Synthesis, biological evaluation, and molecular modeling of of new naphthalene-chalcone derivatives as potential anticancer agents on MCF-7 breast cancer cells by targeting tubulin colchicine binding site

1. Experimental section.

1.1. Chemistry.

All starting materials and reagents were purchased from commercial suppliers. TLC was performed on 0.20 mm Silica Gel 60 F$_{254}$ plates (Qingdao Ocean Chemical Factory, Shandong, China). Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker spectrometer (400 MHz) with TMS as an external reference and reported in parts per million. High resolution mass spectra (HRMS) were recorded on Bruker MicroQTOFII using ESI method.

1-(2-methoxynaphthalen-1-yl)ethan-1-one (2)

To a solution of 1-(2-hydroxynaphthalen-1-yl)ethan-1-one (1, 10 mmol) in acetone (50 mL) was added Cs$_2$CO$_3$ (20 mmol) and methyl iodide (12 mmol) and stirred at room temperature for 12 hours. Then, the reaction mixture was filtered and the solvent was evaporated. The residue was purified by chromatography on silica gel using EtOAc/petroleum ether as eluent to afford 1-(2-methoxynaphthalen-1-yl)ethan-1-one (2).

General procedures for the synthesis of 3a-3t
A mixture of compound 2 (1.0 mmol) and commercially available aryl aldehyde (1.0 mmol) in MeOH (10 mL) was stirred at ice bath for 0.5 h. Then a solution of KOH aqueous (50%, 3 mL) was added dropwise to the reaction and this was stirred at room temperature for a further 24 hours. After completion of reaction, the reaction mixture was poured on crushed ice and neutralized with concentrated HCl. The precipitated solid was filtered and recrystallized from ethanol to provide the target compounds 3a-3t. The most of compounds have not been reported in literature except compounds 3b, 3h, 3k, 3n, 3q and 3r.

\((E)-3-(3\text{-Hydroxy}-4\text{-methoxyphenyl})-1-(2\text{-methoxynaphthalen}-1\text{-yl})\text{prop-2-en-1-one (3a)}\)

Yellow solid, yield = 59 %, mp 135-136 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.91 (d, 1H, \(J = 8.8\) Hz, ArH), 7.80 (d, 1H, \(J = 8.0\) Hz, ArH), 7.66 (d, 1H, \(J = 8.4\) Hz, ArH), 7.40-7.44 (m, 1H, ArH), 7.35-7.37 (m, 1H, ArH), 7.31 (d, 1H, \(J = 8.8\) Hz, ArH), 7.21 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 7.16 (d, 1H, \(J = 2.0\) Hz, ArH), 6.96 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 6.95 (dd, 1H, \(J = 8.0\) Hz, 2.4 Hz, ArH), 6.78 (d, 1H, \(J = 8.4\) Hz, ArH), 5.64 (s, 1H, OH), 3.91 (s, 3H, OCH\(_3\)), 3.89 (s, 3H, OCH\(_3\)); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 197.53, 154.09, 148.90, 146.08, 145.91, 131.63, 131.21, 128.89, 128.31, 128.13, 127.50, 127.30, 124.27, 124.14, 123.77, 122.57, 113.44, 113.24, 110.55, 56.75, 56.10; HRMS (TOF) calcd for [M+Na]\(^+\) \(\text{C}_{21}\text{H}_{18}\text{NaO}_4^+\): 357.1097 found 357.1098.

