Supporting Information

Synthesis and Evaluation of Selenium-containing Indole Chalcone and Diarylketone Derivatives as Tubulin Polymerization Inhibition Agents

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1. Chemistry

All chemicals were analytically pure without further purification as commercially available unless otherwise noted. Nuclear magnetic resonance spectra for proton (^{1}H) and carbon (^{13}C) were recorded in $CDCl_3$ on a Bruker AvanceIII spectrometer, and chemical shifts are expressed in parts per million (ppm) with TMS as the internal standard. Melting points (MP) were determined on SRS-OptiMelt automated melting point instrument. The purity of each compound (>95%)was determined on high-performance liquid chromatography (HPLC), which were recorded using an Agilent LC–MS 6120 instrument and were run on Eclipse Plus C8 column (4.6 × 150 mm, 5 μm) with two different solvent gradients (acetonitrile/water=90:10), and a flow rate of 0.20mL/min.

1.1. Synthesis procedure of 1-(4-hydroxy-3-methoxy-5-nitrophenyl)ethan-1-one ***(2)***

To a solution of 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one **1** (8.31g, 50.0mmol) in 100 mL of acetic acid at 0 °C, HNO_3 (4ml, 60%) were added in dropwise and then the reaction was stirred at room temperature for 3h. The resulting mixture was poured into ice water and the precipitate was collected by filtration, dried in vacuum oven to yield **2** as a yellow solid used in the following step without further purification. Yield: 92%.

1.2. Synthesis procedure of 1-(3,4-dimethoxy-5-nitrophenyl)ethan-1-one ***(3)***

Compound **2** (6.33g, 30.0mmol) was dissolved in 100ml of acetone, followed by addition of K_2CO_3 (10.37g, 75.0mmol), dimethylsulfate (4.27ml, 45.0mmol), and then the reaction mixture was stirred at 80°C for two days. After the mixture was cooled to room temperature, ammonium hydroxide was added to remove the excess dimethylsulfate. The mixture was extracted with ethyl acetate, washed with water (twice) and brine (once), dried over anhydrous Na_2SO_4, concentrated in vacuo to produce a dark oil, which was purified by column chromatography (petroleum ether: ethyl acetate= 10: 1) on silica gel to afford the intermediate compound **3** as white solid, Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.72 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.01 (s), 154.01 (s), 146.47 (s), 144.14 (s), 132.11 (s), 116.80 (s), 114.32 (s), 61.99 (s), 56.51 (s), 26.18 (s).

*1.3. Synthesis procedure of 1-(3-amino-4,5-dimethoxyphenyl)ethan-1-one **(4)***

To a stirred solution of **3** (2.25g, 10.0mmol) in acetic acid (25ml), iron power (2.80g, 50.0mmol) and 1ml HCl were added. After stirred for 8h at room temperature, the precipitates were filtered, vacuumed and purified by column chromatographic (petroleum ether: ethyl acetate, 8:1) to provide compound **4** as white solid, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 9.8 Hz, 1H), 4.08 (s, 2H), 3.86 (d, *J* = 6.9 Hz, 6H), 2.49 (d, *J* = 10.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.52 (s), 152.64 (s), 140.50 (s), 139.68 (s), 133.03 (s), 109.69 (s), 101.92 (s), 59.86 (s), 55.77 (s), 26.36 (s).

*1.4. Synthesis procedure of 1-(3,4-dimethoxy-5-selenocyanatophenyl)ethan-1-one (**5**)*

To a suspension of **4** (195mg, 1.0 mmol) in water, 10% HCl (2.5ml) was added in -5 °C. $NaNO_2$ (100mg, 1.2 mmol) was added and the reaction mixture was stirred for 30 min until the suspension completely dissolved and the solution was adjusted to the pH 6 by the addition of aqueous solution of NaOAc. After half one hour later, KSeCN (217mg, 1.5mmol) was added to the solution and the reaction mixture was stirred for another 3 hours. The mixture was filtered to get a brown yellow solid **5,** which was used in next step without further purification. Yield: 88%.

*1.5. Synthesis procedure of 1-(3,4-dimethoxy-5-(methylselanyl)phenyl)ethan-1-one (**6**)*

To a solution of **5** (285mg, 1.0mmol) in 10ml of MeOH, $NaBH_4$ (38mg, 1.0 mmol) and CH_3I (92μL, 1.5 mmol) were added at room temperature in sequence. After stirred 2 minutes, the reaction mixture was diluted with saturated $NaHSO_4$ solution and then extracted with ethyl acetate, the combined extracts were dried, evaporated the solvent and purified by column chromatography (petroleum ether: ethyl acetate/5: 1) to yield the key intermediate **6** as white solid. Yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.60 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.70 (s), 152.07 (s), 150.67 (s), 133.77 (s), 127.80 (s), 121.24 (s), 109.95 (s), 60.17 (s), 56.03 (s), 26.42 (s), 5.14 (s).

*1.6. General procedure for the preparation of **12**, **13** and **14**.*

To a stirred solution of ketone **6** (137 mg, 0.5 mmol) and aldehyde **7** or **8**, **10** and **11** (0.5 mmol), which were synthesized according to a literature method,[1-2] in methanol (8 mL), piperidine (151μL, 1.5mmol) and HOAc (2ml) was added and the resulting mixture was stirred at 95°C for 36-48h. On completion, the slurry was partitioned between water and ethyl acetate, and the mixture was extracted with ethyl acetate (twice). The organic phase were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography (petroleum ether: ethyl acetate=8:1) on silica gel, and then crystallized from ethyl acetate to give target compounds **12**, **13** and **14**).

*1.6.1. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (**12a**)*

Yellow solid, yield: 52%. mp:191.1°C -192.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.10 (d, *J* = 15.5 Hz, 1H), 7.99 (s, 1H), 7.63 (s, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.47 (s, 2H), 7.32 (s, 2H), 3.95 (d, *J* = 3.6 Hz, 6H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.81 (s, 2H), 152.19 (s, 2H), 149.96 (s, 1H), 139.00 (s, 3H), 137.29 (s, 2H), 135.71 (s, 1H), 130.33 (s, 4H), 127.70 (s, 2H), 125.39 (s, 2H), 123.59 (s, 4H), 121.85 (s, 3H), 120.78 (s, 3H), 120.56 (s, 4H), 117.81 (s, 4H), 114.49 (s, 2H), 112.07 (s, 4H), 110.31 (s, 3H), 60.24 (s, 2H), 56.11 (s, 3H), 5.25 (s, 2H). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{19}NO_3Se$, 402.0604; found, 402.0612. Purity: 98.5% (by HPLC).

*1.6.2. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1-methyl-1H-indol-3-yl)prop-2-en-1-one (**12b**)*

Yellow solid, yield: 44%. mp:153.9°C -154.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 15.5 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 3H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.36 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.33 (dd, *J* = 6.7, 1.5 Hz, 1H), 3.98 (s, 6H), 3.86 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.51 (s), 152.17 (s), 149.97 (s), 138.65 (s), 138.32 (s), 135.85 (s), 134.47 (s), 127.57 (s), 126.20 (s), 123.22 (s), 121.64 (s), 120.83 (s), 120.65 (s), 116.99 (s), 113.03 (s), 110.41 (s), 110.19 (s), 60.20 (s), 56.12 (s), 33.29 (s), 5.24 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{21}NO_3Se$, 416.0761; found, 416.0770. Purity: 98.5% (by HPLC). Purity: 99.7% (by HPLC).

*1.6.3. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(4-methoxy-1H-indol-3-yl)prop-2-en-1-one (**12c**)*

Yellow solid, yield: 56%. mp:162.5°C -163.4°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.45 (d, *J* = 15.7 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.53 (d, *J* = 15.8 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.45 (s), 154.80 (s), 152.13 (s), 149.87 (s), 140.65 (s), 138.45 (s), 135.80 (s), 127.43 (s), 125.73 (s), 124.27 (s), 121.12 (s), 119.01 (s), 116.08 (s), 115.01 (s), 110.53 (s), 105.02 (s), 101.89 (s), 60.21 (s), 56.05 (s), 55.35 (s), 5.22 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{21}NO_4Se$, 432.0710; found, 432.0708. Purity: 97.2% (by HPLC).

*1.6.4. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(4-methoxy-1-methyl-1H-indol-3-yl)prop-2-en-1-one (**12d**)*

Yellow solid, yield: 60%. mp:138.8°C -140.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 15.7 Hz, 1H), 7.54 (d, *J* = 1.7 Hz, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 1.5 Hz, 1H), 7.45 (d, *J* = 12.3 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 3.83 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.15 (s), 154.84 (s), 152.09 (s), 149.74 (s), 140.49 (s), 139.43 (s), 135.92 (s), 130.05 (s), 127.32 (s), 123.87 (s), 121.03 (s), 118.10 (s), 116.64 (s), 113.49 (s), 110.50 (s), 103.19 (s), 101.81 (s), 60.18 (s), 56.04 (s), 55.37 (s), 33.56 (s), 5.22 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{23}NO_4Se$, 446.0866; found, 446.0869. Purity: 98.2% (by HPLC).

*1.6.5. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(5-methoxy-1H-indol-3-yl)prop-2-en-1-one (**12e**)*

Yellow solid, yield: 41%. mp:201.7°C -202.5°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.11 (d, *J* = 15.5 Hz, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 15.7 Hz, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.74 (s), 155.68 (s), 152.18 (s), 149.86 (s), 139.12 (s), 135.73 (s), 132.14 (s), 130.46 (s), 127.82 – 127.25 (m), 126.15 (s), 120.59 (s), 117.12 (s), 114.43 – 113.93 (m), 113.40 (s), 112.74 (s), 110.22 (s), 102.69 (s), 60.24 (s), 56.05 (s), 55.85 (s), 5.11 (s). HRMS

(ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{21}H_{21}NO_4Se$, 432.0710; found, 432.0711. Purity: 99.0% (by HPLC).

*1.6.6. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(5-methoxy-1-methyl-1H-indol-3-yl)prop-2-en-1-one (**12f**)*

Yellow solid, yield: 55%. mp:168.5°C -169.9°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 15.5 Hz, 1H), 7.51 (d, *J* = 1.1 Hz, 1H), 7.47 (d, *J* = 1.4 Hz, 1H), 7.46 (s, 1H), 7.40 (d, *J* = 3.0 Hz, 1H), 7.38 (d, *J* = 10.3 Hz, 1H), 7.26 (d, *J* = 2.9 Hz, 1H), 6.98 (dd, *J* = 8.9, 2.1 Hz, 1H), 3.95 (s, 6H), 3.92 (s, 3H), 3.82 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.49 (s), 155.70 (s), 152.16 (s), 149.75 (s), 138.84 (s), 135.89 (s), 134.52 (s), 133.36 (s), 127.59 (s), 126.90 (s), 120.51 (s), 116.17 (s), 112.99 (s), 112.55 (s), 110.98 (s), 110.19 (s), 102.82 (s), 60.21 (s), 56.05 (s), 55.87 (s), 33.54 (s), 5.11 (s). HRMS (ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{22}H_{23}NO_4Se$, 446.0866; found, 446.0865. Purity: 95.8% (by HPLC).

*1.6.7. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(6-methoxy-1H-indol-3-yl)prop-2-en-1-one (**12g**)*

Yellow solid, yield: 39%. mp:179.5°C -180.5°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.04 (d, *J* = 15.5 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.52 (s, 1H), 7.50 (s, 1H), 7.48 (d, *J* = 13.8 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.92 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.95 (s), 157.27 (s), 152.17 (s), 149.91 (s), 139.28 (s), 138.37 (s), 135.76 (s), 129.95 (s), 127.73 (s), 121.18 (s), 120.73 (s), 119.43 (s), 117.40 (s), 114.51 (s), 111.41 (s), 110.28 (s), 95.60 (s), 60.25 (s), 56.10 (s), 55.67 (s), 5.25 (s). HRMS (ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{21}H_{21}NO_4Se$, 432.0710; found, 432.0716. Purity: 97.8% (by HPLC).

*1.6.8. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(6-methoxy-1-methyl-1H-indol-3-yl)prop-2-en-1-one (**12h**)*

Yellow solid, yield: 48%. mp:166.0°C -167.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 15.5 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 7.42 (d, *J* = 15.5 Hz, 1H), 7.38 (s, 1H), 6.96 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 3.95 (s, 6H), 3.91 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.58 (s), 157.19 (s), 152.15 (s), 149.83 (s), 139.30 (s), 138.82 (s), 135.90 (s), 134.08 (s),

127.57 (s), 121.39 (s), 120.69 (s), 120.18 (s), 116.70 (s), 113.13 (s), 110.97 (s), 110.28 (s), 93.97 (s), 60.22 (s), 56.11 (s), 55.76 (s), 33.33 (s), 5.26 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{23}NO_4Se$, 446.0866; found, 446.0853. Purity: 98.6% (by HPLC).

*1.6.9. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1H-indol-4-yl)prop-2-en-1-one (**13a**)*

Yellow solid, yield: 67%. mp:131.7°C -132.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.24 (d, *J* = 15.7 Hz, 1H), 7.66 (d, *J* = 15.6 Hz, 1H), 7.55 (s, 1H), 7.49 (t, *J* = 7.2 Hz, 3H), 7.35 (s, 1H), 7.25 (d, *J* = 2.7 Hz, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.65 (s), 152.22 (s), 150.32 (s), 143.97 (s), 136.41 (s), 135.23 (s), 127.87 (s), 127.39 (s), 127.12 (s), 125.84 (s), 122.14 (s), 122.07 (s), 121.11 (s), 120.89 (s), 113.69 (s), 110.49 (s), 101.40 (s), 60.25 (s), 56.11 (s), 5.25 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{19}NO_3Se$, 402.0604; found, 402.0617. Purity: 98.0% (by HPLC).

*1.6.10. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1-methyl-1H-indol-4-yl)prop-2-en-1-one (**13b**)*

Yellow solid, yield: 59%. mp:130.3°C -131.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 15.7 Hz, 1H), 7.62 (d, *J* = 15.7 Hz, 1H), 7.50 (s, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 2.8 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.57 (s), 152.20 (s), 150.21 (s), 143.89 (s), 137.27 (s), 135.25 (s), 130.42 (s), 127.94 (s), 127.83 (s), 127.16 (s), 122.10 (s), 121.60 (s), 120.98 (s), 120.51 (s), 111.81 (s), 110.38 (s), 99.77 (s), 60.25 (s), 56.11 (s), 33.12 (s), 5.25 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{21}NO_3Se$, 416.0761; found, 416.0766. Purity: 99.4% (by HPLC).

*1.6.11. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1H-indol-5-yl)prop-2-en-1-one (**14a**)*

Yellow solid, yield: 50%. mp:150.3°C -151.8°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.99 (d, *J* = 15.5 Hz, 1H), 7.93 (s, 1H), 7.59 – 7.52 (m, 2H), 7.48 (d, *J* = 4.8 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.27 (s, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 3H), 3.96 – 3.90 (m, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.56 (s), 152.19 (s), 150.26 (s), 147.17 (s), 137.37 (s), 135.40 (s), 128.34 (s), 127.73 (s), 126.98 (s),

125.52 (s), 123.04 (s), 122.03 (s), 121.14 (s), 119.13 (s), 111.73 (s), 110.51 (s), 103.60 (s), 60.23 (s), 56.12 (s), 5.33 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{19}NO_3Se$, 402.0604; found, 402.0612. Purity: 99.4% (by HPLC).

*1.6.12. (E)-1-(3,4-dimethoxy-5-(methylselanyl)phenyl)-3-(1-methyl-1H-indol-5-yl)prop-2-en-1-one (**14b**)*

Yellow solid, yield: 57%. mp:142.7°C -143.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 15.5 Hz, 1H), 7.90 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 3.95 (s, 6H), 3.81 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.42 (s), 152.17 (s), 150.13 (s), 147.19 (s), 138.13 (s), 135.45 (s), 130.21 (s), 128.83 (s), 127.71 (s), 126.43 (s), 123.25 (s), 121.62 (s), 120.99 (s), 118.86 (s), 110.39 (s), 109.86 (s), 102.21 (s), 60.24 (s), 56.12 (s), 33.05 (s), 5.34 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{21}NO_3Se$, 416.0759; found, 416.0761. Purity: 99.2% (by HPLC).

*1.7. Synthesis procedure of 4-bromo-2-methoxyphenol (**16**)*

To a solution of 2-methoxyphenol (**15**, 1.24g, 10.0mmol) and NBS (2.13g, 12.0mmol) in CH3CN at 0 °C for 4h. After the reaction, the solvent diluted with Na_2SO_3 aqueous solution and then extracted with ethyl acetate, the combined extracts were dried. The solvent evaporated and the residue purified by column chromatography (petroleum ether: ethyl acetate=10: 1) to yield 16 as colorless oil, yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 5.1, 2.1 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 5.84 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.34 (s), 144.86 (s), 124.16 (s), 115.90 (s), 114.26 (s), 111.65 (s), 56.17 (s).

*1.8. Synthesis procedure of 4-bromo-2-methoxy-6-nitrophenol (**17**)*

Intermediate **17** were obtained by the same procedure as compound **2**. Yellow solid, yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.12 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.76 (s), 145.74 (s), 134.08 (s), 120.79 (s), 118.15 (s), 110.89 (s), 57.01 (s).

*1.9. Synthesis procedure of 5-bromo-1,2-dimethoxy-3-nitrobenzene (**18**)*

Intermediate **18** were obtained by the same procedure as compound **3**. Colorless oil, yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H).

*1.10. Synthesis procedure of 5-bromo-2,3-dimethoxyaniline (**19**)*

Intermediate **19** were obtained by the same procedure as compound**4**. White solid, yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.45 (s, 1H), 3.88 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.38 (s), 140.67 (s), 133.77 (s), 115.68 (s), 110.50 (s), 104.73 (s), 58.84 (s), 54.90 (s).

*1.11. Synthesis procedure of 5-bromo-1,2-dimethoxy-3-selenocyanatobenzene (**20**)*

Intermediate **20** were obtained by the same procedure as compound **5**. Brown yellow solid, yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.56 (s), 144.02 (s), 122.79 (s), 120.33 (s), 118.09 (s), 116.27 (s), 100.99 (s), 60.80 (s), 56.28 (s).

*1.12. Synthesis procedure of (5-bromo-2,3-dimethoxyphenyl)(methyl)selane (**21**)*

Intermediate **21** were obtained by the same procedure as compound **6**. White solid, yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.75 (s), 145.34 (s), 129.63 (s), 121.87 (s), 117.29 (s), 113.31 (s), 60.00 (s), 56.09 (s), 5.03 (s).

*1.13. General procedure for the preparation of **23**.*

To a solution of (5-bromo-2,3-dimethoxyphenyl)(methyl)selane **21** (310mg, 1.0 mmol) in 20mL of anhydrous THF in nitrogen atmosphere at -78°C, n-butyllithium (0.8mL, 2.5M in hexane) was added in dropwise. After the solution was stirred for 0.5h, **22a-22c**, which were synthesized according to literature methods, [3] was added, and then the reaction mixture was stirred for overnight in darkness. A saturated NH_4Cl solution was added and the mixture was extracted by ethyl acetate. The solvent was evaporated and the crude product was purified by flash column chromatography to get colorless oil **23**.

*1.13.1. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-indol-3-yl)methanol (**23a**)*

Colorless oil, yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 4.0 Hz, 2H), 7.43 (d, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 17.8 Hz, 2H), 5.96 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.16 (s, 3H).

*1.13.2. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-indol-4-yl)methanol (**23b**)*

Colorless oil, yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.53 (d, *J* = 3.8 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 6.78 – 6.71 (m, 3H), 6.02 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.08 (s, 3H).

*1.13.3. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-inden-5-yl)methanol (**23c**)*

Colorless oil, yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 3.7 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.31 (dd, *J* = 8.6, 1.4 Hz, 1H), 6.76 (d, *J* = 10.2 Hz, 2H), 6.62 (d, *J* = 3.6 Hz, 1H), 5.81 (d, *J* = 2.5 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.17 (s, 3H).

*1.14. General procedure for the preparation of **24**.*

The colorless oil **23** was dissolved in THF, and IBX (1.2eq) was added. After stirred for 2 days, the mixture was diluted with ethyl acetate and water, the organic phase was separated, washed with saturated NaCl solution (twice) and dried with anhydrous sodium sulfate. The solvent was removed in vacuum, and the residue was purified by flash column chromatography (petroleum ether: ethyl acetate=8:1) to afford compounds **24**.

*1.14.1. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-indol-3-yl)methanone (**24a**)*

White oil, yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.5 Hz, 1H), 8.01 – 7.91 (m, 2H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.24 (d, *J* = 7.7 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 188.32 (s), 151.14 (s), 148.90 (s), 136.59 (s), 134.42 (s), 134.04 (s), 133.59 (s), 131.94 (s), 128.63 (s), 127.49 (s), 127.24 (s), 126.01 (s), 125.09 (s), 123.90 (s), 121.89 (s), 120.19 (s), 119.50 (s), 112.18 (s), 109.76 (s), 59.20 (s), 55.06 (s), 3.99 (s).

*1.14.2. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-indol-4-yl)methanone (**24b**)*

White oil, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 3.7 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.95 (s), 151.93 (s), 150.12 (s), 138.09 (s), 135.47 (s), 134.14 (s), 130.48 (s), 129.45 (s), 128.09 (s), 126.84 (s), 126.39 (s), 123.72 (s), 122.75 (s), 120.31 (s), 117.23 (s), 113.57 (s), 111.69 (s), 109.28 (s), 102.01 (s), 60.22 (d, J = 4.0 Hz), 56.06 (s), 4.98 (s).

*1.14.3. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-(phenylsulfonyl)-1H-indol-5-yl)methanone (**24c**)*

White oil, yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.14 (d, J = 10.7 Hz, 2H), 6.68 (d, J = 3.6 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.30 (s), 151.91 (s), 149.85 (s), 138.00 (s), 136.97 (s), 134.30 (s), 134.23 (s), 133.21 (s), 130.35 (s), 129.47 (s), 127.76 (s), 127.72 (s), 126.87 (s), 126.48 (s), 124.26 (s), 122.55 (s), 113.21 (s), 111.77 (s), 109.61 (s), 60.21 (s), 56.11

*1.15. General procedure for the preparation of **25**.*

To a solution of **24a-24c** (51.5mg, 0.1mmol) in 10mL of methanol, NaOH (12mg, 0.3mmol) was added and the reaction was stirred for 3h. The mixture was extracted with ethyl acetate (twice) and the organic phase was washed with saturated brine (twice) and dried over Na_2SO_4. The solvent was evaporated in vacuum and the crude product was purified by column chromatography (petroleum ether: ethyl acetate/5:1) over silica gel to give the target compounds **25**.

1.15.1. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1H-indol-3-yl)methanone

(25a)

White soild, yield: 77%. mp:217.6°C -218.9°C. ^{1}H NMR (400 MHz, DMSO) δ 8.25 (dd, *J* = 6.5, 1.9 Hz, 1H), 8.09 (s, 1H), 7.53 (dd, *J* = 6.6, 1.7 Hz, 1H), 7.28 (d, *J* = 1.4 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.20 (d, *J* = 1.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 189.14 (s), 151.97 (s), 147.94 (s), 137.69 (s), 137.02 (s), 136.04 (s), 127.78 (s), 126.78 (s), 123.62 (s), 122.36 (s), 121.90 (s), 119.71 (s), 115.32 (s), 112.66 (s), 110.97 (s), 59.95 (s), 56.36 (s), 4.74 (s). HRMS (ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{18}H_{17}NO_3Se$, 376.0447; found, 376.0441. Purity: 98.9% (by HPLC).

1.15.2. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1H-indol-4-yl)methanone

(25b)

White soild, yield: 71%. mp:139.5°C -140.4°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.30 (m, 3H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.23 (s), 151.84 (s), 149.65 (s), 136.65 (s), 135.39 (s), 129.33 (s), 127.53 (s), 127.35 (s), 126.43 (s), 124.32 (s), 122.69 (s), 120.77 (s), 115.55 (s), 111.88 (s), 103.55 (s), 60.21 (s), 56.05 (s), 4.97 (s). HRMS (ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{18}H_{17}NO_3Se$, 376.0447; found, 376.0442. Purity: 98.7% (by HPLC).

