

Supporting Information

Synthesis and Evaluation of Donepezil-Ferulic Acid Hybrids as Multi-Target-Directed Ligands against Alzheimer's Disease

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EXPERIMENTAL

Chemistry

The structural characterization of compounds was performed by NMR and high-resolution mass spectrometry (HRMS). NMR spectra were recorded on a Bruker AVANCE III-500 spectrometer with tetramethylsilane (TMS) as an internal standard, and chemical shifts are reported in δ (ppm). HRESIMS were collected using an Agilent 6520B UPLC-Q-TOF mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). IR spectra (KBr disks, in cm^{-1}) were recorded on a Bruker Tensor 27 spectrometer (Bruker, Karlsruhe, Germany). The purity of target compounds was determined by HPLC (Agilent 1100 infinity HPLC system). All reactions were monitored by thin layer chromatography (TLC), which was performed on precoated silica gel GF254 plates (Qingdao Haiyang Chemical Plant, Qingdao, China). Detection was done by iodine vapor staining and UV light irradiation (UV lamp). Column chromatography was performed with silica gel silica gel (100-200 mesh and 200-300 mesh; Qingdao Haiyang Chemical Co., Ltd., Qingdao, China). Melting points were determined on an X4-type apparatus and were uncorrected. Unless otherwise stated, all reagents were purchased from commercial sources. If necessary, they were purified and dried by standard methods.

General procedure for the preparation of acetophenone derivatives (4a-4i and 5a-5n)¹

EDCI (1.1 equiv) and HOBt (1.1 equiv) were added at 0 °C to a solution of the appropriate phenylpropenoid derivatives (1 equiv) in the mixture of DCM and DMF.

The mixture was stirred at room temperature for 30 min. The mixture was cooled again to 0 °C and (1-benzylpiperidin-4-yl)amine (**3a**) or 4-(2-amide)-1-benzylpiperidine (**3b**) (1equiv) was added. The mixture was stirred at room temperature until TLC analysis indicated that there was no **3a** or **3b** left. The solvent was removed in vacuo and the resulting residue was dissolved in ethyl acetate and washed with diluted hydrochloric acid, saturated sodium bicarbonate (NaHCO₃) solution and brine. After drying over anhydrous Na₂SO₄, evaporating the solvent, the residue was purified by chromatography (PE/EA/Et₃N) on silica gel to obtain **4a-4i** and **5a-5n**.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (4a):

Yield 76%, colorless oil, IR (KBr) ν 3419, 3273, 2926, 1659, 1594, 1552, 1515, 1454, 1279, 1125, 1031, 748, 701 cm⁻¹. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 7.7 Hz, 1H), 7.33–7.27 (m, 5H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 6.97 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 3.79 (s, 3H), 3.64 (br s, 1H), 3.45 (s, 2H), 2.75 (d, *J* = 11.4 Hz, 2H), 2.03 (t, *J* = 10.8 Hz, 2H), 1.75 (d, *J* = 11.3 Hz, 2H), 1.47–1.37 (m, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.5 (Cq), 160.1 (Cq), 148.2 (Cq), 147.8 (Cq), 138.7 (CH), 138.5 (Cq), 128.7 (2×CH), 128.1 (2×CH), 126.8 (CH), 121.4 (CH), 119.2 (CH), 115.6 (CH), 110.6 (CH), 62.1 (CH₂), 55.5(CH₃), 51.8 (CH₂), 51.6 (CH₂), 45.9 (CH), 31.6 (CH₂), 31.4 (CH₂). HRMS (ESI) *m/z* 367.2014 [M + H]⁺ (calcd for 367.2016, C₂₂H₂₇N₂O₃). HPLC purity of 95.02%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-ethoxy-3-methoxyphenyl)acrylamide (4b): Yield

88%, white solid, m.p. 117–119°C; IR (KBr) ν 3235, 2838, 1766, 1611, 2560, 1512,

1370, 1263, 1216, 1161, 1120, 1032, 972, 905, 700. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 15.7 Hz, 1H), 7.36–7.27 (m, 5H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.12 (q, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 3.67 (br s, 1H), 3.45 (s, 2H), 2.76 (d, *J* = 10.9 Hz, 2H), 2.04 (t, *J* = 10.8 Hz, 2H), 1.77 (d, *J* = 10.9 Hz, 2H), 1.43 (dd, *J* = 20.7, 10.6 Hz, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 168.3 (Cq), 164.0 (Cq), 151.0 (Cq), 140.1 (Cq), 138.6 (Cq), 137.8 (CH), 133.9 (Cq), 128.7 (2×CH), 128.1 (2×CH), 126.8 (CH), 123.2 (CH), 122.7 (CH), 120.0 (CH), 111.3 (CH), 62.1 (CH₂), 55.7 (CH₃), 51.8 (2×CH₂), 46.0 (CH), 31.6 (2×CH₂), 20.3 (CH₃). HRMS (ESI) *m/z* 409.2120 [M + H]⁺ (calcd for 409.2122, C₂₄H₂₉N₂O₄). HPLC purity of 99.42%.

***(E)-N-(1-benzylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)acrylamide (4c)*²**: Yield 90%, light yellow solid, m.p. 117–119°C; IR (KBr) ν 3421, 2921, 1612, 1582, 1536, 1508, 1455, 1418, 1326, 1286, 1240, 1127, 993, 882, 697. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.37–7.27 (m, 5H), 7.25 (d, *J* = 6.9 Hz, 1H), 6.88 (s, 2H), 6.56 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 6H), 3.68 (s, 3H), 3.67–3.63 (m, 1H), 3.45 (s, 2H), 2.75 (d, *J* = 11.3 Hz, 2H), 2.04 (t, *J* = 10.8 Hz, 2H), 1.76 (d, *J* = 10.1 Hz, 2H), 1.42 (td, *J* = 14.3, 3.5 Hz, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.1 (Cq), 153.0 (2×Cq), 138.59 (Cq), 138.57 (Cq), 138.5 (Cq), 130.6 (CH), 128.7 (2×CH), 128.1 (2×CH), 126.8 (CH), 121.9 (CH), 104.9 (2×CH), 62.1 (CH₂), 60.0 (CH₃), 55.8 (2×CH₃), 51.8 (2×CH₂), 46.0 (CH), 31.6 (2×CH₂). HRMS (ESI) *m/z* 411.2277 [M + H]⁺ (calcd for 411.2278, C₂₄H₃₁N₂O₄). HPLC purity of 95.63%.

***(E)-N-(1-benzylpiperidin-4-yl)-3-(3,4-dihydroxyphenyl)acrylamide (4d)*³**: Yield 50%,

deep green solid, m.p. 91–94 °C; IR (KBr) ν 3214, 2714, 1710, 1658, 1559, 1412, 1264, 1163, 1119, 1046, 1013, 983, 815, 750, 701, 656. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 7.97 (d, $J = 7.7$ Hz, 1H), 7.37–7.27 (m, 5H), 7.25 (d, $J = 6.9$ Hz, 1H), 6.88 (s, 2H), 6.56 (d, $J = 15.7$ Hz, 1H), 3.80 (s, 6H), 3.68 (s, 3H), 3.67–3.63 (m, 1H), 3.45 (s, 2H), 2.75 (d, $J = 11.3$ Hz, 2H), 2.04 (t, $J = 10.8$ Hz, 2H), 1.76 (d, $J = 10.1$ Hz, 2H), 1.42 (td, $J = 14.3, 3.5$ Hz, 2H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 164.6 (Cq), 145.8 (Cq), 147.6 (Cq), 139.0 (Cq), 138.6 (Cq), 128.6 (2 \times CH), 128.1 (2 \times CH), 126.7 (CH), 126.2 (CH), 120.1 (CH), 118.5 (CH), 115.9 (CH), 114.0 (CH), 62.1 (CH_2), 51.9 (2 \times CH_2), 45.9 (CH), 31.7 (2 \times CH_2). HRMS (ESI) m/z 353.1861 [$\text{M} + \text{H}$] $^+$ (calcd for 353.1860, $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_3$). HPLC purity of 97.62%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-hydroxyphenyl)acrylamide (4e): Yield 79%, yellow solid, m.p. 125–128 °C; IR (KBr) ν 3273, 3064, 2934, 1656, 1584, 1515, 1451, 1284, 1220, 1171, 1140, 987, 835, 748, 699. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 8.05–7.97 (m, 1H), 7.65–7.56 (m, 2H), 7.40 (d, $J = 15.8$ Hz, 1H), 7.36–7.27 (m, 4H), 7.24 (dd, $J = 10.8, 5.5$ Hz, 3H), 6.57 (d, $J = 15.8$ Hz, 1H), 3.72–3.60 (m, 2H), 3.46 (s, 3H), 2.76 (d, $J = 11.0$ Hz, 2H), 2.05 (t, $J = 10.7$ Hz, 2H), 1.77 (d, $J = 10.8$ Hz, 2H), 1.49–1.38 (m, 2H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 164.6 (Cq), 159.2 (Cq), 138.6 (Cq), 138.5 (Cq), 129.0 (2 \times CH), 128.6 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 125.6 (CH), 118.7 (CH), 115.8 (2 \times CH), 62.1 (CH_2), 51.9 (2 \times CH_2), 45.0 (CH), 31.7 (2 \times CH_2). HRMS (ESI) m/z 337.1909 [$\text{M} + \text{H}$] $^+$ (calcd for 337.1911, $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$). HPLC purity of 97.91%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-fluorophenyl)acrylamide (4f): Yield 83%,

yellow oil; IR (KBr) ν 3299, 3061, 2940, 1658, 1621, 1555, 1509, 1350, 1222, 1158, 1136, 1028, 988, 830, 700. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 8.05–7.97 (m, 1H), 7.65–7.56 (m, 2H), 7.40 (d, $J = 15.8$ Hz, 1H), 7.36–7.27 (m, 4H), 7.24 (dd, $J = 10.8, 5.5$ Hz, 3H), 6.57 (d, $J = 15.8$ Hz, 1H), 3.72–3.60 (m, 2H), 3.46 (s, 3H), 2.76 (d, $J = 11.0$ Hz, 2H), 2.05 (t, $J = 10.7$ Hz, 2H), 1.77 (d, $J = 10.8$ Hz, 2H), 1.49–1.38 (m, 2H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 164.0 (Cq), 138.5 (Cq), 137.2 (Cq), 129.54 (2 \times CH), 129.47 (CH), 128.7 (2 \times CH), 128.1 (2 \times CH), 126.8 (CH), 122.4 (Cq), 115.9 (2 \times CH), 115.7 (CH), 62.1 (CH_2), 51.8 (2 \times CH_2), 46.1 (CH), 31.6 (2 \times CH_2). HRMS (ESI) m/z 339.1866 [$\text{M} + \text{H}$] $^+$ (calcd for 339.1867, $\text{C}_{21}\text{H}_{24}\text{FN}_2\text{O}$). HPLC purity of 97.82%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-chlorophenyl)acrylamide (4g): Yield 83%, yellow oil; IR (KBr) ν 3285, 3063, 2932, 2799, 1655, 1621, 1546, 1492, 1219, 1143, 1091, 972, 821, 730, 699, 665. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 8.05–7.97 (m, 1H), 7.65–7.56 (m, 2H), 7.40 (d, $J = 15.8$ Hz, 1H), 7.36–7.27 (m, 4H), 7.24 (dd, $J = 10.8, 5.5$ Hz, 3H), 6.57 (d, $J = 15.8$ Hz, 1H), 3.72–3.60 (m, 2H), 3.46 (s, 3H), 2.76 (d, $J = 11.0$ Hz, 2H), 2.05 (t, $J = 10.7$ Hz, 2H), 1.77 (d, $J = 10.8$ Hz, 2H), 1.49–1.38 (m, 2H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 163.9 (Cq), 138.6 (Cq), 137.0 (Cq), 133.9 (Cq), 133.7 (CH), 129.1 (2 \times CH), 128.9 (2 \times CH), 128.6 (2 \times CH), 128.1 (2 \times CH), 126.8 (CH), 123.3 (CH), 62.1 (CH_2), 51.8 (2 \times CH_2), 46.1 (CH), 31.6 (2 \times CH_2). HRMS (ESI) m/z 355.1571 [$\text{M} + \text{H}$] $^+$ (calcd for 355.1572, $\text{C}_{21}\text{H}_{24}\text{ClN}_2\text{O}$). HPLC purity of 99.32%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-nitrophenyl)acrylamide (4h): Yield 70%, yellow oil; IR (KBr) ν 3264, 2930, 1666, 1521, 1345, 1112, 986, 848, 749, 703. $^1\text{H-NMR}$

(500 MHz, DMSO- d_6) δ 8.05 – 7.97 (m, 1H), 7.65 – 7.56 (m, 2H), 7.40 (d, J = 15.8 Hz, 1H), 7.36–7.27 (m, 4H), 7.24 (dd, J = 10.8, 5.5 Hz, 3H), 6.57 (d, J = 15.8 Hz, 1H), 3.72–3.60 (m, 2H), 3.46 (s, 3H), 2.76 (d, J = 11.0 Hz, 2H), 2.05 (t, J = 10.7 Hz, 2H), 1.77 (d, J = 10.8 Hz, 2H), 1.49–1.38 (m, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 163.4 (Cq), 147.4 (Cq), 141.6 (Cq), 136.1 (CH), 128.7 (2 \times CH), 128.4 (2 \times CH), 128.1 (2 \times CH), 126.9 (CH), 126.7 (CH), 124.0 (2 \times CH), 62.0 (CH $_2$), 51.7 (CH $_2$), 51.7 (CH $_2$), 46.1 (CH), 31.4 (2 \times CH $_2$). HRMS (ESI) m/z 366.1812 [M+H] $^+$ (calcd for 366.1814, C $_{21}$ H $_{24}$ N $_3$ O $_3$). HPLC purity of 96.32%.

(E)-N-(1-benzylpiperidin-4-yl)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylamide (4i):

Yield 71%, yellow solid, m.p. 123–127 °C; IR (KBr) ν 3255, 1561, 1516, 1455, 1327, 1260, 1211, 1155, 1117, 951, 827, 757. ^1H -NMR (500 MHz, DMSO- d_6) δ 7.87 (d, J = 7.7 Hz, 1H), 7.35–7.27 (m, 5H), 7.24 (t, J = 6.8 Hz, 1H), 6.83 (s, 2H), 6.47 (d, J = 15.7 Hz, 1H), 3.79 (s, 6H), 3.70–3.61 (m, 2H), 3.45 (s, 2H), 2.75 (d, J = 11.5 Hz, 2H), 2.03 (t, J = 10.7 Hz, 2H), 1.75 (d, J = 10.6 Hz, 2H), 1.48–1.36 (m, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 164.5 (Cq), 148.0 (2 \times Cq), 139.0 (Cq), 138.6 (Cq), 128.7 (2 \times CH), 128.1 (2 \times CH), 126.8 (CH), 125.3 (CH), 119.62 (Cq), 119.60 (CH), 105.2 (2 \times CH), 62.1 (CH $_2$), 55.9 (2 \times CH $_3$), 51.8 (2 \times CH $_2$), 45.9 (CH), 31.6 (2 \times CH $_2$). HRMS (ESI) m/z 397.2120 [M+H] $^+$ (calcd for 397.2122, C $_{23}$ H $_{29}$ N $_2$ O $_4$). HPLC purity of 95.88%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide

(5a): Yield 75%, colorless oil; IR (KBr) ν 3264, 2933, 1658, 1516, 1407, 1255, 1160, 1126, 1032, 983, 848, 819, 750, 702. ^1H -NMR (500 MHz, DMSO- d_6) δ 7.93 (t, J =

5.1 Hz, 1H), 7.32–7.28 (m, , 5H), 7.22 (t, $J = 6.9$ Hz, 1H), 7.10 (br s, 1H), 6.96 (br d, $J = 7.3$ Hz, 1H), 6.79 (d, $J = 8.1$ Hz, 1H), 6.41 (d, $J = 15.7$ Hz, 1H), 3.79 (s, 3H), 3.41 (s, 2H), 3.20–3.16 (m, 2H), 2.80–2.71 (m, 2H), 1.87 (t, $J = 11.5$ Hz, 2H), 1.62 (d, $J = 11.8$ Hz, 2H), 1.37 (dd, $J = 13.6, 6.8$ Hz, 2H), 1.26 (br s, 1H), 1.12 (dd, $J = 21.3, 11.3$ Hz, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 165.2 (Cq), 155.1 (Cq), 147.8 (Cq), 144.2 (Cq), 138.7 (CH), 138.6 (Cq), 128.7 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 121.5 (CH), 119.0 (CH), 115.7 (CH), 110.7 (CH), 62.5 (CH₂), 55.5 (CH₃), 53.2 (CH₂), 48.5 (CH₂), 36.2 (CH), 35.9 (CH₂), 32.8 (CH₂), 31.8 (2 \times CH₂). HRMS (ESI) m/z 395.2327 [M+H]⁺ (calcd for 395.2327, C₂₄H₃₁N₂O₃). HPLC purity of 98.55%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(3-hydroxy-4-methoxyphenyl)acrylamide

(5b): Yield 72%, colorless oil, IR (KBr) ν 3422, 2925, 1677, 1512, 1439, 1270, 1202, 1131, 1026, 981, 801, 750, 721, 702. ^1H -NMR (500 MHz, DMSO- d_6) δ 8.00 (t, $J = 5.6$ Hz, 1H), 7.47 (dd, $J = 6.9, 3.6$ Hz, 6H), 7.25 (d, $J = 15.7$ Hz, 1H), 6.94 (t, $J = 11.4$ Hz, 3H), 6.35 (d, $J = 15.7$ Hz, 1H), 3.79 (s, 4H), 3.54 (s, 7H), 3.35 (d, $J = 11.6$ Hz, 2H), 3.19 (dd, $J = 13.3, 7.1$ Hz, 3H), 2.89 (d, $J = 11.8$ Hz, 2H), 1.90 (d, $J = 13.0$ Hz, 2H), 1.55 (d, $J = 23.1$ Hz, 1H), 1.41–1.36 (m, 2H), 1.33 (d, $J = 13.1$ Hz, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 165.1 (Cq), 149.1 (Cq), 146.7 (Cq), 138.6 (Cq), 131.2 (2 \times CH), 129.6 (Cq), 129.5 (CH), 128.8 (2 \times CH), 127.8 (CH), 120.0 (CH), 119.5 (CH), 113.4 (CH), 112.1 (CH), 59.2 (CH₂), 55.6 (CH₃), 51.6 (2 \times CH₂), 35.7 (CH), 35.2 (CH₂), 30.5 (CH₂), 28.6 (2 \times CH₂). HRMS (ESI) m/z 395.2326 [M+H]⁺ (calcd for 395.2329, C₂₄H₃₁N₂O₃). HPLC purity of 98.27%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-hydroxy-3,5-

dimethoxyphenyl)acrylamide (5c): Yield 80%, yellow solid, m.p. 101–102 °C; IR (KBr) ν 3368, 2932, 1658, 1590, 1514, 1454, 1325, 1286, 1214, 1157, 1117, 980, 831, 748, 702. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 7.89 (t, $J = 5.2$ Hz, 1H), 7.29 (dt, $J = 11.5, 5.7$ Hz, 1H), 7.22 (t, $J = 6.9$ Hz, 1H), 6.83 (s, 1H), 6.45 (d, $J = 15.7$ Hz, 1H), 3.79 (s, 1H), 3.42 (s, 1H), 3.18 (dd, $J = 12.7, 6.6$ Hz, 1H), 2.77 (d, $J = 11.2$ Hz, 1H), 1.88 (t, $J = 10.9$ Hz, 1H), 1.63 (d, $J = 11.8$ Hz, 1H), 1.38 (dd, $J = 13.7, 6.8$ Hz, 1H), 1.31–1.24 (m, 1H), 1.19–1.07 (m, 1H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 165.1 (Cq), 148.1 (2 \times Cq), 138.9 (Cq), 138.6 (Cq), 128.6 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 119.4 (CH), 105.2 (2 \times CH), 99.4 (CH), 62.4 (CH₂), 55.9 (CH₃), 53.2 (2 \times CH₂), 36.1 (CH), 35.9 (CH₂), 32.8 (CH₂), 31.8 (2 \times CH₂). HRMS (ESI) m/z 425.2437 [M+H]⁺ (calcd for 425.2435, C₂₅H₃₃N₂O₄). HPLC purity of 97.35%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-hydroxyphenyl)acrylamide (5d): Yield 88%, yellow solid, m.p. 123–125 °C; IR (KBr) ν 3273, 2933, 1654, 1584, 1514, 1454, 1407, 1283, 1225, 1172, 994, 944, 839, 751, 699. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ 7.91 (s, 1H), 7.33–7.25 (m, 4H), 7.23 (d, $J = 6.9$ Hz, 1H), 7.20 (d, $J = 15.7$ Hz, 1H), 6.90 (d, $J = 1.8$ Hz, 1H), 6.78 (dd, $J = 8.1, 1.8$ Hz, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.30 (d, $J = 15.7$ Hz, 1H), 3.42 (s, 2H), 3.17 (dd, $J = 11.0, 7.3$ Hz, 2H), 2.76 (d, $J = 11.3$ Hz, 2H), 1.88 (t, $J = 10.8$ Hz, 2H), 1.63 (d, $J = 11.7$ Hz, 2H), 1.37 (dd, $J = 13.9, 6.9$ Hz, 2H), 1.27 (dd, $J = 7.0, 3.8$ Hz, 1H), 1.18–1.08 (m, 2H). $^{13}\text{C-NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 165.2 (Cq), 158.9 (Cq), 138.6 (Cq), 138.4 (Cq), 129.0 (2 \times CH), 128.6 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 125.8 (CH), 118.7 (CH), 115.7 (2 \times CH), 62.4 (CH₂), 53.2 (2 \times CH₂), 36.2 (CH), 35.9 (CH₂), 32.8 (CH₂), 31.8 (2 \times CH₂). HRMS (ESI)

m/z 365.2222 $[M+H]^+$ (calcd for 365.2224, $C_{23}H_{29}N_2O_2$). HPLC purity of 97.18%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(3,4-dihydroxyphenyl)acrylamide (5e):

