Diastereoselective Reversible C-C Bond Exchange of Oxindole-Thiazolidinediones for Dynamic Combinatorial Chemistry

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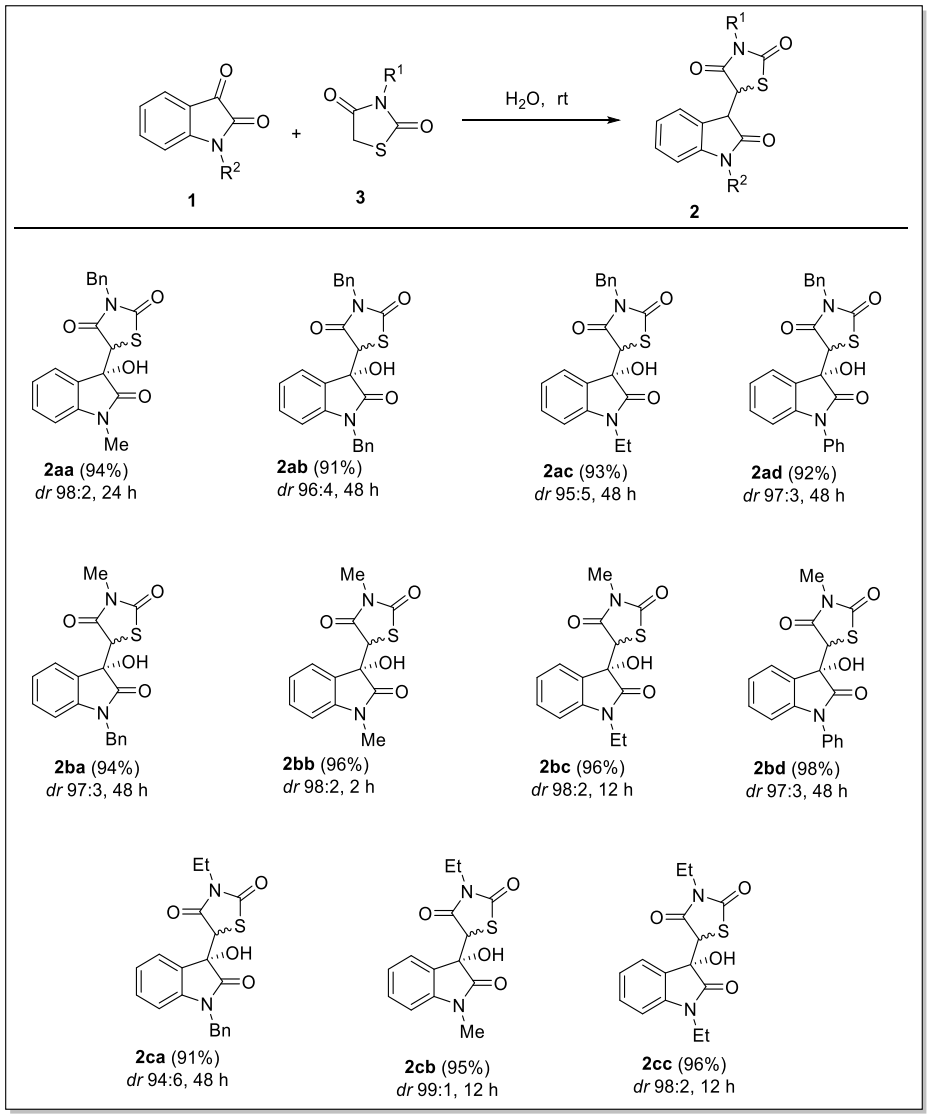
1.0 General information

All experiments were carried out in flame-dried reaction vials. Solvents were dried using standard procedures. All starting materials were obtained from commercial suppliers and used as received. Products were purified by flash chromatography on silica gel (100-200 mesh, Merck). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. **^{1}H NMR** spectra were recorded at 500 MHz using Brüker AVANCE 500 MHz and JEOL 400 MHz instruments at 278 K. Signals are quoted as δ values in ppm using residual protonated solvent signals as internal standard ($CDCl_3$: δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. **^{13}C NMR** spectra were recorded on either a JEOL-400 (100 MHz), or a Brüker AVANCE 500 MHz (125 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.26 ppm). **HRMS** analyses were performed with Q-TOF YA263 high resolution (Water Corporation) instruments by +ve mode electrospray ionization.

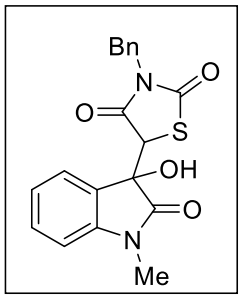
2.0 Synthesis of oxindolyl-thiazolidinediones 2

General procedure for the aldol reaction (GP-1)[19]: To a solution of thiazolidinedione **3** (1.0 equiv) in water was added isatin **1** (1.0 equiv) and stirred at room temperature until the complete consumption of the starting materials. The completion of the reaction was checked by TLC. The reaction mixture was filtered and dried under vacuum to afford the oxindolyl-thiazolidinediones **2** as solid residue in high yields and purity. Compound **2aa** was purified by flash chromatography using ethyl acetate−hexane (Table S1).

Table S1. Synthesis of oxindolyl-thiazolidinedione conjugates via on-water aldol reactions.

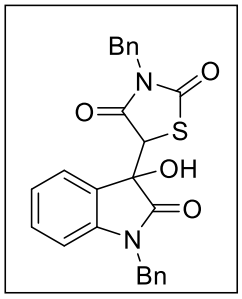


3-Benzyl-5-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (2aa)[19]



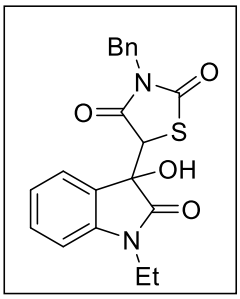
Using the general procedure (**GP-1**), methyl protected isatin **1b** (77.76 mg, 0.48 mmol) and benzyl protected thiazolidinedione **3b** (100 mg, 0.48 mmol) were stirred in water for 24 h. After the completion of the reaction, the crude mixture was extracted with ethyl acetate (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography with ethyl acetate−hexane (5/95 to 20/80) to afford **2aa** (166.9 mg, 94%) as a viscous liquid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.13 (s, 1H), 7.10 (t, *J* = 6.7 Hz, 2H), 7.05 – 6.99 (m, 2H), 6.50 (d, *J* = 7.3 Hz, 2H), 5.26 (s, 1H), 4.45 (m, 2H), 3.15 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 170.9, 169.9, 144.1, 134.8, 130.7, 128.3, 127.1, 126.2, 124.3, 122.4, 108.9, 74.2, 57.9, 43.9, 26.2. HRMS (ESI) calculated for $C_{19}H_{16}N_2KO_4S$ $[M+K]^+$ 407.0462, found 407.0459.

