Supplementary Information for

Synthesis of Functionalized 2,3-Dihydroisoxazoles by Domino Reactions in Water and Unexpected Ring-Opening Reactions of 2,3-Dihydroisoxazoles

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1. General Methods:

NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$(δ = 7.26 ppm) or DMSO-D6 (δ = 2.49 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) or DMSO-D6 (δ = 39.5 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. Commercial grade solvents were dried and purified by standard procedures as specified in Purification of Laboratory Chemicals.

2. Experimental Section

Synthesis of benzaldehyde oxime 3a

Hydroxylamine hydrochloride (345 mg, 5 mmol) was stirred in 5 mL H_2O at room temperature and 1N NaOH was added at a rate such that the reaction pH value reached 12. Then2-benzylidenemalononitrile **1a** (154 mg, 1 mmol) was added to the resulting solution. The mixture was then stirred for 4 h. benzaldehyde oxime **3a** was isolated by flash chromatography on silica gel (10% ethyl acetate/petroleum ether).

benzaldehyde oxime 3a ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.17 (s, 1H), 7.57 (m, 2H), 7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 130.1, 128.8, 127.1, 127.0; ESI-HRMS: calcd. for C_7H_7NO +H 122.0599, found 122.0601.

General procedure for synthesis of multifunctionalized 2,3-dihydroisoxazoles (2a-2h).

Hydroxylamine hydrochloride (345 mg, 5 mmol) was stirred in 5 mL H_2O at room temperature and 1 N NaOH was added at a rate such that the reaction pH value reached 9~10. Then 2-benzylidenemalononitrile **1a** (154 mg, 1 mmol) was added into the resulting solution. The mixture was then stirred for 4 h. The pure 2,3-dihydroisoxazole **2a** was easily isolated by filtration, then washed with water.

5-amino-3-phenyl-2,3-dihydroisoxazole-4-carbonitrile 2a ^{1}H NMR (400 MHz, DMSO) δ 8.72 (s, 1H), 7.30 – 7.38 (m, 5H), 5.23 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.6, 128.5, 127.83, 126.8, 118.4, 109.5, 65.6, 54.9; IR (KBr) cm^{-1} 3356, 3219, 3164, 2918, 2168, 1654, 1600, 1398, 1109, 810, 571; ESI-HRMS: calcd. for $C_{10}H_9N_3O$ +Na 210.0638, found 210.0627.

5-amino-3-(*p*-tolyl)-2,3-dihydroisoxazole-4-carbonitrile 2b ^{1}H NMR (400 MHz, DMSO) δ 8.55 (s, 1H), 7.96 – 6.46 (m, 4H), 5.18 (d, *J* = 8.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 168.5, 129.4, 129.1, 129.1, 128.9, 128.9, 128.3, 127.8, 118.3, 54.9, 20.7; IR (KBr) cm^{-1} 3363, 3220, 3157, 2924, 2179, 1644, 1599, 1400, 1107, 808, 577; ESI-HRMS: calcd. for $C_{11}H_{11}N_3O$ +Na 224.0794, found 224.0797.

5-amino-3-(4-fluorophenyl)-2,3-dihydroisoxazole-4-carbonitrile 2c ^{1}H NMR (400 MHz, DMSO) δ 8.65 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 4H), 7.19 (t, *J* = 8.7 Hz, 2H), 5.24 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.6, 118.2, 115.3, 115.3, 115.1,

109.5, 54.9; IR (KBr) cm^{-1} 3349, 3266, 3225, 2932, 2178, 1639, 1575, 1404, 1116, 809, 799, 601; ESI-HRMS: calcd. for $C_{10}H_8FN_3O$ +Na 228.0545, found 228.0547.

5-amino-3-(4-chlorophenyl)-2,3-dihydroisoxazole-4-carbonitrile 2d ^{1}H NMR (400 MHz, DMSO) δ 8.79 (s, 1H), 7.56 – 7.15 (m, 4H), 5.25 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) 167.5, 131.3, 127.5, 127.5, 127.1, 127.0, 117.3, 53.7; IR (KBr) cm^{-1} 3368, 3270, 3215, 2925, 2181, 1646, 1599, 1408, 1106, 819, 800, 555; ESI-HRMS: calcd. for $C_{10}H_8ClN_3O$ +Na 244.0241, found 224.0248.

5-amino-3-(4-bromophenyl)-2,3-dihydroisoxazole-4-carbonitrile 2e ^{1}H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 7.72 – 7.07 (m, 4H), 5.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.5, 131.4, 130.9, 130.9, 130.2, 130.2, 128.9, 118.3, 54.7; IR (KBr) cm^{-1} 3345, 3267, 3209, 2925, 2179, 1650, 1587, 1421, 1114, 820, 812, 563; ESI-HRMS: calcd. for $C_{10}H_8BrN3O$ +Na 287.9743, found 287.9734.

5-amino-3-(4-(trifluoromethyl)phenyl)-2,3-dihydroisoxazole-4-carbonitrile 2f ^{1}H NMR (400 MHz, DMSO) δ 8.91 (s, 1H), 8.52 – 6.43 (m, 4H), 5.34 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.5, 128.4, 127.2, 125.7, 125.5, 125.5, 125.5, 123.0, 118.2, 64.7, 54.7; IR (KBr) cm^{-1} 3356, 3245, 3209, 2925, 2173, 1651, 1623, 1412, 1137, 807, 756, 498; ESI-HRMS: calcd. for $C_{11}H_8F_3N_3O$ +Na 278.0512, found 278.0510.

5-amino-3-(3-chlorophenyl)-2,3-dihydroisoxazole-4-carbonitrile 2g ^{1}H NMR (400 MHz, DMSO) δ 8.83 (s, 1H), 7.79 – 7.12 (m, 4H), 5.26 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.5, 133.1, 130.5, 127.6, 126.3, 118.2, 64.7, 54.6; IR (KBr) cm^{-1} 3355, 3267, 3225, 2936, 2179, 1643, 1601, 1422, 1121, 809, 795, 601; ESI-HRMS: calcd. for $C_{10}H_8ClN_3O$ +Na 244.0241, found 244.0252.

5-amino-3-(2-chlorophenyl)-2,3-dihydroisoxazole-4-carbonitrile 2h ^{1}H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 7.72 – 6.96 (m, 4H), 5.59 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.9, 129.8, 129.5, 129.4, 127.7, 127.4, 118.0, 62.5, 53.3; IR (KBr) cm^{-1} 3347, 3260, 3211, 2932, 2184, 1647, 1549, 1421, 1110, 823, 810, 521; ESI-HRMS: calcd. for $C_{10}H_8ClN_3O$ +Na 244.0241, found 224.0248.

3. General procedure for synthesis of multifunctionalized 2,3-dihydroisoxazoles (2i-2q) and spiro-2,3-dihydro- isoxazoles (2r-2s).

Hydroxylamine hydrochloride (345 mg, 5 mmol) was stirred in 5 mL solvent (H_2O:THF = 1:1) at room temperature, then 1 N NaOH was added at a rate such that the reaction pH value reached 9~10. α,α-Dicyanoolefin **1i** (168 mg, 1 mmol) was added into the resulting solution.. The mixture was then stirred for 14 h. The mixture was extracted with EtOAc (10 mL), dried with anhydrous sodium sulfate. The solvent was removed and flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave **2i** as a pale yellow solid.

5-amino-3-methyl-3-phenyl-2,3-dihydroisoxazole-4-carbonitrile 2i ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 2H), 7.48 – 7.14 (m, 3H), 6.61 (s, 1H), 5.12 (s, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 129.3, 128.6, 127.8, 126.3, 124.7, 117.6, 106.6, 96.5, 80.2, 26.0; IR (KBr) cm^{-1} 3446, 3428, 3179, 2981, 2179, 1662, 1406, 1049, 818; ESI-HRMS: calcd. for $C_{11}H_{11}N_3O$ +Na 224.0794, found 224.0795.

5-amino-3-methyl-3-(*p*-tolyl)-2,3-dihydroisoxazole-4-carbonitrile 2j ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 2H), 6.59 (s, 1H), 5.20 (s, 2H), 2.34 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 129.2, 126.3, 124.7, 123.4, 121.6, 117.6, 83.2, 25.8, 20.9; IR (KBr) cm^{-1} 3449, 3428, 3176, 2980, 2187, 1671, 145, 1056, 817; ESI-HRMS: calcd. for $C_{12}H_{13}N_3O$ +Na 238.0951, found 238.0946.

5-amino-3-(4-methoxyphenyl)-3-methyl-2,3-dihydroisoxazole-4-carbonitrile 2k ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.54 (s, 1H), 5.05 (s, 2H), 3.81 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 125.9, 118.2, 118.0, 113.3, 113.0, 54.9, 25.6; IR (KBr) cm^{-1} 3451, 3430, 3178, 2982, 2189, 1673, 1407, 1056, 819; ESI-HRMS: calcd. for $C_{12}H_{13}N_3O_2$ +Na 254.0901, found 254.0899.

5-amino-3-(4-chlorophenyl)-3-methyl-2,3-dihydroisoxazole-4-carbonitrile 2l ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.59 (s, 1H), 5.10 (s, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 142.9, 129.0, 128.9, 128.8, 120.6, 117.0, 85.1, 25.9; IR (KBr) cm^{-1} 3433, 3317, 3173, 2977, 2167, 1645, 1401, 1004, 811; ESI-HRMS: calcd. for $C_{11}H_{10}ClN_3O$ +Na 258.0405, found

258.0405.

5-amino-3-(4-bromophenyl)-3-methyl-2,3-dihydroisoxazole-4-carbonitrile 2m ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (q, *J* = 8.7 Hz, 4H), 6.58 (s, 1H), 4.93 (s, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 131.0, 126.7, 126.7, 126.6, 126.6, 126.5, 117.9, 77.3, 77.0, 76.6, 60.7, 25.3; IR (KBr) cm^{-1} 3438, 3331, 3163, 2953, 2169, 1653, 1410, 1007, 821; ESI-HRMS: calcd. for $C_{11}H_{10}BrN_3O$ +Na 301.9900, found 301.9897.

5-amino-3-(3-chlorophenyl)-3-methyl-2,3-dihydroisoxazole-4-carbonitrile 2n ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.33-7.29 (m, 2H), 6.61 (s, 1H), 5.12 (s, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 129.9, 127.6, 124.9, 117.1, 109.9, 25.8; IR (KBr) cm^{-1} 3436, 3325, 3178, 2977, 2172, 1650, 1406, 1009, 815; ESI-HRMS: calcd. for $C_{11}H_{10}ClN_3O$ + Na 258.0405, found 258.0403.

5-amino-3-ethyl-3-phenyl-2,3-dihydroisoxazole-4-carbonitrile 2o ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 1H), 6.69 (s, 1H), 5.24 (s, 2H), 2.08-1.95 (m, 2H), 0.94 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 128.5, 128.1, 127.4, 126.0, 125.6, 118.2, 32.4, 8.6; IR (KBr) cm^{-1} 3446, 3425, 3173, 2977, 2184, 1668, 1402, 1051, 814; ESI-HRMS: calcd. for $C_{12}H_{13}N_3O$ +Na 238.0951, found 238.0946.

5-amino-3-ethyl-3-(p-tolyl)-2,3-dihydroisoxazole-4-carbonitrile 2p ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.66 (s, 1H), 5.20 (s, 2H), 2.34 (s, 3H), 2.22 – 1.93 (m, 2H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 129.3, 126.6, 126.0, 125.7, 125.3, 118.2, 43.3, 20.9, 13.7, 8.6; IR (KBr) cm^{-1} 3438, 3420, 3169, 2965, 2182, 1668, 1400, 1049, 807; ESI-HRMS: calcd. for $C_{13}H_{15}N_3O$ +Na 252.1107, found 252.1106.

5-amino-3-(4-chlorophenyl)-3-ethyl-2,3-dihydroisoxazole-4-carbonitrile 2q ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 1H), 5.41 (s, 1H), 2.04-2.00 (m, 1H), 0.91 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 128.9, 128.58, 128.2, 127.1, 127.0, 126.9, 118.1, 14.0, 8.5; IR (KBr) cm^{-1} 3451, 3432, 3173, 2980, 2187, 1670, 1412, 1058, 817;

ESI-HRMS: calcd. for $C_{12}H_{12}ClN_3O$ + Na 272.0566, found 272.0562.

3-amino-2-oxa-1-azaspiro[4.4]non-3-ene-4-carbonitrile 2r ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (d, *J* = 4.3 Hz, 2H), 1.92 – 1.46 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 117.4, 75.7, 60.8, 37.6, 35.0, 24.7, 24.2; IR (KBr) cm^{-1} 3457, 3418, 3161, 2966, 2119, 1600; ESI-HRMS: calcd. for $C_8H_{11}N_3O$ + Na 188.0794, found 188.0786;

3-amino-2-oxa-1-azaspiro[4.5]dec-3-ene-4-carbonitrile 2s ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 2H), 1.82-1.53 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 117.8, 67.9, 63.3, 31.4, 28.4, 25.5, 24.8; IR (KBr) cm^{-1} 3451, 3419, 3169, 2968, 2117, 1608; ESI-HRMS: calcd. for $C_9H_{13}N_3O$ +Na 202.0951, found 202.0945.

General procedure for synthesis of 2-cyano-3-phenylacrylamides (4a-4h) *via* one-pot tandem reaction

Hydroxylamine hydrochloride (345 mg, 5 mmol) was stirred in 5 mL H_2O at room temperature, then 1 N NaOH was added at a rate such that the reaction pH value reached 9~10. Then 2-benzylidenemalononitrile **1a** (154 mg, 1 mmol) was added into the resulting solution. Hydrochloric acid (2 N HCl) was added at a rate such that the reaction pH value reached 1~3 after the mixture was then stirred for 4 h. The mixture was then stirred for another 30 min extracted with EtOAc (10 mL), and dried with anhydrous sodium sulfate. The solvent was removed and flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave 4a as a white solid.

2-cyano-3-phenylacrylamide 4a ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 25.1 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 2H), 7.55-7.50 (m, 3H), 6.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 153.8, 132.9, 131.4, 130.6, 116.8, 103.2; IR (KBr) cm^{-1} 3388, 3156, 2219, 1693, 1590, 1374, 1182, 815, 610, 459; ESI-HRMS: calcd. for $C_{10}H_8N_2O$ +Na 195.0529, found 195.0530.

2-cyano-3-(*p*-tolyl)acrylamide 4b ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.40 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ 167., 153.9, 144.3, 130.9, 130.9, 130.0, 129.9, 129.9, 128.9, 117.2, 21.8; IR (KBr) cm^{-1} 3390, 3159, 2222, 1698, 1596, 1377, 1185, 821, 616, 461; ESI-HRMS: calcd. for $C_{11}H_{10}N_2O$ + Na 209.0686, found 209.0690.

2-cyano-3-(4-fluorophenyl)acrylamide 4c ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s,

1H), 8.09 – 7.87 (m, 2H), 7.20 (t, *J* = 8.6 Hz, 2H), 6.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 161.7, 161.1, 152.5, 133.3, 133.2, 127.9, 122.6, 116.9, 116.8, 116.8, 116.6, 116.6; IR (KBr) cm^{-1} 3439, 3137, 2190, 1693, 1583, 1329, 809, 447; ESI-HRMS: calcd. for $C_{10}H_7FN_2O$ +Na 213.0435., found 213.0436.

3-(4-chlorophenyl)-2-cyanoacrylamide 4d ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.90 (d, *J* = 10.7 Hz, 2H), 7.49 (d, *J* = 6.8 Hz, 2H), 6.33 (s, 1H), 5.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 150.0, 137.5, 130.9, 130.9, 129.6, 128.6, 128.6, 128.6, 115.7, 104.7; IR (KBr) cm^{-1} 3451, 3149, 2209, 1701, 1600, 1396, 819, 460; ESI-HRMS: calcd. for $C_{10}H_7ClN_2O$ +Na 229.0139., found 229.0139.

3-(4-bromophenyl)-2-cyanoacrylamide 4e ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 6.32 (s, 1H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 150.2, 131.7, 131.0, 130.0, 126.3, 115.8, 104.8; IR (KBr) cm^{-1} 3449, 3146, 2204, 1700, 1599, 1392, 821, 451; ESI-HRMS: calcd. for $C_{10}H_7Br\ N_2O$ +Na 272.9634., found 272.9638.

2-cyano-3-(4-(trifluoromethyl)phenyl)acrylamide 4f ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.35 (m, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 6.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 152.0, 130.7, 126.2, 126.2, 126.1, 126.1, 116.2, 105.9; IR (KBr) cm^{-1} 3447, 3145, 2204, 1707, 1593, 1392, 819, 452; ESI-HRMS: calcd. for $C_{11}H_7F_3N_2O$ +Na 263.0403, found 263.0405.

3-(3-chlorophenyl)-2-cyanoacrylamide 4g ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.97 – 7.78 (m, 2H), 7.49 (dt, *J* = 15.7, 8.0 Hz, 2H), 6.38 (s, 1H), 6.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 152.3, 135.3, 133.1, 132.8, 130.5, 130.4, 130.4, 128.5, 116.4, 104.5; IR (KBr) cm^{-1} 3449, 3147, 2207, 1695, 1598, 1388, 821, 451; ESI-HRMS: calcd. for $C_{10}H_7ClN_2O$ +Na 229.0140, found 229.0142;

3-(2-chlorophenyl)-2-cyanoacrylamide 4h ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.14 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.60 – 7.37 (m, 4H), 6.38 (s, 1H), 6.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 150.4, 150.4, 136.4, 133.4, 133.4, 130.4, 130.3, 130.0, 129.4, 129.4, 127.3, 127.3, 116.3; IR (KBr) cm^{-1} 3451, 3148, 2209, 1701, 1604, 1395, 823, 461; ESI-HRMS: calcd. for $C_{10}H_7ClN_2O$ +Na 229.0140, found 229.0142.

2-cyano-3-(m-tolyl)acrylamide 4t ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.85 –

7.68 (m, 2H), 7.45 – 7.29 (m, 2H), 6.68 (s, 1H), 6.49 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 154.1, 139.0, 133.9, 131.4, 131.3, 129.0, 127.8, 117.0, 102.7, 21.2; IR (KBr) cm^{-1} 3390, 3157, 2220, 1695, 1591, 1377, 1183, 817, 617, 464; ESI-HRMS: calcd. for $C_{11}H_{10}N_2O$ +Na 209.0686, found 209.0689.

2-cyano-3-(3-methoxyphenyl)acrylamide 4u ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.53-7.49 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.07 (m, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 159.8, 154.0, 132.6, 130.2, 130.2, 123.8, 119.7, 117.0, 114.4, 103.11, 55.4; IR (KBr) cm^{-1} 3390, 3160, 2222, 1695, 1592, 1377, 1185, 818, 614, 462; ESI-HRMS: calcd. for $C_{11}H_{10}N_2O_2$ +Na 225.0635, found 225.0636.

General procedure for synthesis of 2-cyanobut-2-enoic acid derivatives 5 *via* one-pot tandem reaction

Hydroxylamine hydrochloride (345 mg, 5 mmol) was stirred in 5 mL solvent (H_2O:THF = 1:1) at room temperature and 1 N NaOH was added at a rate such that the reaction pH value reached 9~10. Then 1 mmol of **1s** was added into the resulting solution. Hydrochloric acid (2 N HCl) was added at a rate such that the reaction pH value reached 1~3 after the mixture was stirred for 14 h. The mixture was then stirred for another 1 h, extracted with EtOAc (10 mL), and dried with anhydrous sodium sulfate. The solvent was removed and flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave **5j** as a white solid.

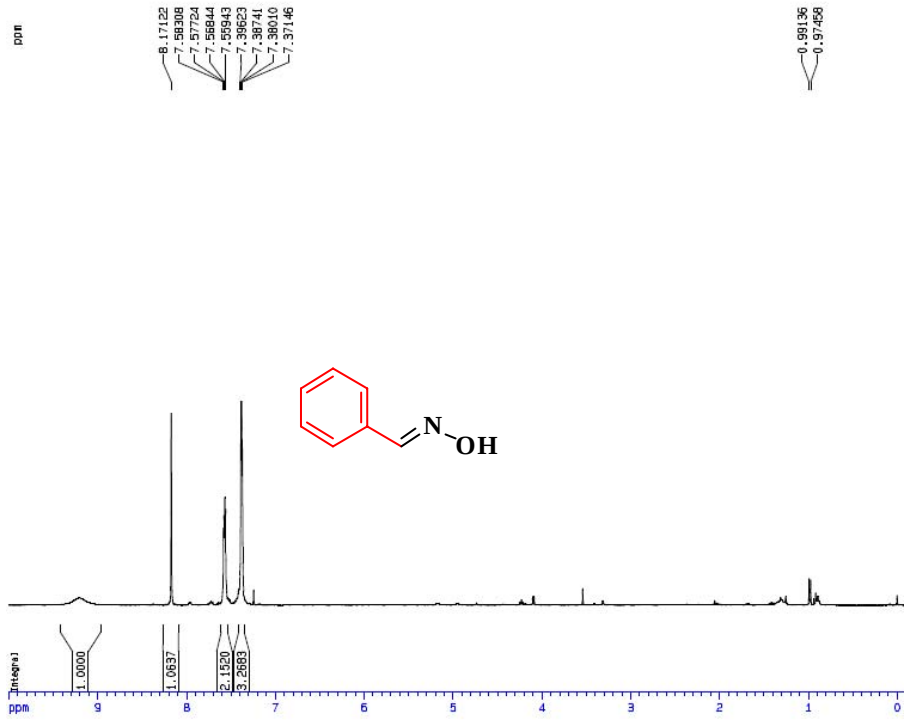
2-cyano-3-(p-tolyl)but-2-enoic acid 5j ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 156.3, 139.7, 134.1, 129.6, 126.4, 129.6, 126.4, 21.7, 12.8; IR (KBr) cm^{-1} 3451, 3172, 2283, 1737, 1602, 1381, 1191, 878, 673, 509.ESI-HRMS: calcd. for $C_{12}H_{11}NO_2$ +Na 224.0682, found 224.0692;

2-cyano-3-phenylpent-2-enoic acid 5o ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.71 – 7.53 (m, 2H), 7.39 (dd, *J* = 5.1, 1.8 Hz, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 161.2, 135.9, 129.6, 129.0, 126.7, 126.7, 20.2, 11.3; IR (KBr) cm^{-1} 3472, 3210, 2327, 1763, 1609, 1451, 1201,901, 667, 518; ESI-HRMS: calcd. for $C_{12}H_{11}NO_2$ +Na 224.0682, found 224.0685.

