Supplementary Information

Racemising 3-aryl-3-hydroxy-2-oxindoles in a Pickering emulsion under acid catalysis and its application to dynamic kinetic resolution

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1. General information

^{1}H, ^{13}C and ^{19}F NMR spectra were measured on a JEOL-ECA500 instrument (^{1}H: 500 MHz, ^{13}C: 126 MHz, ^{19}F: 471 MHz). Chemical shifts were reported in δ (ppm). Chemical shifts were reported in δ (ppm) relative to the deuterated solvents (7.26 ppm (^{1}H) and 77.0 ppm (^{13}C) for $CDCl_3$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. HPLC analyses were carried out using a JASCO LC-2000 Plus system (HPLC pump: PU-2080, UV detector: MD-2018) equipped with a chiral stationary phase column (4.6 × 250 mm). Optical rotations were measured on a JASCO P-1020 polarimeter. High resolution mass spectra were measured on a JEOL JMS-T100LP (ESI) with a time of flight (TOF) mass analyzer.

All reagents were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), FUJIFILM Wako Chemical Co., Ltd. (Osaka, Japan), NACALAI TESQUE, INC. (Kyoto, Japan), and Merck Co., LLC (U.S.A.), and used without further purification. Molecular sieves 4 Å (powder, activated, –325 mesh particle size) was purchased from Merck, treated in a microwave (600 W, 1 min.), and then allowed to cool in vacuo prior to use. Flash chromatography was performed on silica gel 60N (particle size 40–50 μm) purchased from Kanto Chemical Co., Inc. (Tokyo, Japan).

2. Preparation of and characterisation of Pickering emulsions

Silica nanoparticles were prepared according to the literature method with a slight modification.[1,2] In brief, a mixture of EtOH (200 mL), deionised water (50 mL), aq. 27% NH_3 (11.2 mL), and $Si(OEt)_4$ (8.32 g) were stirred 12 h at room temperature. The formed nanoparticles were collected by centrifugation at 12,000 rpm for 5 min (KUBOTA 6200). The precipitate was washed by deionised water for 3 times, and then EtOH for 2 times by centrifugation. Then the precipitate was dried overnight at 120ºC under vacuum (5 mmHg).

Hydrophobic modification of the silica nanoparticles was conducted according to the literature method.[1] The dried silica nanoparticles (1.0 g), $MeSi(OMe)_3$ (3.0 mmol) and Et_3N (3.0 mmol) were added to anhydrous toluene (6 mL), and the resultant suspension was refluxed with vigorous stirring for 4 h under argon atmosphere. After that, the suspension was centrifuged at 12,000 rpm for 10 min, and the precipitate was washed by EtOH for 5 times. The resultant precipitate was dried at 60ºC overnight under vacuum (5 mmHg).

Methyl-modified silica nanoparticles (30 mg) were added to a screw-capped vial (ϕ =15 mm) containing *n*-octane (1.0 mL) and water or an aqueous acid solution (300 μL). The mixture was homogenised at 20,000 rpm for 90 sec using a T10 basic ULTRA-TURRAX homogenizer (IKA) equipped with a S10N-5G Dispersing tool. The prepared emulsion droplets were observed

using an Olympus FSX100 optical microscope (Figure S1). The Pickering emulsions were stable under the reaction conditions (5.0 M H_2SO_4, 80 °C, 18 h), with no colour changes or degradation observed during the reactions. A further increase in acid concentration, i.e. 7.0 M H_2SO_4, resulted in slight browning of the emulsion after 18 h of incubation at 70 °C. These observations suggest that the surface of the methyl-modified silica nanoparticles was partially degraded under higher acid concentration.

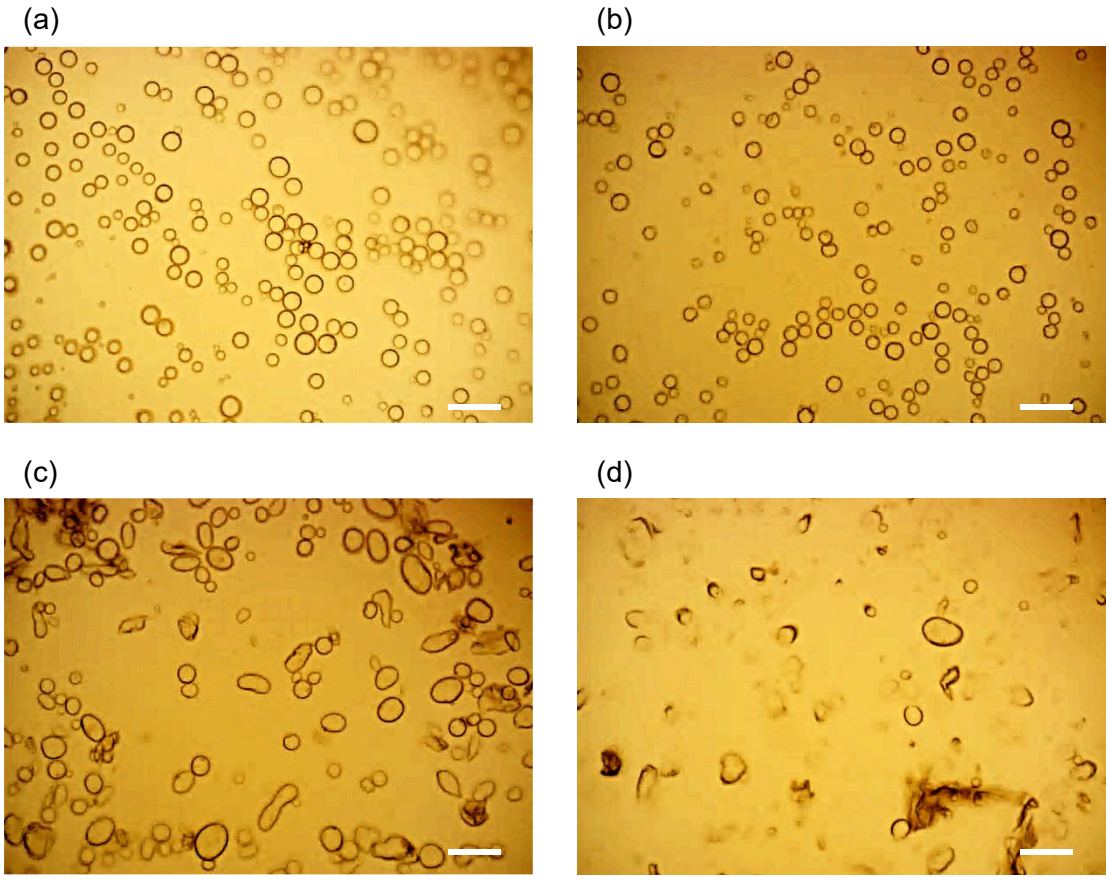
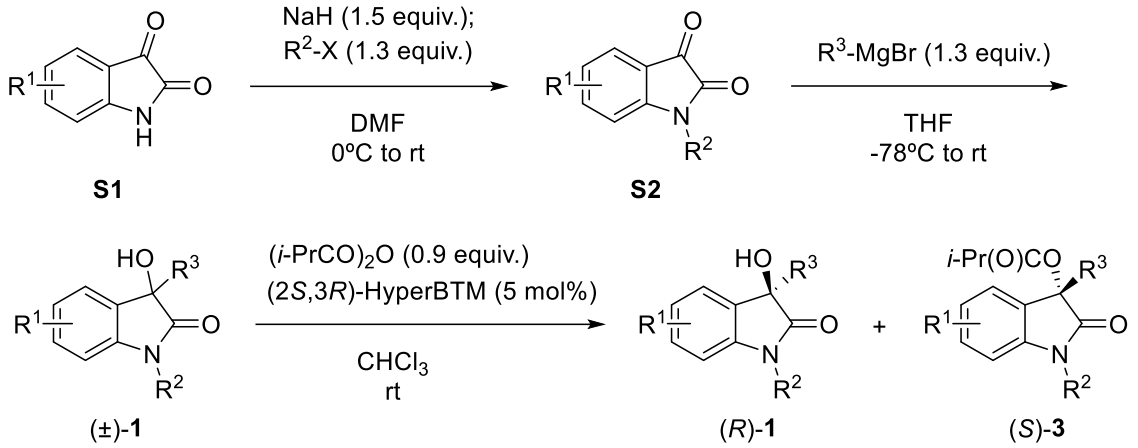


Figure S1. Microscopic image of Pickering emulsions: (a) deionised water as the aqueous phase; (b) 1.0 M H_2SO_4 as the aqueous phase; (c) 1.0 M HCl as the aqueous phase; (d) 1.0 M HNO_3 as the aqueous phase; Scale bars: 200 μm.

3. Substrate synthesis

Alcohols (±)-**1a**–**1m** were synthesised according to the following scheme. The obtained alcohol **1** was then subjected to (2*S*,3*R*)-HyperBTM-catalyzed kinetic resolution[3,6] to give optically active (*R*)-**1** and (*S*)-**3**.

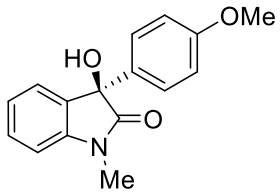


Typical procedure

In a 100-mL flask, sodium hydride (60% dispersion in mineral oil, 600 mg, 15 mmol) was added to a solution of isatin derivatives **S1** (10 mmol) in DMF (40 mL) at 0 ºC. The reaction solution was stirred at room temperature for 30 min. After that, alkyl halide (R^2-X, 12-15 mmol) was added dropwise to the solution. The resultant mixture was stirred at room temperature for 3 h. The reaction was quenched with water under 0 ºC, and the reaction mixture was extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtrated, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give N-substituted isatin **S2**.

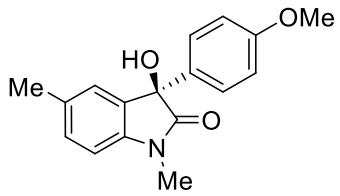
In a 100-mL flask, N-substituted isatin **S2** was dissolved in THF, and the corresponding Grignard reagent (R^3-MgBr, 1.3 equiv) was added dropwise at -78 °C. the solution stirred at -78 ºC for 30 min, then at 0 ºC for 3-10 h. The reaction was quenched with aqueous ammonium chloride solution under 0 ºC, and the reaction mixture was extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous sodium sulfate, filtrated, and evaporated in vacuo. The residue was purified by silica gel column chromatography to give alcohol (±)-**1**.

Alcohol (±)-**1** (1.0 mmol), isobutyric anhydride (150 µL, 0.90 mmol) and (2*S*,3*R*)-HyperBTM (15 mg, 0.05 mmol) were dissolved in $CHCl_3$ (10 mL). After stirring for 16 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography to give alcohol (*R*)-**1** and ester (*S*)-**3**. The enantiomeric excess of (*R*)-**1** was determined by HPLC analysis using chiral stationary phase. The spectroscopic data of (*R*)-**1** matched with those of racemised compounds, which are described in the next section.



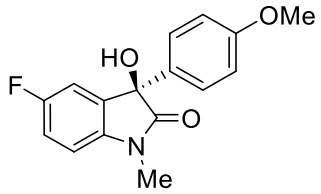
(*R*)-3-Hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((*R*)-1a)

98% ee; HPLC analysis DAICEL CHIRALPAK IE-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 17.9 min (*major*), 22.9 min (*minor*).



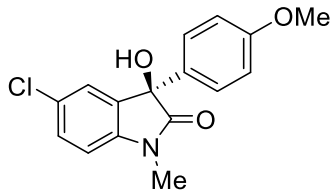
(*R*)-3-Hydroxy-3-(4-methoxyphenyl)-1,5-dimethyloxindole ((*R*)-1b)

99% ee; HPLC analysis DAICEL CHIRALPAK IF-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 13.5 min (*major*), 15.3 min (*minor*).



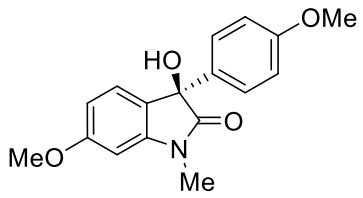
(*R*)-5-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((*R*)-1c)

99% ee; HPLC analysis DAICEL CHIRALPAK IM-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 12.3 min (*major*), 18.6 min (*minor*).



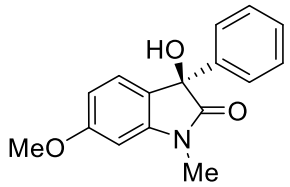
(*R*)-5-Chloro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((*R*)-1d)

99% ee; HPLC analysis DAICEL CHIRALPAK IC-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 17.0 (*major*), 20.3 min (*minor*).



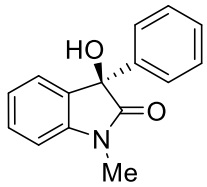
(*R*)-3-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-1-methyloxindole ((*R*)-1e)

99% ee; HPLC analysis DAICEL CHIRALPAK IA-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 13.6 min (*minor*), 14.9 min (*major*).



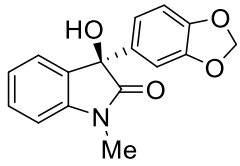
(*R*)-3-Hydroxy-6-methoxy-1-methyl-3-phenyloxindole ((*R*)-1f)

99% ee; HPLC analysis DAICEL CHIRALPAK IM-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 16.5 min (*major*), 23.0 min (*minor*).



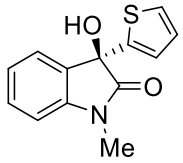
(*R*)-3-Hydroxy-1-methyl-3-phenyloxindole ((*R*)-1g)

99% ee; HPLC analysis DAICEL CHIRALPAK IC-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 12.4 min (*minor*), 16.3 min (*major*).



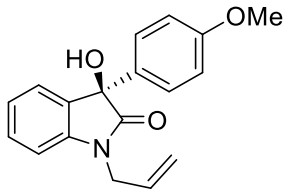
(*R*)-3-(Benzo[d][1,3]dioxo-5-yl)-3-hydroxy-1-methyloxindole ((*R*)-1h)

99% ee; HPLC analysis DAICEL CHIRALPAK IE-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 21.0 min (*major*), 27.1 min (*minor*).



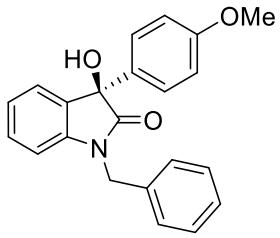
(*R*)-3-Hydroxy-1-methyl-3-(thiophen-2-yl)oxindole ((*R*)-1i)

58% ee; HPLC analysis DAICEL CHIRALPAK IM-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 13.0 min(*major*), 15.3 min (*minor*).



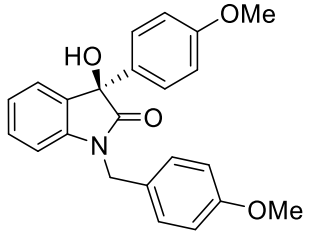
(*R*)-1-Allyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((*R*)-1k)

99% ee; HPLC analysis DAICEL CHIRALPAK IE-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 12.6 min (*major*), 16.1 min (*major*).



(*R*)-1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((*R*)-1l)

99% ee; HPLC analysis DAICEL CHIRALPAK IE-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 21.2 (*major*), 26.4 min (*minor*).



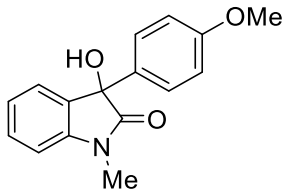
(*R*)-3-Hydroxy-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)oxindole ((*R*)-1m)

71% ee; HPLC analysis DAICEL CHIRALPAK IF-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC), t_R 22.7 min (*major*), 27.4 min (*minor*).

4. Racemisation in Pickering emulsion

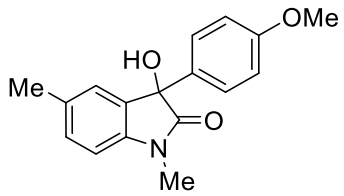
General procedure

A Pickering emulsion was prepared in a screw-capped vial (ϕ =15 mm) by mixing methyl-modified silica nanoparticles (60 mg), aqueous sulfuric acid (1.0–5.0 M, 600 μL), and *n*-octane (2.0 mL) at 20,000 rpm for 90 sec using a T10 basic ULTRA-TURRAX homogenizer (IKA) equipped with a S10N-5G Dispersing tool (ϕ =5 mm). After the supernatant organic layer was removed, toluene (1.2 mL) containing (*R*)-**1** (0.10 mmol) was gently added to the vial. The vial was stood in an incubator at corresponding temperature without stirring. After 18 h, the reaction mixture was diluted with ethyl acetate and naeutralised by solid sodium hydrogen carbonate. The resulting mixture was dried over anhydrous magnesium sulfate, filtrated, and evaporated. The residue was purified by short-path silica gel column chromatography to give racemised alcohol **1**. The ^{1}H NMR spectra of (±)-**1a**, (±)-**1b**, (±)-**1d**, (±)-**1g**, (±)-**1h**, (±)-**1i**, (±)-**1k** and (±)-**1l** were in good agreement with those reported in the literature. Compounds (±)-**1c**, (±)-**1e**, (±)-**1f** and (±)-**1m** were fully characterized by ^{1}H and ^{13}C NMR, and HRMS because they are note reported in the literature.



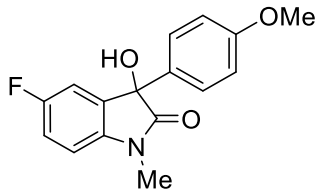
(±)-3-Hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1a) [3]

colourless solid, 26.1 mg (97% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 3.30 (s, 1H), 3.24 (s, 3H).



