Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Silver(I)-Mediated Oxidative C(sp^3)−H Amination of Ethers with Azoles Derivatives Under Mild Conditions

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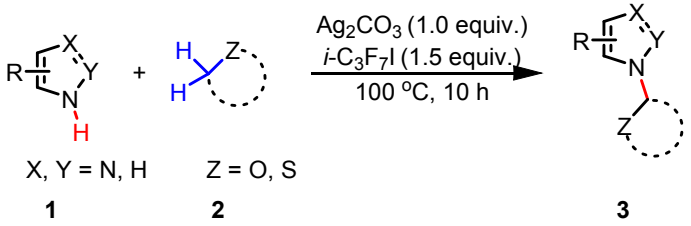
1. GeneralInformation

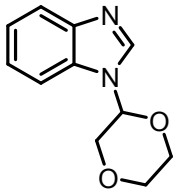
All reactions were carried out with magnetic stirring and in dried glassware. Standard syringe techniques were applied for transfer of dry solvents. All solvents before used were dried and distilled under standard methods. All other commercially available reagents were used as received. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: TMS = 0.00ppm, for ^{13}C NMR: $CDCl_3$ = 77.00 ppm. The following abbreviations were used to explain multiplicities: s = singlet, d=doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Analytical TLC was performed on precoated silica gelplates. 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 General procedure for the N-alkylation of azoles



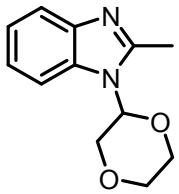
In a 15 mL tube, the corresponding azoles **1** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.2 mmol, 1.0 equiv), *i*-C_3F_7I (0.3 mmol, 1.5 equiv), and ethers **2** (2.0 mL) were added under air. The tube was sealed and the resulting solution was heated in a 100 °C oil bath with vigorous stirring for 10 h. Then the reaction mixture was cooled to room temperature. The mixture was extracted with ethyl acetate (20 mL × 3), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using methanol/dichloromethane (1:10) as eluent to afford the products.



1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3a)

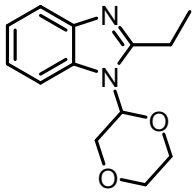
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.85 – 7.77 (m, 1H), 7.57 – 7.45 (m, 1H), 7.34 – 7.25 (m, 2H), 5.67 (t, *J* = 4Hz, 1H), 4.19 – 4.01 (m, 2H), 3.95 – 3.55 (m, 4H); ^{13}C NMR (100 MHz, CDCl3) δ 143.27 , 141.43 , 132.93 , 123.29 , 122.63 , 120.18 , 110.45 , 78.26 , 67.81 , 66.22 ,

63.16; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}N_2O_2$ [M+H]$^+$: 205.0972, found: 205.0983..



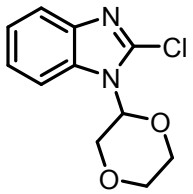
1-(1,4-dioxan-2-yl)-2-methyl-1*H*-benzo[d]imidazole (3b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.58 (m, 2H), 7.26 – 7.16 (m, 2H), 5.66 (dd, *J* = 9.7, 3.2 Hz, 1H), 4.15 – 4.06 (m, 2H), 4.05 – 3.95 (m, 1H), 3.90 – 3.79 (m, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.53 , 142.35 , 133.45 , 122.49 , 122.30 , 119.07 , 111.59 , 80.76 , 67.53 , 67.21 , 65.67 , 14.70 ; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}N_2O_2$ [M+H]$^+$: 219.1128, found: 219.1144.



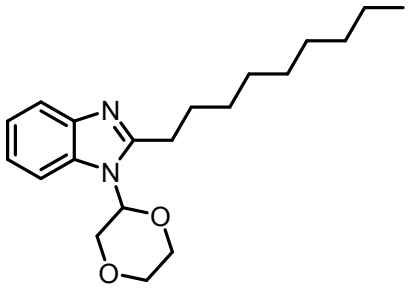
1-(1,4-dioxan-2-yl)-2-ethyl-1*H*-benzo[d]imidazole (3c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.49 (m, 2H), 7.20 – 7.05 (m, 2H), 5.57 (dd, *J* = 9.8, 2.8 Hz, 1H), 4.08 – 3.95 (m, 2H), 3.94 – 3.86 (m, 1H), 3.78 – 3.67 (m, 3H), 2.91 – 2.77 (m, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.97 , 142.67 , 133.39 , 122.25 , 122.00 , 119.25 , 111.82 , 80.43 , 67.47 , 67.21 , 65.55 , 21.41 , 11.80; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{16}N_2O_2$ [M+H]$^+$: 233.1285, found: 233.1304.



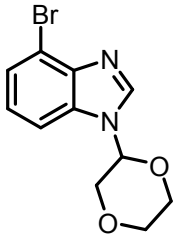
2-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.63 (m, 2H), 7.37 – 7.17 (m, 2H), 5.87 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.19 – 3.96 (m, 3H), 3.97 – 3.77 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 141.87 , 139.06 , 133.50 , 123.51 , 123.11 , 119.63 , 112.27 , 81.22 , 67.34 , 67.20 , 65.70; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}ClN_2O_2$ [M+H]$^+$: 239.0582, found: 239.0589.



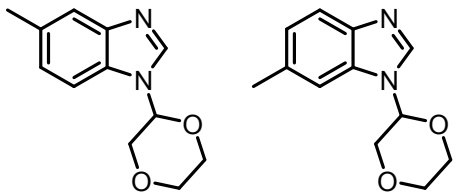
1-(1,4-dioxan-2-yl)-2-nonyl-1*H*-benzo[d]imidazole (3e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.55 (m, 2H), 7.18 – 7.11 (m, 2H), 5.59 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.11 – 3.99 (m, 2H), 3.98 – 3.89 (m, 1H), 3.80 – 3.69 (m, 3H), 2.83 (t, *J* = 4Hz, 2H), 1.83 – 1.71 (m, 2H), 1.41 – 1.16 (m, 12H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.20 , 142.72 , 133.32 , 122.32 , 122.15 , 119.33 , 111.99 , 80.64 , 67.63 , 67.36 , 65.68 , 31.74 , 29.35 , 29.33 , 29.21 , 29.15 , 28.18 , 27.90 , 22.55 , 14.01; HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{30}N_2O_2$ $[M+H]^+$: 331.2380, found: 331.2397.



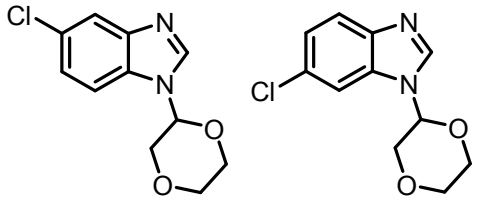
4-bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.53 – 7.40 (t, *J* = 8 Hz, 2H), 7.16 (t, *J* = 7.9 Hz, 1H), 5.67 (t, *J* = 3.6 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.91 – 3.79 (m, 2H), 3.76 – 3.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.85 , 133.46 , 125.61 , 124.23 , 113.45 , 109.95 , 78.41 , 67.54 , 66.18 , 62.80; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}BrN_2O_2$ $[M+H]^+$: 283.0077, found: 283.0083.



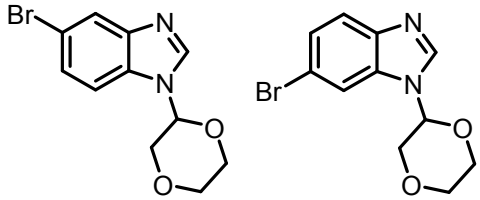
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-benzo[d]imidazole (3g) and 1-(1,4-dioxan-2-yl)-6-methyl-1*H*-benzo[d]imidazole (3g')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.8 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.31 (s, 1H), 7.15 (t, *J* = 16 Hz, 2H), 5.74 – 5.63 (m, 2H), 4.19 – 4.09 (m, 4H), 3.94 – 3.72 (m, 8H), 2.49 (d, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.55 , 141.48 , 141.07 , 133.54 , 133.23 , 132.55 , 131.05 , 124.93 , 124.41 , 119.96 , 119.72 , 110.37 , 110.05 , 78.47 , 78.36 , 67.96 , 66.35 , 63.32 , 21.74 , 21.41; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$: 219.1128, found: 219.1140.



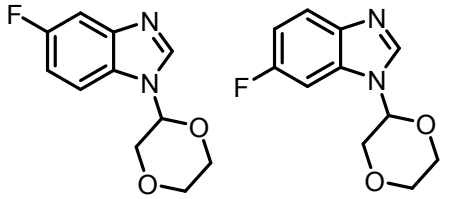
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3h) and 6-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3h')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.2 Hz, 2H), 7.79 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 5.73 – 5.62 (m, 2H), 4.23 – 4.08 (m, 4H), 3.94 – 3.68 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.82 , 142.67 , 142.20 , 141.58 , 133.52 , 131.54 , 129.22 , 128.38 , 123.85 , 123.49 , 120.87 , 119.79 , 111.51 , 110.94 , 78.45 , 67.58 , 67.50 , 66.24 , 62.96; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}N_2O_2$ $[M+H]^+$: 239.0582, found: 239.0584.



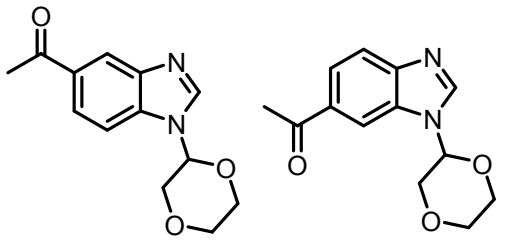
5-bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3i) and 6-bromo-1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazole (3i')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.0 Hz, 2H), 7.85 (s, 1H), 7.60 – 7.57 (m, 1H), 7.55 (s, 1H), 7.34 – 7.27 (m, 3H), 5.59 – 5.51 (m, 2H), 4.11 – 3.98 (m, 4H), 3.82 – 3.71 (m, 4H), 3.68 – 3.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.56 , 142.47 , 142.25 , 142.08 , 134.00 , 131.91 , 126.25 , 125.93 , 122.91 , 121.37 , 116.54 , 115.55 , 113.75 , 111.83 , 78.25 , 78.23 , 67.50 , 67.45 , 66.18 , 62.84 ; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}BrN_2O_2$ $[M+H]^+$: 283.0077, found: 283.0083.



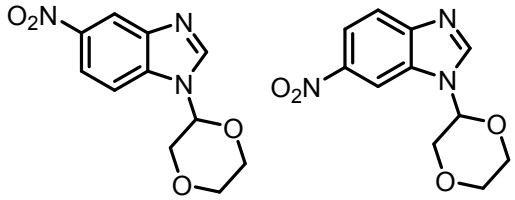
1-(1,4-dioxan-2-yl)-6-fluoro-1*H*-benzo[d]imidazole (3j)
and 1-(1,4-dioxan-2-yl)-5-fluoro-1*H*-benzo[d]imidazole (3j')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.27 (s, 1H), 7.74 (dd, J = 8.8, 4.8 Hz, 1H), 7.53 – 7.40 (m, 2H), 7.22 (dd, J = 8.6, 2.4 Hz, 1H), 7.07 (qd, J = 9.3, 2.4 Hz, 2H), 5.72 – 5.67 (m, 1H), 5.67 – 5.62 (m, 1H), 4.23 – 4.10 (m, 4H), 3.96 – 3.84 (m, 4H), 3.83 – 3.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.92 (d, $J_{C\text{-}F}$ = 240.7 Hz), 159.53 (d, $J_{C\text{-}F}$ = 238.4 Hz), 143.81 (d, $J_{C\text{-}F}$ = 12.7 Hz), 142.91 , 142.10 (d, $J_{C\text{-}F}$ = 2.7 Hz), 139.69 , 133.24 (d, $J_{C\text{-}F}$ = 13.2 Hz), 129.57 , 121.06 (d, $J_{C\text{-}F}$ = 10.0 Hz), 111.87 (d, $J_{C\text{-}F}$ = 26.0 Hz), 111.27 (d, $J_{C\text{-}F}$ = 25.4 Hz), 111.09 (d, $J_{C\text{-}F}$ = 10.7 Hz), 106.05 (d, $J_{C\text{-}F}$ = 24.1 Hz), 97.59 (d, $J_{C\text{-}F}$ = 28.0 Hz), 78.56 , 78.53 , 67.80 , 67.67 , 66.37 , 63.11; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}FN_2O_2$ $[M+H]^+$: 223.0877, found: 223.0890.



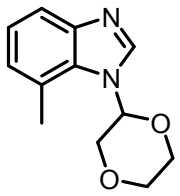
1-(1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazol-5-yl)ethan-1-one (3k) and 1-(1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazol-6-yl)ethan-1-one (3k')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 7.98 – 7.87 (m, 2H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 5.69 (t, *J* = 3.8 Hz, 1H), 5.65 (t, *J* = 3.8 Hz, 1H), 4.17 – 4.01 (m, 4H), 3.86 (s, 6H), 3.84 – 3.62 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.18 , 167.06 , 146.70 , 144.04 , 143.11 , 143.02 , 136.24 , 132.72 , 125.21 , 124.92 , 124.78 , 124.05 , 122.52 , 119.86 , 112.82 , 110.31 , 78.38 , 78.34 , 67.74 , 67.67 , 66.26 , 63.09 , 63.06 , 52.06 , 51.99; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{14}N_2O_3$ $[M+H]^+$: 266.1061, found: 266.1089.



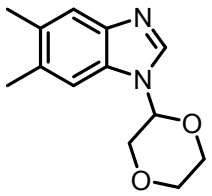
1-(1,4-dioxan-2-yl)-5-nitro-1*H*-benzo[d]imidazole (3l) and 1-(1,4-dioxan-2-yl)-6-nitro-1*H*-benzo[d]imidazole (3l')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.1 Hz, 1H), 8.46 (s, 1H), 8.42 – 8.37 (m, 2H), 8.14 – 8.05 (m, 2H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 5.76 (t, *J* = 3.5 Hz, 1H), 5.72 (t, *J* = 3.6 Hz, 1H), 4.26 – 4.08 (m, 4H), 3.92 – 3.75 (m, 4H), 3.73 – 3.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.58 , 146.11 , 144.95 , 143.73 , 143.69 , 142.66 , 137.16 , 132.36 , 120.16 , 118.78 , 118.18 , 116.57 , 110.82 , 107.75 , 78.45 , 78.42 , 67.30 , 67.29 , 66.22 , 66.20 , 62.73 , 62.67; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}N_3O_4$ $[M+H]^+$: 250.0822, found: 250.0837.



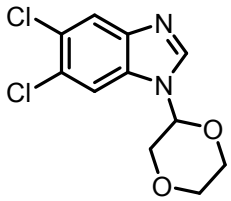
1-(1,4-dioxan-2-yl)-7-methyl-1*H*-benzo[d]imidazole (3m)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.33 (d, *J* = 8Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 5.68 (m, 1H), 4.18 – 4.07 (m, 2H), 3.91 – 3.66 (m, 4H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.50 , 140.57 , 132.66 , 130.26 , 123.41 , 123.17 , 107.98 , 78.55 , 68.05 , 66.35 , 63.43 , 16.59 ; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$: 219.1128, found: 219.1141.



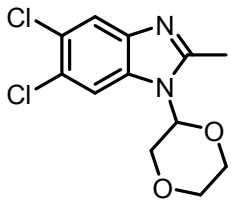
1-(1,4-dioxan-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazole (3n)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.58 (s, 1H), 7.29 (s, 1H), 5.71 – 5.63 (t, *J* = 8 Hz, 1H), 4.21 – 4.09 (m, 2H), 3.95 – 3.73 (m, 4H), 2.39 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.66 , 140.66 , 132.83 , 131.89 , 131.50 , 120.22 , 110.70 , 78.51 , 68.04 , 66.42 , 63.38 , 20.55 , 20.22; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{16}N_2O_2$ $[M+H]^+$: 233.1285, found: 233.1296.



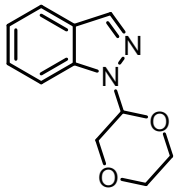
5,6-dichloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3o)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.90 (s, 1H), 7.65 (s, 1H), 5.65 (t, *J* = 3.6 Hz, 1H), 4.28 – 4.10 (m, 2H), 3.98 – 3.82 (m, 2H), 3.81 – 3.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.42 , 142.84 , 132.35 , 127.62 , 127.00 , 121.53 , 112.33 , 78.55 , 67.53 , 66.41 , 62.88; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{10}N_2O_2$ $[M+H]^+$: 273.0192, found: 273.0195.



5,6-dichloro-1-(1,4-dioxan-2-yl)-2-methyl-1*H*-benzo[d]imidazole (3p)

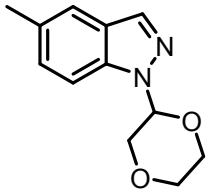
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.62 (s, 1H), 5.51 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.96 – 3.84 (m, 2H), 3.82 – 3.70 (m, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.52 , 141.95 , 132.56 , 126.10 , 120.08 , 113.19 , 80.65 , 67.29 , 66.98 , 65.54 , 14.59; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{12}Cl_2N_2O_2$ $[M+H]^+$: 287.0349, found: 287.0368.



1-(1,4-dioxan-2-yl)-1*H*-indazole (3q)

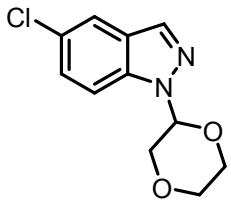
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.85 (dd, *J* = 8.1, 2.8 Hz, 1H), 4.49 (dd, *J* = 11.7, 8.2 Hz, 1H), 4.11 (dd, *J* = 11.7, 2.8 Hz, 1H), 4.03 – 3.93 (m, 2H), 3.88 – 3.79 (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 139.84 , 134.92 , 126.88 , 124.48 , 121.53 , 121.12 , 109.58 , 81.36 , 67.87 , 65.92; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}N_2O_2$ $[M+H]^+$: 205.0972, found: 205.0985.



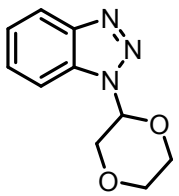
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-indazole (3r)

^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.45 – 7.38 (m, 2H), 7.21 – 7.20 (m, 0.55H), 7.19 – 7.17 (m, 0.45H), 5.75 (dd, *J* = 8.2, 2.8 Hz, 1H), 4.40 (dd, *J* = 11.7, 8.2 Hz, 1H), 4.03 (dd, *J* = 11.7, 2.8 Hz, 1H), 3.94 – 3.85 (m, 2H), 3.82 – 3.71 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.52 , 134.47 , 131.06 , 128.97 , 124.87 , 120.20 , 109.21 , 81.35 , 67.92 , 65.97 , 65.95 , 21.24; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$: 219.1128, found: 219.1140.



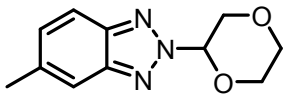
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-indazole (3s)

^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.29 (dd, *J* = 8.9, 1.9 Hz, 1H), 5.73 (dd, *J* = 7.8, 2.9 Hz, 1H), 4.42 – 4.31 (m, 1H), 4.04 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.94 – 3.83 (m, 2H), 3.81 – 3.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.27 , 134.12 , 127.52 , 127.14 , 125.31 , 120.29 , 110.87 , 81.50 , 67.66 , 65.89 , 65.70; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}ClN_2O_2$ $[M+H]^+$: 239.0582, found: 239.0603.



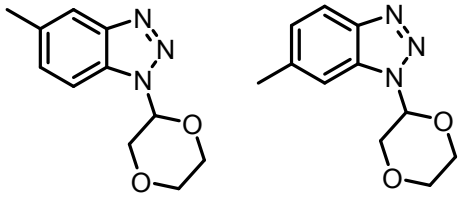
1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3t)

^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 6.09 (d, *J* = 4.8 Hz, 1H), 4.59 – 4.47 (m, 1H), 4.22 (d, *J* = 11.0 Hz, 1H), 4.03 – 3.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.90 , 132.45 , 127.75 , 124.22 , 119.86 , 110.53 , 81.82 , 67.14 , 65.79 , 65.23; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{11}N_3O_2$ $[M+H]^+$: 206.0924, found: 206.0932.



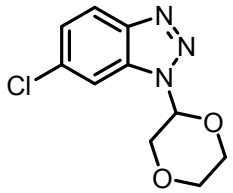
2-(1,4-dioxan-2-yl)-5-methyl-2*H*-benzo[d][1,2,3]triazole (3u)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), 7.16 (dd, *J* = 8.8, 1.4 Hz, 1H), 6.00 (dd, *J* = 6.7, 2.9 Hz, 1H), 4.41 (dd, *J* = 11.9, 6.7 Hz, 1H), 4.12 (dd, *J* = 11.9, 2.9 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.93 – 3.86 (m, 1H), 3.83 – 3.77 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.77 , 142.97 , 137.27 , 130.11 , 117.83 , 116.54 , 86.22 , 67.69 , 65.83 , 65.24 , 22.06; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{13}N_3O_2$ $[M+H]^+$: 220.1081, found: 220.1081.



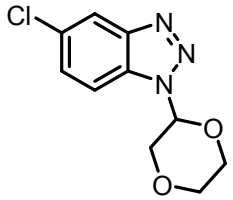
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-benzo[d][1,2,3]triazole (3u') and 1-(1,4-dioxan-2-yl)-6-methyl-1*H*-benzo[d][1,2,3]triazole (3u'')

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.40 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 5.98 – 5.91 (m, 2H), 4.45 – 4.35 (m, 2H), 4.10 (dt, *J* = 11.9, 2.4 Hz, 2H), 3.91 – 3.68 (m, 8H), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 146.39 , 144.44 , 138.48 , 134.26 , 132.84 , 130.85 , 129.85 , 126.47 , 119.19 , 118.66 , 109.97 , 109.59 , 81.74 , 81.62 , 67.09 , 65.74 , 65.29 , 65.16 , 21.79 , 21.23; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{13}N_3O_2$ $[M+H]^+$: 220.1081, found: 220.1099.



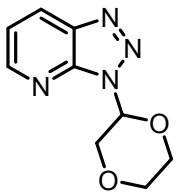
6-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3v)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.69 (s, 1H), 7.26 (dd, *J* = 8.8, 1.8 Hz, 1H), 5.96 (dd, *J* = 6.7, 2.9 Hz, 1H), 4.39 (dd, *J* = 12.0, 6.7 Hz, 1H), 4.15 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.89 – 3.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.37 , 134.25 , 133.03 , 125.58 , 120.73 , 110.65 , 82.04 , 66.95 , 65.81 , 64.99; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{10}N_3O_2$ $[M+H]^+$: 240.0534, found: 240.0553.



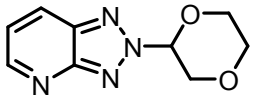
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3v')

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.00 (dd, *J* = 6.7, 2.9 Hz, 1H), 4.42 (dd, *J* = 12.0, 6.7 Hz, 1H), 4.16 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.94 – 3.70 (m, 4H); ^{13}C NMR (100MHz, $CDCl_3$) δ 146.56 , 131.23 , 130.20 , 128.77 , 119.28 , 111.77 , 82.12 , 67.07 , 65.87 , 65.04; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{10}N_3O_2$ $[M+H]^+$: 240.0534, found: 240.0546.



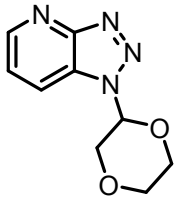
3-(1,4-dioxan-2-yl)-3*H*-[1,2,3]triazolo[4,5-b]pyridine (3w)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.33 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.32 (dd, *J* = 8.3, 4.5 Hz, 1H), 6.26 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.63 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.10 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.05 – 3.94 (m, 2H), 3.89 – 3.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.78 , 145.70 , 136.90 , 128.90 , 120.35 , 79.78 , 67.26 , 66.30 , 65.87; HRMS (ESI-TOF) m/z Calcd for $C_9H_{10}N_4O_2$ $[M+H]^+$: 207.0877, found: 207.0900.



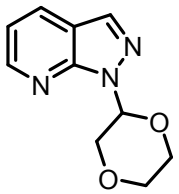
2-(1,4-dioxan-2-yl)-2*H*-[1,2,3]triazolo[4,5-b]pyridine (3w')

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.31 (dd, *J* = 8.6, 4.2 Hz, 1H), 6.07 (dd, *J* = 6.0, 2.9 Hz, 1H), 4.46 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.94 – 3.87 (m, 1H), 3.87 – 3.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.31 , 152.89 , 136.58 , 127.60 , 122.78 , 86.96 , 67.58 , 65.89 , 64.99; HRMS (ESI-TOF) m/z Calcd for $C_9H_{10}N_4O_2$ $[M+H]^+$: 207.0877, found: 207.0891.



1-(1,4-dioxan-2-yl)-1*H*-[1,2,3]triazolo[4,5-b]pyridine (3w'')

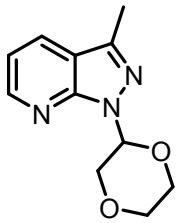
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 4.3, 1.2 Hz, 1H), 8.13 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.39 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.07 (dd, *J* = 6.5, 3.0 Hz, 1H), 4.39 (dd, *J* = 12.0, 6.5 Hz, 1H), 4.20 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.01 – 3.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.59 , 148.53 , 124.96 , 122.57 , 120.22 , 82.77 , 67.03 , 65.90 , 64.97; HRMS (ESI-TOF) m/z Calcd for $C_9H_{10}N_4O_2$ $[M+H]^+$: 207.0877, found: 207.0899.



1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3x)

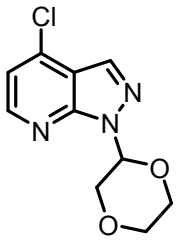
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.01 (s, 1H), 7.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.10 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.22 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.44 (dd, *J* = 11.5, 9.0 Hz, 1H), 4.06 – 3.86 (m, 3H), 3.83 – 3.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.65 , 149.12 ,

134.11 , 130.21 , 117.79 , 115.87 , 78.53 , 67.88 , 66.57 , 65.79; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{11}N_3O_2$ $[M+H]^+$: 206.0924, found: 206.0955.



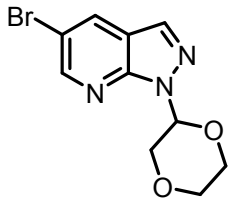
1-(1,4-dioxan-2-yl)-3-methyl-1*H*-pyrazolo[3,4-b]pyridine (3y)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.06 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.15 (dd, *J* = 9.5, 2.8 Hz, 1H), 4.41 (dd, *J* = 11.5, 9.5 Hz, 1H), 4.10 – 3.85 (m, 3H), 3.83 – 3.67 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.44 , 148.98 , 143.09 , 129.55 , 117.06 , 115.77 , 78.46 , 68.08 , 66.91 , 65.73 , 12.49; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{13}N_3O_2$ $[M+H]^+$: 220.1081, found: 220.1103.



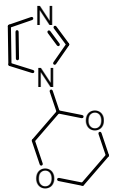
4-chloro-1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3z)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.0 Hz, 1H), 8.18 (s, 1H), 7.21 (d, *J* = 5.0 Hz, 1H), 6.27 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.51 (dd, *J* = 11.6, 8.9 Hz, 1H), 4.12 – 3.99 (m, 3H), 3.90 – 3.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.55 , 149.51 , 138.05 , 132.59 , 117.87 , 115.83 , 78.92 , 67.77 , 66.54 , 65.82; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{10}ClN_3O_2$ $[M+H]^+$: 240.0534, found: 240.0563.



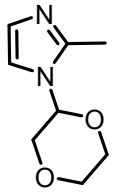
5-bromo-1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3aa)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.1 Hz, 1H), 8.22 (d, *J* = 2.1 Hz, 1H), 8.06 (s, 1H), 6.25 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.50 (dd, *J* = 11.6, 8.9 Hz, 1H), 4.13 – 3.99 (m, 3H), 3.89 – 3.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.06 , 149.12 , 133.33 , 132.04 , 117.31 , 113.46 , 78.73 , 67.79 , 66.57 , 65.83; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{10}BrN_3O_2$ $[M+H]^+$: 284.0029, found: 284.0007.



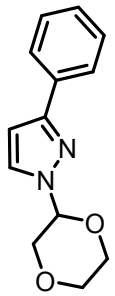
1-(1,4-dioxan-2-yl)-1*H*-imidazole (3ab)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.06 (d, *J* = 28.3 Hz, 2H), 5.37 (s, 1H), 4.13 – 3.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.26 , 129.06 , 117.57 , 79.34 , 68.31 , 65.84 , 63.75; HRMS (ESI-TOF) m/z Calcd for $C_7H_{10}N_2O_2$ $[M+H]^+$: 155.0815, found: 155.0825.



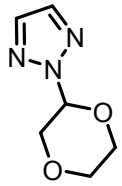
1-(1,4-dioxan-2-yl)-2-methyl-1*H*-imidazole (3ac)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 1.3 Hz, 1H), 6.86 (d, *J* = 1.2 Hz, 1H), 5.28 (dd, *J* = 6.2, 3.0 Hz, 1H), 3.91 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.85 – 3.64 (m, 5H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.07 , 127.15 , 117.13 , 78.27 , 68.41 , 66.05 , 64.19 , 13.12; HRMS (ESI-TOF) m/z Calcd for $C_8H_{12}N_2O_2$ $[M+H]^+$: 169.0972, found: 169.0981.



1-(1,4-dioxan-2-yl)-3-phenyl-1*H*-pyrazole (3ad)

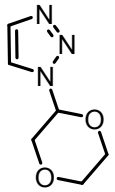
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.64 (d, *J* = 2.5 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 5.52 (dd, *J* = 6.0, 4.1 Hz, 1H), 4.06 – 4.01 (m, 2H), 3.89 – 3.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.20 , 132.89 , 130.20 , 128.49 , 127.87 , 125.76 , 103.55 , 83.39 , 68.41 , 65.92 , 65.05; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{14}N_2O_2$ $[M+H]^+$: 231.1128, found: 231.1151.



2-(1,4-dioxan-2-yl)-2*H*-1,2,3-triazole (3ae)

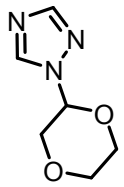
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 2H), 5.76 (dd, *J* = 7.3, 2.9 Hz, 1H), 4.25 (dd, *J* = 11.8, 7.3 Hz, 1H), 4.01 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.94 – 3.81 (m, 2H), 3.79 – 3.69 (m, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 135.20 , 84.77 , 67.48 , 65.83 , 65.40; HRMS (ESI-TOF) m/z Calcd for $C_6H_9N_3O_2$ $[M+H]^+$: 156.0768, found: 156.0781.



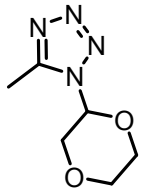
1-(1,4-dioxan-2-yl)-1*H*-1,2,3-triazole (3ae')

^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.0 Hz, 1H), 7.67 (d, *J* = 0.9 Hz, 1H), 5.83 (dd, *J* = 5.9, 3.0 Hz, 1H), 4.10 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.99 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.84 – 3.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.73 , 122.74 , 81.79 , 68.09 , 66.02 , 64.35; HRMS (ESI-TOF) m/z Calcd for $C_6H_9N_3O_2$ $[M+H]^+$: 156.0768, found: 156.0783.



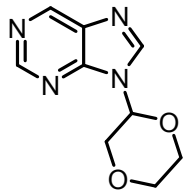
1-(1,4-dioxan-2-yl)-1*H*-1,2,4-triazole(3af)

^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.93 (s, 1H), 5.71 – 5.47 (m, 1H), 4.09 – 3.97 (m, 2H), 3.85 – 3.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.64 , 142.94 , 81.15 , 67.48 , 65.73 , 63.71; HRMS (ESI-TOF) m/z Calcd for $C_6H_9N_3O_2$ $[M+H]^+$: 156.0768, found: 156.0779.



1-(1,4-dioxan-2-yl)-5-methyl-1*H*-tetrazole (3ag)

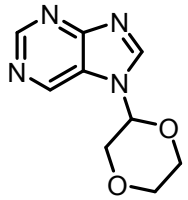
^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 6.0, 2.9 Hz, 1H), 4.35 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.13 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.08 – 4.03 (m, 1H), 3.96 – 3.85 (m, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.21 , 83.57 , 66.98 , 65.80 , 64.79 , 10.87; HRMS (ESI-TOF) m/z Calcd for $C_6H_{10}N_4O_2$ $[M+H]^+$: 171.0877, found: 171.0885.



9-(1,4-dioxan-2-yl)-9*H*-purine (3ah)

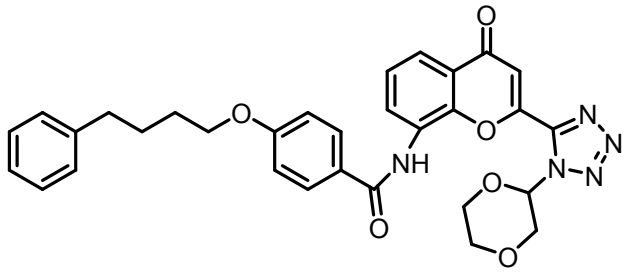
^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.95 (s, 1H), 8.47 (s, 1H), 6.01 (dd, *J* = 5.6, 3.0 Hz, 1H), 4.15 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.06 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.90 – 3.78 (m, 4H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 152.90 , 150.98 , 148.80 , 143.69 , 133.70 , 77.07 , 68.25 , 66.19 , 64.14; HRMS (ESI-TOF) m/z Calcd for $C_9H_{10}N_4O_2$ $[M+H]^+$: 207.0877, found: 207.0882.



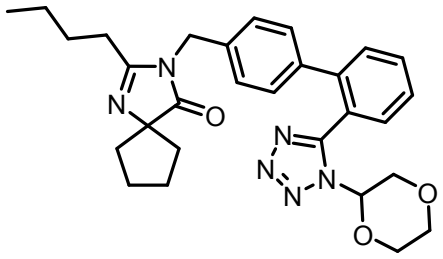
7-(1,4-dioxan-2-yl)-7*H*-purine (3ah')

^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 9.04 (s, 1H), 8.52 (s, 1H), 5.78 (t, *J* = 3.5 Hz, 1H), 4.28 – 4.10 (m, 2H), 3.94 – 3.78 (m, 2H), 3.77 – 3.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.73 , 153.75 , 146.86 , 141.32 , 124.55 , 79.25 , 67.21 , 66.37 , 62.83; HRMS (ESI-TOF) m/z Calcd for $C_9H_{10}N_4O_2$ $[M+H]^+$: 207.0877, found: 207.0880.



N-(2-(1-(1,4-dioxan-2-yl)-1*H*-tetrazol-5-yl)-4-oxo-4*H*-chromen-8-yl)-4-(4-phenylbutoxy)benzamide (3ai)

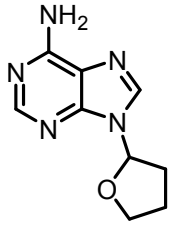
^1H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.82 (m, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.87 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.35 – 7.24 (m, 3H), 7.25 – 7.17 (m, 3H), 6.98 (m, 2H), 6.23 – 6.14 (m, 1H), 4.59 – 4.45 (m, 1H), 4.26 (dd, *J* = 12.4, 2.8 Hz, 1H), 4.15 – 4.01 (m, 3H), 4.00 – 3.84 (m, 3H), 2.72 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.04 , 164.41 , 162.40 , 159.17 , 151.07 , 145.36 , 141.96 , 129.02 , 128.35 , 128.31 , 128.14 , 125.95 , 125.82 , 125.72 , 123.97 , 123.95 , 119.30 , 114.51 , 111.22 , 84.84 , 68.00 , 66.60 , 65.86 , 63.93 , 35.47 , 28.61 , 27.73; HRMS (ESI-TOF) m/z Calcd for $C_{31}H_{29}N_5O_6$ $[M+H]^+$: 568.2191, found: 568.2209.



3-((2'-(1-(1,4-dioxan-2-yl)-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (3aj)

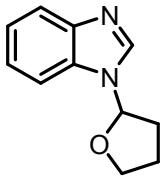
^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.43 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.08 (m, 2H), 5.94 (dd, *J* = 5.4, 2.9 Hz, 1H), 4.68 (s, 2H), 4.16 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.01 (dd, *J* = 12.1, 2.9 Hz, 1H), 3.93 – 3.74 (m, 4H), 2.37 – 2.29

(m, 2H), 2.03 – 1.92 (m, 6H), 1.87 – 1.78 (m, 2H), 1.65 – 1.53 (m, 2H), 1.40 – 1.29 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.46 , 165.15 , 161.89 , 141.40 , 140.41 , 135.17 , 130.67 , 130.40 , 130.18 , 129.76 , 127.66 , 126.16 , 125.75 , 83.75 , 76.37 , 66.87 , 65.78 , 64.35 , 43.23 , 37.34 , 28.70 , 27.71 , 26.02 , 22.27 , 13.68; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{34}N_6O_3$ $[M+H]^+$: 515.2765, found: 515.2797.



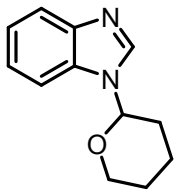
9-(tetrahydrofuran-2-yl)-9*H*-purin-6-amine (3ak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.93 (s, 1H), 6.30 (dd, *J* = 6.3, 3.1 Hz, 1H), 6.24 (s, 2H), 4.34 – 4.20 (m, 1H), 4.12 – 4.01 (m, 1H), 2.65 – 2.39 (m, 2H), 2.23 – 2.06 (m, 2H)； ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.43 , 152.61 , 149.17 , 138.46 , 120.18 , 85.84 , 69.59 , 32.43 , 24.19； HRMS (ESI-TOF) m/z Calcd for $C_9H_{11}N_5O$ $[M+H]^+$: 206.1036, found: 206.1048.



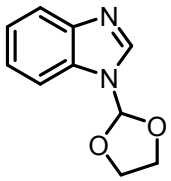
1-(tetrahydrofuran-2-yl)-1*H*-benzo[d]imidazole (4a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.75 – 7.67 (m, 1H), 7.39 – 7.33 (m, 1H), 7.23 – 7.14 (m, 2H), 6.06 (m, 1H), 4.12 – 4.01 (m, 1H), 3.98 – 3.88 (m, 1H), 2.39 – 2.24 (m, 2H), 2.09 – 1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.14 , 140.13 , 132.44 , 122.88 , 122.26 , 120.17 , 110.33 , 85.84 , 68.77 , 31.65 , 24.08; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}N_2O$ $[M+H]^+$: 189.1022, found: 189.1001.



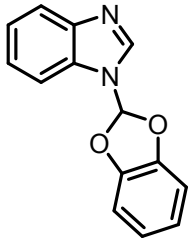
1-(tetrahydro-2H-pyran-2-yl)-1*H*-benzo[d]imidazole (4b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.76 – 7.67 (m, 1H), 7.49 – 7.39 (m, 1H), 7.28 – 7.11 (m, 2H), 5.40 (dd, *J* = 9.8, 2.5 Hz, 1H), 4.11 – 3.96 (m, 1H), 3.75 – 3.59 (m, 1H), 2.20 – 1.93 (m, 3H), 1.76 – 1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.72 , 140.31 , 132.90 , 123.06 , 122.44 , 120.24 , 110.77 , 83.29 , 67.93 , 30.65 , 24.87 , 22.63; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}N_2O$ $[M+H]^+$: 203.1179, found: 203.1156.



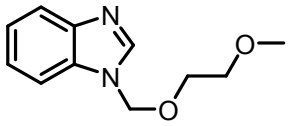
1-(1,3-dioxolan-2-yl)-1*H*-benzo[d]imidazole (4c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.85 – 7.77 (m, 1H), 7.61 – 7.54 (m, 1H), 7.37 – 7.29 (m, 2H), 6.25 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.45 (s, 1H), 5.08 (s, 1H), 4.44 (dd, *J* = 9.7, 2.1 Hz, 1H), 4.22 (dd, *J* = 9.7, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.07 , 141.23 , 132.01 , 123.56 , 122.85 , 120.55 , 110.17 , 96.39 , 81.31 , 69.43; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{10}N_2O_2$ $[M+H]^+$: 191.0815, found: 191.0822.



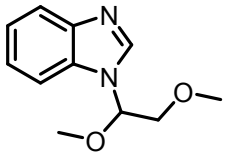
1-(benzo[d][1,3]dioxol-2-yl)-1*H*-benzo[d]imidazole (4d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.85 (s, 1H), 7.82 (m, 1H), 7.37 – 7.29 (m, 1H), 7.28 – 7.25 (m, 2H), 7.05 – 6.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.27 , 144.25 , 140.10 , 131.03 , 124.12 , 123.45 , 122.94 , 120.71 , 111.04 , 109.06 , 107.36; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{10}N_2O_2$ $[M+H]^+$: 239.0815, found: 239.0824.



1-((2-methoxyethoxy)methyl)-1*H*-benzo[d]imidazole (4e)

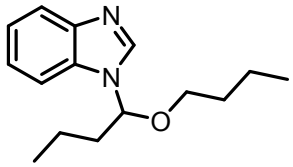
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.42 – 7.30 (m, 2H), 5.68 (s, 2H), 3.64 – 3.53 (m, 2H), 3.51 – 3.44 (m, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.82 , 141.36 , 132.94 , 124.41 , 123.89 , 119.45 , 110.95 , 75.50 , 71.51 , 68.03 , 59.03; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{14}N_2O_2$ $[M+H]^+$: 207.1128, found: 207.1149.



1-(1,2-dimethoxyethyl)-1*H*-benzo[d]imidazole (4e')

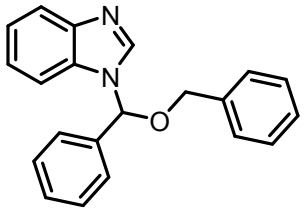
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.81 – 7.73 (m, 1H), 7.52 – 7.45 (m, 1H), 7.24 (m, 2H), 5.43 (t, *J* = 5.6 Hz, 1H), 3.83 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.69 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.27 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.02 , 141.76 , 132.64 , 123.34 , 122.70 ,

120.53 , 110.82 , 86.83 , 73.19 , 59.52 , 56.57; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{14}N_2O_2$ $[M+H]^+$: 207.1128, found: 207.1139.



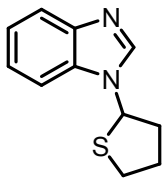
1-(1-butoxybutyl)-1*H*-benzo[d]imidazole (4f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.86 – 7.78 (m, 1H), 7.62 – 7.51 (m, 1H), 7.33 – 7.27 (m, 2H), 5.40 (t, *J* = 6.6 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.30 – 3.19 (m, 1H), 2.21 – 2.07 (m, 1H), 2.04 – 1.87 (m, 1H), 1.57 – 1.46 (m, 2H), 1.44 – 1.16 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.69 , 141.28 , 132.46 , 123.10 , 122.53 , 120.23 , 111.12 , 87.18 , 68.59 , 37.60 , 31.28 , 19.16 , 18.28 , 13.69 , 13.49; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{22}N_2O$ $[M+H]^+$: 247.1805, found: 247.1819.



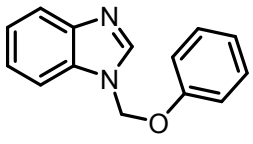
1-((benzyloxy)(phenyl)methyl)-1*H*-benzo[d]imidazole (4g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.42 – 7.26 (m, 12H), 7.23 – 7.18 (m, 1H), 6.56 (s, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.18 , 142.31 , 136.98 , 136.05 , 132.61 , 128.99 , 128.65 , 128.63 , 128.32 , 128.05 , 125.96 , 123.33 , 122.70 , 120.40 , 111.52 , 84.45 , 70.15; HRMS (ESI-TOF) m/z Calcd for $C_{21}H_{18}N_2$ O $[M+H]^+$: 315.1492, found: 315.1523.