3-Benzyl-5-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (2ab)



Using the general procedure (**GP-1**), benzyl protected isatin **2a** (100 mg, 0.4214 mmol) and benzyl protected thiazolidinedione **3b** (87.35 mg, 0.4214 mmol) were stirred for 48 h in water to afford compound **2ab** (170.3 mg, 91%) as an off-white solid. NMR of *anti* diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 4.2 Hz, 4H), 7.37 (dd, *J* = 10.4, 5.8 Hz, 2H), 7.32 (d, *J* = 6.3 Hz, 4H), 7.28 (s, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.07 (d, *J* = 15.7 Hz, 1H), 4.97 (s, 1H), 4.90 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 14.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 171.9, 169.9, 143.7, 135.1, 134.7, 131.4, 129.0, 128.8, 128.2, 128.0, 127.7, 124.5, 123.7, 110.3, 60.7, 45.9, 44.6. HRMS (ESI) calculated for $C_{25}H_{20}N_2NaO_4S$ $[M+Na]^+$ is 467.1041, found 467.1042.

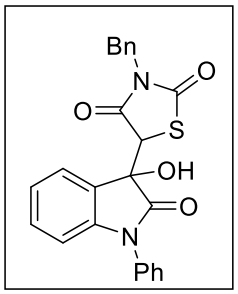
3-Benzyl-5-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (2ac)



Using the general procedure (**GP-1**), ethyl protected isatin **1d** (100 mg, 0.57 mmol) and benzyl protected thiazolidinedione **3b** (118 mg, 0.57 mmol) were stirred in water for 12 hours to afford **2ac** (202.8 mg, 93%) as an orange solid. NMR of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.21 (m, 3H), 7.15 (d, *J* = 3.9 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 4.83 (s, 1H), 4.73 – 4.62 (m, 2H), 3.83 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.69 (dt, *J* = 14.2, 7.2 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 171.7, 170.1, 143.5, 134.7, 131.5, 128.7, 128.2, 126.1, 124.7, 123.5, 109.3, 54.5, 45.6, 35.3, 12.5. HRMS (ESI) calculated for $C_{20}H_{19}N_2O_4S$ $[M+H]^+$ is 383.1066, found 383.1066.

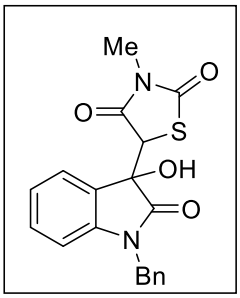
3-Benzyl-5-(3-hydroxy-2-oxo-1-phenylindolin-3-yl)-thiazolidine-2,4-dione (2ad)[19]

Using the general procedure (**GP-1**), phenyl protected isatin **1c** (37.9 mg, 0.17 mmol, 1.0 equiv) and benzyl protected thiazolidinedione **3b** (35.2 mg, 0.17 mmol, 1.0 equiv) were stirred for 48 h in water to afford **2ad** (67.3 mg, 92%) as a colorless solid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) 7.68 (d, 1H, *J* = 8.9 Hz), 7.63 (t, 2H, *J* = 9.6 Hz), 7.51 (t, 1H, *J* = 9.4 Hz), 7.45−7.43 (m, 2H), 7.40−7.38 (m, 1H), 7.14 (d, 1H, *J* = 9.1 Hz), 7.10−7.04 (m, 3H), 6.73 (d, 1H, *J* = 9.9 Hz), 6.50 (d, 2H, *J* = 9.1 Hz), 5.38 (s, 1H), 4.72−4.35 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) 174.2, 170.9, 170.3, 143.8, 134.8, 134.0, 130.9, 129.8, 128.4, 128.3, 127.1, 126.2, 125.9, 124.9, 123.1, 109.3, 74.3, 58.3, 44.0. HRMS (ESI) calculated for $C_{24}H_{19}N_2O_4S$ $[M+H]^+$ 431.1060, found 431.1063.



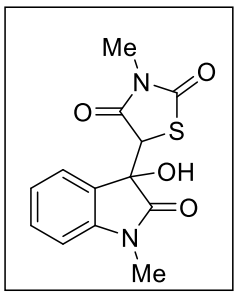
5-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (2ba)

Using the general procedure (**GP-1**), benzyl protected isatin **1a** (147.13 mg, 0.62 mmol) and methyl protected thiazolidinedione **3d** (81.3 mg, 0.62 mmol) were stirred in water for 48 hours to afford **2ba** (214.5 mg, 94%) as an orange solid. NMR of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 4.8, 1.3 Hz, 3H), 7.13 (s, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H),



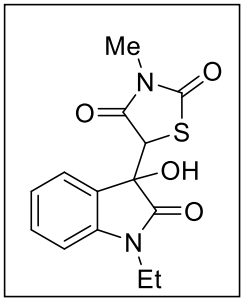
4.86 (s, 1H), 4.72 – 4.60 (m, 2H), 3.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 135.0, 131.5, 129.0, 128.0, 127.5, 124.4, 123.8, 110.3, 53.3, 44.4, 37.5. HRMS (ESI) calculated for $C_{19}H_{17}N_2O_4S$ $[M+H]^+$ is 369.0909, found 369.0974.

5-(3-Hydroxy-1-methyl-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (2bb)[19]



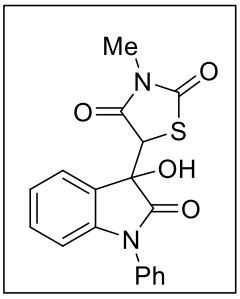
Using the general procedure (**GP-1**), methyl protected isatin **1b** (77.7 mg, 0.4825 mmol) and methyl protected thiazolidinedione **3d** (63.28 mg, 0.4825 mmol) were stirred in water for 12 h. The residue was isolated by filtration to afford **2bb** (137.9 mg, 96%) as a light orange solid. NMR of *anti*-diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.07 (s, 1H), 7.02 (t, J = 7.4 Hz, 2H), 5.15 (s, 1H), 3.15 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 171.1, 170.1, 143.9, 130.6, 126.5, 123.9, 122.4, 108.9, 74.1, 57.3, 27.1, 26.2. HRMS (ESI) calculated for $C_{13}H_{12}N_2NaO_4S$ $[M+Na]^+$ is 315.0415, found 315.0417.

5-(1-Ethyl-3-hydroxy-2-oxoindolin-3-yl)-3-methylthiazolidine-2,4-dione (2bc)[19]



Using the general procedure (**GP-1**), ethyl protected isatin **1d** (146.98 mg, 0.839 mmol) and methyl protected thiazolidinedione **3d** (110 mg, 0.839 mmol) were stirred in water for 12 h to afford **2bc** (248.5 mg, 96%) as a white solid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (d, J = 7.4 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 7.1 Hz, 2H), 7.00 (t, J = 7.5 Hz, 1H), 5.15 (s, 1H), 3.78 – 3.64 (m, 2H), 2.65 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 171.1, 170.0, 143.1, 130.6, 126.7, 124.1, 122.2, 108.9, 74.0, 57.3, 34.3, 27.2, 12.0. HRMS (ESI) calculated for $C_{14}H_{15}N_2O_4S$ $[M+H]^+$ is 307.0747, found 307.0749.