Yield 69%, yellow solid, m.p. 112–115 °C; IR (KBr) ν 3434, 3279, 1646, 1565, 1411, 1335, 1302, 1275, 1211, 1117, 1020, 987, 924, 857, 811, 751, 701. 1H -NMR (500 MHz, $DMSO-d_6$) δ 7.91 (br s, 1H), 7.33–7.25 (m, 4H), 7.23 (d, $J = 6.9$ Hz, 1H), 7.20 (d, $J = 15.7$ Hz, 1H), 6.90 (d, $J = 1.8$ Hz, 1H), 6.78 (dd, $J = 8.1, 1.8$ Hz, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.30 (d, $J = 15.7$ Hz, 1H), 3.42 (s, 2H), 3.17 (dd, $J = 11.0, 7.3$ Hz, 2H), 2.76 (d, $J = 11.3$ Hz, 2H), 1.88 (t, $J = 10.8$ Hz, 2H), 1.63 (d, $J = 11.7$ Hz, 2H), 1.37 (dd, $J = 13.9, 6.9$ Hz, 2H), 1.27 (dd, $J = 7.0, 3.8$ Hz, 1H), 1.18–1.08 (m, 2H). ^{13}C -NMR (126 MHz, $DMSO-d_6$) δ 165.3 (Cq), 148.0 (Cq), 146.0 (Cq), 138.9 (Cq), 138.6 (Cq), 128.6 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 126.1 (CH), 120.1 (CH), 118.3 (CH), 116.1 (CH), 114.3 (CH), 62.5, 53.1(2 \times CH₂), 36.1 (CH), 35.9(CH₂), 32.8(CH₂), 31.8(2 \times CH₂). HRMS (ESI) m/z 381.2171 $[M+H]^+$ (calcd for 381.2173, $C_{23}H_{29}N_2O_3$). HPLC purity of 98.56%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(2-hydroxyphenyl)acrylamide (5f): Yield

72%, colorless oil, IR (KBr) ν 3395, 2923, 1710, 1653, 1604, 1455, 1407, 1340, 1295, 1255, 1156, 1114, 1095, 990, 752, 701. 1H -NMR (500 MHz, $DMSO-d_6$) δ 7.97 (t, $J = 5.4$ Hz, 1H), 7.60 (d, $J = 15.9$ Hz, 1H), 7.40 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.33–7.25 (m, 4H), 7.22 (t, $J = 6.8$ Hz, 1H), 7.19–7.13 (m, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 6.81 (t, $J = 7.4$ Hz, 1H), 6.63 (d, $J = 15.9$ Hz, 1H), 3.42 (s, 3H), 3.21–3.15 (m, 3H), 2.77 (d, $J = 11.3$ Hz, 2H), 1.87 (s, 3H), 1.63 (d, $J = 11.8$ Hz, 2H), 1.38 (dd, $J = 13.9, 6.9$ Hz, 2H), 1.28 (dd, $J = 7.1, 3.8$ Hz, 1H), 1.19–1.08 (m, 2H). ^{13}C -NMR (126 MHz, $DMSO-d_6$) δ

165.4 (Cq), 156.2 (Cq), 138.6 (Cq), 134.2 (CH), 130.2 (Cq), 128.7 (2×CH), 128.1 (CH), 128.0 (2×CH), 126.7 (CH), 121.8 (CH), 121.7 (CH), 119.2 (CH), 116.1 (CH), 62.5 (CH₂), 53.2 (2×CH₂), 36.2 (CH), 35.9 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 365.2222 [M+H]⁺ (calcd for 365.2224, C₂₃H₂₉N₂O₂). HPLC purity of 99.67%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)cinnamamide (5g)⁴: Yield 91%, yellow solid, m.p. 69–71 °C; IR (KBr) ν 3430, 3297, 3063, 2928, 1659, 1622, 1562, 1348, 1229, 1075, 982, 793, 767, 741, 700. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 7.91 (s, 1H), 7.33–7.25 (m, 4H), 7.23 (d, J = 6.9 Hz, 1H), 7.20 (d, J = 15.7 Hz, 1H), 6.90 (d, J = 1.8 Hz, 1H), 6.78 (dd, J = 8.1, 1.8 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.30 (d, J = 15.7 Hz, 1H), 3.42 (s, 2H), 3.17 (dd, J = 11.0, 7.3 Hz, 2H), 2.76 (d, J = 11.3 Hz, 2H), 1.88 (t, J = 10.8 Hz, 2H), 1.63 (d, J = 11.7 Hz, 2H), 1.37 (dd, J = 13.9, 6.9 Hz, 2H), 1.27 (dd, J = 7.0, 3.8 Hz, 1H), 1.18–1.08 (m, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.7 (Cq), 138.6 (Cq), 138.3 (Cq), 134.9 (CH), 129.2 (CH), 128.8 (CH), 128.6 (2×CH), 128.0 (2×CH), 127.4 (CH), 126.7 (CH), 122.4 (CH), 62.4 (CH₂), 53.2 (2×CH₂), 36.2 (CH), 35.8 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 349.2275 [M+H]⁺ (calcd for 349.2274, C₂₃H₂₉N₂O). HPLC purity of 98.67%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-ethoxy-3-methoxyphenyl)acrylamide (5h): Yield 82%, yellow solid, m.p. 94–95 °C; IR (KBr) ν 3294, 2930, 1763, 1656, 1619, 1544, 1511, 1370, 1259, 1217, 1162, 1120, 1033, 974, 906, 703. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.03 (t, J = 5.4 Hz, 1H), 7.39 (d, J = 15.7 Hz, 1H), 7.33–7.25 (m, 5H), 7.23 (t, J = 6.8 Hz, 1H), 7.12 (dd, J = 18.3, 8.1 Hz, 2H), 6.60 (d, J = 15.8 Hz,

1H), 3.81 (s, 3H), 3.42 (s, 2H), 3.20 (dd, $J = 12.9, 6.6$ Hz, 2H), 2.77 (d, $J = 11.0$ Hz, 2H), 2.26 (s, 3H), 1.89 (t, $J = 11.2$ Hz, 2H), 1.64 (d, $J = 12.0$ Hz, 2H), 1.39 (dd, $J = 13.8, 6.9$ Hz, 2H), 1.29 (s, 1H), 1.14 (dd, $J = 21.1, 11.4$ Hz, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 168.3 (Cq), 164.6 (Cq), 151.0 (Cq), 138.6 (Cq), 137.7 (Cq), 133.9 (CH), 128.6 (2 \times CH), 128.0 (2 \times CH), 126.7 (CH), 123.1 (CH), 122.6 (CH), 120.0 (CH), 111.4 (CH), 62.4 (CH $_2$), 55.7 (CH $_3$), 53.2 (2 \times CH $_2$), 36.2 (CH), 35.8 (CH $_2$), 32.8 (CH $_2$), 31.8 (2 \times CH $_2$), 20.3 (CH $_3$). HRMS (ESI) m/z 437.2433 [M+H] $^+$ (calcd for 437.2435, C $_{26}$ H $_{33}$ N $_2$ O $_4$). HPLC purity of 96.20%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(3,4-dimethoxyphenyl)acrylamide (5i):

Yield 87%, yellow solid, m.p. 81–83 °C; IR (KBr) ν 3426, 3325, 2928, 1653, 1621, 1538, 1452, 1261, 1215, 1139, 1026, 971, 846, 799, 740, 699. ^1H -NMR (500 MHz, DMSO- d_6) δ 8.02 (t, $J = 5.4$ Hz, 1H), 7.37 (d, $J = 15.8$ Hz, 1H), 7.33–7.25 (m, 6H), 7.22 (t, $J = 6.9$ Hz, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 7.10 (s, 1H), 6.94 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.61 (d, $J = 15.8$ Hz, 1H), 3.78 (s, 3H), 3.42 (s, 2H), 3.20 (dd, $J = 13.0, 6.7$ Hz, 2H), 2.77 (d, $J = 11.3$ Hz, 2H), 1.88 (t, $J = 10.8$ Hz, 2H), 1.63 (d, $J = 11.9$ Hz, 2H), 1.39 (q, $J = 6.9$ Hz, 2H), 1.33–1.24 (m, 2H), 1.14 (qd, $J = 12.3, 3.5$ Hz, 2H). ^{13}C -NMR (126 MHz, DMSO- d_6) δ 165.0 (Cq), 150.0 (Cq), 148.9 (Cq), 138.3 (Cq), 128.7 (2 \times CH), 128.0 (2 \times CH), 127.8 (Cq), 126.7 (CH), 121.2 (CH), 120.1 (CH), 111.8 (CH), 110.0 (CH), 62.4 (CH $_2$), 55.5 (CH $_3$), 55.4 (CH $_3$), 53.2 (2 \times CH $_2$), 36.2 (CH), 35.9 (CH $_2$), 32.8 (CH $_2$), 31.8 (2 \times CH $_2$). HRMS (ESI) m/z 409.2482 [M+H] $^+$ (calcd for 409.2486, C $_{25}$ H $_{33}$ N $_2$ O $_3$). HPLC purity of 98.88%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(3-methoxyphenyl)acrylamide (5j): Yield

78%, yellow solid, m.p. 62 – 64 °C; IR (KBr) ν 3293, 3059, 2920, 1657, 1622, 1553, 1493, 1451, 1293, 1168, 1034, 981, 851, 787, 741, 701. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.02 (t, *J* = 5.4 Hz, 1H), 7.37 (d, *J* = 15.8 Hz, 1H), 7.33 – 7.25 (m, 6H), 7.22 (t, *J* = 6.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 6.94 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 2H), 3.20 (dd, *J* = 13.0, 6.7 Hz, 2H), 2.77 (d, *J* = 11.3 Hz, 2H), 1.88 (t, *J* = 10.8 Hz, 2H), 1.63 (d, *J* = 11.9 Hz, 2H), 1.39 (q, *J* = 6.9 Hz, 2H), 1.33–1.24 (m, 2H), 1.14 (qd, *J* = 12.3, 3.5 Hz, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.7 (Cq), 159.5 (Cq), 138.6 (Cq), 138.2 (CH), 136.4 (Cq), 129.9 (CH), 128.7 (2×CH), 128.0 (2×CH), 126.7 (CH), 122.7 (CH), 119.8 (CH), 115.1 (CH), 112.5 (CH), 62.4 (CH₂), 55.1 (CH₃), 53.2 (2×CH₂), 36.2 (CH), 35.8 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) *m/z* 379.2378 [M+H]⁺ (calcd for 379.2380, C₂₄H₃₁N₂O₂). HPLC purity of 98.33%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (5k):

Yield 72%, yellow oil, IR (KBr) ν 3369, 3281, 2929, 1660, 1621, 1583, 1505, 1454, 1419, 1279, 1126, 1003, 828, 743, 700. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 7.99 (t, *J* = 5.3 Hz, 1H), 7.34 (d, *J* = 15.9 Hz, 1H), 7.28 (dd, *J* = 12.2, 6.9 Hz, 4H), 7.23 (t, *J* = 6.9 Hz, 1H), 6.88 (s, 2H), 6.56 (d, *J* = 15.7 Hz, 1H), 3.81 (s, 6H), 3.68 (s, 3H), 3.42 (s, 2H), 3.19 (dd, *J* = 12.7, 6.6 Hz, 2H), 2.77 (d, *J* = 11.2 Hz, 2H), 1.87 (d, *J* = 13.5 Hz, 2H), 1.63 (d, *J* = 11.9 Hz, 2H), 1.38 (dd, *J* = 13.7, 6.8 Hz, 2H), 1.33–1.23 (m, 1H), 1.19–1.08 (m, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.8 (Cq), 153.0 (Cq), 138.62 (Cq), 138.60 (Cq), 138.5 (Cq), 130.6 (CH), 128.7 (2×CH), 128.0 (2×CH), 126.7 (CH), 121.7 (CH), 104.9 (2×CH), 62.5 (CH₂), 60.1 (CH₃), 55.9 (CH₃), 53.2 (2×CH₂), 36.2

(CH), 35.9 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 439.2594 [M+H]⁺ (calcd for 439.2591, C₂₆H₃₅N₂O₄). HPLC purity of 96.39%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-fluorophenyl)acrylamide (5l): Yield 82%, yellow oil, IR (KBr) ν 3423, 3278, 2927, 1661, 1620, 1600, 1555, 1451, 1414, 1342, 1226, 1159, 982, 832, 745, 701. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.65–7.57 (m, 2H), 7.39 (d, J = 15.8 Hz, 1H), 7.27 (ddd, J = 20.9, 14.8, 6.9 Hz, 7H), 6.55 (d, J = 15.8 Hz, 1H), 3.42 (s, 2H), 3.19 (dd, J = 12.8, 6.5 Hz, 2H), 2.77 (d, J = 11.0 Hz, 2H), 1.89 (d, J = 12.1 Hz, 3H), 1.63 (d, J = 12.1 Hz, 2H), 1.39 (dd, J = 13.7, 6.8 Hz, 2H), 1.29 (s, 1H), 1.14 (dd, J = 22.0, 10.6 Hz, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.6 (Cq), 138.6 (Cq), 137.1 (Cq), 131.6 (CH), 129.54 (CH), 129.47 (Cq), 128.7 (2×CH), 128.0 (2×CH), 126.7 (CH), 122.3 (CH), 115.9 (CH), 115.7 (CH), 62.4 (CH₂), 53.2 (2×CH₂), 36.2 (CH), 35.8 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 367.2182 [M+H]⁺ (calcd for 367.2180, C₂₃H₂₈N₂O). HPLC purity of 99.52%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-chlorophenyl)acrylamide (5m)⁴: Yield 84%, yellow solid, m.p. 104–106 °C; IR (KBr) ν 3432, 3307, 2931, 1656, 1621, 1546, 1452, 1344, 1222, 1150, 1030, 937, 855, 732. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.05 (t, J = 5.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 15.8 Hz, 1H), 7.33–7.25 (m, 2H), 7.22 (t, J = 6.9 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 3.42 (s, 1H), 3.19 (dd, J = 13.0, 6.7 Hz, 1H), 2.77 (d, J = 11.2 Hz, 1H), 1.88 (t, J = 11.2 Hz, 1H), 1.63 (d, J = 12.1 Hz, 1H), 1.39 (q, J = 6.9 Hz, 1H), 1.33–1.25 (m, 1H), 1.19–1.08 (m, 1H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.5 (Cq), 138.6 (Cq), 136.9 (Cq), 133.9

(Cq), 133.7 (CH), 129.1 (CH), 128.9 (CH), 128.6 (2×CH), 128.0 (2×CH), 126.7 (CH), 123.2 (CH), 62.4 (CH₂), 53.2 (2×CH₂), 36.2 (CH), 35.8 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 383.1884 [M+H]⁺ (calcd for 383.1885, C₂₃H₂₈ClN₂O). HPLC purity of 98.62%.

(E)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-nitrophenyl)acrylamide (5n)⁴: Yield 84%, yellow solid, m.p. 101–103 °C; IR (KBr) ν 3407, 3063, 2925, 1663, 1621, 1597, 1555, 1519, 1451, 1413, 1343, 1226, 1109, 981, 846, 74, 701. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.25 (d, J = 8.7 Hz, 1H), 8.21 (t, J = 5.3 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 15.8 Hz, 1H), 7.33–7.25 (m, 2H), 7.22 (t, J = 6.9 Hz, 1H), 6.80 (d, J = 15.8 Hz, 1H), 3.42 (s, 1H), 3.21 (dd, J = 13.0, 6.7 Hz, 1H), 2.77 (d, J = 11.3 Hz, 1H), 1.87 (d, J = 9.7 Hz, 3H), 1.64 (d, J = 12.0 Hz, 1H), 1.40 (q, J = 6.9 Hz, 1H), 1.34–1.24 (m, 1H), 1.14 (qd, J = 12.2, 3.4 Hz, 1H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 164.0 (Cq), 147.4 (Cq), 141.6 (Cq), 138.6 (Cq), 136.0 (CH), 128.6 (2×CH), 128.4 (2×CH), 128.0 (2×CH), 126.7 (CH), 126.7 (CH), 124.0 (2×CH), 62.4 (CH₂), 53.2 (2×CH₂), 36.3 (CH), 35.7 (CH₂), 32.8 (CH₂), 31.8 (2×CH₂). HRMS (ESI) m/z 394.2127 [M+H]⁺ (calcd for 394.2125, C₂₃H₂₈N₃O₃). HPLC purity of 98.48%.

N-(1-benzylpiperidin-4-yl)-3-(4-hydroxy-3-methoxyphenyl)propanamide (6):

Compound **4a** was dissolved in MeOH under N₂. To this Pd/C (10%) was added. The solution was then stirred under H₂ at normal pressure overnight. The solution was then filtered to remove Pd/C, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/CH₂Cl₂: 2/98) to give **6**. Yield 68%, colorless oil; IR (KBr) ν 3400, 2925, 2850, 1676, 1519, 1455, 1276, 1202,

1128, 1034, 946, 832, 800, 751, 721, 701. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 7.89 (s, 1H), 7.46 (s, 5H), 6.73 (s, 1H), 6.64 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 4.25 (s, 2H), 3.72 (s, 3H), 3.17 (s, 1H), 3.02 (s, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 2H), 1.88 (s, 2H), 1.54 (s, 2H), 1.23 (s, 1H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 171.1 (Cq), 147.3 (Cq), 144.6 (Cq), 132.0 (Cq), 131.2 (2×CH), 129.6 (Cq), 128.80 (Cq), 128.79 (2×CH), 120.3 (CH), 115.2 (CH), 112.4 (CH), 55.5 (CH₃), 50.8 (2×CH₂), 48.6 (CH₂), 37.3 (CH₂), 30.7 (2×CH₂), 28.8 (CH₂). HRMS (ESI) *m/z* 369.2171 [M+H]⁺ (calcd for 369.2173, C₂₂H₂₉N₂O₃). HPLC purity of 97.94%.

***N*-(2-(1-benzylpiperidin-4-yl)ethyl)-3-(4-hydroxy-3-methoxyphenyl)propanamide (7):**

Procedure for synthesis compound **7** was following above. Yield 74%, colorless oil; IR (KBr) ν 3366, 2927, 1678, 1519, 1455, 1277, 1201 1127, 1127, 1034, 945, 831, 800, 750, 720, 702. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 9.55 (s, 1H), 7.74 (t, *J* = 5.5 Hz, 1H), 7.53–7.45 (m, 6H), 6.74 (d, *J* = 1.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.26 (d, *J* = 4.7 Hz, 2H), 4.25–4.23 (m, 1H), 3.73 (s, 4H), 3.70 (s, 2H), 3.32 (d, *J* = 11.8 Hz, 2H), 3.04 (dd, *J* = 12.1, 6.1 Hz, 3H), 2.76 (dd, *J* = 21.4, 10.7 Hz, 2H), 2.76 (d, *J* = 10.7 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 3H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.79 (d, *J* = 11.4 Hz, 2H), 1.79 (d, *J* = 11.4 Hz, 3H), 1.33–1.18 (m, 5H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 171.2 (Cq), 147.2 (Cq), 144.5 (Cq), 138.1 (Cq), 132.0 (Cq), 131.2 (2×CH), 129.5 (CH), 128.8 (2×CH), 120.3 (CH), 115.2 (CH), 112.5 (CH), 59.3 (CH₂), 55.5 (CH₃), 51.6 (2×CH₂), 37.1 (CH), 35.4 (CH₂), 35.1 (CH₂), 30.7 (2×CH₂), 30.2 (CH₂), 28.5 (CH₂). HRMS (ESI) *m/z* 397.2485 [M+H]⁺ (calcd for 397.2486, C₂₄H₃₃N₂O₃). HPLC purity of 97.70%.

Ethyl 3-oxo-4-(triphenylphosphoranylidene)butanoate (9)⁵: Triphenylphosphine (76.2 mmol, 20 g) and 4-chloroacetoacetate (84.5 mmol, 11.42 mL) in 50 mL toluene were stirred for 24 h at 50 °C. The solid product was washed with toluene and then distilled water was added until the solid was dissolved. The mixture was extracted with three portions of diethyl ether followed by adding saturated NaHCO₃ to the aqueous phase until pH 8. The solid product was filtrated through a Buchner funnel, washed twice with distilled water and twice with diethyl ether and evaporated to dryness (22 g, 90%). ¹H-NMR (500 MHz, CDCl₃) δ 7.72–7.60 (m, 6H), 7.60–7.50 (m, 3H), 7.45 (m, 6H), 4.19 (q, *J* = 7.13 Hz, 2H), 3.81 (m, 1H), 3.35 (s, 2H), 1.28 (t, *J* = 7.13 Hz, 3H).

General procedure for the preparation of acetophenone derivatives (10a-10b)⁶

Compound **9** (1.0 equiv) and relevant amine (**3** or **4**) (1.1 equiv) were added together in xylene, and the solution was heated to reflux for 3 h. The solution was then cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash chromatography (MeOH/CH₂Cl₂: 1/30).

N-(2-(1-benzylpiperidin-4-yl)ethyl)-3-oxo-4-

(triphenylphosphoranylidene)butanamide (10a): Yield 64%, off-white solid, ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.12 (d, *J* = 7.2 Hz, 1H), 7.65–7.59 (m, 6H), 7.57 (dd, *J* = 8.2, 6.7 Hz, 3H), 7.47 (td, *J* = 7.7, 2.8 Hz, 6H), 7.30 (dd, *J* = 8.2, 5.2 Hz, 4H), 7.24 (dd, *J* = 6.0, 2.9 Hz, 1H), 3.83–3.76 (m, 1H), 3.50 (s, 2H), 3.25 (s, 2H), 2.76 (d, *J* = 10.6 Hz, 2H), 2.17 (d, *J* = 11.1 Hz, 2H), 1.85 (d, *J* = 10.9 Hz, 3H), 1.48 (dd, *J* = 20.2, 10.0 Hz, 3H).

***N*-(1-benzylpiperidin-4-yl)-3-oxo-4-(triphenylphosphoranylidene)butanamide (10b):**

Yield 58%, off-white solid, ¹H-NMR (500 MHz, DMSO-*d*₆) δ 8.00 (t, *J* = 5.5 Hz, 1H), 7.65 (dd, *J* = 10.0, 4.2 Hz, 3H), 7.62–7.52 (m, 12H), 7.32–7.27 (m, 2H), 7.23 (dd, *J* = 16.7, 7.5 Hz, 3H), 3.36 (s, 3H), 3.08 (dd, *J* = 12.7, 6.6 Hz, 2H), 3.00 (s, 2H), 2.69 (d, *J* = 11.3 Hz, 2H), 1.77 (t, *J* = 10.9 Hz, 3H), 1.56 (d, *J* = 11.9 Hz, 3H), 1.30 (dd, *J* = 13.6, 6.8 Hz, 3H), 1.23 (s, 2H), 1.08 (dd, *J* = 11.7, 9.1 Hz, 3H).

General procedure for the preparation of acetophenone derivatives (11a-11c)⁶

Compound **10** (0.93 mmol) was added to a solution of NaH (0.112 g, 2.81 mmol) in THF (10 mL) and cooled to 0 °C for 30 min. Then relevant benzaldehyde (1.12 mmol) in THF (1.0 mL) was added dropwise. The solution was then cooled to room temperature and stirred overnight following heating the solution to 40°C for 3 h. The reaction was then quenched using NH₄Cl (1.0 mL). The solvent was removed under reduced pressure and the residual oil was purified by flash chromatography.

