

Supporting Information
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Expeditious Synthesis of the Topoisomerase-I Inhibitors Isoindolo[2,1-*b*]-isoquinolin-7(5*H*)-one and the Alkaloid Rosettacin based on Aryl Radical Cyclization of Enamide Generated by using *N*-Acyliminium Chemistry

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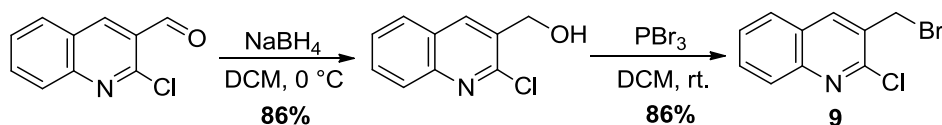
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Dedicated to the memory of our colleague, Professor Jean Morel, deceased on December 12, 2012 in Le Havre, France.

I- Synthesis of the intermediates

3-(Bromomethyl)-2-chloroquinoline (**9**) via 2-(Chloroquinolin-3-yl)methanol



Step 1. To a mixture of 2-chloroquinoline-3-carbaldehyde (1 g, 5.2 mmol), CH₂Cl₂ (20 mL) and MeOH (20 mL) was added dropwise sodium borohydride (590 mg, 15.6 mmol) at 0 °C with string. The mixture was stirred at 0 °C for 2h, poured into ice-cold water and extracted with CH₂Cl₂. The extracted was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. Recrystallization from cyclohexane of the crude reaction mixture gave the expected 2-(chloroquinolin-3-yl)methanol (870 mg, 86%) as white yellow crystals (Mp=151-152 °C; Lit.¹ mp 149 °C) having a R_f value of 0.18 when using a mixture of cyclohexane/AcOEt in 3/2 ratio as the eluent.

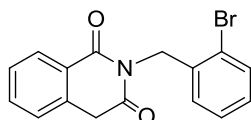
Step 2. To a solution 2-(chloroquinolin-3-yl)methanol (800 mg, 4.1 mmol) in dry CH₂Cl₂ (40 mL) was added dropwise PBr₃ (1.23 mL, 12.4 mmol) at room temperature. The mixture was then stirred for 2 h and the reaction mixture was stirred at 0 °C for 2 h, poured into ice-cold water and extracted with CH₂Cl₂. The extracted organic layer was washed with brine, dried over MgSO₄ and evaporated in vacuo. Recrystallization from cyclohexane of the reaction mixture provides the expected 3-(bromomethyl)-2-chloroquinoline (**9**, 870 mg, 86%) as white crystals (Mp=176-177 °C; Lit.² Mp=179 °C) which have a R_f value of 0.18 with cyclohexane/AcOEt (3/3) as the eluent.

¹H NMR (300 MHz, CDCl₃): δ = 4.74 (s, 2H, CH₂), 7.61 (s, 1H, H_{aro}), 7.77 (dd, *J* = 7.5 Hz and 7.6, 1H, H_{aro}), 7.82 (dd, *J* = 7.5 Hz and 7.4, 1H, H_{aro}), 8.04 (dd, *J* = 5.9 Hz and 7.5, 1H, H_{aro}), 8.24 (d, *J* = 8.2 Hz, 1H, H_{aro}).

¹ Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, 53, 11049–11060.

² Mandhane, P. G.; Joshi, R. S.; Khan, W.; Gill, C. H. *J. Korean Chem. Soc.* **2011**, 55, 656–661.

2-(2-bromobenzyl)isoquinoline-1,3(2H,4H)-dione



To a solution of the commercially available homophthalic anhydride (**4**, 500 mg, 3.1 mmol) and few amounts of *para*-toluenesulfonic acid in dry toluene (10 mL) was added dropwise *o*-bromobenzylamine in 5 mL of toluene. The mixture was heated at reflux under argon for 15 h. The solvent was evaporated under reduced pressure, the reaction residue was dissolved in CH₂Cl₂ (30 mL) and washed successively with saturated NaHCO₃ solution (30 mL) and water (30 mL). The organic layer extracted was dried over MgSO₄ and evaporated under reduced pressure to furnish crude product, which was recrystallised from cyclohexane to afford the desired pure product as a yellow solid product, namely 2-(2-bromobenzyl)isoquinoline-1,3(2H,4H)-dione, (520 mg, 52%) which have a R_f value of 0.26 (cyclohexane/AcOEt: 4/1).

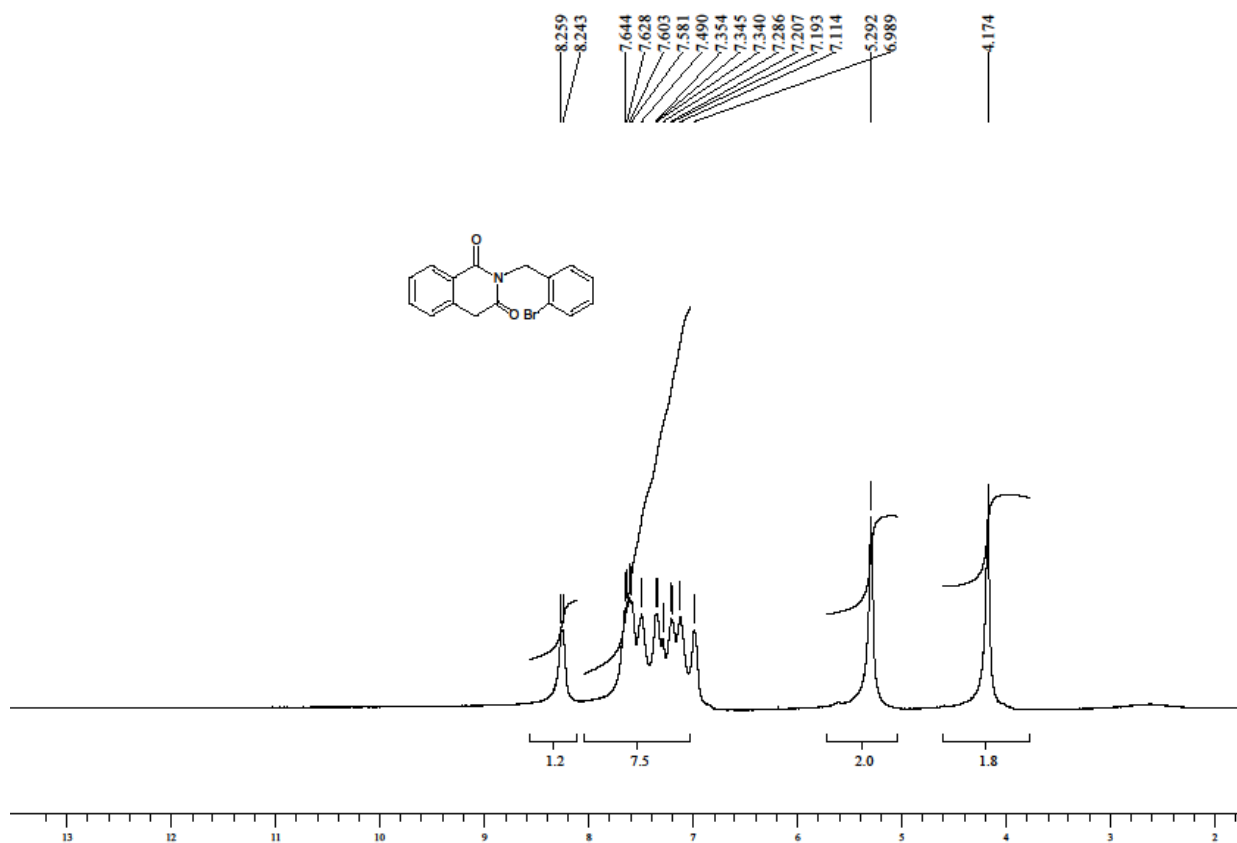
¹H NMR (300 MHz, CDCl₃, 25 °C): δ (ppm) 4.17 (s, 2H, CH₂-CO), 5.29 (s, 2H, CH₂-N), 6.98-7.64 (m, 7H, CH_{aro}), 8.25 (d, 1H, CH_{aro}, *J* = 4.9 Hz).

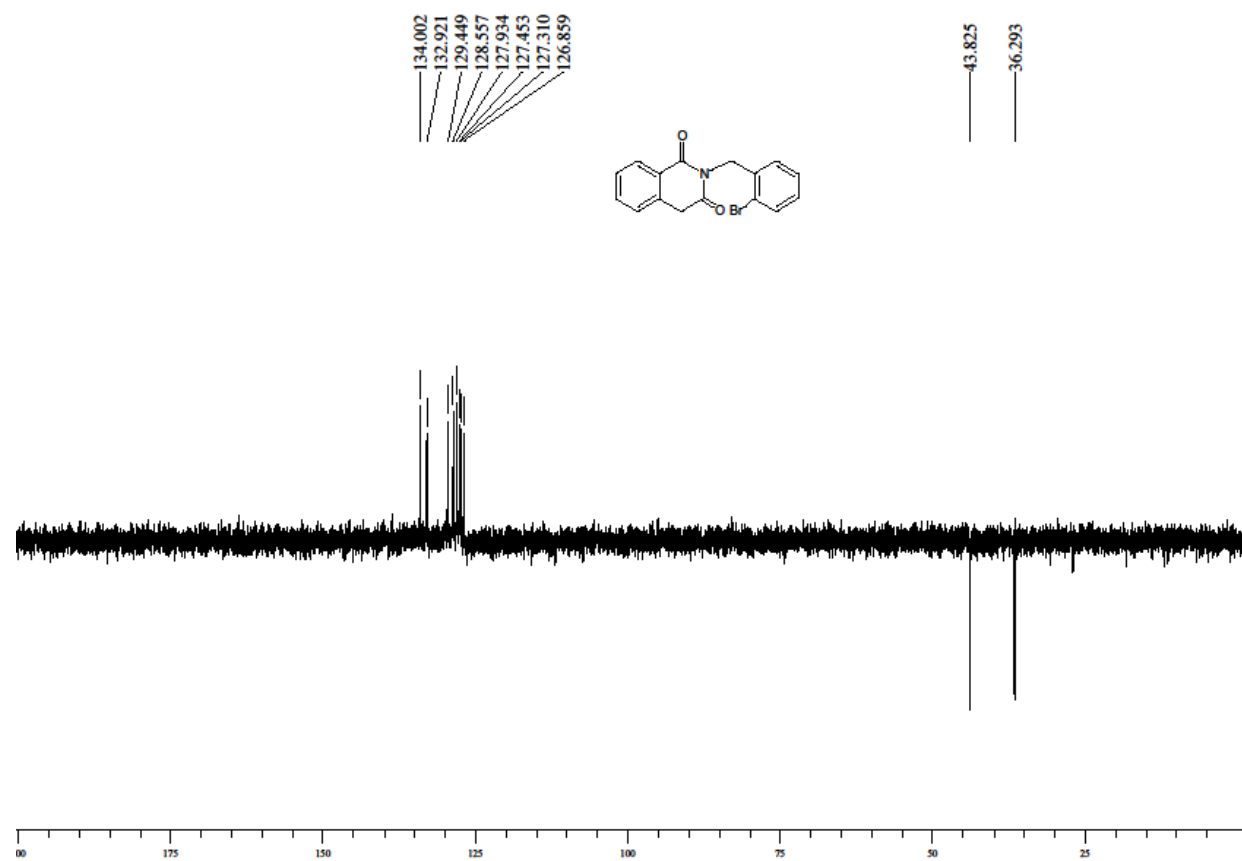
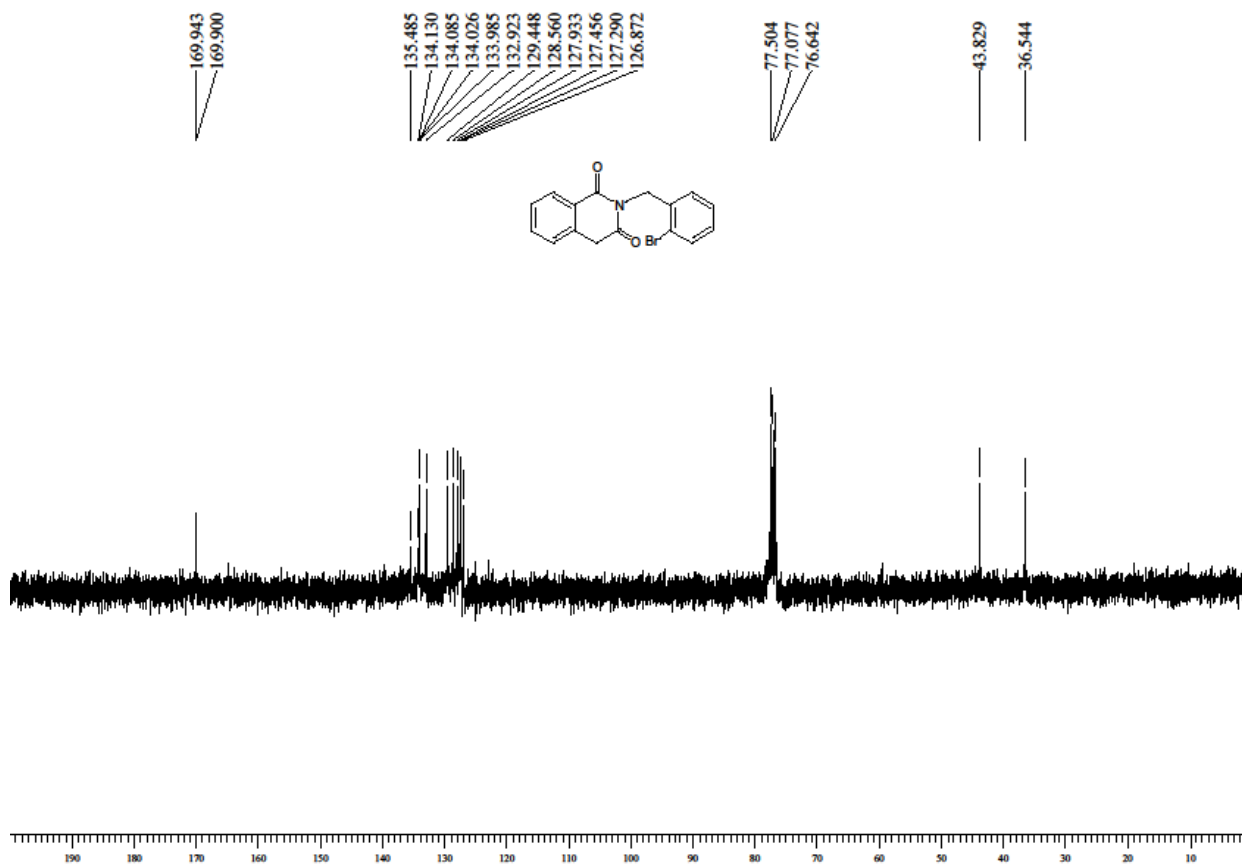
¹³C NMR (75 MHz, CDCl₃, 25 °C): δ (ppm) 36.3 (CH₂-CO), 43.8 (CH₂-N), 126.9 (CH_{aro}), 127.3 (CH_{aro}), 127.4 (CH_{aro}), 127.9 (CH_{aro}), 128.5 (CH_{aro}), 129.4 (CH_{aro}), 132.9 (CH_{aro}), 134.0 (CH_{aro}), 134.1 (C_q), 134.13 (C_q), 135.5 (C_q), 169.9 (CO), 169.94 (CO).

Anal. Calcd for C₁₆H₁₂BrNO₂ (330.18): C, 58.20; H, 3.66; N, 4.24. Found: C, 58.09; H, 3.53; N, 4.13.