1.15.3. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1H-indol-5-yl)methanone

(25c)

White soild, yield: 69%. mp:160.0°C -161.2°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.16 (s, 1H), 7.76 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.27 (d, *J* = 0.7 Hz, 2H), 6.66 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.20 (s), 151.83 (s), 149.34 (s), 138.31 (s), 135.43 (s), 129.80 (s), 127.50 (s), 127.26 (s), 125.81 (s), 124.99 (s), 124.23 (s), 122.35 (s), 111.87 (s), 110.97 (s), 104.25 (s), 60.18 (s), 56.08 (s), 5.03 (s). HRMS (ESI) (*m/z*) [M+H] $^{+}$ calcd for $C_{18}H_{17}NO_3Se$, 376.0447; found, 376.0438. Purity: 98.7% (by HPLC).

1.16. Synthesis procedure of (3,4-dimethoxy-5-(methylselanyl)phenyl) -(1-methyl-1H-indol-4-yl)methanol (26)

Intermediate **26** was obtained by the same procedure as compound **23**.Colorless oil, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 3.0 Hz, 1H), 6.90 (d, *J* = 16.6 Hz, 2H), 6.53 (d, *J* = 2.9 Hz, 1H), 6.15 (s, 1H), 3.81 (s, 3H), 3.77 (s, 6H), 2.18 (s, 3H).

1.17. (3,4-dimethoxy-5-(methylselanyl)phenyl)(1-methyl-1H-indol-4-yl)methanone ***(27)***

Compound **27** was obtained by the same procedure as compound **24**. Yellow oil, yield: 83%. 1H NMR (400 MHz, CDCl3) δ 7.56 (d, J = 8.2 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.33 (s, 2H), 7.31 – 7.27 (m, 1H), 7.20 (d, *J* = 3.1 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.03 (s), 151.83 (s), 149.63 (s), 137.50 (s), 135.47 (s), 131.01 (s), 129.43 (s), 127.90 (s), 127.46 (s), 123.86 (s), 122.66 (s), 120.31 (s), 113.52 (s), 111.89 (s), 102.04 (s), 60.19 (s), 56.05 (s), 33.03 (s), 4.98 (s). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd for $C_{19}H_{19}NO_3Se$, 390.0604; found, 390.0595. Purity: 98.3% (by HPLC).

2. Biological Assays[4]

*2.1. Cell Lines and Culture***.**

The human cancer cell lines (A549, HELA, HEPG2, RKO, HCT116, MGC803, MDAMB231) used in this study were purchased from the Laboratory Animal Service Center at Sun Yat-sen University (Guangzhou, China). Cell lines A549, HELA, RKO, and MDAMB231 were cultivated in DMEM containing 10% (v/v) heat-inactivated fetal bovine serum (FBS), 100 units/mL penicillin, and 100 μg/mL streptomycin. Cell lines HCT116 and HEPG2 were cultivated in RPMI 1640 medium containing 10% (v/v) heat-inactivated FBS, 100 units/mL penicillin, and 100 mg/mL streptomycin. The cells were incubated at 37 °C under a 5% CO_2 and 90% relative humidity (RH) atmosphere.

2.2. **MTT Assay.**

Cells grownin the logarithmic phase were seeded into 96-well plates (5× 10^3 cells/well) for 24 h, and then exposed to different concentrations of the test compounds for 48 h. After attached cells were incubated with 5 mg/mL MTT (Sigma, USA) for another 4 h, the suspension was discarded, and subsequently the dark blue crystals (formazan) were solubilized in dimethyl

sulfoxide (DMSO). The absorbance of the solution at 570 nm was measured using a multifunction microplate reader (Molecular Devices, Flex Station 3), and each experiment was performed at least in triplicate. IC_{50} values, which represent the drug concentrations required to cause 50% cancer cell growth inhibition, were used to express the cytotoxic effects of each compound and were calculated with GraphPad Prism Software version 5.02 (GraphPad Inc., La Jolla, CA, USA).

2.3. In vitro Tubulin Polymerization

Assay. A tubulin polymerization assay was performed by measuring the increase in fluorescence intensity, which can be easily recorded due to the incorporation of a fluorescent reporter, DAPI (4′,6-diamidino-2-phenylindole), a fluorophore that is known to be a DNA intercalator. A commercial kit (cytoskeleton, cat. #BK011P) was used for the tubulin polymerization. The final buffer used for tubulin polymerization contained 80.0 mM piperazine-N, N′-bis(2-ethanesulfonic acid) sequisodium salt (pH 6.9), 2.0 mM MgCl2, 0.5 mM EGTA, 1 mM GTP, and 10.2% glycerol. First, 5 μL of the tested compounds at the indicated concentrations was added, and the mixture was warmed to 37 °C for 1 min; then, the reaction was initiated by the addition of 55 μL of the tubulin solution. The fluorescence intensity enhancement was recorded every 60 sec for 90 min in a multifunction microplate reader (Molecular Devices, Flex Station 3) (emission wavelength at 410 nm, excitation wavelength at 340 nm). The area under the curve was used to determine the concentration that inhibited tubulin polymerization by 50% (IC_{50}) and was calculated using GraphPad Prism Software version 5.02 (GraphPad Inc., La Jolla, CA, USA).

2.4. Immunofluorescence Microscopy.

In a 10 mm confocal culture dish, 3×10^4 cells were grown for 24 h and then incubated in the presence/absence of compound **25b** at the indicated concentrations for another 12 h. After being washed with phosphate-buffered solution (PBS) and fixed in 4% pre-warmed (37 °C) paraformaldehyde for 15 min, the cells were permeabilized with 0.5% Triton X-100 for 15 min and blocked for 30 min in 10% goat serum. Then, the cells were incubated with mouse anti-tubulin antibody (CST, USA) at 4 °C overnight, washed with PBS three times, and incubated with goat anti-mouse IgG/Alexa-Fluor 488 antibody (Invitrogen, USA) for 1 h. The samples were immediately visualized on a Zeiss LSM 570 laser scanning confocal

microscope (Carl Zeiss, Germany) after the nuclei were stained with Hoechst 33342 (Sigma, USA) in the dark at room temperature for 30 min.

2.5. **Cell Cycle Analysis.**

A549 cells were seeded in 6-well plates (3×10^5 cells/well), incubated in the presence/absence of compound **25b** at the indicated concentrations for 24 or 49 h, harvested by centrifugation, and then fixed in ice-cold 70% ethanol overnight. After the ethanol was removed the next day, the cells were re-suspended in ice-cold PBS, treated with RNAse A (Keygen Biotech, China) at 37 °C for 30 min, and then incubated with the DNA staining solution propidium iodide (PI, Keygen Biotech, China) at 4 °C for 30 min. Approximately 10,000 events were detected by flow cytometry (Beckman Coulter, Epics XL) at 488 nm. The data regarding the number of cells in different phases of the cell cycle were analysed using EXPO32 ADC analysis software.

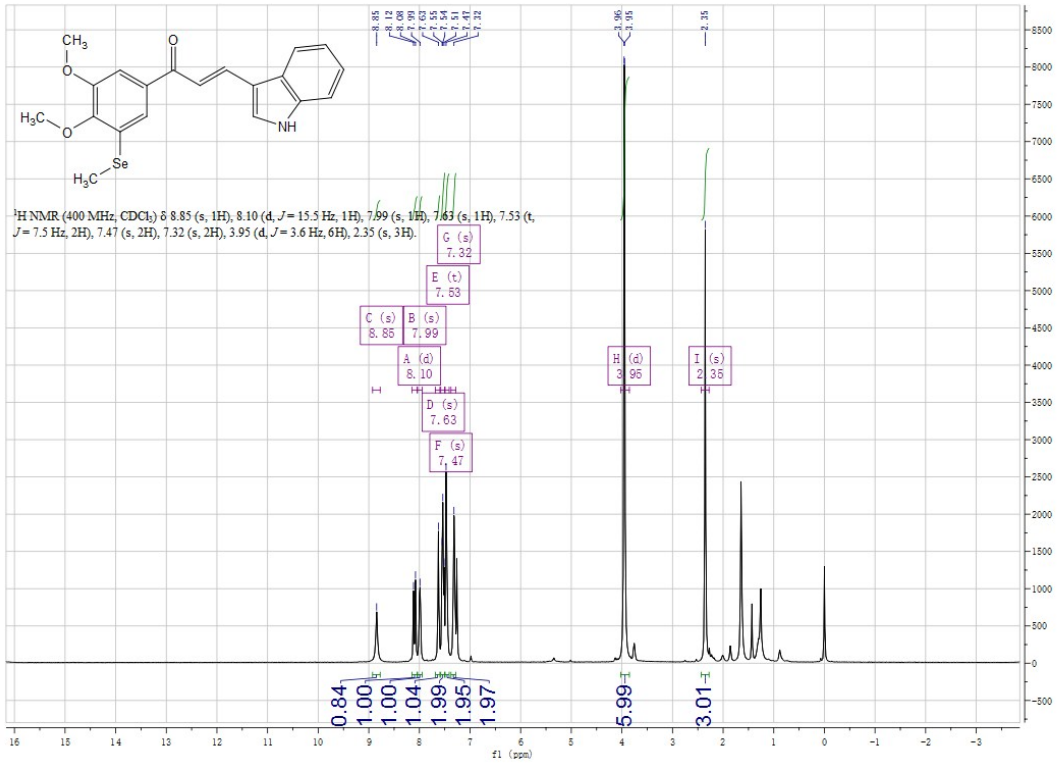
2.6. Effect of 24b on cell apoptosis progression and decreased the mitochondrial membrane potential of A549 cells

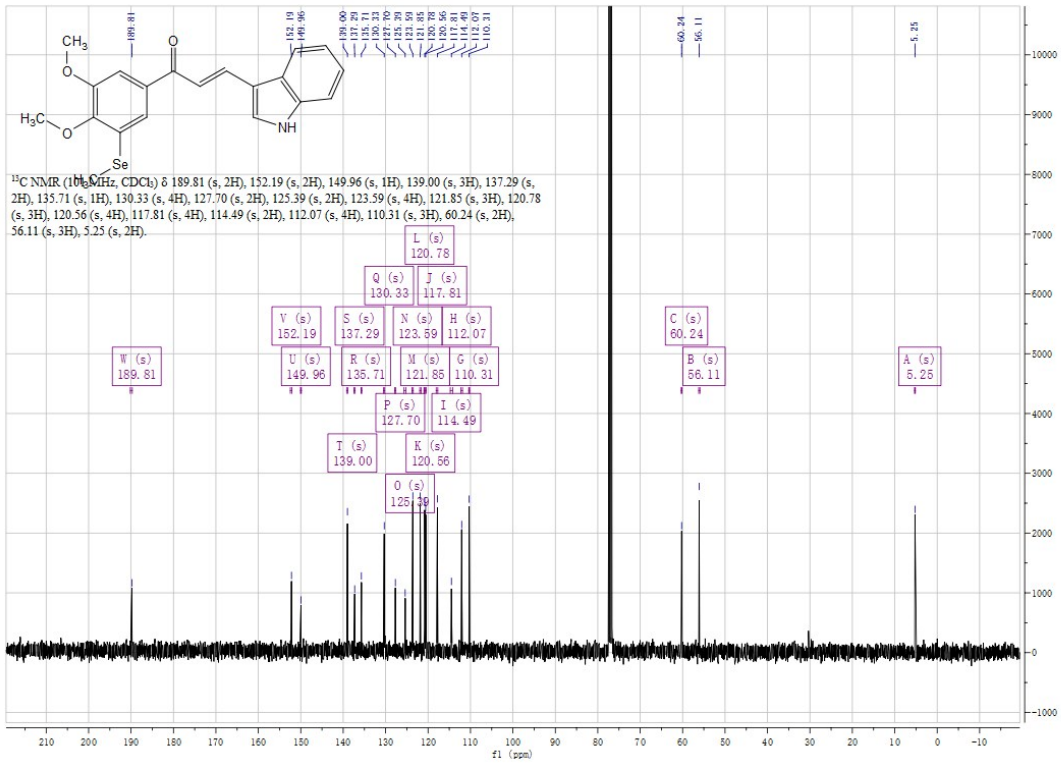
The A549 cell sample was prepared following the same protocols used for the cell cycle analysis. After incubation, cells were harvested and incubated with 5 μL of Annexin-V/FITC (Keygen Biotech, China) in binding buffer (10 mM HEPES, 140 mM NaCl, and 2.5 mM $CaCl_2$ at pH 7.4) at room temperature for 15 min. PI solution was then added to the medium for another 10 min-incubation. Almost 10,000 events were collected for each sample and analysed by flow cytometry (Beckman Coulter, Epics XL). The percentage of apoptotic cells was calculated using EXPO32 ADC Analysis software.

A lipophilic cationic dye, 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethyl-benzimidazolcarbocyanine (JC-1, Beyotime, China) was used to monitor the level of MMP in the cells. At normal state, the MMP is high and JC-1 appears as aggregates, which indicated by red fluorescence. When apoptosis occurs, the MMP reduced and JC-1 displayed as monomers, which indicated by green fluorescence. For the fluorescence microscopy detection, A549 cells were plated in 6-well plates (3×10^5 cells/well) and incubated for 24 h, and treated with **25b** at the indicated concentrations for another 48 h. Then, the cells were stained with 2 μM JC-1 at 37 °C for 30 min, washed with PBS, and then the cell nuclei were stained with Hoechst 33342 (Sigma, USA) for 10 min in the dark. The cell images were immediate detected by a fluorescence microscopy (EVOS FL Auto).

SI1. NMR spectrums of target compounds

12a





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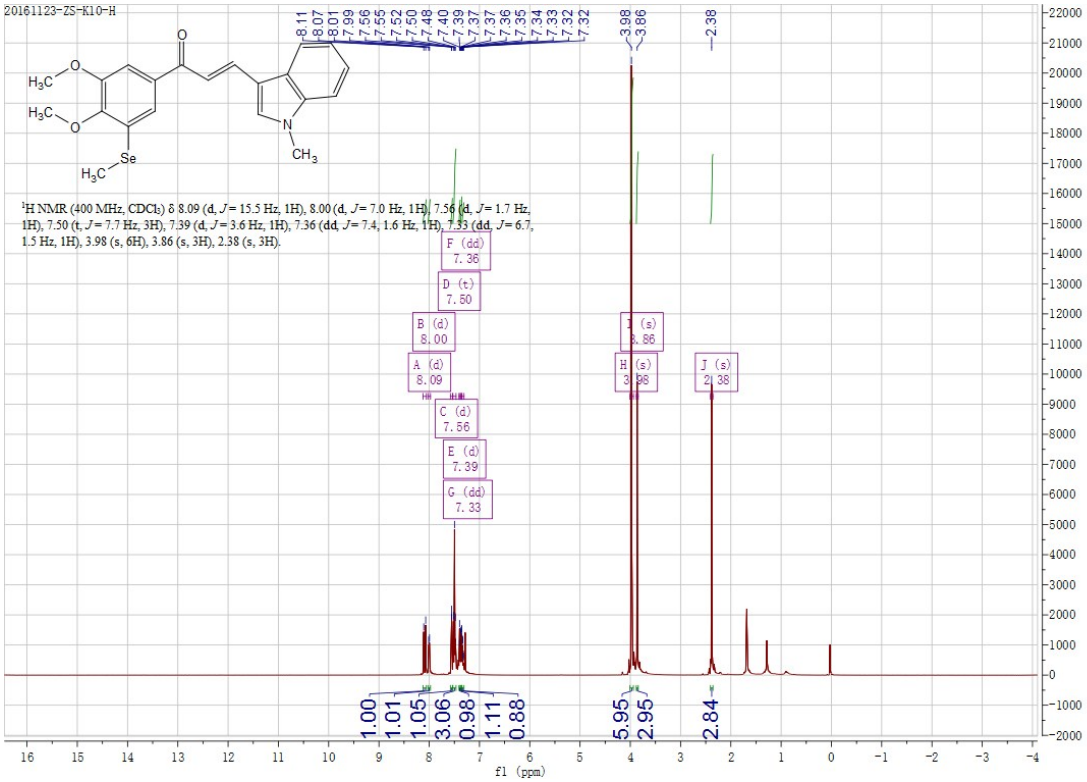
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7.37
7.36
7.35
7.34
7.33
7.32
3.98
3.86
2.38
O
H3C
O
H3C
Se
H3C
N
CH3
1H NMR (400 MHz, CDCl3) δ 8.09 (d, J = 15.5 Hz, 1H), 8.00 (d, J = 7.0 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 3H), 7.39 (d, J = 3.6 Hz, 1H), 7.36 (dd, J = 7.4, 1.6 Hz, 1H), 7.33 (dd, J = 6.7, 1.5 Hz, 1H), 3.98 (s, 6H), 3.86 (s, 3H), 2.38 (s, 3H).
F (dd) 7.36
D (t) 7.50
B (d) 8.00
A (d) 8.09
C (d) 7.56
E (d) 7.39
G (dd) 7.33
I (s) 3.86
H (s) 3.98
J (s) 2.38
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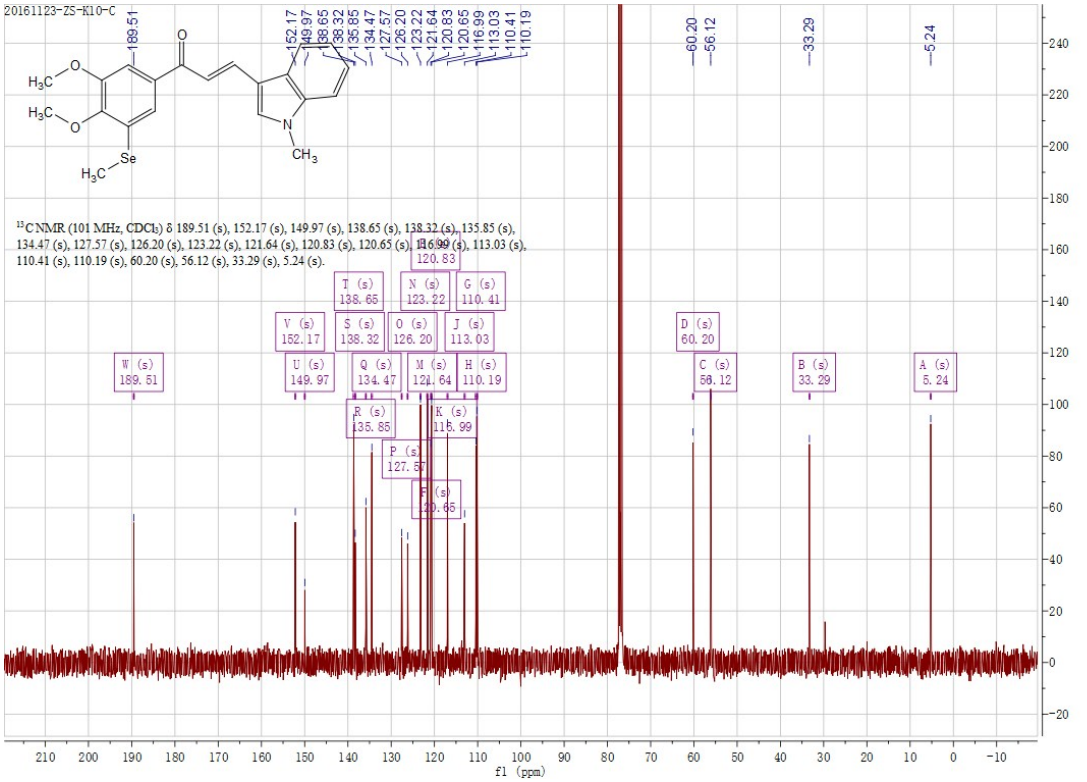
2.95
2.84
f1 (ppm)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120.65
116.99
113.03
110.41
110.19
60.20
56.12
33.29
5.24
O
H3C
O
H3C
Se
H3C
N
CH3
13C NMR (101 MHz, CDCl3) δ 189.51 (s), 152.17 (s), 149.97 (s), 138.65 (s), 138.32 (s), 135.85 (s), 134.47 (s), 127.57 (s), 126.20 (s), 123.22 (s), 121.64 (s), 120.83 (s), 120.65 (s), 116.99 (s), 113.03 (s), 110.41 (s), 110.19 (s), 60.20 (s), 56.12 (s), 33.29 (s), 5.24 (s).
T (s) 138.65
N (s) 123.22
G (s) 110.41
V (s) 152.17
S (s) 138.32
O (s) 126.20
J (s) 113.03
D (s) 60.20
W (s) 189.51
U (s) 149.97
Q (s) 134.47
M (s) 121.64
H (s) 110.19
C (s) 56.12
B (s) 33.29
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P (s) 127.57
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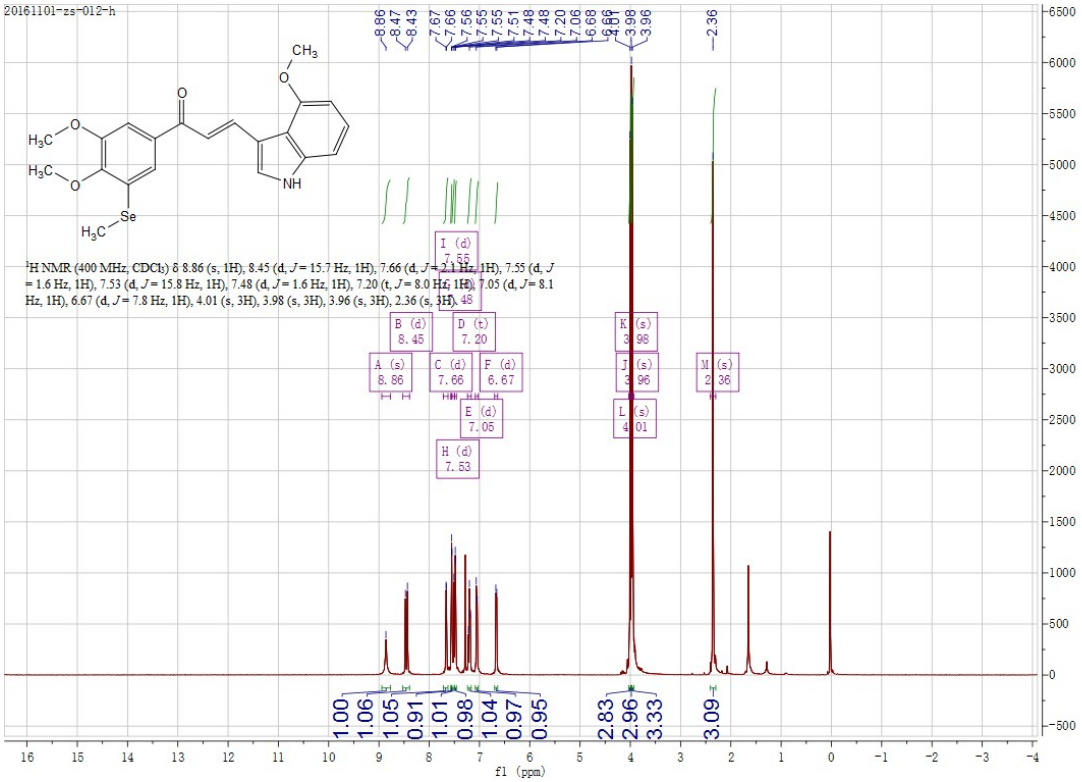
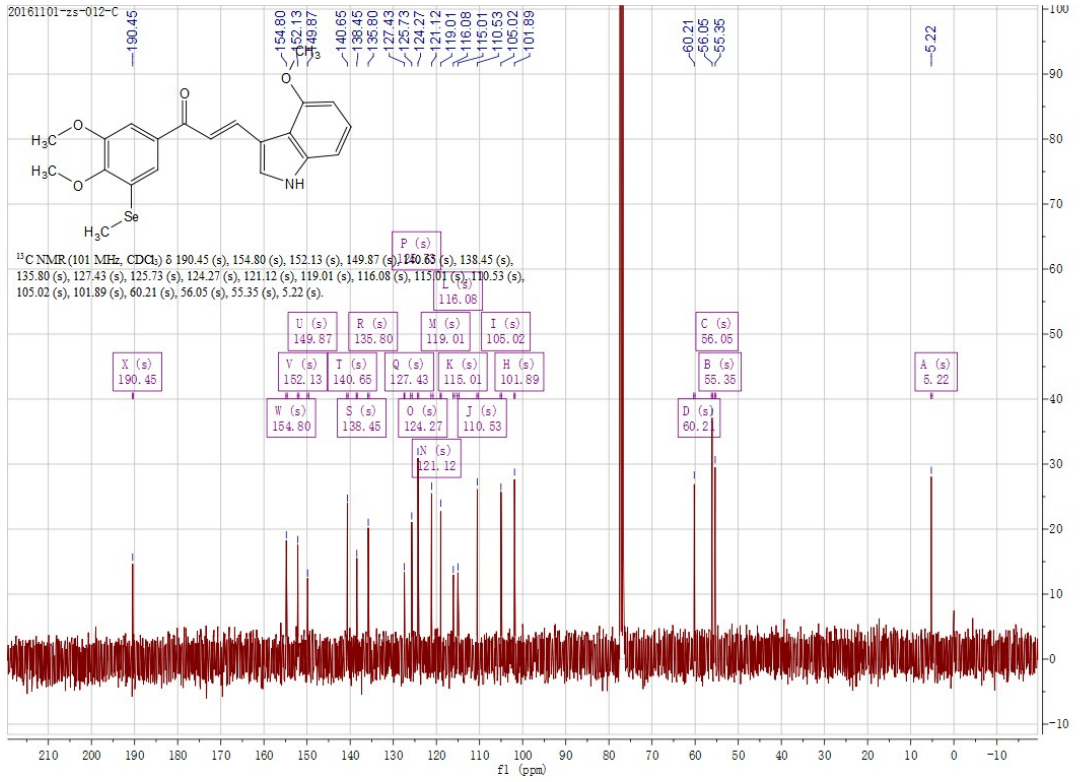
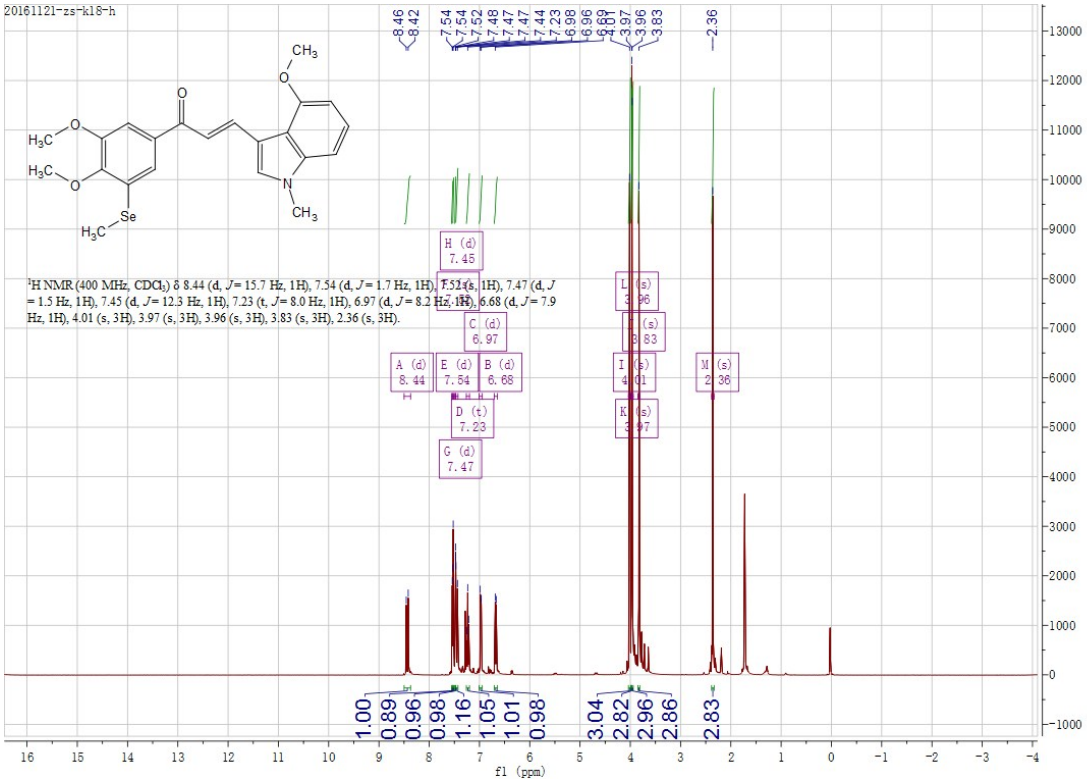
f1 (ppm)

