Supporting Information

New Multi-Target-Directed Small Molecules Against Alzheimer's Disease: The Combination of Resveratrol and Clioquinol

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1 Chemistry

1.1 General information

The ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as the internal standard on a Bruker BioSpin GmbH spectrometer (AvanceIII, Switzerland) at 400.132 MHz and 100.614 MHz. Coupling constants are given in Hz. High-resolution mass spectra were obtained using a Shimadzu LCMS-IT-TOF mass spectrometer. Flash column chromatography was performed using silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd or alumina from Sinopharm Chemical Reagent Co. Ltd. All reactions were monitored by thin layer chromatography using silica gel. The purity of compounds **10a-10e**, **10g**, **13a-e** and **13h-13i** (higher than 95%) was confirmed by HPLC [Agilent technologies 1200 series system (**10a-10c, 10e, 10g**, **13b-13e**, **13h-13i**) or

SHIMADZU LC-20A (**10d, 13a**), TC-C18 column (4.6×250 mm, 5μm)] eluted with CH_3CN:water (50 mM KH_2PO_4, pH=3.0) 70:30-35:65 at a flow rate of 0.5 mL/min or 1.0 mL/min).

1.2 General procedure for the preparation of 2 and 4

The preparation was carried out according to a reported procedure.[1] MOMCl (3.5 mL, 45 mmol) was added dropwise to an ice-cooled solution of diisopropylethylamine (10.5 mL, 60 mmol) and **1, 3** or another phenol (30 mmol) in dry CH_2Cl_2 (40 mL). After complete addition, the reaction mixture was allowed to warm to ambient temperature and stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine before being dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel with petrol/ethyl acetate (10:1) as the elution solvent to afford the major product.

4-(methoxymethoxy)benzaldehyde (2)

Colorless oil, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 5.26 (s, 2H), 3.50 (s, 3H).

Methyl 3,5-bis(methoxymethoxy)benzoate (4)

Colorless oil, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.3 Hz, 2H), 6.92 (t, *J* = 2.2 Hz, 1H), 5.19 (s, 4H), 3.90 (s, 3H), 3.48 (s, 6H).

1.3 The preparation of 3,5-bis(methoxymethoxy)benzaldehyde (5).

The preparation was carried out according to a reported procedure.[1, 2] A solution of methyl 3,5-bis(methoxymethoxy)benzoate **4** (5.33 g, 20.8 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred solution of lithium aluminium hydride (25 mL of a 1.0 M solution in THF, 25 mmol). The reaction mixture was stirred at ambient temperature for 4 h. Water (1 mL), 15% aqueous NaOH (1 mL) and water (3 mL) were sequentially added dropwise. After the final addition, stirring was continued for 1 h, and the mixture was filtered. The solid was washed with THF, and the filtrate was evaporated to provide 3,5-bis(methoxymethoxy)benzyl alcohol as a colourless oil (4.56 g, 96% yield). A solution of 3,5-bis(methoxymethoxy)benzyl alcohol (4.56, 20 mmol) in CH_2Cl_2 (8 mL) was added in one portion to a solution of PCC (8.88 g, 41.2 mmol) and sodium acetate (1.13 g, 13.8 mmol) in CH_2Cl_2 (45 mL). The mixture was stirred under nitrogen for 4 h. Ether (300 mL) was added, and the brown mixture was filtered through filter paper over celite. The filtrate was evaporated to provide a brown oil that was purified by flash chromatography with petrol/ethyl acetate (10:1) as the elution solvent to afford the product 3,5-bis(methoxymethoxy)benzaldehyde **5** as a colourless oil (5.45 g, 90.6% yield).

1.4 General procedure for the preparation of 8

Compounds **7a** and **7b** were prepared according to a reported procedure.[3, 4] Triethyl phosphite (5.2 mL, 30 mmol) was added to a round-bottomed flask charged with **7a** or **7b** (10 mmol), and the mixture was heated to reflux for 5 h. Excess triethyl phosphate was removed by vacuum distillation, and the residue was purified by flash chromatography on silica gel with ethyl acetate as the elution solvent to afford the product diethyl ((8-hydroxyquinolin-5-yl)methyl)phosphonate (2.42 g, 82% yield) or diethyl ((8-hydroxy-2-methylquinolin-5-yl)methyl)phosphonate (2.32 g, 75% yield) as a yellow oil.

Compounds **8a** and **8b** were obtained using the general procedure described for the preparation **2** and **4** and were purified by flash chromatography on silica gel with ethyl acetate as the elution solvent.

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate (8a)

Yellow oil, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.44 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.45 – 7.37 (m, 2H), 5.50 (s, 2H), 4.05 – 3.88 (m, 4H), 3.58 (s, 3H), 3.53 (d, *J* = 21.5 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 6H).

Diethyl ((8-(methoxymethoxy)-2-methylquinolin-5-yl)methyl) phosphonate (8b)

Yellow oil, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.32 (m, 3H), 5.49 (s, 2H), 4.05 – 3.84 (m, 4H), 3.59 (s, 3H), 3.51 (d, *J* = 21.4 Hz, 2H), 2.79 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H).

1.5 General procedure for the preparation of 9

Sodium methoxide (3 mmol) was added to a solution of phosphonic acid diethyl ester **8a** or **8b** (1 mmol) in dry DMF (2 mL). The resulting mixture was stirred at room temperature for 5 min, and the appropriate aldehyde (1.2 mmol) was added at 0°C. The mixture was stirred at room temperature for 0.5 h and then for 12 h at 80°C. The reaction was quenched by pouring into ice-water with stirring. Reactions that gave solids were filtered and dried. Reactions that gave oils were extracted with ethyl acetate, and the ethyl acetate layer was washed with water and brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent afforded the oils. The crude solids or oils were purified by flash chromatography on silica gel with petrol / ethyl acetate (1:1) as the elution solvent to afford the desired product.

(E)-4-(2-(8-(methoxymethoxy)quinolin-5-yl)vinyl)-N,N-dimethylaniline (9a)

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate **8a** was treated with 4-(dimethylamino)benzaldehyde according to general procedure to give the desired product **9a** as a yellow solid, 46% yield; ^{1}H NMR (400 MHz, CDCl3) δ 8.97 (d, J = 3.9 Hz, 1H), 8.55 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.52 – 7.42 (m, 5H), 7.02 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 5.52 (s, 2H), 3.59 (s, 3H), 3.00 (s, 6H).

(E)-N,N-diethyl-4-(2-(8-(methoxymethoxy)quinolin-5-yl)vinyl)aniline (9b)

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate **8a** was treated with 4-(diethylamino)benzaldehyde according to general procedure to give the desired product **9b** as a yellow solid, 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.43 (m, 5H), 7.02 (d, *J* = 15.7 Hz, 1H), 6.73 (s, 2H), 5.53 (s, 2H), 3.60 (s, 3H), 3.41 (s, 4H), 1.21 (t, *J* = 6.3 Hz, 6H).

(E)-4-(2-(8-(methoxymethoxy)quinolin-5-yl)vinyl)phenol (9c)

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate **8a** was treated with 4-(methoxymethoxy)benzaldehyde **2** according to general procedure to give the desired product **9c** as a yellow solid, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.53 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 16.0 Hz, 1H), 7.53 – 7.43 (m, 4H), 7.11 – 7.00 (m, 3H), 5.53 (s, 2H), 5.22 (s, 2H), 3.60 (s, 3H), 3.51 (s, 3H).

(E)-5-(2-(8-(methoxymethoxy)quinolin-5-yl)vinyl)benzene-1,3-diol (9d)

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate **8a** was treated with 3,5-bis(methoxymethoxy)benzaldehyde **5** according to general procedure to give the desired product **9d** as a yellow oil, 31% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.53 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.49 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 15.9 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 2H), 6.70 (t, *J* = 2.2 Hz, 1H), 5.54 (s, 2H), 5.22 (s, 4H), 3.60 (s, 3H), 3.52 (s, 6H).

(E)-4-(2-(8-(methoxymethoxy)-2-methylquinolin-5-yl)vinyl)phenol (9e)

Diethyl ((8-(methoxymethoxy)-2-methylquinolin-5-yl)methyl)phosphonate **8b** was treated with 4-(methoxymethoxy)benzaldehyde **2** according to general procedure to give the desired product **9e** as a yellow solid, 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 16.0 Hz, 1H), 5.52 (s, 2H), 5.21 (s, 2H), 3.60 (s, 3H), 3.50 (s, 3H), 2.80 (s, 3H).

(E)-8-(methoxymethoxy)-5-(3,4,5-trimethoxystyryl)quinoline (9f)

Diethyl ((8-(methoxymethoxy)quinolin-5-yl)methyl)phosphonate **8a** was treated with 3,4,5-trimethoxybenzaldehyde according to general procedure to give the desired product **9f** as a yellow solid,

50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 3.9 Hz, 1H), 8.54 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 15.9 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 15.8 Hz, 1H), 6.80 (s, 2H), 5.54 (s, 2H), 3.95 (s, 6H), 3.89 (s, 3H), 3.60 (s, 3H).

1.6 General procedure for the preparation of 10

A solution of compound **9** (0.5 mmol) in methanol (5 mL) was treated with 6 M HCl (0.5 mL), and the mixture was refluxed for 3 h. The solvent was removed by evaporation, and the residue was neutralised by saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine and dried over Na_2SO_4.The solvent was removed by evaporation, and the residue was purified by flash chromatography on silica gel with petrol / ethyl acetate (1:1) as the elution solvent to afford the desired product **10.**

(E)-5-(4-(dimethylamino)styryl)quinolin-8-ol (10a)

Yellow solid, 87% yield, m.p.=173.4-174.2°C; 1H NMR (400 MHz, CDCl3) δ 8.79 (d, J = 4.2 Hz, 1H), 8.57 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.55 – 7.43 (m, 4H), 7.19 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 3.00 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 151.30, 150.19, 147.57, 138.27, 132.80, 130.59, 127.54 (2C), 126.73, 126.44, 126.10, 124.28, 121.45, 119.53, 112.51 (2C), 110.05, 40.48. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{18}N_2O$, 291.1492. found, 291.1506; Purity: 98.4% (by HPLC).

(E)-5-(4-(diethylamino)styryl)quinolin-8-ol (10b)

Yellow solid, 82% yield, m.p.=137.5-138.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 3.7 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.39 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 15.9 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 3.40 (q, *J* = 7.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.20, 147.55, 147.47, 138.28, 132.83, 130.70, 127.80 (2C), 126.90, 126.44, 125.04, 124.17, 121.41, 118.88, 111.79 (2C), 110.08, 44.44, 12.65. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{22}N_2O$, 319.1805. found, 319.1821; Purity: 97.4% (by HPLC).

(E)-5-(4-hydroxystyryl)quinolin-8-ol (10c)

Yellow solid, 91% yield, m.p.=199.1-200.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.1 Hz, 1H), 8.55 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 157.09, 152.59, 147.91, 138.28, 132.66, 129.15, 128.62 (2C), 127.94, 126.41, 125.32, 123.72, 121.61, 120.35, 115.44 (2C), 111.37. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{17}H_{13}NO_2$, 262.0874. found, 262.0871; Purity: 97.8% (by HPLC).

(E)-5-(2-(8-hydroxyquinolin-5-yl)vinyl)benzene-1,3-diol (10d)

Red solid, 18% yield, m.p.=222.6-223.4°C; ^{1}H NMR (400 MHz, DMSO) δ 9.91 (s, 1H), 9.24 (s, 2H), 8.88 (s, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 1H), 6.55 (s, 2H), 6.18 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 158.46 (2C), 153.06, 147.97, 139.18, 138.26, 132.54, 129.65, 126.50, 124.72, 124.42, 123.09, 121.79, 111.36, 104.82 (2C), 102.15, 40.11, 39.90, 39.69, 39.48, 39.27, 39.06, 38.85. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{17}H_{13}NO_3$, 278.0823. found, 278.0837; Purity: 98.0% (by HPLC).

(E)-5-(4-hydroxystyryl)-2-methylquinolin-8-ol (10e)

Yellow solid, 90% yield, m.p.=161.5-162.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 15.9 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 15.9 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 157.07, 156.41, 151.76, 137.60, 132.74, 128.90, 128.65, 127.91 (2C), 125.19, 124.59, 122.60, 122.39, 120.48, 115.44 (2C), 111.11, 24.46. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{18}H_{15}NO_2$, 276.1030. found, 276.1016; Purity: 98.6% (by HPLC).

(E)-5-(3,4,5-trimethoxystyryl)quinolin-8-ol (10f)

Yellow solid, 87% yield; LC/MS (ESI) m/z: $[M+H]^+$ 338.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 3.9 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 15.9 Hz, 1H), 7.51 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.21 (d,

J = 8.0 Hz, 1H), 7.01 (d, *J* = 15.9 Hz, 1H), 6.79 (s, 2H), 3.94 (s, 6H), 3.89 (s, 3H).

1.7 General procedure for the preparation of 12

Compound **12** was prepared according to a reported procedure[5, 6] with modifications. A mixture of 2-methyl-8-hydroxyquinoline (0.358 g, 2.3 mmol), benzaldehyde (2.3 mmol) and acetic anhydride (8 mL) was heated at 130° C under a nitrogen atmosphere for 24 h (TLC monitoring). The reaction was quenched by pouring into ice-water (50 mL) with stirring. The solids were filtered and dried, and the crude products were purified by recrystallisation from petrol / ethyl acetate.

(E)-2-(2-(8-acetoxyquinolin-2-yl)vinyl)phenyl acetate (12a)

Yellow solid, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.13 (d, *J* = 7.9 Hz, 1H), 2.54 (s, 3H), 2.41 (s, 3H).

(E)-3-(2-(8-acetoxyquinolin-2-yl)vinyl)phenyl acetate(12b)

Yellow solid, 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.32 (d, *J* = 16.1 Hz, 2H), 7.06 (dd, *J* = 7.9, 1.1 Hz, 1H), 2.56 (s, 3H), 2.33 (s, 3H).

(E)-2-(4-bromostyryl)quinolin-8-yl acetate (12c)

Yellow solid, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 6.9 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.65 – 7.40 (m, 6H), 7.32 (d, *J* = 16.2 Hz, 1H), 2.56 (s, 3H).

(E)-2-(4-nitrostyryl)quinolin-8-yl acetate (12d)

Yellow solid, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 8.6 Hz, 1H), 7.77 – 7.69 (m, 4H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.44 (m, 3H), 2.57 (s, 3H).

(E)-4-(2-(8-acetoxyquinolin-2-yl)vinyl)phenyl acetate (12e)

Yellow solid, 65% yield; LC/MS (ESI) m/z: $[M+H]^+$ 306.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.59 (m, 5H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.29 (d, *J* = 16.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 2.56 (s, 3H), 2.32 (s, 3H).

1.8 General procedure for the preparation of 13

Compound **13** was prepared according to a reported procedure[6] with modifications. Compound **12a** (0.8 mol) was dissolved in DMF (8 mL) and concentrated hydrochloric acid (0.8 mL) was added to the solution. The mixture was heated at 100° C for 3 h before the addition of ice-water (20 mL) to the mixture. The pH of the mixture was adjusted to 7-8 with saturated aqueous $NaHCO_3$. The mixture was then extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. Filtration and evaporation of the ethyl acetate afforded a solid that was purified by flash chromatography on silica gel with petrol / ethyl acetate (5:1-1:1) as the elution solvent to afford the desired product **13.**

(E)-2-(2-hydroxystyryl)quinolin-8-ol (13a)

Yellow solid, 82% yield, m.p.=188.5-189.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 16.4 Hz, 1H), 7.67 (t, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 6.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 155.88, 154.22, 152.83, 138.18, 136.33, 130.16, 129.61, 128.23, 128.01, 127.55, 126.78, 123.14, 120.28, 119.41, 117.58, 116.07, 111.25. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}NO_2$, 264.1019. found, 264.1021; Purity: 99.6% (by HPLC).

(E)-2-(3-hydroxystyryl)quinolin-8-ol (13b)

Yellow solid, 80% yield, m.p.=141.5-142.5°C; ^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 2H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.02 (d, *J* = 16.2 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.37 – 7.33 (m, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.77 (dd, *J* = 7.9, 1.6 Hz, 1H). ^{13}C NMR (101 MHz,

DMSO) δ 157.69, 153.39, 152.88, 138.09, 137.75, 136.41, 134.52, 129.80, 127.77, 127.62, 126.98, 120.88, 118.14, 117.51, 115.82, 113.63, 111.16. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{17}H_{13}NO_2$, 262.0874. found, 262.0871; Purity: 99.6% (by HPLC).