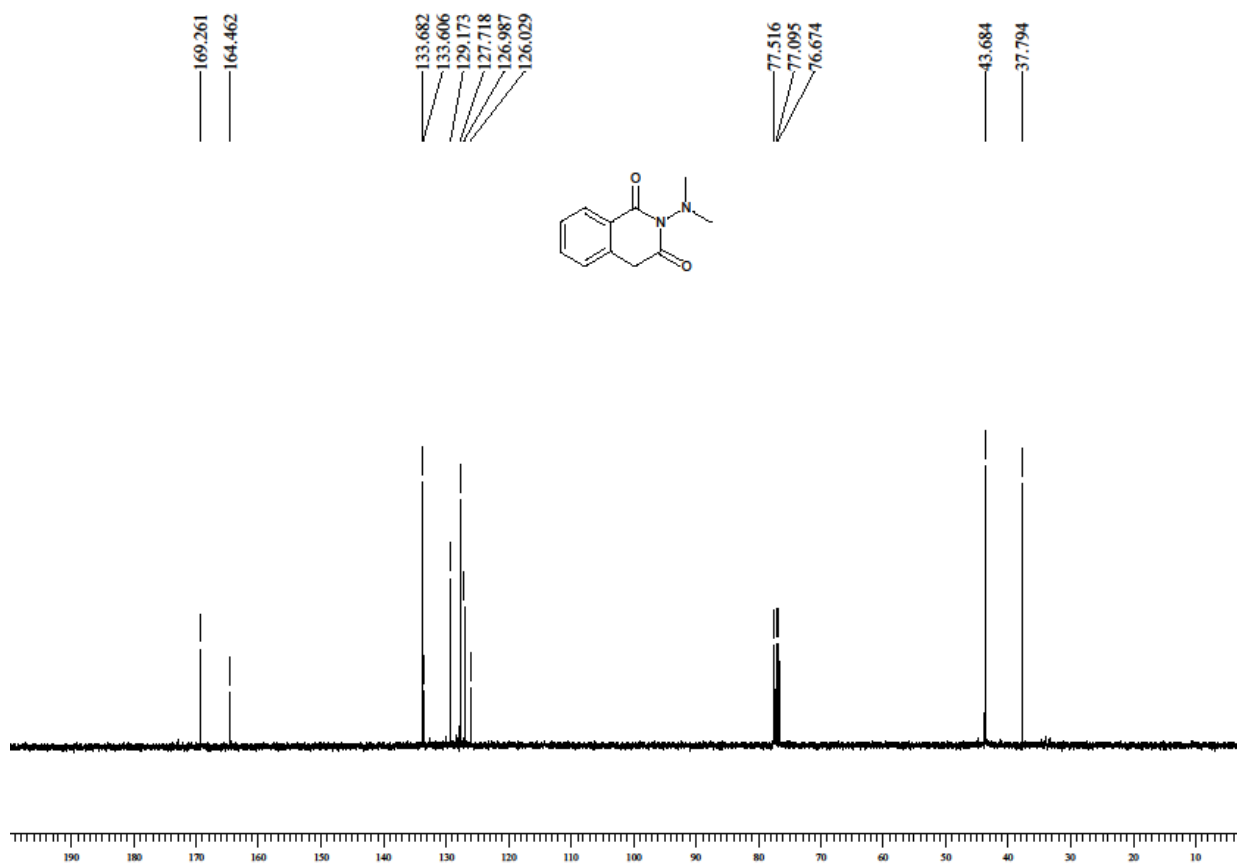
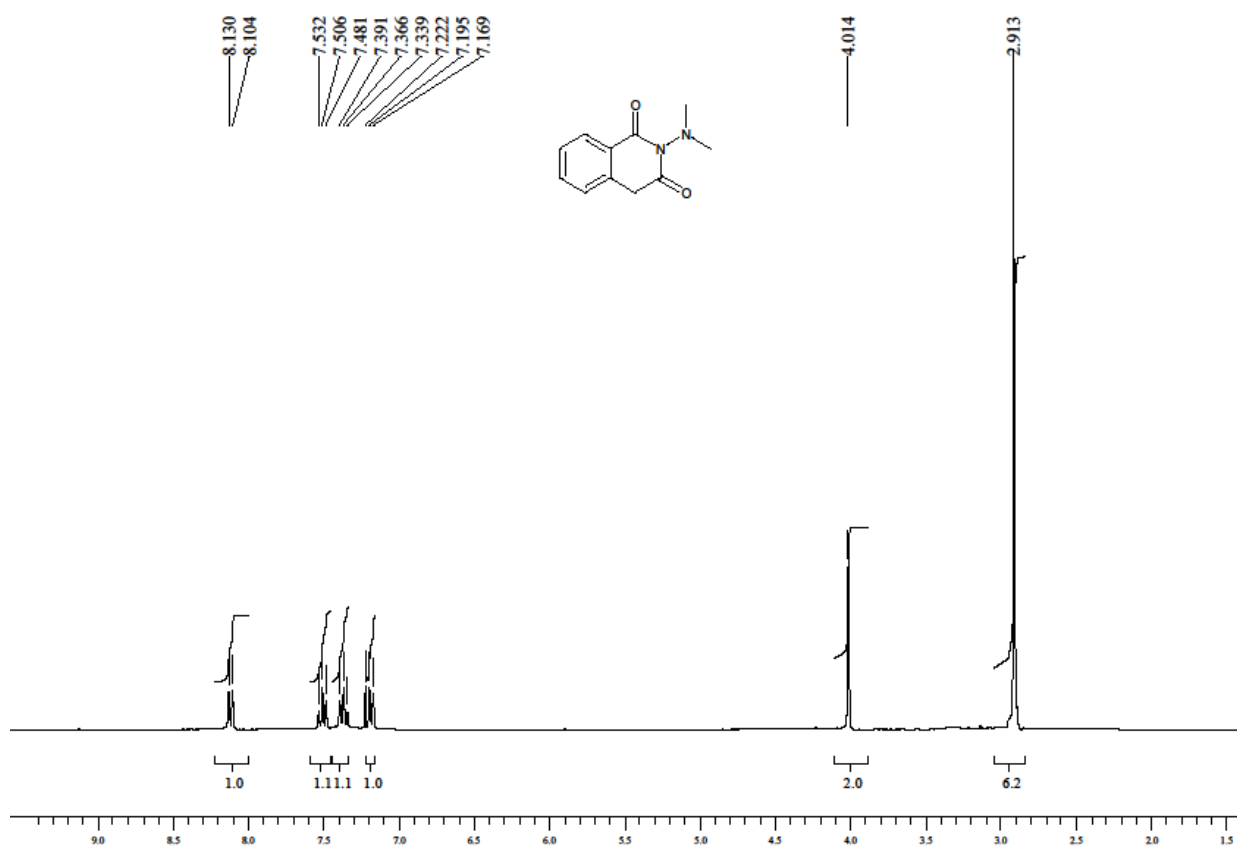
II- ¹H and ¹³C-NMR as well as Dept spectra of new compounds

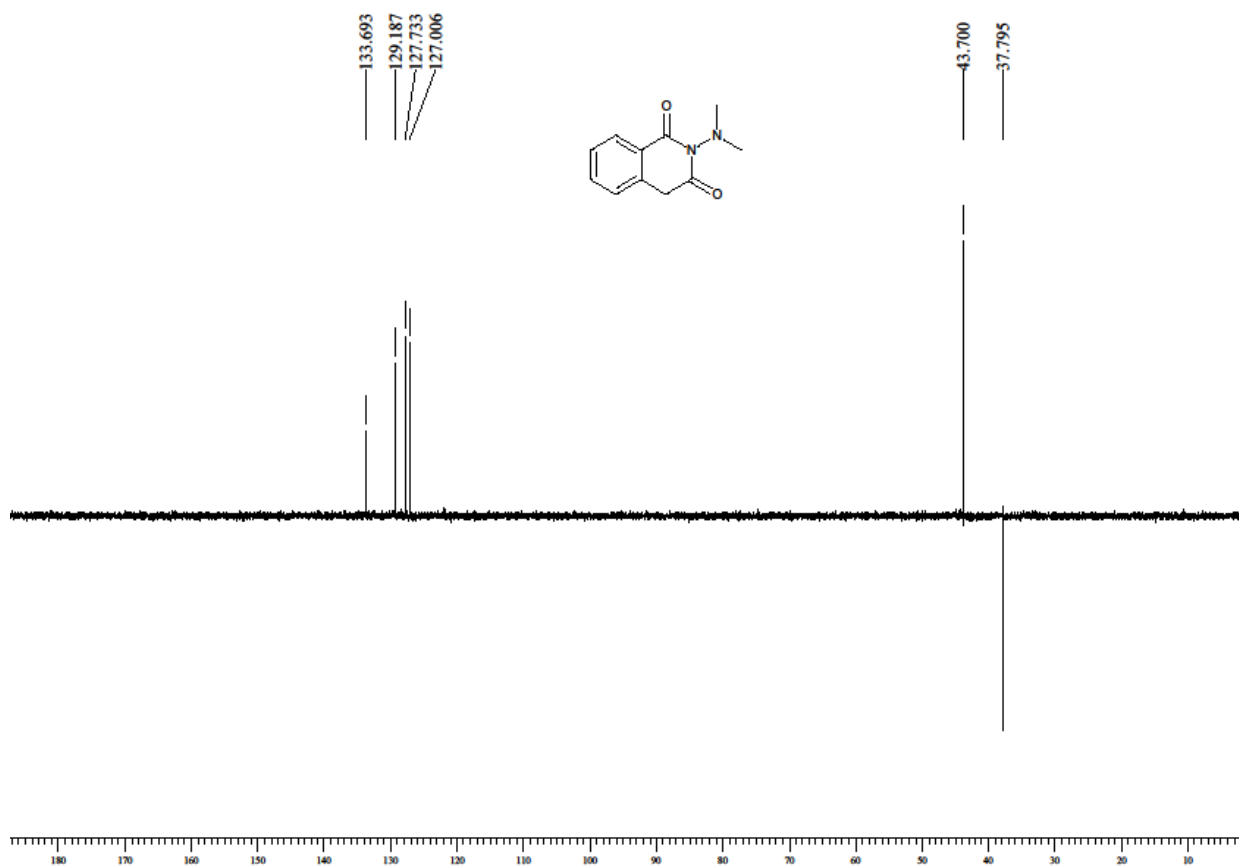
2-(2-Bromobenzyl)isoquinoline-1,3(2H,4H)-dione



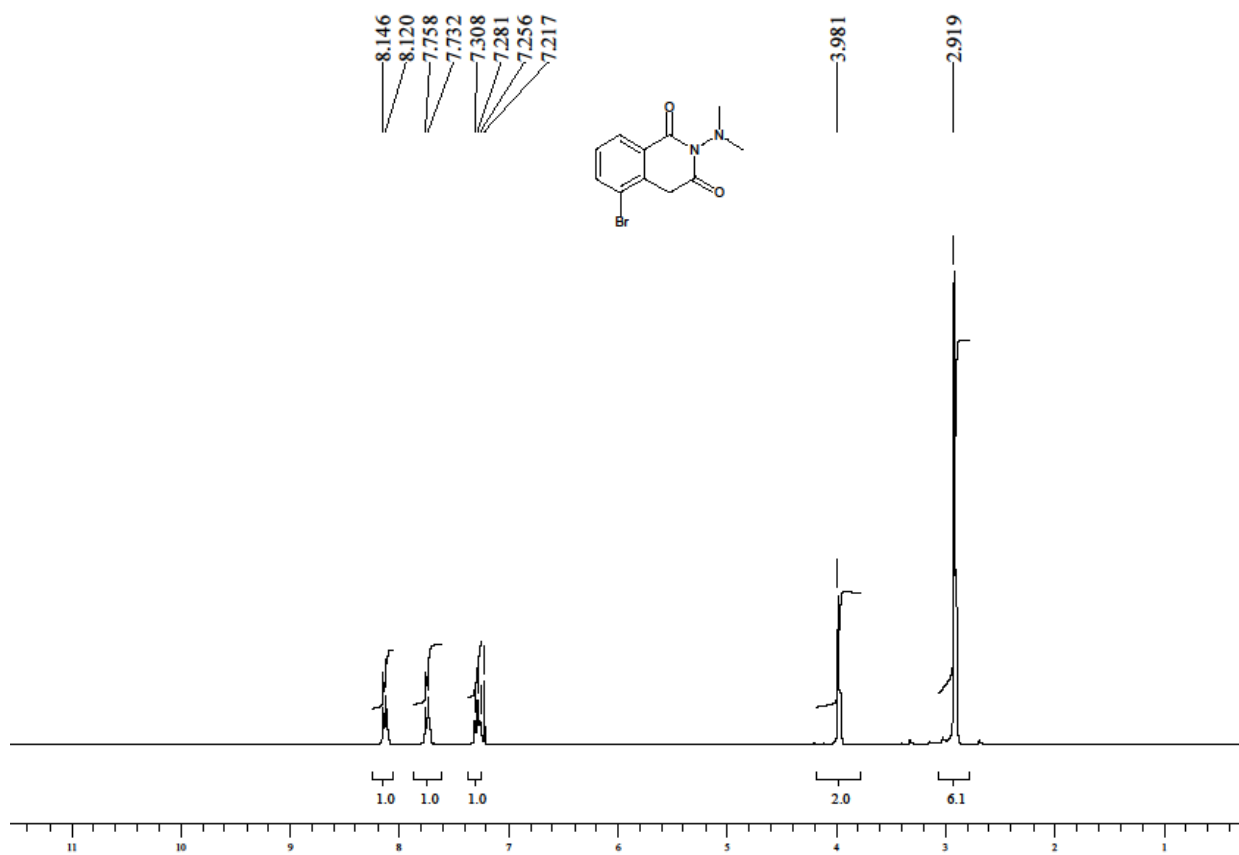


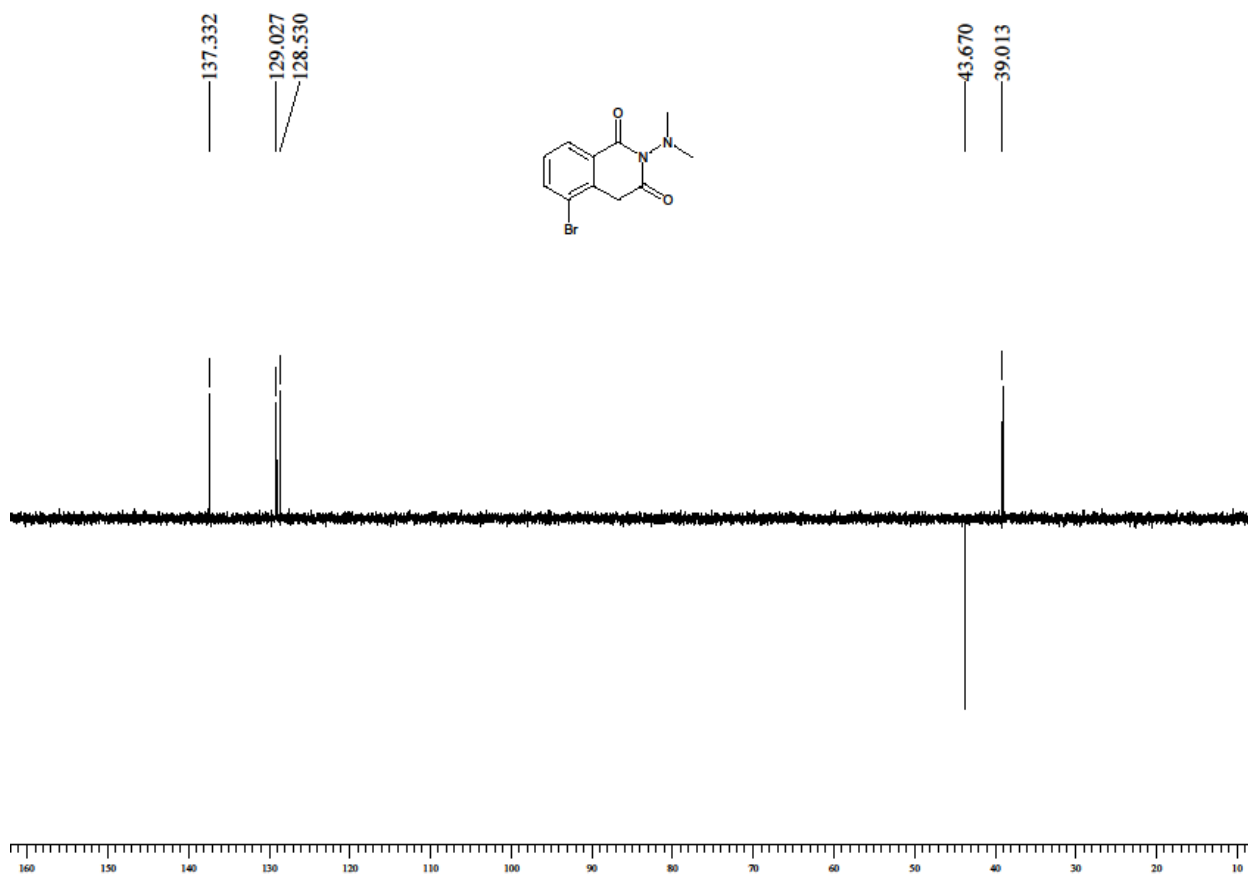
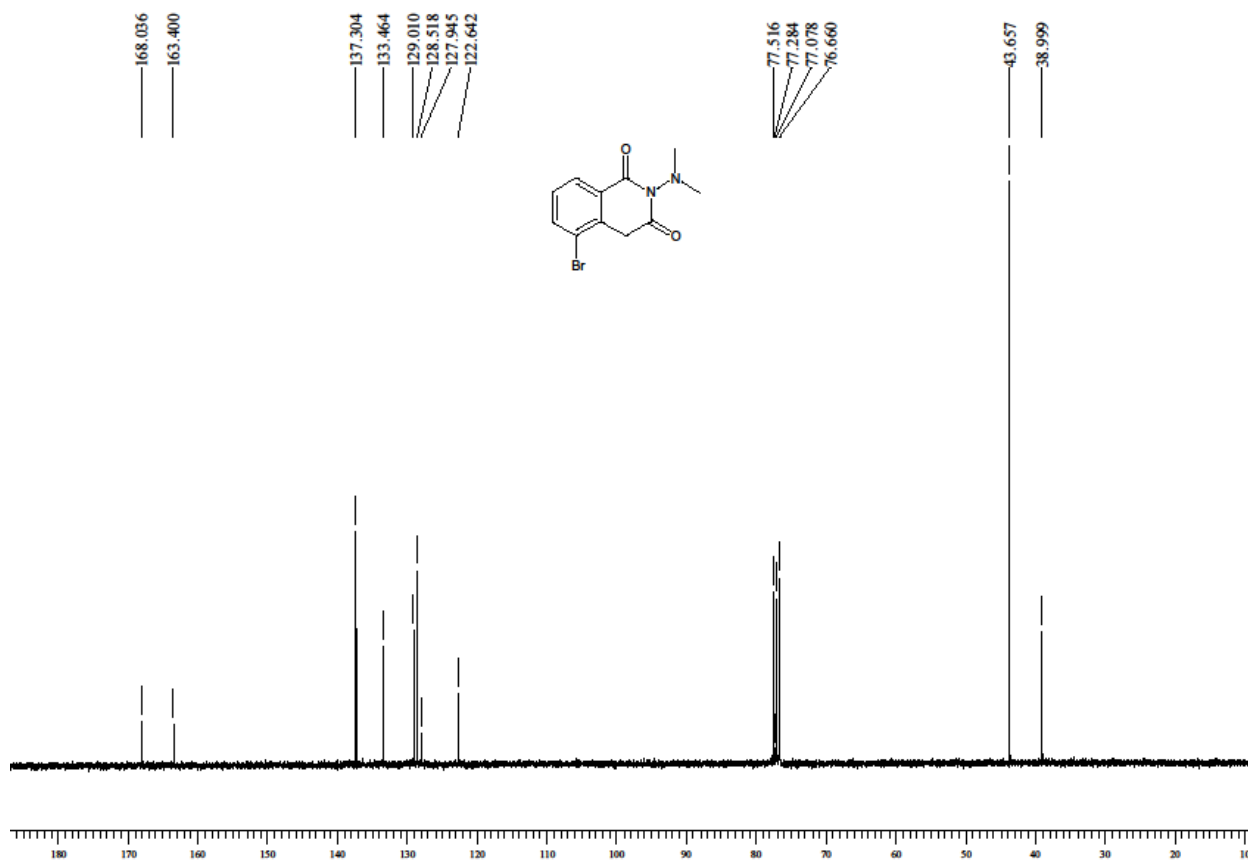
2-(Dimethylamino)isoquinoline-1,3(2H,4H)-dione (6a)



