Palladium-Catalyzed *ortho* C–H Bond Alkylation of Benzylamides with α-Bromo Ketones

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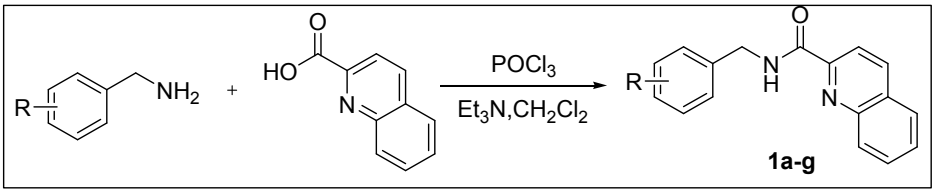
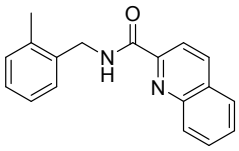
Supporting Information

Content

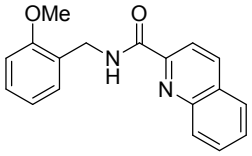
Preparation of Benzylamide Compounds 1a−j.



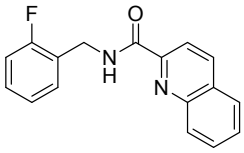
Quinoline-2-carboxylic acid (20 mmol, 3.46 g), benzylamine derivatives (20 mmol), and Et_3N (40 mmol, 5.6 mL) were dissolved in CH_2Cl_2 (40 mL), and addition of $POCl_3$ (3.76 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. Subsequently, the reaction was performed at room temperature for about 2 h until benzylamine derivative was consumed completely. At the conclusion of the reaction, the reaction mixture was allowed to cool to 0 °C, and ice−water was added slowly to quench the reaction. The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with saturated $NaHCO_3$ (2 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography (eluent, ethyl acetate/petroleum ether = 1/6 v/v) to give the desired product.



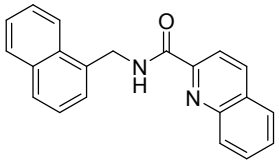
*N-(2-Methylbenzyl)quinoline-2-carboxamide (**1a**, CAS no. 879307-42-3)*. 2.76 g, 50% yield; white solid; mp 95−96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 7.0 Hz, 1H), 7.20 (m, 3H), 4.72 (d, J = 6.0 Hz, 2H), 2.39 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 144.5, 141.3, 132.2, 131.3, 131.2, 130.7, 125.3, 124.8, 124.5, 124.1, 123.3, 122.6, 122.5, 121.0, 113.7, 36.5, 13.9.



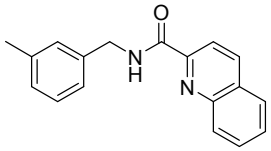
*N-(2-Methoxybenzyl)quinoline-2-carboxamide (**1b**, CAS no. 224796-49-0)*. 3.04 g, 52% yield; white solid; mp 106−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.54 (t, J = 7.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 7.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 4.74 (d , J = 6.0 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 152.5, 144.9, 141.3, 132.1, 124.7, 124.5, 124.3, 124.0, 123.5, 122.5, 122.4, 121.2, 115.4, 113.7, 105.2, 50.2, 34.0.



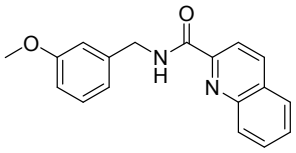
*N-(2-Fluorobenzyl)quinoline-2-carboxamide (**1c**, CAS no. 731012-39-8)*. 3.08 g, 55% yield; white solid; mp 89−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 7.0 Hz, 1H), 7.53 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.03 (m, 2H), 4.76 (d, J = 6.5 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 164.5, 162.0, 161.1, 149.6, 146.5, 137.5, 130.2, 130.1, 130.0, 129.7, 129.4, 129.3, 129.2, 127.9, 127.7, 125.4, 125.3, 124.3, 124.2, 118.9, 115.5, 115.3, 37.5, 37.4.



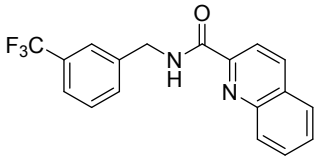
N-((naphthalen-4-yl)methyl)quinoline-2-carboxamide (***1d***). 3.25 g, 52% yield; white solid; mp 154−155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.97 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 6.5 Hz, 1H),7.54 (m, 3H), 7.49(t, J = 8.0 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H),5.17 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 149.6, 146.5, 137.5, 133.9, 133.7, 131.6, 130.0, 129.7, 129.3, 128.8, 128.6, 127.9, 127.7, 126.7, 126.6, 126.0, 125.5, 123.6, 119.0, 41.7. HRMS (ESI) calcd for $C_{21}H_{16}N_2O$ $[M + H]^+$ 313.1335, found 313.1334.



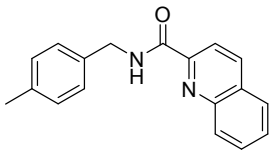
N-(3-methylbenzyl)quinoline-2-carboxamide (***1e***). 2.94 g, 53% yield; white solid; mp 81−82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.17 (m, 4H), 4.69 (d, J = 5.5 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 144.5, 141.3, 133.2, 133.0, 132.2, 124.8, 124.5, 124.1, 123.5, 123.4, 123.0, 122.7, 122.5, 119.7, 113.7, 38.4, 16.2. HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ $[M + H]^+$ 277.1335, found 277.1332.



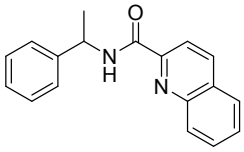
N-(3-methoxybenzyl)quinoline-2-carboxamide (***1f***). 3.97 g, 68% yield; white solid; mp 75−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.29 (t, J = 8.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 6.0 Hz, 1H), 7.71 (t, J = 6.5 Hz, 1H), 7.58 (t, J = 6.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.95(s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.71 (d, J = 5.5 Hz, 2H), 3.78 (d, J = 3.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 160.0, 149.7, 146.5, 140.0, 137.5, 130.1, 129.8, 129.7, 129.4, 127.9, 127.7, 120.1, 119.0, 113.5, 113.0, 55.3, 43.6;HRMS (ESI) calcd for $C_{18}H_{16}N_2O_2$ $[M + H]^+$ 293.1285, found 293.1283.



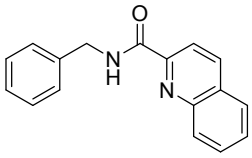
N-(3-(trifluoromethyl)benzyl)quinoline-2-carboxamide (***1g***). 4.55 g, 69% yield; white solid; mp 116−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 7.0 Hz, 1H), 7.64 (s, 1H), 7.60 (t, J = 8.5 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 4.78 (d, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 149.5, 146.5, 139.5, 137.6, 131.4, 131.2, 130.9, 130.6, 130.2, 129.7, 129.4, 129.2, 128.0, 127.7, 127.3, 125.2, 124.7, 124.6, 124.5, 124.4, 124.3, 124.2, 124.1, 124.0, 123.0, 120.8, 118.9, 43.1; HRMS (ESI) calcd for $C_{18}H_{13}F_3N_2O$ $[M + H]^+$ 331.1053, found 331.1050.



*N-(4-methylbenzyl)quinoline-2-carboxamide (**1h**)*. 3.66 g, 66% yield; white solid; mp 77−78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 8.5 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 4.70 (d, J = 6.5 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 144.6, 141.3, 132.2, 131.9, 130.1, 124.8, 124.4, 124.2, 124.1, 122.7, 122.6, 122.5, 113.7, 38.2, 15.9; HRMS (ESI) calcd for $C_{18}H_{16}N_2O$ $[M + H]^+$ 277.1335, found 277.1333.

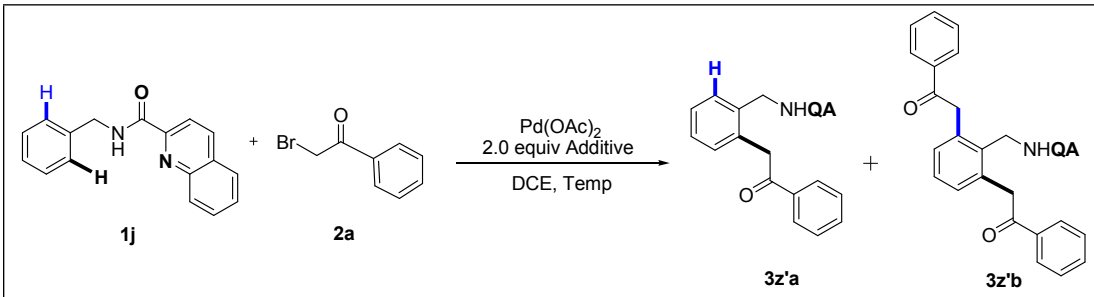


*N-(1-Phenylethyl)quinoline-2-carboxamide (**1i**, CAS no. 361984-03-4)*. 2.98 g, 54% yield; white solid; mp 95−96 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H), 5.40 (quint, J = 7.5 Hz, 1H), 1.63 (d , J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 149.9, 146.5, 143.4, 137.5, 130.1, 129.7, 129.4, 128.7, 127.9, 127.8, 127.4, 126.3, 118.9, 49.0, 22.1.



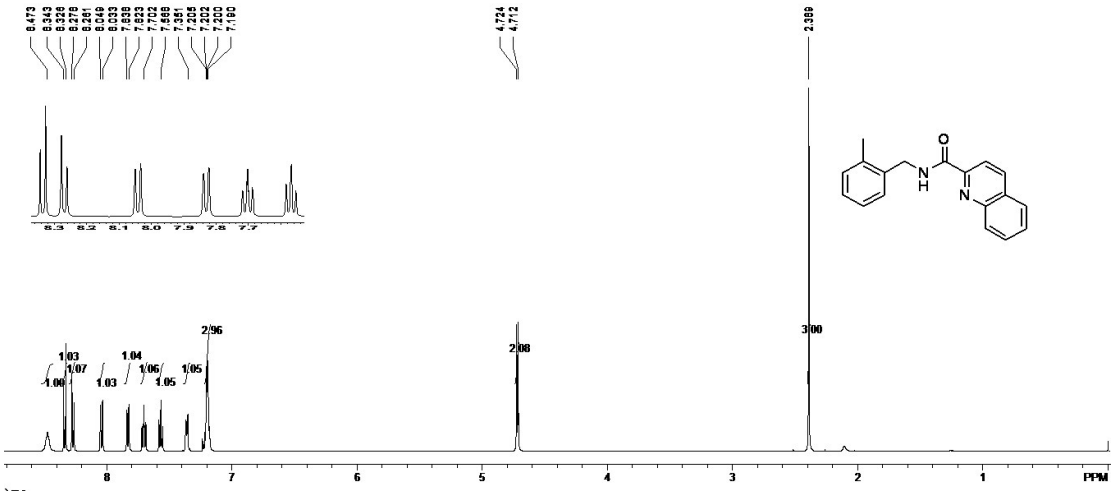
*N-Benzylquinoline-2-carboxamide (**1j**, CAS no. 6019-43-8)*. 2.83 g, 54% yield; white solid; mp 116−117 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.34 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 4.73 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 149.7, 146.5, 138.3, 137.5, 130.1, 129.7, 129.3, 128.8, 128.0, 127.9, 127.8, 127.5, 119.0, 43.6.

Table 3 Optimization of the reaction conditions[a]

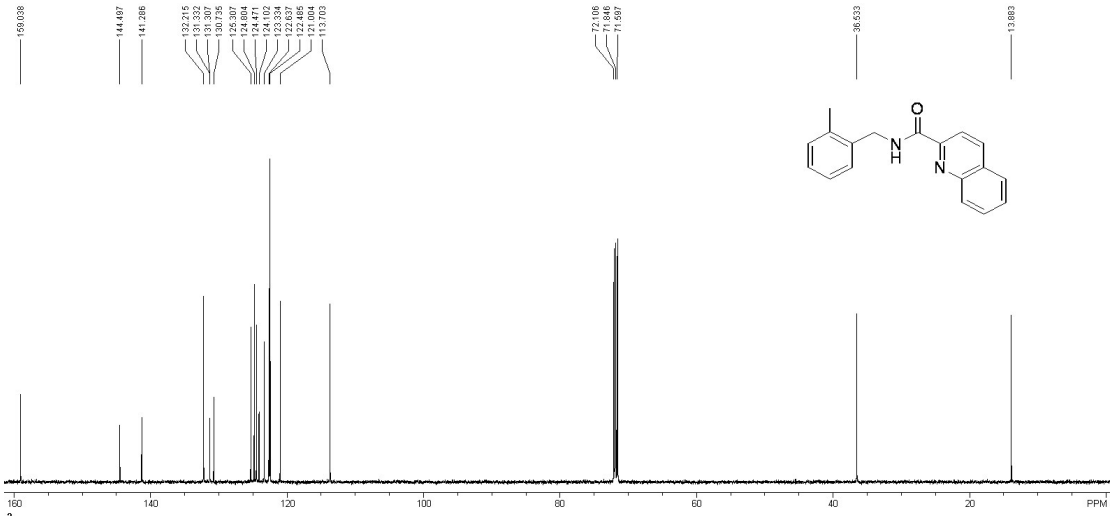


Entry	$Pd(OAc)_2$ (mol %)	Additive	**2a**(equiv)	T(°C)	Time (h)	**3za**(%)[b]	**3zb**(%)[b]
1	10	PhCOOK	3	90	12	34	33
2	10	**Na_2CO_3**	3	90	12	36	38
3	10	PhCOOK	**4**	90	12	38	30
4	10	PhCOOK	3	90	**48**	34	33
5	**15**	PhCOOK	3	**130**	12	35	34
6	**15**	**Na_2CO_3**	3	**130**	12	32	30

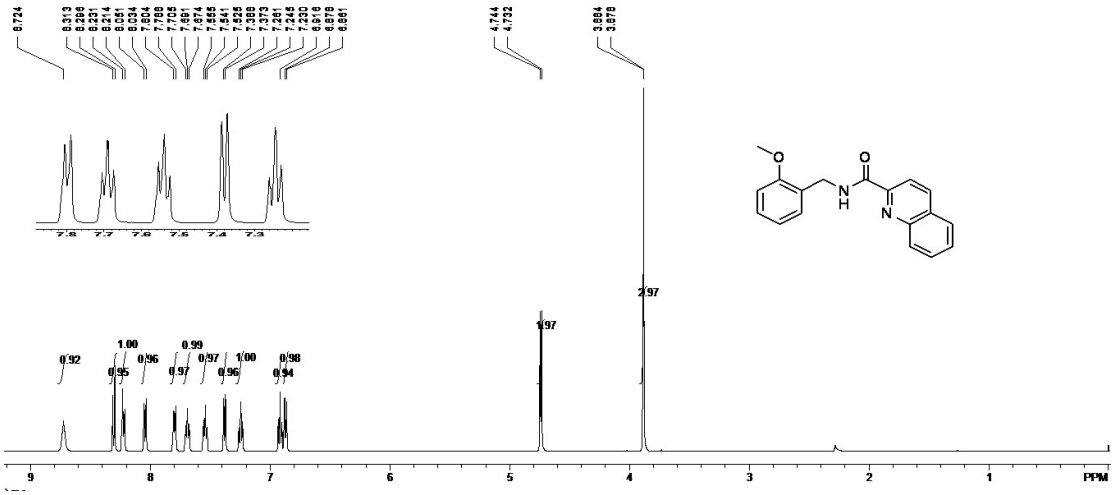
[a]Reaction conditions: **1j** (0.25 mmol, 69 mg), $Pd(OAc)_2$ (0.025 mmol, 6 mg), α-bromo ketones (0.5 mmol), PhCOOK (0.5 mmol, 80 mg), DCE (2 mL), 90 °C, 12 h. [b]Isolated yields.