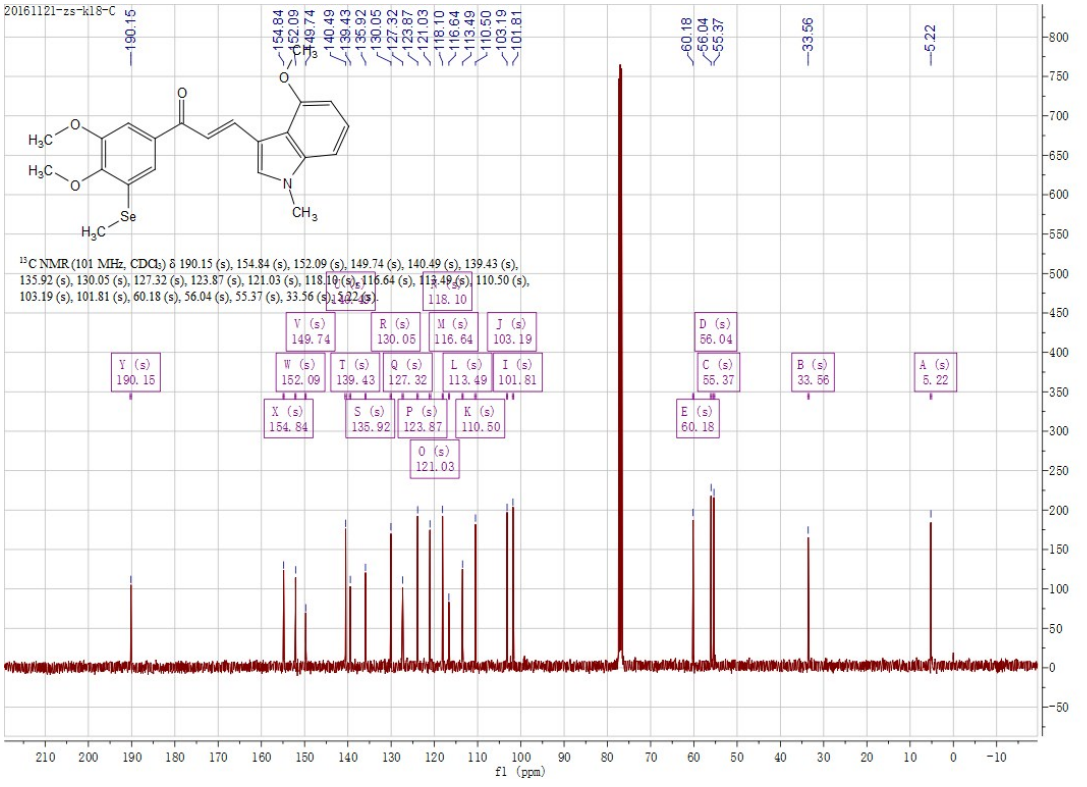
12c


20161101-zs-012-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.86 (s, 1H), 8.45 (d, J = 15.7 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.53 (d, J = 15.8 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 2.36 (s, 3H).
f1 (ppm)

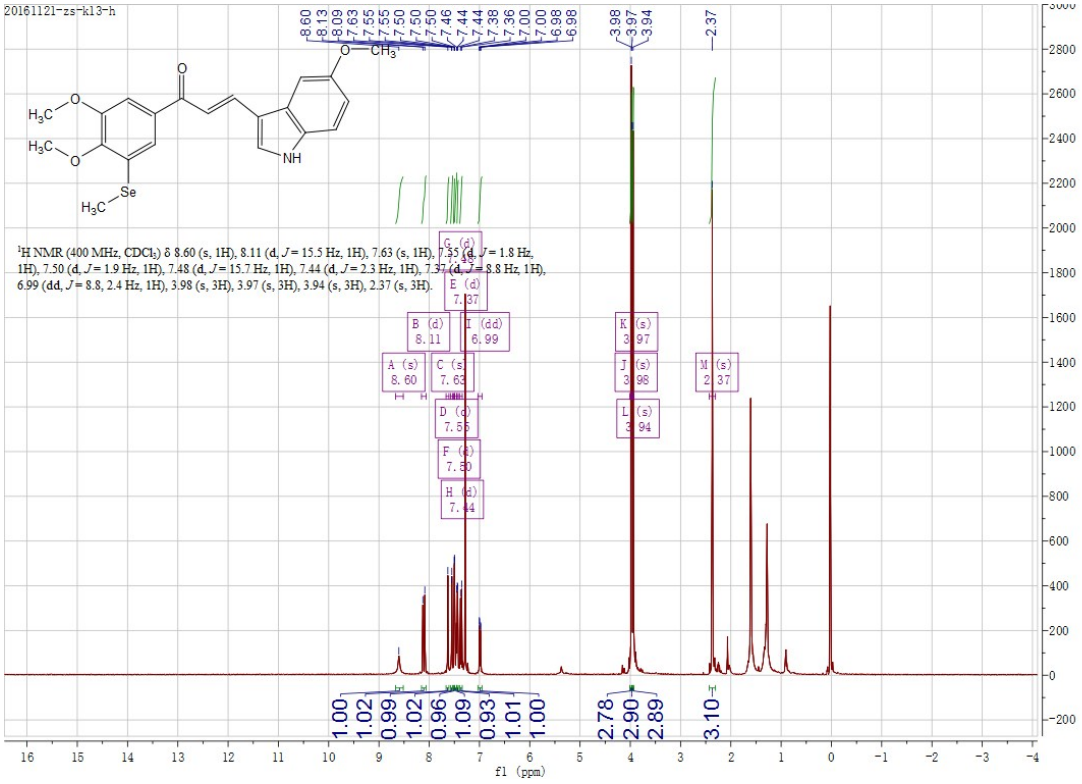

20161101-zs-012-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 190.45 (s), 154.80 (s), 152.13 (s), 149.87 (s), 140.65 (s), 138.45 (s), 135.80 (s), 127.43 (s), 125.73 (s), 124.27 (s), 121.12 (s), 119.01 (s), 116.08 (s), 115.01 (s), 110.53 (s), 105.02 (s), 101.89 (s), 60.21 (s), 56.05 (s), 55.35 (s), 5.22 (s).
f1 (ppm)

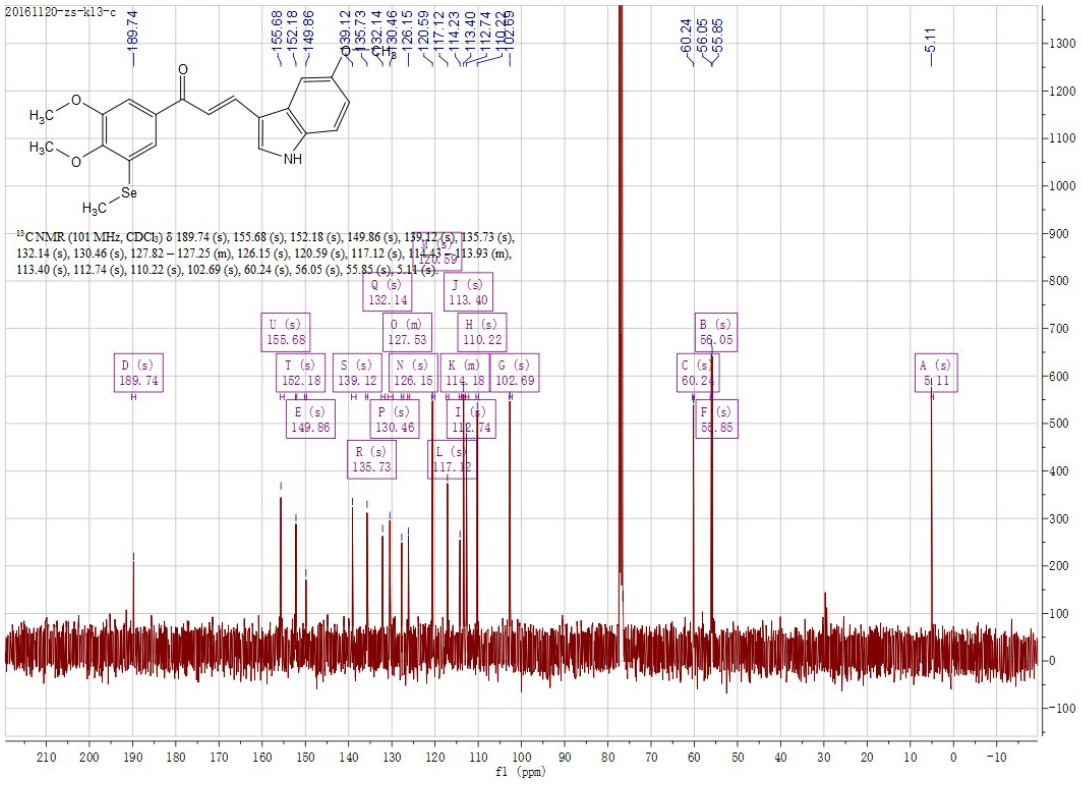
12d


20161121-zs-k18-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.44 (d, J = 15.7 Hz, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.52 (s, 1H), 7.47 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 12.3 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H), 3.83 (s, 3H), 2.36 (s, 3H).
f1 (ppm)

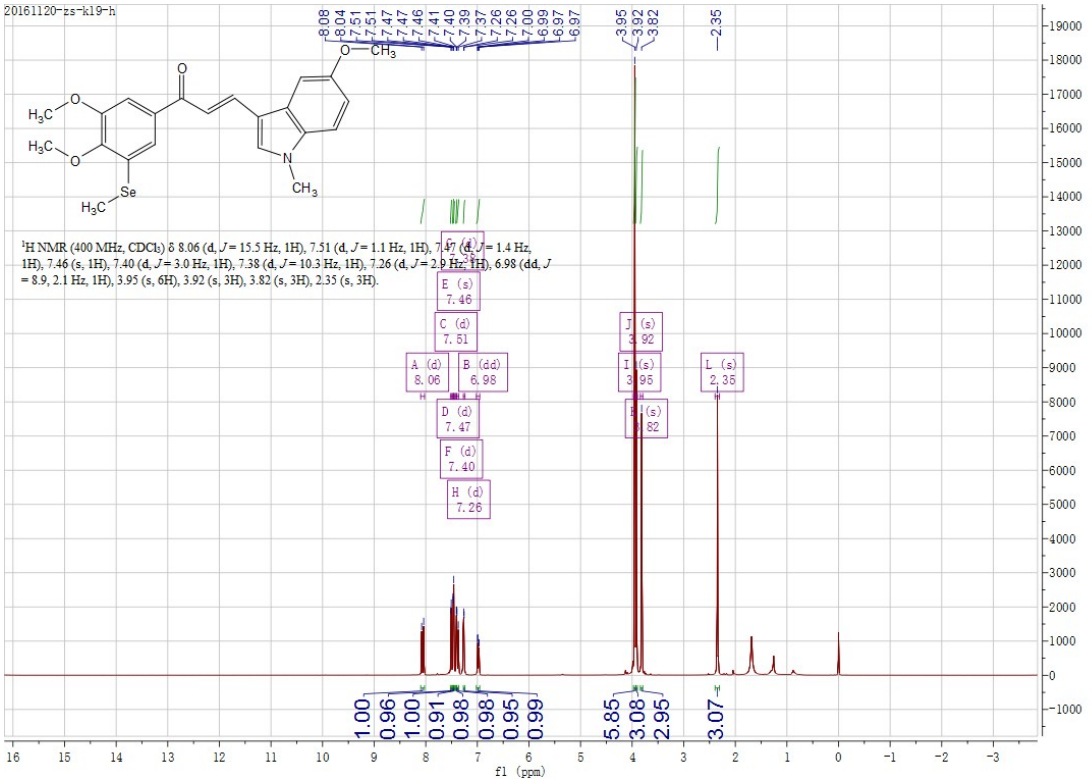

20161121-zs-k18-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 190.15 (s), 154.84 (s), 152.09 (s), 149.74 (s), 140.49 (s), 139.43 (s), 135.92 (s), 130.05 (s), 127.32 (s), 123.87 (s), 121.03 (s), 118.10 (s), 116.64 (s), 113.49 (s), 110.50 (s), 103.19 (s), 101.81 (s), 60.18 (s), 56.04 (s), 55.37 (s), 33.56 (s), 5.22 (s).
f1 (ppm)

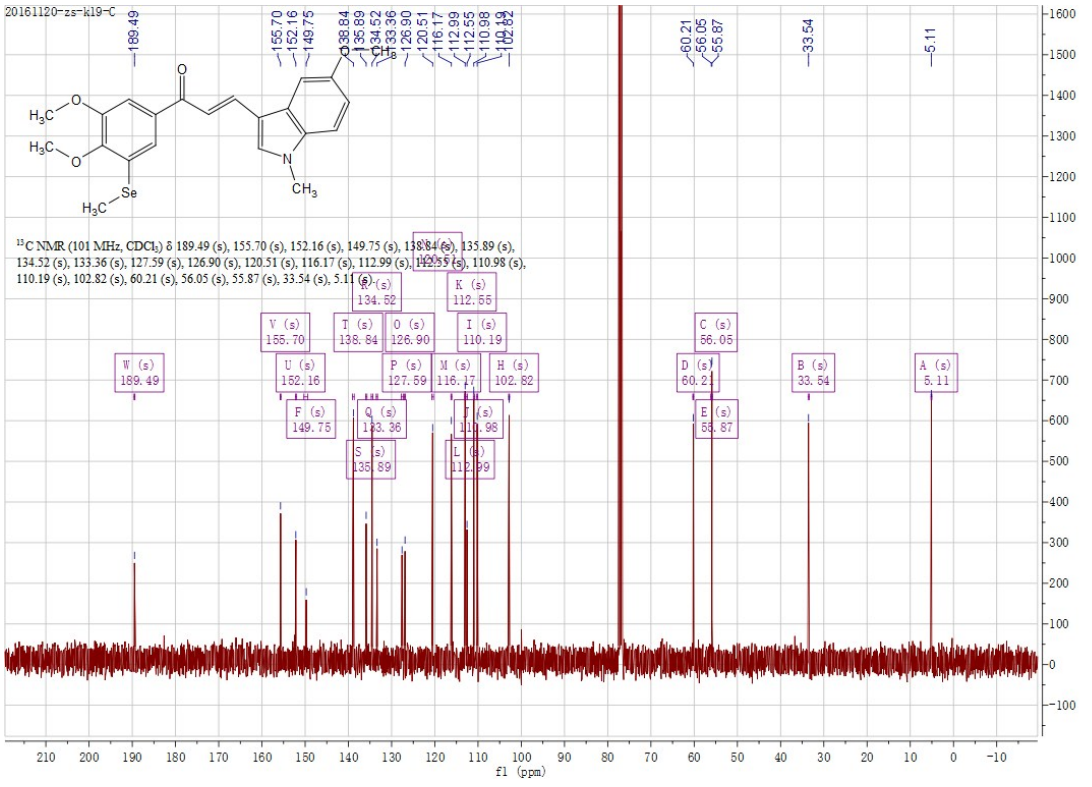
12e


20161121-zs-k13-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.60 (s, 1H), 8.11 (d, J = 15.5 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.48 (d, J = 15.7 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.99 (dd, J = 8.8, 2.4 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 2.37 (s, 3H).
f1 (ppm)

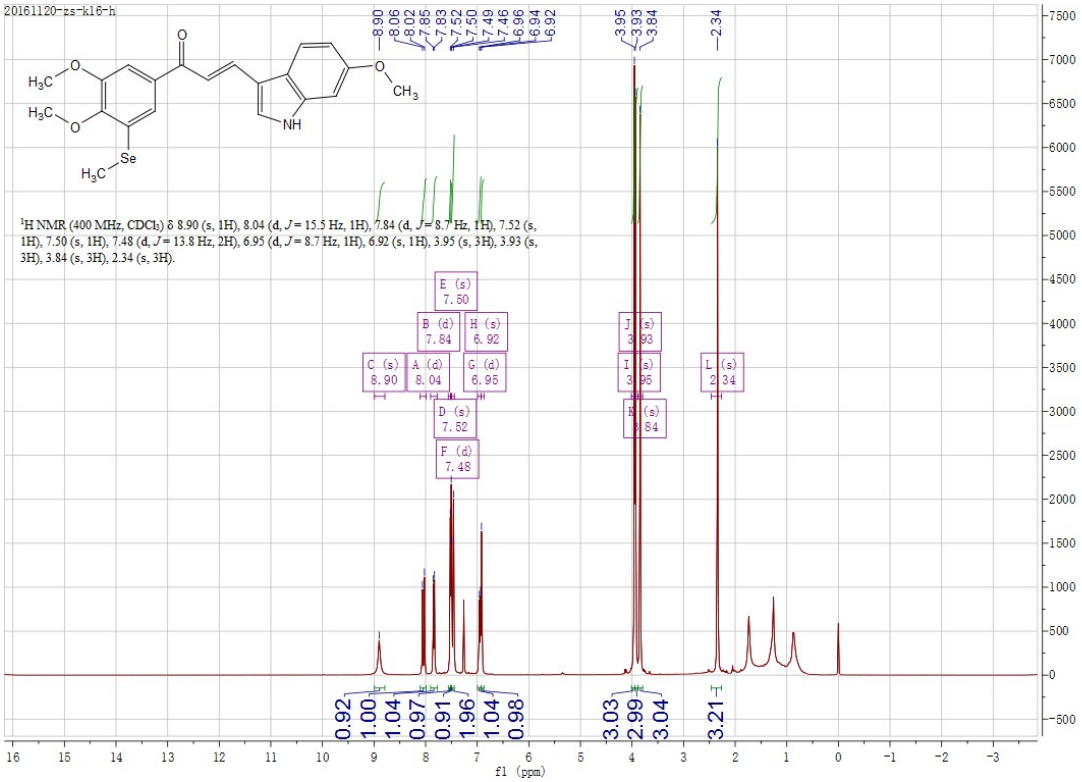

20161120-zs-k13-c
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.74 (s), 155.68 (s), 152.18 (s), 149.86 (s), 139.12 (s), 135.73 (s), 132.14 (s), 130.46 (s), 127.82 – 127.25 (m), 126.15 (s), 120.59 (s), 117.12 (s), 114.43 – 113.93 (m), 113.40 (s), 112.74 (s), 110.22 (s), 102.69 (s), 60.24 (s), 56.05 (s), 55.85 (s), 5.11 (s).
f1 (ppm)

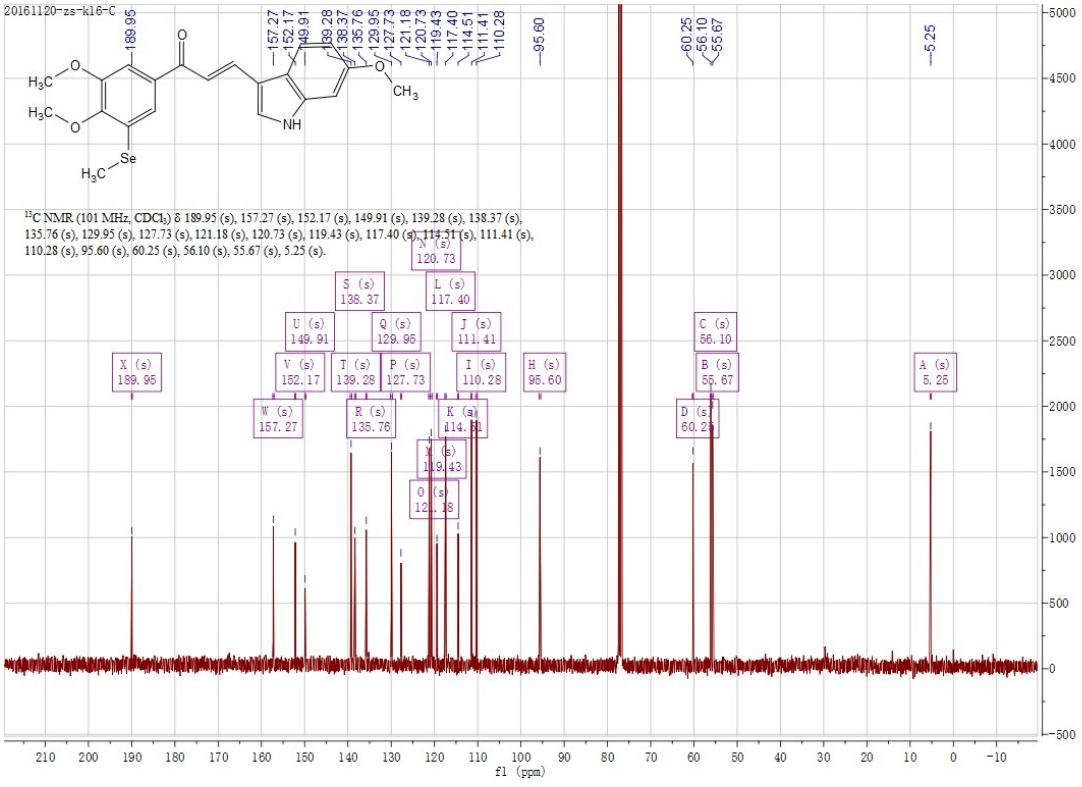
12f


20161120-zs-k19-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06 (d, J = 15.5 Hz, 1H), 7.51 (d, J = 1.1 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.46 (s, 1H), 7.40 (d, J = 3.0 Hz, 1H), 7.38 (d, J = 10.3 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 6.98 (dd, J = 8.9, 2.1 Hz, 1H), 3.95 (s, 6H), 3.92 (s, 3H), 3.82 (s, 3H), 2.35 (s, 3H).
f1 (ppm)