\((E)-3-(4\text{-Bromophenyl})-1-(2\text{-methoxynaphthalen}-1\text{-yl})\text{prop-2-en-1-one (3b)}\)

Yellow solid, yield = 48 %, mp 127-129 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.94 (d, 1H, \(J = 8.8\) Hz, ArH), 7.82 (d, 1H, \(J = 8.0\) Hz, ArH), 7.67 (d, 1H, \(J = 8.4\) Hz, ArH),
7.43-7.50 (m, 3H), 7.33-7.40 (m, 4H, ArH), 7.26 (d, 1H, J = 16.0 Hz, COCH=CH), 7.09 (d, 1H, J = 16.0 Hz, COCH=CH), 3.93 (s, 3H, OCH3);

13C NMR (CDCl3, 100 MHz) δ: 196.71, 153.77, 143.68, 133.11, 131.71, 131.65, 131.07, 131.00, 129.39, 128.78, 128.35, 127.73, 127.65, 127.15, 124.41, 123.71, 123.59, 123.45, 122.75, 112.59, 56.18; HRMS (TOF) calcd for [M+Na]+ C20H15BrNaO2+: 389.0148 found 389.0149.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (3c)

Yellow solid, yield = 63 %, mp 107-108 °C; 1H NMR (CDCl3, 400 MHz) δ: 7.89-7.92 (m, 1H), 7.78-7.81 (m, 1H), 7.67-7.70 (m, 1H), 7.51-7.56 (m, 1H), 7.24-7.43 (m, 4H), 7.06-7.11 (m, 1H), 6.65-6.68 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H); 13C NMR (CDCl3, 100 MHz) δ: 197.92, 155.93, 154.02, 153.59, 142.43, 141.41, 131.69, 131.16, 128.91, 128.13, 127.96, 127.37, 124.31, 124.06, 123.86, 123.56, 121.79, 113.22, 107.78, 61.55, 61.01, 56.73, 56.17; HRMS (TOF) calcd for [M+Na]+ C23H22NaO5+: 401.1359 found 401.1359.

(E)-3-(2-Bromophenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3d)

Yellow solid, yield = 41 %, mp 150-152 °C; 1H NMR (CDCl3, 400 MHz) δ: 7.94 (d, 1H, J = 8.8 Hz, ArH), 7.82 (d, 1H, J = 8.0 Hz, ArH), 7.72 (d, 1H, J = 16.0 Hz, COCH=CH), 7.71 (d, 1H, J = 8.0 Hz, ArH), 7.67 (dd, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.54 (d, 1H, J = 8.0 Hz, ArH), 7.47 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.31-7.39 (m, 3H), 7.21 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.02 (d, 1H, J = 16.0 Hz, COCH=CH), 3.96 (s, 3H, OCH3); 13C NMR (CDCl3, 100 MHz) δ: 196.73, 153.87, 143.64, 134.26, 132.97, 132.88, 131.20, 131.14, 131.03, 130.91, 130.60, 128.36, 127.71, 127.57, 127.48, 127.27, 127.11, 125.26, 123.64, 122.51, 112.43, 56.10; HRMS (TOF) calcd for [M+K]+
$C_{26}H_{15}BrKO_2^+$: 404.9887 found 404.9889.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (3e)

Yellow solid, yield = 62%, mp 162-163 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 8.24 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.96 (d, 1H, $J = 8.8$ Hz, ArH), 7.80-7.91 (m, 6H, ArH), 7.46-7.50 (m, 4H, ArH), 7.24-7.41 (m, 2H, ArH), 7.20 (d, 1H, $J = 16.0$ Hz, COCH=CH), 3.96 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 197.18, 154.46, 142.48, 133.75, 132.04, 131.67, 131.59, 131.29, 130.91, 128.98, 128.86, 128.27, 127.71, 126.95, 126.29, 125.59, 125.46, 124.27, 123.62, 123.27, 113.17, 56.73; HRMS (TOF) calcd for [M+K]$^+$ $C_{24}H_{18}KO_2^+$: 377.0938 found 377.0939.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-(naphthalen-2-yl)prop-2-en-1-one (3f)

