

A Novel Route to Unsymmetrical Disubstituted Ureas and Thioureas by Lewis Base Catalyzed Reductive Alkylation with Trichlorosilane

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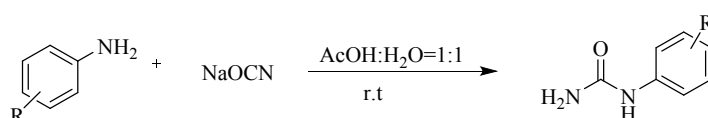
#These authors contributed equally to this work and should be considered co-first authors.

1. General remarks

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Solvents were dried and purified according to the standard procedures before use. Reactions were monitored by TLC. Flash column chromatography was performed on silica gels (200-300 mesh). ¹H NMR and ¹³C NMR (300 or 400 and 75 or 100 MHz, respectively) spectra were recorded on a Bruker 300 MHz or 400 MHz NMR spectrometer in CDCl₃ or DMSO. ¹H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (CDCl₃, δ 7.26 ppm, DMSO-*d*₆ at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, td = triplet of doublets, q = quartet, m = multiplet), coupling constants (Hz) and integration. ¹³C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CDCl₃, δ 77.0 ppm, DMSO – *d*₆ at 39.51 ppm). HRMS data were obtained on X500R QTOFB. Melting points were recorded on Melting Point WRS-2.

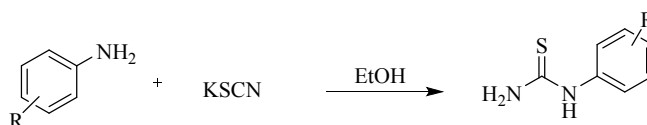
2. Procedures and characterizations data of compounds.

2.1 General chemical method of synthesis the compounds of monosubstituted ureas



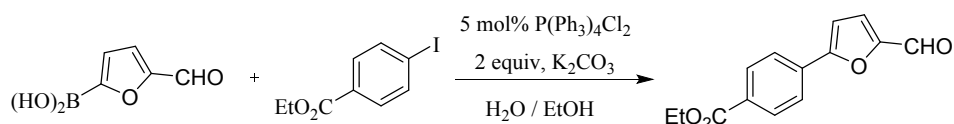
To a stirring solution of substituted amine (10 mmol) in 30 mL solvent (AcOH : H₂O = 1 : 1), sodium cyanate (22 mmol) was added. The reaction mixture was kept stirring at room temperature until full conversion was detected by TLC. The solution was neutralized with Na₂CO₃. The crude product was obtained by simple filtration and purified by silica-gel chromatography with ethyl acetate/petroleum ether.^[1]

2.2 A general chemical method of synthesis the compounds of monosubstituted thioureas



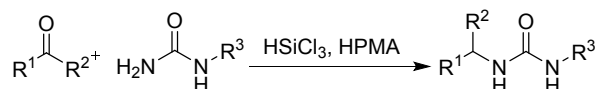
To a stirring solution of substituted amine (5 mmol) in 20 mL EtOH, potassium thiocyanate (7.5 mmol) was added. The reaction mixture was refluxed at 80°C until full conversion was detected by TLC. The reaction mixture was concentrated under reduced pressure. The crude products was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product.^[2]

2.3 Synthesis the compound of ethyl 4-(5-formylfuran-2-yl)benzoate



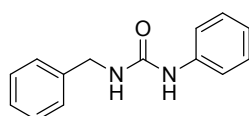
The (5-formylfuran-2-yl) boronic acid (10 mmol, 1.39 g) and ethyl 4-iodobenzoate (11 mmol, 3.04g) were dissolved in 40 mL solvent (EtOH : H₂O = 3 : 1) at round bottom flask. The (PPh₃)₄PdCl₂ (0.5 mmol, 578mg) and K₂CO₃ (2 mmol, 2.76 g) were added to the mixture. Then the mixture was refluxed at 80 °C under argon atmosphere for 5h, monitored by TLC. Then the solids was filtered out, and the mixture was extracted by EtOAc (3 × 30 mL). Then the combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product (6.17mmol, 1.51 g).^[2]

2.4 A general chemical method of synthesis the compounds of disubstituted ureas

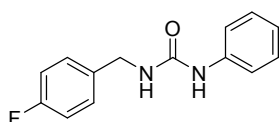


To a stirring solution of aldehyde or ketone (0.24 mmol) and urea (0.2 mmol) in 2 mL DCM, HMPA (0.01 mmol) was added. The solution was stirred at 0 °C for 10 min, and then the HSiCl₃ (0.3 mmol) was added to the mixture and stirred for 12 h. The solution was neutralized with NaHCO₃. The mixture was extracted by EtOAc (3 × 5 mL) and the combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product.

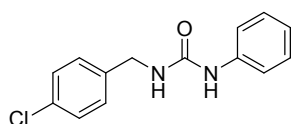
2.5 The characterizations data of disubstituted ureas



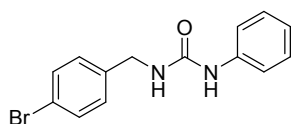
Benzyl-3-phenylurea (P1) : white solid, yield: 98 %. ¹H NMR (400 MHz, DMSO – *d*₆) δ 8.56 (s, 1H), 7.45–7.38 (m, 2H), 7.38–7.29 (m, 4H), 7.24 (m, *J* = 8.4, 7.2, 1.8 Hz, 3H), 6.96– 6.84 (m, 1H), 6.62 (t, *J* = 6.0 Hz, 1H), 4.31 (d, *J* = 5.9 Hz, 2H). HRMS (ESI) Calcd for [C₁₄H₁₄N₂O + H] + 227.1179; Found: 227.1171. M.p: 118.5– 119.1 °C.



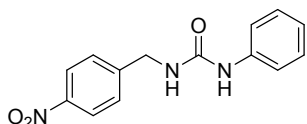
(4-fluorobenzyl)-3-phenylurea (P2): white solid, yield: 83 %. ¹H NMR (400 MHz, DMSO – *d*₆) δ 8.57 (s, 1H), 7.41 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.27 – 7.11 (m, 4H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.63 (t, *J* = 6.0 Hz, 1H), 4.28 (d, *J* = 5.9 Hz, 2H). HRMS (ESI) Calcd for [C₁₄H₁₃FN₂O + H] + 245.1085; Found: 245.1080. M.p: 158.9 - 160.2 °C.



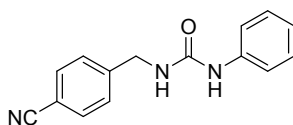
1-(4-chlorobenzyl)-3-phenylurea (P3): white solid, yield: 94 %. ¹H NMR (400 MHz, DMSO – *d*₆) δ 8.60 (s, 1H), 7.41 (dd, *J* = 8.6, 2.1 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.19 (m, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.66 (t, *J* = 6.0 Hz, 1H), 4.29 (d, *J* = 6.0 Hz, 2H). HRMS (ESI) Calcd for [C₁₄H₁₃ClN₂O + H] + 261.0784; Found: 261.0786. M.p: 139.8-139.9 °C.



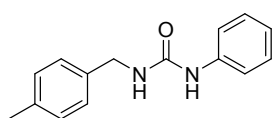
1-(4-bromobenzyl)-3-phenylurea (P4): white solid, yield: 81 %. ^1H NMR (400 MHz, DMSO – d_6) δ 8.62 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.32 – 7.19 (m, 4H), 6.90 (t, J = 7.2 Hz, 1H), 6.67 (t, J = 5.8 Hz, 1H), 4.27 (d, J = 6.0 Hz, 2H). HRMS (ESI) Calcd for $[\text{C}_{14}\text{H}_{13}\text{BrN}_2\text{O} + \text{H}] + 305.0284$; Found: 305.0281. M.p: 181.1-182.3 °C.



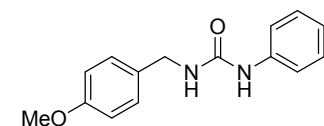
1-(4-nitrobenzyl)-3-phenylurea (P5): white solid, yield: 89 %. ^1H NMR (400 MHz, DMSO – d_6) δ 8.73 (s, 1H), 8.23 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.80 (t, J = 6.0 Hz, 1H), 4.44 (d, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 155.76, 149.38, 146.81, 140.80, 129.13, 128.45, 123.97, 121.72, 118.28, 42.81. HRMS (ESI) Calcd for $[\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3 + \text{H}] + 272.1030$; Found: 272.1025. M.p: 198.8 – 199.5 °C.



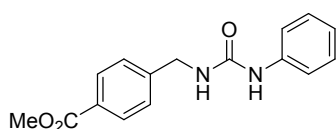
1-(4-cyanobenzyl)-3-phenylurea (P6): white solid, yield: 78%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.68 (s, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.45 (dd, J = 35.0, 7.4 Hz, 4H), 7.23 (d, J = 7.1 Hz, 2H), 7.02 – 6.62 (m, 2H), 4.38 (d, J = 5.1 Hz, 2H). M.p: 137.1-137.9 °C.



1-(4-methylbenzyl)-3-phenylurea (P7): white solid, yield: 82%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.53 (s, 1H), 7.44 – 7.37 (m, 2H), 7.2 – 7.10 (m, 6H), 6.90 (t, J = 7.3 Hz, 1H), 6.55 (t, J = 5.9 Hz, 1H), 4.25 (d, J = 5.9 Hz, 2H), 2.29 (s, 3H). HRMS (ESI) Calcd for $[\text{C}_{15}\text{H}_{16}\text{N}_2\text{O} + \text{H}] + 241.1335$; Found: 241.1334. M.p: 183.5-184.8 °C.

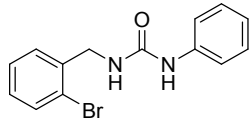


1-(4-methoxybenzyl)-3-phenylurea (P8): white solid, yield: 93%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.50 (s, 1H), 7.40 (dd, J = 8.6, 1.0 Hz, 2H), 7.30 – 7.17 (m, 4H), 7.01 – 6.75 (m, 3H), 6.52 (t, J = 5.8 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 3.74 (s, 3H). HRMS (ESI) Calcd for $[\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2 + \text{H}] + 257.1285$; Found: 257.1281. M.p: 158.3-158.6 °C.

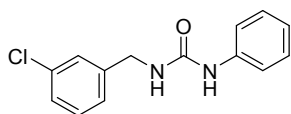


Methyl-4-((3-phenylureido)methyl)benzo-ate (P9): white solid, yield: 87%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.66 (s, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.43 (dd, J = 13.8, 8.2 Hz, 4H), 7.23 (t, J

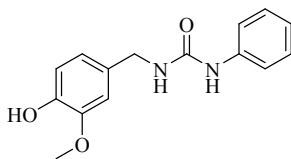
= 7.8 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.73 (t, J = 6.0 Hz, 1H), 4.39 (d, J = 6.0 Hz, 2H), 3.85 (s, 3H). HRMS (ESI) Calcd for $[C_{16}H_{16}N_2O_3 + H]^+$ + 285.1234; Found: 285.1229. M.p: 175.4-176.6 °C.



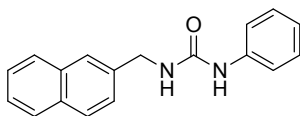
1-(2-bromobenzyl)-3-phenylurea (P10): white solid, yield: 77 %. 1H NMR (400 MHz, DMSO- d_6) δ 8.72 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.48 – 7.34 (m, 4H), 7.28 – 7.18 (m, 3H), 6.91 (t, J = 7.3 Hz, 1H), 6.68 (t, J = 5.9 Hz, 1H), 4.34 (d, J = 6.0 Hz, 2H). HRMS (ESI) Calcd for $[C_{14}H_{13}BrN_2O + H]^+$ + 305.0287; Found: 305.0285. M.p: 172.5-173 °C.



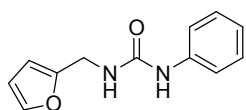
1-(3-chlorobenzyl)-3-phenylurea (P11): white solid, yield: 85 %. 1H NMR (400 MHz, DMSO- d_6) δ 8.63 (s, 1H), 7.39 (dd, J = 17.9, 7.6 Hz, 4H), 7.27 (m, J = 22.4, 8.3 Hz, 4H), 6.91 (t, J = 7.3 Hz, 1H), 6.70 (t, J = 5.9 Hz, 1H), 4.31 (d, J = 6.0 Hz, 2H). HRMS (ESI) Calcd for $[C_{14}H_{13}ClN_2O + H]^+$ + 261.0789; Found: 261.0788. M.p: 158.1-158.8 °C.



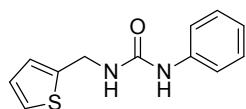
1-(4-hydroxy-3-methoxybenzyl)-3-phenylurea (P12) : white solid, Yield: 83%. 1H NMR (400 MHz, DMSO- d_6) δ 8.86 (s, 1H), 8.48 (s, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.22 (t, J = 7.9 Hz, 2H), 6.89 (dd, J = 8.3, 4.2 Hz, 2H), 6.75 – 6.70 (m, 2H), 6.46 (t, J = 5.7 Hz, 1H), 4.18 (d, J = 5.7 Hz, 2H), 3.75 (s, 3H), 3.37 (s, 1H). M.p: 262.3-262.5 °C.



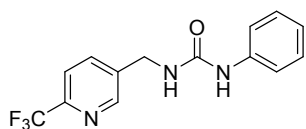
1-(naphthalen-2-ylmethyl)-3-phenylurea (P13): white solid, yield: 90%. 1H NMR (400 MHz, DMSO- d_6) δ 8.63 (s, 1H), 7.90 (d, J = 8.6 Hz, 3H), 7.80 (s, 1H), 7.54 – 7.36 (m, 5H), 7.24 (t, J = 7.8 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.74 (t, J = 5.8 Hz, 1H), 4.49 (d, J = 5.8 Hz, 2H). HRMS (ESI) Calcd for $[C_{18}H_{16}N_2O + H]^+$ + 277.1335; Found: 277.1331. M.p: 181.0 – 181.3 °C.



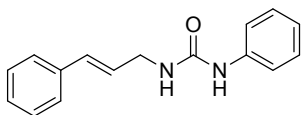
1-(furan-2-yl-methyl)-3-phenylurea (P14): white solid, yield: 88%. 1H NMR (400 MHz, DMSO- d_6) δ 8.52 (s, 1H), 7.60 (s, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.54 (t, J = 5.6 Hz, 1H), 6.41 (dd, J = 2.8, 1.9 Hz, 1H), 6.27 (d, J = 3.0 Hz, 1H), 4.29 (d, J = 5.8 Hz, 2H). HRMS (ESI) Calcd for $[C_{12}H_{12}N_2OS + H]^+$ + 233.0743; Found: 233.0739. M.p: 114.2-114.9 °C.



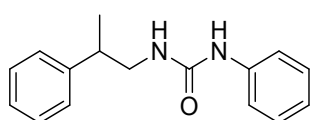
1-phenyl-3-(thiophen-2-ylmethyl)urea (P15): white solid, yield: 85%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.56 (s, 1H), 7.52 – 7.33 (m, 3H), 7.23 (t, J = 7.9 Hz, 2H), 7.04 – 6.95 (m, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.66 (t, J = 5.9 Hz, 1H), 4.47 (d, J = 5.9 Hz, 2H). HRMS (ESI) Calcd for $[\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS} + \text{H}]^+$ + 233.0743; Found: 233.0739. M.p: 166.3-167.4 °C.



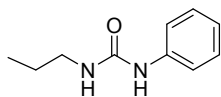
1-phenyl-3-((6-(trifluoromethyl)pyridin-3-yl)methyl)urea (P16): white solide, yield: 78%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 8.62 (s, 1H), 7.82 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.31 (dd, J = 13.4, 6.2 Hz, 3H), 7.12 (t, J = 7.1 Hz, 1H), 6.86 (s, 1H), 5.52 (t, J = 5.7 Hz, 1H), 4.47 (d, J = 5.9 Hz, 2H).



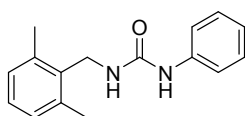
Cinnamyl-3-phenylurea (P17): white solid, yield: 88%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.54 (s, 1H), 7.43 (t, J = 7.4 Hz, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 – 7.19 (m, 3H), 6.90 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.45 – 6.22 (m, 2H), 3.91 (t, J = 6.2 Hz, 2H). HRMS (ESI) Calcd for $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O} + \text{H}]^+$ + 253.1335; Found: 253.1332. M.p: 134.8-135.9 °C.



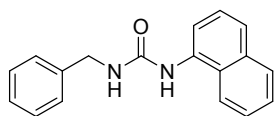
1-phenyl-3-(2-phenylpropyl)urea (P18): white solid, yied: 54%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.43 (s, 1H), 7.42 – 7.30 (m, 4H), 7.30 – 7.16 (m, 5H), 6.88 (t, J = 7.2 Hz, 1H), 6.03 (t, J = 5.8 Hz, 1H), 3.34 – 3.21 (m, 2H), 2.89 (q, J = 7.2 Hz, 1H), 1.21 (d, J = 7.0 Hz, 3H). HRMS (ESI) Calcd for $[\text{C}_{16}\text{H}_{18}\text{N}_2\text{O} + \text{H}]^+$ + 255.1492; Found: 255.1488. M.p: 118.1-118.5 °C.



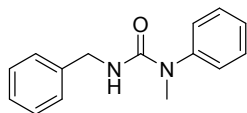
1-phenyl-3-propylurea (P19): white solid, yield: 68%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.39 (s, 1H), 7.38 (dd, J = 8.6, 1.0 Hz, 2H), 7.28 – 7.15 (m, 2H), 6.88 (t, J = 7.2 Hz, 1H), 6.13 (t, J = 5.8 Hz, 1H), 3.04 (q, J = 6.8 Hz, 2H), 1.44 (q, J = 7.2 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H). HRMS (ESI) Calcd for $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O} + \text{H}]^+$ + 253.1335; Found: 253.1332. M.p: 112.7-113.7 °C.



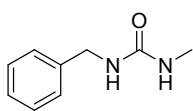
1-(2,6-dimethylbenzyl)-3-phenylurea(P20): white solid, yield: 67%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.25 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.22 (t, J = 7.7 Hz, 2H), 7.13 – 7.00 (m, 3H), 6.89 (t, J = 7.3 Hz, 1H), 6.23 (t, J = 4.9 Hz, 1H), 4.30 (d, J = 4.9 Hz, 2H), 2.37 (s, 6H). M.p: 139.8-140.6 °C.



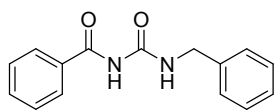
1-benzyl-3-(naphthalen-1-yl)urea (P21): white solid, yield: 81%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.65 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.93 (dd, J = 21.0, 7.6 Hz, 2H), 7.59 – 7.50 (m, 4H), 7.43 (t, J = 7.9 Hz, 1H), 7.37 (d, J = 4.2 Hz, 4H), 7.28 (dd, J = 8.2, 4.0 Hz, 1H), 7.07 (t, J = 5.4 Hz, 1H), 4.38 (d, J = 5.7 Hz, 2H). M.p: 195.9-196.1 °C.



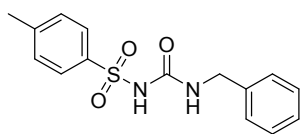
3-benzyl-1-methyl-1-phenylurea (P22): colorless oil, yield: 91%. ^1H NMR (400 MHz, DMSO – d_6) δ 7.39 (t, J = 7.8 Hz, 2H), 7.32 – 7.17 (m, 8H), 6.54 (t, J = 5.8 Hz, 1H), 4.21 (d, J = 6.0 Hz, 2H), 3.17 (s, 3H).



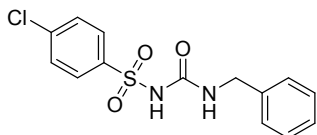
1-benzyl-3-methylurea (P23): white solid, yield: 87%. ^1H NMR (400 MHz, CDCl_3 – d_3) δ 7.34 – 7.31 (m, 1H), 7.29 (d, J = 5.1 Hz, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 4.83 (s, 1H), 4.49 (s, 1H), 4.35 (d, J = 5.8 Hz, 2H), 2.75 (d, J = 4.9 Hz, 3H). M.p 93.1-94.0 °C.



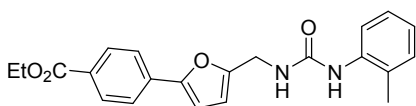
N-(benzylcarbamoyl)benzamide (P24): white solid, yield: 80%. ^1H NMR (400 MHz, DMSO – d_6) δ 10.78 (s, 1H), 9.08 (t, J = 5.8 Hz, 1H), 7.96 (t, J = 8.9 Hz, 3H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (td, J = 7.7, 1.9 Hz, 3H), 7.36 – 7.34 (m, 3H), 4.46 (d, J = 6.0 Hz, 2H). M.p: 172.1-172.8 °C.



N-(benzylcarbamoyl)-4-methylbenzenesulfonamide (P25): white solid, yield, 75%. ^1H NMR (400 MHz, DMSO – d_6) δ 7.79 (d, J = 8.3 Hz, 2H), 7.42 (dd, J = 13.6, 4.6 Hz, 3H), 7.30 – 7.19 (m, 3H), 7.12 (d, J = 6.9 Hz, 2H), 7.00 (t, J = 5.8 Hz, 1H), 4.16 (t, J = 6.2 Hz, 2H), 2.40 (s, 3H). M.p: 176.2-176.7 °C.

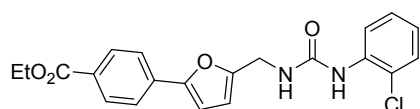


N-(benzylcarbamoyl)-4-chlorobenzenesulfonamide (P26): white solid, yield: 75%. ^1H NMR (400 MHz, DMSO – d_6) δ 10.91 (s, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.25 (dq, J = 14.3, 7.1 Hz, 3H), 7.12 (dd, J = 16.8, 6.5 Hz, 3H), 4.16 (d, J = 5.9 Hz, 2H). M.p: 165.3-165.5 °C.



Ethyl-4-(5-((3-(o-tolyl)ureido)methyl)furan-2-yl)benzoate (P27): beige solid, yield: 78%. ^1H NMR (400

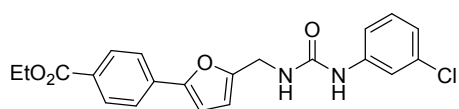
MHz, DMSO – d_6) δ 8.02 (s, 1H), 8.00 (s, 1H), 7.88 – 7.80 (m, 3H), 7.77 (s, 1H), 7.09 (m, J = 22.8, 10.6, 6.5 Hz, 4H), 6.90 (t, J = 7.4 Hz, 1H), 6.48 (d, J = 3.3 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.84, 155.62, 155.11, 152.83, 151.53, 138.45, 134.78, 130.57, 130.34, 128.56, 127.43, 126.57, 123.57, 122.61, 121.09, 109.84, 109.81, 61.20, 55.39, 36.90, 18.35, 14.68. HRMS (ESI) Calcd for $[\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4 + \text{H}]^+$ + 379.1652; Found: 379.1652. M.p: 176.3-177.5 °C.



Ethyl-4-(5-((3-(2-chlorophenyl)ureido)methyl) furan-2-

yl)benzoate (P28): white solid, yield: 78%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.33 – 8.10 (m, 2H), 8.00 (d, J = 8.6

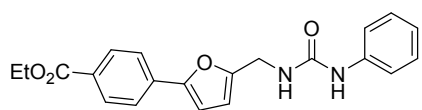
Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 5.6 Hz, 1H), 7.41 (dd, J = 8.0, 1.4 Hz, 1H), 7.37 – 7.21 (m, 1H), 7.12 (d, J = 3.4 Hz, 1H), 6.98 (td, J = 7.8, 1.6 Hz, 1H), 6.50 (d, J = 3.4 Hz, 1H), 4.43 (d, J = 5.6 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 155.06, 154.59, 151.65, 136.99, 134.74, 130.33, 129.57, 128.60, 127.95, 123.59, 123.18, 121.83, 121.37, 110.02, 109.75, 61.19, 36.85, 14.67. HRMS (ESI) Calcd for $[\text{C}_{21}\text{H}_{18}\text{ClN}_2\text{O}_4 + \text{H}]^+$ + 399.1106; Found: 399.1104. M.p: 184.4-185.4 °C.



Ethyl-4-(5-((3-(3-chlorophenyl)ureido)methyl) furan-2-

yl)benzoate (P29): yellow solid, yield: 87%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.83 (s, 1H), 8.00 (d, J = 8.4

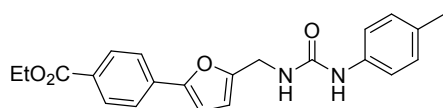
Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.70 (t, J = 1.8 Hz, 1H), 7.36 – 7.15 (m, 2H), 7.10 (d, J = 3.2 Hz, 1H), 6.95 (m, J = 35.6, 18.6, 16.8 Hz, 1H), 6.78 (dd, J = 14.6, 8.8 Hz, 1H), 6.46 (d, J = 3.4 Hz, 1H), 4.40 (d, J = 5.8 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 155.23, 154.91, 151.48, 142.33, 134.77, 133.60, 130.74, 130.33, 128.54, 123.54, 121.32, 119.73, 117.60, 116.62, 109.76, 61.18, 36.88, 14.67. HRMS (ESI) Calcd for $[\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4 + \text{H}]^+$ + 399.1106; Found: 399.1105. M.p: 181.4-182.1 °C.



Methyl-4-(5-((3-phenylureido)methyl)furan-2-

yl)benzoate (P30): light green solid, yield: 70%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.60 (s, 1H), 8.00 (d, J = 8.5 Hz,

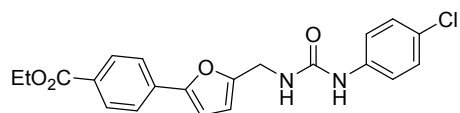
2H), 7.82 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.9 Hz, 2H), 7.11 (d, J = 3.3 Hz, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.67 (t, J = 5.7 Hz, 1H), 6.45 (d, J = 3.3 Hz, 1H), 4.39 (d, J = 5.7 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). HRMS (ESI) Calcd for $[\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4 + \text{H}]^+$ + 365.1496; Found: 365.1498. M.p: 188.2-189.0 °C.



Ethyl-4-(5-((3-(p-tolyl)ureido)methyl)furan-2-

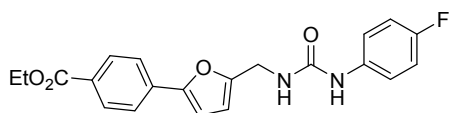
yl)benzoate (P31): white solid, yield: 79%. ^1H NMR (400MHz, DMSO – d_6) δ 8.47 (s, 1H), 8.08 – 7.94 (m,

2H), 7.80 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 3.4$ Hz, 1H), 7.04 (d, $J = 8.2$ Hz, 2H), 6.61 (t, $J = 5.6$ Hz, 1H), 6.45 (d, $J = 3.4$ Hz, 1H), 4.42 – 4.34 (m, 2H), 4.32 (q, $J = 7.0$ Hz, 2H), 2.22 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 4H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.84, 155.50, 155.19, 151.44, 138.20, 134.79, 130.39, 129.54, 128.52, 123.53, 118.35, 109.73, 61.18, 36.87, 20.77, 14.67. HRMS (ESI) Calcd for $[\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4 + \text{H}]^+$ 379.1652; Found: 379.1652. M.p: 167.3- 168.2 °C.



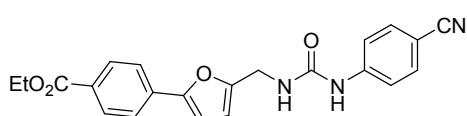
Ethyl-4-(5-((3-(4-chlorophenyl)ureido)methyl)furan-2-yl)benzoate (P32): light solid, yield: 68%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.43 (d, $J = 2.2$ Hz, 1H), 8.21 – 8.05 (m, 1H), 8.03 (t, $J = 16.8$ Hz, 2H), 7.89 – 7.74 (m,

2H), 7.29 – 7.00 (m, 4H), 7.03 – 6.85 (m, 1H), 6.48 (d, $J = 3.2$ Hz, 1H), 4.42 (d, $J = 5.6$ Hz, 2H), 4.33 (q, $J = 7.0$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 155.12, 154.71, 151.60, 134.74, 130.33, 128.58, 124.89, 124.86, 123.57, 122.35, 122.27, 120.78, 115.40, 115.21, 109.86, 109.75, 61.19, 36.85, 14.67. HRMS (ESI) Calcd for $[\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4 + \text{H}]^+$ 399.1106; Found: 399.1105. M.p: 171.3-171.5 °C.



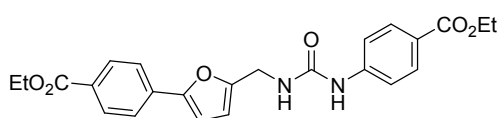
Ethyl-4-(5-((3-(4-fluorophenyl)ureido)methyl)furan-2-yl)benzoate (P33): red solid, yield: 80%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.80 (d, $J = 32.8$ Hz, 1H), 8.00 (d, $J =$

8.4 Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 9.0$ Hz, 2H), 7.09 (d, $J = 3.4$ Hz, 1H), 6.85 – 6.69 (m, 1H), 6.45 (d, $J = 3.2$ Hz, 1H), 4.40 (d, $J = 5.6$ Hz, 2H), 4.33 (q, $J = 7.0$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 155.30, 154.98, 151.48, 139.78, 134.76, 130.32, 128.97, 128.54, 125.20, 123.53, 119.73, 109.75, 61.18, 36.88, 14.67. M.p: 183.8-184.6 °C.



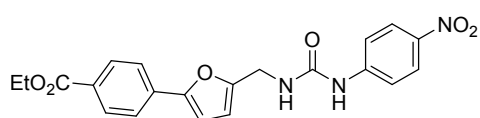
Ethyl-4-(5-((3-(4-cyanophenyl)ureido)methyl)furan-2-yl)benzoate (P34): faint yellow solid, yield: 77%.

^1H NMR (400 MHz, DMSO – d_6) δ 8.75 (s, 1H), 8.00 (d, $J = 8.6$ Hz, 2H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.48 – 7.42 (m, 2H), 7.31 – 7.25 (m, 2H), 7.10 (d, $J = 3.4$ Hz, 1H), 6.73 (t, $J = 5.8$ Hz, 1H), 6.45 (d, $J = 3.2$ Hz, 1H), 4.39 (d, $J = 5.6$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 155.30, 154.98, 139.78, 134.77, 130.32, 128.97, 128.54, 126.20, 123.53, 119.73, 109.75, 61.18, 36.88, 14.67. M.p: 172.8-173.5 °C.



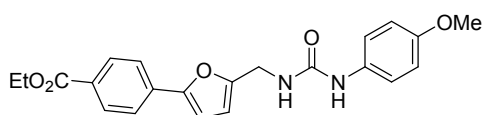
Ethyl-4-3-((5-(4-(ethoxycarbonyl)phenyl)furan-2-yl)methyl)ureido)benzoate (P35): yellow solid, yield: 85%. ^1H NMR (400 MHz, DMSO – d_6) δ 9.04 (s, 1H),

8.02 – 7.96 (m, 2H), 7.87 – 7.78 (m, 4H), 7.57 – 7.51 (m, 2H), 7.10 (d, $J = 3.3$ Hz, 1H), 6.84 (t, $J = 5.7$ Hz, 1H), 6.46 (d, $J = 3.4$ Hz, 1H), 4.41 (d, $J = 5.7$ Hz, 2H), 4.29 (dq, $J = 22.1, 7.1$ Hz, 4H), 1.32 (dt, $J = 11.9, 7.1$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.94, 165.83, 155.02, 154.80, 151.52, 145.37, 134.75, 130.79, 130.32, 128.55, 123.54, 122.66, 117.32, 109.99, 109.75, 61.18, 60.67, 36.88, 14.72, 14.66. HRMS (ESI) Calcd for $[\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_6 + \text{H}]^+$ + 437.1707; Found: 437.1709. M.p: 171.8-172.5 °C.



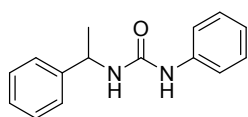
Ethyl-4-(5-((3-(4-nitrophenyl)ureido)methyl)furan-2-yl)benzoate (P36): beige power, yield: 89%.

^1H NMR (400 MHz, DMSO – d_6) δ 9.45 (s, 1H), 8.16 (d, $J = 9.2$ Hz, 2H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.66 (d, $J = 9.2$ Hz, 2H), 7.17 – 6.97 (m, 2H), 6.48 (d, $J = 3.4$ Hz, 1H), 4.43 (d, $J = 5.6$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 165.83, 154.77, 154.56, 151.56, 147.44, 141.07, 134.74, 130.33, 128.57, 125.61, 123.56, 117.48, 109.99, 109.76, 61.19, 36.93, 14.67. M.p: 211.3-212.3 °C.

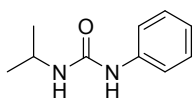


Ethyl-4-(5-((3-(4-methoxyphenyl)ureido)-methyl)furan-2-yl)benzoate (P37): yellow solid, yield: 80%.

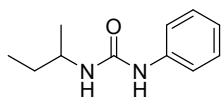
^1H NMR (400 MHz, DMSO – d_6) δ 8.37 (s, 1H), 7.99 (d, $J = 8.6$ Hz, 2H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.30 (t, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 3.3$ Hz, 1H), 6.83 (d, $J = 9.0$ Hz, 2H), 6.55 (t, $J = 5.7$ Hz, 1H), 6.43 (d, $J = 3.4$ Hz, 1H), 4.38 – 4.35 (m, 2H), 4.31 (t, $J = 7.1$ Hz, 2H), 3.70 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H). M.p: 193.1-194.0 °C.



