Highly efficient synthesis of 2,5-disubstitutedpyrazines from (Z)-β-haloenol acetates

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Supporting Information

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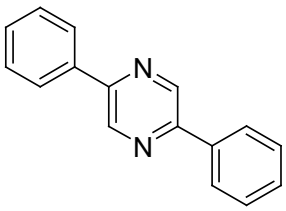
A. General method

^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, chloroform is solvent with TMS as the internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A spectrometer at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). Elemental analyses were performed with a Vario EL elemental analyzer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254) and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

B. General procedure for synthesis of 2,5-disubstitutedpyrazines

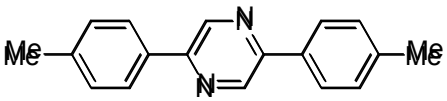
The mixture of (Z)-β-haloenol acetates (0.5 mmol), ammonium formate (0.5 mmol) and DMF (1 mL) were stirred at 120 ^{o}C for 6 h in a 25 mL schlenk tube. Water (8 mL) was added after completion of the reaction, the aqueous solution was extracted with diethyl ether (3×5 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give the pure sample.

C. Analytical data



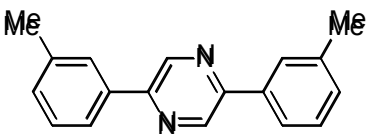
2,5-diphenylpyrazine (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 2H), 8.05 (d, *J* = 7.2 Hz, 4H), 7.46-7.53 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 141.2, 136.3, 129.7, 129.0, 126.8. MS (EI) m/z: 232, 204, 178, 155, 102, 76, 51. Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.47; H, 5.29; N, 12.01.



2,5-di*p*-tolylpyrazine (2b)

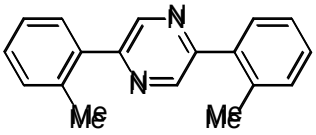
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (s, 2H), 8.03 (d, *J* = 8.4 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 4H), 2.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 140.0, 139.2, 133.8, 129.7, 126.9, 21.3. MS (EI) m/z: 260, 245, 229, 218, 164, 115, 89. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.49; H, 6.04; N, 10.67.



2,5-di*m*-tolylpyrazine (2c)

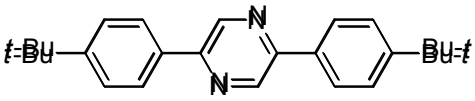
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 2H), 7.92 (t, *J* = 8.0 Hz, 4H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 2.46 (s,

2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 139.8, 138.7, 136.5, 130.6, 128.9, 128.7, 124.2, 21.6. MS (EI) m/z: 260, 245, 207, 169, 130, 115, 89. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.51; H, 6.02; N, 10.83.



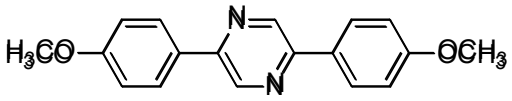
2,5-di*o*-tolylpyrazine (2d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 2H), 7.46-7.48 (m, 2H), 7.28-7.37 (m, 6H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 142.0, 136.8, 136.4, 131.1, 130.0, 129.2, 126.1, 20.5. MS (EI) m/z: 260, 245, 207, 169, 130, 115, 89. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.65; H, 6.00; N, 10.62.



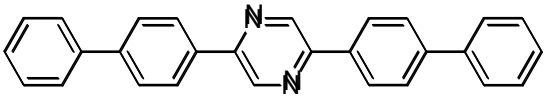
2,5-bis(4-butylphenyl)pyrazine (2e)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 2H), 8.07 (d, *J* = 8.4 Hz, 4H), 7.54 (d, *J* = 8.4 Hz, 4H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 151.6, 139.2, 133.8, 126.7, 125.9, 34.8, 31.2. MS (EI) m/z: 344, 329, 316, 301, 264, 239, 212, 185, 172, 158, 145, 133, 105. Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.45; H, 8.31; N, 8.06.



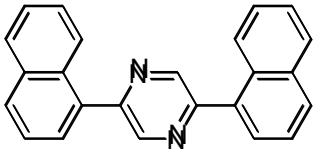
2,5-bis(4-methoxyphenyl)pyrazine (2f)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 2H), 8.09 (d, *J* = 8.8 Hz, 4H), 7.03 (d, *J* = 8.8 Hz, 4H), 3.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =161.1, 151.0, 138.4, 129.2, 128.3, 114.3, 55.4. MS (EI) m/z: 292, 277, 249, 206, 158, 132, 89, 63. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.70; H, 5.59; N, 9.51.



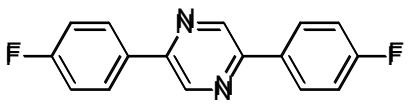
2,5-di([1,1'-biphenyl]-4-yl)pyrazine (2g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (s, 2H), 8.24 (d, *J* = 8.4 Hz, 4H), 7.76 (d, *J* = 8.4 Hz, 4H), 7.67 (t, *J* = 7.2 Hz, 4H), 7.47 (t, *J* = 7.6 Hz, 4H), 7.38 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 142.7, 140.3, 139.7, 135.3, 128.9, 127.7, 127.7, 127.4, 127.1. MS (EI) m/z: 384, 307, 230, 204, 178, 155, 77, 51. Anal. Calcd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.68; H, 5.17; N, 7.33.



2,5-di(naphthalen-1-yl)pyrazine (2h)

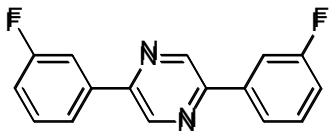
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (s, 2H), 8.64 (s, 2H), 8.31-8.33 (m, 4H), 8.01 (t, *J* = 4.0 Hz, 4H), 7.89-7.91 (m, 2H), 7.53-7.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 140.1, 134.0, 133.8, 133.4, 128.8, 128.8, 127.8, 127.1, 126.8, 126.6, 124.2. MS (EI) m/z: 332, 280, 228, 206, 180, 153, 102, 77. Anal. Calcd for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43. Found: C, 86.39; H, 4.97; N, 8.35.



2,5-bis(4-fluorophenyl)pyrazine (2i)

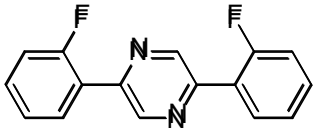
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 2H), 8.09-8.12 (m, 4H), 7.16-7.24 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 162.8, 150.6, 139.4, 132.5, 132.5, 128.9, 128.8, 116.1, 115.9. MS (EI) m/z: 268, 240, 214, 173,

120, 94, 74, 50. Anal. Calcd for $C_{16}H_{10}F_2N_2$: C, 71.64; H, 3.76; N, 10.44. Found: C, 71.43; H, 3.85; N, 10.49.



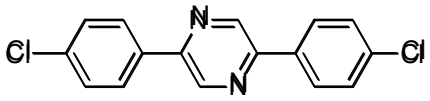
2,5-bis(3-fluorophenyl)pyrazine (2j)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 2H), 7.84-7.88 (m, 4H), 7.47-7.51 (m, 2H), 7.16-7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 162.1, 150.3, 150.3, 140.2, 138.5, 138.4, 130.6, 130.5, 122.5, 122.4, 117.1, 116.9, 114.1, 113.9. MS (EI) m/z: 268, 240, 214, 173, 120, 94, 74, 50. Anal. Calcd for $C_{16}H_{10}F_2N_2$: C, 71.64; H, 3.76; N, 10.44. Found: C, 71.37; H, 3.90; N, 10.29.



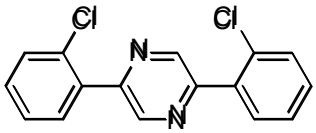
2,5-bis(2-fluorophenyl)pyrazine (2k)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 2H), 8.16-8.21 (m, 2H), 7.46-7.52 (m, 2H), 7.34-7.38 (m, 2H), 7.26-7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 159.4, 148.5, 144.8, 144.7, 143.4, 143.3, 131.5, 131.5, 131.4, 131.0, 131.0, 124.8, 124.8, 124.4, 124.3, 116.5, 116.3. MS (EI) m/z: 268, 240, 214, 173, 120, 94, 74, 50. Anal. Calcd for $C_{16}H_{10}F_2N_2$: C, 71.64; H, 3.76; N, 10.44. Found: C, 71.34; H, 3.93; N, 10.47.



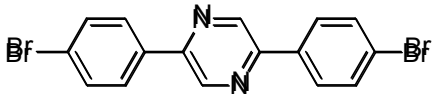
2,5-bis(4-chlorophenyl)pyrazine (2l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 2H), 8.04-8.06 (m, 4H), 7.47-7.49 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 139.7, 136.3, 134.6, 129.3, 128.2. MS (EI) m/z: 300, 265, 136, 101, 75, 51. Anal. Calcd for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.45; H, 3.47; N, 9.25.



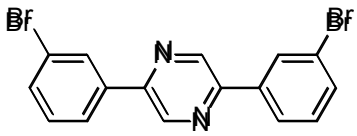
2,5-bis(2-chlorophenyl)pyrazine (2m)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (s, 2H), 8.12 (t, *J* = 1.2 Hz, 2H), 7.97-7.99 (m, 2H), 7.45-7.46 (t, *J* = 4.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 140.4, 138.0, 135.2, 130.3, 130.1, 127.2, 125.0. MS (EI) m/z: 300, 265, 136, 101, 75, 51. Anal. Calcd for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.55; H, 3.43; N, 9.41.



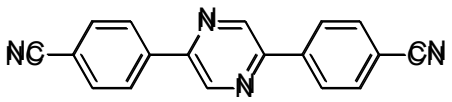
2,5-bis(4-bromophenyl)pyrazine (2n)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 2H), 7.98 (d, *J* = 8.8 Hz, 4H), 7.64 (d, *J* = 8.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 139.8, 135.1, 132.2, 128.5, 124.7. MS (EI) m/z: 390, 309, 229, 182, 127, 101, 75, 51. Anal. Calcd for $C_{16}H_{10}Br_2N_2$: C, 49.27; H, 2.58; N, 7.18. Found: C, 49.44; H, 2.50; N, 7.26.



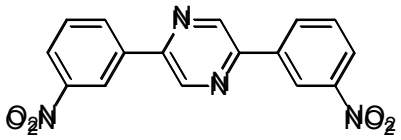
2,5-bis(3-bromophenyl)pyrazine (2o)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 2H), 8.24 (t, *J* = 1.6 Hz, 2H), 7.98-8.01 (m, 2H), 7.57-7.60 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 140.4, 138.1, 133.0, 130.5, 130.0, 125.5, 123.3. MS (EI) m/z: 390, 309, 229, 182, 127, 101, 75, 51. Anal. Calcd for $C_{16}H_{10}Br_2N_2$: C, 49.27; H, 2.58; N, 7.18. Found: C, 49.57; H, 2.49; N, 7.07.



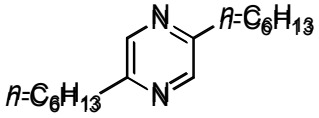
4,4'-(pyrazine-2,5-diyl)dibenzonitrile (2p)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 2H), 8.25 (d, *J* = 8.4 Hz, 4H), 7.83 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 141.3, 140.0, 132.8, 127.5, 118.3, 113.9. MS (EI) m/z: 282, 256, 230, 207, 169, 130, 89, 51. Anal. Calcd for $C_{18}H_{10}N_4$: C, 76.58; H, 3.57; N, 19.85. Found: C, 76.31; H, 3.63; N, 19.80.



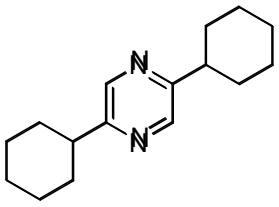
2,5-bis(3-nitrophenyl)pyrazine (2q)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 2H), 8.99 (t, *J* = 2.0 Hz, 2H), 8.50-8.52 (m, 2H), 8.36-8.38 (m, 2H), 7.76 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 148.9, 141.1, 137.6, 132.8, 130.3, 124.8, 121.9. MS (EI) m/z: 322, 306, 290, 276, 234, 206, 179, 101, 77. Anal. Calcd for $C_{16}H_{10}N_4O_4$: C, 59.63; H, 3.13; N, 17.38. Found: C, 59.29; H, 3.27; N, 17.23.



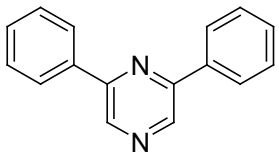
2,5-dihexylpyrazine (2r)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 2H), 2.74 (t, *J* = 7.6 Hz, 4H), 1.65-1.72 (m, 4H), 1.26-1.33 (m, 12H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 141.2, 35.5, 31.6, 29.6, 28.9, 22.5, 14.0. MS (EI) m/z: 248, 233, 219, 205, 191, 178, 163, 149, 135, 121, 108, 94, 81, 66, 53. Anal. Calcd for $C_{16}H_{28}N_2$: C, 77.36; H, 11.36; N, 11.28. Found: C, 77.58; H, 11.27; N, 11.34.



2,5-dicyclohexylpyrazine (2s)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 2H), 2.64-2.71 (m, 2H), 1.81-1.93 (m, 8H), 1.36-1.57 (m, 8H), 1.22-1.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 140.0, 44.1, 32.5, 26.3, 25.9. MS (EI) m/z: 244, 229, 215, 203, 189, 176, 161, 145, 133, 120, 107, 91, 79, 67, 55. Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.38; H, 9.97; N, 11.38.