(E)-2-(4-bromostyryl)quinolin-8-ol (13c)

Yellow solid, 90% yield, m.p.=135.7-136.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.64 (t, *J* = 13.0 Hz, 2H), 7.56 – 7.53 (m, 2H), 7.52 – 7.47 (m, 2H), 7.44 – 7.38 (m, 1H), 7.36 – 7.28 (m, 2H), 7.17 (dd, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.20, 152.06, 138.03, 136.51, 135.32, 132.97, 132.00 (2C), 128.74, 128.66 (2C), 127.54, 127.47, 122.67, 120.40, 117.69, 110.24. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{12}BrNO$, 326.0175. found, 326.0190; Purity: 99.1% (by HPLC).

(E)-2-(4-nitrostyryl)quinolin-8-ol (13d)

Yellow solid, 93% yield, m.p.=198.5-199.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.32, 152.17, 147.48, 142.77, 138.10, 136.79, 132.31, 131.58, 128.05, 127.85, 127.66 (2C), 124.22 (2C), 120.67, 117.76, 110.49. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_{17}H_{12}N_2O_3$, 291.0775. found, 291.0762; Purity: 98.5% (by HPLC).

(E)-2-(4-hydroxystyryl)quinolin-8-ol (13e)

Yellow solid, two steps yield 41% yield, m.p.=168.5-169.7°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 16.3 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.23 (s, 1H), 7.20 – 7.14 (m, 1H), 6.89 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 158.21, 153.96, 152.71, 138.08, 136.26, 134.50, 128.74, 127.51, 127.37, 126.60, 124.66, 120.62, 117.51, 115.75, 111.04. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}NO_2$, 264.1019. found, 264.020; Purity: 99.5% (by HPLC).

(E)-2-(3,5-dimethoxystyryl)quinolin-8-ol (13f)

Yellow solid, two steps yield 38% yield; LC/MS (ESI) m/z: $[M+H]^+$ 308.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 6.2 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.34 (s, 1H), 7.32 – 7.29 (m, 1H), 7.17 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 2H), 6.47 (s, 1H), 3.86 (s, 6H).

(E)-2-(3,4,5-trimethoxystyryl)quinolin-8-ol (13g)

Yellow solid, 86% yield; LC/MS (ESI) m/z: $[M+H]^+$ 338.1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 11.4 Hz, 1H), 7.63 (d, *J* = 3.8 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 11.4 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.88 (s, 2H), 3.96 (s, 6H), 3.90 (s, 3H).

1.9 General procedure for the preparation of 10g and 13h-13i

BBr_3 (5-7.5 eq.) was added dropwise at -78°C under nitrogen to a solution of dried CH_2Cl_2 containing compound **10f** or **13f-13g** (0.5 mmol). The resulting solution was slowly warmed to room temperature and stirred overnight. After monitoring the reaction progress by TLC, water was added slowly. The mixture was neutralised by saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate layer was washed with water then dried over Na_2SO_4.The solvent was removed by evaporation, and the residue was purified by flash chromatography on silica gel with CH_2Cl_2 / methanol (10:1-5:1) as the elution solvent to afford the desired product **10g** or **13h-13i.**

(E)-5-(2-(8-hydroxyquinolin-5-yl)vinyl)benzene-1,2,3-triol (10g)

Red solid, 53% yield, m.p.=218.25-219.1°C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.61 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 15.9 Hz, 1H), 6.64 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 154.16, 149.69, 147.92, 139.84, 135.18, 134.65, 131.95, 130.12, 128.23, 127.20, 125.85, 123.56, 122.14, 113.33, 107.73. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}NO_4$, 296.0717. found, 296.0717; Purity: 98.6% (by HPLC).

(E)-5-(2-(8-hydroxyquinolin-2-yl)vinyl)benzene-1,3-diol (13h)

Red solid, 63% yield, m.p.=229.2-229.9°C; ^{1}H NMR (400 MHz, DMSO) δ 9.39 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H),

7.89 (d, *J* = 16.2 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.27 (d, *J* = 16.2 Hz, 1H), 7.08 (dd, *J* = 7.0, 1.6 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 2H), 6.25 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 160.49, 160.35, 155.34, 154.62, 140.03, 139.91, 138.25, 136.72, 129.45 (2C), 128.82, 122.67, 119.42, 112.99, 107.22, 107.14, 105.08. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}NO_3$, 280.0968. found, 280.0971; Purity: 98.7% (by HPLC).

(E)-5-(2-(8-hydroxyquinolin-2-yl)vinyl)benzene-1,2,3-triol (13i)

Red solid, 51% yield, m.p.=194.7.5-195.3°C; ^{1}H NMR (400 MHz, DMSO) δ 8.19 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 16.1 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.05 (dd, *J* = 15.0, 9.0 Hz, 2H), 6.66 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 155.85, 154.47, 147.93, 139.90, 138.06, 137.14, 136.40, 129.21, 128.90, 128.43, 126.59, 122.42, 119.40, 112.87, 108.33. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}NO_4$, 296.0917. found, 296.0918; Purity: 97.1% (by HPLC).

2 Biological Assays

2.1 ThT assay[7]

A hexafluoro-2-propanol (HFIP) pretreated $A\beta_{1-42}$ sample (Sigma, CA, US) was dissolved in ammonium hydroxide (1% v/v) to give a stock solution (2000μM) that was aliquoted into small samples and stored at -80°C.

For the inhibition of self-mediated $A\beta_{1-42}$ aggregation experiment, the $A\beta_{1-42}$ stock solution was diluted with 50 mM phosphate buffer (pH 7.4) to 50μM before use. A mixture of the peptide (10μL, 25μM and final concentration) with or without the test compound (10μL, 20μM and final concentration) was incubated at 37°C for 48 h. Blanks using 50 mM phosphate buffer (pH 7.4) instead of $A\beta_{1-42}$ in the presence or absence of compounds were also carried out. Then, the samples were diluted to a final volume of 200 μL with 50 mM glycine-NaOH buffer (pH 8.0) containing thioflavin T (5 μM). The fluorescence intensity was recorded 5 min later (λex = 450 nm, λem = 485 nm). The percentage of inhibition of aggregation was calculated according to the following formula: $(1 - F_{Sample} / F_{Control}) \times 100$, where F_{Sample} and $F_{Control}$ are the fluorescence intensity of $A\beta_{1-42}$ in the presence and absence of inhibitors after subtracting the background, respectively.

For the inhibition of the copper(II)-induced $A\beta_{1-42}$ aggregation experiment, the $A\beta_{1-42}$ stock solution was diluted in 20μM HEPES (pH 6.6) with 150 μM NaCl. The mixture of the peptide (10 μL, 25 μM and final concentration) with or without copper(II) (10 μL, 25 μM and final concentration) and the test compound (10 μL, 50 μM and final concentration) was incubated at 37°C for 24 h. Then, 20 μL of the sample was diluted to a final volume of 200μL with 50 mM glycine-NaOH buffer (pH 8.0) containing thioflavin-T (5μM). The detection method was the same as the self-mediated $A\beta_{1-42}$ aggregation experiment.

For the disaggregation of the self-mediated $A\beta_{1-42}$ fibrils experiment, the $A\beta_{1-42}$ stock solution was diluted with 10 mM phosphate buffer (pH 7.4). The peptide (15 μL and 50 μM) was incubated at 37°C for 24 h. The test compound (15 μL and 50 μM) was then added and incubated at 37°C for another 24 h. Then, 20 μL of the sample was diluted to a final volume of 200 μL with 50 mM glycine-NaOH buffer (pH 8.0) containing thioflavin-T (5 μM). The detection method was the same as above.

For the disaggregation of the copper(II)-induced $A\beta_{1-42}$ fibrils experiment, the $A\beta_{1-42}$ stock solution was diluted in 20 μM HEPES (pH 6.6) with 150 μM NaCl. The mixture of the peptide (10 μL, 25 μM and final concentration) with copper(II) (10 μL, 25 μM and final concentration) was incubated at 37°C for 24 h. The test compound (10 μL, 50 μM and final concentration) was then added and incubated at 37°C for another 24 h.[30] Then, 20 μL of the sample was diluted to a final volume of 200 μL with 50 mM glycine-NaOH buffer (pH 8.0) containing thioflavin-T (5 μM). The detection method was the same as above.

2.2 TEM assay[8-10]

For the metal-free experiment, the $A\beta_{1-42}$ stock solution was diluted with 10 mM phosphate buffer (pH 7.4). For the copper(II)-induced experiment, the $A\beta_{1-42}$ stock solution was diluted with 20 μM HEPES (pH 6.6) and 150 μM

NaCl. The sample preparation was the same as for the ThT assay. Aliquots (10 μL) of the samples were placed on a carbon-coated copper/rhodium grid for 2 min. Each grid was stained with uranyl acetate (1%, 5μL) for 2 min. After draining off the excess staining solution, the specimen was transferred for imaging by transmission electron microscopy (JEOL JEM-1400). All compounds were solubilised in the buffer used for the experiment.

2.3 Oxygen radical absorbance capacity (ORAC-FL) assay [11-13]

The tested compound and fluorescein (FL) stock solution were diluted with 75 mM phosphate buffer (pH 7.4) to 10 μM and 0.117 μM, respectively. The solution of (±)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) was diluted with the same buffer to 100, 80, 60, 50, 40, 20, and 10 μM. The solution of 2,2'-azobis-(amidinopropane)dihydrochloride (AAPH) was prepared before the experiment by dissolving 108.4 mg AAPH in 10 mL 75 mM phosphate buffer (pH 7.4) to a final concentration of 40 mM. The mixture of the tested compound (20 μL) and FL (120 μL; 70 nM, final concentration) was pre-incubated for 10 min at 37ºC, and then 60 μL of the AAPH solution was added. The fluorescence was recorded every minute for 120 min (excitation, 485 nm; emission, 520 nm). A blank using phosphate buffer instead of the tested compound was also carried out. All reaction mixtures were prepared triple and at least three independent runs were performed for each sample. The Antioxidant curves (fluorescence versus time) were normalized to the curve of the blank. The area under the fluorescence decay curve (AUC) was calculated as following equation:

$$AUC = 1 + \sum_{i=1}^{i=120} (f_i / f_0)$$

Where f_0 is the initial fluorescence reading at 0 min and f_i is the fluorescence reading at time i. The net AUC was calculated by the expression: $AUC_{sample} - AUC_{blank}$. Regression equations between net AUC and Trolox concentrations were calculated. ORAC-FL value for each sample were calculated by using the standard curve which means the ORAC-FL value of tested compound expressed as Trolox equivalents.

2.4 Metal chelation

The complexation studies were performed in HEPES buffer solution (20 mM, containing 150 mM NaCl, pH=7.4) at 298 K using a UV-vis spectrophotometer (SHIMADZC UV-2450PC) at wavelengths ranging from 200 to 650 nm. Compound **10c** was dissolved in DMSO and diluted with HEPES buffer solution (PH=7.4) to a concentration of 50 μM. Then, 100 μL of HEPES buffer solution and 100 μL of metal solution (200 μM of $CuSO_4$, $FeSO_4$, or $ZnCl_2$) were added to the mixture containing 800 μL of the test compound solution. The solution was incubated at 298 K for 10 min and the absorption spectra were recorded at 298 K in a 1 cm quartz cell using a blank containing 4 μL DMSO in 996 μL HEPES (pH=7.4). The blank absorption spectrum was subtracted from all of the absorption spectra.

The stoichiometry of the **10c**-copper(II) complex was determined by employing Job's method. A series of solutions were prepared in HEPES buffer with the condition that the sum of the concentrations of compound **10c** and copper(II) was constant in all samples and that the proportions of both them varied between 0 and 100%. The absorbance differences at 445 nm were plotted versus the mole fraction of copper(II)**.**

2.5 Ascorbate studies

All of the solutions, except $CuSO_4$ (Milli-Q water only) and **10c (**dissolved in methanol and diluted in PBS), were mixed and diluted in a phosphate (20 mM), NaCl (100 mM) buffer (PBS) at pH 7.4 with a final sample volume of 200 μL.[14] Each experiment was performed in triplicate. Hydroxyl radical production was measured as the conversion of CCA into 7-hydroxy-CCA (λexcitation = 395 nm, λemission = 450 nm). The general order of addition was as follows: CCA [50 μM], ligand [15 μM] or copper [5 μM], and then ascorbate [150 μM]. All of the test solutions contained 1 μM desferryl and 0.1% methanol.

2.6 In vitro Blood-Brain Barrier Permeation Assay

The brain penetration of the compounds was evaluated using a parallel artificial membrane permeation assay (PAMPA) similar to the procedure described by Di et al.[15] Commercial drugs were purchased from Sigma and Alfa Aesar. The porcine brain lipid (PBL) was obtained from Avanti Polar Lipids. The donor microplate (PVDF membrane, pore size 0.45 mm) and the acceptor microplate were obtained from Millipore. The 96-well UV plate (COSTAR®) was obtained from Corning Incorporated. The acceptor 96-well microplate was filled with 300 µL of PBS/EtOH (7:3), and the filter membrane was impregnated with 4 µL of PBL in dodecane (20 mg mL^{-1}). The compounds were dissolved in DMSO at 5 mg mL^{-1} and diluted 50-fold in PBS/EtOH (7:3) to achieve a concentration of 100 mg mL^{-1} before 200 µL was added to the donor wells. The acceptor filter plate was carefully placed on the donor plate to form a sandwich, which was left undisturbed for 10 h at 25°C. After incubation, the donor plate was carefully removed, and the concentration of compounds in the acceptor wells was determined using the UV plate reader (Flexstation® 3). Every sample was analysed at five wavelengths in four wells and in at least three independent runs, and the results are given as the means ± standard deviation. In each experiment, 13 quality control standards of known BBB permeability (Table S2) were included to validate the analysis set. P_e can be calculated from the following equation as reported by Faller et al.[16] and Sugano et al.[17]

$$P_e = -\left(\frac{V_d \times V_a}{(V_d + V_a)\ A \times t}\right) \times \ln\left(1 - \frac{[drug]_{acceptor}}{[drug]_{equilibrium}}\right)$$

where V_d is the volume of donor well, V_a is the volume in acceptor well, A is the filter area, t is the permeation time, $[drug]_{acceptor}$ is the absorbance of compound found in the acceptor well, and $[drug]_{equilibrium}$ is the theoretical equilibrium absorbance.

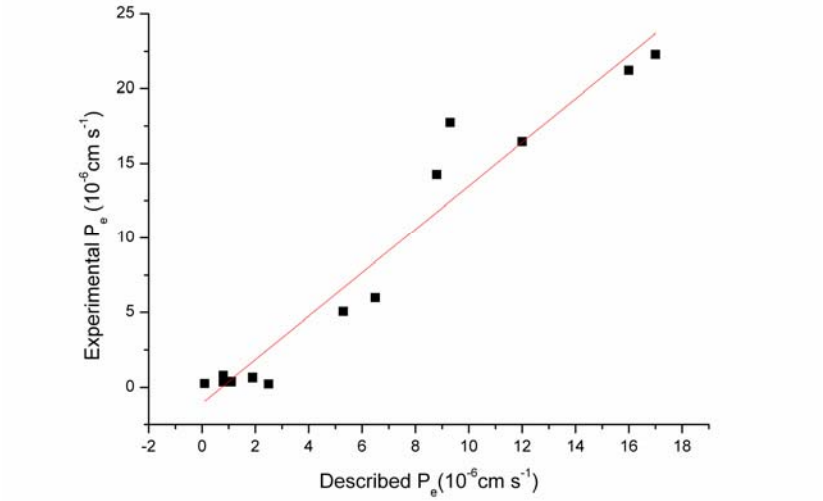


Figure S1. Lineal correlation between experimental and reported permeability of commercial drugs using the PAMPA-BBB assay. P_e (exp.)=1.4574*P*e (bibl.) - 1.0773 (R^2=0.9427).

Table S1. Ranges of Permeability of PAMPA-BBB Assays (P_e, 10^{-6} cm s^{-1})

Compounds of high BBB permeation (CNS+)	P_e >4.7
Compounds of uncertain BBB permeation (CNS+/-)	4.7> P_e >1.8
Compounds of low BBB permeation (CNS-)	P_e <1.8

Table S2 Permeability ($P_e \times 10^{-6}$ cm s^{-1}) in the PAMPA-BBB assay for 13 commercial drugs, used in the

Experiment Validation.