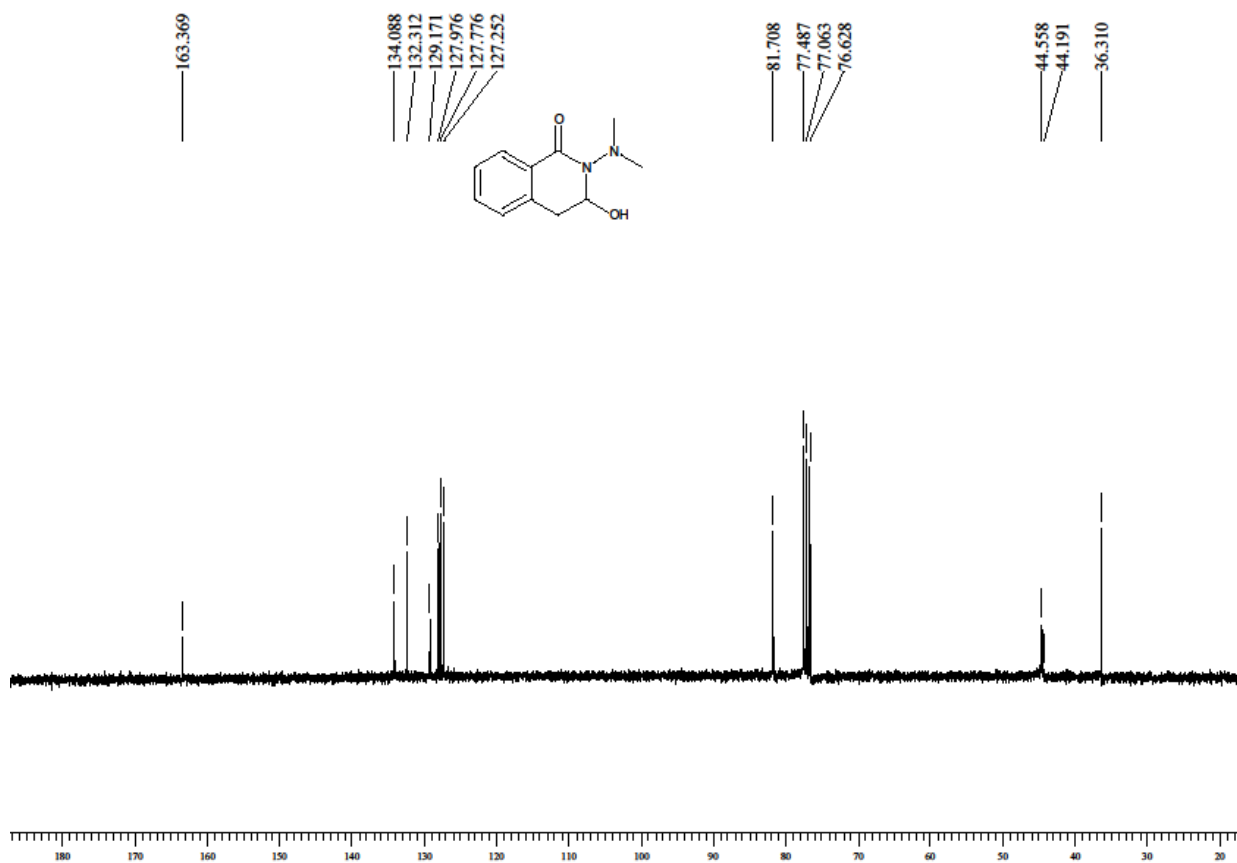
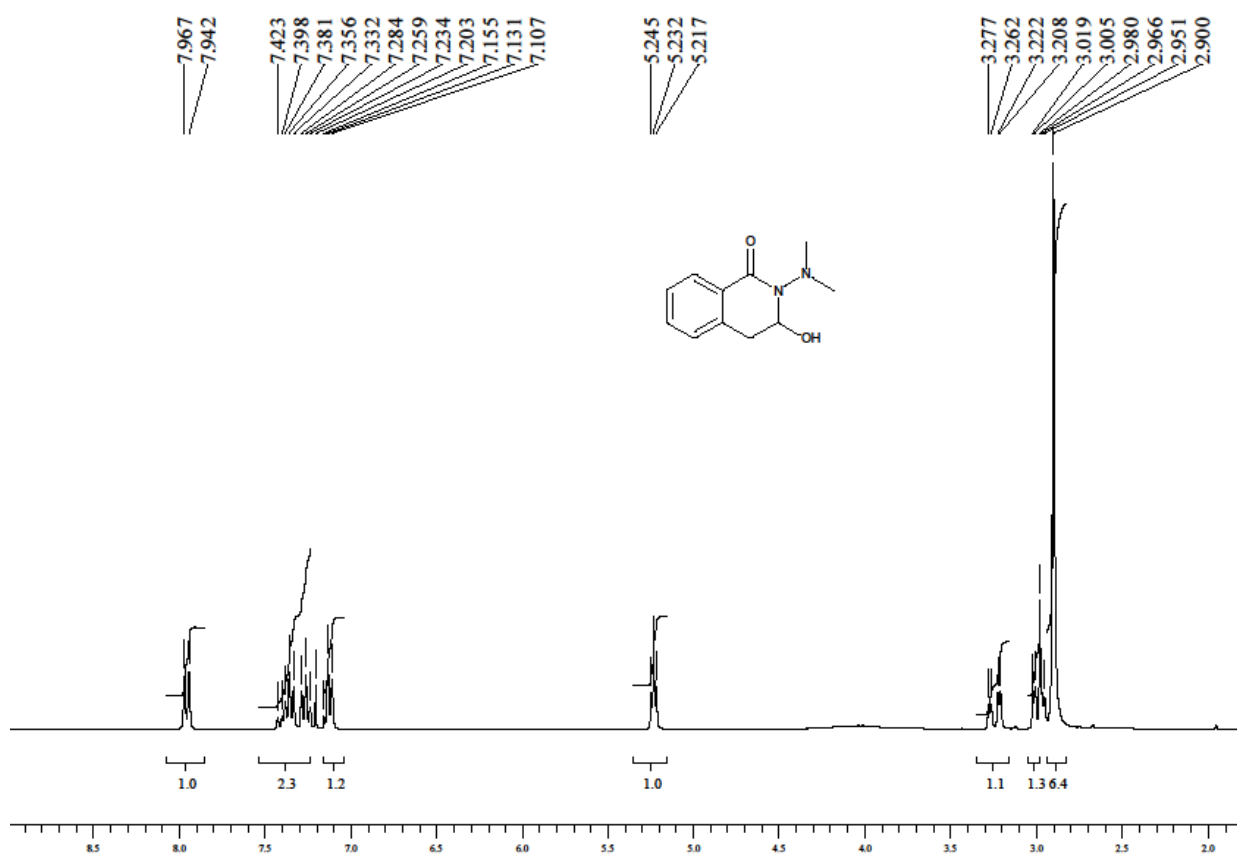


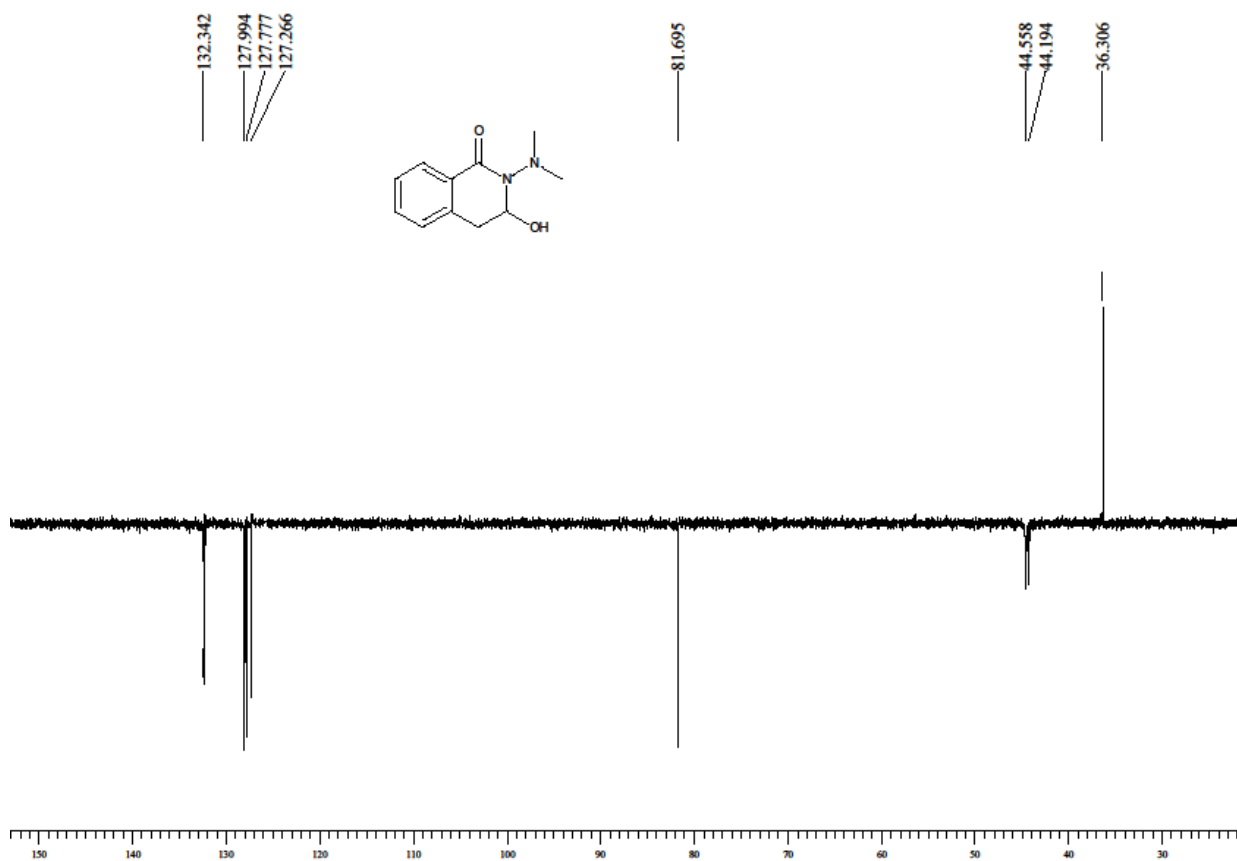
5-Bromo-2-(dimethylamino)isoquinoline-1,3(2H,4H)-dione (6b)