***(E)*-7-((1-benzylpiperidin-4-yl)amino)-1-(4-hydroxy-3-methoxyphenyl)hept-1-ene-**

3,5-dione (11a): Yield 67%, colorless oil; IR (KBr) ν 3441, 2851, 251, 2312, 1679, 1516, 1455, 1294, 1201, 1130, 800, 751, 720, 702, 420. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 9.76 (d, *J* = 7.8 Hz, 1H), 8.24 (t, *J* = 5.6 Hz, 1H), 7.52–7.47 (m, 6H), 7.23 (d, *J* = 1.4 Hz, 1H), 7.10 (br d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 4.28 (s, 1H), 3.73 (s, 1H), 3.27 (s, 1H), 3.23–3.18 (m, 1H), 2.82 (d, *J* = 12.1 Hz, 1H), 2.31 (s, 1H), 1.86 (d, *J* = 13.4 Hz, 1H), 1.50 (s, 1H), 1.38 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.31 (d, *J* = 11.8 Hz, 1H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 190.9 (Cq), 167.3 (Cq), 153.0 (Cq), 149.3 (Cq), 147.4 (Cq), 139.3 (Cq), 135.1 (CH), 131.2 (2×CH), 129.6 (CH), 129.5 (CH),

128.8 (2×CH), 124.6 (CH), 115.5 (CH), 115.4 (CH), 59.2 (CH₂), 55.5 (CH₃), 51.7 (2×CH₂), 48.5 (CH), 35.9 (CH₂), 34.5 (CH₂), 28.6 (2×CH₂), 26.1 (CH₂). HRMS (ESI) *m/z* 437.2436 [M+H]⁺ (calcd for 437.2435, C₂₆H₃₃N₂O₄). HPLC purity of 97.50%.

(E)-N-(1-benzylpiperidin-4-yl)-5-(4-hydroxy-3-methoxyphenyl)-3-oxopent-4-enamide (11b): Yield 84%, colorless oil; IR (KBr) ν 3436, 2925, 2848, 2340, 2310, 1676, 1589, 1517, 1292, 1202, 1131, 1031, 947, 800, 753, 721, 701, 419. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 11.93 (s, 1H), 10.65 (s, 1H), 9.75 (s, 1H), 8.48 (br s, 1H), 7.61–7.58 (m, 2H), 7.46–7.41 (m, 4H), 7.23 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.23 (br s, 2H), 3.92 (br s, 1H), 3.03 (br s, 2H), 2.30 (s, 3H), 1.96 (br s, 2H), 182–1.78 (m, 2H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 195.5 (Cq), 171.9 (Cq), 149.4 (Cq), 147.5 (Cq), 139.4 (Cq), 139.3 (Cq), 134.7 (CH), 131.3 (CH), 131.2 (2×CH), 128.7 (2×CH), 124.57 (CH), 124.53 (CH), 115.6 (CH), 114.0 (CH), 55.6 (CH₃), 50.5 (2×CH₂), 50.4 (CH₂), 46.0 (CH), 36.3 (CH₂), 34.1 (CH₂), 26.1 (CH₂). HRMS (ESI) *m/z* 409.2120 [M+H]⁺ (calcd for 409.2122, C₂₄H₂₉N₂O₄). HPLC purity of 97.37%.

(E)-N-(1-benzylpiperidin-4-yl)-5-(4-hydroxyphenyl)-3-oxopent-4-enamide (11c): Yield 79%, colorless oil; IR (KBr) ν 3438, 2922, 2851, 2318, 1677, 1513, 1455, 1258, 1204, 1176, 1131, 837, 420. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 8.43 (d, *J* = 7.4 Hz, 1H), 7.6–7.34 (m, 7H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.28 (s, 1H), 3.98–3.92 (m, 1H), 3.38 (d, *J* = 12.2 Hz, 1H), 3.09 (dd, *J* = 21.9, 10.5 Hz, 1H), 2.30 (s, 1H), 2.02 (d, *J* = 12.7 Hz, 1H), 1.60 (dd, *J* = 24.4, 11.2 Hz, 1H). ¹³C-NMR (126 MHz, DMSO-*d*₆) δ 195.4 (Cq), 167.0 (Cq), 159.8 (Cq), 139.0 (Cq), 134.5 (Cq), 132.2 (2×CH),

131.2 (2×CH), 129.5 (CH), 128.8 (2×CH), 124.0 (CH), 115.8 (CH), 115.6 (2×CH), 59.1 (CH₂), 50.7 (2×CH₂), 43.8 (CH), 28.1 (2×CH₂), 26.1 (CH₂). HRMS (ESI) *m/z* 379.2014 [M+H]⁺ (calcd for 379.2016, C₂₃H₂₇N₂O₃). HPLC purity of 97.00%.

Bioactivity

***In vitro* inhibition studies on eeChEs and hChEs.**

Acetylcholinesterase (AChE, E.C. 3.1.1.7) from electric eel and human erythrocytes, butyrylcholinesterase (BuChE, E.C. 3.1.1.8) from equine serum and human serum, S-butyrylthiocholine iodide (BTCI), acetylthiocholine iodide (ATCI), 5, 5'-dithiobis-(2-nitrobenzoic acid) (Ellman's reagent, DTNB) and donepezil hydrochloride were purchased from Sigma Aldrich (St. Louis, MO, USA). The inhibitory activities of test compounds was evaluated by Ellman's method.⁷ The compounds were dissolved in DMSO and diluted with the buffer solution (50 mM Tris-HCl, pH = 8.0, 0.1 M NaCl, 0.02 M MgCl₂•6H₂O) to yield corresponding test concentrations (DMSO less than 0.01%). In each well of the plate, 160μL of 1.5 mM DTNB, 50 μL of AChE (0.22 U/mL eeAChE or 0.05 U/mL hAChE) or 50μL of BuChE (0.12 U/mL eqBuChE or 0.024 U/mL hBuChE) were incubated with 10μL of different concentrations of test compounds (0.001-200mM) at 37 °C for 5 min. After this period, acetylthiocholine iodide (15 mM) or S-butyrylthiocholine iodide (15 mM) as the substrate (30 μL) was added and the absorbance was measured with a wavelength of 405 nm at different time intervals (0, 60, 120, and 180 s). IC₅₀ values were calculated as concentration of compound that produces 50% enzyme activity inhibition, using the Graph Pad Prism 4.03 software (San Diego, CA, USA). Results

are expressed as the mean \pm SD of at least three different experiments performed in triplicate.

***In vitro* antioxidant activity assays**

ABTS radical cation scavenging method⁸: ABTS scavenging activity was accessed using the method as described in the literature. ABTS radical cation (ABTS^{•+}) was generated by reacting 7 mM ABTS stock solution with 2.45 mM potassium persulfate (final concentration) and allowing the mixture to stand in the dark at room temperature for 16 h before use. The ABTS stock solution was serially diluted with sodium phosphate buffer (50 mM, pH 7.4) to 100 μ M. Trolox and all target compounds at different concentrations (total volume of 50 μ L) were added to 150 μ L of 100 μ M ABTS solution, respectively. After the addition of either trolox or another antioxidant to the ABTS solution, complete mixing of reactants was achieved by bubbling three to four times using plastic pipettes. The optical absorbance of ABTS at 734 nm was measured at 6 min after addition and equilibrated at 23 °C. Each individual treatment was repeated for three times and the results of the experiments were compared.

DPPH radical scavenging method⁹: DPPH is one of the few stable and commercially available organic nitrogen radicals and has a UV-vis absorption maximum at 517 nm. Upon reduction, the solution color fades; the reaction progress is conveniently monitored by a spectrophotometer. To test free radicals scavenging effects, all target and reference compounds were adjusted with 80% ethanol solution to final concentrations of 0–200 mM. 80% ethanol DPPH (150 mM) was used in the

reaction mixture. Serial dilutions of the test sample (20 μL) were combined with the DPPH (180 μL , 150 mM) solution in a 96-well microtitre plate. 80% ethanol was used as a negative control and ferulic acid was used as positive control. The reaction mixtures were incubated for 30 min at 37 °C in the dark and the change in absorbance at 517 nm was measured. Mean values were obtained from triplicate experiments. Inhibition percent was calculated using the equation: DPPH radical-scavenging rate^{1/4} $[1 - (A - C)/B] \times 100\%$, where A is the absorbance of the sample (DPPH + compounds), B is the absorbance of the DPPH radical–80% ethanol solution, and C is the absorbance of the sample (compounds) alone. Percent inhibition was plotted against concentration, and the equation for the line was used to obtain the IC_{50} value. The IC_{50} values of samples were compared against the standard, ferulic acid, and the lower the IC_{50} of synthesized compounds, the better it is as an antioxidant.

Kinetic Analysis of ChEs Inhibition

Kinetic characterization of ChEs was performed using Ellman's method with three different concentrations (0.2, 0.4 and 0.8 μM for AChE and 0.5, 1.0 and 2.0 μM for BuChE) of Compound **5c**.¹⁰ Lineweaver-Burk reciprocal plots were constructed by plotting $1/\text{velocity}$ against $1/[\text{substrate}]$ at varying concentrations of the substrate ATCI or BTCl, respectively (0.05-0.5 mM). The plots were assessed by a weighted least-squares analysis that assumed the variance of velocity (v) to be a constant percentage of v for the entire data set. Data analysis was performed with Graph Pad Prism 4.03 software (San Diego, CA, USA).

Molecular docking study with AChE

Molecular docking studies were performed using Molecular Operating Environment (MOE) software version 2008.10 (Chemical Computing Group, Montreal, Canada).^{11, 12} The X-ray crystal structure of recombinant human acetylcholinesterase in complex with donepezil (hAChE, PDB code 1EVE) was obtained from the Protein Data Base (PDB). Hydrogens and partial charges were added using protonate 3D application in MOE. The compound **5c** was constructed using the MOE builder module and energy minimized using Merck Molecular forcefield (MMFF94x, RMSD gradient: 0.05 kcal mol⁻¹ Å⁻¹). The MOE Dock application was used for docking **5c** into the active site of the protein. The poses were generated by the Triangle Matcher placement method and then were rescored using ASE scoring function. The Force field was selected as the refinement method. The retained best poses were visually inspected and the interactions with binding pocket residues were analyzed.

Cell culture and measurement of cell viability

PC12 cells were obtained from the Shanghai Institute of Cell Biology, Chinese Academy of Sciences and grown in RPMI-1640 medium containing 10% (v/v) foetal bovine serum, 100 U penicillin/mL and 100 mg streptomycin/mL under 5% CO₂ at 37 °C. The culture media were changed every other day. The cells were plated in 96-well microplates at a density of 1×10⁵ cells mL⁻¹ (100 μL per well). After attachment, the cells were pretreated with different concentrations of test compounds (1.0–20 μM) for 4 h. Then, 10 μL of H₂O₂ (diluted with medium to a final concentration of 100 μM) solution was added. The cell viability was measured by MTT assay after 20 h.¹³

Briefly, 10 μL of 5 mg/ml MTT was added to each well and incubated for 4 h at 37 °C. Then, 200 μL of dimethylsulfoxide (DMSO) was added to dissolve the dark blue formazan crystals formed in intact cells, and the absorbance at 570 nm was detected by a microplate reader. PC 12 cells were cultured without test compound and H_2O_2 as control group and the results were expressed by percentage of control.

Metal Chelation

The study of metal chelation was performed in methanol at 298 K using UV-vis spectrophotometer (SHIMADZU UV-2450PC) with wavelength ranging from 200 to 400 nm.^{14, 15} The absorption spectra of compound **5c** (75 μM , final concentration) alone or in the presence of CuSO_4 , FeSO_4 , FeCl_3 , or ZnCl_2 (150 μM , final concentration) for 30min in methanol were recorded 1 cm-quartz cells.

***In vitro* blood–brain barrier permeation assay**

The ability of test compounds that penetrate into brain was evaluated using a parallel artificial membrane permeation assay (PAMPA) for blood–brain barrier according to the method established by Di *et al.*¹⁶ Commercial drugs were purchased from Sigma and Aladdin. Porcine brain lipid (PBL) was acquired from Avanti Polar Lipids. The donor microplate (96-wellfilter plate, PVDF membrane, pore size is 0.45mm) and the acceptor microplate (indented 96-well plate) were both from Millipore. The 96-well UV plate (COSTAR) was obtained from Corning Inc. The 96-well UV plate (COSTAR®) was 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 10mL of PBL in dodecane (20 mg/mL). The compound was firstly

dissolved in DMSO at a concentration of 5 mg/mL followed diluting 50-fold with a mixture of PBS/EtOH (70 : 30) to give a final concentration of 100 $\mu\text{g/mL}$. After that, 200 μL of diluted solution and 300 μL of PBS/EtOH (70 : 30) were added to the donor wells. The donor filter plate was carefully placed on the acceptor plate to make the underside of filter membrane can contact with buffer solution. After leaving this sandwich assembly undisturbedly for 16 h at 25 °C, the donor plate was carefully removed, and the concentrations of test compound in the acceptor, donor and reference wells were measured with a UV plate reader (SpectraMax Plus 384, Molecular Devices, Sunnyvale, CA, USA). Each sample was analyzed at least three independent runs in four wells, and the results are given as the means \pm SD. A plot of the experimental P_e values of 9 standard drugs versus their bibliographic values provided a good linear correlation, $P_e(\text{exp}) = 1.0416 P_e(\text{Bibl.}) - 0.8567$ ($R^2 = 0.9443$)

References

- 1 U. Reichman, K. A. Watanabe and J. J. Fox, *Carbohydr. Res.*, 1975, **42**, 233-240.
- 2 G. Giichi, N. Akinobu, *Eur. Pat.* 330026, 1989.
- 3 T. Tetsuji, H. Ichiro, Y. Shuji, T. Michio, *Jpn. Kokai Tokkyo Koho* 62012757, 1987.
- 4 W. L. Caulfield, I. T. Collie, R. S. Dickins, O. Epemolu, R. McGuire, D. R. Hill, G. McVey, J. R. Morphy, Z. Rankovic and H. Sundaram, *J. Med. Chem.*, 2001, **44**, 2679-2682.
- 5 A. Stergiou, A. Bariotaki, D. Kalaitzakis and I. Smonou, *J. Org. Chem.*, 2013, **78**, 7268-7273.
- 6 J. E. Chojnacki, K. Liu, X. Yan, S. Toldo, T. Selden, M. Estrada, M. Isabel Rodriguez-Franco, M. S. Halquist, D. Ye and S. Zhang, *ACS Chem. Neurosci.*, 2014, **5**, 690-699.
- 7 G. L. Ellman, K. D. Courtney, V. Andres, Jr. and R. M. Feather-Stone, *Biochem. Pharmacol.*, 1961, **7**, 88-95.
- 8 N. J. Miller and C. A. RiceEvans, *Free Radical Res.*, 1997, **26**, 195-199.
- 9 R. A. Himes, G. Y. Park, G. S. Siluvai, N. J. Blackburn and K. D. Karlin, *Angew. Chem.*, 2008, **47**, 9224-9227.
- 10 S.-S. Xie, J.-S. Lan, X.-B. Wang, N. Jiang, G. Dong, Z.-R. Li, K. D. G. Wang, P.-P. Guo and L.-Y. Kong, *Eur. J. Med. Chem.*, 2015, **93**, 42-50.
- 11 M. Y. Wu, G. Esteban, S. Brogi, M. Shionoya, L. Wang, G. Campiani, M. Unzeta, T. Inokuchi, S. Butini and J. Marco-Contelles, *Eur. J. Med. Chem.*, 2015, DOI: 10.1016/j.ejmech.2015.10.001.

- 12 I. Bolea, J. Juarez-Jimenez, C. de Los Rios, M. Chioua, R. Pouplana, F. J. Luque, M. Unzeta, J. Marco-Contelles and A. Samadi, *J. Med. Chem.*, 2011, **54**, 8251-8270.
- 13 S.-L. Hwang and G.-C. Yen, *J. Agric. Food. Chem.*, 2008, **56**, 859-864.
- 14 J. A. Duce and A. I. Bush, *Progress in neurobiology*, 2010, **92**, 1-18.
- 15 C. Lu, Y. Guo, J. Yan, Z. Luo, H.-B. Luo, M. Yan, L. Huang and X. Li, *J. Med. Chem.*, 2013, **56**, 5843-5859.
- 16 L. Di, E. H. Kerns, K. Fan, O. J. McConnell and G. T. Carter, *Eur. J. Med. Chem.*, 2003, **38**, 223-232.

Legends

Figure S1-1. ^1H NMR spectrum of compound **4g** (DMSO, 500 MHz).

Figure S1-2. ^{13}C NMR spectrum of compound **4g** (DMSO, 125 MHz).

Figure S1-3. HRMS (ESI) spectrum of compound **4g**.

Figure S2-1. ^1H NMR spectrum of compound **4i** (DMSO, 500 MHz).

Figure S2-2. ^{13}C NMR spectrum of compound **4i** (DMSO, 125 MHz).

Figure S2-3. HRMS (ESI) spectrum of compound **4i**.

Figure S3-1. ^1H NMR spectrum of compound **5c** (DMSO, 500 MHz).

Figure S3-2. ^{13}C NMR spectrum of compound **5c** (DMSO, 125 MHz).

Figure S3-3. HRMS (ESI) spectrum of compound **5c**.

Figure S4-1. ^1H NMR spectrum of compound **5g** (DMSO, 500 MHz).

Figure S4-2. ^{13}C NMR spectrum of compound **5g** (DMSO, 125 MHz).

Figure S4-3. HRMS (ESI) spectrum of compound **5g**.

Figure S5-1. ^1H NMR spectrum of compound **5h** (DMSO, 500 MHz).

Figure S5-2. ^{13}C NMR spectrum of compound **5h** (DMSO, 125 MHz).

Figure S5-3. HRMS (ESI) spectrum of compound **5h**.

Figure S6-1. ^1H NMR spectrum of compound **5m** (DMSO, 500 MHz).

Figure S6-2. ^{13}C NMR spectrum of compound **5m** (DMSO, 125 MHz).

Figure S6-3. HRMS (ESI) spectrum of compound **5m**.

Figure S7-1. ^1H NMR spectrum of compound **6** (DMSO, 500 MHz).

Figure S7-2. ^{13}C NMR spectrum of compound **6** (DMSO, 125 MHz).

Figure S7-3. HRMS (ESI) spectrum of compound **6**.

Figure S8-1. ^1H NMR spectrum of compound **11b** (DMSO, 500 MHz).

Figure S8-2. ^{13}C NMR spectrum of compound **11b** (DMSO, 125 MHz).

Figure S8-3. HRMS (ESI) spectrum of compound **11b**.

Figure S9. HPLC spectrum of compound **4a**.

Figure S10. HPLC spectrum of compound **4b**.

Figure S11. HPLC spectrum of compound **4c**.

Figure S12. HPLC spectrum of compound **4d**.

Figure S13. HPLC spectrum of compound **4e**.
Figure S14. HPLC spectrum of compound **4f**.
Figure S15. HPLC spectrum of compound **4g**.
Figure S16. HPLC spectrum of compound **4h**.
Figure S17. HPLC spectrum of compound **4i**.
Figure S18. HPLC spectrum of compound **5a**.
Figure S19. HPLC spectrum of compound **5b**.
Figure S20. HPLC spectrum of compound **5c**.
Figure S21. HPLC spectrum of compound **5d**.
Figure S22. HPLC spectrum of compound **5e**.
Figure S23. HPLC spectrum of compound **5f**.
Figure S24. HPLC spectrum of compound **5g**.
Figure S25. HPLC spectrum of compound **5h**.
Figure S26. HPLC spectrum of compound **5i**.
Figure S27. HPLC spectrum of compound **5j**.
Figure S28. HPLC spectrum of compound **5k**.
Figure S29. HPLC spectrum of compound **5l**.
Figure S30. HPLC spectrum of compound **5m**.
Figure S31. HPLC spectrum of compound **5n**.
Figure S32. HPLC spectrum of compound **6**.
Figure S33. HPLC spectrum of compound **7**.
Figure S34. HPLC spectrum of compound **11a**.
Figure S35. HPLC spectrum of compound **11b**.
Figure S36. HPLC spectrum of compound **11c**.

Spectra of some selected compounds

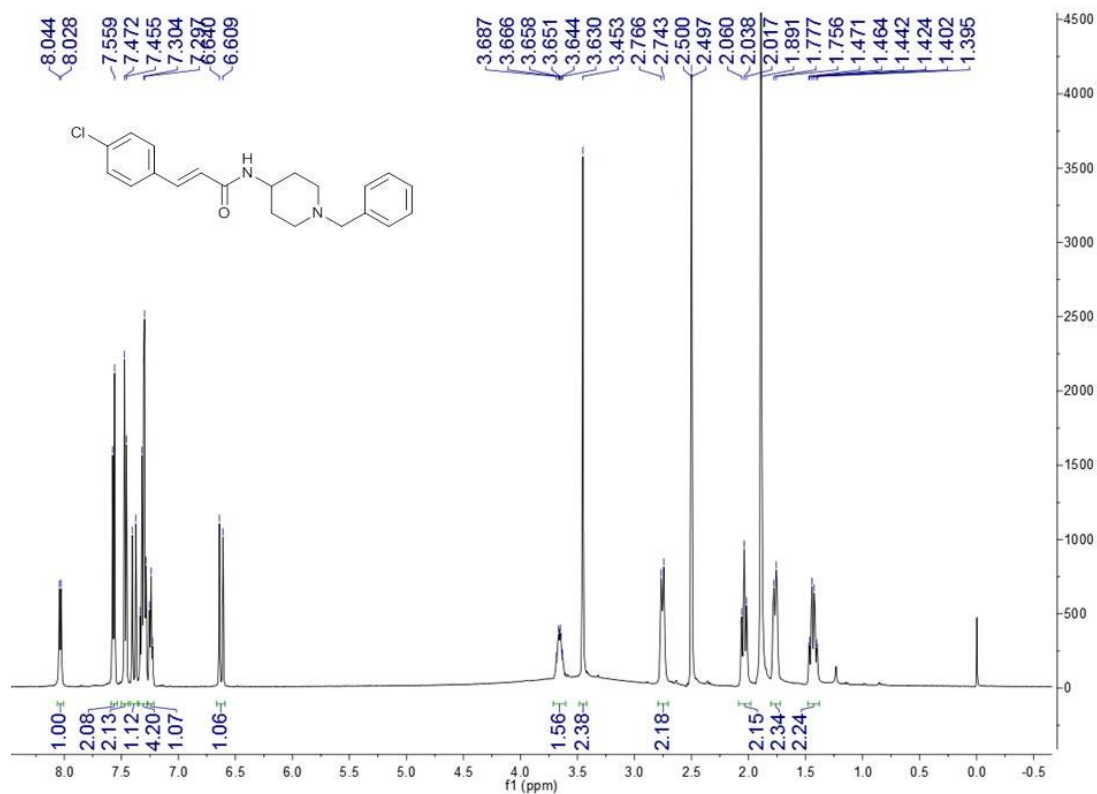


Figure S1-1. ¹H NMR spectrum of compound 4g.