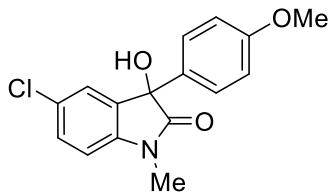
(±)-3-Hydroxy-3-(4-methoxyphenyl)-1,5-dimethyloxindole ((±)-1b) [4]

pale-yellow solid, 24.4 mg (85% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.15-7.12 (m, 2H), 6.87-6.84 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 3.23 (s, 3H), 3.10 (s, 1H), 2.31 (s, 3H).



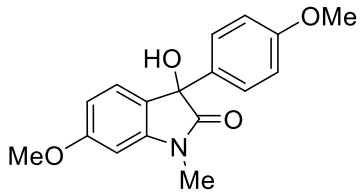
(±)-5-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1c)

colourless solid, 27.2 mg (95% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.06-7.03 (m, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.83 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.78 (s, 3H), 3.36 (s, 1H), 3.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.2, 158.9, 158.3, 138.9, 138.9, 135.1, 135.0, 133.5, 129.4, 114.6, 114.4, 113.9, 113.7, 109.0, 109.0, 61.5, 61.5, 55.2, 26.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ –119.1 (td, *J* = 8.3, 4.0 Hz); HRMS (ESI) *m/z* calcd. for $C_{16}H_{14}FNO_3Na$ $[M+Na]^+$: 310.0849, found: 310.0849.



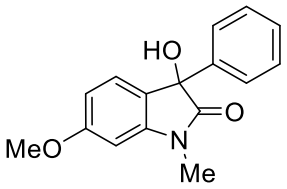
(±)-5-Chloro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1d) [4]

yellow solid, 28.0 mg (92% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 4H), 6.88-6.85 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.39 (s, 1H), 3.23 (s, 3H).



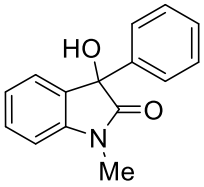
(±)-3-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1e)

colourless solid, 29.9 mg (>99% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.86-6.83 (m, 2H), 6.58 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.47 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.21 (s, 3H), 3.01 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 161.6, 159.7, 145.1, 132.5, 127.0, 125.9, 123.7, 114.1, 107.1, 96.9, 55.7, 55.4, 26.6; HRMS (ESI) *m/z* calcd. for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$: 322.1050, found: 322.1050.



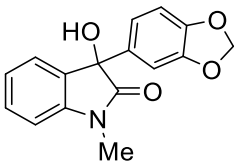
(±)-3-Hydroxy-6-methoxy-1-methyl-3-phenyloxindole ((±)-1f)

colourless solid, 25.3 mg (94% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.34-7.27 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.57 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 3.84 (s, 3H), 3.24 (s, 3H), 3.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 161.3, 144.9, 140.5, 128.4, 128.0, 125.8, 125.5, 123.9, 107.0, 96.7, 77.7, 55.6, 26.4; HRMS (ESI) *m/z* calcd. for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$: 292.0944, found: 292.0946.



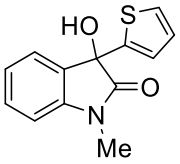
(±)-3-Hydroxy-1-methyl-3-phenyloxindole ((±)-1g) [3]

pale-yellow solid, 23.9 mg (>99% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 7H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 3.27 (s, 1H), 3.26 (s, 3H).



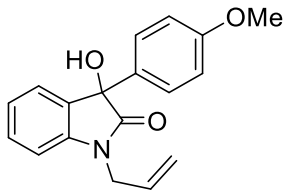
(±)-3-(Benzo[d][1,3]dioxo-5-yl)-3-hydroxy-1-methyloxindole ((±)-1h) [5]

colourless solid, 22.9 mg (81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.8, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.10 (td, *J* = 7.6, 0.9 Hz, 1H), 6.91-6.89 (m, 2H), 6.83 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.93 (q, *J* = 1.6 Hz, 2H), 3.28 (s, 1H), 3.24 (s, 3H).



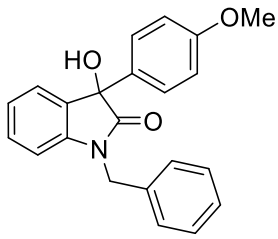
(±)-3-Hydroxy-1-methyl-3-(thiophen-2-yl)oxindole ((±)-1i) [3]

pale-yellow solid, 23.3 mg (95% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.93 (dd, *J* = 4.9, 3.7 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 3.66 (s, 1H), 3.22 (s, 3H).



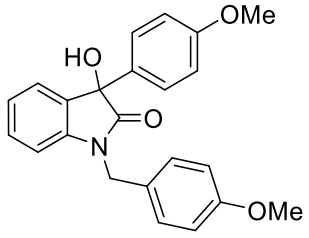
(±)-1-Allyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((±)-1k) [6]

colourless solid, 29.5 mg (>99% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.29 (m, 4H), 7.08 (td, *J* = 7.5, 0.9 Hz, 1H), 6.90-6.88 (m, 1H), 6.88-6.85 (m, 2H), 5.90-5.82 (m, 1H), 5.28-5.23 (m, 2H), 4.45 (dtd, *J* = 16.3, 3.4, 1.7 Hz, 1H), 4.27 (dtd, *J* = 16.3, 3.4, 1.7 Hz, 1H), 3.78 (s, 3H), 3.23 (s, 1H).



(±)-1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((±)-1l) [7]

pale-yellow solid, 25.2 mg (73% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 8H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 7.05 (td, *J* = 7.6, 0.8 Hz, 1H), 6.89-6.86 (m, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 3.79 (s, 3H), 3.25 (s, 1H).



(±)- **3-Hydroxy-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)oxindole ((±)-1m)**

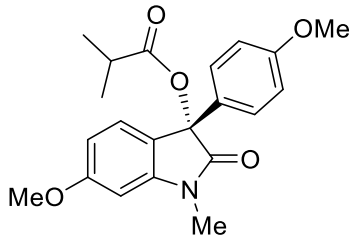
pale-yellow solid, 37.1 mg (99% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.29 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.25-7.21 (m, 3H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 6.89-6.83 (m, 4H), 6.80 (d, *J* = 7.9 Hz, 1H), 4.96 (d, *J* = 15.3 Hz, 1H), 4.77 (d, *J* = 15.3 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.20 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 159.7, 159.3, 142.7, 132.3, 131.8, 129.8, 128.8, 127.6, 126.9, 125.1, 123.6, 114.4, 114.2, 109.9, 77.7, 55.4, 55.4, 43.6; HRMS (ESI) *m/z* calcd. for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$: 398.1358, found: 398.1362.

Large-scale experiment

A Pickering emulsion was prepared in a 250-mL beaker by mixing methyl-modified silica nanoparticles (1.8 g), aqueous sulfuric acid (5.0 M, 18 mL), and *n*-octane (60 mL) at 20,000 rpm for 90 sec using a T10 basic ULTRA-TURRAX homogenizer (IKA) equipped with a S10N-8G Dispersing tool (ϕ = 8 mm). After the supernatant organic layer was removed, toluene (36 mL) containing (*R*)-**1a** (3.0 mmol, 808 mg) was gently added to the beaker. The beaker was stood in an incubator at 50ºC without stirring. After 18 h, the reaction mixture was diluted with diethyl ether and naturized by aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with ethyl acetate (10 mL x3). The combined organic layers were dried over anhydrous sodium sulfate, filtrated, and evaporated in vacuo. The residue was purified by short-path silica gel column chromatography to give racemised alcohol (±)-**1a** (736 mg, 91% yield, <1% ee).

5. Dynamic kinetic resolution in Pickering emulsion

A Pickering emulsion was prepared in a screw-capped vial (ϕ =15 mm) by mixing methyl-modified silica nanoparticles (20 mg), aqueous sulfuric acid (5.0 M, 0.2 mL), and *n*-octane (1.0 mL) at 20,000 rpm for 90 sec using a T10 basic ULTRA-TURRAX homogenizer (IKA) equipped with a S10N-5G Dispersing tool (ϕ =5 mm). After the supernatant organic layer was removed, toluene (600 μL) containing (±)-**1e** (0.10 mmol) and isobutyric anhydride **2** (100 μL, 0.60 mmol) was gently added to the vial. Sodium isobutyrate (50 mg) and molecular sieves 4 Å (powder, 50 mg) were placed on top of the emulsion to cover the droplets, followed by addition of (2*S*,3*R*)-HyperBTM (3.0 mg, 10 mol%). The vial was stood in an incubator at 25 ºC without stirring. After 2 h, the reaction mixture was diluted with chloroform and neutralised by solid sodium hydrogen carbonate. The resulting mixture was dried over anhydrous magnesium sulfate, filtrated, and evaporated. The residue was purified by silica gel column chromatography to give ester (*S*)-**3e** (21.4 mg, 58% yield, 97% ee) and the recovered alcohol **1e** (7.6 mg, 28% yield, 62% ee). The absolute configuration of **3e** was assigned as *S* based on the previously reported HyperBTM catalyzed kinetic resolution of isatin derivatives.[3,6]



(*S*)-6-Methoxy-3-(4-methoxyphenyl)-1-methyl-2-oxoindolin-3-yl isobutyrate ((*S*)-3e)

pale-yellow oil, 21.4 mg (58% yield); 97% ee; optical rotation $[\alpha]_D^{27}$ = +72.2 (*c* 1.0, $CHCl_3$); HPLC analysis DAICEL CHIRALPAK IA-3 (Hexane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm, 30ºC) t_R 6.0 min (*major*), 7.4 min (*minor*); 97% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.84-6.81 (m, 2H), 6.64 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 161.7, 159.7, 146.0, 130.9, 128.0, 126.8, 119.5, 113.8, 106.9, 96.6, 83.4, 55.7, 55.4, 53.0, 26.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}NO_5Na$ $[M+Na]^+$: 392.1468, found: 392.1465.

6. References

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[2] W. Stöber, A. Fink and E. Bohn, *J. Colloid Interface Sci.*, 1968, **26**, 62–69.

[3] S. M. Smith, M. D. Greenhalgh, T. Feoktistova, D. M. Walden, J. E. Taylor, D. B. Cordes, A. M. Z. Slawin, P. H.-Y. Cheong and A. D. Smith, *Eur. J. Org. Chem.*, 2022, **2022**, e202101111.

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[5] A. Nasim, G. T. Thomas, J. S. Ovens and S. G. Newman, *Org. Lett.*, 2022, **24**, 7232–7236.

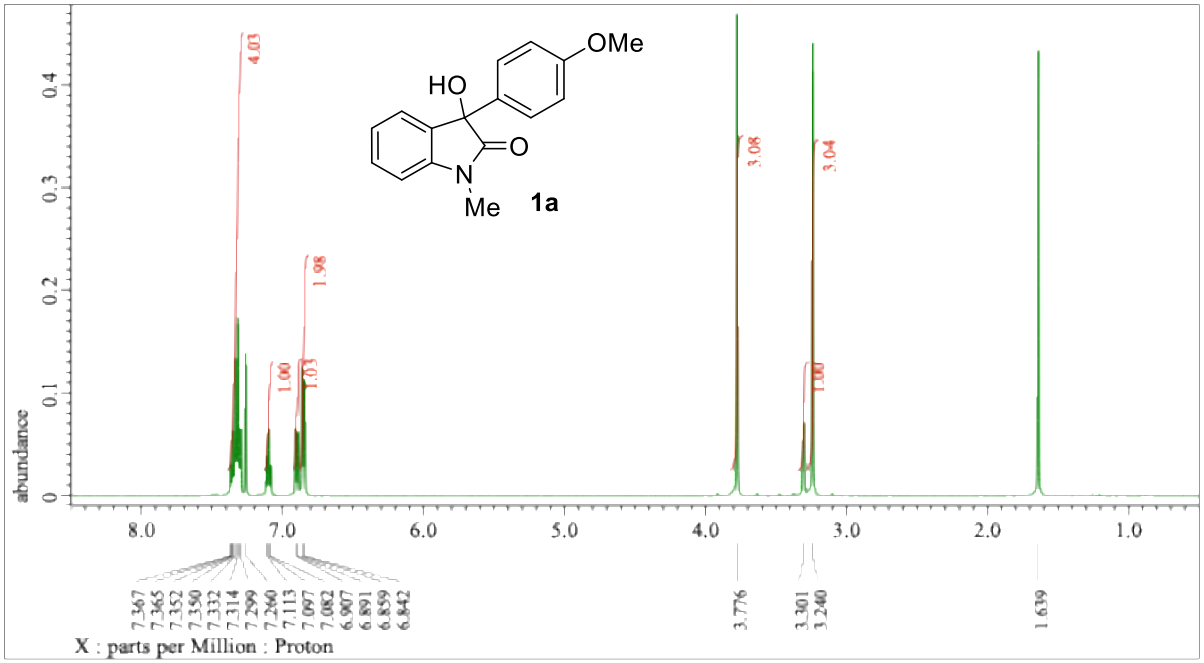
[6] M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H.-Y. Cheong and A. D. Smith, *Angew. Chem. Int. Ed.,* 2018, **57**, 3200–3206.

[7] G. R. Boyce, S. F. Musolino, J. Yang, A. D. Smith and J. E. Taylor, *J. Org. Chem.*, 2022, **87**, 13367–13374.

7. NMR and HPLC charts

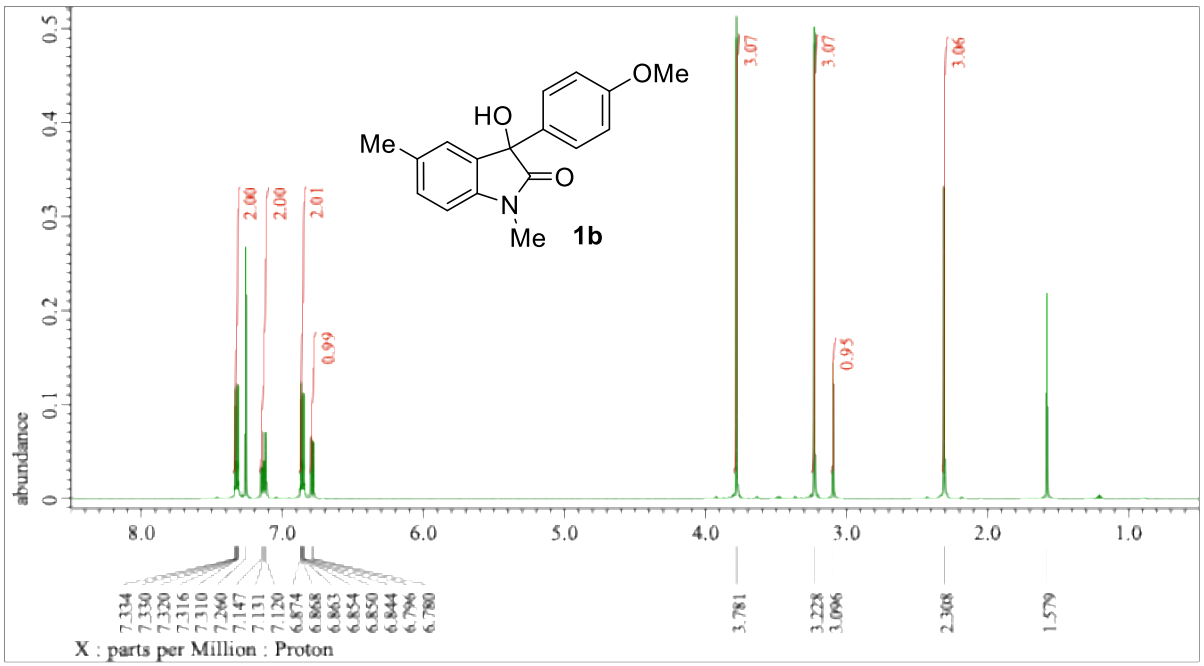
(±)-3-Hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1a)

^{1}H NMR



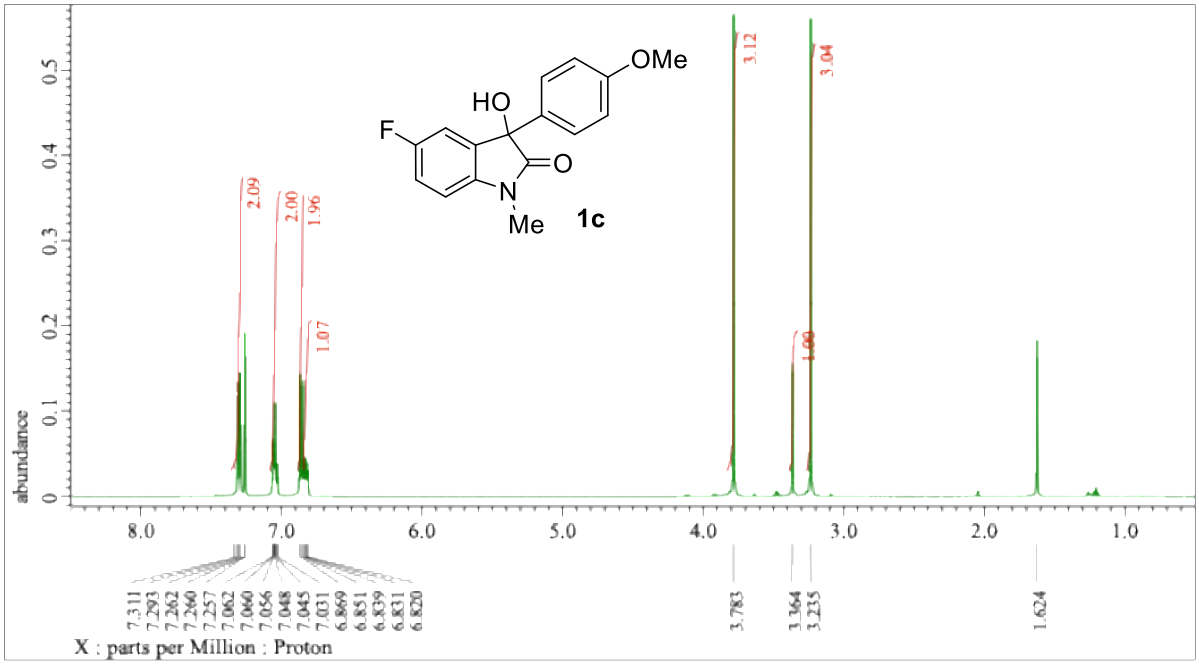
(±)-3-Hydroxy-3-(4-methoxyphenyl)-1,5-dimethyloxindole ((±)-1b)