1-(tetrahydrothiophen-2-yl)-1*H*-benzo[d]imidazole (4h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.87 – 7.71 (m, 1H), 7.51 – 7.39 (m, 1H), 7.35 – 7.24 (m, 2H), 6.04 (m, 1H), 3.32 – 3.23 (m, 1H), 3.08 – 2.96 (m, 1H), 2.47 – 2.15 (m, 3H), 2.12 – 1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.47 , 141.74 , 133.19 , 122.79 , 122.34 , 120.45 , 109.92 , 62.92 , 38.15 , 32.91 , 28.60; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}N_2S$ $[M+H]^+$: 205.0794, found: 205.0770.

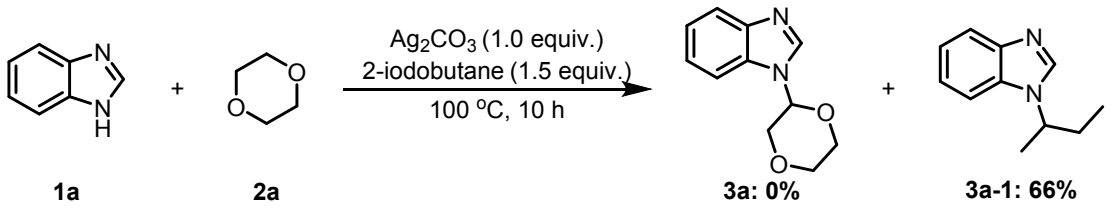


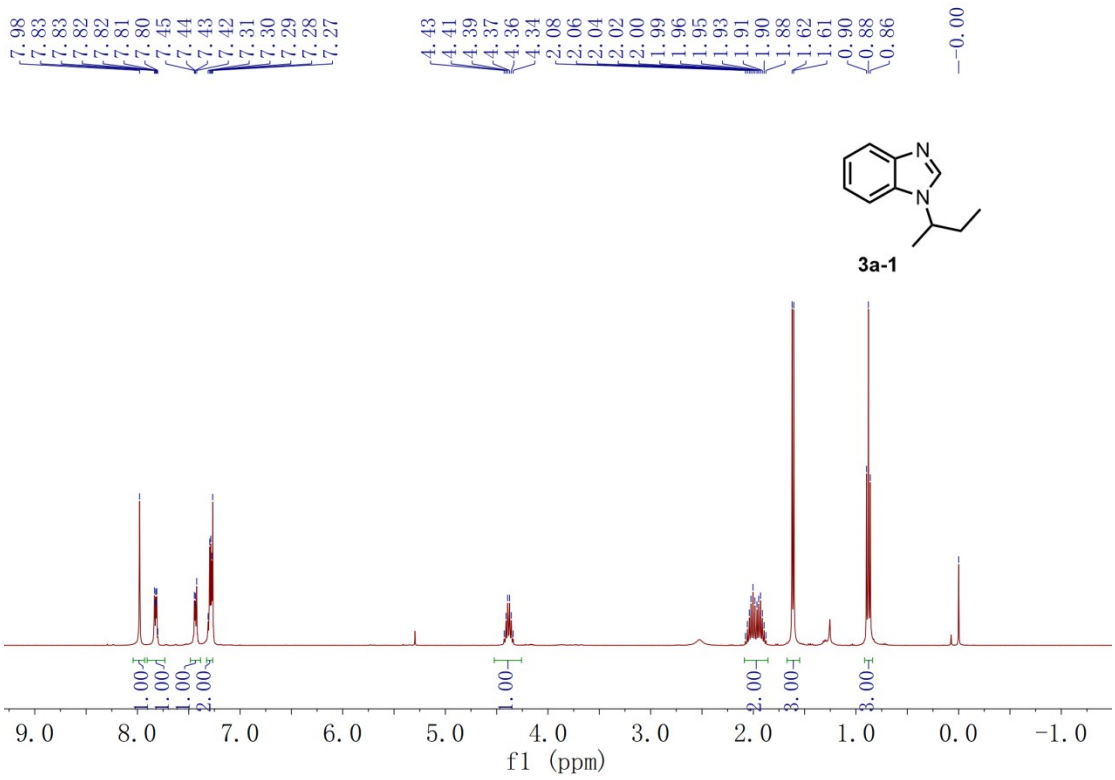
1-(phenoxymethyl)-1*H*-benzo[d]imidazole (4i)

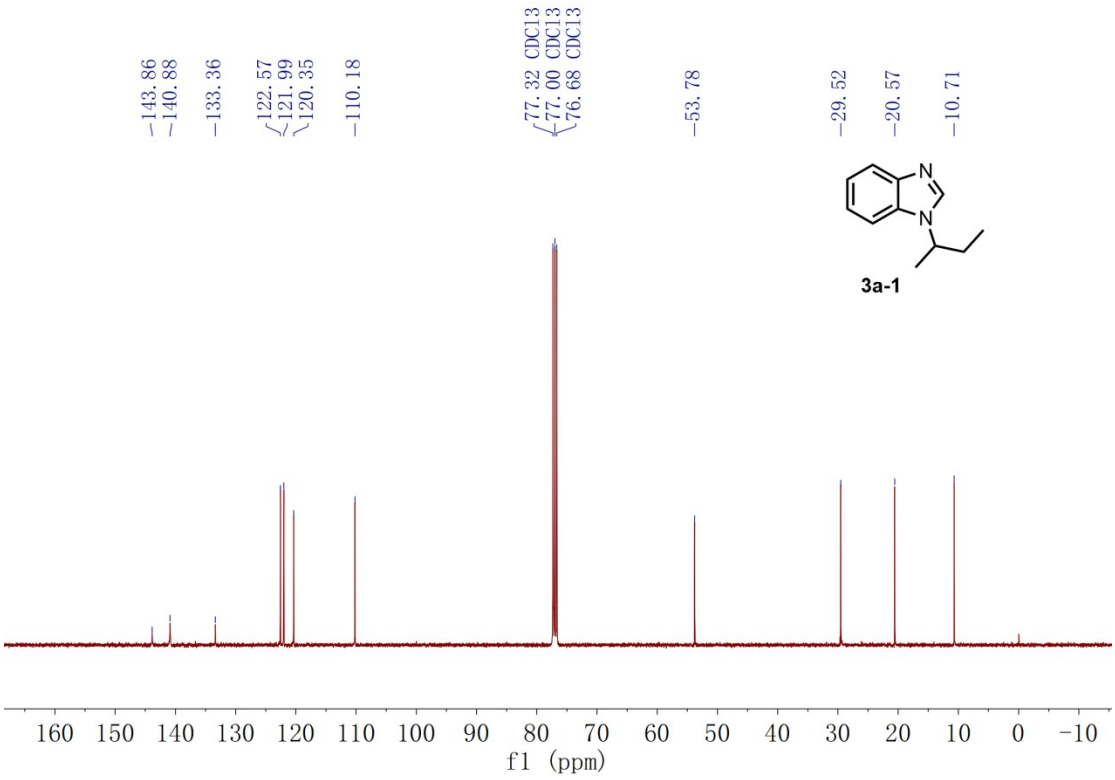
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.85 – 7.78 (m, 1H), 7.54 – 7.47 (m, 1H), 7.37 – 7.27 (m, 4H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.94 – 6.86 (m, 2H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.04 , 143.70 , 142.80 , 133.25 , 129.84 , 123.73 , 123.38 , 122.95 , 120.41 , 117.08 , 110.14 , 73.34; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{12}N_2O$ $[M+H]^+$: 225.1022, found: 225.1019.

2.2 Control experiments

To a mixture of benzimidazole **1a** (0.2 mmol, 1.0 equiv.), Ag_2CO_3 (0.2 mmol, 1.0 equiv.), and 2-iodobutane (0.3 mmol, 1.5 equiv.) was added 1,4-dioxane **2a** (2.0 mL) under air. The resultant mixture was heated in a preheated oil bath at 100 °C for 10 h. Then the reaction mixture was cooled to room temperature. The mixture was extracted with ethyl acetate (20 mL × 3), and the combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The crude product was obtained by purifying over a column of silica gel and eluted with methanol/dichloromethane (1:10) to give the expected product in 66% yield (**3a-1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.87 – 7.76 (m, 1H), 7.47 – 7.39 (m, 1H), 7.33 – 7.27 (m, 2H), 4.48 – 4.20 (m, 1H), 2.16 – 1.80 (m, 2H), 1.61 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.86 , 140.88 , 133.36 , 122.57 , 121.99 , 120.35 , 110.18 , 53.78 , 29.52 , 20.57 , 10.71； HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{14}N_2$ $[M+H]^+$: 175.1230, found: 175.1223.




7.98
7.83
7.83
7.82
7.82
7.81
7.80
7.45
7.44
7.43
7.42
7.31
7.30
7.29
7.28
7.27
4.43
4.41
4.39
4.37
4.36
4.34
2.08
2.06
2.04
2.02
2.00
1.99
1.96
1.95
1.93
1.91
1.90
1.88
1.62
1.61
0.90
0.88
0.86
-0.00
3a-1
1.00
1.00
1.00
2.00
1.00
2.00
3.00
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)


143.86
140.88
133.36
122.57
121.99
120.35
110.18
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
53.78
29.52
20.57
10.71
3a-1
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2.3 Electrospray Ionization-Time-of-Flight-Mass Spectrometry (ESI-TOF-MS) of compound 5

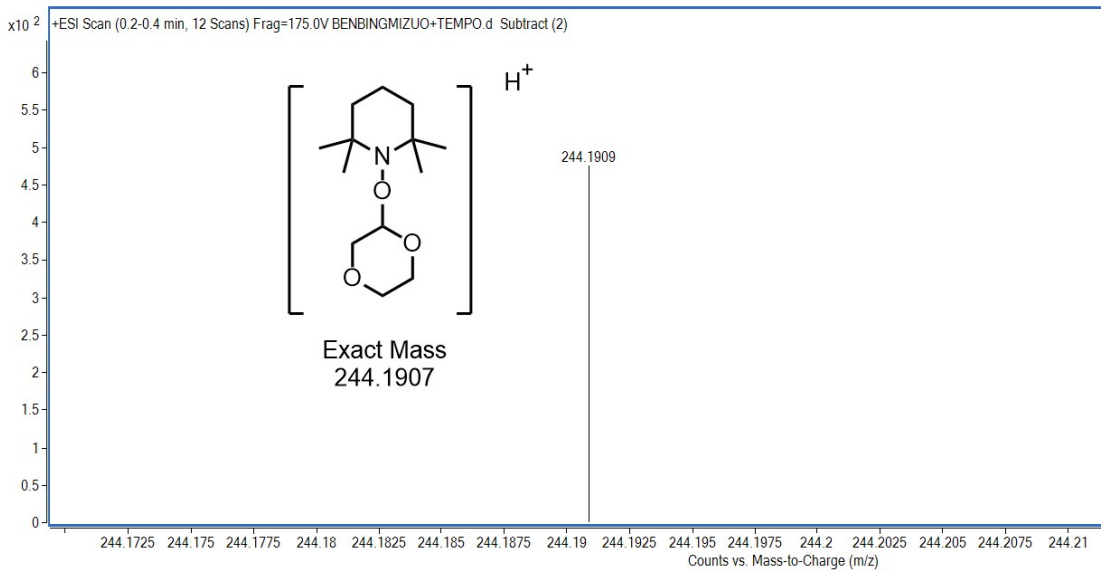
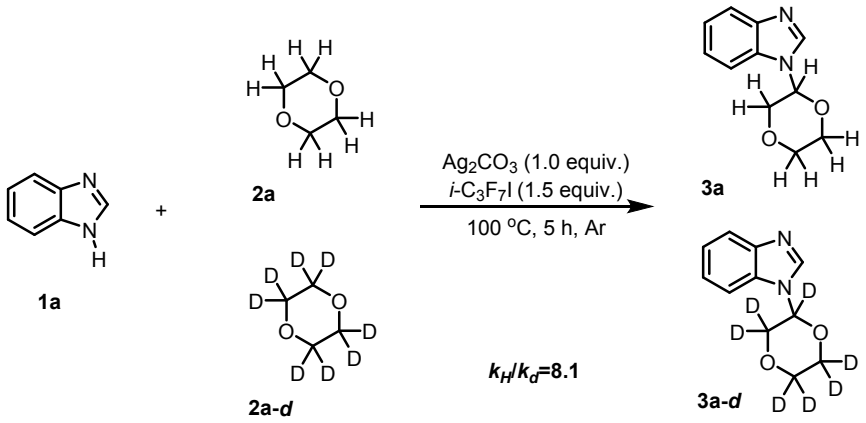


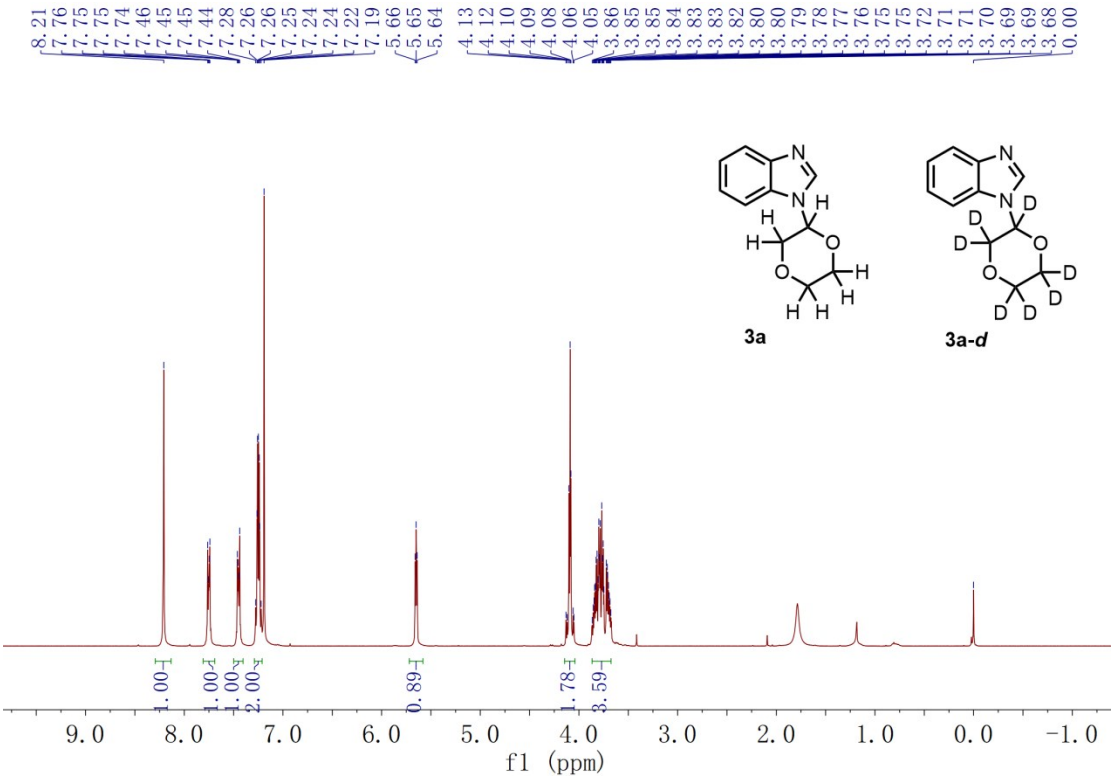
Figure1. HRMS spectrum of compound **5**

2.4 Kinetic isotope effect studies

To a mixture of benzimidazole **1a** (0.2 mmol, 1.0 equiv.), Ag_2CO_3 (0.2 mmol, 1.0 equiv.), and *i*-C_3F_7I (0.3 mmol, 1.5 equiv.) was added an equivalent of 1,4-dioxane **2a** (1.0 mL) and d_8-1,4-dioxane **2a-*d*** (1.0 mL) under air. The resultant mixture was heated in a preheated oil bath at 100 °C for 10 h. Then the reaction mixture was cooled to room temperature. The mixture was extracted with ethyl acetate (20 mL × 3), and the combined organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The crude product was obtained by purifying over a column of silica gel and eluted with methanol/dichloromethane (1:10) to give the expected product in 32% yield (**3a** and **3a-*d***). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.81 – 7.69 (m, 1H), 7.50 – 7.42 (m, 1H), 7.29 – 7.21 (m, 2H), 5.71 – 5.62 (m, 0.89H), 4.16 – 4.02 (m, 1.78H), 3.91 – 3.65 (m, 3.59H).

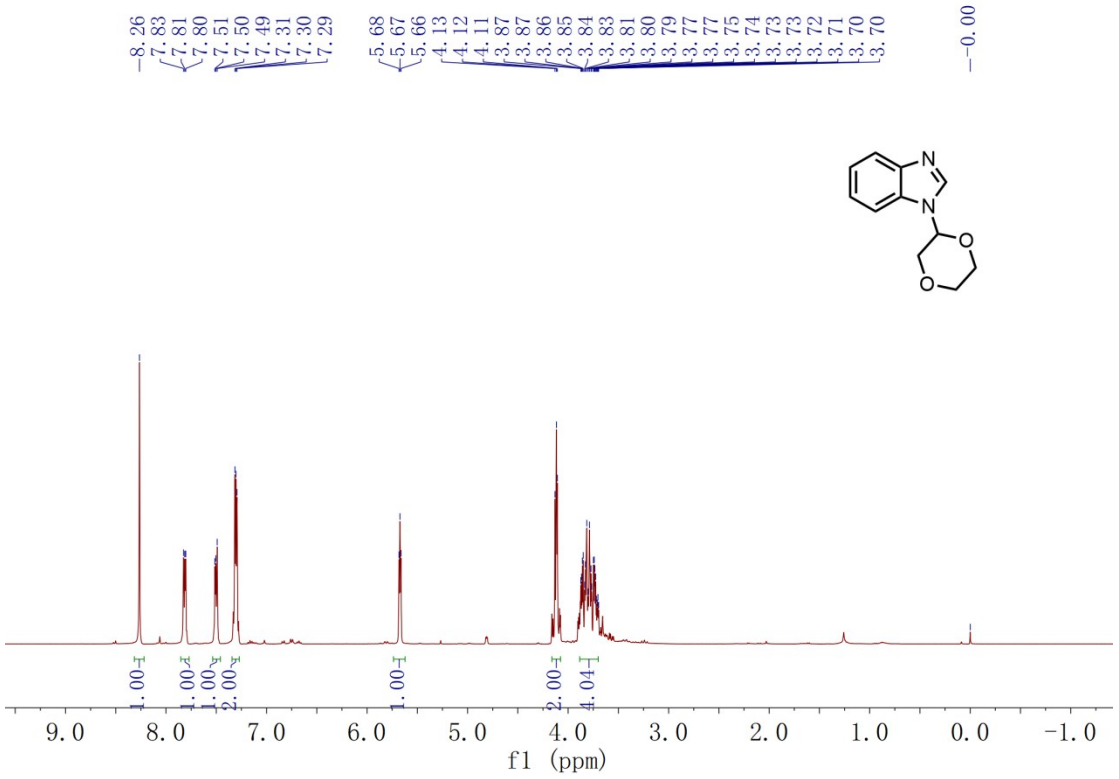
The KIE value was calculated as k_H/k_D = 8.1.

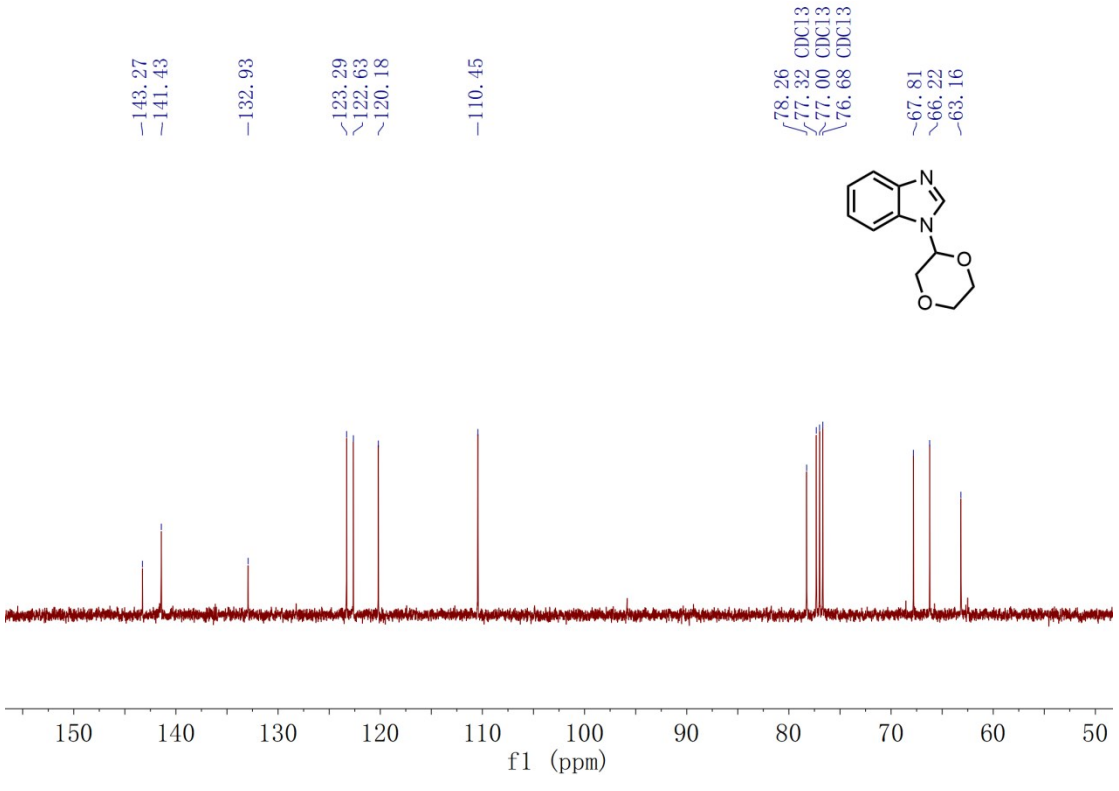

1a
2a
2a-d
Ag2CO3 (1.0 equiv.)
i-C3F7I (1.5 equiv.)
100 °C, 5 h, Ar
kH/kd=8.1
3a
3a-d


8.21
7.76
7.75
7.75
7.74
7.46
7.45
7.45
7.44
7.28
7.26
7.26
7.25
7.24
7.24
7.22
7.19
5.66
5.65
5.64
4.13
4.12
4.10
4.09
4.08
4.06
4.05
3.86
3.85
3.85
3.84
3.83
3.83
3.82
3.80
3.80
3.79
3.78
3.77
3.76
3.75
3.75
3.72
3.71
3.71
3.70
3.69
3.69
3.68
0.00
3a
3a-d
1.00
1.00
1.00
2.00
0.89
1.78
3.59
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)

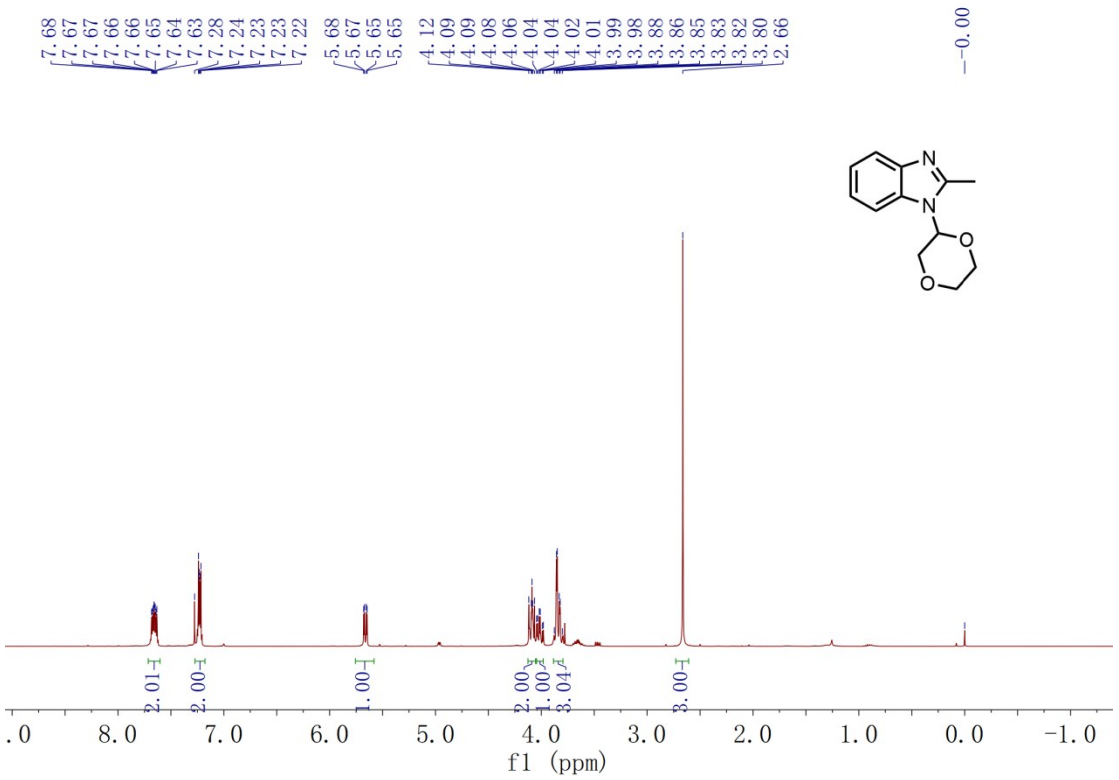
3. ^{1}H and ^{13}C NMR spectra

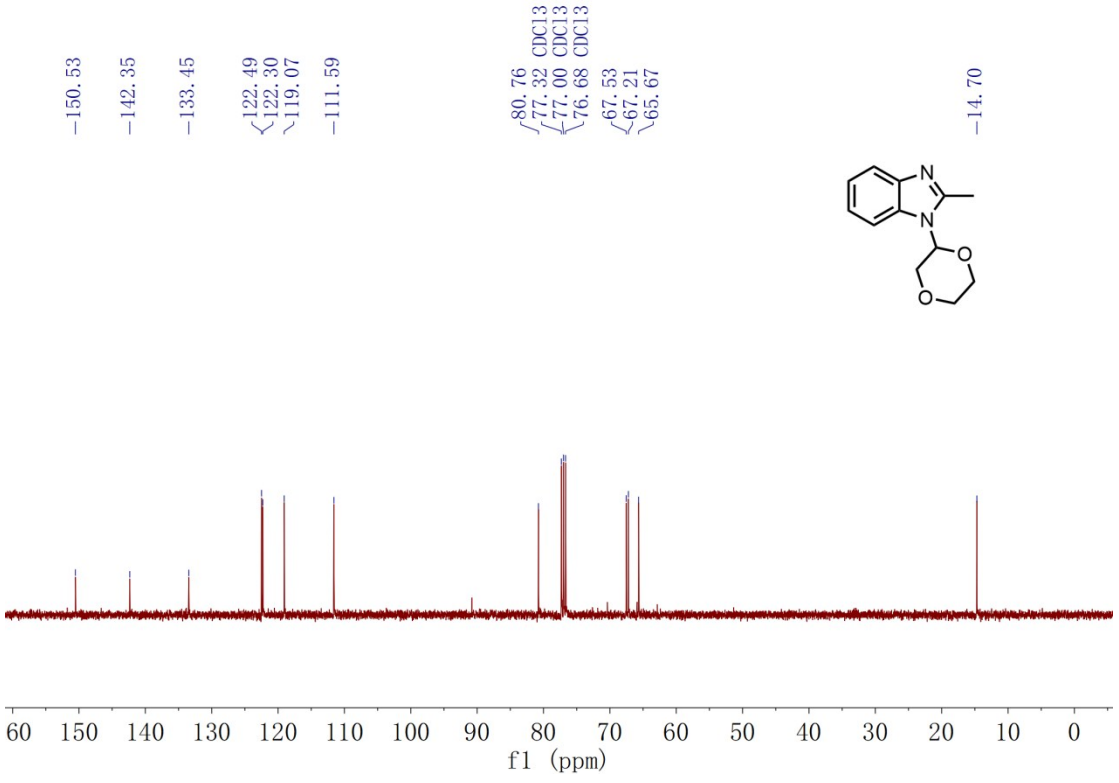
1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3a)



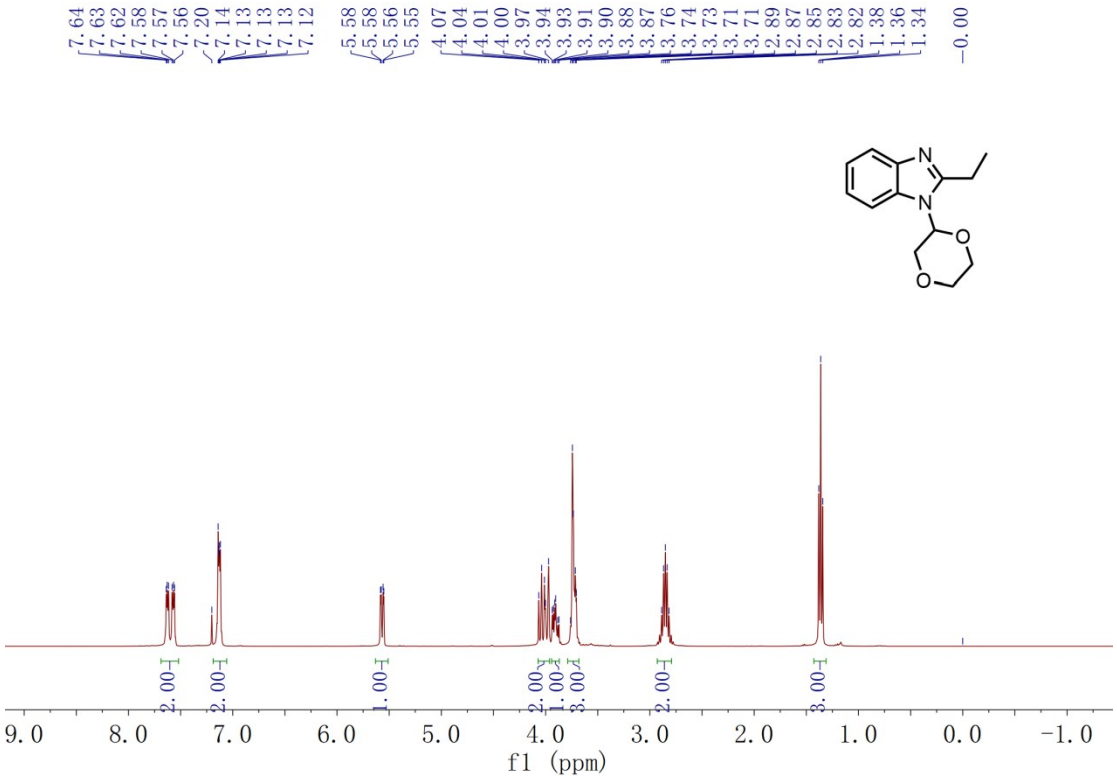


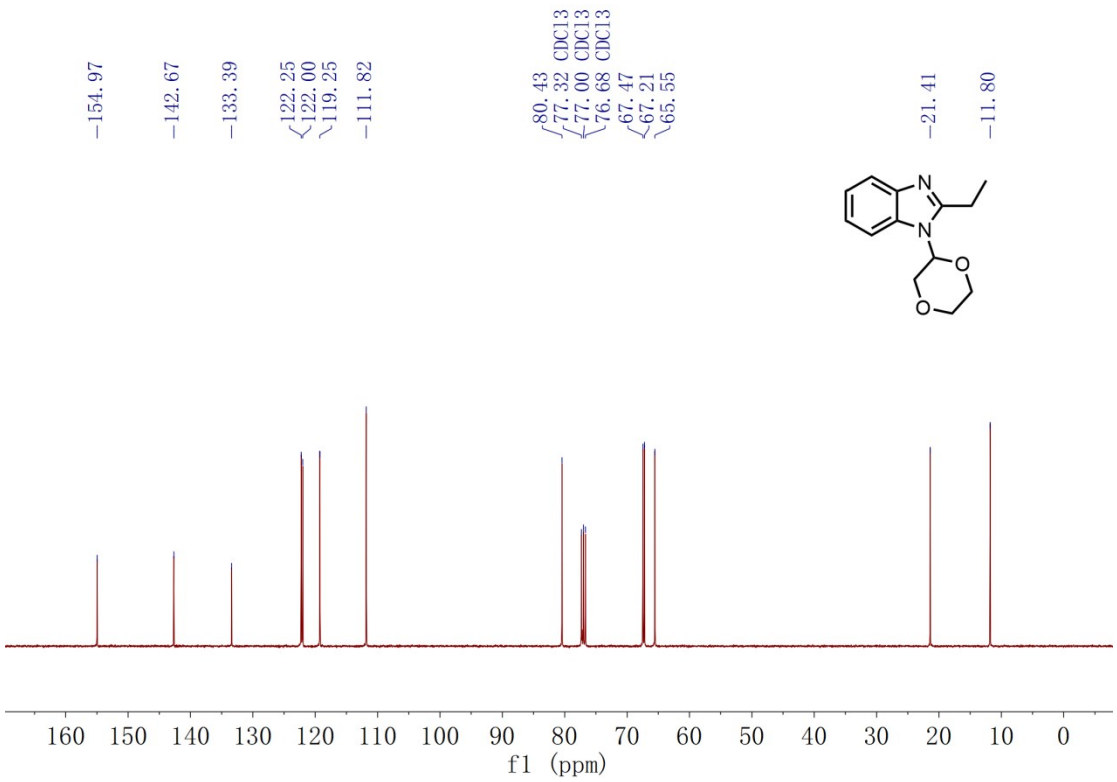
1-(1,4-dioxan-2-yl)-2-methyl-1*H*-benzo[d]imidazole (3b)



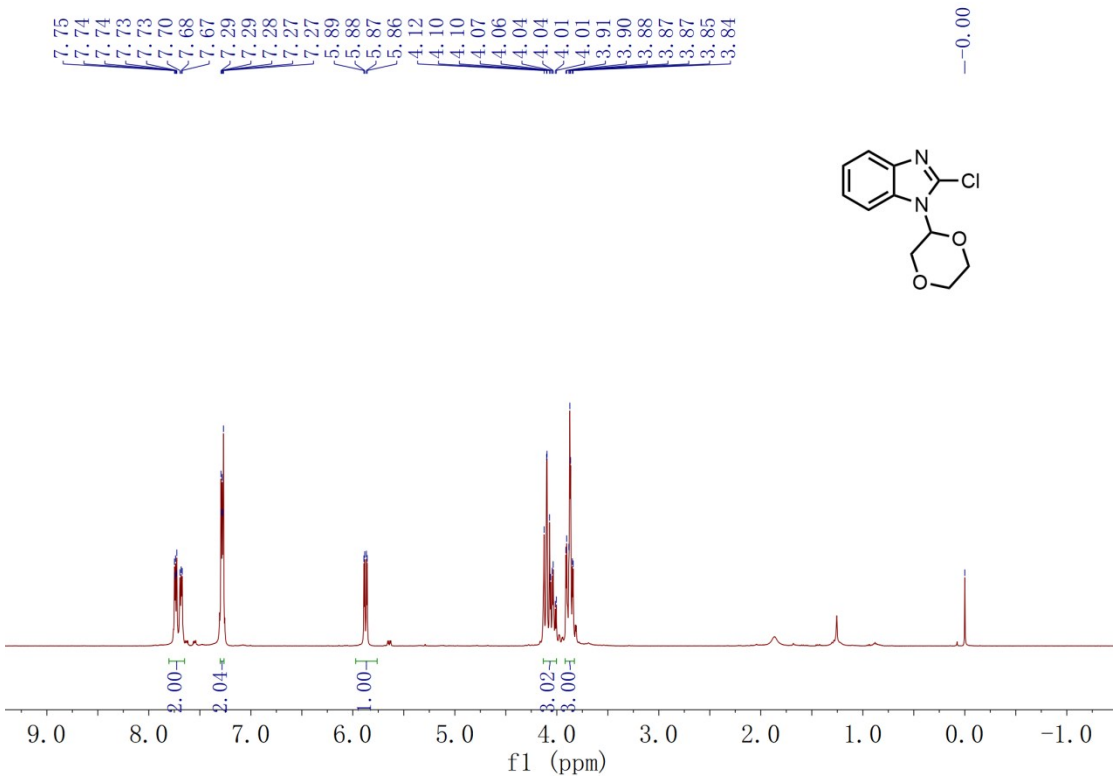


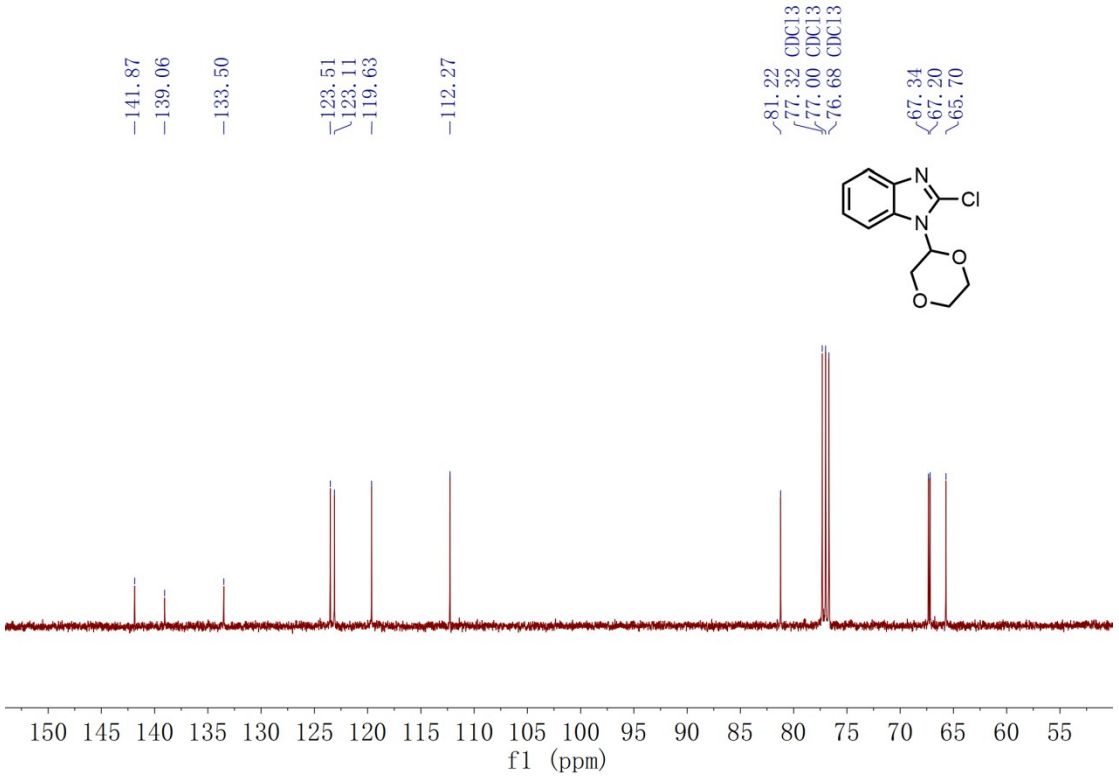
1-(1,4-dioxan-2-yl)-2-ethyl-1*H*-benzo[d]imidazole (3c)



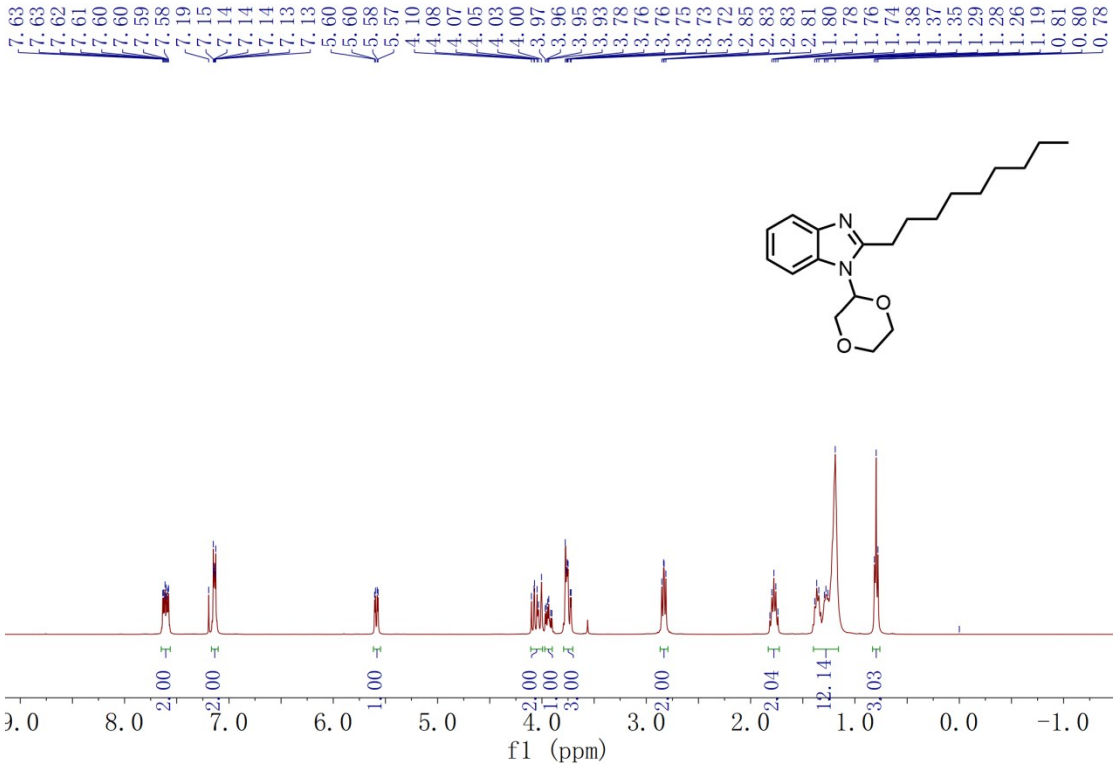


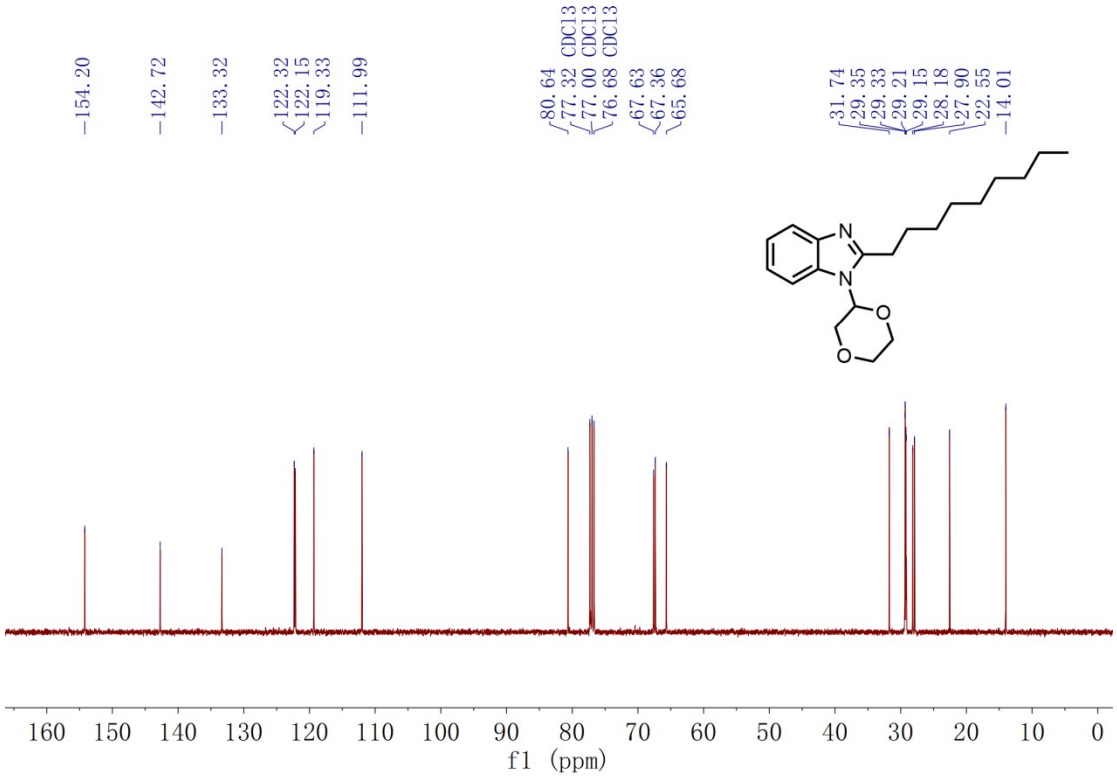
2-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3d)