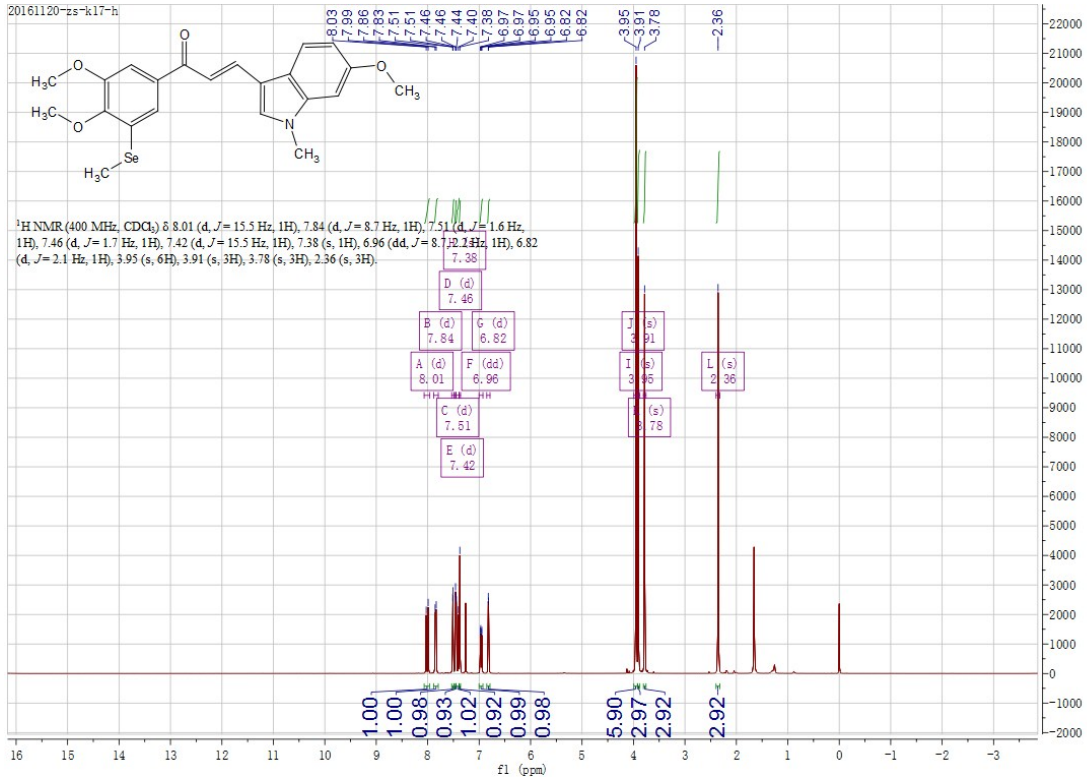

20161120-zs-k19-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.49 (s), 155.70 (s), 152.16 (s), 149.75 (s), 138.84 (s), 135.89 (s), 134.52 (s), 133.36 (s), 127.59 (s), 126.90 (s), 120.51 (s), 116.17 (s), 112.99 (s), 112.55 (s), 110.98 (s), 110.19 (s), 102.82 (s), 60.21 (s), 56.05 (s), 55.87 (s), 33.54 (s), 5.11 (s).
f1 (ppm)

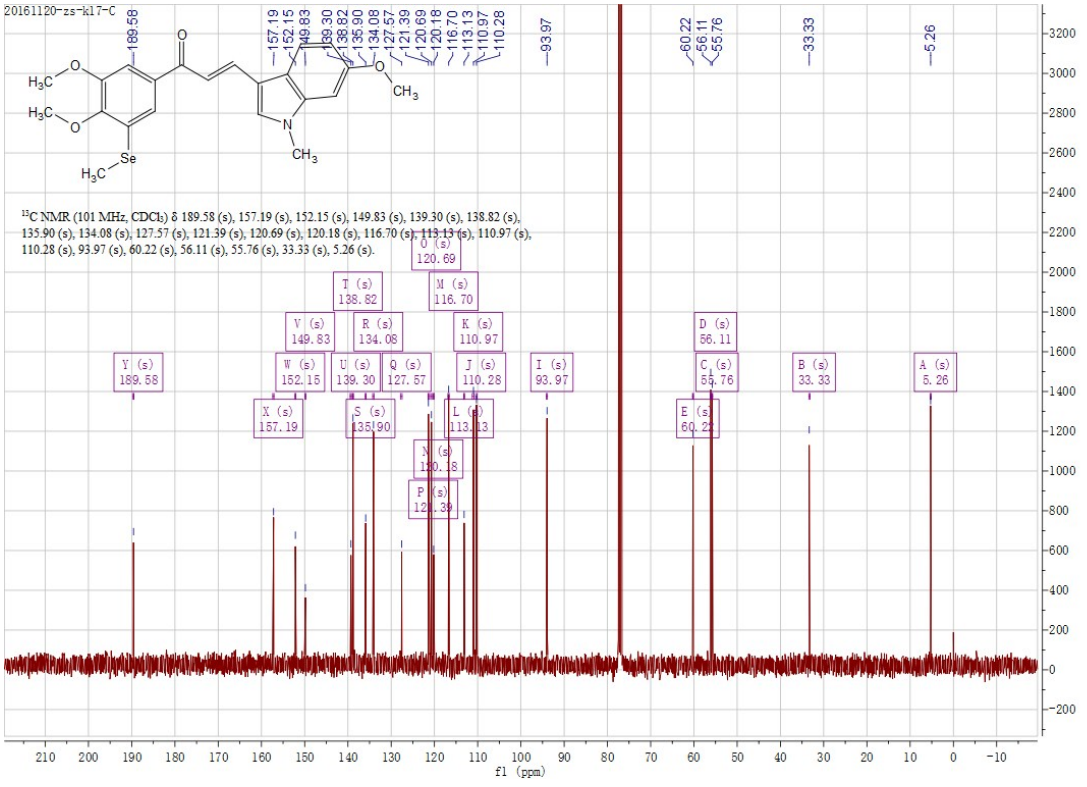
12g


20161120-zs-k16-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (s, 1H), 8.04 (d, J = 15.5 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.50 (s, 1H), 7.48 (d, J = 13.8 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.92 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 2.34 (s, 3H).
f1 (ppm)

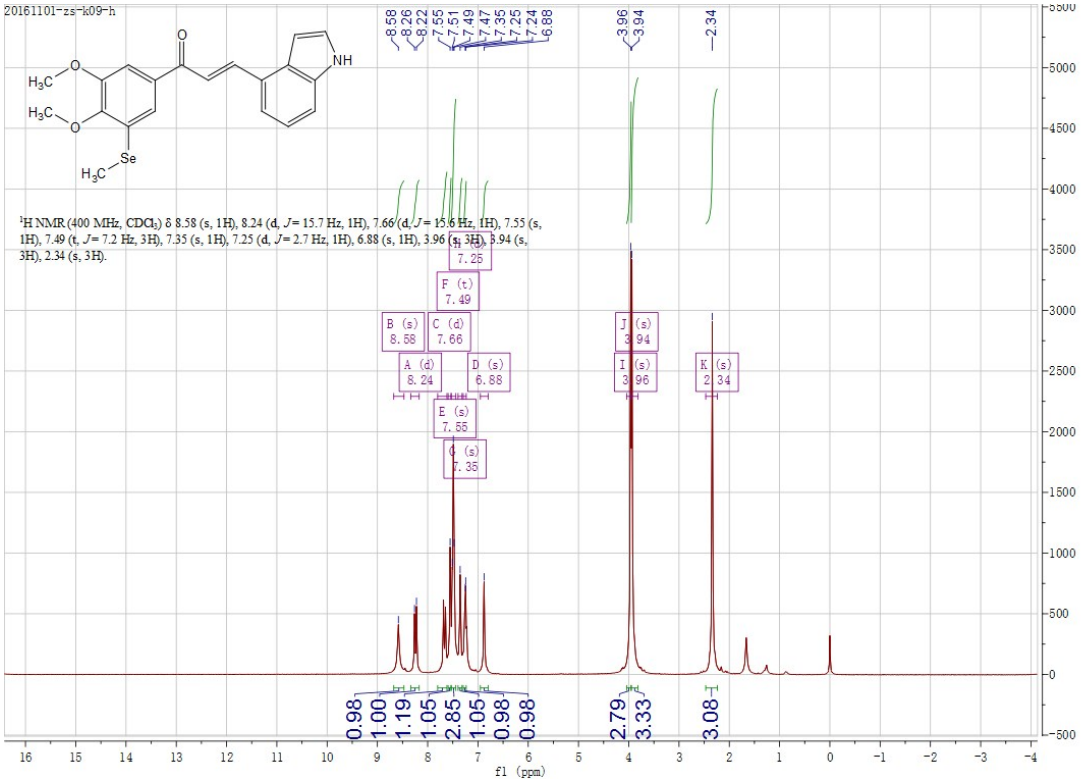

20161120-zs-k16-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.95 (s), 157.27 (s), 152.17 (s), 149.91 (s), 139.28 (s), 138.37 (s), 135.76 (s), 129.95 (s), 127.73 (s), 121.18 (s), 120.73 (s), 119.43 (s), 117.40 (s), 114.51 (s), 111.41 (s), 110.28 (s), 95.60 (s), 60.25 (s), 56.10 (s), 55.67 (s), 5.25 (s).
f1 (ppm)

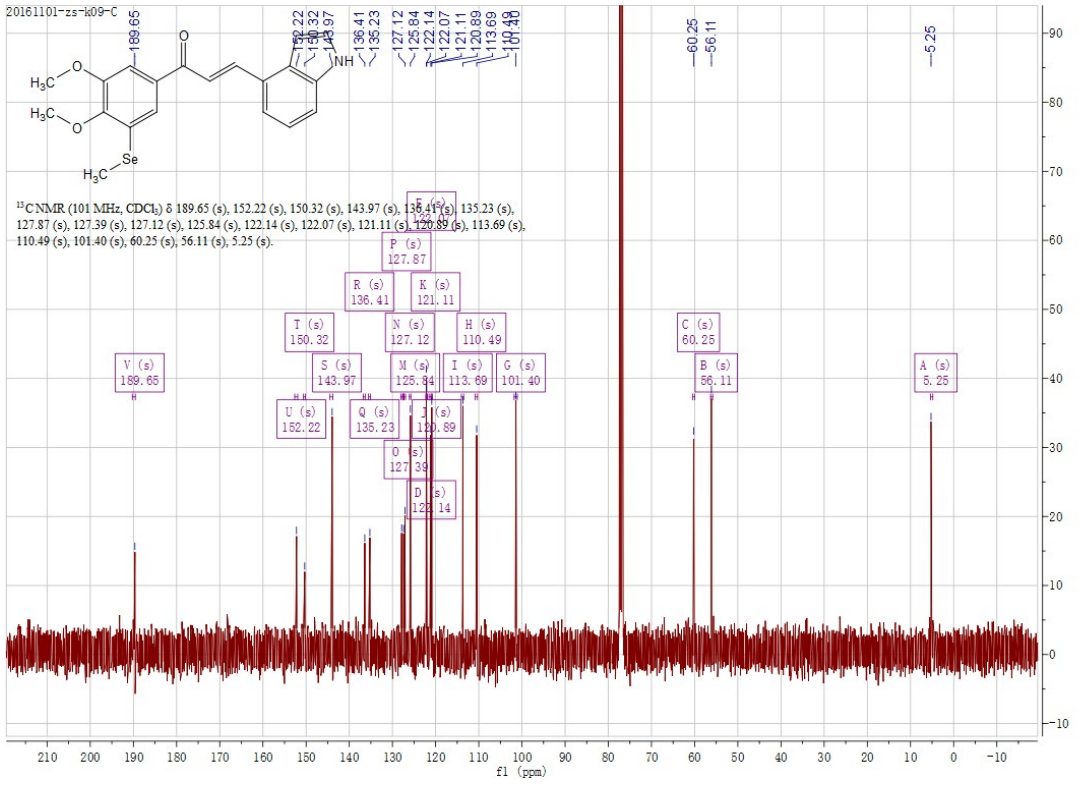
12h


20161120-zs-k17-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, J = 15.5 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.42 (d, J = 15.5 Hz, 1H), 7.38 (s, 1H), 6.96 (dd, J = 8.7, 2.2 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 3.95 (s, 6H), 3.91 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H).
f1 (ppm)

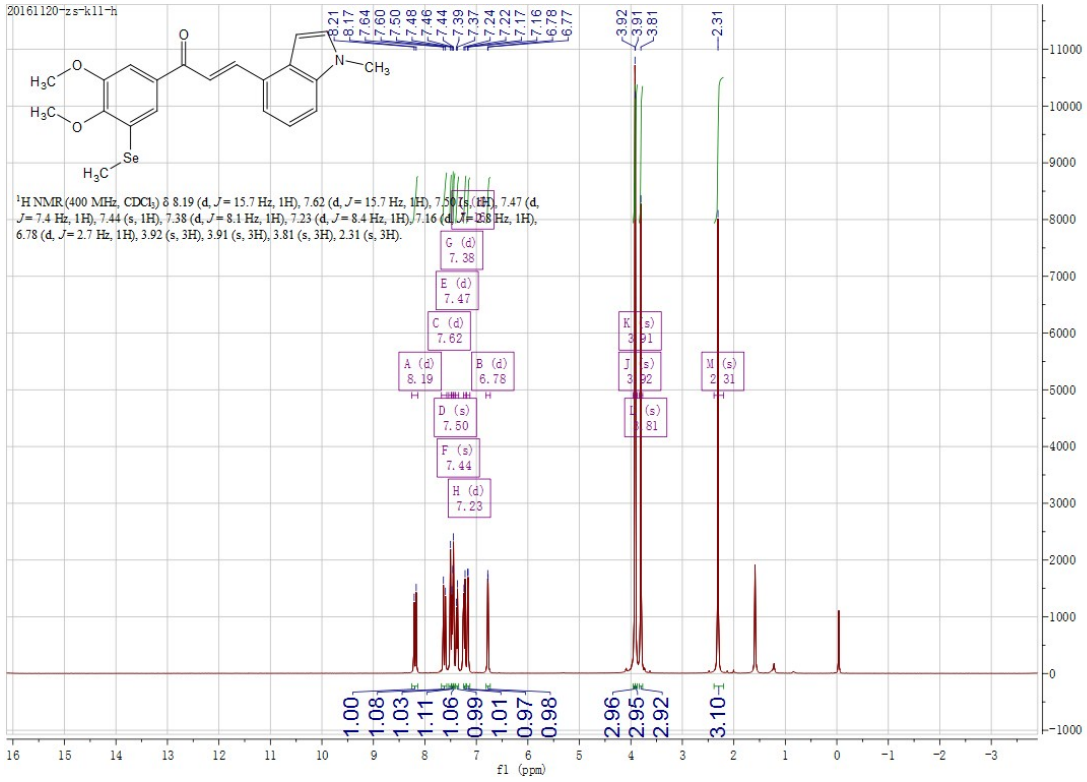

20161120-zs-k17-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.58 (s), 157.19 (s), 152.15 (s), 149.83 (s), 139.30 (s), 138.82 (s), 135.90 (s), 134.08 (s), 127.57 (s), 121.39 (s), 120.69 (s), 120.18 (s), 116.70 (s), 113.13 (s), 110.97 (s), 110.28 (s), 93.97 (s), 60.22 (s), 56.11 (s), 55.76 (s), 33.33 (s), 5.26 (s).
f1 (ppm)

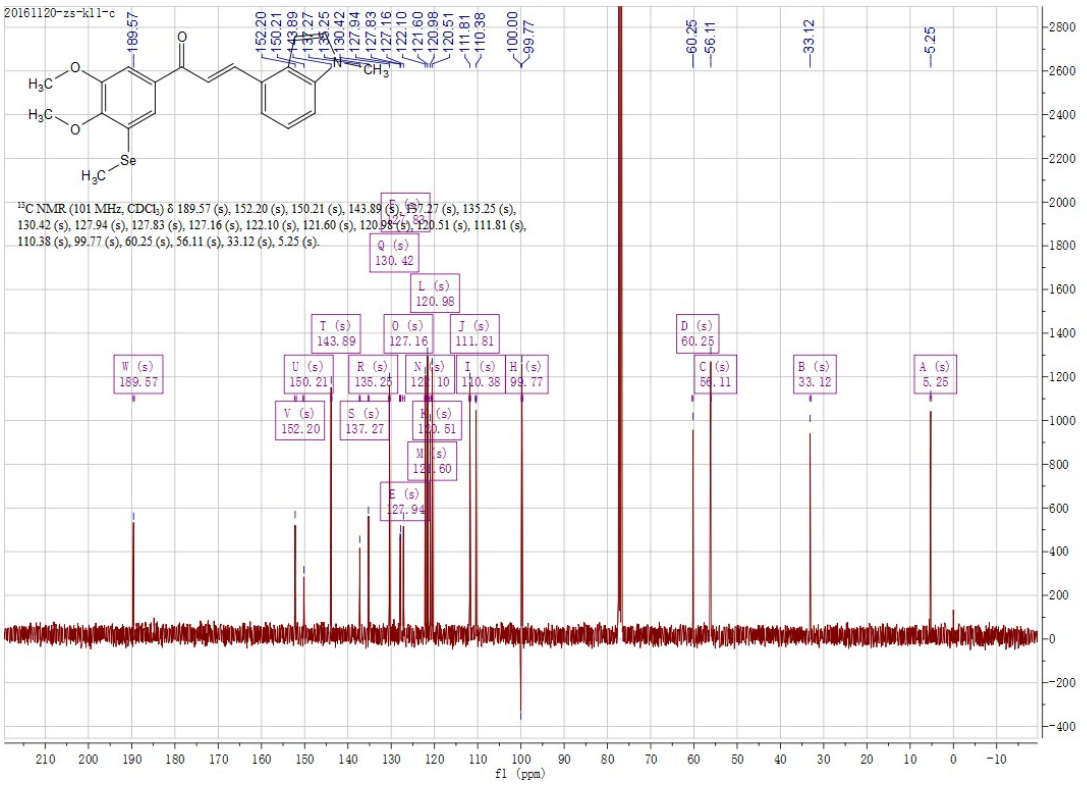
13a


20161101-zs-k09-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.58 (s, 1H), 8.24 (d, J = 15.7 Hz, 1H), 7.66 (d, J = 15.6 Hz, 1H), 7.55 (s, 1H), 7.49 (t, J = 7.2 Hz, 3H), 7.35 (s, 1H), 7.25 (d, J = 2.7 Hz, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.34 (s, 3H).
f1 (ppm)

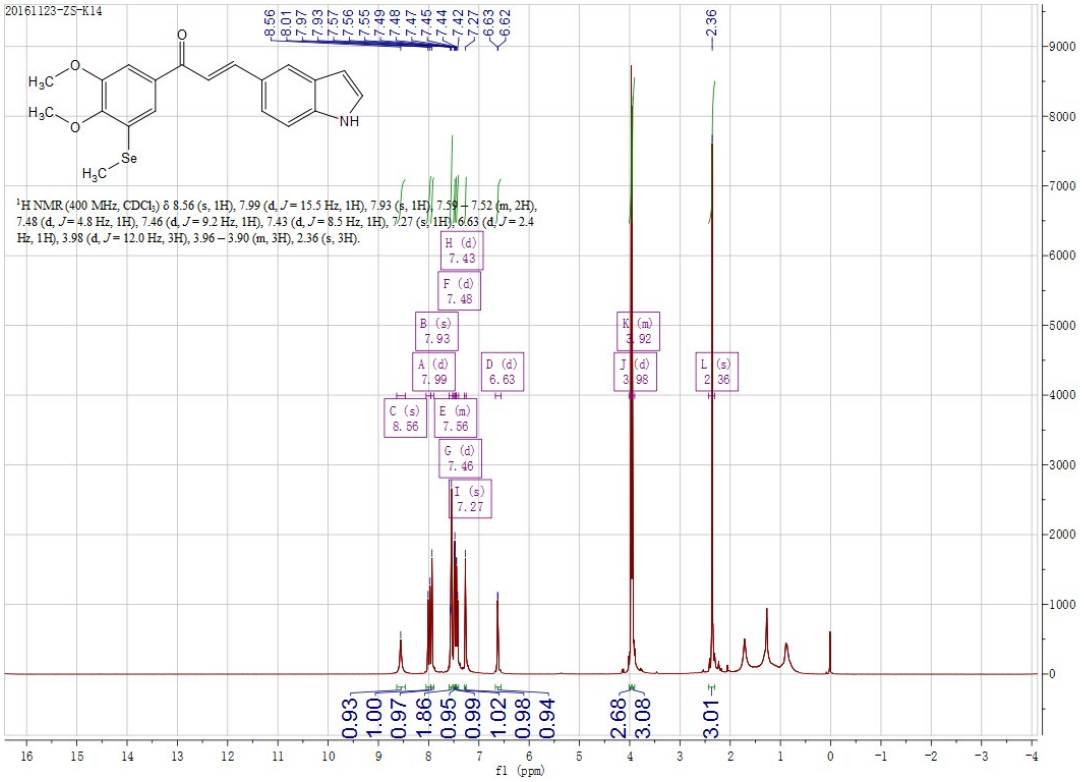

20161101-zs-k09-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.65 (s), 152.22 (s), 150.32 (s), 143.97 (s), 136.41 (s), 135.23 (s), 127.87 (s), 127.39 (s), 127.12 (s), 125.84 (s), 122.14 (s), 122.07 (s), 121.11 (s), 120.89 (s), 113.69 (s), 110.49 (s), 101.40 (s), 60.25 (s), 56.11 (s), 5.25 (s).
f1 (ppm)

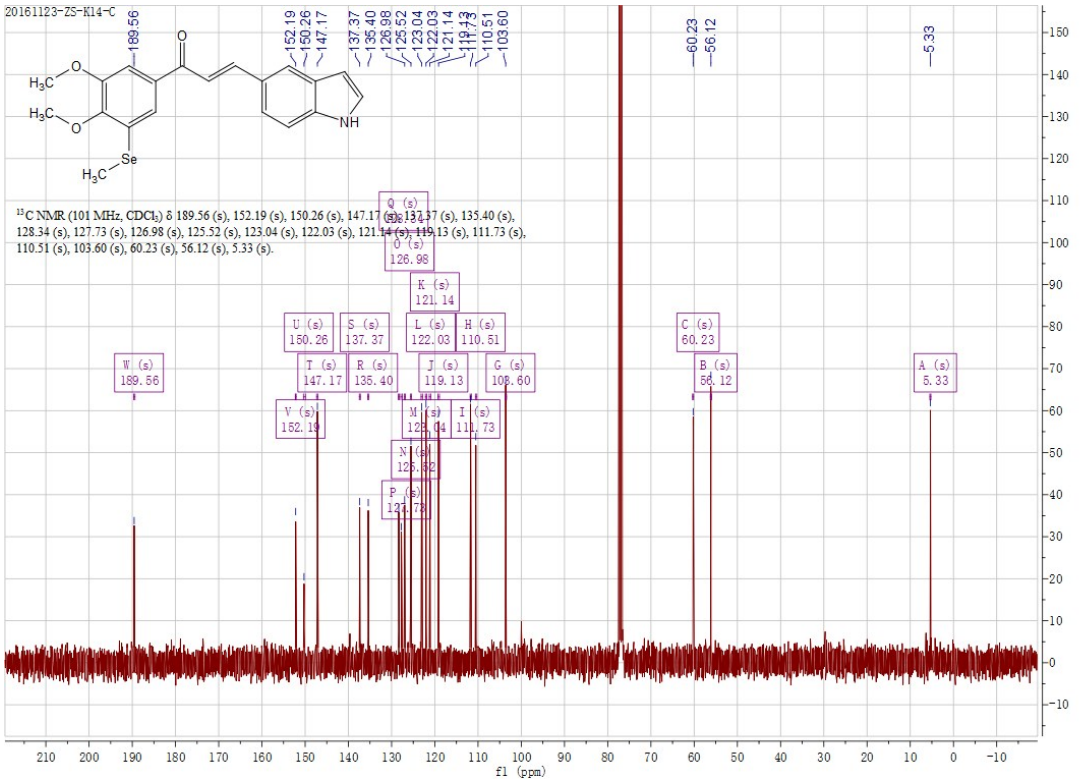
13b


20161120-zs-k11-h
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 15.7 Hz, 1H), 7.62 (d, J = 15.7 Hz, 1H), 7.50 (s, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.44 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 2.7 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 2.31 (s, 3H).
f1 (ppm)