^{1}H NMR

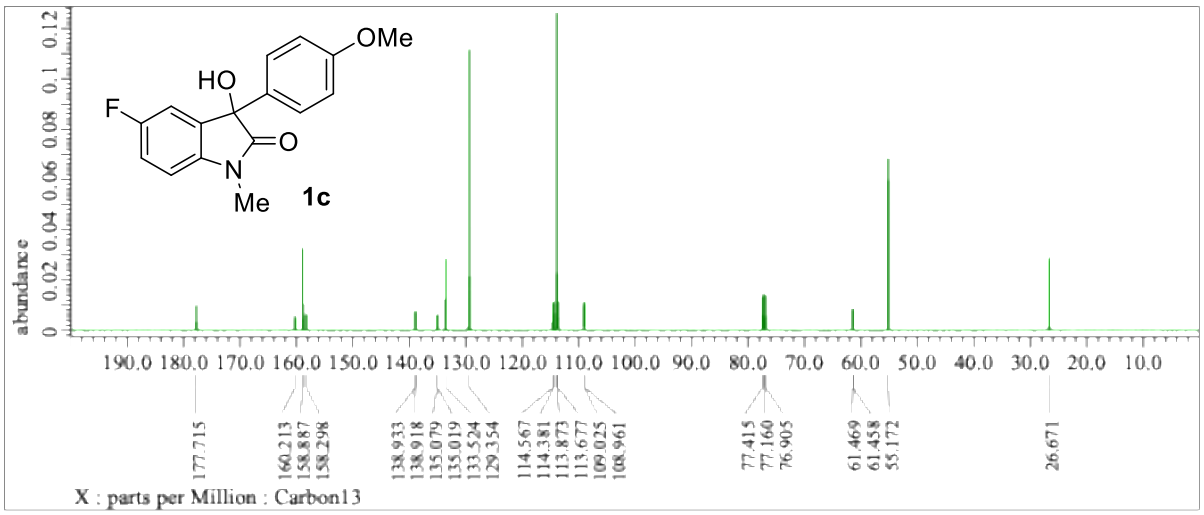


(±)-5-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1c)

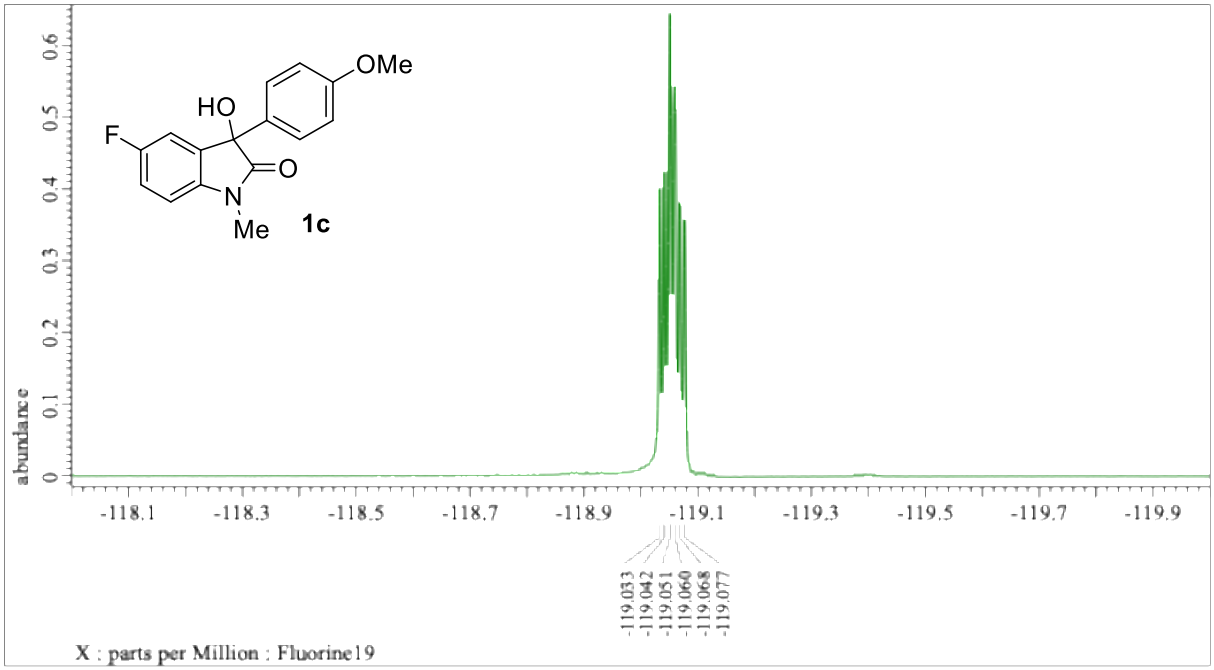
^{1}H NMR



^{13}C NMR

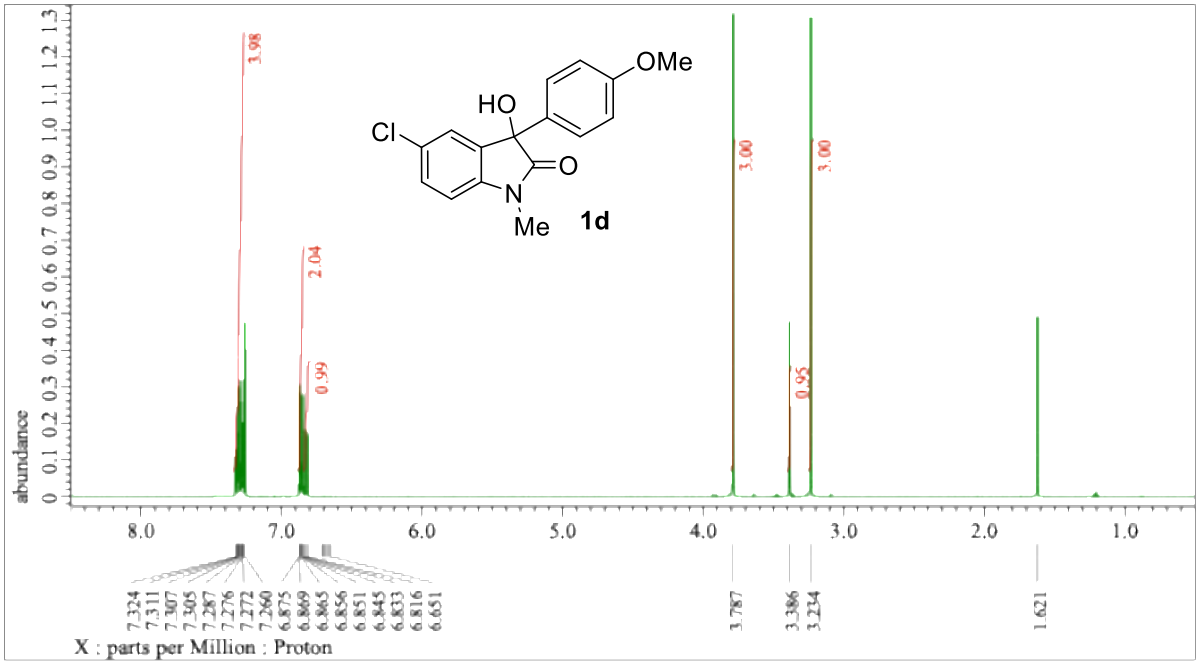


^{19}F NMR



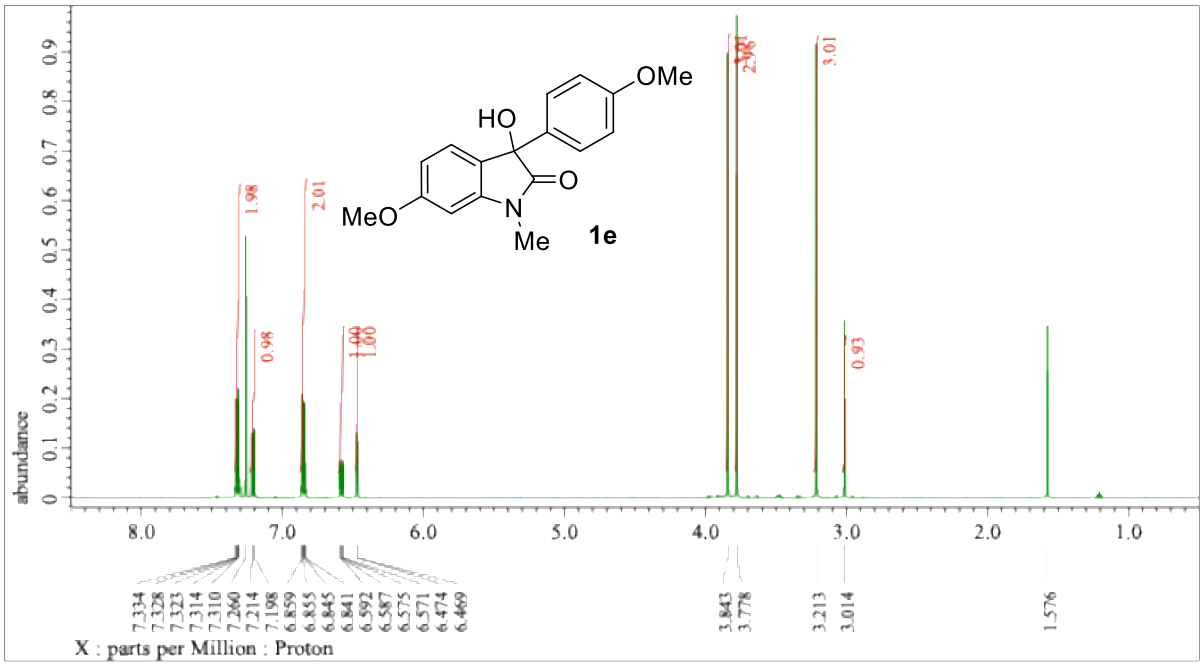
(±)-5-Chloro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1d)

^{1}H NMR

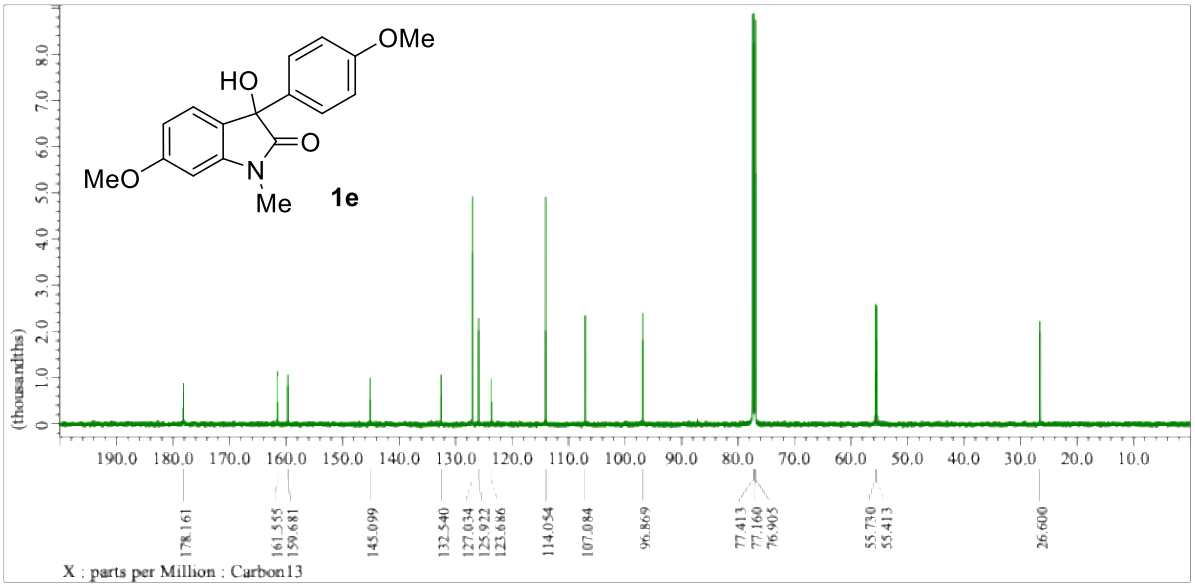


(±)-3-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-1-methyloxindole ((±)-1e)

^{1}H NMR

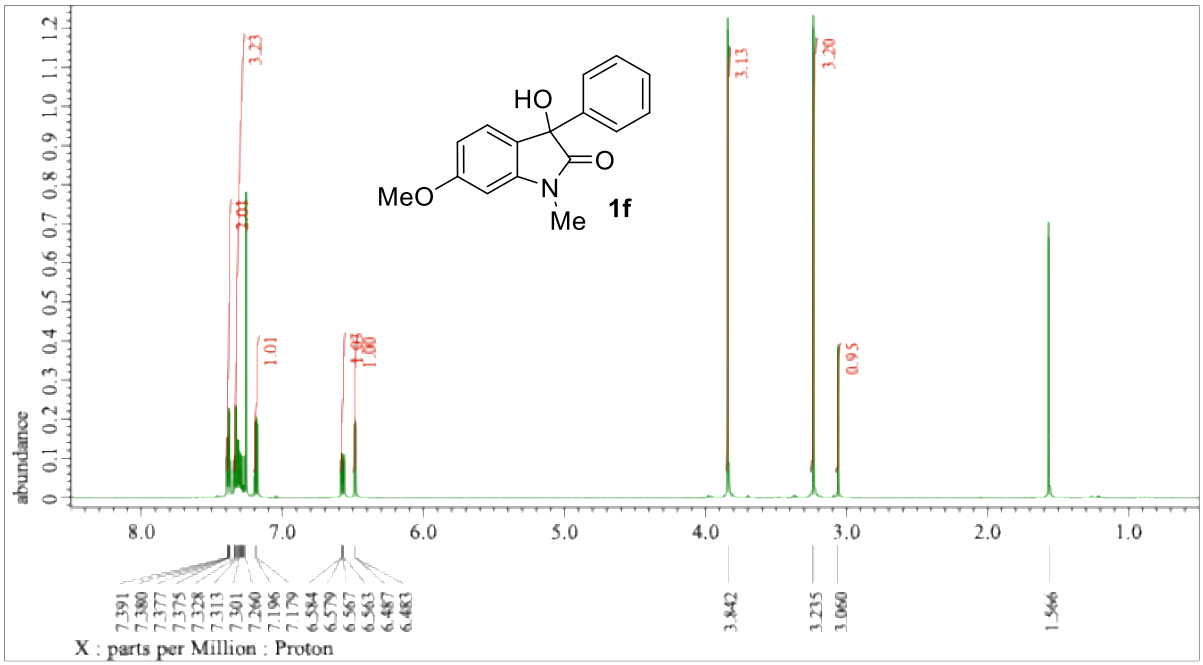


^{13}C NMR

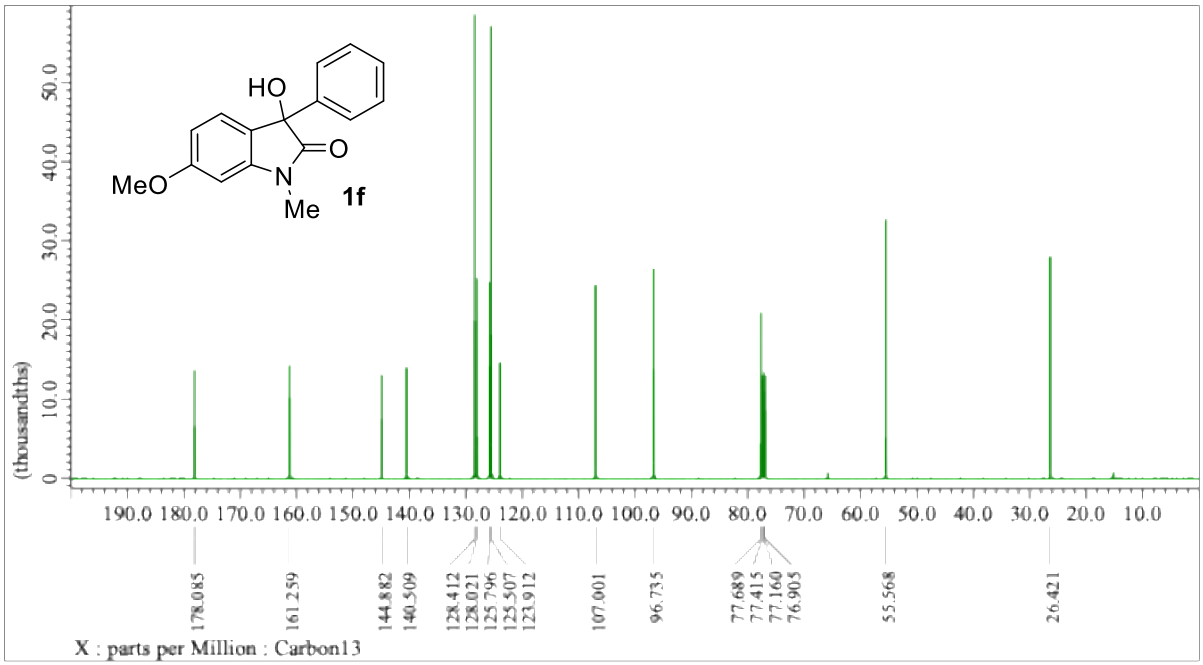


(±)-3-Hydroxy-6-methoxy-1-methyl-3-phenyloxindole ((±)-1f)