Yellow solid, yield = 59%, mp 107-109 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.94 (d, 1H, $J = 8.8$ Hz, ArH), 7.77-7.85 (m, 6H, ArH), 7.68-7.72 (m, 2H, ArH), 7.43-7.51 (m, 4H, ArH), 7.34-7.39 (m, 2H, ArH), 7.21 (d, 1H, $J = 16.0$ Hz, COCH=CH), 3.94 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 197.65, 154.22, 146.13, 134.45, 133.31, 132.25, 131.65, 131.39, 130.82, 129.07, 128.93, 128.78, 128.67, 128.21, 127.88, 127.62, 127.50, 126.82, 124.22, 123.76, 123.58, 113.23, 56.77; HRMS (TOF) calcd for [M+Na]$^+$ $C_{24}H_{18}NaO_2^+$: 361.1199 found 361.1198.

(E)-3-(3-Bromo-4-methoxyphenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3g)

Yellow solid, yield = 60%, mp 168-169 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.92 (d, 1H, $J = 8.8$ Hz, ArH), 7.81 (d, 1H, $J = 8.4$ Hz, ArH), 7.64-7.69 (m, 2H, ArH), 7.41-7.45 (m, 2H, ArH), 7.31-7.38 (m, 2H, ArH), 7.18 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.97 (d,
(E)-1-(2-Methoxynaphthalen-1-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (3h)

Yellow solid, yield = 42 %, mp 109-110 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.93 (d, 1H, \(J = 8.8\) Hz, ArH), 7.81 (d, 1H, \(J = 8.4\) Hz, ArH), 7.66 (d, 1H, \(J = 8.0\) Hz, ArH), 7.42-7.46 (m, 1H, ArH), 7.36-7.39 (m, 1H, ArH), 7.24-7.34 (m, 3H, ArH), 7.08 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 7.07 (d, 1H, \(J = 8.0\) Hz, ArH), 7.00-7.01 (m, 1H, ArH), 6.90 (dd, 1H, \(J = 8.0\) Hz, 2.0 Hz, ArH), 3.92 (s, 3H, OCH\(_3\)), 3.79 (s, 3H, OCH\(_3\)); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 197.70, 159.92, 154.20, 145.95, 136.06, 131.59, 131.41, 129.96, 129.14, 128.87, 128.19, 127.63, 124.16, 123.42, 121.34, 116.75, 113.18, 77.45, 77.13, 76.81, 56.72, 55.41; HRMS (TOF) calcd for [M+Na]\(^+\) C\(_{21}\)H\(_{18}\)NaO\(_3\): 341.1148 found 341.1149.

(E)-3-(4-Methoxy-3-nitrophenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3i)

Yellow solid, yield = 55 %, mp 157-159 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.95 (d, 1H, \(J = 8.8\) Hz, ArH), 7.95 (d, 1H, \(J = 2.0\) Hz, ArH), 7.83 (d, 1H, \(J = 8.0\) Hz, ArH), 7.70 (dd, 1H, \(J = 8.8\) Hz, 2.0 Hz, ArH), 7.67 (d, 1H, \(J = 8.4\) Hz, ArH), 7.46 (dt, 1H, \(J = 8.0\) Hz, 1.2 Hz, ArH), 7.38 (t, 1H, \(J = 8.4\) Hz, ArH), 7.33 (d, 1H, \(J = 8.8\) Hz, ArH), 7.26 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 7.09 (d, 1H, \(J = 8.8\) Hz, ArH), 7.05 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 3.99 (s, 3H, OCH\(_3\)), 3.94 (s, 3H, OCH\(_3\)); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\):
HRMS (TOF) calcd for \([\text{M+Na}^+ \text{C}_{21}\text{H}_{17}\text{NaO}_5]^+\): 386.0999 found 386.0999.