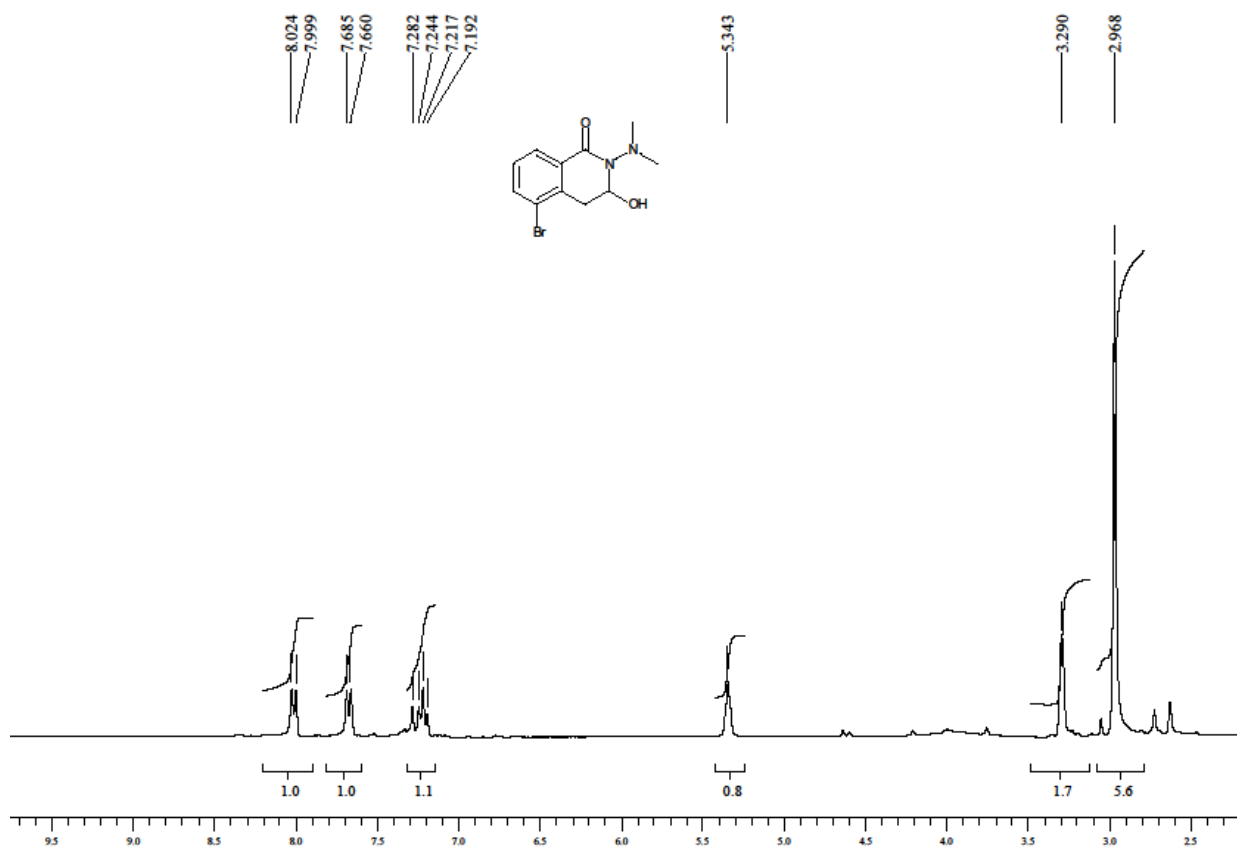


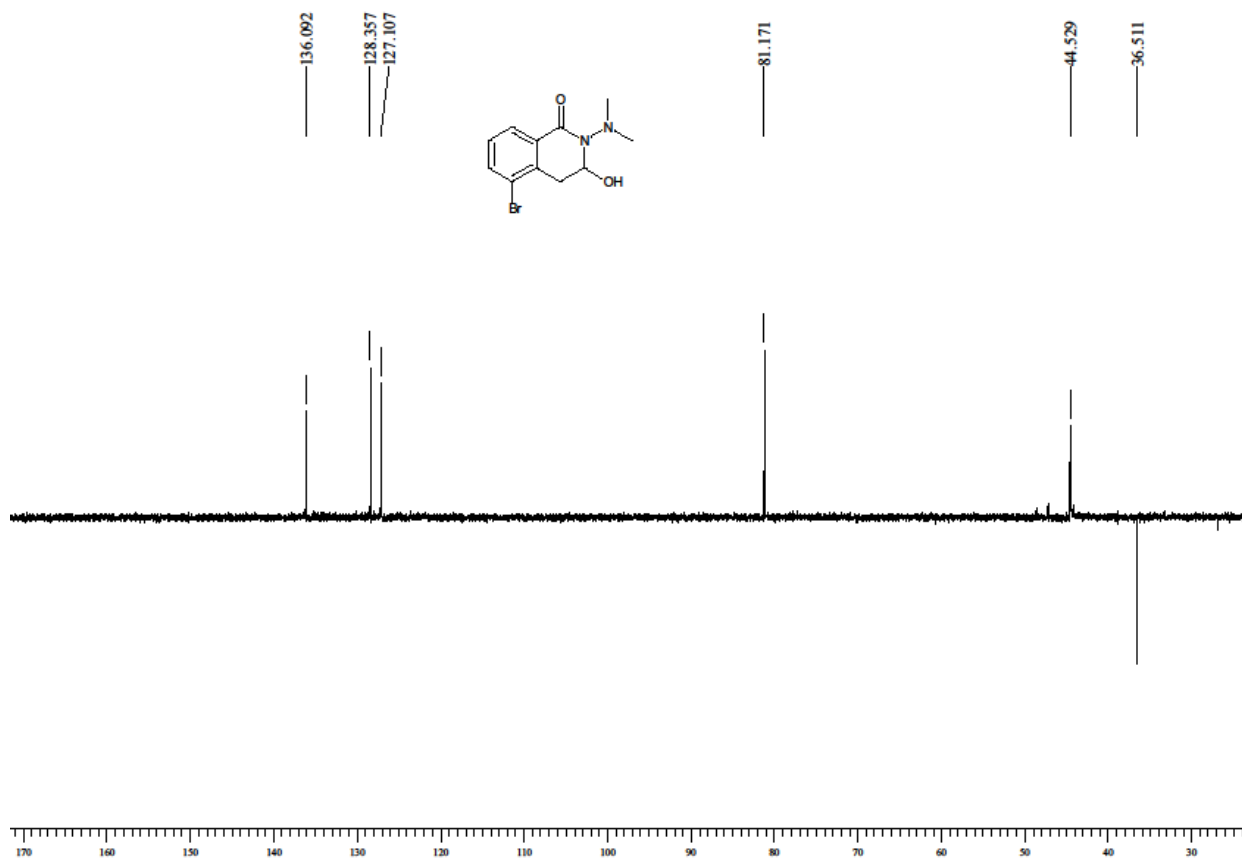
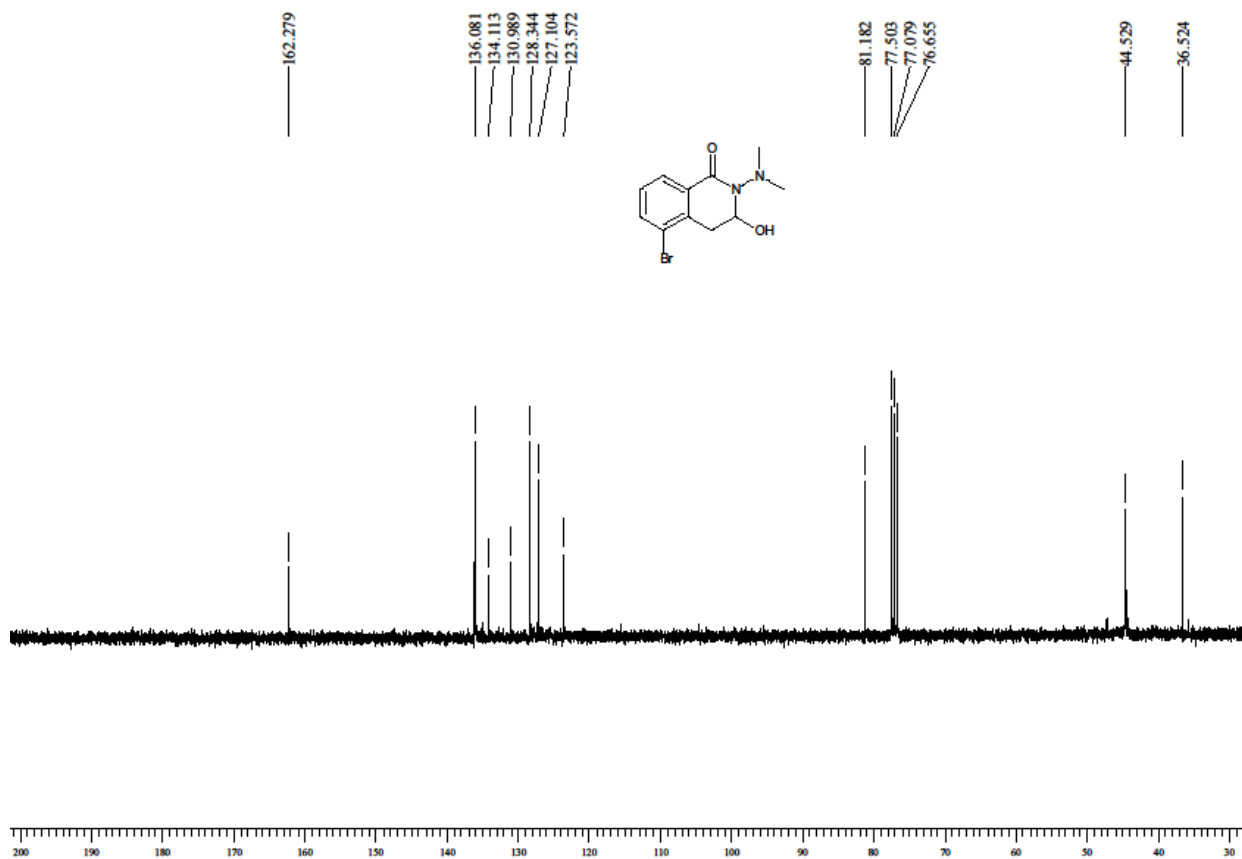
2-(Dimethylamino)-3-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (14a)



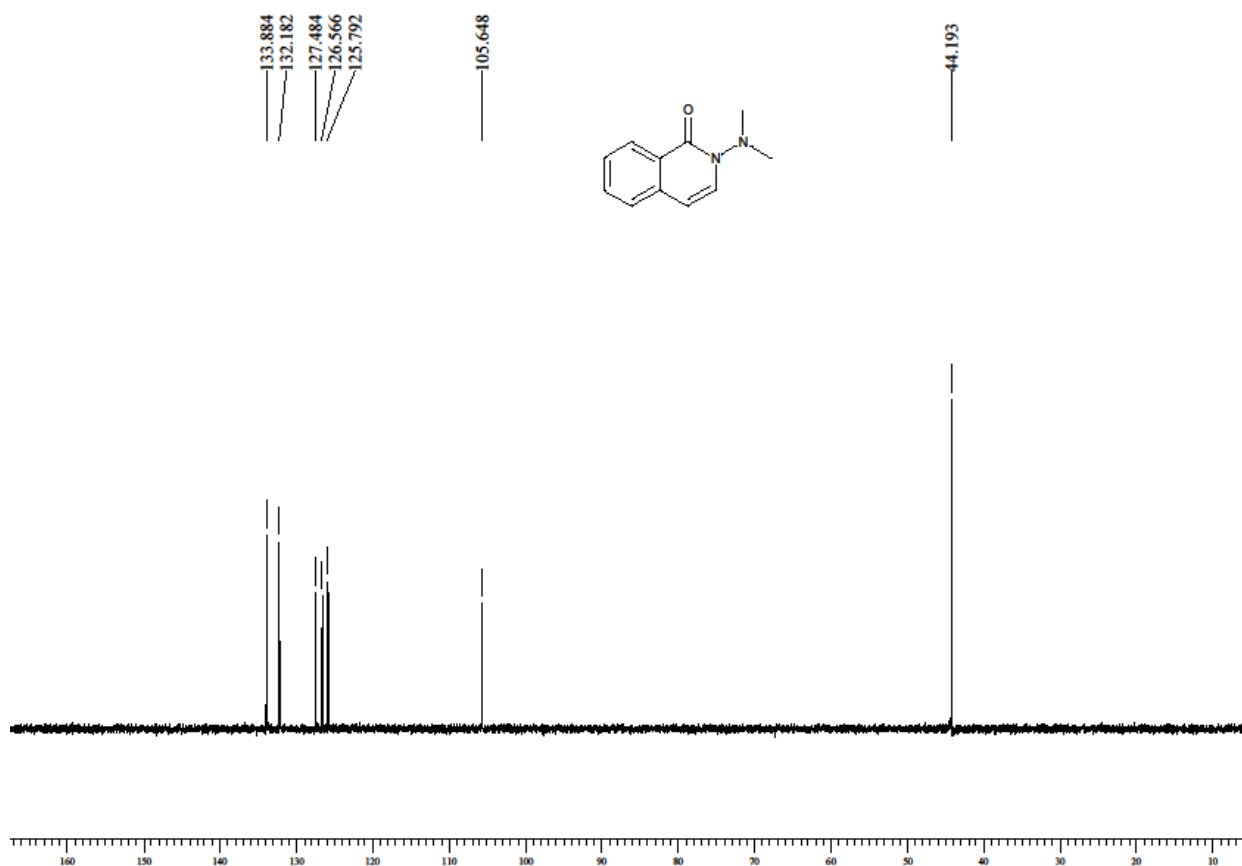
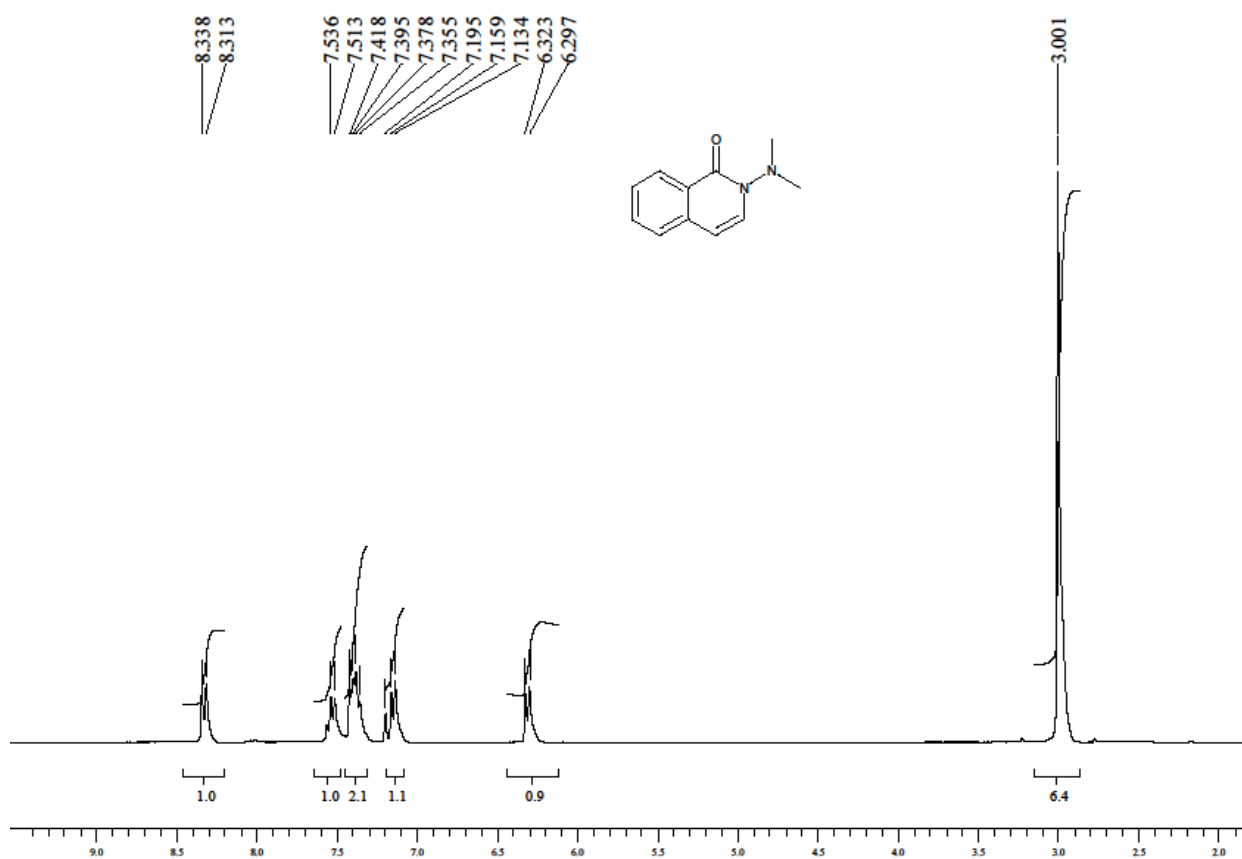


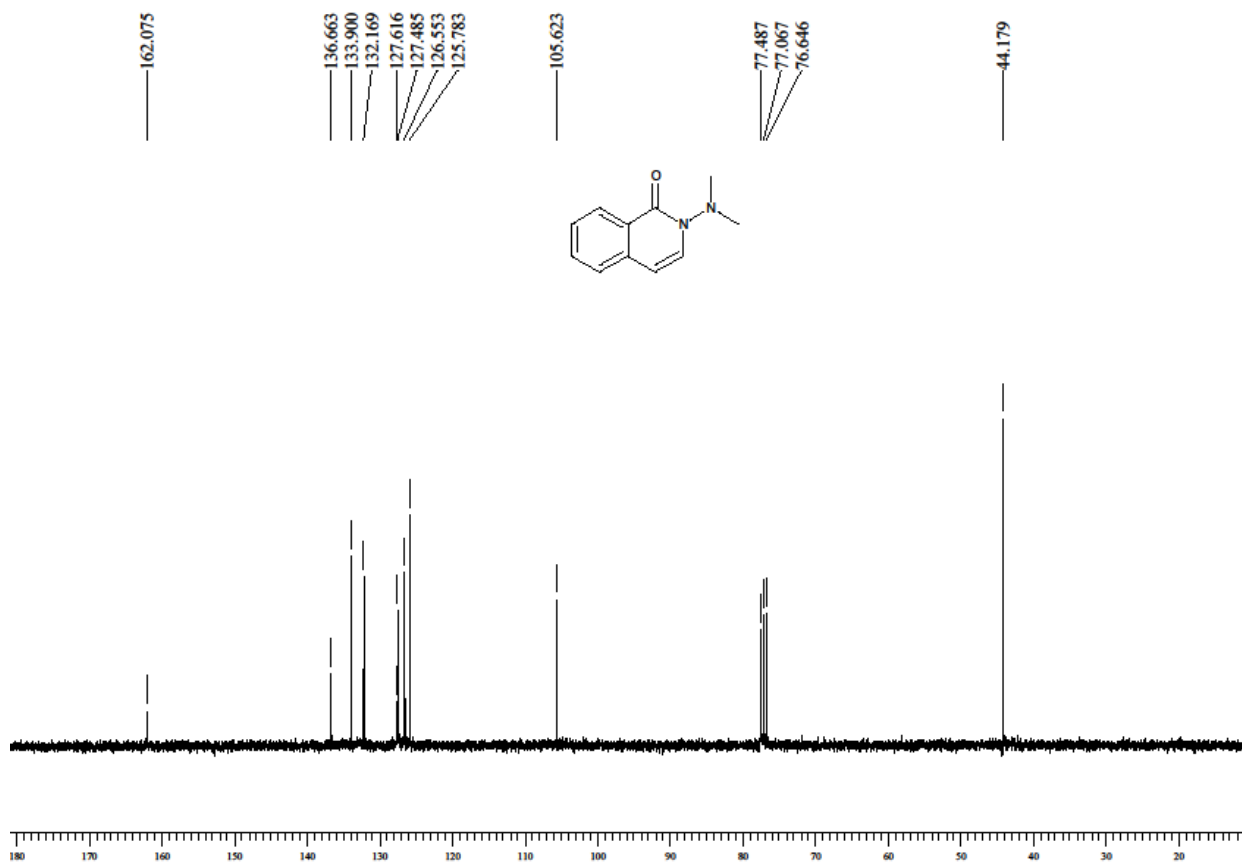
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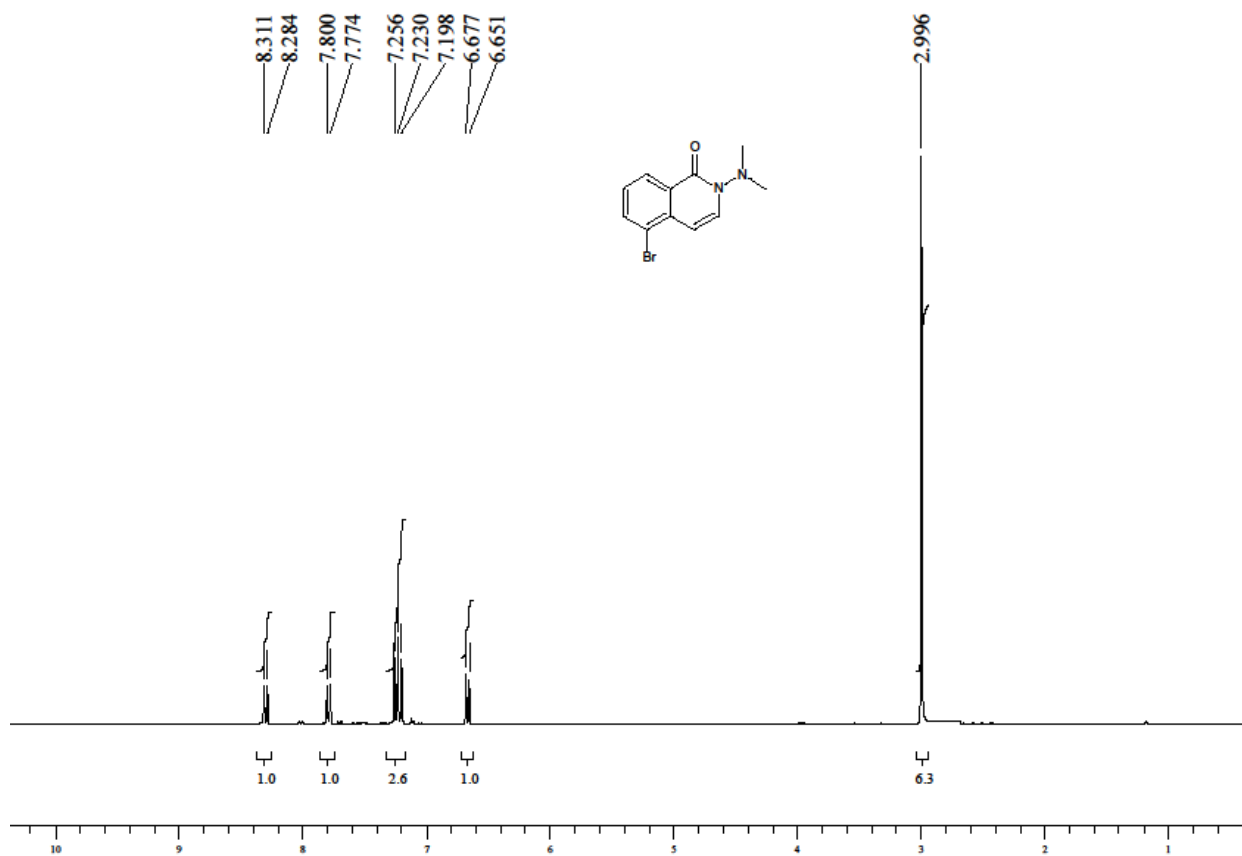


