Three-Component, One-Pot Synthesis of 2,4,5-Substituted Pyrimidines Library for Screening against Human Hepatocellular Carcinoma BEL-7402 Cells

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Supporting information

Experimental section

General methods. ^{1}H (300 MHz) and ^{13}C (100 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm from internal TMS (δ). Melting points (uncorrected) were determined on a Buchi-510 capillary apparatus. Mass spectra were recorded on a Finnigan-4201 spectrometer (EI). Column chromatography was performed with 200-300 mesh silica gel using flash column techniques. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

General procedure for the synthesis of 2,4,5-substituted pyrimidine library: Substrate **A** (1.20 mmol), arylboronic acids (1.1 equiv) and K_2CO_3 (2.0 equiv) were dissolved in THF (4 mL) and water (1 mL), then $Pd(PPh_3)_4$ (0.02 mmol) was added to the mixture. The reaction mixture was stirred at 50-60 ^{0}C. The reaction was monitored by TLC. After the reaction was complete, the reaction solution was split into six portions, then amidines hydrochloride or hydroiodide **f-k** (0.3 mmol) and

1,8-diazabicyclo[5.4.0]undec-7-ene(DBU, 0.3 mmol or 0.6 mmol) were added, respectively. The mixture was stirred at 50-60 ^{0}C for about 10 hours, then the organic layer was diluted with water and extracted with ethyl acetate and dried over $MgSO_4$. Upon removal of the solvent, the corresponding pyrimidine was obtained after flash chromatography on silica gel (petrol ether/ethyl acetate).

Large scale preparation of ak: iodochromone (30 mmol), 4-methoxyphenylboronic acid f (1.1 equiv) and K_2CO_3 (2.0 equiv) were dissolved in CH_3CN (40 mL) and water (10 mL), then 10% Pd/C (0.02 mmol) was added to the mixture. The reaction mixture was stirred at 50-60 ^{0}C for about 8 hours. After the reaction was complete, Pd/C was filtered, and the flitrate was diluted with water and extracted with ethyl acetate two times. The collected organic extracts were dried over $MgSO_4$. Intermediate 4´-methoxyisoflvone was obtained after the solvent was evaporated. The crude product (7.11 g, 28.2 mmol), acetamidine hydrochloride k (1.5 equiv) and K_2CO_3 (2.0 equiv) were dissolved in DMF (50 mL). The mixture was stirred at 50-60 ^{0}C for about 10 hours, the organic layer was diluted with water and extracted with ethyl acetate two times. The collected organic extracts were dried over $MgSO_4$. Upon removal of the solvent, the compound ak (6.75 g, 23.1 mmol) was obtained in 77% yield (over two steps) after flash chromatography on silica gel (4:1 petrol ether : ethyl acetate).

Compound af: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 32.6 mg of **af** (46%) as a light yellow solid; mp 129-130 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.84 (s, 1H), 8.80 (s, 1H), 8.38-8.43 (m, 2H), 7.53-7.56 (m, 3H), 7.24-7.29 (m, 3H), 7.04-7.09 (m, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.55 (dt, *J* = 7.8, 1.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.33, 160.69, 160.32, 159.33, 158.90, 135.86, 131.93, 130.93, 130.83, 129.82, 129.69, 128.54, 128.49, 127.63, 118.15, 118.01, 114.29, 54.91; MS (EI) m/z 354 (M^+).

Compound ag: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 33.9 mg of **ag** (48%) as a colorless solid; mp 201-202 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.24 (s, 1H), 8.85(s, 1H), 8.83 (d, *J* = 6.1 Hz, 2H), 8.24 (d, *J* = 6.2 Hz, 2H), 7.24-7.31(m, 3H), 7.06 (dt, *J* = 7.2, 1.2 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.57 (dt, *J* = 7.3, 0.9 Hz, 1H), 3.87 (s, 3H); MS (EI) m/z 355 (M^+).

Compound ah: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 38.1 mg of **ah** (52%) as a tan solid; mp 218-219 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.13 (s, 1H), 8.70 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 2H), 7.19-7.25 (m, 3H), 7.01-7.07 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.53 (dt, *J* = 7.7, 1.2 Hz, 1H), 4.02 (br, 2H), 3.85 (s, 3H); MS (EI) m/z 369 (M^+).

Compound ai: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 39.0 mg of **ai** (50%) as a solid; mp 149-150 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.55 (s, 1H), 8.78 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.21-7.29 (m, 3H), 7.05 (dt, *J* = 7.3, 1.3 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.55 (dt, *J* = 7.6, 1.2 Hz, 1H), 3.86 (s, 3H); MS (EI) m/z 388 (M^+).

Compound aj: Purified by flash chromatography (20:1 petrol ether : ethyl acetate) to afford 32.6 mg of **aj** (49%) as a solid; mp 93-94 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.31 (s, 1H), 8.68 (s, 1H), 7.18-7.25 (m, 3H), 7.03(dd, *J* = 8.1, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.50 (dt, *J* = 7.7, 1.2 Hz, 1H), 3.86 (s, 3H), 1.50 (s, 9H); MS (EI) m/z 334 (M^+).

Compound ak: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 27.4 mg of **ak** (47%) as a solid; mp 121-122 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.96 (s, 1H), 8.61 (s, 1H), 7.17-7.25 (m, 3H), 6.99-7.03 (m, 2H), 6.945 (d, *J* = 8.8 Hz, 2H), 6.50 (dt, *J* = 7.7, 1.4 Hz, 1H), 3.85 (s, 3H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.73, 161.18, 159.83, 159.31, 159.28, 131.91, 130.90, 129.83, 128.90, 128.63, 118.14, 118.00, 117.88, 114.32, 54.91, 25.00; MS (EI) m/z 292 (M^+).

Compound bf: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 38.0 mg of **bf** (49%) as a solid; mp 168-170 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.59 (s, 1H), 8.81 (s, 1H), 8.40-8.45 (m, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.53-7.60 (m, 3H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.28 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.55 (dt, *J* = 7.7, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 162.16, 162.10, 160.51, 159.29, 140.72, 135.94, 132.80, 131.63, 131.40, 130.49 (q, $^2J_{CF}$ = 32.4 Hz, 1C), 129.46, 129.03, 128.96, 128.23, 126.18 (d, $^3J_{CF}$ = 3.6 Hz, 2C), 123.94 (q, $^1J_{CF}$ = 270.5 Hz, 1C), 118.65, 117.92; MS (EI) m/z 392 (M^+).

Compound bg: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to

afford 35.4 mg of **bg** (45%) as a solid; mp 208-210 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 11.98 (s, 1H), 8.86 (s, 1H), 8.83 (d, *J* = 6.1 Hz, 2H), 8.25 (d, *J* = 6.2 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.30 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.58 (dt, *J* = 7.6, 1.5 Hz, 1H); MS (EI) m/z 393 (M^+).

Compound bh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 35.9 mg of **bh** (44%) as a solid; mp 205-206 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.85 (s, 1H), 8.70 (s, 1H), 8.24 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.25 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.53 (dt, *J* = 7.6, 1.2 Hz, 1H), 4.07 (br, 2H); MS (EI) m/z 407 (M^+).

Compound bi: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 39.4 mg of **bi** (46%) as a solid; mp 209-210 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.29 (s, 1H), 8.80 (s, 1H), 8.37 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.56(dt, *J* = 7.6, 1.3 Hz, 1H); MS (EI) m/z 426 (M^+).

Compound bj: Purified by flash chromatography (20:1 petrol ether : ethyl acetate) to afford 36.4 mg of **bj** (49%) as a solid; mp 137-138 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.05 (s, 1H), 8.68 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.24 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.50 (t, *J* = 7.5 Hz, 1H), 1.51 (s, 9H); MS (EI) m/z 372 (M^+).

Compound bk: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 36.6 mg of **bk** (55%) as a solid; mp 113-115 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 1H), 8.62 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.24 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.50 (dt, *J* = 7.7, 1.2 Hz, 1H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.30, 161.90, 160.00, 159.60, 140.76, 132.76, 131.29, 130.45 (q, $^2J_{CF}$ = 32.8 Hz, 1C), 129.43, 128.20, 126.17 (d, $^3J_{CF}$ = 3.7 Hz, 2C), 123.90 (q, $^1J_{CF}$ = 270.5 Hz, 1C), 118.74, 118.49, 117.56, 25.47; MS (EI) m/z 330 (M^+).

Compound cf: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to

afford 41.9 mg of **cf** (61%) as a solid; mp 151-153 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.71 (s, 1H), 8.80 (s, 1H), 8.38-8.45 (m, 2H), 7.51-7.59 (m, 3H), 7.32 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.27 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.14 (t, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.55 (dt, *J* = 7.7, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 162.80 (d, $^1J_{CF}$ = 247.3 Hz, 1C), 161.95, 161.62, 160.62, 159.33, 136.10, 132.82 (d, $^4J_{CF}$ = 3.2 Hz, 1C), 132.56, 131.44, 131.31, 130.83 (d, $^3J_{CF}$ = 8.2 Hz, 2C), 129.37, 128.99, 128.13, 118.55, 118.48, 118.23, 116.40 (d, $^2J_{CF}$ = 21.4 Hz, 2C); MS (EI) m/z 342 (M^+).

Compound cg: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 34.6 mg of **cg** (51%) as a solid; mp 204-206 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.10 (s, 1H), 8.84 (s, 1H), 8.82 (d, *J* = 6.2 Hz, 2H), 8.24 (d, *J* = 6.2 Hz, 2H), 7.32 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.28 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.14 (t, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.58 (dt, *J* = 7.6, 1.2 Hz, 1H); MS (EI) m/z 343 (M^+).

Compound ch: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 37.1 mg of **ch** (52%) as a solid; mp 205-206 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.30 (s, 1H), 8.69 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.24 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 7.05 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.94 (d, *J* = 8.0, 1.8 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.53 (dt, *J* = 7.6, 1.4 Hz, 1H), 4.03 (br, 2H); MS (EI) m/z 357 (M^+).

Compound ci: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 34.7 mg of **ci** (46%) as a solid; mp 183-184 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.42 (s, 1H), 8.78 (s, 1H), 8.35 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.27 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.14 (t, *J* = 8.5 Hz, 2H), 7.07 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.56 (dt, *J* = 7.6, 1.4 Hz, 1H); MS (EI) m/z 376 (M^+).

Compound cj: Purified by flash chromatography (20:1 petrol ether : ethyl acetate) to afford 26.3 mg of **cj** (41%) as a solid; mp 184-186 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.17 (s, 1H), 8.67 (s, 1H), 7.28 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.23 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.13 (t, *J* = 8.7 Hz, 2H), 7.03 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.50 (dt, *J* = 7.6, 1.3 Hz, 1H), 1.51 (s, 9H); MS (EI) m/z 322 (M^+).

Compound ck: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 29.5 mg of **ck** (53%) as a solid; mp 118-119 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.81 (s, 1H), 8.60 (s, 1H), 7.26 (dd, *J* = 9.0, 5.3 Hz, 2H), 7.22 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.50 (dt, *J* = 7.7, 1.3 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.70, 162.74 (d, $^1J_{CF}$ = 246.8 Hz, 1C), 161.74, 160.12, 159.64, 132.85 (d, $^4J_{CF}$ = 3.7 Hz, 1C), 132.52, 131.19, 130.77 (d, $^3J_{CF}$ = 8.2 Hz, 2C), 128.57, 118.64, 118.61, 117.86, 116.36 (d, $^2J_{CF}$ = 21.4 Hz, 2C), 25.41; MS (EI) m/z 280 (M^+).

Compound df: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 34.6 mg of **df** (46%) as a solid; mp 144-145 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.89 (s, 1H), 8.82 (s, 1H), 8.37-8.46 (m, 2H), 7.51-7.59 (m, 3H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.25 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.52 (dt, *J* = 7.7, 1.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.90, 161.25, 160.76, 159.38, 151.58, 136.31, 133.78, 132.36, 131.51, 131.26, 130.37, 128.96, 128.69, 128.09, 126.15, 118.51, 118.39, 118.33, 34.72, 31.33; MS (EI) m/z 380 (M^+).

Compound dg: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 30.2 mg of **dg** (40%) as a solid; mp 227-228 ^{0}C. ^{1}H NMR (DMSO) δ 8.96 (s, 1H), 8.77 (d, *J* = 6.0 Hz, 2H), 8.28 (d, *J* = 6.1 Hz, 2H), 7.20-7.36 (m, 6H), 6.87 (dt, *J* = 7.5, 0.9 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 1.24 (s, 9H); MS (EI) m/z 381 (M^+).

Compound dh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 35.3 mg of **dh** (45%) as a solid; mp 202-204 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.17 (s, 1H), 8.73 (s, 1H), 8.23 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.19-7.27 (m, 3H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.49 (dt, *J* = 7.7, 1.4 Hz, 1H), 4.03 (br, 2H), 1.36 (s, 9H); ^{13}C NMR (DMSO) δ 162.39, 162.08, 157.75, 154.85, 151.53, 149.79, 133.83, 130.59, 130.33, 129.96, 129.34, 128.15, 125.49, 125.19, 124.23, 118.87, 115.85, 113.49, 34.31, 31.16; MS (EI) m/z 395 (M^+).

Compound di: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 43.3 mg of **di** (52%) as a solid; mp 176-178 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.60 (s, 1H),

8.81 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.22-7.29 (m, 3H), 7.06 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.52 (dt, 7.6, 1.3 Hz, 1H), 1.37 (s, 9H); MS (EI) m/z 414 (M^+).

Compound dj: Purified by flash chromatography (20:1 petrol ether : ethyl acetate) to afford 33.1 mg of **dj** (46%) as a solid; mp 130-132 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.34 (s, 1H), 8.70 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.18-7.25 (m, 3H), 7.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.46(dt, *J* = 7.6, 1.4 Hz, 1H), 1.51 (s, 9H), 1.36 (s, 9H); MS (EI) m/z 360 (M^+).

Compound dk: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 27.6 mg of **dk** (43%) as a solid; mp 78-80 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.00 (s, 1H), 8.63 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.18-7.24 (m, 3H), 7.01 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.97 (d, *J* = 8.2, 1.4 Hz, 1H), 6.47 (dt, *J* = 7.6, 1.4 Hz, 1H), 2.81 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.17, 161.66, 160.18, 159.70, 151.46, 133.81, 132.31, 131.39, 129.50, 128.63, 126.11, 118.48, 118.16, 118.11, 34.68, 31.29, 25.39; MS (EI) m/z 318 (M^+).

Compound ef: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 31.2 mg of **ef** (47%) as a solid; mp 145-147 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.71 (s, 1H), 8.87(s, 1H), 8.37-8.44 (m ,2H), 7.51-7.58 (m ,3H), 7.40 (s, 1H), 7.39 (d, *J* = 0.7 Hz, 1H), 7.29 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.09 (m ,2H), 6.95 (d, *J* = 6.4 Hz, 1H), 6.61 (dt, *J* = 7.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.44, 160.98, 160.01, 158.75, 136.53, 135.75, 132.21, 130.94, 130.47, 128.55, 127.72, 127.68, 126.56, 125.14, 123.42, 118.16, 117.96; MS (EI) m/z 330 (M^+).

Compound eg: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 26.5 mg of **eg** (40%) as a solid; mp 237-238 ^{0}C. ^{1}H NMR (DMSO) δ 9.13 (s, 1H), 8.76 (d, *J* = 6.3 Hz, 2H), 8.27 (d, *J* = 6.1 Hz, 2H), 7.87 (dd, *J* = 3.0, 1.6 Hz, 1H), 7.49 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.27-7.33 (m, 2H), 6.90-6.96 (m, 2H), 6.84 (d, *J* =8.5 Hz, 1H); MS (EI) m/z 331 (M^+).

