Supporting Information

For

Rhodium (III)-catalyzed regioselective C2-amidation of indoles with *N*-(2,4,6-trichlorobenzoyloxy)amides and its synthetic application in the development of novel potential PPARγ modulator

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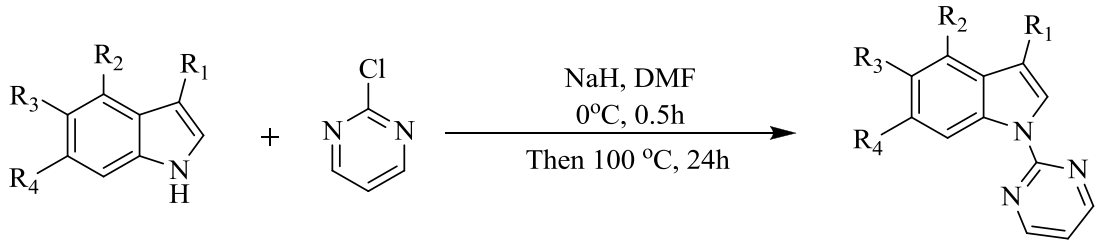
General methods and materials:

$AgSbF_6$ was purchased from Aldrich and used without further purification. $[Cp^*Rh(MeCN)_3](SbF_6)_2$ and $[Cp^*RhCl_2]_2$,[S1] substrate 1-(Pyrimidin-2-yl)-1H-indole [S2-4] and N-(2,4,6-trichlorobenzoyloxy)amide [S5] were synthesized according to published procedures. Other chemicals were purchased from commercial suppliers and were dried and purified when necessary. The water used was re-distillated and ion-free.

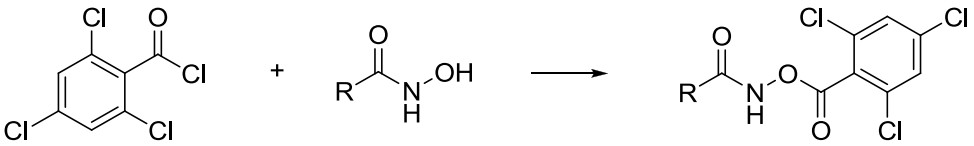
Melting points were determined on a WRS-1B digital instrument without correction. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-Plus 400 NMR and Varian Mercury-Plus 500 NMR instruments (^1H 400 MHz; ^{13}C 125 MHz) in either $CDCl_3$ or DMSO-d_6. Abbreviations for data quoted are s, singlet; brs, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. Mass spectra and high-resolution mass spectra were measured on a agilent TOF-G6230B mass spectrometer. Thin-layer chromatographies were done on pre-coated silica gel 60 F254 plates (Merck). Silica gel 60H (200-300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography.

General procedure for synthesis of the starting materials 1:[S2-S4]



NaH (60% dispersion in mineral oil, 11.0 mmol) was added in portions at 0 ℃ to a stirred solution of indoles (10.0 mmol) in dry DMF (25 mL). After stirring for 30 min at 0 ℃, 2-chloropyrimidine (12.0 mmol) was added and then the mixture was stirred at 100 ℃ for 24 h. Then, the reaction mixture was cooled to ambient temperature, poured into H_2O (300 mL) and extracted with EtOAc (250 mL). The organic phase was dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, the crude product was purified on a silica gel column using EtOAc/petroleum ether (1:10) to get the corresponding product. Characterization of these compounds have been described in the previous report.[S2- S4]

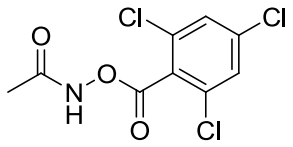
General procedure for synthesis of the starting materials 2a-2f:



Hydroxycarbamate (1.0 equiv) was dissolved in dry CH_2Cl_2 and triethylamine (1.15 equiv) was added. After cooling to 0 ℃, 2,4,6-trichlorobenzoyl chloride (1.0 equiv) was added slowly and the mixture was allowed to warm to room temperature and stirred 2 h. The reaction mixture was then

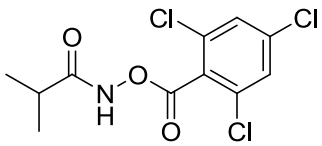
diluted with CH_2Cl_2, transferred to a separatory funnel and extracted with water and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography (silica, pentane/ethyl acetate 95:5) afforded the compound as a colorless solid.

2a: N-(2,4,6-trichlorobenzoyloxy)acetamide



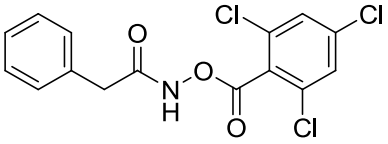
This compound was obtained in 88% yield as a white solid. Mp 141-143 ^{o}C. ^{1}H NMR (400 MHz, Methanol-d_4) δ: 12.23 (s, 1H), 7.88 (s, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 137.8, 133.7, 128.5, 128.3, 128.0, 19.8. HRMS (ESI) calcd for 281.9492 ($[M+H]^+$), found 281.9499 ($[M+H]^+$).

2b: N-(2,4,6-trichlorobenzoyloxy)isobutyramide



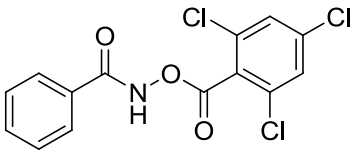
This compound was obtained in 76% yield as a white solid. Mp 119-121 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 7.39 (s, 2H), 2.62–2.55 (m, 1H), 1.26 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 137.7, 133.7, 128.6, 128.3, 128.0, 32.7, 19.2; HRMS (ESI) calcd for 309.9805 ($[M+H]^+$), found 309.9794 ($[M+H]^+$).

2c: 2-phenyl-N-(2,4,6-trichlorobenzoyloxy)acetamide



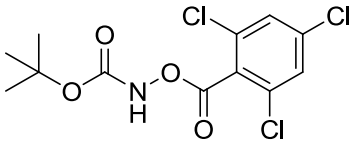
This compound was obtained in 80% yield as a white solid. Mp 143-145 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (s, 1H), 7.48–7.30 (m, 7H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 137.5, 133.6, 133.5, 129.2, 128.9, 128.7, 128.2, 127.2, 39.7; HRMS (ESI) calcd for 357.9805 ($[M+H]^+$), found 357.9801 ($[M+H]^+$).

2d: N-(2,4,6-trichlorobenzoyloxy)benzamide



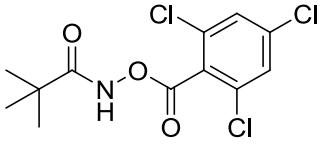
This compound was obtained in 80% yield as a white solid. Mp 118-120 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.94 (s, 1H), 7.94 (s, 2H), 7.88 (d, J = 7.6 Hz, 2H), 7.66–7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.2, 162.6, 137.8, 133.8, 133.0, 130.3, 128.9, 128.6, 128.3, 127.7; HRMS (ESI) calcd for 343.9648 ([M+H]$^{+}$), found 343.9644 ([M+H]$^{+}$).

2e: tert-butyl 2,4,6-trichlorobenzoyloxycarbamate



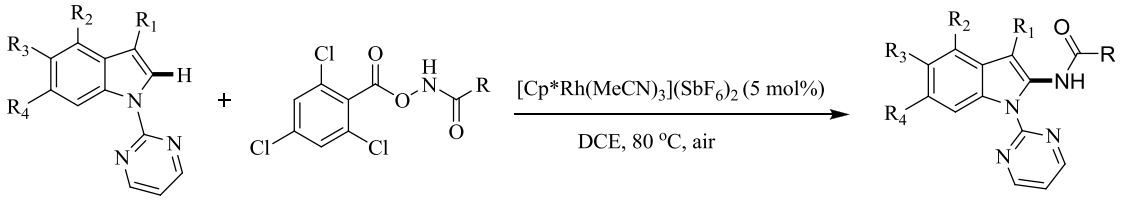
This compound was obtained in 76% yield as a white solid. Mp 76-78 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.24 (s, 1H), 7.90 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 154.8, 137.6, 133.7, 128.8, 128.3, 83.9, 28.1; HRMS (ESI) calcd for 339.9910 ([M+H]$^{+}$), found 339.9907 ([M+H]$^{+}$).

2f: N-(2,4,6-trichlorobenzoyloxy)pivalamide



This compound was obtained in 72% yield as a white solid. Mp 143-144 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 7.40 (s, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.5, 162.6, 137.7, 133.8, 128.7, 128.3, 38.9, 27.2; ^{1}HRMS (ESI) calcd for 323.9961 ([M+H]$^{+}$), found 323.9968 ([M+H]$^{+}$).

General procedure for C-H amidation reaction:

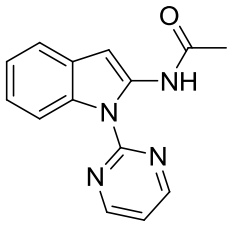


The mixture of [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (8.3 mg, 0.01mmol, 0.05 equiv), substrate A (0.20 mmol,

1.0 equiv), B (0.24 mmol, 1.2 equiv) and DCE (1 mL) were stirred at 80 ℃ for 5h under air. The resulting mixture was cooled to room temperature, silica gel column directly to give the desired product.

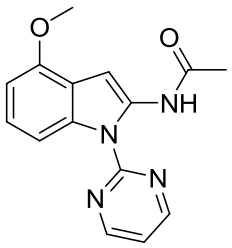
Characterizations of products

N-(1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3a)



This compound was obtained in 81% yield as a white solid. Mp 116-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.96 (s, 1H), 8.76 (d, *J* = 4.8 Hz, 2H), 8.69–8.53 (m, 1H), 7.67–7.45 (m, 1H), 7.29–7.19 (m, 3H), 7.14 (t, *J* = 4.8 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 158.9, 157.7, 135.0, 132.5, 129.9, 123.1, 122.4, 119.9, 116.2, 116.1, 95.8, 25.0; IR (KBr): 2923.56, 2601.50, 1778.05, 1733.69, 1668.12, 1567.84, 1546.63, 1457.92, 1427.07, 1376.93, 1238.08, 1103.08, 850.45, 788.74, 746.32; HRMS (ESI) calcd for 253.1089 ($[M+H]^+$), found 253.1086 ($[M+H]^+$).

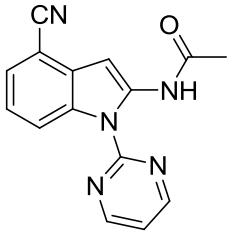
N-(4-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3f)



This compound was obtained in 79% yield as a white solid. Mp 166-168 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.27 (s, 1H), 8.96 (d, *J* = 4.8 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 4.8 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.5, 159.3, 157.8, 152.2, 133.7, 133.6, 123.3, 118.9, 118.3, 108.6, 103.7, 92.4, 55.7, 24.6; IR (KBr): 3365.17, 3089.40, 2921.63, 2850.27, 1689.34, 1571.70,

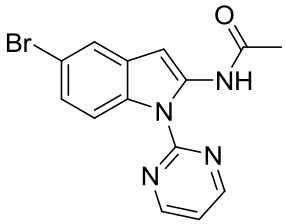
1538.92, 1434.78, 1417.42, 1373.07, 1247.72, 1079.94, 788.74, 738.60; HRMS (ESI) calcd for 283.1195 ($[M+H]^+$), found 283.1192 ($[M+H]^+$).

N-(4-cyano-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3g)



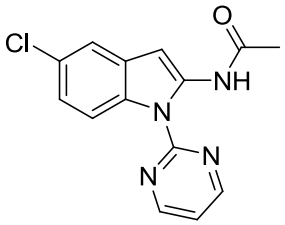
This compound was obtained in 72% yield as a white solid. Mp 203-204 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.64 (s, 1H), 8.98 (d, *J* = 4.8 Hz, 2H), 8.63 (d, *J* = 8.4 Hz, 1H), 7.62–7.49 (m, 2H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ:167.9, 159.4, 157.4, 138.4, 132.0, 131.4, 127.2, 122.3, 120.2, 119.0, 118.7, 100.6, 91.7, 24.8; IR (KBr): 3432.67, 3158.83, 2921.63, 2219.67, 1697.05, 1579.41, 1536.99, 1434.78, 1373.07, 1241.93, 788.74, 744.39; HRMS (ESI) calcd for 278.1042 ($[M+H]^+$), found 278.1037 ($[M+H]^+$).

N-(5-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3h)



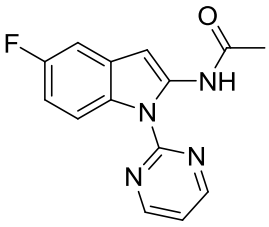
This compound was obtained in 80% yield as a white solid. Mp 199-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.90 (s, 1H), 8.61 (d, *J* = 4.8 Hz, 2H), 8.40 (d, *J* = 8.8 Hz, 1H), 7.45 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.05–7.04 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.6, 153.2, 152.3, 130.9, 126.5, 125.8, 119.6, 116.8, 112.6, 111.1, 111.0, 89.3, 19.8; IR (KBr): 3046.98, 2923.56, 1589.06, 1563.99, 1446.35, 1428.99, 798.39; HRMS (ESI) calcd for 331.0194 ($[M+H]^+$), found 331.0200 ($[M+H]^+$).

N-(5-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3i)



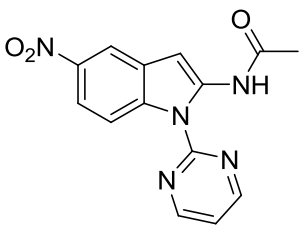
This compound was obtained in 82% yield as a white solid. Mp 196-197 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.98 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 2H), 8.52 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.19–7.05 (m, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 158.5, 157.6, 136.3, 131.3, 130.7, 128.4, 122.2, 119.1, 117.5, 116.4, 94.7, 25.0; IR (KBr): 3185.83, 3048.91, 1587.13, 1563.99, 1448.28, 1427.07, 798.39; HRMS (ESI) calcd for 287.0700 ($[M+H]^+$), found 287.0702 ($[M+H]^+$).

N-(5-fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3j)



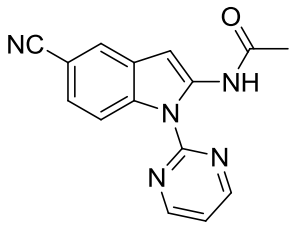
This compound was obtained in 85% yield as a white solid. Mp 176-177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.99 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 2H), 8.57 (dd, *J* = 9.2 and 4.8 Hz, 1H), 7.22–7.04 (m, 3H), 6.87 (td, *J* = 9.2 and 2.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 159.4 (d, *J* = 237.5 Hz), 158.5, 157.6, 136.6, 131.0 (d, *J* = 10.0 Hz), 128.6, 117.4 (d, *J* = 8.7 Hz), 116.2, 109.5 (d, *J* = 24.3 Hz), 105.1 (d, *J* = 24.1 Hz), 95.2 (d, *J* = 3.7 Hz), 25.0; IR (KBr): 3102.90, 2923.56, 1691.27, 1585.20, 1554.34, 1450.21, 1425.14, 1371.14, 1182.15, 790.67; HRMS (ESI) calcd for 271.0995 ($[M+H]^+$), found 271.0999 ($[M+H]^+$).

N-(5-nitro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3k)



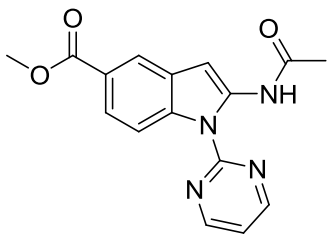
This compound was obtained in 79% yield as a white solid. Mp 282-283 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.28 (s, 1H), 9.02 (d, J = 4.8 Hz, 2H), 8.51–8.40 (m, 2H), 8.04 (dd, J = 9.2 and 2.4 Hz, 1H), 7.57 (t, J = 4.8 Hz, 1H), 7.17 (s, 1H), 2.16 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 168.0, 159.7, 157.1, 143.3, 137.8, 135.9, 129.2, 119.5, 117.5, 116.0, 115.2, 95.4, 24.6; IR (KBr): 3423.03, 3087.48, 1689.34, 1579.41, 1540.84, 1519.63, 1448.28, 1419.35, 1334.50, 1247.72, 813.81, 730.89; HRMS (ESI) calcd for 298.0940 ([M+H]$^{+}$), found 298.0944 ([M+H]$^{+}$).

N-(5-cyano-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3l)



This compound was obtained in 76% yield as a white solid. Mp 244-245 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.35 (s, 1H), 9.02 (d, J = 4.8 Hz, 2H), 8.47 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 1.2 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.08 (s, 1H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.9, 159.6, 157.2, 137.2, 134.6, 129.4, 125.5, 124.5, 120.4, 119.2, 116.0, 105.0, 94.5, 24.6; IR (KBr): 2923.56, 2852.20, 2223.52, 1693.19, 1581.34, 1544.70, 1467.56, 1419.35, 811.88; HRMS (ESI) calcd for 278.1042 ([M+H]$^{+}$), found 278.1050 ([M+H]$^{+}$).

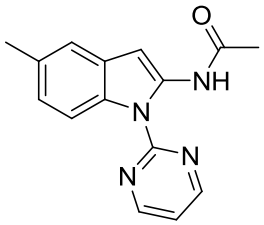
methyl 2-acetamido-1-(pyrimidin-2-yl)-1H-indole-5-carboxylate (3m)



This compound was obtained in 79% yield as a white solid. Mp 218-219 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.31 (s, 1H), 8.99 (d, J = 4.8 Hz, 2H), 8.41 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 7.77 (dd, J = 8.8 and 1.8 Hz, 1H), 7.52 (t, J = 4.8 Hz, 1H), 7.07 (s, 1H), 3.86 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 167.3, 166.7, 159.0, 156.9, 135.9, 134.8, 128.5, 123.7,

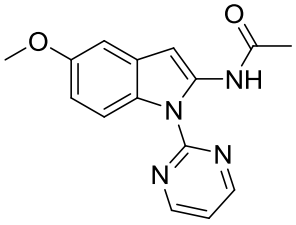
122.9, 121.2, 118.4, 114.4, 94.9, 51.9, 24.1; IR (KBr): 3056.63, 2923.56, 2852.20, 1714.41, 1583.27, 1567.84, 1446.35, 1419.35, 1259.29, 761.74; HRMS (ESI) calcd for 311.1144 ($[M+H]^+$), found 311.1142 ($[M+H]^+$).

