Step economical synthesis of *o*-aryl benzamides via C-H activation relayed by the *in situ* installation of directing group: a multicomponent method

Yunyun Liu,[a] Yi Zhang,[a] Meiying Huang,[a] and Jie-Ping Wan*,[a]

[a]*Key Laboratory of Functional Small Organic Molecules, Ministry of Education, and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P.R. China. Email: wanjieping@jxnu.edu.cn*

Contents

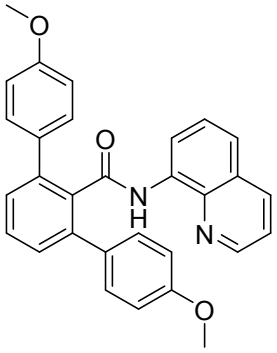
General experimental information

All chemicals and solvents used in the experiments were obtained from commercial sources and used directly without further treatment. All reactions were performed in open air conditions. The ^{1}H and ^{13}C NMR were recorded in 400 MHz apparatus using $CDCl_3$ as solvent, the frequency for ^{1}H NMR and ^{13}C NMR test are 400 MHz and 100 MHz, respectively. The chemical shifts were reported in ppm using TMS as internal standard. HRMS results were tested under ESI model in a spectrometer equipped with TOF analyzer. Melting points were tested in X-4A instrument without correcting temperature.

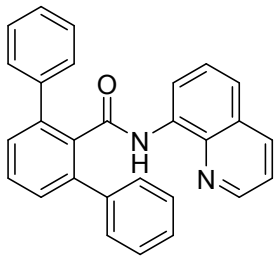
General procedure for the synthesis of benzamides 4 and 5

In a 25 mL round bottom flask equipped with a condenser were located 8-aminoquinoline **1** (0.3 mmol), acyl chloride **2** (0.3 mmol), iodobenzene **3** (0.9 mmol)/(0.45 mmol in the synthesis of **5**), $Pd(OAc)_2$ (0.009 mmol), K_2CO_3 (0.6 mmol) and xylene (2 mL). The mixture was stirred at 120 ^oC for 12h. Upon completion (TCL), the reaction was allowed to cool down to room temperature, and 10 mL water was added. The heterogeneous mixture was extracted with ethyl acetate (3 ×10 mL). The combined organic phase was dried over Na_2SO_4. After filtering, the acquired solution was collected and the solvent was removed at reduced pressure. The residue was subjected to silica gel column chromatography to give pure products by using mixed petroleum ether and ethyl acetate (V_{PET}: V_{EA} = 5:1).

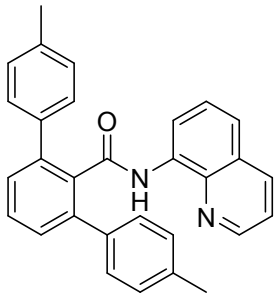
Characterization data



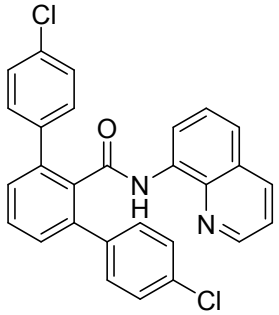
***N*-(Quinolin-8-yl)-2,6-di(*p*-methoxyphenyl) benzamide** (**4a**).[1] White solid, mp 181-182 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1 H), 8.59-8.55 (m, 2 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 4 H), 7.43-7.40 (m, 4 H), 7.34 (q, *J* = 4.1 Hz, 1 H), 6.78 (d, 4 H), 3.67 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 158.9, 147.8, 140.2, 138.4, 136.1, 136.0, 134.4, 132.9, 129.8, 129.2, 129.1, 127.7, 127.2, 121.4, 121.3, 116.5, 113.7, 55.1.



***N*-(Quinolin-8-yl)-2,6-diphenyl benzamide** (**4b**).[2] White solid, mp 205-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 8.58-8.53 (m, 2 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 4 H), 7.48 (d, *J* = 7.2 Hz, 2 H), 7.40 (d, *J* = 6.8 Hz, 2 H), 7.32 (q, *J* = 4.3 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 4 H), 7.16 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 147.8, 140.6, 140.4, 138.2, 136.2, 136.0, 134.3, 129.4, 129.3, 128.7, 128.2, 127.7, 127.3, 127.2, 121.5, 121.3, 116.4.

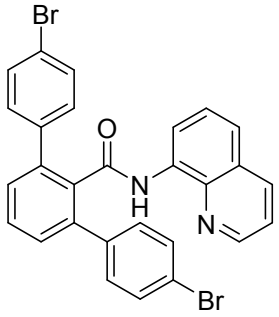


***N*-(Quinolin-8-yl)-2,6-ditolyl benzamide** (**4c**). White solid, mp 115-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.57-8.53 (m, 2 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.43-7.40 (m, 8 H), 7.32 (q, *J* = 4.1 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 4 H), 2.18 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 147.7, 140.5, 138.3, 137.6, 137.0, 136.0, 134.4, 129.2, 128.9, 128.8, 128.6, 127.7, 127.3, 124.4, 121.4, 121.3, 116.6, 21.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{30}H_{25}N_2O$: 429.1967; found: 429.1980.

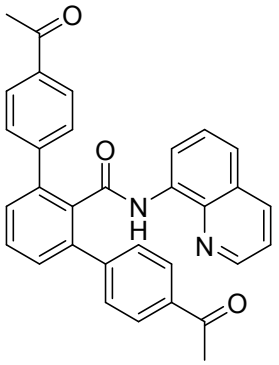


***N*-(Quinolin-8-yl)-2,6-di(*p*-chlorophenyl) benzamide** (**4d**). White solid, mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.57 (dd, *J* = 4.0, 1.6 Hz, 1 H), 8.51-8.49 (m, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.48-7.42 (m, 8 H), 7.37 (q, *J* = 4.1 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 147.9, 139.4, 138.7, 136.2, 136.0, 133.9, 133.7, 130.3, 130.0, 129.6, 128.6, 128.5, 127.8, 127.2, 121.9, 121.5, 116.7; HRMS (ESI): m/z $[M + H]^+$ calcd for

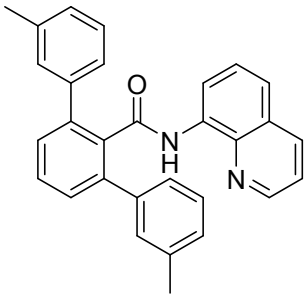
$C_{28}H_{19}Cl_2N_2O$: 496.0874; found: 496.0896.



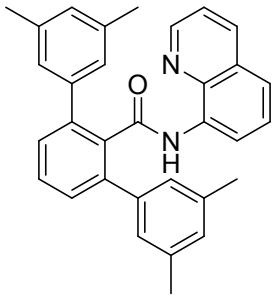
***N*-(Quinolin-8-yl)-2,6-di(*p*-bromoxyphenyl) benzamide** (**4e**). White solid, mp 215-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.57 (dd, *J* = 4.0, 1.2 Hz, 1 H), 8.51-8.48 (m, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.46-7.44 (m, 3 H), 7.42 (s, 2 H), 7.39 (d, *J* = 5.6 Hz, 6 H), 7.36 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 147.9, 139.5, 139.1, 138.2, 136.3, 136.1, 135.9, 133.9, 131.4, 130.4, 129.5, 127.8, 127.2, 122.0, 121.9, 121.5, 116.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{18}Br_2N_2NaO$: 578.9684; found: 578.9686.



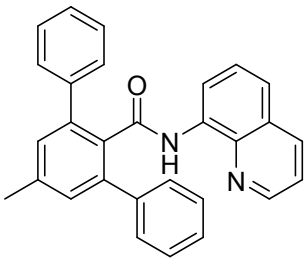
***N*-(Quinolin-8-yl)-2,6-di(*p*-acetylphenyl) benzamide** (**4f**). Pale yellow solid, mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 8.56-8.47 (m, 2 H), 8.07 (d, *J* = 7.2 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 4 H), 7.64 (d, *J* = 8.0 Hz, 5 H), 7.51 (d, *J* = 7.6 Hz, 2 H), 7.44 (s, 2 H), 7.35 (q, *J* = 4.0 Hz, 1 H), 2.47 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 166.9, 147.9, 145.0, 139.7, 136.4, 136.0, 135.9, 133.8, 129.9, 129.7, 129.0, 128.9, 128.4, 127.7, 127.3, 122.0, 121.5, 116.8, 26.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{24}N_2NaO_3$: 507.1685; found: 507.1691.



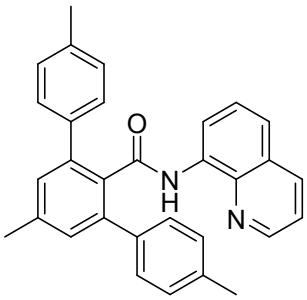
***N*-(Quinolin-8-yl)-2,6-di(*m*-methylphenyl) benzamide** (**4g**). White solid, mp 134-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.60-8.52 (m, 2 H), 8.05-8.02 (m, 1 H), 7.57-7.53 (m, 1 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.42-7.32 (m, 7 H), 7.12 (t, *J* = 7.6 Hz, 2 H), 6.96 (d, *J* = 7.6 Hz, 2 H), 2.21 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 147.7, 140.7, 140.4, 137.7, 136.2, 136.2, 136.1, 134.4, 129.6, 129.3, 129.2, 128.1, 128.0, 127.7, 127.2, 125.8, 121.4, 121.3, 116.4, 21.3; HRMS (ESI): m/z [M + H]$^{+}$ calcd for $C_{30}H_{25}N_2O$: 429.1967; found: 429.1982.



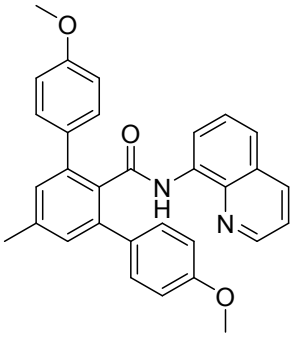
***N*-(Quinolin-8-yl)-2,6-di(3,5-dimethylphenyl) benzamide** (**4h**). White solid, mp 190-192 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1 H), 8.59-8.58 (m, 1 H), 8.50 (dd, *J* = 7.2, 1.6 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 7.52-7.48 (m, 1 H), 7.43-7.34 (m, 4 H), 7.30 (q, *J* = 4.1 Hz, 1 H), 7.15 (s, 4 H), 6.73 (s, 2 H), 2.12 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 147.7, 140.8, 140.4, 138.4, 137.6, 136.2, 136.1, 134.5, 129.2, 129.1, 129.0, 127.7, 127.2, 126.7, 121.4, 121.3, 116.4, 21.3; HRMS (ESI): m/z [M + H]$^{+}$ calcd for $C_{32}H_{29}N_2O$: 457.2280; found: 457.2303.



***N*-(Quinolin-8-yl)-2,6-diphenyl 4-methylbenzamide** (**4i**). White solid, mp 160-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1 H), 8.55-8.50 (m, 2 H), 8.03-8.01 (m, 1 H), 7.54-7.52 (m, 4 H), 7.41-7.36 (m, 2 H), 7.31 (q, *J* = 4.1 Hz, 1 H), 7.28 (s, 2 H), 7.25-7.21 (m, 4 H), 7.13 (t, *J* = 7.4 Hz, 2 H), 2.48 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =167.7, 147.7, 140.6, 140.5, 139.2, 138.2, 136.0, 134.4, 133.6, 130.1, 128.7, 128.1, 127.6, 127.3, 121.3, 116.3, 21.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{23}N_2O$: 415.1810; found: 415.1804.

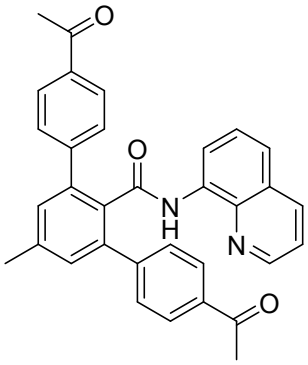


***N*-(Quinolin-8-yl)-2,6-ditolyl 4-methylbenzamide** (**4j**). White solid, mp 179-180 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1 H), 8.55-8.54 (m, 2 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.42-7.38 (m, 6 H), 7.32 (q, *J* = 3.9 Hz, 1 H), 7.24 (s, 2 H), 7.03 (d, *J* = 7.6 Hz, 4 H), 2.46 (s, 3 H), 2.18 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 147.7, 140.6, 139.1, 138.3, 137.7, 136.9, 136.0, 134.5, 133.5, 130.0, 128.9, 128.5, 127.6, 127.3, 121.3, 121.3, 116.4, 21.4, 21.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{31}H_{27}N_2O$: 443.2123; found: 443.2133.

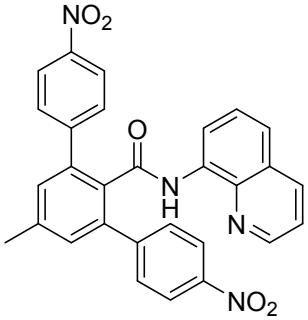


***N*-(Quinolin-8-yl)-2,6-di(*p*-methoxylphenyl) 4-methylbenzamide** (**4k**).[1] White solid, mp 198-199 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.60-8.59 (m, 2 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.49-7.44 (m, 6 H), 7.37 (q, *J* = 3.9 Hz, 1 H), 7.25 (s, 2 H), 6.79 (d, *J* = 8.0 Hz, 4 H), 3.69 (s, 6 H), 2.49 (s, 3 H); ^{13}C NMR (100 MHz,

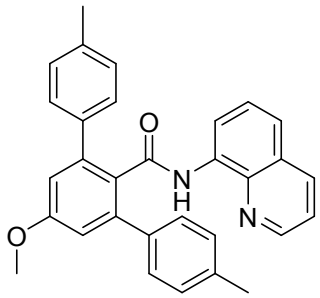
$CDCl_3$): δ = 168.2, 158.9, 147.8, 140.2, 139.1, 138.3, 136.0, 134.5, 133.5, 133.0, 129.8, 127.7, 127.3, 121.3, 116.4, 113.7, 55.1, 21.4.



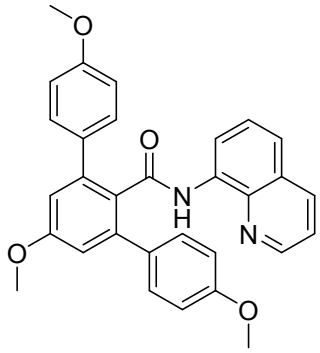
***N*-(Quinolin-8-yl)-2,6-di(*p*-acetylphenyl) 4-methylbenzamide** (**4l**). Pale yellow solid, mp 205-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1 H), 8.55-8.47 (m, 2 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 4 H), 7.63 (d, *J* = 8.4 Hz, 4 H), 7.44 (s, 2 H), 7.37-7.33 (m, 3 H), 2.52 (s, 3 H), 2.47 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 167.1, 147.9, 145.2, 139.8, 139.7, 135.9, 133.9, 133.4, 130.5, 128.9, 128.4, 127.7, 127.2, 121.9, 121.5, 116.6, 26.6, 21.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{33}H_{26}N_2O_3Na$: 521.1836; found: 521.1850.



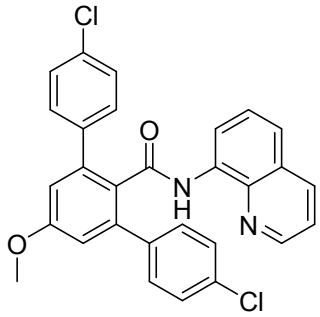
***N*-(Quinolin-8-yl)-2,6-di(*p*-nitroxylphenyl) 4-methylbenzamide** (**4m**). Pale yellow solid, mp 250-252 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 8.54 (d, *J* = 2.8 Hz, 1 H), 8.45 (d, *J* = 5.2 Hz, 1 H), 8.12 (d, *J* = 8.8 Hz, 5 H), 7.70 (d, *J* = 8.8 Hz, 4 H), 7.45-7.36 (m, 5 H), 2.55 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 147.9, 147.2, 146.8, 140.3, 138.8, 138.0, 136.6, 133.4, 130.9, 129.6, 129.3, 127.8, 127.3, 123.5, 122.4, 121.7, 116.8, 21.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{21}N_4O_5$: 505.1512; found: 505.1510.



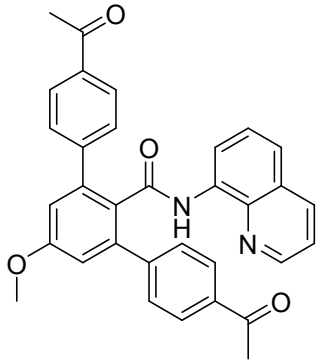
***N*-(Quinolin-8-yl)-2,6-ditolyl 4-methoxylbenzamide** (**4n**). White solid, mp 159-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1 H), 8.55-8.54 (m, 2 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 3 H), 7.40-7.35 (m, 3 H), 7.29 (q, *J* = 4.1 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 4 H), 6.95 (s, 2 H), 3.88 (s, 3 H), 2.17 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 159.6, 147.8, 142.4, 138.3, 137.7, 137.1, 135.9, 134.6, 129.3, 129.0, 128.5, 127.6, 127.3, 121.3, 116.3, 114.6, 55.5, 21.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_2$: 459.2073; found: 459.2066.



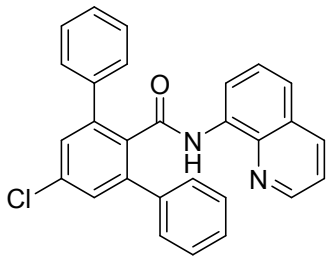
***N*-(Quinolin-8-yl)-2,6-di(*p*-methoxylphenyl) 4-methoxylbenzamide** (**4o**). White solid, mp 157-159 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 8.58-8.55 (m, 2 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 4 H), 7.43-7.36 (m, 2 H), 7.30 (q, *J* = 4.1 Hz, 1 H), 6.93 (s, 2 H), 6.77 (d, *J* = 8.4 Hz, 4 H), 3.88 (s, 3 H), 3.63 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 159.6, 159.0, 147.8, 142.0, 138.3, 136.0, 134.5, 133.0, 129.7, 129.6, 129.3, 127.7, 127.3, 121.3, 116.3, 114.4, 113.7, 55.5, 55.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_4$: 491.1971; found: 491.1965.



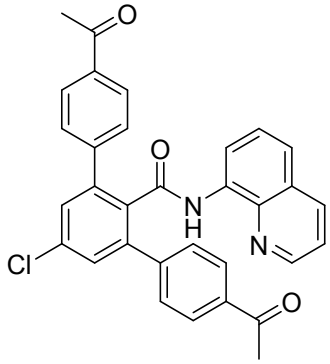
***N*-(Quinolin-8-yl)-2,6-di(*p*-chlorophenyl) 4-methoxylbenzamide** (**4p**). White solid, mp 156-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (s, 1 H), 8.55-8.48 (m,2 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.47-7.41 (m, 6 H), 7.33 (dd, *J* = 8.0, 4.4 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 4H), 6.93 (s, 2 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 159.8, 147.9, 141.3, 138.8, 138.2, 136.2, 134.1, 133.7, 129.9, 129.1, 128.5, 127.7, 127.2, 121.8, 121.5, 116.5, 114.9, 55.6; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{29}H_{20}Cl_2N_2O_2Na$: 521.0794; found: 499.0988.



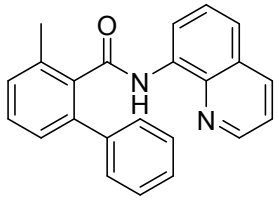
***N*-(Quinolin-8-yl)-2,6-di(*p*-acetylphenyl) 4-methoxylbenzamide** (**4q**). Pale yellow solid, mp 204-205 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H), 8.53-8.45 (m, 2 H), 8.03 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 4 H), 7.62 (d, *J* = 8.0 Hz, 4 H), 7.41 (s, 2 H), 7.33 (q, *J* = 3.7 Hz, 1 H), 7.00 (s, 2 H), 3.92 (s, 3 H), 2.45 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 166.9, 159.9, 147.8, 145.1, 141.6, 136.3, 136.2, 136.1, 134.0, 128.8, 128.7, 128.4, 127.7, 127.2, 121.8, 121.5, 116.5, 115.2, 55.7, 26.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{33}H_{26}N_2NaO_4$: 537.1790; found: 537.1808.



***N*-(Quinolin-8-yl)-2,6-diphenyl 4-chlorobenzamide** (**4r**). White solid, mp 148-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 1 H), 8.57 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.49-8.47 (m, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 4 H), 7.46 (s, 2 H), 7.41 (d, *J* = 3.6 Hz, 2 H), 7.35 (q, *J* = 4.0 Hz, 1 H), 7.27-7.23 (m, 4 H), 7.17 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 147.8, 142.3, 139.1, 138.1, 136.1, 134.9, 134.6, 134.0, 129.2, 128.5, 128.3, 127.9, 127.6, 127.2, 121.6, 121.4, 116.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{19}ClN_2NaO$: 457.1084; found: 457.1110.