2-cyano-2-cyclohexylideneacetic acid 5s ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 3.07 – 2.96 (m, 1H), 2.76 – 2.63 (m, 1H), 2.55 (t, *J* = 6.0 Hz, 1H), 2.26 (t, *J* = 6.1 Hz, 1H), 1.91 – 1.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 167.1, 116.2, 102.5, 66.1, 37.4, 33.8, 30.6, 27.1, 27.0, 25.0; IR (KBr) cm^{-1} 3420, 3208, 2278, 1701, 1609, 1387; ESI-HRMS: calcd. for $C_9H_{11}NO_2$ +Na 188.0682, found 188.0692.

3. ^{1}H NMR, ^{13}CNMR

3a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7
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5
4
3
2
1
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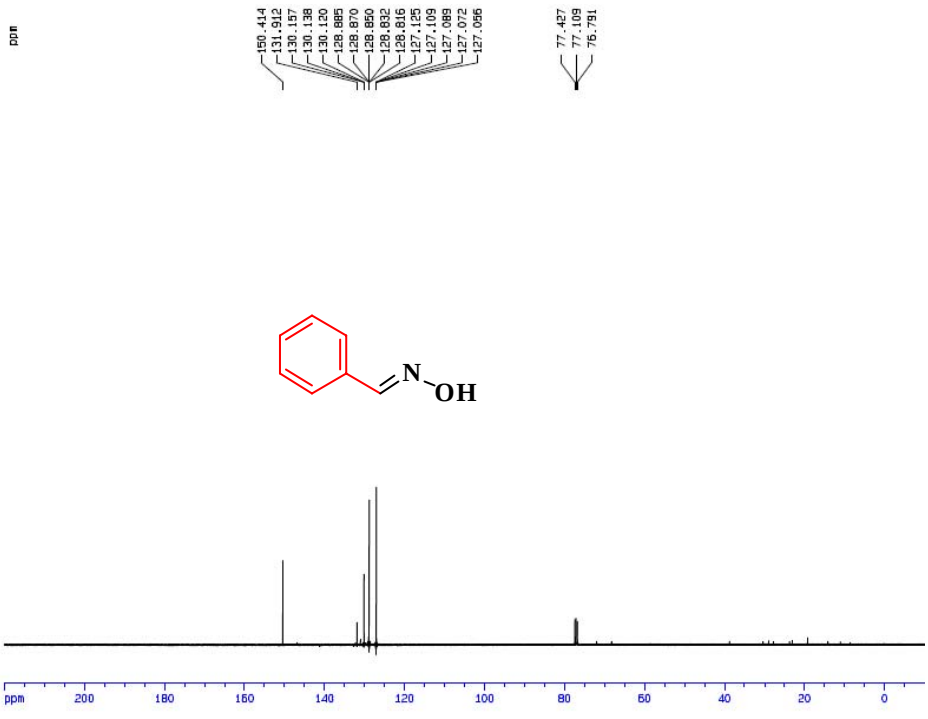
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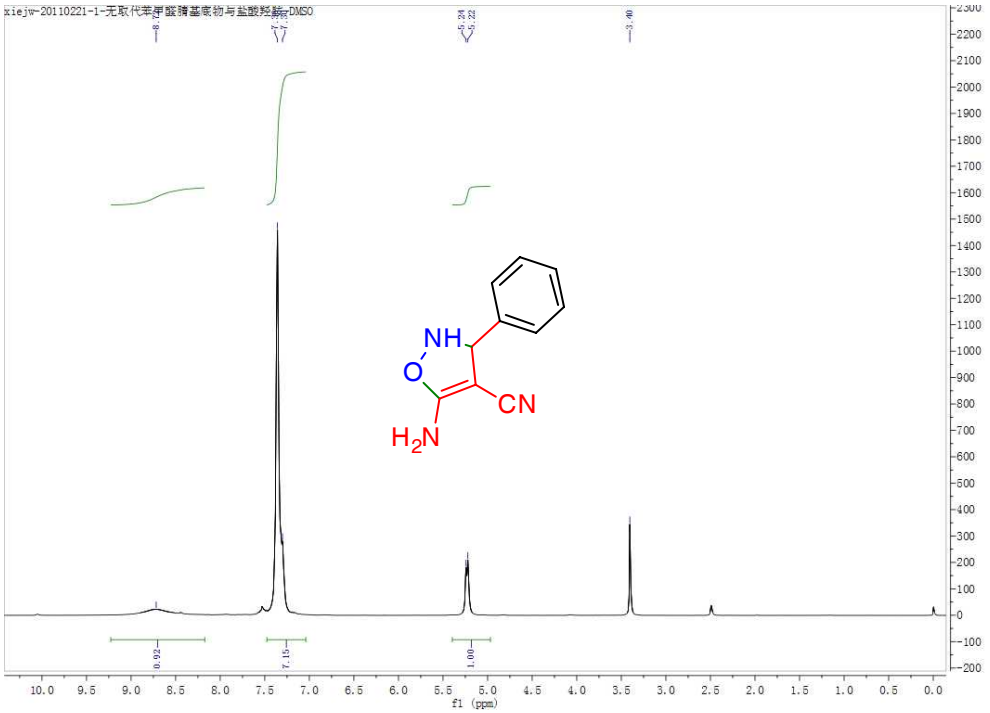
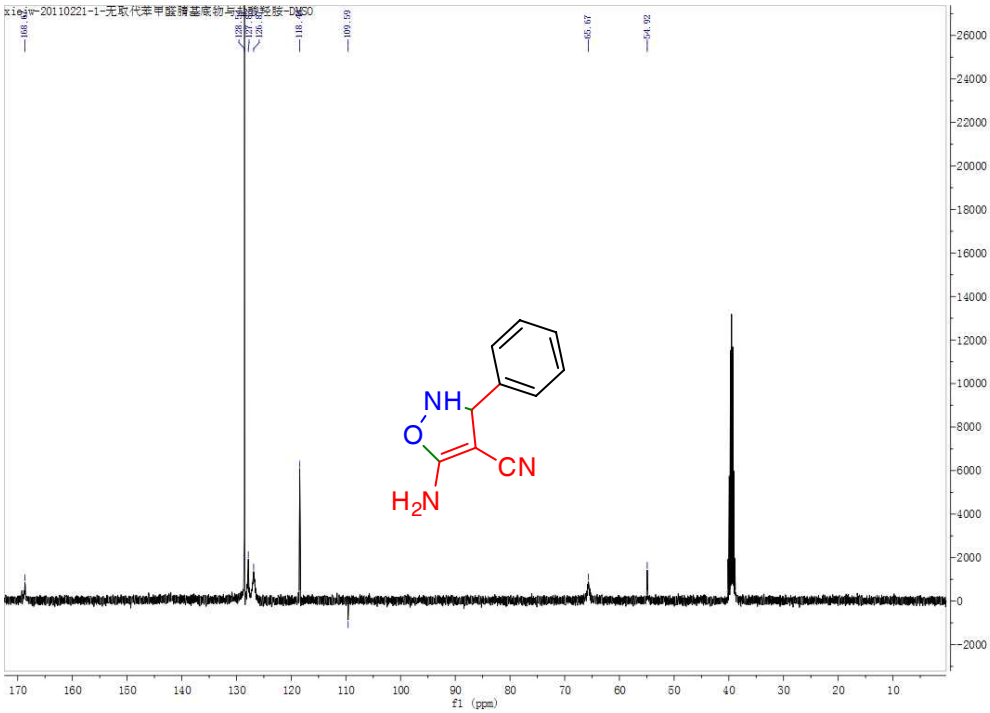
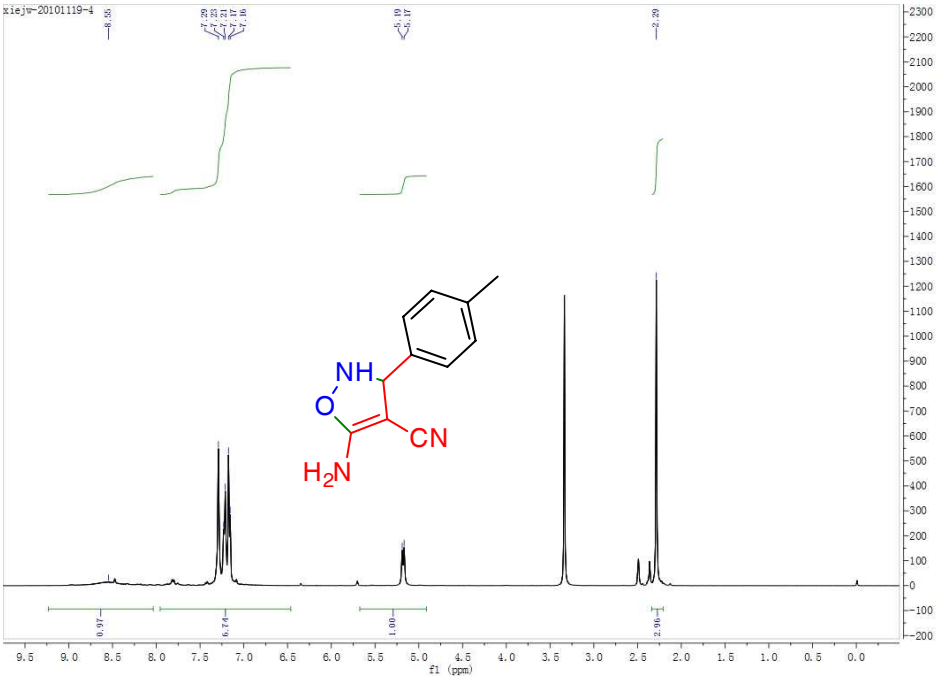
2a





2b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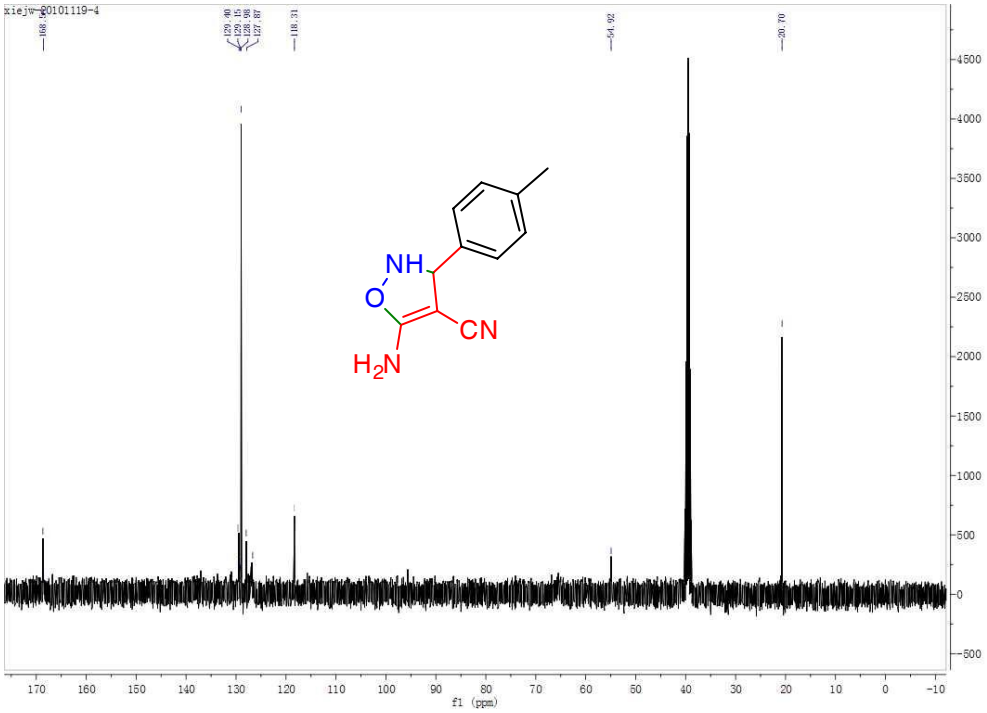
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CN
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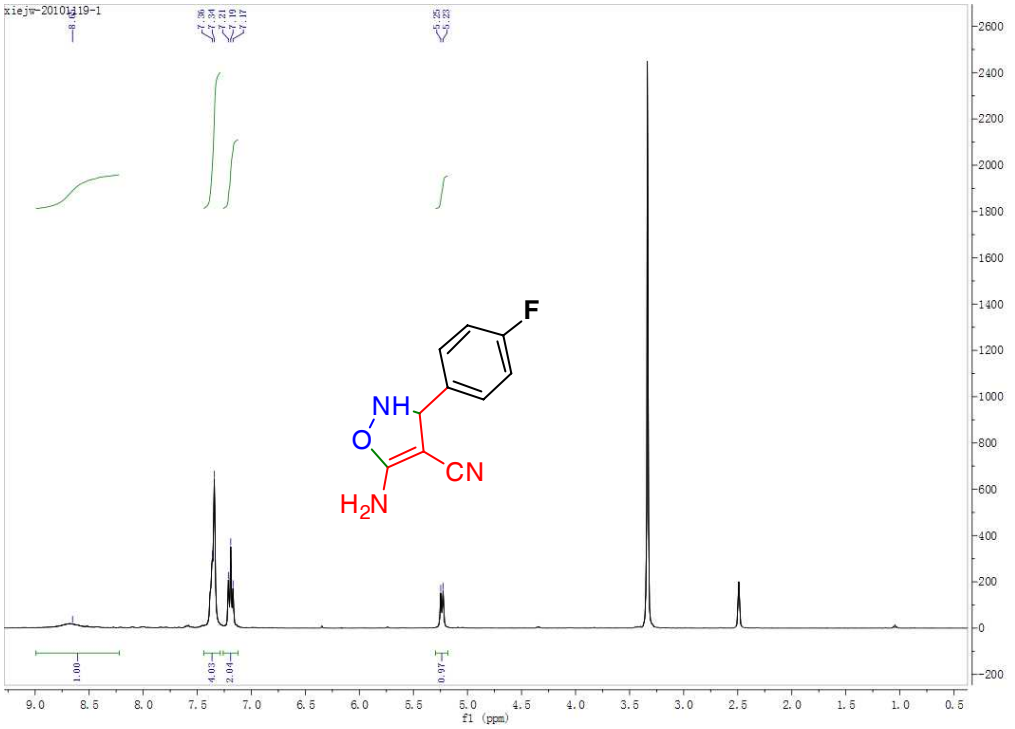
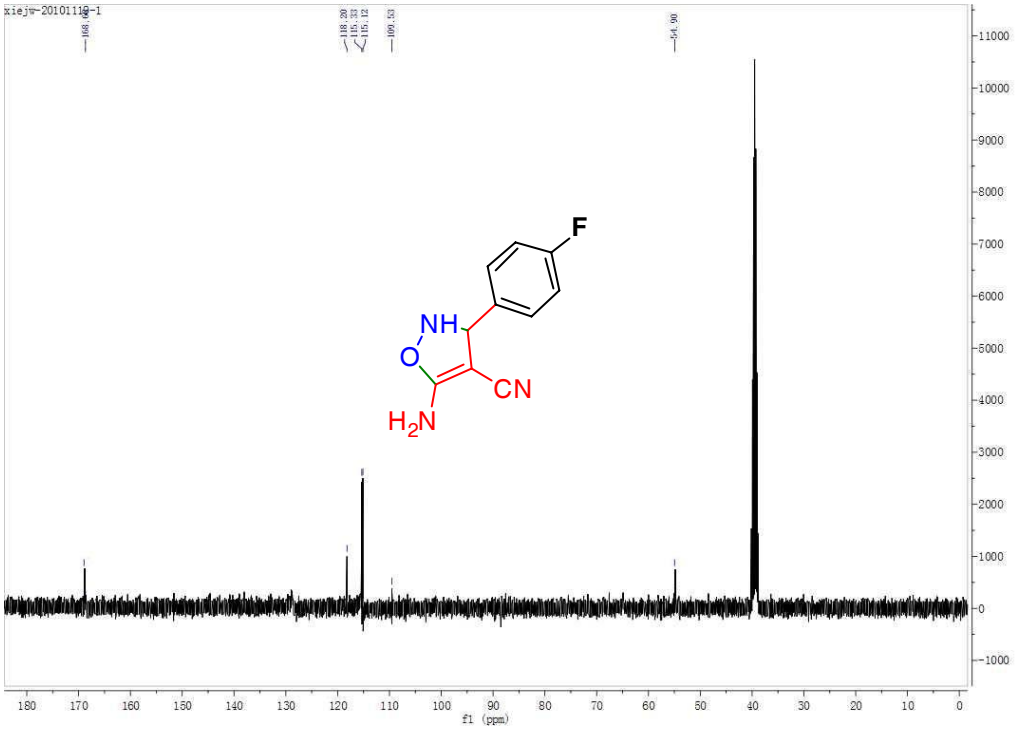
f1 (ppm)

2c





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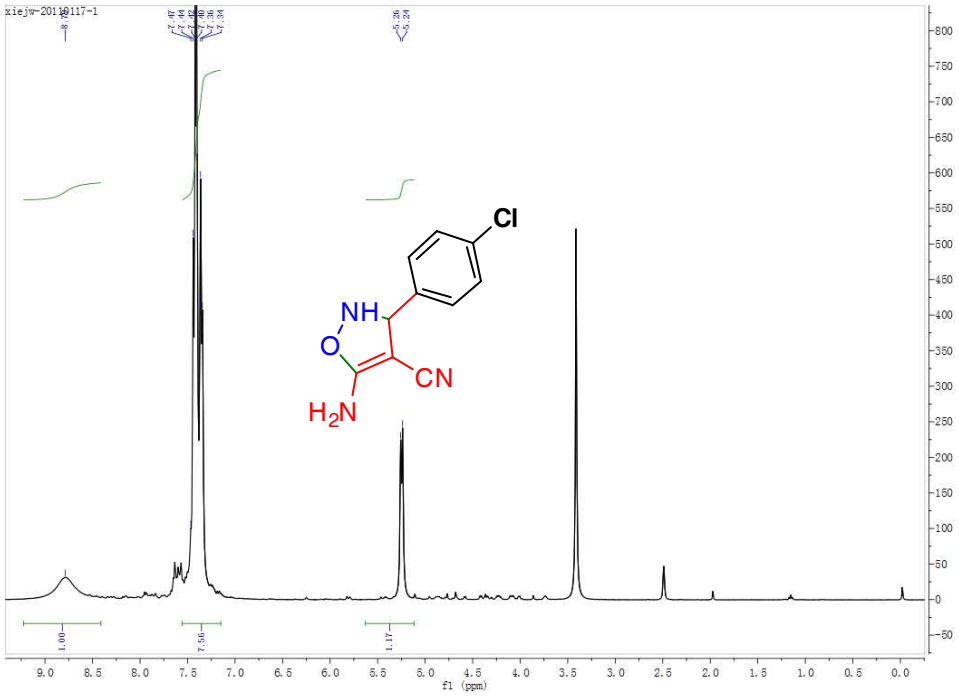

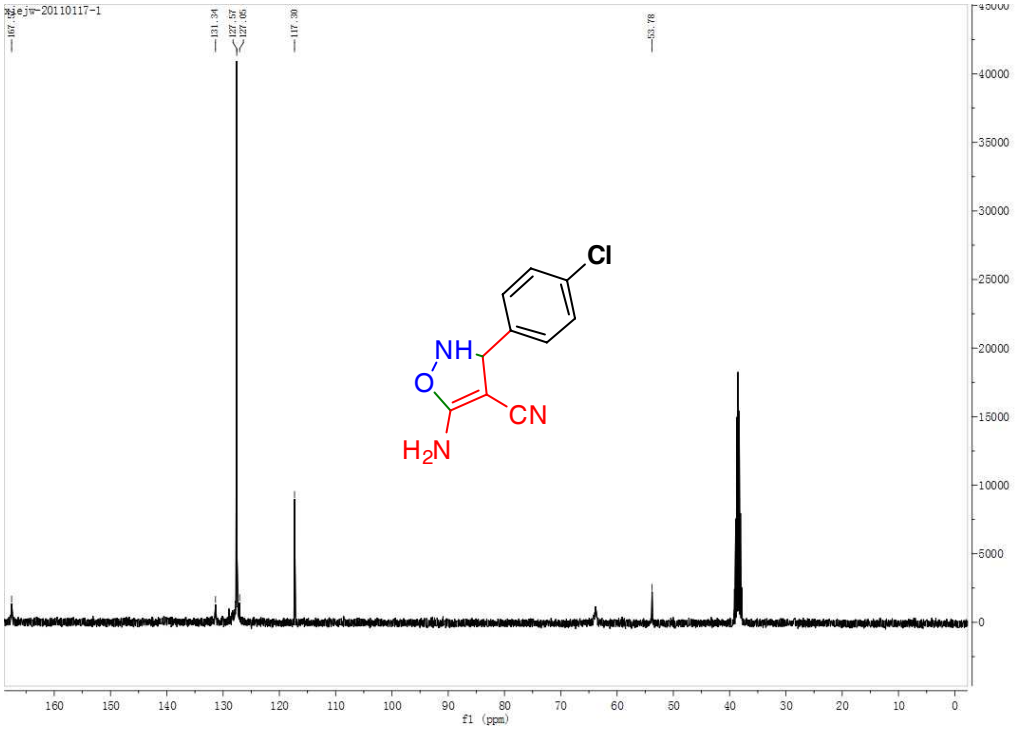

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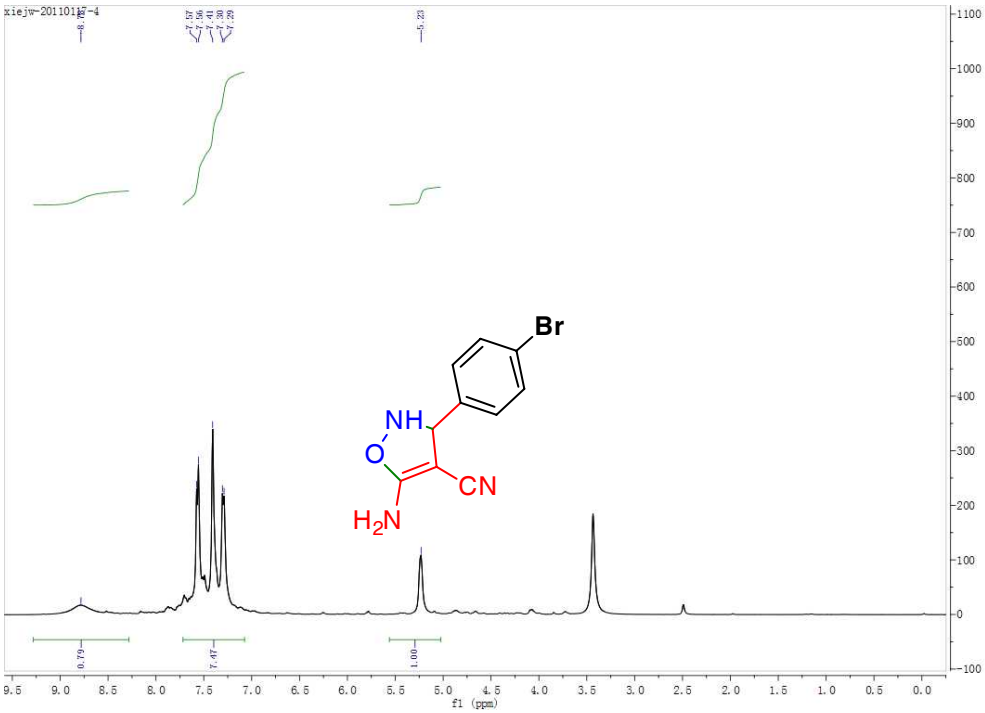