1-phenyl-3-(1-phenylethyl)urea (P38): white solid, yield 30%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.36 (s, 1H), 7.35 (t, $J = 6.5$ Hz, 6H), 7.27 – 7.17 (m, 3H), 6.88 (t, $J = 7.3$ Hz, 1H), 6.60 (d, $J = 7.8$ Hz, 1H), 4.82 (p, $J = 7.0$ Hz, 1H), 1.39 (d, $J = 6.9$ Hz, 3H). M.p: 130.3-131.4 °C.

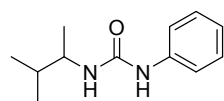


1-isopropyl-3-phenylurea (P39): White solid, Yield: 53%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.25 (s, 1H), 7.36 (d, $J = 7.9$ Hz, 2H), 7.20 (t, $J = 7.8$ Hz, 2H), 6.87 (t, $J = 7.3$ Hz, 1H), 5.97 (d, $J = 7.4$ Hz, 1H), 3.74 (dd, $J = 13.4, 6.7$ Hz, 1H), 1.09 (d, $J = 6.5$ Hz, 6H). M.p: 151.9-152.8 °C.

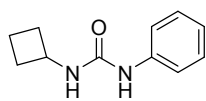


1-(sec-butyl)-3-phenylurea (P40): white solide, yield: 73%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.32 (d, $J = 5.9$ Hz, 3H), 7.09 (dd, $J = 7.3, 4.7$ Hz, 1H),

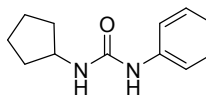
6.56 (s, 1H), 4.72 (s, 1H), 3.84 (dd, $J = 13.1, 6.5$ Hz, 1H), 1.65 (s, 1H), 1.48 (m, $J = 7.3$ Hz, 2H), 1.16 (d, $J = 6.5$ Hz, 3H), 0.94 (t, $J = 7.4$ Hz, 3H).



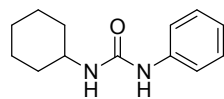
1-(3-methylbutan-2-yl)-3-phenylurea (P41): white solide, yield: 68%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.31 (dd, $J = 5.4, 4.2$ Hz, 3H), 7.06 (dd, $J = 9.3, 4.2$ Hz, 2H), 5.12 (d, $J = 7.7$ Hz, 1H), 3.77 (dd, $J = 13.1, 6.6$ Hz, 1H), 1.77 (s, 1H), 1.70 (dd, $J = 12.8, 6.6$ Hz, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 6H).



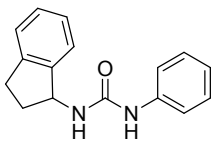
1-cyclobutyl-3-phenylurea (P42): colorless oil, yield: 82%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 8.28 (s, 1H), 7.36 (d, $J = 7.7$ Hz, 2H), 7.20 (t, $J = 7.9$ Hz, 2H), 6.88 (t, $J = 7.3$ Hz, 1H), 6.37 (d, $J = 8.0$ Hz, 1H), 4.12 (dd, $J = 16.3, 8.2$ Hz, 1H), 2.18 (m, $J = 10.2, 5.2, 2.6$ Hz, 2H), 1.89 – 1.77 (m, 2H), 1.66 – 1.56 (m, 2H).



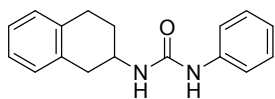
1-cyclopentyl-3-phenylurea (P43): white solid. yield: 81%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 8.23 (s, 1H), 7.36 (d, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.9$ Hz, 2H), 6.87 (t, $J = 7.3$ Hz, 1H), 6.14 (d, $J = 7.1$ Hz, 1H), 3.98 – 3.87 (m, 1H), 1.83 (td, $J = 12.1, 6.7$ Hz, 2H), 1.70 – 1.60 (m, 2H), 1.54 (m, $J = 9.0, 5.8, 2.5$ Hz, 2H), 1.42 – 1.32 (m, 2H). M.p: 195.2-195.5 °C.



1-cyclohexyl-3-phenylurea (P44): White solid. Yield: 88%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 8.28 (s, 1H), 7.43 – 7.28 (m, 2H), 7.21 (t, $J = 7.9$ Hz, 2H), 6.87 (t, $J = 6.9$ Hz, 1H), 6.06 (d, $J = 7.8$ Hz, 1H), 3.47 (td, $J = 14.0, 6.9$ Hz, 1H), 1.86 – 1.74 (m, 2H), 1.72 – 1.59 (m, 2H), 1.54 (dd, $J = 8.4, 4.0$ Hz, 1H), 1.37 – 1.12 (m, 5H). M.p: 167.8-168.1 °C.



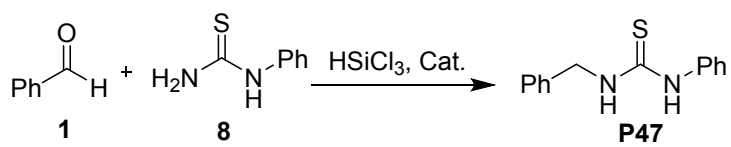
1-(2,3-dihydro-1H-inden-1-yl)-3-phenylurea (P45): white solid, yield: 33%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 8.37 (s, 1H), 7.42 (d, $J = 7.6$ Hz, 2H), 7.31 – 7.20 (m, 6H), 6.91 (t, $J = 7.3$ Hz, 1H), 6.49 (d, $J = 8.1$ Hz, 1H), 5.18 (q, $J = 7.7$ Hz, 1H), 2.93 (ddd, $J = 15.8, 8.7, 3.5$ Hz, 1H), 2.86 – 2.77 (m, 1H), 2.48 – 2.41 (m, 1H), 1.77 (dq, $J = 12.5, 8.5$ Hz, 1H). M.p: 183.2-184.1 °C.



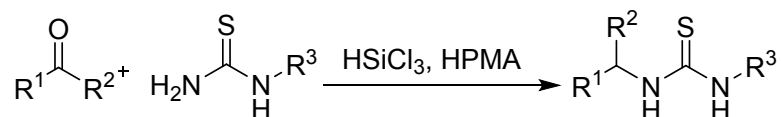
1-phenyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)urea (P46): white solid, yield: 98%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 8.37 (s, 1H), 7.38 (d, $J = 7.7$ Hz, 2H), 7.22 (t, $J = 7.9$ Hz, 2H), 7.11 (t, $J = 4.0$ Hz, 4H), 6.89 (t, $J = 7.3$ Hz, 1H), 6.25 (d, $J = 7.5$ Hz, 1H), 4.04 – 3.88 (m, 1H), 3.04 (m, $J = 16.4$,

4.9 Hz, 1H), 2.84 (t, $J = 6.2$ Hz, 2H), 2.64 (m, $J = 16.4, 7.7$ Hz, 1H), 1.97 (m, $J = 12.3, 7.4, 4.7$ Hz, 1H), 1.72 (m, $J = 15.2, 7.4$ Hz, 1H). M.p: 159.7-161.1 °C.

3. Reaction conditions optimization for the reductive alkylation of thiourea

						
Entry	1:2	HSiCl ₃	Temp(°C)	Cat. (%)	Sol.	Yield(%)
1	1.2	1.5	0	HMPA(5)	DCM	24
2	1	1.5	r.t	HMPA(5)	DCM	68
3	1.2	1.5	r.t	HMPA(5)	DCM	73
4	1.5	1.5	r.t	HMPA(5)	DCM	77
5	2	1.5	r.t	HMPA(5)	DCM	99
6	2	1.5	-10	HMPA(5)	DCM	70
7	2	1.5	0	HMPA(5)	DCM	81
8	2	1	r.t	HMPA(5)	DCM	85
9	2	1.1	r.t	HMPA(5)	DCM	89
10	2	1.2	r.t	HMPA(5)	DCM	94
11	2	2	r.t	HMPA(5)	DCM	98
12	2	1.5	r.t	HMPA(1)	DCM	45
13	2	1.5	r.t	HMPA(2)	DCM	57
14	2	1.5	r.t	HMPA(10)	DCM	98

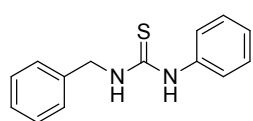
3.1 A general chemical method of synthesis the compounds of disubstituted thioureas



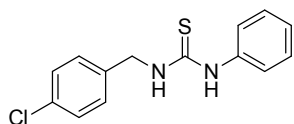
To a stirring solution of aldehyde or ketone (0.4 mmol) and urea (0.2 mmol) in 2 mL DCM, HMPA (0.01 mmol) was added. The solution was stirred at 0 °C for 10 min, and then the

HSiCl₃ was added to the mixture and stirred for 12 h at room temperature. The solution was neutralized with NaHCO₃. The mixture was extracted by EtOAc (3 × 5 mL) and the combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product.

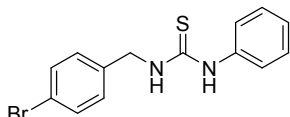
3.2 The characterizations data of disubstituted thioureas



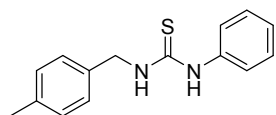
1-benzyl-3-phenylthiourea (P47): white solid, yield: 99%. ¹H NMR (400 MHz, DMSO – *d*₆) δ 9.65 (s, 1H), 8.18 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 4.0 Hz, 6H), 7.30 – 7.24 (m, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 2H). HRMS (ESI) Calcd for [C₁₄H₁₄N₂S + H] + 243.0950; Found: 243.0948. M.p: 145.4-146.0 °C.



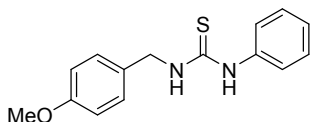
(4-chlorobenzyl)-3-phenylthiourea (P48): white solid, yield: 98%. ¹H NMR (400 MHz, DMSO – *d*₆) δ 9.68 (s, 1H), 8.21 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 4H), 7.39 – 7.31 (m, 4H), 7.14 (t, *J* = 7.3 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 2H). HRMS (ESI) Calcd for [C₁₄H₁₃ClN₂S + H] + 277.0561; Found: 277.0556. M.p: 135.3-136.4 °C.



1-(4-bromobenzyl)-3-phenylthiourea (P49): white solid, yield: 87%. ¹H NMR (400 MHz, DMSO – *d*₆) δ 9.67 (s, 1H), 8.20 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.26 (m, 4H), 7.13 (t, *J* = 7.3 Hz, 1H), 4.71 (d, *J* = 5.7 Hz, 2H). m.p: 141.5-142.3 °C.

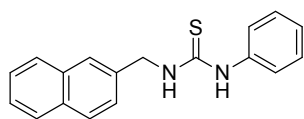


(4-methylbenzyl)-3-phenylthiourea (P50): white solid, yield: 92%. ¹H NMR (400 MHz, DMSO – *d*₆) δ 9.59 (s, 1H), 8.11 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.09 (m, 3H), 4.86 – 4.57 (m, 2H), 2.30 (s, 3H). HRMS (ESI) Calcd for [C₁₅H₁₆N₂S + H] + 257.1135; Found: 257.1131. M.p: 140.2-141.1 °C.



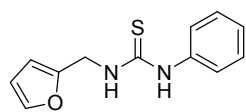
1-benzyl-3-(4-methoxyphenyl)thiourea (P51): white solide, Yield: 95%. ¹H NMR (400 MHz, DMSO – *d*₆) δ 9.42 (s, 1H), 7.96 (s, 1H), 7.34 – 7.29 (m, 4H), 7.25 (d, *J* = 8.8 Hz, 3H), 6.91 (d, *J* = 8.9

Hz, 2H), 4.72 (d, $J = 5.6$ Hz, 2H), 3.73 (s, 3H). HRMS (ESI) Calcd for $[C_{15}H_{16}N_2OS + H]^+$ + 273.1056; Found: 273.1058. M.p: 107.8-109.5 °C.

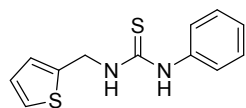


1-(naphthalen-2-ylmethyl)-3-phenylthiourea (P52): white solid, yield: 98%. 1H NMR (400 MHz, DMSO- d_6) δ 9.70 (s, 1H), 8.30 (s, 1H), 7.95 – 7.87 (m, 3H), 7.82 (s, 1H), 7.57 – 7.43 (m, 5H), 7.35 (t, $J = 7.8$ Hz, 2H), 7.14 (t, $J = 7.4$ Hz, 1H), 4.93 (d, $J = 5.4$ Hz, 2H).

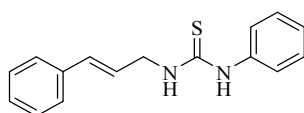
HRMS (ESI) Calcd for $[C_{18}H_{16}N_2S + H]^+$ + 293.1107; Found: 293.1103. M.p: 163.7-164.3 °C.



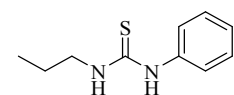
1-(furan-2-yl-methyl)-3-phenylthiourea (P53): white solide, yield: 78%. 1H NMR (400 MHz, DMSO- d_6) δ 9.59 (s, 1H), 8.08 (s, 1H), 7.61 (dd, $J = 1.8, 0.8$ Hz, 1H), 7.44 (dd, $J = 8.4, 0.8$ Hz, 2H), 7.36 – 7.28 (m, 2H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.42 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.33 (dd, $J = 3.2, 0.6$ Hz, 1H), 4.72 (d, $J = 5.4$ Hz, 2H). M.p: 133.3-134.5 °C.



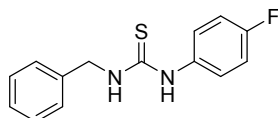
1-phenyl-3-(thiophen-2-ylmethyl)thiourea (P54): yellow solide, yield: 80%. 1H NMR (400 MHz, DMSO- d_6) δ 9.63 (s, 1H), 8.19 (s, 1H), 7.42 – 7.37 (m, 3H), 7.35 – 7.29 (m, 2H), 7.12 (t, $J = 7.3$ Hz, 1H), 7.05 (dd, $J = 3.4, 1.0$ Hz, 1H), 6.97 (dd, $J = 5.1, 3.4$ Hz, 1H), 4.90 (d, $J = 5.7$ Hz, 2H). M.p: 121.6-130.1 °C.



1-cinnamyl-3-phenylthiourea (P55): yellow solide, Yield: 68%. 1H NMR (400 MHz, DMSO- d_6) δ 7.43 (dd, $J = 10.5, 6.5$ Hz, 4H), 7.33 (dd, $J = 12.4, 7.1$ Hz, 4H), 7.26 – 7.21 (m, 1H), 7.12 (t, $J = 7.3$ Hz, 1H), 6.55 (d, $J = 16.0$ Hz, 2H), 6.42 – 6.31 (m, 2H), 4.87 (t, $J = 5.5$ Hz, 1H), 4.32 (s, 1H), 4.12 (td, $J = 5.3, 1.4$ Hz, 2H). M.p: 128.5-129.0 °C.

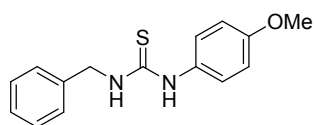


1-phenyl-3-propylthiourea (P56): white solid, yield: 62%. 1H NMR (400 MHz, DMSO- d_6) δ 9.45 (s, 1H), 7.75 (s, 1H), 7.40 (d, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.9$ Hz, 2H), 7.09 (t, $J = 7.3$ Hz, 1H), 3.47 – 3.36 (m, 2H), 1.60 – 1.48 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). M.p: 80.0-80.3 °C.

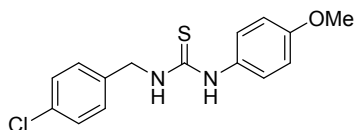


1-benzyl-3-(4-fluorophenyl)thiourea (P57): white solide, yield: 88%. 1H NMR (400 MHz, DMSO- d_6) δ 9.57 (s, 1H), 8.14 (s, 1H), 7.42 (dd,

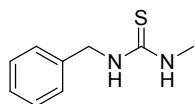
$J = 8.9, 5.0$ Hz, 2H), 7.36 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 7.20 – 7.13 (m, 2H), 4.73 (d, $J = 5.5$ Hz, 2H). M.p: 142.3-143.0 °C.



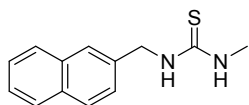
1-benzyl-3-(4-methoxyphenyl)thiourea (P58): white solide, yield: 95%. ^1H NMR (400 MHz, DMSO – d_6) δ 9.42 (s, 1H), 7.96 (s, 1H), 7.34 – 7.29 (m, 4H), 7.25 (d, $J = 8.8$ Hz, 3H), 6.91 (d, $J = 8.9$ Hz, 2H), 4.72 (d, $J = 5.6$ Hz, 2H), 3.73 (s, 3H). M.p: 107.8-109.5 °C.



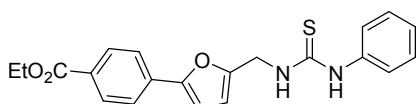
1-(4-chlorobenzyl)-3-(4-methoxyphenyl)thiourea (P59): white solide, yield: 90%. ^1H NMR (400 MHz, DMSO – d_6) δ 9.47 (s, 1H), 7.98 (s, 1H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.9$ Hz, 2H), 6.91 (d, $J = 8.9$ Hz, 2H), 4.70 (d, $J = 5.7$ Hz, 2H), 3.74 (s, 3H). M.p: 134.8-135.8 °C.



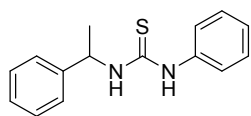
1-benzyl-3-methylthiourea (P60): white oil, yield: 85%. ^1H NMR (400 MHz, DMSO – d_6) δ 7.34 (t, $J = 7.2$ Hz, 3H), 7.30 – 7.28 (m, 1H), 7.21 – 7.18 (m, 2H), 4.40 (s, 1H), 4.28 (s, 3H).



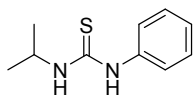
1-methyl-3-(naphthalen-2-ylmethyl)thiourea (P61): white solide, yield: 78%. ^1H NMR (400 MHz, DMSO – d_6) δ 8.04 (s, 1H), 7.90 – 7.86 (m, 3H), 7.75 (s, 1H), 7.49 (dd, $J = 11.6, 6.3$ Hz, 4H), 4.83 (s, 2H), 2.87 (s, 3H). M.p: 108.8-109.2 °C.



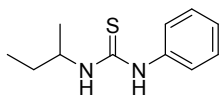
Ethyl-4-(5-((3-phenylthioureido)methyl)furan-2-yl)benzoate (P62): yellow solid, yield: 73%. ^1H NMR (400 MHz, DMSO – d_6) δ 9.68 (s, 1H), 8.22 (s, 1H), 8.00 (d, $J = 8.5$ Hz, 2H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.34 (dd, $J = 10.7, 5.1$ Hz, 2H), 7.13 (dd, $J = 8.9, 5.4$ Hz, 2H), 6.51 (d, $J = 3.4$ Hz, 1H), 4.82 (d, $J = 5.3$ Hz, 2H), 4.37 – 4.28 (m, 2H), 1.33 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO – d_6) δ 181.23, 165.83, 153.67, 151.55, 134.74, 130.34, 129.10, 128.56, 124.84, 123.57, 110.55, 109.78, 61.20, 14.67. HRMS (ESI) Calcd for $[\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{S} + \text{H}]^+$ + 381.1267; Found: 381.1269. M.p: 149.5-155.2 °C.



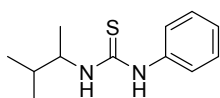
1-phenyl-3-(1-phenylethyl)thiourea (P63): white solide, yield: 65%. ^1H NMR (300 MHz, $\text{CDCl}_3 - d_3$) δ 7.74 (s, 1H), 7.49 – 7.25 (m, 8H), 7.17 (d, $J = 7.3$ Hz, 2H), 6.24 (s, 1H), 5.67 (s, 1H), 1.54 (d, $J = 6.9$ Hz, 2H). M.p: 121.3-122.1 °C.



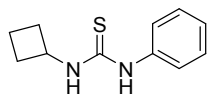
1-isopropyl-3-phenylthiourea (P64): yellow solide, yield: 44%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.86 (s, 1H), 7.45 (t, $J = 7.5$ Hz, 2H), 7.31 (dd, $J = 13.5, 6.0$ Hz, 1H), 7.21 (d, $J = 7.7$ Hz, 2H), 5.83 (s, 1H), 4.61 (dd, $J = 13.4, 6.7$ Hz, 1H), 1.22 (d, $J = 6.5$ Hz, 6H).



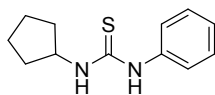
1-(sec-butyl)-3-phenylthiourea (P65): yellow solide, yield: 47%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.78 (s, 1H), 7.46 (dd, $J = 10.7, 4.9$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.21 (d, $J = 7.5$ Hz, 2H), 5.80 (d, $J = 6.6$ Hz, 1H), 4.60 – 4.40 (m, 1H), 1.60 – 1.51 (m, 2H), 1.19 (d, $J = 6.6$ Hz, 3H), 0.93 (t, $J = 7.5$ Hz, 3H).



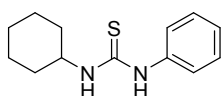
1-(3-methylbutan-2-yl)-3-phenylthiourea (P66): yellow solide, yield: 34%. ^1H NMR (300 MHz, $\text{CDCl}_3 - d_3$) δ 7.83 (s, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.30 (t, $J = 7.2$ Hz, 1H), 7.20 (d, $J = 7.5$ Hz, 2H), 5.85 (s, 1H), 4.40 (s, 1H), 1.88 – 1.76 (m, 1H), 1.69 – 1.57 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.87 (dd, $J = 6.8, 2.9$ Hz, 6H).



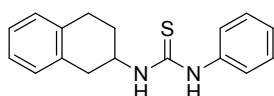
1-cyclobutyl-3-phenylthiourea (P67): yellow solide, yield: 53%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 8.07 (s, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.31 (dd, $J = 12.9, 5.4$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 2H), 6.17 (s, 1H), 4.79 (s, 1H), 2.44 (ddd, $J = 11.6, 8.3, 5.7$ Hz, 2H), 1.82 (dd, $J = 18.7, 9.5$ Hz, 2H), 1.77 – 1.67 (m, 2H).



1-cyclopentyl-3-phenylthiourea (P68): yellow solide, yield: 51%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.86 (s, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.33 – 7.27 (m, 1H), 7.21 (d, $J = 7.7$ Hz, 2H), 6.00 (s, 1H), 4.69 (d, $J = 6.2$ Hz, 1H), 2.11 (dd, $J = 13.1, 6.7$ Hz, 2H), 1.62 (dd, $J = 6.7, 3.7$ Hz, 4H), 1.40 (dd, $J = 12.9, 6.6$ Hz, 2H).

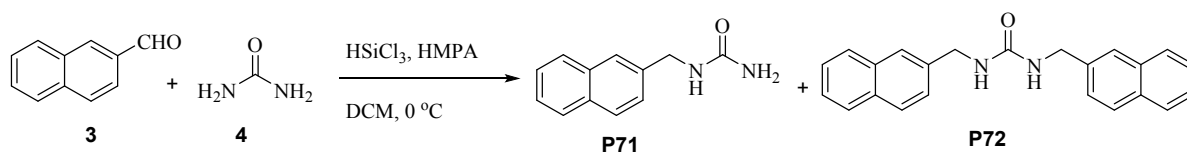


1-cyclohexyl-3-phenylthiourea (P69): white solid. yield: 58%. ^1H NMR (400 MHz, $\text{DMSO} - d_6$) δ 9.34 (s, 1H), 7.63 (d, $J = 6.9$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 2H), 7.30 (t, $J = 7.9$ Hz, 2H), 7.08 (t, $J = 7.4$ Hz, 1H), 4.07 (m, $J = 34.7, 18.0, 6.2$ Hz, 1H), 1.92 (d, $J = 3.2$ Hz, 2H), 1.69 (dd, $J = 9.0, 3.4$ Hz, 2H), 1.57 (dd, $J = 9.4, 3.2$ Hz, 1H), 1.33 – 1.12 (m, 5H). M.p: 141.5-142.3 °C.

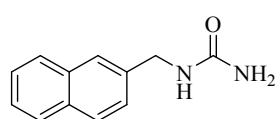


1-phenyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)thiourea (P70): yellow solide, yield: 51%. ^1H NMR (400 MHz, $\text{CDCl}_3 - d_3$) δ 7.78 (s, 1H), 7.39 (dd, $J = 11.8, 5.9$ Hz, 2H), 7.31 – 7.26 (m, 2H), 7.16 – 7.06 (m, 5H), 6.07 (d, $J = 7.3$ Hz, 1H), 4.99 – 4.77 (m, 1H), 3.25 (dd, $J = 16.1, 4.8$ Hz, 1H), 3.13 – 2.91 (m, 2H), 2.90 – 2.66 (m, 2H), 1.91 – 1.73 (m, 2H).

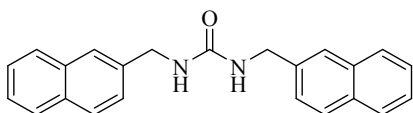
4. The procedure for reductive alkylation of urea 4 to synthesize P71/72



To a stirring solution of 2-naphthaldehyde (0.4 mmol) and urea (0.8 mmol) in 2 mL DCM, HMPA (0.02 mmol) was added. The solution was stirred at 0 °C for 10 min, and then the HSiCl₃ (0.6 mmol) was added to the mixture and stirred for 12 h at 0 °C. The solution was neutralized with NaHCO₃. The mixture was extracted by EtOAc (3 × 5 mL) and the combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the main product (yield: **P71** 43%, **P72** 23%).

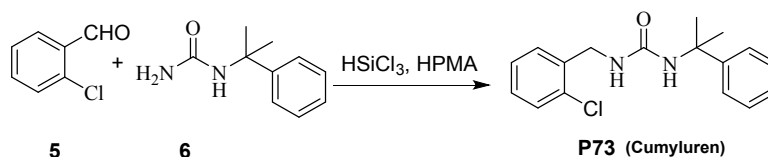


1-(naphthalen-2-ylmethyl)urea (P71): white solide, yield: 43%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 - 7.86 (m, 3H), 7.73 (s, 1H), 7.53 - 7.42 (m, 3H), 6.54 (t, *J* = 5.5 Hz, 1H), 5.58 (s, 2H), 4.35 (d, *J* = 5.92 Hz, 2H). M.p 193.1-195 °C.



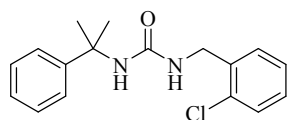
1,3-bis(naphthalen-2-ylmethyl)urea (P72): white solid, yield: 70%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (dd, *J* = 8.5, 6.3 Hz, 6H), 7.83 (s, 2H), 7.53 - 7.45 (m, 6H), 5.34 (t, *J* = 5.7 Hz, 2H), 4.67 (d, *J* = 5.7 Hz, 4H). M.p: 80.6-81.0 °C

5. The procedure for gram-scale synthesis of Cumyluren



4-Cl-Benzaldehyde (6 mmol, 705 μL) and 1-(2-phenylpropan-2-yl)urea (5 mmol, 860 mg) were dissolved in 30 mL of DCM, HMPA (0.25 mmol, 45 μL) was added to the mixture and stirred at 0 °C for 10 min. The HSiCl₃ (6 mmol, 604 μL) was added to the mixture and stirred for 12 h. Then the water (10 mL) was added to the mixture and stirred for 10 min. The solution was neutralized with NaHCO₃. The mixture was extracted by EtOAc (3 × 20 mL) and the

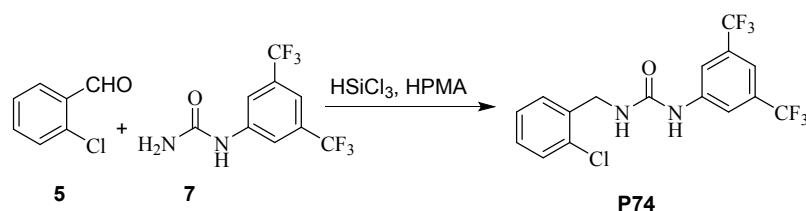
combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product (1.09g, 0.41 mmol).



1-(2-chlorobenzyl)-3-(2-phenylpropan-2-yl)urea (Cumyluren):

white solide, yield: 81%. ¹H NMR (400 MHz, CDCl₃ – d₃) δ 7.42 – 7.26 (m, 8H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.52 (s, 1H), 6.33 (t, *J* = 6.0 Hz, 1H), 4.21 (d, *J* = 6.0 Hz, 1H), 1.54 (s, 6H).

5.1 The procedure for gram-scale synthesis of P74



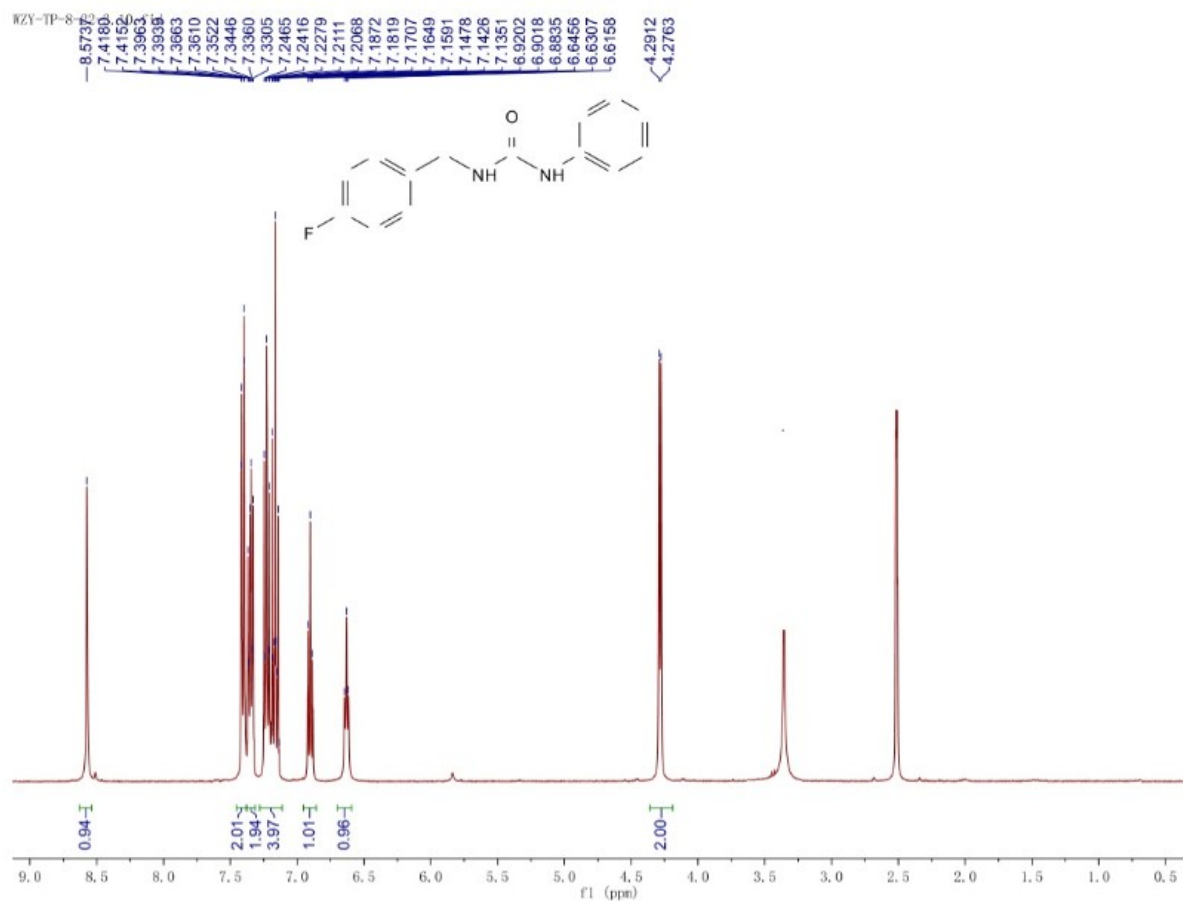
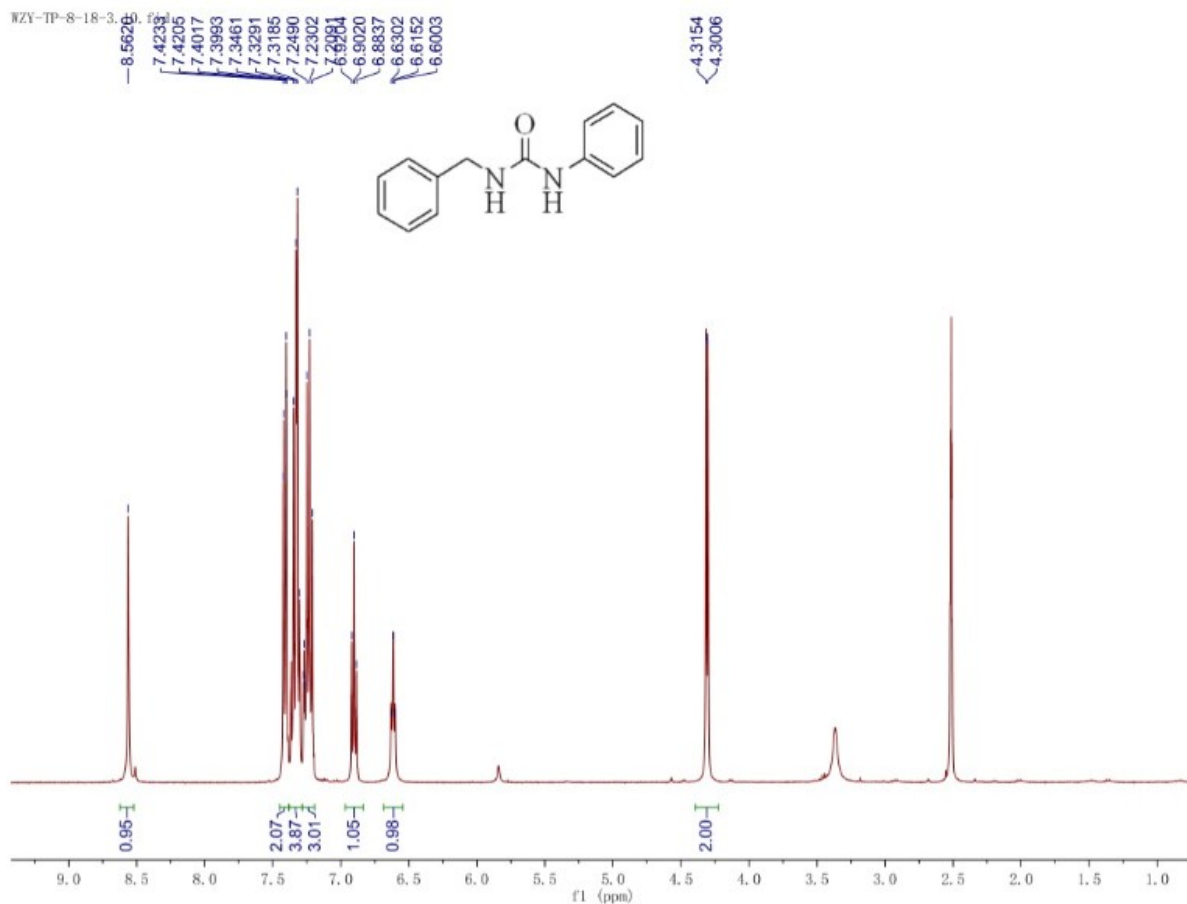
4-Cl-Benzaldehyde (4.8 mmol, 470 μL) and 1-(2-phenylpropan-2-yl)urea (4 mmol, 1.09 g) were dissolved in 30 mL of DCM, HMPA (0.25 mmol, 45 μL) was added to the mixture and stirred at 0 °C for 10 min. The HSiCl₃ (4.8 mmol, 483 μL) was added to the mixture and stirred for 12 h. Then the water (10 mL) was added to the mixture and stirred for 10 min. The solution was neutralized with NaHCO₃. The mixture was extracted by EtOAc (3 × 20 mL) and the combined organic layer was dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product (1.39g, 3.5 mmol).

