Supplementary data

Design, synthesis and antiproliferative activity studies of 1,2,3-triazole-chalcones

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1. General Experimental

The reaction process was monitored by TLC with silica gel plates (thickness 250μm, Indicator F-254). The target analogues were purified by column chromatography with silica gel (300 meshes). Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. The novel structures of target analogues were characterized by NMR (400 and 100 MHz) in Acetone-d_6, DMSO-d_6 or $CDCl_3$ with TMS as an internal standard and HRMS. The purity of all biologically evaluated compounds was determined to be >95% by reverse phase high performance liquid chromatography (HPLC) analysis. HPLC measurement was performed with a Phenomenex column (C_{18}, 5.0 μm, 4.60 mm × 250 mm) on Dionex UltiMate 3000 UHPLC instrument from Thermo-Fisher. The signal was monitored at 254 nm with a UV dector. A flow rate of 0.5 ml/min was used with mobile phase of MeOH in H_2O (60:40, v/v).

2. Experimental Procedures and Analytical Data

General Procedure for the Synthesis of Compounds 5a-e

To a magnetically stirred solution of aryl bromides (3 mmol) in CH_3CN (15 mL), sodium azide (9 mmol) and tetrabutylammonium bromide(1 mmol) were added carefully and the reaction mixture was refluxed for 10 h. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc (30 mL) and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compounds **5a-e**, which were used in the next reaction without further purification (yield:

87.4%~92.6%).

General Procedure for the Synthesis of Compounds 6a-c

p-aminoacetophenone (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml). The mixture was allowed to stir for 3 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product (yield: 80.4%~86.9%).

General Procedure for the Synthesis of Compounds 9a-g

propargyl bromide (1 mmol), *p*-acetylphenol (1mmol), K_2CO_3 (1 mmol) were dissolved in acetone (10 ml) and the reaction mixture was refluxed for 8 h. Upon completion, the precipitated product was filtered off and washed with ethylacetate to afford the crude product **7**. compound **7** (1.05 mmol), **5a** (1mmol), $CuSO_4.5H_2O$ (0.2 mmol) and sodium ascorbate (0.1 mmol) were dissolved in THF/H_2O (5 ml/5 ml) to stir for 7 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product **8**. Compound **8** (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml) to stir at room temperature. The reaction was monitored by TLC till the reaction was finished. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford **9a-g** which were purified with column chromatography (total yield: 62.2%~71.3%).

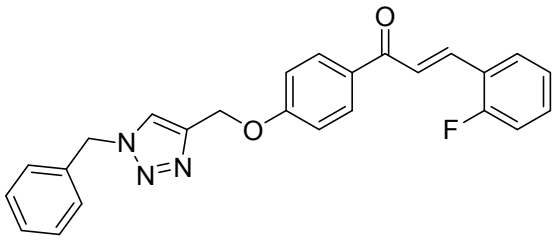
General Procedure for the Synthesis of Compounds 12a-n

propargyl bromide (1mmol), *p*-aminoacetophenone (1 mmol), K_2CO_3 (1 mmol) were dissolved in acetone (10 ml) and the reaction mixture was refluxed for 8 h. Upon completion, the precipitated product was filtered off and washed with ethylacetate to afford the crude product **10**. compound **10** (1.05 mmol), azide derivatives (1 mmol), $CuSO_4.5H_2O$ (0.2 mmol) and sodium ascorbate (0.1 mmol) were dissolved in THF/H_2O (5 ml/5 ml) to stir for 7 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product **11a-e**. Compound **11a-e** (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml) to stir at room temperature. The reaction was monitored by TLC till the reaction was finished.

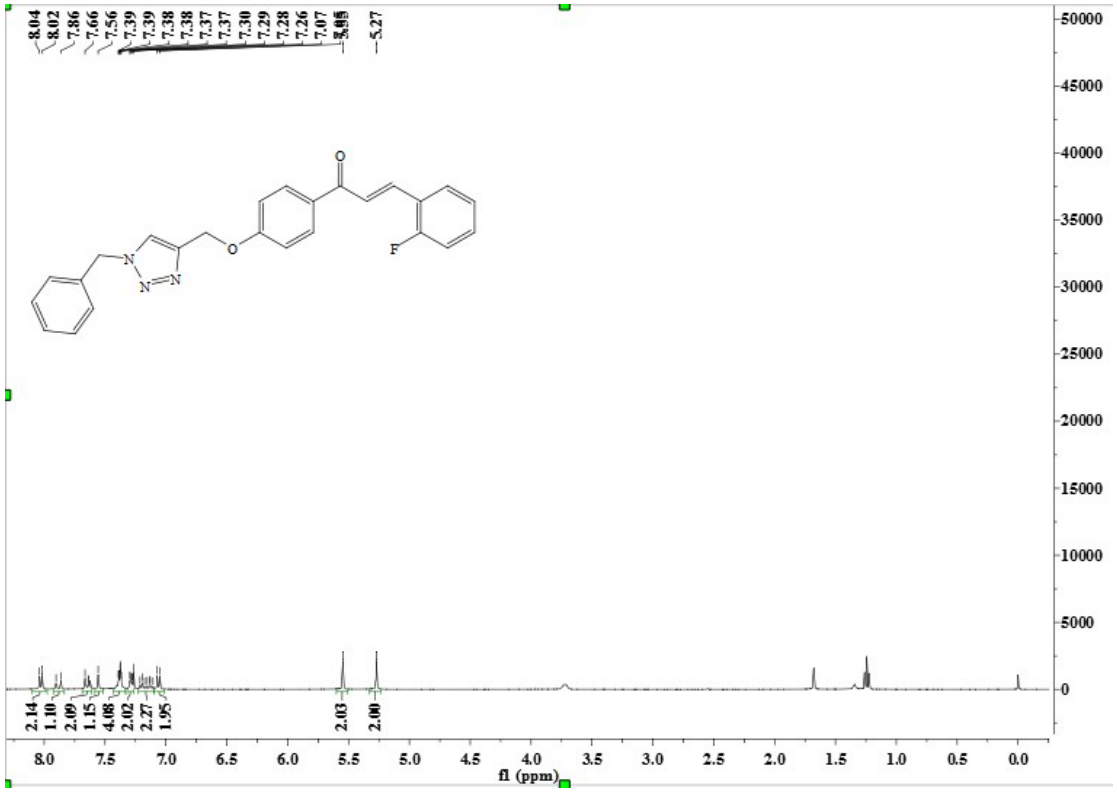
Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compounds **12a-n** which were purified with column chromatography (68.9%~77.5%).

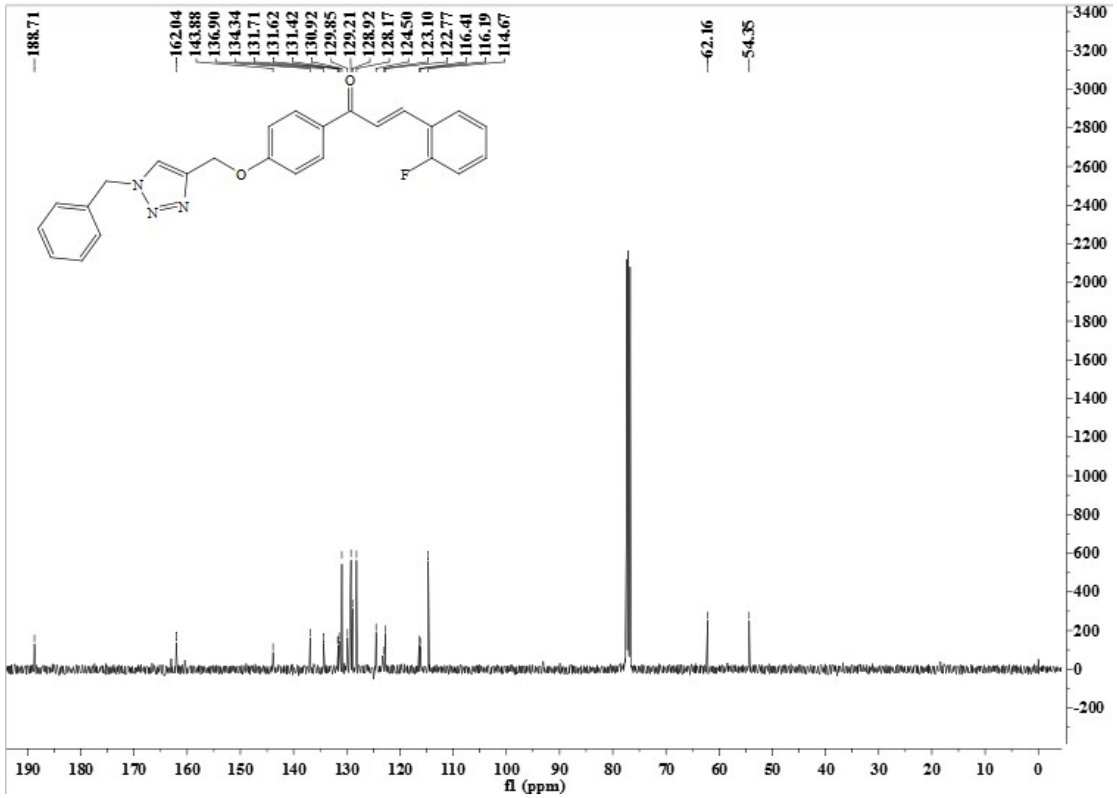
^{1}H, ^{13}C NMR and HRMS Spectra for all new compounds

(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2-fluorophenyl)prop-2-en-1-one (**9a**)

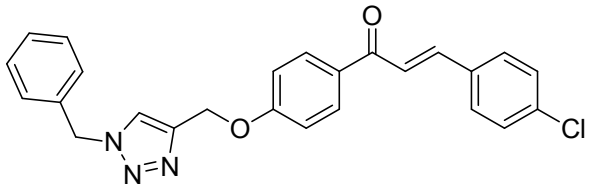


White solid，yield：85%，m.p：249.6~253.2 °C. purity: 98.23 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 2H), 7.88 (d, *J* = 15.9 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.56 (s, 1H), 7.38 (dt, *J* = 7.0, 2.2 Hz, 4H), 7.28 (dd, *J* = 7.2, 2.1 Hz, 2H), 7.23 – 7.10 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.71, 162.04, 143.88, 136.90, 134.34, 131.71, 131.62, 131.42, 130.92, 129.85, 129.21, 128.92, 128.17, 124.50, 123.10, 122.77, 116.41, 116.19, 114.67, 62.16, 54.35. HRMS (ESI) calcd for $C_{25}H_{20}FN_3O_2$ [M+H]+: 414.1618, found: 414.1616.

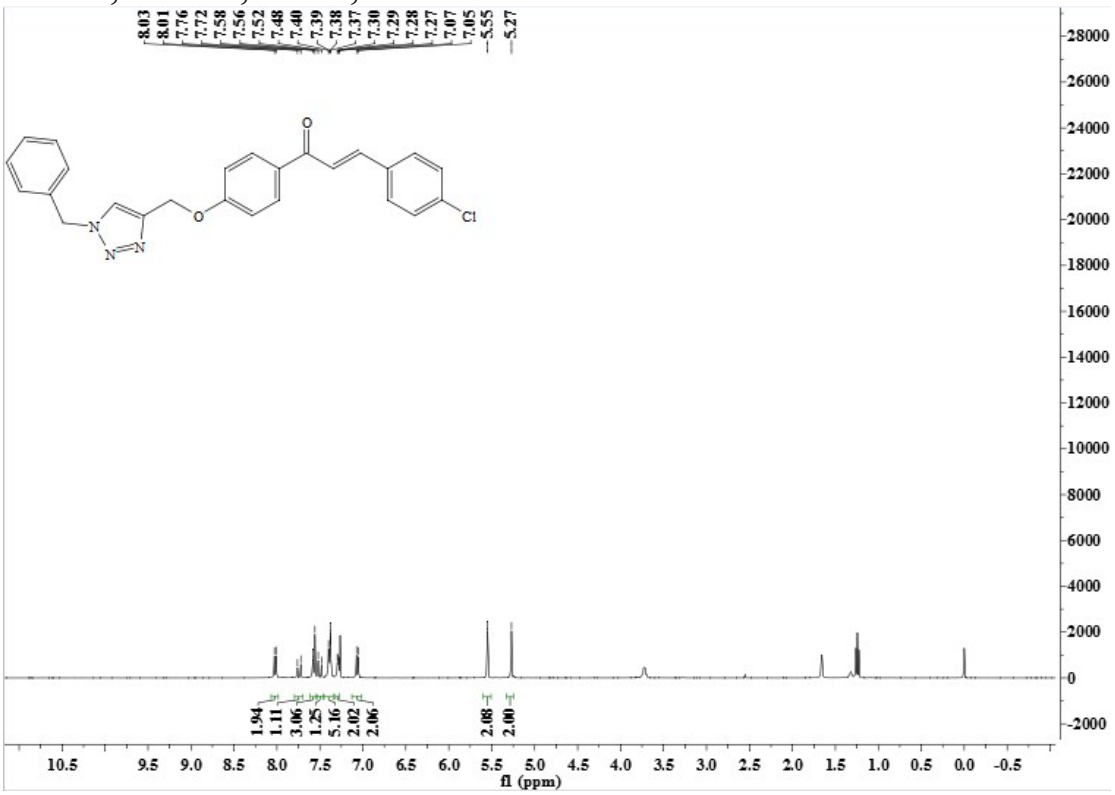


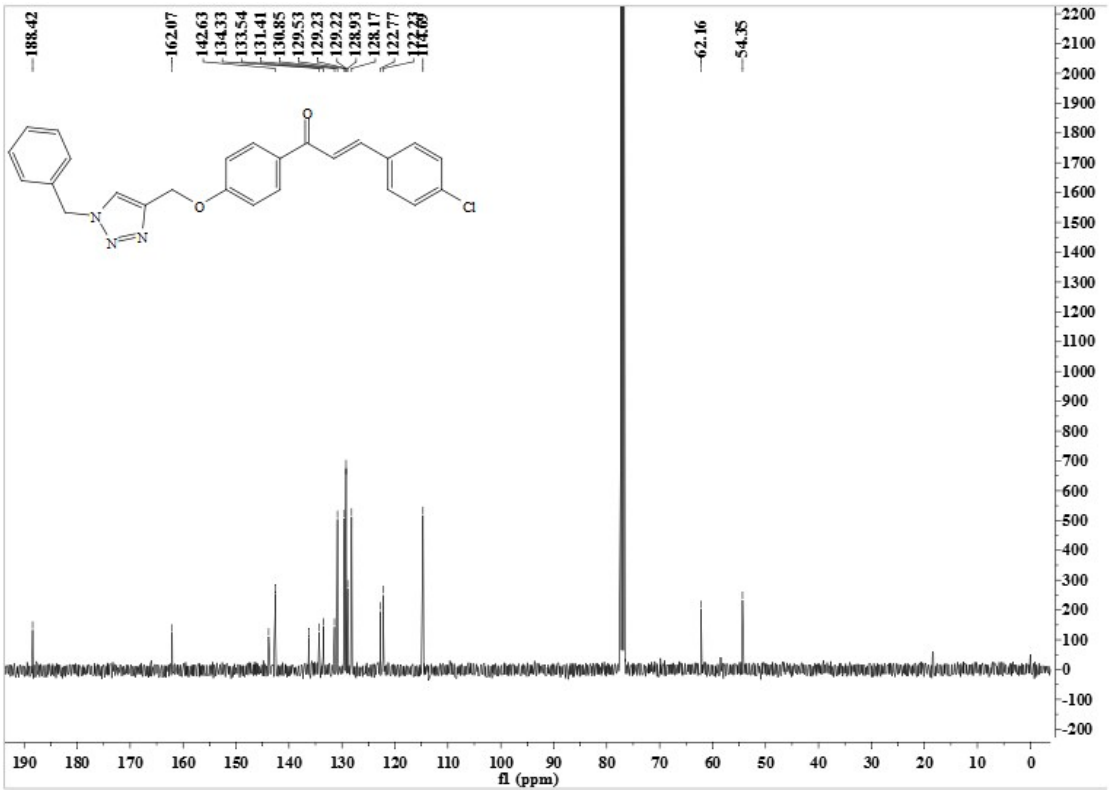


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**9b**)

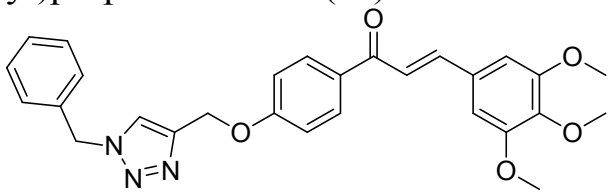


White solid，yield：86%，m.p：182.3~184.4 °C. purity: 98.04 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 15.6 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 3H), 7.50 (d, *J* = 15.6 Hz, 1H), 7.39 (dd, *J* = 7.9, 1.9 Hz, 5H), 7.28 (dd, *J* = 7.2, 2.2 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.42, 162.07, 143.84, 142.63, 136.26, 134.33, 133.54, 131.41, 130.85, 129.53, 129.23, 129.22, 128.93, 128.17, 122.77, 122.23, 114.69, 62.16, 54.35.

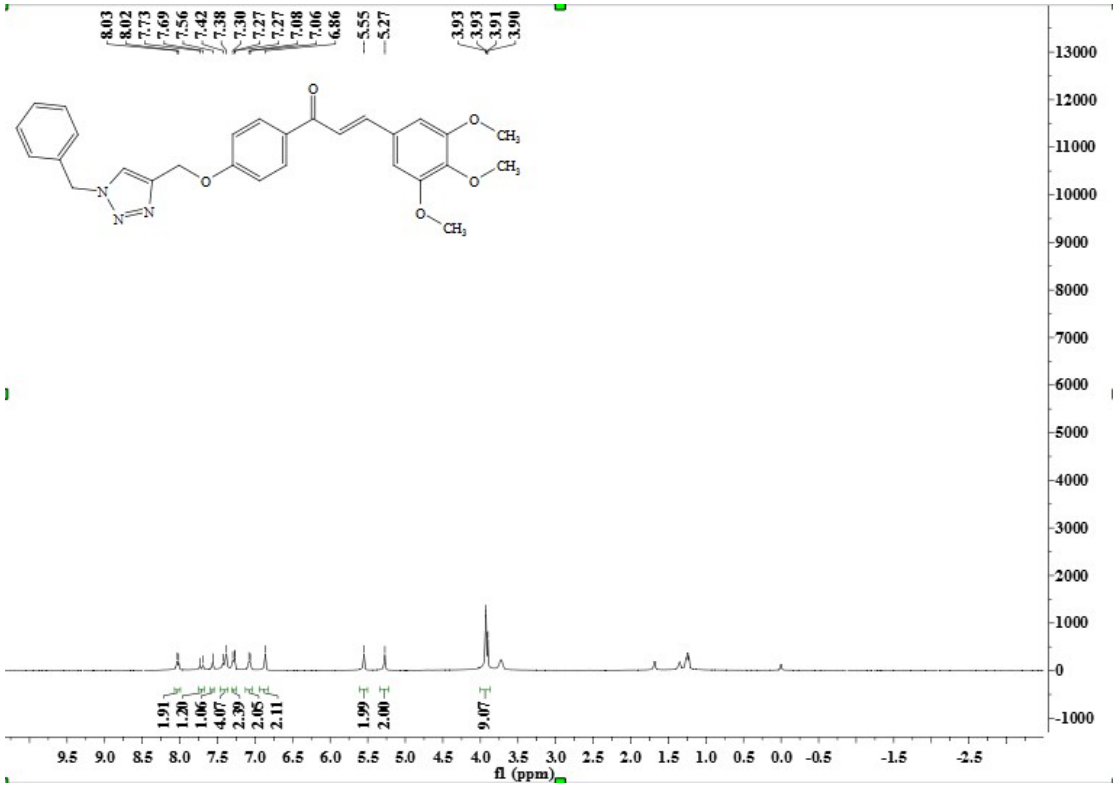


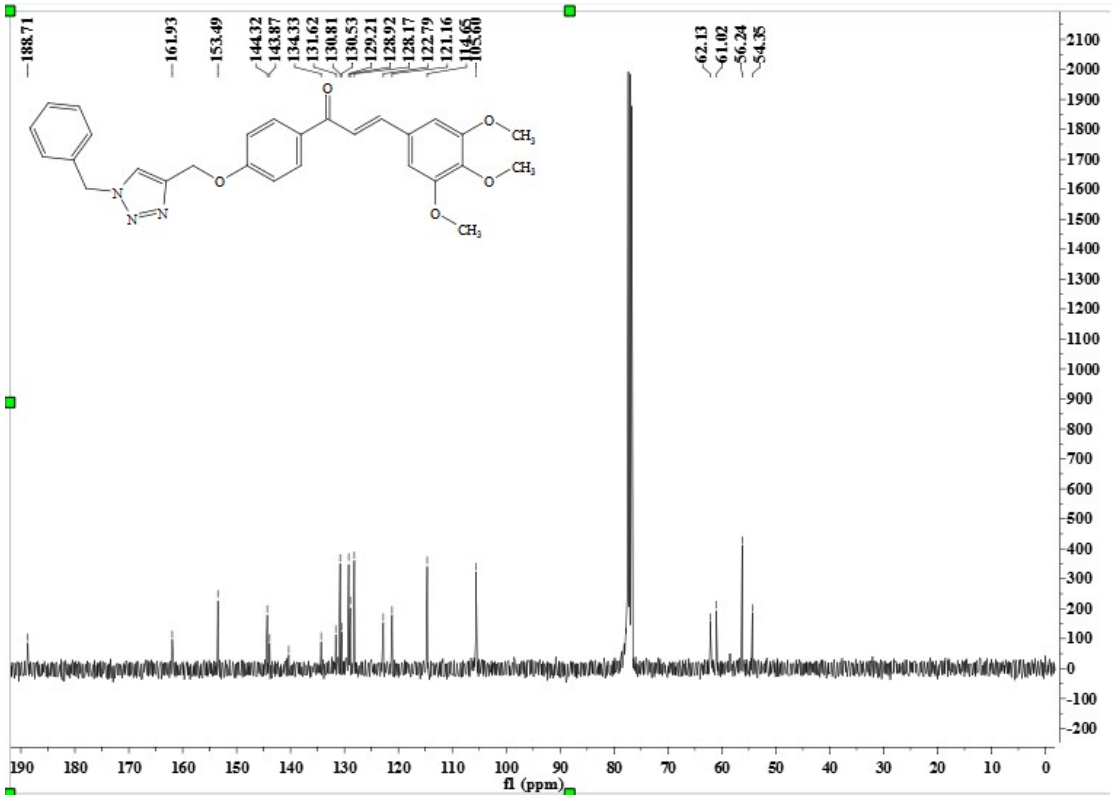


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9c**)

