Elucidating the mechanism, origin of regioselectivity and substrate scope of structurally diverse 1,2,4-triazoles synthesis via rare type of diazo compounds reactivity

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Supporting Information

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1. Experimental procedures and characterization data

General considerations. All reagents were used as purchased from commercial suppliers without further purification. Dichloromethane (DCM) was freshly distilled over P_2O_5. NMR spectra were recorded using Bruker Avance III spectrometer in $CDCl_3$ or DMSO-d_6 (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; ^{19}F 376.50 MHz); chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standard: 7.26 or 2.5 for ^{1}H and 77.16 or 39.7 ppm for ^{13}C in $CDCl_3$ or DMSO-d_6, respectively; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet/doublets of doublets; coupling constants, *J*, are reported in Hz. Mass spectra were recorded using Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Analytical thin-layer chromatography was carried out on UV-254 silica gel plates using appropriate eluents. Compounds were visualized with short-wavelength UV light. Column chromatography was performed using silica gel Merk grade 60 (0.040−0.063 mm) 230−400 mesh. For gradient mode chromatography, a mixture of *n*-hexane/acetone or petroleum ether/acetone was used as eluent. *n*-Pentane or *n*-heptane can also be used instead of *n*-hexane as a non-polar phase.

Synthesis of starting materials

Almost all of the starting *N*-acylated amino acids **1 (Figure S1)** are known and synthetically available compounds. Most of them were synthesized using well-known methods from the corresponding amino acids and chloroanhydrides[1]. *N*-Acylated amino acids **1g**, **1m**, **1o - 1q**, **1x**, **1ac - 1af** were obtained using alternative methods as described below. Diazo reagents **3 (Figure S2)** were obtained using known methods from the corresponding carbonyl compounds via the diazo transfer reaction[2,3].

Figure S1. Scope of *N*-acylated amino acids used

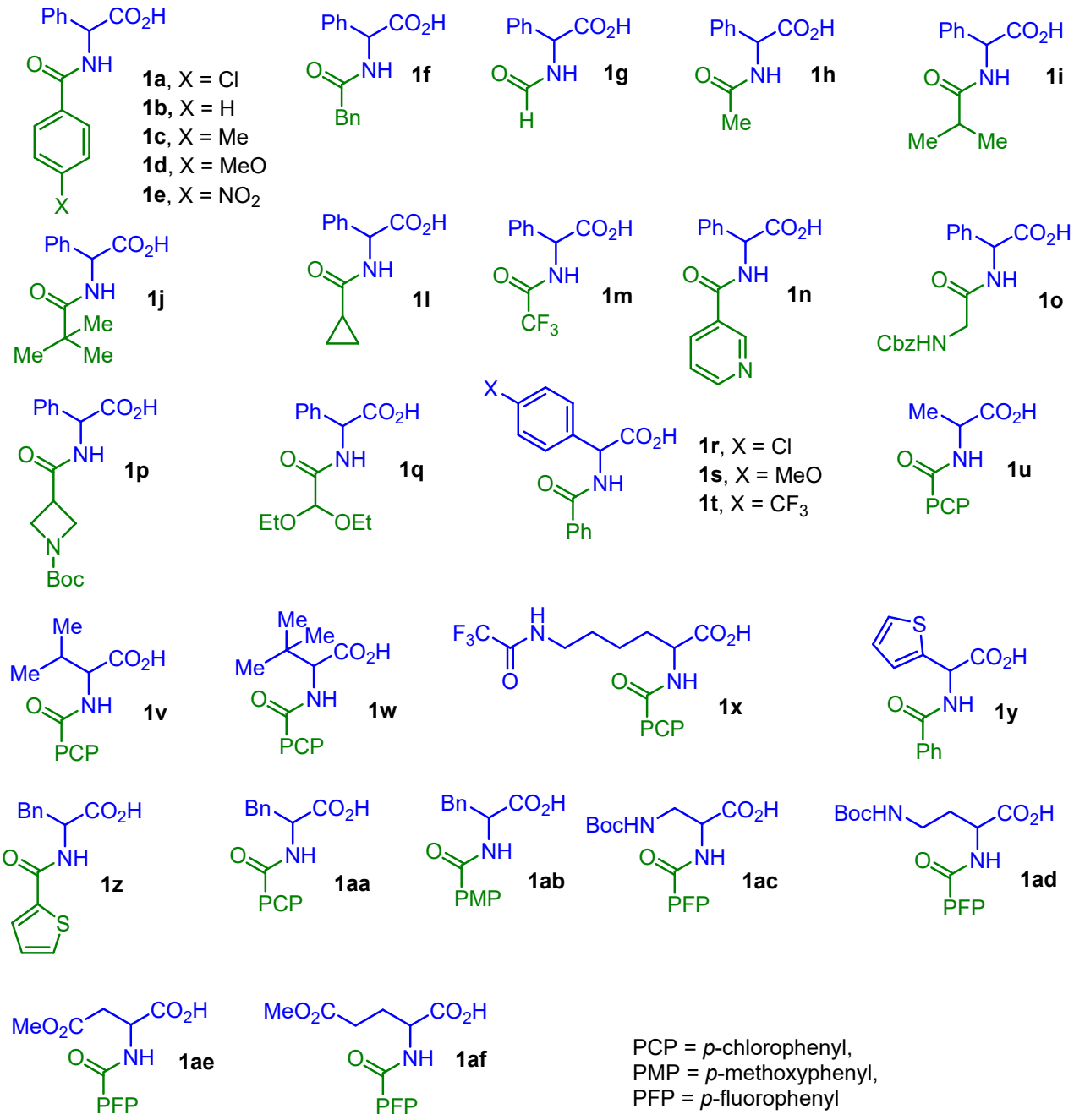
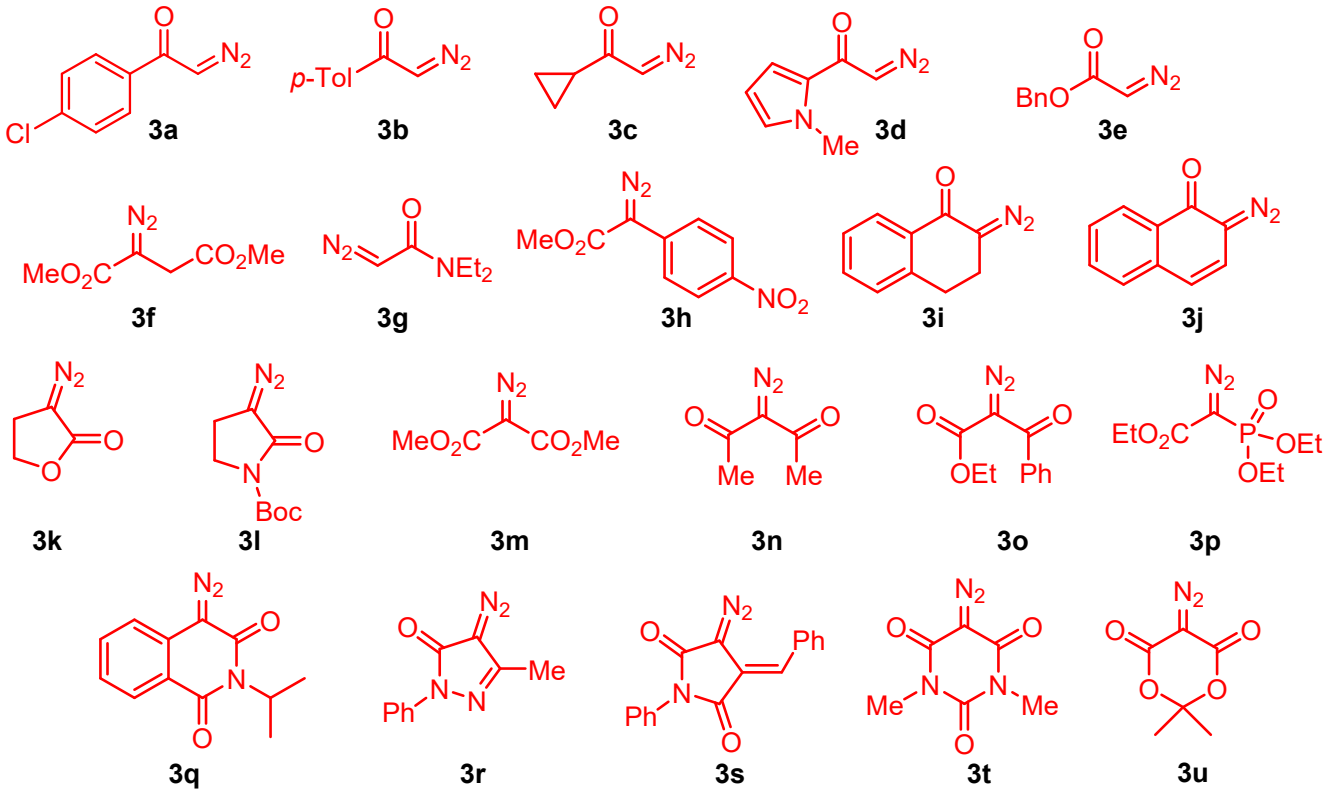
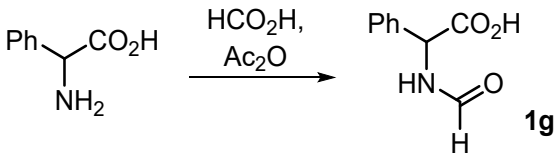


Figure S2. Scope of diazo compounds used

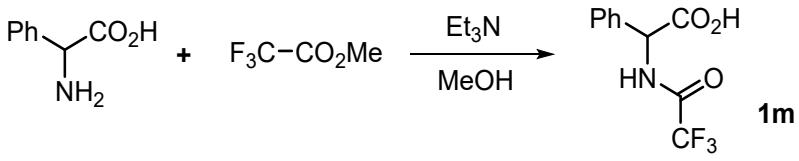


Synthesis of *N*-acylated amino acid 1g



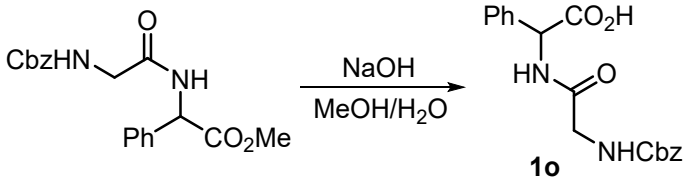
2-Formamido-2-phenylacetic acid (1g). Acetic anhydride (17 mL) was added dropwise to a solution of phenylglycine (3.775 g, 25 mmol) in formic acid (50 mL) while cooling with an ice bath. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 1 hour. Then, 20 mL of ice-cold water was added to the reaction mixture, and it was evaporated to dryness using a rotary evaporator to obtain the pure product. Yield: 4.41 g (98%). White crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 8.91 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.44 – 7.30 (m, 5H), 5.39 (d, J = 7.8 Hz, 1H) ppm.

Synthesis of *N*-acylated amino acid 1m



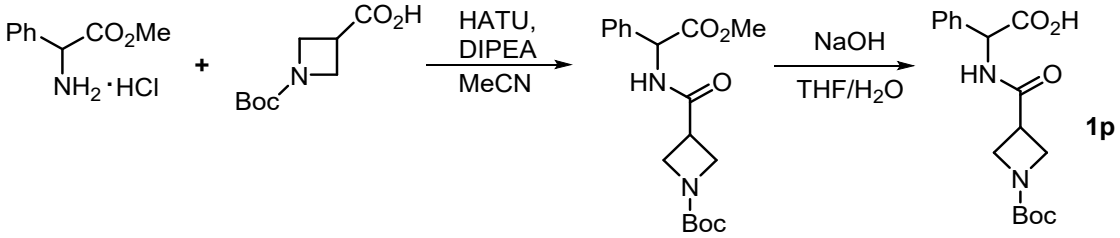
2-Phenyl-2-(2,2,2-trifluoroacetamido)acetic acid (1m). To a suspension of phenylglycine (1.51 g, 10 mmol) in methanol (10 mL) was added triethylamine (2.1 mL), the resulting reaction mixture was stirred for 5 minutes at room temperature. Then ethyl trifluoroacetate (1.51 mL, 15 mmol) was added, the reaction mixture was stirred for 2 days at room temperature. After evaporation under reduced pressure, the resulting yellow oil was dissolved in 30 mL of 10% HCl, resulting in the formation of a white precipitate. The precipitate was extracted with ethyl acetate (3×10 mL), and the organic phase was washed with brine (2×10 mL) and dried over anhydrous Na_2SO_4. The substance was crystallized from chloroform. Yield: 2.30 g (93%). White crystals, m.p. 155-157 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.6 (d, J = 7.5 Hz, 1H), 7.4 – 7.3 (m, 2H), 7.3 – 7.2 (m, 3H), 5.4 (d, J = 7.4 Hz, 1H) ppm.

Synthesis of *N*-acylated amino acid 1o



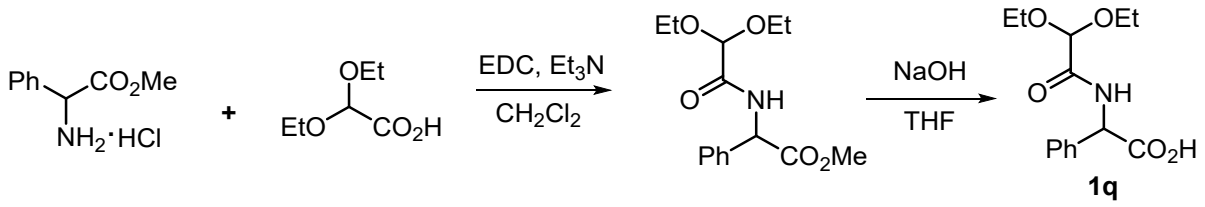
2-(2-(((Benzyloxy)carbonyl)amino)acetamido)-2-phenylacetic acid (1o). To a solution of Cbz-protected dipeptide (1.78 g, 5 mmol) in methanol (20 mL), an aqueous solution of NaOH (260 mg, 6.5 mmol in 5 mL of water) was added. The yellow solution was stirred for 1.5 hours at room temperature. The resulting solution was concenrated on a rotary evaporator, acidified with 10% citric acid to pH 3, and the oil was extracted with 70 mL of ethyl acetate. The organic phase was washed with water (2×25 mL) and brine (25 mL). The solution was dried with anhydrous Na_2SO_4 and evaporated on a rotary evaporator to obtain the pure product. Yield: 1.19 g (70%). White crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.57 (d, J = 7.5 Hz, 1H), 7.43 – 7.25 (m, 10H), 5.36 (d, J = 7.4 Hz, 1H), 5.04 (s, 2H), 3.73 (d, J = 6.2 Hz, 2H) ppm.

Synthesis of *N*-acylated amino acid 1p



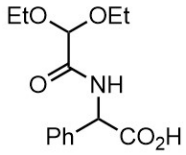
2-(1-(*tert*-Butoxycarbonyl)azetidine-3-carboxamido)-2-phenylacetic acid (1p). To a stirred mixture of *N*-Boc-azetidine-3-carboxylic acid (1.1 g, 5.5 mmol), methyl 2-amino-2-phenylacetate hydrochloride (1.0 g, 5 mmol) and DIPEA (15 mmol) in MeCN (15 mL), HATU (2.85 g, 7.5 mmol) was added in portions. The resulting solution was stirred at room temperature overnight. The resulting mixture was concentrated under reduced pressure, the residue was dissolved in DCM (40 mL), washed with water (20 mL), 1M HCl (20 mL), $NaHCO_3$ (20 mL) and brine (20 mL), and dried with anhydrous Na_2SO_4. The resulting solution was evaporated on a rotary evaporator to yield a dark red oil (3.70 g). The resulting oil was suspended in THF (8 mL), a solution of NaOH (350 mg in 20 mL of water) was added and the mixture was stirred for 3.5 hours at room temperature. The resulting mixture was extracted with DCM (3×10 mL) and the organic washings were discarded. The aqueous solution was acidified with diluted HCl to adjust pH 3 and extracted with chloroform (3×10 mL)/. Combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, and evaporated to obtain the pure product. Yield: 1.515 g (65%). Amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.49 (s, 1H), 7.41 – 7.28 (m, 5H), 7.08 (d, *J* = 7.2 Hz, 1H), 5.60 (d, *J* = 7.1 Hz, 1H), 4.19 – 3.80 (m, 4H), 3.35 – 3.15 (m, 1H), 1.38 (s, 9H) ppm.

Synthesis of *N*-acylated amino acid 1q



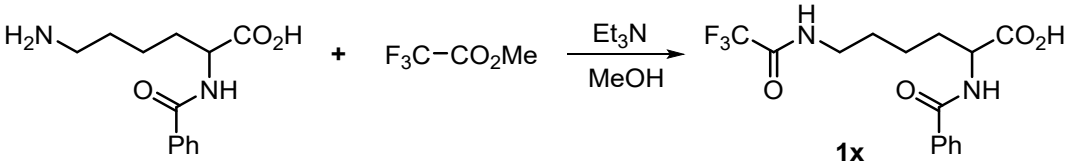
2-(2,2-Diethoxyacetamido)-2-phenylacetic acid (1q)

1st Step: To a suspension of methyl 2-amino-2-phenylacetate hydrochloride (1.21 g, 6 mmol) in DCM (40 mL) was added the solution of 2,2-diethoxyacetic acid (978 mg, 6.6 mmol), followed by addition of Et_3N (707 mg, 7 mmol). To this stirring mixture EDC (1.08 g, 7 mmol) was added at once. Stirring was continued for 18 h. The resulting mixture was washed with water (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($CaCl_2$) and evaporated the product of the first step. Yield: 1.47 g (83%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.31 (m, 5H), 5.57 (d, *J* = 7.5 Hz, 1H), 4.83 (s, 1H), 3.73 (s, 3H), 3.71 – 3.56 (m, 4H), 1.33 – 1.16 (m, 6H) ppm.



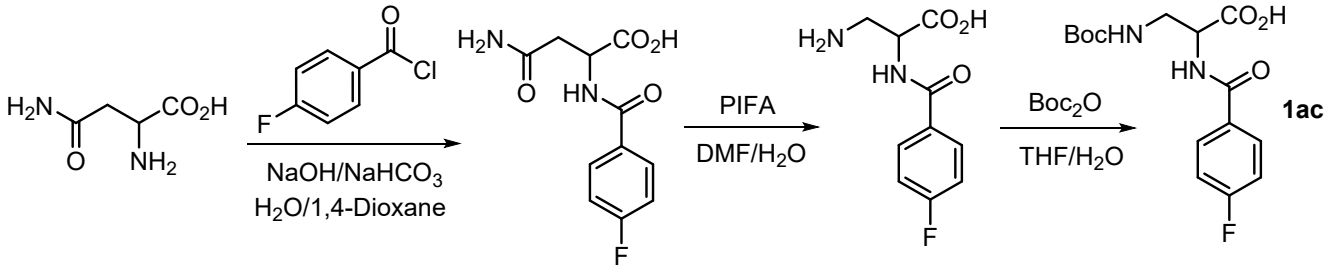
2st Step: Under ice-cooling, to the solution of the obtained substance in THF (5 mL) was added 1M aq. NaOH (10 mL). The mixture was stirred at room temperature for 3 h. THF was removed under reduced pressure, the residual solution was washed with diethyl ether (2×5 mL), cooled with ice bath and acidified with 6M HCl to adjust pH 3. Oily precipitate slowly solidified and was stirred for 20 min in ice bath, then filtered, washed with water and dried in air at 60 °C to give pure acid **1q**. Yield: 1.08 g (64% over 2 steps). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.20 (d, *J* = 7.3 Hz, 1H), 7.49 – 7.21 (m, 5H), 5.32 (d, *J* = 7.3 Hz, 1H), 4.85 (s, 1H), 3.71 – 3.39 (m, 4H), 1.26 – 1.01 (m, 6H) ppm.

Synthesis of *N*-acylated amino acid 1x



***N*^{2}-Benzoyl-*N*^{6}-(2,2,2-trifluoroacetyl)lysine (1x).** To a suspension of *N*-benzoyl lysine (2.5 g, 10 mmol) in methanol (25 mL), triethylamine (2.1 mL, 15 mmol) was added, and the reaction mixture was stirred for 5 minutes at room temperature. Then, methyl trifluoroacetate (1.92 g, 15 mmol) was added. The resulting suspension was stirred at room temperature for 3 days. The resulting colorless solution was evaporated on a rotary evaporator, and the resulting yellow oil was dissolved in ethyl acetate (15 mL), washed with 10% hydrochloric acid (30 mL), extracted with of ethyl acetate (2×10 mL), and the combined organic phases were washed with brine (2×15 mL) and dried with anhydrous Na_2SO_4. The resulting solution was evaporated to afford pure compound **1x**. Yield: 3.307 g (96%). White solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (br.s, 1H), 9.66 (d, J = 7.7 Hz, 1H), 8.44 (t, J = 5.7 Hz, 1H), 7.88 – 7.74 (m, 2H), 7.54 – 7.40 (m, 3H), 4.31 – 4.16 (m, 1H), 3.29 – 3.19 (m, 2H), 1.96 – 1.68 (m, 2H), 1.62 – 1.45 (m, 2H), 1.43 – 1.25 (m, 2H) ppm.

Synthesis of *N*-acylated amino acid 1ac

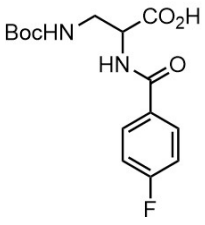


3-((*tert*-Butoxycarbonyl)amino)-2-(4-fluorobenzamido)propanoic acid (1ac)

1st Step: To a stirred ice-cooled solution of asparagine (4.50 g, 30 mmol) and NaOH (2.40 g, 60 mmol) in sat. aq. $NaHCO_3$ (80 mL) was slowly added 4-fluorobenzoyl chloride (4.76 g, 30 mmol) in 1,4-dioxane (10 mL) during 30 min. The reaction mixture was stirred at room temperature overnight, and a suspension was formed. The reaction mixture was acidified with conc. HCl, resulting in the formation of a white precipitate. Upon cooling to 5 °C crystals were filtered, washed with water (2×30 mL), and dried at 60 °C to give pure substance for the next step. Yield: 7.15 g (94%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.69 (d, J = 7.7 Hz, 1H), 7.92 (dd, J = 8.6, 5.5 Hz, 2H), 7.39 (s, 1H), 7.31 (t, J = 8.7 Hz, 2H), 6.93 (s, 1H), 4.73 (td, J = 7.8, 5.4 Hz, 1H), 2.77 – 2.65 (m, 1H), 2.65 – 2.54 (m, 1H) ppm.

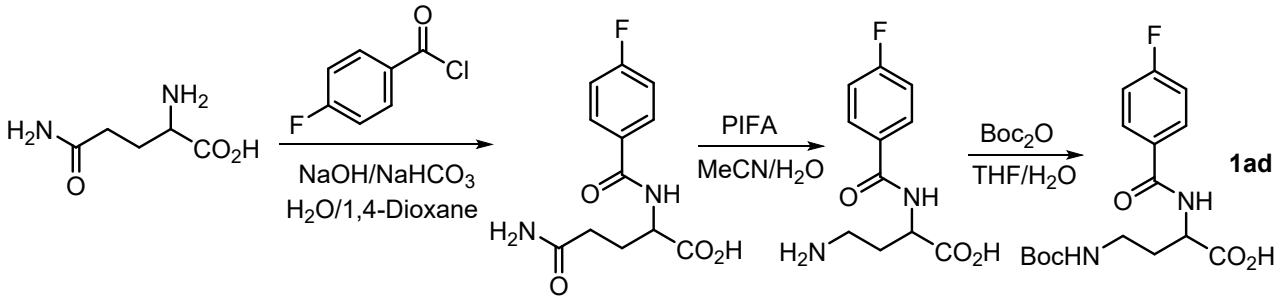
2st Step: To a stirred solution of the obtained *N*-acylated acid (763 mg, 3 mmol) in DMF (14 mL)/H_2O (7 mL) was added at ambient temperature PIFA (1.94 g, 4.5 mmol). After 10 min, pyridine (500 mg, 6.3 mmol) was added and stirring was continued for overnight (18 h). The solvents were removed *in vacuo* (50 °C). The residue was dissolved in water (10 mL), washed with diethyl ether (3×5 mL) and the aqueous layer was evaporated. Brown residual oil was dissolved in EtOH (5 mL) and the product was precipitated with Et_2O (15 mL). White solid was filtered, washed with Et_2O (5 mL) and dried in air.

Yield: 480 mg (70%). White solid. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.95 – 7.86 (m, 2H), 7.33 – 7.21 (m, 2H), 4.71 (t, *J* = 6.9 Hz, 1H), 3.56 (dd, *J* = 13.2, 5.8 Hz, 1H), 3.38 (dd, *J* = 13.2, 7.7 Hz, 1H) ppm.



3st Step: Solid $NaHCO_3$ (420 mg, 5 mmol) was added to a suspension of reactant (452 mg, 2 mmol) in a 1:1 (v:v) mixture of water and THF (10 mL), followed by addition of the solution of Boc_2O (873 mg, 4 mmol) in THF (3 mL). Gas evolution was observed and all solids gradually dissolved. The reaction mixture was stirred at room temperature for 20 h and evaporated partially to remove THF. Aqueous solution was washed with Et_2O (2×10 mL) to removed the excess of Boc_2O. Under ice-cooling, aq. phase was acidified with 6M HCl to adjust pH 3, and a precipitate formed. The mixture was extracted with Et_2O (3×10 mL), combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated to afford pure acid **1ac**. Yield: 540 mg (83%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.53 (d, *J* = 7.7 Hz, 1H), 7.94 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.32 (t, *J* = 8.8 Hz, 2H), 7.00 (t, *J* = 6.0 Hz, 1H), 4.46 (td, *J* = 7.3, 4.9 Hz, 1H), 3.49 – 3.40 (m, 2H), 1.35 (s, 9H) ppm.

Synthesis of *N*-acylated amino acid 1ad

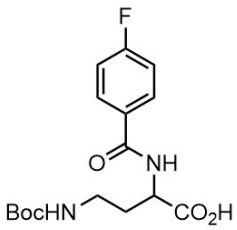


4-((*tert*-Butoxycarbonyl)amino)-2-(4-fluorobenzamido)butanoic acid (1ad)

1st Step: To a stirred ice-cooled solution of glutamine (4.40 g, 30 mmol) and NaOH (2.40 g, 60 mmol) in sat. aq. $NaHCO_3$ (80 mL) was slowly added 4-fluorobenzoyl chloride (4.76 g, 30 mmol) in 1,4-dioxane (10 mL) during 30 min. The reaction mixture was stirred at room temperature overnight, and a suspension was formed. Then the resulting mixture was acidified with conc. HCl, and the suspension dissolved. When the resulting solution was ultrasonicated, a precipitate formed. The suspension was cooled with ice, the precipitate was filtered, washed with water (2×30 mL), and dried at 60 °C. to yield *N*-acylated glutamine pure enough for the next step. Yield: 6.55 g (81%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.77 (d, *J* = 7.4 Hz, 1H), 8.05 – 7.90 (m, 2H), 7.45 – 7.22 (m, 3H), 6.83 (s, 1H), 4.41 – 4.29 (m, 1H), 2.30 – 2.17 (m, 2H), 2.16 – 2.03 (m, 1H), 2.02 – 1.87 (m, 1H) ppm

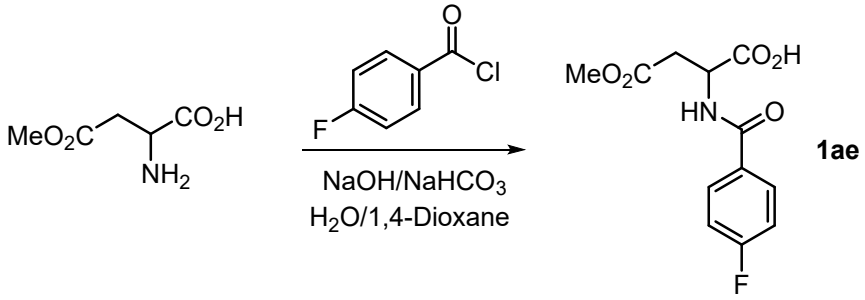
2st Step: To a solution of product from previous step (1.34 g, 5 mmol) in MeCN (20 mL)/H_2O (5 mL) under ice-cooling was added PIFA (2.58 g, 6 mmol). The reaction mixture was stirred at room temperature overnight and for 30 minutes at 80 °C. The reaction progress was monitored by TLC ($CHCl_3$-MeOH-AcOH, 90:9:1). Most of the solvents were evaporated under reduced pressure (at 50 °C), and the semi-solid residue was dissolved in conc. HCl (3 mL), washed with Et_2O (2×20 mL), and evaporated to dryness to give the corresponding γ-amino acid. Yield: 1.2 g (98%). White amorphous solid. ^{1}H NMR

(400 MHz, DMSO-d_6) δ 8.94 (d, J = 7.5 Hz, 1H), 8.20 (s, 2H), 8.09 – 7.98 (m, 2H), 7.37 – 7.27 (m, 2H), 4.51 – 4.37 (m, 1H), 2.99 – 2.77 (m, 2H), 2.24 – 2.02 (m, 2H) ppm.



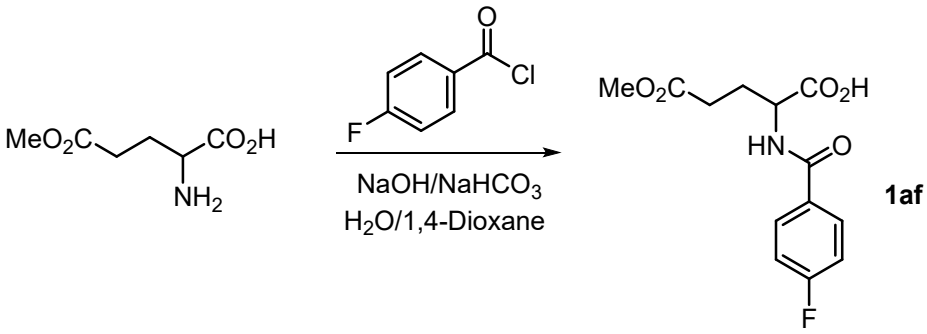
3st Step: Solid $NaHCO_3$ (1.26 g, 15 mmol) was added to a solution of reactant (1.2 g, 5 mmol) in a 1:1 (v:v) mixture of water and THF (20 mL), followed by addition of the solution of Boc_2O (2.18 g, 10 mmol) in THF (6 mL). The reaction mixture was stirred at room temperature for 20 h and evaporated partially to remove THF. The aqueous solution was washed with Et_2O (2×10 mL) to removed the excess of Boc_2O. Under ice-cooling, the aqueous phase was acidified with 6M HCl to adjust pH 3 and extracted with Et_2O (3×20 mL). Combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated to afford compound **1ad**. Yield: 940 mg (55%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.62 (d, J = 7.7 Hz, 1H), 8.05 – 7.87 (m, 2H), 7.39 – 7.25 (m, 2H), 6.83 (t, J = 5.6 Hz, 1H), 4.46 – 4.30 (m, 1H), 3.16 – 2.94 (m, 2H), 2.08 – 1.92 (m, 1H), 1.93 – 1.79 (m, 1H), 1.36 (s, 9H) ppm.

Synthesis of *N*-acylated amino acid 1ae



2-(4-Fluorobenzamido)-4-methoxy-4-oxobutanoic acid (1ae). To a stirred ice-cooled solution of aspartic acid monomethyl ester (3.64 g, 20 mmol) and NaOH (1.60 g, 40 mmol) in sat. aq. $NaHCO_3$ (70 mL) was slowly added 4-fluorobenzoyl chloride (3.17 g, 20 mmol) in 1,4-dioxane (10 mL) during 30 min. The reaction mixture was stirred at room temperature overnight, washed with ethyl acetate (2×25 mL), the aqueous phase was acidified with conc. HCl, and the precipitate was cooled with ice bath, filtered, washed with water (2×30 mL), and dried at 60 °C. Yield: 3.66 g (68%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 8.83 (d, J = 7.9 Hz, 1H), 7.98 – 7.84 (m, 2H), 7.32 (t, J = 8.8 Hz, 2H), 4.79 (td, J = 7.9, 5.8 Hz, 1H), 3.62 (s, 3H), 2.94 (dd, J = 16.2, 5.9 Hz, 1H), 2.80 (dd, J = 16.2, 8.1 Hz, 1H) ppm.

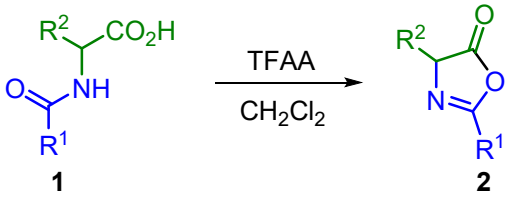
Synthesis of *N*-acylated amino acid 1af



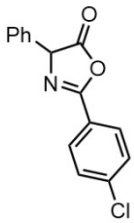
2-(4-Fluorobenzamido)-5-methoxy-5-oxopentanoic acid (1af). To a stirred ice-cooled solution of glutamic acid monomethyl ester (2.5 g, 12.6 mmol) and NaOH (1.04 g, 26 mmol) in sat. aq. $NaHCO_3$ (50 mL) was slowly added 4-fluorobenzoyl chloride (2.0 g, 12.6 mmol) in 1,4-dioxane (10 mL) during 30 min. The reaction mixture was stirred at room temperature overnight. It was then washed with ethyl acetate (2×20 mL), and acidified with conc. HCl. The precipitate formed was cooled with ice, filtered, washed with water (2×20 mL) and dried at 60 °C. Yield: 2.4 g (67%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.65 (d, J = 7.7 Hz, 1H), 8.05 – 7.87 (m, 2H), 7.31 (t, J = 8.9 Hz, 2H), 4.48 – 4.34 (m, 1H), 3.59 (s, 3H), 2.50 – 2.38 (m, 2H), 2.24 – 2.08 (m, 1H), 2.08 – 1.93 (m, 1H) ppm.

Synthesis of azlactones 2

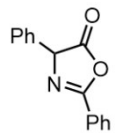
General procedure GP1 for the preparation of compounds 2a-2d



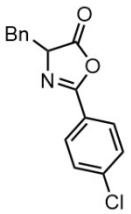
To a suspension of *N*-acylated amino acid **1** (1 equiv.) in DCM (20 mL), trifluoroacetic anhydride (2 equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature. The resulting mixture was washed with soda (2×25 mL) and brine (25 mL). The organic layer was dried with anhydrous Na_2SO_4. To obtain the pure product, the resulting solution was concentrated using a rotary evaporator.



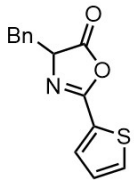
2-(4-Chlorophenyl)-4-phenyloxazol-5(4*H*)-one (2a). Yield: 698 mg (70%). Yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.46 – 7.35 (m, 5H), 5.54 (s, 1H) ppm.



2,4-Diphenyloxazol-5(4*H*)-one (2b). Yield: 1.104 g (93%). White solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.06 (m, 2H), 7.65 – 7.59 (m, 1H), 7.53 (dd, J = 8.3, 6.9 Hz, 2H), 7.47 – 7.36 (m, 5H), 5.54 (s, 1H) ppm.

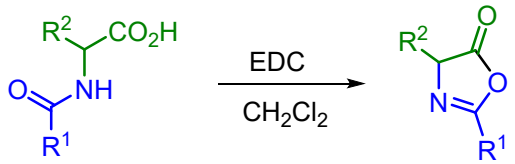


4-Benzyl-2-(4-chlorophenyl)oxazol-5(4*H*)-one (2c). Yield: 714 mg (50%). White solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.15 (m, 5H), 4.69 (dd, *J* = 6.7, 4.9 Hz, 1H), 3.37 (dd, *J* = 14.0, 4.9 Hz, 1H), 3.19 (dd, *J* = 14.0, 6.7 Hz, 1H) ppm.



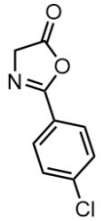
4-Benzyl-2-(thiophen-2-yl)oxazol-5(4*H*)-one (2d). Yield: 600 mg (47%). Light-brown solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.57 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.31 – 7.20 (m, 6H), 7.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.68 (dd, *J* = 6.3, 5.1 Hz, 1H), 3.36 (dd, *J* = 14.0, 5.1 Hz, 1H), 3.20 (dd, *J* = 14.0, 6.3 Hz, 1H) ppm.

General procedure GP2 for the preparation of compounds 2e-2f

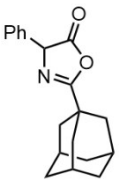


1 **2**

To a suspension of *N*-acylated amino acid **1** (1 equiv.) in DCM (2 mL per 1 mmol), EDC (1.2 equiv.) was added at 0 °C, and the resulting reaction mixture was stirred for 2 hours at 0 °C. Then, 20 mL of water was added to the reaction mixture, and the organic layer was washed with 10 mL of water and 15 mL of brine, and dried with anhydrous Na_2SO_4. To obtain the pure product, the solvent was removed under reduced pressure.

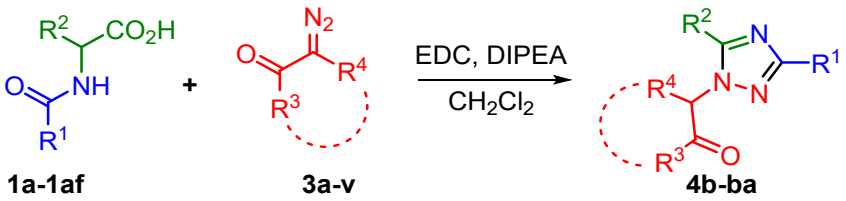


2-(4-Chlorophenyl)oxazol-5(4*H*)-one (2e). Yield: 1.342 g (89%). White solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.42 (s, 2H) ppm.



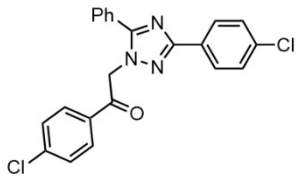
2-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-4-phenyloxazol-5(4*H*)-one (2f). Yield: 420 mg (42%). Yellow viscous oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.35 (m, 2H), 7.60 – 7.43 (m, 3H), 5.59 (s, 1H), 2.14 – 1.58 (m, 15H) ppm.

Synthesis of 1,2,4-Triazole Derivatives 4

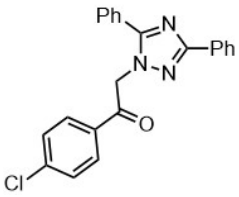


General procedure GP3 for the preparation of compounds 4a-4j, 4l-4ba.

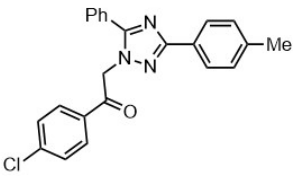
A solution or suspension of the corresponding *N*-acylated amino acid **1** (0.8 mmol, 2 equiv.) and EDC hydrochloride (0.9 mmol, 2.25 equiv.) in dry DCM (3 mL) was placed in a screw-cap, thick-walled vial and stirred at 40 °C using heating block. The corresponding diazo compound **3** (0.4 mmol, 1 equiv.) and DIPEA (0.4 mmol, 1 equiv.) were added sequentially. In most cases, gas evolution was observed upon the addition of DIPEA. The reaction mixture was then sealed and stirred at 40 °C for 6–20 hours. After the complete conversion of the diazo reagent (controlled by TLC), the reaction mixture was directly subjected to silica gel column chromatography (eluting with petroleum ether/acetone) to obtain the pure target compound.



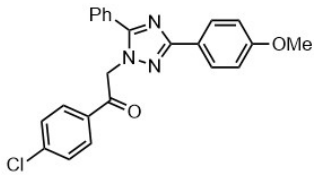
1-(4-Chlorophenyl)-2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4a). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 145 mg (89%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.68 – 7.58 (m, 2H), 7.55 – 7.44 (m, 5H), 7.41 (d, *J* = 8.6 Hz, 2H), 5.64 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.1, 160.5, 157.2, 141.2, 135.5, 132.4, 130.8, 129.6, 129.5, 129.1, 128.8, 128.8, 128.7, 128.0, 127.0, 55.3 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2N_3O$ $[M+H]^+$ 408.0665. found 408.0666.



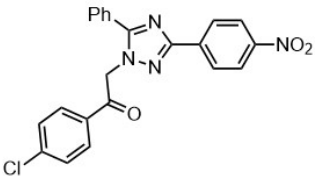
1-(4-Chlorophenyl)-2-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4b). Prepared according to GP3 using *N*-acylated amino acid **1b** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 120 mg (80%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 6.4 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.63 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.55 – 7.29 (m, 8H), 5.63 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.4, 161.8, 157.2, 141.0, 132.5, 130.7, 130.5, 129.5, 129.5, 129.4, 129.0, 128.6, 128.6, 127.7, 126.6, 55.2 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{17}ClN_3O$ $[M+H]^+$ 374.1055 found 374.1062.



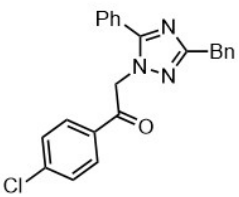
1-(4-Chlorophenyl)-2-(5-phenyl-3-(*p*-tolyl)-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4c). Prepared according to GP3 using *N*-acylated amino acid **1c** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 135 mg (87%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 7.9 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.73 – 7.59 (m, 2H), 7.57 – 7.41 (m, 5H), 7.27 (d, *J* = 7.8 Hz, 2H), 5.64 (s, 2H), 2.42 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.4, 161.9, 157.1, 141.0, 139.4, 132.6, 130.5, 129.5, 129.4, 129.3, 129.0, 128.6, 127.9, 127.7, 126.5, 55.2, 21.4 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O$ $[M+H]^+$ 388.1211 found 388.1217.



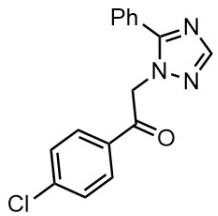
1-(4-Chlorophenyl)-2-(3-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4d). Prepared according to GP3 using *N*-acylated amino acid **1d** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 139 mg (86%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.71 – 7.55 (m, 2H), 7.55 – 7.33 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.60 (s, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.4, 161.7, 160.7, 157.1, 141.0, 132.6, 130.5, 129.5, 129.4, 129.0, 128.6, 128.0, 127.7, 123.4, 113.9, 55.3, 55.1 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O_2$ $[M+H]^+$ 404.1160 found 404.1168.



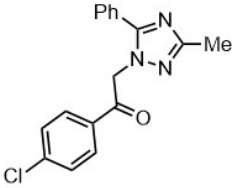
1-(4-Chlorophenyl)-2-(3-(4-nitrophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4e). Prepared according to GP3 using *N*-acylated amino acid **1e** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 150 mg (89%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 – 8.18 (m, 4H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.58 (m, 2H), 7.59 – 7.35 (m, 5H), 5.69 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.1, 159.9, 157.9, 148.3, 141.3, 136.8, 132.3, 130.8, 129.6, 129.6, 129.2, 128.6, 127.2, 127.2, 123.9, 55.3 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{16}ClN_4O_3$ $[M+H]^+$ 419.0905 found 419.0913.



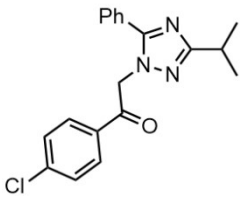
2-(3-Benzyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)ethan-1-one (4f). Prepared according to GP3 using *N*-acylated amino acid **1f** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 137 mg (88%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.54 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.52 – 7.34 (m, 7H), 7.34 – 7.17 (m, 3H), 5.55 (s, 2H), 4.15 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.6, 163.0, 156.9, 140.9, 138.1, 132.5, 130.4, 129.5, 129.4, 129.0, 129.0, 128.5, 128.5, 127.7, 126.5, 55.0, 34.8 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O$ $[M+H]^+$ 388.1211 found 388.1210.



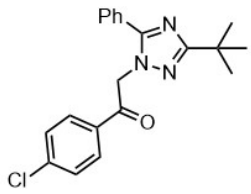
1-(4-Chlorophenyl)-2-(5-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4g). Prepared according to GP3 using *N*-acylated amino acid **1g** and diazo reagent **3a**; eluent – petroleum ether–acetone (15% to 70% of acetone). Yield: 88 mg (74%). Yellow-green oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.56 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.53 – 7.40 (m, 5H), 5.62 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.3, 156.4, 151.5, 141.1, 132.5, 130.5, 129.5, 129.5, 129.0, 128.5, 127.6, 55.1 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{13}ClN_3O$ $[M+H]^+$ 298.0742 found 298.0741.



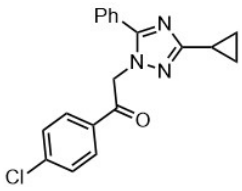
1-(4-Chlorophenyl)-2-(3-methyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4h). Prepared according to GP3 using *N*-acylated amino acid **1h** and diazo reagent **3a**; eluent – diethyl ether. Yield: 92 mg (74%). Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.6 Hz, 2H), 7.55 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.49 – 7.43 (m, 5H), 5.54 (s, 2H), 2.47 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.6, 160.7, 156.7, 141.0, 132.5, 130.4, 129.5, 129.4, 129.0, 128.4, 127.7, 54.8, 13.9 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{15}ClN_3O$ $[M+H]^+$ 312.0898 found 312.0899.



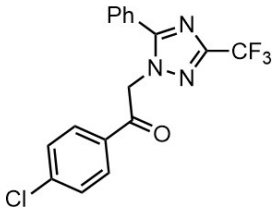
1-(4-Chlorophenyl)-2-(3-isopropyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4i). Prepared according to GP3 using *N*-acylated amino acid **1i** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 130 mg (99%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.56 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.52 – 7.37 (m, 5H), 5.55 (s, 2H), 3.15 (p, *J* = 7.0 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.7, 169.1, 156.5, 140.8, 132.5, 130.2, 129.5, 129.3, 128.9, 128.5, 127.9, 54.9, 28.2, 21.6 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{19}ClN_3O$ $[M+H]^+$ 340.1211 found 340.1217.



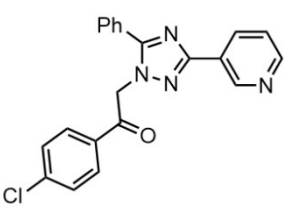
2-(3-(*tert*-Butyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)ethan-1-one (4j). Prepared according to GP3 using *N*-acylated amino acid **1j** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 119 mg (84%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.54 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.44 – 7.39 (m, 3H), 5.53 (s, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.7, 171.7, 156.5, 140.8, 132.6, 130.1, 129.5, 129.3, 128.9, 128.6, 128.2, 54.9, 32.8, 29.6 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClN_3O$ $[M+H]^+$ 354.1368 found 354.1367.



1-(4-Chlorophenyl)-2-(3-cyclopropyl-5-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4l). Prepared according to GP3 using *N*-acylated amino acid **1l** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 133 mg (99%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.51 – 7.37 (m, 5H), 5.50 (s, 2H), 2.09 (tt, *J* = 8.4, 5.0 Hz, 1H), 1.12 – 1.03 (m, 2H), 1.03 – 0.95 (m, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.7, 165.8, 156.5, 140.9, 132.5, 130.3, 129.5, 129.4, 128.9, 128.5, 127.9, 54.8, 9.0, 7.9 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}ClN_3O$ $[M+H]^+$ 338.1055 found 338.1057.

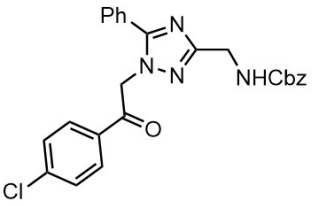


1-(4-Chlorophenyl)-2-(5-phenyl-3-(trifluoromethyl)-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4m). Prepared according to GP3 using *N*-acylated amino acid **1m** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 140 mg (96%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.55 (m, 2H), 7.55 – 7.39 (m, 5H), 5.68 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.3, 158.3, 153.7 (q, $^{2}J_{C-F}$ = 39.9 Hz), 141.5, 132.1, 131.2, 129.6, 129.5, 129.2, 128.6, 126.3, 119.2 (q, $^{1}J_{C-F}$ = 270.2 Hz), 55.6 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -65.34 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{12}ClF_3N_3O$ $[M+H]^+$ 366.0616 found 366.0622.

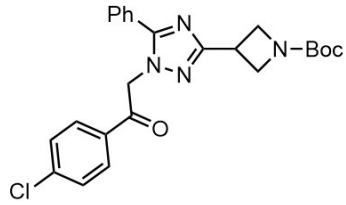


1-(4-Chlorophenyl)-2-(5-phenyl-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4n). Prepared according to GP3 using *N*-acylated amino acid **1n** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 48 mg (32%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.39 (s, 1H), 8.72 – 8.57 (m, 1H), 8.46 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.72 – 7.57 (m, 2H), 7.49 (t, *J* = 8.1 Hz, 5H), 7.41 (dd, *J* = 8.0, 4.9 Hz, 1H), 5.67 (s, 2H) ppm. ^{13}C NMR

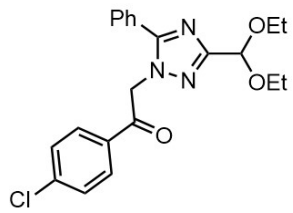
(101 MHz, Chloroform-*d*) δ 190.2, 159.5, 157.7, 149.9, 147.7, 141.2, 134.1, 132.4, 130.7, 129.6, 129.5, 129.1, 128.6, 127.5, 127.0, 123.5, 55.3 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{16}ClN_4O$ $[M+H]^+$ 375.1007 found 375.1015.



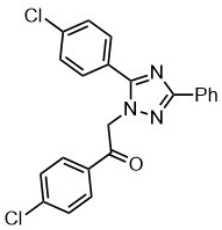
Benzyl ((1-(2-(4-chlorophenyl)-2-oxoethyl)-5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)carbamate (4o). Prepared according to GP3 using *N*-acylated amino acid **1o** and diazo reagent **3a**; eluent – petroleum ether–acetone (15% to 70% of acetone). Yield: 165 mg (90%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.79 (m, 2H), 7.57 – 7.51 (m, 2H), 7.51 – 7.40 (m, 5H), 7.39 – 7.28 (m, 6H), 5.59 (s, 1H), 5.56 (s, 2H), 5.13 (s, 2H), 4.56 (d, *J* = 5.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.2, 160.4, 157.1, 156.3, 141.2, 136.5, 132.4, 130.7, 129.5, 129.5, 129.1, 128.5, 128.1, 128.0, 127.1, 66.9, 55.1, 39.0 ppm. HRMS (ESI), *m/z* calcd for $C_{25}H_{22}ClN_4O_3$ $[M+H]^+$ 461.1375 found 461.1372.



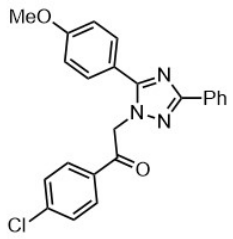
***tert*-Butyl 3-(1-(2-(4-chlorophenyl)-2-oxoethyl)-5-phenyl-1*H*-1,2,4-triazol-3-yl)azetidine-1-carboxylate (4p)**. Prepared according to GP3 using *N*-acylated amino acid **1p** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 157 mg (87%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.80 (m, 2H), 7.61 – 7.51 (m, 2H), 7.52 – 7.38 (m, 5H), 5.57 (s, 2H), 4.28 (d, *J* = 8.2 Hz, 4H), 3.92 (p, *J* = 7.5 Hz, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.4, 163.9, 157.3, 156.2, 141.2, 132.4, 130.6, 129.5, 129.5, 129.1, 128.5, 127.5, 79.4, 54.9, 54.2, 54.2, 28.4, 27.3 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{26}ClN_4O_3$ $[M+H]^+$ 453.1685 found 453.1682.



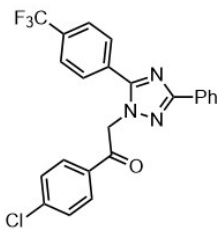
1-(4-Chlorophenyl)-2-(3-(diethoxymethyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4q). Prepared according to GP3 using *N*-acylated amino acid **1q** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 158 mg (99%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.88 – 7.75 (m, 2H), 7.61 – 7.47 (m, 2H), 7.47 – 7.32 (m, 5H), 5.70 (s, 1H), 5.60 (s, 2H), 3.71 (dddd, J = 16.7, 9.6, 7.1, 2.6 Hz, 4H), 1.23 (t, J = 7.1 Hz, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.2, 161.0, 157.0, 140.9, 132.4, 130.4, 129.4, 129.4, 128.9, 128.6, 127.5, 96.7, 61.6, 55.2, 15.1 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{23}ClN_3O_3$ $[M+H]^+$ 400.1423 found 400.1418.



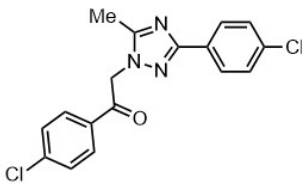
1-(4-Chlorophenyl)-2-(5-(4-chlorophenyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4r). Prepared according to GP3 using *N*-acylated amino acid **1r** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 132 mg (81%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.05 (m, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.54 – 7.35 (m, 7H), 5.61 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.3, 161.9, 156.3, 141.2, 136.8, 132.4, 130.6, 129.9, 129.6, 129.5, 129.5, 129.4, 128.6, 126.5, 126.2, 55.2 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2N_3O$ $[M+H]^+$ 408.0665 found 408.0675.



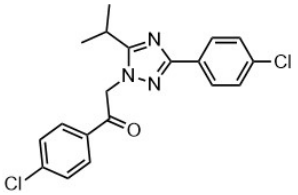
1-(4-Chlorophenyl)-2-(5-(4-methoxyphenyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4s). Prepared according to GP3 using *N*-acylated amino acid **1s** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 138 mg (85%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 6.4 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.52 – 7.36 (m, 5H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.62 (s, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.5, 161.7, 161.3, 157.1, 141.0, 132.6, 130.8, 130.1, 129.6, 129.4, 129.3, 128.5, 126.6, 119.9, 114.5, 55.4, 55.2 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O_2$ $[M+H]^+$ 404.1160 found 404.1163.