^{1}H NMR

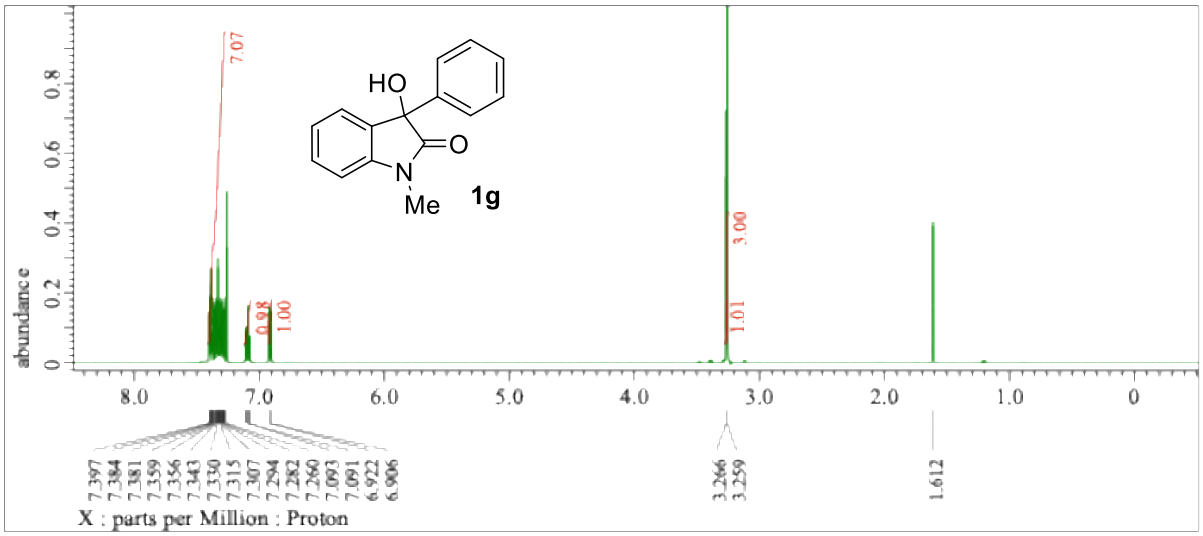


^{13}C NMR



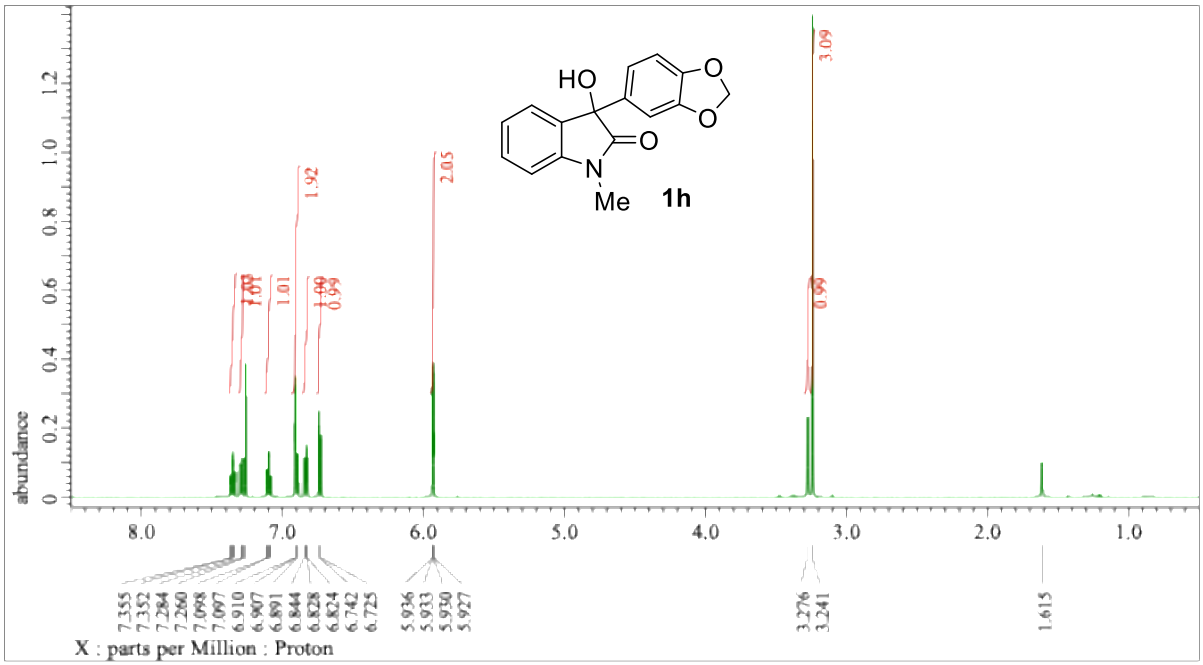
(±)-3-Hydroxy-1-methyl-3-phenyloxindole ((±)-1g)

^{1}H NMR



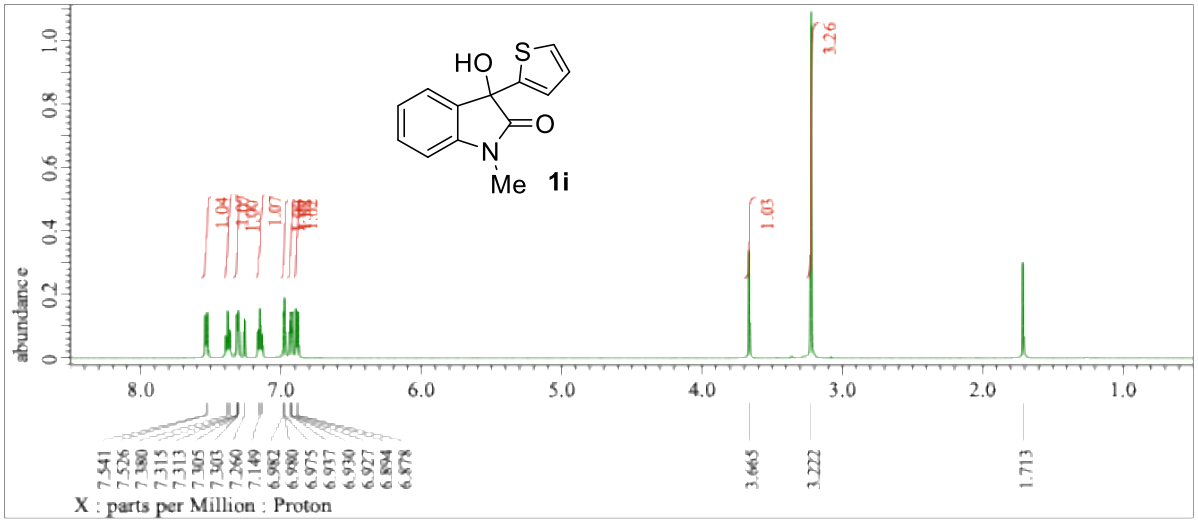
(±)- 3-(Benzo[d][1,3]dioxo-5-yl)-3-hydroxy-1-methyloxindole ((±)-1h)

^{1}H NMR



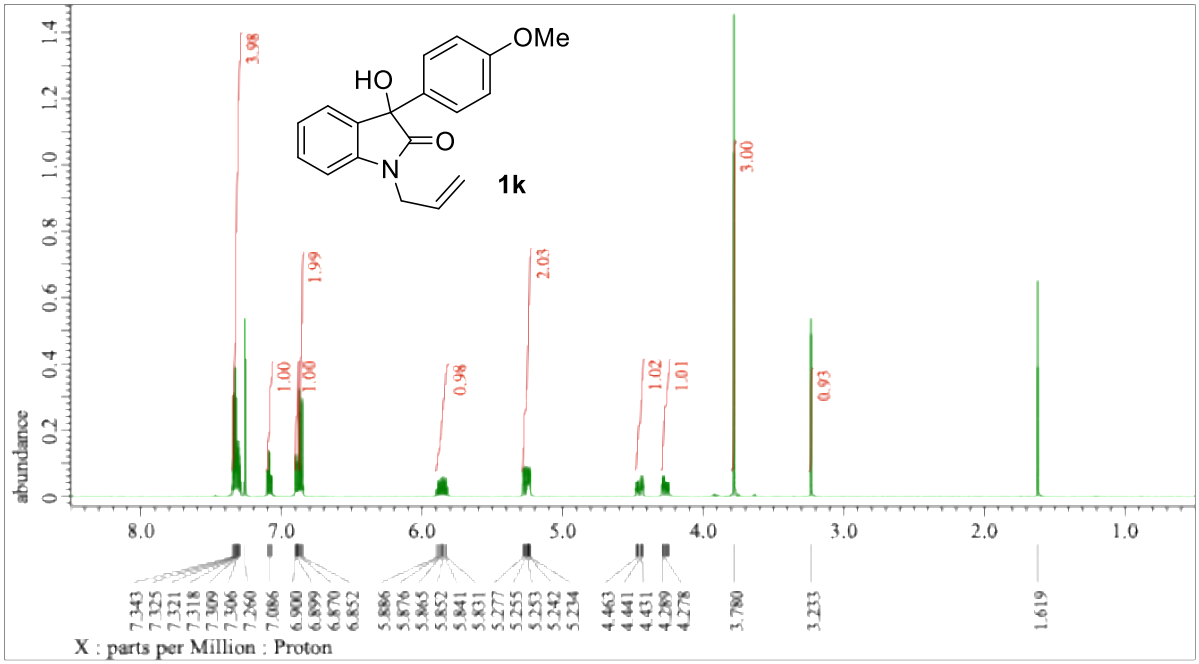
(±)- 3-Hydroxy-1-methyl-3-(thiophen-2-yl)oxindole ((±)-1i)

^{1}H NMR



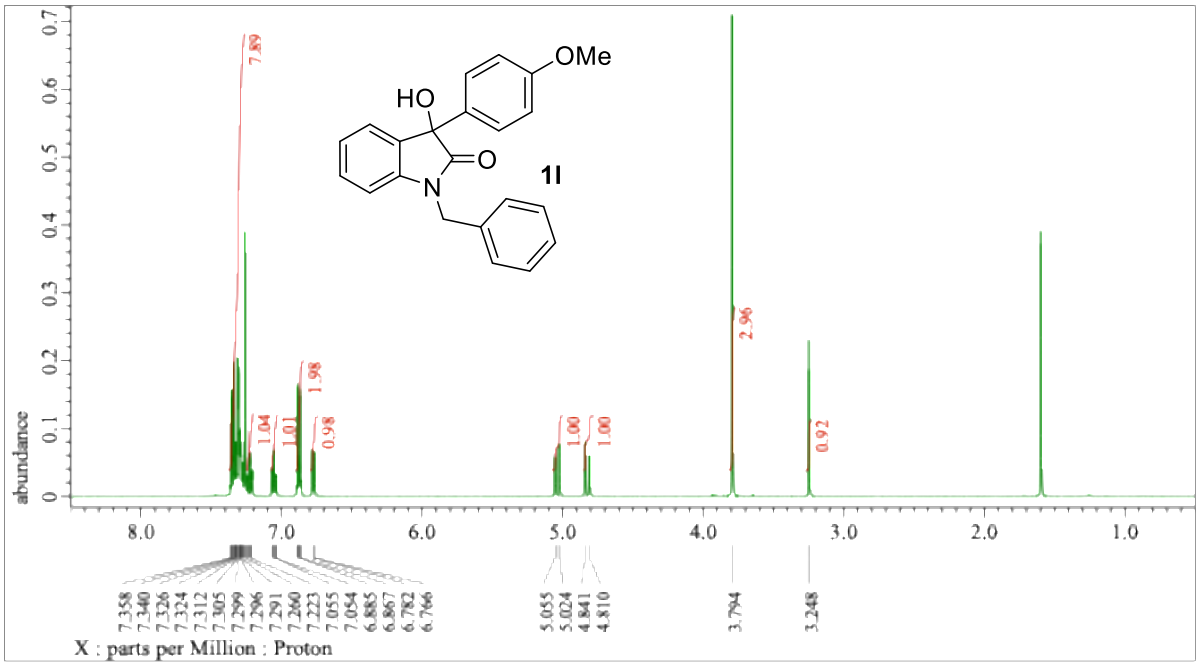
(±)-1-Allyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((±)-1k)

^{1}H NMR



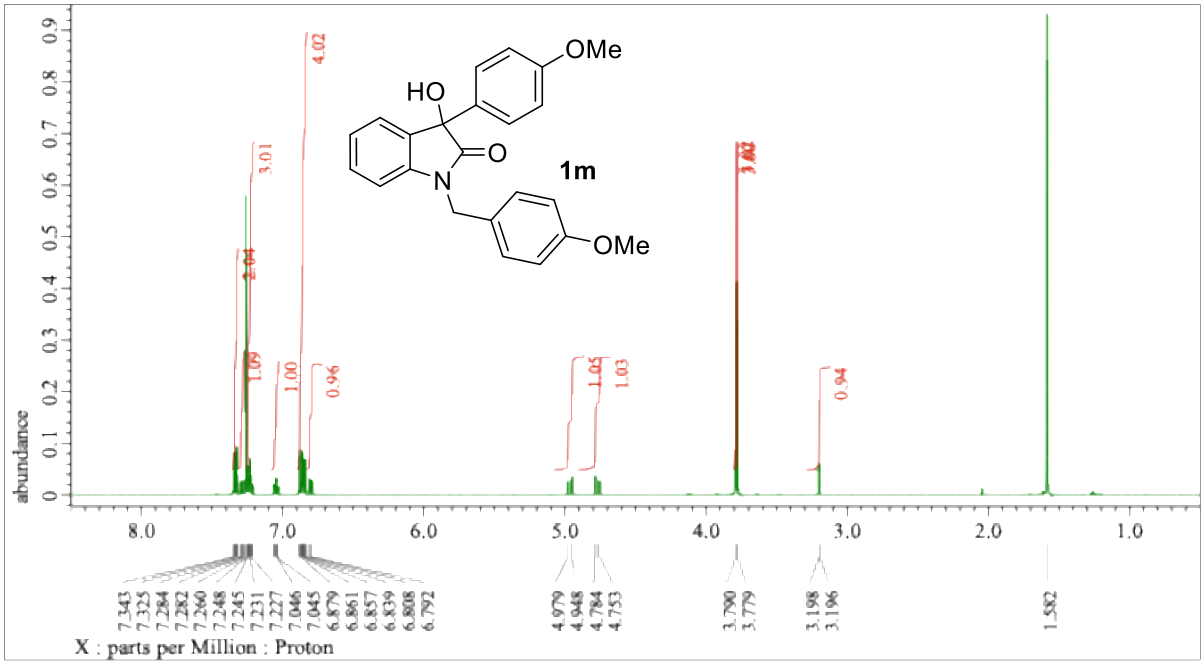
(±)-1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)oxindole ((±)-1l)

^{1}H NMR

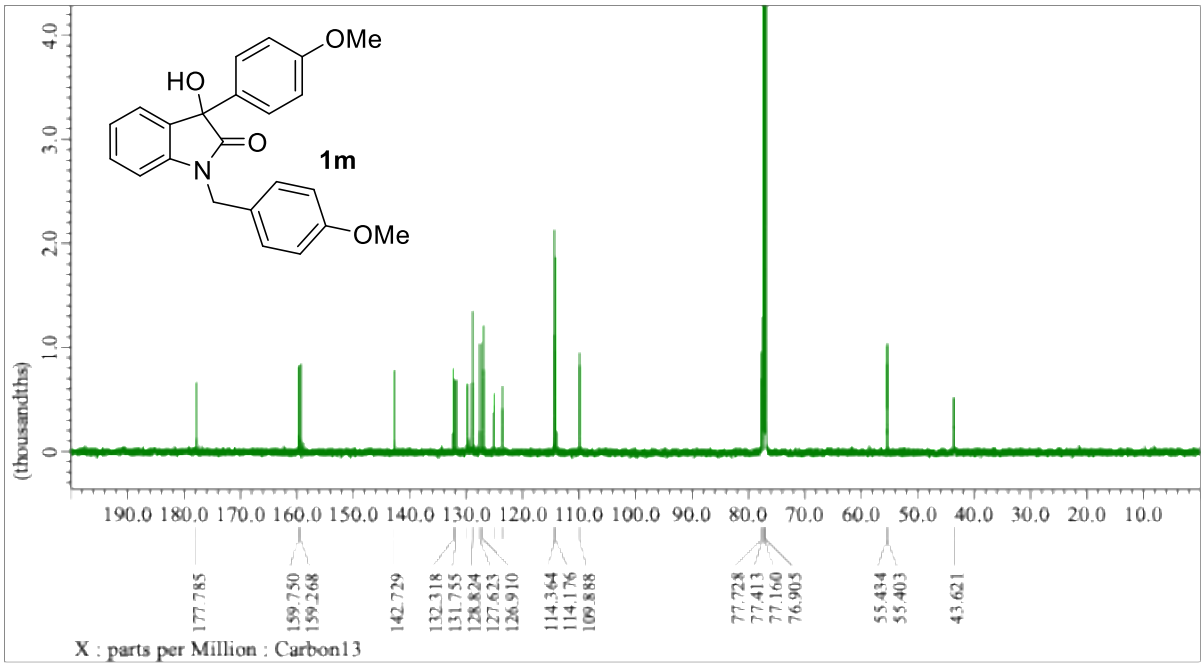


(±)- 3-Hydroxy-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)oxindole ((±)-1m)