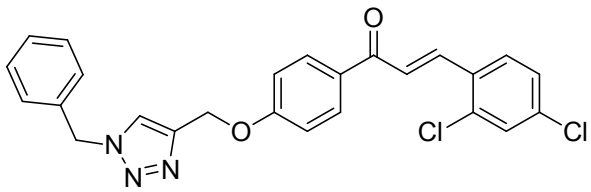


White solid，yield：75%，m.p：156.6~158.2 °C. purity: 99.13 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 15.8 Hz, 1H), 7.56 (s, 1H), 7.40 (d, *J* = 16.0 Hz, 4H), 7.31 – 7.25 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.86 (s, 2H), 5.55 (s, 2H), 5.27 (s, 2H), 3.92 (dd, *J* = 9.4, 1.4 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.71, 161.93, 153.49, 144.32, 143.87, 140.33, 134.33, 131.62, 130.81, 130.53, 129.21, 128.92, 128.17, 122.79, 121.16, 114.65, 105.60, 62.13, 61.02, 56.24, 54.35. HRMS (ESI) calcd for $C_{28}H_{27}N_3O_5$ [M+H]+: 486.2029, found: 486.2028.

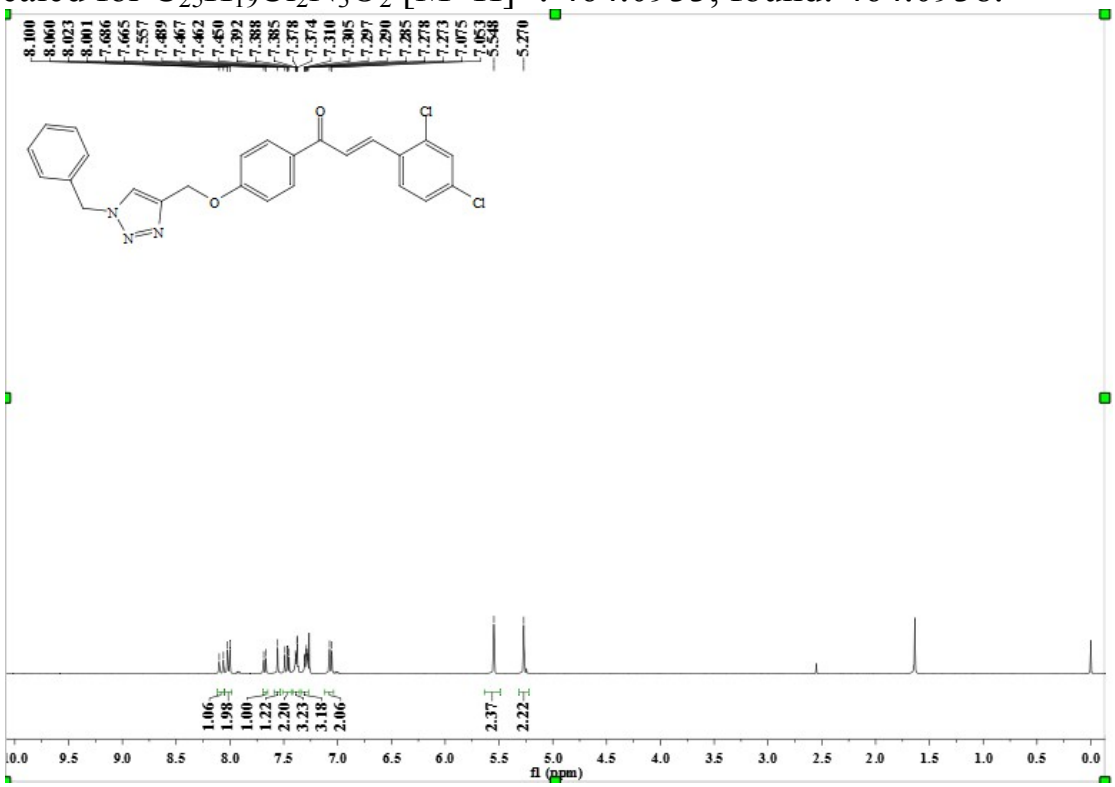


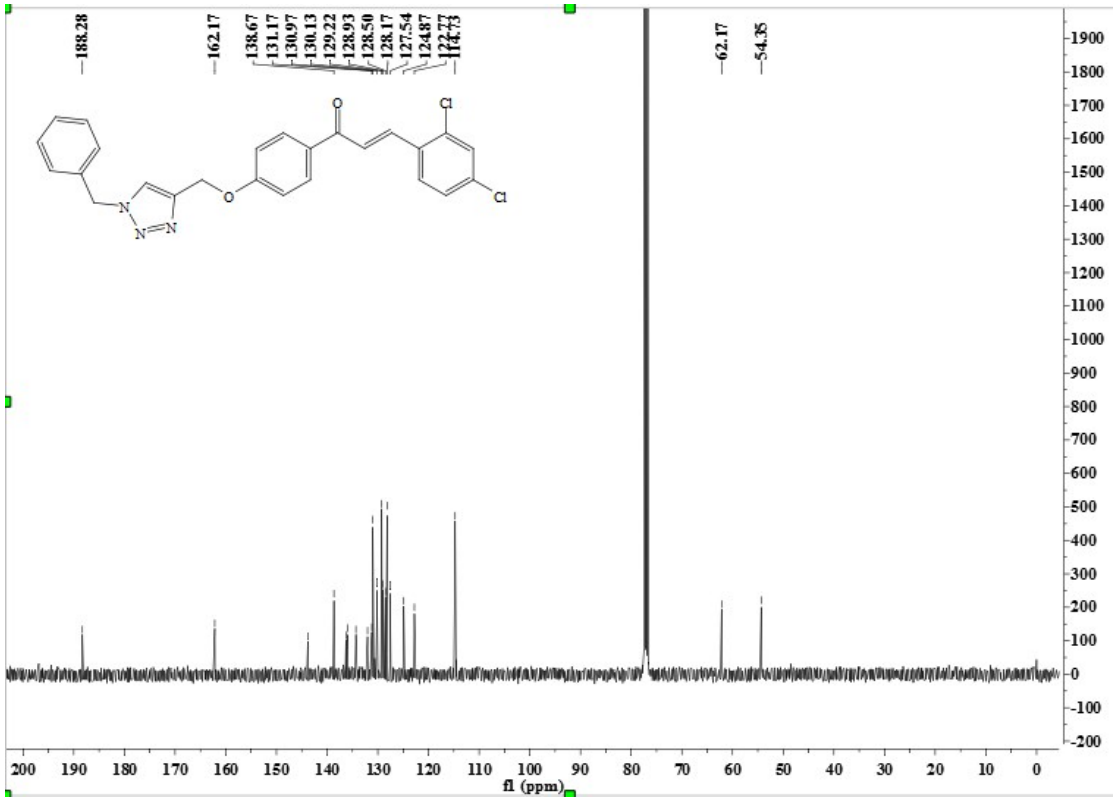


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one (**9d**)

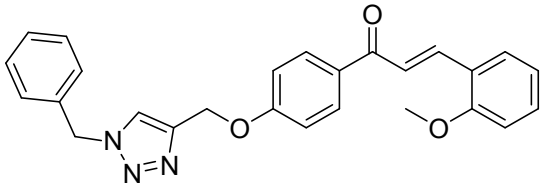


White solid, yield：84%, m.p：145.6~147.2 °C. purity: 97.17 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 15.7 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.47 (dd, *J* = 8.9, 6.8 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.29 (ddd, *J* = 6.7, 4.9, 2.0 Hz, 3H), 7.06 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.28, 162.17, 143.81, 138.67, 136.30, 135.99, 134.32, 132.02, 131.17, 130.97, 130.13, 129.22, 128.93, 128.50, 128.17, 127.54, 124.87, 122.77, 114.73, 62.17, 54.35. HRMS (ESI) calcd for $C_{25}H_{19}Cl_2N_3O_2$ [M+H]+: 464.0933, found: 464.0938.

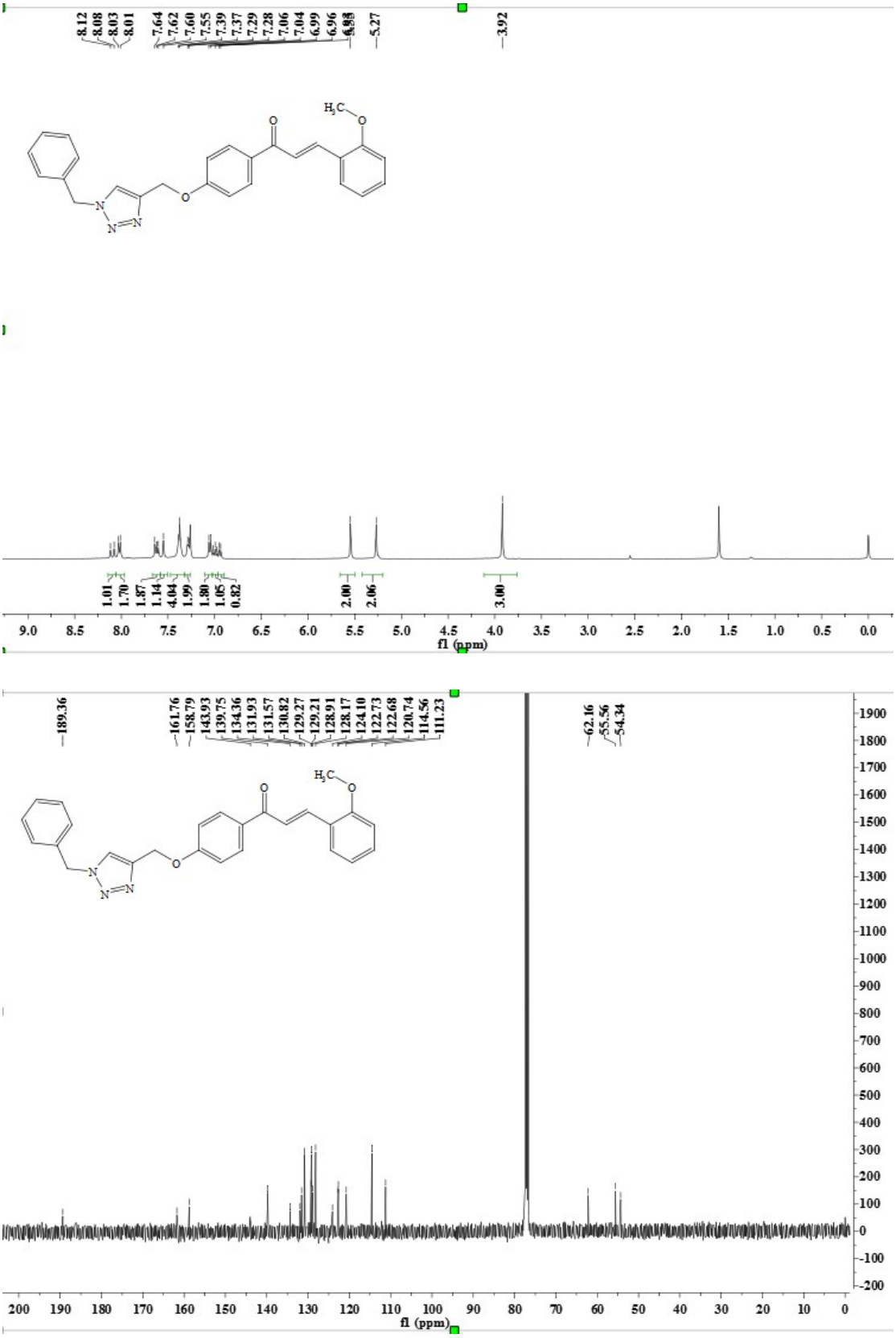




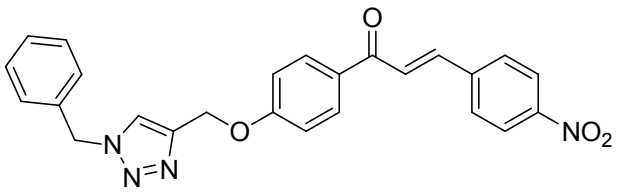
(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**9e**)



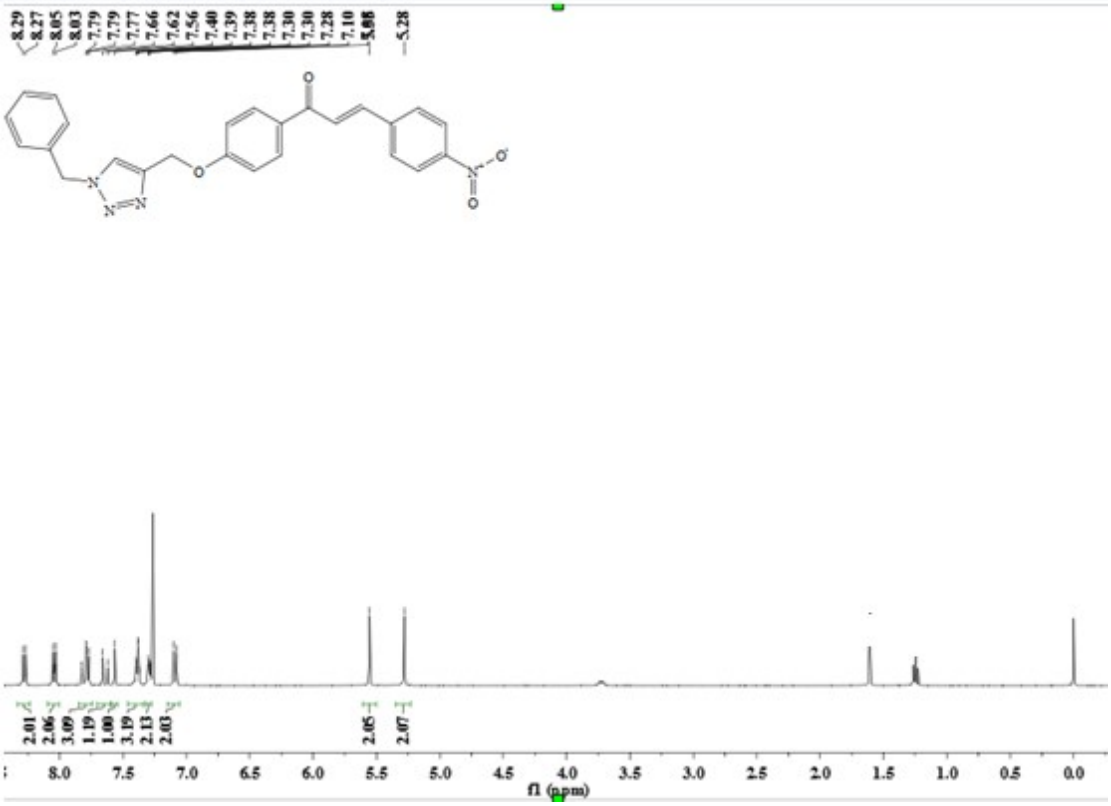
White solid, yield：75%, m.p：130.6~132.4 °C. purity: 98.65 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.8 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.55 (s, 1H), 7.38 (d, *J* = 6.5 Hz, 4H), 7.28 (d, *J* = 5.5 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.55 (s, 2H), 5.27 (s, 2H), 3.92 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 189.36, 161.76, 161.27, 158.79, 139.75, 134.36, 131.93, 131.57, 130.82, 129.27, 129.21, 128.91, 128.17, 127.50, 124.10, 122.68, 120.74, 114.56, 111.23, 62.16, 55.56, 54.34. HRMS (ESI) calcd for $C_{26}H_{23}N_3O_3$ [M+H]+: 426.1818, found: 426.1819.

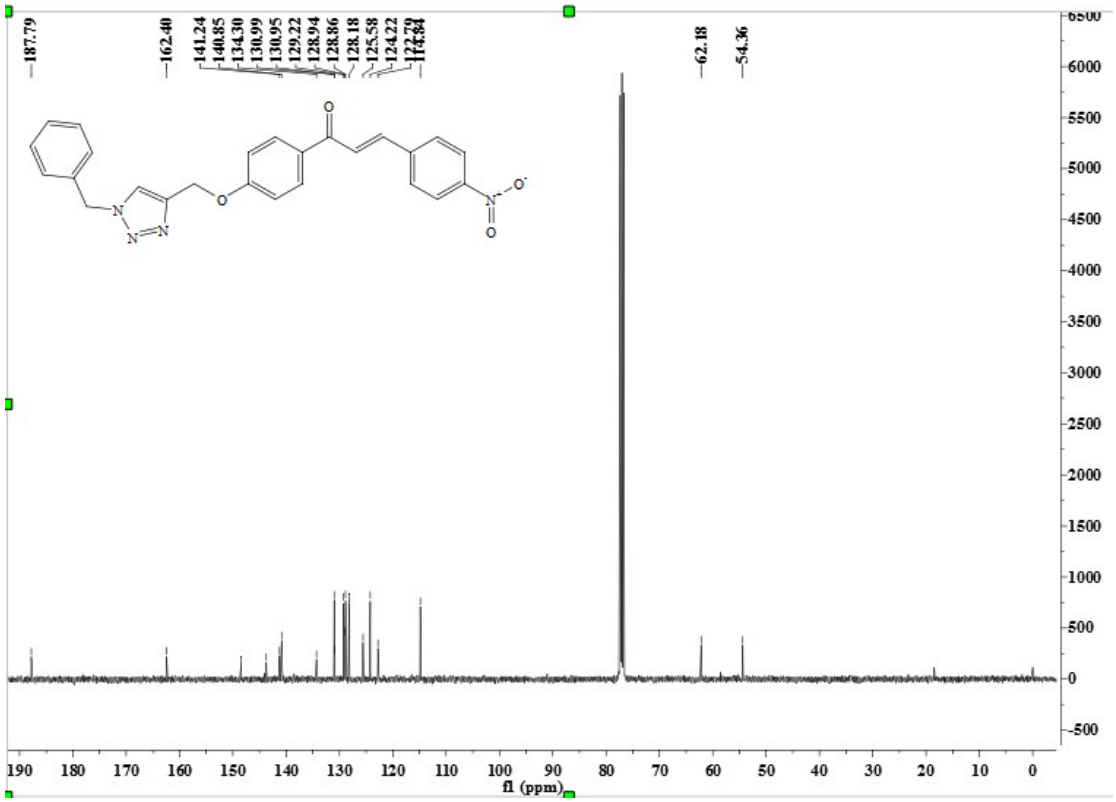


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (**9f**)

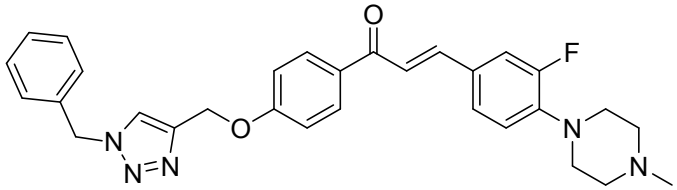


White solid, yield：89%, m.p：203.6~205.4 °C. purity: 98.93 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.09 – 8.00 (m, 2H), 7.79 (dd, *J* = 12.0, 9.9 Hz, 3H), 7.64 (d, *J* = 15.7 Hz, 1H), 7.56 (s, 1H), 7.38 (dt, *J* = 4.5, 2.4 Hz, 3H), 7.32 – 7.27 (m, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.79, 162.40, 148.48, 143.72, 141.24, 140.85, 134.30, 130.99, 130.95, 129.22, 128.94, 128.86, 128.18, 125.58, 124.22, 122.79, 114.84, 62.18, 54.36. HRMS (ESI) calcd for $C_{25}H_{20}N_4O_4$ [M+H]+: 441.1563, found: 441.1567.