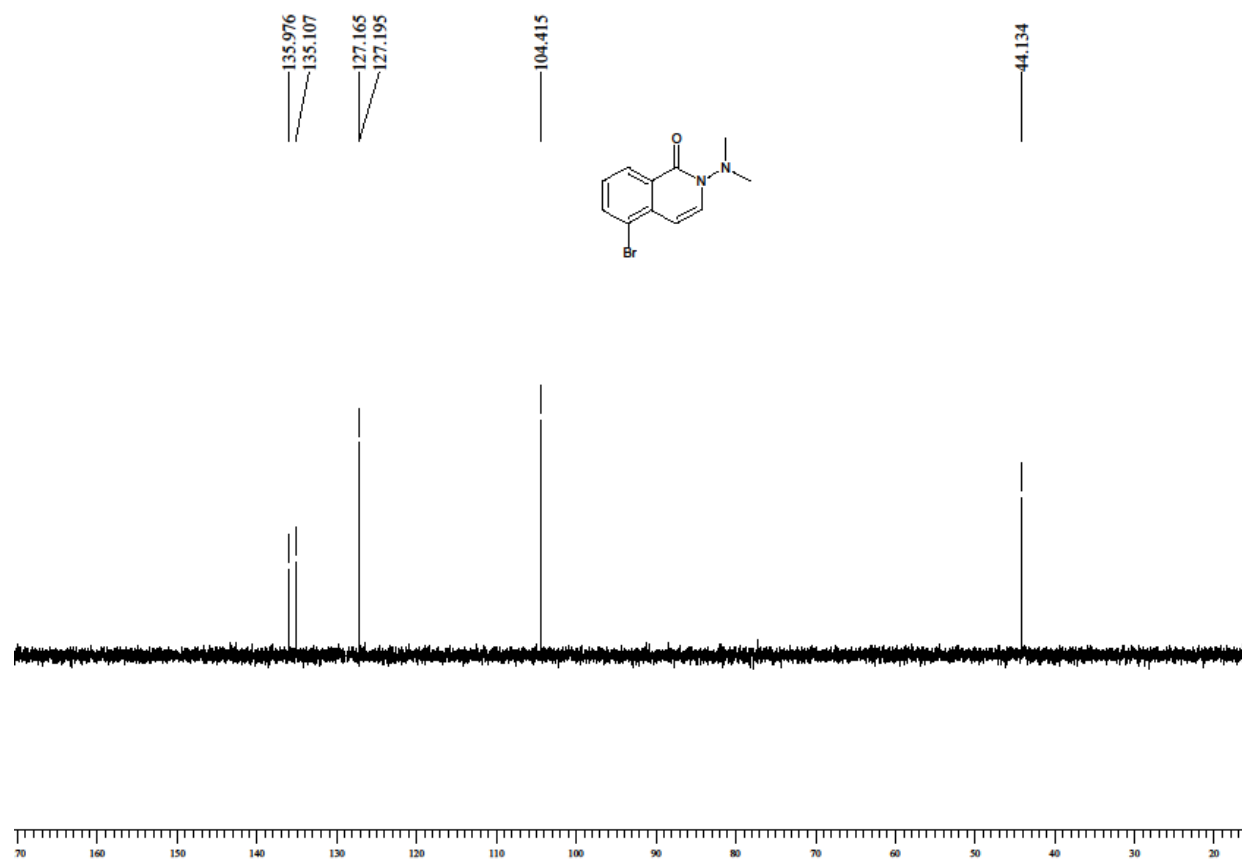
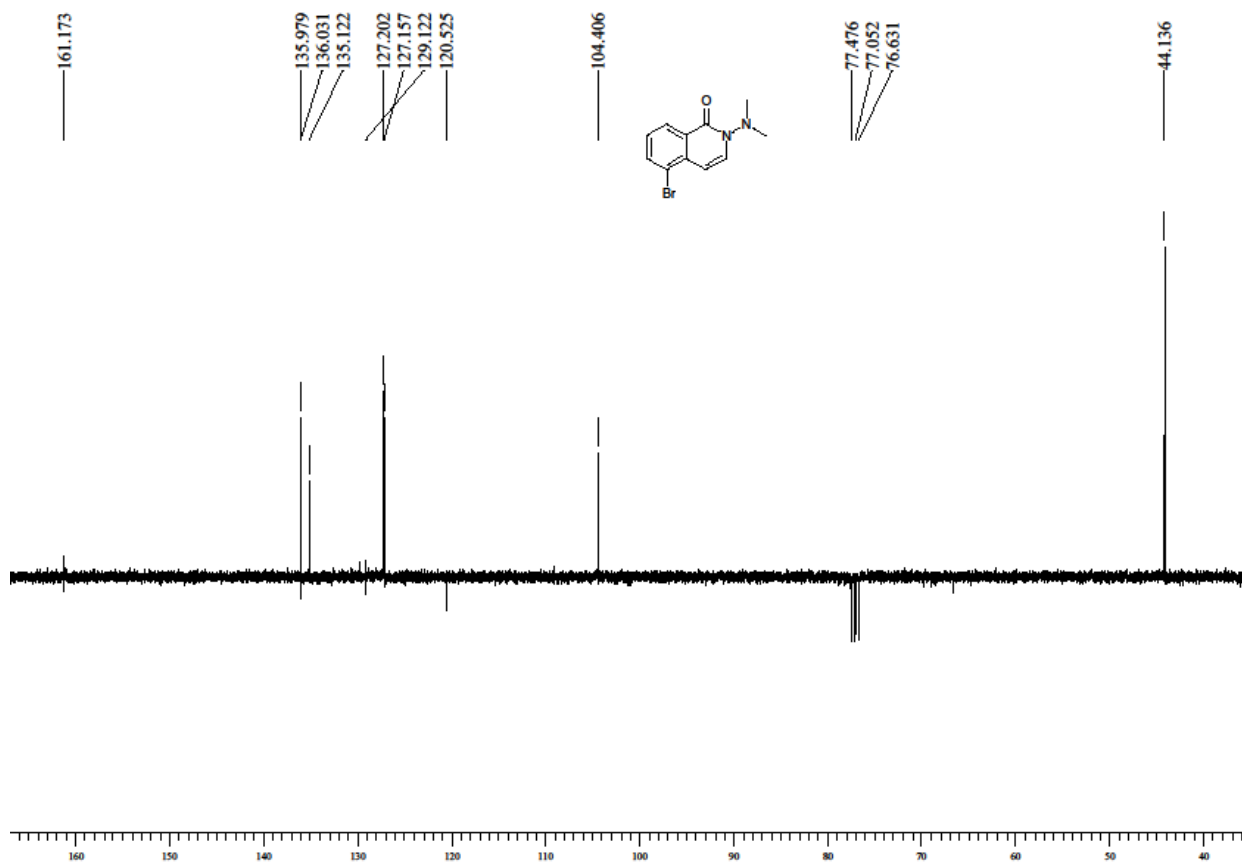
2-(Dimethylamino)isoquinolin-1(2H)-one (7a)



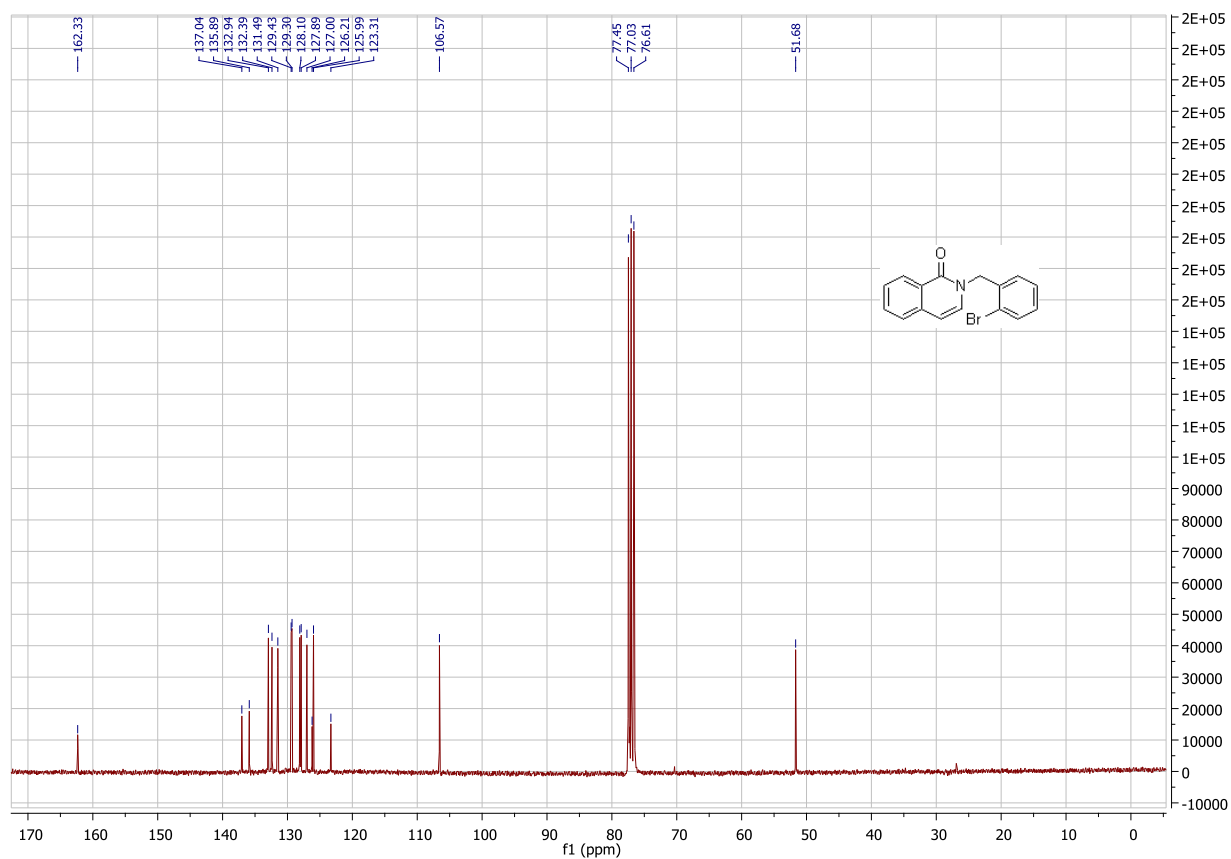
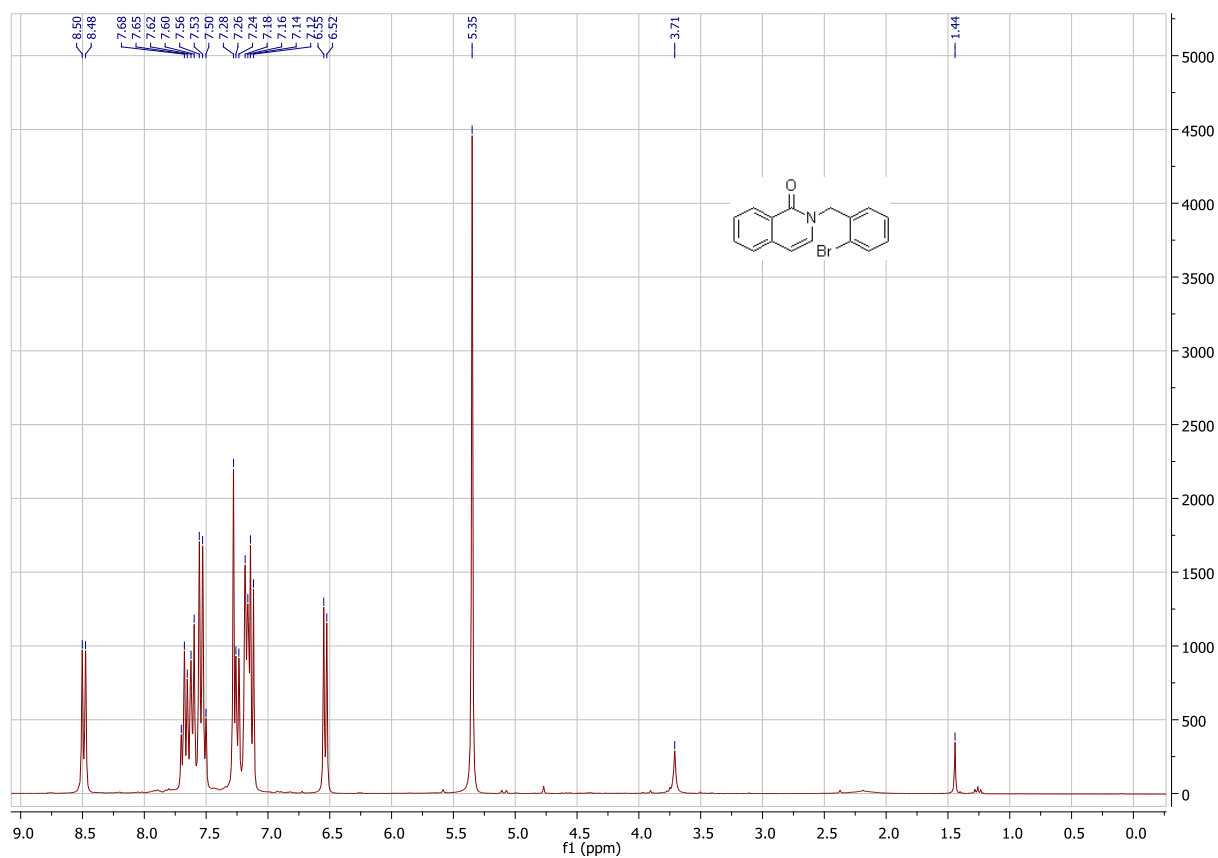