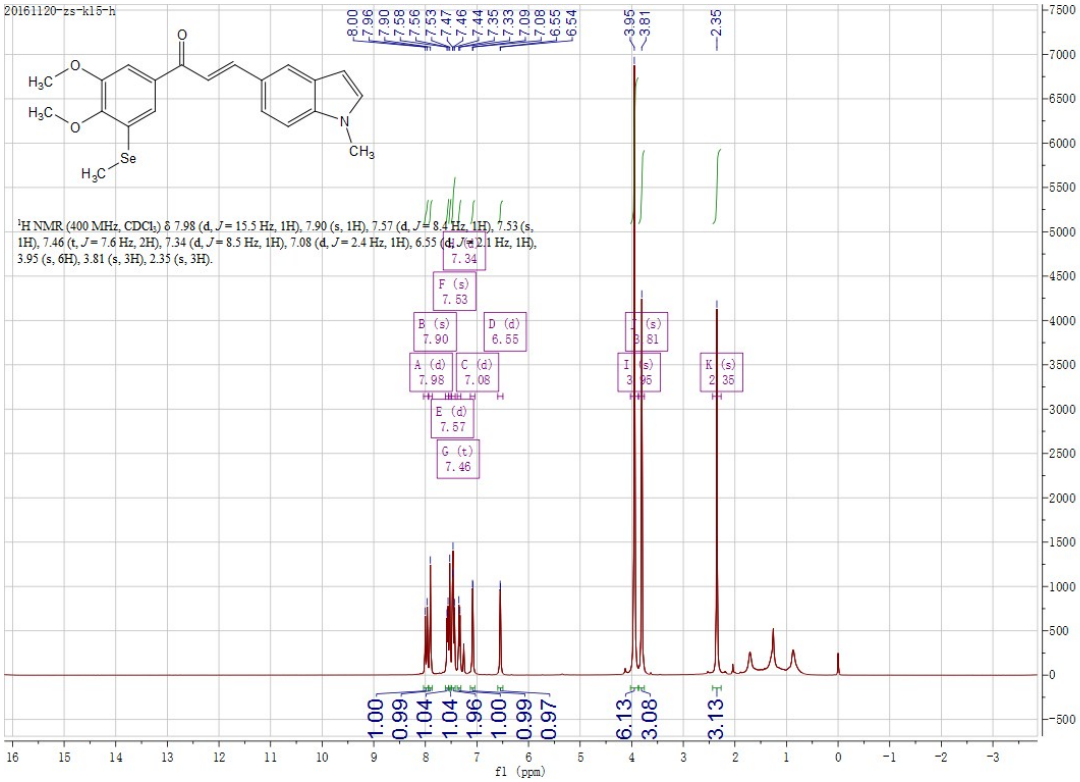

20161120-zs-k11-c
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.57 (s), 152.20 (s), 150.21 (s), 143.89 (s), 137.27 (s), 135.25 (s), 130.42 (s), 127.94 (s), 127.83 (s), 127.16 (s), 122.10 (s), 121.60 (s), 120.98 (s), 120.51 (s), 111.81 (s), 110.38 (s), 99.77 (s), 60.25 (s), 56.11 (s), 33.12 (s), 5.25 (s).
f1 (ppm)

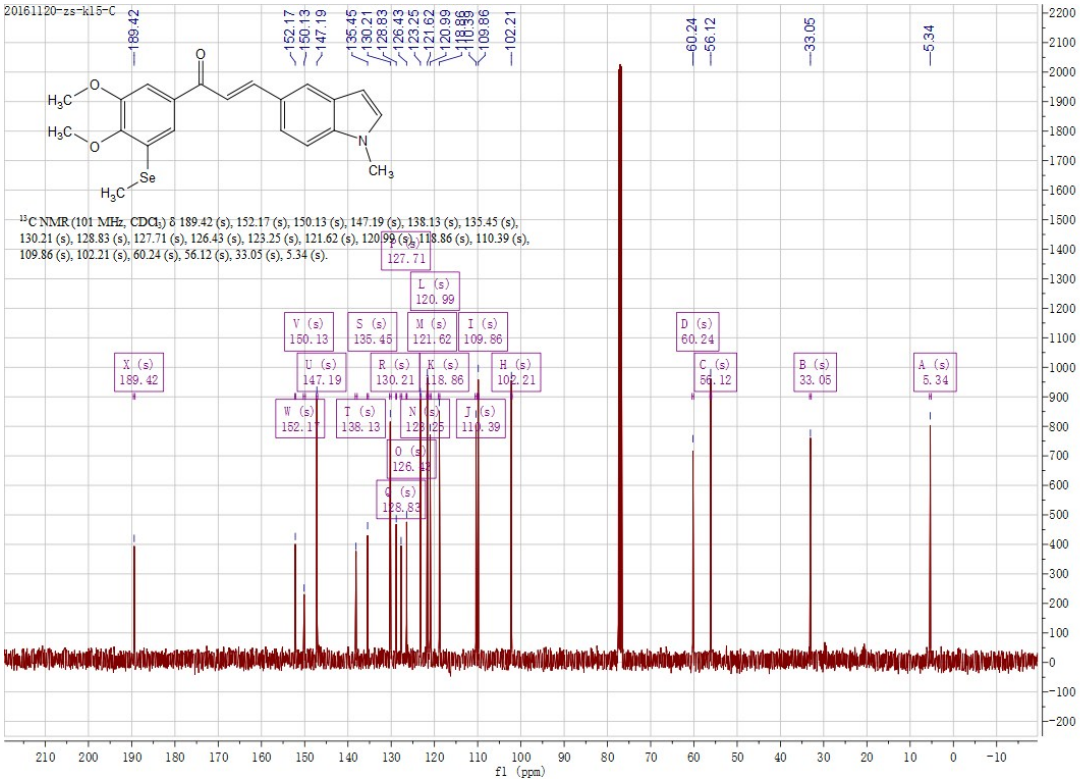
14a


20161123-ZS-K14
8.56
8.01
7.97
7.93
7.57
7.56
7.55
7.49
7.48
7.47
7.45
7.44
7.42
7.27
6.63
6.62
2.36
O
H3C
O
H3C
O
Se
H3C
NH
1H NMR (400 MHz, CDCl3) δ 8.56 (s, 1H), 7.99 (d, J = 15.5 Hz, 1H), 7.93 (s, 1H), 7.59 – 7.52 (m, 2H), 7.48 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.27 (s, 1H), 6.63 (d, J = 2.4 Hz, 1H), 3.98 (d, J = 12.0 Hz, 3H), 3.96 – 3.90 (m, 3H), 2.36 (s, 3H).
H (d) 7.43
F (d) 7.48
B (s) 7.93
A (d) 7.99
D (d) 6.63
C (s) 8.56
E (m) 7.56
G (d) 7.46
I (s) 7.27
K (m) 3.92
J (d) 3.98
L (s) 2.36
0.93
1.00
0.97
1.86
0.95
0.99
1.02
0.98
0.94
2.68
3.08
3.01
f1 (ppm)

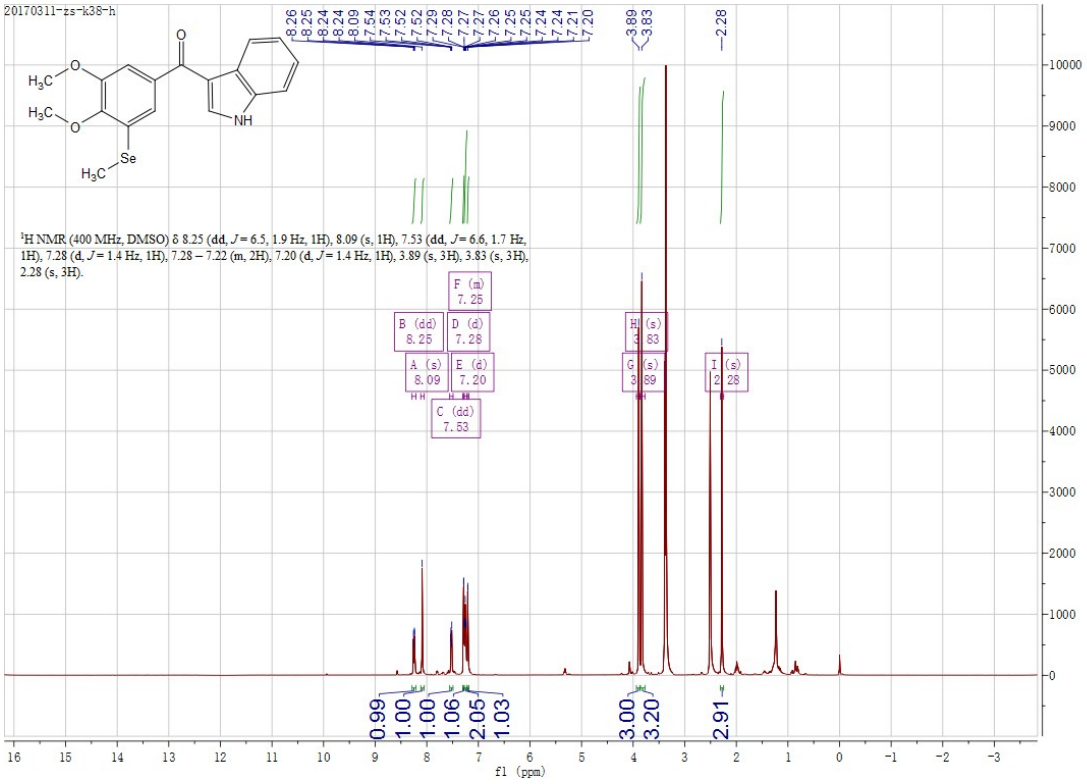

20161123-ZS-K14-C
189.56
152.19
150.26
147.17
137.37
135.40
128.98
125.52
123.04
122.03
121.14
119.13
111.73
110.51
103.60
60.23
56.12
5.33
O
H3C
O
H3C
O
Se
H3C
NH
13C NMR (101 MHz, CDCl3) δ 189.56 (s), 152.19 (s), 150.26 (s), 147.17 (s), 137.37 (s), 135.40 (s), 128.34 (s), 127.73 (s), 126.98 (s), 125.52 (s), 123.04 (s), 122.02 (s), 121.14 (s), 119.13 (s), 111.73 (s), 110.51 (s), 103.60 (s), 60.23 (s), 56.12 (s), 5.33 (s).
Q (s) 128.34
O (s) 126.98
K (s) 121.14
U (s) 150.26
S (s) 137.37
L (s) 122.03
H (s) 110.51
C (s) 60.23
W (s) 189.56
T (s) 147.17
R (s) 135.40
J (s) 119.13
G (s) 103.60
B (s) 56.12
A (s) 5.33
V (s) 152.19
M (s) 123.04
I (s) 111.73
N (s) 125.52
P (s) 127.73
f1 (ppm)

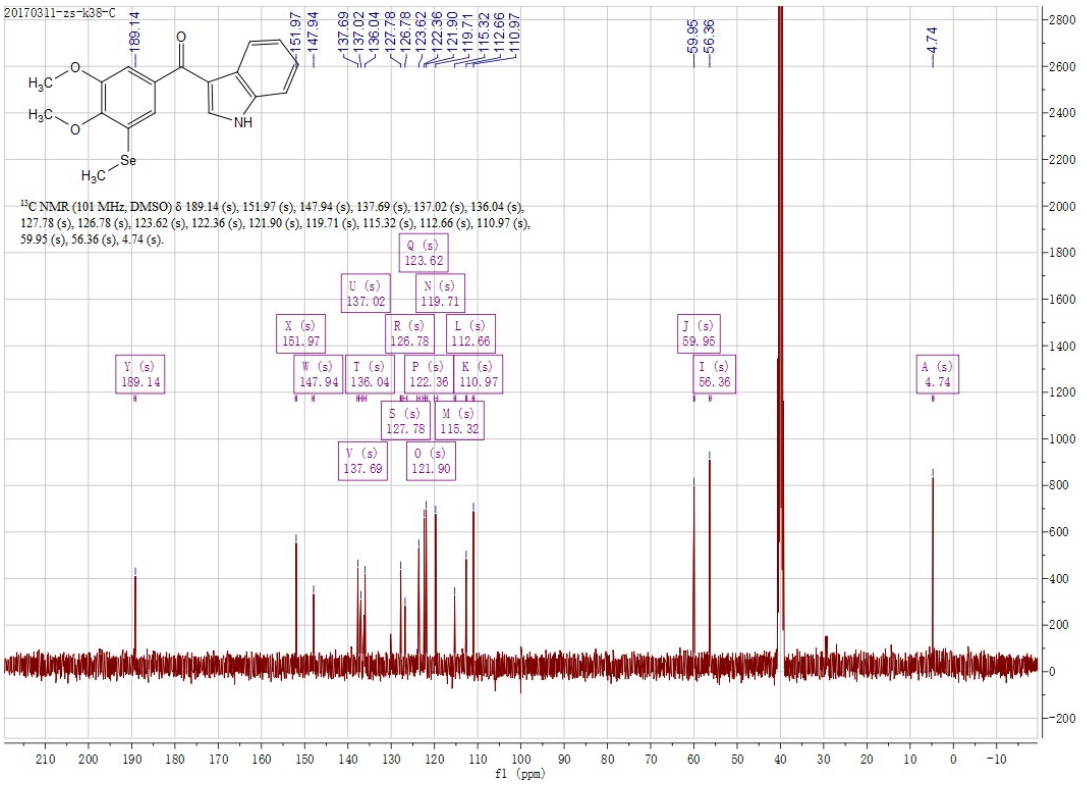
14b


20161120-zs-k15-h
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, J = 15.5 Hz, 1H), 7.90 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 3.95 (s, 6H), 3.81 (s, 3H), 2.35 (s, 3H).
f1 (ppm)

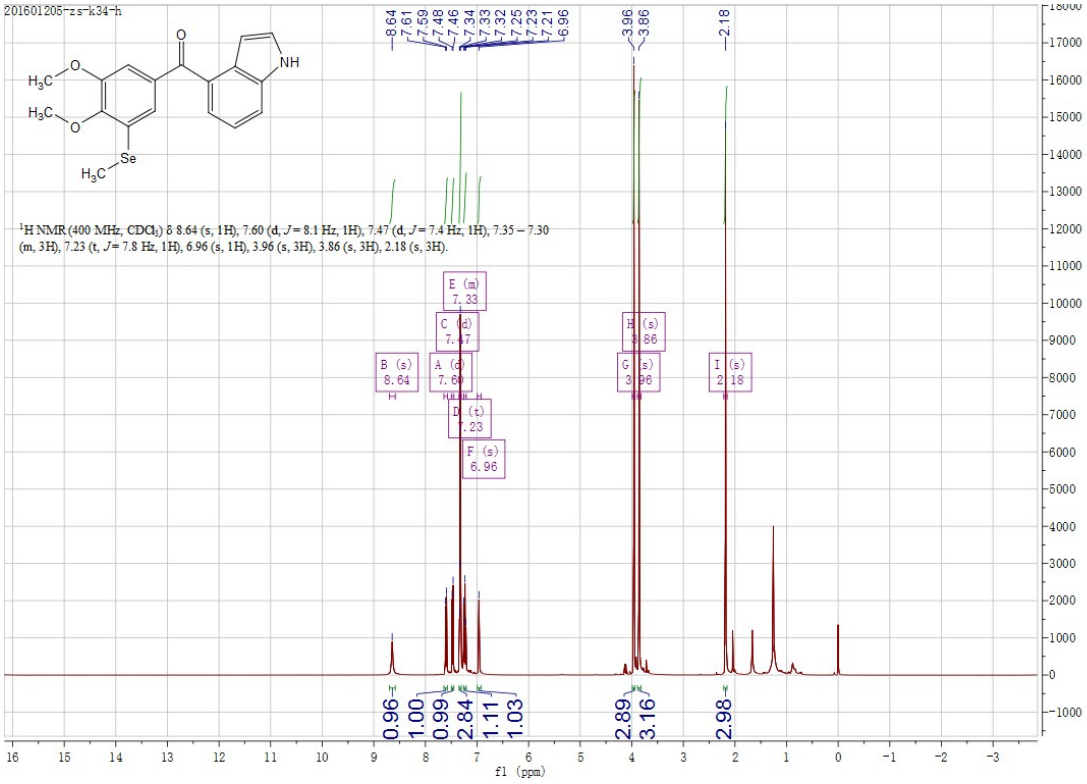

20161120-zs-k15-C
^{13}C NMR (101 MHz, CDCl$_3$) δ 189.42 (s), 152.17 (s), 150.13 (s), 147.19 (s), 138.13 (s), 135.45 (s), 130.21 (s), 128.83 (s), 127.71 (s), 126.43 (s), 123.25 (s), 121.62 (s), 120.99 (s), 118.86 (s), 110.39 (s), 109.86 (s), 102.21 (s), 60.24 (s), 56.12 (s), 33.05 (s), 5.34 (s).
f1 (ppm)

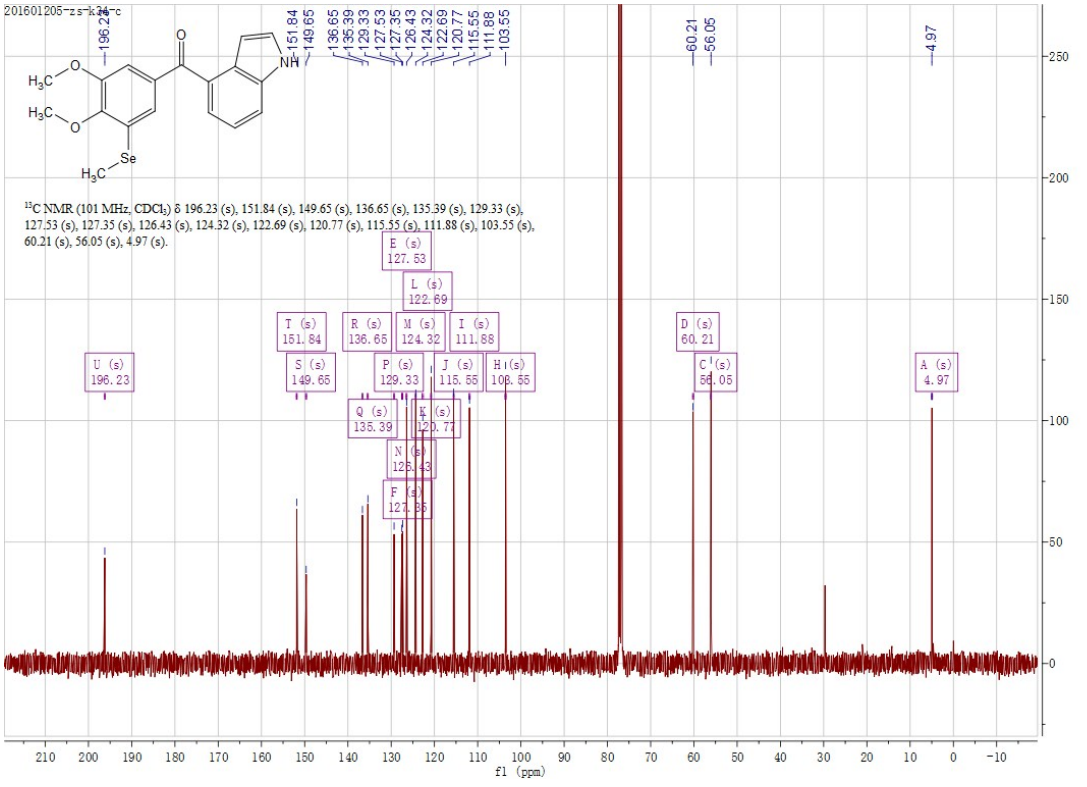
25a


20170311-zs-k38-h
^{1}H NMR (400 MHz, DMSO) δ 8.25 (dd, J = 6.5, 1.9 Hz, 1H), 8.09 (s, 1H), 7.53 (dd, J = 6.6, 1.7 Hz, 1H), 7.28 (d, J = 1.4 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.20 (d, J = 1.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.28 (s, 3H).
f1 (ppm)

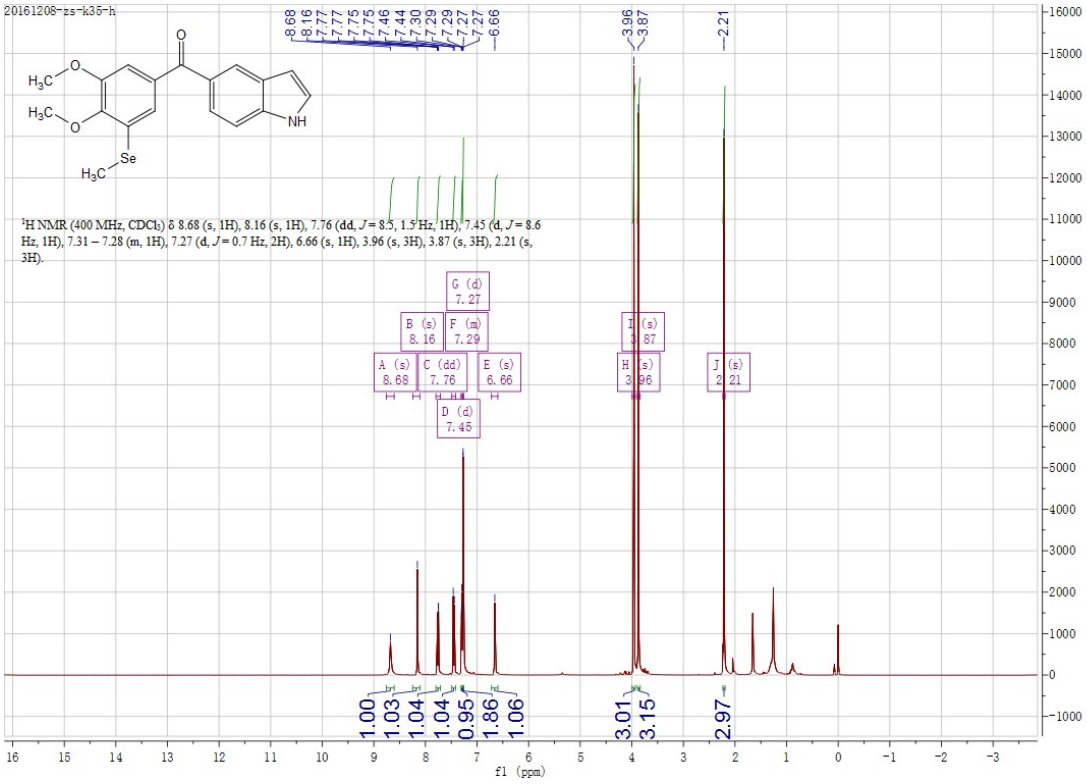

20170311-zs-k38-C
^{13}C NMR (101 MHz, DMSO) δ 189.14 (s), 151.97 (s), 147.94 (s), 137.69 (s), 137.02 (s), 136.04 (s), 127.78 (s), 126.78 (s), 123.62 (s), 122.36 (s), 121.90 (s), 119.71 (s), 115.32 (s), 112.66 (s), 110.97 (s), 59.95 (s), 56.36 (s), 4.74 (s).
f1 (ppm)