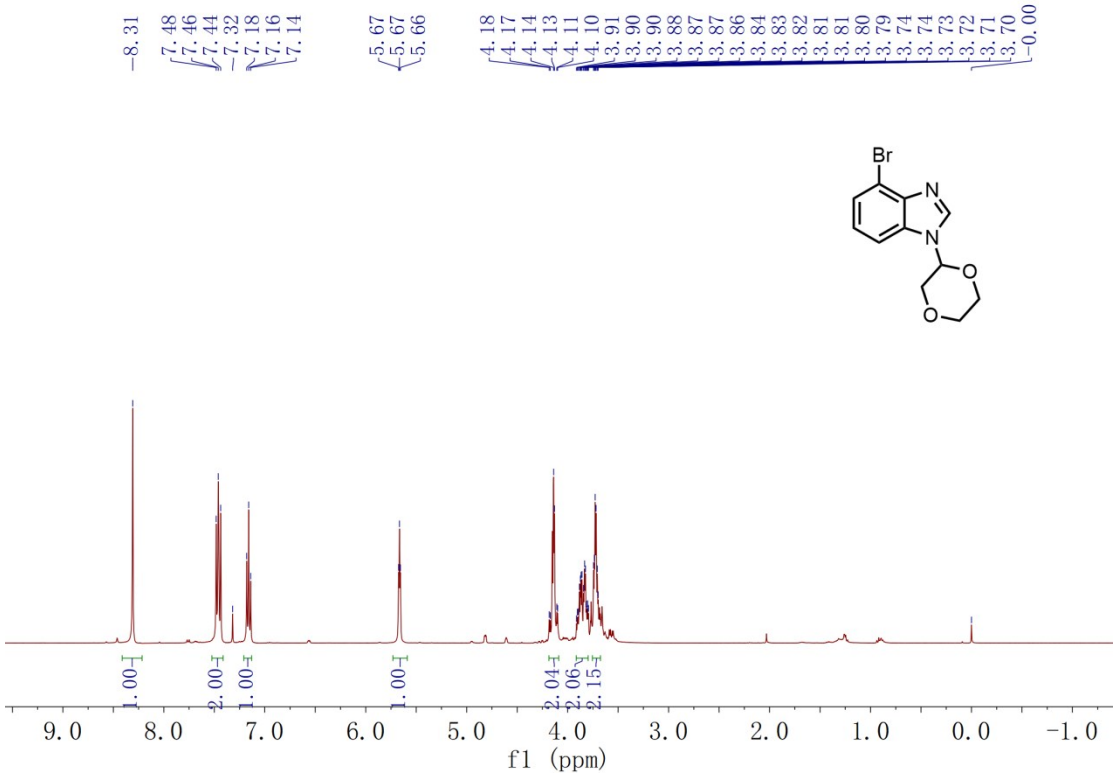


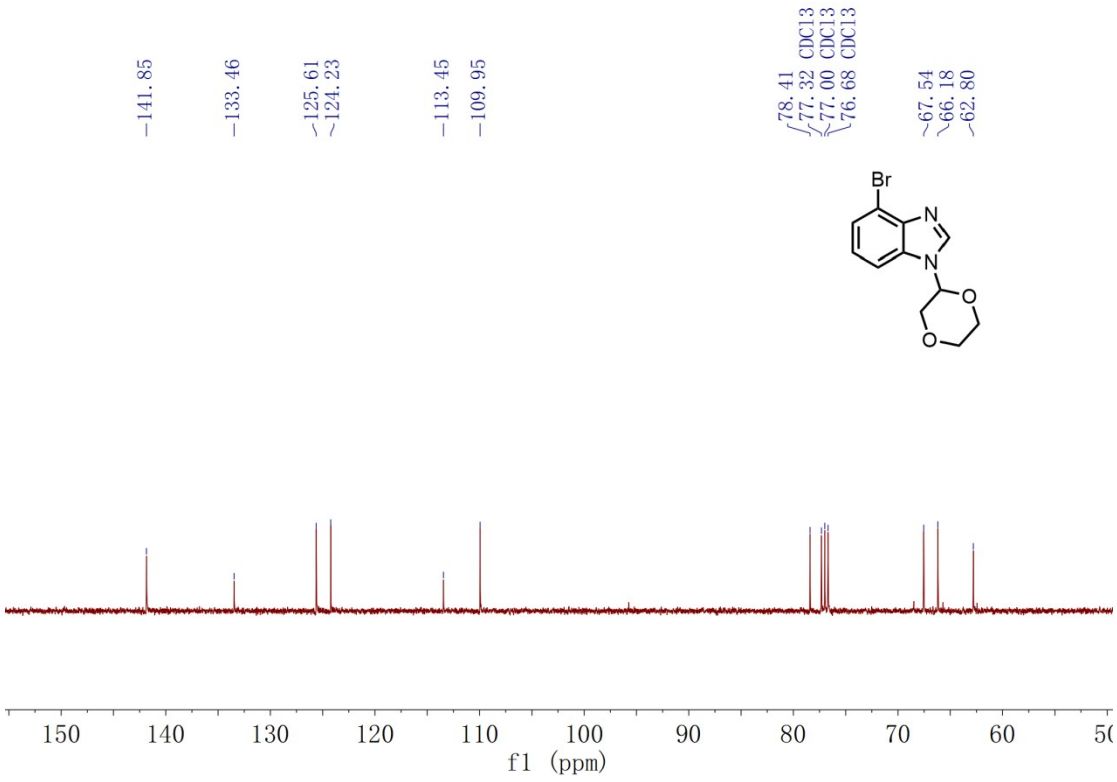
1-(1,4-dioxan-2-yl)-2-nonyl-1*H*-benzo[d]imidazole (3e)



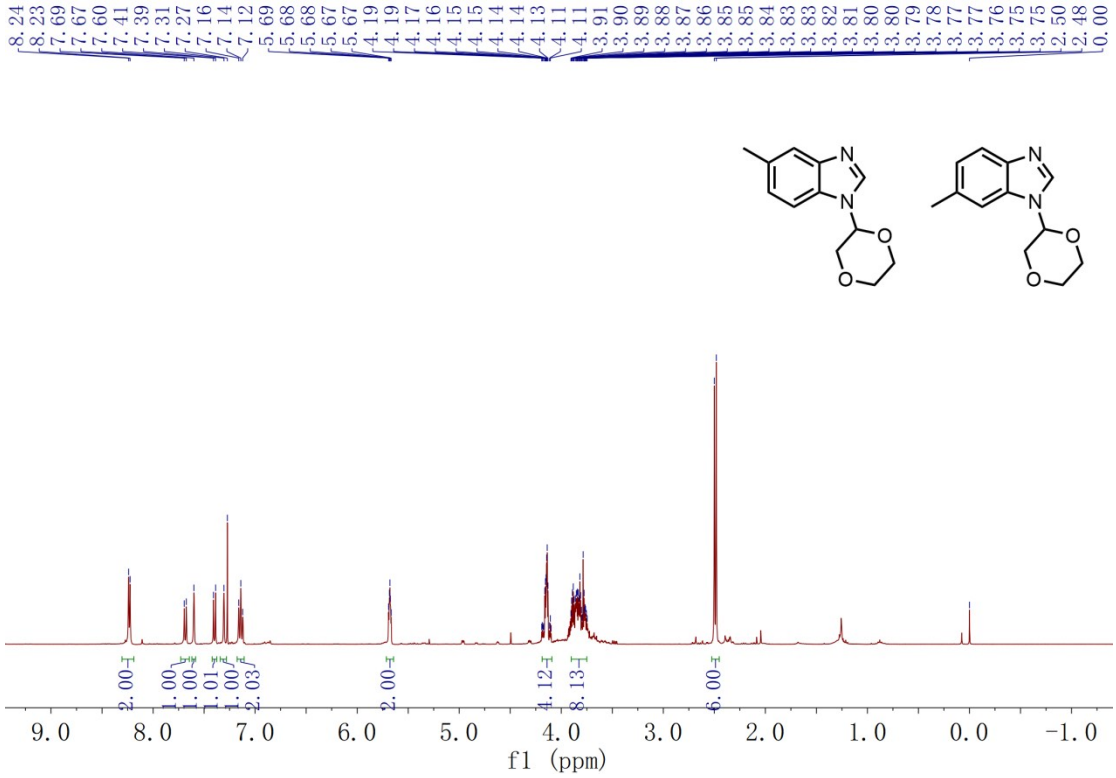


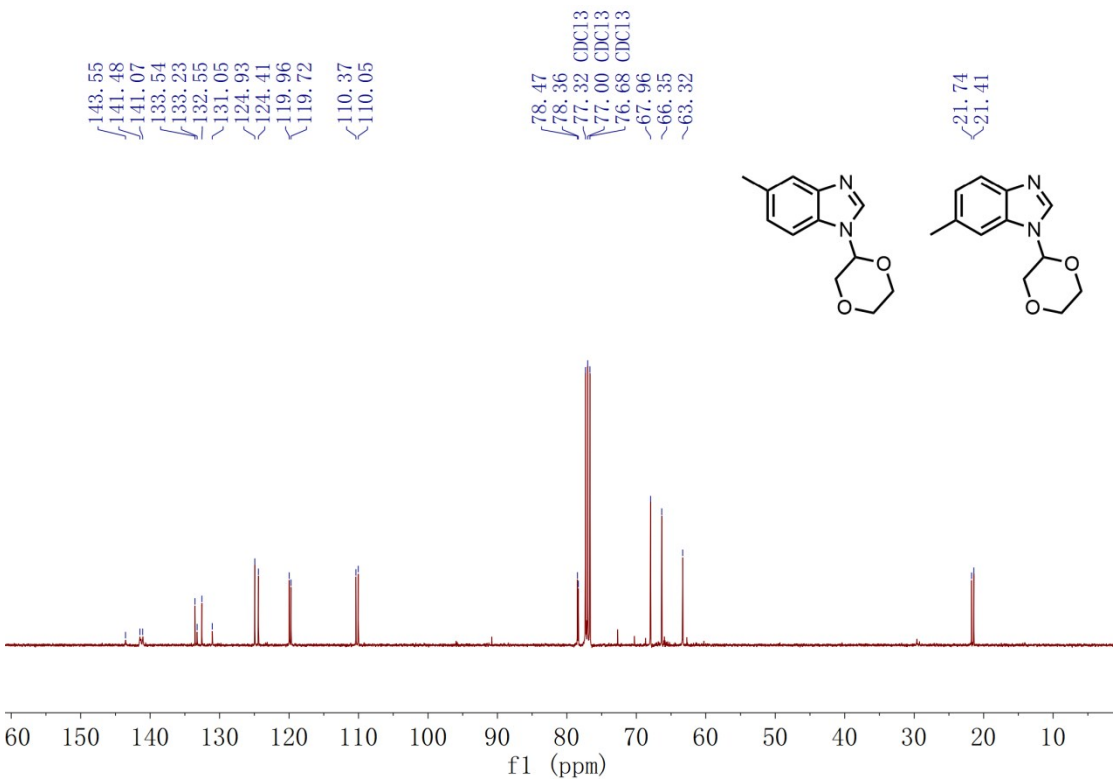
4-bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3f)



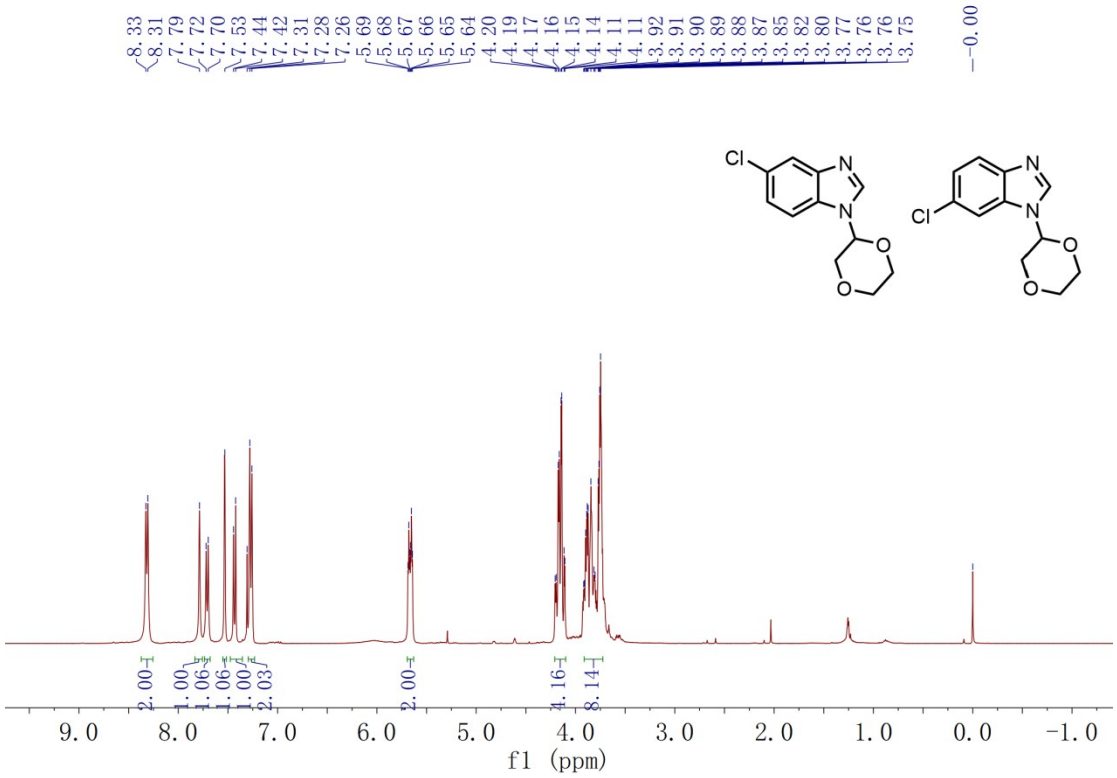


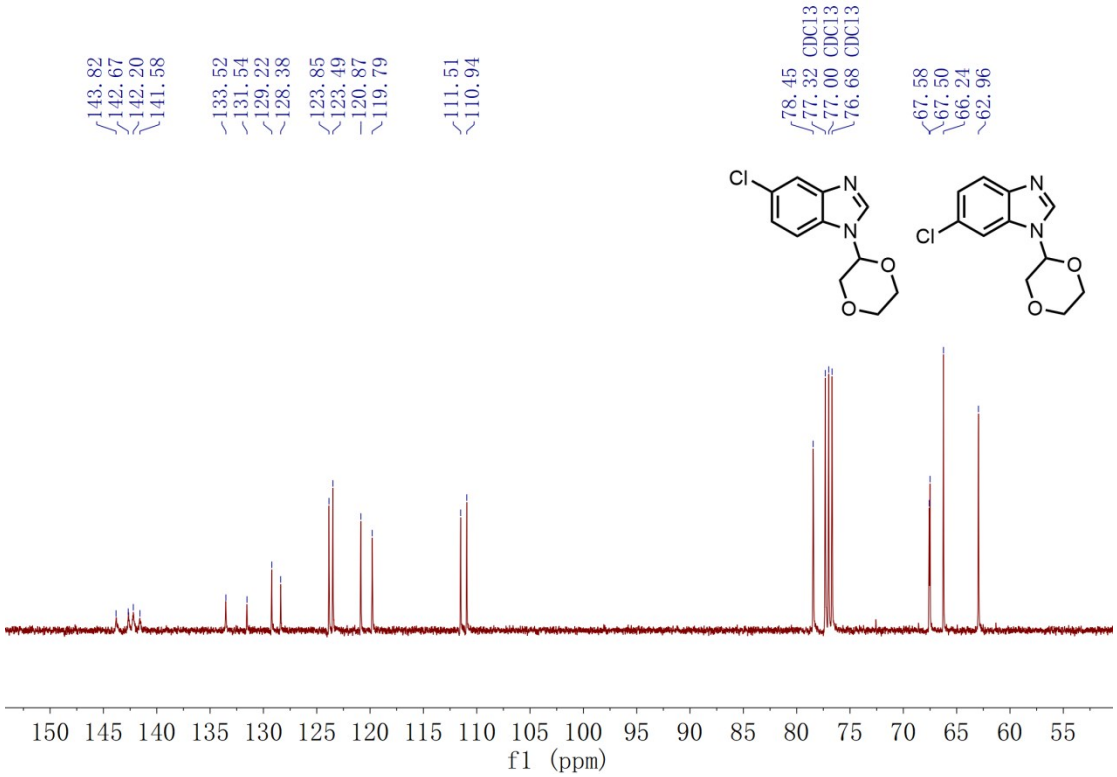
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-benzo[d]imidazole (3g) and 1-(1,4-dioxan-2-yl)-6-methyl-1*H*-benzo[d]imidazole (3g')



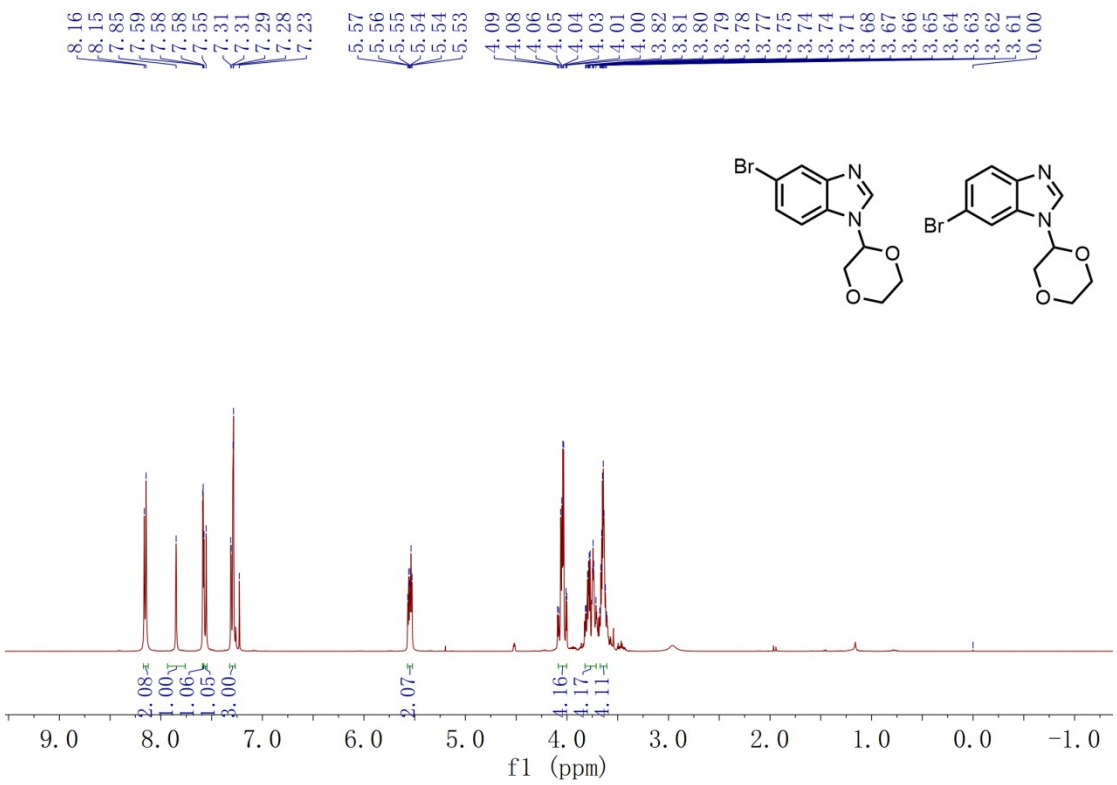


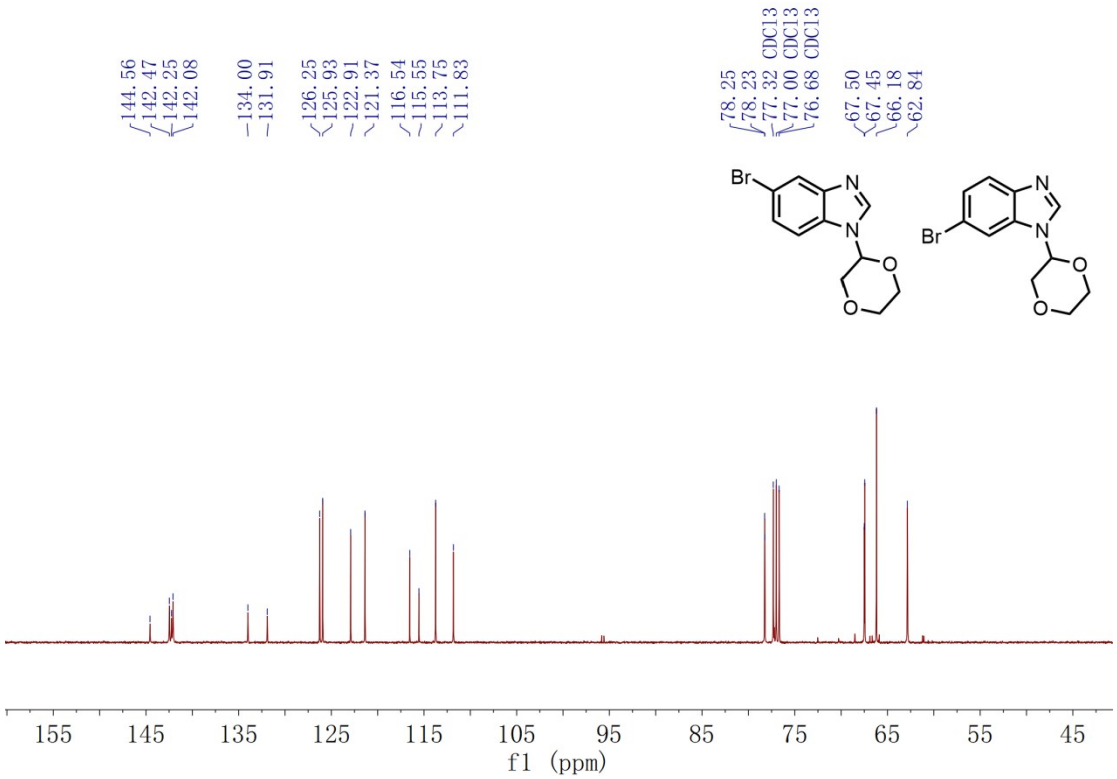
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3h) and 6-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3h')





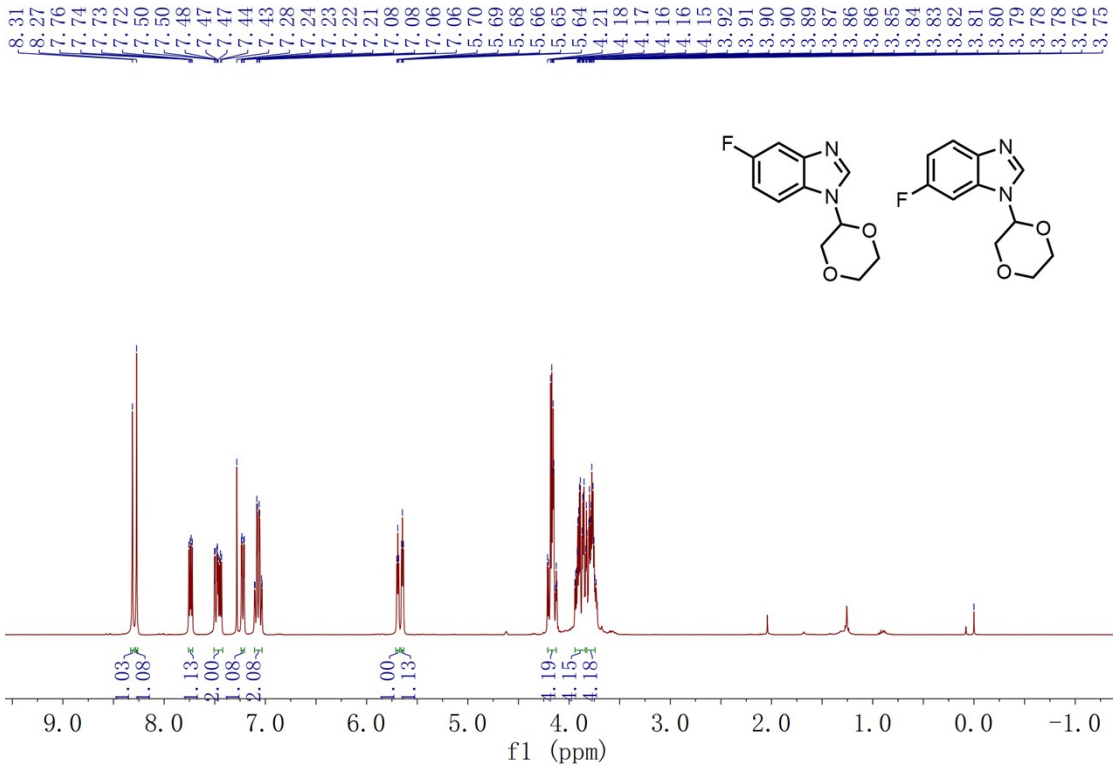
5-bromo-1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazole (3i) and 6-bromo-1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazole (3i')

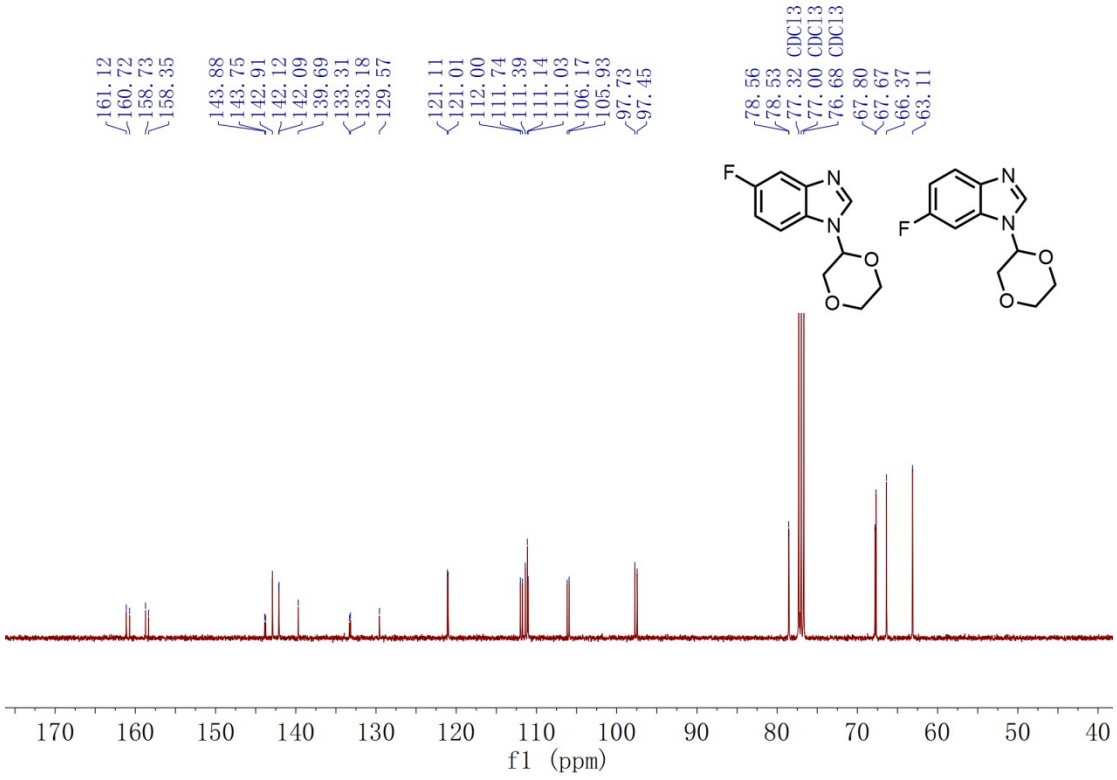




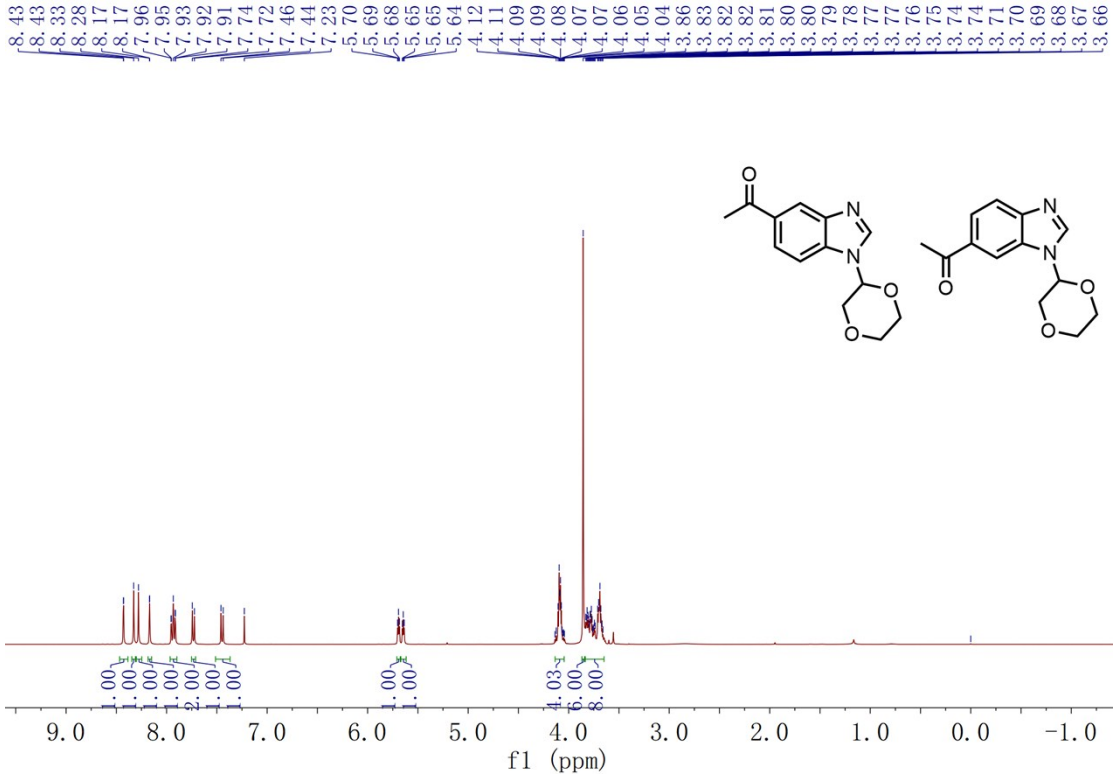
1-(1,4-dioxan-2-yl)-6-fluoro-1*H*-benzo[d]imidazole (3j)

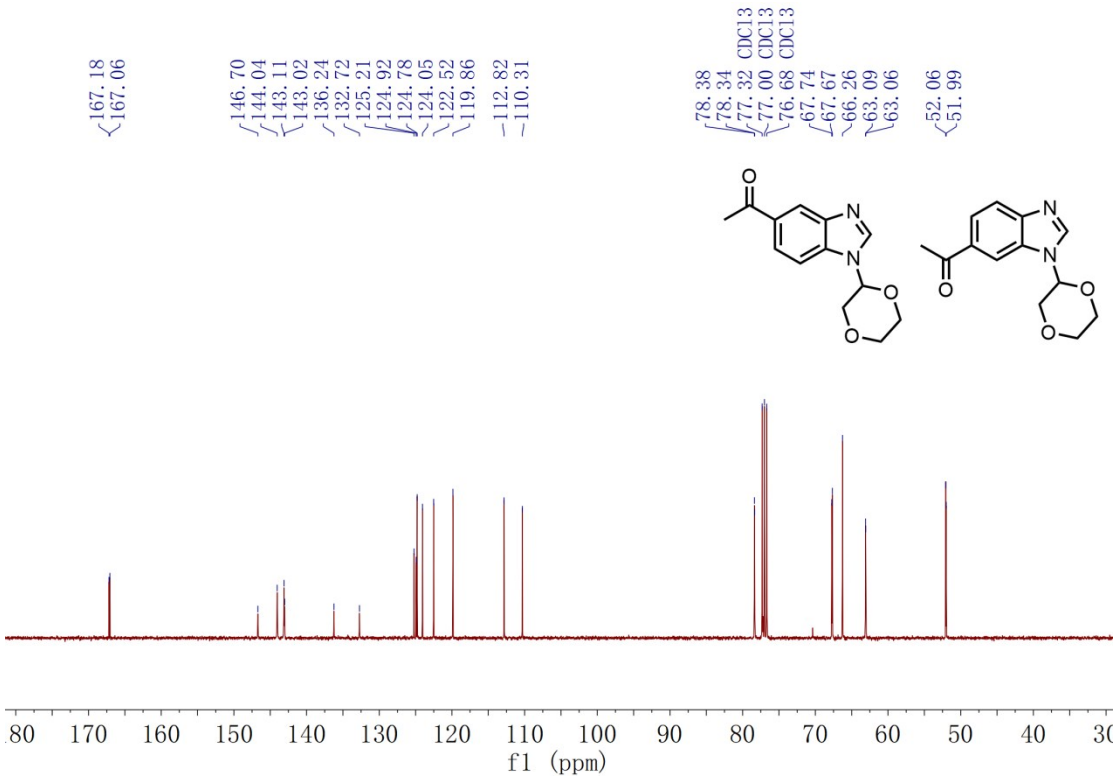
And 1-(1,4-dioxan-2-yl)-5-fluoro-1*H*-benzo[d]imidazole (3j')



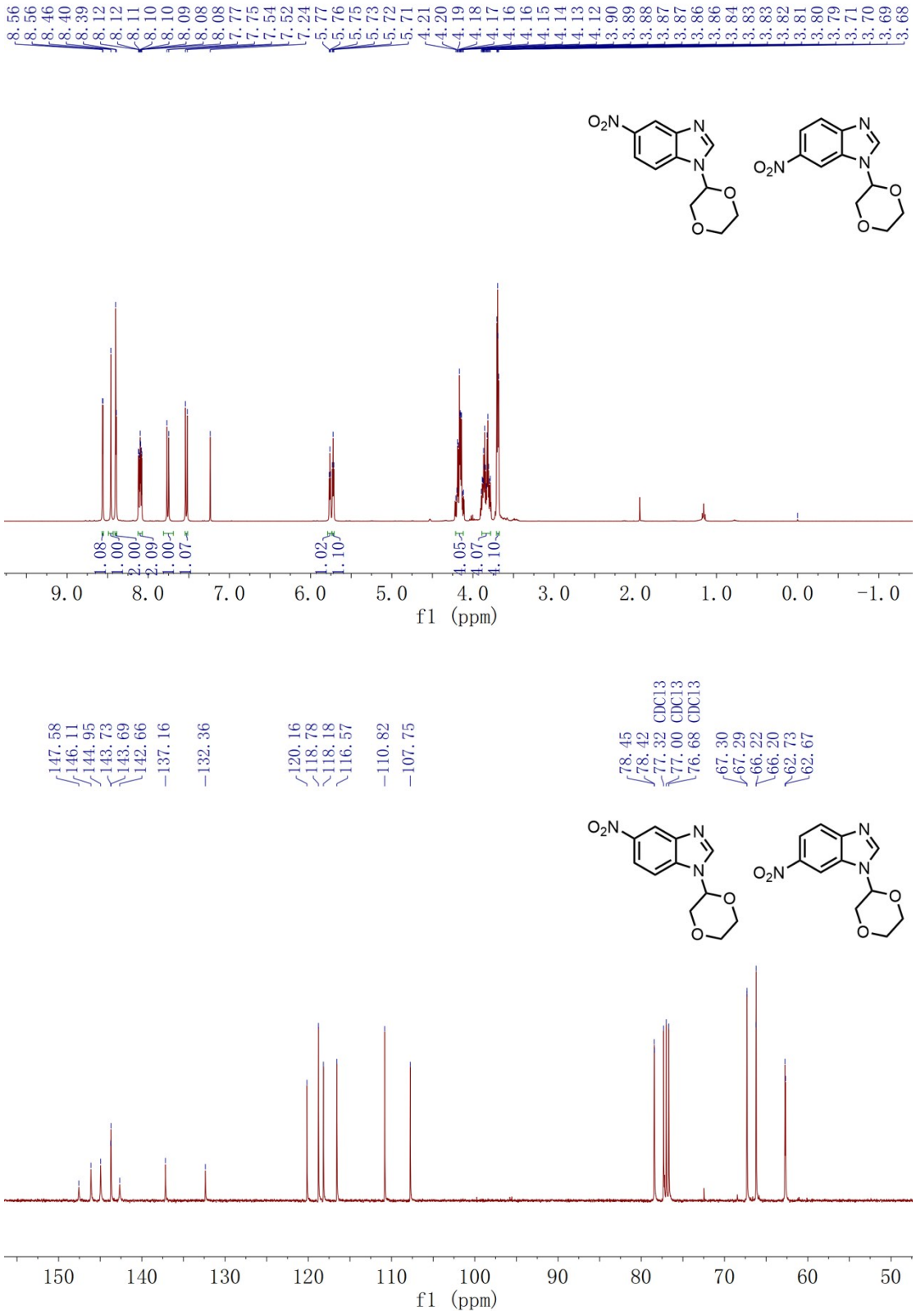


1-(1-(1,4-dioxan-2-yl)-1*H*-benzo[d]imidazol-5-yl)ethan-1-one (3k) and 1-(1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazol-6-yl)ethan-1-one (3k')

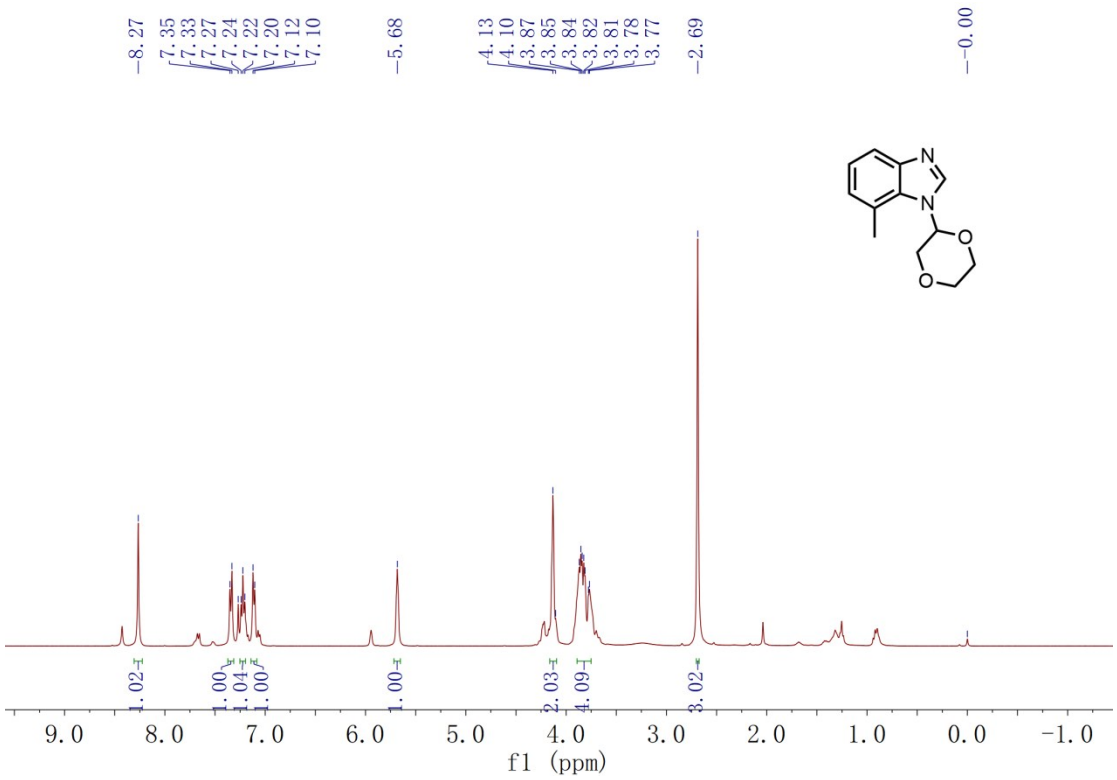


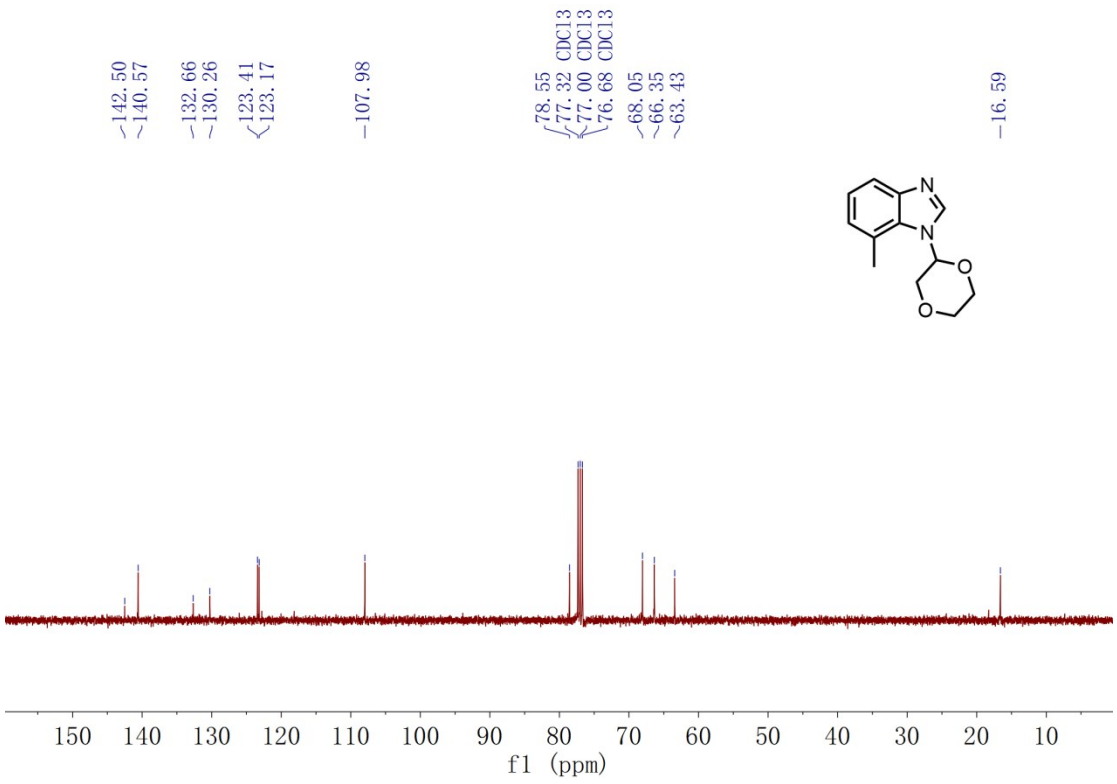


1-(1,4-dioxan-2-yl)-5-nitro-1*H*-benzo[d]imidazole (3l) and 1-(1,4-dioxan-2-yl)-6-nitro-1*H*-benzo[d]imidazole (3l')