N-(5-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3n)



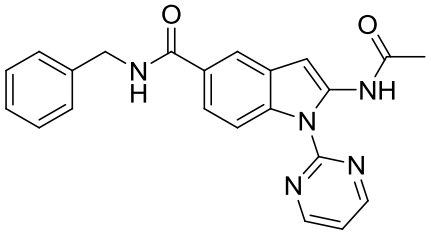
This compound was obtained in 80% yield as a white solid. Mp 136-137 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.00 (s, 1H), 8.73 (d, *J* = 4.8 Hz, 2H), 8.52 (d, *J* = 8.4 Hz, 1H), 7.30 (s, 1H), 7.17 (s, 1H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 2.43 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 158.4, 157.1, 134.7, 132.1, 130.1, 129.6, 123.2, 119.4, 115.4, 115.4, 95.0, 24.5, 20.9; IR (KBr): 2923.56, 2854.13, 1733.69, 1666.20, 1585.20, 1546.63, 1446.35, 1425.14, 1376.93, 1270.86, 1122.37, 846.60, 792.60; HRMS (ESI) calcd for 267.1246 ($[M+H]^+$), found 267.1241 ($[M+H]^+$).

N-(5-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3o)



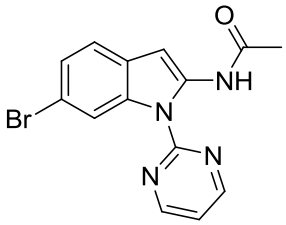
This compound was obtained in 77% yield as a white solid. Mp 169-171 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.04 (s, 1H), 8.69 (d, *J* = 4.8 Hz, 2H), 8.55 (d, *J* = 9.2 Hz, 1H), 7.18 (s, 1H), 7.07 (t, *J* = 4.8 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.80 (dd, *J* = 9.2 and 2.7 Hz, 1H), 3.86 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 158.7, 157.5, 156.1, 135.8, 130.9, 127.0, 117.2, 115.8, 110.5, 102.7, 95.6, 55.6, 25.0; IR (KBr): 3176.18, 2933.20, 1693.19, 1600.19, 160.63, 1585.20, 1563.99, 1536.99, 1479.13, 1425.14, 1209.15, 1174.44, 796.46; HRMS (ESI) calcd for 283.1195 ($[M+H]^+$), found 283.1188 ($[M+H]^+$).

2-acetamido-N-benzyl-1-(pyrimidin-2-yl)-1H-indole-5-carboxamide (3p)



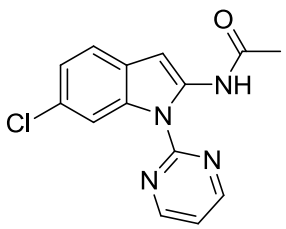
This compound was obtained in 82% yield as a white solid. Mp 218-219 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.36 (s, 1H), 9.01–8.98 (m, 3H), 8.42 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.74 (dd, J = 8.8 and 1.8 Hz, 1H), 7.51 (t, J = 4.8 Hz, 1H), 7.39–7.20 (m, 5H), 7.04 (s, 1H), 4.51 (d, J = 6.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 167.3, 166.6, 159.0, 157.1, 139.9, 135.7, 133.7, 128.7, 128.2, 127.2, 126.6, 121.4, 118.8, 118.2, 114.2, 94.9, 42.6, 24.1; IR (KBr): 3376.75, 2923.56, 1583.27, 1563.99, 1535.06, 1419.35, 1280.50, 792.60; HRMS (ESI) calcd for 386.1617 ([M+H]$^{+}$), found 386.1611 ([M+H]$^{+}$).

N-(6-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3q)



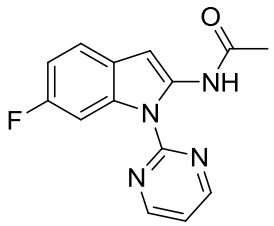
This compound was obtained in 67% yield as a white solid. Mp 185-187 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.94 (s, 1H), 8.82 (s, 1H), 8.69 (d, J = 4.8 Hz, 2H), 7.34–7.28 (m, 2H), 7.16 (s, 1H), 7.10 (t, J = 4.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 158.0, 157.2, 135.2, 132.5, 128.3, 125.7, 120.3, 118.8, 116.0, 115.0, 94.7, 24.6; IR (KBr): 3176.18, 2921.63, 1683.55, 1581.34, 1521.56, 1452.14, 1425.14, 1348.00, 1263.15, 802.24; HRMS (ESI) calcd for 331.0194 ([M+H]$^{+}$), found 331.0197 ([M+H]$^{+}$).

N-(6-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3r)



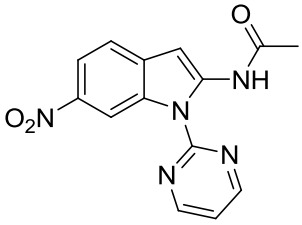
This compound was obtained in 76% yield as a white solid. Mp 171-172 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.92 (s, 1H), 8.73–8.60 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19–7.13 (m, 2H), 7.08 (t, *J* = 4.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 158.5, 157.6, 135.8, 132.6, 128.4, 127.7, 123.4, 120.2, 116.6, 116.4, 95.1, 25.0; IR (KBr):3127.97, 2923.56, 1693.19, 1585.20, 1549.84, 1538.92, 1419.35, 1346.07, 1259.29, 794.53; HRMS (ESI) calcd for 287.0700 ($[M+H]^+$), found 287.0692 ($[M+H]^+$).

N-(6-fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3s)



This compound was obtained in 80% yield as a white solid. Mp 168-170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.89 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 1H), 8.42 (dd, *J* = 11.2 and 1.6 Hz, 1H), 7.37 (dd, *J* = 8.4 and 5.6 Hz, 1H), 7.17 (s, 1H), 7.12–7.05 (m, 2H), 6.96 (td, *J* = 8.8 and 2.5 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.6, 159.6 (d, *J* = 235.9 Hz), 158.6, 157.6, 135.4 (d, *J* = 3.6 Hz), 132.3 (d, *J* = 13.2 Hz), 126.0, 119.9 (d, *J* = 9.5 Hz), 116.3, 110.8 (d, *J* = 23.7 Hz), 104.0 (d, *J* = 30.1 Hz), 95.2, 24.9; IR (KBr): 3131.83, 2923.56, 1689.34, 1587.13, 1569.77, 1544.70, 1425.14, 798.39; HRMS (ESI) calcd for 271.0995 ($[M+H]^+$), found 271.1001 ($[M+H]^+$).

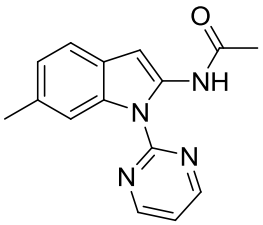
N-(6-nitro-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3t)



This compound was obtained in 84% yield as a white solid. Mp 274-276 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.76 (s, 1H), 9.30 (s, 1H), 9.05 (d, *J* = 4.8 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.73–7.51 (m, 2H), 7.19 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.0, 159.6, 157.4, 142.5, 140.7, 135.3, 131.0, 119.8, 119.2, 118.5, 111.8, 94.7, 24.8; IR (KBr): 3428.81,

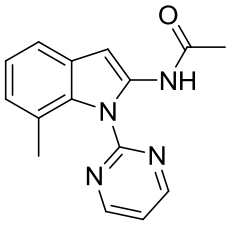
3141.47, 1573.63, 1531.20, 1500.35, 1425.14, 1328.71, 1257.36, 1072.23, 792.60; HRMS (ESI) calcd for 298.0940 ($[M+H]^+$), found 298.0935 ($[M+H]^+$).

N-(6-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3u)



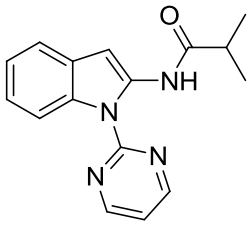
This compound was obtained in 79% yield as a white solid. Mp 139-140 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ: 11.88 (s, 1H), 8.77 (d, *J* = 4.8 Hz, 2H), 8.47 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 158.4, 157.2, 134.0, 132.3, 131.7, 127.0, 123.9, 119.0, 115.8, 115.5, 95.3, 24.5, 21.7; IR (KBr): 3112.55, 2921.63, 1679.69, 1587.13, 1569.77, 1538.92, 1430.92, 1371.14, 813.81; HRMS (ESI) calcd for 267.1246 ($[M+H]^+$), found 267.1253 ($[M+H]^+$).

N-(7-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (3v)



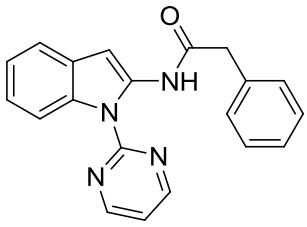
This compound was obtained in 78% yield as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 10.35 (s, 1H), 8.82 (d, *J* = 4.8 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 2.20 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.5, 158.2, 157.6, 134.7, 132.4, 131.1, 125.5, 123.9, 123.2, 118.0, 117.5, 94.6, 24.7, 21.6; IR (KBr): 2921.63, 2852.20, 1691.27, 1519.63, 1457.92, 1255.43, 1085.73, 802.24; HRMS (ESI) calcd for 267.1246 ($[M+H]^+$), found 267.1250 ($[M+H]^+$).

N-(1-(pyrimidin-2-yl)-1H-indol-2-yl)isobutyramide (4b)



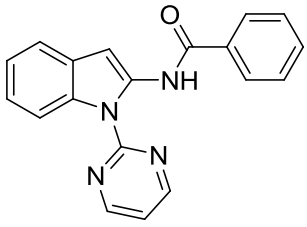
This compound was obtained in 54% yield as a white solid. Mp 119-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, *J* = 4.8 Hz, 2H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.40–7.31 (m, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 6.94 (s, 1H), 5.97 (d, *J* = 8.0 Hz, 1H), 4.31–4.18 (m, 1H), 1.28 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.3, 158.0, 157.4, 137.5, 134.9, 128.0, 125.3, 122.5, 121.6, 117.6, 113.9, 109.1, 41.8, 22.6; IR (KBr): 2923.56, 2852.18, 1733.61, 1660.29, 1579.20, 1446.92, 1376.29, 1288.36, 1123.27, 845.92, 792.48; HRMS (ESI) calcd for 281.1402 ($[M+H]^+$), found 281.1403 ($[M+H]^+$).

2-phenyl-N-(1-(pyrimidin-2-yl)-1H-indol-2-yl)acetamide (4c)



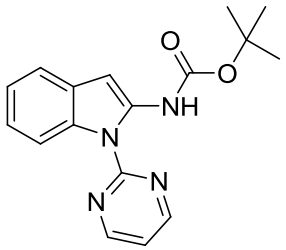
This compound was obtained in 83% yield as a white solid. Mp 139-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.72 (s, 1H), 8.66–8.56 (m, 1H), 8.27 (d, *J* = 4.8 Hz, 2H), 7.53–7.36 (m, 6H), 7.33 (s, 1H), 7.23–7.16 (m, 2H), 6.93 (t, *J* = 4.8 Hz, 1H), 3.88 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 158.4, 157.3, 135.1, 134.3, 132.5, 130.5, 129.8, 129.1, 127.5, 123.0, 122.4, 119.9, 116.1, 115.7, 95.8, 45.2; IR (KBr): 3430.74, 3050.83, 1668.12, 1454.06, 1430.92, 790.67, 744.39, 701.96; HRMS (ESI) calcd for 329.1402 ($[M+H]^+$), found 329.1399 ($[M+H]^+$).

N-(1-(pyrimidin-2-yl)-1H-indol-2-yl)benzamide (4d)



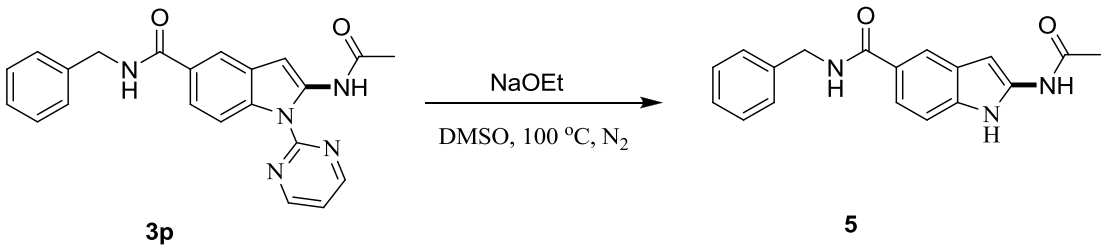
This compound was obtained in 61% yield as a white solid. Mp 123-124 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.07 (s, 1H), 8.78–8.69 (m, 3H), 8.02–7.97 (m, 2H), 7.60–7.50 (m, 4H), 7.45 (s, 1H), 7.26–7.21 (m, 2H), 7.13 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.3, 158.5, 157.2, 135.1, 134.2, 132.2, 131.5, 129.6, 128.4, 126.7, 122.8, 122.1, 119.5, 115.9, 115.7, 95.5; IR (KBr): 3046.98, 2921.63, 1666.20, 1587.13, 1565.91, 1540.84, 1425.14, 1348.00, 1276.65, 792.60, 742.46, 696.18; HRMS (ESI) calcd for 329.1402 ($[M+H]^+$), found 329.1399 ($[M+H]^+$).

tert-butyl 1-(pyrimidin-2-yl)-1H-indol-2-ylcarbamate (4e)



This compound was obtained in 76% yield as a white solid. Mp 163-165 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.93 (s, 1H), 8.74 (d, *J* = 4.8 Hz, 2H), 8.63–8.57 (m, 1H), 7.50–7.44 (m, 1H), 7.24–7.15 (m, 2H), 7.10 (t, *J* = 4.8 Hz, 1H), 6.90 (s, 1H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.6, 157.7, 151.9, 135.9, 132.6, 130.0, 122.9, 121.7, 119.2, 116.1, 115.7, 93.1, 80.8, 28.3; IR (KBr): 3208.97, 2983.34, 1725.98, 1515.77, 1457.92, 1428.99, 1249.65, 1157.08, 1062.59, 786.81, 742.46; HRMS (ESI) calcd for 311.1508 ($[M+H]^+$), found 311.1504 ($[M+H]^+$).

Procedure for deprotection:

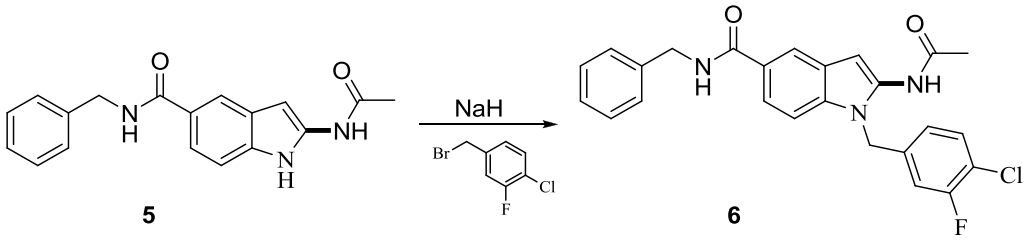


3p **5**

A suspension of **3p** (385 mg, 1 mmol) and NaOEt (340 mg, 5 mmol) in dry DMSO (5 mL) under N_2 was stirred at 100^{o}C until consumption of the starting material (typically 10 min). It was

allowed to reach room temperature, diluted with EtOAc (10 mL) and washed brine. The combined organic phase was dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, the crude product was purified on a silica gel column on a silica gel column to afford the product **5** as pale yellow solid. Yield 192 mg (62%). Mp 232-233^oC; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.21 (s, 1H), 10.77 (s, 1H), 8.81 (t, *J* = 6.0 Hz, 1H), 7.98 (s, 1H), 7.54 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.35–7.19 (m, 4H), 6.05 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.10 (s, 3H); HRMS (ESI) calcd for 210.0633 ($[M+H]^+$), found 210.0635 ($[M+H]^+$).

Procedure for synthesis of 6:



5 **6**

A suspension of **5** (61 mg, 0.20 mmol) and NaH (60 % in oil, 9 mg, 0.22 mmol) in dry DMF (2 mL) under N_2 was stirred at 0^oC for 30 min, then the 4-(bromomethyl)-1-chloro-2-fluorobenzene (44 mg, 0.20 mmol) was added and the mixture was allowed to warm to room temperature and stirred 1 h, diluted with EtOAc (10 mL) and washed brine. The combined organic phase was dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, the crude product was purified on a silica gel column on a silica gel column to afford the product **6** as pale yellow solid. Yield 49 mg (55%). Mp 262-263^oC; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.41 (s, 1H), 10.31 (d, *J* = 2.0 Hz, 1H), 8.81 (s, 1H), 7.88 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.37 (m, 2H), 7.33 – 7.17 (m, 5H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.09 (s, 2H), 2.13 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ: 169.6, 167.6, 157.5 (d, *J* = 245.6 Hz), 143.9 (d, *J* = 6.2 Hz), 140.6, 134.9, 133.3, 130.7, 128.7, 127.6, 127.1, 126.3, 125.8 (d, *J* = 2.6 Hz), 125.7, 120.1, 117.6, 116.9 (d, *J* = 17.3 Hz), 116.8 (d, *J* = 20.5 Hz), 111.2, 99.3, 43.0, 28.0, 23.6. IR (KBr): 3274.54, 2919.70, 2850.27, 1666.20, 1631.48, 1608.34, 1535.06, 1496.49, 1454.06, 1267.00, 1060.66, 696.1; HRMS (ESI) calcd for 450.1385 ($[M+H]^+$), found 450.1379 ($[M+H]^+$).

Bioactivity Assays:[S6]

Transient Co-transfection Assays

Cos-7 cells from ATCC were grown to 70% confluence in DMEM containing 10% fetal bovine serum (FBS). For assessing full-length PPAR receptors, Cos-7 cells were transiently co-transfected with a plasmid containing the luciferase gene under the control of three tandem PPAR response elements (100 ng) (PPRE × 3 TK-luciferase) and 50 ng of full-length hPPARγ plasmids using lipofectamine 2000 (Invitrogen) along with the standard 10 ng of renilla luciferase gene. 24 hrs after transfection the cells were treated with 0.1, 1 and 10 μM concentrations of rosiglitazone and compound **6**, for 24 hours. Reporter luciferase assay kits from Promega were used to measure the luciferase activity, according to the manufacturer's instructions, with a luminometer (Envision, Perkin–Elmer). Luciferase activity was normalized by renilla units. Each condition was performed with $n \geq 3$ for each experiment.

