Supporting information

Synthesis and biological evaluation of (*E*)-4-(3-arylvinyl-1*H*-indazol-6-yl)pyrimidin-2-amine derivatives as PLK4 inhibitors for the treatment of breast cancer

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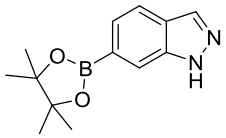
1. General Information

All reactions were carried out with magnetic stir and in dried glassware. Standard syringe techniques were applied for transfer of dry solvents. All solvents before used were dried and distilled under standard methods. All materials were from commercial suppliers and used without purification. We used DMSO-d_6 as the solvent of all products for the ^{1}H and ^{13}C NMR assays, which spectra were recorded on a Bruker AVANCEIII 400 spectrometer. Chemical shifts (δ) were reported in ppm relative to Me_4Si (internal standard) and coupling constants (*J*) were reported in Hz. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 101MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Thin layer chromatography (TLC) and column chromatography were used Qingdao Haiyang Silica gel F-254 plates and Qingdao Haiyang Silica gel 60 (300-400 mesh). HPLC analysis was performed on an UltiMate 3000 HPLC system (Dionex, USA). High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experimental Section

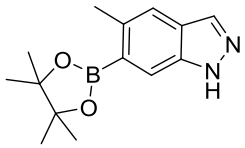
2.1 Synthesis of 9a -9b

6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **9a**



To a solution of 6-bromo-1*H*-indazole **8a** (8.0 g, 40 mmol), bis(pinacolato)-diboron (15.2 g, 60 mmol) and KOAc (7.84 g, 80 mmol) in 1,4-dioxane (100 mL), $Pd(dppf)Cl_2$ (1.46 g, 2 mmol) was added and the mixture was degassed for 5 min. The mixture was heated to 90 ℃ for 8 h and cooled to r.t. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed successively with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography eluting with Pet:EtOAc=2.5:1 to give the product as an off-white waxy solid (7.12 g, 73%); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.17 (brs, 1H), 8.09 (s, 1H), 7.75 (s, 1H), 7.73 (d, *J*=8.8 Hz, 1H), 7.23 (dd, 1H); 1.36 (s, 12H); MS (ESI) *m/z* Calcd for $C_{13}H_{18}BN_2O_2$ $[M + H]^+$: 245.1, found: 245.1.

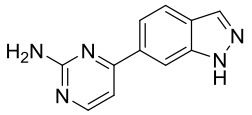
5-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **9b**



The title compound **9b** was prepared from **8b** following synthesis of **8a**. Yellow solid; yield 70.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ13.23 (s, 1H), 8.01 (s, 1H), 7.73 (s, 1H), 7.23 (d, 1H), 2.36(s, 3H) 1.35 (s, 12H); MS (ESI) *m/z* Calcd for $C_{14}H_{20}BN_2O_2$ $[M + H]^+$: 259.2, found: 259.1.

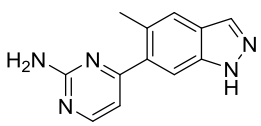
2.2 Synthesis of 11a -11d

4-(1*H*-indazol-6-yl)pyrimidin-2-amine **11a**



To a solution of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **9a** (3.66 g, 15 mmol), 4-chloropyrimidin-2-amine **10a** (1.62 g, 12.5 mmol) and KOAc (2.34 g, 30 mmol) in 1,4-dioxane (100 mL), $Pd(dppf)Cl_2$ (0.45 g, 0.62 mmol) was added and the mixture was degassed for 5 min. The mixture was heated to 100 ℃ for 3 h and cooled to r.t. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed successively with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography eluting with DCM:CH_3OH=12:1 to afford the title compound as a brown solid (1.74 g, 55%); ^{1}H NMR (400 MHz, DMSO-d_6)δ 13.17 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 8.10 (s, 1H) 7.86 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 5.3 Hz, 1H), 6.73 (s, 2H); MS (ESI) *m/z* Calcd for $C_{11}H_9N_5Na$ $[M + Na]^+$: 234.1, found: 234. 6.

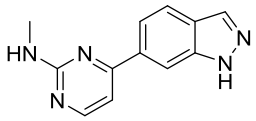
4-(5-methyl-1*H*-indazol-6-yl)pyrimidin-2-amine **11b**



The title compound **11b** was prepared from **9b** and **10a** following synthesis of **11a**. Light brown solid; yield 49.7%.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 8.02 (s, 1H), 7.63 (s, 1H), 7.50 (s,

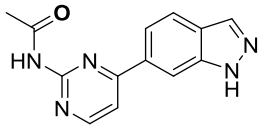
1H), 6.73 (d, *J* = 5.1 Hz, 1H), 6.66 (s, 2H), 2.40 (s, 3H); MS (ESI) *m/z* Calcd for $C_{12}H_{12}N_5$ $[M + H]^+$: 226.1, found: 226. 1.

4-(1*H*-indazol-6-yl)-*N*-methylpyrimidin-2-amine **11c**



The title compound **11c** was prepared from **9a** and 4-chloro-*N*-methylpyrimidin-2-amine **10b** following synthesis of **11a**. Brown solid; yield 41.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.35 – 8.24 (m, 2H), 8.02 (s, 1H) 7.86 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 5.3 Hz, 1H), 2.88 (s, 3H); MS (ESI) *m/z* Calcd for $C_{12}H_{11}N_5Na$ $[M + Na]^+$: 248.1, found: 248. 3.

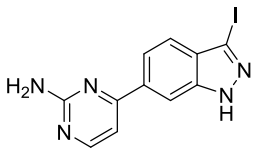
N-(4-(1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **11d**



The title compound **11d** was prepared from **9a** and *N*-(4-chloropyrimidin-2-yl)acetamide **10c** following synthesis of **11a**. Brown solid; yield 55.1%.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 10.61 (s, 1H), 8.72 (d, *J* = 5.3 Hz, 1H), 8.43 (s, 1H), 8.17 (s, 1H), 7.94 – 7.85 (m, 2H), 7.82 (d, *J* = 5.2 Hz, 1H), 2.29 (s, 3H); MS (ESI) *m/z* Calcd for $C_{13}H_{12}N_5O$ $[M + H]^+$: 254. 1, found: 254. 1.

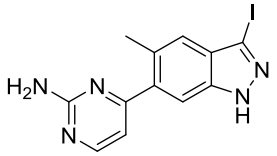
2.3 Synthesis of 12a -12d

4-(3-iodo-1*H*-indazol-6-yl)pyrimidin-2-amine **12a**



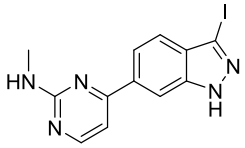
4-(1*H*-indazol-6-yl)pyrimidin-2-amine **11a** (1.7 g, 8.0 mmol) and K_2CO_3(2.24 g, 16 mmol) were combined in DMF (15 mL), and I_2(4. 0 g, 16 mmol) dissolved in DMF (2 mL) was added dropwise to the mixture, then stirred 10 h at 65 ℃. The reaction was then poured into a solution of sodium dithionite (3.0 g) and K_2CO_3 (1.1 g) in 50 mL water. A white precipitate formed and was stirred at room temperature for 30 min. Product was isolated by filtration. Light yellow solid; yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H); 7.66 (s, 1H), 7.41 (s, 1H), 6.79 (d, *J* = 5.1 Hz, 1H), 6.74 (s, 2H); MS (ESI) *m/z* Calcd for $C_{11}H_8IN_5Na$ $[M + Na]^+$: 360.0, found: 360. 4.

4-(3-iodo-5-methyl-1*H*-indazol-6-yl)pyrimidin-2-amine **12b**



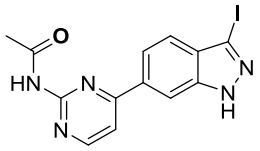
The title compound **12b** was prepared from **11b** following synthesis of **12a**. Light yellow solid; yield 73.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 6.83 (d, *J* = 5.1 Hz, 1H), 6.71 (s, 2H), 2.39 (s, 3H); MS (ESI) *m/z* Calcd for $C_{12}H_{11}IN_5$ $[M + H]^+$: 352.0, found: 352.0.

4-(3-iodo-1*H*-indazol-6-yl)-*N*-methylpyrimidin-2-amine **12c**



The title compound **12c** was prepared from **11c** following synthesis of **12a**. White solid; yield 81.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.35 – 8.24 (m, 2H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 5.3 Hz, 1H), 2.91 (s, 3H); MS (ESI) *m/z* Calcd for $C_{12}H_{11}IN_5$ $[M + H]^+$: 352.0, found: 352.1.

N-(4-(3-iodo-1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **12d**

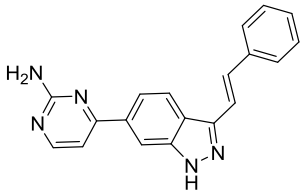


The title compound **12d** was prepared from **11d** following synthesis of **12a**. Light yellow solid; yield 80.1%.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.85 (s, 1H), 10.63 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 8.43 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 5.3 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 2.28 (s, 3H); MS (ESI) *m/z* Calcd for $C_{13}H_{10}IN_5ONa$ $[M + Na]^+$: 402.0, found: 402.0.

2.4 Synthesis of 14a-14y, 15a-15d.

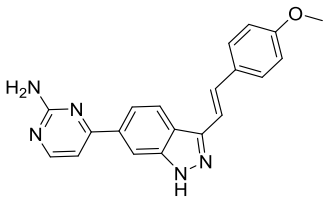
To a solution of 4-(3-iodo-1*H*-indazol-6-yl)pyrimidin-2-amine **12a** (120 mg, 0.36 mmol), *trans*-arylvinylboronates or *trans*-hetarylvinylboronates **13a**-**13y** (0.43 mmol) and cesium carbonate (234 mg, 0.72 mmol) in 1,4-dioxane:H_2O=4:1 (15 mL), Pd(dppf)Cl_2 (29 mg, 0.04 mmol) was added and the mixture was degassed for 5 min. The mixture was heated to 100 ℃ for 8 h and cooled to r.t. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed successively with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography eluting with DCM:CH_3OH=10:1 to afford the title compounds **14a**-**14y**.

(*E*)-4-(3-styryl-1*H*-indazol-6-yl)pyrimidin-2-amine **14a**



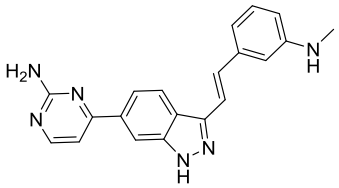
Light yellow solid; yield 33.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 8.38 (d, *J* = 5.1 Hz, 1H), 8.34 – 8.25 (m, 2H), 7.96 – 7.87 (m, 1H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.59 (d, *J* = 3.2 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 5.1 Hz, 1H), 6.73 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.32 , 164.12 , 159.53 , 142.84 , 142.04 , 137.55 , 135.66 , 130.15 , 129.19 , 128.20 , 126.95 , 122.32 , 121.40 , 120.79 , 120.05 , 109.28 , 106.77; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}N_5$ $[M+H]^+$: 314.1406, found: 314.1395.

(*E*)-4-(3-(4-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14b**



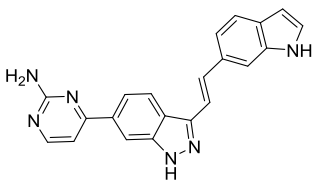
Yellow solid; yield 40.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.26 (t, *J* = 4.1 Hz, 2H), 7.88 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 16.7 Hz, 1H), 7.42 (d, *J* = 16.7 Hz, 1H), 7.24 (d, *J* = 5.2 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.72 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.13 , 159.58 , 159.54 , 143.12 , 142.00 , 135.57 , 130.21 , 129.88 , 128.29 , 121.43 , 119.85 , 118.54 , 114.66 , 109.20 , 106.69 , 55.65 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{18}N_5O$ $[M+H]^+$: 344.1512, found: 344.1506.

(*E*)-4-(3-(3-(methylamino)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14c**



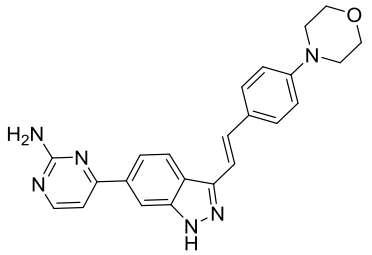
Brown solid; yield 29.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.39 (s, 1H), 8.35 – 8.23 (m, 2H), 7.91 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.48 (s, 2H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.88 (t, *J* = 1.9 Hz, 1H), 6.74 (s, 2H), 6.53 (dd, *J* = 8.0, 2.2 Hz, 1H), 5.66 (d, *J* = 5.1 Hz, 1H), 2.76 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.34 , 164.15 , 159.51 , 150.68 , 143.03 , 142.06 , 138.03 , 135.62 , 131.25 , 129.60 , 122.25 , 121.43 , 119.98 , 119.92 , 114.78 , 112.44 , 109.64 , 109.27 , 106.78 , 30.30 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{19}N_6$ $[M+H]^+$: 343.1672, found: 343.1678.

(*E*)-4-(3-(2-(1*H*-indol-6-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14d**



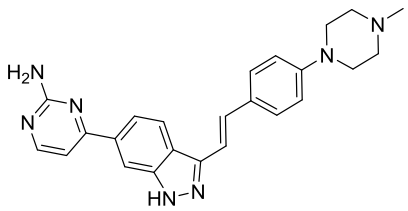
Brown solid; yield 41.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 11.19 (s, 1H), 8.35 (d, J = 5.1 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.27 (s, 1H), 7.90 (dd, J = 8.6, 1.4 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.57 (d, J = 8.2 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.38 (t, J = 2.7 Hz, 1H), 7.25 (d, J = 5.3 Hz, 1H), 6.72 (s, 2H), 6.45 (t, J = 2.4 Hz, 1H);^{13}C NMR (101 MHz, DMSO-d_6) δ 164.23 , 159.57 , 142.05 , 136.72 , 135.55 , 131.98 , 130.72 , 128.20 , 126.83 , 121.53 , 120.72 , 119.86 , 118.02 , 117.90 , 110.78 , 109.22 , 106.74 , 101.86 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{16}N_6Na$ $[M+Na]^+$: 375.1334, found: 375.1325.

(*E*)-4-(3-(4-morpholinostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14e**



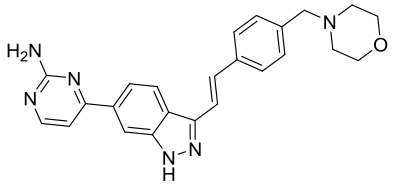
Yellow solid; yield 47.3% ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.29 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 16.6 Hz, 1H), 7.43 (d, J = 16.8 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.77 (s, 2H), 3.81 (t, J = 4.8 Hz, 4H), 3.22 (t, J = 4.8 Hz, 4H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.28 , 159.59 , 151.10 , 143.33 , 142.02 , 137.63, 135.54 , 134.36 , 130.19 , 128.39 , 127.89 , 122.21 , 121.46 , 119.79 , 117.44 , 115.34 , 113.77 , 109.19 , 106.70 , 66.52 , 48.49 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{23}N_6O$ $[M+H]^+$: 399.1934, found: 399.1947.

(*E*)-4-(3-(4-(4-methylpiperazin-1-yl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14f**



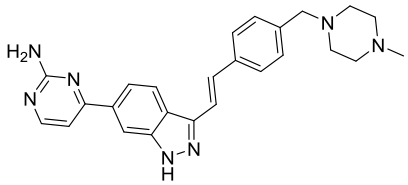
Yellow solid; yield 24.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.24 (d, J = 8.7 Hz, 2H), 7.87 (dd, J = 8.5, 1.5 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 16.6 Hz, 1H), 7.35 (d, J = 16.7 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.72 (s, 2H), 3.21 (t, J = 4.8 Hz, 4H), 2.50 – 2.42 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.15 , 159.57 , 150.96 , 135.52 , 130.22 , 127.97 , 127.87 , 121.44 , 119.75 , 117.22 , 115.53 , 109.17 , 106.68 , 54.93 , 48.03 , 46.14; HRMS (ESI-TOF) *m/z* Calcd for $C_{24}H_{26}N_7$ $[M+H]^+$: 412.2250, found: 412.2243.

(*E*)-4-(3-(4-(morpholinomethyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14g**



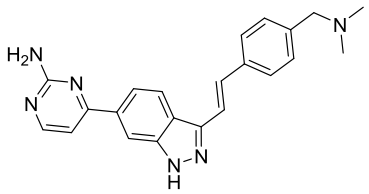
Light brown solid; yield 41.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.31 – 8.22 (m, 2H), 7.90 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.55 (s, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 2H), 3.59 (t, *J* = 4.6 Hz, 4H), 3.48 (s, 2H), 2.37 (t, *J* = 4.6 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.93 , 148.99 , 148.87 , 142.82 , 142.24 , 137.93 , 137.19 , 136.40 , 129.90 , 129.77 , 126.79 , 121.90 , 121.16 , 120.55 , 120.31 , 110.91 , 108.43 , 105.93 , 66.69 , 62.67 , 53.66; HRMS (ESI-TOF) *m/z* Calcd for $C_{24}H_{25}N_6O$ $[M+H]^+$: 413.2091, found: 413.2095.

(*E*)-4-(3-(4-((4-methylpiperazin-1-yl)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14h**



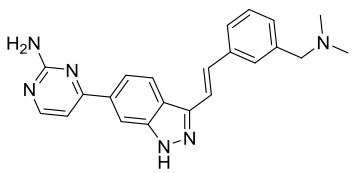
Brown solid; yield 28.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.27 (t, *J* = 4.2 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.55 (s, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 2H), 3.49 (s, 2H), 3.39 (s, 4H), 2.44 (s, 4H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.19 , 159.52 , 138.02 , 138.00 , 136.41 , 136.35 ,135.63 , 135.28 , 132.07 , 130.01 , 129.81 , 129.33 , 129.25 , 126.81 , 121.42 , 120.08 , 119.30 , 106.78 , 63.20 , 54.68 , 52.23 , 45.41; HRMS (ESI-TOF) *m/z* Calcd for $C_{25}H_{28}N_7$ $[M+H]^+$: 426.2407, found: 426.2410.

(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14i**



Light brown solid; yield 36.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.27 (dd, *J* = 4.9, 3.4 Hz, 2H), 7.90 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 2.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 5.3 Hz, 1H), 6.71 (s, 2H), 3.51 (s, 2H), 2.23 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.26 , 164.03 , 159.62 , 142.64, 142.03 , 138.79 , 135.72 , 131.77 , 129.17 , 127.30 , 122.34 , 122.09 , 121.37 , 120.17 , 109.32 , 106.71 , 60.11 , 42.39; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{23}N_6$ $[M+H]^+$: 371.1985, found: 371.1978.

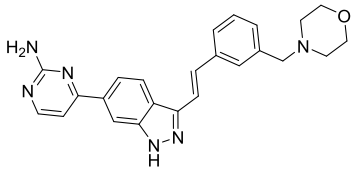
(*E*)-4-(3-(3-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14j**



Light brown solid; yield 28.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.33 – 8.23 (m, 2H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.60 (m, 2H), 7.57 (s, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.18 (m, 2H), 6.73 (s, 2H), 3.51 (s, 2H), 2.23 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.28 , 164.09 , 159.60 , 137.49 ,

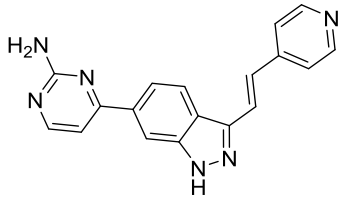
135.64 , 130.11 , 129.07 , 128.83 , 127.56 , 125.72 , 122.25 , 121.48 , 120.84 , 120.05 , 106.70 , 63.56 , 45.24; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{23}N_6$ $[M+H]^+$: 371.1985, found: 371.1981.

(*E*)-4-(3-(3-(morpholinomethyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14k**



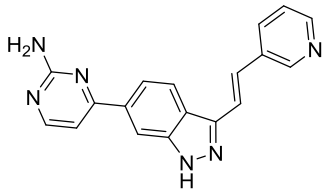
Light brown solid; yield 34.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 1.3 Hz, 1H), 7.90 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 2H), 7.56 (s, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.72 (s, 2H), 3.60 (t, *J* = 4.6 Hz, 4H), 3.51 (s, 2H), 2.40 (t, *J* = 4.5 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.25 , 164.11 , 159.60 , 142.85，142.04 , 142.03 , 137.48 , 135.65 , 130.14 , 129.10 , 127.74 , 125.65 , 122.25 , 121.49 , 120.88 , 120.06 , 109.27 , 106.73 , 66.59 , 53.62 , 40.49; HRMS (ESI-TOF) *m/z* Calcd for $C_{24}H_{25}N_6O$ $[M+H]^+$: 413.2091, found: 413.2087.

(*E*)-4-(3-(2-(pyridin-4-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14l**



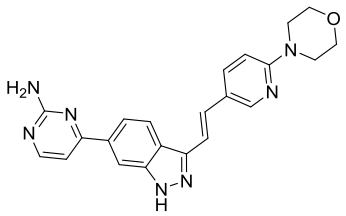
Brown solid; yield 45.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.59 (s, 1H), 8.49 – 8.23 (m, 3H), 8.01 – 7.89 (m, 2H), 7.87 (s, 1H), 7.77 (s, 2H), 7.54 (d, *J* = 16.7 Hz, 2H), 7.26 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.31 , 163.99 , 159.59 , 150.43 , 142.21 , 142.07 , 135.83 , 127.48 , 125.32 , 122.48 , 121.38 (d, *J* = 24.2 Hz,) , 120.43 , 109.41 , 106.77; HRMS (ESI-TOF) *m/z* Calcd for $C_{18}H_{14}N_6Na$ $[M+Na]^+$: 337.1178, found: 337.1171.

(*E*)-4-(3-(2-(pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14m**



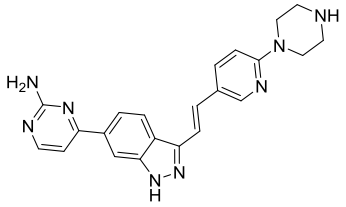
Brown solid; yield 50.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.53 (s, 1H), 9.02 (s, 1H), 8.59 (s, 1H), 8.38 (s, 1H), 8.36 – 8.23 (m, 2H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 16.8 Hz, 1H), 7.68 – 7.46 (m, 3H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.82 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.31 ,164.01 , 159.14 , 148.41 , 142.54 , 142.01 , 135.62 , 133.61 , 126.45 , 123.06 , 122.40 , 121.42 , 120.24 , 109.44 , 106.78; HRMS (ESI-TOF) *m/z* Calcd for $C_{18}H_{15}N_6$ $[M+H]^+$: 315.1359, found: 315.1362.

(*E*)-4-(3-(2-(6-morpholinopyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14n**



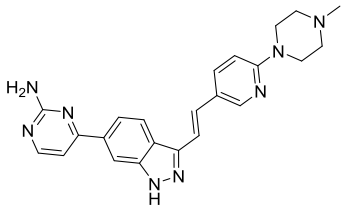
Light yellow solid; yield 54.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.42 (d, *J* = 2.3 Hz, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 8.03 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 3.4 Hz, 2H), 7.24 (d, *J* = 5.2 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.72 (s, 2H), 3.72 (t, *J* = 4.8 Hz, 4H), 3.51 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27, 164.27, 159.57 , 158.89 , 147.59 , 143.20 , 142.00 , 135.57 , 134.71 , 127.14 , 123.34 , 122.19, 121.41 , 119.81 , 117.93 , 109.20 , 107.51 , 106.71 , 66.41 , 45.54; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}N_7O$ $[M+H]^+$: 400.1887, found: 400.1904.

(*E*)-4-(3-(2-(6-(piperazin-1-yl)pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14o**



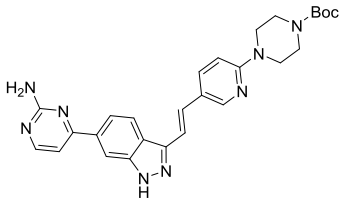
Yellow solid; yield 21.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H), 8.46 – 8.32 (m, 2H), 8.32 – 8.19 (m, 2H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.38 (m, 2H), 7.24 (d, *J* = 5.3 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.73 (s, 2H), 3.58 (s, 1H), 3.53 – 3.43 (m, 4H), 2.81 (s, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.26 , 164.17 , 159.57 , 158.99 , 147.68 , 143.15 , 142.10 , 135.55 , 134.57 , 127.28 , 122.62 , 122.16 , 121.42 , 119.79 , 117.39 , 109.31 , 107.37 , 106.71 , 46.11 , 45.78; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}N_8Na$ $[M+Na]^+$: 421.1865, found: 421.1874.