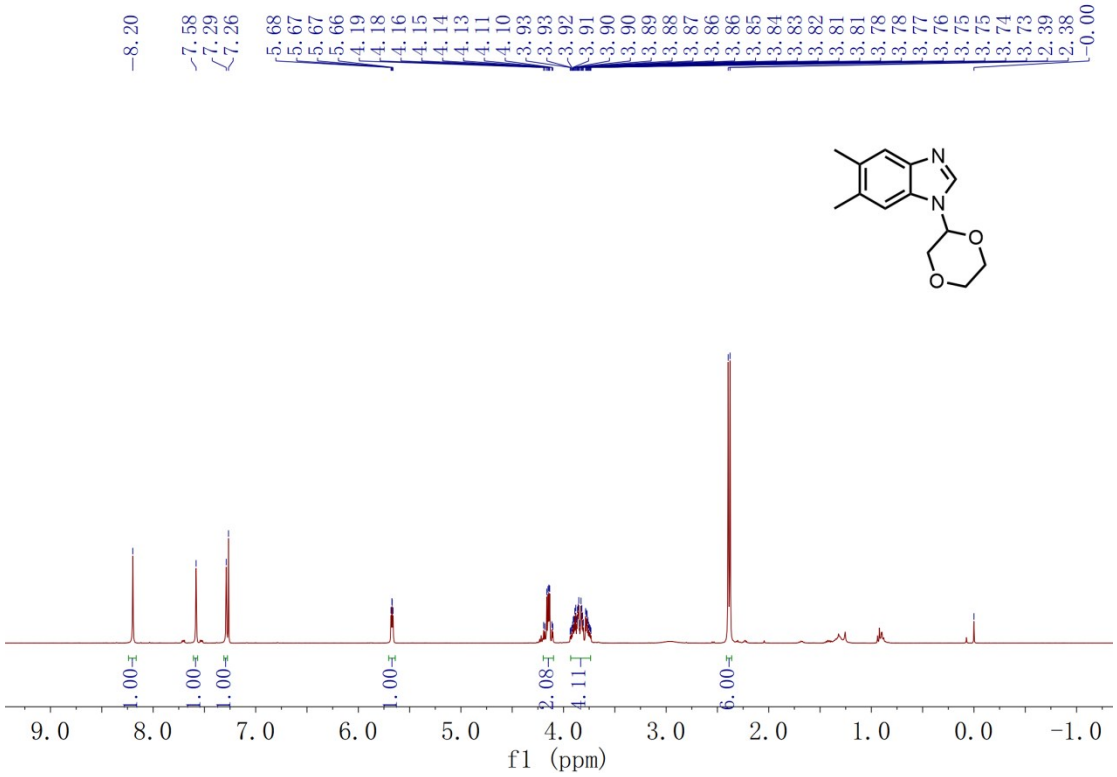


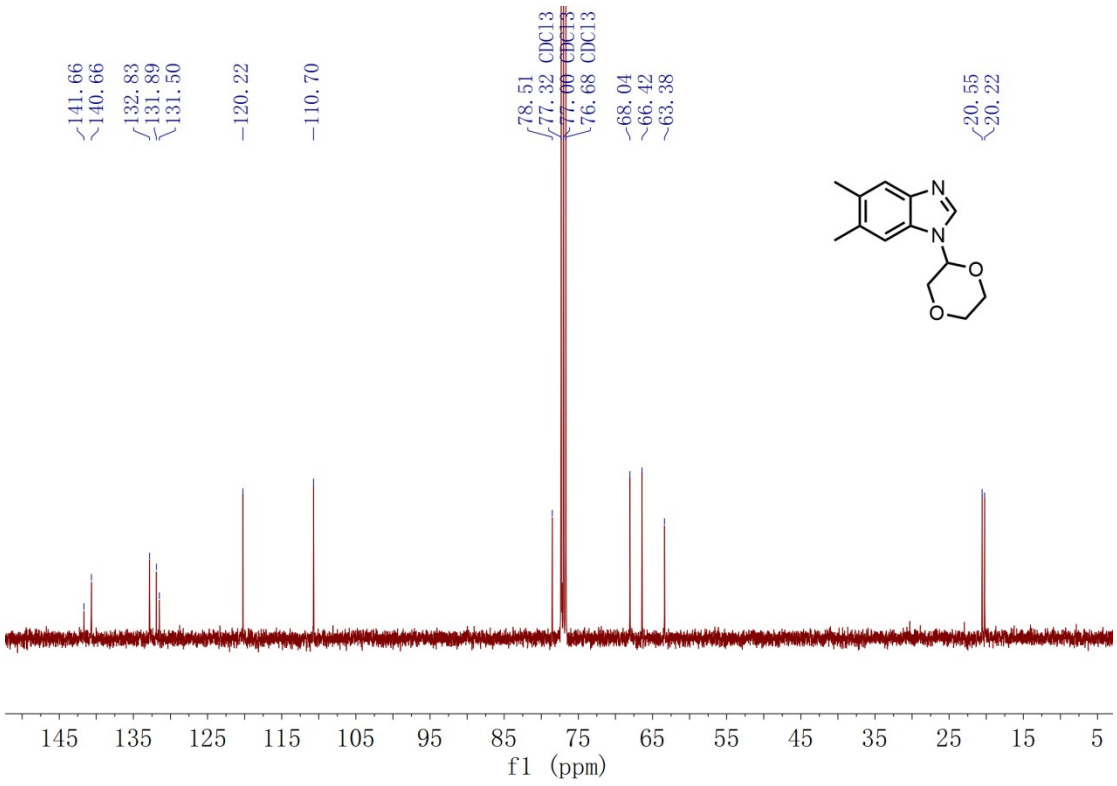
1-(1,4-dioxan-2-yl)-7-methyl-1*H*-benzo[d]imidazole (3m)



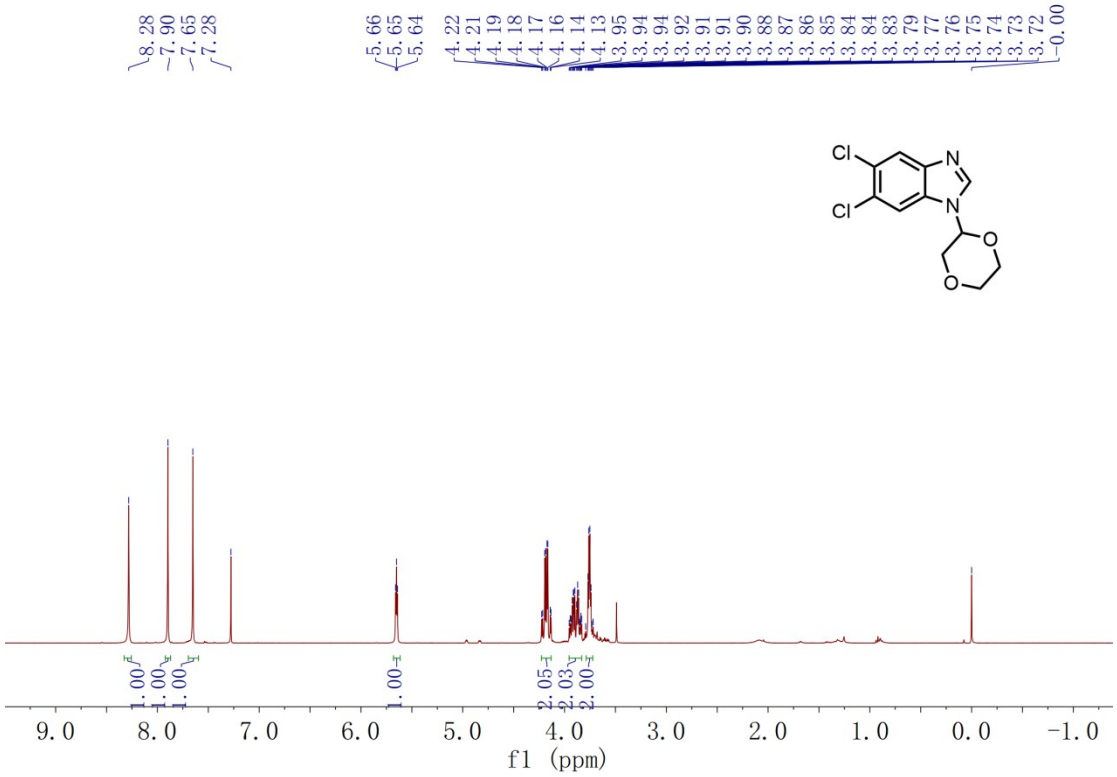


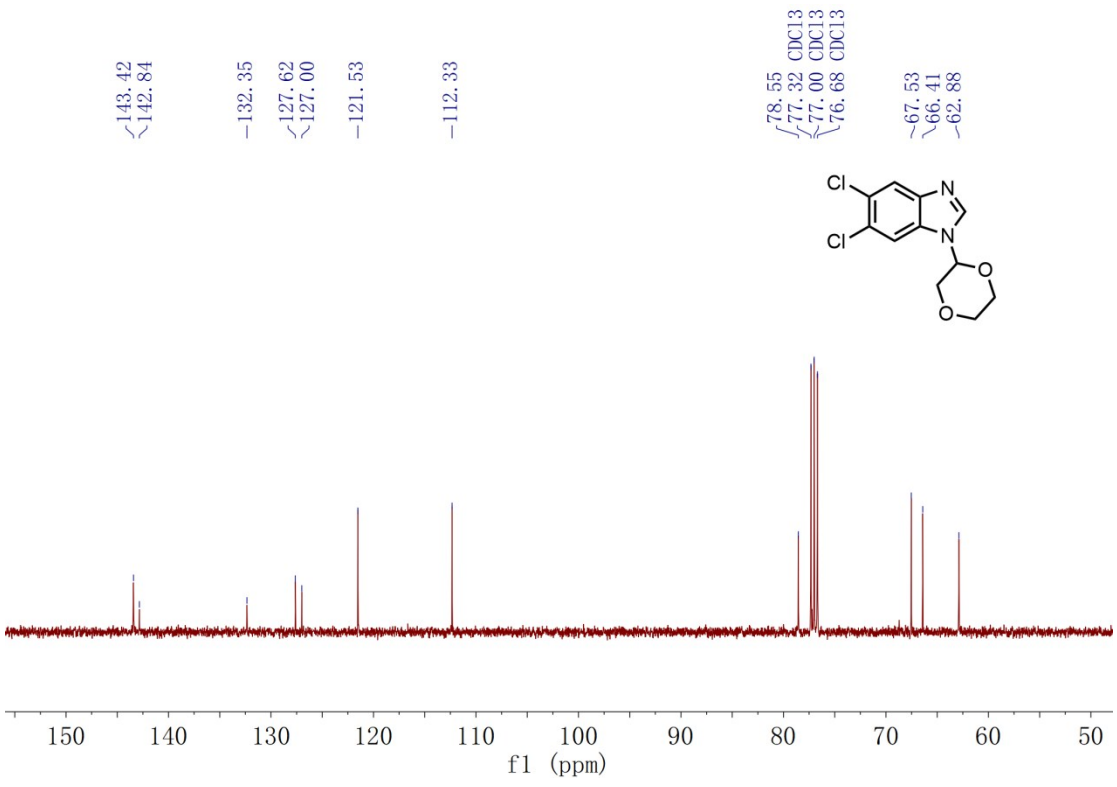
1-(1,4-dioxan-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazole (3n)



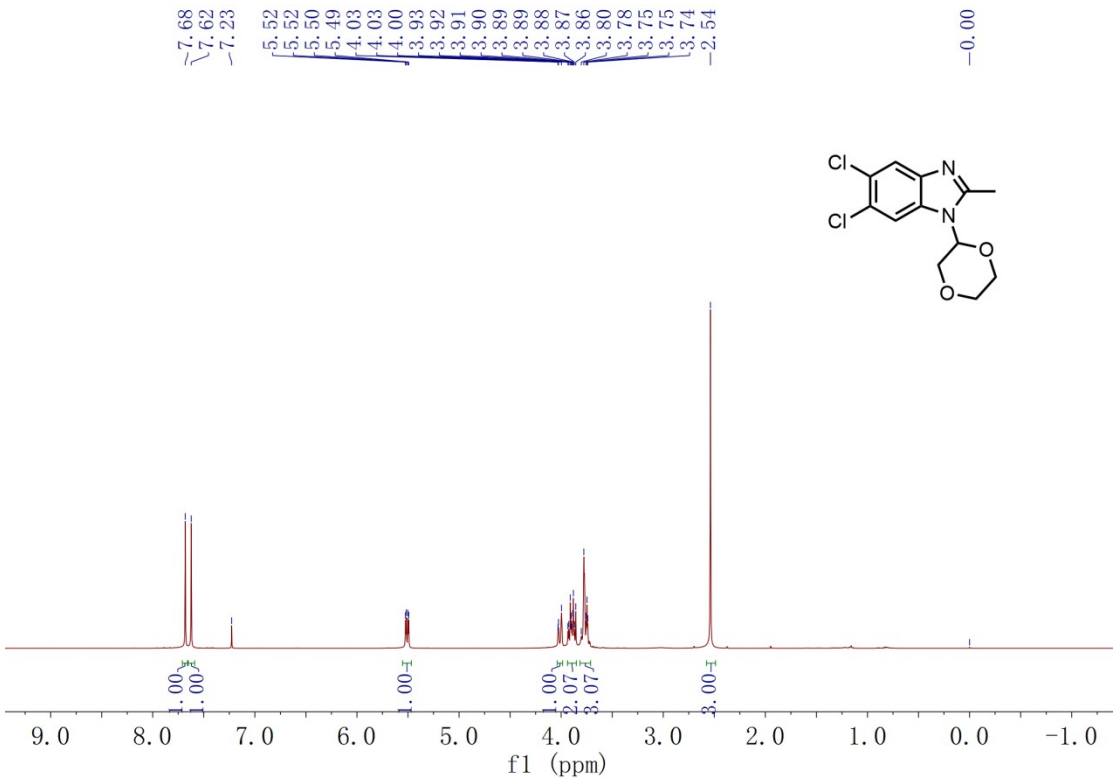


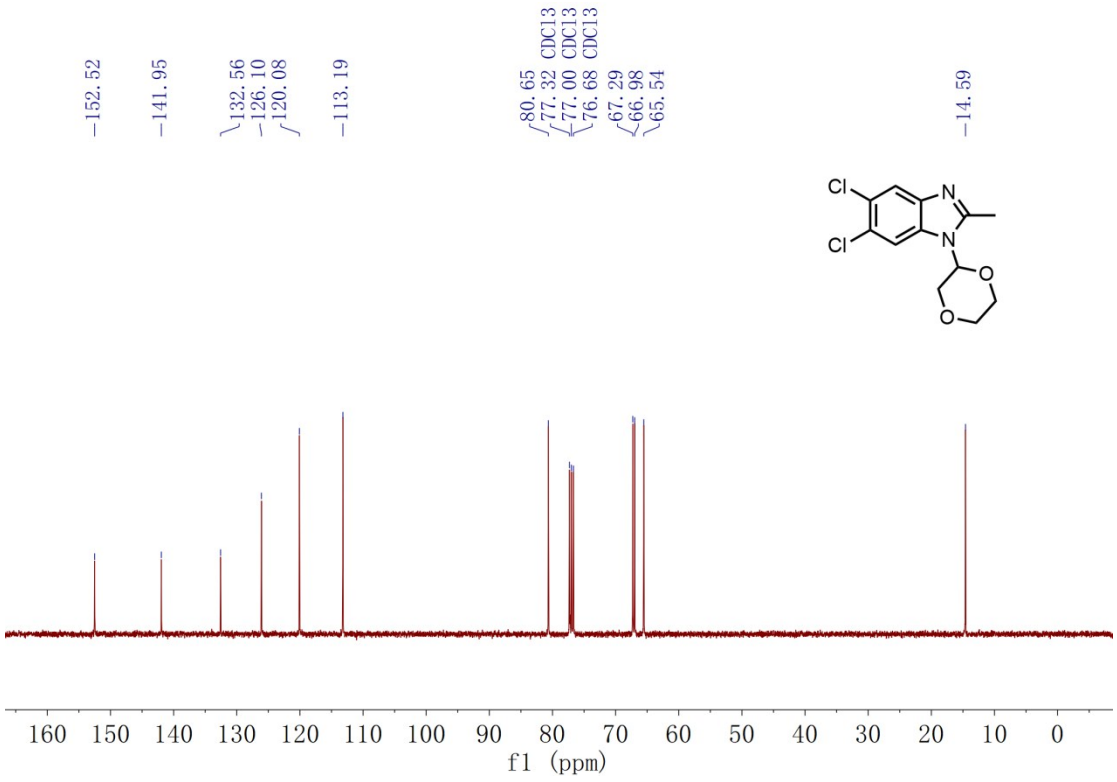
5,6-dichloro-1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazole (3o)



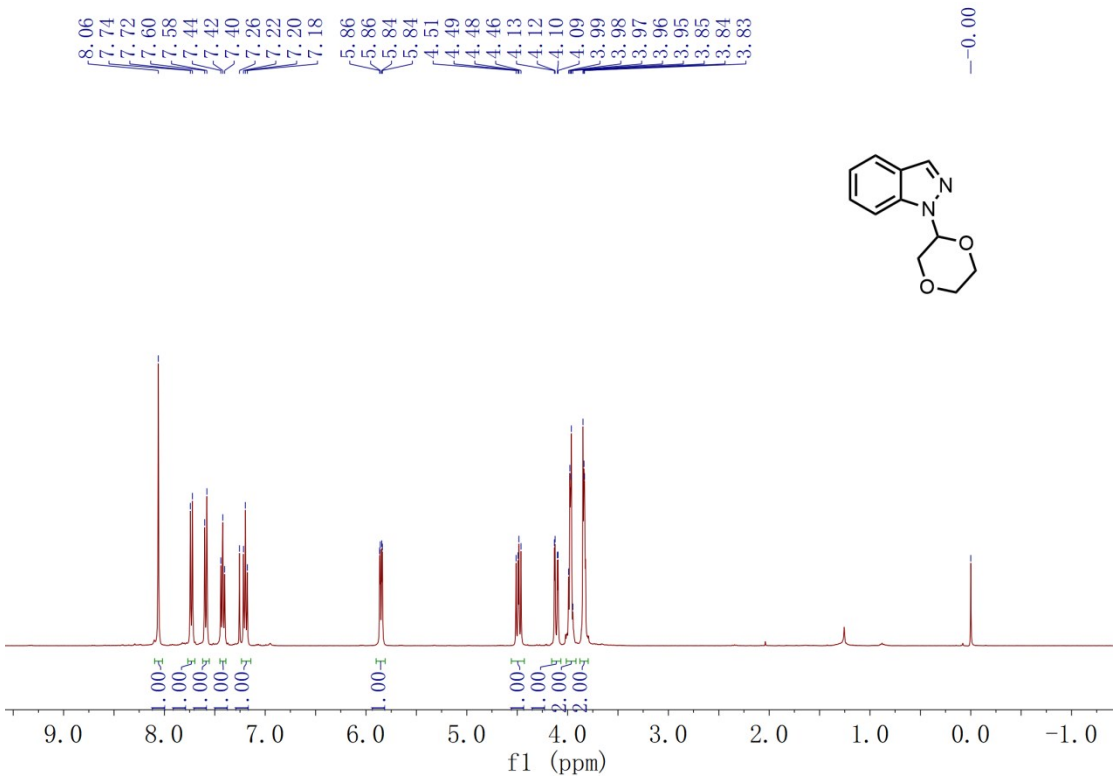


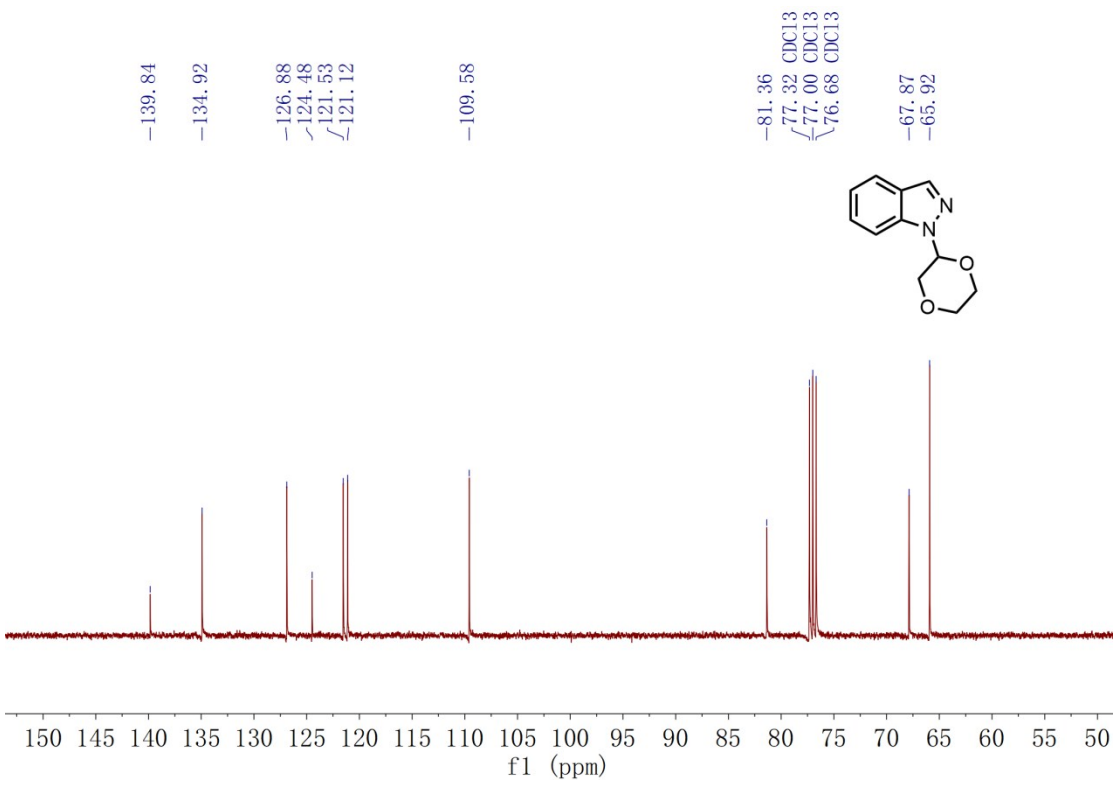
5,6-dichloro-1-(1,4-dioxan-2-yl)-2-methyl-1*H*-benzo[d]imidazole (3p)



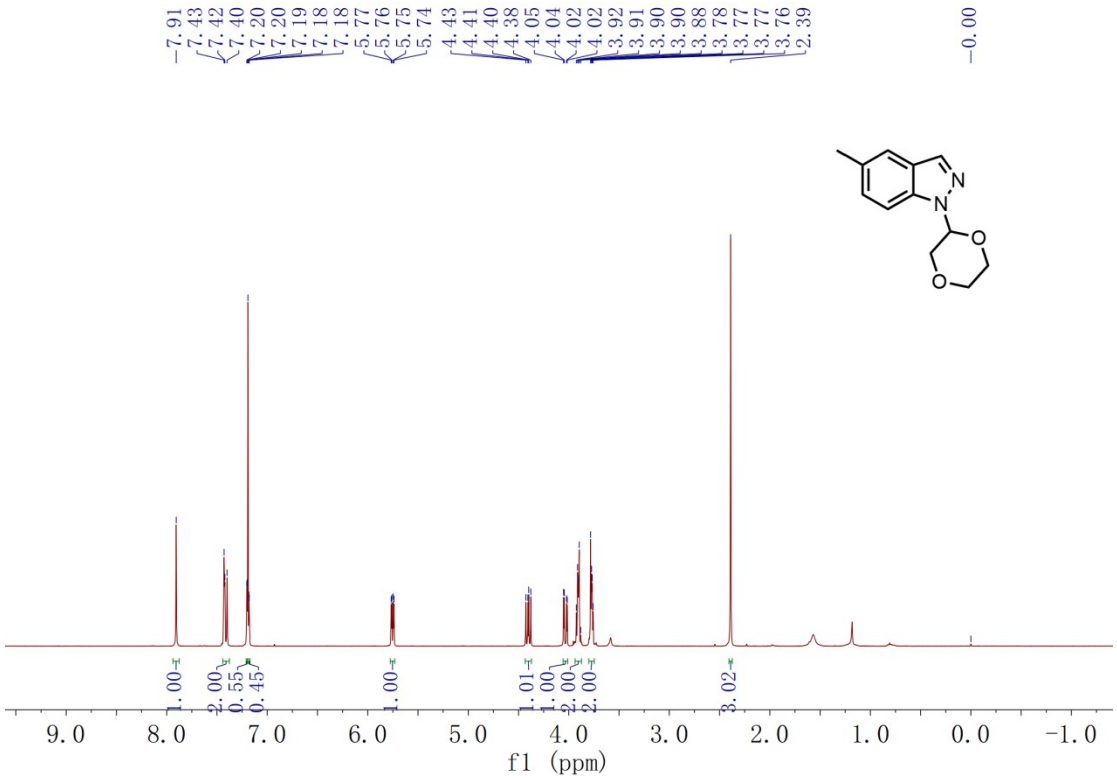


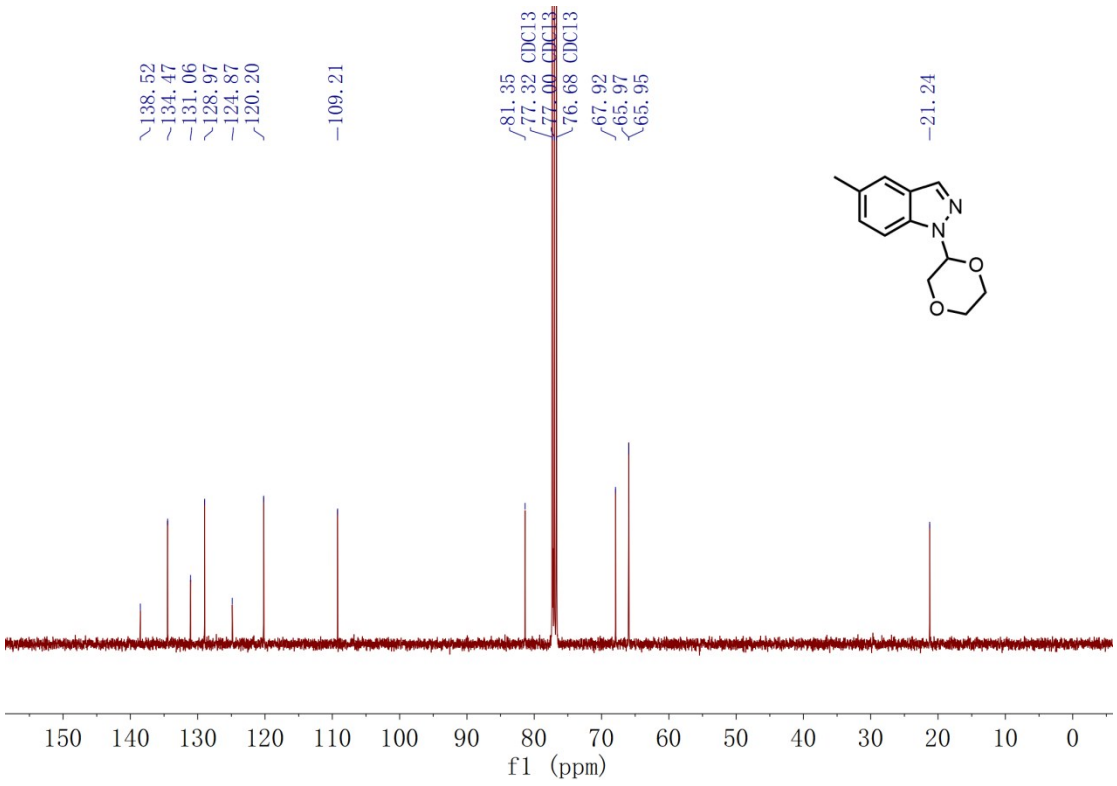
1-(1,4-dioxan-2-yl)-1*H*-indazole (3q)



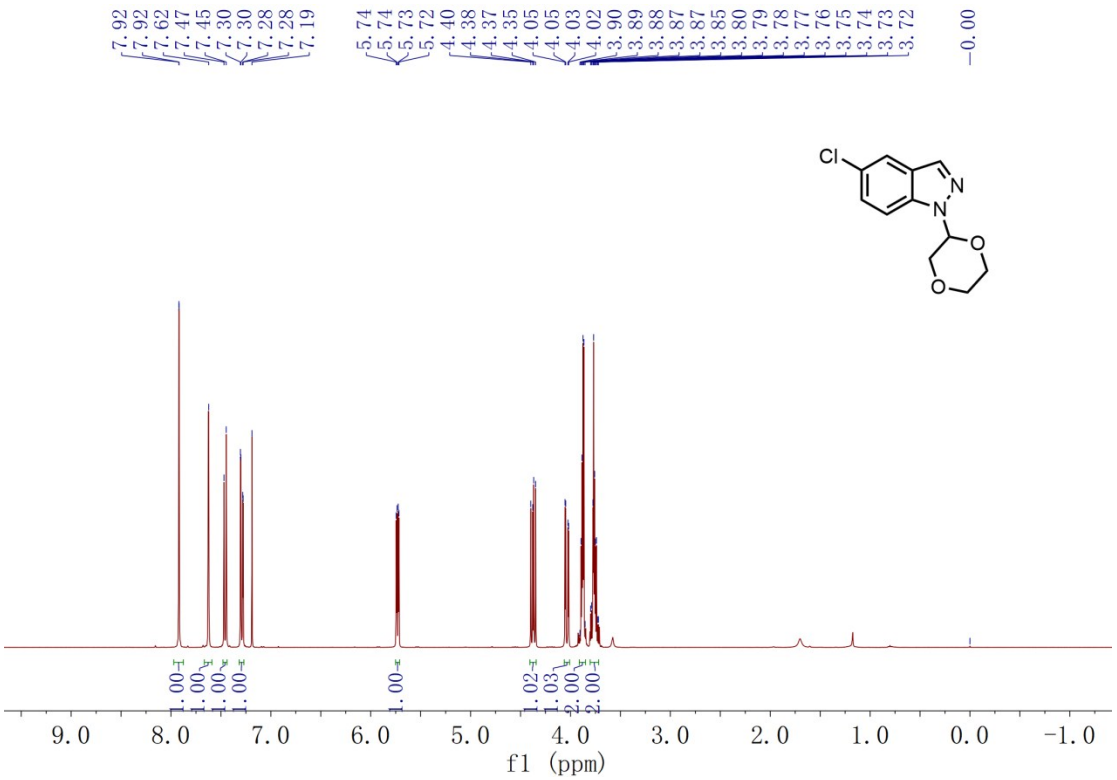


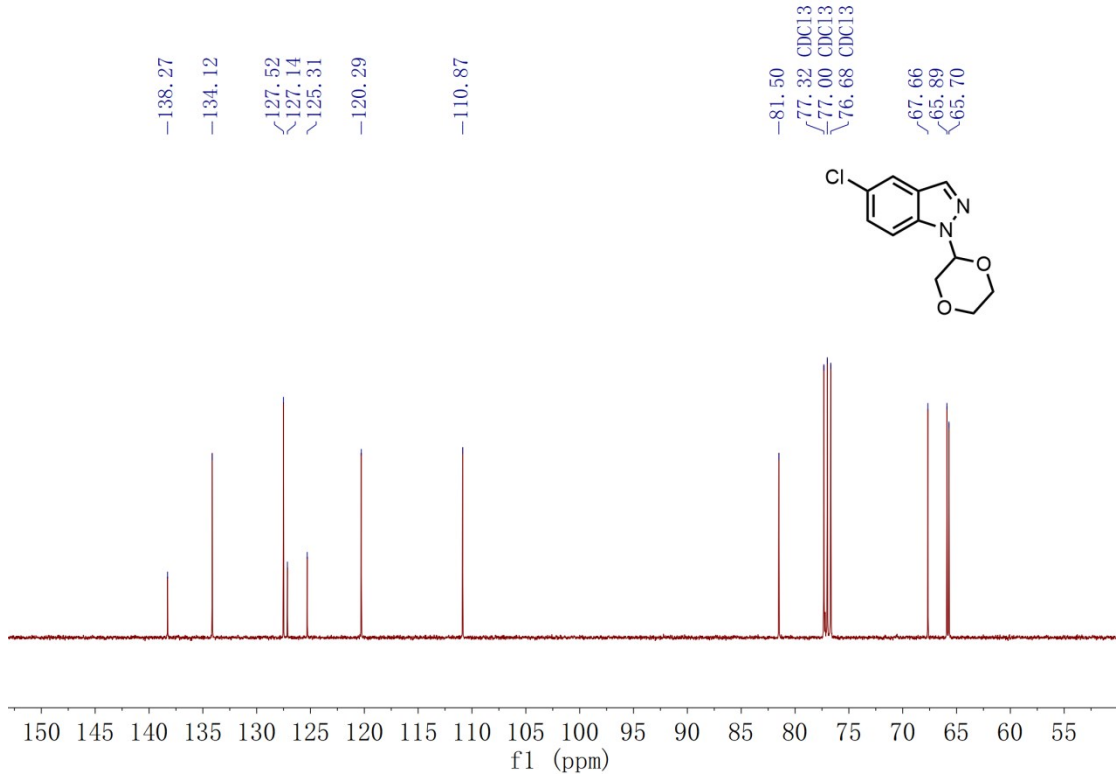
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-indazole (3r)



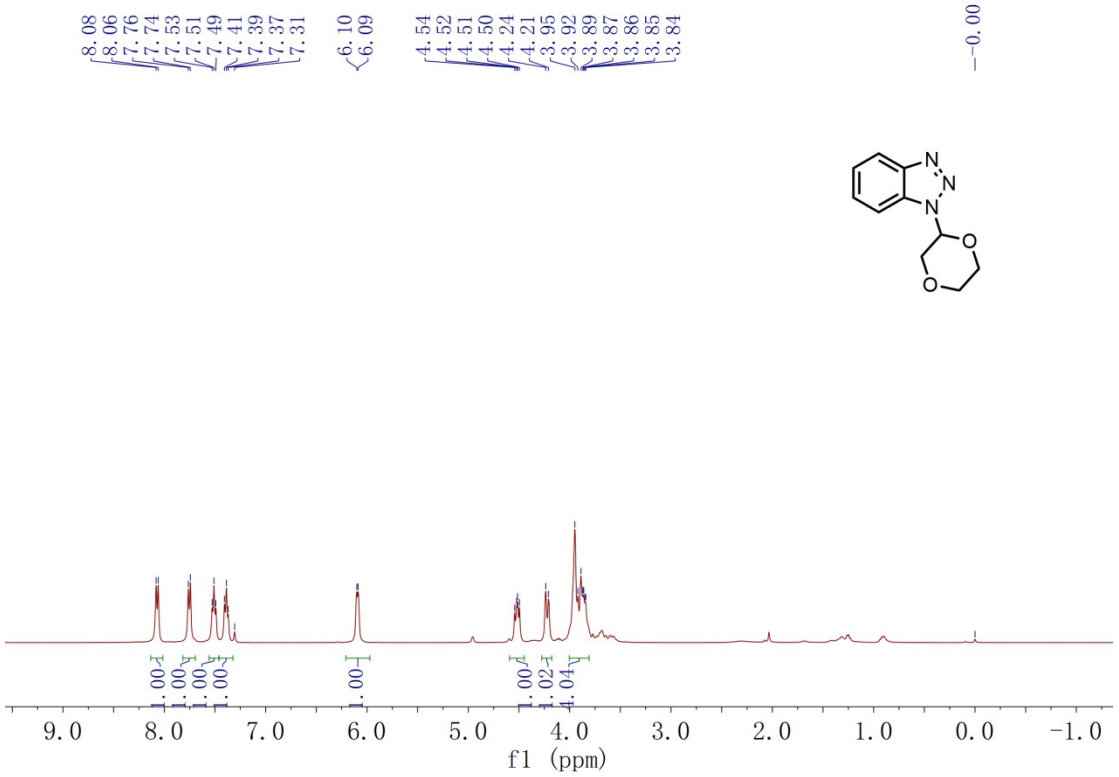


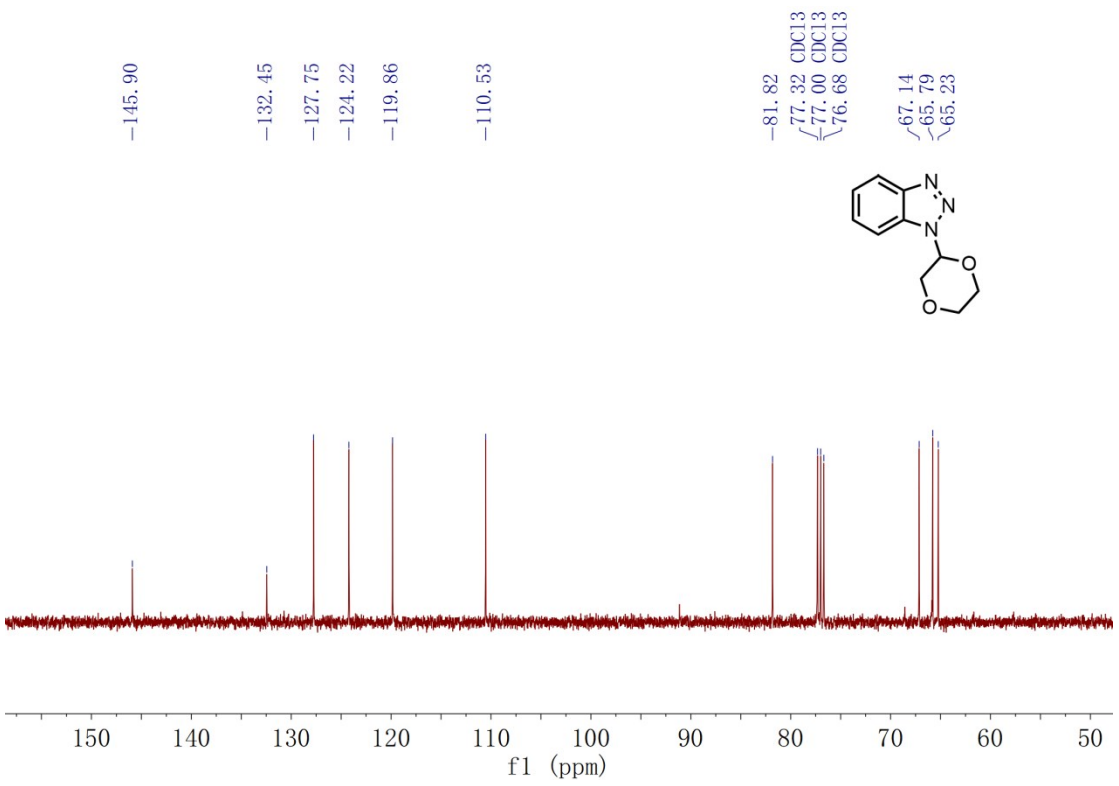
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-indazole (3s)



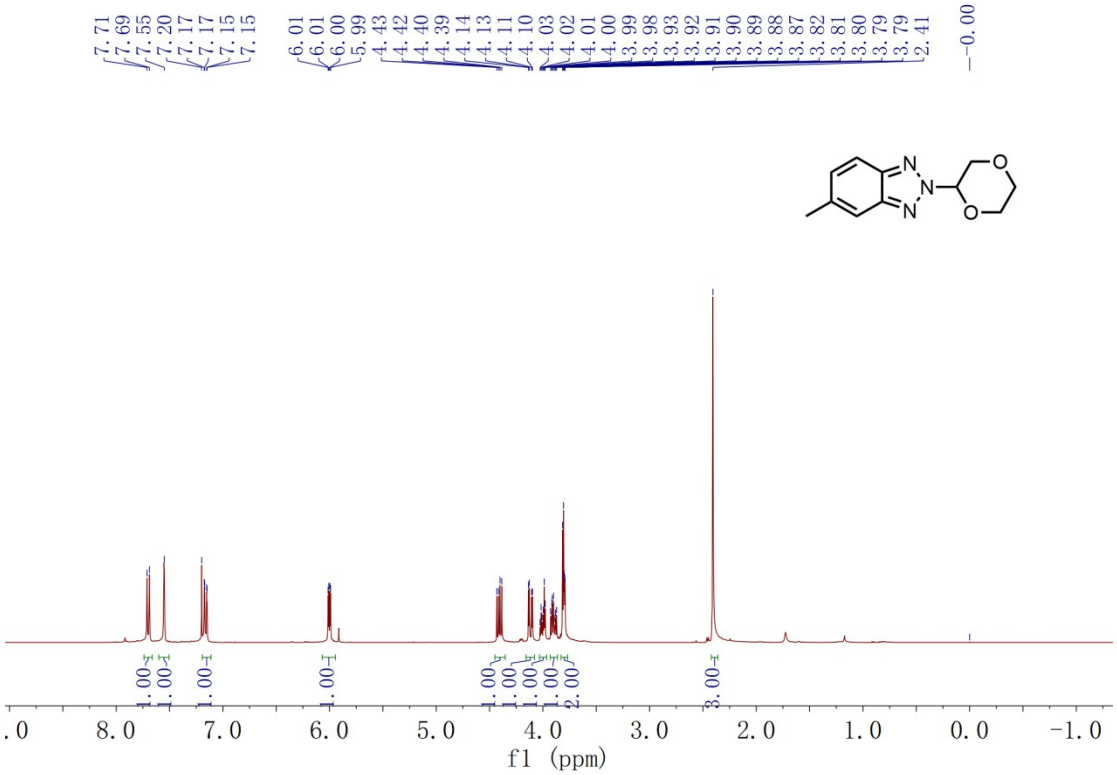


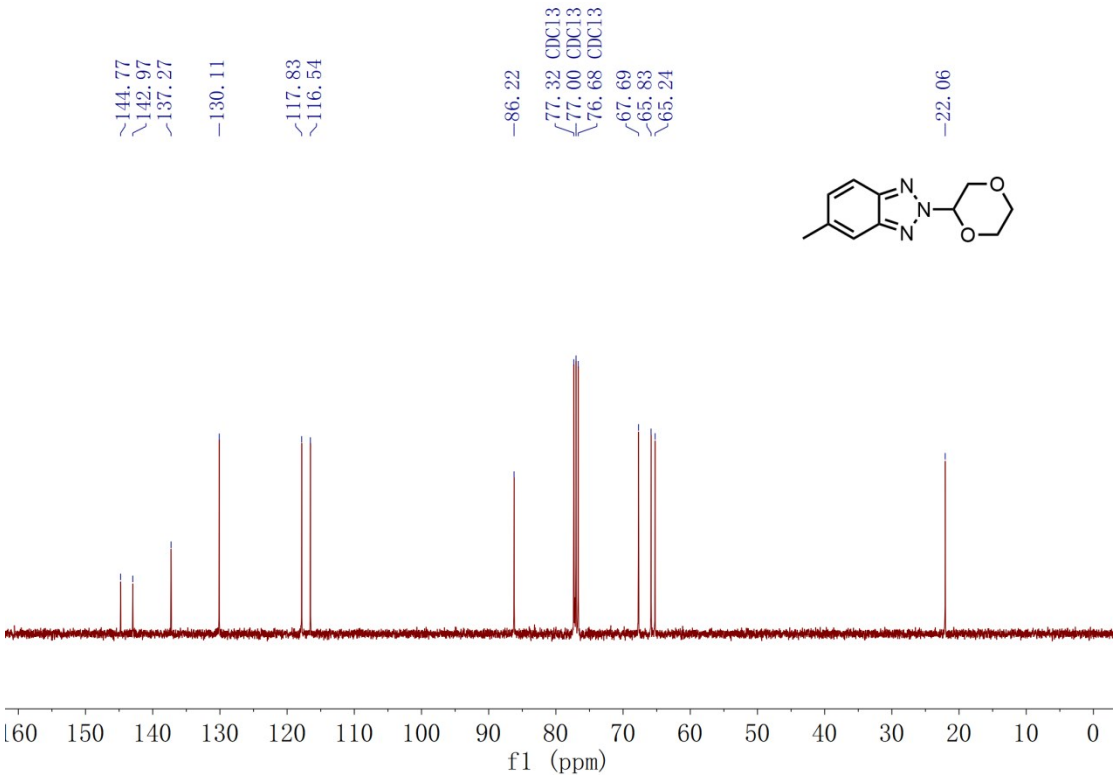
1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3t)