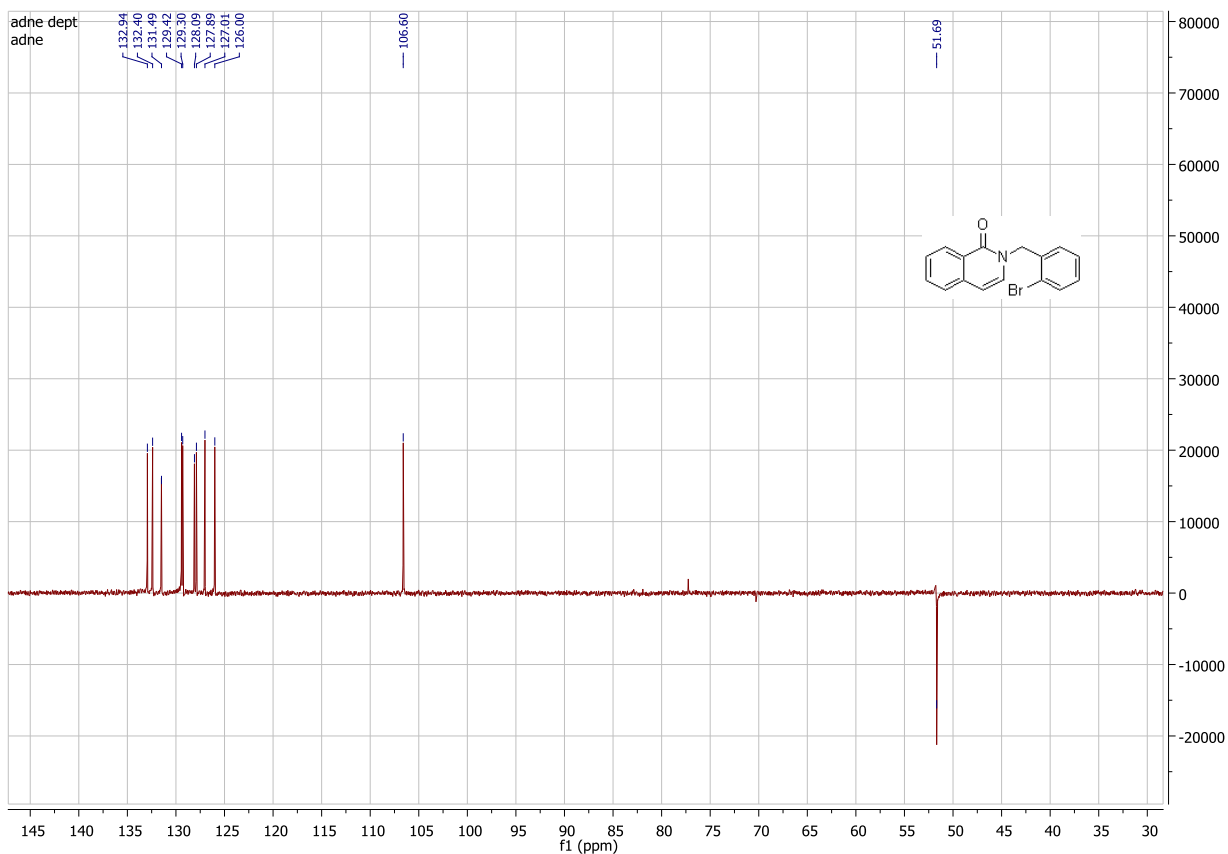
5-Bromo-2-(dimethylamino)isoquinolin-1(2H)-one (7b)



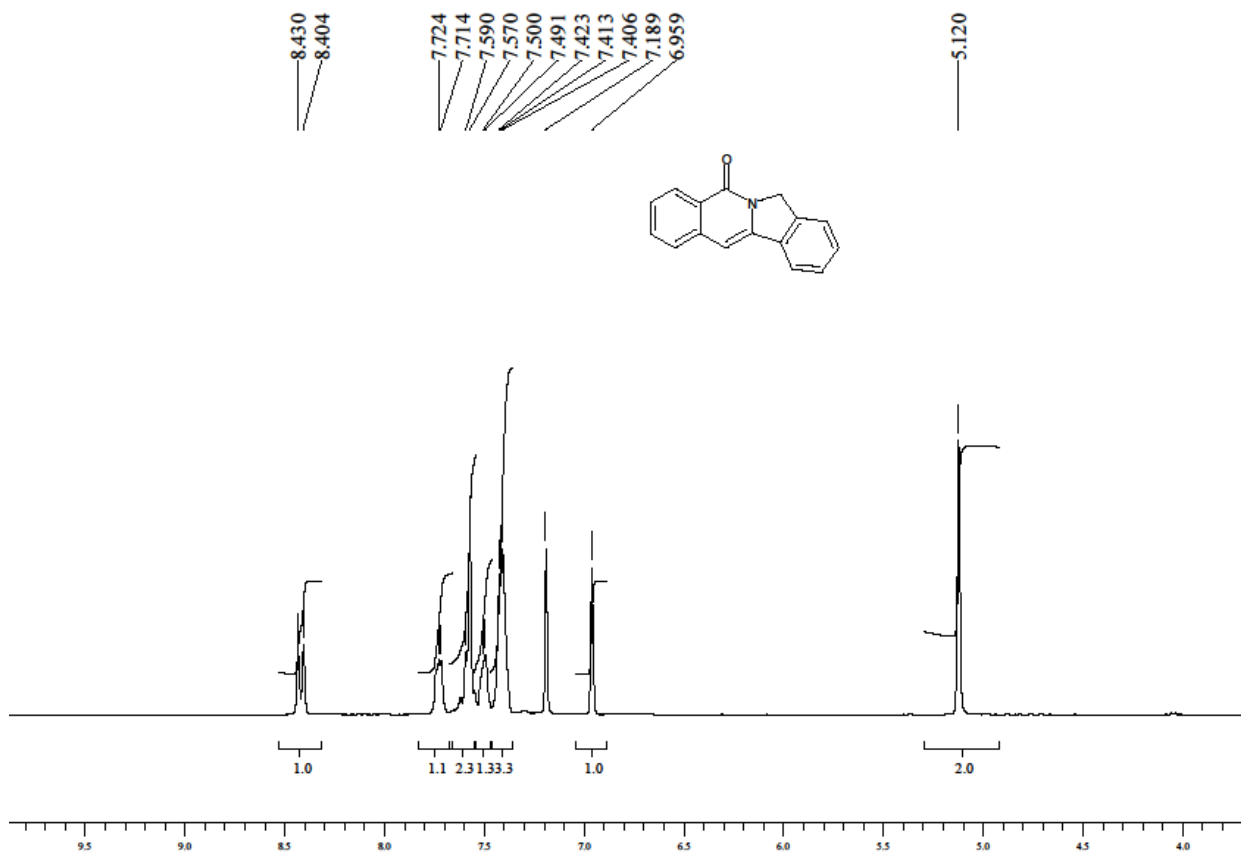


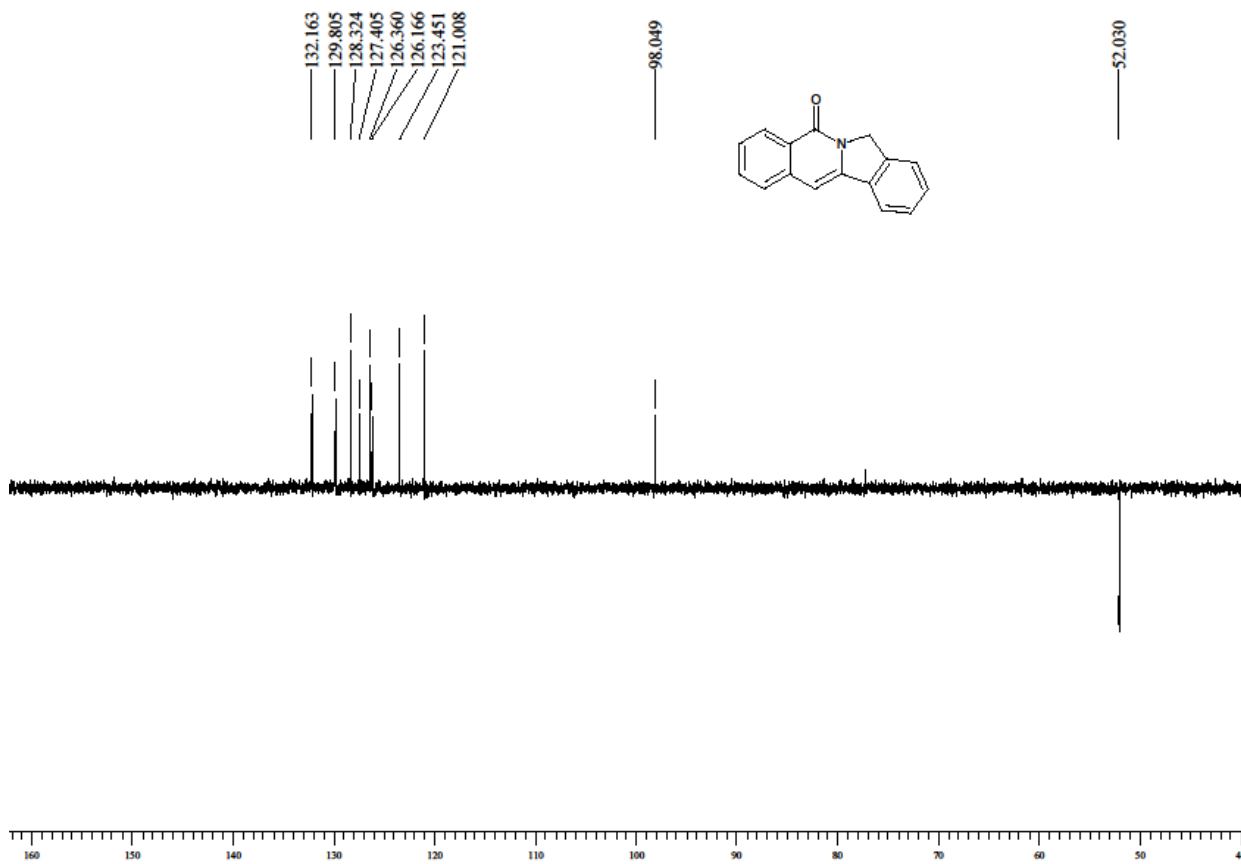
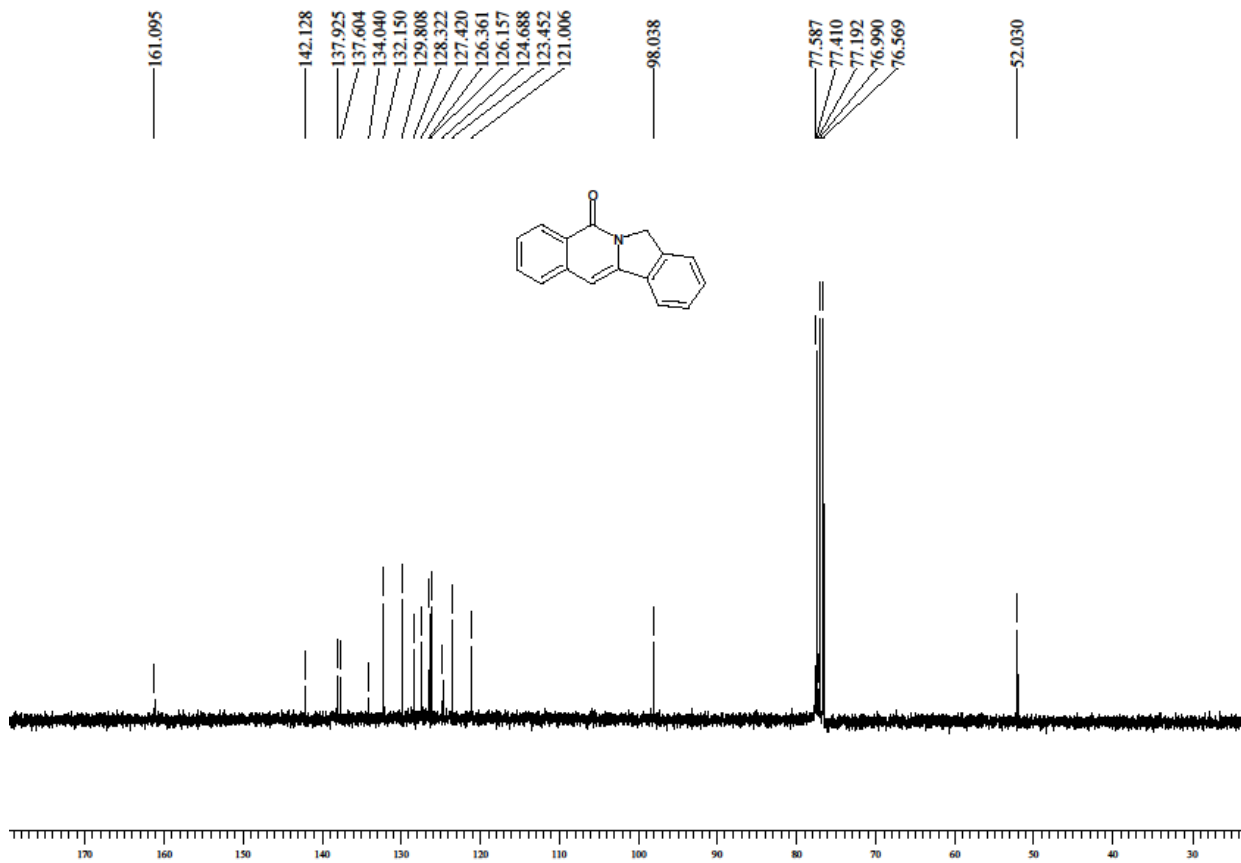
2-(2-Bromobenzyl)isoquinolin-1(2H)-one (10)



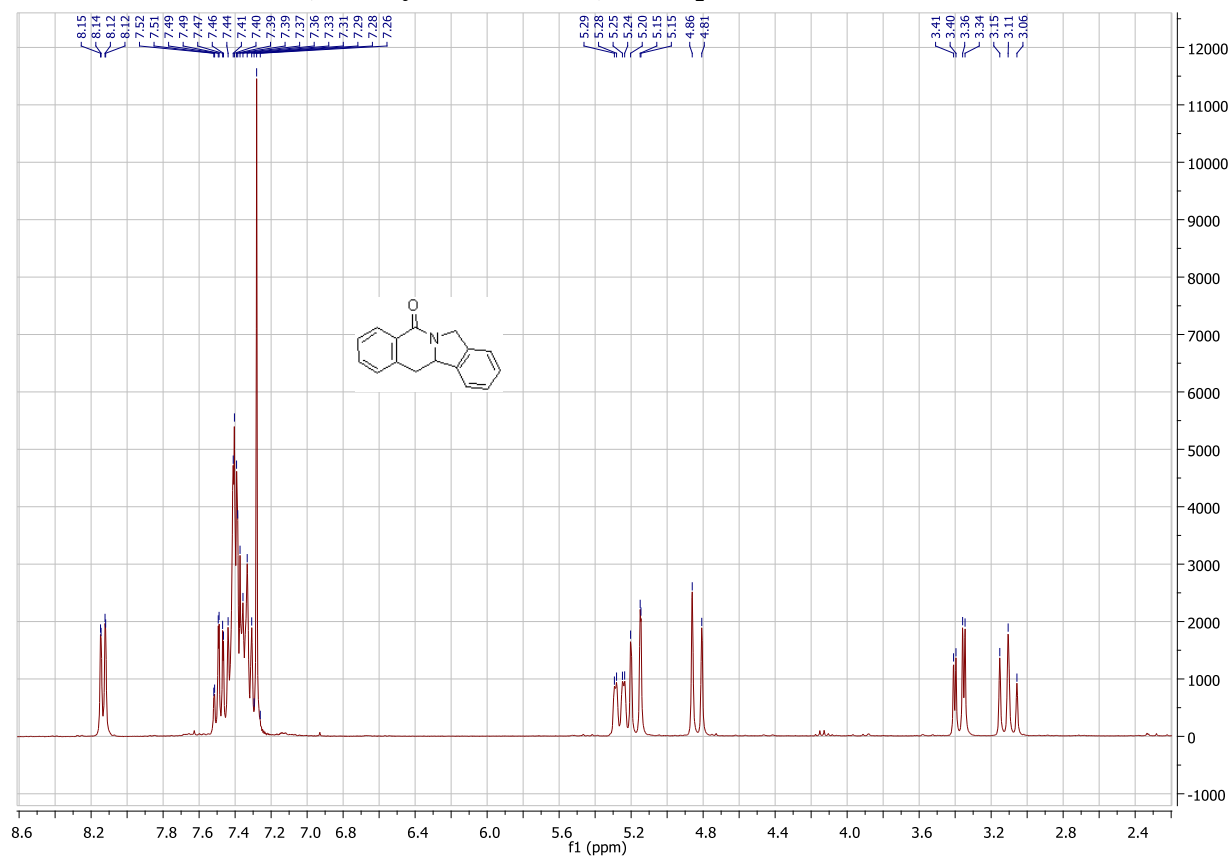


Isoindolo[2,1-b]isoquinolin-5(7H)-one (11)