Compound eh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 30.1 mg of **eh** (44%) as a solid; mp 220-221 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.99 (s, 1H), 8.76 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.33-7.38 (m, 2H), 7.27 (dt, *J* = 7.7, 1.5 Hz,

1H), 7.07 (m, 2H), 6.93 (dd, *J* = 4.8, 1.5 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.59 (dt, *J* = 7.6, 1.4 Hz, 1H), 4.04 (br, 2H); MS (EI) m/z 345 (M^+).

Compound ei: Purified by flash chromatography (8:1 petrol ether : ethyl acetate) to afford 33.7 mg of **ei** (46%) as a solid; mp160-161 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.40 (s, 1H), 8.84 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 3.4 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.03-7.13 (m, 2H), 6.93 (t, *J* = 3.1 Hz, 1H), 6.61 (t, *J* = 7.7 Hz, 1H); MS (EI) m/z 364 (M^+).

Compound ej: Purified by flash chromatography (20:1 petrol ether : ethyl acetate) to afford 25.6 mg of **ej** (41%) as a solid; mp 119-121 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.18 (s, 1H), 8.74 (s, 1H), 7.38 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.34 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.25 (dt, *J* =7.7, 1.7 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.56 (dt, *J* = 7.6, 1.3 Hz, 1H), 1.50 (s, 9H); MS (EI) m/z 310 (M^+).

Compound ek: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 22.7 mg of **ek** (42%) as a solid; mp 156-157 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 12.82 (s, 1H), 8.67 (s, 1H), 7.38 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.33 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.25 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.03 (dt, *J* = 7.8, 1.3 Hz, 2H), 6.90 (dd, *J* = 4.9, 1.4 Hz, 1H), 6.56 (dt, *J* = 7.6, 1.3 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.99, 161.20, 159.42, 158.95, 136.41, 132.04, 130.22, 127.58, 126.46, 124.21, 123.11, 117.92, 117.88, 117.69, 24.90; MS (EI) m/z 268 (M^+).

Compound 1ak: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 31.9 mg of **1ak** (50%) as a solid; mp 99-101 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 1H), 6.83 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.55 (d, *J* = 3.0 Hz, 1H), 3.84 (s, 3H), 3.20 (s, 3H), 2.81 (s, 3H); MS (EI) m/z 322 (M^+).

Compound 2ak: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 30.1 mg of **2ak** (46%) as a solid; mp 139-141 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.15(dd, *J* = 8.6, 2.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.96 (s, 1H), 6.93 (m, 1H), 3.86 (s, 3H), 2.81 (s, 3H); MS (EI) m/z 326 (M^+).

Compound 3ak: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to

afford 23.3 mg of **3ak** (35%) as a solid; mp 202-203 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.09 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.05 (d, *J* = 2.6 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 9.1 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.85 (s, 3H); MS (EI) m/z 337 (M^+).

Compound 4ak: Purified by flash chromatography (4:1 petrol ether : ethyl acetate) to afford 27.2 mg of **4ak** (44%) as a solid; mp 76-78 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.02 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.755 (d, *J* = 1.6 Hz, 1H), 3.86 (s, 3H), 2.80 (s, 3H), 1.90 (s, 3H); MS (EI) m/z 306 (M^+).

Compound 1dh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 37.9 mg of **1dh** (45%) as a solid; mp 167-169 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.24 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.84 (dd, *J* = 9.2, 3.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 2.8 Hz, 1H), 3.09 (s, 3H), 1.34 (s, 9H); MS (EI) m/z 425 (M^+).

Compound 2dh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 35.8 mg of **2dh** (42%) as a solid; mp 207-208 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.79-6.84 (m, 3H), 1.38 (s, 9H); MS (EI) m/z 429 (M^+).

Compound 3dh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 29.3 mg of **3dh** (33%) as a solid; mp 268-270 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1H), 8.20 (d, *J* = 8.7 Hz, 2H), 8.09 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.94 (d, *J* = 2.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.256 (d, *J*= 8.1 Hz, 2H), 7.08 (d, *J* = 9.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 1.38 (s, 9H); MS (EI) m/z 440 (M^+).

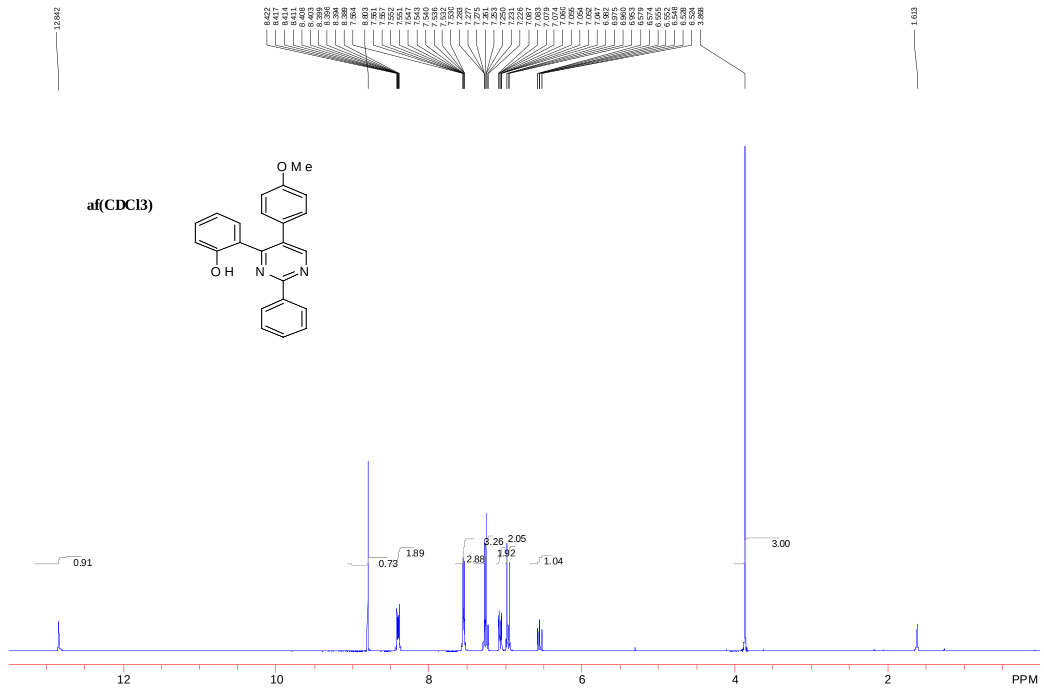
Compound 4dh: Purified by flash chromatography (2:1 petrol ether : ethyl acetate) to afford 45.2 mg of **4dh** (55%) as a solid; mp 224-226 ^{0}C. ^{1}H NMR ($CDCl_3$) δ 13.02 (s, 1H), 8.75 (s, 1H), 8.22 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.02 (dd, *J* = 8.5, 2.0Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.64 (d, *J* = 1.6 Hz, 1H), 4.01 (br, 2H), 1.85 (s, 3H), 1.37 (s, 9H); MS (EI) m/z 409 (M^+).

Cytotoxicity Assay

Cytotoxicity of compounds against human hepatocellular carcinoma BEL-7402 cells was determined by sulforhodamine B (SRB) assay.[1] Cells were plated in 96-well plate 24 h before treatment and continuously exposed to different concentrations of compounds for 72 h. After compound treatment, cells were fixed and stained with SRB as described in Monks *et al*.[1]