^{1}H NMR of product **1a**

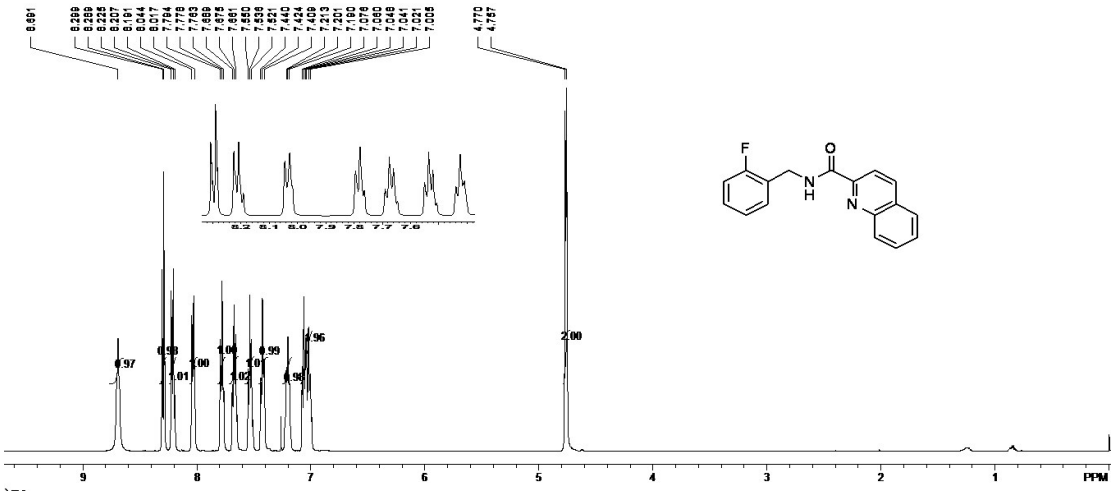


^{13}C NMR of product **1a**

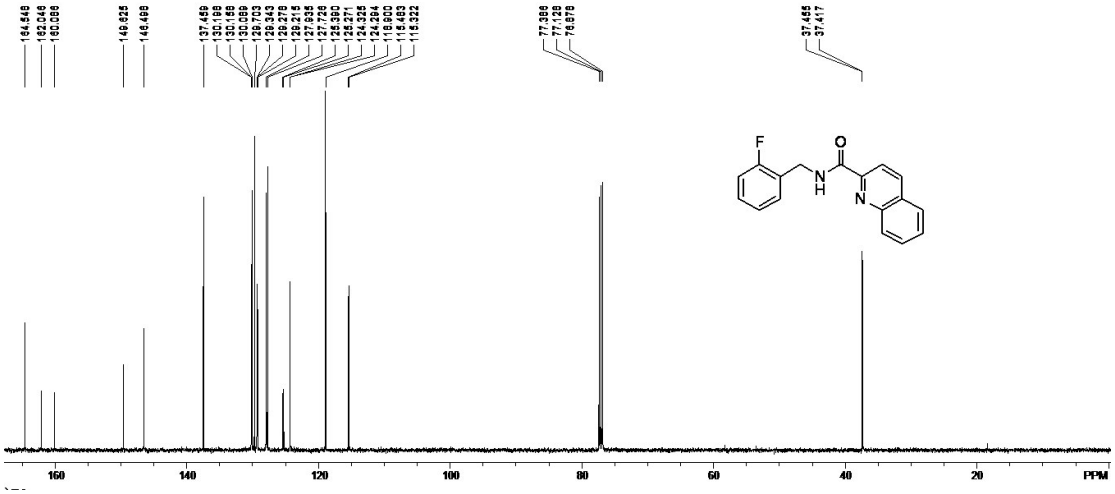


^{1}H NMR of product **1b**

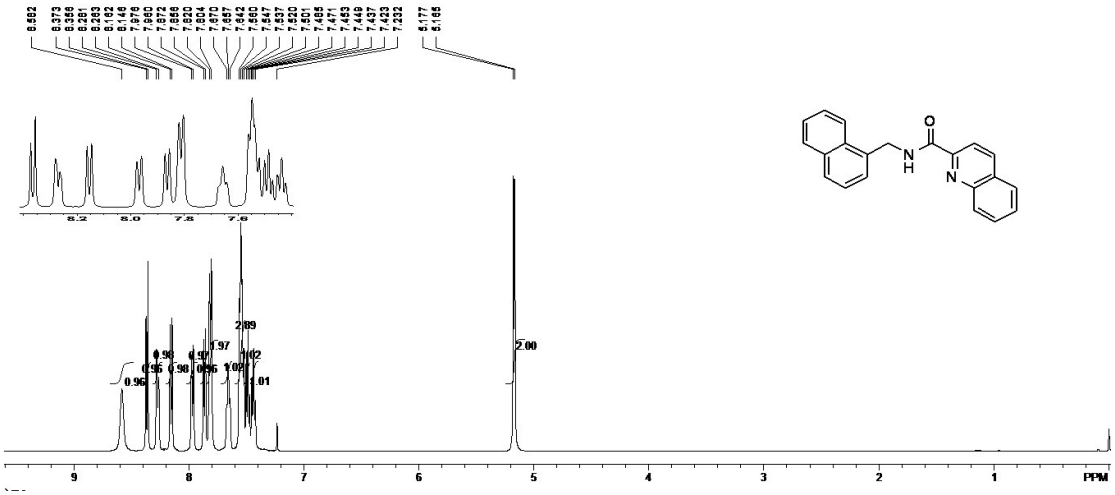
^{13}C NMR of product **1b**



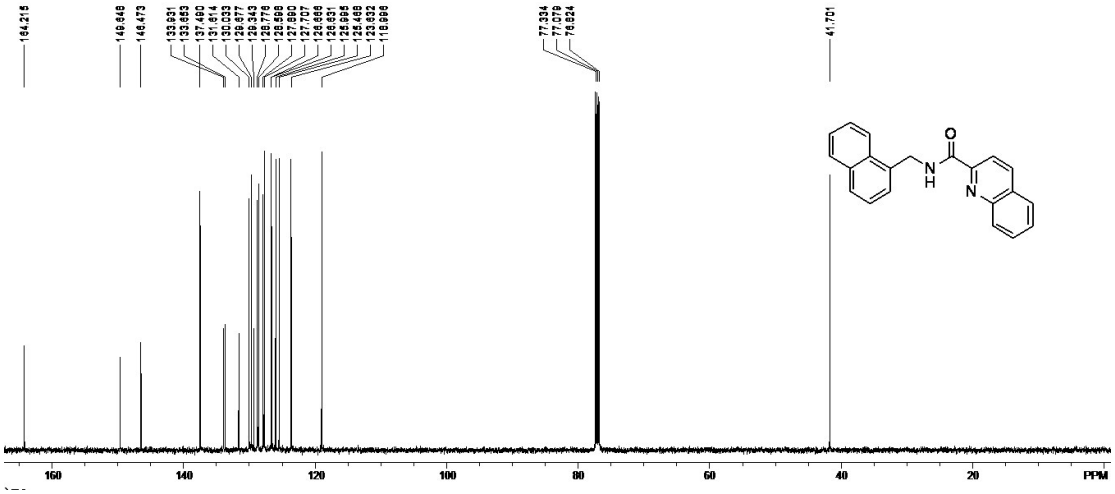
^{1}H NMR of product **1c**



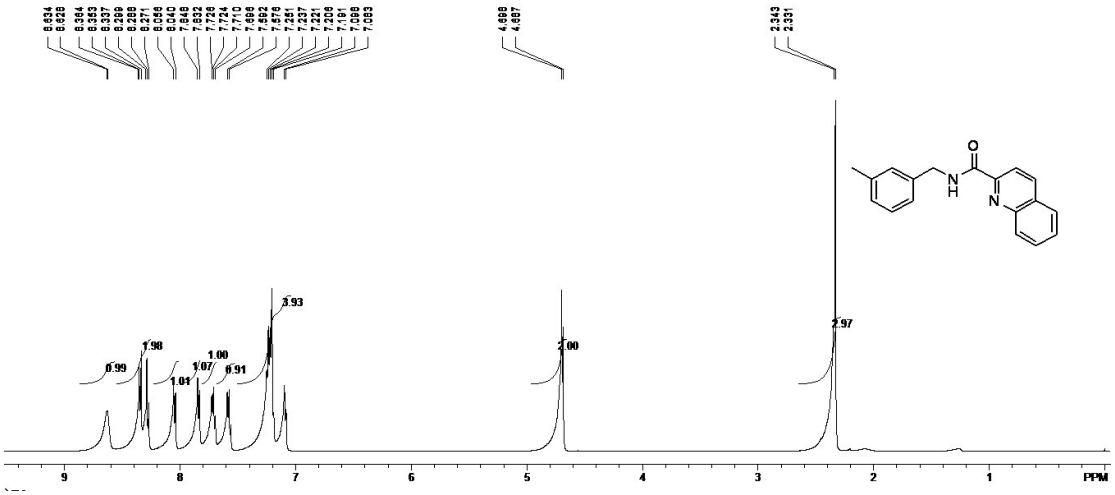
^{13}C NMR of product **1c**



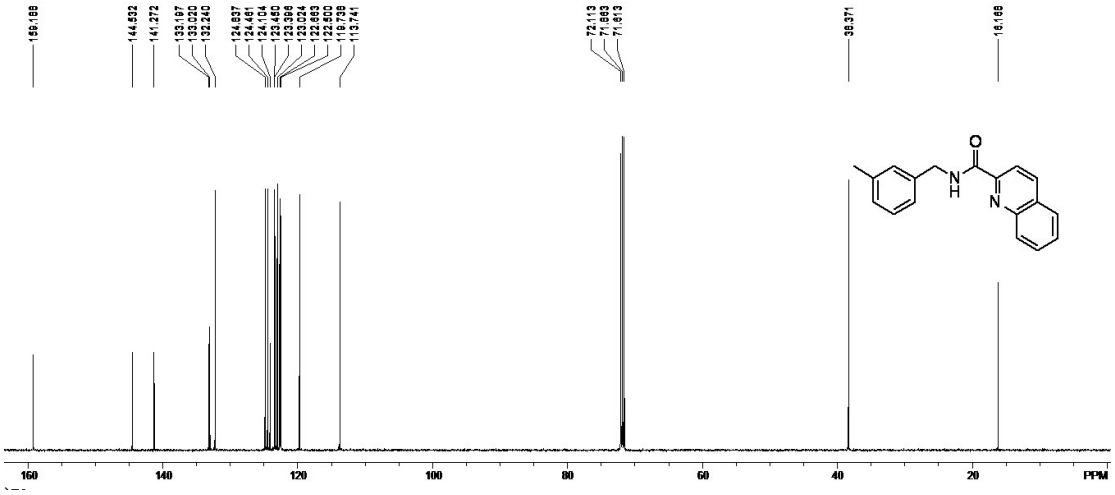
^{1}H NMR of product **1d**



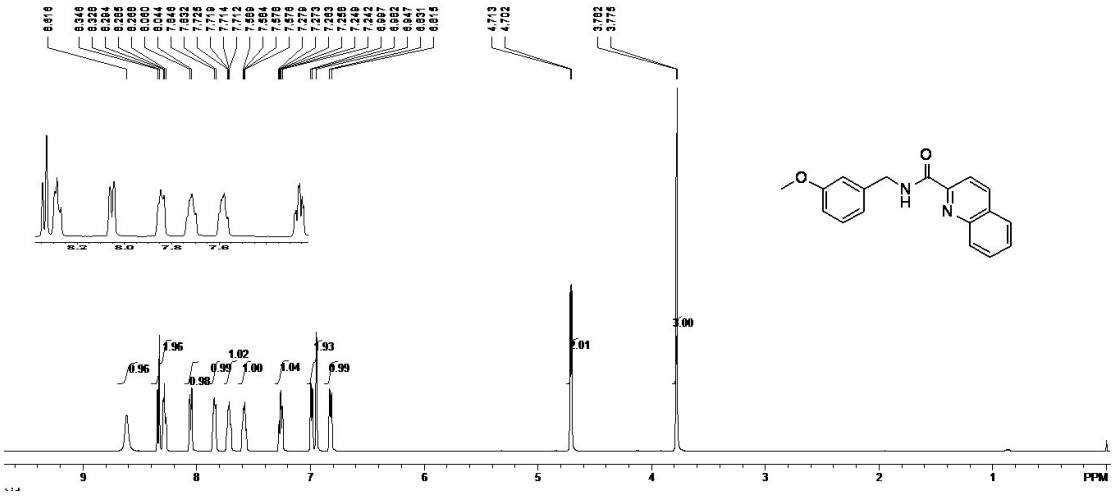
^{13}C NMR of product **1d**



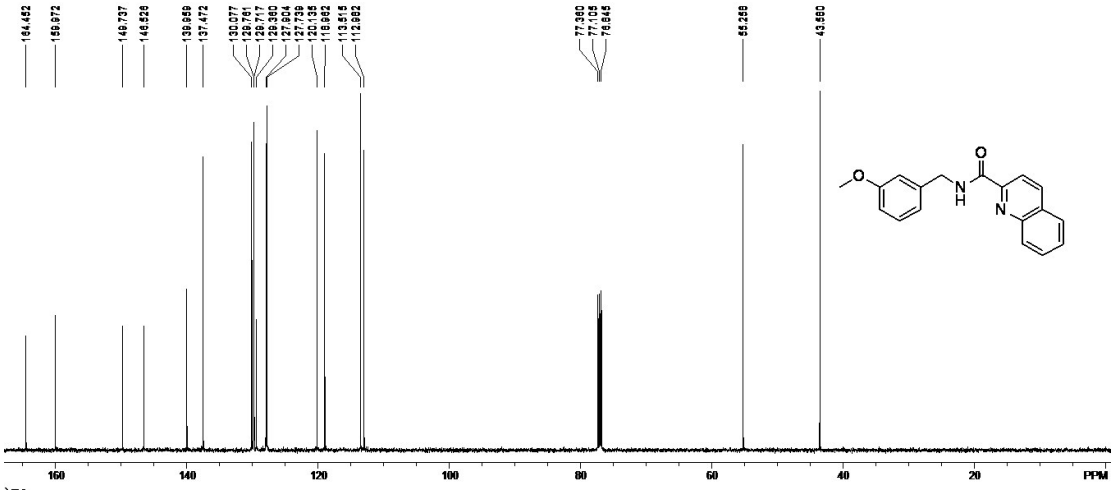
^{1}H NMR of product **1e**



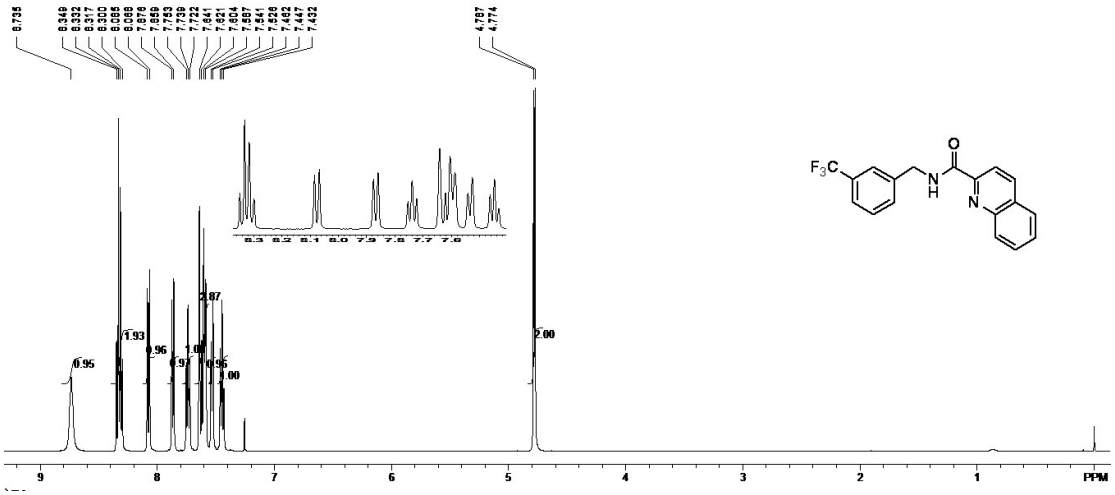
^{13}C NMR of product **1e**



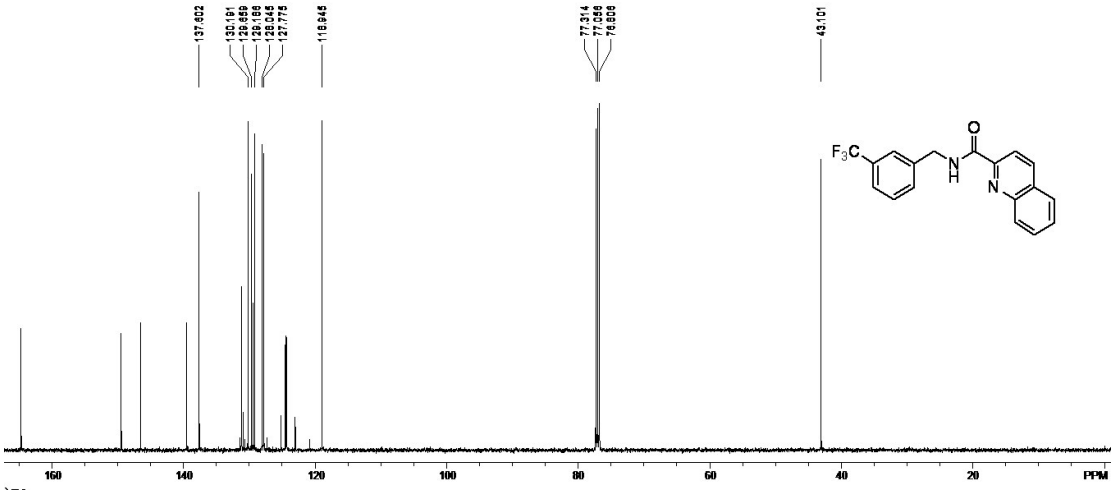
^{1}H NMR of product **1f**



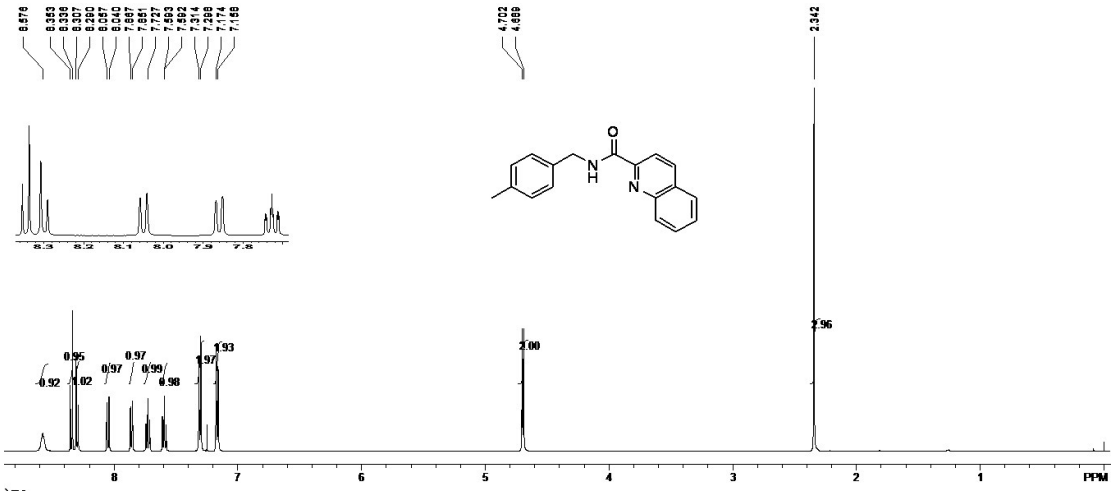
^{13}C NMR of product **1f**



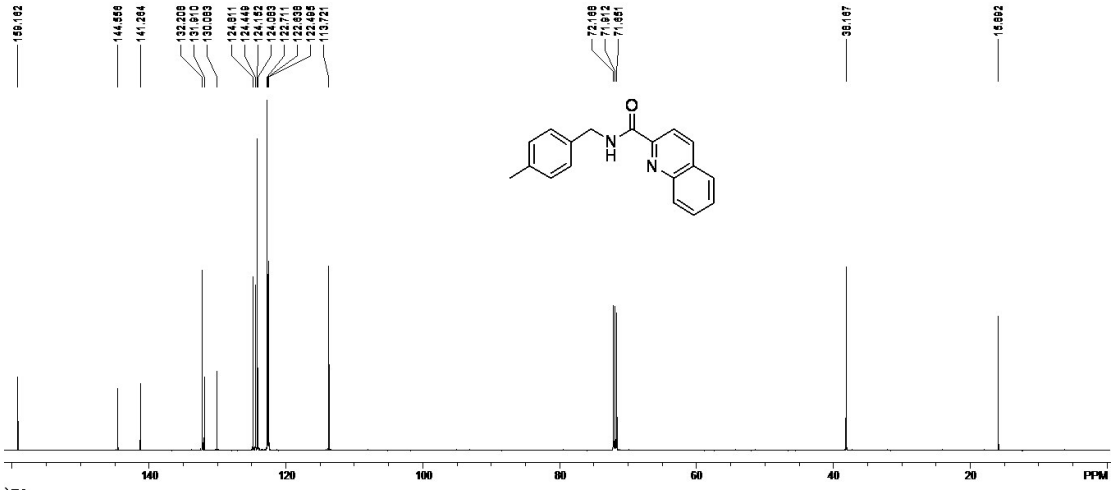
^{1}H NMR of product **1g**



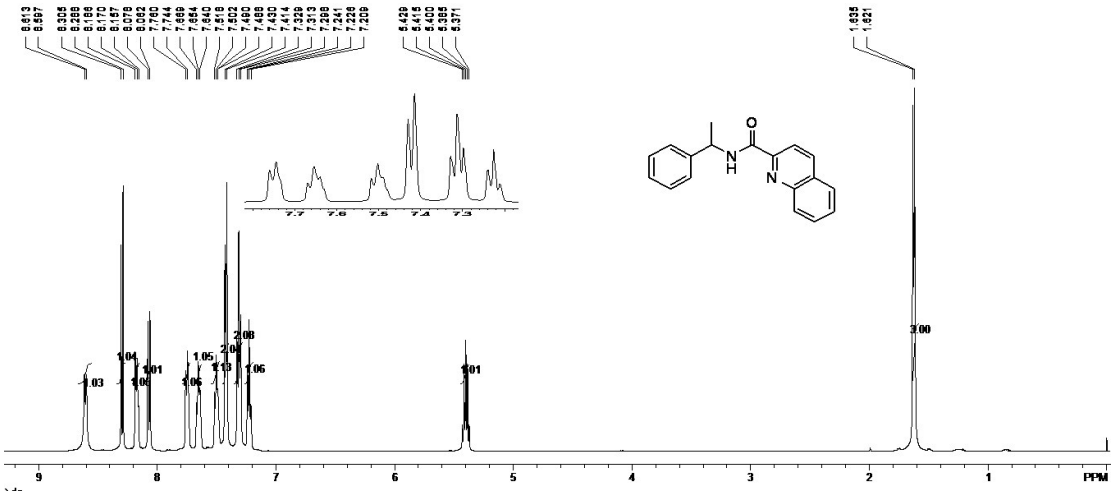