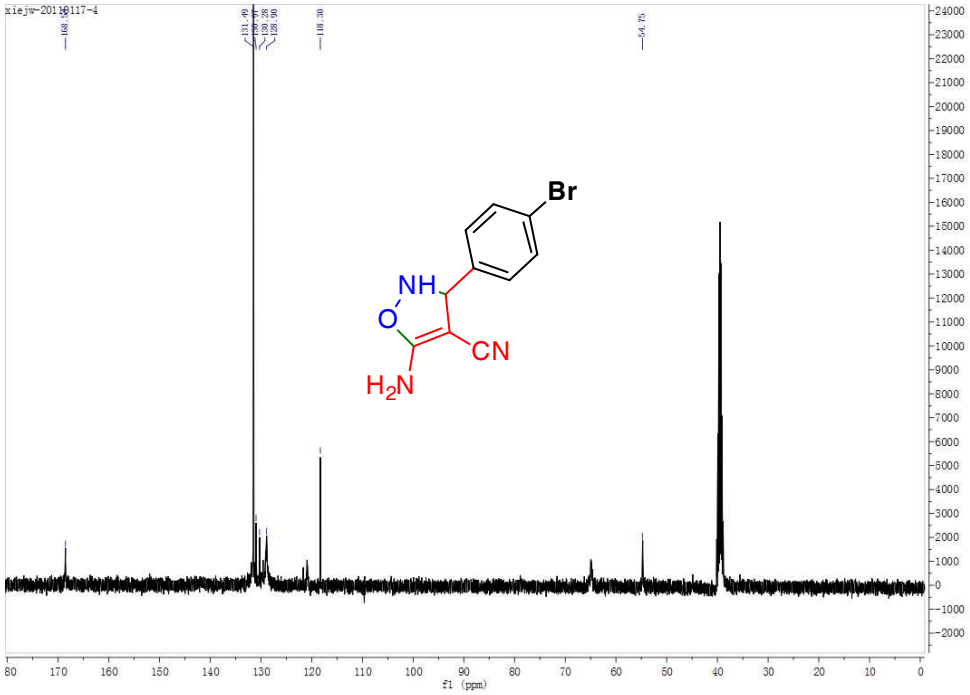

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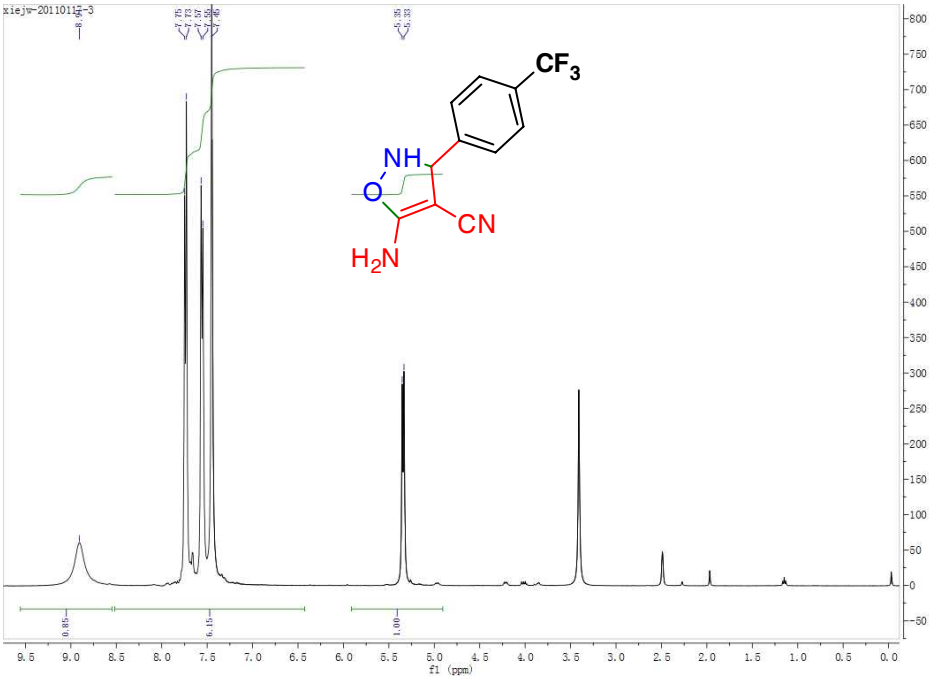

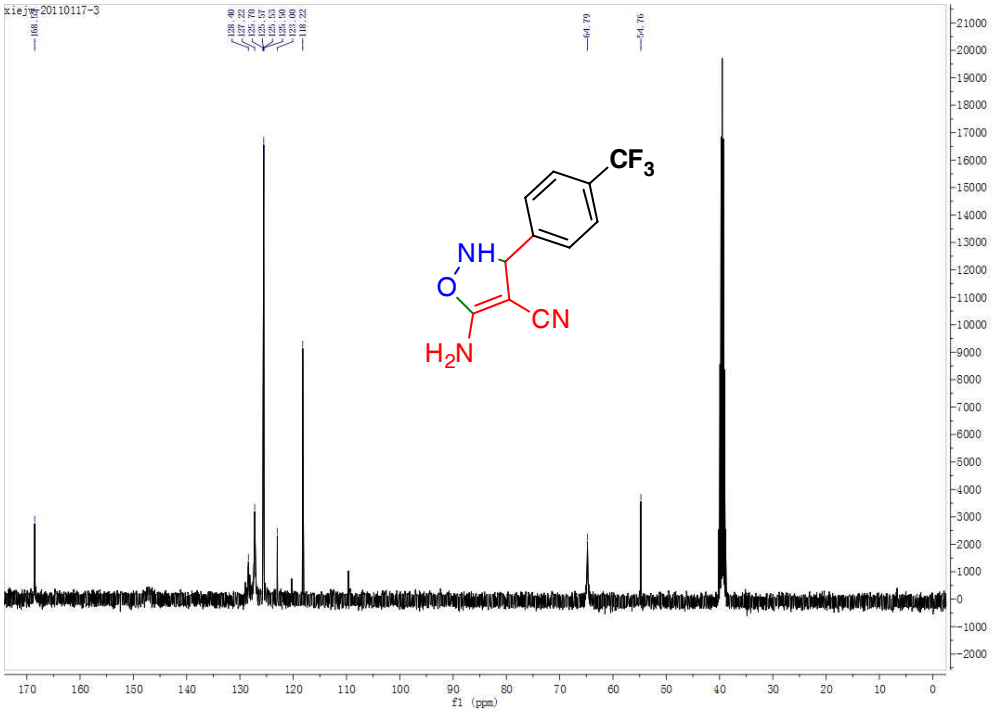

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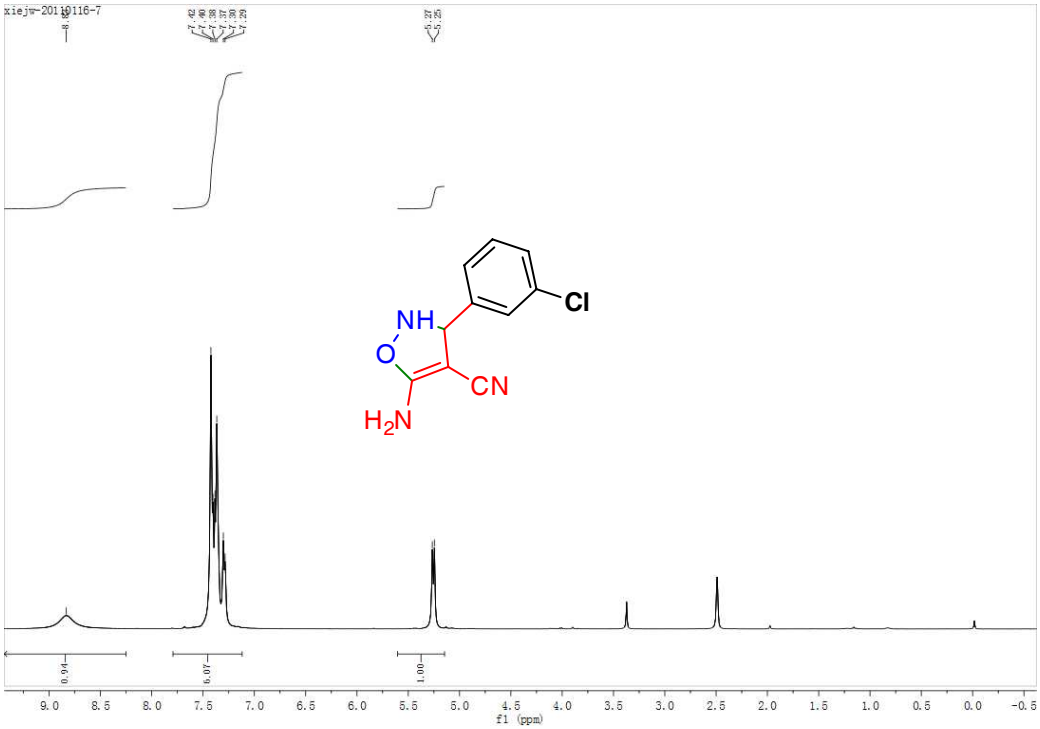

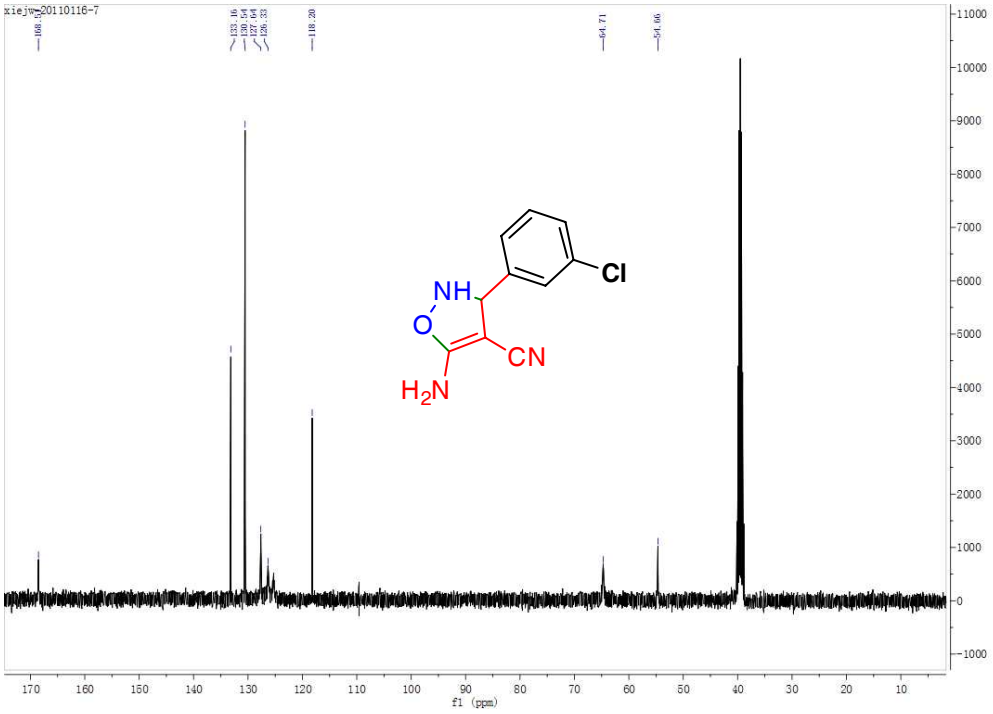

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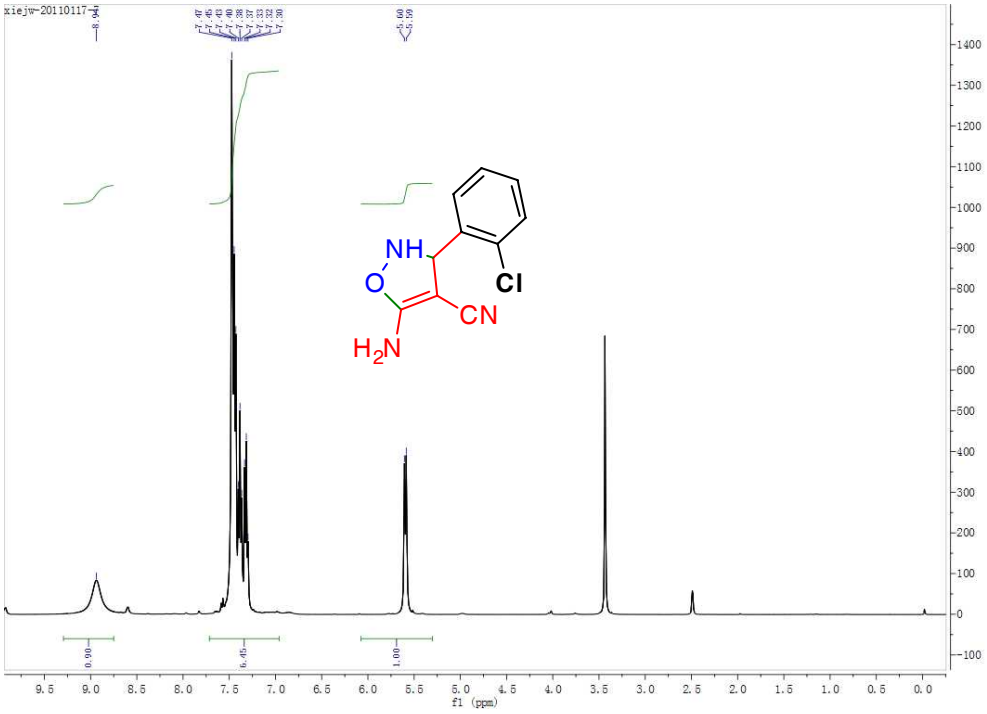

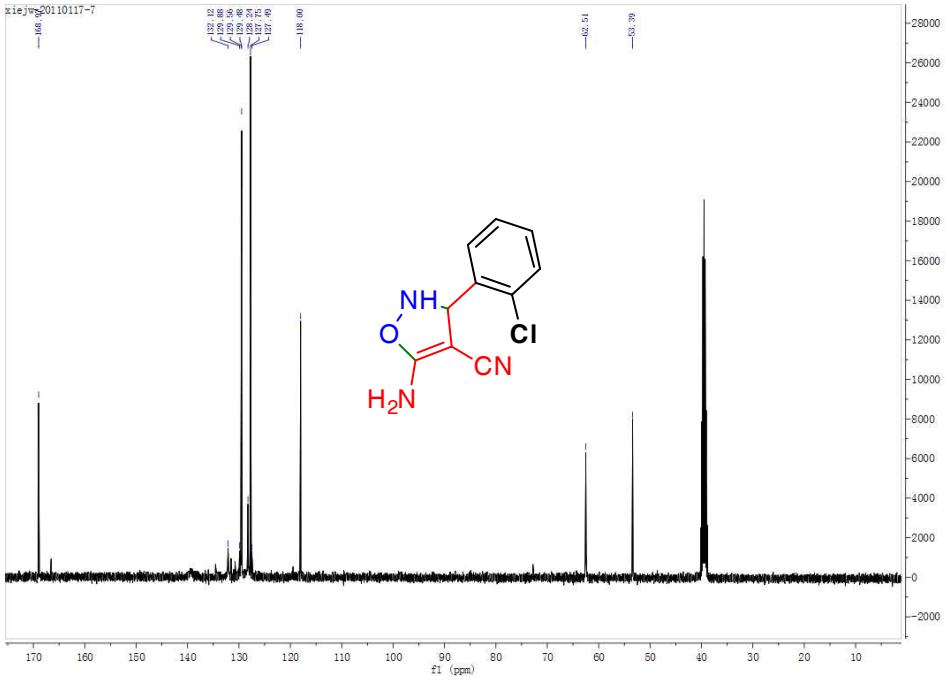

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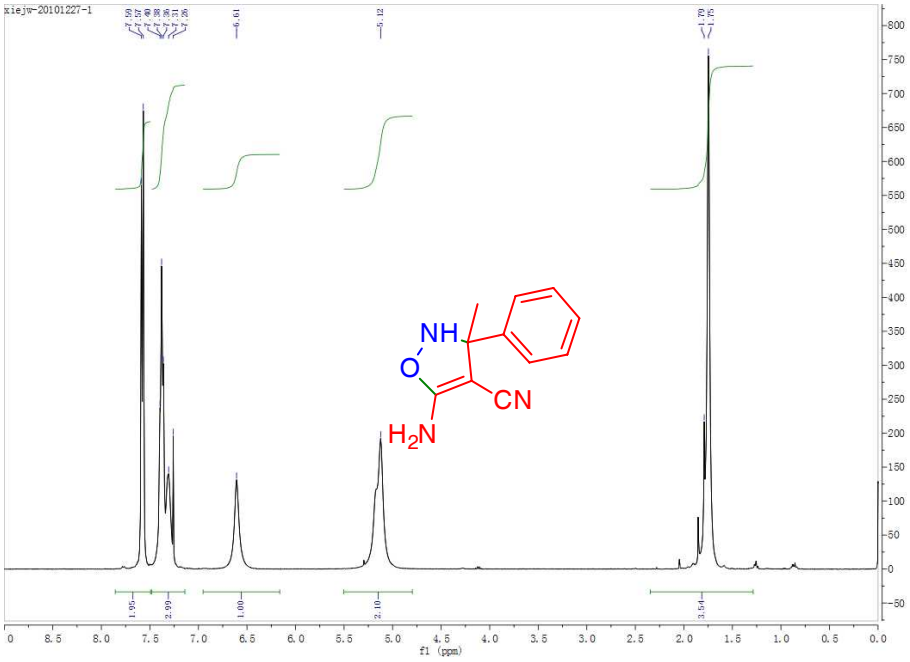
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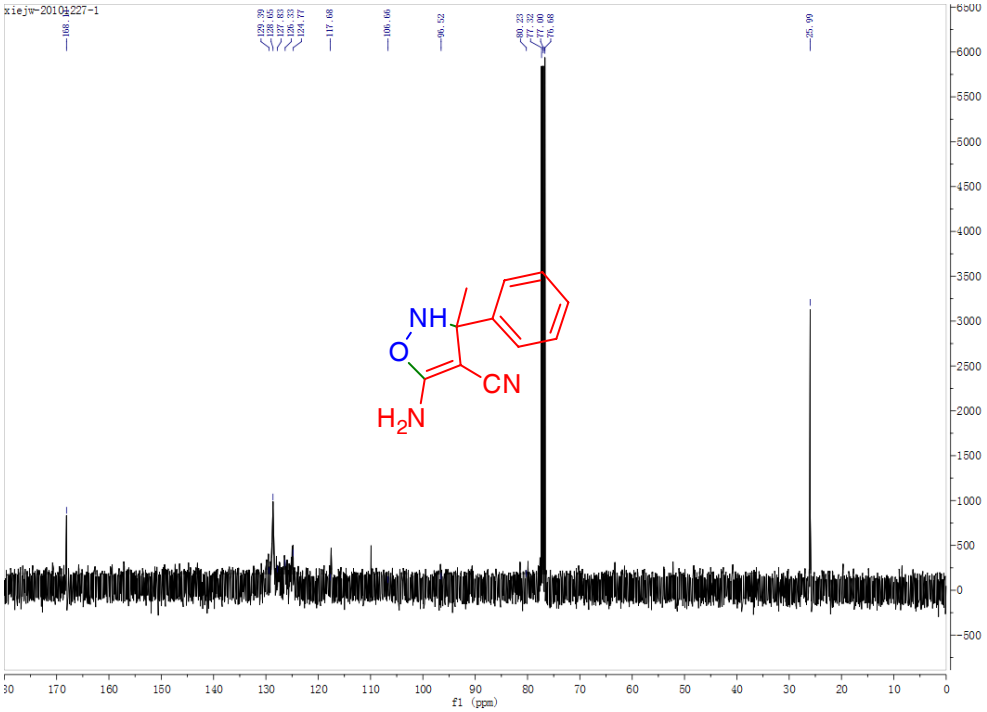
O
CN
H2N
f1 (ppm)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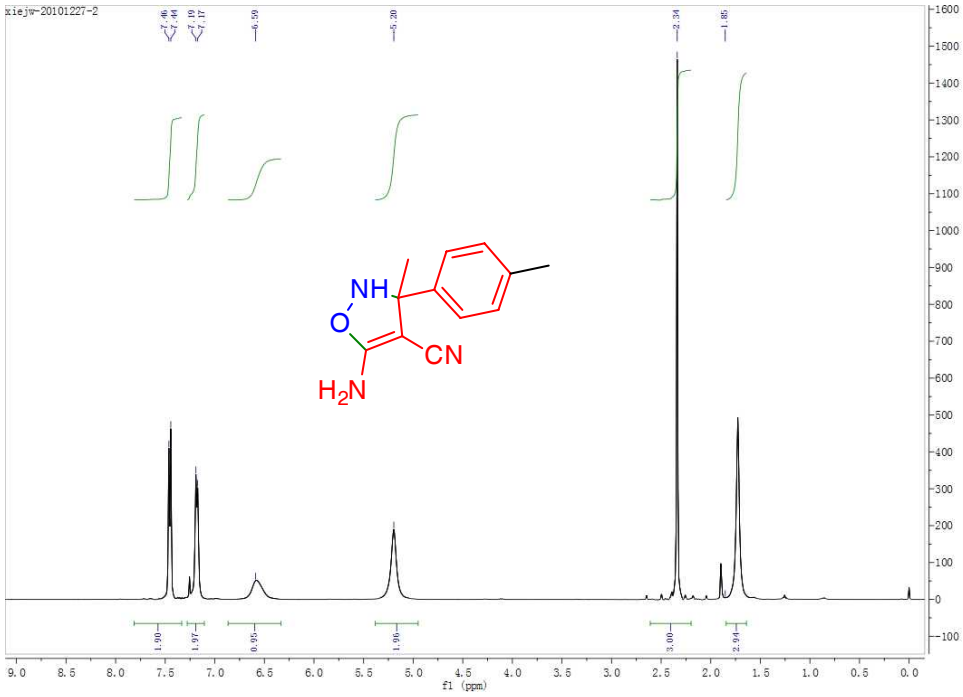
O
CN
H2N
f1 (ppm)