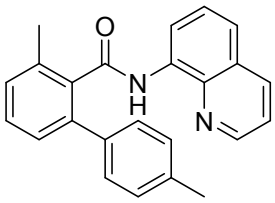


,6-di(*p*-acetylphenyl) 4-chlorobenzamide (**4s**). Pale yellow solid, mp 216-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 8.56 (d, *J* = 2.8 Hz, 1 H), 8.44 (d, *J* = 5.2 Hz, 1 H), 8.07 (d, *J* = 6.8 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 4 H), 7.63 (d, *J* = 8.0 Hz, 4 H), 7.51 (s, 2 H), 7.44-7.35 (m, 3 H), 2.47 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 164.8, 146.9, 142.5, 140.3, 137.0, 135.4, 135.2, 134.3, 133.4, 132.6, 128.5, 127.8, 127.3, 126.6, 126.1, 121.0, 120.4, 115.7, 25.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{32}H_{23}ClN_2NaO_3$: 541.1295; found: 541.1308.

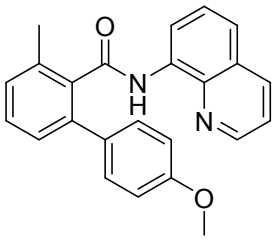


***N*-(Quinolin-8-yl)-2-methyl-6-phenyl benzamide** (**5a**).[1] Colorless oil; ^{1}H NMR (400

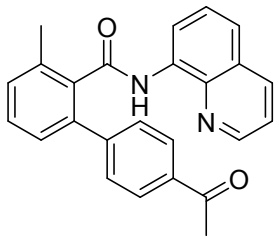
MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.77 (d, *J* = 7.6 Hz, 1 H), 8.57 (s, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 2 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.42-7.37 (m, 2 H), 7.29 (d, *J* = 4.4 Hz, 3 H), 7.19 (t, *J* = 6.6 Hz, 2 H), 7.07 (t, *J* = 6.8 Hz, 1 H), 2.53 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 148.0, 140.4, 139.7, 138.4, 136.9, 136.1, 135.9, 134.4, 129.5, 129.2, 128.7, 128.2, 127.8, 127.6, 127.3, 127.3, 121.7, 121.5, 116.5, 19.8.



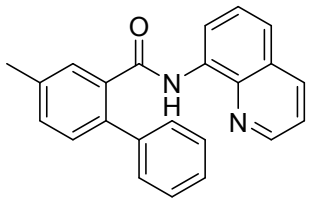
***N*-(Quinolin-8-yl)-2-methyl-6-(*p*-tolyl) benzamide** (**5b**).[2] White solid, mp 118-120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 8.79 (d, *J* = 7.2 Hz, 1 H), 8.57 (s, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.43-7.39 (m, 3 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.28-7.23 (m, 3 H), 7.00 (d, *J* = 6.8 Hz, 2 H), 2.52 (s, 3 H), 2.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 148.0, 139.7, 138.4, 137.5, 136.9, 136.9, 136.1, 135.7, 134.5, 129.3, 129.2, 129.0, 128.6, 127.8, 127.7, 127.3, 121.7, 121.4, 116.6, 21.0, 19.8.



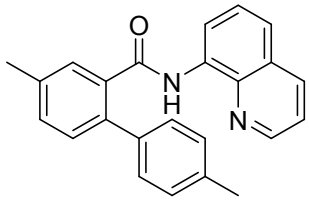
***N*-(Quinolin-8-yl)-2-methyl-6-(*p*-methoxylphenyl) benzamide** (**5c**).[2] White solid, mp 146-147 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 8.69 (d, *J* = 7.6 Hz, 1 H), 8.47 (d, *J* = 4.0 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.40-7.34 (m, 2 H), 7.32-7.24 (m, 2 H), 7.20-7.12 (m, 4 H), 6.64 (d, *J* = 8.4 Hz, 2 H), 3.47 (s, 3 H) 2.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 157.8, 146.9, 138.1, 137.2, 135.7, 135.0, 134.6, 133.3, 131.7, 128.7, 128.1, 128.0, 126.7, 126.5, 126.1, 120.7, 120.4, 115.4, 112.6, 53.9, 18.7.



***N*-(Quinolin-8-yl)-2-methyl-6-(*p*-acetylphenyl) benzamide** (**5d**).[2] White solid, mp 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 8.76 (d, *J* = 6.8 Hz, 1 H), 8.60(d, *J* = 4.0 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.52-7.41 (m, 3 H), 7.36-7.29 (m, 3 H), 2.54 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 168.0, 148.1, 145.3, 138.5, 138.3, 136.7, 136.2, 136.1, 135.8, 134.1, 130.3, 129.4, 128.9, 128.3, 127.8, 127.5, 127.2, 122.0, 121.6, 116.6, 26.6, 19.8.

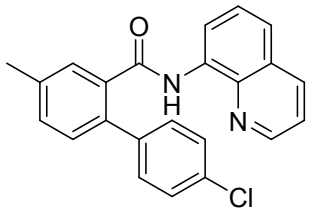


***N*-(Quinolin-8-yl)-2-phenyl-5-methyl benzamide** (**5e**).[1] White solid, mp 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 8.82 (d, *J* = 7.6 Hz, 1 H), 8.48 (dd, *J* = 4.0, 1.6 Hz, 1 H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.72 (s, 1 H), 7.51-7.46 (m, 3 H), 7.42-7.33 (m, 3 H), 7.30-7.23 (m, 3 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 2.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 147.2, 139.5, 137.9, 137.0, 136.9, 135.5, 134.1, 130.8, 130.2, 129.3, 128.5, 127.9, 127.2, 126.9, 126.8, 121.0, 120.9, 115.8, 20.6.

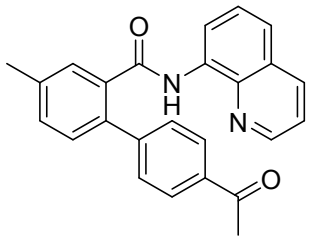


***N*-(Quinolin-8-yl)-2-(*p*-tolyl)-5-methyl benzamide** (**5f**). White solid, mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 8.81 (d, *J* = 4.8 Hz, 1 H), 8.50 (s, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.70 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.38-7.34 (m, 5 H), 7.05 (d, *J* = 5.2 Hz, 2 H), 2.45 (s, 3 H), 2.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 147.6, 138.5, 137.5, 137.2, 137.1, 136.0, 135.9, 134.7, 131.2, 130.6, 129.7, 129.1, 128.9, 127.7, 127.3, 121.4, 121.3, 116.4, 21.0;

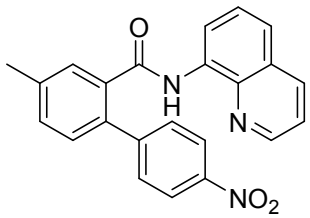
HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{20}N_2NaO$: 375.1473; found: 375.1495.



***N*-(Quinolin-8-yl)-2-(*p*-chlorophenyl)-5-methyl benzamide** (**5g**).[1] White solid, mp 158-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 8.79 (d, *J* = 7.2 Hz, 1 H), 8.55-8.54 (m, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.72 (s, 1 H), 7.55-7.47 (m, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.38-7.32 (m, 3 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 2.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 147.9, 138.5, 138.4, 138.0, 136.1, 135.8, 134.4, 133.6, 131.5, 130.5, 130.4, 129.9, 128.6, 127.8, 127.3, 121.8, 121.5, 116.5, 21.1.



***N*-(Quinolin-8-yl)-2-(*p*-acetylphenyl)-5-methyl benzamide** (**5h**).[3] Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 8.78 (d, *J* = 7.2 Hz, 1 H), 8.49 (d, *J* = 2.4 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 2 H), 7.72 (s, 1 H), 7.57 (d, *J* = 7.6 Hz, 2 H), 7.52-7.44 (m, 2 H), 7.37 (s, 2 H), 7.32 (q, *J* = 4.3 Hz, 1 H), 2.47 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 167.6, 147.8, 145.0, 141.8, 138.4, 138.4, 136.3, 136.1, 136.0, 134.4, 131.4, 130.4, 129.7, 129.2, 128.4, 127.8, 127.3, 121.7, 121.4, 116.4, 26.5, 21.1.



***N*-(Quinolin-8-yl)-2-(*p*-nitrophenyl)-5-methyl benzamide** (**5i**). Pale yellow solid, mp 156-157; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 8.75 (d, *J* = 6.4 Hz, 1 H), 8.54 (s, 1 H), 8.10 (t, *J* = 8.4 Hz, 3 H), 7.73 (s, 1 H), 7.63 (d, *J* = 6.4 Hz, 2 H), 7.50 (d,

J = 6.8 Hz, 2 H), 7.41-7.36 (m, 3 H), 2.50 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 147.9, 147.1, 147.0, 139.2, 138.3, 136.4, 136.1, 135.3, 134.1, 131.6, 130.4, 129.8, 127.8, 127.3, 123.6, 122.1, 121.7, 116.6, 21.1; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{23}H_{17}N_3NaO_3$: 406.1168; found: 406.1180.

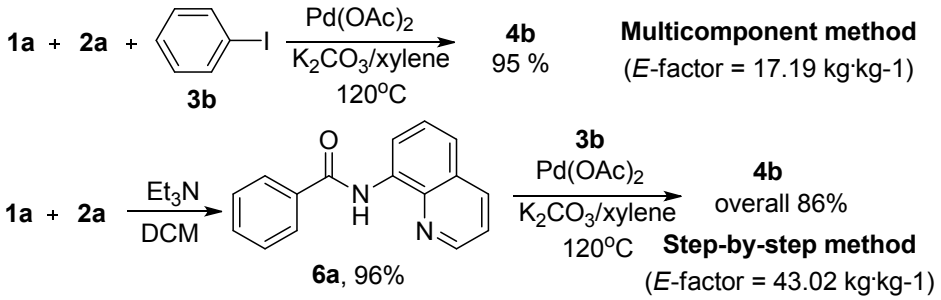
References

(1) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349.

(2) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922.

(3) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664.

Calculation and comparison of *E*-factor



Calculation of *E*-factor

(1) **The one-pot procedure: 1a** (0.3 mmol = 43 mg), **2a** (0.3 mmol = 42 mg), **3b** (0.9 mmol = 184 mg), $Pd(OAc)_2$ (0.009 mmol = 2 mg), K_2CO_3 (0.6 mmol = 83 mg), xylene (2 mL = 1.72g), **4** (114 mg).

Amount of materials used in the synthesis: 43 mg + 42 mg + 184 mg + 2 mg + 83 mg + 1.72 g = 2074 mg

Amount of Product: 114 mg

Amount of wastes produced from the reaction: 2074 – 114 = 1960 mg

E-factor = 1960/114 = 17.19 kg·kg^{-1}

(2) **The step-by-step procedure: 1** (0.3 mmol = 43 mg), **2** (0.3 mmol = 42 mg), **3** (0.9 mmol = 184 mg), Et_3N (0.3 mmol = 30 mg), CH_2Cl_2 (2 mL = 2.65 g), $Pd(OAc)_2$ (0.009 mmol = 2 mg), K_2CO_3 (0.6 mmol = 83 mg), xylene (2 mL = 1.72g), **4** (108

mg).

Amount of materials used in the synthesis: 43 mg + 42 mg + 184 mg + 30 mg + 2.65 g + 2 mg + 83 mg + 1.72 g = 4754 mg

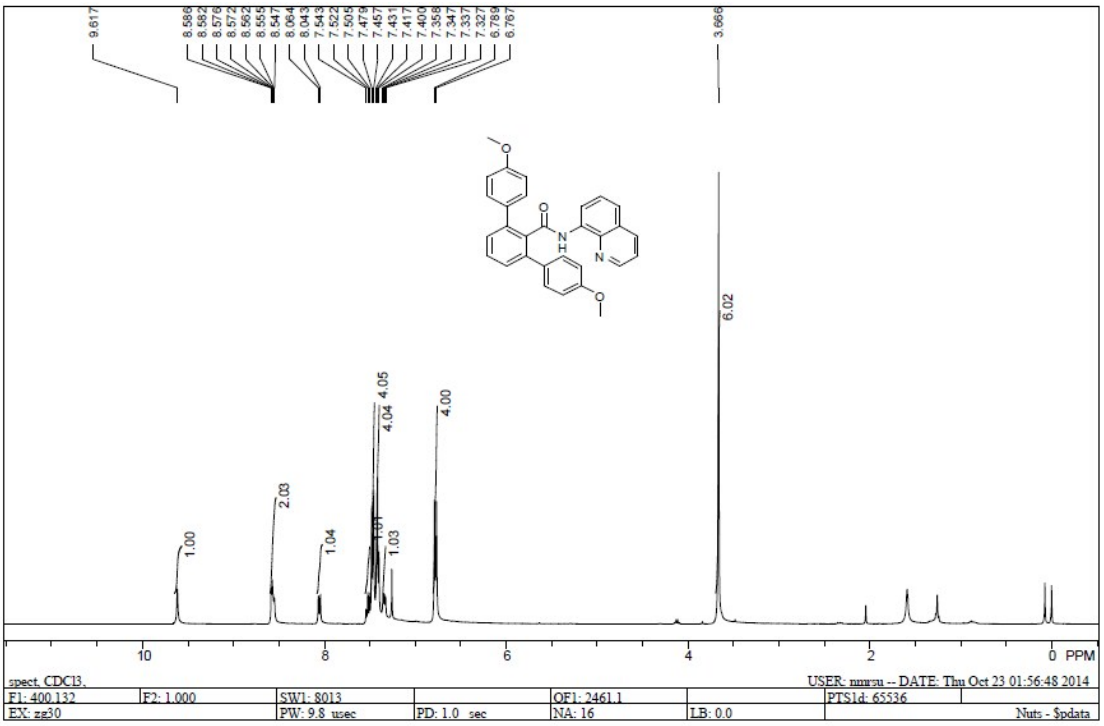
Amount of Product: 108 mg

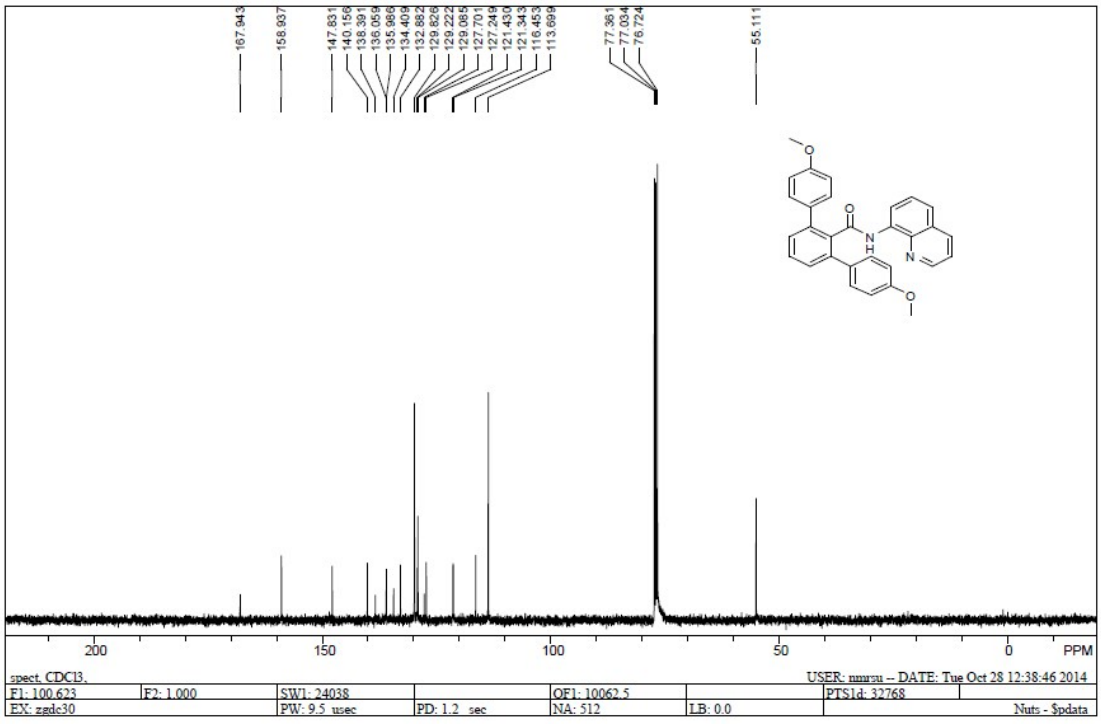
Amount of wastes produced from the reaction: 4754 – 108 = 4646 mg