^{13}C NMR of product **1g**



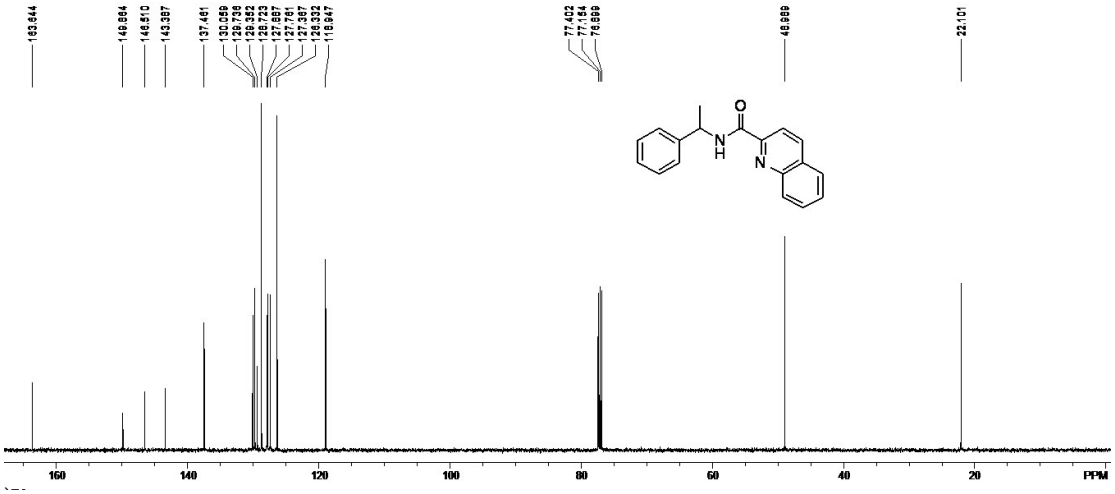
^{1}H NMR of product **1h**



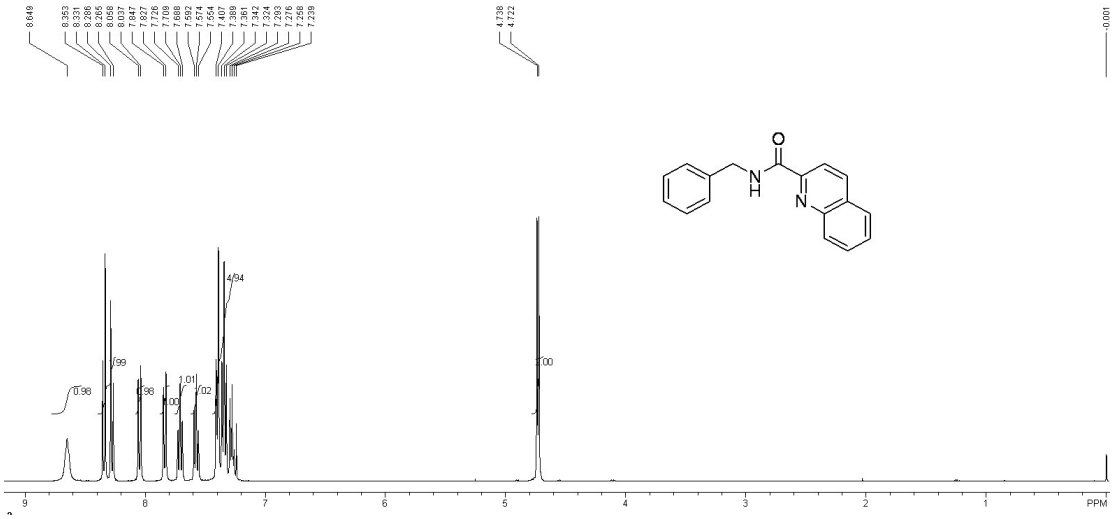
^{13}C NMR of product **1h**



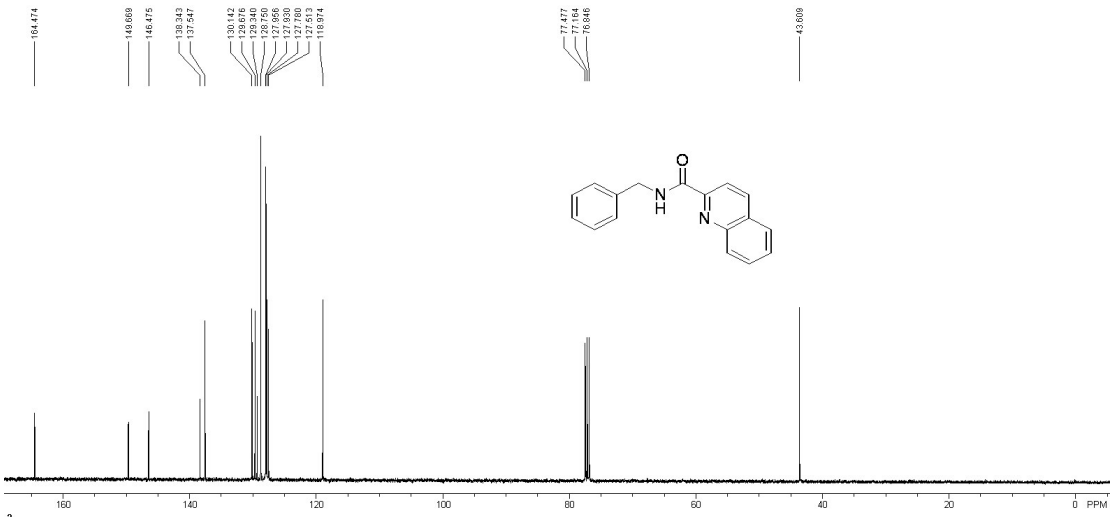
^{1}H NMR of product **1i**



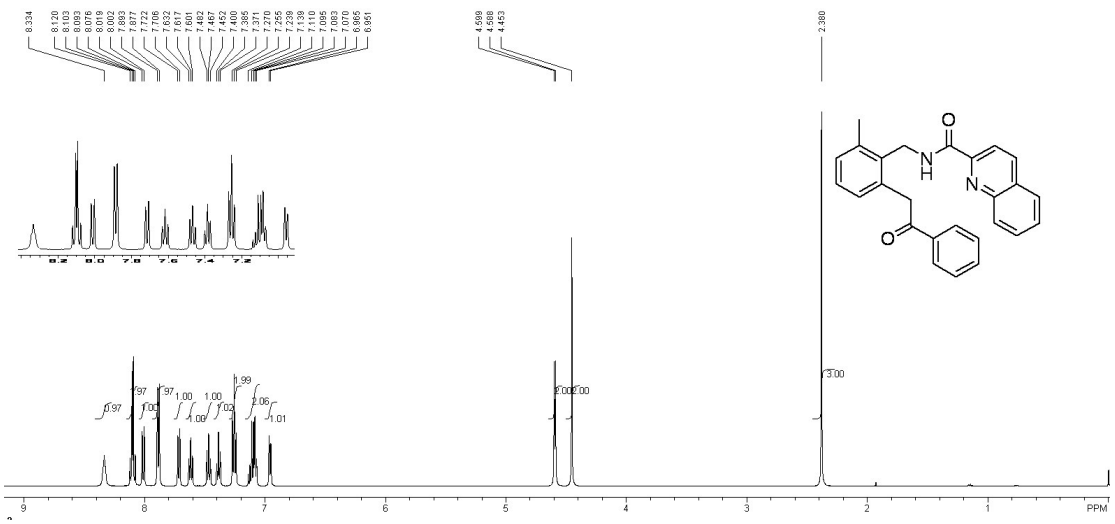
^{13}C NMR of product **1i**



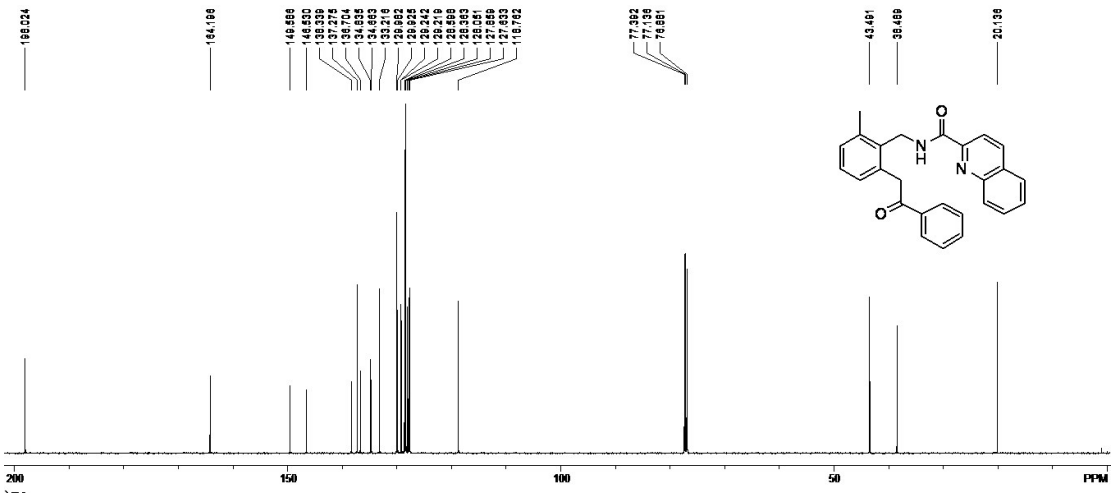
^{1}H NMR of product **1j**



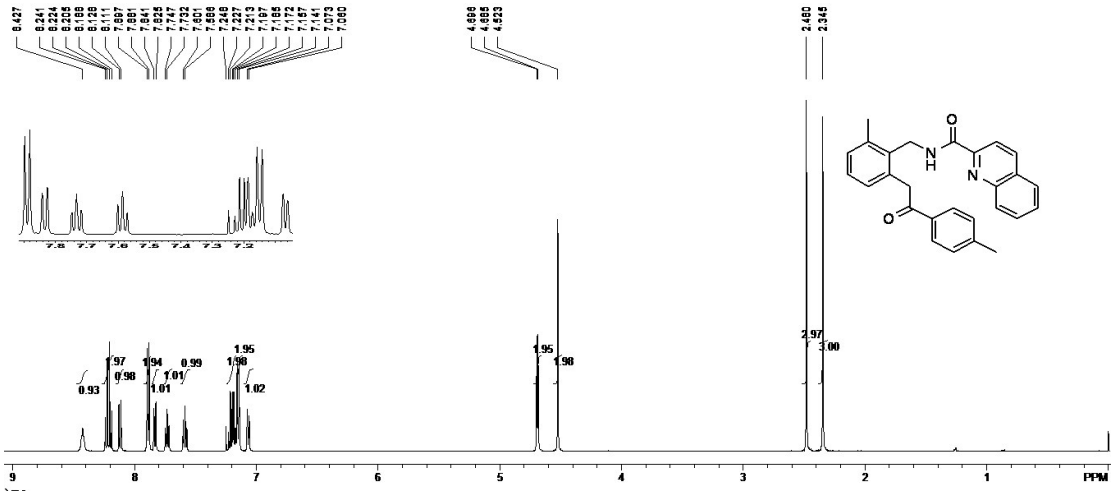
^{13}C NMR of product **1j**



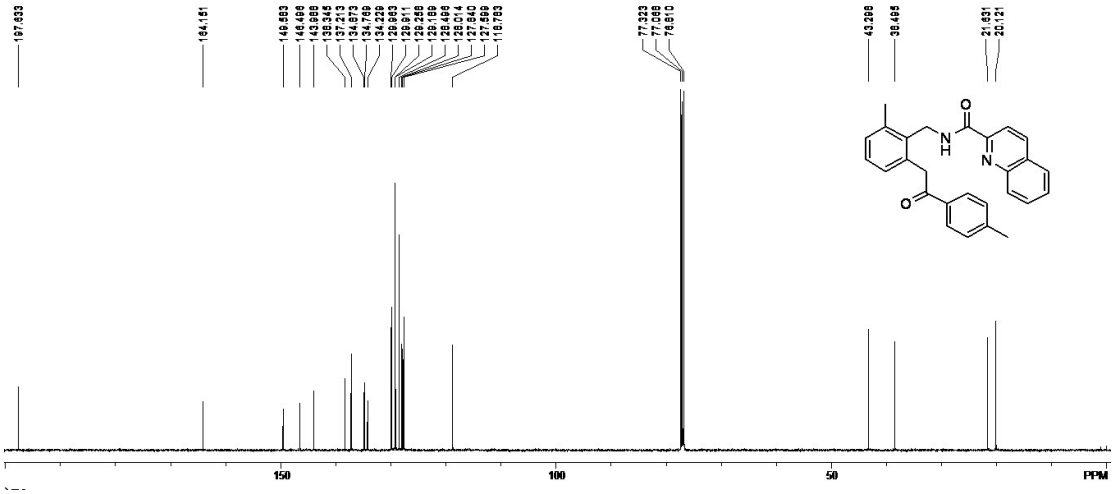
^{1}H NMR of product **3a**



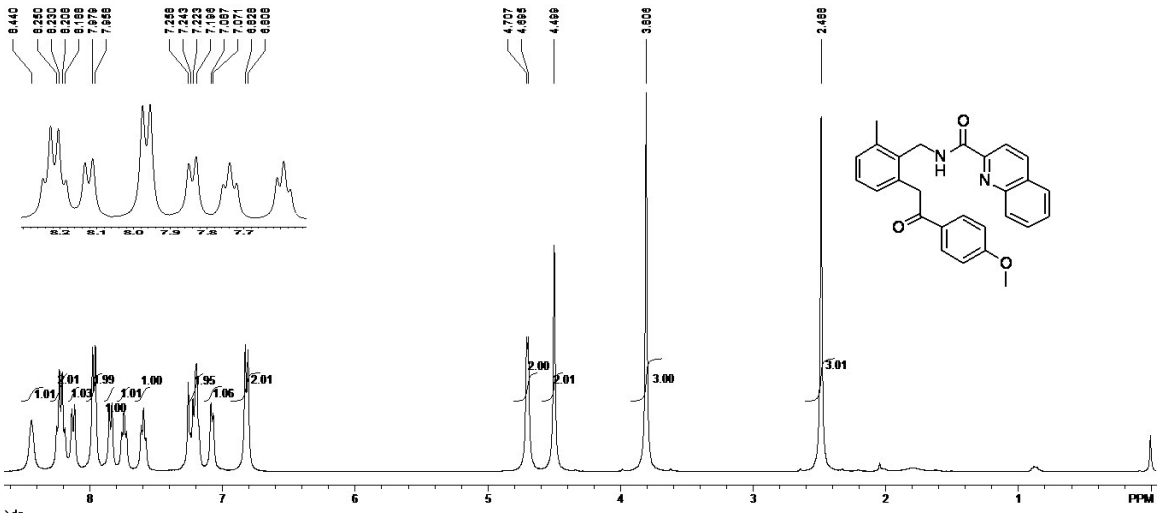
^{13}C NMR of product **3a**



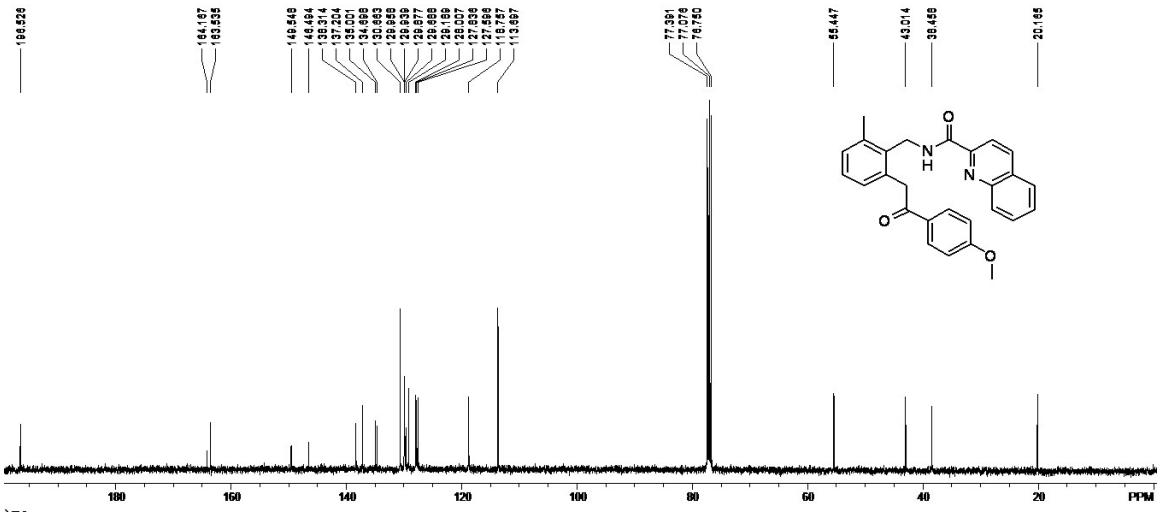
^{1}H NMR of product **3b**



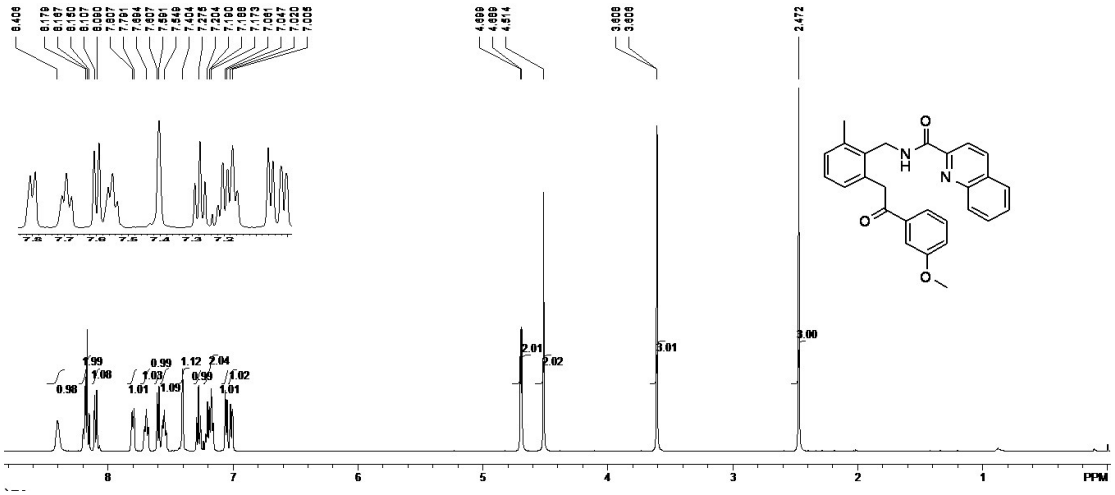
^{13}C NMR of product **3b**



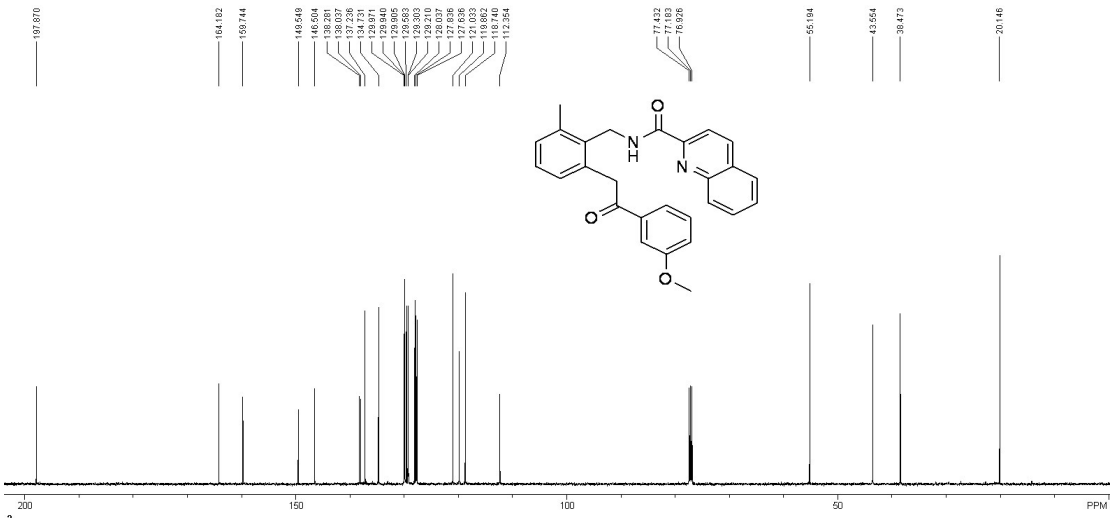
^{1}H NMR of product **3c**



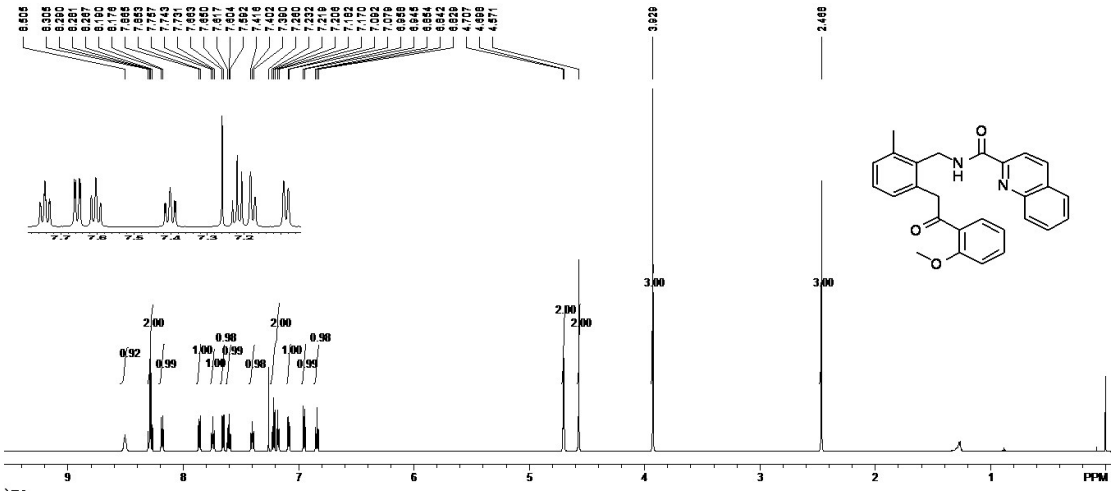
^{13}C NMR of product **3c**



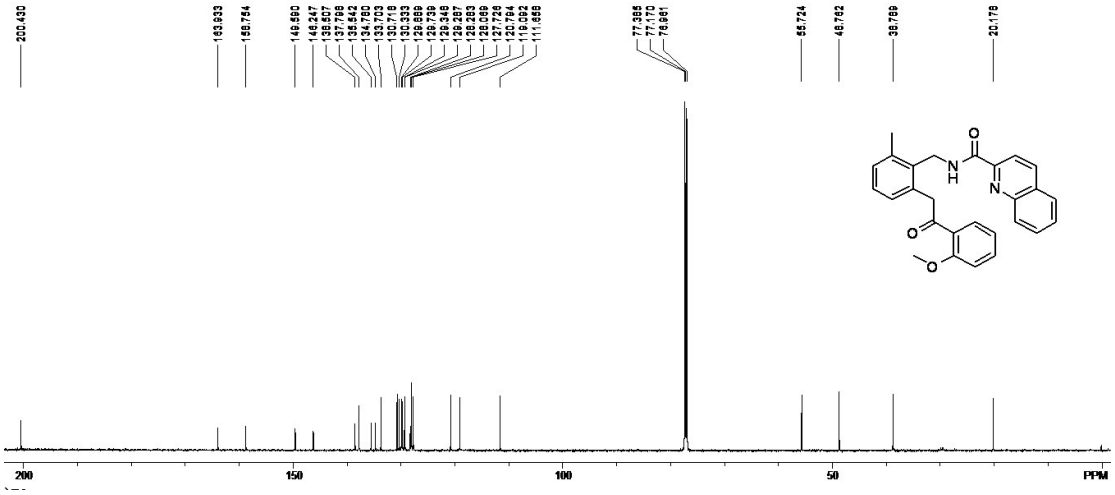