(*E*)-4-(3-(2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14p**



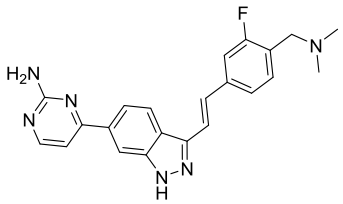
Brown solid; yield 34.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.46 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 8.22 (d, *J*=8.6 Hz, 1H), 7.89 (dd, *J* = 18.1, 8.2 Hz, 2H), 7.70 (d, *J* = 16.5 Hz, 1H), 7.54 (d, *J* = 16.4 Hz, 1H), 7.35-7.14 (m, 3H), 6.72 (s, 2H), 3.60 (s, 4H), 2.33 (s, 4H), 2.21(s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.09 , 159.60 , 158.16 , 153.09 , 151.47 , 145.10 , 137.73 , 135.65 , 130.58 , 130.24 , 124.00 , 121.47 , 119.99 , 119.17 , 109.31 , 109.14 , 106.71 , 54.81 , 49.02, 45.52 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{25}N_8$ $[M+H]^+$: 413.2203, found: 413.2212.

Tert-butyl (*E*)-4-(5-(2-(6-(2-aminopyrimidin-4-yl)-1*H*-indazol-3-yl)vinyl)pyridin-2-yl)piperazine-1-carboxylate **14q**



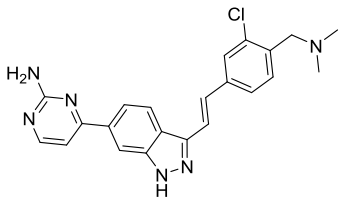
Yellow solid; yield 47.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 2H), 8.02 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.87 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 2H), 7.24 (d, *J* = 5.2 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 1H), 6.71 (s, 2H), 3.56 (dd, *J* = 6.8, 3.7 Hz, 4H), 3.44 (dd, *J* = 6.6, 3.8 Hz, 4H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.26 , 164.14 , 159.57 , 158.50 ,154.42 , 147.61 , 143.20 , 141.99 , 135.57,134.78 , 127.13 , 123.17, 122.19 , 121.42 , 119.81 , 117.89 , 109.20 , 107.72 , 106.70 , 79.51 , 44.85 , 28.56; HRMS (ESI-TOF) *m/z* Calcd for $C_{27}H_{31}N_8O_2$ $[M+H]^+$: 499.2571, found: 499.2551.

(*E*)-4-(3-(4-((dimethylamino)methyl)-3-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14r**



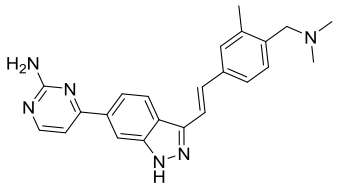
Beige solid; yield 35.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.32 – 8.25 (m, 2H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.60 – 7.52 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.73 (s, 2H), 3.68 (s, 2H), 2.32 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.05 , 159.61 , 154.56 , 135.69 , 134.37 , 132.73 , 128.56 , 123.00 , 122.39 , 121.37 , 120.16 , 116.85 , 113.19 (d, *J* = 24.4 Hz), 109.32 , 106.71 , 52.48 , 45.94; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}FN_6$ $[M+H]^+$: 389.1891, found: 389.1906.

(*E*)-4-(3-(3-chloro-4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14s**



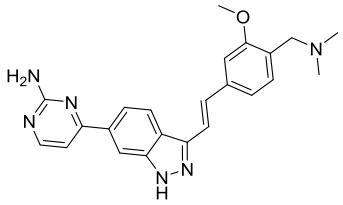
Yellow solid; yield 30.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.42 – 8.20 (m, 3H), 7.90 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.76 – 7.61 (m, 2H), 7.58 – 7.45 (m, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 6.71 (s, 2H), 3.53 (s, 2H), 2.24 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.26 , 164.07 , 159.61 , 152.95, 146.10, 142.10, 138.48, 135.68, 134.31, 128.33, 127.62 , 125.23 , 121.45, 120.13 , 106.72 , 60.72, 45.42 . HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}ClN_6$ $[M+H]^+$: 405.1595, found: 405.1584 .

(*E*)-4-(3-(4-((dimethylamino)methyl)-3-methylstyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14t**



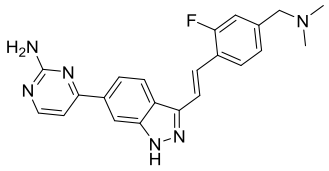
Yellow solid; yield 28.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.30 – 8.23 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.59 – 7.46 (m, 4H), 7.29 – 7.22 (m, 2H), 6.72 (s, 2H), 3.40 (s, 2H), 2.37 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.11 , 159.59 , 142.92 , 137.86 , 135.62 , 130.57 , 130.03 , 128.66 , 124.12 , 121.39 , 120.00 , 109.28 , 106.71 , 61.60, 45.52 , 19.27 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{24}N_6Na$ $[M+Na]^+$: 407.1960, found: 407.1971.

(*E*)-4-(3-(4-((dimethylamino)methyl)-3-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14u**



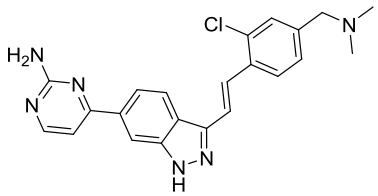
Light brown solid; yield 17.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.40 – 8.26 (m, 3H), 7.91 (dd, J = 8.6, 1.4 Hz, 1H), 7.67 (d, J = 16.7 Hz, 1H), 7.57 (d, J = 16.7 Hz, 1H), 7.44 (s, 1H), 7.41 – 7.32 (m, 2H), 7.25 (d, J = 5.2 Hz, 1H), 6.72 (s, 2H), 3.93 (s, 3H), 3.83 (s, 2H), 2.46 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.07 , 159.61 , 158.41 , 152.60 , 142.78 , 139.52 , 135.69 , 131.96 , 129.89 , 122.27 , 121.45 , 120.06 , 119.26 , 109.37 , 106.73 , 102.77 , 63.26, 56.16 , 44.19; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{25}N_6O$ $[M+H]^+$: 401.2091, found: 401.2096.

(*E*)-4-(3-(4-((dimethylamino)methyl)-2-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14v**



Brown solid; yield 30.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.28 (s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.96 – 7.84 (m, 2H), 7.66 (d, J = 16.8 Hz, 1H), 7.57 (d, J = 16.8 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.72 (s, 2H), 3.44 (s, 2H), 2.18 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.04 , 161.33 , 159.61 , 158.86 , 149.15 , 142.62 , 135.72 , 131.88 , 127.66 , 125.38 , 123.52 , 122.35 , 121.68 , 121.01 , 120.28 , 116.14 (d, J = 22.0 Hz), 106.70 , 62.92 , 45.40; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}FN_6$ $[M+H]^+$: 389.1891, found: 389.1885.

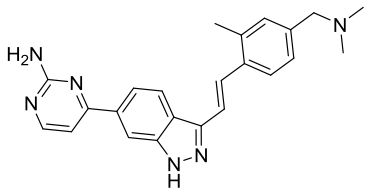
(*E*)-4-(3-(2-chloro-4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14w**



Light brown solid; yield 27.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.31(d, 2H), 7.92 (d, J = 8.6 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.74 – 7.61 (m, 2H), 7.55 (d, 1H), 7.25 (d, J = 5.2 Hz, 1H), 6.72 (s, 2H), 3.57 (s, 2H), 2.17 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.05 , 159.60 , 142.58 , 142.06 , 138.26 , 135.68 , 135.22 , 134.23 , 131.47 , 128.38 , 127.60 , 125.19 , 122.36 , 121.93 , 121.45 , 120.11 ,

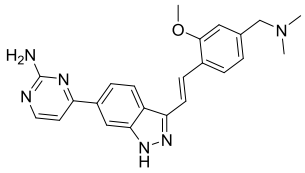
109.29 , 106.71 , 58.92 , 46.16 ; Brown solid; yield 25.6%; HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{22}ClN_6$ $[M+H]^+$: 405.1595, found: 405.1605.

(*E*)-4-(3-(4-((dimethylamino)methyl)-2-methylstyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14x**



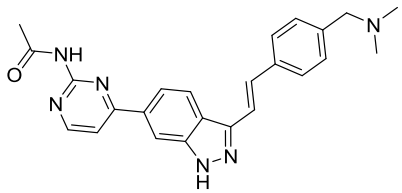
Brown solid; yield 36.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.90 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 16.4 Hz, 1H), 7.45 (d, *J* = 16.5 Hz, 1H), 7.24 (d, *J* = 5.2 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.72 (s, 2H), 3.41 (s, 2H), 2.46 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.27 , 164.10 , 159.60 , 135.68 , 135.63 , 134.99 , 131.39 , 127.42 , 127.28 , 125.29 , 122.32 , 121.17 , 120.13 , 106.68 , 63.48 , 45.34 , 20.07 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{25}N_6$ $[M+H]^+$: 385.2141, found: 385.2157.

(*E*)-4-(3-(4-((dimethylamino)methyl)-2-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14y**



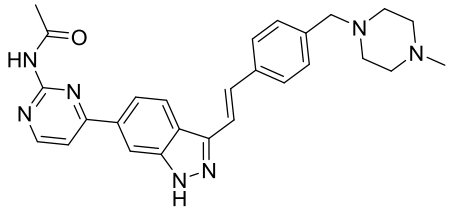
Brown solid; yield 28.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.27 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.90 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.54 (d, *J* = 16.8 Hz, 1H), 7.23 (d, *J* = 5.3 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.71 (s, 2H), 3.90 (s, 3H), 3.43 (s, 2H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.24 , 164.13 , 159.59 , 156.98 , 135.61 , 126.61 , 124.69 , 122.31 , 121.66 , 120.99 , 120.06 , 112.16 , 106.72 , 63.62 , 56.07 , 45.27. HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{24}N_6ONa$ $[M+Na]^+$: 423.1910, found: 423.1924.

(*E*)-*N*-(4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **15a**



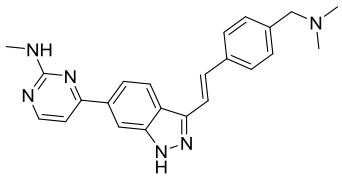
The title compound **15a-15b** was prepared from **12d** following synthesis of **14a-14y.** Yellow solid; yield 31.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.53 (s, 1H), 10.61 (s, 1H), 8.73 (d, *J* = 5.3 Hz, 1H), 8.43 (s, 1H), 8.38 – 8.30 (m, 1H), 8.07 – 7.99 (m, 1H), 7.86 (d, *J* = 5.3 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 5.2 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 3.83 (s, 2H), 2.40 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.71 , 164.41 , 164.26 , 164.09 , 159.81 , 159.59 , 158.40 , 136.59 , 134.53 , 131.98 , 130.11 , 130.02 , 129.88 , 129.12 , 126.87 , 121.73 , 120.11 , 112.61 , 60.38 , 45.00 , 25.38 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{24}H_{25}N_6O$ $[M+H]^+$: 413.2091, found: 413.2085.

(*E*)-*N*-(4-(3-(4-((dimethylamino)methyl)-3-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **15b**



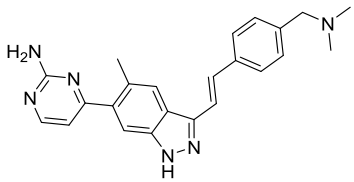
Brown solid; yield 28.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.44 – 8.22 (m, 3H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.56 (s, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 3.53 (s, 2H), 3.37 (s, 4H), 2.92 (s, 3H), 2.68 (s, 4H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.43 , 159.42 , 136.52 , 135.69 , 129.90 , 129.80 , 126.85 , 122.30, 121.42 , 120.56 , 120.48 , 120.03 , 109.36 , 106.25 , 63.26 , 61.75 , 54.32 , 51.64 , 28.38; HRMS (ESI-TOF) *m/z* Calcd for $C_{27}H_{30}N_7O$ $[M+H]^+$: 468.2513, found: 468.2517.

(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)-*N*-methylpyrimidin-2-amine **15c**



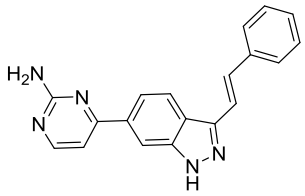
The title compound **15c** was prepared from **12c** following synthesis of **14a-14y.** Brown solid; yield 34.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.35 – 8.24 (m, 2H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 1.9 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 4.8 Hz, 1H), 3.52 (d, *J* = 4.5 Hz, 2H), 2.92 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.44, 159.40, 156.60, 142.88, 137.53,136.60, 135.68, 129.88 , 126.85, 122.35, 121.42 , 120.03 , 106.25 , 67.03 , 45.03 , 28.38; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{24}N_6Na$ $[M+Na]^+$: 407.1960, found: 407.1953.

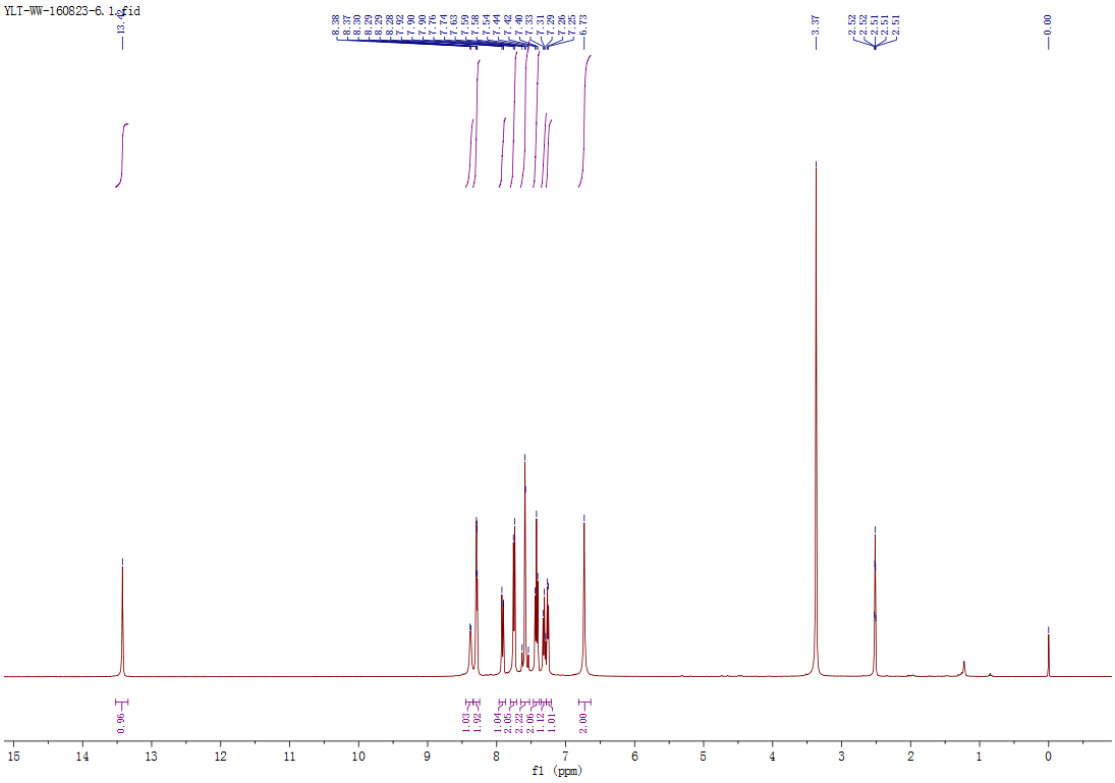
(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-5-methyl-1*H*-indazol-6-yl)pyrimidin-2-amine **15d**

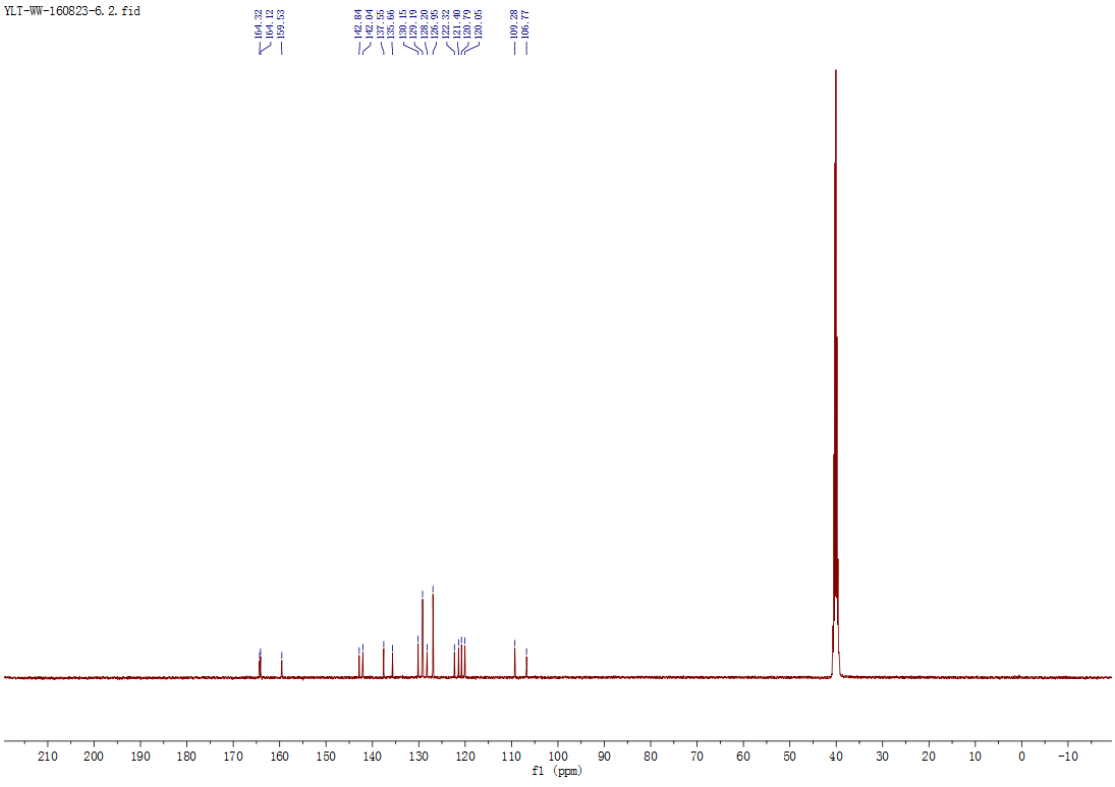


The title compound **15d** was prepared from **12b** following synthesis of **14a-14y.** Brown solid; yield 31.5%; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.34 (d, *J* = 5.1 Hz, 1H), 8.03 – 7.98 (m, 1H), 7.65 (s, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 16.5 Hz, 2H), 7.47 (d, *J* = 16.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 5.1 Hz, 1H), 3.54 (s, 2H), 2.53 – 2.47 (m, 3H), 2.30 (s, 6H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 169.01 , 163.08 , 158.09 , 138.34 , 136.85 , 136.51 , 130.25 , 129.86 , 128.61 , 126.18 , 121.51 , 121.12 , 119.57 , 110.57 , 63.06 , 43.66 , 19.43 ; HRMS (ESI-TOF) *m/z* Calcd for $C_{23}H_{25}N_6$ $[M+H]^+$: 385.2141, found: 385.2153.

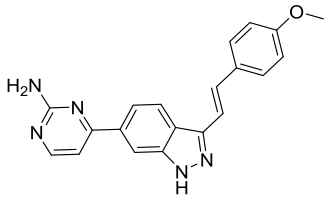
(*E*)-4-(3-styryl-1*H*-indazol-6-yl)pyrimidin-2-amine **14a**

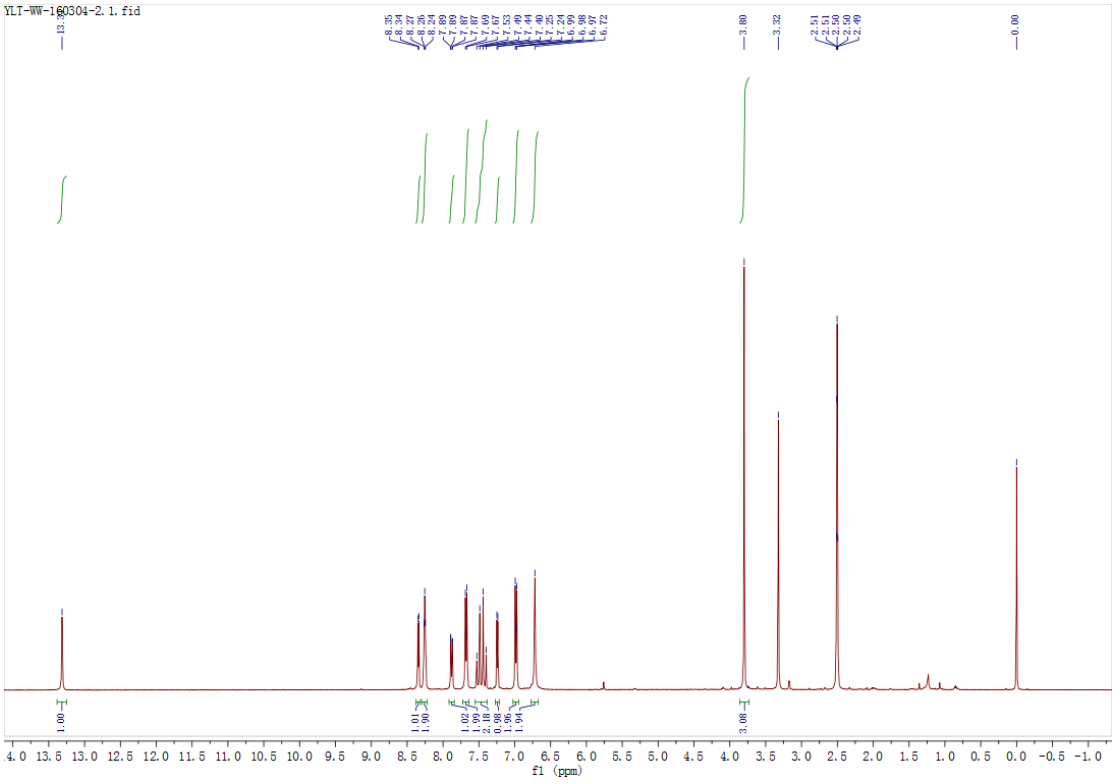


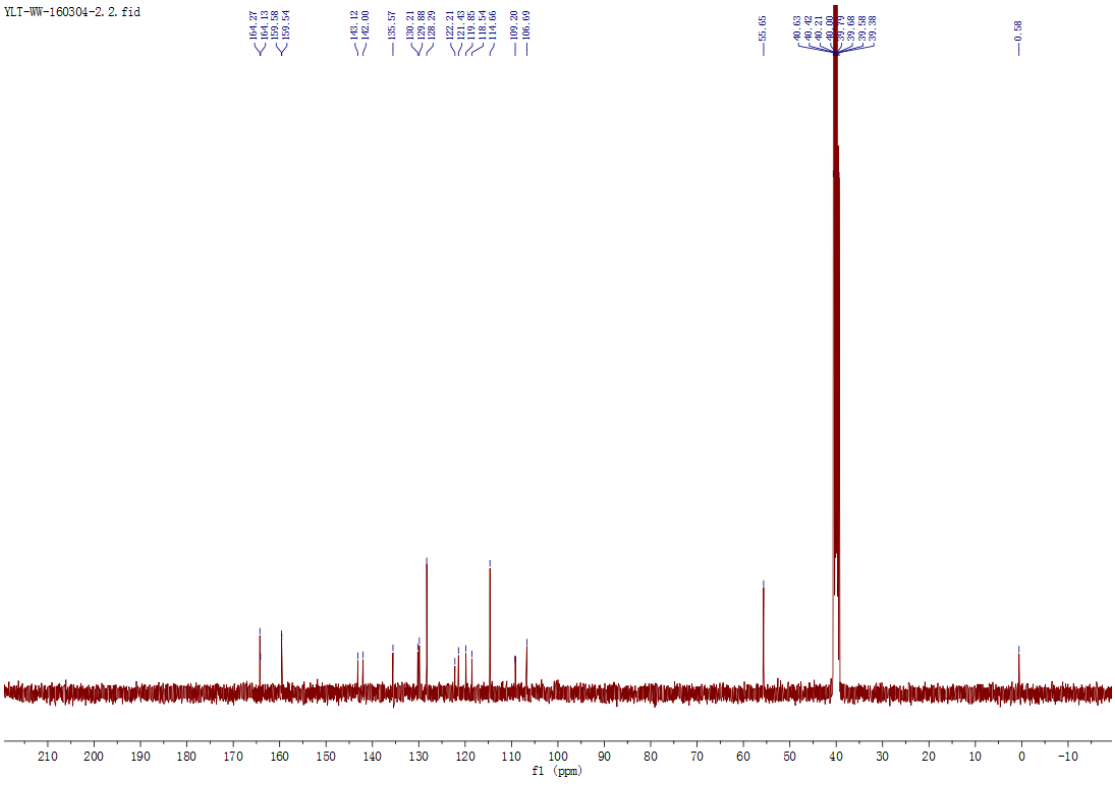




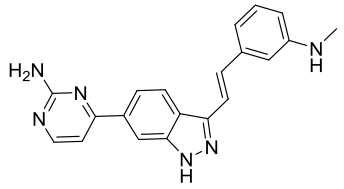
(*E*)-4-(3-(4-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14b**