5-(3-Hydroxy-2-oxo-1-phenylindolin-3-yl)-3-methylthiazolidine-2,4-dione (2bd) [19]

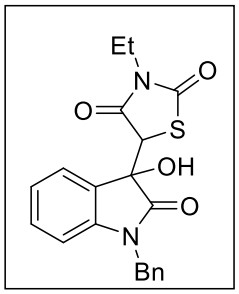


Using the general procedure (**GP-1**), phenyl protected isatin **1c** (138.2 mg, 0.62 mmol) and methyl protected thiazolidinedione **3d** (81.3 mg, 0.62 mmol) were stirred in water for 48 h to afford **2bd** (210.8 mg, 98%) as a white solid.

NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 – 7.61 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 2H), 5.28 (s, 1H), 2.69 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.1, 171.1, 170.4, 143.8, 134.0, 130.7, 129.8, 128.4, 126.6, 126.2, 124.5, 123.0, 109.3, 74.1, 57.8, 27.3. HRMS (ESI) calcd for $C_{18}H_{15}N_2O_4S$ $[M+H]^+$ 355.0747, found 355.0745.

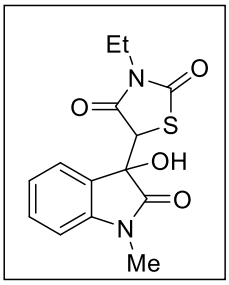
5-(1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)-3-ethylthiazolidine-2,4-dione (2ca)[19]

Using the general procedure (**GP-1**), benzyl protected isatin **1a** (147 mg, 0.62 mmol) and ethyl protected thiazolidinedione **3a** (90 mg, 0.62 mmol) and were stirred in water for 48 h to provide **2ca** (215.6 mg, 91%) as a light brown solid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 (m, 2H), 7.24 (s, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 5.19 (s, 1H), 4.99 – 4.95 (m, 2H), 3.24 (tt, 2H, *J* = 6.8, 13.6 Hz, 2H), 0.51 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.7, 170.9, 169.8, 143.2, 135.9, 130.4, 128.5, 127.4, 127.3, 126.5, 124.0, 122.4, 109.5, 74.4, 57.2, 43.2, 35.8, 11.8. HRMS (ESI) calculated for $C_{20}H_{18}N_2NaO_4S$ $[M+Na]^+$ is 405.0885, found 405.0886.

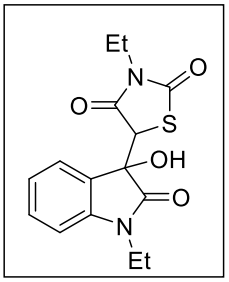


3-Ethyl-5-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-thiazolidine-2,4-dione (2cb)[19]

Using the general procedure (**GP-1**), methyl protected isatin **1b** (100 mg, 0.62 mmol) and ethyl protected thiazolidinedione **3a** (90 mg, 0.62 mmol) were stirred in water for 12 h to afford **2cb** (180.3 mg, 95%) as a white solid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 7.03 – 7.01 (m, 2H), 5.08 (s, 1H), 3.29 – 3.15 (m, 2H), 3.14 (s, 3H), 0.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 171.0, 169.7, 144.0, 130.6, 126.2, 123.9, 122.3, 108.8, 74.4, 57.5, 35.8, 26.2, 11.8. HRMS (ESI) calcd for $C_{14}H_{14}KN_2O_4S$ $[M+K]^+$ 345.0306, found 345.0327.



3-Ethyl-5-(1-ethyl-3-hydroxy-2-oxoindolin-3-yl)thiazolidine-2,4-dione (2cc) [19]



Using the general procedure (**GP-1**), ethyl protected isatin **1d** (107.6 mg, 0.62 mmol) and ethyl protected thiazolidinedione **3a** (90 mg, 0.62 mmol) were stirred in water for 12 h to afford **2cc** (190.3 mg, 96%) as a white solid. NMR of major diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.07 (s, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 5.08 (s, 1H), 3.64 – 3.76 (m, 2H), 3.19 – 3.16 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 171.0, 169.6, 143.0, 130.5, 126.4, 124.1, 122.1, 108.9, 74.2, 57.4, 35.8, 34.3, 12.0, 11.7. HRMS (ESI) calcd for $C_{15}H_{20}N_2O_4S$ $[M+NH_4]^+$ 338.1169, found 338.1185.

3.0 Solvent optimization for reversible exchange reaction

Table S2: Solvent optimization for reversible exchange reaction

entry	Solvent	temp. (°C)	time (h)	Conversion (**2aa**:**2ab**)[a]
1	H_2O (pH=7)	25	12	87:13
2	50% i-PrOH	25	12	34:66
3	20% i-PrOH	25	12	51:49
4	10% i-PrOH	25	12	54:46
5	5% i-PrOH	25	24	15:85
6	20% t-BuOH	25	12	67:33
7	10% EtOH	25	36	56:44
8	3% DMSO	25	12	100:0

4.0 Optimization of exchange reaction condition in aqueous media

A solution of oxindolyl-thiazolidinedione isatin **1a** (50 mg, 0.21 mmol, 1 equiv) and **2aa** (*dr* = 98:2, 77.36 mg, 0.21 mmol, 1 equiv) in a mixture of acetate buffer at pH 4 (5 mL, 0.1 M) was

stirred at room temperature for 48 h. The pH was raised to 8 by adding a saturated solution of $NaHCO_3$ and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, followed by filtered and concentrated. The residue was purified by column chromatography (20:80 EtOAc-Hexane) followed by analysis (Table 1). The distribution ratio at equilibrium was determined by HPLC.

For the reverse reaction, a solution of oxindolyl-thiazolidinedione methyl protected isatin **1b** (34 mg, 0.21 mmol, 1 equiv) and **2ab** (*dr* = 96:4, 93.34 mg, 0.21 mmol, 1 equiv) in a mixture of acetate buffer at pH 6 (5 mL, 0.1 M) was stirred at room temperature for 48 h (Table 2). Equilibrium distribution ratio was analyzed by HPLC.

5.0 Reversible exchange reactions at optimised condition

5.1 General procedure for the oxindolyl-thiazolidinedione and isatin library exchange (GP-2)

A solution of isatin **1R^3** (0.21 mmol, 1 equiv) and oxindolyl-thiazolidinedione **2R^{1}R^2** (0.21 mmol, 1 equiv) in acetate buffer of pH 6 (5 mL, 0.1 M) was stirred at room temperature for 24 h (Scheme 3). After 24 h, the crude mixture was extracted with ethyl acetate (3 × 10 mL). Equilibrium distribution ratio was analyzed by HPLC.

5.2 Exchange between oxindolyl-thiazolidinedione and thiazolidinedione (GP-3)

A solution of oxindolyl-thiazolidinedione **2aa** (*dr* = 98:2, 84.6 mg, 0.23 mmol, 1 equiv), *N*-ethyl thiazolidinedione **3a** (33.4 mg, 0.23 mmol, 1 equiv) in acetate buffer of pH 6 (5 mL, 0.1 M) was stirred at room temperature for 24 h (Scheme 4a). After 24 h, the crude mixture was extracted with ethyl acetate (3 × 10 mL). Equilibrium distribution ratio was analyzed by HPLC.