^{1}H NMR of product **3d**



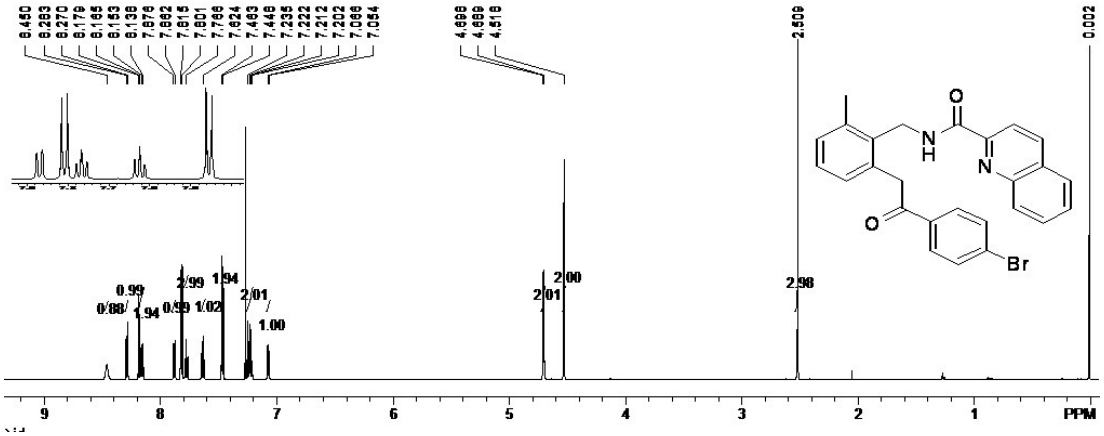
^{13}C NMR of product **3d**



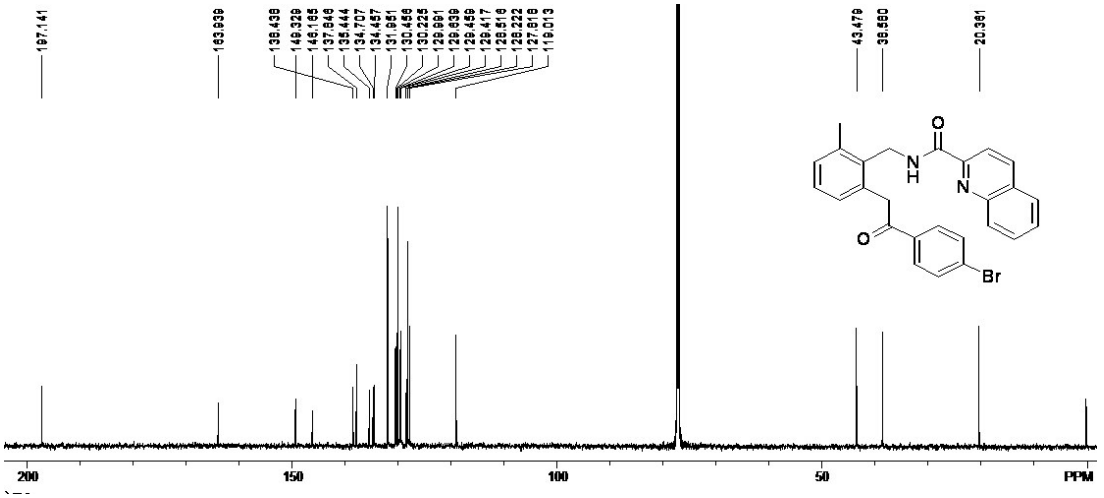
^{1}H NMR of product **3e**



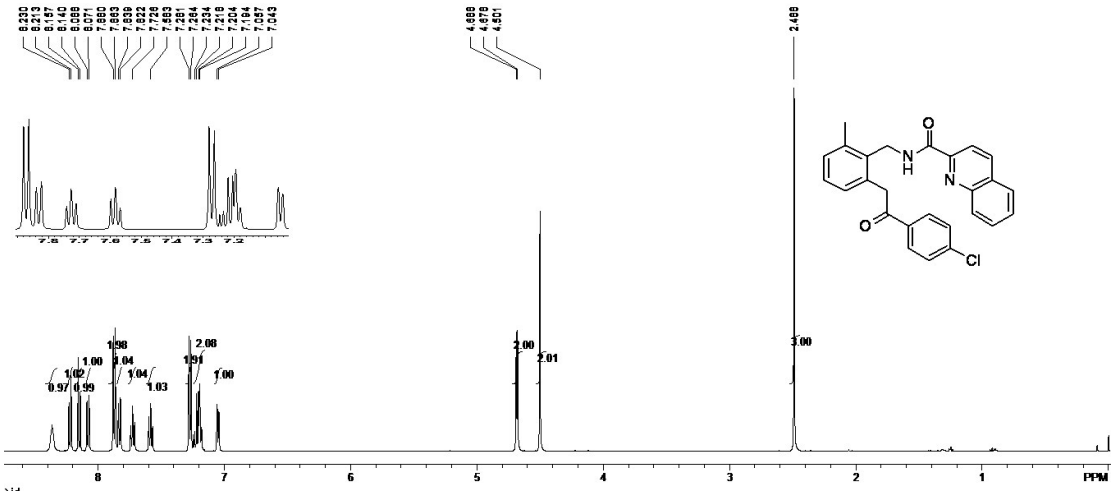
^{13}C NMR of product **3e**



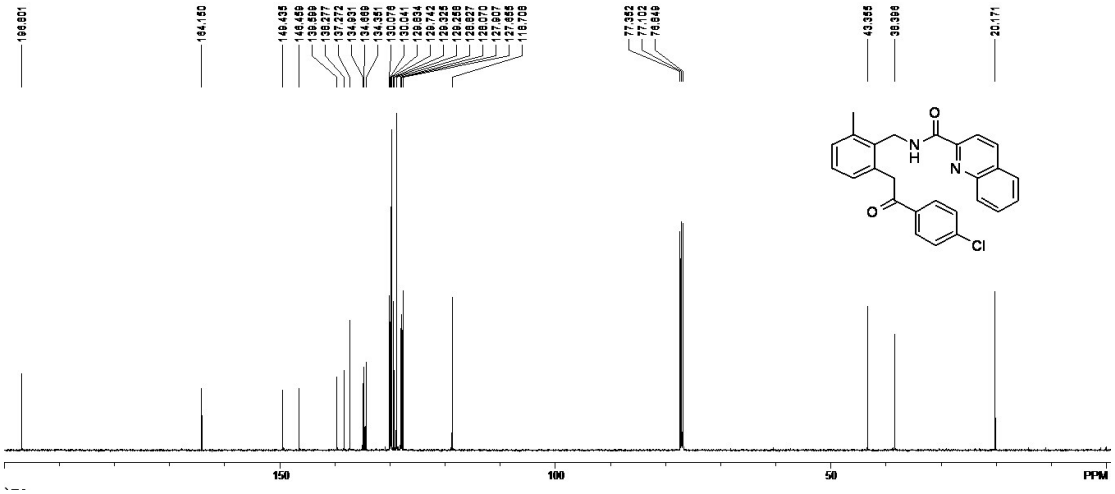
^{1}H NMR of product **3f**



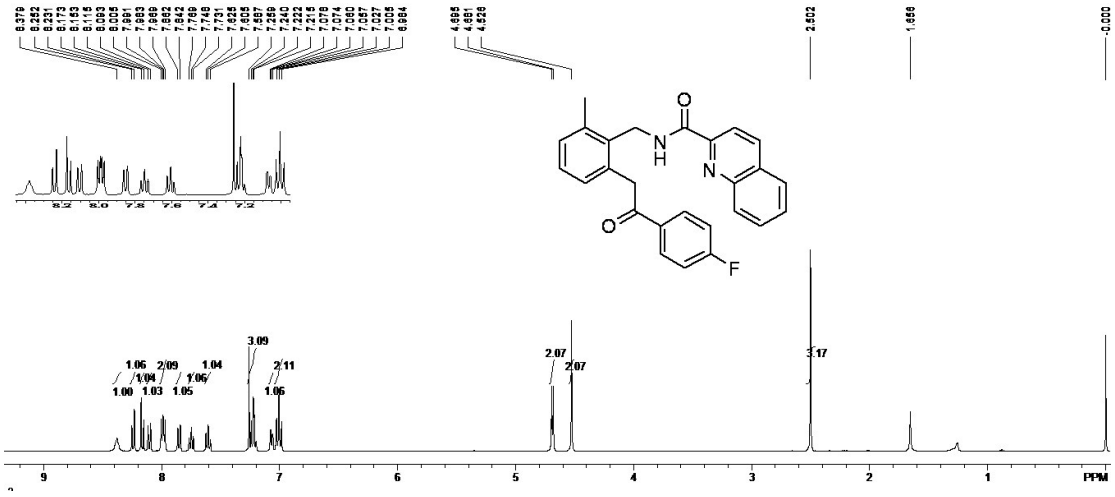
^{13}C NMR of product **3f**



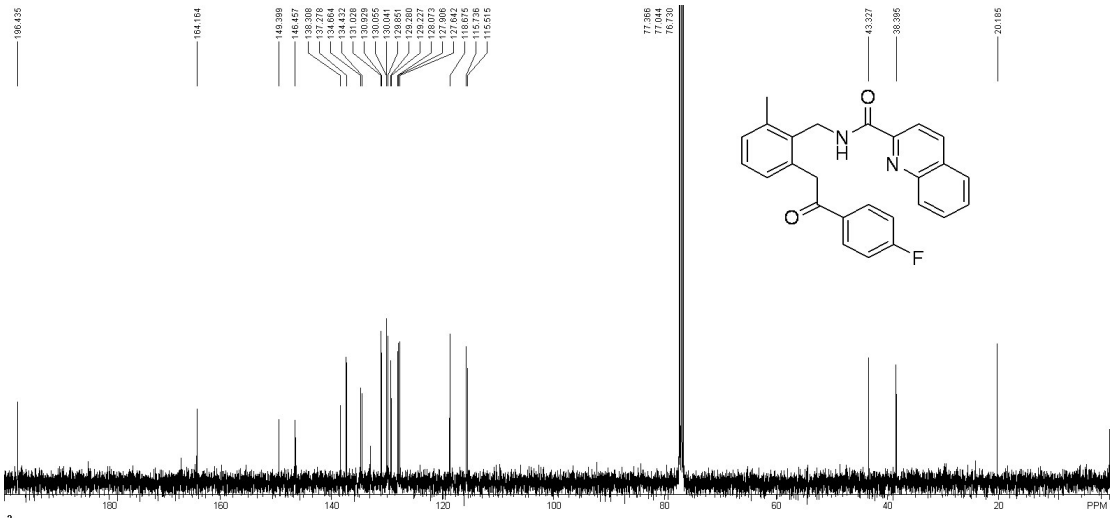
^{1}H NMR of product **3g**



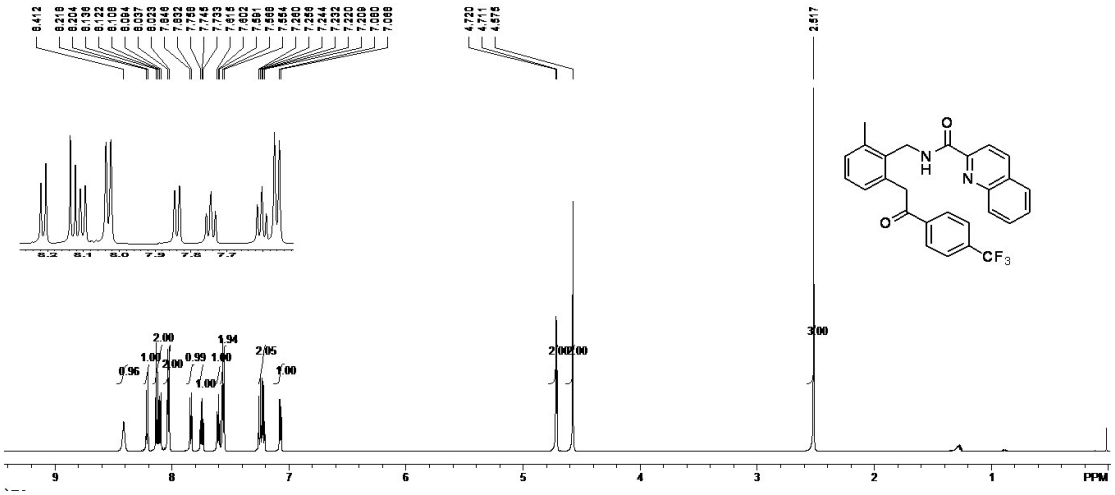
^{13}C NMR of product **3g**



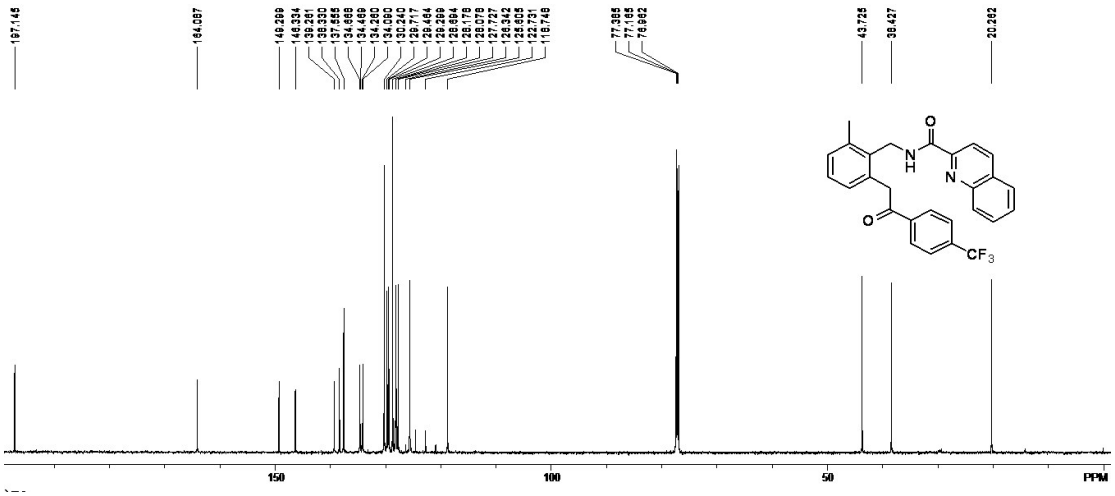
^{1}H NMR of product **3h**



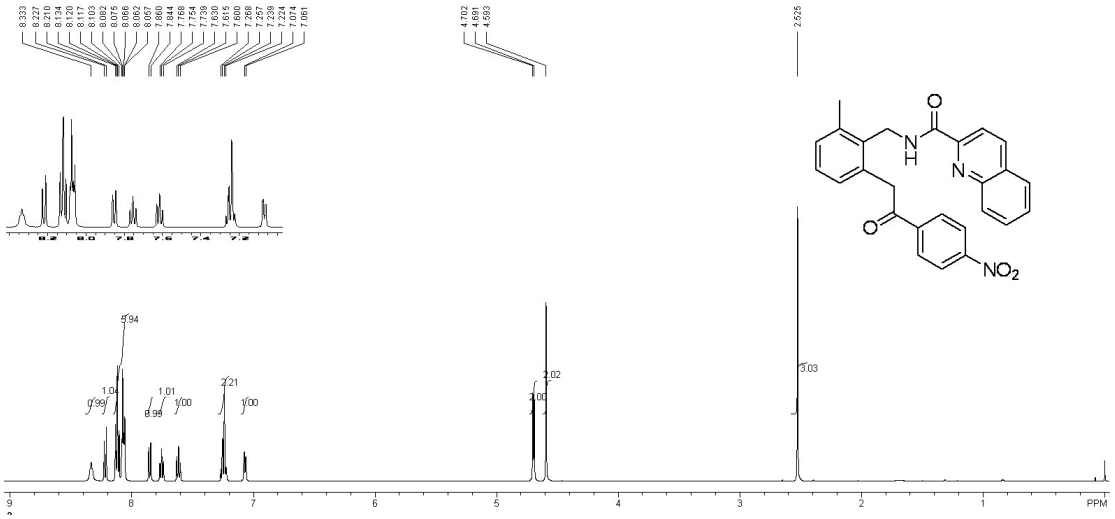
^{13}C NMR of product **3h**



^{1}H NMR of product **3i**



^{13}C NMR of product **3i**



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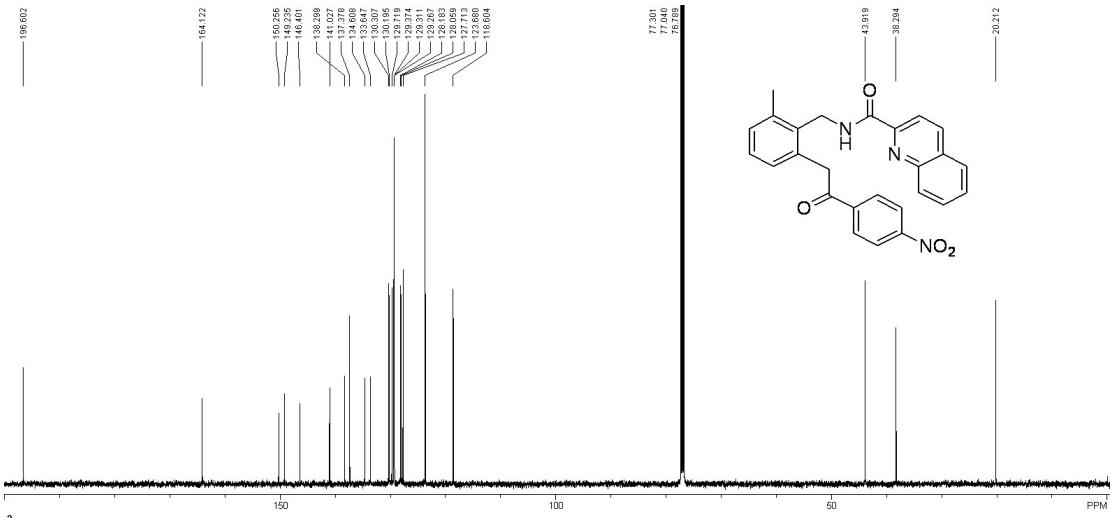
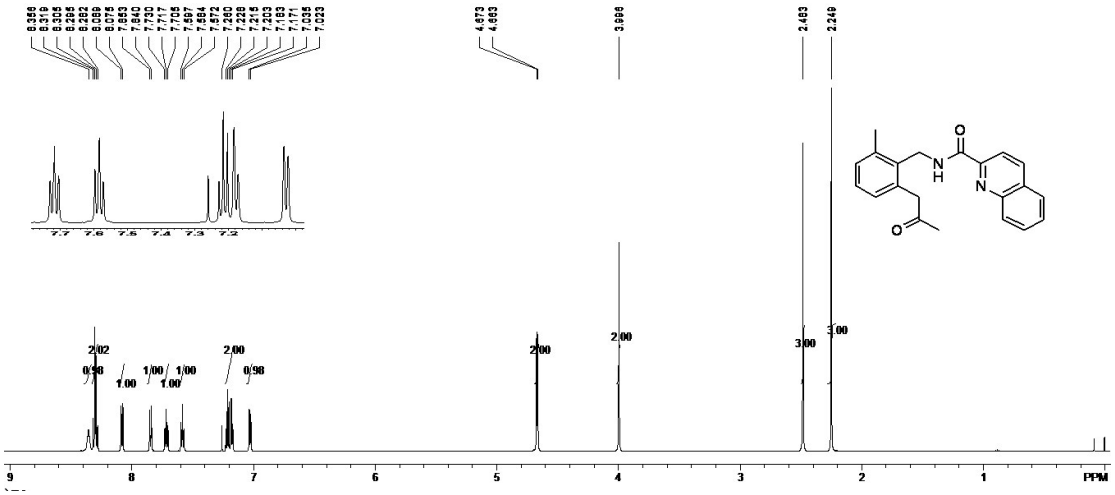
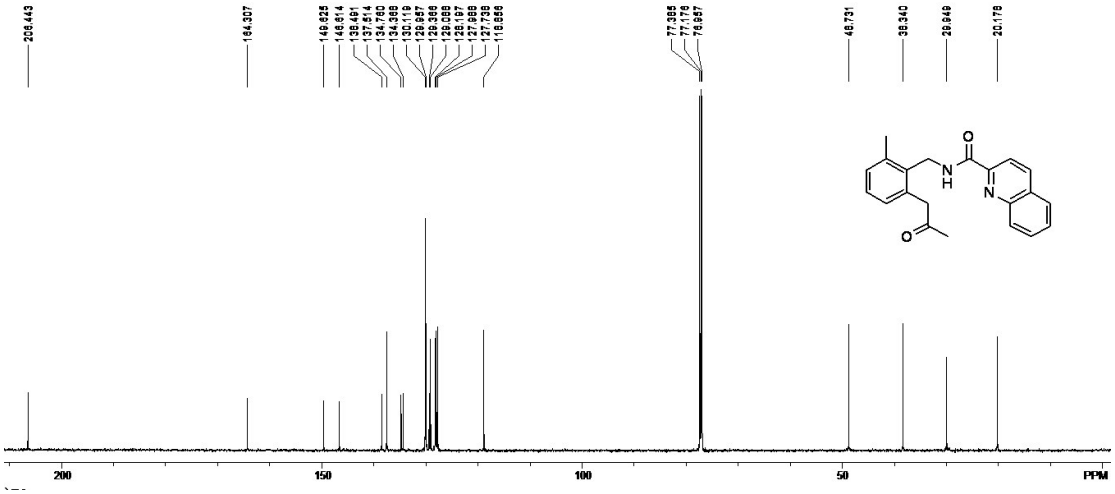