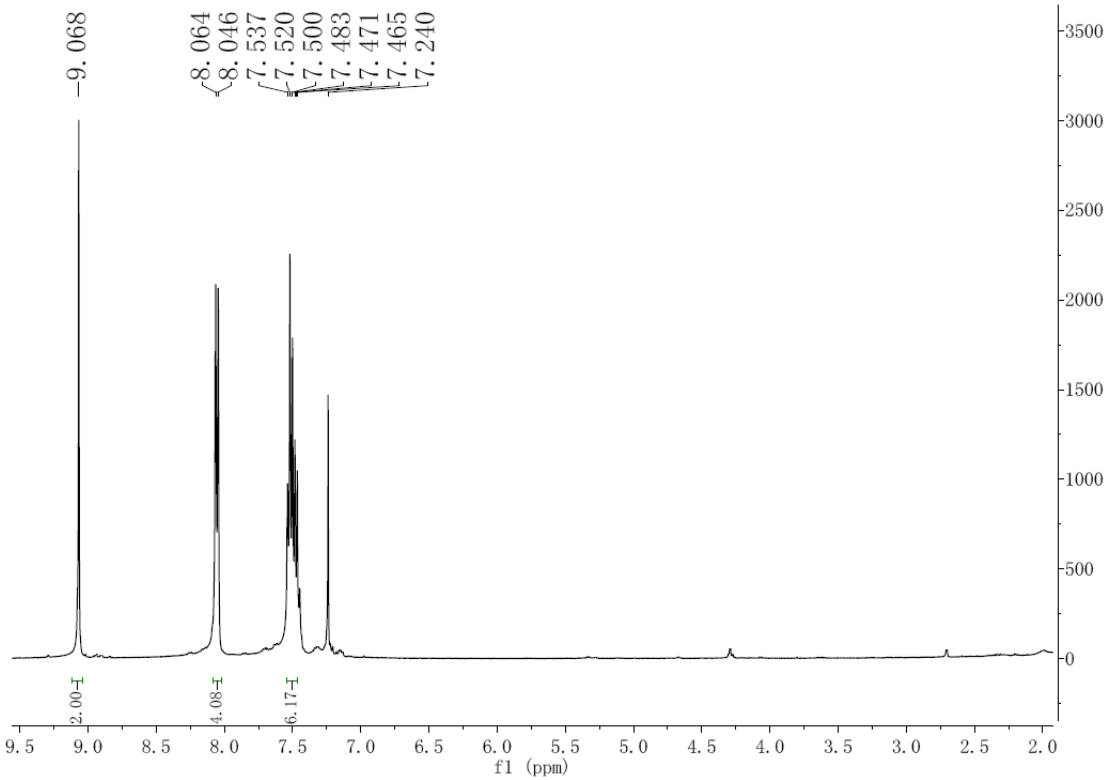


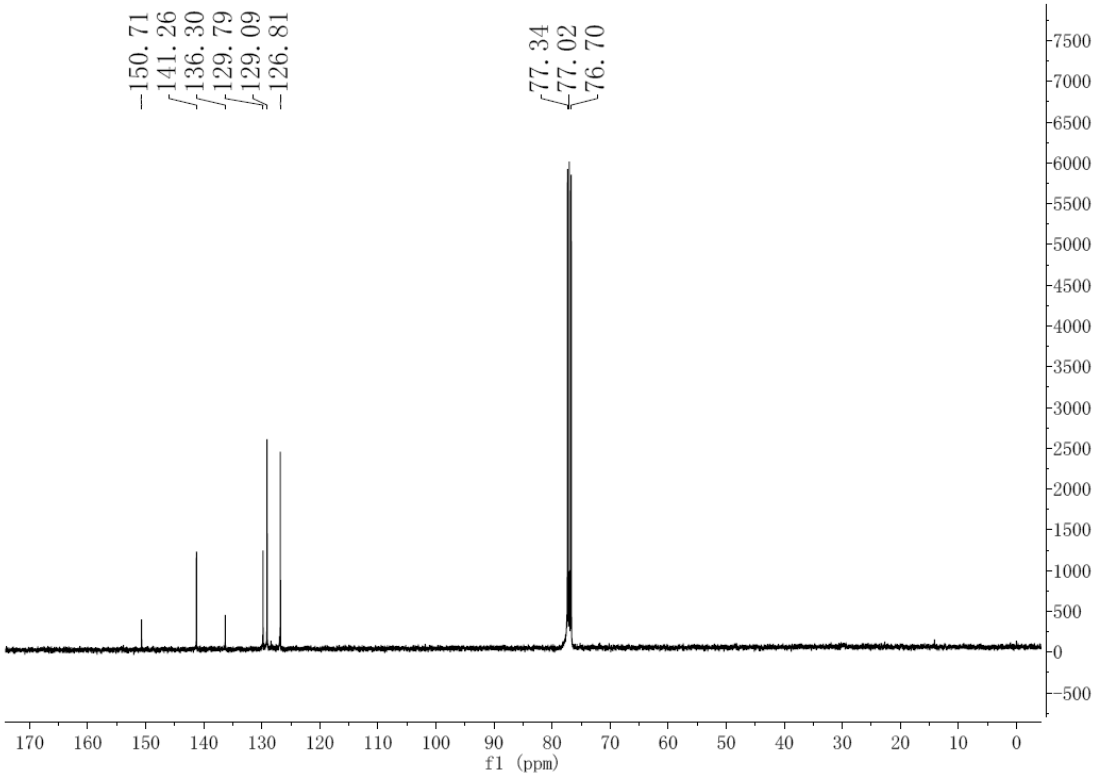
2,6-diphenylpyrazine (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (s, 2H), 8.14 (d, *J* = 6.8 Hz, 4H), 7.45-7.54 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 139.8, 136.5, 129.9, 129.0, 127.0. MS (EI) m/z: 232, 204, 178, 155, 102, 76, 51. Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.45; H, 5.12; N, 12.13.

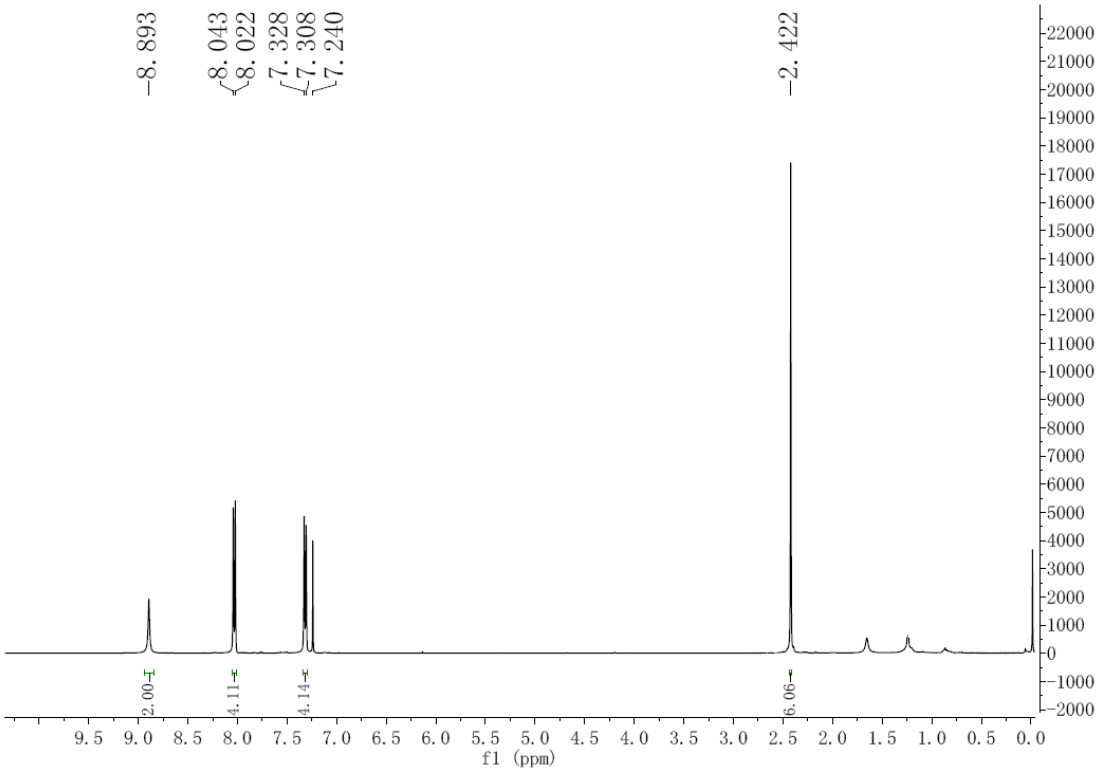
D. NMR Spectra

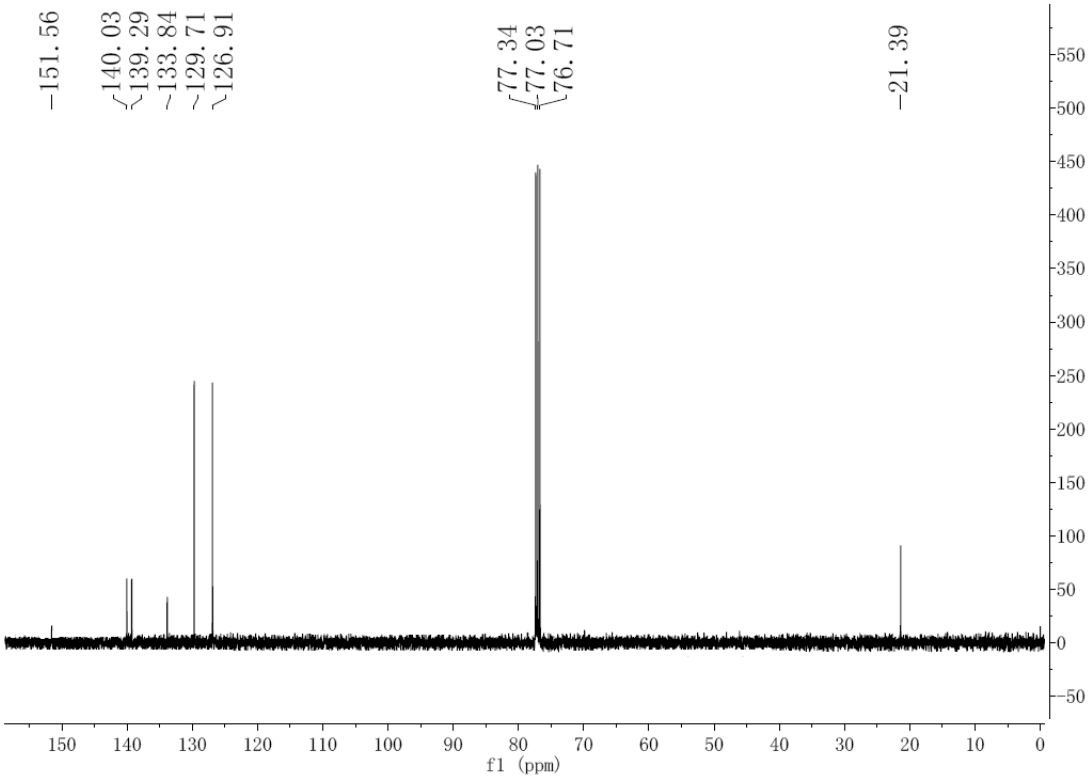
^{1}H NMR and ^{13}C NMR of 2,5-diphenylpyrazine (2a)



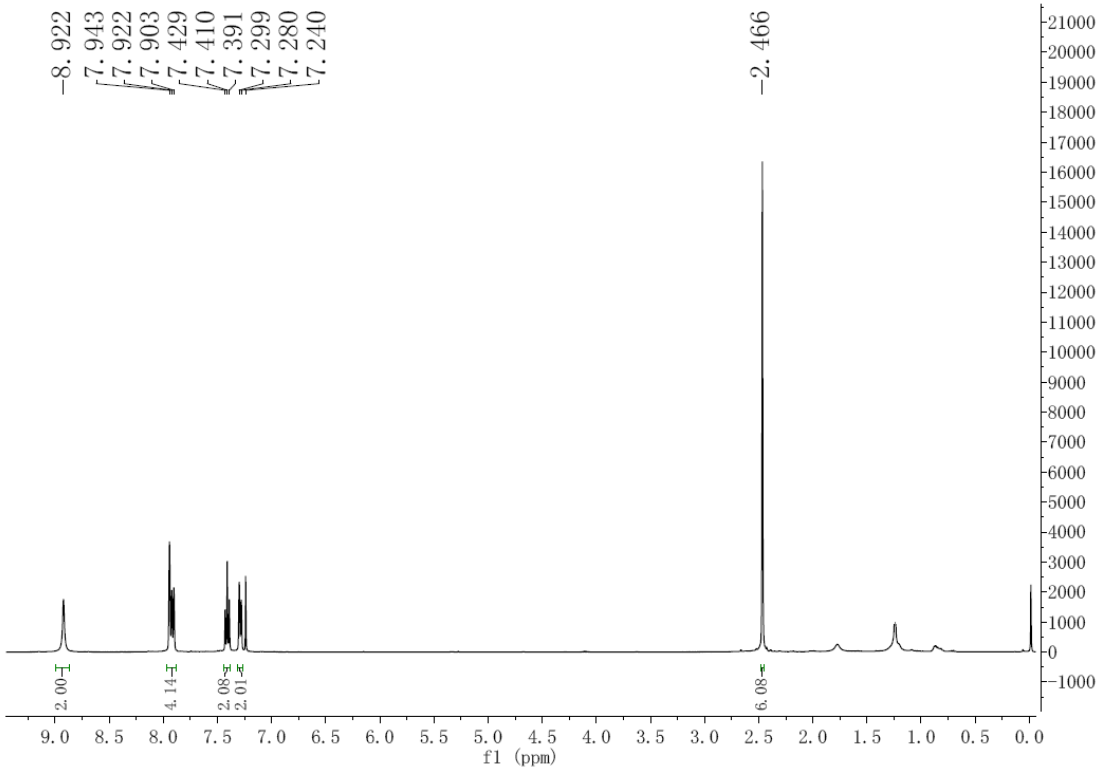


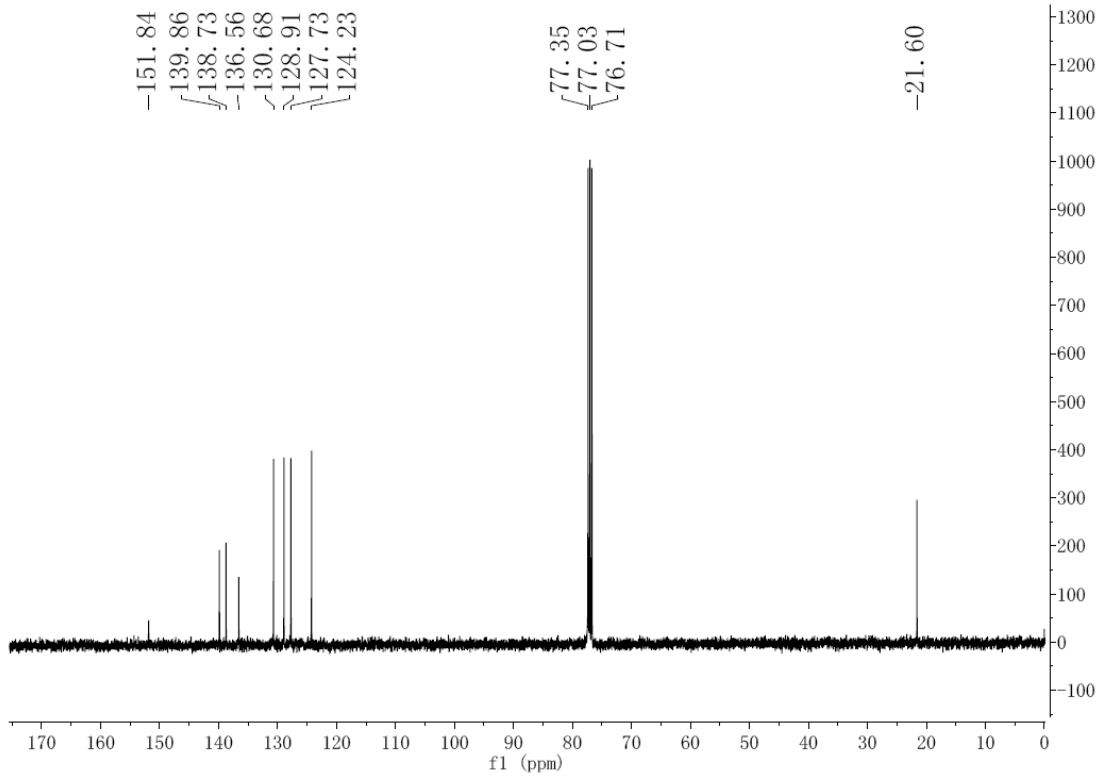
^{1}H NMR and ^{13}C NMR of 2,5-di*p*-tolylpyrazine (2b)