^{1}H NMR

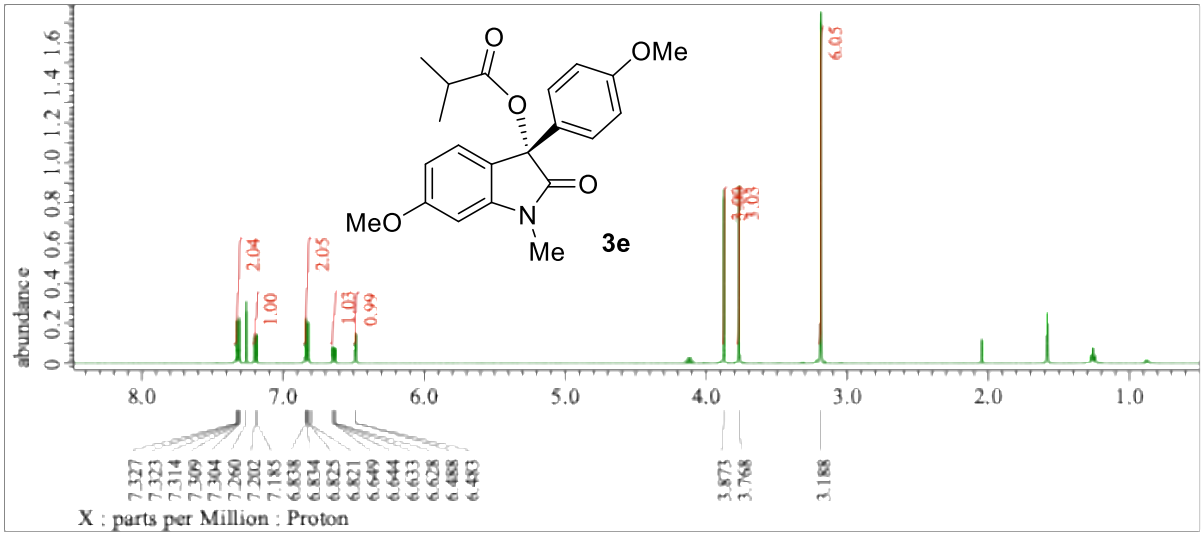


^{13}C NMR

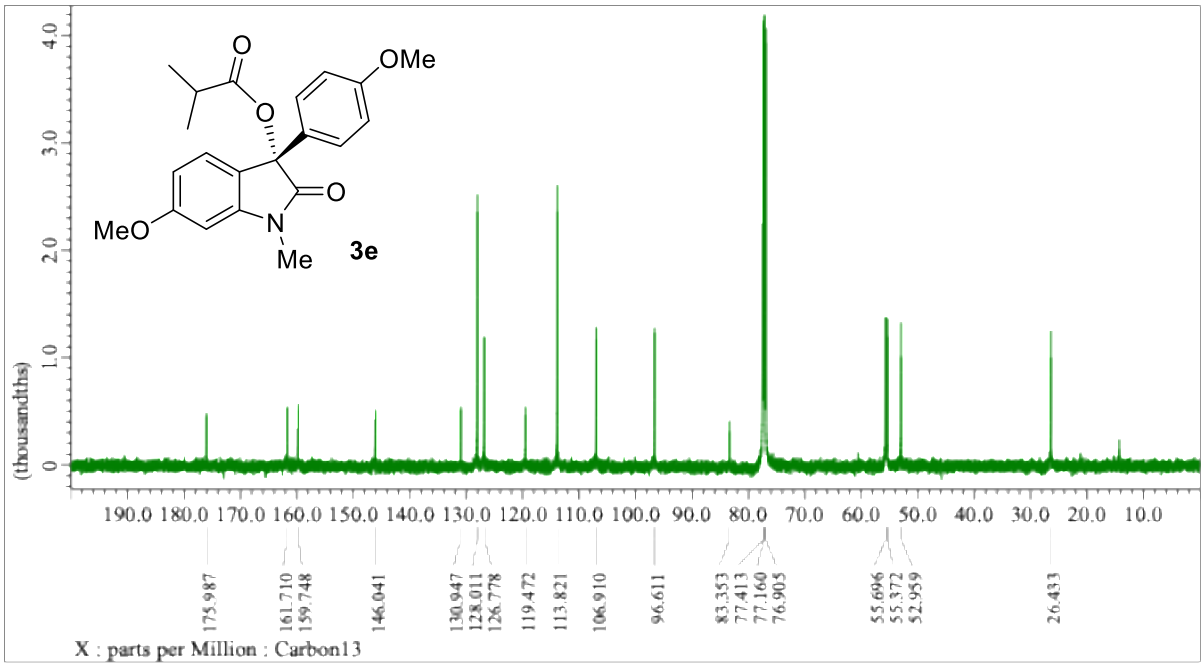


(*S*)-6-Methoxy-3-(4-methoxyphenyl)-1-methyl-2-oxoindolin-3-yl isobutyrate ((*S*)-3e)

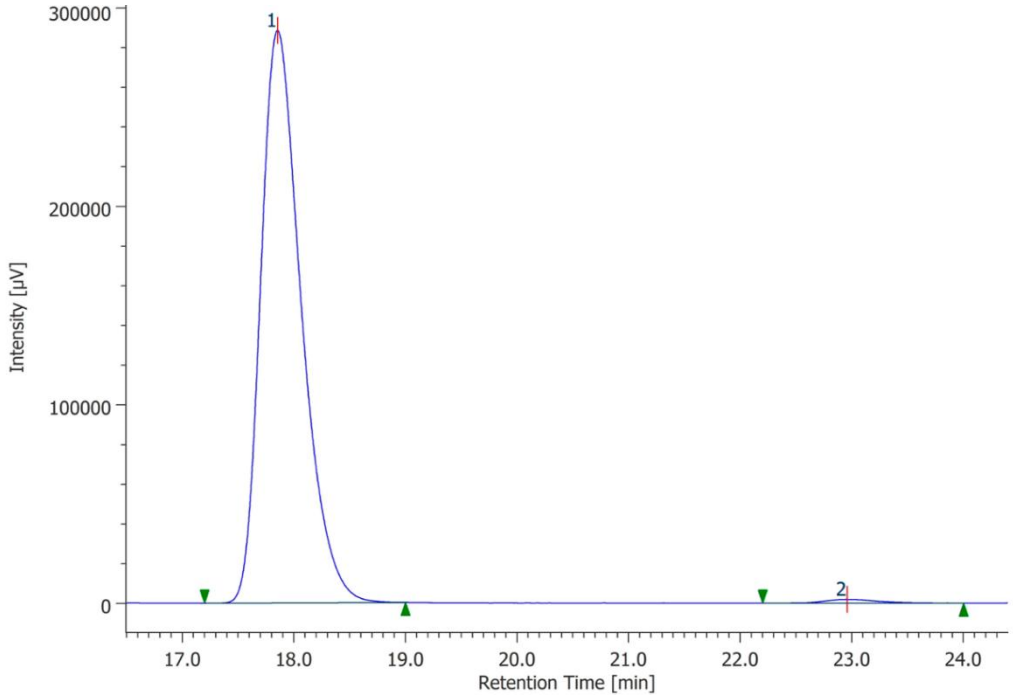
^{1}H NMR

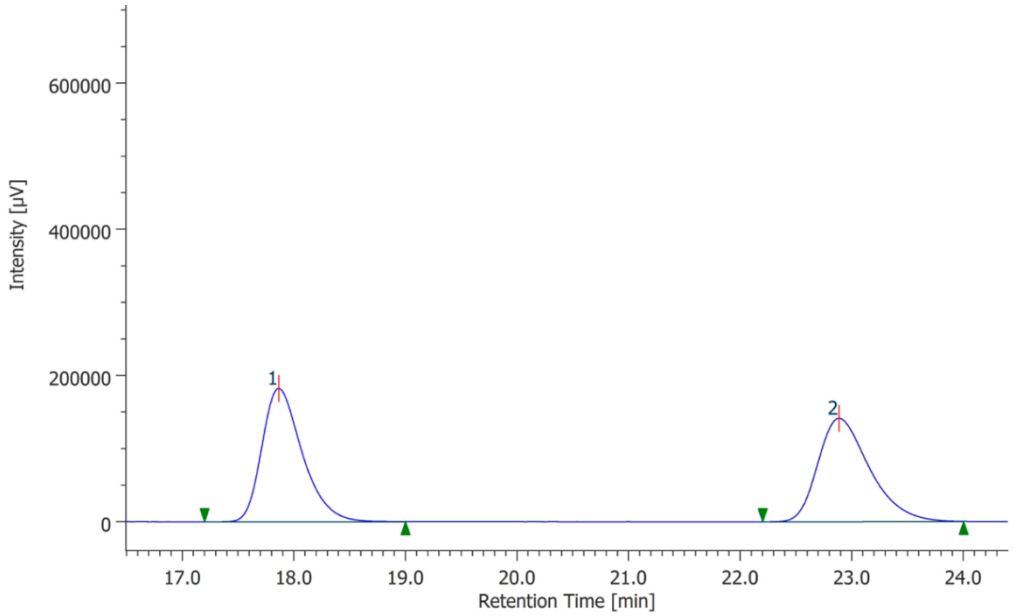


^{13}C NMR


O
OMe
O
O
MeO
N
Me
3e
(thousandths)
4.0
3.0
2.0
1.0
0
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
175.987
161.710
159.748
146.041
130.947
128.011
126.778
119.472
113.821
106.910
96.611
83.353
77.413
77.160
76.905
55.696
55.372
52.959
26.433
X : parts per Million : Carbon13

3-Hydroxy-3-(4-methoxyphenyl)-1-methyloxindole (1a)





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2	Unknown	6	22.957	63140	1882	0.860	0.649	N/A	12226	N/A	1.255	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
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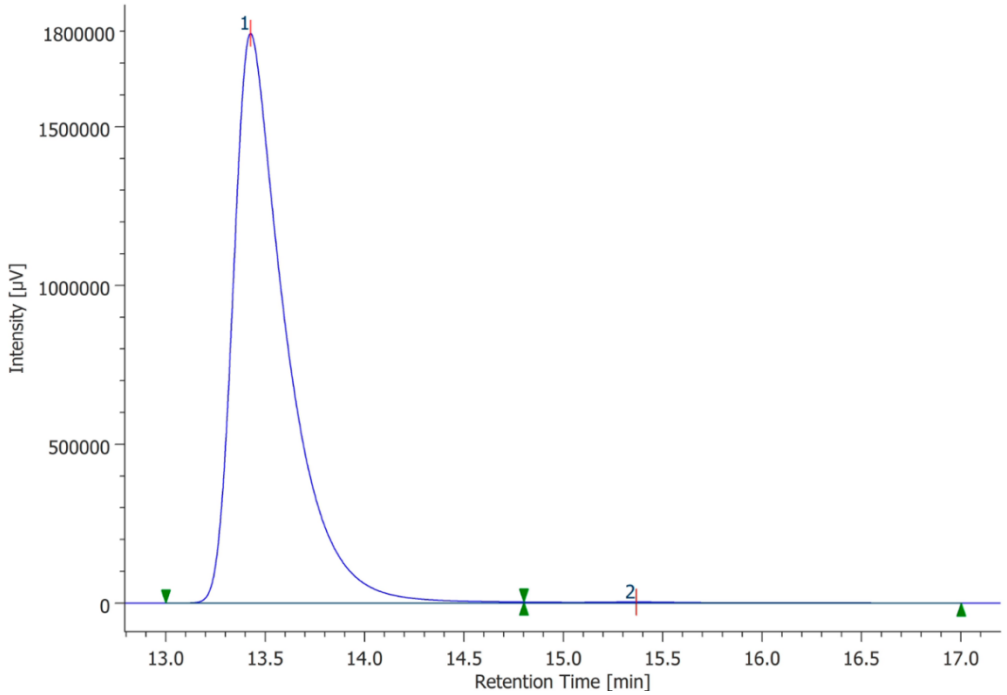
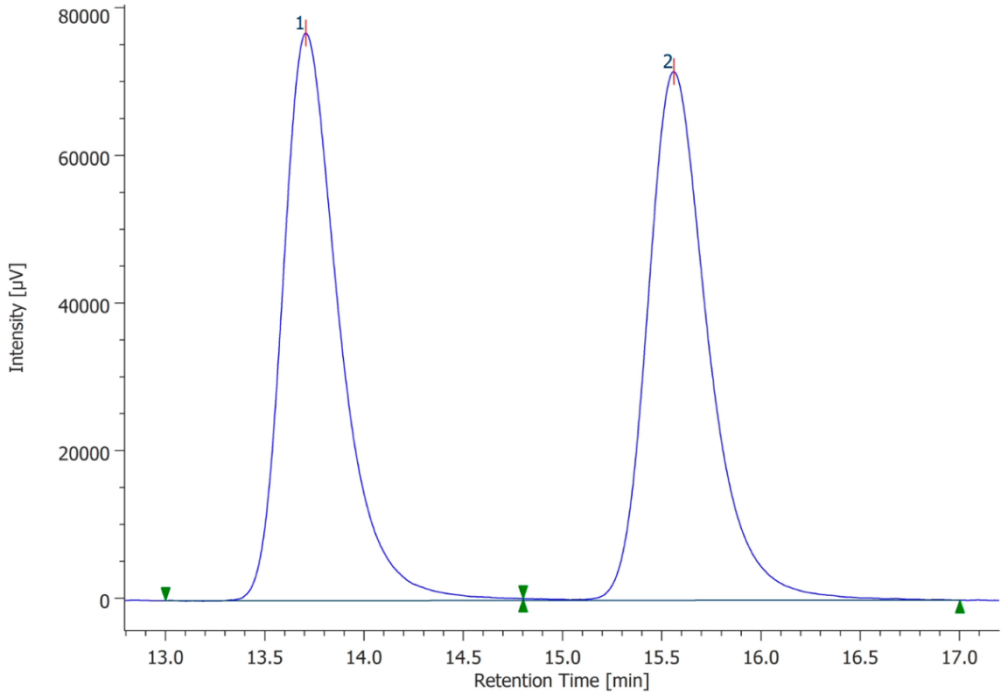
2	Unknown	6	22.883	4532541	141251	49.780	43.645	N/A	12109	N/A	1.389	

3-Hydroxy-3-(4-methoxyphenyl)-1,5-dimethyloxindole (1b)





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2	Unknown	6	15.367	155803	3157	0.466	0.176	N/A	N/A	N/A	N/A	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
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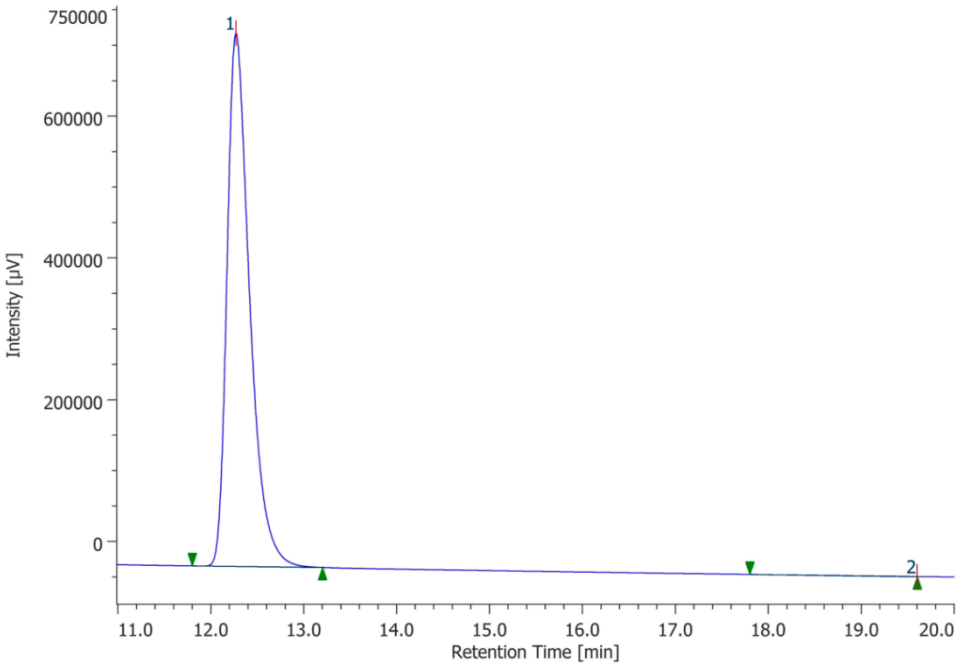
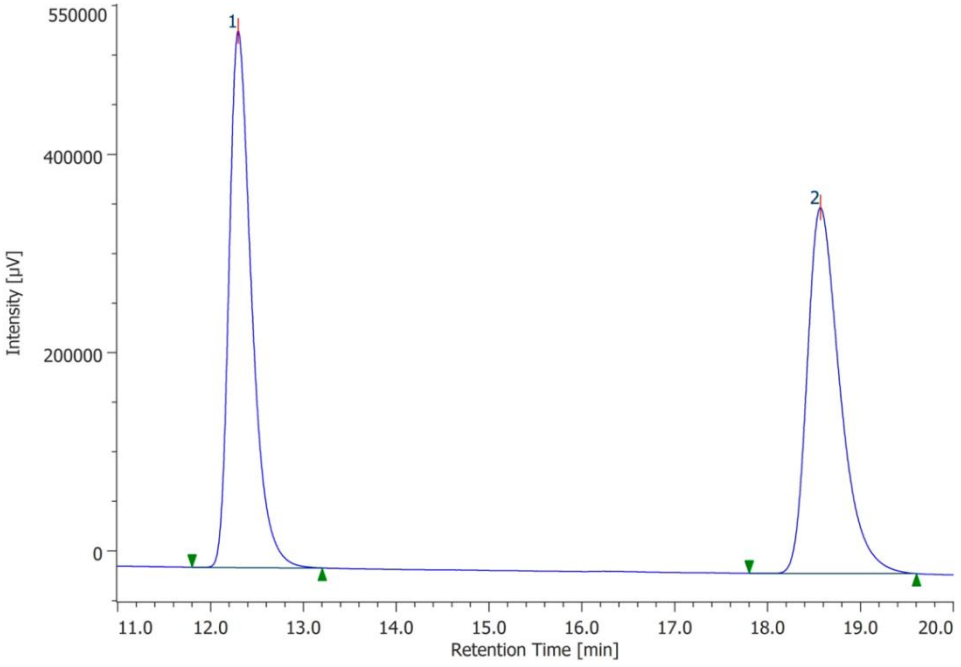
2	Unknown	6	15.560	1525901	71580	50.014	48.222	N/A	13610	N/A	1.327	