TR-FRET Competitive Binding Assay

The GST PPARγ-LBD was labeled with a terbium-linked antibody and a fluorescent small molecule pan-PPAR ligand (Fluormone™ Pan-PPAR Green) is used as a tracer that is displaced by the ligand binding domain upon agonist binding. Excitation of the terbium at 340 nm results in FRET to the fluorescent tracer, with emissions detected at 520 nm and 495 nm. Upon ligand binding, the tracer is displaced from the PPARγ-LBD and there is a loss of FRET signal between the terbium label and the fluorescent tracer.

3T3-L1 differentiation assay

3T3-L1 preadipocytes from ATCC were maintained in DMEM containing 10% FBS and antibiotics. For differentiation DMI (Dexamethazone 1 μM, 3-isobutyl-1-methyxanthine (IBMX) 0.5 mM and Insulin 850 nM) and 1μM of rosiglitazone were used as positive controls for the assay. Compound **6** was used at a 1μM concentration. All the treatments have insulin at 850nM concentration. Media with DMSO was used as a negative control. Differentiation was induced by treating post-confluent cultures with media containing the respective ligands for two days. The media was changed every two days, and on day 8 cells were stained with Oil red O and DAPI to estimate the lipid accumulation. The amount stained by Oil Red to DAPI is differentiation ratio.

References

[S1] Y. Li, B.-J. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2011, **50**, 2115.

[S2] L. Ackermann and A. V. Lygin, *Org. Lett.*, 2011, **13**, 3332.

[S3] J.-J. Shi, B. Zhou, Y.-X. Yang and Y.-C. Li, *Org. Biomol. Chem.*, 2012, **10**, 8953.

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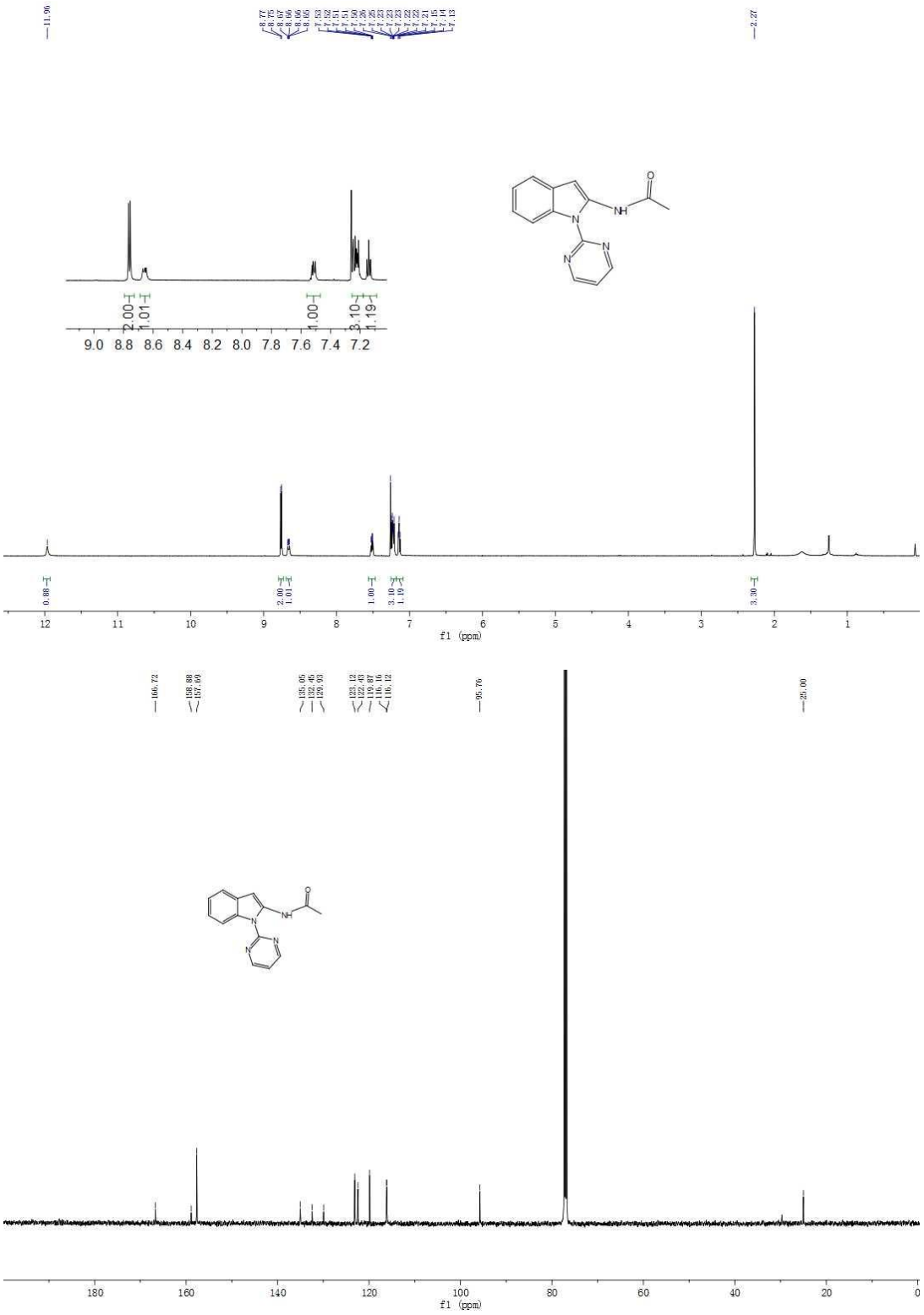
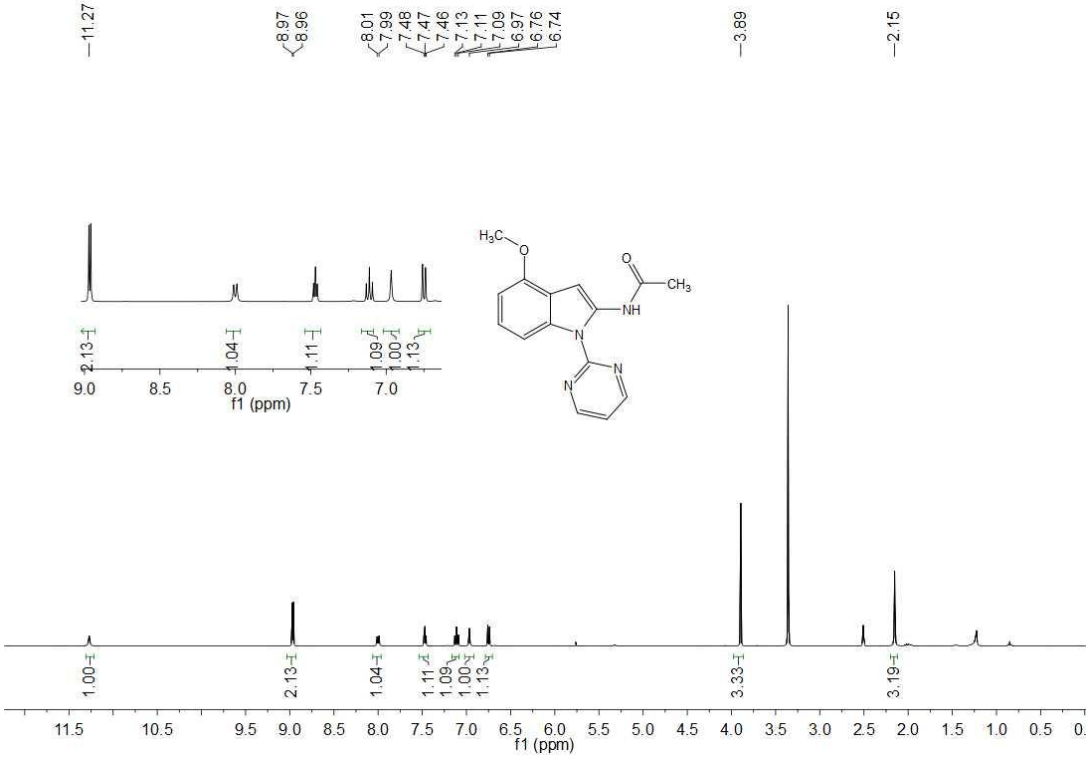
^{1}H and ^{13}C NMR spectra of products

3a



3f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8.96
8.01
7.99
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7.11
7.09
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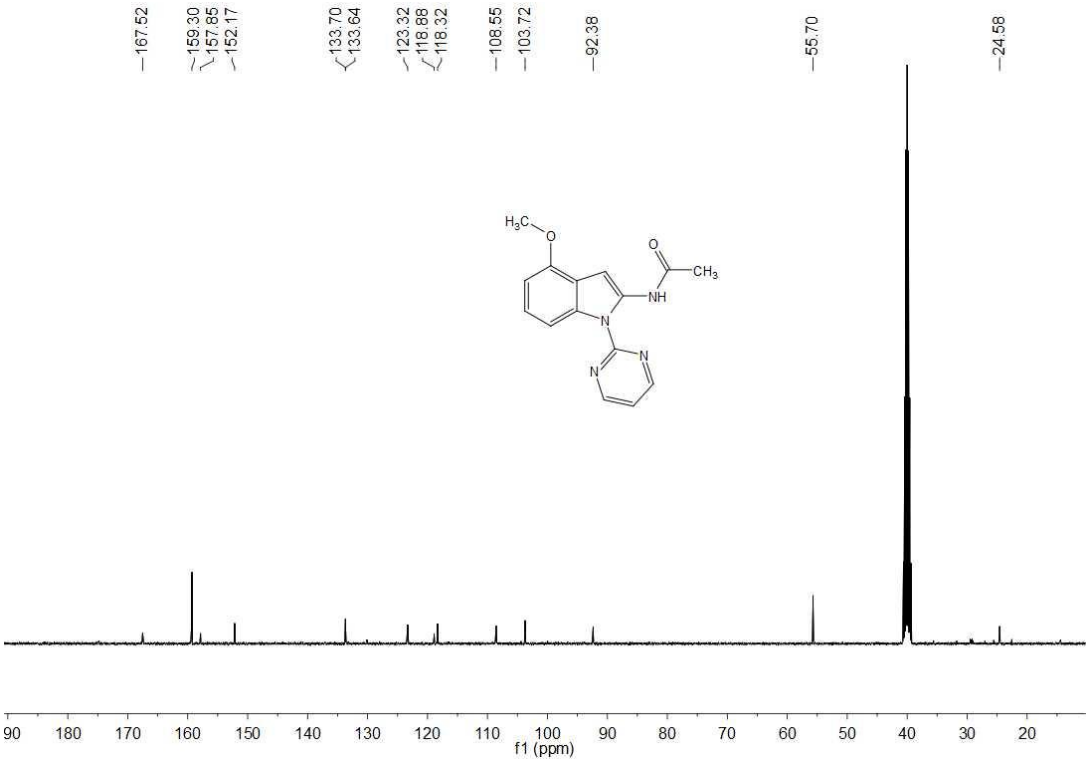
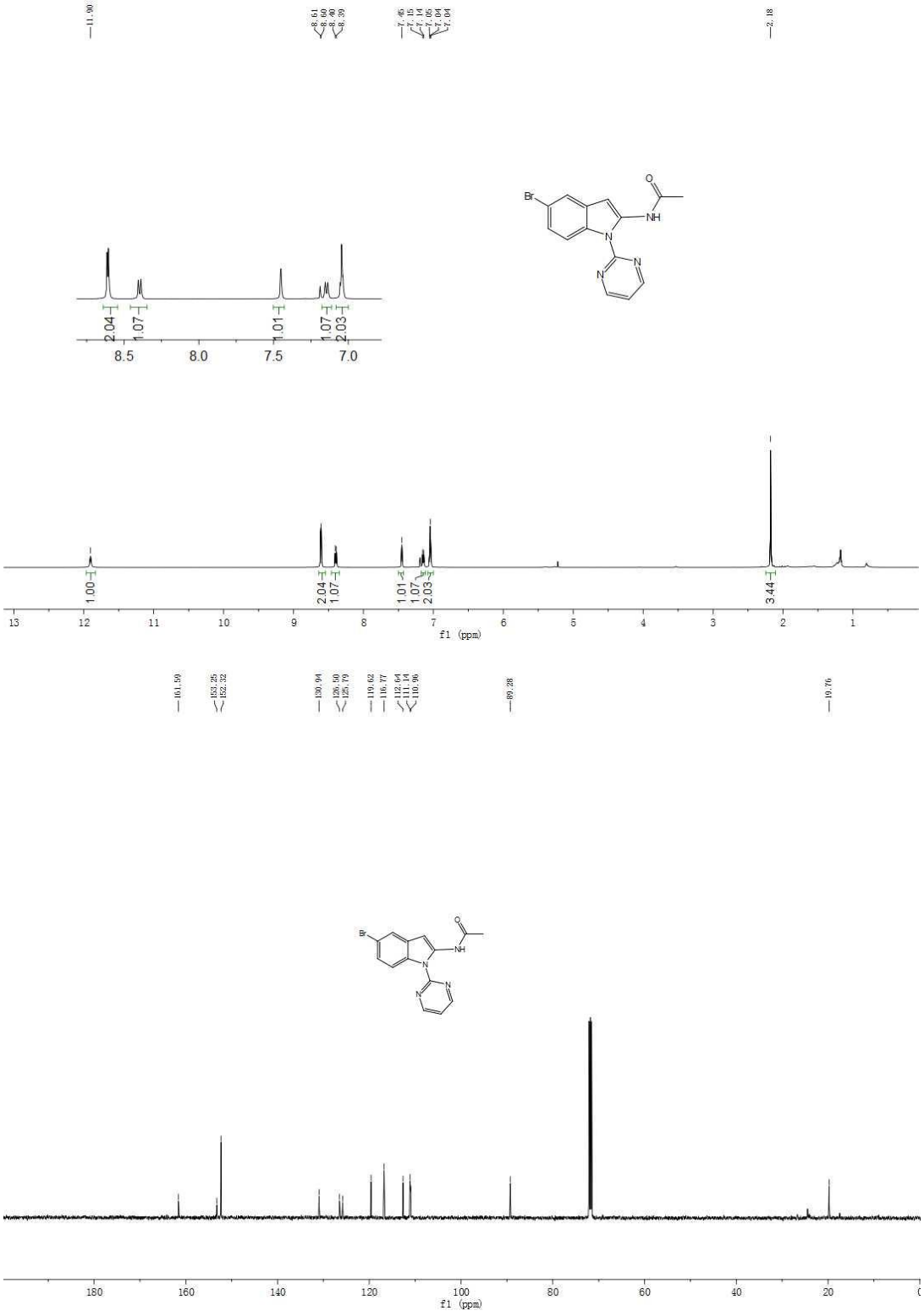
6.76
6.74
3.89
2.15
f1 (ppm)


167.52
159.30
157.85
152.17
133.70
133.64
123.32
118.88
118.32
108.55
103.72
92.38
55.70
24.58
f1 (ppm)

3g


11.64
8.98
8.97
8.64
8.62
7.61
7.59
7.54
7.53
7.52
7.27
7.25
7.23
7.06
2.22
1.95
1.00
1.93
1.01
0.91
f1 (ppm)
N
O
CH3
NH
N
N
0.94
1.95
1.00
1.93
1.01
0.91
3.03
f1 (ppm)
167.90
159.40
157.37
138.37
132.05
131.45
127.25
122.33
120.22
118.96
118.67
100.61
91.69
24.82
f1 (ppm)

3h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8.61
8.60
8.40
8.39
7.45
7.15
7.14
7.06
7.05
7.04
2.18
Br
O
NH
N
N
N
2.04
1.07
1.01
1.07
2.03
8.5
8.0
7.5
7.0
1.00
2.04
1.07
1.01
1.07
2.03
3.44
13
12
11
10
9
8
7
6
5
4
3
2
1
f1 (ppm)
161.59
153.25
152.32
130.94
126.50
125.79
119.62
116.77
112.64
111.14
110.96
89.28
30.76
Br
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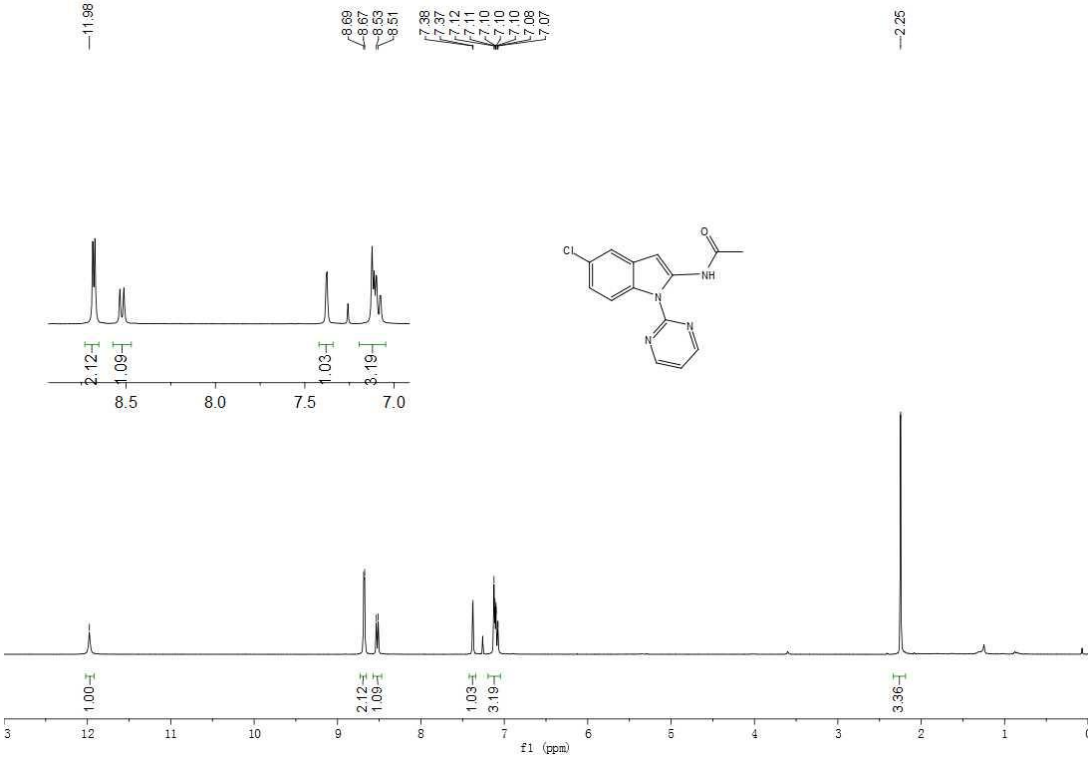
N
N
N
180
160
140
120
100
80
60
40
20
f1 (ppm)