1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-chlorobenzyl)urea: white solide, yield: 89%. ¹H NMR (400 MHz, CDCl₃ – d₃) δ 9.48 (s, 1H), 8.10 (s, 2H), 7.57 (s, 1H), 7.45 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.04 (t, *J* = 5.8 Hz, 1H), 4.40 (d, *J* = 5.5 Hz, 1H).

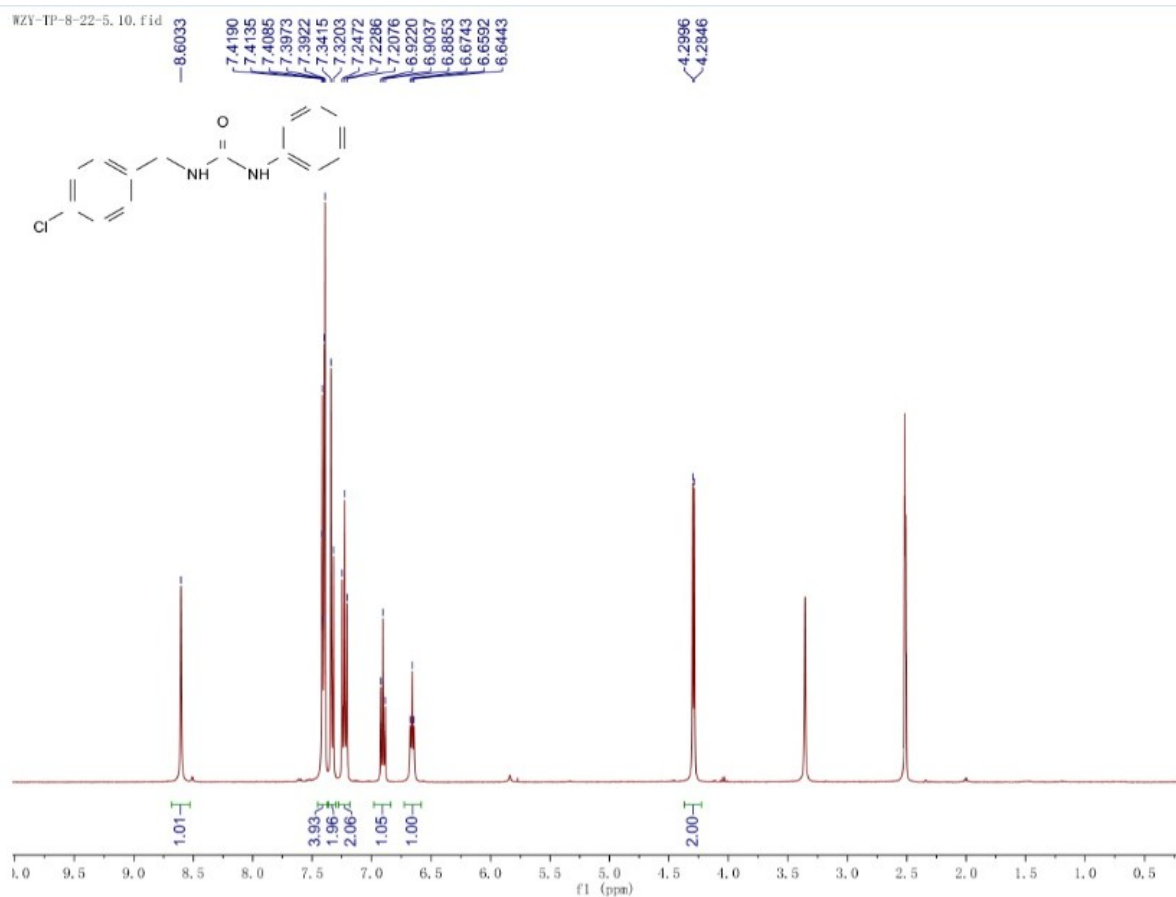
References:

1. L. Tiwari, V. Kumar, B. Kumar, D. Mahajan, *RSC Adv*, 2018, 8, 21585-21595.
2. H. Hammoud, K. Elhabazi, R. Quillet, I. Bertin, V. Utard, E. Laboureyras, J.-J. Bourguignon, F. Bihel, G. Simonnet, F. Simonin, M. Schmitt, *ACS Chem. Neurosci.* 2018, 9, 2599-2609
3. V. Pascanu, P. R. Hansen, A. Bermejo Gómez, C. Ayats, A. E. Platero-Prats, M. J. Johansson, M. À. Pericàs, B M.-Matute, *ChemSusChem*, 2015, 8, 123-130.

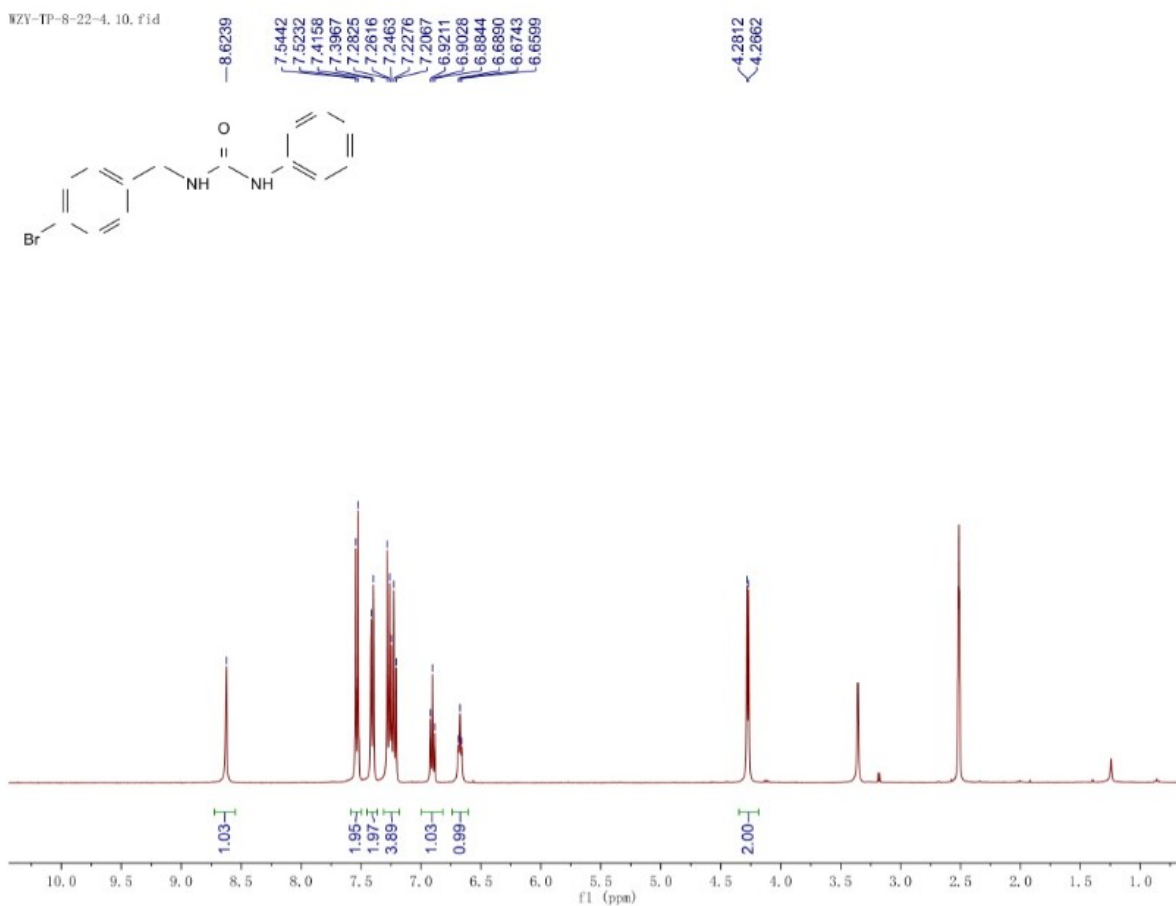
6. ^1H NMR and ^{13}C NMR spectra



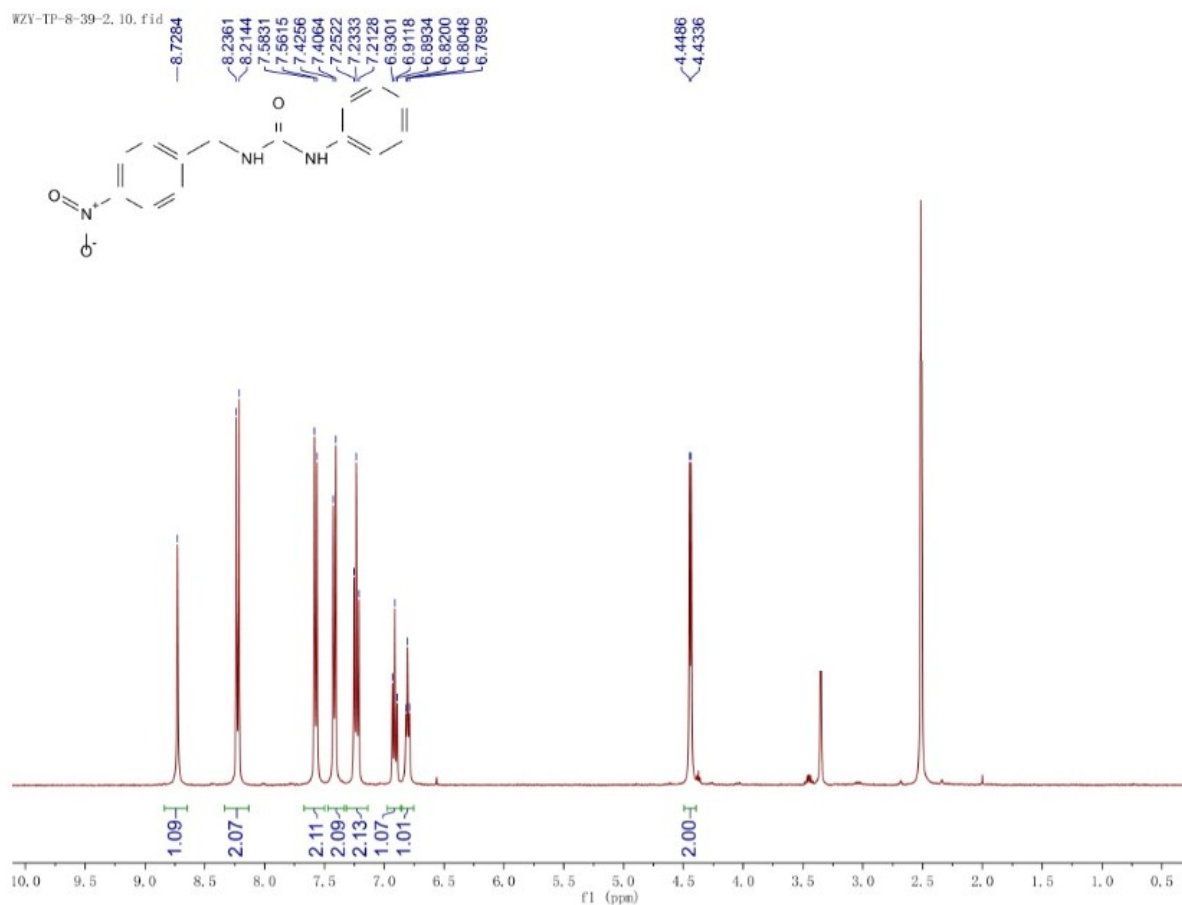
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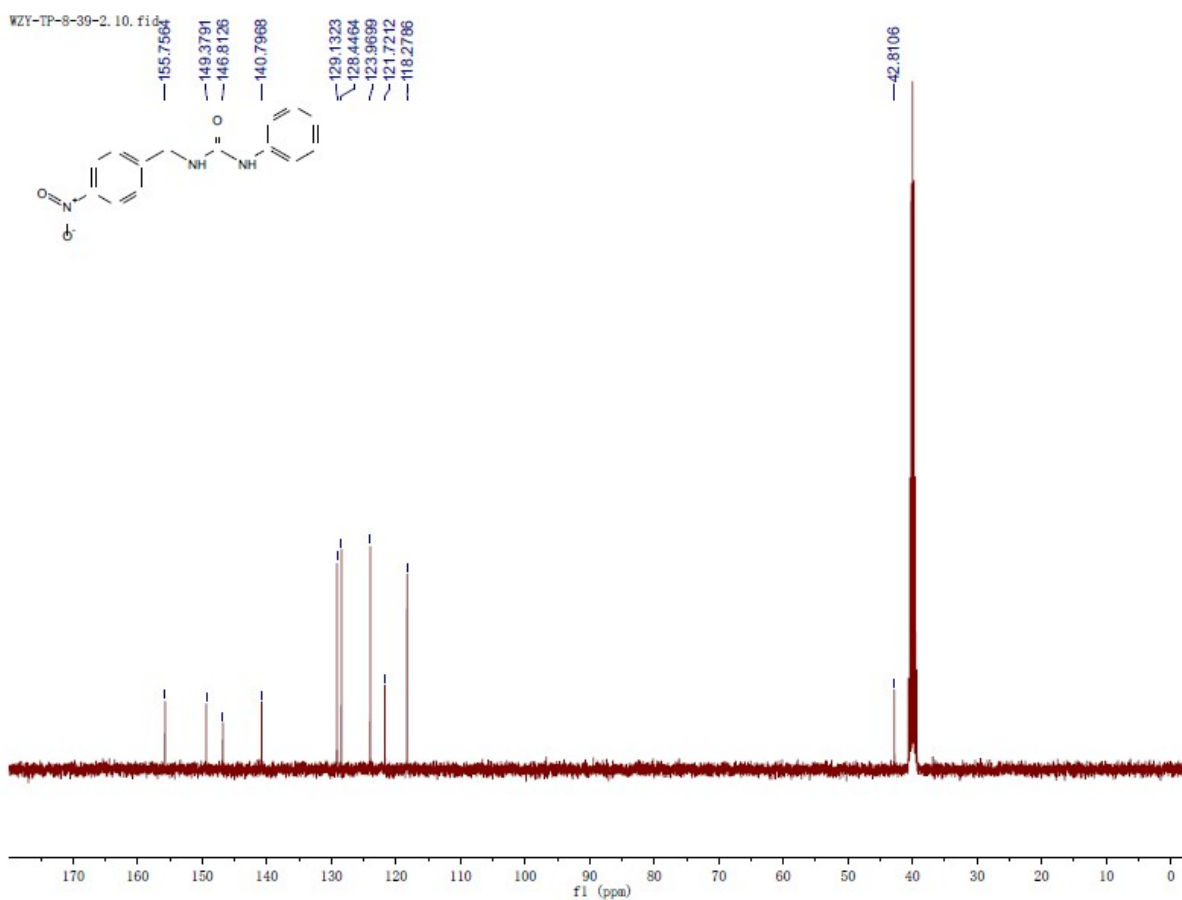
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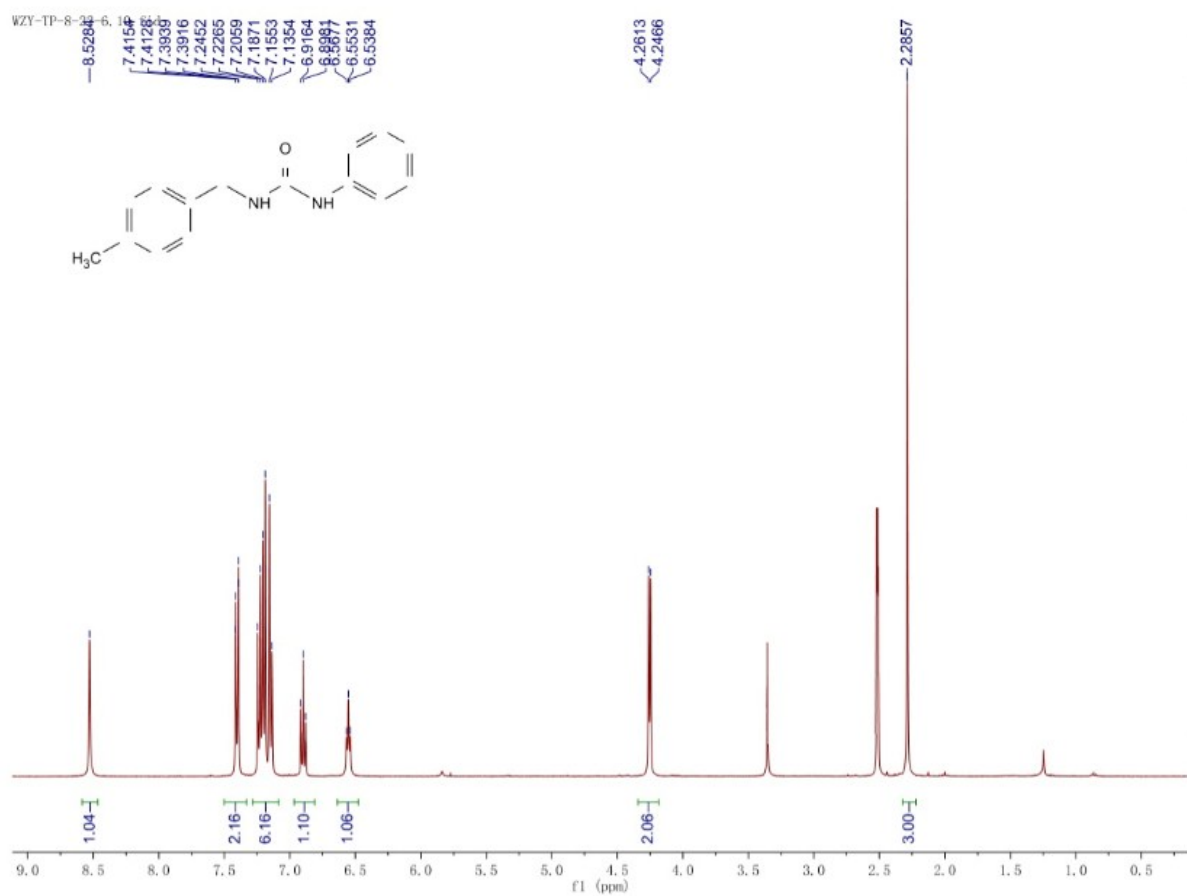
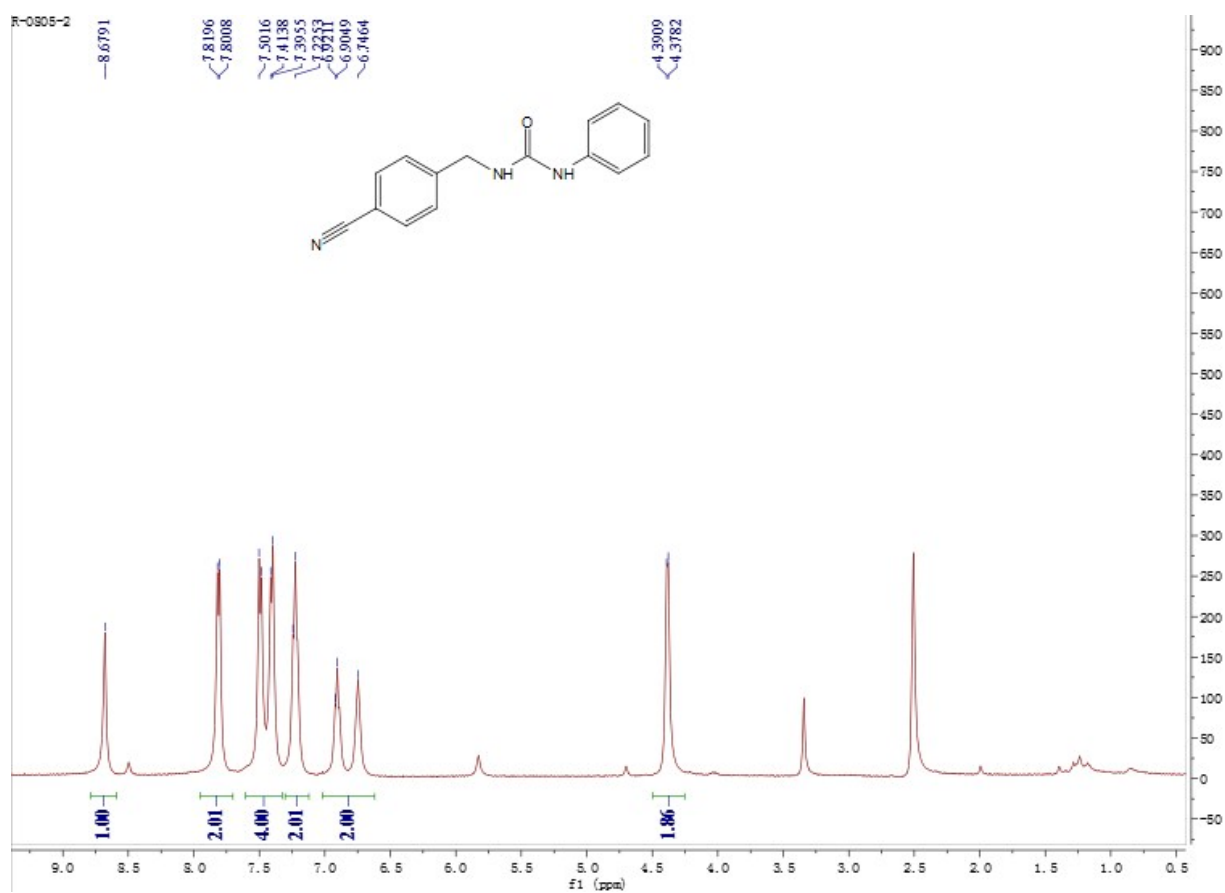


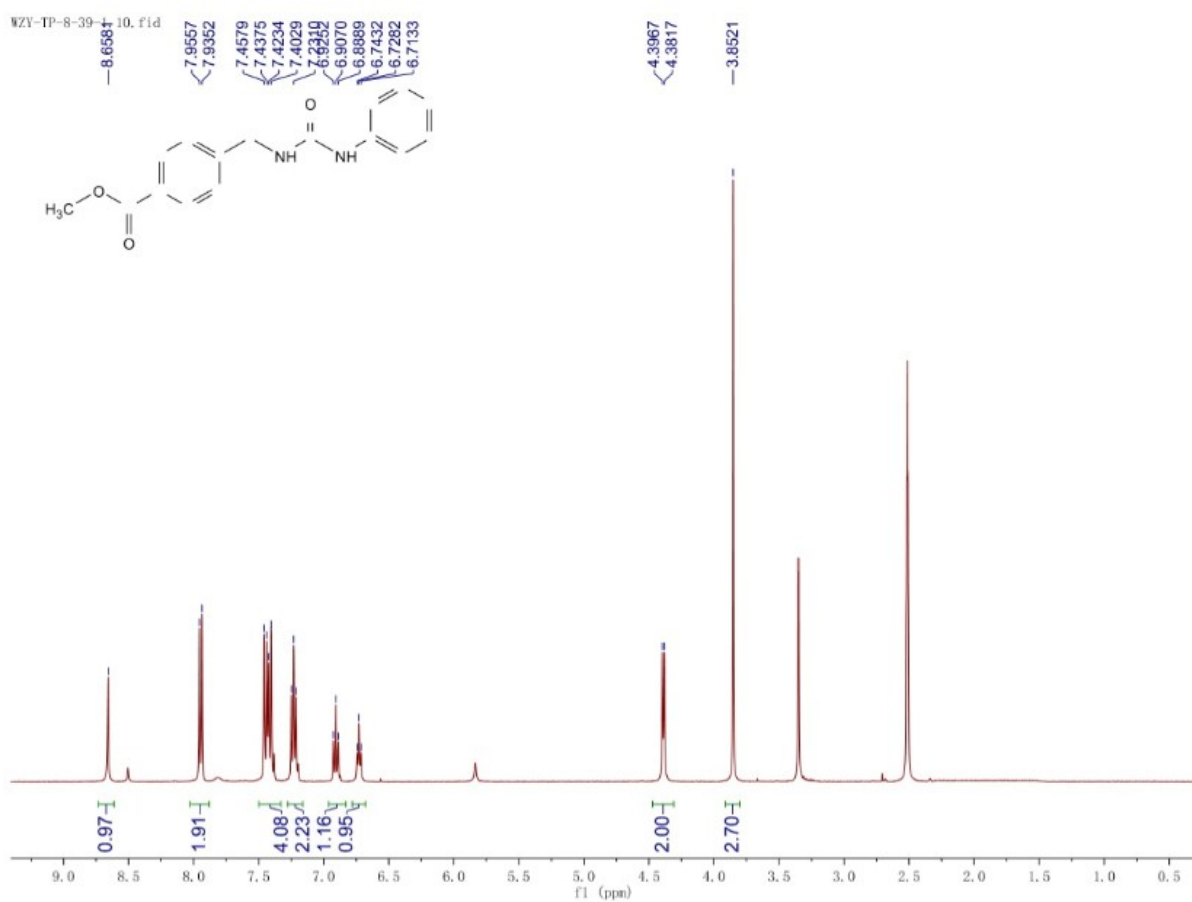
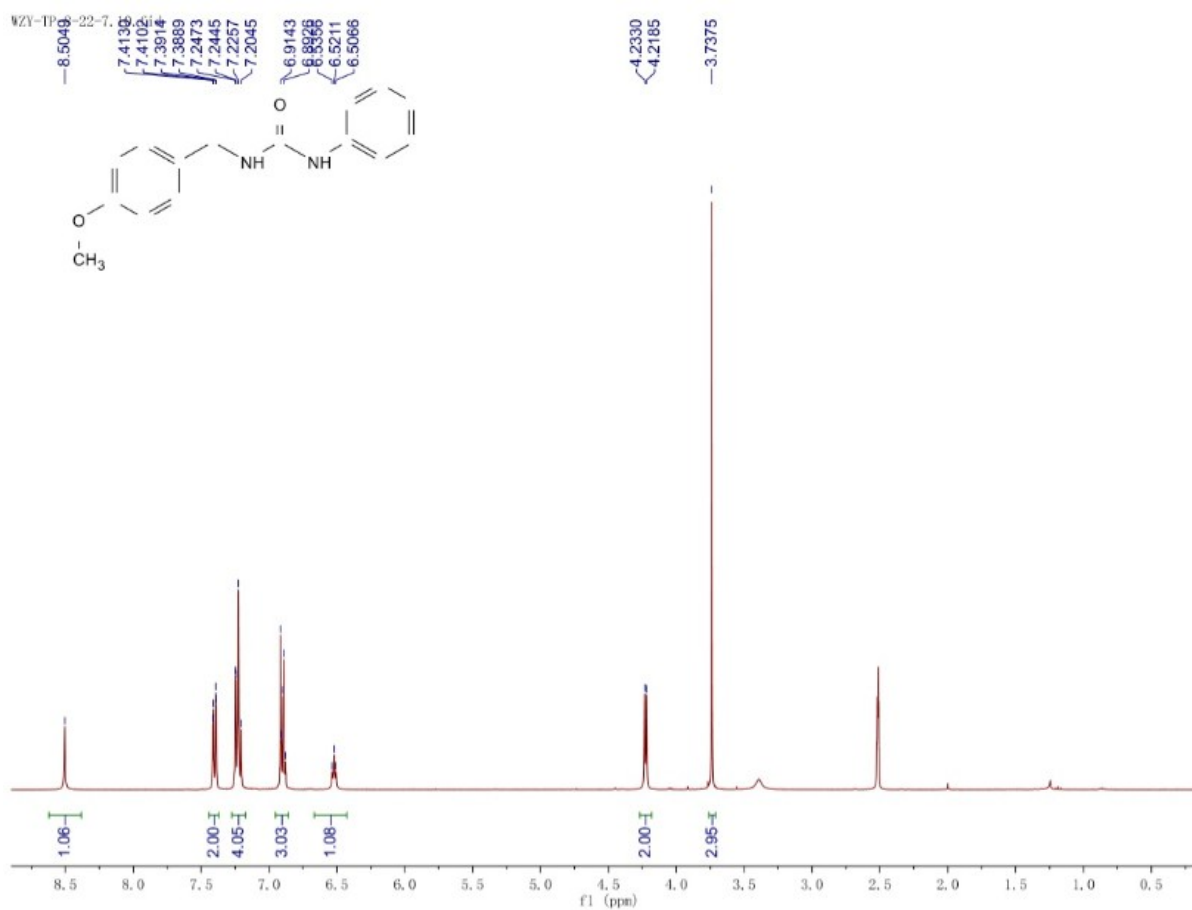
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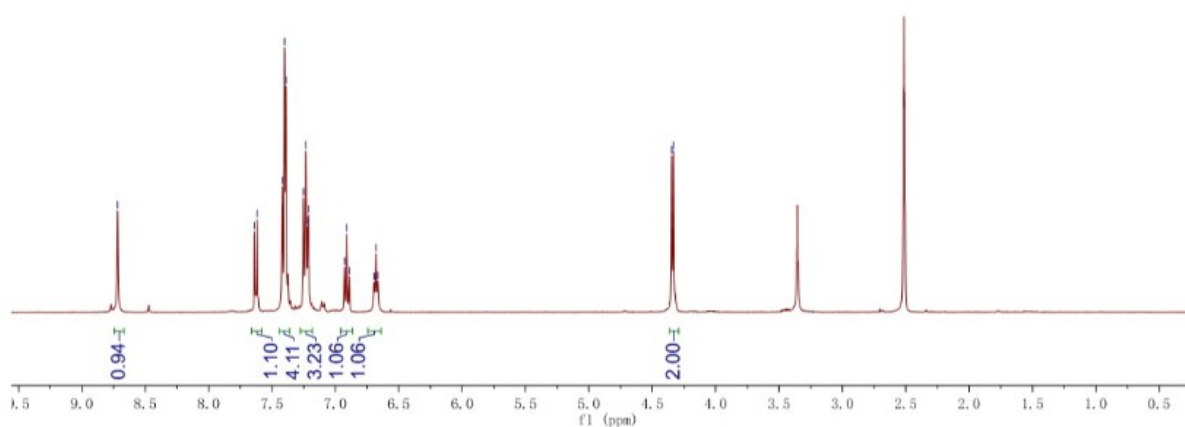
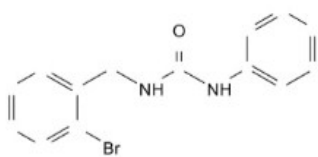