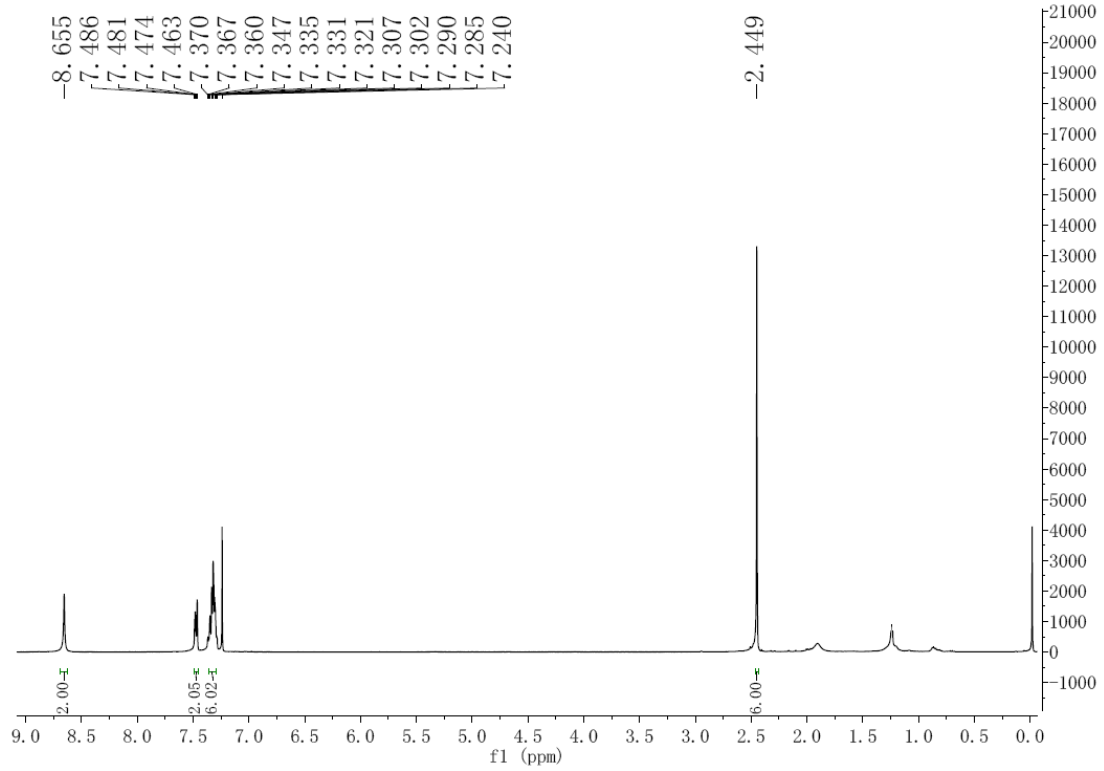


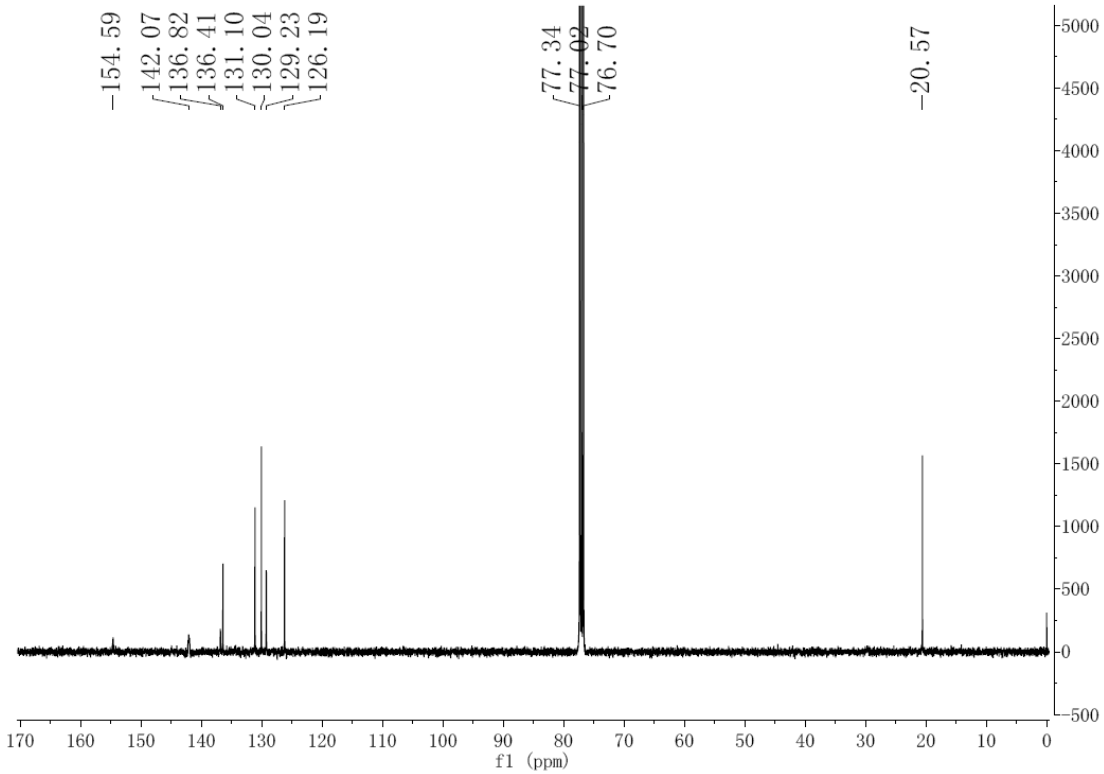
^{1}H NMR and ^{13}C NMR of 2,5-di*m*-tolylpyrazine (2c)



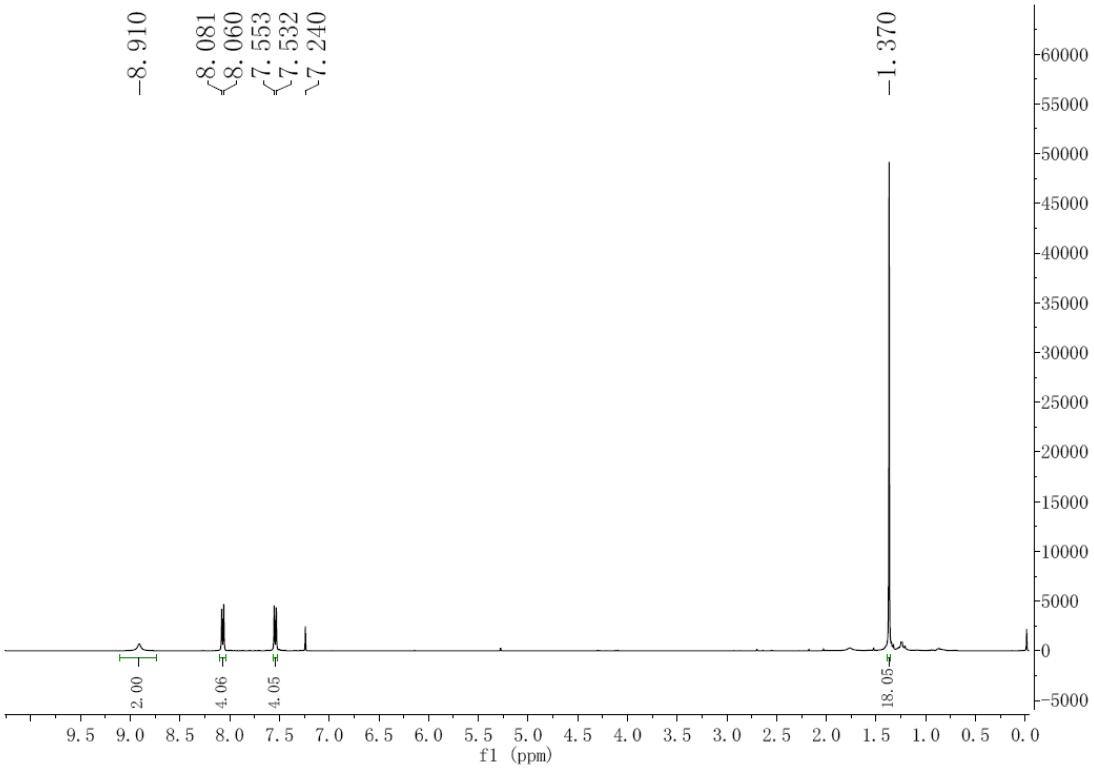


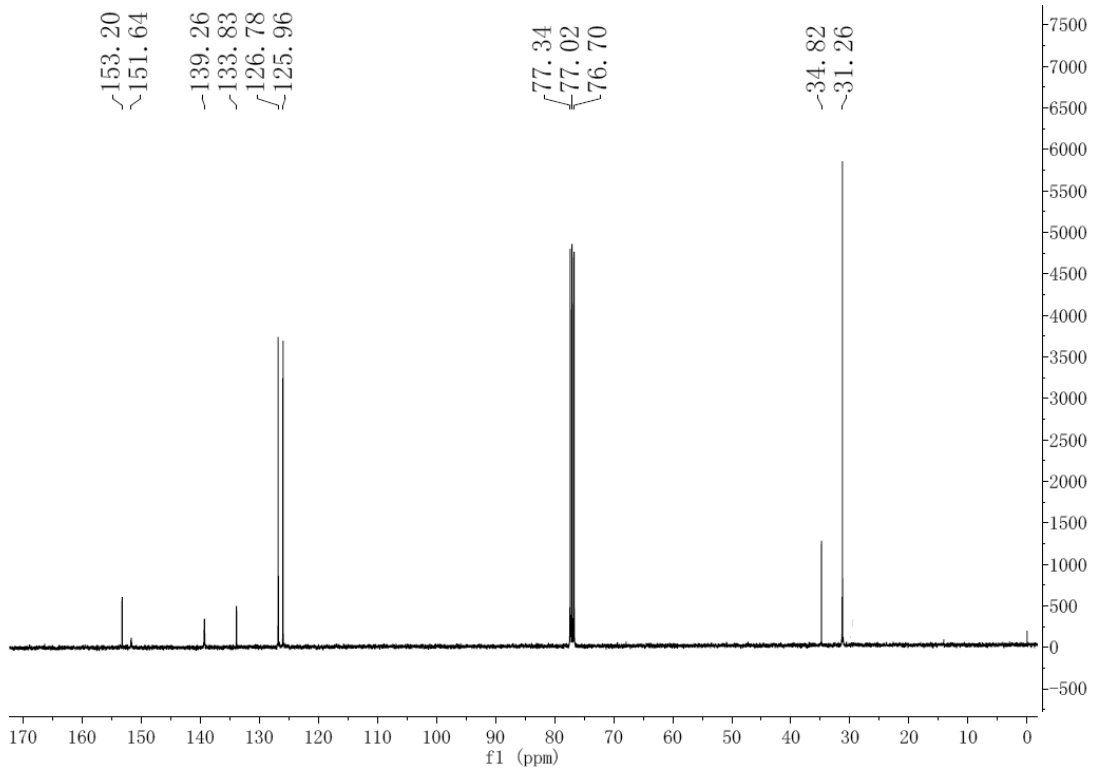
^{1}H NMR and ^{13}C NMR of 2,5-di*o*-tolylpyrazine (2d)



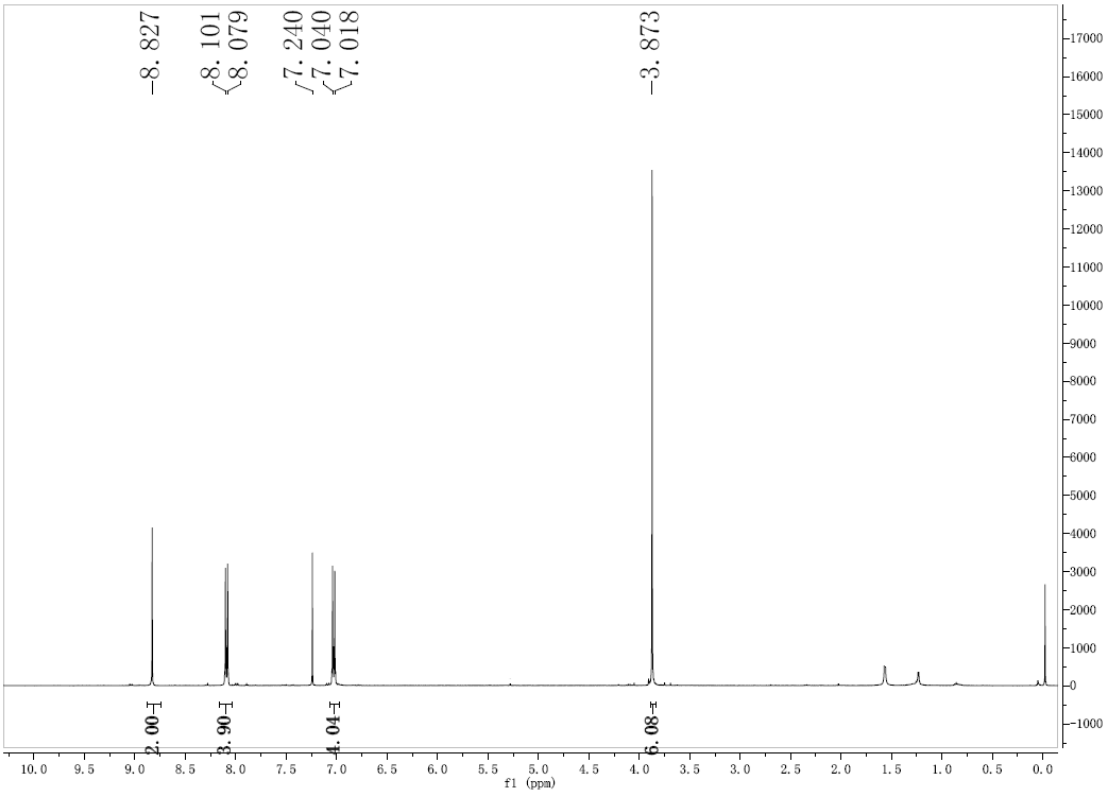


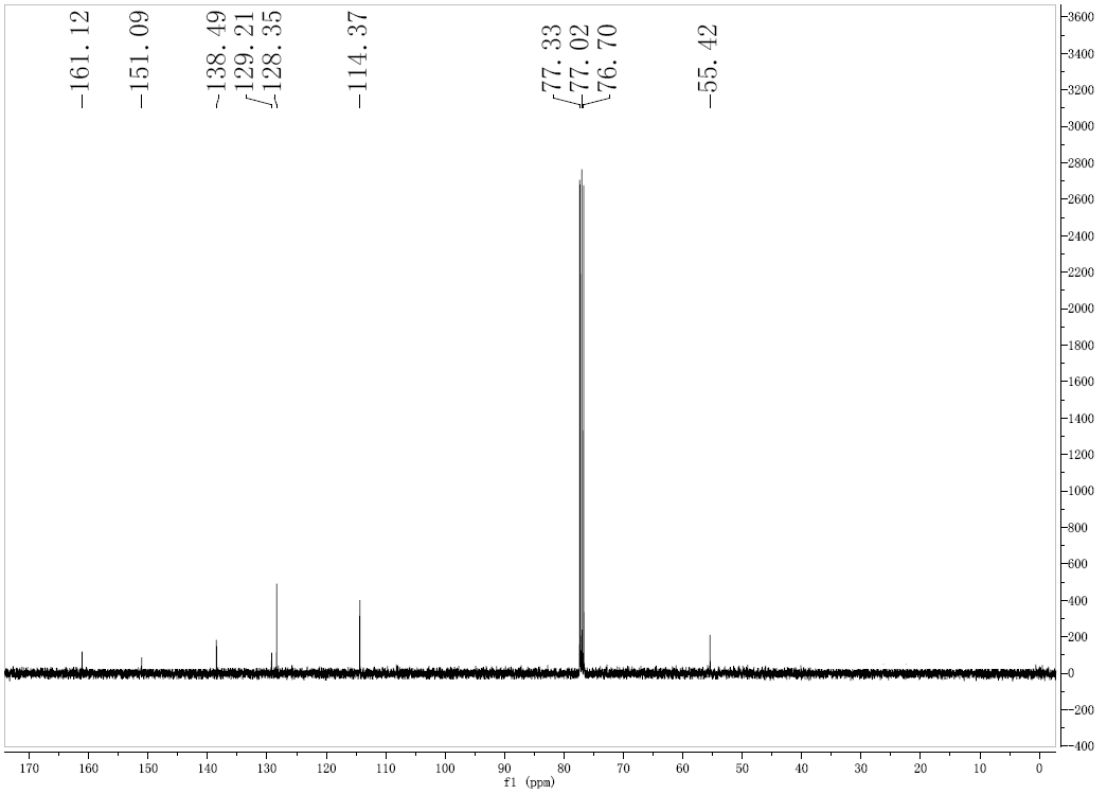
^{1}H NMR and ^{13}C NMR of 2,5-bis(4-butylphenyl)pyrazine (2e)