3i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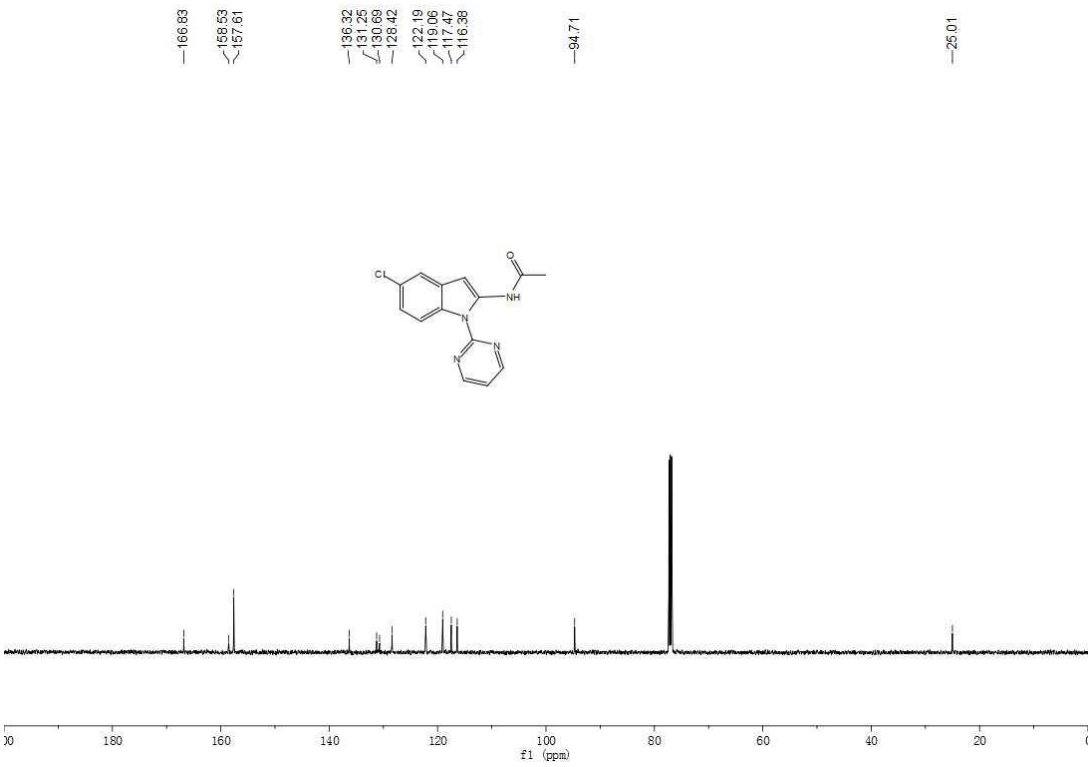
8.69
8.67
8.53
8.51
7.38
7.37
7.12
7.11
7.10
7.10
7.10
7.08
7.07
2.25
2.12
1.09
1.03
3.19
8.5
8.0
7.5
7.0
Cl
O
NH
N
N
1.00
2.12
1.09
1.03
3.19
3.36
f1 (ppm)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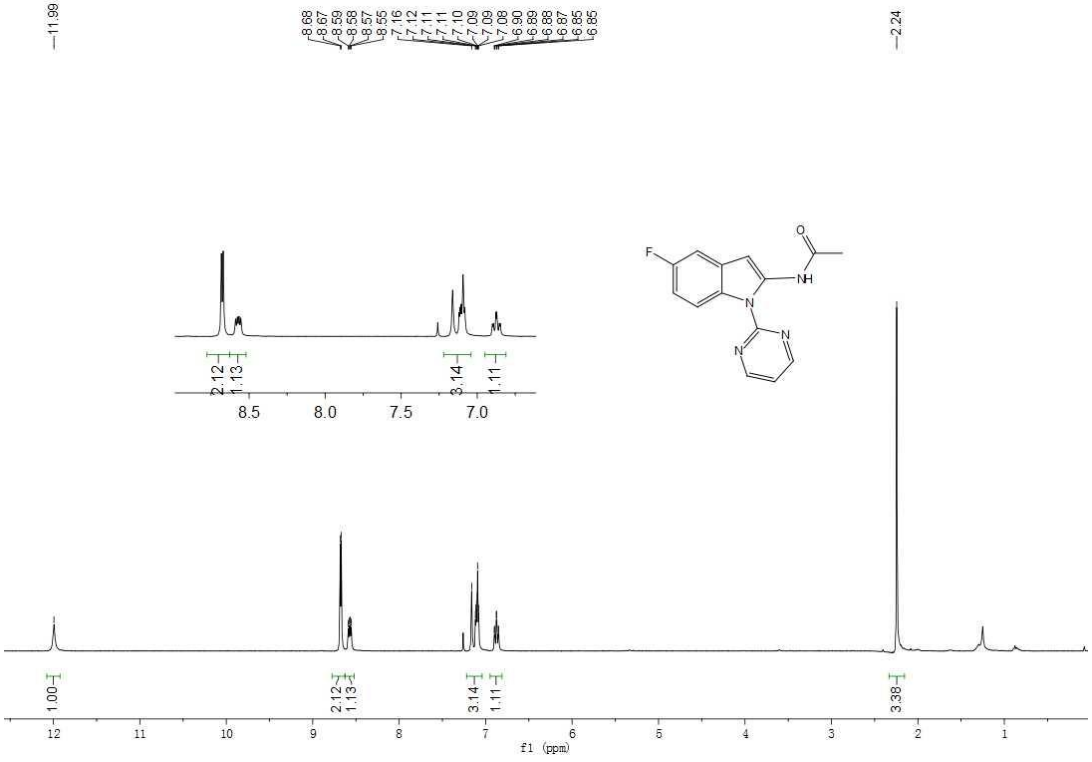
158.53
157.61
136.32
131.25
130.69
128.42
122.19
119.06
117.47
116.38
94.71
25.01
Cl
O
NH
N
N
f1 (ppm)

3j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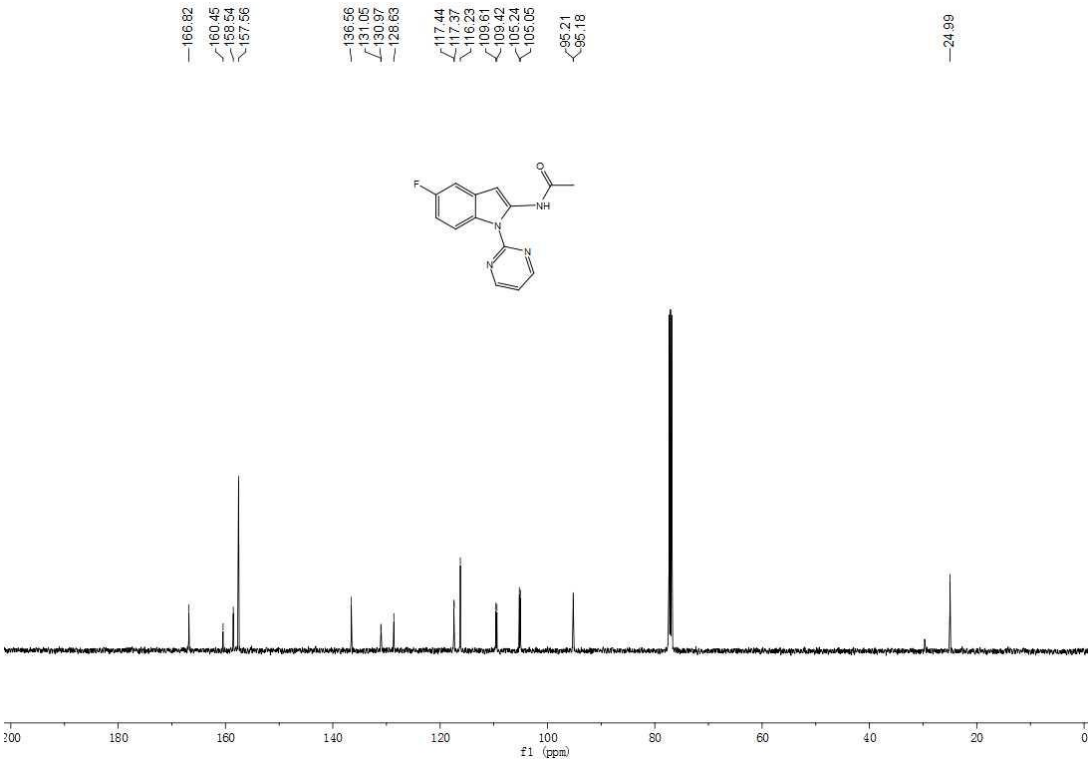
8.67
8.59
8.58
8.57
8.55
7.16
7.12
7.11
7.11
7.10
7.09
7.09
7.08
6.90
6.89
6.88
6.87
6.85
6.85
2.24
F
O
NH
N
N
N
2.12
1.13
3.14
1.11
8.5
8.0
7.5
7.0
1.00
2.12
1.13
3.14
1.11
3.38
12
11
10
9
8
7
6
5
4
3
2
1
f1 (ppm)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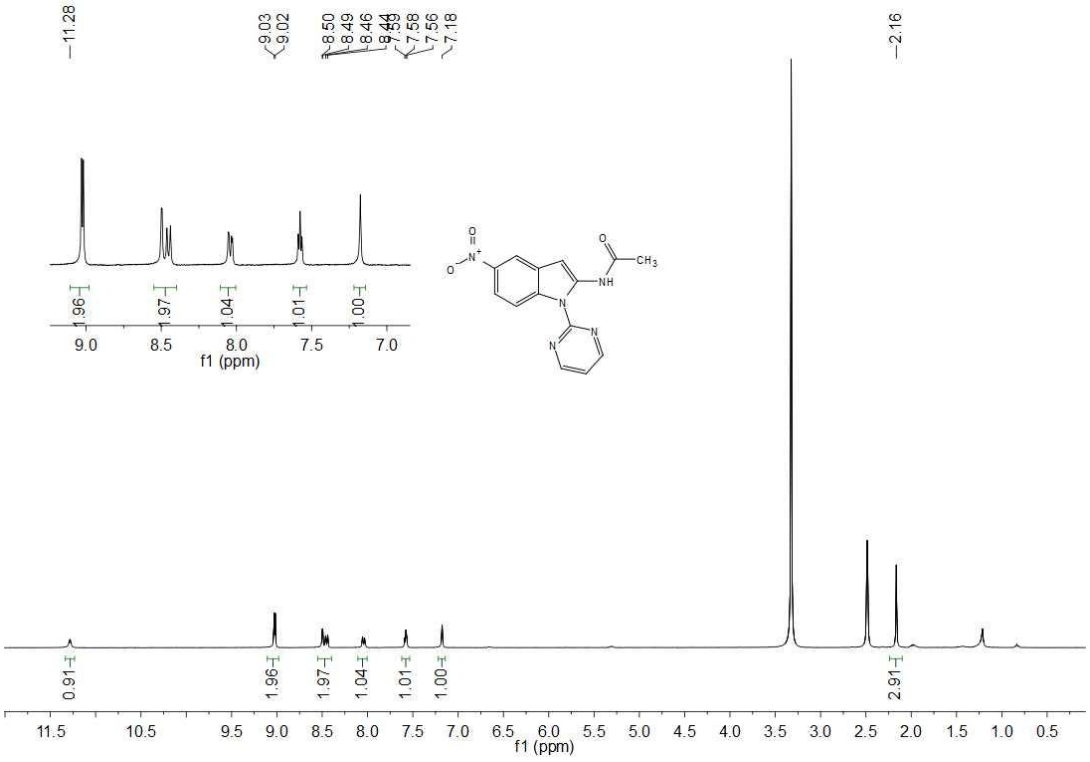
160.45
158.54
157.56
136.56
131.05
130.97
128.63
117.44
117.37
116.23
109.61
109.42
105.24
105.05
95.21
95.18
24.99
F
O
NH
N
N
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

3k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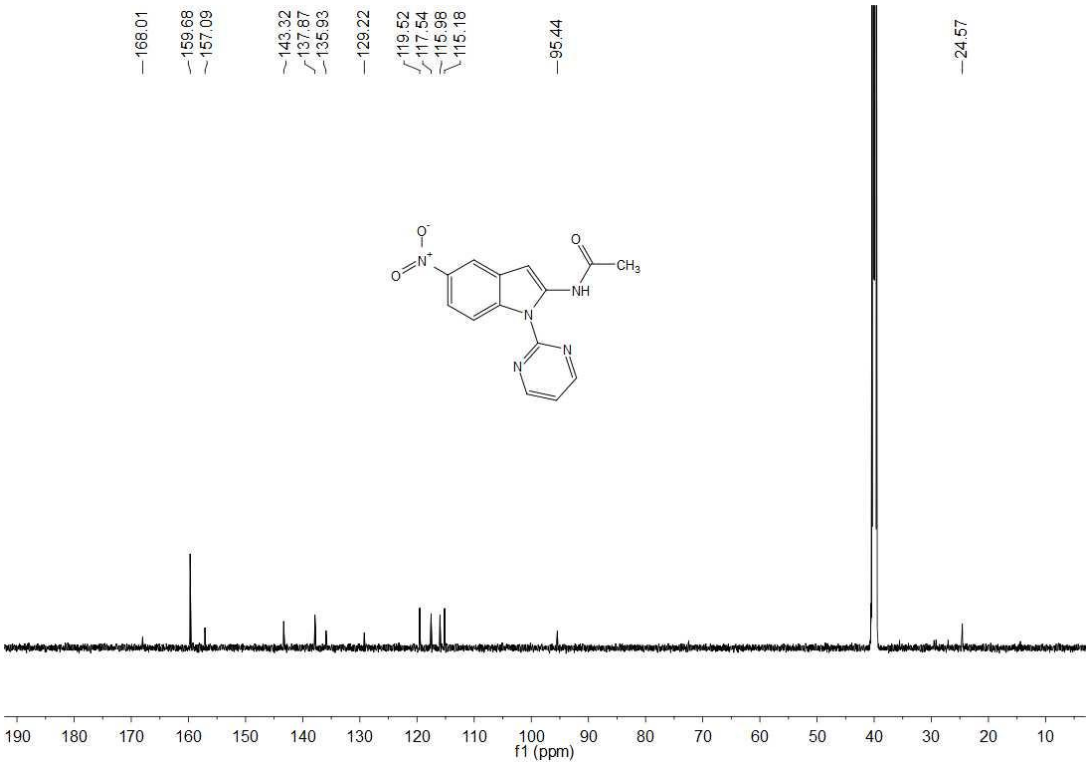
9.03
9.02
8.50
8.49
8.46
8.44
7.59
7.58
7.56
7.18
2.16
1.96
1.97
1.04
1.01
1.00
f1 (ppm)
0.91
1.96
1.97
1.04
1.01
1.00
2.91
f1 (ppm)


168.01
159.68
157.09
143.32
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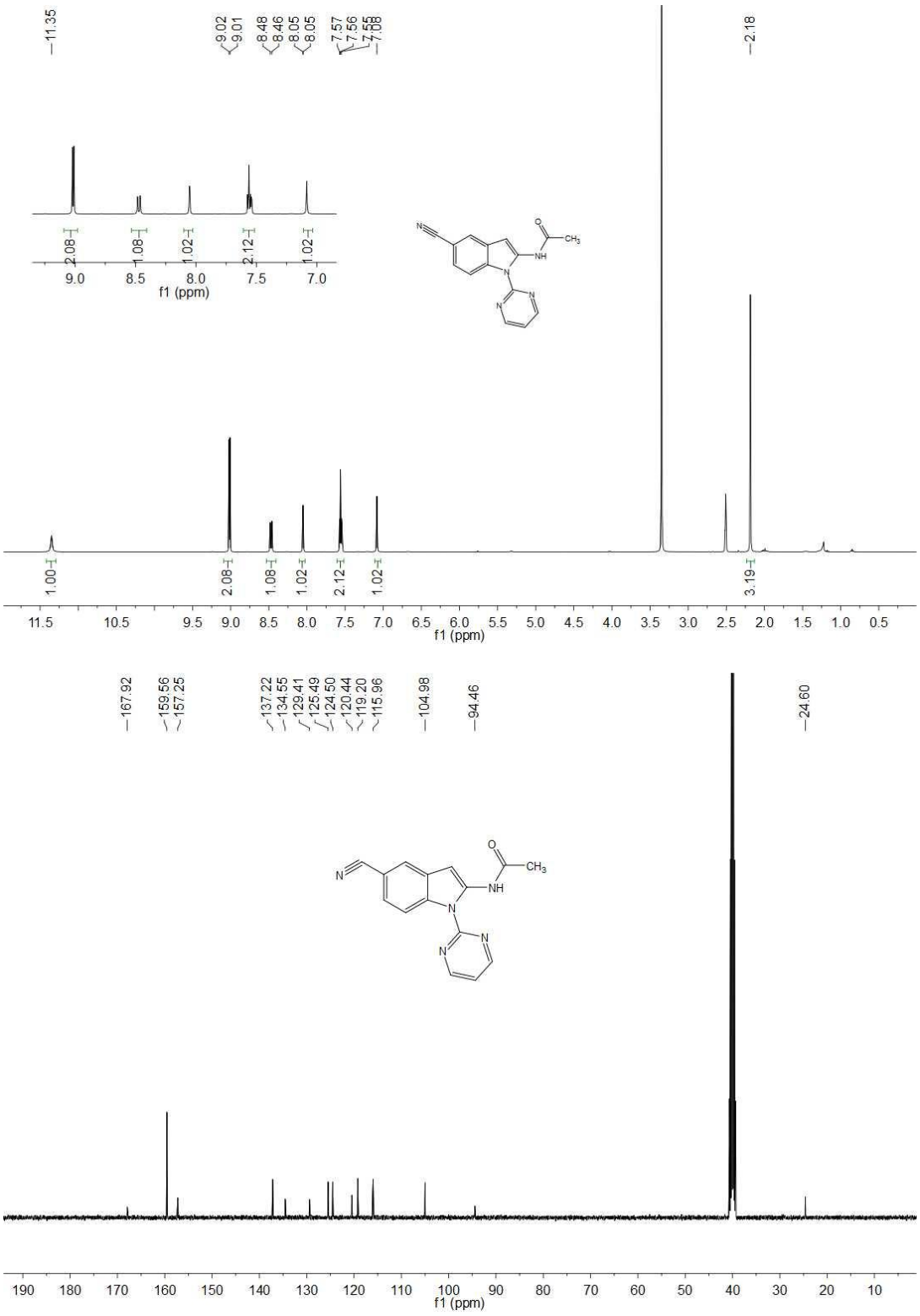
129.22
119.52
117.54
115.98
115.18
95.44
24.57
f1 (ppm)