Reference

1. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; et al. Feasibility of a high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines. *J. Natl. Cancer Inst*. **1991**, *83*, 757-766.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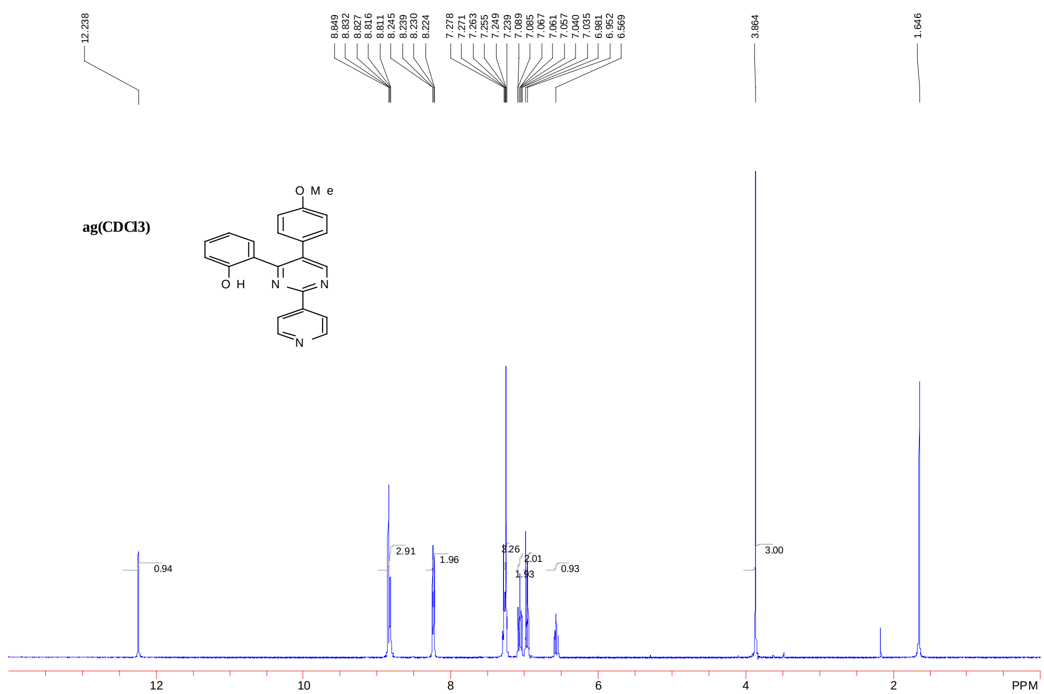
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N
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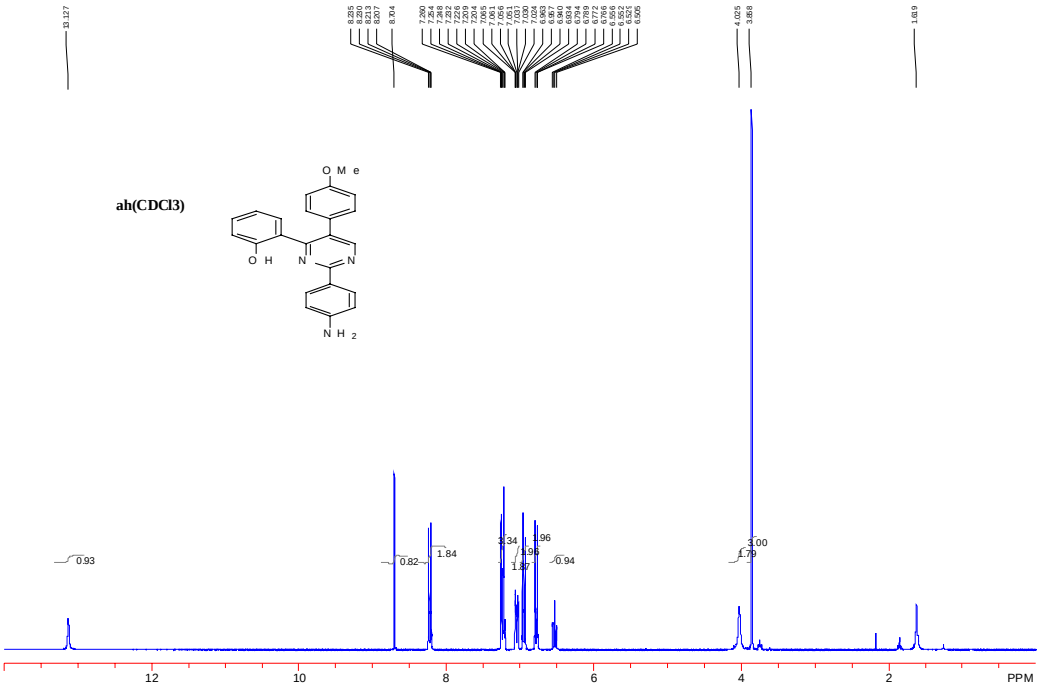
N
PPM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6.794
6.779
6.772
6.756
6.556
6.552
6.536
6.505
4.025
3.868
1.619
0.93
0.82
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10
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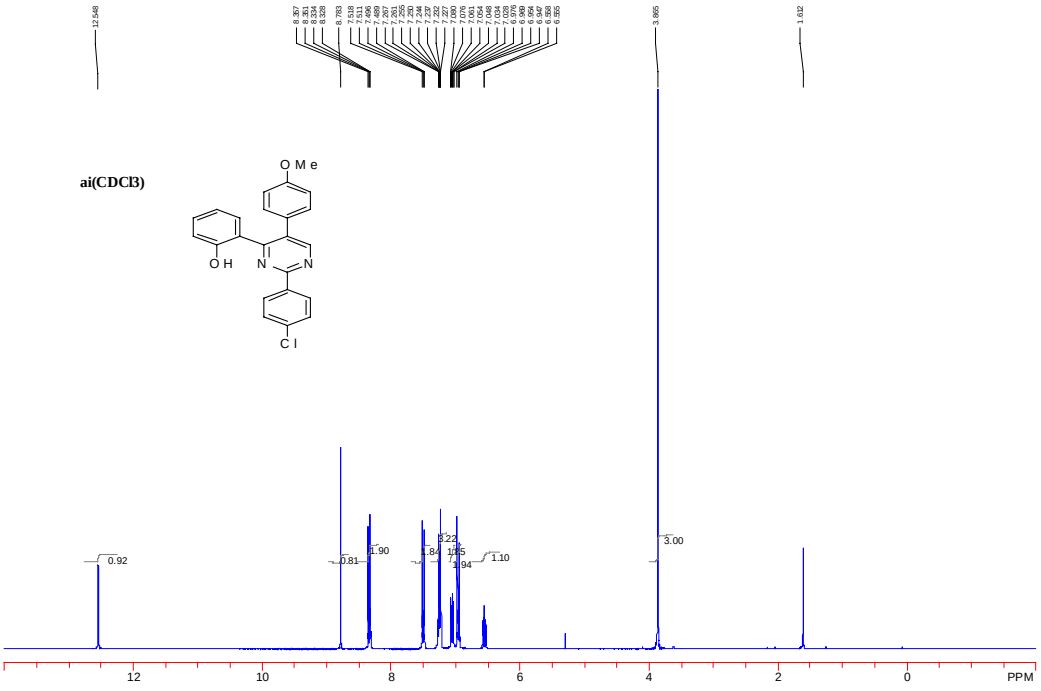
6
4
2
PPM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7.227
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7.048
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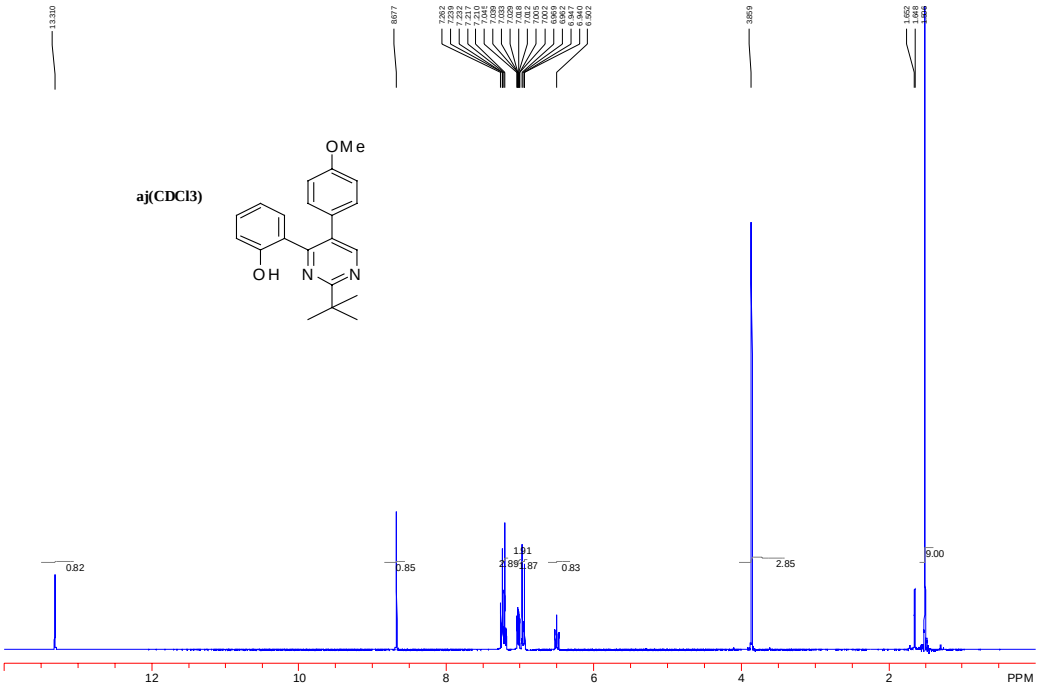
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7.018
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7.005
7.002
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6.947
6.940
6.422
3.859
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4
2
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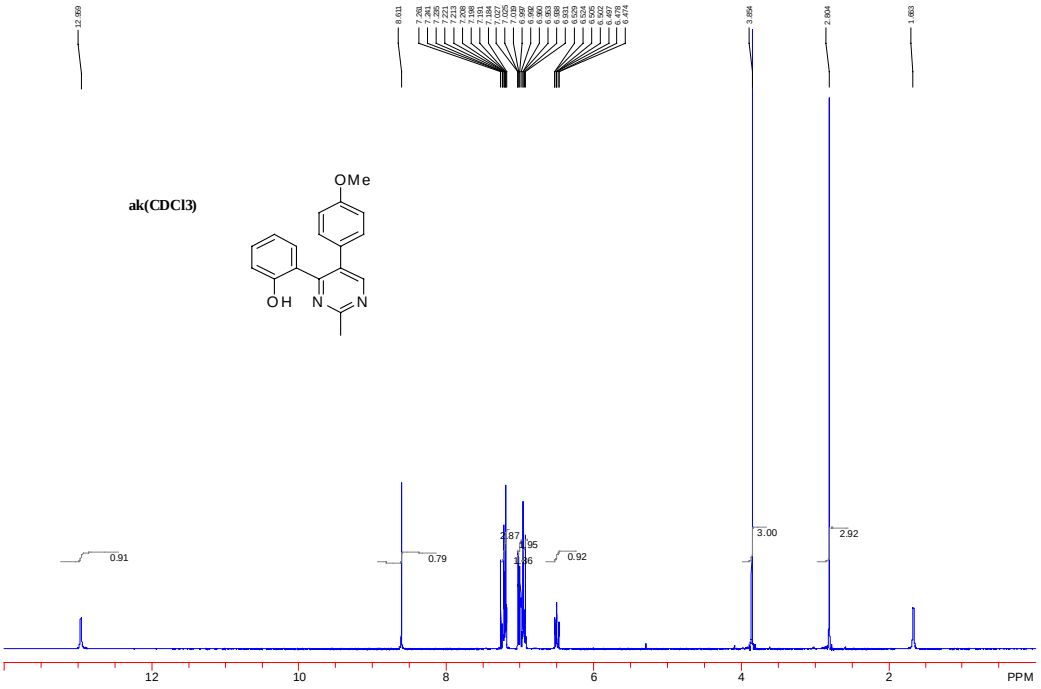
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2
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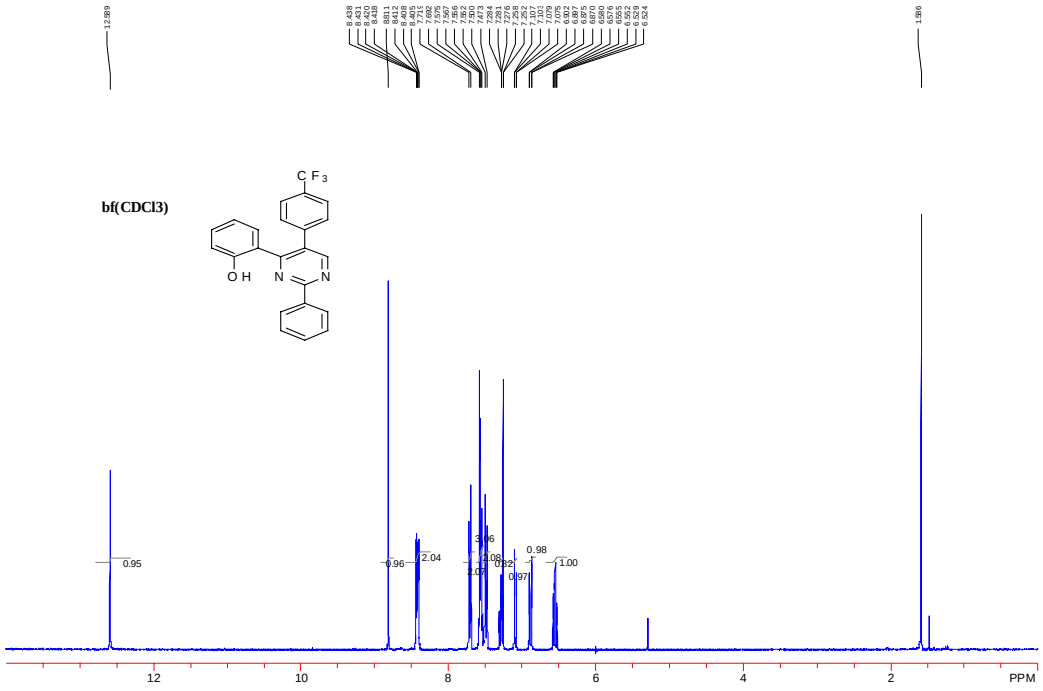
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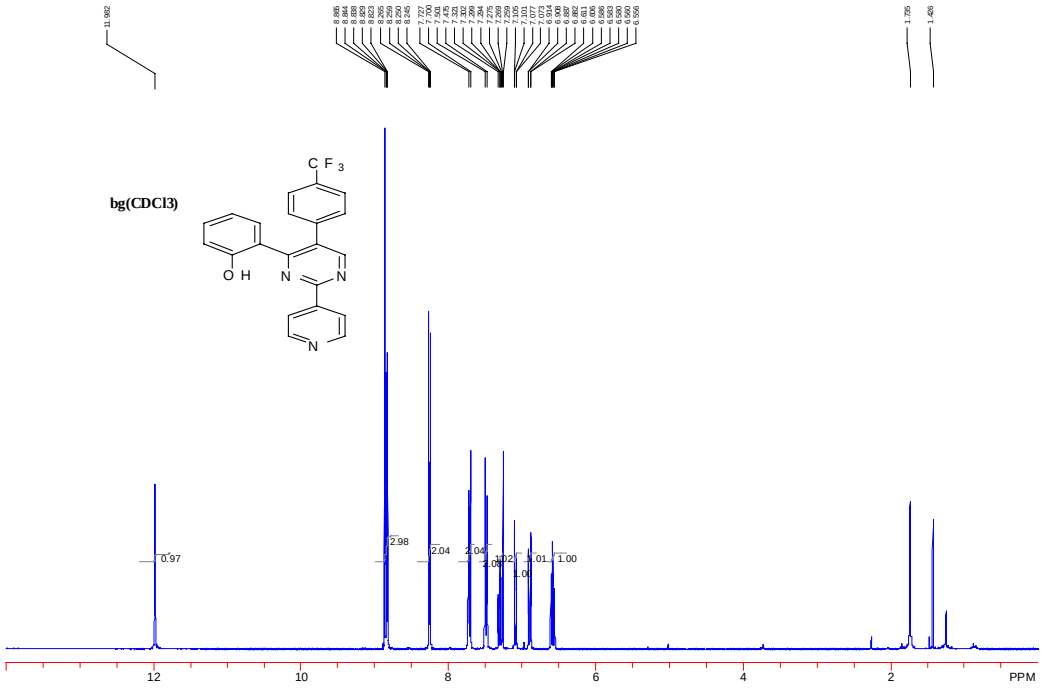
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1.00
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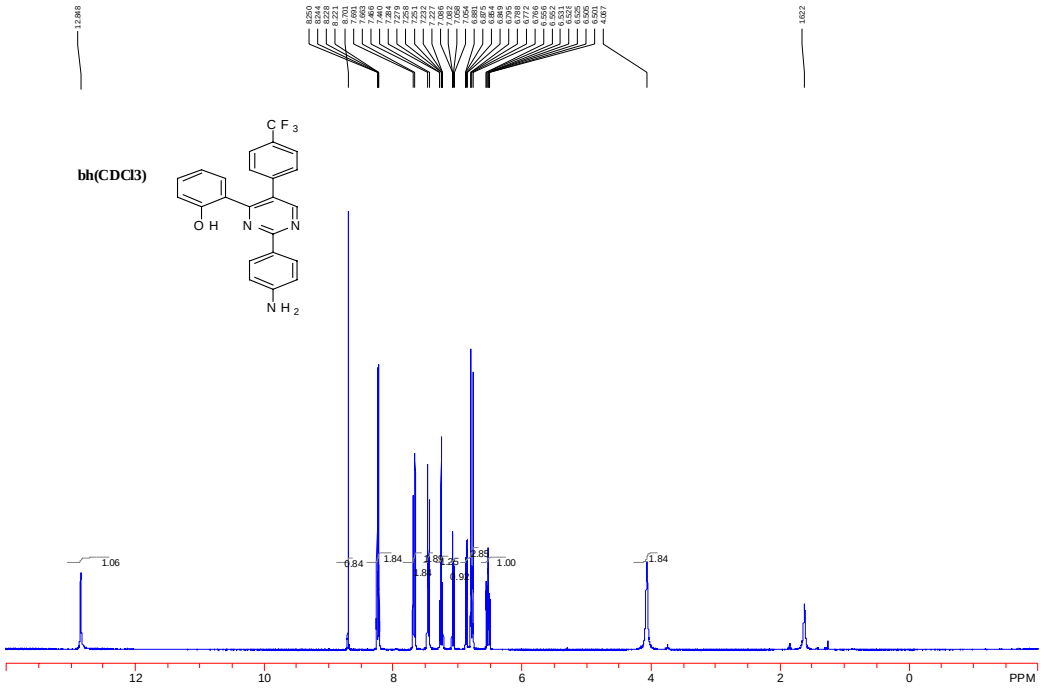
6
4
2
PPM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N
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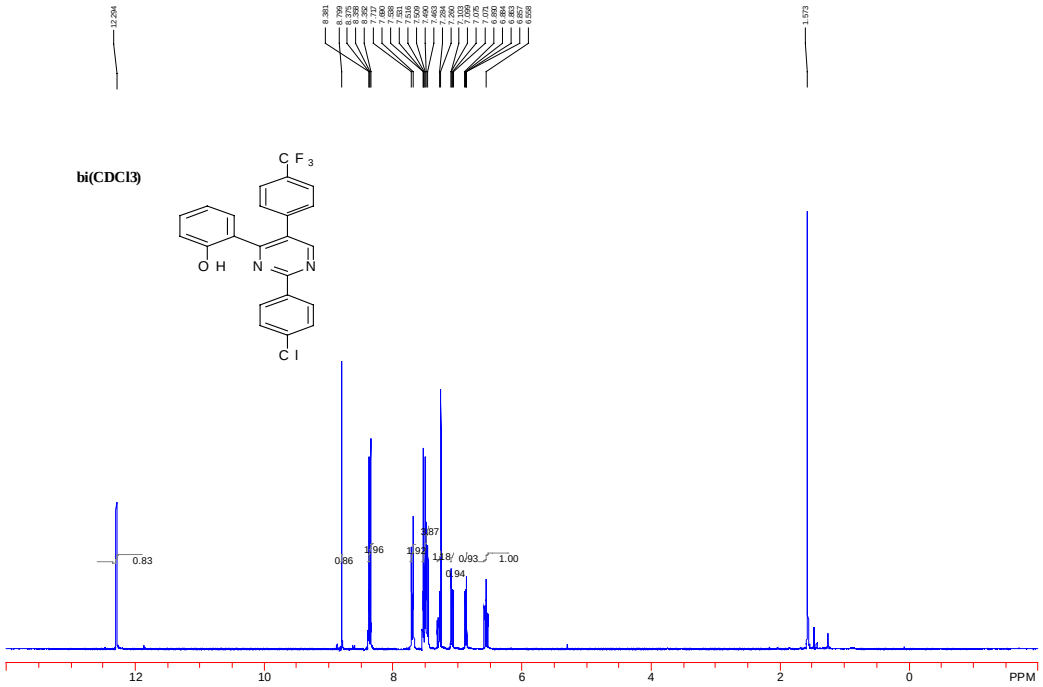
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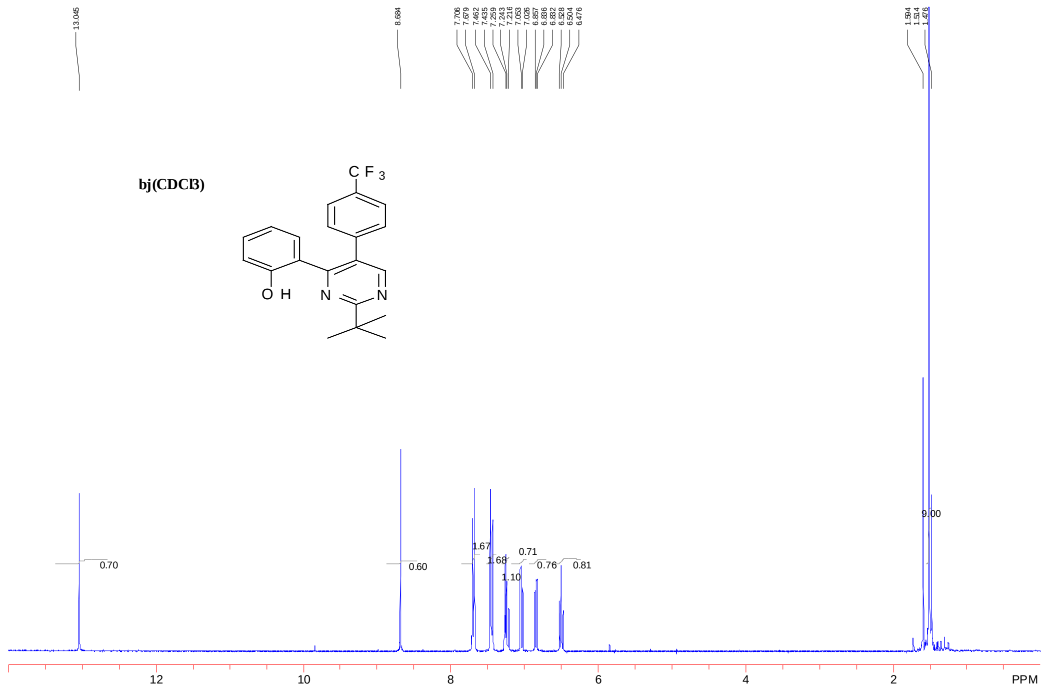
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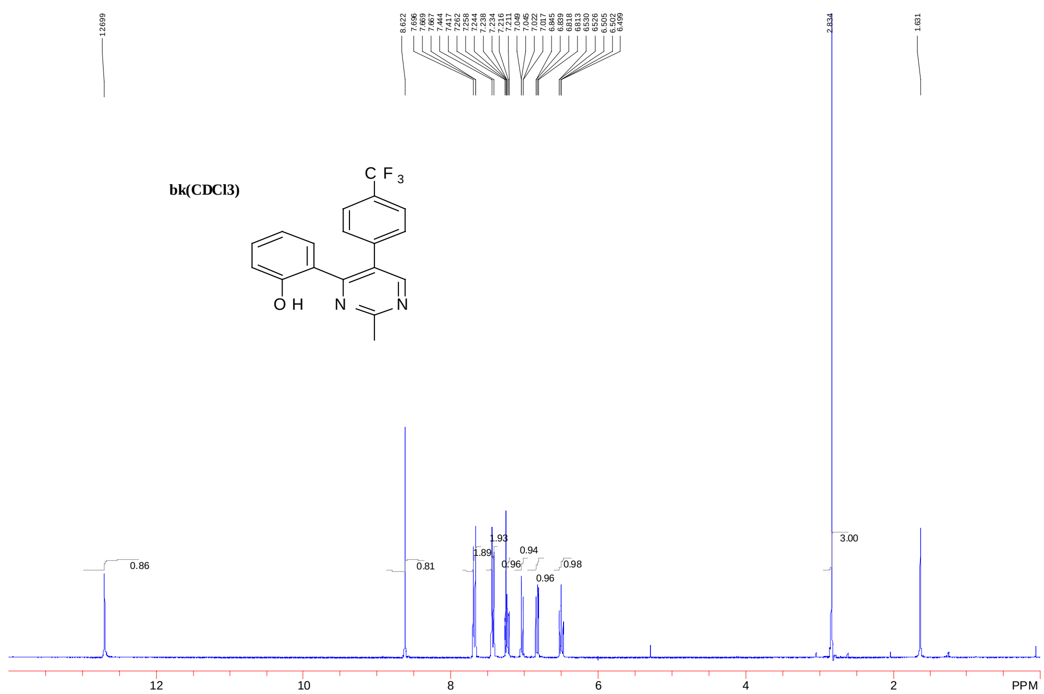
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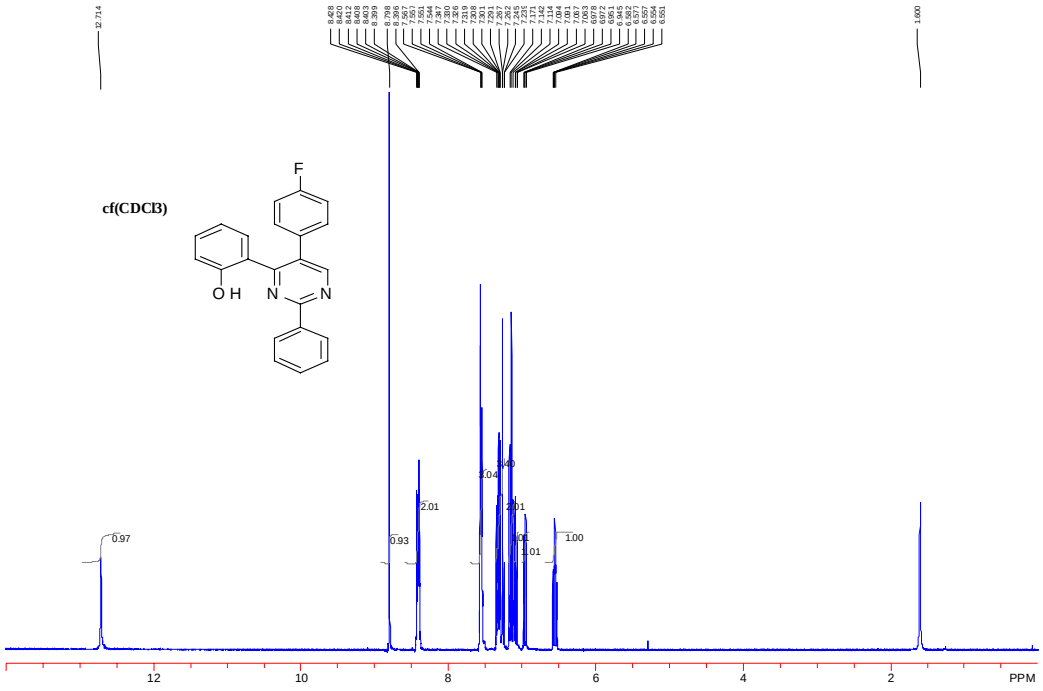
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6
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2
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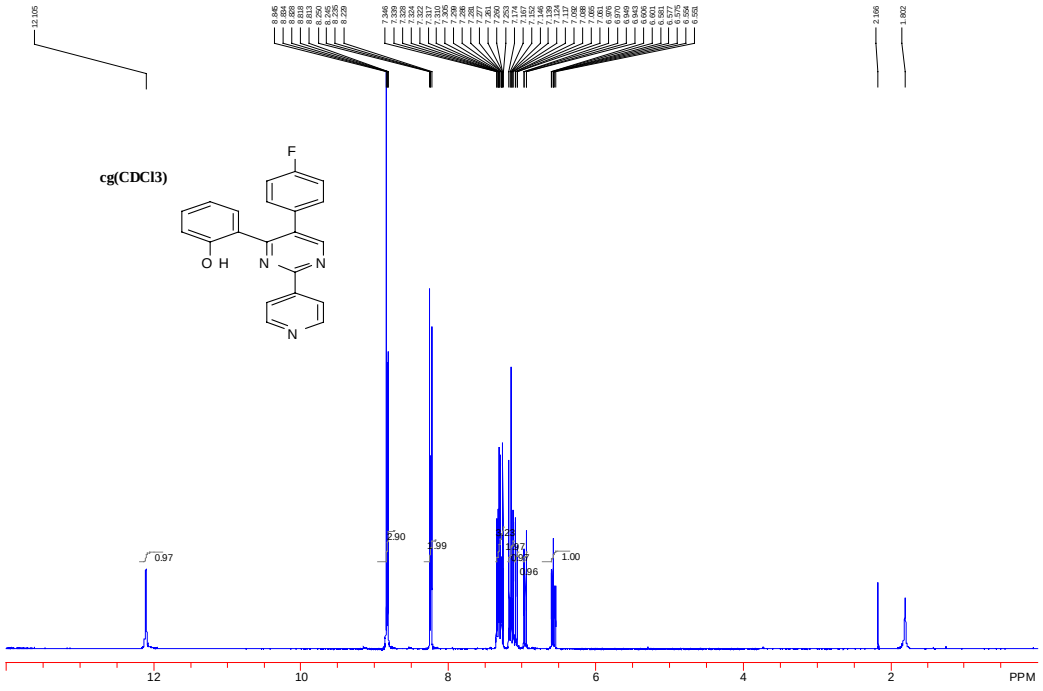
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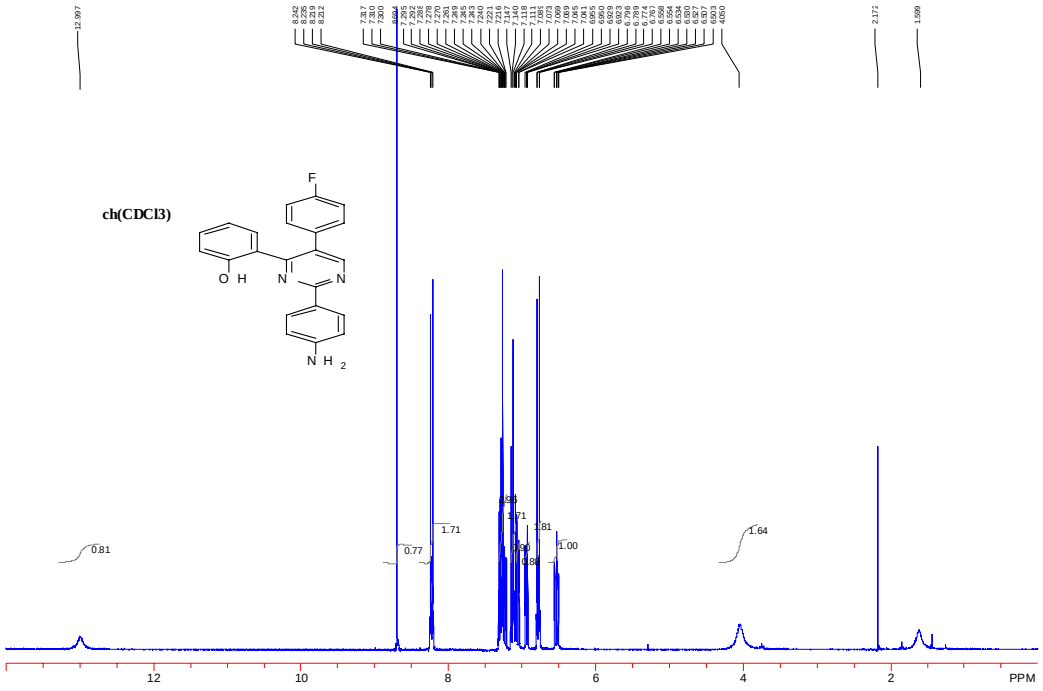
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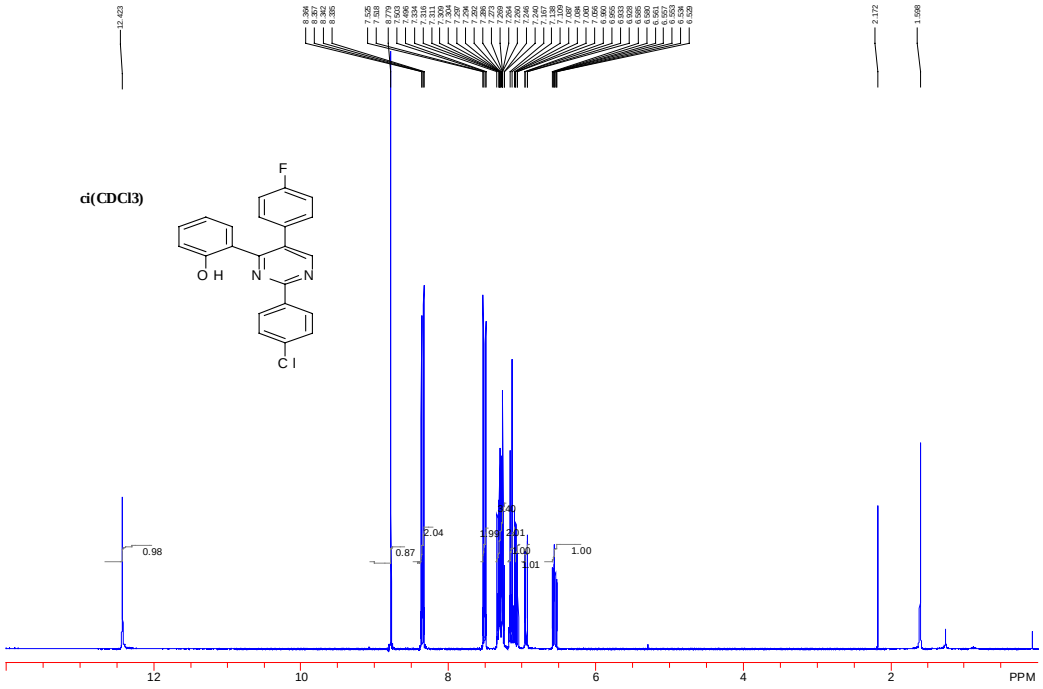
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2
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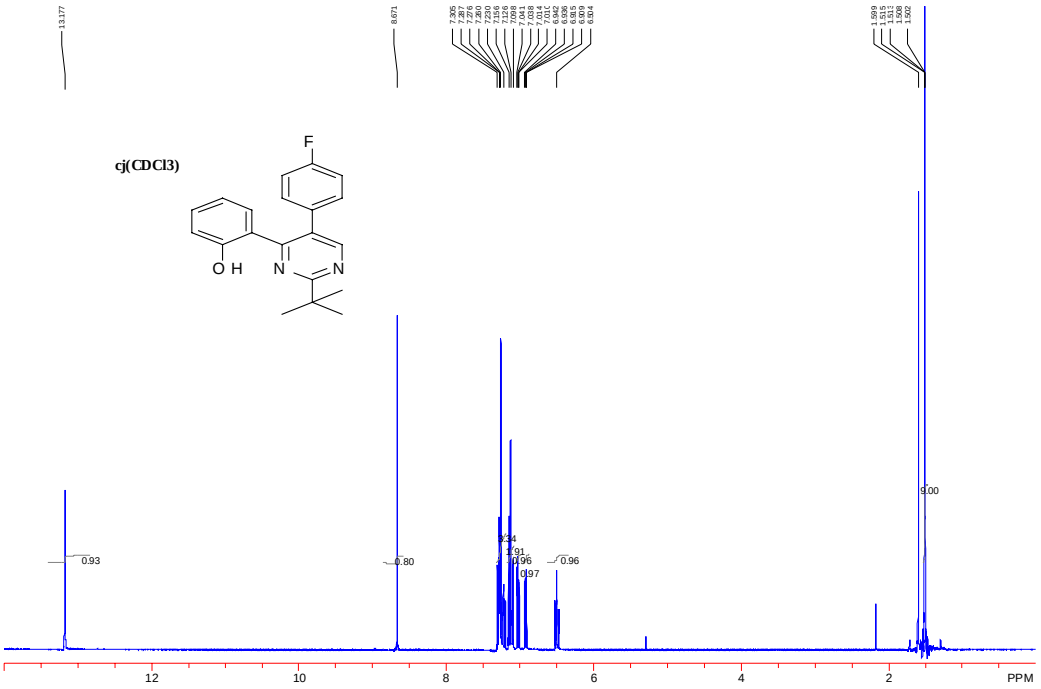
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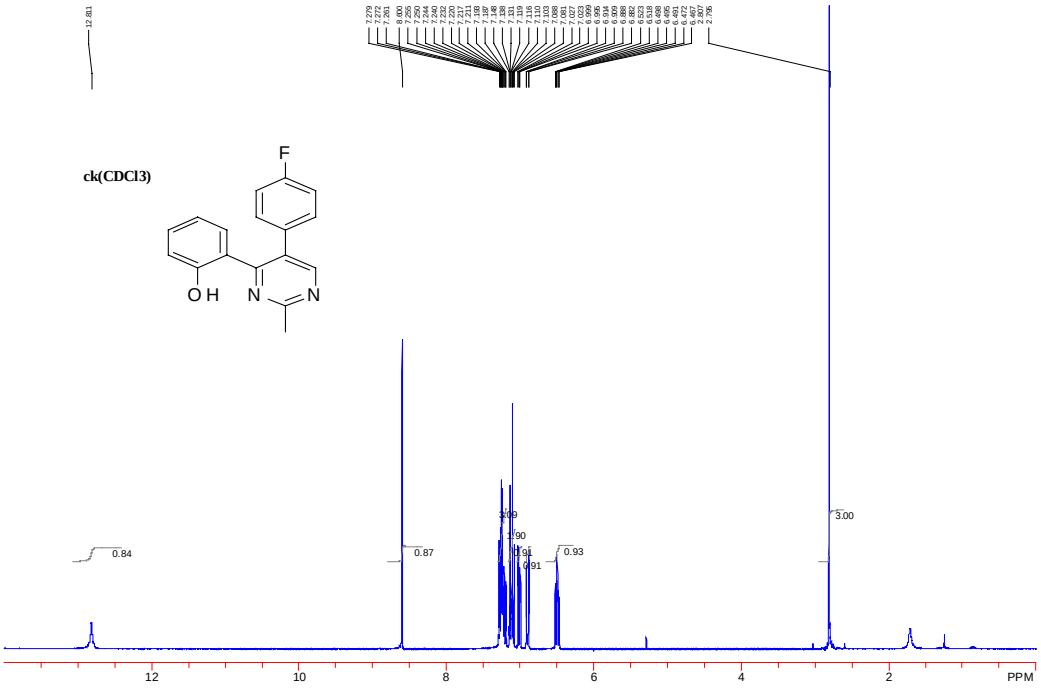
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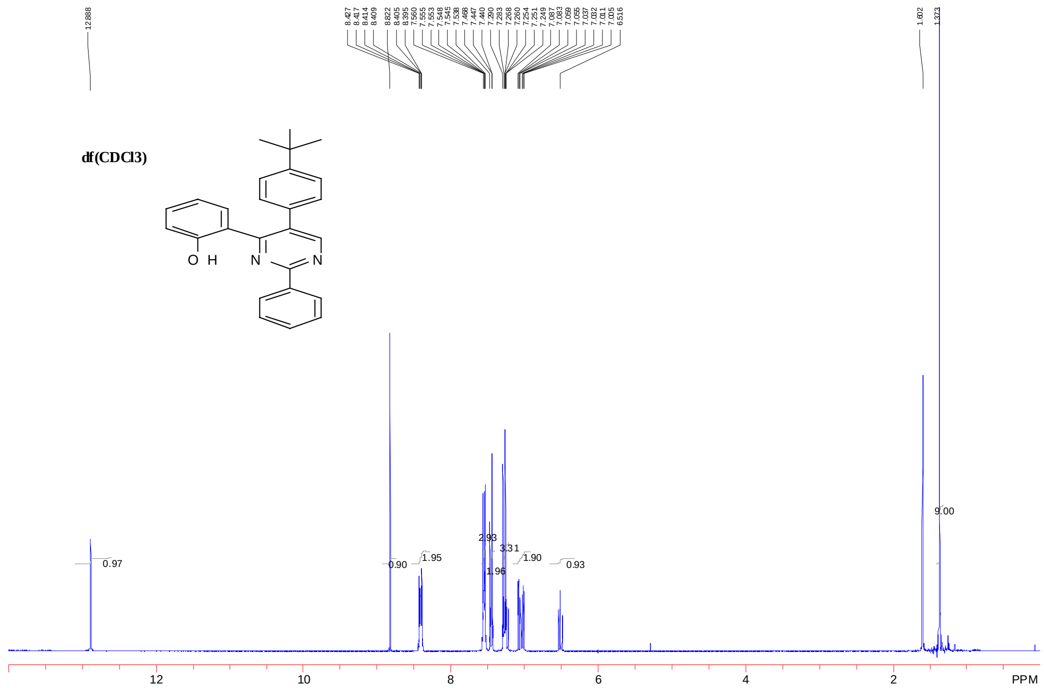