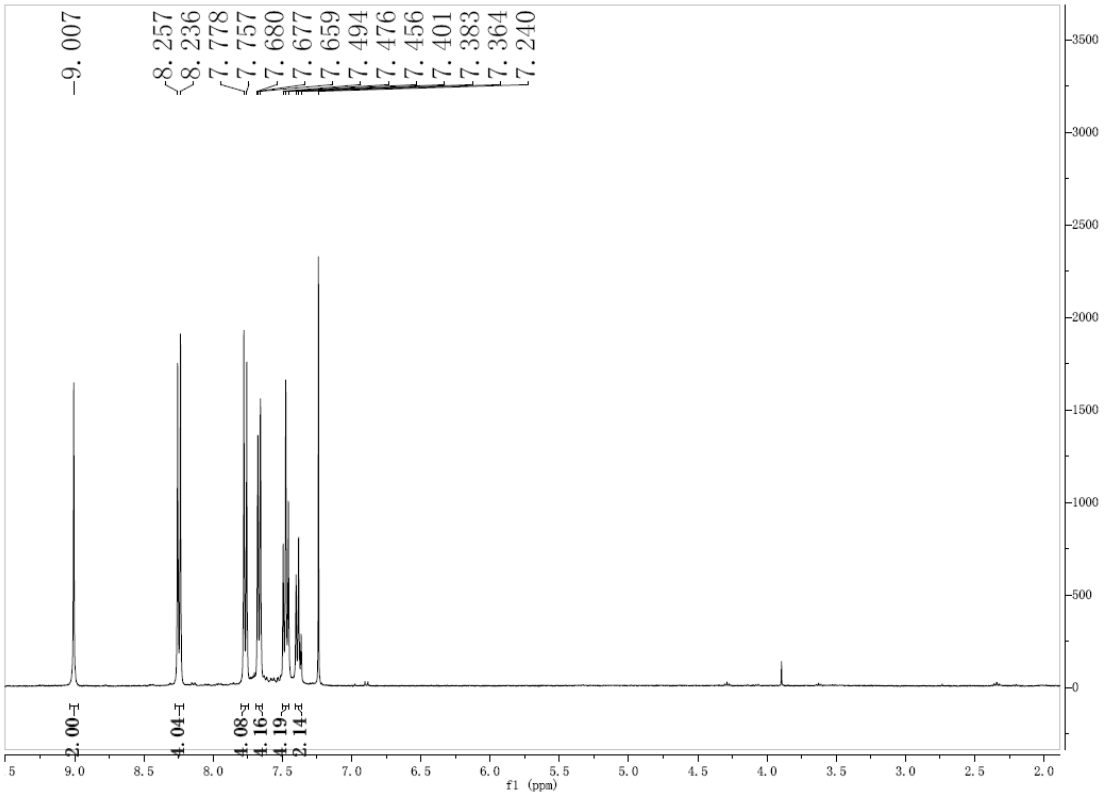


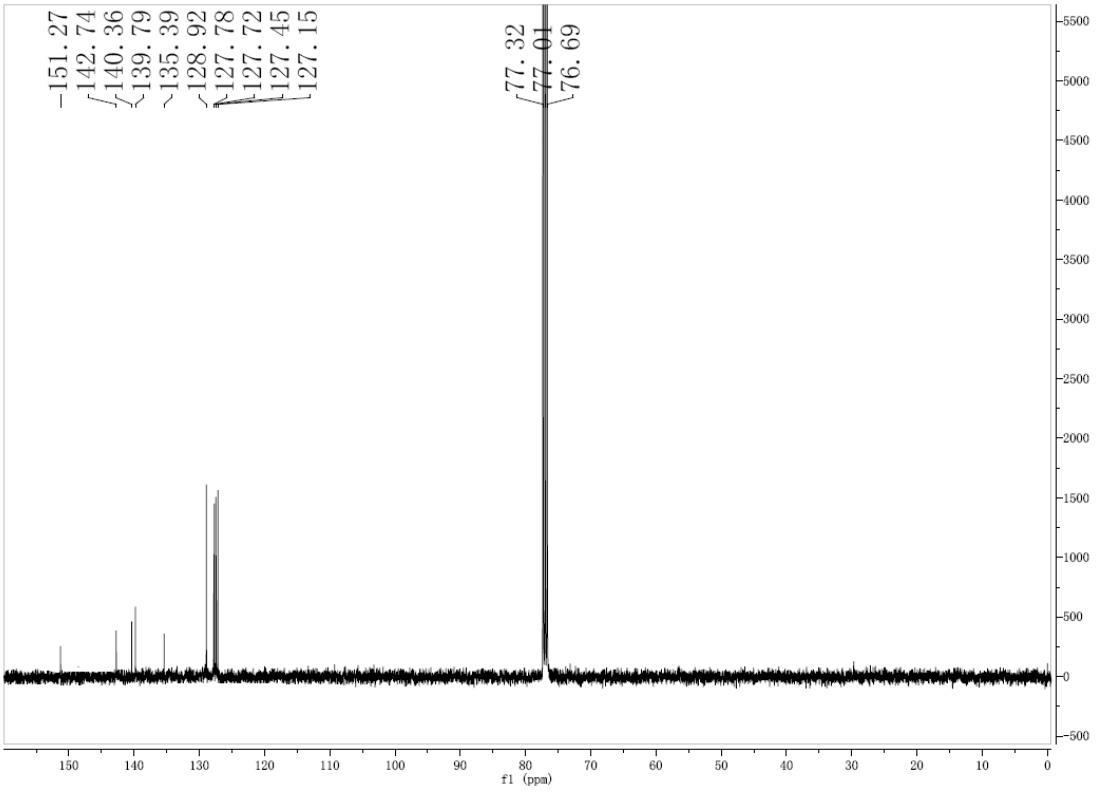
^{1}H NMR and ^{13}C NMR of 2,5-bis(4-methoxyphenyl)pyrazine (2f)



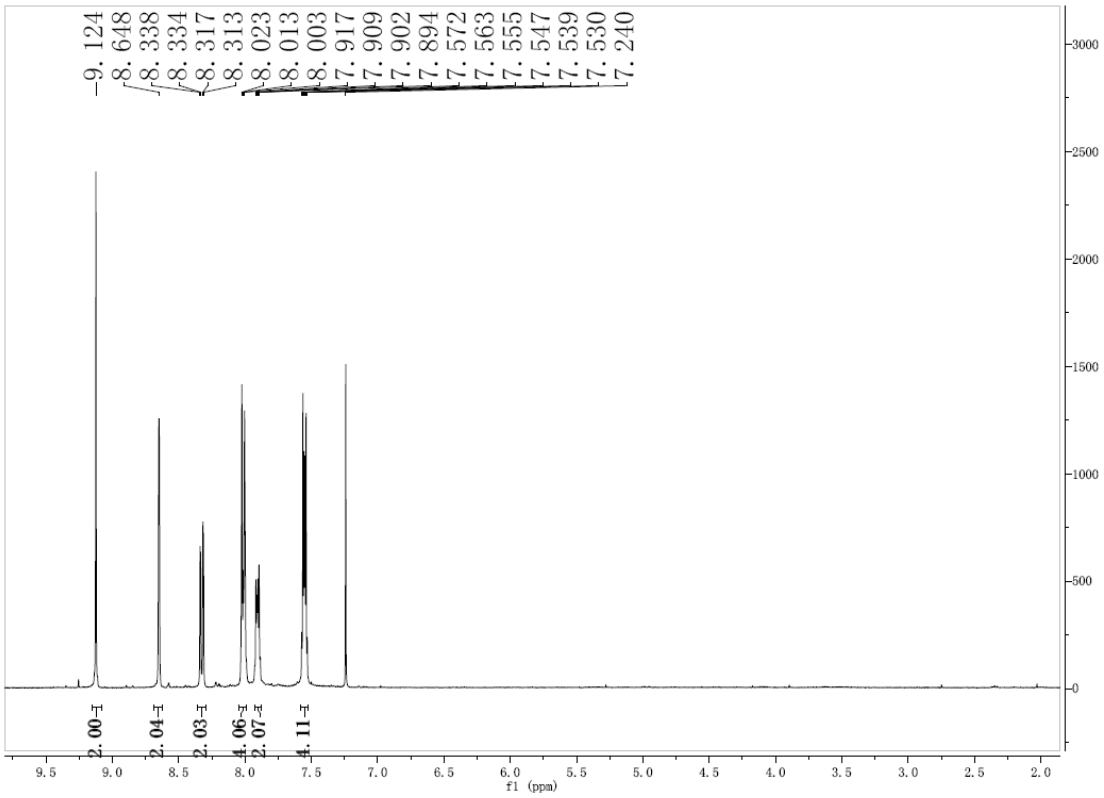


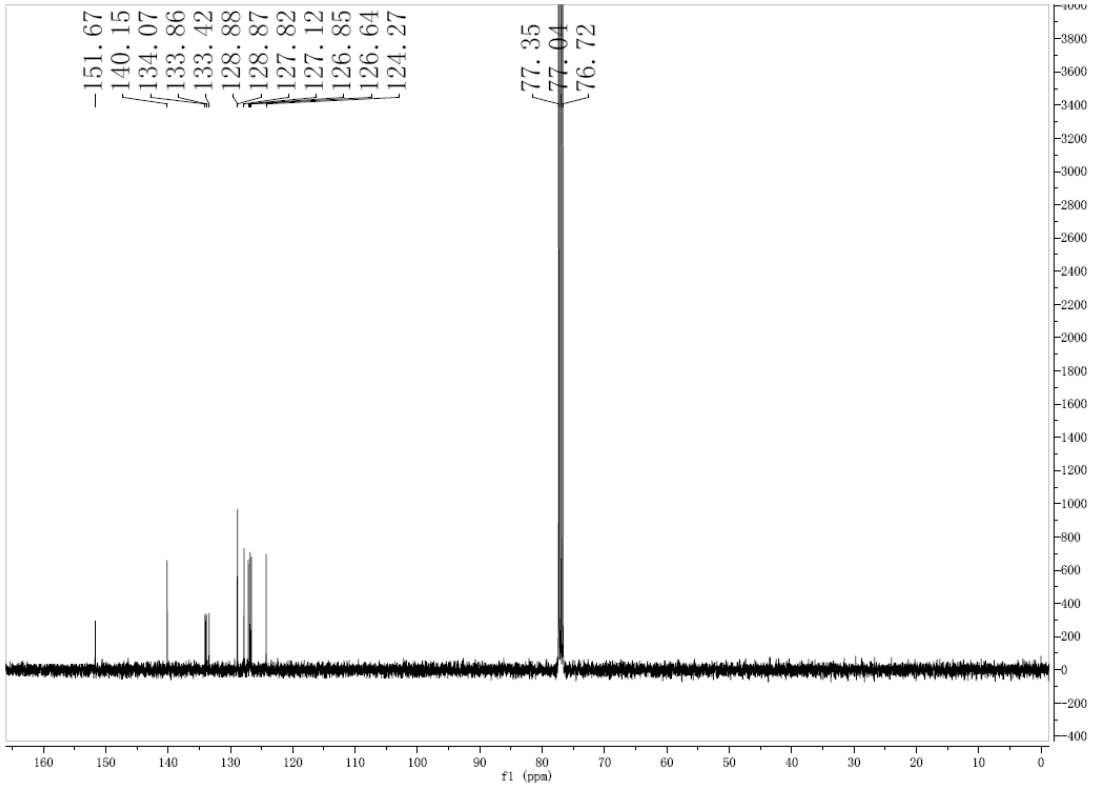
^{1}H NMR and ^{13}C NMR of 2,5-di([1,1'-biphenyl]-4-yl)pyrazine (2g)