3l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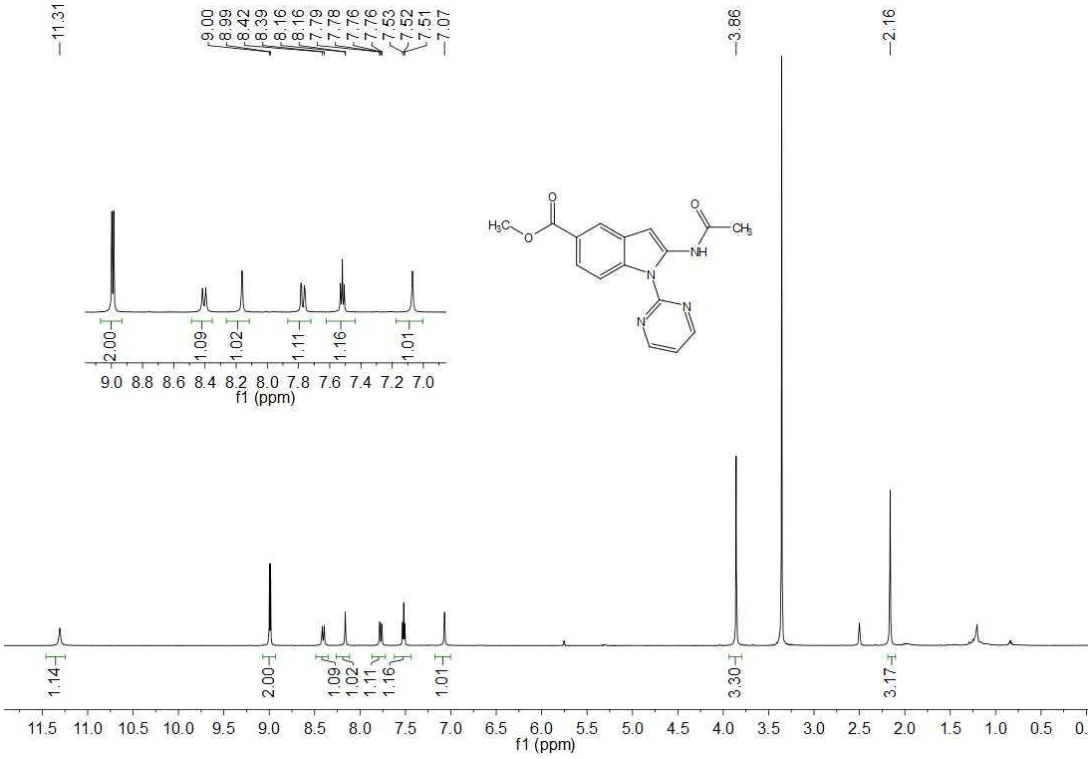
9.02
9.01
8.48
8.46
8.05
8.05
7.57
7.56
7.55
7.53
2.18
2.08
1.08
1.02
2.12
1.02
9.0
8.5
8.0
7.5
7.0
f1 (ppm)
1.00
2.08
1.08
1.02
2.12
1.02
3.19
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
167.92
159.56
157.25
137.22
134.55
129.41
125.49
124.50
120.44
119.20
115.96
104.98
94.46
24.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

3m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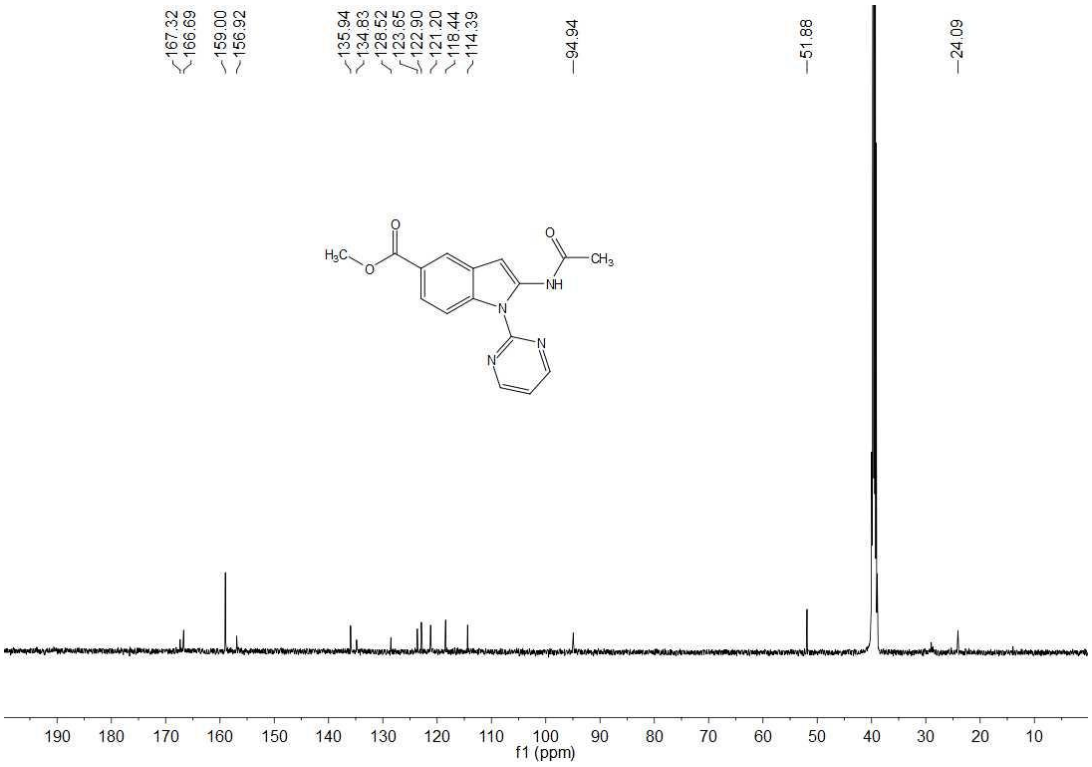
8.42
8.39
8.16
8.16
7.79
7.78
7.76
7.76
7.53
7.52
7.51
7.07
3.86
2.16
2.00
1.09
1.02
1.11
1.16
1.01
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)
1.14
2.00
1.09
1.02
1.11
1.16
1.01
3.30
3.17
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)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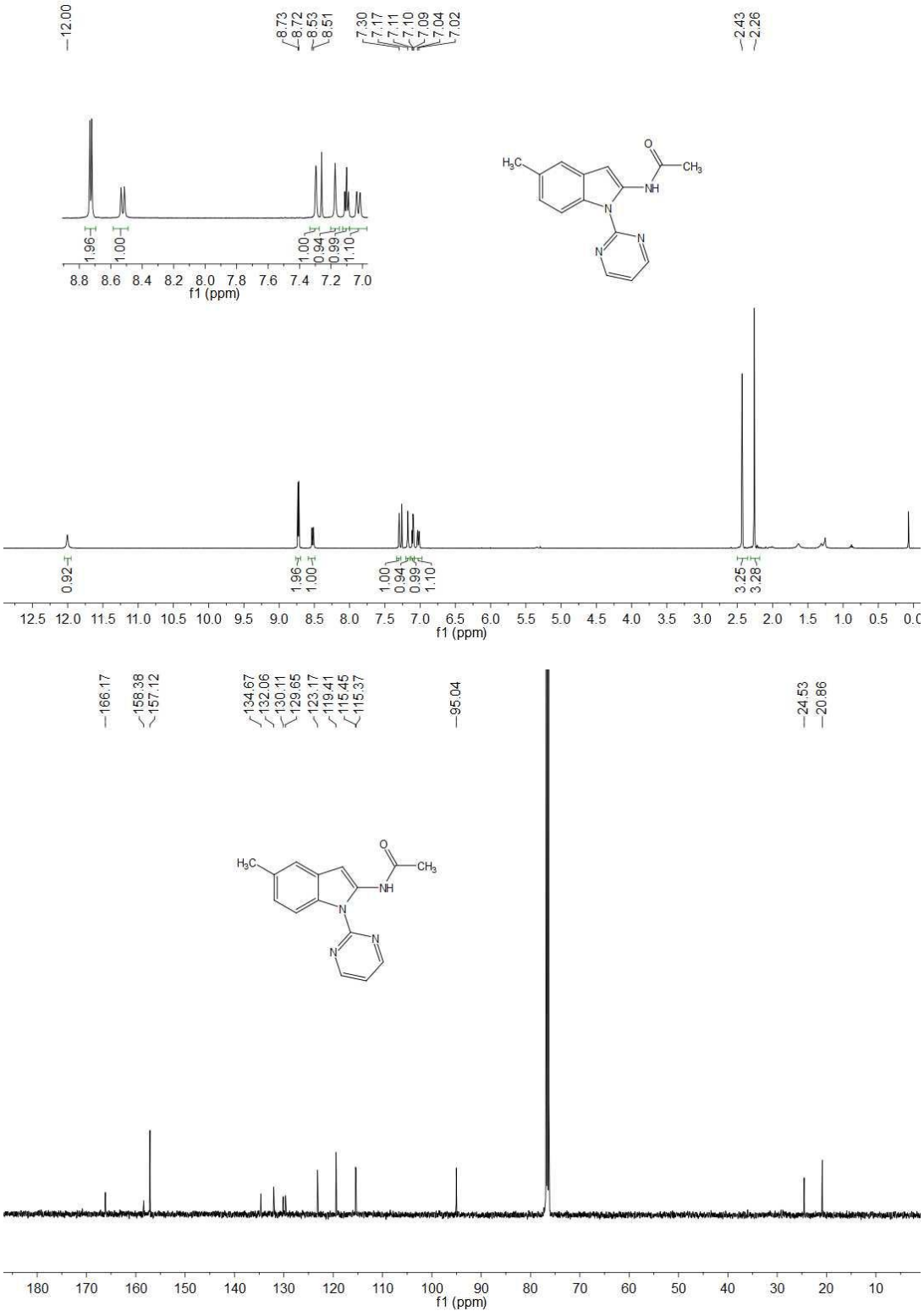
166.69
159.00
156.92
135.94
134.83
128.52
123.65
122.90
121.20
118.44
114.39
94.94
51.88
24.09
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

3n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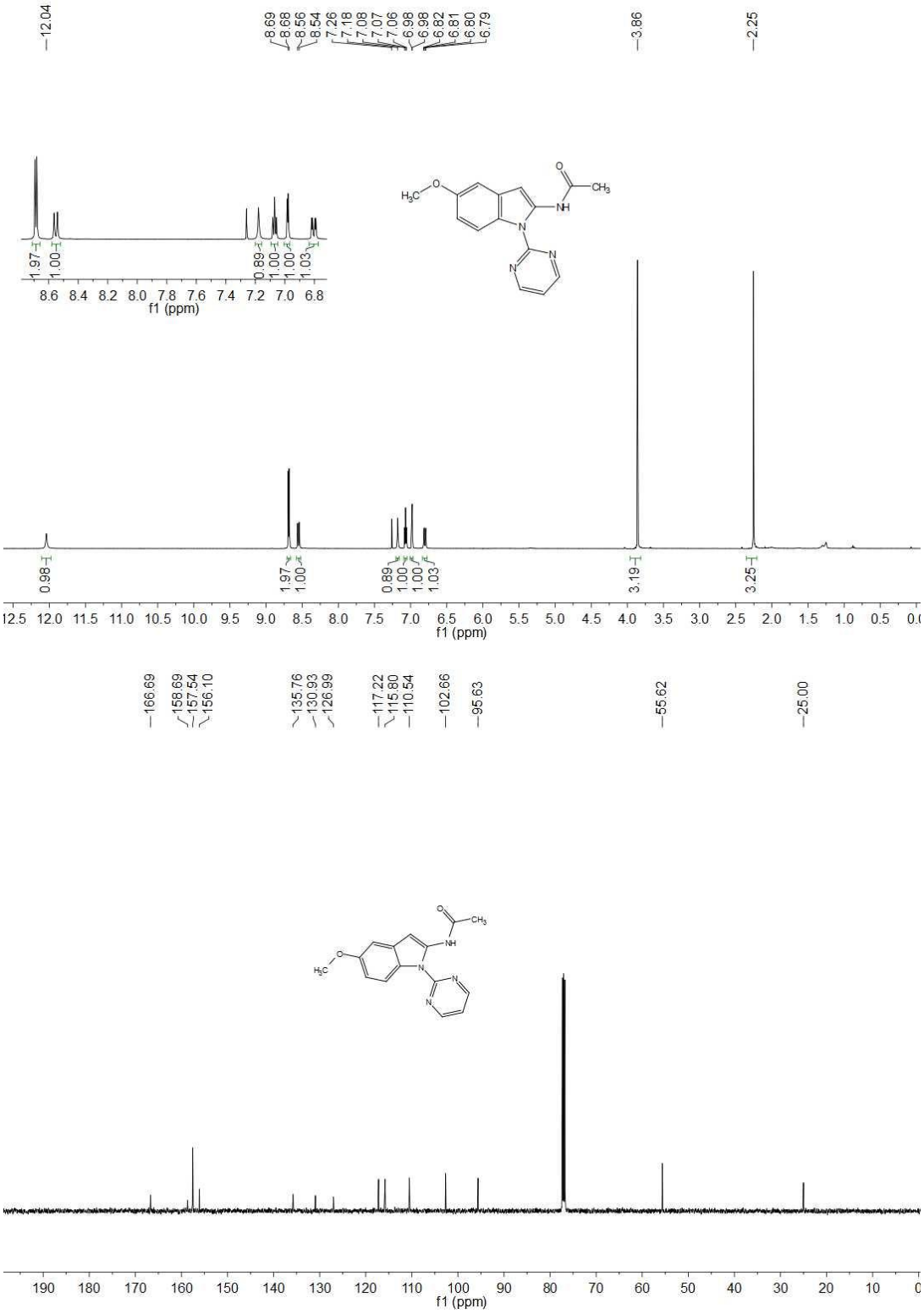
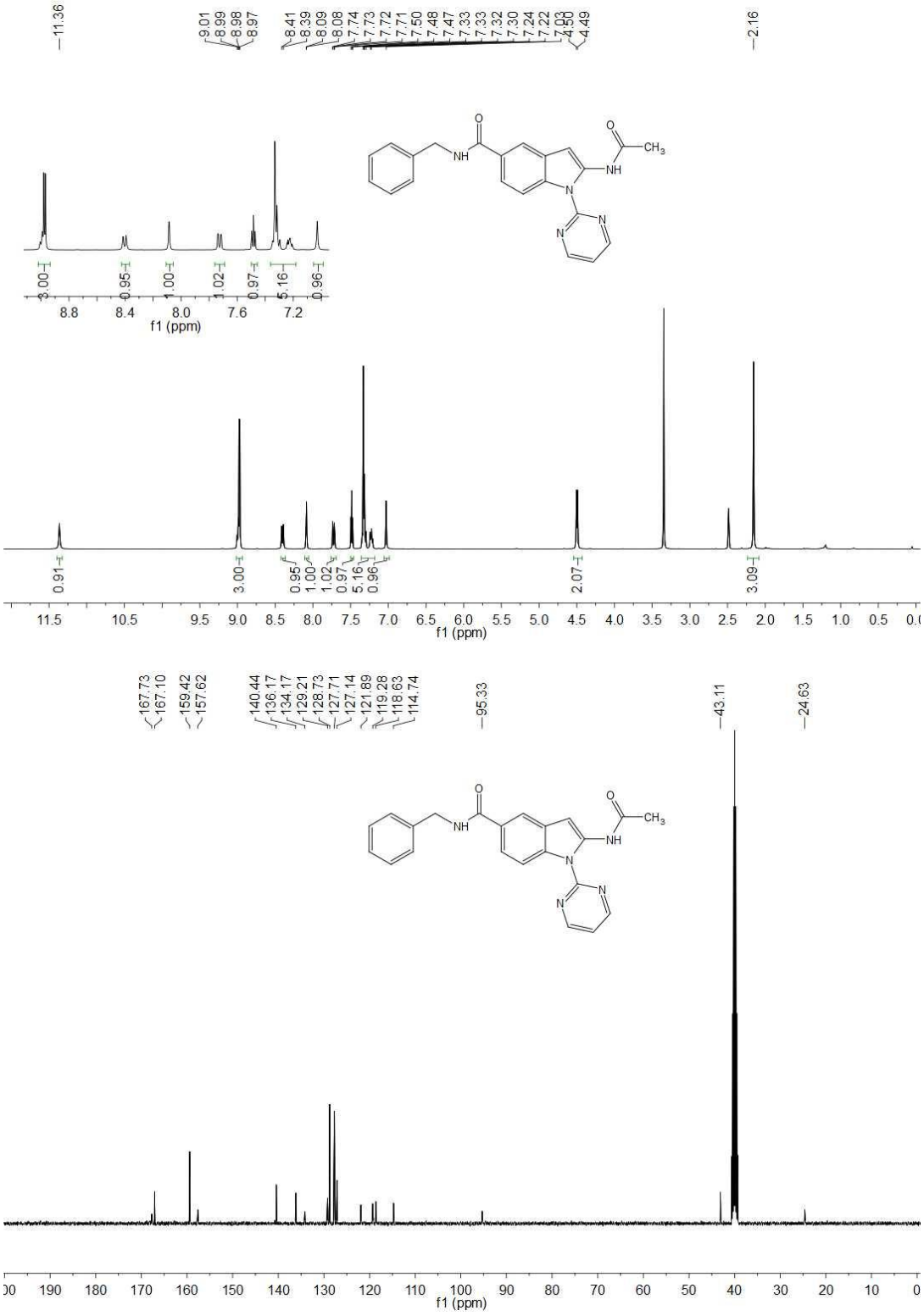
8.73
8.72
8.53
8.51
7.30
7.17
7.11
7.10
7.09
7.04
7.02
2.43
2.26
1.96
1.00
1.00
0.94
0.99
1.10
f1 (ppm)
0.92
1.96
1.00
1.00
0.94
0.99
1.10
3.25
3.28
f1 (ppm)
166.17
158.38
157.12
134.67
132.06
130.11
129.65
123.17
119.41
115.45
115.37
95.04
24.53
20.86
f1 (ppm)