5-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole (1c)





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2	Unknown	6	19.597	4	9	0.000	0.001	N/A	N/A	N/A	N/A	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
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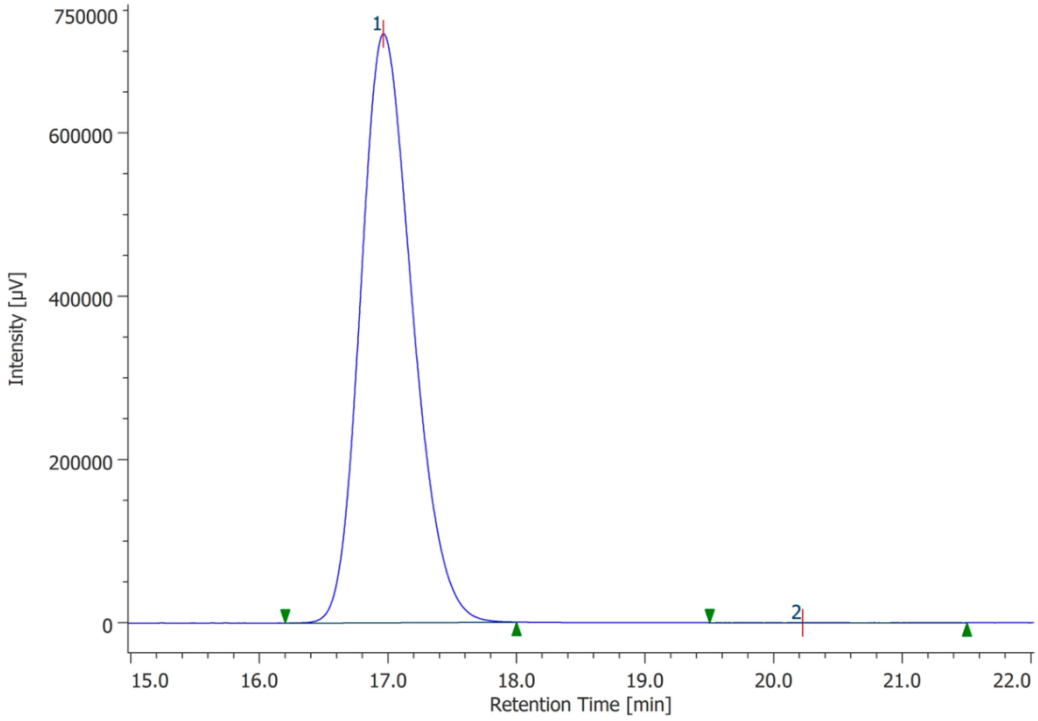
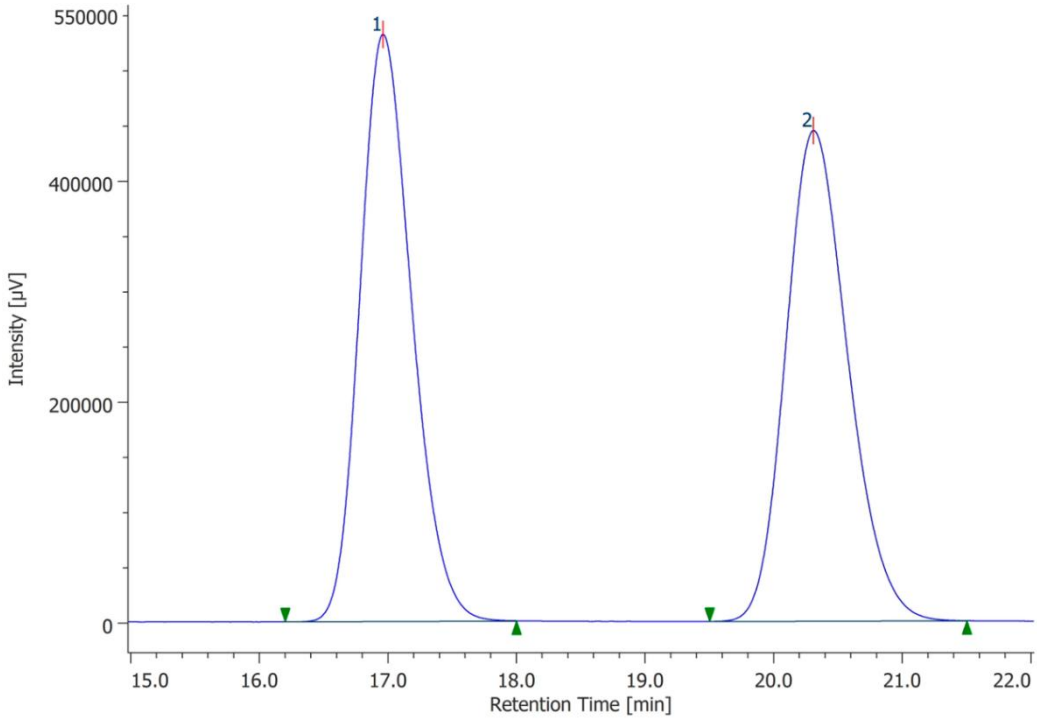
2	Unknown	6	18.567	9087142	368858	49.867	40.551	N/A	13987	N/A	1.443	

Chloro-3-hydroxy-3-(4-methoxyphenyl)-1-methyloxindole (1d)

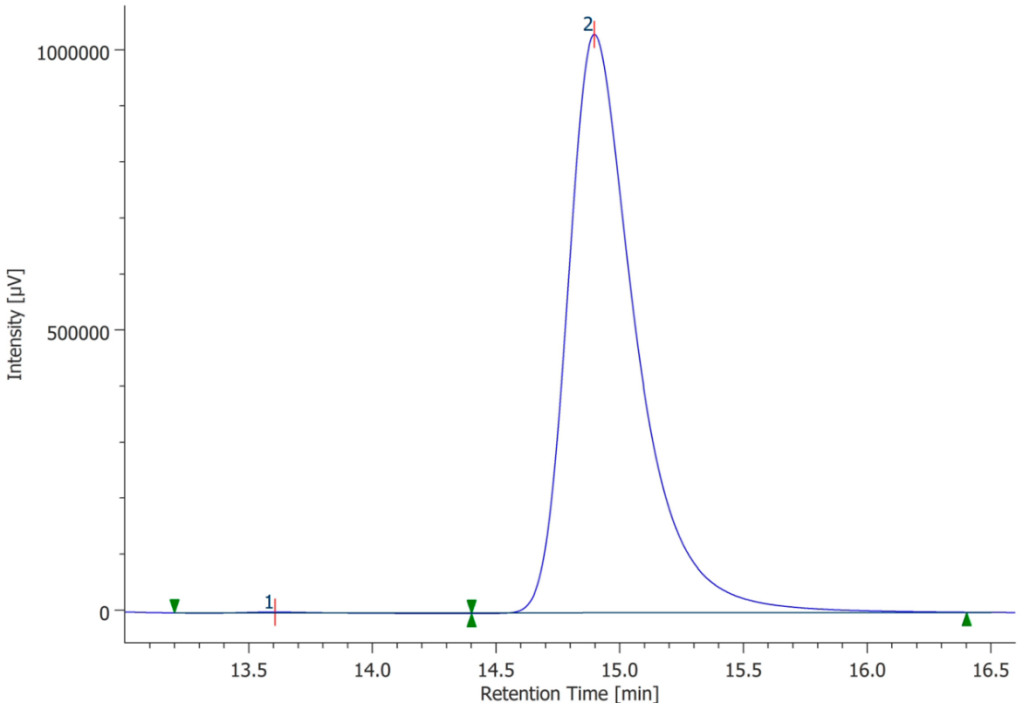


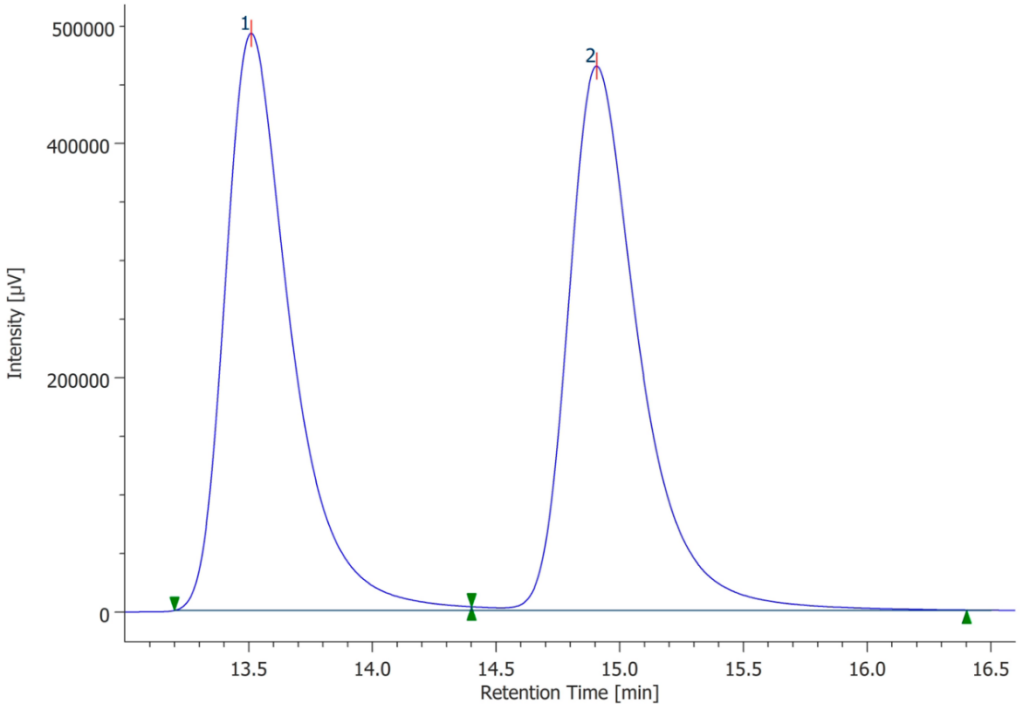


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	16.963	20205289	720868	99.980	99.980	N/A	8499	3.070	1.223	
2	Unknown	6	20.223	4025	143	0.020	0.020	N/A	3369	N/A	1.437	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	16.960	14929586	531400	49.999	54.470	N/A	8445	4.139	1.211	
2	Unknown	6	20.307	14930024	444185	50.001	45.530	N/A	8461	N/A	1.206	

3-Hydroxy-6-methoxy-3-(4-methoxyphenyl)-1-methyloxindole (1e)

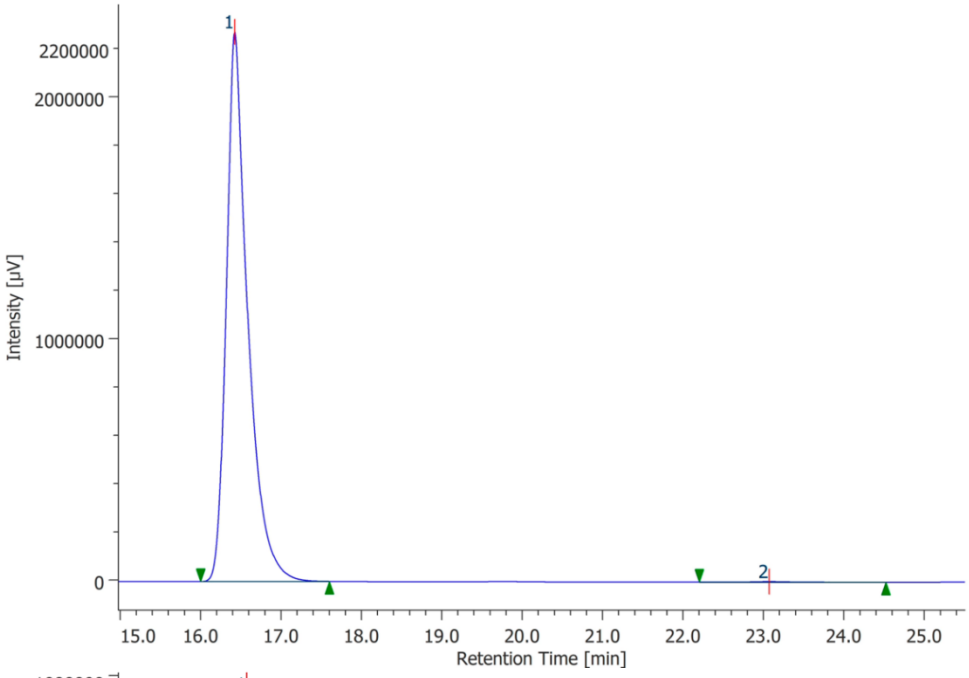


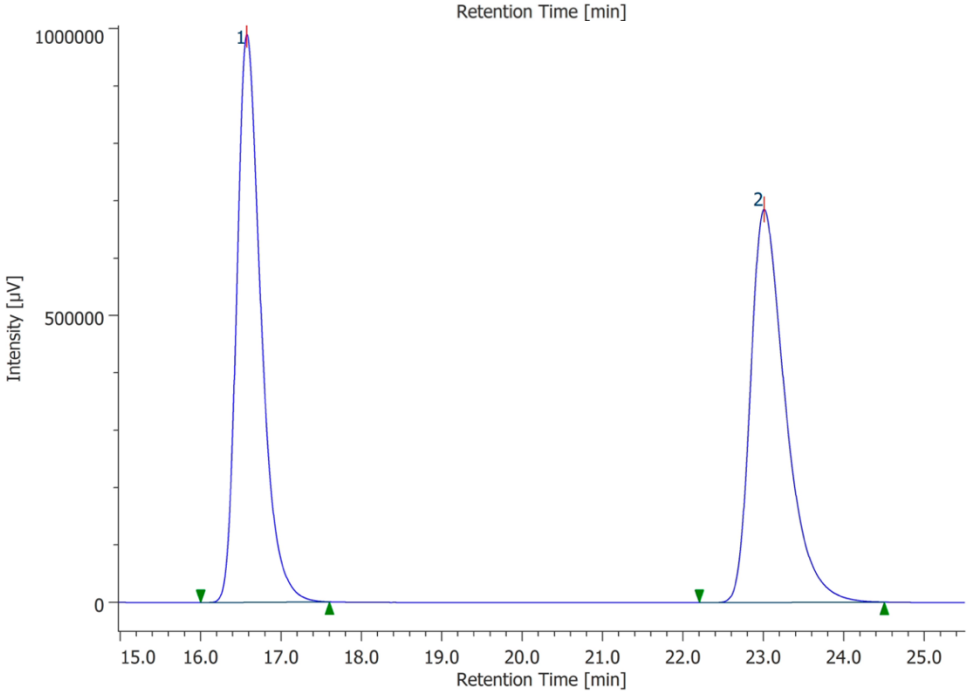


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	13.607	19866	1465	0.100	0.142	N/A	19646	2.994	1.077	
2	Unknown	6	14.897	19943215	1031670	99.900	99.858	N/A	15691	N/A	1.552	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	13.510	9186840	492470	49.528	51.464	N/A	13750	2.931	1.547	
2	Unknown	6	14.907	9361966	464457	50.472	48.536	N/A	14523	N/A	1.497	

3-Hydroxy-6-methoxy-1-methyl-3-phenyloxindole (1f)