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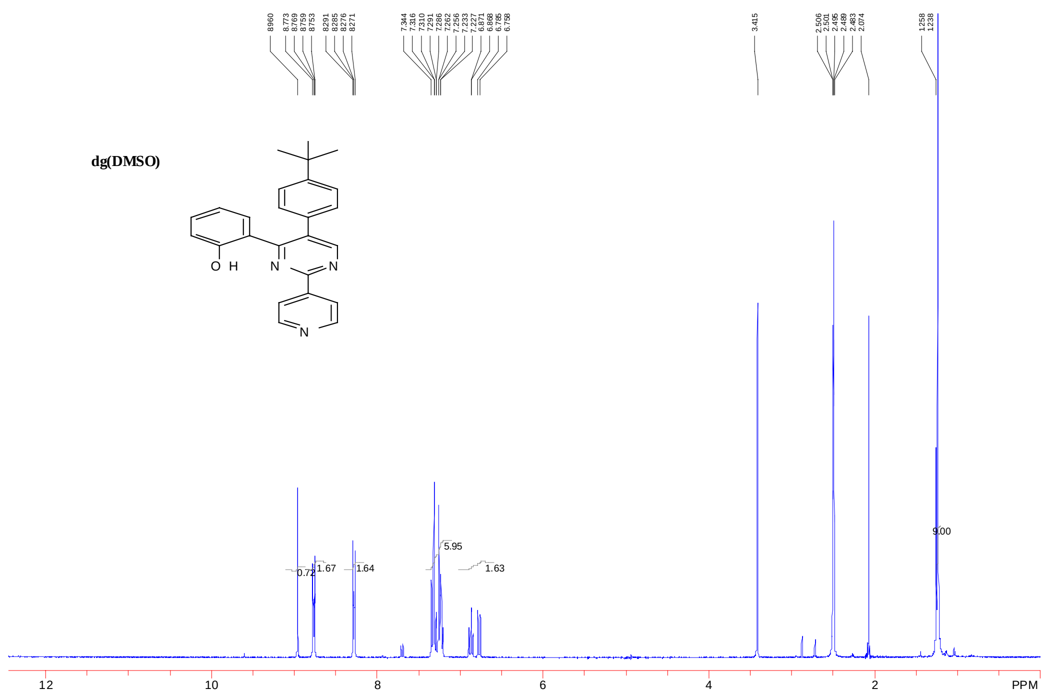