\((E)-1-(2\text{-Methoxynaphthalen-1-yl})-3-(\text{thiophen}-2\text{-yl})\text{prop-2-en-1-one (3j)}\)

Yellow solid, yield = 65 %, mp 149-150 °C; \(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.92 (d, 1H, \(J = 8.8\) Hz, ArH), 7.81 (d, 1H, \(J = 8.0\) Hz, ArH), 7.67 (d, 1H, \(J = 8.8\) Hz, ArH), 7.31-7.46 (m, 5H, ArH), 7.17 (d, 1H, \(J = 3.6\) Hz, ArH), 7.01 (dd, 1H, \(J = 4.8\) Hz, 3.6 Hz, ArH), 6.90 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 3.92 (s, 3H, OCH\(_3\)); \(^1\text{C}\) NMR (CDCl\(_3\), 100 MHz) \(\delta\): 197.06, 154.18, 140.09, 138.41, 131.95, 131.59, 131.39, 129.47, 128.86, 128.39, 128.18, 127.86, 127.62, 124.21, 124.18, 123.30, 113.16, 56.73; HRMS (TOF) calcd for \([\text{M+Na}^+ \text{C}_{18}\text{H}_{14}\text{NaO}_2S]^+\): 317.0607 found 317.0607.

\((E)-3-(4\text{-Chlorophenyl})-1-(2\text{-methoxynaphthalen-1-yl})\text{prop-2-en-1-one (3k)}\)

Yellow solid, yield = 58 %, mp 142-143 °C; \(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.93 (d, 1H, \(J = 8.8\) Hz, ArH), 7.81 (d, 1H, \(J = 8.0\) Hz, ArH), 7.66 (d, 1H, \(J = 8.4\) Hz, ArH), 7.41-7.46 (m, 3H, ArH), 7.36-7.39 (m, 1H, ArH), 7.33-7.35 (m, 2H, ArH), 7.31 (d, 1H, \(J = 2.4\) Hz, ArH), 7.26 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 7.06 (d, 1H, \(J = 16.0\) Hz, COCH=CH), 3.92 (s, 3H, OCH\(_3\)); \(^1\text{C}\) NMR (CDCl\(_3\), 100 MHz) \(\delta\): 197.31, 154.28, 144.23, 136.56, 133.21, 131.57, 129.75, 129.25, 128.88, 128.23, 127.69, 124.26, 124.08, 123.28, 113.11, 77.44, 77.13, 76.81, 56.72; HRMS (TOF) calcd for \([\text{M+Na}^+ \text{C}_{20}\text{H}_{15}\text{ClNaO}_2]^+\): 345.0653 found 345.0653.

\((E)-1-(2\text{-Methoxynaphthalen-1-yl})-3-(2,4,5\text{-trimethoxyphenyl})\text{prop-2-en-1-one (3l)}\)

Yellow solid, yield = 63 %, mp 147-149 °C; \(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.92 (d,
$^{1}$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.93 (d, 1H, $J = 8.8$ Hz, ArH), 7.82 (d, 1H, $J = 8.0$ Hz, ArH), 7.70 (d, 1H, $J = 8.4$ Hz, ArH), 7.63 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.44 (t, 1H, $J = 8.0$ Hz, ArH), 7.36 (t, 1H, $J = 8.0$ Hz, ArH), 7.33 (d, 1H, $J = 8.8$ Hz, ArH), 7.07 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.02 (s, 1H, ArH), 6.44 (s, 1H, ArH), 3.93 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.76 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 198.01, 154.46, 153.93, 152.62, 143.26, 141.44, 131.71, 130.95, 128.92, 128.07, 127.34, 127.01, 124.44, 124.17, 115.09, 113.46, 110.85, 110.01, 96.72, 56.83, 56.45, 56.41, 56.14; HRMS (TOF) calcd for [M+Na]$^+$ C$_{23}$H$_{22}$NaO$_5^+$: 401.1359 found 401.1360.