2j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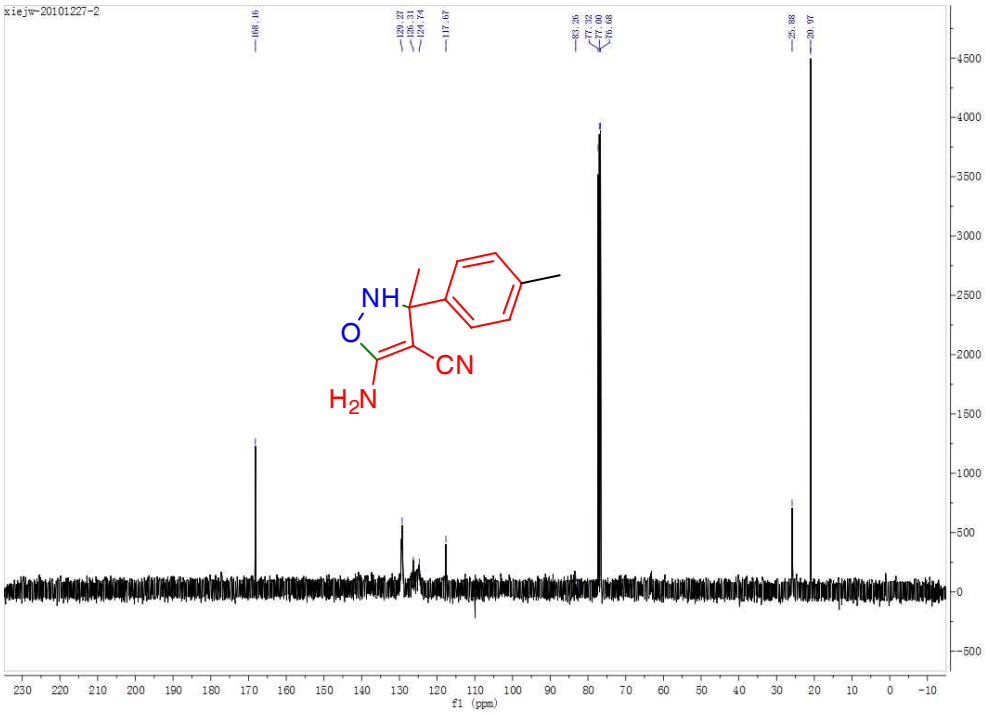
CN
H2N
f1 (ppm)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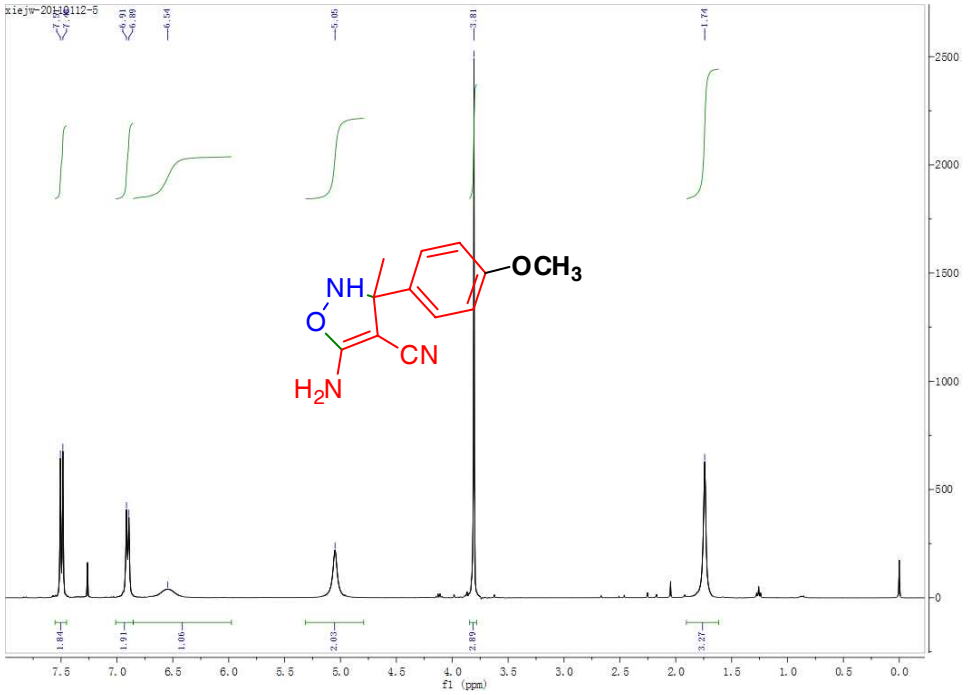
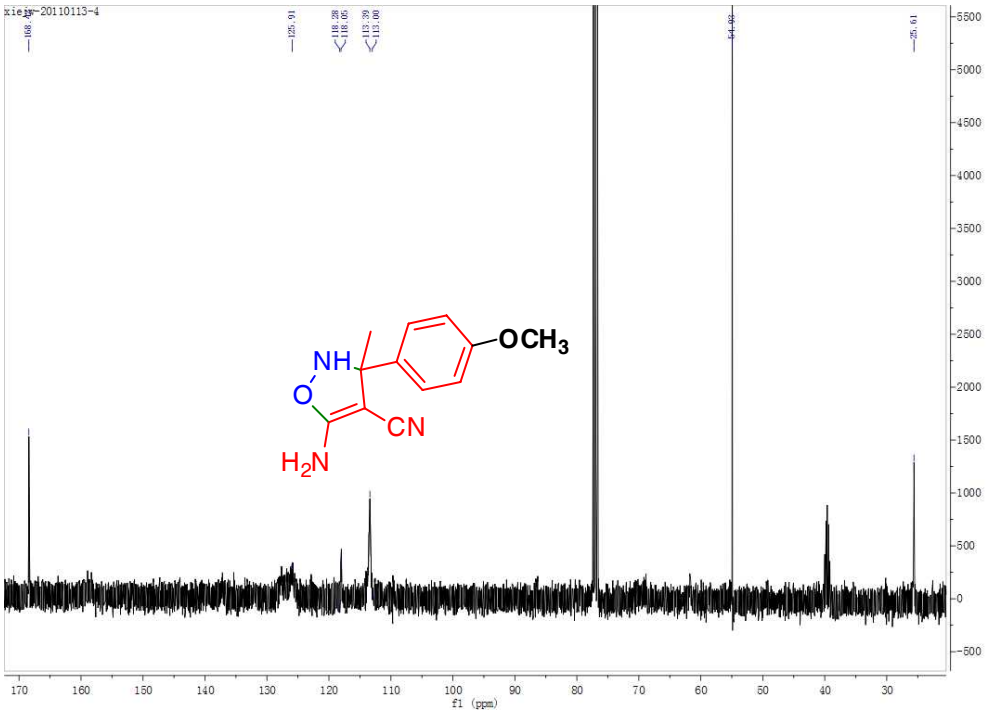
O
CN
H2N
f1 (ppm)

2k





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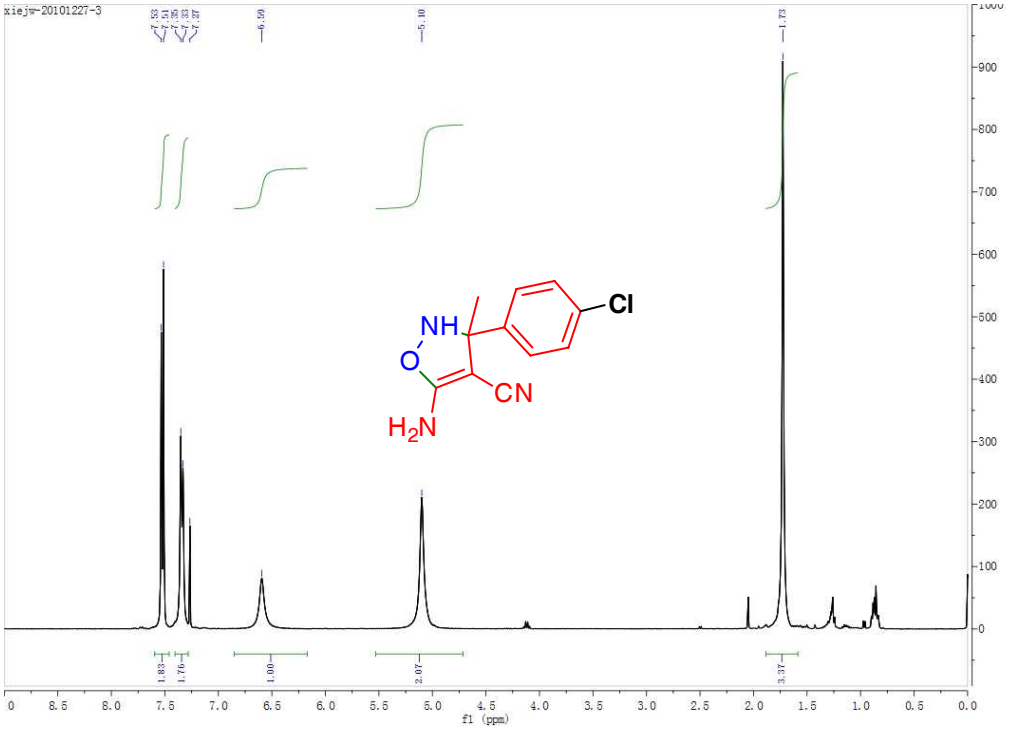
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O
CN
H2N
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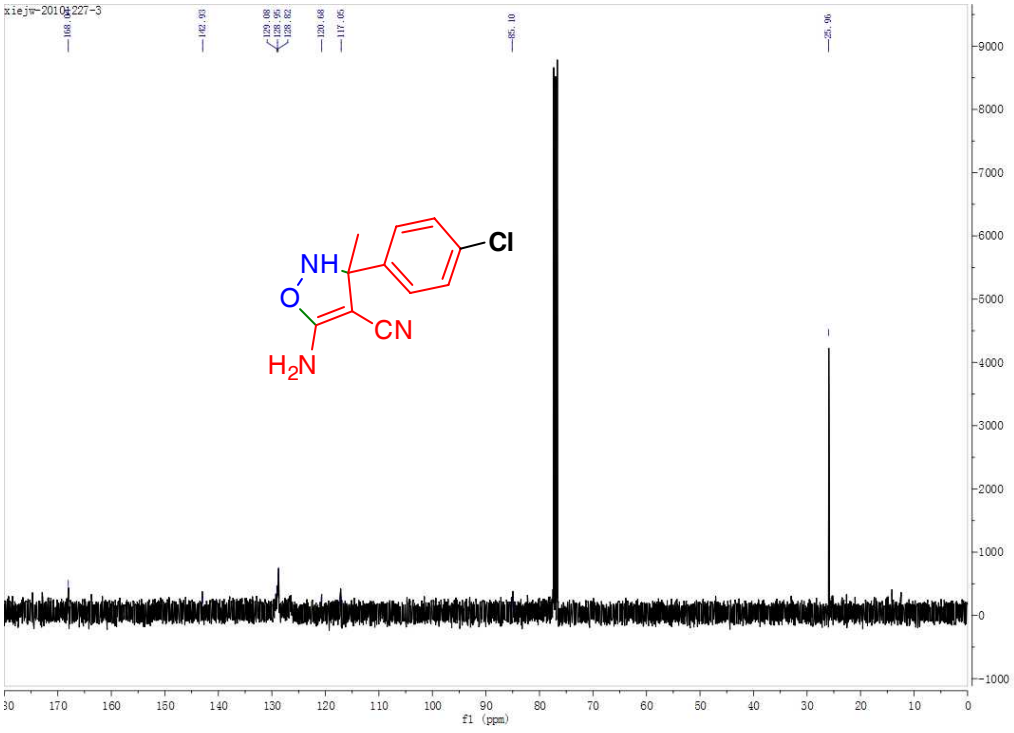
3.37
f1 (ppm)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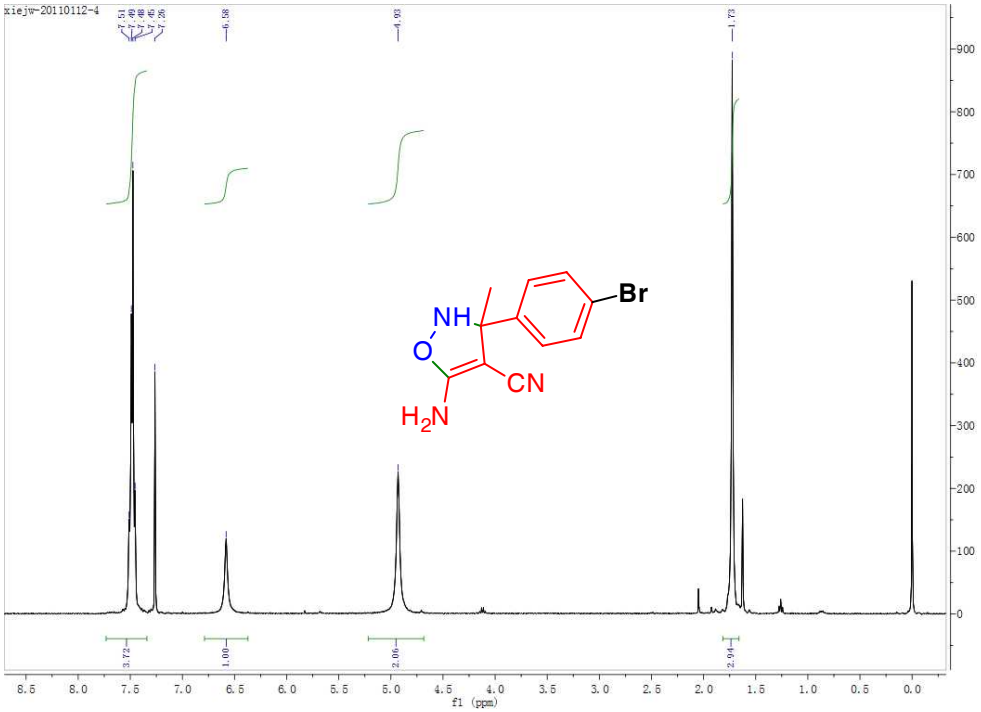
25.96
Cl
NH
O
CN
H2N
f1 (ppm)

22

2m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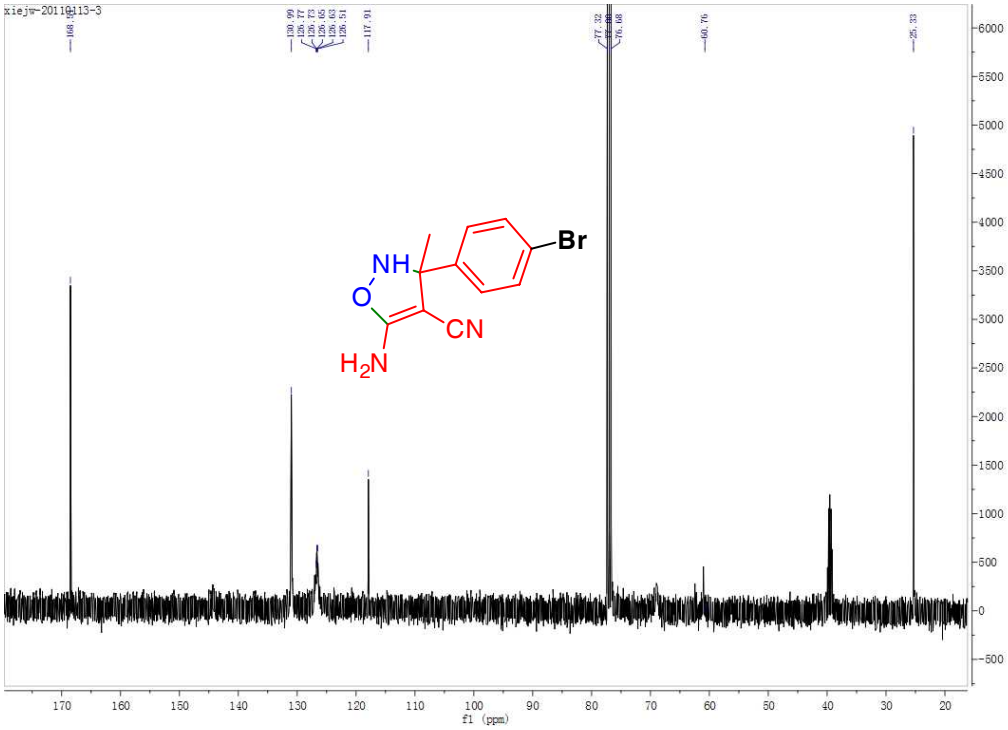
O
CN
H2N
f1 (ppm)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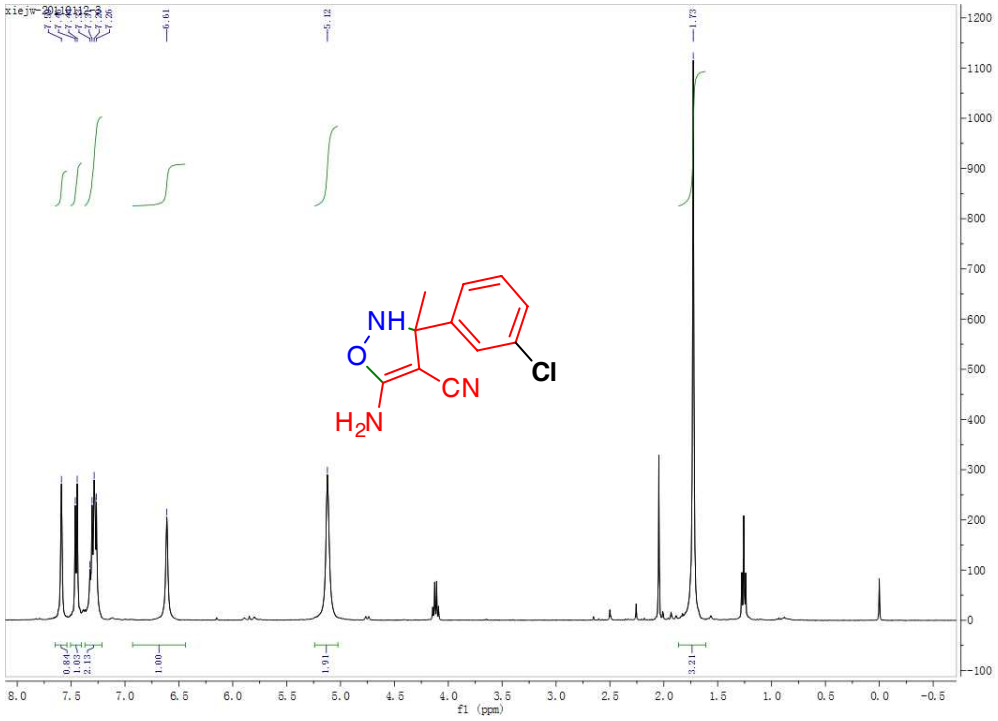
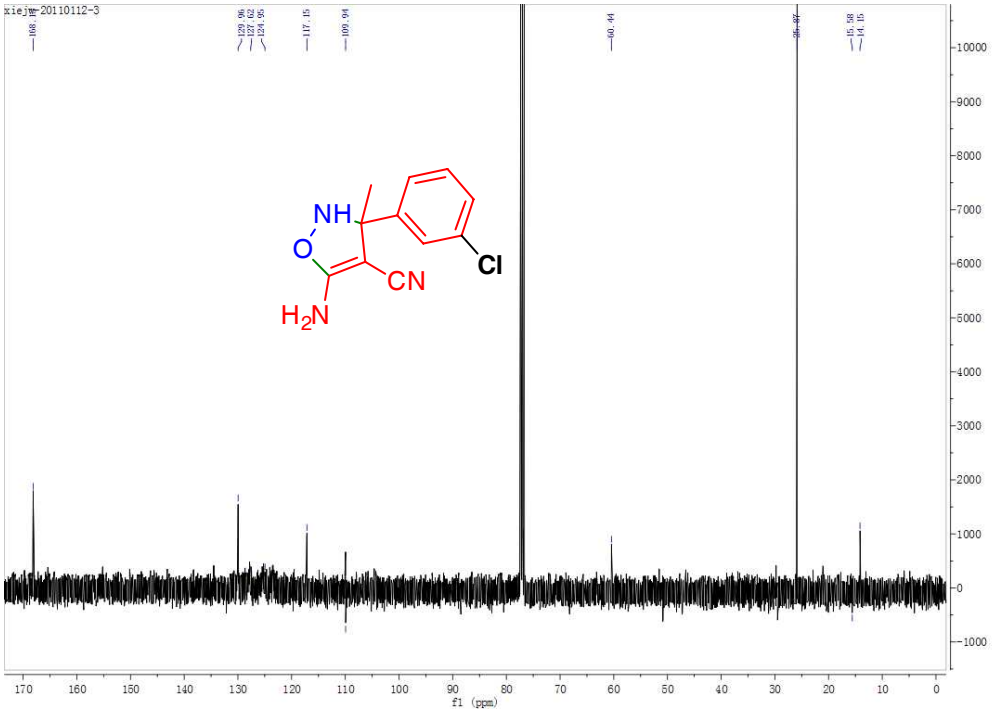
CN
H2N
f1 (ppm)

2n





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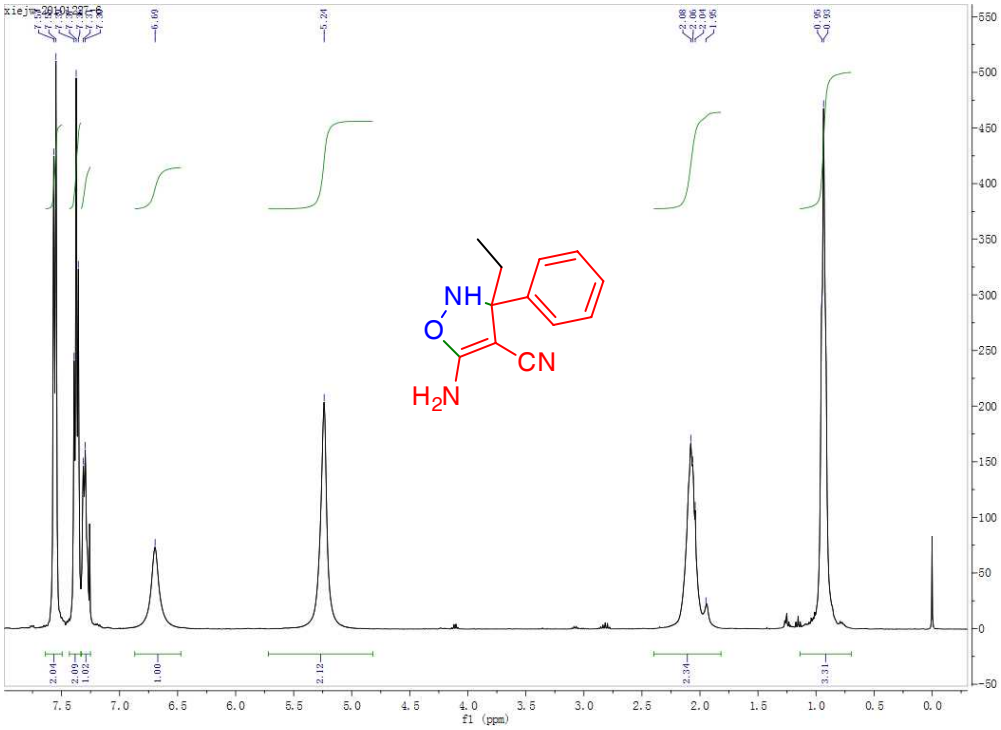

