Electronic Supplementary Material (ESI) for RSC Advances.

Synthetic- and DFT modelling studies on regioselective modified Mannich reactions of hydroxy-KYNA derivatives

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Contents

1. Synthetic procedures……2.
1.1. General procedure for the synthesis of 5-, 6-, 7-hydroxy-substituted kynurenic acid derivatives (2a–c)……..2.
1.2. General procedure for the synthesis of methyl and ethyl esters of 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxilic acid (8a,b)……2.
2. Experimental steps for computational study……3.
3. ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds……4.

1. Synthetic procedures

1.1 General procedure for the synthesis of 5-, 6-, 7-hydroxy-substituted kynurenic acid derivatives (2a–c).

Diethyl acetylenedicarboxylate (1 g, 5.9 mmol) and 500 mg (4.6 mmol) of the corresponding aniline derivatives (3-aminophenol or 4-aminophenol) were put in a 35-mL microwave tube with 10 mg *p*-TsOH (0.06 mmol) and 10 mL 1,2-dichlorobenzene. The mixture was kept at 190 °C for 30 minutes in a microwave reactor (300 W). Work-up procedures were carried out as described at the corresponding derivatives.

Ethyl 6-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2a)

Work-up procedure: crystallisation from 1,2-dichlorobenzene. Yield: 0.66 g (62%); M.p. 277–280 °C. ^{1}H NMR (DMSO-d_6); 1.37 (3H, t, J = 7.0 *Hz*); 4.41 (2H, q, J = 7.1 *Hz*); 6.56 (1H, s); 7.24 (1H, d, J = 8.7 *Hz*); 7.39 (1H, s); 7.84 (1H, d, J = 8.9 *Hz*); 9.87 (1H, brs); 11.93 (1H, brs); ^{13}C NMR (DMSO-d6); 14.4; 62.9; 107.4; 108.6; 121.7; 123.5; 128.1; 134.0; 137.0; 154.9; 162.9; 177.3

Ethyl 5-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2b)

Reflux time for ring closure: 48 h. Eluent for second column chromatography: EtOAc:*n*-hexane 8:1. Yield: 214 mg (20%); M.p. 191–197 °C (lit[38]: 280-281 °C). ^{1}H NMR (DMSO-d_6); 1.38 (3H, t, J = 7.0 *Hz*); 4.43 (2H, q, J = 7.2 *Hz*); 6.62 (1H, d, J= 8.1 *Hz*); 6.65 (1H, s); 7.34 (1H, d, J = 8.2 *Hz*); 7.56 (1H, t, J = 8.2 *Hz*); 12.44 (1H, brs); 14.00 (1H, brs); ^{13}C NMR (DMSO-d6); 14.3; 63.3; 108.7; 108.8; 109.0; 114.4; 135.2; 139.6; 141.4; 161.0; 161.9; 183.4

Ethyl 7-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2c)

Reflux time for ring closure: 48 h. Eluent for second column chromatography: EtOAc:*n*-hexane 8:1. Yield: 461 mg (43%); M.p. 233–236 °C. ^{1}H NMR (DMSO-d_6); 1.36 (3H, t, J = 7.3 *Hz*); 4.40 (2H, q, J = 7.1 *Hz*); 6.51 (1H, s); 6.83 (1H, d, J = 6.8 *Hz*) 7.20 (1H, s); 7.91 (1H, d, J = 8.8 *Hz*); 10.38 (1H, brs); 11.67 (1H, brs); ^{13}C NMR (DMSO-d6); 14.4; 62.9; 102.7; 110.4; 115.4; 120.2; 127.2; 137.9; 142.5; 161.6; 162.8; 177.4

1.2. General procedure for the synthesis of methyl and ethyl esters of 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxilic acid (8a,b)

Xanthurenic acid (**6**, 410 mg, 2.0 mmol) was put in a 100 mL, three-necked round bottom flask with 40 mL MeOH or EtOH, one neck with a stopper, one with a reflux column and one with a thermometer under water-free conditions. The reaction mixture was cooled with ice-salt mixture to –15 °C and 1mL $SOCl_2$ was added gradually in 2 minutes. The mixture was stirred for 4 h and then heated at reflux temperature for 6 h. After evaporation of the solvent, the residue was purified using column chromatography (eluent: DCM:MeOH 20:1 or DCM:EtOH 20:1). The solvent of the collected fractions was evaporated and the residue was crystallised from EtOAc (10 mL).

Ethyl 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (8a)

Solvent: EtOH, eluent: DCM:EtOH 20:1. Yield: 168 mg (72%); M.p. 265–268 °C. ^{1}H NMR (DMSO-d_6); 1.37 (3H, t, J = 7.1 *Hz*); 4.42 (2H, q, J = 7.1 *Hz*); 6.59 (1H, s); 7.25 (1H, d, J = 7.7 *Hz*); 7.22 (1H, s); 7.54 (1H, d, J = 7.8 *Hz*); 9.74 (1H, brs); 10.98 (1H, brs); ^{13}C NMR (DMSO-d6); 14.4; 63.1; 109.6; 114.8; 115.6; 125.2; 126.8; 130.6; 137.4; 147.7; 162.9; 177.9

Methyl 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (8b)

Solvent: MeOH, eluent: DCM:MeOH 20:1. Yield: 201 mg (77%); M.p. 260–265 °C (lit [29]: 262 °C). ^{1}H NMR (DMSO-d_6); 3.96 (3H, s); 7.15 (1H, d, J = 7.6 *Hz*); 7.25 (1H, s); 7.54 (1H, d, J = 8.3 *Hz*); ^{13}C NMR (DMSO-d6); 54.1; 110.3; 115.2; 116.1; 124.8; 127.3; 130.2; 137.1; 147.2; 163.0; 178.1

2. Experimental steps for the computational study

In the course of DFT calculations the optimised structures were localised as local minima on the potential energy surface (PES) by B3LYP (Becke, 3-parameter, Lee–Yang–Parr) exchange-correlation hybrid functional[1-3] using 6-31+G(d,p) basis set with diffuse functions on elements other than H atom as well as polarisation functions d and p on C, N and O atoms and on H atom, respectively.[4] All the computations were supported by IEFPCM solvent model[5] using the dielectric constant of the appropriate solvent (ε: 24.50 for ethanol; 2.25 for 1,4-dioxane; 2.38 for toluene and 37.5 for acetonitrile) to represent the polarity of the reaction mixtures. On the optimised structures frequency calculations were carried out employing the same functional, basis set and solvent model with the dielectric constant of the appropriate solvent to obtain the Gibbs free energy values. In the course of the calculations molecular orbitals (MO's) were accumulated in the checkpoint files. Using downloaded „formchk.exe" utility the checkpoint files were then converted into a formatted file suitable for visualisation. From the set of MO's HOMO was selected and visualised. Natural bond analysis[6] was run simultaneously with geometry optimisation of the anionic models providing NBO charges. All calculations were performed by the Gaussian 09 software (Gaussian Incorporation, Pittsburgh, U.S.) package.[7]

References:

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3. ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds

Ethyl 6-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2a)

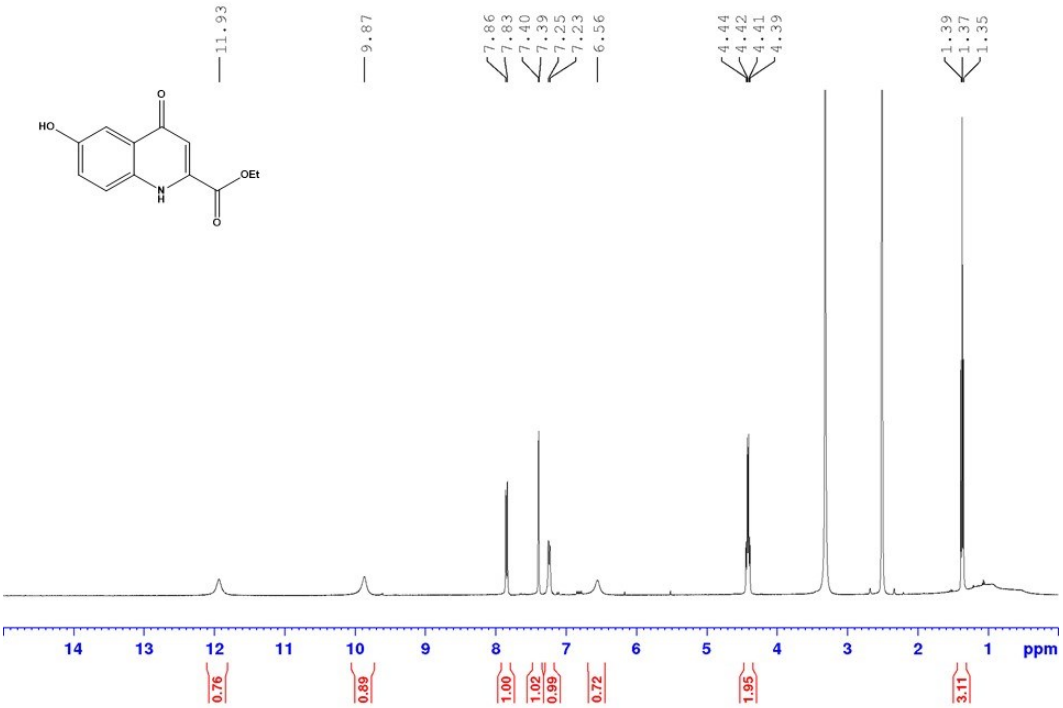

Figure S1. ^{1}H-NMR spectrum of **2a**

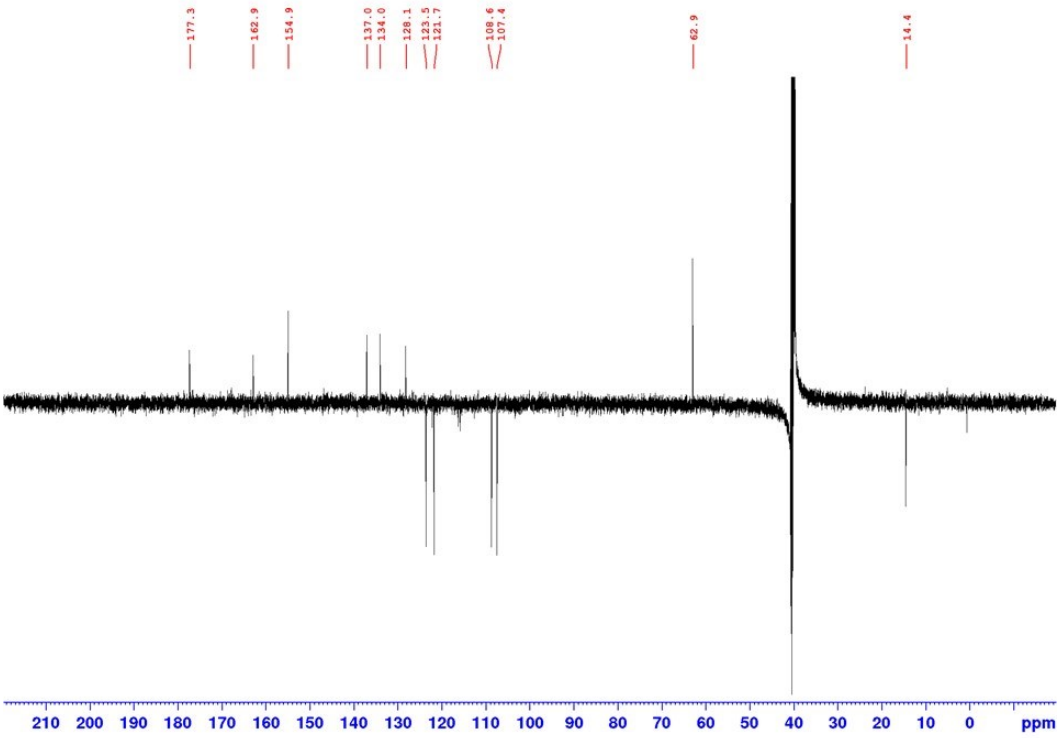

Figure S2. ^{13}C-NMR spectrum of **2a**

Ethyl 5-hydroxy-4-oxo-1,4-dihydroquinoline-2-zcarboxylate (2b)