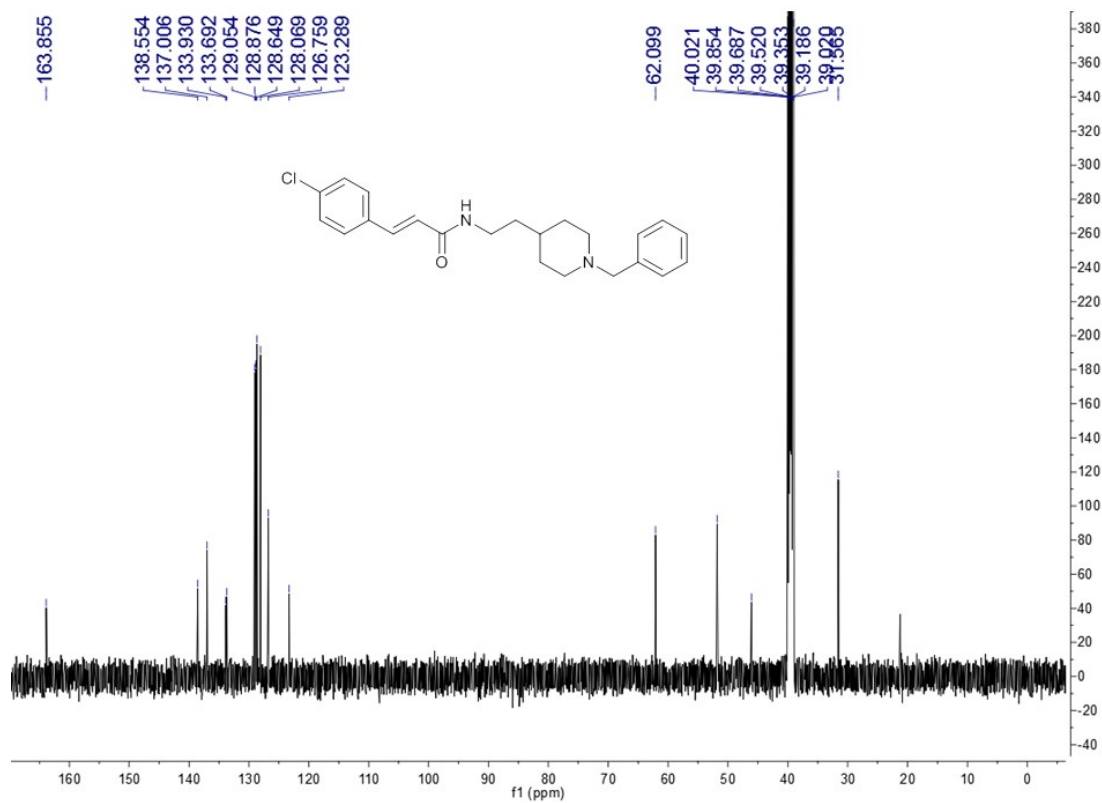
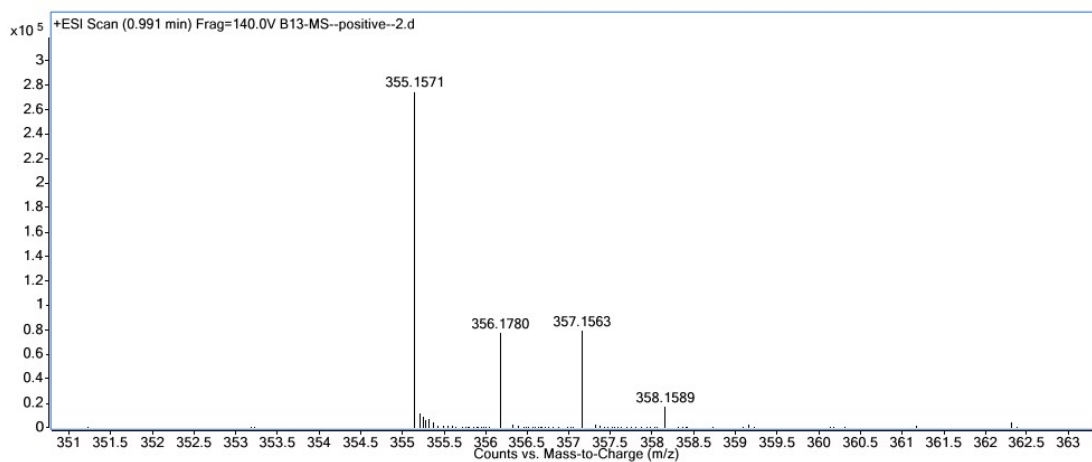
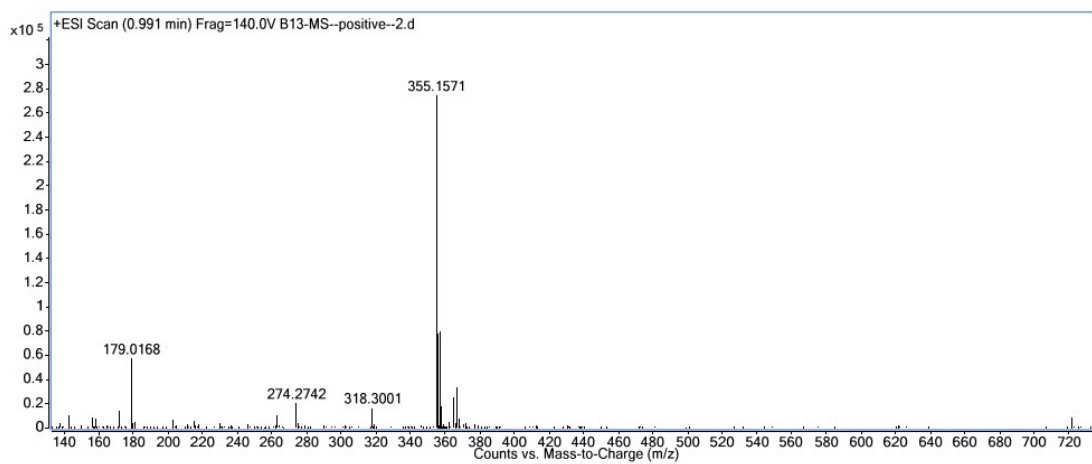


Figure S1-2. ¹³C NMR spectrum of compound 4g.



Elemental Composition Calculator

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Elements:	C (0-80); H (0-120); O (0-30); N(0-10); Cl (0-5)				
Ion Formula	Calculated m/z		PPM Error		
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Figure S1-3. HRMS (ESI) spectrum of compound **4g**.

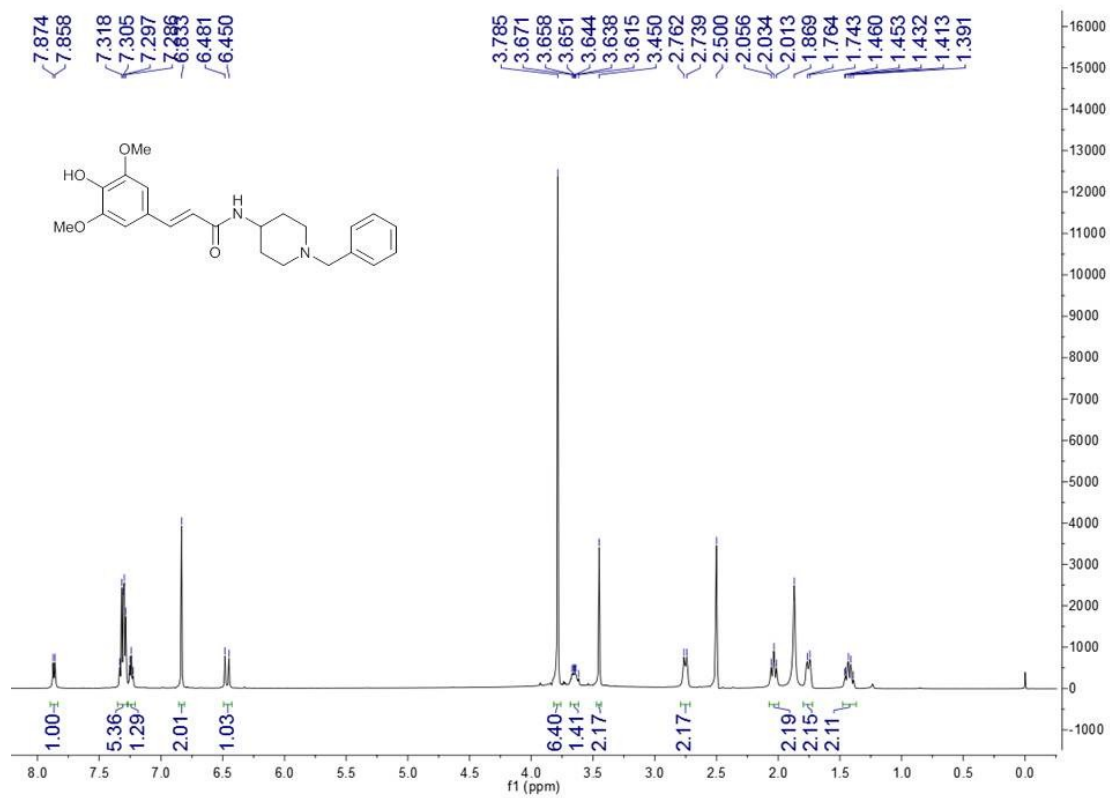


Figure S2-1. ¹H NMR spectrum of compound 4i.

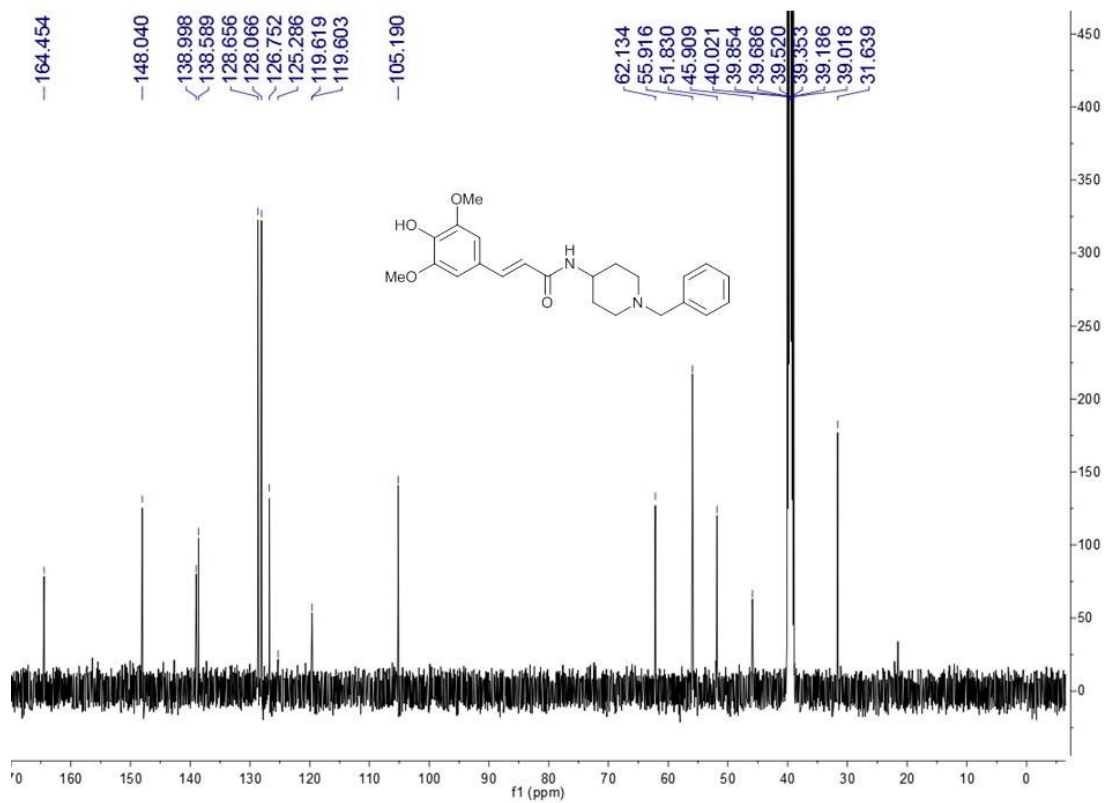
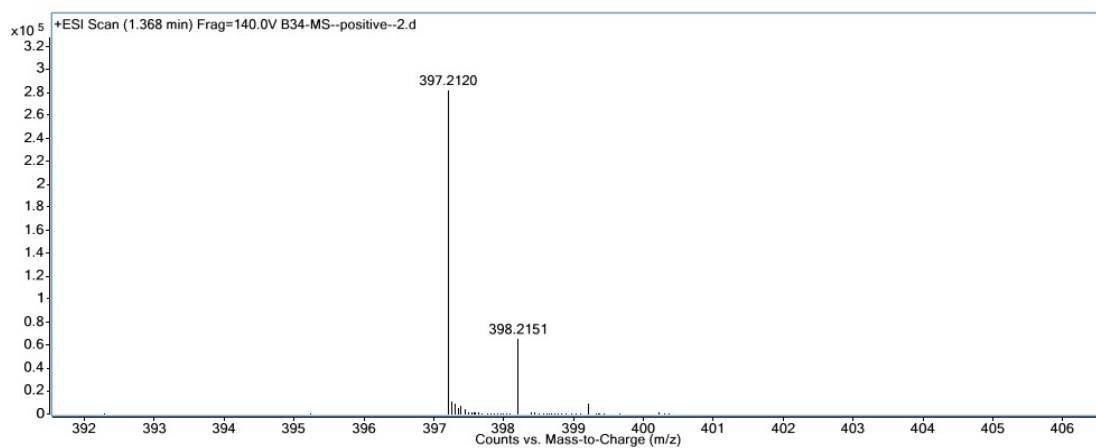
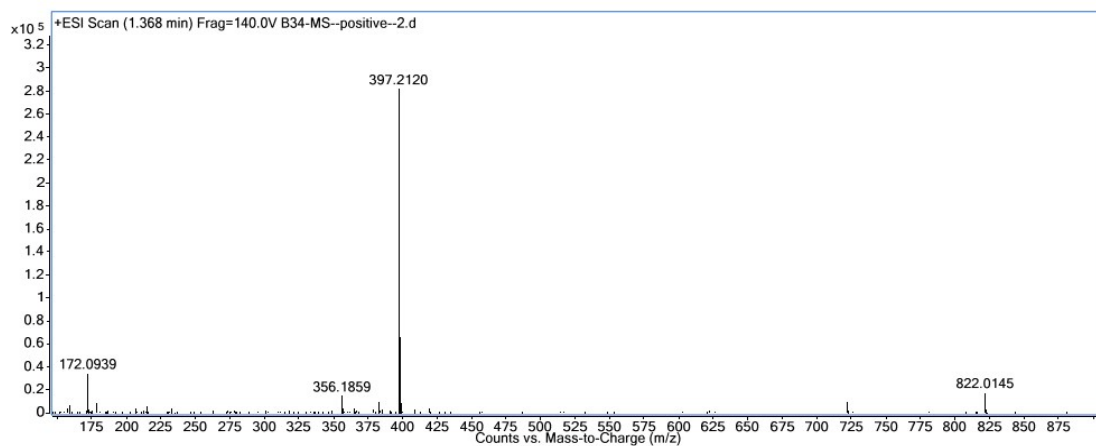


Figure S2-2. ¹³C NMR spectrum of compound 4i.



Elemental Composition Calculator

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Figure S2-3. HRMS (ESI) spectrum of compound **4i**.

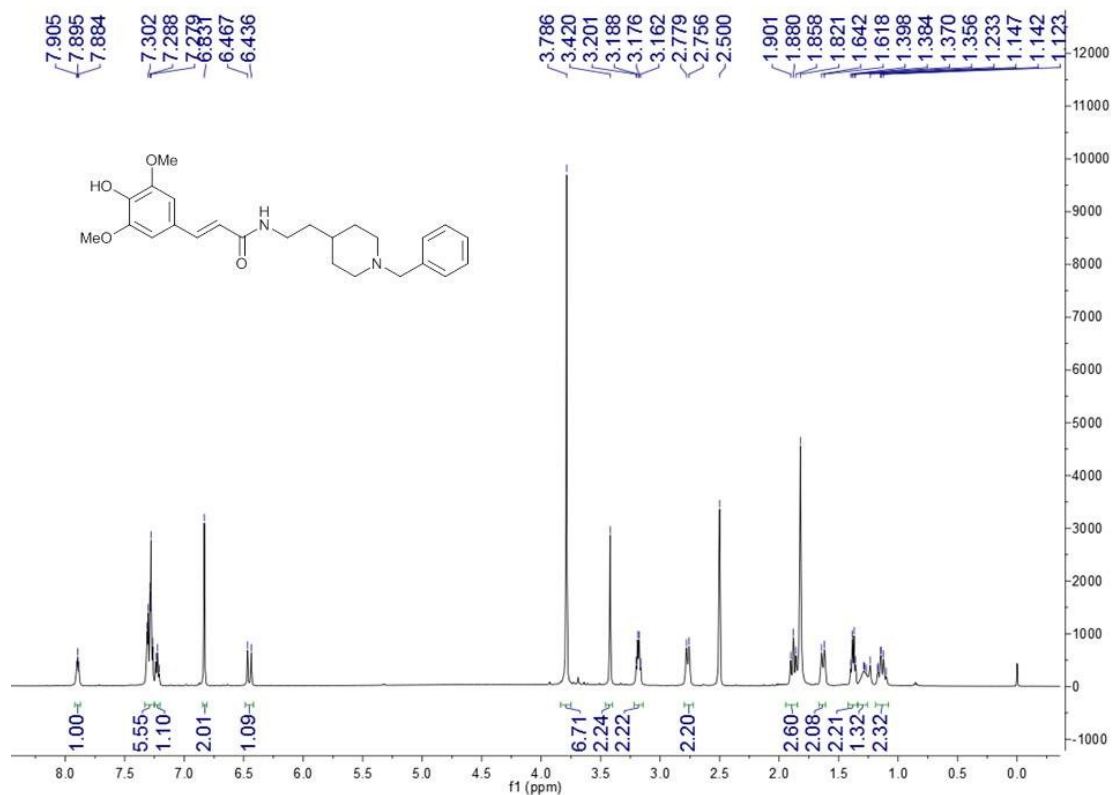


Figure S3-1. ¹H NMR spectrum of compound 5c.

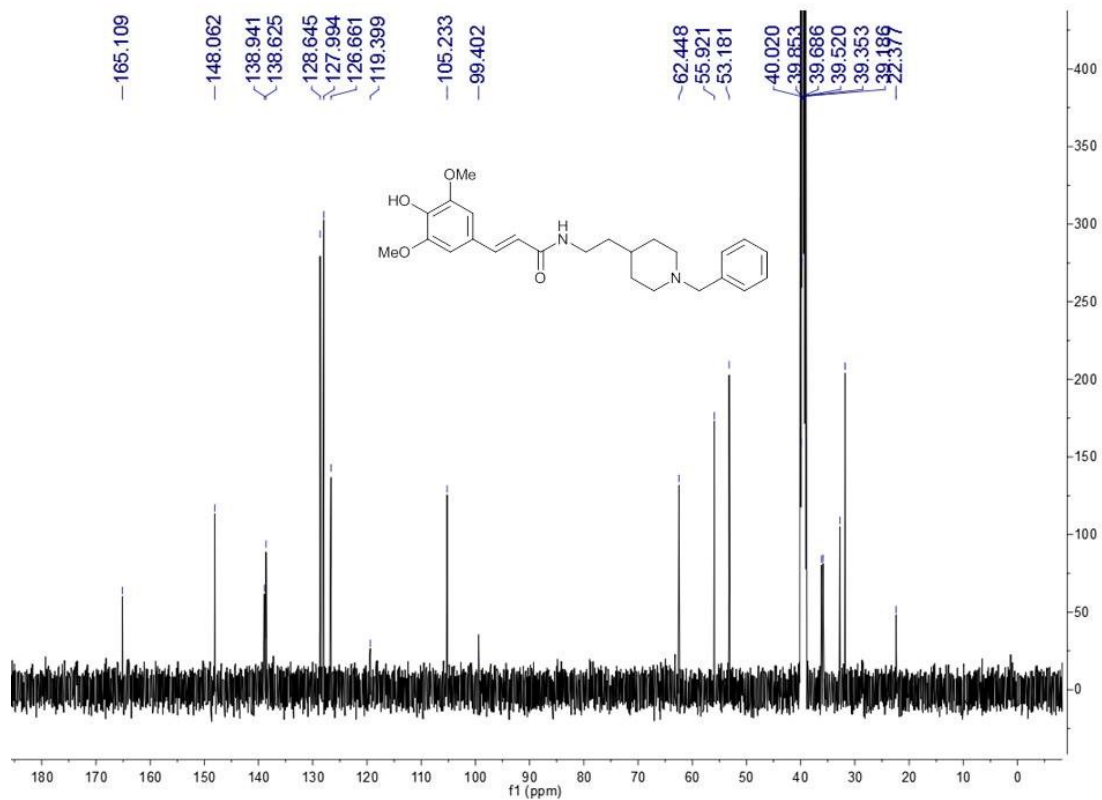
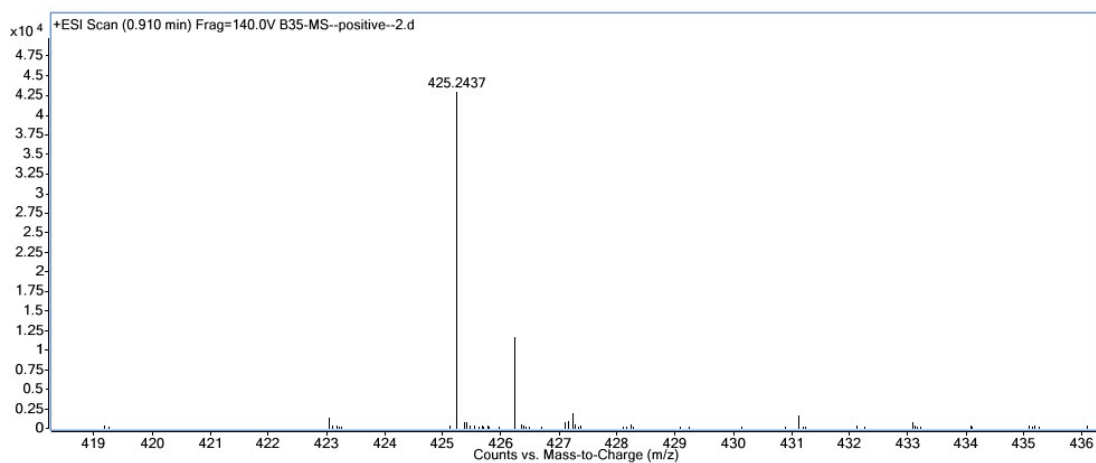
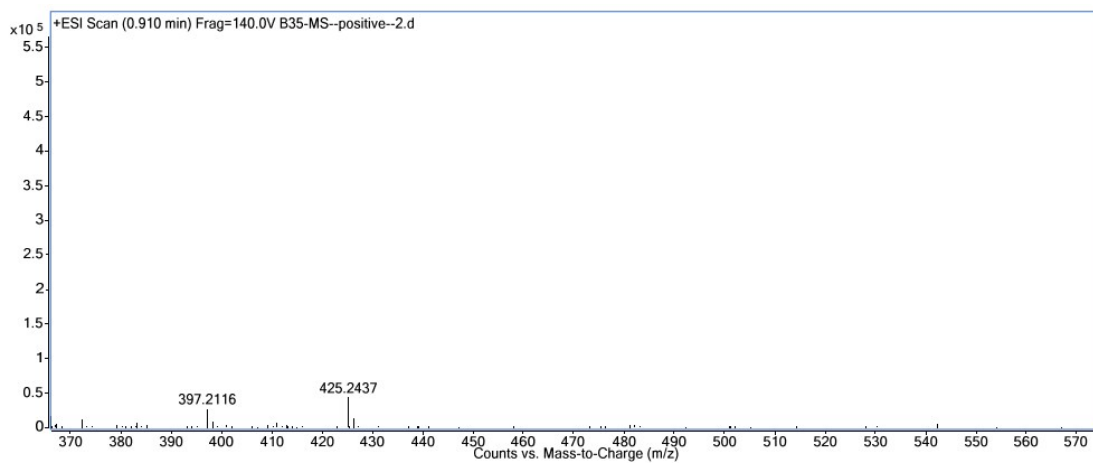


Figure S3-2. ¹³C NMR spectrum of compound 5c.