3o


12.04
8.69
8.68
8.56
8.54
7.26
7.18
7.08
7.07
7.06
6.98
6.98
6.82
6.81
6.80
6.79
3.86
2.25
1.97
1.00
0.89
1.00
1.00
1.03
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8
f1 (ppm)
H3C
O
NH
CH3
N
N
0.98
1.97
1.00
0.89
1.00
1.00
1.03
3.19
3.25
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
166.69
158.69
157.54
156.10
135.76
130.93
126.99
117.22
115.80
110.54
102.66
95.63
55.62
25.00
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

3p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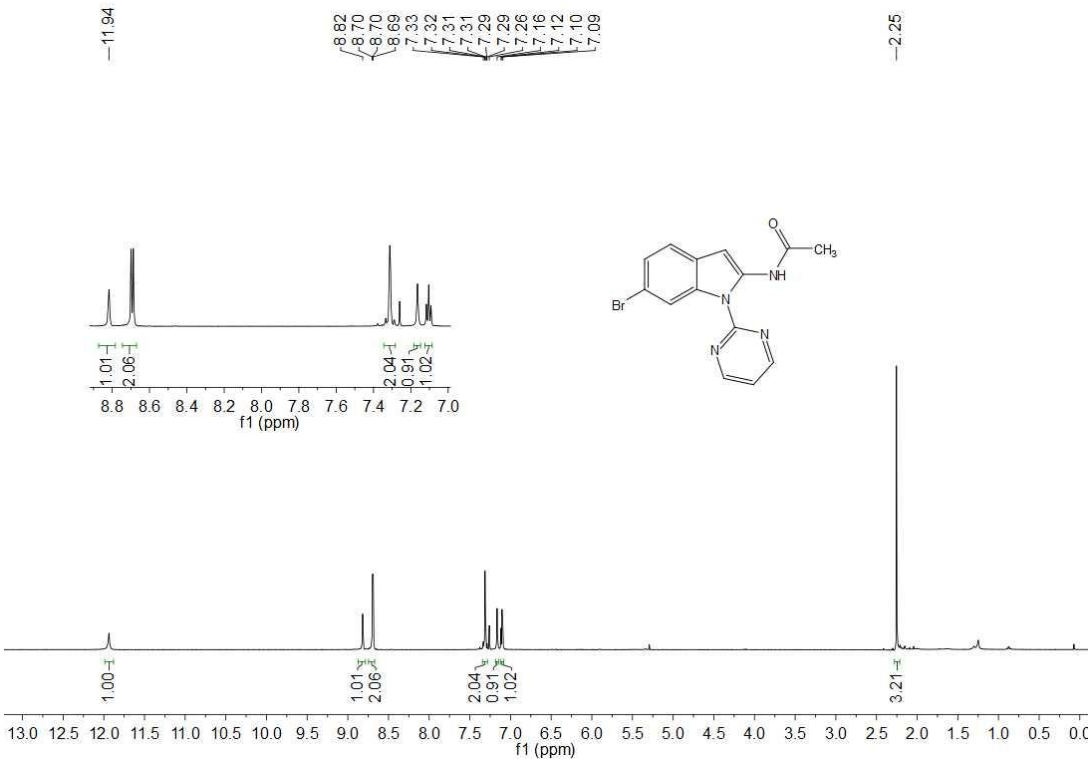
8.09
8.08
7.74
7.73
7.72
7.71
7.50
7.48
7.47
7.33
7.32
7.30
7.24
7.22
7.03
4.49
2.16
NH
O
CH3
N
f1 (ppm)
0.91
3.00
0.95
1.00
1.02
0.97
5.16
0.96
2.07
3.09
167.73
167.10
159.42
157.62
140.44
136.17
134.17
129.21
128.73
127.71
127.14
121.89
119.28
118.63
114.74
95.33
43.11
24.63

3q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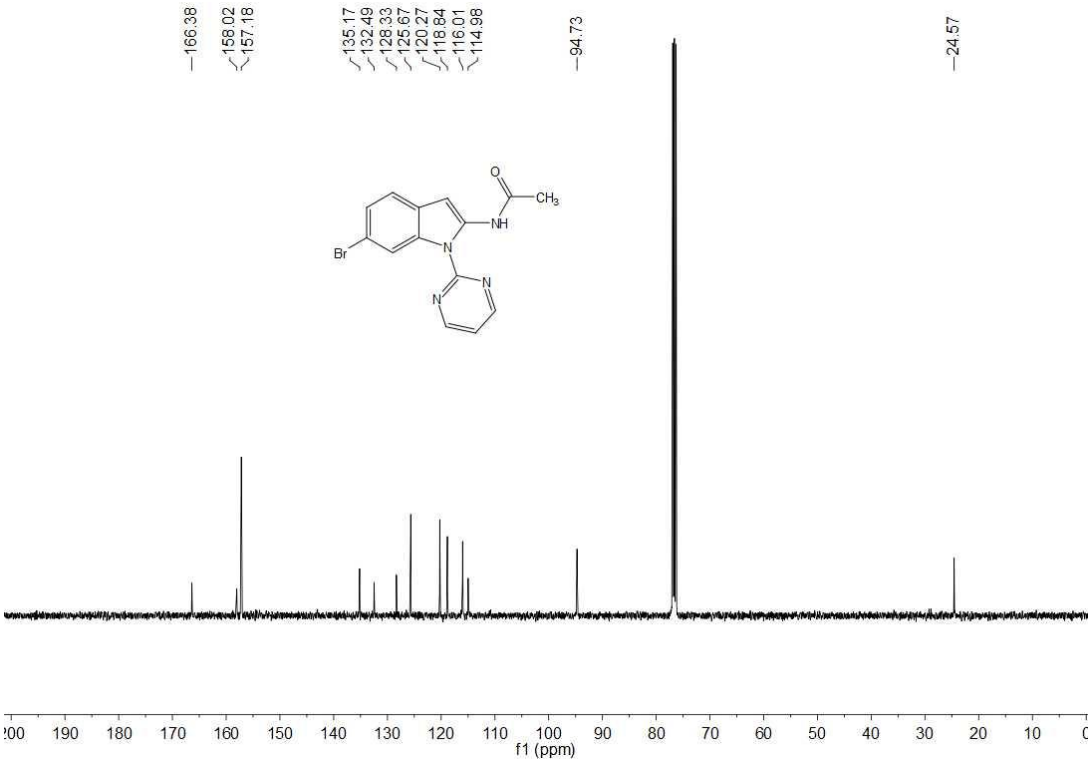
8.70
8.69
7.33
7.32
7.31
7.31
7.29
7.29
7.26
7.16
7.12
7.10
7.09
2.25
1.01
2.06
2.04
0.91
1.02
f1 (ppm)
O
CH3
NH
Br
N
N
N
1.00
1.01
2.06
2.04
0.91
1.02
3.21
f1 (ppm)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135.17
132.49
128.33
125.67
120.27
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116.01
114.98
94.73
24.57
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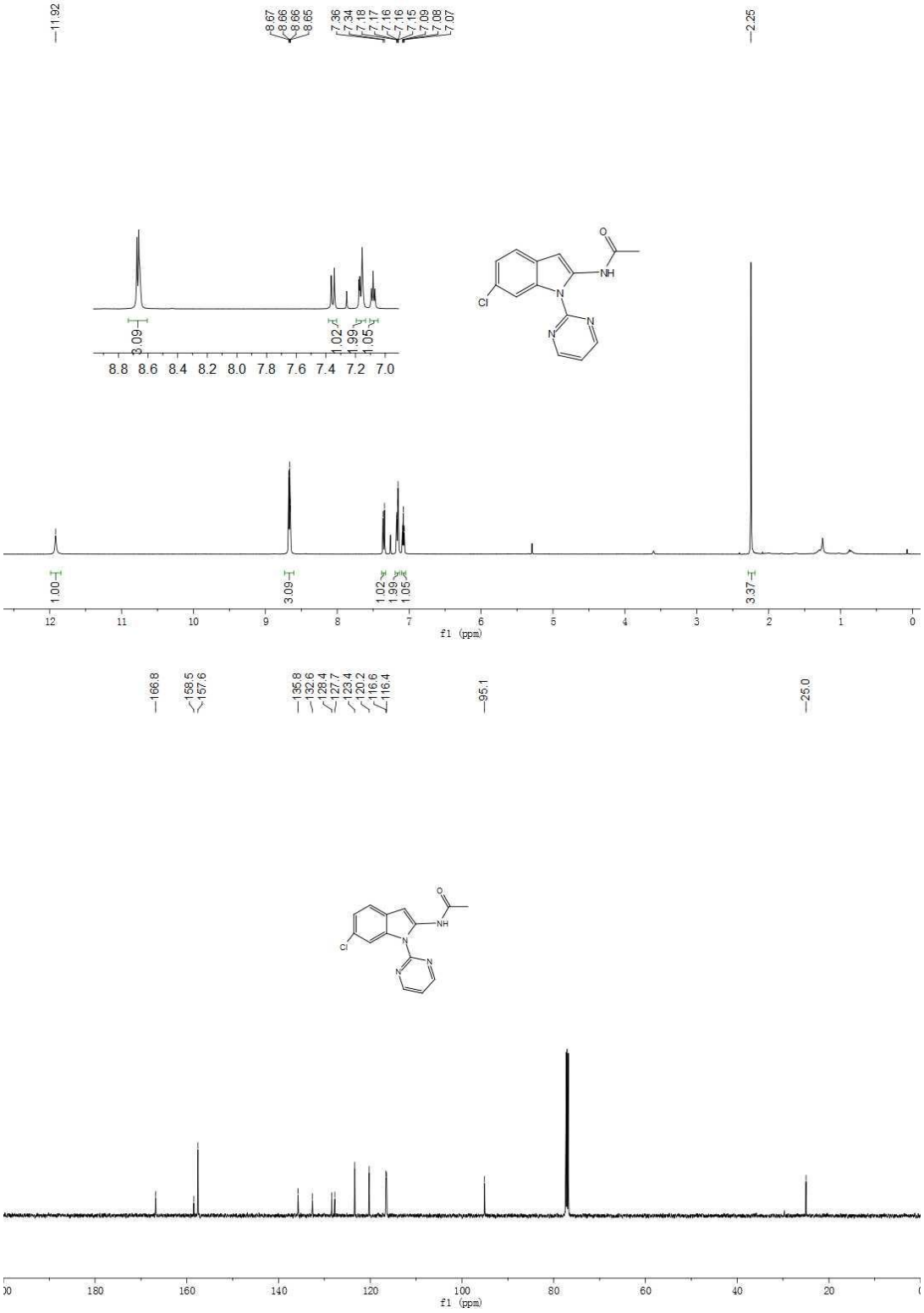
CH3
NH
Br
N
N
N
f1 (ppm)

3r


11.92
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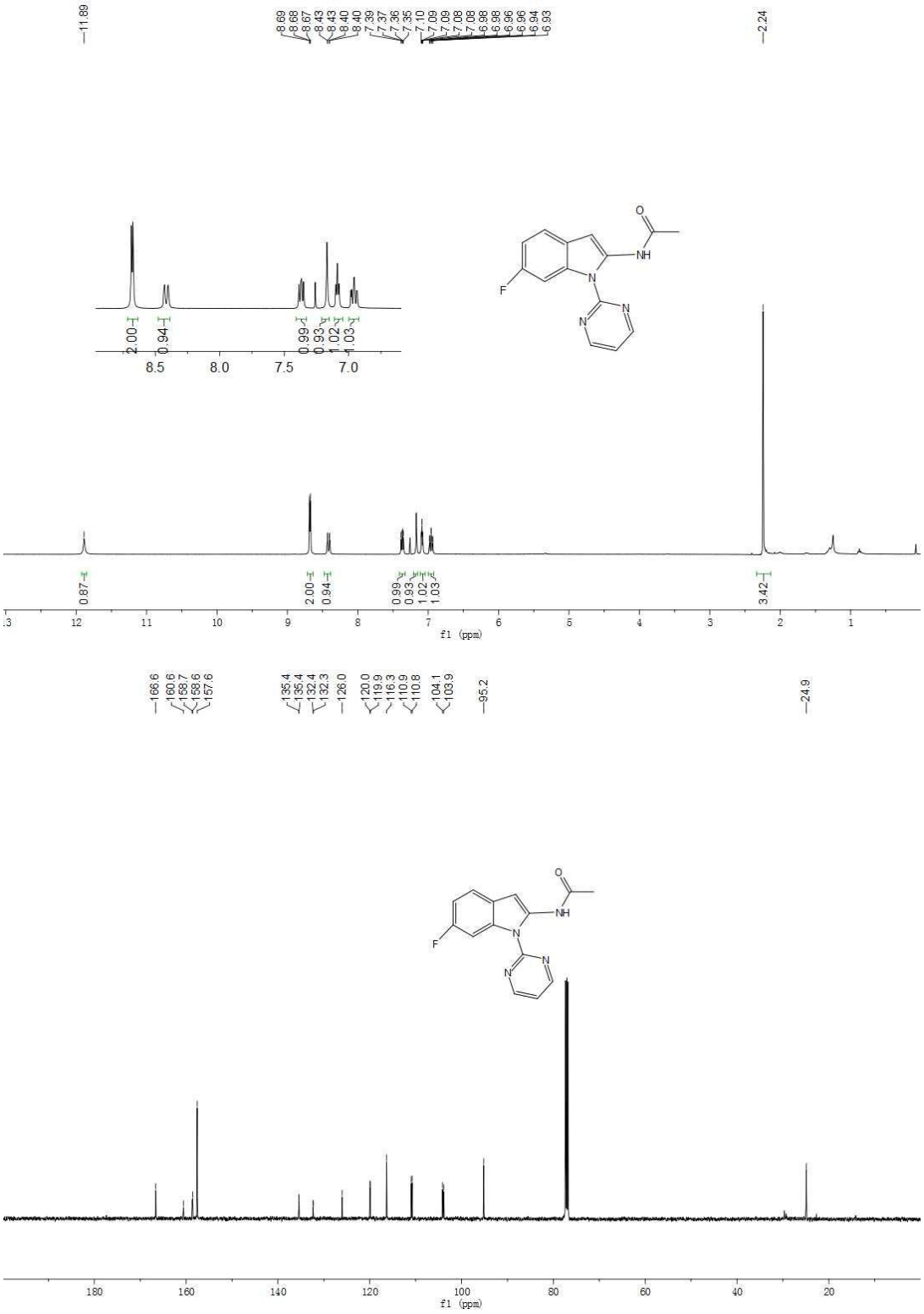
8.66
8.65
7.36
7.34
7.18
7.17
7.16
7.16
7.15
7.09
7.08
7.07
2.25
3.09
1.02
1.99
1.05
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
O
NH
Cl
N
N
1.00
3.09
1.02
1.99
1.05
3.37
12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)
166.8
158.5
157.6
135.8
132.6
128.4
127.7
123.4
120.2
116.6
116.4
95.1
25.0
180 160 140 120 100 80 60 40 20
f1 (ppm)