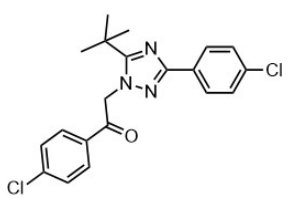
1-(4-Chlorophenyl)-2-(3-phenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4t). Prepared according to GP3 using *N*-acylated amino acid **1t** and diazo reagent **3a**; eluent – petroleum ether-acetone (5% to 30% of acetone). Yield: 143 mg (81%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.08 (m, 2H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.47 (m, 2H), 7.48 – 7.38 (m, 3H), 5.64 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.1, 162.1, 155.9, 141.3, 132.4 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 132.3, 131.3, 130.4, 129.6, 129.6, 129.5, 129.1, 128.6, 126.6, 126.0 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.6 (q, $^{1}J_{C\text{-}F}$ = 272.6 Hz), 55.3 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.0 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{16}ClF_3N_3O$ $[M+H]^+$ 442.0929 found 442.0939.



1-(4-Chlorophenyl)-2-(3-(4-chlorophenyl)-5-methyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-one (4u). Prepared according to GP3 using *N*-acylated amino acid **1u** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 116 mg (84%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.55 (s, 2H), 2.46 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.5, 160.1, 154.8, 141.2, 135.1, 132.3, 129.6, 129.5, 129.3, 128.8, 127.6, 54.4, 12.0 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{14}Cl_2N_3O$ $[M+H]^+$ 346.0508 found 346.0509.

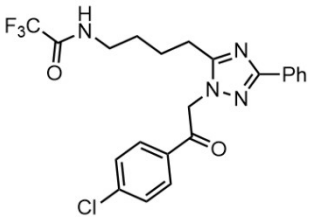


1-(4-Chlorophenyl)-2-(3-(4-chlorophenyl)-5-isopropyl-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4v). Prepared according to GP3 using *N*-acylated amino acid **1v** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 133 mg (87%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 5.56 (s, 2H), 3.05 – 2.73 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.9, 163.1, 160.3, 141.1, 134.9, 132.5, 132.5, 129.6, 129.5, 128.7, 127.8, 54.1, 26.1, 21.4 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{18}Cl_2N_3O$ $[M+H]^+$ 374.0821 found 374.0817.

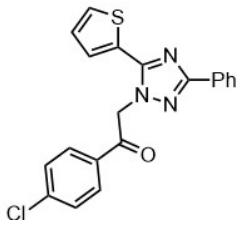


2-(5-(*tert*-Butyl)-3-(4-chlorophenyl)-1*H*-1,2,4-triazol-1-yl)-1-(4-chloro-phenyl)-ethan-1-one (4w). Prepared according to GP3 using *N*-acylated amino acid **1w** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of

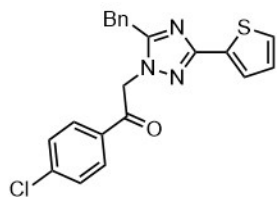
acetone). Yield: 96 mg (62%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 5.73 (s, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.3, 164.3, 159.3, 141.0, 134.8, 132.6, 129.7, 129.5, 129.4, 128.6, 127.8, 56.5, 33.0, 29.5 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{20}Cl_2N_3O$ $[M+H]^+$ 388.0978 found 388.0976.



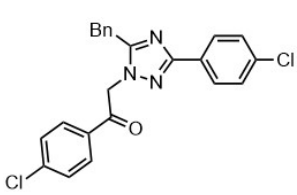
***N*-(4-(1-(2-(4-Chlorophenyl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-butyl)-2,2,2-trifluoroacetamide (4x)**. Prepared according to GP3 using *N*-acylated amino acid **1x** and diazo reagent **3a**; eluent – petroleum ether–acetone (15% to 70% of acetone). Yield: 155 mg (83%). Yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (t, *J* = 5.7 Hz, 1H), 8.11 – 7.98 (m, 2H), 7.86 – 7.75 (m, 2H), 7.73 – 7.65 (m, 2H), 7.55 – 7.47 (m, 1H), 7.43 (dd, *J* = 8.2, 6.6 Hz, 2H), 6.16 (s, 2H), 3.28 (q, *J* = 6.5 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.72 (p, *J* = 7.7 Hz, 2H), 1.65 – 1.51 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.6, 166.6, 160.5, 151.7 (d, $^2J_{C\text{-}F}$ = 38.2 Hz), 139.8, 135.1, 133.1, 131.4, 130.7, 129.5, 128.6, 127.6, 119.9 (d, $^1J_{C\text{-}F}$ = 269.4 Hz), 55.7, 39.1, 29.1, 24.9, 24.7 ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ -64.07 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{21}ClF_3N_4O_2$ $[M+H]^+$ 465.1300 found 465.1301.



1-(4-Chlorophenyl)-2-(3-phenyl-5-(thiophen-2-yl)-1*H*-1,2,4-triazol-1-yl)ethan-1-one (4y). Prepared according to GP3 using *N*-acylated amino acid **1y** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 120 mg (79%). Violet amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 6.8 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.32 (m, 7H), 7.09 (t, *J* = 4.4 Hz, 1H), 5.76 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.9, 161.7, 151.4, 141.1, 132.4, 130.4, 129.6, 129.5, 129.5, 129.0, 128.9, 128.6, 128.4, 128.0, 126.6, 55.7 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{15}ClN_3OS$ $[M+H]^+$ 380.0619 found 380.0617.

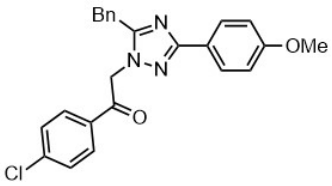


2-(5-Benzyl-3-(thiophen-2-yl)-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)-ethan-1-one (4z). Prepared according to GP3 using *N*-acylated amino acid **1z** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 131 mg (83%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.22 – 7.15 (m, 2H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.30 (s, 2H), 4.23 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.4, 157.4, 156.2, 141.0, 134.7, 133.5, 132.3, 129.4, 129.4, 129.0, 128.6, 127.7, 127.4, 126.4, 126.3, 54.7, 32.7 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{17}ClN_3OS$ $[M+H]^+$ 394.0775 found 394.0779.

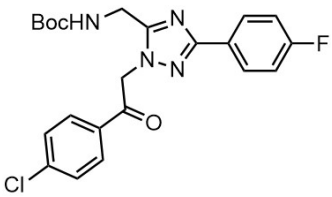


2-(5-Benzyl-3-(4-chlorophenyl)-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)-ethan-1-one (4aa). Prepared according to GP3 using *N*-acylated amino acid **1aa** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 144 mg (85%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 6.9 Hz, 3H), 7.22 – 7.12 (m, 2H), 5.30 (s, 2H), 4.21

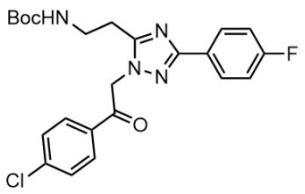
(s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.6, 160.4, 156.4, 141.0, 135.1, 134.8, 132.3, 129.4, 129.4, 129.4, 129.0, 128.8, 128.6, 127.7, 127.4, 54.8, 32.8 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{18}Cl_2N_3O$ $[M+H]^+$ 422.0821 found 422.0828.



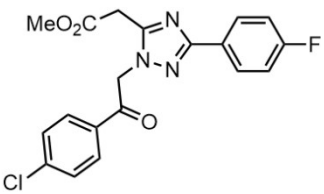
2-(5-Benzyl-3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)ethan-1-one (4ab). Prepared according to GP3 using *N*-acylated amino acid **1ab** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 133 mg (80%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.22 (m, 3H), 7.23 – 7.16 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.31 (s, 2H), 4.23 (s, 2H), 3.87 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.7, 161.0, 160.6, 156.0, 140.9, 134.9, 132.4, 129.5, 129.4, 129.0, 128.6, 127.9, 127.3, 114.0, 55.3, 54.7, 32.7 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{21}ClN_3O_2$ $[M+H]^+$ 418.1317 found 418.1315.



***tert*-Butyl ((1-(2-(4-chlorophenyl)-2-oxoethyl)-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)methyl)carbamate (4ac)**. Prepared according to GP3 using *N*-acylated amino acid **1ac** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 91 mg (51%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (dd, J = 8.7, 5.6 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.09 (t, J = 8.7 Hz, 2H), 5.84 (s, 2H), 5.41 (s, 1H), 4.43 (d, J = 6.2 Hz, 2H), 1.31 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.1, 163.6 (d, $^1J_{C\text{-}F}$ = 248.6 Hz), 160.5, 155.9, 155.2, 141.0, 132.5, 129.6, 129.4, 128.3 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 126.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 80.4, 54.9, 35.7, 28.2 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.77 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{23}ClFN_4O_3$ $[M+H]^+$ 445.1437 found 445.1447.

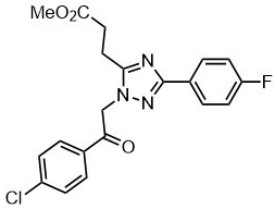


***tert*-Butyl (2-(1-(2-(4-chlorophenyl)-2-oxoethyl)-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate (4ad)**. Prepared according to GP3 using *N*-acylated amino acid **1ad** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 152 mg (83%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 5.60 (s, 2H), 5.31 (s, 1H), 3.60 (q, *J* = 6.3 Hz, 2H), 2.88 (t, *J* = 6.3 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.8, 163.6 (d, $^1J_{C\text{-}F}$ = 248.3 Hz), 160.4, 156.2, 156.1, 141.2, 132.4, 129.6, 129.5, 128.3 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 126.9 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 79.6, 54.2, 38.1, 28.4, 26.5 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.91 ppm.

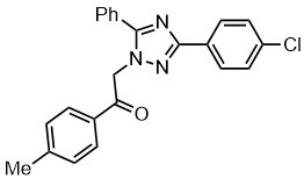


Methyl 2-(1-(2-(4-chlorophenyl)-2-oxoethyl)-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)acetate (4ae). Prepared according to GP3 using *N*-acylated amino acid **1ae** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 101 mg (65%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 5.72 (s, 2H), 3.93 (s, 2H), 3.71 (s, 3H) ppm.

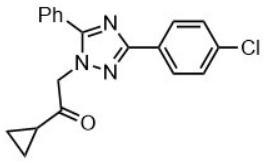
^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.8, 168.2, 163.6 (d, $^{1}J_{C\text{-}F}$ = 248.5 Hz), 160.6, 151.0, 141.2, 132.4, 129.6, 129.5, 128.3 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 126.7 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 55.0, 52.8, 32.8 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.87 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{15}ClFN_3NaO_3$ $[M+Na]^+$ 410.0678 found 410.0686.



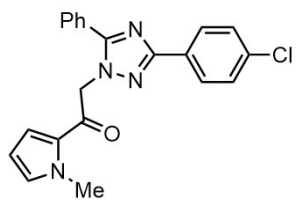
Methyl 3-(1-(2-(4-chlorophenyl)-2-oxoethyl)-3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yl)propanoate (4af). Prepared according to GP3 using *N*-acylated amino acid **1af** and diazo reagent **3a**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 133 mg (83%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.08 (t, *J* = 8.8 Hz, 2H), 5.71 (s, 2H), 3.66 (s, 3H), 2.96 (s, 4H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.0, 173.1, 163.5 (d, $^{1}J_{C\text{-}F}$ = 248.2 Hz), 160.4, 156.9, 141.1, 132.4, 129.6, 129.5, 128.2 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 127.1 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 54.5, 52.0, 31.6, 21.1 ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.15 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{17}ClFN_3NaO_3$ $[M+Na]^+$ 424.0835 found 424.0841.



2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-(*p*-tolyl)ethan-1-one (4ag). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3b**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 140 mg (90%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.53 – 7.36 (m, 5H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.64 (s, 2H), 2.43 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.9, 160.7, 157.3, 145.6, 135.2, 131.7, 130.5, 129.8, 129.3, 129.0, 128.7, 128.6, 128.3, 127.9, 127.6, 55.3, 21.8 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O$ $[M+H]^+$ 388.1211 found 388.1218.

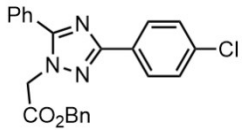


2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-cyclopropylethan-1-one (4ah). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3c**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 140 mg (99%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.67 – 7.56 (m, 2H), 7.55 – 7.46 (m, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 2H), 1.93 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.22 – 1.11 (m, 2H), 1.06 – 0.94 (m, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.9, 160.8, 157.0, 135.3, 130.6, 129.2, 129.0, 128.8, 128.6, 127.9, 127.4, 58.5, 18.4, 12.2 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}ClN_3O$ $[M+H]^+$ 338.1055 found 338.1054.

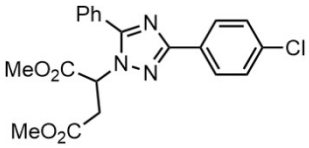


2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-(1-methyl-1*H*-pyrrol-2-yl)ethan-1-one (4ai). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3d**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 160 mg (99%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.77 – 7.63 (m, 2H), 7.48 (dt, *J* = 5.4, 2.6 Hz, 3H), 7.43 – 7.36 (m, 2H), 7.00 (dd, *J* = 4.2, 1.6 Hz, 1H), 6.92 (t, *J* = 2.0 Hz, 1H), 6.19 (dd, *J* = 4.2, 2.5 Hz, 1H), 5.47 (s, 2H), 3.94 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*)

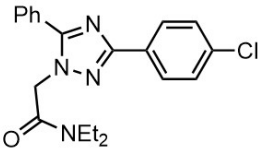
δ 181.2, 160.7, 157.4, 135.1, 132.5, 130.4, 129.5, 128.9, 128.8, 128.7, 127.9, 127.9, 127.7, 119.6, 109.0, 54.6, 37.6 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{18}ClN_4O$ $[M+H]^+$ 377.1164 found 377.1173.



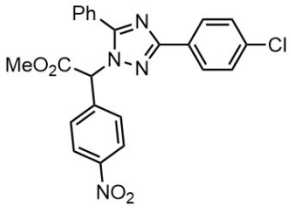
Benzyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)acetate (4aj). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3e**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 133 mg (83%). White amorphous solid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.70 – 7.56 (m, 2H), 7.55 – 7.39 (m, 5H), 7.34 (dtt, *J* = 9.9, 6.2, 2.9 Hz, 5H), 5.24 (s, 2H), 5.02 (s, 2H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.9, 160.9, 157.0, 135.3, 134.7, 130.6, 129.2, 129.1, 128.8, 128.8, 128.7, 128.7, 128.5, 127.9, 127.3, 67.9, 50.8 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}ClN_3O_2$ $[M+H]^+$ 404.1160 found 404.1161.



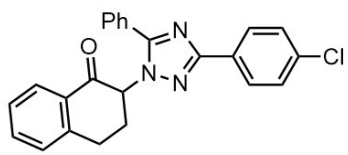
Dimethyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)succinate (4ak). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3f**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 144 mg (90%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.03 (m, 2H), 7.83 – 7.73 (m, 2H), 7.62 – 7.52 (m, 3H), 7.46 – 7.36 (m, 2H), 5.57 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.44 (d, *J* = 7.0 Hz, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.3, 168.3, 160.8, 157.5, 135.3, 130.6, 129.2, 129.1, 129.0, 128.7, 128.0, 127.5, 57.1, 53.4, 52.3, 35.4 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{19}ClN_3O_4$ $[M+H]^+$ 400.1059 found 400.1062.



2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-*N*,*N*-diethylacetamide (4al). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3g**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 97 mg (66%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.6 Hz, 2H), 7.79 – 7.71 (m, 2H), 7.49 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.99 (s, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.18 – 1.10 (m, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.9, 160.6, 157.1, 135.0, 130.3, 129.6, 128.9, 128.9, 128.6, 127.9, 127.9, 50.4, 41.7, 41.0, 14.3, 12.9 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{22}ClN_4O$ $[M+H]^+$ 369.1477 found 369.1478.

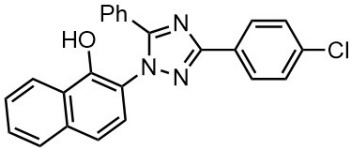


Methyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2-(4-nitrophenyl)acetate (4am). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3h**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 176 mg (98%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.65 – 7.49 (m, 5H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.0, 161.3, 157.2, 148.3, 140.4, 135.6, 131.0, 130.0, 129.3, 129.0, 128.9, 128.8, 128.0, 127.2, 123.9, 63.8, 53.7 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{18}ClN_4O_4$ $[M+H]^+$ 449.1011 found 449.1009.

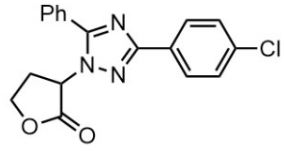


2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (4an). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3i**; eluent – petroleum ether–acetone (5%

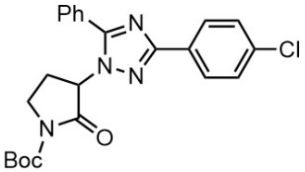
to 30% of acetone). Yield: 150 mg (94%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.02 (m, 3H), 7.78 – 7.63 (m, 2H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.50 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.43 – 7.34 (m, 3H), 7.31 (d, *J* = 7.7 Hz, 1H), 5.26 – 5.06 (m, 1H), 3.27 – 3.01 (m, 3H), 2.61 – 2.45 (m, 1H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 191.9, 160.6, 143.5, 135.0, 134.5, 131.4, 130.5, 129.6, 129.0, 129.0, 128.9, 128.7, 128.4, 127.9, 127.9, 127.2, 63.9, 29.7, 28.5 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{19}ClN_3O$ $[M+H]^+$ 400.1211 found 400.1209.



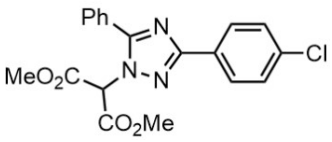
2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)naphthalen-1-ol (4ao). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3j**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 79 mg (50%). White-pink amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.24 (s, 1H), 8.57 – 8.35 (m, 1H), 8.18 (d, *J* = 8.6 Hz, 2H), 7.86 – 7.72 (m, 1H), 7.71 – 7.52 (m, 4H), 7.53 – 7.30 (m, 5H), 7.30 – 7.16 (m, 1H), 6.95 (d, *J* = 8.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.2, 155.5, 146.3, 136.0, 133.9, 130.6, 129.2, 129.0, 129.0, 128.8, 128.3, 128.0, 127.6, 127.4, 126.2, 125.9, 123.1, 122.1, 119.7, 118.1 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{17}ClN_3O$ $[M+H]^+$ 398.1055 found 398.1050.



3-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)dihydrofuran-2(3*H*)-one (4aq). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3k**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 134 mg (98%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 3.8 Hz, 2H), 7.65 – 7.48 (m, 3H), 7.41 (d, *J* = 8.3 Hz, 2H), 5.24 (t, *J* = 8.8 Hz, 1H), 4.77 (td, *J* = 8.8, 3.9 Hz, 1H), 4.43 (q, *J* = 8.2 Hz, 1H), 3.12 (dq, *J* = 12.4, 8.4 Hz, 1H), 2.74 (ddt, *J* = 12.2, 8.4, 4.3 Hz, 1H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.9, 161.3, 157.5, 135.4, 130.9, 129.2, 129.2, 129.1, 128.8, 128.0, 127.1, 66.4, 56.1, 28.9 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{15}ClN_3O_2$ [M+H]+ 340.0847 found 340.0848.

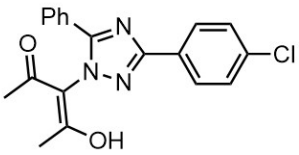


***tert*-Butyl 3-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2-oxopyrrolidine-1-carboxylate (4ar)**. Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3l**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 79 mg (50%). Yield: 116 mg (66 %). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.89 – 7.71 (m, 2H), 7.52 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.39 (d, *J* = 8.5 Hz, 2H), 5.18 (t, *J* = 9.2 Hz, 1H), 4.12 (ddd, *J* = 10.8, 9.1, 3.0 Hz, 1H), 3.71 (ddd, *J* = 10.8, 8.7, 7.4 Hz, 1H), 3.00 – 2.82 (m, 1H), 2.57 – 2.40 (m, 1H), 1.56 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.2, 161.0, 157.6, 149.8, 135.3, 130.7, 129.3, 129.3, 129.1, 128.7, 128.0, 127.3, 84.1, 59.7, 43.2, 28.0, 24.4 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{24}ClN_4O_3$ $[M+H]^+$ 439.1531 found 439.1542.

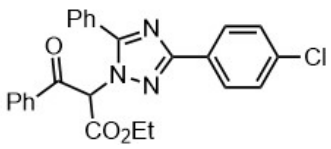


Dimethyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)malonate (4as). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3m**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 131 mg (85%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.67 – 7.60 (m, 2H), 7.58 – 7.50 (m, 3H), 7.41 (d, *J* = 8.6 Hz, 2H), 5.82 (s, 1H),

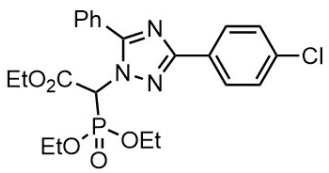
3.83 (s, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.1, 161.0, 157.2, 135.5, 131.0, 129.2, 128.9, 128.9, 128.7, 128.2, 126.8, 63.7, 53.8 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}ClN_3O_4$ $[M+H]^+$ 386.0902 found 386.0899.



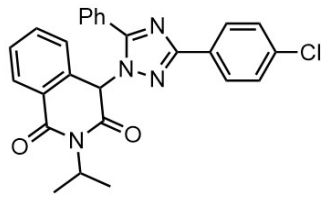
3-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-4-hydroxypent-3-en-2-one (4at). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3n**; eluent – petroleum ether–acetone (0% to 40% of acetone). Yield: 107 mg (75%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 15.91 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.83 – 7.75 (m, 2H), 7.53 – 7.42 (m, 5H), 1.92 (s, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.8, 161.8, 156.9, 135.7, 130.8, 129.2, 128.9, 128.9, 127.9, 127.8, 127.1, 116.2, 22.0 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{17}ClN_3O_2$ $[M+H]^+$ 354.1004 found 354.0999.



Ethyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-3-oxo-3-phenylpropanoate (4au). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3o**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 112 mg (63%). Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.24 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.29 (m, 6H), 7.24 – 7.15 (m, 4H), 4.36 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.0 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 170.2, 161.1, 157.7, 135.5, 131.6, 131.5, 130.2, 129.2, 128.8, 128.5, 128.5, 128.0, 127.9, 127.7, 127.4, 104.6, 62.2, 14.0 ppm. HRMS (ESI), *m/z* calcd for $C_{25}H_{21}ClN_3O_3$ $[M+H]^+$ 446.1266 found 446.1265.

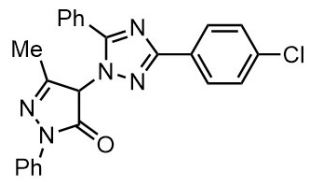


Ethyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2-(diethoxyphosphoryl)acetate (4av). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3p**; eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 187 mg (98%). Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.52 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.43 – 7.35 (m, 2H), 5.49 (d, *J* = 23.1 Hz, 1H), 4.46 – 4.08 (m, 6H), 1.39 – 1.19 (m, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.3 (d, $^2J_{C\text{-}P}$ = 2.9 Hz), 160.9, 157.6 (d, $^3J_{C\text{-}P}$ = 4.6 Hz), 135.3, 130.8, 129.3, 129.2, 128.9, 128.7, 128.0, 127.1, 64.5 (d, $^2J_{C\text{-}P}$ = 6.5 Hz), 64.3 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 63.0, 59.8 (d, $^1J_{C\text{-}P}$ = 153.4 Hz), 16.4 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 16.3 (d, $^3J_{C\text{-}P}$ = 6.1 Hz), 14.0 ppm. ^{31}P NMR (162 MHz, Chloroform-*d*) δ 11.61 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{26}ClN_3O_5P$ $[M+H]^+$ 478.1293 found 478.1287.

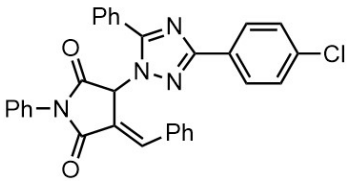


4-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2-isopropyl-isoquinoline-1,3(2*H*,4*H*)-dione (4aw). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3q**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 114 mg (62%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (dd, *J* = 7.4, 1.9 Hz, 1H), 8.09 – 7.96 (m, 2H), 7.80 – 7.71 (m, 2H), 7.61 – 7.45 (m, 5H), 7.40 – 7.32 (m, 2H), 6.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.35 (s, 1H), 5.19 (hept, *J* = 7.0 Hz, 1H), 1.48 (dd, *J* = 11.4, 6.9 Hz, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.1, 163.5, 161.4, 158.2, 135.4, 134.1, 133.7, 130.9, 129.5, 129.4, 129.3, 129.1,

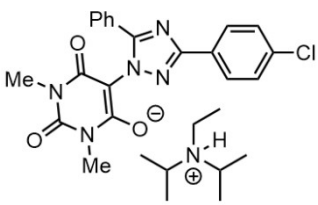
129.1, 128.7, 128.0, 127.4, 126.1, 125.8, 59.8, 46.5, 19.7, 19.4 ppm. HRMS (ESI), *m/z* calcd for $C_{31}H_{22}ClN_4O_2$ $[M+H]^+$ 457.1426 found 457.1425.



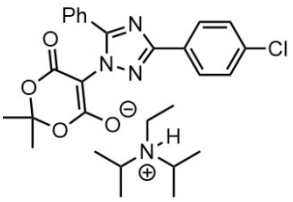
4-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4ax). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3r**; eluent – petroleum ether–acetone (5% to 40% of acetone). Yield: 104 mg (61%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.90 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.22 (dt, *J* = 16.1, 8.3 Hz, 4H), 1.86 (s, 3H) ppm. ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.2, 156.4, 144.7, 138.0, 136.3, 130.9, 129.0, 129.0, 128.7, 128.0, 127.7, 127.0, 126.9, 125.4, 122.4, 11.6 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{19}ClN_5O$ $[M+H]^+$ 428.1273 found 428.1272.



(*E*)-3-Benzylidene-4-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-phenylpyrrolidine-2,5-dione (4ay). Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3s**; eluent – petroleum ether–acetone (5% to 60% of acetone). Yield: 148 mg (71%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 7.87 (m, 5H), 7.63 (p, *J* = 3.8 Hz, 3H), 7.55 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.30 (d, *J* = 2.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 167.9, 161.3, 157.8, 140.3, 135.5, 132.2, 131.5, 131.2, 131.0, 129.8, 129.5, 129.3, 129.3, 129.1, 128.9, 128.8, 128.7, 128.0, 127.1, 126.4, 122.8, 57.2 ppm. HRMS (ESI), *m/z* calcd for $C_{31}H_{22}ClN_4O_2$ $[M+H]^+$ 517.1426 found 517.1435.



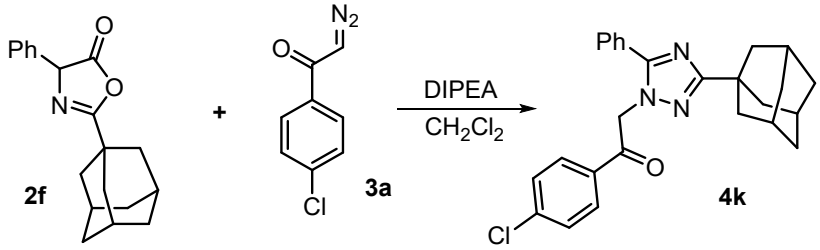
***N*-Ethyl-*N*-isopropylpropan-2-aminium 5-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (4az)**. Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3s**; eluent – petroleum ether–acetone (15% to 100% of acetone). Yield: 214 mg (99%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 2H), 7.82 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.43 – 7.30 (m, 5H), 3.25 (s, 8H), 2.76 (dd, *J* = 7.3, 3.1 Hz, 2H), 1.10 (dd, *J* = 14.8, 7.1 Hz, 14H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.2, 157.9, 152.9, 134.8, 130.0, 129.8, 128.7, 128.5, 128.4, 128.0, 127.5, 94.5, 53.9, 42.0, 27.9, 18.4, 17.2, 11.8 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{17}ClN_5O_3$ $[M+H]^+$ 410.1014 found 410.1013.



***N*-Ethyl-*N*-isopropylpropan-2-aminium 5-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-olate (4ba)**. Prepared according to GP3 using *N*-acylated amino acid **1a** and diazo reagent **3u**; eluent – petroleum ether–acetone (15% to 100% of acetone). Yield: 155 mg (97%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.76 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.39 (m, 3H), 3.67 – 3.51 (m, 2H), 3.33 (s, 1H), 3.12 (t, *J* = 7.5 Hz, 2H), 1.60 (s, 3H), 1.47 (s, 3H), 1.22 (q, *J* = 7.7, 6.0 Hz, 13H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.7, 158.6, 158.0, 133.6,

131.1, 129.9, 129.5, 129.2, 128.7, 128.6, 127.8, 100.9, 83.1, 54.1, 42.3, 26.6, 26.4, 18.5, 17.2, 12.9 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{22}ClN_4O$ $[M+H]^+$ 398.0902 found 398.0899.

Synthesis of 1,2,4-Triazole Derivatives 4k



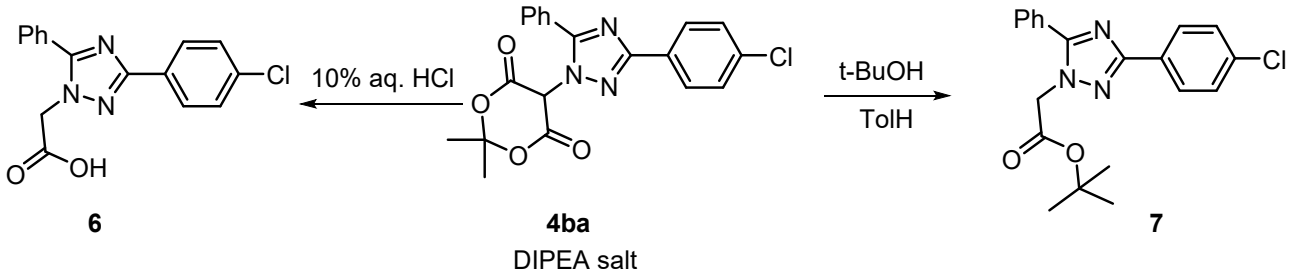
2-(3-Adamantan-1-yl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-1-(4-chlorophenyl)ethan-1-one (4k). To a solution of azlactone **2f** (152 mg, 0.5 mmol) in DCM (3 mL) stirred at 40 °C, diazo ketone **3a** (45 mg, 0.25 mmol) and DIPEA (0.04 mL, 0.25 mmol) were added. The reaction mixture was stirred at 40 °C for 4 days, and the complete conversion of diazo ketone was monitored using TLC. After complete conversion of the diazo reagent, the reaction mixture was subjected to column chromatography to obtain the pure product. Eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 65 mg (60%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.54 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 5.54 (s, 2H), 2.23 – 2.00 (m, 9H), 1.79 (s, 6H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.6, 171.5, 156.3, 140.8, 132.7, 130.1, 129.5, 129.3, 128.9, 128.6, 128.2, 55.0, 41.4, 36.8, 34.7, 28.4 ppm. HRMS (ESI), *m/z* calcd for $C_{26}H_{27}ClN_3O$ $[M+H]^+$ 432.1837 found 432.1839.

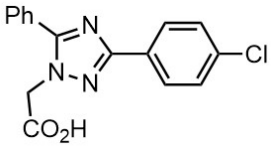
General procedure GP4 for the large-scale synthesis of compounds 4a and 4ba

A solution or suspension of the corresponding *N*-acylated amino acid **1a** (4.8 mmol, 2 equiv.) and EDC hydrochloride (5.4 mmol, 2.2 equiv.) in dry DCM (18 mL) was placed in a screw-cap, thick-walled vial and stirred at 40 °C using heating block. The corresponding diazo reagent (2.4 mmol, 1 equiv.) and DIPEA (2.4 mmol, 1 equiv.) were added sequentially. The reaction mixture was then sealed and stirred at 40 °C until the diazo reagent was completely consumed (control by TLC). The resulting mixture was washed with water (20 mL), 1N aq. citric acid (20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residual solid was triturated with diethyl ether (5 mL) and dried *in vacuo*. Yield of compound **4a**: 686 mg (70%); yield of compound **4ba**: 1.075 g (85%). The spectral data were in accordance with previously obtained.

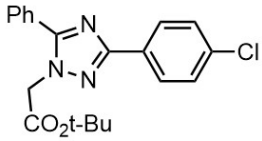
Post-modifications

Preparation of compounds 6 and 7



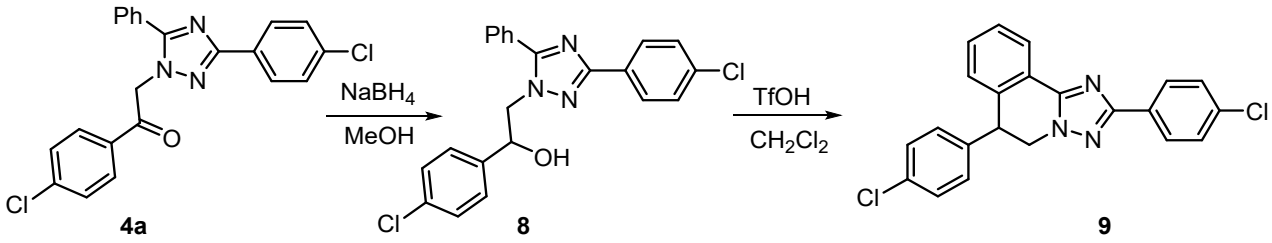


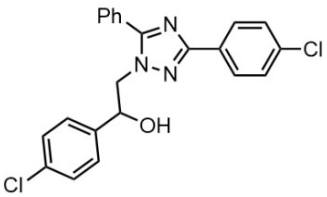
2-(3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)acetic acid (6). Derivative **4ba** (100 mg, 0.3 mmol) was suspended in 5 mL of 10% HCl. The reaction mixture was stirred for 2 days at 80 °C. White precipitate formed, and the solid was filtered, washed with water, and dried at 60 °C. Yield: 60 mg (64%). White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.41 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.87 – 7.69 (m, 2H), 7.57 (dd, J = 10.4, 5.9 Hz, 5H), 5.16 (s, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2, 159.6, 156.6, 134.4, 130.9, 129.9, 129.5, 129.4, 128.8, 128.0, 127.8, 51.6 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{13}ClN_3O_2$ $[M+H]^+$ 314.0691 found 314.0690.



***tert*-Butyl 2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)acetate (7).** To a solution of the starting triazole **4ba** (100 mg, 0.3 mmol) in toluene (3 mL), added *tert*-butanol (782 mg, 10.5 mmol), stirred the reaction mixture for 3 days at 110 °C. The reaction progress was monitored by TLC. The reaction mixture was evaporated and subjected to silica gel column chromatography to obtain the pure product. Eluent – petroleum ether–acetone (0% to 25% of acetone). Yield: 53 mg (58%). Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, J = 8.4 Hz, 2H), 7.72 – 7.62 (m, 2H), 7.51 (dd, J = 5.2, 1.9 Hz, 3H), 7.41 (d, J = 8.4 Hz, 2H), 4.89 (s, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.0, 160.6, 156.7, 135.2, 130.5, 129.3, 129.0, 128.8, 128.6, 127.9, 127.6, 83.5, 51.6, 27.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{13}ClN_3O_2$ $[M+H]^+$ 314.0691 found 314.0690. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}ClN_3O_2$ $[M+H]^+$ 370.1317 found 370.1319.

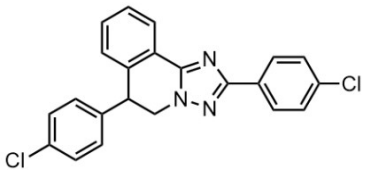
Preparation of compound 9





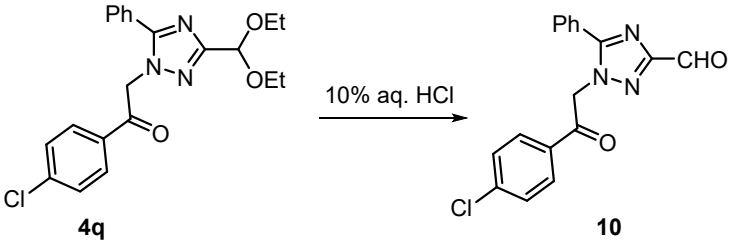
1-(4-Chlorophenyl)-2-(3-(4-chlorophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)-ethan-1-ol (8). To a suspension of the starting ketone **4a** (50 mg, 0.1 mmol) in methanol (3 mL), stirred at 0 °C, $NaBH_4$ (5 mg, 0.1 mmol) was added to give a clear light-yellow solution. The reaction mixture was stirred for 2 hours at room temperature, and the reaction progress was monitored by TLC. The reaction mixture was quenched with 20 mL of water, extracted with DCM (3×20 mL), and the organic

extracts were washed with brine (2×15 mL) and dried with anhydrous Na_2SO_4. The resulting solution was evaporated to obtain compound **8**. Yield: 49 mg (100%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.51 (m, 2H), 7.51 – 7.39 (m, 5H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.21 (dd, *J* = 8.1, 3.7 Hz, 1H), 4.75 (s, 1H), 4.41 – 4.19 (m, 2H) ppm.



2,6-Bis(4-chlorophenyl)-5,6-dihydro-[1,2,4]triazolo[5,1-*a*]isoquinoline (9). To a solution of alcohol **8** (57 mg, 0.1 mmol) in DCM (3 mL) under stirring at –20 °C was added TfOH (1 mL, 11.3 mmol). The reaction mixture was stirred for 1.5 hours at –20 °C. The resulting mixture was quenched with 20 mL of ice-cold $NaHCO_3$ solution and extracted with DCM (3×20 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude material was subjected to silica gel column chromatography to obtain a pure product **9**. Eluent – petroleum ether–acetone (5% to 30% of acetone). Yield: 21 mg (54%). White amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.17 – 8.06 (m, 2H), 7.51 – 7.37 (m, 4H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.13 – 7.03 (m, 3H), 4.69 (dd, *J* = 11.9, 5.3 Hz, 1H), 4.57 (ddt, *J* = 18.9, 11.9, 6.3 Hz, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.9, 151.6, 138.4, 136.0, 135.5, 133.8, 131.2, 129.5, 129.4, 128.9, 128.9, 128.6, 128.5, 127.8, 125.5, 124.0, 51.8, 44.1 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{16}Cl_2N_3$ $[M+H]^+$ 392.0716 found 392.0714.

Hydrolysis of acetal 4q



4q **10**

1-(2-(4-Chlorophenyl)-2-oxoethyl)-5-phenyl-1*H*-1,2,4-triazole-3-carbaldehyde (10). A mixture of 10% HCl (10 mL) and acetal **4q** (67 mg, 0.2 mmol) was stirred for 4 hours at room temperature. The reaction was monitored using TLC. A solution of soda was added to the reaction mixture to adjust pH 7, it was extracted with ethyl acetate (3×15 mL) and the combined organic phases were dried with anhydrous Na_2SO_4. The resulting solution was evaporated, and the solid residue was dissolved in 2.5 mL of DCM and subjected to silica gel column chromatography to obtain the pure aldehyde **10**. Eluent – petroleum ether–acetone (5% to 35% of acetone). Yield: 31 mg (56%). Yellow amorphous solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.55 – 7.43 (m, 5H), 5.74 (s, 2H) ppm. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.5, 183.8, 159.6, 158.5, 141.5, 132.1, 131.1, 129.6, 129.5, 129.2, 128.6, 126.5, 55.8 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{13}ClN_3O_2$ $[M+H]^+$ 326.0691 found 326.0689.

2. Crystallographic data for compounds 4aq and 4t

X-ray Single Crystal analysis was performed on SuperNova, Single source at offset/far, HyPix3000 diffractometer. Crystal growth was performed by slow evaporation of solution in chloroform at room temperature. The crystal was kept at 100 K during data collection. Using Olex2[4], the structure was solved with the SHELXT[5] structure solution program using Dual Space and refined with the SHELXL[6] refinement package using Least Squares minimization. Hydrogen atoms in all structures were placed in ideally calculated positions according to neutron diffraction statistical data[7] and refined as colliding atoms with the parameters of relative isotropic displacement. The main data of crystallography and details of refinement are presented in **Table S1** in Supporting Information.

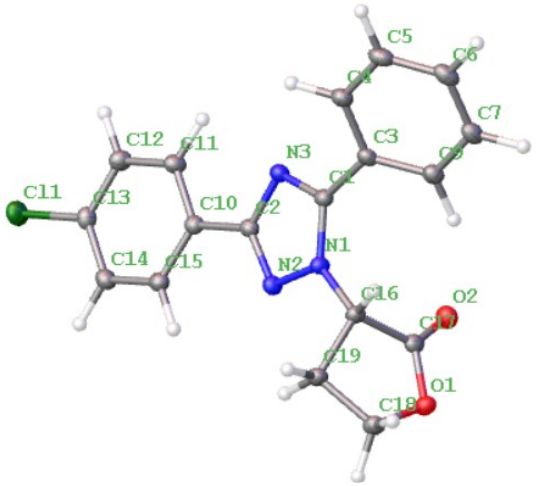


Figure S3. ORTEP representation of compound **4aq** displaying thermal ellipsoids at 50%

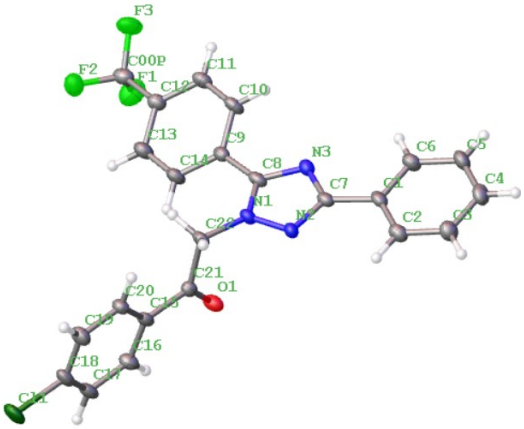


Figure S4. ORTEP representation of compound **4t** displaying thermal ellipsoids at 50%

Table S1. Crystal data and structure refinement for **4aq** and **4t**

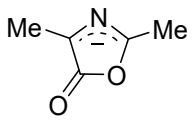
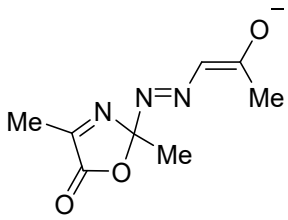
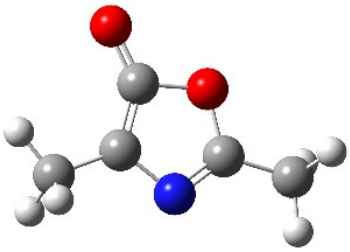
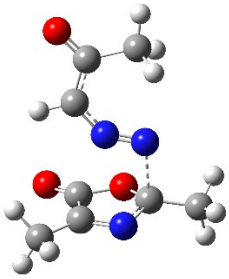
Identification code	**4aq**	**4t**
Empirical Formula	$C_{18}H_{14}ClN_3O_2$	$C_{23}H_{15}ClF_3N_3O$
Formula weight	339.78	441.83
Temperature, K	100(2)	100(2)
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a/Å	18.05750(10)	21.1094(9)
b/Å	9.68530(10)	4.6693(4)
c/Å	9.10770(10)	20.8977(11)
α/°	90	90
β/°	104.0140(10)	107.207(5)
γ/°	90	90
Volume/Å^3	1545.46(3)	1967.6(2)
Z	7	4
ρ_{calc}g/cm^3	1.460	1.492

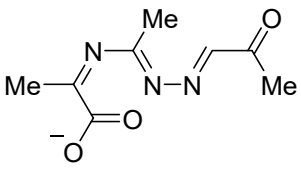
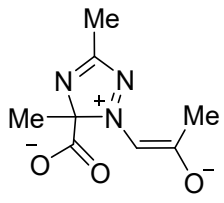
μ/mm^{-1}	2.328	2.162
F(000)	704.0	904.0
Radiation	Cu Kα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.044 to 159.846	4.382 to 160.46
Index ranges	$-22 \leq h \leq 22$, $-11 \leq k \leq 12$, $-9 \leq l \leq 11$	$-26 \leq h \leq 26$, $-5 \leq k \leq 5$, $-25 \leq l \leq 17$
Reflections collected	30604	15490
Independent reflections	3270 [R_{int} = 0.0428, R_{sigma} = 0.0213]	3983 [R_{int} = 0.1005, R_{sigma} = 0.0820]
Data/restraints/parameters	3270/0/217	3983/0/280
Goodness-of-fit on F^2	1.076	1.122
Final R indexes [I>=2σ (I)]	R_1 = 0.0359, wR_2 = 0.0982	R_1 = 0.0770, wR_2 = 0.1736
Final R indexes [all data]	R_1 = 0.0372, wR_2 = 0.0995	R_1 = 0.1074, wR_2 = 0.1887
Largest diff. peak/hole / e $Å^{-3}$	0.32/-0.23	0.52/-0.51
CCDC	**2488000**	**2488001**

3. Computation details

All calculations were performed by using the Gaussian 09 suite of quantum chemical programs.[8] Geometry optimizations and energy calculations for compounds 2–7,4', CO_2, and transition states TS1–TS7 were performed at the DFT B3LYP-D3/6-311+G(d,p) level using PCM model for dichloromethane (T = 313 K). Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate.

Table S2. Energies (au) and cartesian coordinates of stationary points for compounds **A-E'**, 3', CO_2, and transition states TS1–TS7

Anion **A**	Enolate **B**
	
Zero-point correction = 0.103722 Thermal correction to Energy = 0.112241 Thermal correction to Enthalpy = 0.113233 Thermal correction to Gibbs Free Energy = 0.069239 E_0 = -399.493816, E = -399.485297, H = -399.484305, G = -399.528299. Imaginary frequency = 0.	Zero-point correction = 0.176525 Thermal correction to Energy = 0.191880 Thermal correction to Enthalpy = 0.192872 Thermal correction to Gibbs Free Energy = 0.132198 E_0 = -700.927068, E = -700.911712, H = -700.910721, G = -700.971394. Imaginary frequency = 0.
	
O 1.50877200 1.81399600 -0.00013600 C 0.86121000 -0.56053200 -0.00000800 C 0.74332600 0.82021500 -0.00008000 O -0.68603700 1.05039300 -0.00002800 C -1.26319600 -0.18488000	O -2.16722290 -1.90476276 1.43587240 C -2.31906590 -1.09732276 -0.88143660 C -2.20830390 -1.04200576 0.57288540 O -2.23947090 0.31157724 0.87098940 C -2.16452290 0.97417924 -0.35824760

0.00005400 N -0.40723700 -1.15708200 0.00006300 C -2.74978900 -0.25608700 0.00005100 C 2.12183200 -1.36265400 0.00006500 H -3.06097100 -1.30134800 0.00025100 H -3.17478400 0.23530400 -0.88237900 H -3.17480800 0.23565600 0.88227000 H 2.20475200 -2.01283500 -0.88145800 H 2.98903500 -0.69666600 -0.00047500 H 2.20524700 -2.01201100 0.88215900	N -2.43980090 0.12171524 -1.37696660 N -0.21746390 1.00505124 -0.51943160 N 0.09251810 -0.14106376 -0.38372160 C 1.17099210 -0.92812676 -0.27187660 C 2.52224410 -0.45876376 -0.26727860 O 3.48181810 -1.24848976 -0.15851060 C -2.56080690 2.40834924 -0.33973660 C -2.38666590 -2.36397576 -1.66356260 C 2.77415910 1.03375524 -0.39980560 H 0.97603910 -1.98693276 -0.16465960 H -2.35884990 2.84402324 -1.31896360 H -1.97985890 2.94621024 0.41170440 H -3.62515590 2.52228124 -0.11300360 H -2.36911290 -2.15012076 -2.73278960 H -1.54194190 -3.01402176 -1.41915860 H -3.29972390 -2.92304876 -1.43085760 H 2.35801210 1.41646024 -1.33659560 H 2.27894110 1.58529624 0.40497740 H 3.84742510 1.22117424 -0.36975760
Carboxylate **C**  Zero-point correction = 0.177324 Thermal correction to Energy = 0.193785 Thermal correction to Enthalpy = 0.194777	Carboxylate **D**  Zero-point correction = 0.179531 Thermal correction to Energy = 0.194855 Thermal correction to Enthalpy = 0.195847

Thermal correction to Gibbs Free Energy = 0.130993

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H = -700.943977, G = -701.007761.
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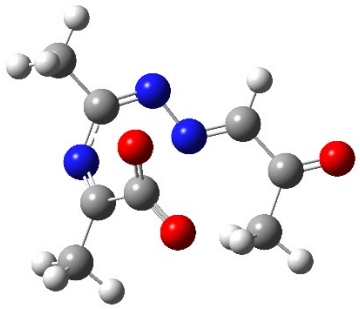

O	-0.55142923	-2.46414902	0.85160038
C	-1.89953523	-1.28589702	-0.69312362
C	-1.37855623	-1.52911702	0.74861438
O	-1.83930323	-0.77192202	1.63028038
C	-1.76650023	1.07687498	-0.58709662
N	-2.09007523	-0.11867102	-1.16819262
N	-0.54990123	1.52469998	-0.39515762
N	0.41988377	0.59452098	-0.66609462
C	1.57086377	0.83245398	-0.15446462
C	2.66798677	-0.14333502	-0.35122262
O	3.78079177	0.10931198	0.09807138
C	-2.91179723	1.99227398	-0.28255862
C	-2.17999123	-2.49155902	-1.53830362
C	2.35298977	-1.43726502	-1.05794562
H	1.78064777	1.71065698	0.46063438
H	-3.55572123	2.10136398	-1.15877762
H	-2.54778623	2.96862598	0.03497738
H	-3.51032923	1.55008498	

Thermal correction to Gibbs Free Energy = 0.135744

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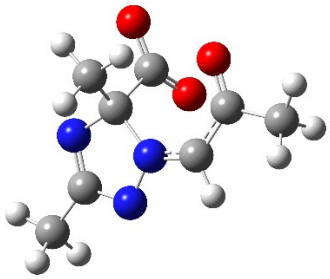

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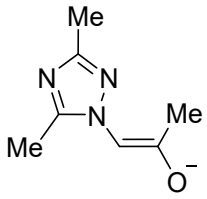
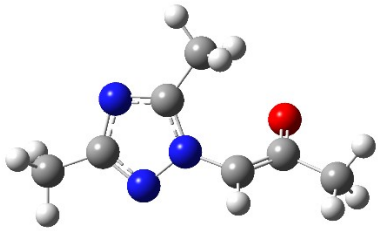
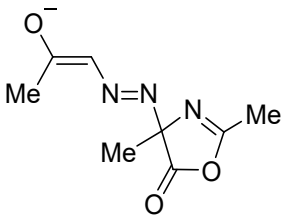
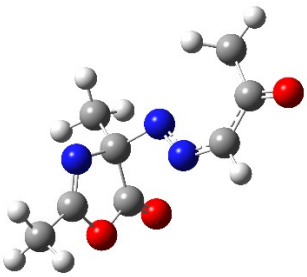
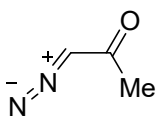
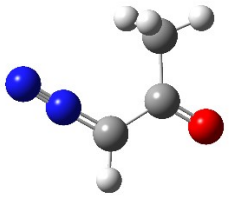
C	-0.58797818	0.81834670	0.59858967
C	-0.08400718	1.86055770	-0.55090033
O	-0.01475218	3.03432370	-0.15485533
C	-2.29119018	-0.48016530	0.13398767
N	-2.01882818	0.73436170	0.48356067
N	-1.20934918	-1.33387130	-0.01113633
N	-0.15239818	-0.59247430	0.25671067
C	1.07720282	-1.09762230	0.15377267
C	2.31998982	-0.36935830	0.23249567
O	2.42634282	0.83256670	0.48818067
C	-3.66116118	-1.01497530	-0.12087133
C	-0.17356818	1.19576770	2.01785567
C	3.55461582	-1.19768230	-0.08845833
H	1.09672082	-2.14376430	-0.11884333
H	-3.86023918	-1.87440630	0.52489767
H	-3.74862118	-1.35443230	-1.15649133

0.51919438 H -2.57482323 -2.20547702 -2.51340562 H -1.25812423 -3.06510002 -1.65933062 H -2.89187223 -3.14892902 -1.02909762 H 1.56844077 -1.96766902 -0.50771762 H 1.95393577 -1.23724102 -2.05538162 H 3.25450977 -2.04531702 -1.12626662	H -4.40558018 -0.24231430 0.06606567 H -0.58486018 2.18216670 2.22400167 H -0.58895218 0.47556670 2.72756467 H 0.90766482 1.23505870 2.10833367 H 4.43268682 -0.71643330 0.34210467 H 3.47582182 -2.22364830 0.27832067 H 3.68254582 -1.24107030 -1.17543033
Enolate **E**  Zero-point correction = 0.165853 Thermal correction to Energy = 0.178234 Thermal correction to Enthalpy = 0.179225 Thermal correction to Gibbs Free Energy = 0.125936 E_0 = -512.357240, E = -512.344859, H = -512.343867, G = -512.397157. Imaginary frequency = 0.  C -0.65672270 0.57688395 0.25544621 C -2.26462670 -0.77821205 -0.02307179 N -1.96670170 0.55128295 -0.01132779 N -1.22311970 -1.56762305	Enolate **B'**  Zero-point correction = 0.178657 Thermal correction to Energy = 0.193967 Thermal correction to Enthalpy = 0.194959 Thermal correction to Gibbs Free Energy = 0.134082 E_0 = -700.936395, E = -700.921085, H = -700.920093, G = -700.980970. Imaginary frequency = 0.  O 1.71060568 1.20632871 1.85581347 C 1.20607668 0.79379071 -0.55053353 C 1.84840968 0.59848771 0.83267747 O 2.69646168 -0.48464229 0.73410247

0.19991921 N -0.18597670 -0.68250205 0.37808021 C 1.14193230 -1.11751505 0.64489821 C 2.20400330 -0.75457905 - 0.16251579 O 2.14885530 -0.01109905 - 1.19981879 C -3.64280370 -1.30517205 - 0.26332379 C 0.18501130 1.79011195 0.42400021 C 3.57946930 -1.28180505 0.24635421 H 1.23643930 -1.80863005 1.47047321 H -3.64154470 -2.39585905 - 0.25042579 H -4.02195870 -0.96722905 - 1.23190579 H -4.33588670 -0.94697705 0.50365221 H -0.44414070 2.68003795 0.41101821 H 0.73046430 1.74236095 1.37140421 H 0.93265230 1.83815295 - 0.37233779 H 4.24442730 -0.43739005 0.45704321 H 3.55240530 -1.93239705 1.12485221 H 4.01606430 -1.83612105 - 0.59071879	C 2.63838268 -0.89480729 - 0.60766553 N 1.88467768 -0.22970629 - 1.37616853 N -0.24788432 0.56546571 - 0.49958053 N -0.50494532 -0.49743729 0.19459847 C -1.74524032 -0.96133929 0.37513647 C -3.01279332 -0.49505129 - 0.12080653 O -4.06806532 -1.09581929 0.18356647 C 3.49681368 -2.06368229 - 0.92192553 C 1.46752568 2.19510471 - 1.08923053 C -3.09218232 0.72036071 - 1.02195753 H -1.79878332 -1.84760729 1.00144447 H 3.39972268 -2.31905929 - 1.97560653 H 3.19948468 -2.91809029 - 0.30829253 H 4.54108968 -1.83652329 - 0.69212753 H 1.00124768 2.28481971 - 2.07178353 H 1.02385068 2.93152771 - 0.41647853 H 2.53801968 2.39121271 - 1.18284153 H -2.71060332 1.60413371 - 0.50374853 H -2.44805932 0.59510971 - 1.89589353 H -4.12945132 0.87518971 - 1.32494653
Diazoacetone (**3'**)  Zero-point correction = 0.070409 Thermal correction to Energy = 0.077238 Thermal correction to Enthalpy = 0.078230	CO_2 Zero-point correction = 0.011584 Thermal correction to Energy = 0.014377 Thermal correction to Enthalpy = 0.015369 Thermal correction to Gibbs Free Energy = -0.011025 E_0 = -188.637930, E = -188.635137, H = -188.634146, G = -188.660539.

