Supporting information for

Synthesis and Herbicidal Activity of Triketone-Quinoline Hybrids as Novel 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors

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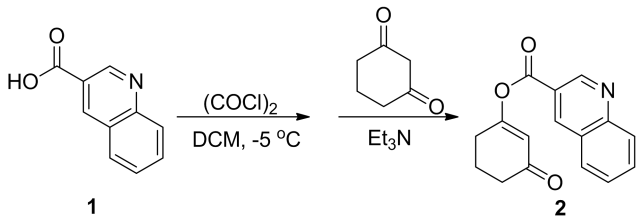
Contents:

Table S1. Calculated ClogP of compounds **I** to **VI**.

compound	R^1	R^2	R^3	CLogP[a]
I	H	H	H	1.9226
II-a	5,5-diCH_3	OCH_3	6-OCH_3	3.9804
II-b	5,5-diCH_3	OCH_3	7-OCH_3	3.9804
II-c	5,5-diCH_3	OCH_3	6-Cl	4.4540
II-d	5,5-diCH_3	OCH_3	7-SH_3	4.4311
II-e	5,5-diCH_3	OCH_3	8-CH_2CH_3	4.7624
II-f	5,5-diCH_3	OCH_3	8-$CH(CH_3)_2$	5.1614
II-g	5,5-diCH_3	OCH_3	7-F-8-CH_3	4.3830
II-h	5,5-diCH_3	OCH_3	7-Cl-8-CH_3	4.9530
II-i	5,5-diCH_3	OCH_3	7-Br-8-CH_3	5.1030
II-j	5,5-diCH_3	OCH_3	8-CH_3	4.2334
II-k	5-CH_3	OCH_3	8-CH_3	3.7144
II-l	6,6-diCH_3	OCH_3	8-CH_3	4.2334
III-a	H	OCH_3	8-CH_3	3.1954
III-b	H	OCH_2H_3	8-CH_3	3.7244
III-c	H	O-*n*-Pr	8-CH_3	4.2534
III-d	H	OCH_2Ph	8-CH_3	4.5634
III-e	H	OCH_3	H	2.6964
III-f	H	OCH_3	6-CH_3	3.1954
III-g	H	OCH_3	7-CH_3	3.1954
III-h	H	OCH_3	6-OCH_3	2.9424
III-i	H	OCH_3	7-OCH_3	2.9424
III-j	H	OCH_3	6-Cl	3.4160
III-k	H	OCH_3	7-Cl	3.4160
III-l	H	OCH_3	7-SCH_3	3.3931
III-m	H	OCH_3	8-CH_2CH_3	3.7244
III-n	H	OCH_3	8-$CH(CH_3)_2$	4.1234
III-o	H	OCH_3	5,8-diCH_3	3.6944
III-p	H	OCH_3	6,8-diCH_3	3.6944
III-q	H	OCH_3	7,8-diCH_3	3.6444
III-r	H	OCH_3	7-F-8-CH_3	3.3450
III-s	H	OCH_3	7-Cl-8-CH_3	3.9150
III-t	H	OCH_3	7-Br-8-CH_3	4.0650
IV-a	H	CH_3	8-CH_3	2.9206
IV-b	5-CH_3	CH_3	8-CH_3	3.4396
V	H	CF_3	8-CH_3	3.3699
VI-a	H	CN	8-CH_3	2.1686
VI-b	5-CH_3	CN	8-CH_3	2.6876

[a]Data calculated by ChemBioDraw Ultra 12.0 version.

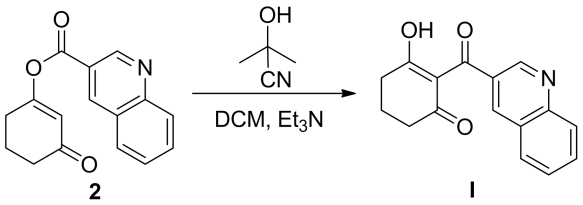
Materials and instrumentation. All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried and redistilled before use. Silica gel column chromatography (CC) (silica gel 200–300 mesh) (Qingdao Makall Group Co., Ltd, Qingdao, China). ^{1}H NMR spectra were recorded on a VARIAN Mercury-Plus 600 or 400 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference, ^{13}C NMR spectra were recorded in $CDCl_3$ on a VARIAN Mercury-Plus 400 (101 MHz) spectrometer, and chemical shifts (δ) are given in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on an Agilent 6224 TOF LC/MS (USA). Melting points were taken on a Buchi B-545 melting point apparatus and are uncorrected.



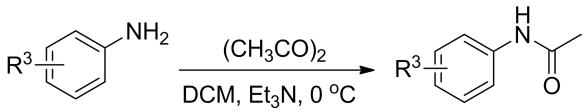
Synthesis of 3-oxocyclohex-1-en-1-yl quinoline-3-carboxylate 2.[1] Quinoline-3-carboxylic acid **1** (2 mmol), DMF (0.05 mL) and DCM (40 mL) were added to a round bottom flask. The resulting mixture was cooled to -5 °C, then $(COCl)_2$ (3 mmol) was added to the mixture over 10 min with stirring. The suspension was then stirred at this temperature for another 5 h. The solvent of the reaction was removed under reduced pressure to afford quinoline-3-carbonyl chloride; the acid chloride was then dissolved in DCM (20 mL). And the solution was added drop-wise to a solution of cyclohexane-1,3-dione (2 mmol) and Et_3N (4 mmol) in DCM (20 mL) at 0 °C. The mixture was further stirred at this temperature for 30 min. After the reaction was completed according to the TLC detection, water (40 mL) was

(1) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490-3493.

added to the solution, and the mixture was stirred for another 30 min. The organic layer was washed successively with sat. aqueous $NaHCO_3$ (40 mL) for two times, brine (40 mL), dried by anhydrous Na_2SO_4, concentrated by rotary evaporation. The residue was purified *via* flash chromatography to give intermediate **2** as white solid (0.43 g, yield 80%), mp 120-122 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.96 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.93 (t, J = 7.8 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 6.14 (s, 1H), 2.76 (t, J = 6.0 Hz, 2H), 2.51 (t, J = 6.6 Hz, 2H), 2.19 (quintuplet, J = 6.6 Hz, 2H).



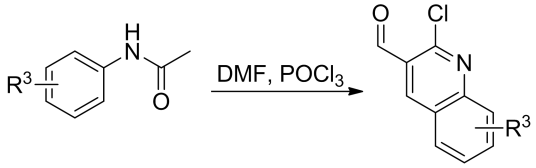
Synthesis of lead compound 3-hydroxy-2-(quinoline-3-carbonyl)cyclohex-2-enone I. **Intermediate 2** (0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) with stirring, Et_3N (1.5 mmol) and acetone cyanohydrin (0.05 mmol) were added to the solution, and the mixture was stirred under N_2 atmosphere for 12 h. After completion of the reaction according to TLC detection, the reaction solution was washed by aqueous HCl solution (20 mL, 1 mol/L) for three times, and brine (20 mL) for two times, dried by anhydrous Na_2SO_4 and concentrated by rotary evaporation. The residue was purified *via* flash chromatography to give **I** as light yellow solid (0.11g, yield 68%), mp 150-152 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 17.00 (s, 1H), 8.95 (s, 1H), 8.46 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 2.81 (brs, 2H), 2.58 (brs, 2H), 2.14 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.29, 195.32, 148.81, 148.55, 136.65, 131.19, 128.93, 128.85, 126.96, 126.45, 113.18, 35.01, 18.78. HRMS (ESI): calcd for $C_{16}H_{13}NO_3$ $[M+H]^+$ 268.0974, found: 268.0947.



3a-q **4a-q**

General procedure for the preparation of (substituted) *N*-phenylacetamides 4a-q.

The known compounds **4a-q** were prepared according to the following reported method:[1,2,3] to a solution of (substituted) anilines **3a-q** (50 mmol), Et_3N (150 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Ac_2O (75 mmol) with stirring. After the reaction was completed based on the TLC detection, the mixture was poured into ice (150 g) and stirred vigorously for another 30 min. The organic layer was then washed sequentially with HCl (100 mL, 1 mol/L), sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried by anhydrous Na_2SO_4 and concentrated by rotary evaporation to generate the corresponding **4a-q**.



4a-q **5a-q**

General procedure for the preparation of intermediates 5a-q. In a round bottom flask equipped with a mechanical stirrer and a reflux condenser was added DMF (100 mmol) at 0 °C, and $POCl_3$ (280 mmol) was added drop-wise to the solution over 30 min; the reaction mixture was then stirred for another 30 min at this temperature. **4a-q** (40 mmol) was added to the mixture over 10 min, and then the reaction solution was slowly heated to 80 °C for 6 h.

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(1) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475.

(2) Rizvi, S. U. F.; Siddiqui, H. L.; Nisar, M.; Khan, N.; Khan, I. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 942-944.

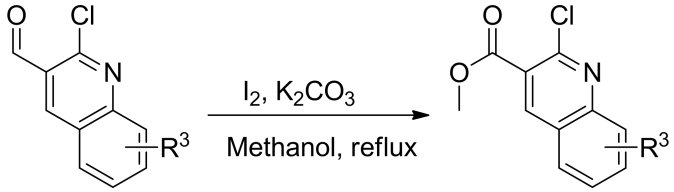
(3) Havlík, M.; Král, V.; Kaplánek, R.; Dolenský, B. *Org. Lett.* **2008**, *10*, 4767-4769.

After completing the reaction according to TLC detection, the mixture was poured into ice (500 g), and stirred vigorously for another 30 min. The resulted solid was filtrated, washed with H_2O (100 mL) and dried in vacuum, recrystallized from ethyl acetate to afford **5a-q** in yields of 30-80%.

Table S2. Chemical Structures, Physical and ^{1}H NMR data of intermediates 5a-q.

compound	R^3	Appearance	Yield/%	mp/°C	^{1}H NMR
5a	6-OCH_3	light yellow solid	60	145-147	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.66 (s, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.53 (dd, J = 9.0, 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H).
5b	7-OCH_3	light yellow solid	48	195-197	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.67 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.38 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H).
5c	6-Cl	light brown solid	48	188-190	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.68 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 7.82 (dd, J = 9.0, 2.0 Hz, 1H).
5d	7-SCH_3	yellow solid	67	193-195	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.66 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 2.62 (s, 3H).
5e	8-CH_2CH_3	light yellow solid	70	98-100	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.73 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 3.28 (q, J = 7.2 Hz, 2H), 1.58 (s, 2H), 1.38 (t, J = 7.8 Hz, 3H).
5f	8-$CH(CH_3)_2$	white solid	58	93-95	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.73 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 4.20-4.20 (m, 1H), 1.38 (d, J = 7.2 Hz, 6H).
5g	7-F-8-CH_3	light yellow solid	65	160-162	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.71 (s, 1H), 7.83 (dd, J = 9.0, 6.0 Hz, 1H), 7.41 (t, J = 9.0 Hz, 1H), 2.68 (d, J = 1.8 Hz, 3H).
5h	7-Cl-8-CH_3	light brown solid	50	160-162	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.69 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 2.85 (s, 3H).

5i	7-Br-8-CH_3	light yellow solid	60	159-161	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.69 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 2.90 (s, 3H).
5j	8-CH_3	white solid	68	135-137	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.71 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 2.79 (s, 3H).
5k	H	light brown solid	80	146-148	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.77 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.90 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H).
5l	6-CH_3	white solid	80	122-124	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.66 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 10.8 Hz, 2H), 2.57 (s, 3H).
5m	7-CH_3	white solid	60	145-147	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.68 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.74 (s, 1H), 7.72 (d, J = 9.0 Hz, 1H), 2.57 (s, 3H).
5n	7-Cl	light yellow solid	60	159-161	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.06 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 4.02 (s, 3H).
5o	5,8-di-CH_3	light brown solid	67	184-186	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.90 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 2.74 (s, 3H), 2.71 (s, 3H).
5p	6,8-di-CH_3	light yellow solid	50	111-113	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.63 (s, 1H), 7.57 (s, 2H), 2.76 (s, 3H), 2.52 (s, 3H).
5q	7,8-di-CH_3	light yellow solid	63	154-156	^{1}H NMR (600 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.67 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 2.73 (s, 3H), 2.54 (s, 3H).



5a-q **6a-q**

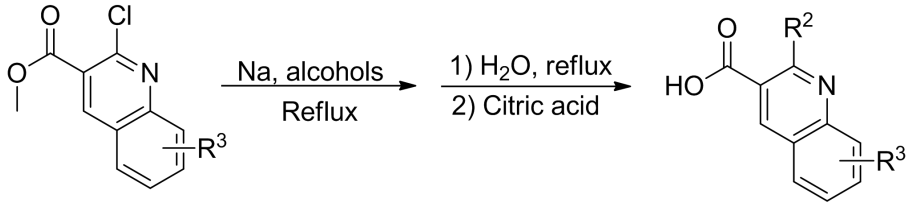
General procedure for the preparation of intermediates 6a-q. In a round bottom flask were added **5a-q** (20 mmol), I_2 (50 mmol), methanol

(40 mL) and K_2CO_3 (50 mmol). The suspension was heated to reflux with stirring for 10 h. After completion the reaction according to TLC detection, the mixture was cooled to room temperature, and quenched with sat. aqueous $Na_2S_2O_3$ (50 mL). The resulted solid was collected by filtration and washed with water, then dried under vacuum to afford the corresponding **6a-q** in yields of 70-98%.

Table S3. Chemical Structures, Physical and ^{1}H NMR data of intermediates 6a-q.

compound	R^3	Appearance	Yield/%	mp/°C	^{1}H NMR
6a	6-OCH_3	light yellow solid	90	104-106	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 4.00 (s, 3H), 3.97 (s, 3H).
6b	7-OCH_3	light yellow solid	78	117-119	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H).
6c	6-Cl	white solid	80	135-137	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.88 (s, 1H), 7.77 (d, J = 9.0 Hz, 1H), 4.02 (s 3H).
6d	7-SCH_3	light yellow solid	90	143-145	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.44 (d, J = 9.0 Hz, 1H), 4.00 (s, 3H), 2.61 (s, 3H).
6e	8-CH_2CH_3	light yellow solid	80	51-53	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 6.6 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 4.01 (s, 3H), 3.26 (q, J = 7.8 Hz, 2H), 1.37 (t, J = 7.8 Hz, 3H).
6f	8-$CH(CH_3)_2$	light brown solid	85	49-51	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.75 – 7.69 (m, 2H), 7.58 (t, J = 7.8 Hz, 1H), 4.28 – 4.20 (m, 1H), 4.01 (s, 3H), 1.37 (d, J = 7.2 Hz, 6H).
6g	7-F-8-CH_3	white solid	88	152-154	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.74 (dd, J = 9.0, 6.0 Hz, 1H), 7.38 (t, J = 9.0 Hz, 1H), 4.01 (s, 3H), 2.67 (d, J = 1.8 Hz, 3H).
6h	7-Cl-8-CH_3	white solid	70	145-147	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 2.84 (s, 3H).
6i	7-Br-8-CH_3	white solid	93	148-150	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 2.88 (s, 3H).
6j	8-CH_3	white solid	98	103-105	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68

					(d, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 4.01 (s, 3H), 2.78 (s, 3H).
6k	H	white solid	95	79-81	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 4.02 (s, 3H).
6l	6-CH_3	white solid	84	76-78	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.62 (m, 2H), 4.01 (s, 3H), 2.55 (s, 3H).
6m	7-CH_3	white solid	97	64-66	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.84 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 4.01 (s, 3H), 2.59 (s, 3H).
6n	7-Cl	light yellow soli	90	120-122	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.06 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.4Hz, 1H), 4.02 (s, 3H).
6o	5,8-di-CH_3	white solid	95	164-166	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 4.02 (s, 3H), 2.72 (s, 3H), 2.67 (s, 3H).
6p	6,8-di-CH_3	white soild	98	100-102	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 4.00 (s, 3H), 2.74 (s, 3H), 2.50 (s, 3H).
6q	7,8-di-CH_3	white solid	90	106-108	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 3H), 2.72 (s, 3H), 2.53 (s, 3H).



6a-q **7a-t**

General procedure for the preparation of intermediates 7a-t. In a round bottom flask was added appropriate alcohols (methanol, ethanol, n-propanol or phenylmethanol) (20 mL), and Na (25 mmol) was added into the solution with stirring. After stirring at room temperature for 30 min, **6a-q** (10 mmol) was added to the solution, and then the mixture was heated to reflux for 6 h. After completing the reaction according to

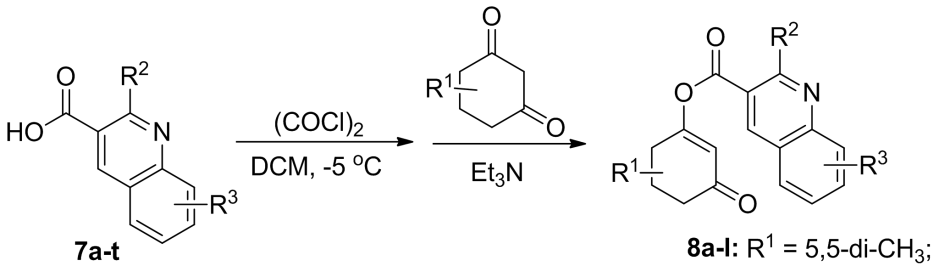
TLC detection, water (20 mL) was added to the solution, the reaction mixture was then heated to reflux for another 3 h. After the reaction was completed according to TLC detection, the solvent of the reaction was condensed to 20 mL under reduced pressure. The mixture was then acidified with saturated aqueous citric acid to pH = 2-3. The resulted solid was collected by filtration, washed with water, dried in vacuum, recrystallized from methanol to afford **7a-t** in yields of 64-98%.