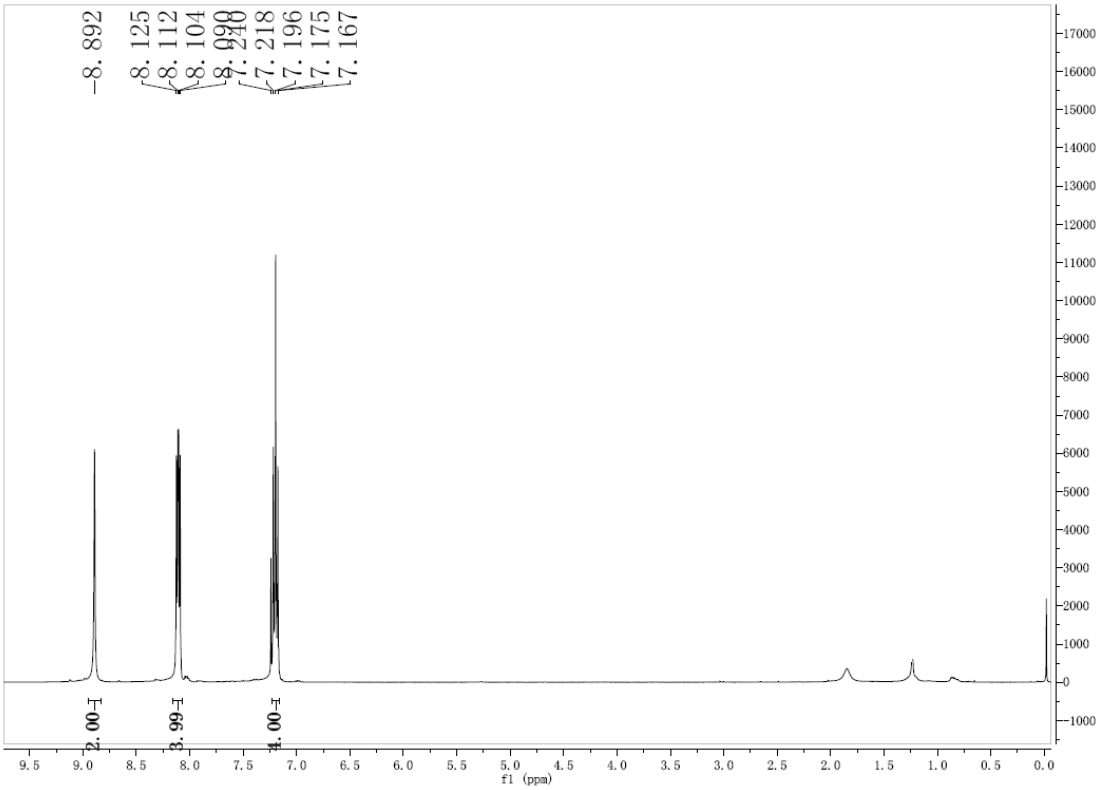


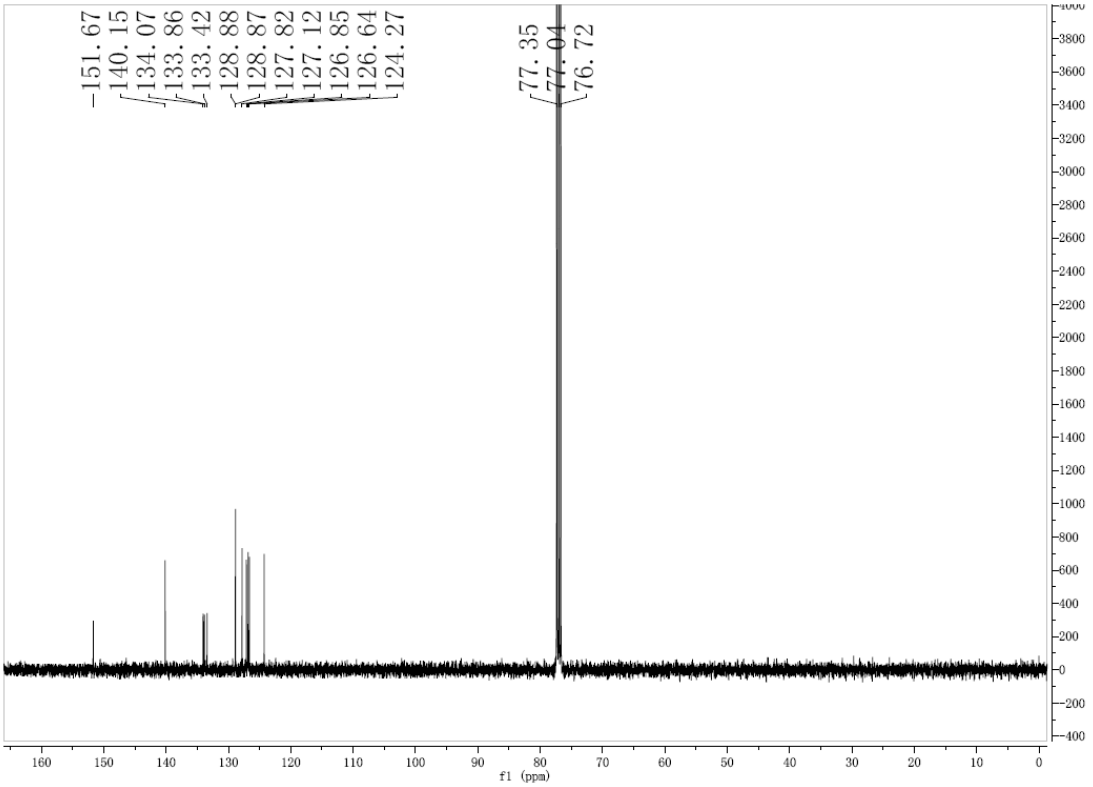
^{1}H NMR and ^{13}C NMR of 2,5-di(naphthalen-1-yl)pyrazine (2h)



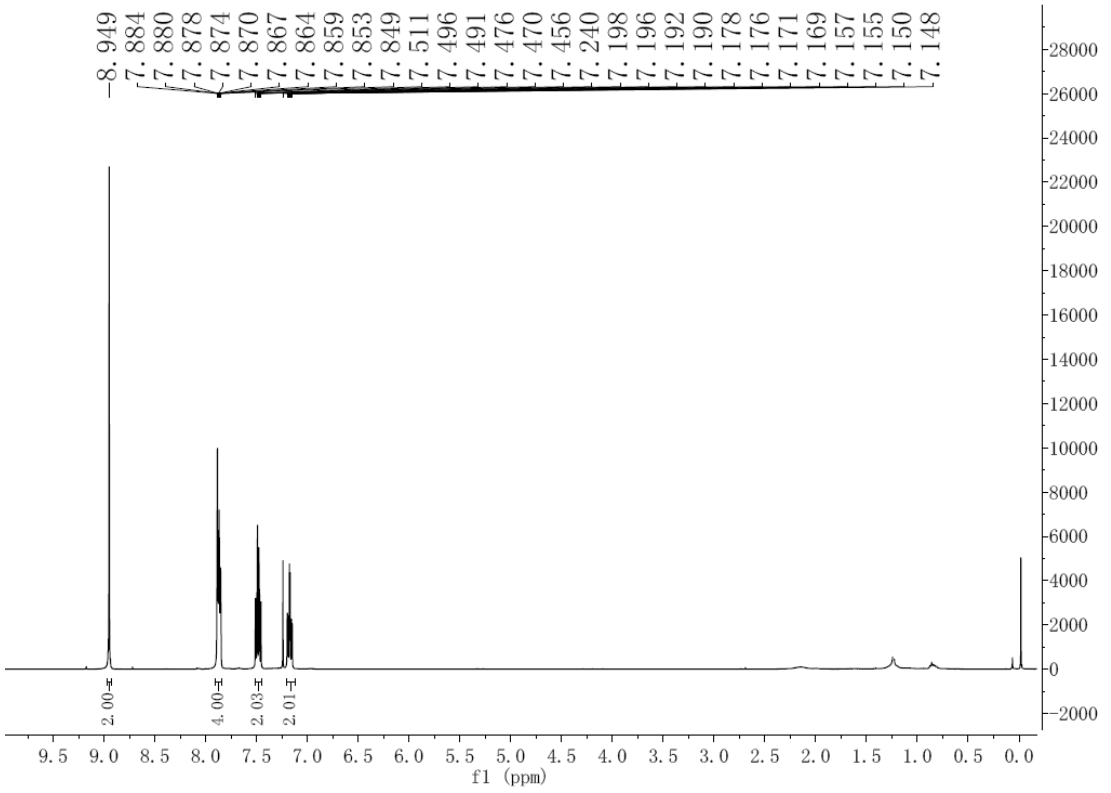


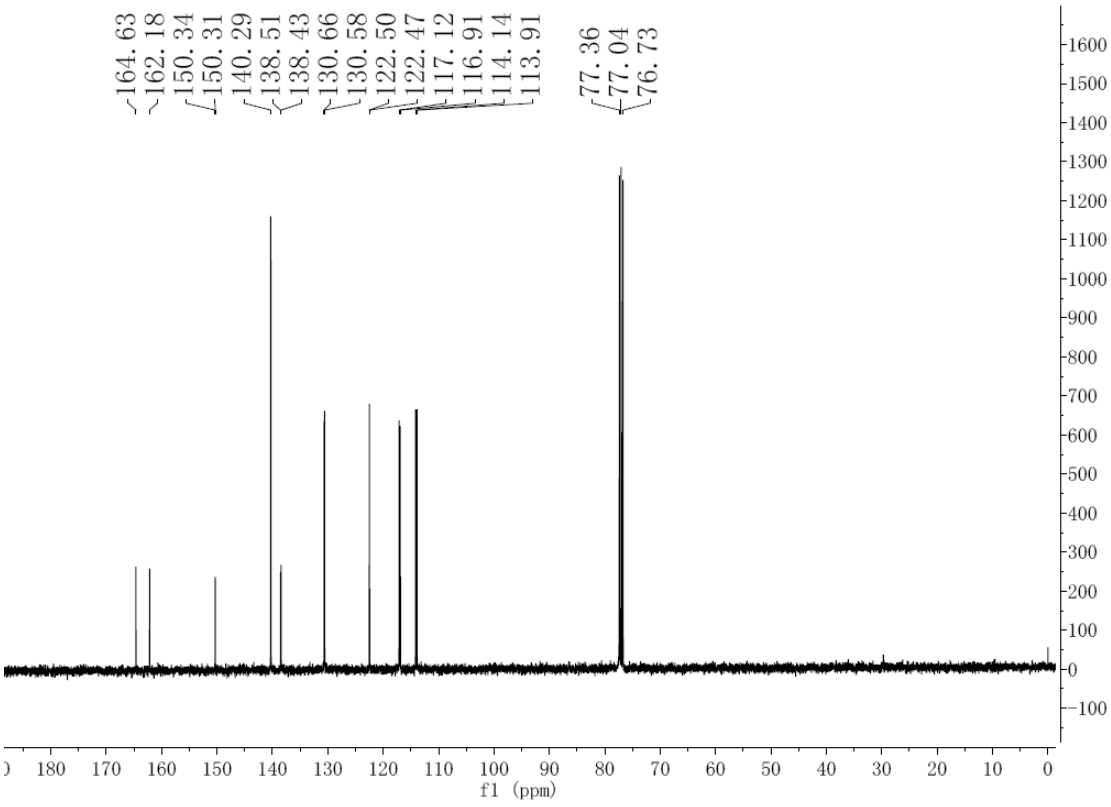
^{1}H NMR and ^{13}C NMR of 2,5-bis(4-fluorophenyl)pyrazine (2i)



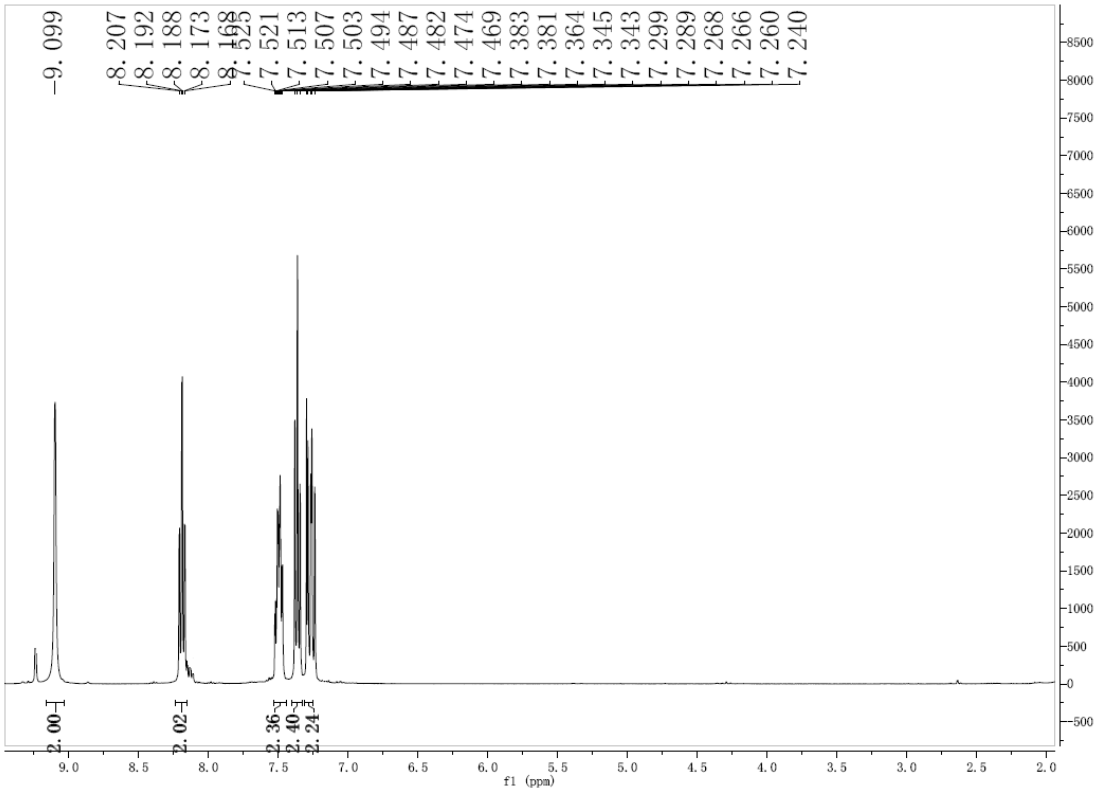


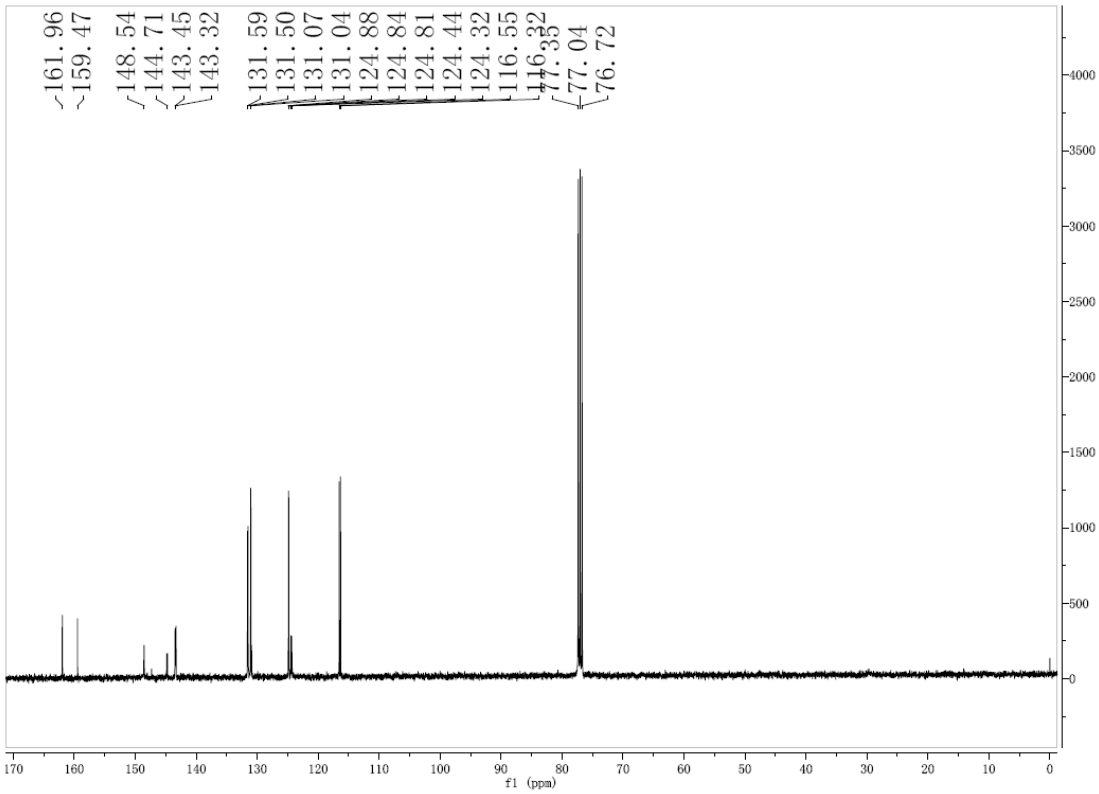
^{1}H NMR and ^{13}C NMR of 2,5-bis(3-fluorophenyl)pyrazine (2j)