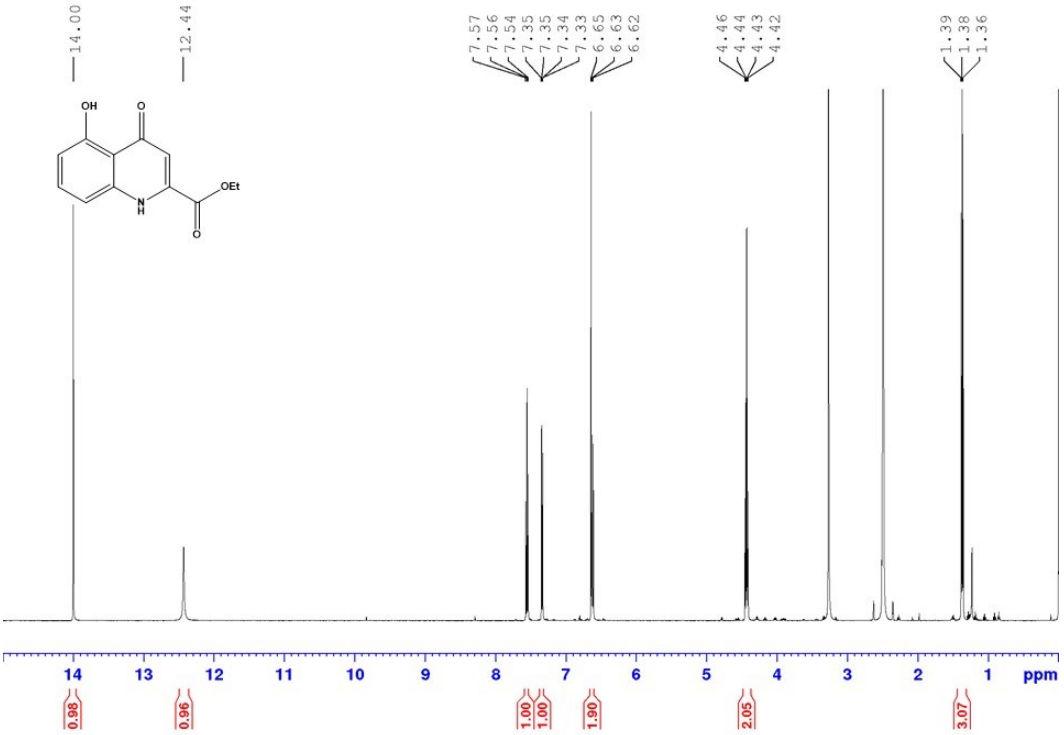

Figure S3. ^{1}H-NMR spectrum of **2b**

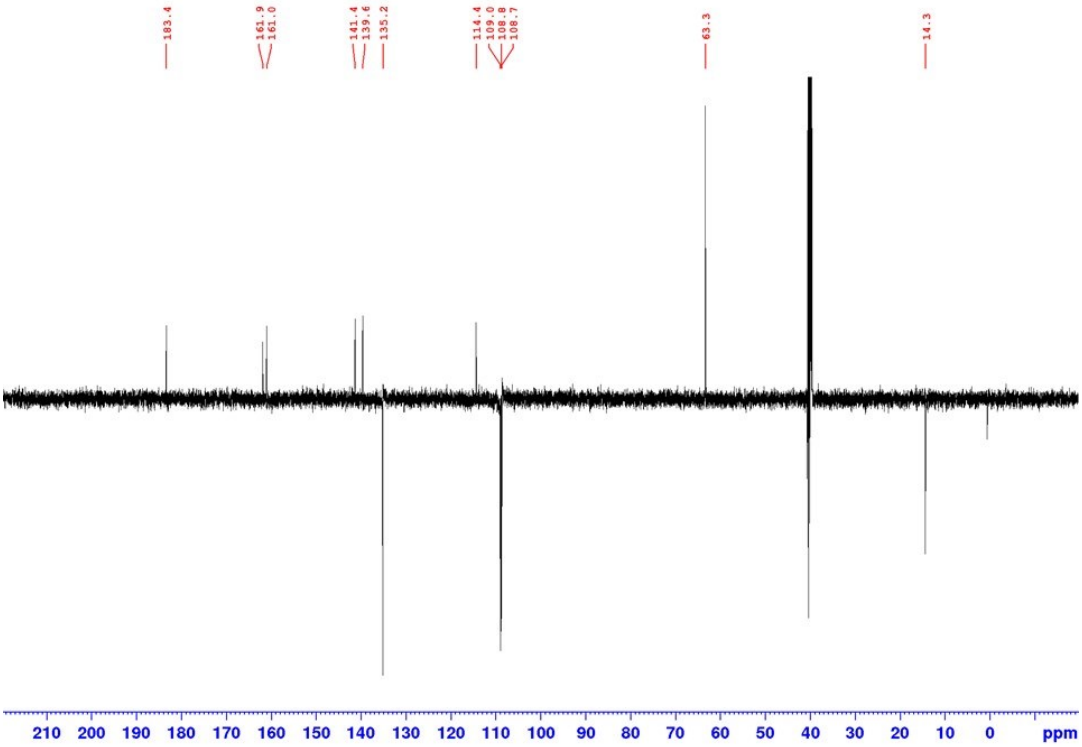

Figure S4. ^{13}C-NMR spectrum of **2b**

Ethyl 7-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2c)

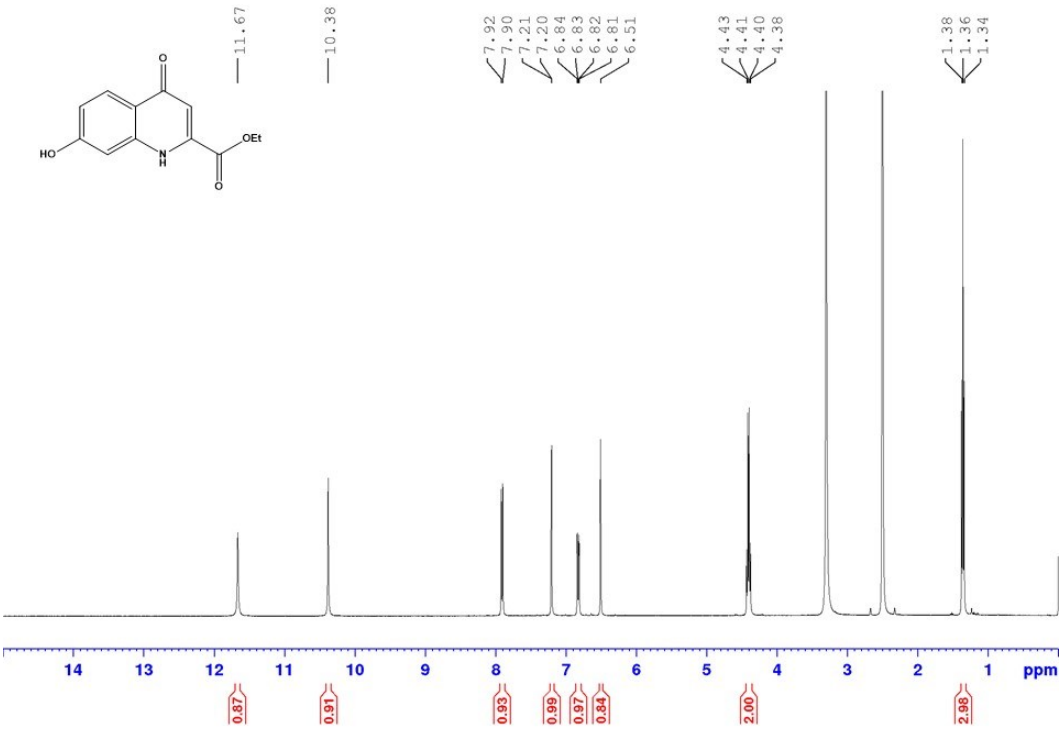

Figure S5. ^{1}H-NMR spectrum of **2c**

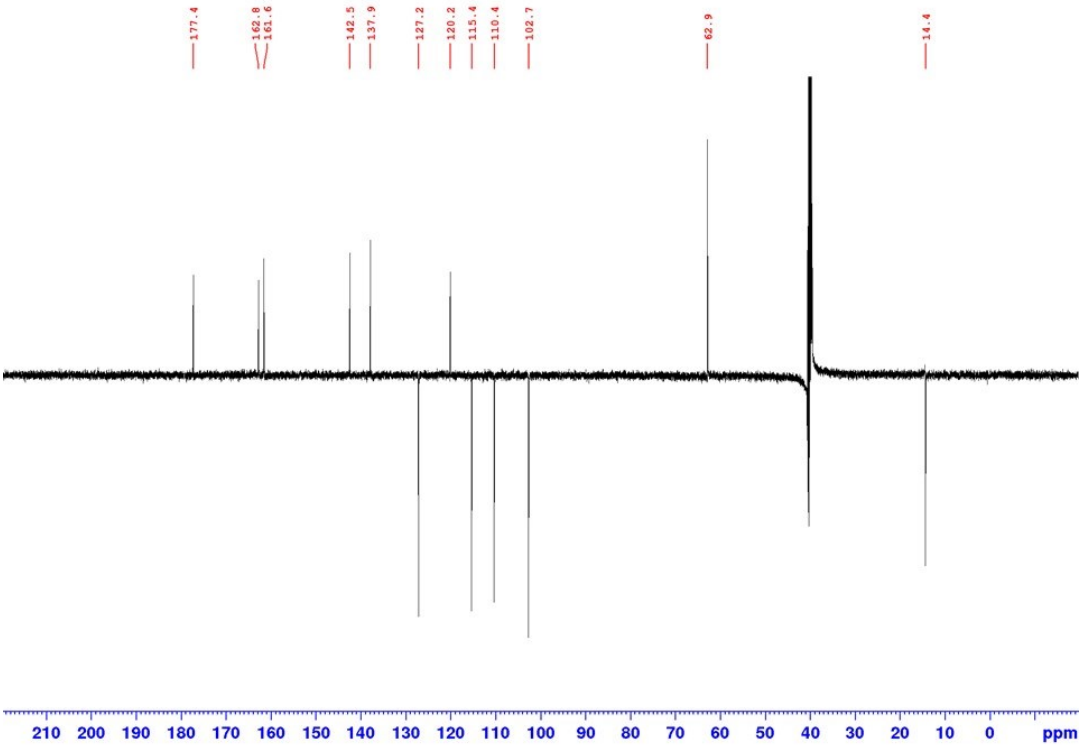

Figure S6. ^{13}C-NMR spectrum of **2c**

6-Hydroxy-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (3a)