5.3 Procedure for the cross-exchange reaction

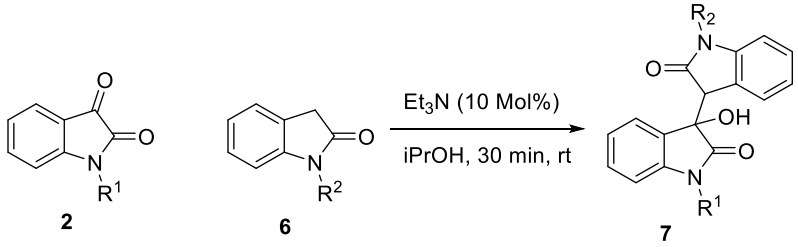
A mixture of oxindolyl-thiazolidinedione **2aa** (*dr* = 98:2, 50 mg, 0.136 mmol, 1 equiv), oxindolyl-thiazolidinedione **2bb** (*dr* = 98:2, 50 mg, 0.136 mmol, 1 equiv) in acetate buffer solution (25 mL, 0.1 M) adjusted to pH 6 was stirred at room temperature for 24 h (Scheme 4b). Then, the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The equilibrium distribution ratio of crude mixture was calculated using HPLC.

5.4 Exchange between oxindolyl-thiazolidinedione and aromatic aldehydes

A mixture of oxindolyl-thiazolidinedione **2aa** (*dr* = 98:2, 50 mg, 0.136 mmol, 1 equiv), aromatic aldehydes **6** (1 equiv) in acetate buffer solution (25 mL, 0.1 M) adjusted to pH 6 was stirred at room temperature for 24 h (Scheme 4c). Then, the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The residue was purified by chromatography (30% EtOAc-Hexane) and analyzed by ^{1}H NMR.

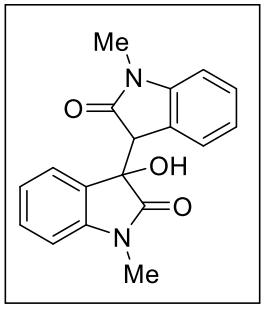
6.0 Synthesis of bi-indolinedione derivatives (GP-4)

A mixture of isatin derivative **1** (1.0 equiv) and oxindole derivative **6** (1.0 equiv) was stirred on isopropanol (2 mL) in 10 mol% Et_3N at room temperature for 30 min. Petrolium ether was added to the crude mixture to obtain the 3-hydroxybiindolinedione derivatives **7** (Scheme S1). The crude product was purified by washing the solid with petroleum ether−isopropyl alcohol (1:1) (3 × 2 mL) and characterized by ^{1}H and ^{13}C NMR.



Scheme S1. Synthesis of 3-hydroxybiindolinedione derivatives.

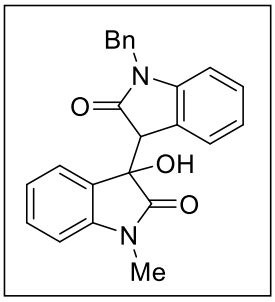
3-Hydroxy-1,1'-dimethyl-[3,3'-biindoline]-2,2'-dione (7aa)



Using the general procedure (**GP-2**), a mixture of methyl protected isatin **1b** (100 mg, 0.62 mmol) and methyl protected oxindole **6a** (91.2 mg, 0.62 mmol) afforded compound **7aa** (*dr* = 98:2, 130 mg, 68%) as an off-white solid. NMR of *anti* diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 16.1, 7.8 Hz, 2H), 7.21 (dd, *J* = 15.2, 7.6 Hz, 2H), 6.83 – 6.77 (m, 2H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.04 (d, *J* = 10.6 Hz, 2H), 3.95 (s,

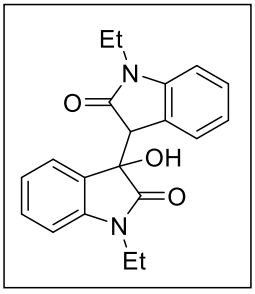
1H), 3.25 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 175.0, 145.1, 130.9, 129.2, 128.0, 124.6, 124.2, 123.6, 123.0, 122.5, 108.7, 49.8, 26.5, 25.9. HRMS (ESI) calculated for $C_{18}H_{16}N_2NaO_3$ $[M+Na]^+$ is 331.1059, found 331.1059.

1'-Benzyl-3-hydroxy-1-methyl-[3,3'-biindoline]-2,2'-dione (7da)



Using the general procedure (**GP-2**), a mixture of methyl protected isatin **1b** (100 mg, 0.62 mmol) and benzyl protected oxindole **6d** (138.4 mg, 0.62 mmol) provided compound **7da** (*dr* = 95:5, 147.9 mg, 62%) as an off-white solid. NMR of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.27 (s, 1H), 7.25 – 7.21 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.10 (dd, *J* = 10.4, 7.7 Hz, 2H), 6.83 – 6.77 (m, 2H), 6.63 (q, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 5.8 Hz, 1H), 4.98 (d, *J* = 12.6 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.12 (s, 1H), 3.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 175.0, 144.4, 144.0, 135.2, 130.6, 128.9, 128.7, 127.5, 127.4, 127.2, 124.6, 124.3, 123.2, 123.2, 122.4, 109.5, 108.5, 50.3, 43.9, 26.0. HRMS (ESI) calculated for $C_{24}H_{20}N_2NaO_3$ $[M+Na]^+$ is 407.4170, found 407.4138.

1,1'-Diethyl-3-hydroxy-[3,3'-biindoline]-2,2'-dione (7bb)