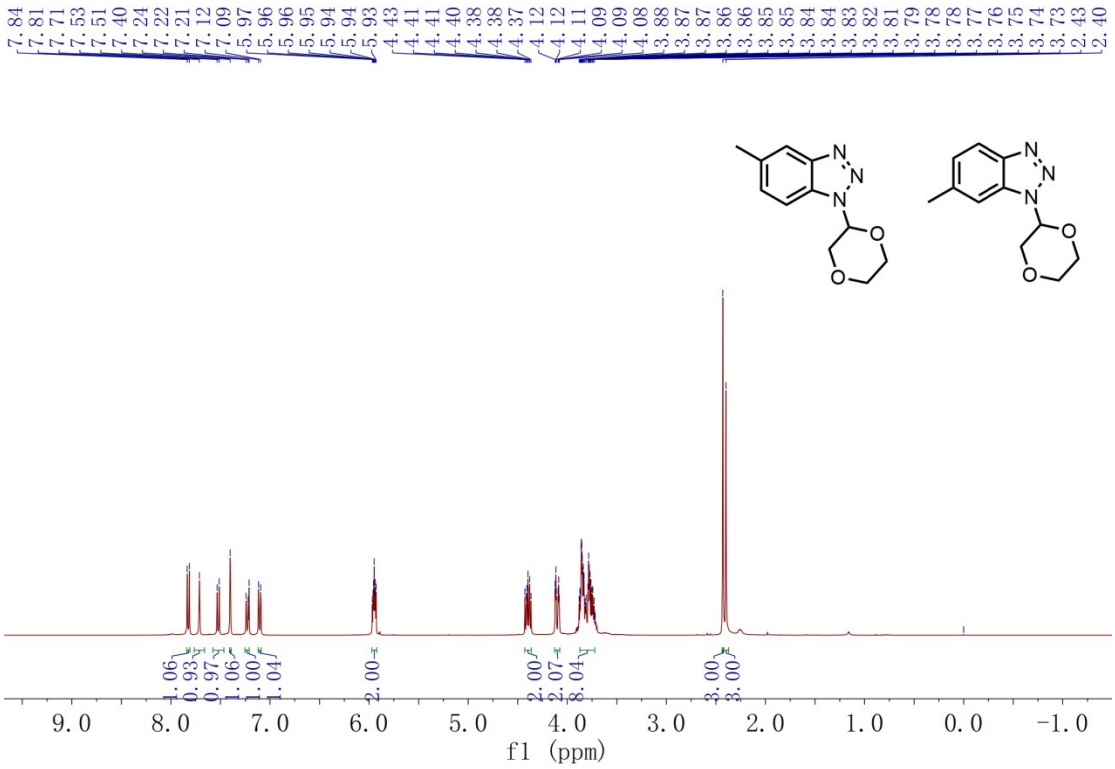


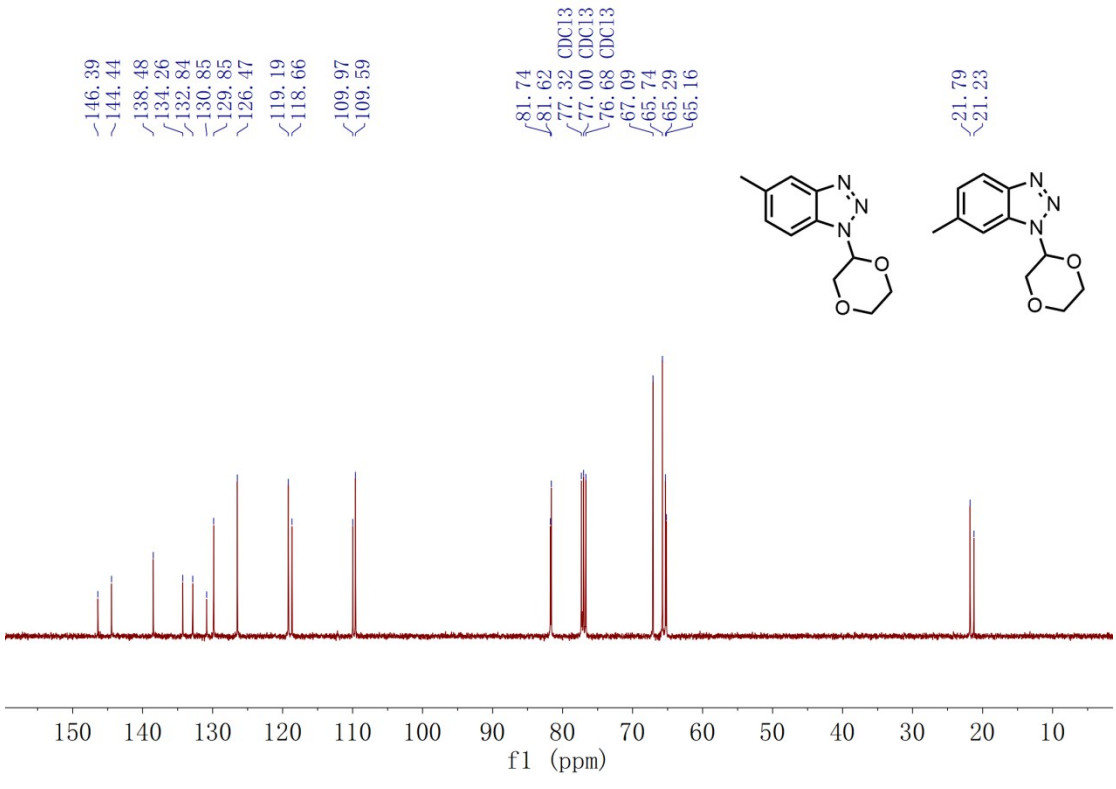
2-(1,4-dioxan-2-yl)-5-methyl-2*H*-benzo[d][1,2,3]triazole (3u)



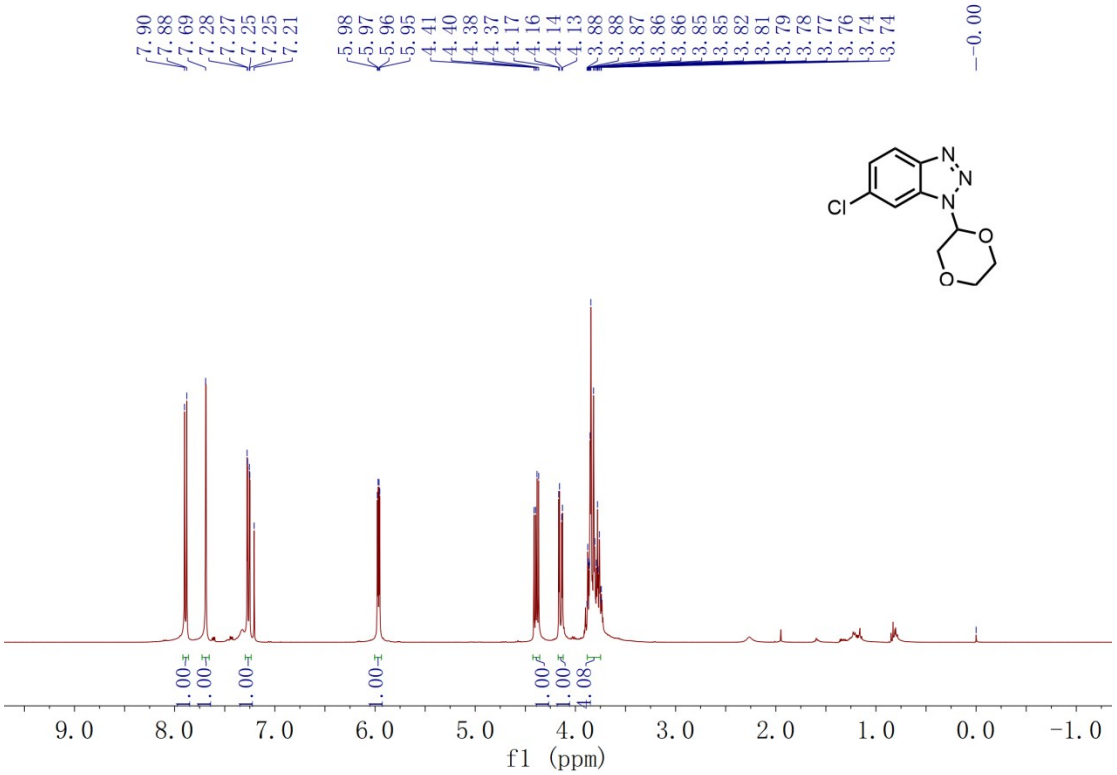


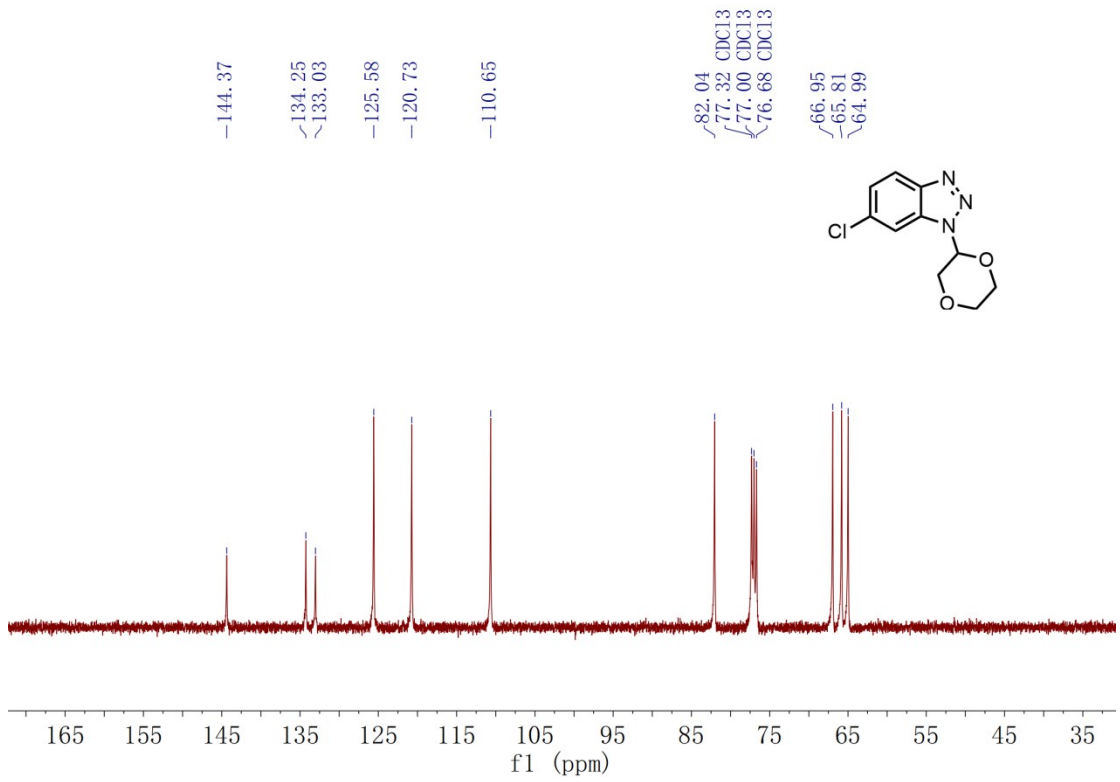
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-benzo[d][1,2,3]triazole(3u') and 1-(1,4-dioxan-2-yl)-6-methyl-1*H*-benzo[d][1,2,3]triazole(3u'')



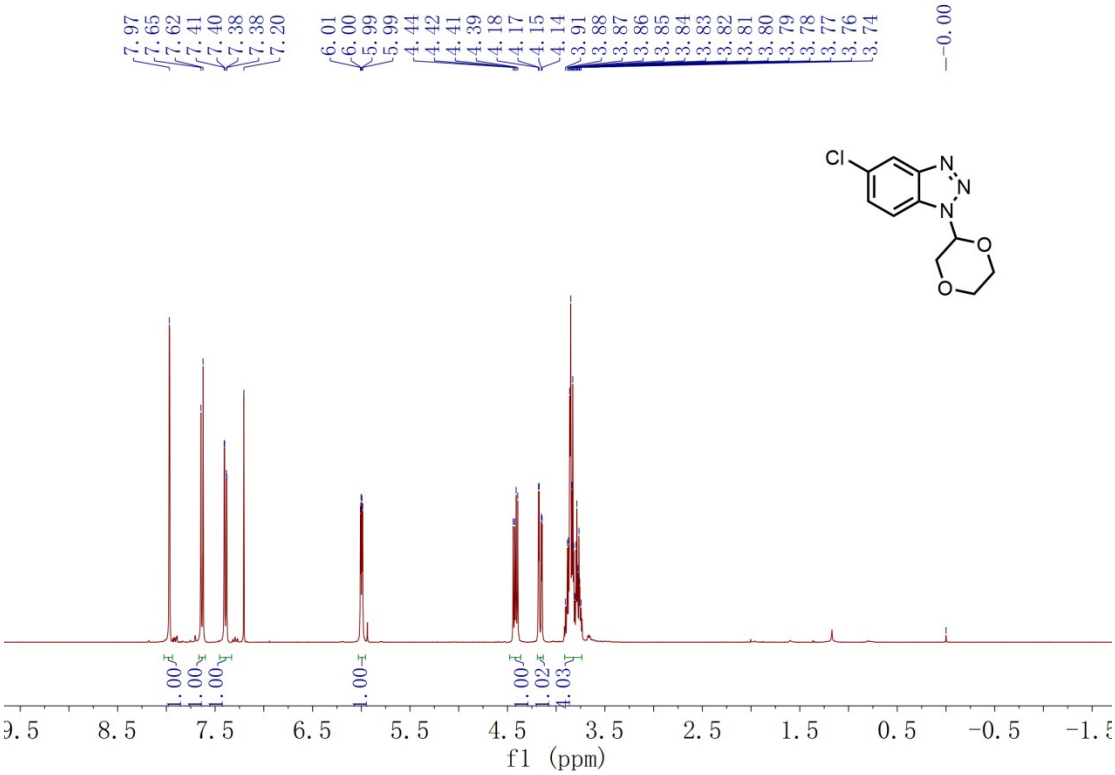


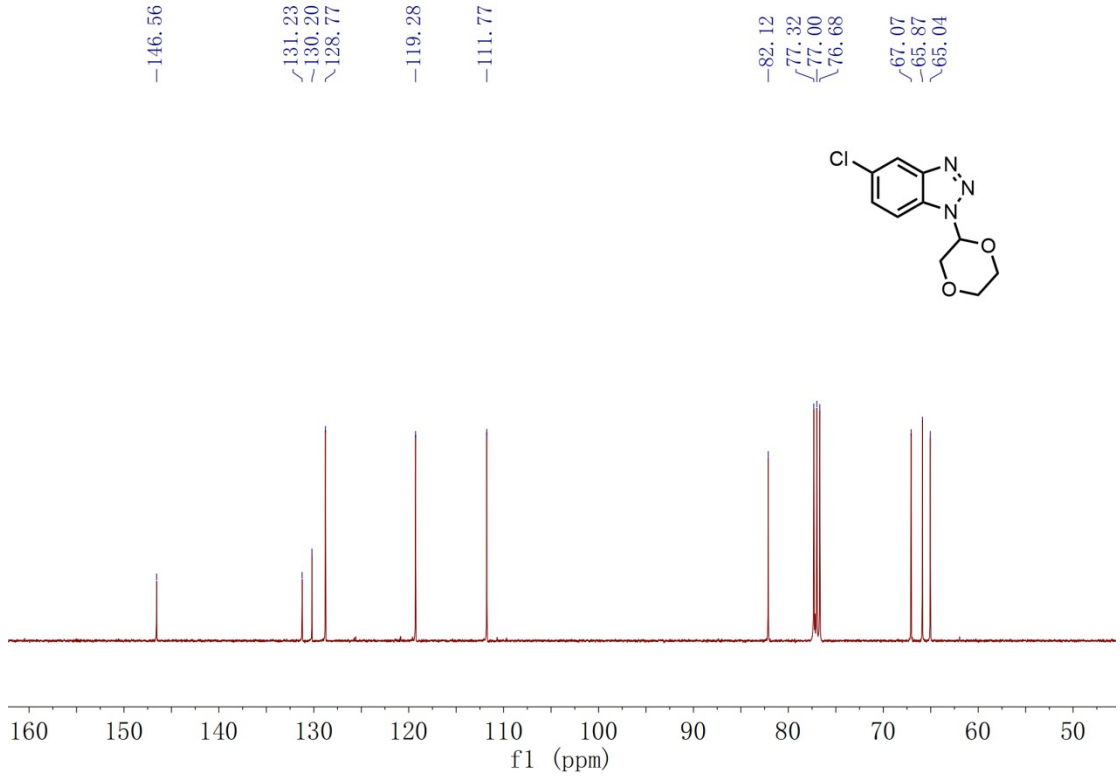
6-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3v)



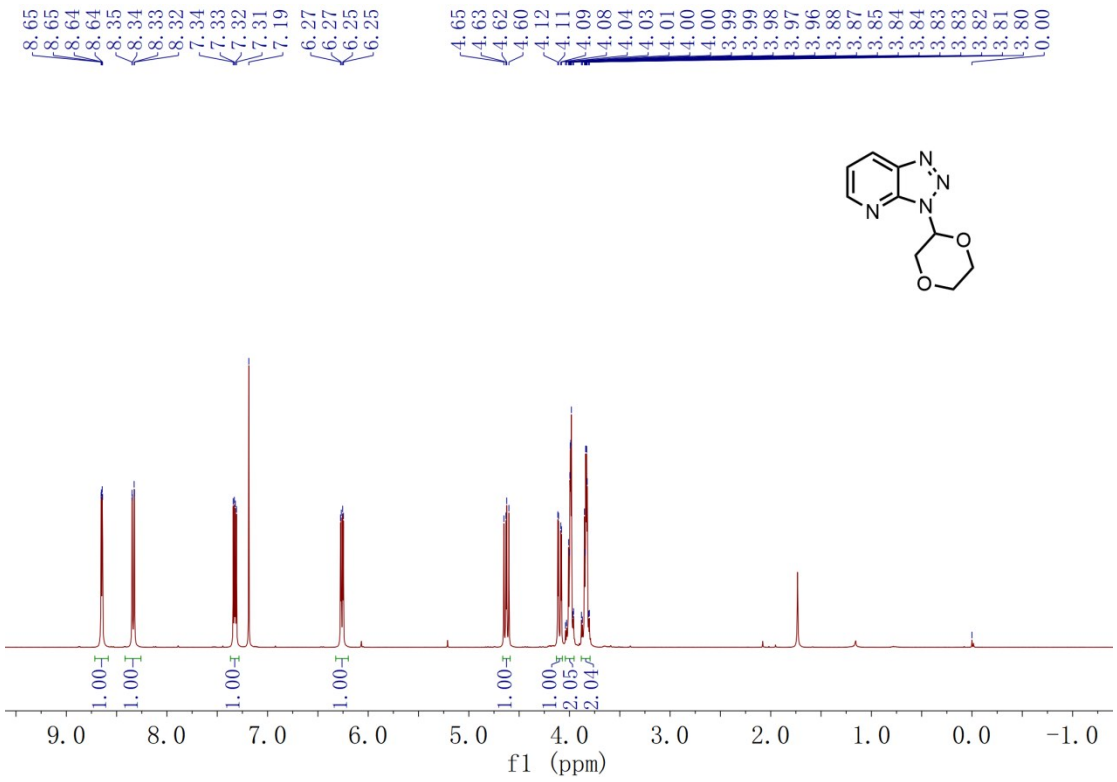


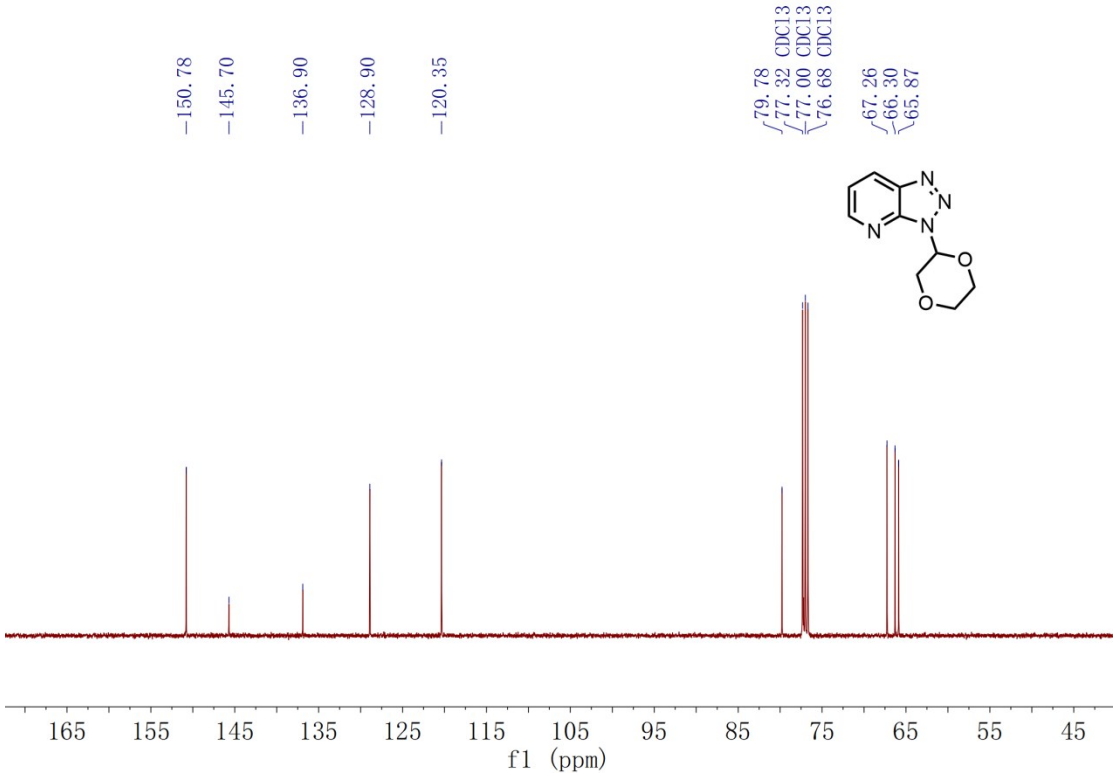
5-chloro-1-(1,4-dioxan-2-yl)-1*H*-benzo[d][1,2,3]triazole (3v')



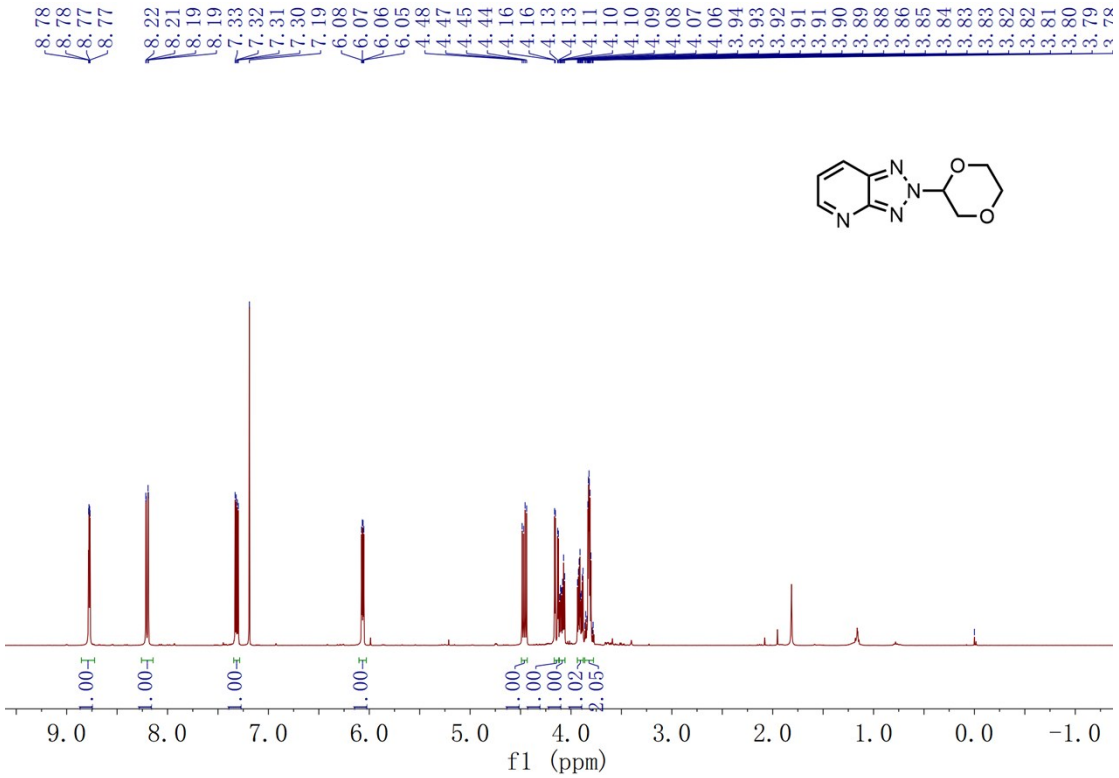


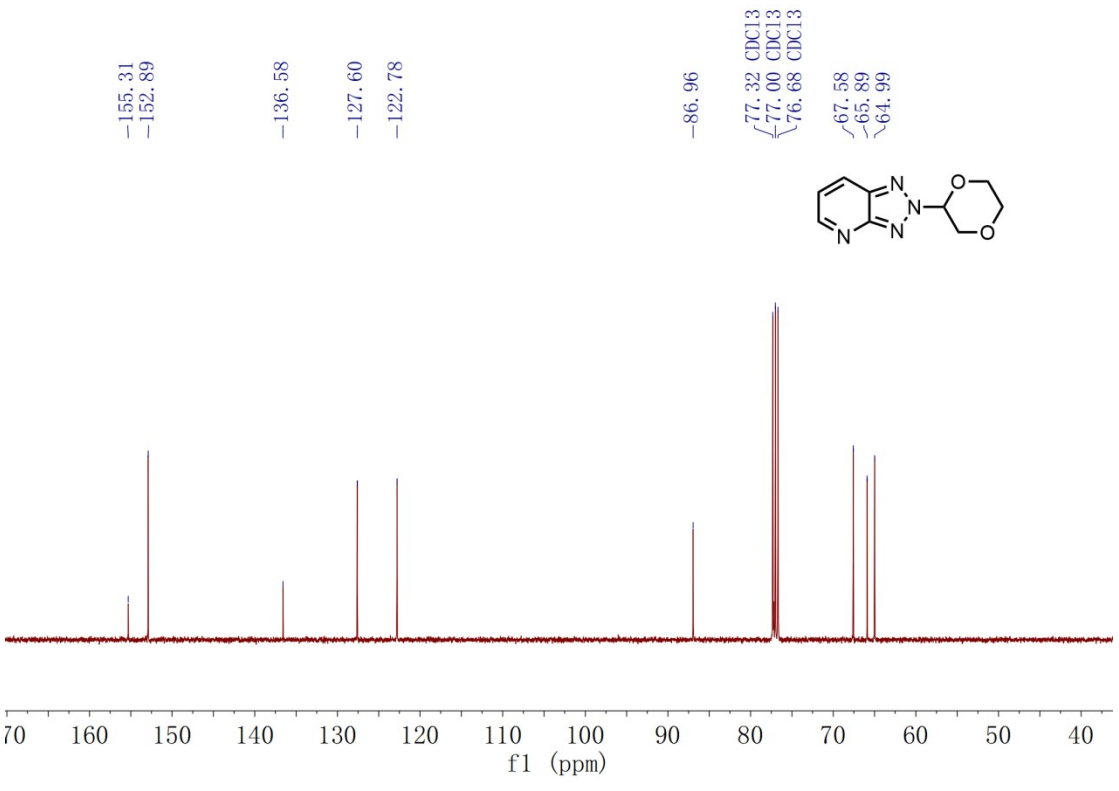
3-(1,4-dioxan-2-yl)-3*H*-[1,2,3]triazolo[4,5-b]pyridine (3w)



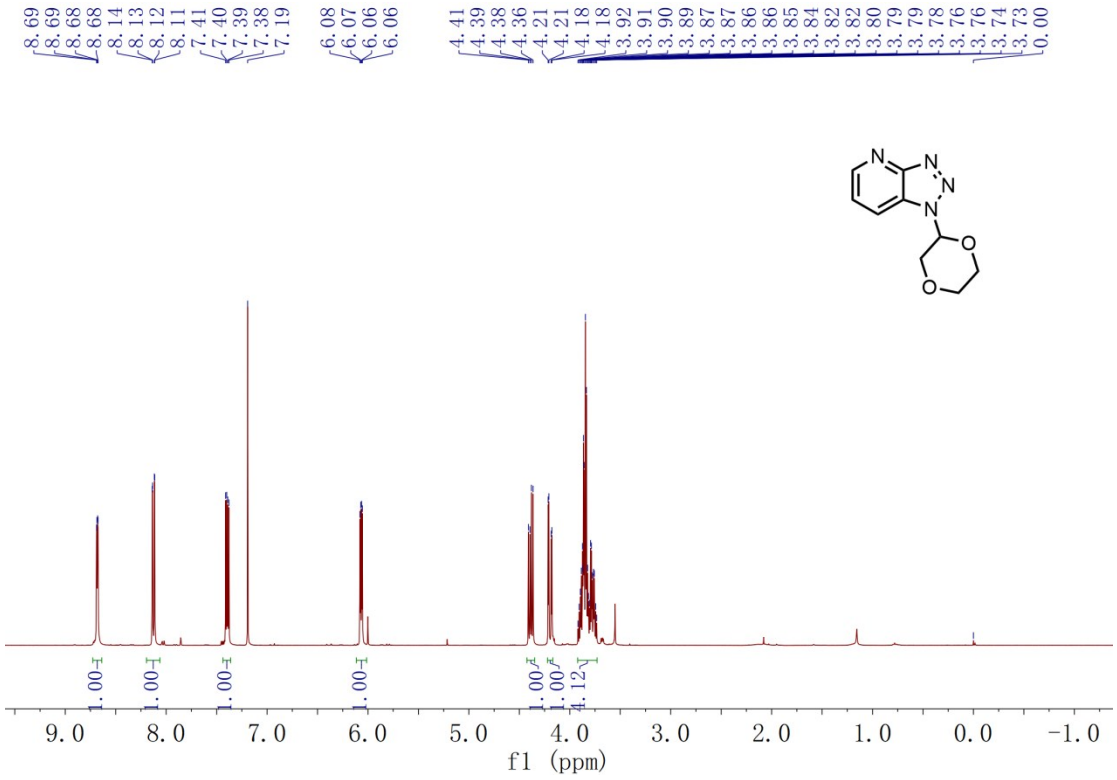


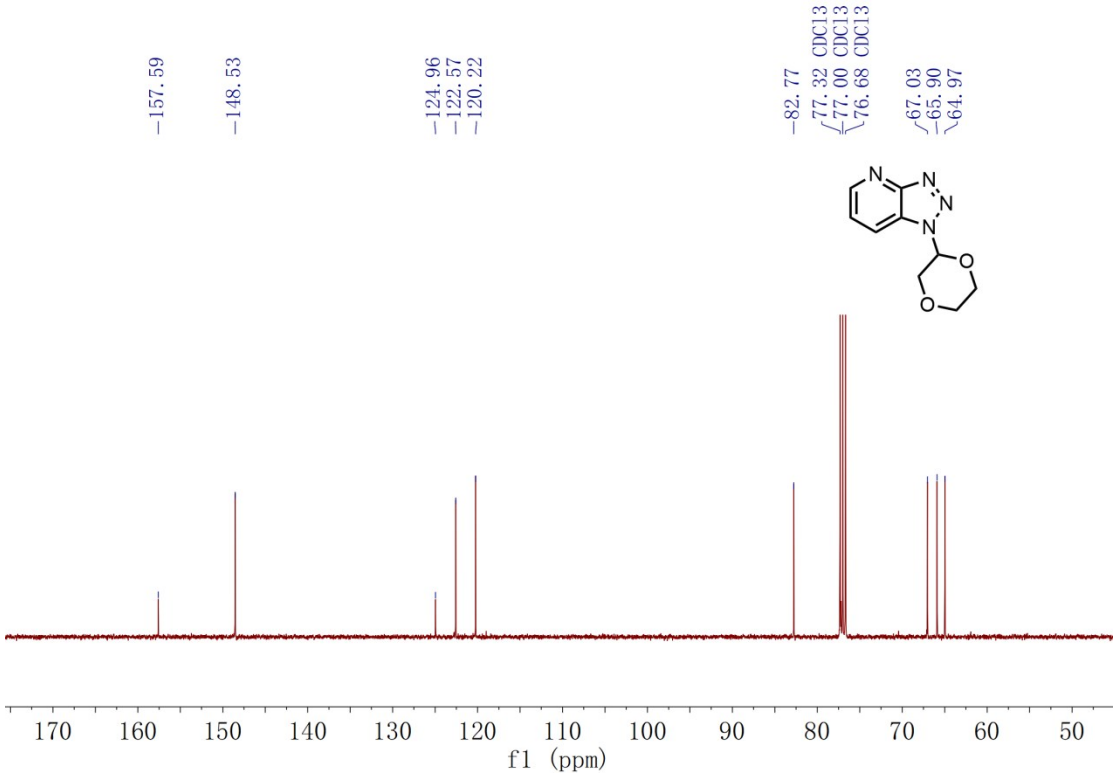
2-(1,4-dioxan-2-yl)-2*H*-[1,2,3]triazolo[4,5-b]pyridine (3w')



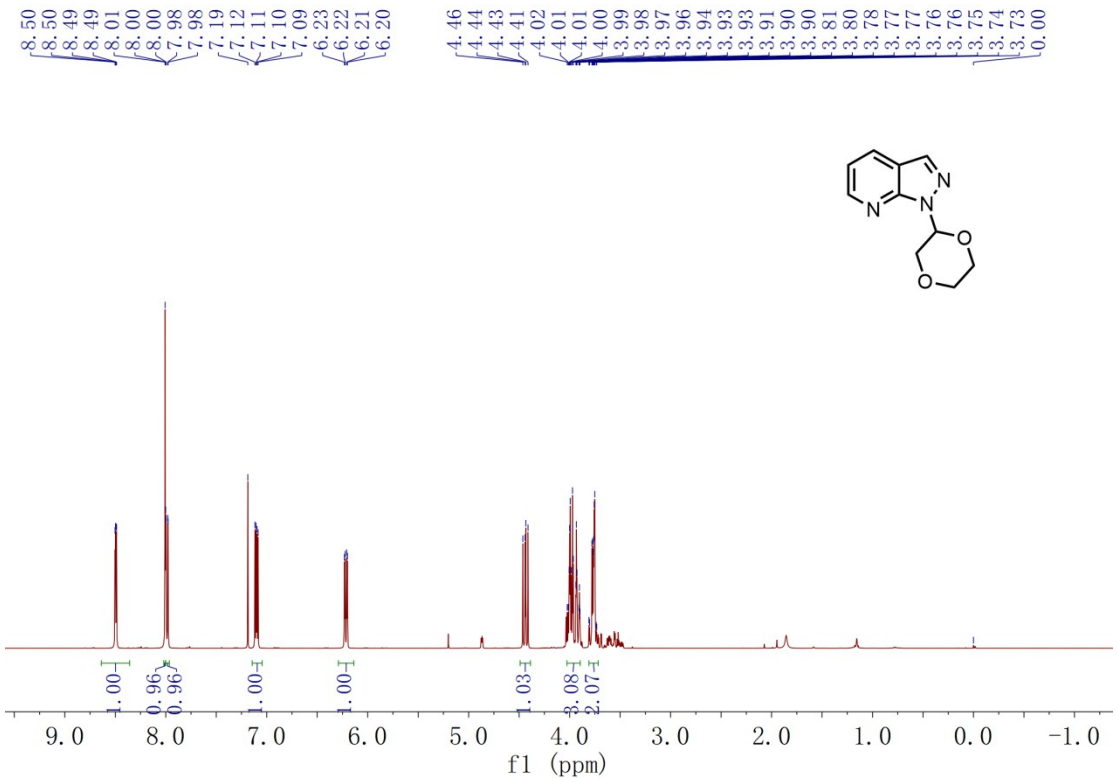


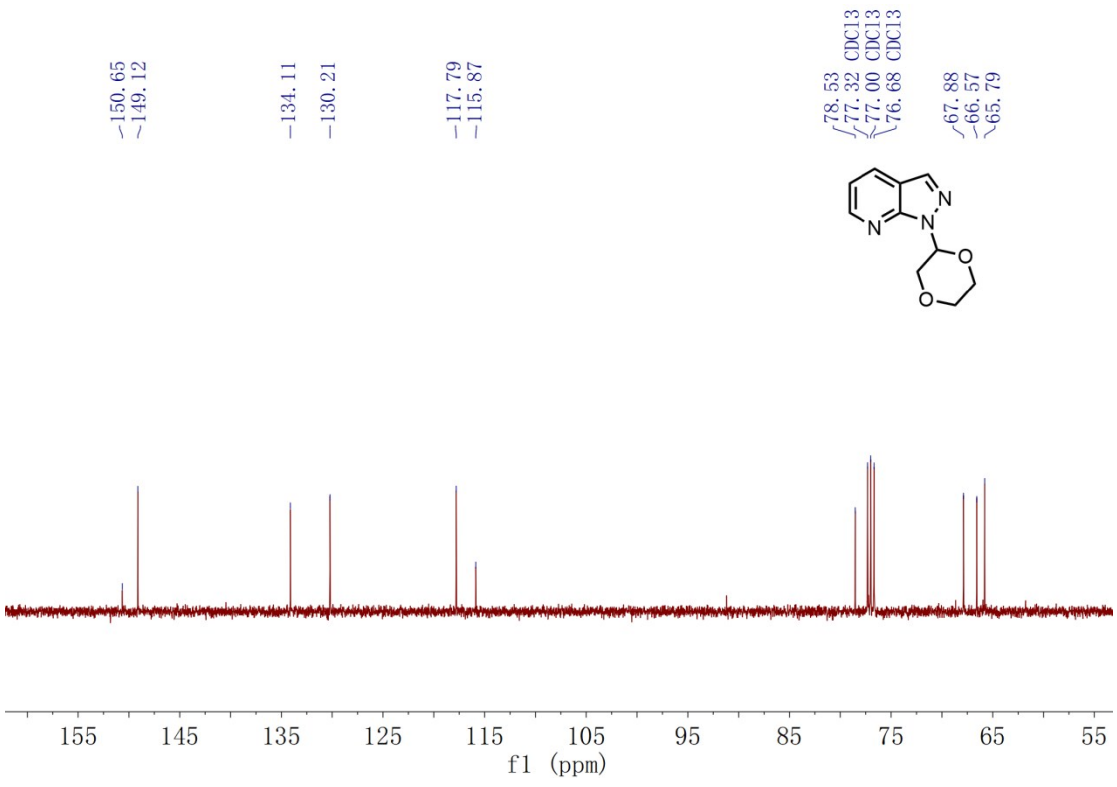
1-(1,4-dioxan-2-yl)-1*H*-[1,2,3]triazolo[4,5-b]pyridine (3w'')