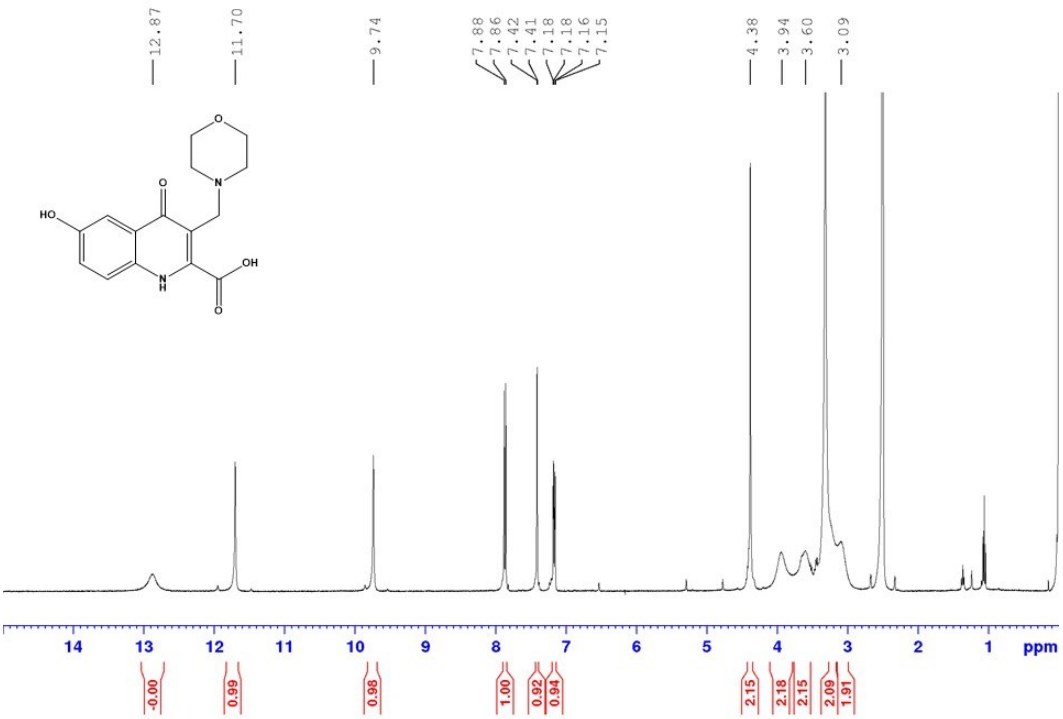

Figure S7. ^{1}H-NMR spectrum of **3a**

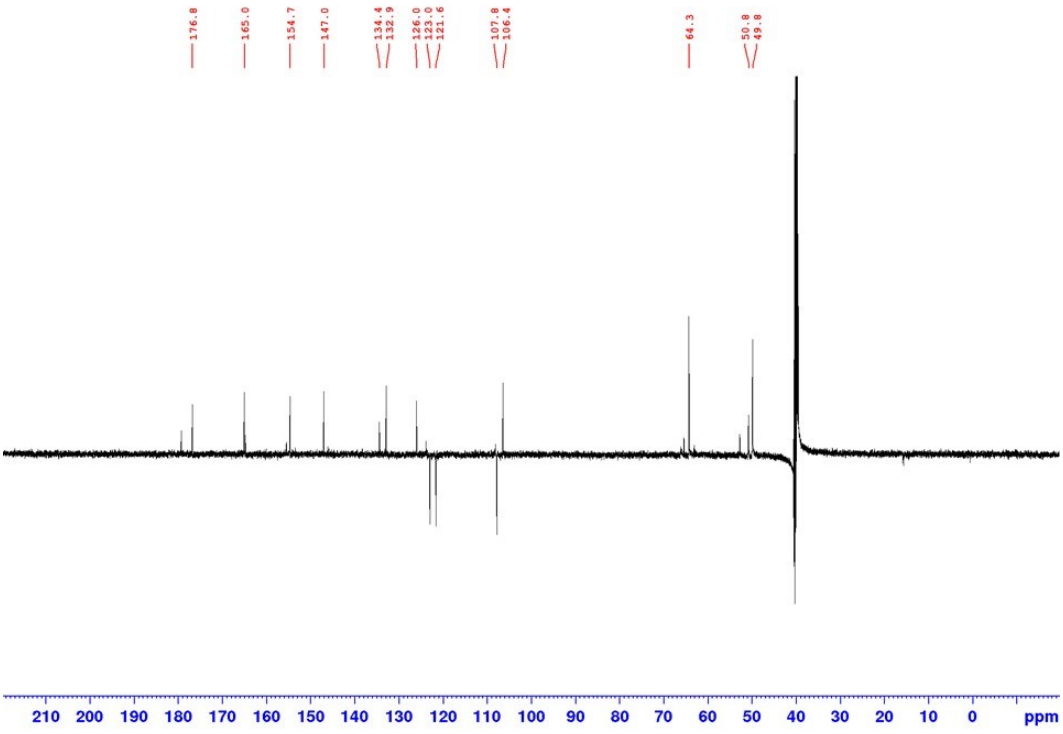

Figure S8. ^{13}C-NMR spectrum of **3a**

6-Hydroxy-3,5-bis(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (3b)

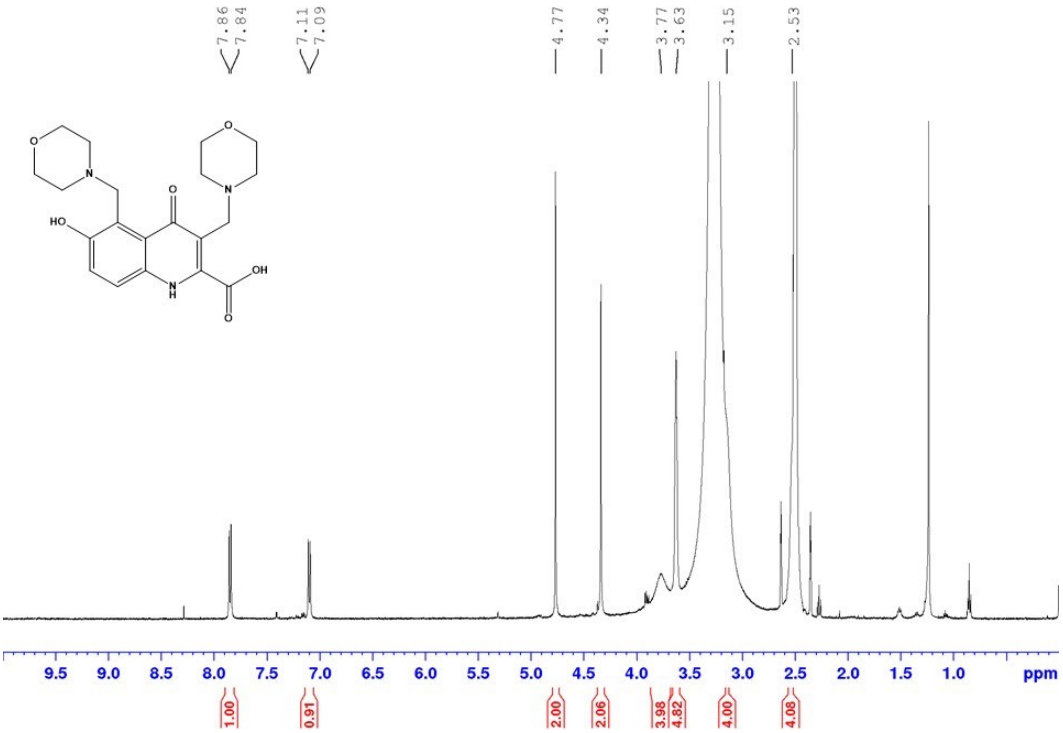

Figure S9. ^{1}H-NMR spectrum of **3b**

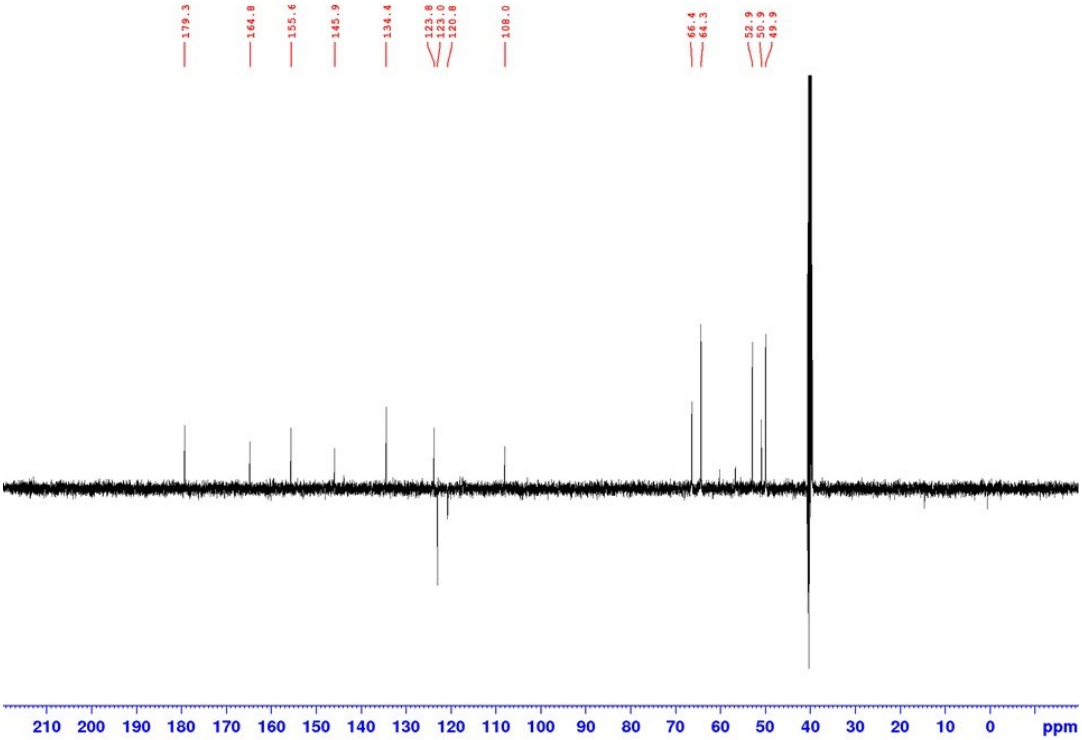

Figure S10. ^{13}C-NMR spectrum of **3b**

Ethyl 5-hydroxy-6-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylate (4a)