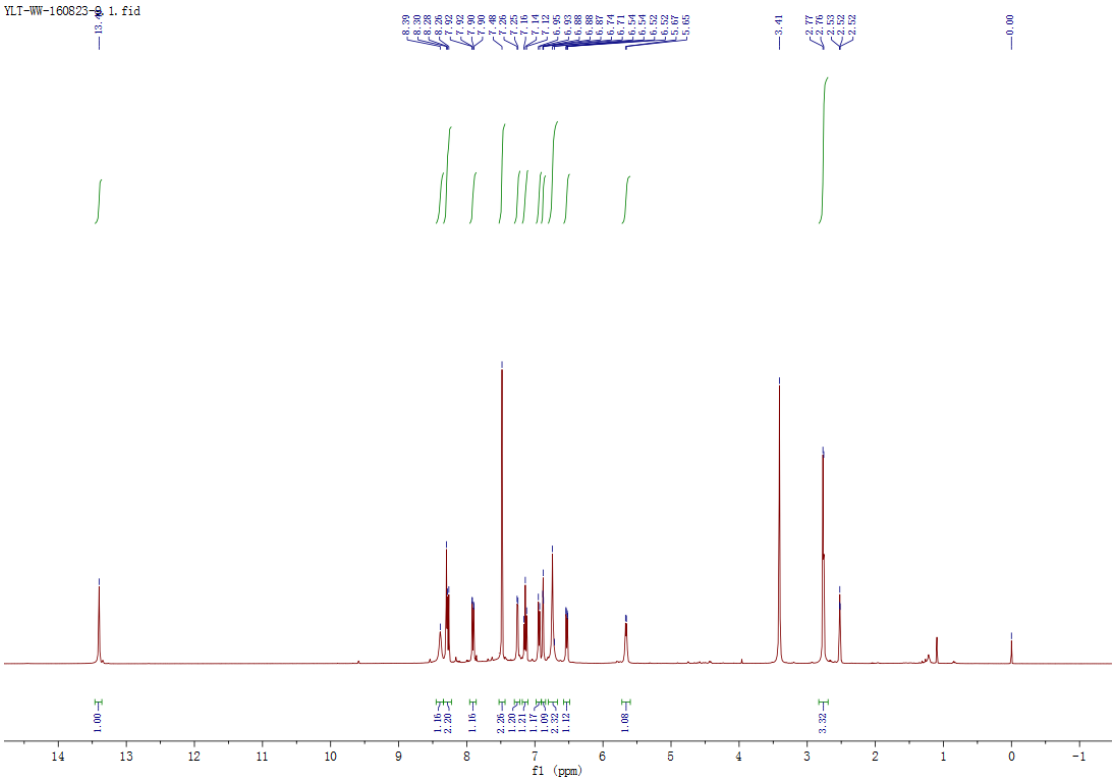


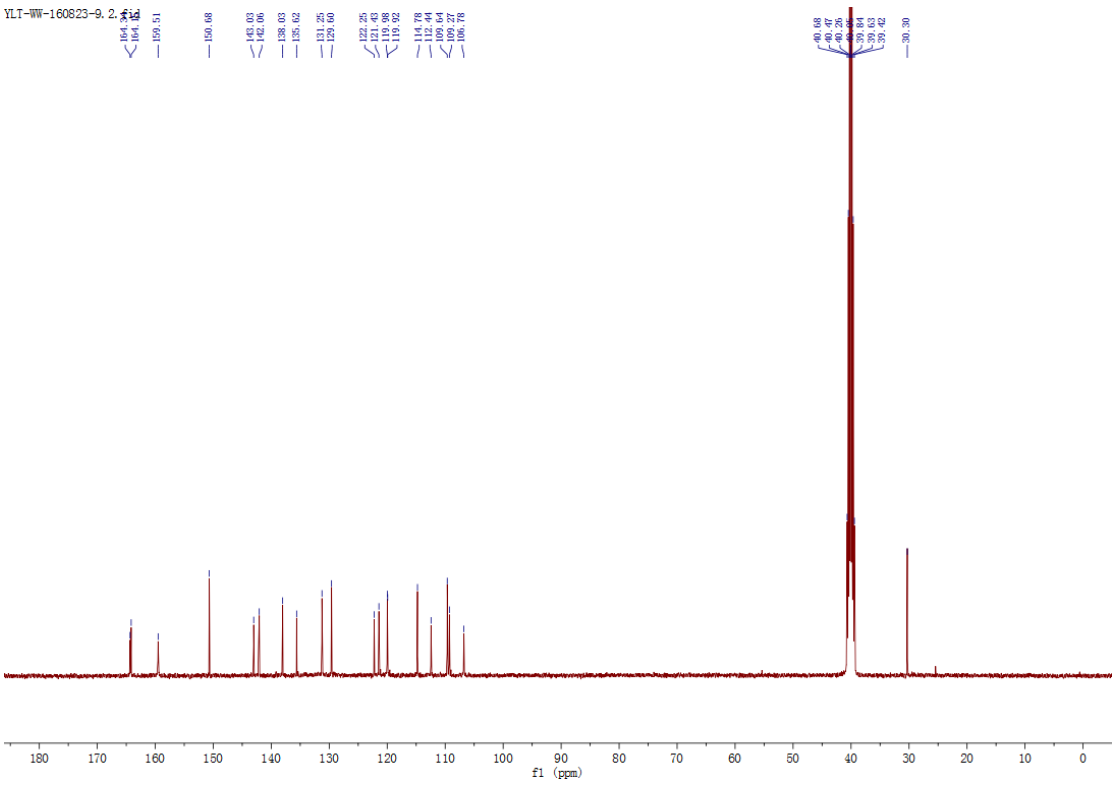




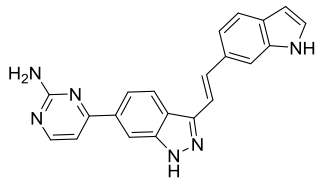
(*E*)-4-(3-(3-(methylamino)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14c**

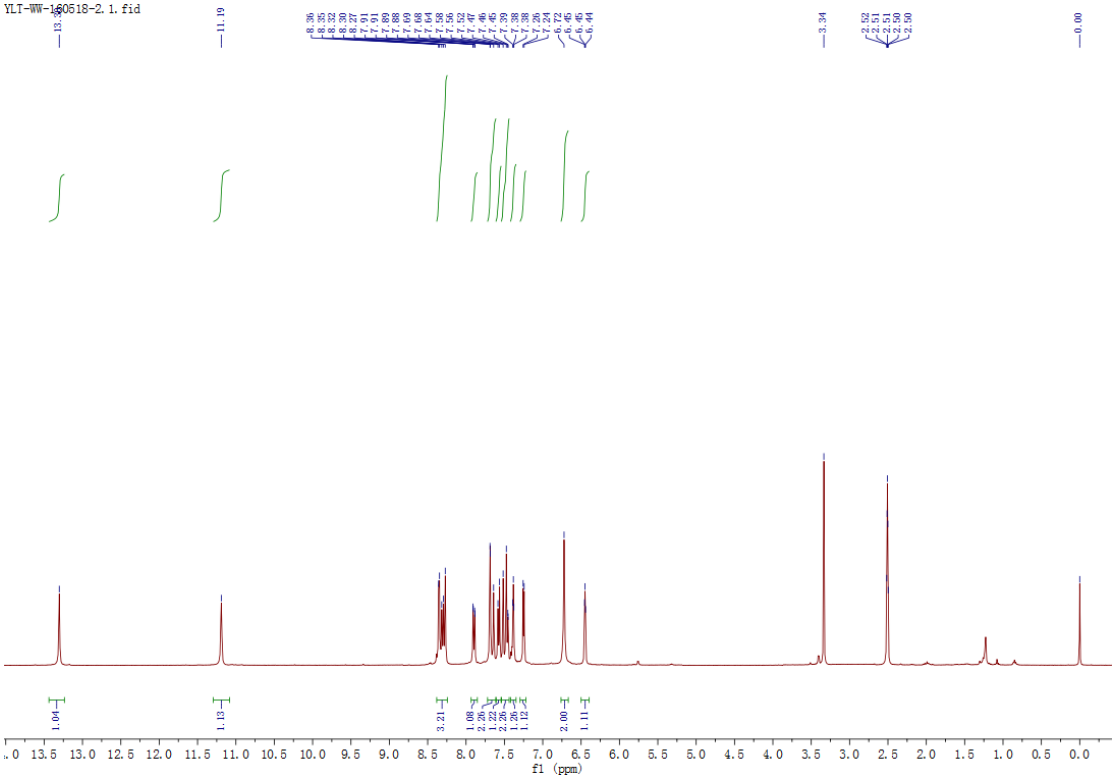


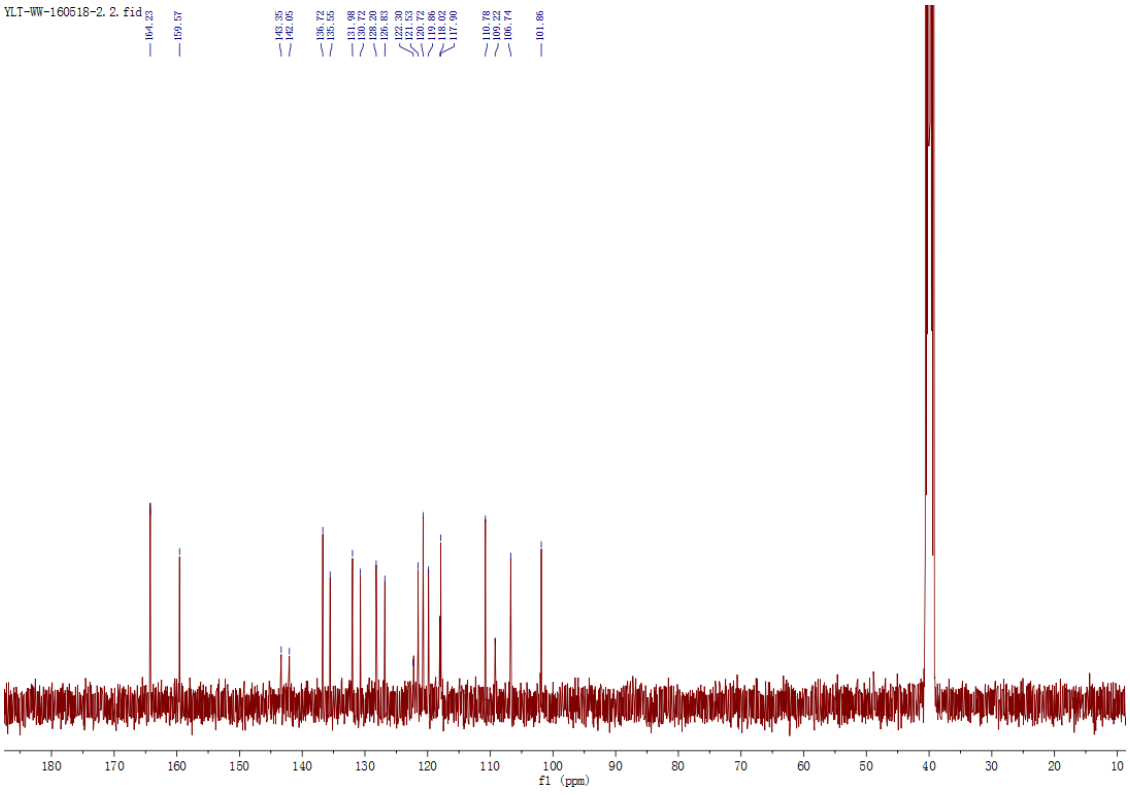




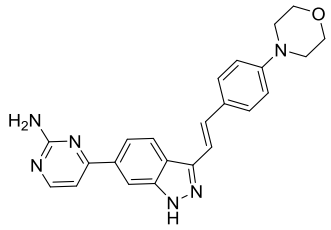
(*E*)-4-(3-(2-(1*H*-indol-6-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14d**

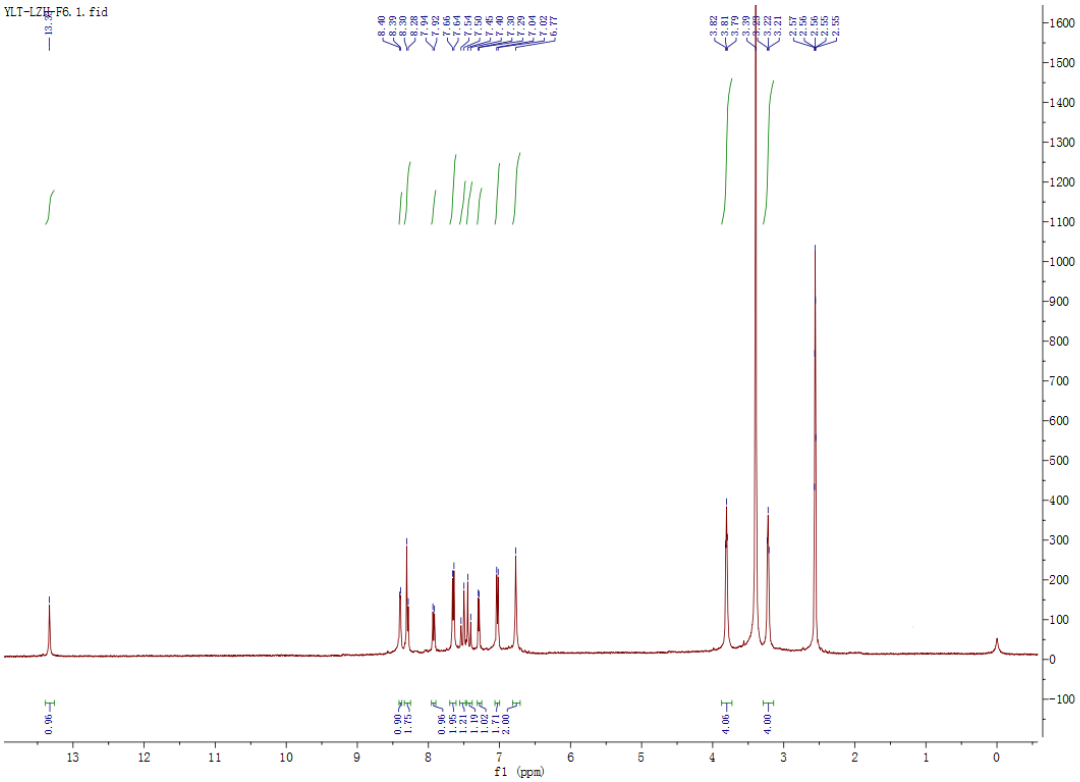


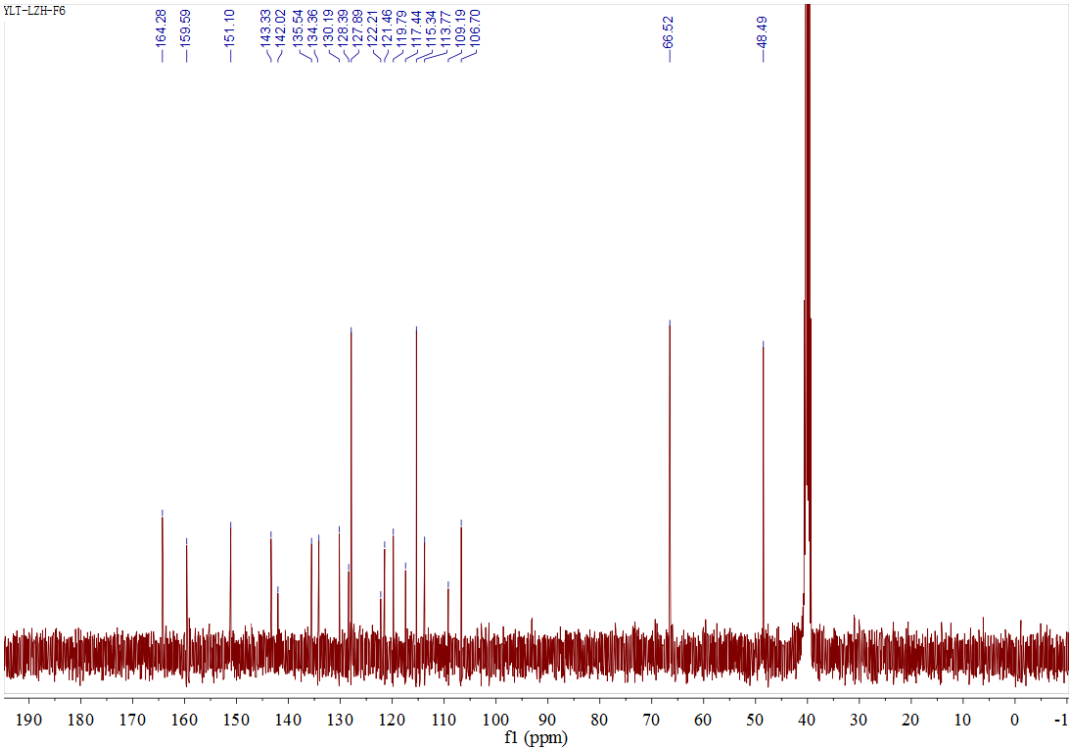




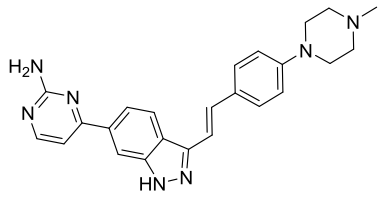
(*E*)-4-(3-(4-morpholinostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14e**

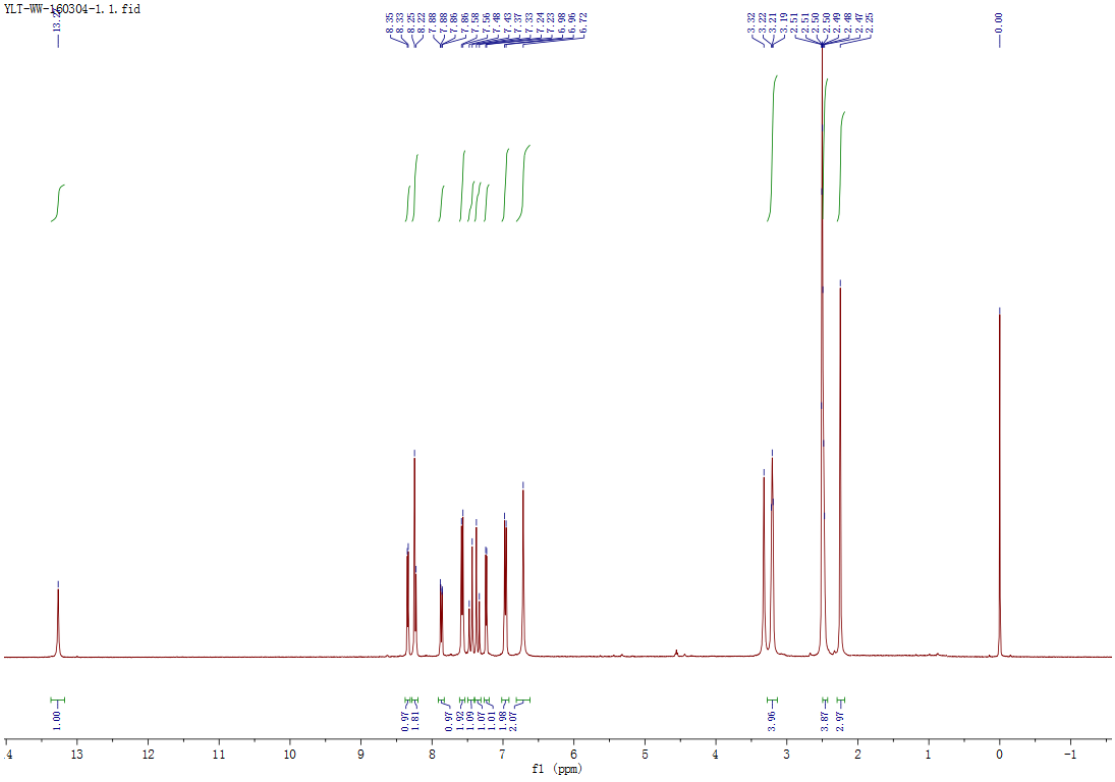


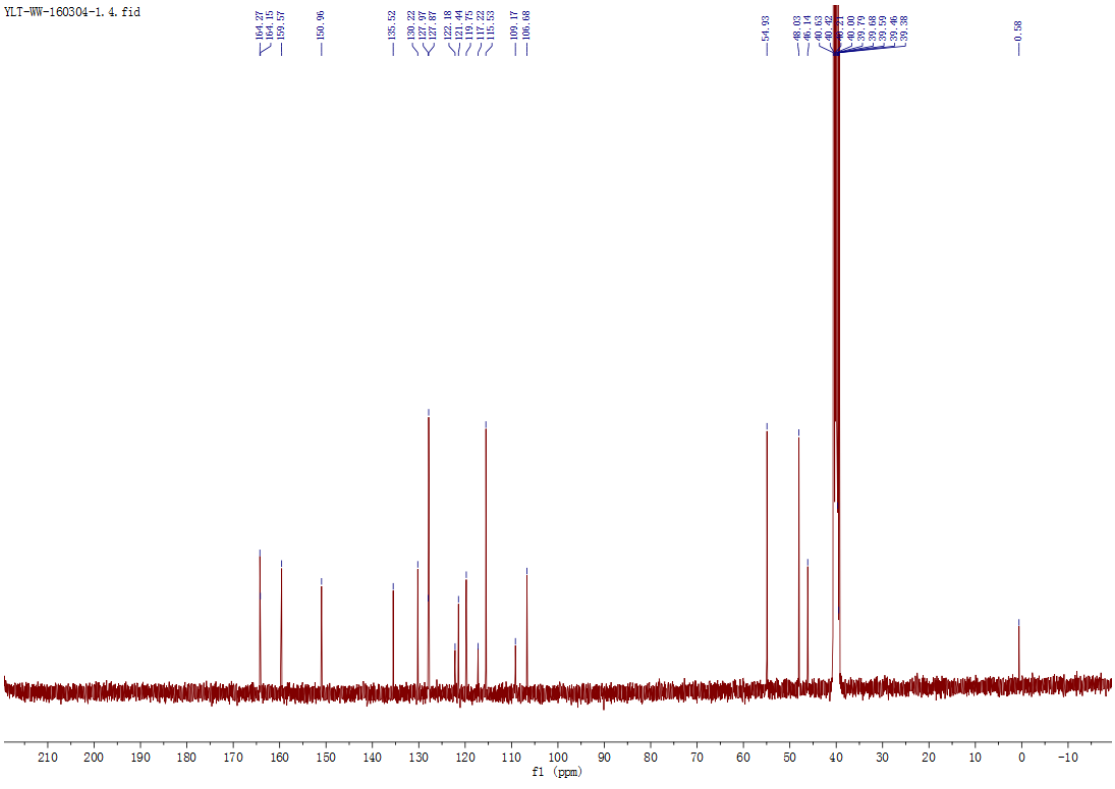




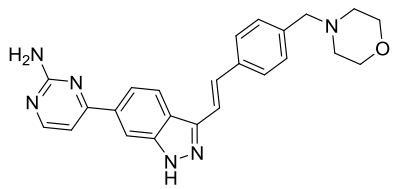
(*E*)-4-(3-(4-(4-methylpiperazin-1-yl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14f**