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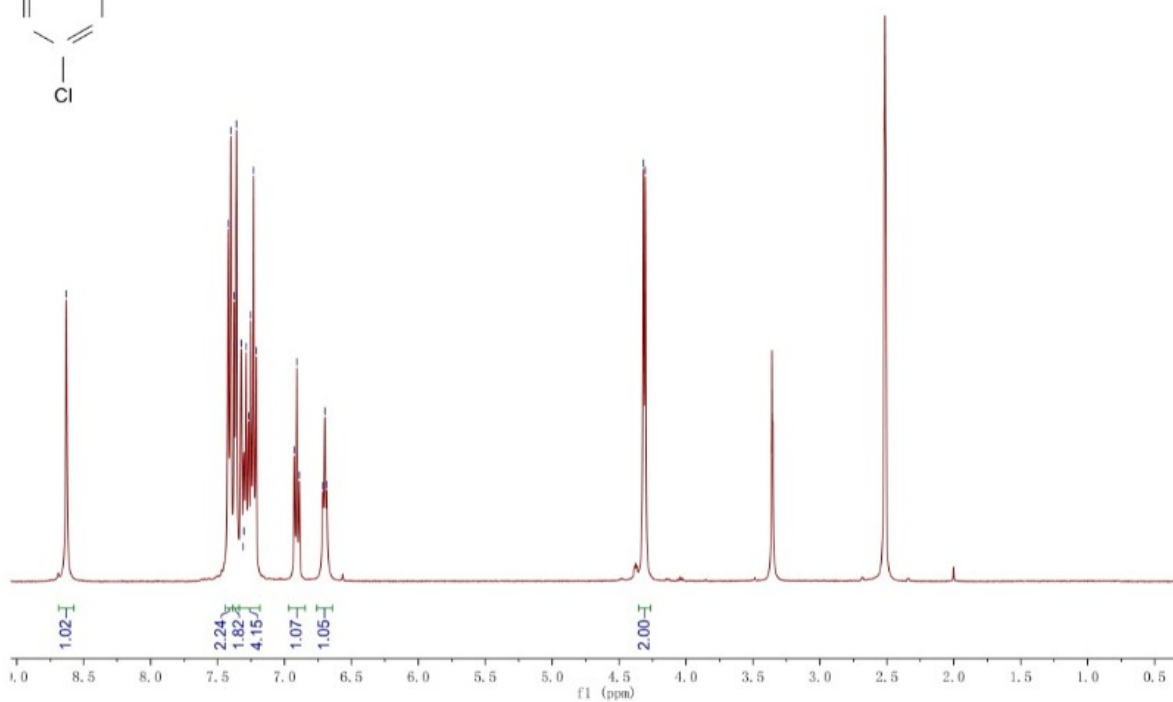
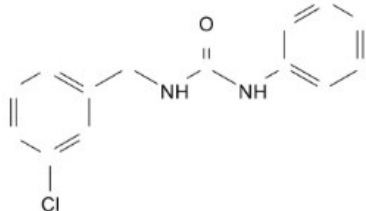
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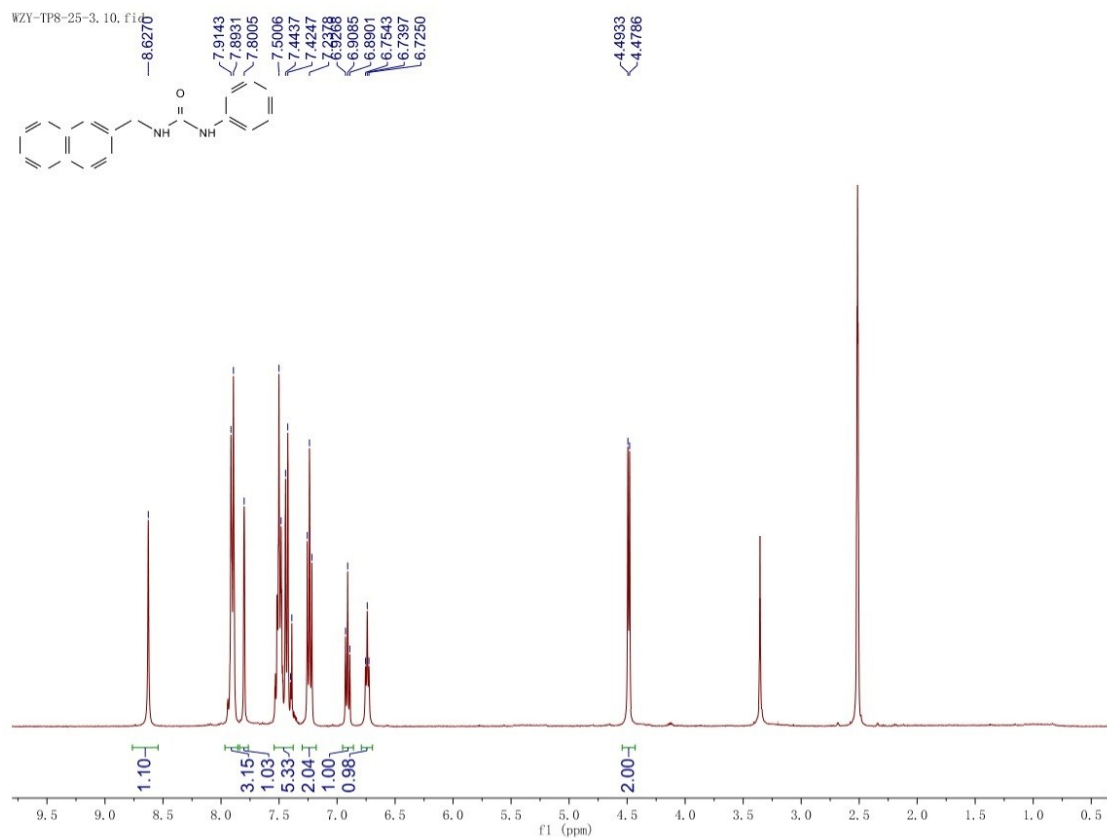
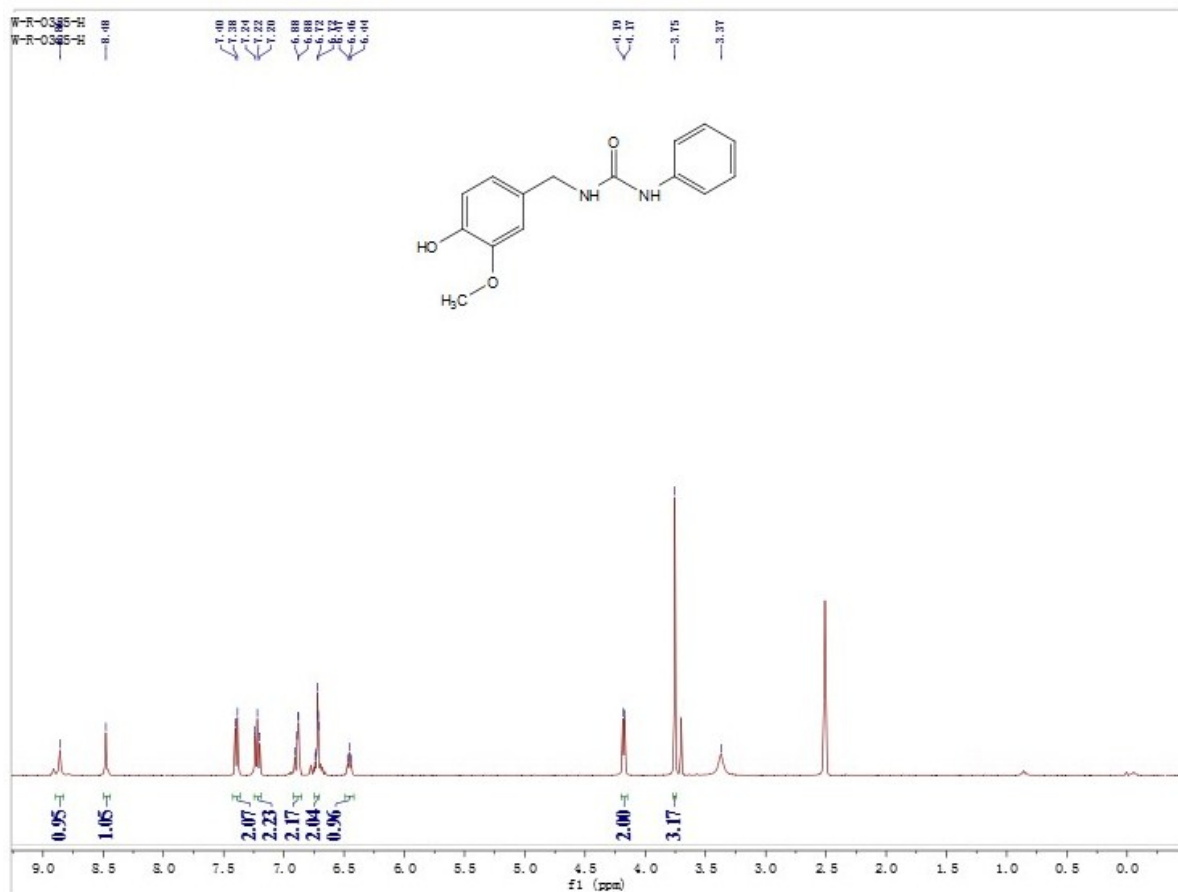


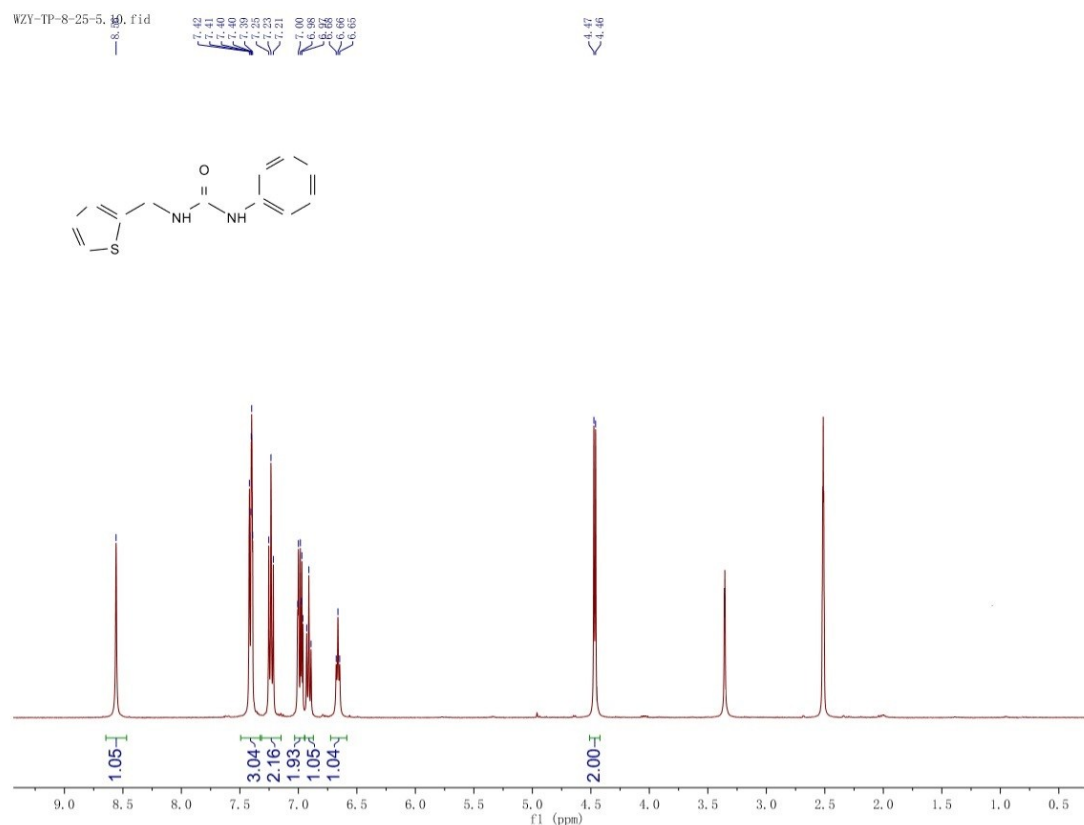
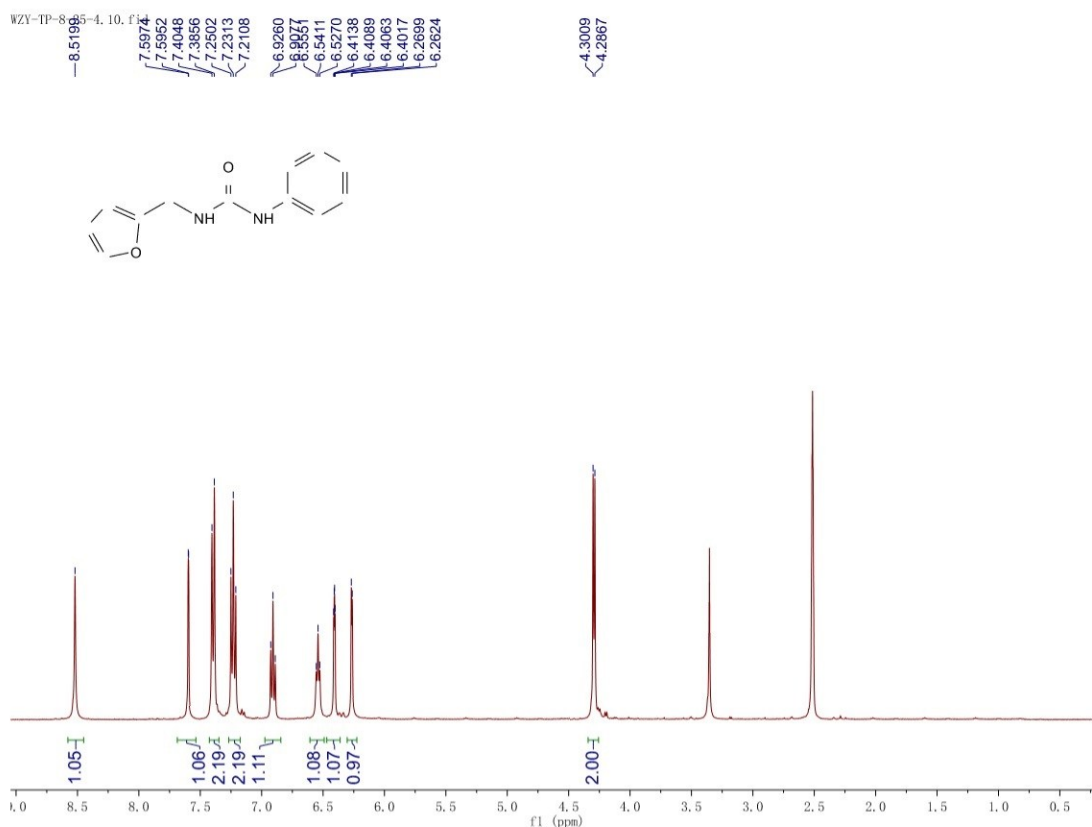
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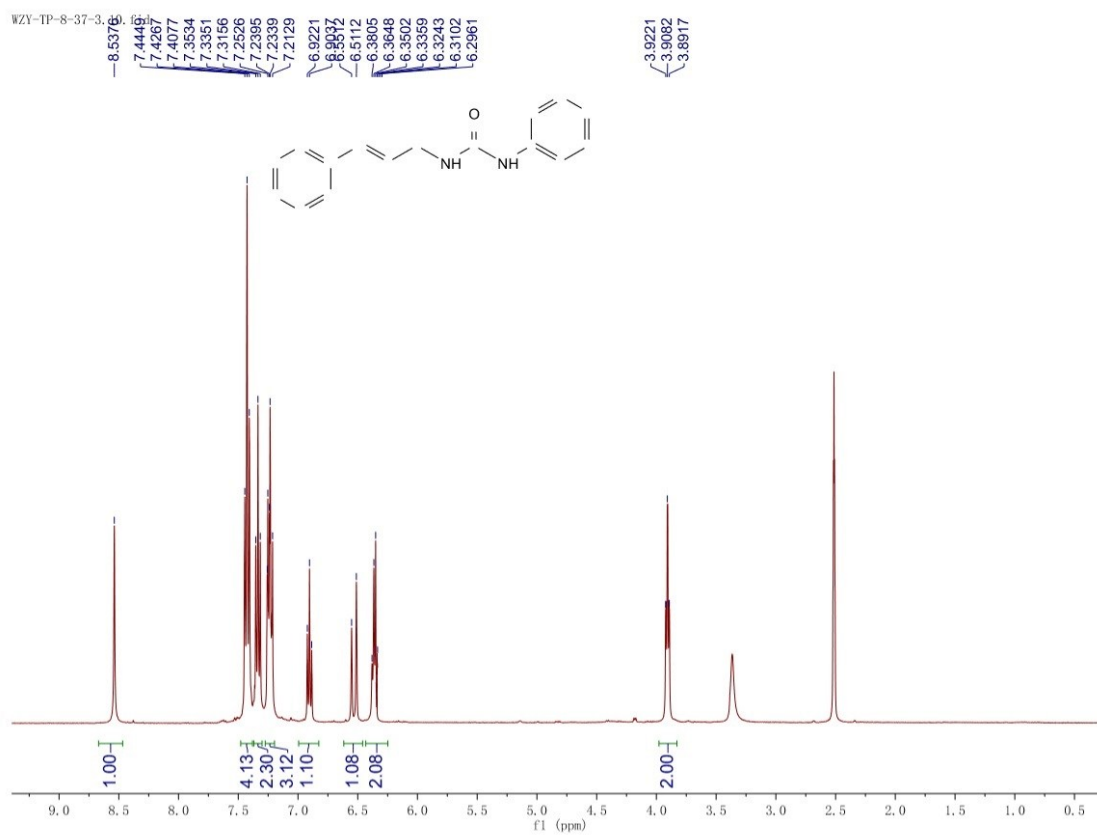
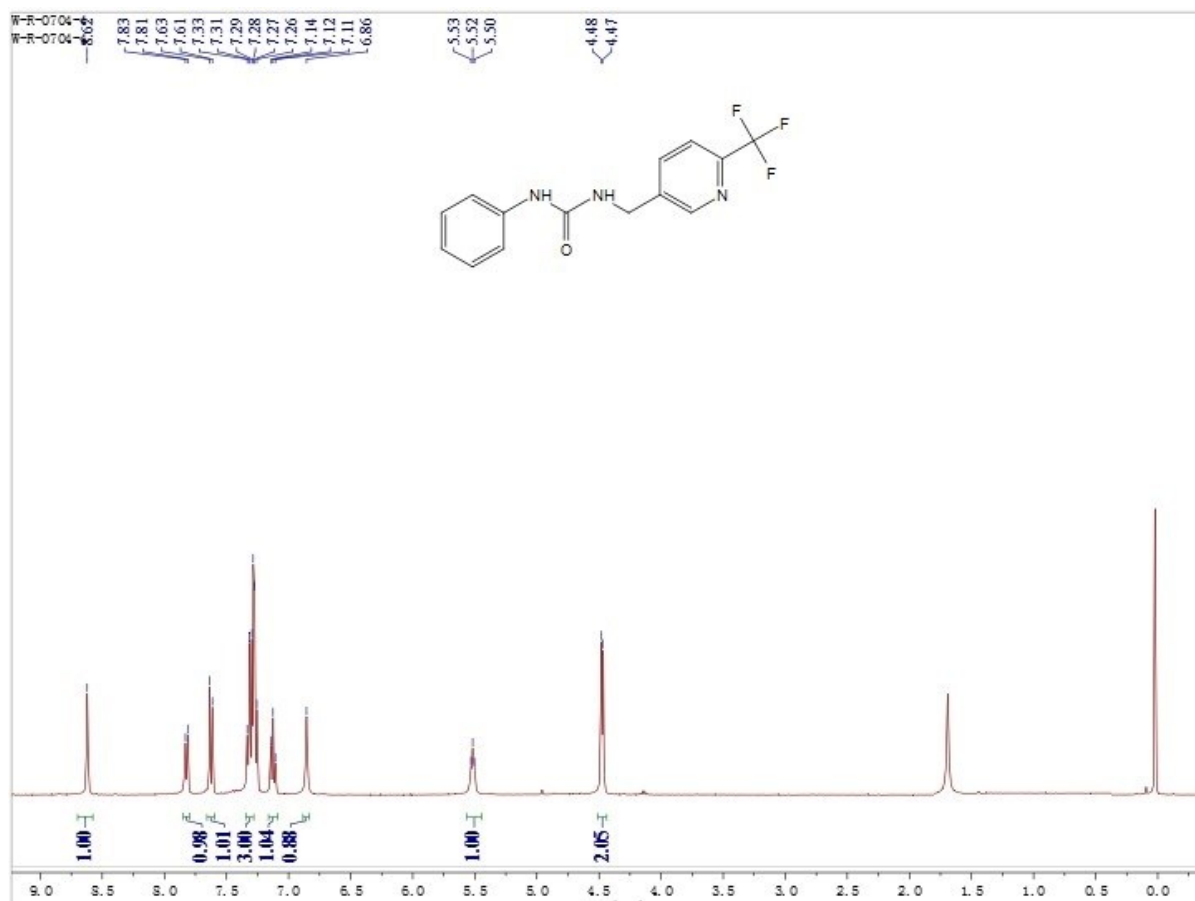
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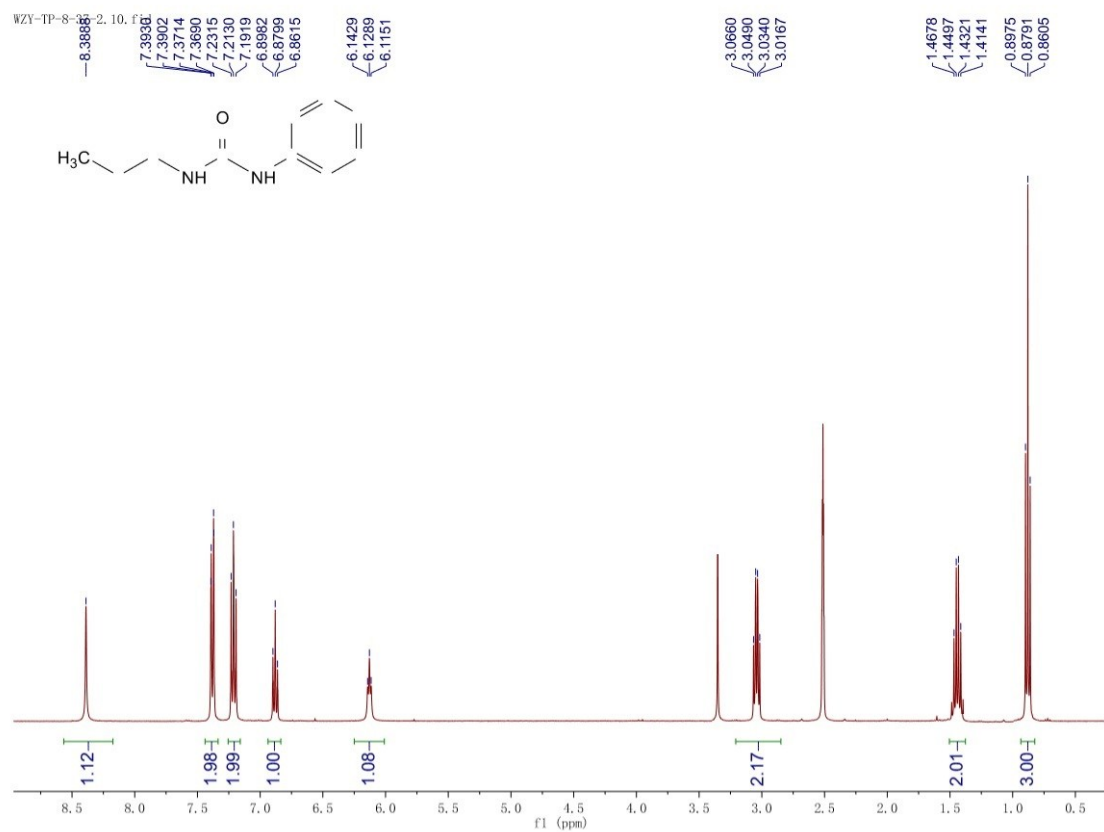
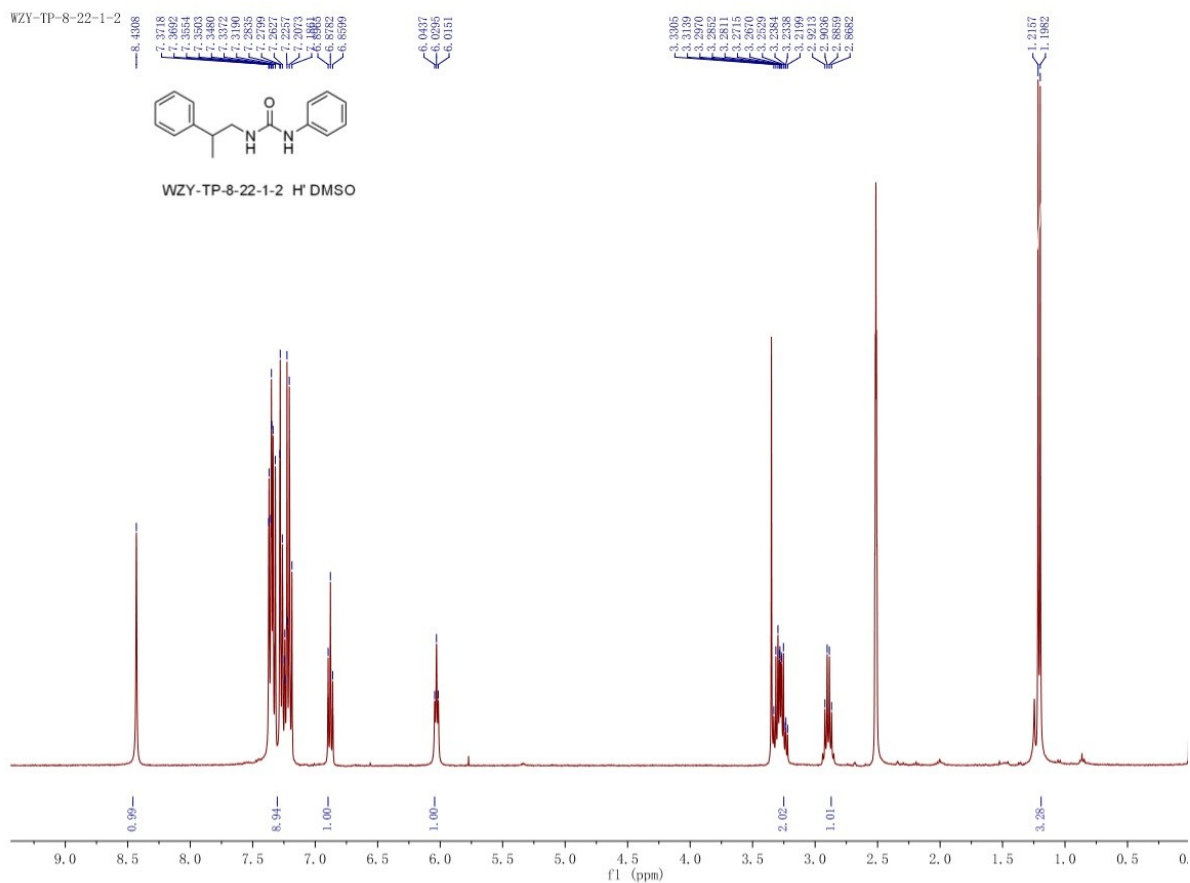
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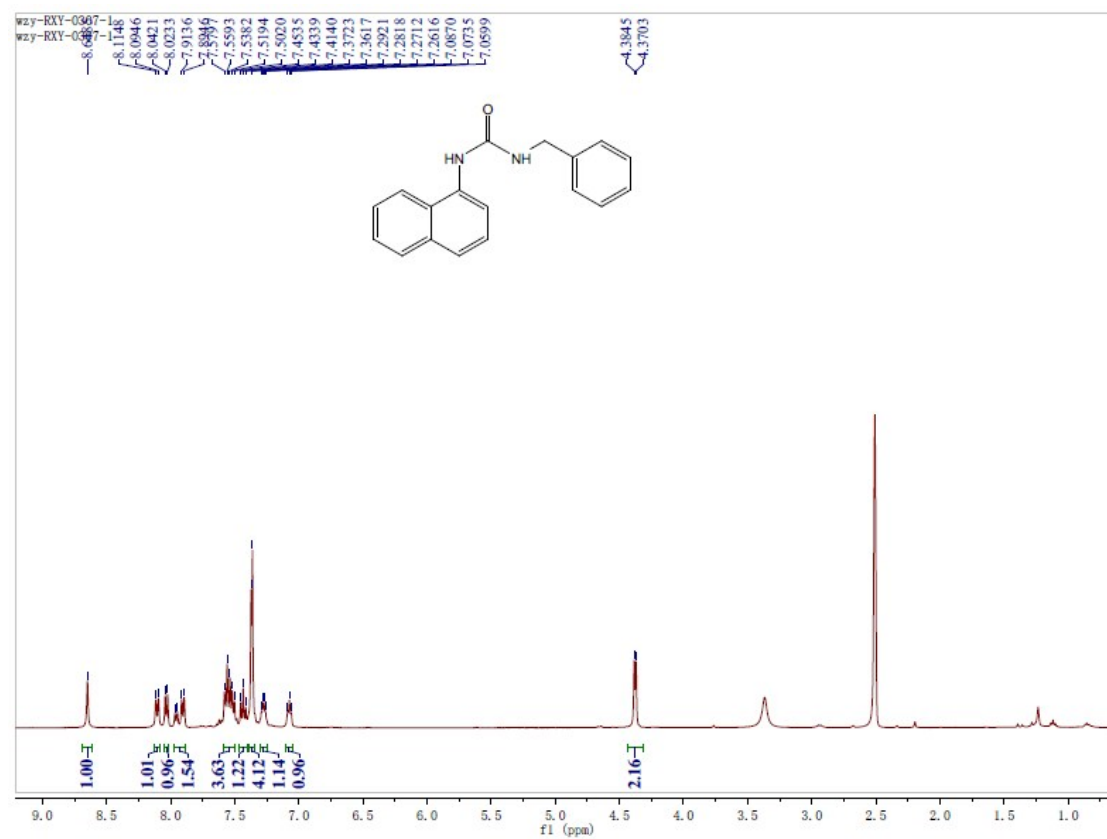
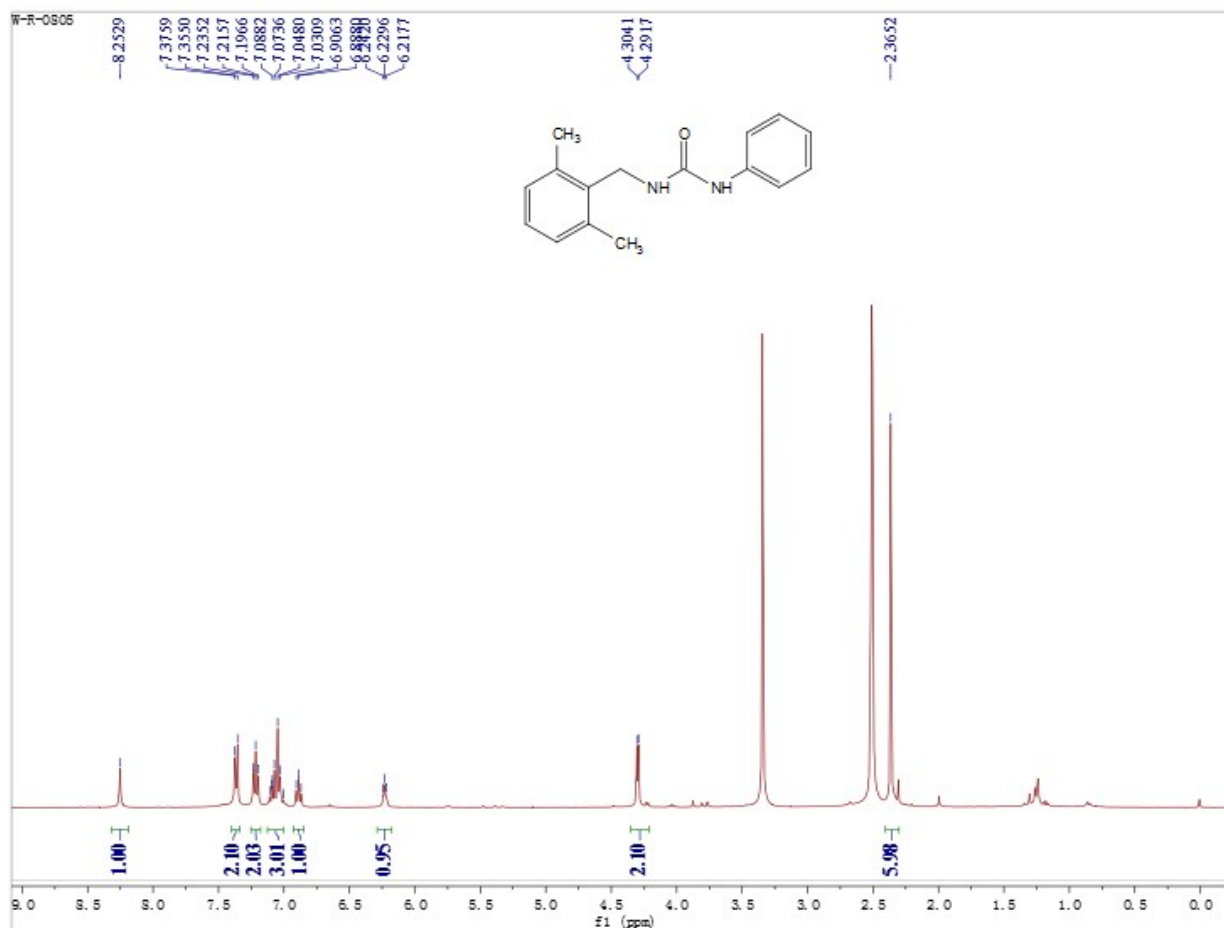