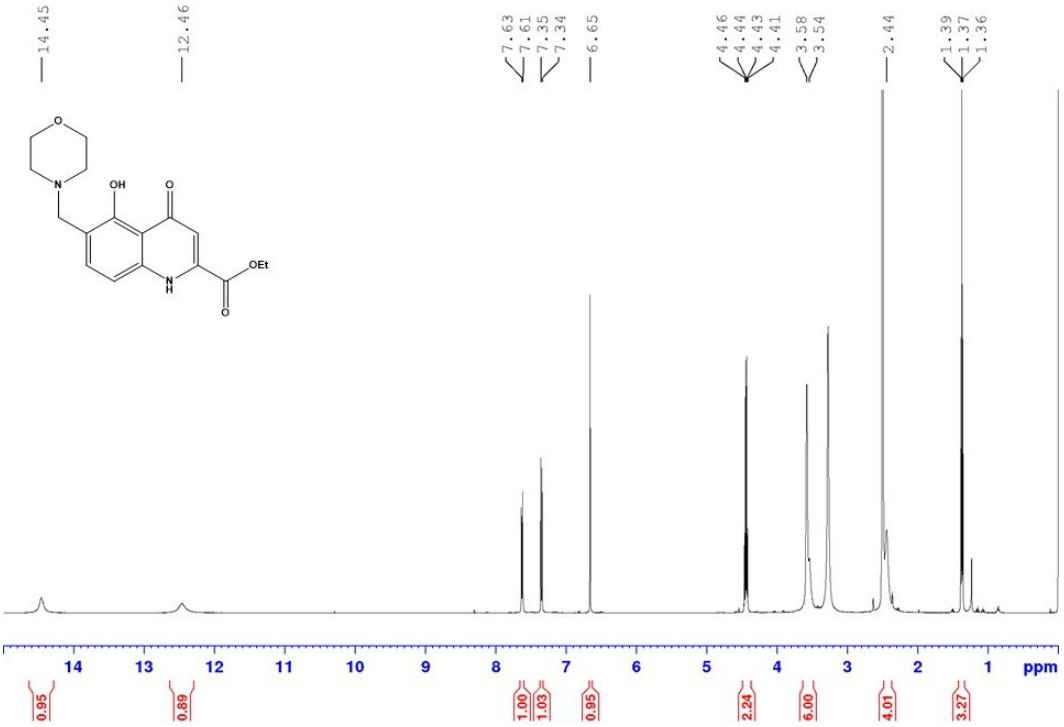

Figure S11. ^{1}H-NMR spectrum of **4a**

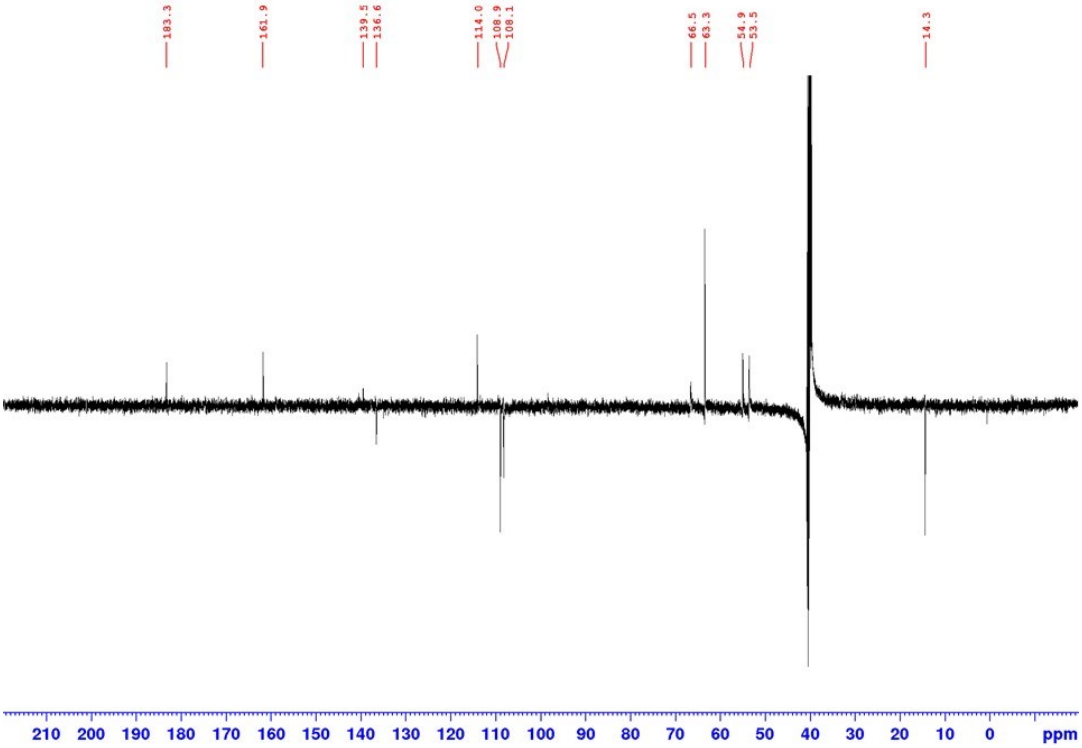

Figure S12. ^{13}C-NMR spectrum of **4a**

5-Hydroxy-3,6-bis(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (4b)

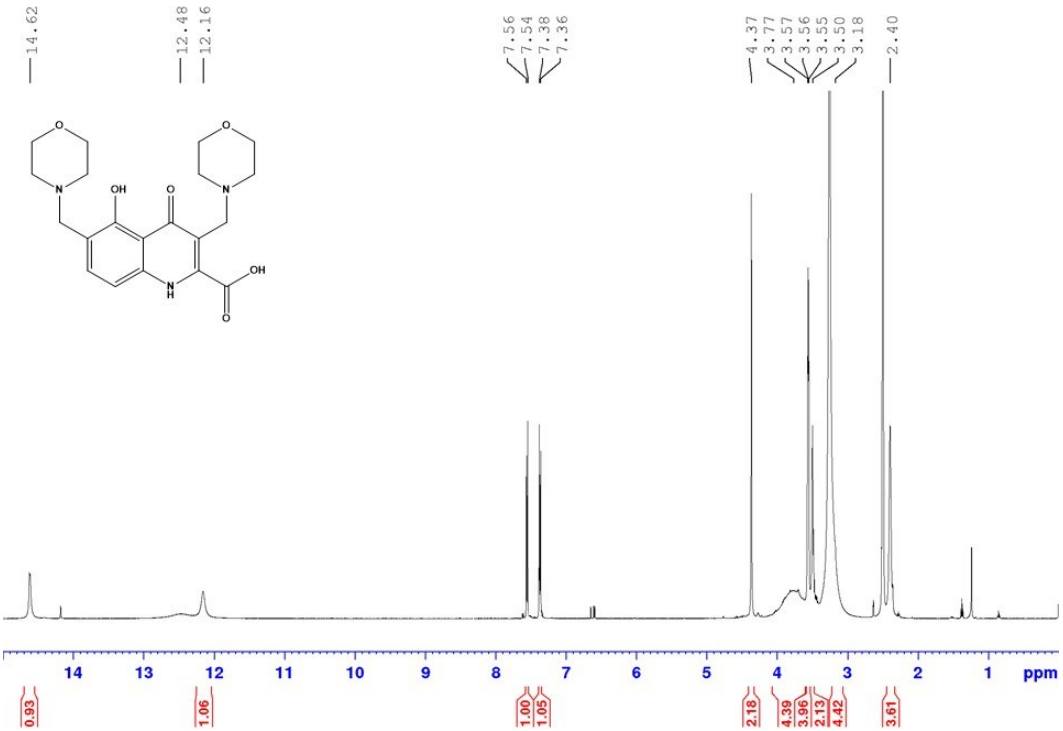

Figure S13. ^{1}H-NMR spectrum of **4b**

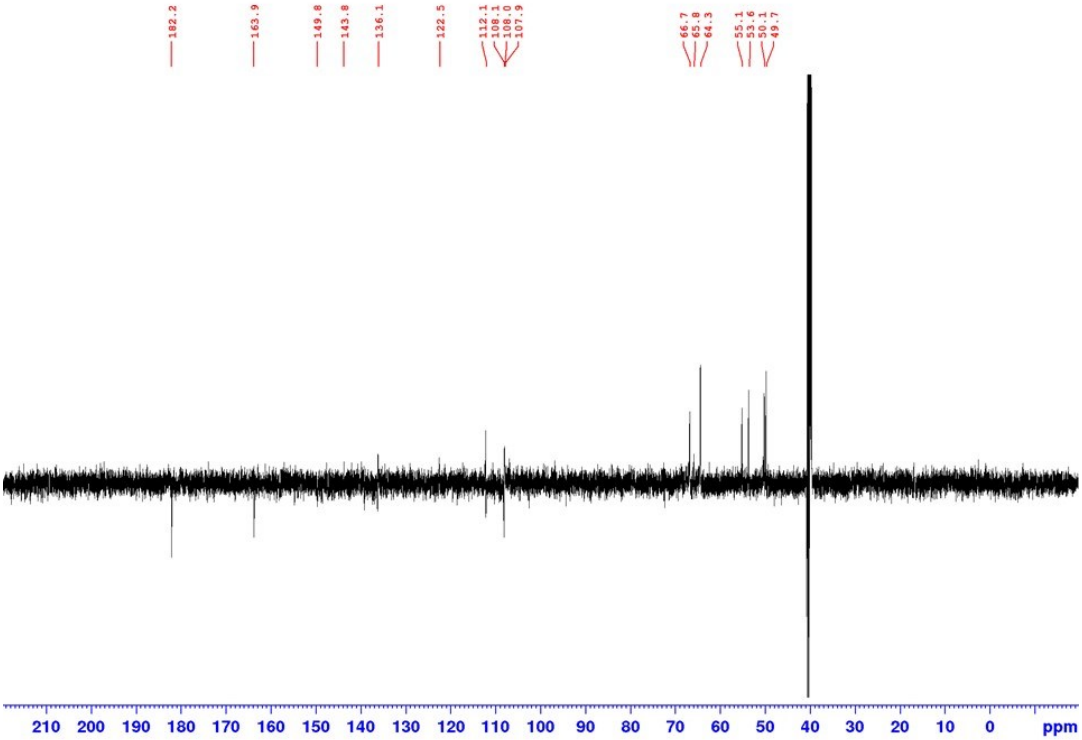

Figure S14. ^{13}C-NMR spectrum of **4b**

Ethyl 7-hydroxy-8-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylate (5a)