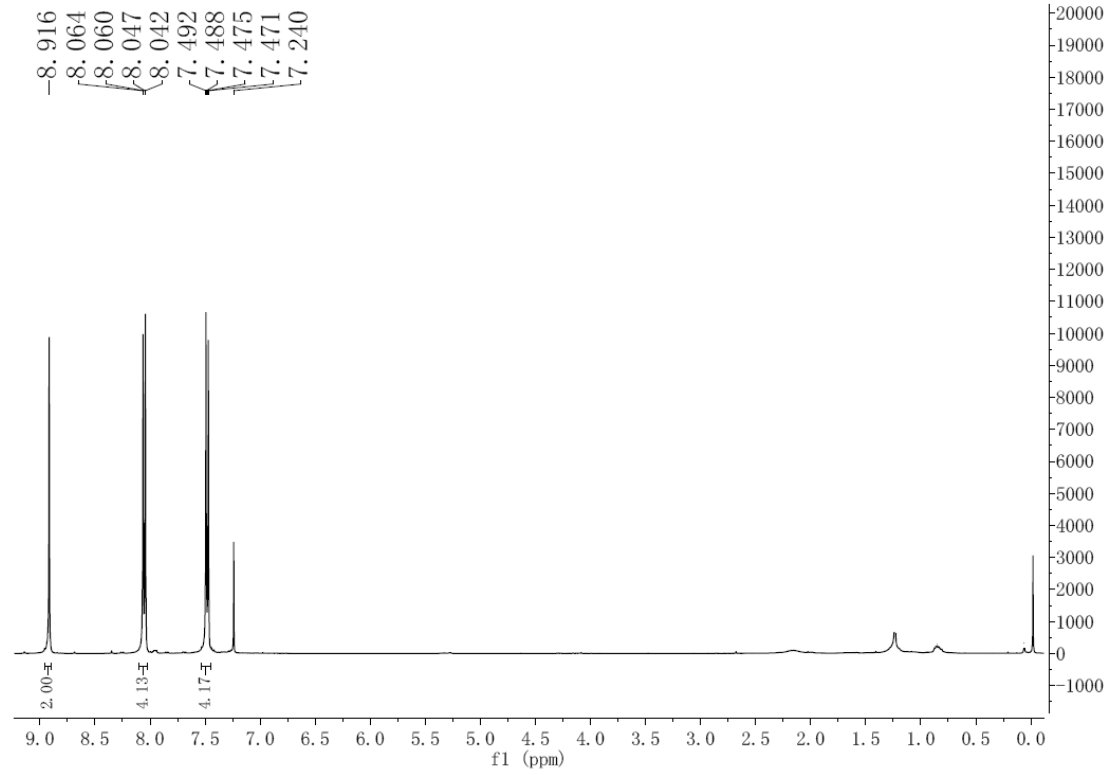


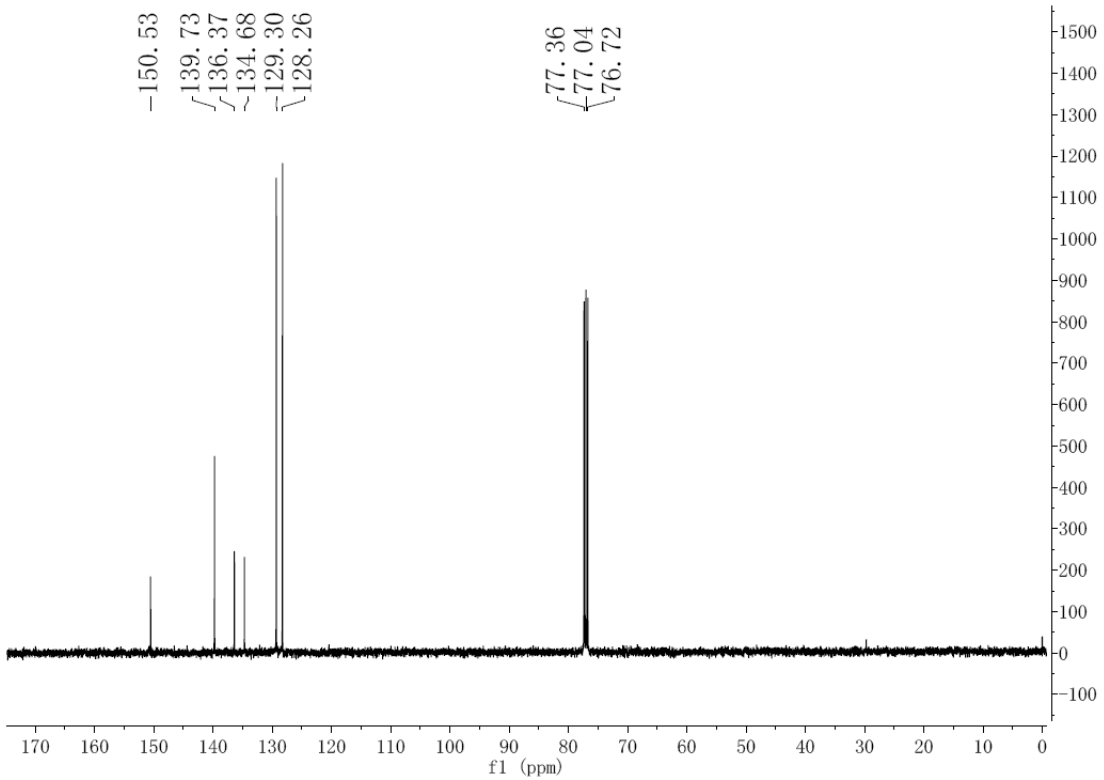
^{1}H NMR and ^{13}C NMR of 2,5-bis(2-fluorophenyl)pyrazine (2k)



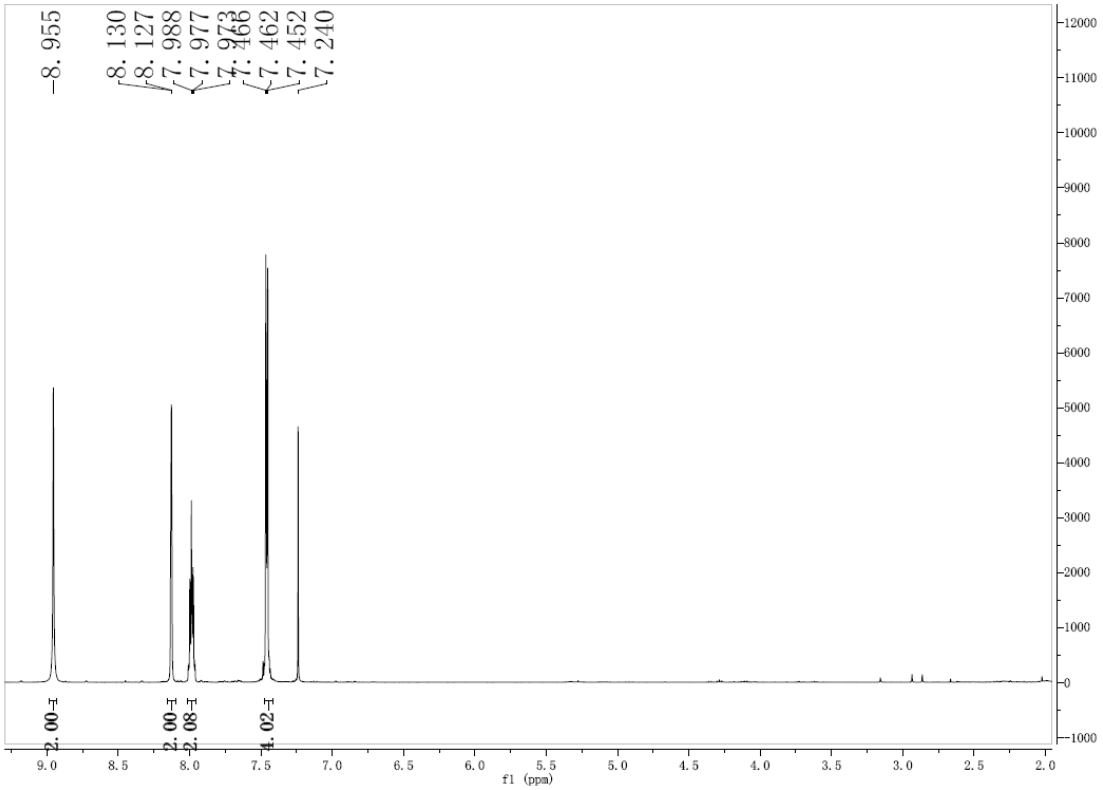


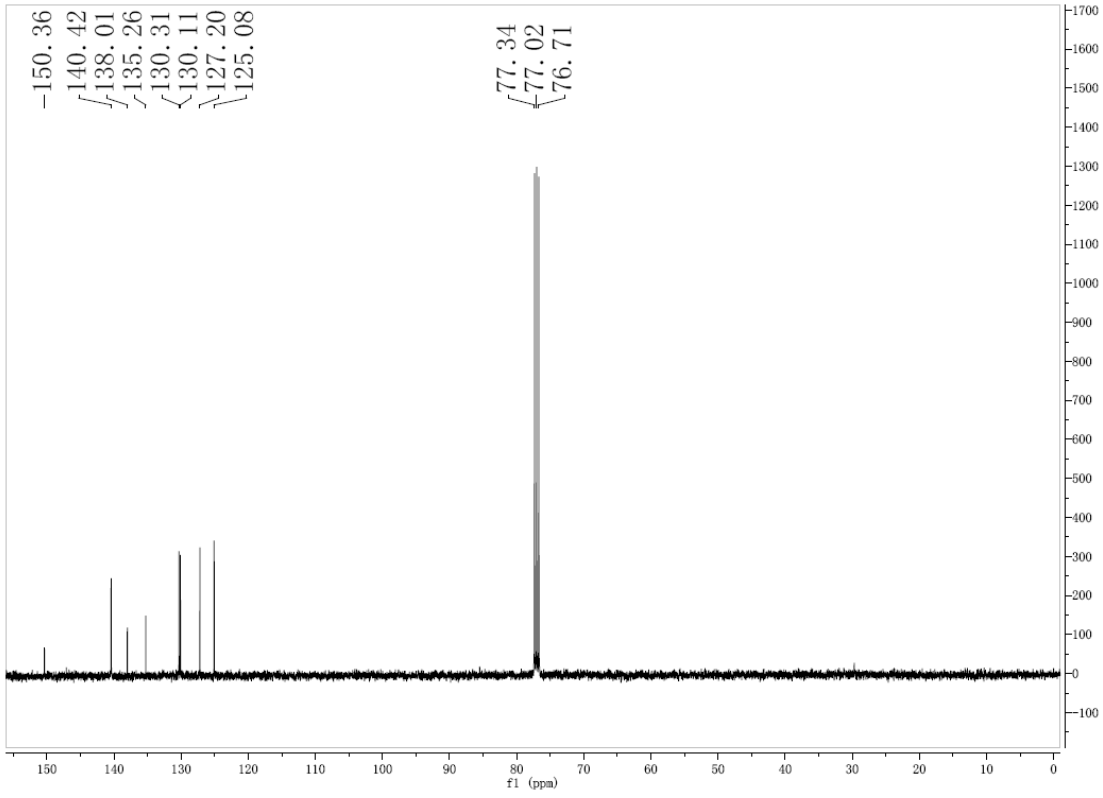
^{1}H NMR and ^{13}C NMR of 2,5-bis(4-chlorophenyl)pyrazine (2l)



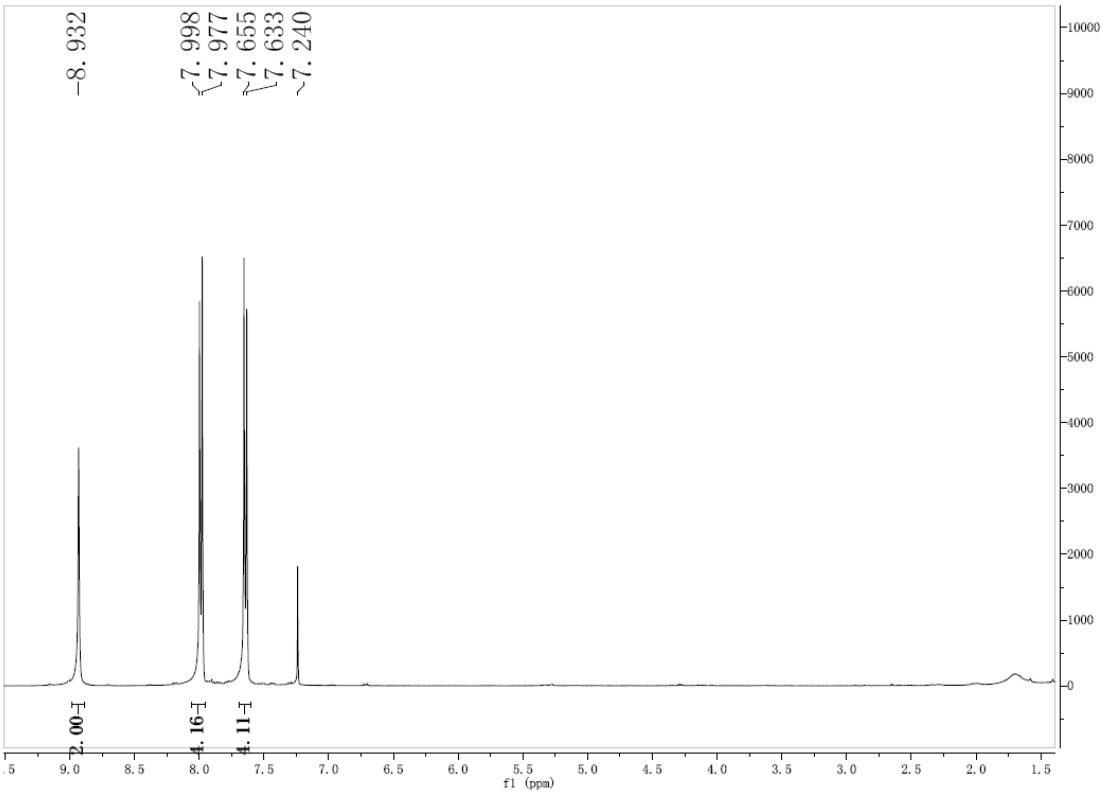


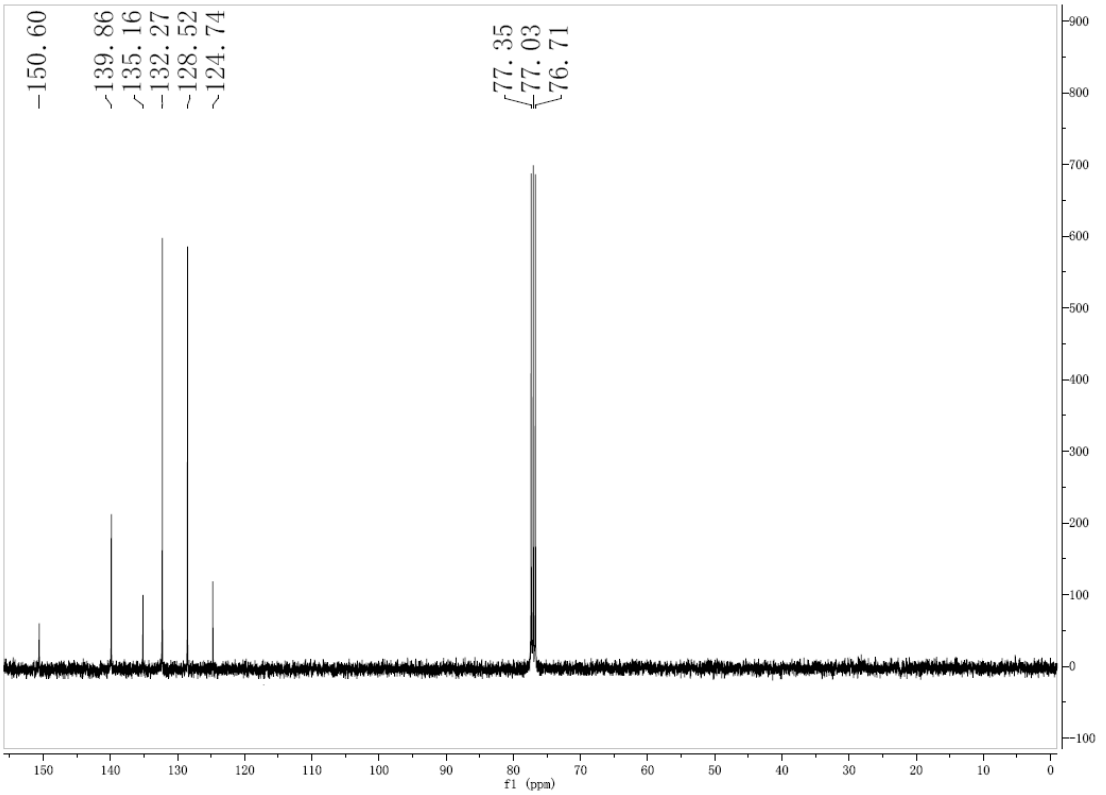
^{1}H NMR and ^{13}C NMR of 2,5-bis(2-chlorophenyl)pyrazine (2m)