3s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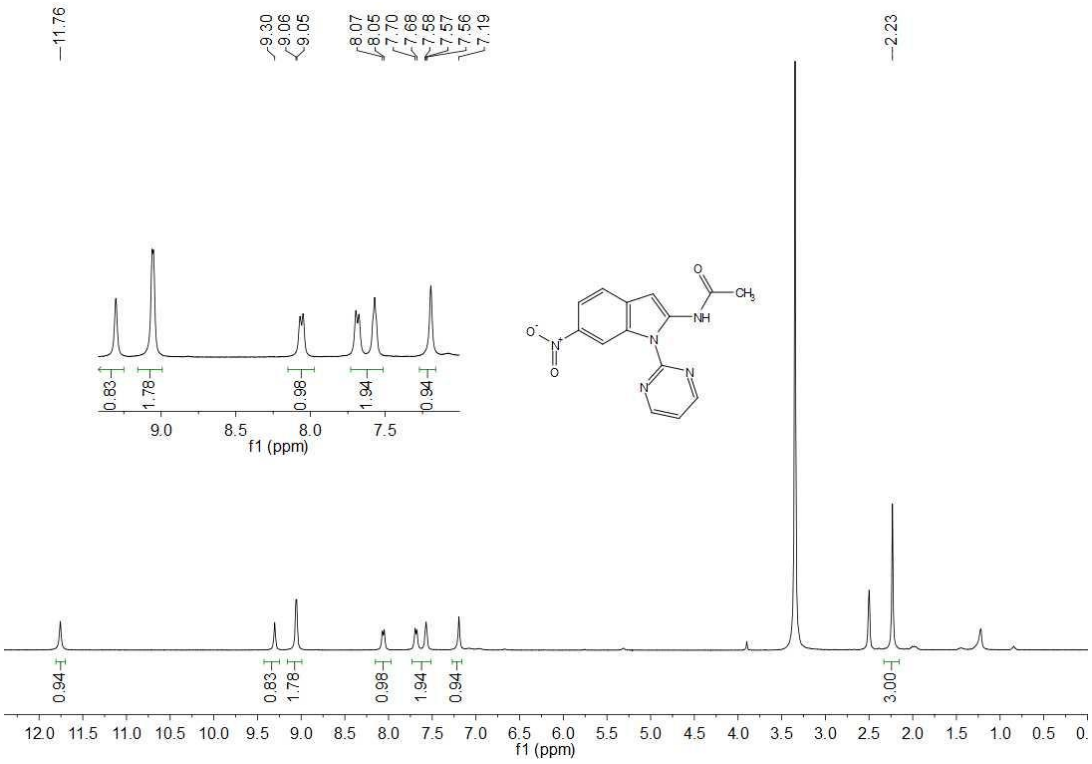
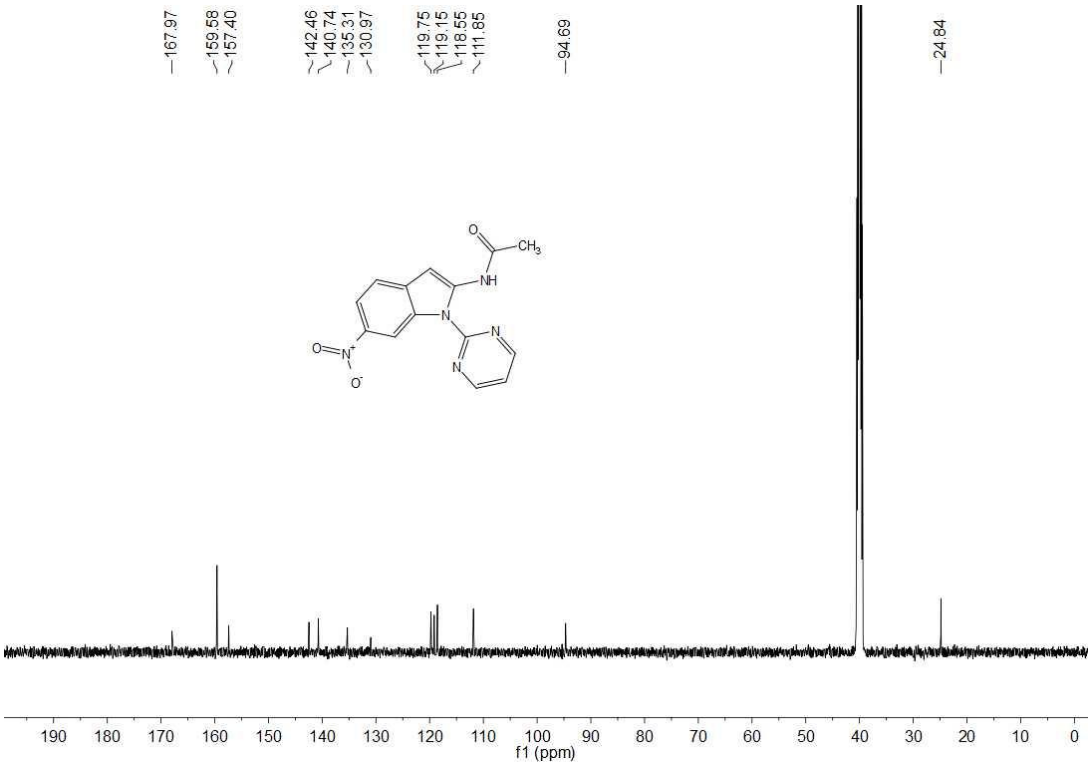
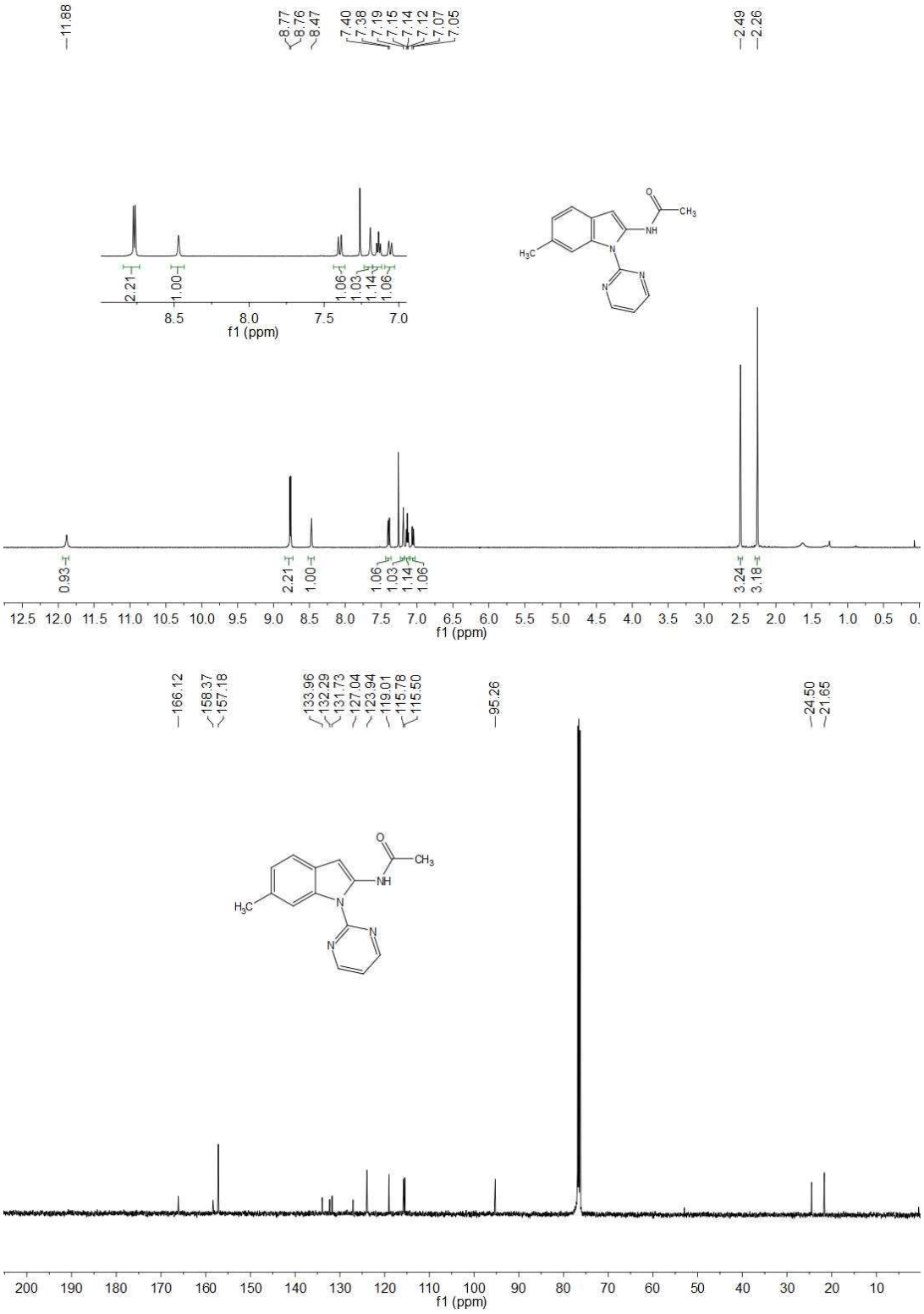
8.69
8.68
8.67
8.43
8.40
8.40
7.39
7.37
7.36
7.35
7.10
7.09
7.09
7.08
7.08
7.08
6.98
6.98
6.96
6.96
6.94
6.93
2.24
O
NH
F
N
N
2.00
0.94
0.99
0.93
1.02
1.03
8.5
8.0
7.5
7.0
0.87
2.00
0.94
0.99
0.93
1.02
1.03
3.42
f1 (ppm)
166.6
160.6
158.7
158.6
157.6
135.4
135.4
132.4
132.3
126.0
120.0
119.9
116.3
110.9
110.8
104.1
103.9
95.2
24.9
f1 (ppm)

3t

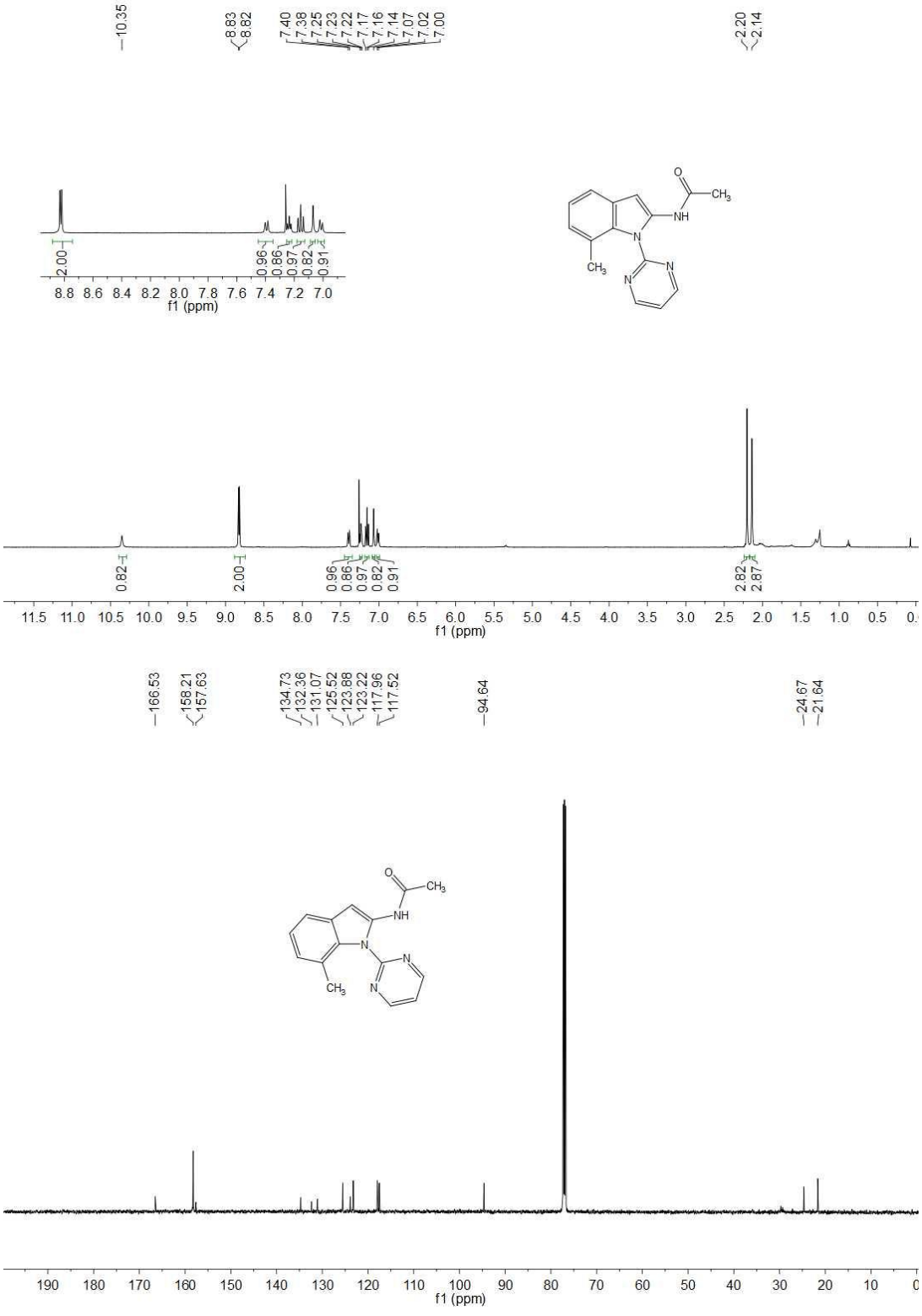

11.76
9.30
9.06
9.05
8.07
8.05
7.70
7.68
7.58
7.57
7.56
7.19
2.23
0.83
1.78
0.98
1.94
0.94
3.00
f1 (ppm)


167.97
159.58
157.40
142.46
140.74
135.31
130.97
119.75
119.15
118.55
111.85
94.69
24.84
f1 (ppm)

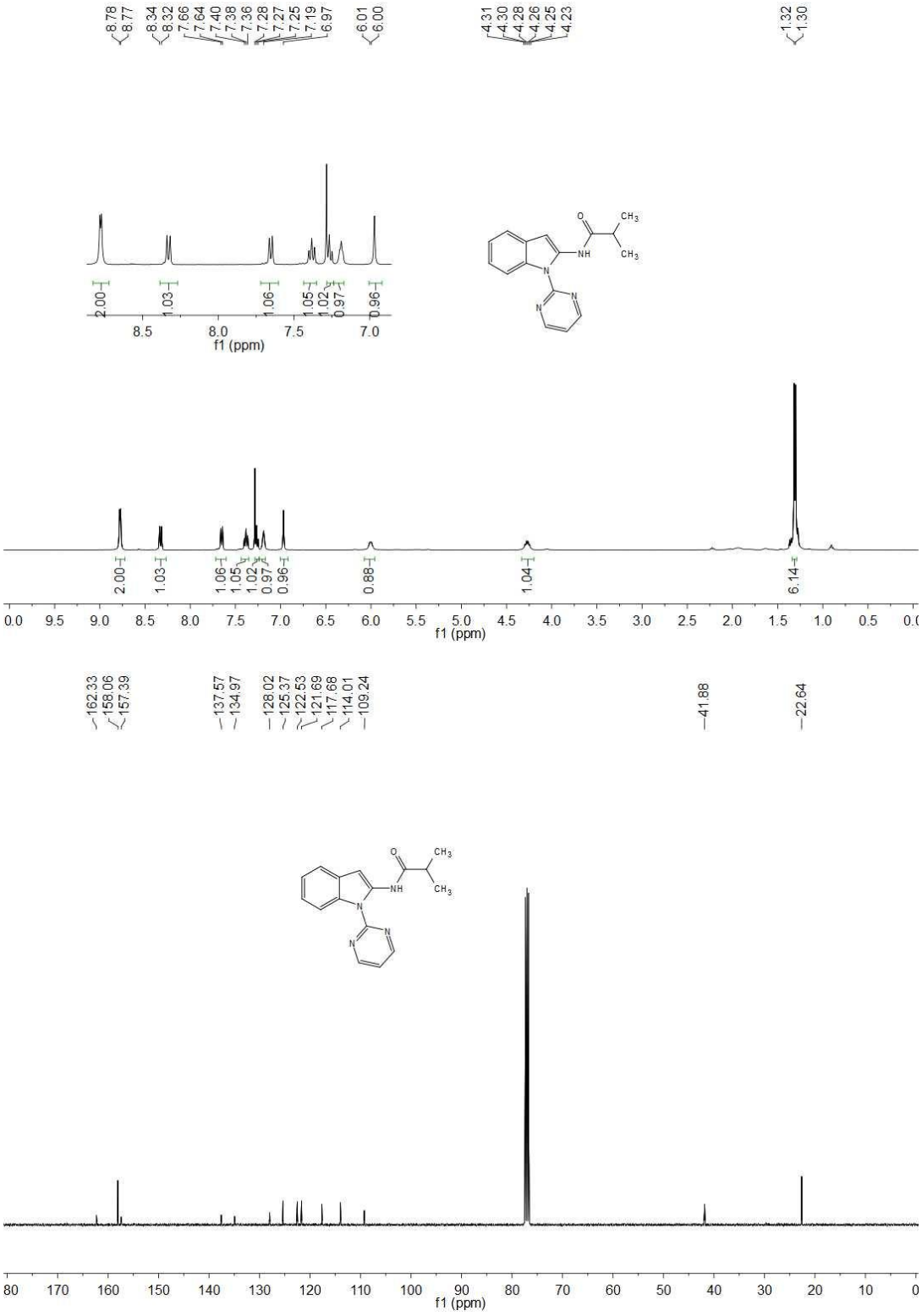
3u


11.88
8.77
8.76
8.47
7.40
7.38
7.19
7.15
7.14
7.12
7.07
7.05
2.49
2.26
2.21
1.00
1.06
1.03
1.14
1.06
8.5
8.0
7.5
7.0
f1 (ppm)
0.93
2.21
1.00
1.06
1.03
1.14
1.06
3.24
3.18
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)
166.12
158.37
157.18
133.96
132.29
131.73
127.04
123.94
119.01
115.78
115.50
95.26
24.50
21.65
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

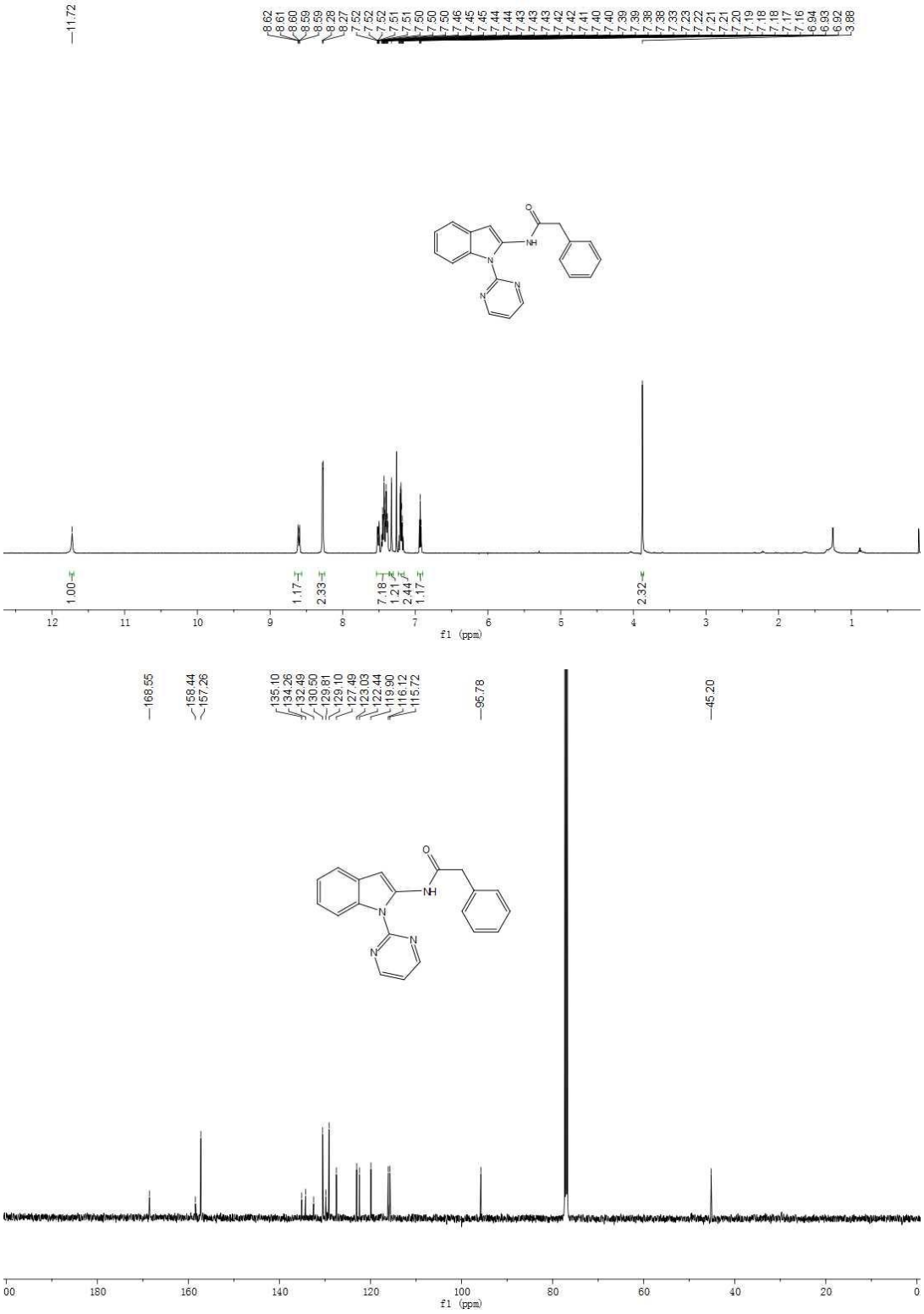
3v


10.35
8.83
8.82
7.40
7.38
7.25
7.23
7.22
7.17
7.16
7.14
7.07
7.02
7.00
2.20
2.14
2.00
0.96
0.86
0.97
0.82
0.91
f1 (ppm)
O
CH3
NH
N
CH3
N
N
0.82
2.00
0.96
0.86
0.97
0.82
0.91
2.82
2.87
f1 (ppm)
166.53
158.21
157.63
134.73
132.36
131.07
125.52
123.88
123.22
117.96
117.52
94.64
24.67
21.64
O
CH3
NH
N
CH3
N
N
f1 (ppm)