E-factor = 4646/108 = 43.02 $kg \cdot kg^{-1}$

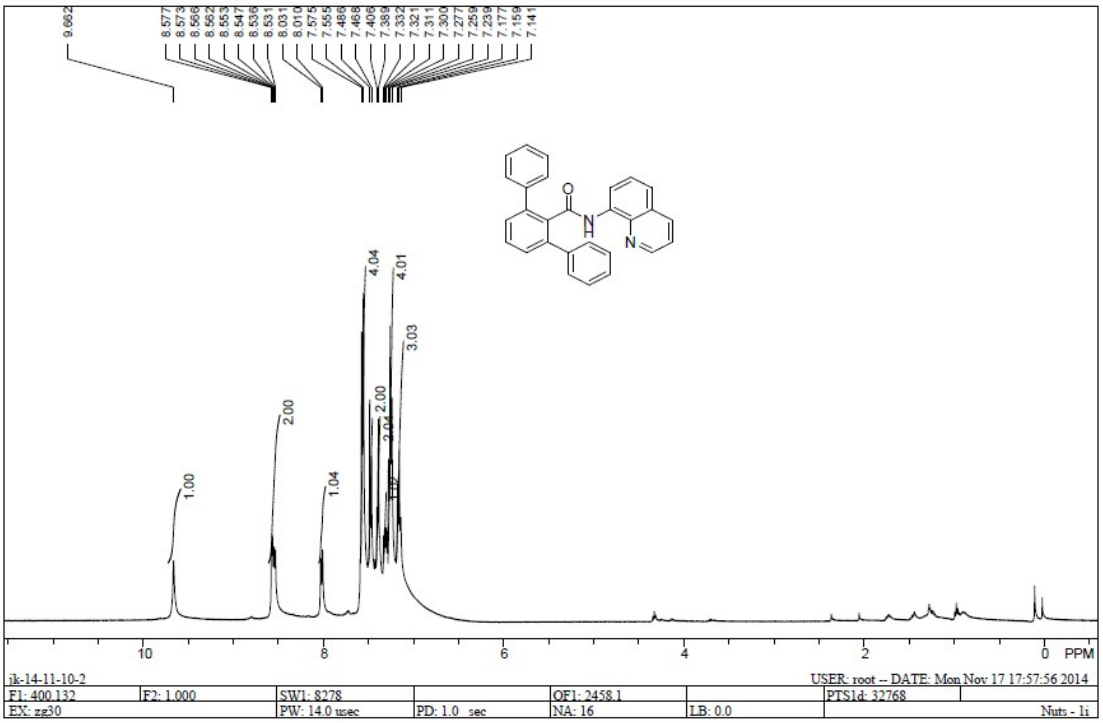
^{1}H and ^{13}C NMR of all products

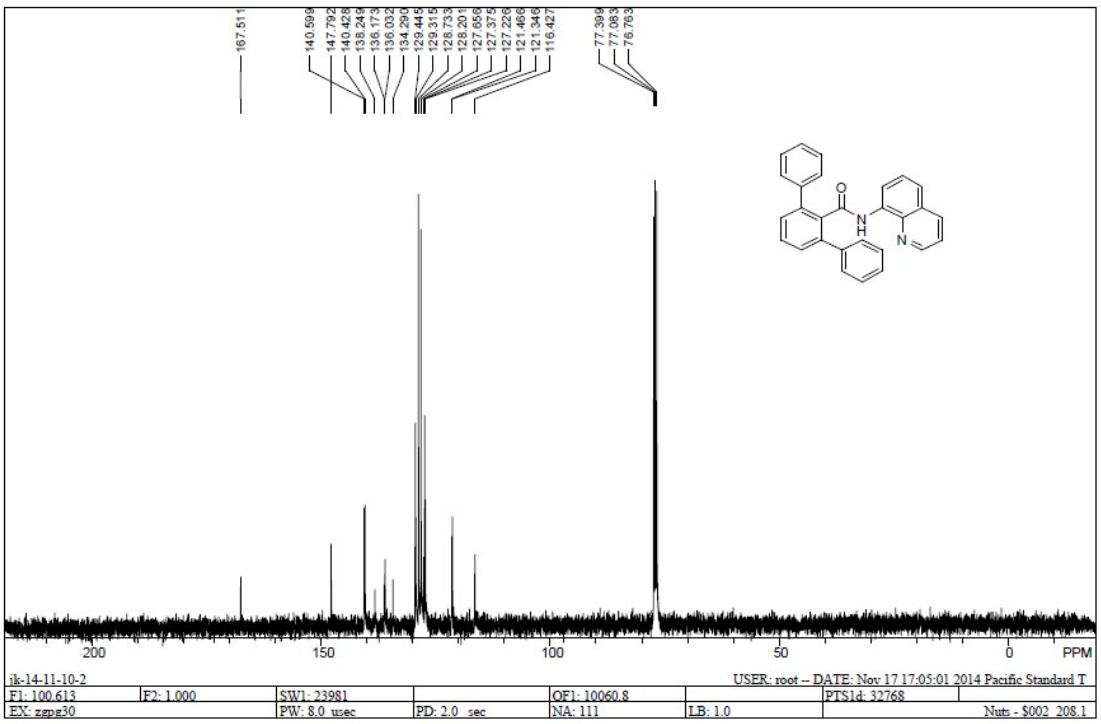
^{1}H and ^{13}C NMR of 4a



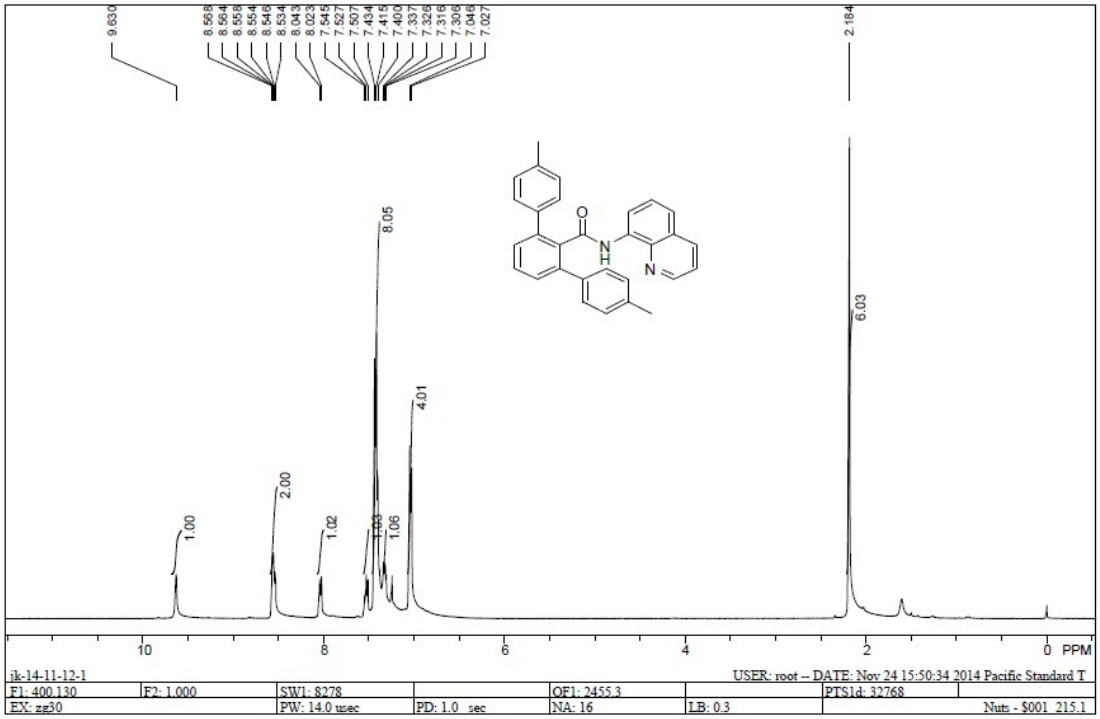


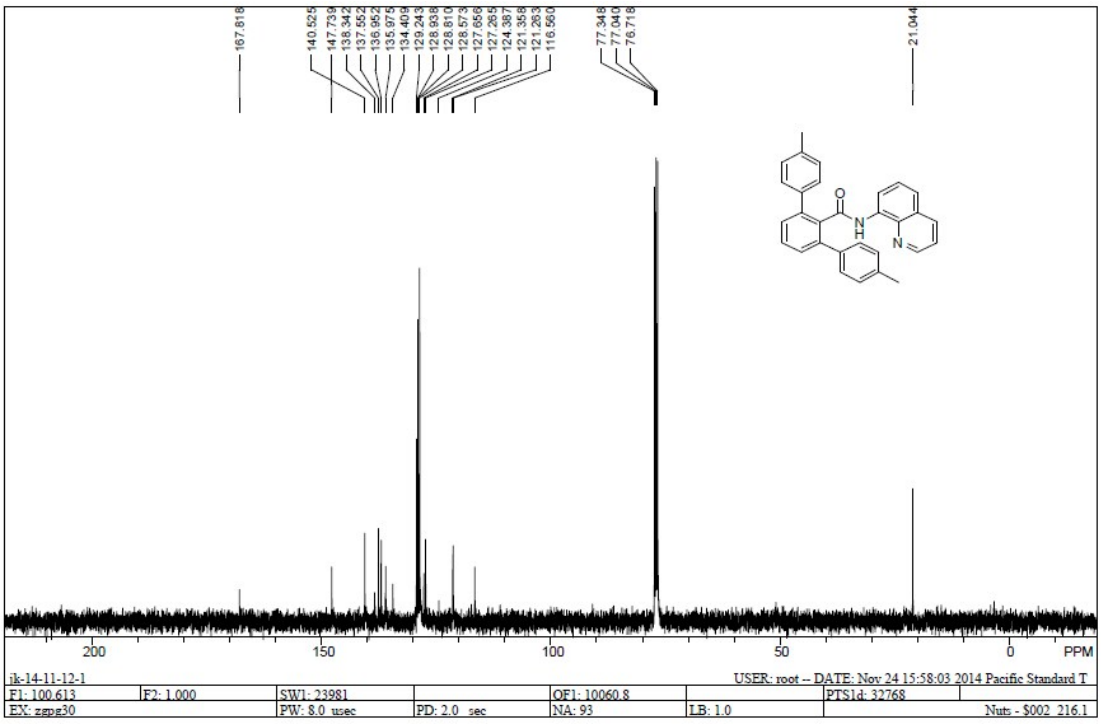
^{1}H and ^{13}C NMR of 4b



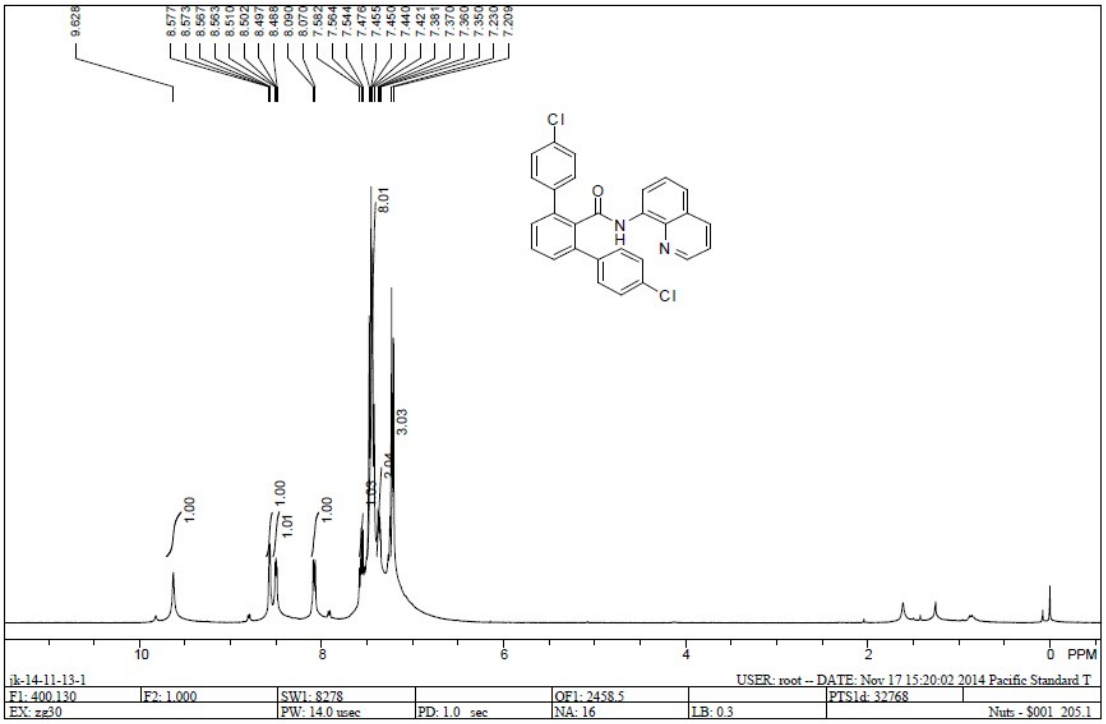


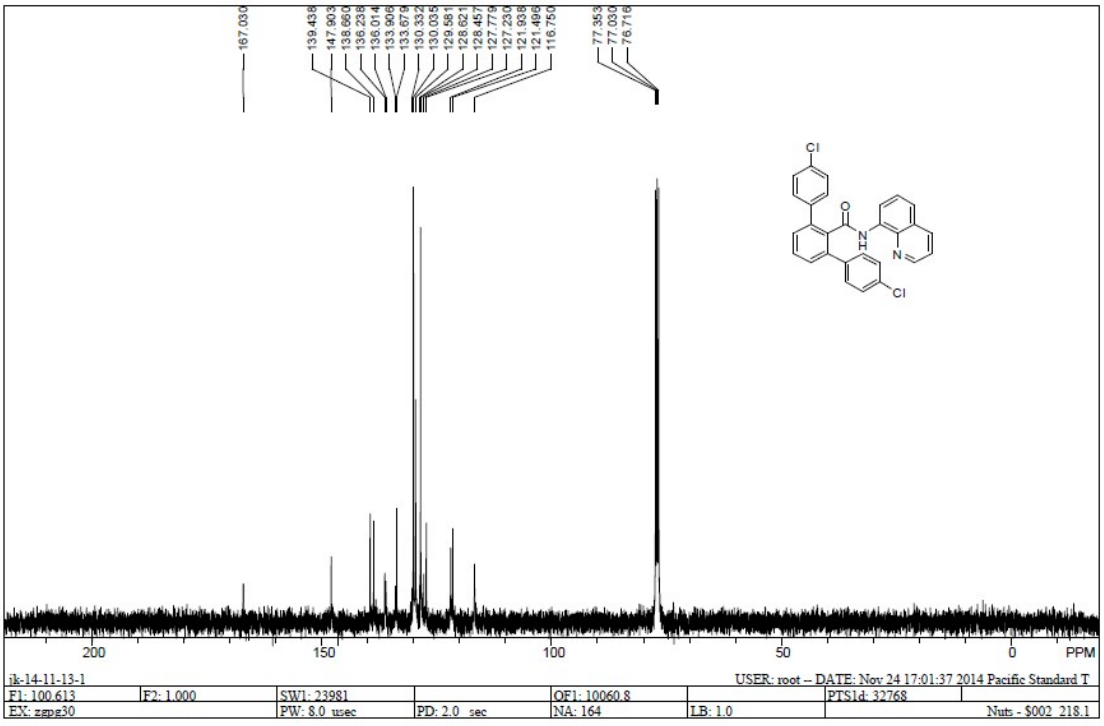
^{1}H and ^{13}C NMR of 4c



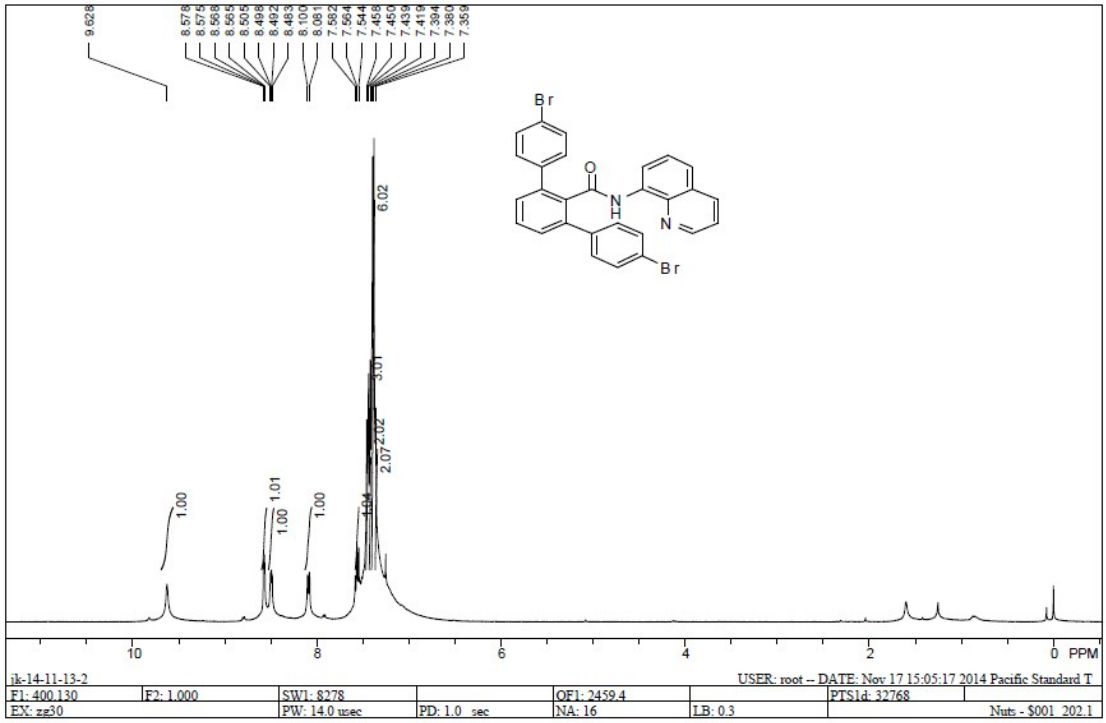


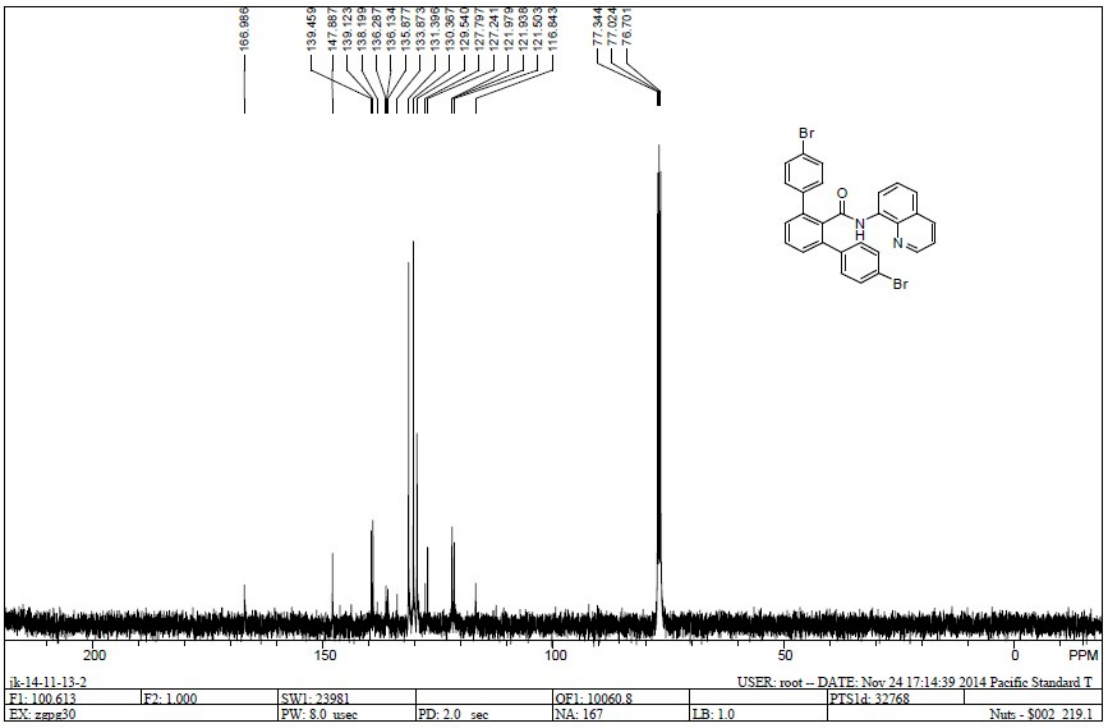