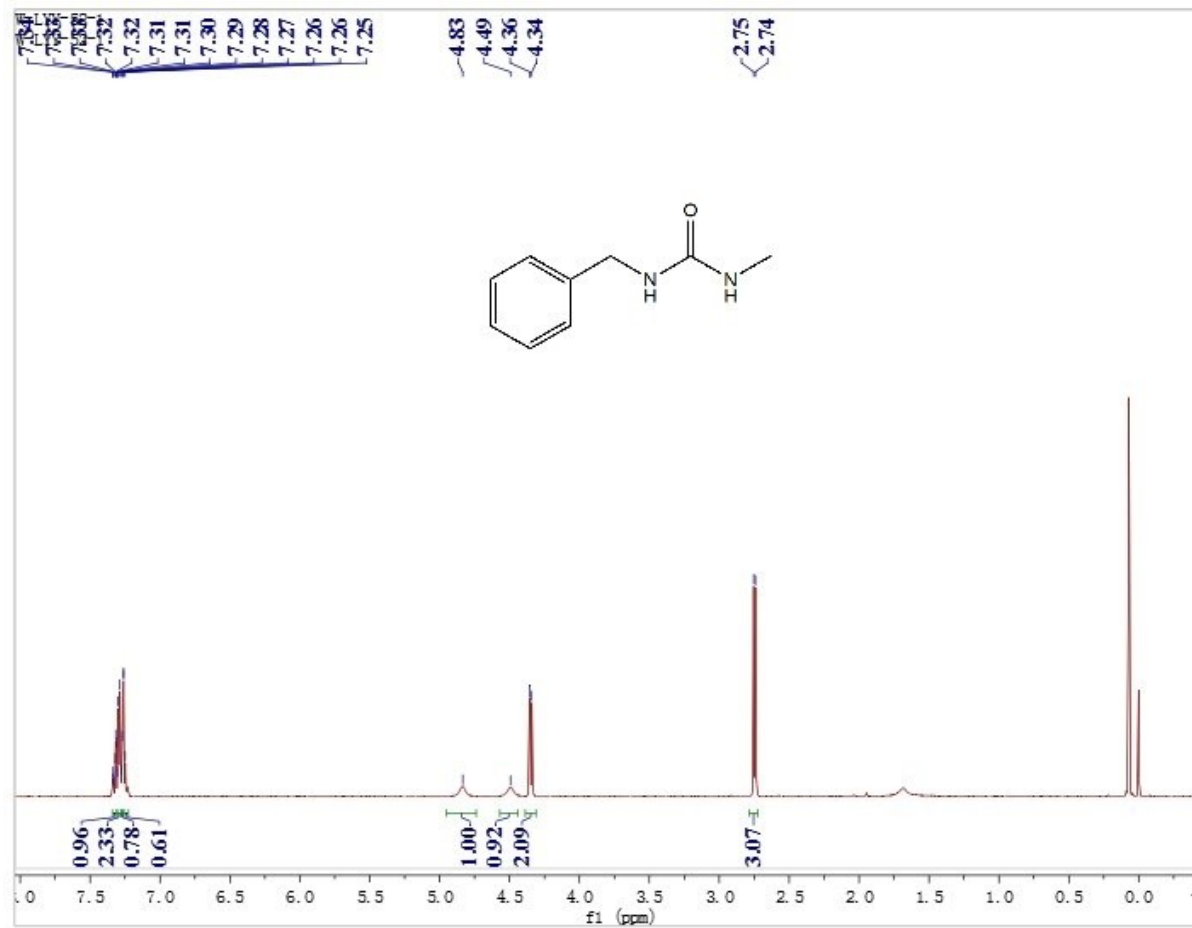
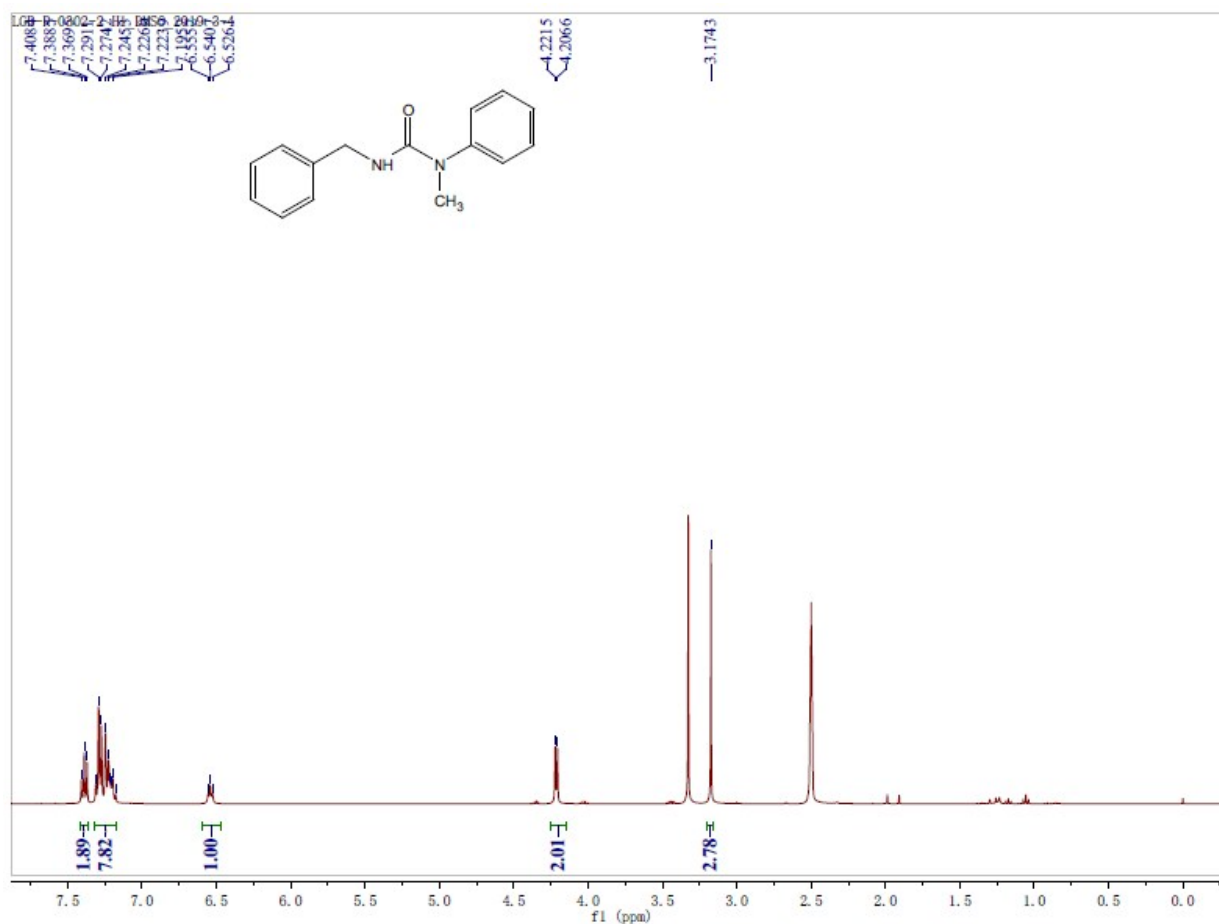


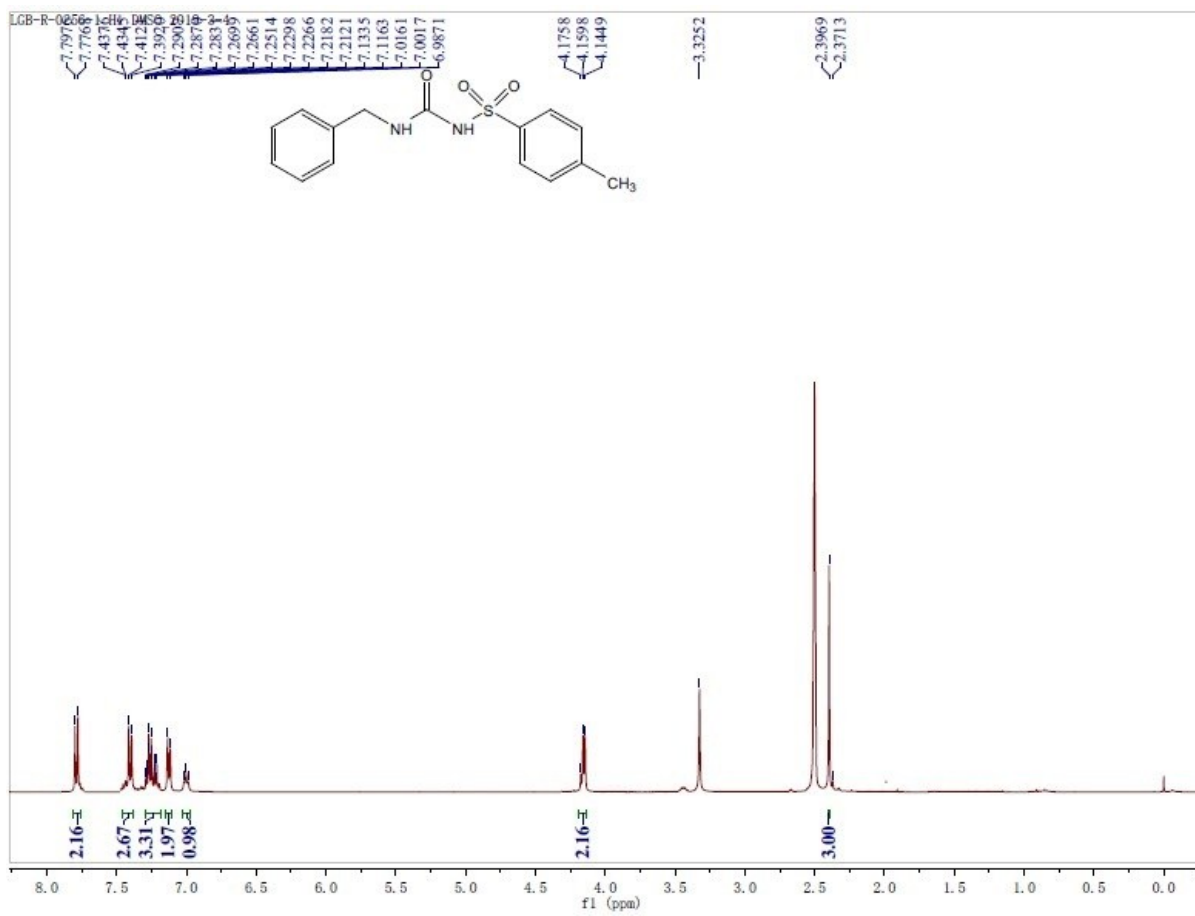
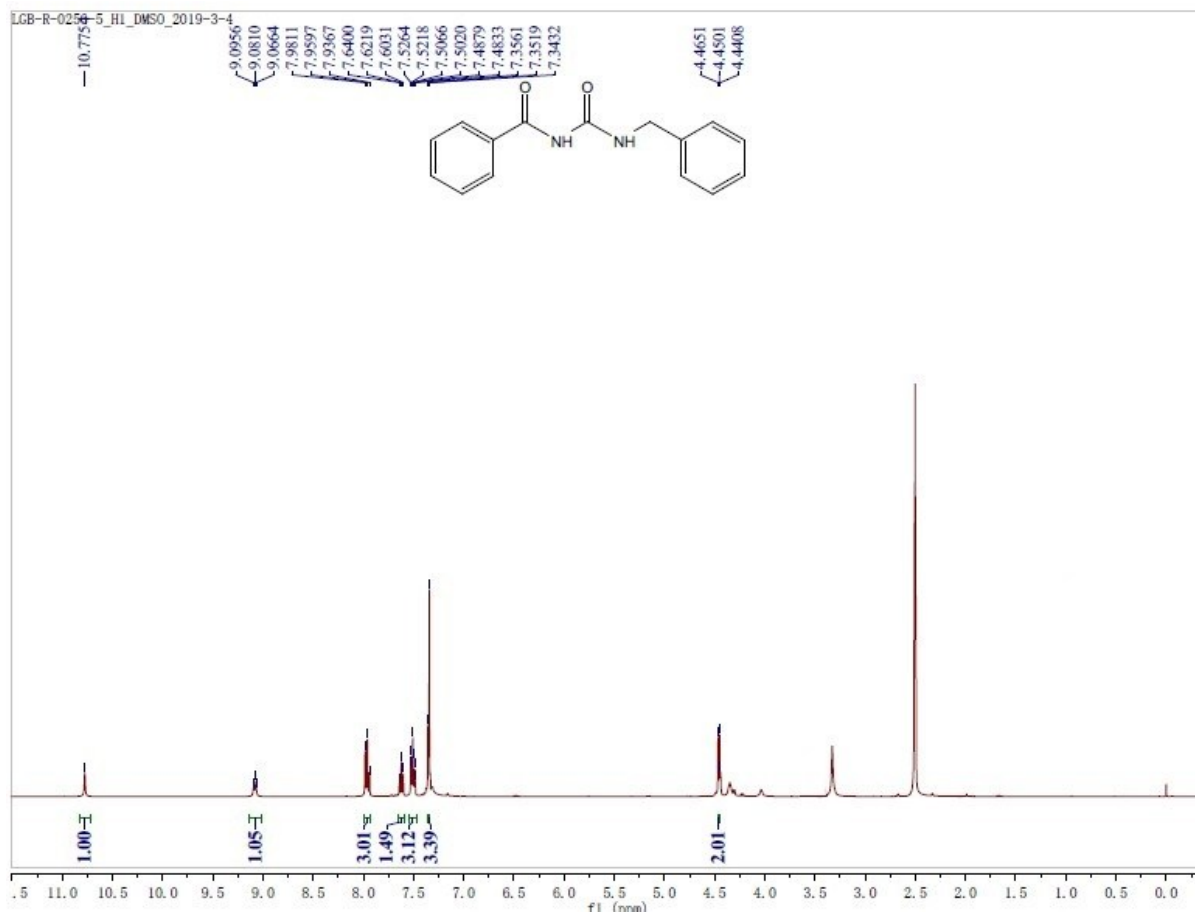


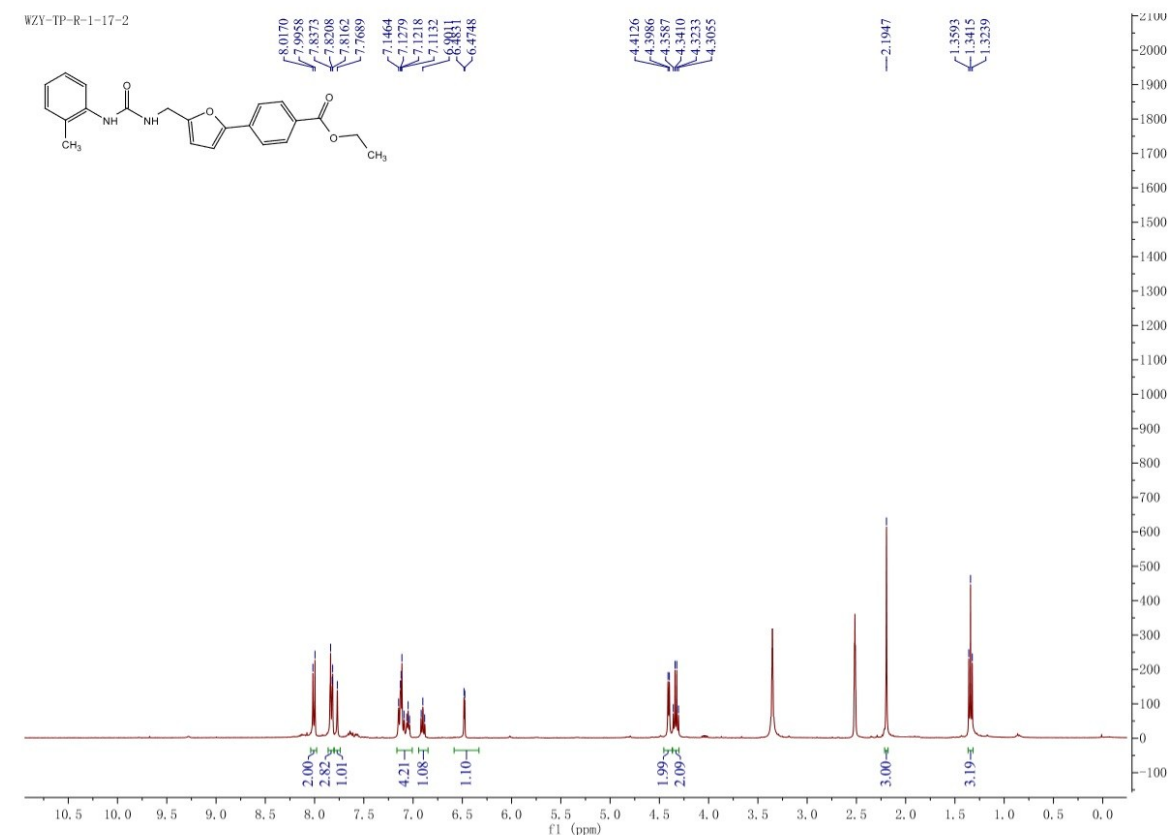
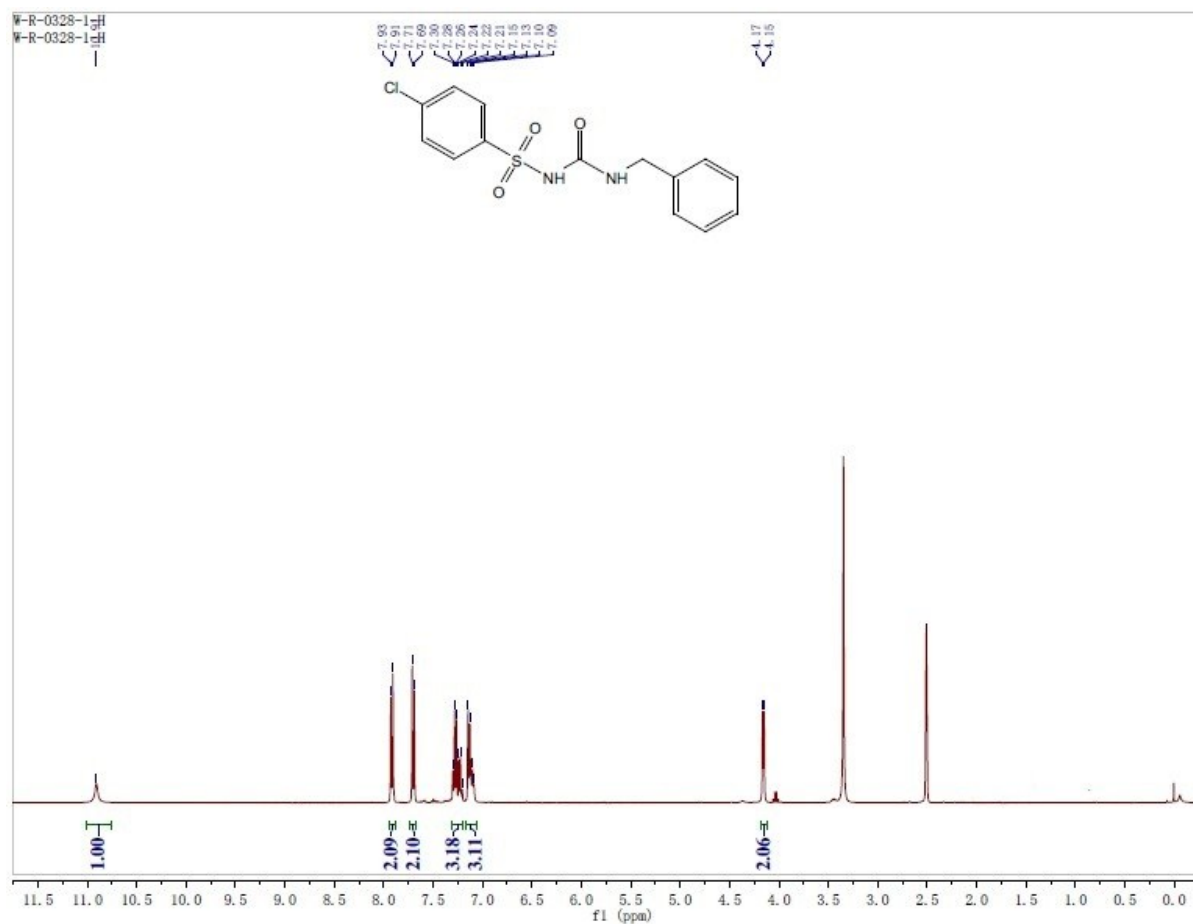


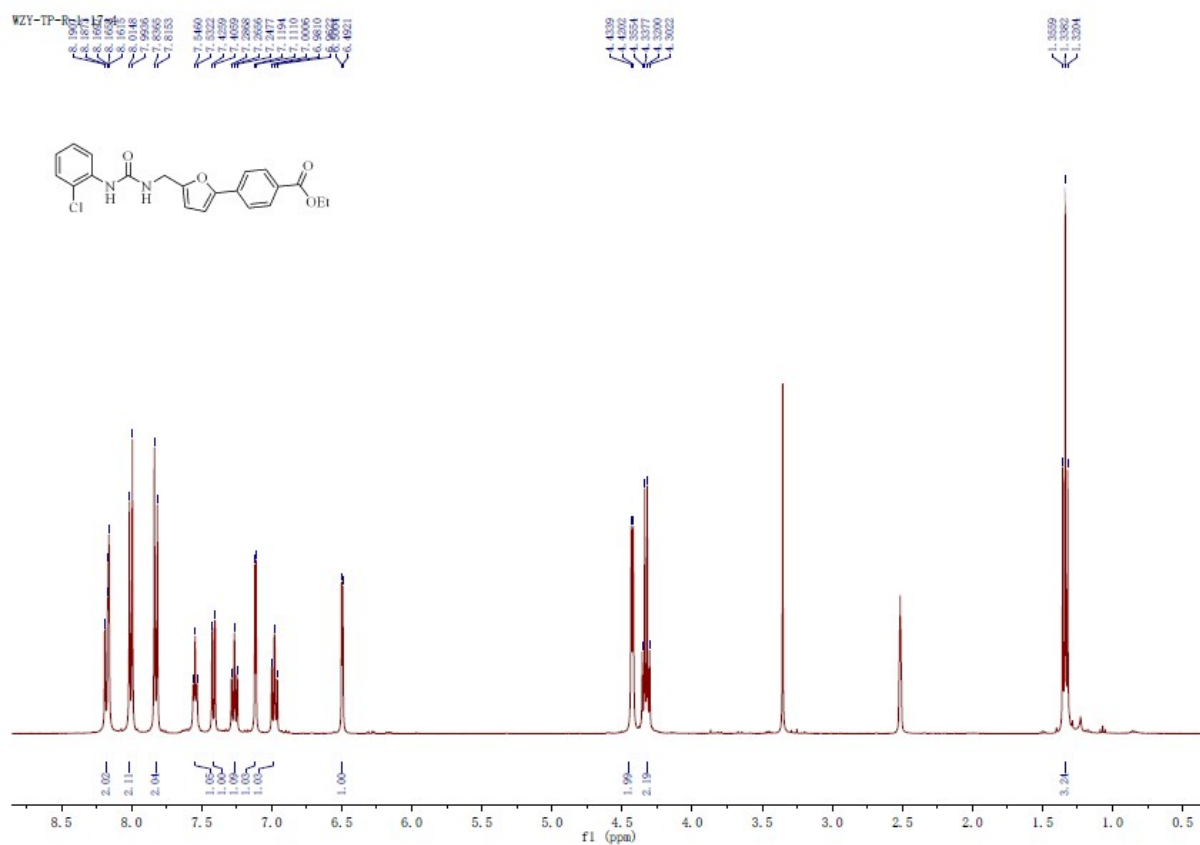
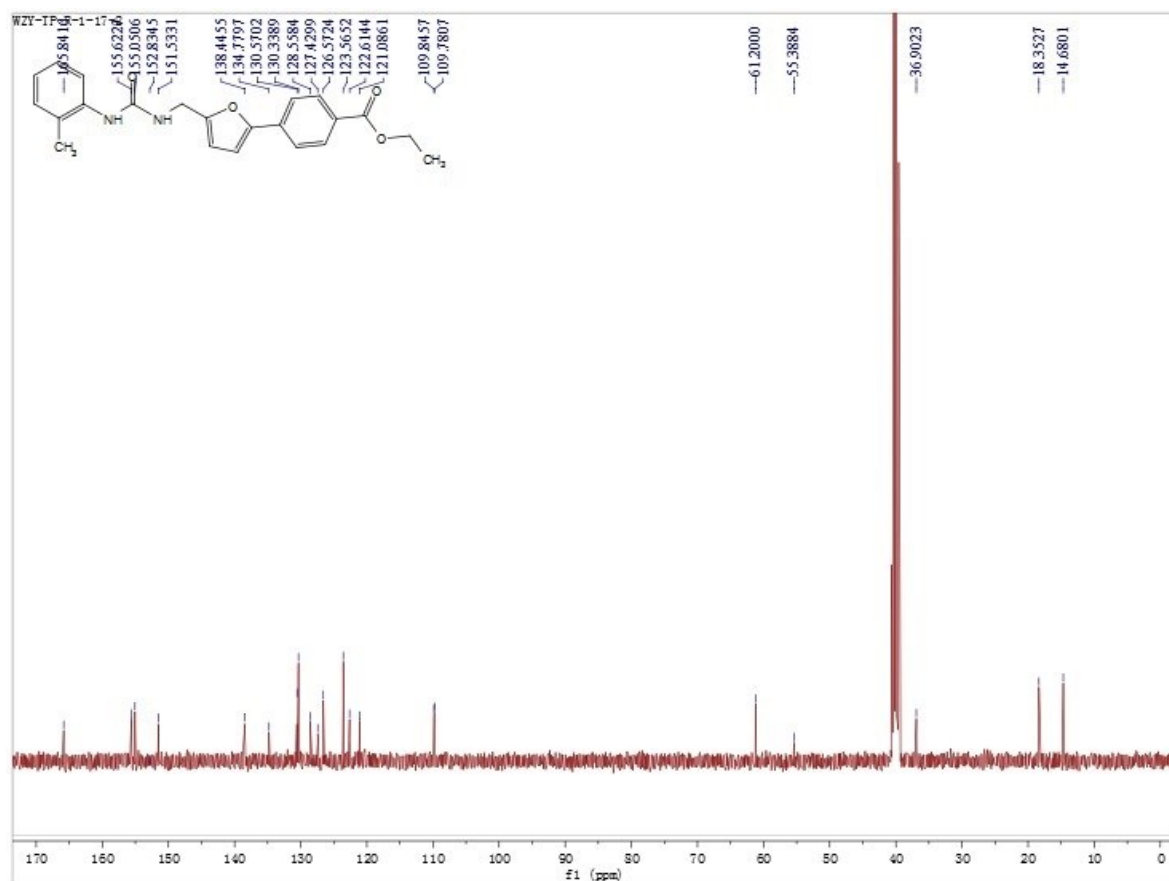


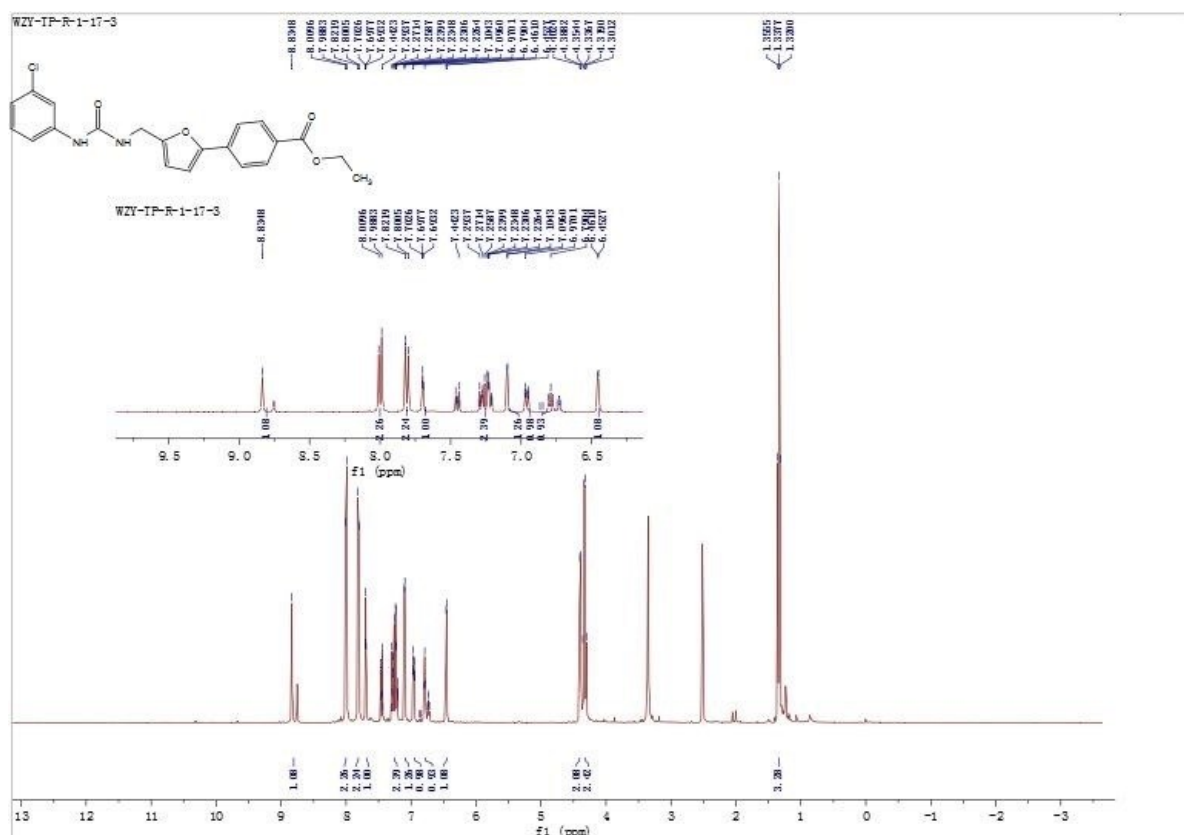
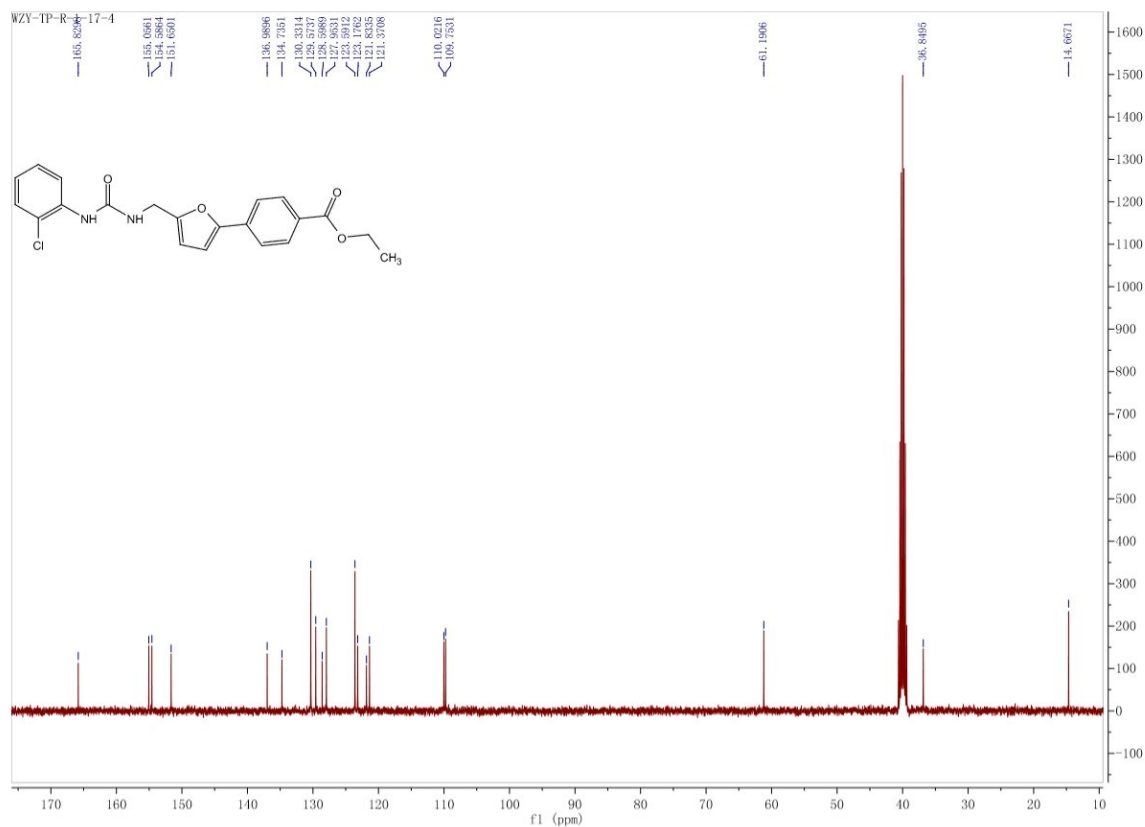