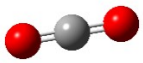
Thermal correction to Gibbs Free Energy = 0.038432

E_0 = -301.429428, E = -301.422599,
H = -301.421607, G = -301.461404.
Imaginary frequency = 0.

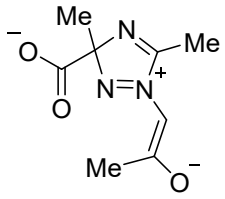
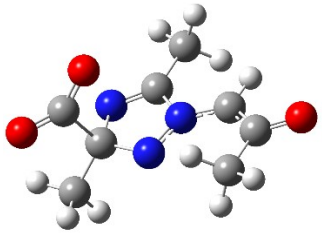


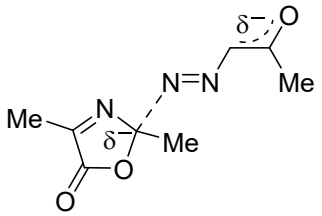
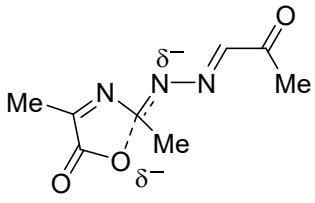
O	-1.91696229	-1.76381172	1.79304666
C	-1.86901529	-0.91213572	-0.50596034
C	-1.81088029	-0.85504372	0.99963066
O	-1.65591129	0.42887328	1.32312566
C	-1.44611629	1.20108928	0.05111566
N	-1.73558729	0.24771028	-1.01482834
N	-0.07606929	1.68319928	-0.00959134
N	0.75810271	0.69541028	0.06322566
C	2.05702171	0.95415028	0.04394366
C	3.02243171	-0.09745272	0.12860366
O	4.24963171	0.13947928	0.10855566
C	-2.41480629	2.36246428	0.05980866
C	-2.07622329	-2.18796772	-1.24302634
C	2.56359571	-1.54313972	0.24574266
H	2.42312071	1.98073228	-0.03340134
H	-2.30193129	2.92596428	-0.86736134
H	-2.18631329	3.01597528	0.90299366
H	-3.44215429	2.00354028	0.14194666
H	-2.12114629	-2.00915372	-

Imaginary frequency = 0.

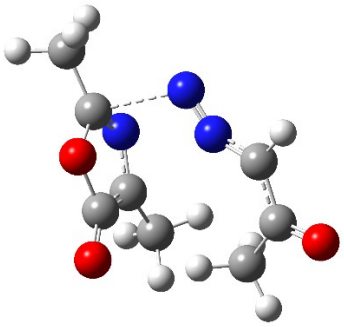


C	0.00000000	0.00000000	0.00000000
O	0.00000000	0.00000000	-1.16080200
O	0.00000000	0.00000000	1.16080200

2.31674834 H -1.25640829 -2.87876872 -1.02470634 H -2.99860229 -2.67278672 -0.91107234 H 1.47979571 -1.64140872 0.26999766 H 2.96439271 -2.10734772 -0.60161834 H 2.99228371 -1.97341972 1.15551366	
Carboxylate **D'**  Zero-point correction = 0.179232 Thermal correction to Energy = 0.194491 Thermal correction to Enthalpy = 0.195482 Thermal correction to Gibbs Free Energy = 0.134709 E_0 = -700.952301, E = -700.937042, H = -700.936050, G = -700.996823. Imaginary frequency = 0.  O -3.28244520 -1.60276743 0.64271157 C -1.67479320 -0.27161143 -0.69536843 C -2.29545020 -0.87359243 0.77871657 O -1.65185820 -0.49657543 1.76247457 C -0.46545520 1.48226757 -0.26473443 N -1.66467020 1.15628257 -0.52954843	

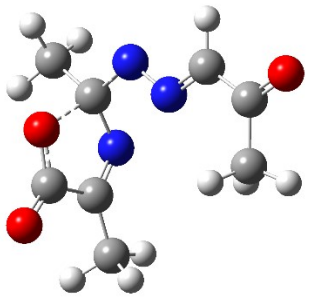
N -0.31352720 -0.72072843 -0.73247243 N 0.39947580 0.29936357 -0.36854743 C 1.73592980 0.34902757 -0.12023443 C 2.65390180 -0.74377143 -0.10160143 O 3.86358280 -0.52010343 0.11618757 C 0.06839680 2.81814757 0.10322557 C -2.49359020 -0.75808343 -1.87687543 C 2.18219880 -2.16459443 -0.32927543 H 2.12412380 1.33099657 0.09491257 H 0.83344780 3.14968657 -0.60345343 H 0.51735380 2.79213257 1.09992857 H -0.75171720 3.53402657 0.10380757 H -2.09511220 -0.34788943 -2.80856143 H -2.46351020 -1.84631843 -1.91947143 H -3.53034120 -0.44648343 -1.75612843 H 1.34095780 -2.41053043 0.32287657 H 1.81559680 -2.28749243 -1.35211643 H 3.01705280 -2.84240043 -0.15001843	
TS1  Zero-point correction = 0.176130 Thermal correction to Energy = 0.191722 Thermal correction to Enthalpy = 0.192713 Thermal correction to Gibbs Free Energy = 0.132092 E_0 = -700.924671, E = -700.909080,	**TS2**  Zero-point correction = 0.177260 Thermal correction to Energy = 0.192493 Thermal correction to Enthalpy = 0.193485 Thermal correction to Gibbs Free Energy = 0.132600

H = -700.908088, G = -700.968709.
Imaginary frequency = 1.

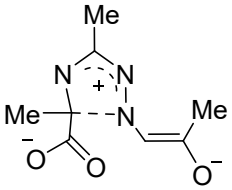
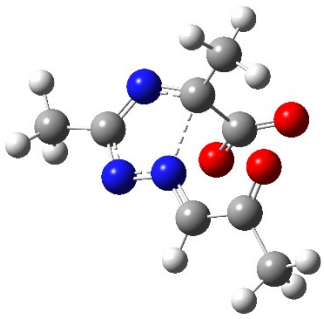
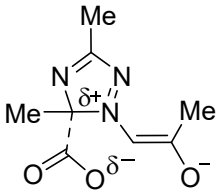
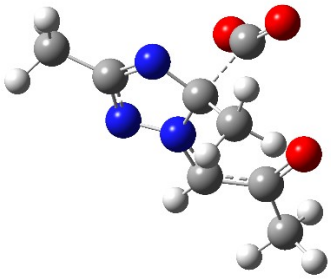


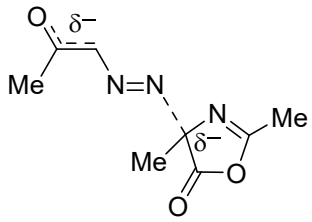
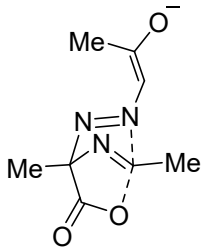
O	0.36759404	2.06939014	2.01844150
C	1.04364504	1.58680614	-0.29391150
C	0.92006504	1.43828414	1.11104050
O	1.67021404	0.26846214	1.40455750
C	2.15051304	-0.18447286	0.20661350
N	1.84284404	0.60599814	-0.79840550
N	0.28436104	-1.60480486	-0.17802750
N	-0.70832396	-1.03406486	-0.02634350
C	-2.03520596	-1.09039386	0.14052450
C	-2.92756096	0.02051114	0.25029150
O	-4.14231896	-0.19408386	0.41904950
C	3.15492904	-1.27582086	0.23349950
C	0.52728004	2.72523814	-1.10916350
C	-2.41467796	1.43801114	0.14038650
H	-2.44327196	-2.09533986	0.18134550
H	3.36146804	-1.59947286	-0.78678050
H	2.78183404	-2.12875286	0.80619450
H	4.09114604	-0.93917486	0.69277050

E_0 = -700.948326, E = -700.933093,
H = -700.932102, G = -700.992986.
Imaginary frequency = 1.

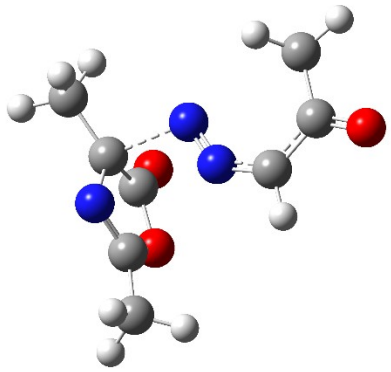


O	-2.35063700	-1.57933100	1.63425700
C	-1.78473400	-0.82094000	-0.60459700
C	-1.94429100	-0.68096300	0.90460500
O	-1.60372700	0.51731800	1.25503100
C	-1.03873700	1.28132700	-0.24075900
N	-1.33227300	0.22614300	-1.16262900
N	0.27582300	1.65049900	-0.05351200
N	1.09600200	0.60979900	-0.09325800
C	2.37029400	0.84480400	0.06732200
C	3.32236900	-0.24619800	0.04908400
O	4.53521200	-0.03170100	0.19252200
C	-1.98142400	2.45486400	-0.34977300
C	-2.15231600	-2.07959200	-1.31125400
C	2.81304200	-1.66633200	-0.12660900
H	2.75516700	1.85552500	0.22466000
H	-1.79654600	2.96885600	-1.29616200
H	-1.79324100	3.14697800	0.47070800
H	-3.01977200	2.12342400	-0.32201900

H 0.00718204 2.37700714 -2.00727350 H -0.16894296 3.32673914 -0.52244750 H 1.34066804 3.38294514 -1.43943850 H -1.65975996 1.64989714 -0.89992850 H -1.95102396 1.59952214 -0.83430350 H -3.25485996 2.12236314 -0.25795950	H -2.01663100 -1.97504200 -2.38719600 H -1.53283800 -2.90309100 -0.94399300 H -3.19043900 -2.34486200 -1.09252300 H 2.09800100 -1.73423700 -0.94769700 H 3.65921800 -2.33113000 -0.30193900 H 2.28822000 -1.98359900 -0.77935600
TS3  Zero-point correction = 0.176861 Thermal correction to Energy = 0.192379 Thermal correction to Enthalpy = 0.193370 Thermal correction to Gibbs Free Energy = 0.131857 E_0 = -700.944805, E = -700.929288, H = -700.928296, G = -700.989809. Imaginary frequency = 1.  O 0.80454576 1.33167617 1.87907401 C 0.68553076 1.38563917 -0.53406399 C 0.26032476 1.89761117 0.91285901 O -0.55314224 2.84490017 0.89309101 C 1.92465876 -0.49354883 -0.22002399 N 1.83313276 0.73689017 -0.65126299	**TS4**  Zero-point correction = 0.178233 Thermal correction to Energy = 0.193347 Thermal correction to Enthalpy = 0.194338 Thermal correction to Gibbs Free Energy = 0.134787 E_0 = -700.960745, E = -700.945632, H = -700.944640, G = -701.004191. Imaginary frequency = 1.  O -0.18878462 1.58617877 -2.08769269 C -0.56457762 0.97830377 0.39187831 C -0.17540962 2.16338477 -1.02041069 O -0.06793662 3.28310977 -0.56626969 C -2.25131162 -0.24453723 -0.18950769 N -1.97035662 0.92197477 0.32985131

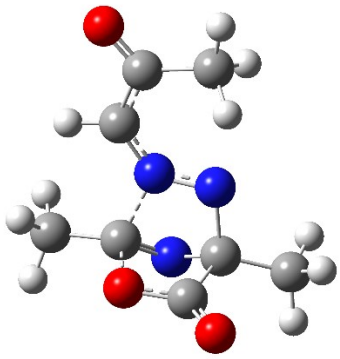
N 0.79014776 -1.22705483 -0.01412399 N -0.28696824 -0.52187183 -0.24890599 C -1.46134124 -0.92185283 0.15345501 C -2.68195924 -0.22415883 -0.24848399 O -2.71926524 0.63823017 -1.12400999 C 3.23671876 -1.17891883 -0.02461999 C 0.13922676 2.12245017 -1.71459899 C -3.93522424 -0.63716183 0.49934901 H -1.53625824 -1.78747883 0.80845301 H 3.19306376 -2.20778683 -0.38711599 H 3.47177476 -1.21167483 1.04370601 H 4.03123976 -0.63540183 -0.53530499 H 0.55911676 3.13431217 -1.71913299 H 0.40532076 1.61916517 -2.64514599 H -0.94048324 2.20427217 -1.61781899 H -4.81205424 -0.19604683 0.02681301 H -4.03652124 -1.72588383 0.52941101 H -3.87170024 -0.28979983 1.53608401	N -1.16619362 -1.04280323 -0.43918569 N -0.12306462 -0.32132923 -0.04467169 C 1.13584138 -0.82556923 -0.18084469 C 2.33459138 -0.06850823 -0.22242969 O 2.42014438 1.16943477 -0.08949469 C -3.62340662 -0.72426923 -0.53238969 C 0.02368538 1.51649977 1.67625431 C 3.60582338 -0.86238423 -0.49962769 H 1.14267738 -1.86601923 -0.46872769 H -3.79553462 -1.72490723 -0.12842769 H -3.74890062 -0.77942023 -1.61761569 H -4.36917262 -0.03938023 -0.12968669 H -0.44395662 2.47851377 1.87988431 H -0.19988762 0.82954377 2.49857331 H 1.09667738 1.65277677 1.58365431 H 4.32768238 -0.66262323 0.29720731 H 3.44347338 -1.93945723 -0.56975669 H 4.04575838 -0.50755623 -1.43631269
TS5  Zero-point correction = 0.176670 Thermal correction to Energy = 0.191920 Thermal correction to Enthalpy = 0.192912 Thermal correction to Gibbs Free Energy = 0.132836 E_0 = -700.924847, E = -700.909597,	**TS6**  Zero-point correction = 0.178069 Thermal correction to Energy = 0.192494 Thermal correction to Enthalpy = 0.193486 Thermal correction to Gibbs Free Energy = 0.135972

H = -700.908606, G = -700.968681.
Imaginary frequency = 1.

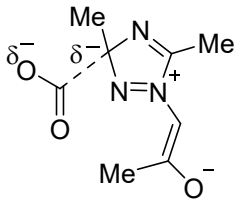
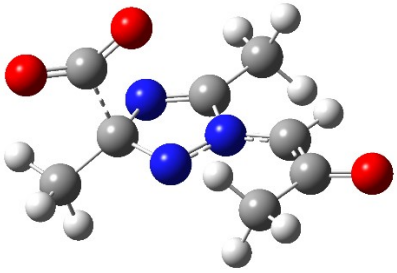


O	-1.98263818	-1.81609426	1.56818952
C	-1.60868018	-1.27495926	-0.80296248
C	-1.87229918	-1.07044126	0.61590052
O	-1.87861518	0.32036174	0.76941052
C	-1.79496718	0.83631174	-0.51678148
N	-1.78822818	-0.05109126	-1.45190748
N	0.30672882	-1.31546226	-0.52615848
N	0.69578082	-0.17850726	-0.40943548
C	1.88830082	0.42277274	-0.25887748
C	3.15913082	-0.23126326	-0.21518148
O	4.21770982	0.41827874	-0.07928748
C	-1.89223218	2.31151274	-0.63437848
C	-1.85822618	-2.57438326	-1.49278848
C	3.21257682	-1.74467726	-0.33851848
H	1.86018582	1.50205074	-0.17527548
H	-1.78465818	2.60077274	-1.67887648
H	-1.11148718	2.79497774	-0.04299848
H	-2.85944918	2.66174074	-

E_0 = -700.905723, E = -700.891297,
H = -700.890305, G = -700.947820.
Imaginary frequency = 1.



O	-2.52937422	-1.09391921	1.88588023
C	-1.77153622	-0.60499421	-0.44013077
C	-2.03712922	-0.32720521	1.07422223
O	-1.56224422	0.87303179	1.33760923
C	-1.12722622	1.36079579	-0.22874777
N	-1.91590722	0.70770779	-1.01943077
N	-0.25688322	-0.88145721	-0.39458877
N	0.25626978	0.26038279	-0.18915077
C	1.51400978	0.63714679	0.04716723
C	2.66875278	-0.20759321	0.19240423
O	3.78681478	0.30316979	0.38855623
C	-0.80076322	2.80818779	-0.18480177
C	-2.52013222	-1.74776321	-1.06849277
C	2.52172378	-1.71162821	0.11501623
H	1.66729278	1.70405279	0.13057823
H	-0.32651322	3.10913079	-1.12058377
H	-0.12982022	3.02774479	0.64546823

0.25960248 H -1.34731018 -2.58485126 -2.45794948 H -1.47146518 -3.39555326 -0.88592148 H -2.92659718 -2.74193826 -1.66113048 H 2.63198782 -2.22035926 0.45736252 H 2.76571482 -2.07480726 -1.28125448 H 4.25118382 -2.07227226 -0.28681448	H -1.72070622 3.37974379 -0.04886777 H -2.18916522 -1.88541321 -2.10002777 H -2.33931422 -2.66875021 -0.51152677 H -3.59234122 -1.54312921 -1.06380177 H 1.76521178 -2.06382121 0.82095423 H 2.16736878 -2.00968921 -0.87575277 H 3.48589678 -2.17555521 0.32408423
TS7  Zero-point correction = 0.178423 Thermal correction to Energy = 0.193230 Thermal correction to Enthalpy = 0.194222 Thermal correction to Gibbs Free Energy = 0.134981 E_0 = -700.952947, E = -700.938139, H = -700.937148, G = -700.996389. Imaginary frequency = 1.  O -3.05603359 -1.47859744 0.83398518 C -1.51541459 -0.17369144 -0.69742982 C -2.08987559 -0.73203344 0.92452318 O -1.39913159 -0.27494644 1.82482718	

C	-0.33781559 1.58187456 -0.26462982	
N	-1.53572259 1.24037156 -0.55680982	
N	-0.16992259 -0.61310344 -0.71382582	
N	0.53090741 0.42176856 -0.34307382	
C	1.86890241 0.47542456 -0.06318882	
C	2.79150041 -0.60493044 -0.03593782	
O	3.99708141 -0.38135444 0.22464618	
C	0.16550441 2.92580956 0.11695018	
C	-2.39566559 -0.75931544 -1.77801582	
C	2.34297141 -2.02686244 -0.31157682	
H	2.24156941 1.45927956 0.17077718	
H	0.94596341 3.26954356 -0.56705682	
H	0.58707441 2.90677256 1.12608218	
H	-0.66402659 3.63056056 0.09456518	
H	-2.06860059 -0.41355144 -2.76251782	
H	-2.34768459 -1.84744544 -1.74565382	
H	-3.42874459 -0.45546544 -1.61360282	
H	1.50706041 -2.30939644 0.33266218	
H	1.97933641 -2.12551444 -1.33797282	
H	3.18934041 -2.69544344 -0.15218382	

4. References

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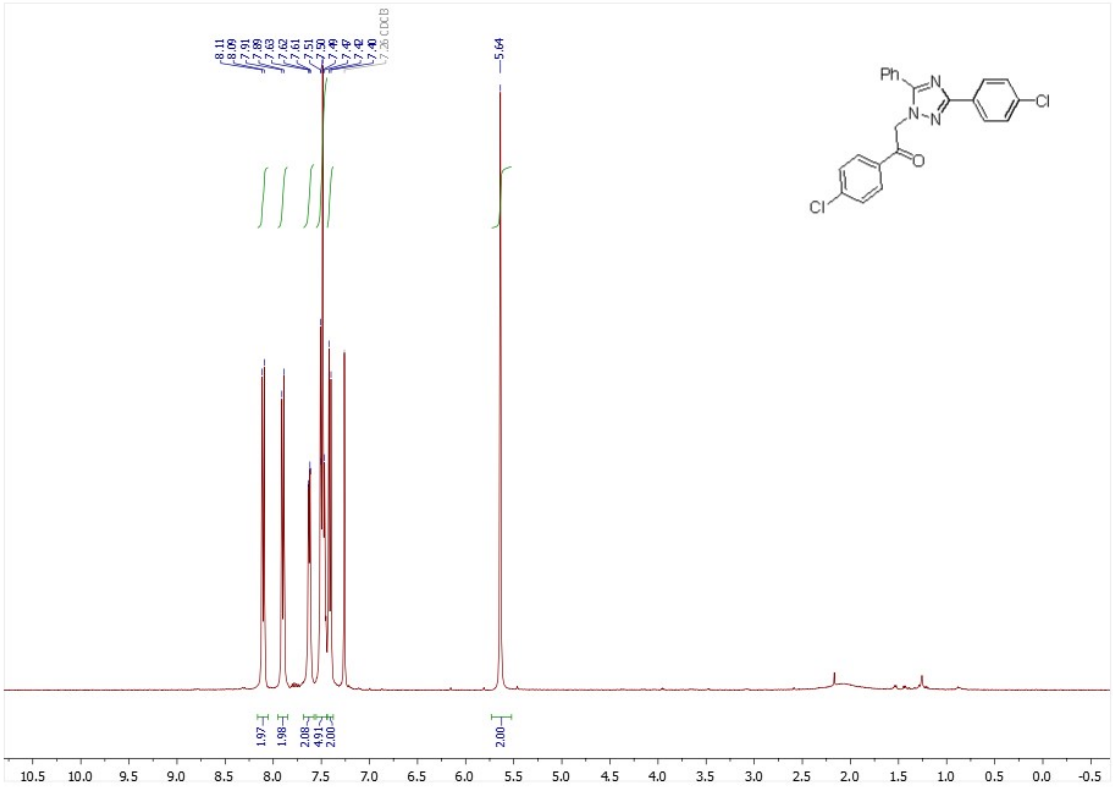
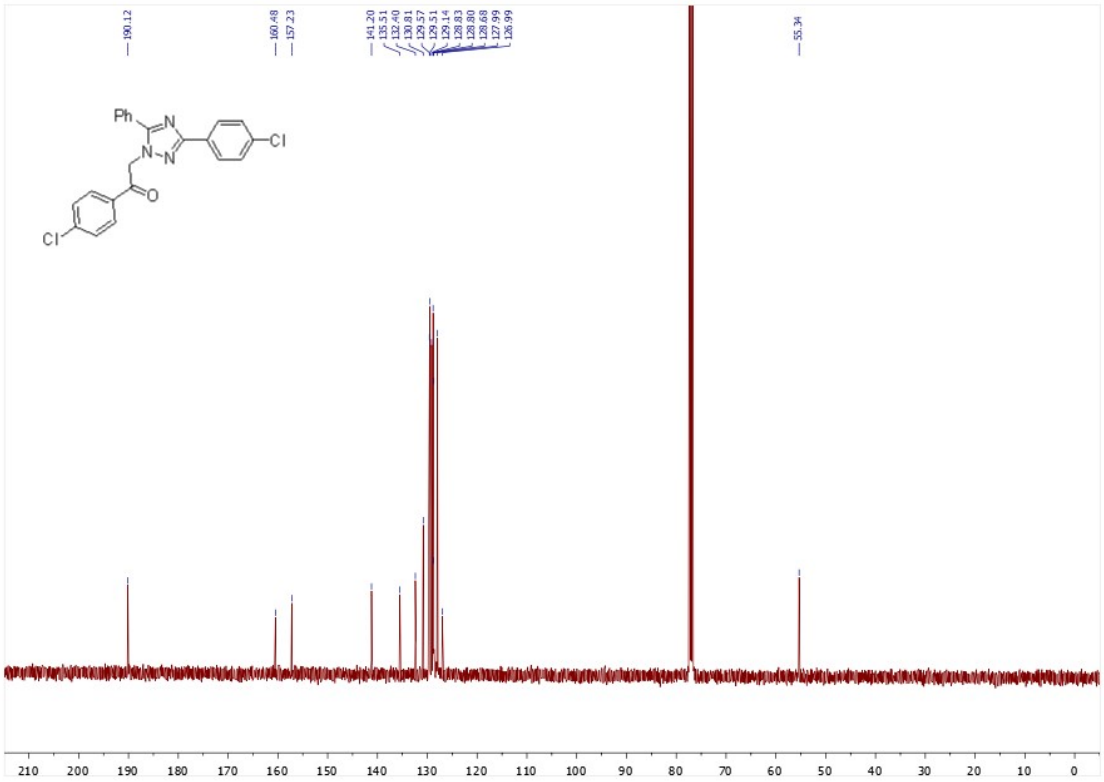
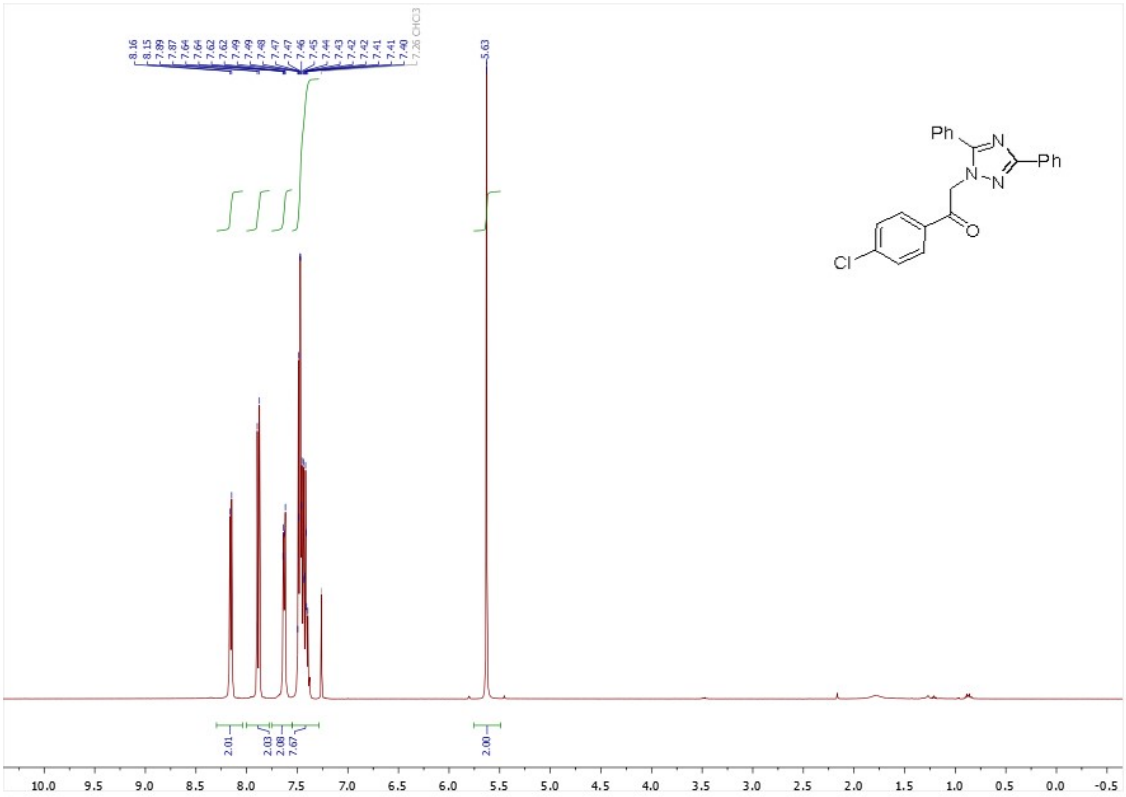
5. Copies of ^{1}H and ^{13}C NMR spectra

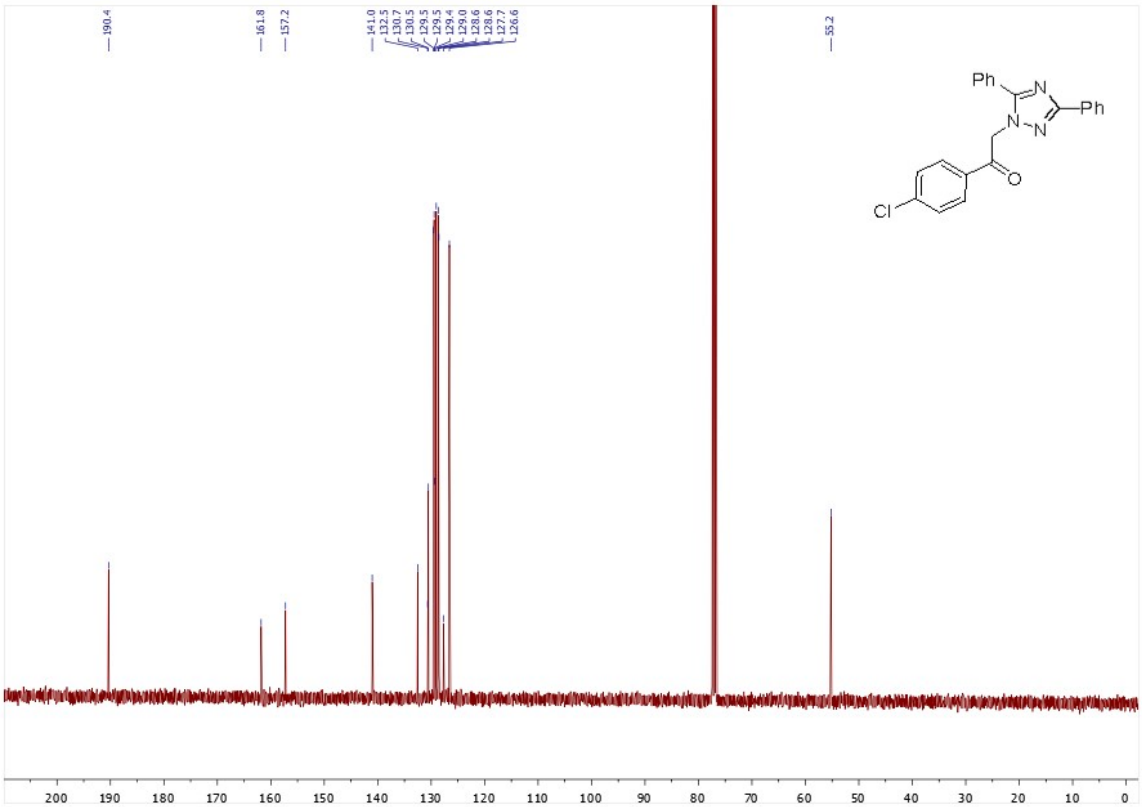
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4a**



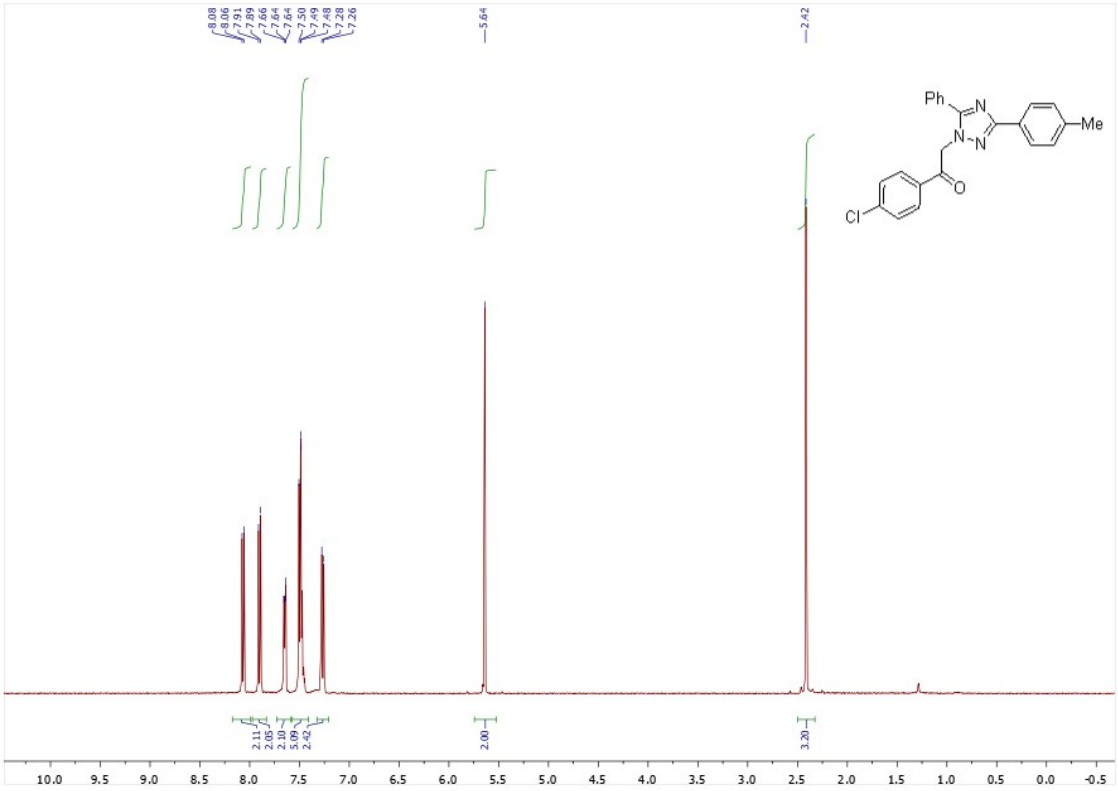


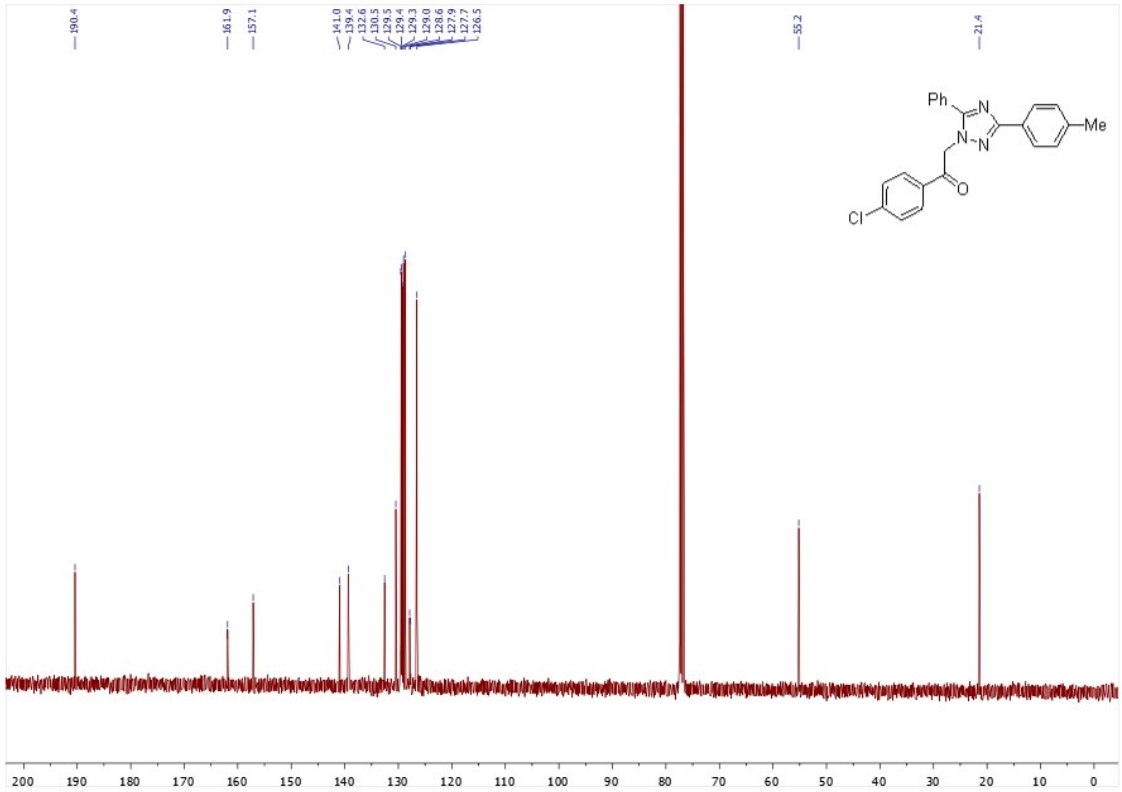
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4b**



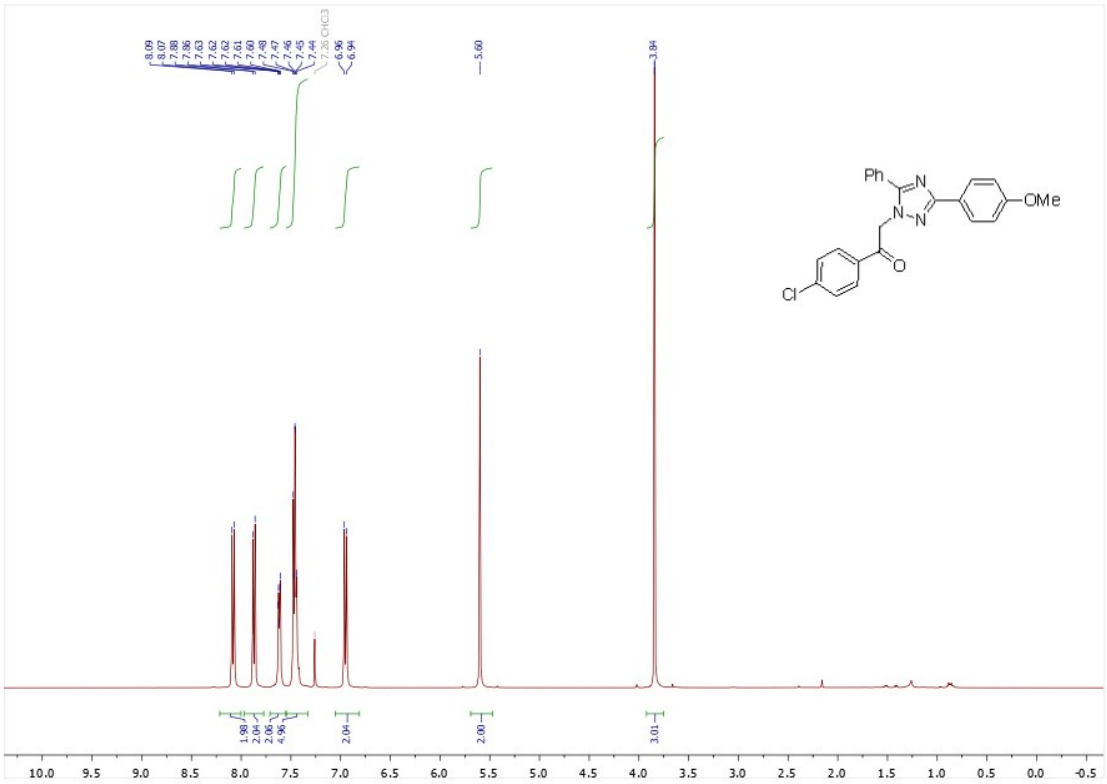


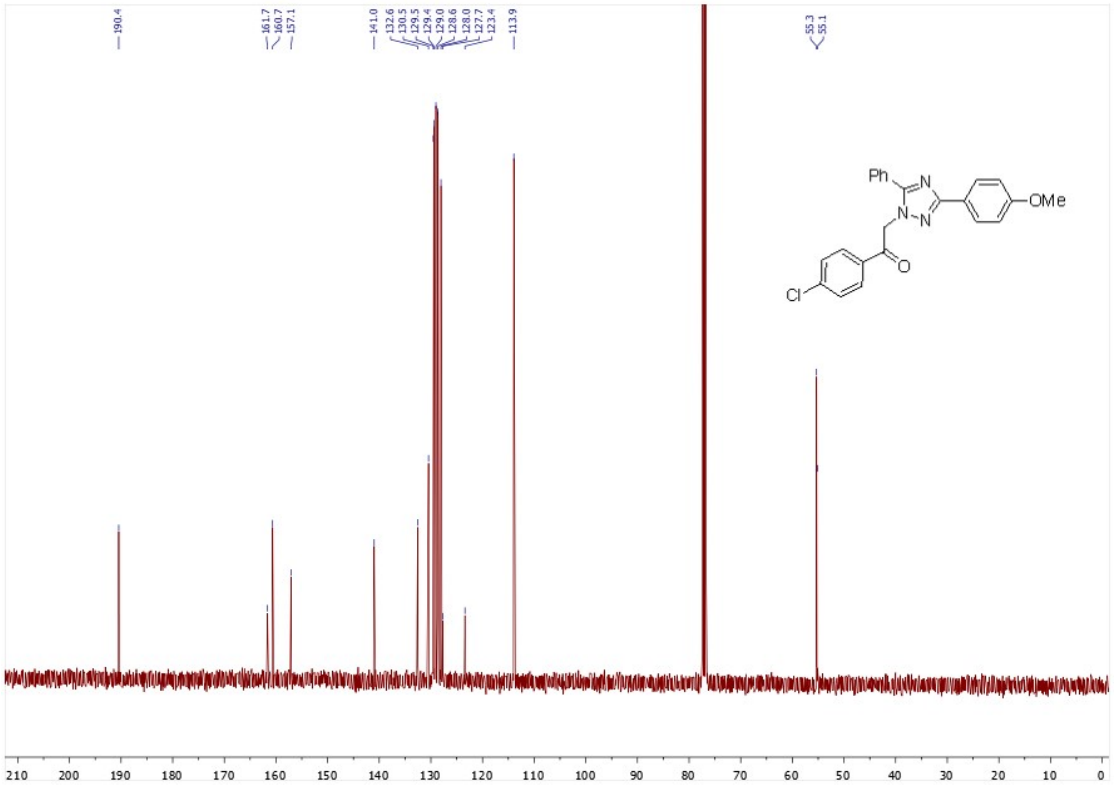
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4c**



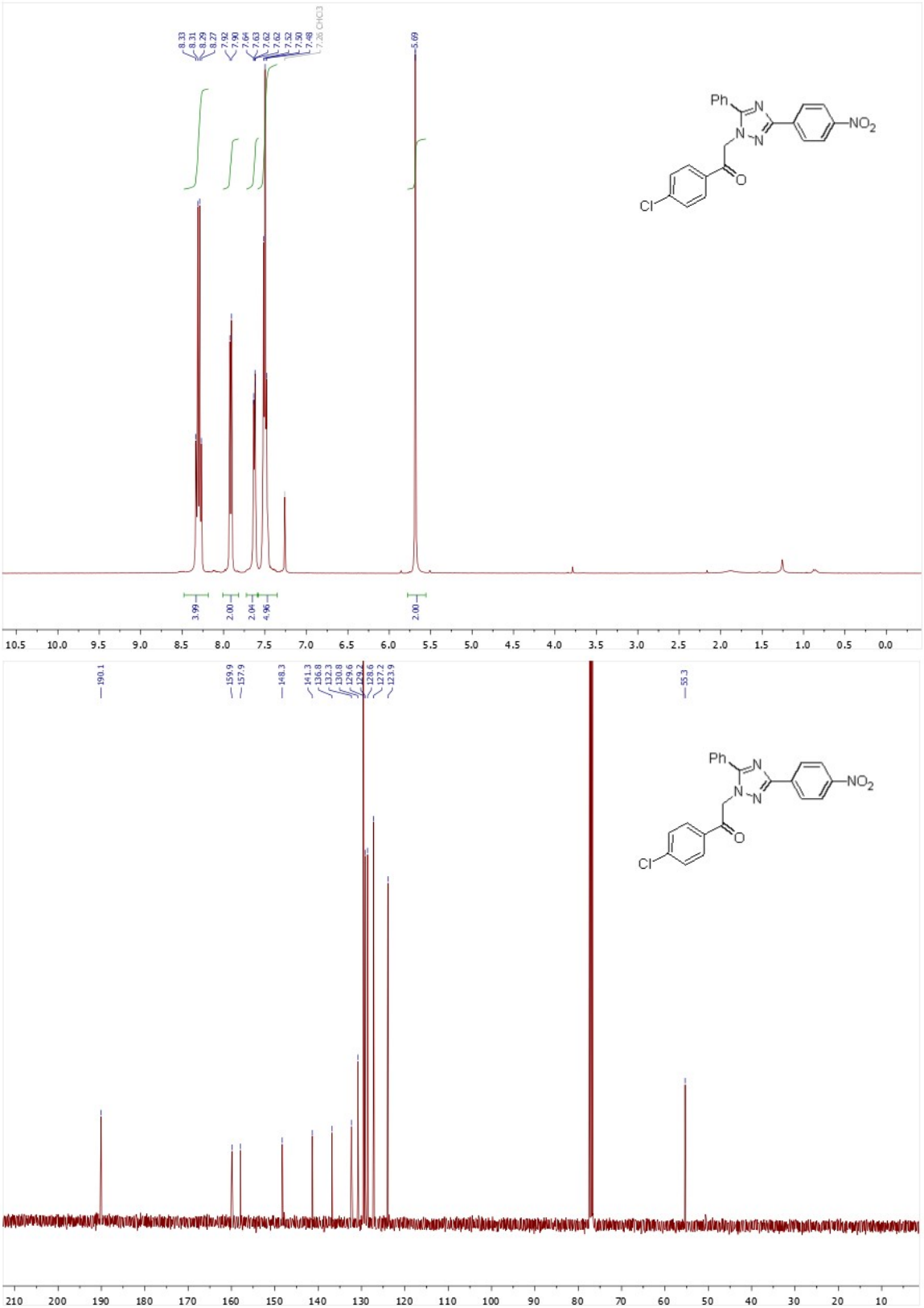


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4d**

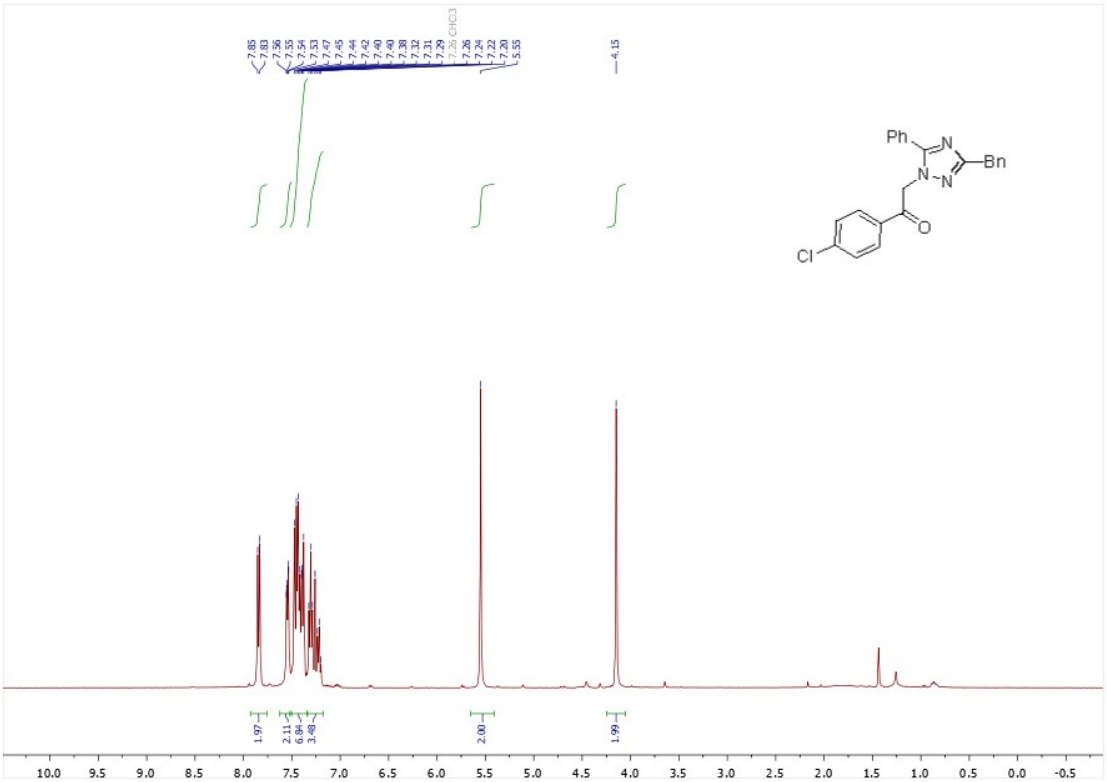


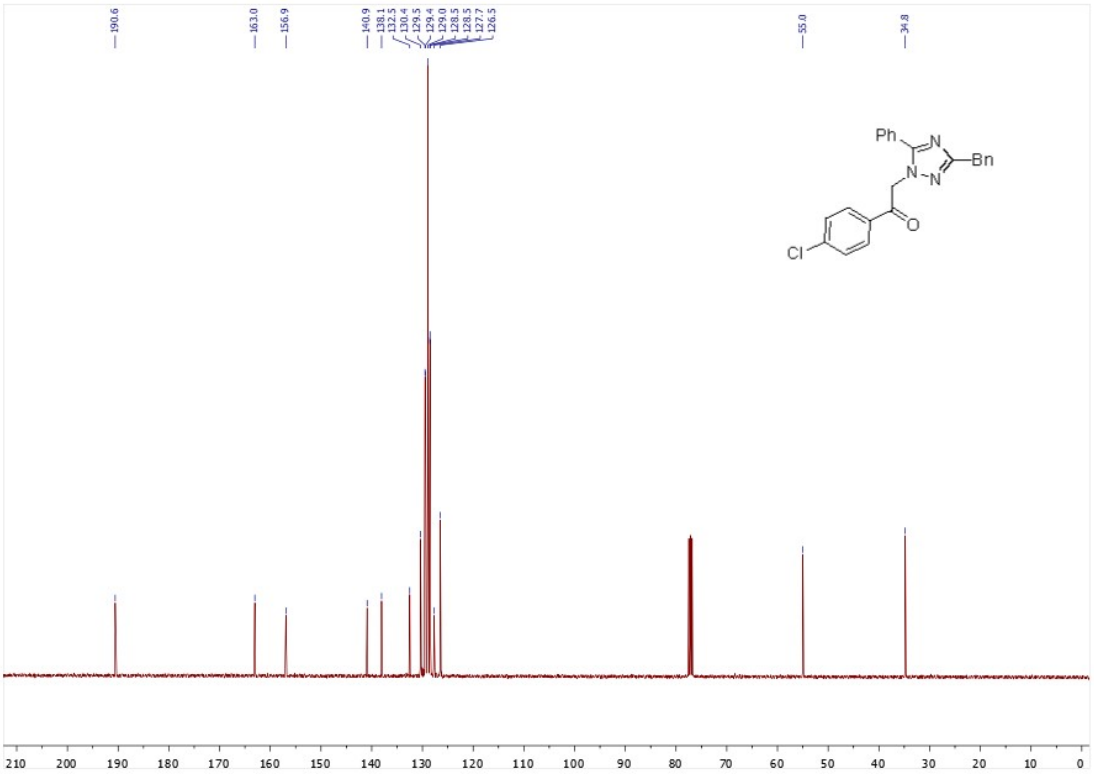


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4e**

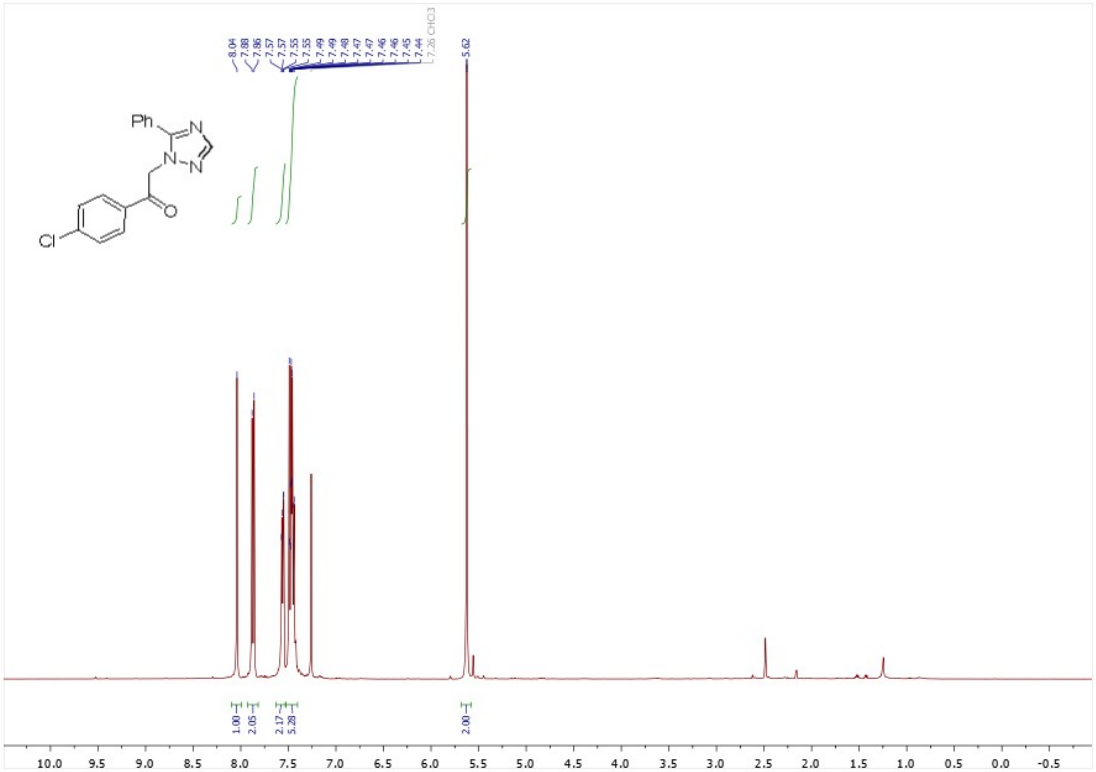


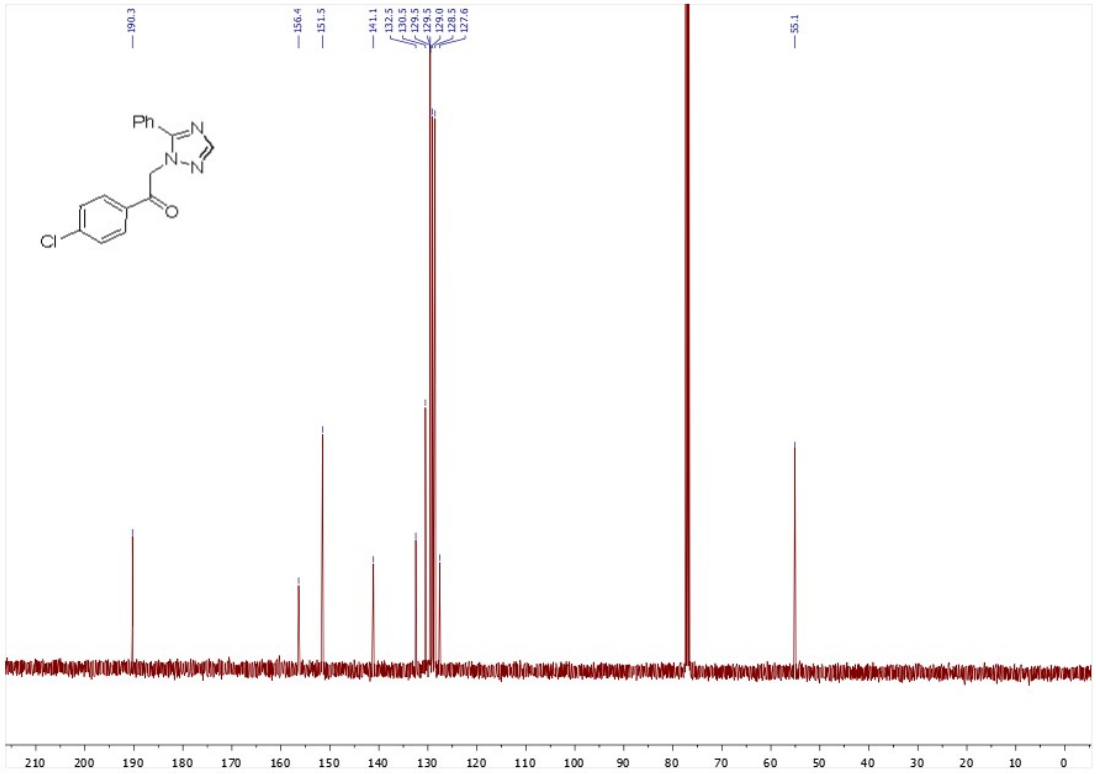
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4f**