Commercial drugs	Bibl [a]	PBS : EtOH (70 : 30) [b]
testosterone	17	22.3 ± 1.4
verapamil	16	21.2 ± 1.9
desipramine	12	16.4 ± 1.2
progesterone	9.3	17.7 ± 1.2
promazine	8.8	14.3 ± 0.5
chlorpromazine	6.5	6.0 ± 0.3
clonidine	5.3	5.1 ± 0.3
piroxicam	2.5	0.24 ± 0.01
hydrocortisone	1.9	0.65 ± 0.01
lomefloxacin	1.1	0.37 ± 0.02
atnolol	0.8	0.78 ± 0.02
ofloxacin	0.8	0.37 ± 0.02
theophylline	0.1	0.26 ± 0.01

[a] The date were taken from ref 10. [b] Data are the mean ± SD of three independent experiments.

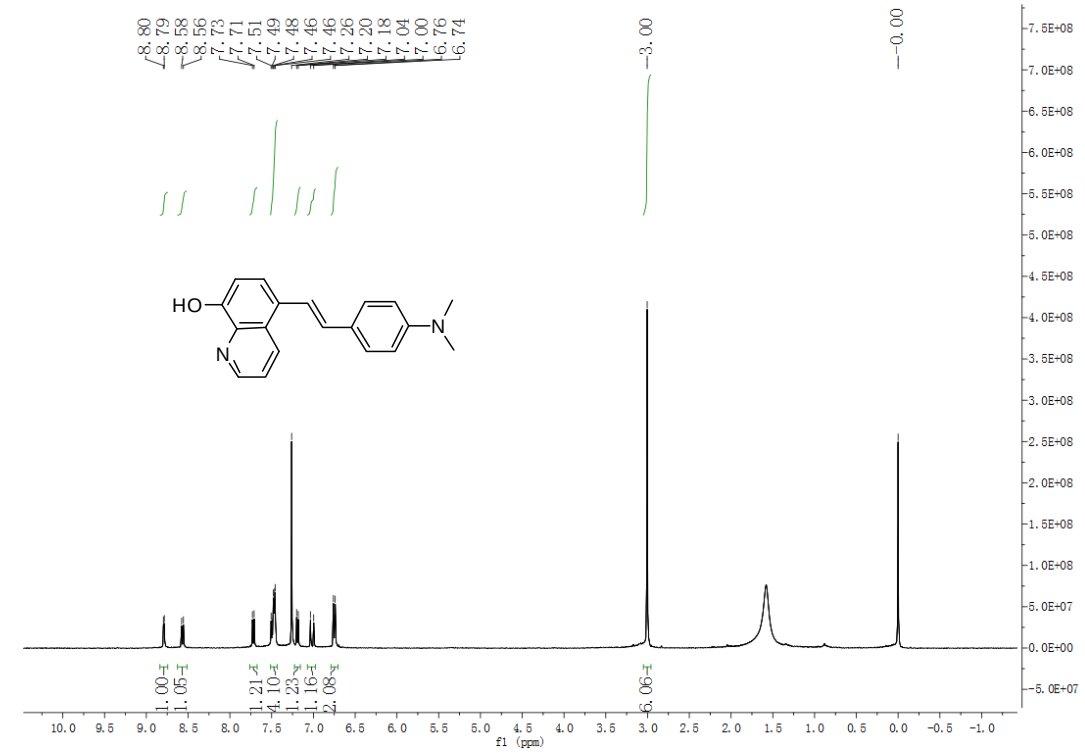
2.7 Statistical Analysis

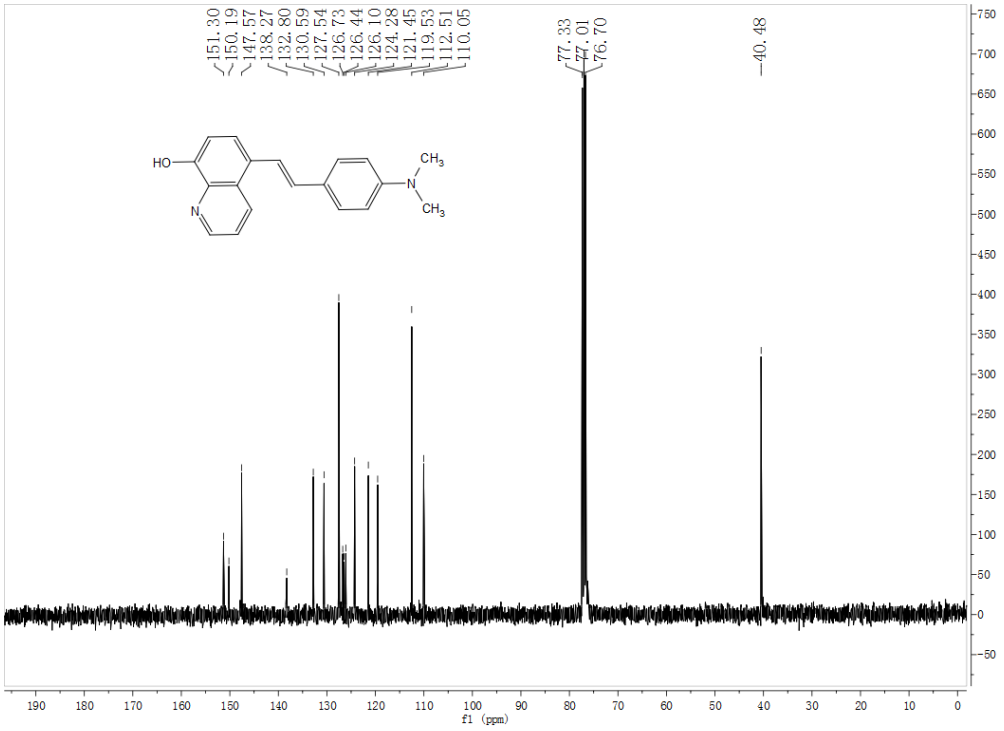
The results are expressed as the mean ± SD of at least three independent experiments. Data were subjected to one-way analysis of variance (ANOVA) followed by Dunnett's test. *P* values less than 0.05 were accepted to indicate the significance.

3 Acute Toxicity Assay

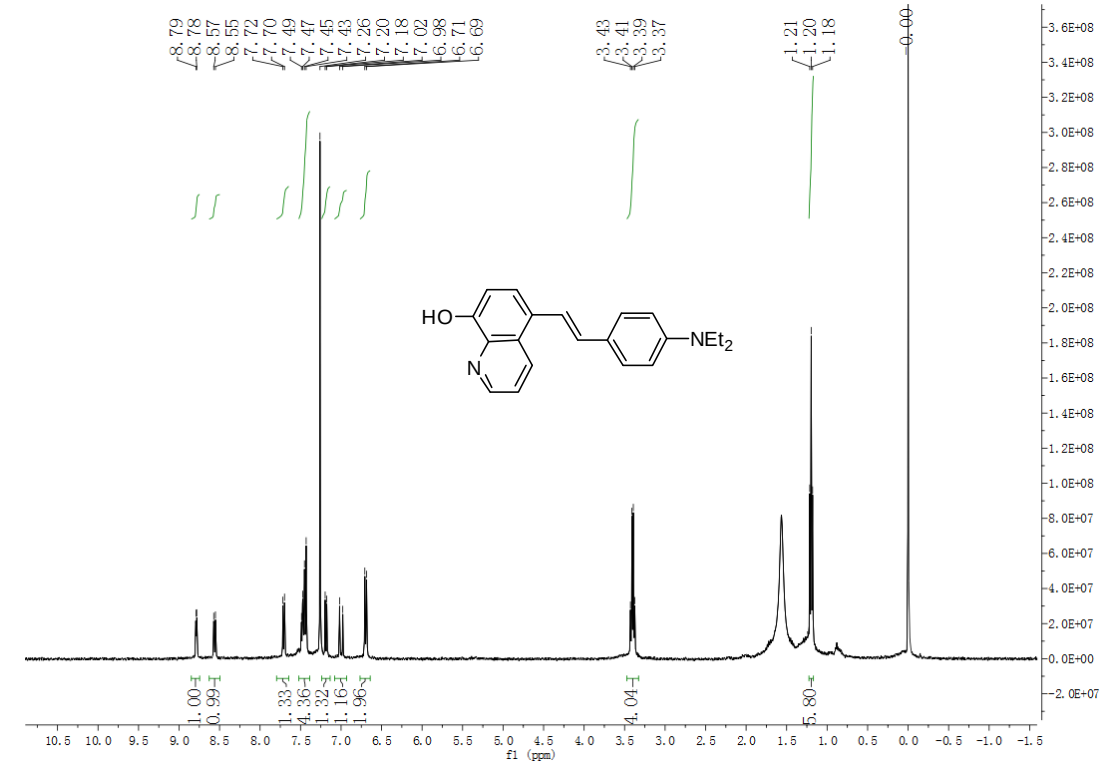
Twenty KM mice (22 days, 18-20 g), purchased from the laboratory animal center of Sun Yat-sen University (Guangzhou, China), were used to evaluate the acute toxicity of compound **10c**. Mice were maintained on a 12 h light/dark cycle (light from 07:00 to 19:00) at 20°C -22°C and 60-70% relative humidity. Sterile food and water were provided according to institutional guidelines. Prior to each experiment, mice were fasted overnight and allowed free access to water. Compound **10c** was dissolved in 0.5% carboxymethyl cellulose sodium (CMC-Na) salt solution and given via oral administration to different experimental groups. After administration of the compound, mice were observed continuously for the first 4 h for any abnormal behavior and mortality changes, intermittently for the next 24 h and occasionally thereafter for 14 days for the onset of any delayed effects. All animals were sacrificed on the 14th day after drug administration and macroscopically evaluated for possible damage to the heart, liver, and kidneys.[18]

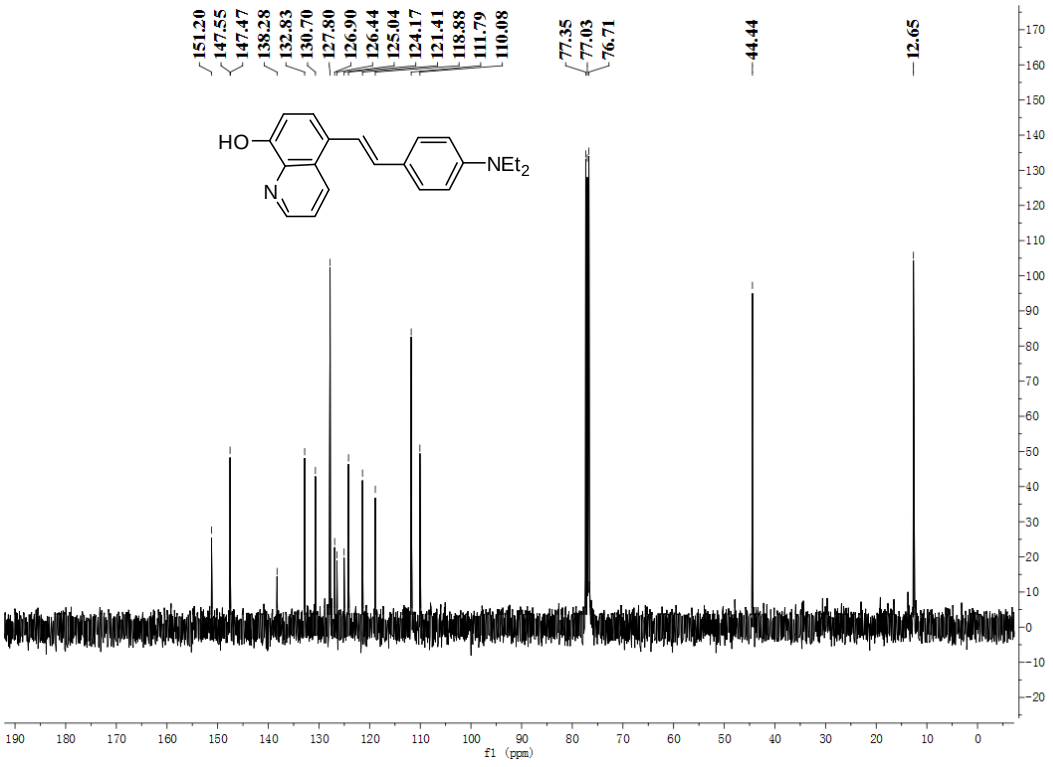
4 NMR spectra of compounds 10a-10e, 10g, 13a-e and 13h-13i