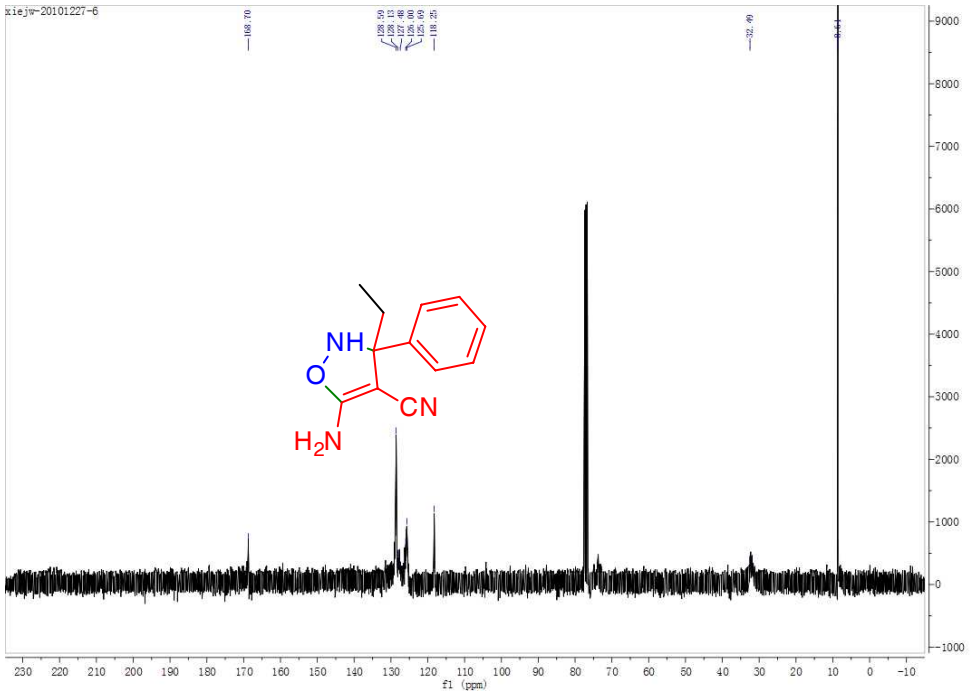

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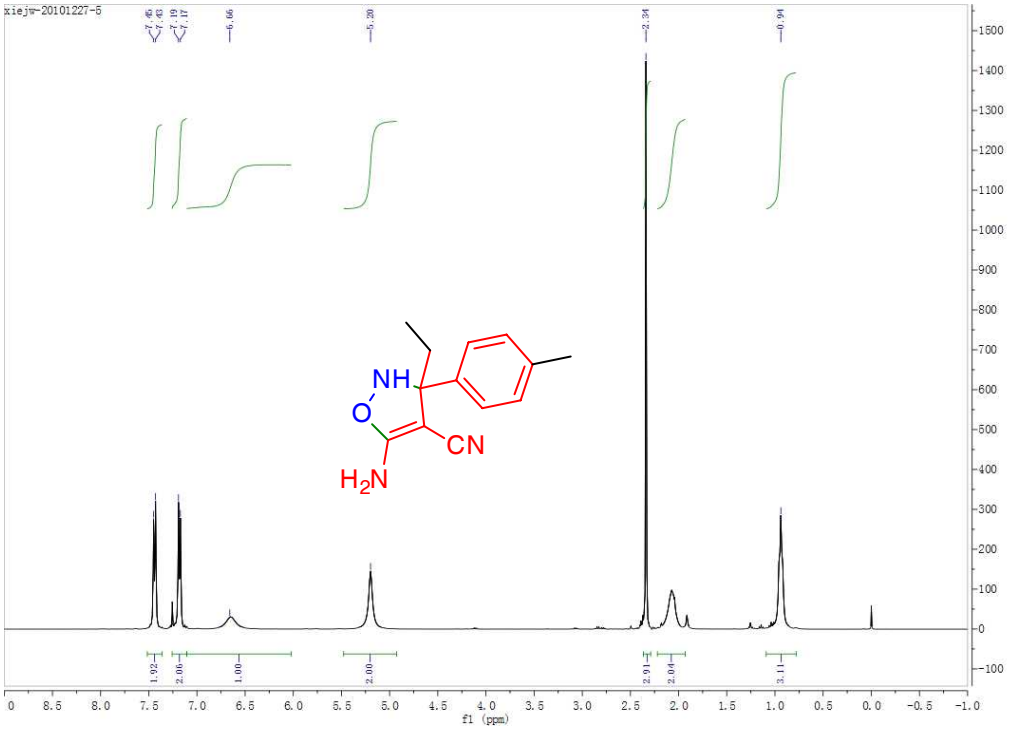
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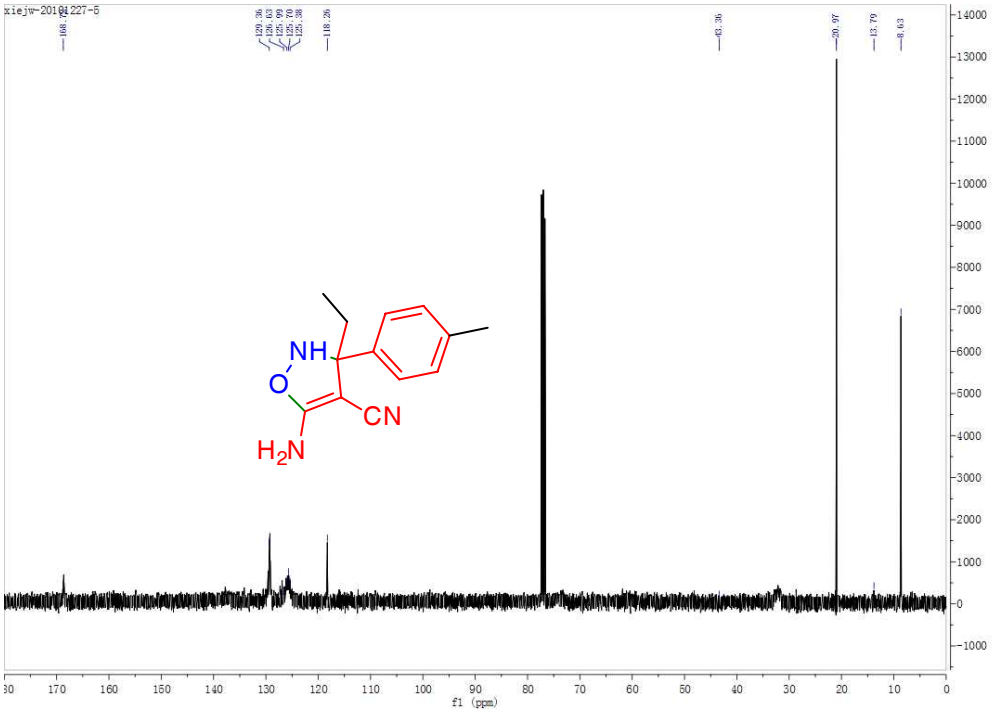
H2N
f1 (ppm)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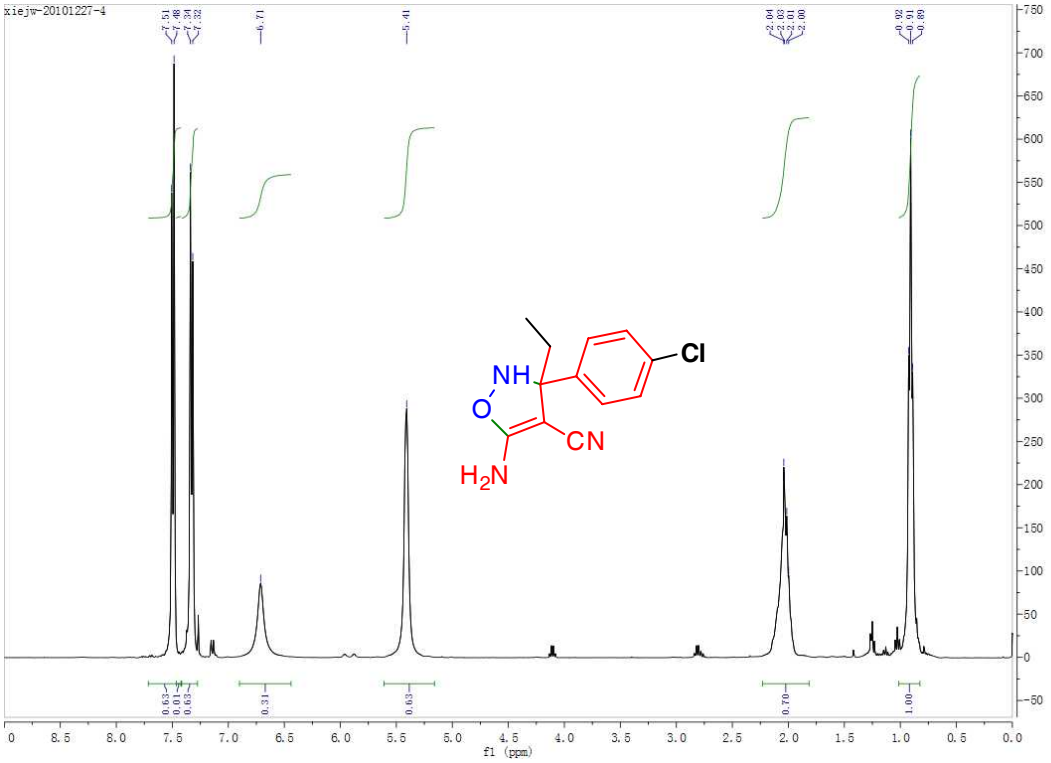
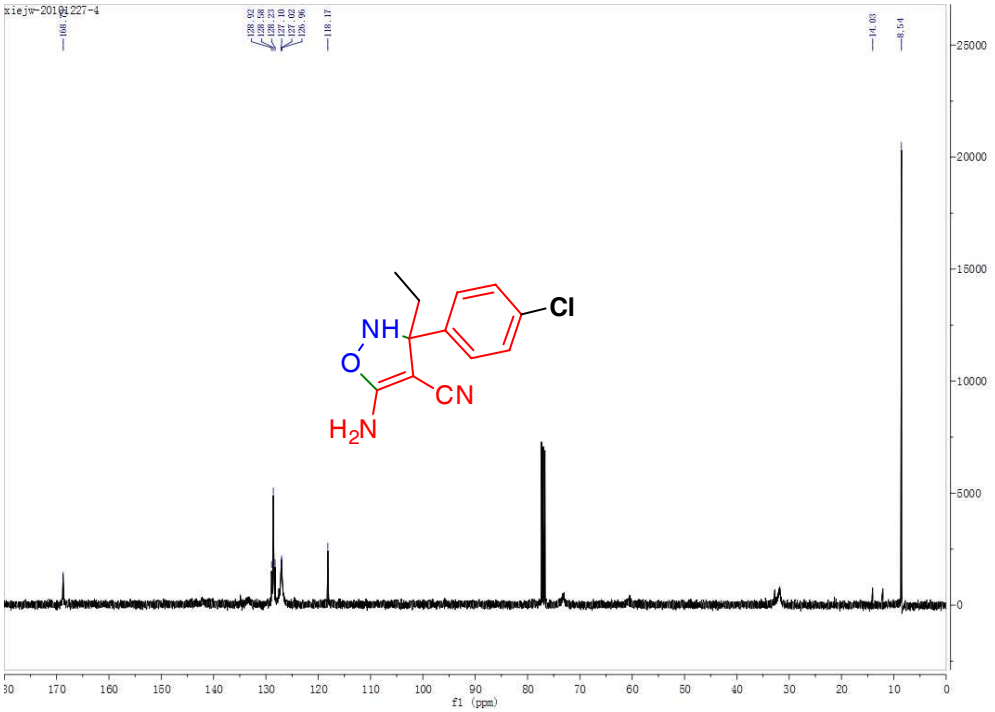
CN
H2N
f1 (ppm)

2q





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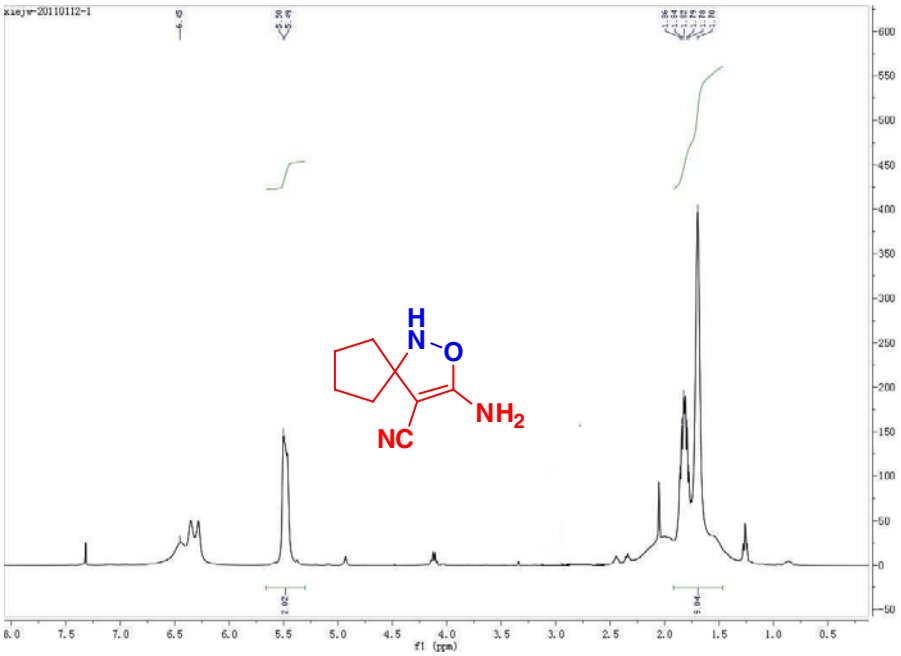
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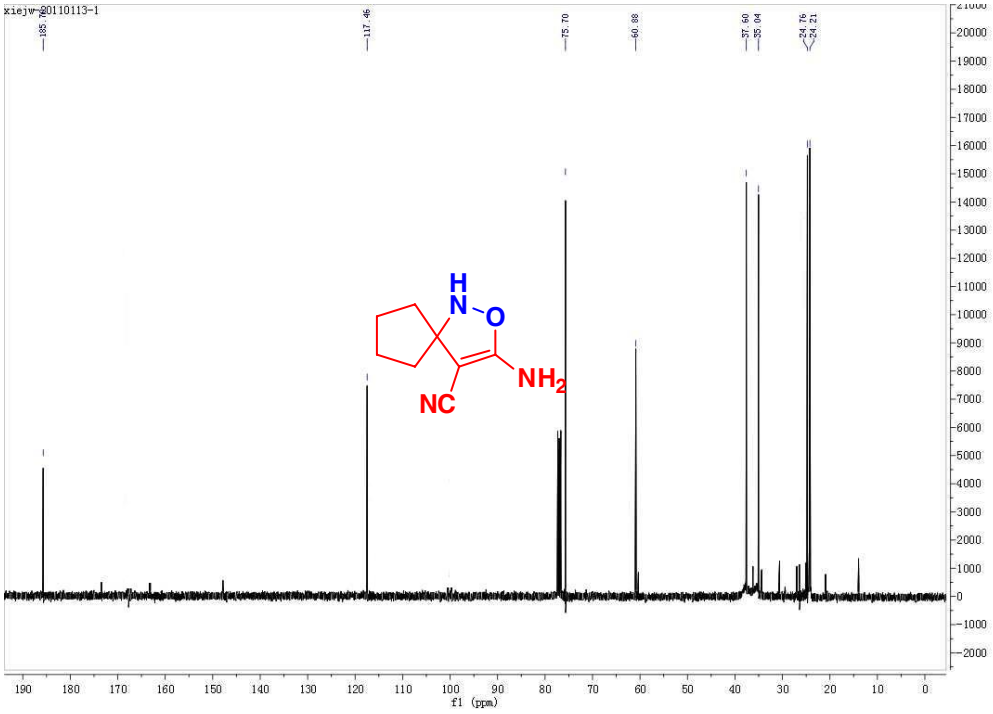
O
NH2
NC
f1 (ppm)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O
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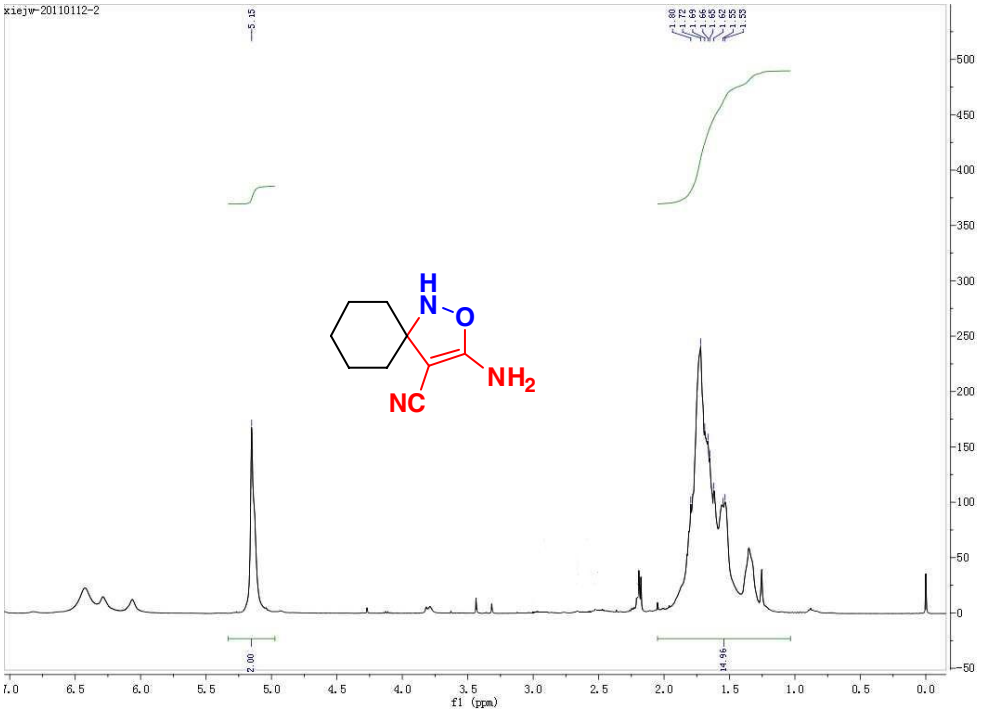
NC
f1 (ppm)