(E)-3-(2-Fluorophenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3m)

Yellow solid, yield = 59 %, mp 146-147 °C; $^{1}$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.93 (d, 1H, $J = 8.8$ Hz, ArH), 7.81 (d, 1H, $J = 8.0$ Hz, ArH), 7.69 (d, 1H, $J = 8.4$ Hz, ArH), 7.56 (dt, 1H, $J = 8.0$ Hz, 1.2 Hz, ArH), 7.49 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.45 (dt, 1H, $J = 8.0$ Hz, 1.2 Hz, ArH), 7.31-7.38 (m, 3H, ArH), 7.18 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.14 (t, 1H, $J = 8.0$ Hz, ArH), 7.02-7.07 (m, 1H, ArH), 3.93 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 197.48, 160.21 (d, 1C, $J = 253.2$ Hz), 154.41, 137.91, 132.05 (d, 1C, $J = 8.7$ Hz), 131.65, 131.57 (d, 1C, $J = 8.1$ Hz), 130.93 (d, 1C, $J = 6.0$ Hz), 129.23, 129.21, 128.93, 128.24, 127.67, 124.53 (d, 1C, $J = 3.6$ Hz), 124.23, 124.10, 123.21, 122.82 (d, 1C, $J = 11.4$ Hz), 116.17 (d, 1C, $J = 21.7$ Hz), 113.13, 56.69; HRMS (TOF) calcd for [M+Na]$^+$ C$_{20}$H$_{15}$FNaO$_2^+$: 329.0948 found 329.0948.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-phenylprop-2-en-1-one (3n)

Yellow solid, yield = 61 %, mp 142-144 °C; $^{1}$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.93 (d, 1H, $J = 8.8$ Hz, ArH), 7.82 (d, 1H, $J = 8.4$ Hz, ArH), 7.69 (d, 1H, $J = 8.4$ Hz, ArH),
7.48-7.50 (m, 2H, ArH), 7.44 (dt, 1H, $J = 8.0$ Hz, 1.2 Hz, ArH), 7.35-7.38 (m, 4H, ArH), 7.30 (d, 1H, $J = 7.2$ Hz, ArH), 7.11 (d, 1H, $J = 16.0$ Hz, COCH=CH), 3.93 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 197.73, 154.20, 146.06, 134.69, 131.60, 131.41, 130.73, 128.99, 128.89, 128.63, 128.20, 127.62, 124.21, 123.45, 113.17, 77.47, 77.15, 76.83, 56.72; HRMS (TOF) calcd for [M+Na]$^+$ C$_{20}$H$_{16}$NaO$_2$+: 311.1043 found 311.1044.

(E)-3-(3-Fluorophenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3o)

Yellow solid, yield = 66 %, mp 142-143 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ: 7.94 (d, 1H, $J = 8.8$ Hz, ArH), 7.82 (d, 1H, $J = 8.0$ Hz, ArH), 7.67 (d, 1H, $J = 8.8$ Hz, ArH), 7.45 (dt, 1H, $J = 8.0$ Hz, 1.2 Hz, ArH), 7.27-7.39 (m, 5H, ArH), 7.18-7.21 (m, 1H, ArH), 7.08 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.03-7.06 (m, 1H, ArH), 3.93 (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: $^{13}$C NMR (101 MHz, ) δ 197.24, 161.80 (d, 1C, $J = 245.7$ Hz), 154.36, 144.07, 136.97 (d, 1C, $J = 7.6$ Hz), 131.66, 131.53, 130.46 (d, 1C, $J = 8.6$ Hz), 129.92, 128.88, 128.25, 127.73, 124.56 (d, 1C, $J = 2.3$ Hz), 124.27, 124.05, 123.19, 117.37 (d, 1C, $J = 21.5$ Hz), 114.65 (d, 1C, $J = 21.8$ Hz), 113.08, 56.70; HRMS (TOF) calcd for [M+K]$^+$ C$_{20}$H$_{15}$FKO$_2$+: 345.0688 found 345.0689.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3p)