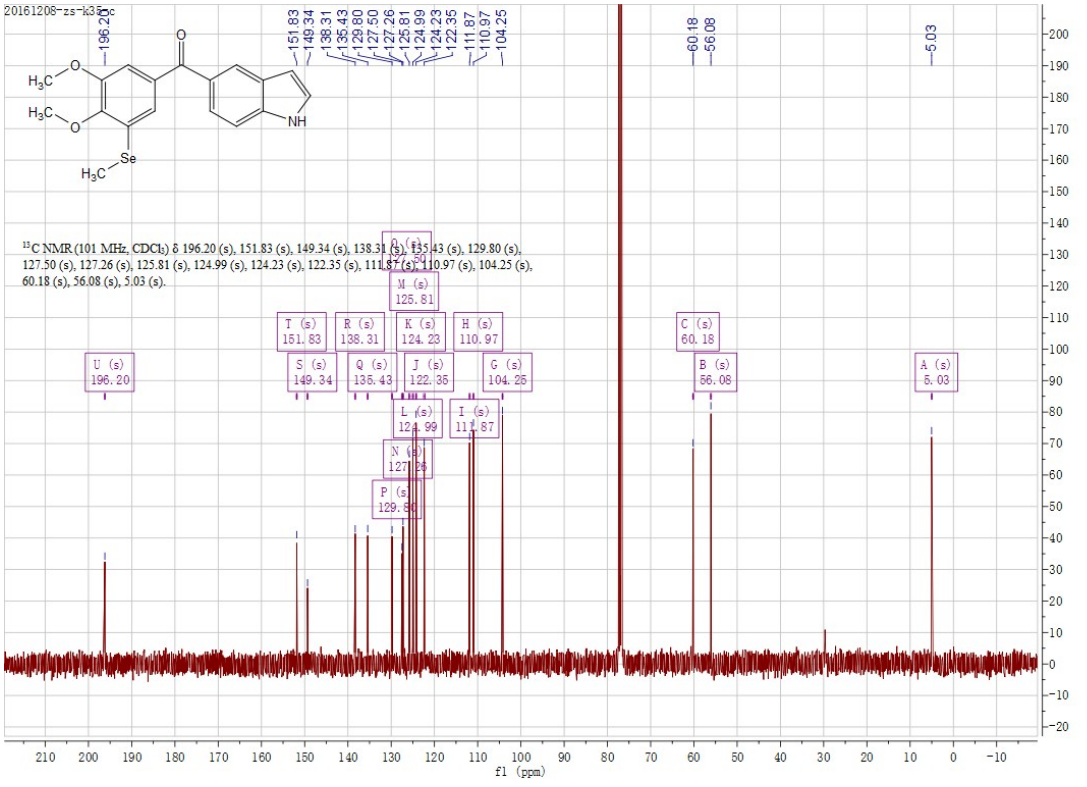
25b


201601205-zs-k34-h
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.35 – 7.30 (m, 3H), 7.23 (t, J = 7.8 Hz, 1H), 6.96 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.18 (s, 3H).
f1 (ppm)

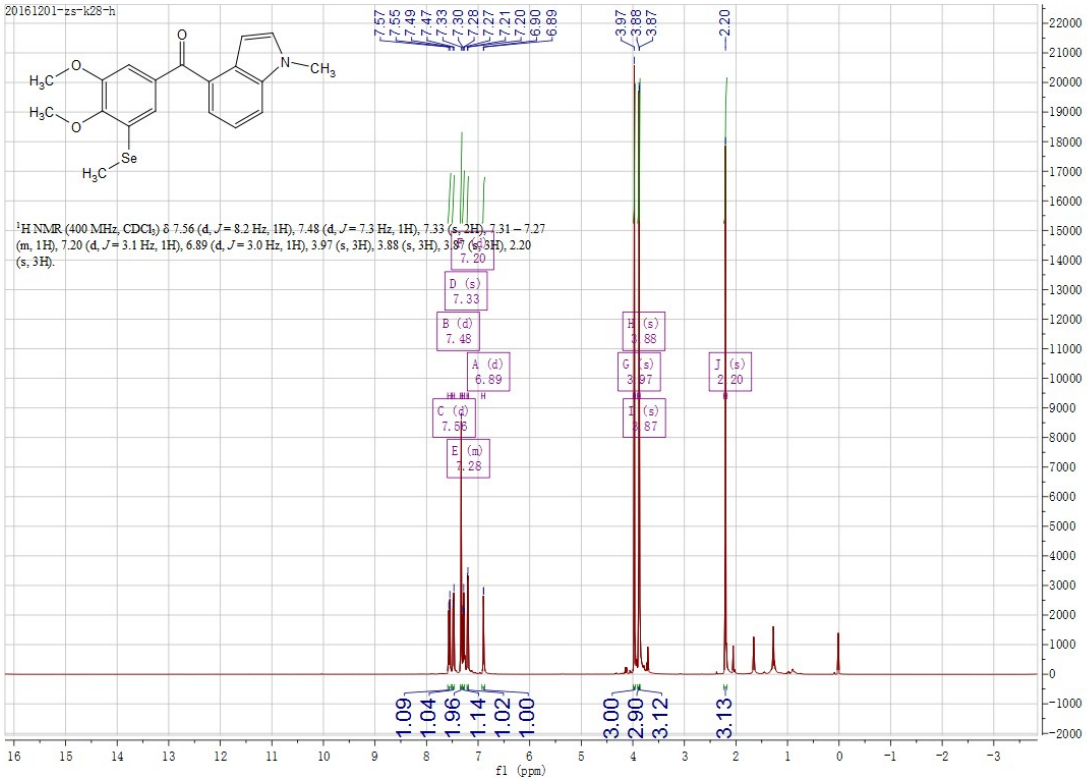

201601205-zs-k34-c
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.23 (s), 151.84 (s), 149.65 (s), 136.65 (s), 135.39 (s), 129.33 (s), 127.53 (s), 127.35 (s), 126.43 (s), 124.32 (s), 122.69 (s), 120.77 (s), 115.55 (s), 111.88 (s), 103.55 (s), 60.21 (s), 56.05 (s), 4.97 (s).
f1 (ppm)

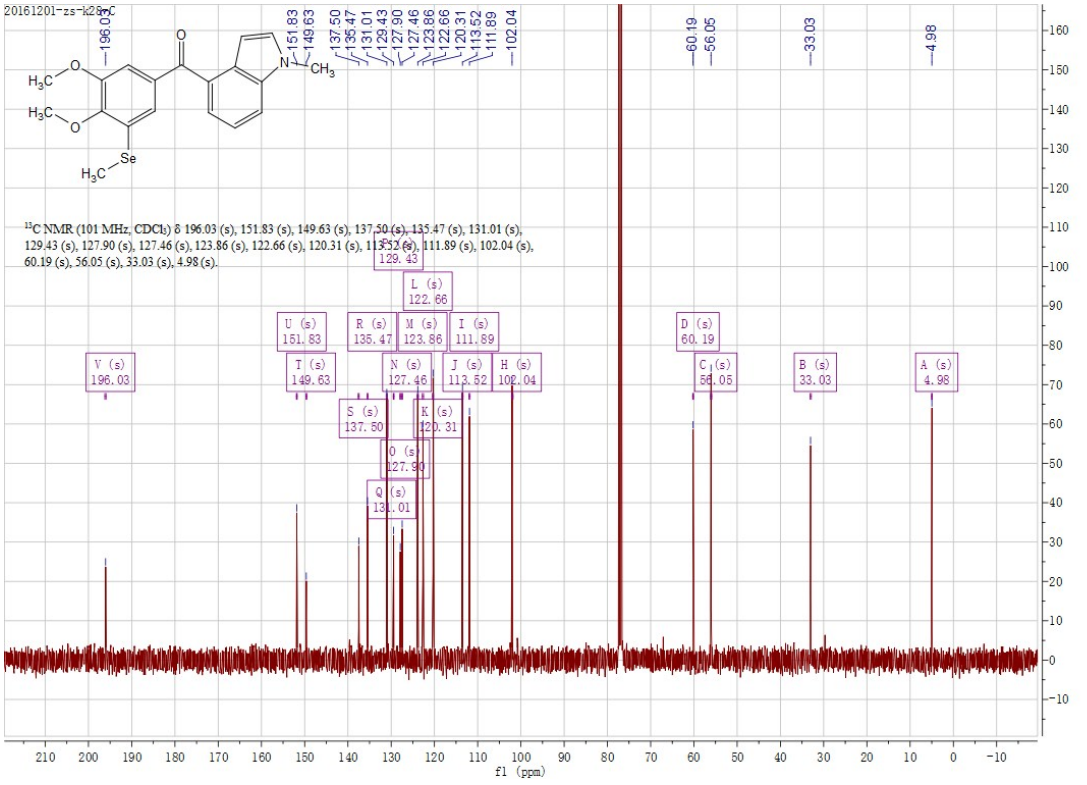
25c


20161208-zs-k35-h
8.68
8.16
7.77
7.75
7.46
7.44
7.30
7.29
7.27
6.66
3.96
3.87
2.21
O
H3C
O
H3C
O
NH
Se
H3C
¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 1H), 8.16 (s, 1H), 7.76 (dd, J = 8.5, 1.5 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.27 (d, J = 0.7 Hz, 2H), 6.66 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 2.21 (s, 3H).
G (d) 7.27
B (s) 8.16
F (m) 7.29
I (s) 3.87
A (s) 8.68
C (dd) 7.76
E (s) 6.66
H (s) 3.96
J (s) 2.21
D (d) 7.45
1.00
1.03
1.04
1.04
0.95
1.86
1.06
3.01
3.15
2.97
f1 (ppm)


20161208-zs-k35-c
196.20
151.83
149.34
138.31
135.43
129.80
127.50
127.26
125.81
124.99
124.23
122.35
111.87
110.97
104.25
60.18
56.08
5.03
O
H3C
O
H3C
O
NH
Se
H3C
¹³C NMR (101 MHz, CDCl₃) δ 196.20 (s), 151.83 (s), 149.34 (s), 138.31 (s), 135.43 (s), 129.80 (s), 127.50 (s), 127.26 (s), 125.81 (s), 124.99 (s), 124.23 (s), 122.35 (s), 111.87 (s), 110.97 (s), 104.25 (s), 60.18 (s), 56.08 (s), 5.03 (s).
M (s) 125.81
T (s) 151.83
R (s) 138.31
K (s) 124.23
H (s) 110.97
C (s) 60.18
U (s) 196.20
S (s) 149.34
Q (s) 135.43
J (s) 122.35
G (s) 104.25
B (s) 56.08
A (s) 5.03
L (s) 124.99
I (s) 111.87
N (s) 127.26
P (s) 129.80
f1 (ppm)

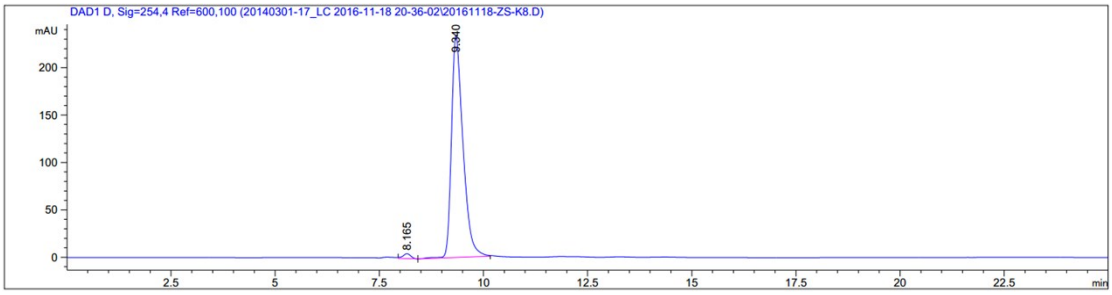
27


20161201-zs-k28-h
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.33 (s, 2H), 7.31 – 7.27 (m, 1H), 7.20 (d, J = 3.1 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.20 (s, 3H).
f1 (ppm)


20161201-zs-k28-C
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.03 (s), 151.83 (s), 149.63 (s), 137.50 (s), 135.47 (s), 131.01 (s), 129.43 (s), 127.90 (s), 127.46 (s), 123.86 (s), 122.66 (s), 120.31 (s), 113.52 (s), 111.89 (s), 102.04 (s), 60.19 (s), 56.05 (s), 33.03 (s), 4.98 (s).
f1 (ppm)

SI3. HPLC chromatograms of target compounds.

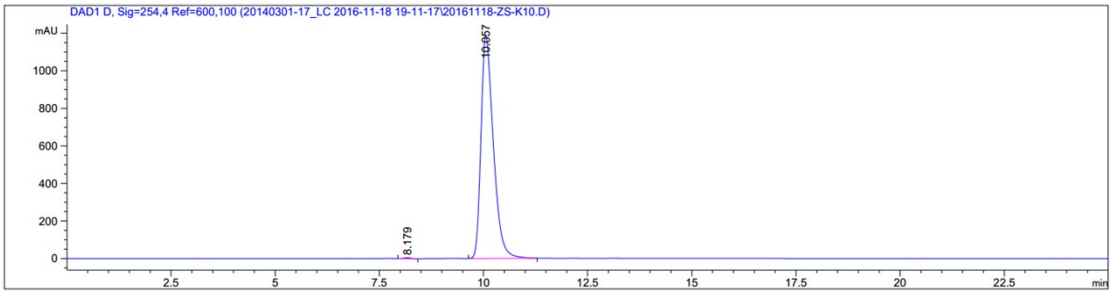
12a



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.165	BV	0.1970	67.00445	5.17786	1.4714
2	9.340	VB	0.2856	4486.91357	234.13512	98.5286
总量：				4553.91802	239.31297	

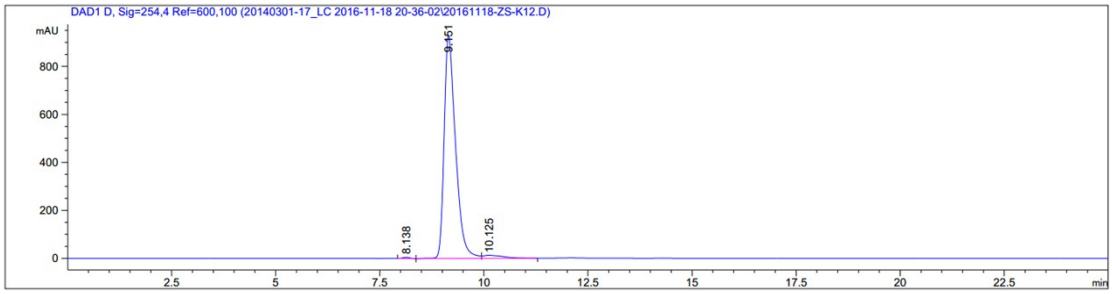
12b



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.179	BV	0.2088	73.55861	5.40434	0.3007
2	10.057	BB	0.3095	2.43891e4	1187.92786	99.6993
总量：				2.44626e4	1193.33220	

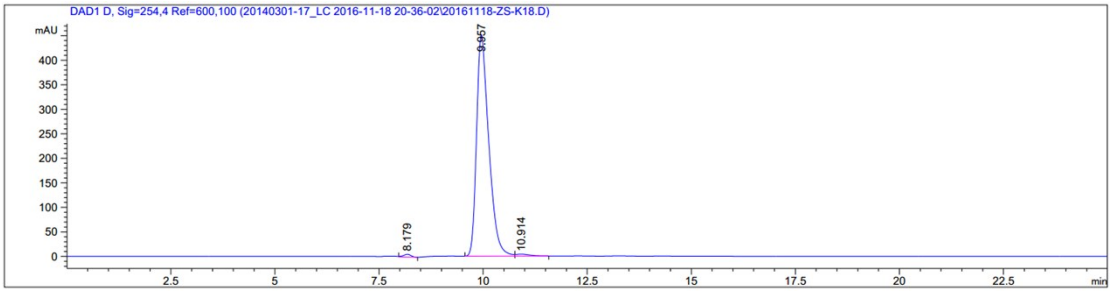
12c



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.138	BV	0.1933	67.26139	5.32593	0.3697
2	9.151	VV	0.2798	1.76861e4	930.24316	97.2094
3	10.125	VB	0.4454	440.45602	13.12862	2.4209
总量：				1.81938e4	948.69771	

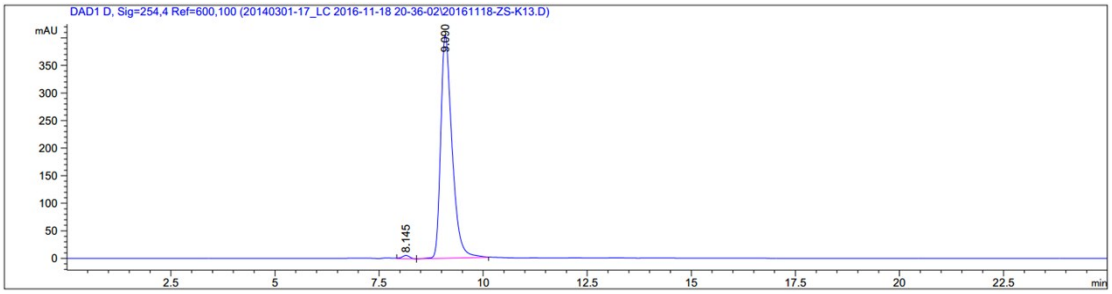
12d



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.179	BV	0.2005	70.70094	5.41041	0.7568
2	9.957	BB	0.3013	9181.02930	451.31256	98.2700
3	10.914	BB	0.3214	90.92791	3.96668	0.9733
总量：				9342.65815	460.68965	

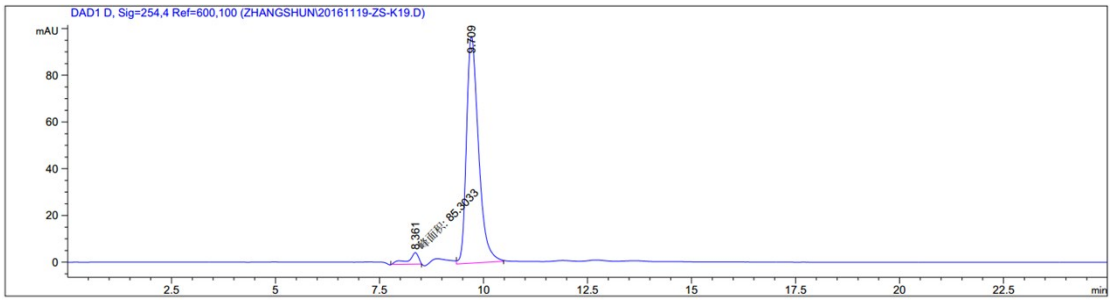
12e



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.145	BV	0.2003	76.09689	5.90598	0.9855
2	9.090	VB	0.2803	7645.70947	404.81860	99.0145
总量 :				7721.80637	410.72459	

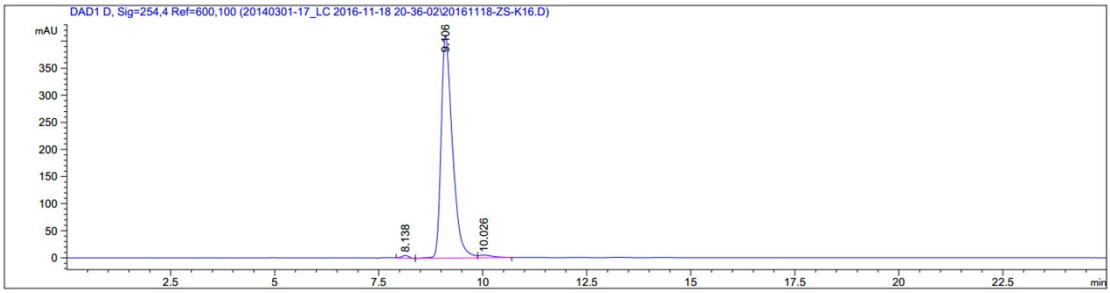
12f



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.361	MM	0.2887	85.30326	4.92386	4.1880
2	9.709	BB	0.3106	1951.53650	97.06363	95.8120
总量 :				2036.83976	101.98749	

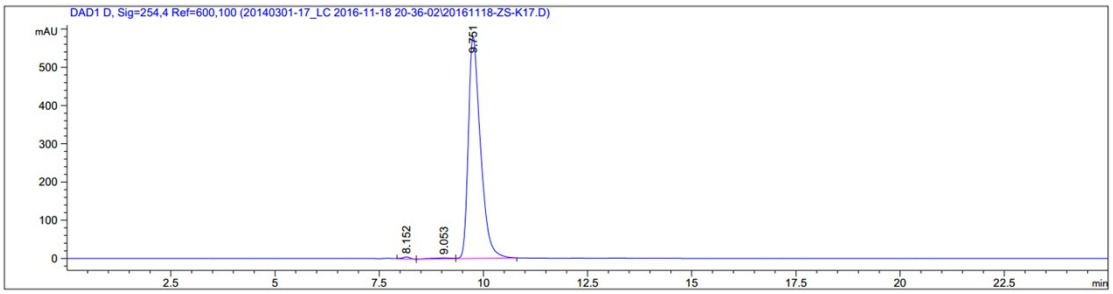
12g



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.138	BV	0.1829	55.53136	4.80186	0.6977
2	9.106	VB	0.2789	7784.39307	411.21252	97.8075
3	10.026	BB	0.3509	118.96532	4.83712	1.4947
总量 :				7958.88974	420.85151	

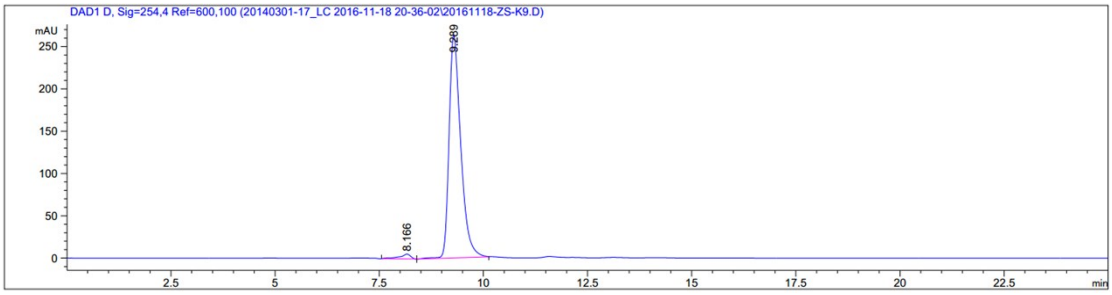
12h



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.152	BV	0.1965	68.20457	5.28724	0.5732
2	9.053	VV	0.4694	88.49655	2.54707	0.7437
3	9.751	VB	0.2976	1.17428e4	581.52692	98.6831
总量 :				1.18995e4	589.36122	

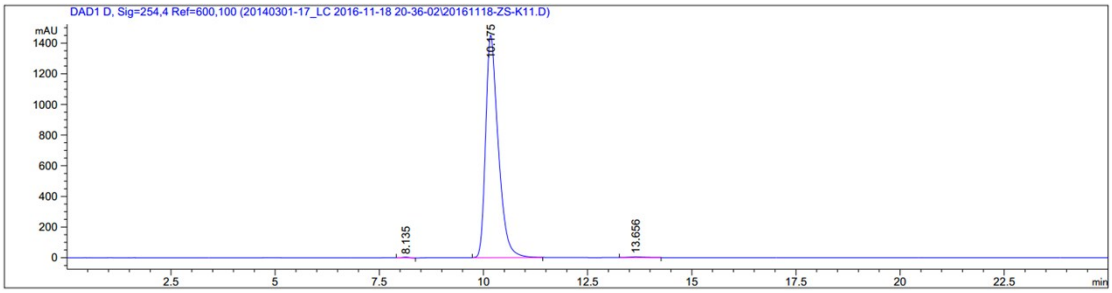
13a



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.166	BV	0.2678	106.48360	5.65262	2.0353
2	9.289	VB	0.2933	5125.34082	263.03516	97.9647
总量 :				5231.82442	268.68777	

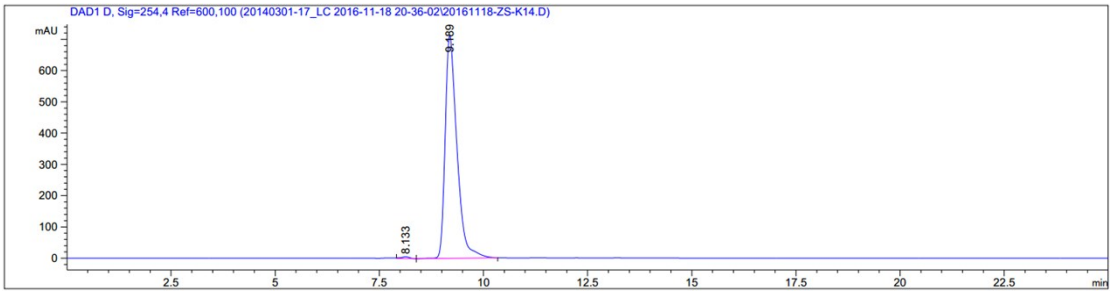
13b



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.135	BV	0.1986	67.54684	5.23152	0.2208
2	10.175	BB	0.3088	3.04227e4	1450.09656	99.4347
3	13.656	BB	0.3643	105.40075	4.29526	0.3445
总量 :				3.05957e4	1459.62333	