Table S4. Chemical Structures, Physical and ^{1}H NMR data of intermediates 7a-t.

compound	R^2	R^3	Appearance	Yield/%	mp/°C	^{1}H NMR
7a	OCH_3	6-OCH_3	yellow solid	88	167-169	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.62 (s, 1H), 7.73 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.41 (dd, J = 9.0, 3.0 Hz, 1H), 4.00 (s, 3H), 3.87 (s, 3H).
7b	OCH_3	7-OCH_3	light brown solid	82	154-156	^{1}H NMR (600 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.67 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.12 (dd, J = 9.0, 1.8 Hz, 1H), 4.02 (s, 3H), 3.93 (s, 3H).
7c	OCH_3	6-Cl	white solid	85	156-158	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.04 (brs, 1H), 8.70 (s, 1H), 8.17 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 9.0, 2.4 Hz, 1H), 4.03 (s, 3H).
7d	OCH_3	7-SCH_3	light brown solid	92	159-161	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.67 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H), 2.62 (s, 3H).
7e	OCH_3	7-CH_2CH_3	white solid	97	154-156	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (brs, 1H), 8.62 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 6.8 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 4.04 (s, 3H), 3.13 (dd, J = 14.8, 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H).
7f	OCH_3	7-$CH(CH_3)_2$	white solid	81	132-134	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.15 (brs, 1H), 8.70 (s, 1H),

						7.85 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 4.07-4.01 (m, 4H), 1.35 (d, *J* = 6.6 Hz, 6H).
7g	OCH_3	7-F-8-CH_3	white solid	97	214-216	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.75 (s, 1H), 7.97 – 7.92 (m, 1H), 7.38 (t, *J* = 9.2 Hz, 1H), 4.06 (s, 3H), 2.53 (s, 3H).
7h	OCH_3	7-Cl-8-CH_3	white solid	91	220-222	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.32 (brs, 1H), 8.72 (s, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 4.06 (s, 3H), 2.71 (s, 3H).
7i	OCH_3	7-Br-8-CH_3	white solid	98	203-205	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.31 (s, 1H), 8.72 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 4.06 (s, 3H), 2.73 (s, 3H).
7j	OCH_3	8-CH_3	white solid	78	190-192	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.15 (brs, 1H), 8.70 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 4.05 (s, 3H), 2.65 (s, 3H).
7k	OEt	8-CH_3	light brown solid	98	170-172	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.09 (brs, 1H), 8.66 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 4.55 (q, *J* = 7.2 Hz, 2H), 2.63 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).
7l	O-*n*-Pr	8-CH_3	light brown solid	95	118-120	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (brs, 1H), 8.66 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 4.45 (t, *J* = 6.6 Hz, 2H), 2.62 (s, 3H), 1.86 – 1.77 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H).
7m	O-CH_2Ph	8-CH_3	white solid	64	162-164	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.19 (brs, 1H), 8.72 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 6.6 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.42-7.36 (m, 3H), 7.31 (t, *J* = 7.2 Hz, 1H), 5.62 (s, 2H), 2.63 (s, 3H).
7n	O-CH_3	H	white solid	98	186-188	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.72 (s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 4.03 (s, 3H).

7o	O-CH_3	6-CH_3	white solid	76	178-180	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.60 (s, 1H), 7.77 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 2.46 (s, 3H).
7p	O-CH_3	7-CH_3	white solid	70	199-201	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (brs, 1H), 8.65 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.33 (dd, J = 8.0, 1.6 Hz, 1H), 4.01 (s, 3H).
7q	O-CH_3	7-Cl	white solid	86	197-199	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (brs, 1H), 8.65 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.33 (dd, J = 8.0, 1.6 Hz, 1H), 4.01 (s, 3H).
7r	O-CH_3	5,8-di-CH_3	light yellow solid	90	197-199	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.70 (s, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 4.05 (s, 3H), 2.61 (s, 3H), 2.60 (s, 3H).
7s	O-CH_3	6,8-di-CH_3	white solid,	88	215-217	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.19 (brs, 2H), 8.35 (s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 3.99 (s, 3H), 2.60 (s, 3H), 2.41 (s, 3H).
7t	O-CH_3	7,8-di-CH_3	white solid	94	176-178	^{1}H NMR (600 MHz, DMSO-d_6) δ 13.09 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 4.05 (s, 3H), 2.60 (s, 3H), 2.45 (s, 3H).



7a-t

8a-l: R^1 = 5,5-di-CH_3; 5-CH_3; 6,6-di-CH_3

9a-t: R^1 = H;

General procedure for the preparation of intermediates 8a-l and 9a-t. The key intermediates **8a-l** and **9a-t** were obtained by using the same method as the preparation of compound **2**.

Table S5. Chemical Structures, Physical and ^{1}H NMR data of intermediates 8a-l and 9a-t.

compound	R^1	R^2	R^3	Appearance	Yield/%	mp/°C	^{1}H NMR
8a	5,5-di-CH_3	OCH_3	6-OCH_3	white solid	58	103-105	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.42 (dd, J = 9.0, 2.4 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.06 (s, 1H), 4.15 (s, 3H), 3.92 (s, 3H), 2.61 (s, 2H), 2.35 (s, 2H), 1.18 (s, 6H).
8b	5,5-di-CH_3	OCH_3	7-OCH_3	white solid	79	120-122	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.11 (dd, J = 9.0, 2.4 Hz, 1H), 6.05 (s, 1H), 4.23 (s, 3H), 3.99 (s, 3H), 2.60 (s, 2H), 2.34 (s, 2H), 1.17 (s, 6H).
8c	5,5-di-CH_3	OCH_3	6-Cl	white solid	48	121-123	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.84 – 7.79 (m, 2H), 7.70 (dd, J = 9.0, 1.8 Hz, 1H), 6.07 (s, 1H), 4.17 (s, 3H), 2.60 (s, 2H), 2.35 (s, 2H), 1.18 (s, 6H).
8d	5,5-di-CH_3	OCH_3	7-SH_3	light yellow solid	68	111-113	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.30 (dd, J = 8.4, 1.8 Hz, 1H), 6.05 (s, 1H), 4.18 (s, 3H), 2.63 (s, 3H), 2.60 (s, 2H), 2.34 (s, 2H), 1.17 (s, 6H).
8e	5,5-di-CH_3	OCH_3	8-CH_2CH_3	light yellow oil	70		^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 6.07 (s, 1H), 4.18 (s, 3H), 3.19 (q, J = 7.2 Hz, 2H), 2.61 (s, 2H), 2.35 (s, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.18 (s, 6H).
8f	5,5-di-CH_3	OCH_3	8-$CH(CH_3)_2$	yellow oil;	72		^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.69 –

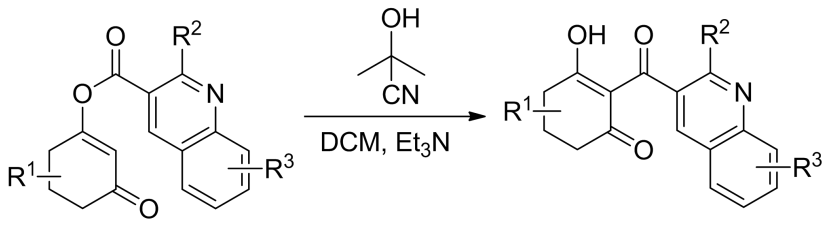
							7.64 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 6.07 (s, 1H), 4.18 (s, 3H), 4.17 – 4.08 (m, 1H), 2.61 (s, 2H), 2.35 (s, 2H), 1.39 (d, *J* = 6.6 Hz, 6H), 1.18 (s, 6H).
8g	5,5-di-CH_3	OCH_3	7-F-8-CH_3	white solid	64	106-108	1H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.67 (dd, *J* = 9.0, 6.0 Hz, 1H), 7.22 (t, *J* = 9.0 Hz, 1H), 6.06 (s, 1H), 4.20 (s, 3H), 2.61 (s, 5H), 2.35 (s, 2H), 1.18 (s, 6H).
8h	5,5-di-CH_3	OCH_3	7-Cl-8-CH_3	white solid	85	121-123	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.07 (s, 1H), 4.19 (s, 3H), 2.78 (s, 3H), 2.60 (s, 2H), 2.35 (s, 2H), 1.18 (s, 6H).
8i	5,5-di-CH_3	OCH_3	7-Br-8-CH_3	white solid	64	138-140	^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 6.04 (s, 1H), 4.09 (s, 3H), 2.75 (s, 3H), 2.60 (s, 2H), 2.31 (s, 2H), 1.09 (s, 6H).
8j	5,5-di-CH_3	OCH_3	8-CH_3	white solid	88	84-86	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 6.6 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 6.07 (s, 1H), 4.19 (s, 3H), 2.71 (s, 3H), 2.61 (s, 2H), 2.35 (s, 2H), 1.18 (s, 6H).
8k	5-CH_3	OCH_3	8-CH_3	white solid	78	87-89	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 6.6 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 6.06 (s, 1H), 4.19 (s, 3H), 2.74 – 2.65 (m, 4H), 2.59 – 2.51 (m, 2H), 2.47 – 2.36 (m, 1H), 2.20 (dd, *J* = 16.4, 12.0 Hz, 1H), 1.16 (d, *J* = 6.6 Hz, 3H).
8l	6,6-di-CH_3	OCH_3	8-CH_3	white solid	80	82-84	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 5.95 (s, 1H), 4.18 (s, 3H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.71 (s, 3H), 1.95 (t, *J* = 6.0 Hz, 2H),

							1.19 (s, 6H).
9a	H	OCH_3	8-CH_3	white solid	78	94-96	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 6.6 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.07 (s, 1H), 4.18 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.71 (s, 3H), 2.48 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9b	H	OEt	8-CH_3	light brown soild	76	100-102	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 6.08 (s, 1H), 4.66 (q, J = 7.2 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.69 (s, 3H), 2.48 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H).
9c	H	O-*n*-Pr	8-CH_3	white solid	80	72-74	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 6.08 (s, 1H), 4.54 (t, J = 6.6 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.69 (s, 3H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H), 1.96-1.86 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H).
9d	H	OCH_2Ph	8-CH_3	colorless oil	42		^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.31 (t, J = 7.2 Hz, 1H), 6.08 (s, 1H), 5.68 (s, 2H), 2.72 (s, 3H), 2.67 (t, J = 6.0 Hz, 2H), 2.47 (t, J = 6.0 Hz, 2H), 2.11 (quintuplet, J = 6.6 Hz, 2H).
9e	H	OCH_3	H	white solid	80	102-104	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.77 – 7.72 (m, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.06 (s, 1H), 4.16 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.47 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).

9f	H	OCH_3	6-CH_3	white solid	90	132-134	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 6.06 (s, 1H), 4.16 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.51 (s, 3H), 2.48 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9g	H	OCH_3	7-CH_3	white solid	90	102-104	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 6.06 (s, 1H), 4.18 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.56 (s, 3H), 2.48 (t, J = 6.6 Hz, 2H), 2.14 (quintuplet, J = 6.6 Hz, 2H).
9h	H	OCH_3	6-OCH_3	white solid	73	129-131	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.79 (d, J = 9.6 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.11 (s, 1H), 6.06 (s, 1H), 4.14 (s, 3H), 3.92 (s, 3H), 2.73 (t, J = 5.4 Hz, 2H), 2.48 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9i	H	OCH_3	7-OCH_3	white solid	58	126-128	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 9.0, 2.4 Hz, 1H), 6.05 (s, 1H), 4.18 (s, 3H), 3.98 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.48 (t, J = 6.6 Hz, 2H), 2.14 (quintuplet, J = 6.6 Hz, 2H).
9j	H	OCH_3	6-Cl	white solid	75	109-111	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.82 (d, J = 10.8 Hz, 2H), 7.69 (d, J = 9.0 Hz, 1H), 6.06 (s, 1H), 4.16 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9k	H	OCH_3	7-Cl	white solid	56	113-115	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.89 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.4, 1.2 Hz, 1H), 6.06 (s, 1H), 4.16 (s, 3H), 2.72 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J

							= 6.6 Hz, 2H).
9l	H	OCH_3	7-SCH_3	light yellow solid	50	128-130	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.30 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.05 (s, 1H), 4.17 (s, 3H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.63 (s, 3H), 2.46 (t, *J* = 6.6 Hz, 2H), 2.15 (t, *J* = 6.6 Hz, 2H).
9m	H	OCH_3	8-CH_2CH_3	white solid	86	62-64	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 6.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 6.07 (s, 1H), 4.18 (s, 3H), 3.19 (q, *J* = 7.8 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 2.15 (quintuplet, *J* = 6.6 Hz, 2H), 1.37 (t, *J* = 7.8 Hz, 3H).
9n	H	OCH_3	8-$CH(CH_3)_2$	white solid	78	80-82	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.69 – 7.65 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 6.07 (s, 1H), 4.18 (s, 3H), 4.15-4.07 (m, 1H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 2.15 (quintuplet, *J* = 6.6 Hz, 2H), 1.39 (d, *J* = 7.2 Hz, 6H).
9o	H	OCH_3	5,8-di-CH_3	white solid	50	119-121	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.07 (s, 1H), 4.17 (s, 3H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.66 (s, 3H), 2.66 (s, 3H), 2.49 (t, *J* = 6.0 Hz, 2H), 2.16 (quintuplet, *J* = 6.6 Hz, 2H).
9p	H	OCH_3	6,8-di-CH_3	light yellow solid	60	118-120	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 6.06 (s, 1H), 4.16 (s, 3H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.67 (s, 3H), 2.45 (m, 5H), 2.15 (quintuplet, *J* = 6.6 Hz, 2H).
9q	H	OCH_3	7,8-di-CH_3	white solid	68	128-130	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.06 (s, 1H), 4.19 (s, 3H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.66 (s, 3H),

							2.51 (s, 3H), 2.48 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9r	H	OCH_3	7-F-8-CH_3	white solid	65	112-114	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.67 (dd, J = 8.4, 6.0 Hz, 1H), 7.22 (t, J = 9.0 Hz, 1H), 6.06 (s, 1H), 4.19 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.60 (d, J = 1.8 Hz, 3H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9s	H	OCH_3	7-Cl-8-CH_3	white solid	78	141-143	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 6.06 (s, 1H), 4.19 (s, 3H), 2.78 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).
9t	H	OCH_3	7-Br-8-CH_3	white solid	78	163-165	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.06 (s, 1H), 4.19 (s, 3H), 2.82 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H).



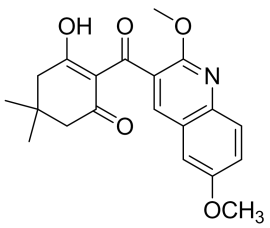
8a-l: R^1 = 5,5-di-CH_3; 5-CH_3; 6,6-di-CH_3

9a-t: R^1 = H;

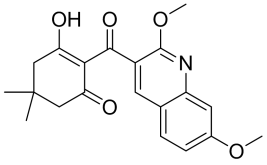
II: R^1 = 5,5-di-CH_3; 5-CH_3; 6,6-di-CH_3

III: R^1= H

General procedure for the preparation of title compounds II and III. The title compounds **II** and **III** were obtained by using the same method as the preparation of lead compound **I**.

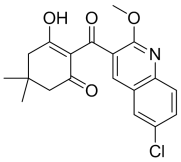


2-(2,6-dimethoxyquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-a)***. Yield, 83%; bierge solid; mp, 132-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.73 (s, 1H), 7.98 (s, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.34 (dd, J = 9.0, 2.4 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 4.04 (s, 3H), 3.89 (s, 3H), 2.64 (s, 2H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.37, 193.92, 193.75, 156.77, 156.26, 142.51, 136.27, 128.38, 125.55, 124.92, 122.41, 114.02, 106.75, 55.50, 53.41, 51.41, 45.56, 31.00, 28.15. HRMS (ESI): calcd for $C_{20}H_{21}NO_5$ $[M+H]^+$ 356.1498, found 356.1492.

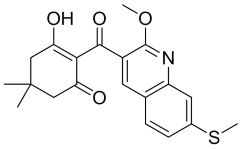


2-(2,7-dimethoxyquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-b)***. Yield, 80%; light yellow solid; mp, 132-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.79 (s, 1H), 8.04 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.41 (s, 1H), 7.05 (dd, J = 8.4, 1.8 Hz, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 2.63 (s, 2H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.86, 193.96, 193.57, 162.06, 158.73, 149.20, 137.49, 129.41, 122.71, 119.09, 116.71, 114.02,

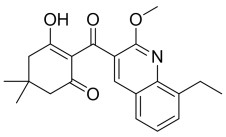
106.38, 55.47, 53.40, 51.46, 45.59, 30.93, 28.14. HRMS (ESI): calcd for $C_{20}H_{21}NO_5$ $[M+H]^+$ 356.1498, found 356.1488.



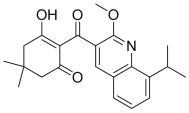
2-(6-chloro-2-methoxyquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-c)***. Yield, 80%; bierge solid; mp, 168-170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.72 (s, 1H), 7.91 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.59 (d, J = 9.0 Hz, 1H), 3.98 (s, 3H), 2.64 (s, 2H), 2.31 (s, 2H), 1.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.03, 194.05, 193.91, 158.26, 145.33, 135.84, 131.16, 129.75, 128.66, 126.84, 126.64, 125.01, 113.86, 53.72, 51.39, 45.51, 31.04, 28.14. HRMS (ESI): calcd for $C_{19}H_{18}ClNO_4$ $[M+H]^+$ 360.1003, found 360.0994.



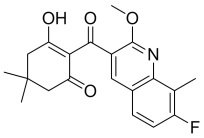
3-hydroxy-2-(2-methoxy-7-(methylthio)quinoline-3-carbonyl)-5,5-dimethylcyclohex-2-eno ne ***(II-d)***. Yield, 70%; light brown solid; mp, 139-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.79 (s, 1H), 7.98 (s, 1H), 7.64-7.57 (m, 2H), 7.25 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 2.63 (s, 2H), 2.61 (s, 3H), 2.32 (s, 2H), 1.15 (s, 6H). ^{13}C NMR (101 MHz, CDC_3) δ 194.84, 193.91, 193.71, 158.64, 147.59, 142.96, 137.22, 128.10, 124.32, 123.39, 121.65, 121.28, 113.98, 53.51, 51.42, 45.56, 30.96, 28.13, 14.99. HRMS (ESI): calcd for $C_{20}H_{21}NO_4S$ $[M+H]^+$ 372.1270, found 372.1260.