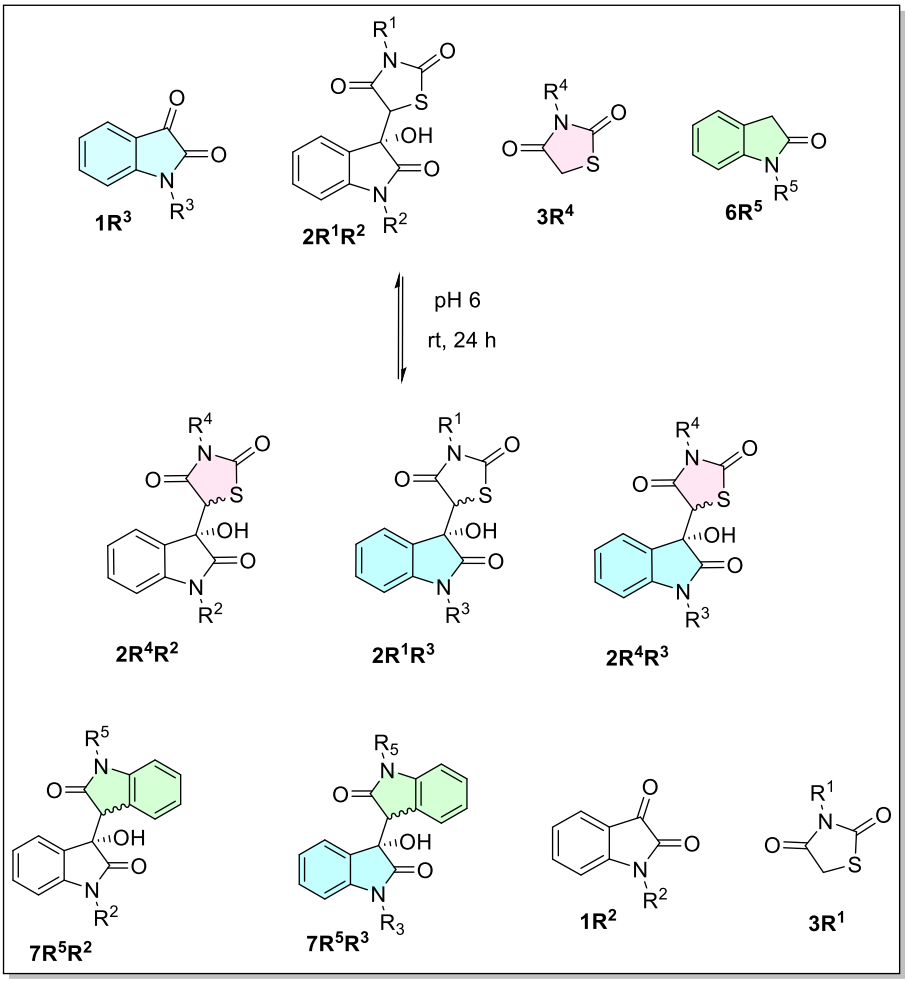


Using the general procedure (**GP-2**), a mixture of ethyl protected isatin **1d** (108.6 mg, 0.62 mmol) and ethyl protected oxindole **6b** (100 mg, 0.62 mmol) provided compound **7bb** (*dr* = 96:4, 133.5 mg, 64%) as a black solid. NMR of major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 6.1 Hz, 3H), 7.09 (s, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 4.87 (s, 1H), 4.69 – 4.58 (m, 2H), 3.83 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.67 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.30 – 1.25 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 170.4, 143.4, 134.7, 131.4, 128.6, 124.8, 123.6, 109.2, 45.4, 35.3, 12.4. HRMS (ESI) calculated for $C_{20}H_{20}N_2NaO_3$ $[M+Na]^+$ is 359.1372, found 359.1374.

6.1 Exchange between oxindole and oxindolyl-thiazolidinedione (GP-5)

A mixture of oxindolyl-thiazolidinedione **2** (0.23 mmol, 1 equiv) and *N*-substituted oxindole **6** (0.23 mmol, 1 equiv) in acetate buffer of pH 6 (25 mL, 0.1 M) was stirred at room temperature for 24 h (Scheme 5). After 24 h, reaction mixture was extracted with ethyl acetate (3 × 10 mL) and the equilibrium distribution ratio of crude mixture was calculated using HPLC.

7.0 Potential Dynamic Combinatorial Library



Scheme S2. Potential Dynamic Combinatorial Library.

8.0 HPLC data:

The Compounds are identified by running pure compounds in HPLC using CHIRALCEL OD column (0.46cm ID × 25 cm) using an isocratic system isopropanol/*n*-Hexanes (10:90), wavelength (λ) = 200 nm.