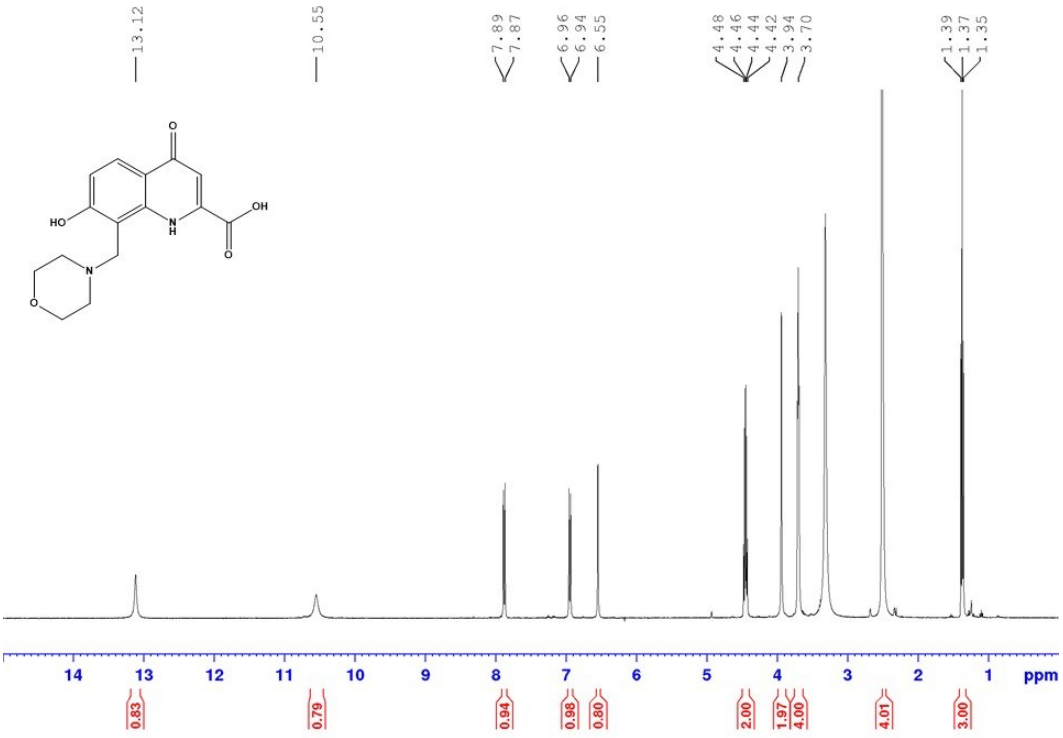

Figure S15. ^{1}H-NMR spectrum of **5a**

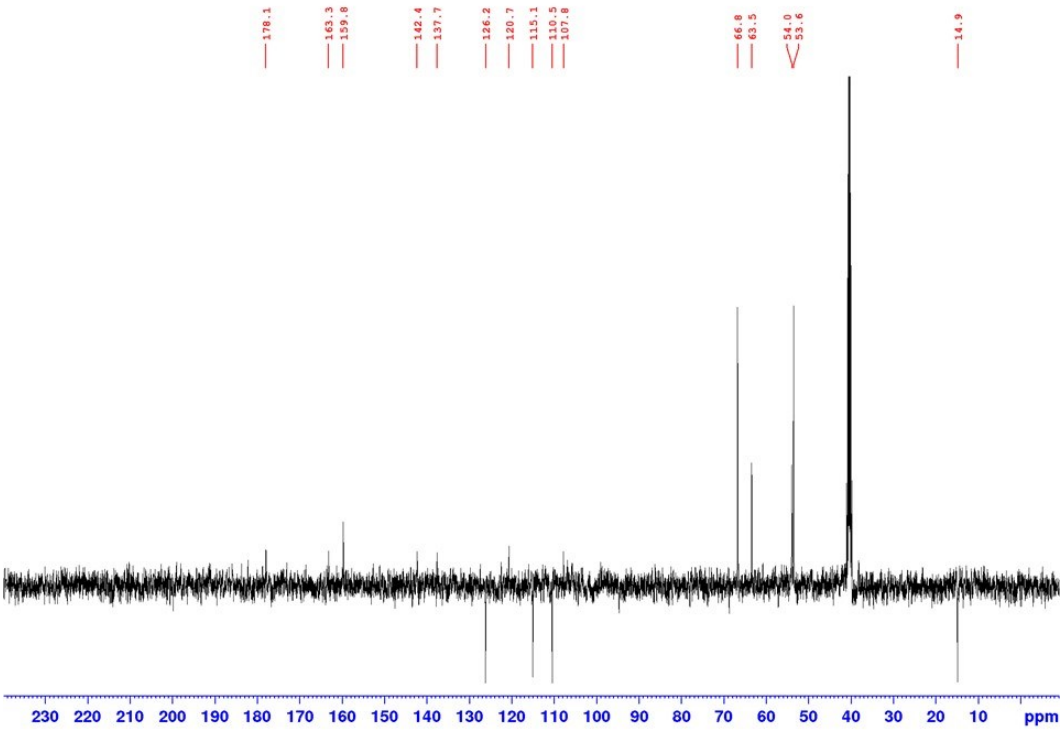

Figure S16. ^{13}C-NMR spectrum of **5a**

7-Hydroxy-3,8-bis(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (5b)

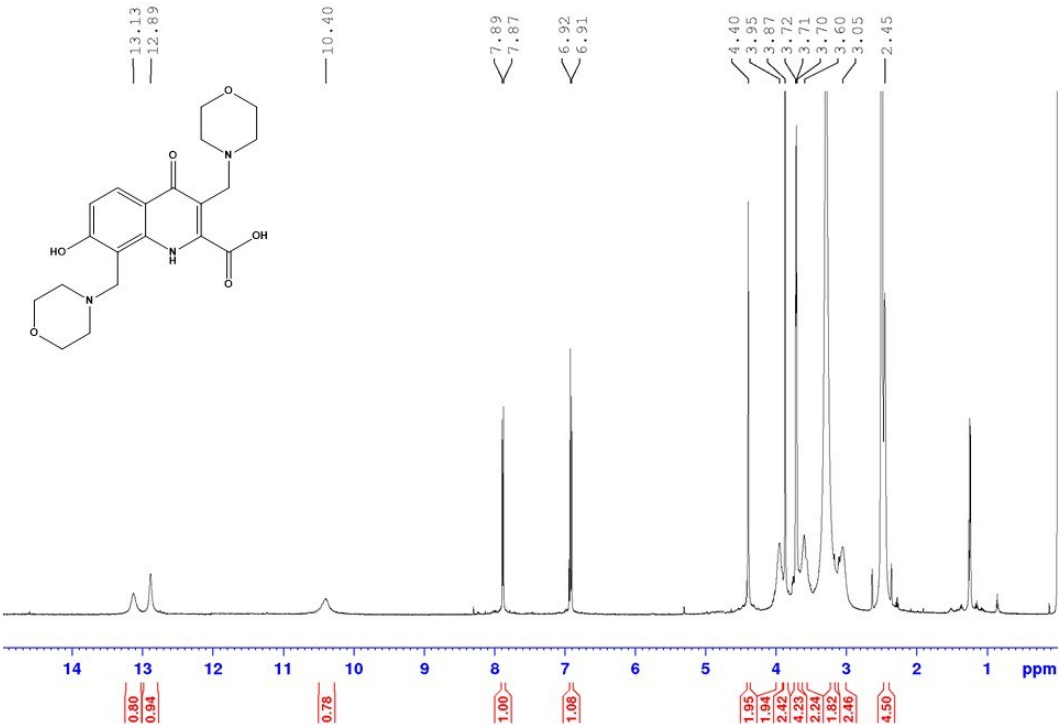

Figure S17. ^{1}H-NMR spectrum of **5b**

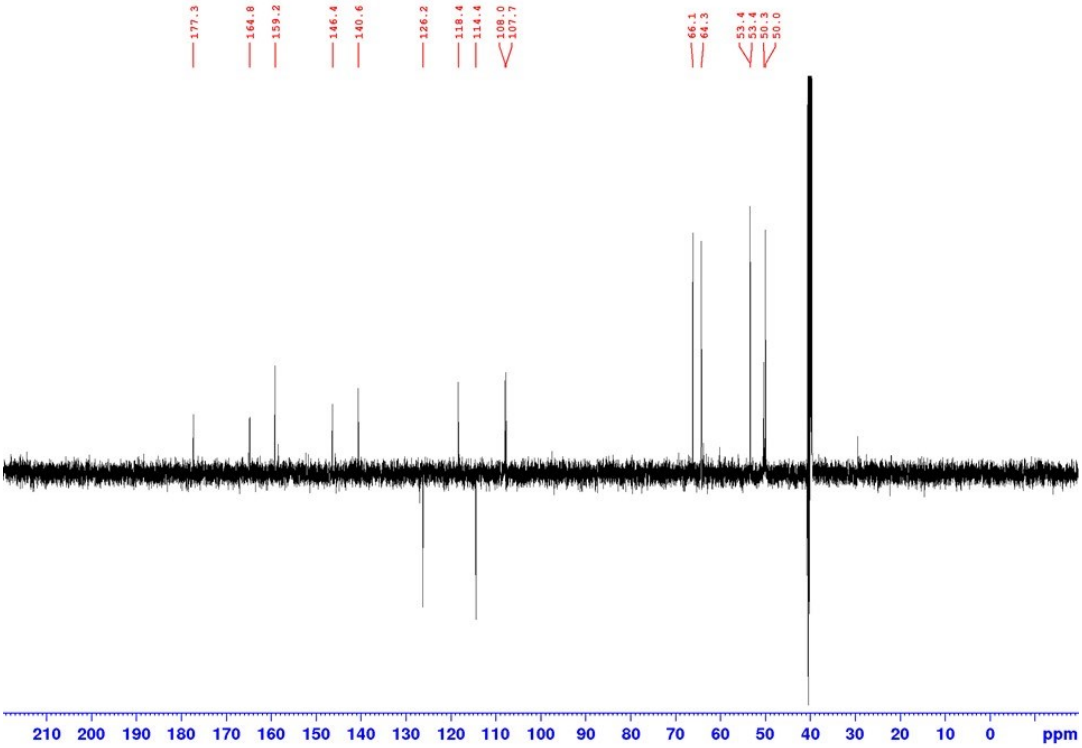

Figure S18. ^{13}C-NMR spectrum of **5b**

Ethyl 4-ethoxy-8-hydroxyquinoline-2-carboxylate (7a)