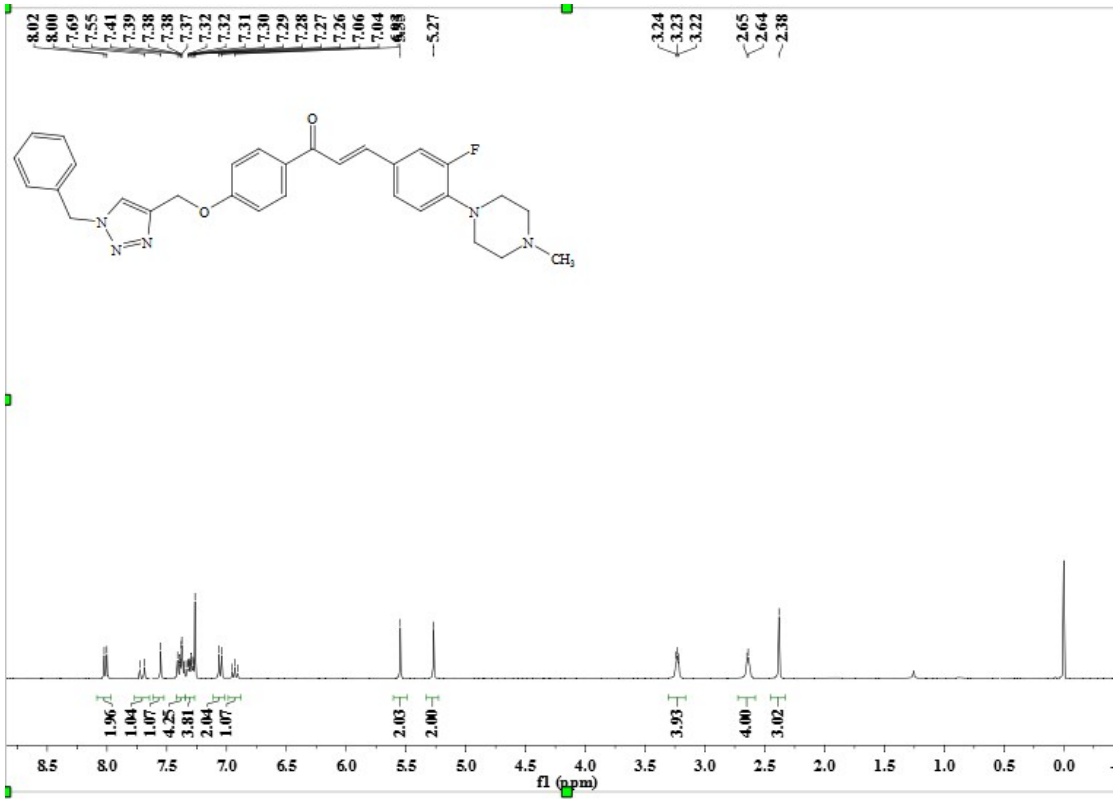


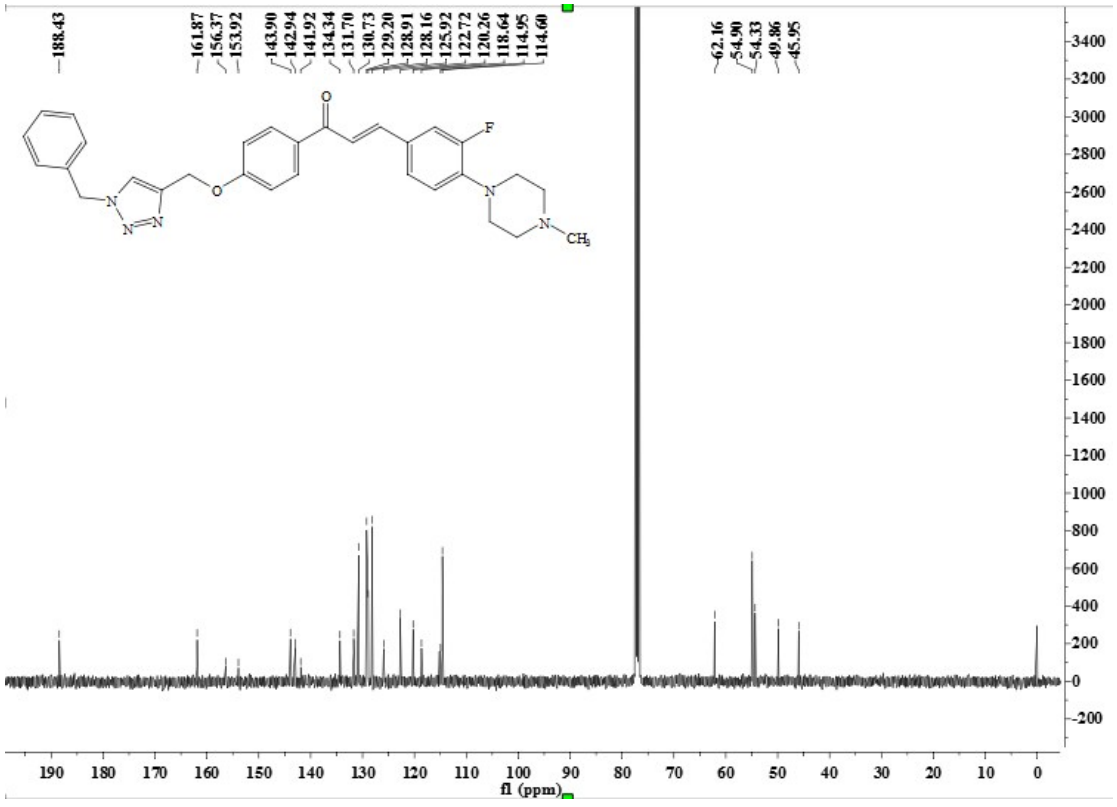


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)prop-2-en-1-one (**9g**)

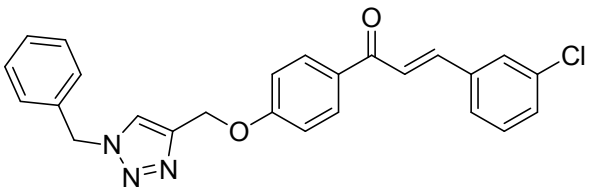


White solid, yield：71%, m.p：163.4~165.9 °C. purity: 96.38 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 15.5 Hz, 1H), 7.55 (s, 1H), 7.42 – 7.35 (m, 4H), 7.35 – 7.27 (m, 4H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.93 (t, *J* = 8.8 Hz, 1H), 5.55 (s, 2H), 5.27 (s, 2H), 3.31 – 3.16 (m, 4H), 2.64 (d, *J* = 4.4 Hz, 4H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.43, 161.87, 156.37, 153.92, 143.90, 142.94, 141.92, 134.34, 131.70, 130.73, 129.20, 128.91, 128.16, 125.92, 122.72, 120.26, 118.64, 114.95, 114.60, 62.16, 54.90, 54.33, 49.86, 45.95. HRMS (ESI) calcd for $C_{30}H_{30}FN_5O_2$ [M+H]+: 512.2462, found: 512.2463.

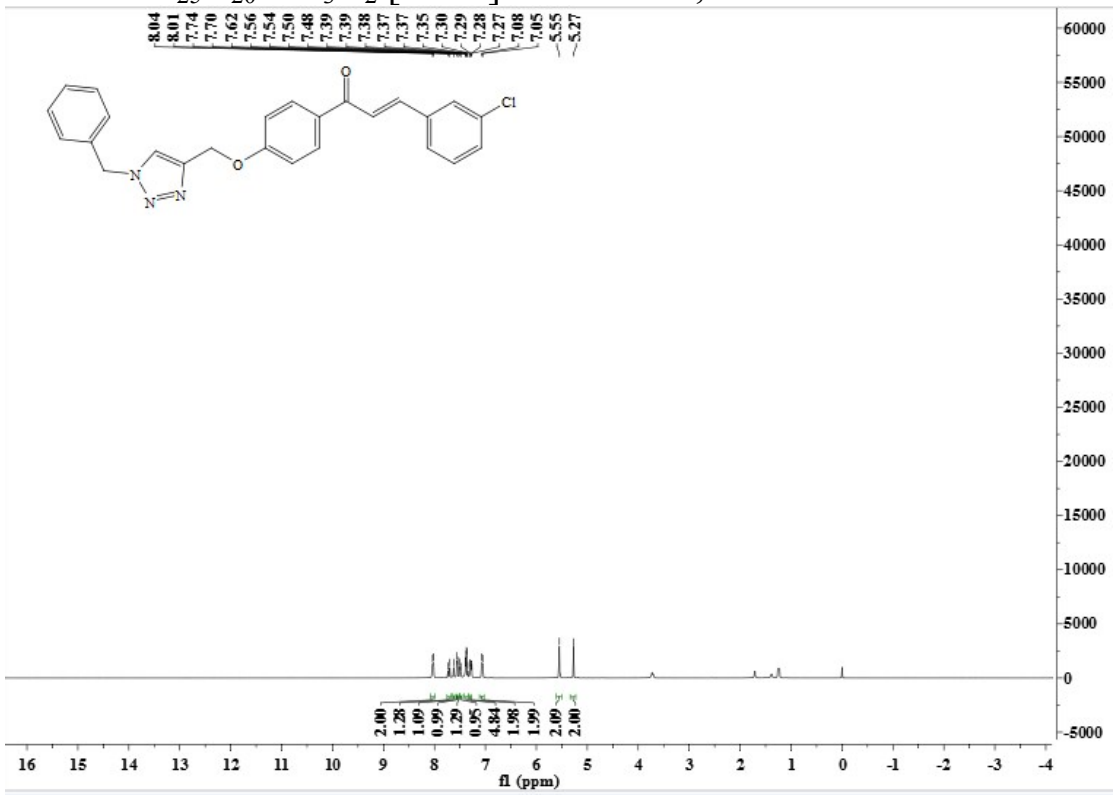


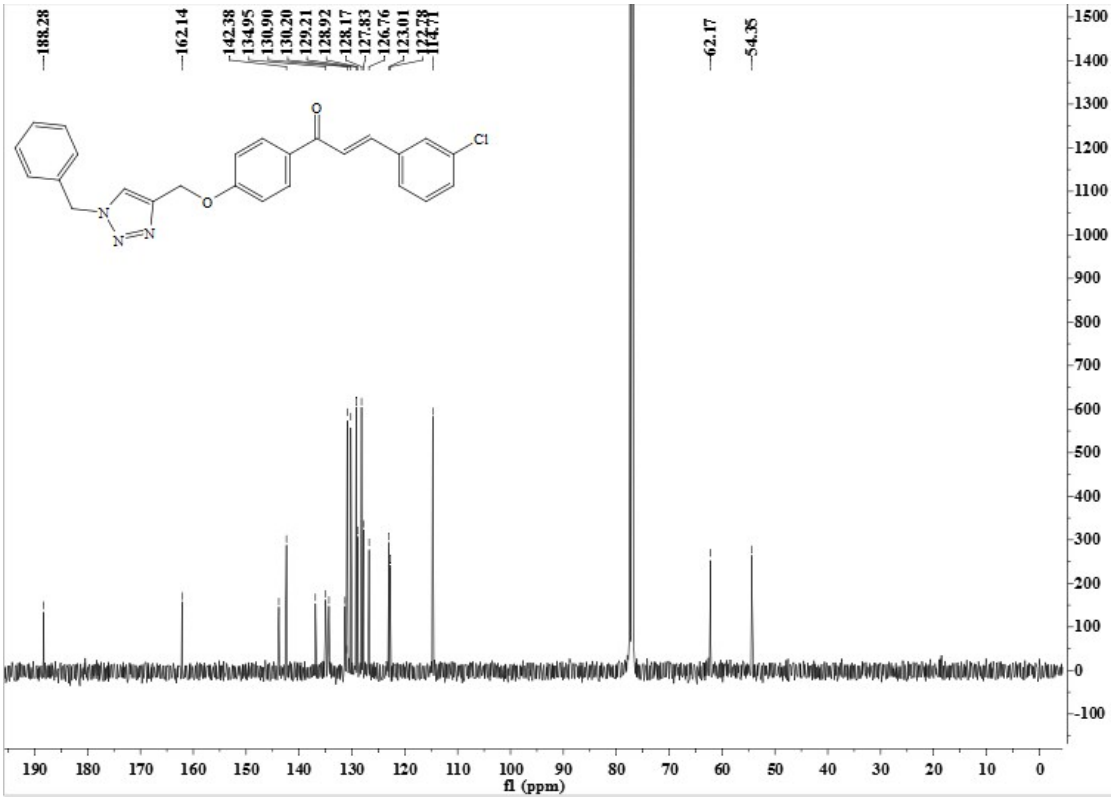


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3-chlorophenyl)prop-2-en-1-one (**9h**)

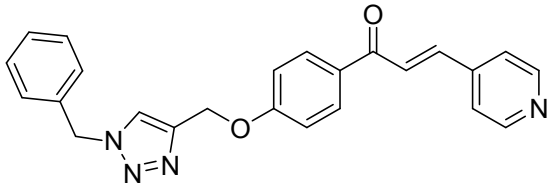


White solid, yield：68%, m.p：151.4~153.4 °C. purity: 97.62 %.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 15.7 Hz, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.52 (d, *J* = 15.7 Hz, 1H), 7.48 (s, 1H), 7.37 (dt, *J* = 10.3, 4.6 Hz, 5H), 7.28 (dd, *J* = 7.1, 2.1 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.28, 162.14, 143.82, 142.38, 136.89, 134.95, 134.34, 131.30, 130.99, 130.90, 130.20, 129.21, 128.92, 128.17, 127.83, 126.76, 123.01, 122.78, 114.71, 62.17, 54.35. HRMS (ESI) calcd for $C_{25}H_{20}ClN_3O_2$ [M+H]+: 430.1322, found: 430.1324.

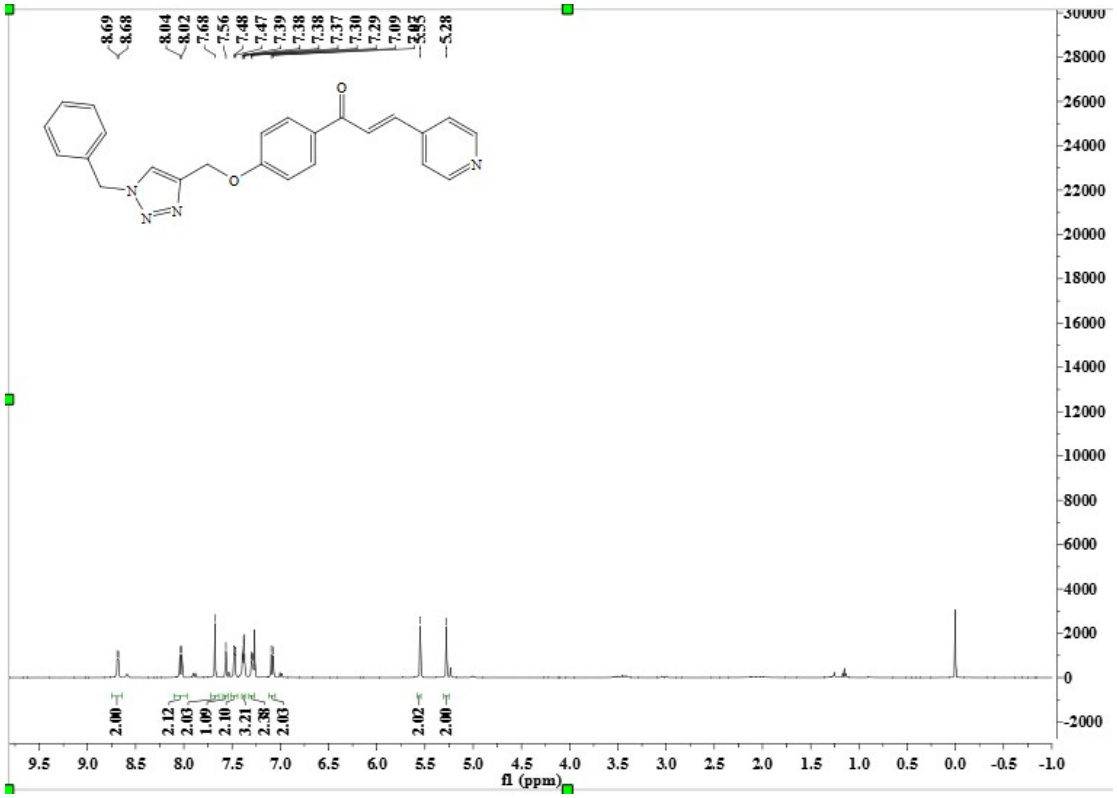


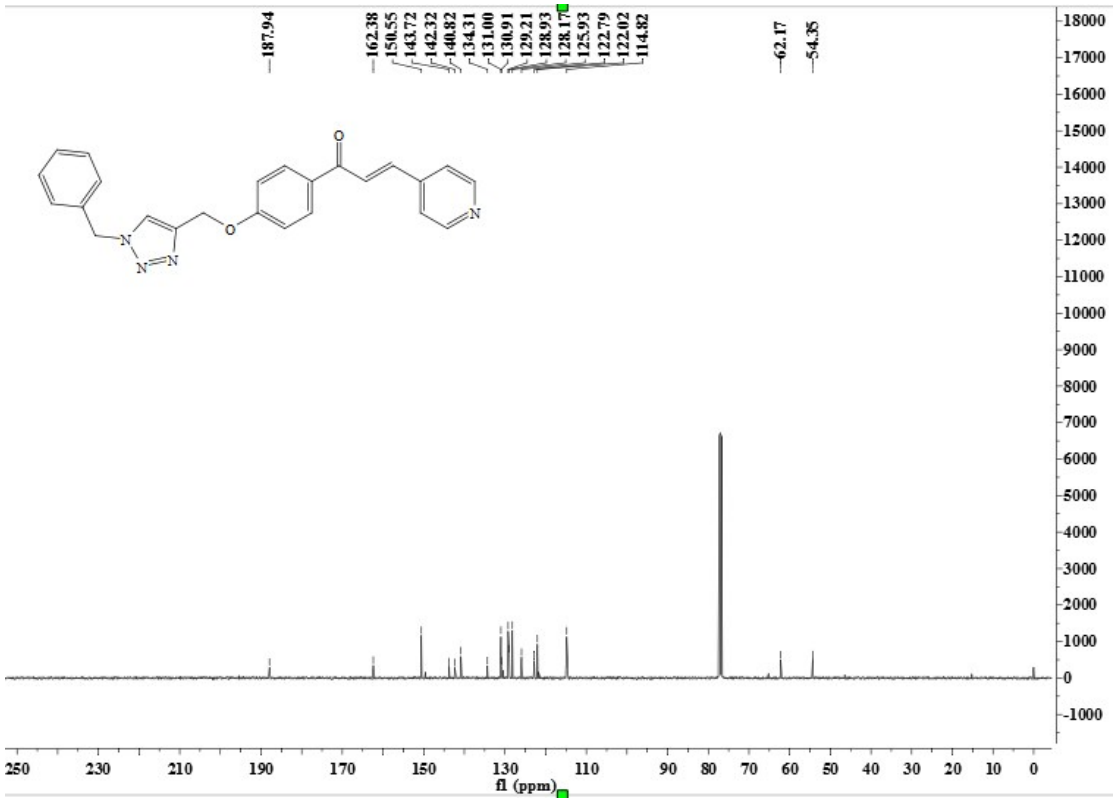


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(pyridin-4-yl)prop-2-en-1-one (**9i**)

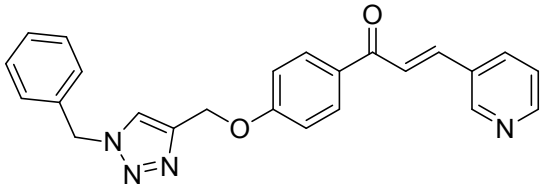


White solid, yield：65%, m.p：126.6~128.4 °C. purity: 98.74 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 5.9 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.68 (s, 2H), 7.56 (s, 1H), 7.47 (d, *J* = 6.0 Hz, 2H), 7.40 – 7.37 (m, 3H), 7.32 – 7.27 (m, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.94, 162.38, 150.55, 143.72, 142.32, 140.82, 134.31, 131.00, 130.91, 129.21, 128.93, 128.17, 125.93, 122.79, 122.02, 114.82, 62.17, 54.35. HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2$ [M+H]+: 397.1665, found: 397.1666.