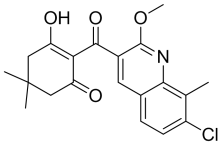
2-(8-ethyl-2-methoxyquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-e)***. Yield, 85%; light brown solid; mp, 120-122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.86 (s, 1H), 8.04 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 3.99 (s, 3H), 3.18 (q, J = 7.2 Hz, 2H), 2.64 (s, 2H), 2.33 (s, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.28, 193.96, 193.88, 156.92, 145.32, 141.02, 137.80, 129.40, 126.14, 124.92, 124.27, 124.17, 114.07, 53.23, 51.48, 45.66, 31.00, 28.18, 24.60, 14.59. HRMS (ESI): calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$ 354.1705, found 354.1699.



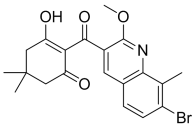
3-hydroxy-2-(8-isopropyl-2-methoxyquinoline-3-carbonyl)-5,5-dimethylcyclohex-2-enone ***(II-f)***. Yield, 79%; white solid; mp, 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.87 (s, 1H), 8.04 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 4.18-4.09 (m, 1H), 3.99 (s, 3H), 2.62 (s, 2H), 2.32 (s, 2H), 1.37 (d, J = 6.8 Hz, 6H), 1.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.26, 193.96, 193.91, 156.78, 145.20, 144.75, 137.90, 126.72, 126.00, 124.81, 124.31, 124.26, 114.07, 53.28, 51.48, 45.67, 31.01, 28.18, 27.82, 23.00. HRMS (ESI): calcd for $C_{22}H_{25}NO_4$ $[M+H]^+$ 368.1862, found 368.1854.



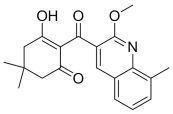
2-(7-fluoro-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-g)***. Yield, 58%; light yellow solid; mp, 134-136 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.79 (s, 1H), 8.01 (s, 1H), 7.58 (dd, J = 8.4, 6.6 Hz, 1H), 7.14 (t, J = 9.0 Hz, 1H), 4.00 (s, 3H), 2.64 (s, 2H), 2.59 (d, J = 1.8 Hz, 3H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.04, 194.07, 193.75, 163.20, 160.75, 157.77, 147.18, 147.07, 137.53, 126.94, 126.83, 124.02, 120.91, 119.87, 119.71, 113.94, 113.68, 53.34, 51.35, 45.45, 30.96, 28.09. HRMS (ESI): calcd for $C_{20}H_{20}FNO_4$ $[M+H]^+$ 358.1455, found 358.1446.



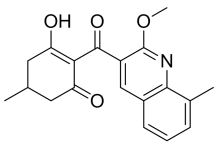
2-(7-chloro-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-h)***. Yield, 85%; light brown solid; mp, 136-138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.77 (s, 1H), 7.99 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 2.76 (s, 3H), 2.64 (s, 2H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.00, 193.99, 193.88, 157.64, 146.35, 137.42, 136.26, 133.04, 126.29, 125.51, 124.97, 122.66, 113.97, 53.43, 51.43, 45.56, 31.01, 28.15, 14.29. HRMS (ESI): calcd for $C_{20}H_{20}ClNO_4$ $[M+H]^+$ 374.1159, found 374.1154.



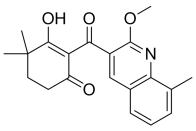
2-(7-bromo-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone ***(II-i)***. Yield, 80%; white solid; mp, 142-144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.76 (s, 1H), 7.98 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 4.00 (s, 3H), 2.80 (s, 3H), 2.64 (s, 2H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.02, 193.99, 193.90, 157.58, 146.22, 137.47, 135.17, 128.39, 127.29, 126.51, 125.18, 123.09, 113.96, 53.44, 51.41, 45.55, 31.02, 28.15, 17.38. HRMS (ESI): calcd for $C_{20}H_{20}BrNO_4$ $[M+H]^+$ 418.0654, found: 418.0643.



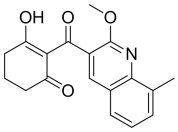
3-hydroxy-2-(2-methoxy-8-methylquinoline-3-carbonyl)-5,5-dimethylcyclohex-2-enone ***(II-j)***. Yield, 75%; light yellow solid; mp, 114-116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.83 (s, 1H), 8.03 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 3.99 (s, 3H), 2.69 (s, 3H), 2.63 (s, 2H), 2.32 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.28, 193.96, 193.82, 157.00, 145.89, 137.67, 135.24, 130.90, 126.08, 124.95, 124.14, 123.98, 114.05, 53.22, 51.45, 45.62, 30.98, 28.15, 17.60. HRMS (ESI): calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1549, found 340.1543.



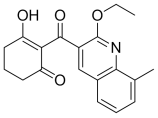
3-hydroxy-2-(2-methoxy-8-methylquinoline-3-carbonyl)-5-methylcyclohex-2-enone ***(II-k)***. Yield, 72%, light brown solid; mp, 108-110 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.87 (s, 1H), 8.01 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 4.01 (s, 3H), 2.81 (dd, J = 17.8, 2.4 Hz, 1H), 2.69 (s, 3H), 2.58-2.43 (m, 2H), 2.43-2.22 (m, 1H), 2.19 (dd, J = 15.7, 11.6 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.59, 194.34, 194.01, 156.95, 145.80, 137.52, 135.21, 130.85, 126.02, 124.93, 124.09, 123.96, 114.43, 53.30, 45.80, 39.87, 26.61, 20.68, 17.63. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1387.



3-hydroxy-2-(2-methoxy-8-methylquinoline-3-carbonyl)-4,4-dimethylcyclohex-2-enone ***(II-l)***. Yield, 80%, light brown solid; mp, 126-128 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 17.39 (s, 0.3H), 16.87 (s, 0.7H), 8.01 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.53-7.48 (m, 1H), 7.30-7.27 (m, 1H), 4.02 (s, 0.8H), 3.98 (s, 2.2H), 2.79 (t, J = 6.6 Hz, 1.5H), 2.69 (s, 3H), 2.51 (t, J = 6.6 Hz, 0.5H), 1.92 (t, J = 6.6 Hz, 0.6H), 1.89 (t, J = 6.6 Hz, 1.4H), 1.39 (s, 1.6H), 1.16 (s, 4.4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.84, 199.23, 196.70, 195.60, 194.32, 193.49, 156.81, 156.69, 145.66, 137.54, 137.42, 135.16, 130.76, 125.95, 125.42, 124.84, 124.14, 124.08, 123.93, 113.34, 113.08, 53.27, 53.07, 40.88, 38.04, 34.24, 33.58, 32.76, 28.55, 25.37, 24.42, 17.60. HRMS (ESI): calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1549, found 340.1543.

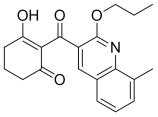


3-hydroxy-2-(2-methoxy-8-methylquinoline-3-carbonyl)cyclohex-2-enone ***(III-a)***. Yield, 75%; white solid; mp, 113-115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 8.01 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 4.01 (s, 3H), 2.77 (t, J = 6.6 Hz, 2H), 2.69 (s, 3H), 2.46 (t, J = 6.6 Hz, 2H), 2.10 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.81, 195.06, 194.22, 156.96, 145.84, 137.51, 135.27, 130.88, 126.05, 124.95, 124.12, 124.00, 114.94, 53.29, 37.68, 32.12, 19.22, 17.63. HRMS (ESI): calcd for $C_{18}H_{17}NO_4$ $[M+H]^+$ 312.1236, found 312.1231.

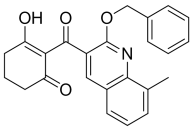


2-(2-ethoxy-8-methylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-b)***. Yield, 80%; light yellow soild; mp, 96-98 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 8.02 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.25 (t, J = 7.2 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.67 (s, 3H), 2.44 (t, J = 6.0 Hz, 2H), 2.04 (quintuplet, J = 6.6 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.78, 194.77, 194.06, 156.61, 145.89, 137.77, 135.11, 130.87, 126.07, 125.08, 124.01, 123.86, 115.06, 61.84, 37.71, 32.09, 19.22, 17.65, 14.35. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found

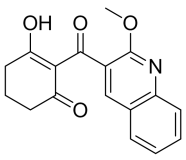
326.1386.



3-hydroxy-2-(8-methyl-2-propoxyquinoline-3-carbonyl)cyclohex-2-enone ***(III-c)***. Yield, 77%; white solid; mp, 69-71 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 17.02 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 6.6 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 4.40 (t, J = 6.6 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.67 (s, 3H), 2.43 (t, J = 6.0 Hz, 2H), 2.02 (quintuplet, J = 6.6 Hz, 2H), 1.81 – 1.69 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.01, 195.11, 193.85, 156.77, 145.78, 137.46, 135.07, 130.80, 126.00, 125.25, 123.96, 123.82, 114.86, 67.62, 37.71, 32.13, 22.14, 19.14, 17.65, 10.64. HRMS (ESI): calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1549, found 340.1544.

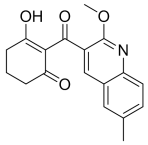


2-(2-(benzyloxy)-8-methylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-d)***. Yield, 75%; light brown solid; mp, 139-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.82 (s, 1H), 8.07 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 6.6 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 5.47 (s, 2H), 2.71 (s, 3H), 2.59 (t, J = 6.0 Hz, 2H), 2.17 (t, J = 6.6 Hz, 2H), 1.72 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.61, 194.74, 194.21, 156.46, 145.85, 138.06, 137.14, 135.24, 131.02, 128.43, 128.26, 127.81, 126.14, 125.13, 124.29, 124.10, 115.08, 67.98, 37.55, 31.98, 18.81, 17.76. HRMS (ESI): calcd for $C_{24}H_{21}NO_4$ $[M+H]^+$ 388.1549, found 388.1541.

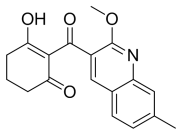


3-hydroxy-2-(2-methoxyquinoline-3-carbonyl)cyclohex-2-enone ***(III-e)***. Yield 84%; light yellow solid; mp 112-114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.87 (s, 1H), 8.00 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 4.00 (s, 3H), 2.76 (t, J = 6.6 Hz, 2H), 2.45 (t, J = 6.6 Hz, 2H), 2.09 – 2.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.73, 195.14, 194.10, 158.01, 146.99, 136.95, 130.59, 128.21, 127.11, 125.60, 124.37, 124.34, 114.84, 53.52, 37.64, 32.08, 19.19. HRMS (ESI): calcd for

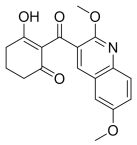
$C_{17}H_{15}NO_4$ $[M+H]^+$ 298.1079, found 298.1073.



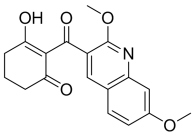
3-hydroxy-2-(2-methoxy-6-methylquinoline-3-carbonyl)cyclohex-2-enone ***(III-f)***. Yield, 78%; light yellow solid; mp, 126-128 °C;^{1}H NMR (600 MHz, $CDCl_3$) δ 16.87 (s, 1H), 7.93 (s, 1H), 7.79 (t, J = 6.6 Hz, 1H), 7.52 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 2.77 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.45 (t, J = 6.0 Hz, 2H), 2.11 – 1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.76, 195.01, 194.04, 157.57, 145.28, 136.60, 133.96, 132.68, 127.28, 126.75, 125.38, 124.28, 114.87, 53.44, 37.62, 32.05, 21.17, 19.17. HRMS (ESI): calcd for $C_{18}H_{17}NO_4$ $[M+H]^+$ 312.1236, found 312.1230.



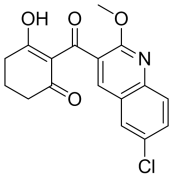
3-hydroxy-2-(2-methoxy-7-methylquinoline-3-carbonyl)cyclohex-2-enone ***(III-g)***. Yield, 76%; light brown solid; mp, 152-154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.88 (s, 1H), 7.98 (s, 1H), 7.66 – 7.61 (m, 2H), 7.21 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 2.52 (s, 3H), 2.45 (t, J = 6.6 Hz, 2H), 2.09 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.67, 194.93, 194.09, 158.17, 147.29, 141.27, 137.03, 127.94, 126.54, 126.45, 124.56, 122.29, 114.94, 53.41, 37.68, 32.11, 21.90, 19.22. HRMS (ESI): calcd for $C_{18}H_{17}NO_4$ $[M+H]^+$ 312.1236, found 312.1230.



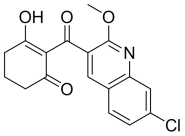
2-(2,6-dimethoxyquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-h)***. Yield, 81%; light yellow solid; mp, 154-156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.85 (s, 1H), 7.93 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.32 (dd, J = 9.0, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 2.77 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.6 Hz, 2H), 2.07 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.70, 195.04, 194.18, 156.69, 156.26, 142.06, 136.24, 128.13, 125.56, 124.83, 122.43, 114.83, 106.66, 55.47, 53.75, 37.59, 32.01, 19.15. HRMS (ESI): calcd for $C_{18}H_{17}NO_5$ $[M+H]^+$ 328.1185, found 328.1179.



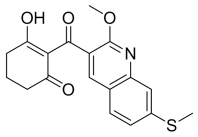
2-(2,7-dimethoxyquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-i)***. Yield, 71%, yellow solid; mp, 136-138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.88 (s, 1H), 7.99 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.24 (s, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.6 Hz, 2H), 2.07 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.38, 194.76, 194.24, 162.07, 158.70, 149.19, 137.38, 129.41, 122.71, 119.10, 116.74, 114.96, 106.39, 77.32, 77.00, 76.68, 55.49, 53.43, 37.69, 32.09, 19.22. HRMS (ESI): calcd for $C_{18}H_{17}NO_5$ $[M+H]^+$ 328.1185, found 328.1179.



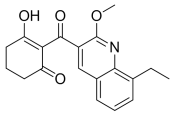
2-(6-chloro-2-methoxyquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-j)***. Yield, 75%; light brown solid; mp, 155-157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.81 (s, 1H), 7.88 (s, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 2.78 (t, J = 6.0 Hz, 2H), 2.45 (t, J = 6.0 Hz, 2H), 2.10 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.55, 195.34, 194.01, 158.25, 145.31, 135.55, 131.08, 129.73, 128.66, 126.78, 126.67, 125.00, 114.73, 53.67, 37.60, 32.04, 19.17. HRMS (ESI): calcd for $C_{17}H_{14}ClNO_4$ $[M+H]^+$ 332.0690, found 332.0683.



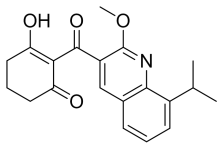
2-(7-chloro-2-methoxyquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-k)***. Yield, 68%; bierge solid; mp,134-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.82 (s, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 9.0, 1.2 Hz, 1H), 3.99 (s, 3H), 2.78 (t, J = 6.0 Hz, 2H), 2.45 (t, J = 6.6 Hz, 2H), 2.07 (t, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.44, 195.27, 194.12, 158.76, 147.44, 136.48, 136.44, 129.25, 126.39, 126.36, 125.29, 122.71, 114.75, 77.32, 77.00, 76.68, 53.77, 37.62, 32.05, 19.18. HRMS (ESI): calcd for $C_{17}H_{14}ClNO_4$ $[M+H]^+$ 332.0690, found 332.0682.



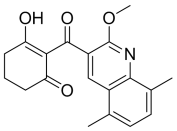
3-hydroxy-2-(2-methoxy-7-(methylthio)quinoline-3-carbonyl)cyclohex-2-enone ***(III-l)***. Yield, 75%; yellow solid; mp, 116-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.85 (s, 1H), 7.96 (s, 1H), 7.61 (d, J = 9.0 Hz, 2H), 7.25 (dd, J = 9.0, 1.8 Hz, 1H), 4.01 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 2.61 (s, 3H), 2.45 (t, J = 6.6 Hz, 2H), 2.06 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.34, 194.95, 194.14, 158.59, 147.52, 142.93, 137.07, 128.06, 124.31, 123.39, 121.61, 121.22, 114.85, 77.32, 77.00, 76.68, 53.55, 37.62, 32.04, 19.17, 14.97. HRMS (ESI): calcd for $C_{18}H_{17}NO_4S$ $[M+H]^+$ 344.0957, found 344.0951



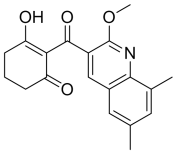
2-(8-ethyl-2-methoxyquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-m)***. Yield, 65%; light brown solid; mp, 84-96 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.93 (s, 1H), 8.01 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 6.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 4.00 (s, 3H), 3.18 (q, J =7.2 Hz, 2H), 2.76 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.0 Hz, 2H), 2.10 – 2.00 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.78, 195.10, 194.16, 156.89, 145.27, 141.03, 137.63, 129.38, 126.10, 124.92, 124.26, 124.18, 114.96, 53.30, 37.69, 32.16, 24.62, 19.24, 14.60. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1386.



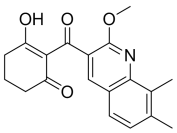
3-hydroxy-2-(8-isopropyl-2-methoxyquinoline-3-carbonyl)cyclohex-2-enone ***(III-n)***. Yield, 76%; light brown solid; mp, 125-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.95 (s, 1H), 8.02 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.01 (s, 3H), 2.77 (t, J = 6.0 Hz, 2H), 2.47 (t, J = 6.0 Hz, 2H), 2.08 (quintuplet, J = 6.0 Hz, 2H), 1.37 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.75, 195.13, 194.17, 156.72, 145.20, 144.68, 137.74, 126.69, 125.95, 124.80, 124.28, 124.26, 114.95, 53.32, 37.68, 32.15, 27.83, 22.98, 19.22. HRMS (ESI): calcd for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.1549, found 340.1541.