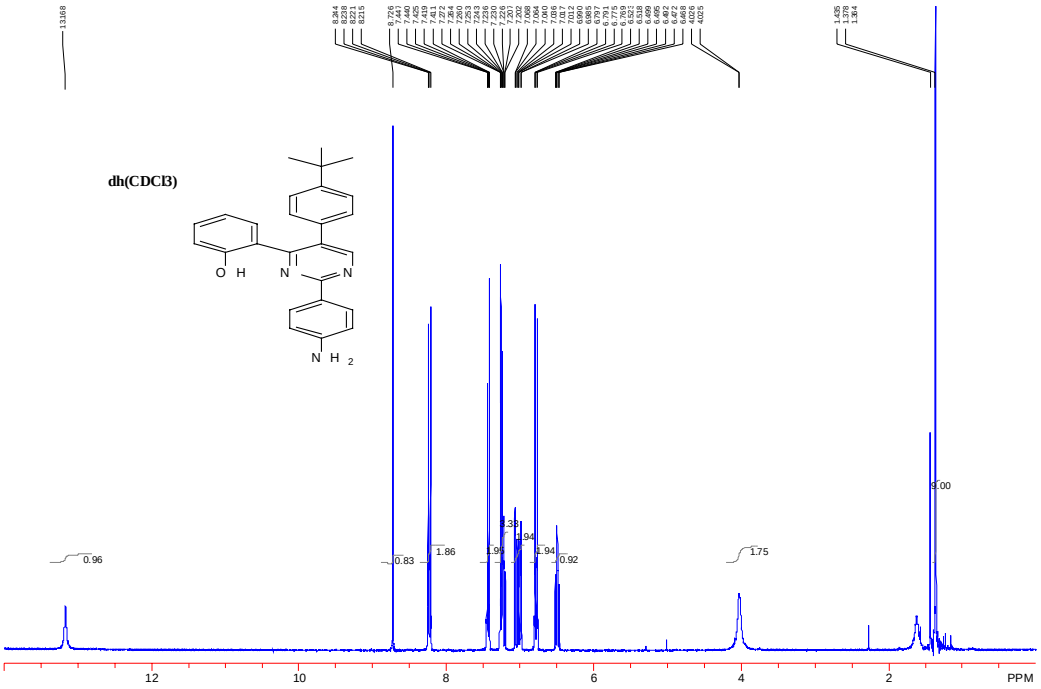
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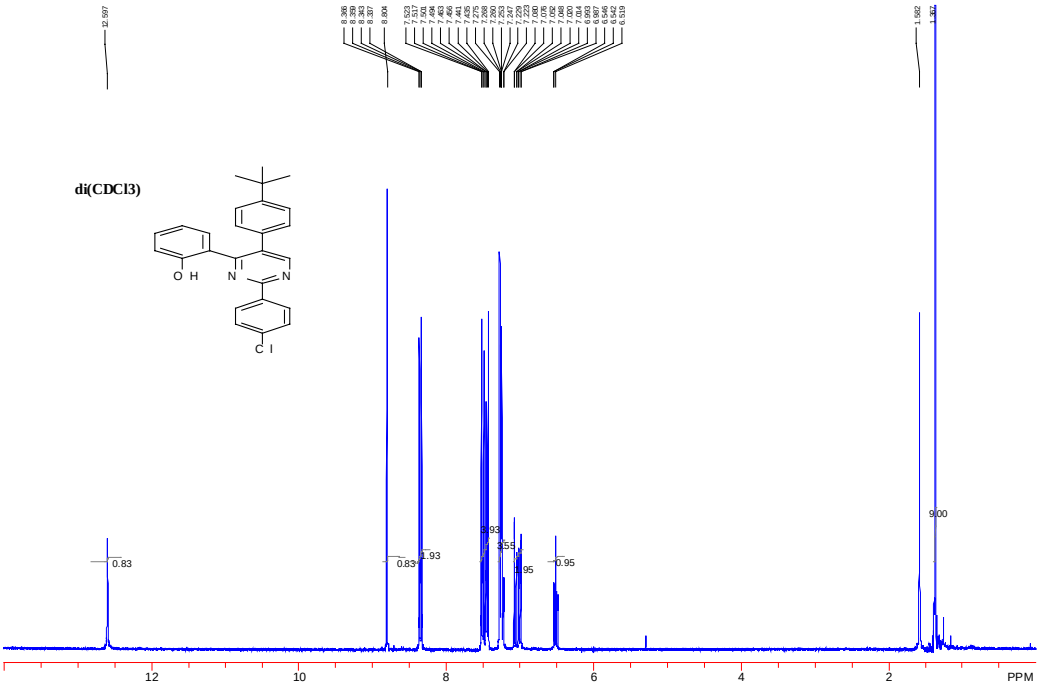
4
2
PPM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6
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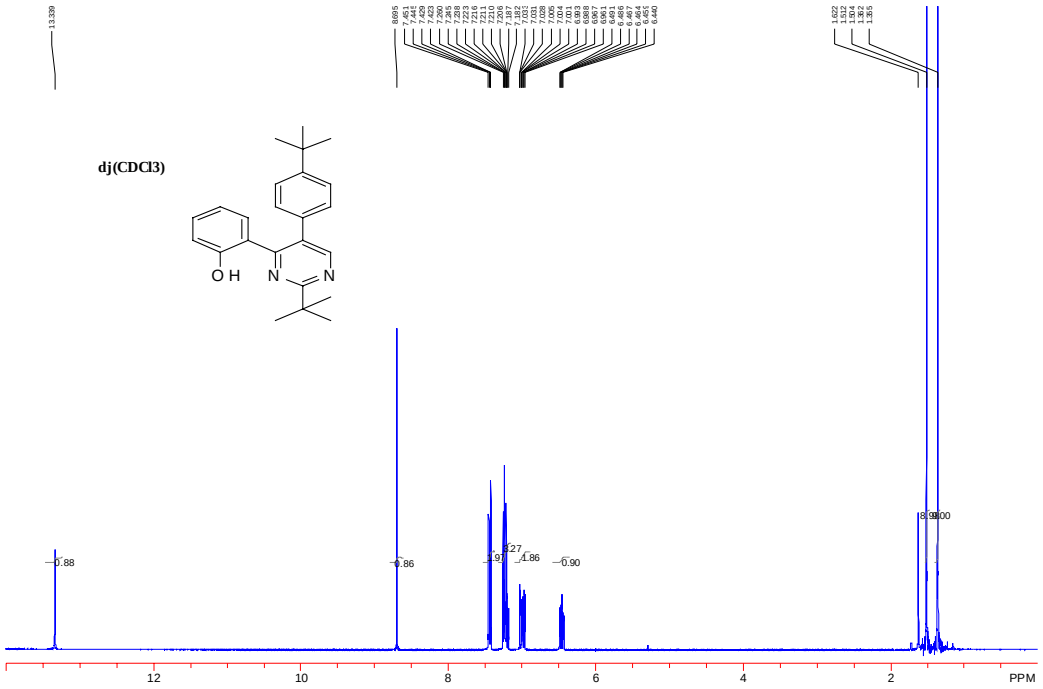
PPM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2
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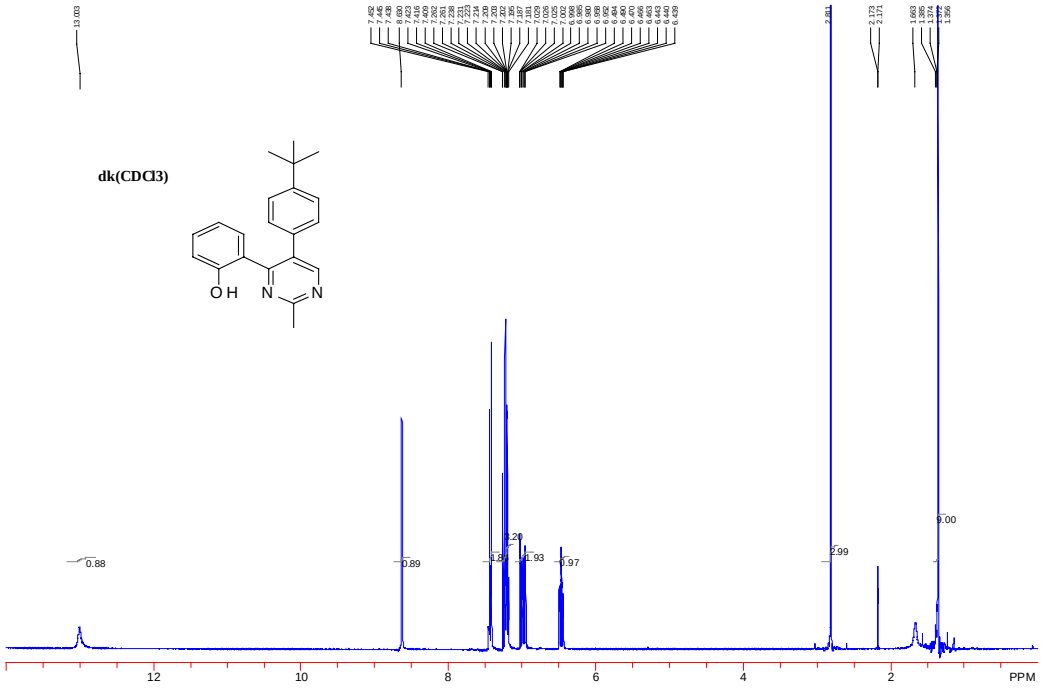
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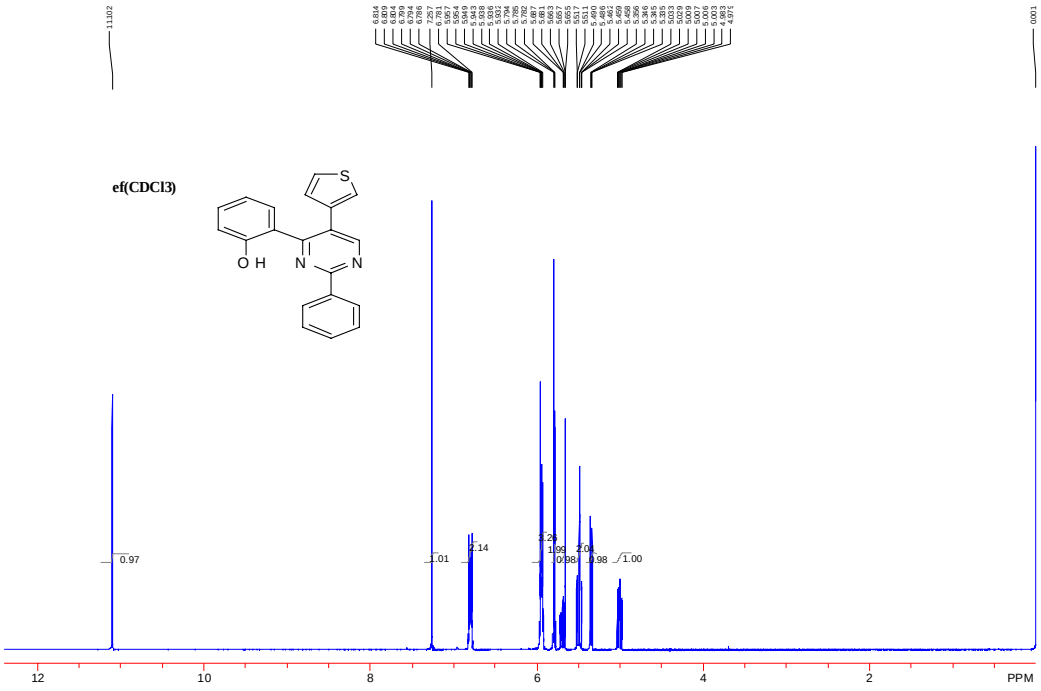
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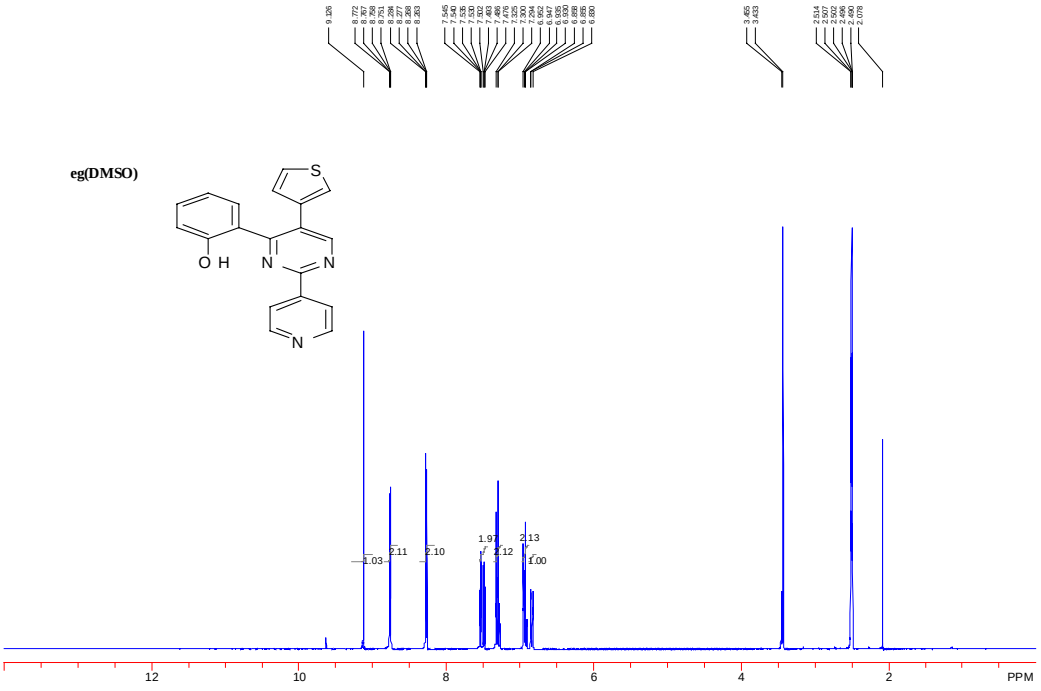
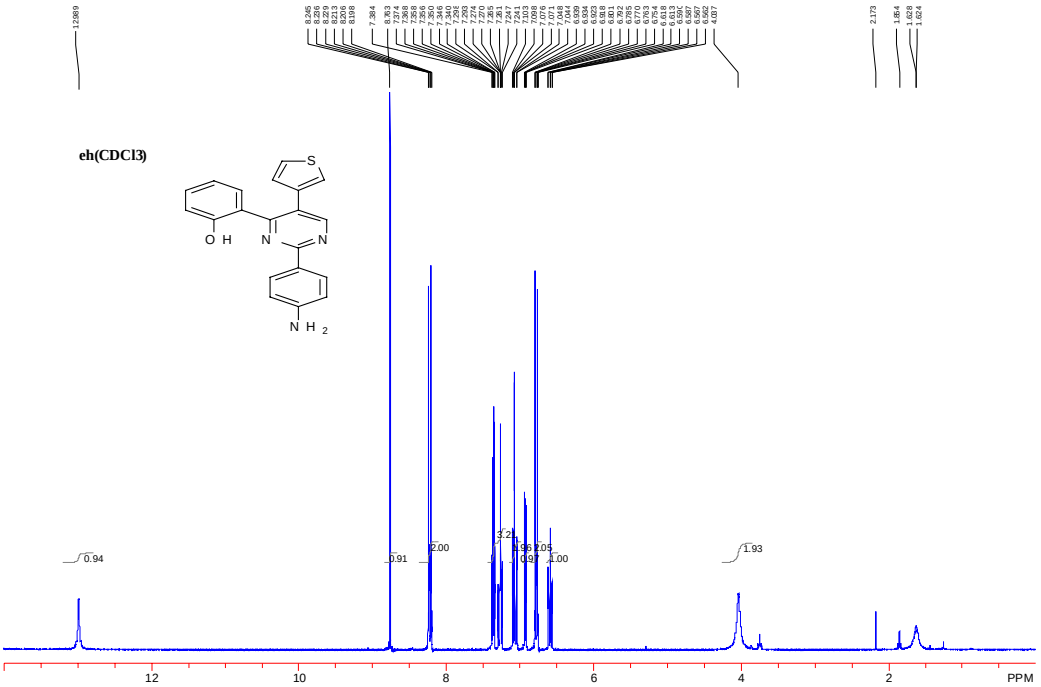
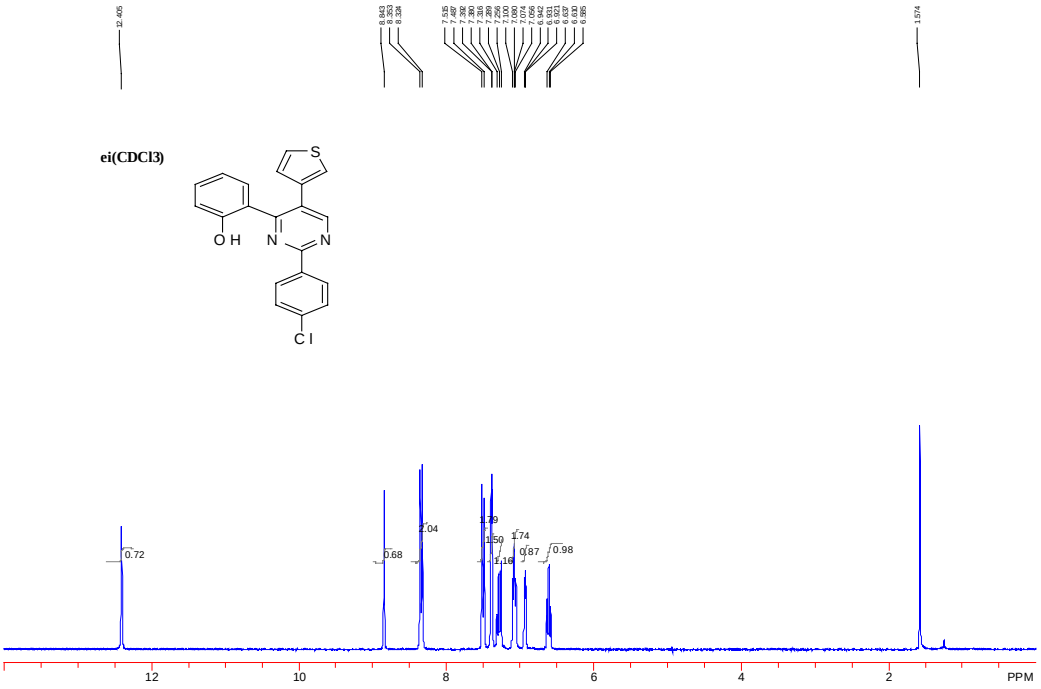
1.00
12
10
8
6
4
2
PPM