^{1}H and ^{13}C NMR of 4d



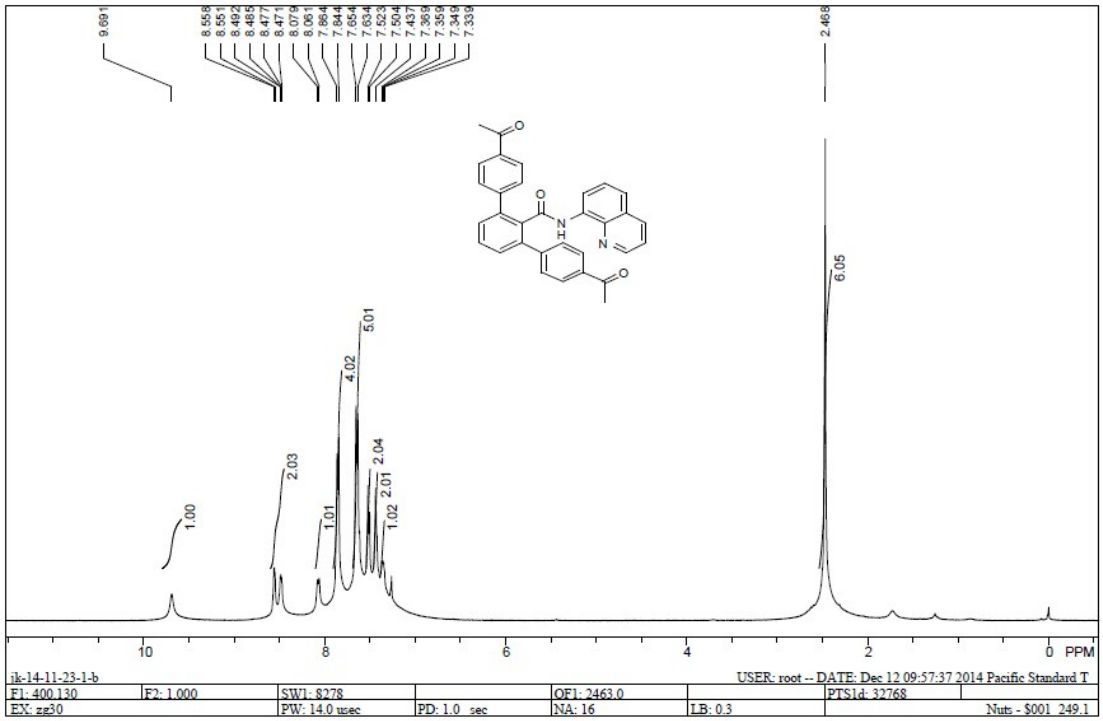


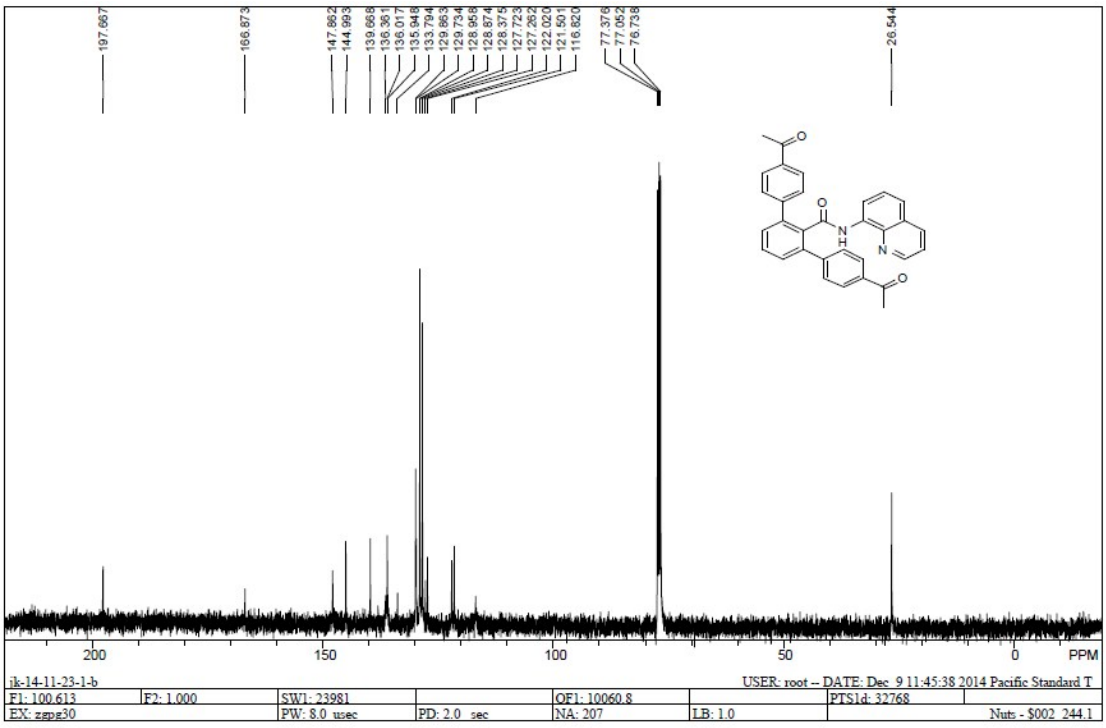
^{1}H and ^{13}C NMR of 4e



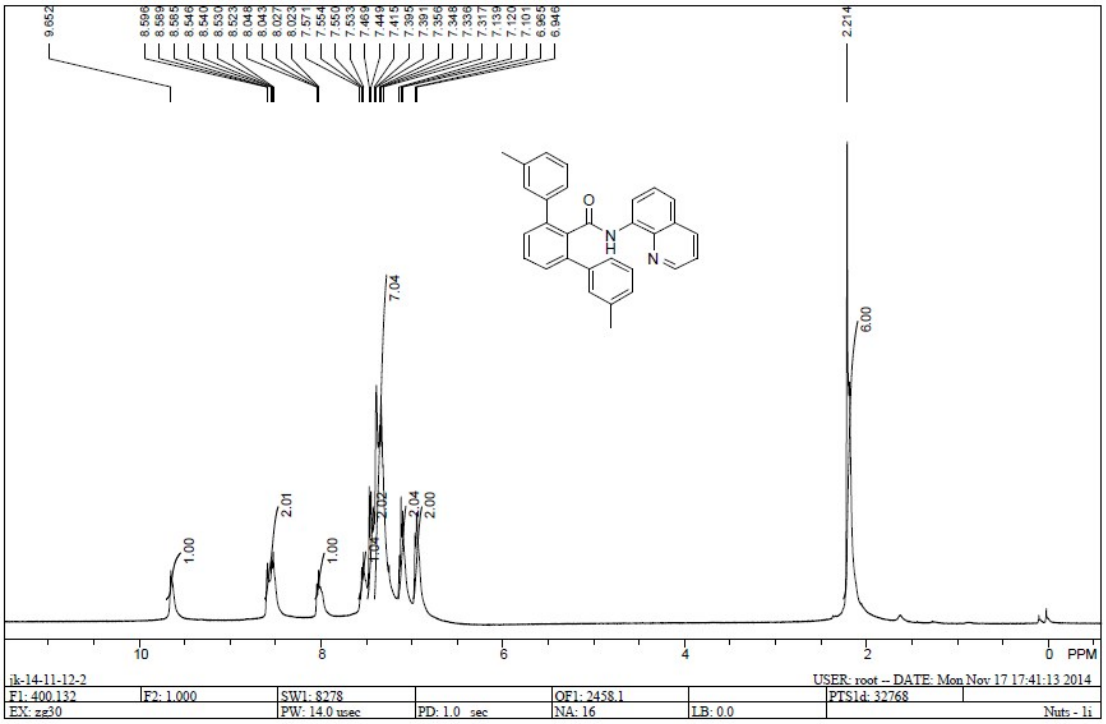


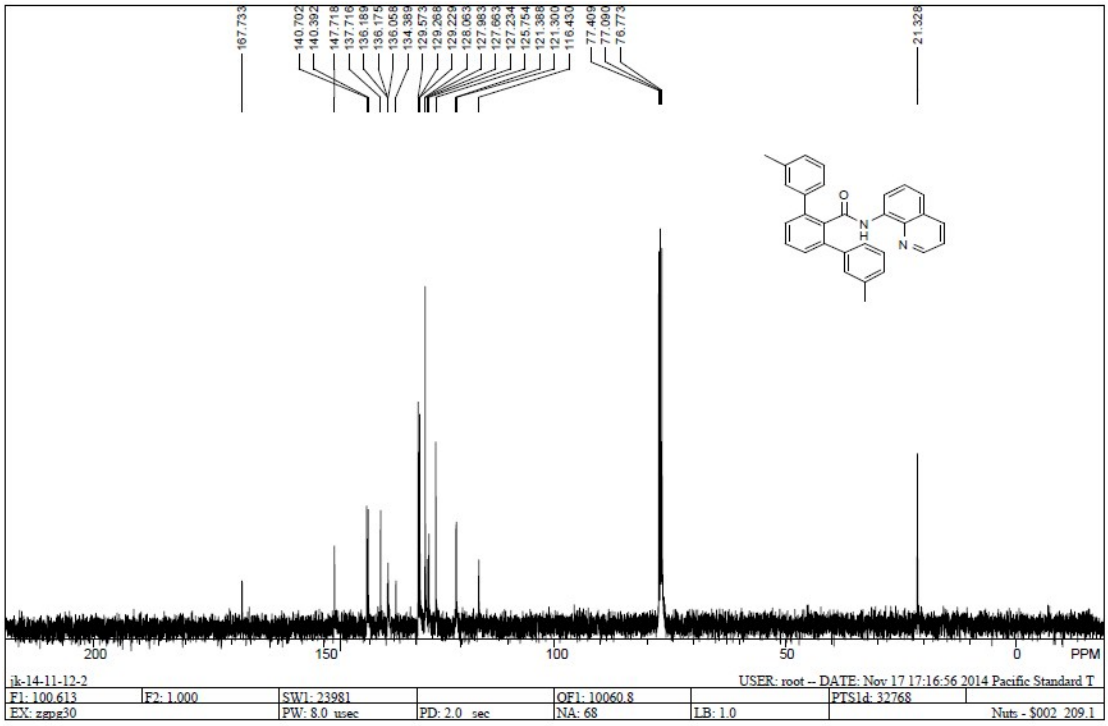
^{1}H and ^{13}C NMR of 4f



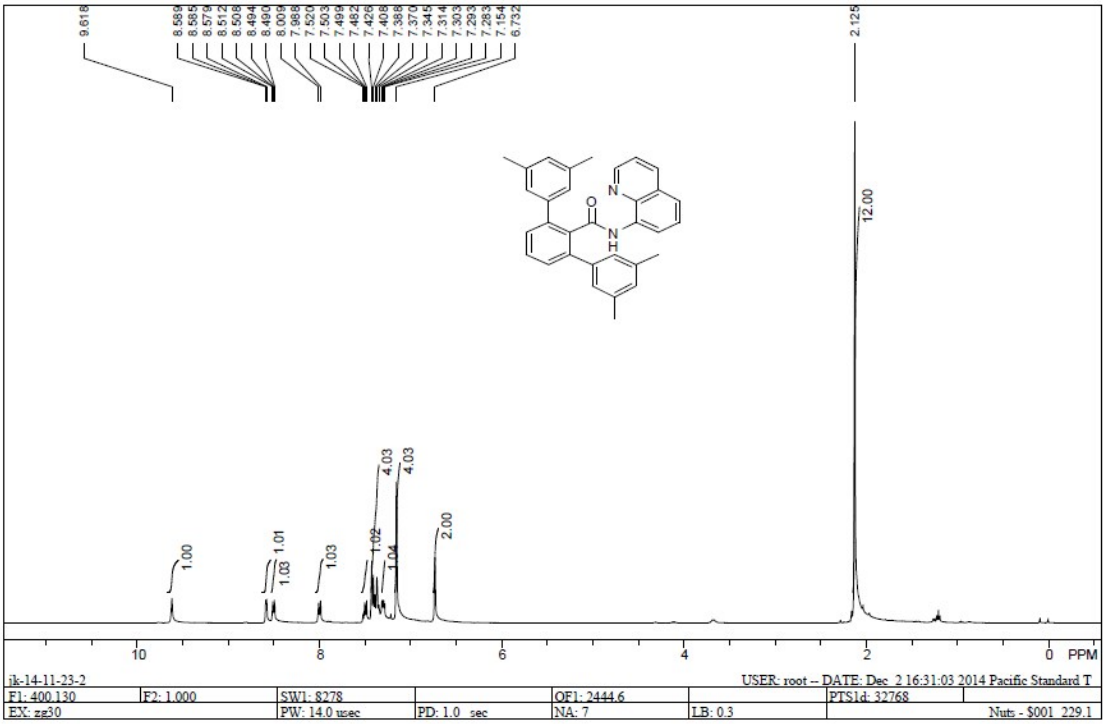


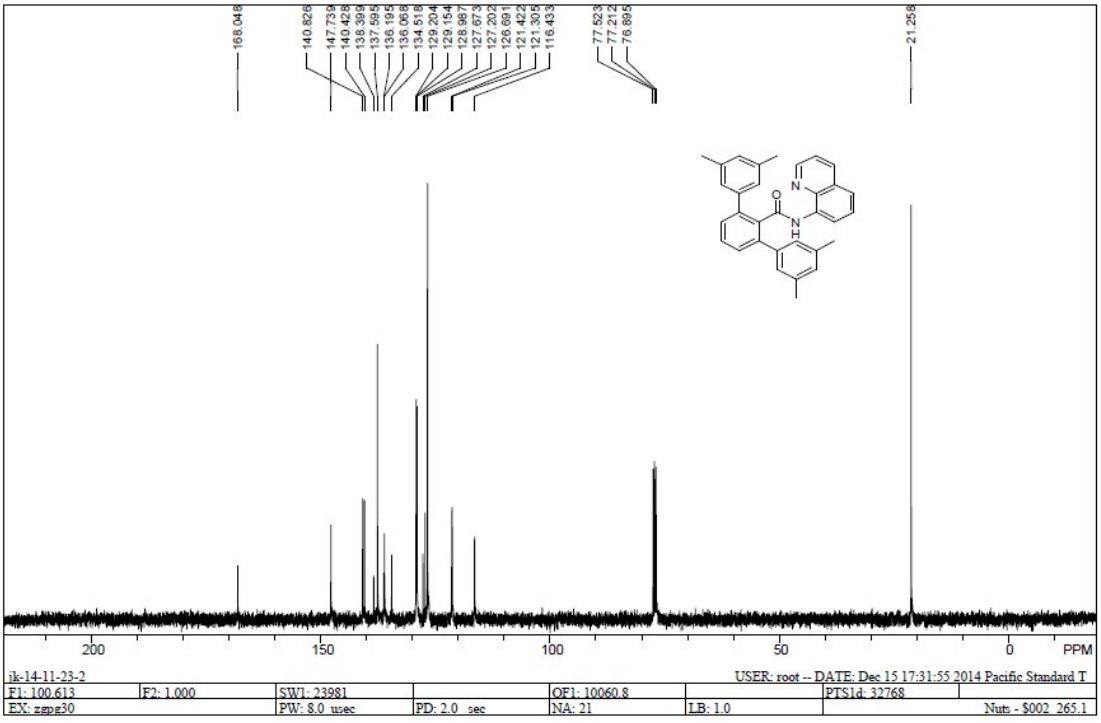
^{1}H and ^{13}C NMR of 4g



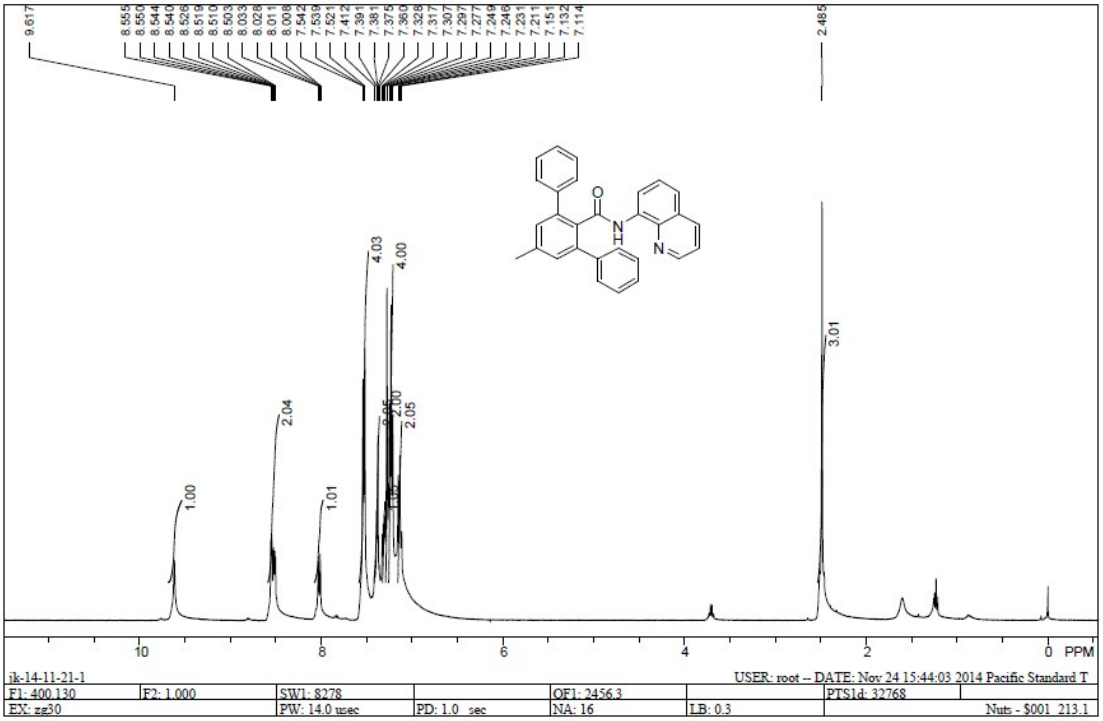


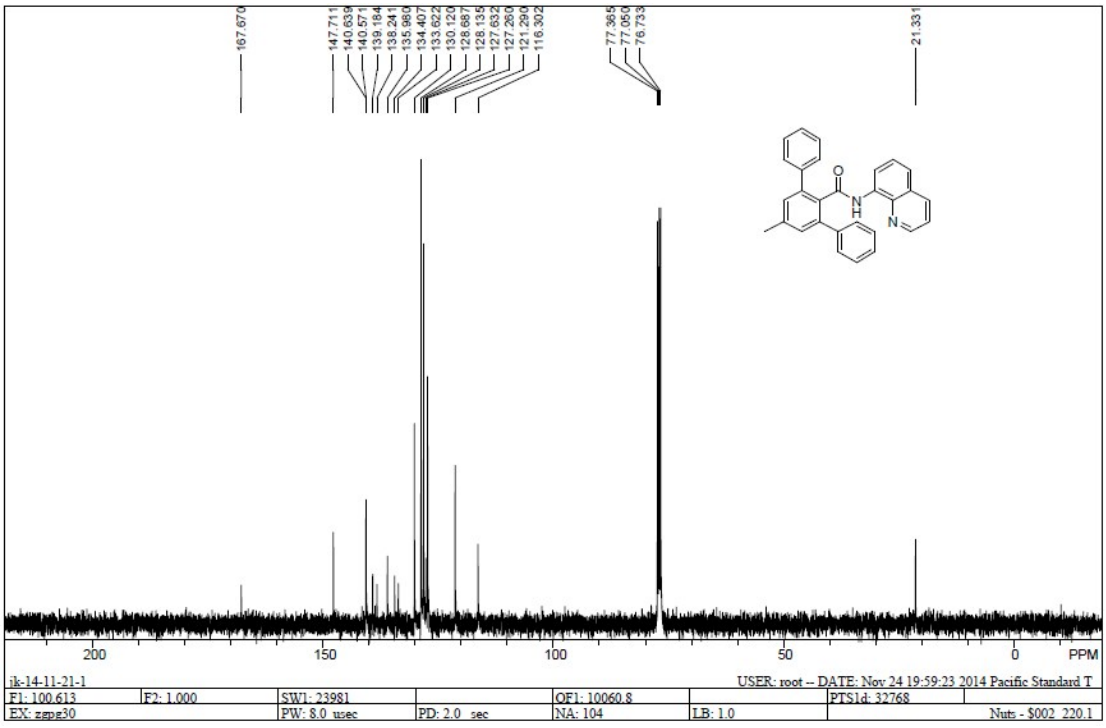
^{1}H and ^{13}C NMR of 4h



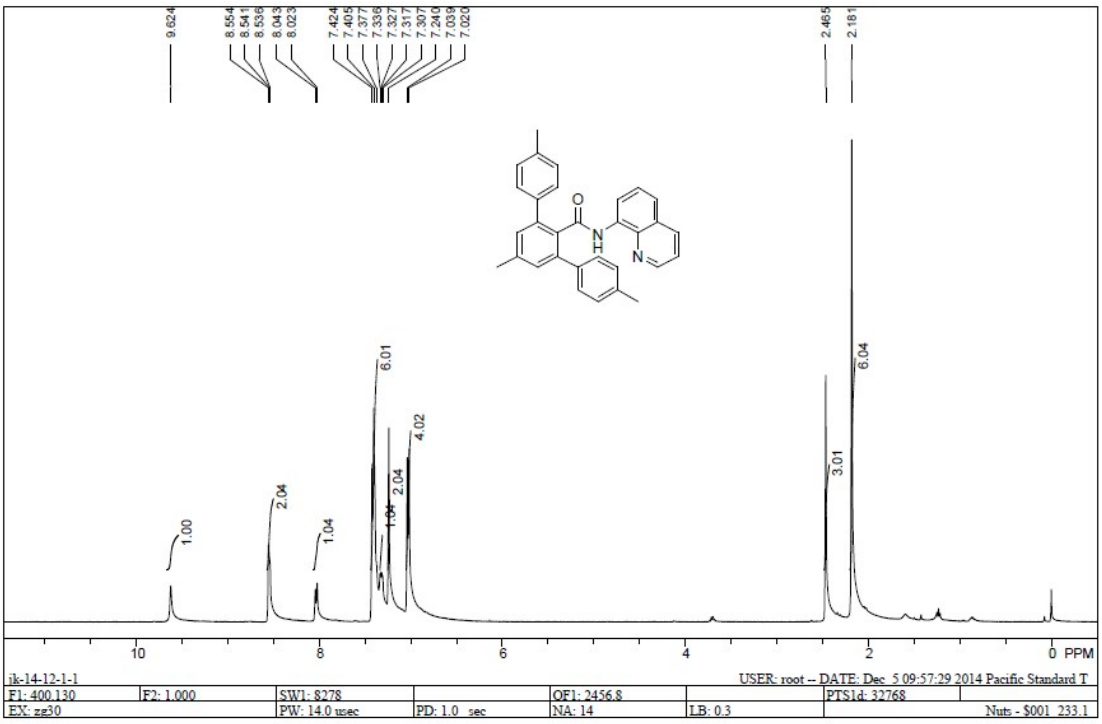