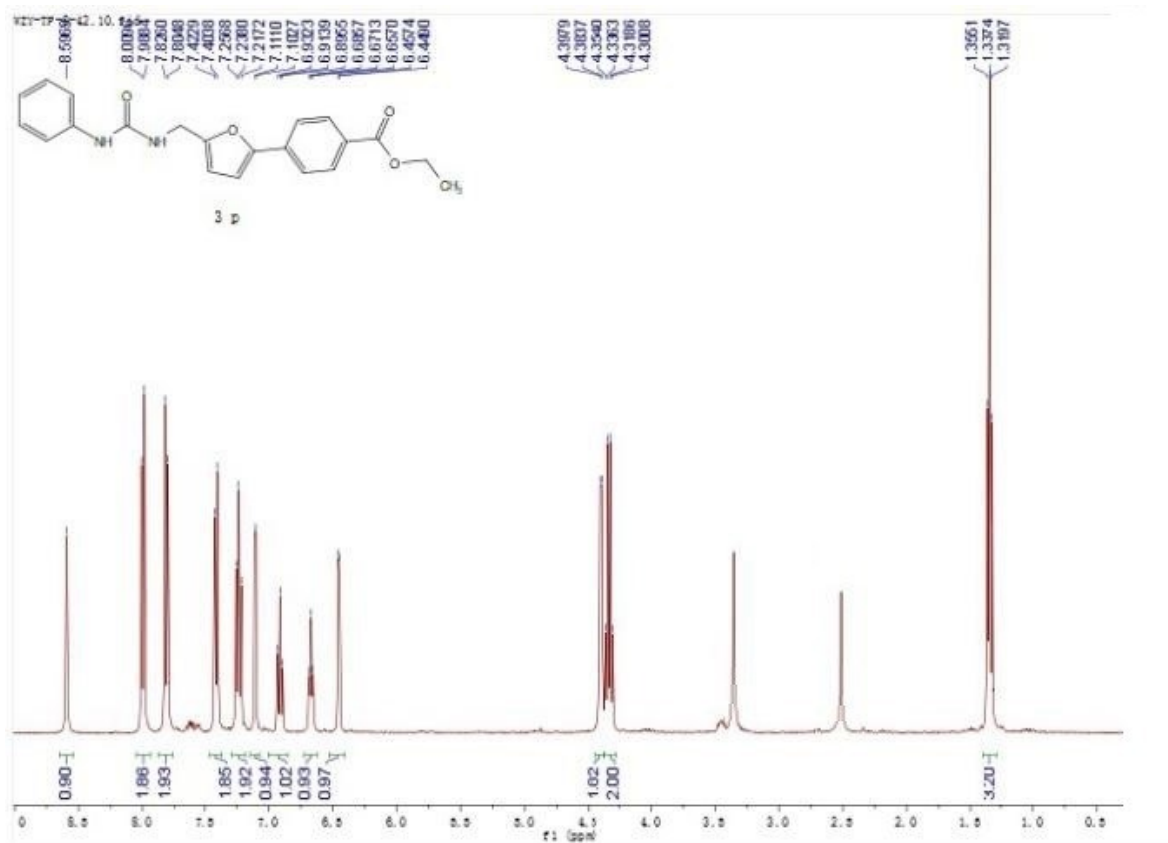
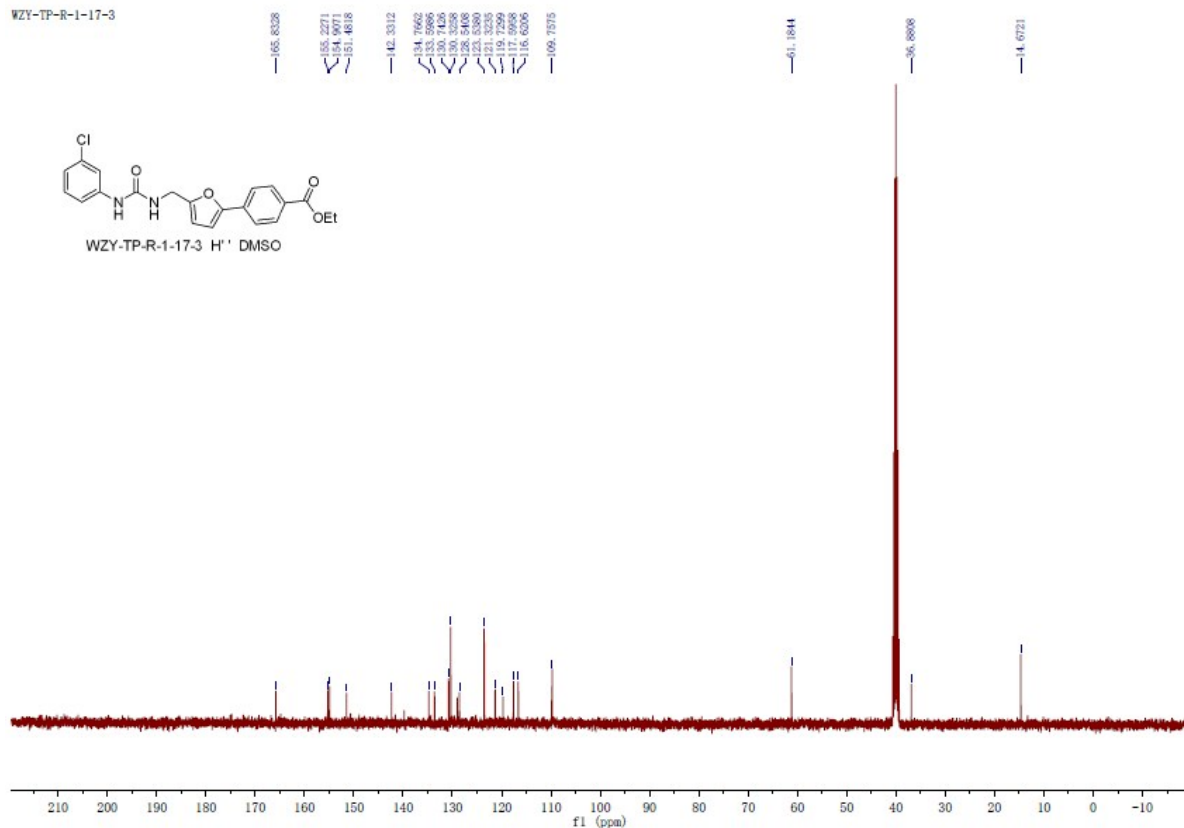




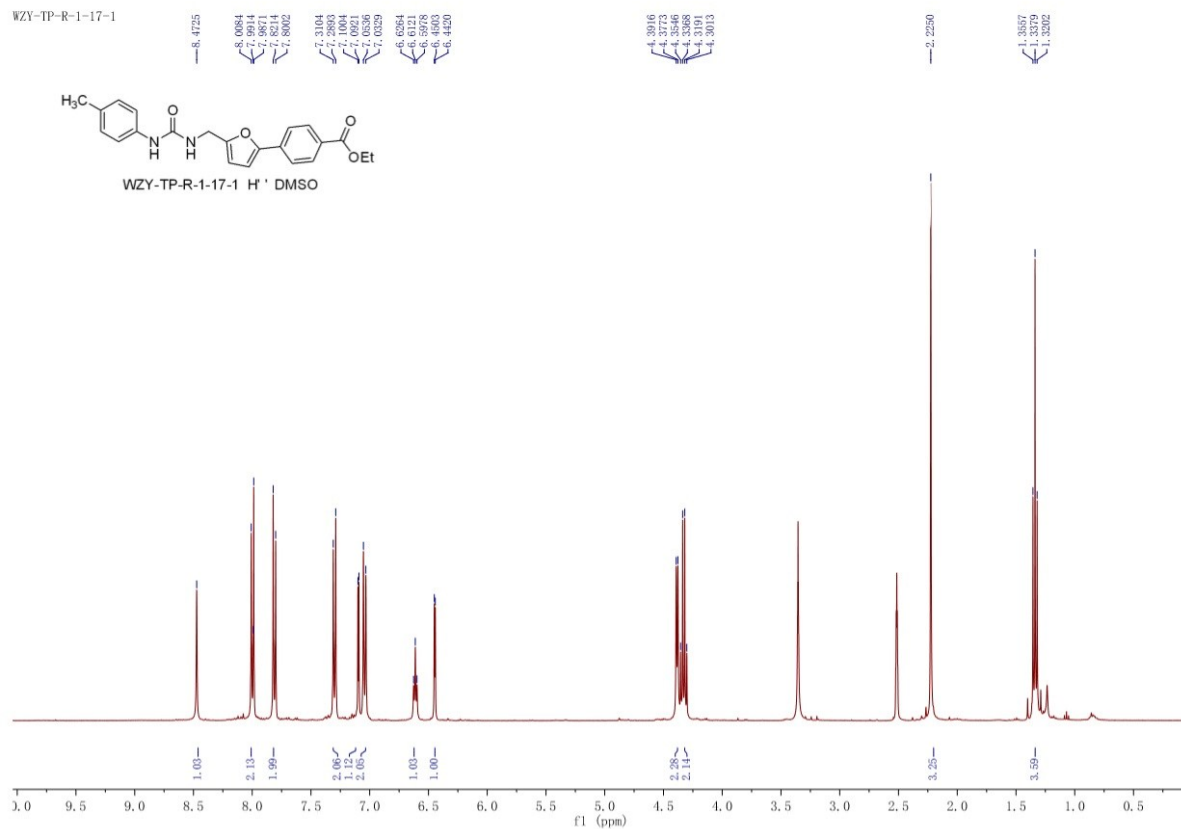




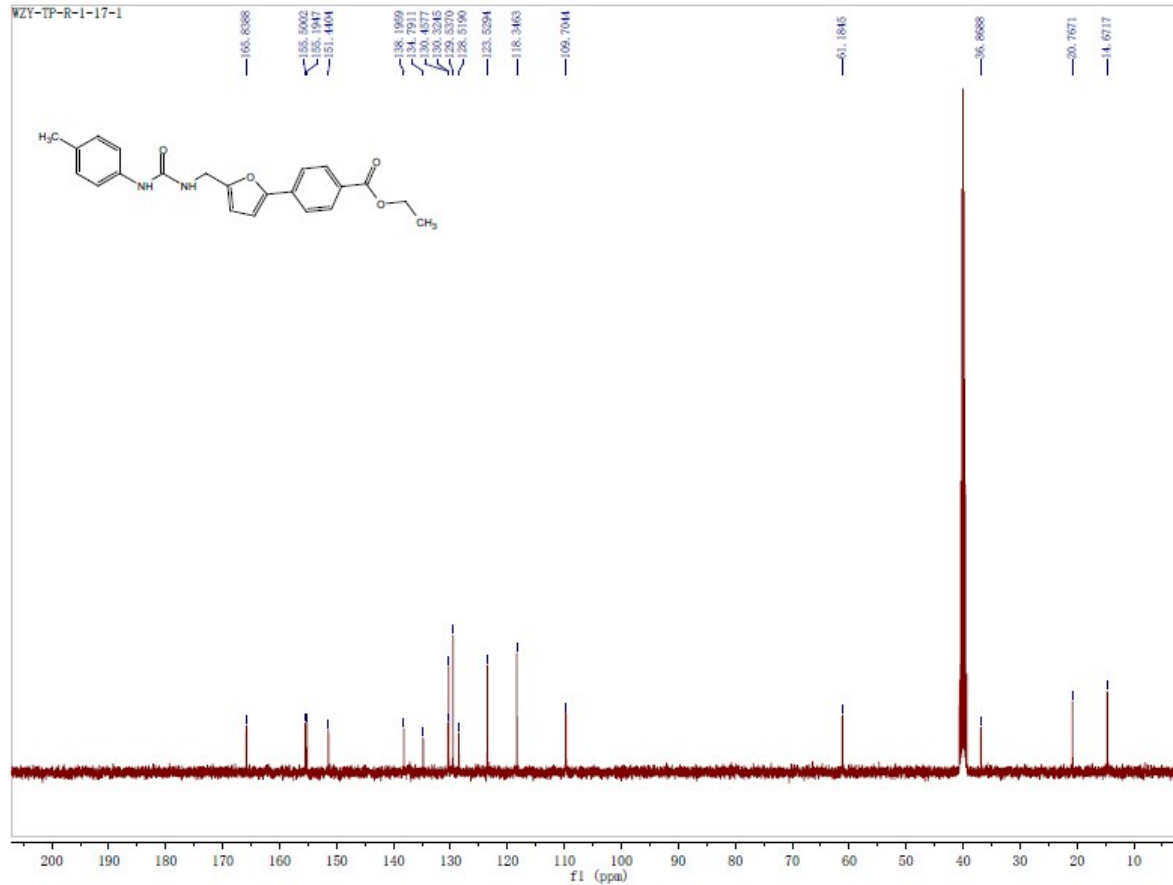
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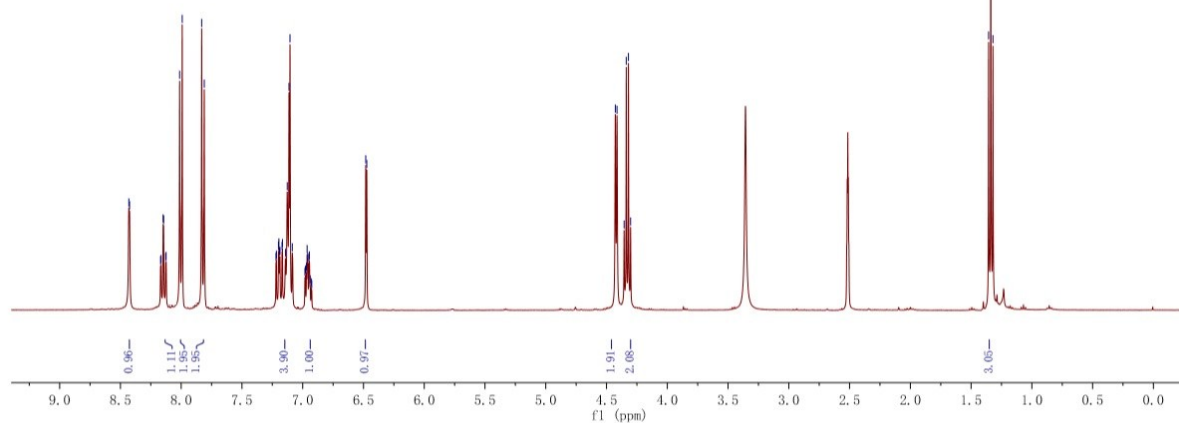
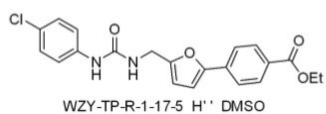


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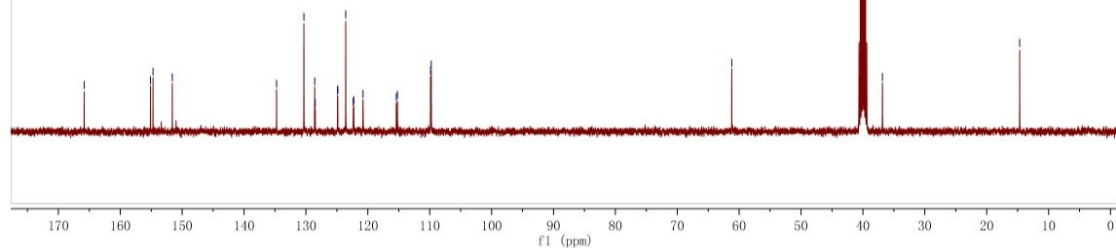
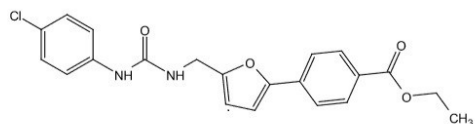
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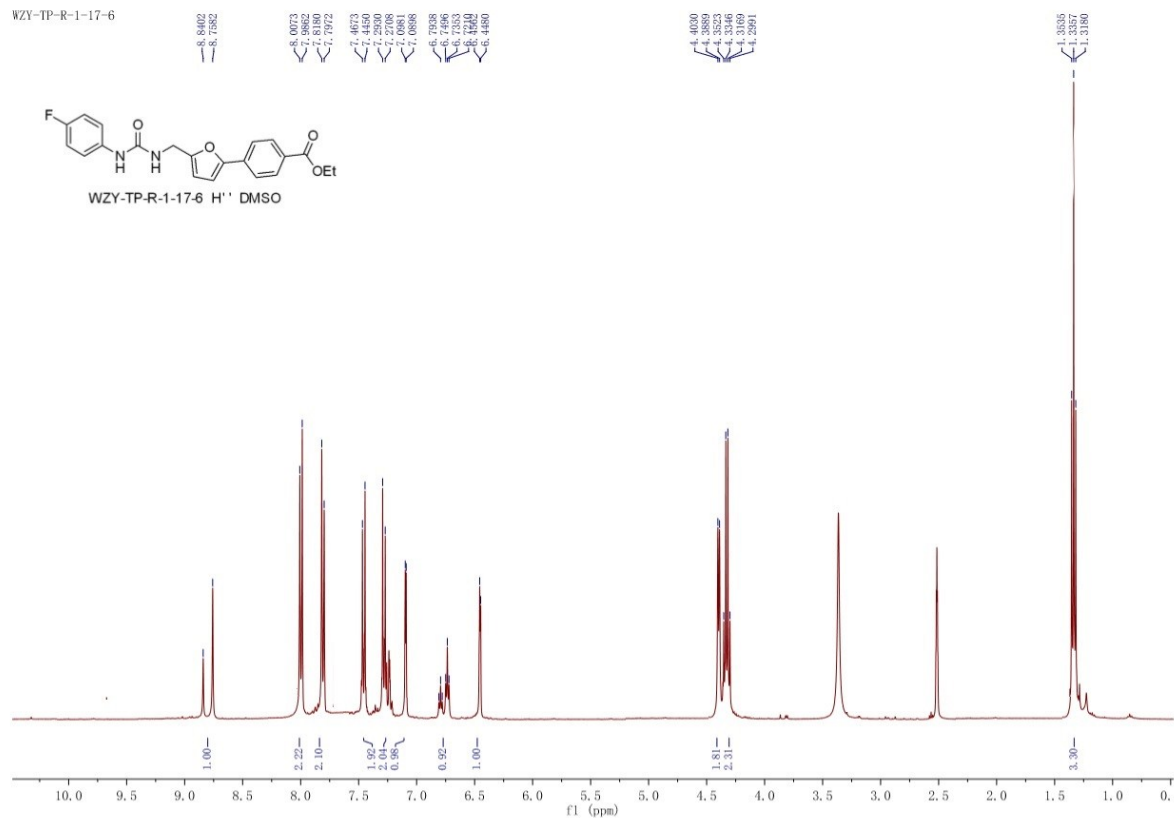


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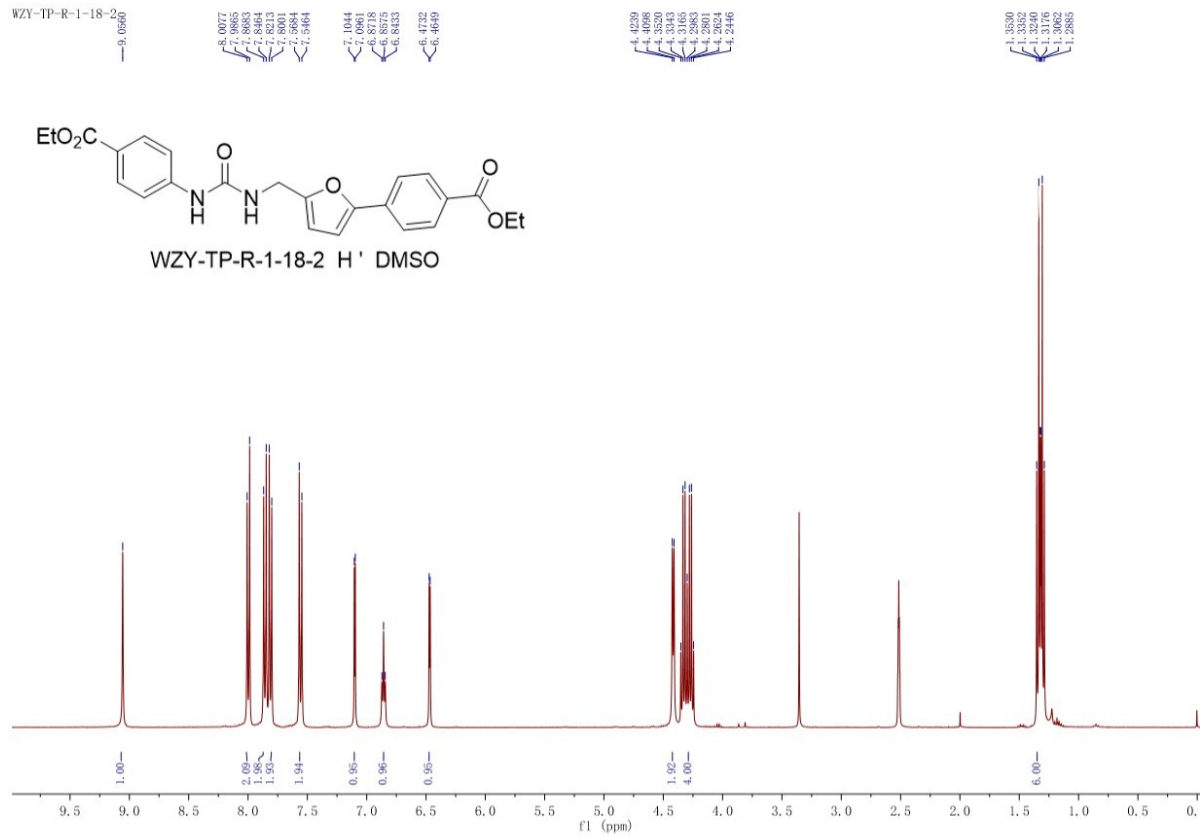
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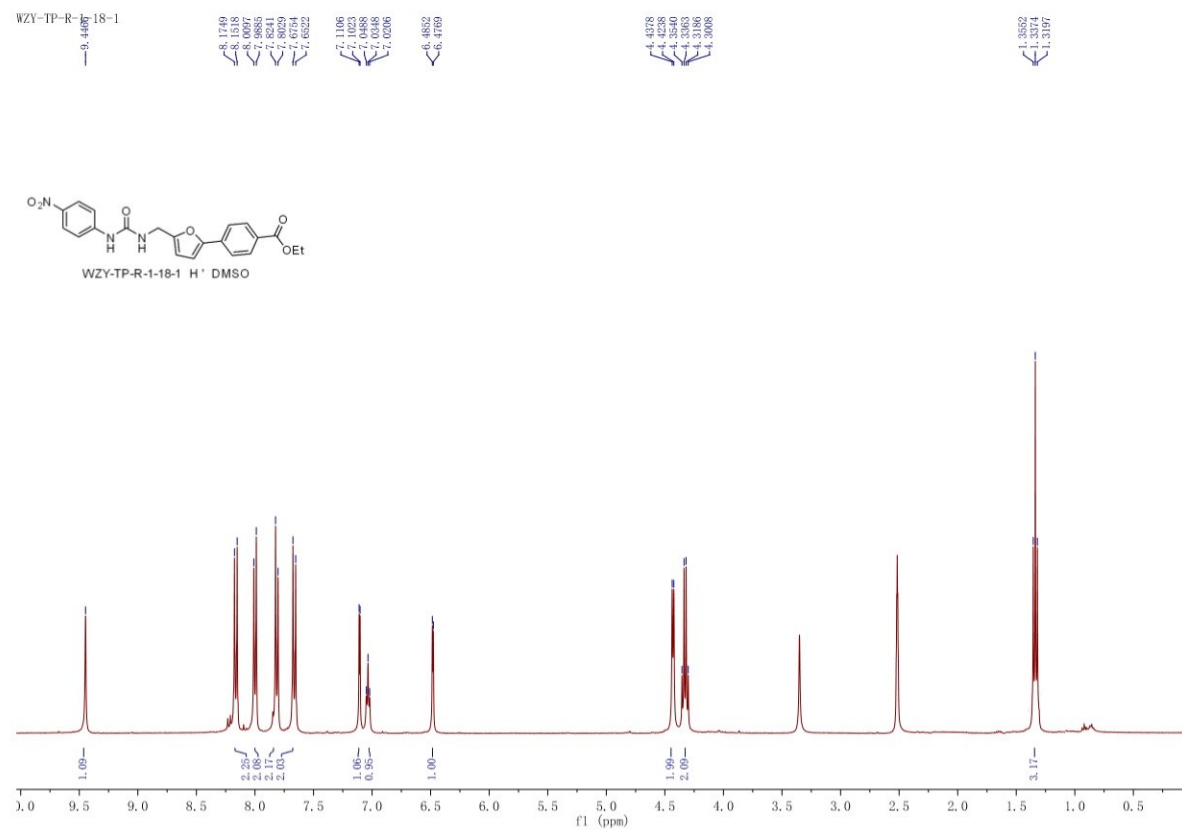
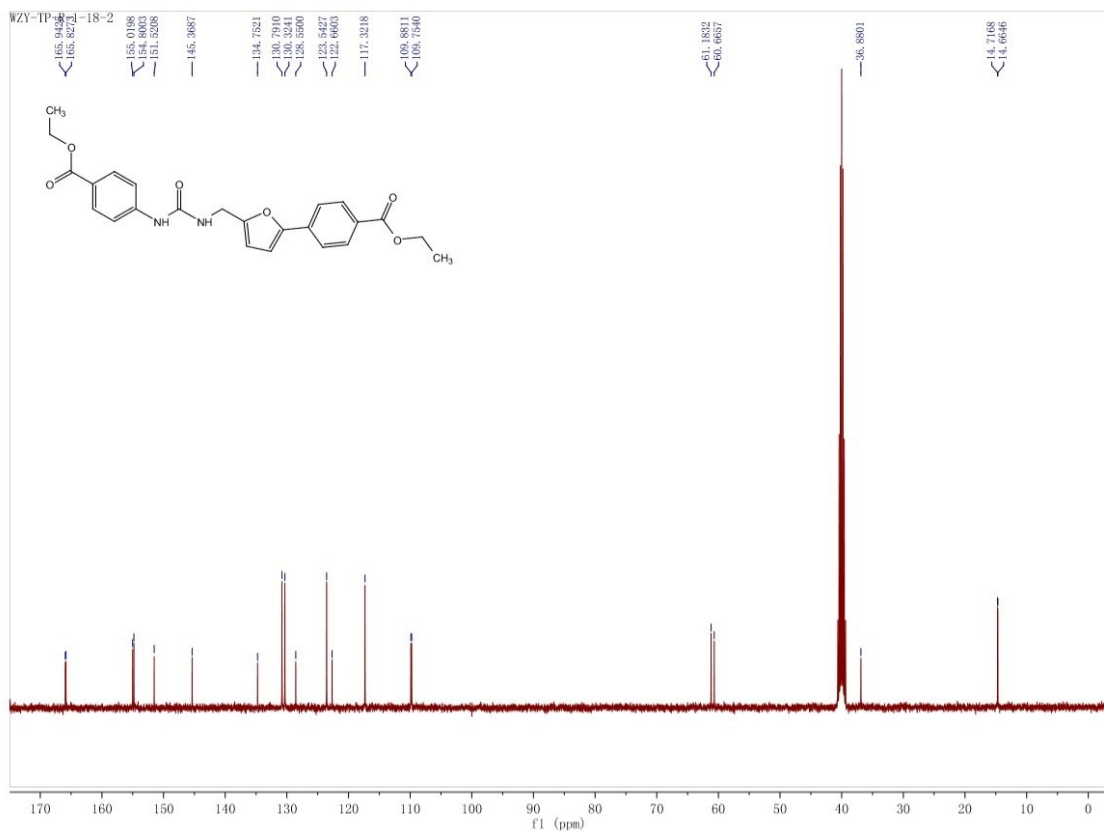