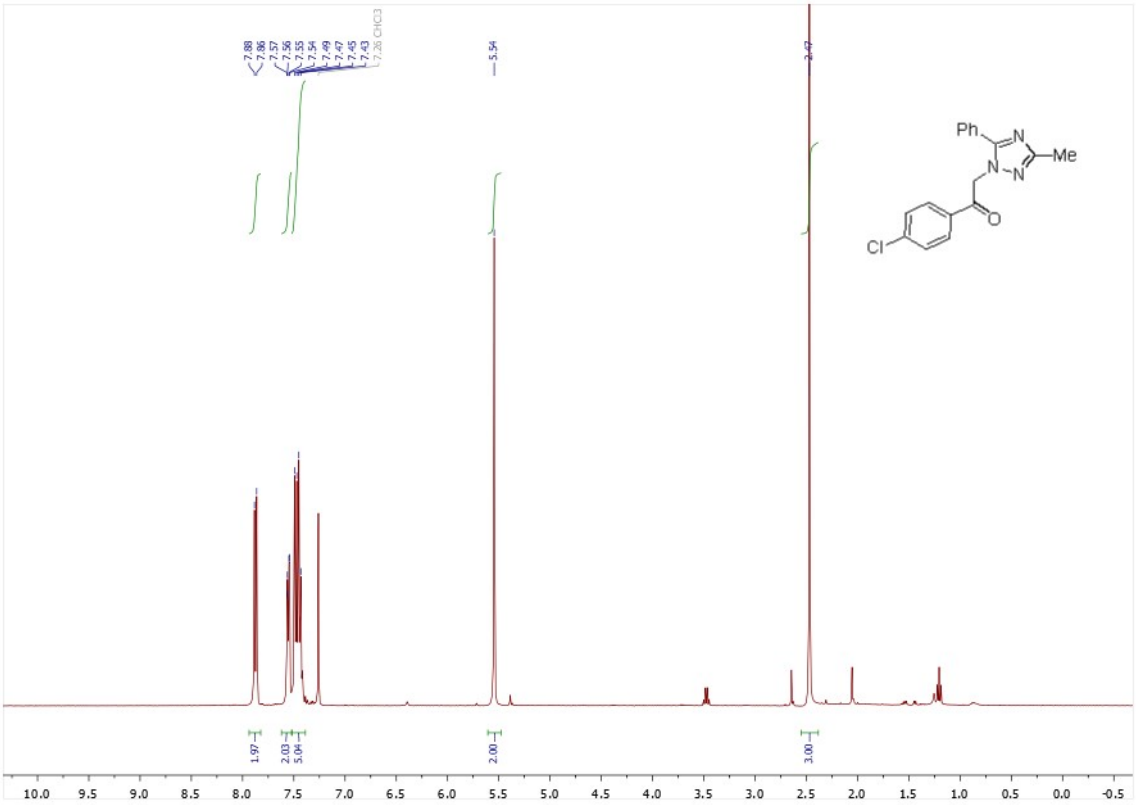


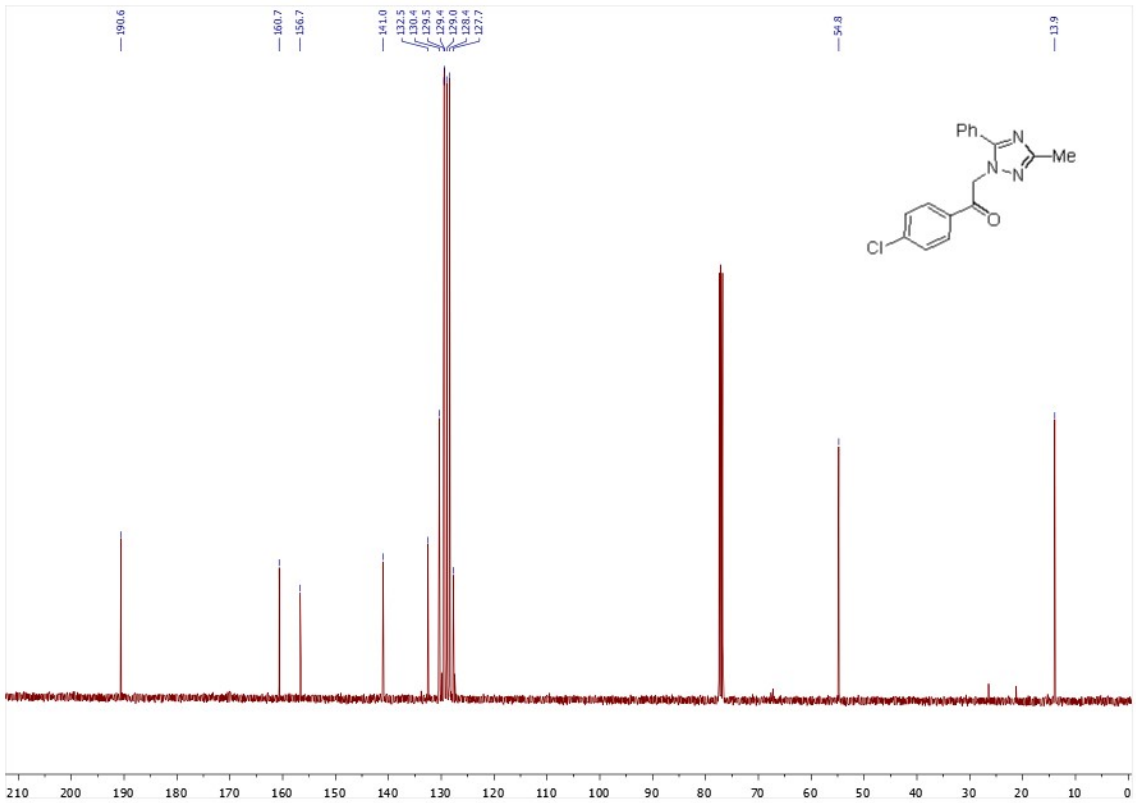
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4g**



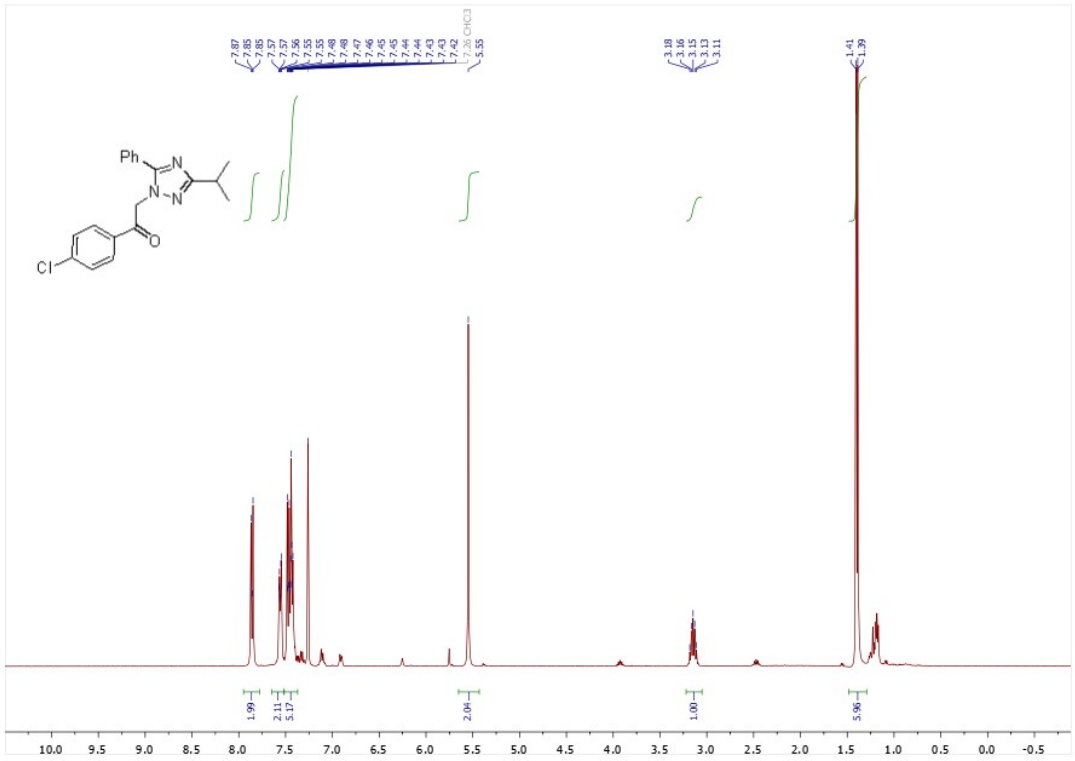


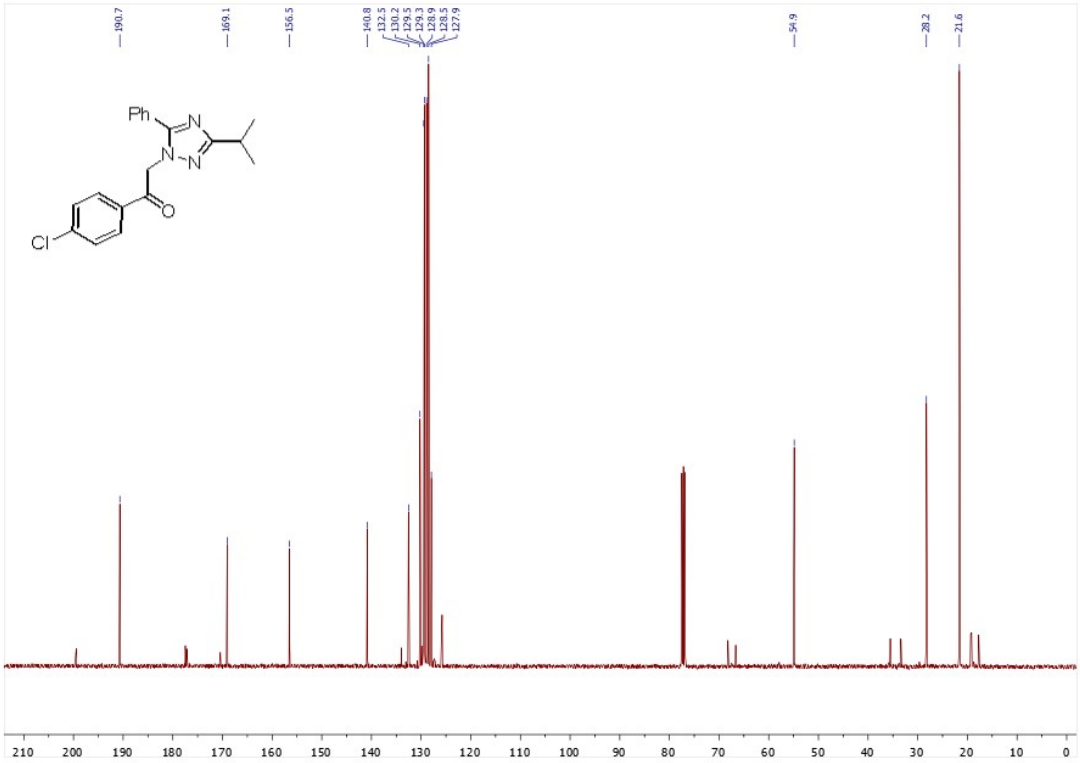
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4h**



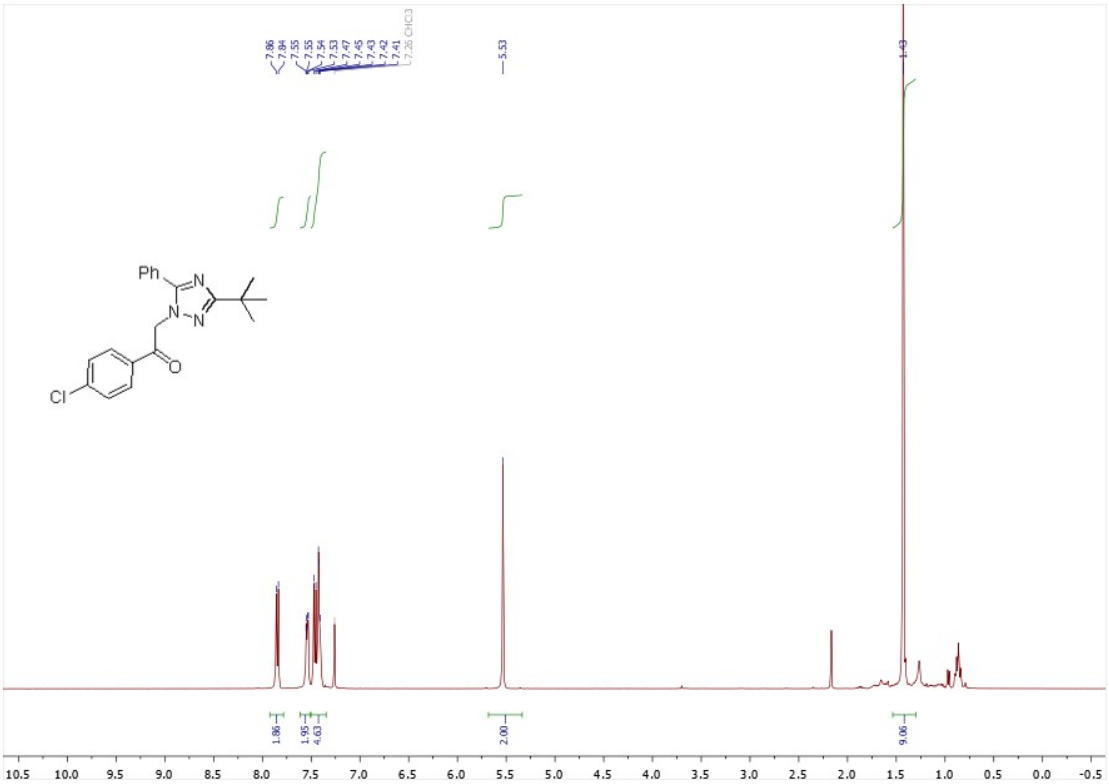


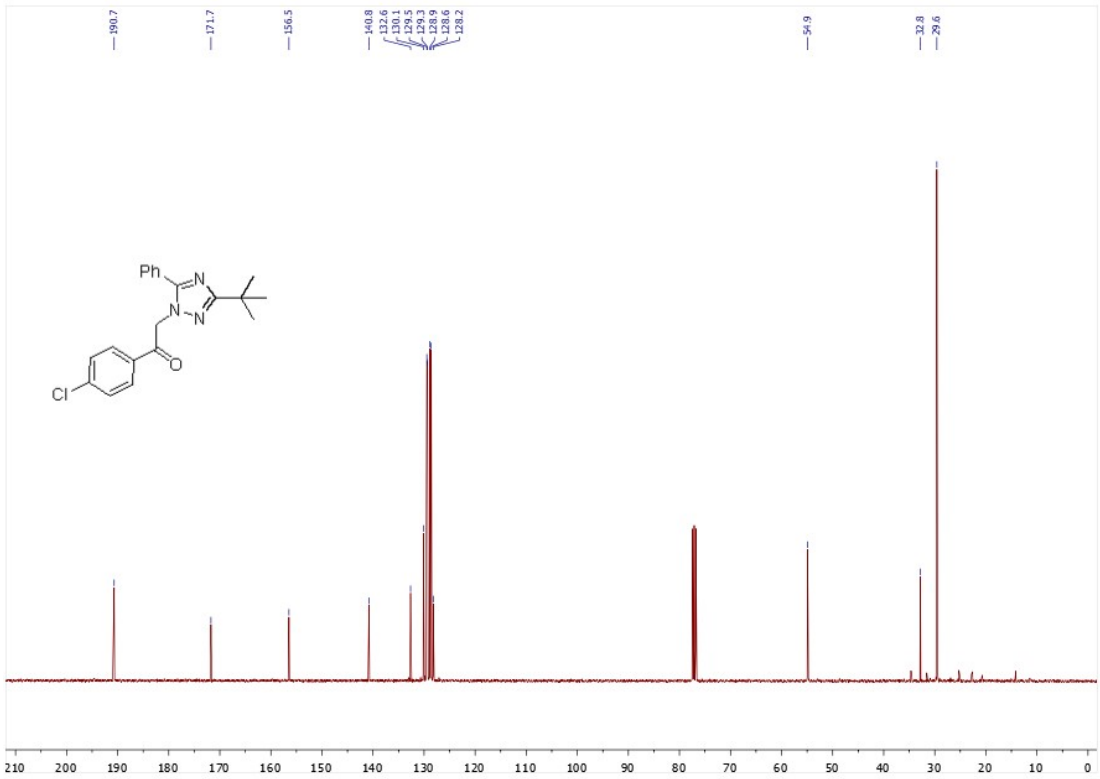
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4i**



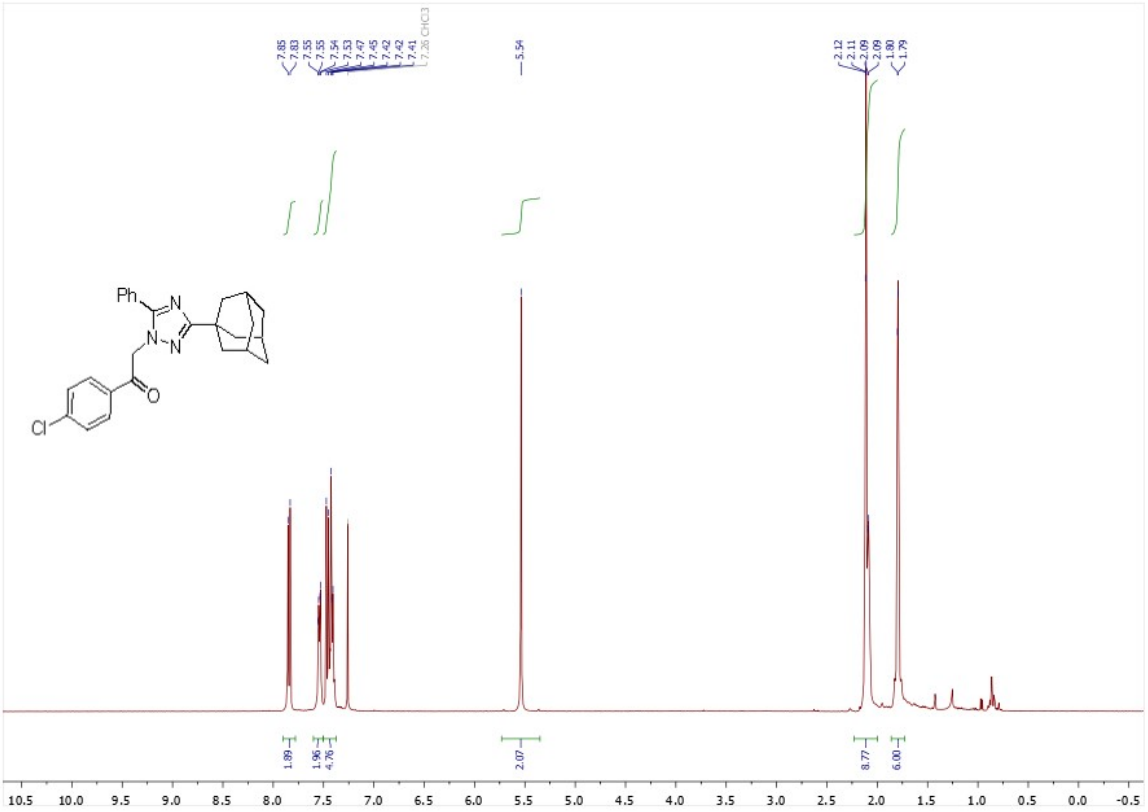


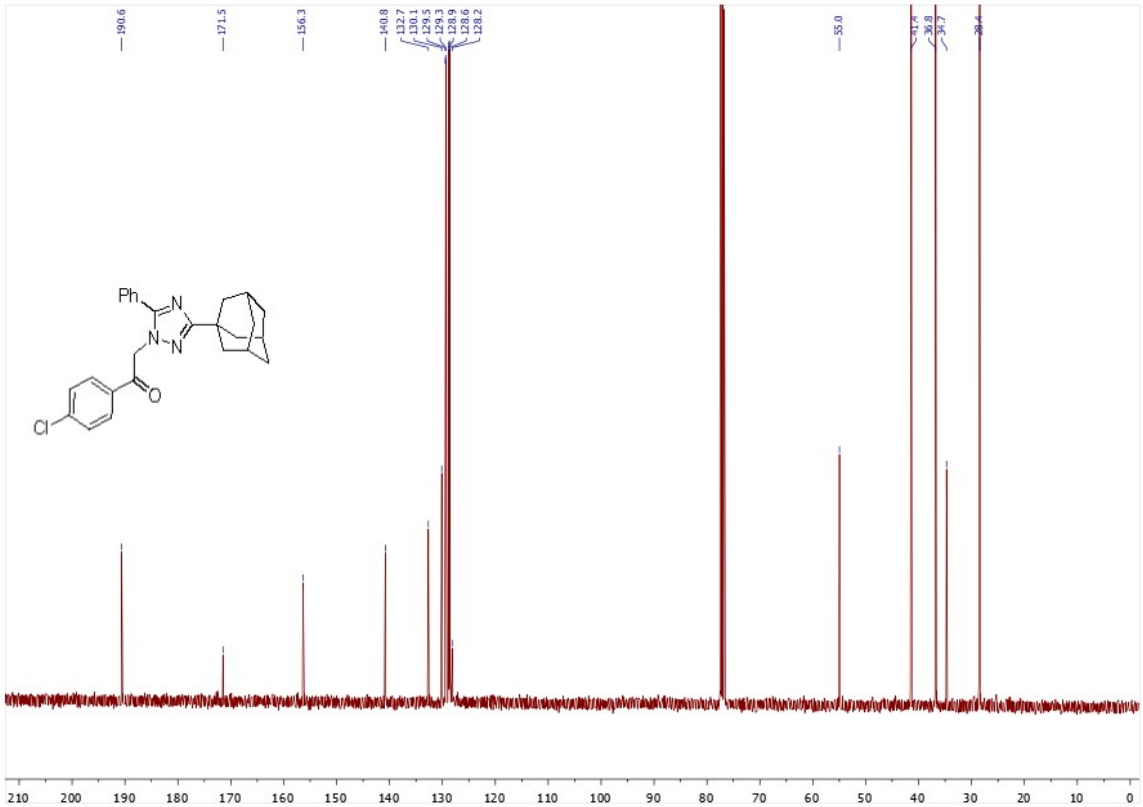
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4j**



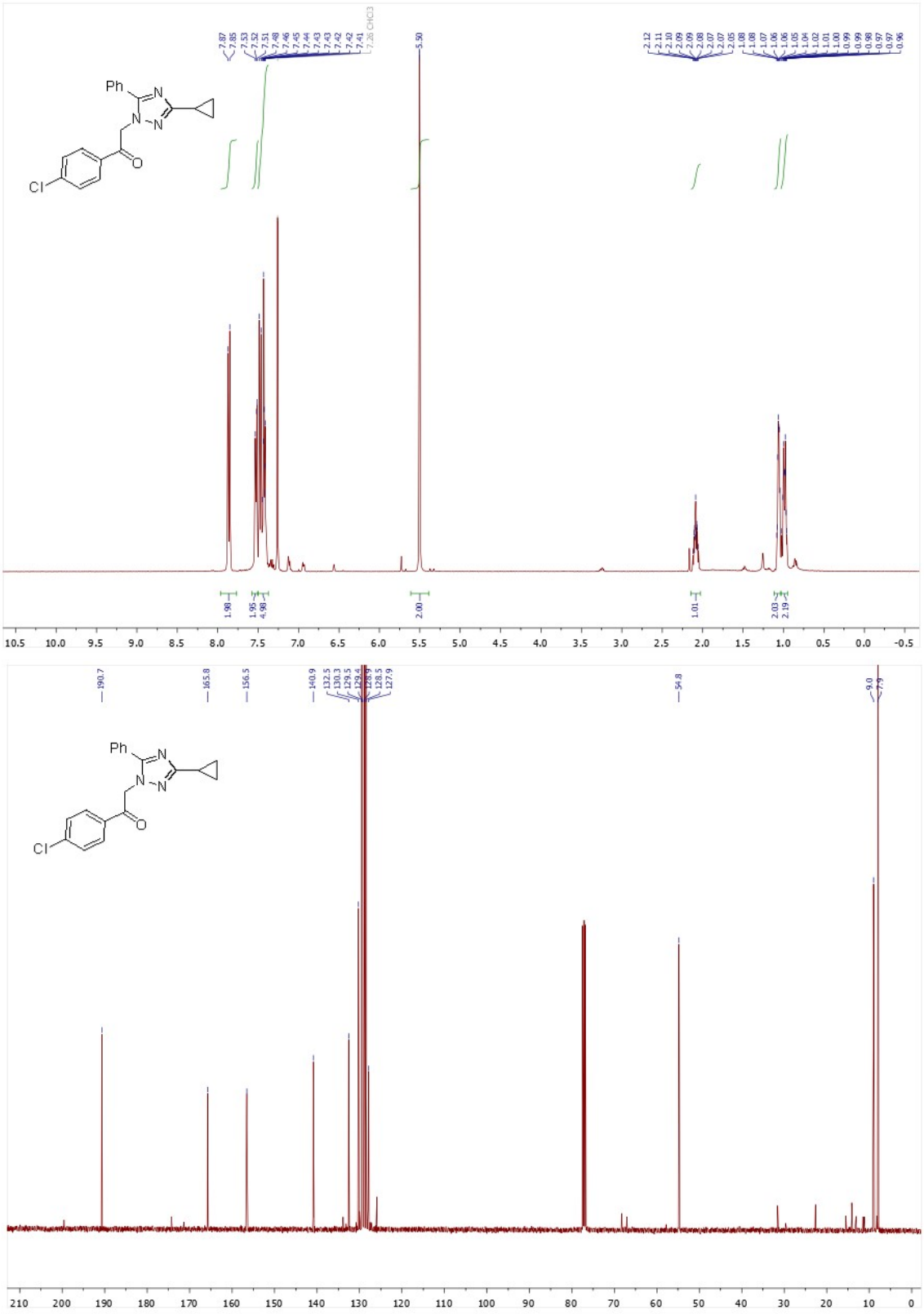


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4k**

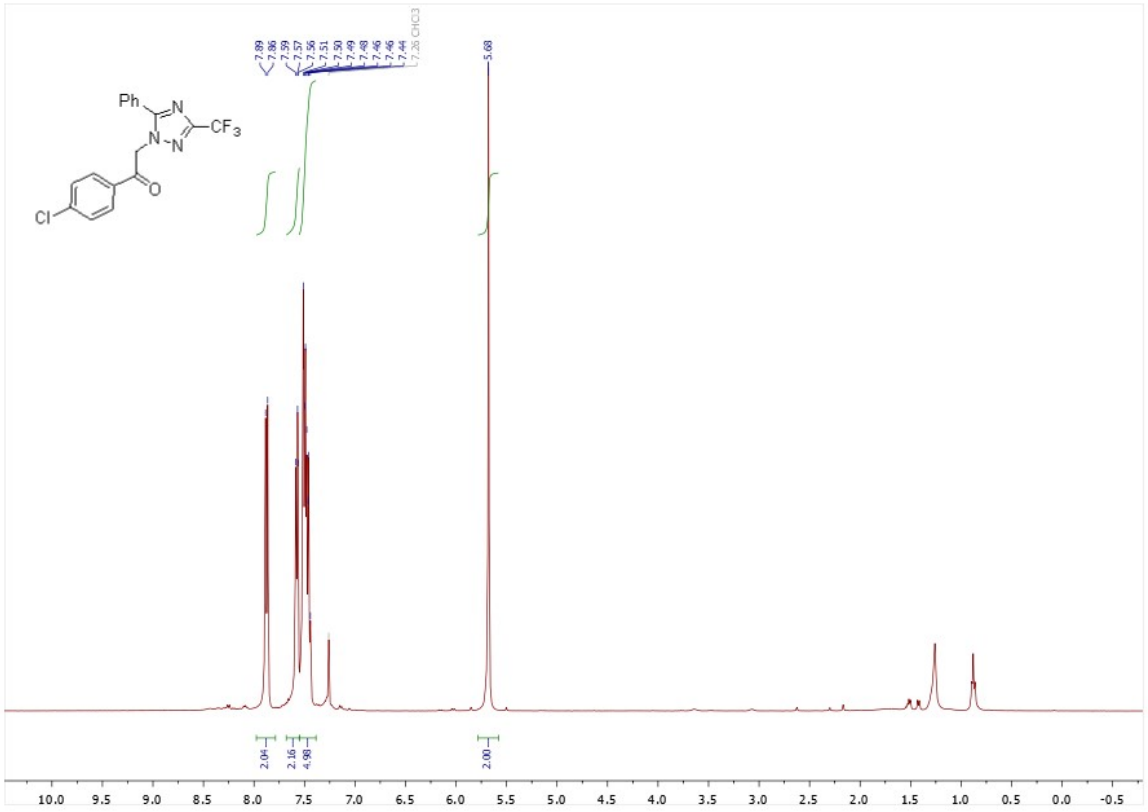


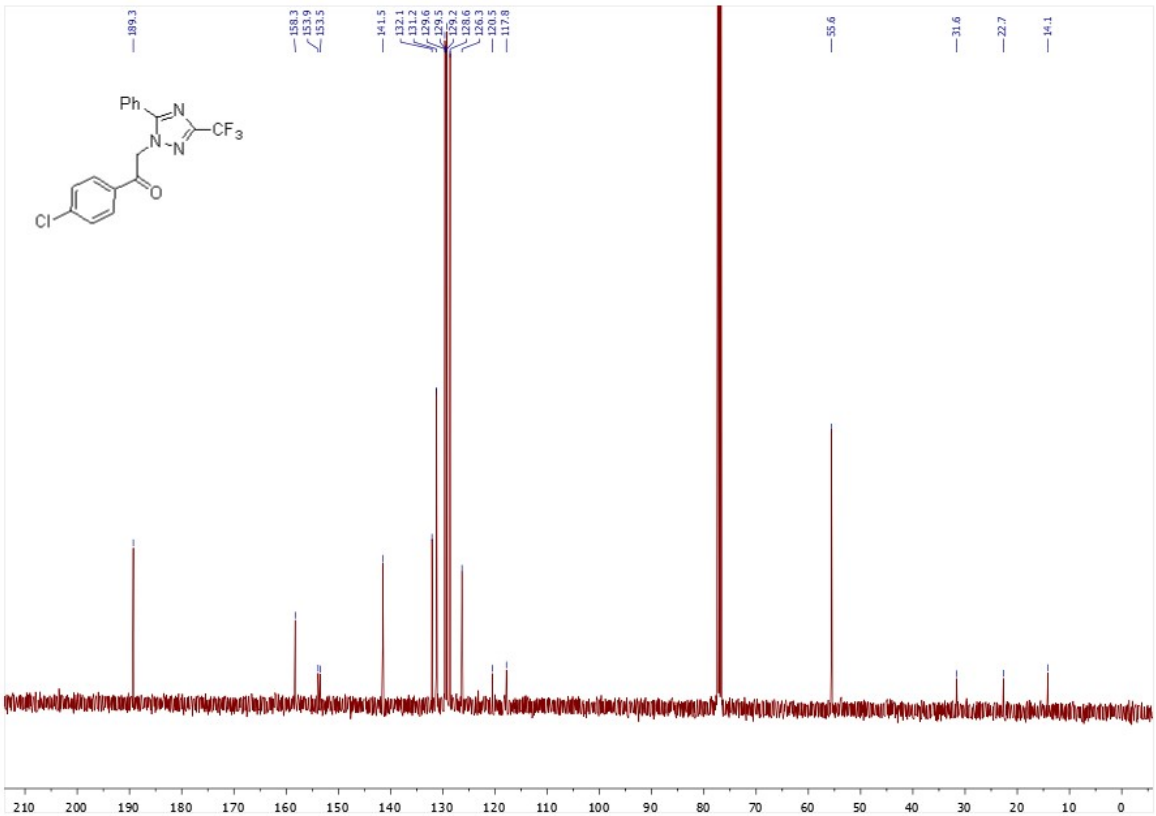


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4l**

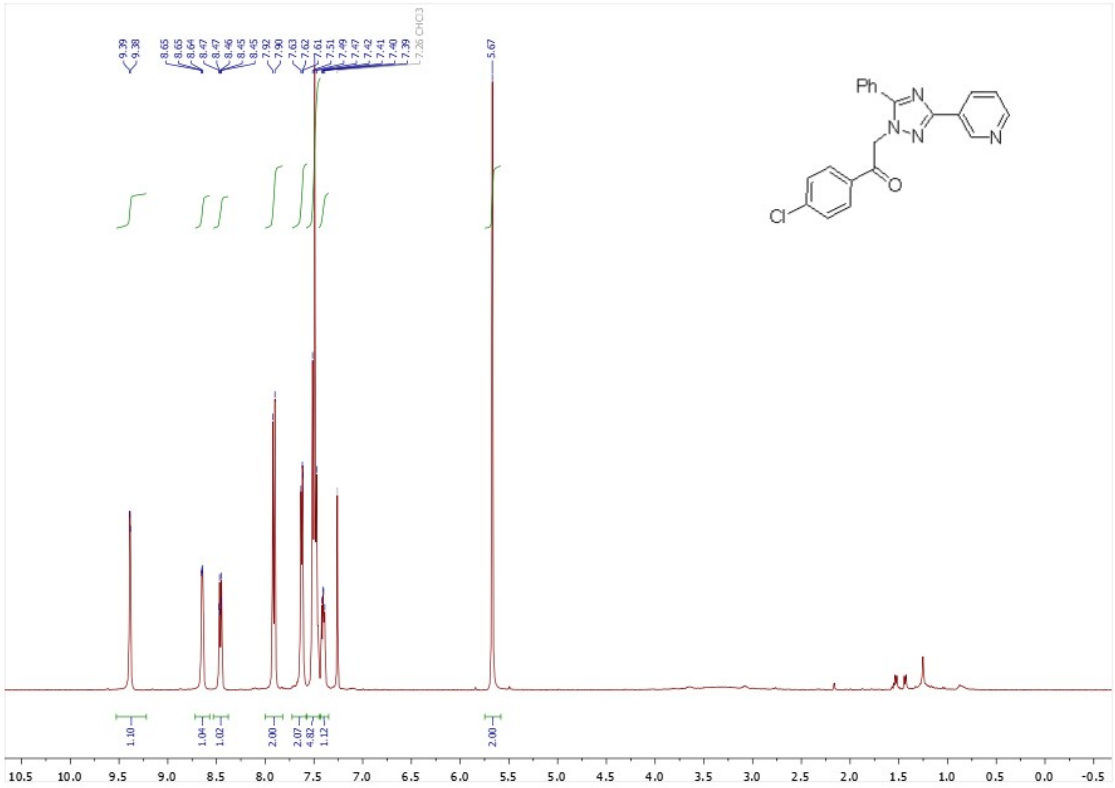


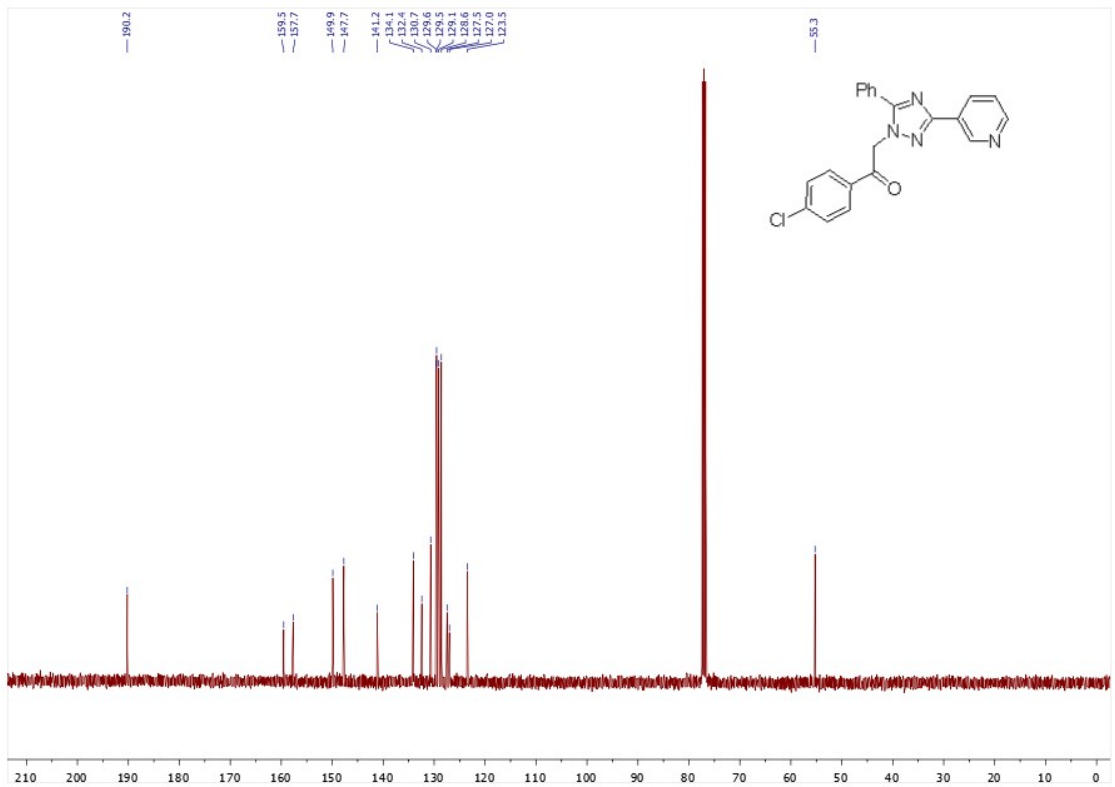
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4m**



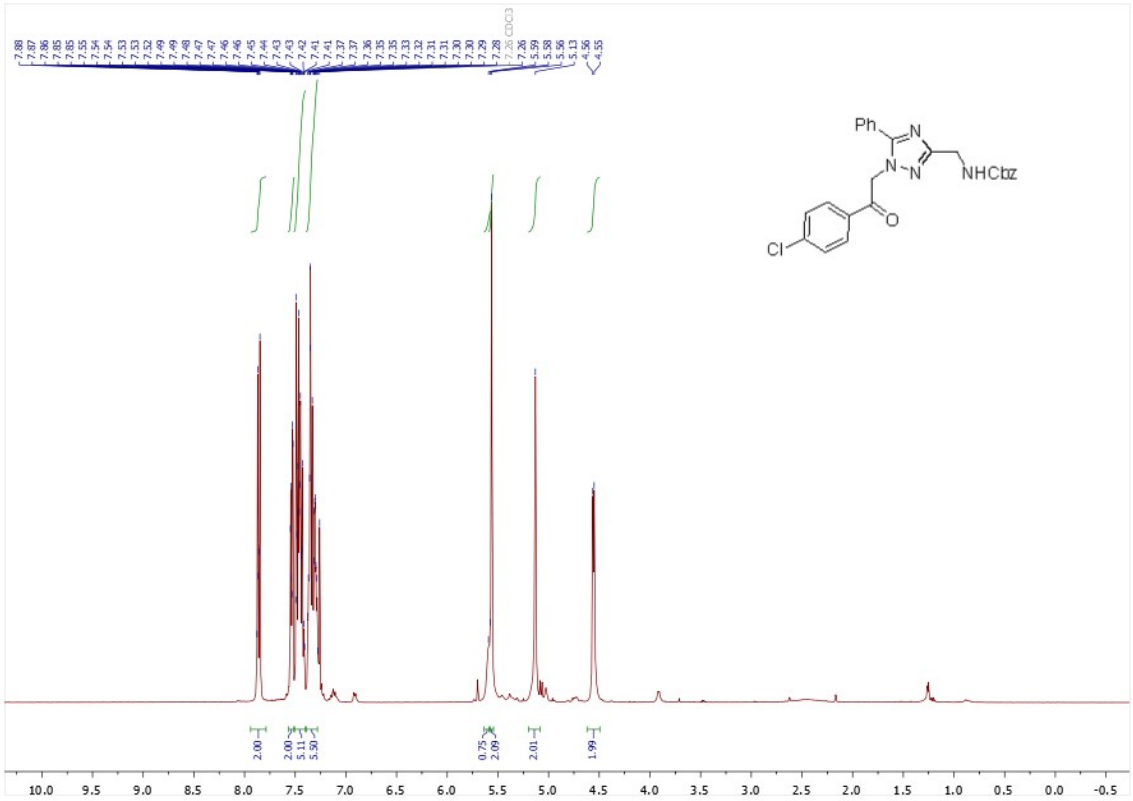


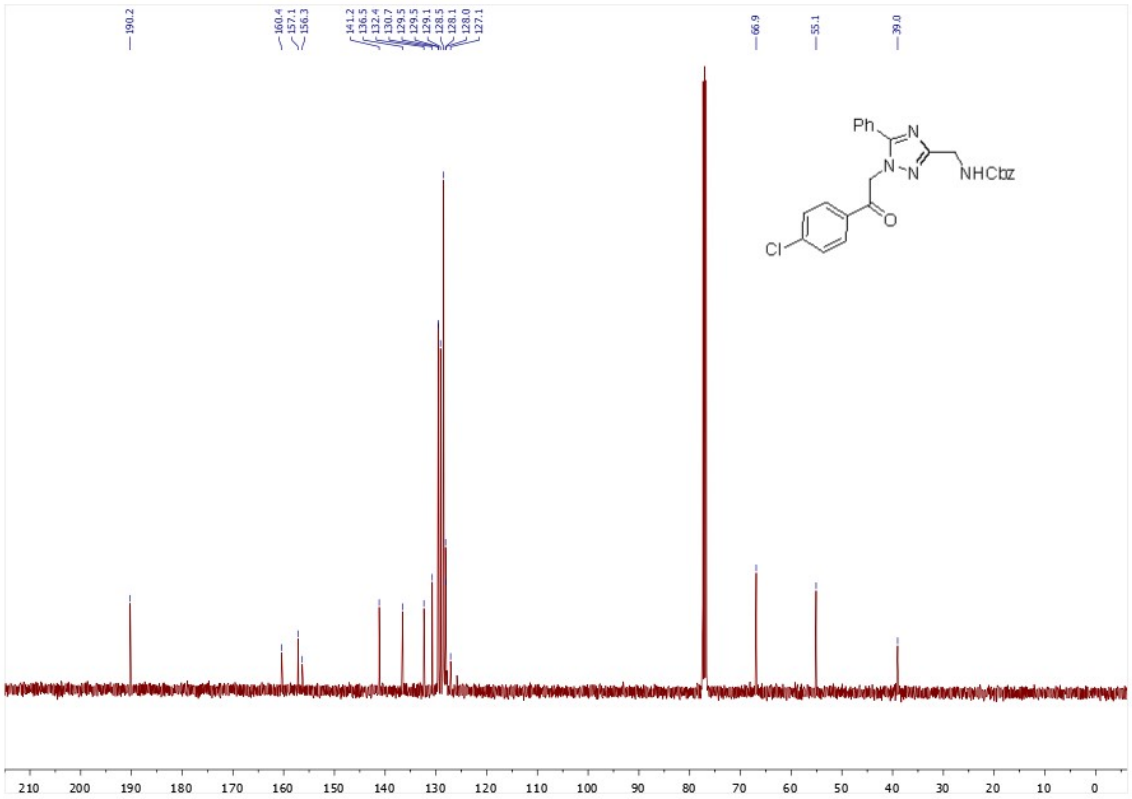
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4n**



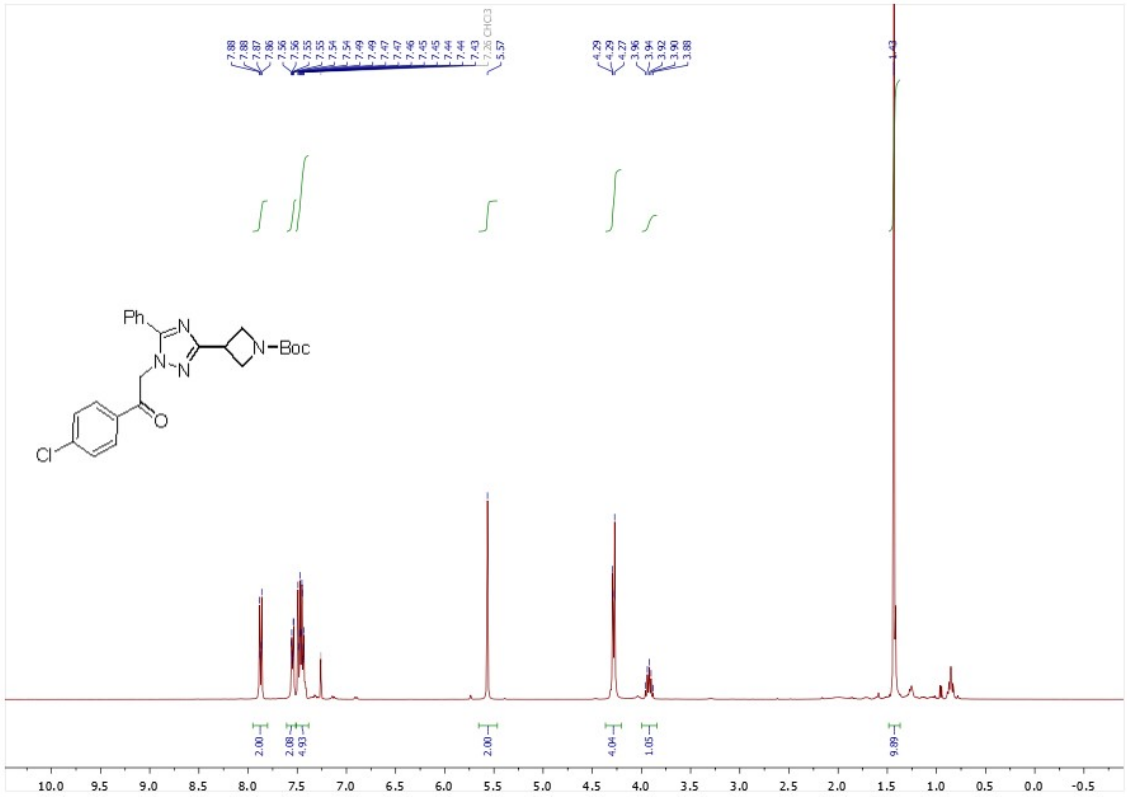


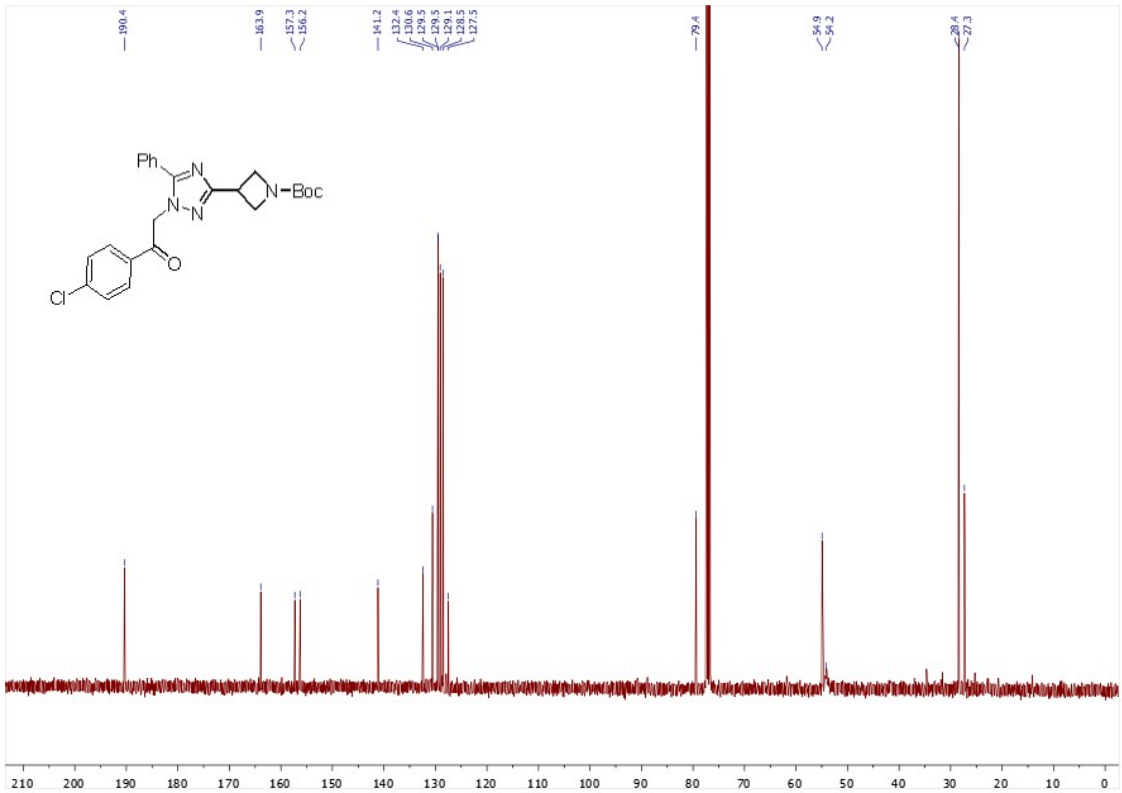
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4o**