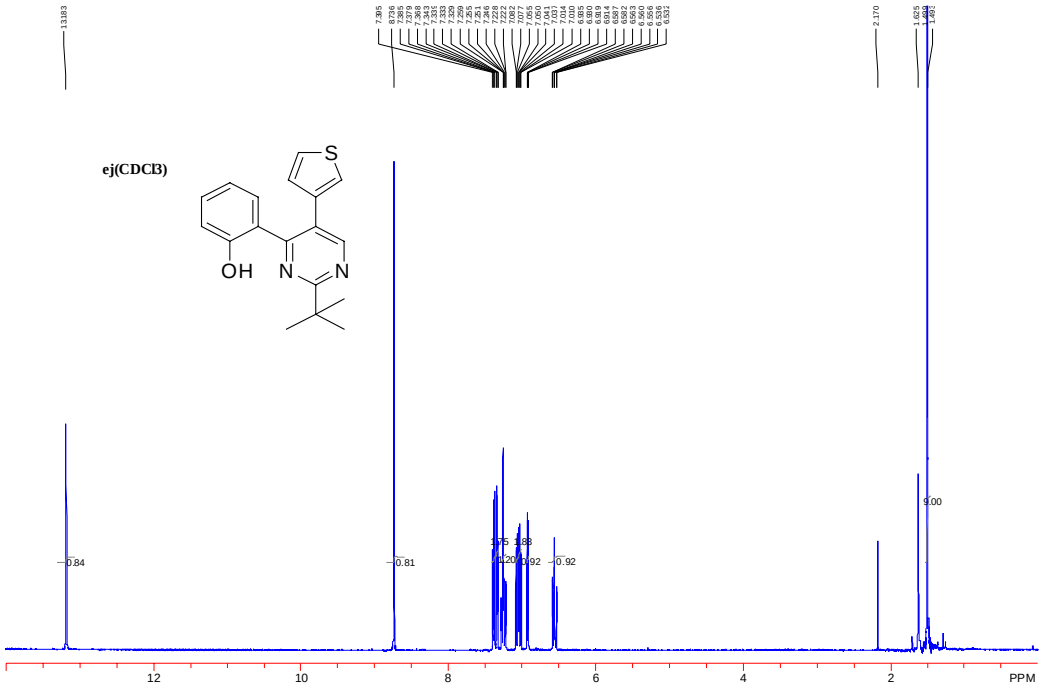

eg(DMSO)
S
O H
N
N
N
1.03
2.11
2.10
1.97
2.12
2.13
1.00
12
10
8
6
4
2
PPM

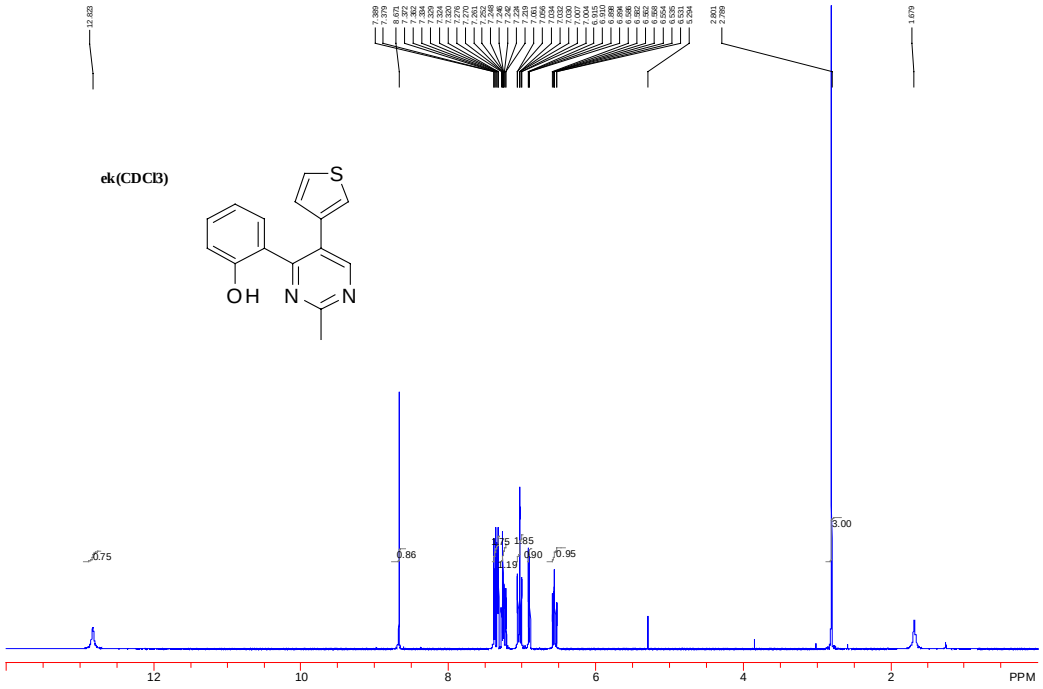
eh(CDCl3)



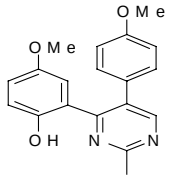
ei(CDCl3)



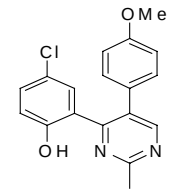

ej(CDCl3)
S
OH
N
N
13.183
7.395
8.736
7.385
7.379
7.372
7.368
7.343
7.335
7.333
7.329
7.299
7.255
7.251
7.246
7.229
7.223
7.092
7.077
7.055
7.050
7.041
7.037
7.014
7.010
6.985
6.980
6.919
6.914
6.897
6.682
6.663
6.560
6.556
6.538
6.531
2.170
1.605
1.484
1.481
0.84
0.81
1.75
1.88
1.20
0.92
0.92
9.00
12
10
8
6
4
2
PPM


ek(CDCl3)
S
OH
N
N
12.683
7.399
7.379
7.373
7.372
7.362
7.334
7.329
7.324
7.320
7.276
7.270
7.261
7.252
7.248
7.246
7.228
7.219
7.216
7.066
7.034
7.032
7.030
7.027
7.004
6.915
6.910
6.889
6.884
6.598
6.592
6.589
6.584
6.556
6.555
6.531
5.294
2.801
2.789
1.679
0.75
0.86
1.75
1.85
1.19
0.90
0.95
3.00
12
10
8
6
4
2
PPM

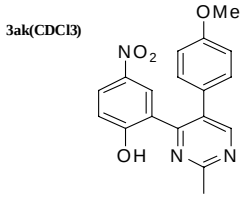
1ak(CDCl3)



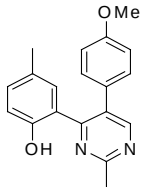
2ak(CDCl3)



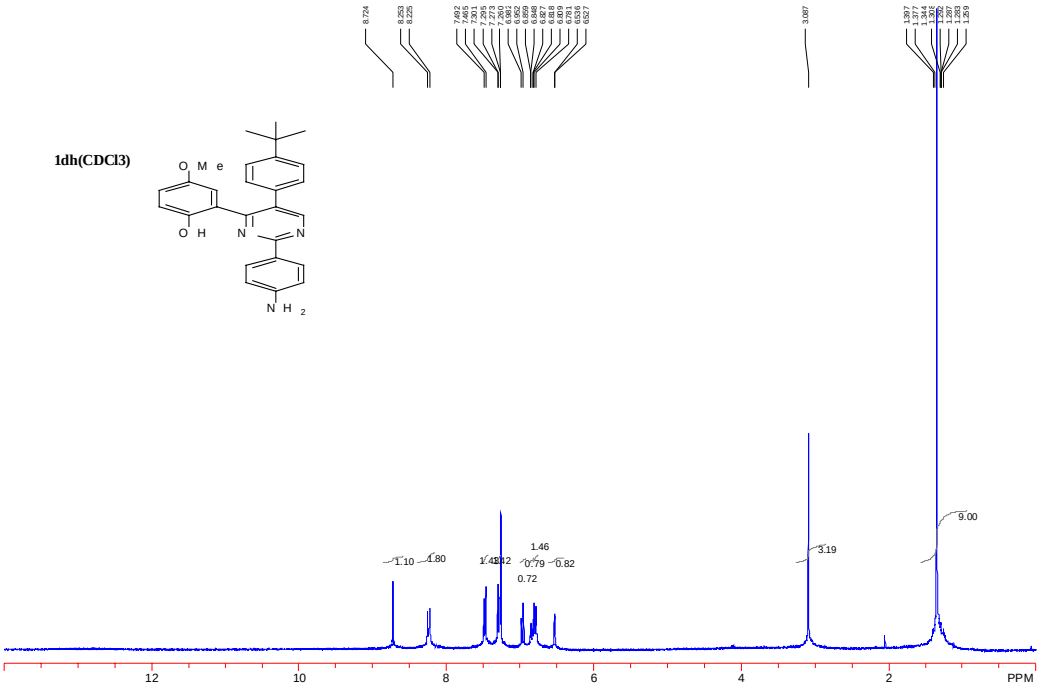
3ak(CDCl3)