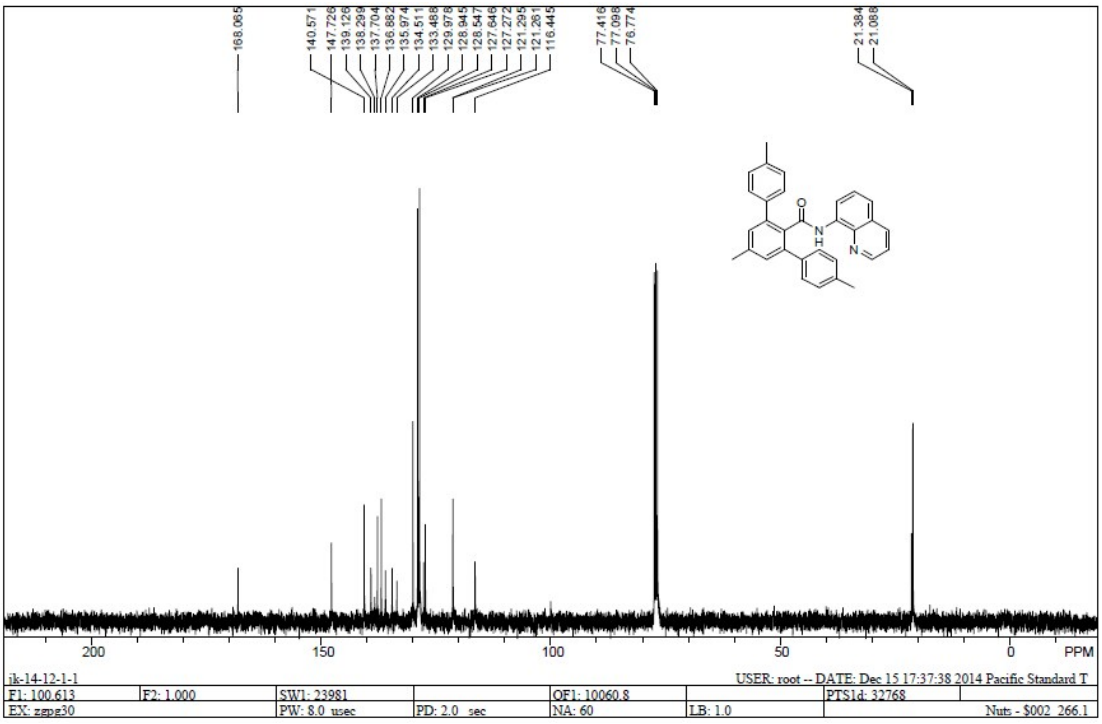
^{1}H and ^{13}C NMR of 4i



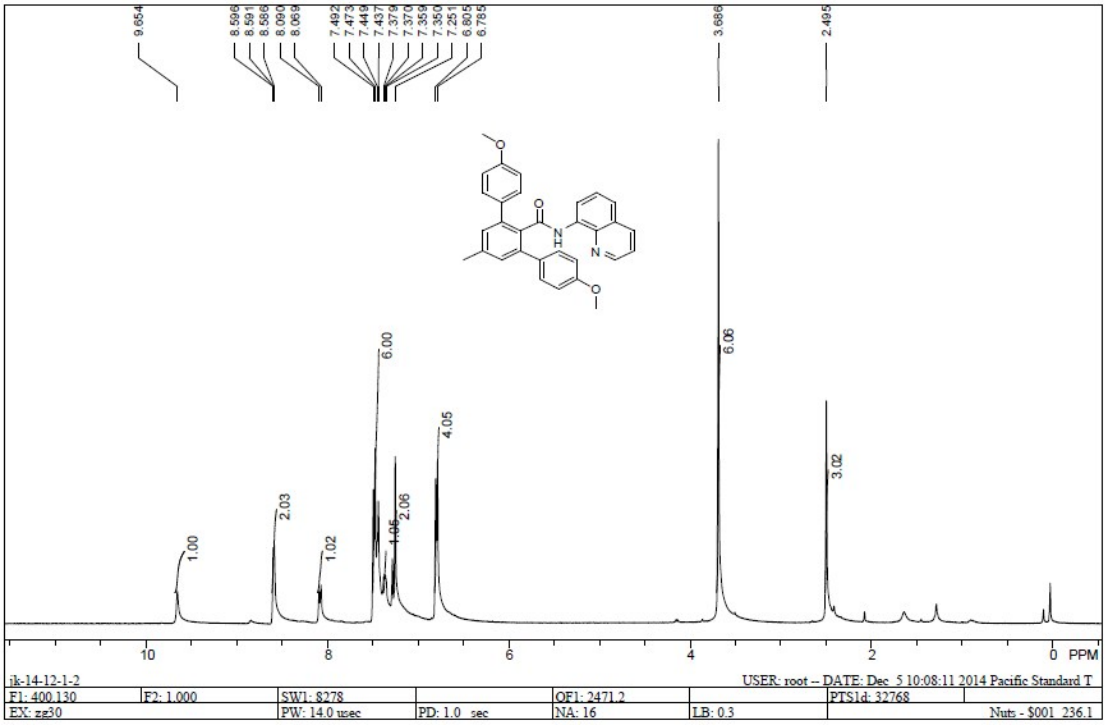


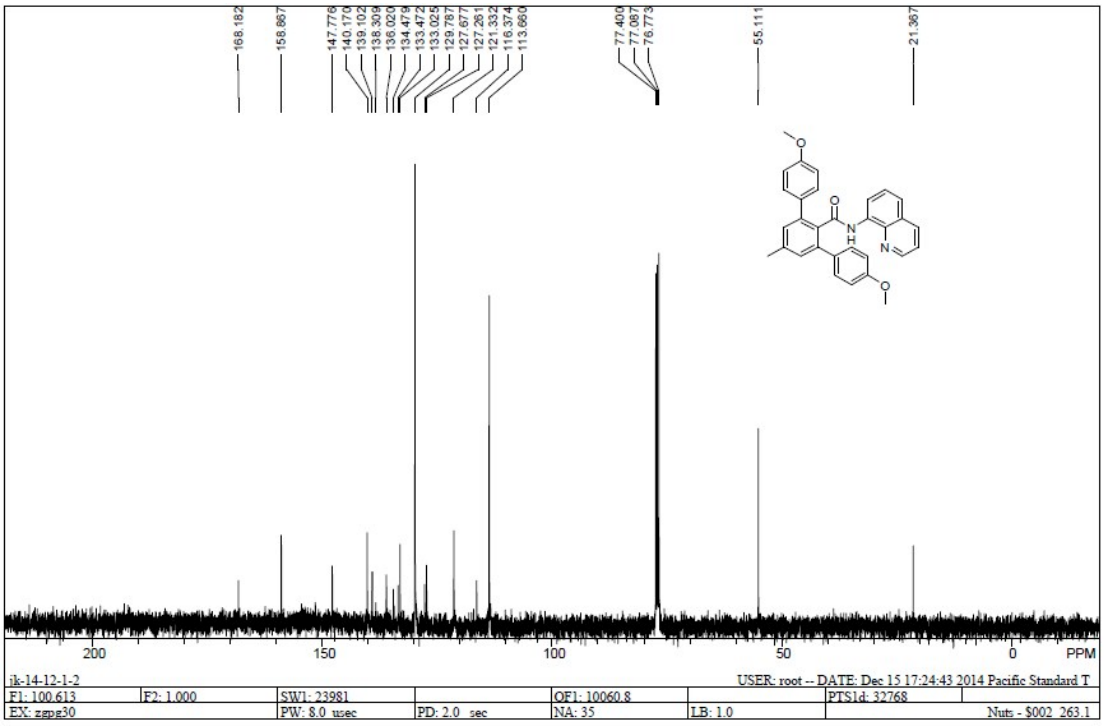
^{1}H and ^{13}C NMR of 4j



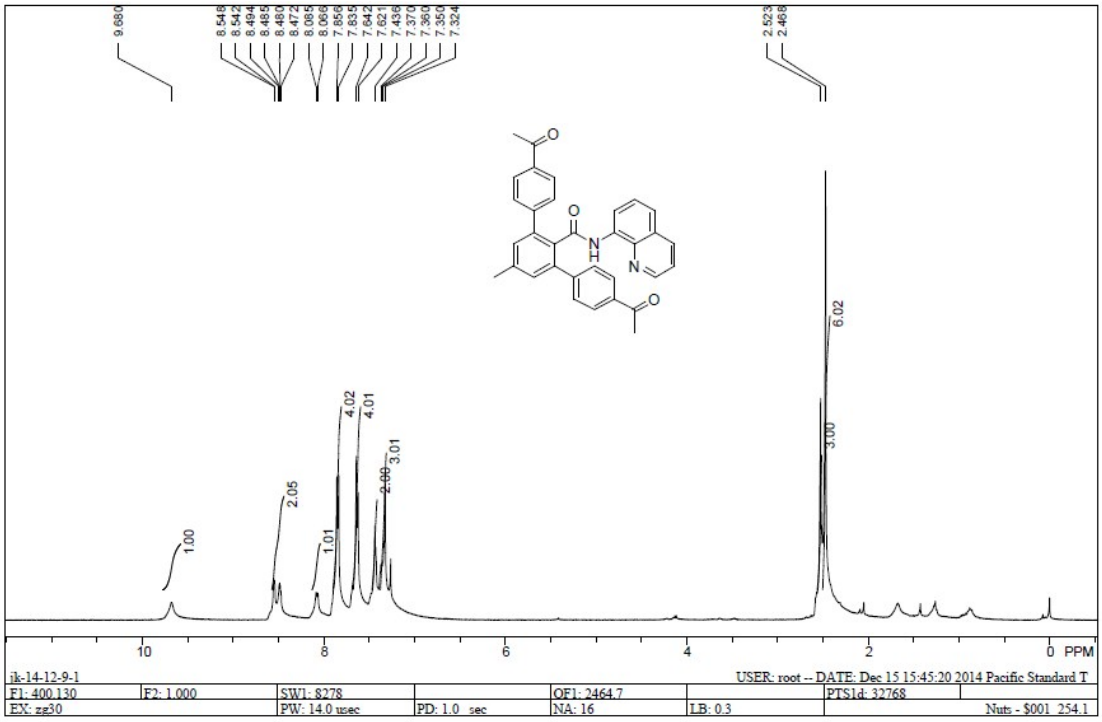


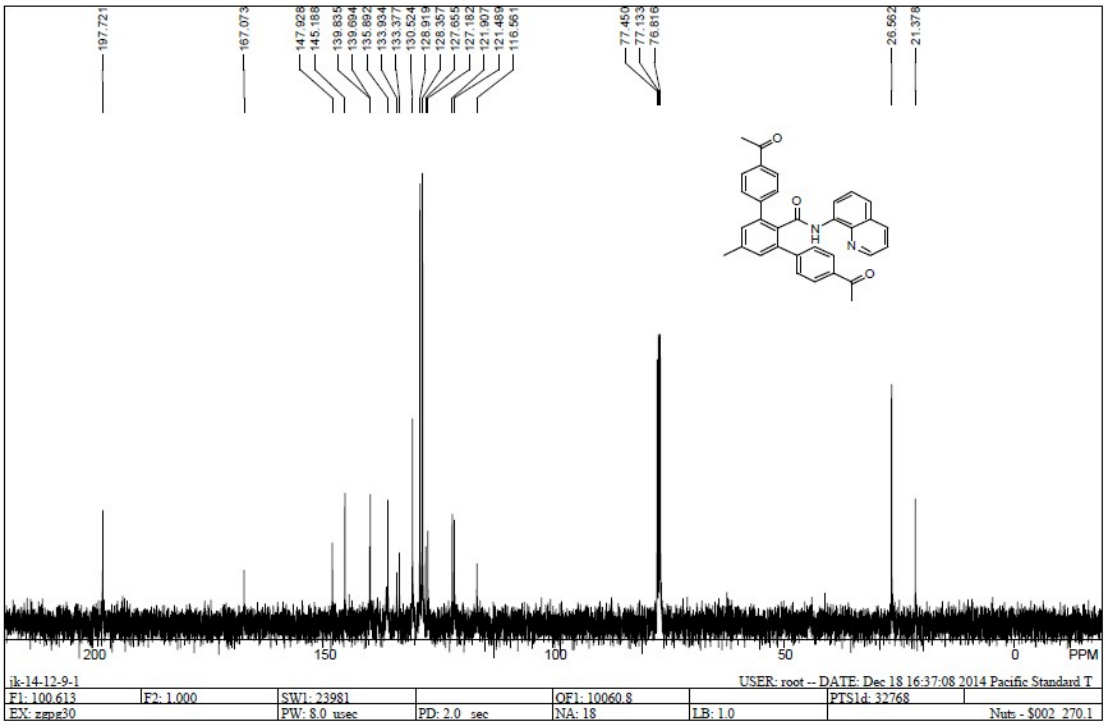
^{1}H and ^{13}C NMR of 4k



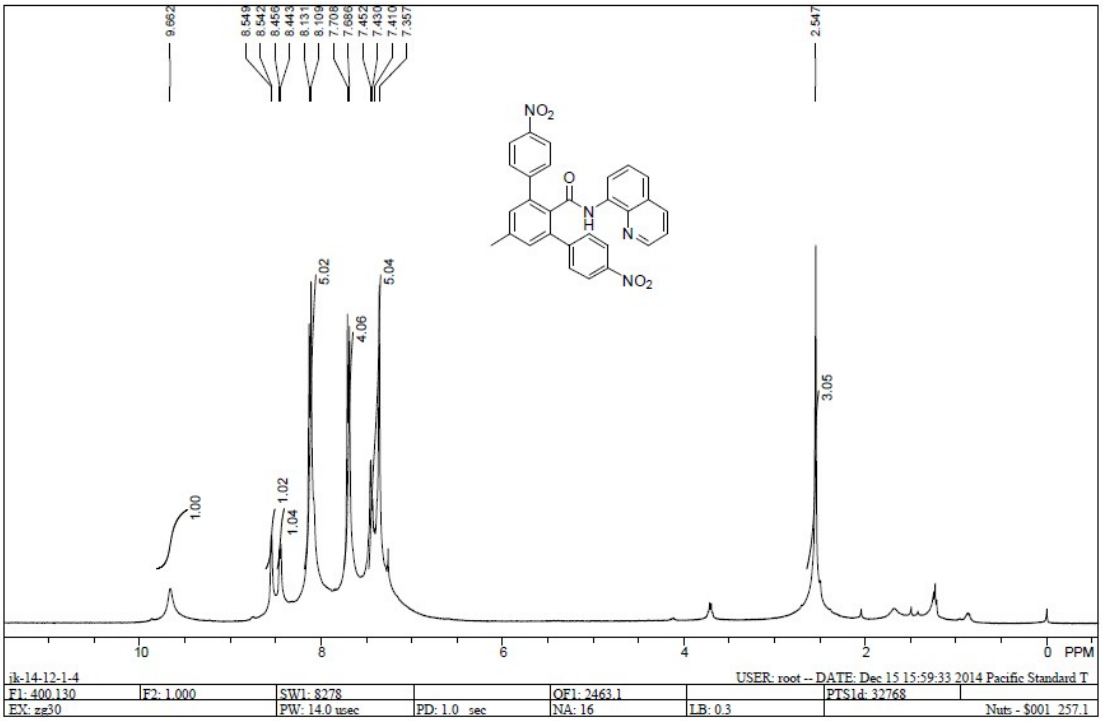


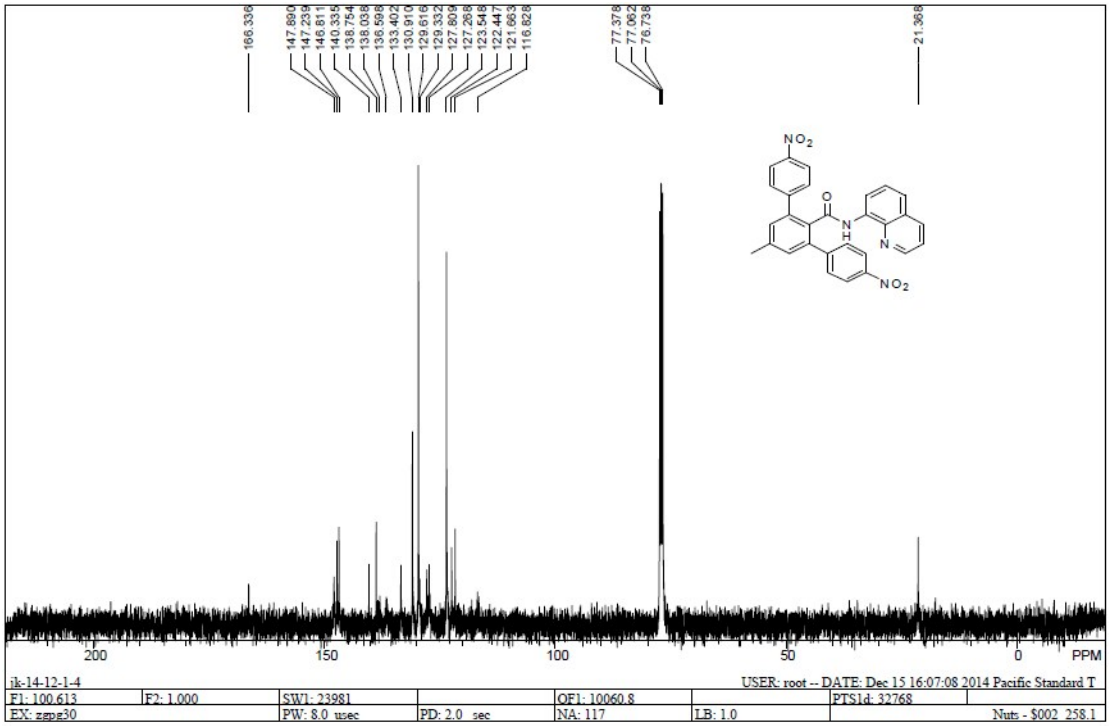
^{1}H and ^{13}C NMR of 4l



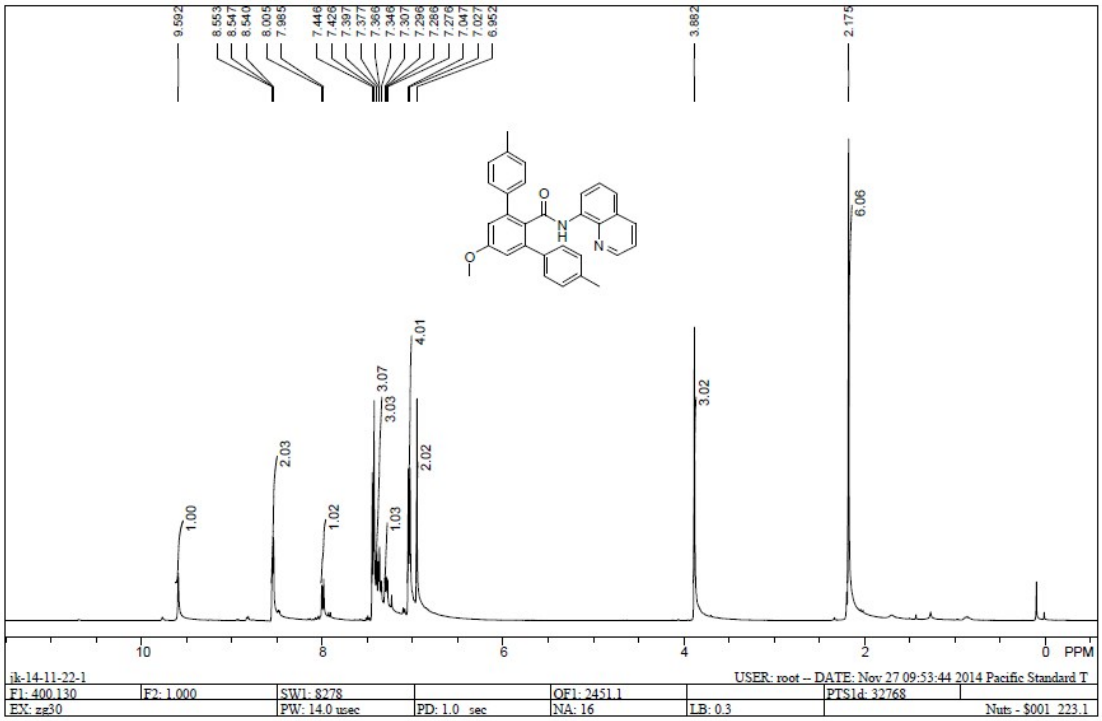


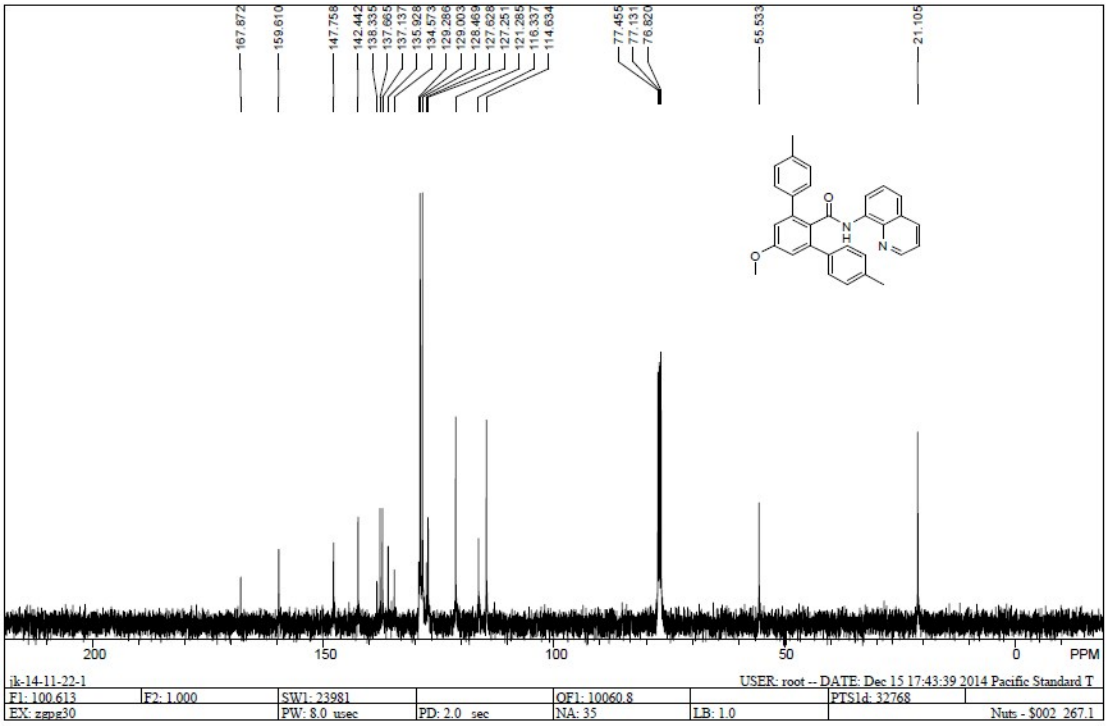
^{1}H and ^{13}C NMR of 4m