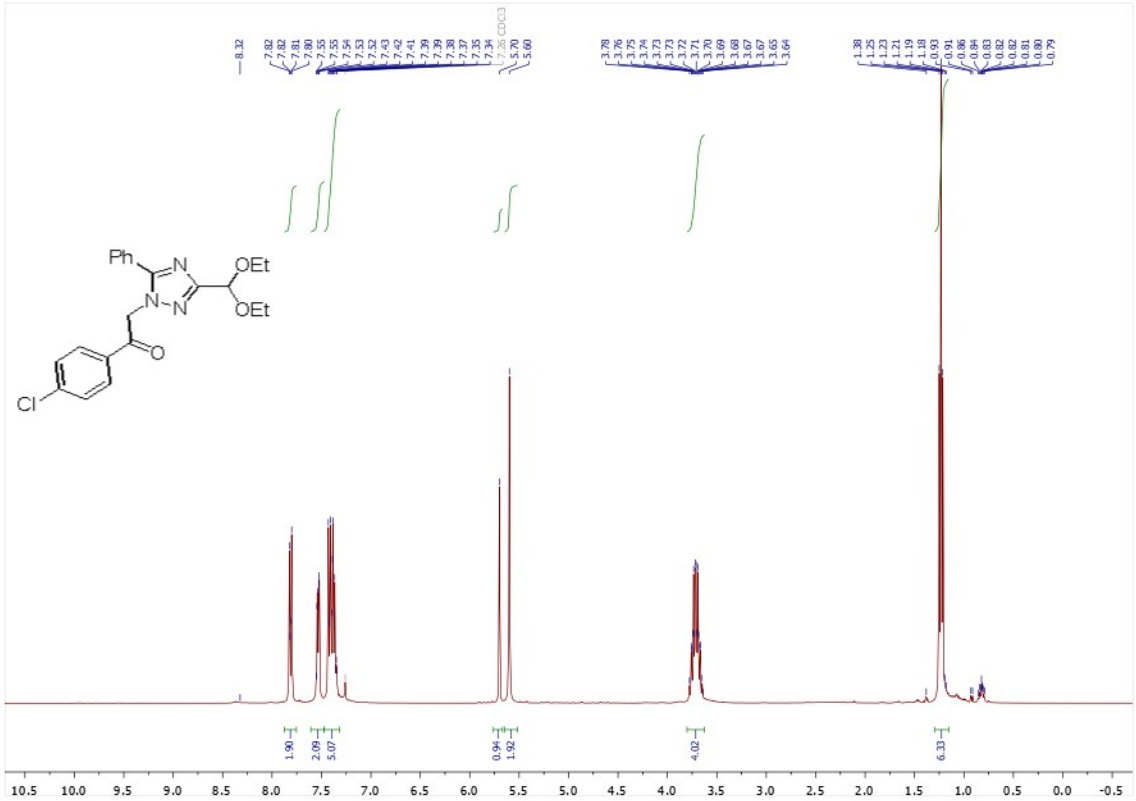


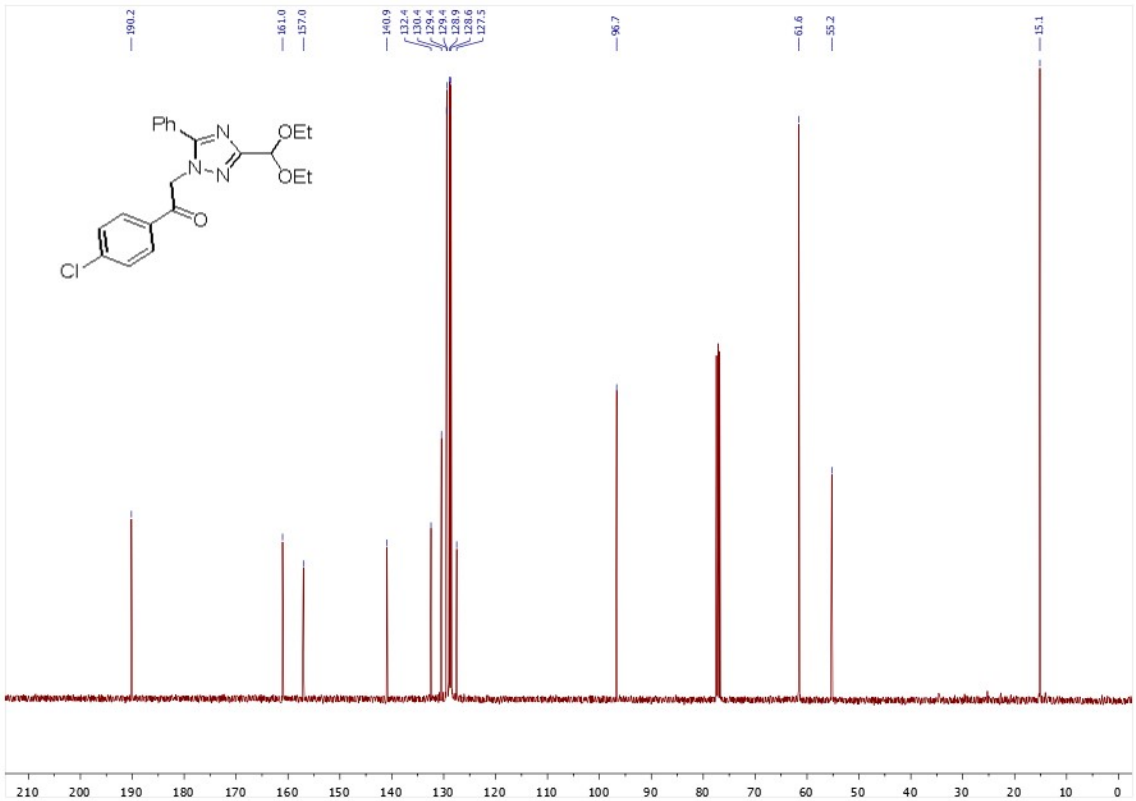
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4p**



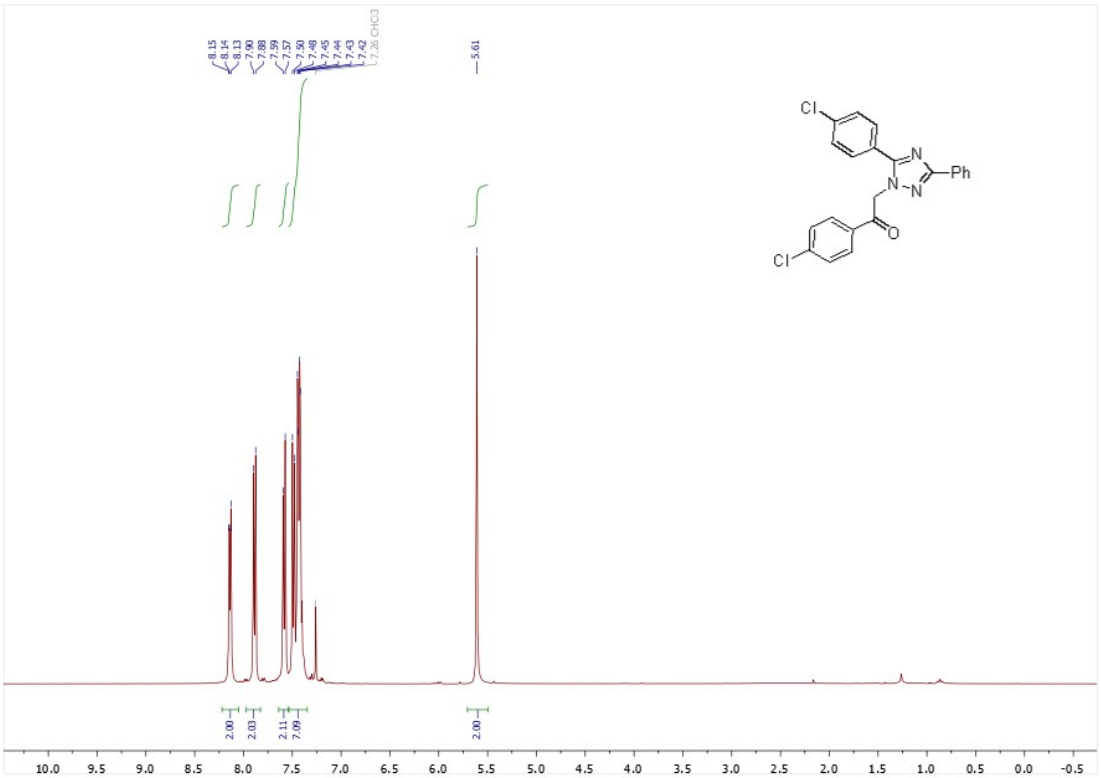


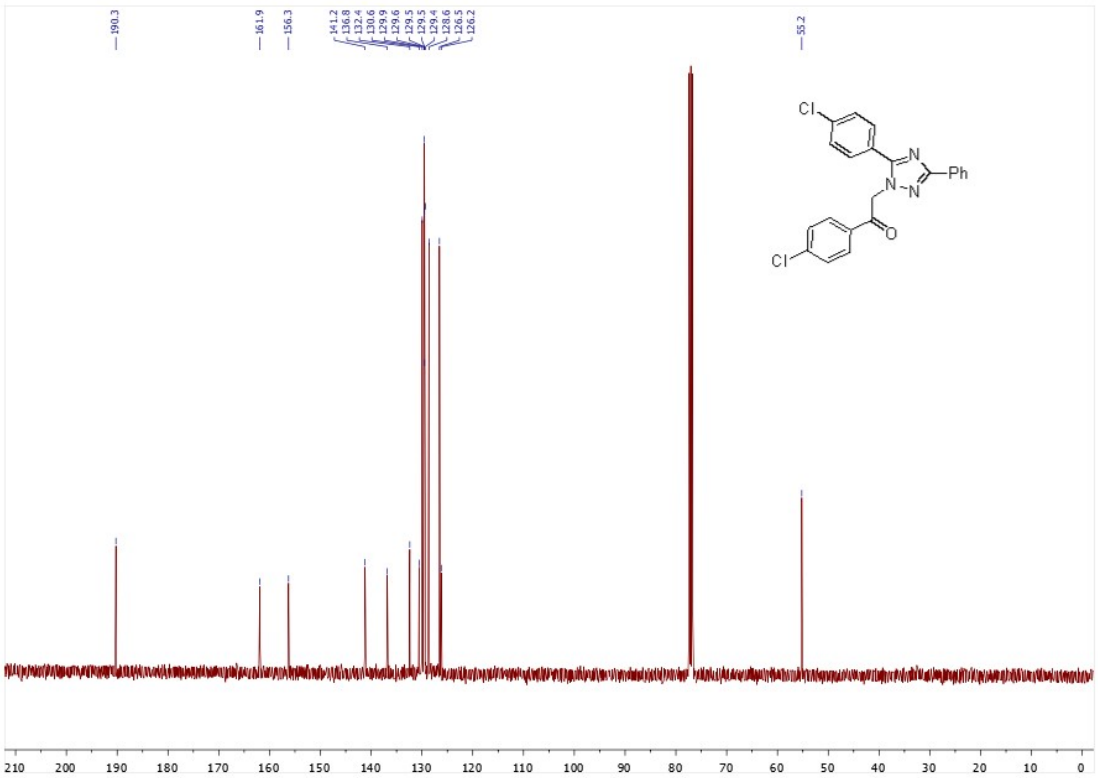
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4q**



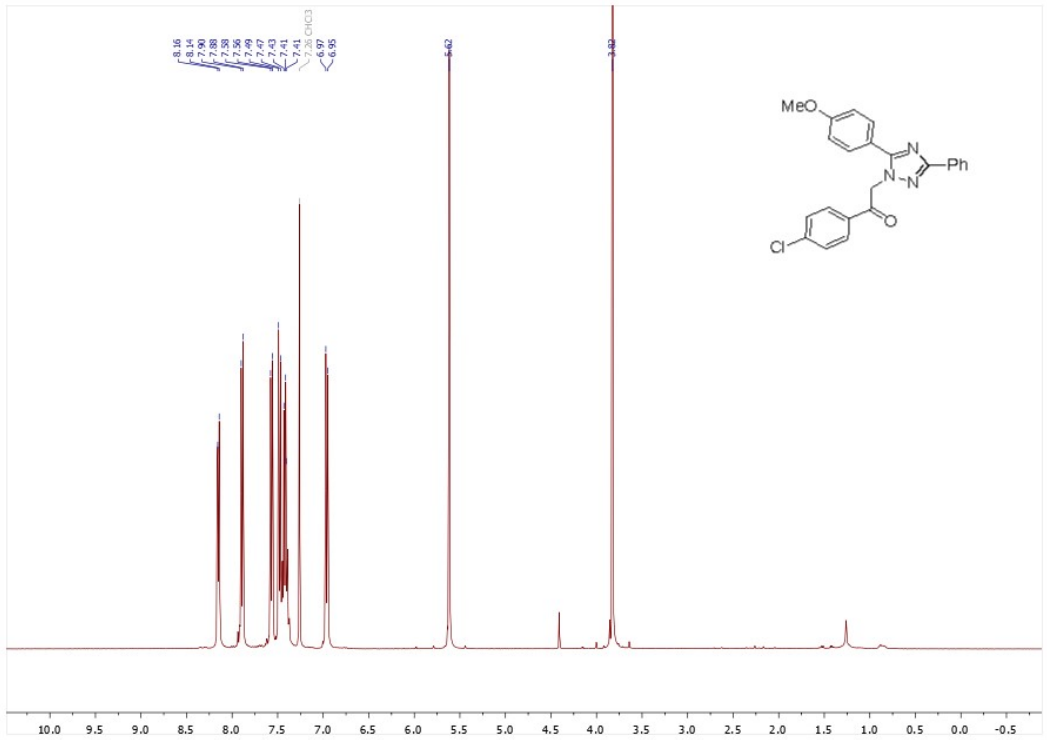


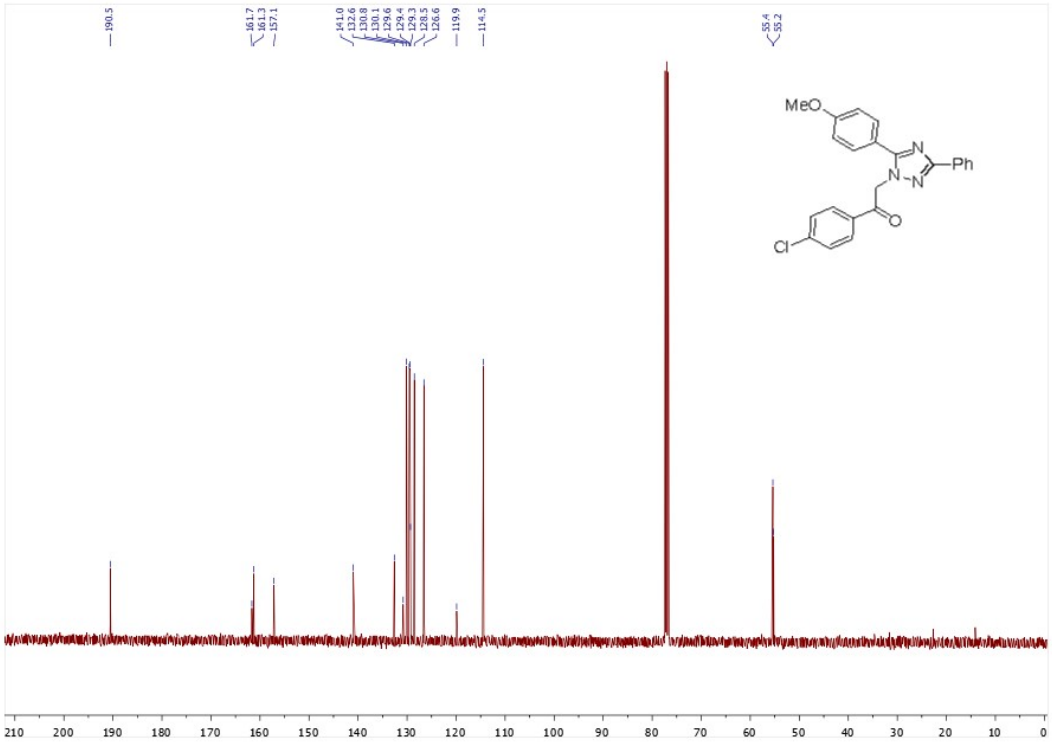
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4r**



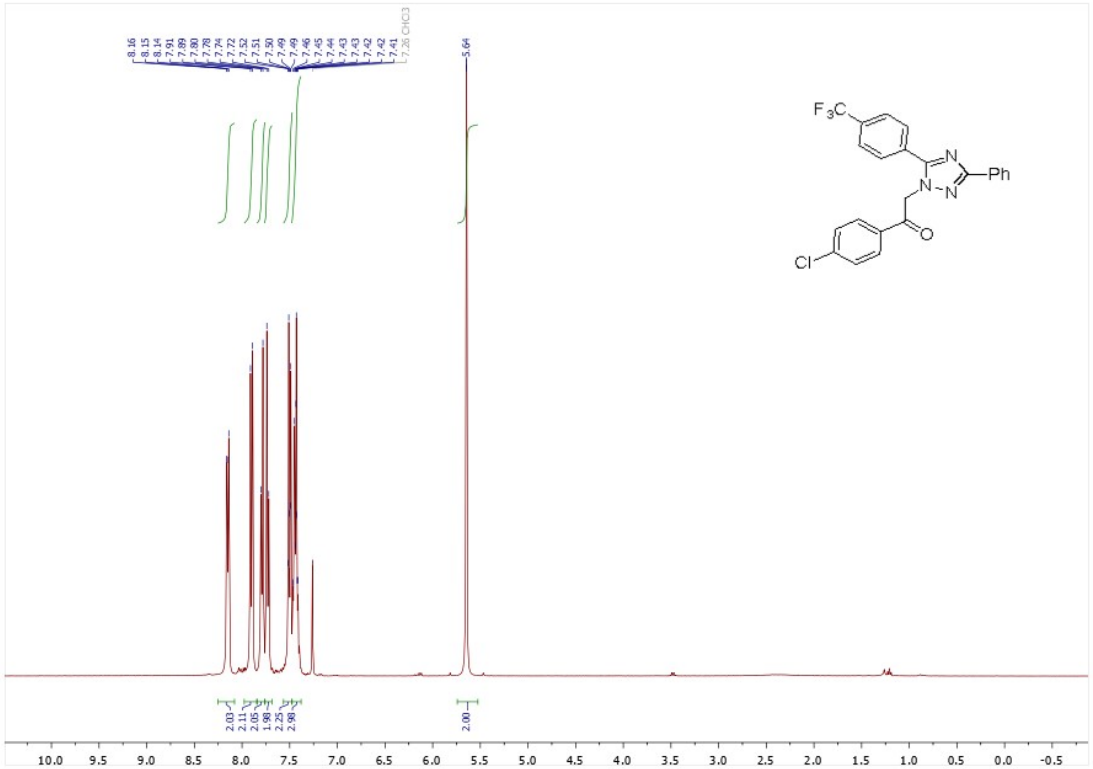


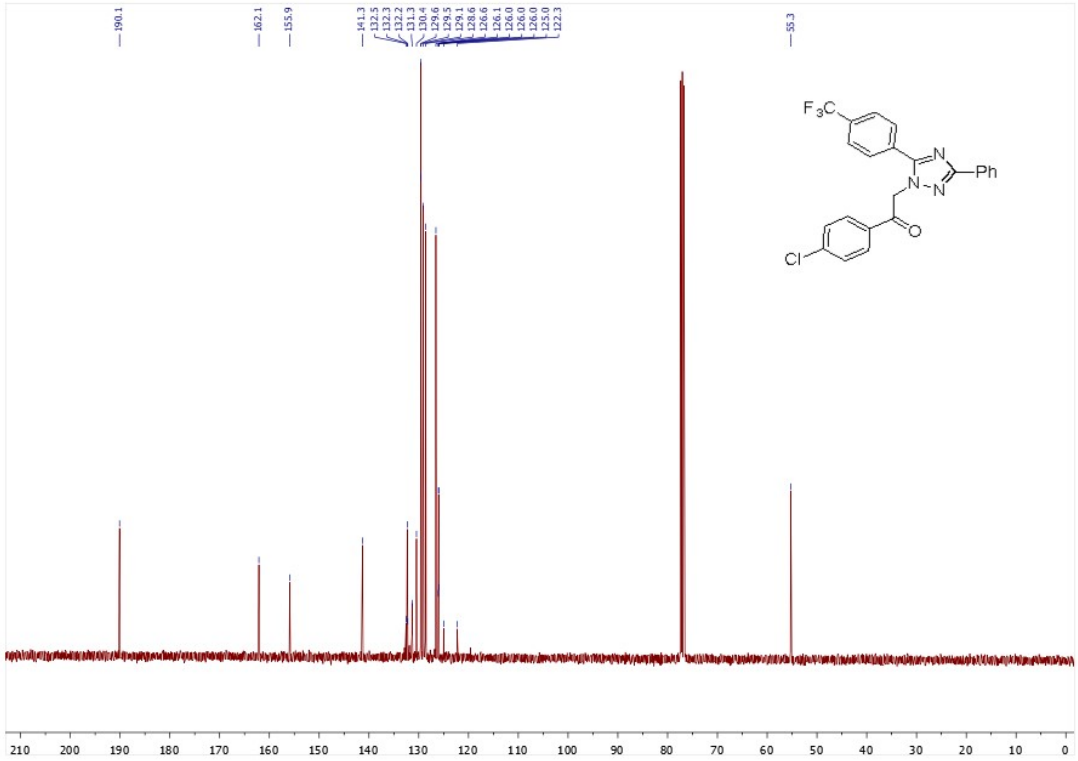
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4s**



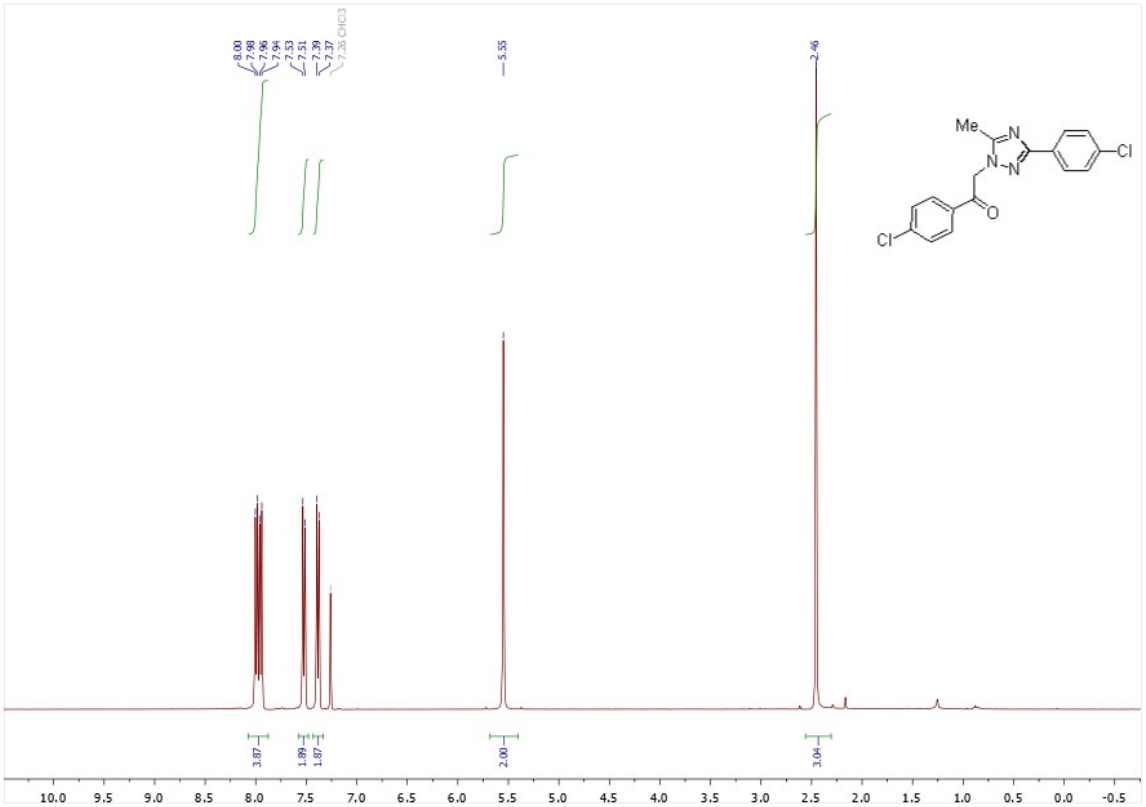


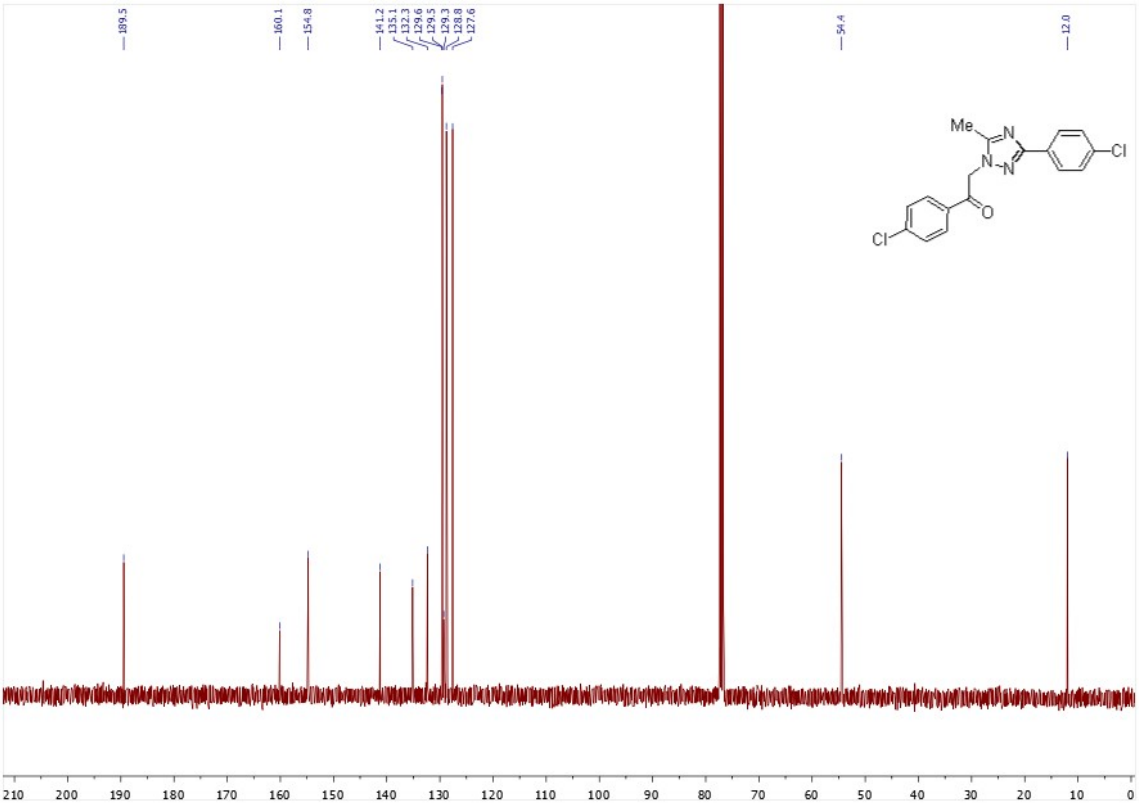
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4t**



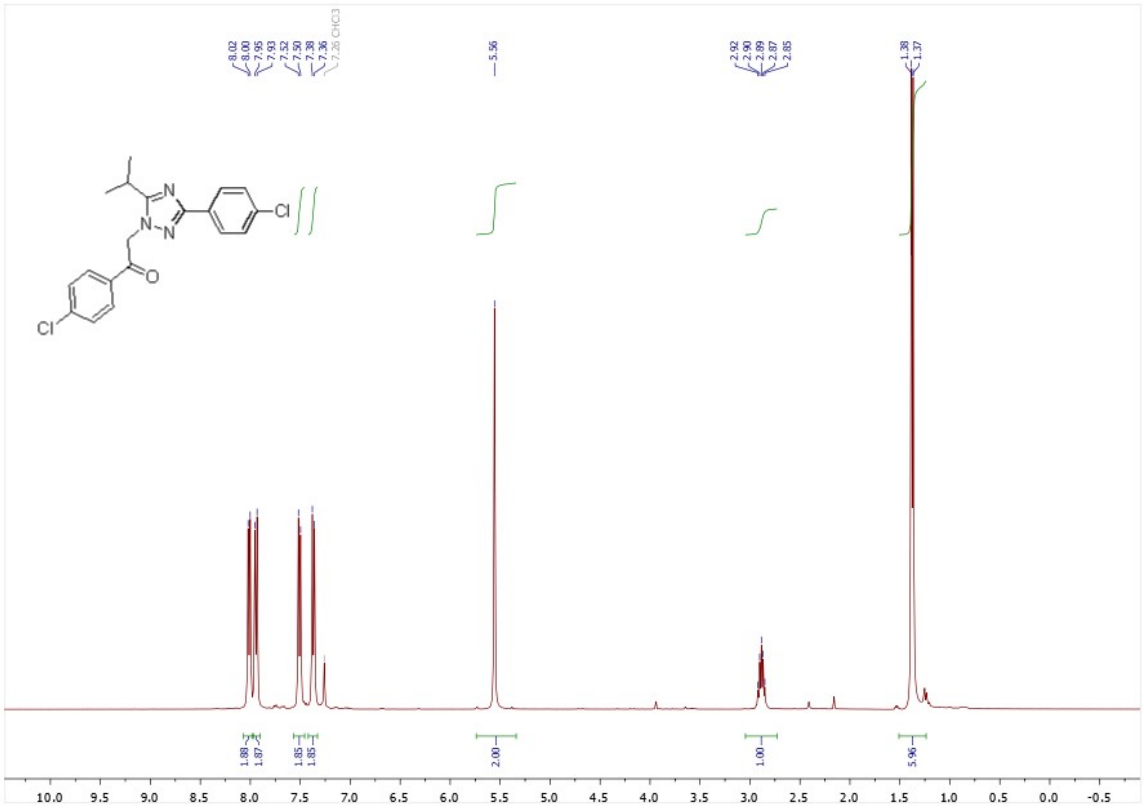


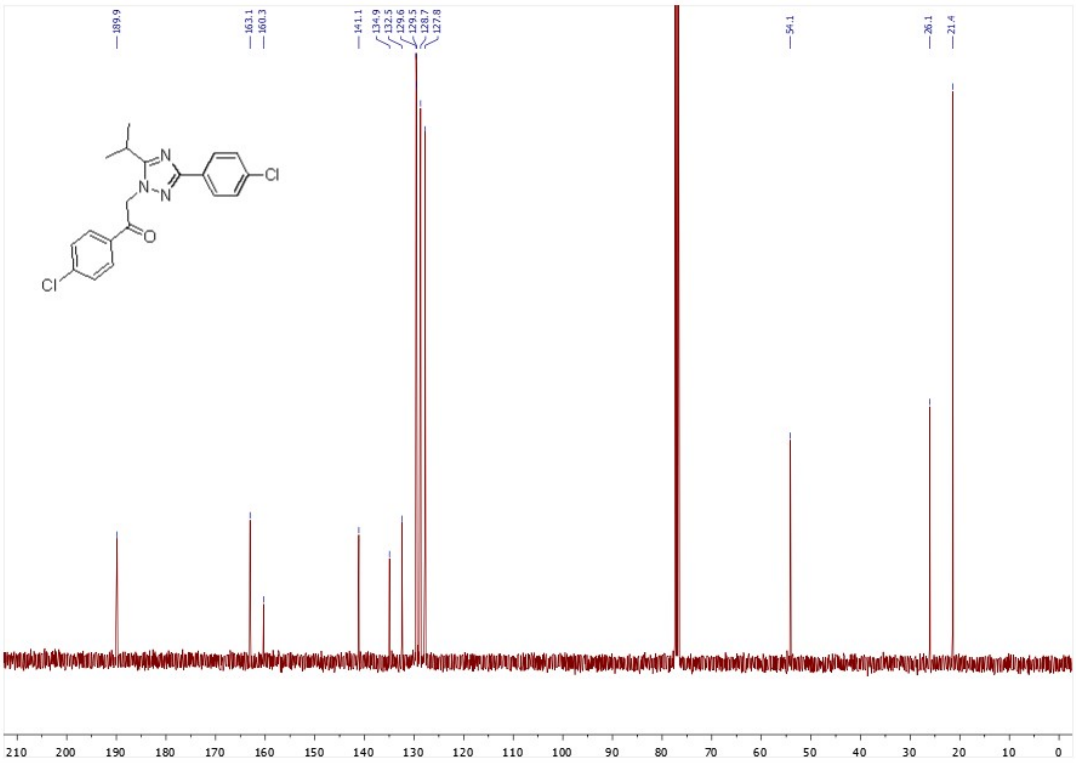
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4u**



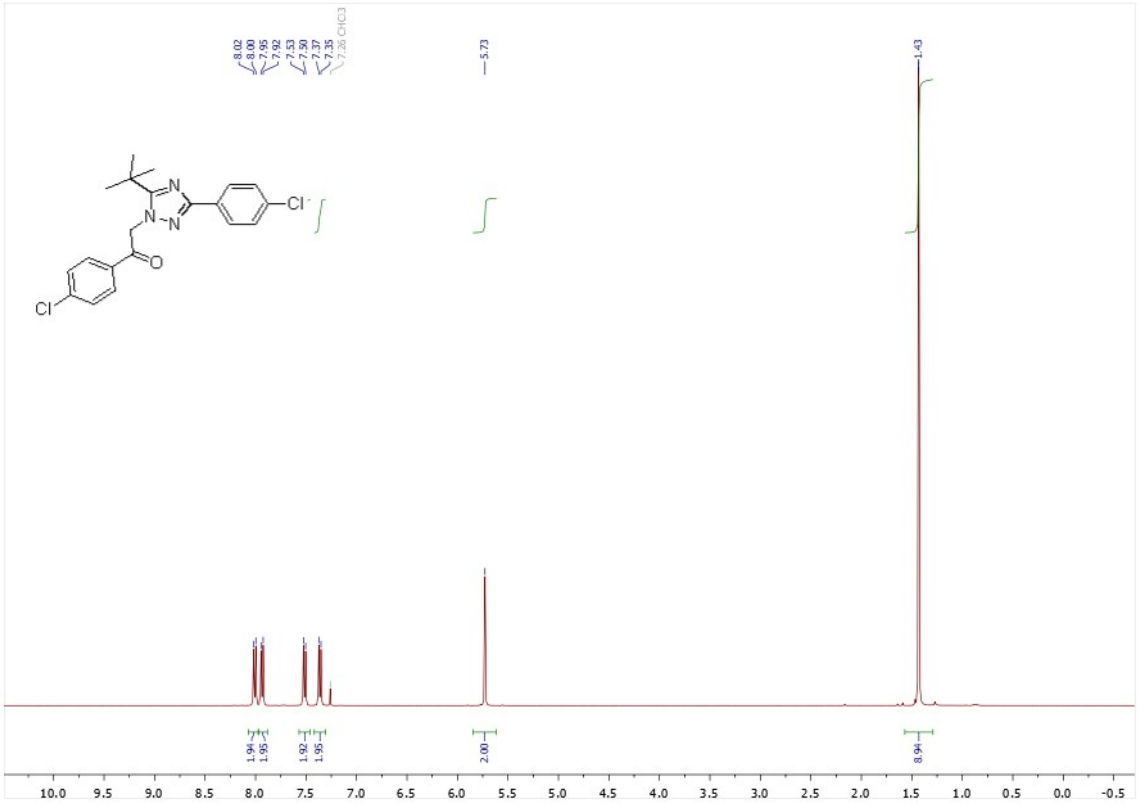


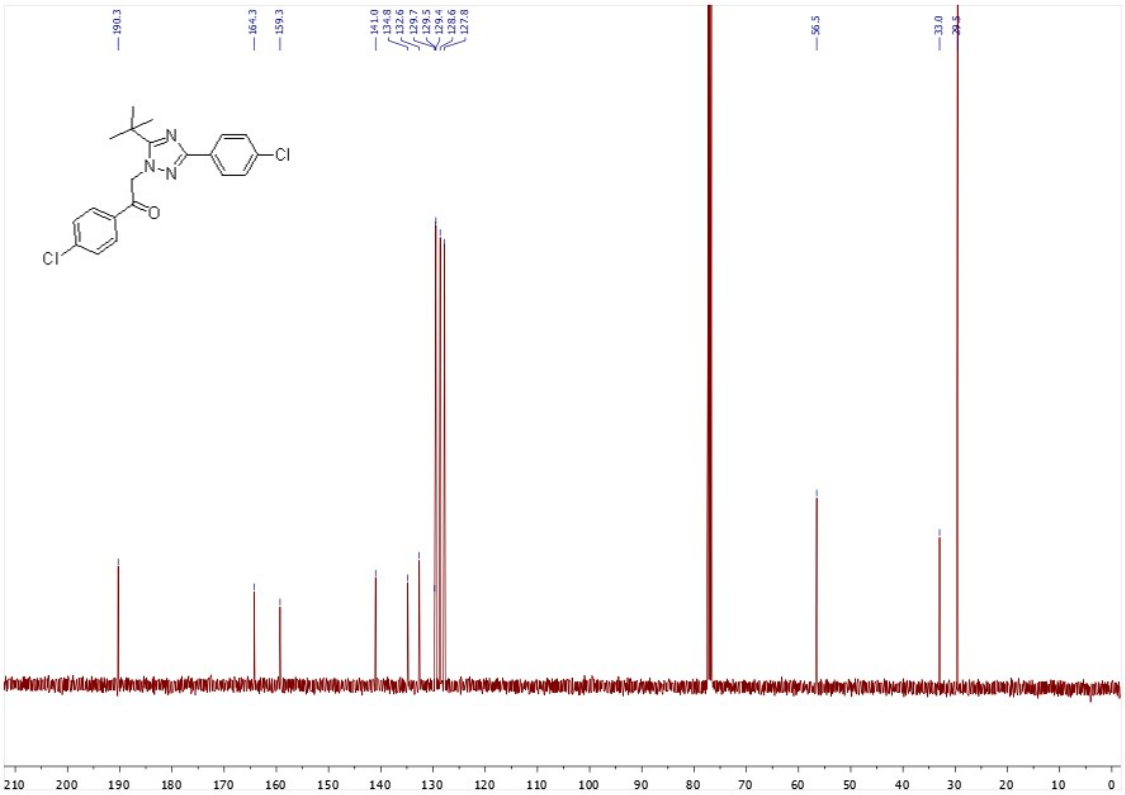
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4v**



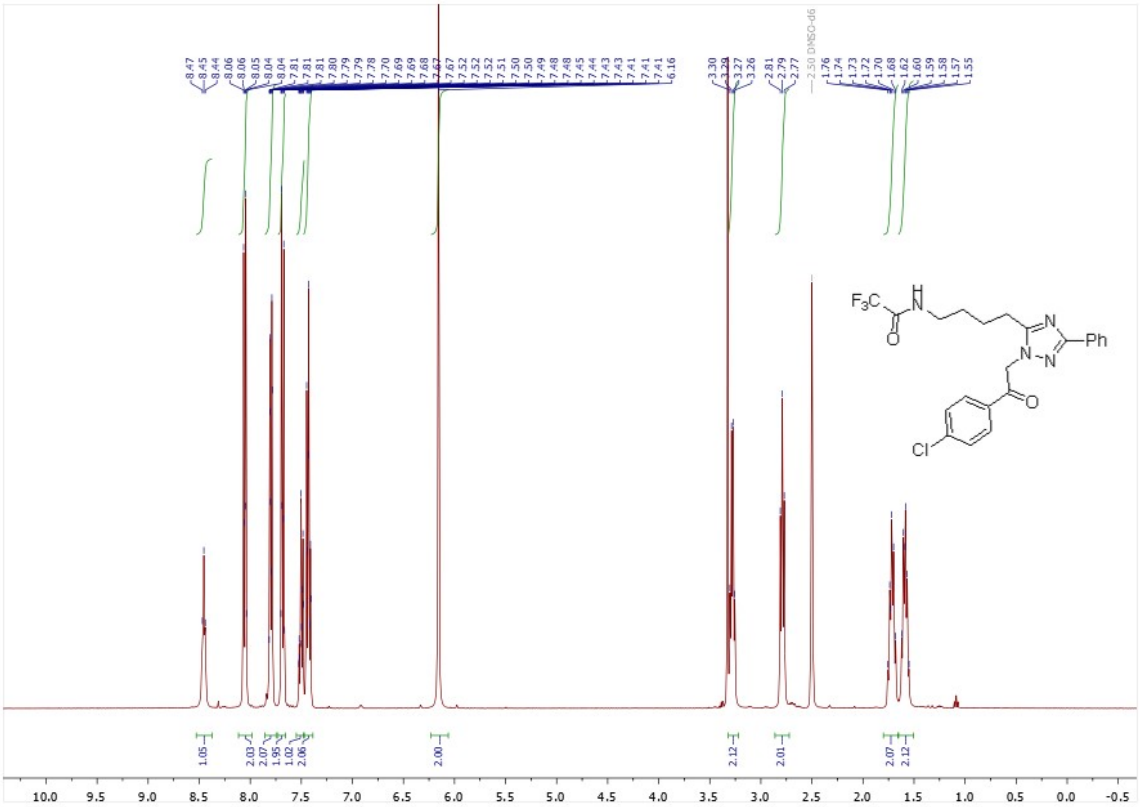


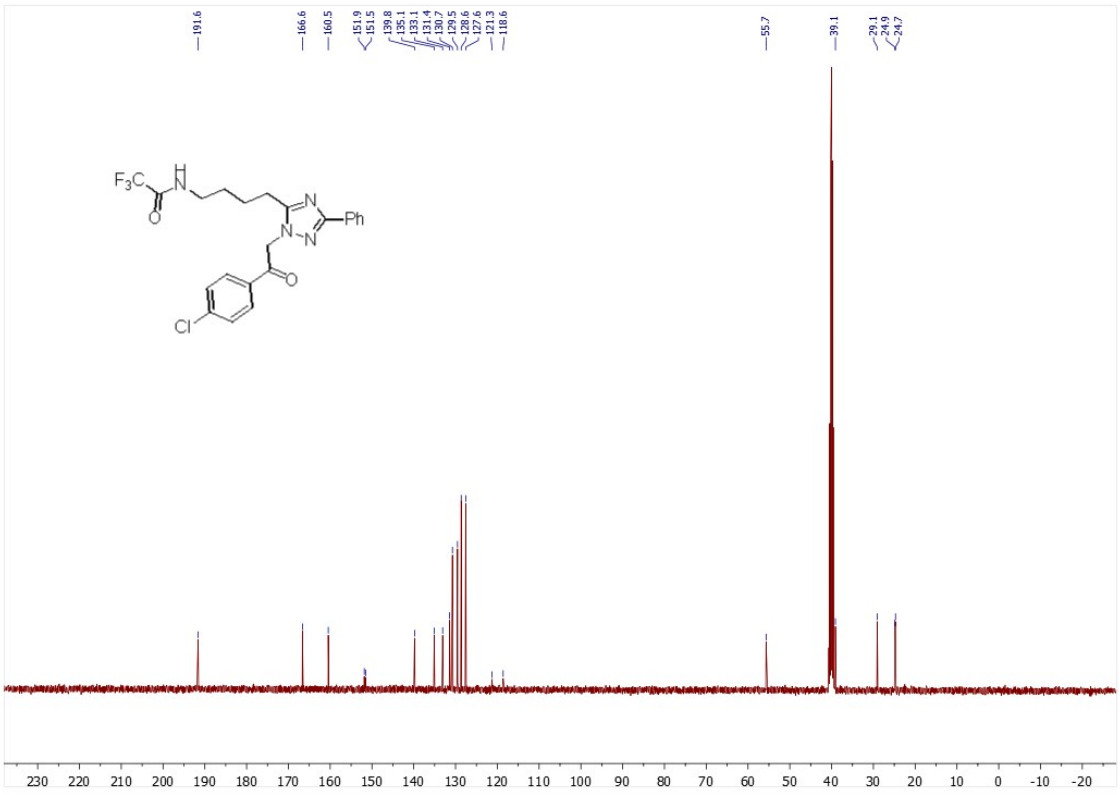
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4w**



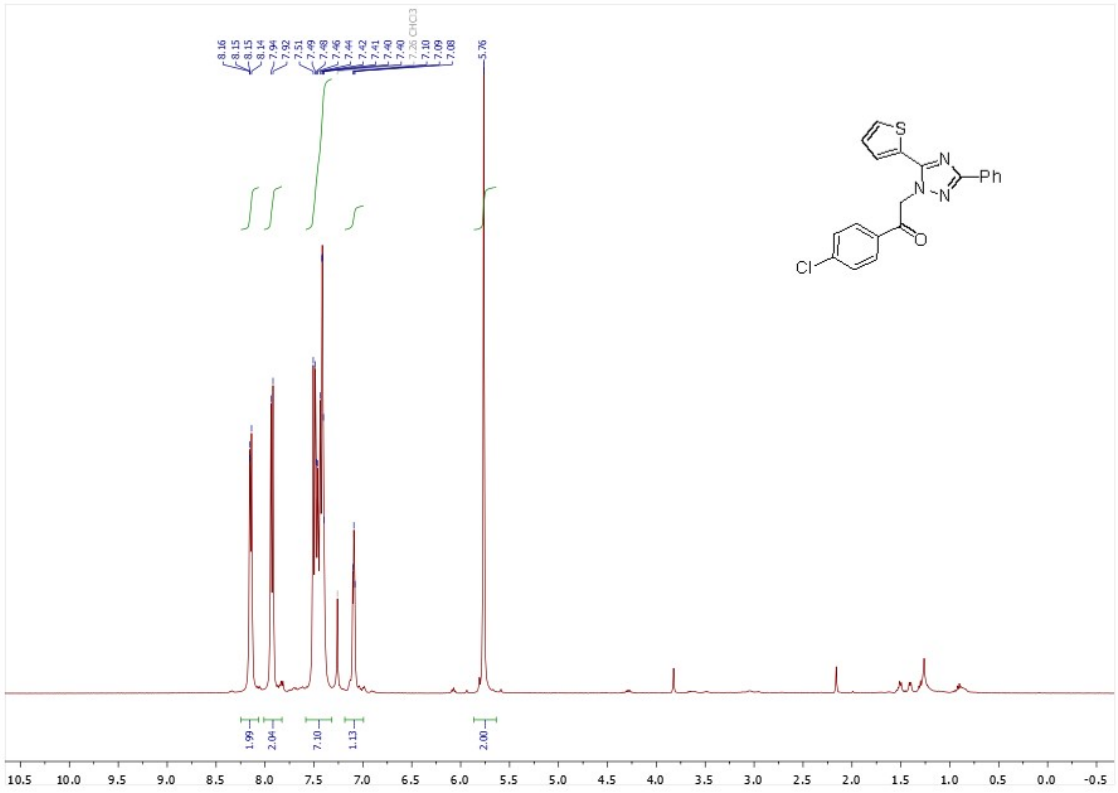


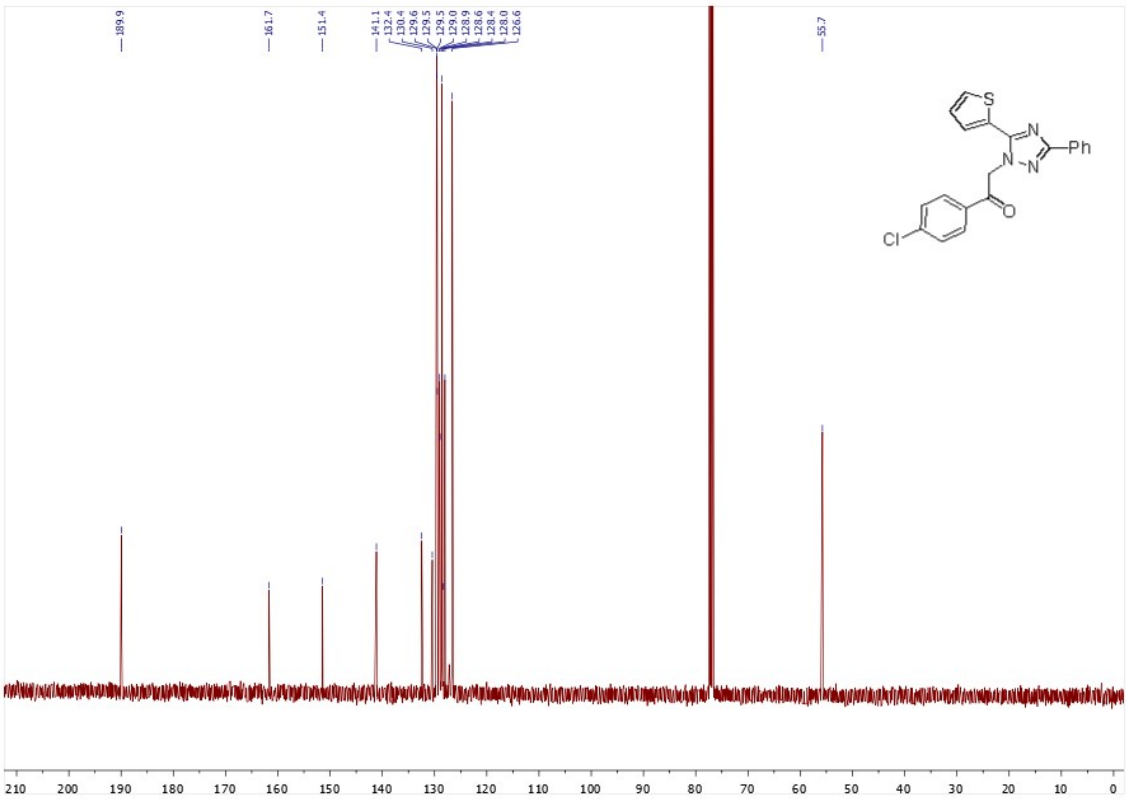
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4x**



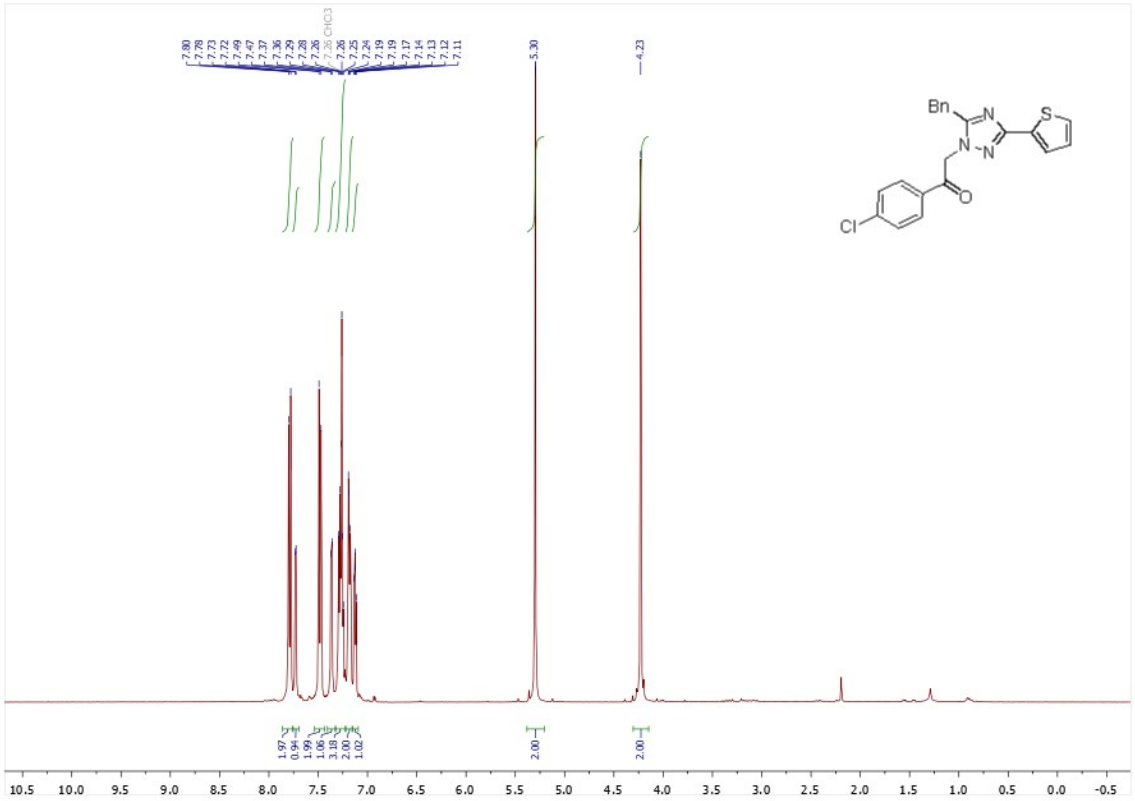


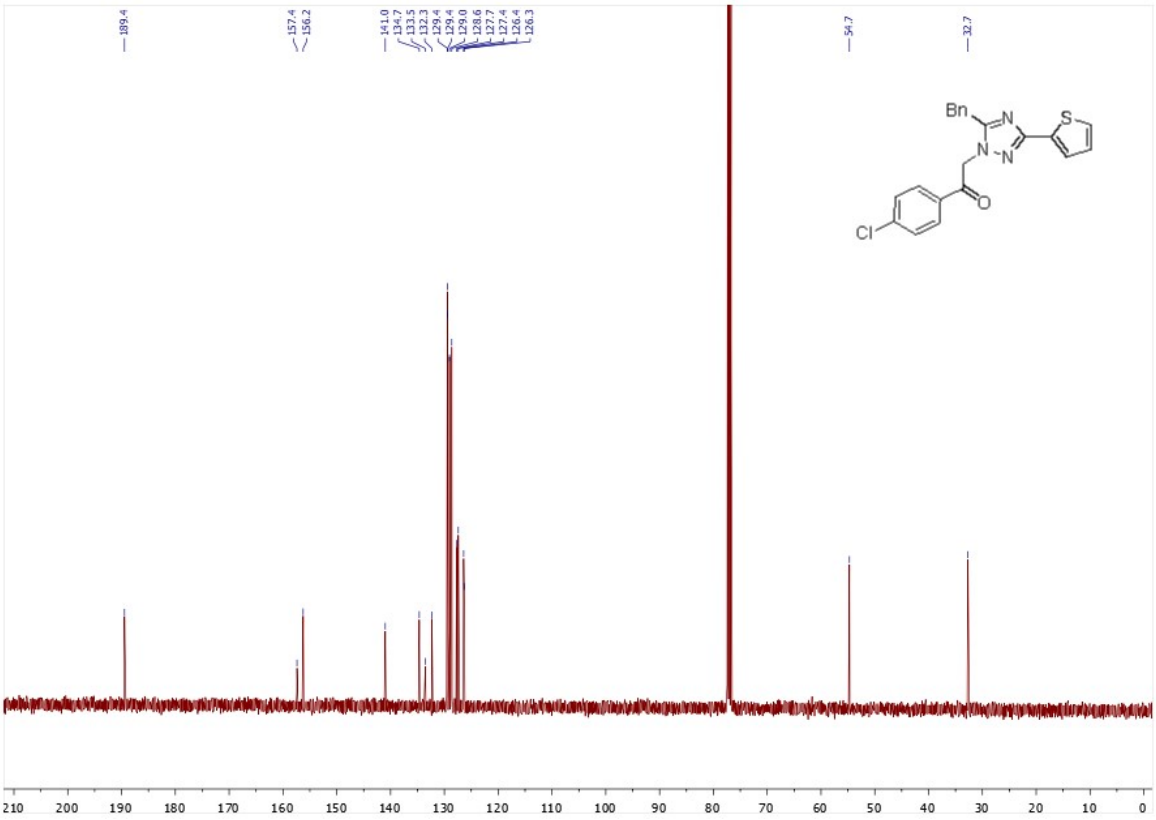
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4y**