2s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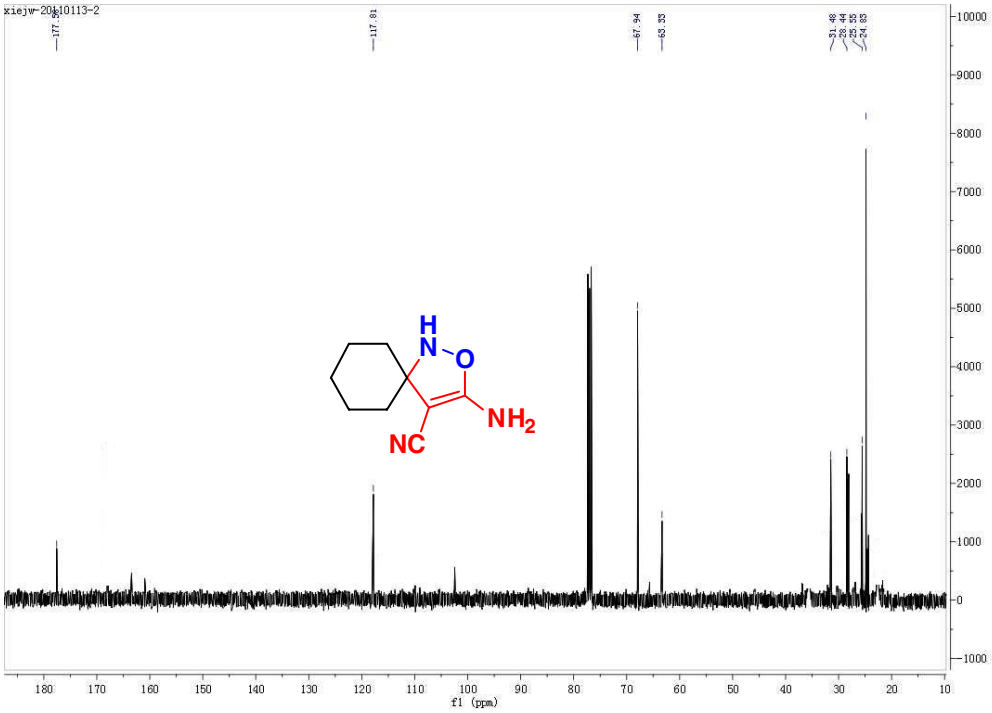
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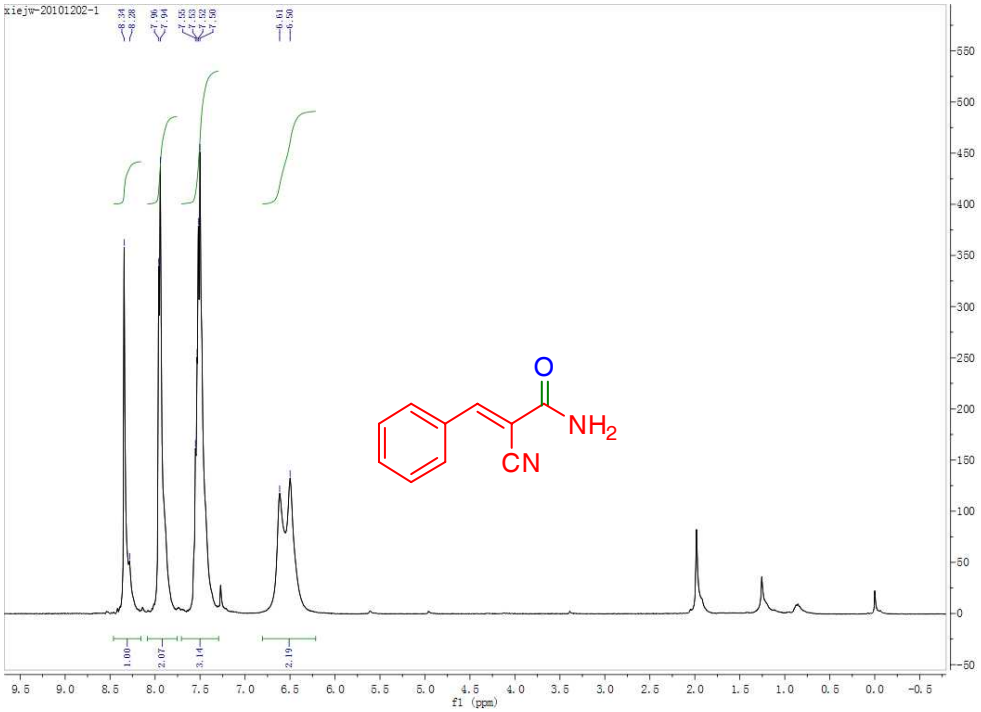
4a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O
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CN
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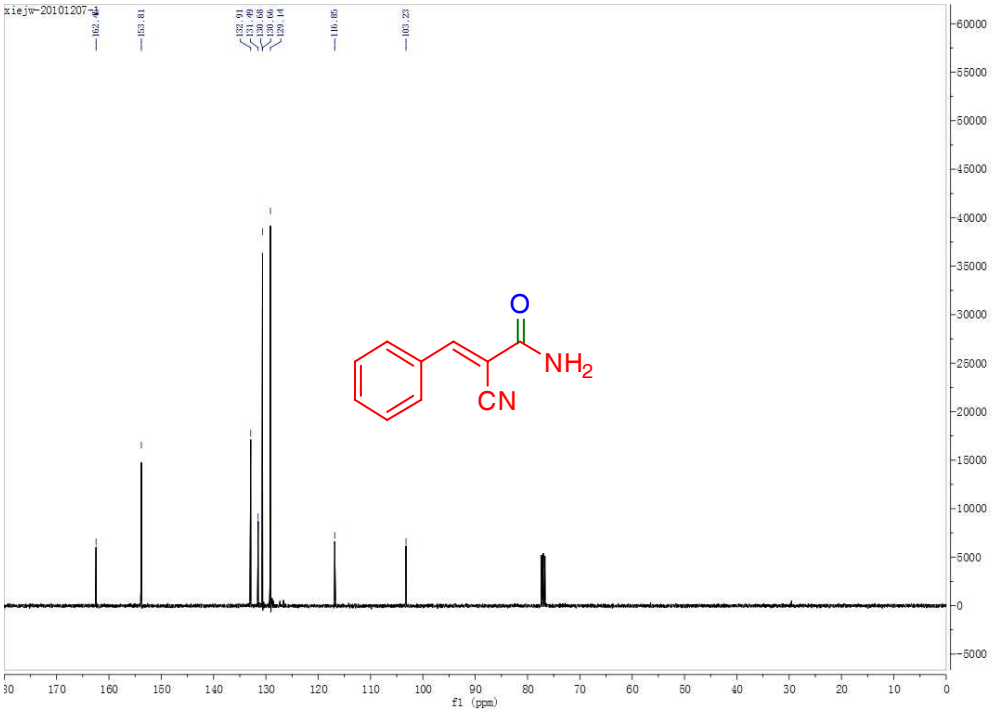
2.19
f1 (ppm)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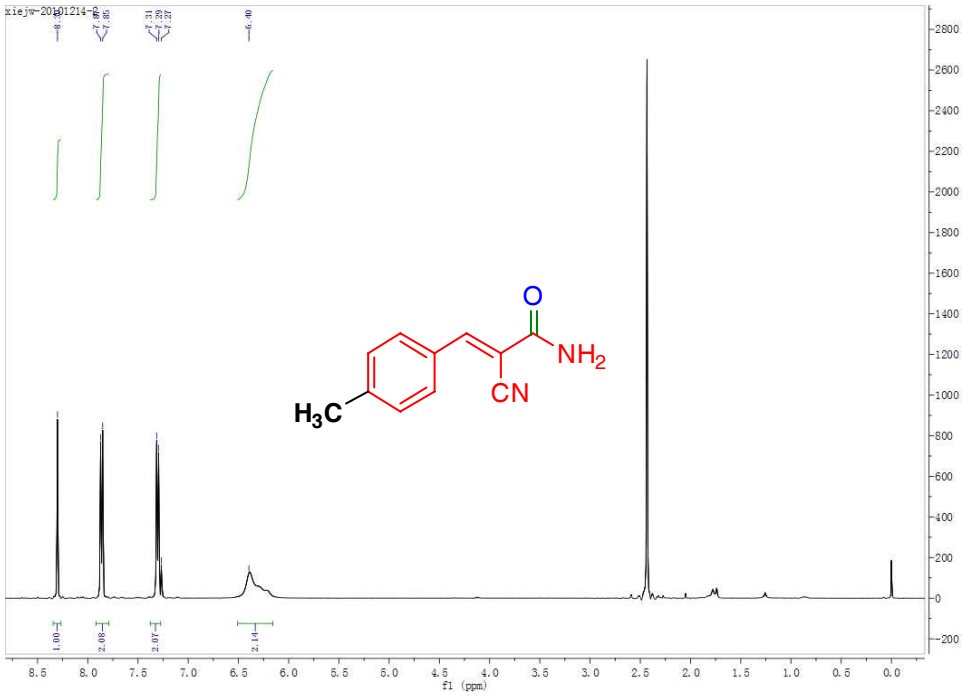
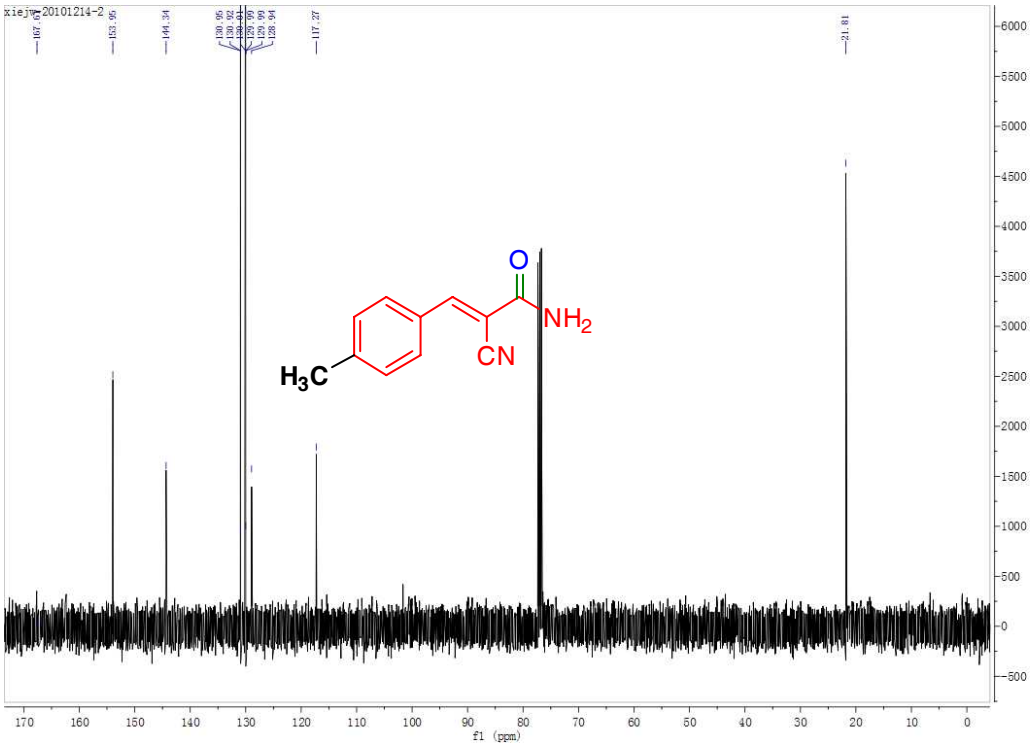
O
NH2
CN
f1 (ppm)

4b





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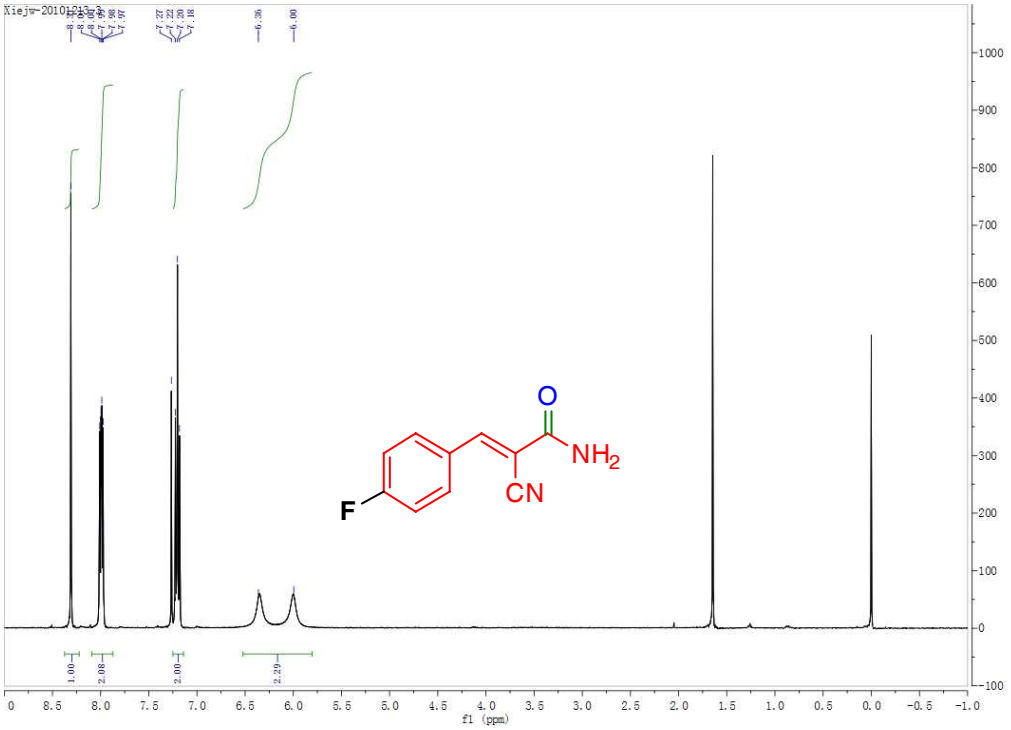
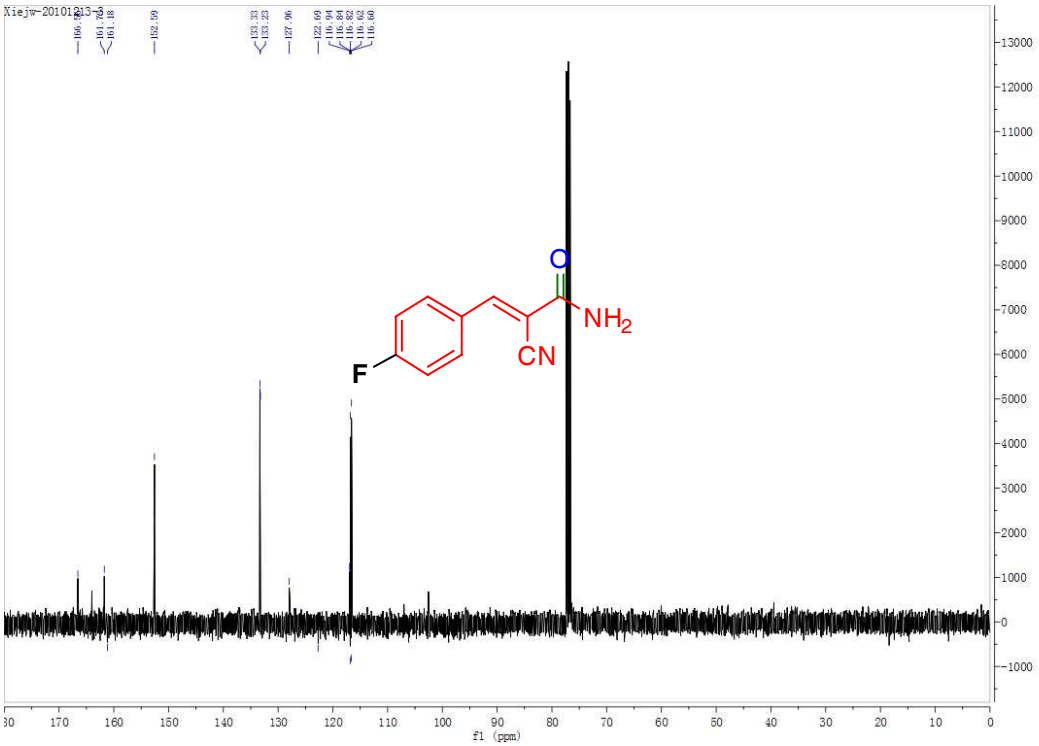
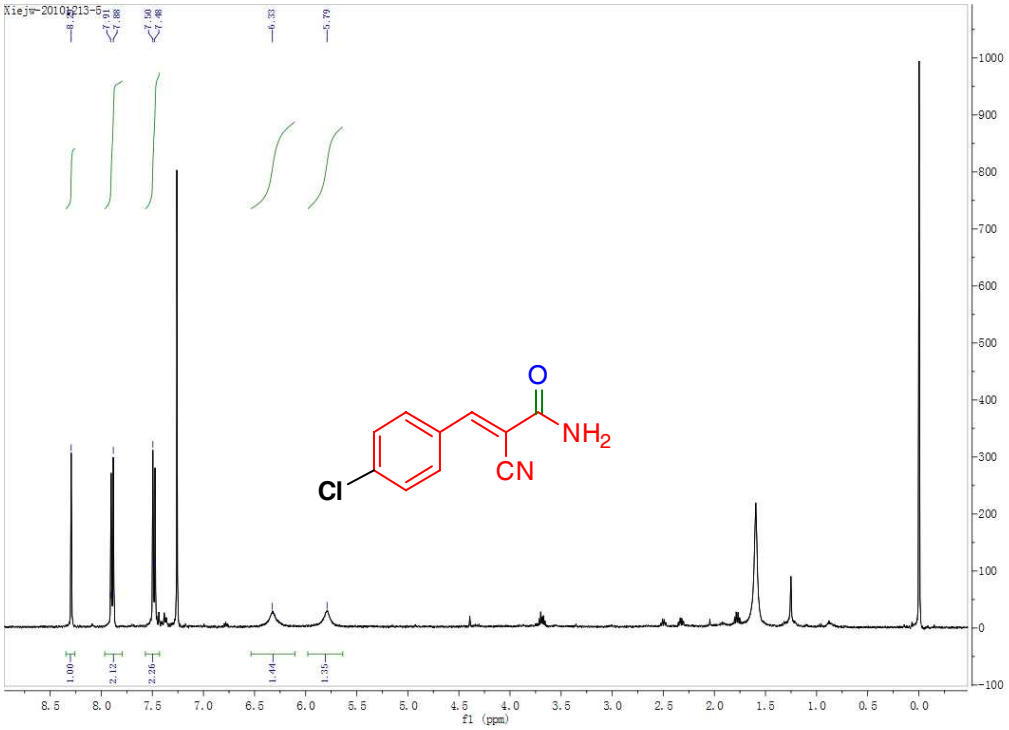
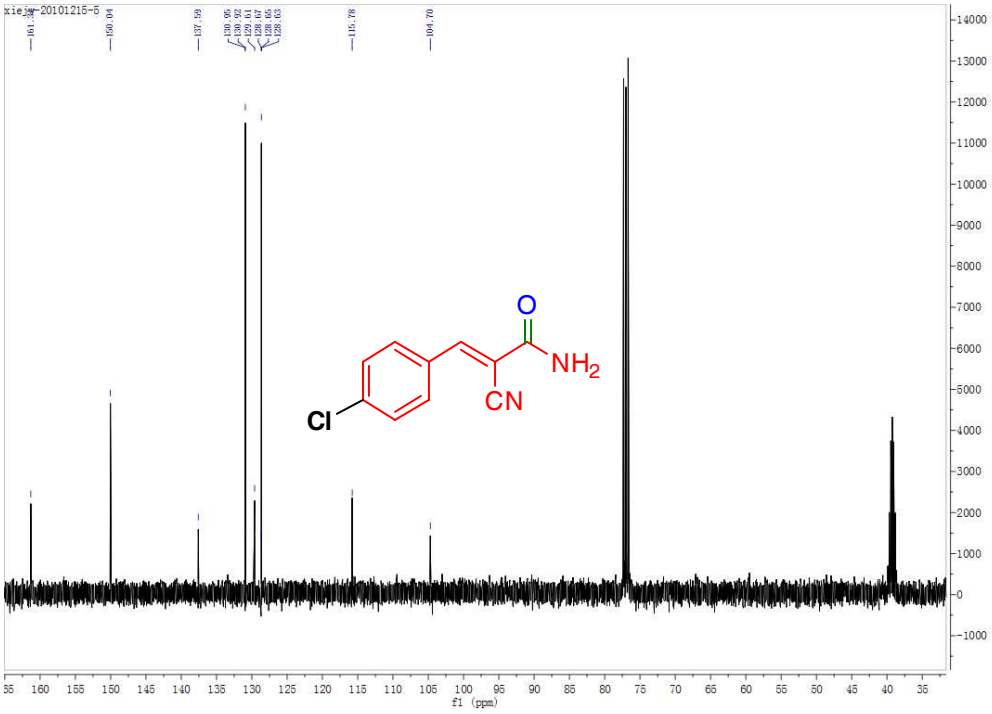