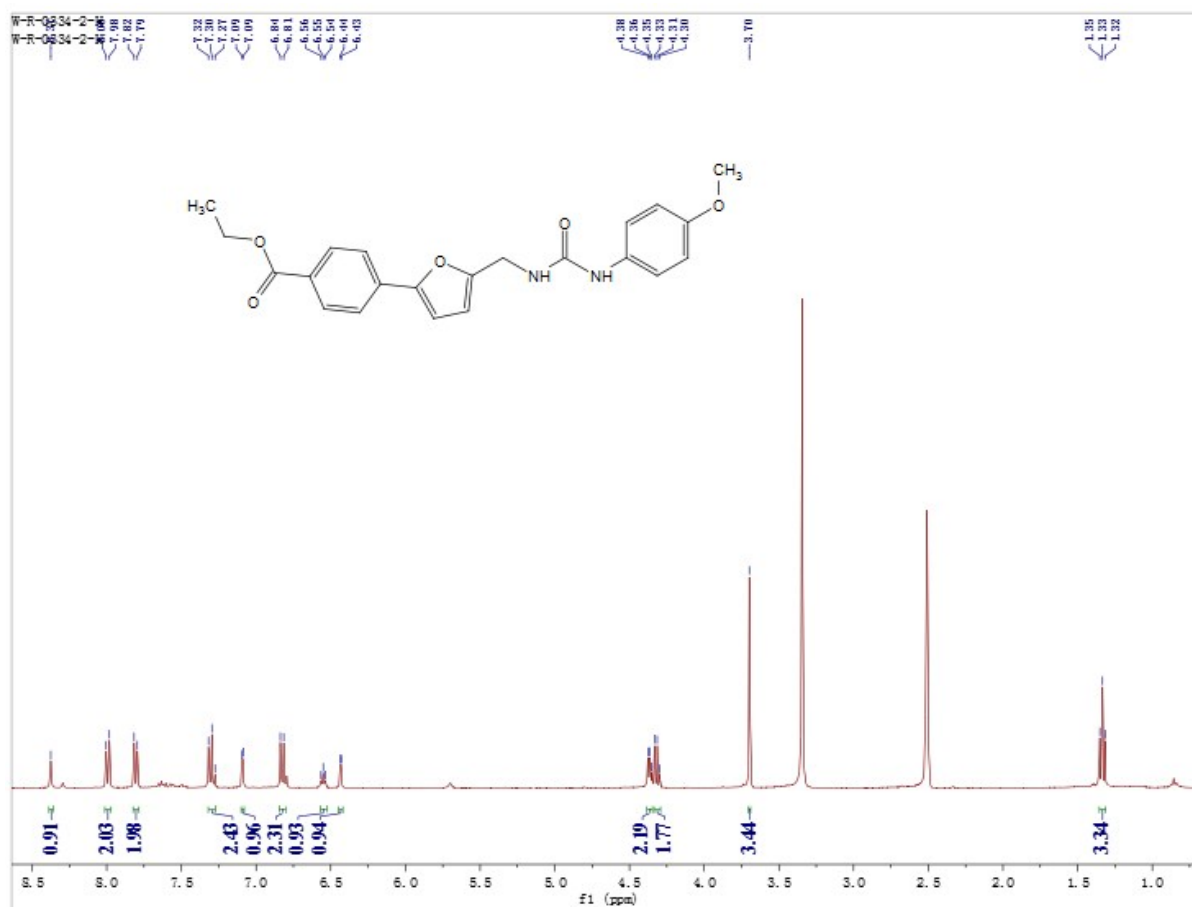
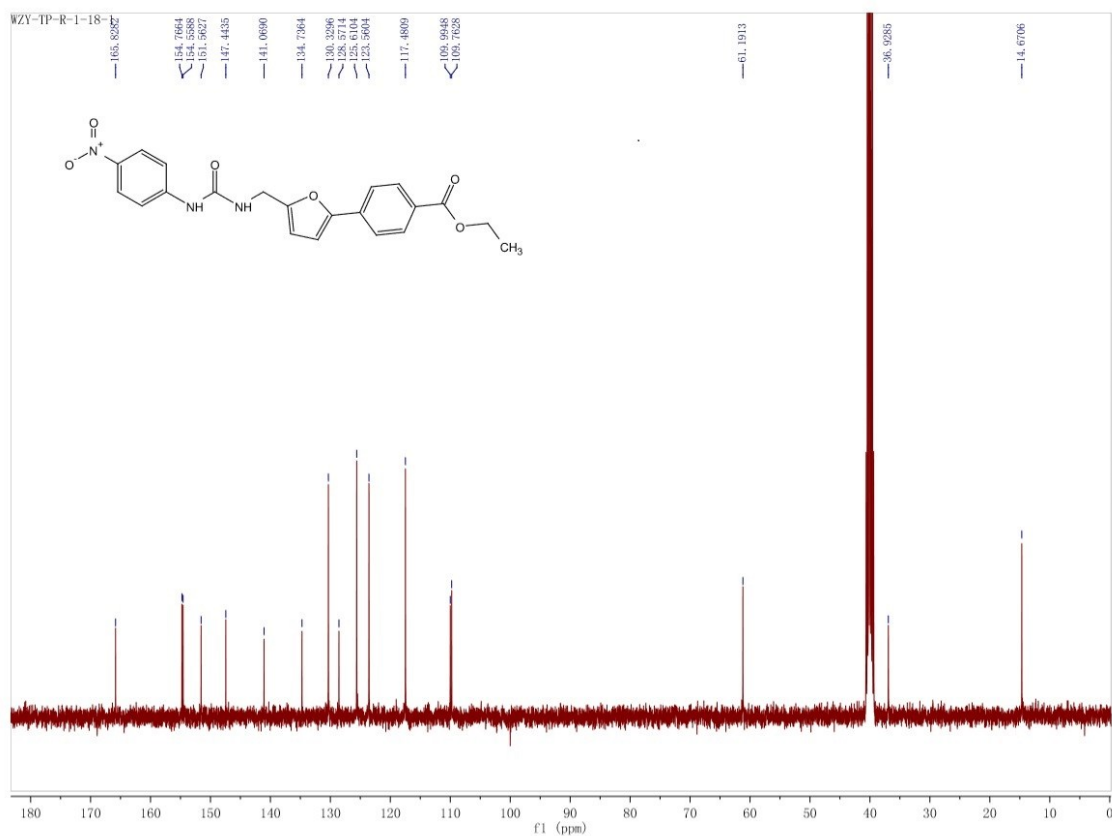
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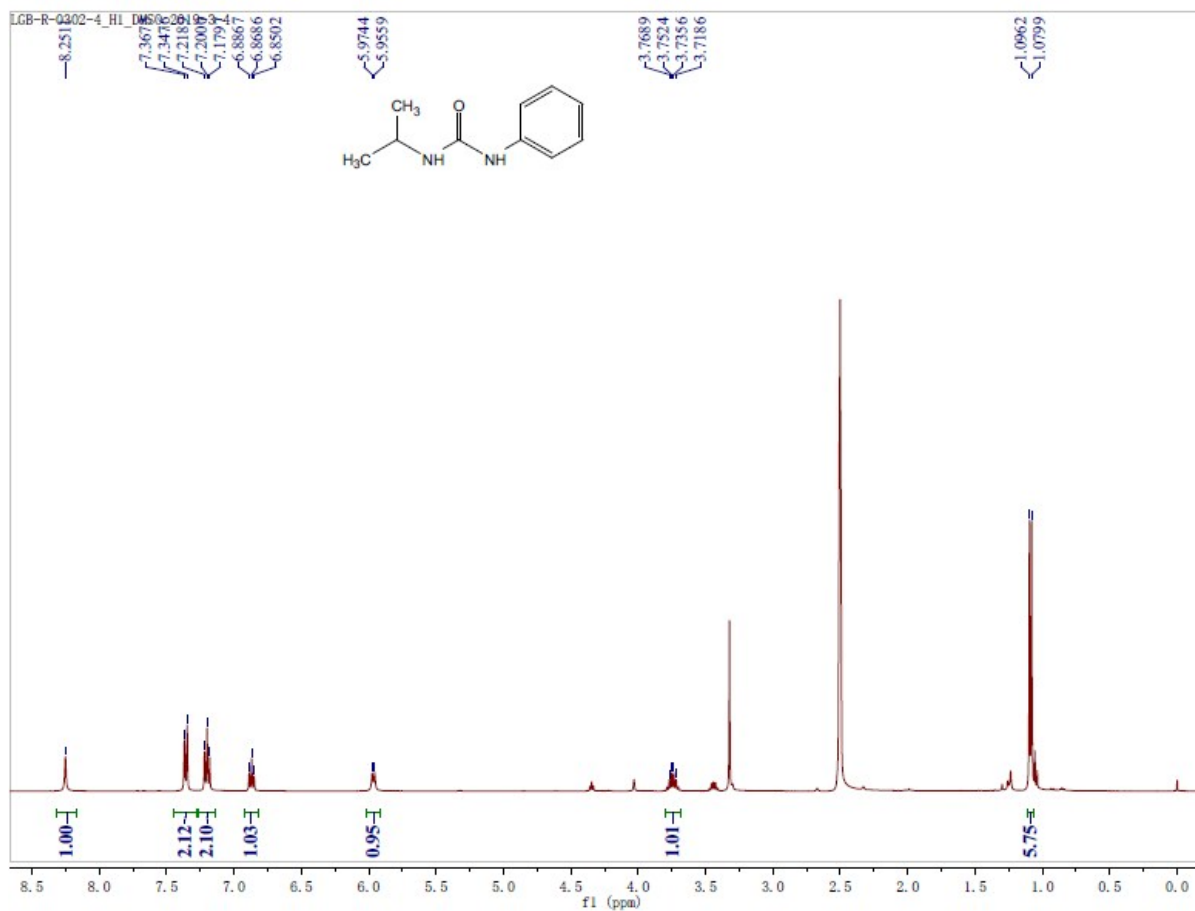
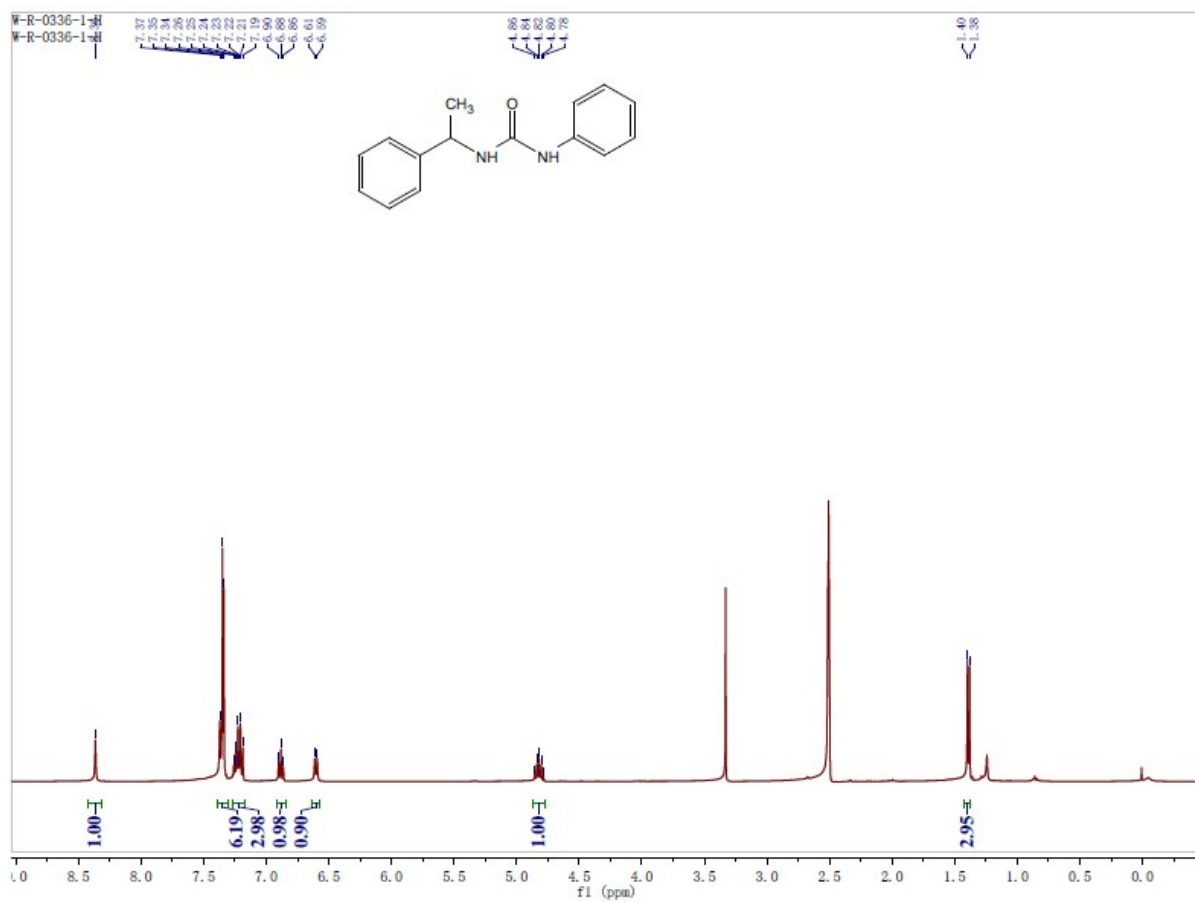


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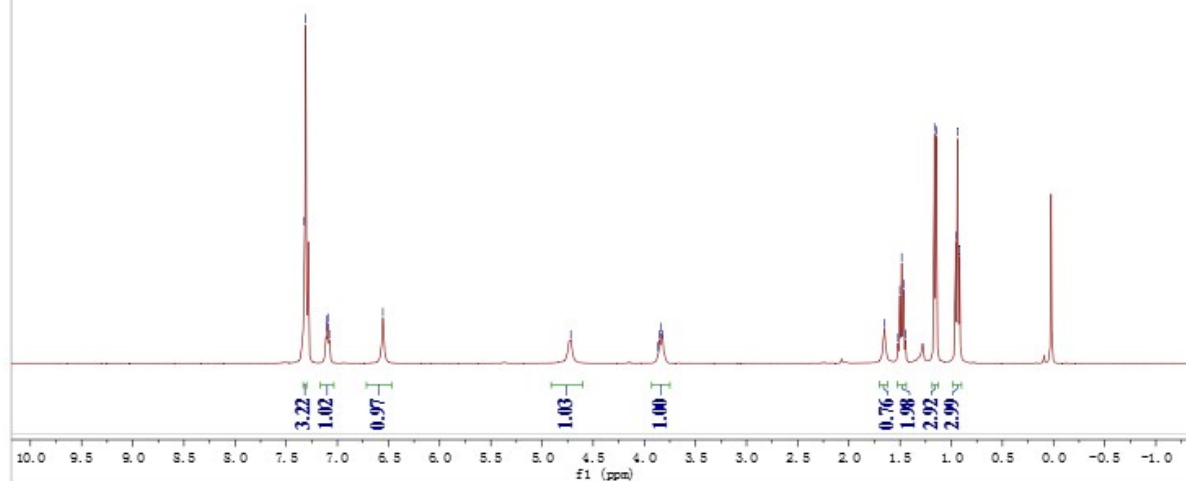
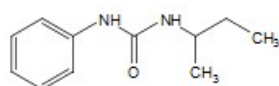






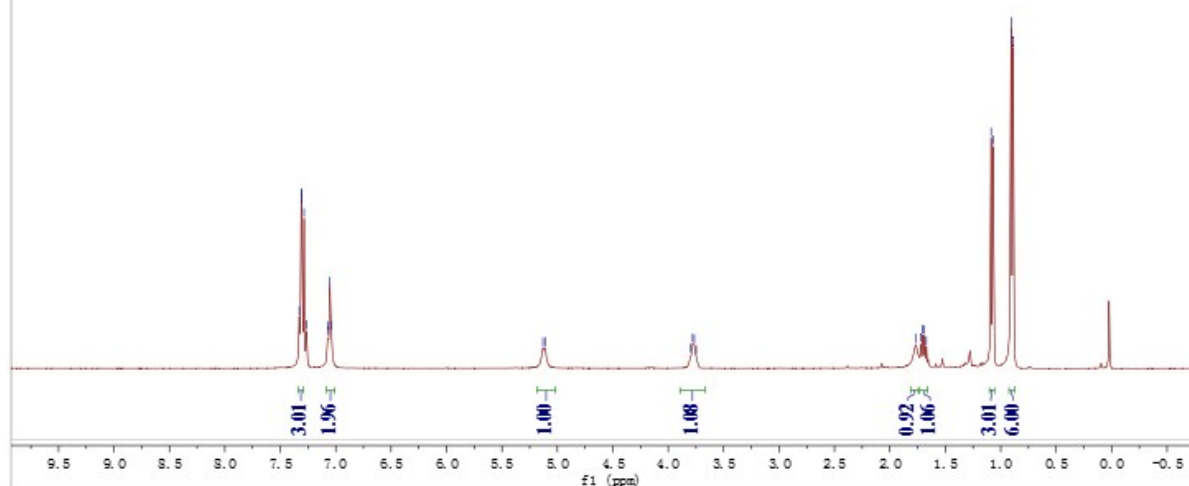
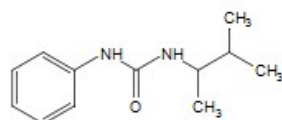
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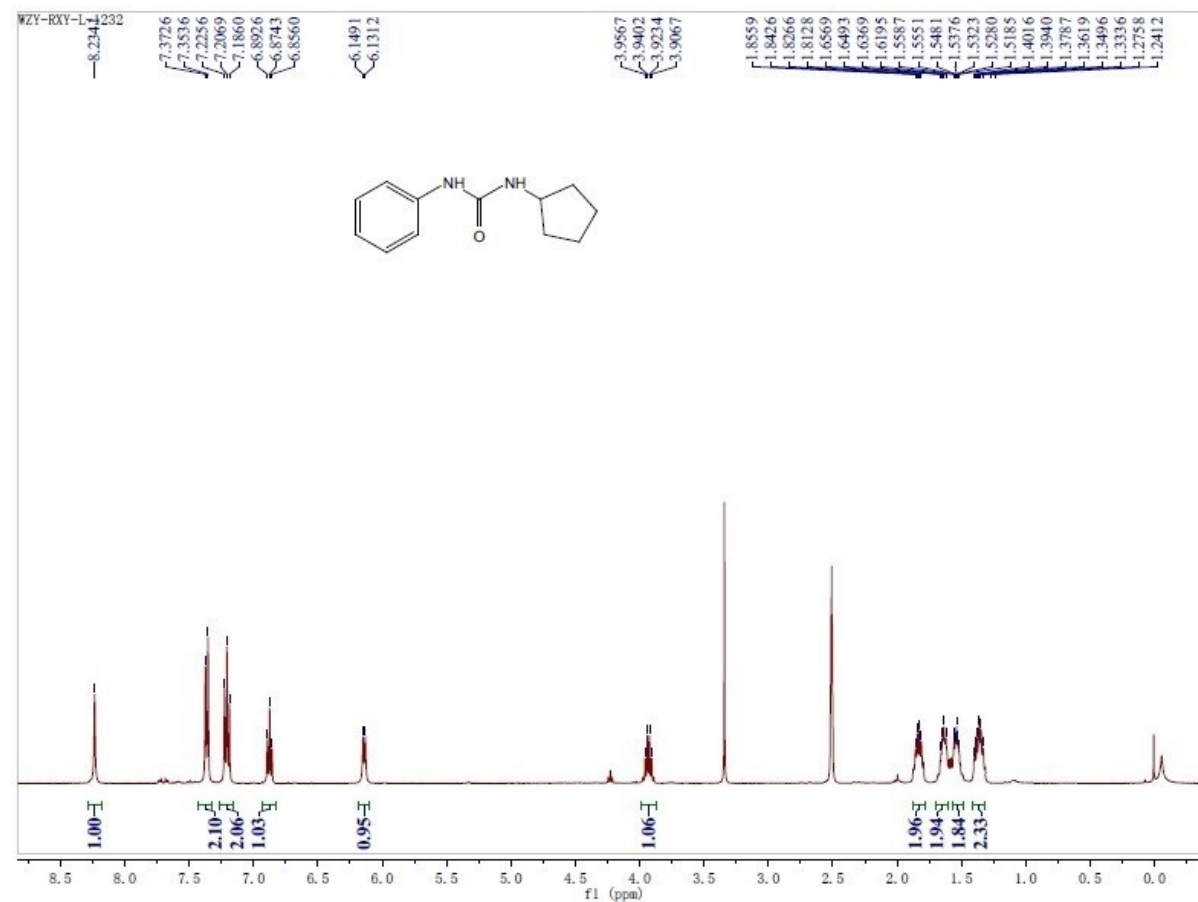
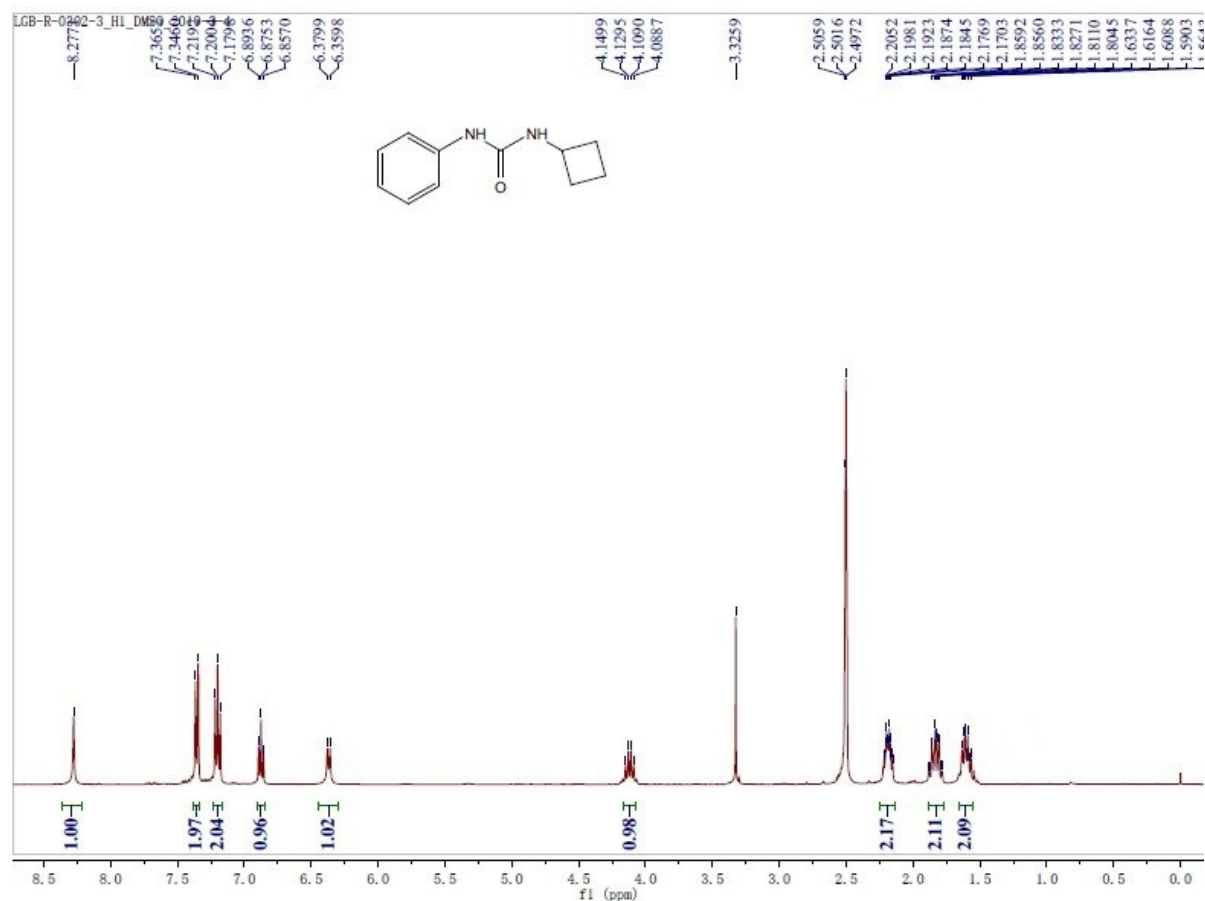
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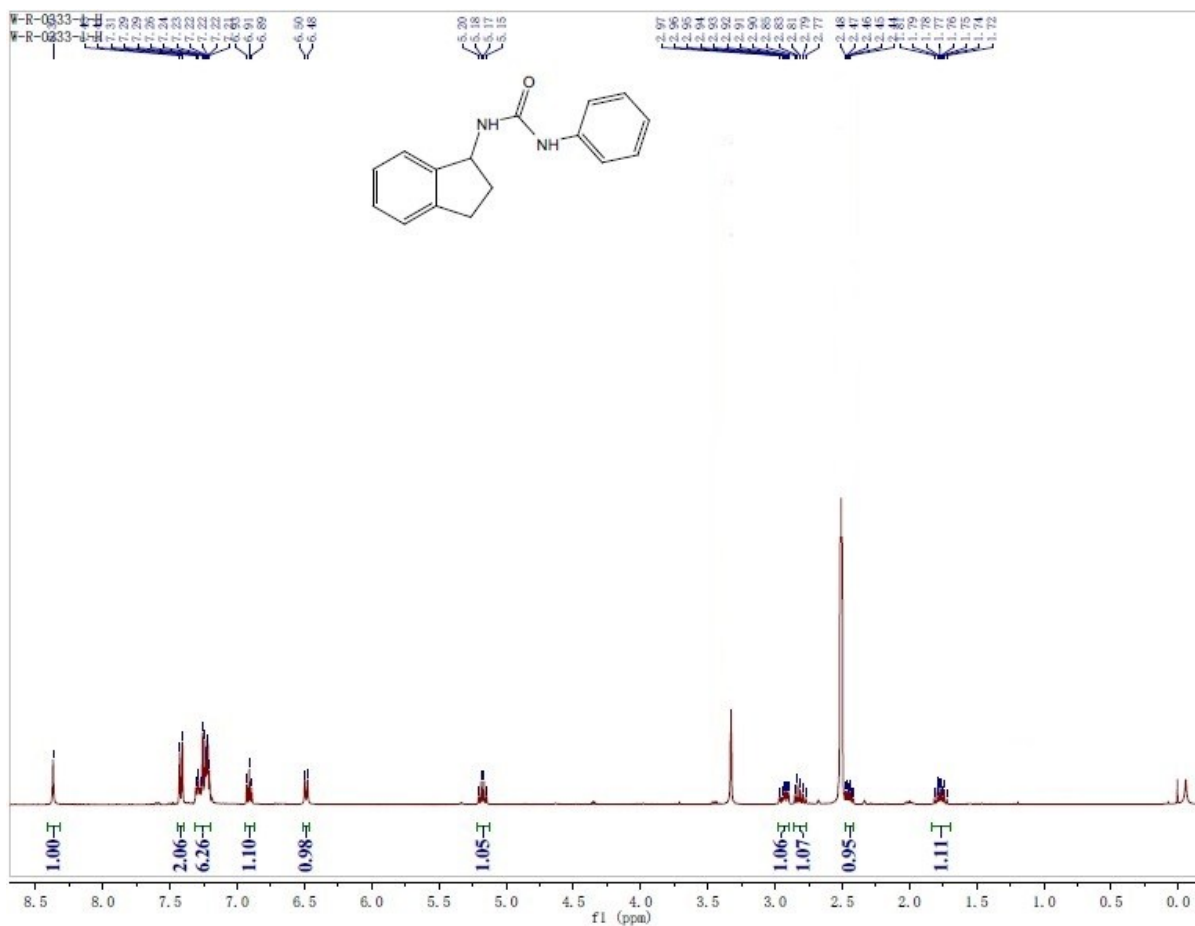
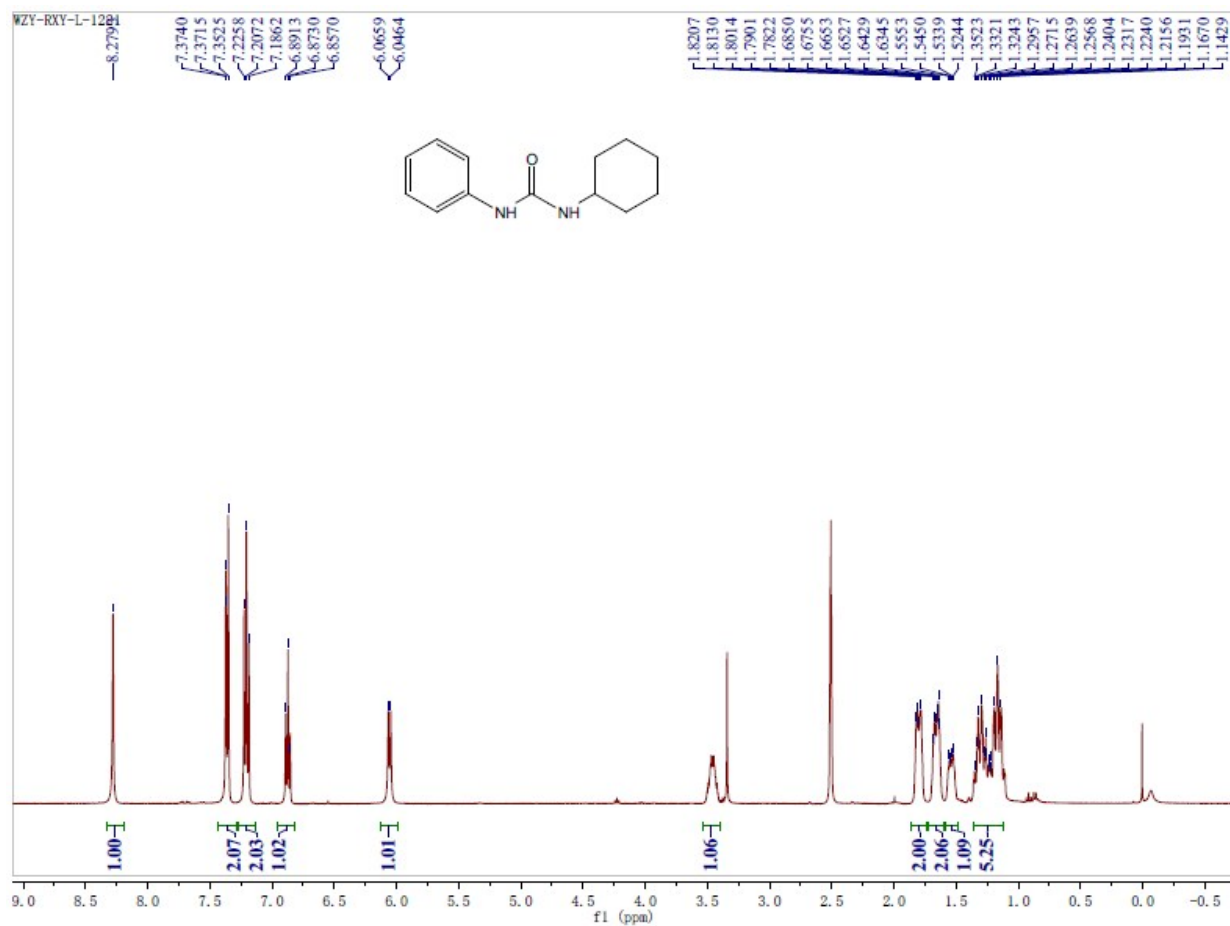


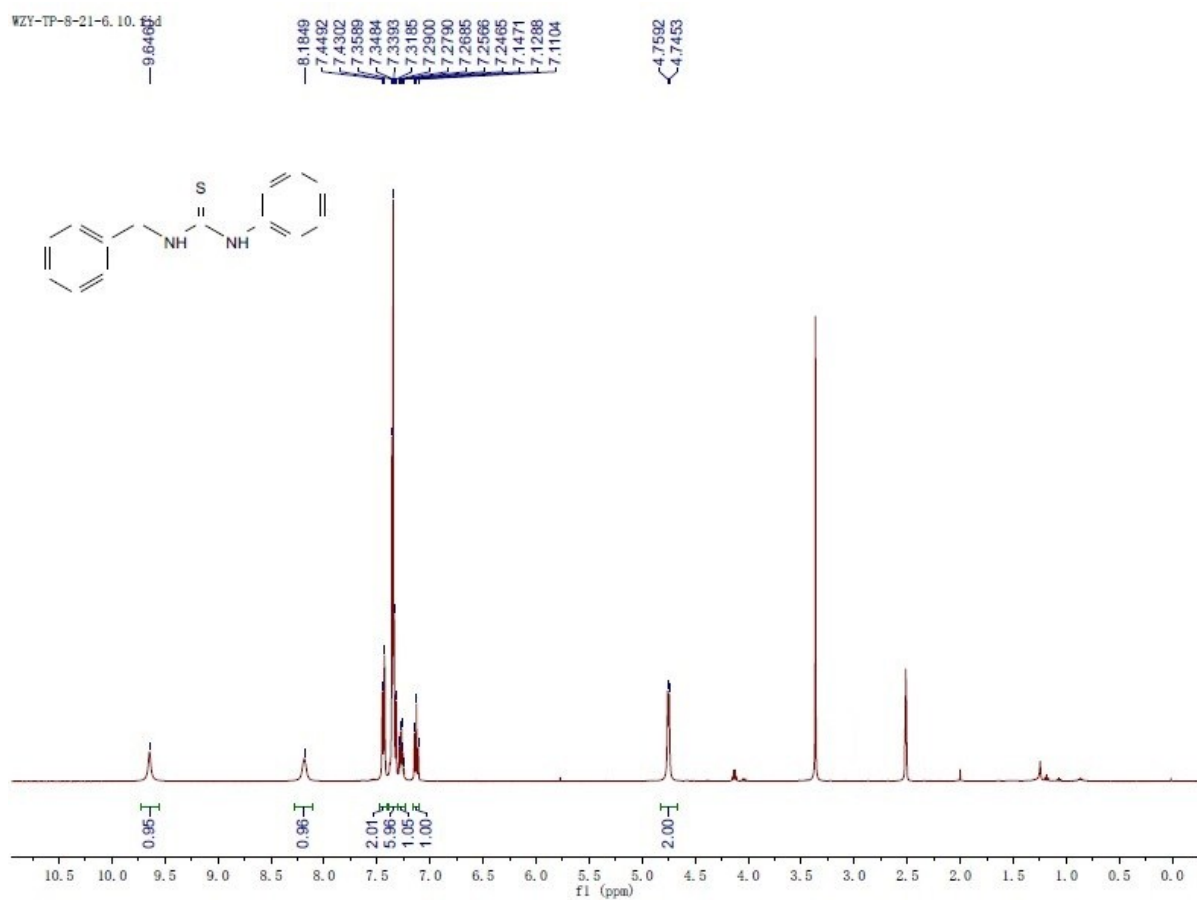
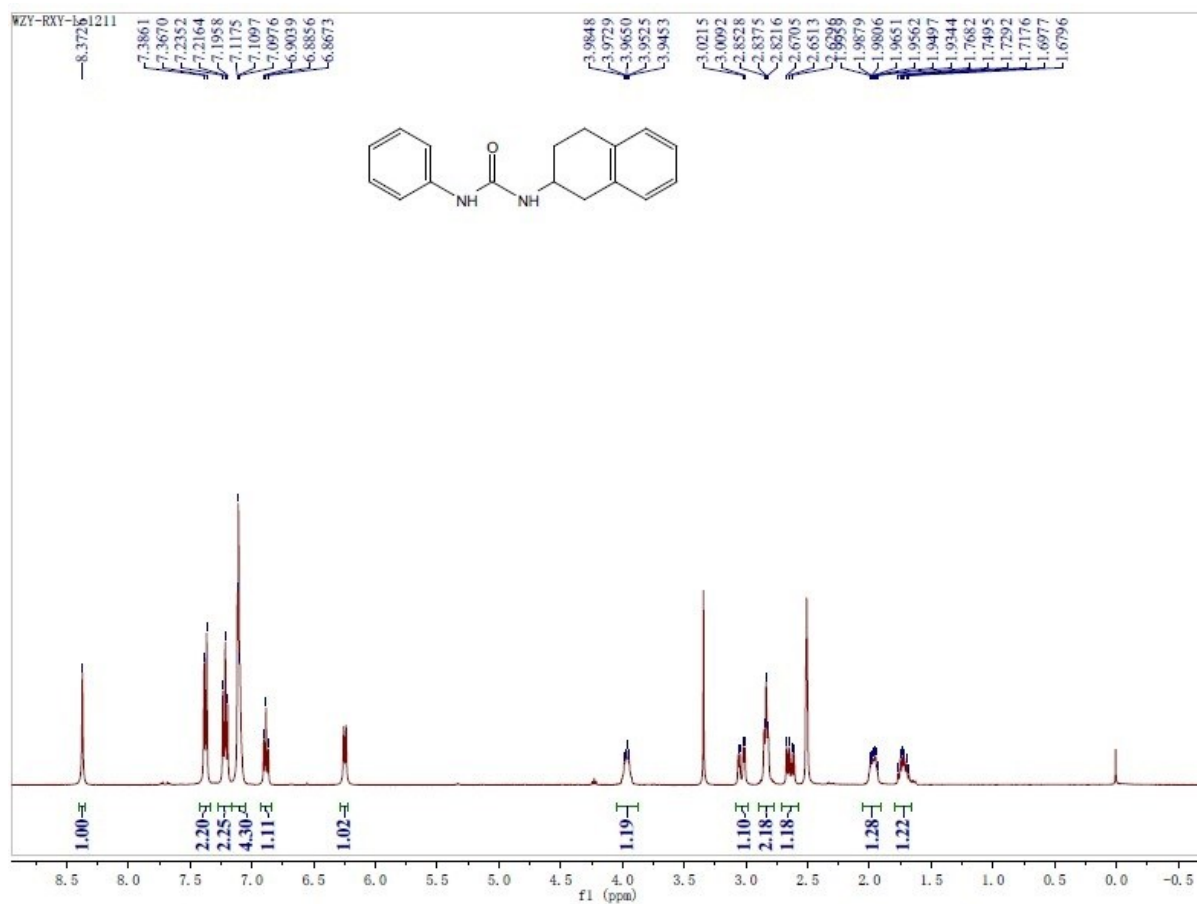
W-R-0704-3
W-R-0704-3

7.33
7.31
7.31
7.30
7.29
7.26
7.07
7.07
7.05
7.04
5.13
5.11
3.80
3.78
3.76
3.75
1.77
1.72
1.70
1.69
1.67
1.09
1.07
0.91
0.89