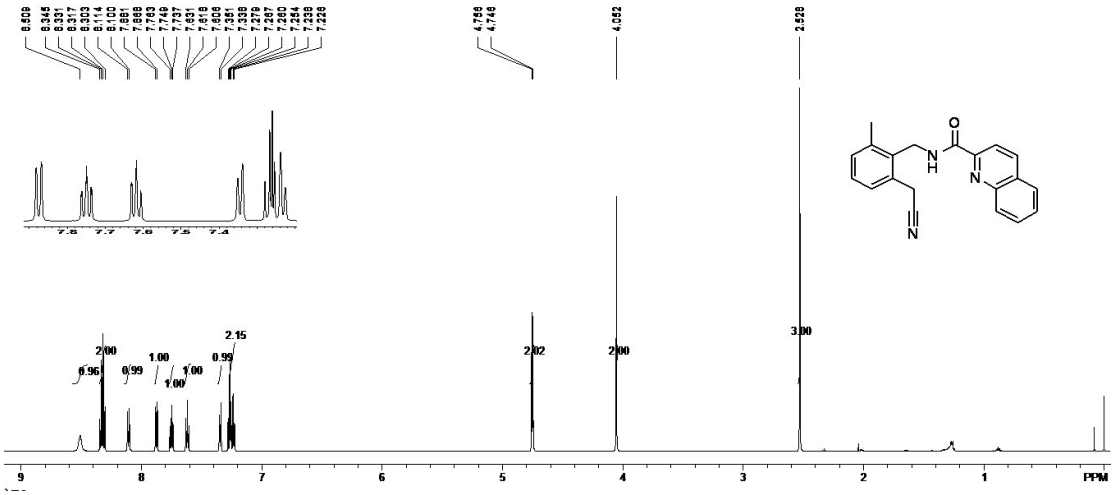
^{13}C NMR of product **3j**



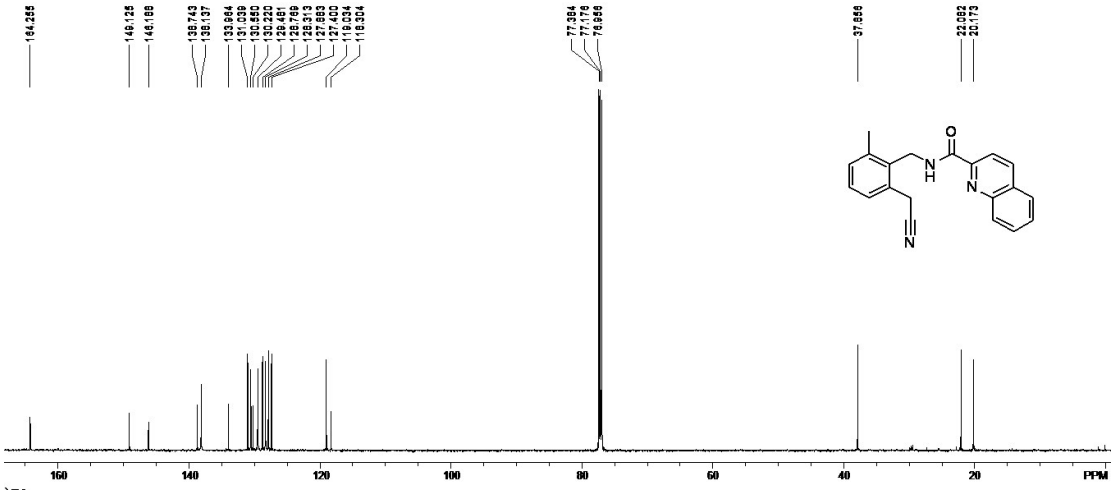
^{1}H NMR of product **3k**



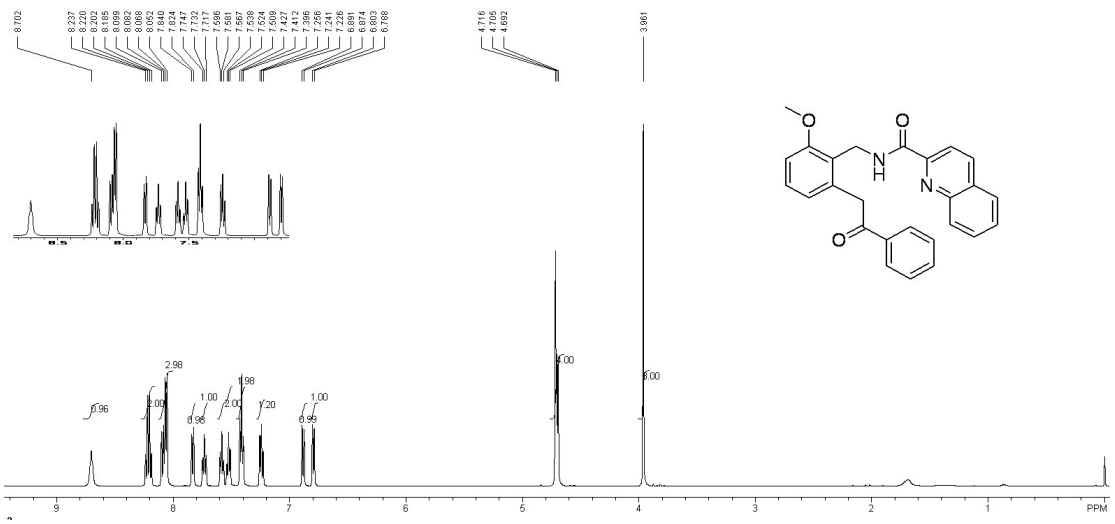
^{13}C NMR of product **3k**



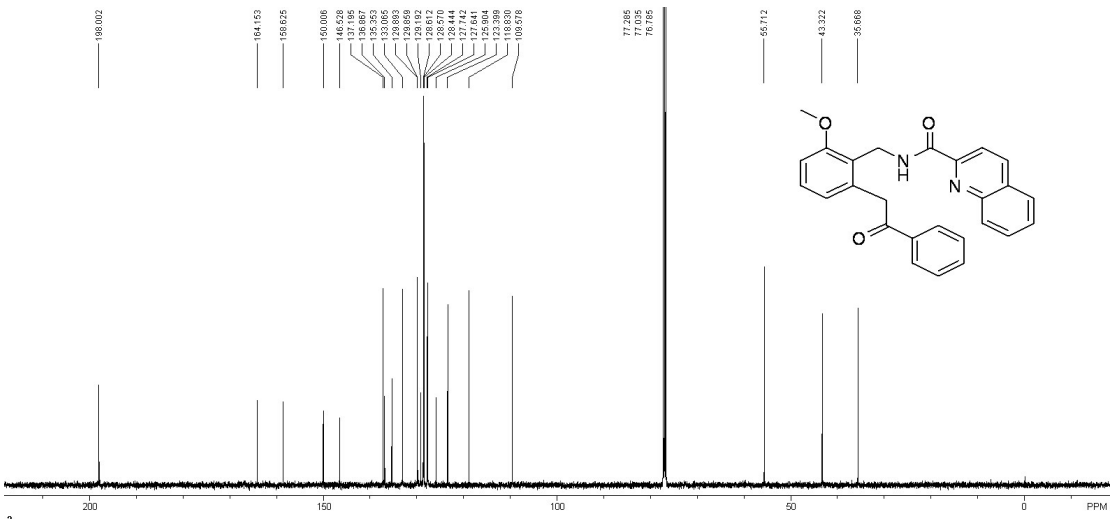
^{1}H NMR of product **3l**



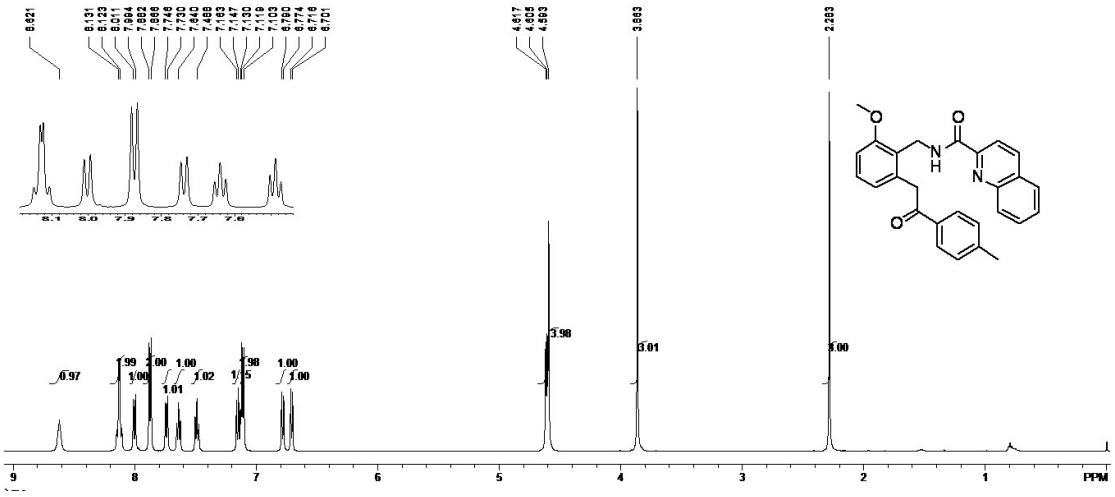
^{13}C NMR of product **3l**



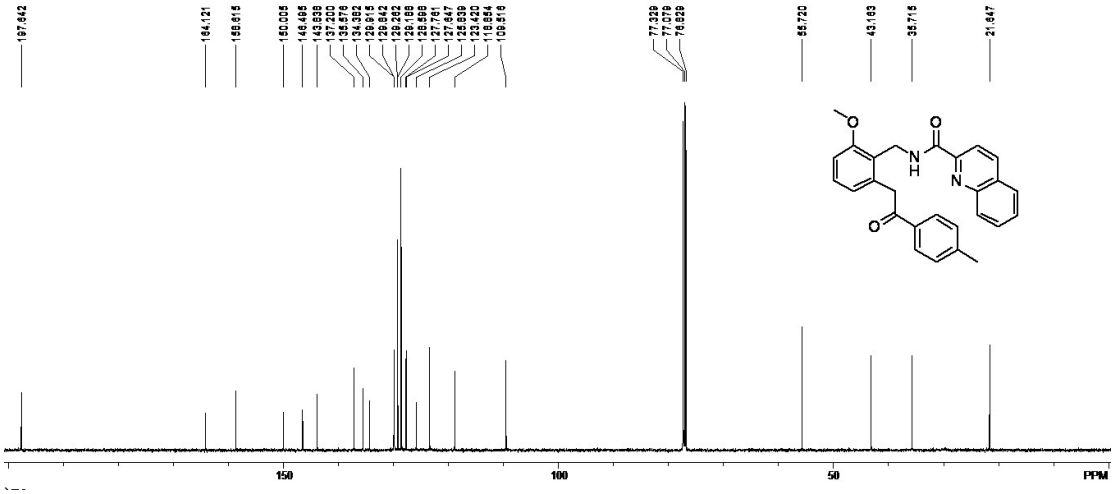
^{1}H NMR of product **3m**



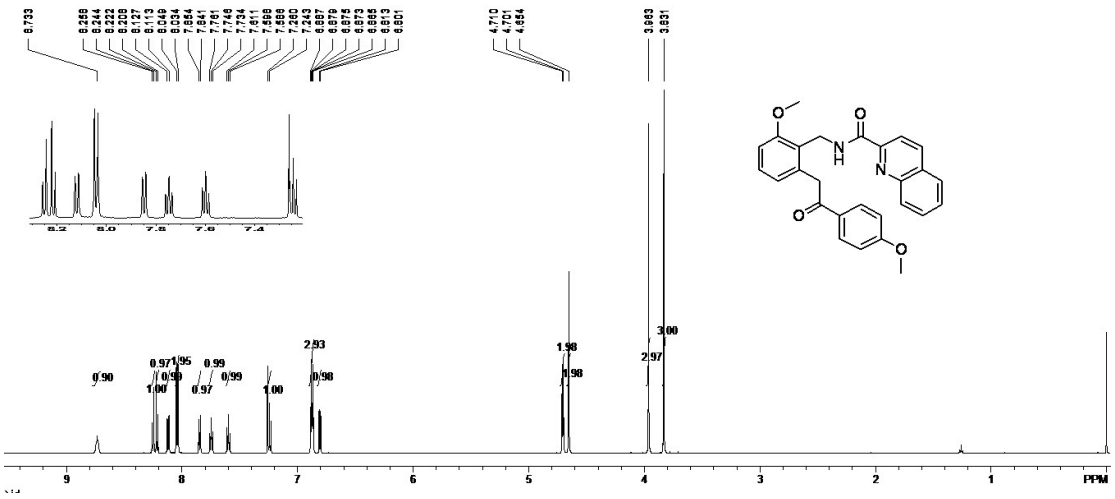
^{13}C NMR of product **3m**



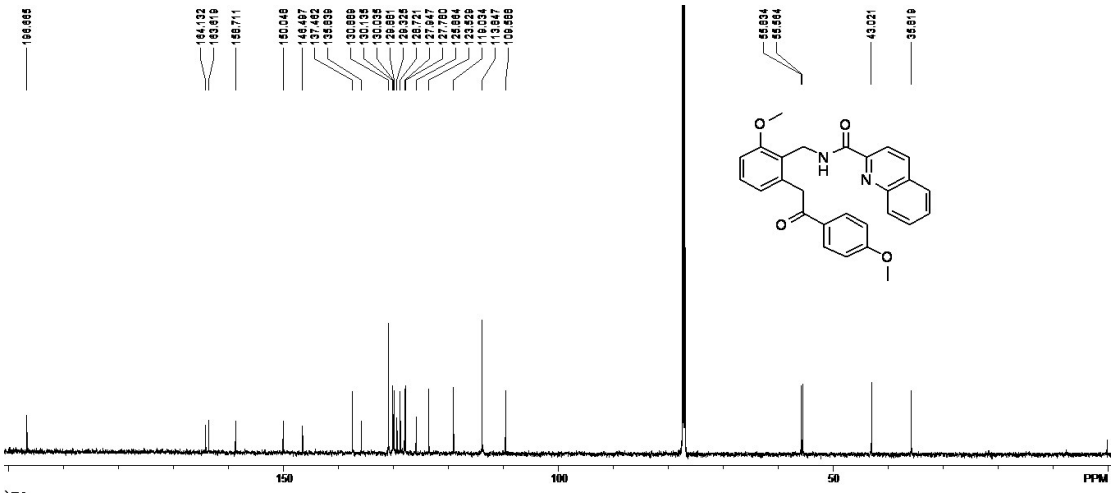
^{1}H NMR of product **3n**



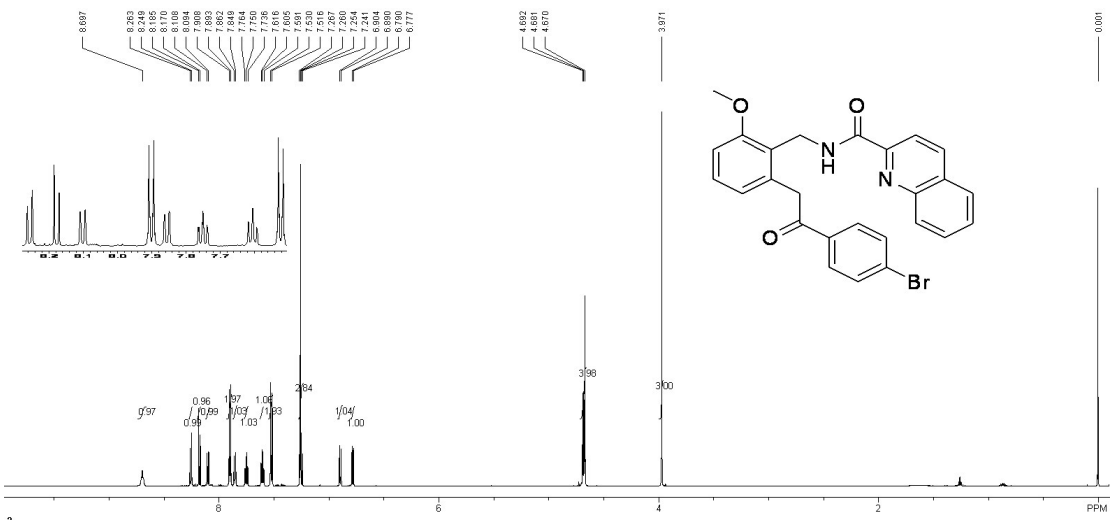
^{13}C NMR of product **3n**



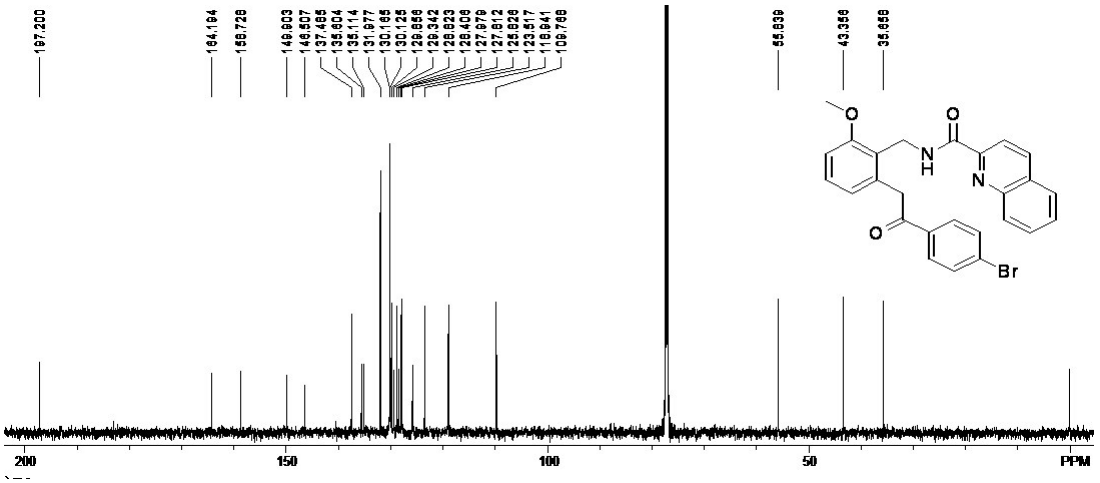
^{1}H NMR of product **3o**



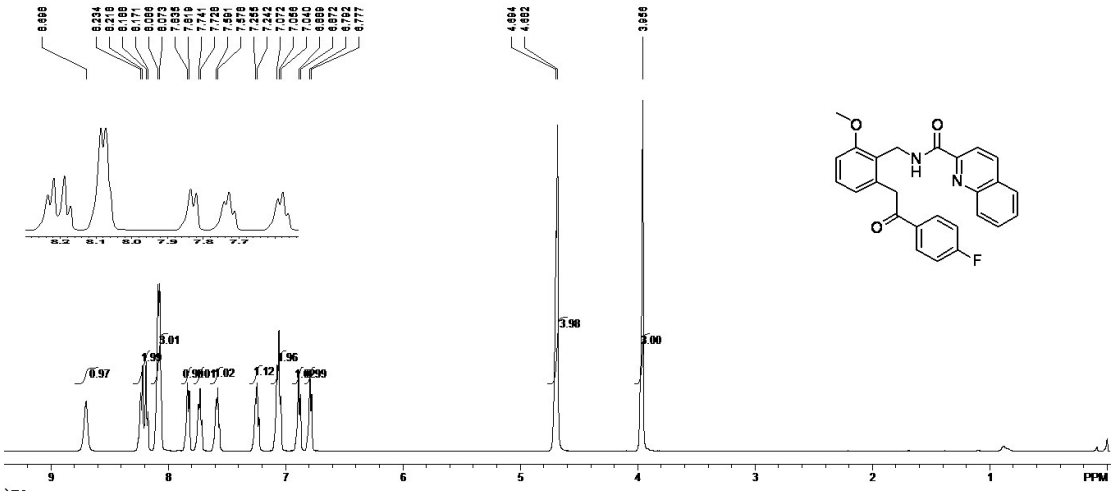
^{13}C NMR of product **3o**