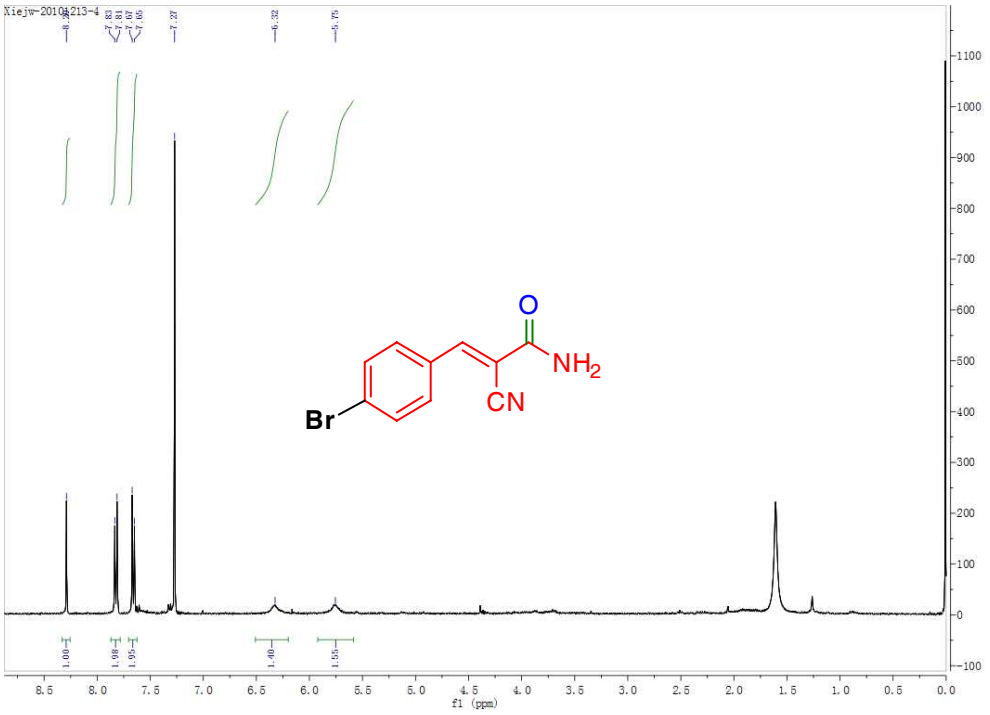


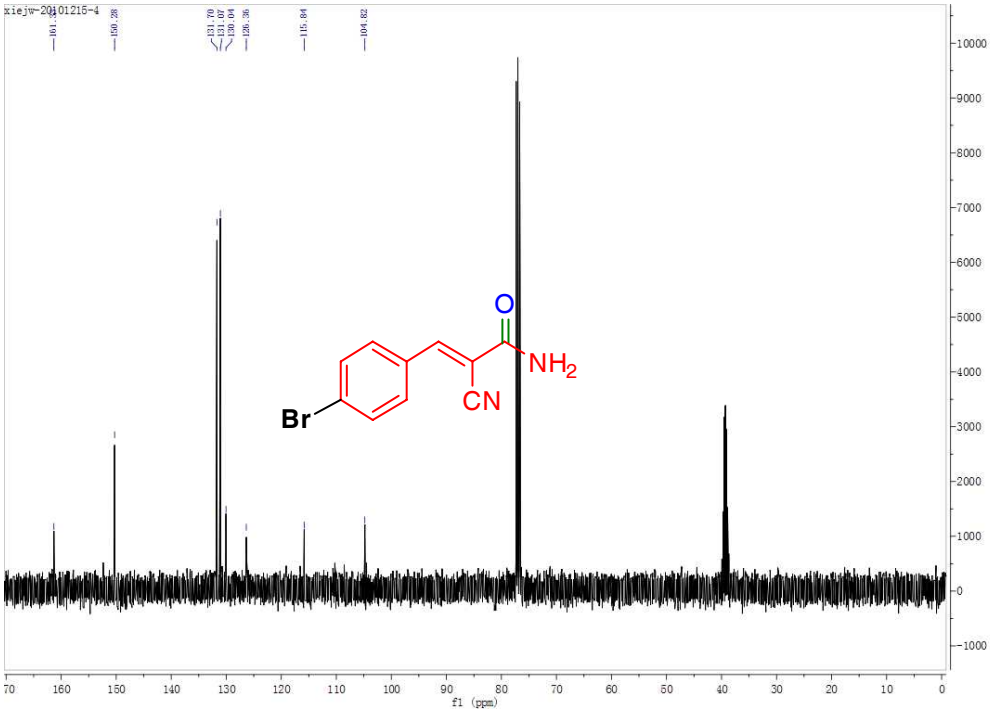
4d



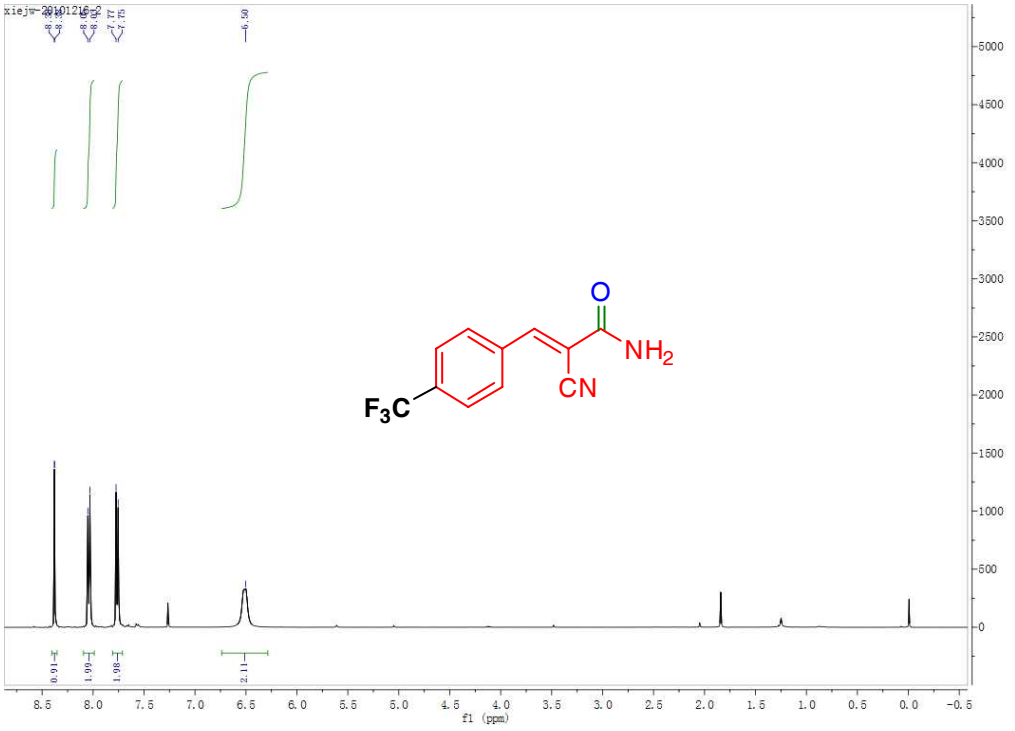


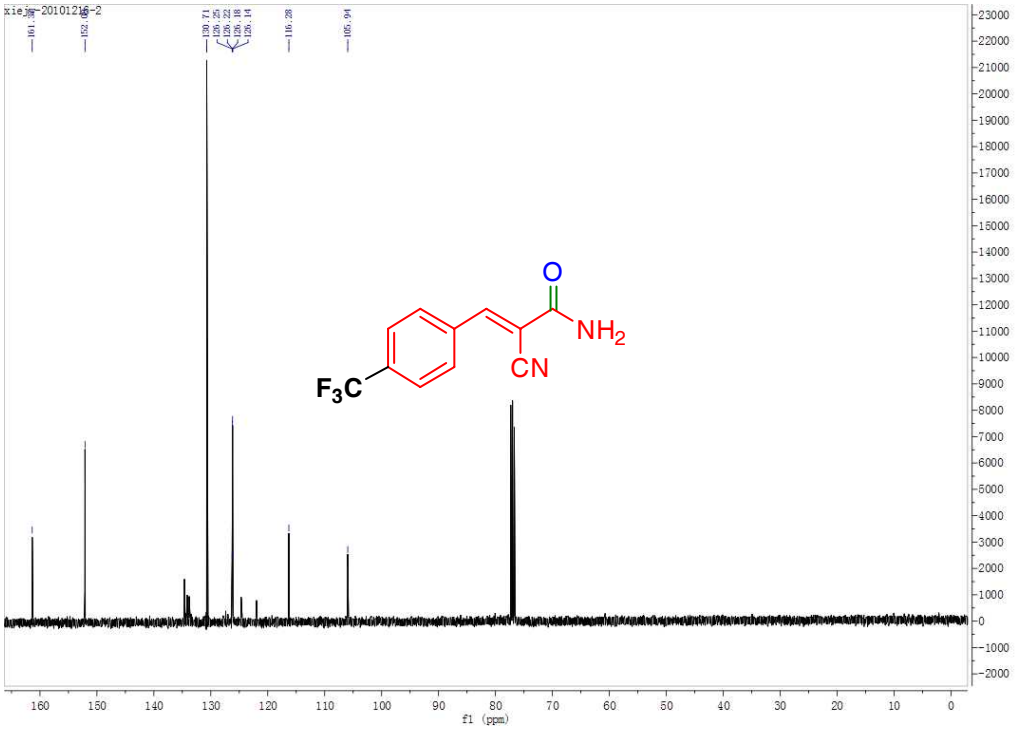
4e


Xiejw-20101213-4
8.22
7.83
7.81
7.67
7.65
7.27
6.32
6.75
1.00
1.98
1.95
1.40
1.55
O
NH2
CN
Br
f1 (ppm)

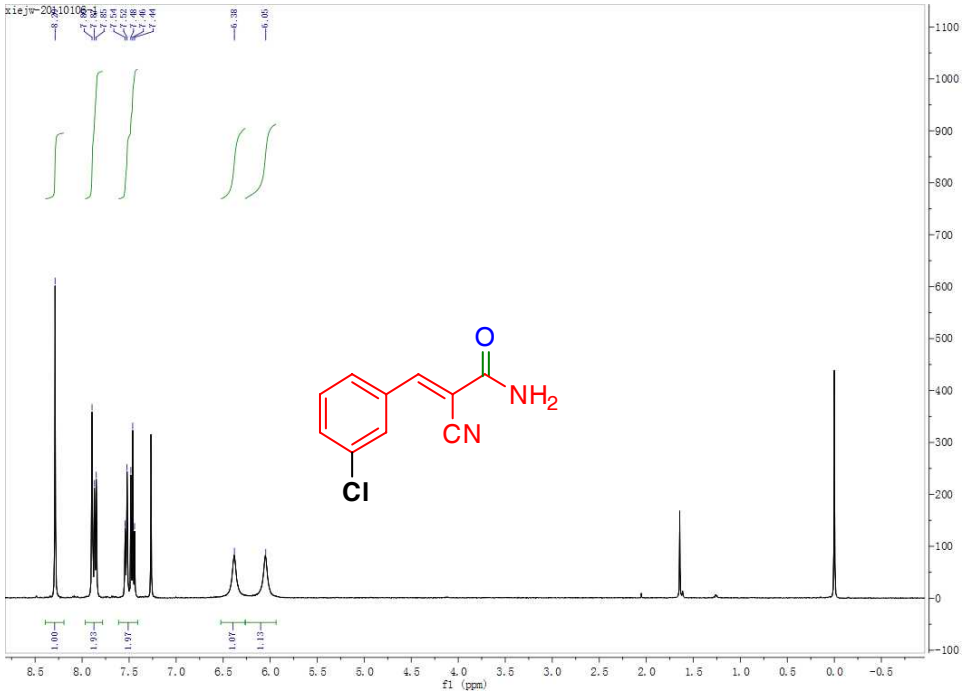

xiejw-20101215-4
161.13
150.28
131.70
131.07
130.84
126.36
115.84
104.82
O
NH2
CN
Br
f1 (ppm)

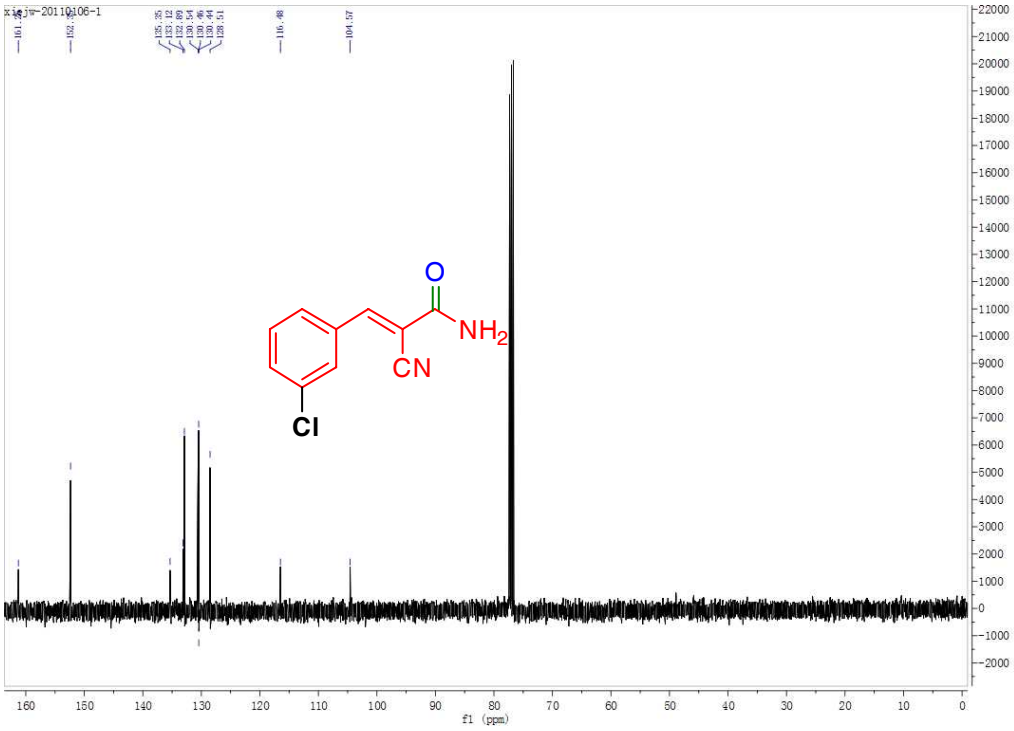
4f



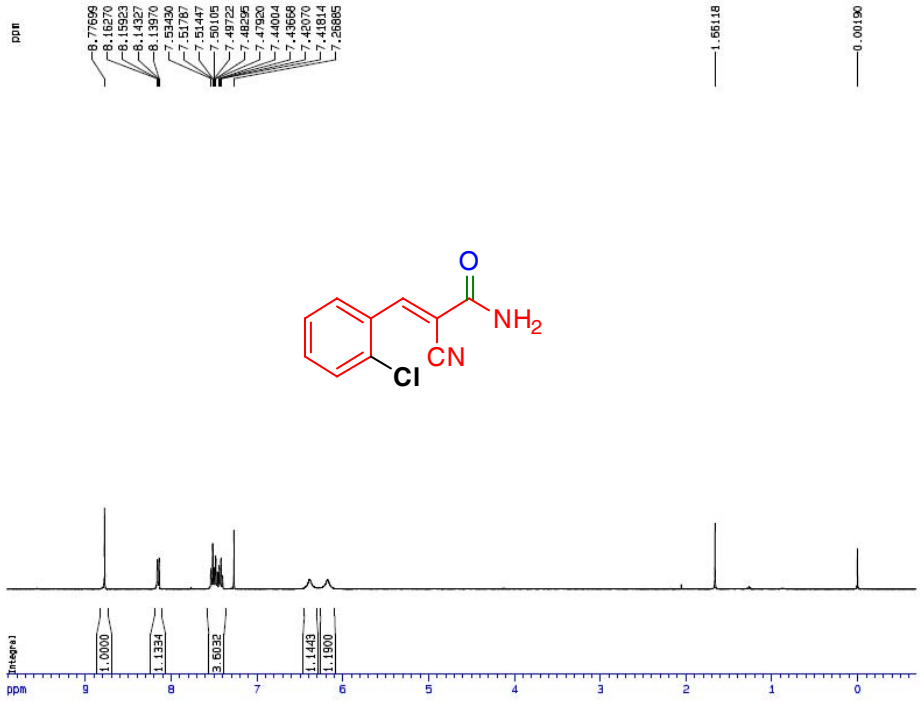


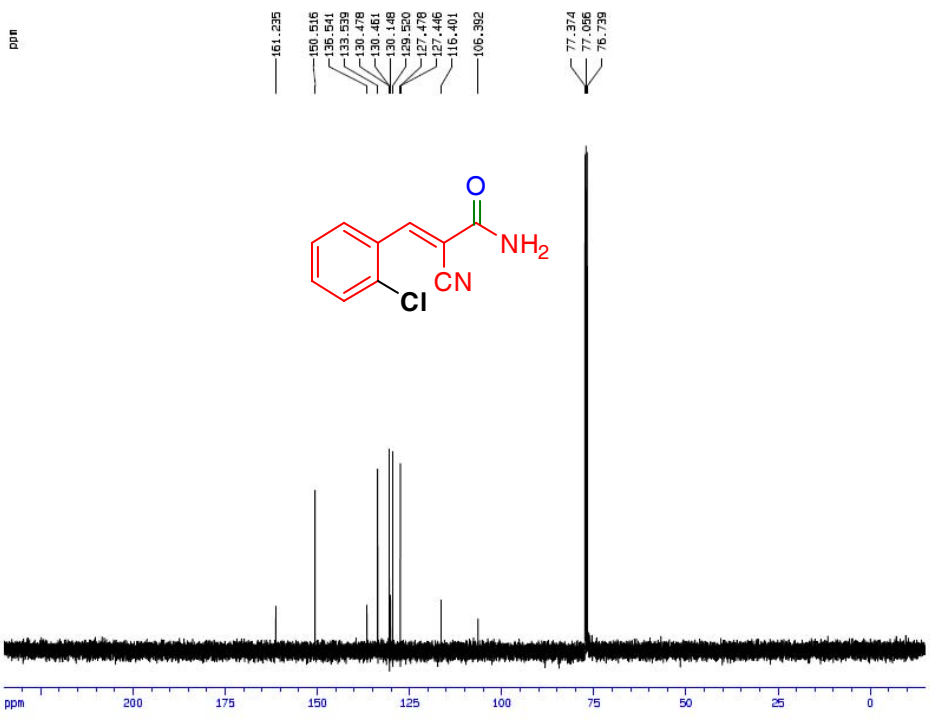
4g



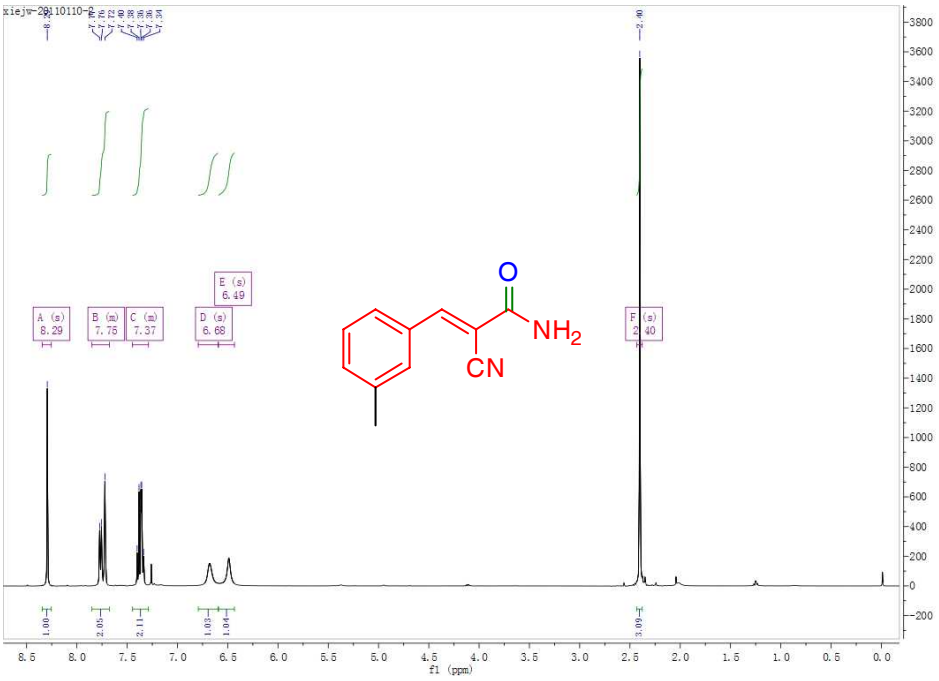


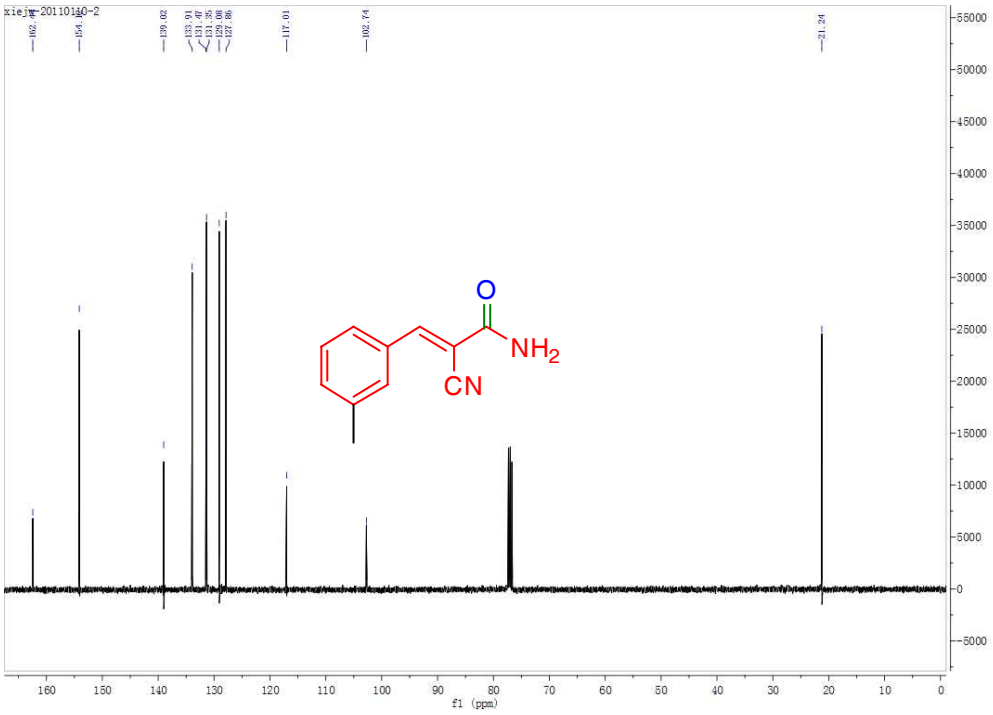
4h


ppm
8.77699
8.16270
8.15923
8.14327
8.13970
7.53430
7.51787
7.51447
7.50105
7.49722
7.48295
7.47920
7.44004
7.43668
7.42070
7.41814
7.26885
1.65118
0.00190
O
NH2
CN
Cl
Integral
1.0000
1.1334
3.6032
1.1443
1.1900
ppm
9
8
7
6
5
4
3
2
1
0

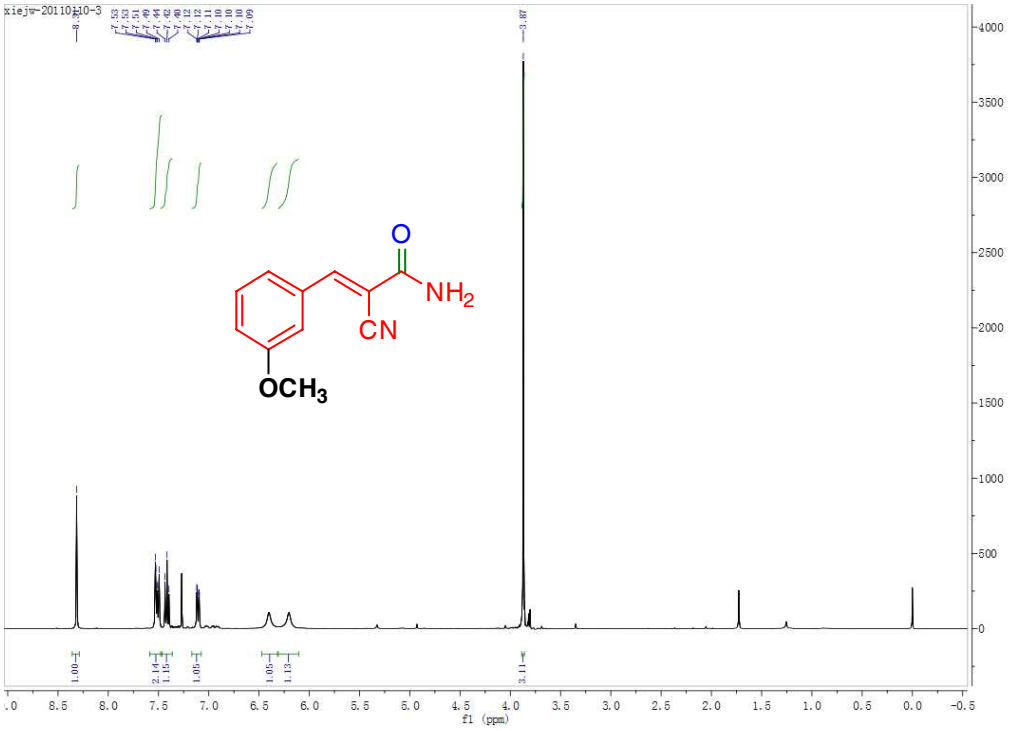

ppm
161.235
150.516
136.541
133.559
130.478
130.461
130.148
129.520
127.478
127.446
116.401
106.392
77.374
77.056
76.739
O
NH2
CN
Cl
ppm
200
175
150
125
100
75
50
25
0

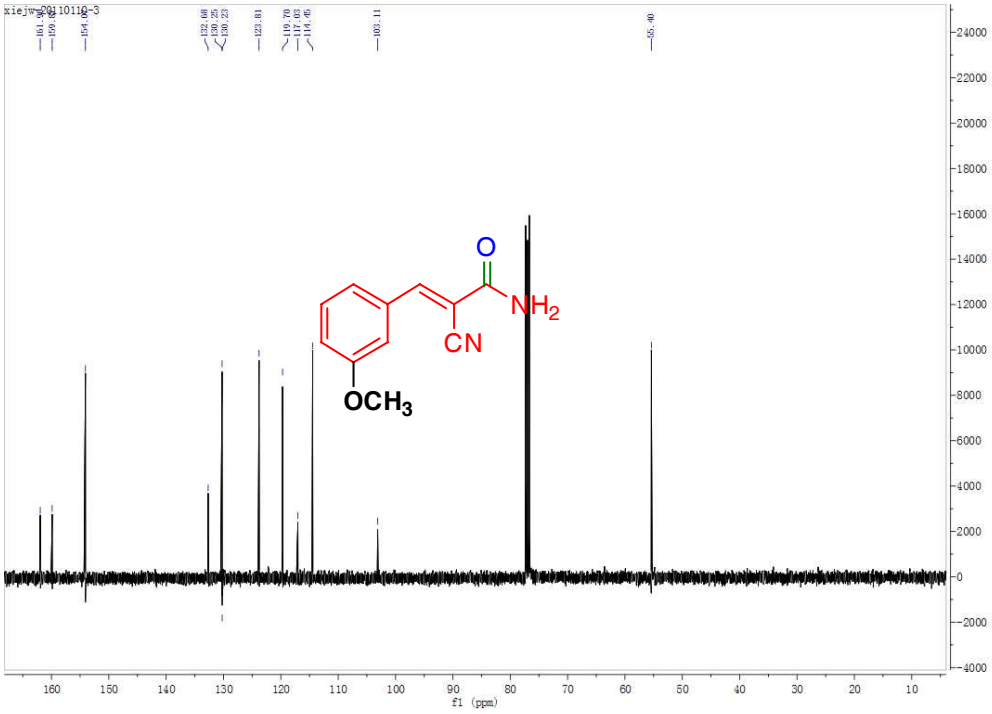
4t


A (s) 8.29
B (m) 7.75
C (m) 7.37
D (s) 6.68
E (s) 6.49
F (s) 2.40
O
NH2
CN
f1 (ppm)