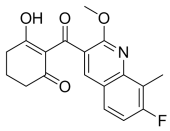
*3-hydroxy-2-(2-methoxy-5,8-dimethylquinoline-3-carbonyl)cyclohex-2-enone (**III-o**).* Yield, 67%; light yellow solid; mp, 168-170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 8.20 (s, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 4.00 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.64 (s, 3H), 2.58 (s, 3H), 2.45 (t, J = 6.0 Hz, 2H), 2.04 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.87, 194.83, 194.23, 156.51, 146.19, 134.33, 133.07, 132.91, 130.63, 124.67, 124.03, 123.40, 114.98, 53.17, 37.61, 32.02, 19.17, 18.53, 17.56. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1387.



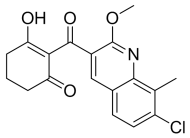
*3-hydroxy-2-(2-methoxy-6,8-dimethylquinoline-3-carbonyl)cyclohex-2-enone (**III-p**).* Yield, 84%; light yellow solid; mp, 147-149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 7.92 (s, 1H), 7.35 (s, 2H), 3.98 (s, 3H), 2.74 (t, J = 6.0 Hz, 2H), 2.65 (s, 3H), 2.44 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H), 2.04 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.85, 194.92, 194.17, 156.50, 144.22, 137.08, 134.83, 133.43, 133.05, 125.05, 124.72, 124.12, 114.96, 53.14, 37.65, 32.08, 21.19, 19.19, 17.46. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1388.



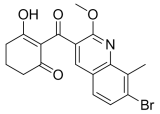
3-hydroxy-2-(2-methoxy-7,8-dimethylquinoline-3-carbonyl)cyclohex-2-enone (**III-q**). Yield, 70%; light yellow solid; mp, 138-140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 7.99 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.63 (s, 3H), 2.48 – 2.40 (m, 5H), 2.04 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.68, 194.83, 194.21, 156.95, 145.74, 138.95, 137.78, 132.72, 126.94, 125.15, 123.75, 122.42, 114.97, 53.16, 37.64, 32.07, 20.74, 19.19, 13.09. HRMS (ESI): calcd for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1387.



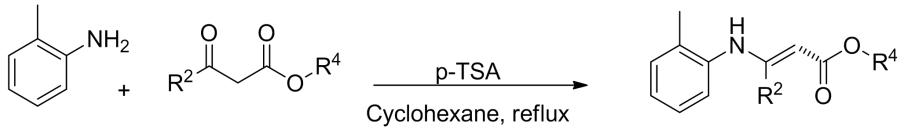
2-(7-fluoro-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-r)***. Yield, 75%; light yellow solid; mp, 131-133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.87 (s, 1H), 7.99 (s, 1H), 7.57 (dd, J = 8.4, 6.0 Hz, 1H), 7.14 (t, J = 9.0 Hz, 1H), 4.02 (s, 3H), 2.77 (t, J = 6.0 Hz, 3H), 2.59 (s, 3H), 2.46 (t, J = 6.6 Hz, 2H), 2.07 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.55, 195.03, 194.26, 163.21, 160.75, 157.76, 147.15, 147.04, 137.37, 126.90, 126.79, 124.02, 120.92, 119.92, 119.75, 114.84, 113.97, 113.71, 53.41, 37.63, 32.03, 19.17, 8.94. HRMS (ESI): calcd for $C_{18}H_{16}FNO_4$ $[M+H]^+$ 330.1142, found 330.1134.



2-(7-chloro-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-s)***. Yield, 84%; light yellow solid; mp, 175-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.85 (s, 1H), 7.96 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H), 2.80 – 2.74 (m, 5H), 2.46 (t, J = 6.0 Hz, 2H), 2.11 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.55, 195.17, 194.19, 157.64, 146.32, 137.23, 136.24, 133.07, 126.26, 125.53, 125.00, 122.67, 114.87, 53.48, 37.65, 32.08, 19.21, 14.29. HRMS (ESI): calcd for $C_{18}H_{16}ClNO_4$ $[M+H]^+$ 346.0846, found 346.0838.



2-(7-bromo-2-methoxy-8-methylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone ***(III-t)***. Yield, 52%, white solid; mp, 178-180 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.85 (s, 1H), 7.96 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 2.80 (s, 3H), 2.78 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.0 Hz, 2H), 2.07 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.51, 195.16, 194.22, 157.47, 146.08, 137.23, 135.10, 128.33, 127.21, 126.45, 125.13, 122.99, 114.79, 53.51, 44.19, 37.60, 32.01, 19.15, 17.36. HRMS (ESI): calcd for $C_{18}H_{16}BrNO_4$ $[M+H]^+$ 390.0341, found 390.0330.

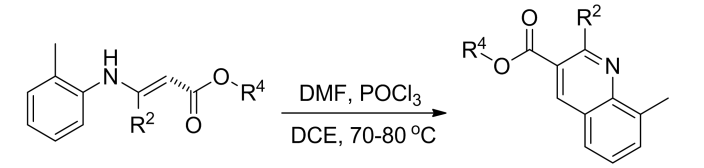


3j **10a**: $R^4 = CH_3$, $R^4 = CH_3$; **10b**: $R^4 = CF_3$, $R^4 = C_2H_5$ **11a**: $R^2 = CH_3$, $R^4 = CH_3$; **11b**: $R^2 = CF_3$, $R^4 = C_2H_5$

General procedure for the preparation of intermediates 11a and 11b. In a round bottom flask were added *o*-toluidine (30 mmol), methyl acetoacetate **10a** (45 mmol) or ethyl trifluoroacetoacetate **10b** (45 mmol), $MgSO_4$ (10 mmol), *p*-TSA (0.3 mmol) and toluene (90 mL). The reaction mixture was stirred at reflux for 6 h. After the reaction was completed according to TLC detection, the suspension was cooled to room temperature, and filtrated through a bed of celite. The resulted solution was concentrated under reduced pressure, and purified *via* flash chromatography to give **11a** and **11b**.

*Data for **11a**:* yield 88%; colorless oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.16 – 7.12 (m, 1H), 4.71 (s, 1H), 3.58 (s, 3H), 2.22 (s, 3H), 1.87 (s, 3H).

*Data for **11b**:* yield 66%; light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.23-7.16 (m, 4H), 5.34 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H).



11a: $R^2 = CH_3$, $R^4 = CH_3$; **11b**: $R^2 = CF_3$, $R^4 = C_2H_5$ **12a**: $R^2 = CH_3$, $R^4 = CH_3$; **12b**: $R^2 = CF_3$, $R^4 = C_2H_5$

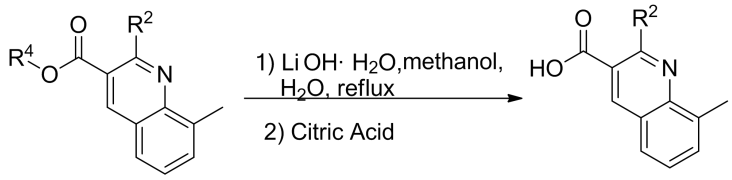
General procedure for the preparation of intermediates 12a and 12b.[1] DMF (15 mmol) and $ClCH_2CH_2Cl$ (10 mL) were added to a round bottom flask at 0 °C. $POCl_3$ (22.5 mmol)

(1) Bouchoul, A.; Benathmane, M.; Benboudiaf, A.; Bouaoud, S.; Ouahab, L.; Djebbar, K. E.*Asian J. Chem.* **2007**, *19*, 5429-5434.

was added drop-wise to the solution over 10 min; the reaction mixture was stirred for another 30 min at this temperature. **11a** or **11b** (15 mmol) in $ClCH_2CH_2Cl$ (10 mL) was added drop-wise to the reaction mixture over 10 min, and the reaction solution was then heated to 80 °C for 6 h. After completing the reaction according to TLC detection, the mixture was poured into ice (100 g), and stirred vigorously for 30 min. The organic layer was separated, the aqueous layer was washed with $ClCH_2CH_2Cl$ (20 mL) for two times. The combined organic layer was dried by anhydrous Na_2SO_4, concentrated under reduced pressure, purified *via* flash chromatography to give intermediates **12a** and **12b**.

*Data for **12a**:* yield 90%; white solid; mp 109-111 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 6.0 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 4.00 (s, 3H), 3.14 (s, 3H), 2.90 (s, 3H).

*Data for **12a**:* yield 50%; white solid; mp 71-73 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 2.85 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H).



12a: $R^2 = CH_3$, $R^4 = CH_3$; **12b**: $R^2 = CF_3$, $R^4 = C_2H_5$

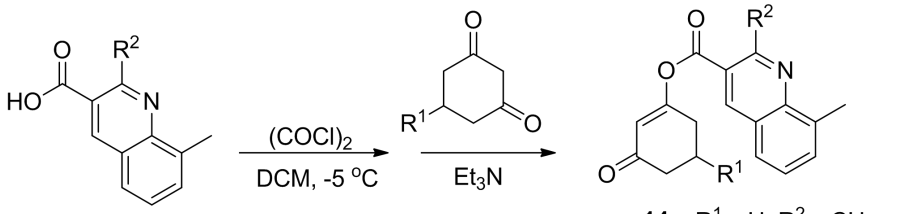
13a: $R^2 = CH_3$; **13b**: $R^2 = CF_3$

General procedure for the preparation of intermediates 13a and 13b. To a solution of **12a** or **12b** (5 mmol), $LiOH·H_2O$ (10 mmol), methanol (20 mL) and H_2O (20 mL) was heated to reflux for 3 h. After completing the reaction according to TLC detection, methanol was removed under reduced pressure; the resulted solution was acidified with sat. aqueous citric acid to pH = 2-3. The solid was collected by filtration and washed with water, dried in

vacuum to afford **13a** or **13b**.

*Data for **13a**:* yield 90%; light brown solid; mp 229-231 ° C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.29 (s, 1H), 8.82 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 2.90 (s, 3H), 2.71 (s, 3H).

*Data for **13b**:* yield 85%; light brown solid; mp 208-210 ° C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.93 (s, 1H), 9.00 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 6.6 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 2.77 (s, 3H).



13a: $R^2 = CH_3$;
13b: $R^2 = CF_3$

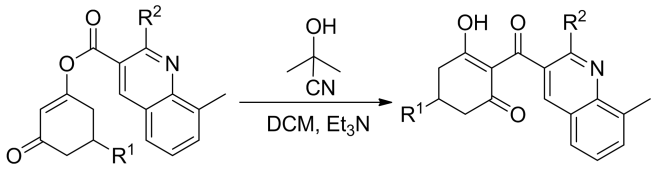
14a: R^1 = H, $R^2 = CH_3$;
14b: $R^1 = CH_3$, $R^2 = CH_3$;
15: R^2 = H, $R^2 = CF_3$

General procedure for the preparation of key intermediates 14a, 14b and 15. The key intermediates **14a**, **14b** and **15** were obtained by using the same method as the preparation of compound **2**.

Table S6. Chemical Structures, Physical and ^{1}H NMR data of intermediates 14a, 14b and 15.

compound	R^1	R^2	Appearance	Yield/%	mp/°C	^{1}H NMR
14a	H	CH_3	light yellow solid	60	99-101	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 6.6 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 6.09 (s, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 2.74 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 6.6 Hz, 2H), 2.17 (quintuplet, J = 6.6 Hz, 2H).
14b	CH_3	CH_3	light brown solid	77	94-96	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 6.08 (s,

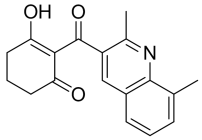
						1H), 3.10 (s, 3H), 2.87 (s, 3H), 2.69 (dd, *J* = 17.4, 4.8 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.50 – 2.39 (m, 1H), 2.22 (dd, *J* = 16.2, 12.0 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H).
15	H	CF_3	light brown solid	70	101-103	^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 6.13 (s, 1H), 2.87 (s, 3H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.50 (t, *J* = 6.6 Hz, 2H), 2.17 (quintuplet, *J* = 6.6 Hz).



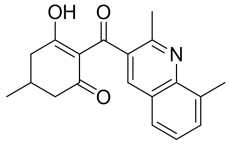
14a: R^1 = H, R^2 = CH_3;
14b: R^1 = CH_3, R^2 = CH_3;
15: R^2 = H, R^2 = CF_3

IV-a: R^1 = H, R^2 = CH_3;
IV-b: R^1 = CH_3, R^2 = CH_3;
V: R^1 = H, R^2 = CF_3

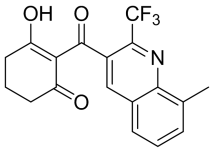
General procedure for the preparation of title compounds IV and V. The title compounds **IV** and **V** were obtained by using the same method as the preparation of lead compound **I**.



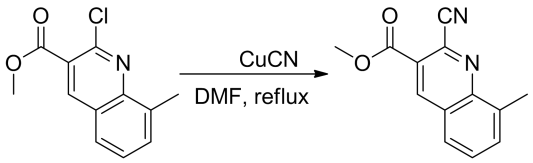
*2-(2,8-dimethylquinoline-3-carbonyl)-3-hydroxycyclohex-2-enone (**IV-a**)*. Yield, 75%; white solid; mp, 80-82 ^{o}C.^{1}H NMR (600 MHz, $CDCl_3$) δ 17.57 (s, 1H), 7.85 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 6.6 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 2.83 (s, 5H), 2.67 (s, 3H), 2.45 (brs, 2H), 2.13 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.70, 152.88, 146.16, 136.20, 133.47, 133.06, 130.33, 125.73, 125.19, 113.87, 23.44, 18.77, 17.80. HRMS (ESI): calcd for $C_{18}H_{17}NO_3$ $[M+H]^+$ 296.1287, found 296.1279.



2-(2,8-dimethylquinoline-3-carbonyl)-3-hydroxy-5-methylcyclohex-2-enone ***(IV-b)***. Yield, 90%; white solid; mp, 129-131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 17.56 (s, 1H), 7.84 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 6.0 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 2.90 – 2.77 (m, 4H), 2.65 (s, 3H), 2.50-2.45 (m, 2H), 2.38 – 2.29 (m, 1H), 2.17 (t, J = 12.0 Hz, 1H), 1.14 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.49, 152.82, 146.19, 136.21, 133.47, 132.99, 130.29, 125.71, 125.17, 113.34, 26.27, 23.44, 20.51, 17.78. HRMS (ESI): calcd for $C_{19}H_{19}NO_3$ $[M+H]^+$ 310.1443, found 310.1436.



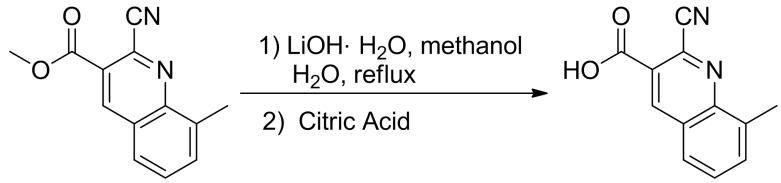
*3-hydroxy-2-(8-methyl-2-(trifluoromethyl)quinoline-3-carbonyl)cyclohex-2-enone(****V****)*. Yield, 55%; white solid; mp, 117-119 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.91 (s, 1H), 8.00 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 6.6 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 2.85 (s, 3H), 2.83 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 6.6 Hz, 2H), 2.07 (quintuplet, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.23, 196.80, 193.54, 145.50, 142.28, 141.93, 141.59, 141.24, 138.53, 134.85, 131.14, 130.81, 128.83, 127.55, 125.62, 122.82, 120.07, 117.33, 113.90, 37.70, 32.22, 19.05, 17.51. HRMS (ESI): calcd for $C_{18}H_{14}F_3NO_3$ $[M+H]^+$ 350.1004, found 350.1008.



6j **16**

Synthesis of methyl 2-cyano-8-methylquinoline-3-carboxylate 16. To a solution of methyl 2-chloro-8-methylquinoline-3-carboxylate **6j (**10 mmol**)**, CuCN (12 mmol) and DMF (15 mL) was heated to reflux under N_2 atmosphere for 3 h. After completing the reaction according to TLC detection, the reaction mixture was cooled to room temperature and poured to ammonium hydroxide (30 mL), and stirred vigorously for 30 min. The solution was extracted by EtOAc (30 mL) for three times, the combined organic layer was then washed by H_2O (30 mL) for three times, brine (30 mL) for two times, dried by anhydrous Na_2SO_4,

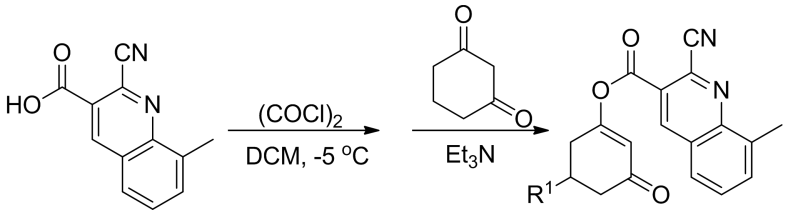
concentrated under reduced pressure, purified *via* flash chromatography to give **16** as white solid (2.0 g, yield 88%), mp 132-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 6.6 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 4.09 (s, 3H), 2.85 (s, 3H).



16 **17**

Synthesis of 2-cyano-8-methylquinoline-3-carboxylic acid 17. The carboxylic acid **17** was obtained by using the same method as the preparation of intermediates **13a** and **13b**.

*Data for **17**:* yield 85%; mp 206-208 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 14.16 (s, 1H), 9.18 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.78 (t, J = 7.2 Hz, 1H), 2.76 (s, 3H).



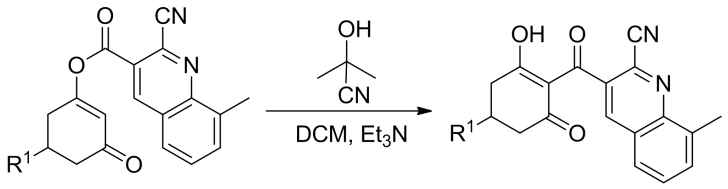
17

18a: R^2 = H;
18b: R^2 = CH_3

Synthesis of intermediates 18a and 18b. The synthetic method for intermediates **18a** and **18b** was the same as the preparation of compound **2**.

*Data for **18a***: yield 70%; light brown solid; mp 188-190 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 6.22 (s, 1H), 2.87 (s, 3H), 2.81 (t, J = 6.0 Hz, 2H), 2.51 (t, J = 6.6 Hz, 2H), 2.19 (quintuplet, J = 6.6 Hz, 2H).