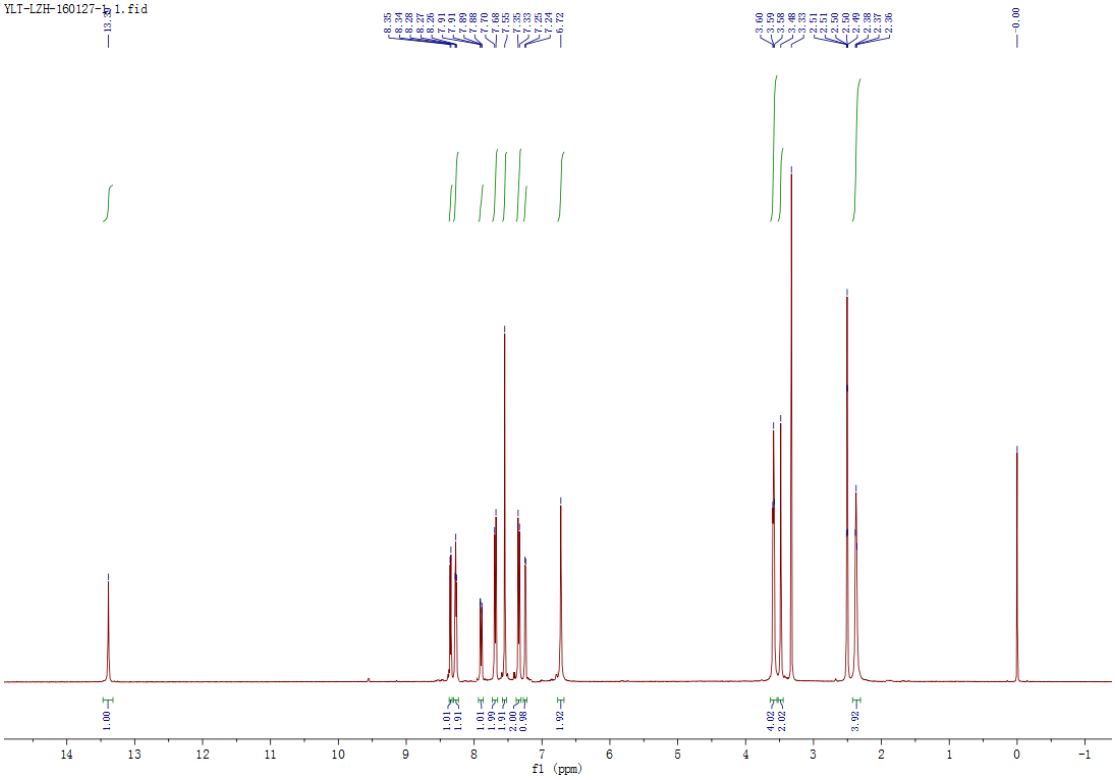


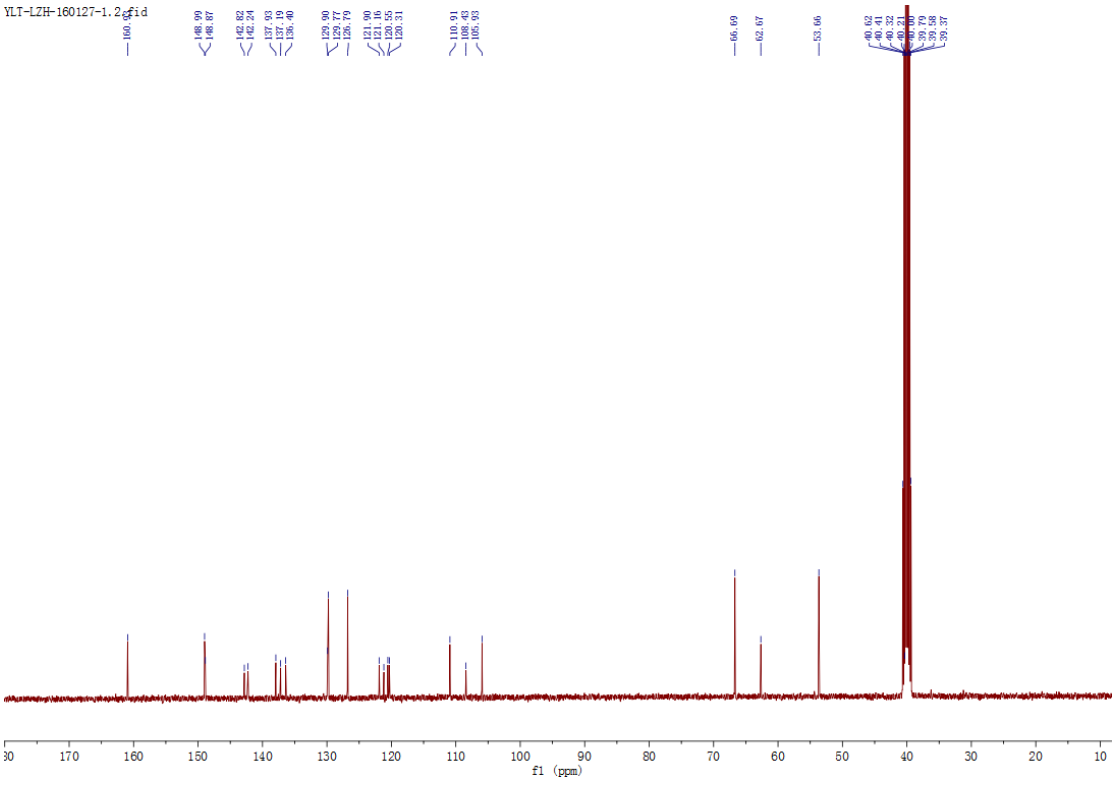




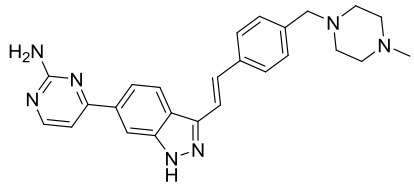
(*E*)-4-(3-(4-(morpholinomethyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14g**

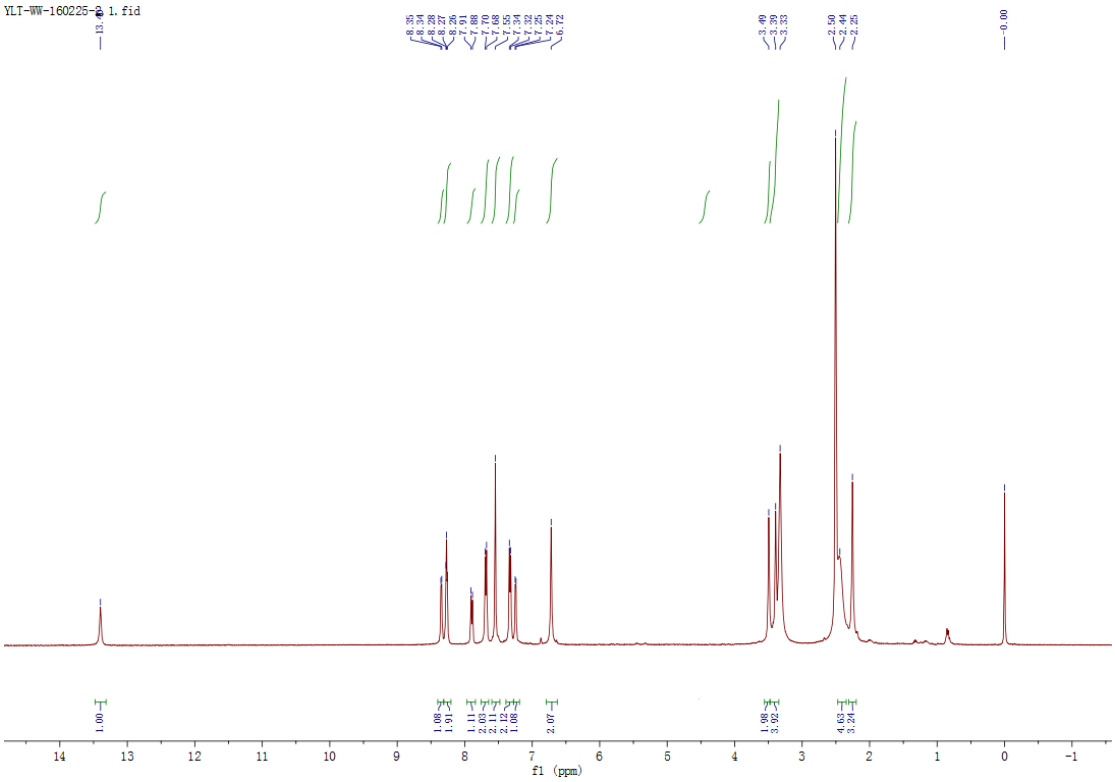


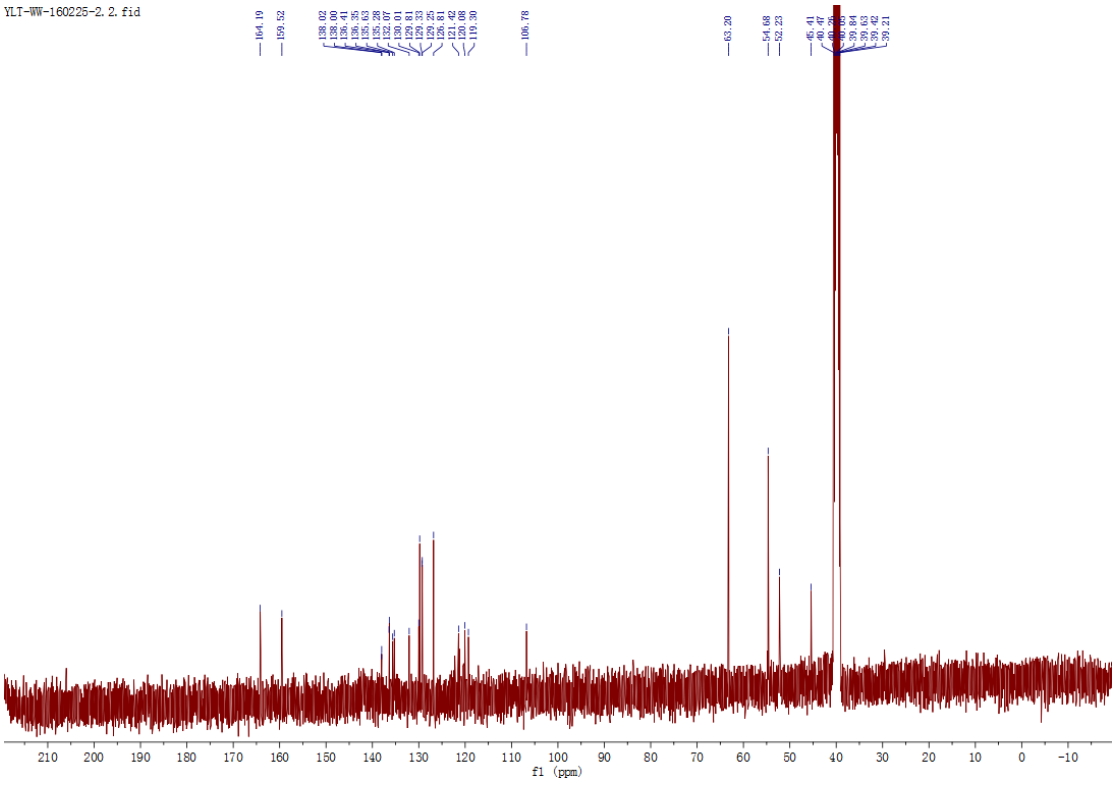




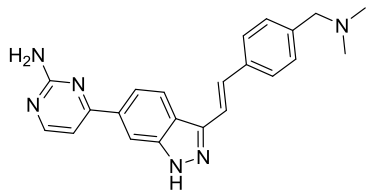
(*E*)-4-(3-(4-((4-methylpiperazin-1-yl)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14h**

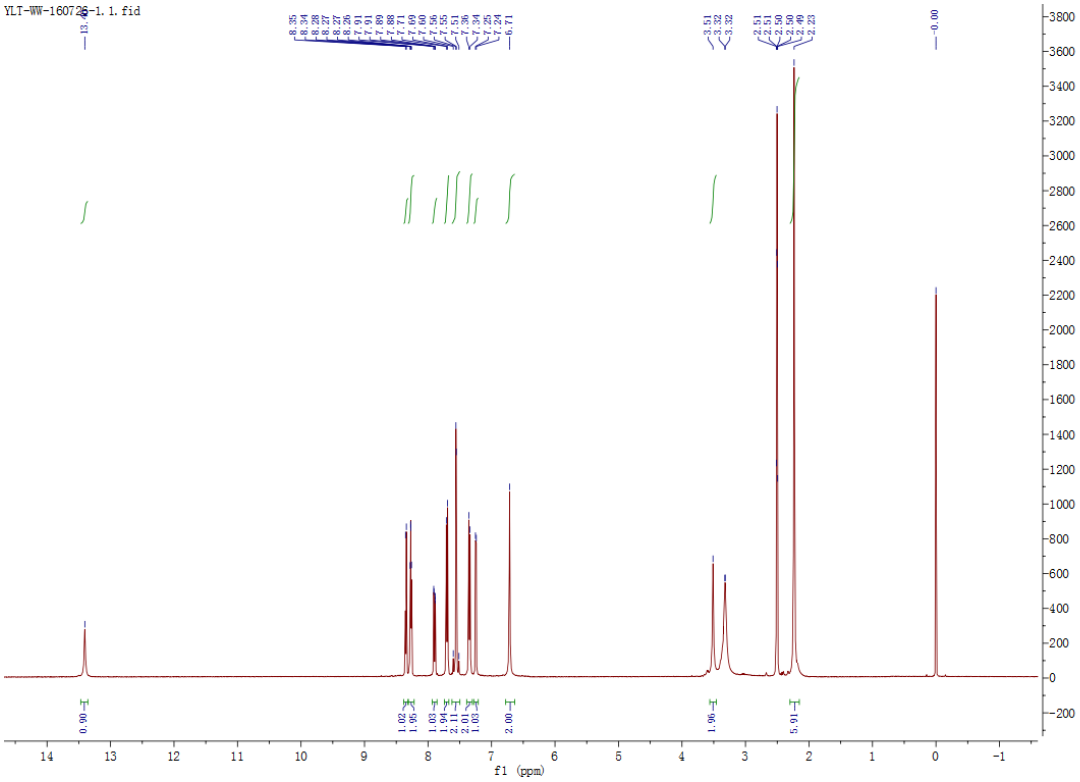


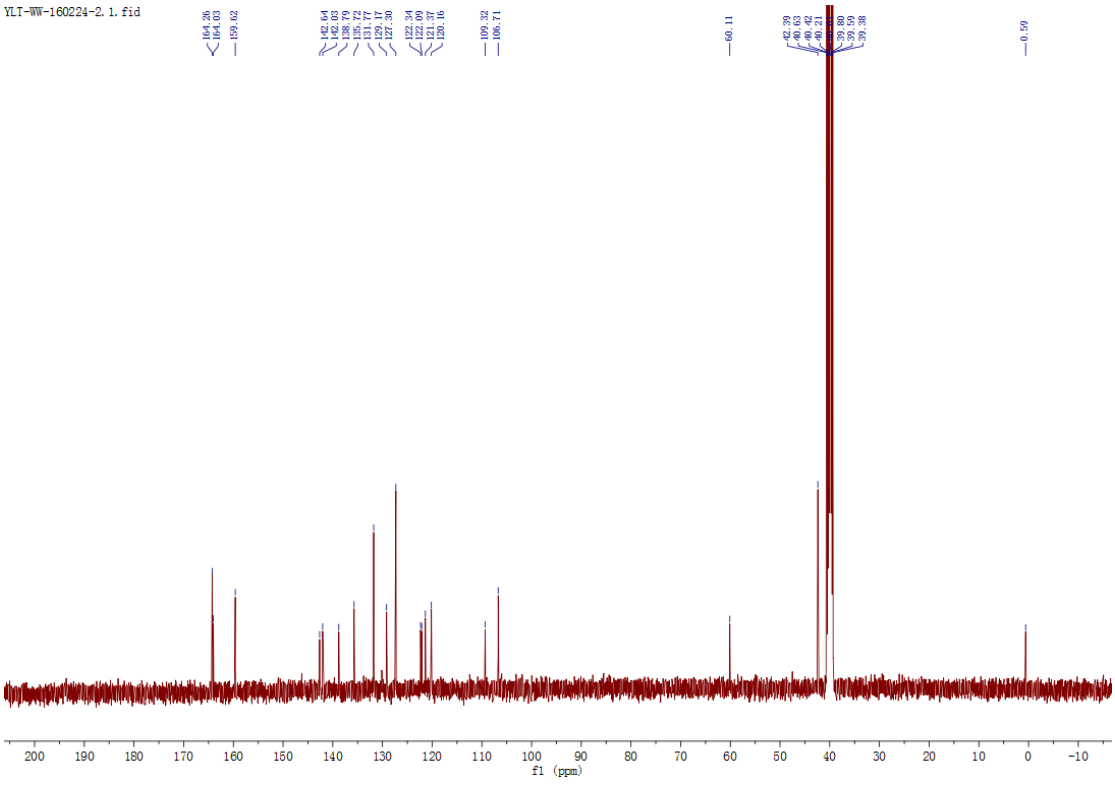




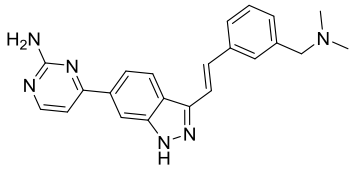
(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14i**

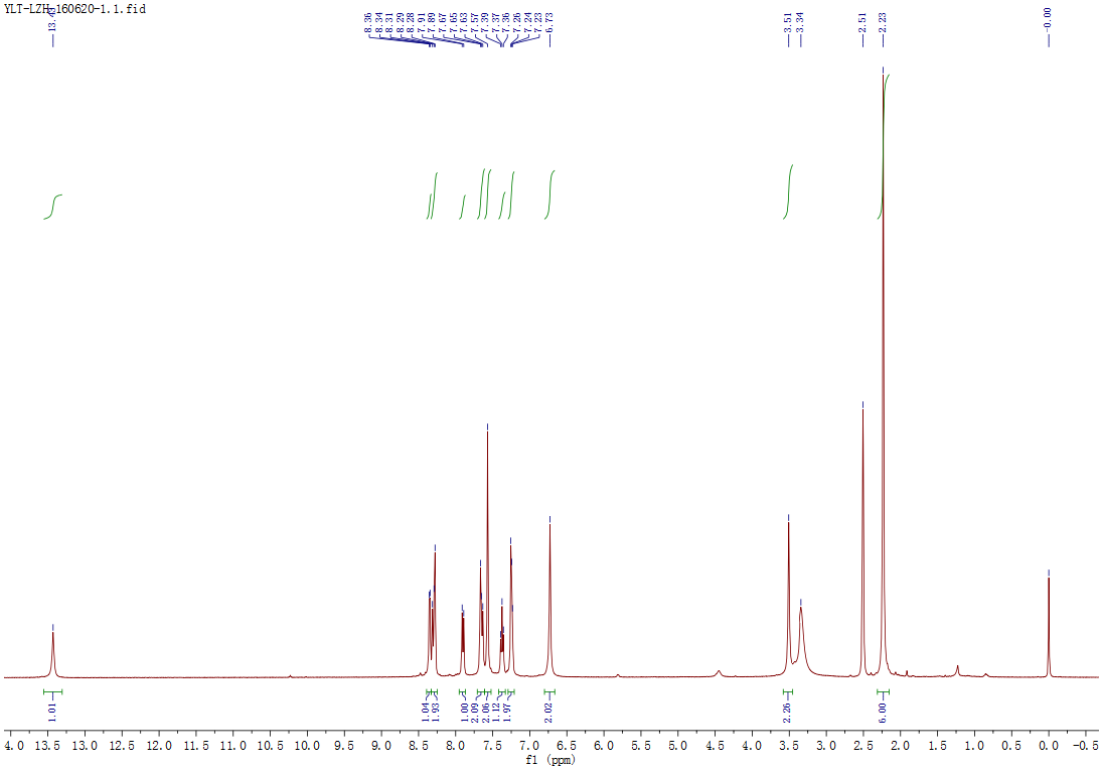


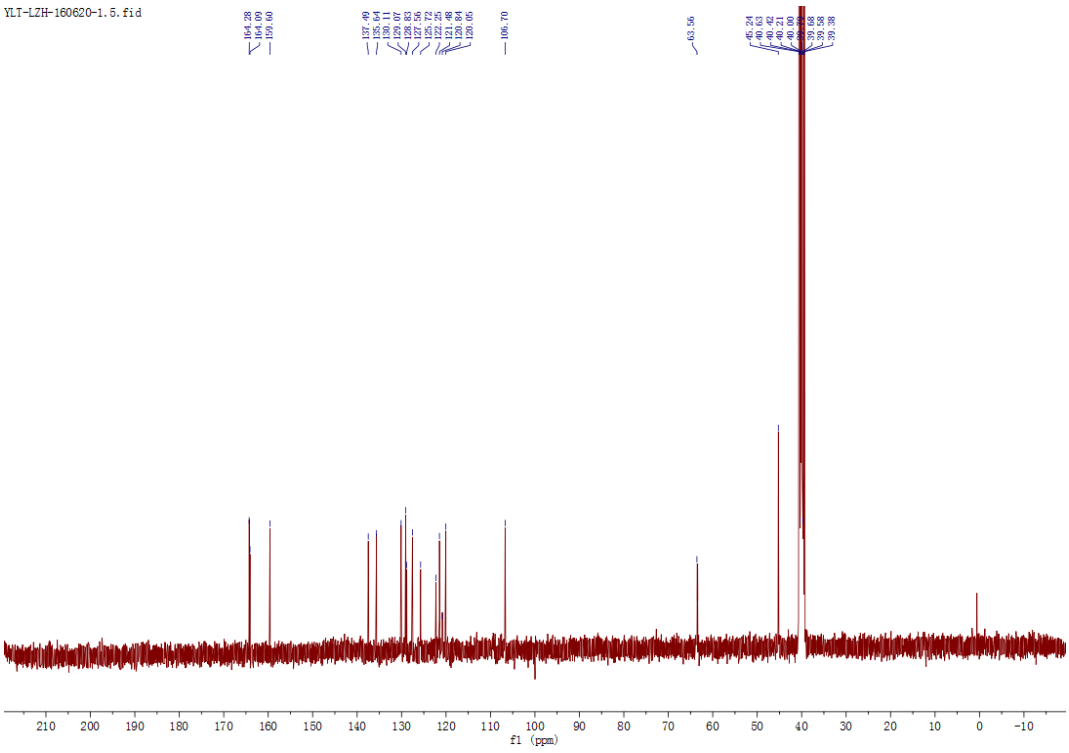




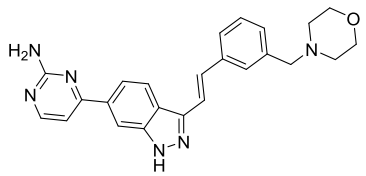
(*E*)-4-(3-(3-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14j**

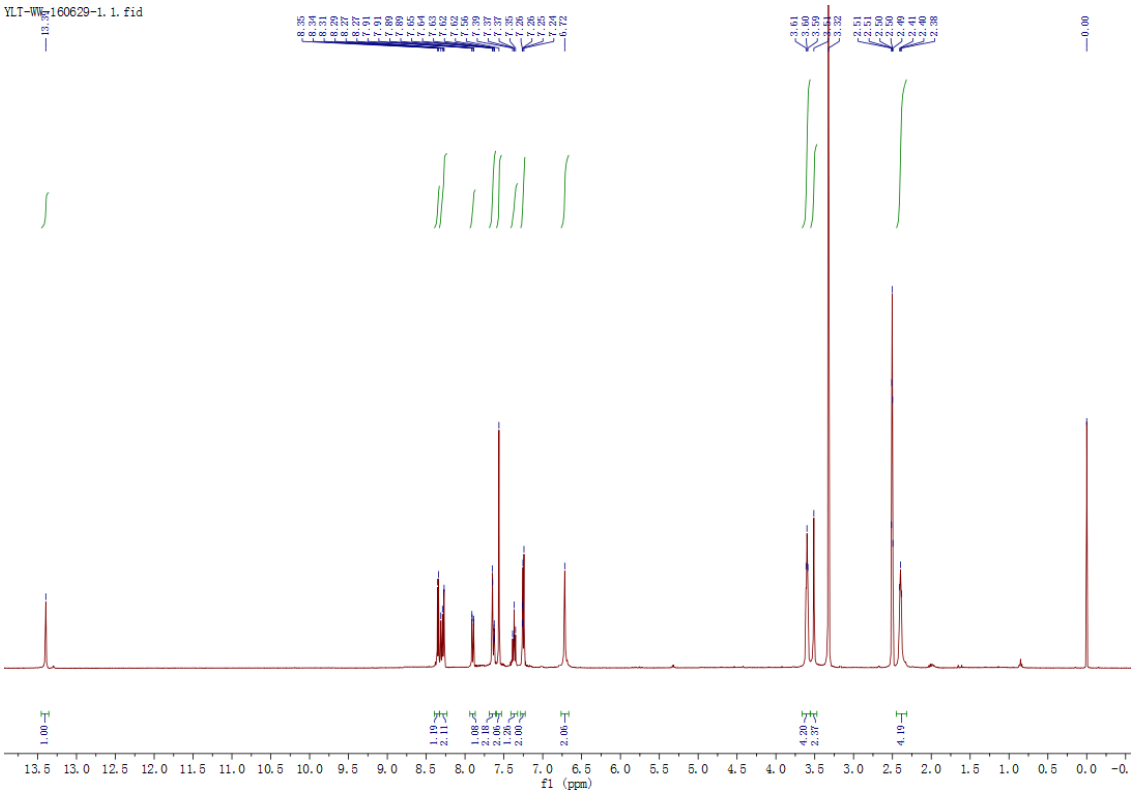


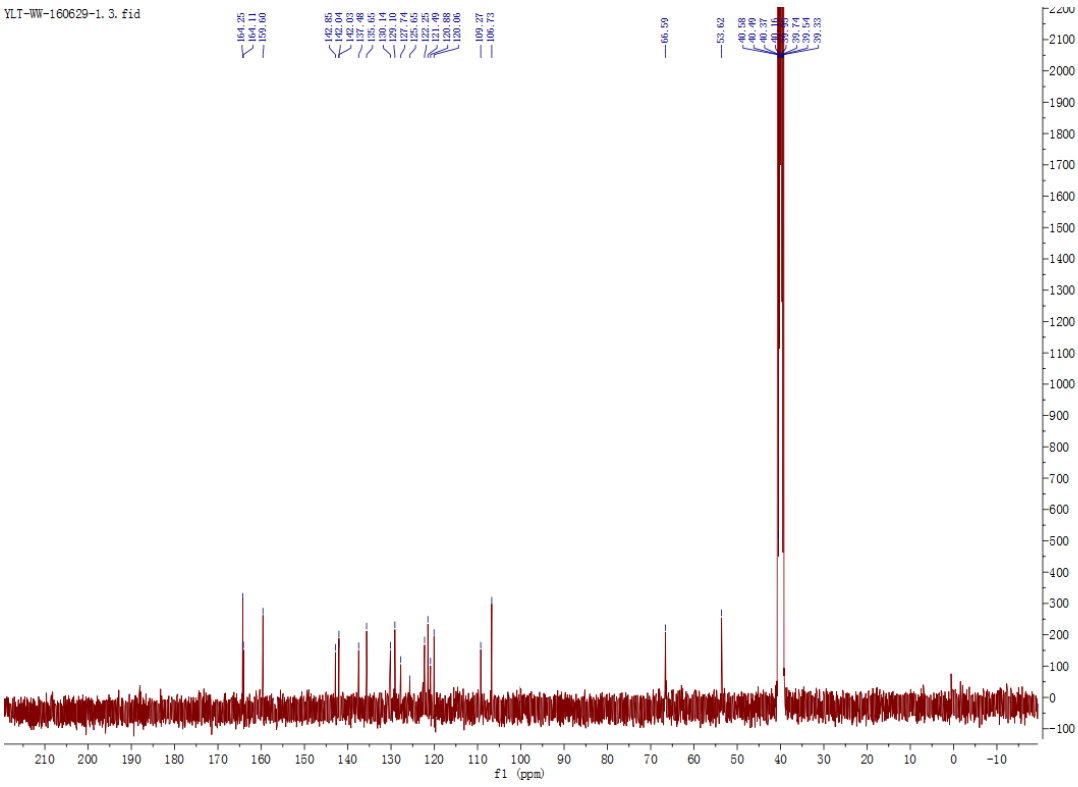




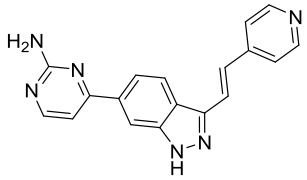
(*E*)-4-(3-(3-(morpholinomethyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14k**