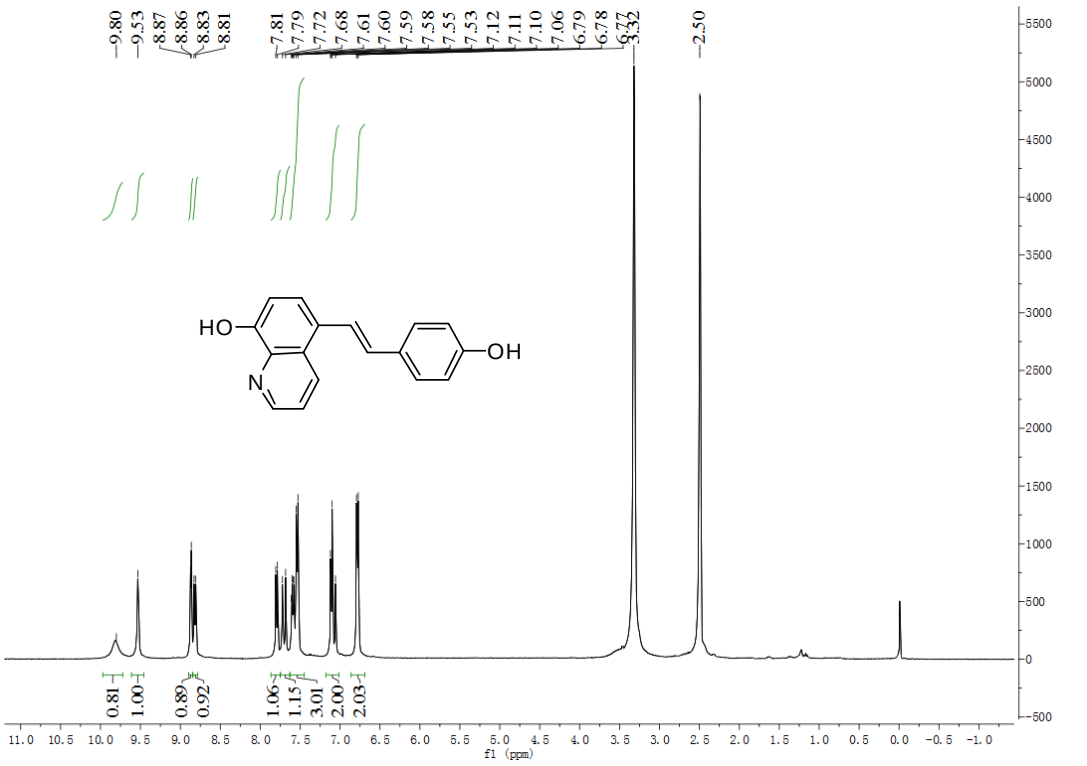


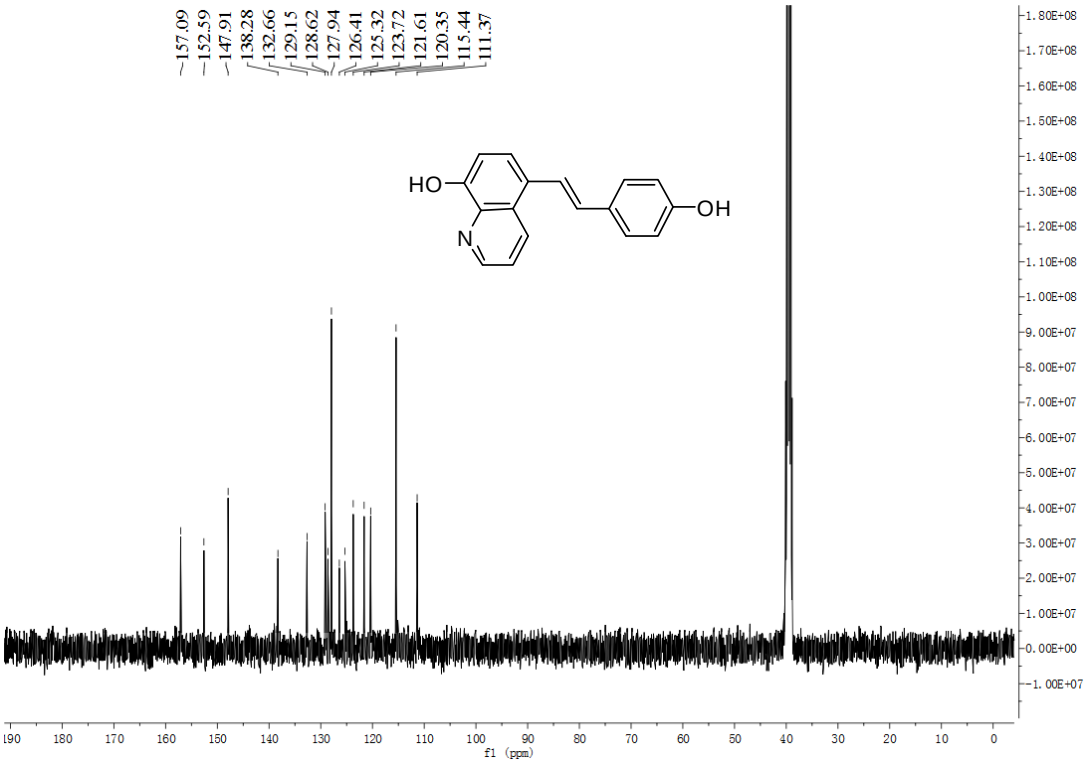
NMR spectra of compounds **10a**



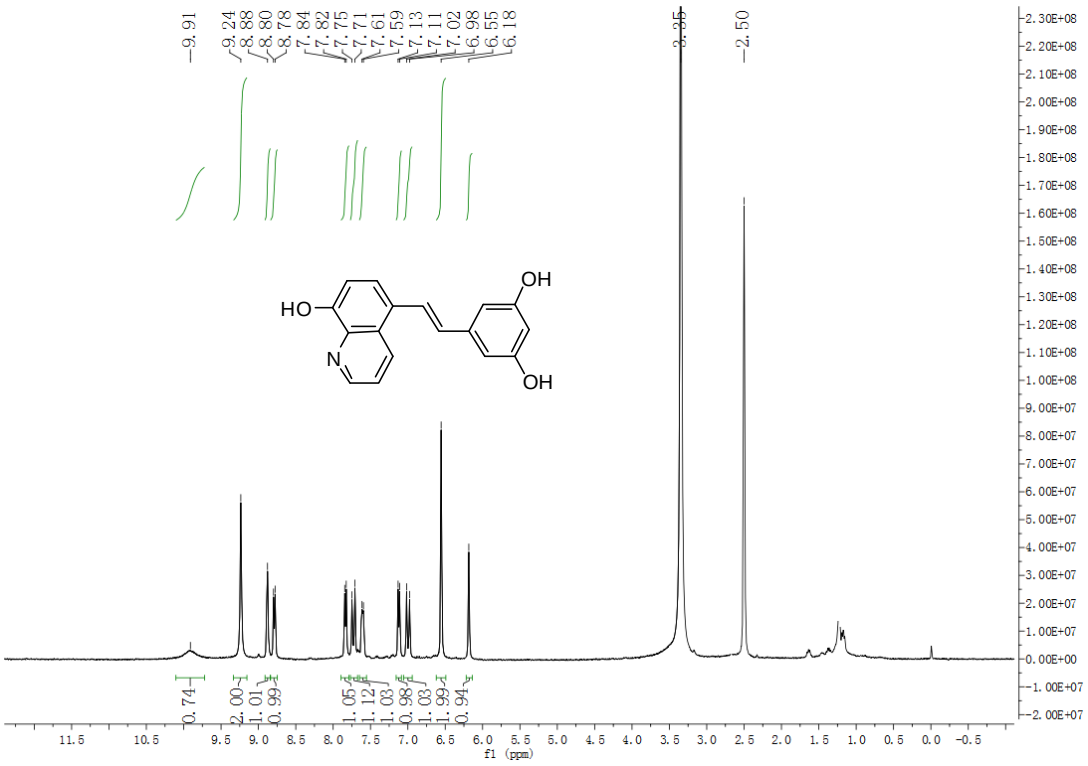


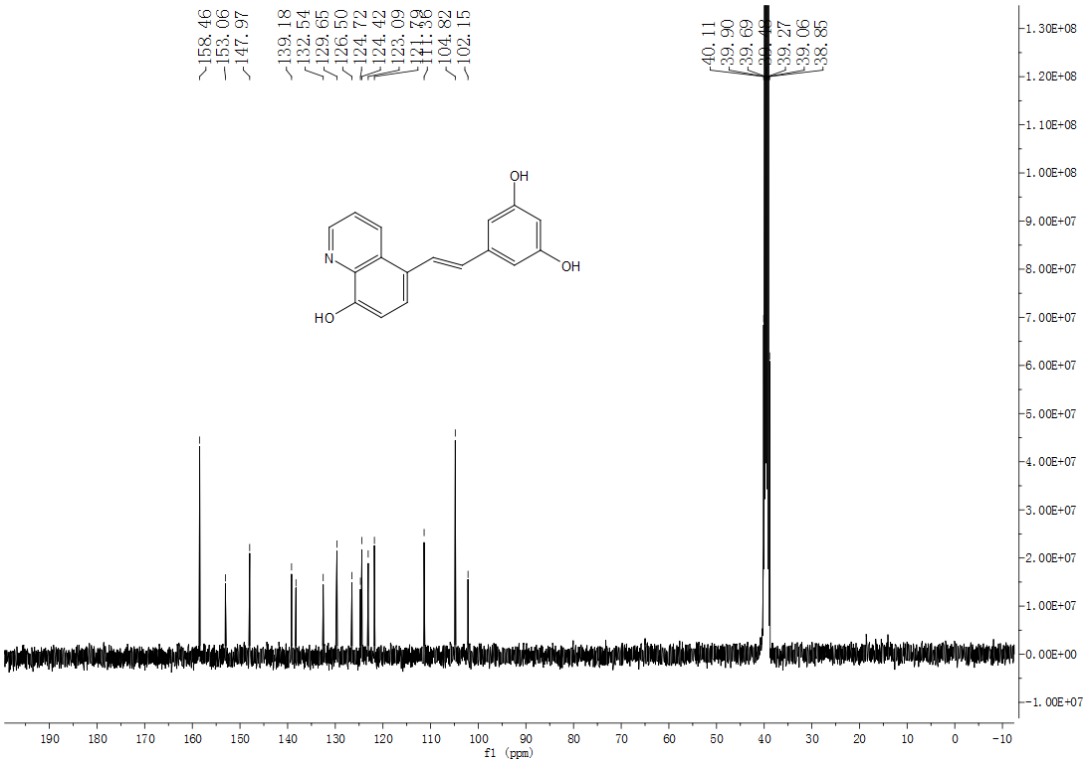
NMR spectra of compounds **10b**



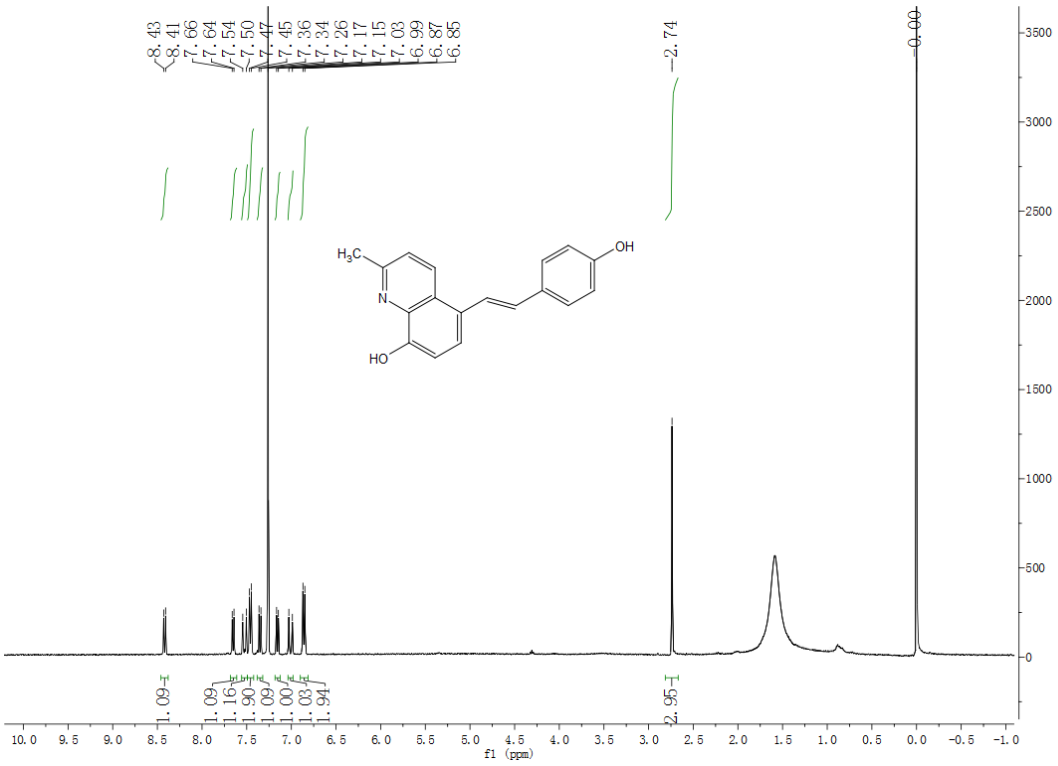


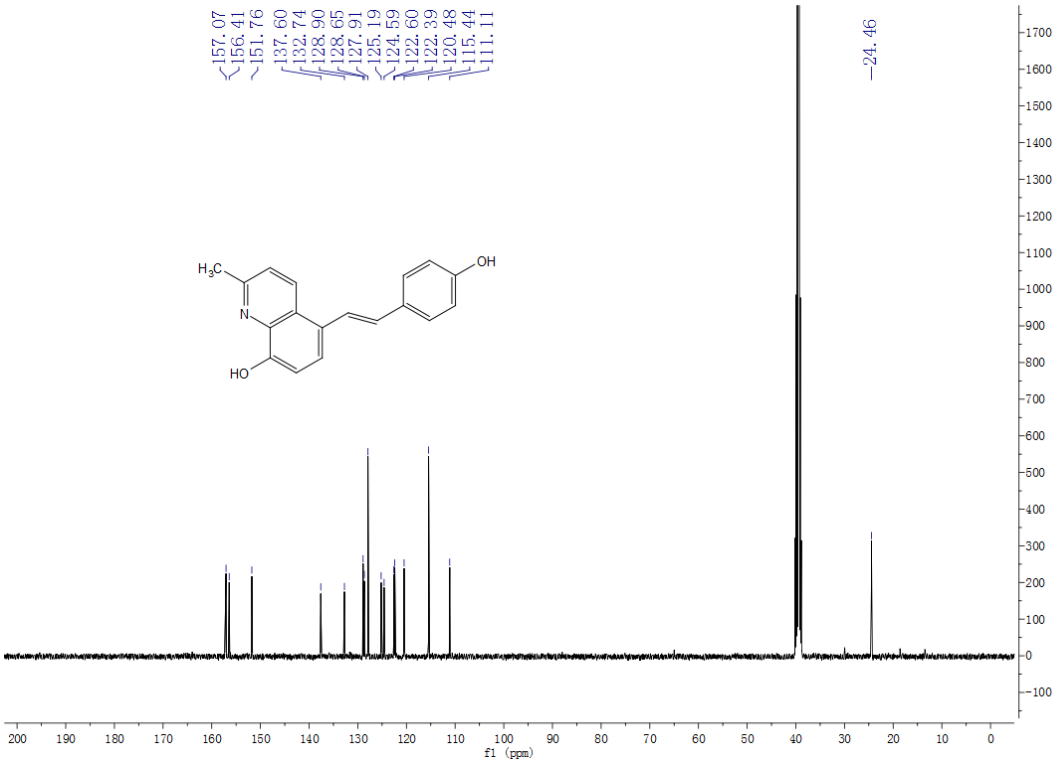
NMR spectra of compounds **10c**



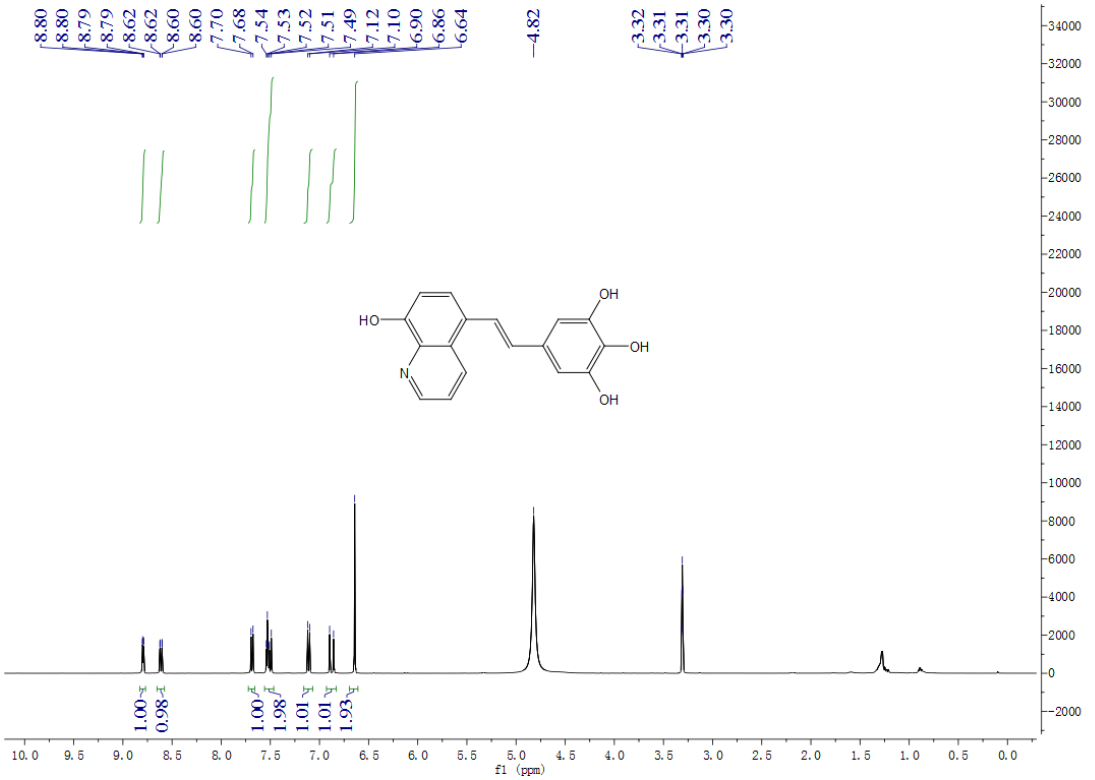


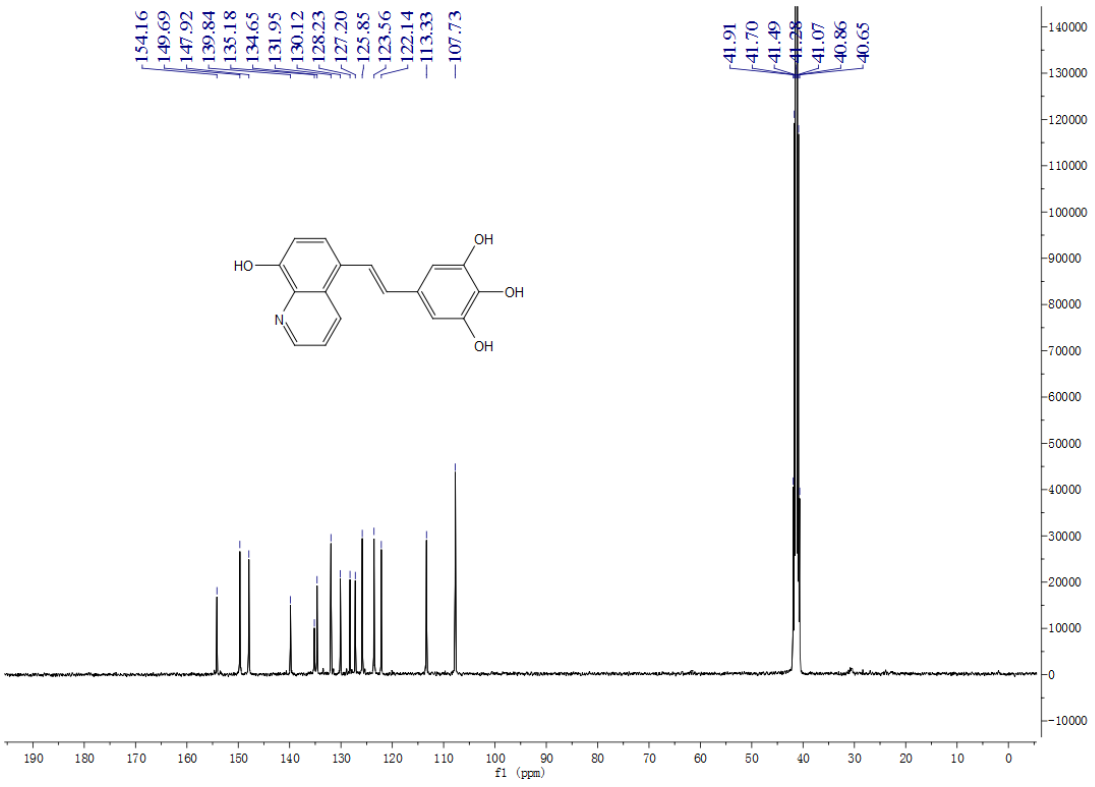
NMR spectra of compounds **10d**



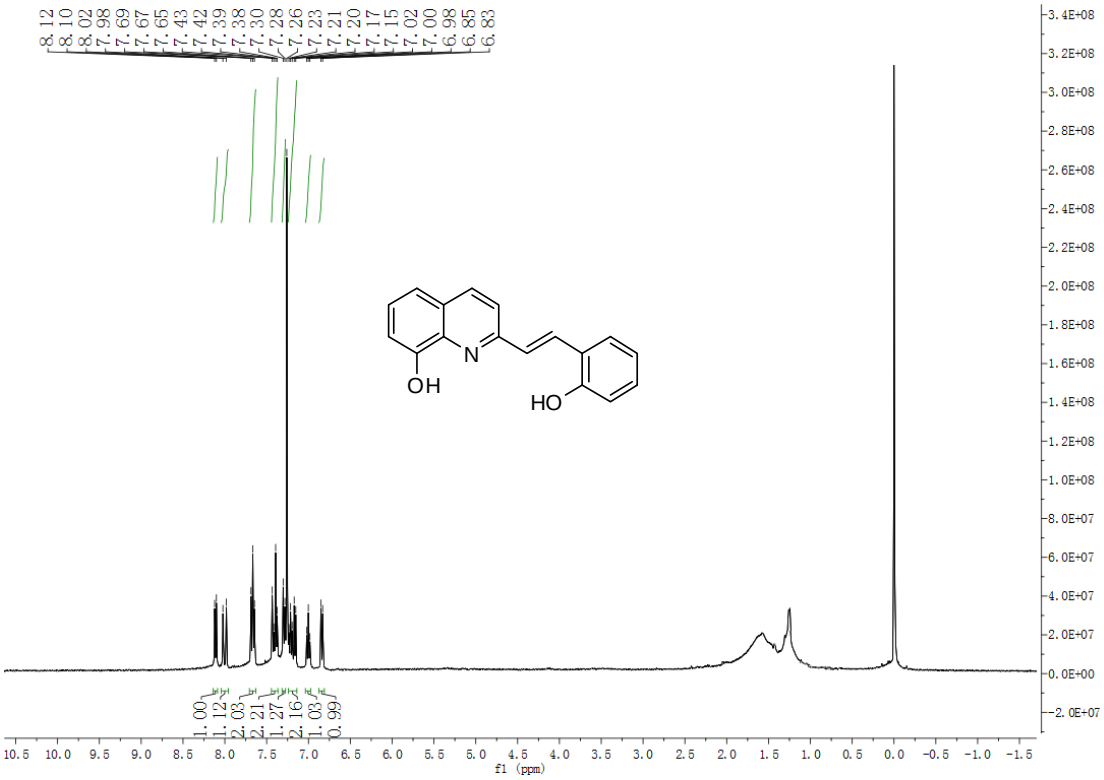


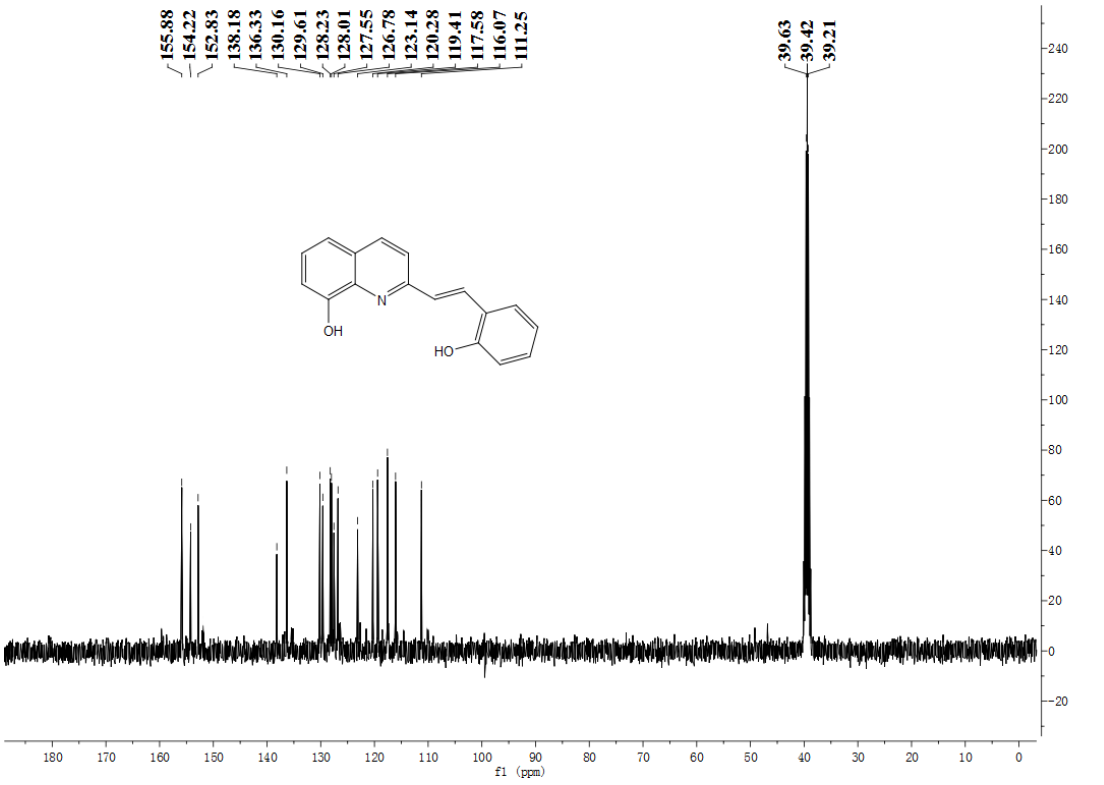
NMR spectra of compounds **10e**



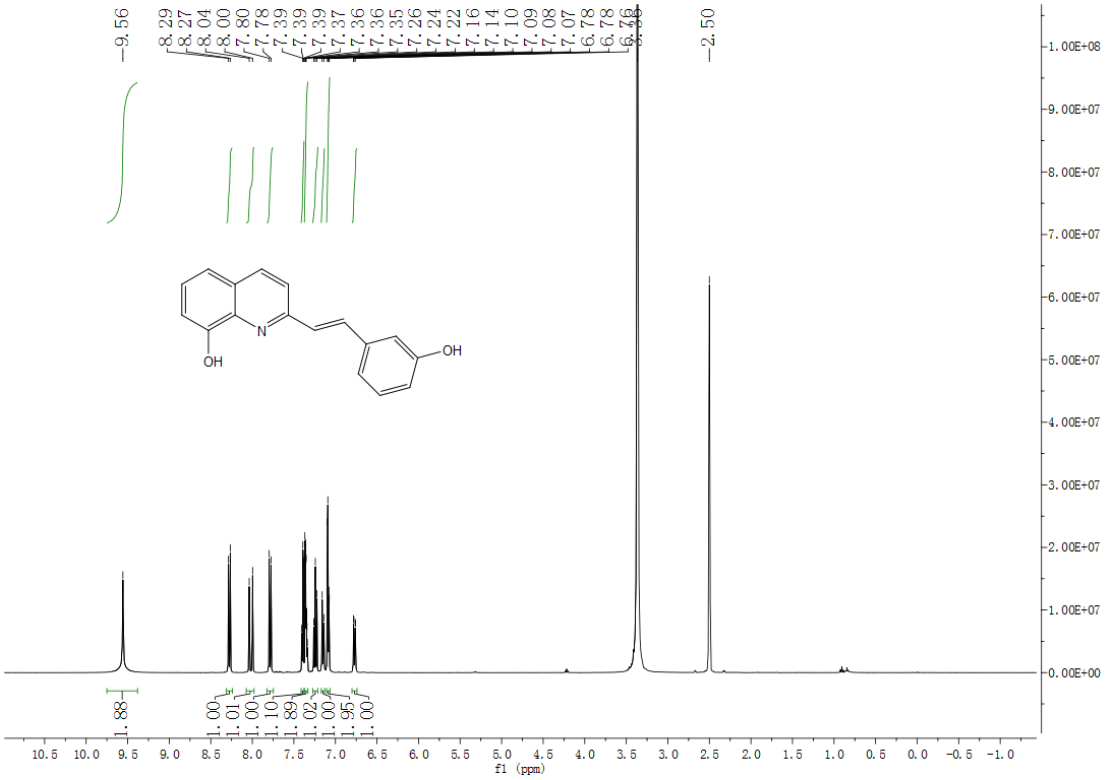


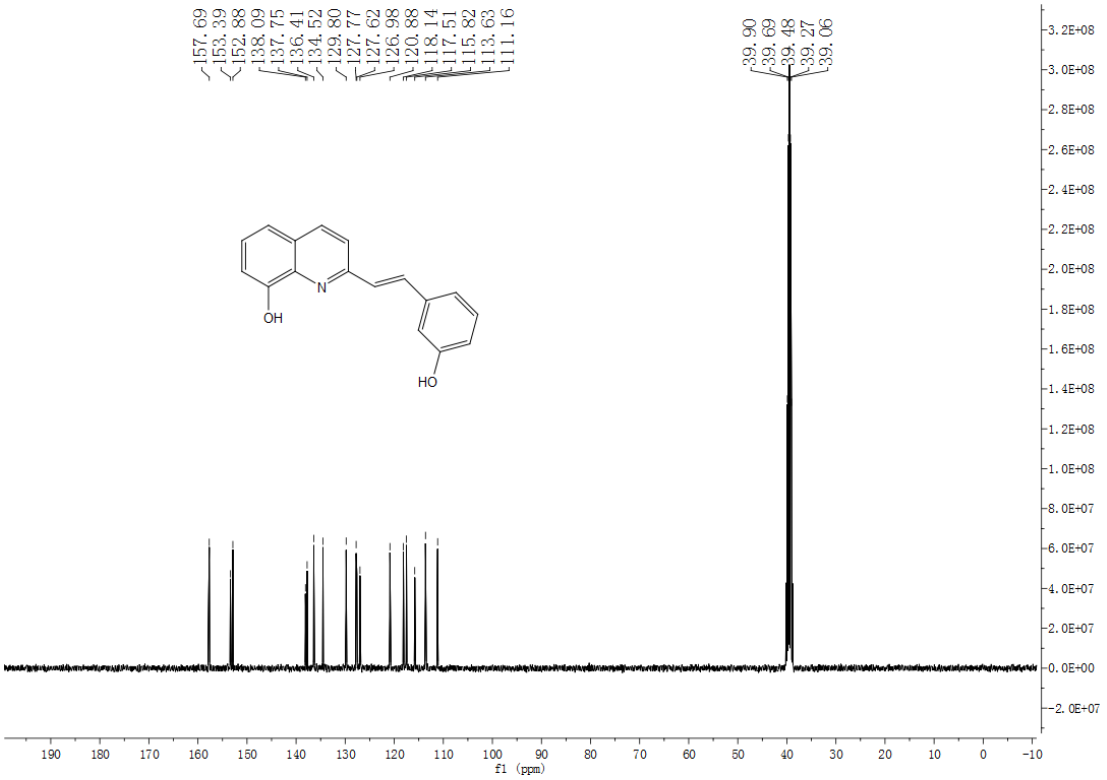
NMR spectra of compounds **10g**



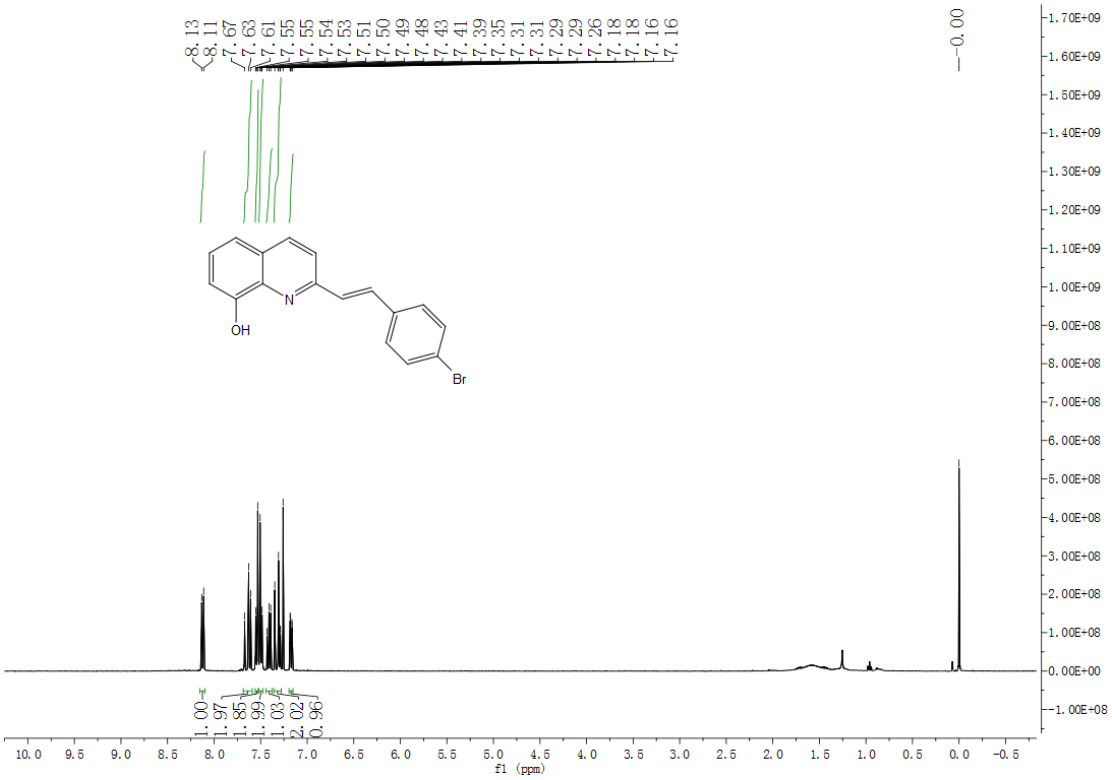


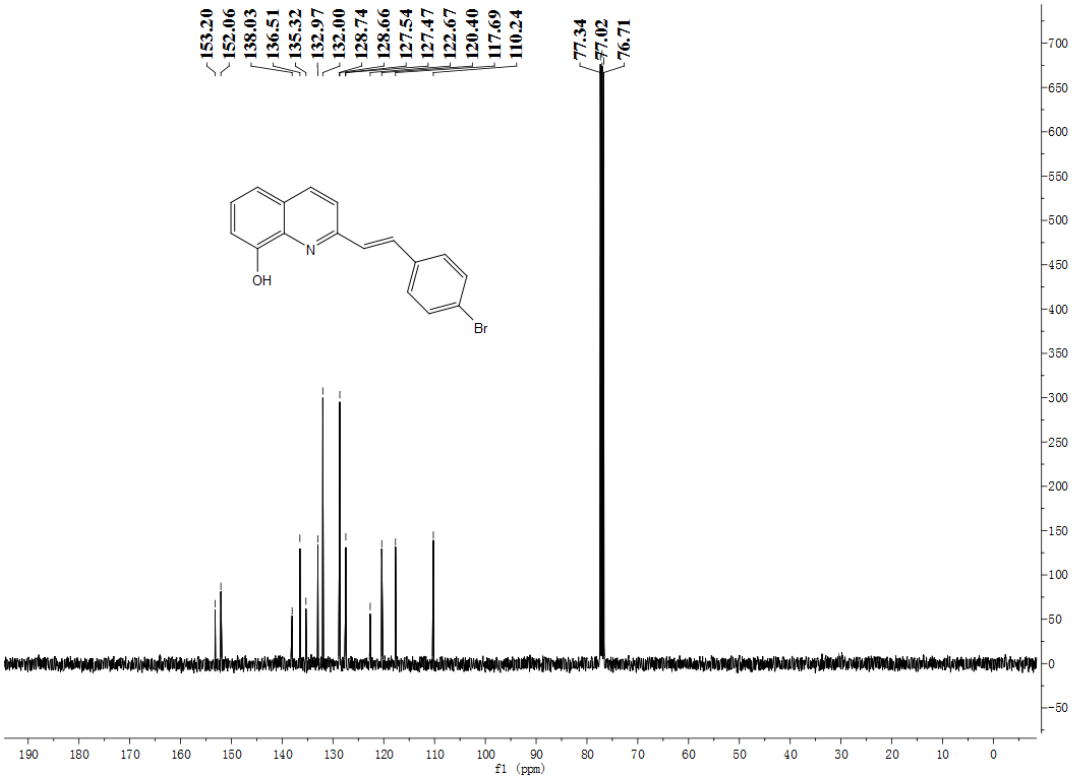