Yellow solid, yield = 49 %, mp 113-114 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ: 7.93 (d, 1H, $J = 8.8$ Hz, ArH), 7.82 (d, 1H, $J = 8.0$ Hz, ArH), 7.65 (d, 1H, $J = 8.4$ Hz, ArH), 7.44 (dt, 1H, $J = 8.0$ Hz, 1.2 Hz, ArH), 7.36-7.39 (m, 1H, ArH), 7.33 (d, 1H, $J = 8.8$ Hz, ArH), 7.18 (d, 1H, $J = 16.0$ Hz, COCH=CH), 7.00 (d, 1H, $J = 16.0$ Hz, COCH=CH), 6.71 (s, 2H, ArH), 3.92 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 3.83 (s, 6H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 197.53, 154.11, 153.48, 146.20, 140.51, 131.63, 131.23, 130.13,
HRMS (TOF) calcd for [M+K]^+ C_{23}H_{22}KO_5^+: 417.1099 found 417.1099.

(E)-1-(2-Methoxynaphthalen-1-yl)-3-(2-methoxyphenyl)prop-2-en-1-one (3q)

Yellow solid, yield = 62 %, mp 124-126 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.91 (d, 1H, J = 8.8 Hz, ArH), 7.80 (d, 1H, J = 8.4 Hz, ArH), 7.69 (d, 1H, J = 8.4 Hz, ArH), 7.66 (d, 1H, J = 16.0 Hz, COCH=CH), 7.49 (dd, 1H, J = 8.0 Hz, 1.6 Hz, ArH), 7.43 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.32-7.37 (m, 3H, ArH), 7.21 (d, 1H, J = 16.0 Hz, COCH=CH), 6.93 (t, 1H, J = 8.0 Hz, ArH), 6.85 (d, 1H, J = 8.4 Hz, ArH), 3.91 (s, 3H, OCH\(_3\)), 3.78 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 198.22, 158.68, 154.16, 141.59, 132.00, 131.68, 131.22, 129.41, 128.93, 128.13, 127.45, 124.36, 124.11, 123.85, 123.61, 120.77, 113.29, 111.22, 77.47, 77.16, 76.84, 56.77, 55.53; HRMS (TOF) calcd for [M+K]^+ C_{21}H_{18}KO_3^+: 357.0888 found 357.0886.

(E)-3-(4-(Dimethylamino)phenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3r)

Yellow solid, yield = 57 %, mp 147-148 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.89 (d, 1H, J = 8.8 Hz, ArH), 7.80 (d, 1H, J = 8.4 Hz, ArH), 7.67 (d, 1H, J = 8.4 Hz, ArH), 7.31-7.43 (m, 5H, ArH), 7.20 (d, 1H, J = 16.0 Hz, COCH=CH), 6.93 (d, 1H, J = 16.0 Hz, COCH=CH), 6.62 (d, 2H, J = 8.4 Hz, ArH), 3.91 (s, 3H, OCH\(_3\)), 3.00 (s, 6H, NCH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 197.70, 153.77, 147.73, 131.76, 130.75, 130.58, 128.87, 128.04, 127.31, 124.52, 124.23, 124.04, 113.35, 111.90, 56.79, 40.31; HRMS (TOF) calcd for [M+Na]^+ C_{22}H_{21}NNaO_2^+: 354.1465 found 354.1466.

(E)-3-(4-(Diethylamino)phenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3s)

Yellow solid, yield = 64 %, mp 142-144 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.89 (d,
1H, J = 8.8 Hz, ArH), 7.80 (d, 1H, J = 8.0 Hz, ArH), 7.67 (d, 1H, J = 8.4 Hz, ArH), 7.40 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.31-7.35 (m, 4H, ArH), 7.17 (d, 1H, J = 16.0 Hz, COCH=CH), 6.90 (d, 1H, J = 16.0 Hz, COCH=CH), 6.56 (d, 2H, J = 8.8 Hz, ArH), 3.90 (s, 3H, OCH₃), 3.34 (q, 4H, J = 7.2 Hz, NCH₂CH₃), 1.15 (t, 6H, J = 7.2 Hz, NCH₂CH₃);

13C NMR (CDCl₃, 100 MHz) δ: 197.70, 153.72, 149.77, 147.97, 131.79, 130.93, 130.65, 128.86, 128.00, 127.26, 124.57, 124.34, 124.01, 123.57, 121.35, 113.36, 111.24, 56.78, 44.61, 12.65; HRMS (TOF) calcd for [M+K]⁺ C₂₄H₂₅KNO₂⁺: 398.1517 found 398.1518.