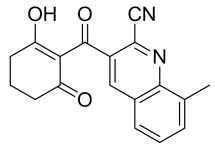
Data for ***18b***: yield 54%; light brown solid; mp 190-192 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 6.20 (d, J = 1.8 Hz, 1H), 2.87 (s, 3H), 2.78 (dd, J = 18.0, 4.2 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.50 – 2.40 (m, 1H), 2.22 (dd, J = 16.8, 12.0 Hz, 1H), 1.18 (d, J = 6.6 Hz, 3H).



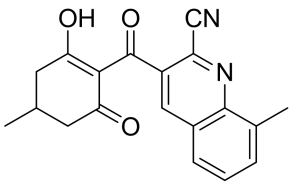
18a: R^2 = H;
18b: R^2 = CH_3

VI-a: R^2 = H;
VI-b: R^2 = CH_3

Synthesis of target compounds VI. The synthetic method for title compounds **VI** was the same as the preparation of lead compound **I**.



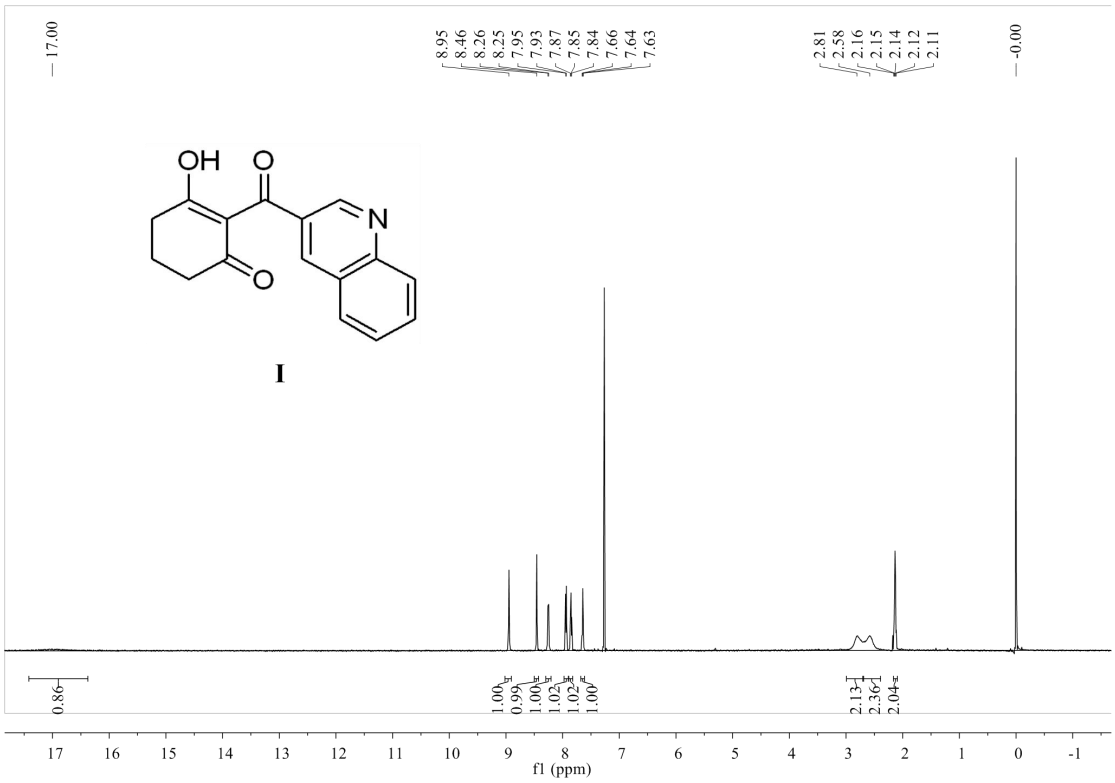
*Data for **VI-a***: yield, 50%; light brown solid; mp 167-169 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.71 (s, 1H), 8.26 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 2.85 (t, J = 6.0 Hz, 2H), 2.82 (s, 3H), 2.57 (t, J = 6.6 Hz, 2H), 2.15 (quintuplet, J = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, CDC_3) δ 197.21, 194.79, 194.40, 146.83, 138.45, 136.21, 134.38, 132.13, 129.65, 129.33, 127.71, 126.27, 116.54, 114.18, 37.46, 32.26, 18.76, 17.68. HRMS (ESI): calcd for $C_{18}H_{14}N_2O_3$ $[M+H]^+$ 307.1083, found 307.1073.

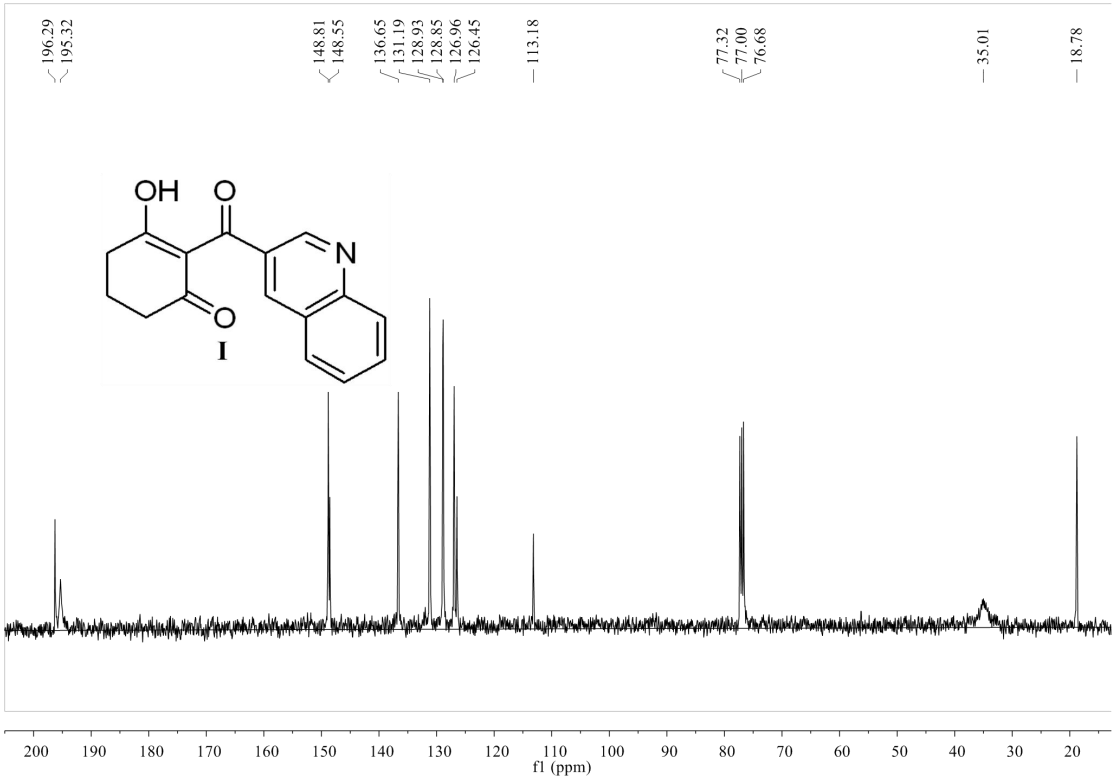


*Data for **VI-b***: yield 80%; light brown solid; mp 175-177 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.72 (s, 1H), 8.26 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 6.6 Hz, 1H), 7.61 (t, J = 7.2

Hz, 1H), 2.91-2.85 (m, 1H), 2.82 (s, 3H), 2.67-2.61 (m, 1H), 2.56 (dd, J = 18.6, 10.8 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.27 (dd, J = 16.8, 12.0 Hz, 1H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.79, 194.69, 194.25, 146.81, 138.43, 136.20, 134.34, 132.11, 129.63, 129.32, 127.69, 126.25, 116.52, 113.67, 45.64, 40.06, 26.37, 20.73, 17.66. HRMS (ESI): calcd for $C_{19}H_{16}N_2O_3$ $[M+H]^+$ 321.1239, found 321.1236.

^{1}H NMR and ^{13}C NMR spectral data for representative compounds.






16.83
8.03
7.61
7.60
7.52
7.51
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7.28
7.26
3.99
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O
O
N
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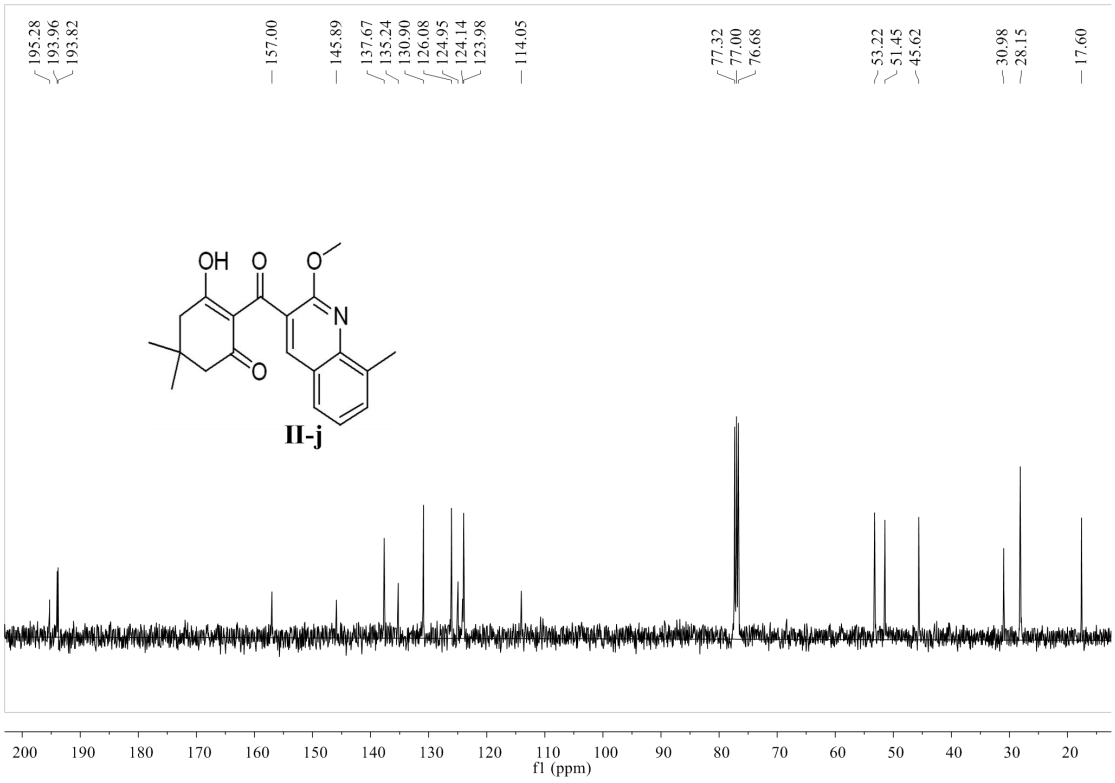
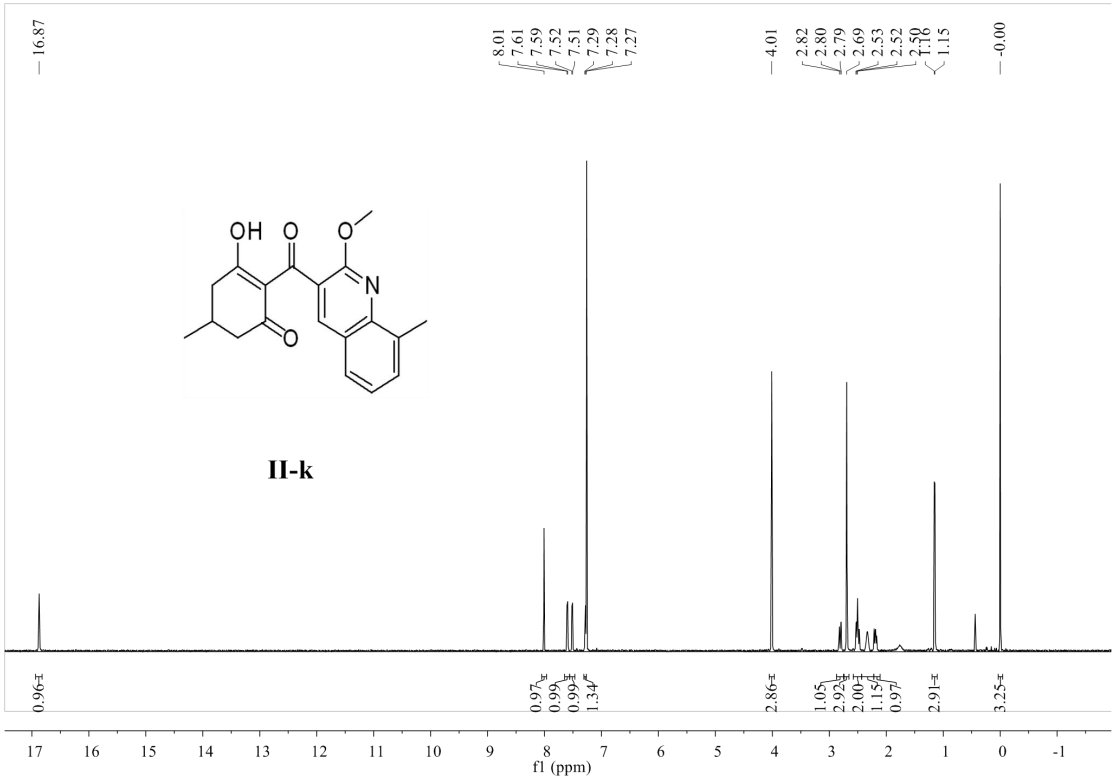
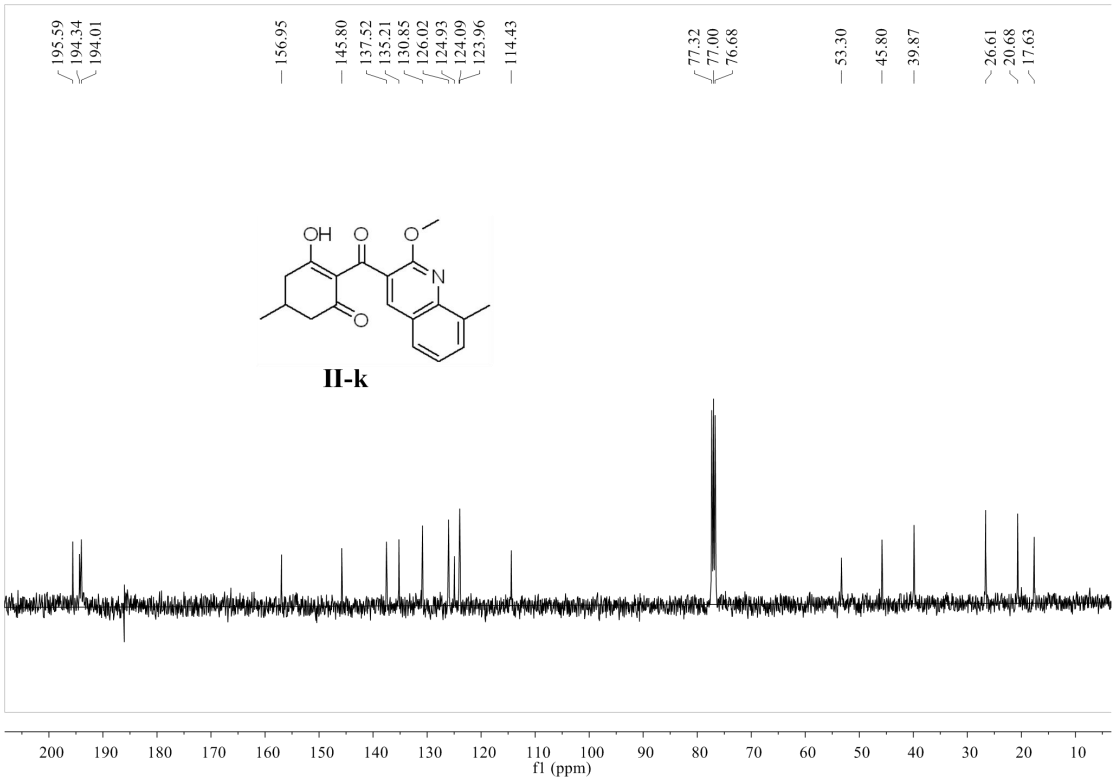
1.04
1.00
1.00
1.02
0.86
3.07
3.09
2.07
2.01
6.13
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