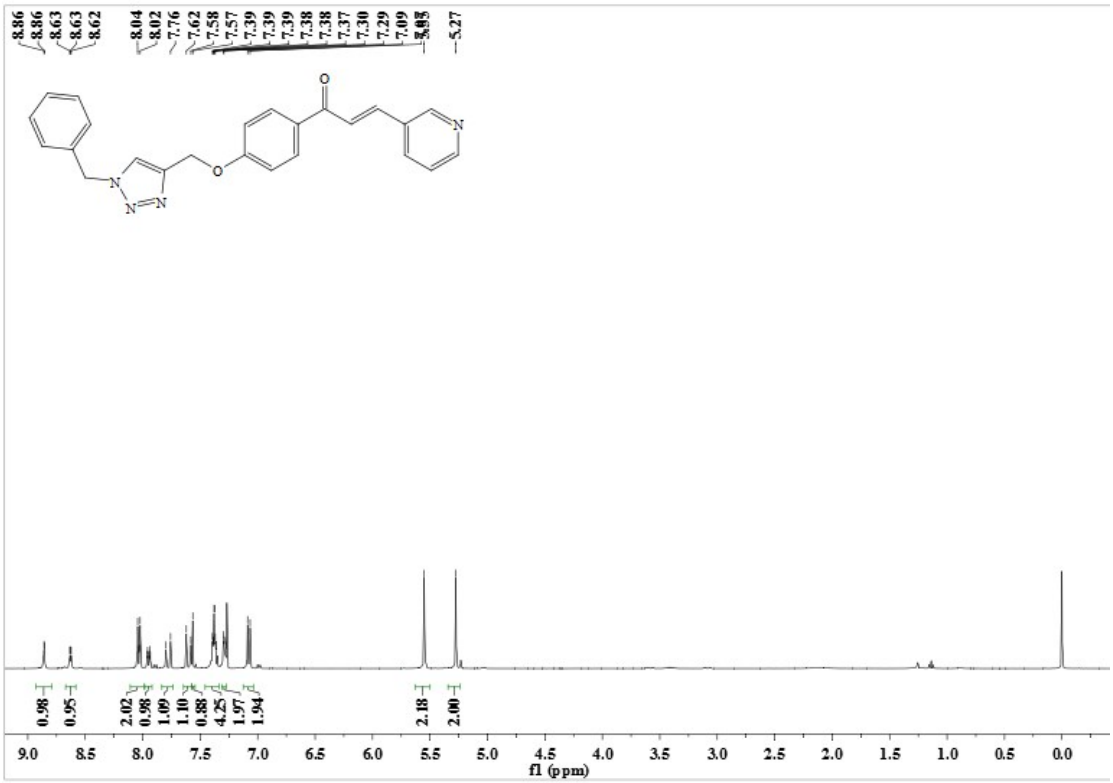


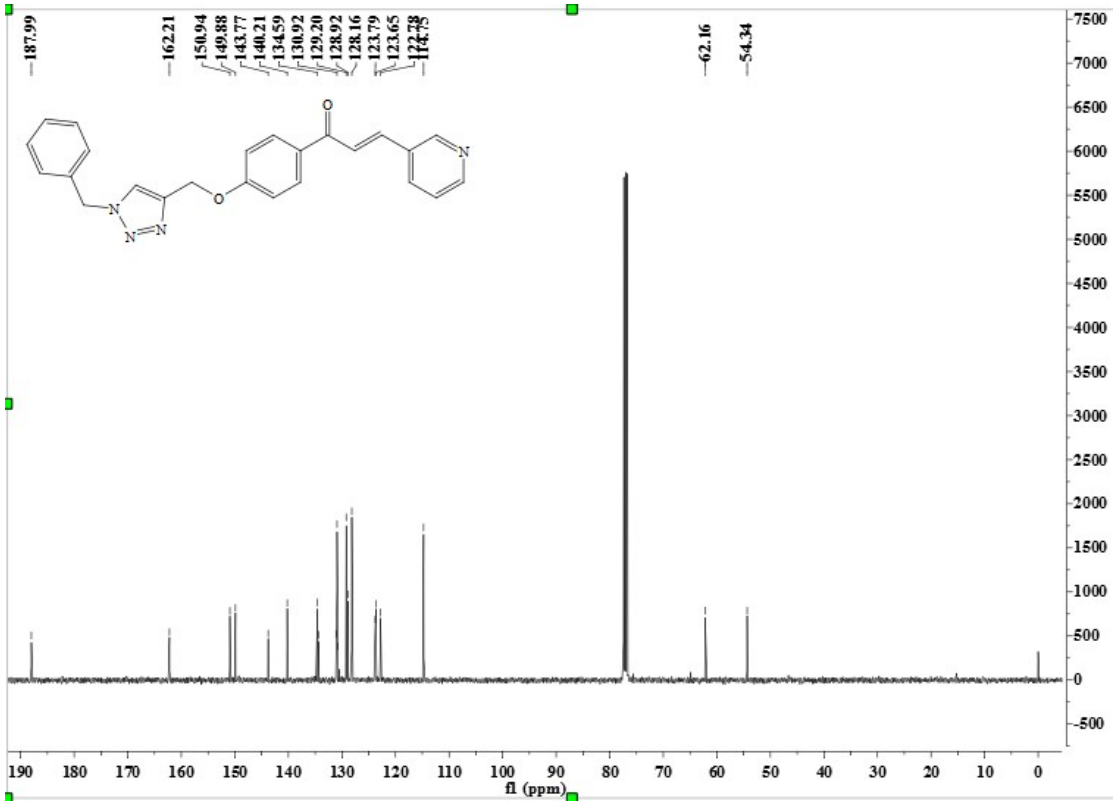


(*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(pyridin -3-yl)prop-2-en-1-one (**9j**)

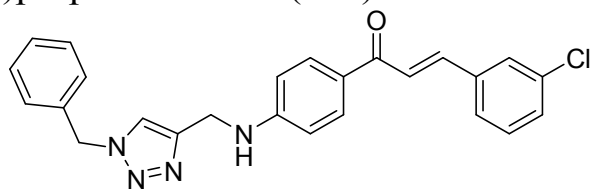


White solid, yield：79%, m.p：168.3~170.4 °C. purity: 98.57 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 1.5 Hz, 1H), 8.67 – 8.58 (m, 1H), 8.11 – 7.99 (m, 2H), 7.95 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.60 (d, *J* = 15.8 Hz, 1H), 7.57 (s, 1H), 7.46 – 7.33 (m, 4H), 7.29 (dd, *J* = 7.2, 2.3 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.99, 162.21, 150.94, 149.88, 143.77, 140.21, 134.59, 134.32, 131.12, 130.92, 130.83, 129.20, 128.92, 128.16, 123.79, 123.65, 122.78, 114.75, 62.16, 54.34. HRMS (ESI) calcd for $C_{24}H_{20}N_4O_2$ [M+H]+: 397.1665, found: 397.1665.

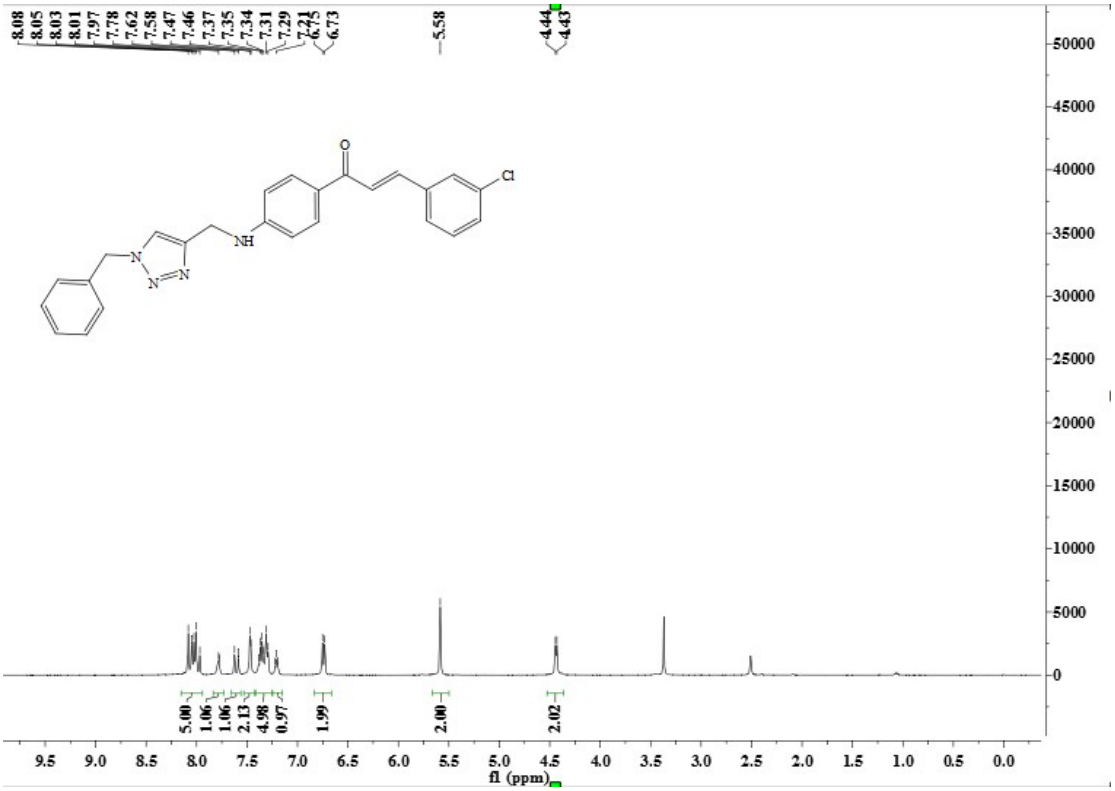


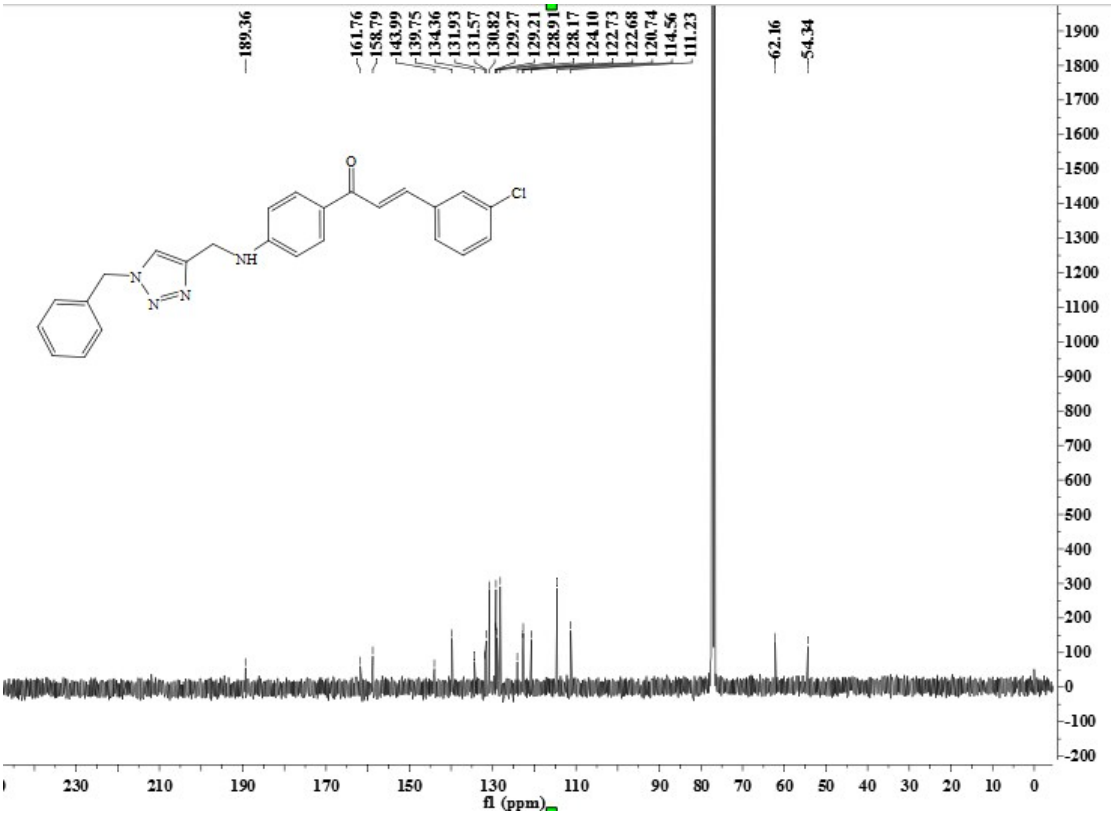


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(3-chlorophenyl)prop-2-en-1-one (**12a**)

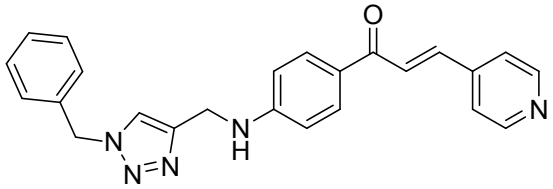


White solid, yield：80%, m.p：177.5~179.4 °C. purity: 96.90 %.^{1}H NMR (400 MHz, DMSO) δ 8.15 – 7.94 (m, 5H), 7.78 (d, *J* = 3.0 Hz, 1H), 7.60 (d, *J* = 15.6 Hz, 1H), 7.47 (d, *J* = 4.7 Hz, 2H), 7.34 (dt, *J* = 17.4, 7.1 Hz, 5H), 7.21 (t, *J* = 5.6 Hz, 1H, D_2O exchangeable), 6.74 (d, *J* = 8.7 Hz, 2H), 5.58 (s, 2H), 4.44 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.36, 161.76, 158.79, 143.99, 139.75, 134.36, 131.93, 131.57, 130.82, 129.27, 129.21, 128.91, 128.17, 124.10, 122.73, 122.68, 120.74, 114.56, 111.23, 62.16, 54.34. HRMS (ESI) calcd for $C_{25}H_{21}ClN_4O$ [M+H]+: 429.1482, found: 429.1485.

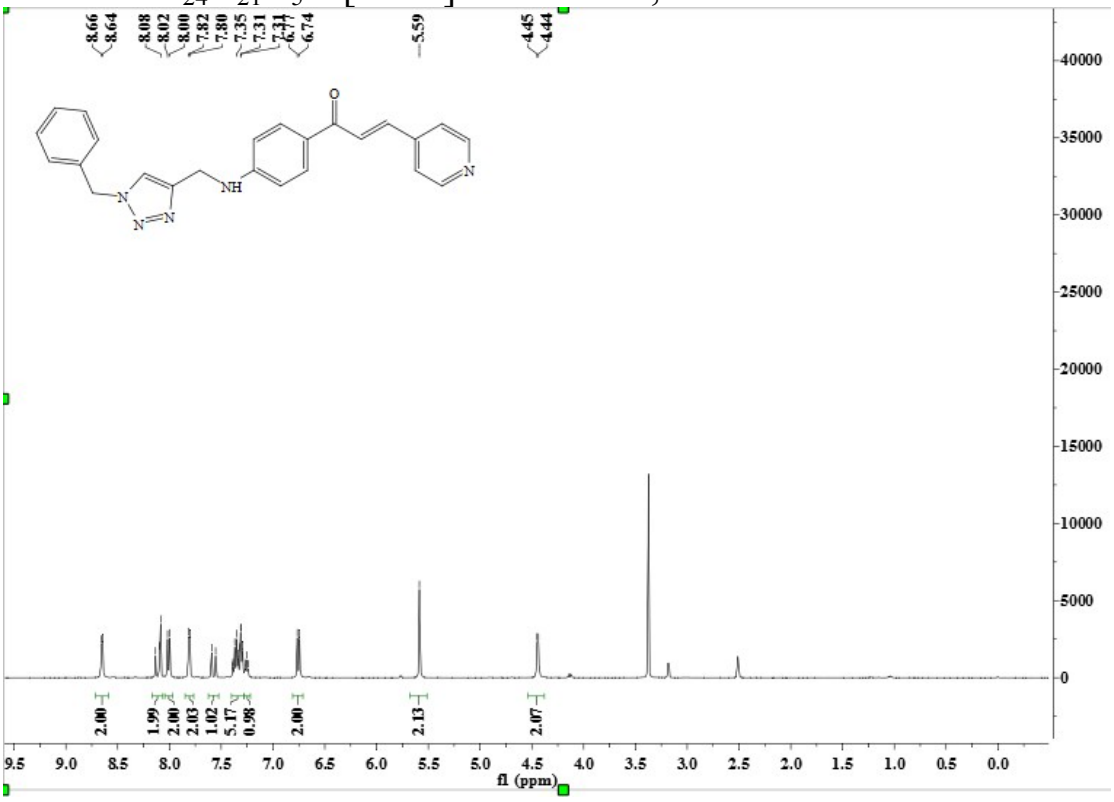


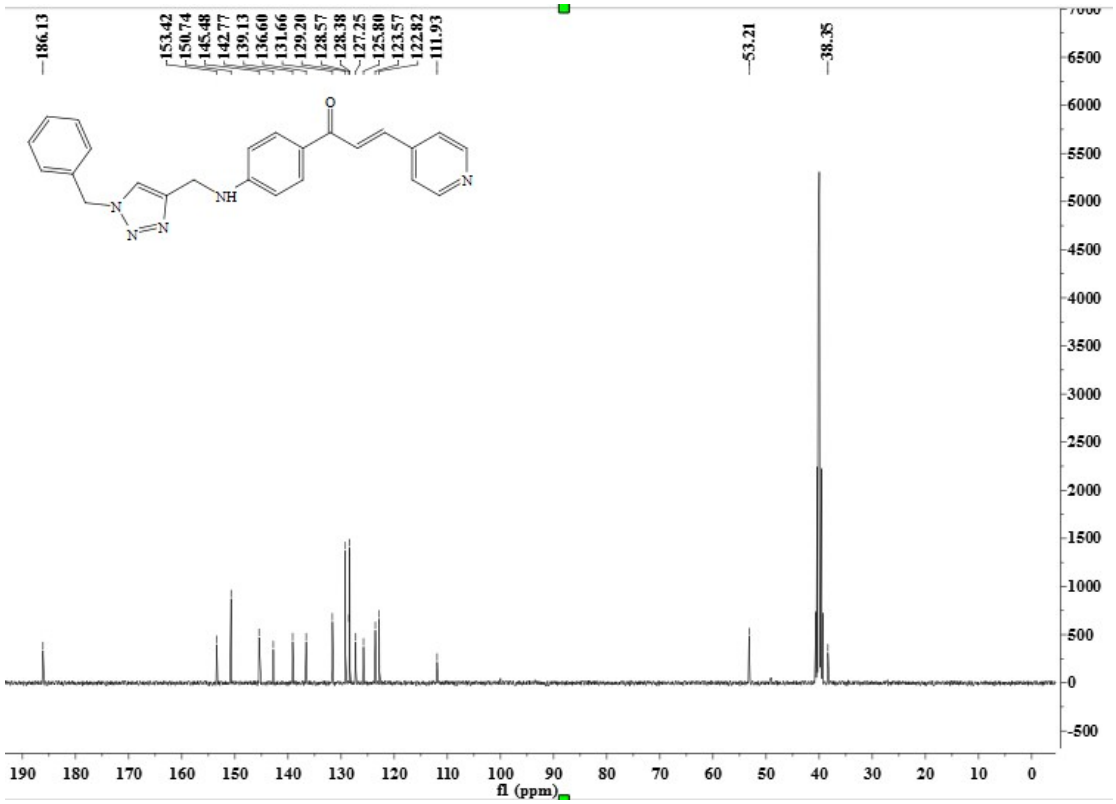


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(pyridin-4-yl)prop-2-en-1-one (**12b**)

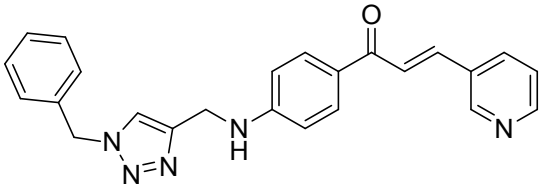


White solid, yield：71%, m.p：164.0~166.2 °C. purity: 99.14 %. ^{1}H NMR (400 MHz, DMSO) δ 8.65 (d, *J* = 5.5 Hz, 2H), 8.17 – 8.06 (m, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 5.8 Hz, 2H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.26 (t, *J* = 5.7 Hz, 1H, D_2O exchangeable), 6.75 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 2H), 4.44 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 186.13, 153.42, 150.74, 145.48, 142.77, 139.13, 136.60, 131.66, 129.20, 128.57, 128.38, 127.25, 125.80, 123.57, 122.82, 111.93, 53.21, 38.35. HRMS (ESI) calcd for $C_{24}H_{21}N_5O$ [M+H]+: 396.1824, found: 396.1825.