Elemental Composition Calculator

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Figure S3-3. HRMS (ESI) spectrum of compound 5c.

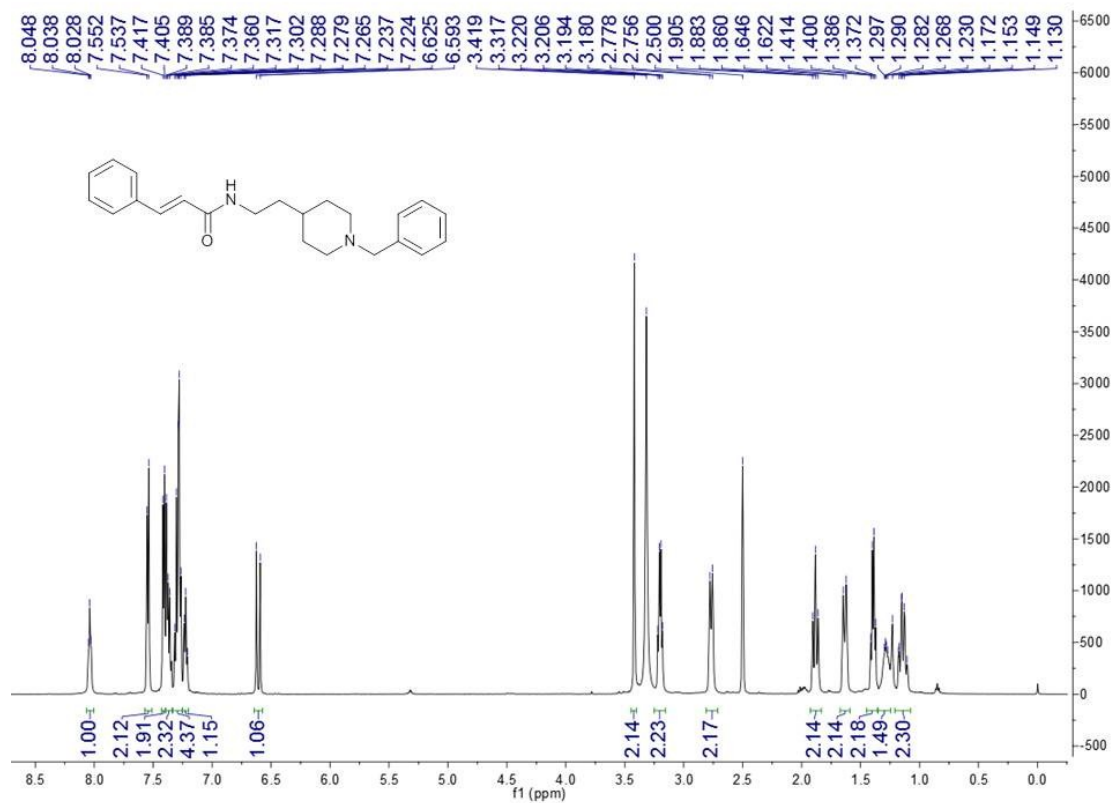


Figure S4-1. ^1H NMR spectrum of compound 5g.

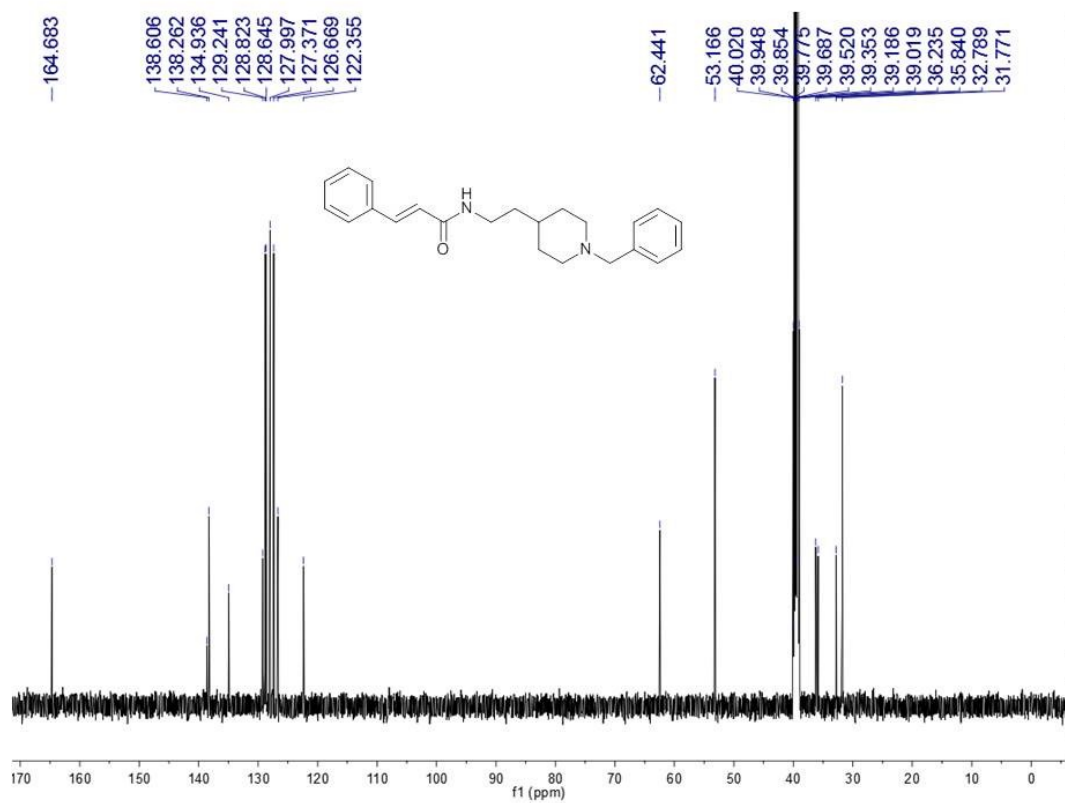
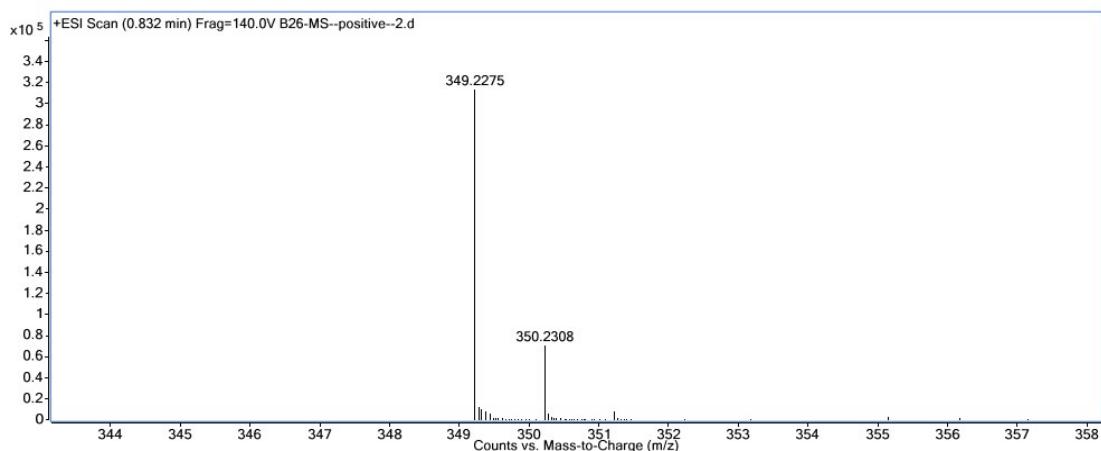
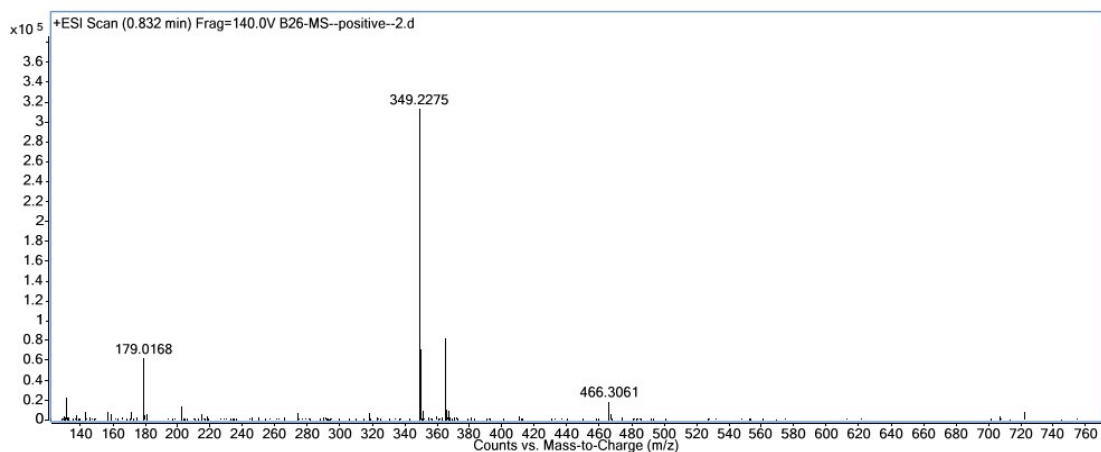


Figure S4-2. ^{13}C NMR spectrum of compound 5g.



Elemental Composition Calculator

Target m/z:	349.2275	Result type:	Positive ions	Species:	[M+H] ⁺
Elements:	C (0-80); H (0-120); O (0-30); N(0-10);Na (0-5)				
Ion Formula	Calculated m/z		PPM Error		
C ₂₃ H ₂₉ N ₂ O	349.2274		-0.05		

Figure S4-3. HRMS (ESI) spectrum of compound **5g**.

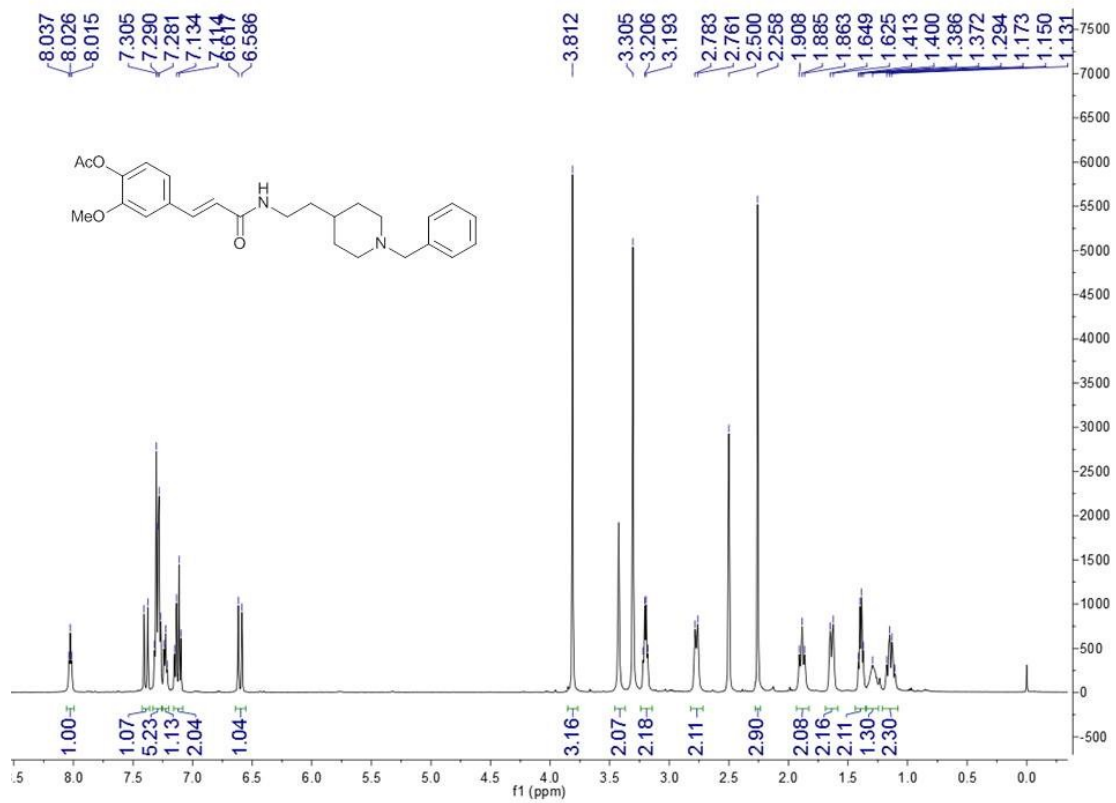


Figure S5-1. ¹H NMR spectrum of compound 5h.

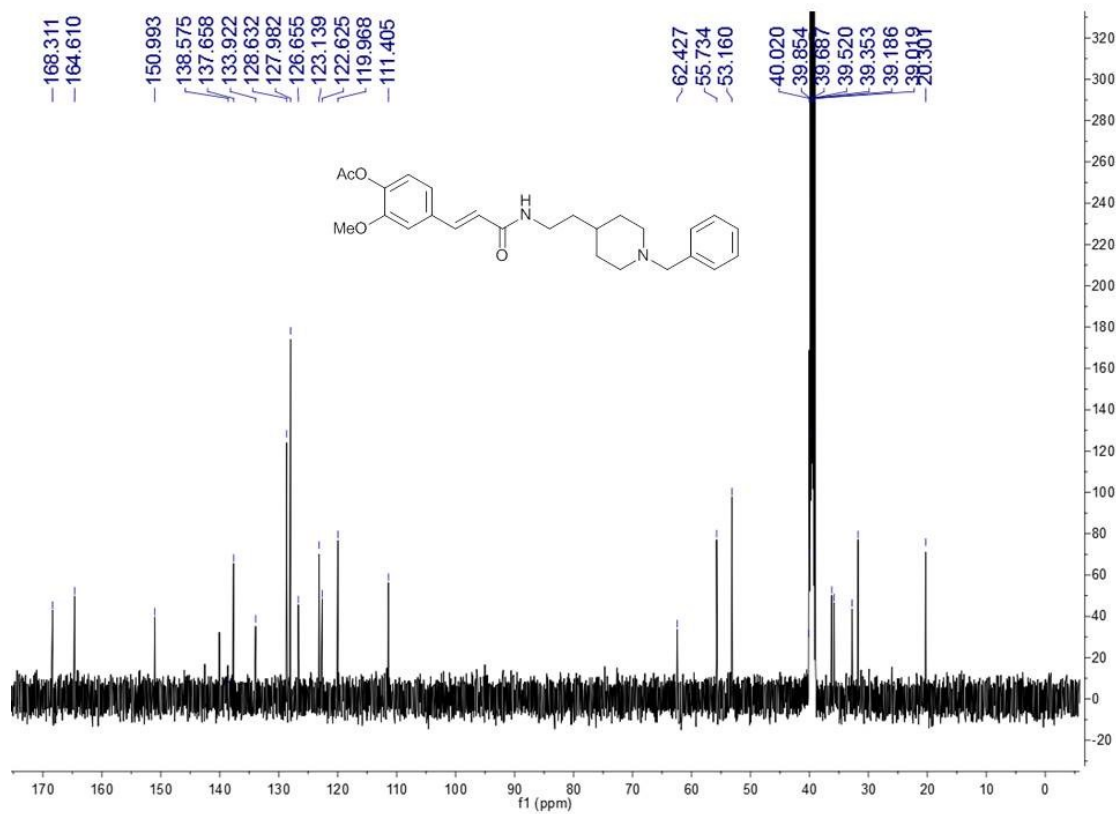
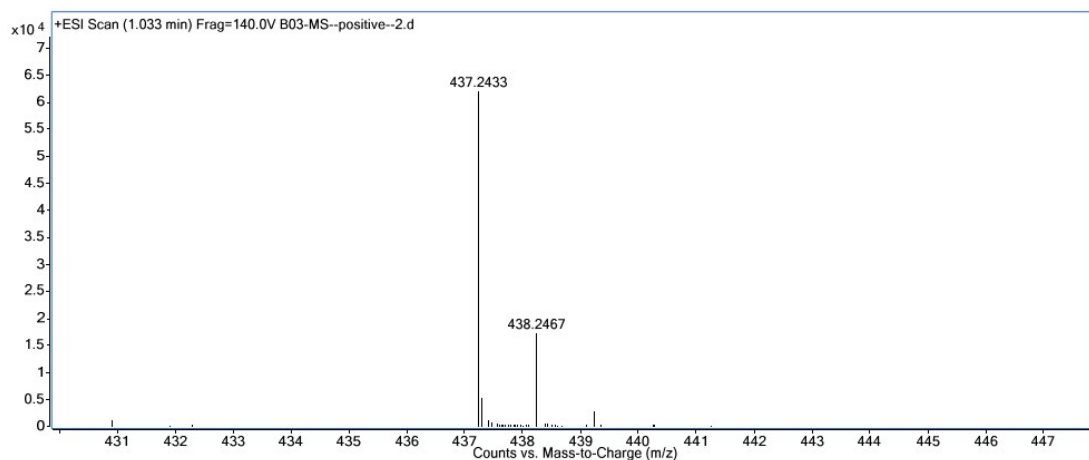
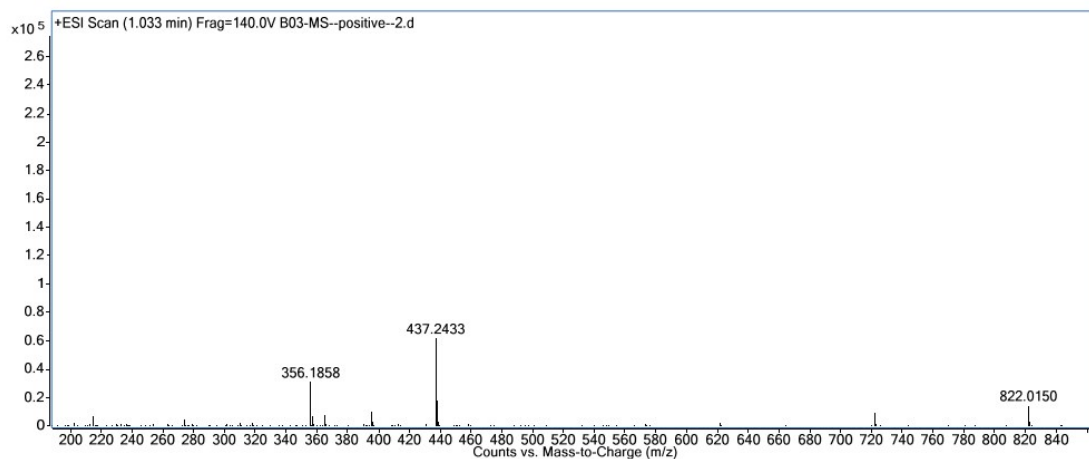


Figure S5-2. ¹³C NMR spectrum of compound 5h.



Elemental Composition Calculator

Target m/z:	437.2433	Result type:	Positive ions	Species:	[M+H] ⁺
Elements:	C (0-80); H (0-120); O (0-30); N(0-10); Na (0-5)				
Ion Formula	Calculated m/z		PPM Error		
C ₂₆ H ₃₃ N ₂ O ₄	437.2435		0.49		

Figure S5-3. HRMS (ESI) spectrum of compound **5h**.

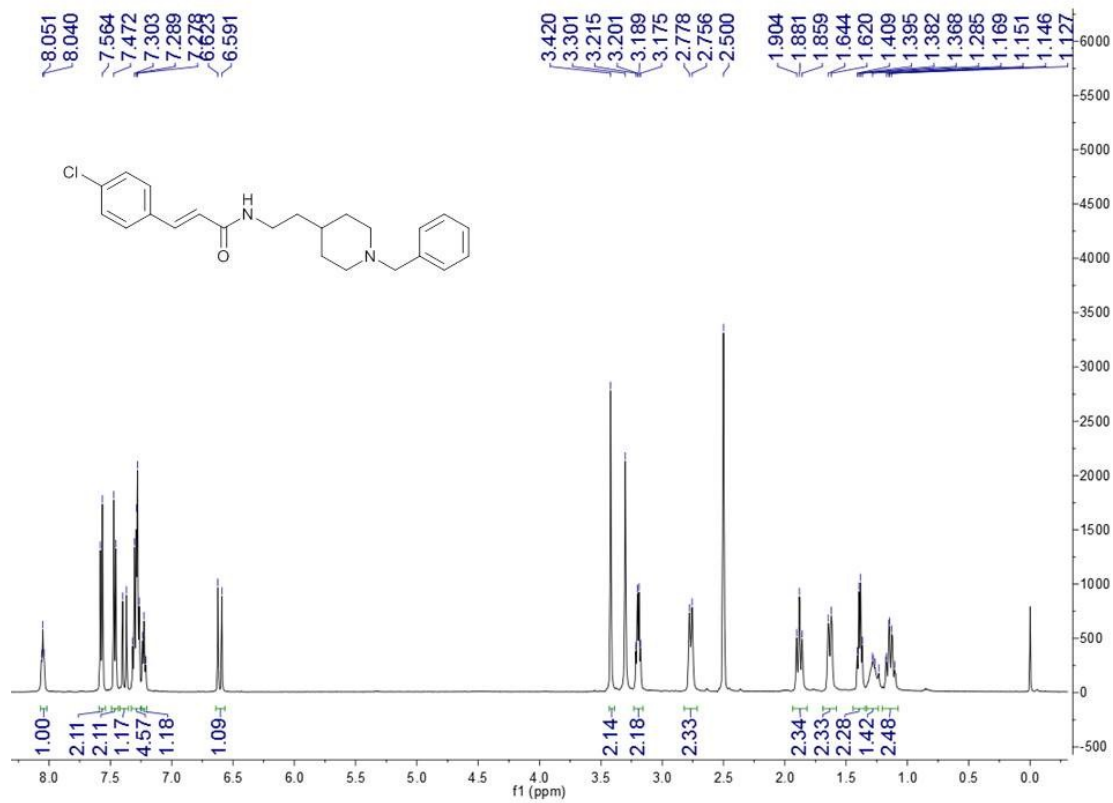


Figure S6-1. ¹H NMR spectrum of compound 5m.