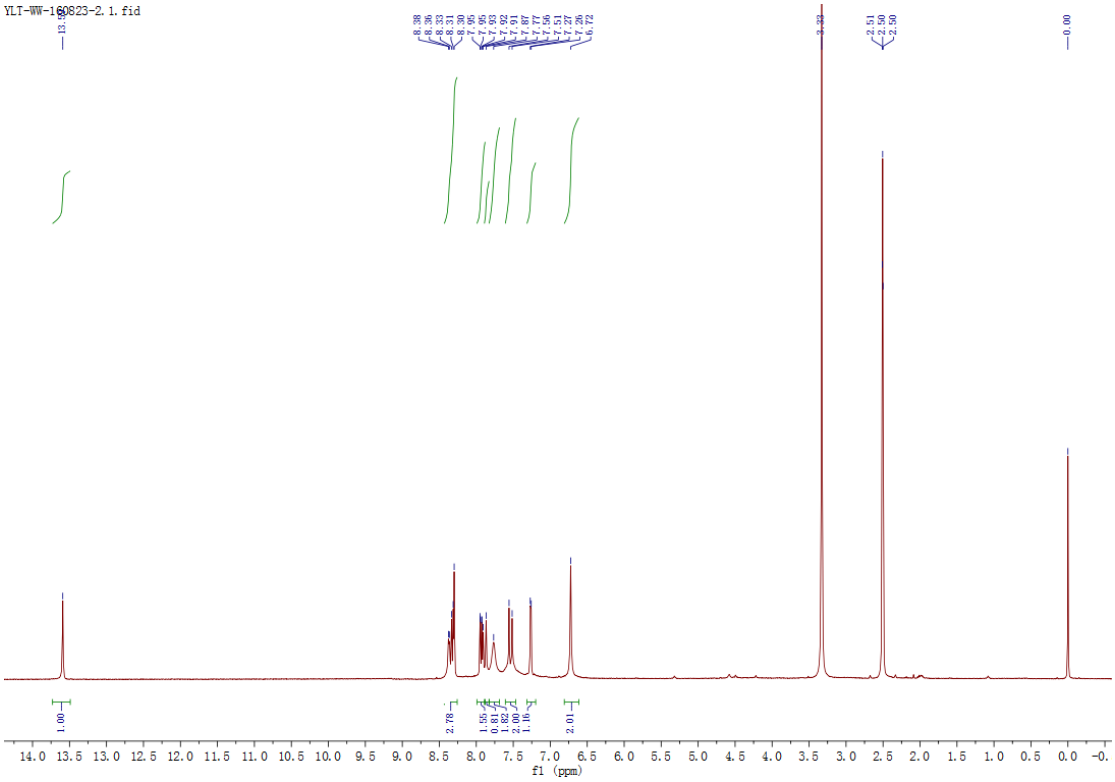


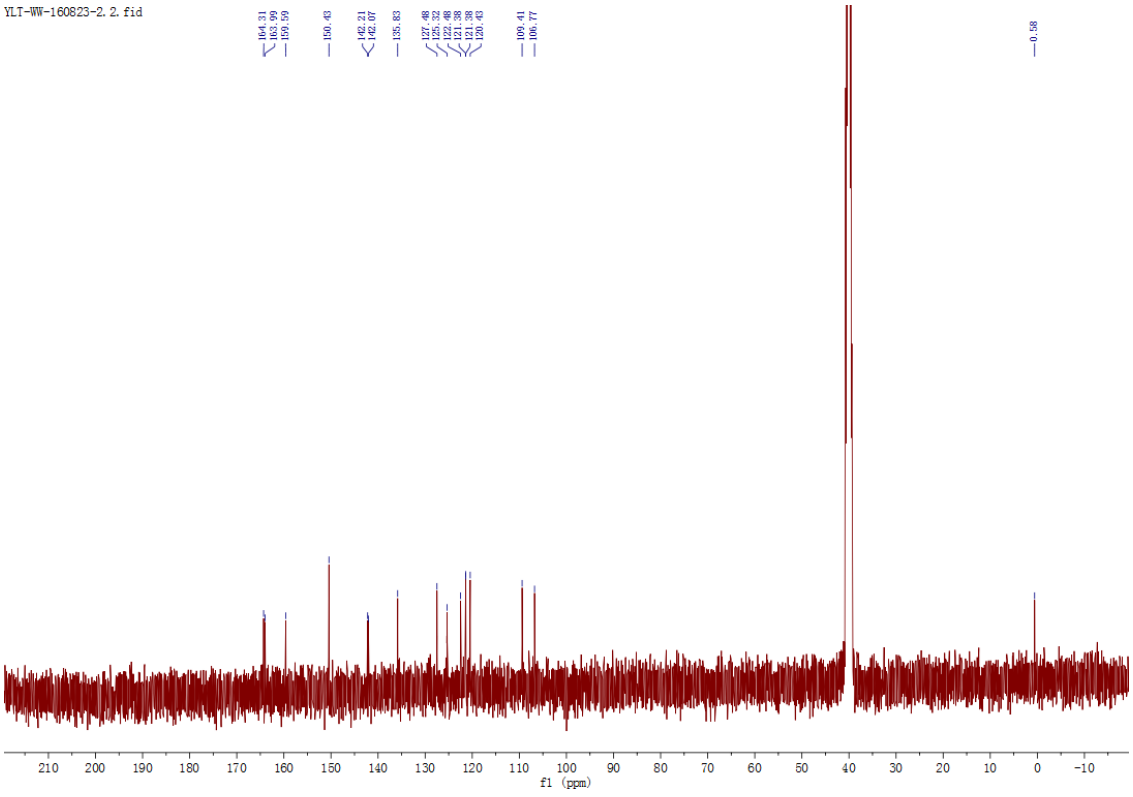




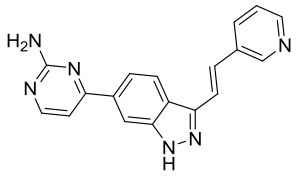
(*E*)-4-(3-(2-(pyridin-4-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14l**

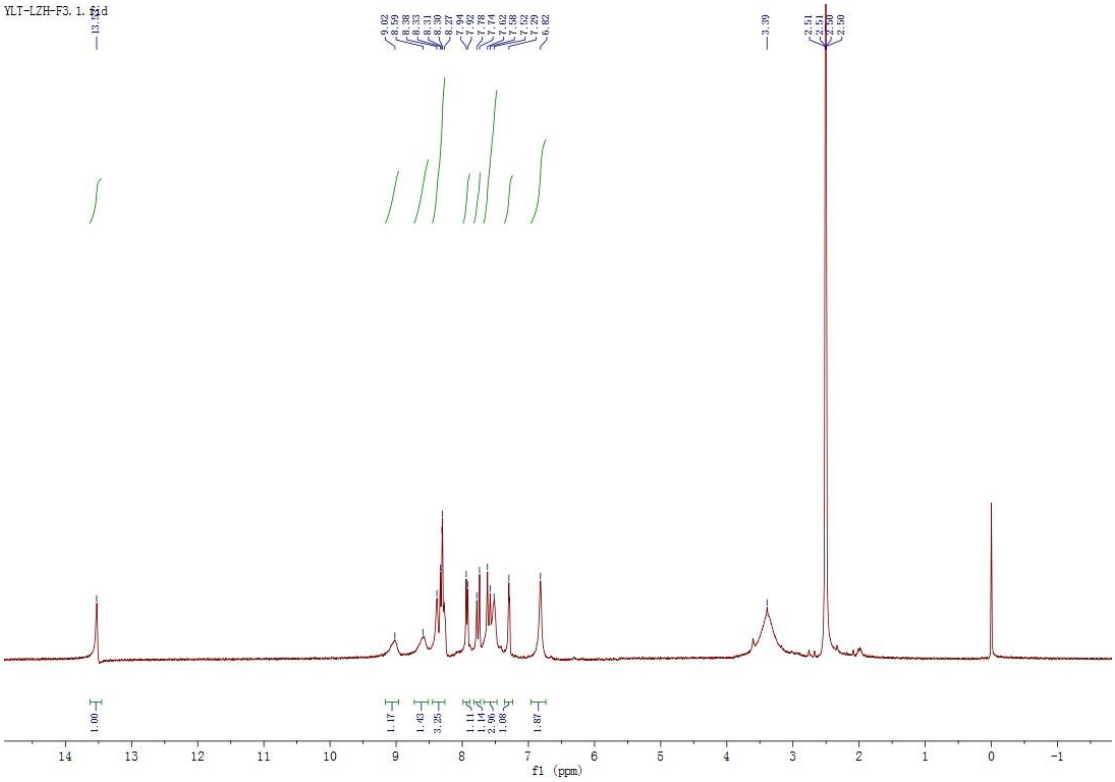


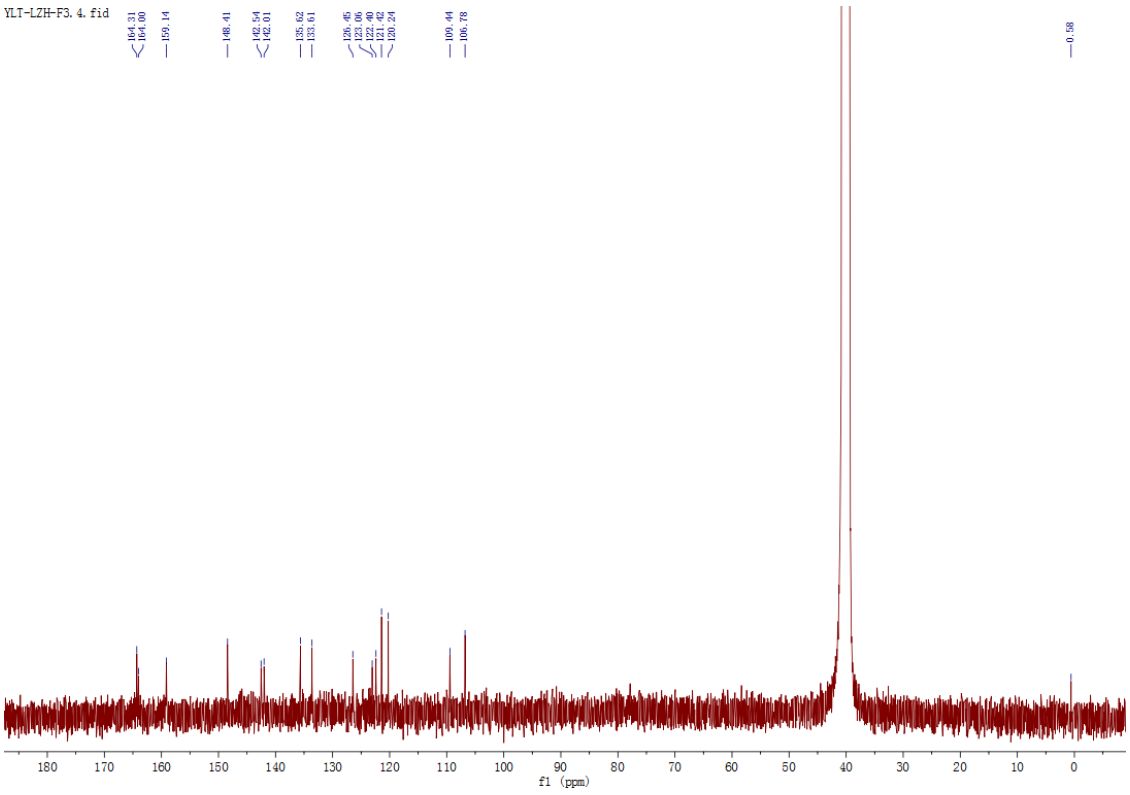




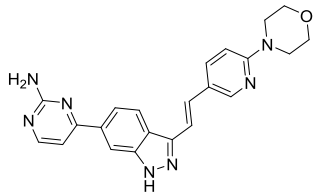
(*E*)-4-(3-(2-(pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14m**

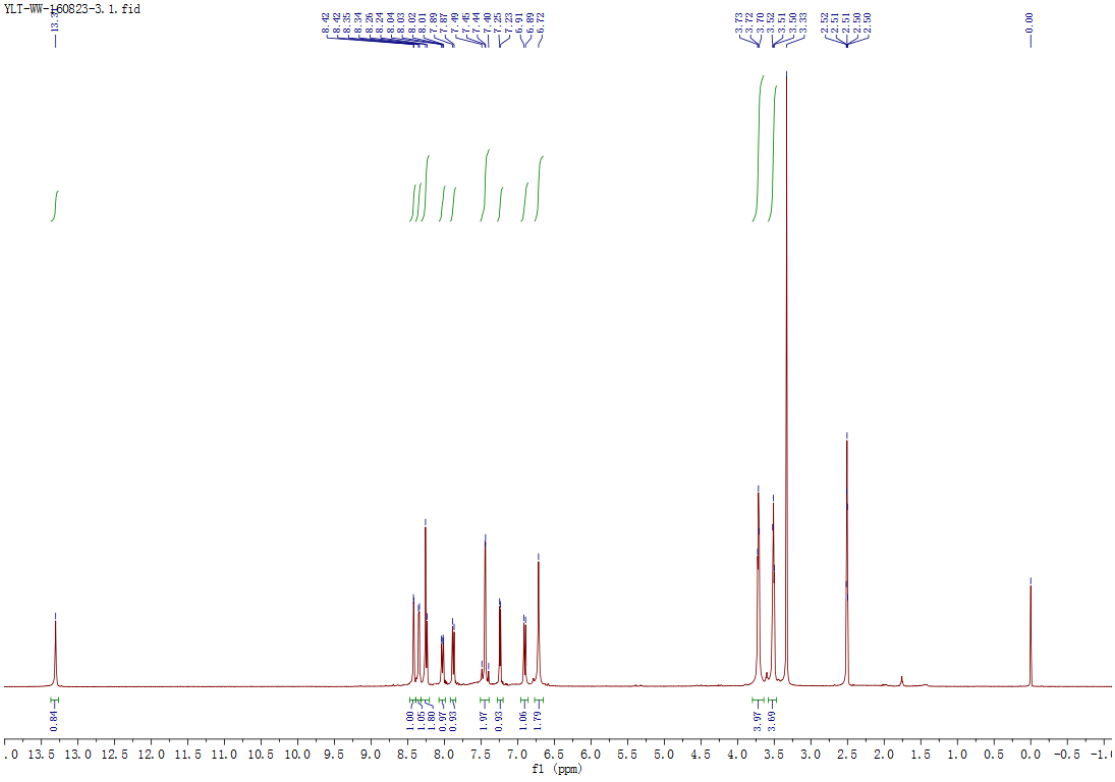


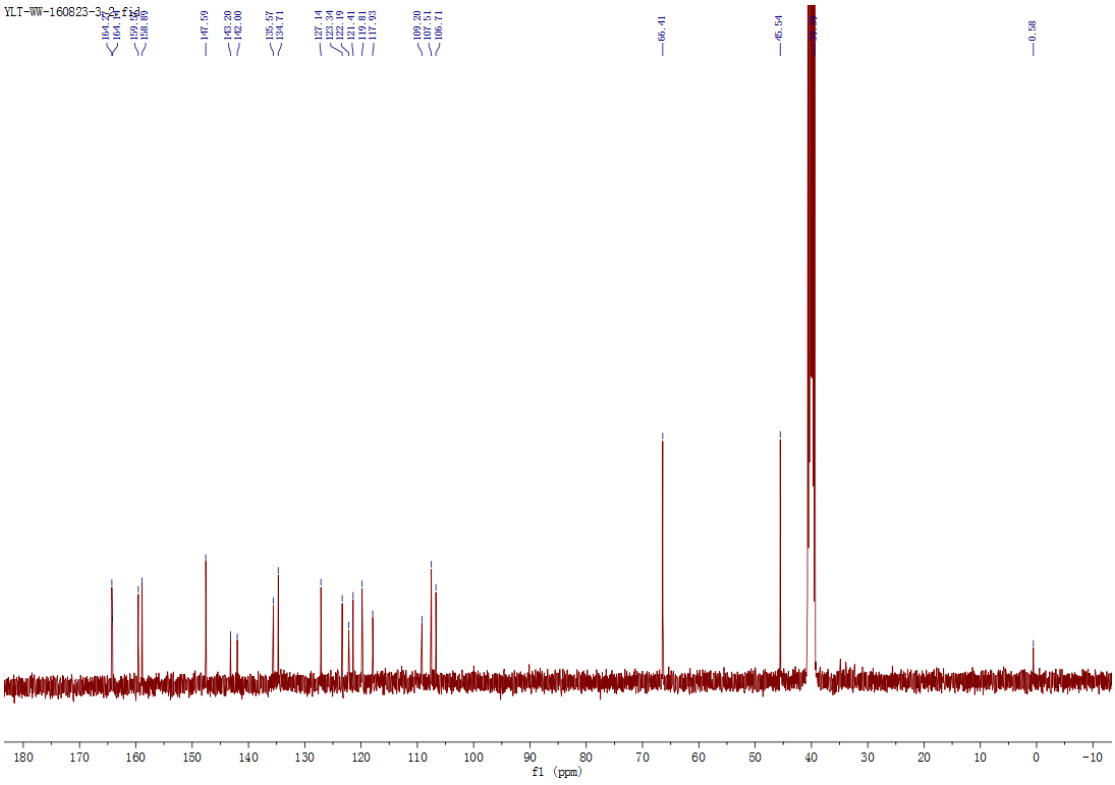




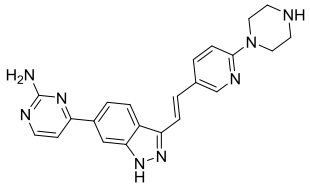
(*E*)-4-(3-(2-(6-morpholinopyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14n**

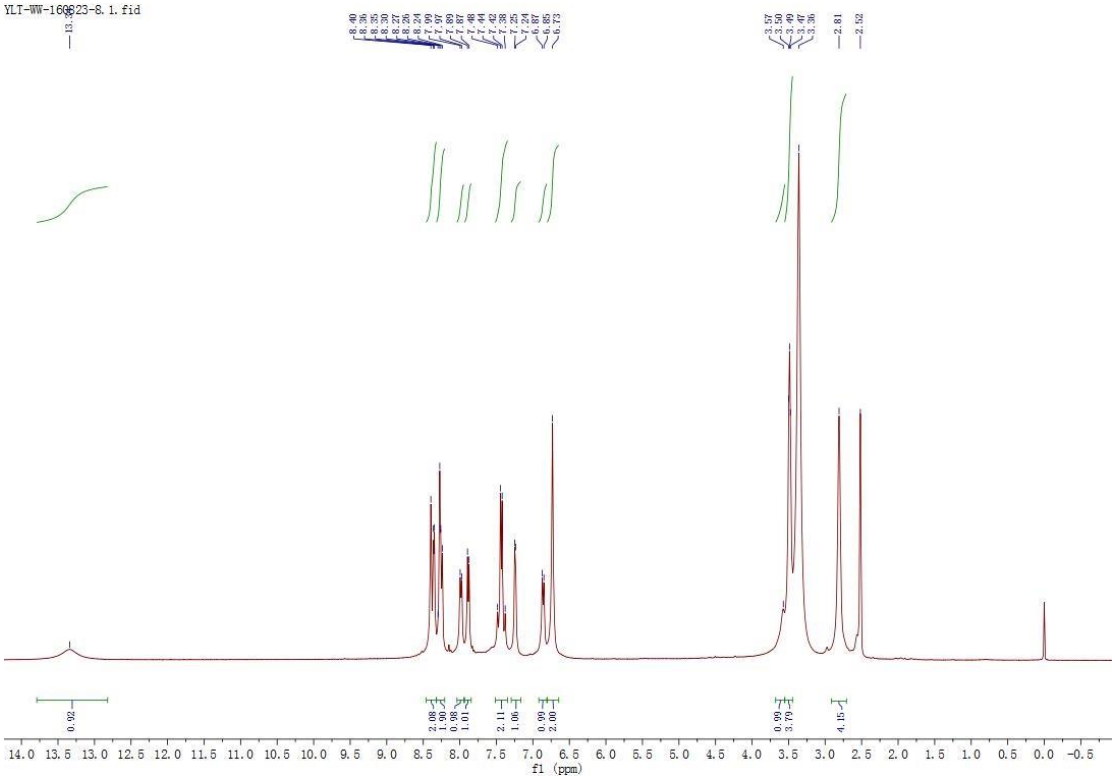


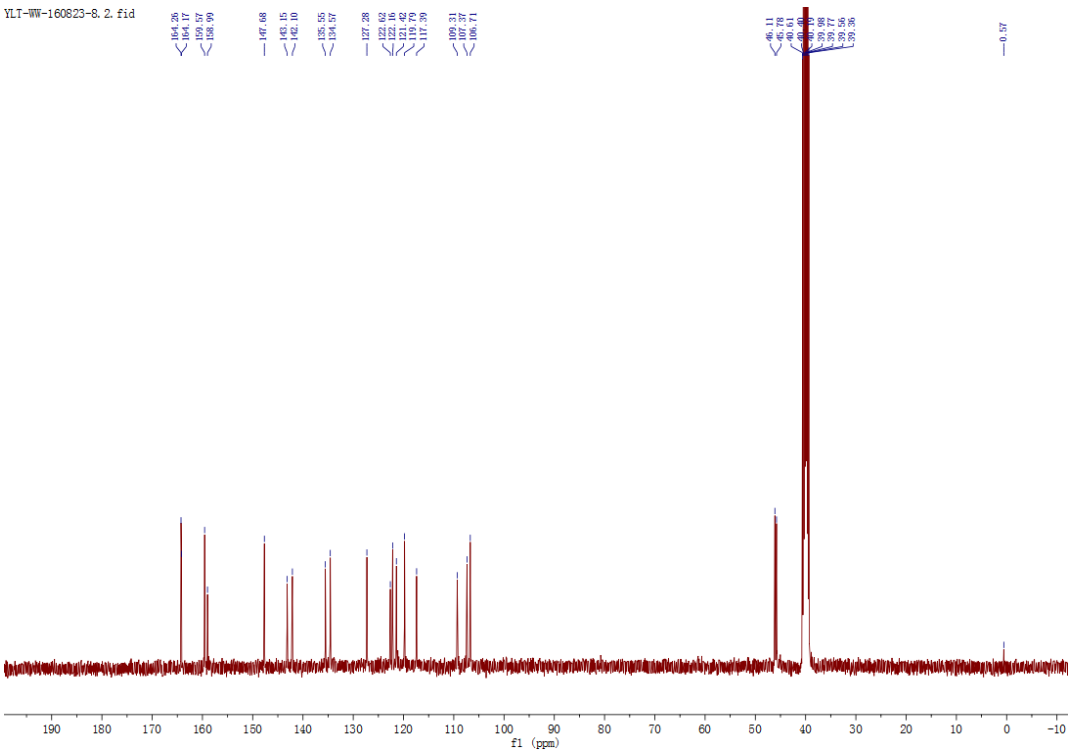




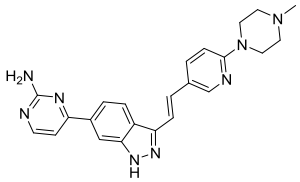
(*E*)-4-(3-(2-(6-(piperazin-1-yl)pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14o**