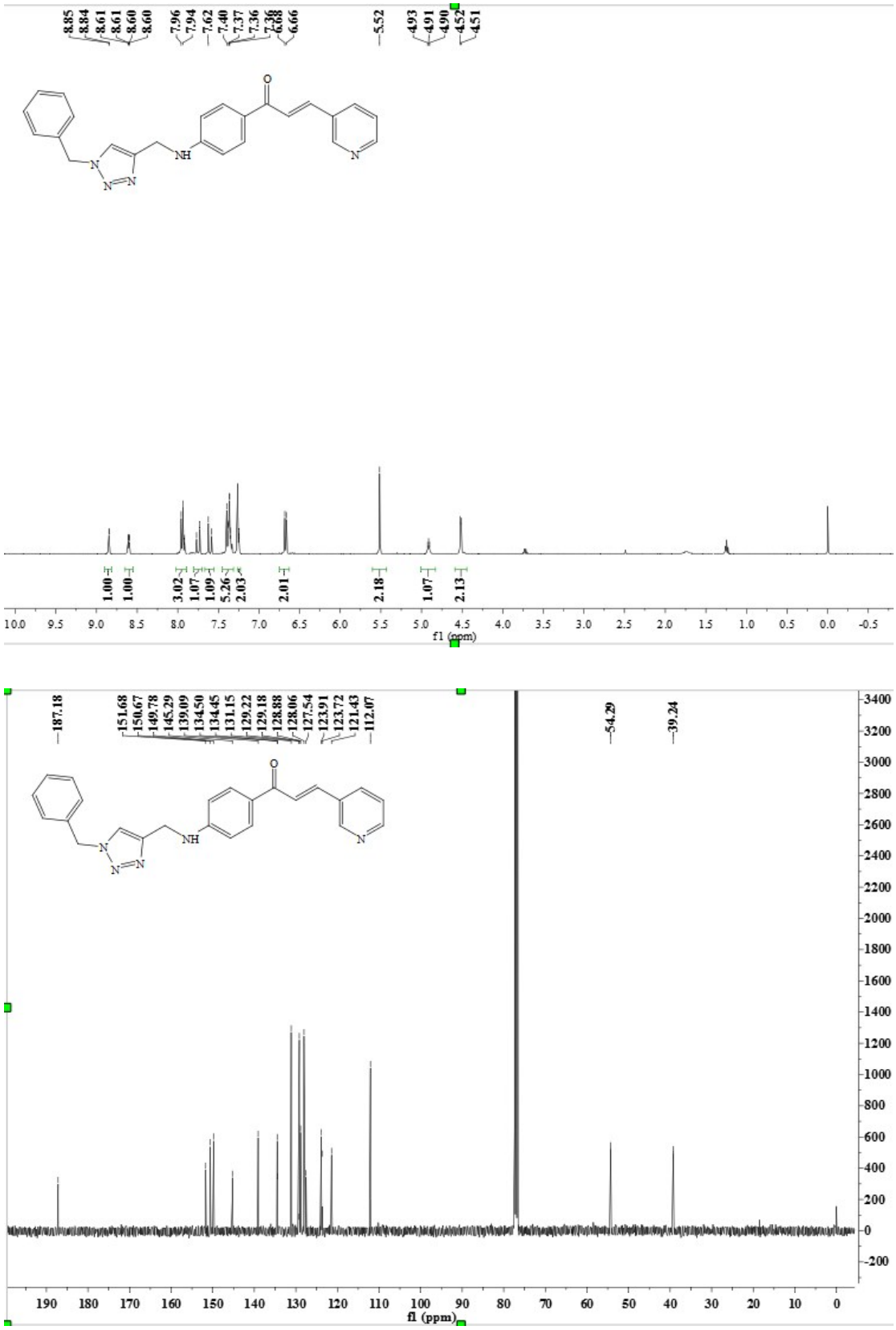




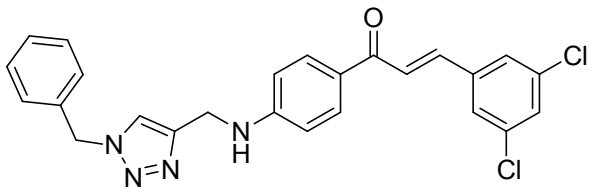
(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (**12c**)



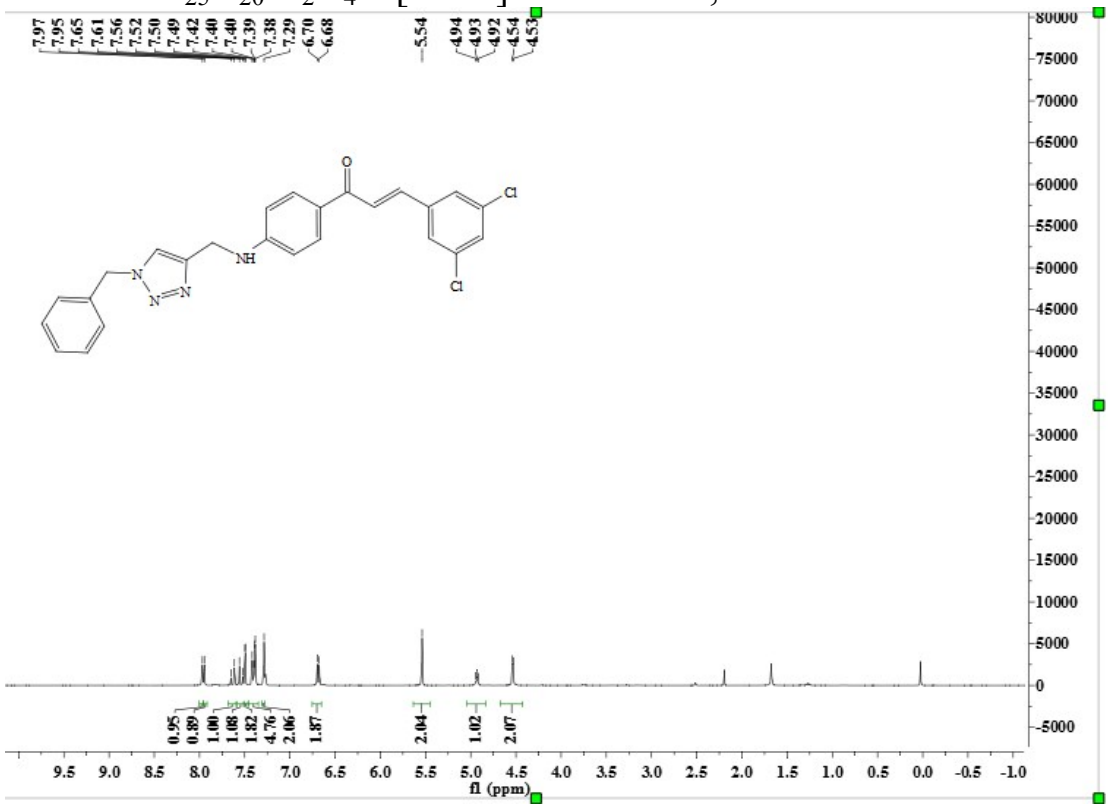
White solid, yield：78%, m.p：178.9~181.2 ^{o}C. purity: 98.92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 1.7 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.93 (dd, *J* = 11.6, 5.3 Hz, 3H), 7.75 (d, *J* = 15.7 Hz, 1H), 7.60 (d, *J* = 15.7 Hz, 1H), 7.46 – 7.31 (m, 5H), 7.25 (d, *J* = 1.9 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.52 (s, 2H), 4.91 (t, *J* = 5.2 Hz, 1H, D_2O exchangeable), 4.52 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.18, 151.68, 150.67, 149.78, 145.29, 139.09, 134.50, 134.45, 131.15, 129.22, 129.18, 128.88, 128.06, 127.54, 123.91, 123.72, 121.43, 112.07, 54.29, 39.24.

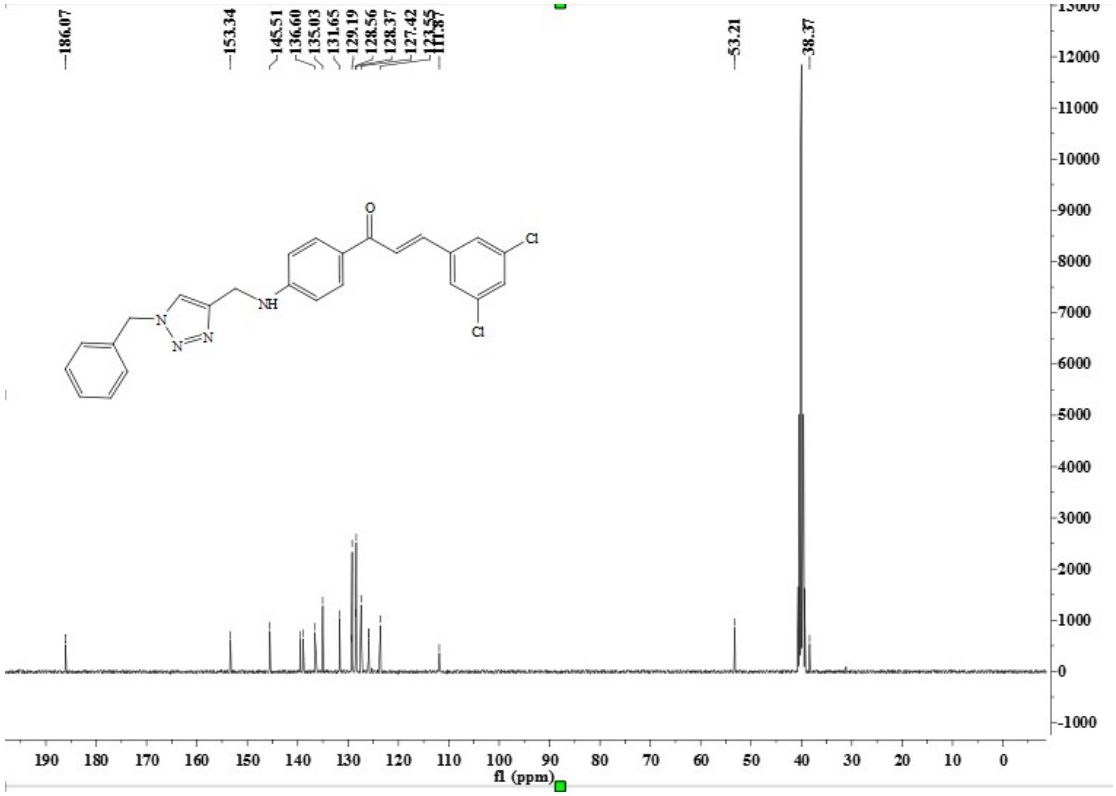


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(3,5-dichlorophenyl)prop-2-en-1-one (**12d**)

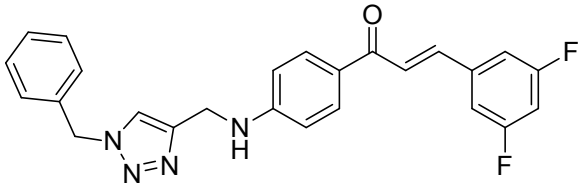


White solid, yield：69%, m.p：189.4~190.3 °C. purity: 98.84 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 2H), 7.46 – 7.35 (m, 5H), 7.29 (s, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.54 (s, 2H), 4.93 (t, *J* = 5.5 Hz, 1H, D_2O exchangeable), 4.53 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 186.07, 153.34, 145.51, 139.45, 138.90, 136.60, 135.03, 131.65, 129.29, 129.19, 128.56, 128.37, 127.42, 125.96, 125.89, 123.55, 111.87, 53.21, 38.37. HRMS (ESI) calcd for $C_{25}H_{20}Cl_2N_4O$ [M+H]+: 463.1092, found: 463.1093.

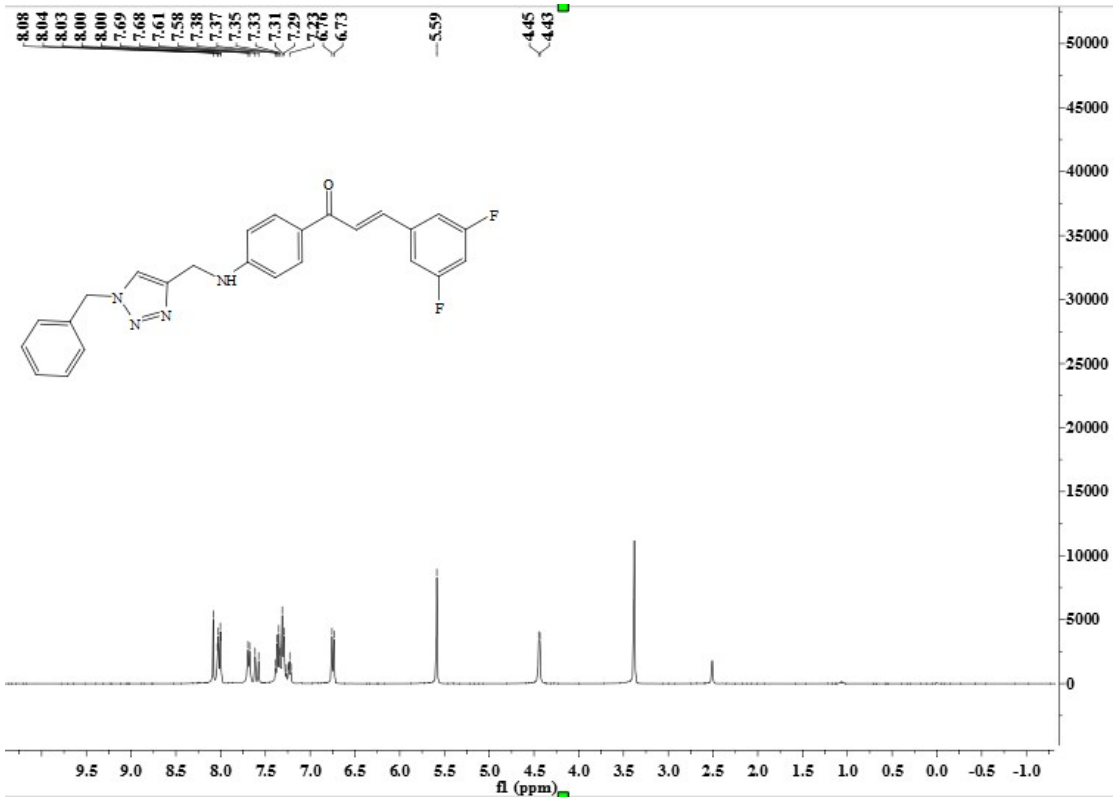


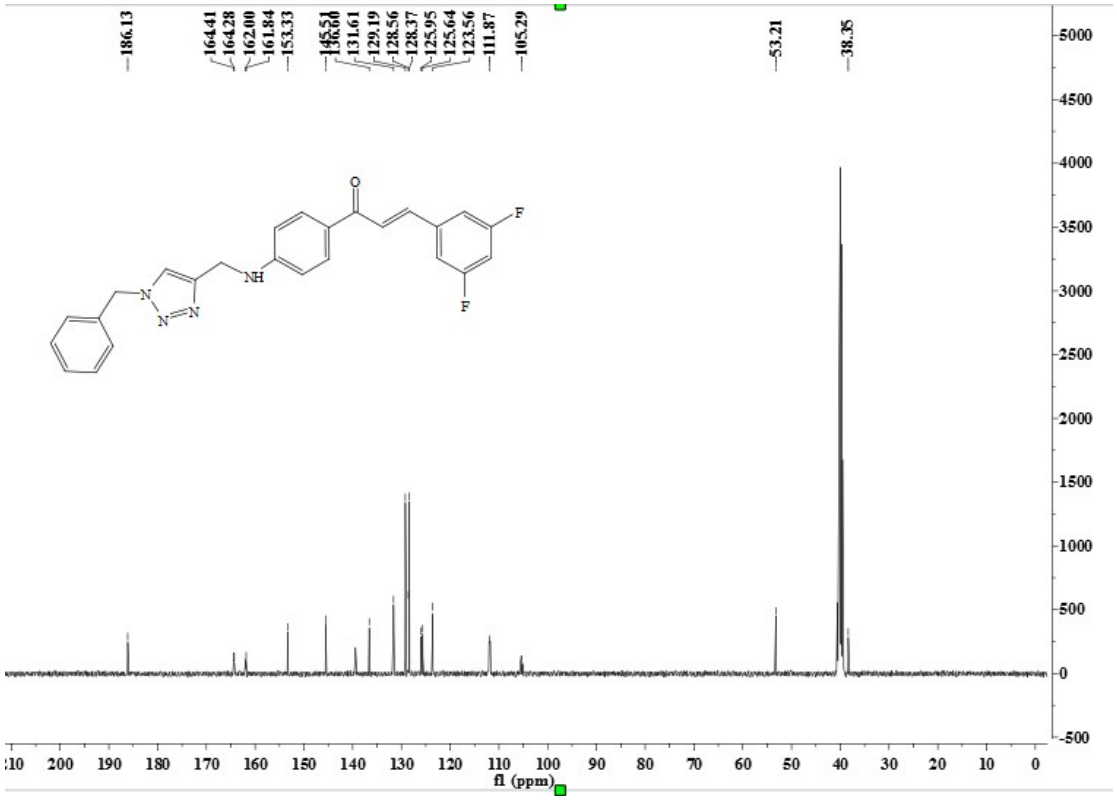


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(3,5-difluorophenyl)prop-2-en-1-one (**12e**)

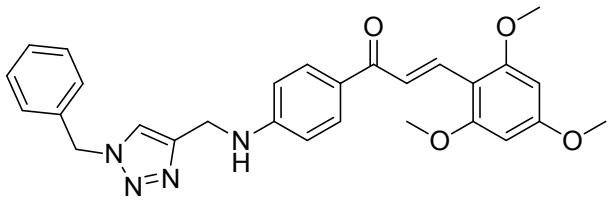


White solid, yield：82%, m.p：172.6~174.4 °C. purity: 97.45 %. ^{1}H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 8.02 (dd, *J* = 12.1, 3.2 Hz, 3H), 7.69 (d, *J* = 6.9 Hz, 2H), 7.60 (d, *J* = 15.5 Hz, 1H), 7.41 – 7.25 (m, 6H), 7.23 (t, *J* = 5.6 Hz, 1H, D_2O exchangeable), 6.75 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 2H), 4.44 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 186.13, 164.41, 164.28, 162.00, 161.84, 153.33, 145.51, 136.60, 131.61, 129.19, 128.56, 128.37, 125.95, 125.64, 123.56, 111.87, 105.29, 53.21, 38.35. HRMS (ESI) calcd for $C_{25}H_{20}F_2N_4O$ [M+H]+: 431.1683, found: 431.1684.