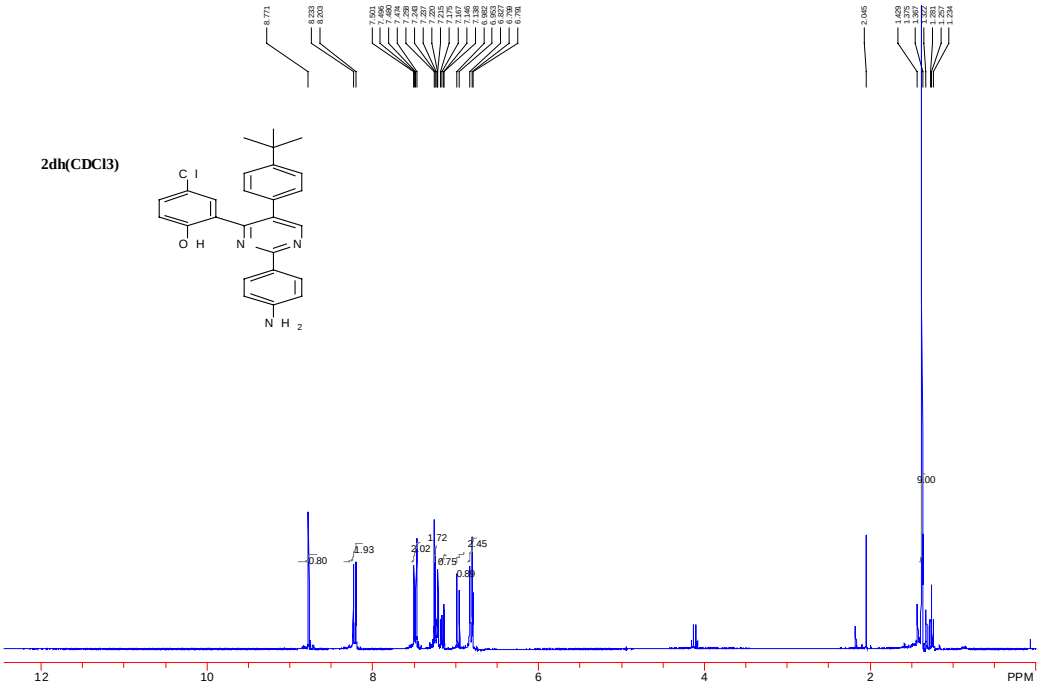
4ak(CDCl3)

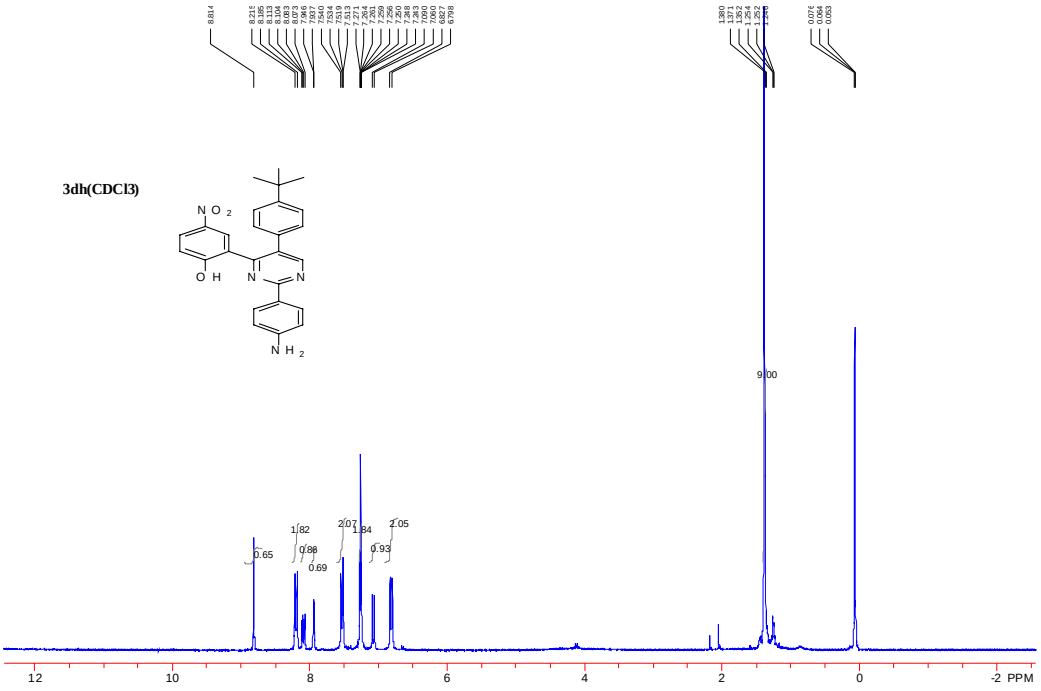


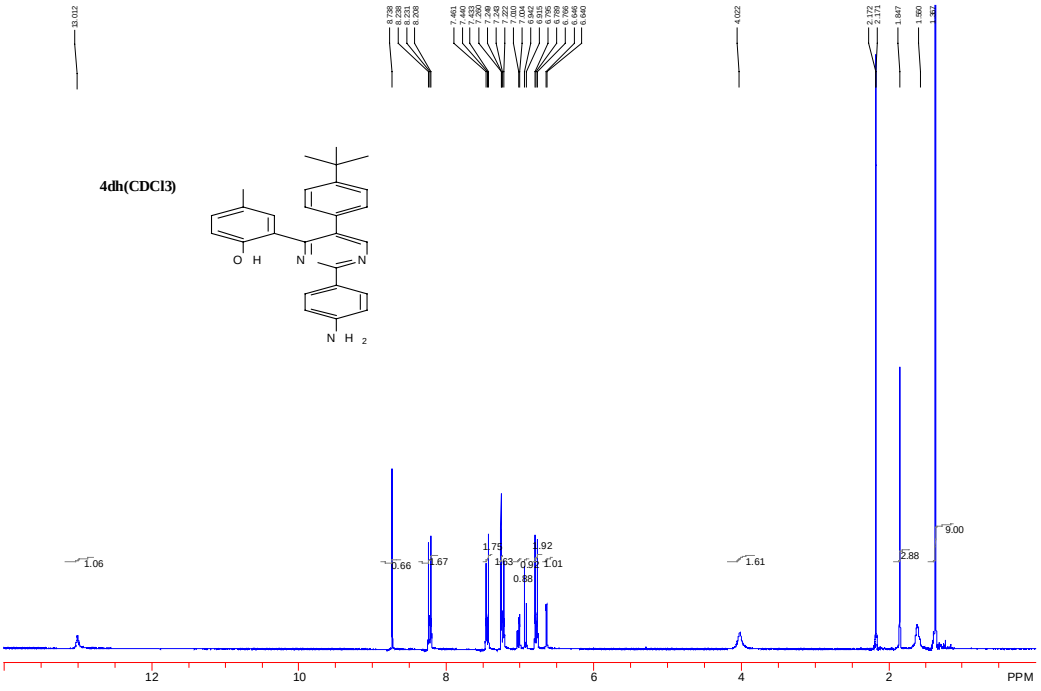
1dh(CDCl3)

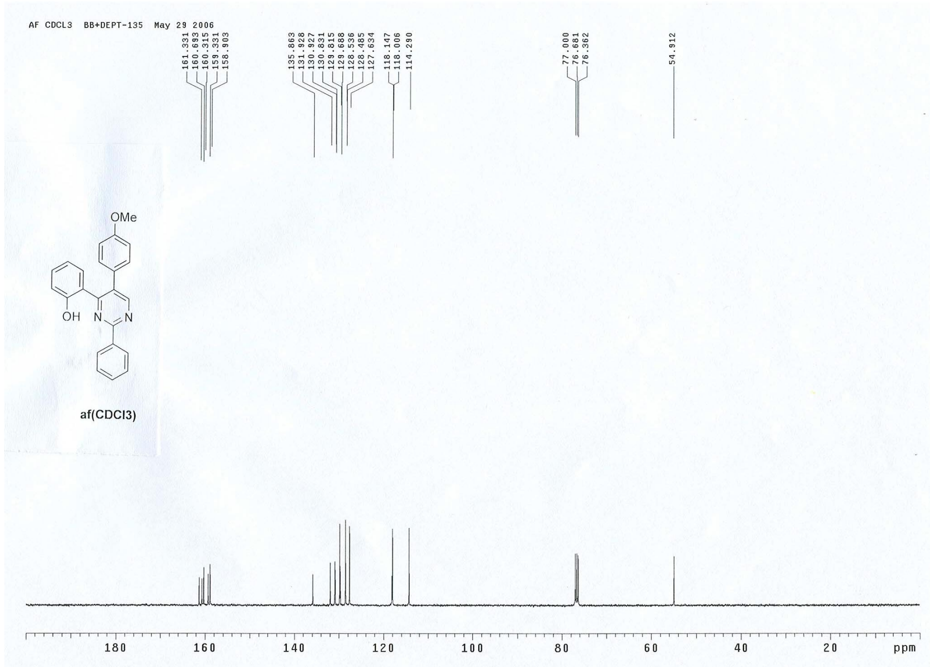


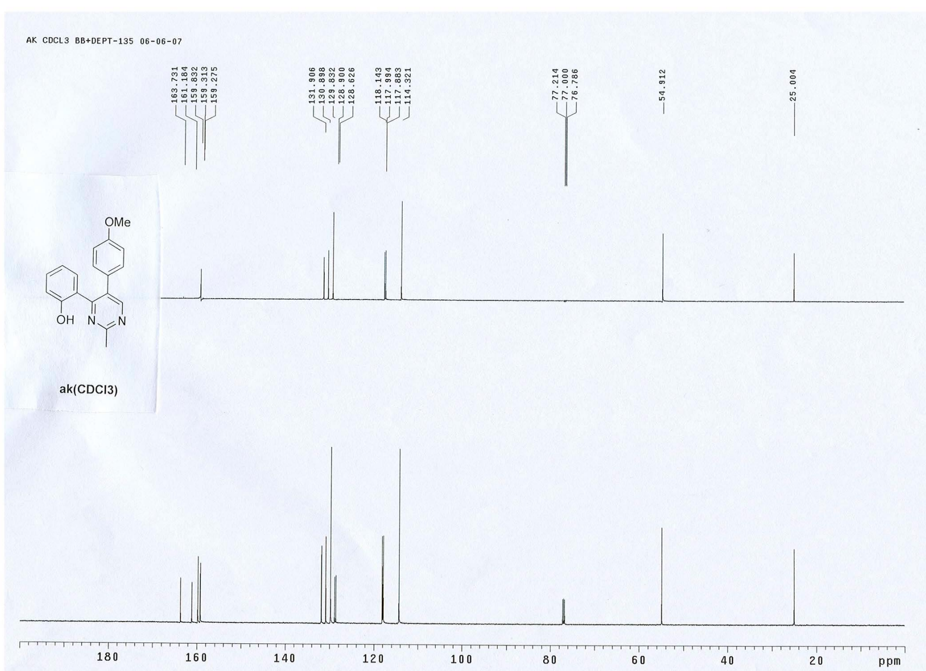
2dh(CDCl3)

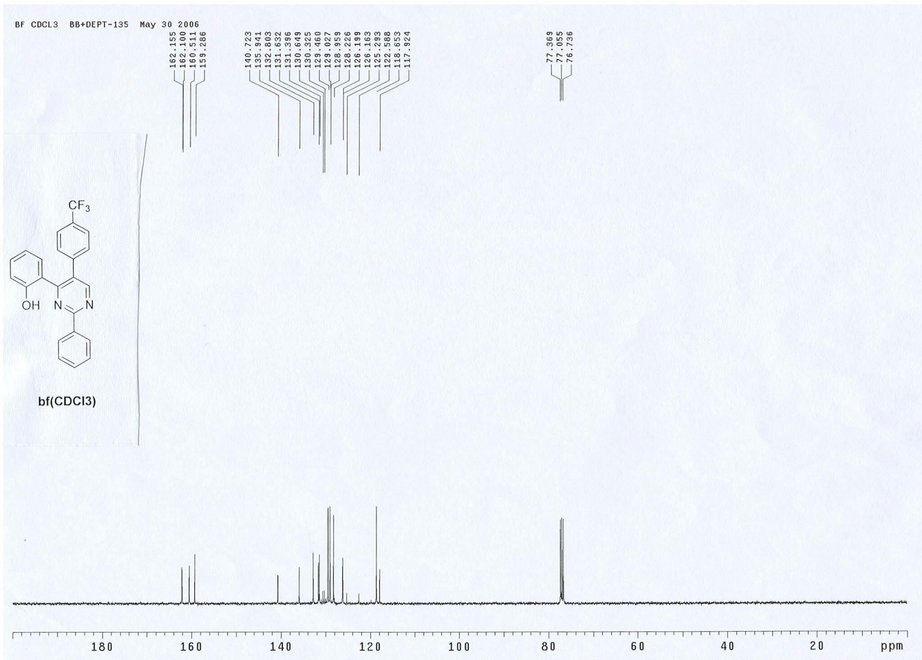


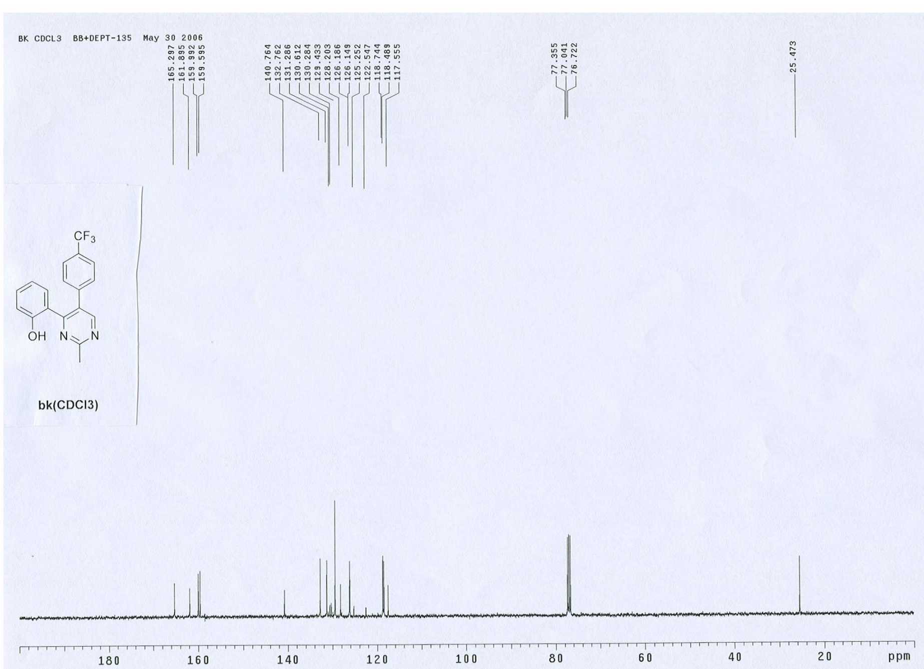

3dh(CDCl3)
NO2
OH
N
N
NH2
9.00
0.65
1.82
0.88
0.69
2.07
1.84
0.93
2.05
12
10
8
6
4
2
0
-2 PPM

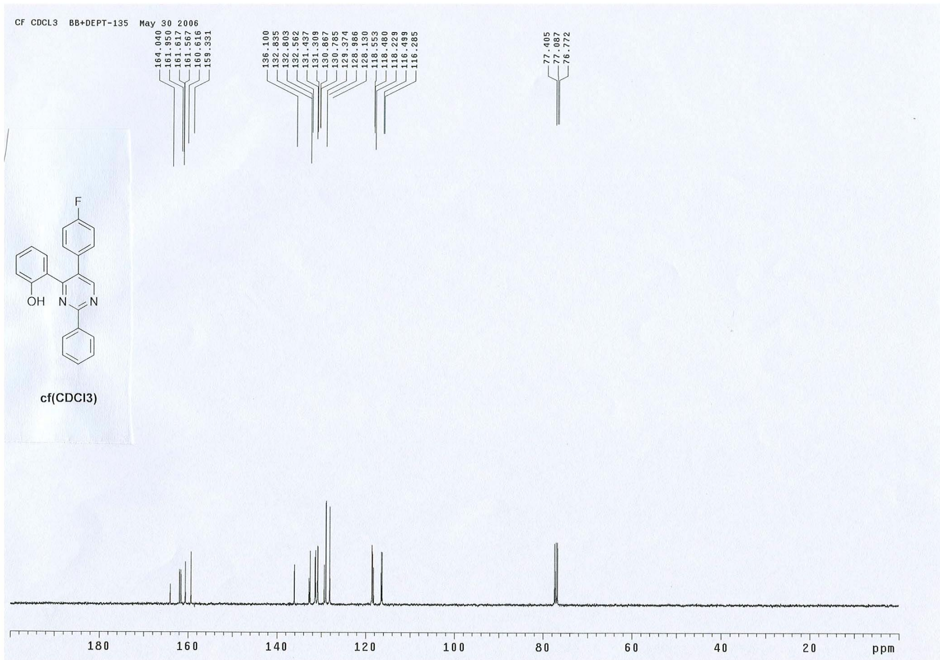

4dh(CDCl3)
OH
N
N
NH2
1.06
0.66
1.67
1.75
1.63
0.92
0.88
1.92
1.01
1.61
2.88
9.00
12
10
8
6
4
2
PPM