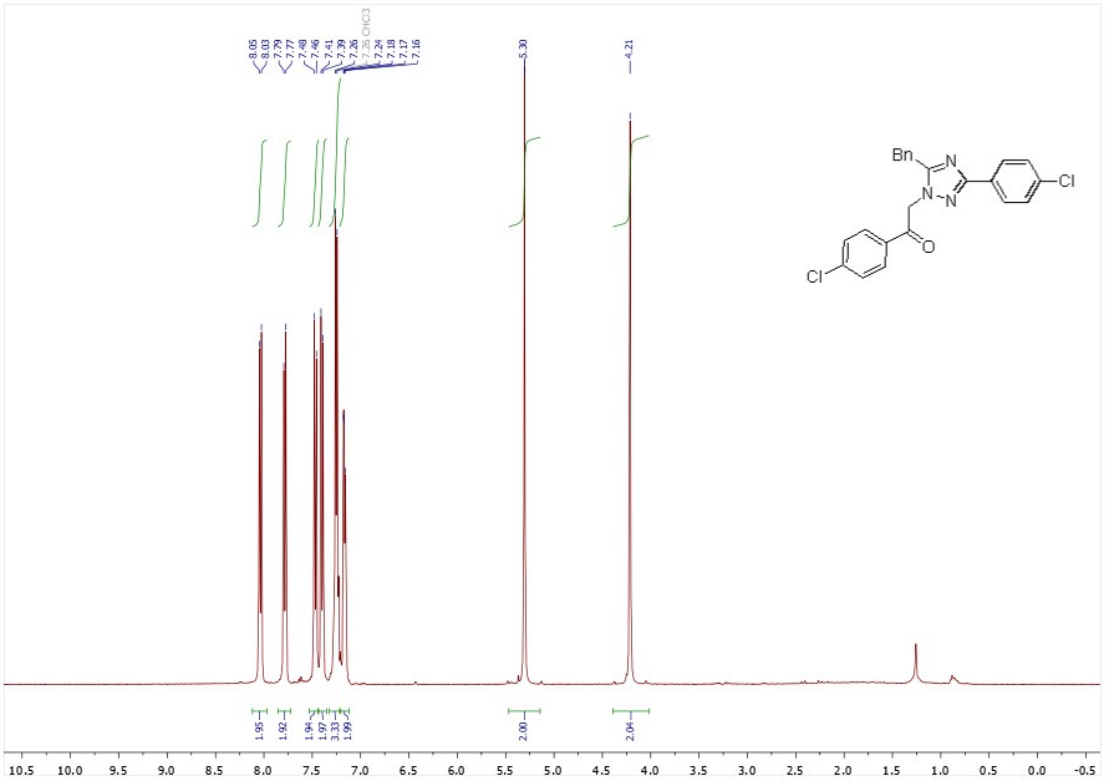


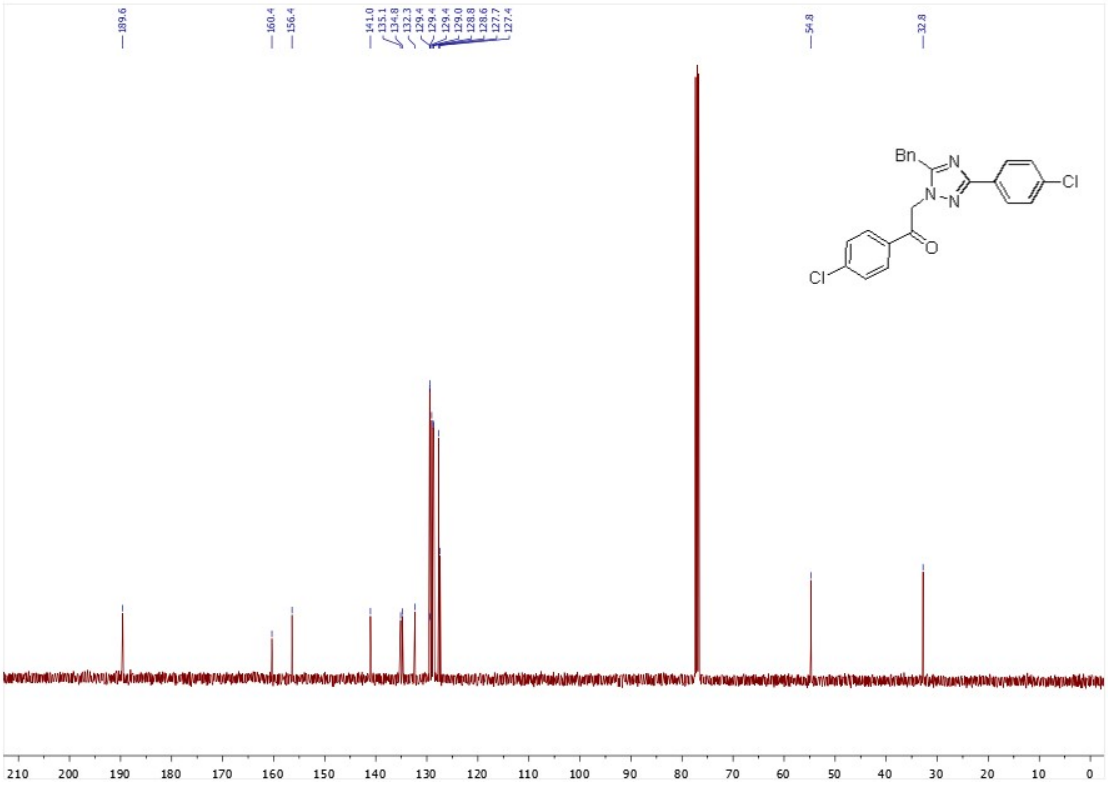
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4z**



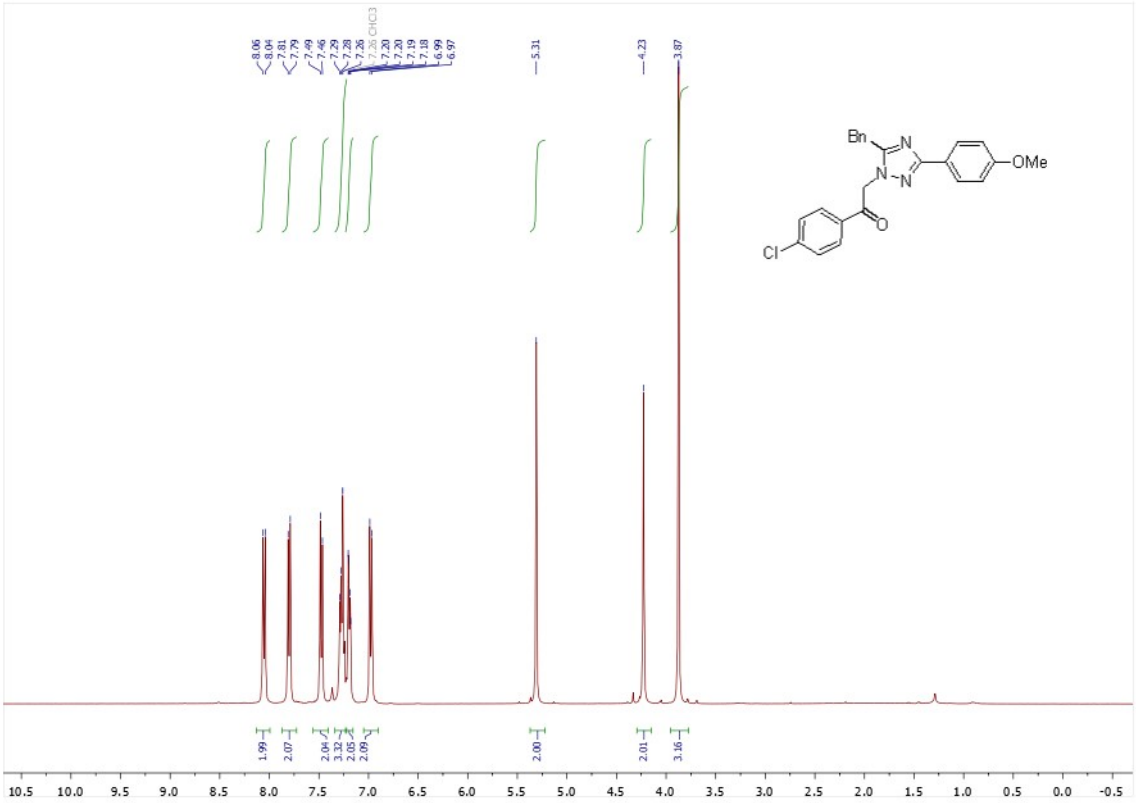


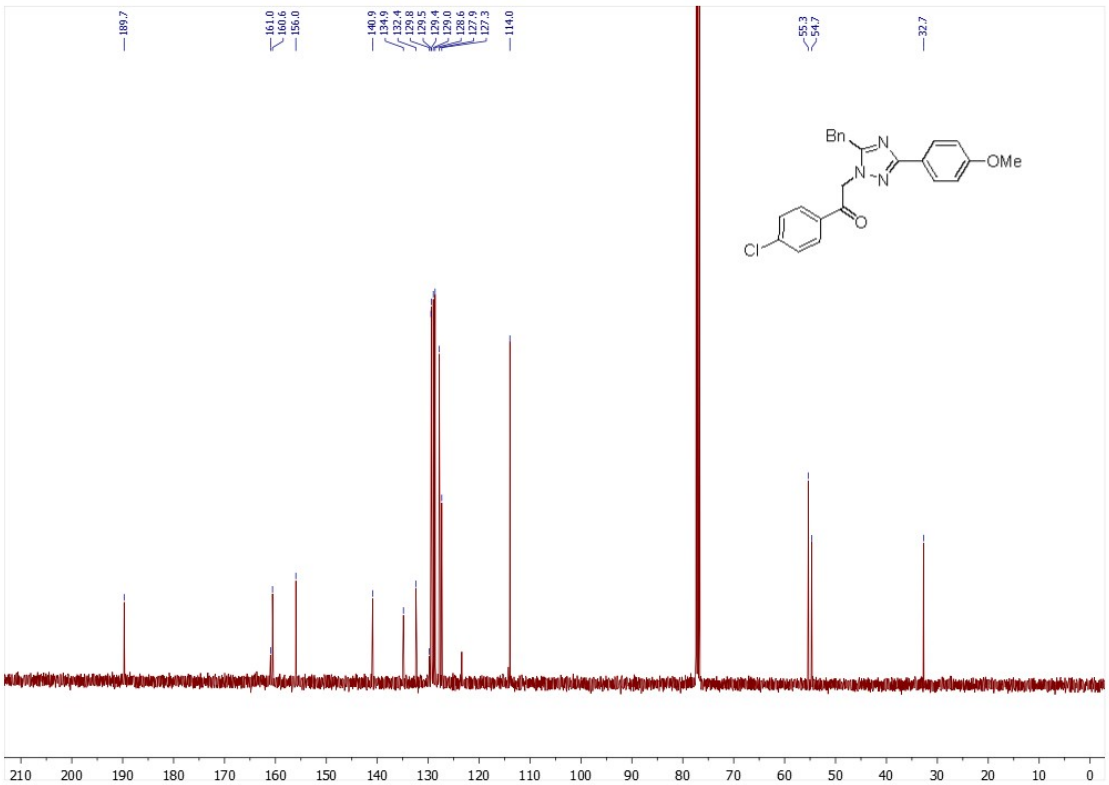
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4aa**



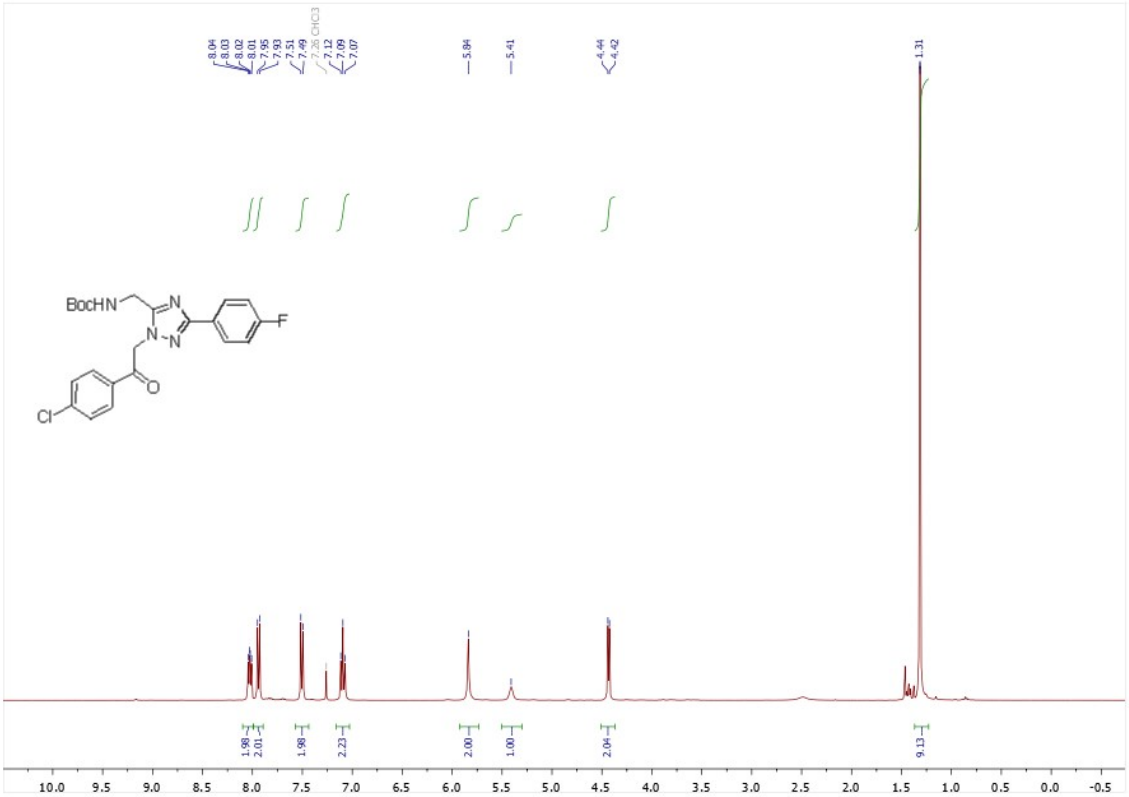


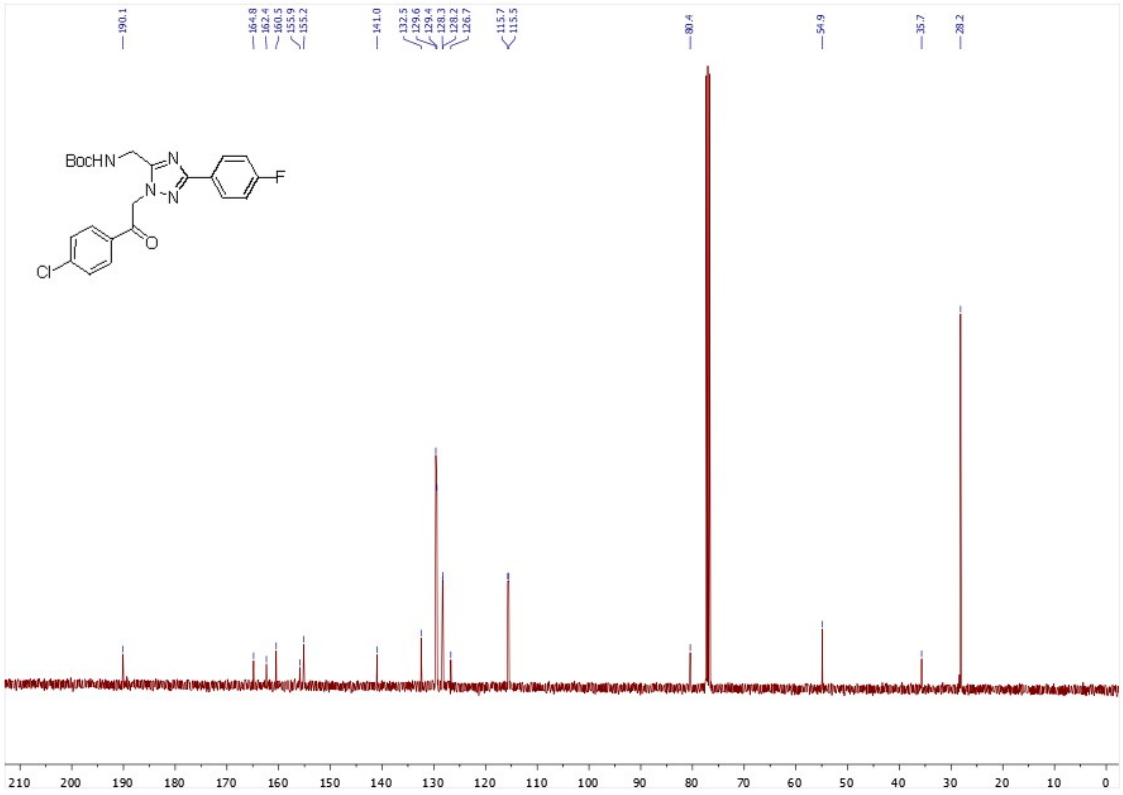
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ab**



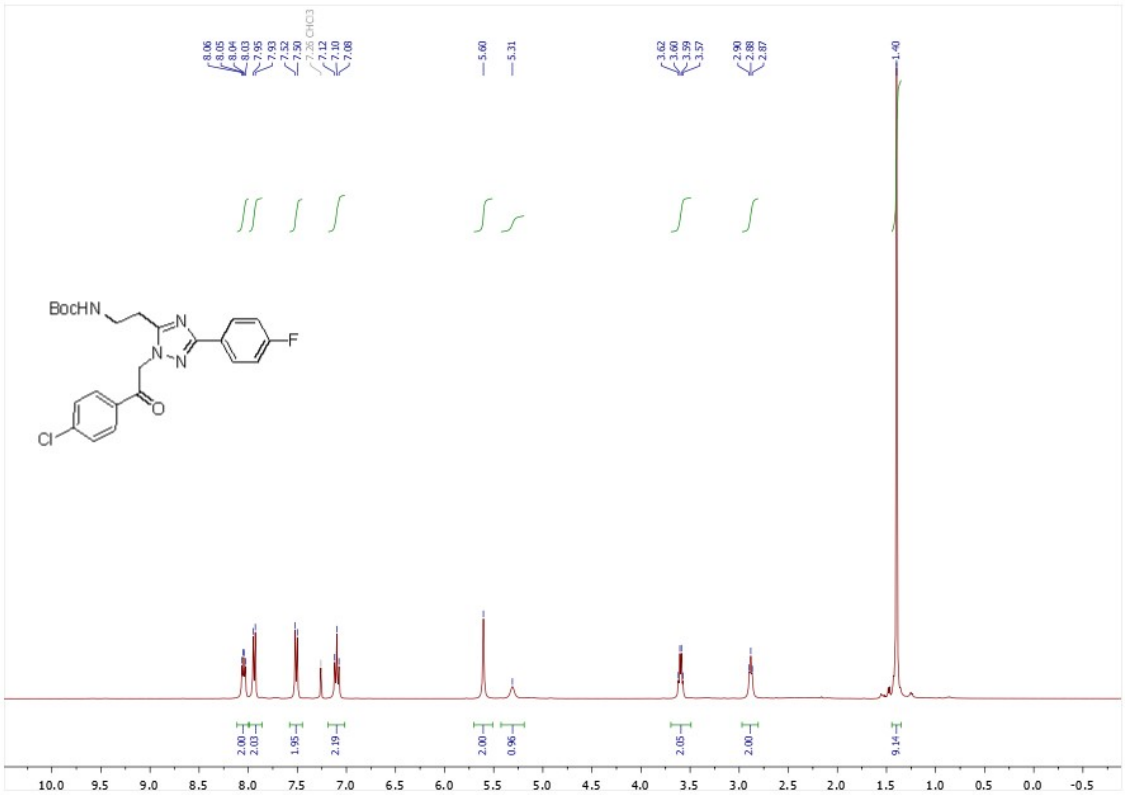


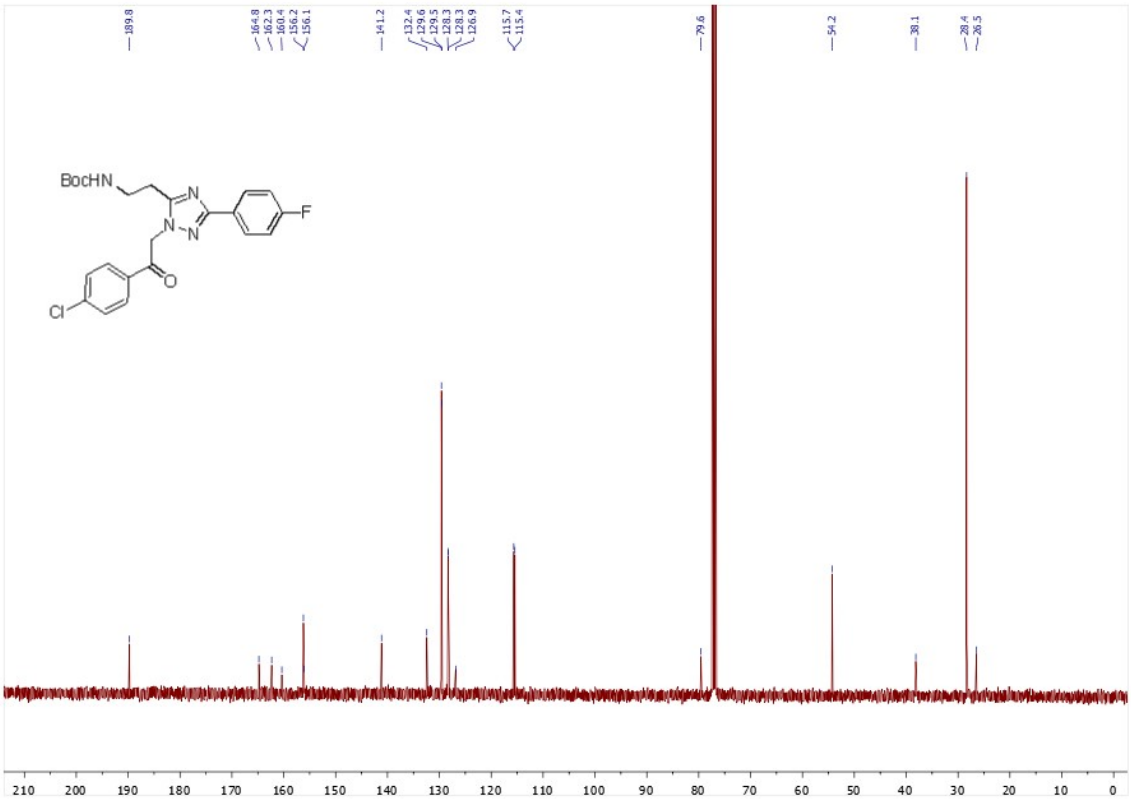
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ac**



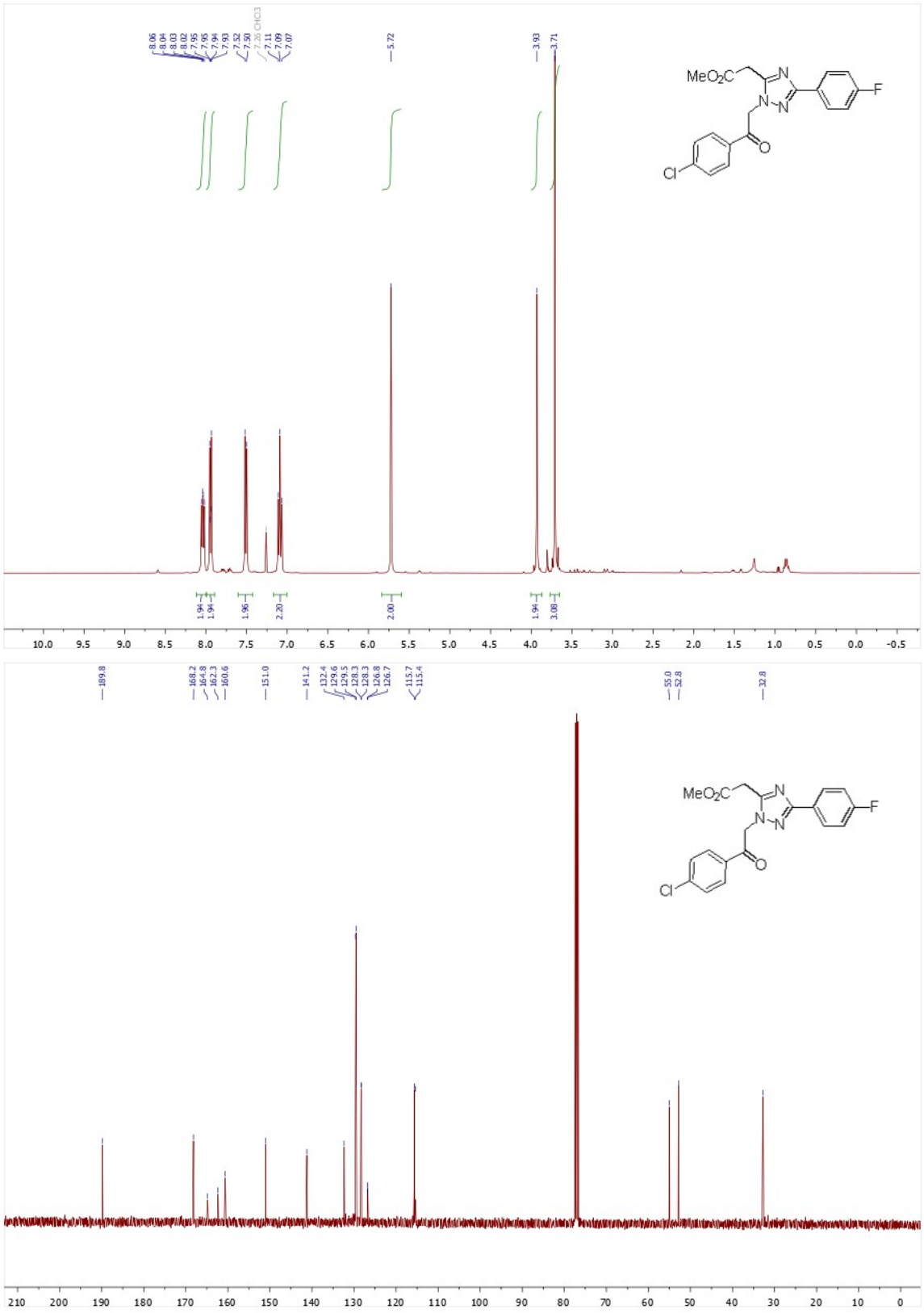


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ad**

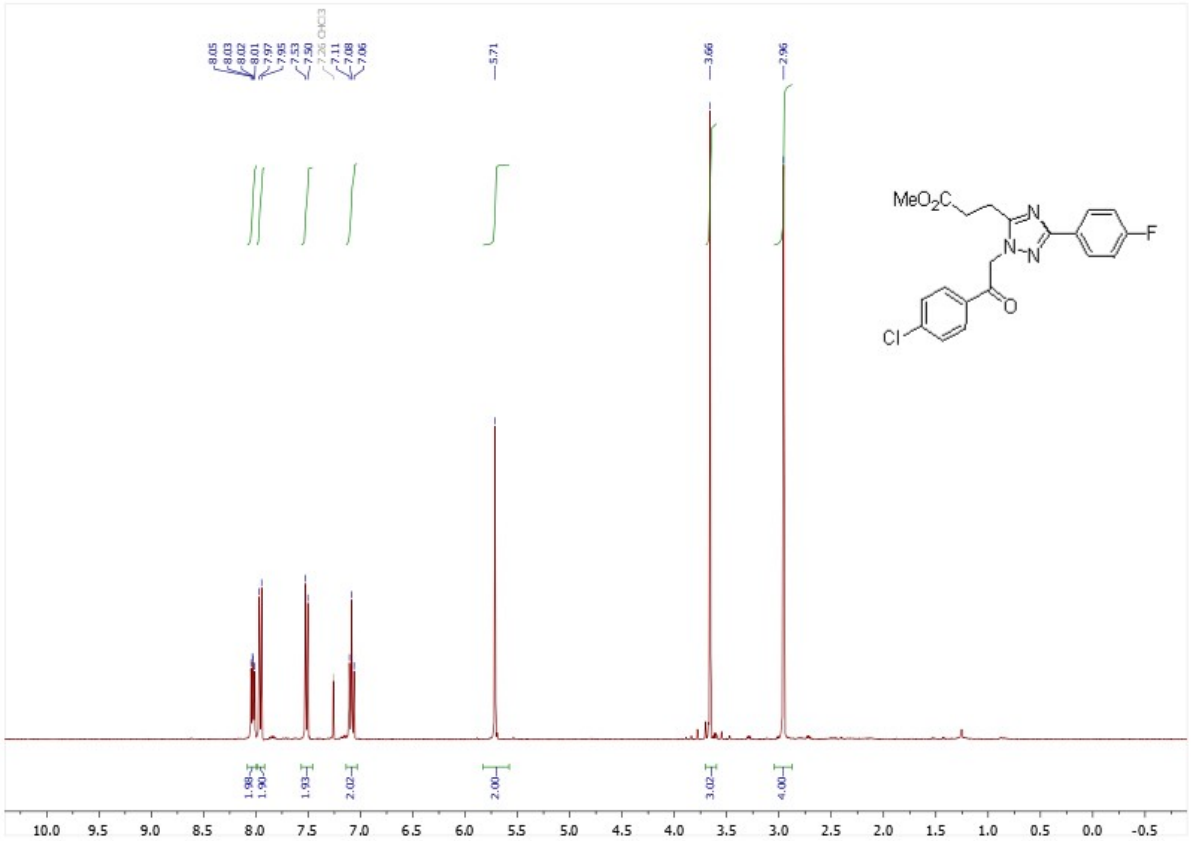


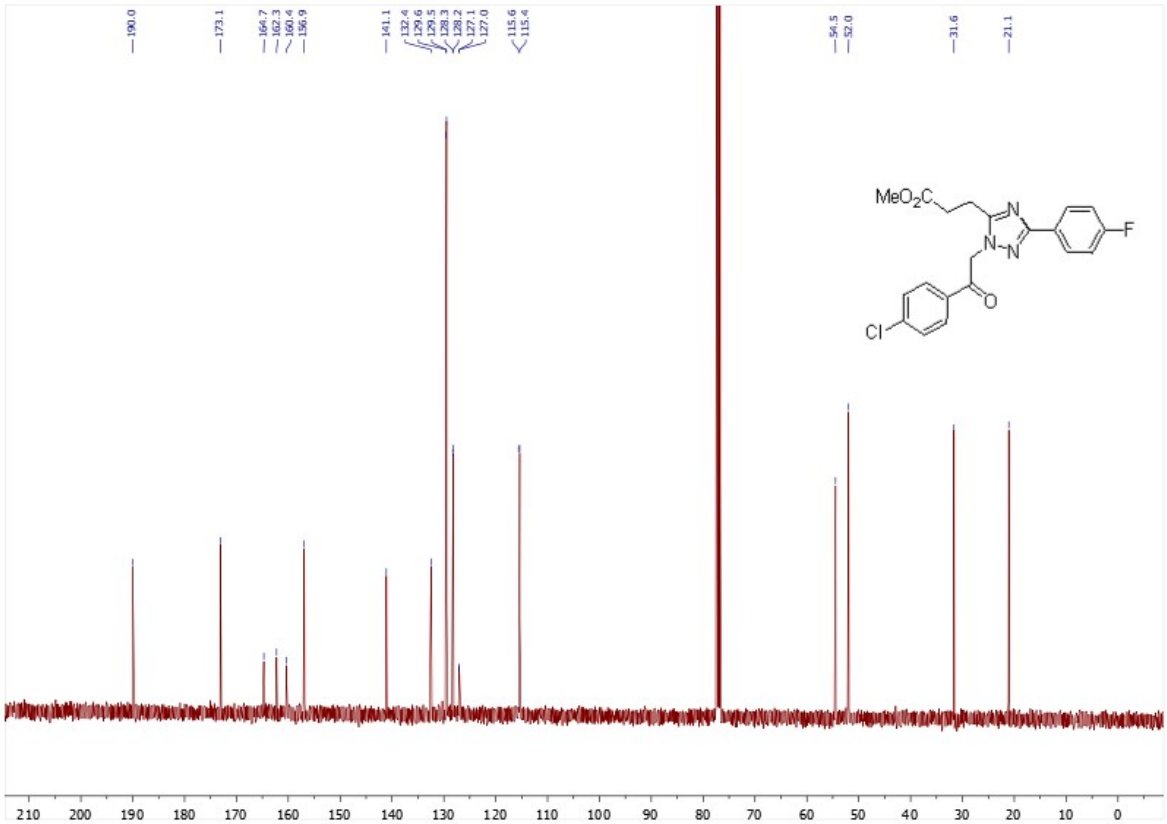


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ae**

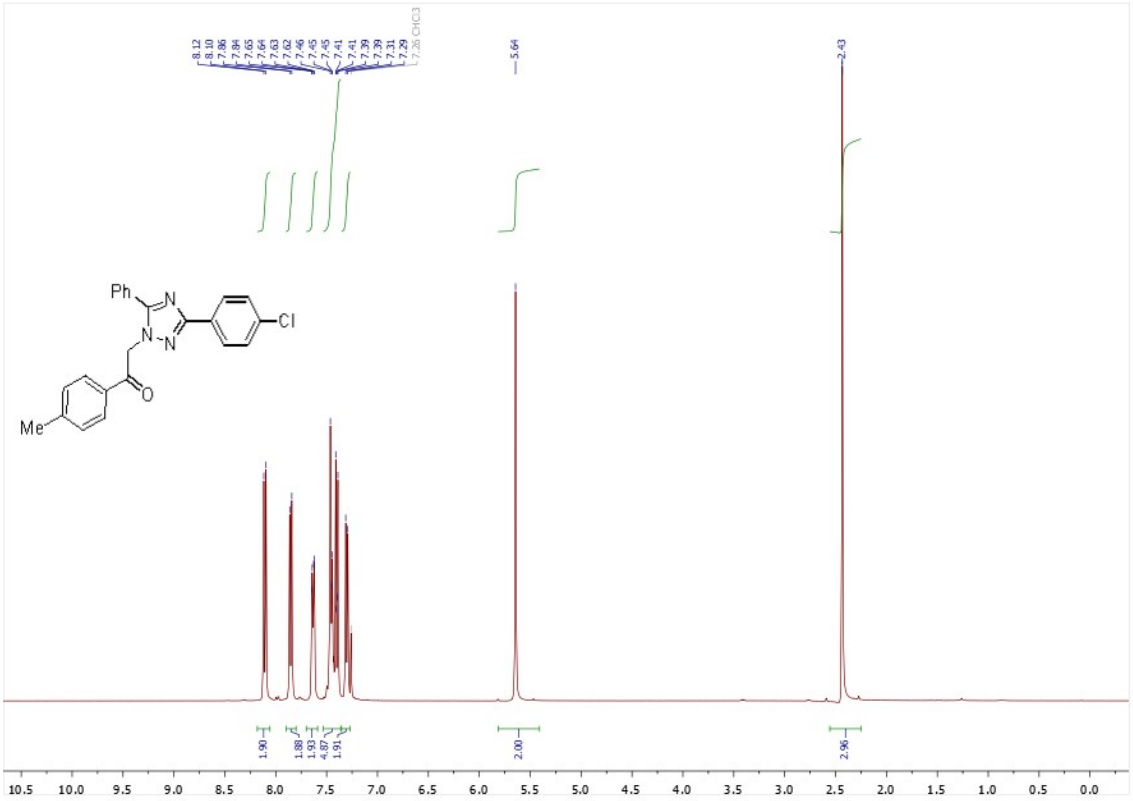


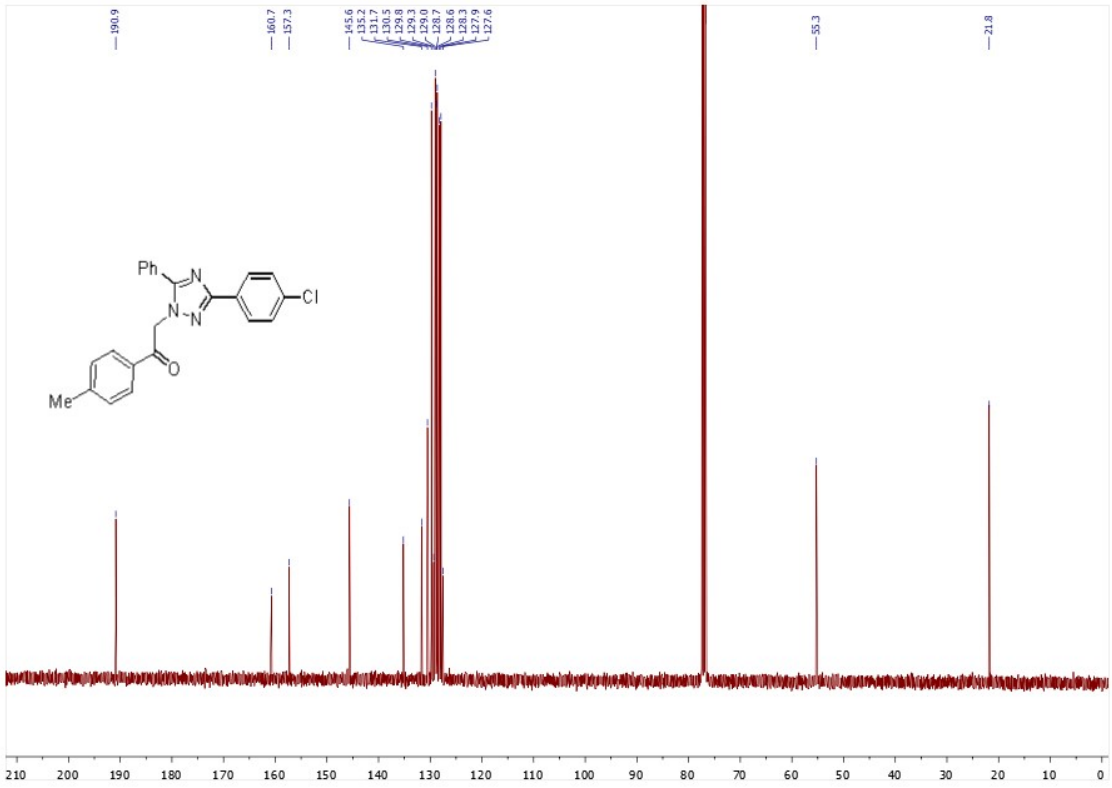
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4af**



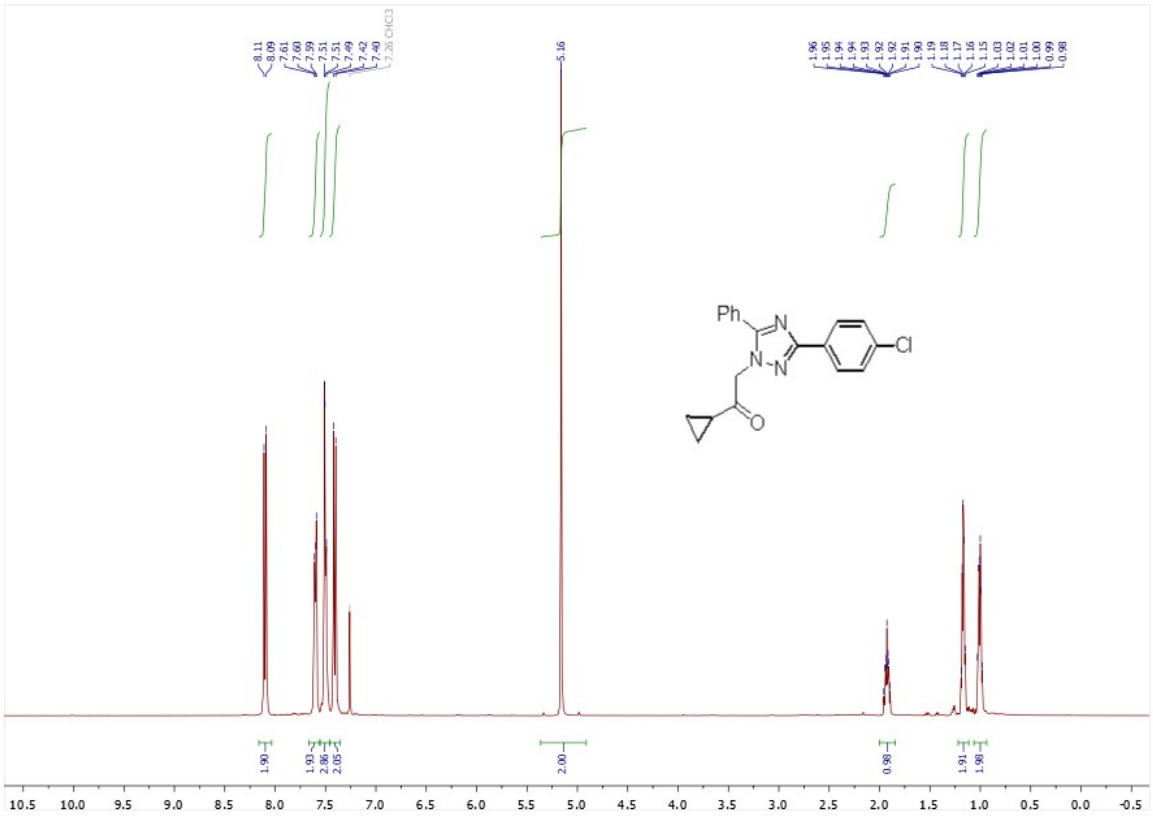


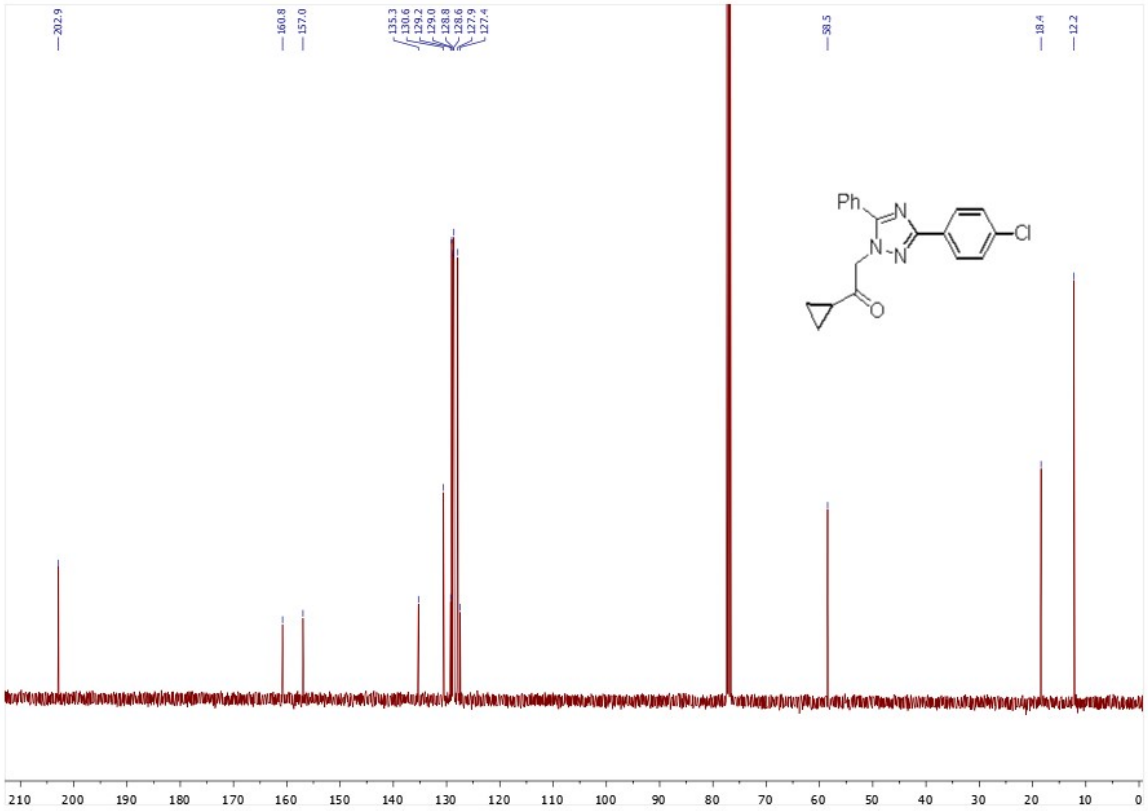
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ag**



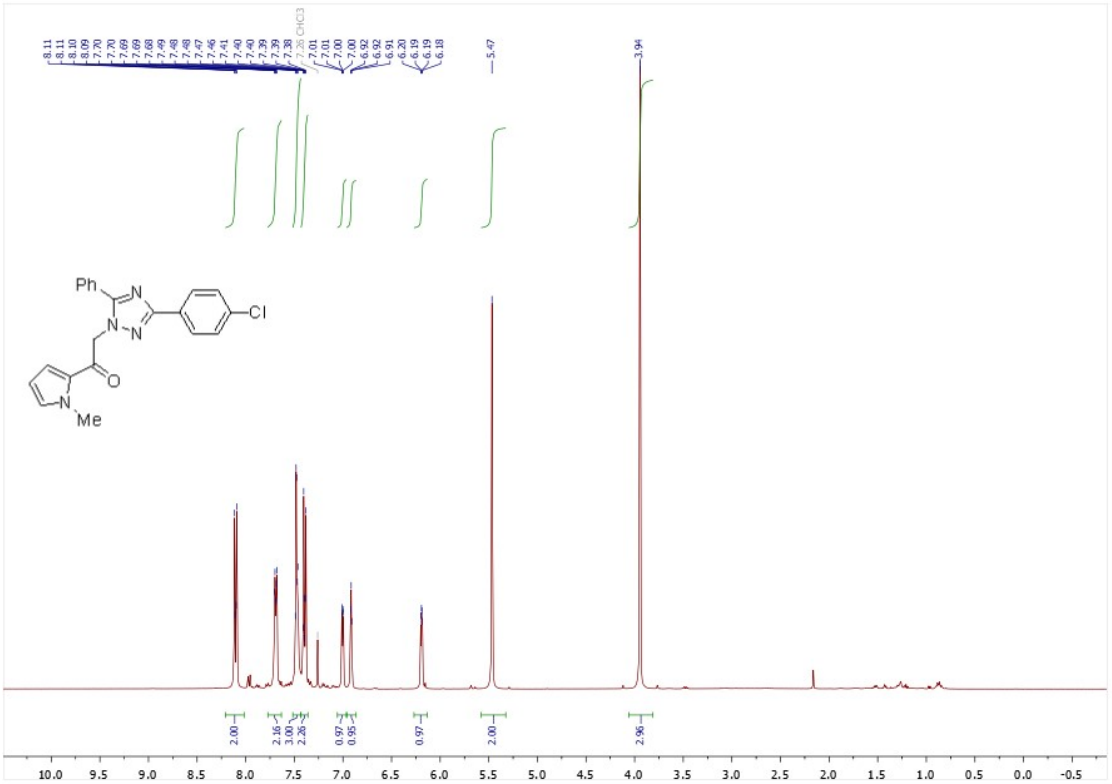


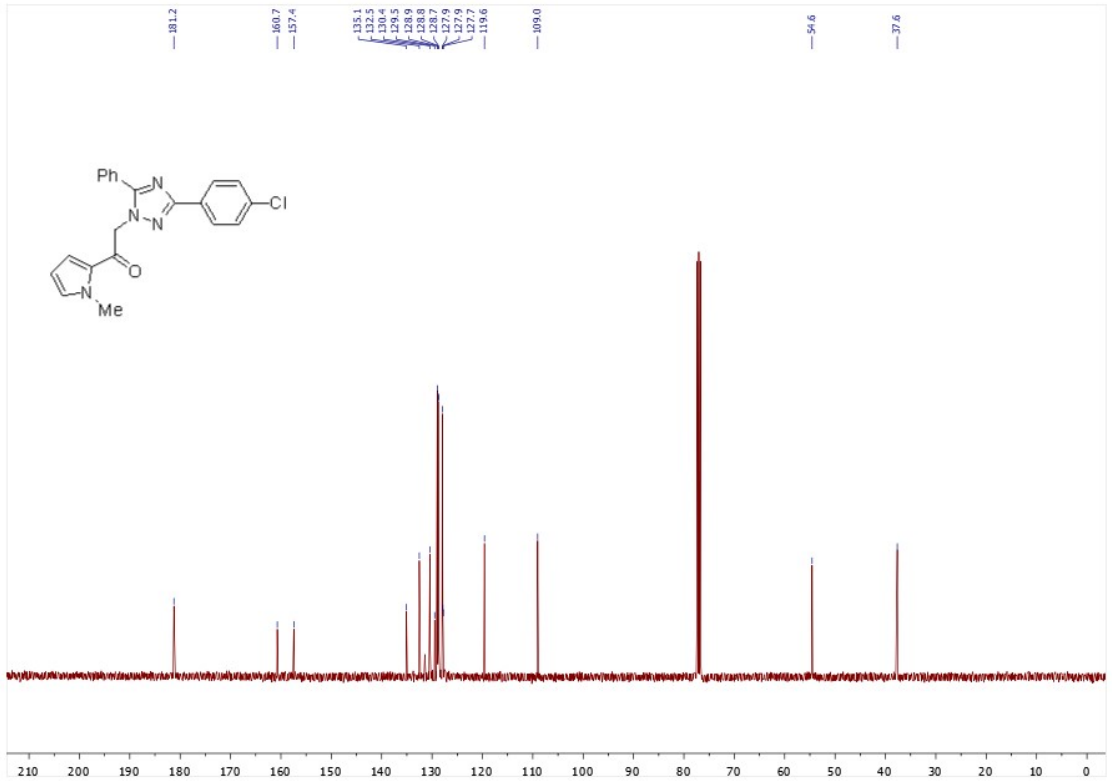
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ah**