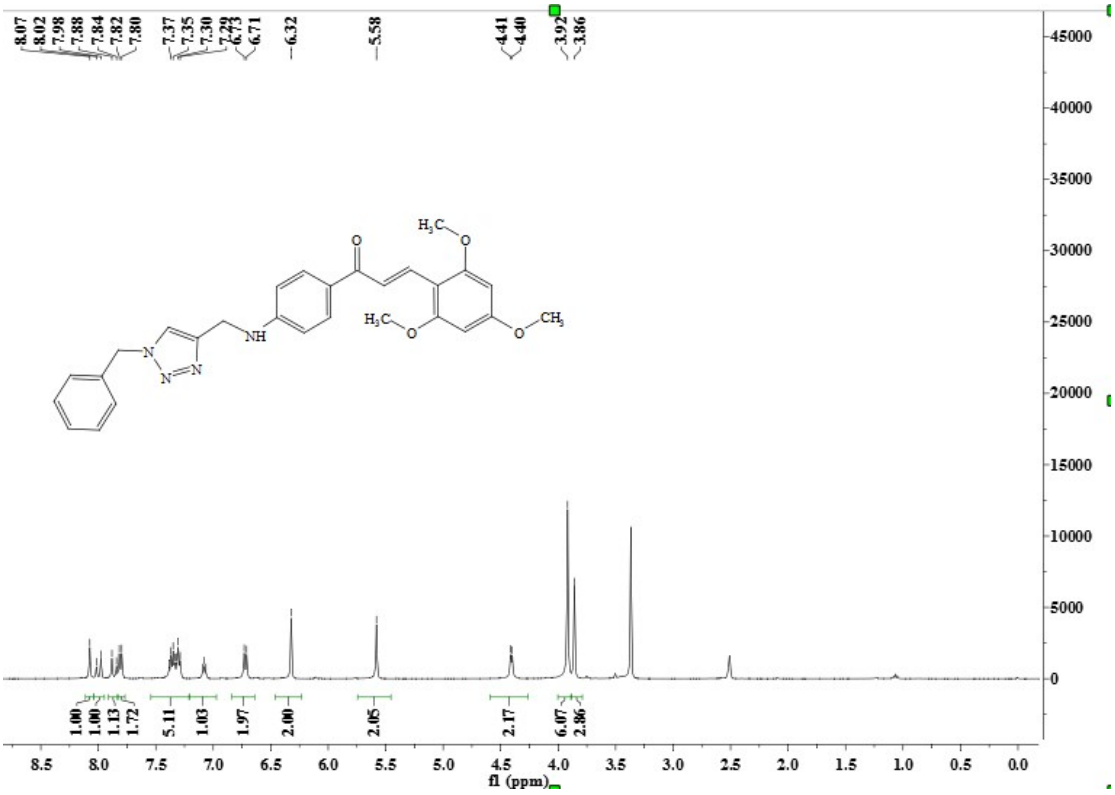


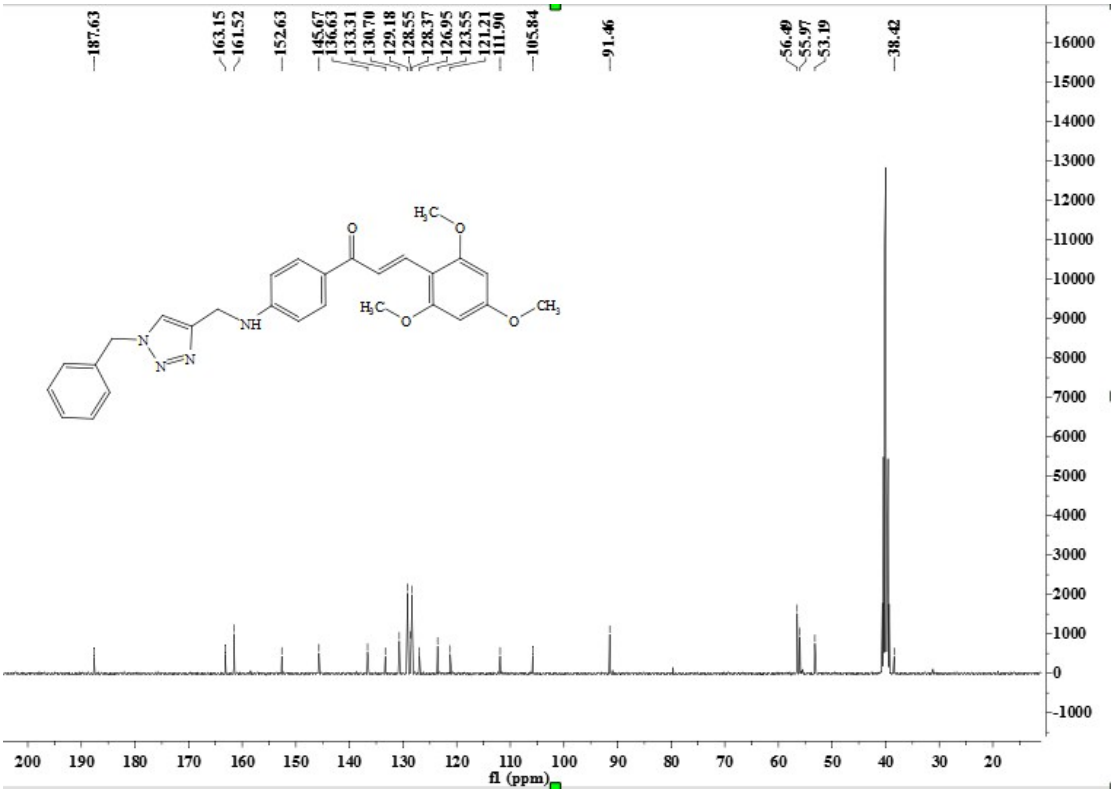


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (**12f**)

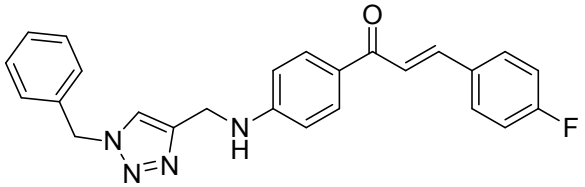


White solid, yield：73%, m.p：182.3~184.4 °C. purity: 99.13%. ^{1}H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 8.00 (d, *J* = 15.7 Hz, 1H), 7.86 (d, *J* = 15.7 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.20 (m, 5H), 7.08 (t, *J* = 5.6 Hz, 1H, D_2O exchangeable), 6.72 (d, *J* = 8.7 Hz, 2H), 6.32 (s, 2H), 5.58 (s, 2H), 4.41 (d, *J* = 5.6 Hz, 2H), 3.92 (s, 6H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 187.63, 163.15, 161.52, 152.63, 145.67, 136.63, 133.31, 130.70, 129.18, 128.55, 128.37, 126.95, 123.55, 121.21, 111.90, 105.84, 91.46, 56.49, 55.97, 53.19, 38.42. HRMS (ESI) calcd for $C_{28}H_{28}N_4O_4$ [M+H]+: 485.2189, found: 485.2188.

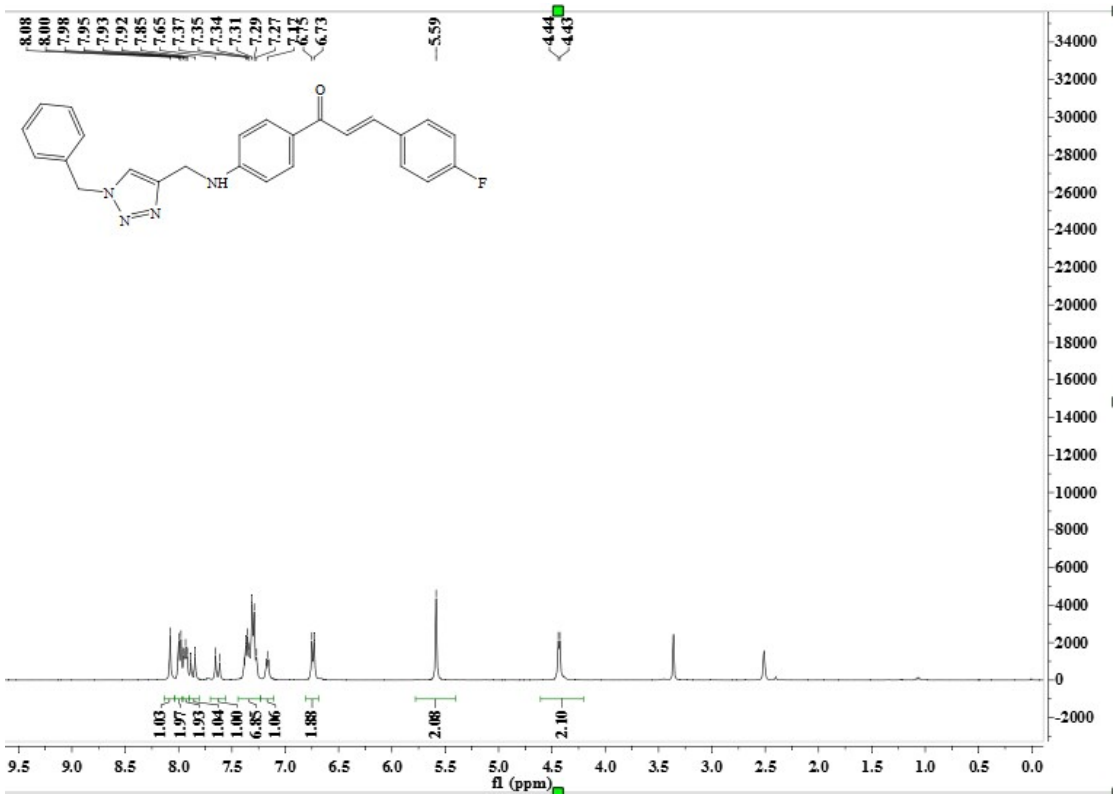


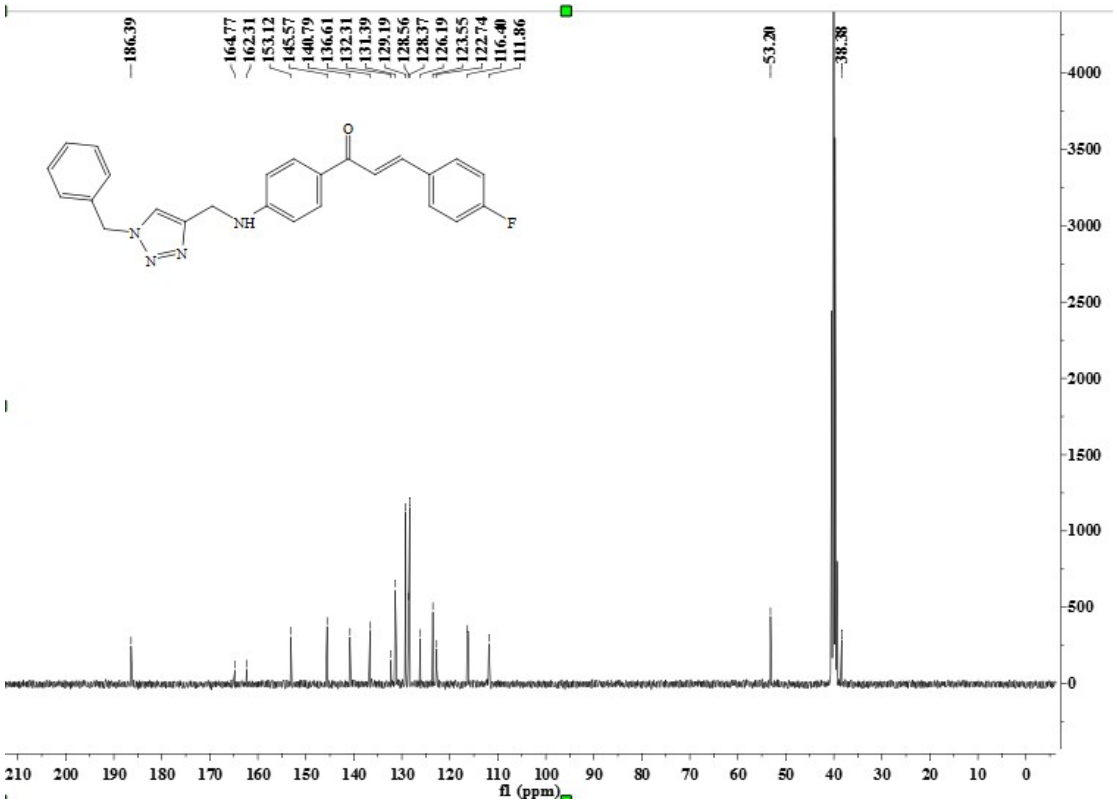


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**12g**)

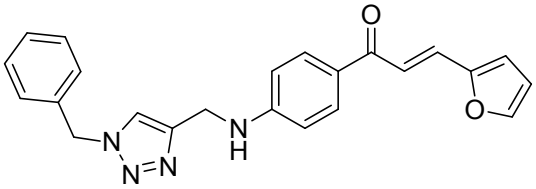


White solid, yield：72%, m.p：165.3~167.4 °C. purity: 97.98 %. ^{1}H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.97 – 7.90 (m, 2H), 7.87 (d, *J* = 15.5 Hz, 1H), 7.63 (d, *J* = 15.5 Hz, 1H), 7.44 – 7.23 (m, 7H), 7.17 (t, *J* = 5.3 Hz, 1H, D_2O exchangeable), 6.74 (d, *J* = 8.5 Hz, 2H), 5.59 (s, 2H), 4.43 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 186.39, 164.77, 162.31, 153.12, 145.57, 140.79, 136.61, 132.31, 131.39, 129.19, 128.56, 128.37, 126.19, 123.55, 122.74, 116.40, 111.86, 53.20, 38.38. HRMS (ESI) calcd for $C_{25}H_{21}FN_4O$ [M+H]+: 413.1778, found: 413.1779.

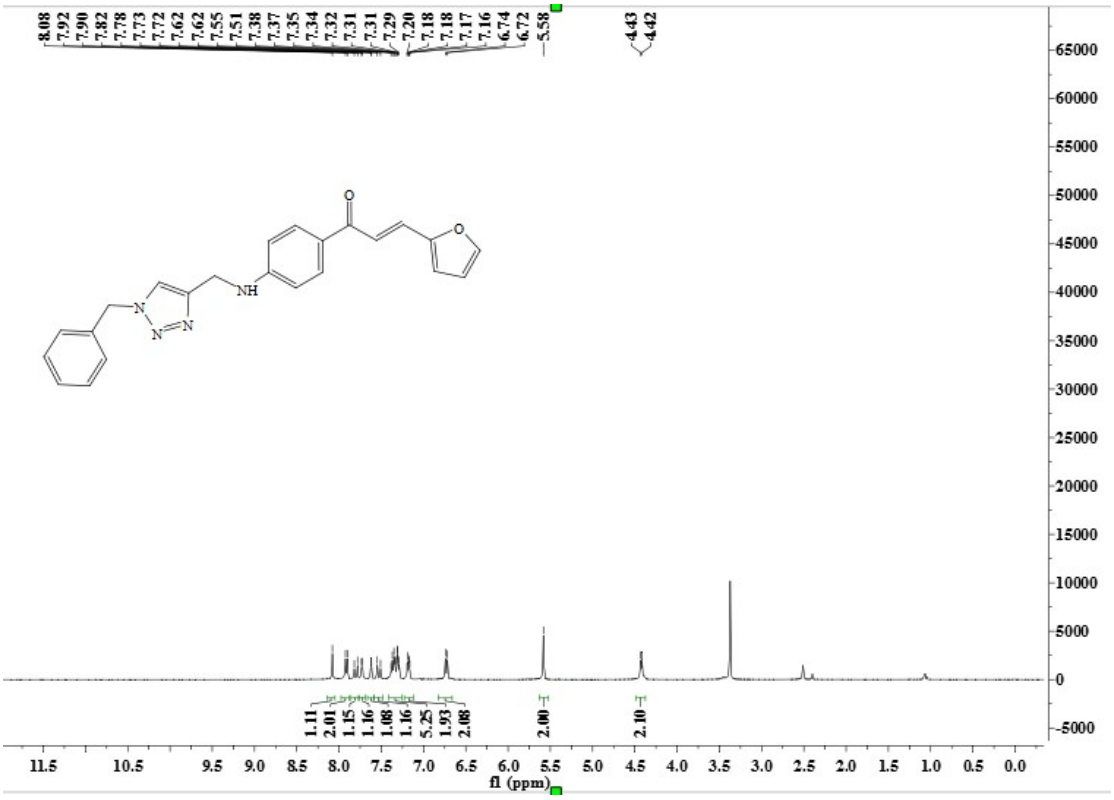


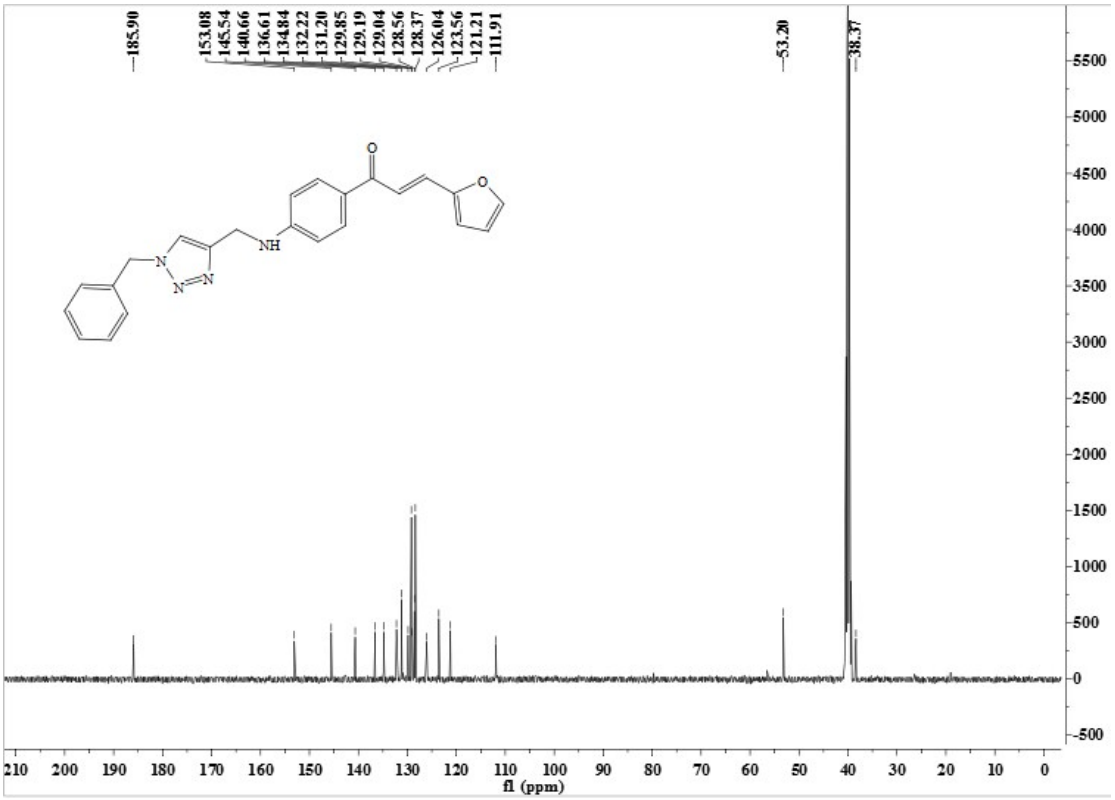


(*E*)-1-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(furan-2-yl)prop-2-en-1-one (**12h**)

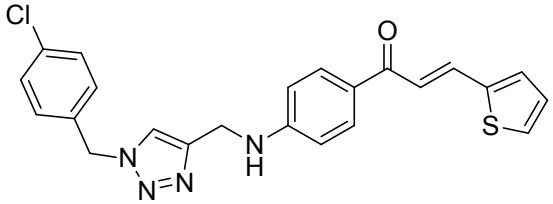


White solid, yield：48%, m.p：165.4~167.0 °C. purity: 97.99 %. ^{1}H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 15.2 Hz, 1H), 7.73 (d, *J* = 4.9 Hz, 1H), 7.62 (d, *J* = 3.3 Hz, 1H), 7.53 (d, *J* = 15.3 Hz, 1H), 7.33 (ddd, *J* = 12.0, 10.9, 6.6 Hz, 5H), 7.23 – 7.12 (m, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.58 (s, 2H), 4.42 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 185.90, 153.08, 145.54, 140.66, 136.61, 134.84, 132.22, 131.20, 129.85, 129.19, 129.04, 128.56, 128.37, 126.04, 123.56, 121.21, 111.91, 53.20, 38.37. HRMS (ESI) calcd for $C_{23}H_{20}N_4O_2$ [M+H]+: 385.1665, found: 385.1667.