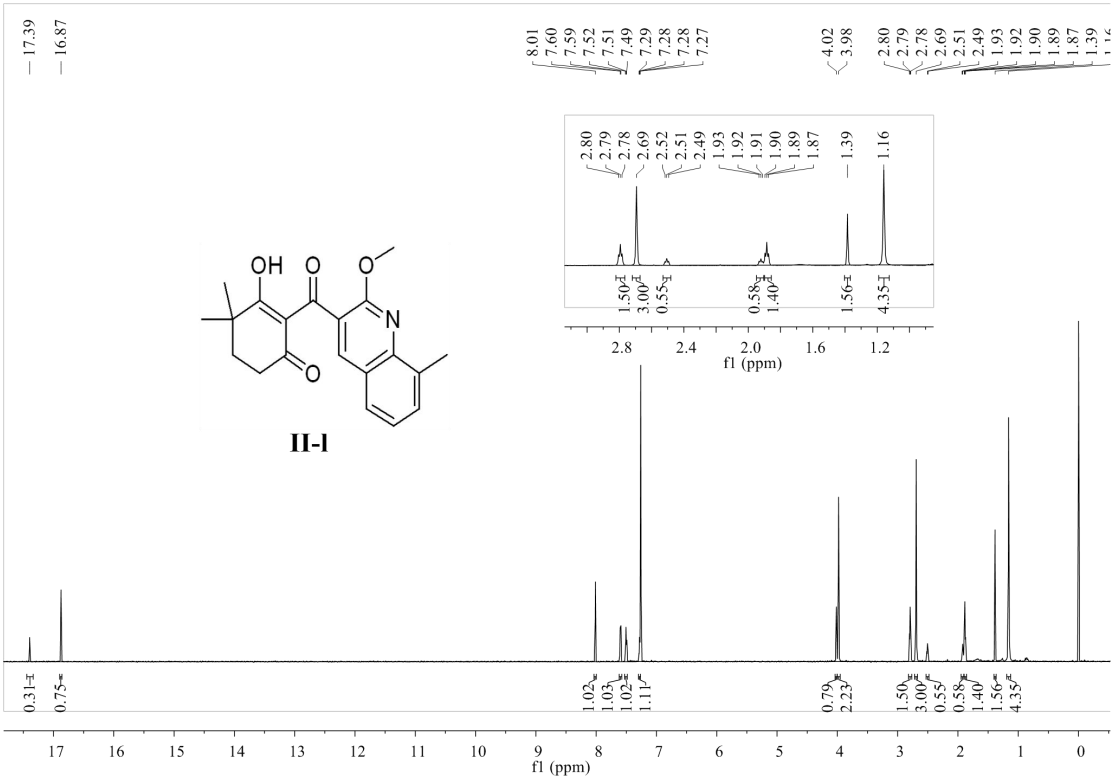
II-j

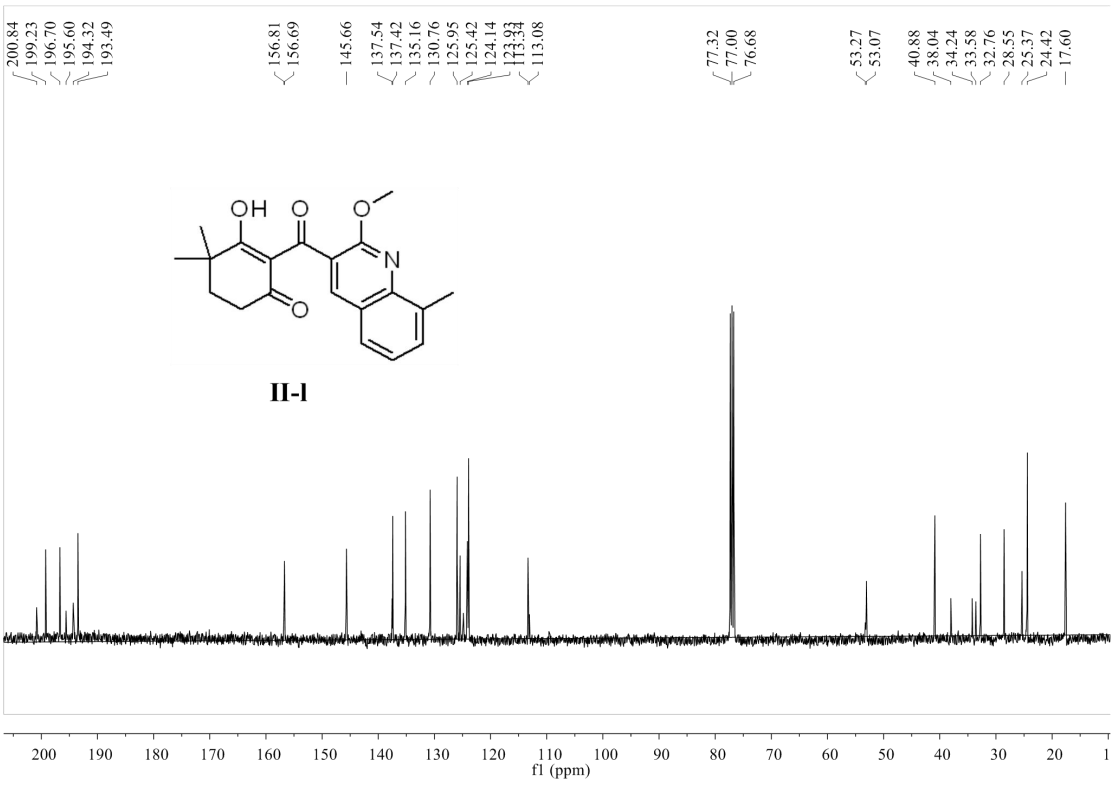

195.28
193.96
193.82
157.00
145.89
137.67
135.24
130.90
126.08
124.95
124.14
123.98
114.05
77.32
77.00
76.68
53.22
51.45
45.62
30.98
28.15
17.60
OH
O
O
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

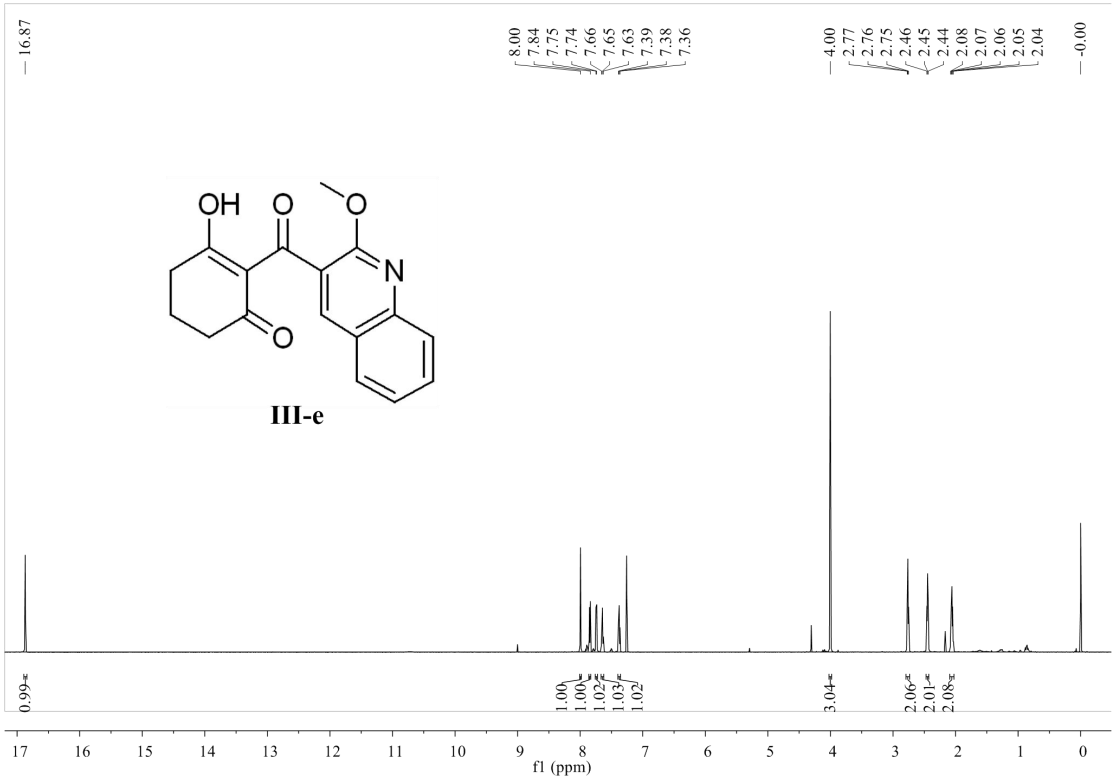
II-j

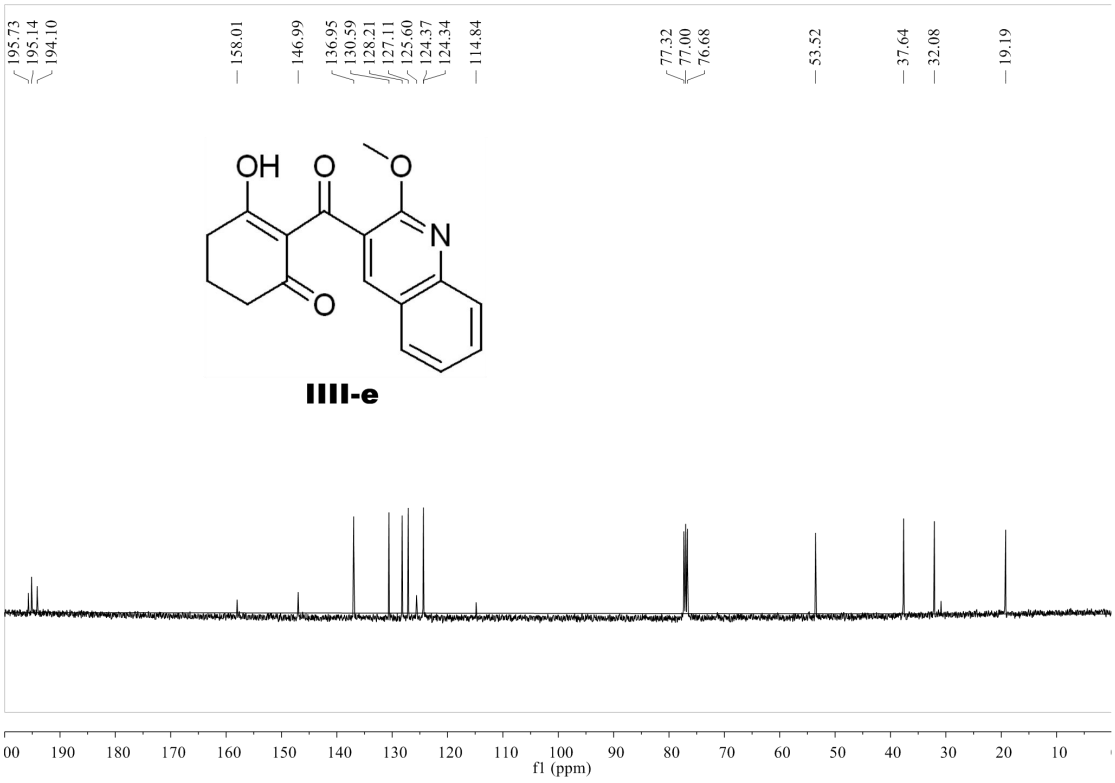

16.87
8.01
7.61
7.59
7.52
7.51
7.29
7.28
7.27
4.01
2.82
2.80
2.79
2.69
2.53
2.52
1.16
1.15
-0.00
OH
O
O
N
O
II-k
0.96
0.97
0.99
0.99
1.34
2.86
1.05
2.92
2.00
1.15
0.97
2.91
3.25
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

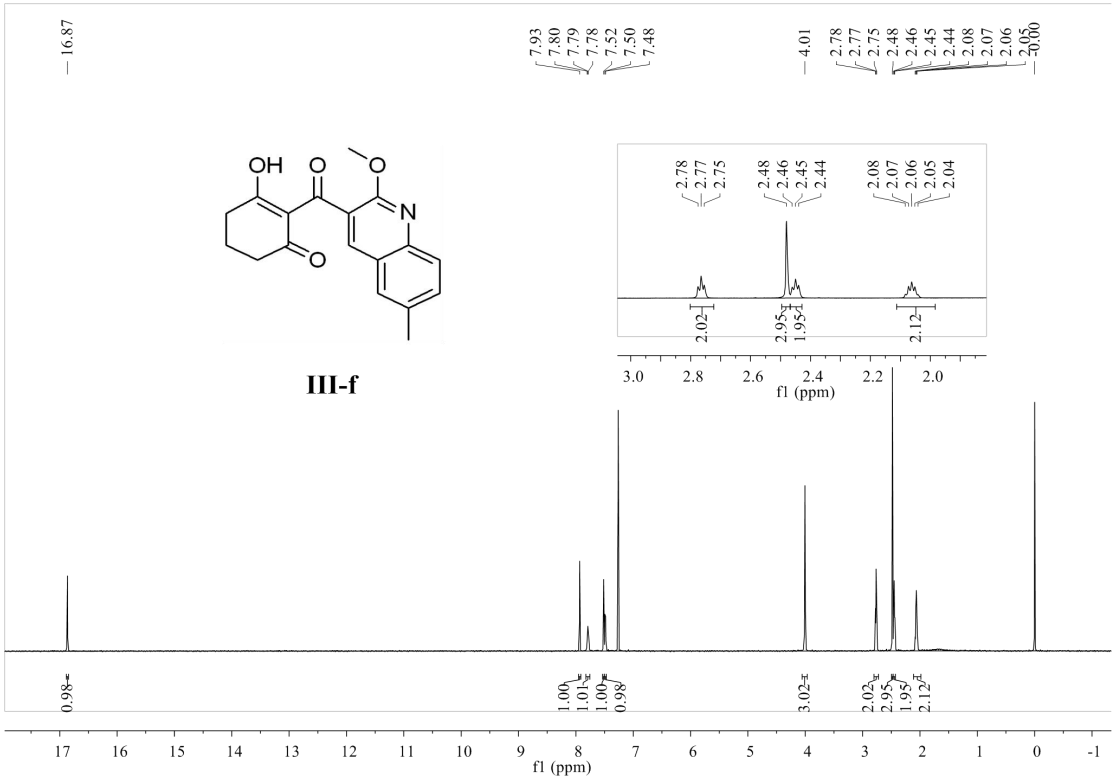

195.59
194.34
194.01
156.95
145.80
137.52
135.21
130.85
126.02
124.93
124.09
123.96
114.43
77.32
77.00
76.68
53.30
45.80
39.87
26.61
20.68
17.63
OH
O
O
N
O
II-k
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

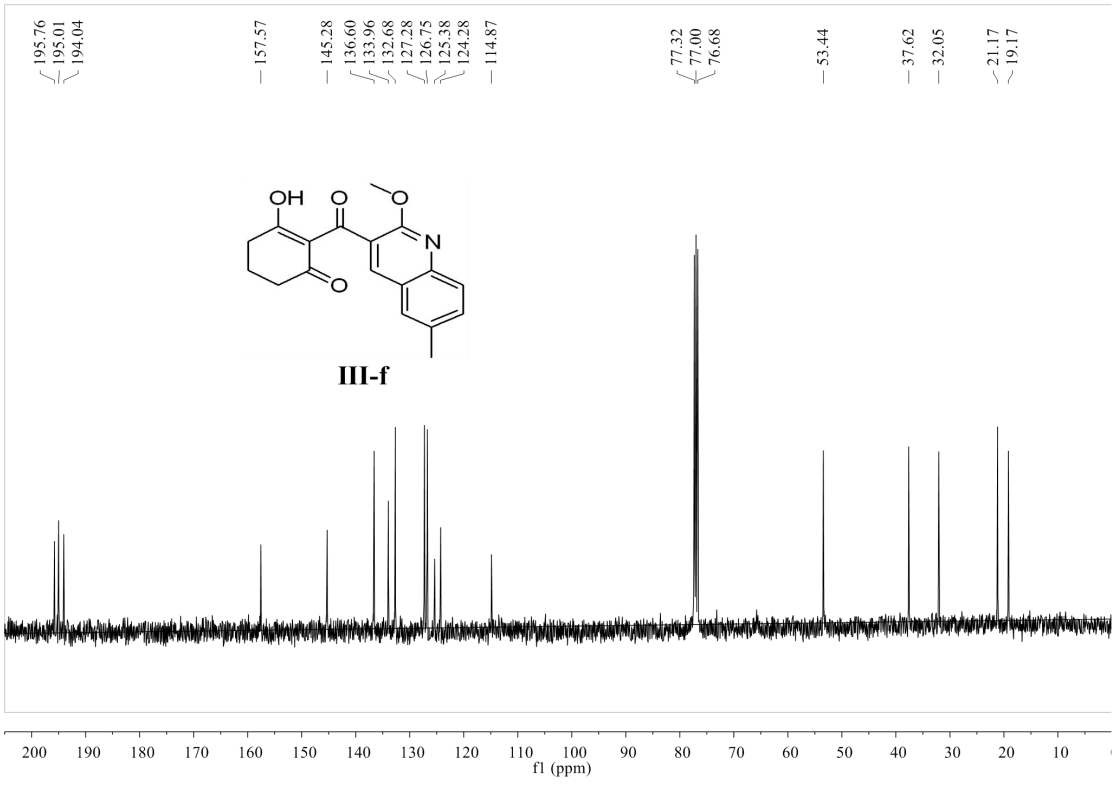

OH
O
O
N
O
II-l
fl (ppm)

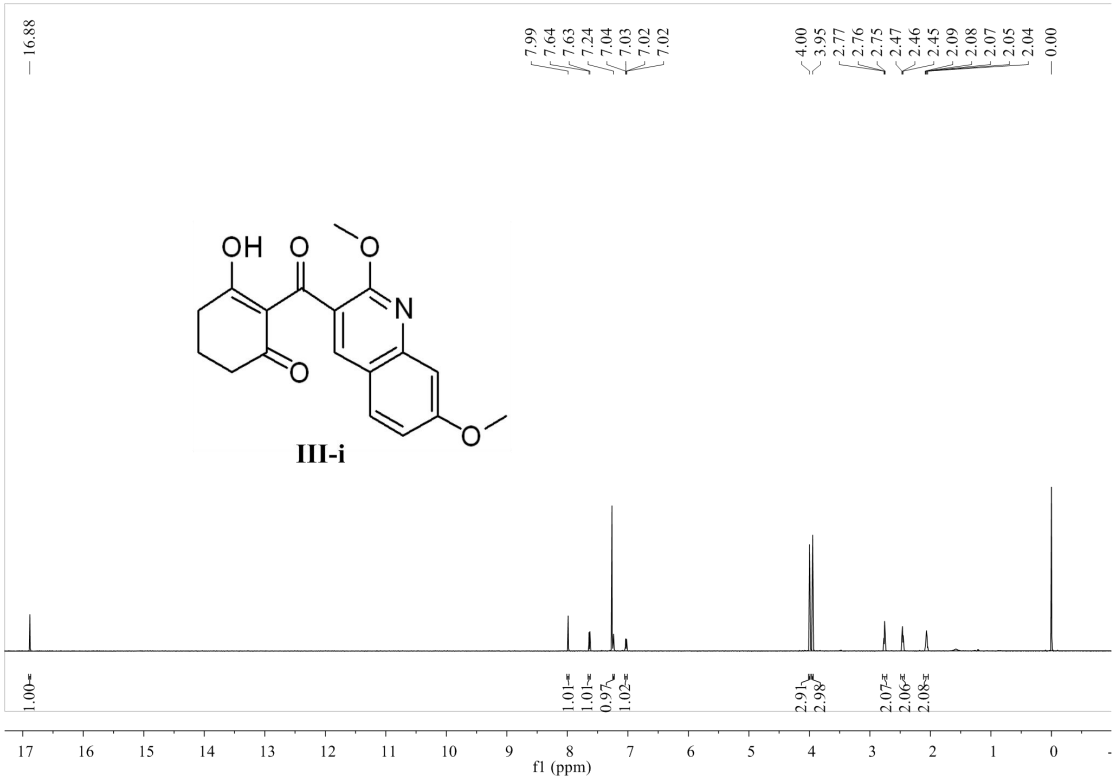

OH
O
O
N
O
II-l
fl (ppm)