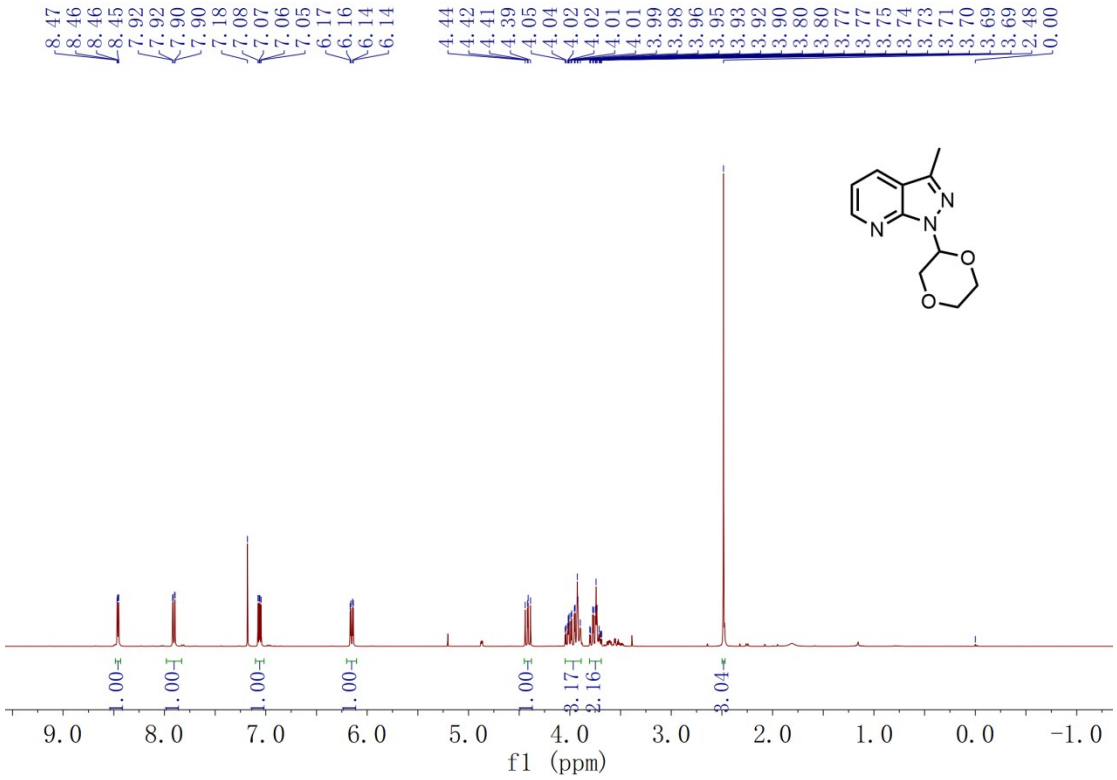


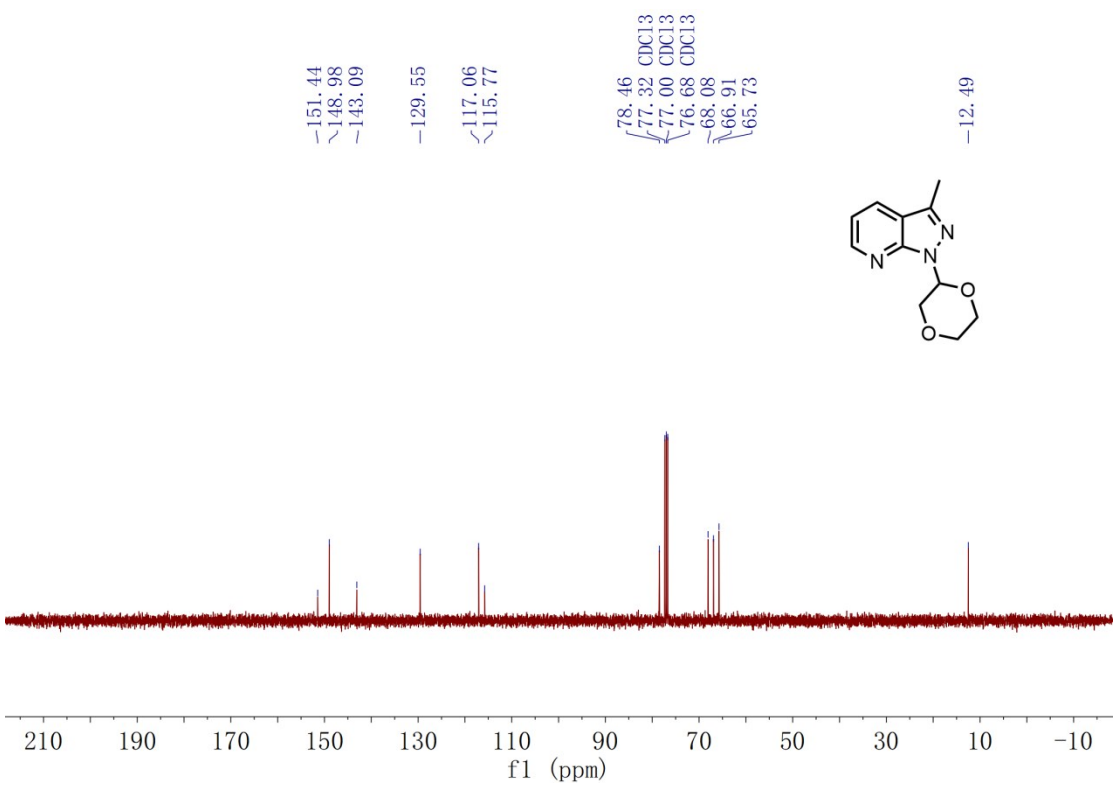
1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3x)



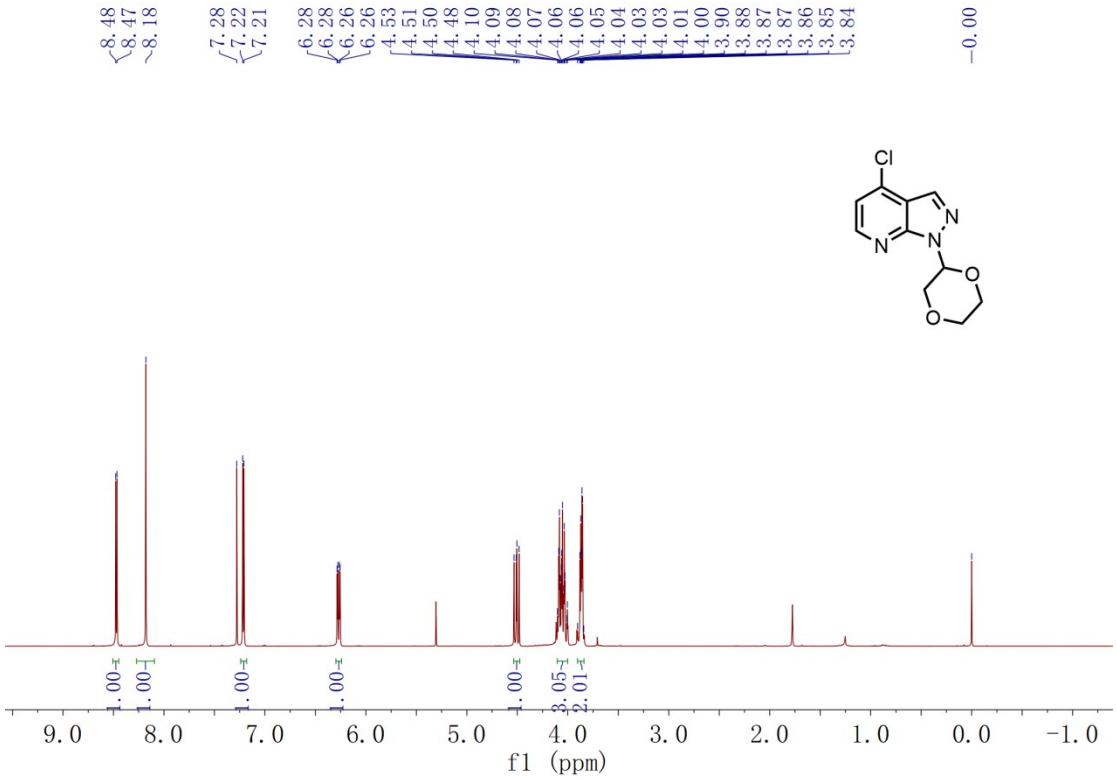


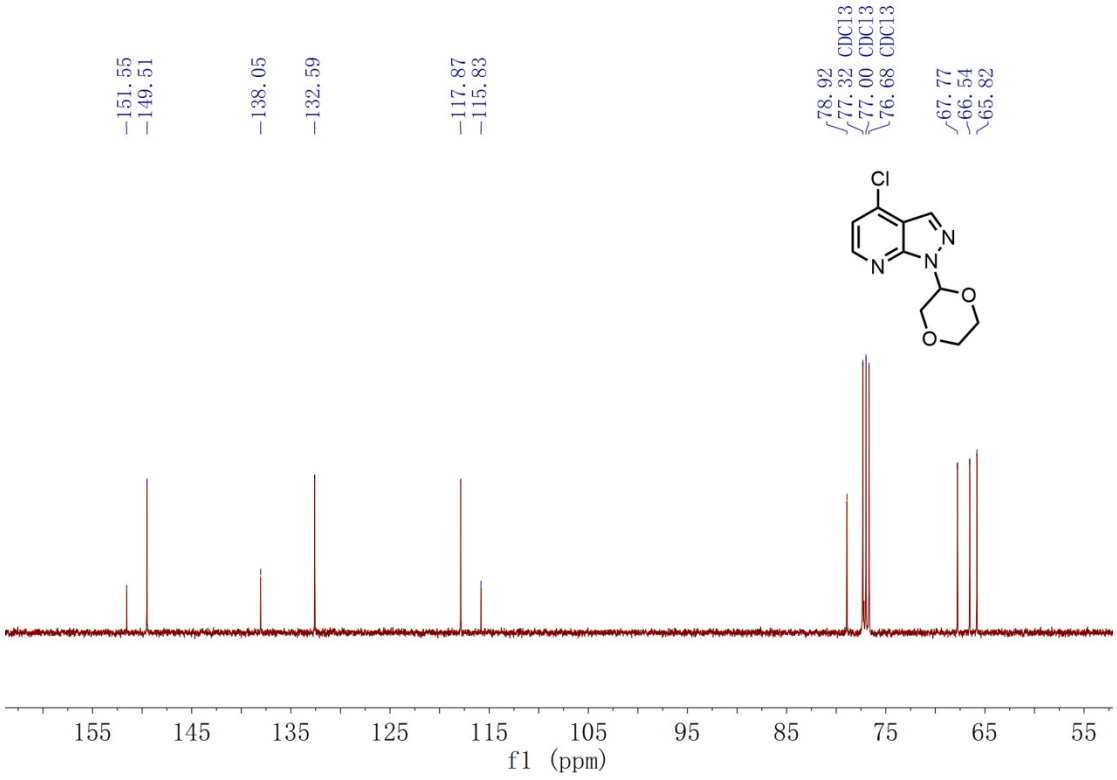
1-(1,4-dioxan-2-yl)-3-methyl-1*H*-pyrazolo[3,4-b]pyridine (3y)



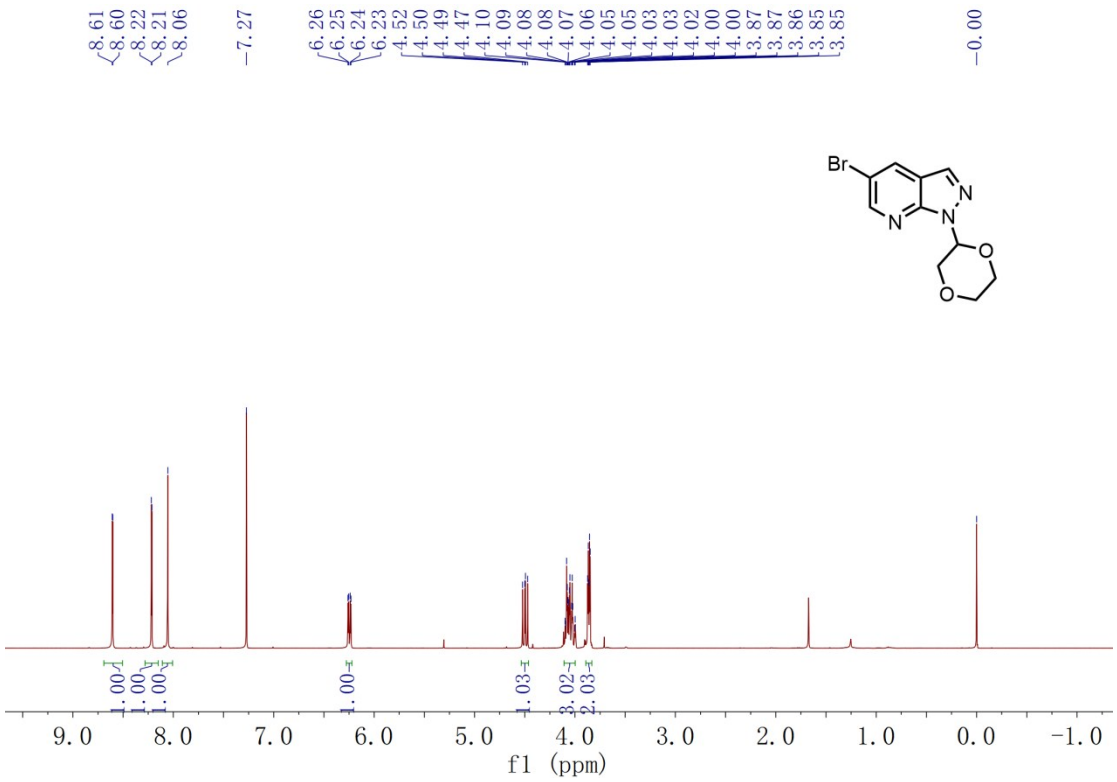


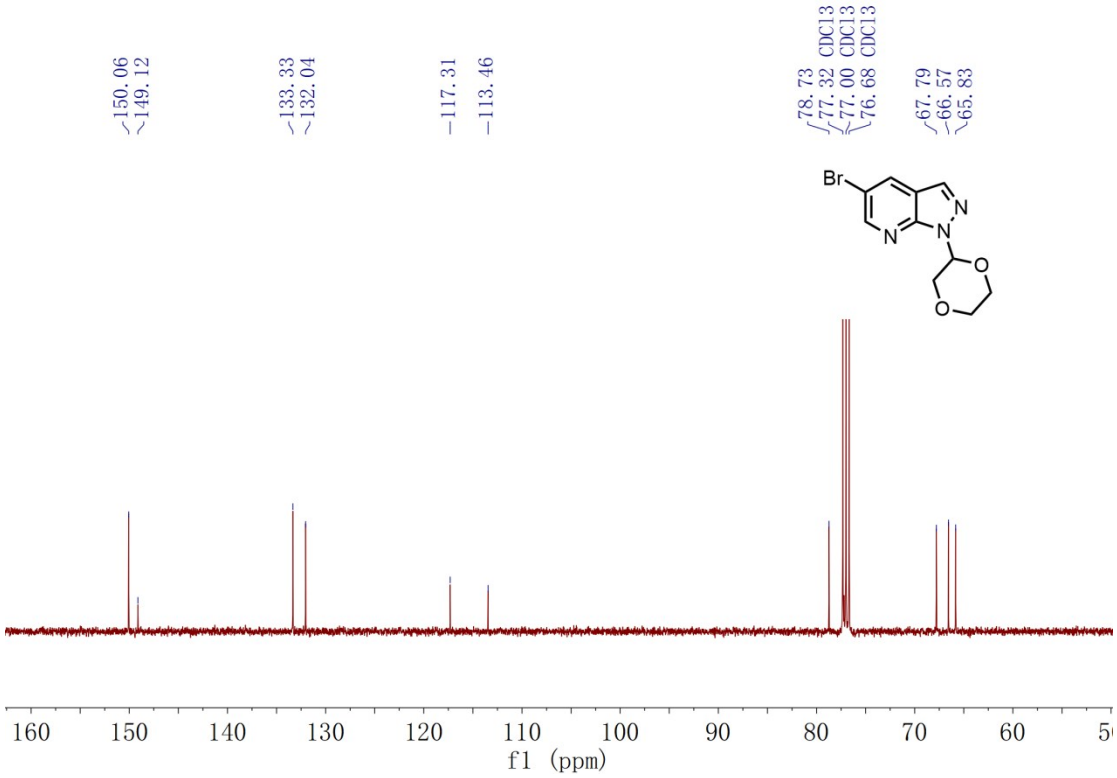
4-chloro-1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3z)



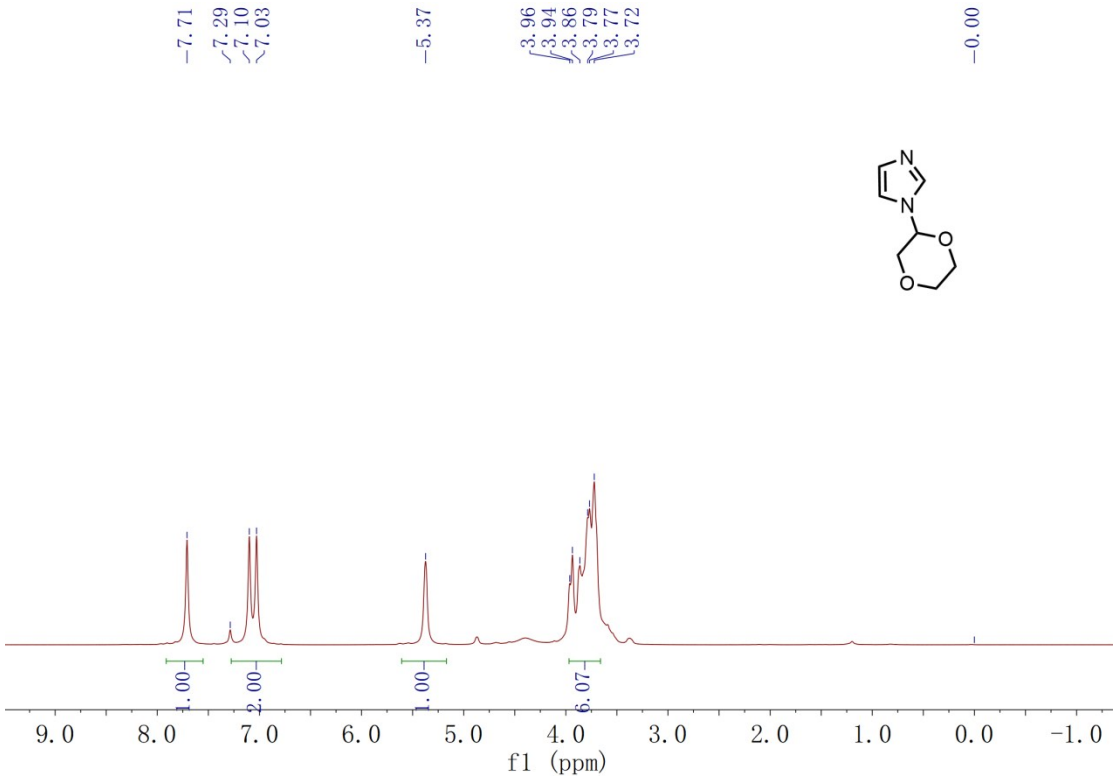


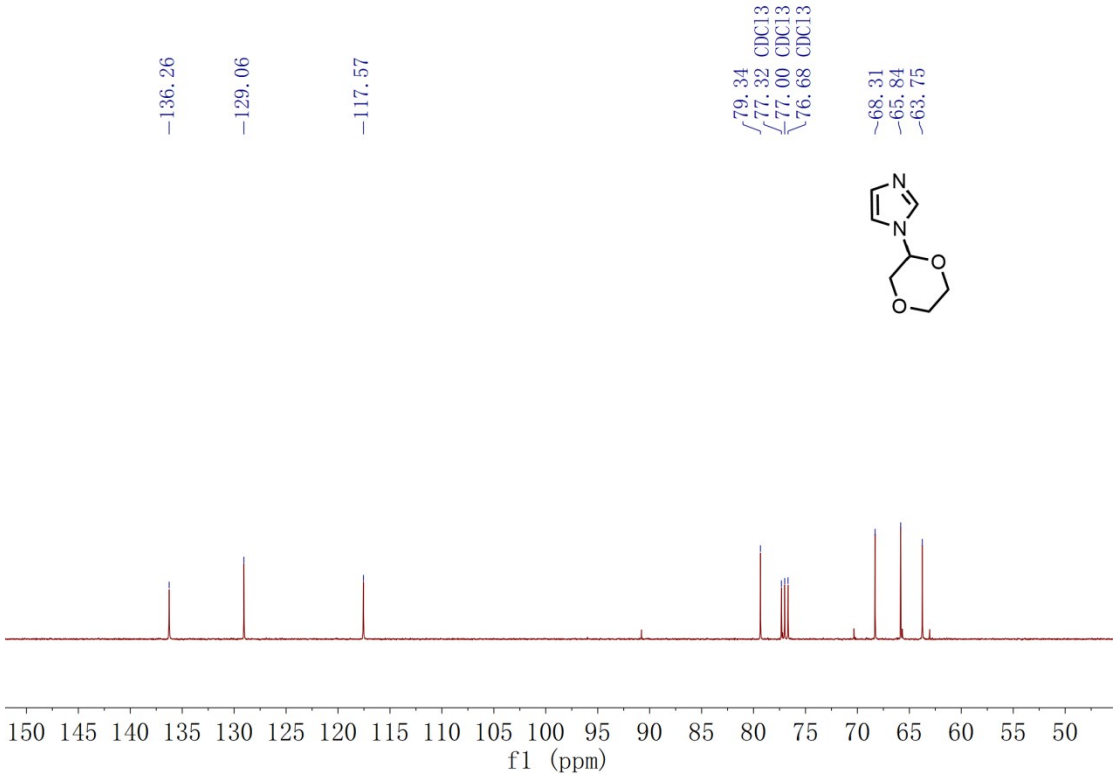
5-bromo-1-(1,4-dioxan-2-yl)-1*H*-pyrazolo[3,4-b]pyridine (3aa)



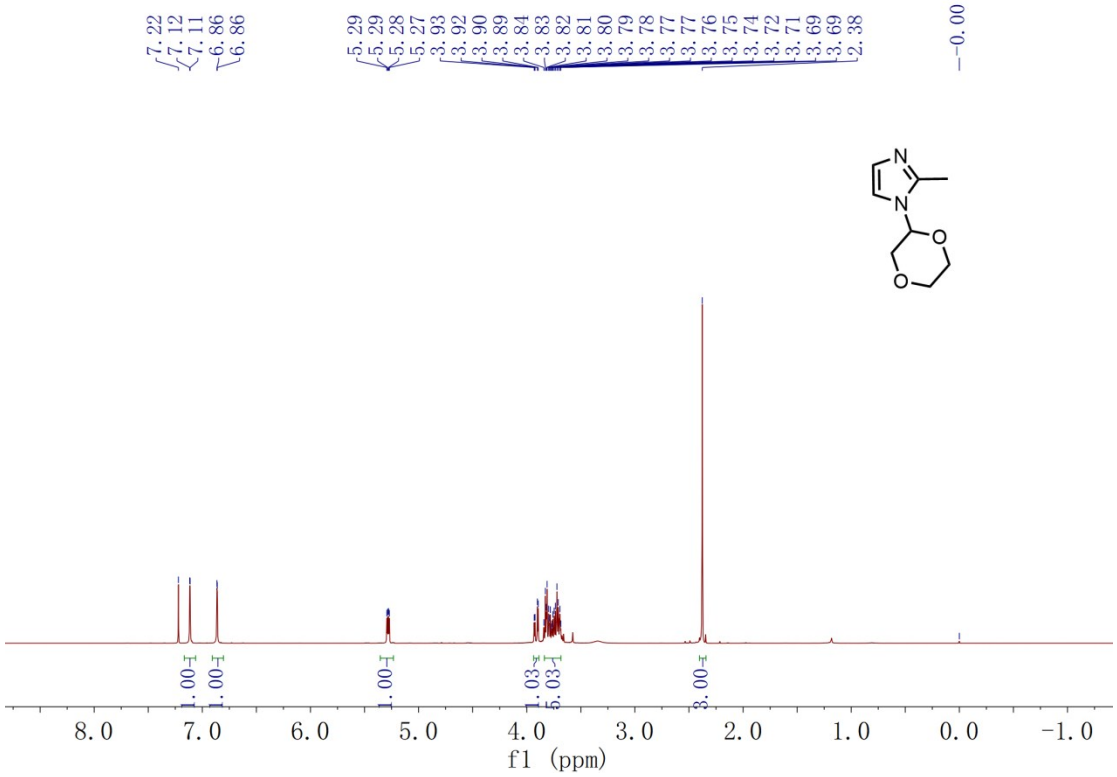


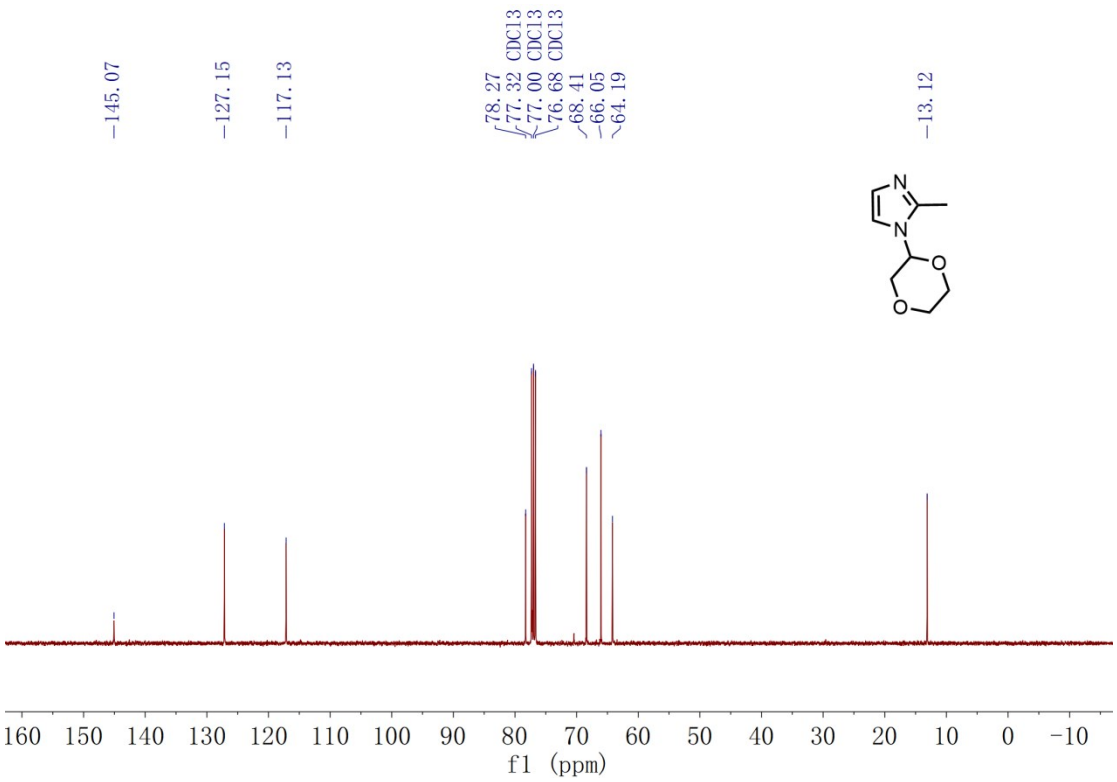
1-(1,4-dioxan-2-yl)-1*H*-imidazole (3ab)



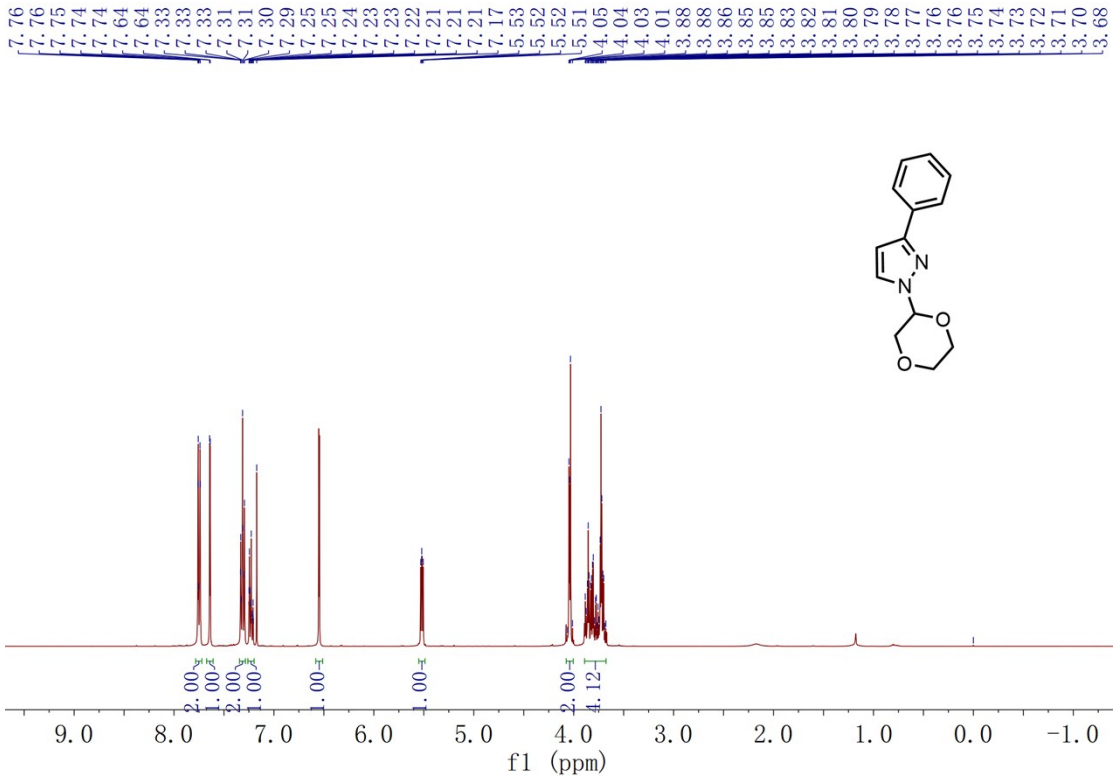


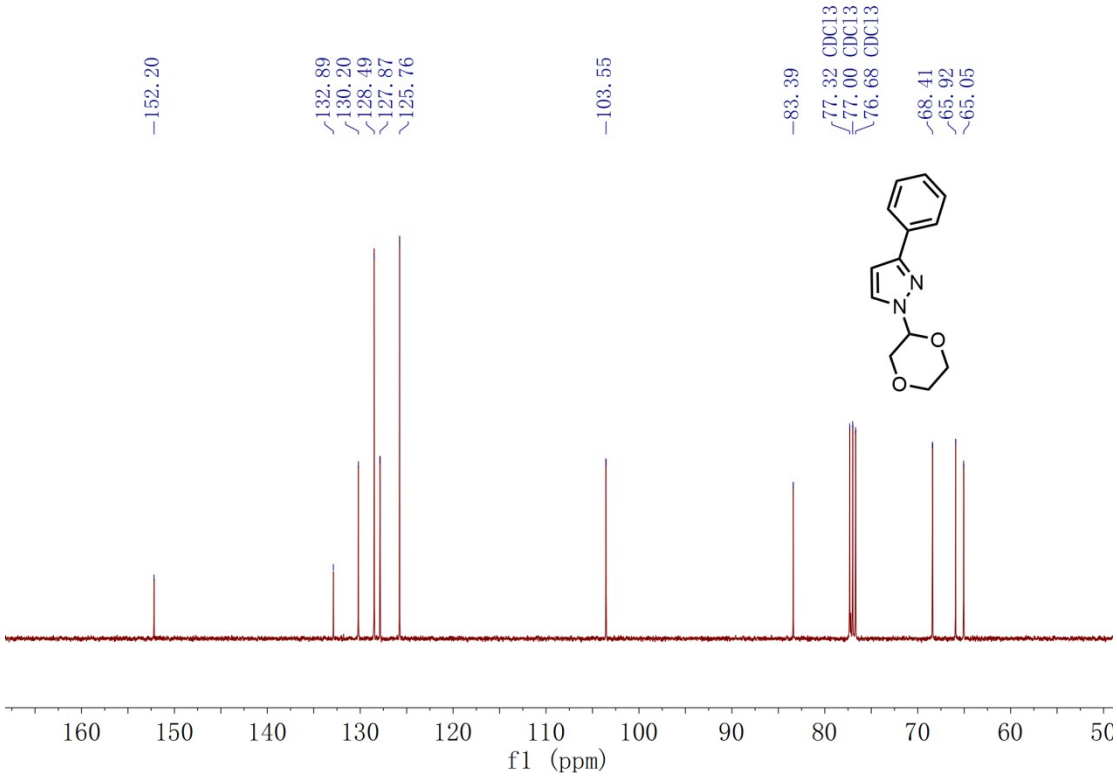
1-(1,4-dioxan-2-yl)-2-methyl-1*H*-imidazole (3ac)



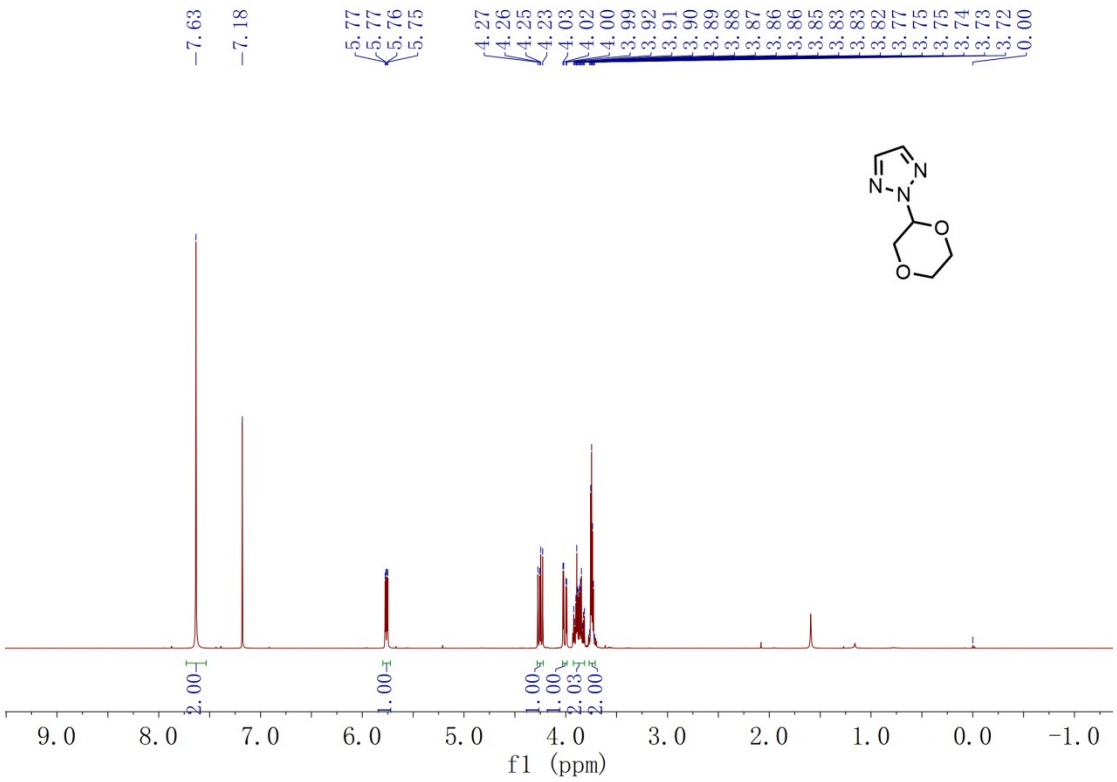


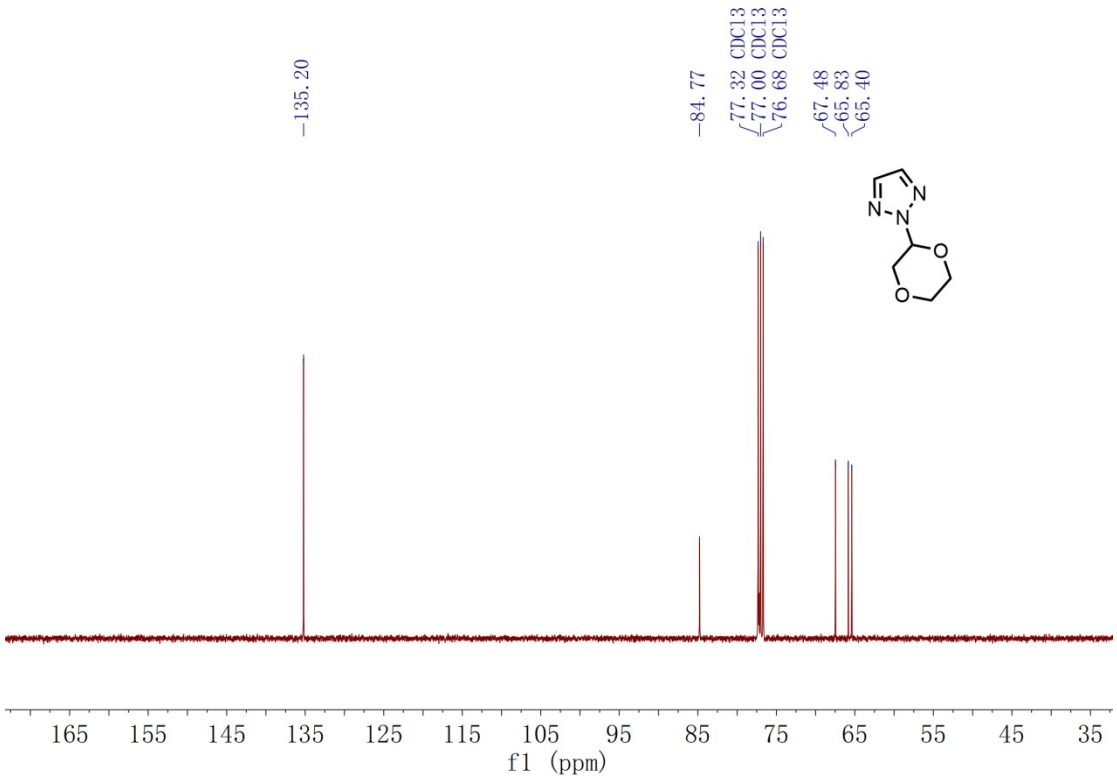
1-(1,4-dioxan-2-yl)-3-phenyl-1*H*-pyrazole (3ad)



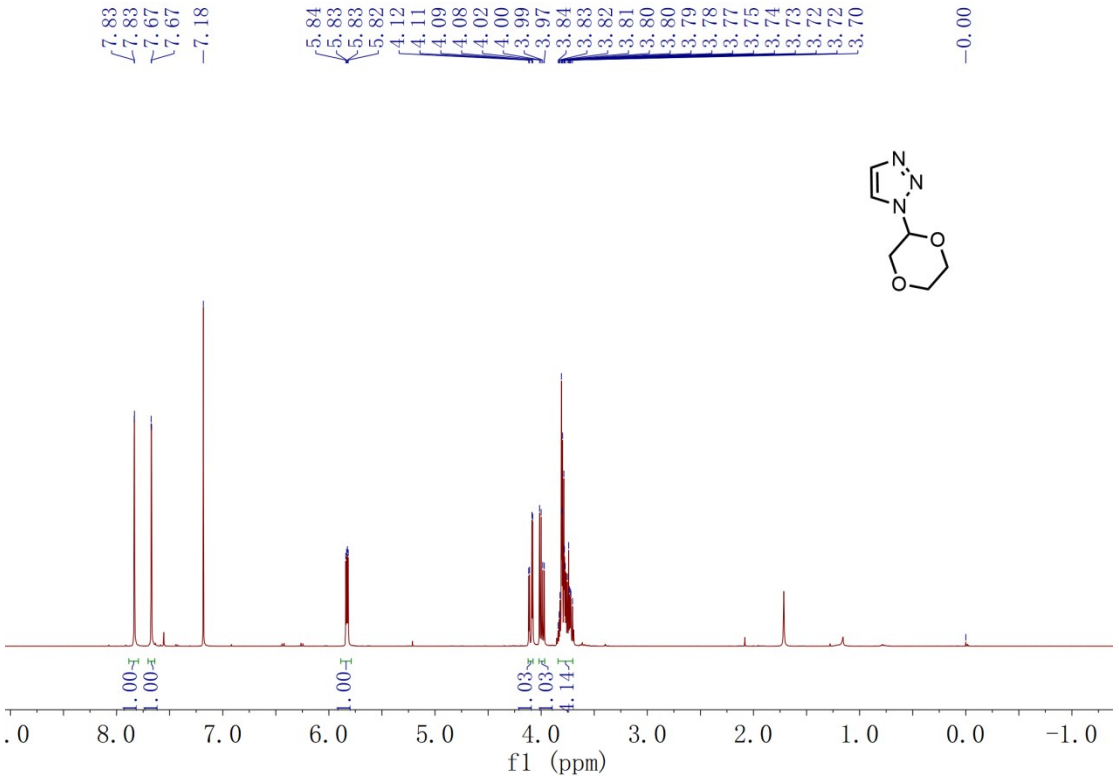


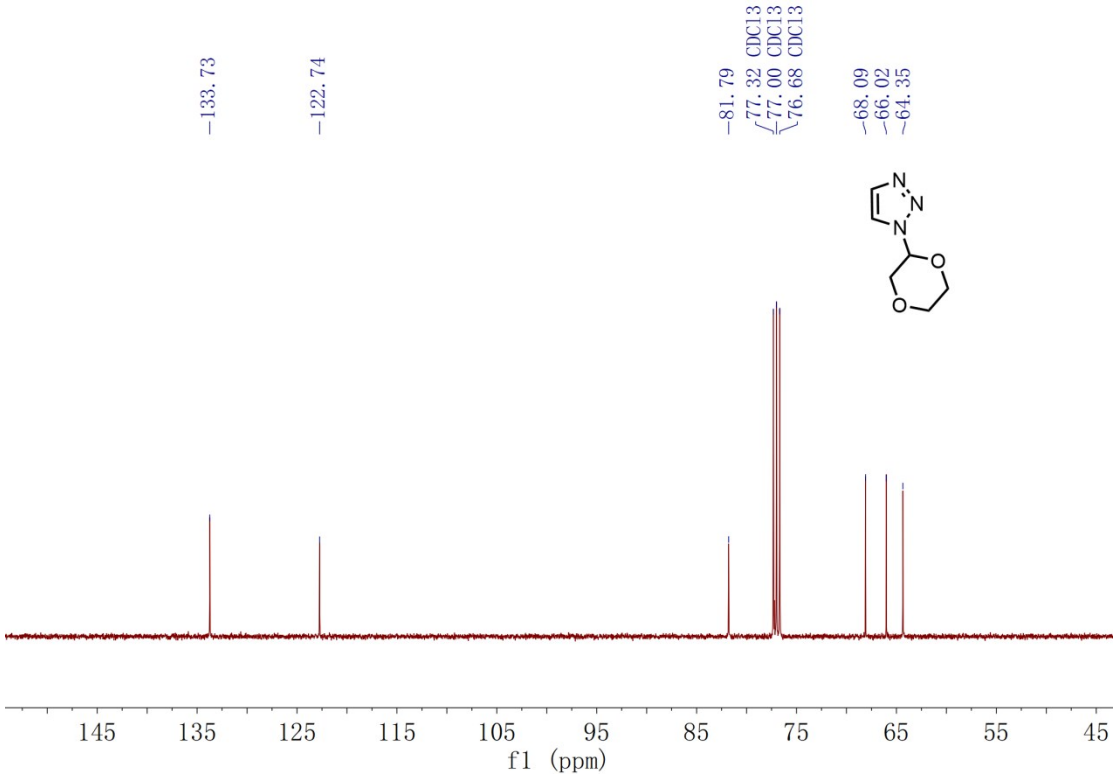
2-(1,4-dioxan-2-yl)-2*H*-1,2,3-triazole (3ae)