NMR spectra of compounds **13a**



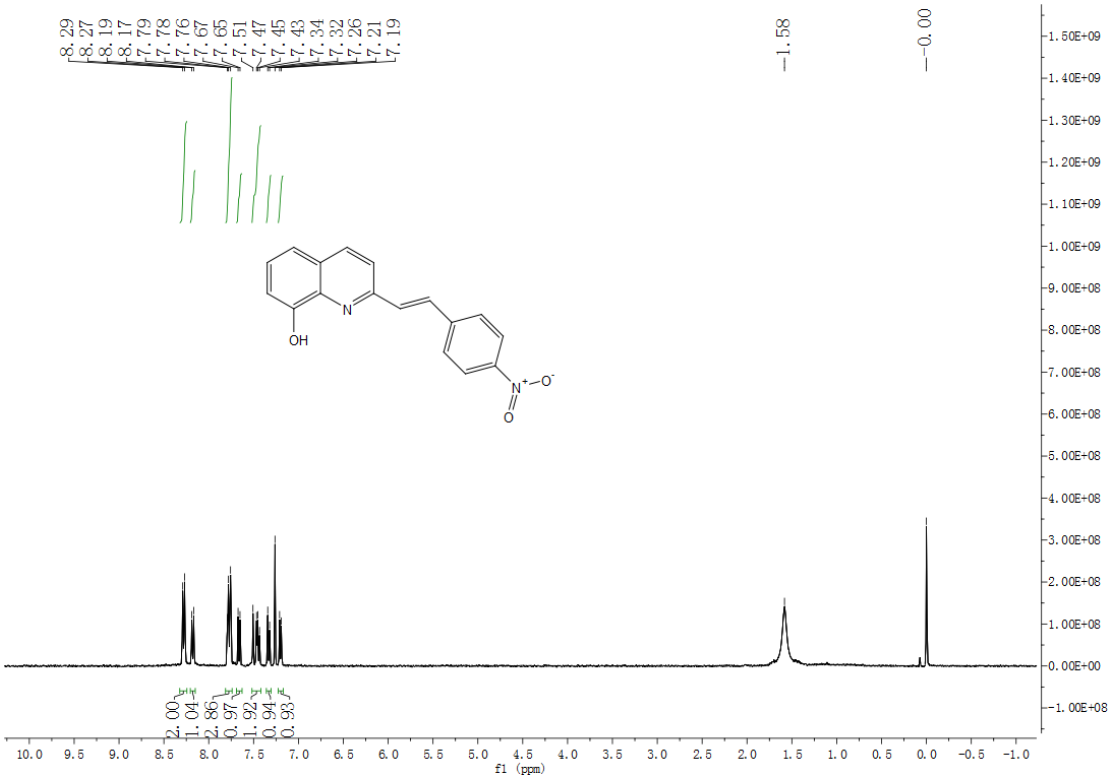


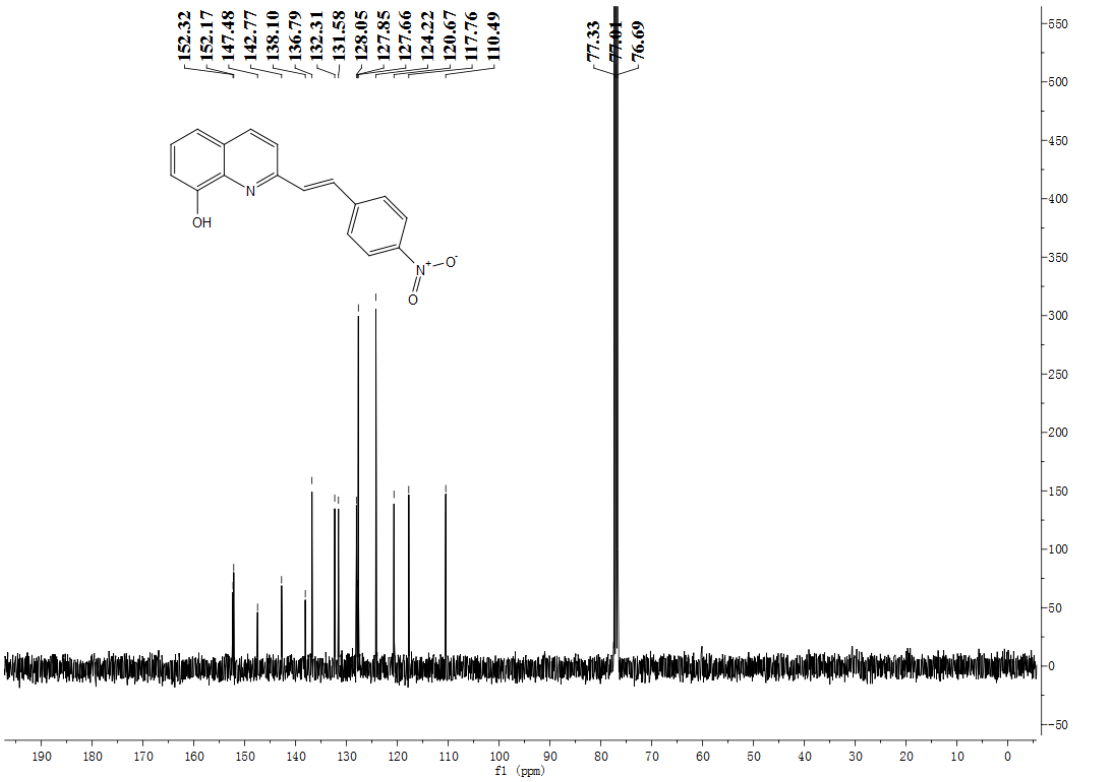
NMR spectra of compounds **13b**



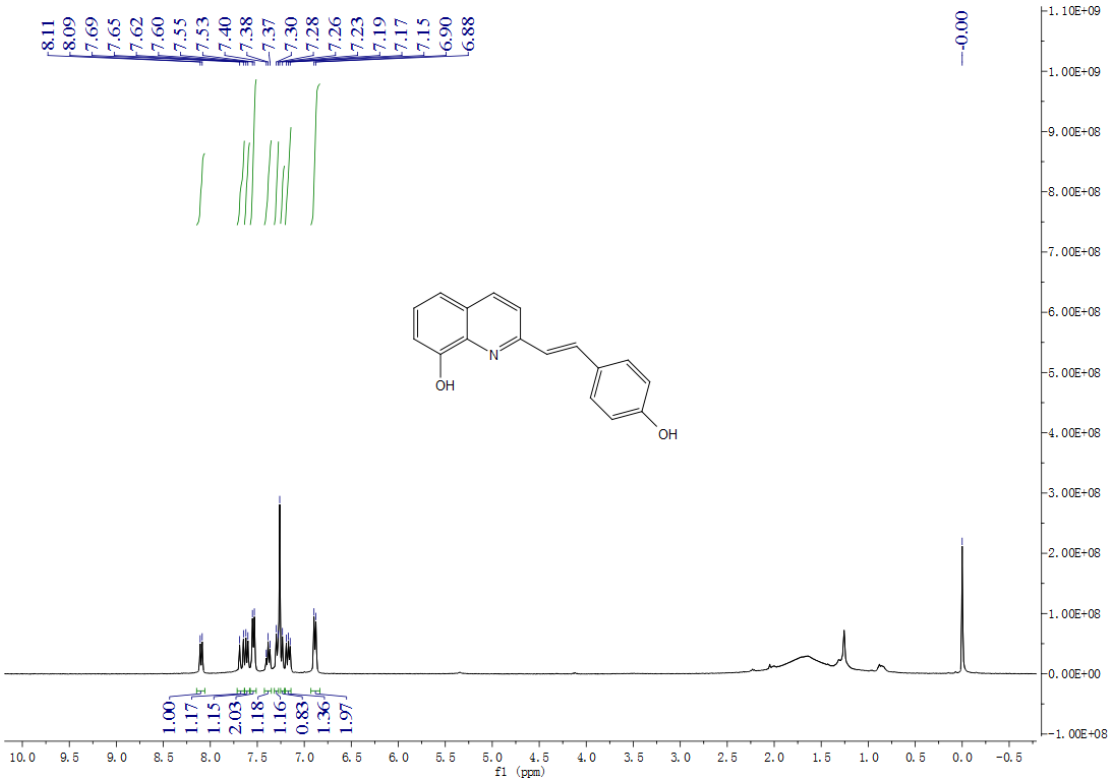


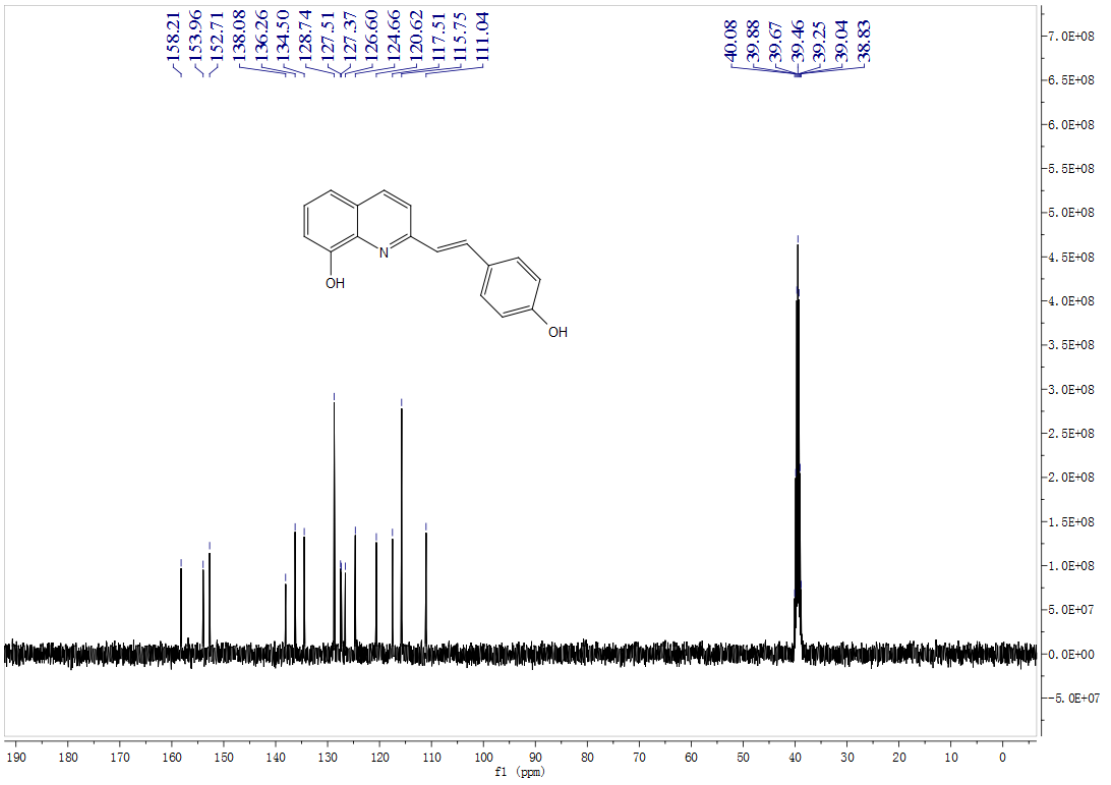
NMR spectra of compounds **13c**



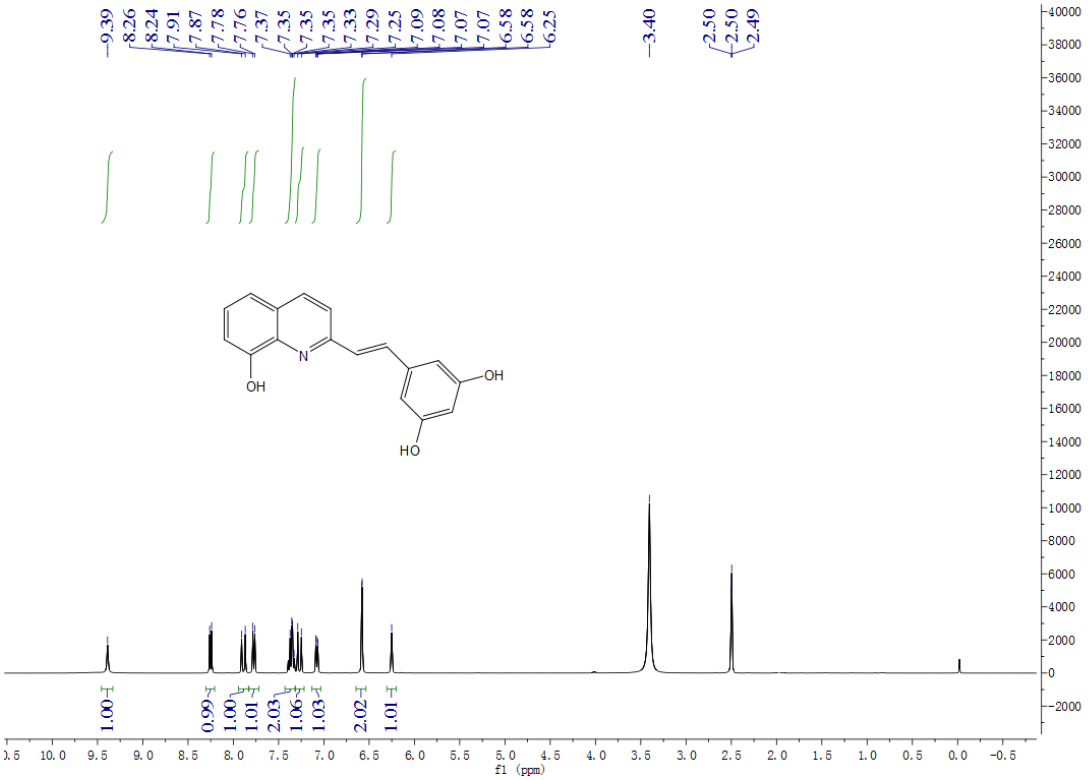


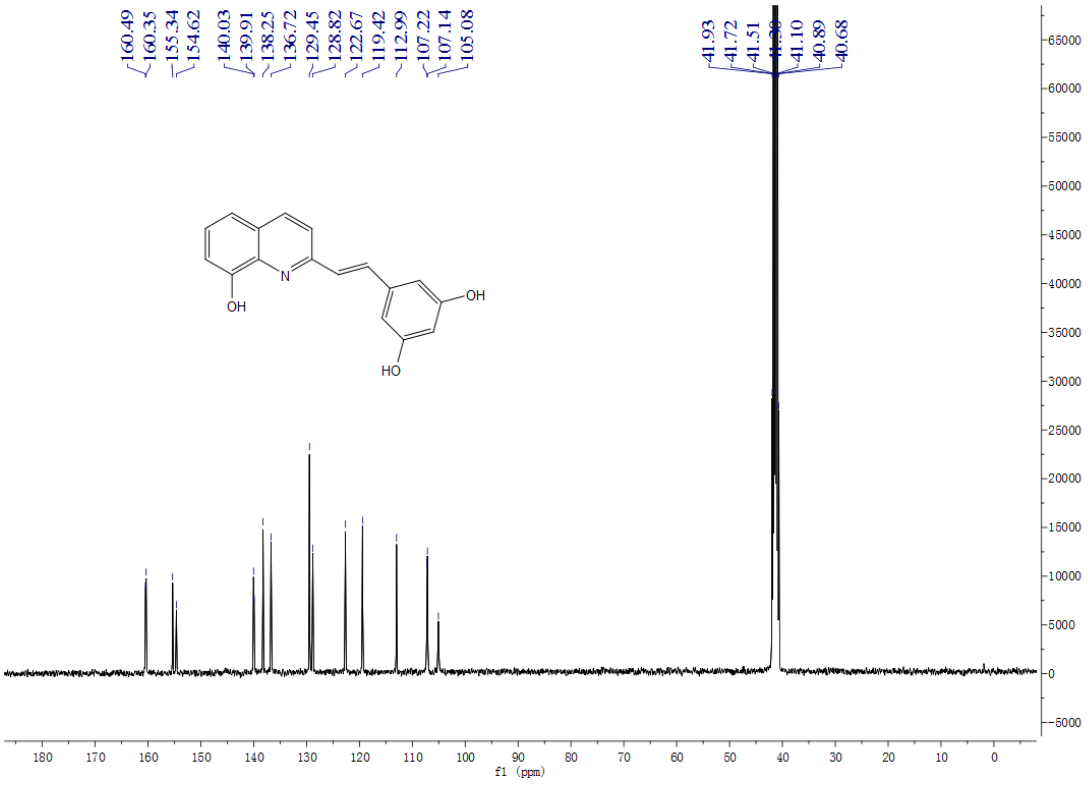
NMR spectra of compounds **13d**



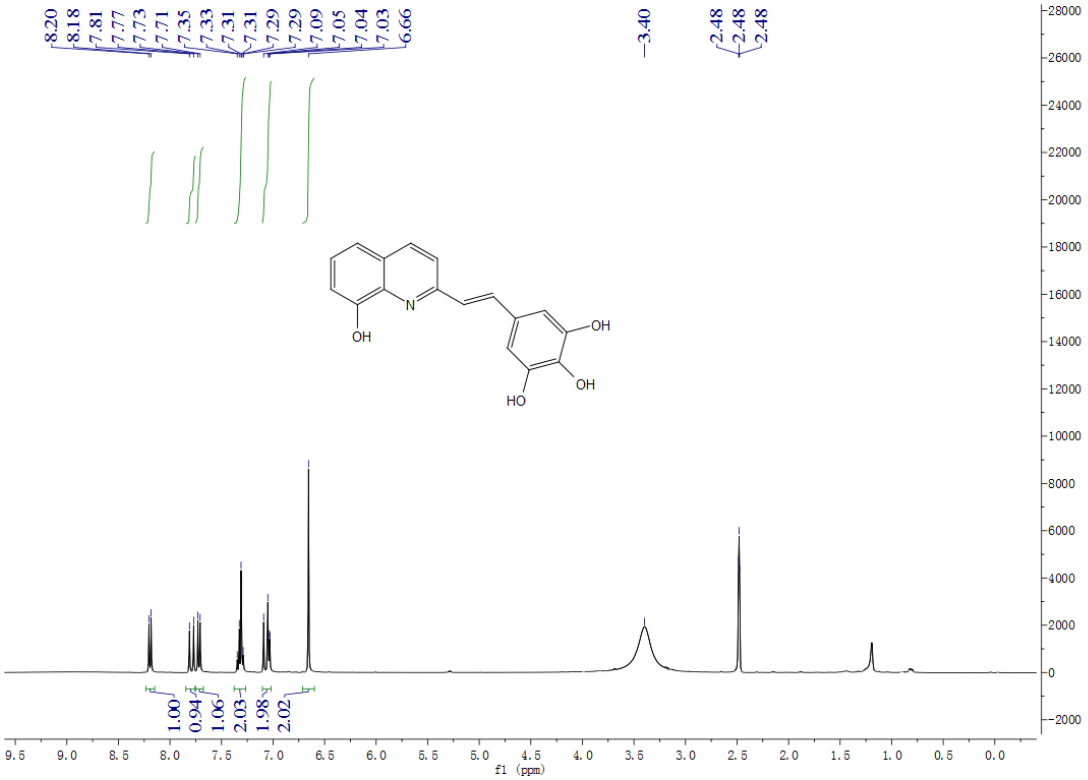


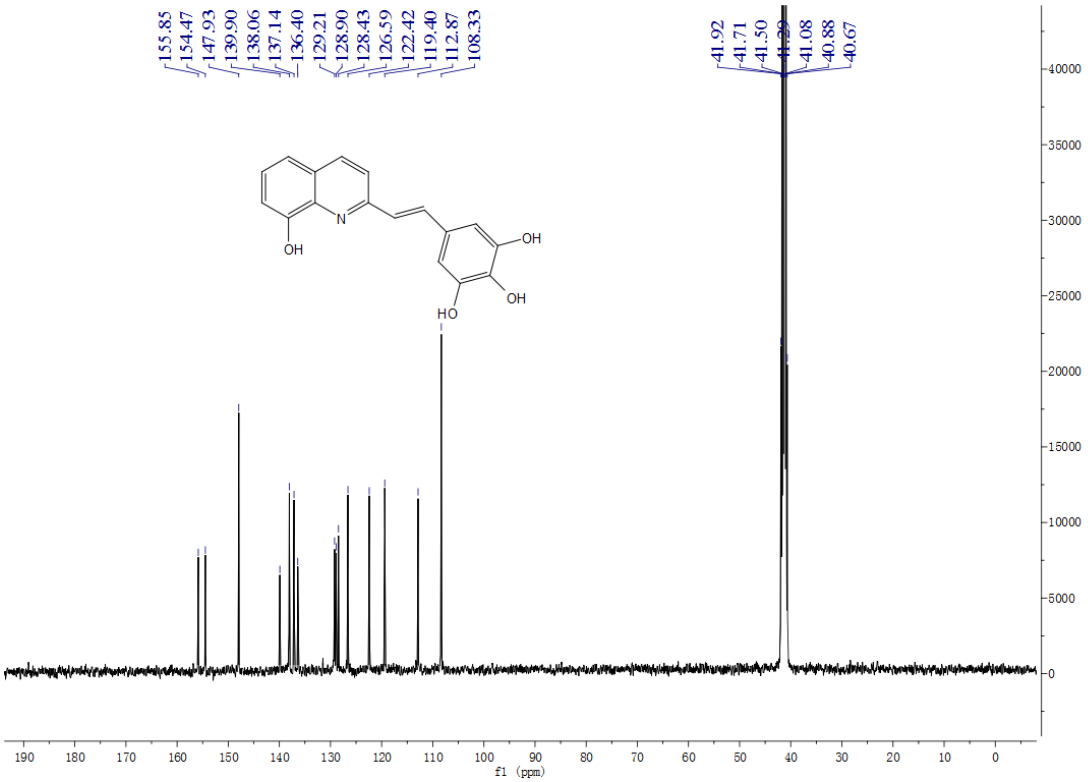
NMR spectra of compounds **13e**





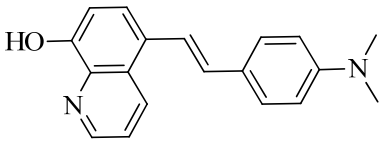
NMR spectra of compounds **13h**





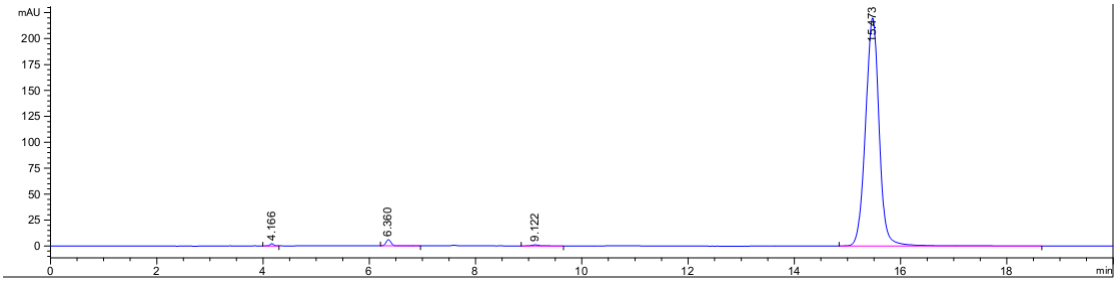
NMR spectra of compounds **13i**

5 HPLC chromatograms of compounds 10a-10e, 10g, 13a-e and 13h-13i.

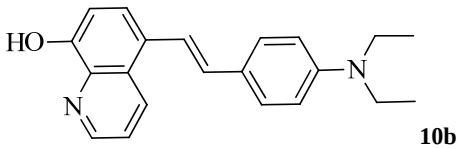


10a

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 15.473.