16.87
8.00
7.84
7.75
7.74
7.66
7.65
7.63
7.39
7.38
7.36
4.00
2.77
2.76
2.75
2.46
2.45
2.44
2.08
2.07
2.06
2.05
2.04
-0.00
OH
O
O
N
O
III-e
0.99
1.00
1.00
1.02
1.03
1.02
3.04
2.06
2.01
2.08
fl (ppm)

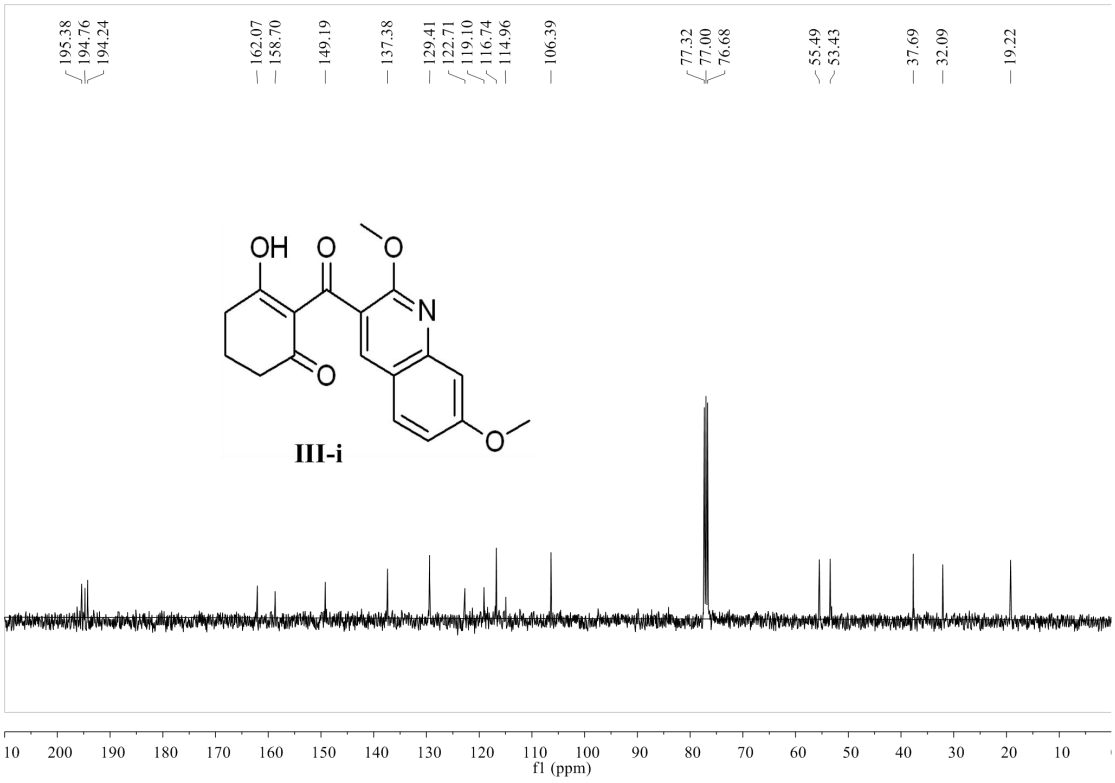

195.73
195.14
194.10
158.01
146.99
136.95
130.59
128.21
127.11
125.60
124.37
124.34
114.84
77.32
77.00
76.68
53.52
37.64
32.08
19.19
OH
O
O
N
O
IIII-e
fl (ppm)


16.87
7.93
7.80
7.79
7.78
7.52
7.50
7.48
4.01
2.78
2.77
2.75
2.48
2.46
2.45
2.44
2.08
2.07
2.06
2.05
2.04
0.00
OH
O
O
N
O
III-f
2.02
2.95
1.95
2.12
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)
0.98
1.00
1.01
1.00
0.98
3.02
2.02
2.95
1.95
2.12
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

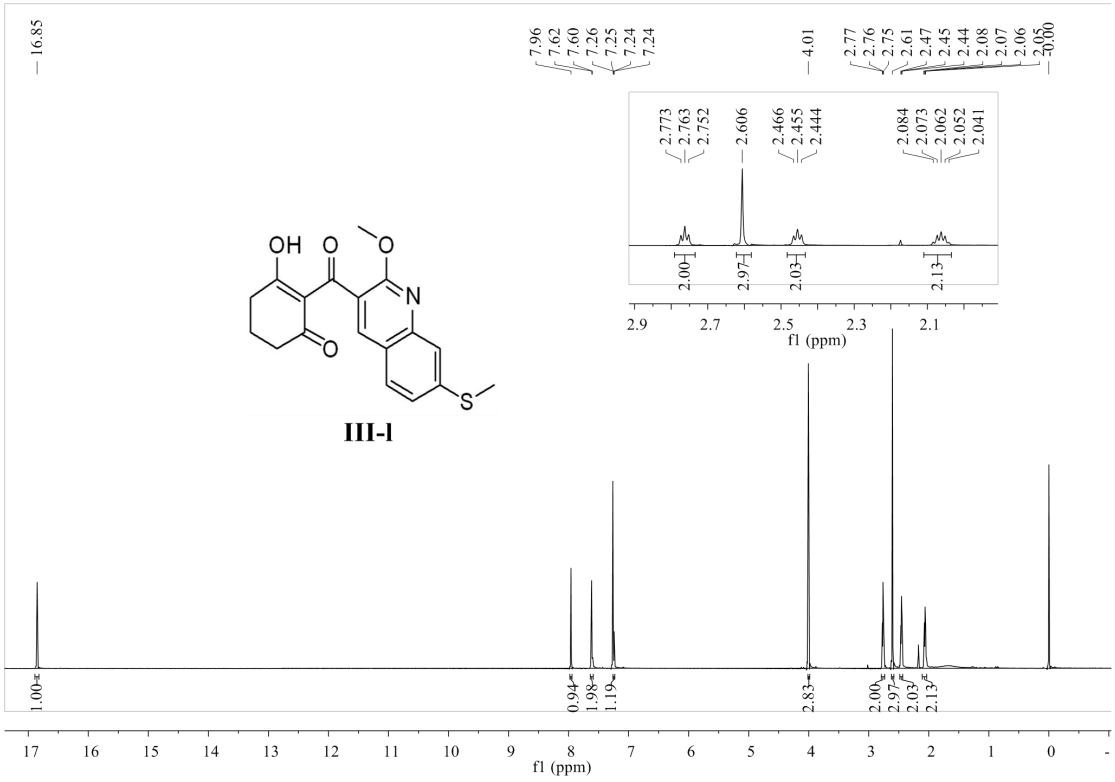

195.76
195.01
194.04
157.57
145.28
136.60
133.96
132.68
127.28
126.75
125.38
124.28
114.87
77.32
77.00
76.68
53.44
37.62
32.05
21.17
19.17
OH
O
O
N
O
III-f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

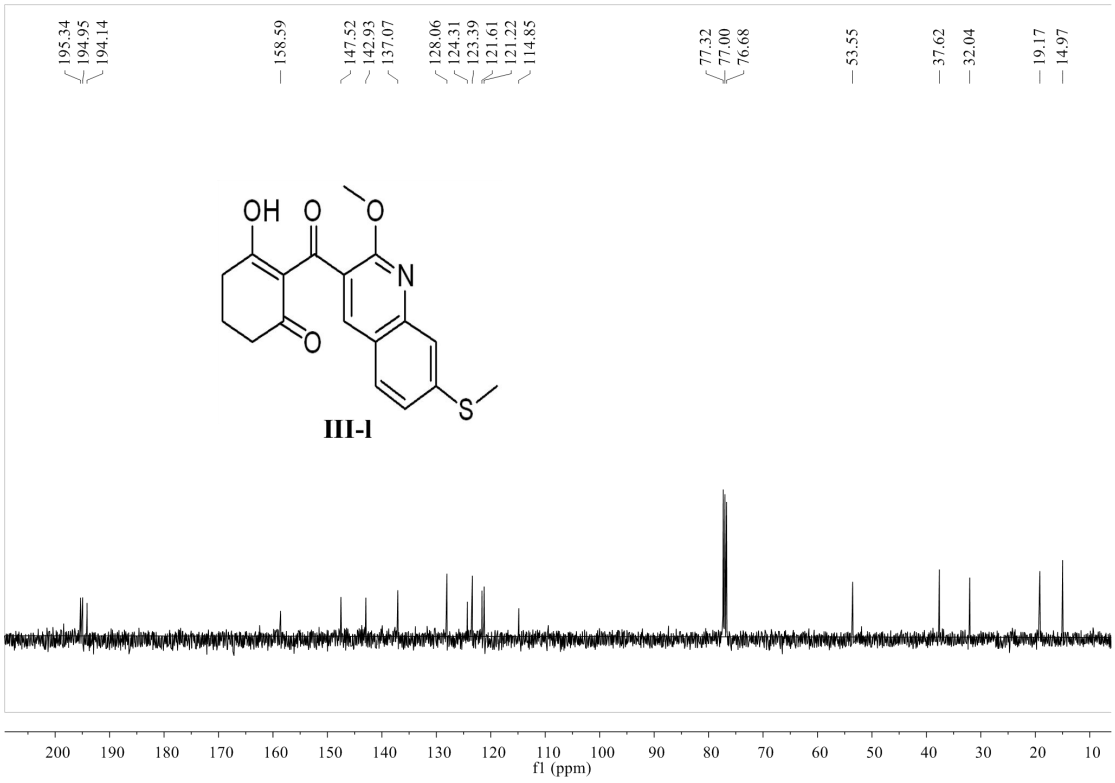

16.88
7.99
7.64
7.63
7.24
7.04
7.03
7.02
7.02
4.00
3.95
2.77
2.76
2.75
2.47
2.46
2.45
2.09
2.08
2.07
2.05
2.04
0.00
OH
O
O
N
O
O
1.00
1.01
1.01
0.97
1.02
2.91
2.98
2.07
2.06
2.08
fl (ppm)

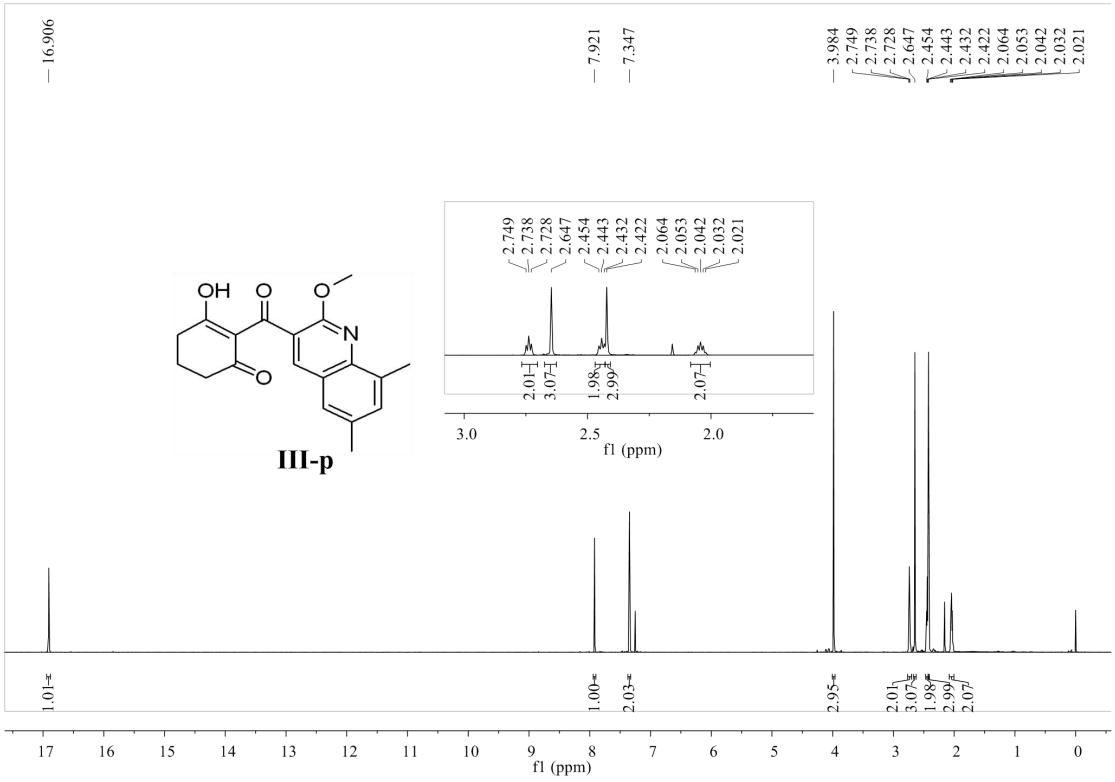
III-i

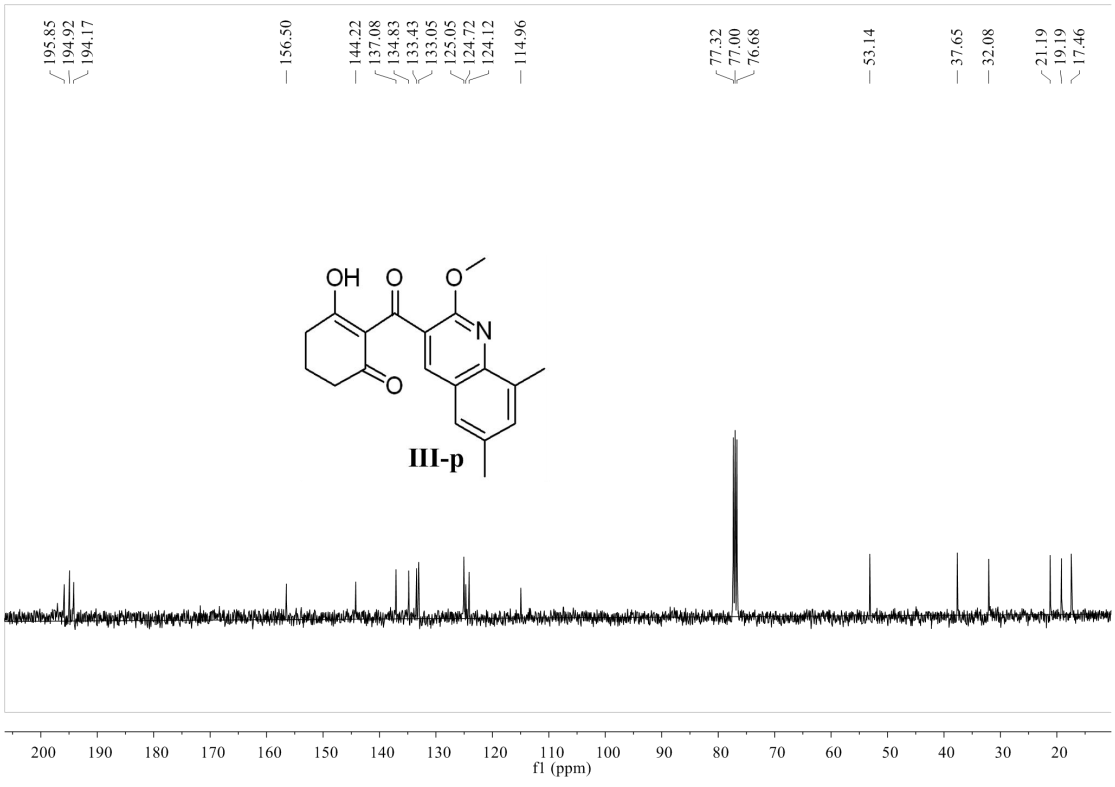

195.38
194.76
194.24
162.07
158.70
149.19
137.38
129.41
122.71
119.10
116.74
114.96
106.39
77.32
77.00
76.68
55.49
53.43
37.69
32.09
19.22
OH
O
O
N
O
O
fl (ppm)