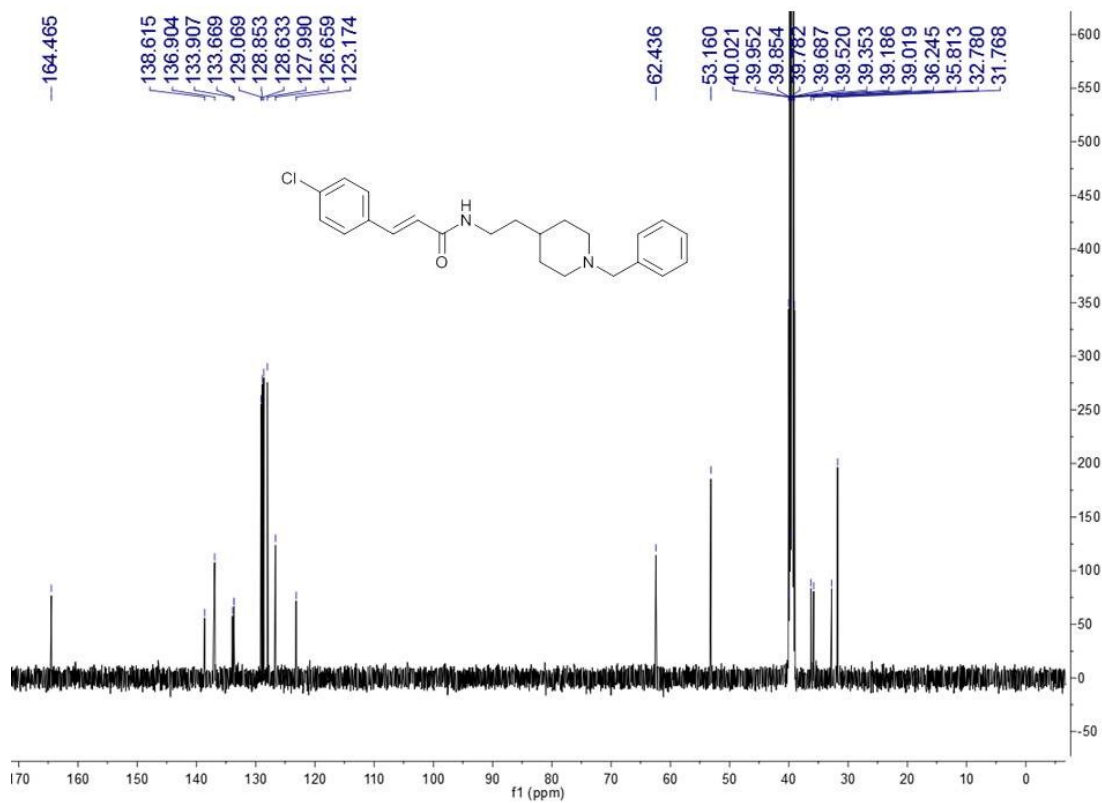
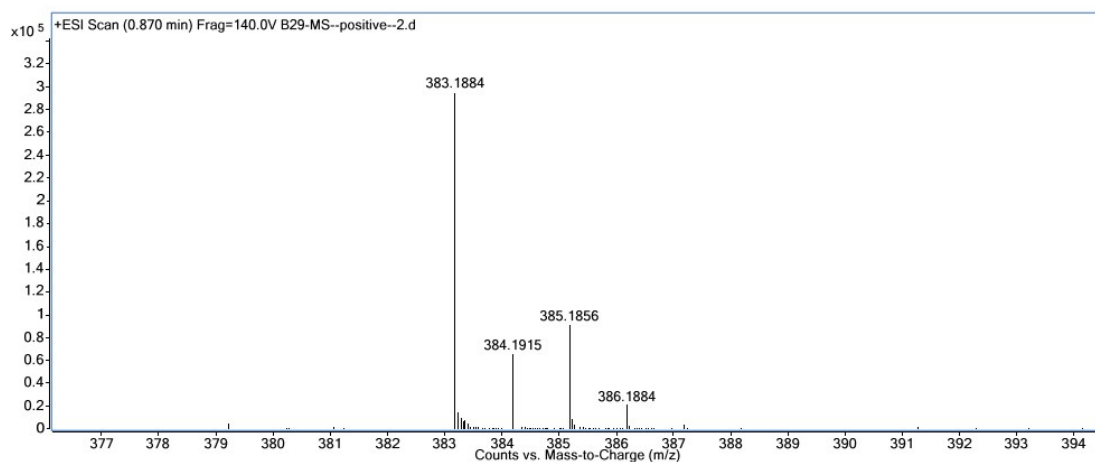
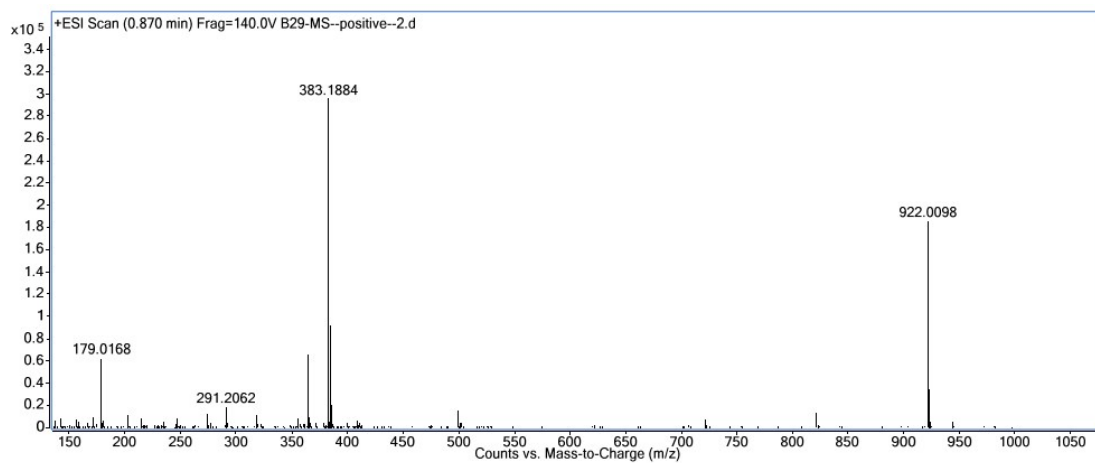


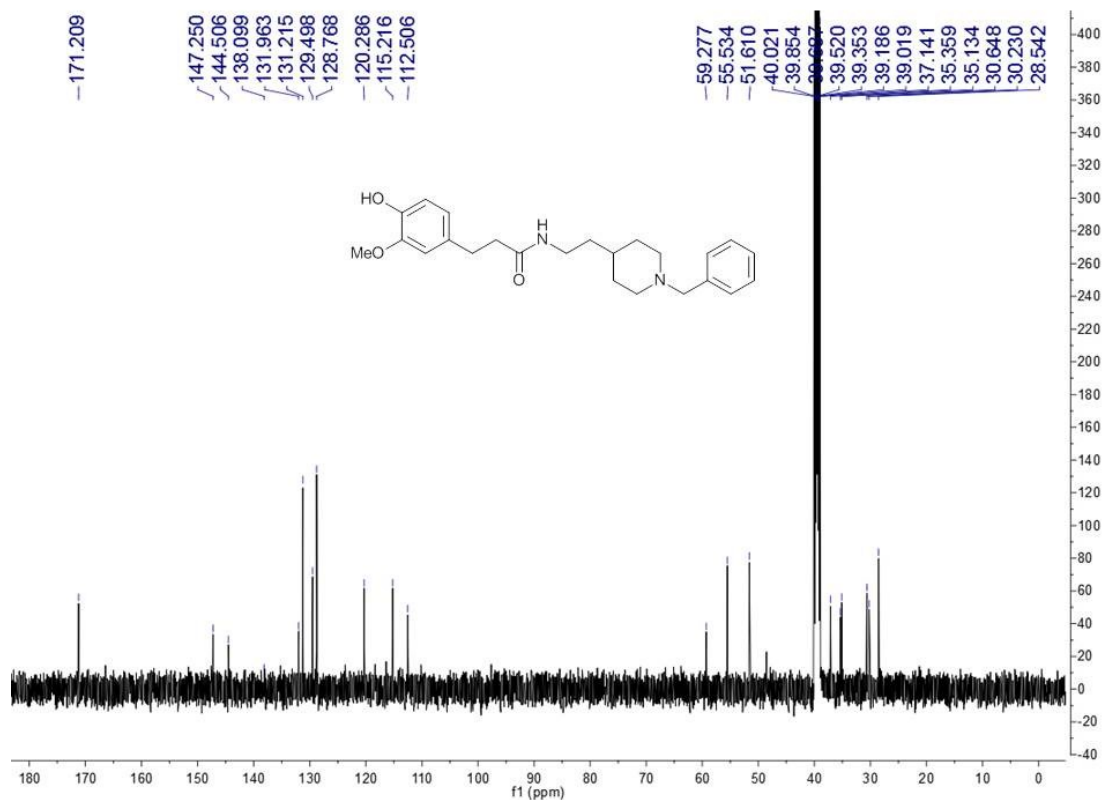
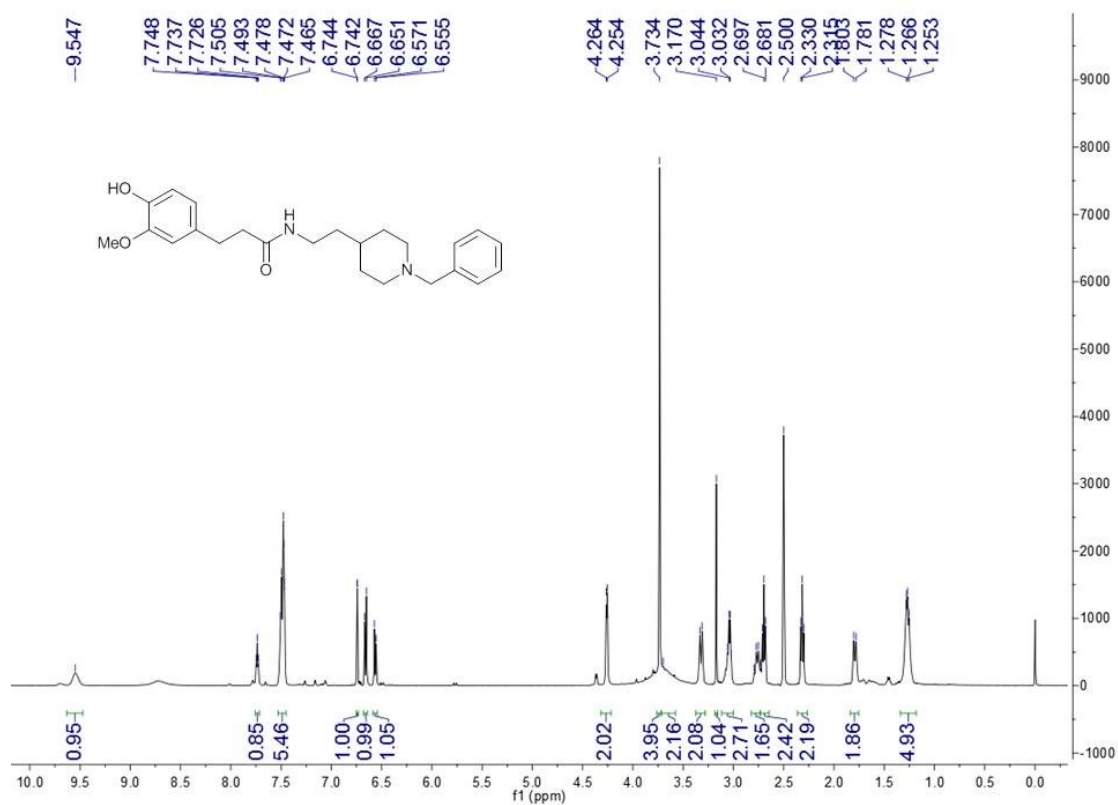
Figure S6-2. ¹³C NMR spectrum of compound 5m.

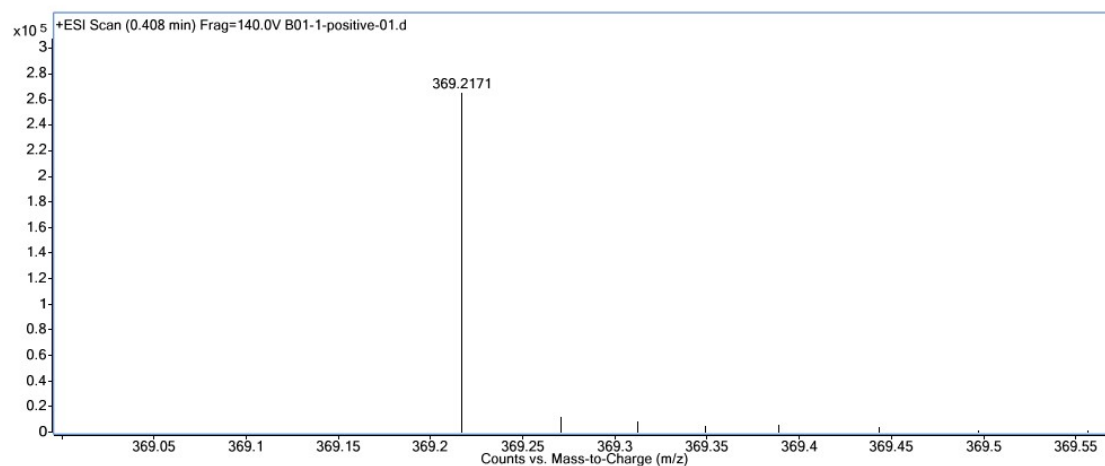
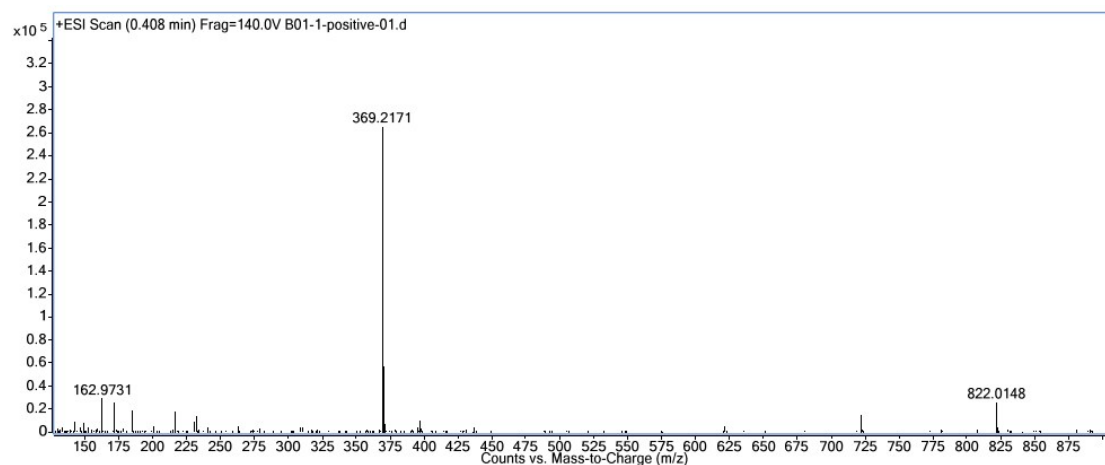


Elemental Composition Calculator

Target m/z:	383.1884	Result type:	Positive ions	Species:	[M+H] ⁺
Elements:	C (0-80); H (0-120); O (0-30); N(0-10);Cl (0-5)				
Ion Formula	Calculated m/z		PPM Error		
C ₂₃ H ₂₈ CIN ₂ O	383.1885		0.12		

Figure S6-3. HRMS (ESI) spectrum of compound **5m**.





Elemental Composition Calculator

Target m/z:	369.2171	Result type:	Positive ions	Species:	[M+H] ⁺
Elements:	C (0-80); H (0-120); O (0-30); N(0-10); Na(0-6);				
Ion Formula	Calculated m/z	PPM Error			
C ₂₂ H ₂₉ N ₂ O ₃	369.2173	0.53			

Figure S7-3. HRMS (ESI) spectrum of compound 6.

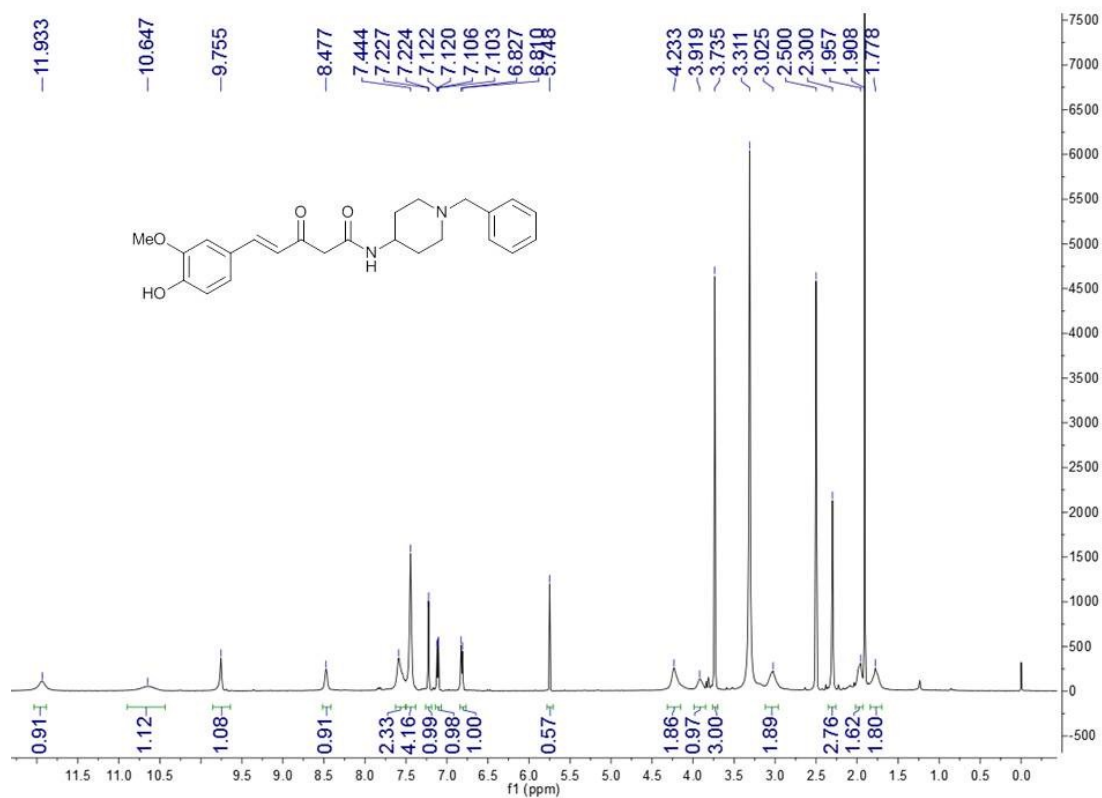


Figure S8-1. ^1H NMR spectrum of compound 11b.

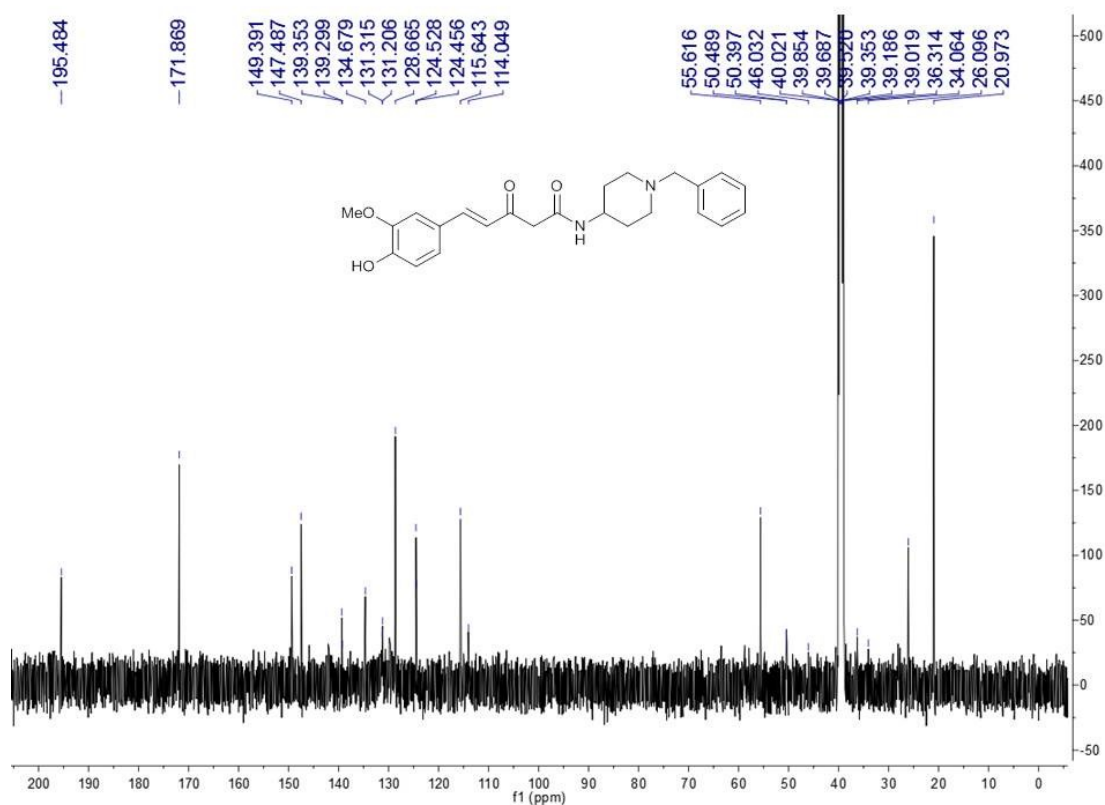
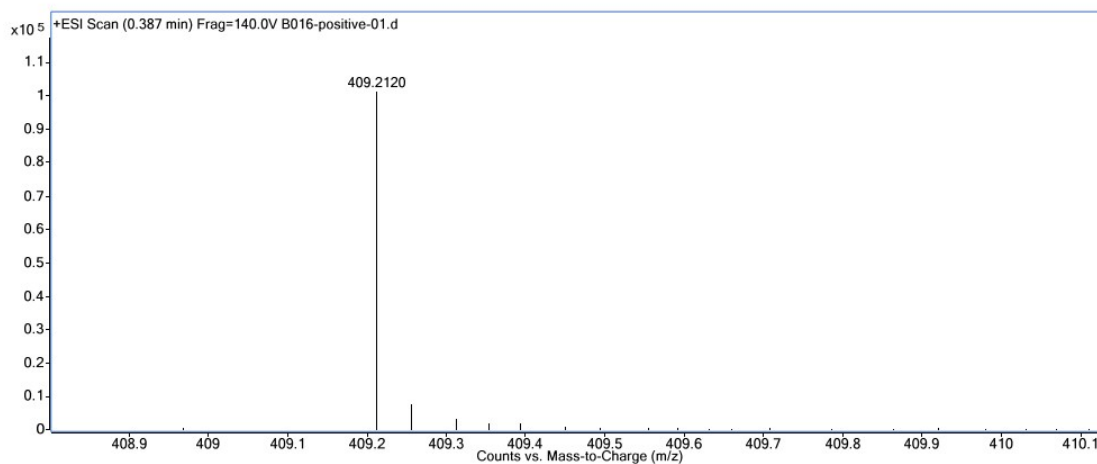
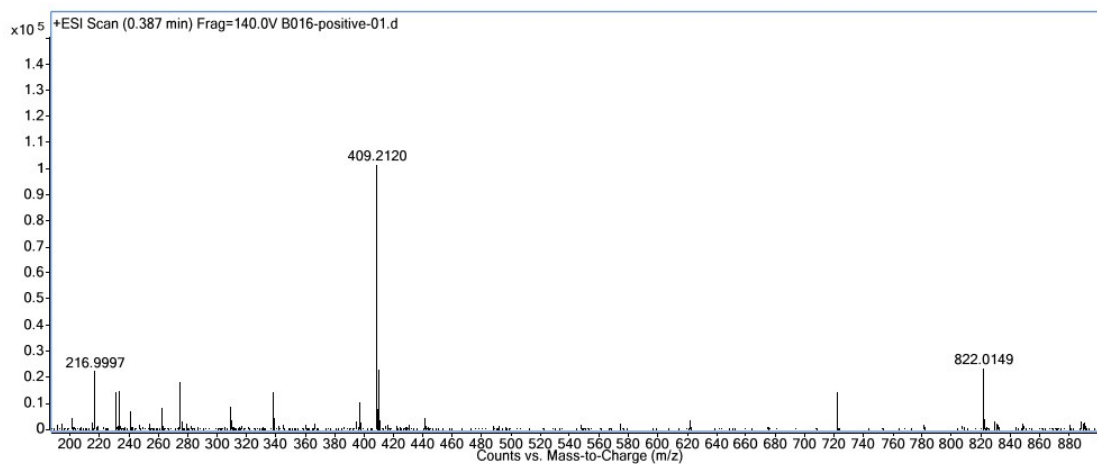


Figure S8-2. ^{13}C NMR spectrum of compound 11b.