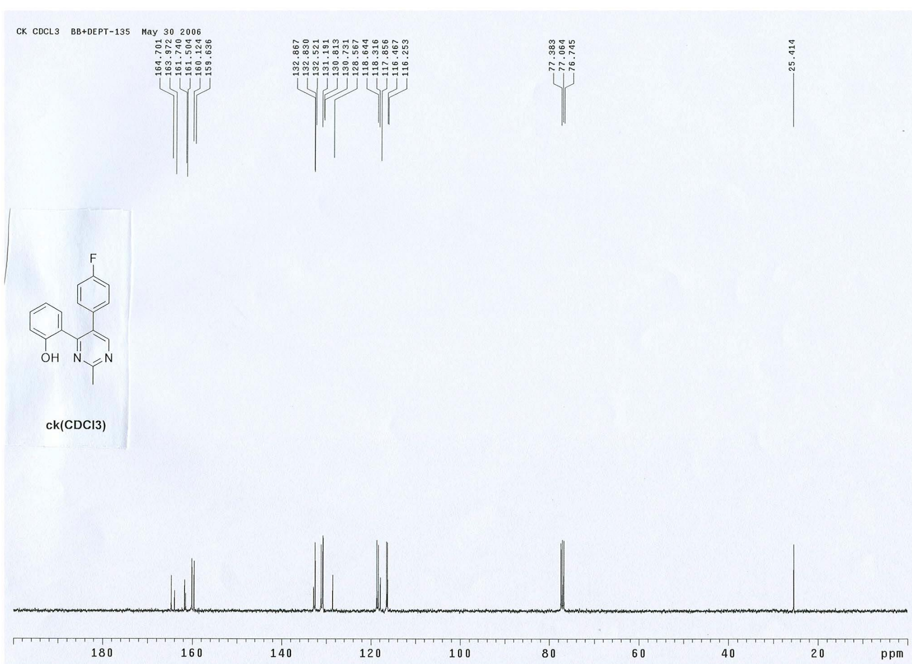

AF CDCL3 BB+DEPT-135 May 29 2006
161.331
160.693
160.315
159.331
158.903
135.863
131.928
130.927
130.831
129.815
129.688
128.536
128.485
127.634
118.147
118.006
114.290
77.000
76.681
76.362
54.912
OMe
OH
N
N
af(CDCl3)
180
160
140
120
100
80
60
40
20
ppm

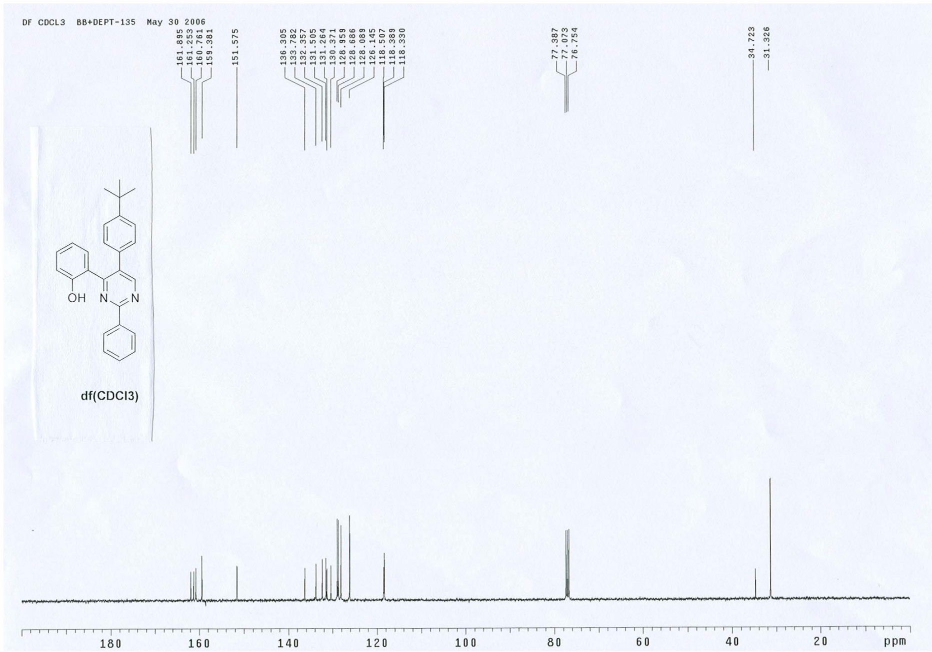

AK CDCL3 BB+DEPT-135 06-06-07
163.731
161.184
159.832
159.313
159.275
131.906
130.898
129.832
128.900
128.626
118.143
117.994
117.883
114.321
77.214
77.000
76.786
54.912
25.004
OMe
OH
N
N
ak(CDCl3)
180
160
140
120
100
80
60
40
20
ppm

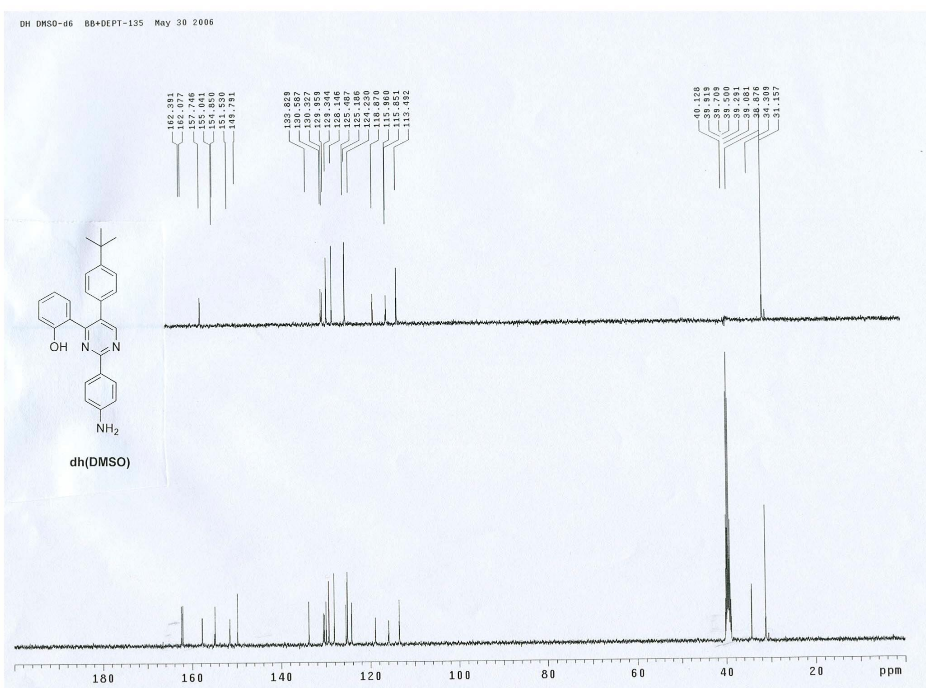

BF CDCL3 BB+DEPT-135 May 30 2006
CF3
OH
N
N
bf(CDCl3)
180
160
140
120
100
80
60
40
20
ppm

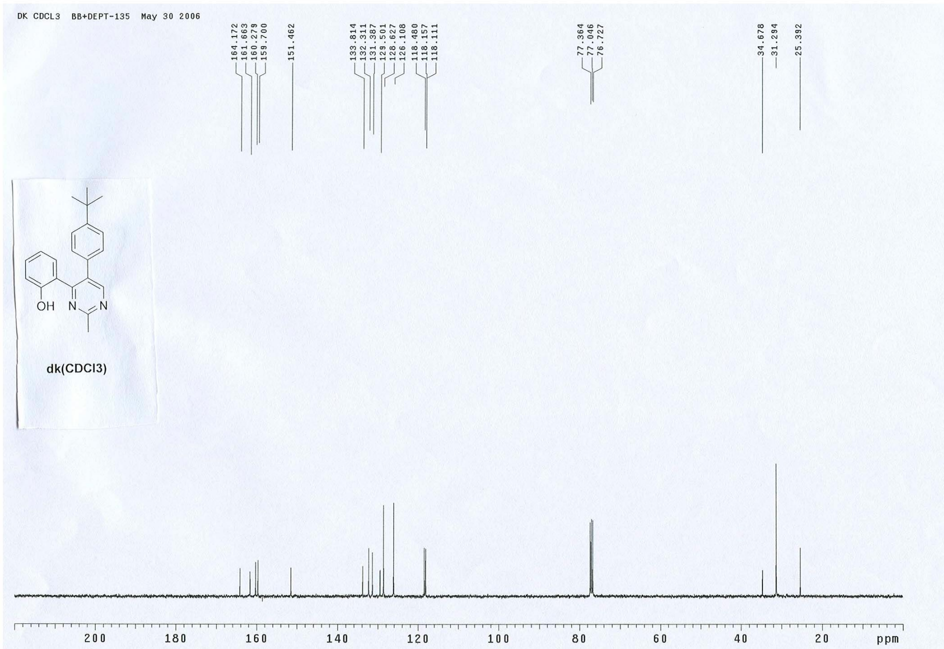

BK CDCL3 BB+DEPT-135 May 30 2006
CF3
OH
N
N
bk(CDCl3)
180
160
140
120
100
80
60
40
20
ppm

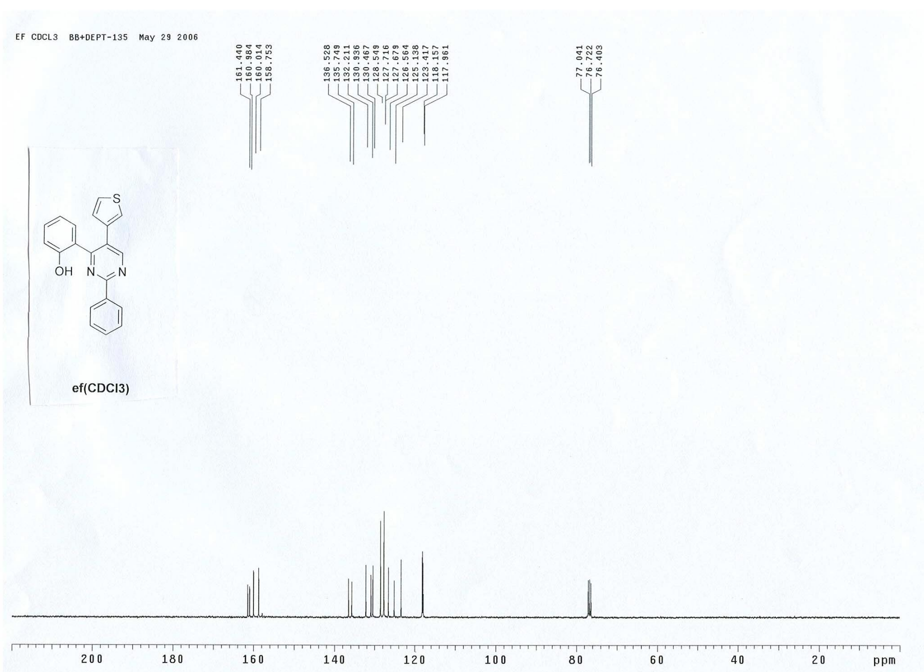

CF CDCL3 BB+DEPT-135 May 30 2006
cf(CDCl3)
ppm

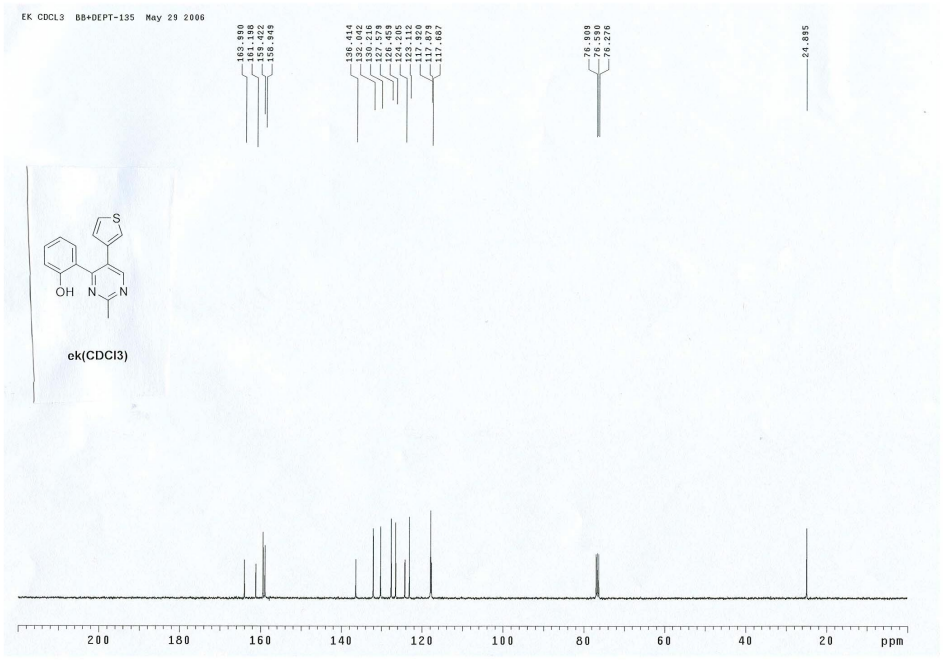

CK CDCL3 BB+DEPT-135 May 30 2006
ck(CDCl3)
ppm


DF CDCL3 BB+DEPT-135 May 30 2006
161.895
161.253
160.761
159.381
151.575
136.305
133.782
132.357
131.505
131.264
130.371
128.959
128.686
128.089
126.145
118.507
118.389
118.330
77.387
77.073
76.754
34.723
31.326
OH
N
N
df(CDCl3)
180
160
140
120
100
80
60
40
20
ppm


DH DMSO-d6 BB+DEPT-135 May 30 2006
162.391
162.077
157.746
155.041
154.850
151.530
149.791
133.829
130.587
130.327
129.959
129.344
128.146
125.487
125.186
124.230
118.870
115.960
115.851
113.492
40.128
39.919
39.709
39.500
39.291
39.081
38.876
34.309
31.157
OH
N
N
NH2
dh(DMSO)
180
160
140
120
100
80
60
40
20
ppm






EK CDCL3 BB+DEPT-135 May 29 2006
163.990
161.196
159.422
158.949
136.414
132.042
130.216
127.573
126.455
124.205
123.112
122.850
117.879
117.687
76.909
76.590
76.276
24.895
S
OH
N
N
ek(CDCl3)
200
180
160
140
120
100
80
60
40
20
ppm