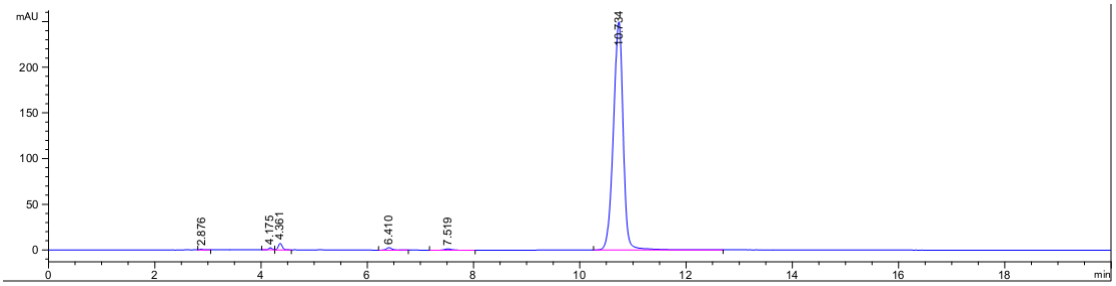


#	[min]		[min]	[mAU*s]	[mAU]	%
1	4.166	BB	0.0777	11.18623	2.26227	0.2800
2	6.360	VB	0.1034	41.18663	6.05134	1.0309
3	9.122	BB	0.1685	11.86876	1.06074	0.2971
4	15.473	BB	0.2744	3931.14795	220.08394	98.3921

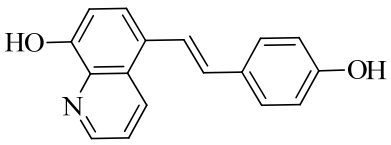


10b

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 10.734.

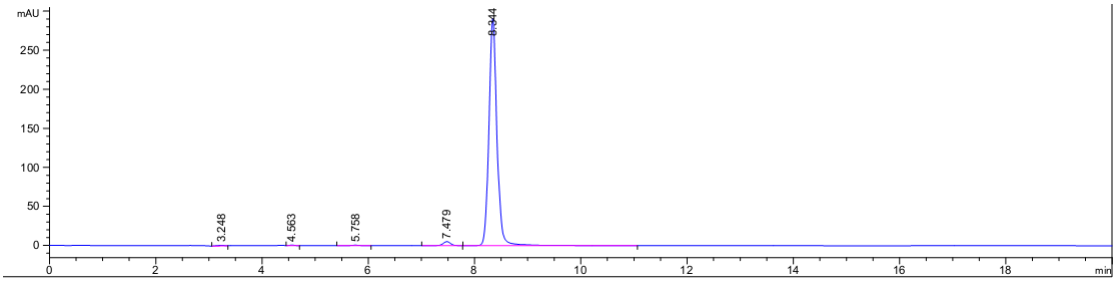


#	[min]		[min]	[mAU*s]	[mAU]	%
1	2.876	VV	0.0702	3.64030	7.83018e-1	0.1109
2	4.175	BV	0.0781	11.62552	2.33380	0.3542
3	4.361	VB	0.0822	38.41744	7.20907	1.1706
4	6.410	BB	0.1108	19.48757	2.68030	0.5938
5	7.519	BB	0.1328	12.50029	1.39204	0.3809
6	10.734	VB	0.1974	3196.09790	249.59860	97.3895

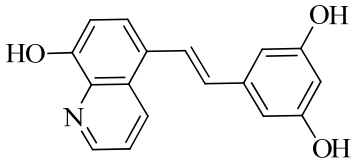


10c