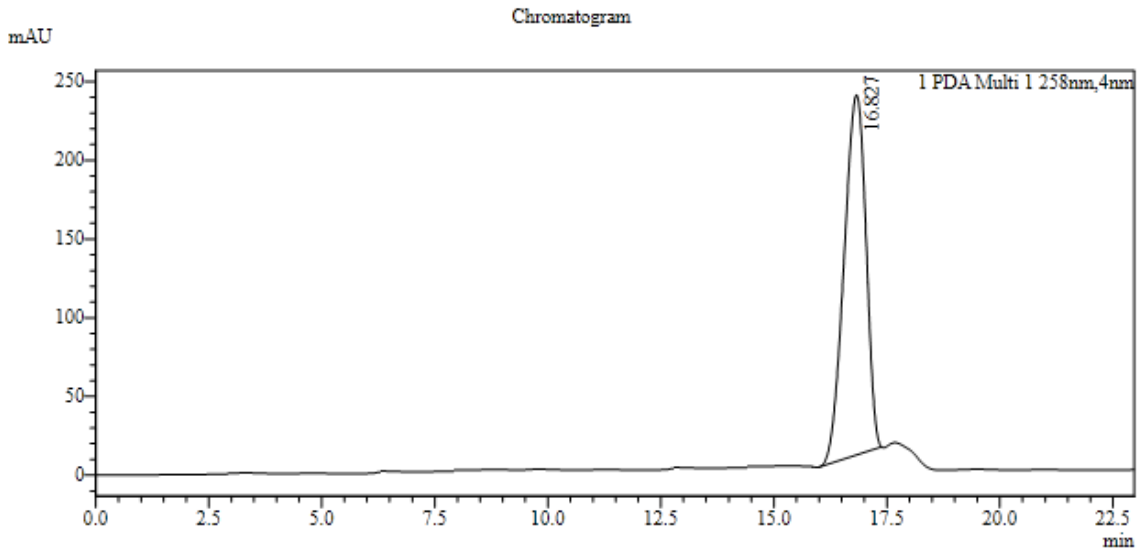


Figure S1. HPLC of compound **2aa**

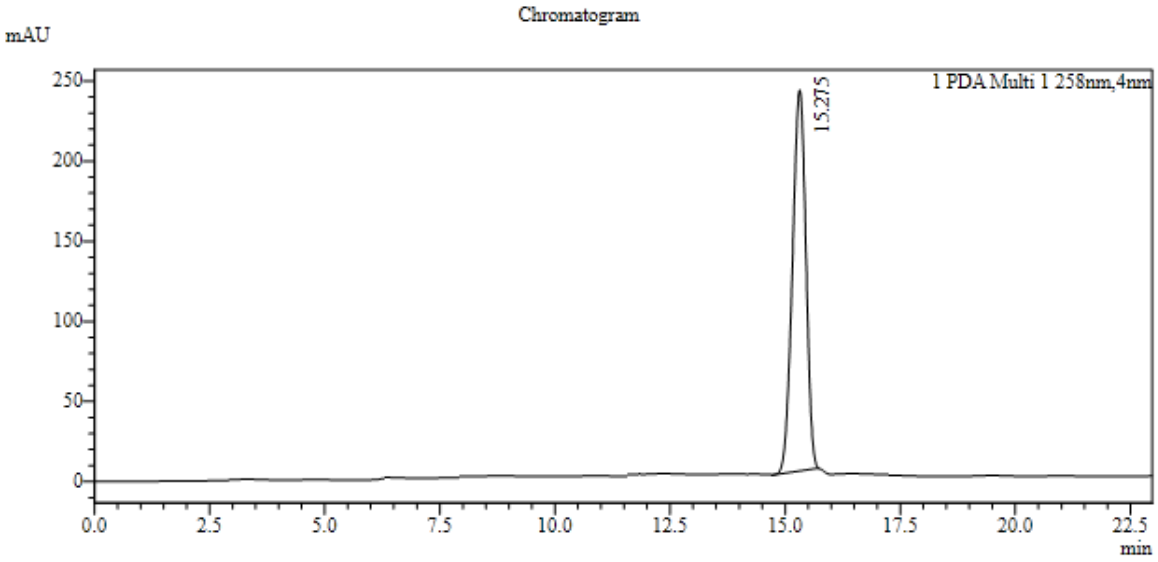


Figure S2. HPLC of compound **2ab**

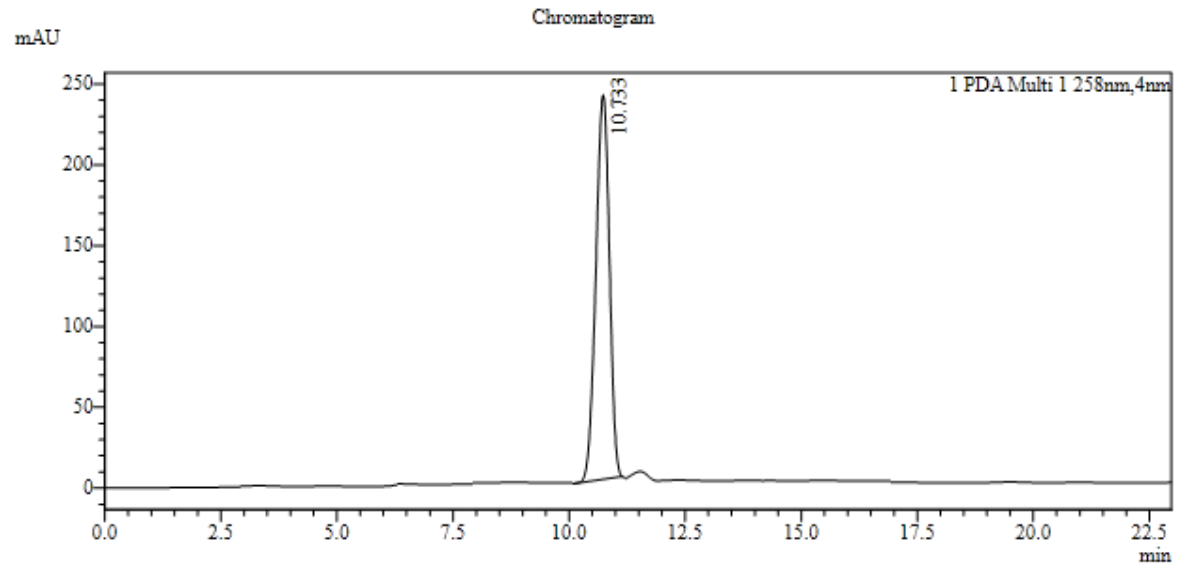


Figure S3. HPLC of compound **2ba**

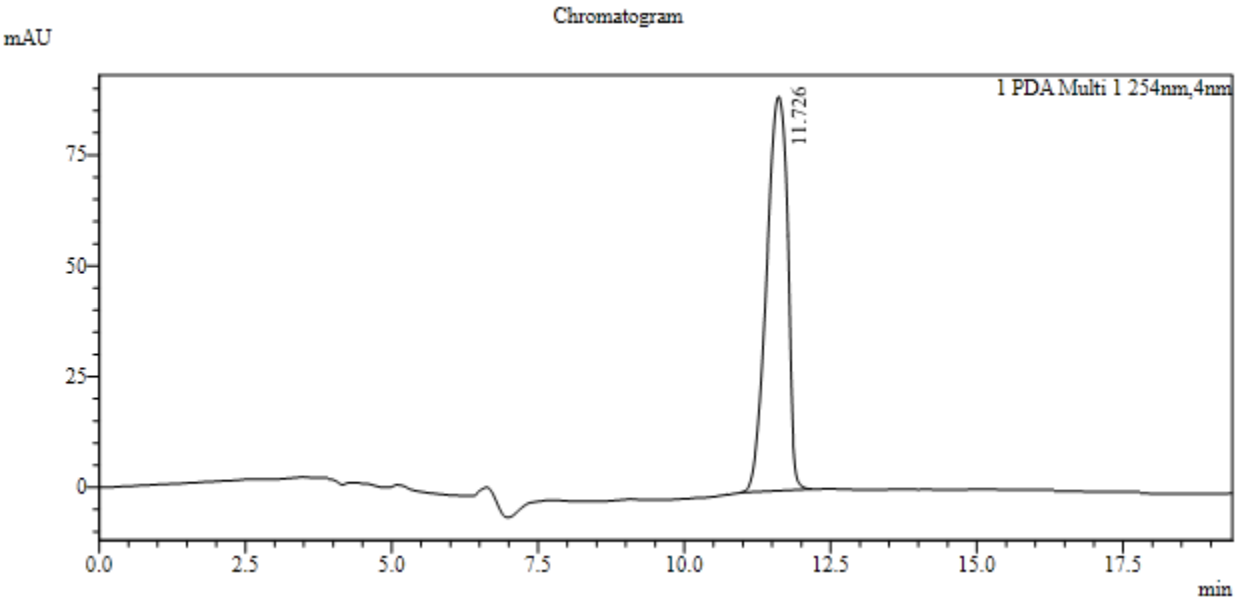


Figure S4. HPLC of compound **2bb**

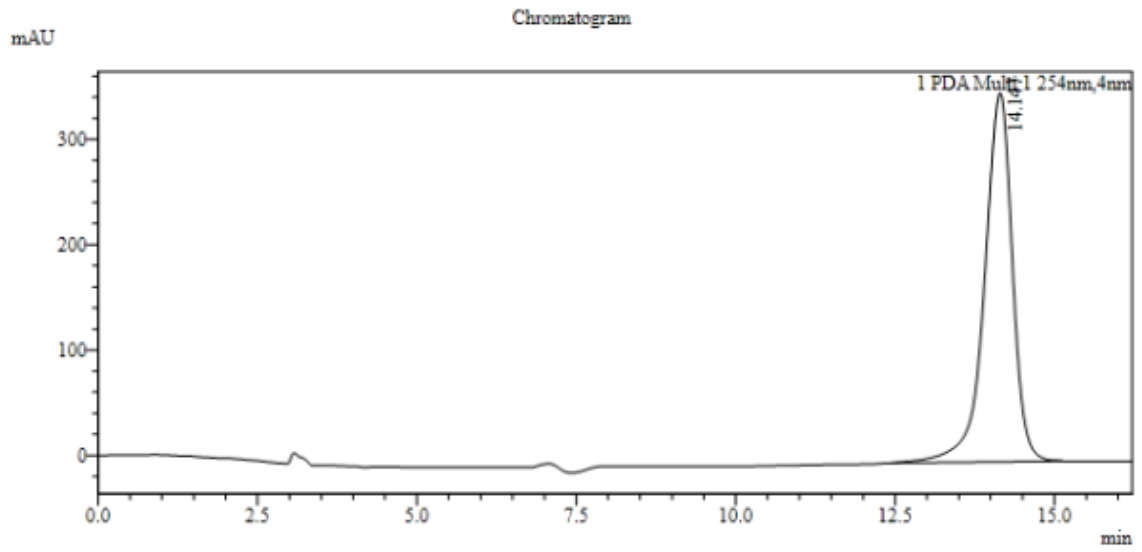


Figure S5. HPLC of compound **2bc**

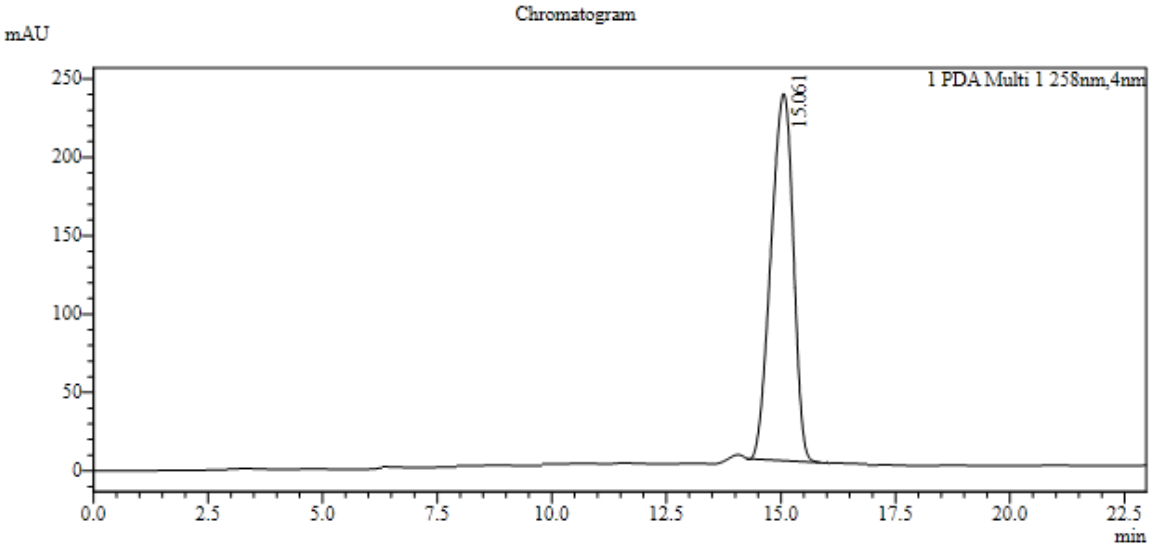