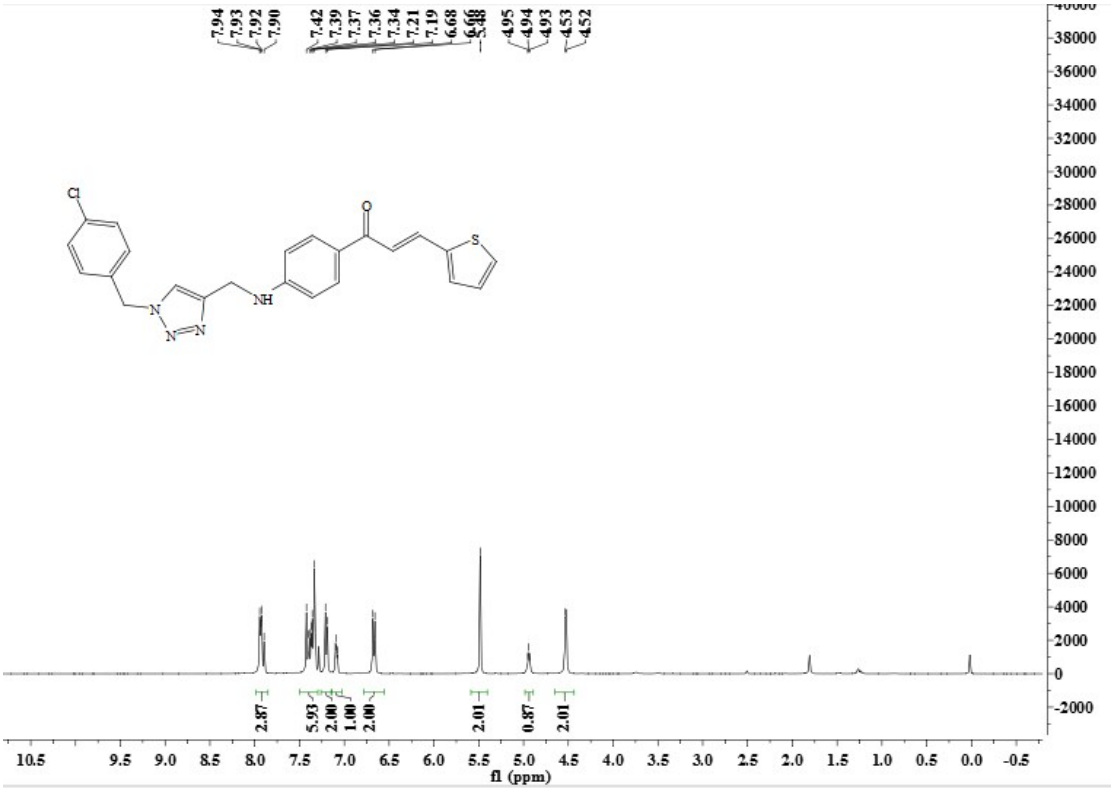


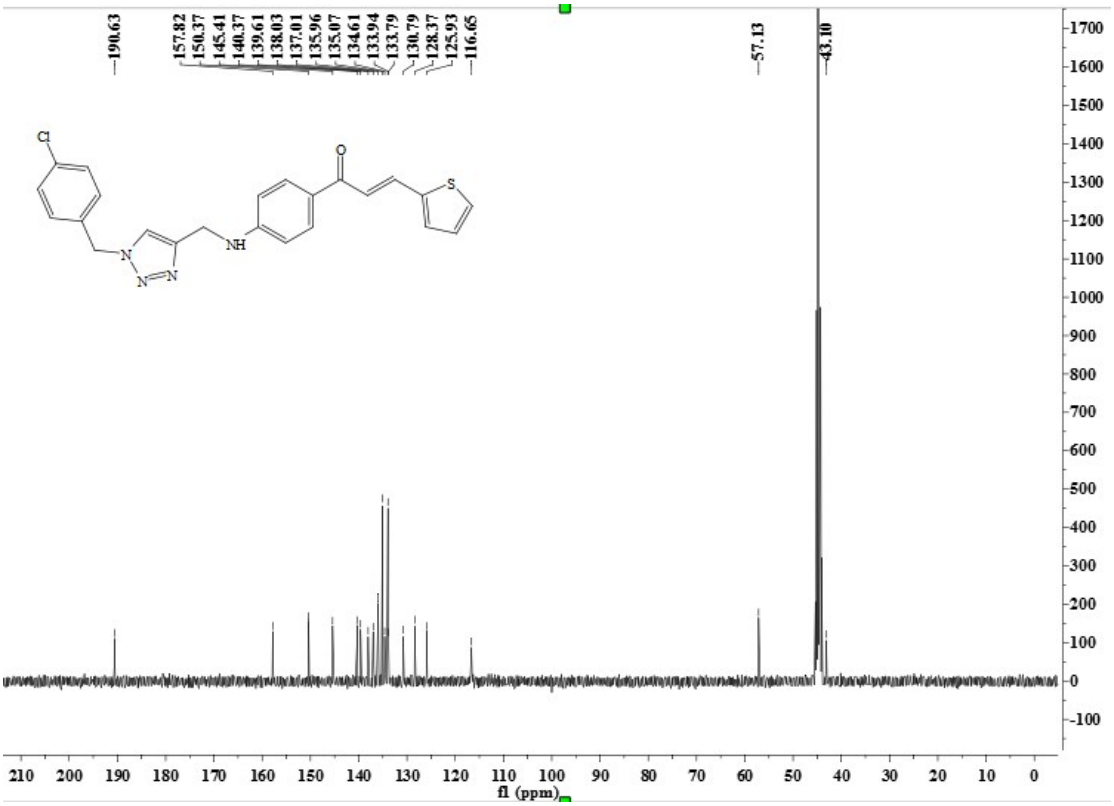


(*E*)-1-(4-(((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino) phenyl)-3-(thiophen-2-yl)prop-2-en-1-one (**12i**)

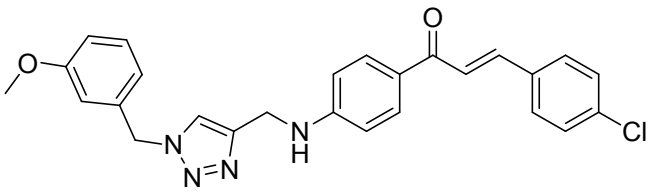


White solid, yield：69%, m.p：159~160 ^{o}C. purity: 98.05 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 11.7, 8.0 Hz, 3H), 7.50 – 7.29 (m, 6H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.03 (m, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 5.48 (s, 2H), 4.94 (t, *J* = 5.4 Hz, 1H, D_2O exchangeable), 4.53 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.63, 157.82, 150.37, 145.41, 140.37, 139.61, 138.03, 137.01, 135.96, 135.07, 134.61, 133.94, 133.79, 130.79, 128.37, 125.93, 116.65, 57.13, 43.10. HRMS (ESI) calcd for $C_{23}H_{19}ClN_4OS$ [M+H]+: 435.1046, found: 435.1044.

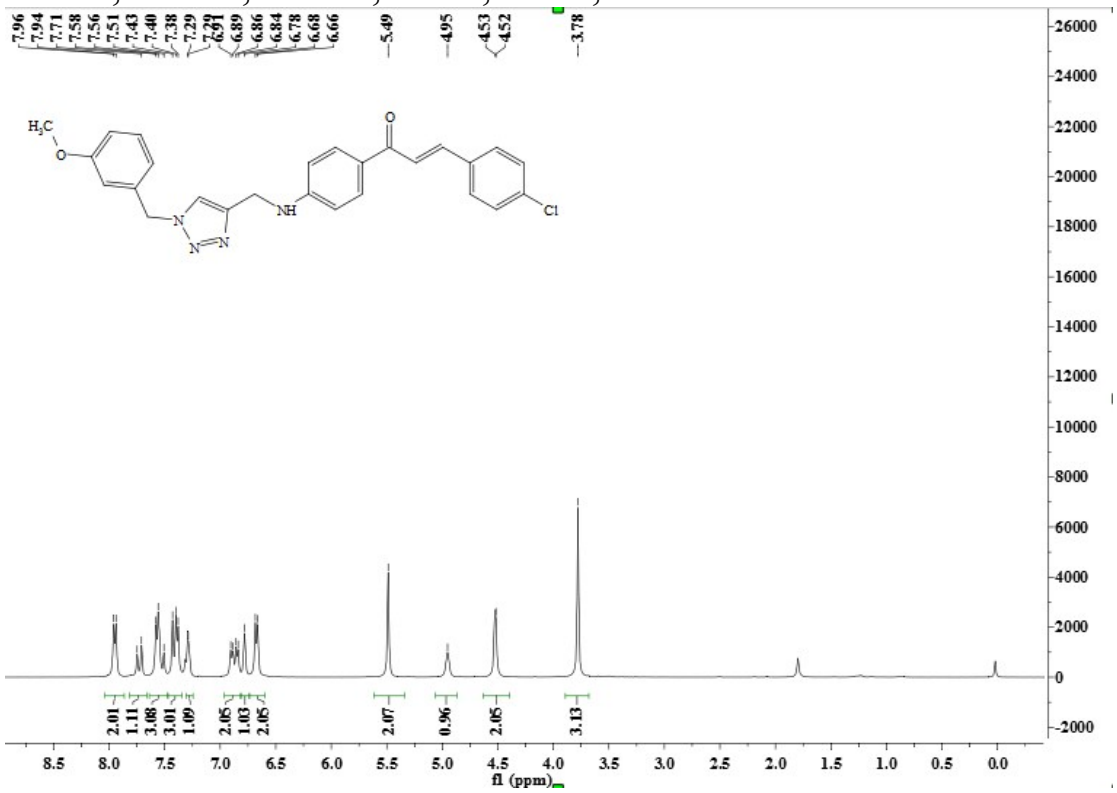


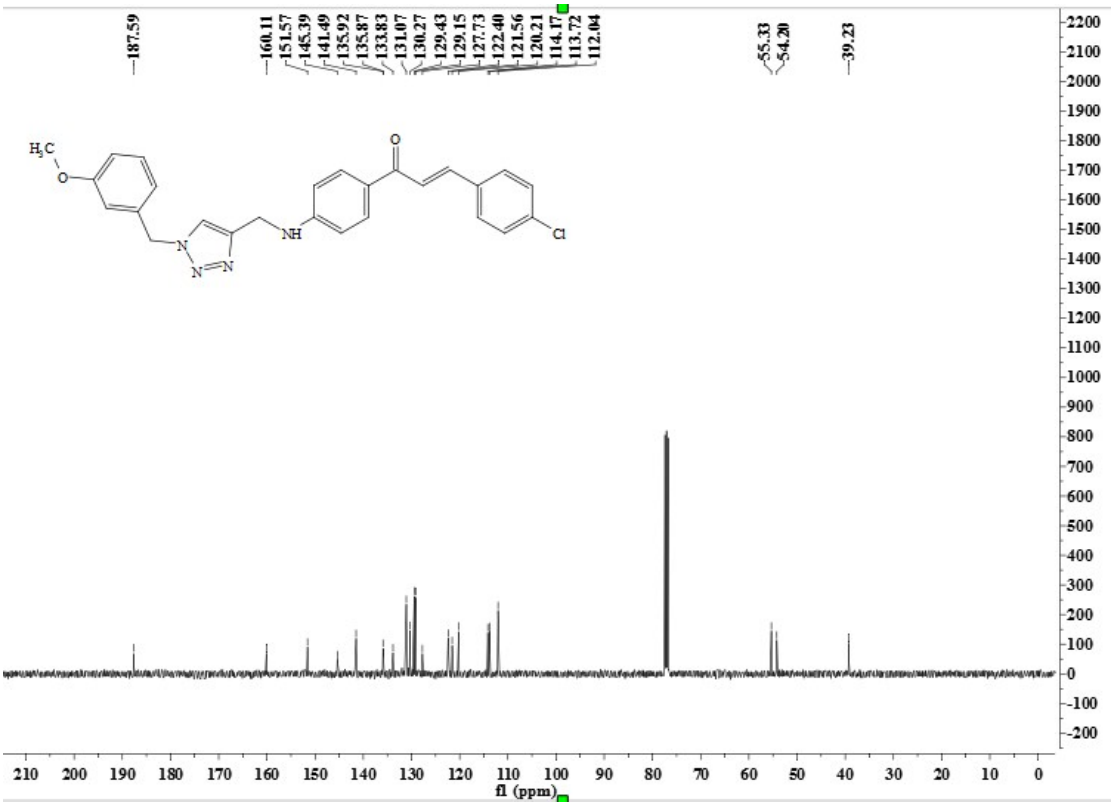


(*E*)-3-(4-chlorophenyl)-1-(4-(((1-(3-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)prop-2-en-1-one (**12j**)

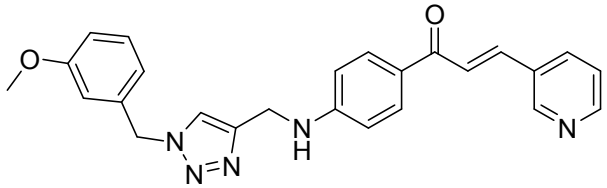


White solid, yield：51%, m.p：145.7~147.3 °C. purity: 97.83 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.55 (t, *J* = 14.4 Hz, 3H), 7.47 – 7.34 (m, 3H), 7.29 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 19.0, 7.5 Hz, 2H), 6.78 (s, 1H), 6.67 (d, *J* = 8.1 Hz, 2H), 5.49 (s, 2H), 4.95 (s, 1H, D_2O exchangeable), 4.52 (d, *J* = 4.7 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.59, 160.11, 151.57, 145.39, 141.49, 135.92, 135.87, 133.83, 131.07, 130.27, 129.43, 129.15, 127.73, 122.40, 121.56, 120.21, 114.17, 113.72, 112.04, 55.33, 54.20, 39.23.

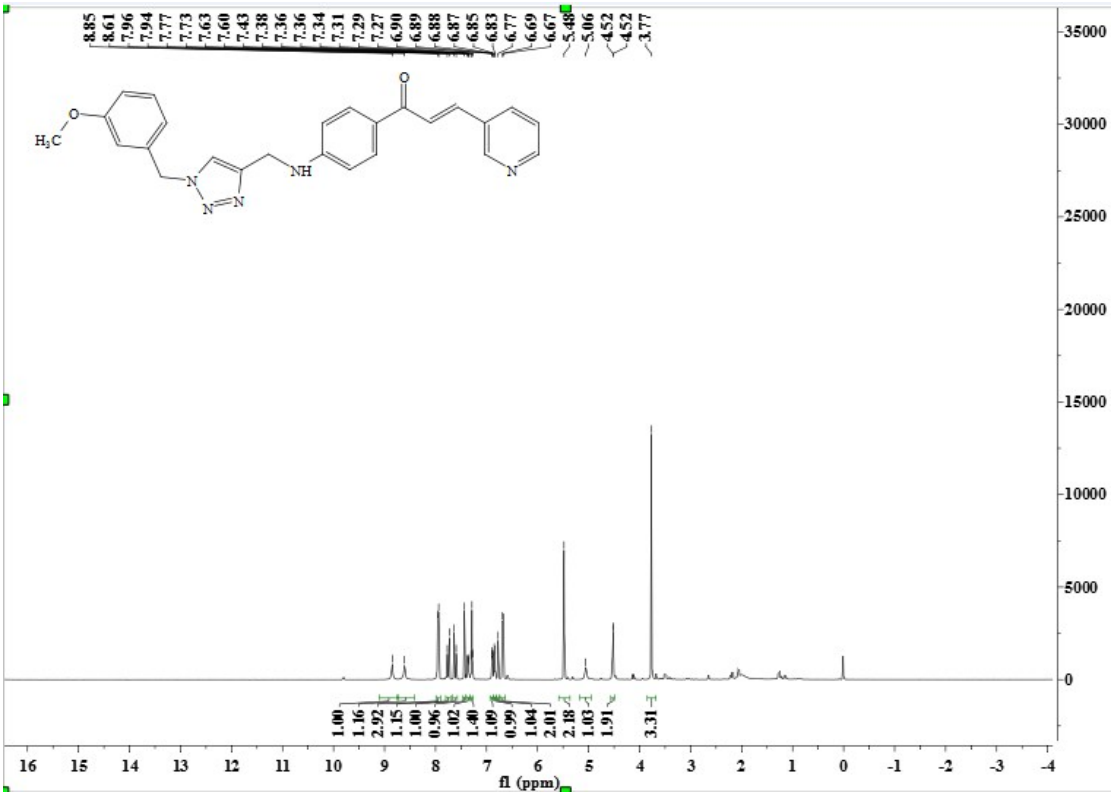


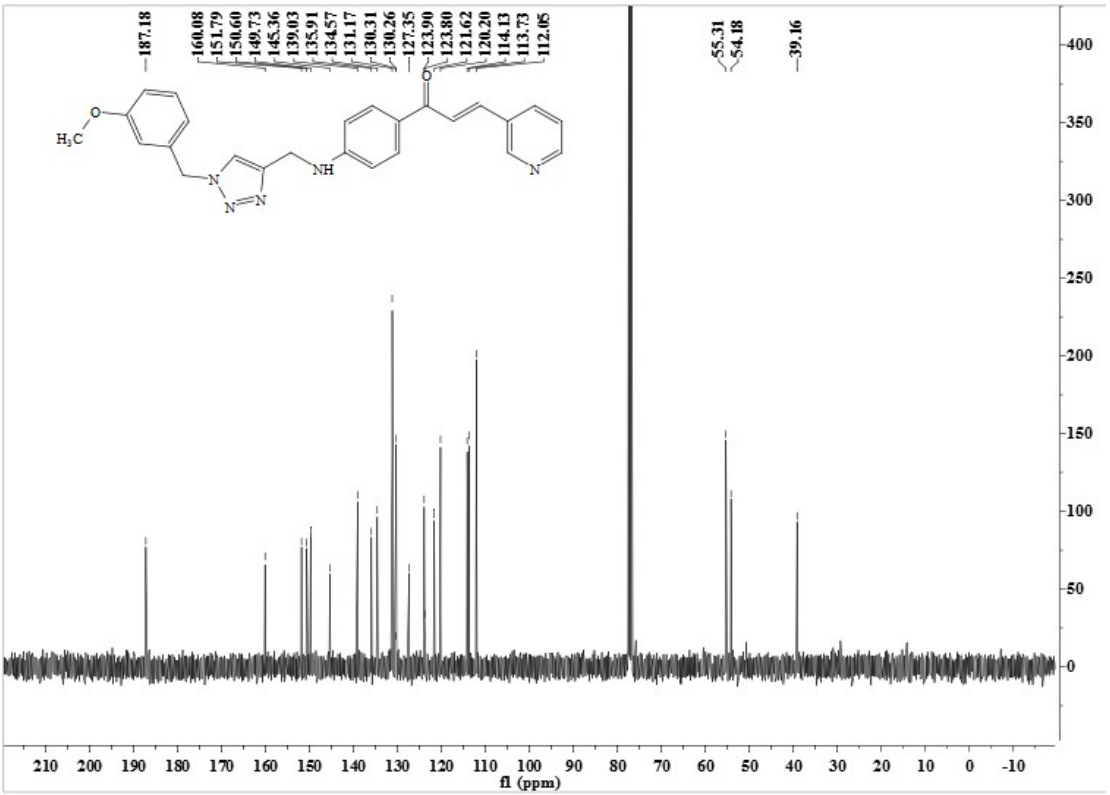


(*E*)-1-(4-(((1-(3-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl) amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (**12k**)

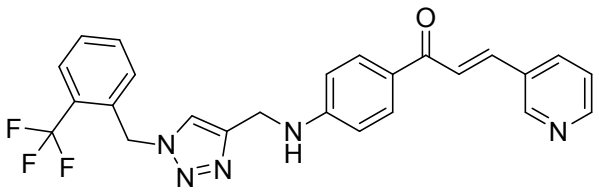


yellow liquid, yield：50%. m.p：179.7~180.3 °C purity: 99.03 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.61 (s, 1H), 7.95 (d, *J* = 8.7 Hz, 3H), 7.75 (d, *J* = 15.8 Hz, 1H), 7.61 (d, *J* = 15.7 Hz, 1H), 7.43 (s, 1H), 7.36 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.77 (s, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 5.48 (s, 2H), 5.06 (s, 1H), 4.52 (d, *J* = 2.6 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.18, 160.08, 151.79, 150.60, 149.73, 145.36, 139.03, 135.91, 134.57, 131.17, 130.31, 130.26, 127.35, 123.90, 123.80, 121.62, 120.20, 114.13, 113.73, 112.05, 55.31, 54.18, 39.16. HRMS (ESI) calcd for $C_{25}H_{23}N_5O_2$ [M+H]+: 426.1930, found: 426.1931.