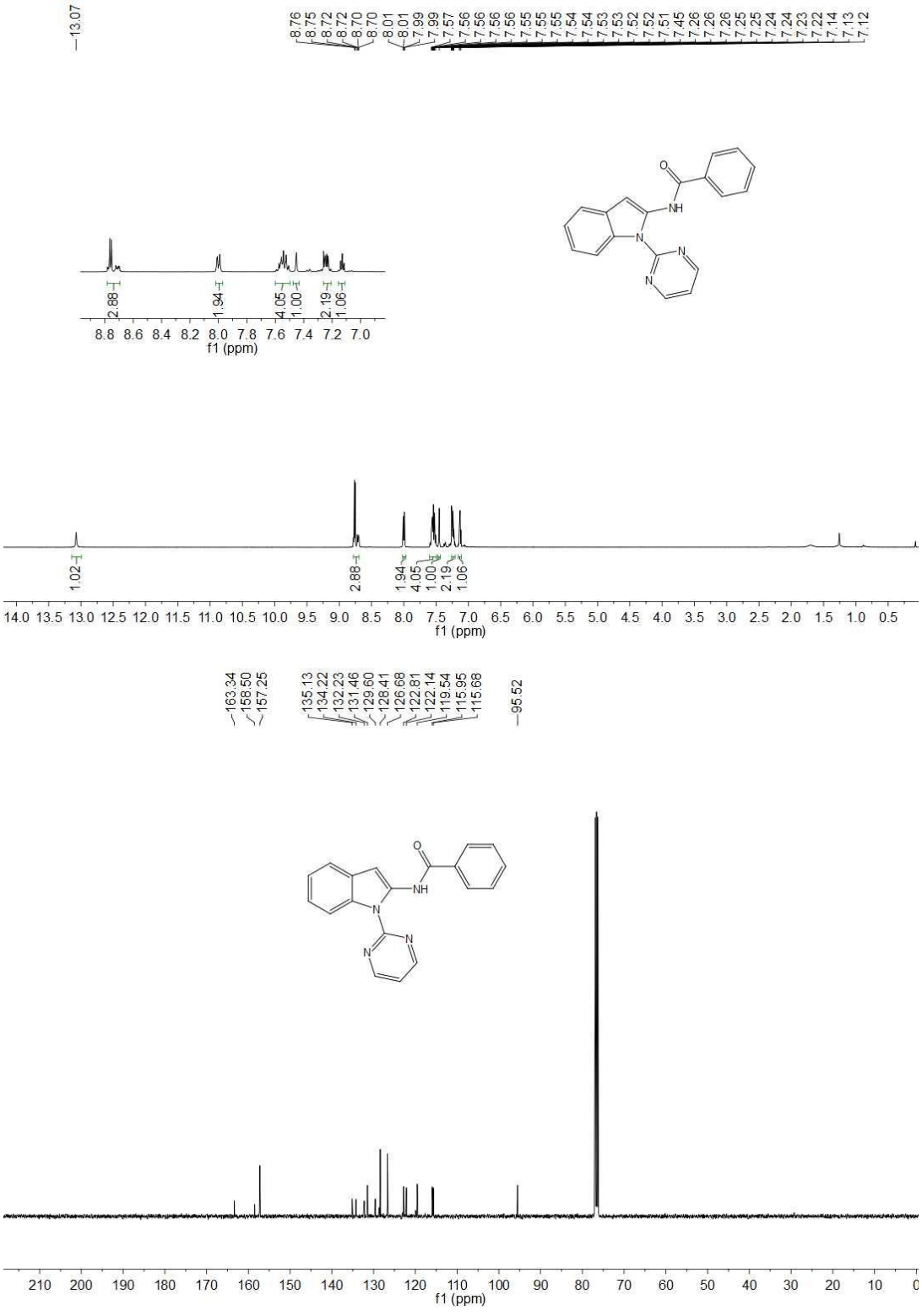
4b


8.78
8.77
8.34
8.32
7.66
7.64
7.40
7.38
7.36
7.28
7.27
7.25
7.19
6.97
6.01
6.00
4.31
4.30
4.28
4.26
4.25
4.23
1.32
1.30
2.00
1.03
1.06
1.05
1.02
0.97
0.96
0.88
1.04
6.14
f1 (ppm)
162.33
158.06
157.39
137.57
134.97
128.02
125.37
122.53
121.69
117.68
114.01
109.24
41.88
22.64
f1 (ppm)

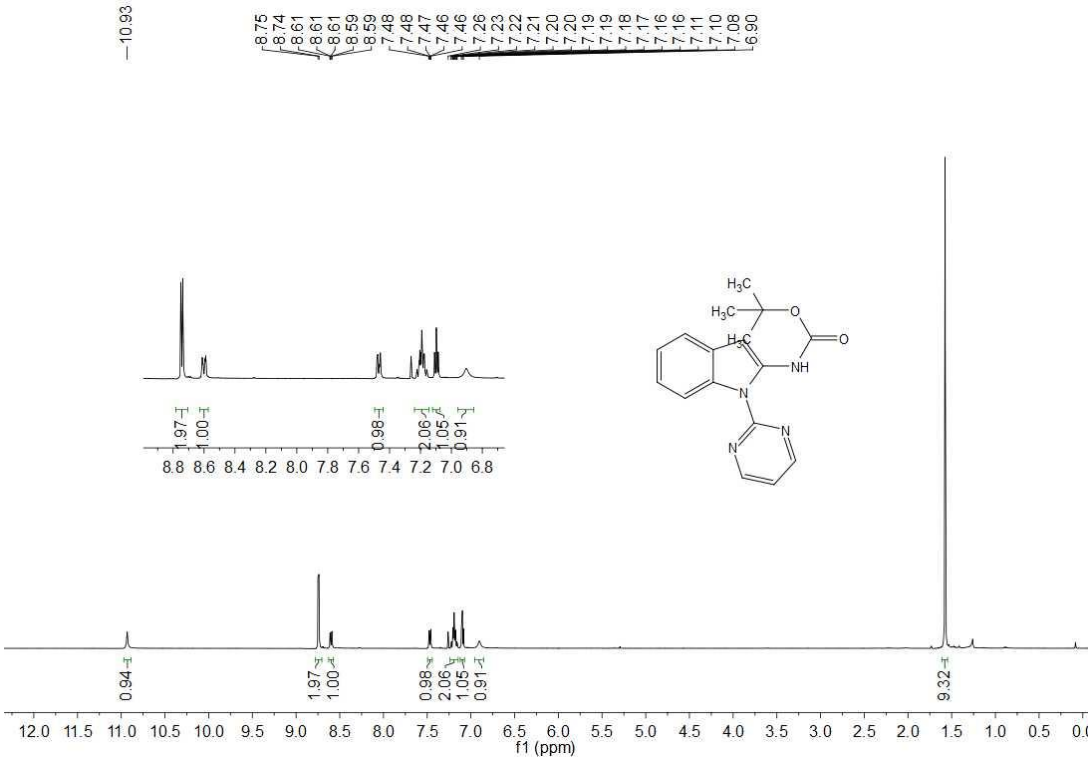
4c

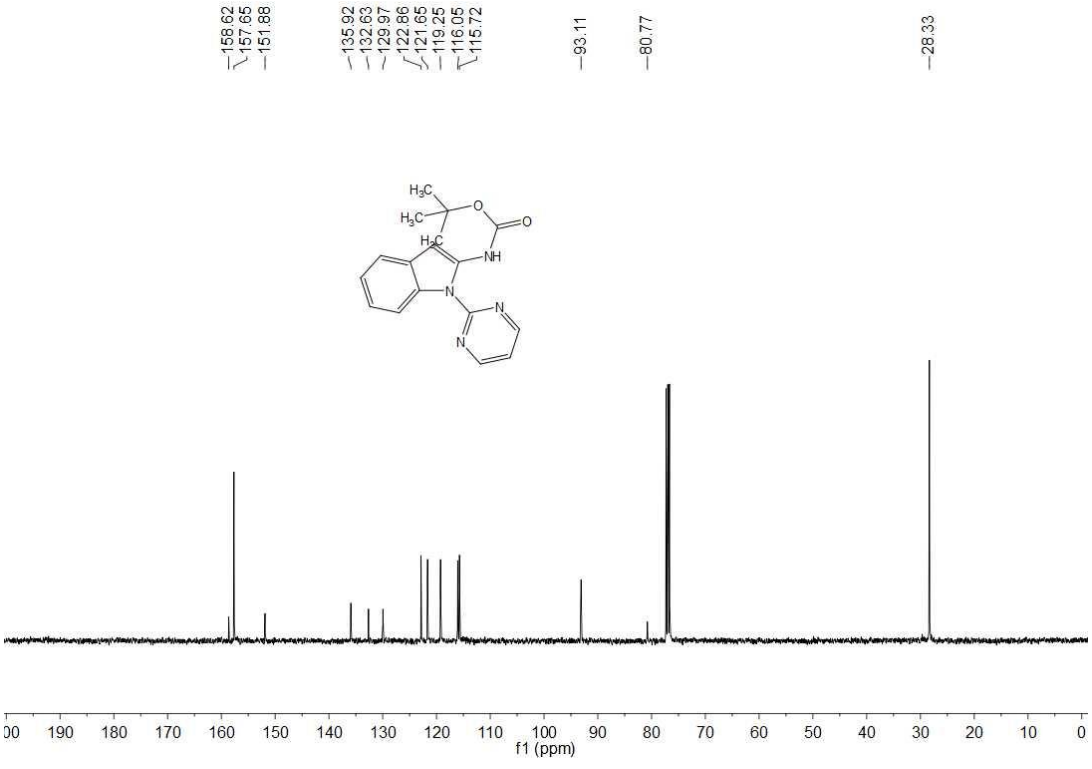

11.72
8.62
8.61
8.60
8.59
8.59
8.28
8.27
7.52
7.52
7.52
7.51
7.51
7.50
7.50
7.50
7.46
7.45
7.45
7.44
7.44
7.43
7.43
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.33
7.23
7.22
7.21
7.21
7.20
7.19
7.18
7.17
7.16
6.94
6.93
6.92
3.88
NH
O
N
N
1.00
1.17
2.33
7.18
1.21
2.44
1.17
2.32
f1 (ppm)
168.55
158.44
157.26
135.10
134.26
132.49
130.50
129.81
129.10
127.49
123.03
122.44
119.90
116.12
115.72
96.78
45.20
f1 (ppm)

4d

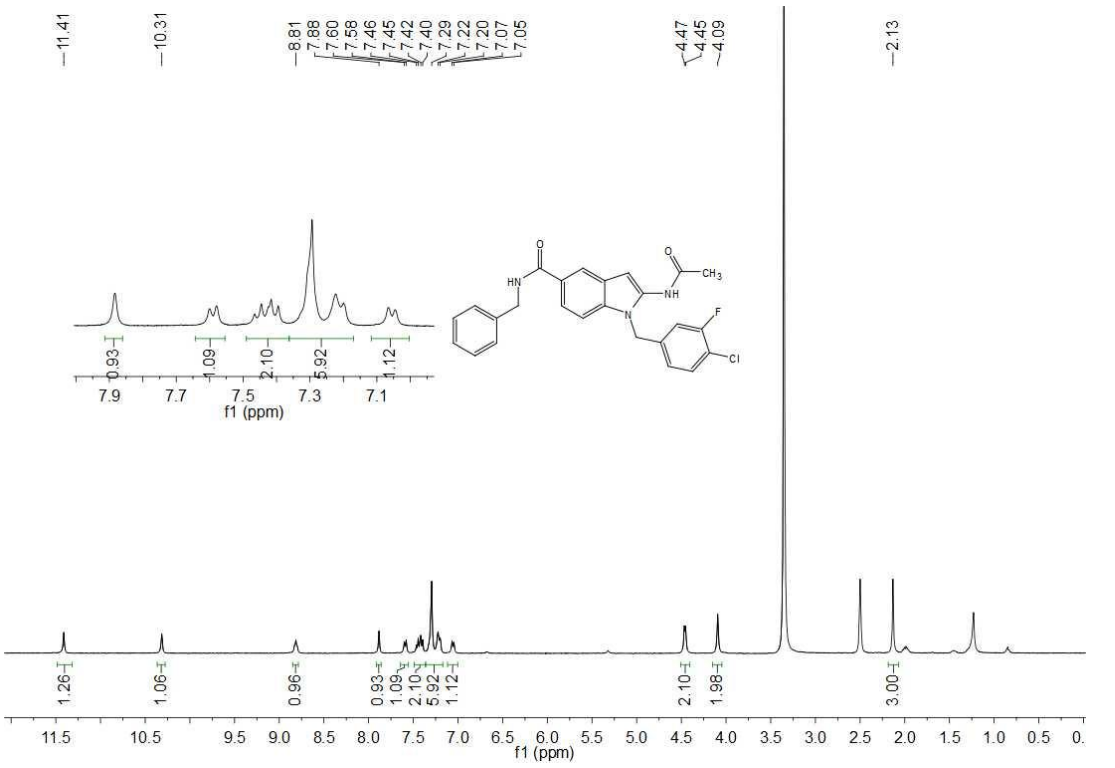

13.07
8.76 8.75 8.72 8.72 8.70 8.70 8.01 8.01 7.99 7.99 7.57 7.56 7.56 7.56 7.56 7.55 7.55 7.55 7.54 7.54 7.53 7.53 7.52 7.52 7.51 7.45 7.26 7.26 7.25 7.25 7.24 7.24 7.23 7.22 7.14 7.13 7.12
2.88 1.94 4.05 1.00 2.19 1.06
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0
f1 (ppm)
O
NH
N
N
N
1.02 2.88 1.94 4.05 1.00 2.19 1.06
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
163.34 158.50 157.25 135.13 134.22 132.23 131.46 129.60 128.41 126.68 122.81 122.14 119.54 115.95 115.68 95.52
O
NH
N
N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

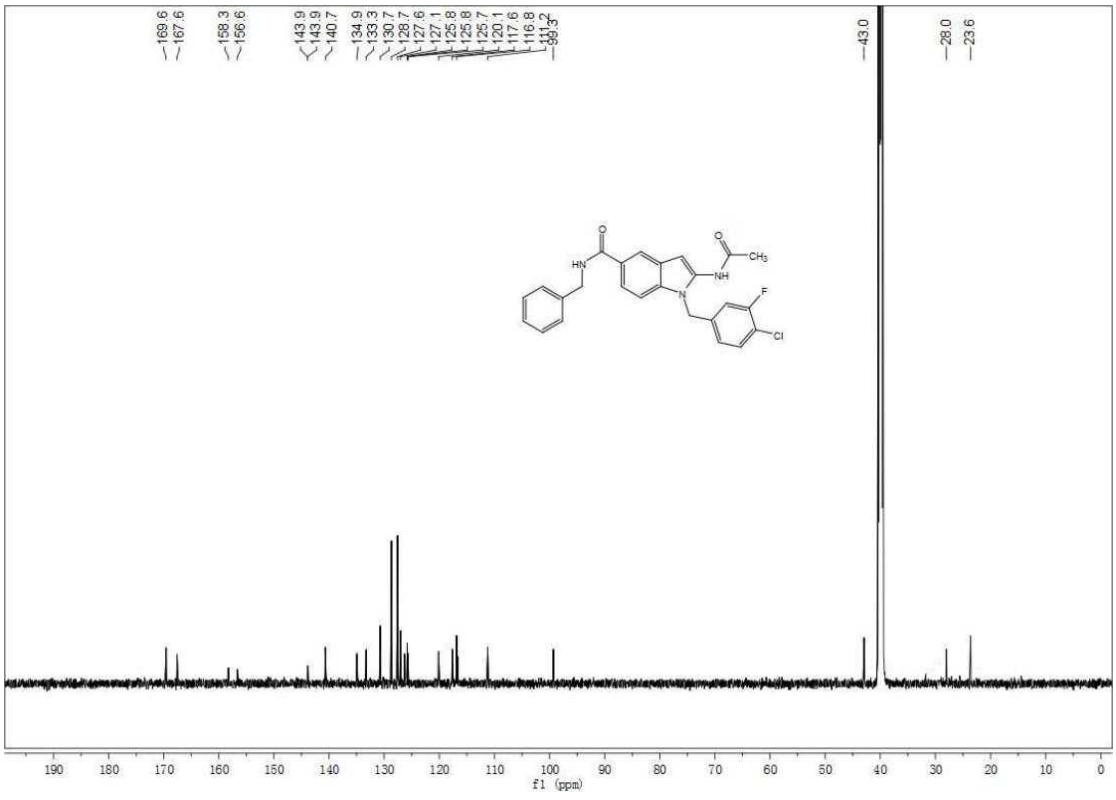
4e


10.93
8.75
8.74
8.61
8.61
8.61
8.59
8.59
7.48
7.48
7.47
7.46
7.46
7.26
7.23
7.22
7.21
7.20
7.20
7.19
7.19
7.18
7.17
7.16
7.16
7.11
7.10
7.08
6.90
1.97
1.00
0.98
2.06
1.05
0.91
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8
H3C
H3C
O
O
H3C
NH
N
N
N
0.94
1.97
1.00
0.98
2.06
1.05
0.91
9.32
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


158.62
157.65
151.88
135.92
132.63
129.97
122.86
121.65
119.25
116.05
115.72
93.11
80.77
28.33
H3C
H3C
O
O
H3C
NH
N
N
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

6


11.41
10.31
8.81
7.88
7.60
7.58
7.46
7.45
7.42
7.40
7.29
7.22
7.20
7.07
7.05
4.47
4.45
4.09
2.13
0.93
1.09
2.10
5.92
1.12
7.9
7.7
7.5
7.3
7.1
f1 (ppm)
HN
O
NH
CH3
F
Cl
1.26
1.06
0.96
0.93
1.09
2.10
5.92
1.12
2.10
1.98
3.00
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


169.6
167.6
158.3
156.6
143.9
143.9
140.7
134.9
133.3
130.7
128.7
127.6
127.1
125.8
125.8
125.7
120.1
117.6
116.8
111.2
99.3
43.0
28.0
23.6
HN
O
NH
CH3
F
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)