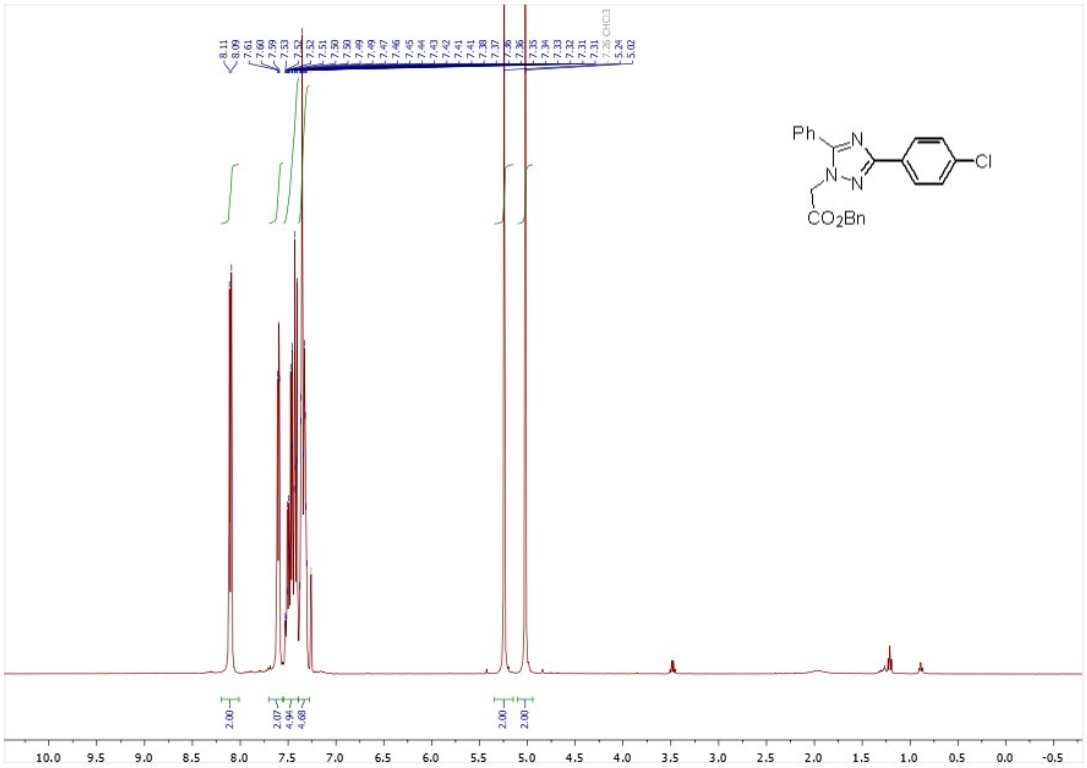


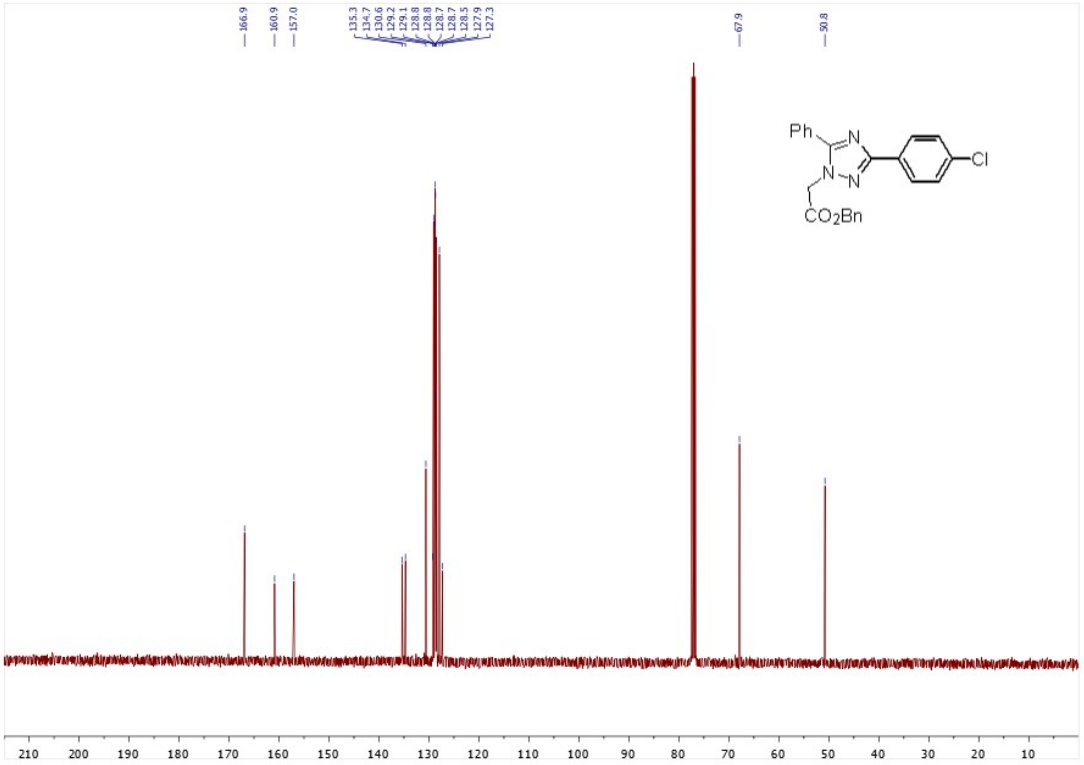
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ai**



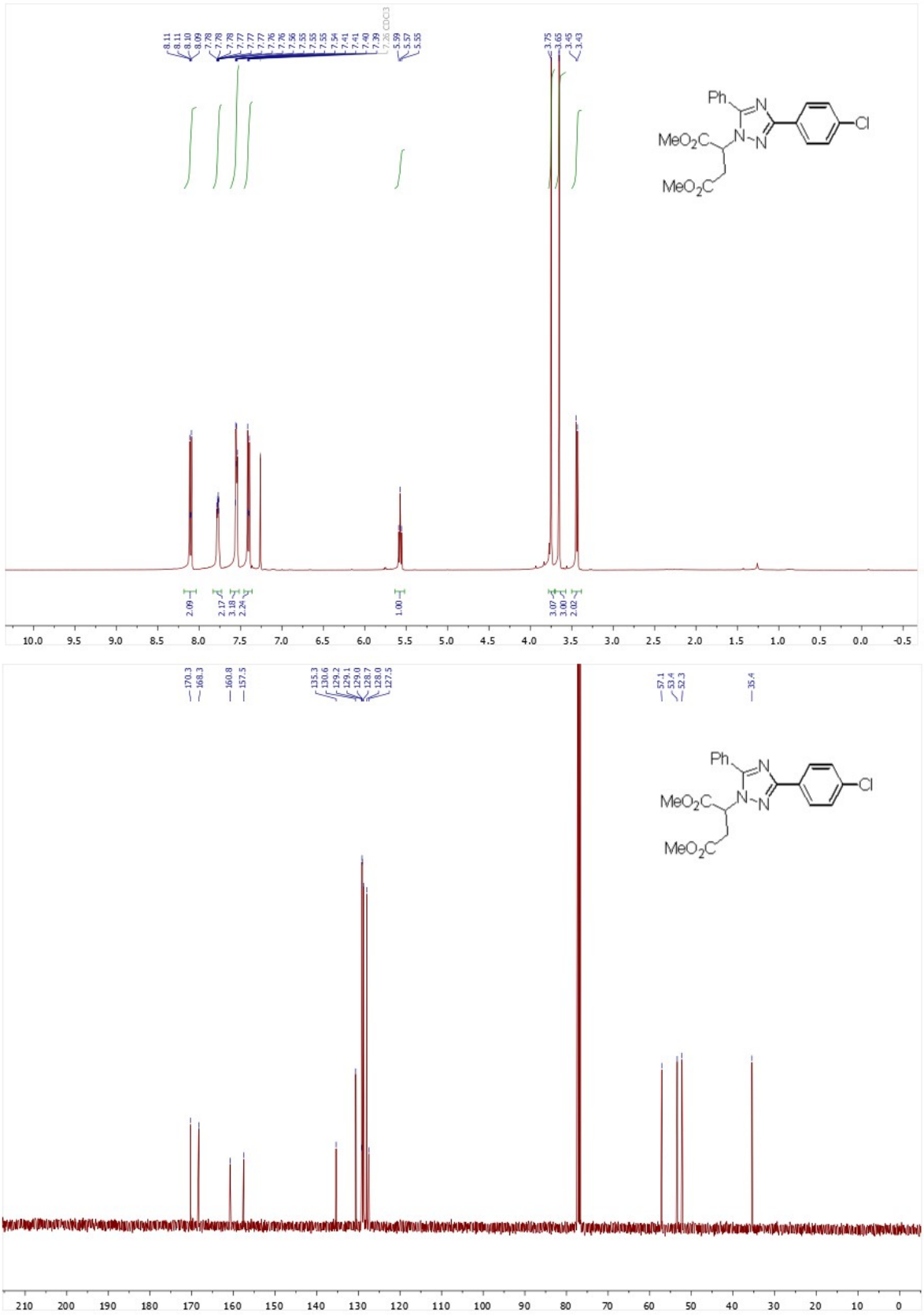


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4aj**

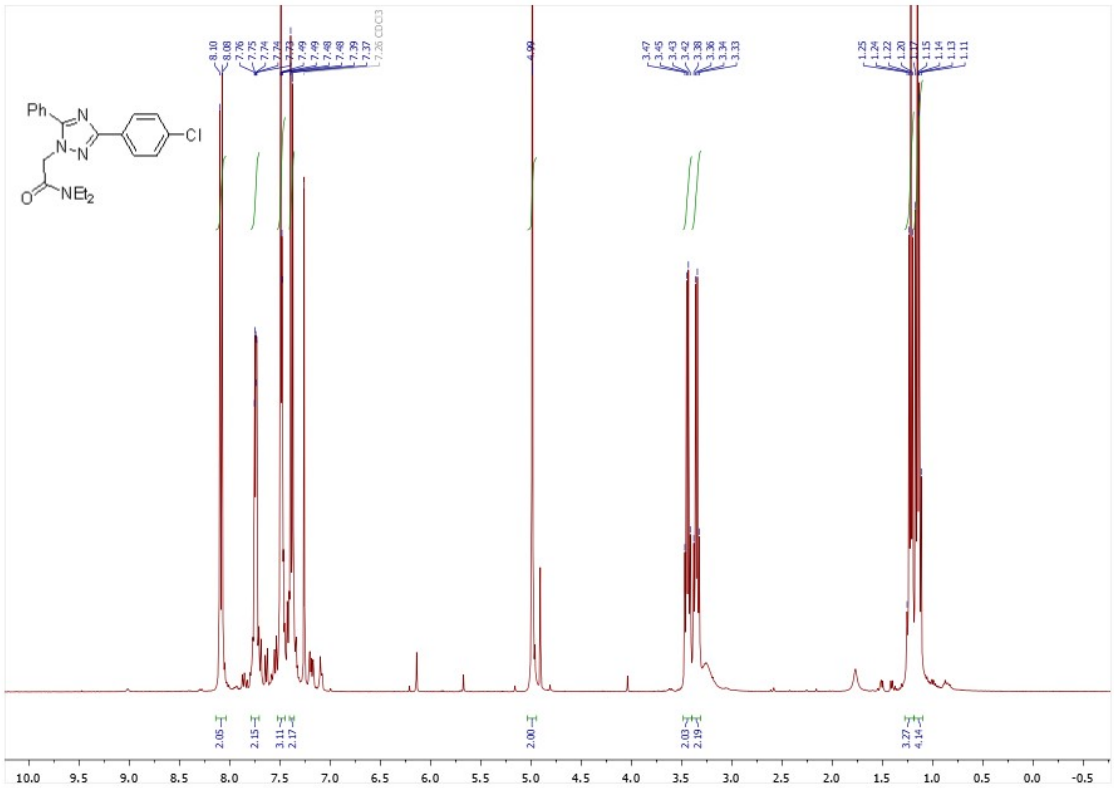


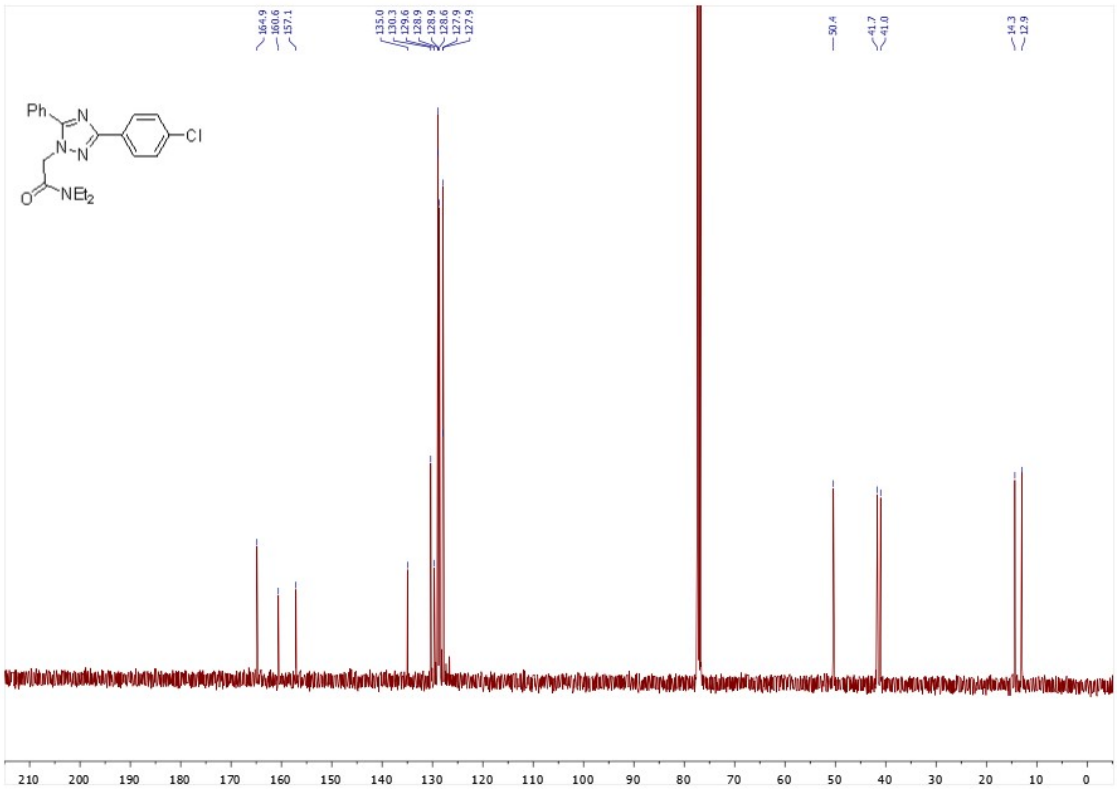


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ak**

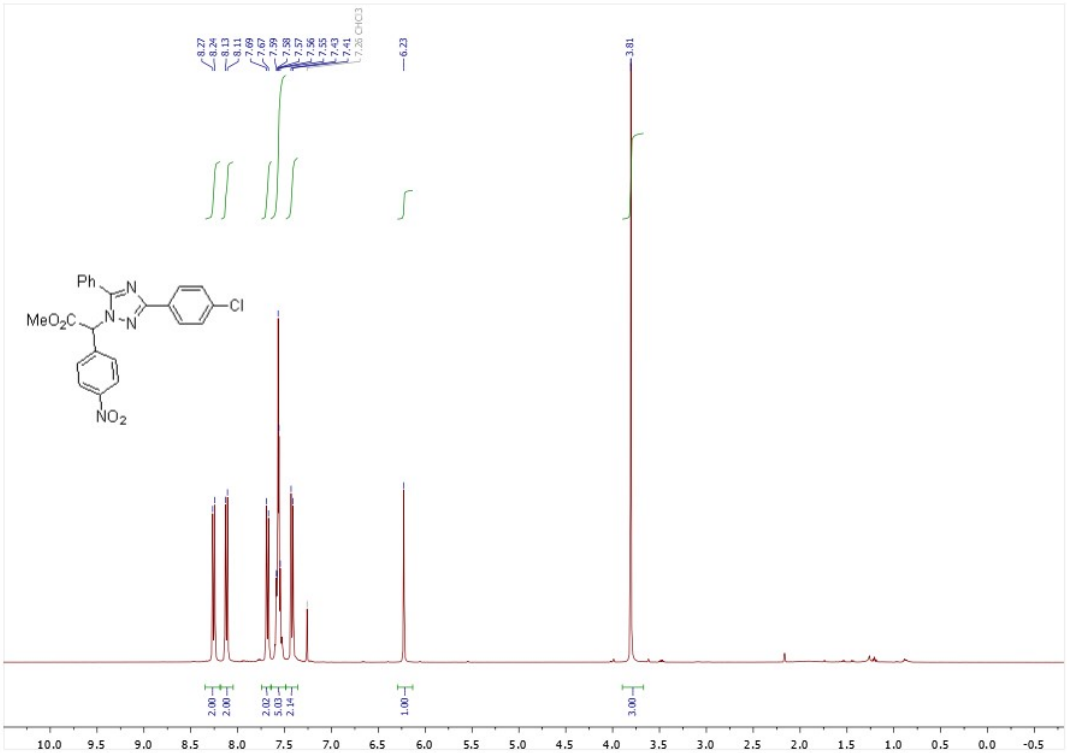


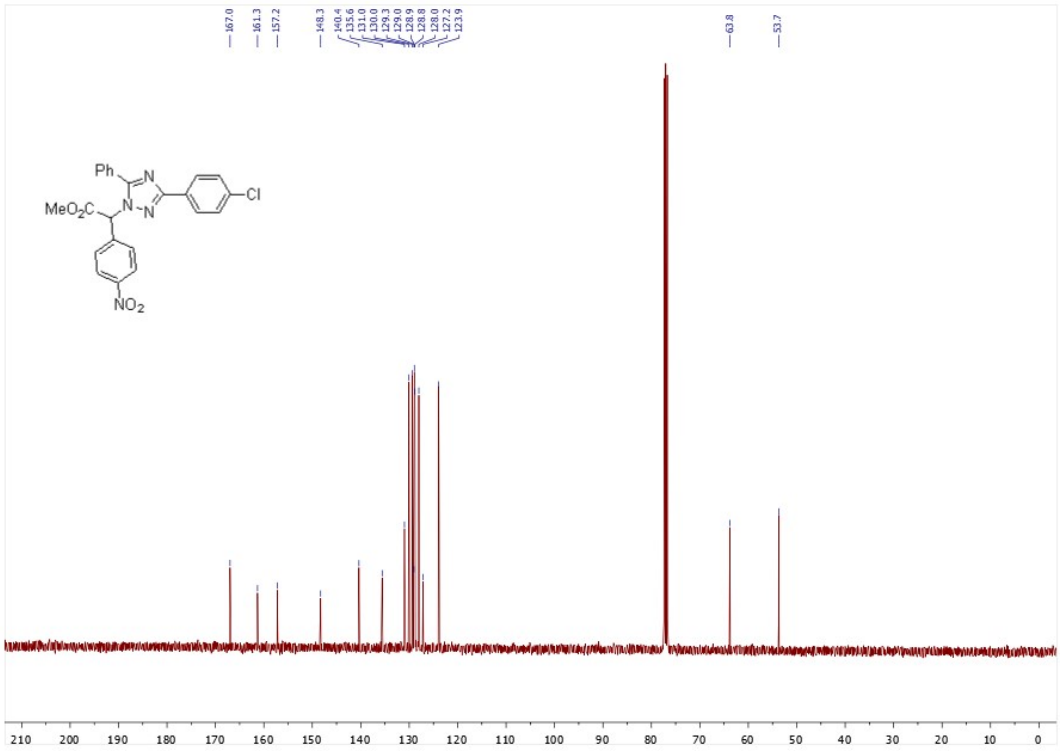
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4al**



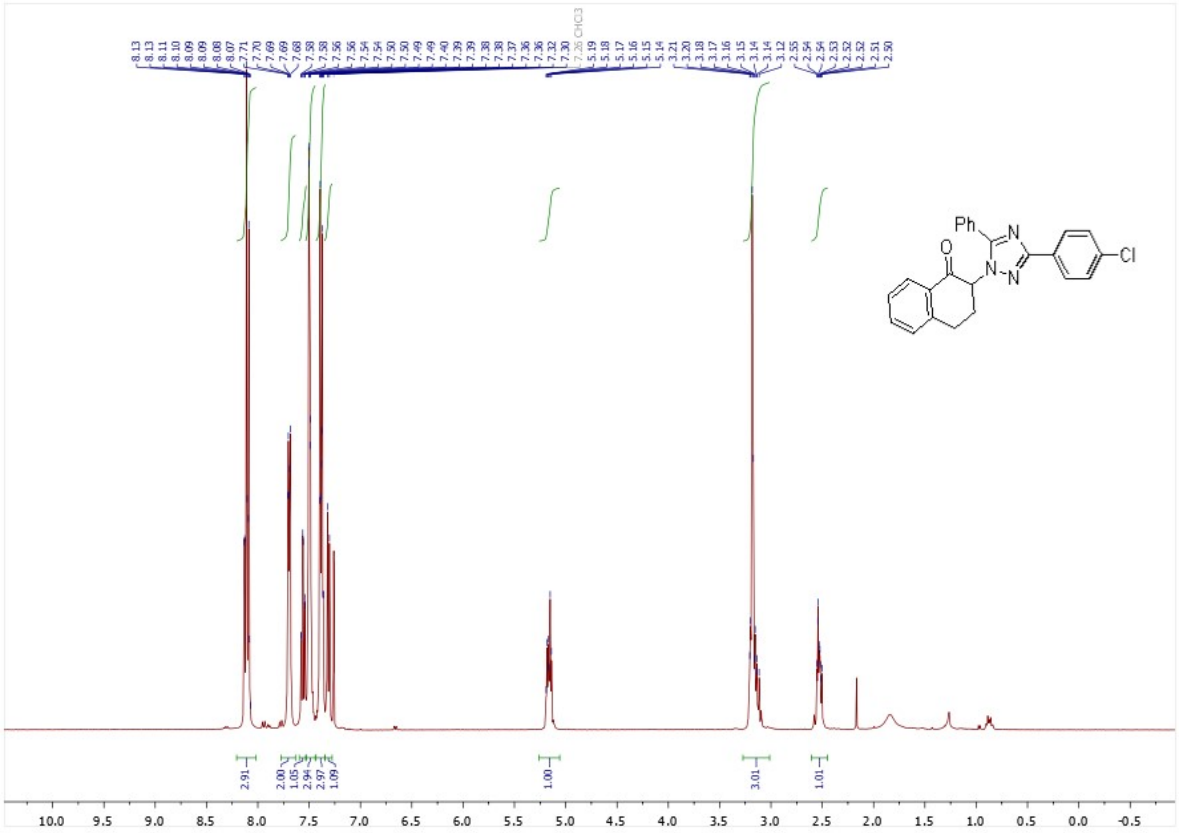


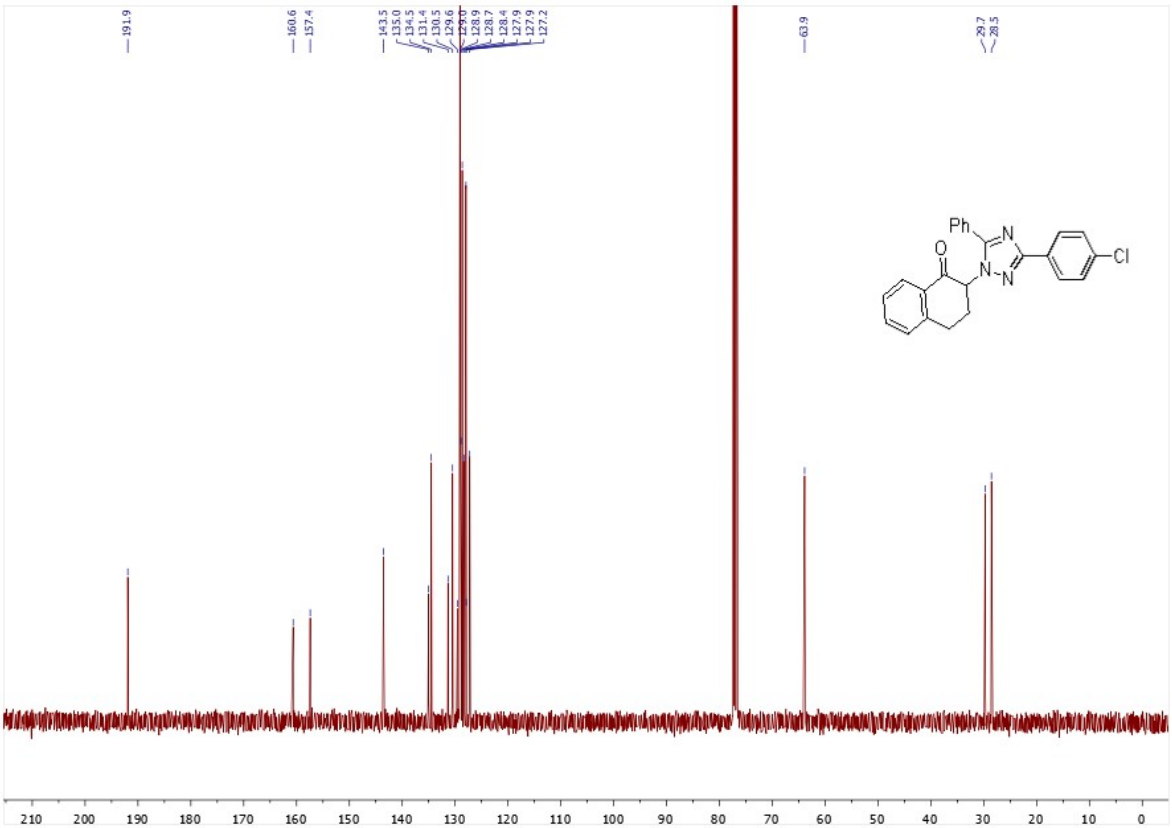
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4am**



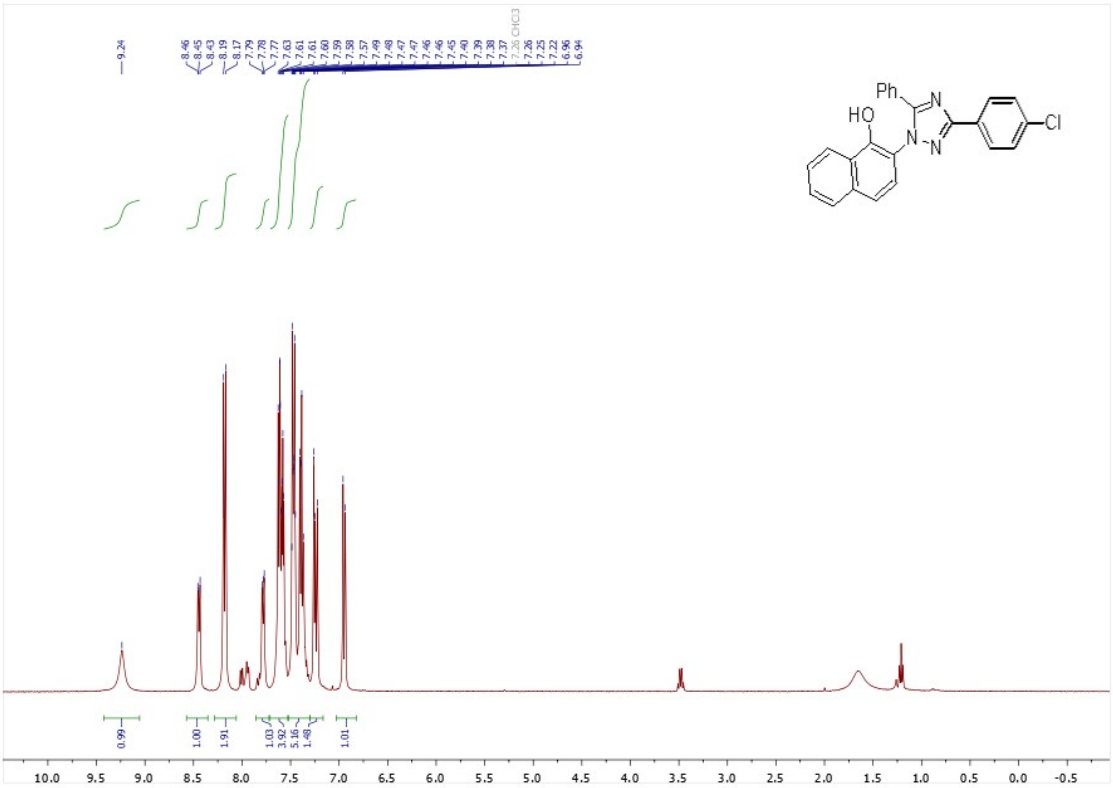


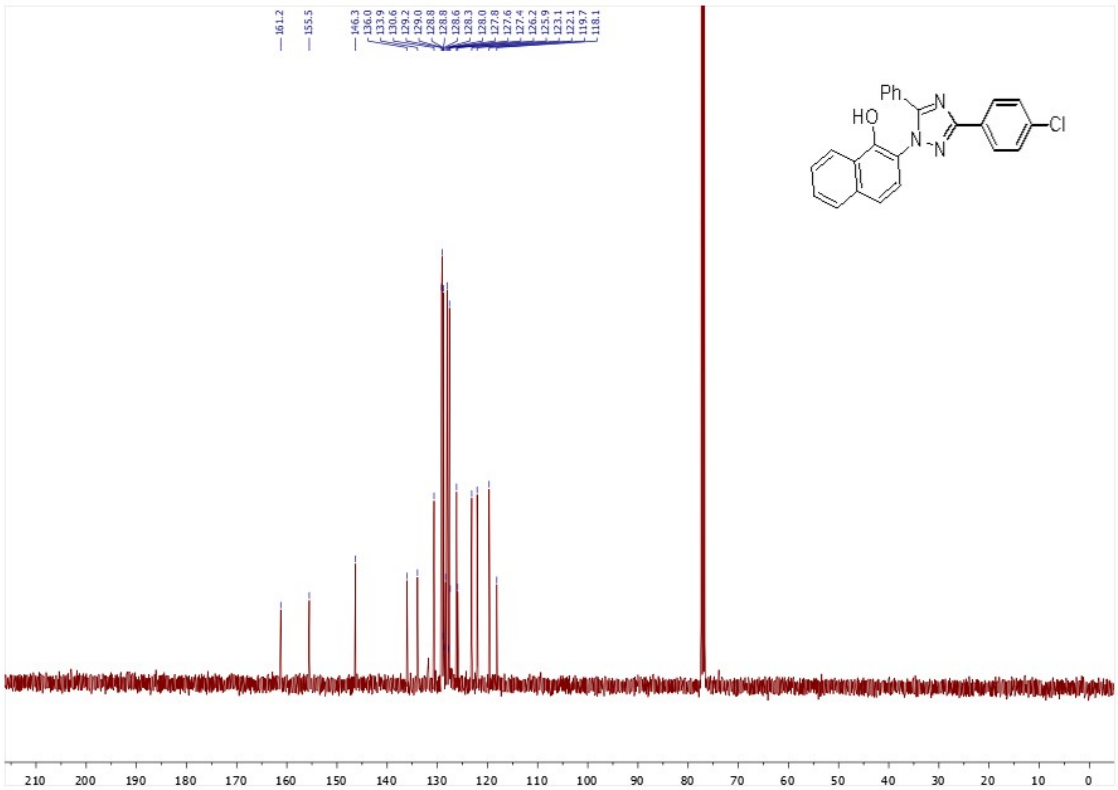
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4an**



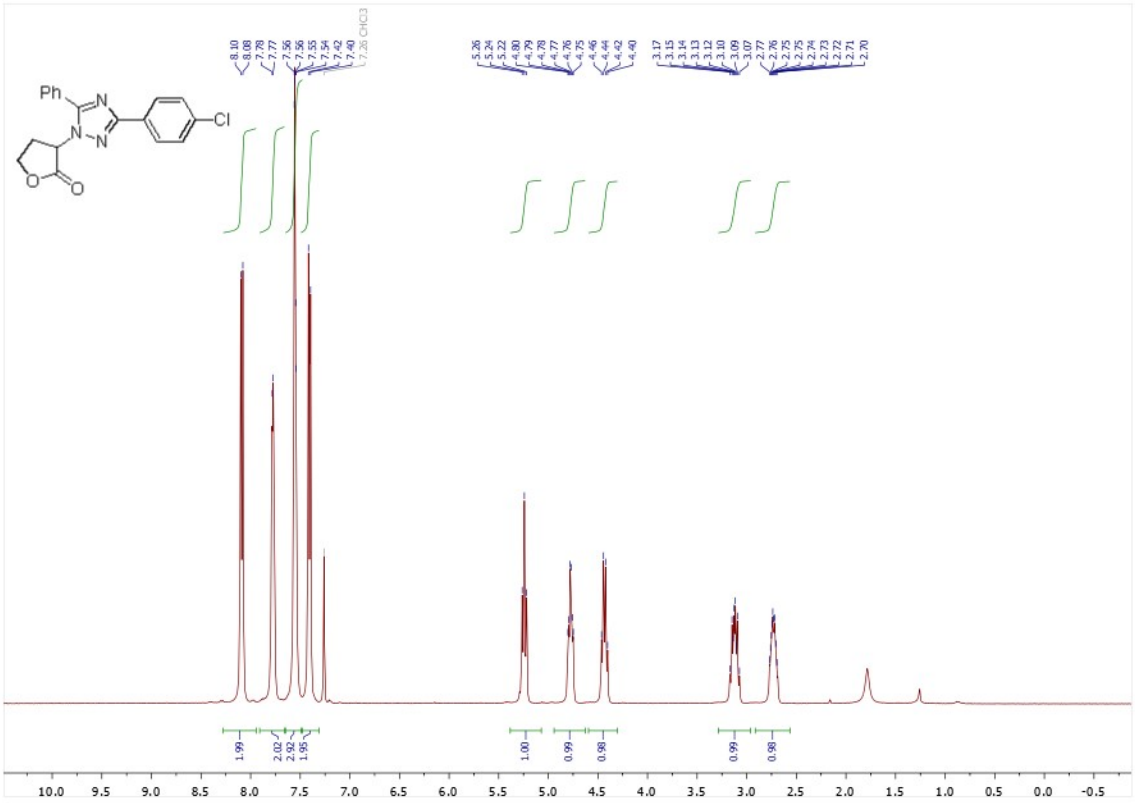


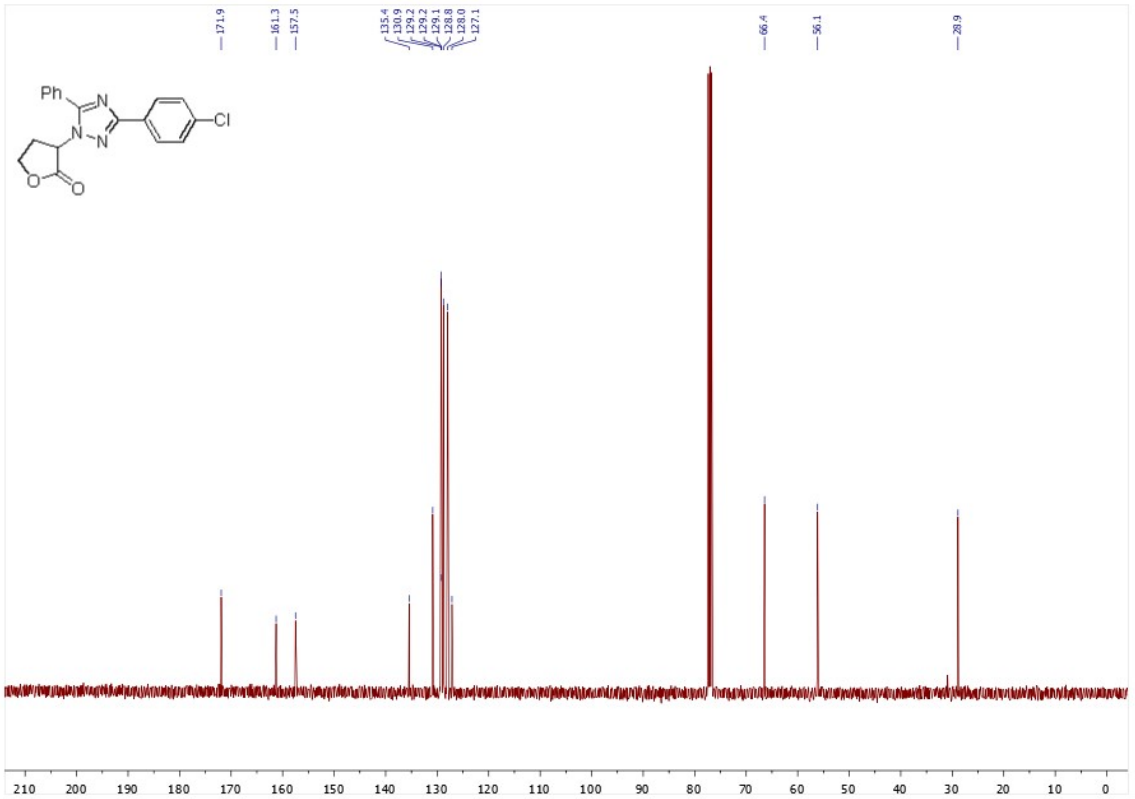
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ao**



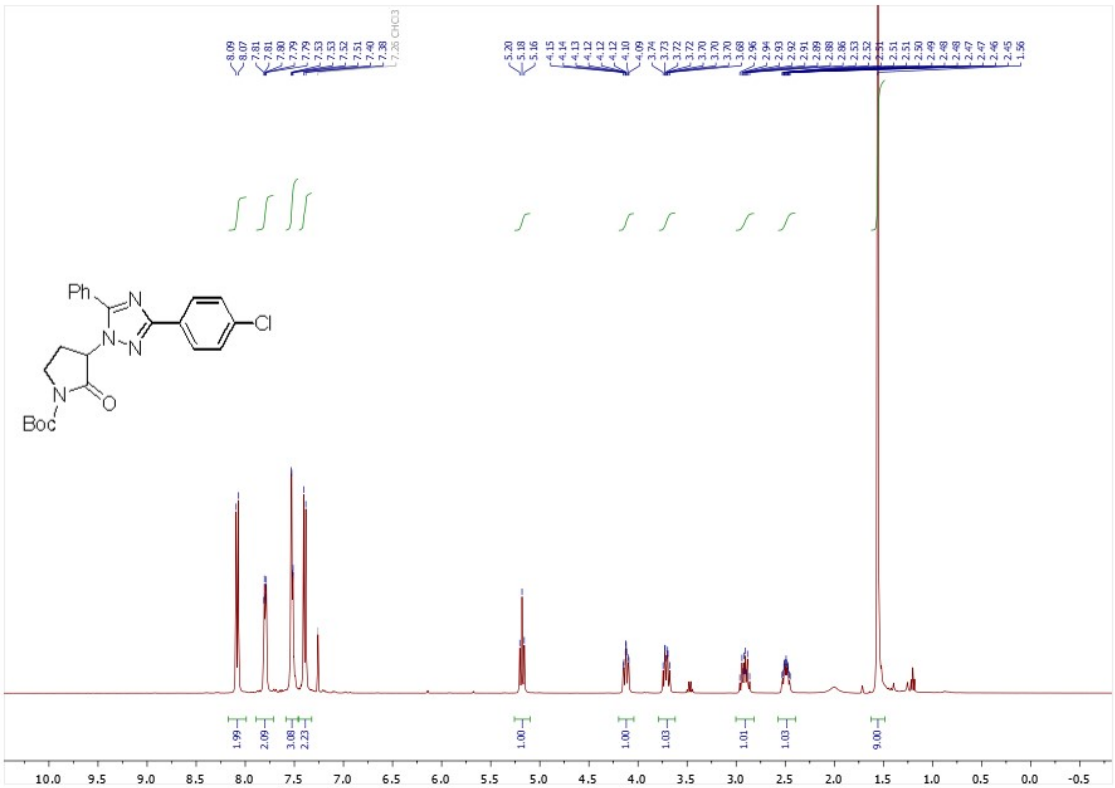


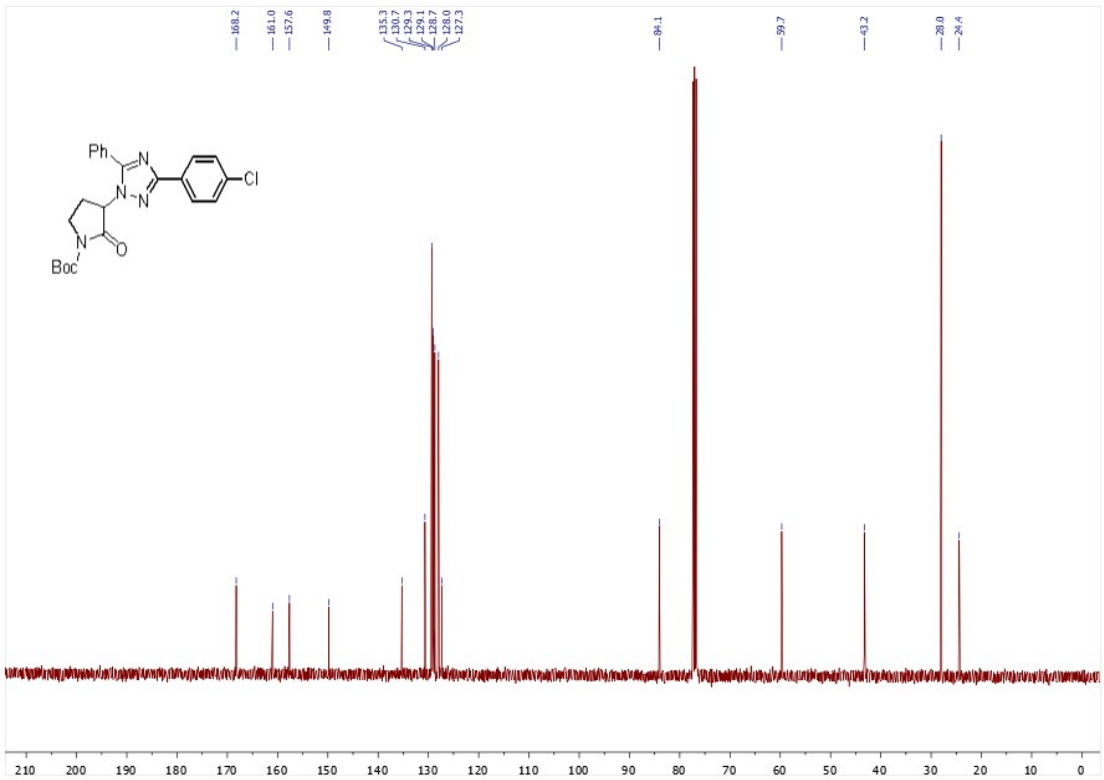
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4aq**



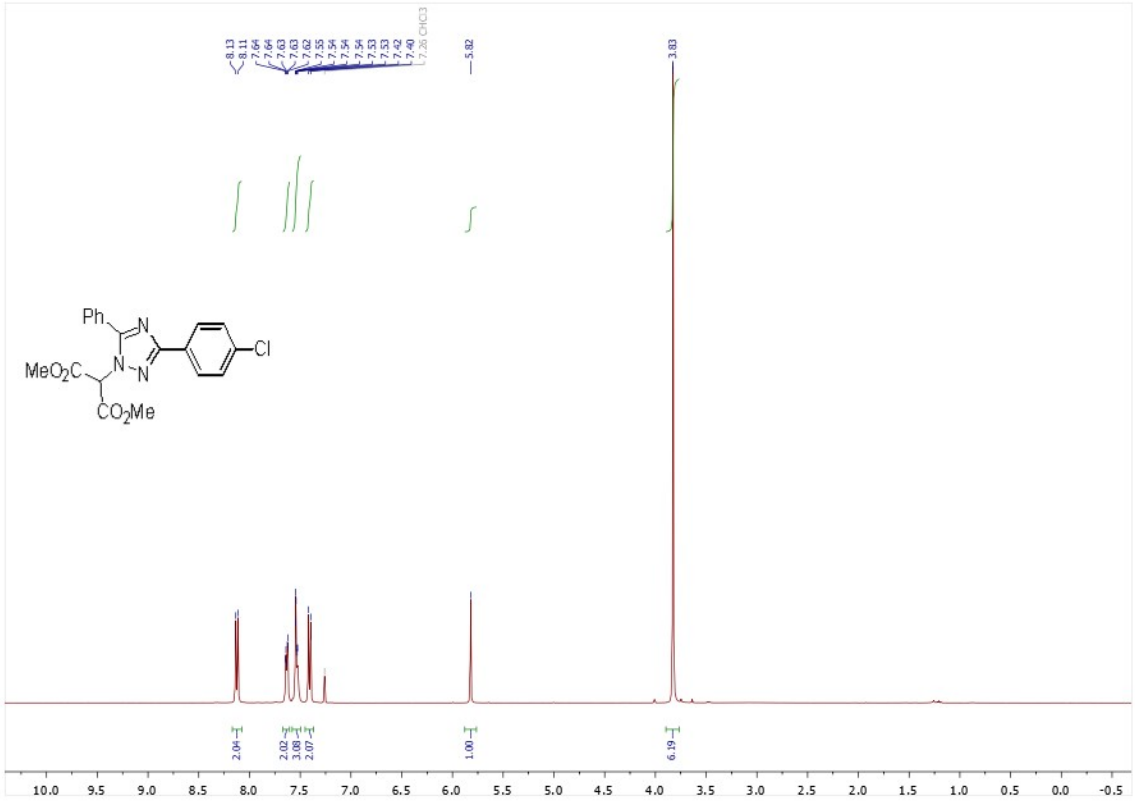


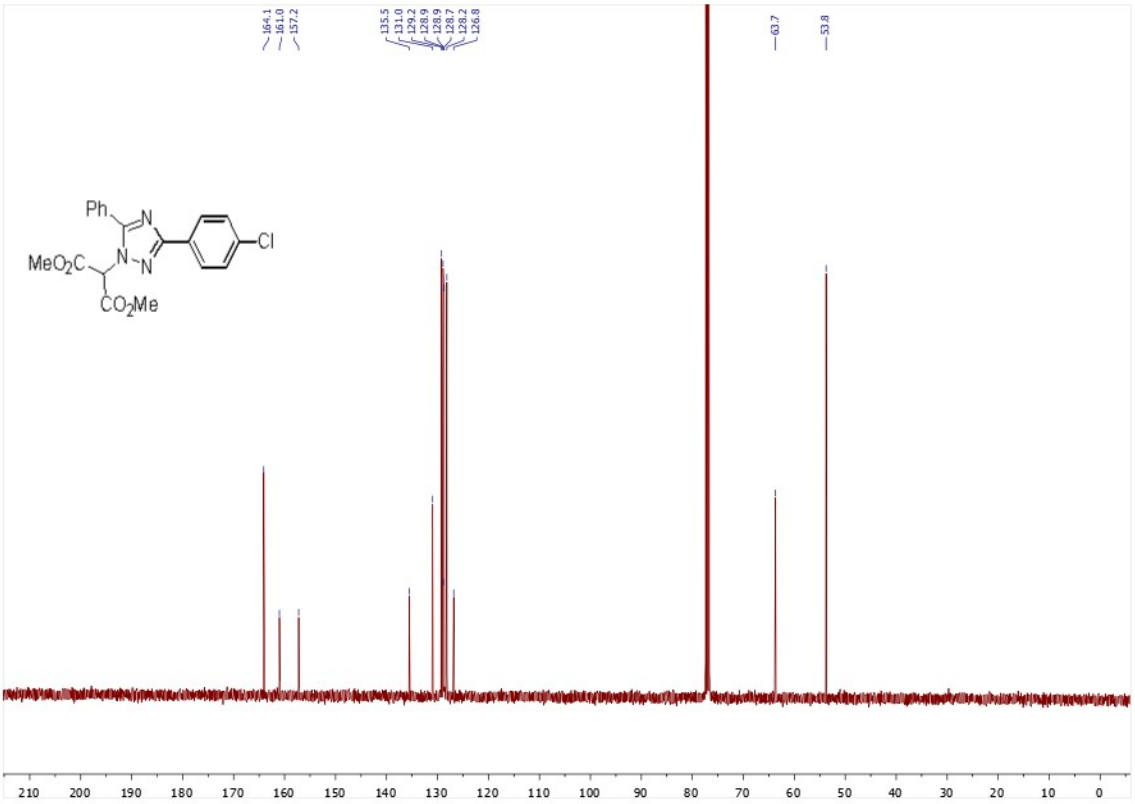
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ar**



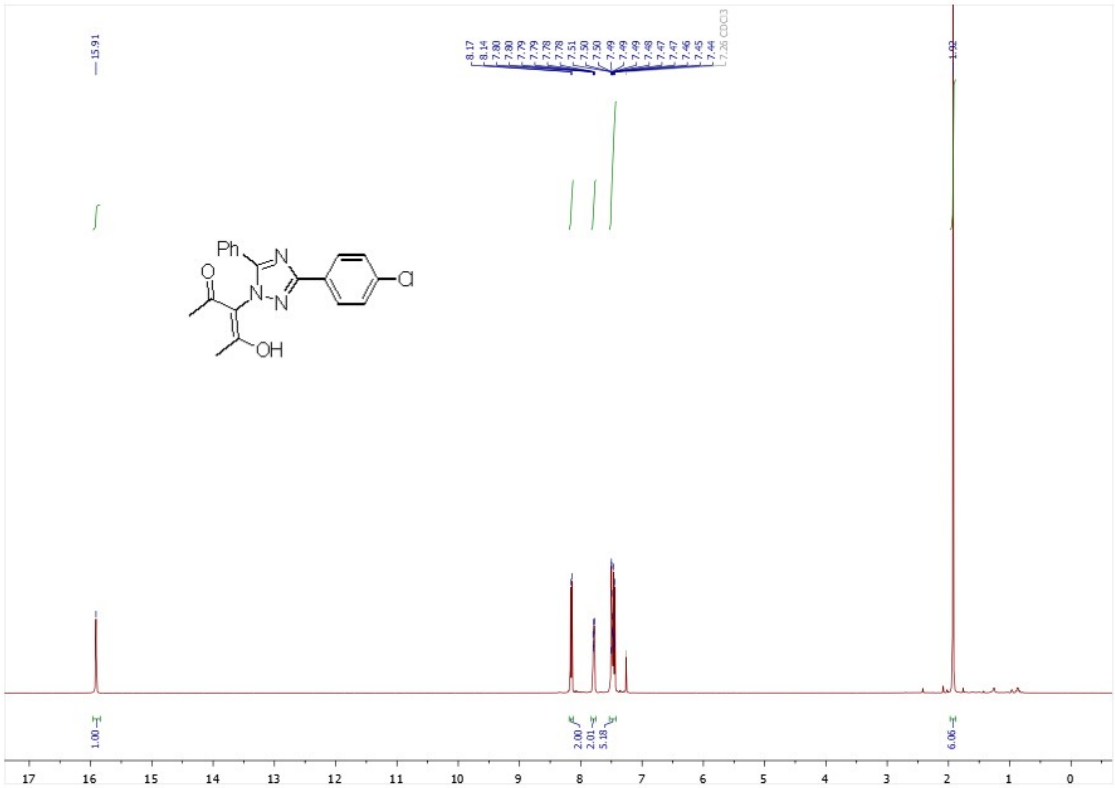


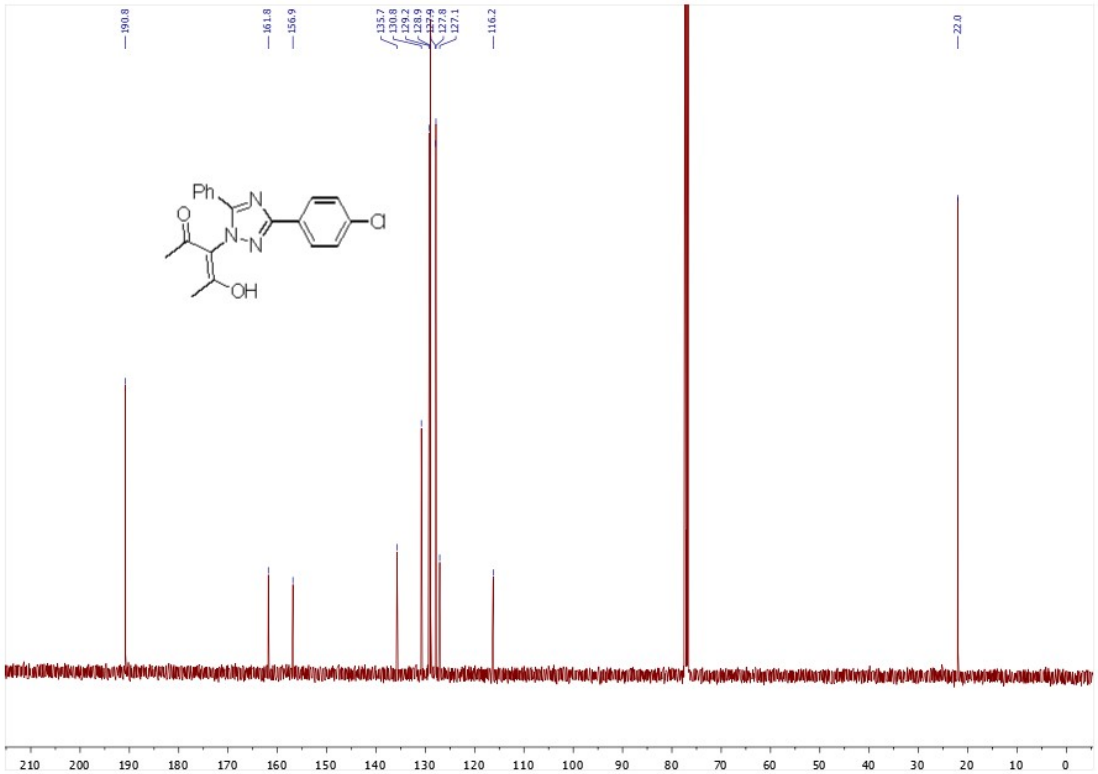
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4as**