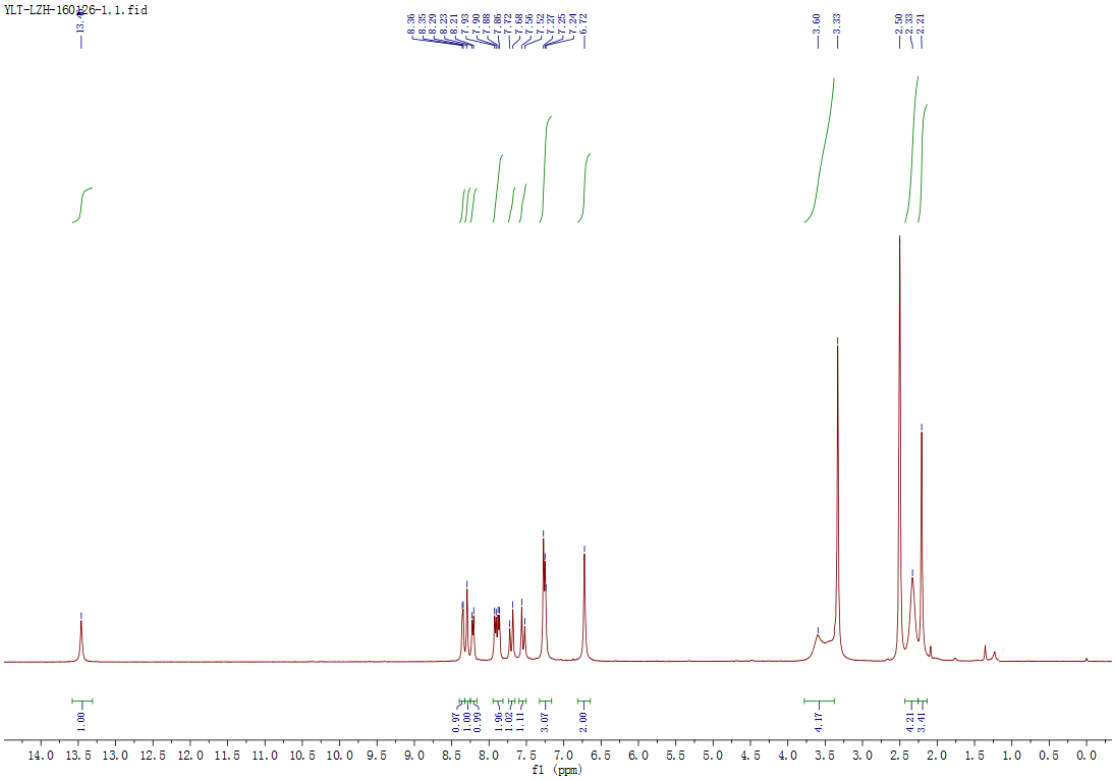


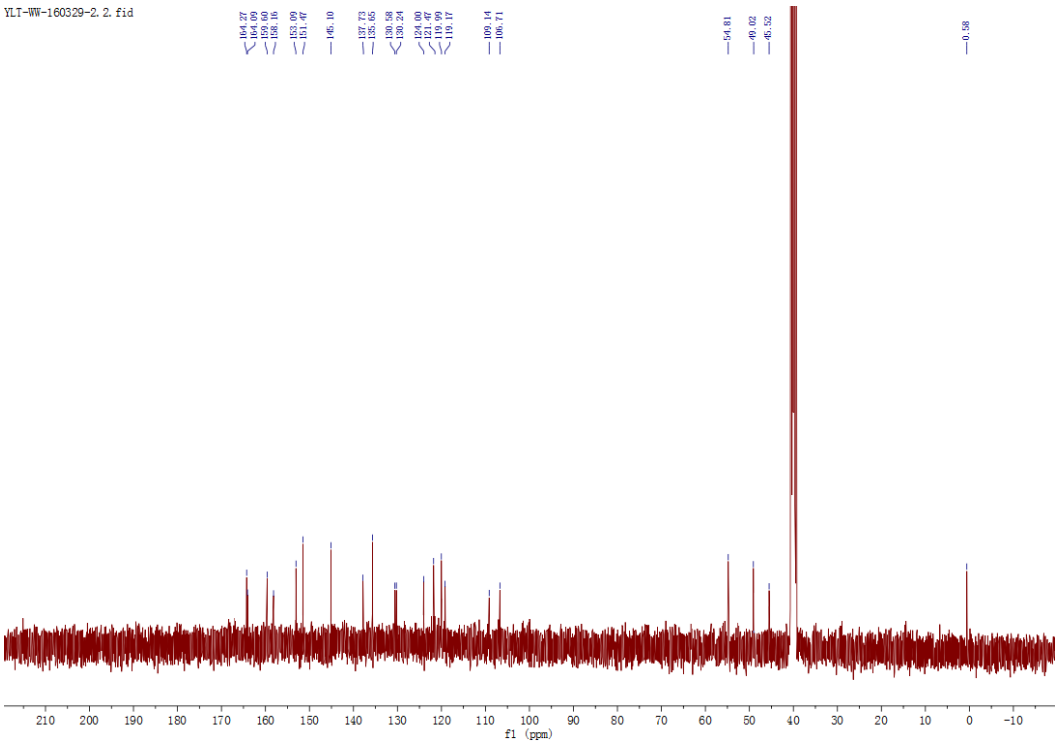




(*E*)-4-(3-(2-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)vinyl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14p**

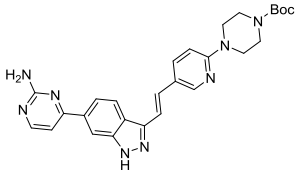


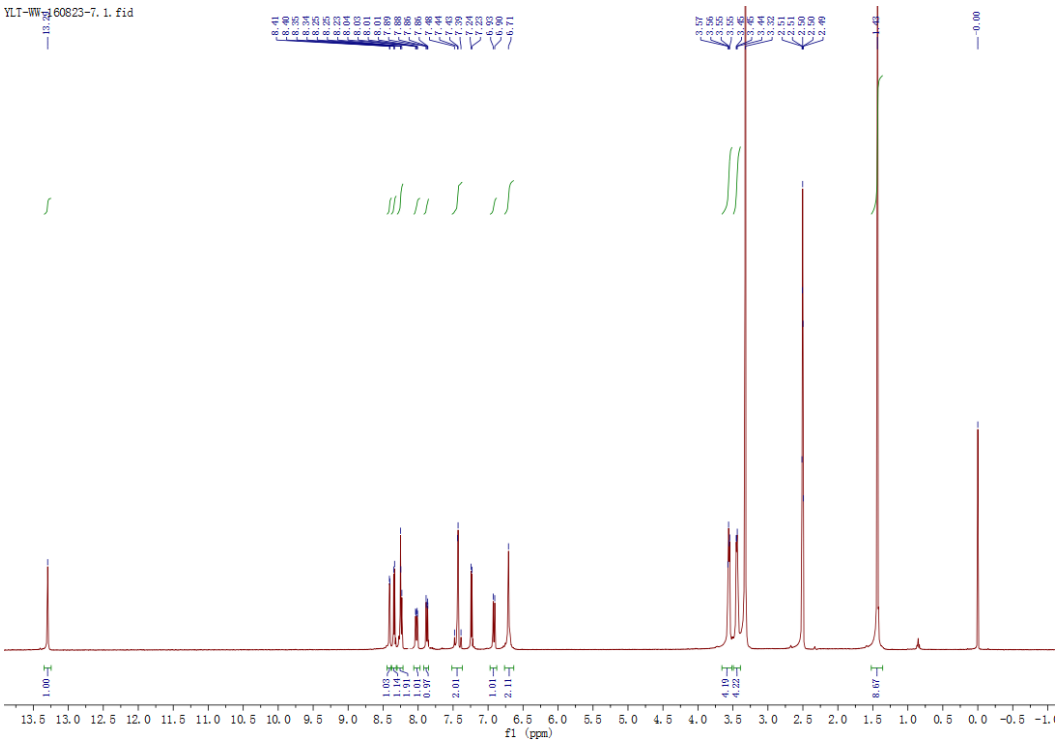


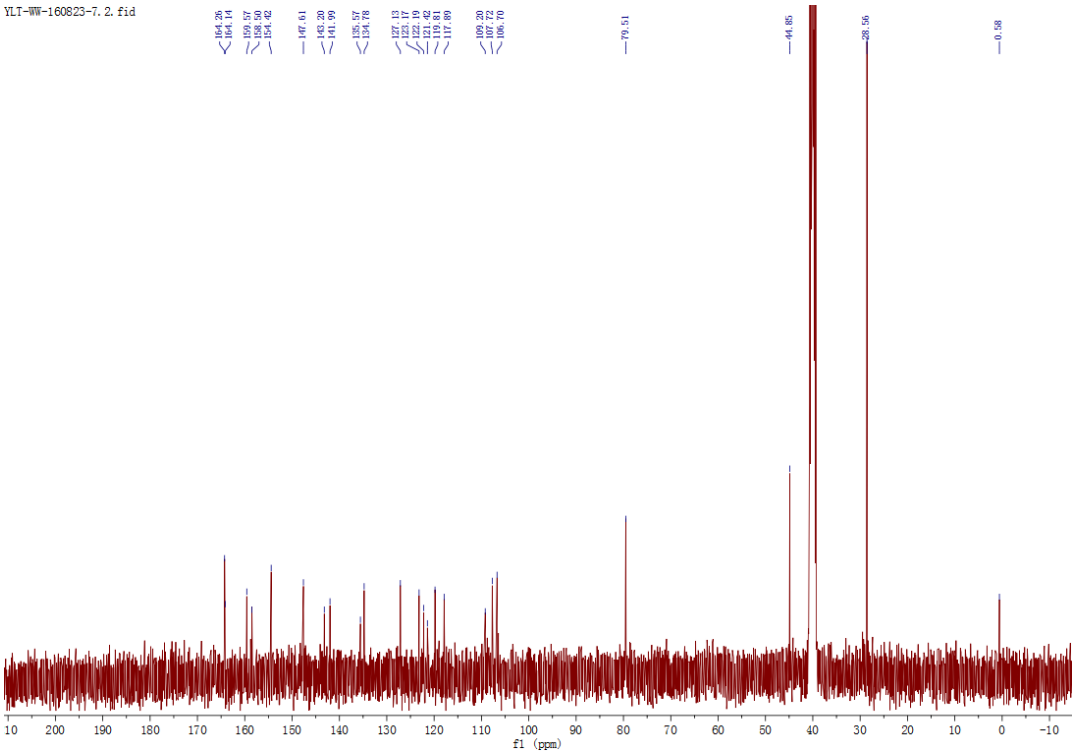


Tert-butyl (*E*)-4-(5-(2-(6-(2-aminopyrimidin-4-yl)-1*H*-indazol-3-yl)vinyl)pyridin-2-yl)piperazine-1-carboxylate

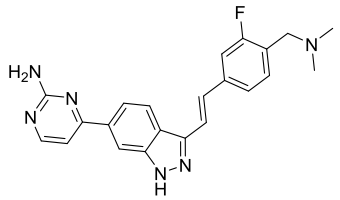
14q

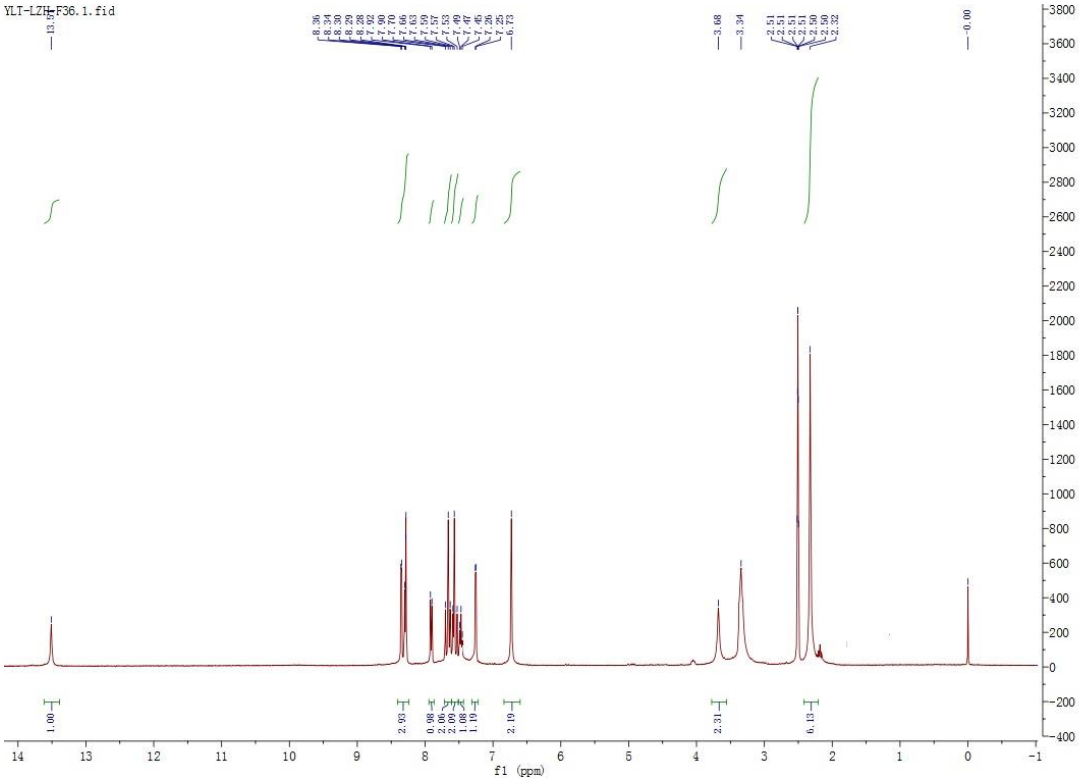


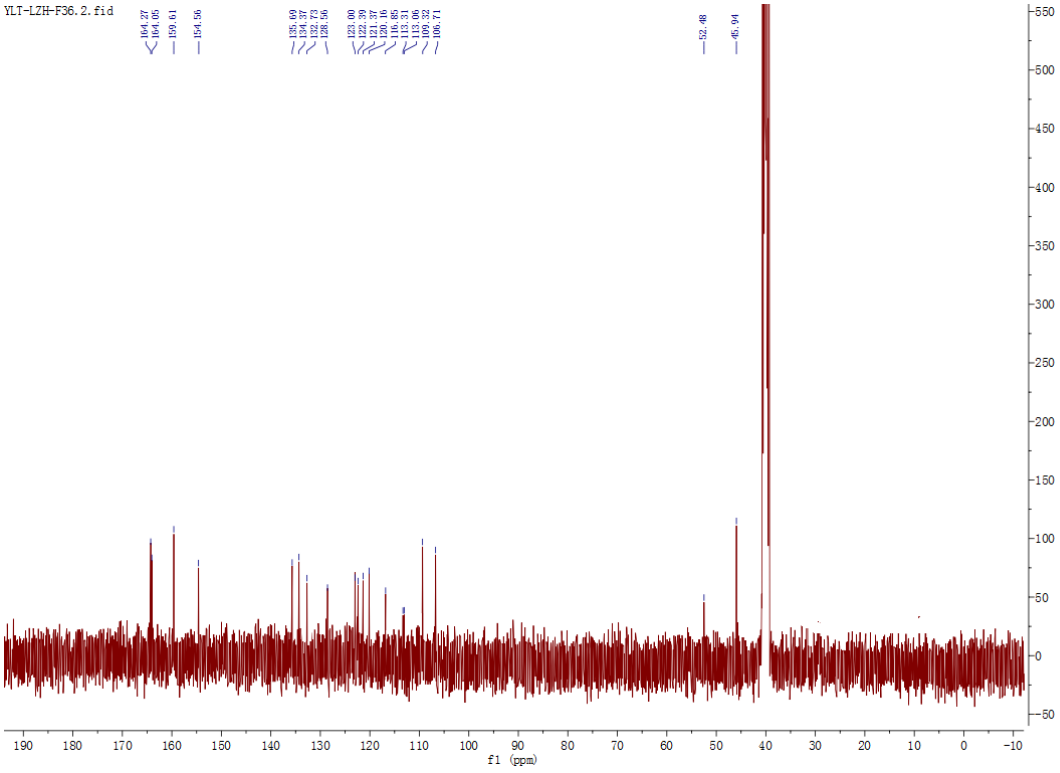




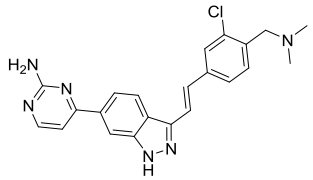
(*E*)-4-(3-(4-((dimethylamino)methyl)-3-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14r**

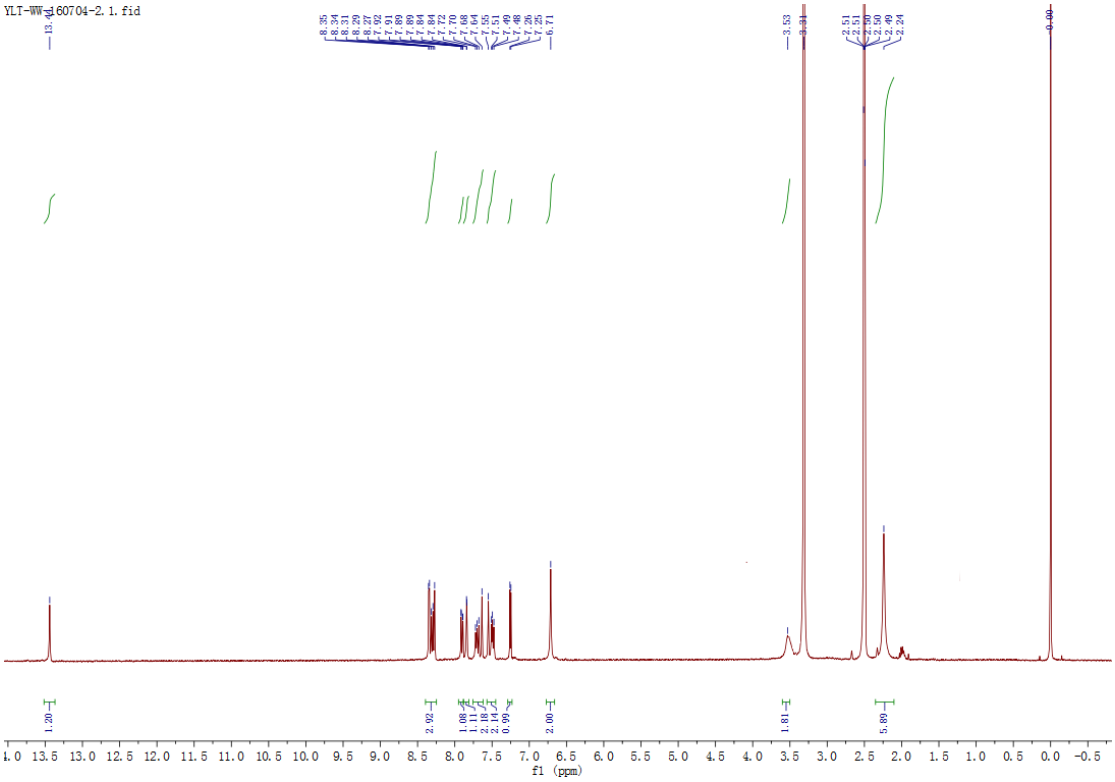


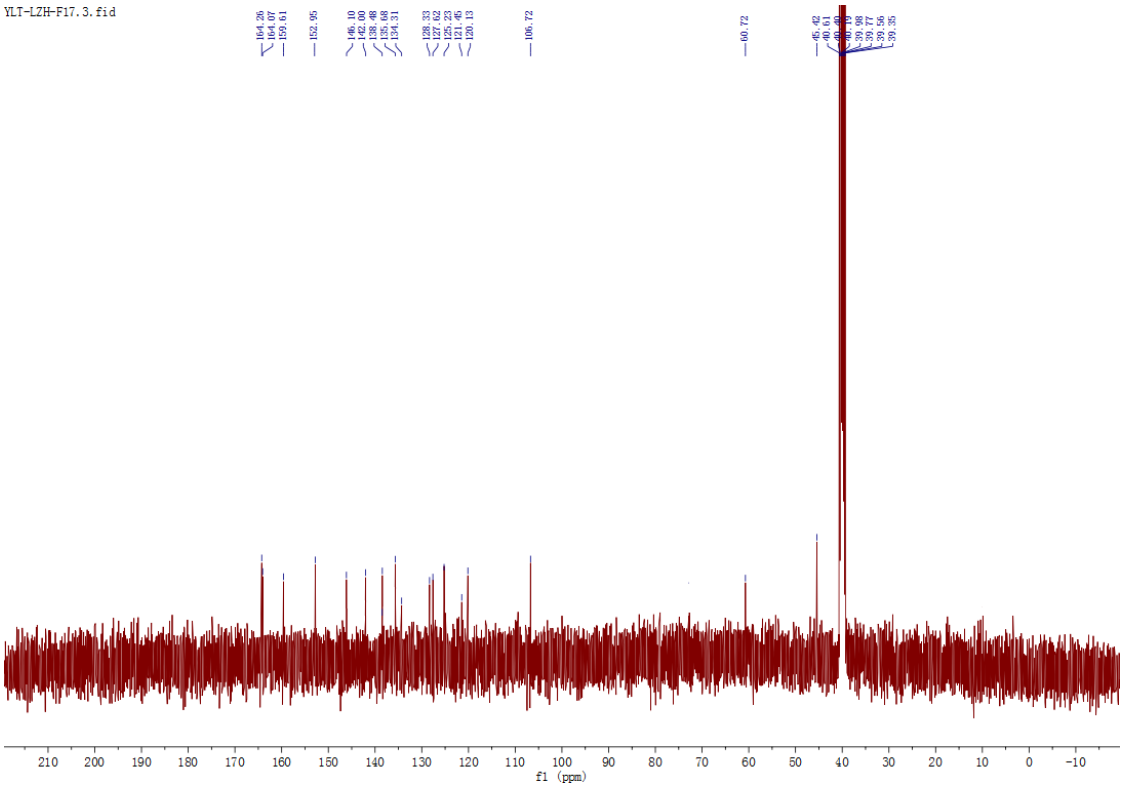




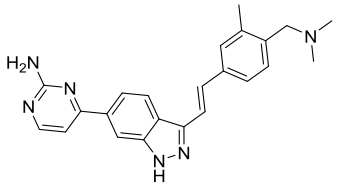
(*E*)-4-(3-(3-chloro-4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14s**