Figure S6. HPLC of compound **2cb**

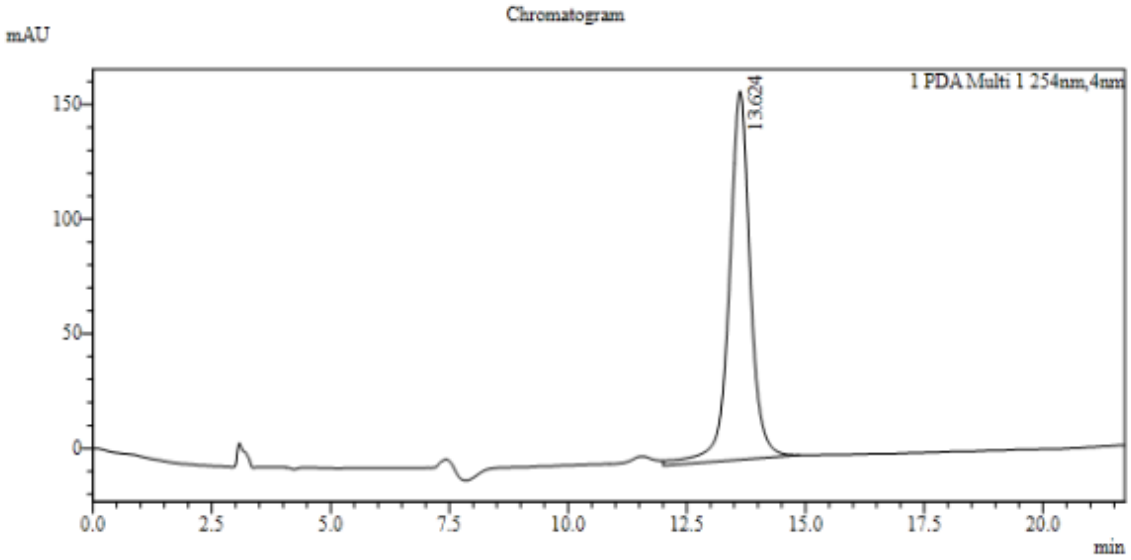


Figure S7. HPLC of compound **2cc**

Exchange reaction between oxindolyl-thiazolidinedione (**2aa**) with isatin (**1a**)

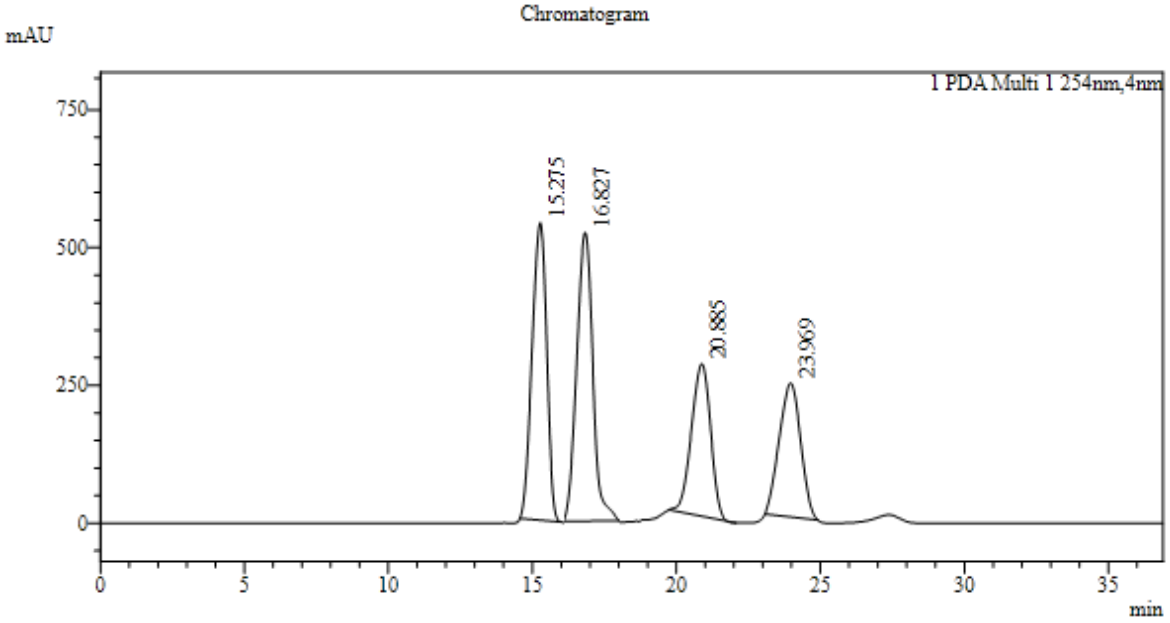


Figure S8. HPLC of crude reaction mixture at 24 h, pH 6. [2aa: R_t = 16.827 min, 1a: R_t = 20.885 min, 2ab: R_t = 15.275 min, 1b: R_t = 23.969 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2aa**) with isatin (**1c**)