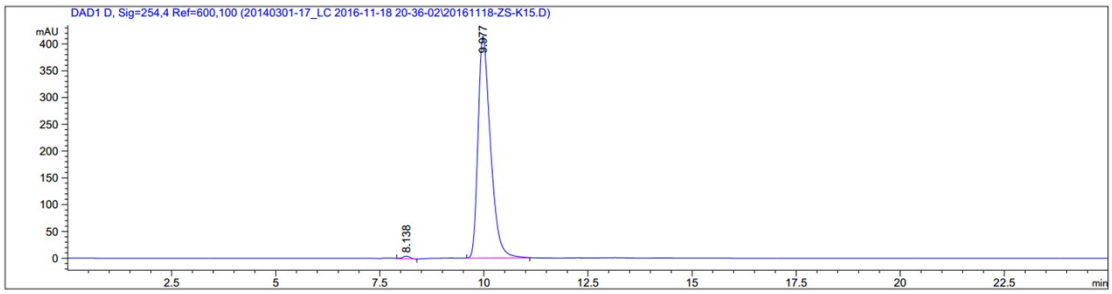
14a



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.133	BV	0.2138	80.13026	5.63687	0.5709
2	9.189	VB	0.2903	1.39568e4	713.20044	99.4291
总量：				1.40370e4	718.83731	

14b

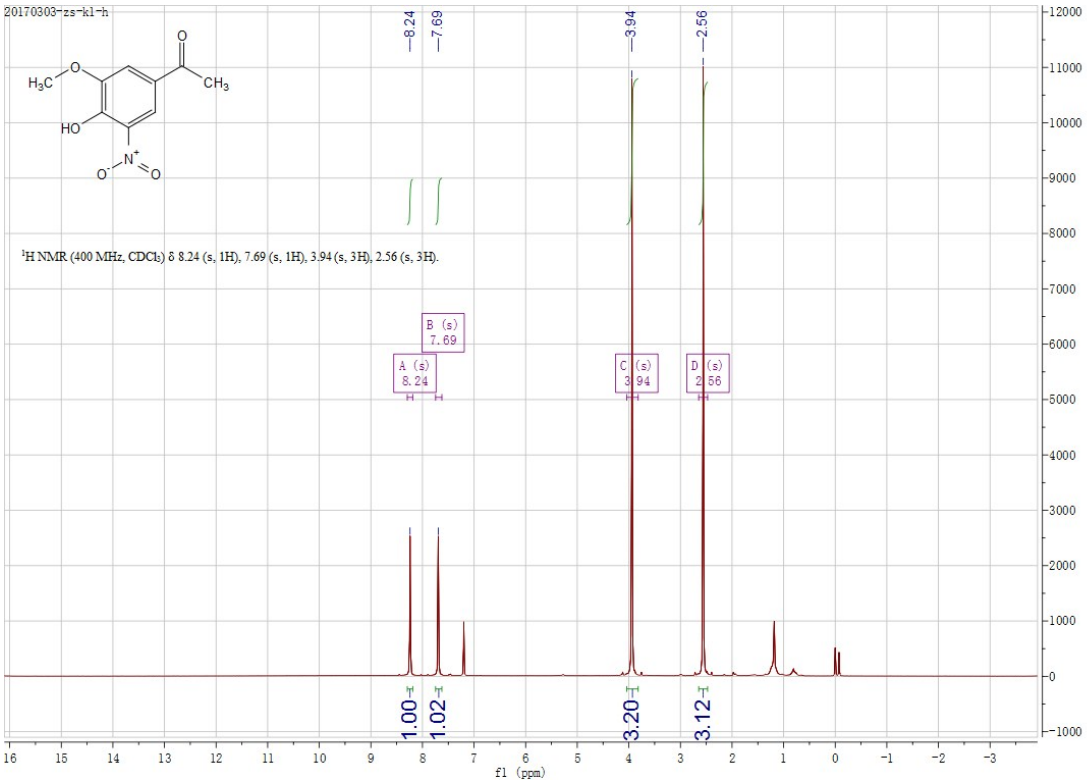


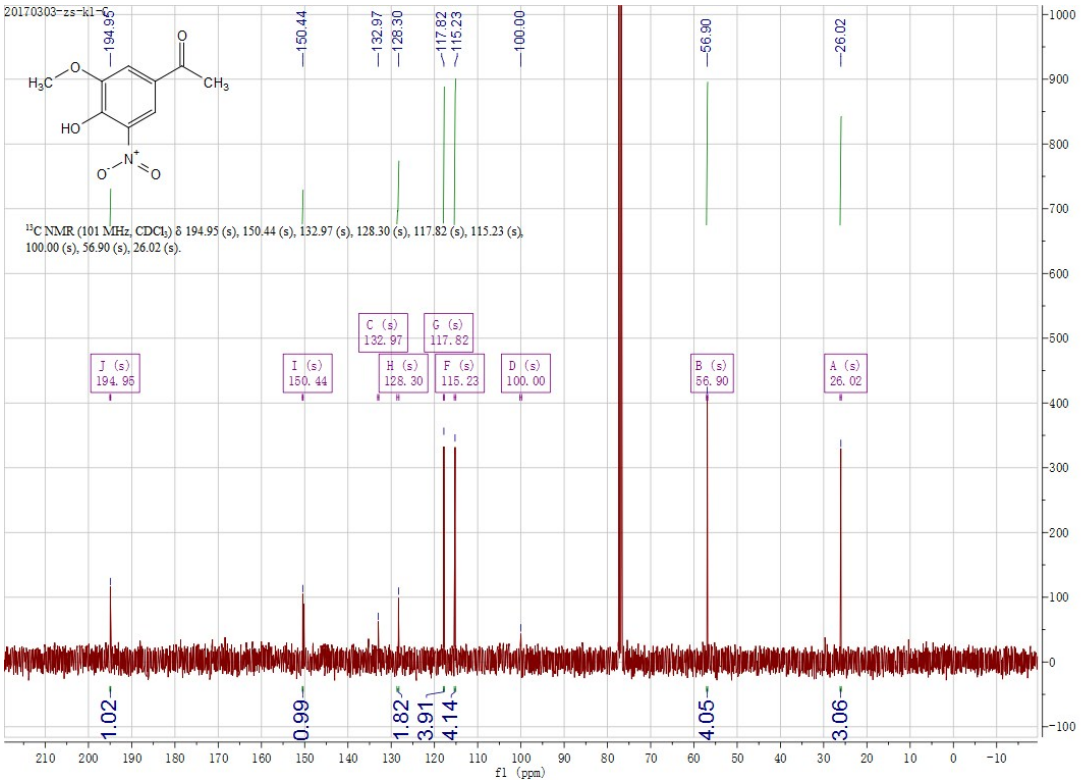
信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.138	BV	0.1960	63.72637	4.95745	0.7339
2	9.977	BB	0.3129	8619.78613	414.03085	99.2661
总量：				8683.51250	418.98830	

Intermediate

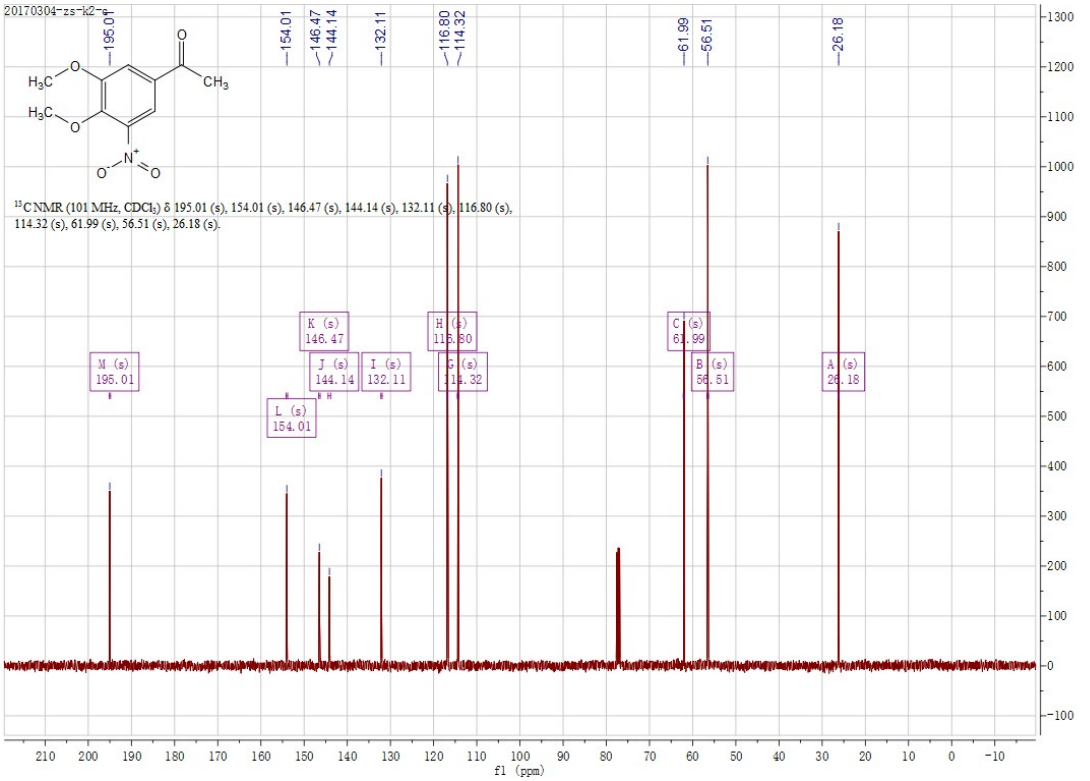
2





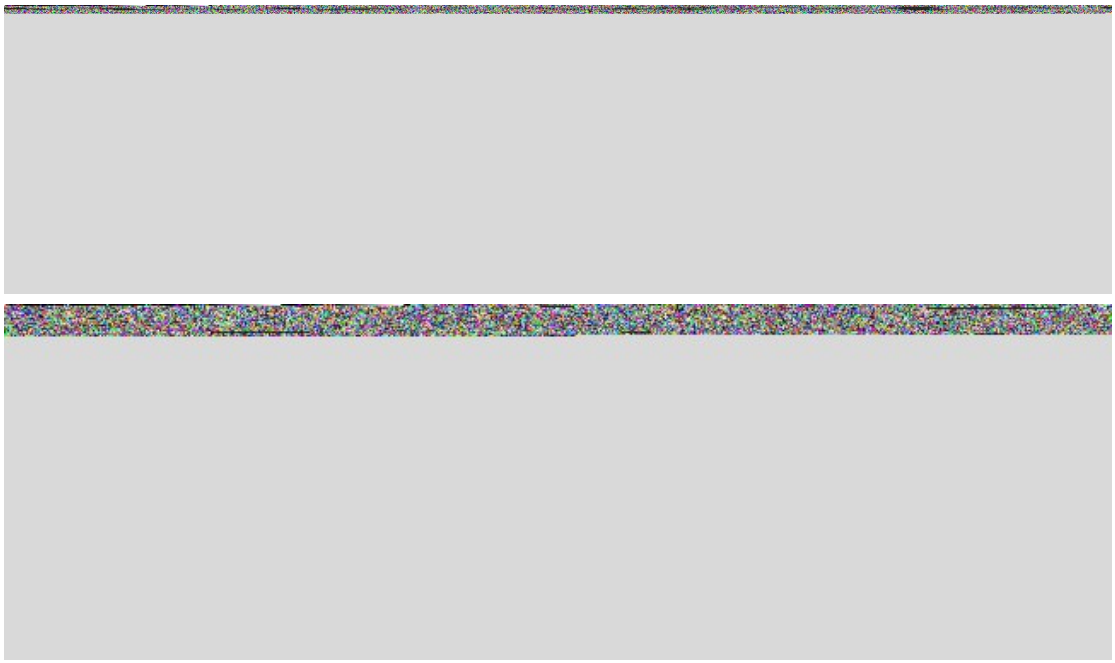
3


20170304-zs-k2
7.88
7.72
4.04
4.01
2.63
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (s, 1H), 7.72 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 2.63 (s, 3H).
B (s) 7.72
A (s) 7.88
D (s) 4.01
C (s) 4.04
E (s) 2.63
1.00
1.00
3.00
3.15
3.11
f1 (ppm)

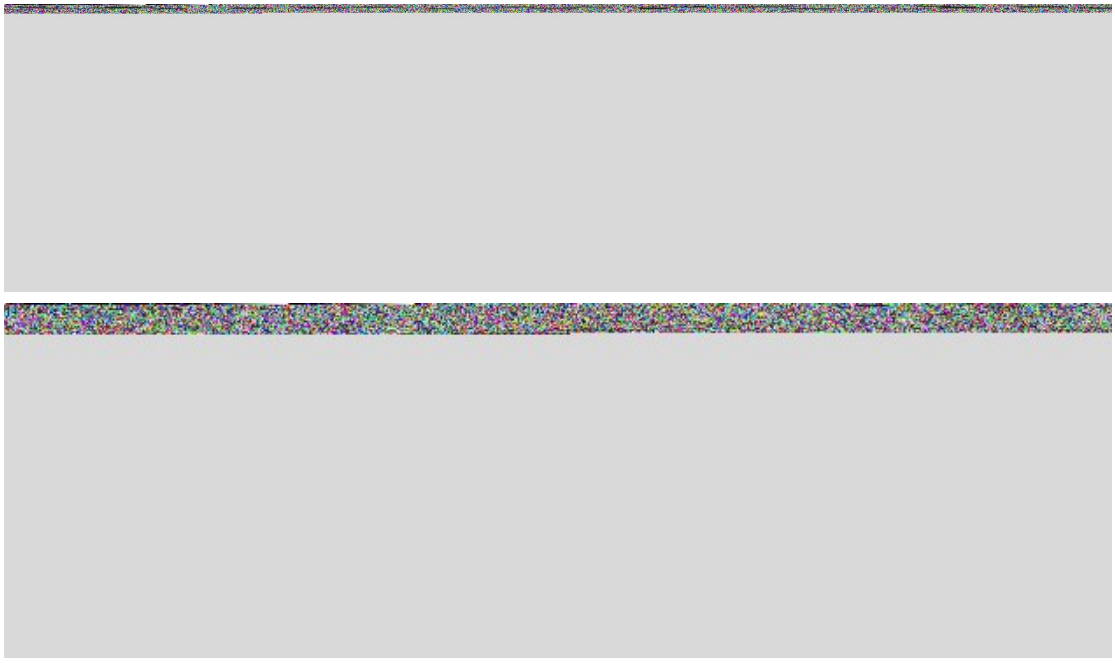

20170304-zs-k2-
195.01
154.01
146.47
144.14
132.11
116.80
114.32
61.99
56.51
26.18
^{13}C NMR (101 MHz, CDCl$_3$) δ 195.01 (s), 154.01 (s), 146.47 (s), 144.14 (s), 132.11 (s), 116.80 (s), 114.32 (s), 61.99 (s), 56.51 (s), 26.18 (s).
M (s) 195.01
L (s) 154.01
K (s) 146.47
J (s) 144.14
I (s) 132.11
H (s) 116.80
G (s) 114.32
C (s) 61.99
B (s) 56.51
A (s) 26.18
f1 (ppm)

SI3. HPLC chromatograms of target compounds

12a



12b



12c

12d

12e

12f

12g

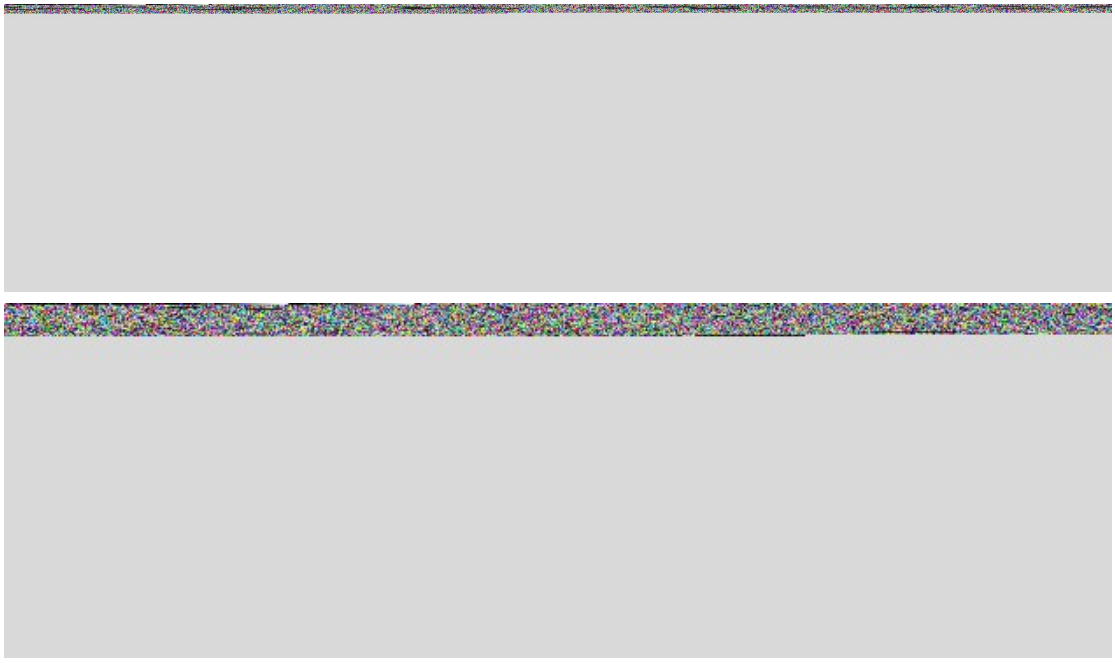
12h

13a

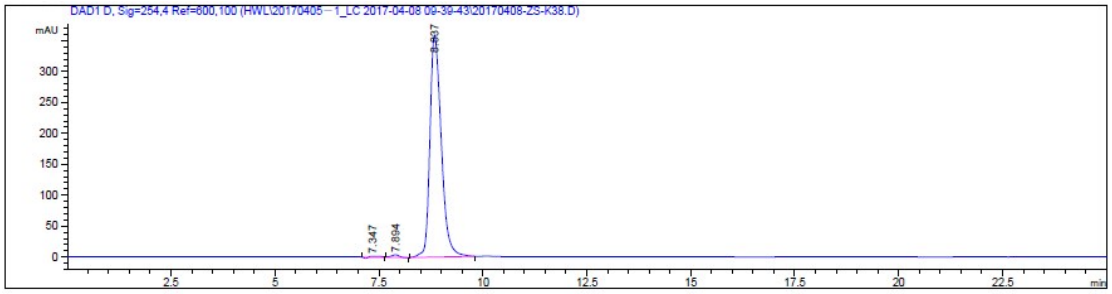
13b

14a

14b



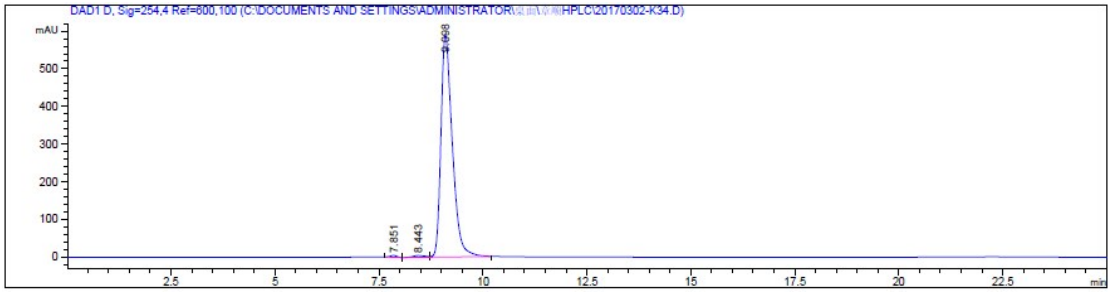
25a



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.347	BB	0.2049	22.68031	1.64424	0.3287
2	7.894	BB	0.1914	54.67888	4.32884	0.7925
3	8.837	BB	0.2953	6822.19580	359.69595	98.8788
总量 :				6899.55499	365.66903	

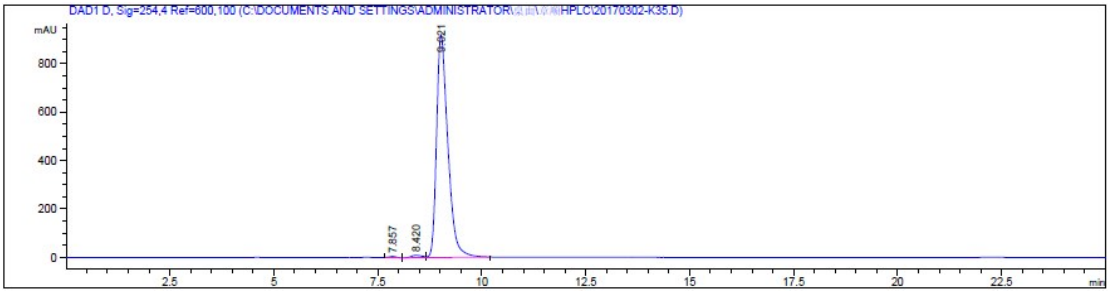
25b



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.851	BV	0.1720	52.59585	4.71885	0.4622
2	8.443	VV	0.2959	97.33435	4.81411	0.8553
3	9.098	VB	0.2817	1.12302e4	591.02191	98.6825
总量 :				1.13801e4	600.55487	

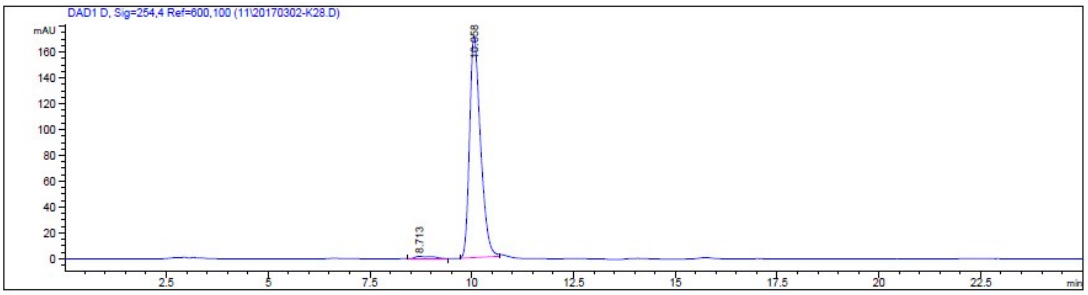
25c



信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.851	BV	0.1720	52.59585	4.71885	0.4622
2	8.443	VV	0.2959	97.33435	4.81411	0.8553
3	9.098	VB	0.2817	1.12302e4	591.02191	98.6825
总量 :				1.13801e4	600.55487	

27

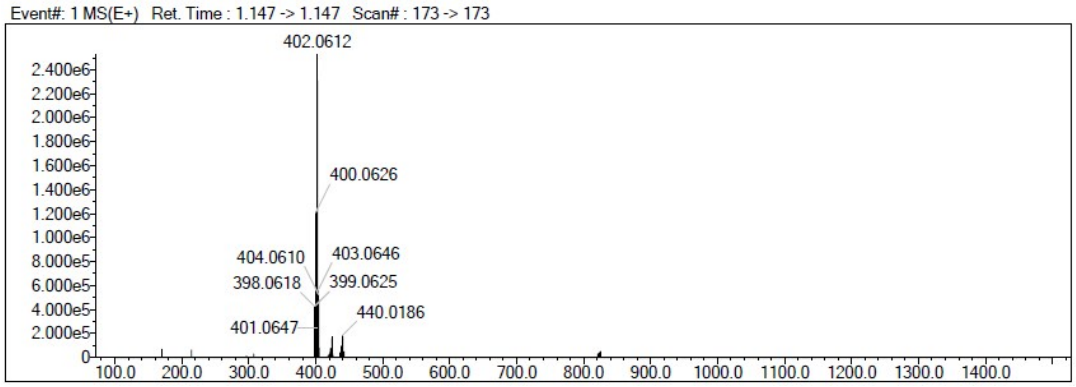


信号 1: DAD1 D, Sig=254,4 Ref=600,100

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	8.713	BB	0.4158	54.50431	1.74787	1.6700
2	10.058	BB	0.2803	3209.15015	171.52037	98.3300
总量 :				3263.65446	173.26824	