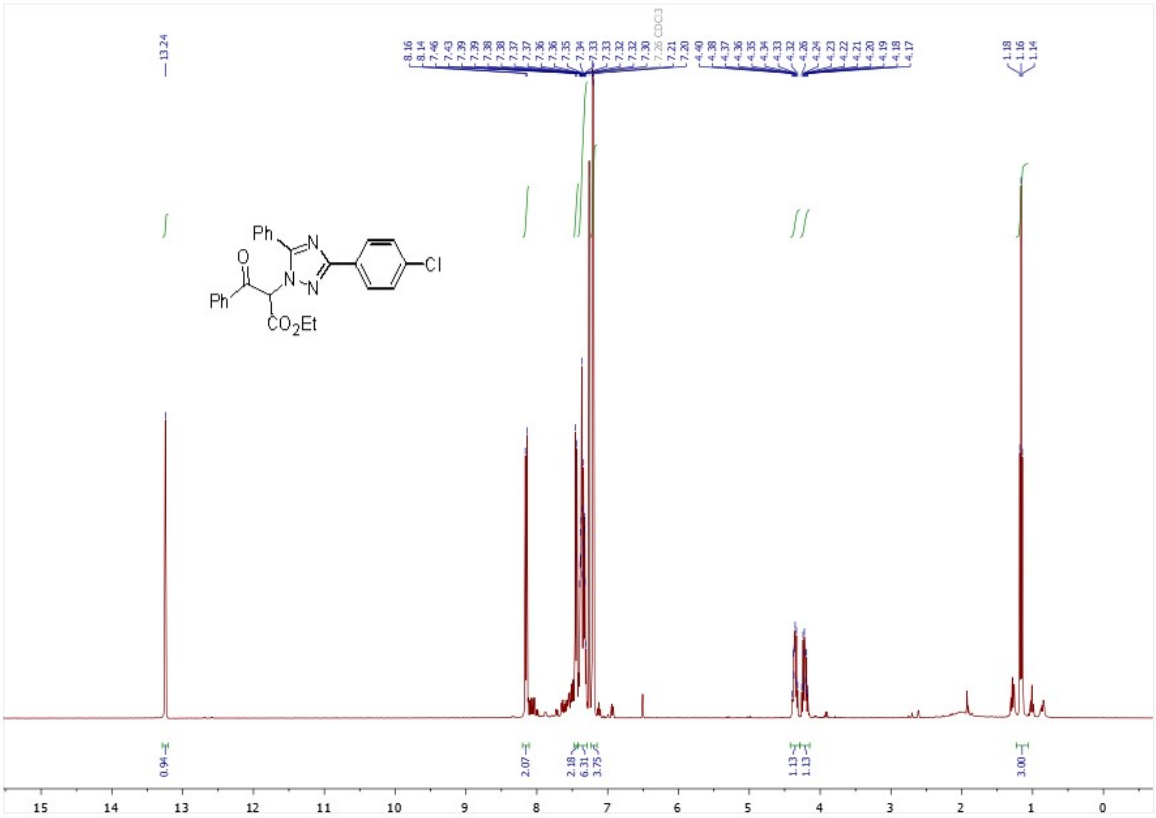


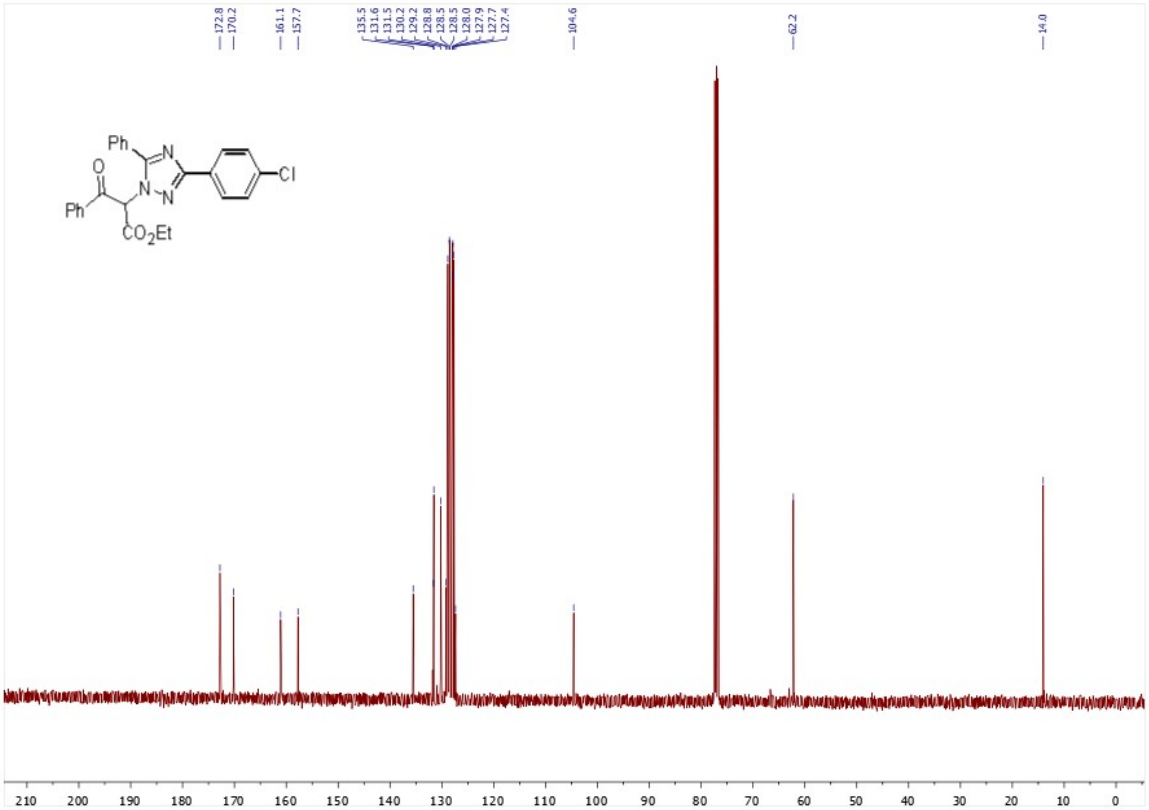
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4at**



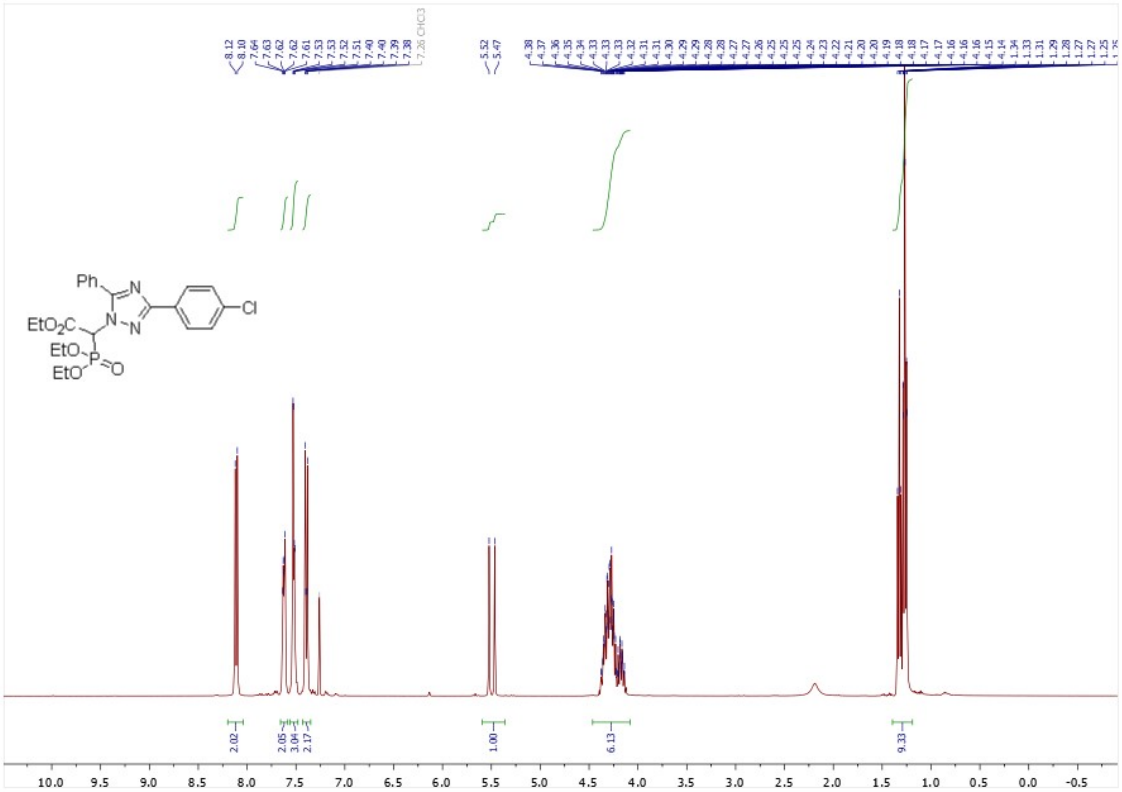


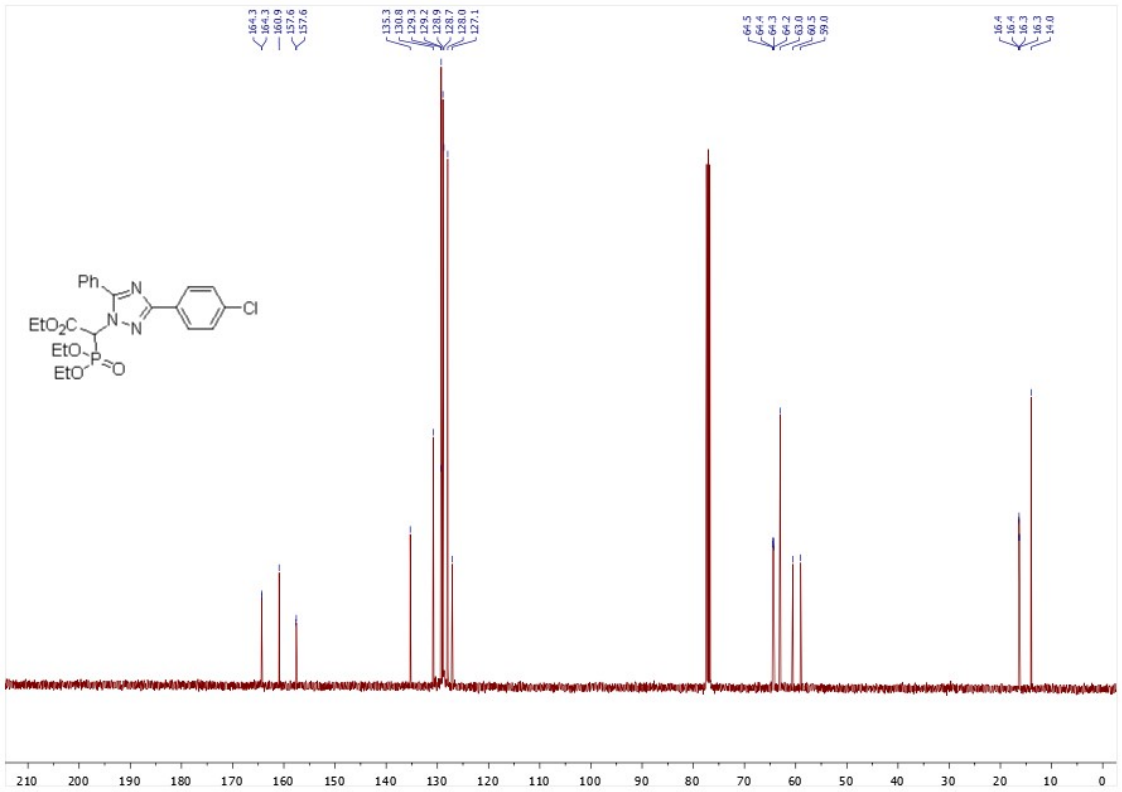
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4au**



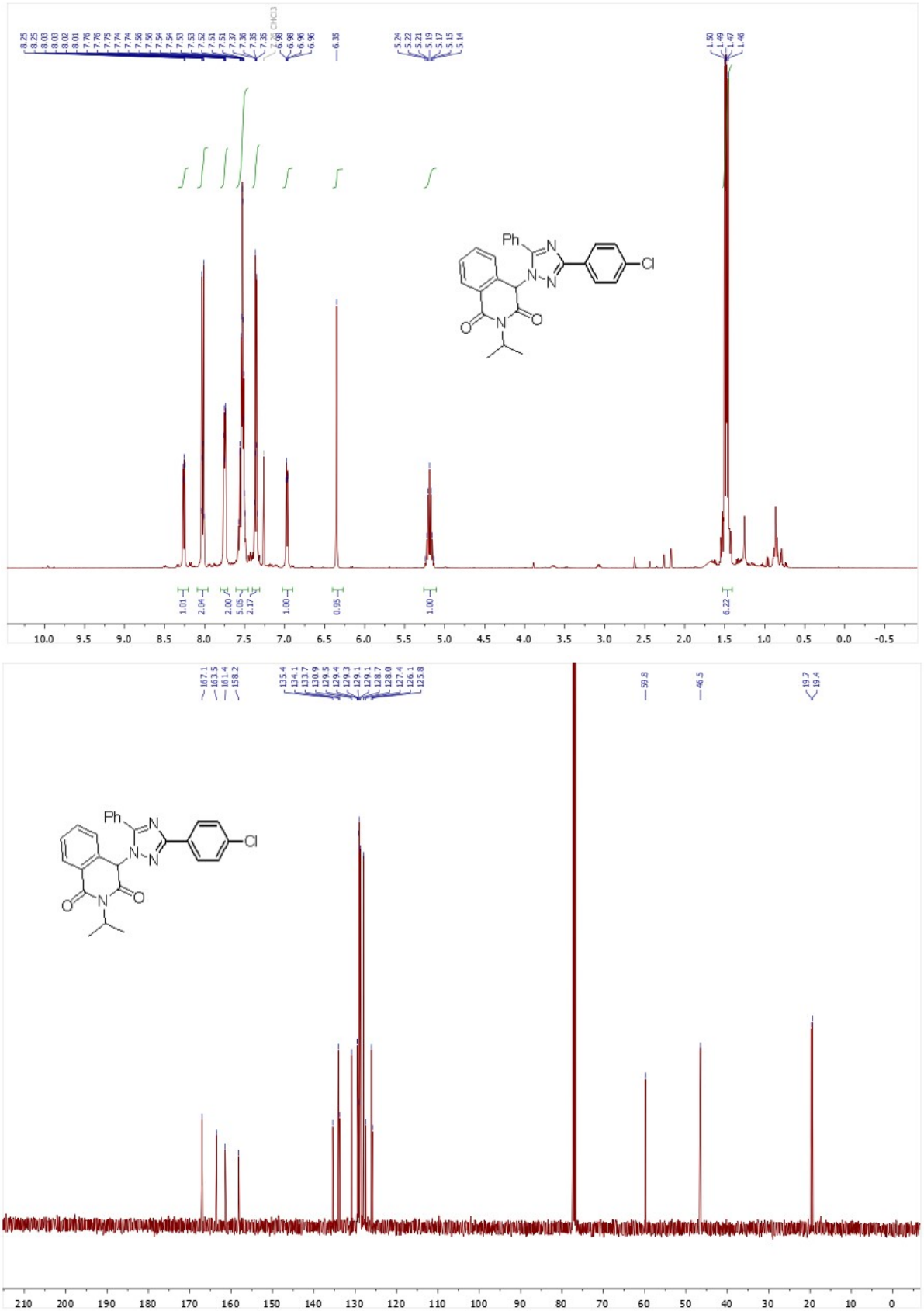


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4av**

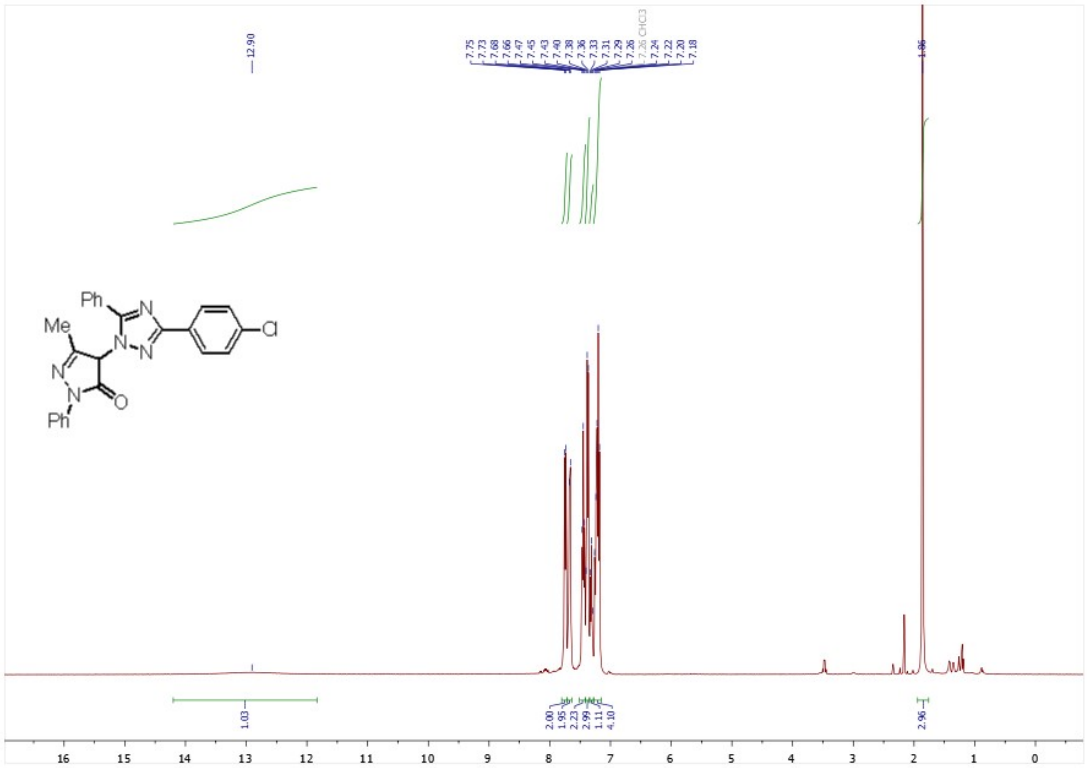


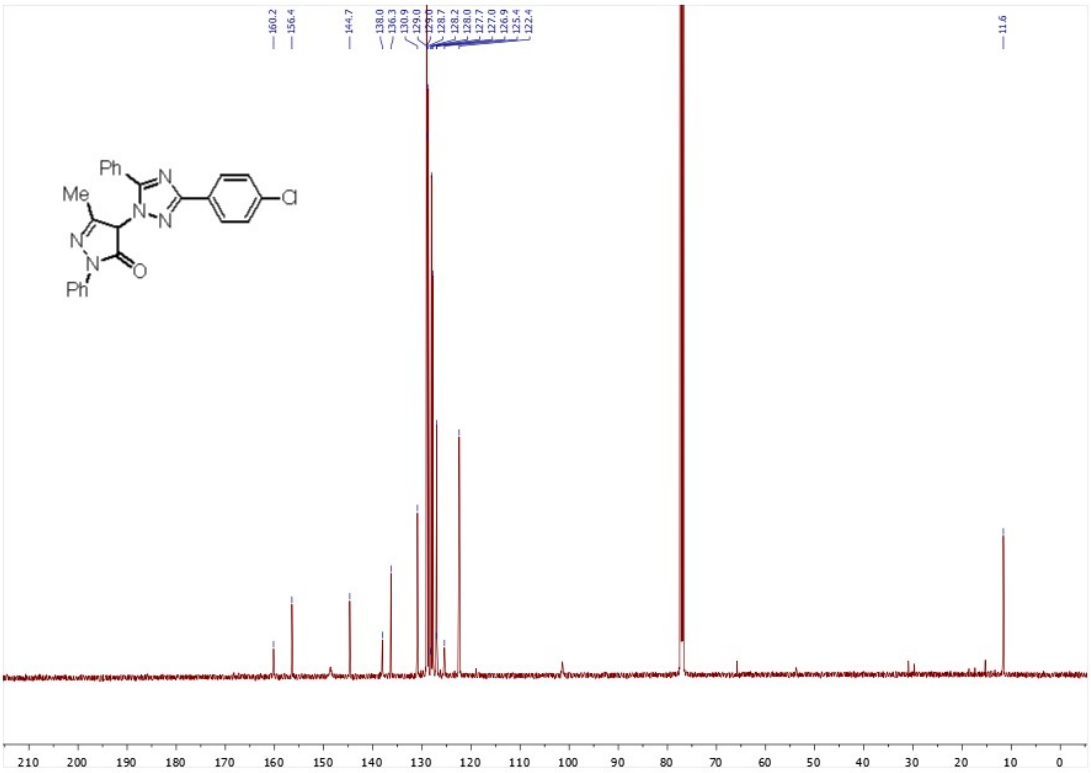


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4aw**

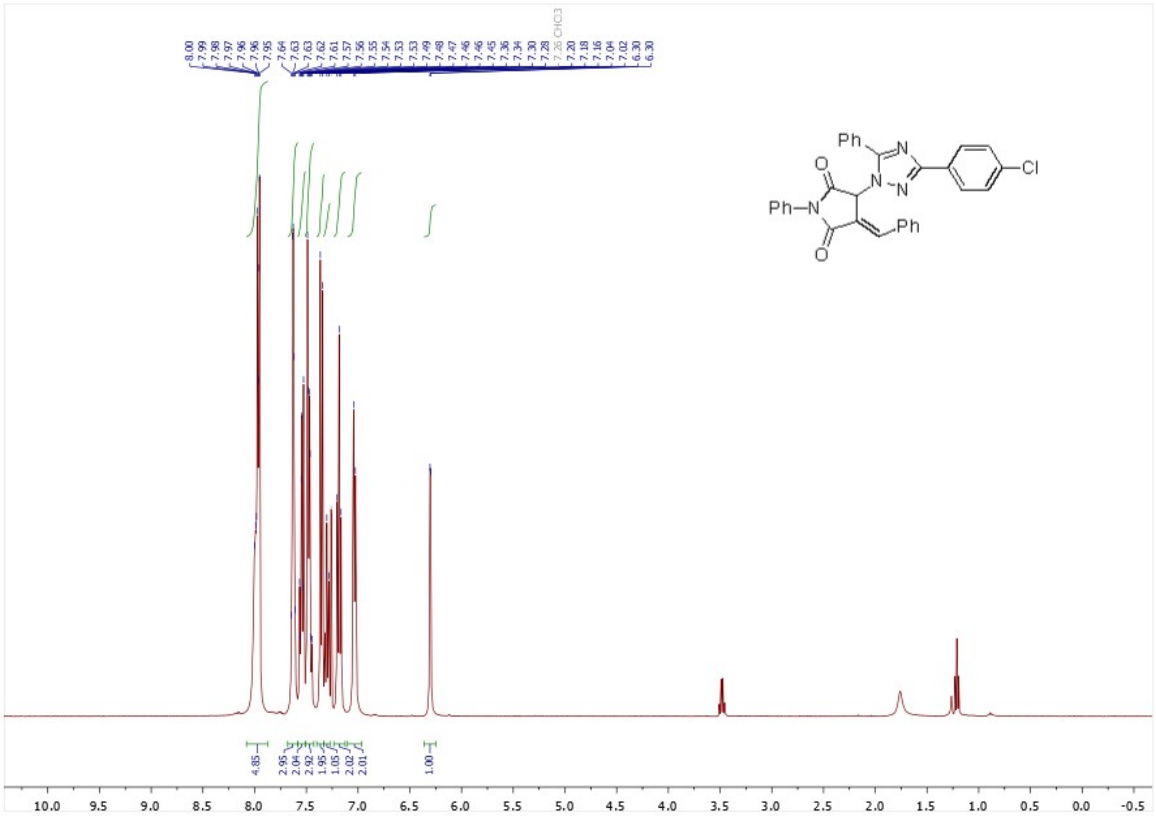


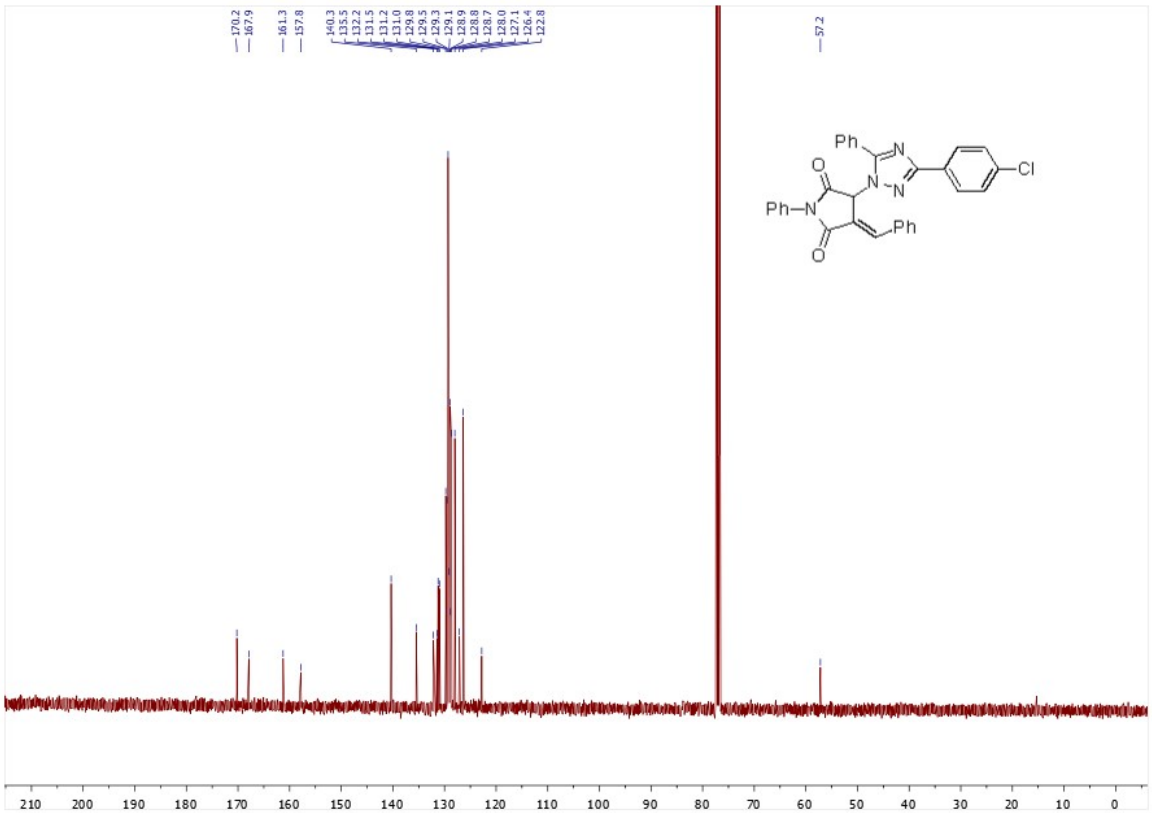
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ax**



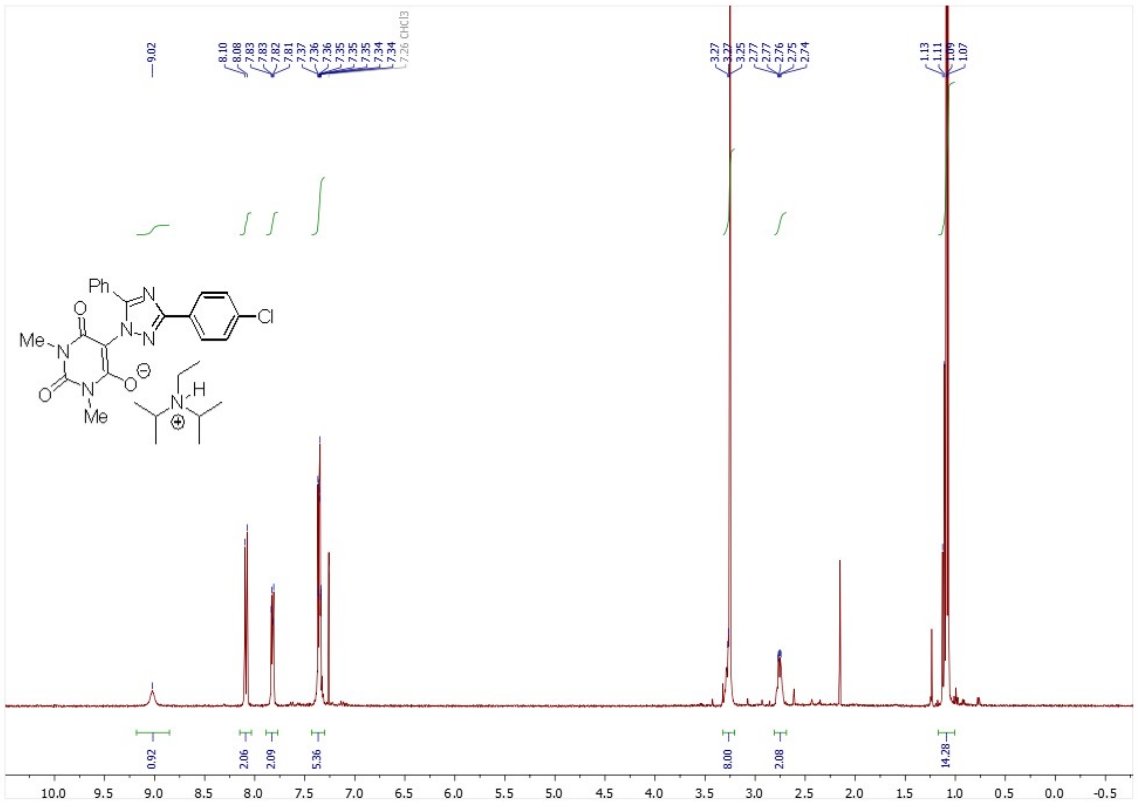


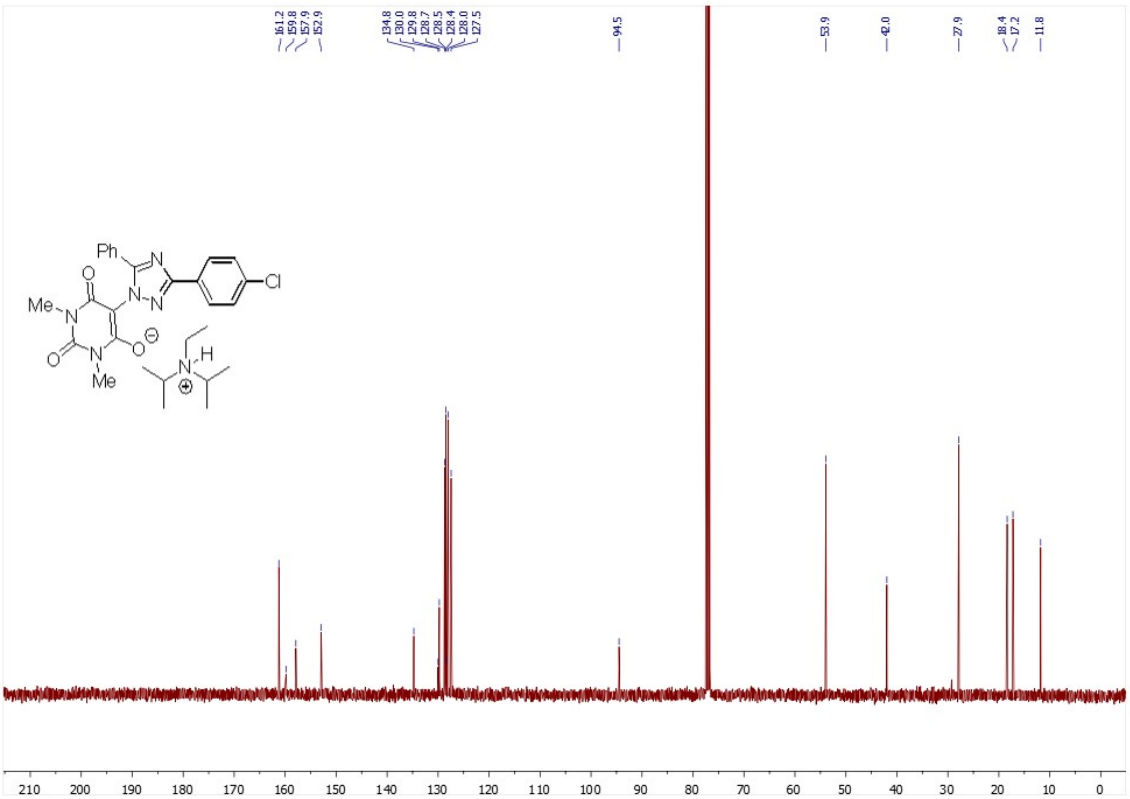
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4ay**



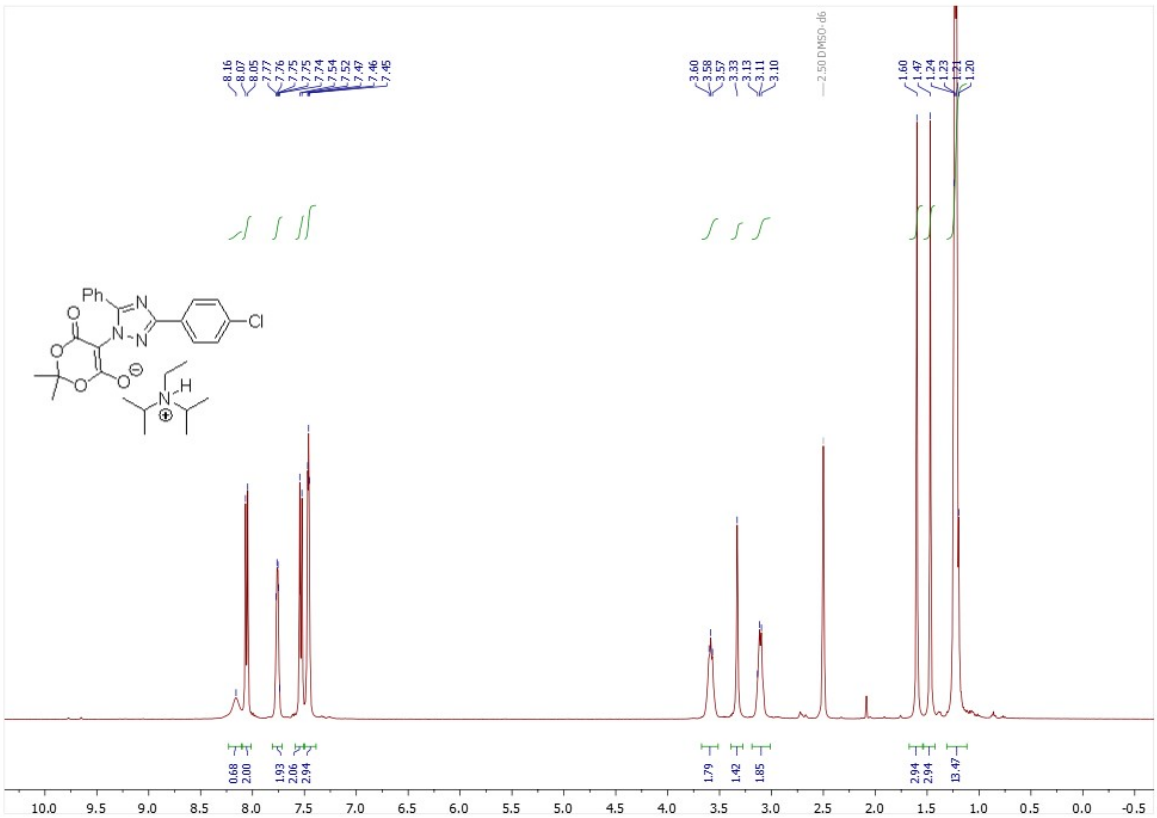


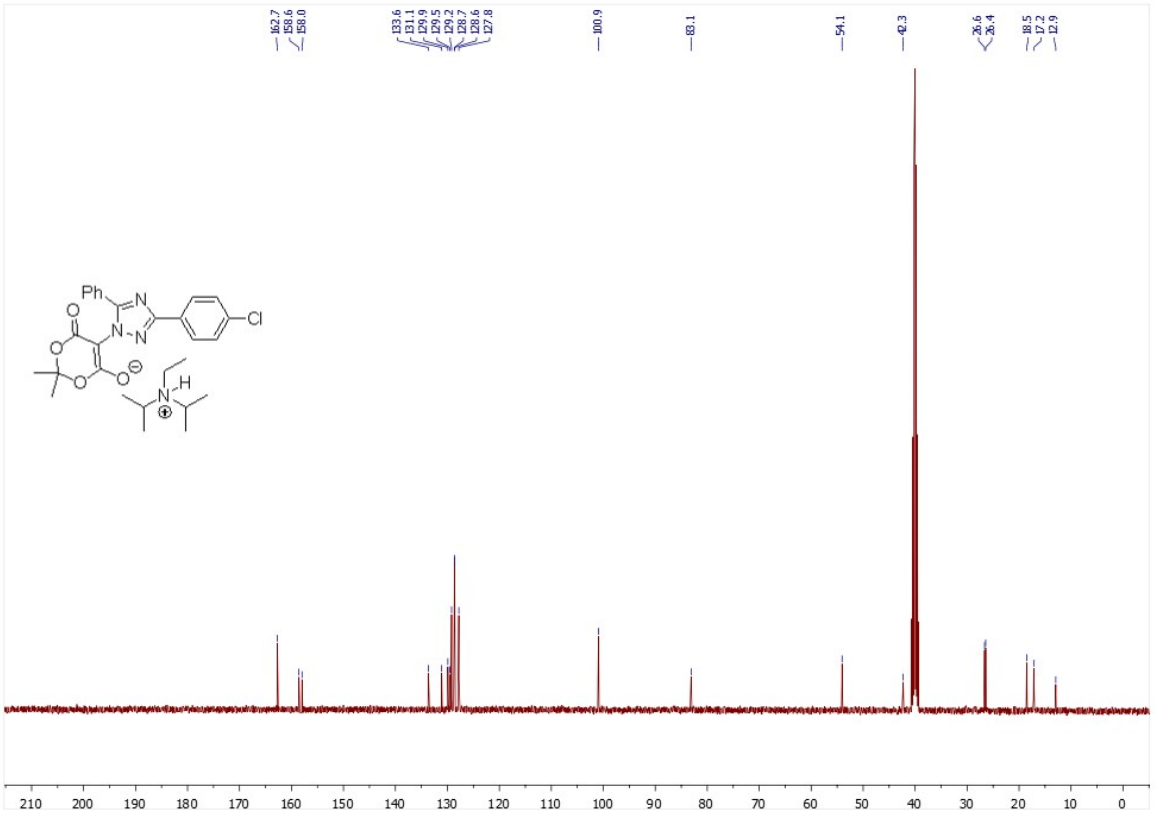
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4az**



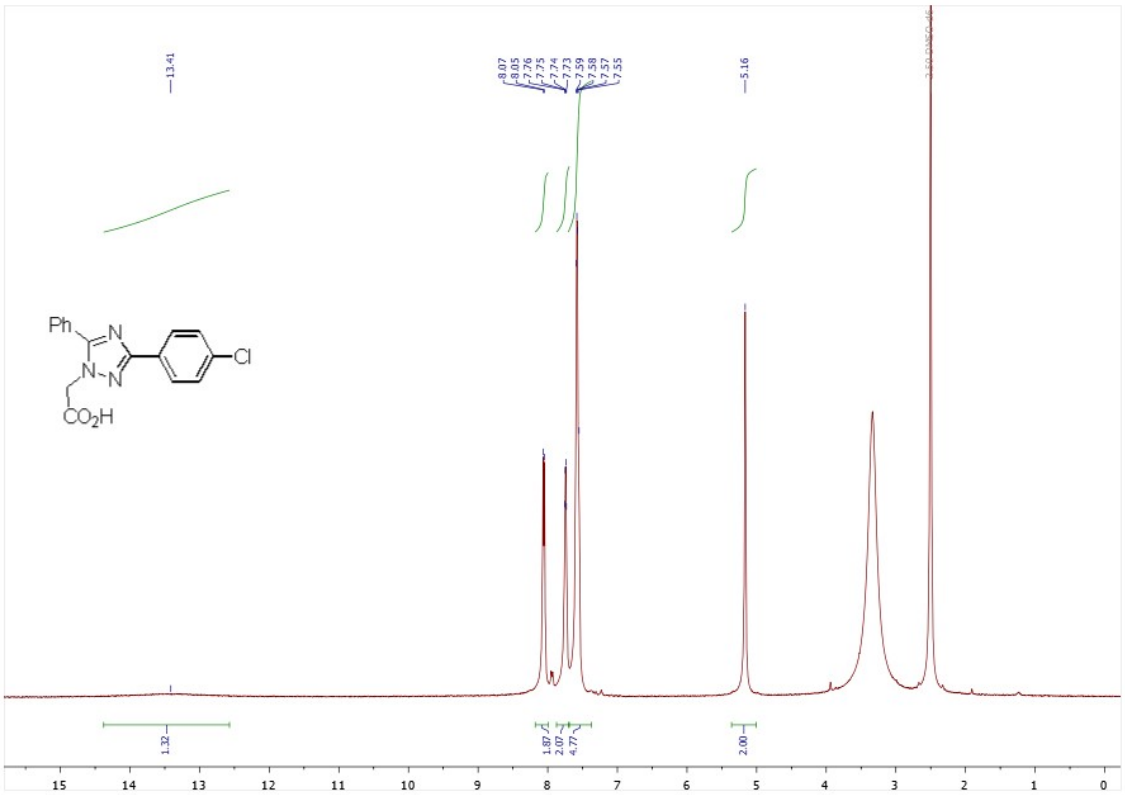


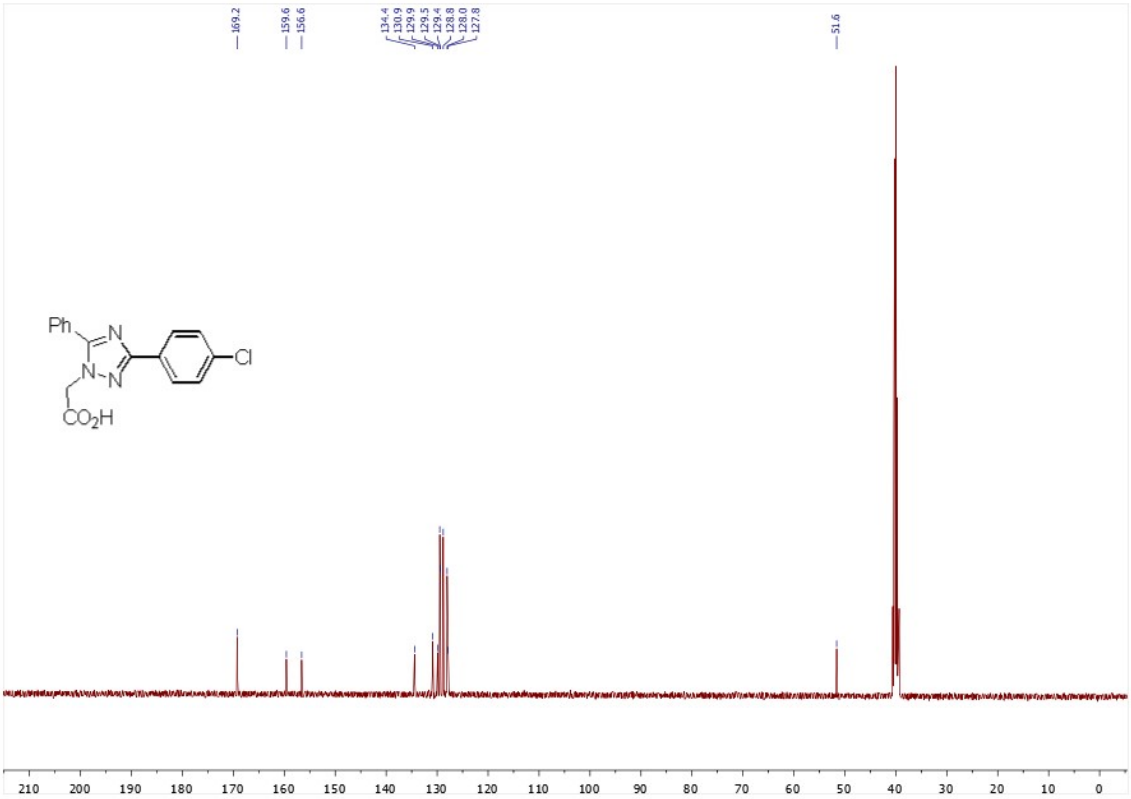
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **4ba**



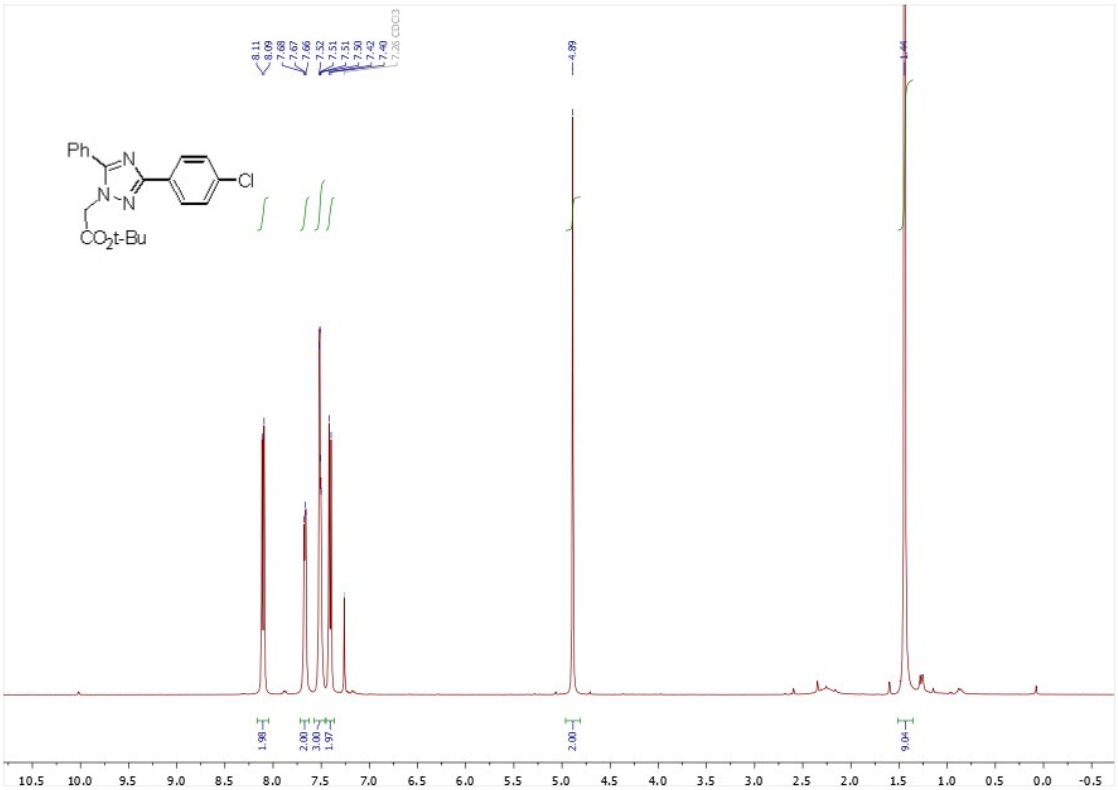


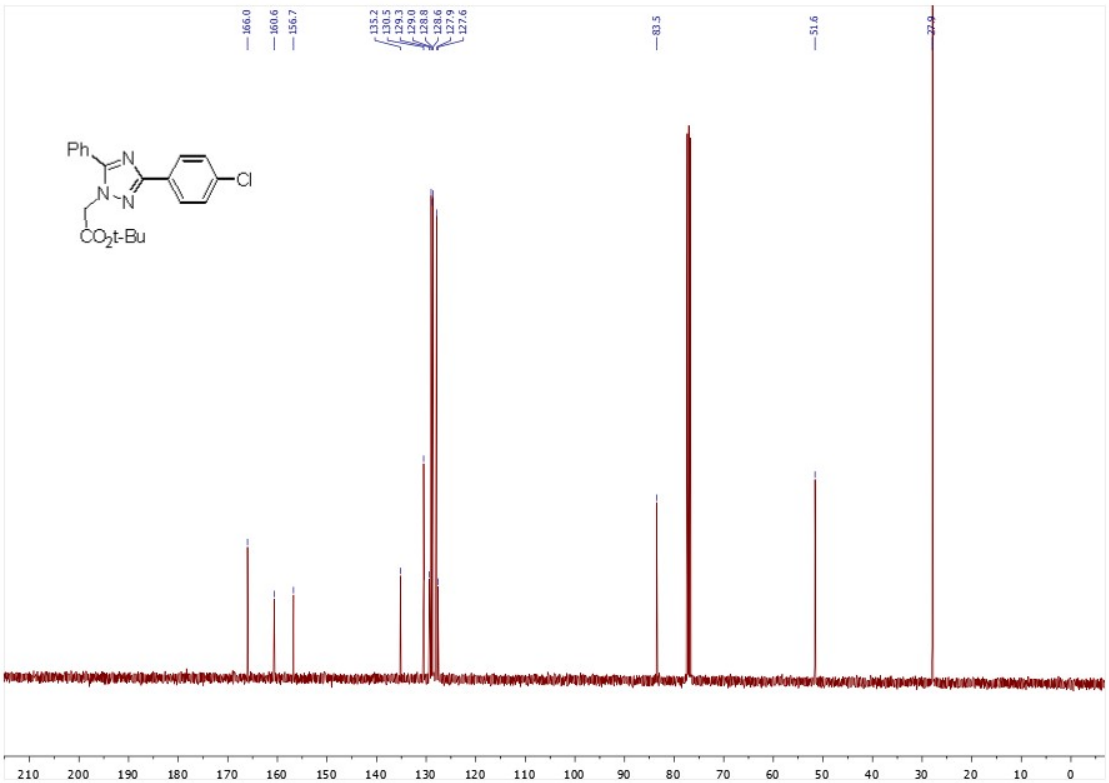
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, DMSO-d_6) spectra of **6**



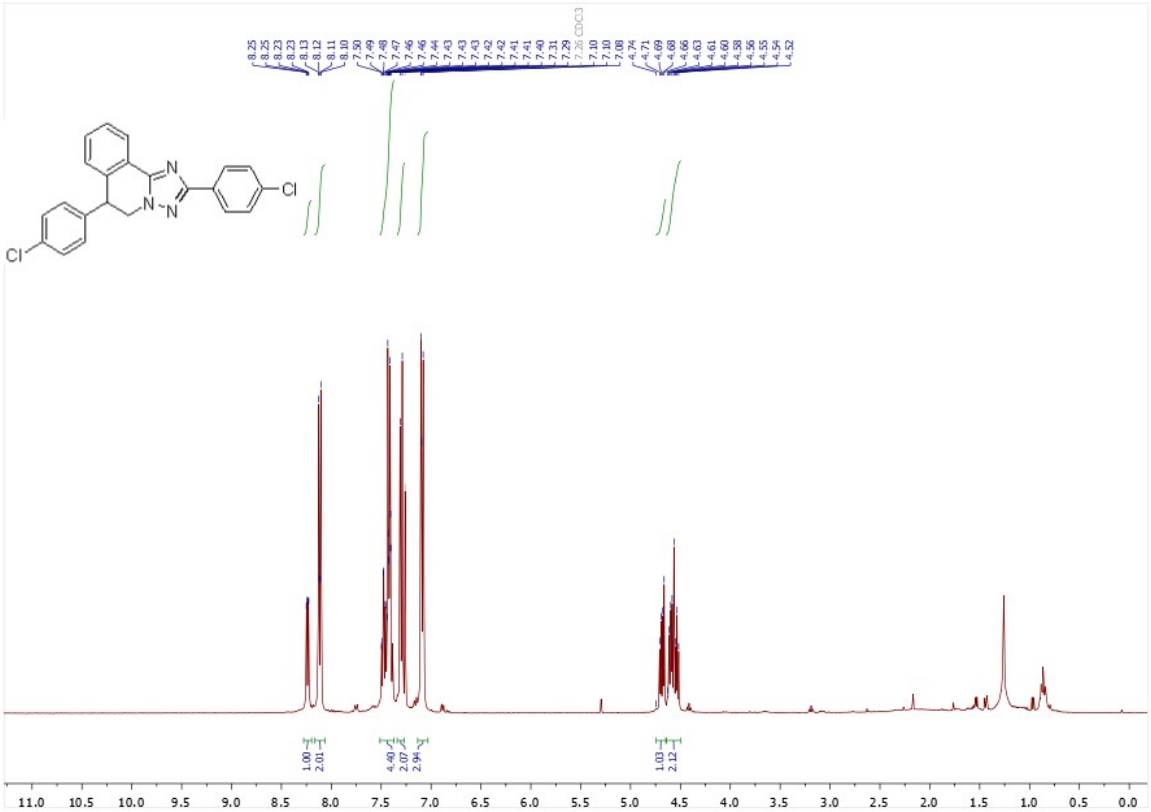


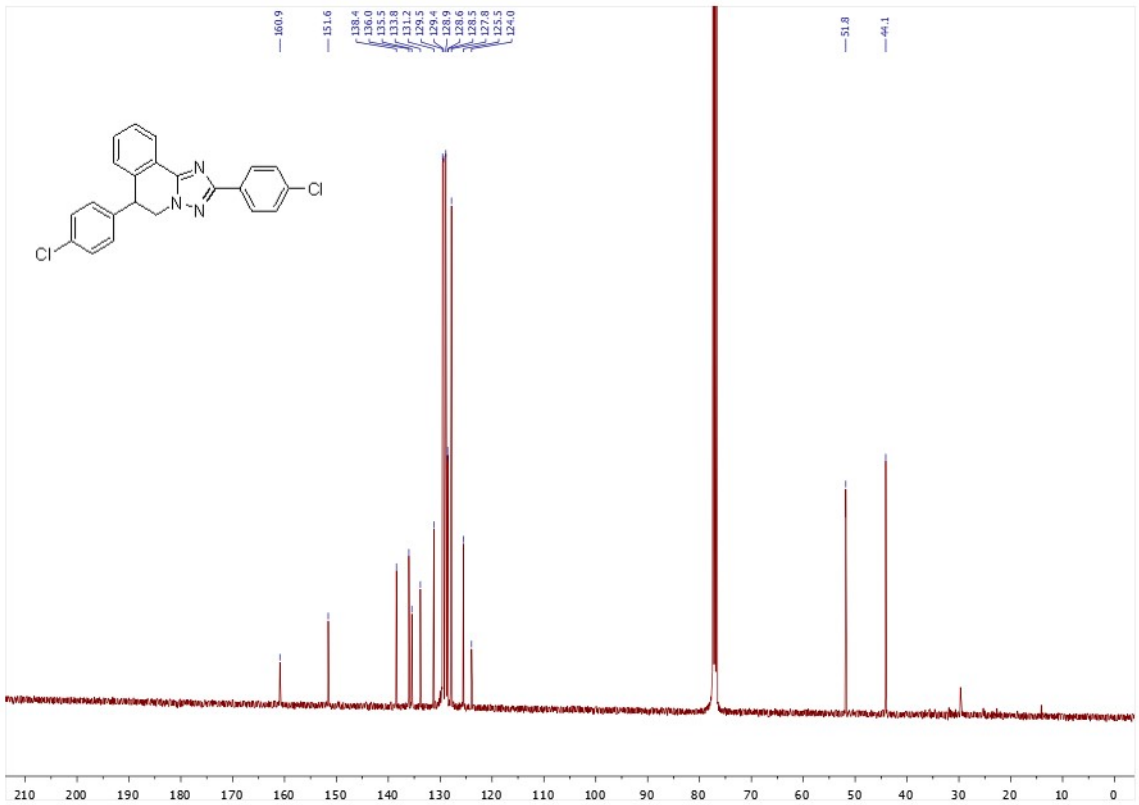
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **7**





Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **9**





Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **10**