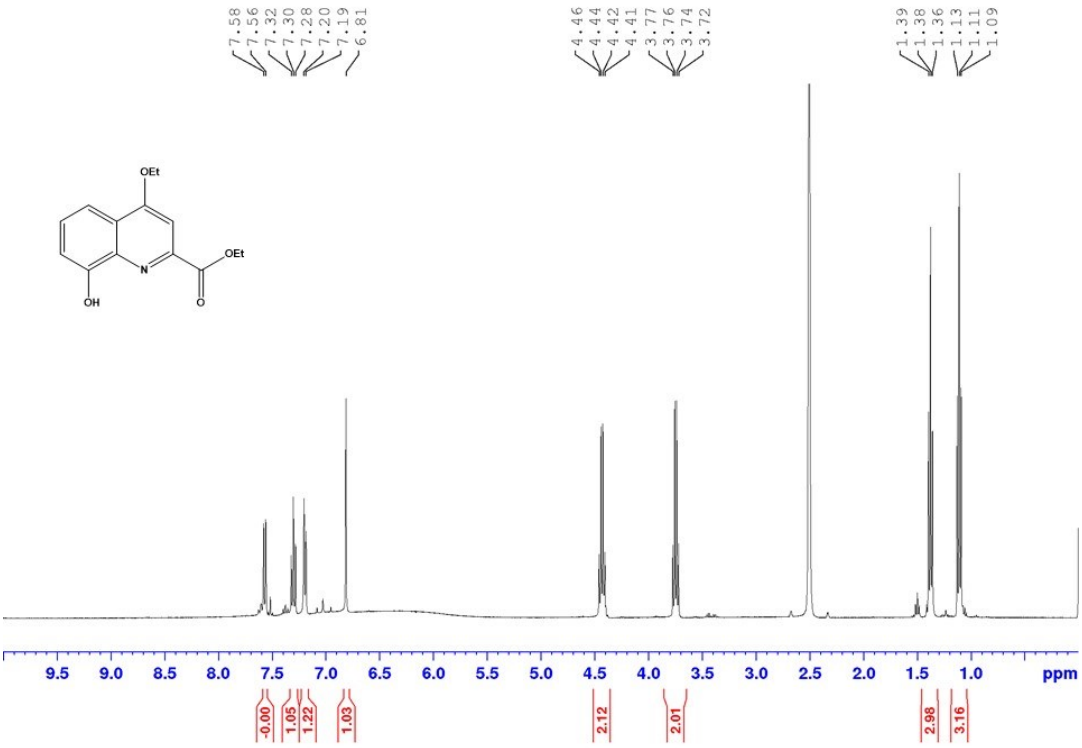

Figure S19. ^{1}H-NMR spectrum of **7a**

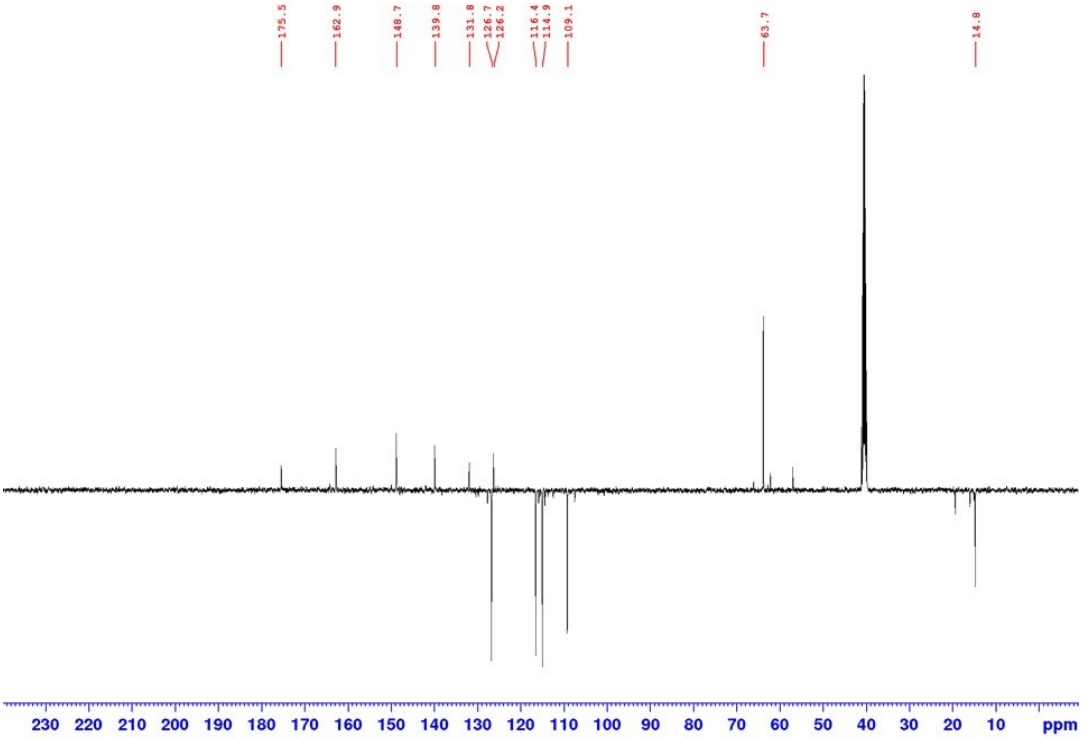

Figure S20. ^{13}C-NMR spectrum of **7a**

Methyl 8-hydroxy-4-methoxyquinoline-2-carboxylate (7b)

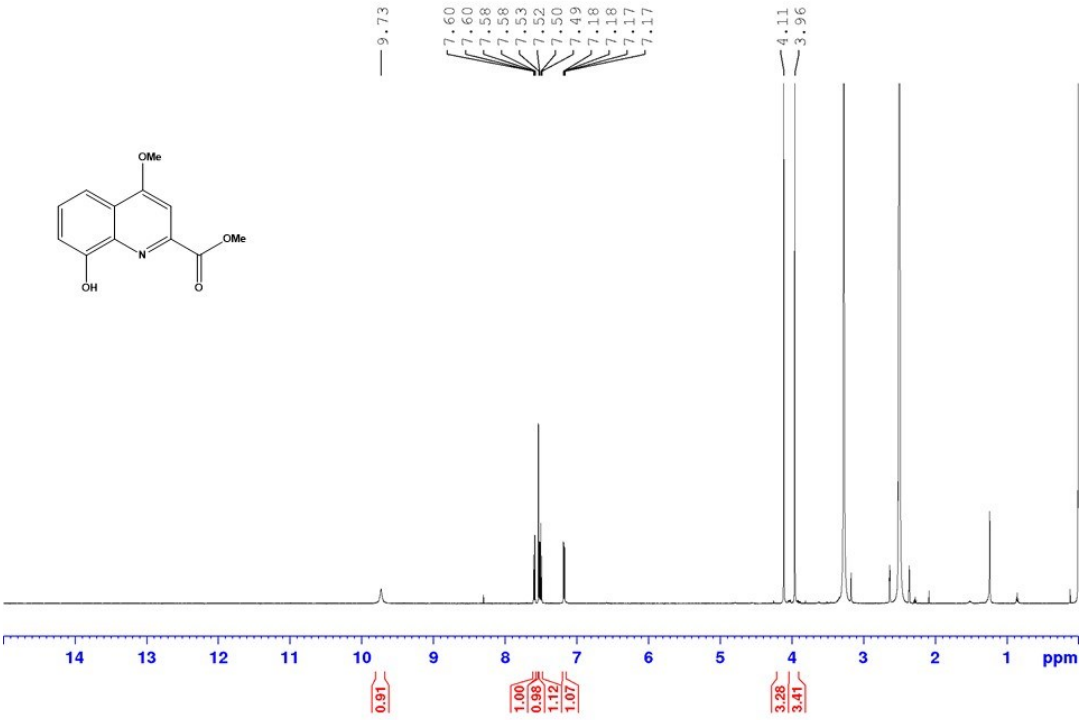

Figure S21. ^{1}H-NMR spectrum of **7b**

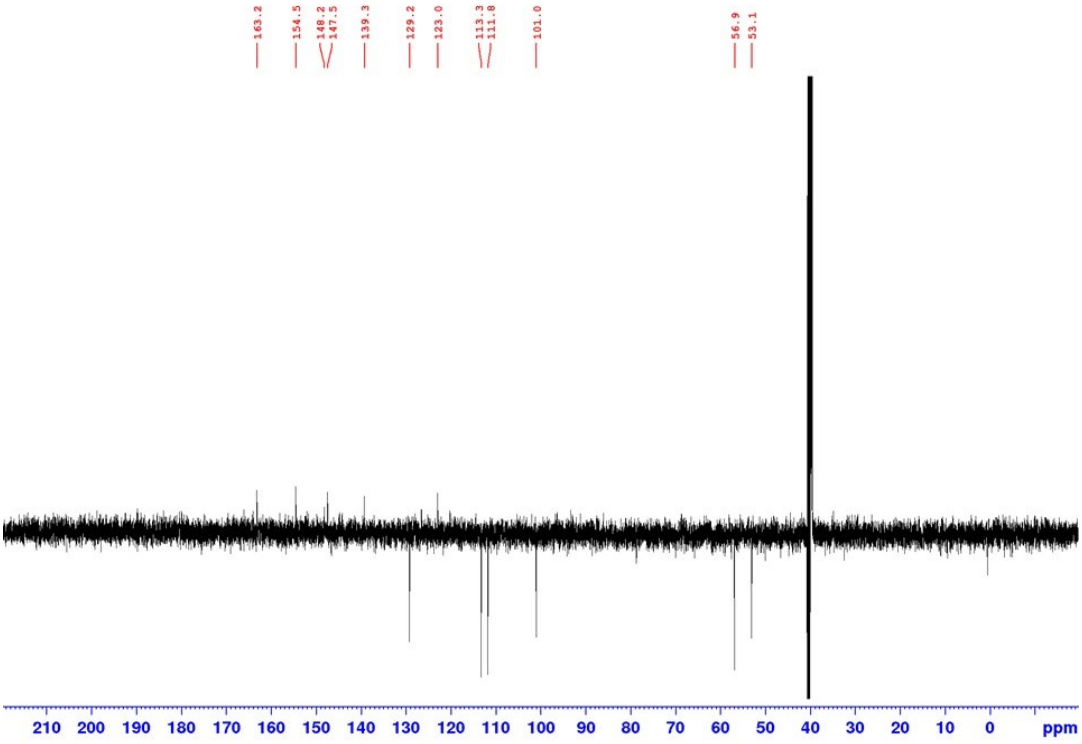

Figure S22. ^{13}C-NMR spectrum of **7b**

Ethyl 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (8a)