Elemental Composition Calculator

Target m/z:	409.2120	Result type:	Positive ions	Species:	[M+H] ⁺
Elements:	C (0-80); H (0-120); O (0-30); N(0-10); Na(0-6);				
Ion Formula	Calculated m/z		PPM Error		
C ₂₄ H ₂₉ N ₂ O ₄	409.2122		0.46		

Figure S8-3. HRMS (ESI) spectrum of compound **11b**.

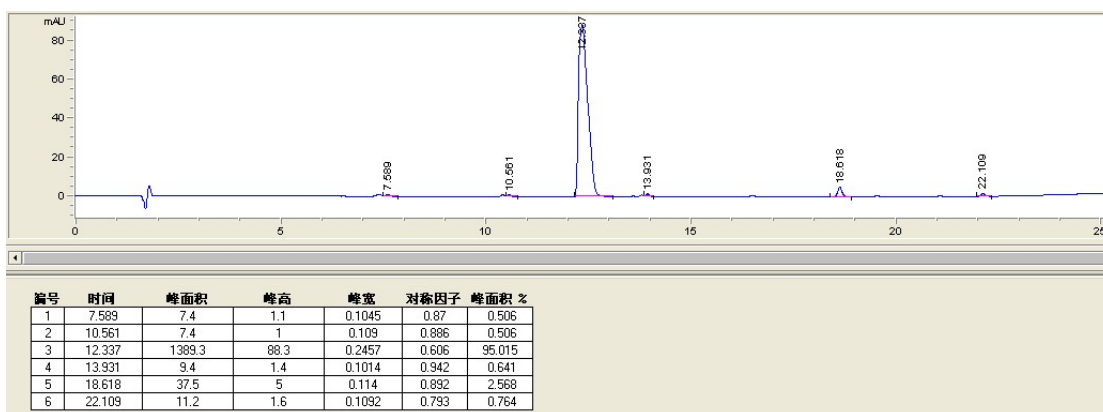


Figure S9. HPLC spectrum of compound 4a.

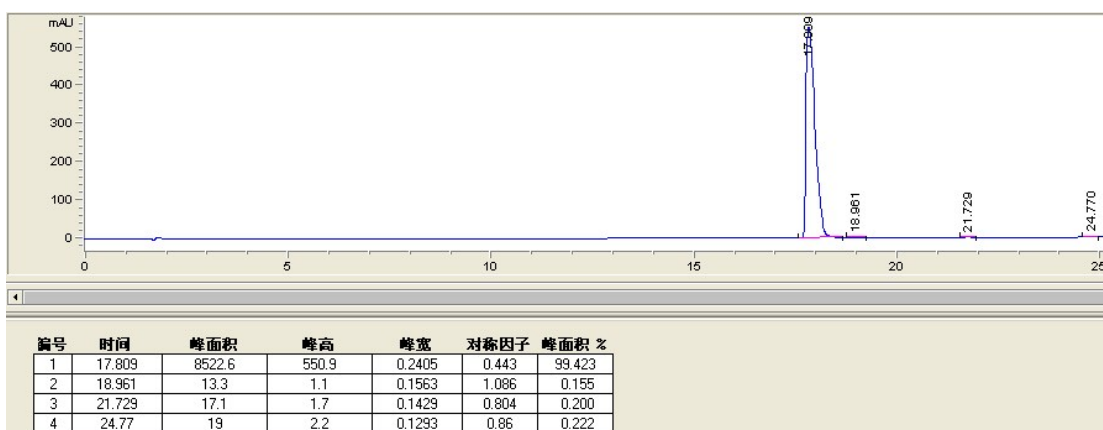


Figure S10. HPLC spectrum of compound 4b.

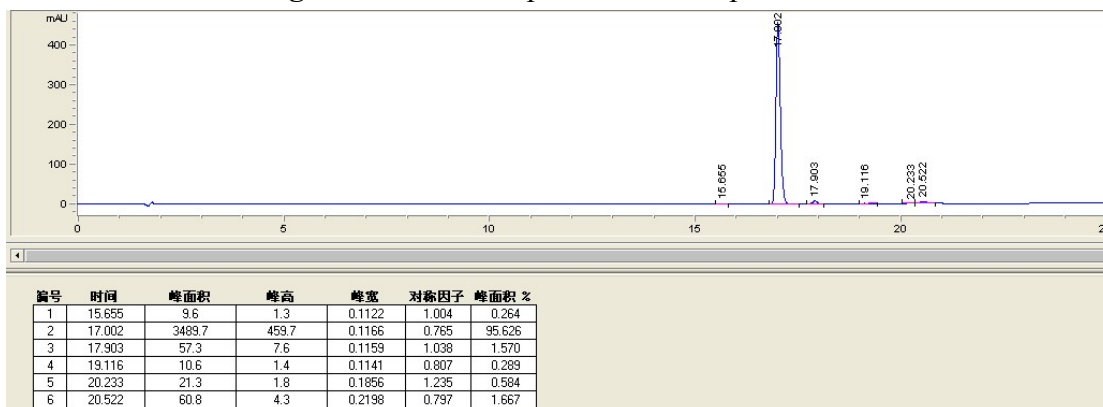


Figure S11. HPLC spectrum of compound 4c.

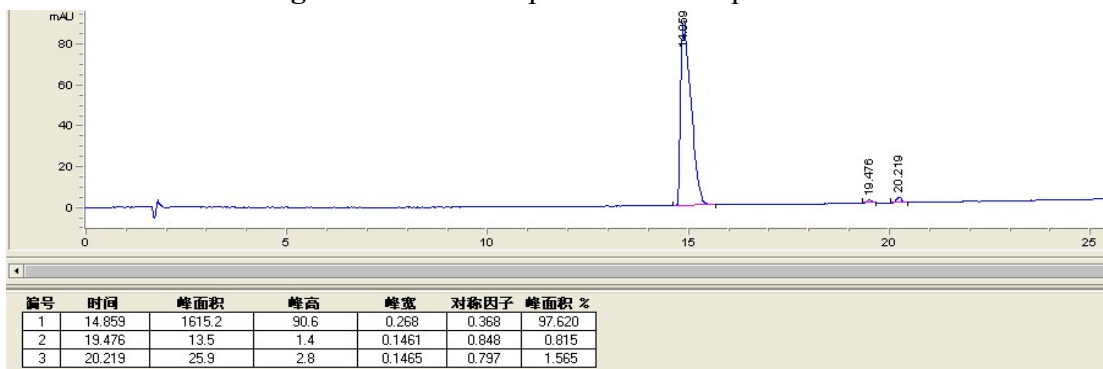


Figure S12. HPLC spectrum of compound 4d.

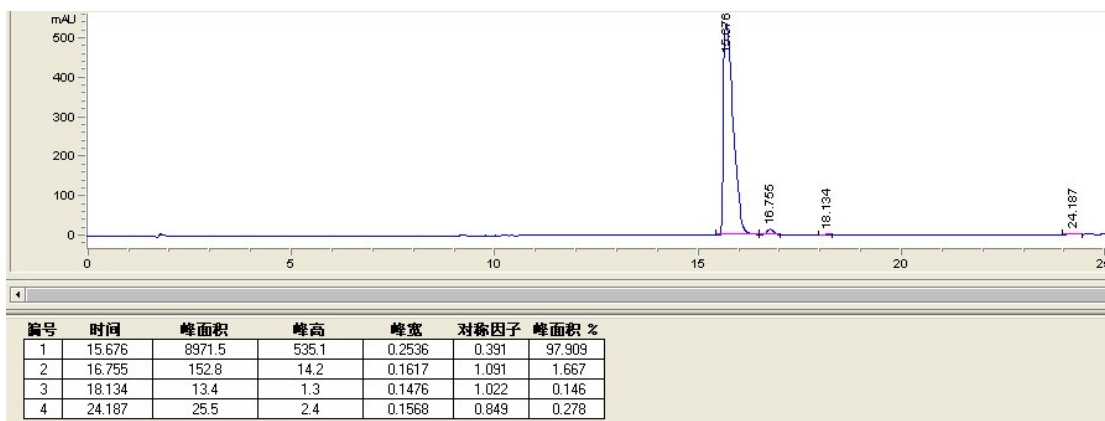


Figure S13. HPLC spectrum of compound 4e.

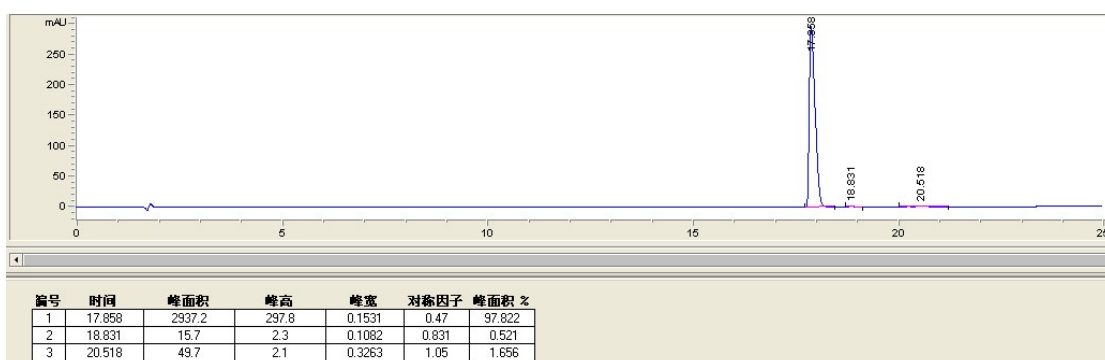


Figure S14. HPLC spectrum of compound 4f.

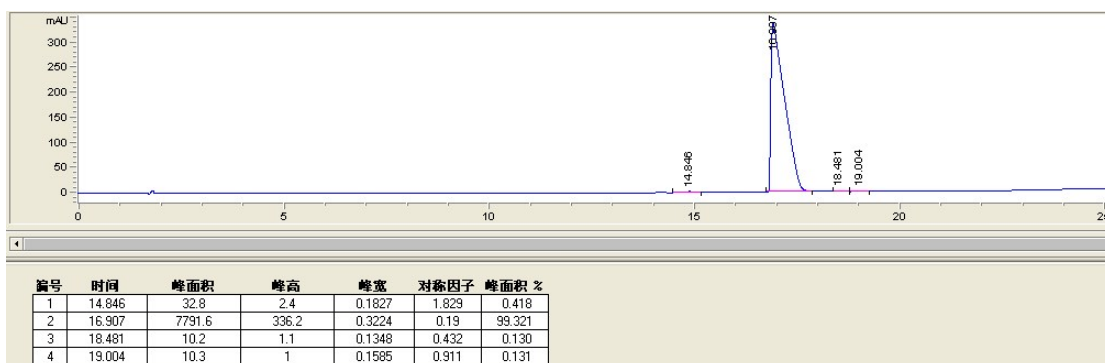


Figure S15. HPLC spectrum of compound 4g.

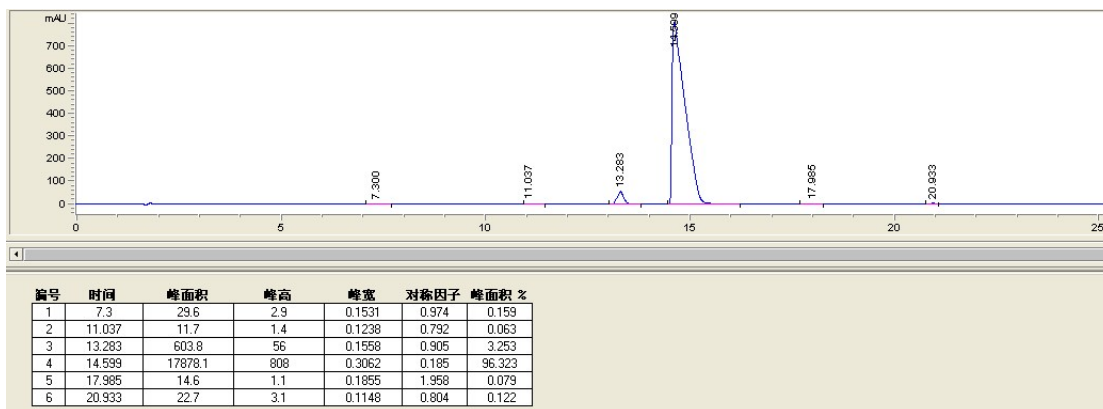


Figure S16. HPLC spectrum of compound 4h.

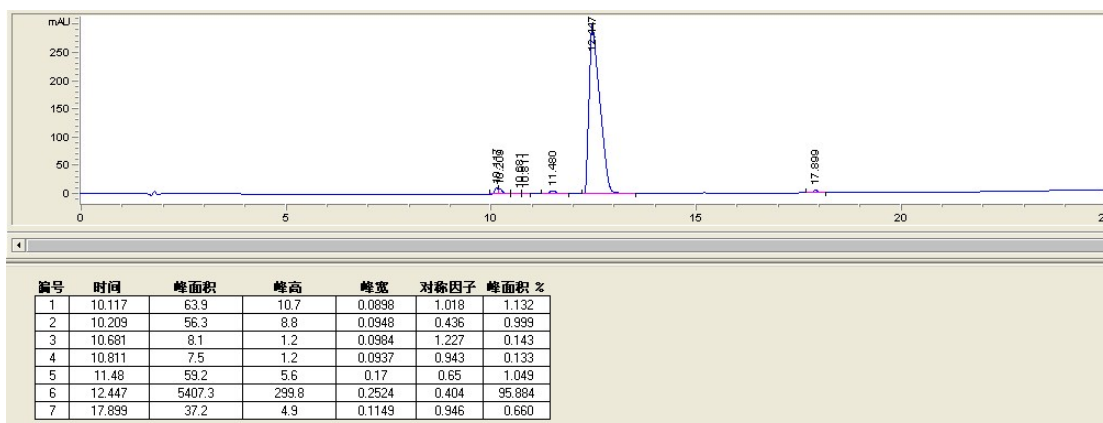


Figure S17. HPLC spectrum of compound 4i.

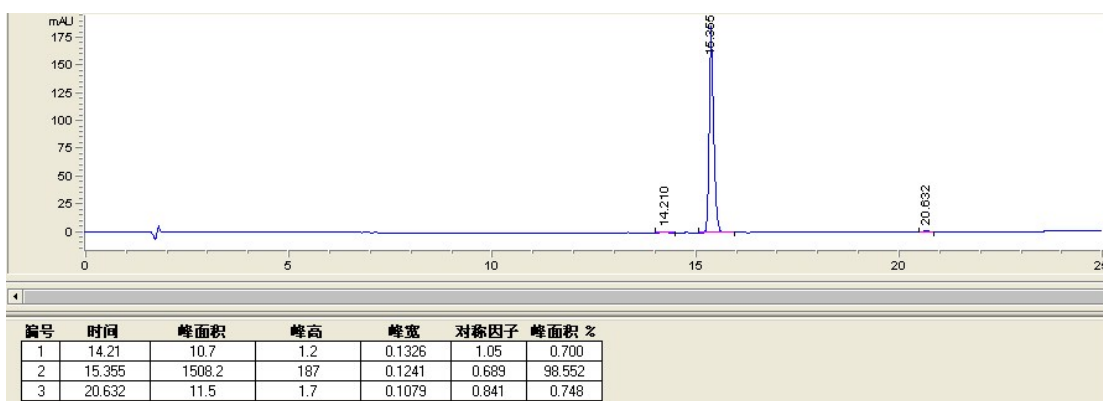


Figure S18. HPLC spectrum of compound 5a.

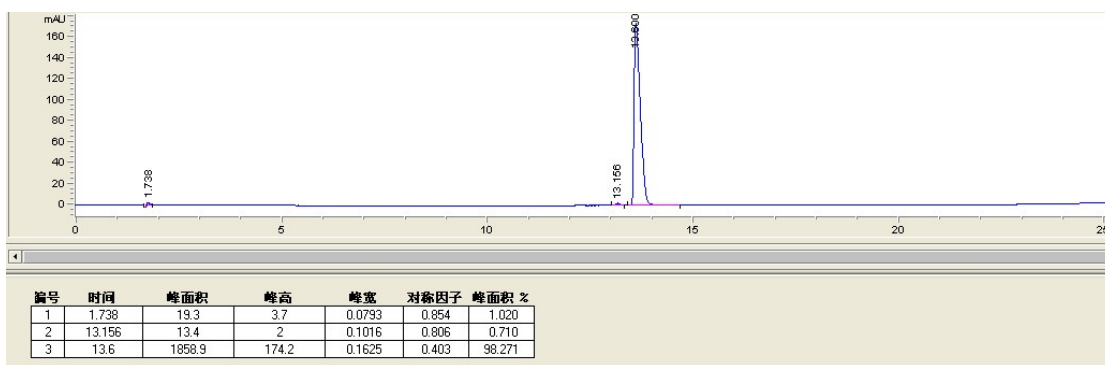


Figure S19. HPLC spectrum of compound 5b.

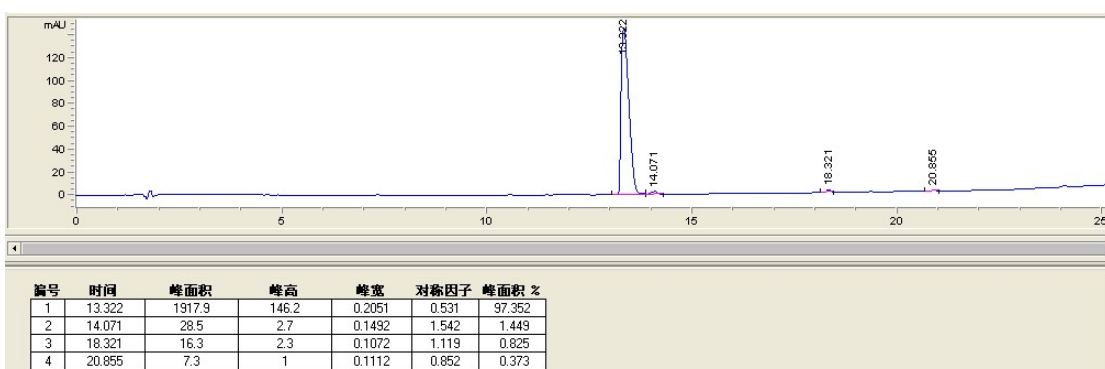


Figure S20. HPLC spectrum of compound 5c.

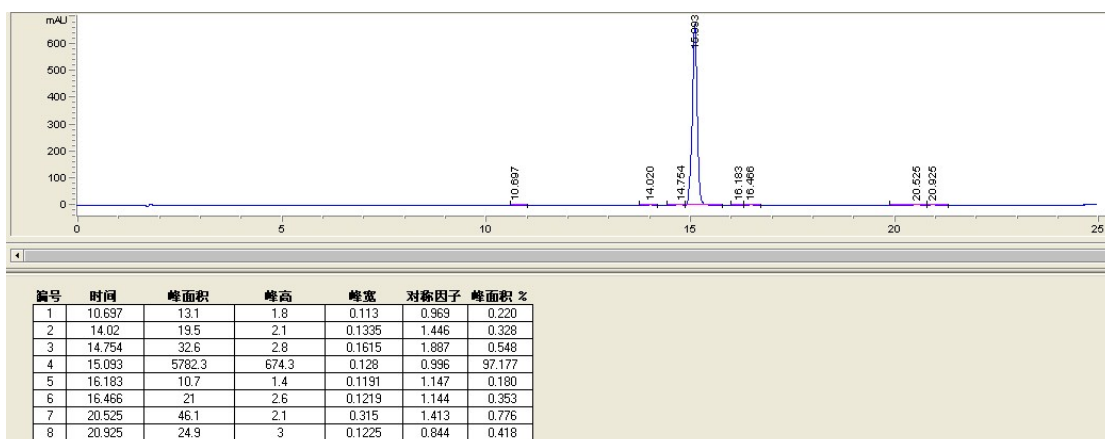


Figure S21. HPLC spectrum of compound 5d.