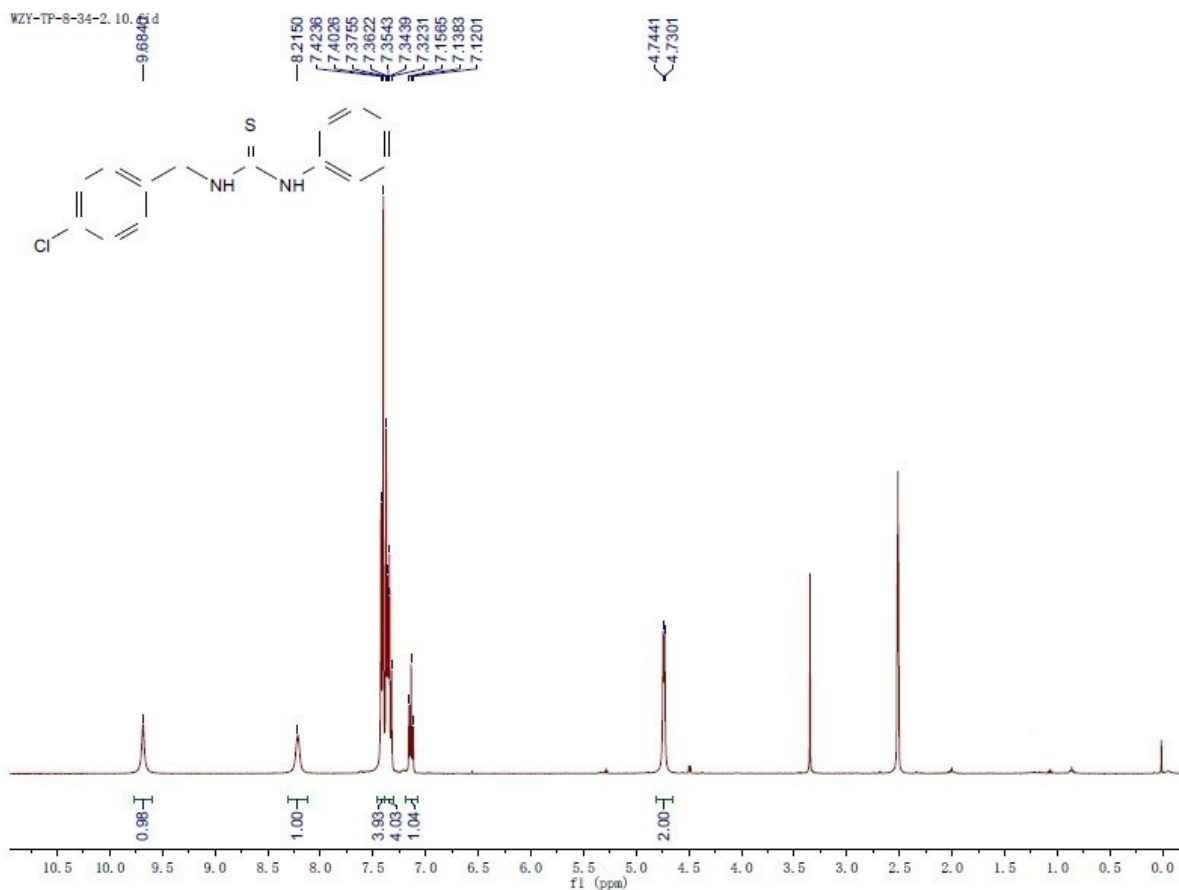




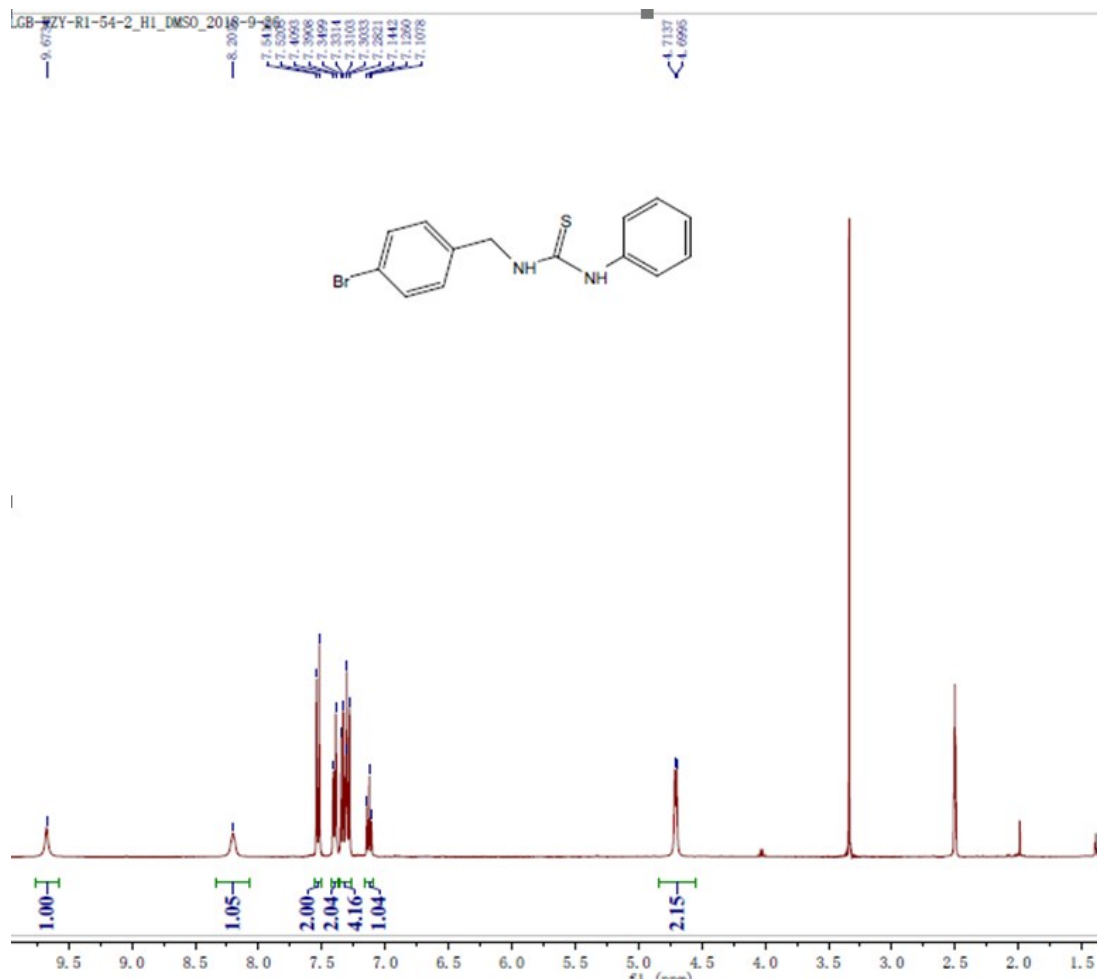


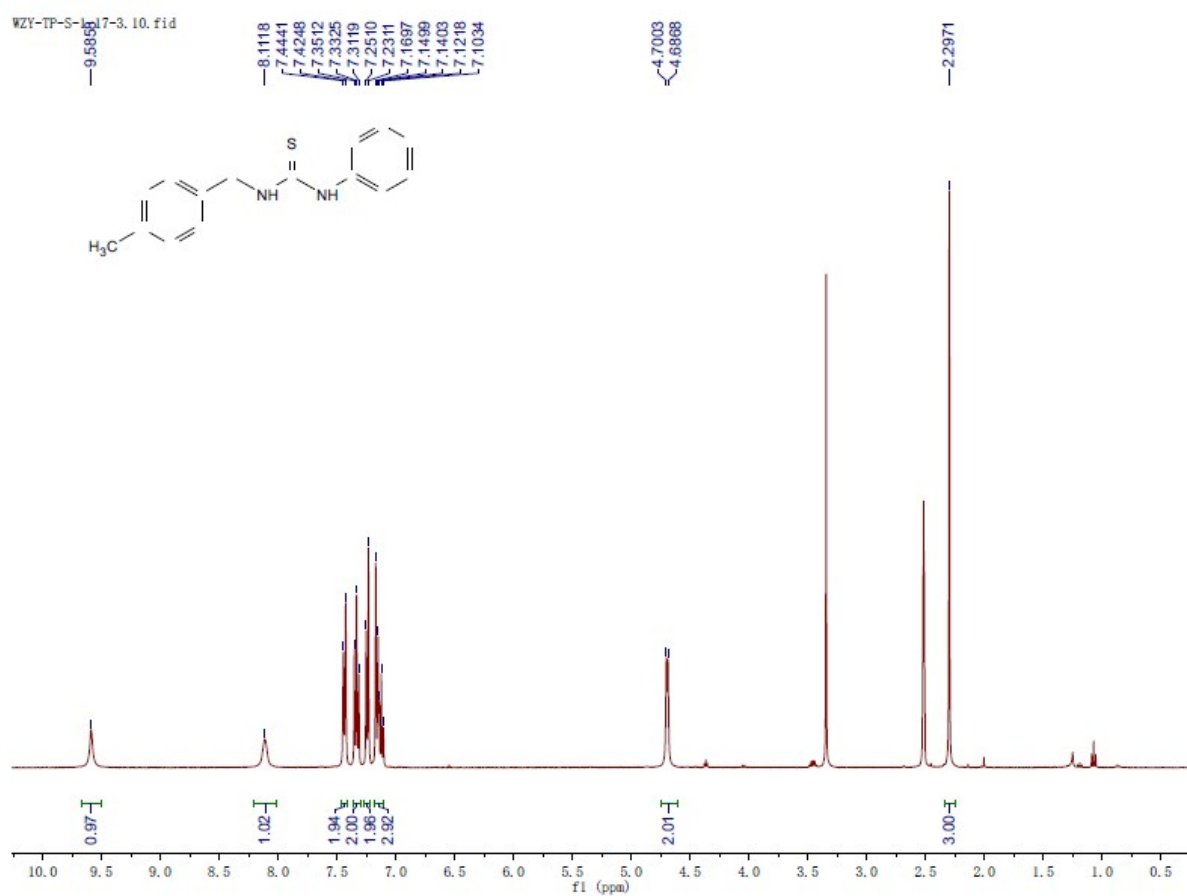
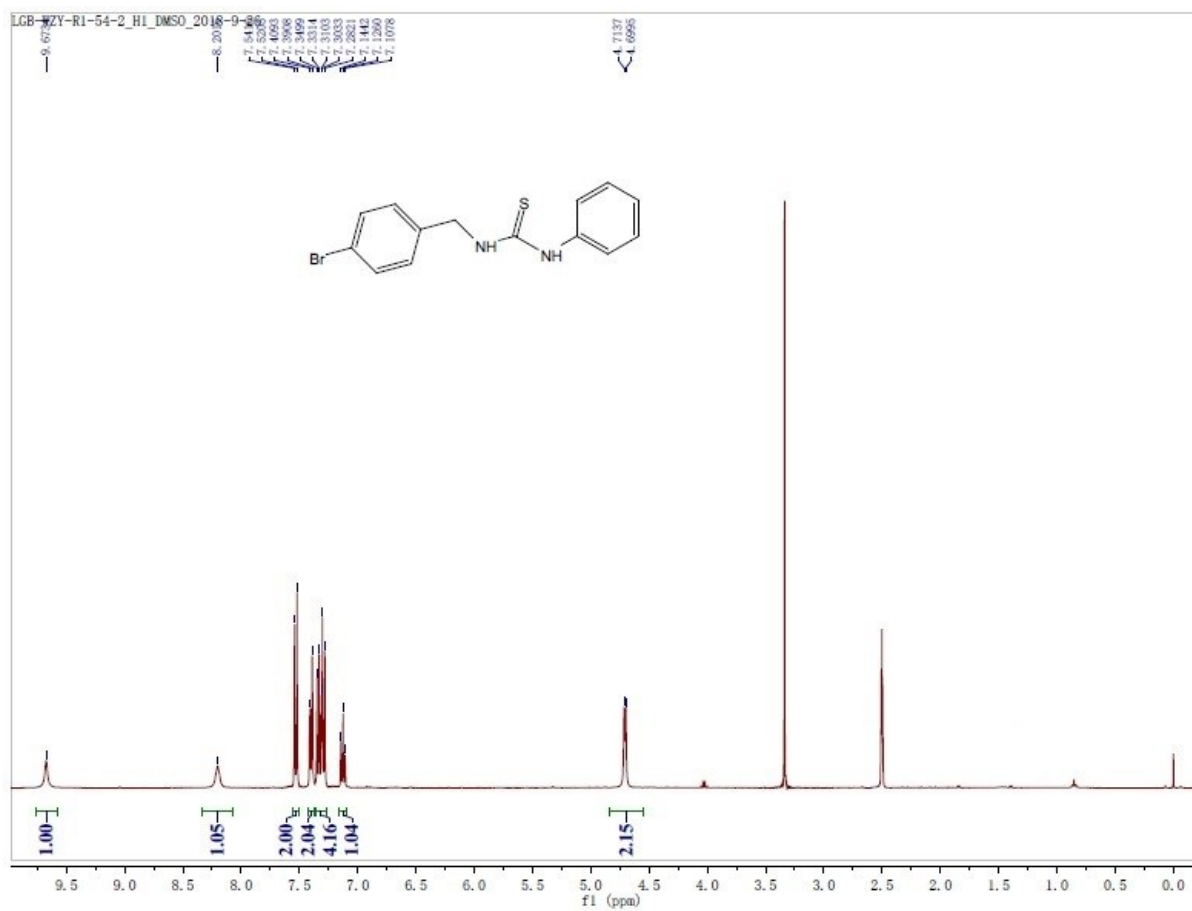


WZY-TP-8-34-2, 10, d

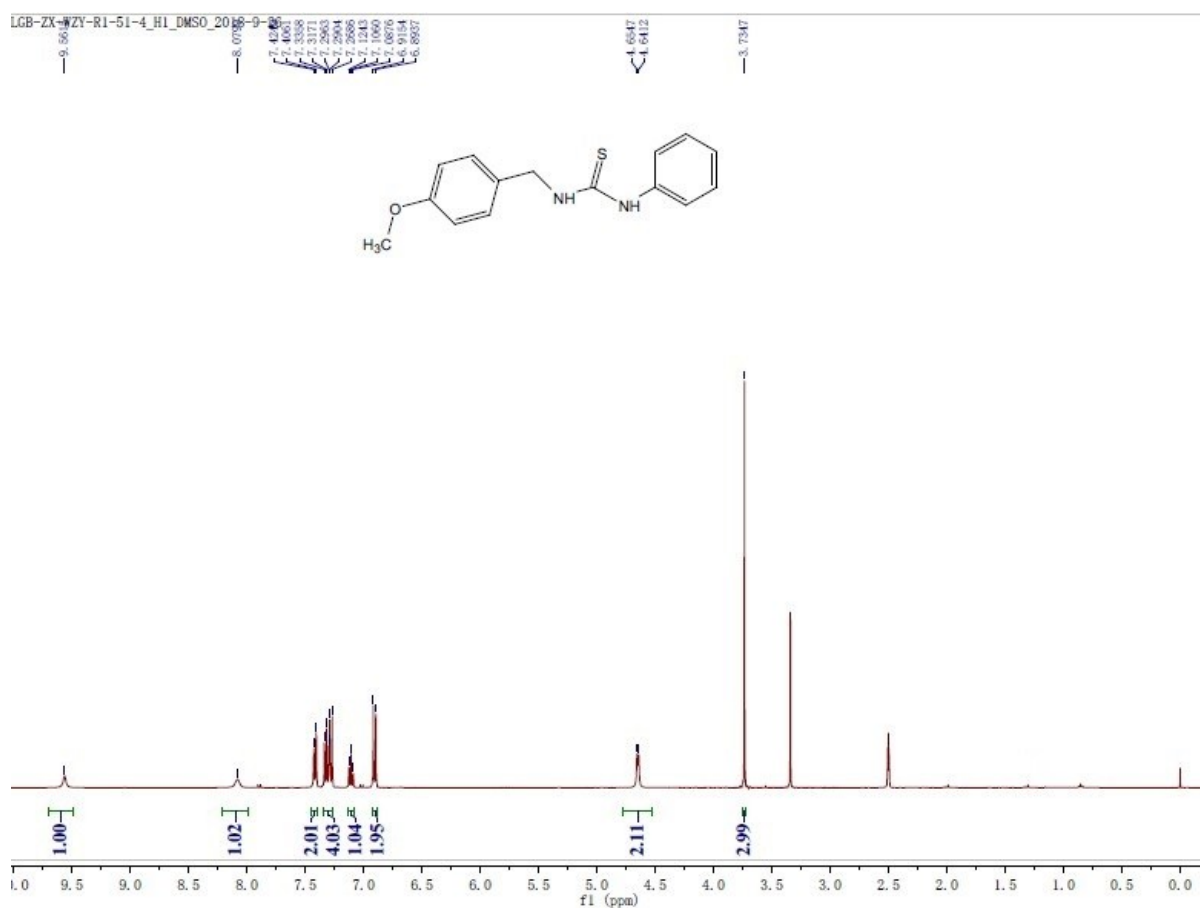


LGB-WZY-R1-54-2, HI, DMSO, 2018-9-8, d

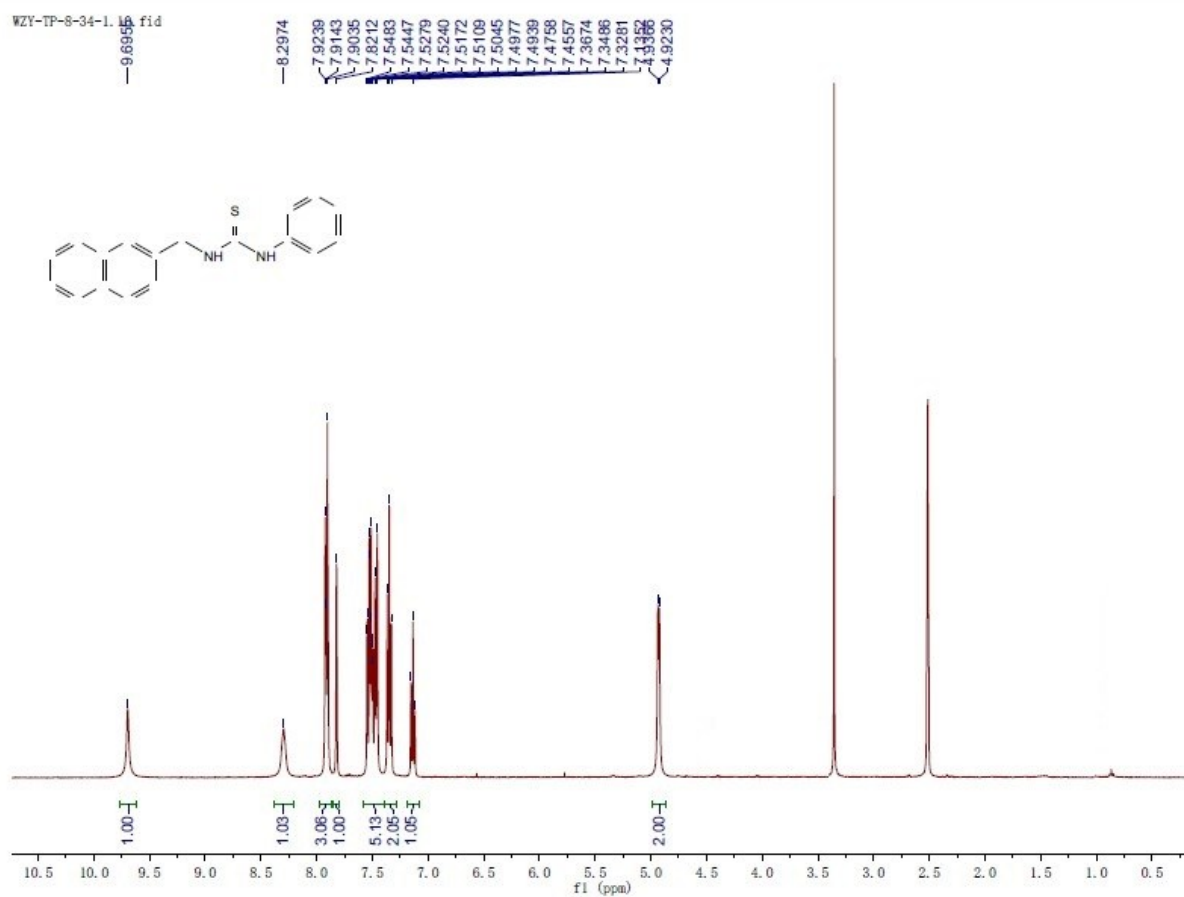


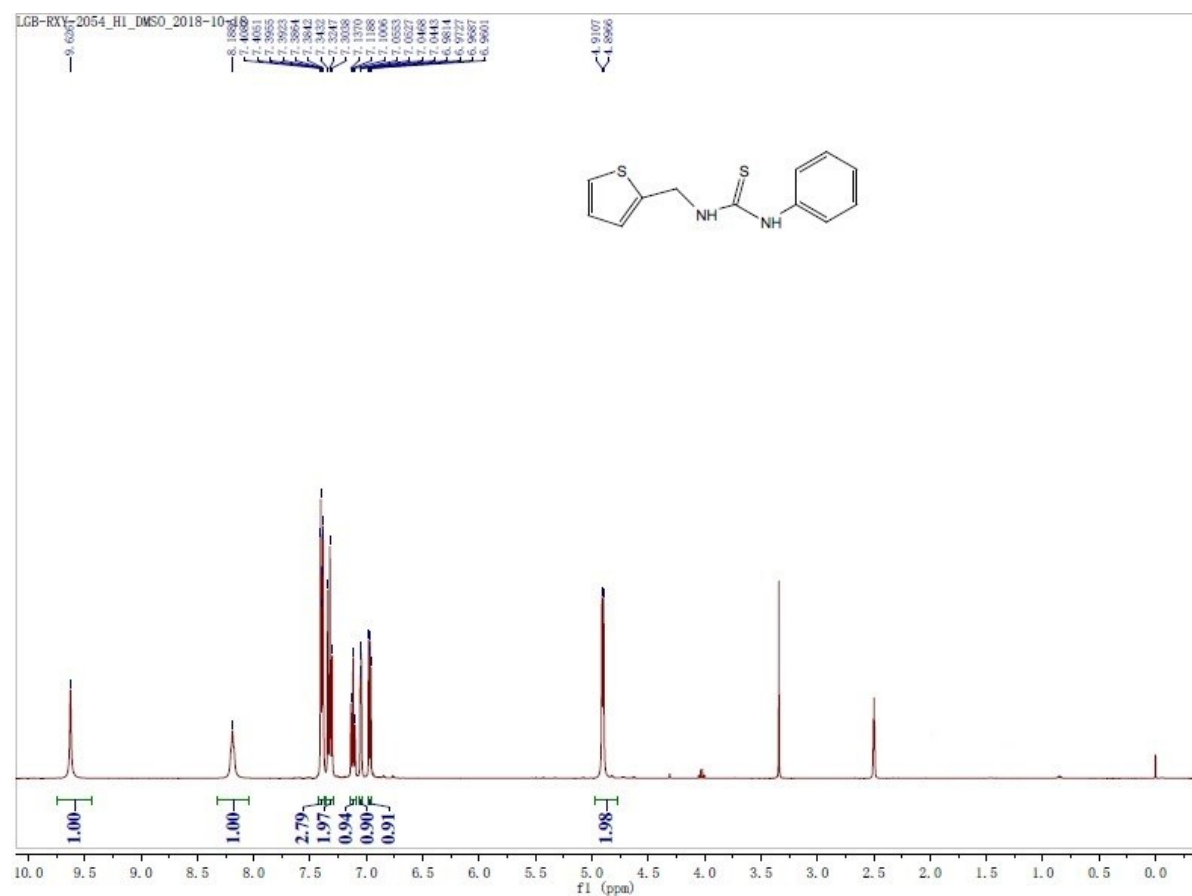
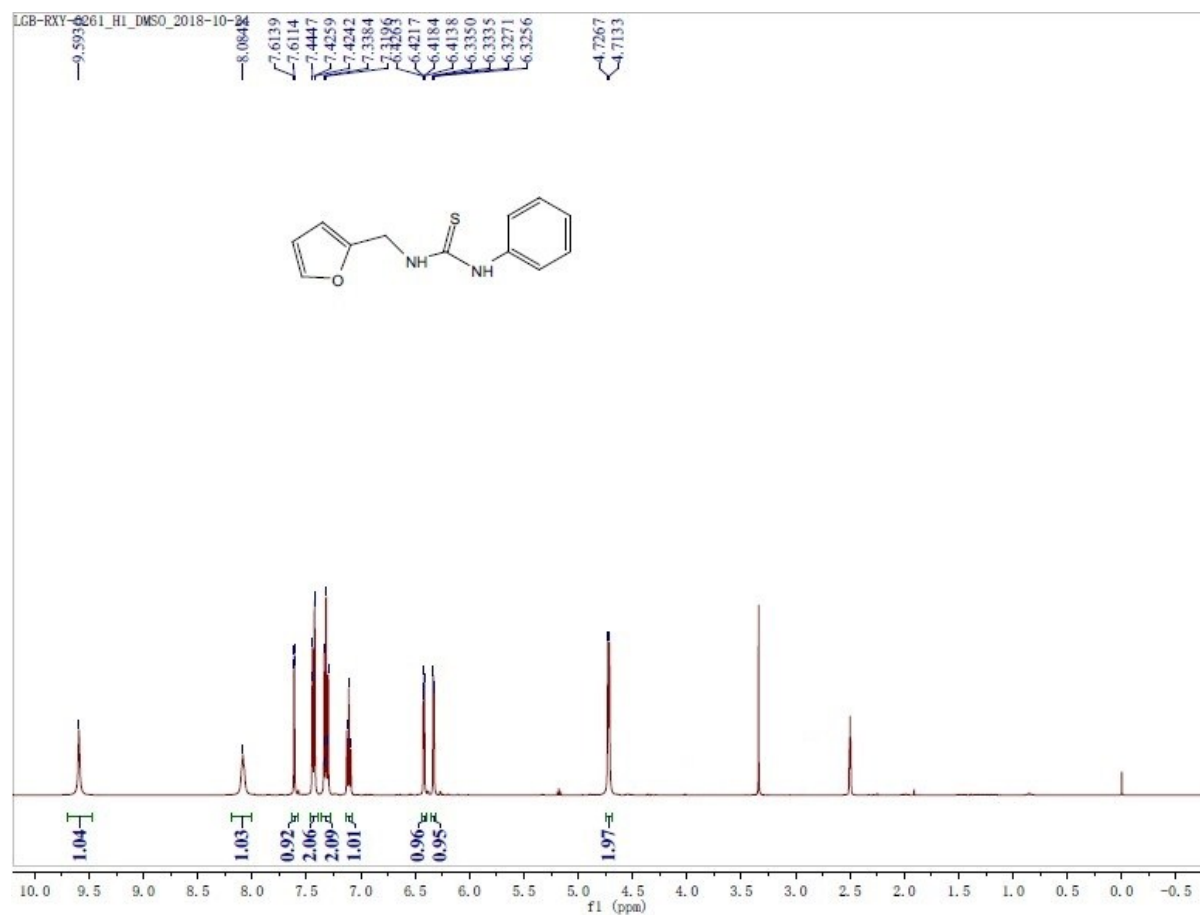


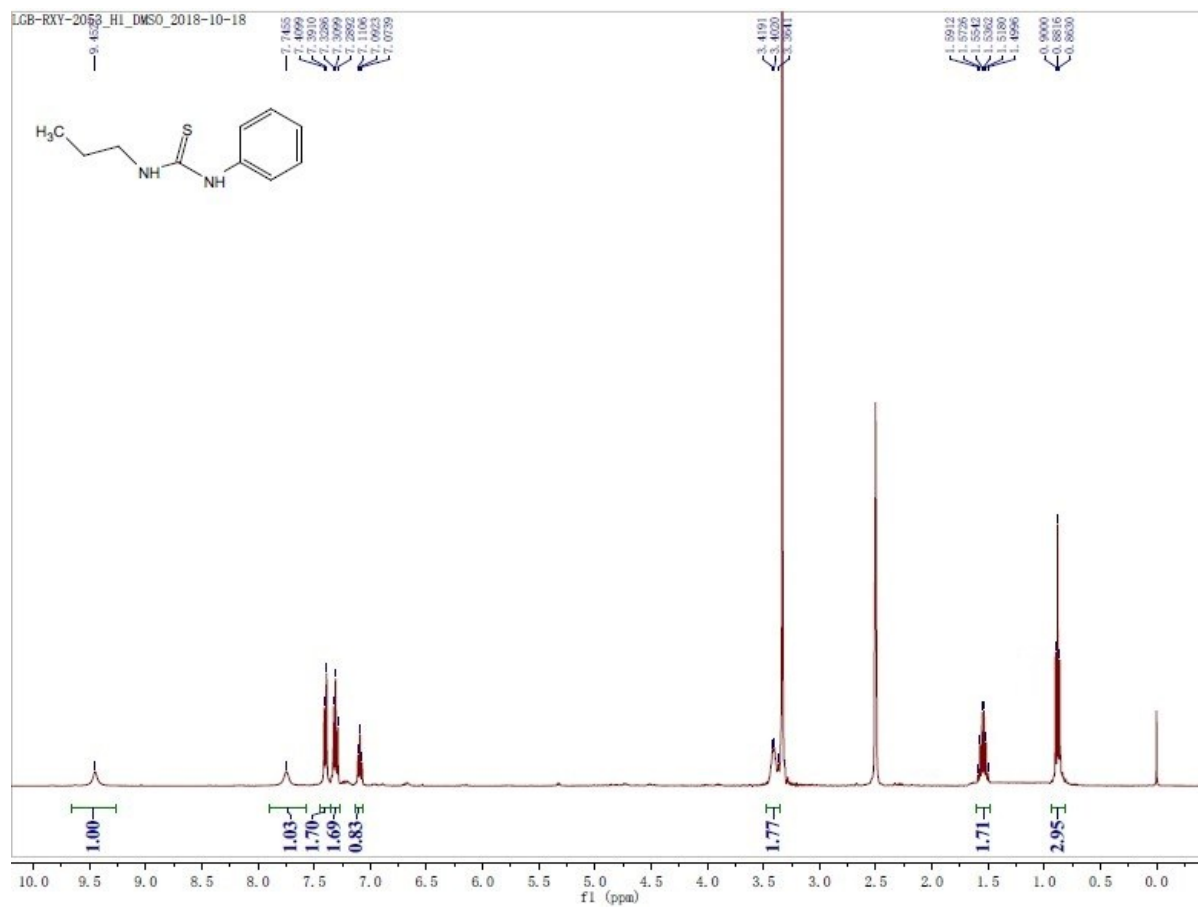
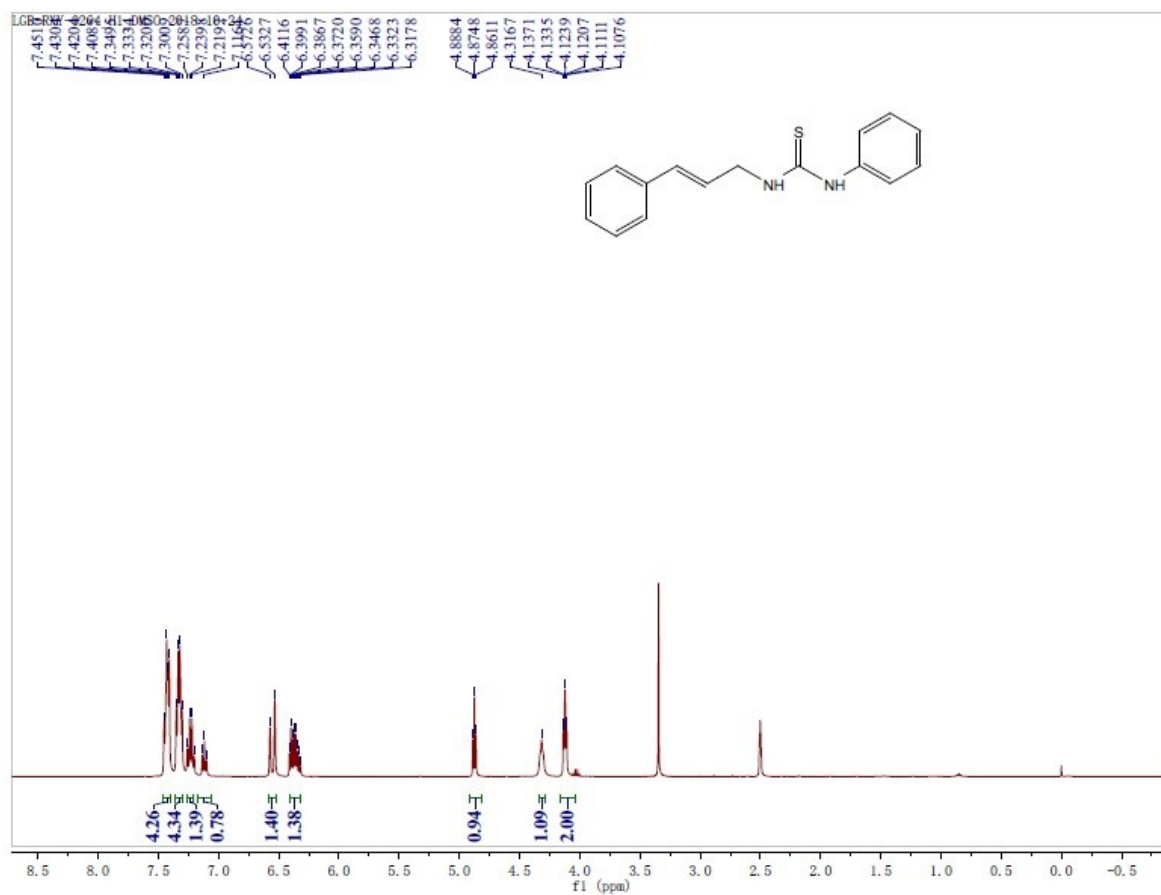
LGB-ZX-WZY-R1-51-4_H1_DMSO_2016-09-09



WZY-TP-8-34-1.fid







LGB-RXY-2092_HI_DMSO_2018-10-18