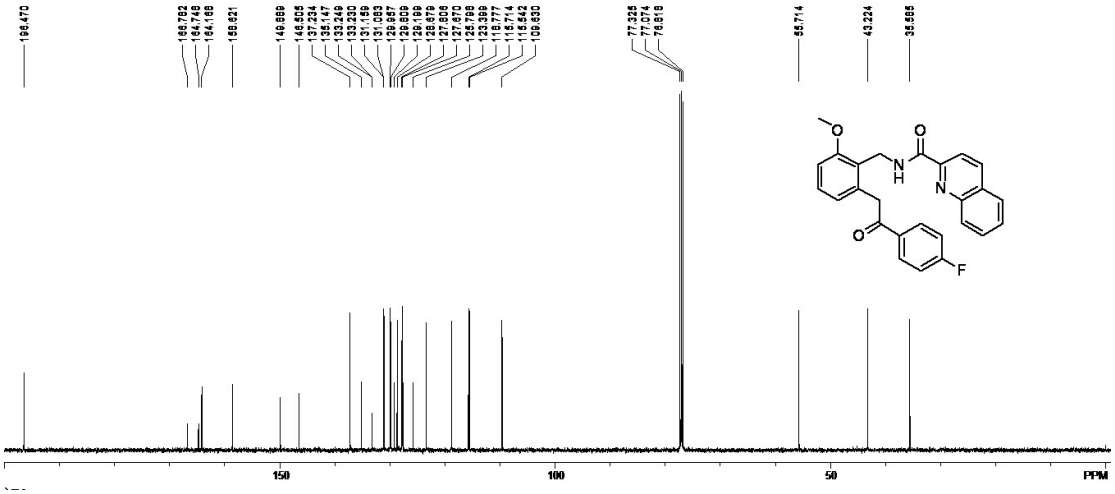
^{1}H NMR of product **3p**



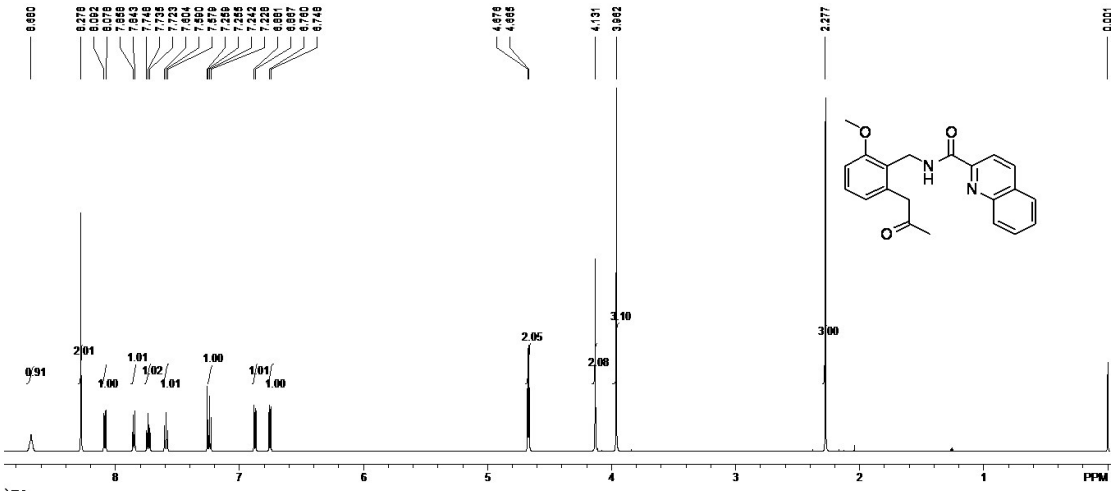
^{13}C NMR of product **3p**



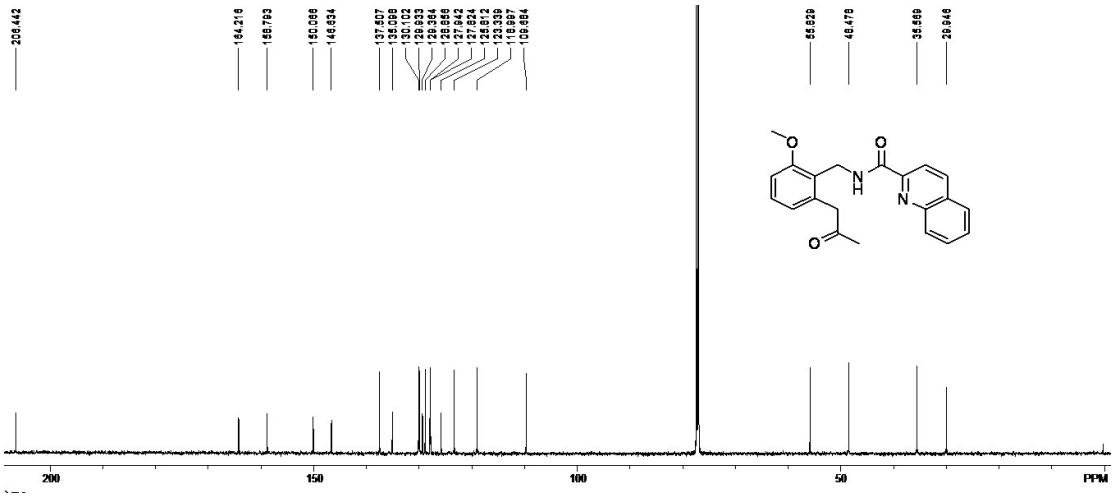
^{1}H NMR of product **3q**



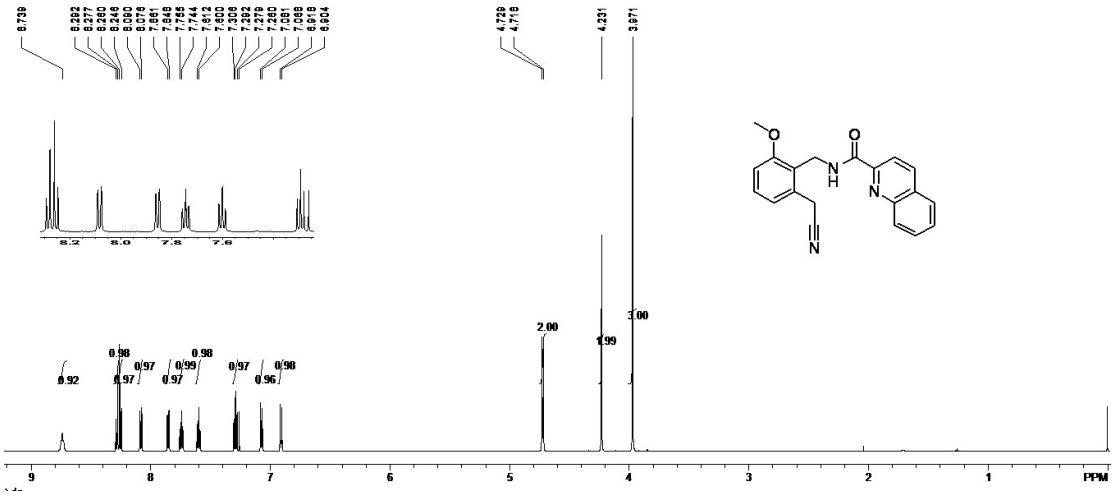
^{13}C NMR of product **3q**



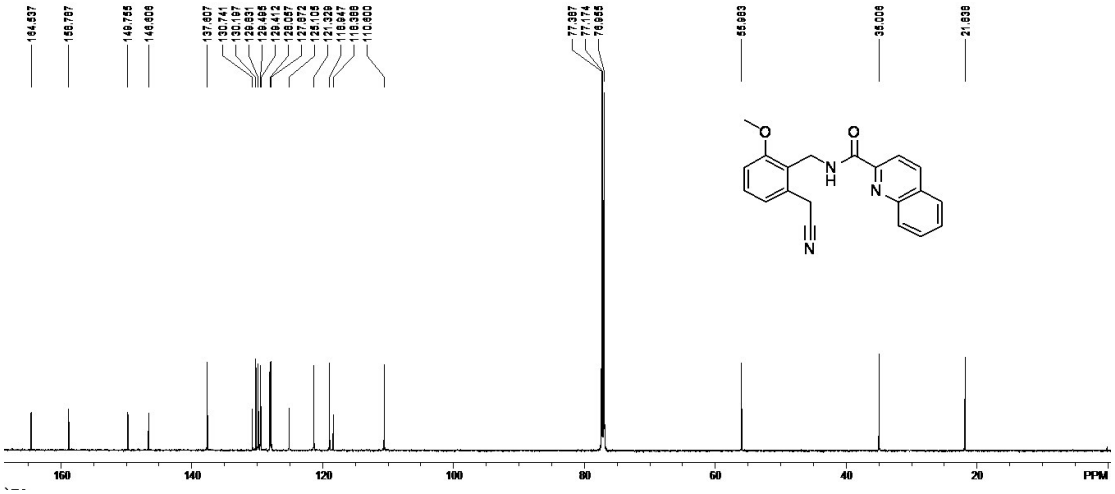
^{1}H NMR of product **3r**



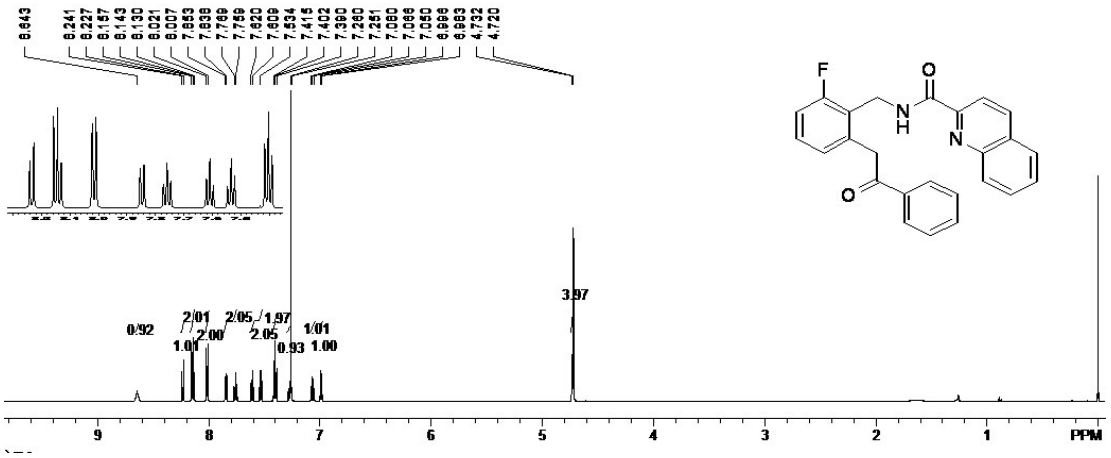
^{13}C NMR of product **3r**



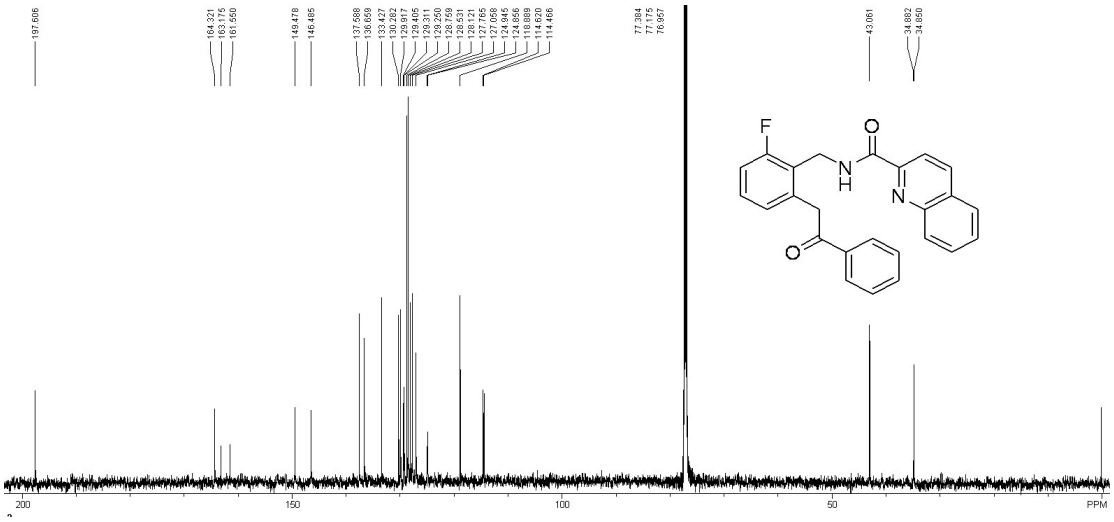
^{1}H NMR of product **3s**



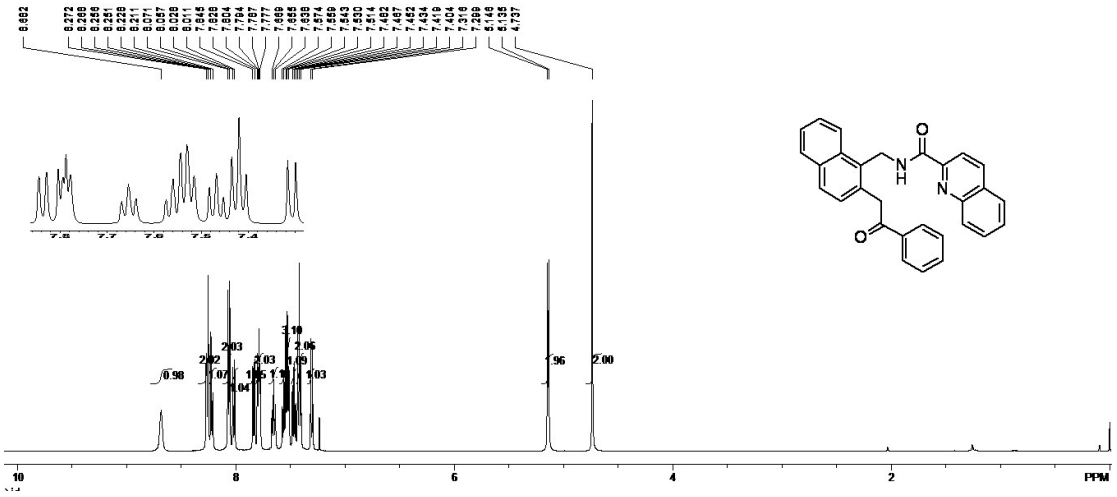
^{13}C NMR of product **3s**



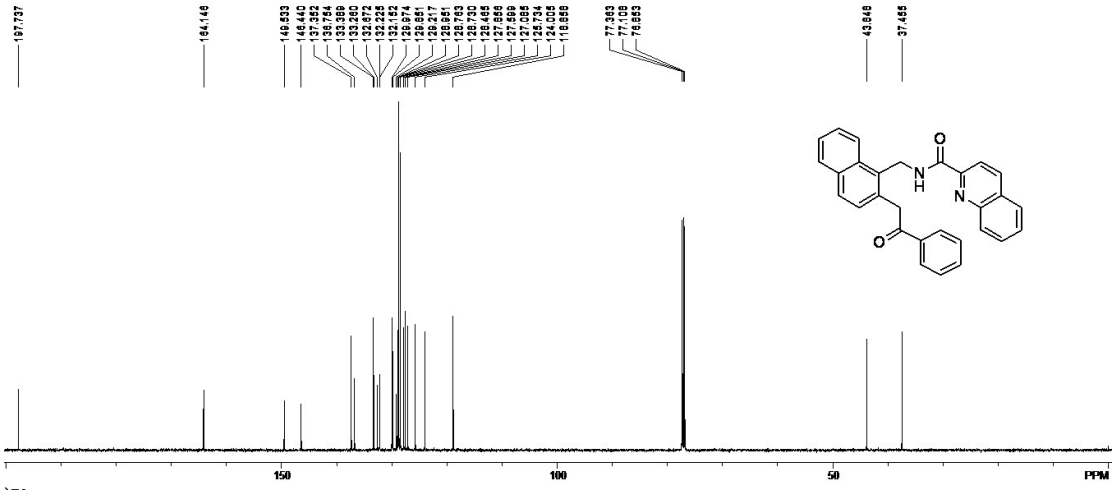
^{1}H NMR of product **3t**



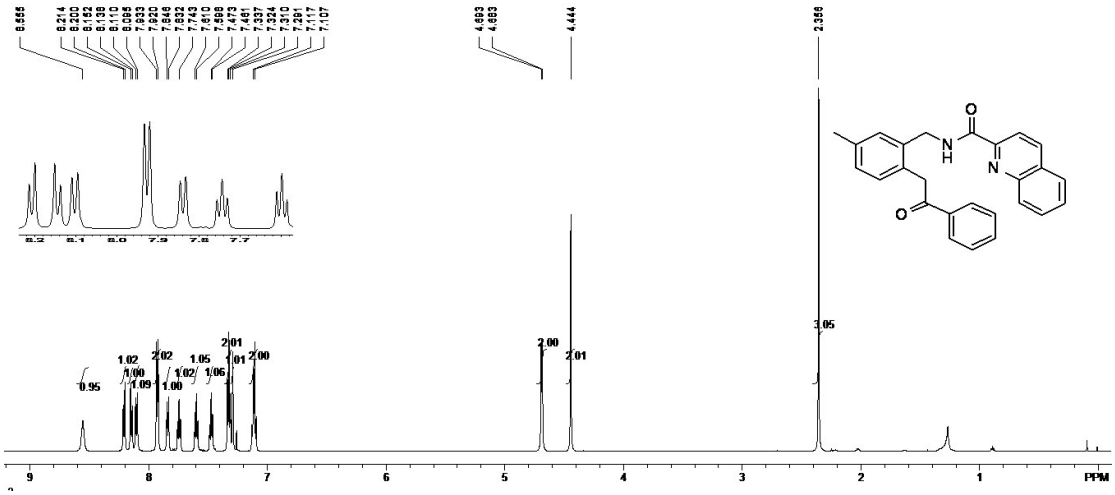
^{13}C NMR of product **3t**



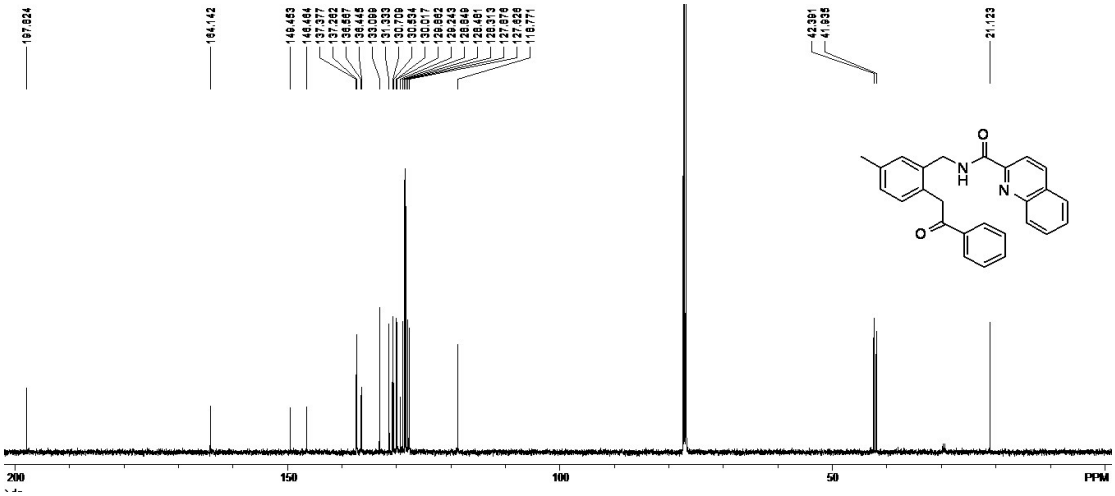
^{1}H NMR of product **3u**



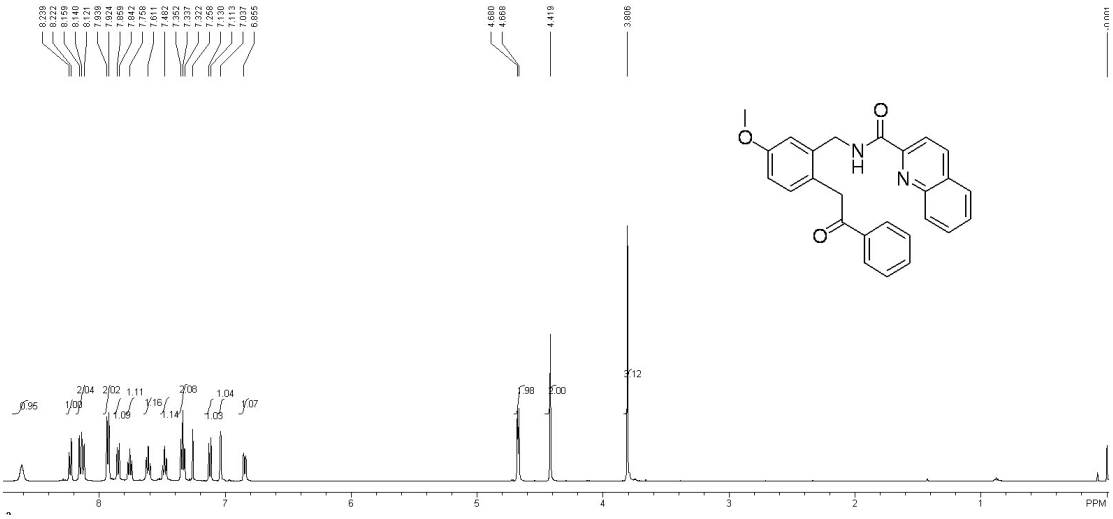