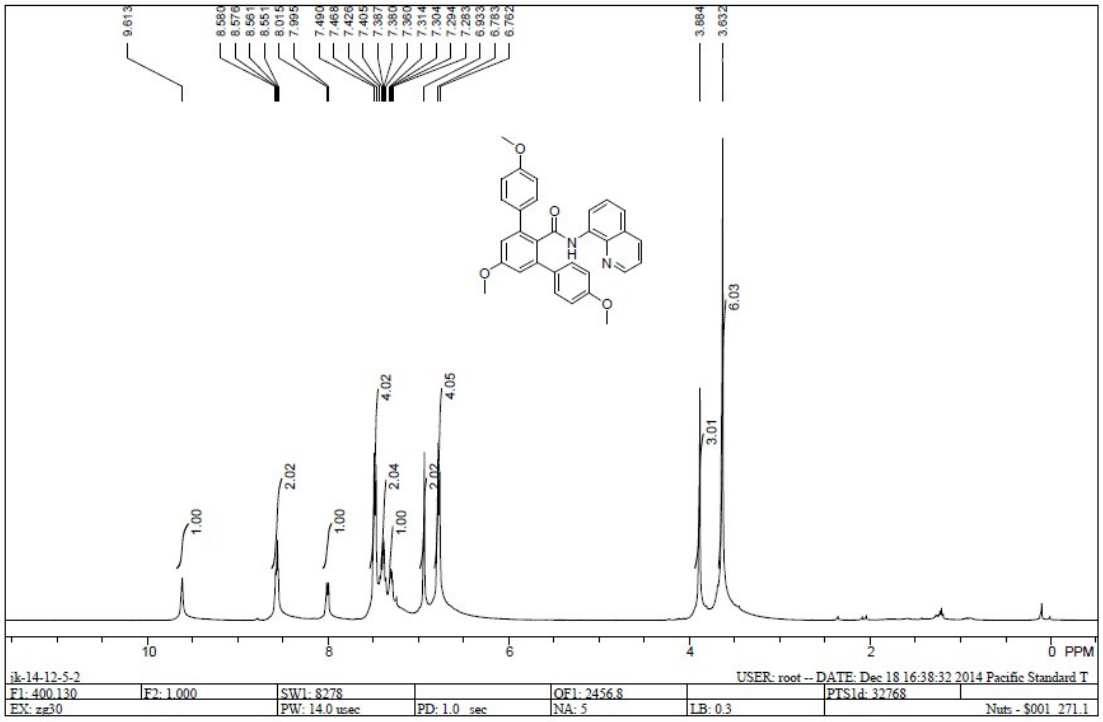


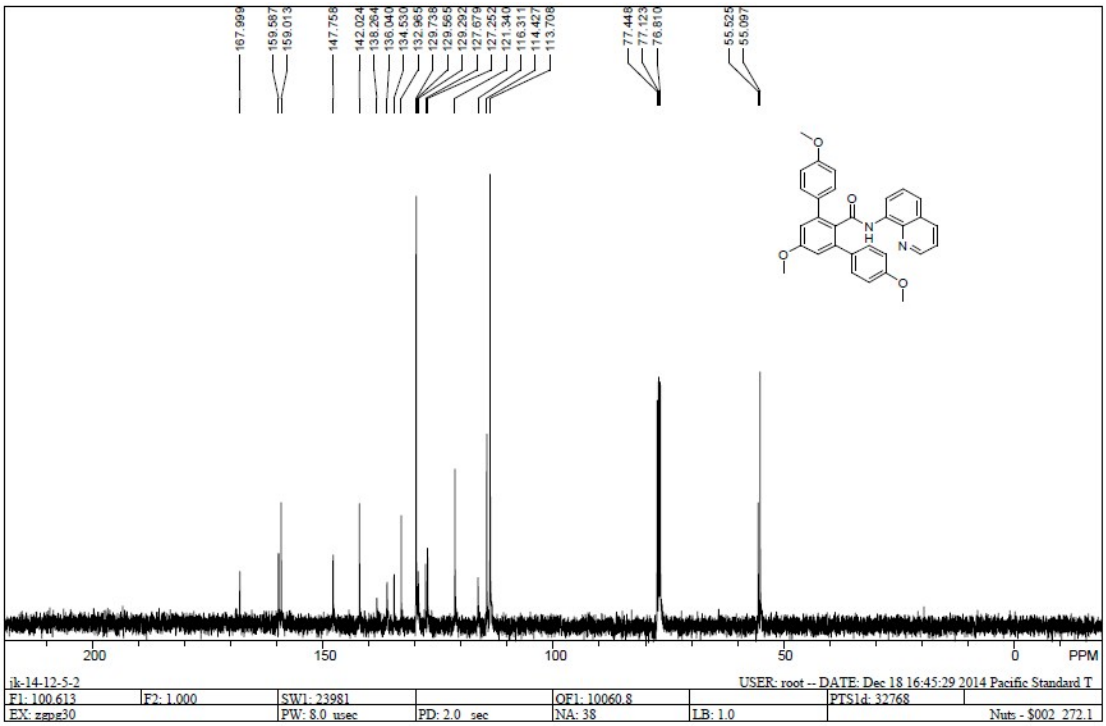
^{1}H and ^{13}C NMR of 4n



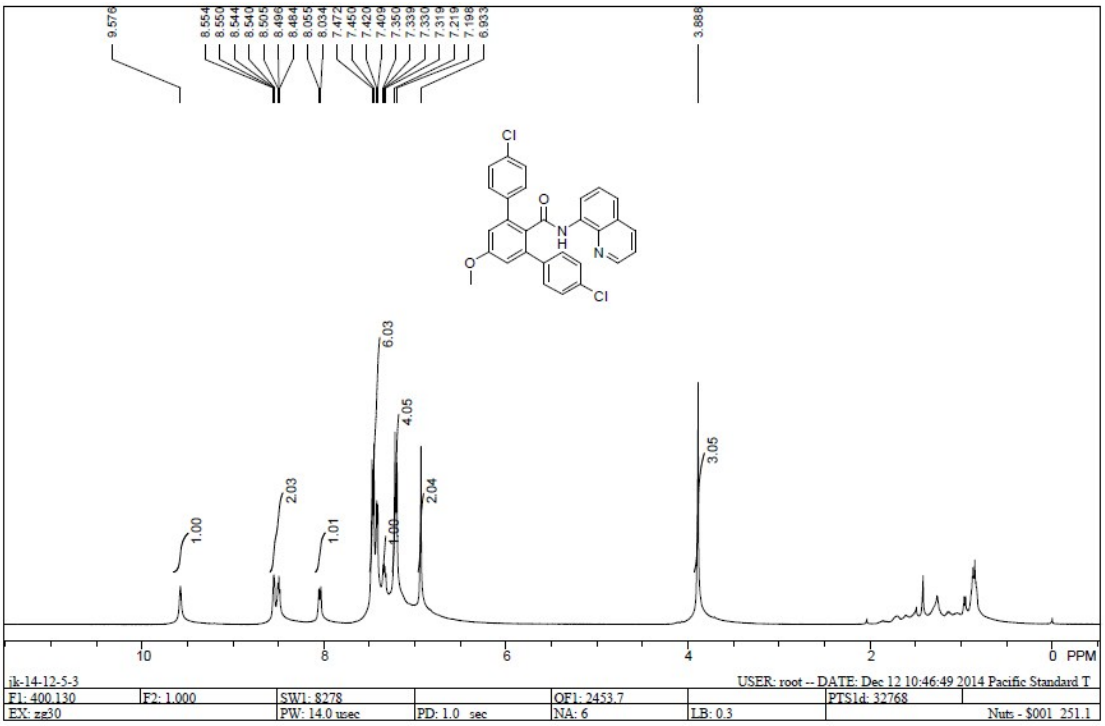


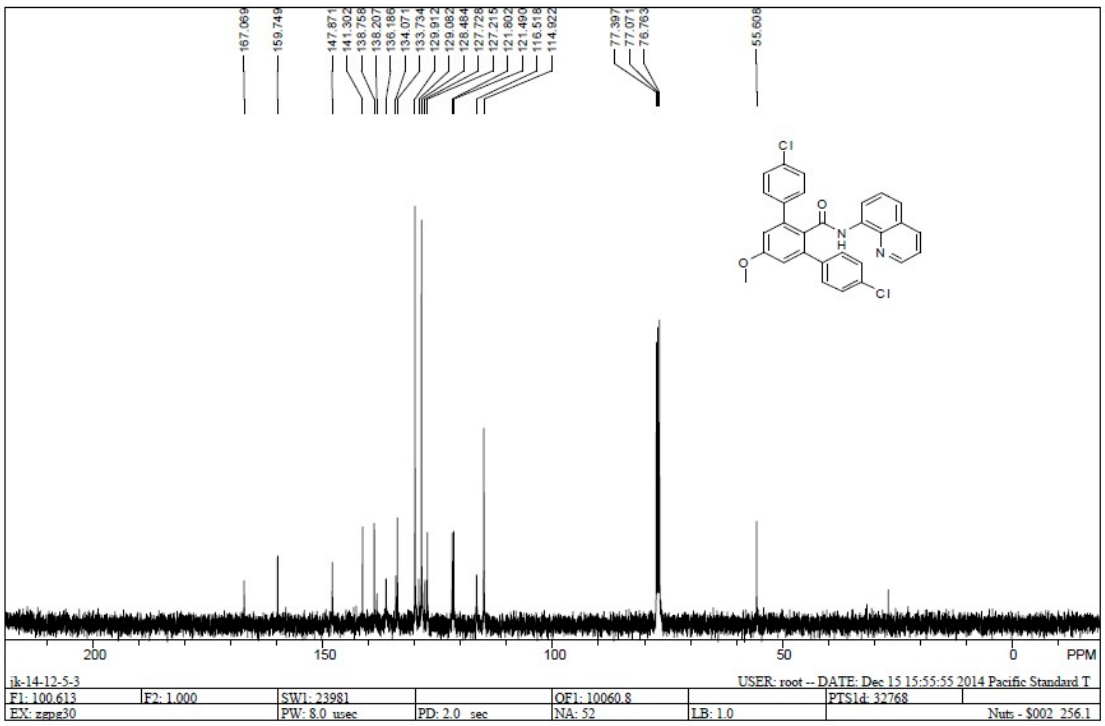
^{1}H and ^{13}C NMR of 4o



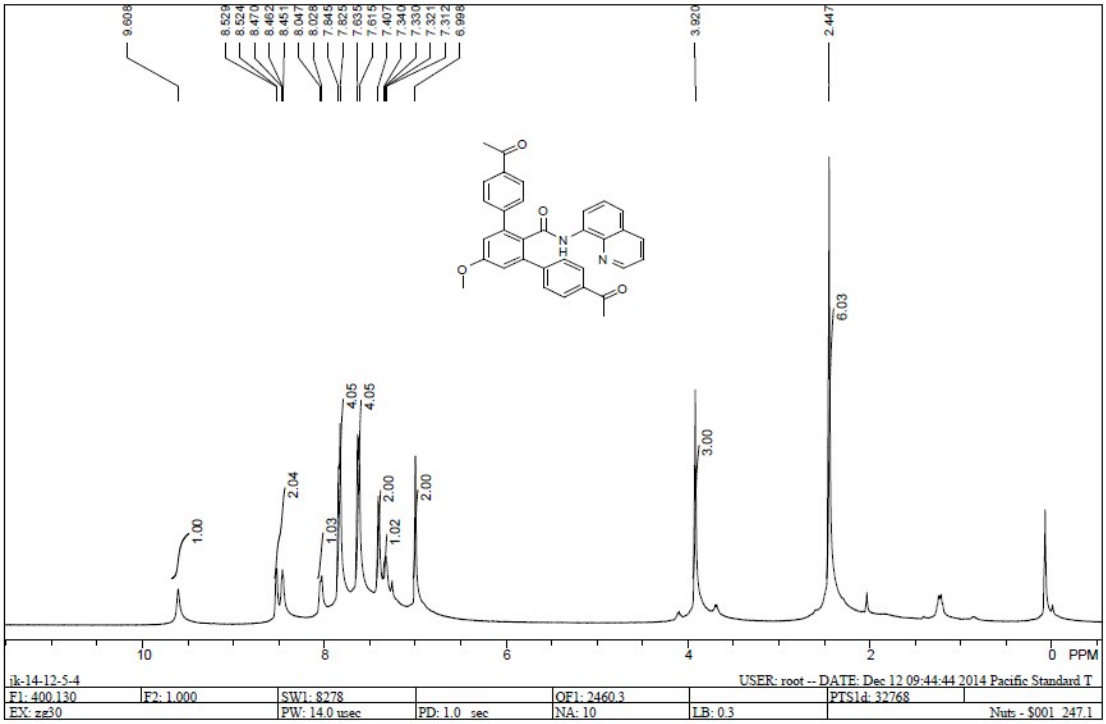


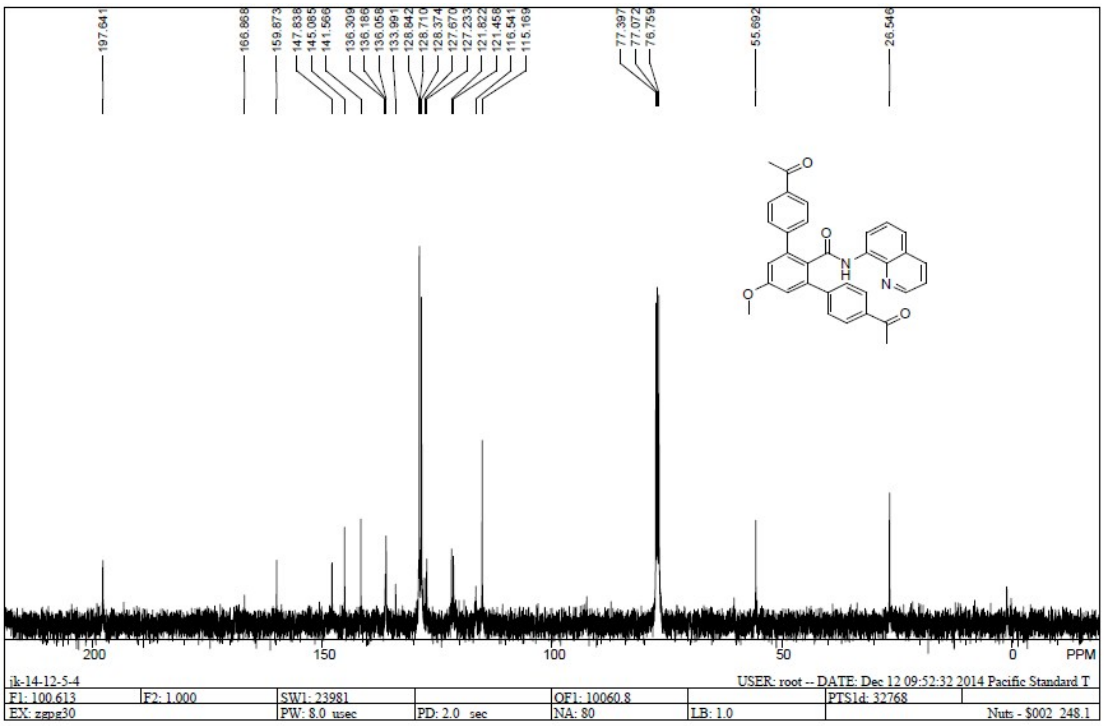
^{1}H and ^{13}C NMR of 4p



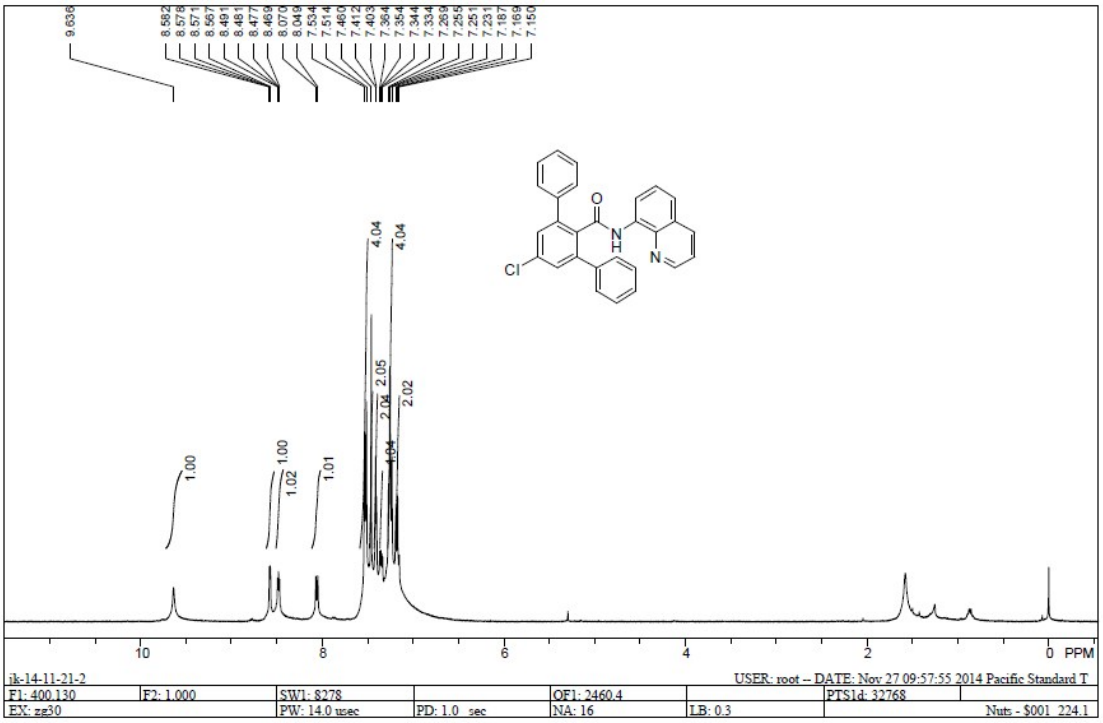


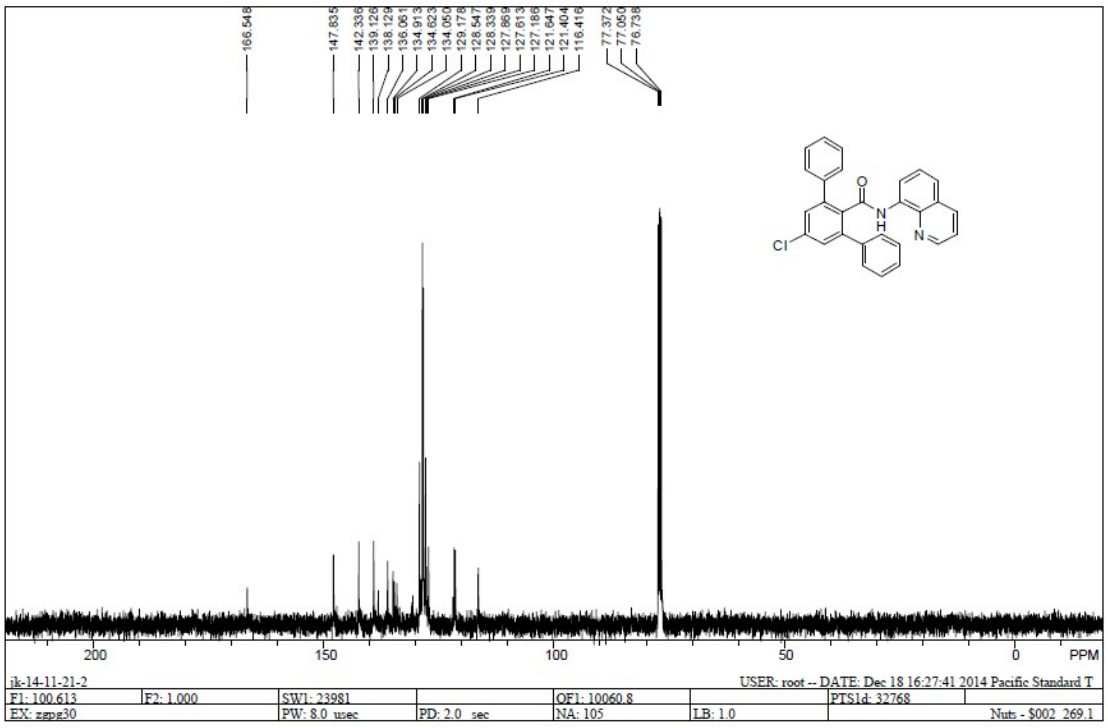
^{1}H and ^{13}C NMR of 4q



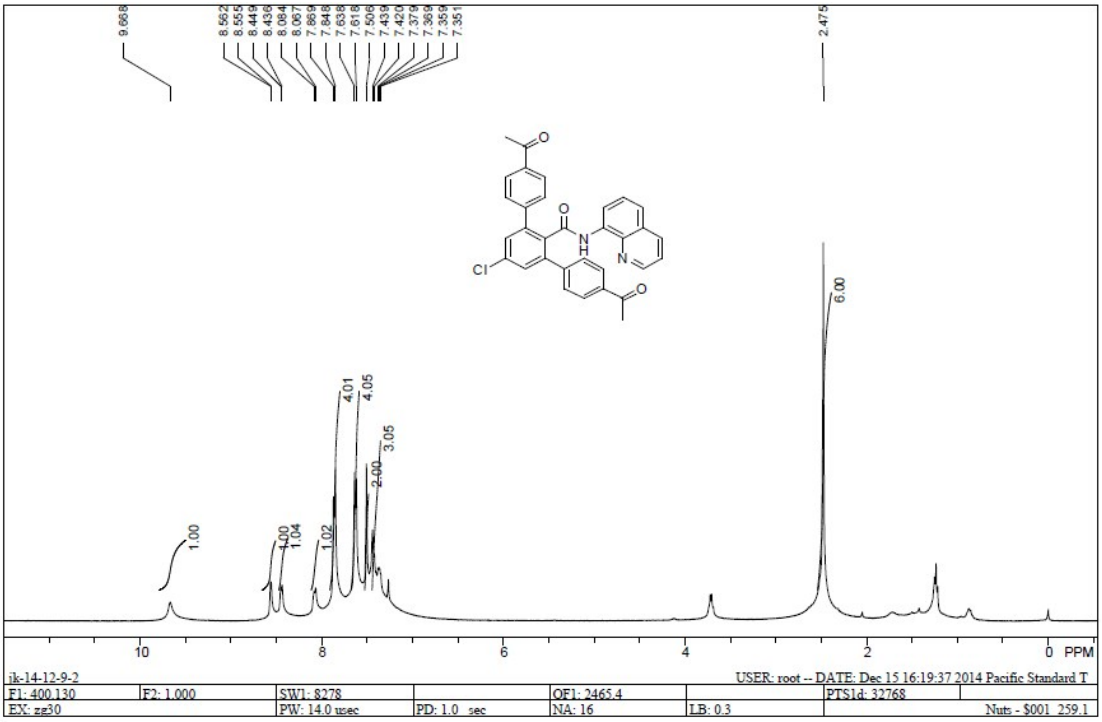