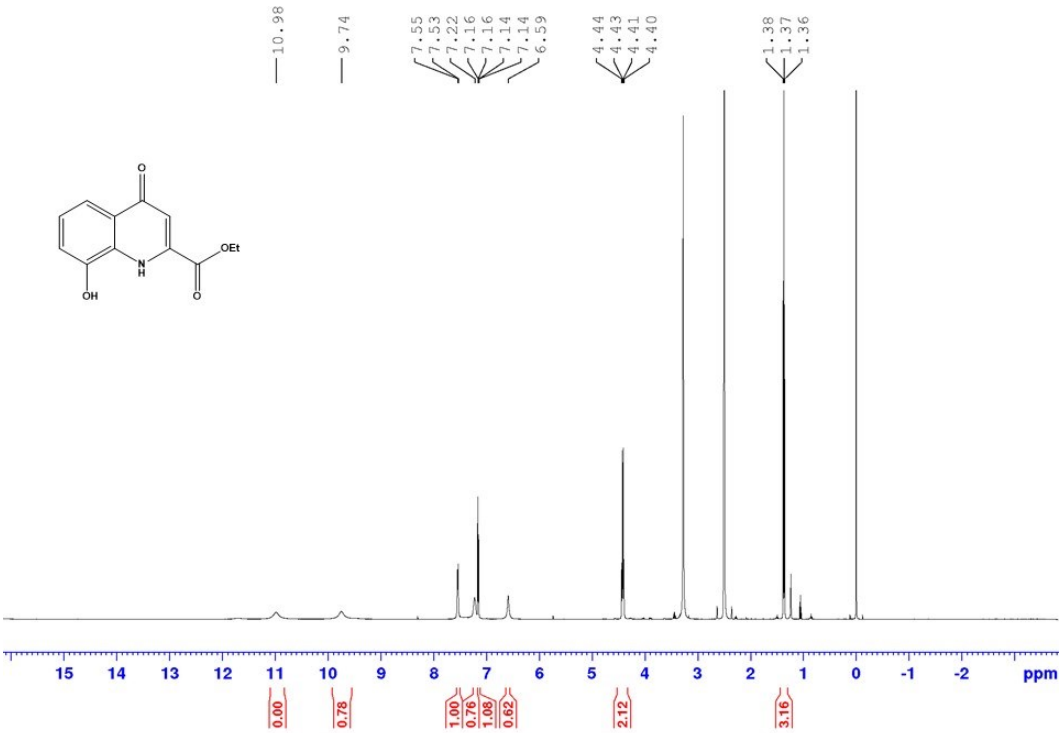

Figure S23. ^{1}H-NMR spectrum of **8a**

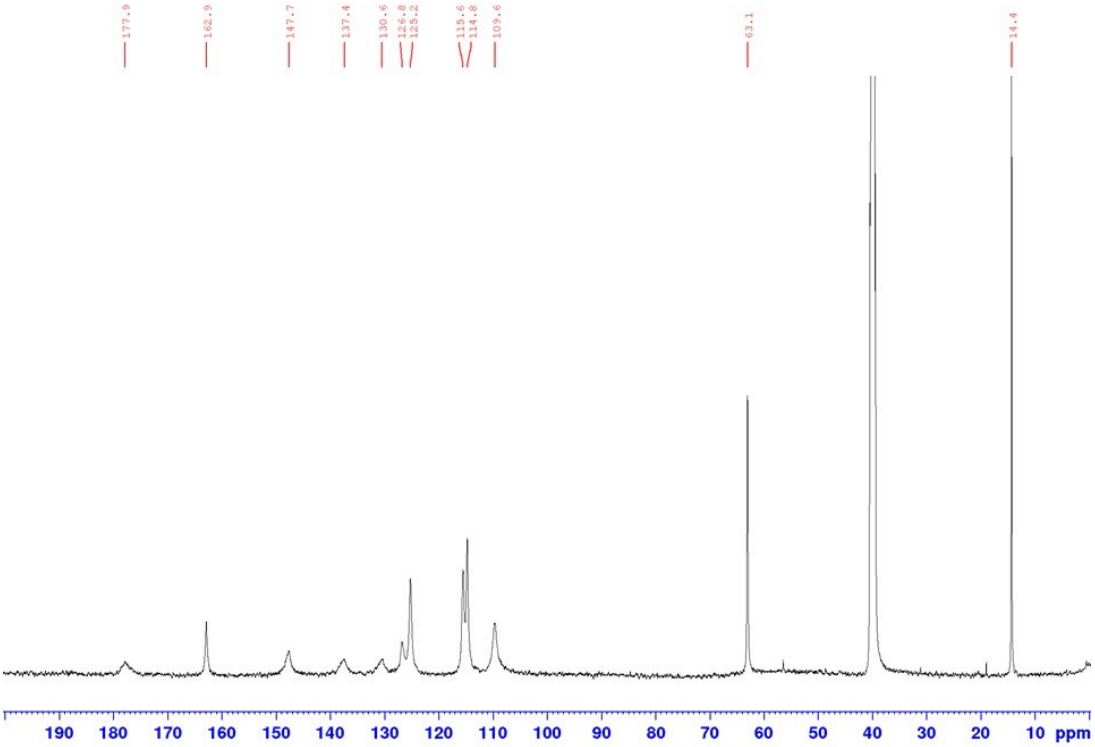

Figure S24. ^{13}C-NMR spectrum of **8a**

Methyl 8-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (8b)

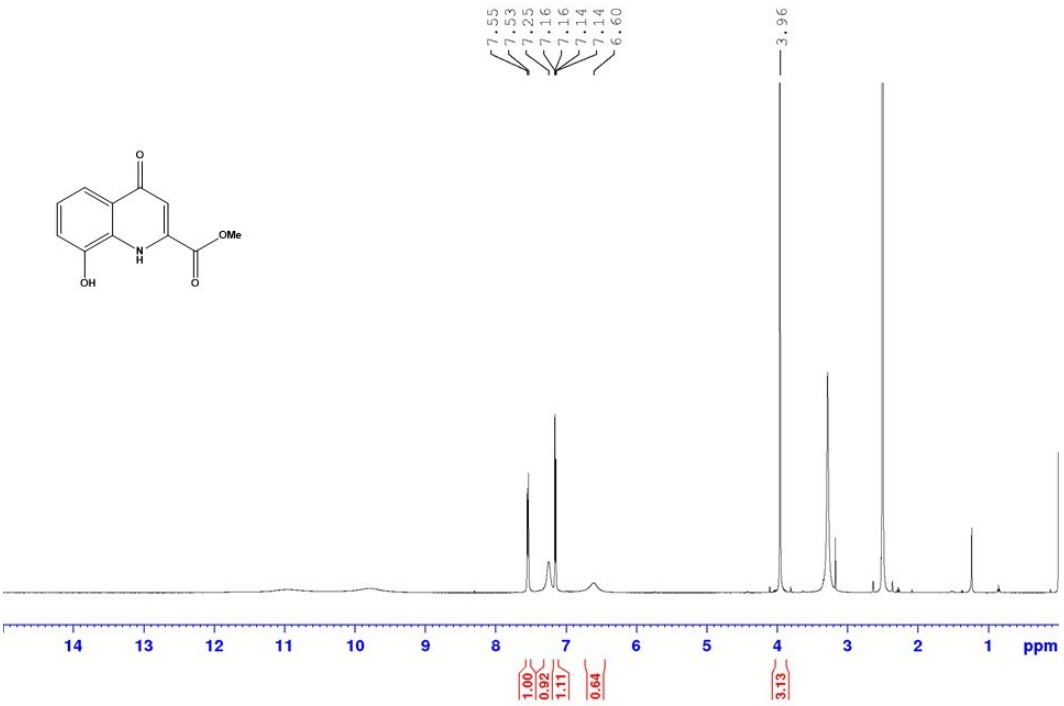

Figure S25. ^{1}H-NMR spectrum of **8b**

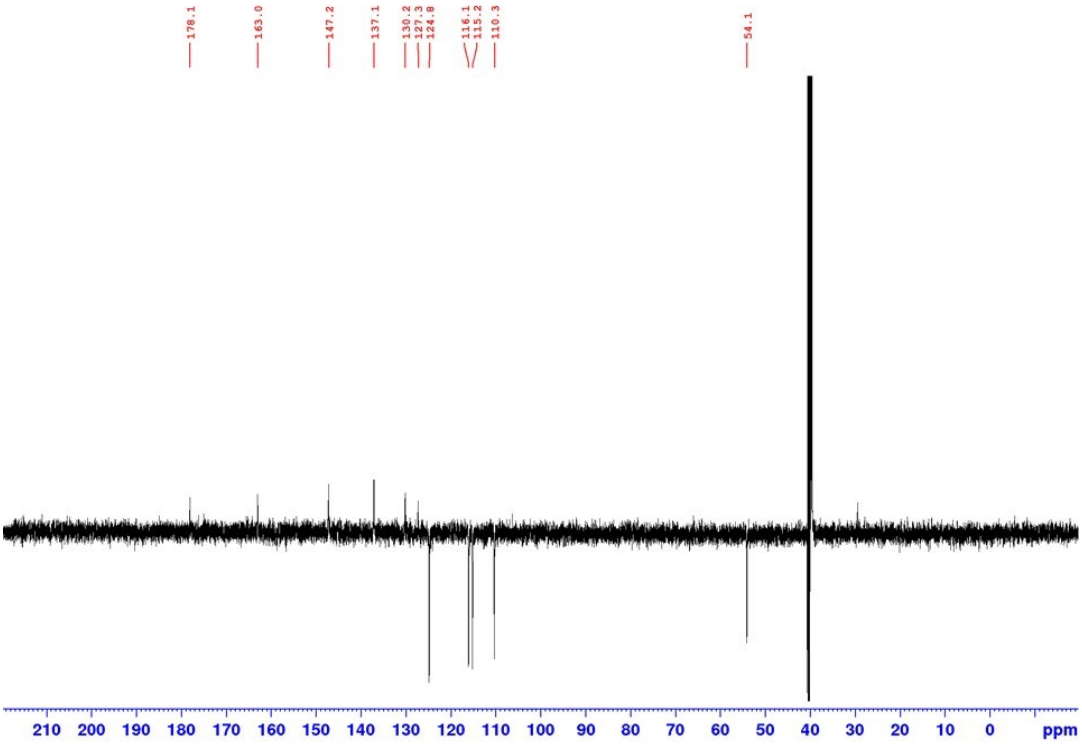

Figure S26. ^{13}C-NMR spectrum of **8b**

8-Hydroxy-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (9a)