^{13}C NMR of product **3u**



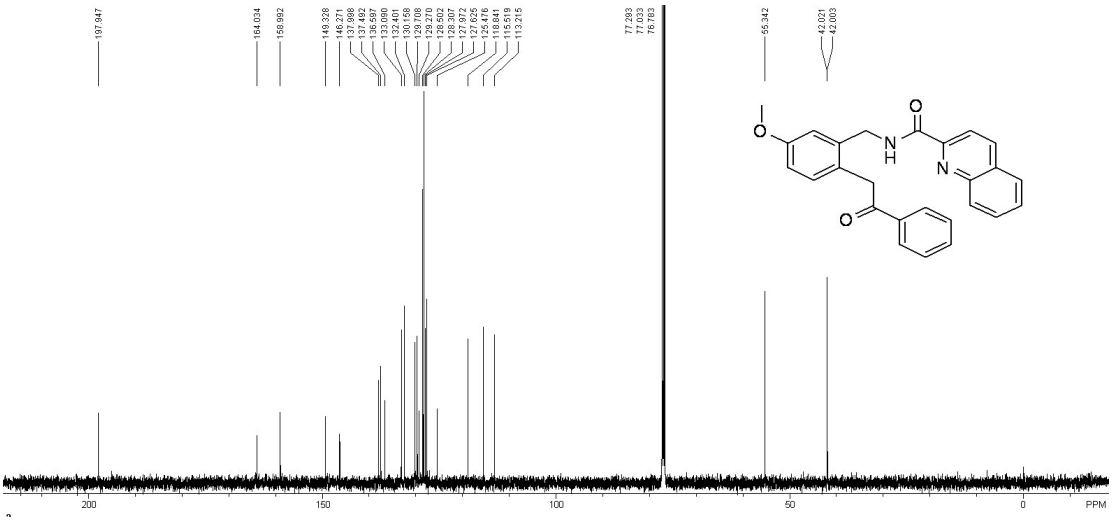
^{1}H NMR of product **3v**



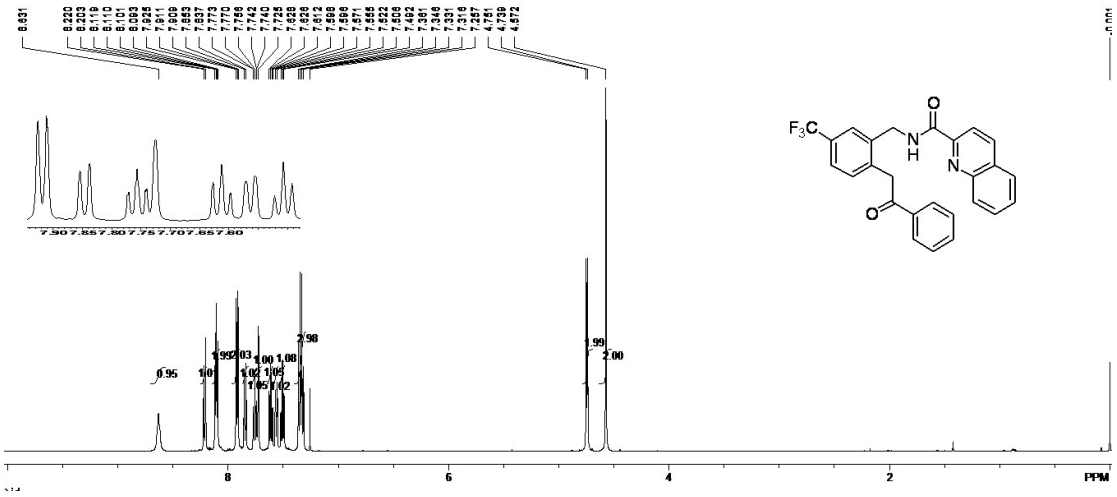
^{13}C NMR of product **3v**



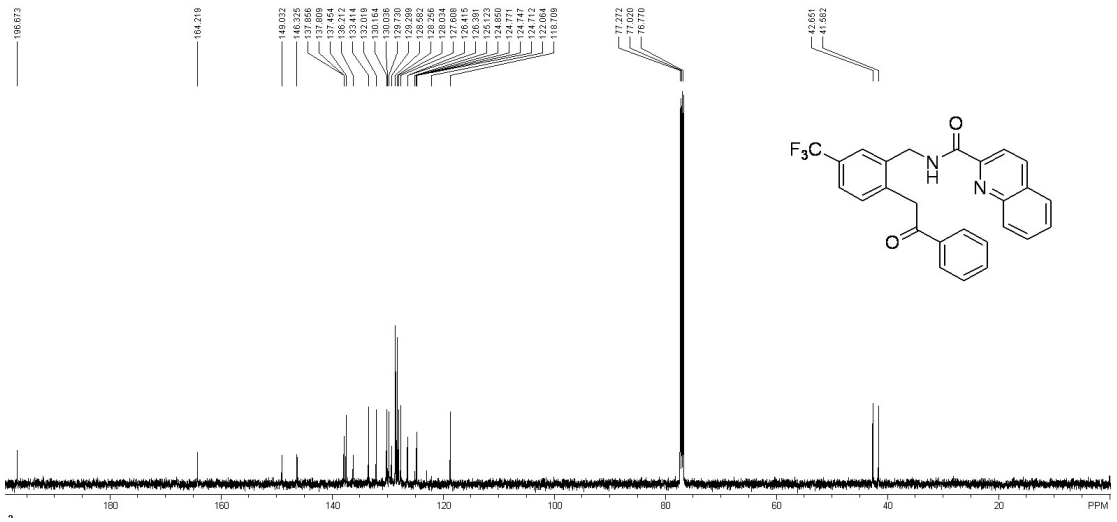
^{1}H NMR of product **3w**



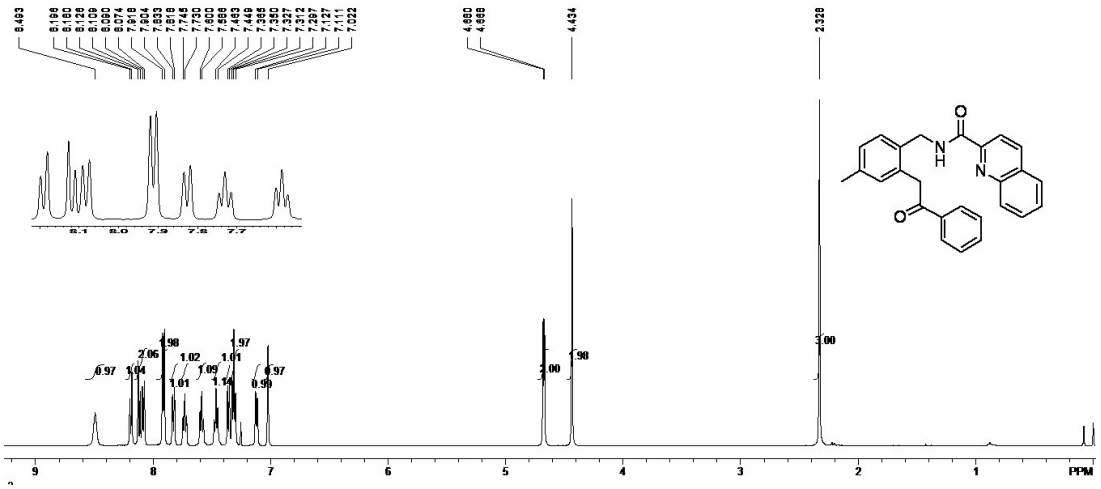
^{13}C NMR of product **3w**



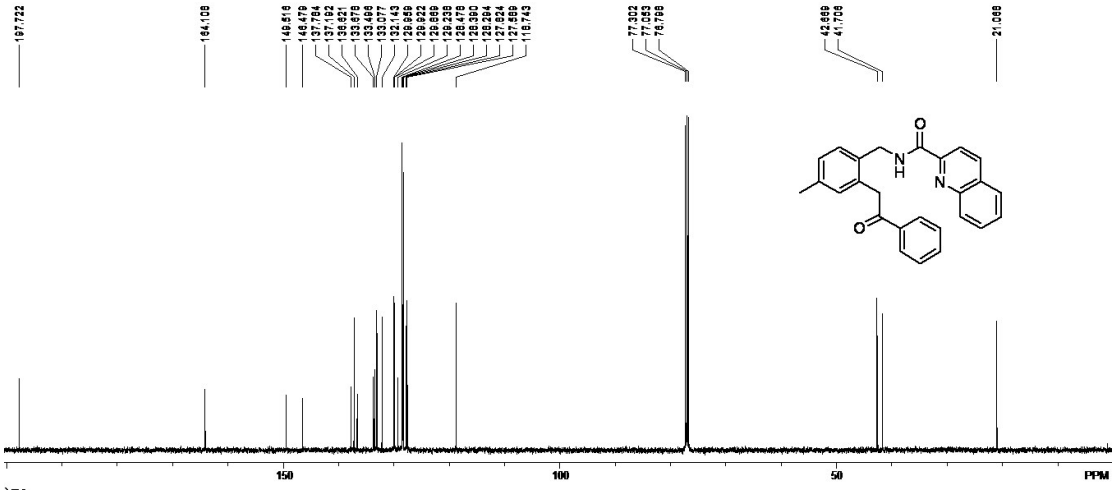
^{1}H NMR of product **3x**



^{13}C NMR of product **3x**



^{1}H NMR of product **3ya**



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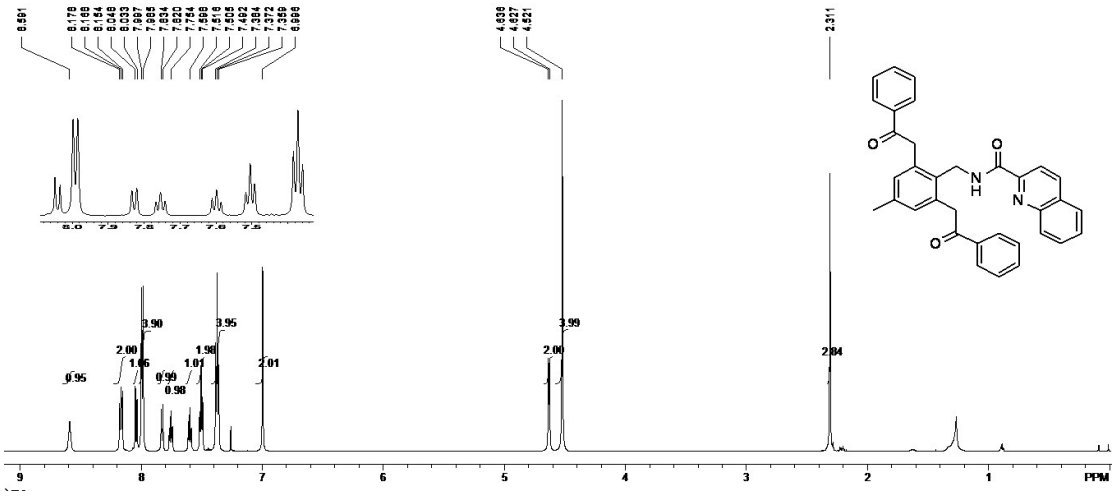
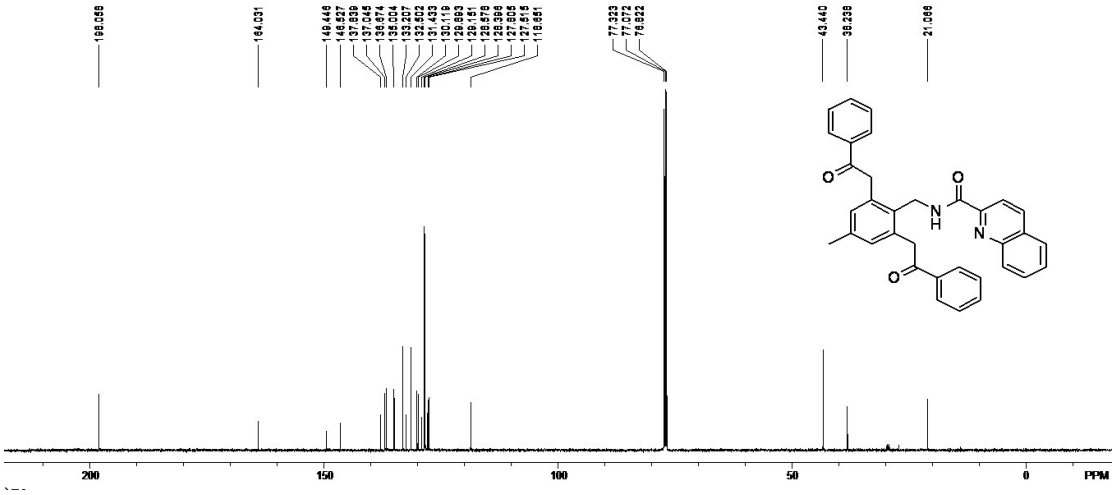


^{1}H NMR of product **3yb**



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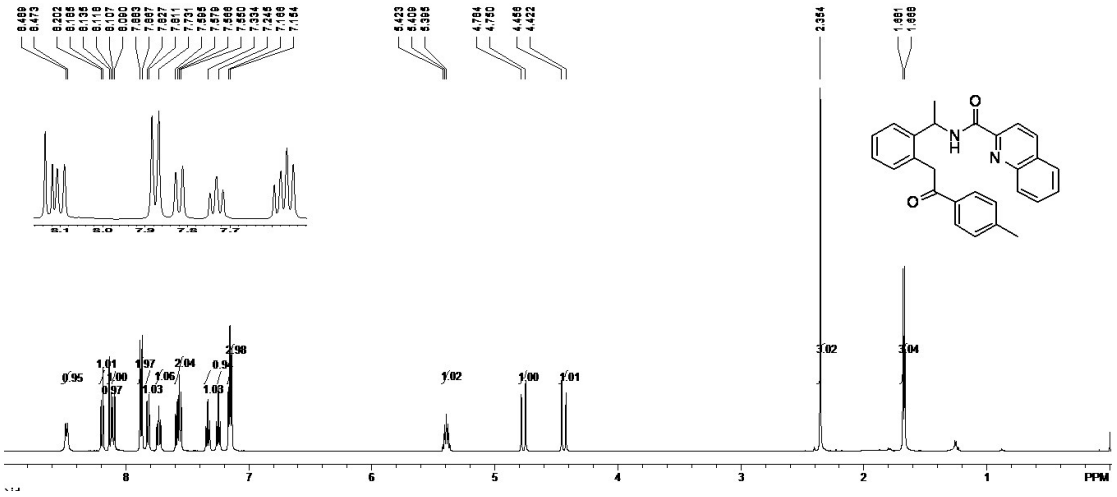
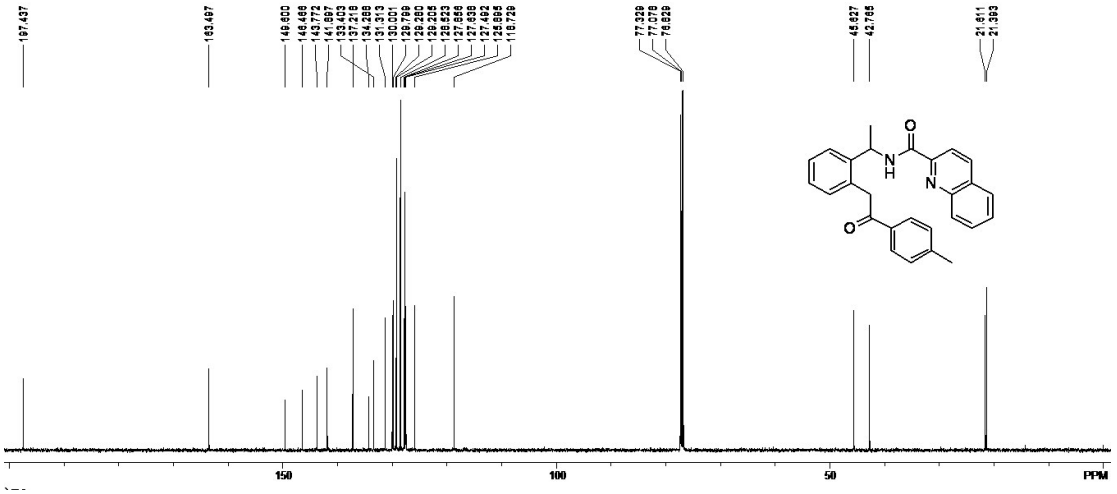
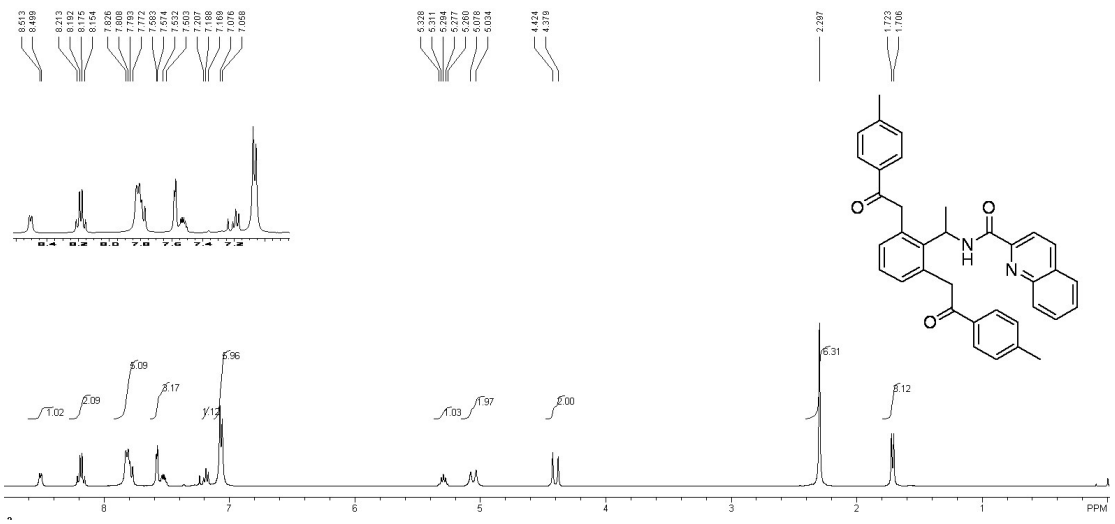