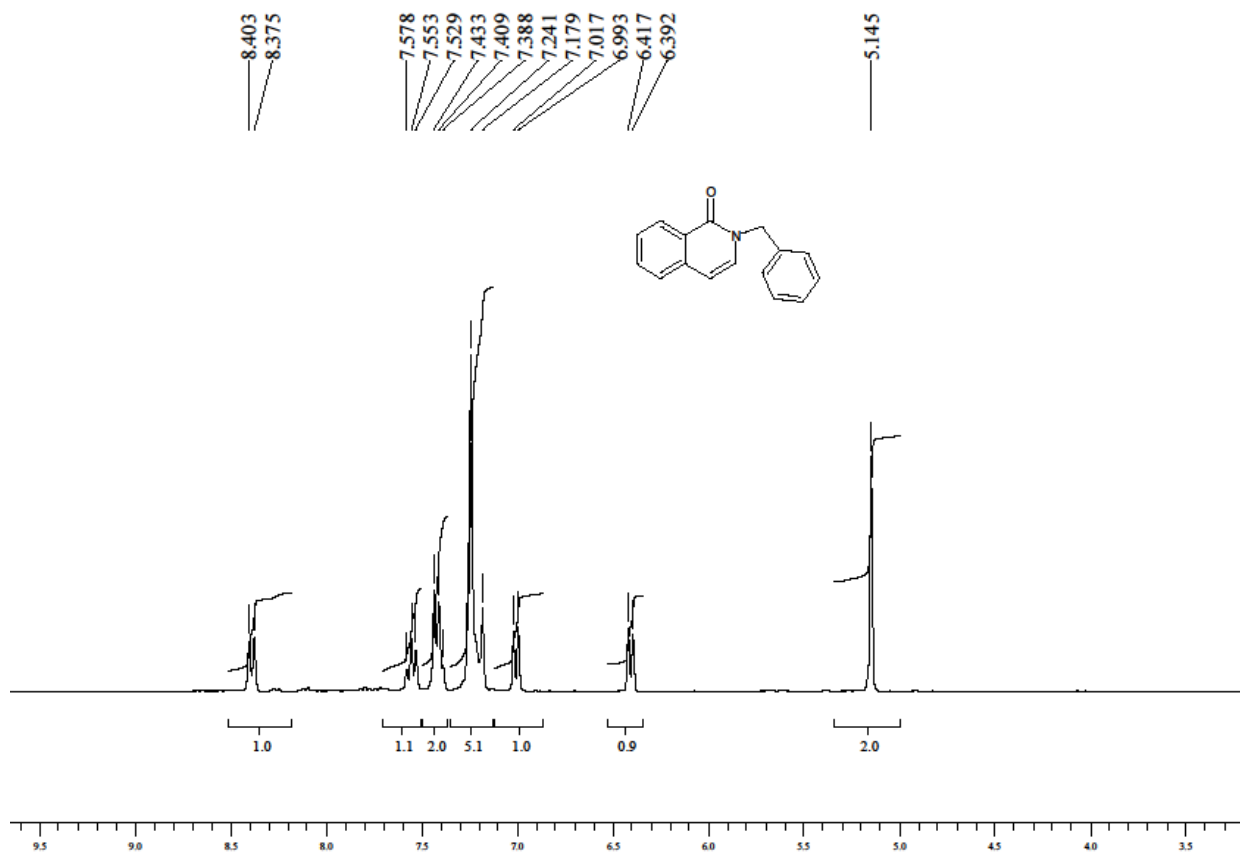


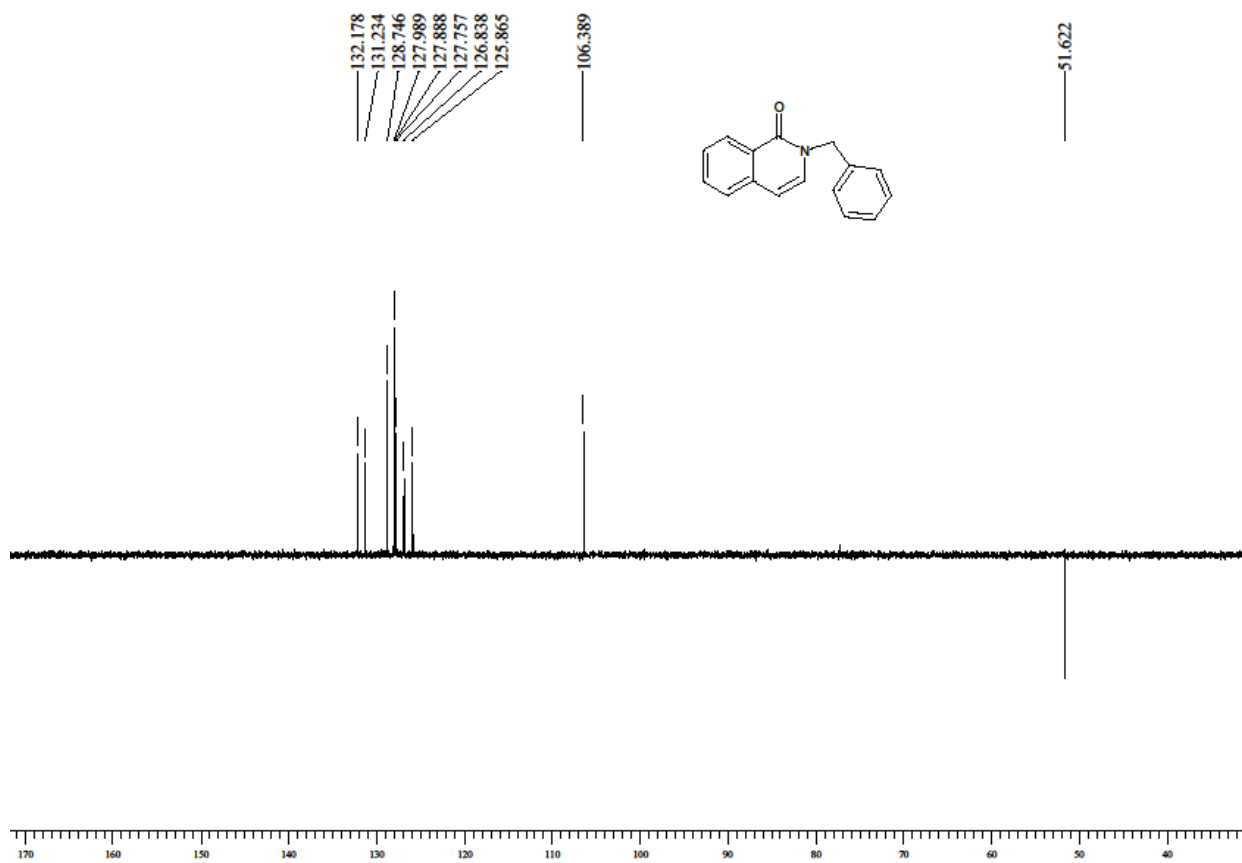
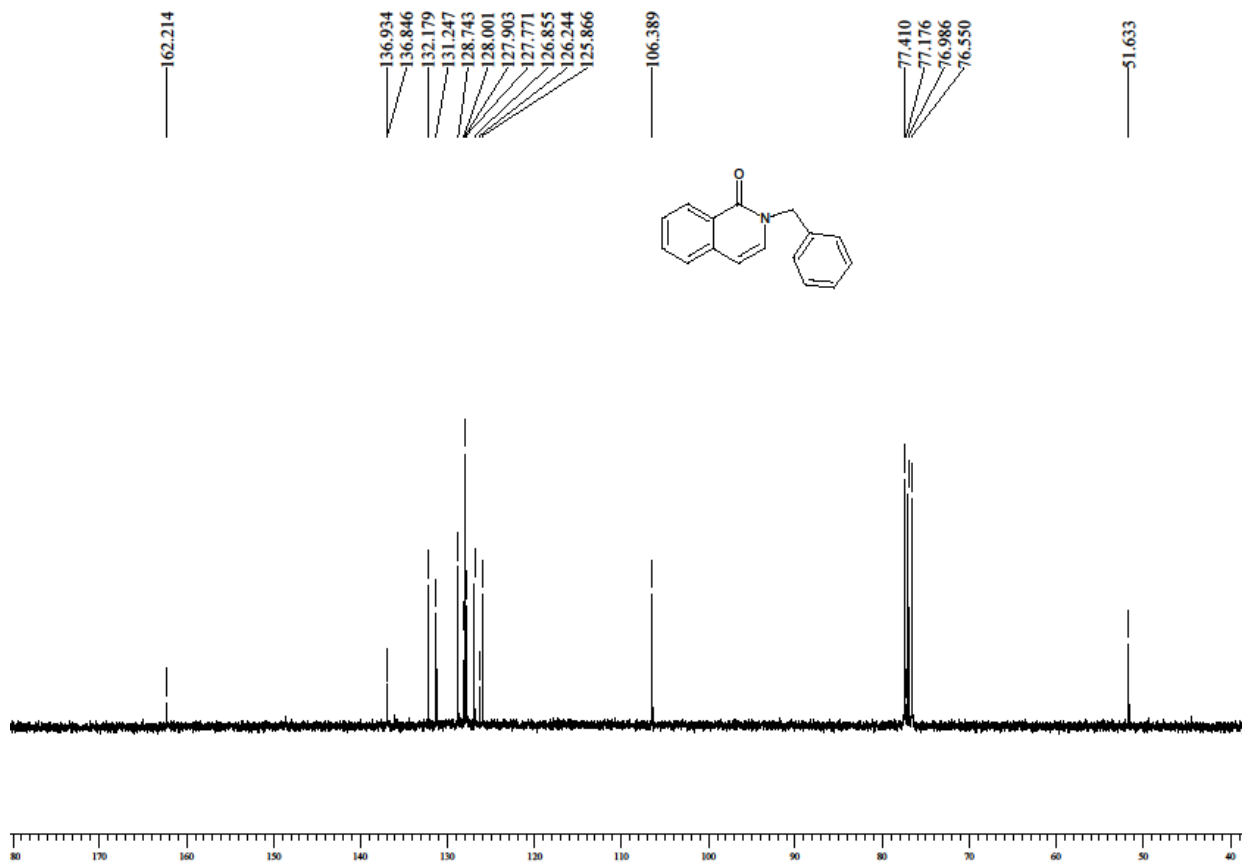


11b,12-Dihydroisoindolo[2,1-b]isoquinolin-5(7H)-one (15)

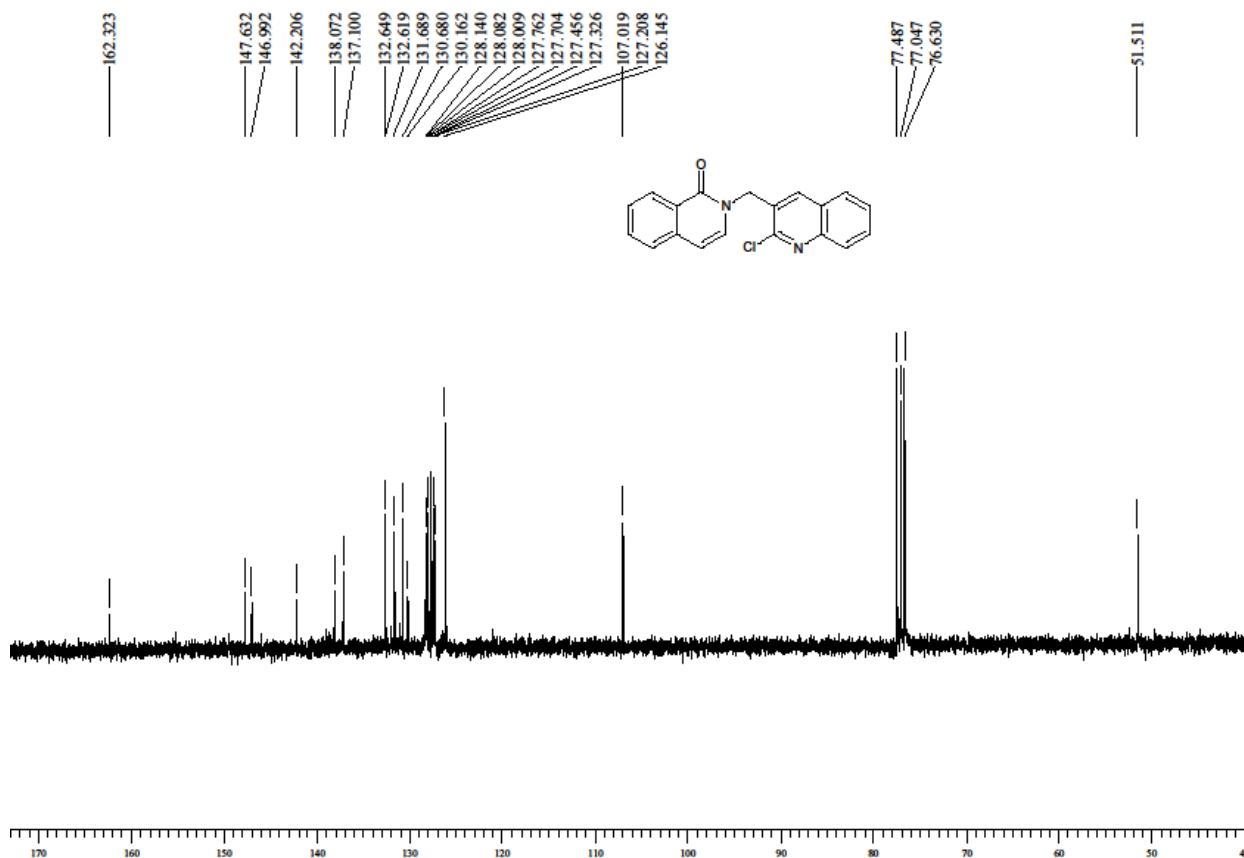
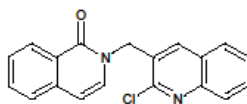
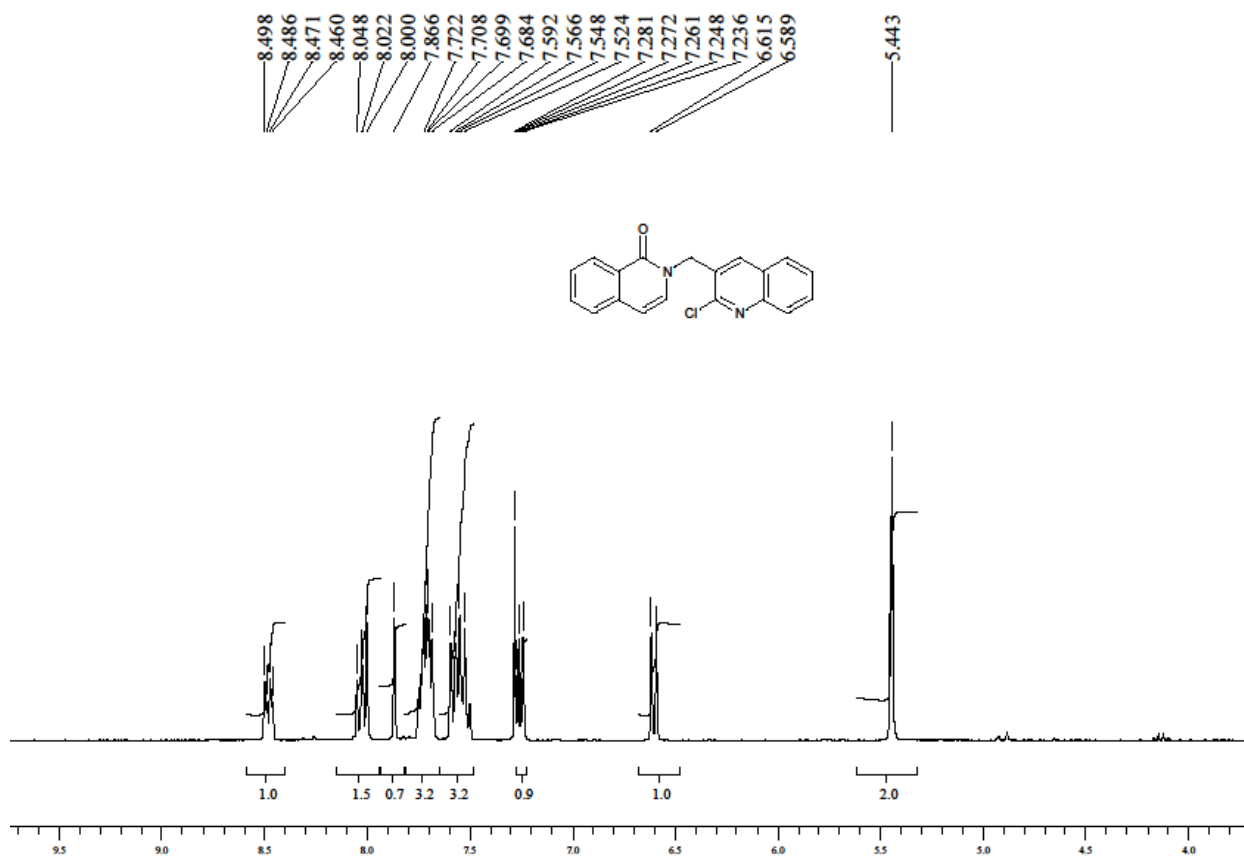