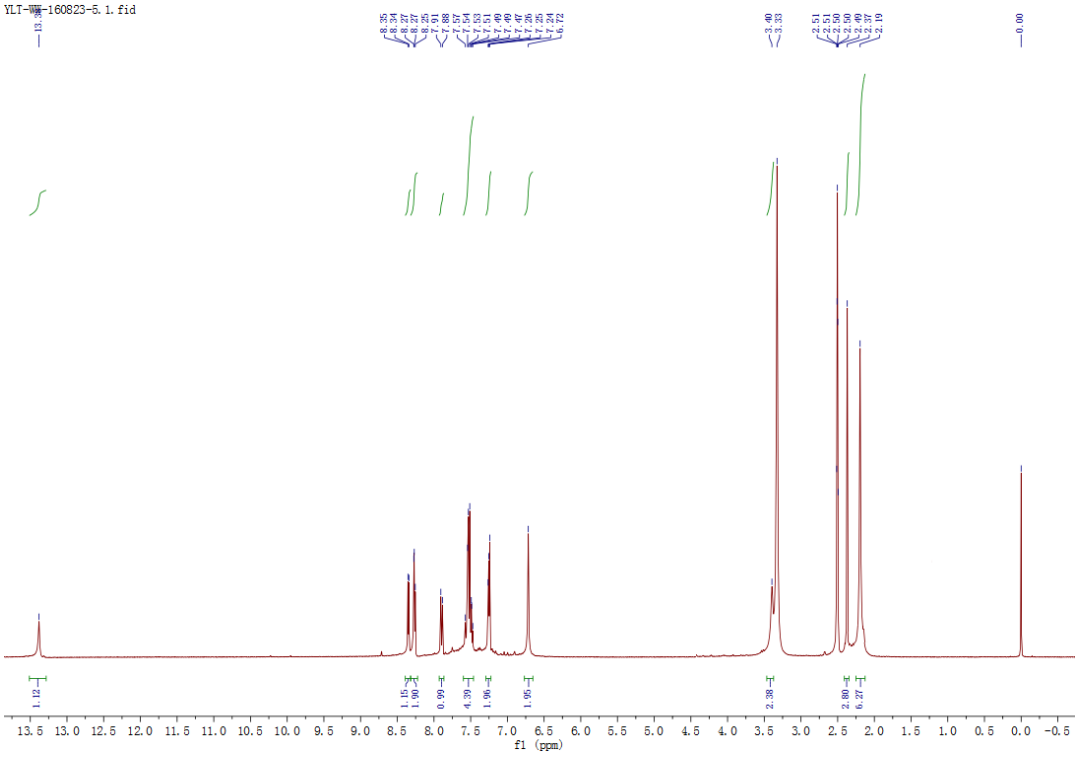


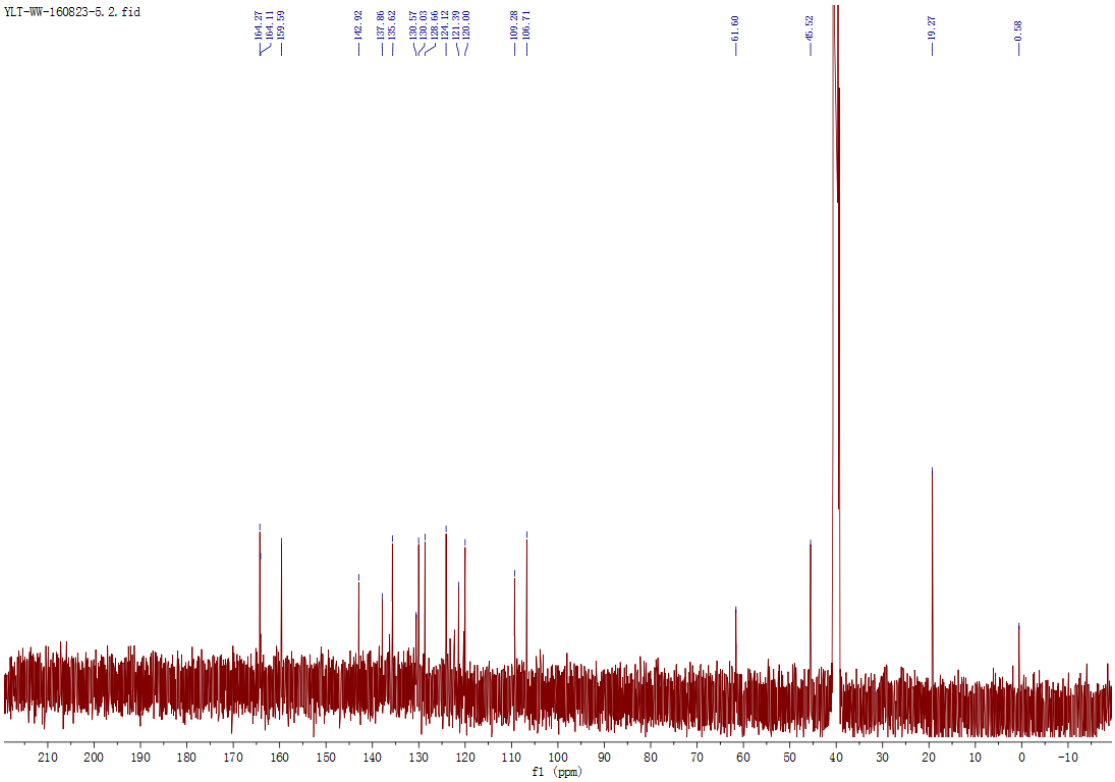




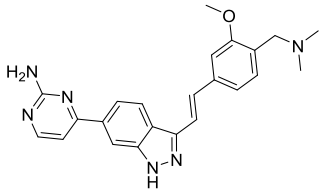
(*E*)-4-(3-(4-((dimethylamino)methyl)-3-methylstyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14t**

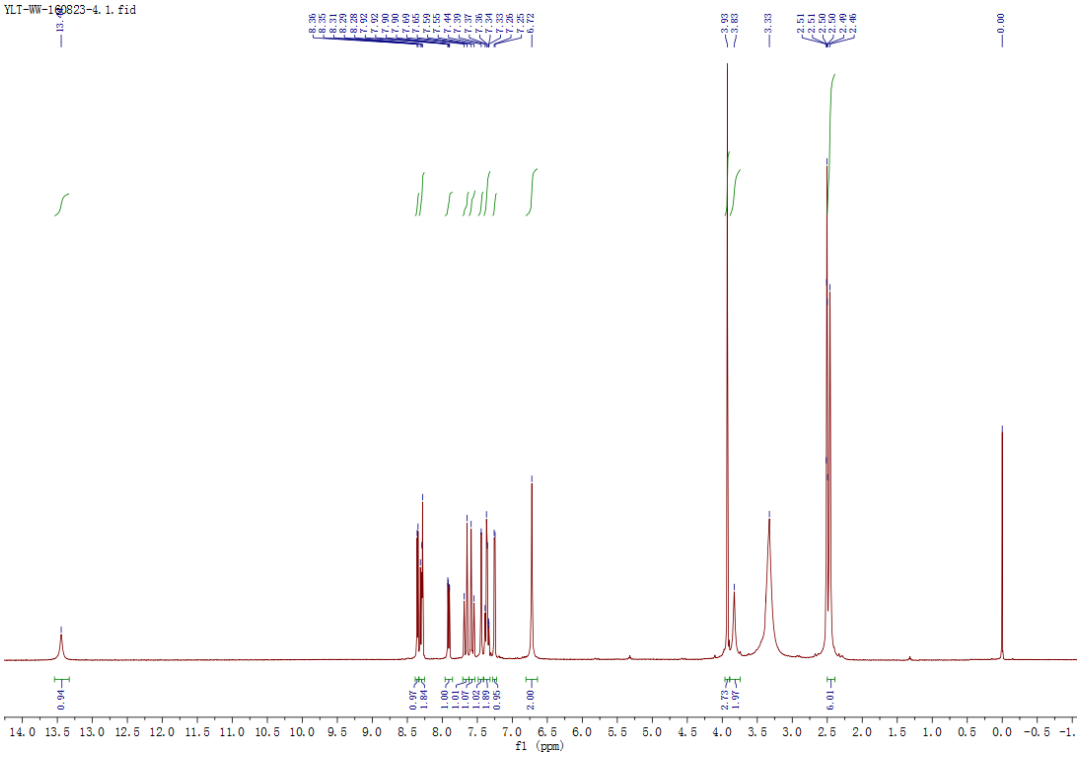


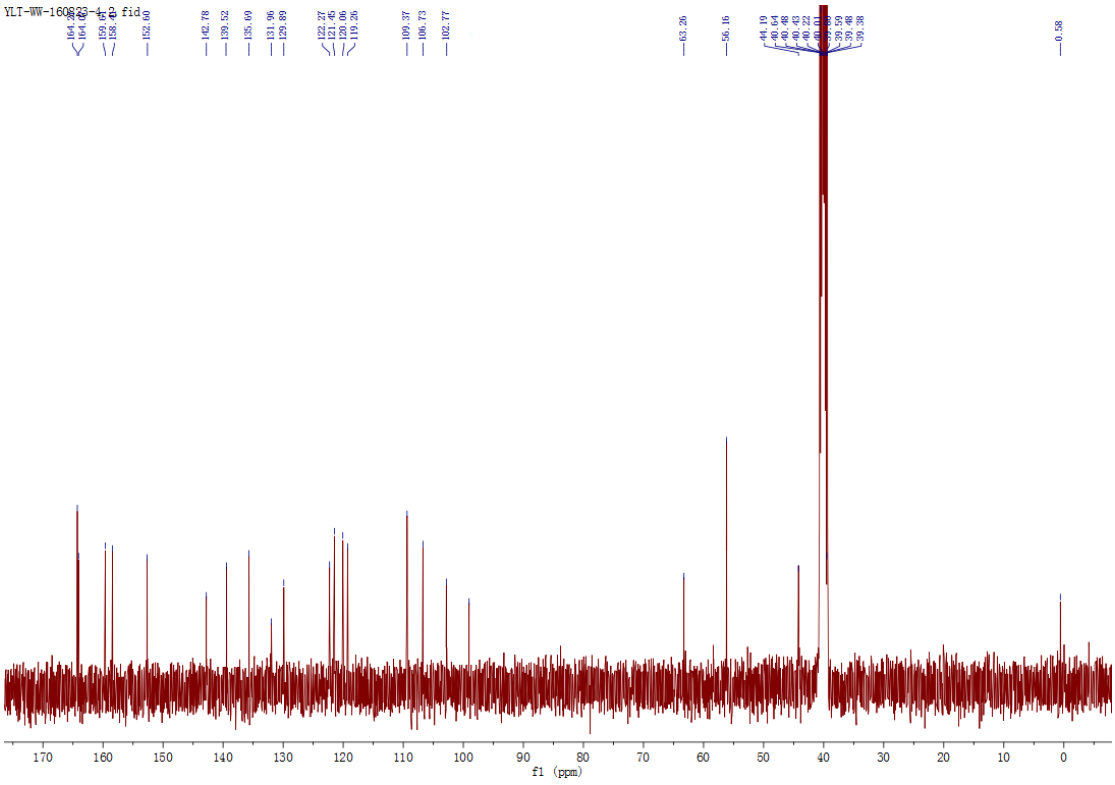




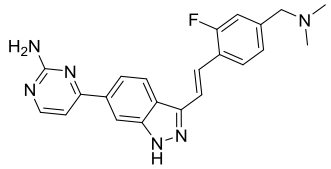
(*E*)-4-(3-(4-((dimethylamino)methyl)-3-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14u**

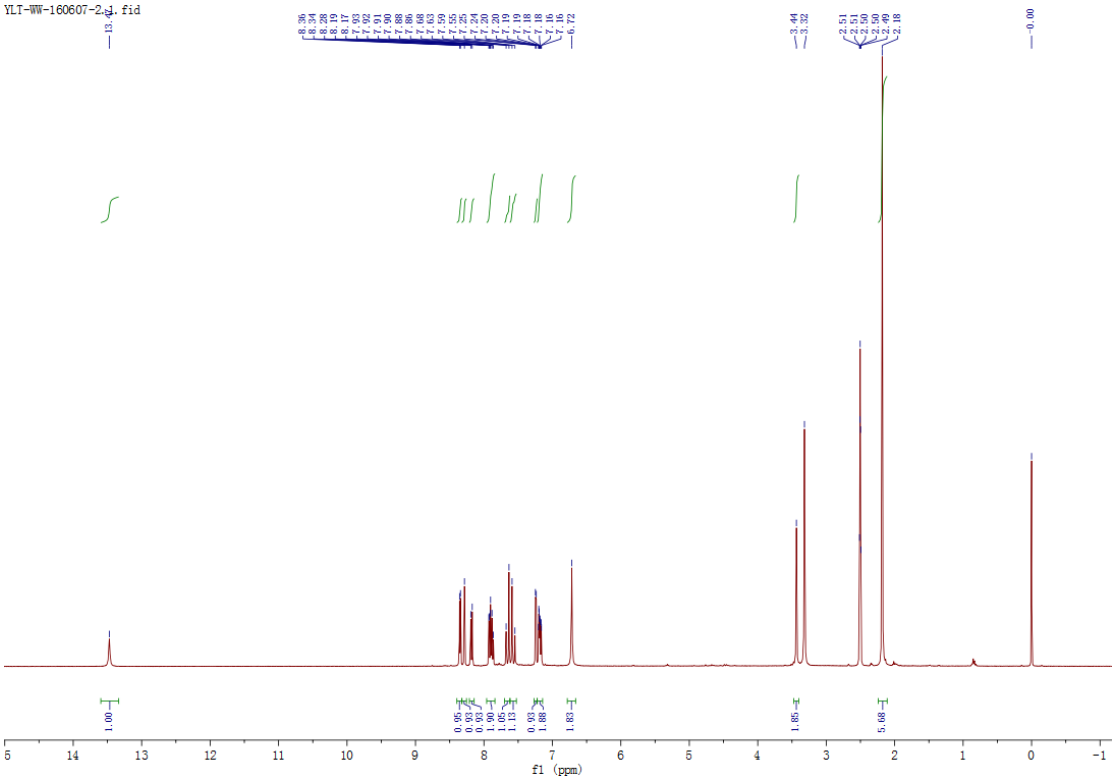


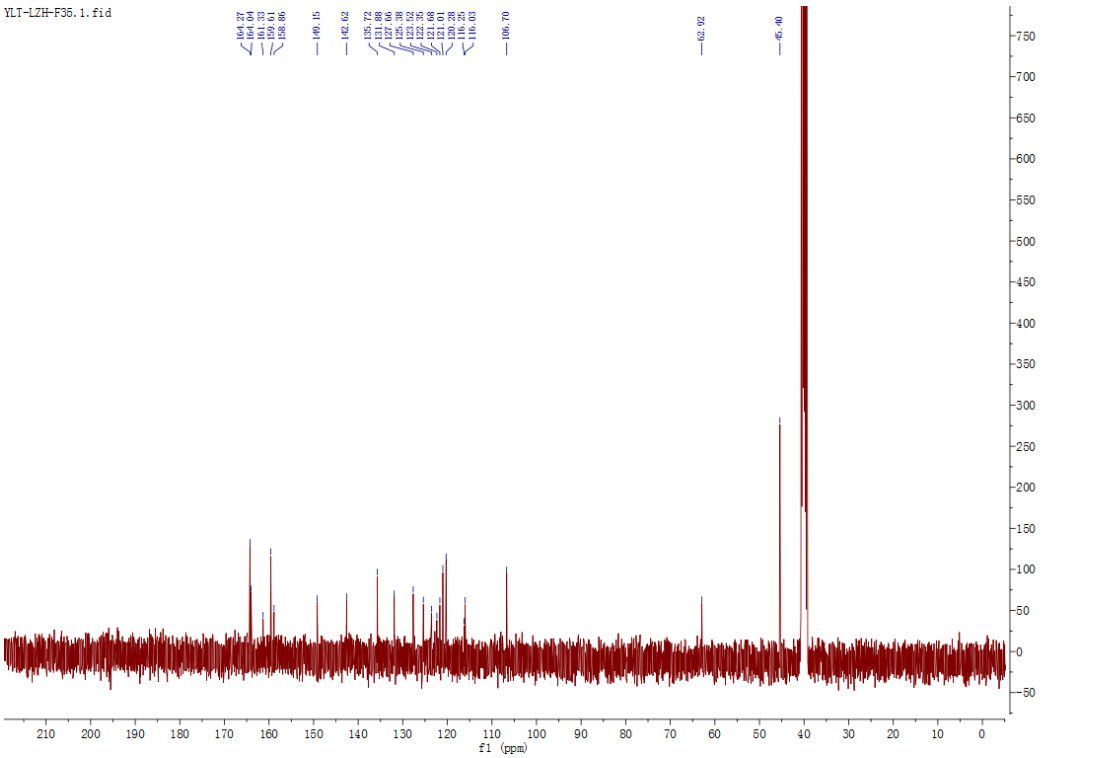




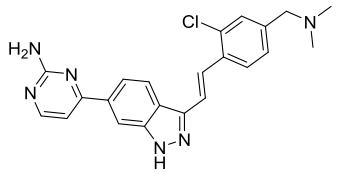
(*E*)-4-(3-(4-((dimethylamino)methyl)-2-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14v**

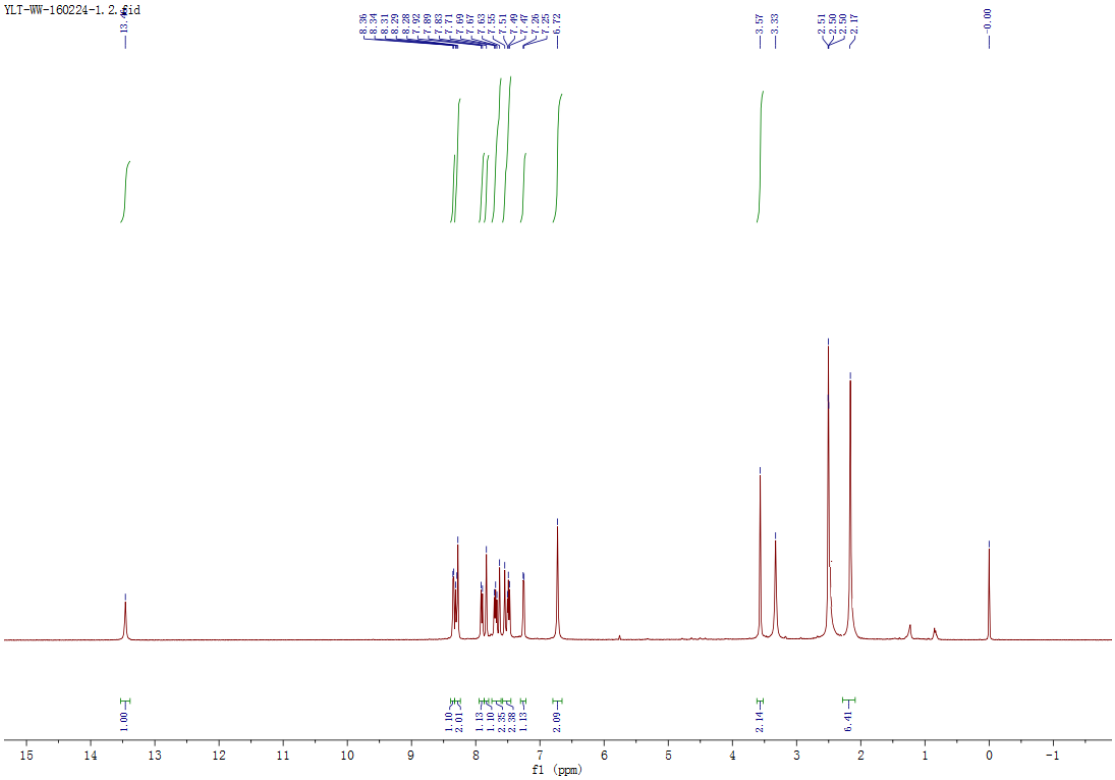


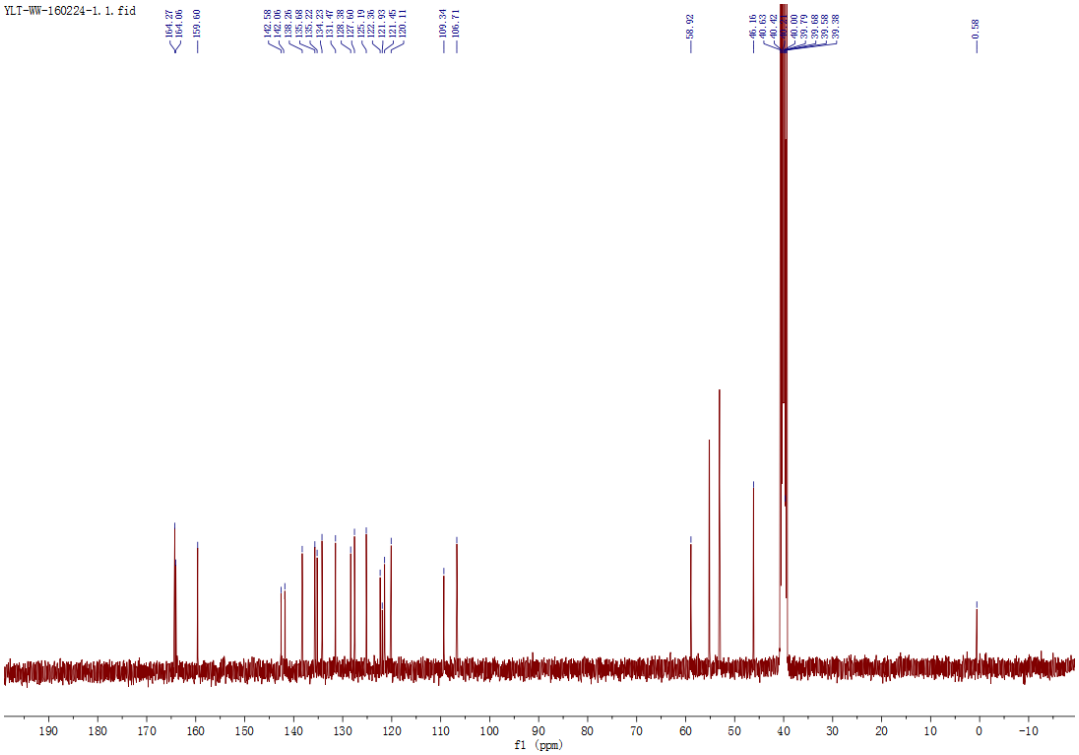




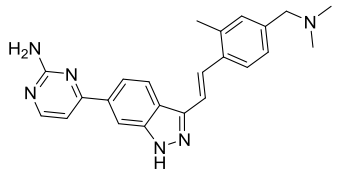
(*E*)-4-(3-(2-chloro-4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14w**

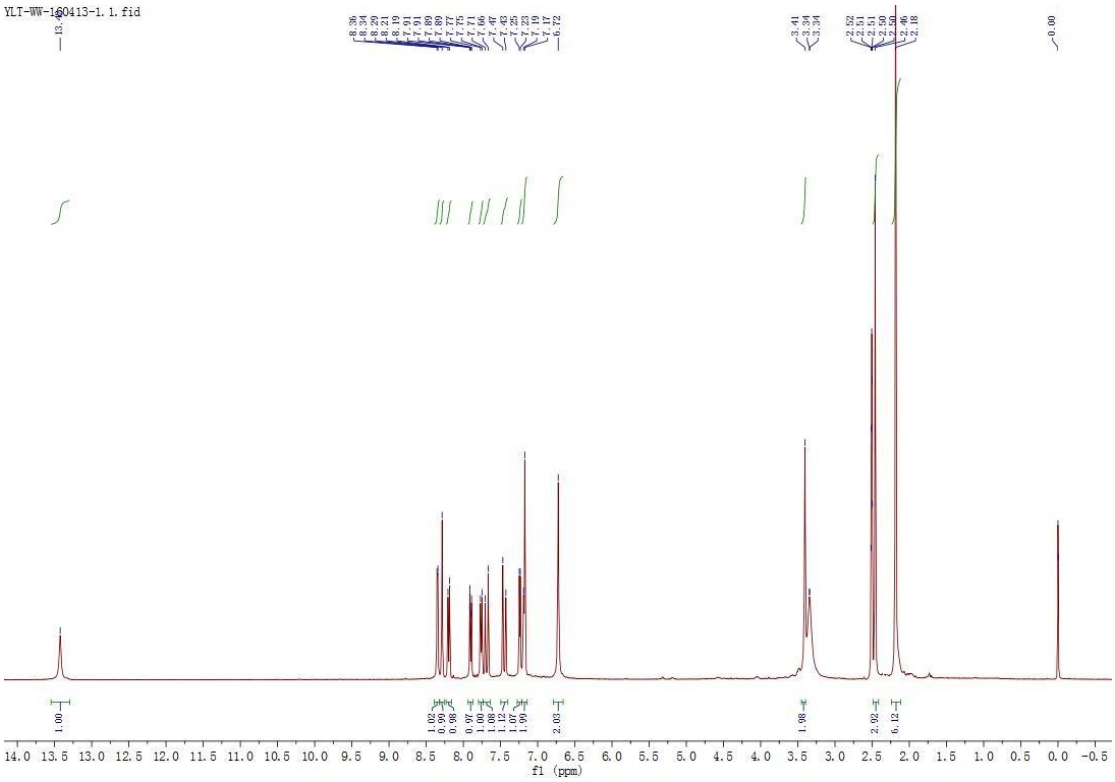


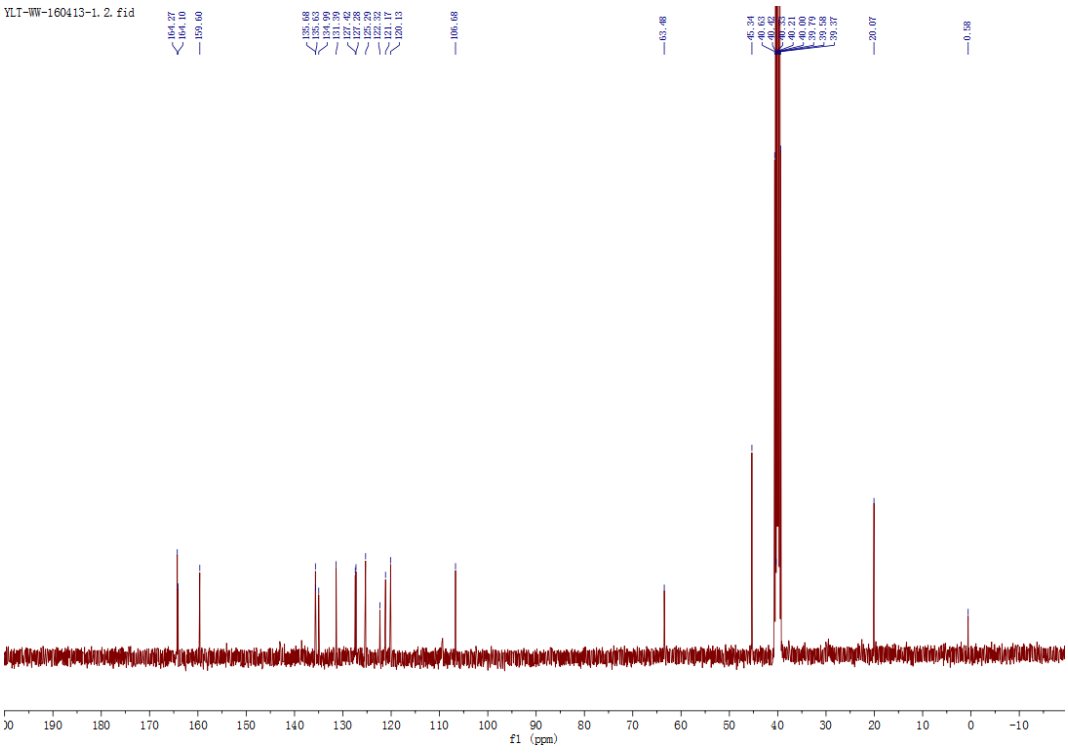




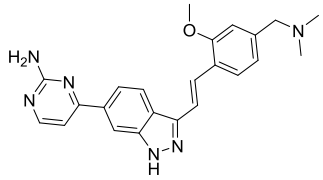
(*E*)-4-(3-(4-((dimethylamino)methyl)-2-methylstyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14x**