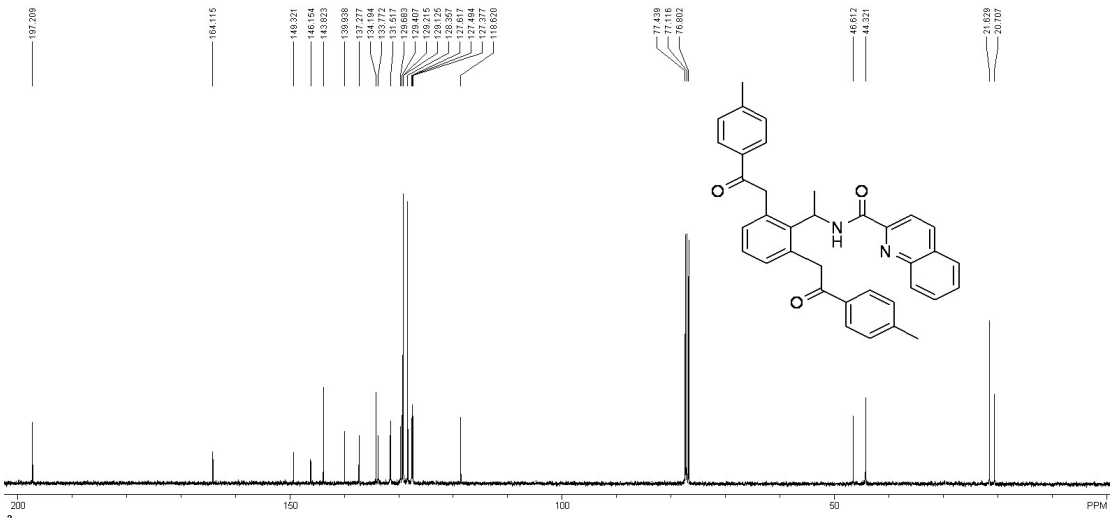
^{1}H NMR of product **3za**



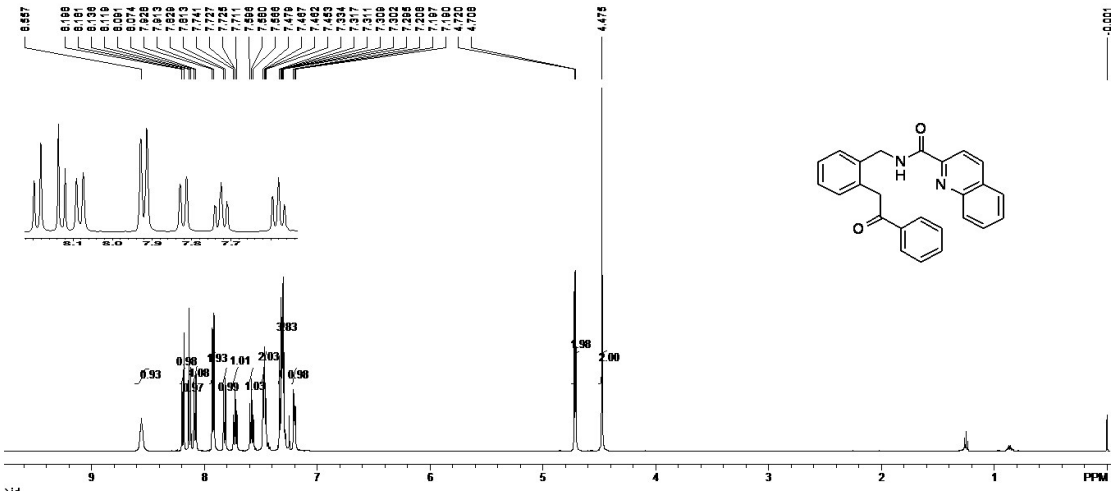
^{13}C NMR of product **3za**



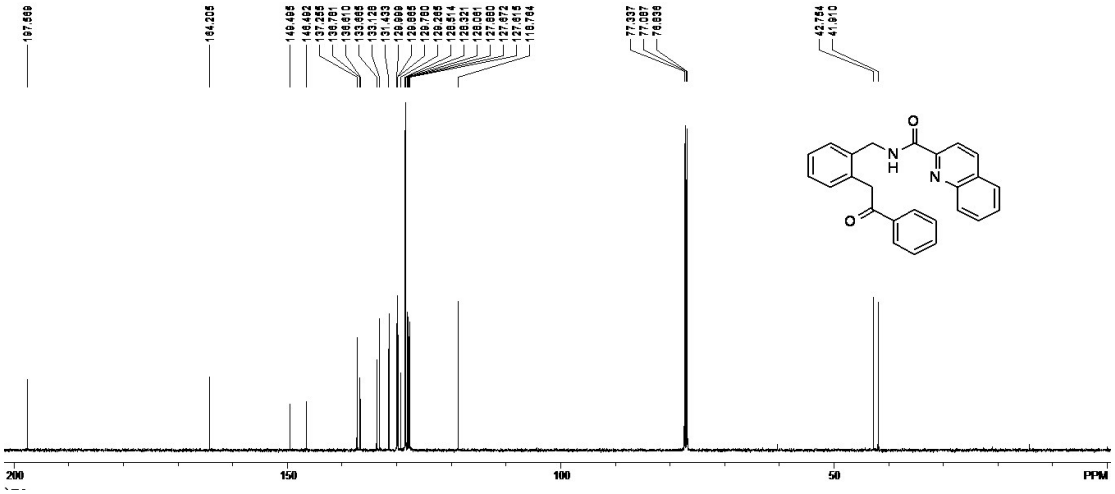
^{1}H NMR of product **3zb**



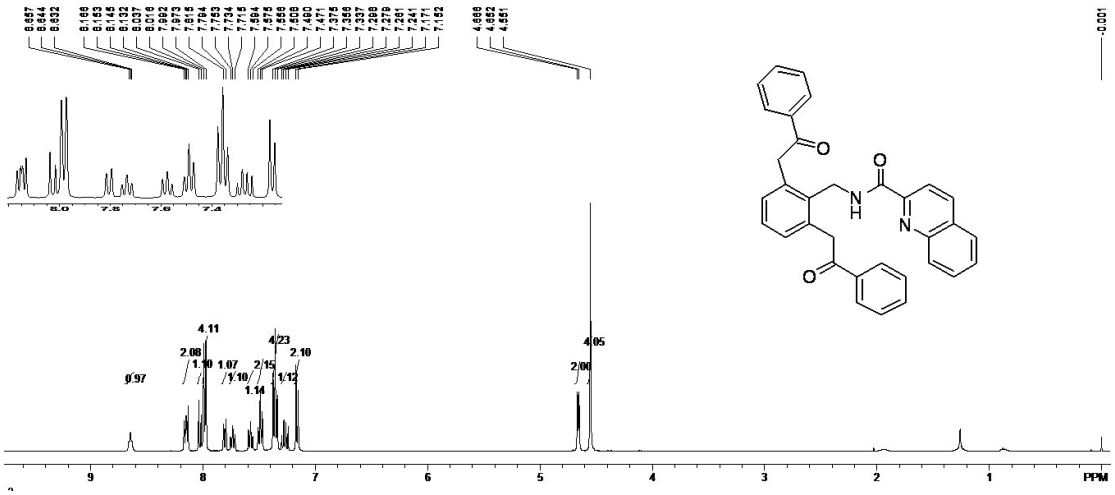
^{13}C NMR of product **3zb**



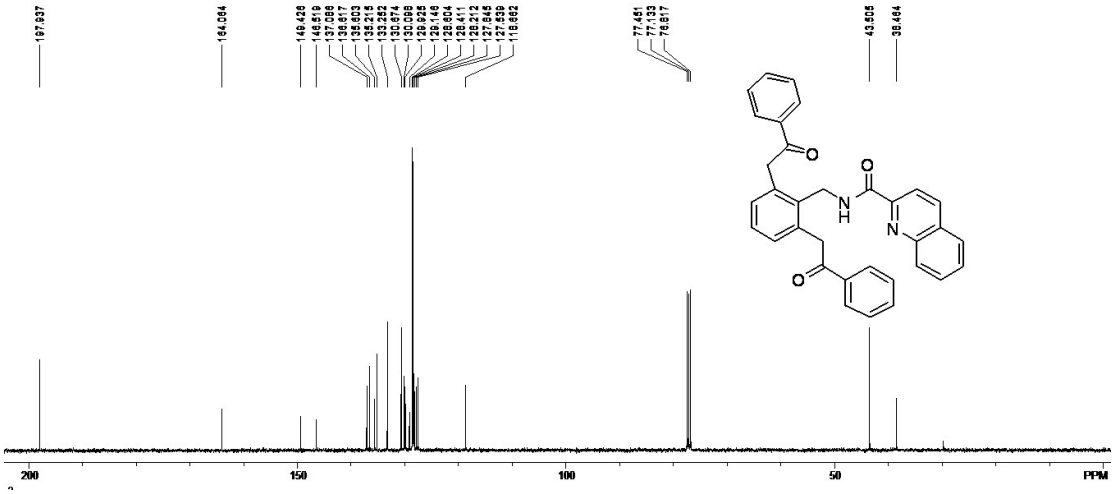
^{1}H NMR of product **3z'a**



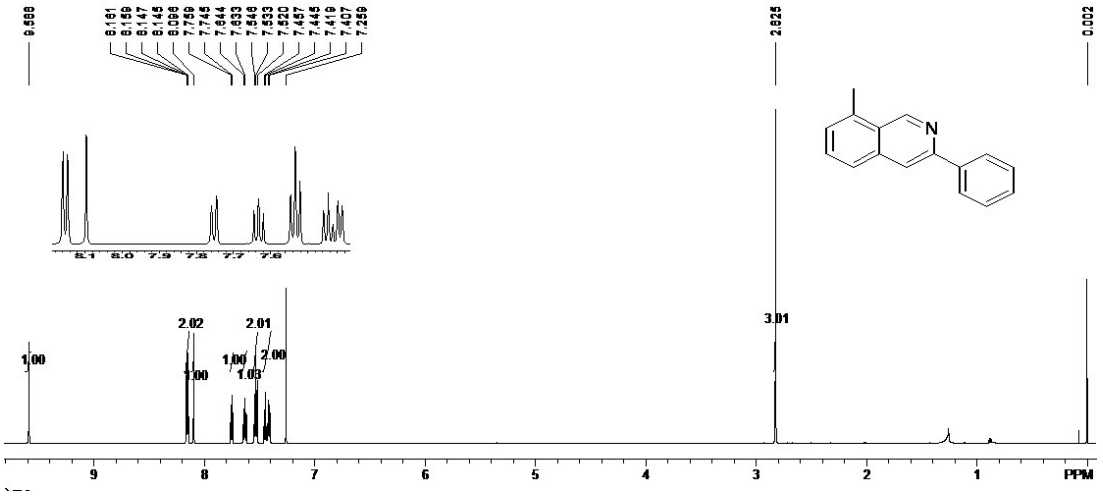
^{13}C NMR of product **3 z'a**



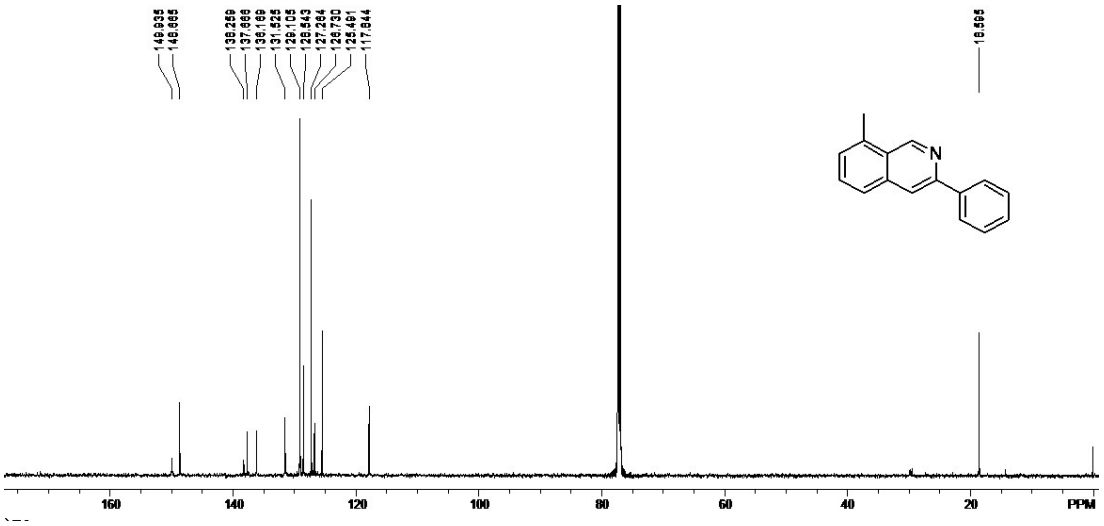
^{1}H NMR of product **3 z'b**



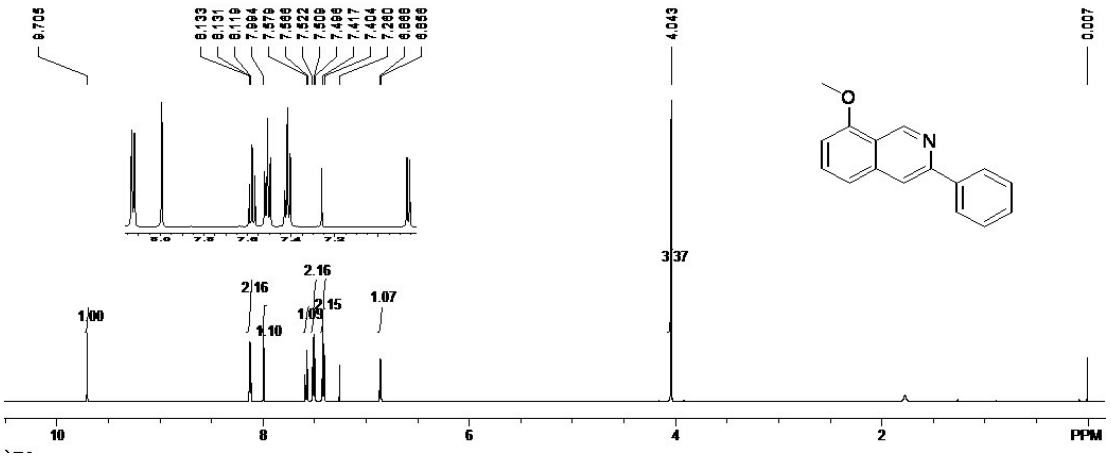
^{13}C NMR of product **3 z'b**



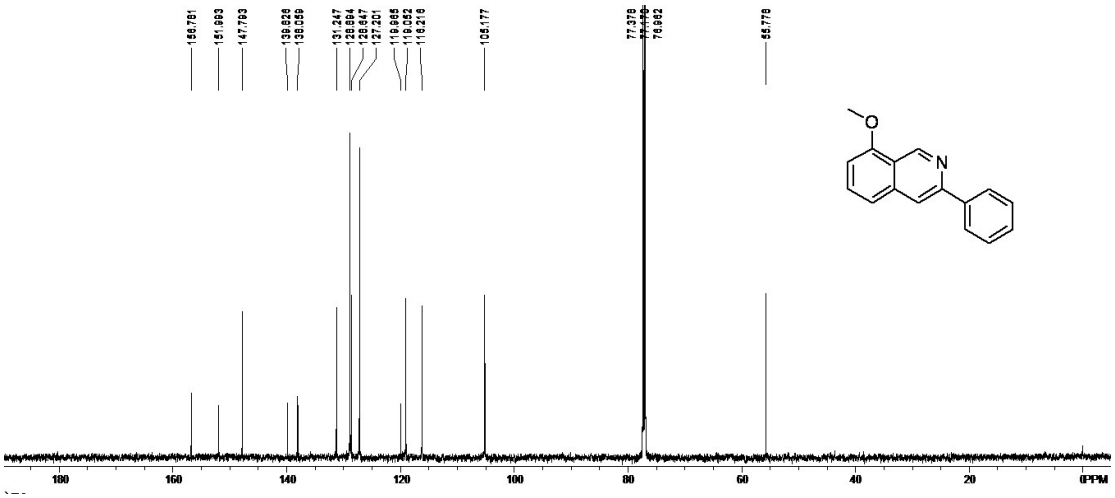
^{1}H NMR of product **4a**



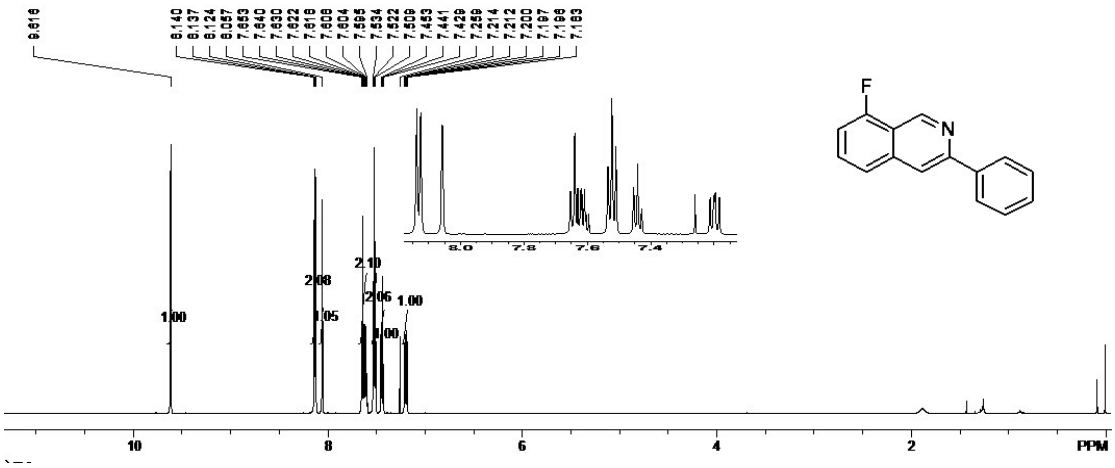
^{13}C NMR of product **4a**



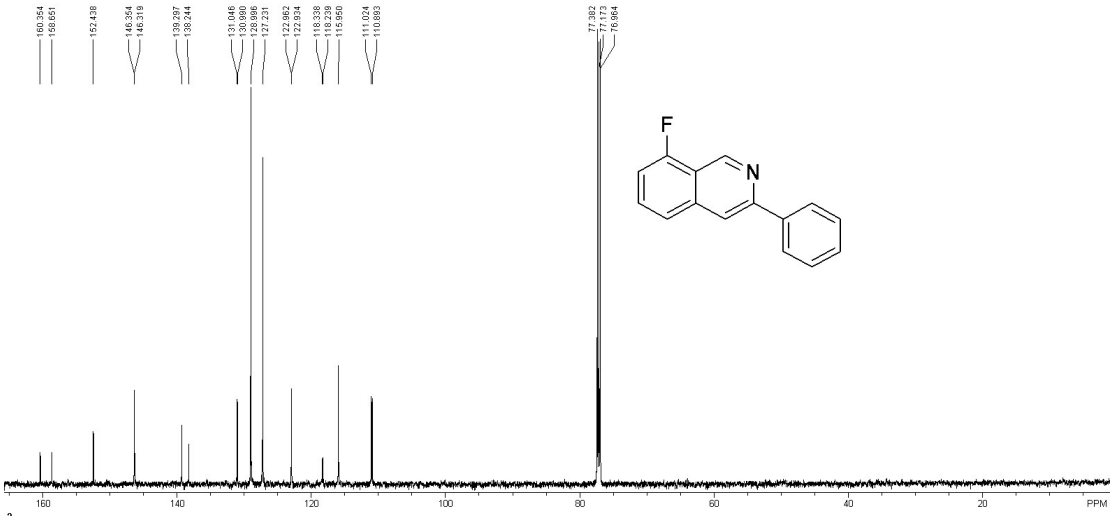
^{1}H NMR of product **4b**



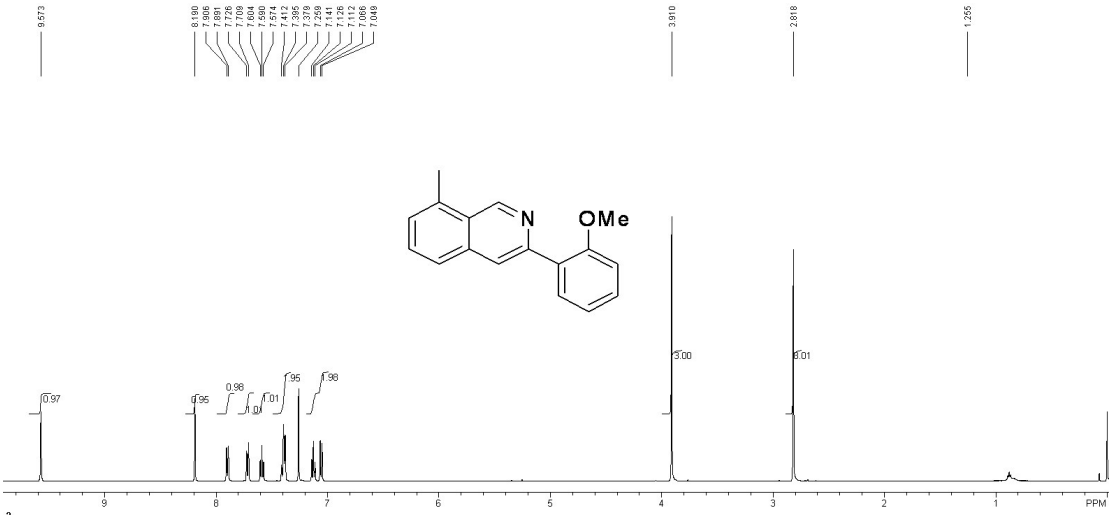
^{13}C NMR of product **4b**



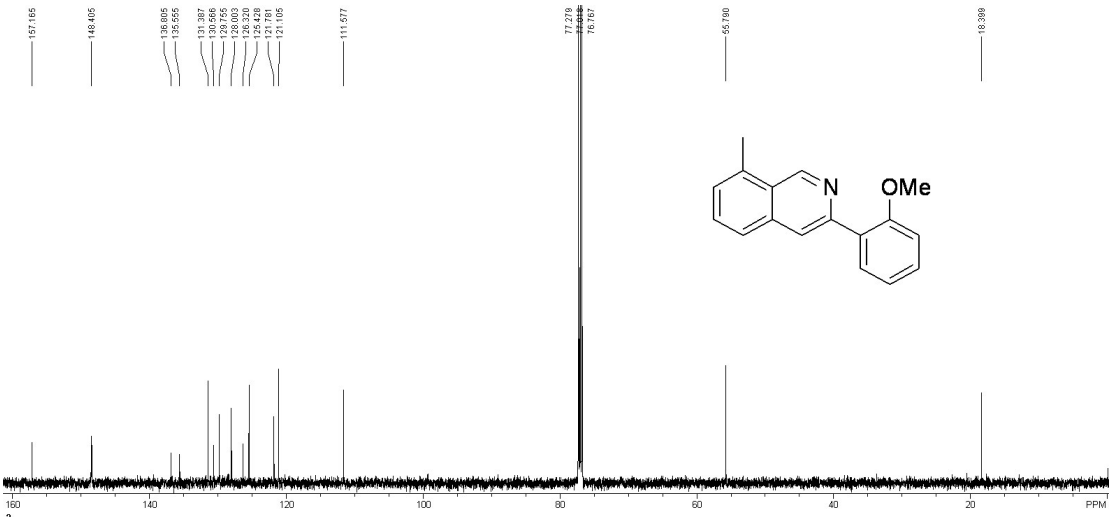
^{1}H NMR of product **4c**



^{13}C NMR of product **4c**



^{1}H NMR of product **4d**



^{13}C NMR of product **4d**