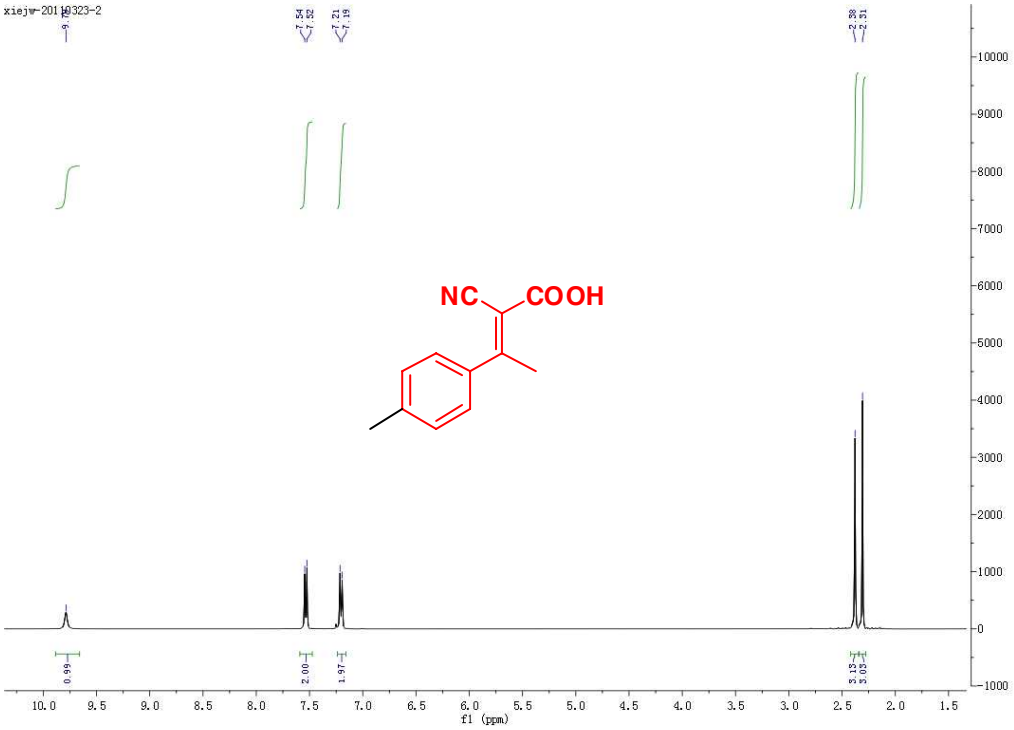

O
NH2
CN
f1 (ppm)

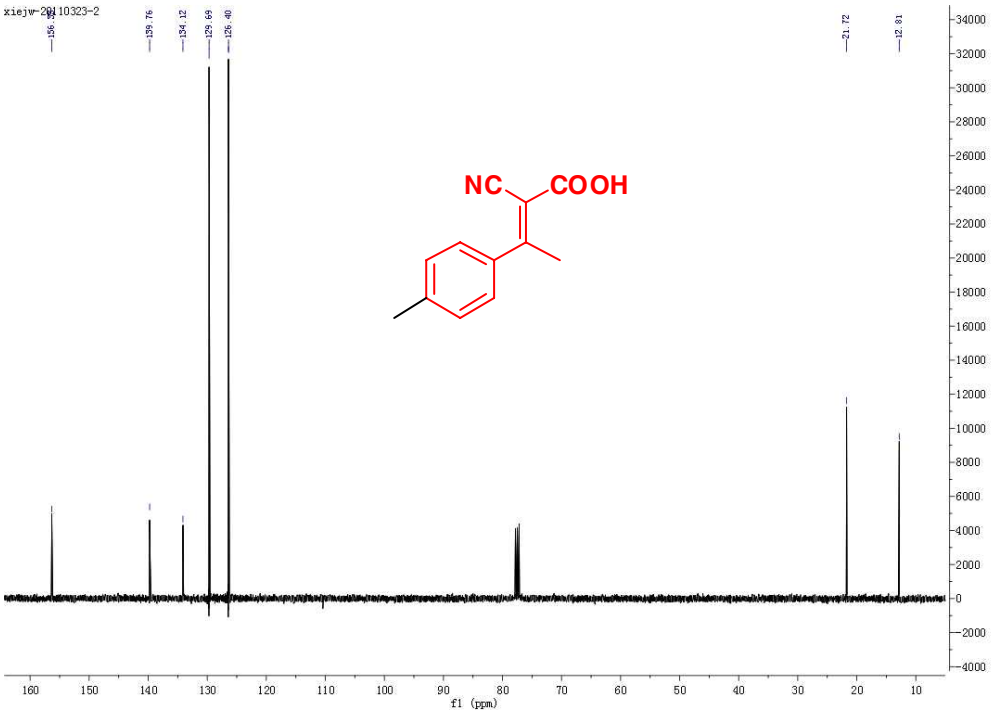
4u



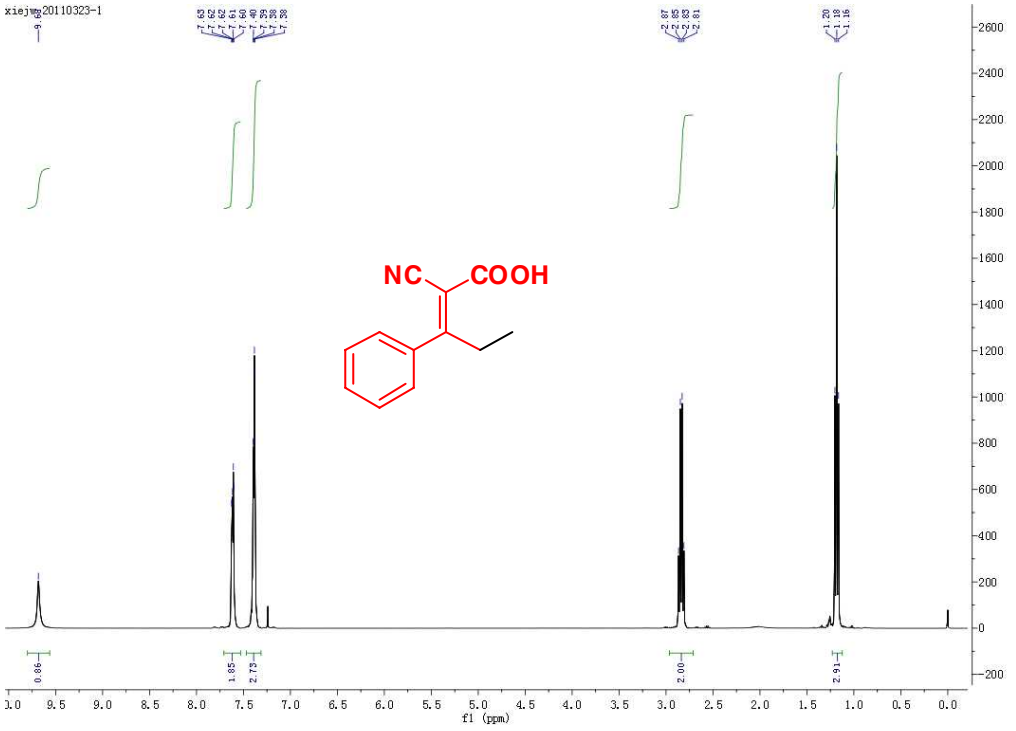


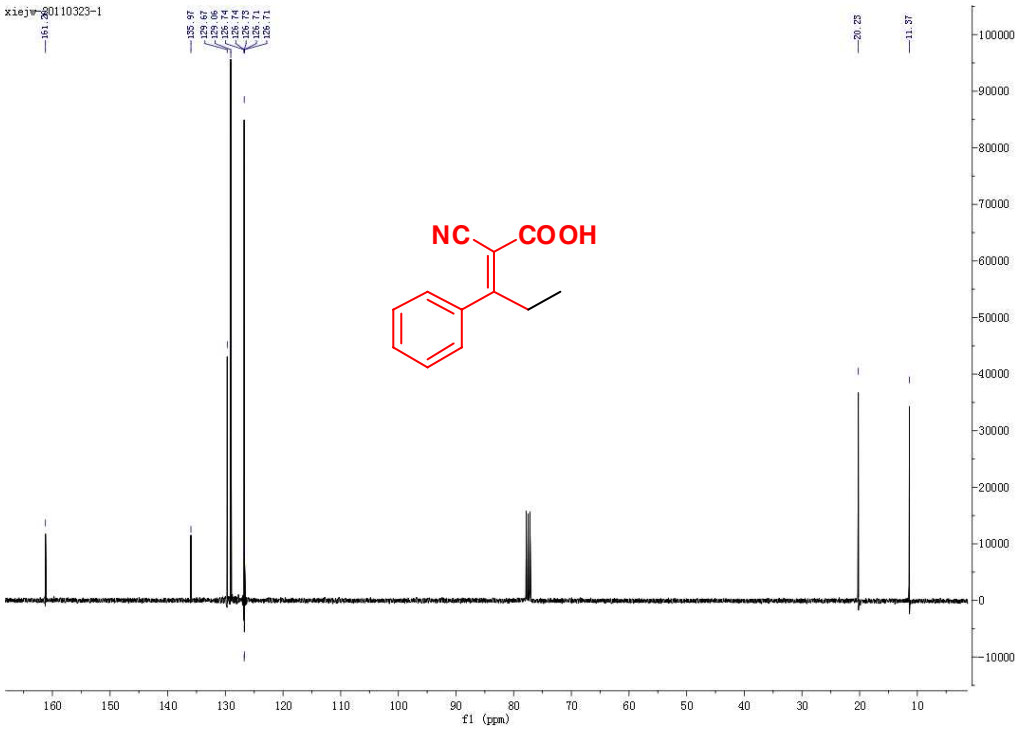
5j


xiejw-20110323-2
NC
COOH
f1 (ppm)

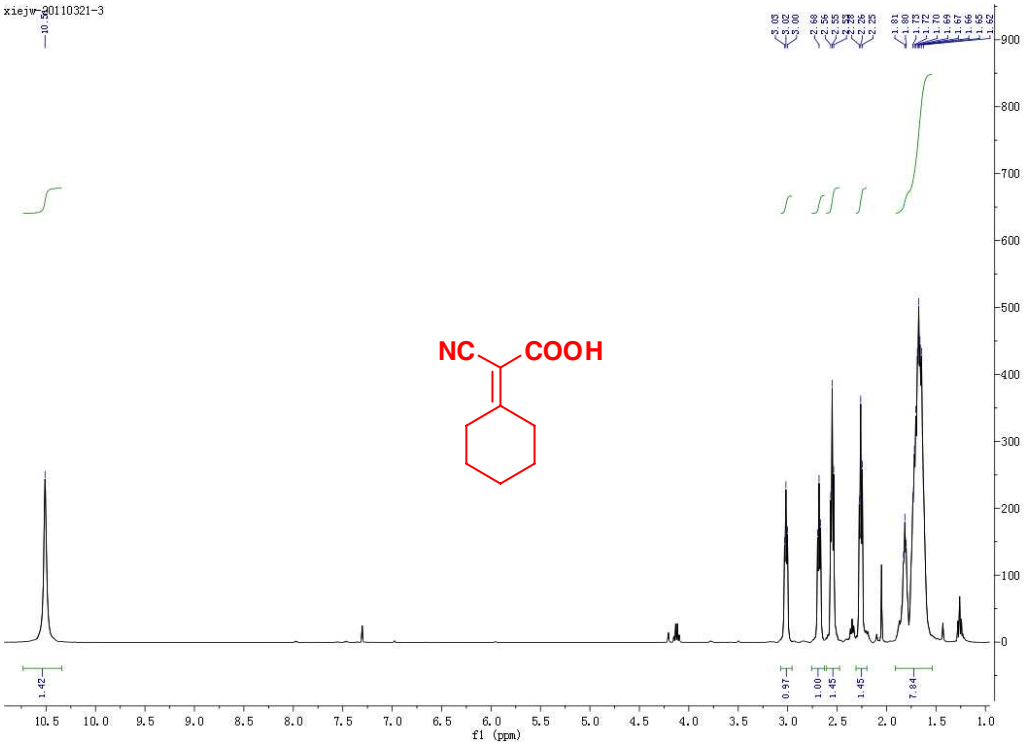

xiejw-20110323-2
NC
COOH
f1 (ppm)

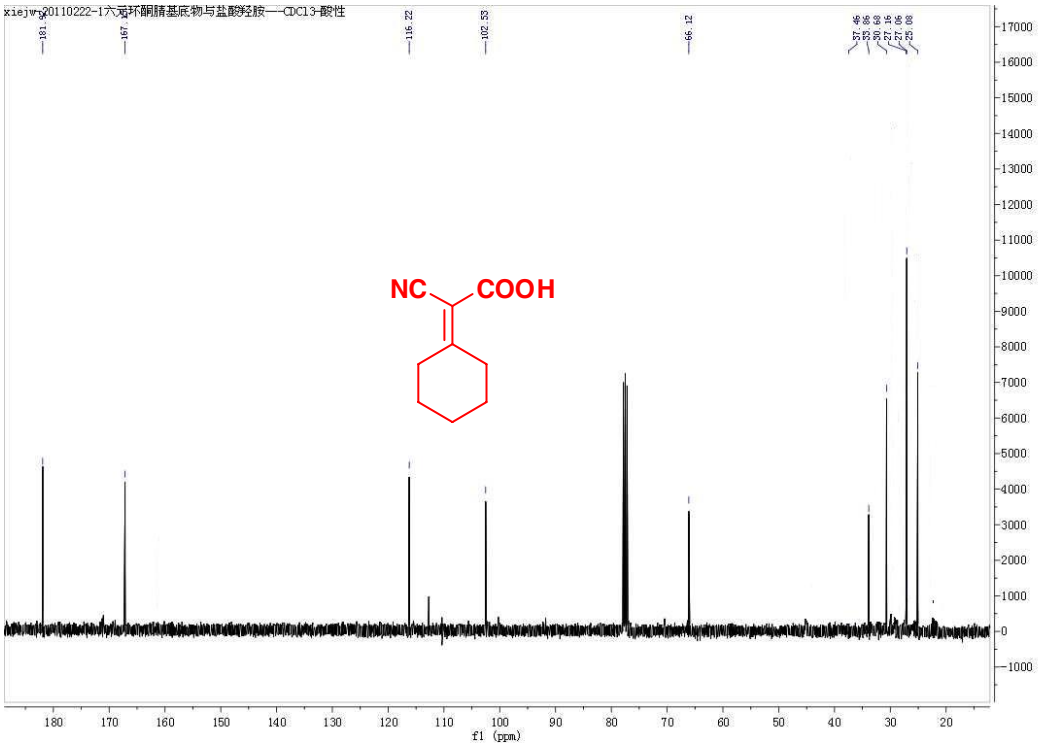
5o



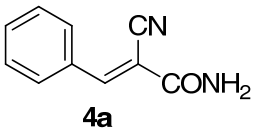


5s


xiejw-20110321-3
NC
COOH
f1 (ppm)


xiejw-20110222-1六元环酮腈基底物与盐酸羟胺---CDCl3-酸性
NC
COOH
f1 (ppm)

4. X-ray crystal data of compound 4a



4a

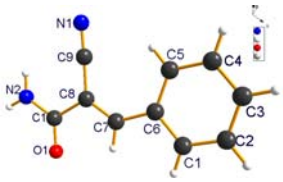


Figure 1. X-ray Crystal Structure of 4a.

Crystal data for **4a** $C_{10}H_8N_2O$ (172.18), Monoclinic, space group P2(1)/n, a = 10.3225(7) Å, b = 11.2447(8) Å, c = 16.7681(11) Å, U = 1776.5(2) Å^3, Z = 8, specimen 0.492 x 0.453 x 0.259 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.086 mm^{-1}, reflections collected 26305, independent reflections 4096 [R(int) = 0.0497], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 4096 / 0 / 235, goodness-of-fit on F^2 = 1.010, final R indices [I>2σ(I)] R1 = 0.0483, wR2 = 0.1209, R indices (all data) R1 = 0.1016, wR2 = 0.1477, largest diff. peak and hole 0.129 and -0.175 e Å^{-3}.

5. Photo of the reactions of 1a (15.4 g, 0.1 mol) with NH_2OH. HCl

Before reaction *After 4 h*

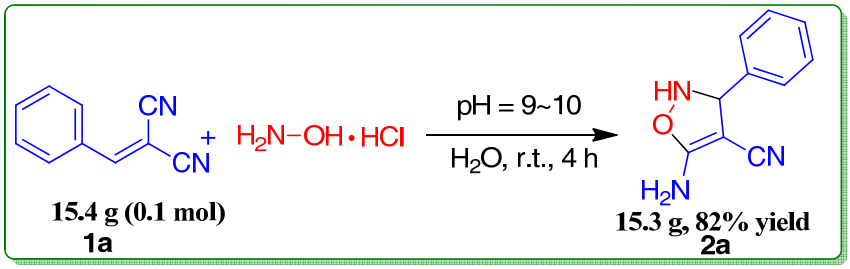


Figure 2 Photo of the reactions of **1a** with **NH_2OH. HCl**

A pale yellow precipitate was formed when the reactions were carried out at room temperature for 4 h and 2,3-dihydroisoxazoles were easily isolated by filtration, then washed with water to give the pure 2,3-dihydroisoxazoles in excellent yields.

6. DFT Calculations

All calculations were performed based on the density functional theory, using the program package of DMol^3 in the Materials Studio of Accelrys Inc. In $DMol_3$ the physical wave functions were expanded in terms of the doubled numerical basis set with p-polarization function for hydrogen and d-polarization functions for other atoms (DNP). The generalized gradient corrected functional by Perdew andWang (PW91) was employed. The tolerances of energy, maximum force, and displacement convergence are 10^{-5} Ha, 2×10^{-3} Ha/Å, and 5×10^{-3} Å, respectively. The real space cutoff of atomic orbital was set at 3.7 Å, and a Fermi smearing of 0.01 Ha was used to count the orbital occupancy. The linear synchronous transit/quadratic synchronous transit (LST/QST) method at the same level was used for the calculation of reaction transition states. The activation barrier was defined as the total energy difference between the transition state and the corresponding initial stable structure. Frequency analysis was carried out to ensure that there is no imaginary frequency for the stable structures, while there is a single imaginary one for the TS structure.

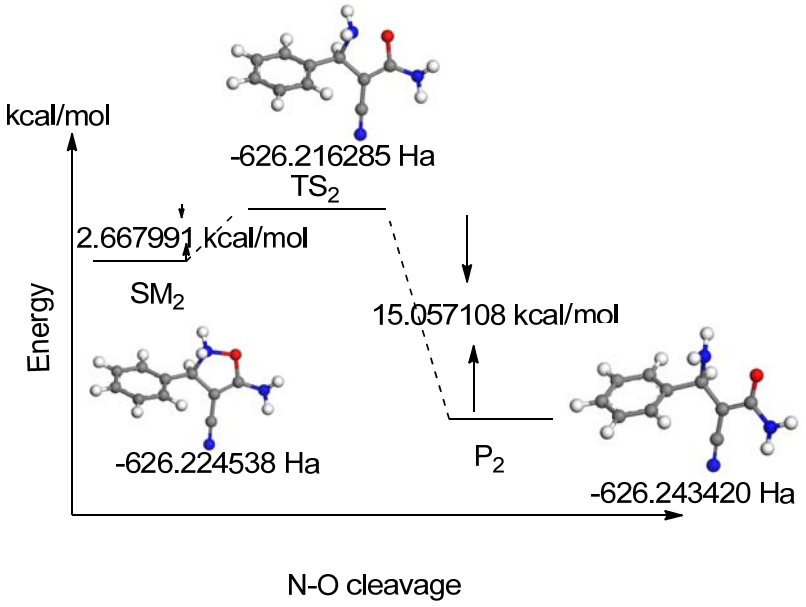


Figure 2a Path A

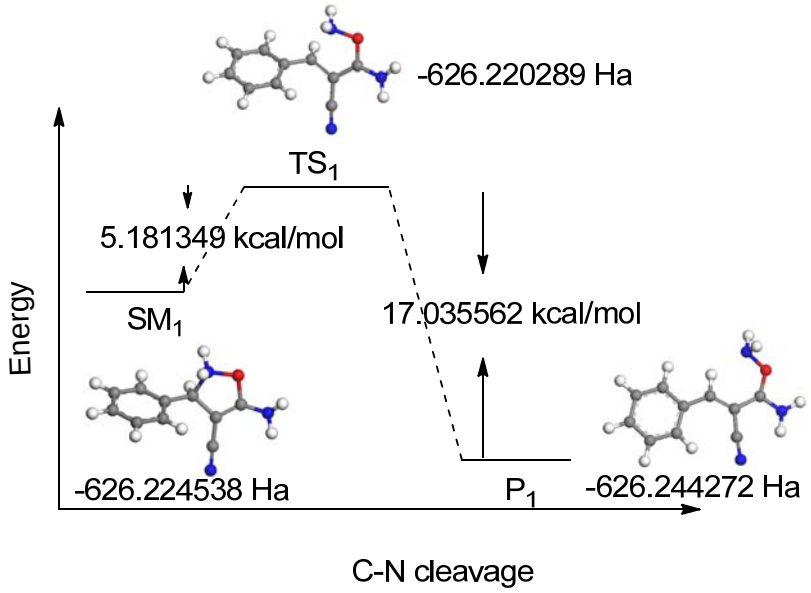


Figure 2b Path B

Compared Path A with Path B, the activation energy of Path A (N-O cleavage) is lower than Path the activation energy of Path B (C-N cleavage). Therefore, the Path A is more preferable than Path B.