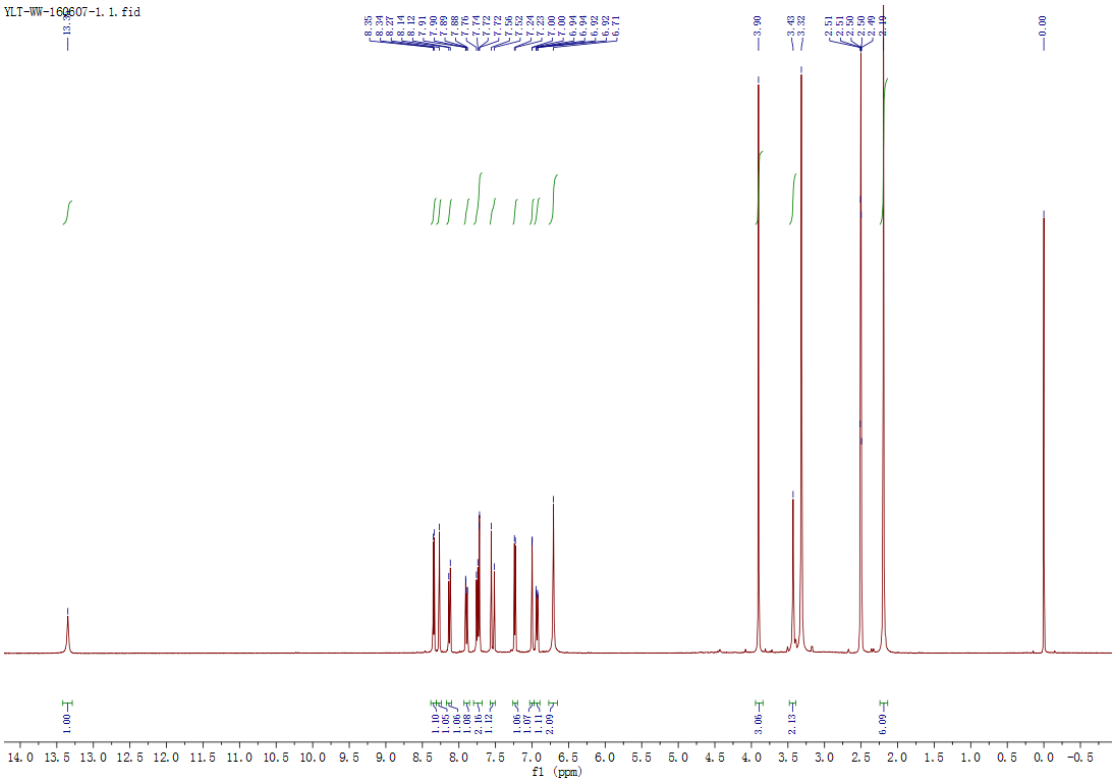


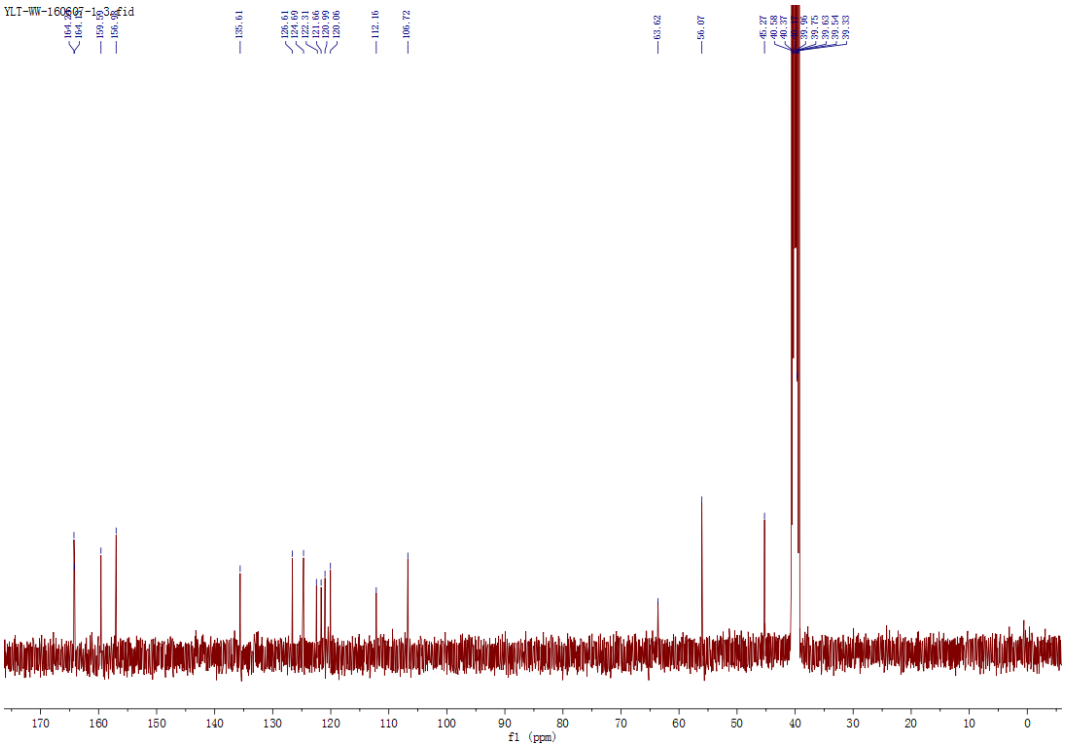




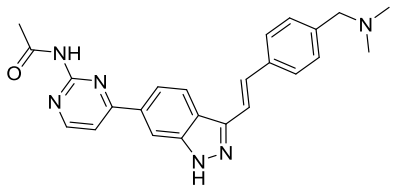
(*E*)-4-(3-(4-((dimethylamino)methyl)-2-methoxystyryl)-1*H*-indazol-6-yl)pyrimidin-2-amine **14y**

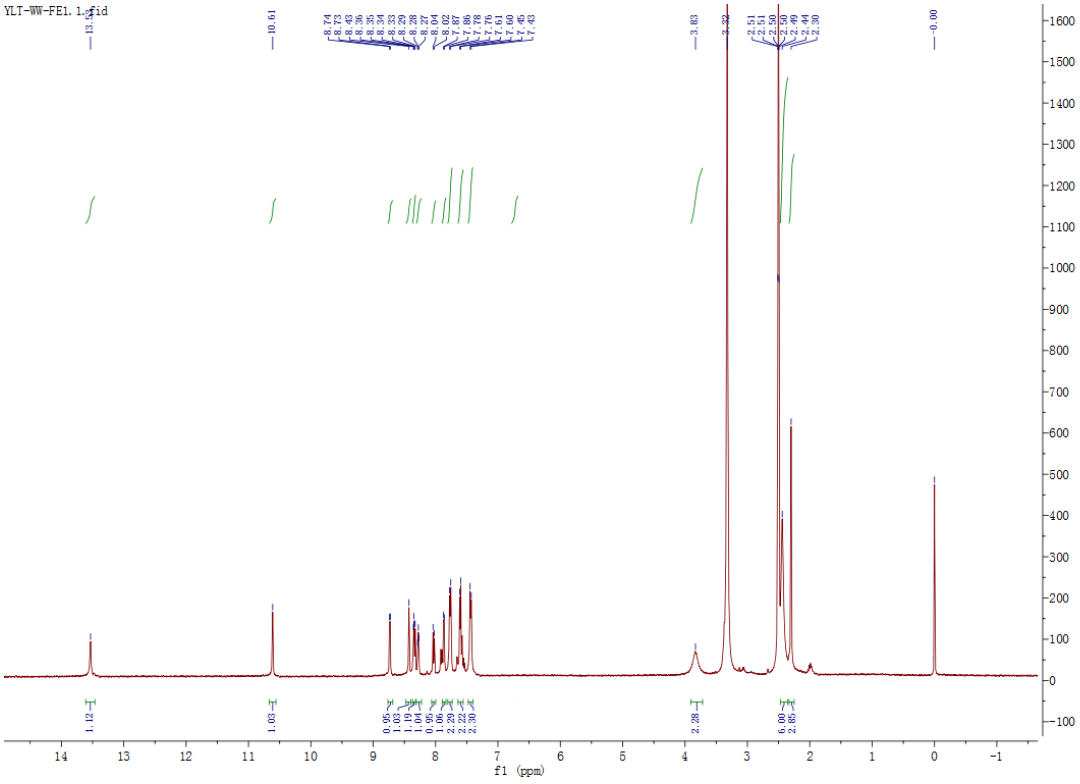


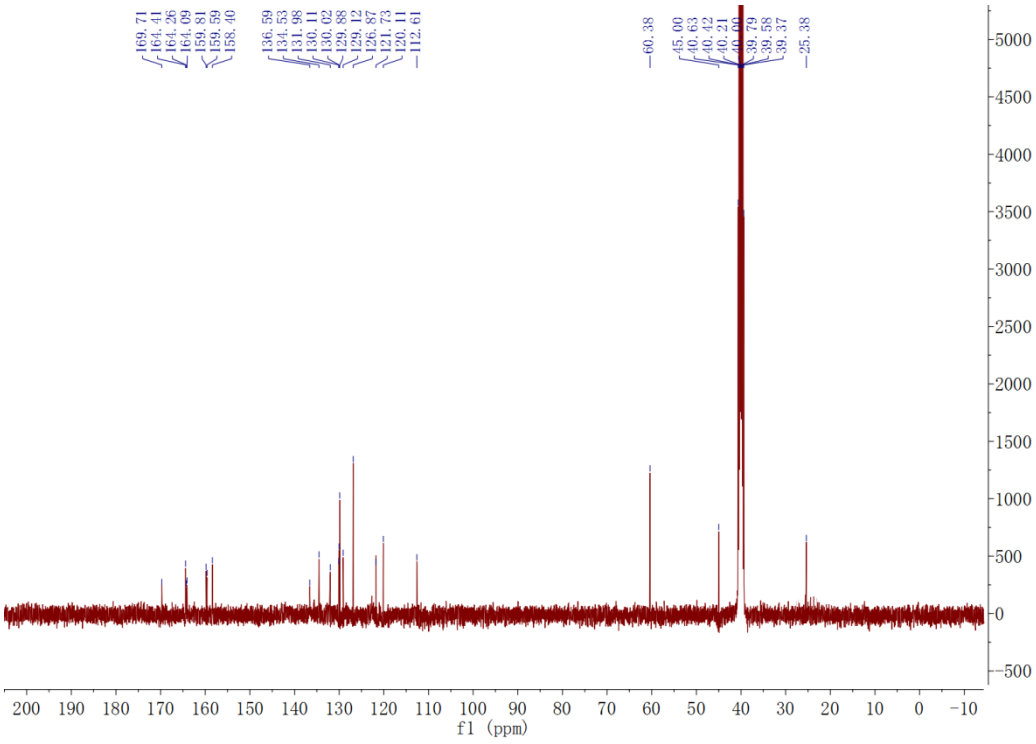




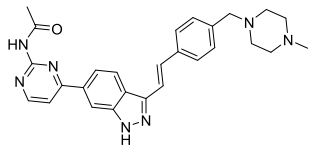
(*E*)-*N*-(4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **15a**

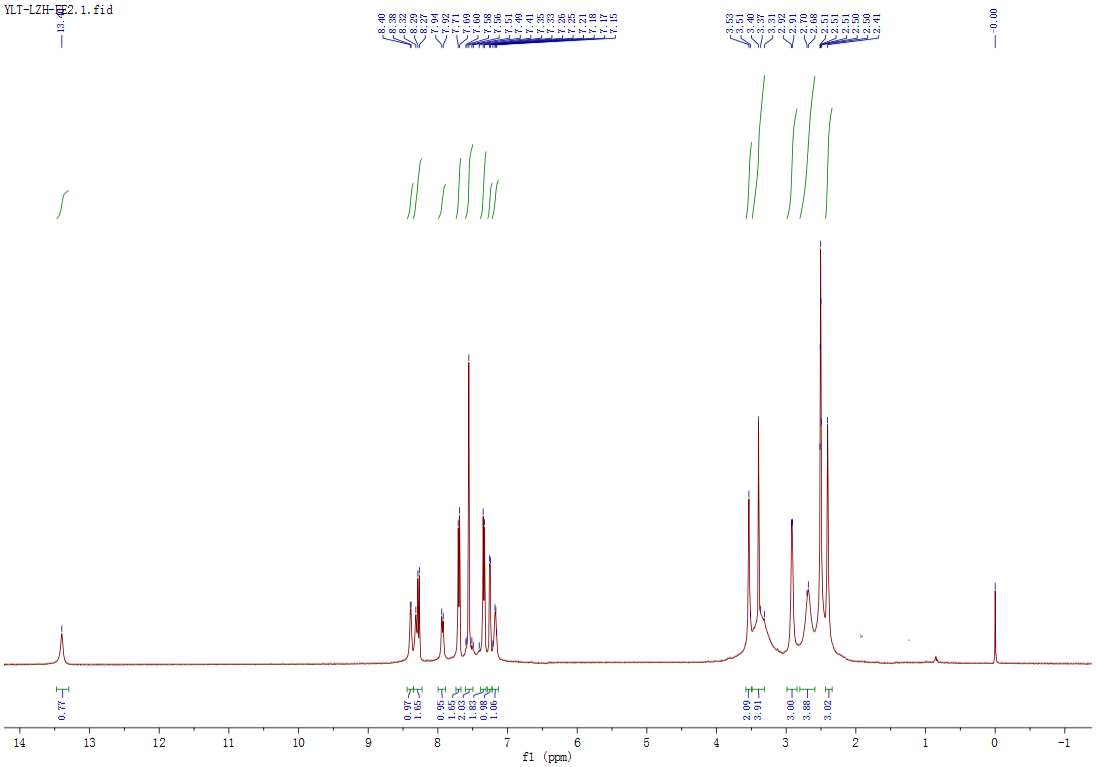


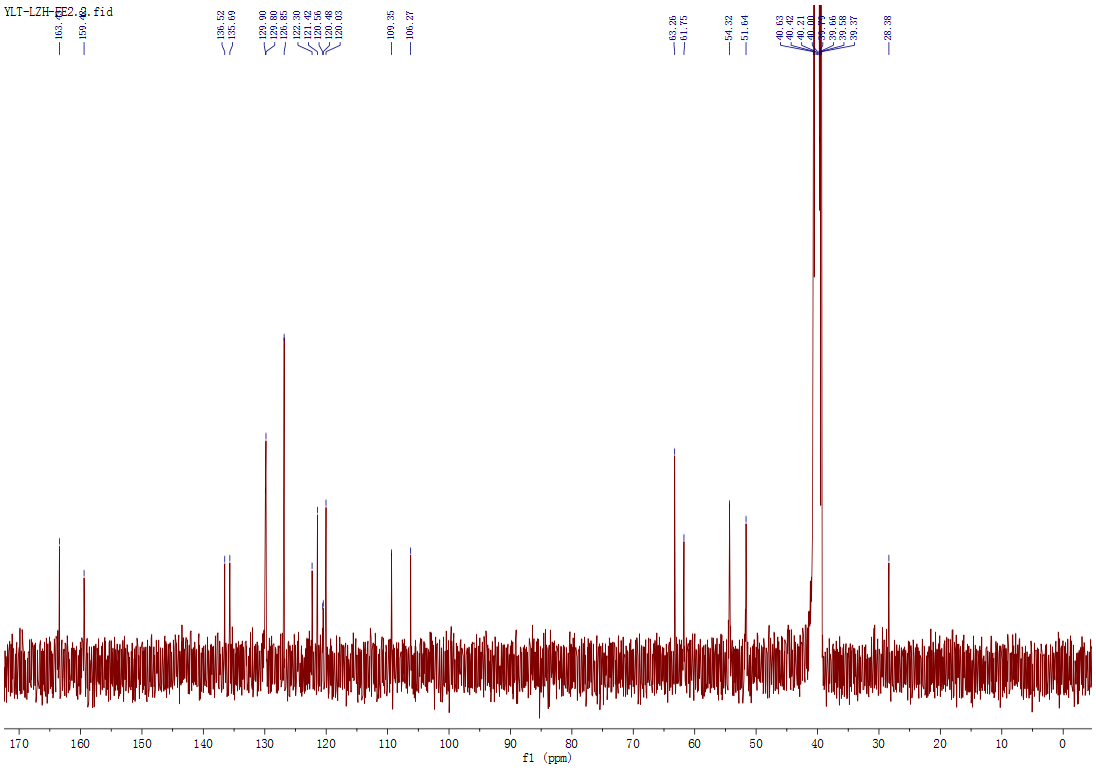




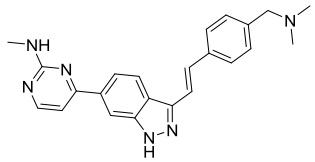
(*E*)-*N*-(4-(3-(4-((dimethylamino)methyl)-3-fluorostyryl)-1*H*-indazol-6-yl)pyrimidin-2-yl)acetamide **15b**

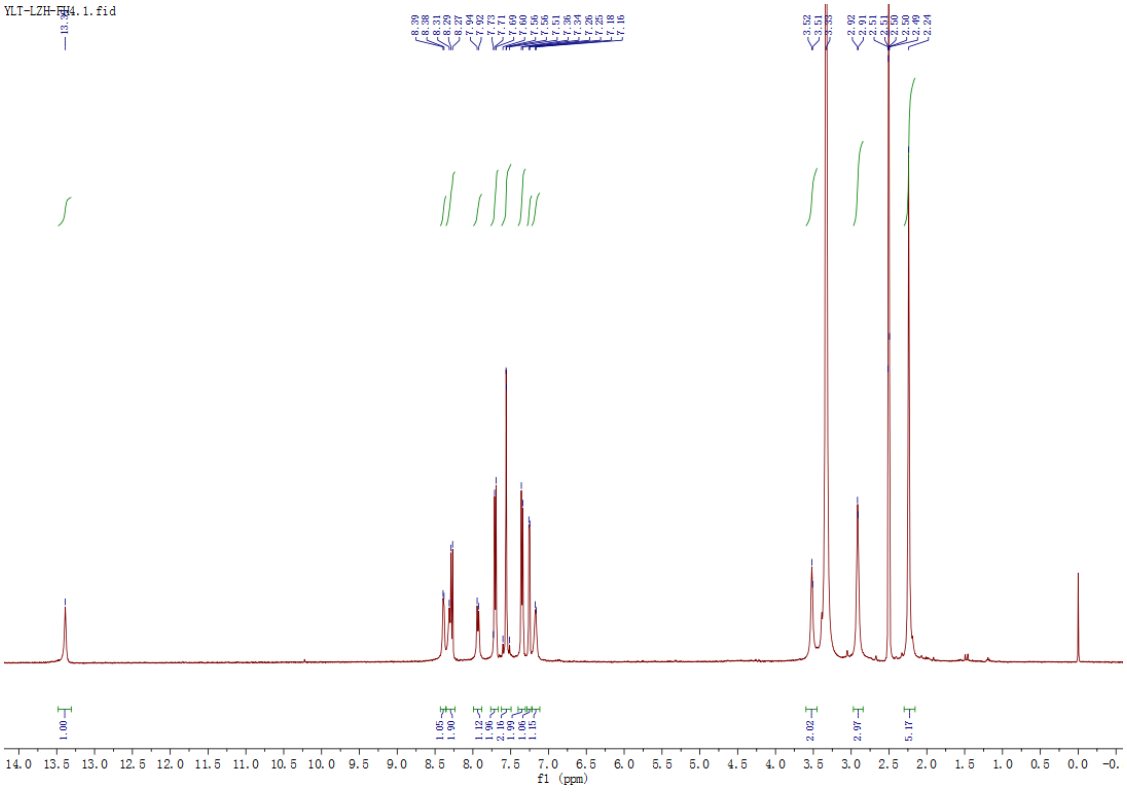


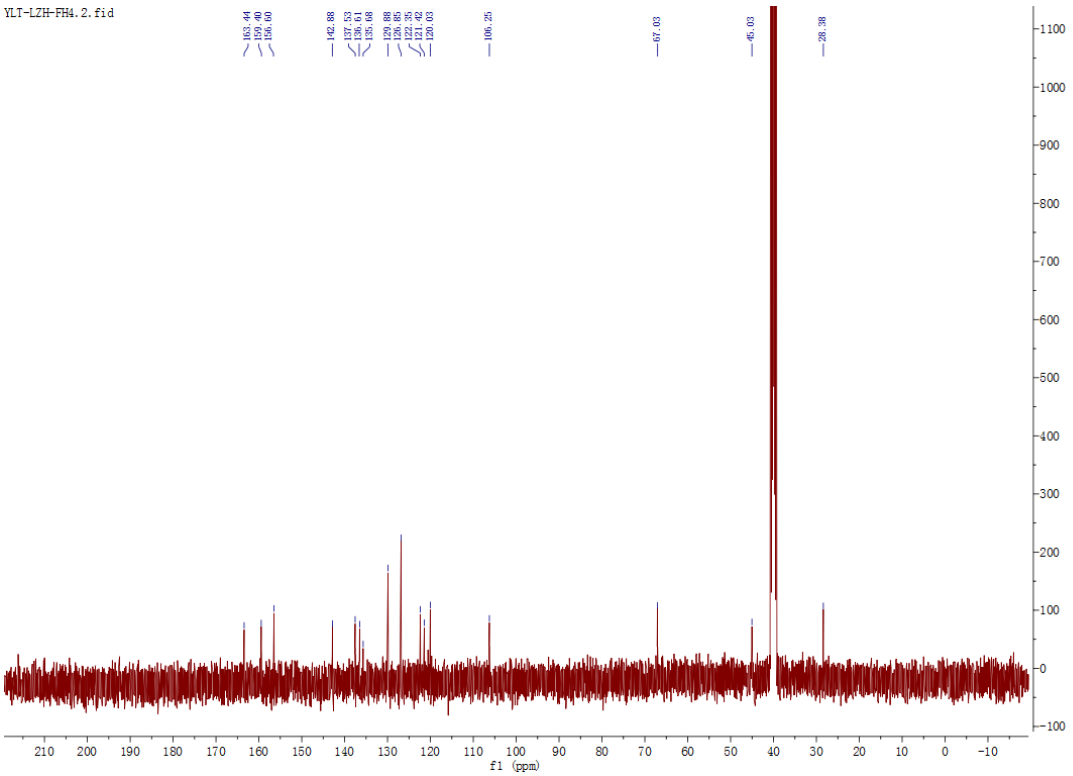




(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-1*H*-indazol-6-yl)-*N*-methylpyrimidin-2-amine **15c**







(*E*)-4-(3-(4-((dimethylamino)methyl)styryl)-5-methyl-1*H*-indazol-6-yl)pyrimidin-2-amine**15d**