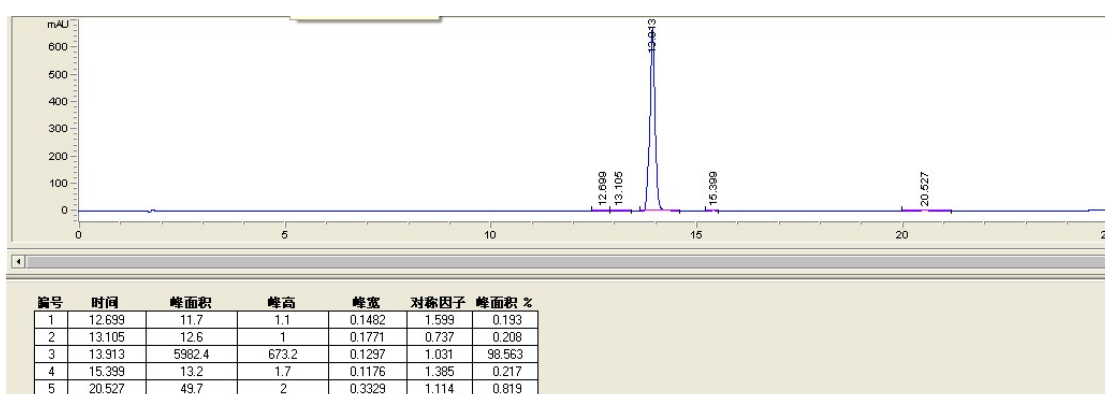


Figure S22. HPLC spectrum of compound 5e.

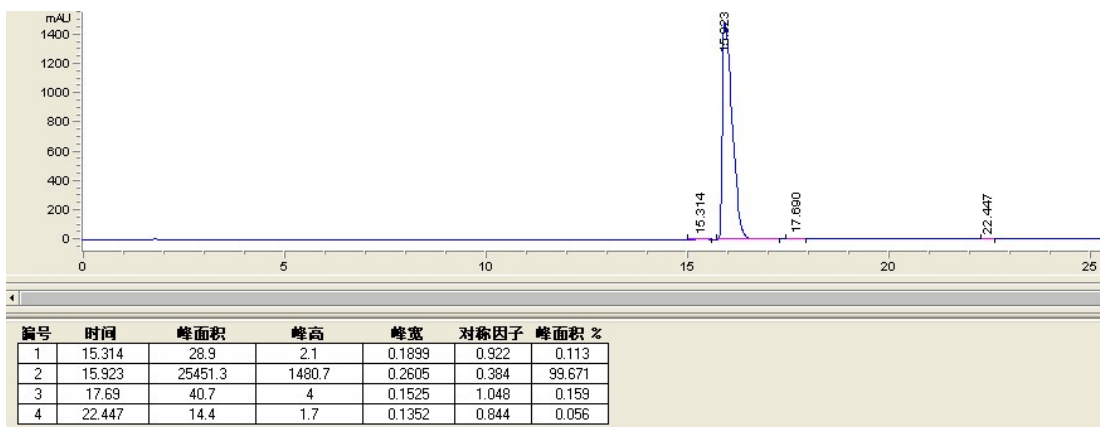


Figure S23. HPLC spectrum of compound 5f.

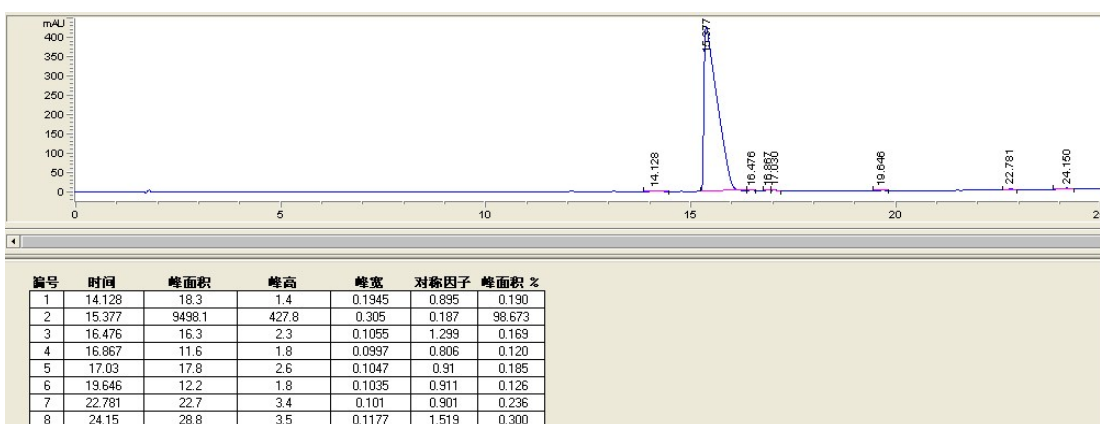


Figure S24. HPLC spectrum of compound 5g.

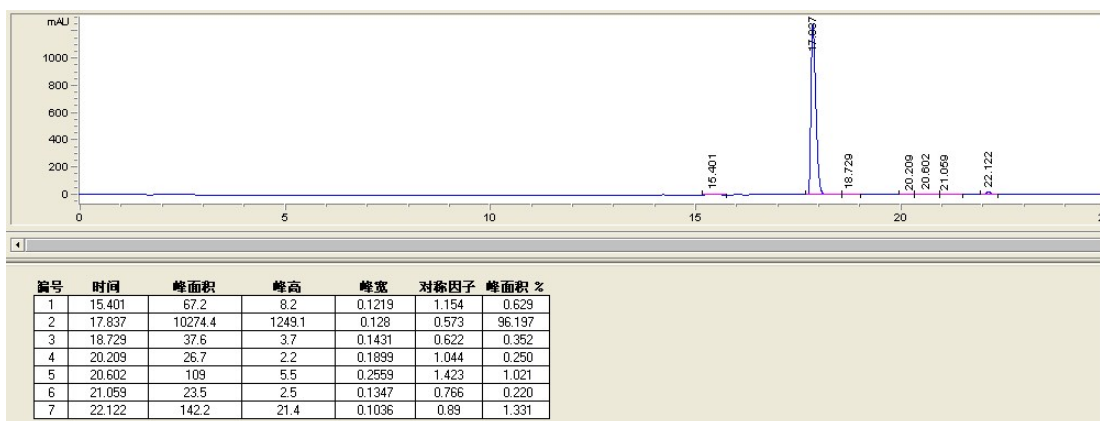


Figure S25. HPLC spectrum of compound 5h.

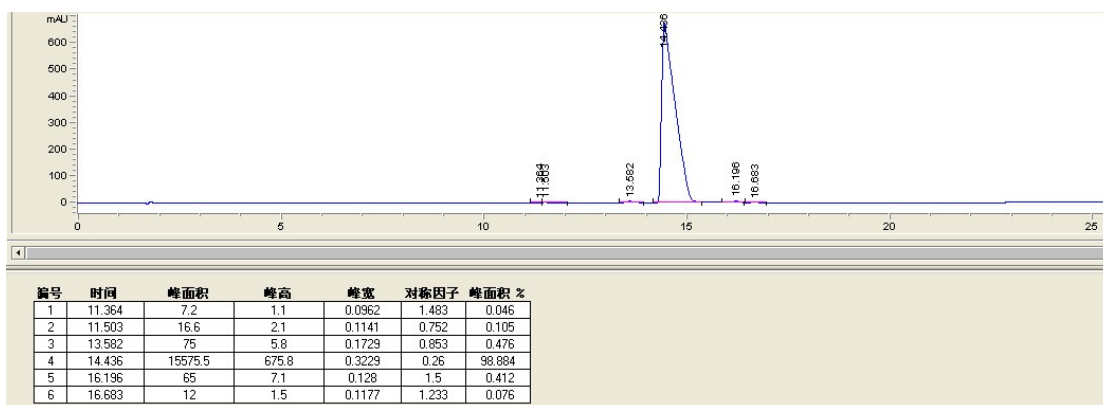


Figure S26. HPLC spectrum of compound 5i

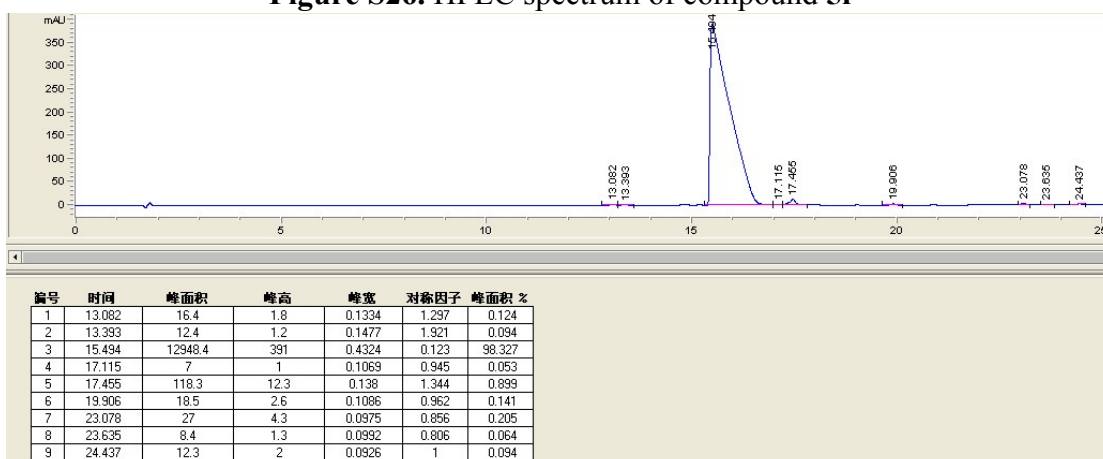


Figure S27. HPLC spectrum of compound 5j.

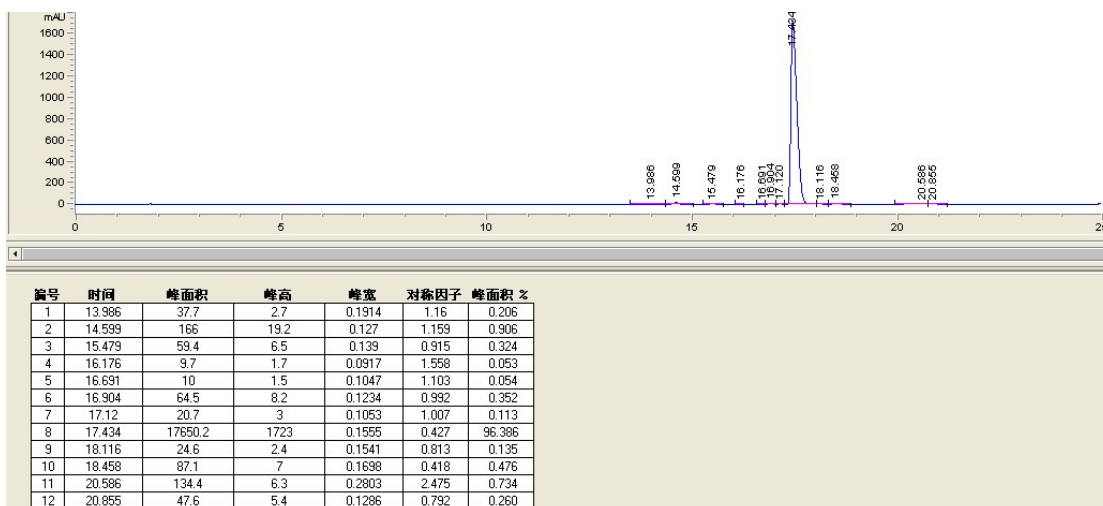


Figure S28. HPLC spectrum of compound 5k.

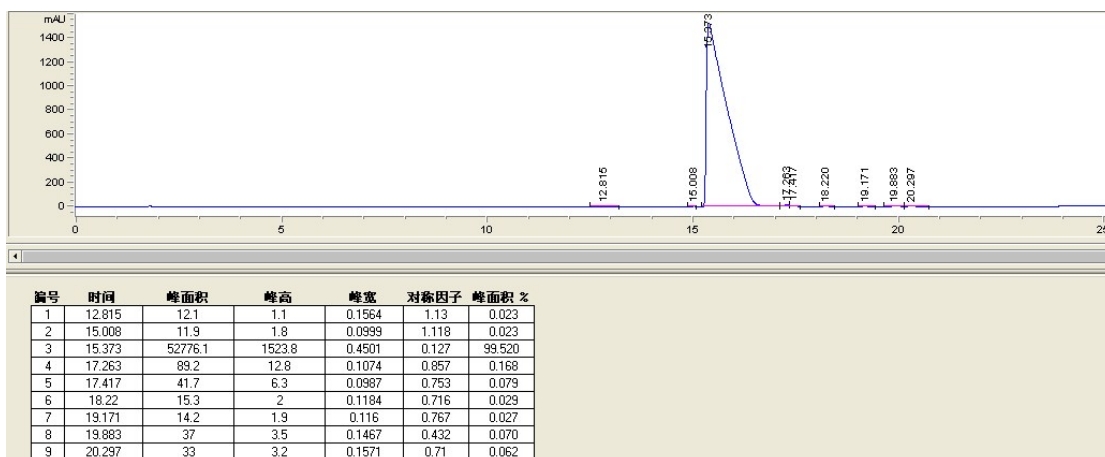


Figure S29. HPLC spectrum of compound 5l.

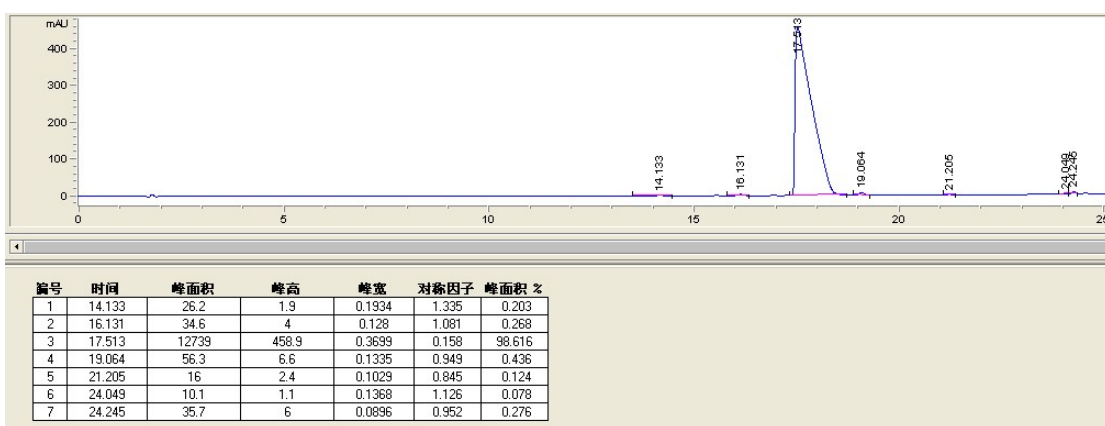


Figure S30. HPLC spectrum of compound 5m.

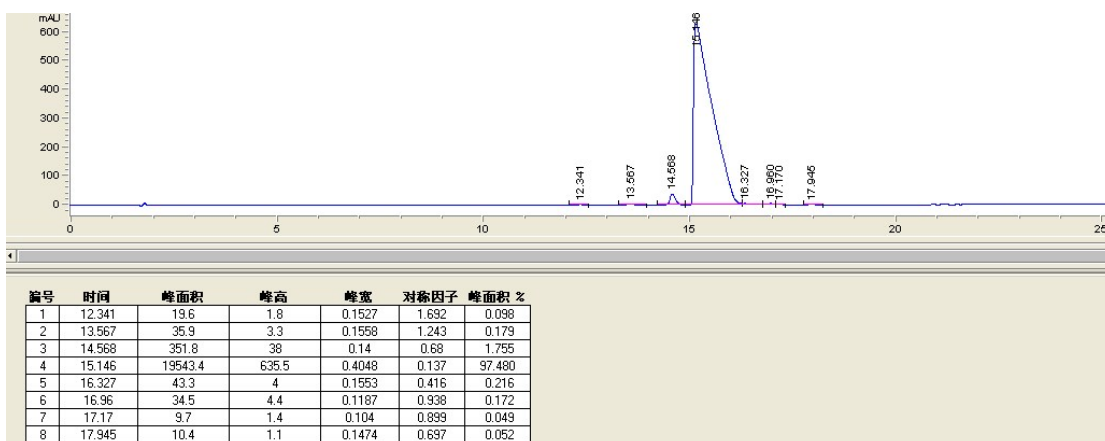


Figure S31. HPLC spectrum of compound 5n.

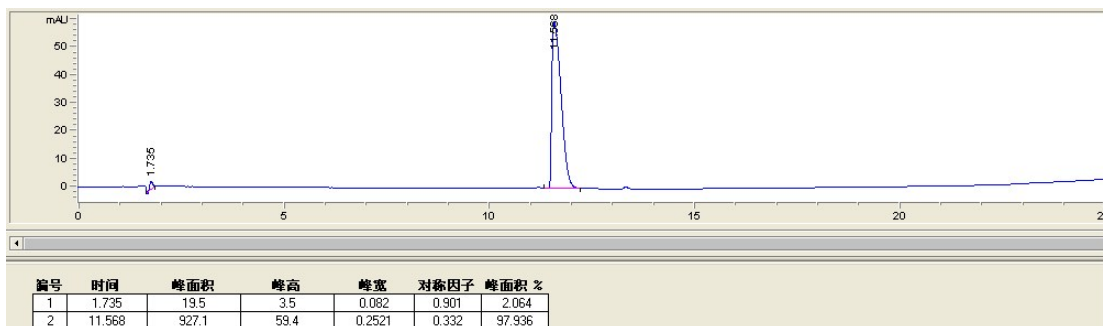


Figure S32. HPLC spectrum of compound 6.

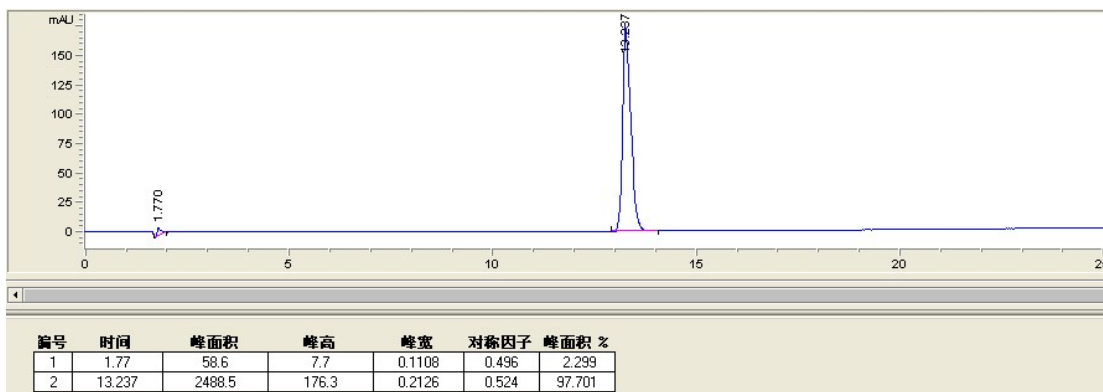


Figure S33. HPLC spectrum of compound 7.

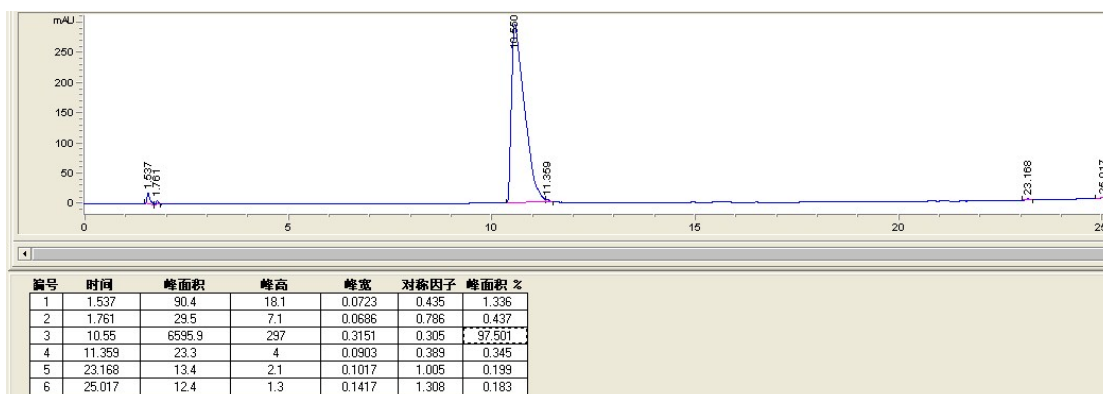


Figure S34. HPLC spectrum of compound 11a.

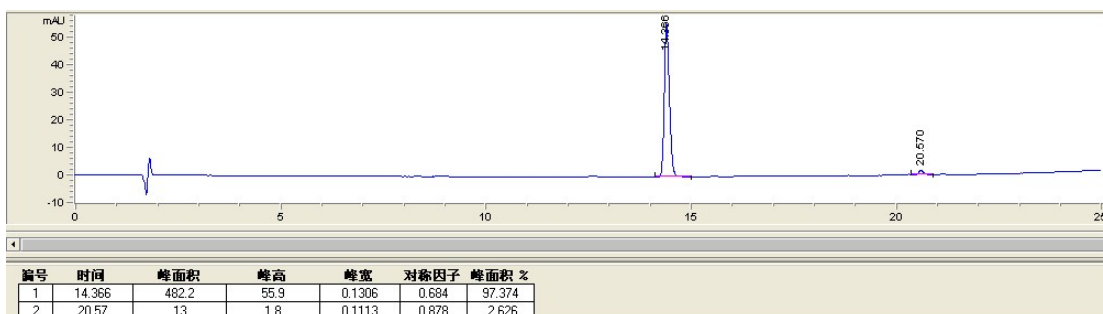


Figure S35. HPLC spectrum of compound 11b.

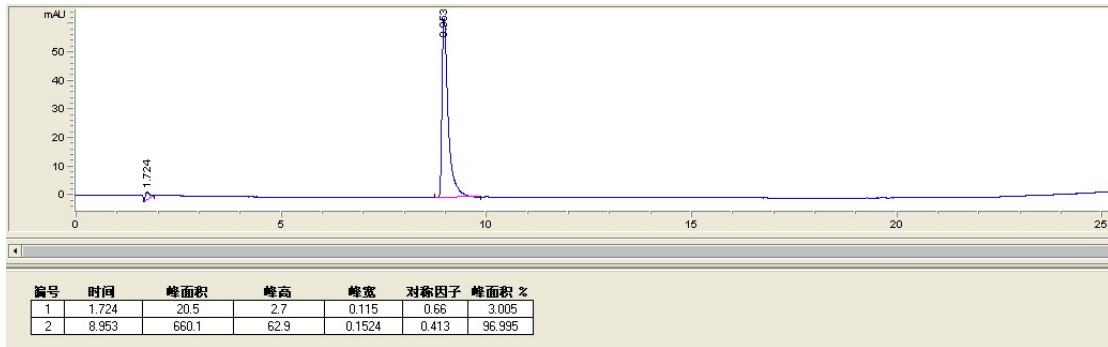


Figure S36. HPLC spectrum of compound **11c**.