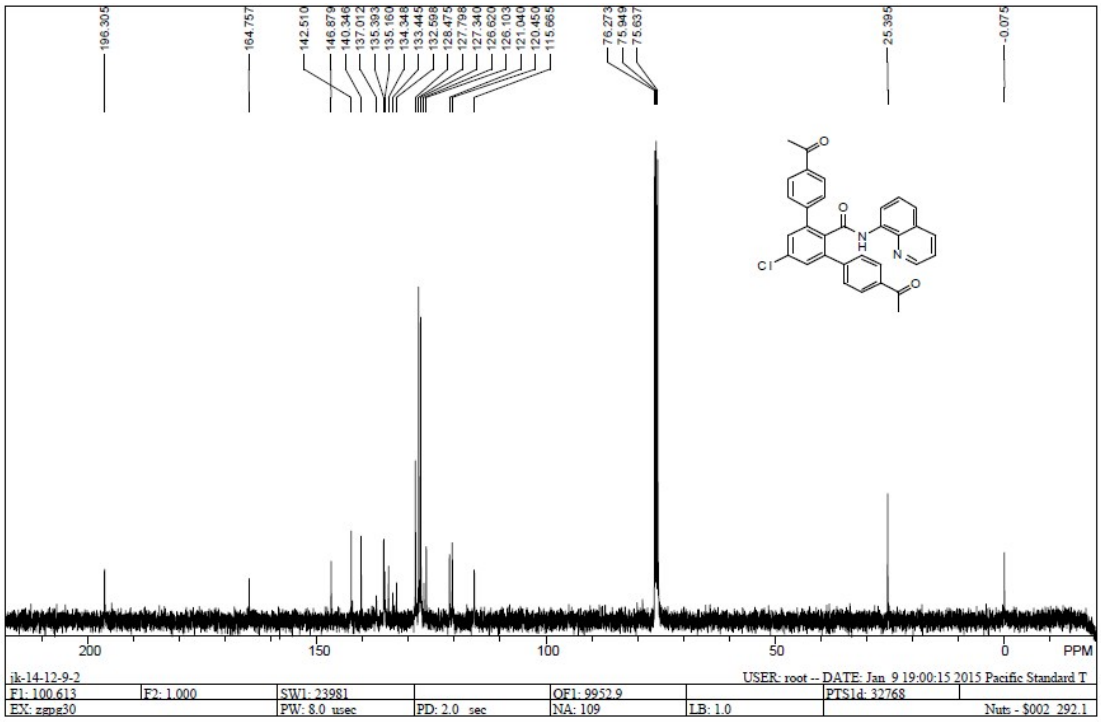
^{1}H and ^{13}C NMR of 4r



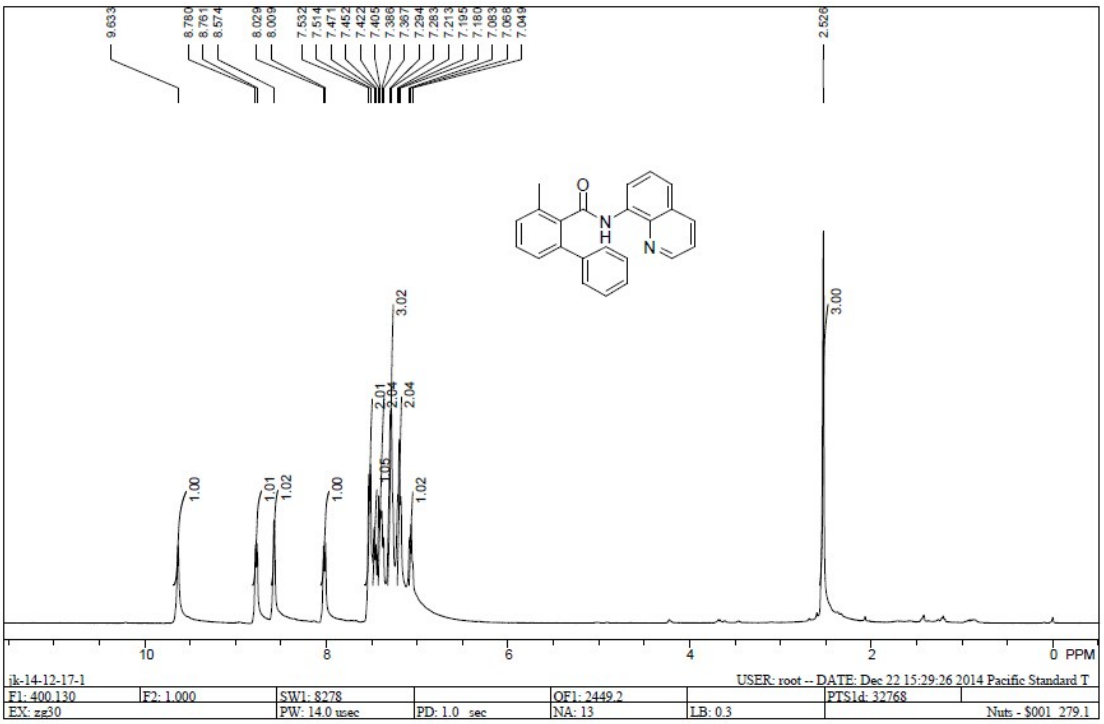


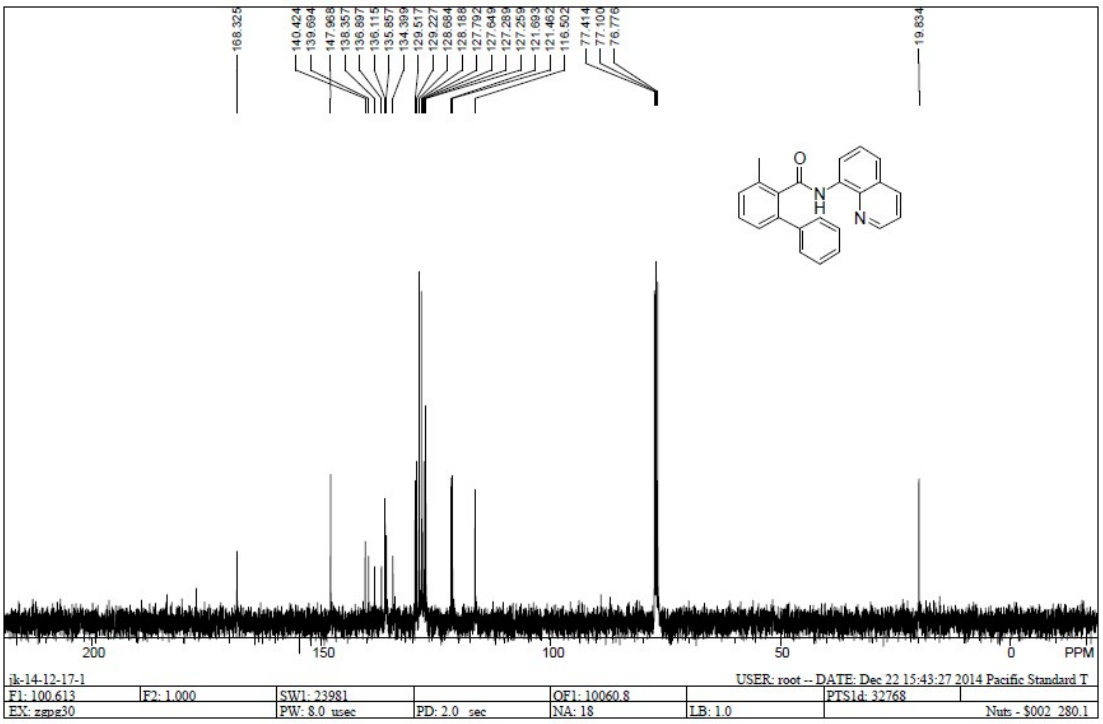
^{1}H and ^{13}C NMR of 4s



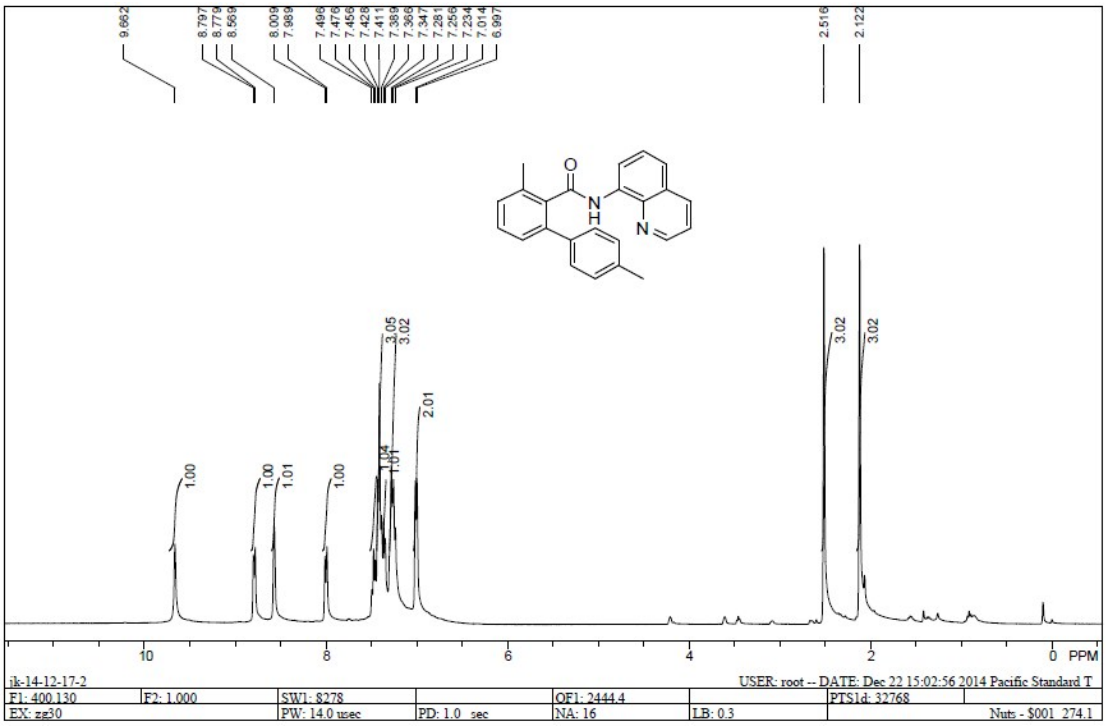


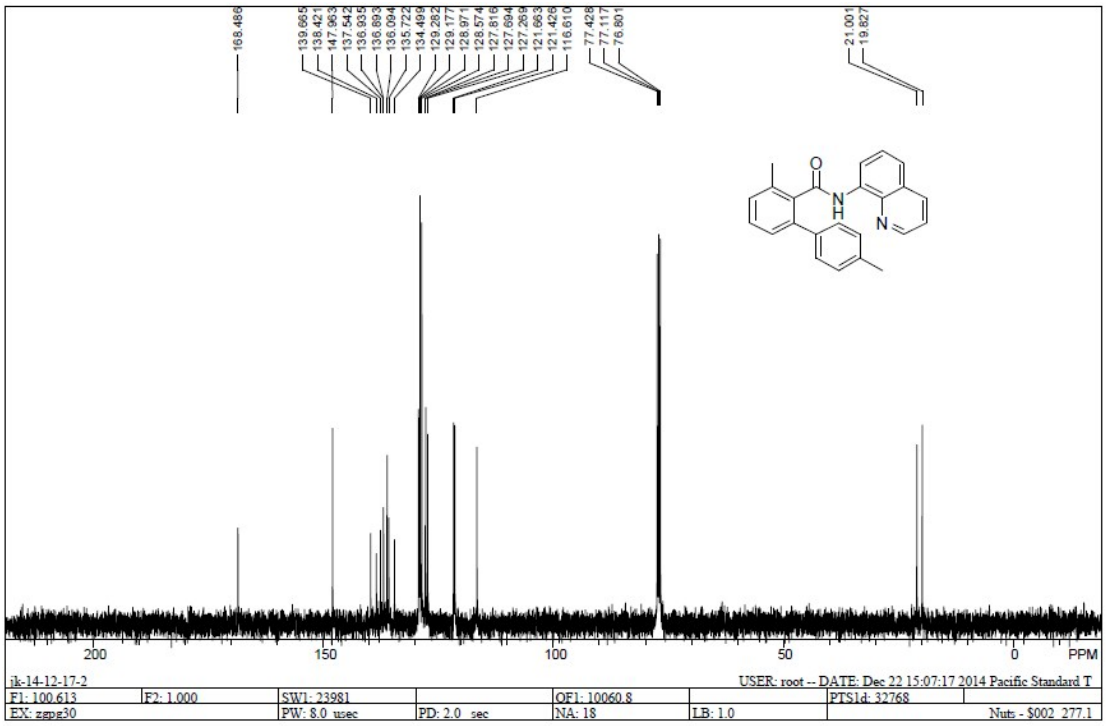
^{1}H and ^{13}C NMR of 5a



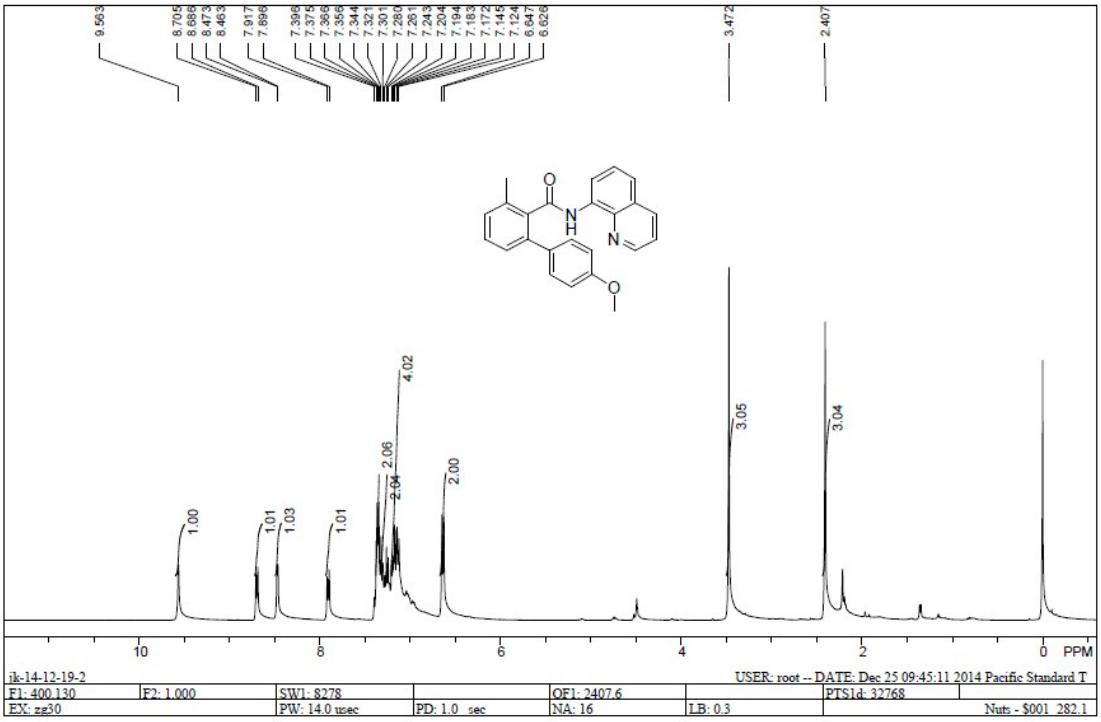


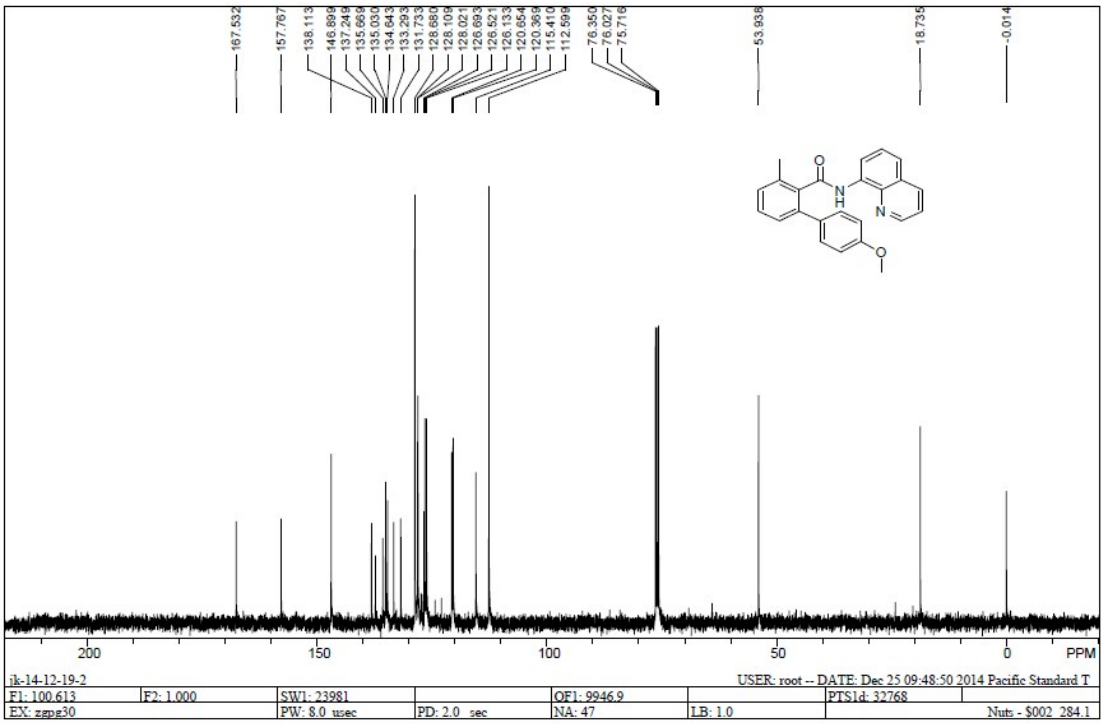
^{1}H and ^{13}C NMR of 5b



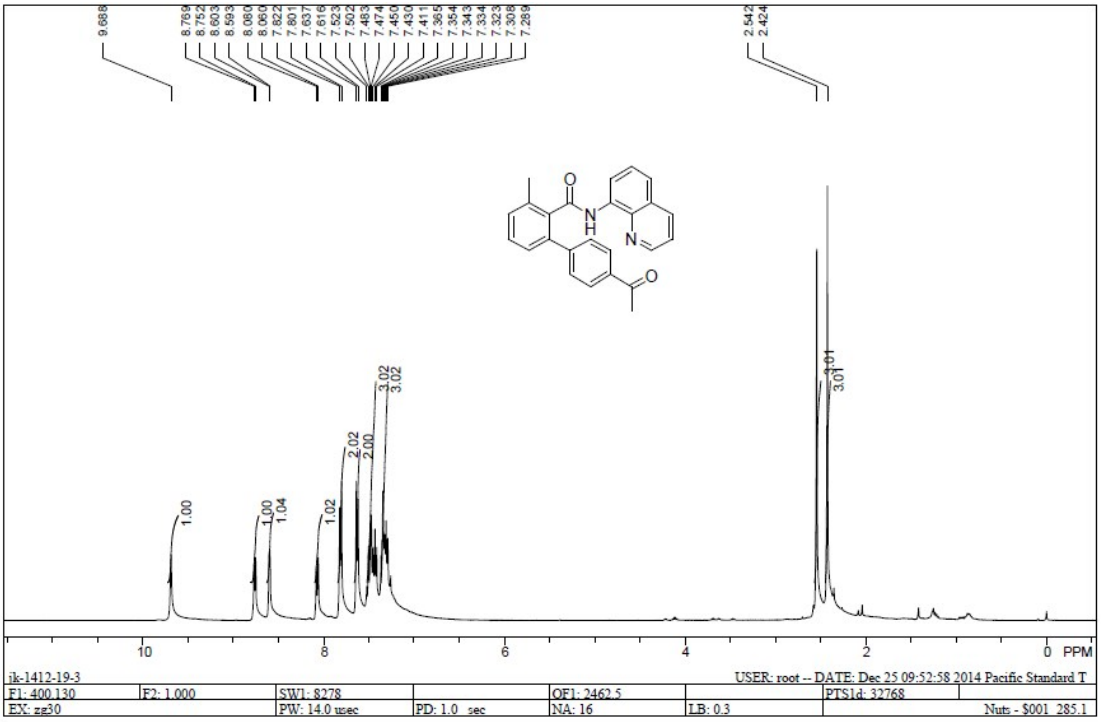


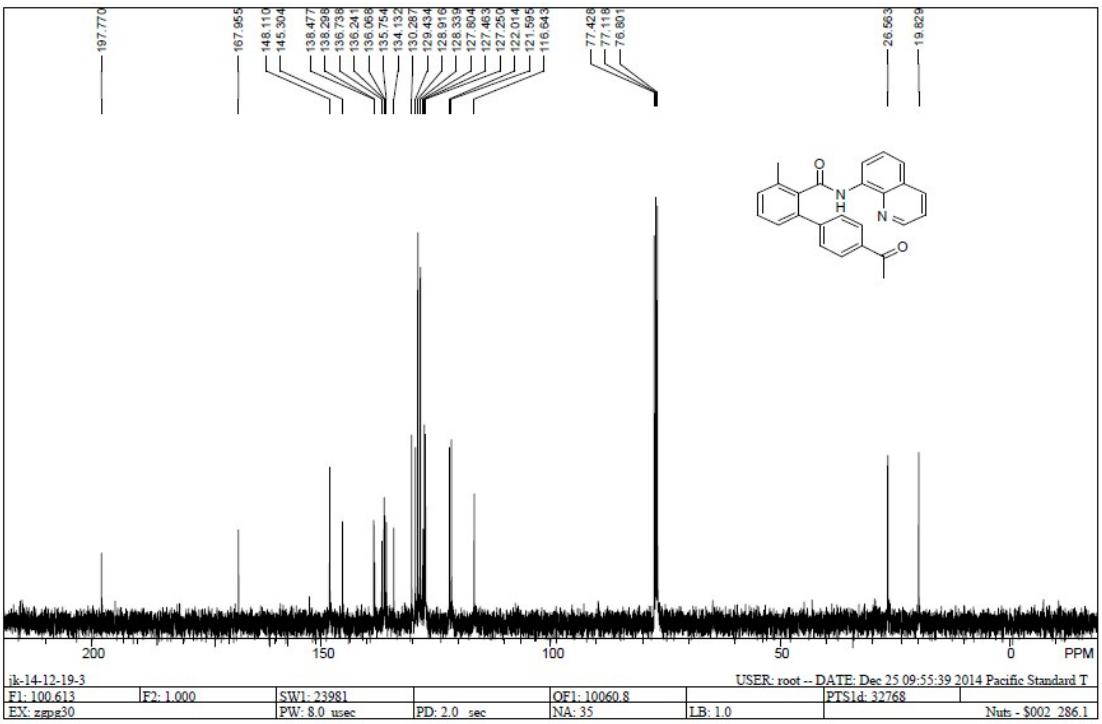
^{1}H and ^{13}C NMR of 5c