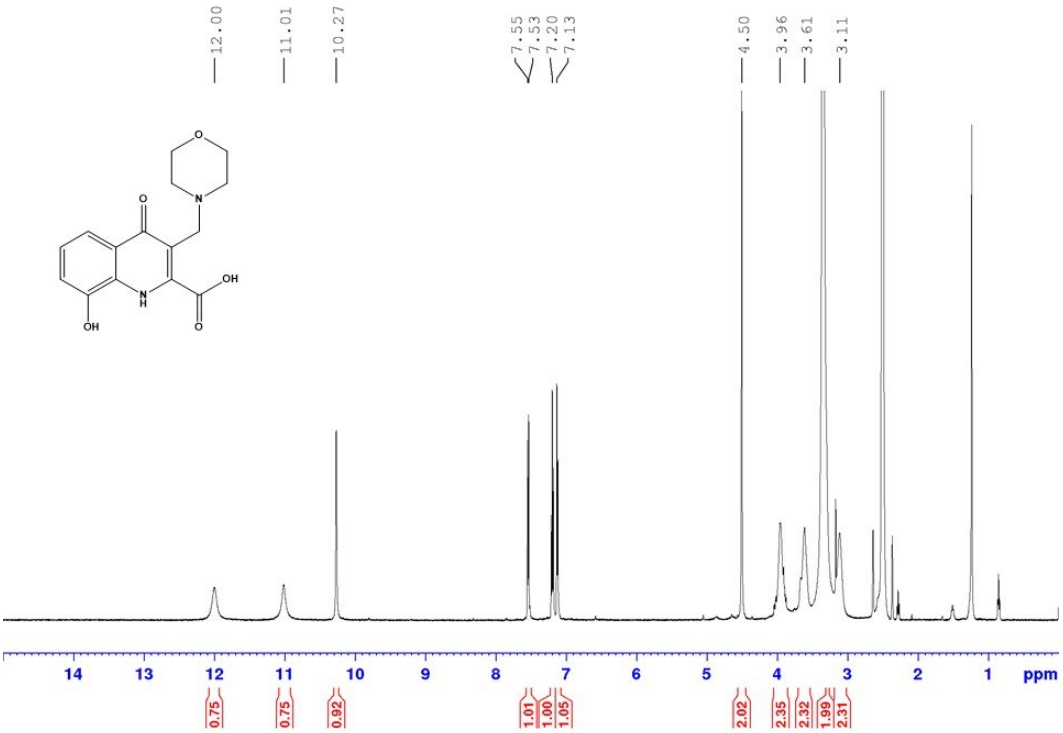

Figure S27. ^{1}H-NMR spectrum of **9a**

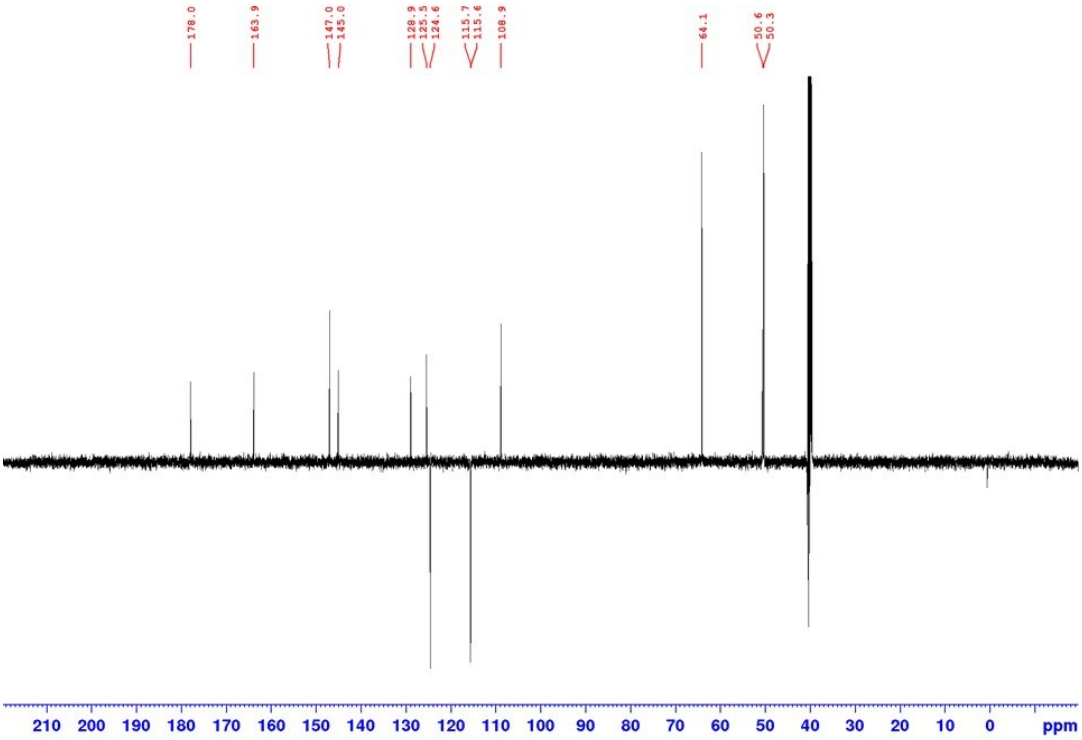

Figure S28. ^{13}C-NMR spectrum of **9a**

8-Hydroxy-3,7-bis(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxylic acid (9b)

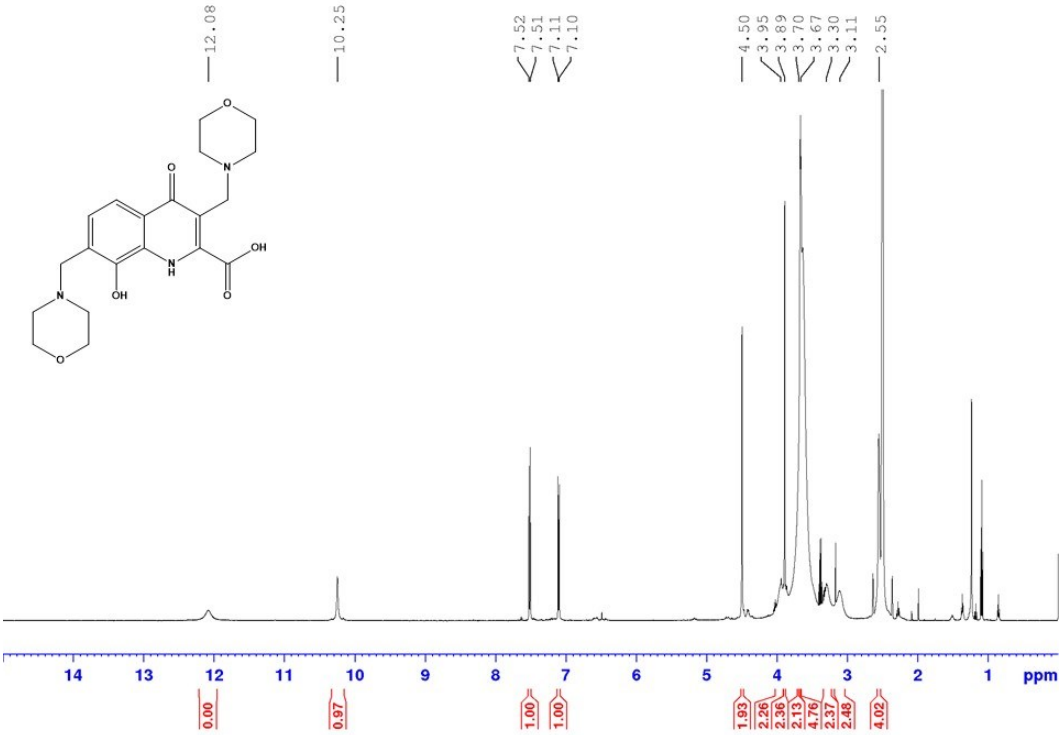

Figure S29. ^{1}H-NMR spectrum of **9b**

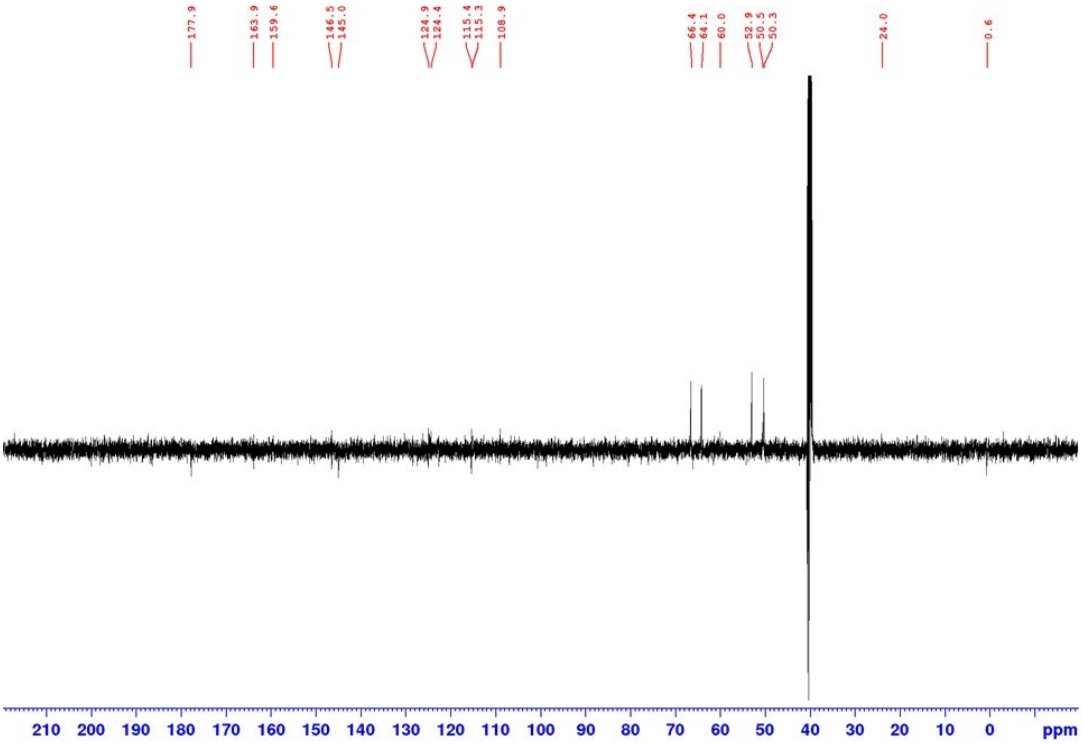

Figure S30. ^{13}C-NMR spectrum of **9b**