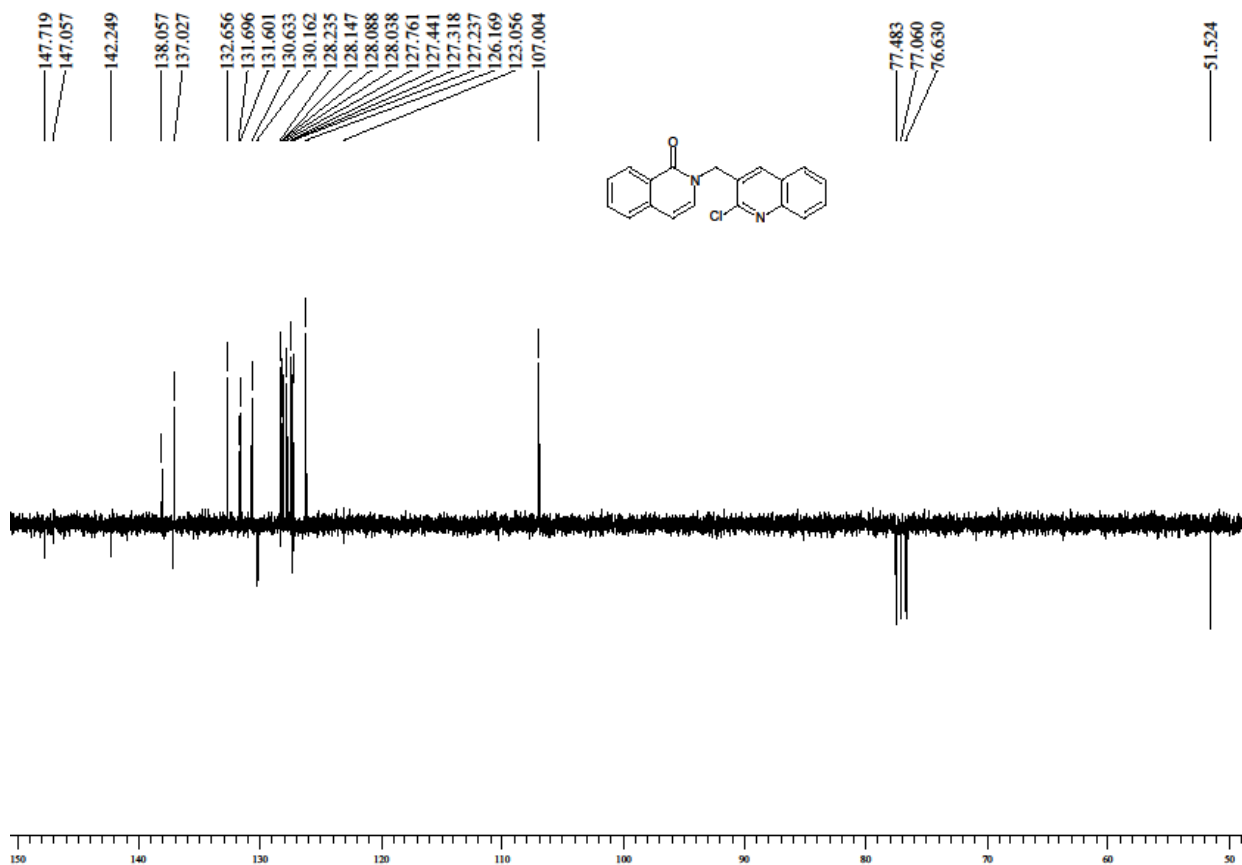
2-Benzylisoquinolin-1(2H)-one (16)



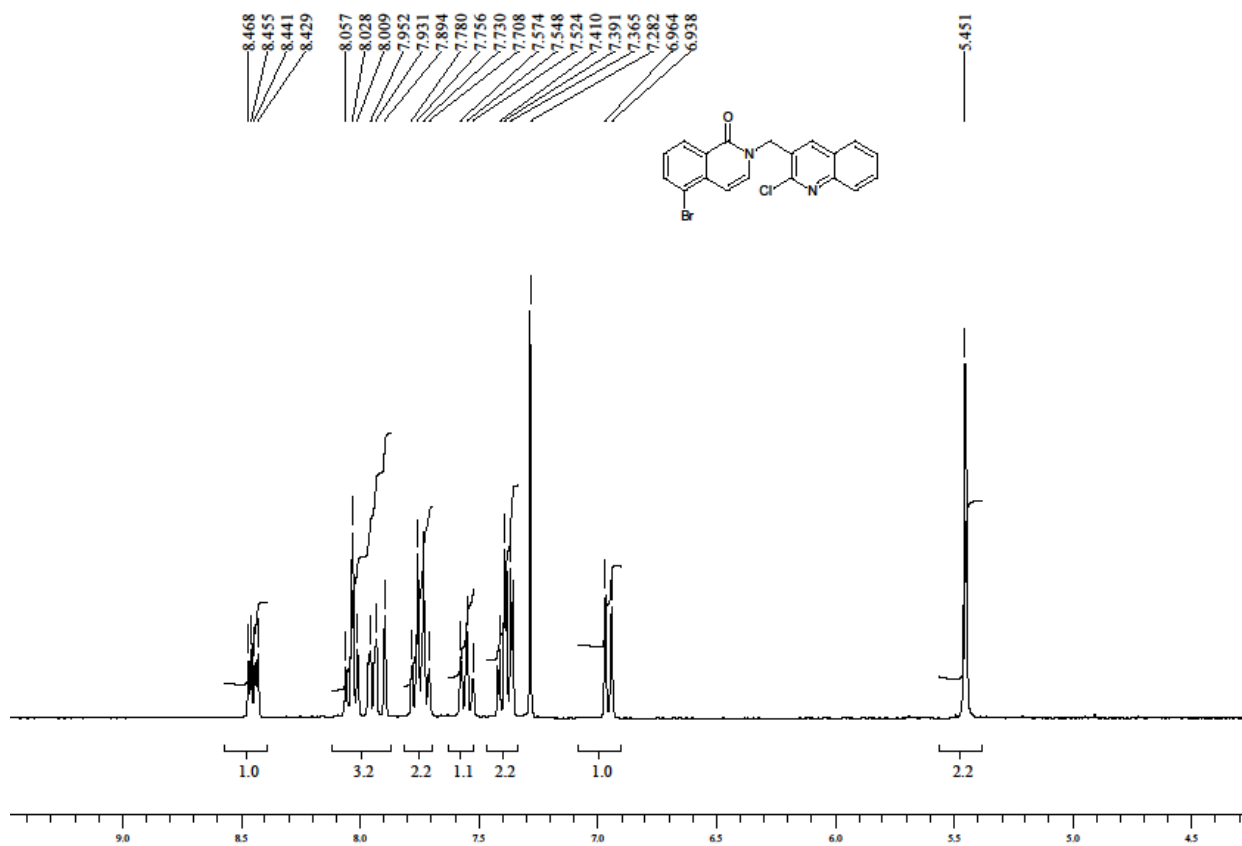


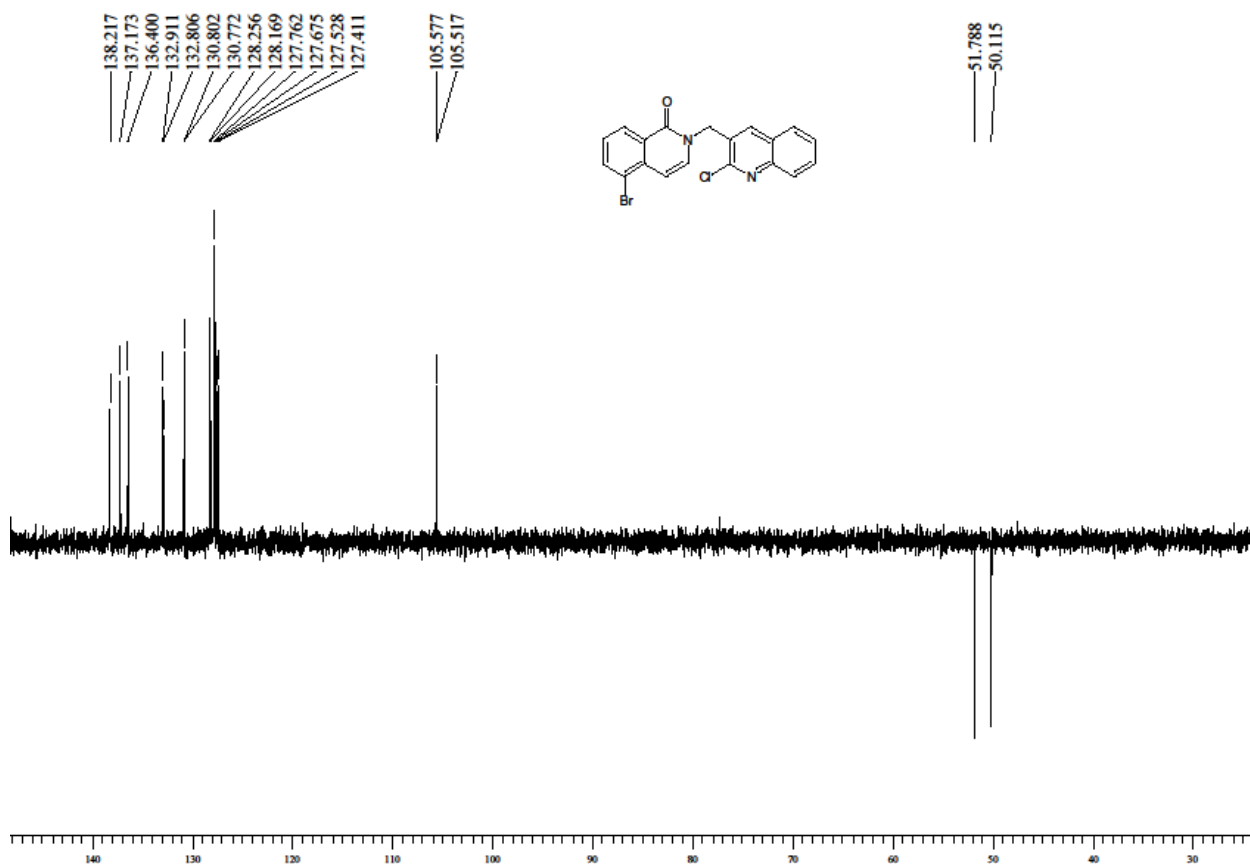
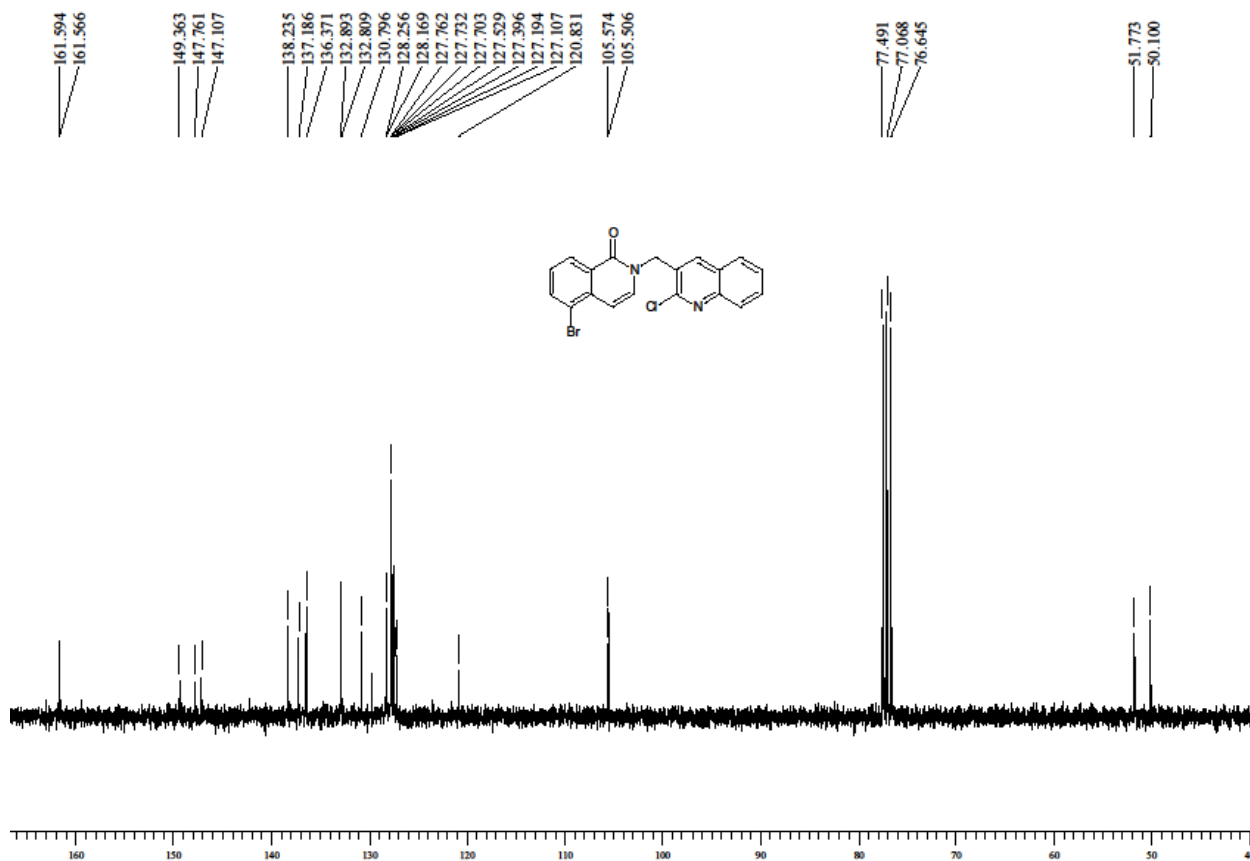
2-((2-Chloroquinolin-3-yl)methyl)isoquinolin-1(2H)-one (13a)



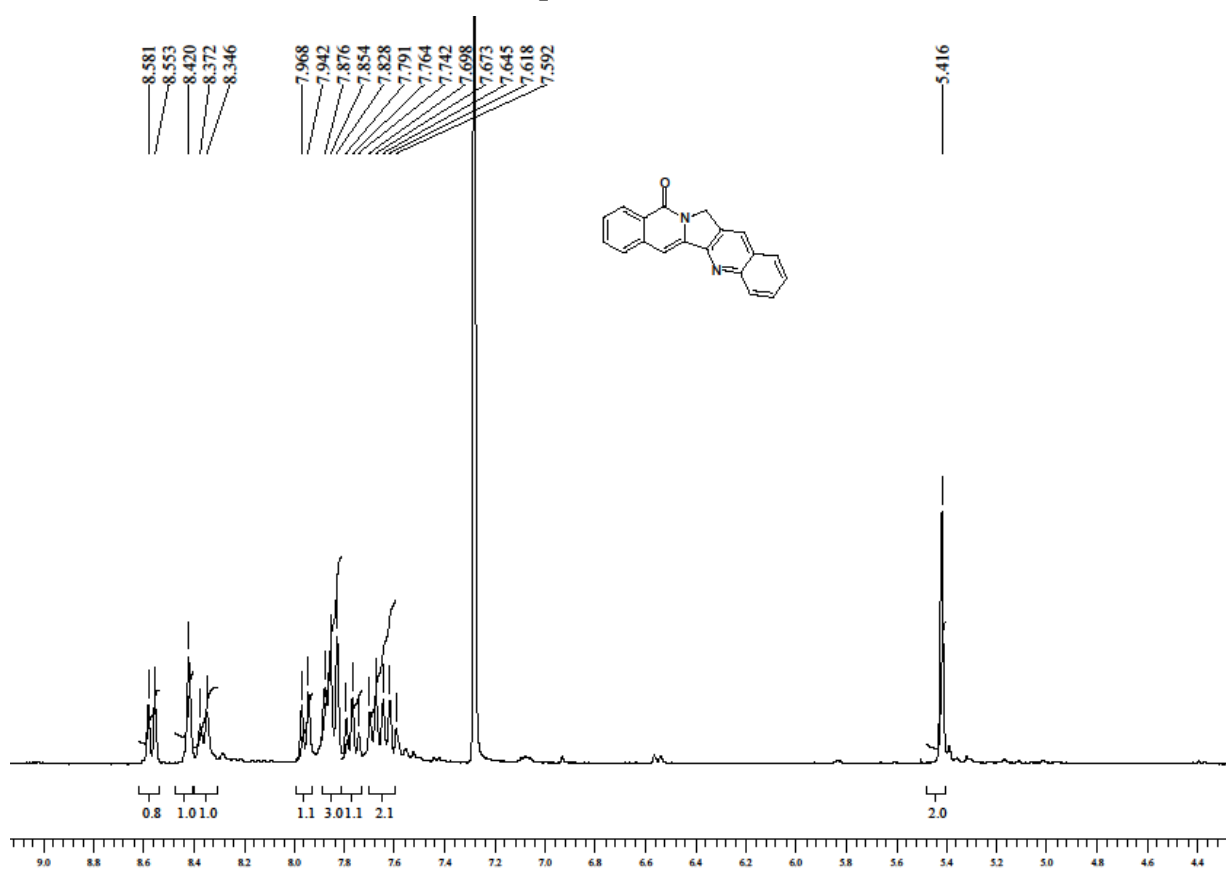


5-Bromo-2-((2-chloroquinolin-3-yl)methyl)isoquinolin-1(2H)-one (13b)





Benzo[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-one or Rosettacin (3a)



2-(Quinolin-3-ylmethyl)isoquinolin-1(2*H*)-one (17)