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 40:60, t_{major} = 8.344.

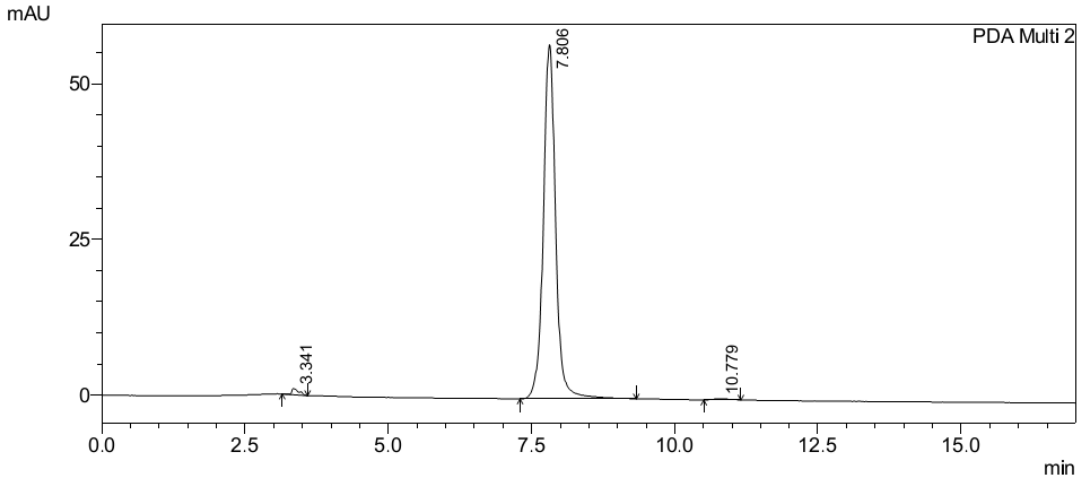


#	[min]		[min]	[mAU*s]	[mAU]	%
1	3.248	BV	0.1598	8.40397	6.82049e-1	0.2697
2	4.563	VB	0.0953	4.71989	7.72000e-1	0.1515
3	5.758	BB	0.1354	6.01826	6.54046e-1	0.1931
4	7.479	BB	0.1511	49.14451	5.06836	1.5772
5	8.344	BB	0.1583	3047.74146	290.82968	97.8085



10d

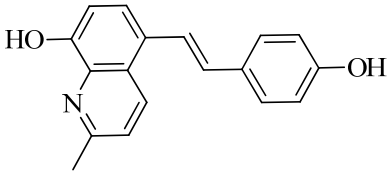
CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 35:65, t_{major} = 7.806.



PeakTable

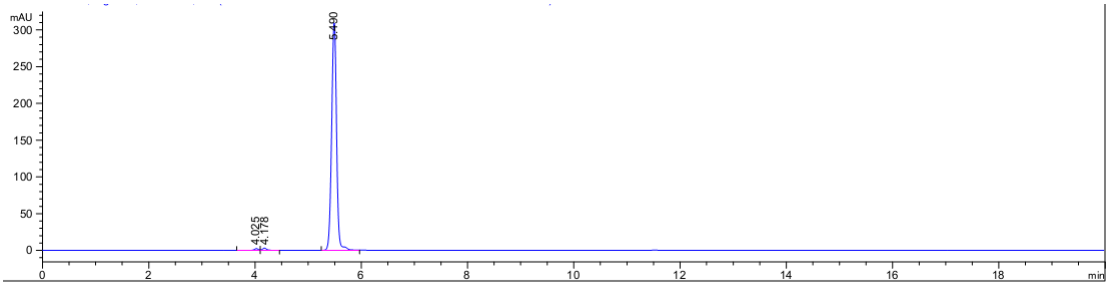
PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.341	8517	969	0.987	1.671
2	7.806	850803	56843	98.619	98.000
3	10.779	3401	191	0.394	0.329
Total		862721	58003	100.000	100.000

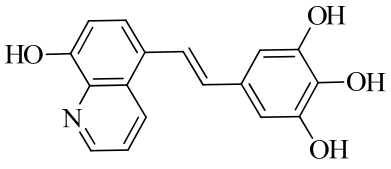


10e

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 5.490.