(E)-3-(3-Amino-4-methoxyphenyl)-1-(2-methoxynaphthalen-1-yl)prop-2-en-1-one (3t)

Yellow oil, yield = 43 %; ¹H NMR (CDCl₃, 400 MHz) δ: 7.90 (d, 1H, J = 8.8 Hz, ArH), 7.79 (d, 1H, J = 8.0 Hz, ArH), 7.64 (d, 1H, J = 8.4 Hz, ArH), 7.41 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.34 (dt, 1H, J = 8.0 Hz, 1.2 Hz, ArH), 7.29 (d, 1H, J = 7.2 Hz, ArH), 7.15 (d, 1H, J = 16.0 Hz, COCH=CH), 6.96 (d, 1H, J = 2.0 Hz, ArH), 6.92 (d, 1H, J = 16.0 Hz, COCH=CH), 6.88 (dd, 1H, J = 8.4 Hz, 1.2 Hz, ArH), 6.71 (d, 1H, J = 8.8 Hz, ArH), 4.10 (s, 2H, NH₂), 3.89 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ: 197.86, 153.99, 150.34, 146.77, 134.58, 131.63, 131.13, 128.85, 128.13, 127.68, 127.48, 126.81, 124.27, 124.13, 123.69, 122.30, 114.78, 113.23, 110.36, 77.46, 77.14, 76.83, 56.72, 55.75; HRMS (ESI) calcd for [M+H]⁺ C₂₁H₂₀NO₃⁺: 334.1438 found 334.1438.

1.2 In vitro anticancer assay

Human breast carcinoma (MCF-7) cells were seeded in 96-well plates at 1 × 10⁴ cells/well, and cultured in RPMI-1640 with 10% fetal bovine serum for 24 h. Then,
different concentrations (0.3125, 0.625, 1.25, 2.5, 5.0, 10 and 20 μM) of the tested compounds (3a-3t) or positive control (cisplatin) were added. After 48 h of culture, the culture medium was removed, and cells were incubated with tetrazolium dye [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)] solution for 4 h. Then, the supernatant was removed and the precipitates (formazan crystal) were dissolved in DMSO. The optical densitys (OD) at a wavelength of 570 nm were measured by the Spectramax M5 Microtiter Plate Luminometer (Molecular Devices, USA).

1.3 *In vitro* tubulin polymerization assay

To evaluate the effect of the compound 3a on tubulin assembly *in vitro*, varying concentrations of compound 3a, colchicine (Aladdin, Shanghai, China) or vehicle DMSO were incubated with purified tubulin protein in PEM buffer [100 mM PIPES (1,4-Piperazinediethanesulfonic acid), 1 mM MgCl₂, and 1 mM EGTA(ethylene glycol tetraacetic acid)] containing 1 mM GTP and 5 % glycerol. Tubulin assembly was monitored by a spectrophotometer (SPECTRA MAX 190) in absorbance at 340 nm for 20 minutes.

1.4 Cell cycle analysis

MCF-7 cells were seeded in 6-well plates and incubated at 37 °C for overnight and treatment with DMSO or compound 3a (0.5, 2.0 and 10.0 μM) for 24 h. The cells were washed twice with PBS, and incubated for 0.5 h at 37 °C in a PBS solution containing 1 mg/mL RNase A and propidium iodide (PI). Cell cycle was analyzed by flow cytometry (TASC240, USA).
1.5 Apoptosis assay

MCF-7 cells were grown in 6-well plates and treated with compound 3a (0.5, 2.0 and 10.0 μM) or DMSO for 24 h. After treatment, the cells were collected and stained with PI (propidium iodide) for 20 min. Apoptosis was analyzed using a flow cytometer.