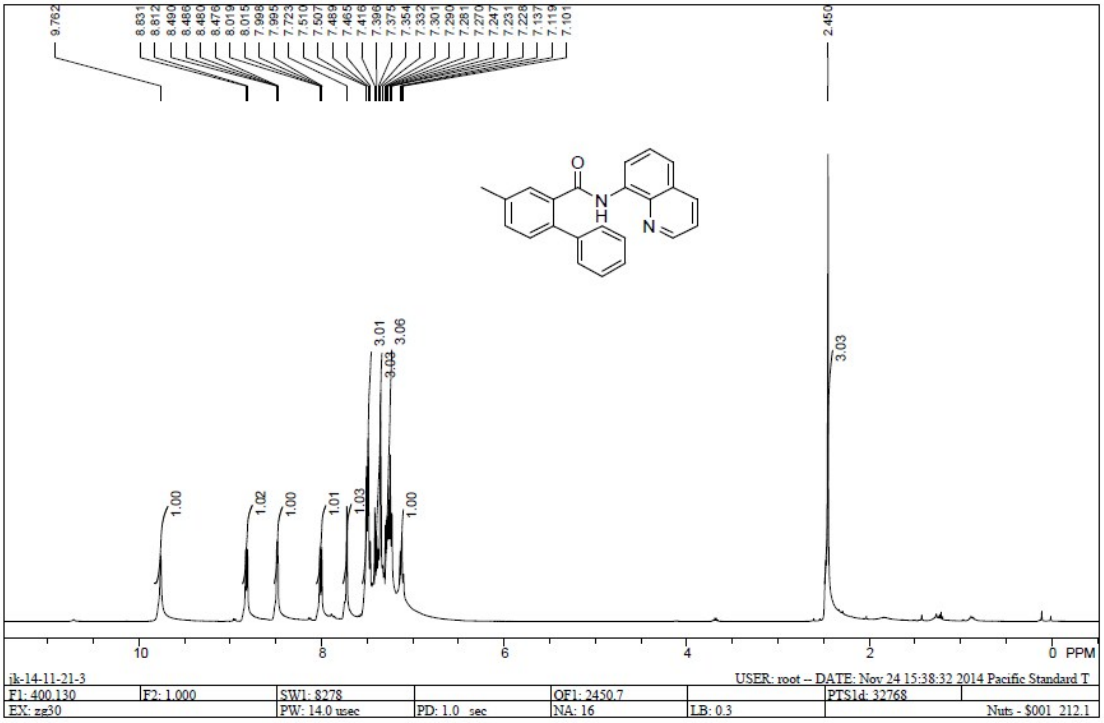


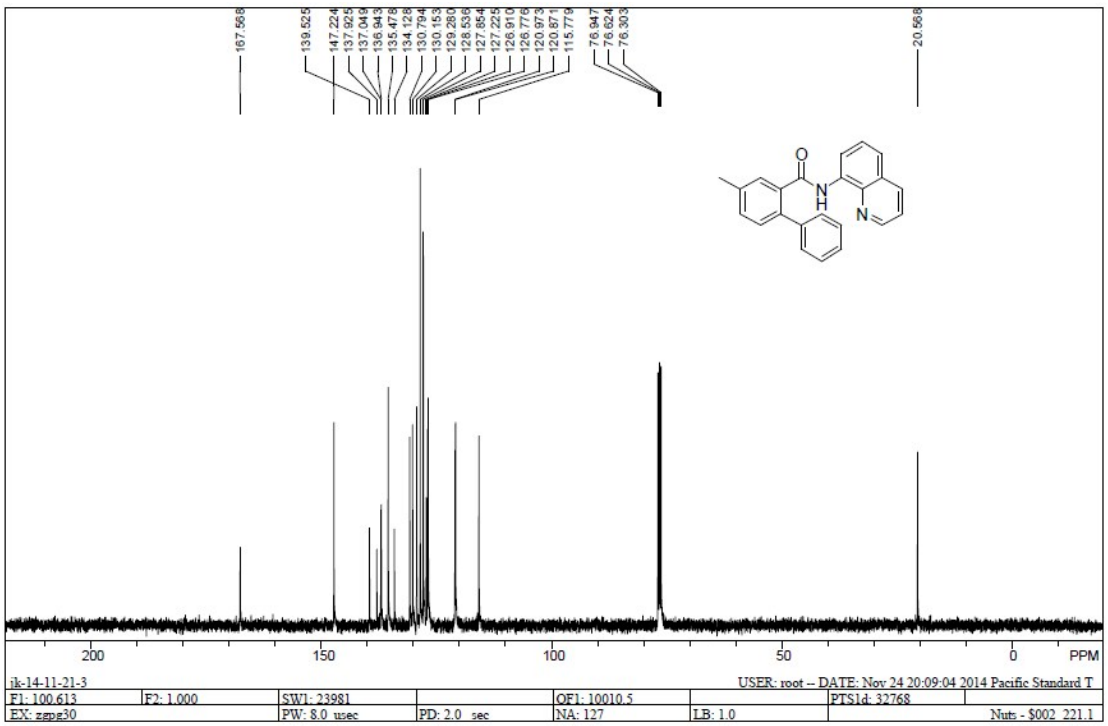
^{1}H and ^{13}C NMR of 5d



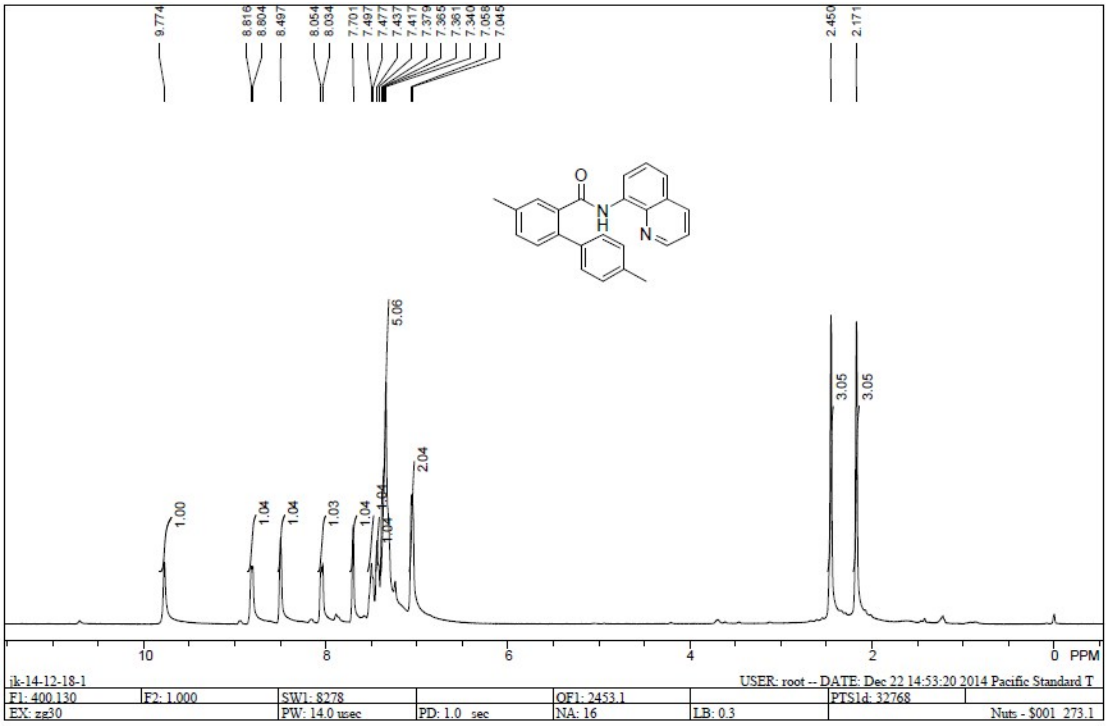


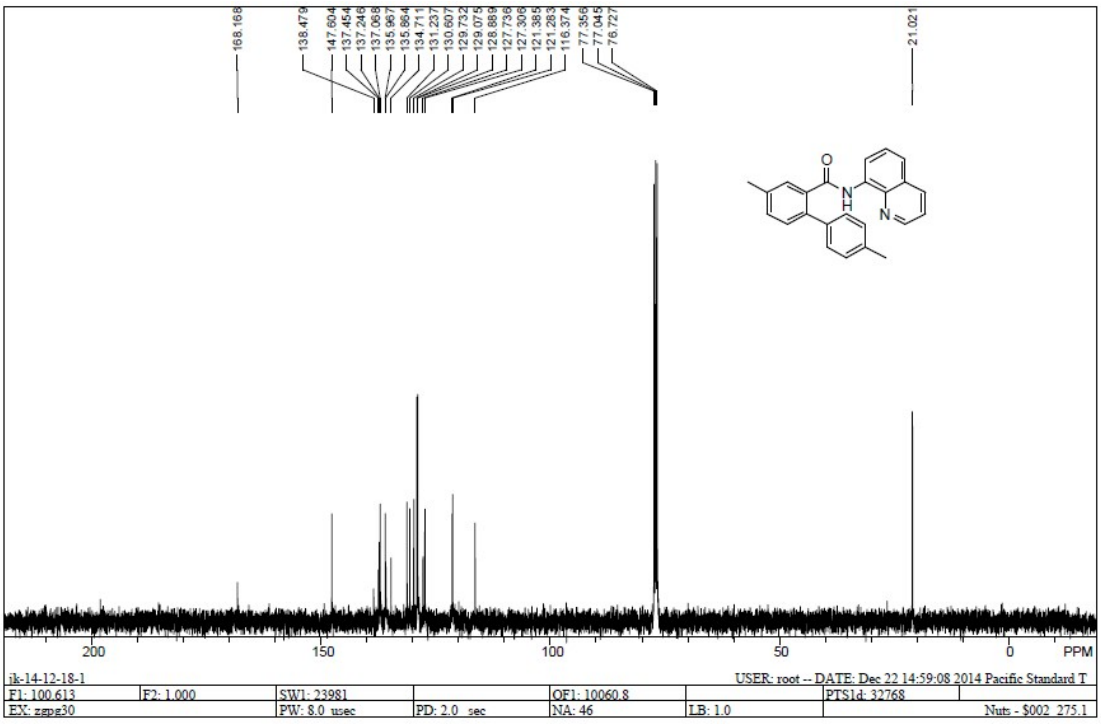
^{1}H and ^{13}C NMR of 5e



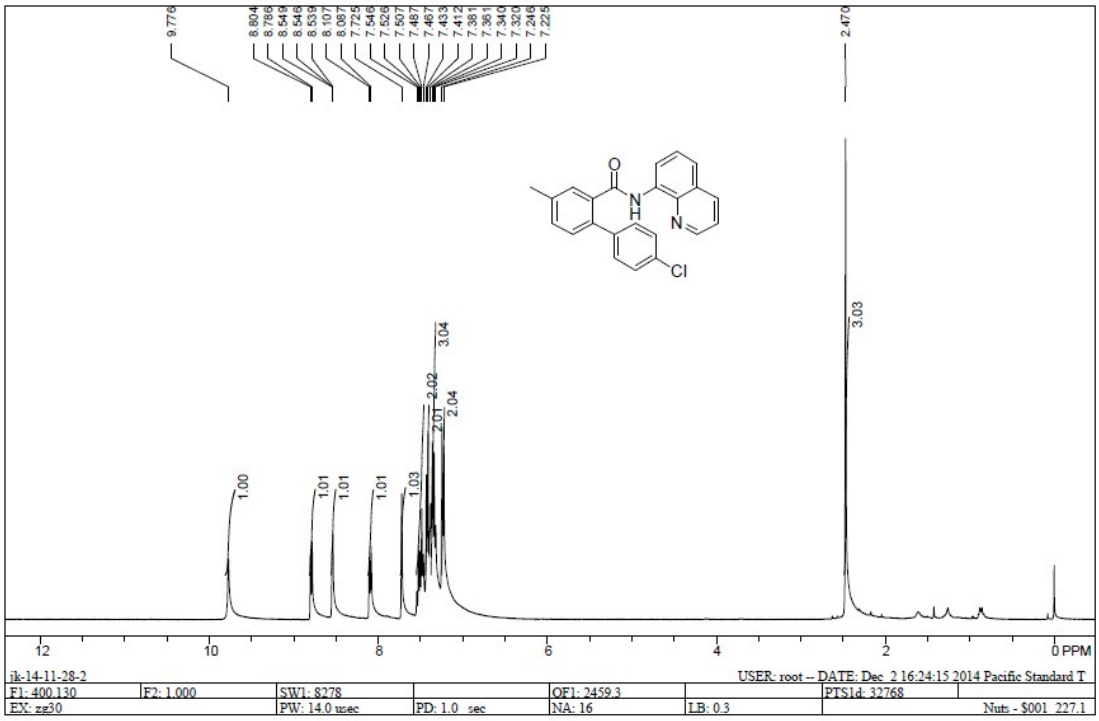


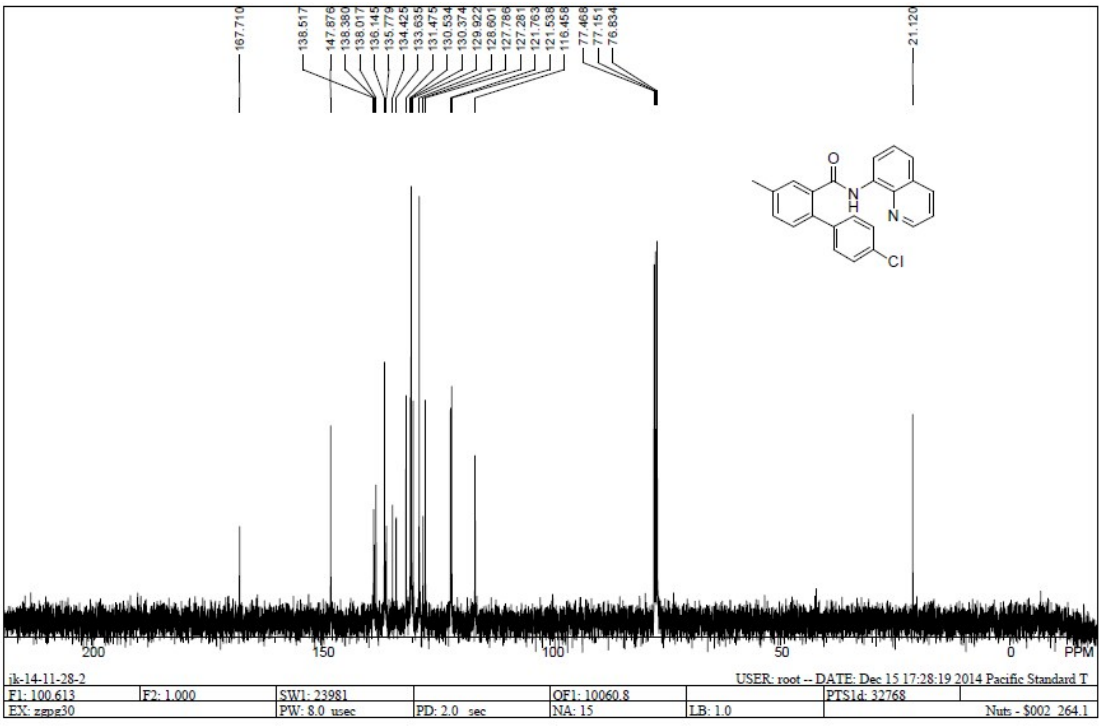
^{1}H and ^{13}C NMR of 5f



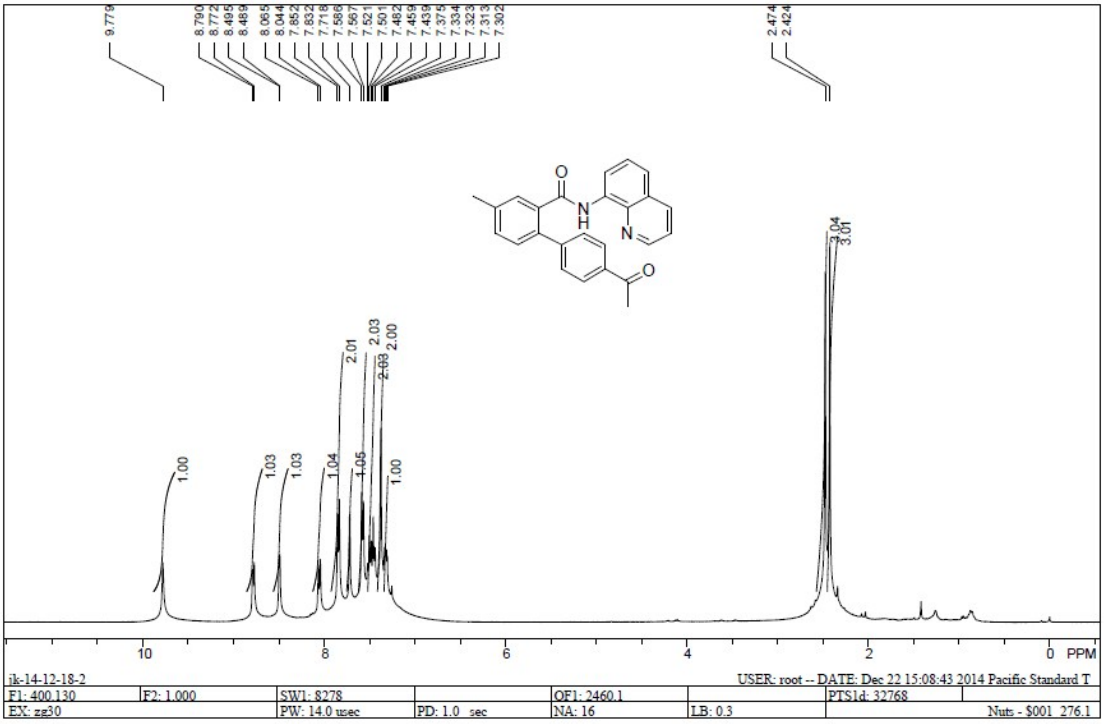


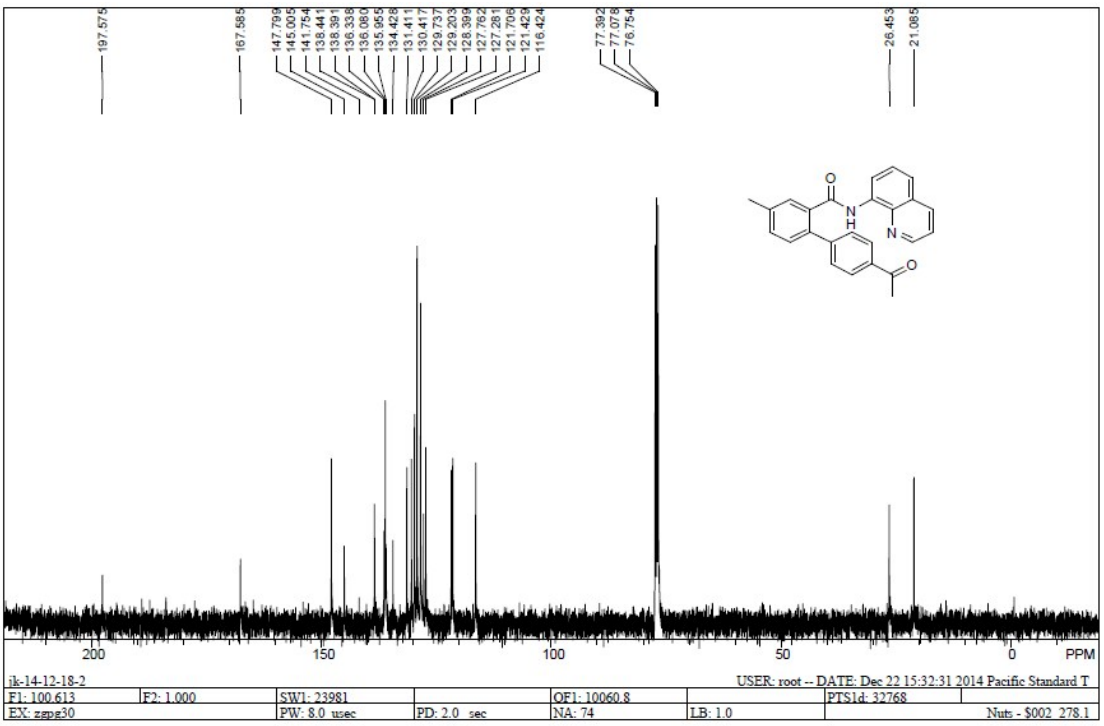
^{1}H and ^{13}C NMR of 5g





^{1}H and ^{13}C NMR of 5h





^{1}H and ^{13}C NMR of 5i