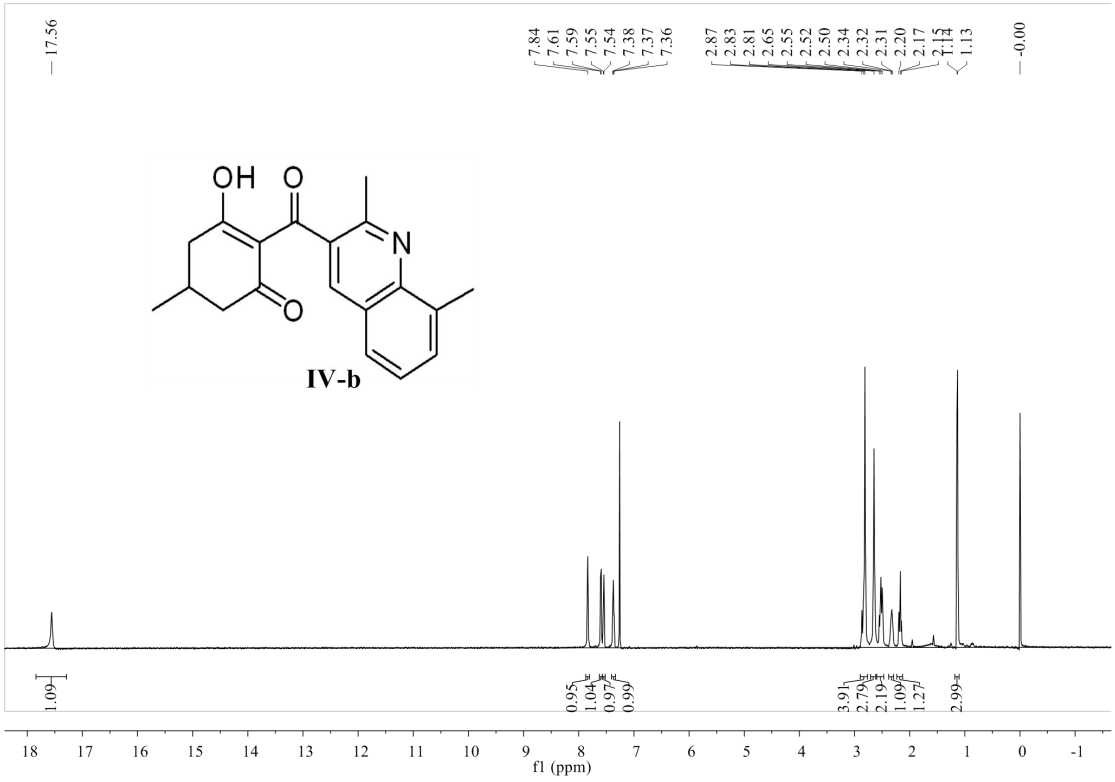
III-i

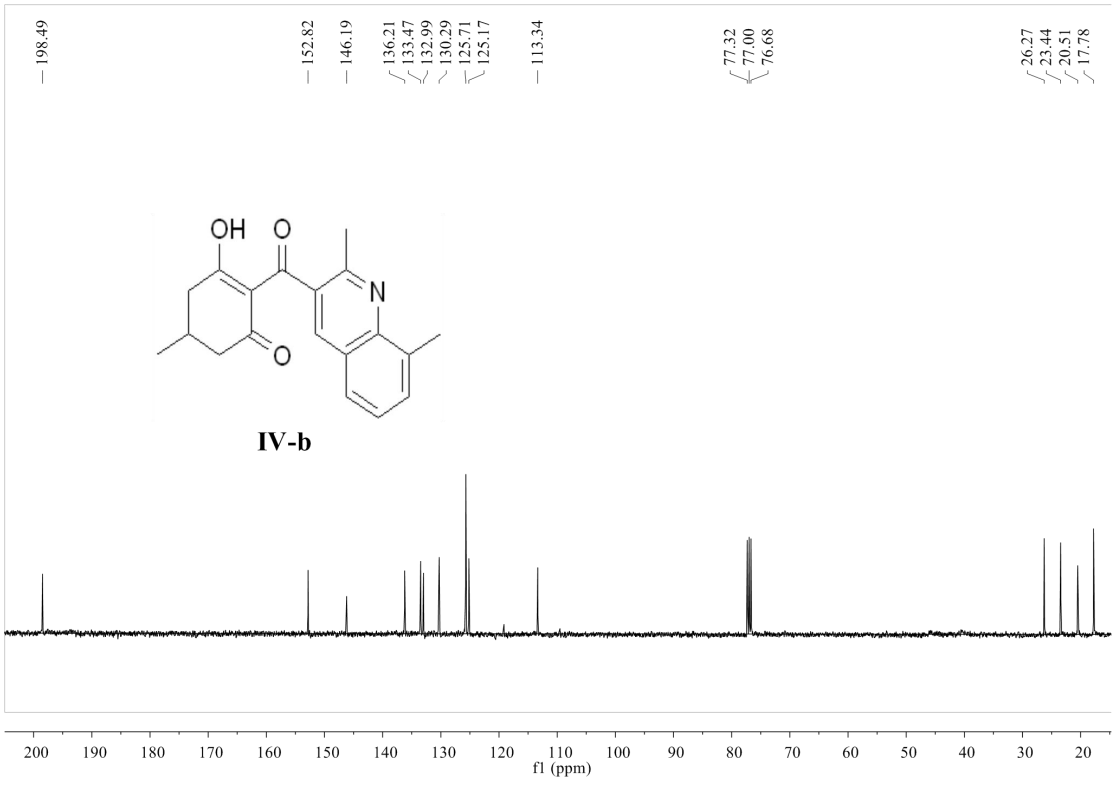

16.85
7.96
7.62
7.60
7.26
7.25
7.24
7.24
4.01
2.77
2.76
2.75
2.61
2.47
2.45
2.44
2.08
2.07
2.06
2.05
0.00
2.773
2.763
2.752
2.606
2.466
2.455
2.444
2.084
2.073
2.062
2.052
2.041
OH
O
O
N
O
S
III-l
2.00
2.97
2.03
2.13
2.9
2.7
2.5
2.3
2.1
f1 (ppm)
1.00
0.94
1.98
1.19
2.83
2.00
2.97
2.03
2.13
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

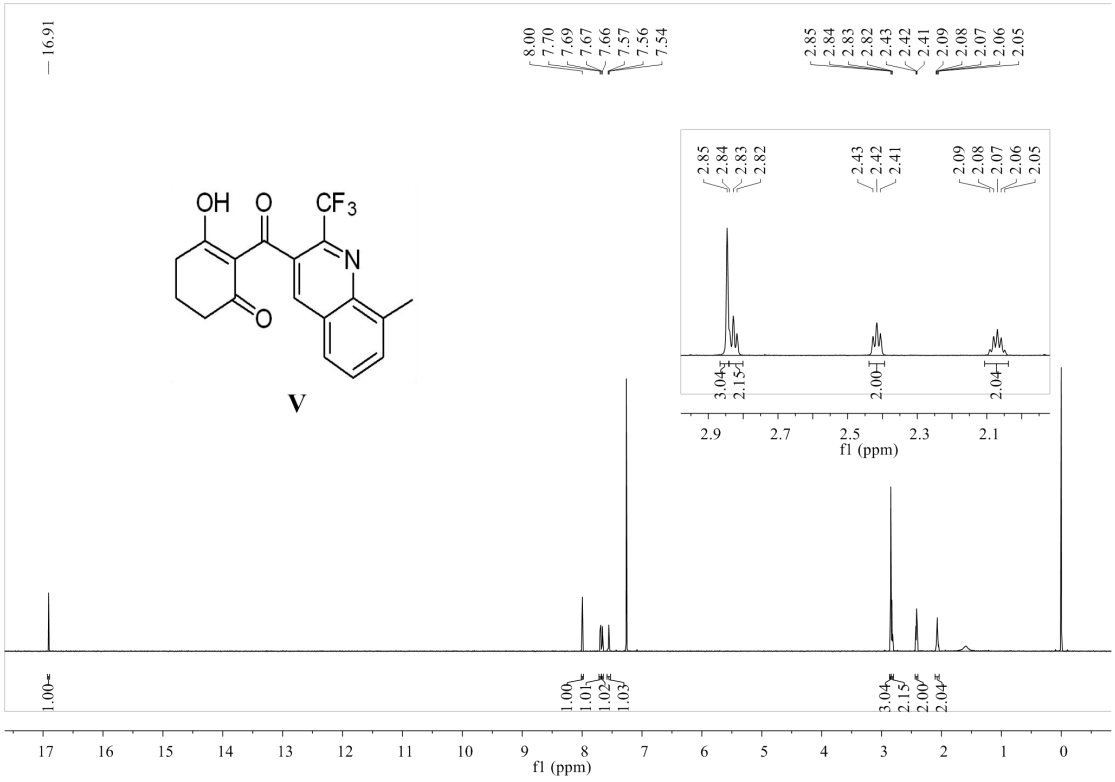

195.34
194.95
194.14
158.59
147.52
142.93
137.07
128.06
124.31
123.39
121.61
121.22
114.85
77.32
77.00
76.68
53.55
37.62
32.04
19.17
14.97
OH
O
O
N
O
S
III-l
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

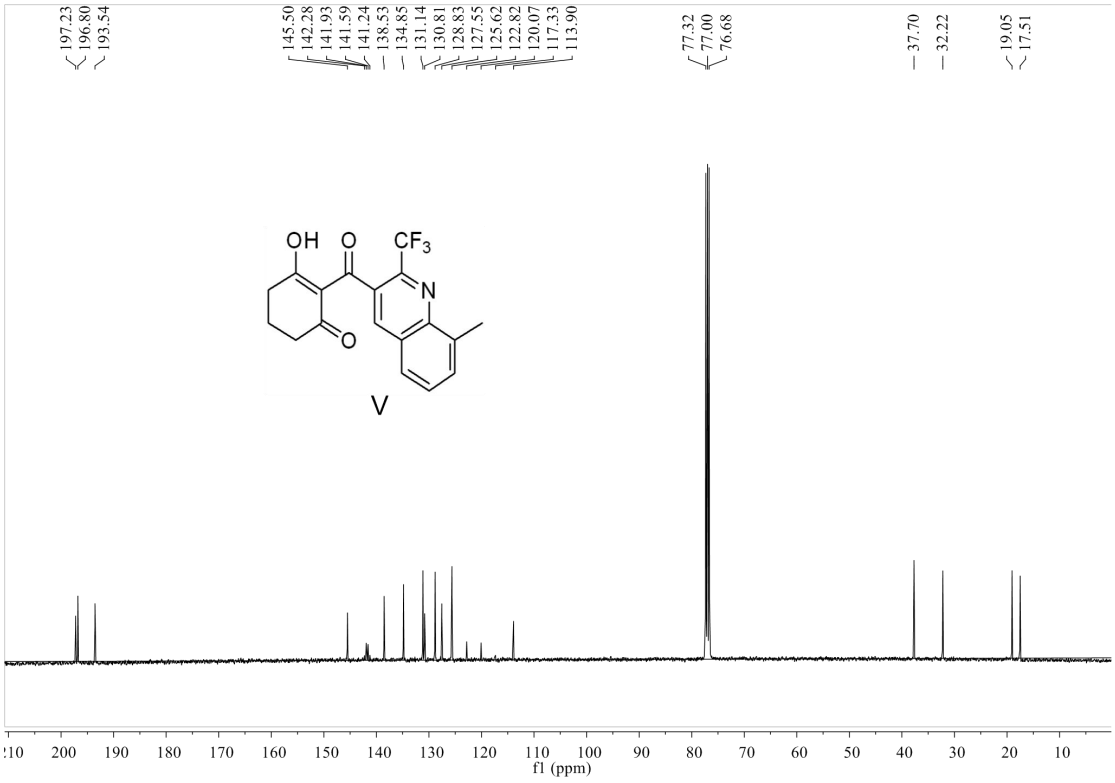

16.906
7.921
7.347
3.984
2.749
2.738
2.728
2.647
2.454
2.443
2.432
2.422
2.064
2.053
2.042
2.032
2.021
OH
O
O
N
O
III-p
2.01
3.07
1.98
2.99
2.07
3.0
2.5
2.0
f1 (ppm)
1.01
1.00
2.03
2.95
2.01
3.07
1.98
2.99
2.07
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

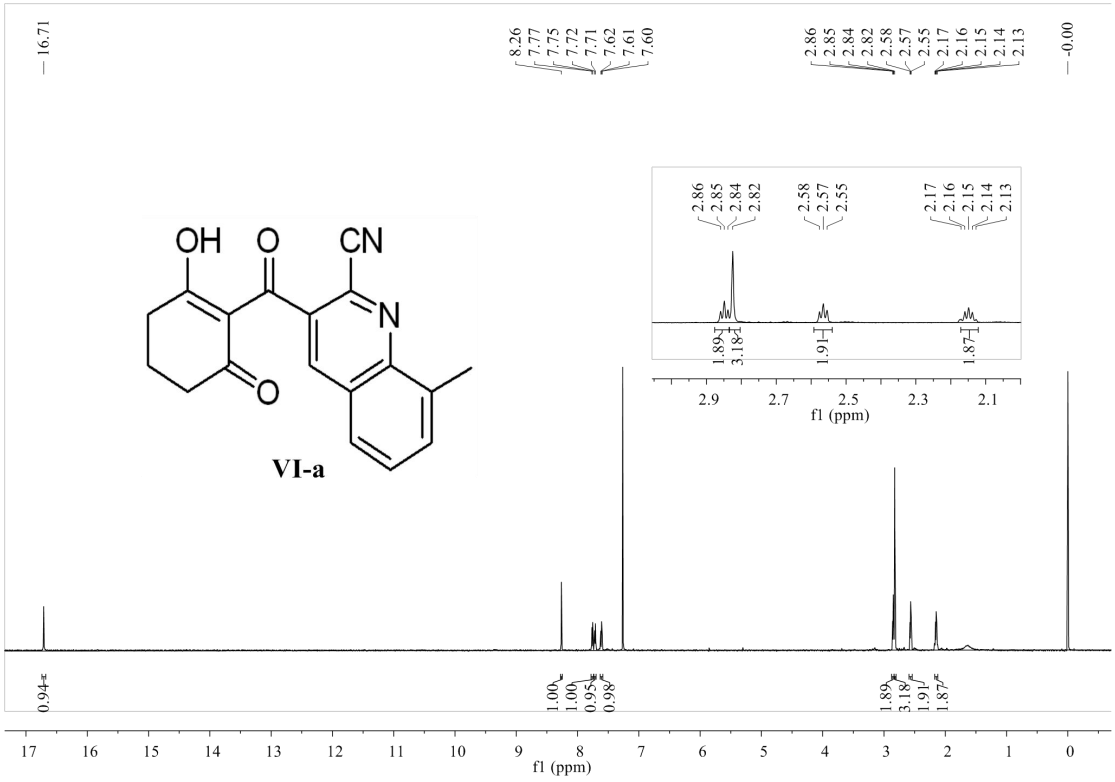

195.85
194.92
194.17
156.50
144.22
137.08
134.83
133.43
133.05
125.05
124.72
124.12
114.96
77.32
77.00
76.68
53.14
37.65
32.08
21.19
19.19
17.46
OH
O
O
N
O
III-p
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

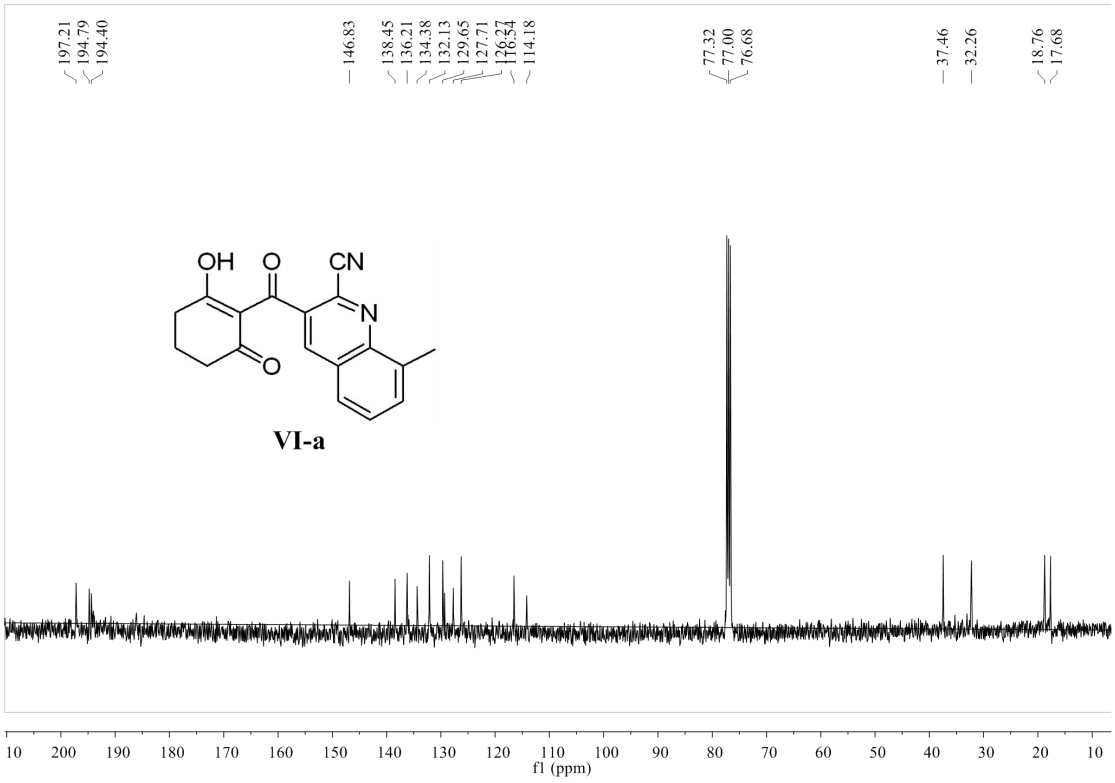

17.56
7.84
7.61
7.59
7.55
7.54
7.38
7.37
7.36
2.87
2.83
2.81
2.65
2.55
2.52
2.50
2.34
2.32
2.31
2.20
2.17
1.13
-0.00
OH
O
N
O
IV-b
1.09
0.95
1.04
0.97
0.99
3.91
2.79
2.19
1.09
1.27
2.99
18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


198.49
152.82
146.19
136.21
133.47
132.99
130.29
125.71
125.17
113.34
77.32
77.00
76.68
26.27
23.44
20.51
17.78
OH
O
N
O
IV-b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


16.91
8.00
7.70
7.69
7.67
7.66
7.57
7.56
7.54
2.85
2.84
2.83
2.82
2.43
2.42
2.41
2.09
2.08
2.07
2.06
2.05
OH
O
CF3
N
O
V
3.04
2.15
2.00
2.04
2.9
2.7
2.5
2.3
2.1
f1 (ppm)
1.00
1.00
1.01
1.02
1.03
3.04
2.15
2.00
2.04
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


197.23
196.80
193.54
145.50
142.28
141.93
141.59
141.24
138.53
134.85
131.14
130.81
128.83
127.55
125.62
122.82
120.07
117.33
113.90
77.32
77.00
76.68
37.70
32.22
19.05
17.51
OH
O
CF3
N
O
V
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


16.71
8.26
7.77
7.75
7.72
7.71
7.62
7.61
7.60
2.86
2.85
2.84
2.82
2.58
2.57
2.55
2.17
2.16
2.15
2.14
2.13
-0.00
OH
O
CN
N
O
VI-a
1.89
3.18
1.91
1.87
f1 (ppm)
0.94
1.00
1.00
0.95
0.98
1.89
3.18
1.91
1.87
f1 (ppm)


197.21
194.79
194.40
146.83
138.45
136.21
134.38
132.13
129.65
127.71
126.27
116.54
114.18
77.32
77.00
76.68
37.46
32.26
18.76
17.68
OH
O
CN
N
O
VI-a
f1 (ppm)