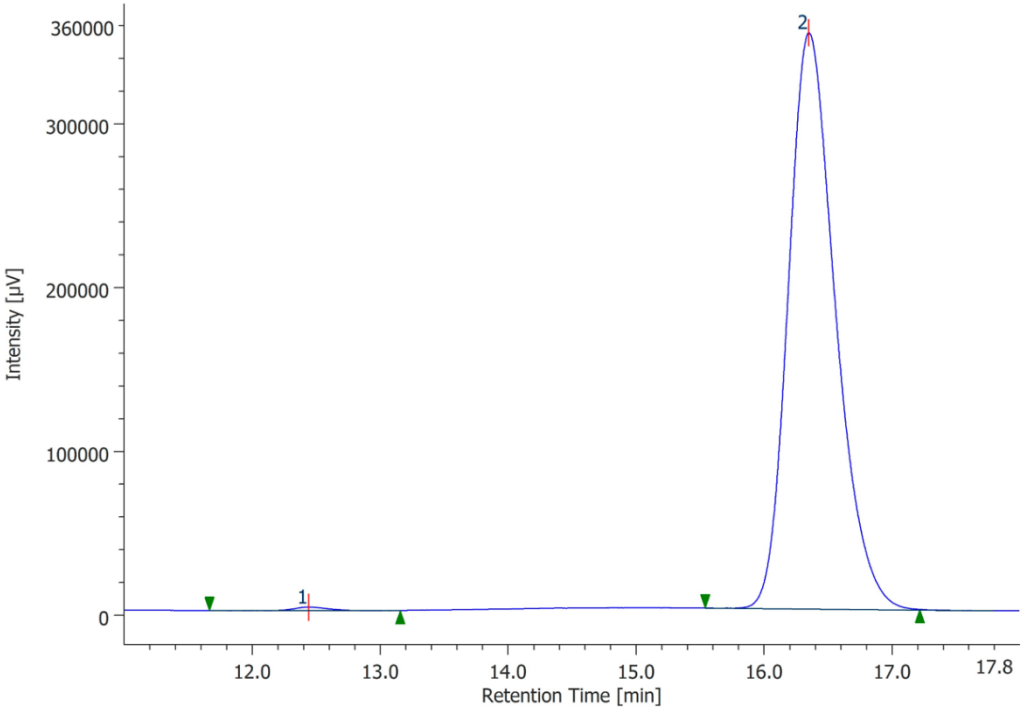


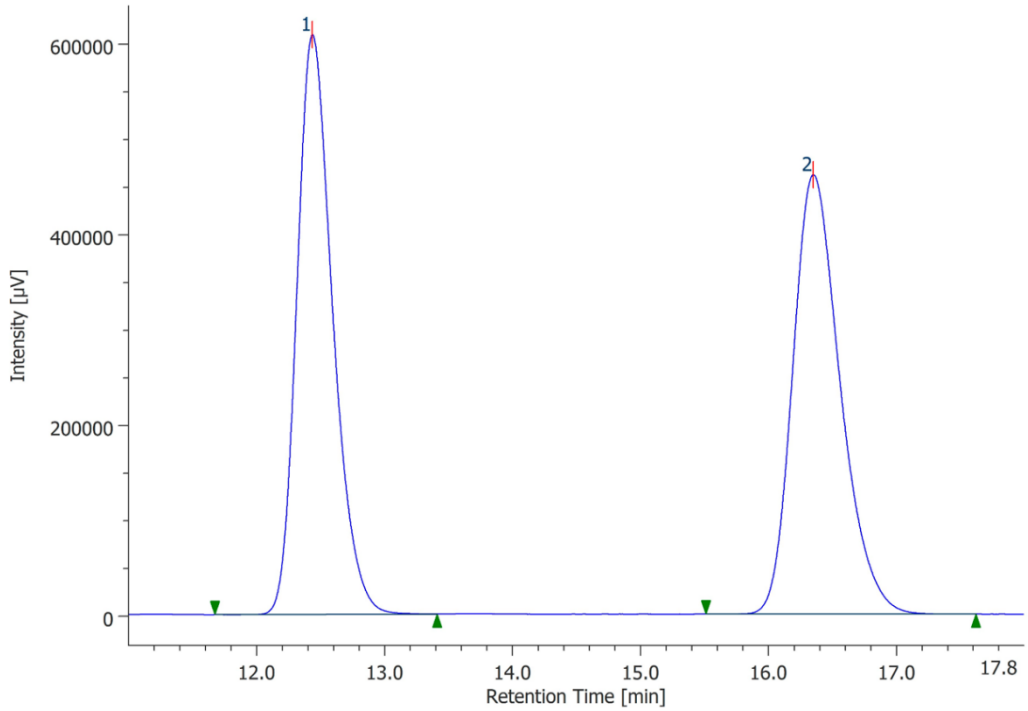


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	16.423	42063154	2273757	99.836	99.899	N/A	21205	11.120	1.494	
2	Unknown	6	23.070	69227	2303	0.164	0.101	N/A	15240	N/A	1.728	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	16.573	20766980	989290	50.078	59.085	N/A	15432	9.928	1.387	
2	Unknown	6	23.007	20702203	685049	49.922	40.915	N/A	14442	N/A	1.518	

3-Hydroxy-1-methyl-3-phenyloxindole (1g)

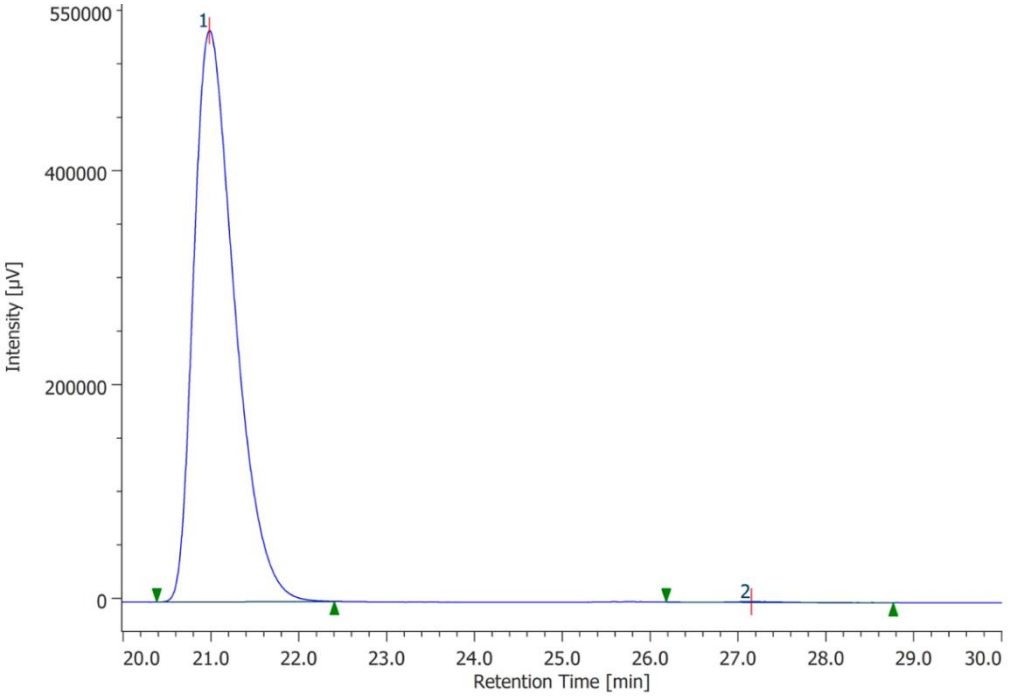


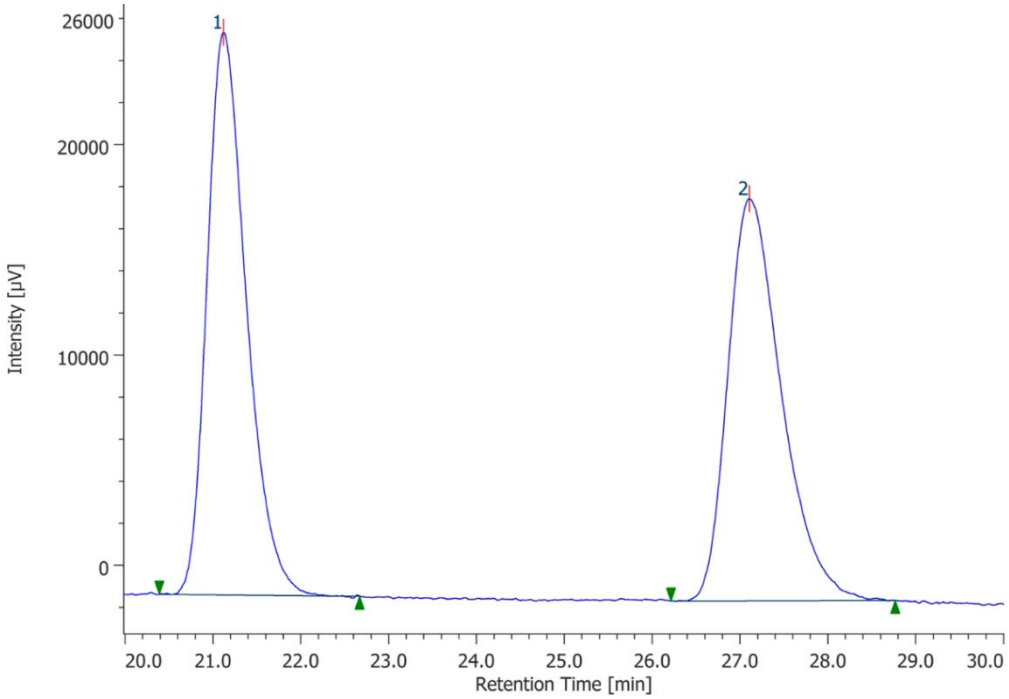


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	12.440	36702	2118	0.407	0.599	N/A	11614	6.969	1.158	
2	Unknown	6	16.347	8980377	351706	99.593	99.401	N/A	9743	N/A	1.258	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	12.433	11815186	608252	49.894	56.891	N/A	9756	6.695	1.272	
2	Unknown	6	16.347	11865520	460895	50.106	43.109	N/A	9562	N/A	1.275	

3-(Benzo[d][1,3]dioxo-5-yl)-3-hydroxy-1-methyloxindole (1h)

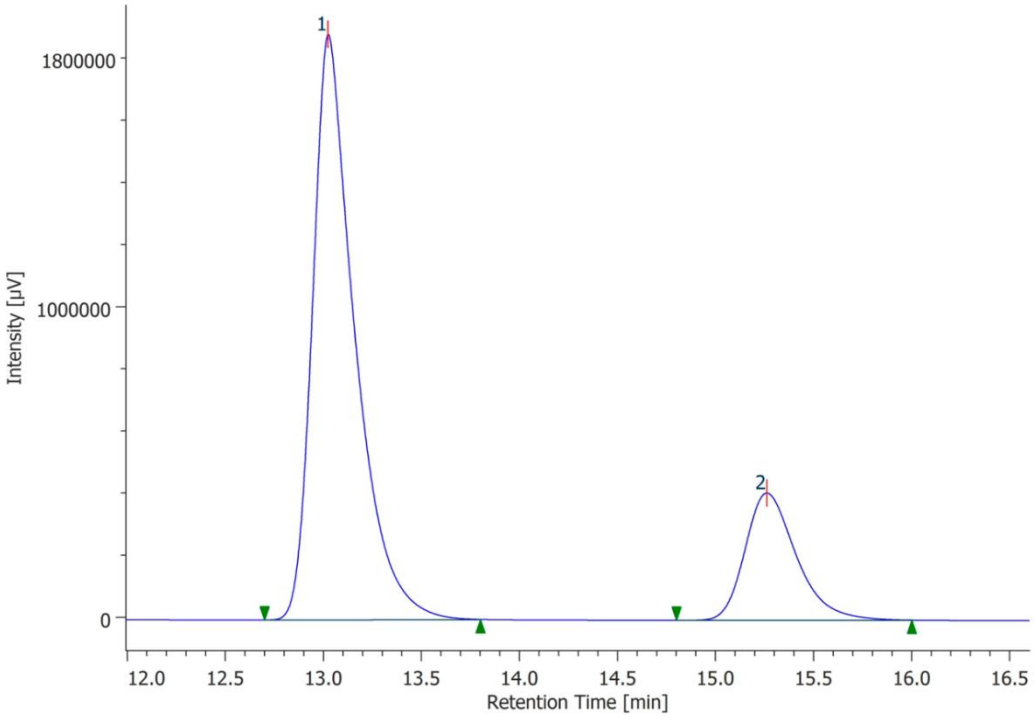


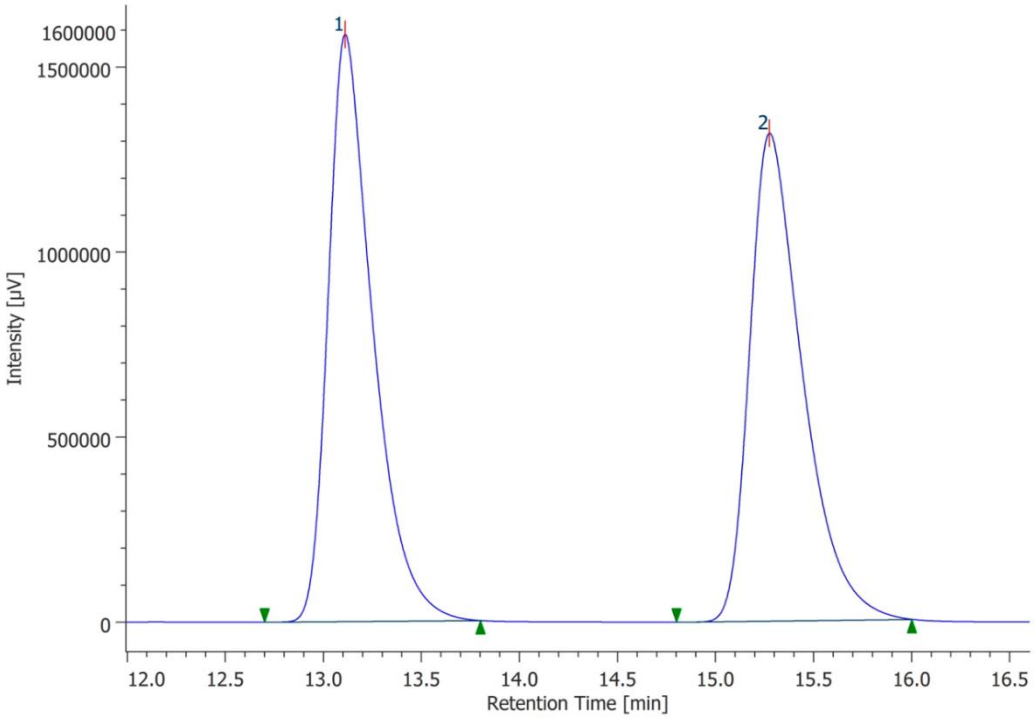


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	20.983	17285027	534095	99.911	99.912	N/A	9854	6.926	1.511	
2	Unknown	6	27.150	15463	471	0.089	0.088	N/A	13347	N/A	1.321	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	21.120	832793	26735	50.702	58.320	N/A	10913	6.297	1.329	
2	Unknown	6	27.103	809736	19107	49.298	41.680	N/A	9772	N/A	1.409	

3-Hydroxy-1-methyl-3-(thiophen-2-yl)oxindole (1i)

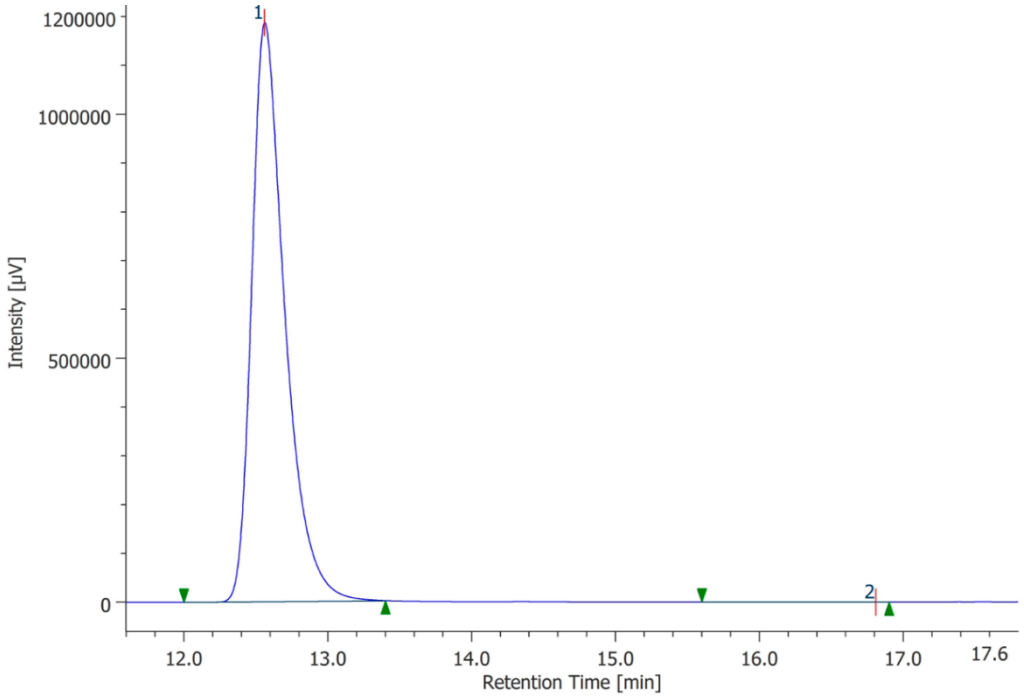


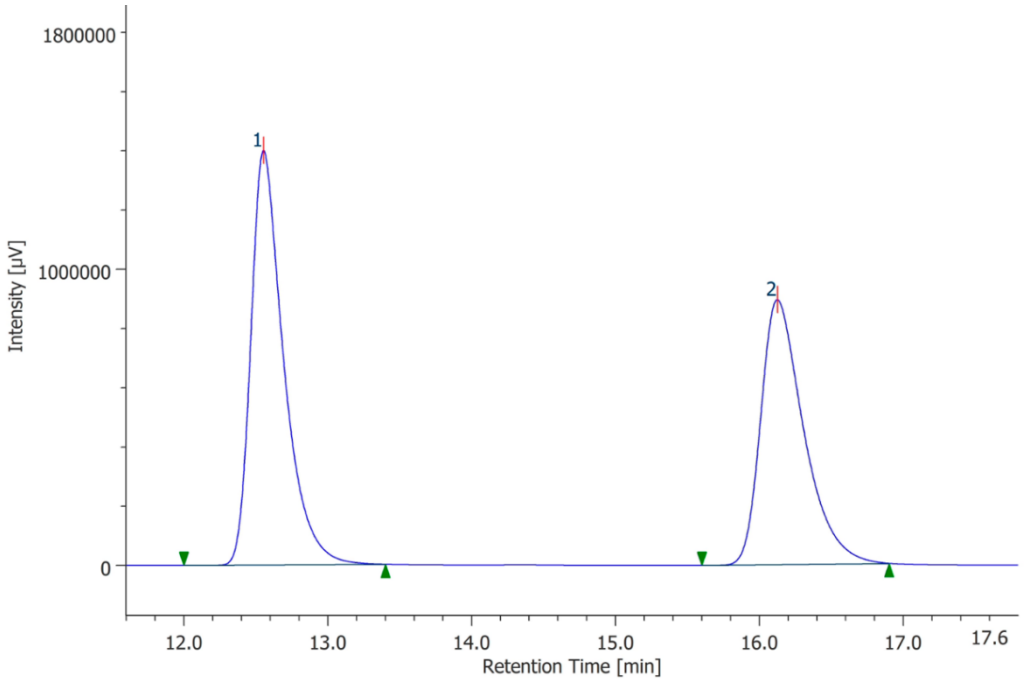


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	13.023	28129244	1884659	79.043	82.144	N/A	19835	5.375	1.580	
2	Unknown	6	15.260	7457825	409668	20.957	17.856	N/A	17258	N/A	1.341	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	13.110	25135577	1586350	50.412	54.611	N/A	17124	4.936	1.528	
2	Unknown	6	15.273	24724982	1318470	49.588	45.389	N/A	16331	N/A	1.545	