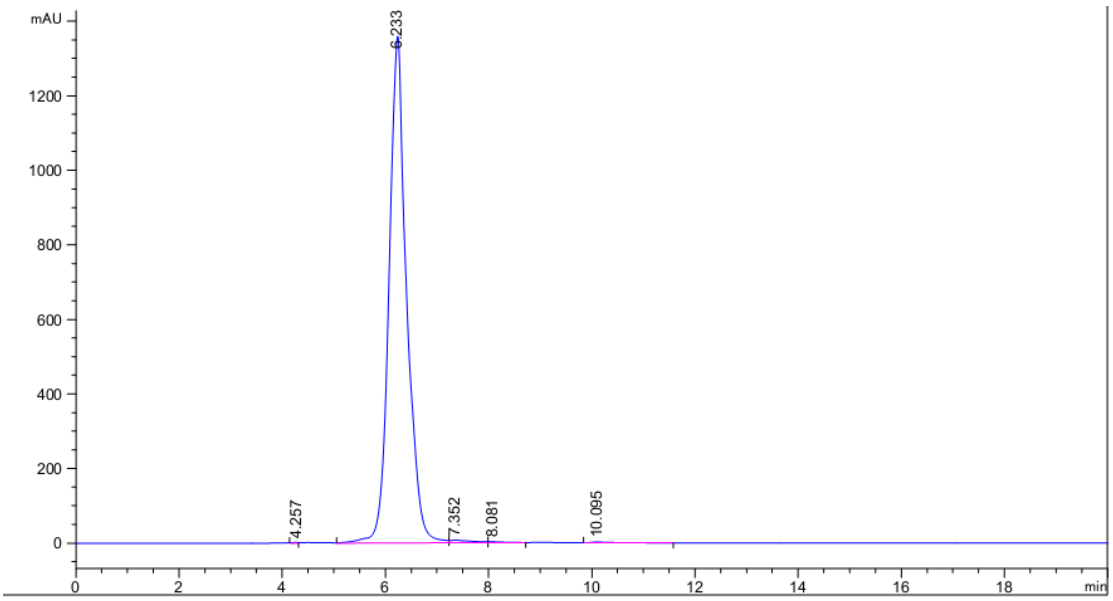


#	[min]		[min]	[mAU*s]	[mAU]	%
1	4.025	BV	0.0822	12.23592	2.29480	0.6087
2	4.178	VB	0.0844	16.52155	2.99337	0.8218
3	5.490	BV	0.0985	1981.57947	310.19400	98.5695

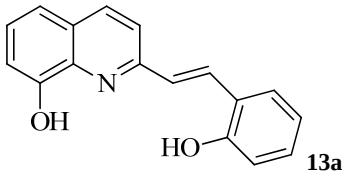


10g

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 60:40, t_{major} = 6.233.

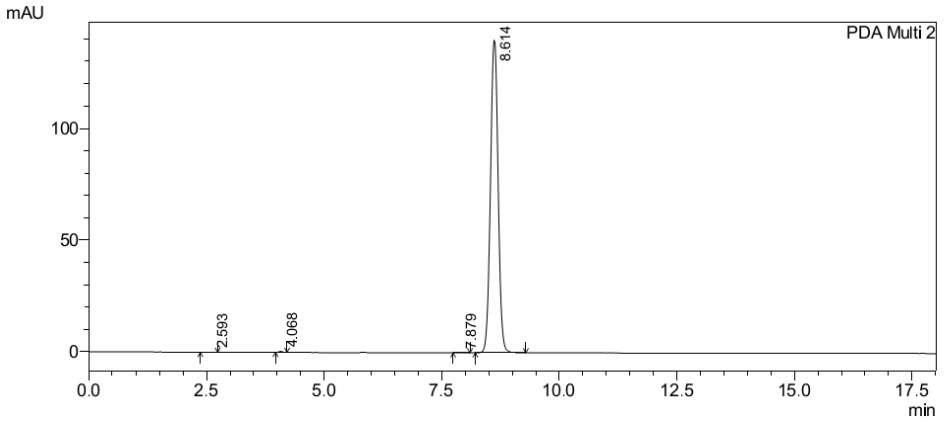


#	[min]		[min]	[mAU*s]	[mAU]	%
1	4.257	VV	0.1180	17.27767	2.01507	0.0527
2	6.233	VV	0.3471	3.23157e4	1360.54871	98.5732
3	7.352	VV	0.4043	252.77437	7.96309	0.7710
4	8.081	VV	0.3807	98.01311	3.33694	0.2990
5	10.095	VB	0.5063	99.68001	2.51567	0.3041



13a

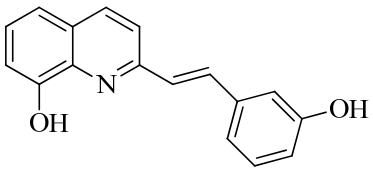
CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 8.614.



PeakTable

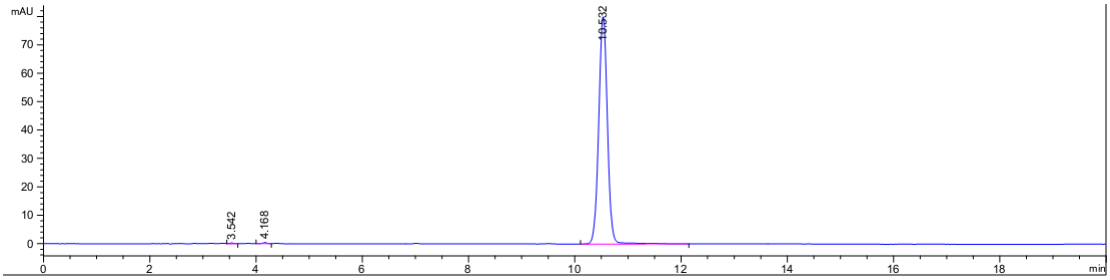
PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.593	1326	83	0.085	0.059
2	4.068	2379	408	0.152	0.291
3	7.879	1048	106	0.067	0.076
4	8.614	1562398	139948	99.697	99.575
Total		1567150	140545	100.000	100.000

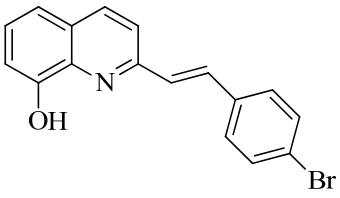


13b

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 10.532.

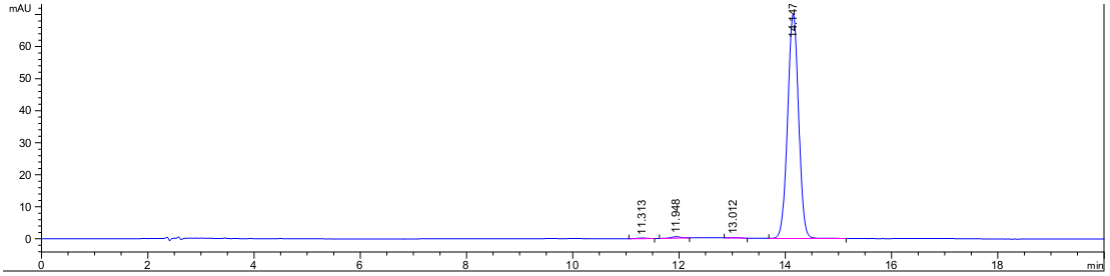


#	[min]		[min]	[mAU*s]	[mAU]	%
1	3.542	VB	0.0744	1.39508	2.78840e-1	0.1519
2	4.168	VV	0.0840	2.30054	4.19163e-1	0.2504
3	10.532	BB	0.1774	914.96210	80.01949	99.5977

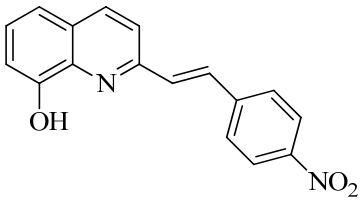


13c

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 70:30, t_{major} = 14.147.

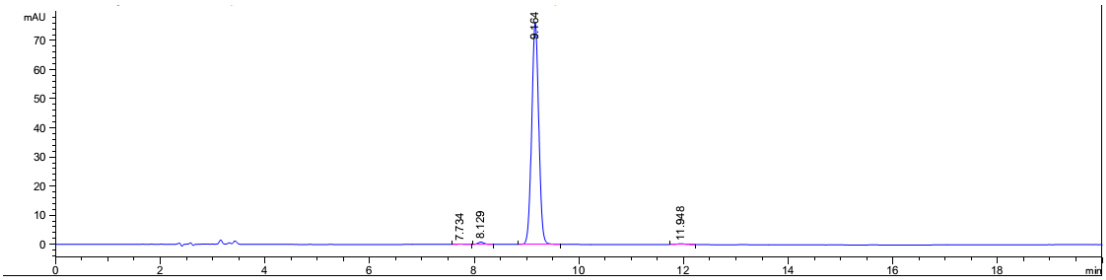


#	[min]		[min]	[mAU*s]	[mAU]	%
1	11.313	BB	0.1553	2.26491	1.98240e-1	0.2227
2	11.948	BB	0.1929	5.72655	4.54835e-1	0.5631
3	13.012	BB	0.1526	1.43528	1.22616e-1	0.1411
4	14.147	BB	0.2237	1007.49750	70.09422	99.0730

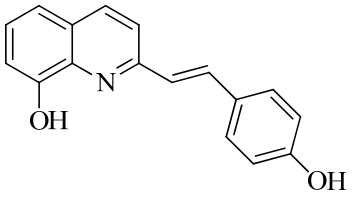


13d

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 70:30, t_{major} = 9.164.

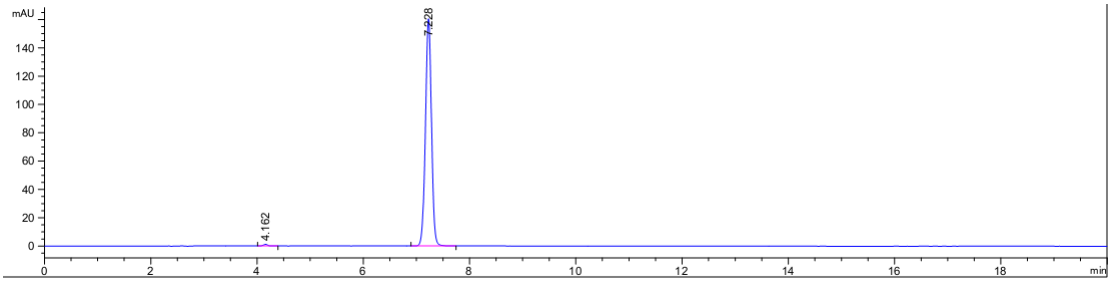


#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.734	BB	0.1263	1.10371	1.31032e-1	0.1518
2	8.129	BB	0.1297	6.72495	8.02943e-1	0.9247
3	9.164	BB	0.1456	716.02985	76.23078	98.4569
4	11.948	BB	0.1668	3.39393	2.85277e-1	0.4667

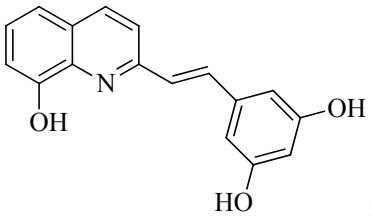


13e

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 50:50, t_{major} = 7.228.

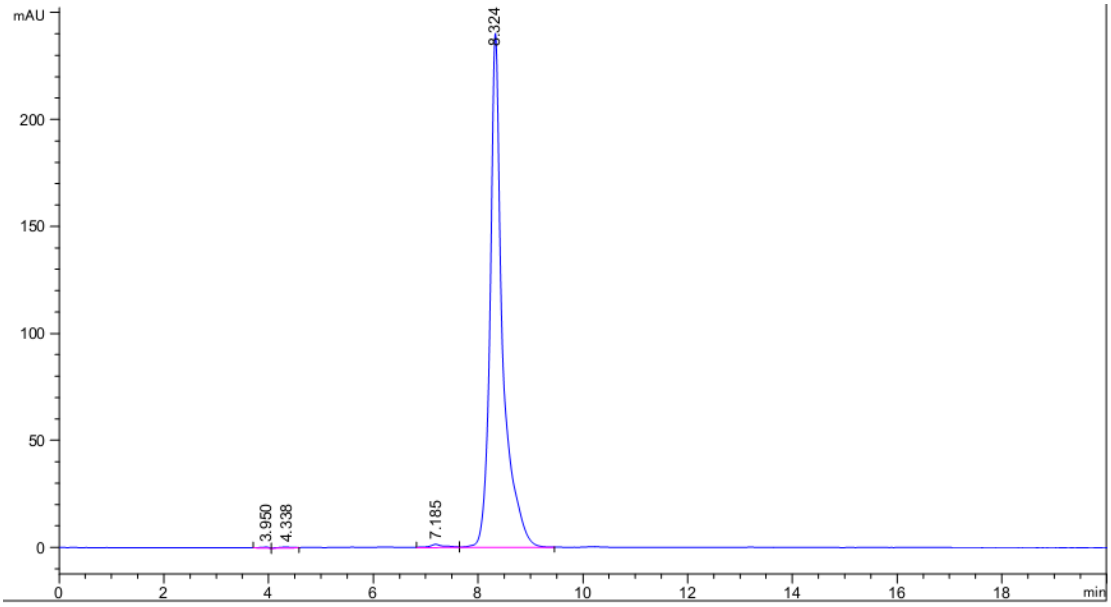


#	[min]		[min]	[mAU*s]	[mAU]	%
1	4.162	BB	0.0918	6.97870	1.16573	0.5454
2	7.228	BV	0.1224	1272.57288	160.63252	99.4546

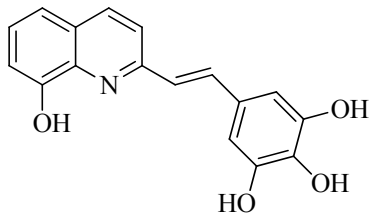


13h

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 60:40, t_{major} = 8.324.

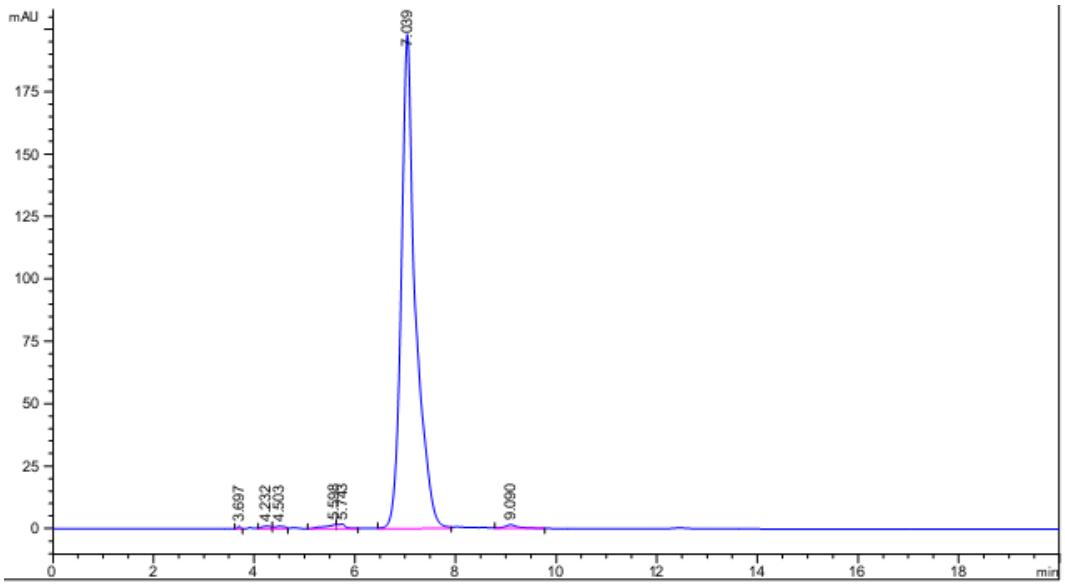


#	[min]		[min]	[mAU*s]	[mAU]	%
1	3.950	BV	0.1597	5.97931	5.54792e-1	0.1474
2	4.338	VV	0.2900	11.81271	5.18155e-1	0.2913
3	7.185	BV	0.2901	34.71926	1.60665	0.8561
4	8.324	VB	0.2343	4002.86963	240.40729	98.7051



13i

CH_3CN/water (50 mM KH_2PO_4, pH=3.0) = 60:40, t_{major} = 7.039.



#	[min]		[min]	[mAU*s]	[mAU]	%
1	3.697	BV	0.0525	3.54074	1.07191	0.0878
2	4.232	VV	0.1650	13.98283	1.09502	0.3466
3	4.503	VV	0.1894	15.33303	1.10839	0.3801
4	5.598	VV	0.2110	28.78130	1.70432	0.7135
5	5.743	VB	0.1700	23.68266	1.89265	0.5871
6	7.039	BV	0.2805	3915.63940	198.14890	97.0654

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