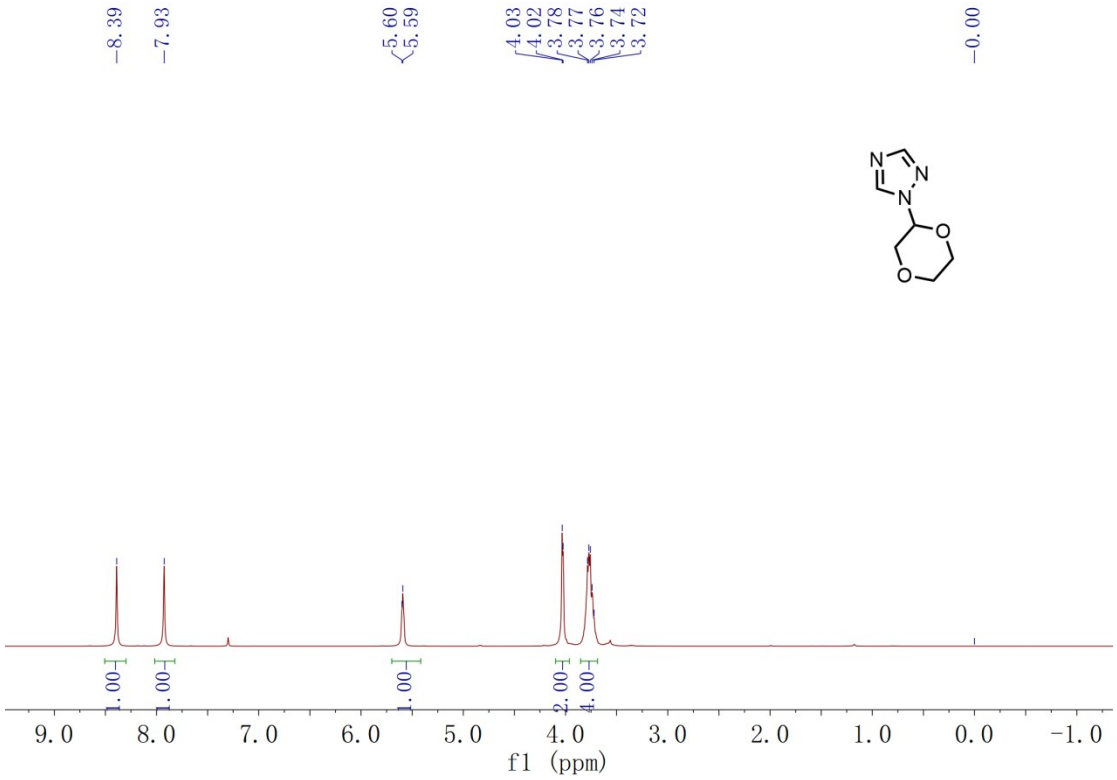


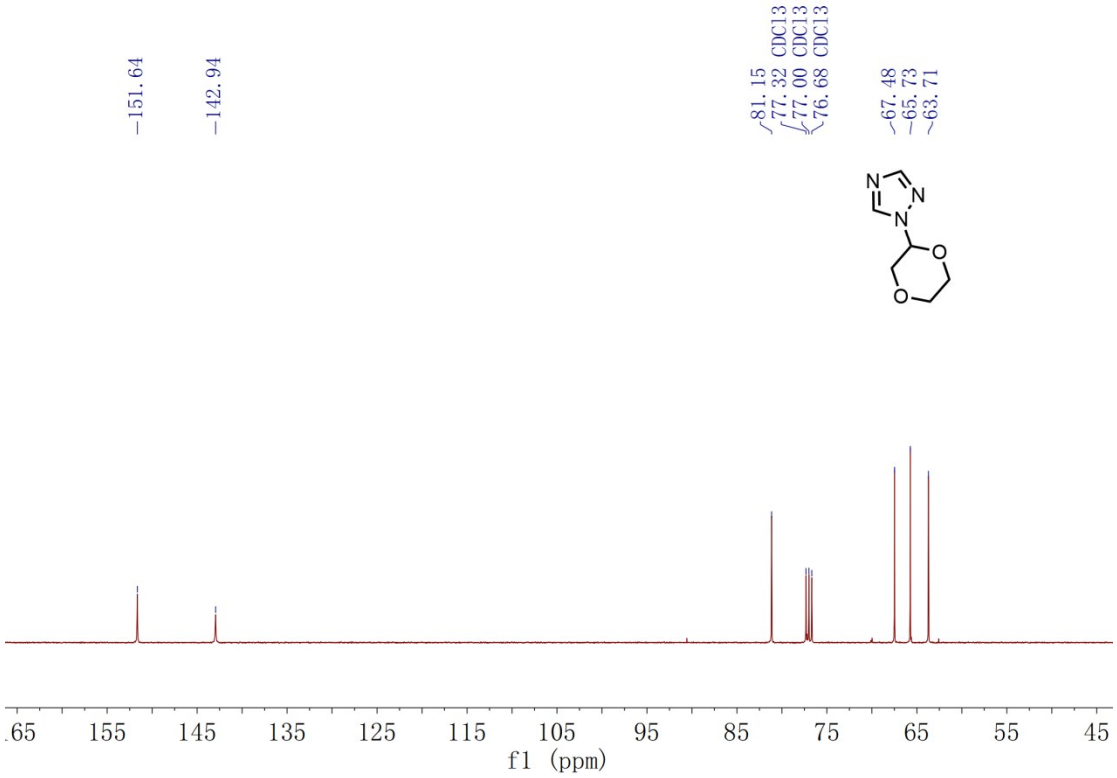
1-(1,4-dioxan-2-yl)-1*H*-1,2,3-triazole (3ae')



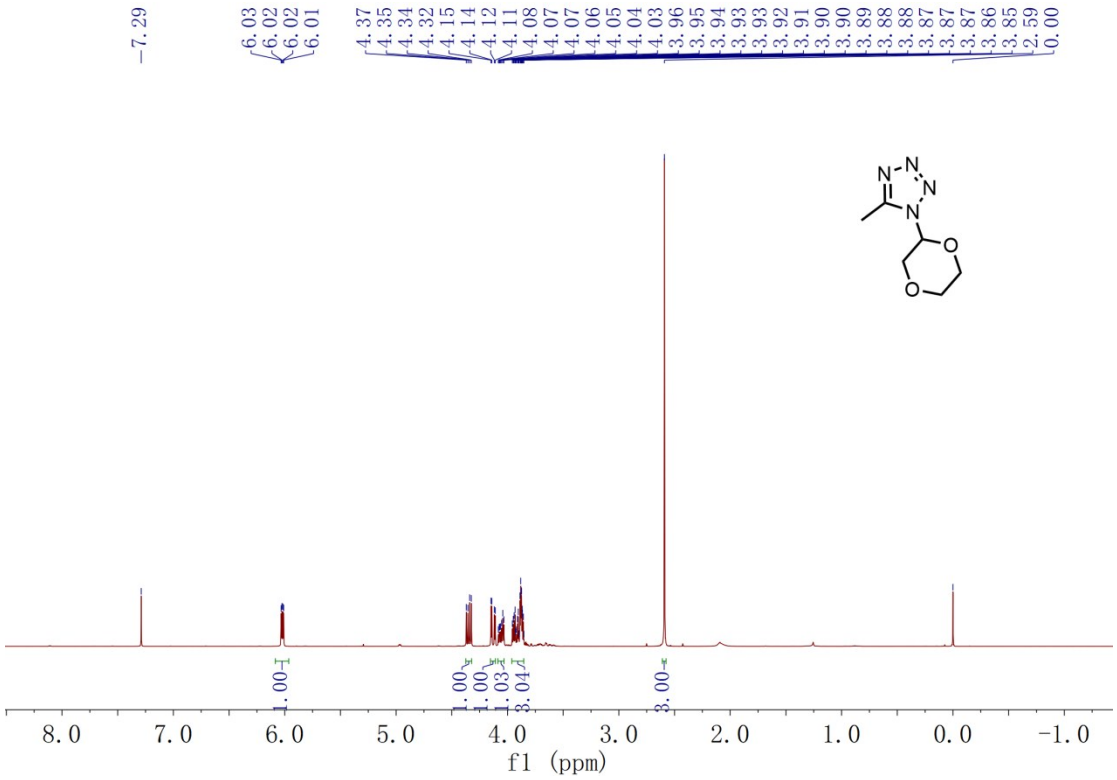


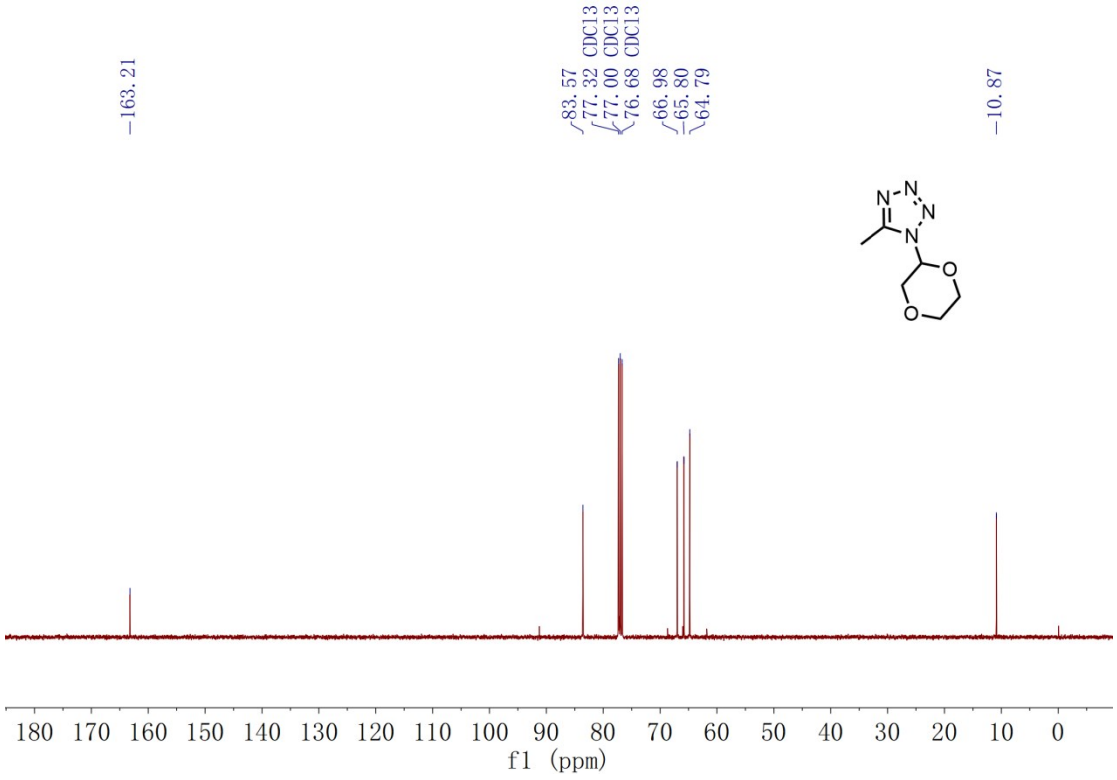
1-(1,4-dioxan-2-yl)-1*H*-1,2,4-triazole (3af)



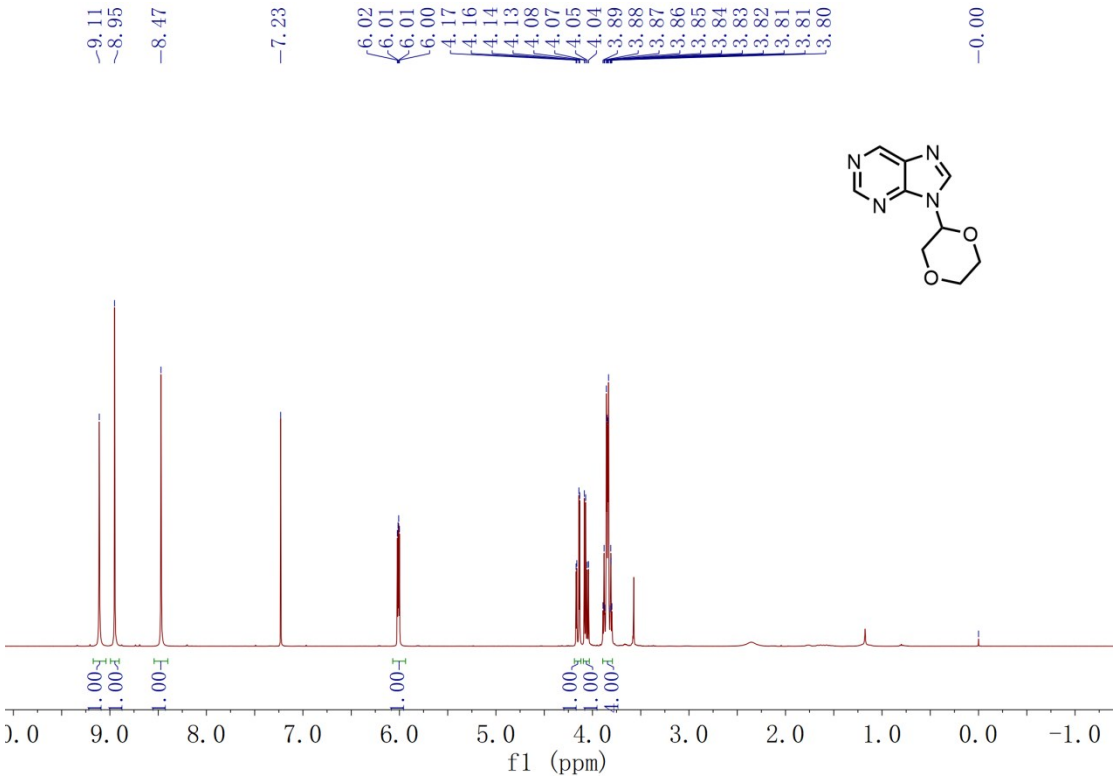


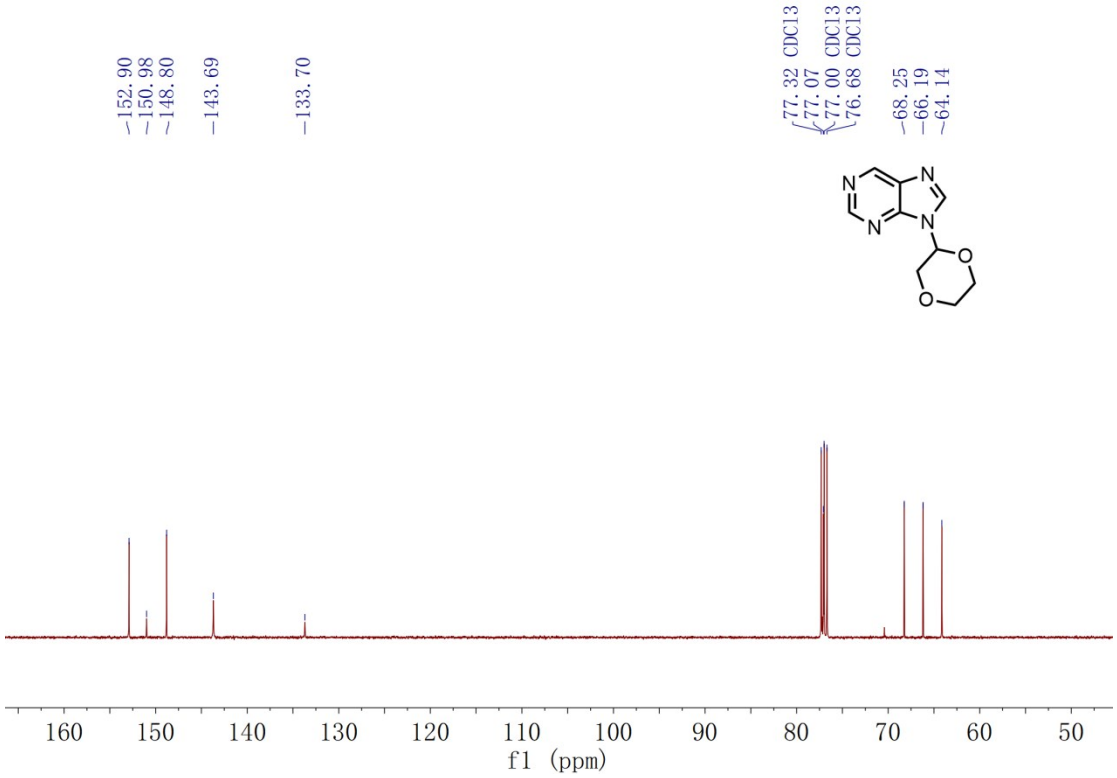
1-(1,4-dioxan-2-yl)-5-methyl-1*H*-tetrazole (3ag)



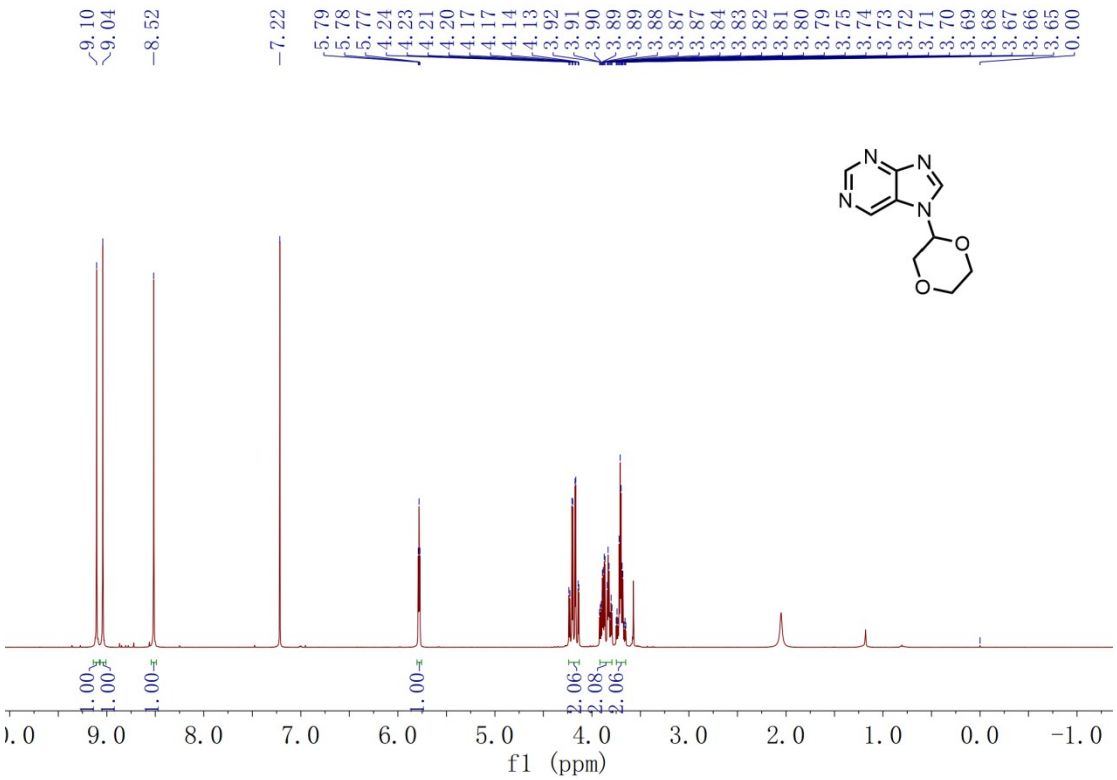


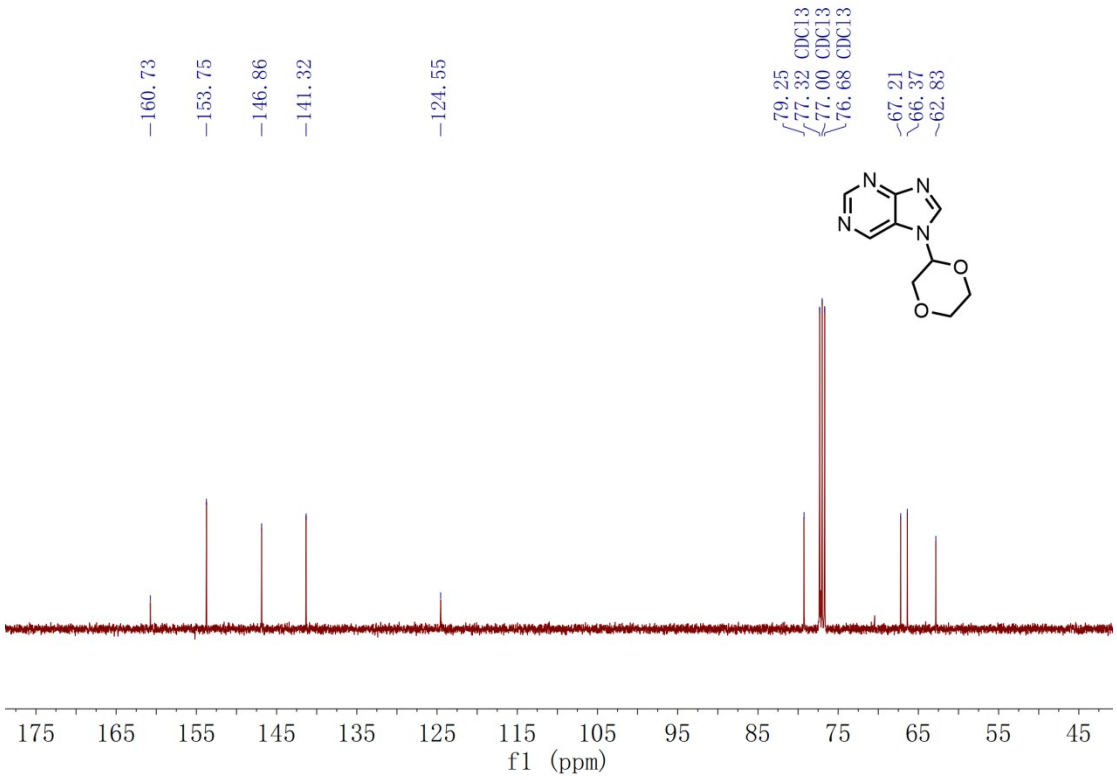
9-(1,4-dioxan-2-yl)-9*H*-purine (3ah)



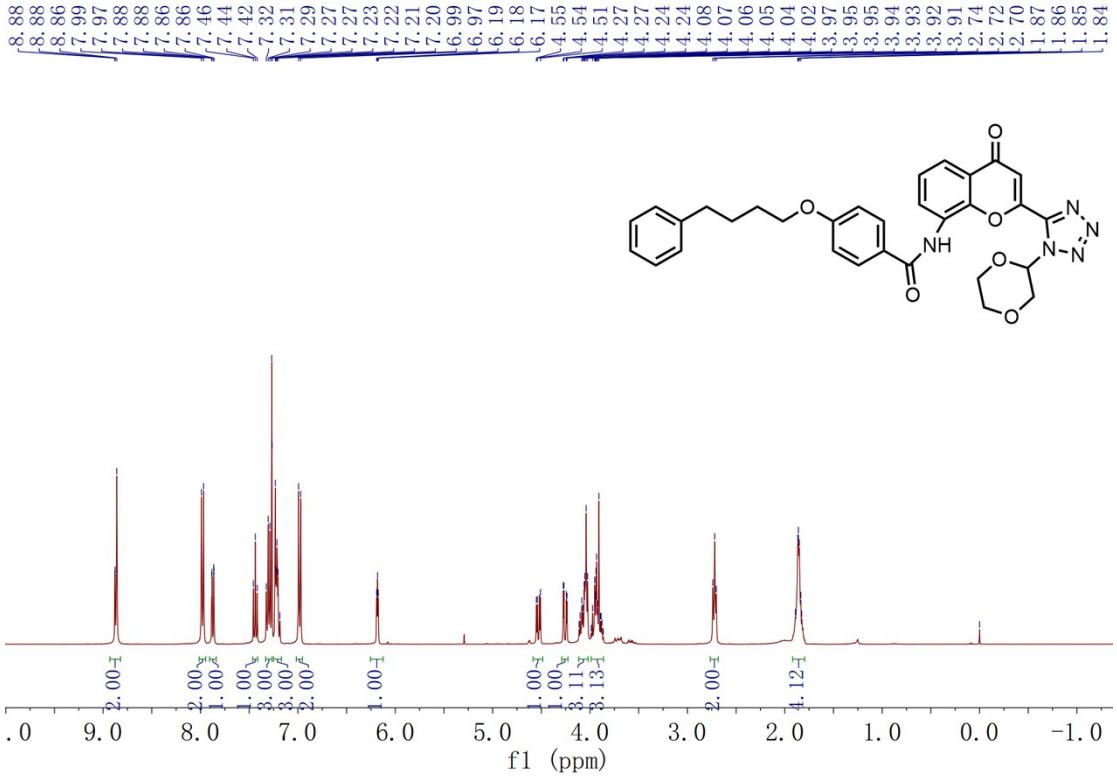


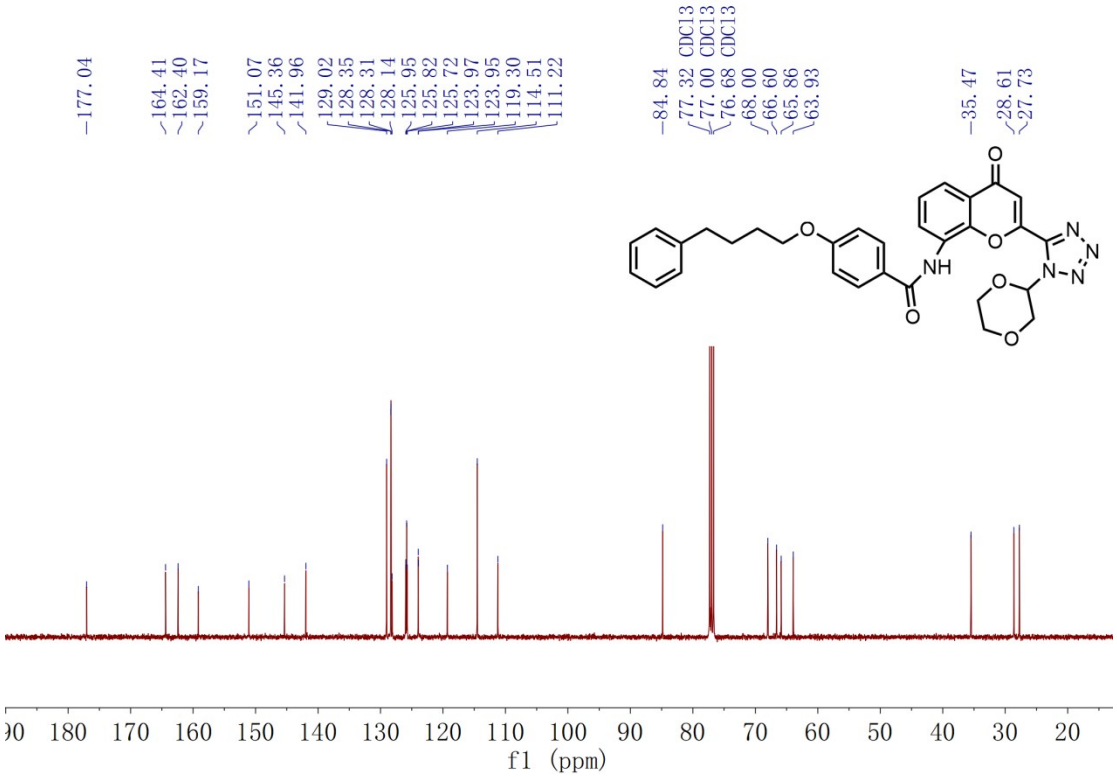
7-(1,4-dioxan-2-yl)-7*H*-purine (3ah')



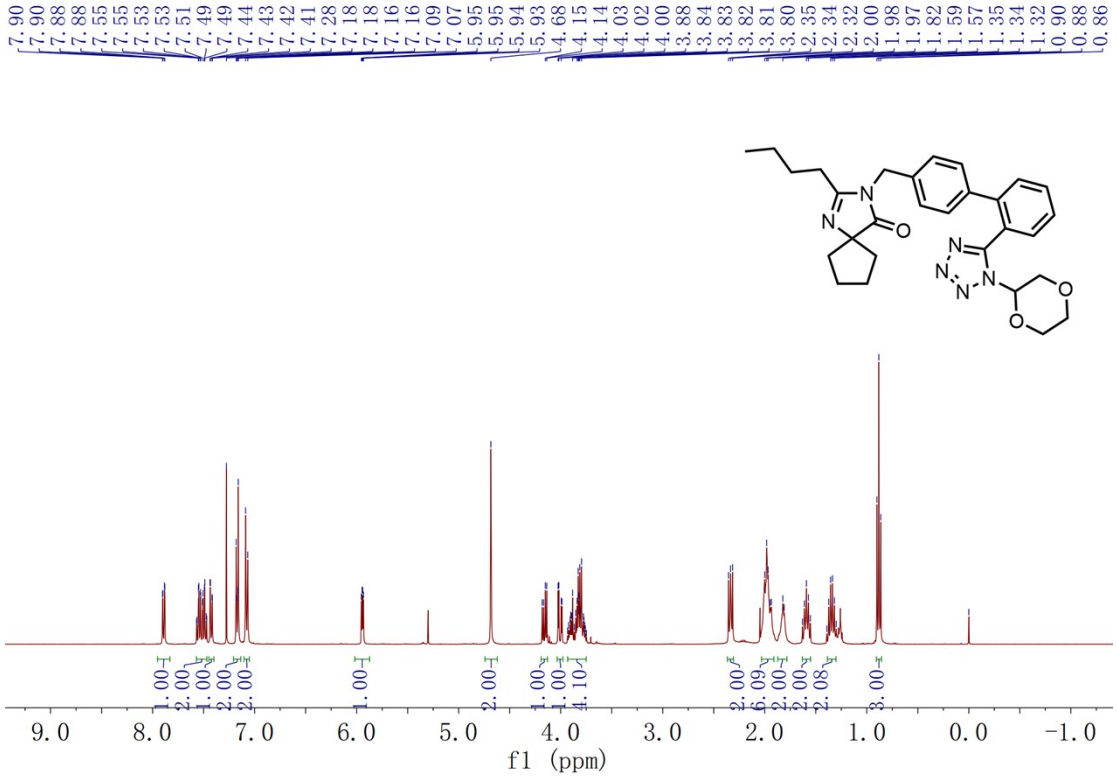


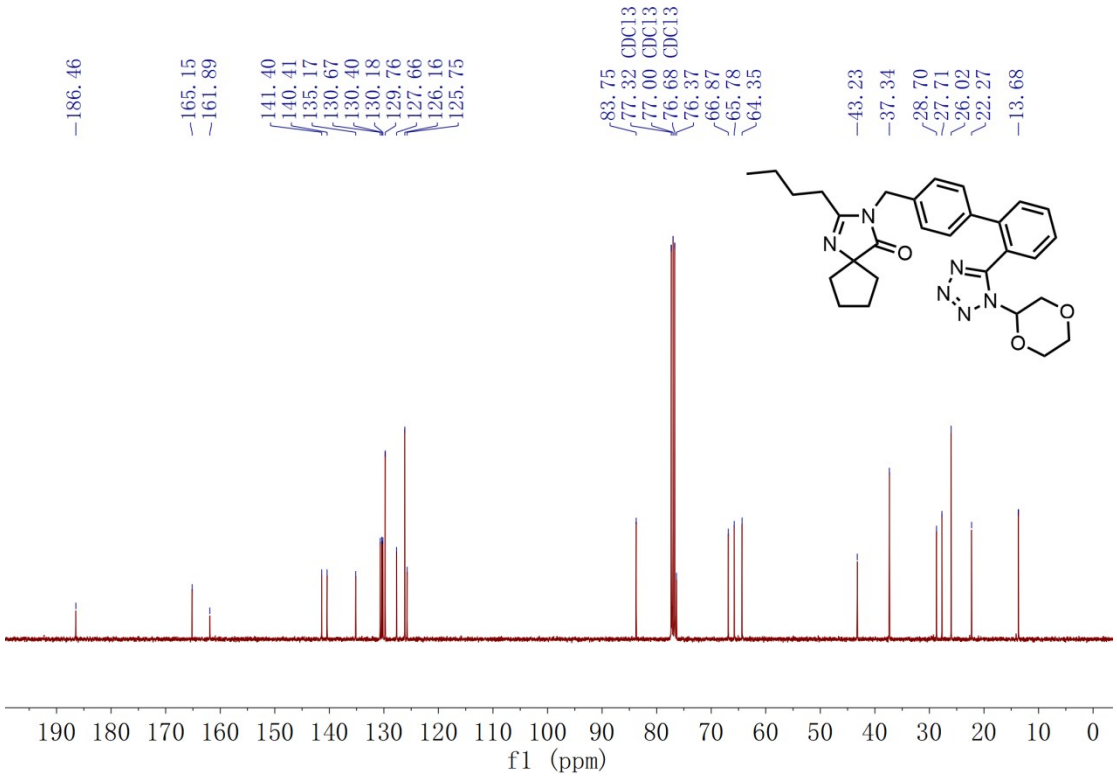
N-(2-(1-(1,4-dioxan-2-yl)-1*H*-tetrazol-5-yl)-4-oxo-4*H*-chromen-8-yl)-4-(4-phenylbutoxy)benzamide (3ai)



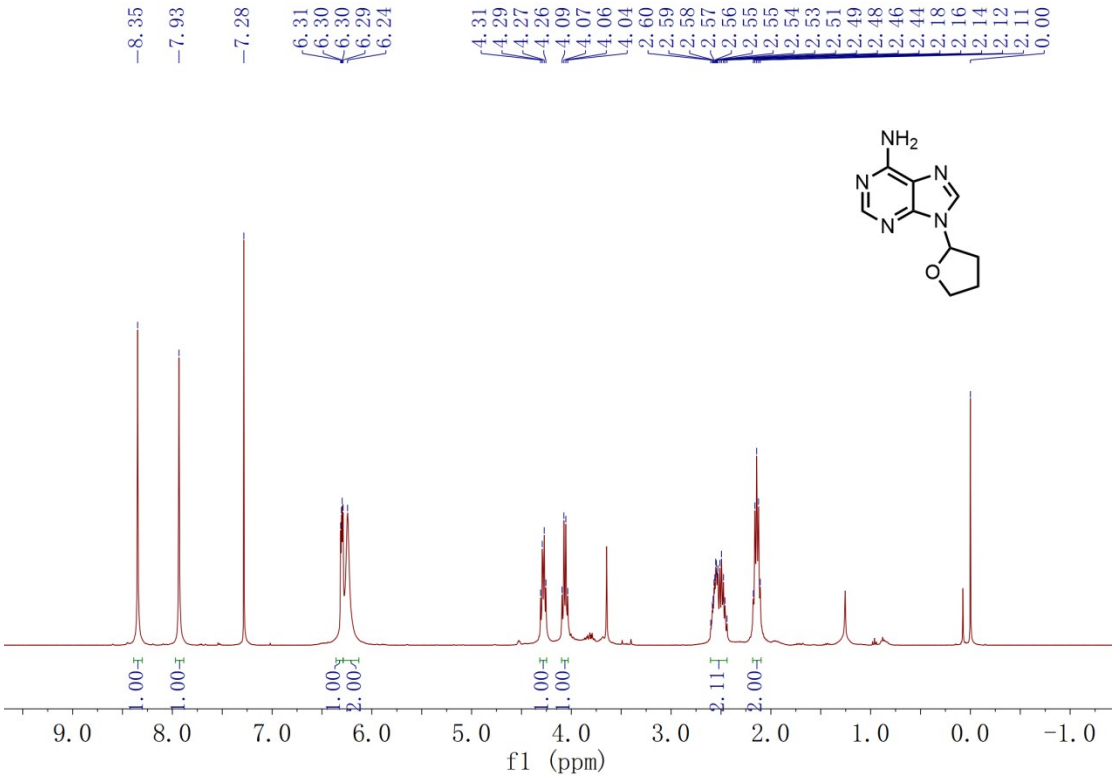


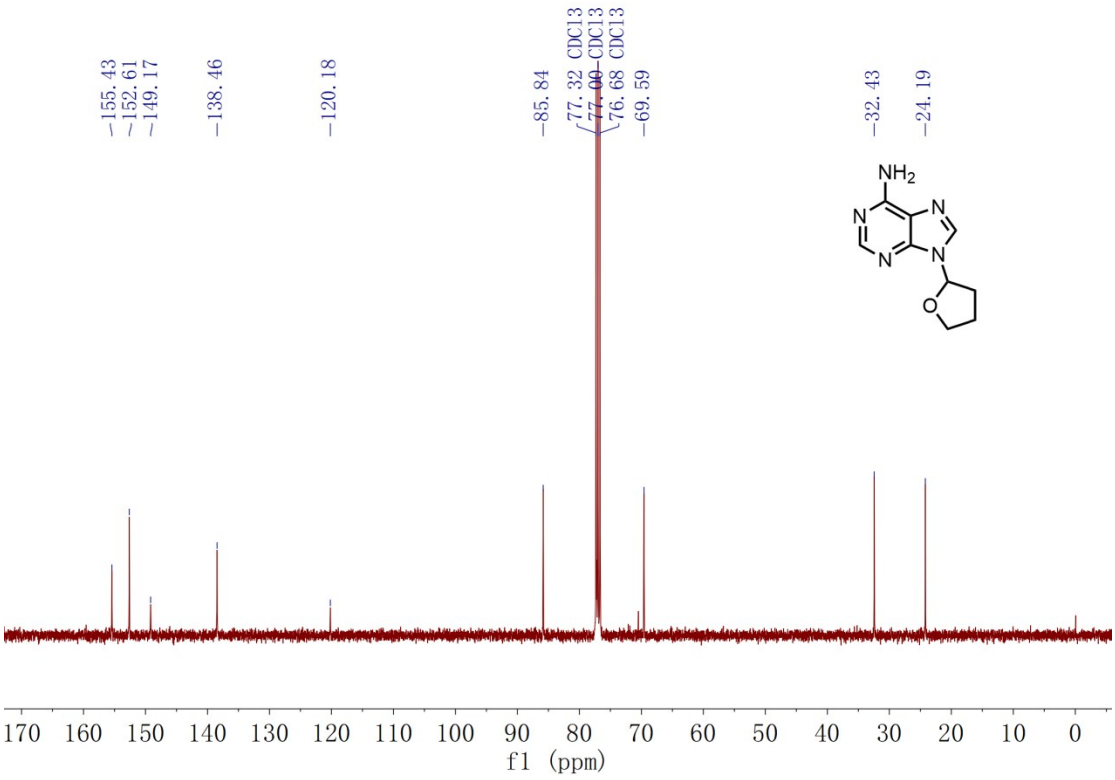
3-((2'-(1-(1,4-dioxan-2-yl)-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (3aj)



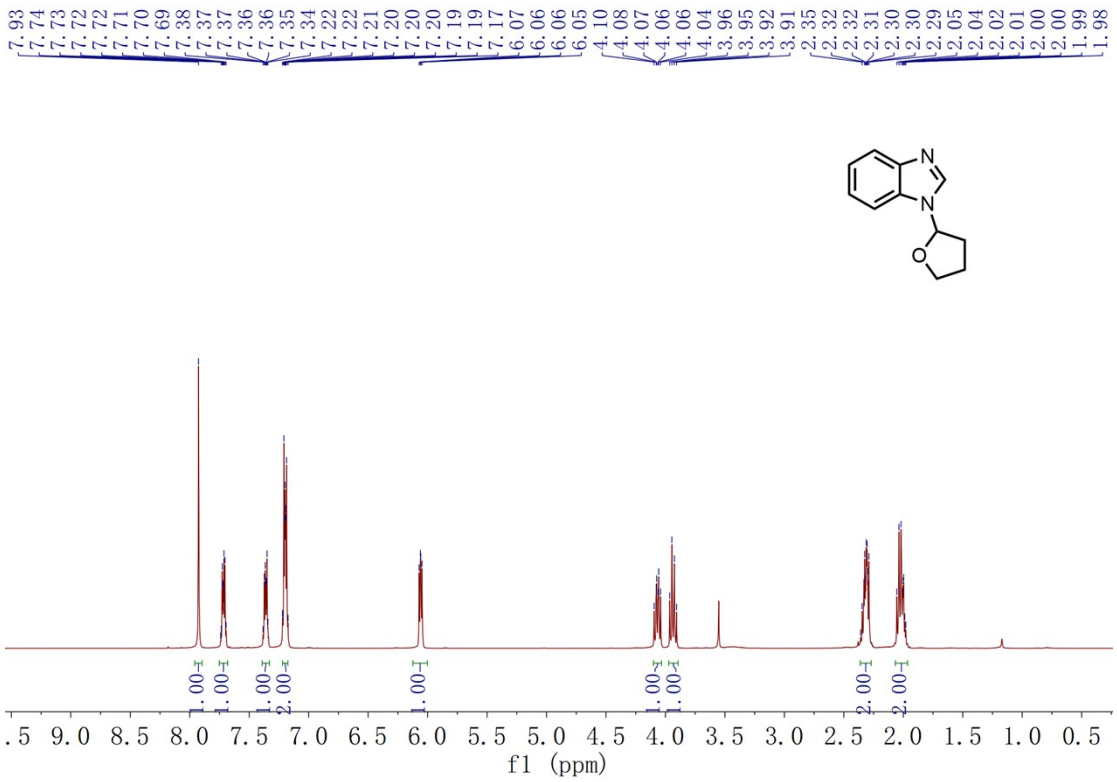


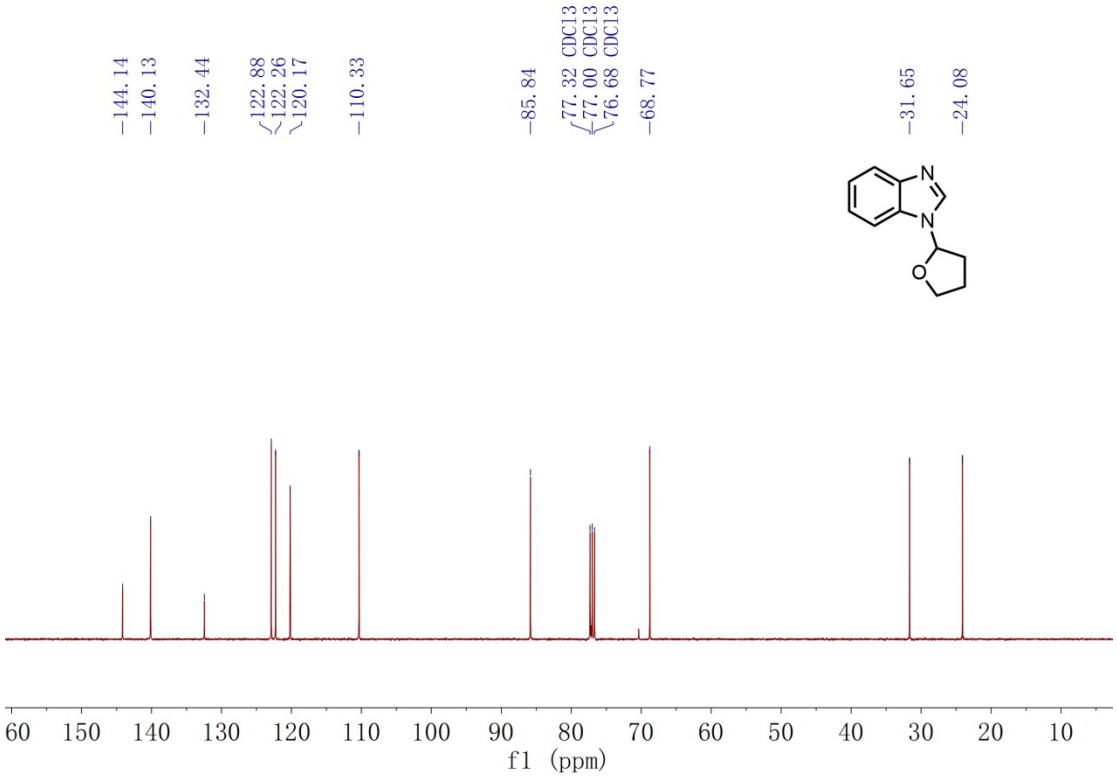
9-(tetrahydrofuran-2-yl)-9*H*-purin-6-amine (3ak)