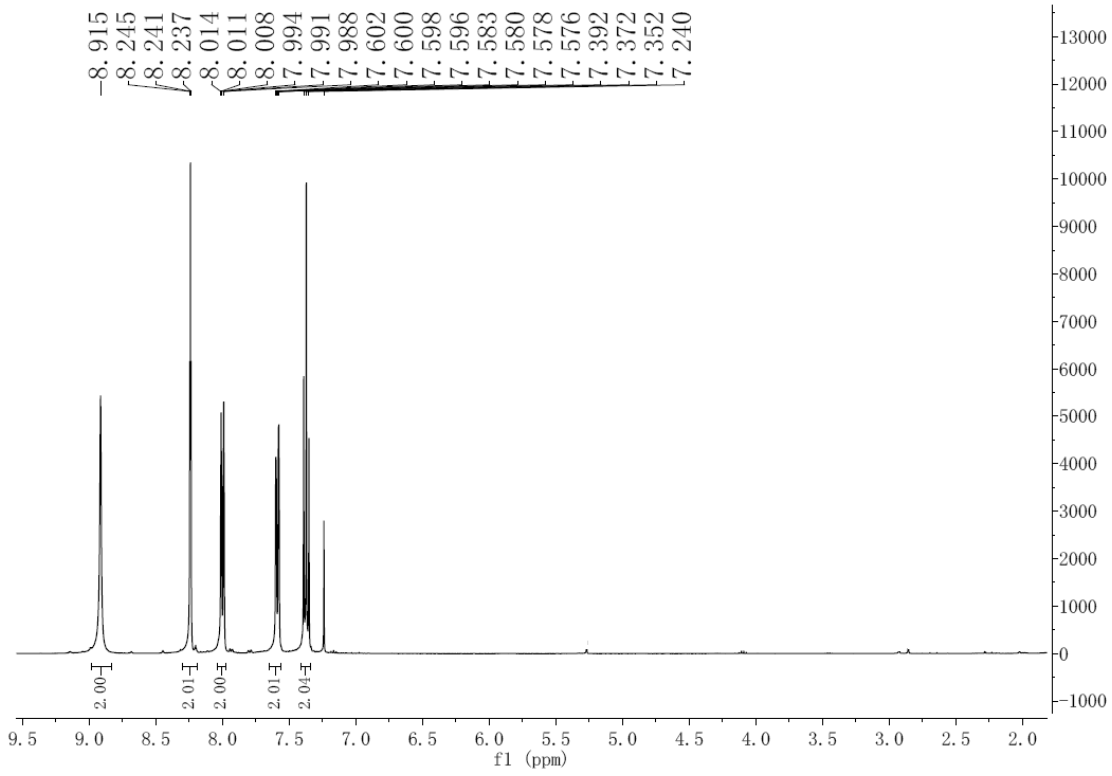


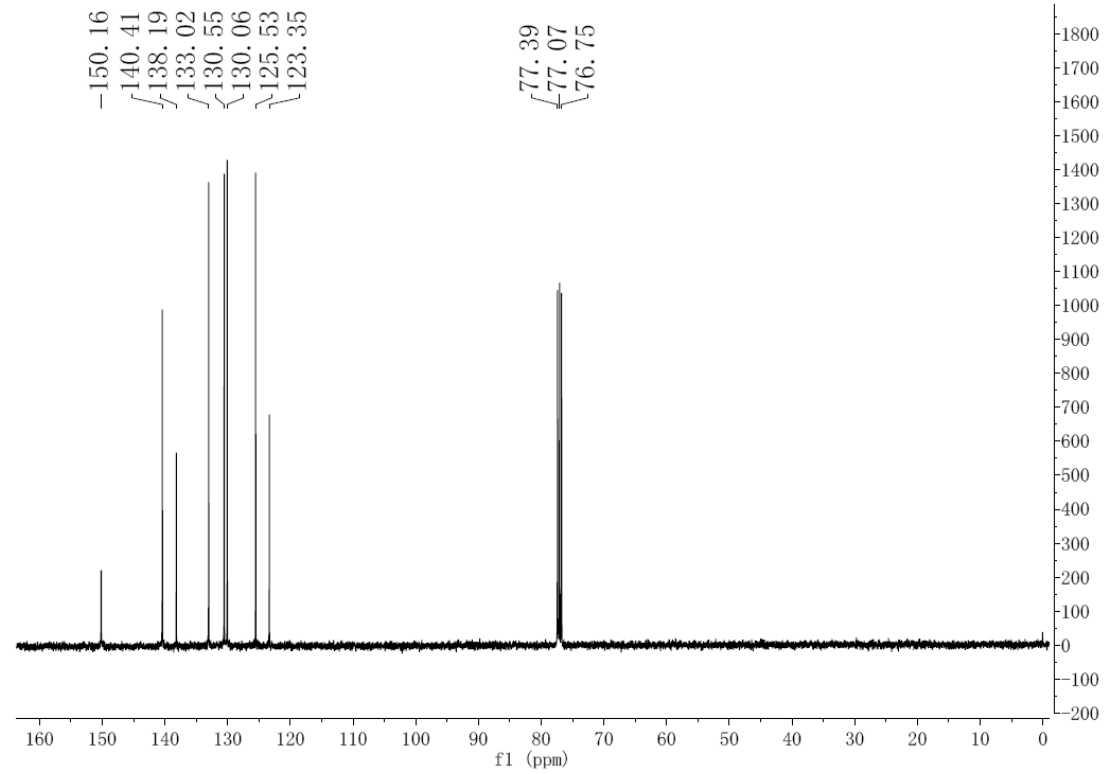
^{1}H NMR and ^{13}C NMR of 2,5-bis(4-bromophenyl)pyrazine (2n)



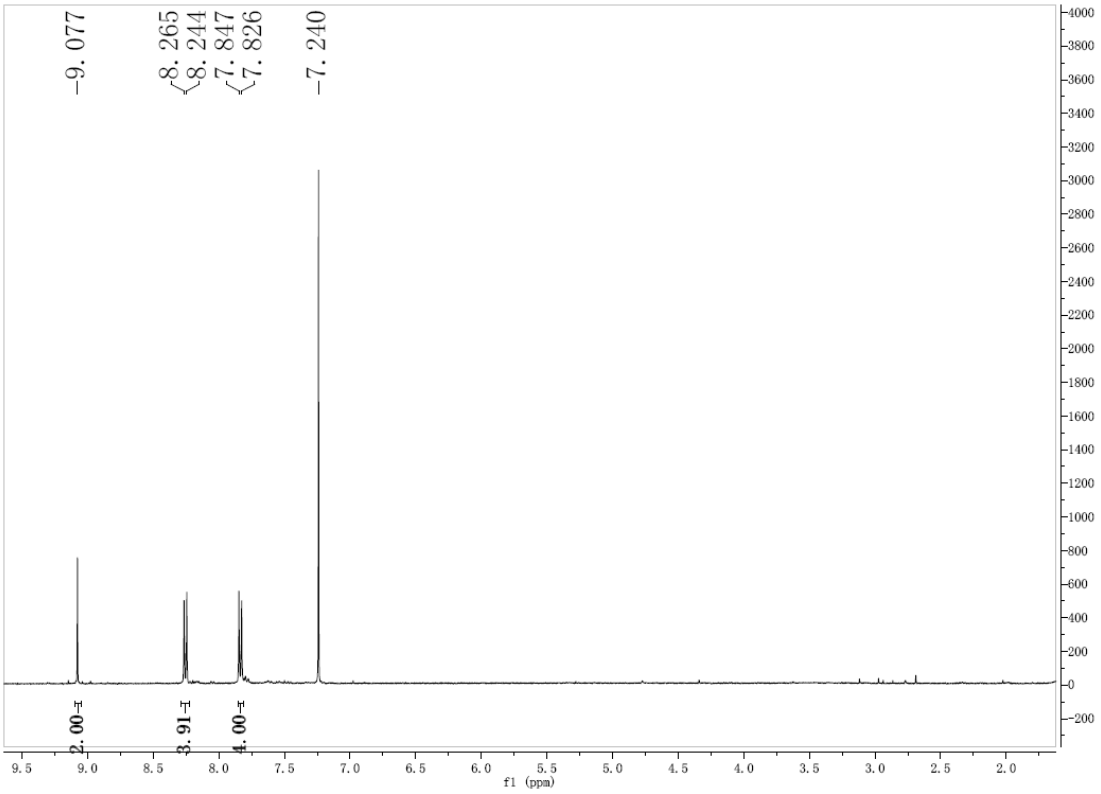


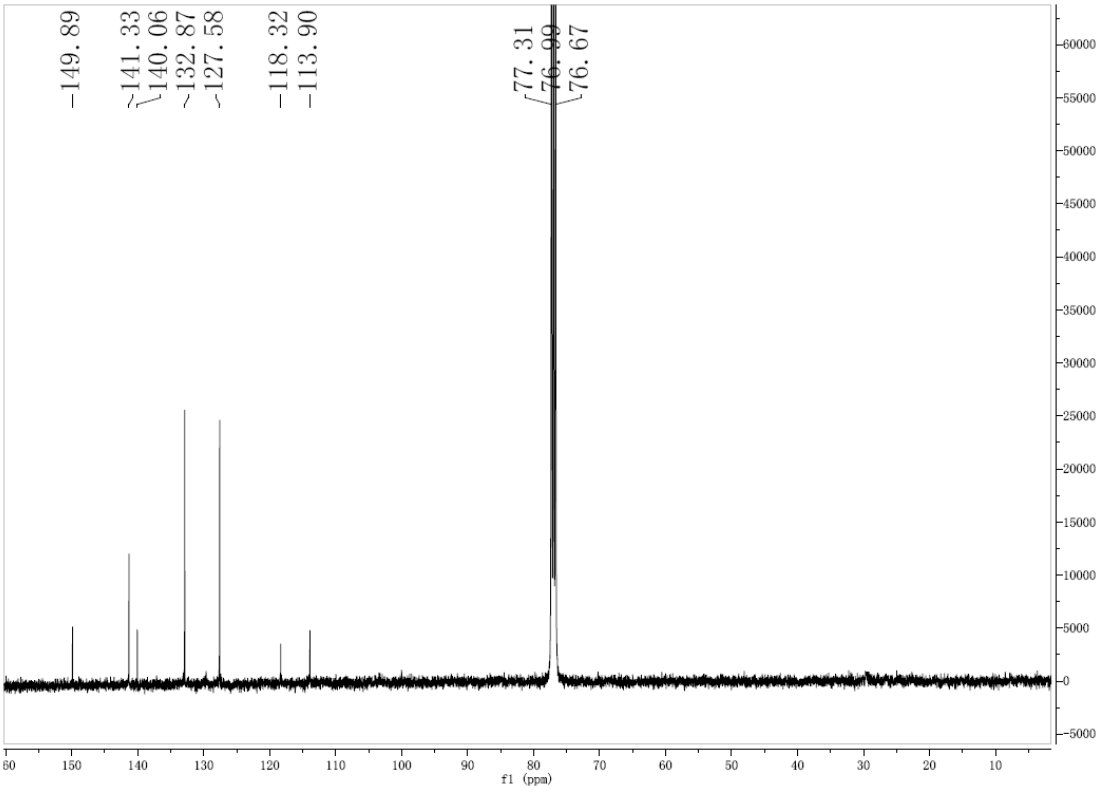
^{1}H NMR and ^{13}C NMR of 2,5-bis(3-bromophenyl)pyrazine (2o)