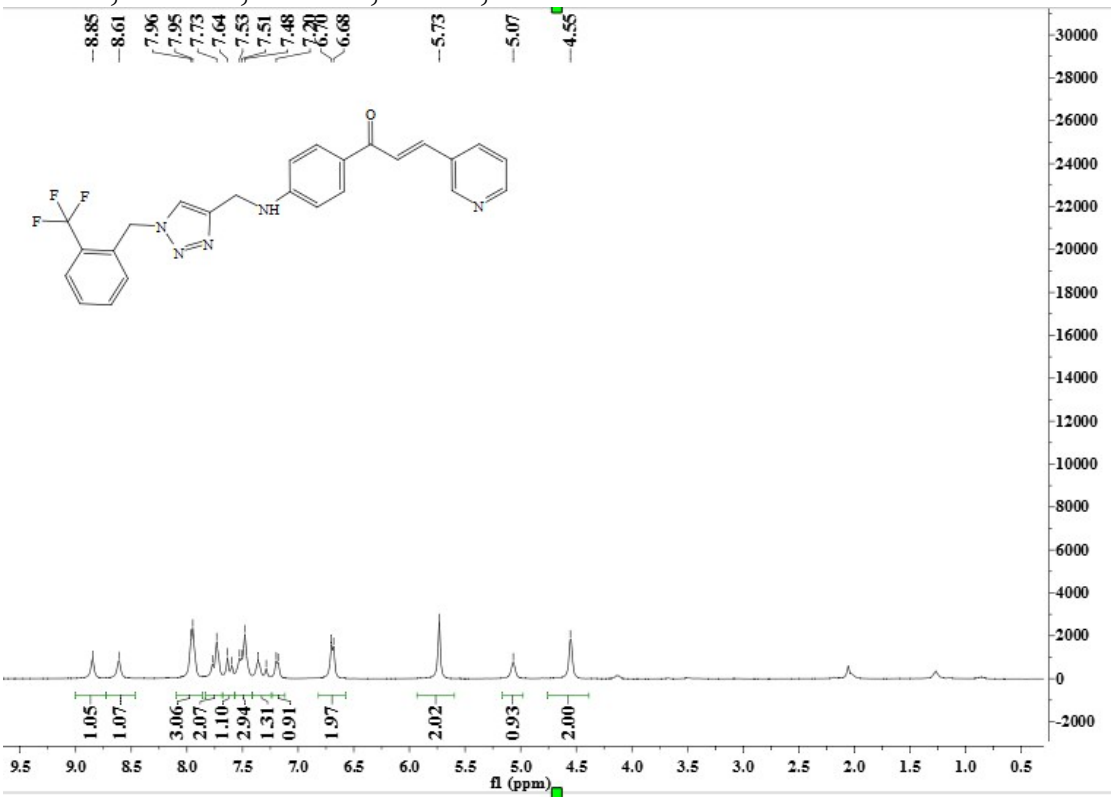


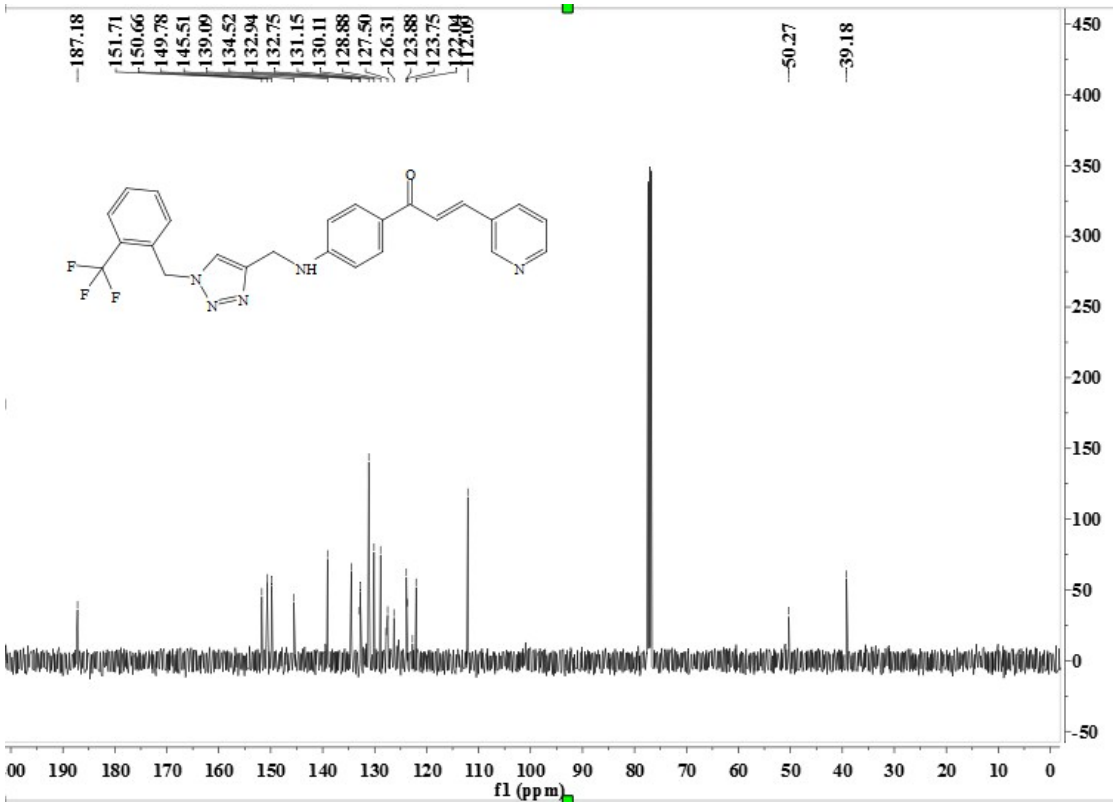


(*E*)-3-(pyridin-3-yl)-1-(4-(((1-(2-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)prop-2-en-1-one (**12l**)

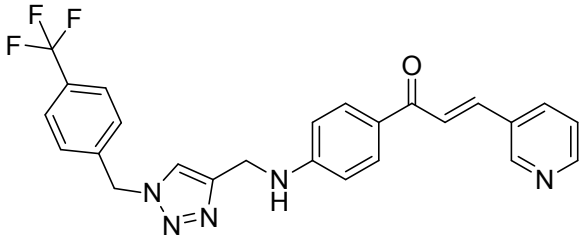


Yellow solid, yield：67%, m.p：189.6~191.4 °C. purity: 98.03 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.61 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 3H), 7.75 (d, *J* = 15.3 Hz, 2H), 7.62 (d, *J* = 15.6 Hz, 1H), 7.57 – 7.41 (m, 3H), 7.32 (d, *J* = 28.6 Hz, 1H), 7.19 (d, *J* = 6.5 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 2H), 5.73 (s, 2H), 5.07 (s, 1H, D_2O exchangeable), 4.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.18, 151.71, 150.66, 149.78, 145.51, 139.09, 134.52, 132.94, 132.75, 131.15, 130.11, 128.88, 127.79, 127.50, 126.31, 123.88, 123.75, 122.71, 122.04, 112.09, 50.27, 39.18.

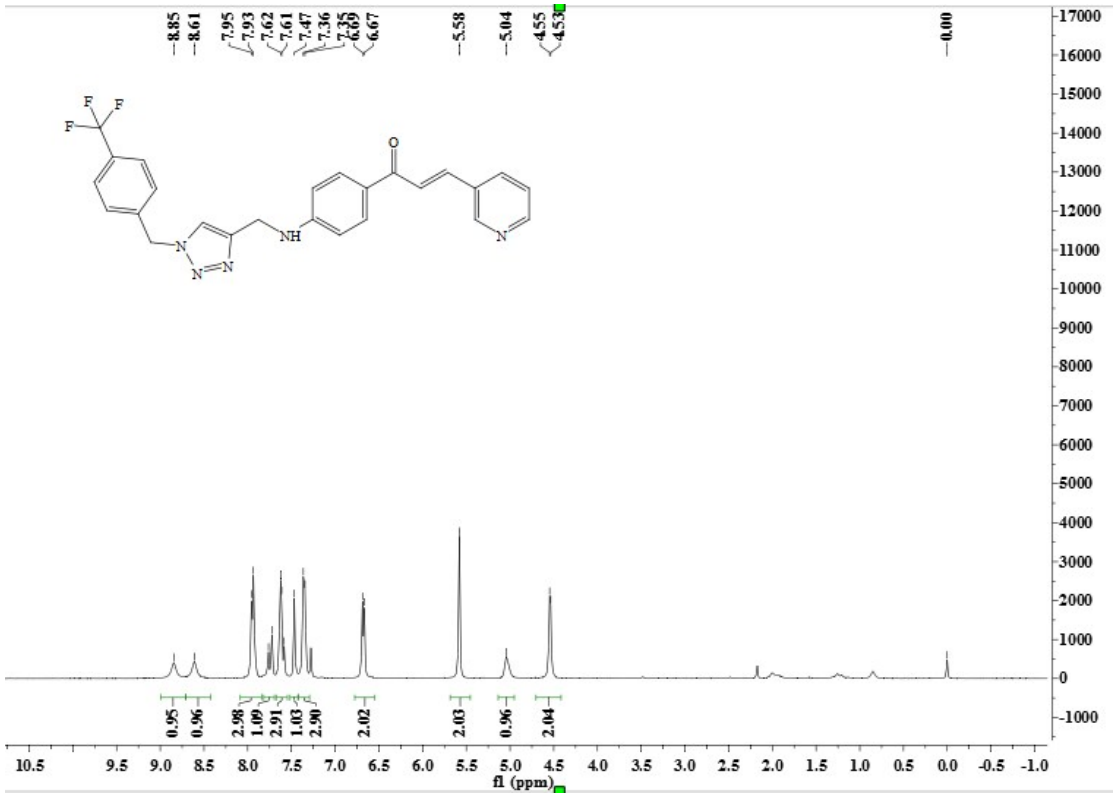


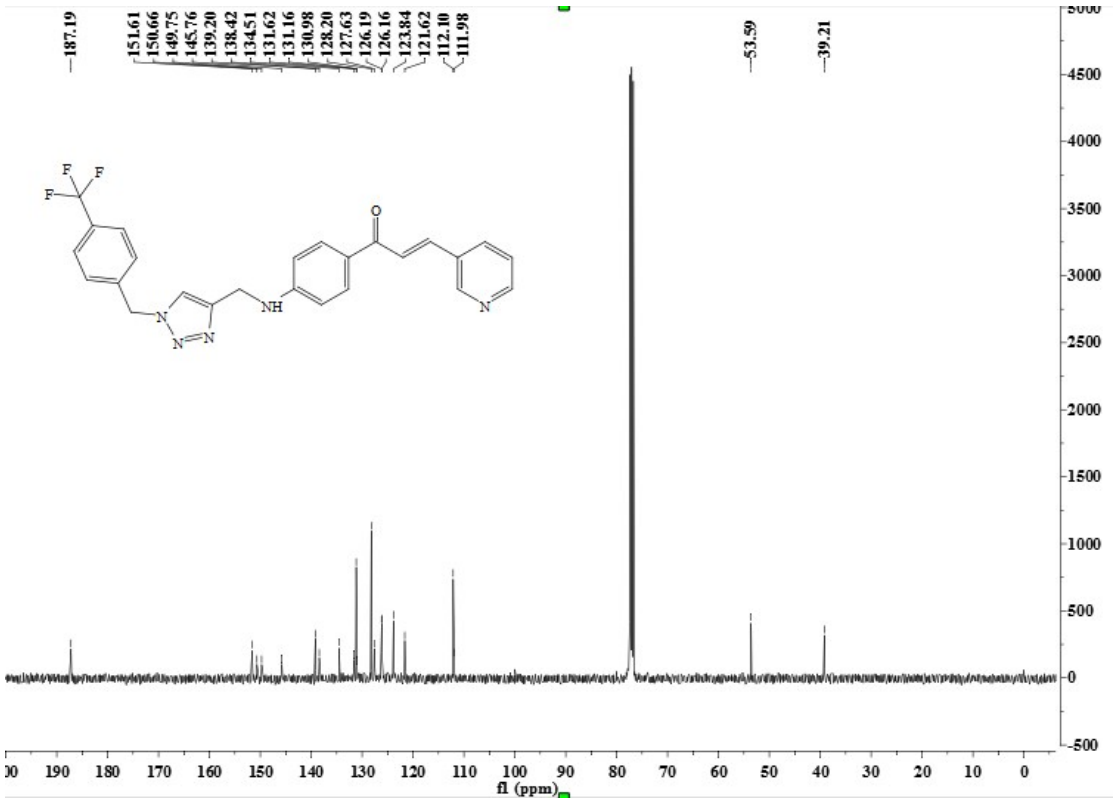


(*E*)-3-(pyridin-3-yl)-1-(4-(((1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)phenyl)prop-2-en-1-one (**12m**)

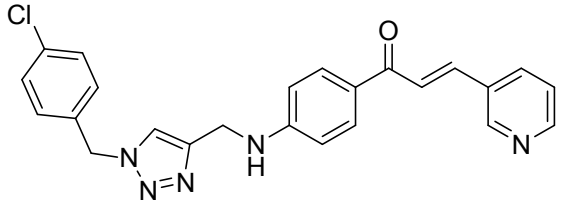


White solid, yield：68%, m.p：181.7~182.4 °C. purity: 97.99 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.61 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 3H), 7.74 (d, *J* = 15.6 Hz, 1H), 7.68 – 7.54 (m, 3H), 7.47 (s, 1H), 7.35 (d, *J* = 7.4 Hz, 3H), 6.68 (d, *J* = 8.3 Hz, 2H), 5.58 (s, 2H), 5.04 (s, 1H, D_2O exchangeable), 4.54 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.19, 151.61, 150.66, 149.75, 145.76, 139.20, 138.42, 134.51, 131.62, 131.16, 130.98, 128.20, 127.63, 126.19, 126.16, 123.84, 121.62, 112.10, 111.98, 53.59, 39.21. HRMS (ESI) calcd for $C_{25}H_{20}F_3N_5O$ [M+H]+: 464.1698, found: 464.1699.

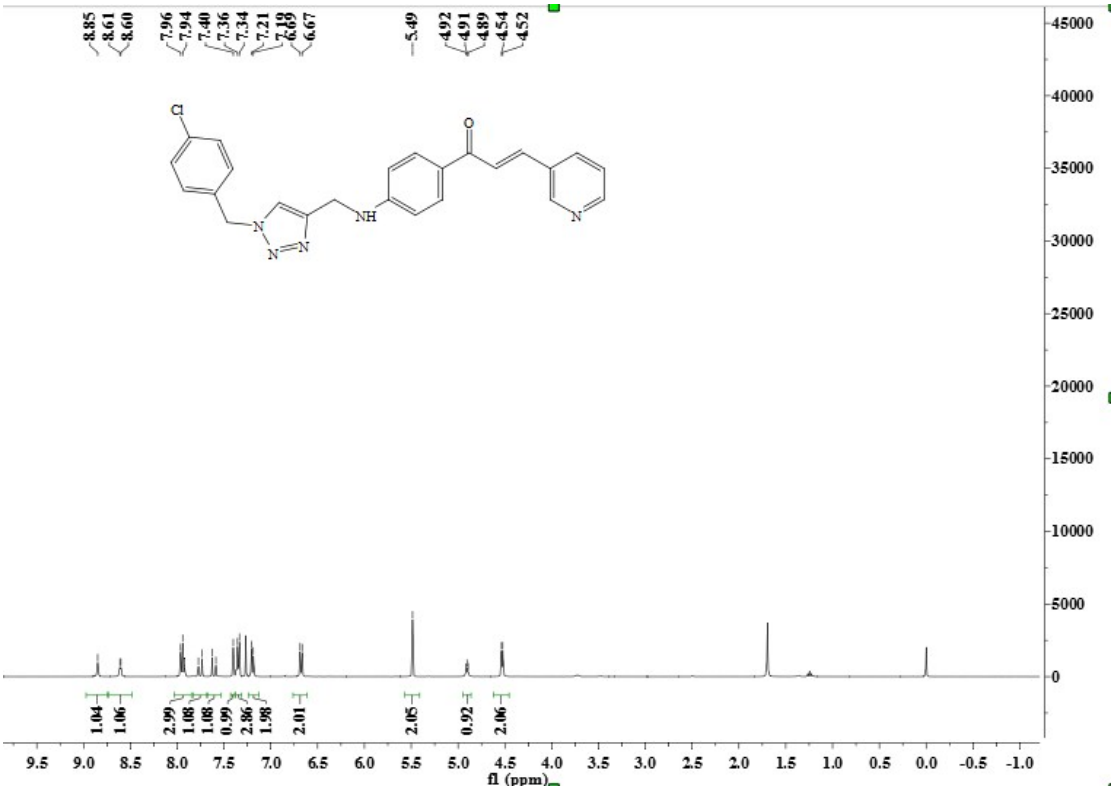


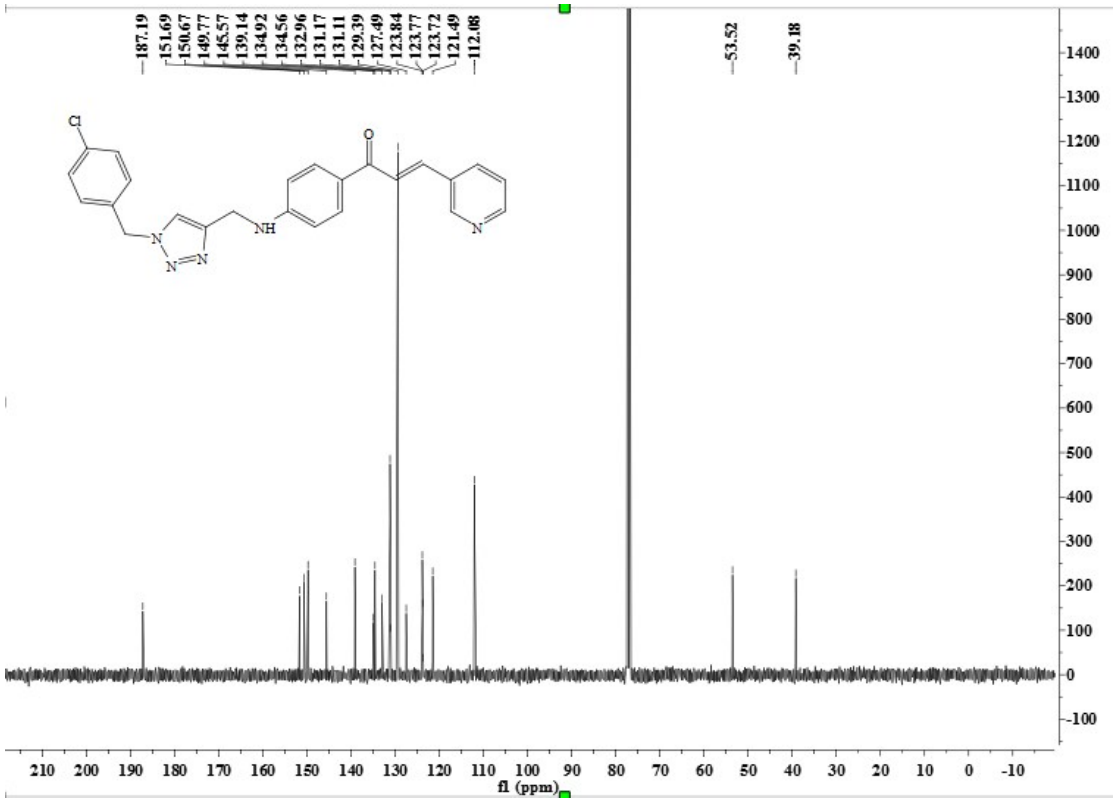


(*E*)-1-(4-(((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4- yl)methyl)amino) phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (**12n**)



White solid, yield：76%, m.p：115.6~116.2 °C. purity: 98.40 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.61 (d, *J* = 4.4 Hz, 1H), 7.94 (t, *J* = 8.4 Hz, 3H), 7.75 (d, *J* = 15.7 Hz, 1H), 7.61 (d, *J* = 15.7 Hz, 1H), 7.40 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 3H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 2H), 4.91 (t, *J* = 5.4 Hz, 1H, D_2O exchangeable), 4.53 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.19, 151.69, 150.67, 149.77, 145.57, 139.14, 134.92, 134.56, 132.96, 131.17, 131.11, 129.39, 127.49, 123.84，123.77, 123.72, 121.49, 112.08, 53.52, 39.18. HRMS (ESI) calcd for $C_{24}H_{20}ClN_5O$ [M+H]+: 430.1435, found: 430.1434.




187.19
151.69
150.67
149.77
145.57
139.14
134.92
134.56
132.96
131.17
131.11
129.39
127.49
123.84
123.77
123.72
121.49
112.08
53.52
39.18
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N
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800
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600
500
400
300
200
100
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210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)