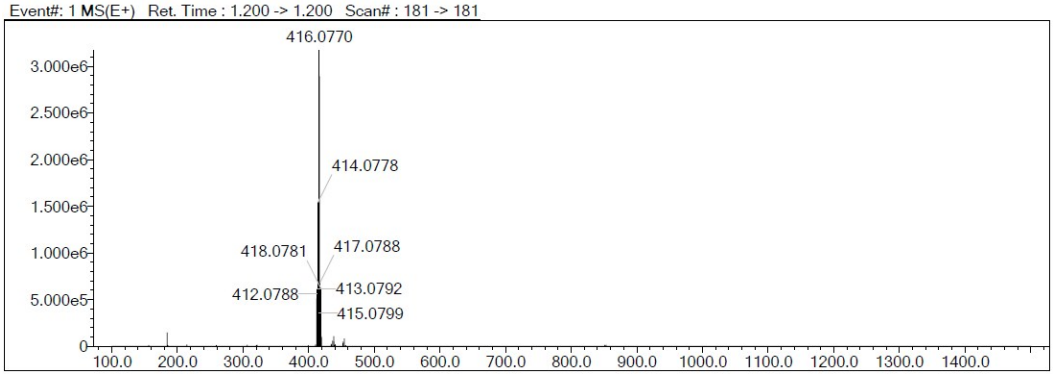
SI4. HR-MS of target compounds

12a



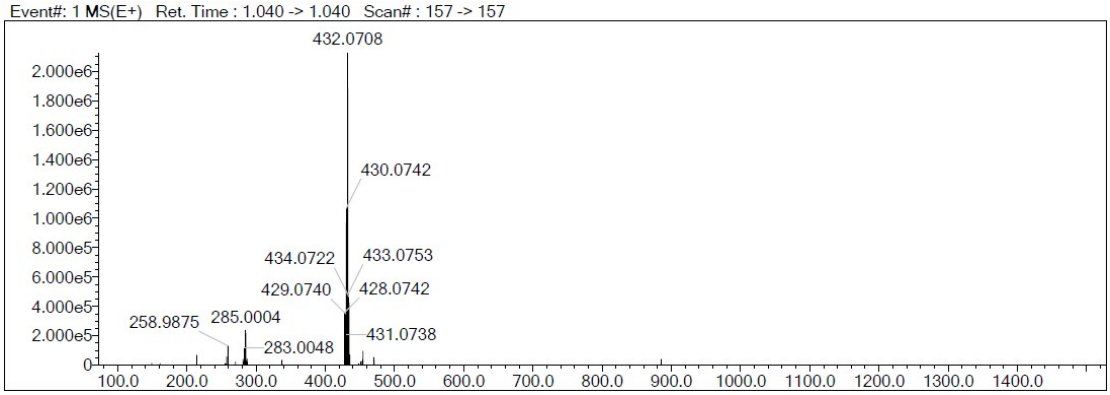
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	97.53	C20 H19 N O3 Se	[M+H]+	402.0612	402.0604	0.8	1.99	100.00	12.0

12b



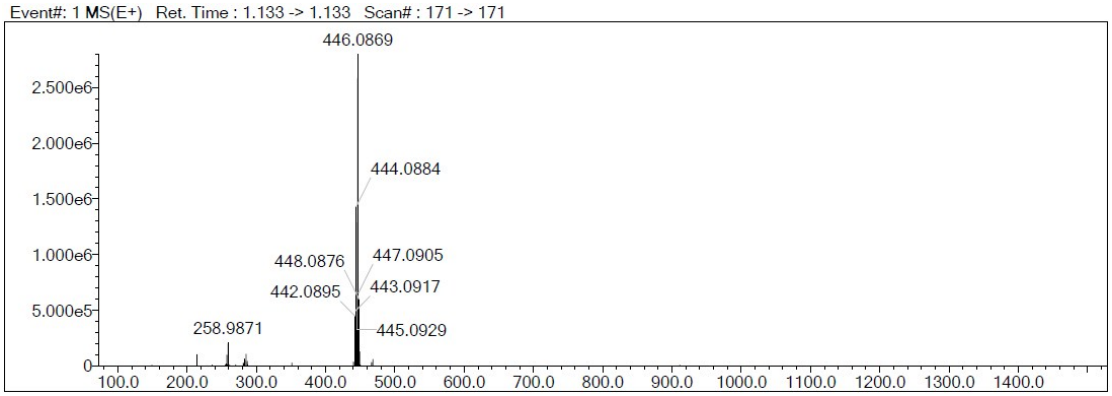
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	97.10	C21 H21 N O3 Se	[M+H]+	416.0770	416.0761	0.9	2.16	100.00	12.0

12c



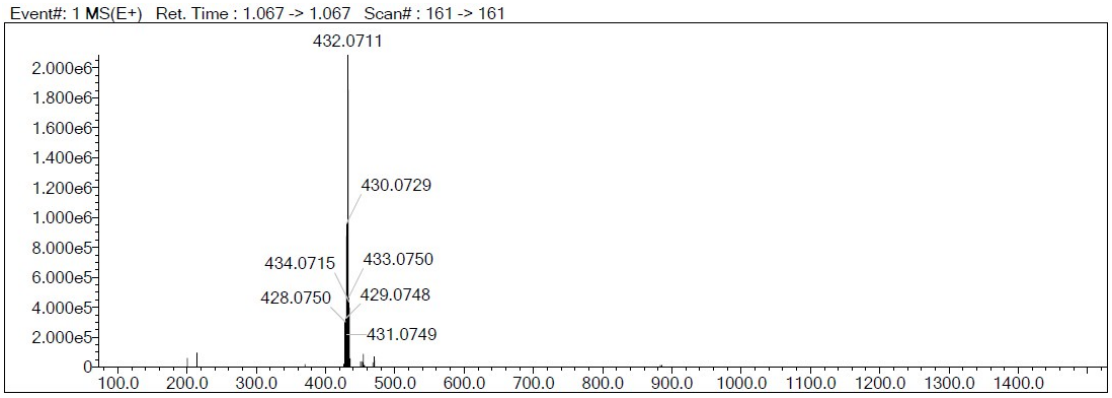
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	100.00	C21 H21 N O4 Se	[M+H]+	432.0708	432.0710	-0.2	-0.46	100.00	12.0

12d



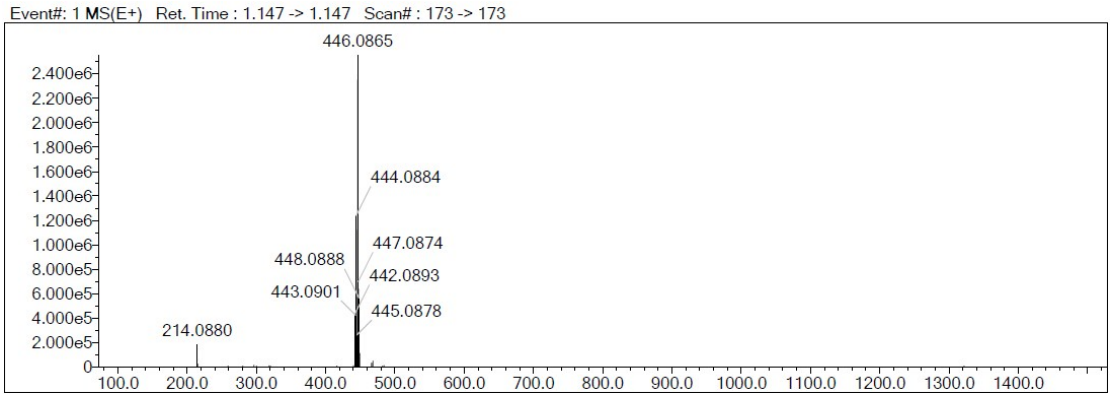
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	100.00	C22 H23 N O4 Se	[M+H]+	446.0869	446.0866	0.3	0.67	100.00	12.0

12e



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	99.48	C21 H21 N O4 Se	[M+H]+	432.0711	432.0710	0.1	0.23	99.48	12.0

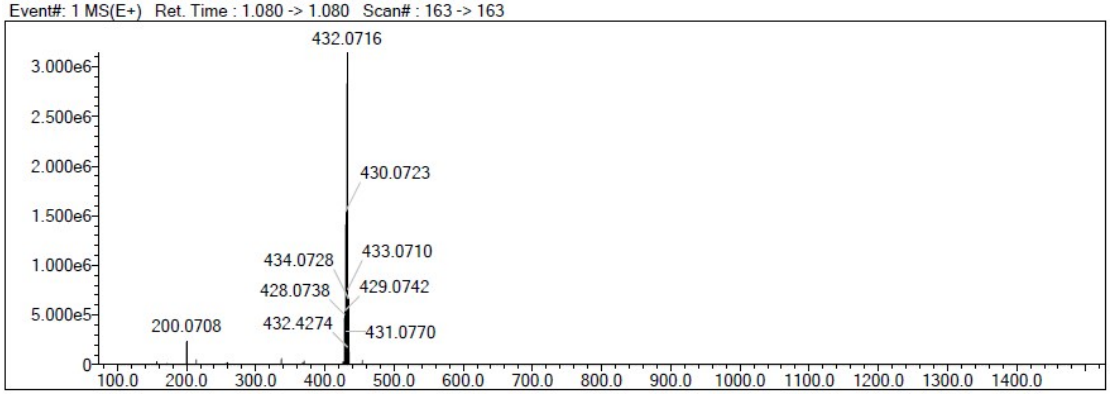
12f



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	100.00	C22 H23 N O4 Se	[M+H]+	446.0865	446.0866	-0.1	-0.22	100.00	12.0

12g

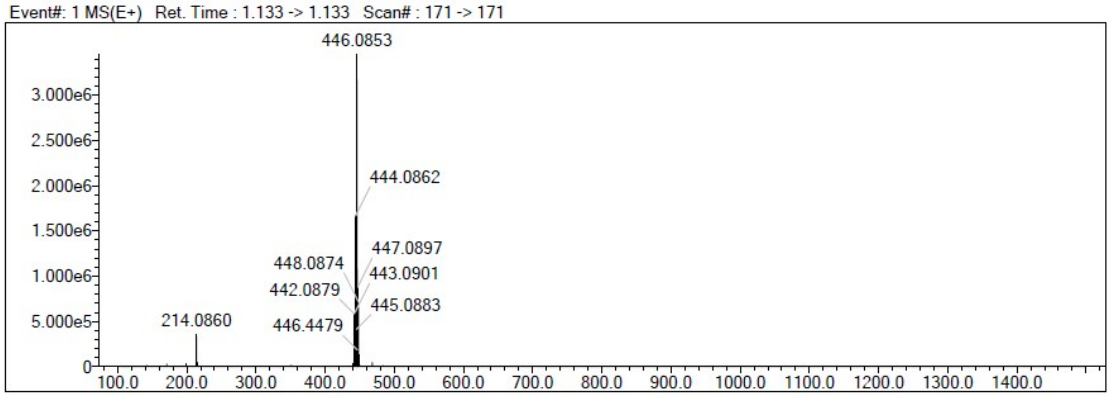
Event#: 1 MS(E+) Ret. Time : 1.080 -> 1.080 Scan# : 163 -> 163



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	99.03	C21 H21 N O4 Se	[M+H]+	432.0716	432.0710	0.6	1.39	100.00	12.0

12h

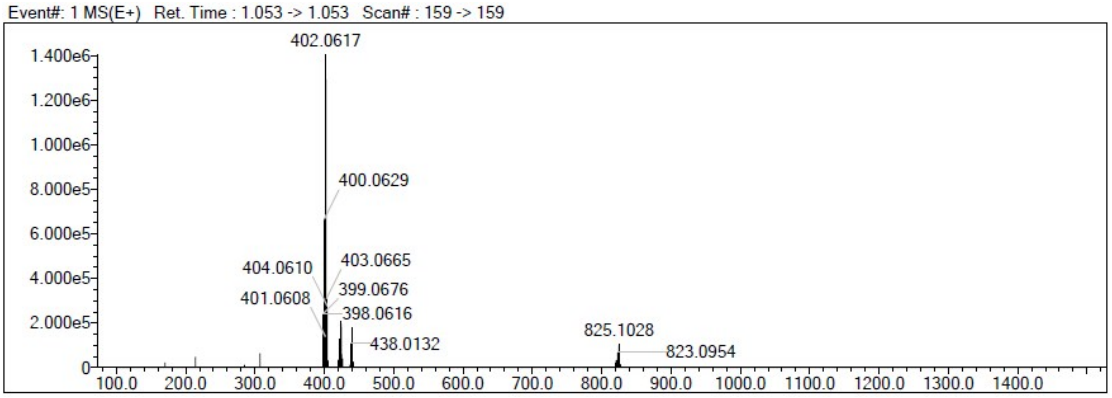
Event#: 1 MS(E+) Ret. Time : 1.133 -> 1.133 Scan# : 171 -> 171



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	95.22	C22 H23 N O4 Se	[M+H]+	446.0853	446.0866	-1.3	-2.91	100.00	12.0

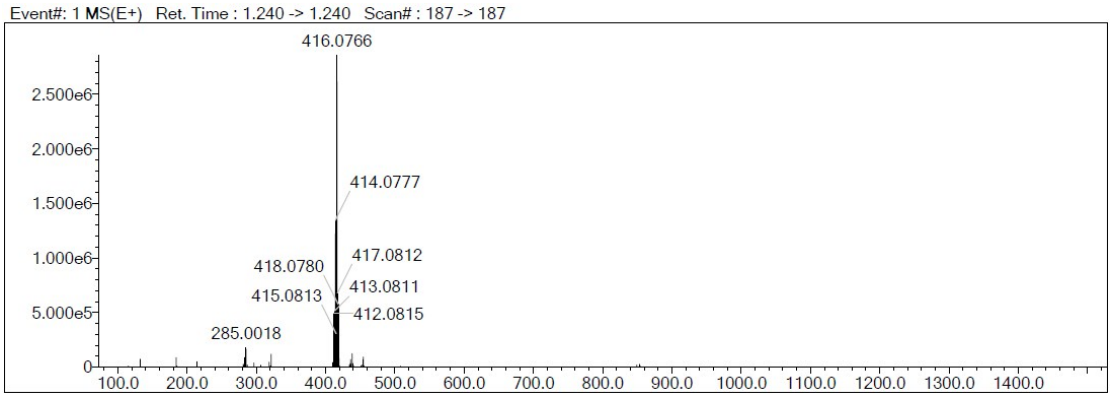
13a

Event#: 1 MS(E+) Ret. Time : 1.053 -> 1.053 Scan# : 159 -> 159



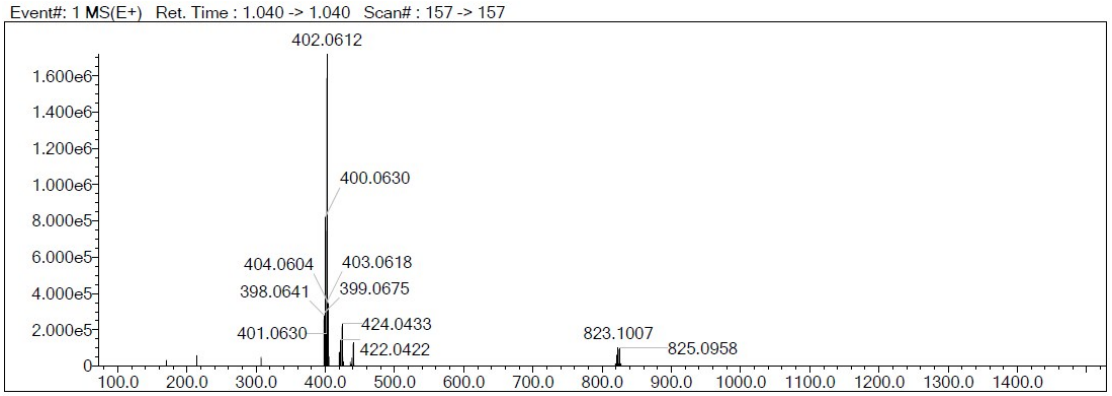
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	94.42	C20 H19 N O3 Se	[M+H]+	402.0617	402.0604	1.3	3.23	100.00	12.0

13b



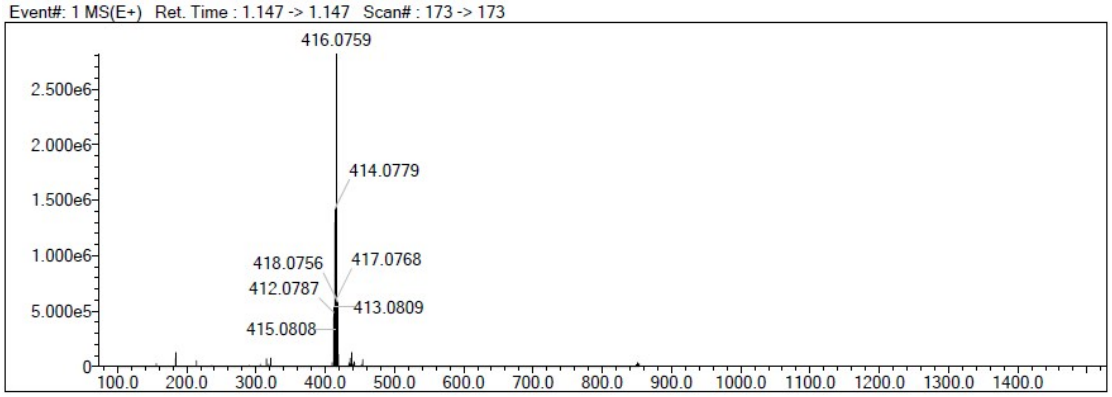
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	99.50	C21 H21 N O3 Se	[M+H]+	416.0766	416.0761	0.5	1.20	100.00	12.0

14a



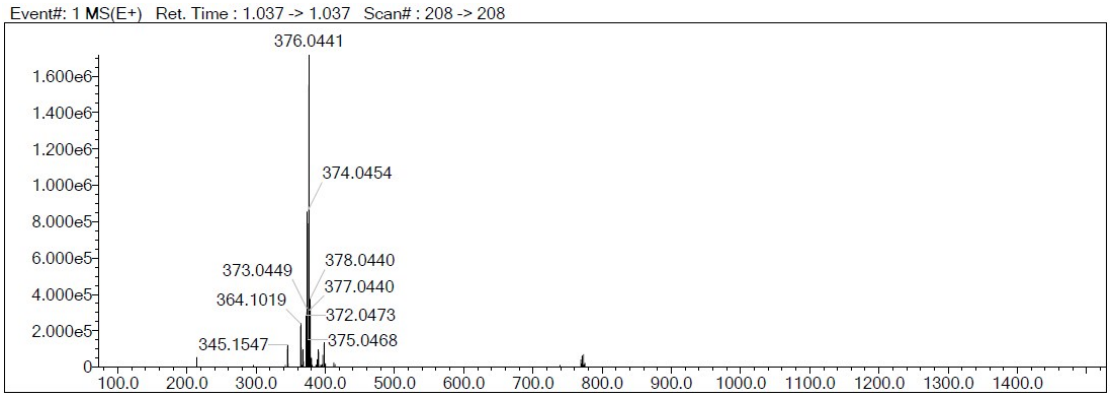
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	97.53	C20 H19 N O3 Se	[M+H]+	402.0612	402.0604	0.8	1.99	100.00	12.0

14b



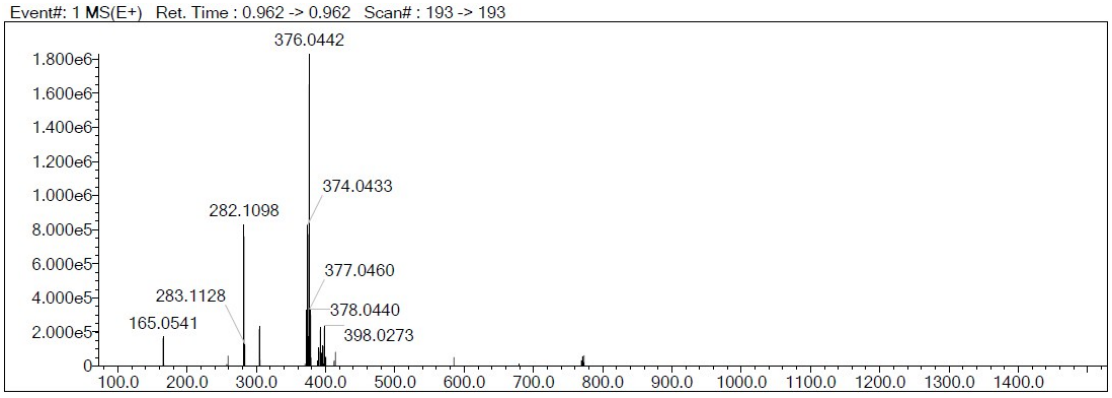
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	100.00	C21 H21 N O3 Se	[M+H]+	416.0759	416.0761	-0.2	-0.48	100.00	12.0

25a



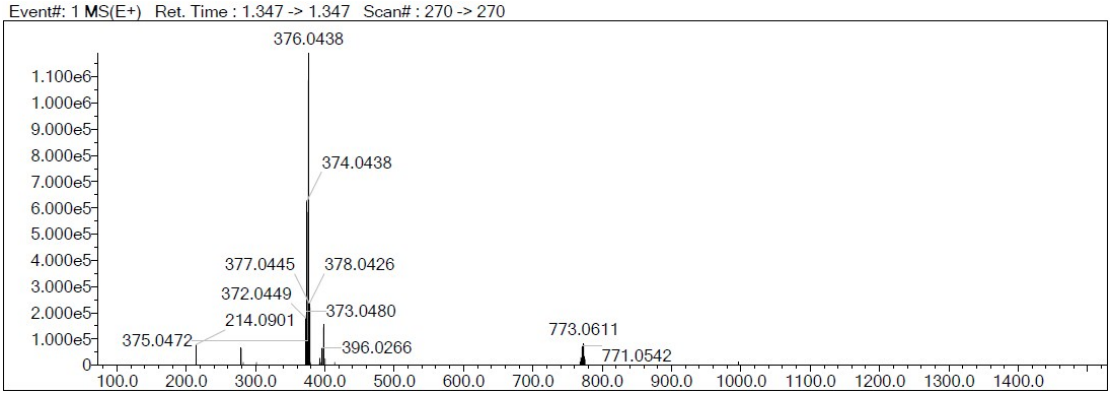
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.50	C18 H17 N O3 Se	[M+H]+	376.0441	376.0447	-0.6	-1.60	100.00	11.0

25b



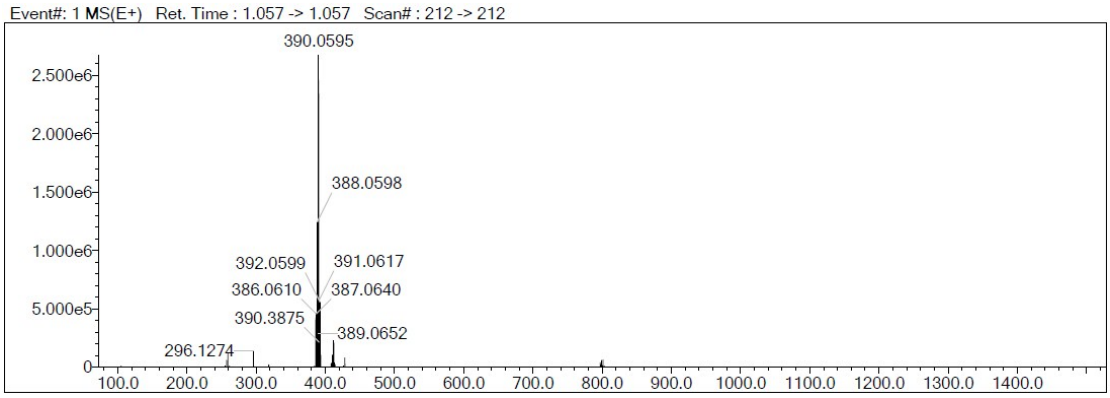
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	99.17	C18 H17 N O3 Se	[M+H]+	376.0442	376.0447	-0.5	-1.33	100.00	11.0

25c



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	96.53	C18 H17 N O3 Se	[M+H]+	376.0438	376.0447	-0.9	-2.39	100.00	11.0

27



Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	96.72	C19 H19 N O3 Se	[M+H]+	390.0595	390.0604	-0.9	-2.31	100.00	11.0

Reference;

1 C. J. Trabbic, J. H. Overmeyer, E. M. Alexander, E. J. Crissman, H. M. Kvale, M. A. Smith, P. W. Erhardt, W. A. Maltese, *J. Med. Chem.*, 2015, **58**, 2489-512.

2 M. S. Pedras, A. Abdoli, *Bioorg. Med. Chem.*, 2013**, 21**, 4541-4549.

3 M. Z. Zhan, Q. Chen, N. Mulholland, *Eur. J. Med. Chem.*, 2012, **53**, 283-291.

4 J. Yan, J. Chen, S. Zhang, J. Hu, L. Huang, X. Li, *J. Med. Chem.*, 2016, **59**, 5264−5283.