1.6 Docking studies

The 3D structure of tubulin (1SA0) was downloaded from the Protein Data Bank (www.rcsb.org). The docking procedure was performed using Autodock vina 1.1.2. The search grid of the tubulin was identified as center_x: 118.921, center_y: 89.718, and center_z: 5.932 with dimensions size_x: 15, size_y: 15, and size_z: 15. The result of molecular docking study was visualized using PyMOL.
Figure S1: $^1$H NMR of Compound 3a

Figure S2: $^{13}$C NMR of Compound 3a
Figure S3: HRMS of Compound 3a
Figure S4: $^1$H NMR of Compound 3b

Figure S5: $^{13}$C NMR of Compound 3b
Figure S6: HRMS of Compound 3b
Figure S7: $^1$H NMR of Compound 3c

Figure S8: $^{13}$C NMR of Compound 3c
Figure S9: HRMS of Compound 3c
Figure S10: $^1$H NMR of Compound 3d

Figure S11: $^{13}$C NMR of Compound 3d
**Figure S12: HRMS of Compound 3d**
Figure S13: $^1$H NMR of Compound 3e

Figure S14: $^{13}$C NMR of Compound 3e
Figure S15: HRMS of Compound 3e
Figure S16: $^1$H NMR of Compound 3f

Figure S17: $^{13}$C NMR of Compound 3f
Figure S18: HRMS of Compound 3f
Figure S19 : $^1$H NMR of Compound 3g

Figure S20 : $^{13}$C NMR of Compound 3g
Figure S21: HRMS of Compound 3g
Figure S22: $^1$H NMR of Compound 3h

Figure S23: $^{13}$C NMR of Compound 3h
Figure S24: HRMS of Compound 3h
Figure S25: $^1$H NMR of Compound 3i

Figure S26: $^{13}$C NMR of Compound 3i
Figure S27: HRMS of Compound 3i
Figure S28: $^1$H NMR of Compound 3j

Figure S29: $^{13}$C NMR of Compound 3j
Figure S30: HRMS of Compound 3j
Figure S31: $^1$H NMR of Compound 3k

Figure S32: $^{13}$C NMR of Compound 3k
Figure S33: HRMS of Compound 3k
Figure S34: $^1$H NMR of Compound 3l

Figure S35: $^{13}$C NMR of Compound 3l
Figure S36: HRMS of Compound 3l
Figure S37: $^1$H NMR of Compound 3m

Figure S38: $^{13}$C NMR of Compound 3m
Figure S39: HRMS of Compound 3m
Figure S40: $^1$H NMR of Compound 3n

Figure S41: $^{13}$C NMR of Compound 3n
Figure S42: HRMS of Compound 3n
Figure S43: $^1$H NMR of Compound 3o

Figure S44: $^{13}$C NMR of Compound 3o
Figure S45: HRMS of Compound 3o
Figure S46: $^1$H NMR of Compound 3p

Figure S47: $^{13}$C NMR of Compound 3p
Figure S48: HRMS of Compound 3p
Figure S49: $^1$H NMR of Compound 3q

Figure S50: $^{13}$C NMR of Compound 3q
Figure S51: HRMS of Compound 3q
Figure S52: $^1$H NMR of Compound 3r

Figure S53: $^{13}$C NMR of Compound 3r
Figure S54: HRMS of Compound 3r
Figure S55: $^1$H NMR of Compound 3s

Figure S56: $^{13}$C NMR of Compound 3s
Figure S57: HRMS of Compound 3s
Figure S58: $^1$H NMR of Compound 3t

Figure S59: $^{13}$C NMR of Compound 3t
Figure S60 : HRMS of Compound 3t