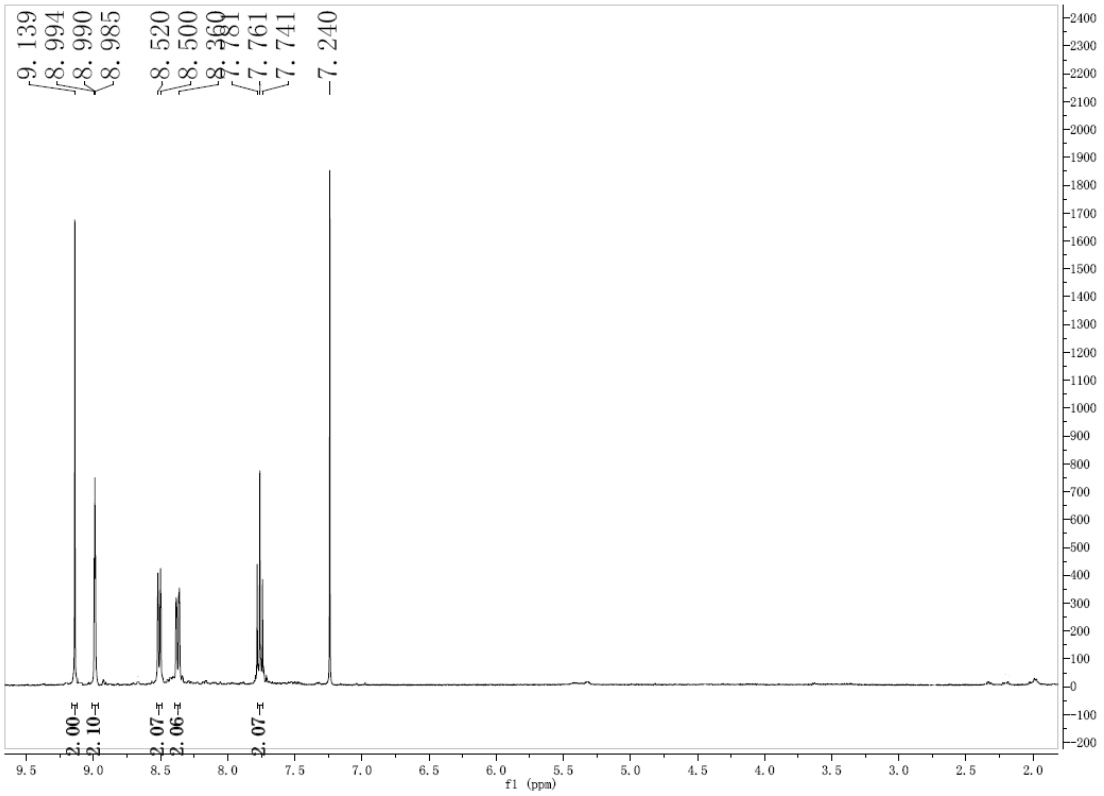


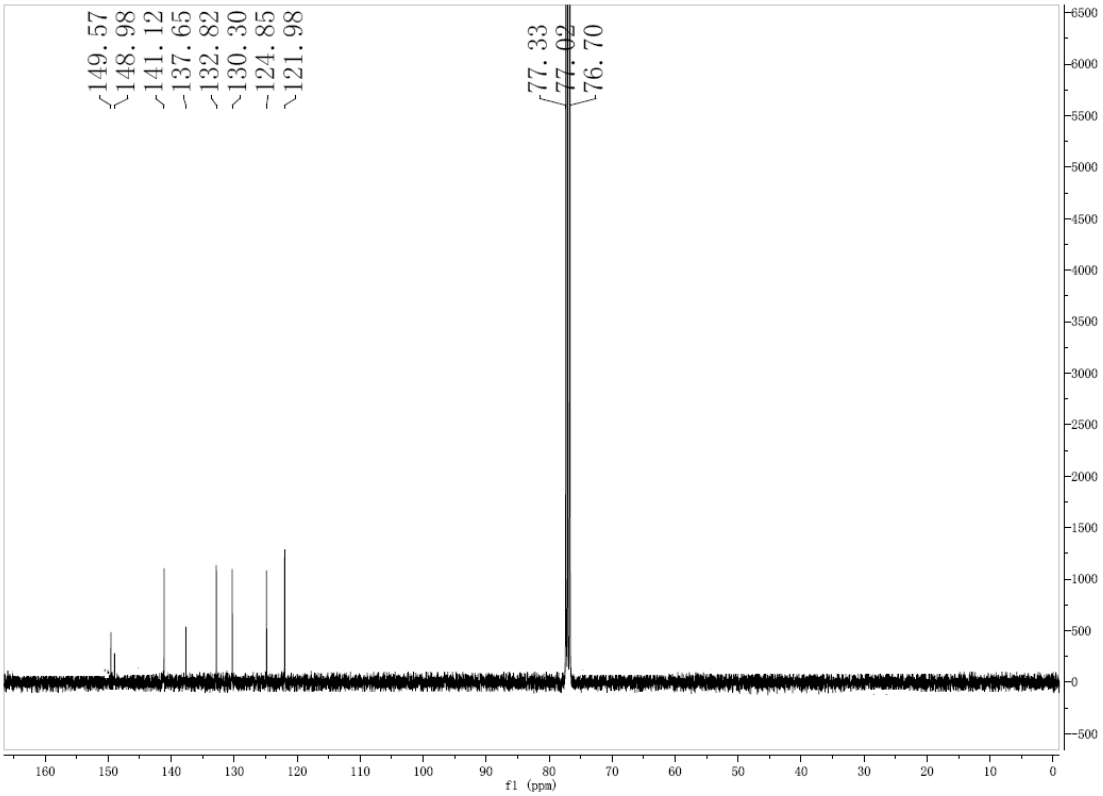
^{1}H NMR and ^{13}C NMR of 4,4'-(pyrazine-2,5-diyl)dibenzonitrile (2p)



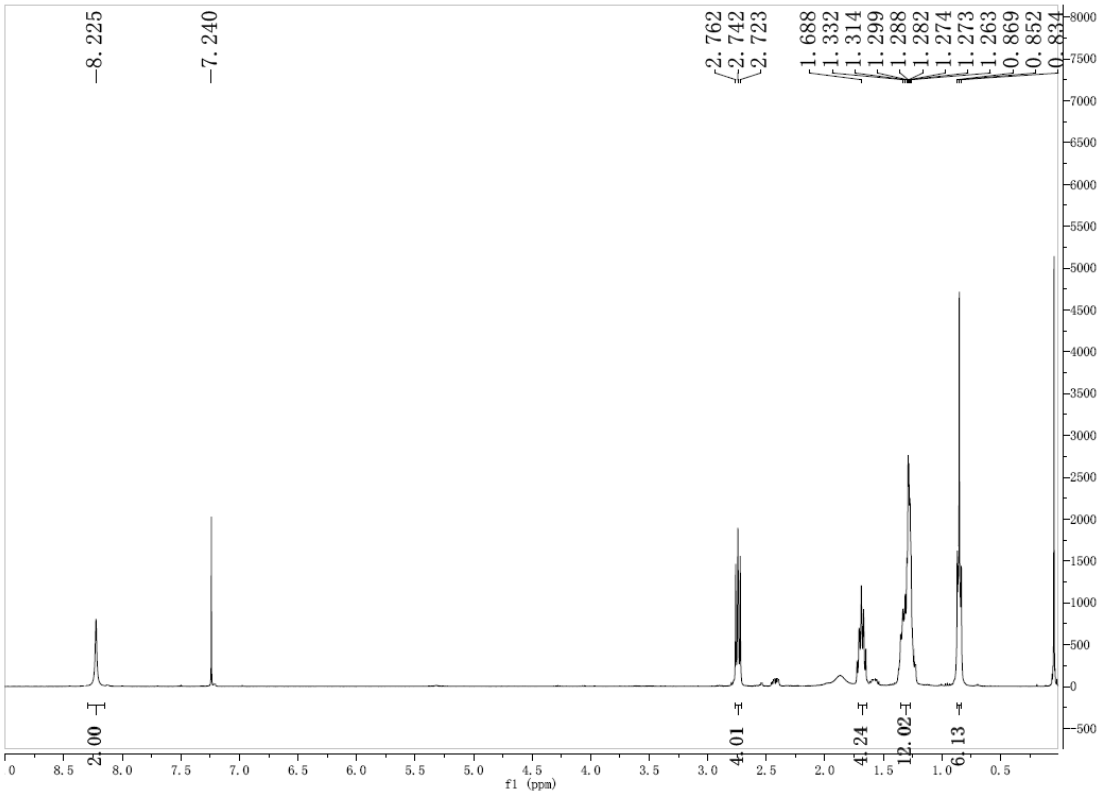


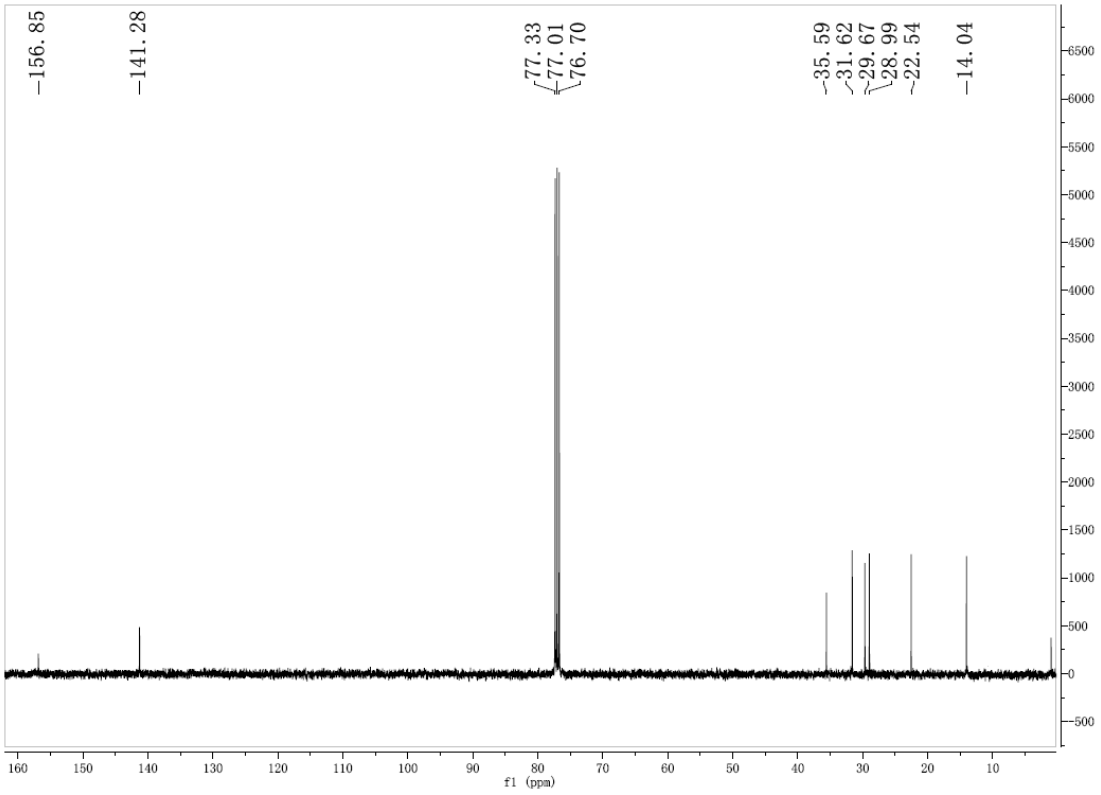
^{1}H NMR and ^{13}C NMR of 2,5-bis(3-nitrophenyl)pyrazine (2q)



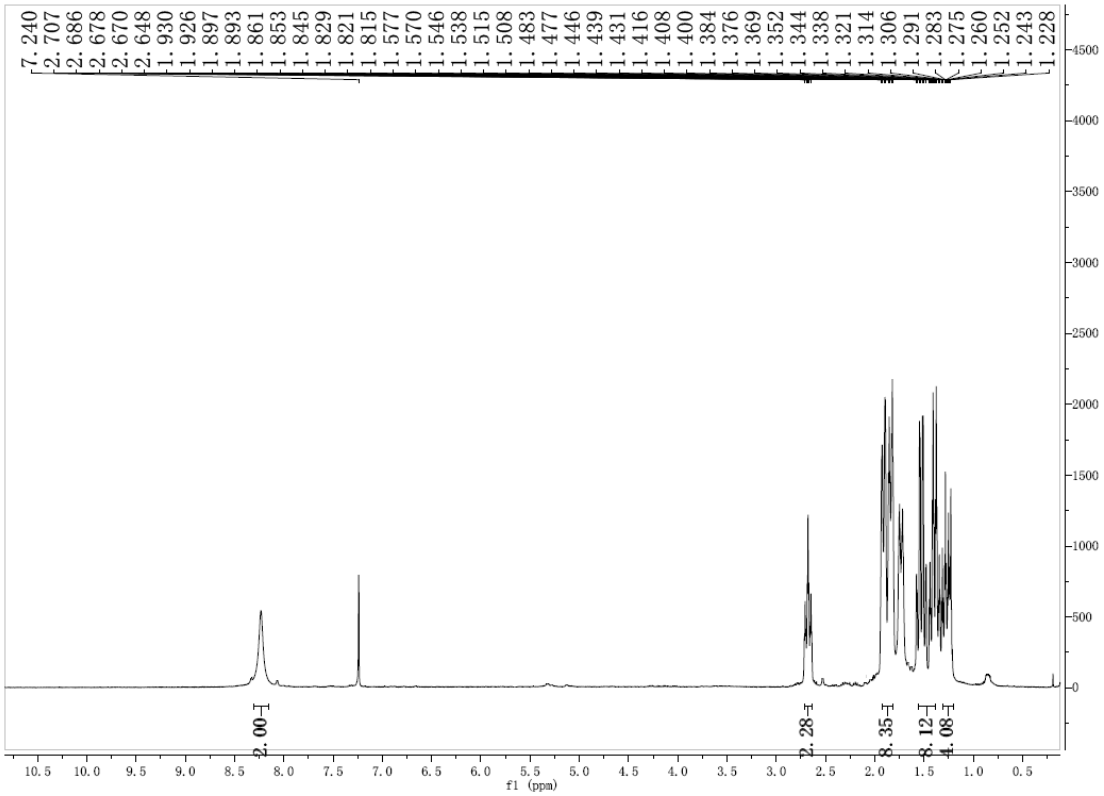


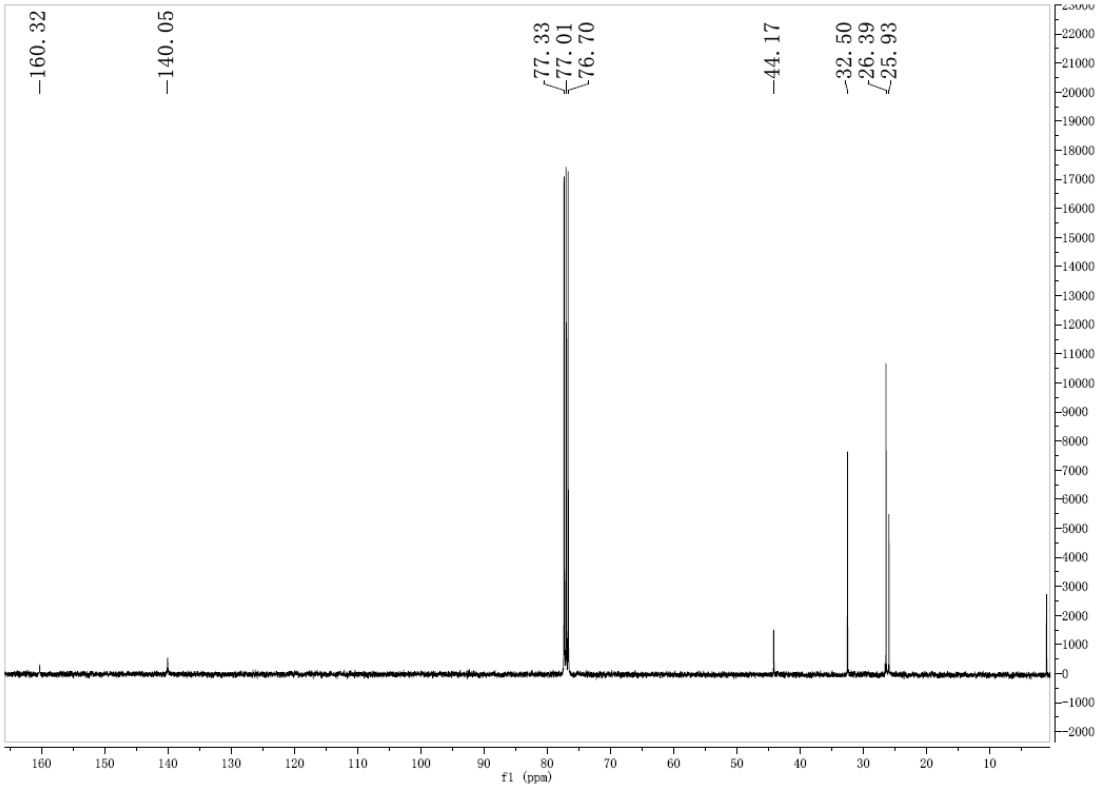
^{1}H NMR and ^{13}C NMR of 2,5-dihexylpyrazine (2r)





^{1}H NMR and ^{13}C NMR of 2,5-dicyclohexylpyrazine (2s)





^{1}H NMR and ^{13}C NMR of 2,6-diphenylpyrazine (3a)