1-Allyl-3-hydroxy-3-(4-methoxyphenyl)oxindole (1k)

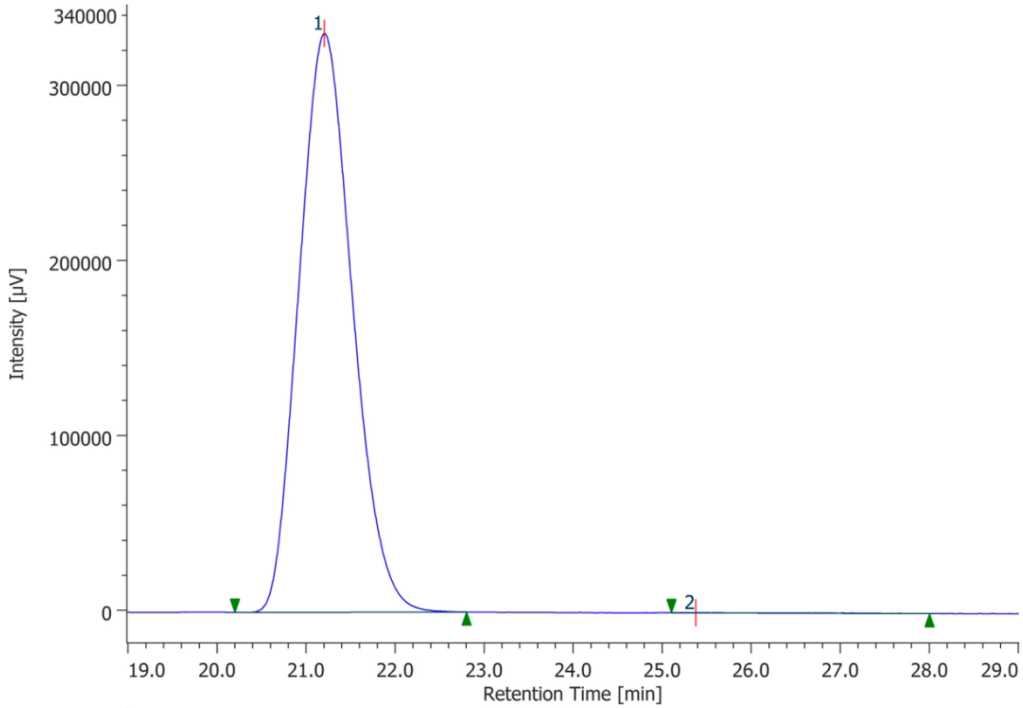


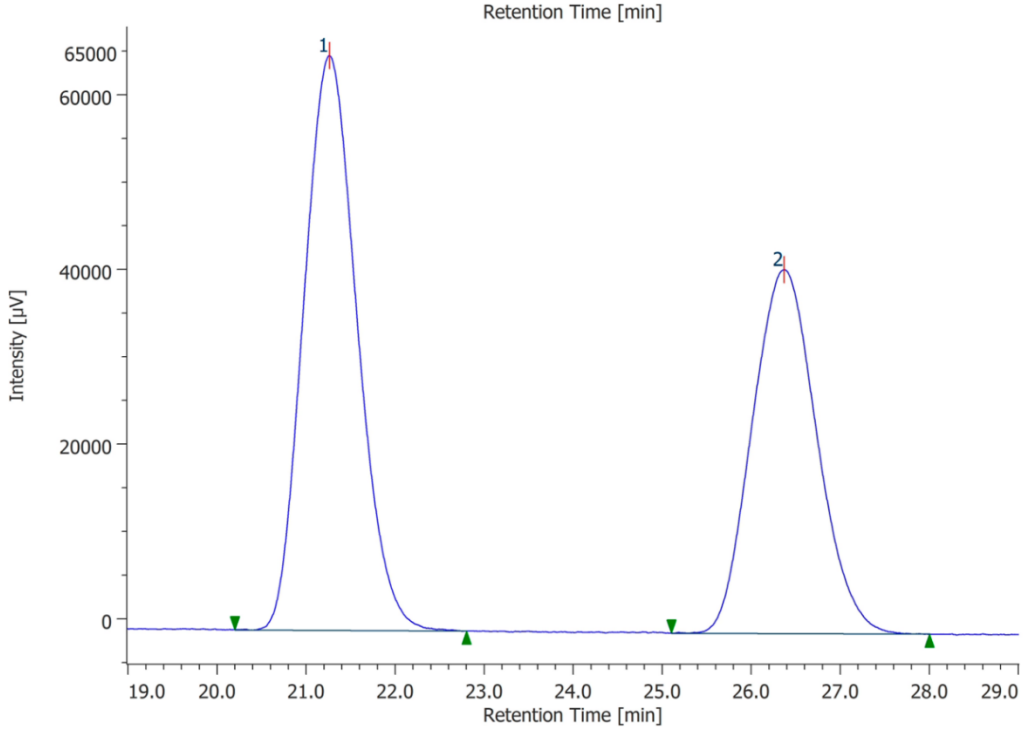


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	12.560	19004811	1186543	100.000	99.998	N/A	15588	4.119	1.503	
2	Unknown	6	16.807	67	26	0.000	0.002	N/A	1630	N/A	0.537	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	12.553	22140801	1399706	54.428	61.011	N/A	16138	7.752	1.517	
2	Unknown	6	16.123	18538094	894470	45.572	38.989	N/A	14908	N/A	1.502	

1-Benzyl-3-hydroxy-3-(4-methoxyphenyl)oxindole (1l)

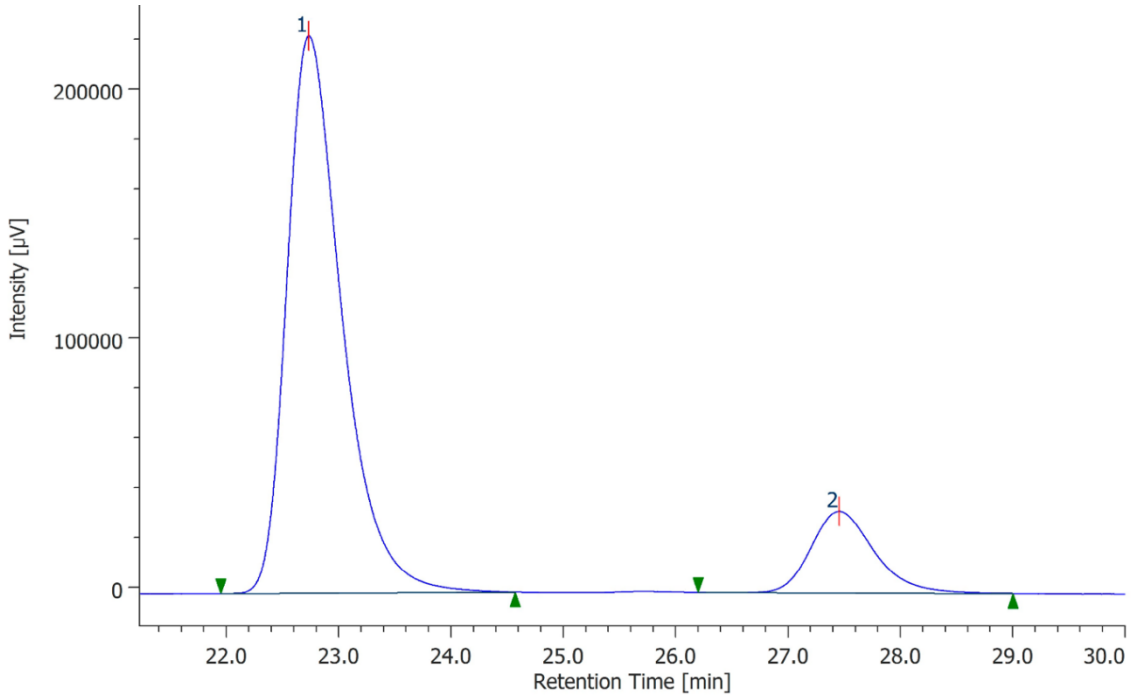


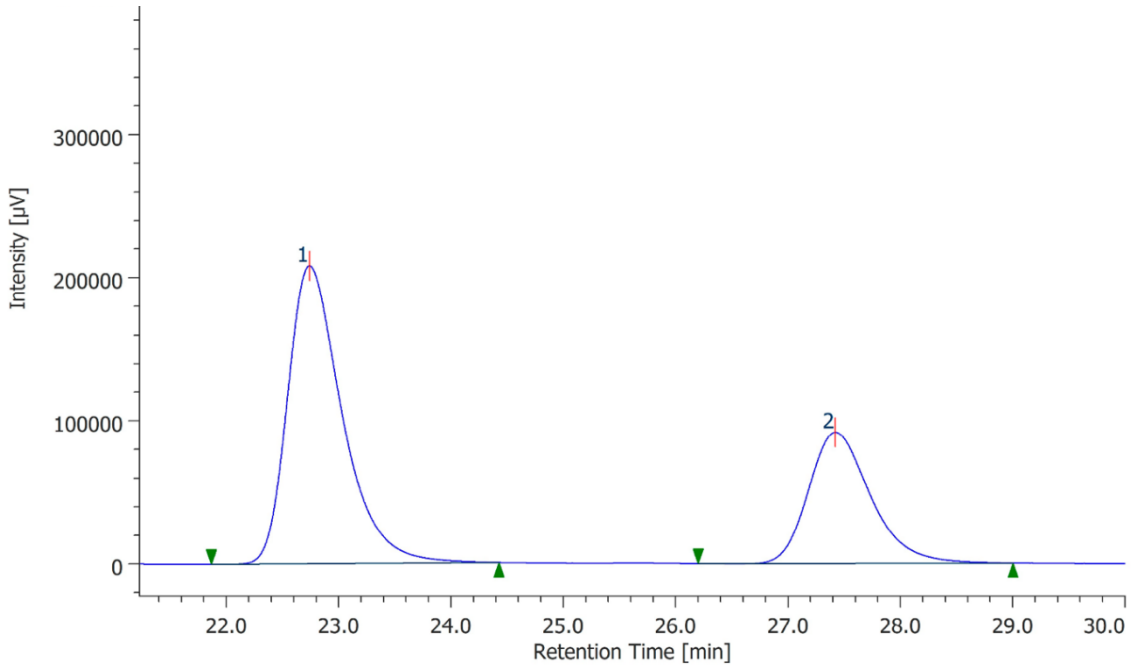


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	21.203	13759179	330708	99.935	99.975	N/A	5840	1.466	1.159	
2	Unknown	6	25.373	8901	82	0.065	0.025	N/A	488	N/A	5.340	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	21.263	2729438	65765	56.515	61.225	N/A	5908	4.158	1.133	
2	Unknown	6	26.367	2100126	41651	43.485	38.775	N/A	6062	N/A	1.102	

3-Hydroxy-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)oxindole (1m)

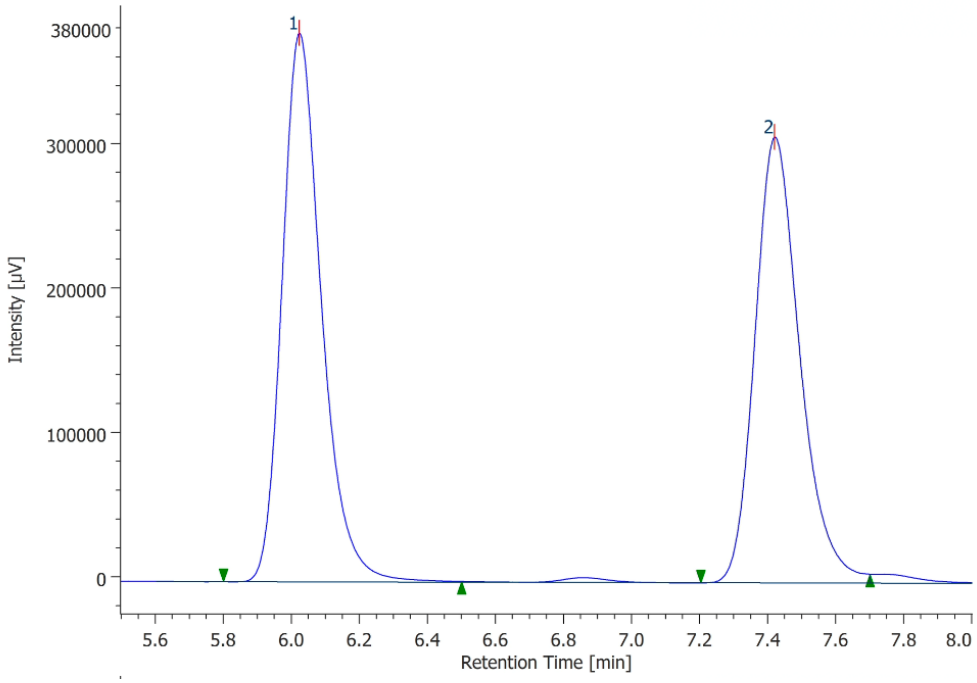


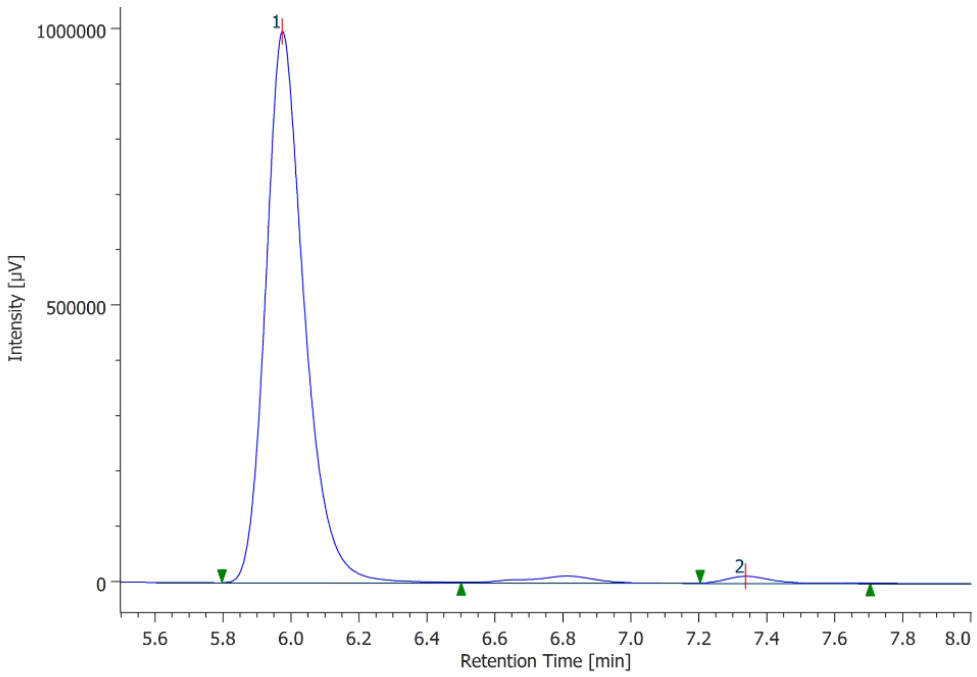


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	22.733	7603603	223583	85.590	87.226	N/A	11120	5.081	1.467	
2	Unknown	6	27.453	1280163	32742	14.410	12.774	N/A	12042	N/A	1.255	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	22.740	7007307	207920	66.577	69.442	N/A	11302	5.094	1.451	
2	Unknown	6	27.420	3517757	91494	33.423	30.558	N/A	12353	N/A	1.298	

6-Methoxy-3-(4-methoxyphenyl)-1-methyl-2-oxoindolin-3-yl isobutyrate (3e)





#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	6.023	3054720	379869	51.887	55.179	N/A	13911	6.380	1.277	
2	Unknown	6	7.420	2832552	308560	48.113	44.821	N/A	15987	N/A	1.270	

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	6	5.973	7858193	996799	98.437	98.731	N/A	14499	6.230	1.289	
2	Unknown	6	7.337	124751	12814	1.563	1.269	N/A	14905	N/A	N/A	