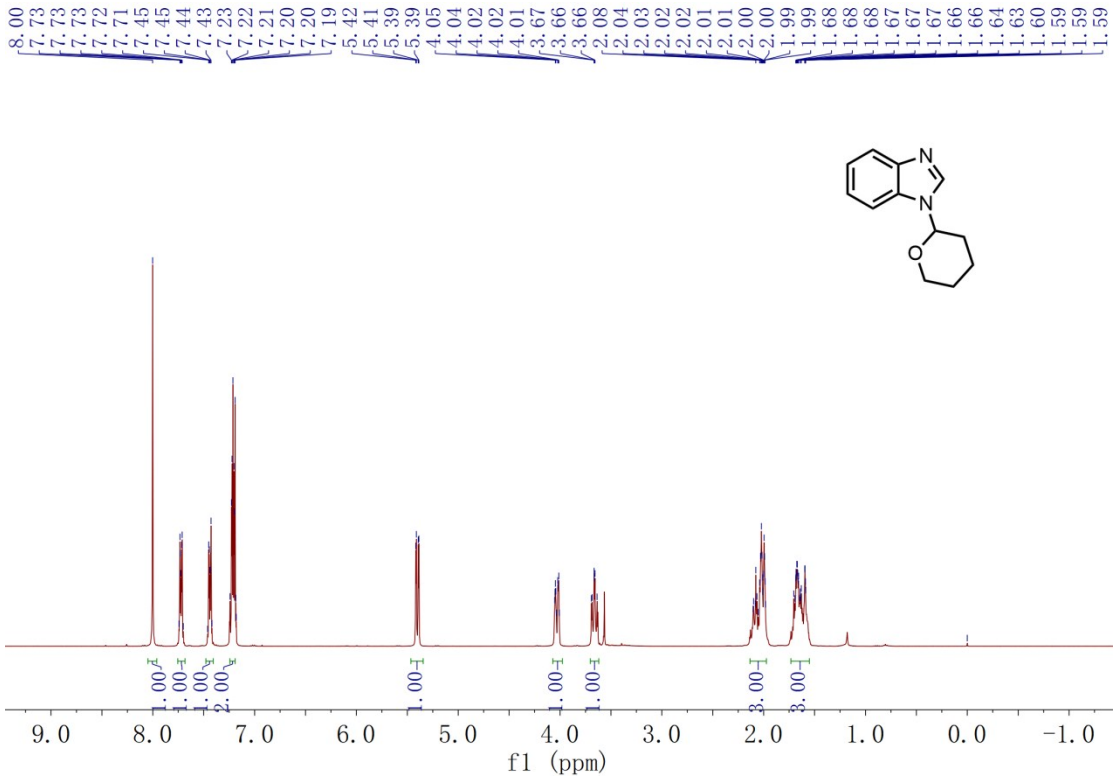


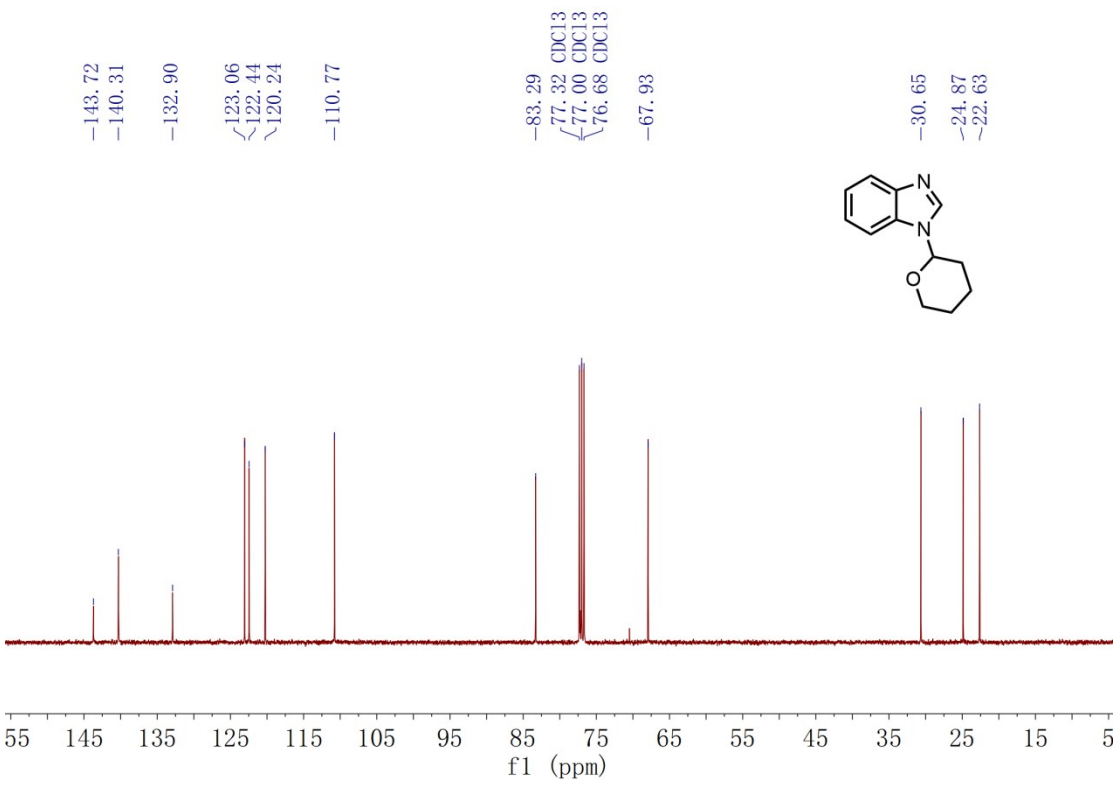
1-(tetrahydrofuran-2-yl)-1*H*-benzo[d]imidazole(4a)



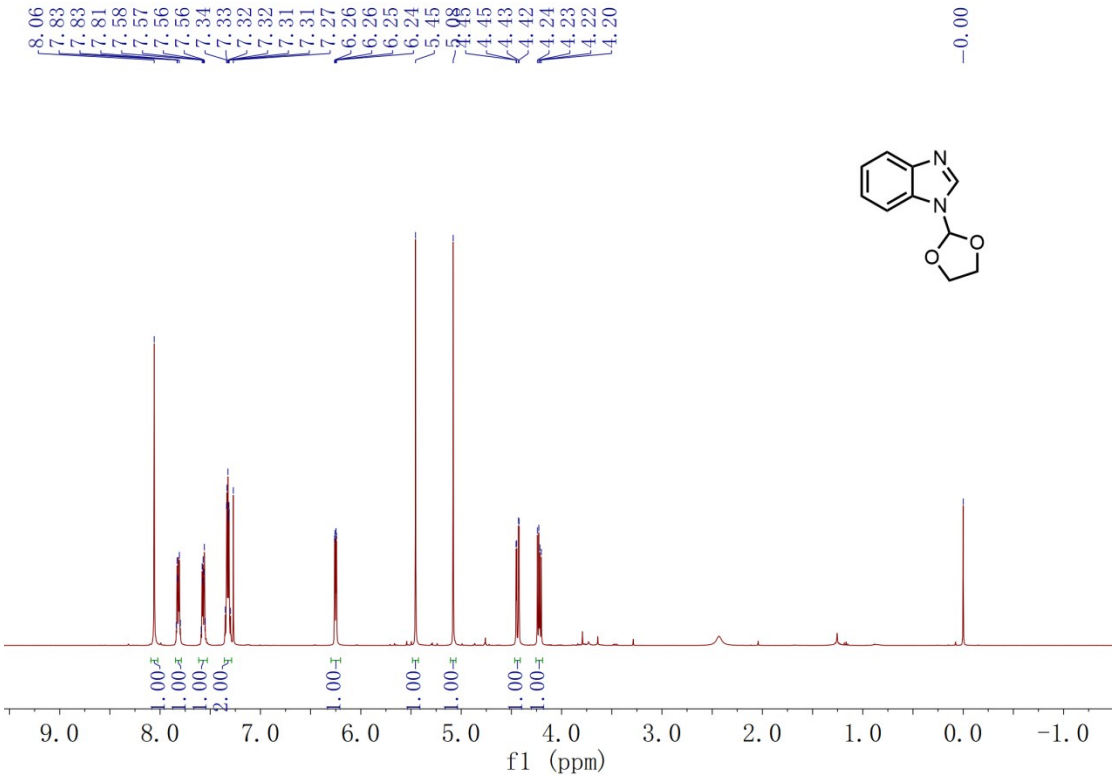


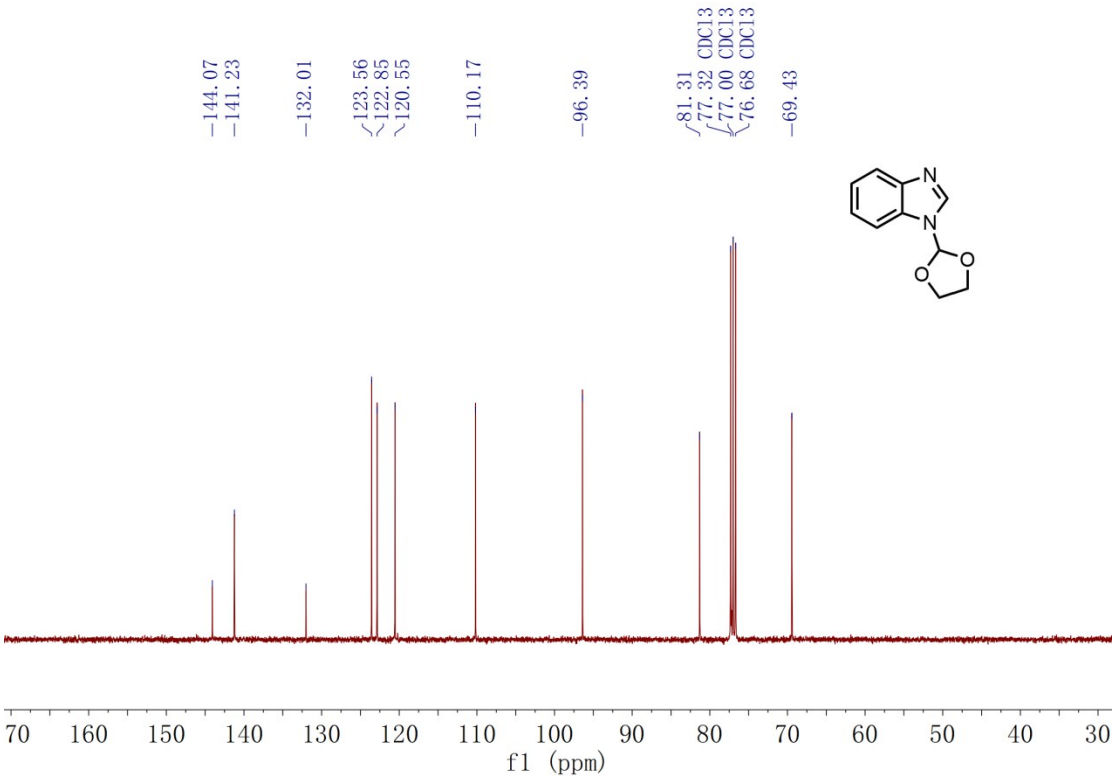
1-(tetrahydro-2H-pyran-2-yl)-1*H*-benzo[d]imidazole(4b)



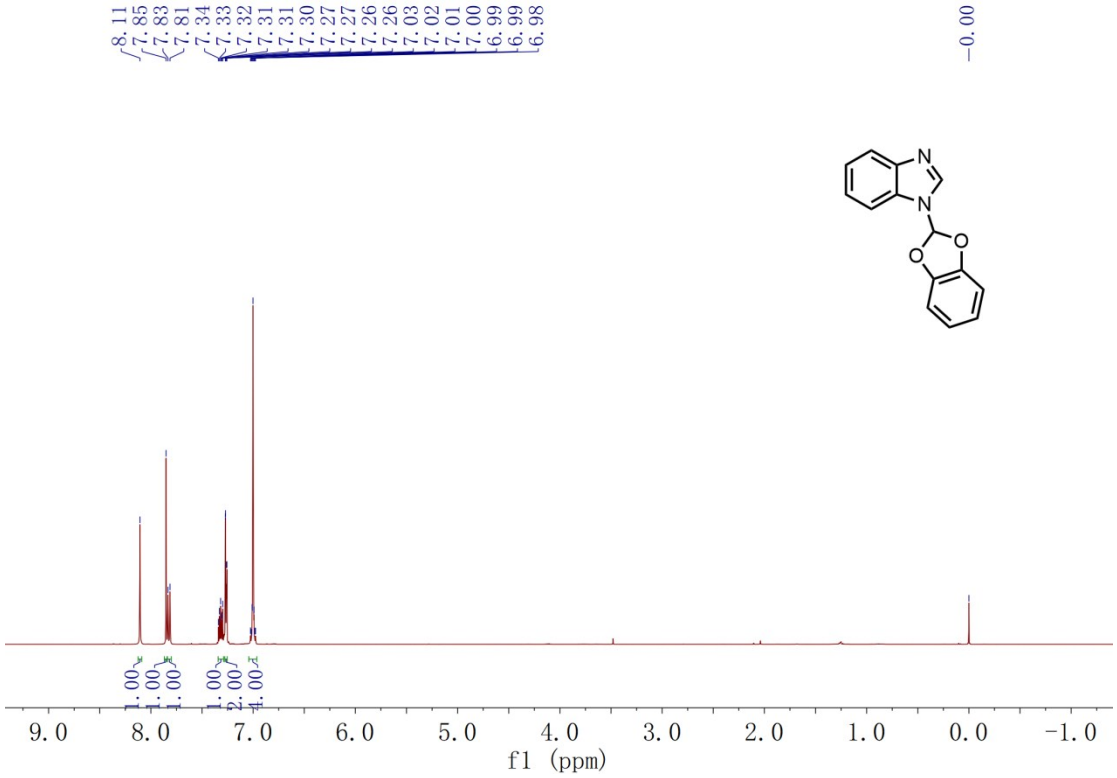


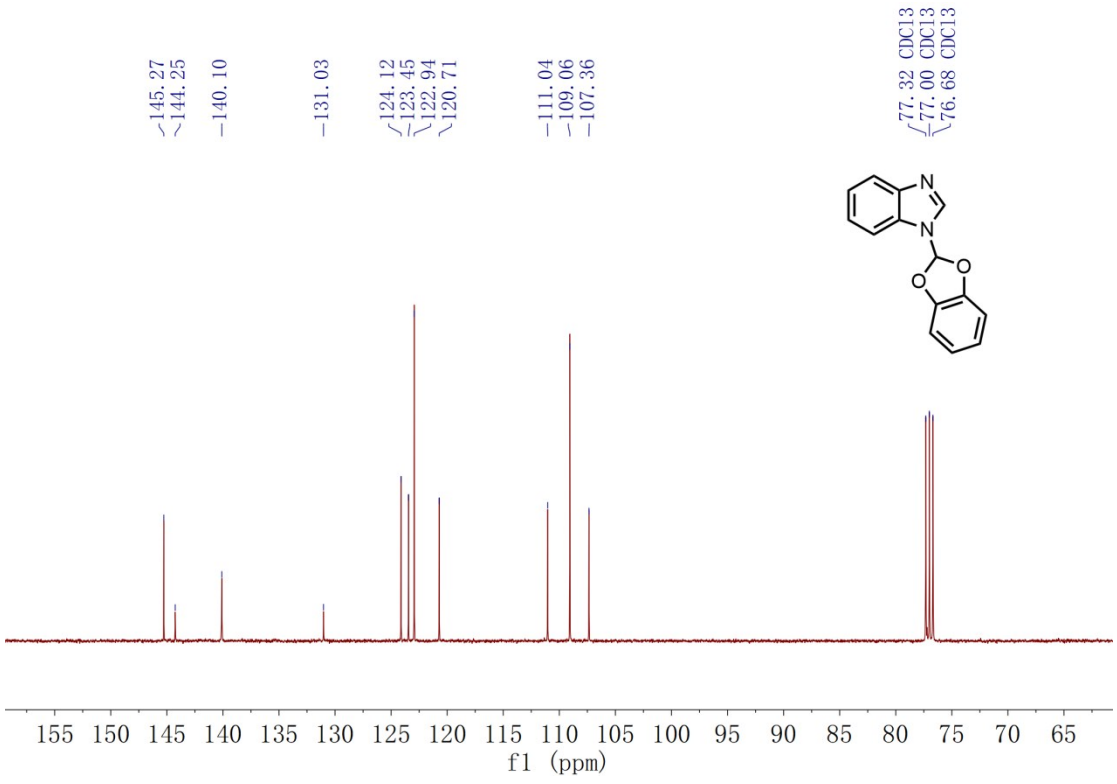
1-(1,3-dioxolan-2-yl)-1*H*-benzo[d]imidazole (4c)



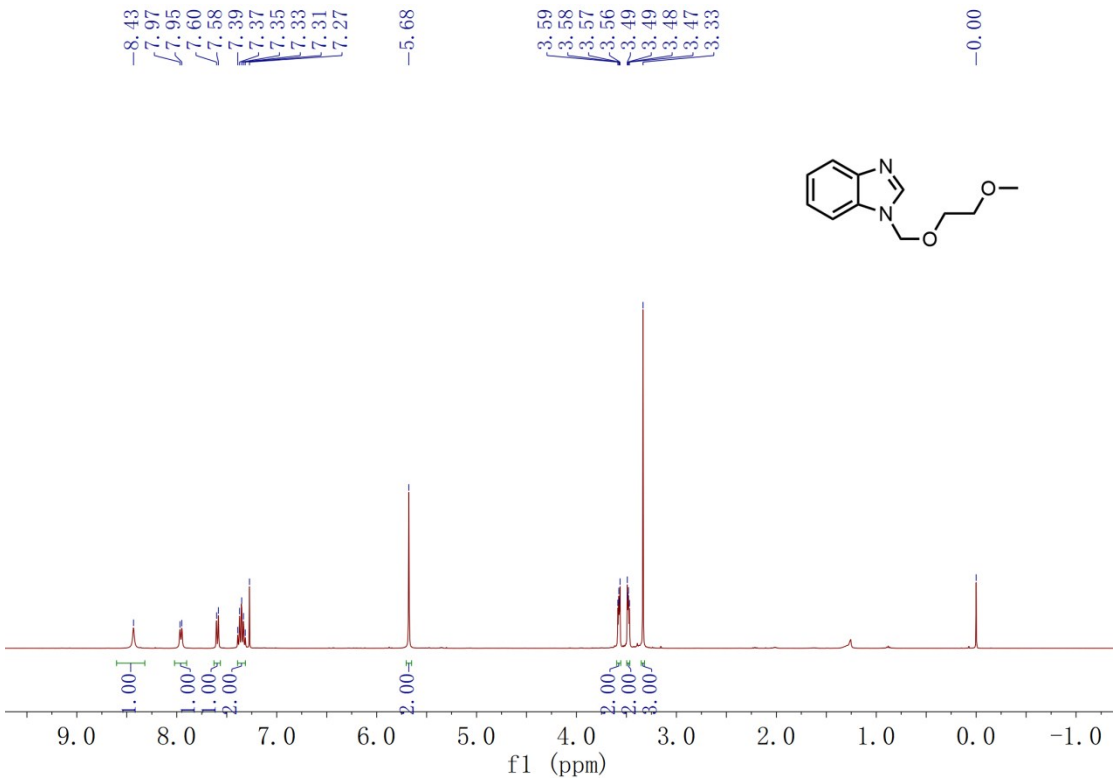


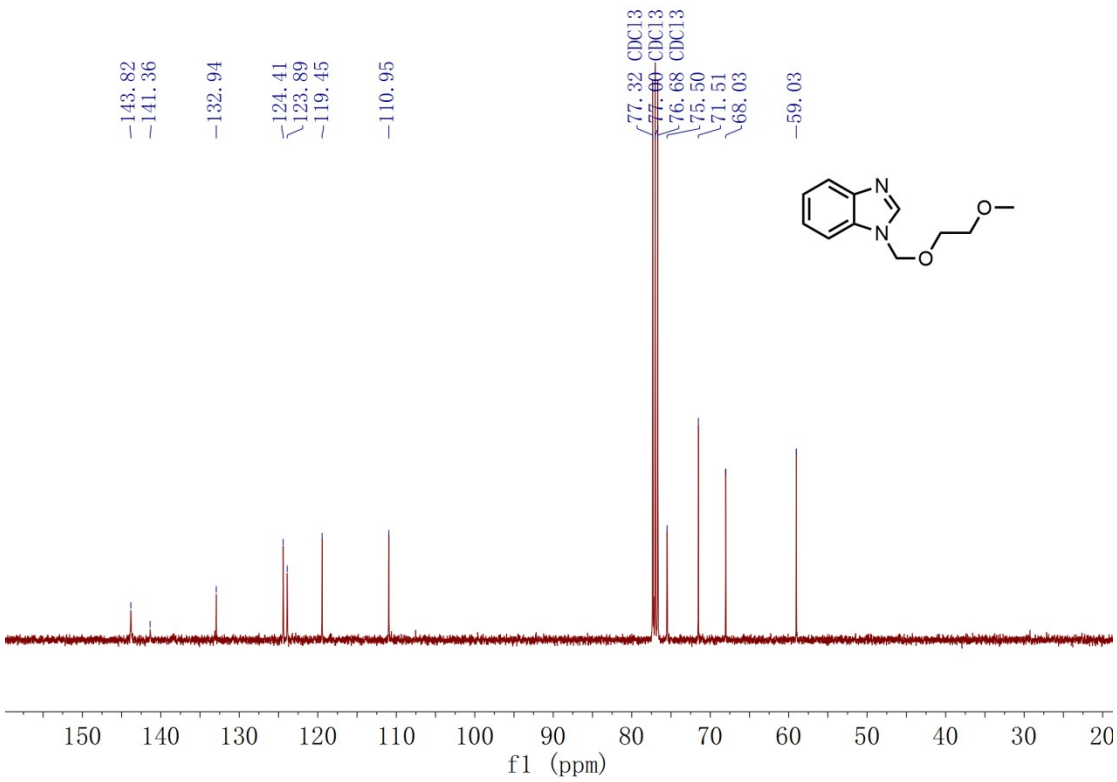
1-(benzo[d][1,3]dioxol-2-yl)-1*H*-benzo[d]imidazole(4d)



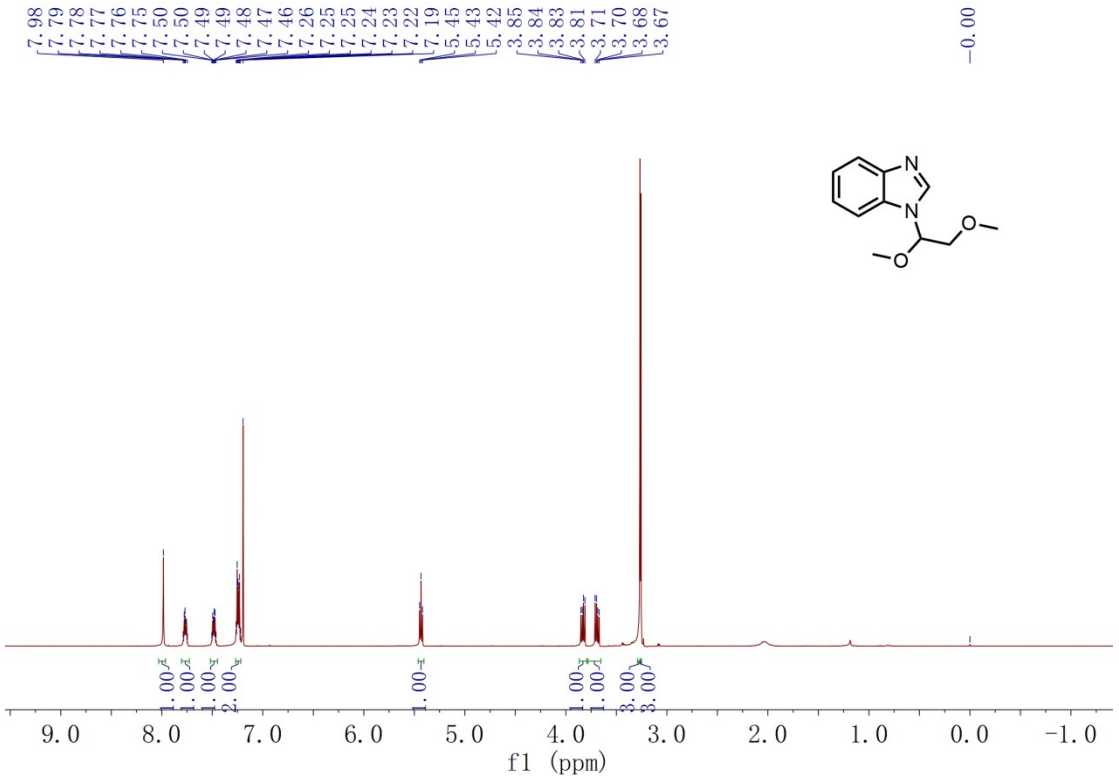


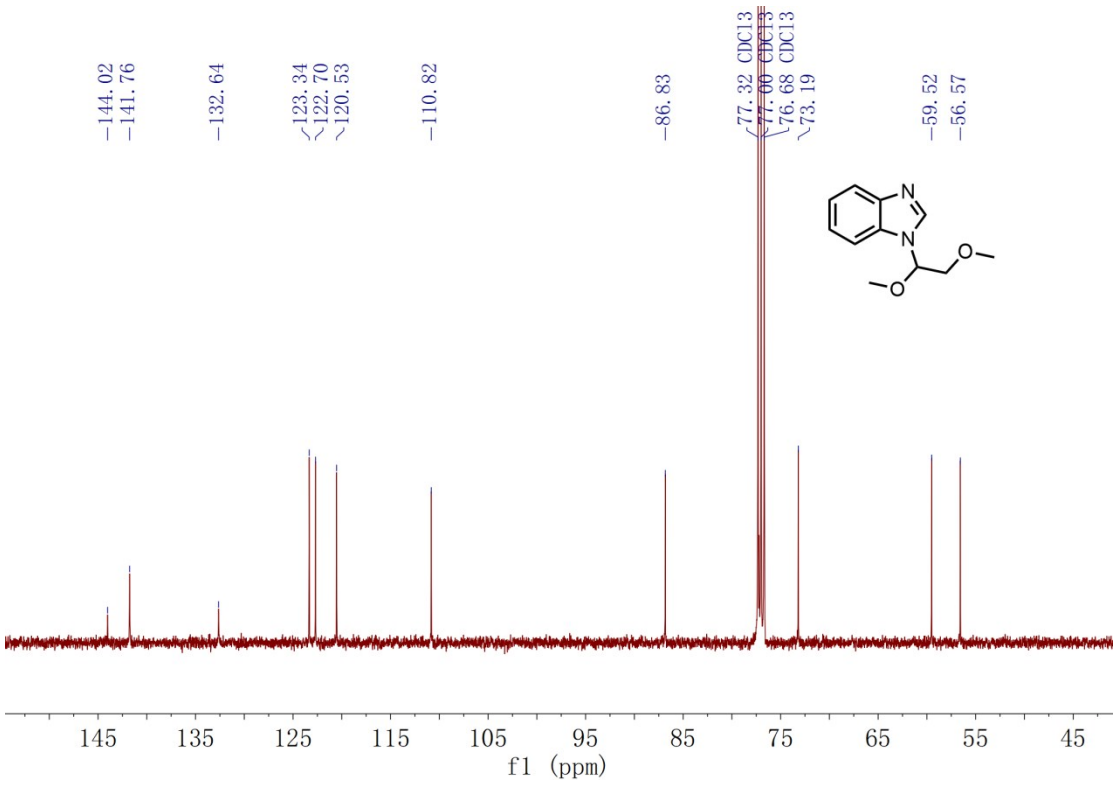
1-((2-methoxyethoxy)methyl)-1*H*-benzo[d]imidazole(4e)



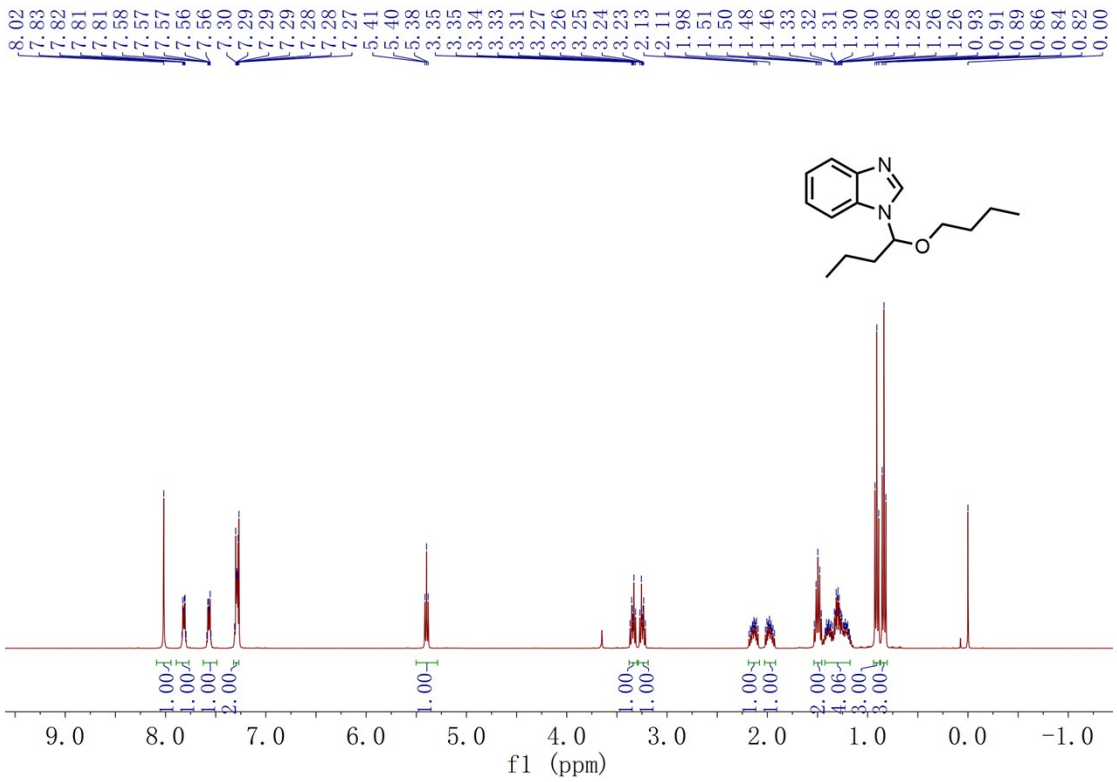


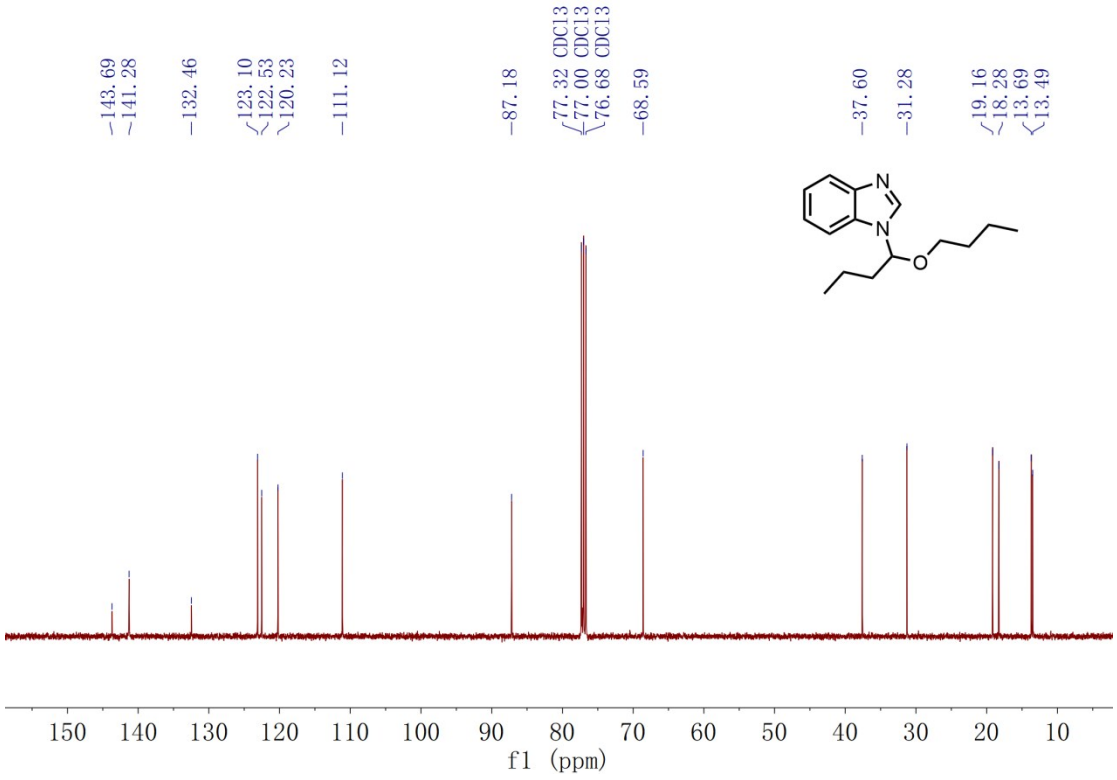
1-(1,2-dimethoxyethyl)-1*H*-benzo[d]imidazole(4e')



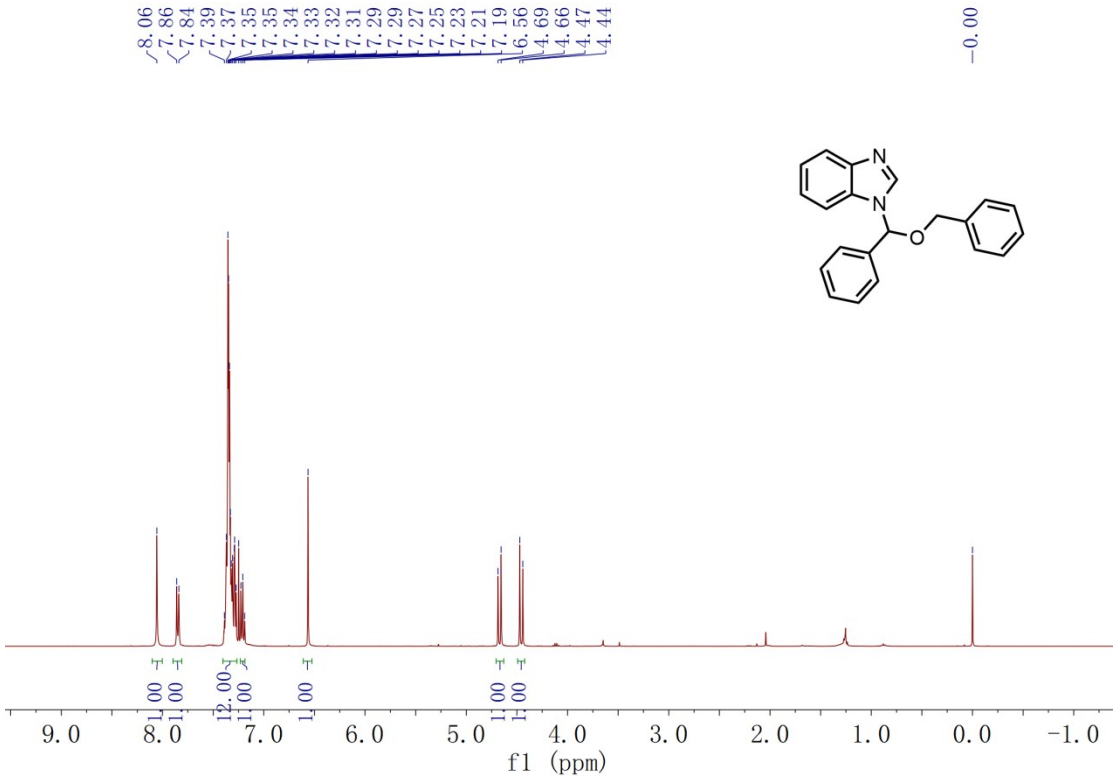


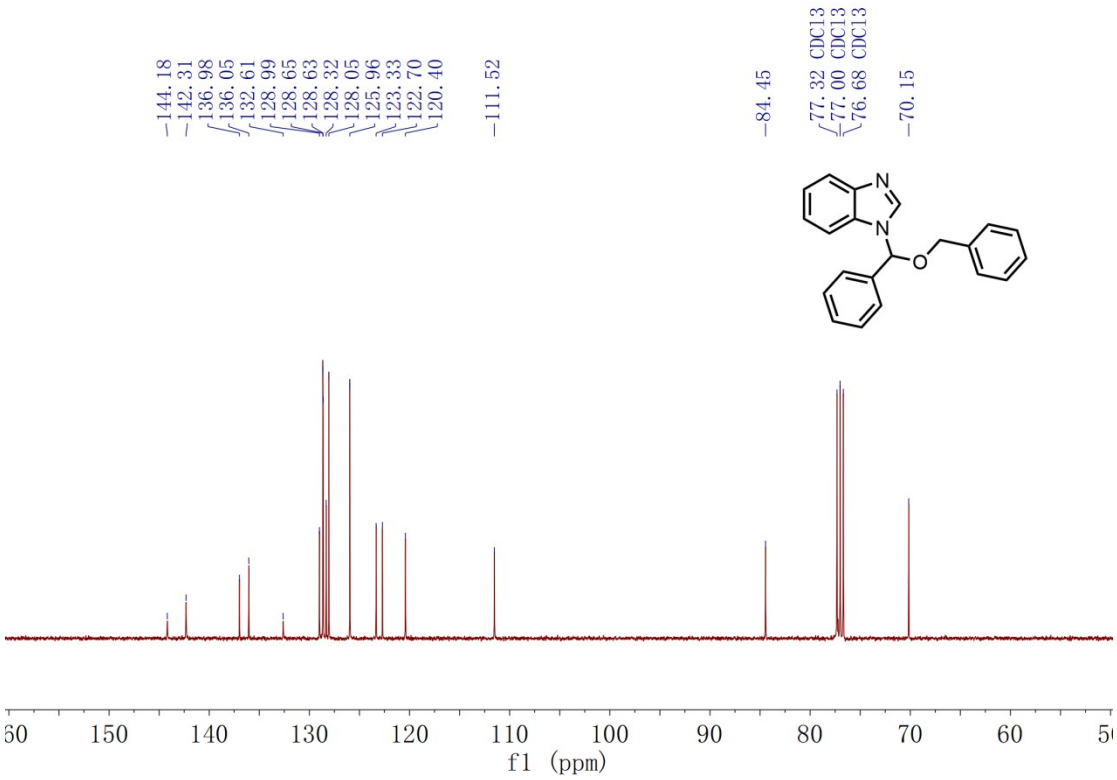
1-(1-butoxybutyl)-1*H*-benzo[d]imidazole(4f)



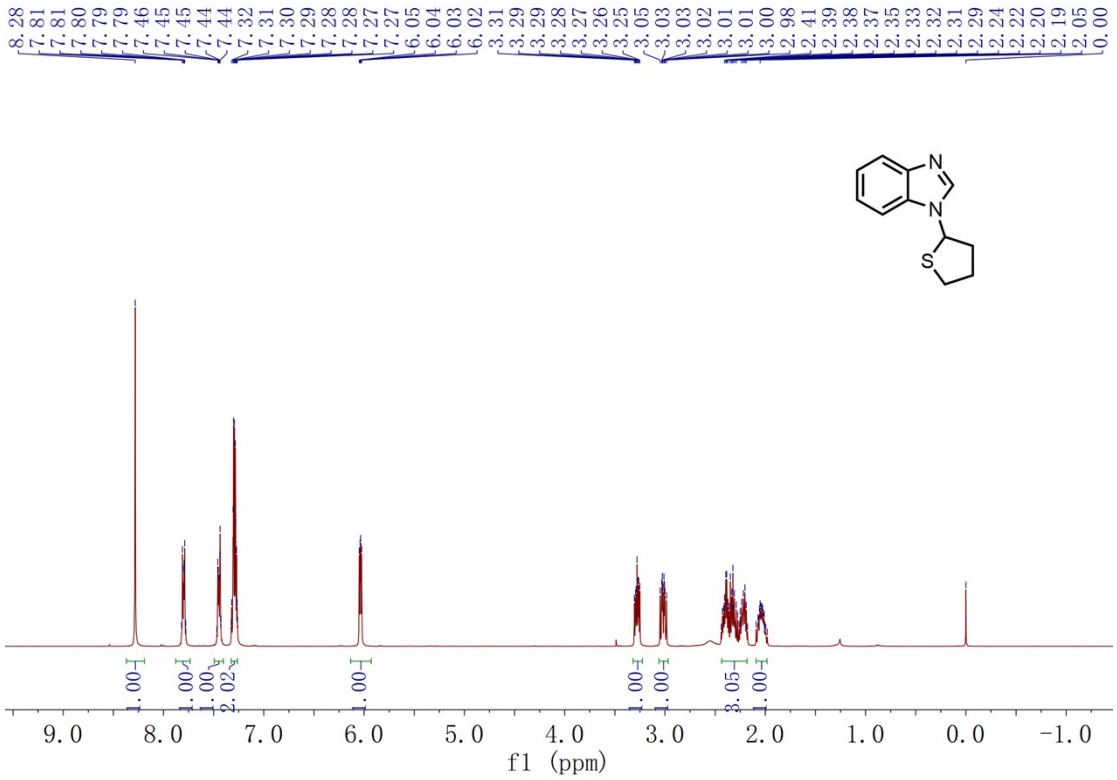


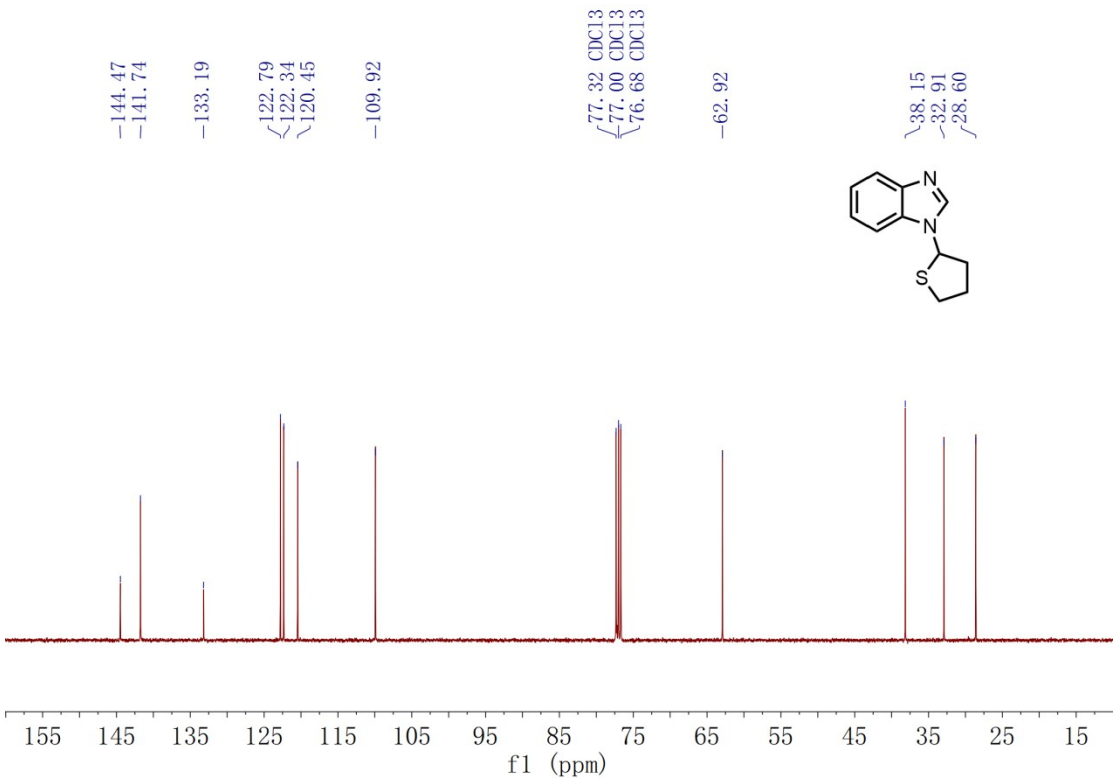
1-((benzyloxy)(phenyl)methyl)-1*H*-benzo[d]imidazole(4g)





1-(tetrahydrothiophen-2-yl)-1*H*-benzo[d]imidazole(4h)





1-(phenoxymethyl)-1*H*-benzo[d]imidazole (4i)