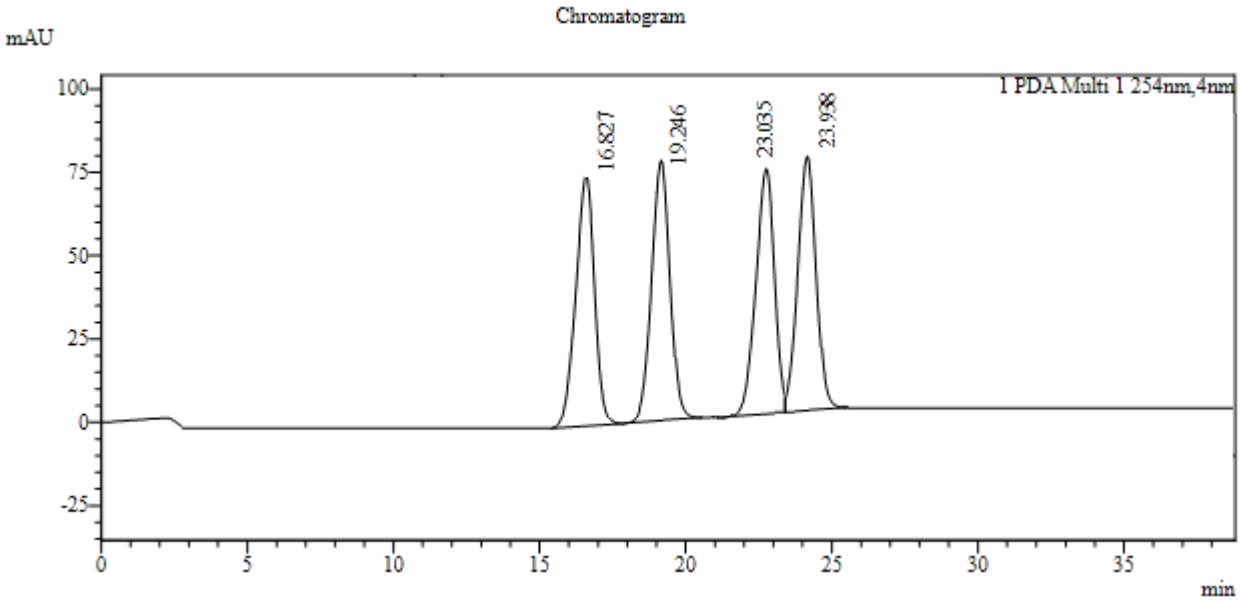


Figure S9. HPLC of crude reaction mixture at 24 h, pH 6. [2aa: R_t = 16.827 min, 1c: R_t = 23.035 min, 2ac: R_t = 19.246 min, 1b: R_t = 23.938 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2ca**) with isatin (**1c**)

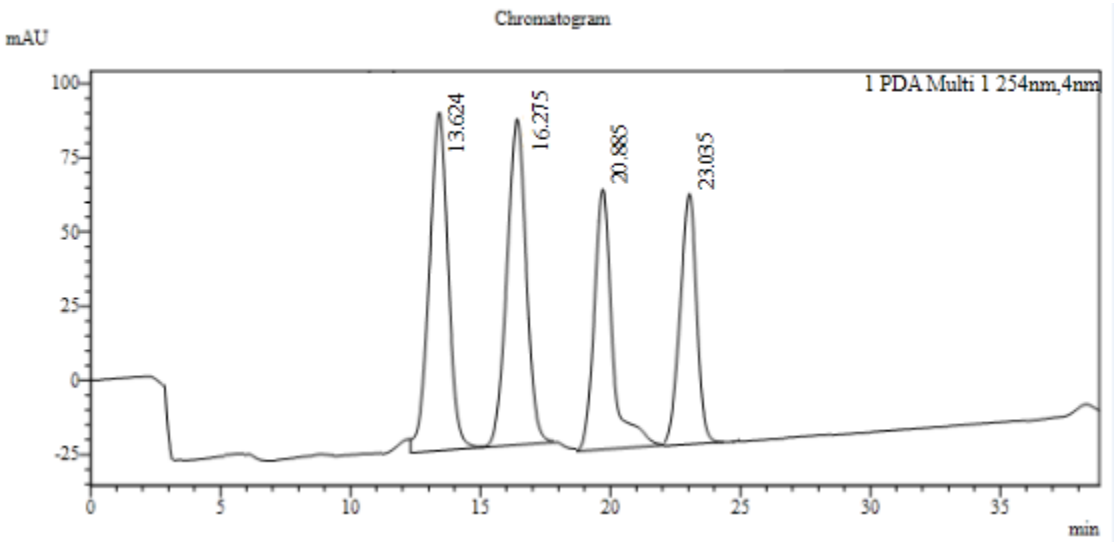


Figure S10. HPLC of crude reaction mixture at 24 h, pH 6. [2ca: R_t = 16.275 min, 1c: R_t = 23.035 min, 2cc: R_t = 13.624 min, 1a: R_t = 20.885 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2bd**) with isatin (**1b**)

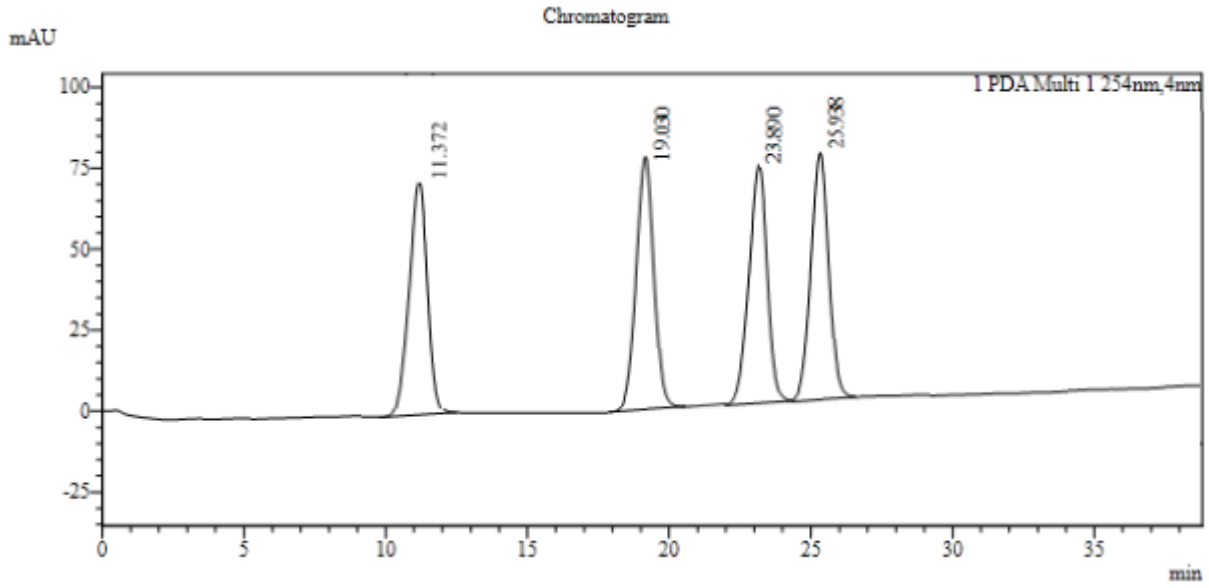


Figure S11. HPLC of crude reaction mixture at 24 h, pH 6. [2bd: R_t = 19.030 min, 1b: R_t = 23.890 min, 2bb: R_t = 11.372 min, 1d: R_t = 25.938 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2cb**) with isatin (**1c**)

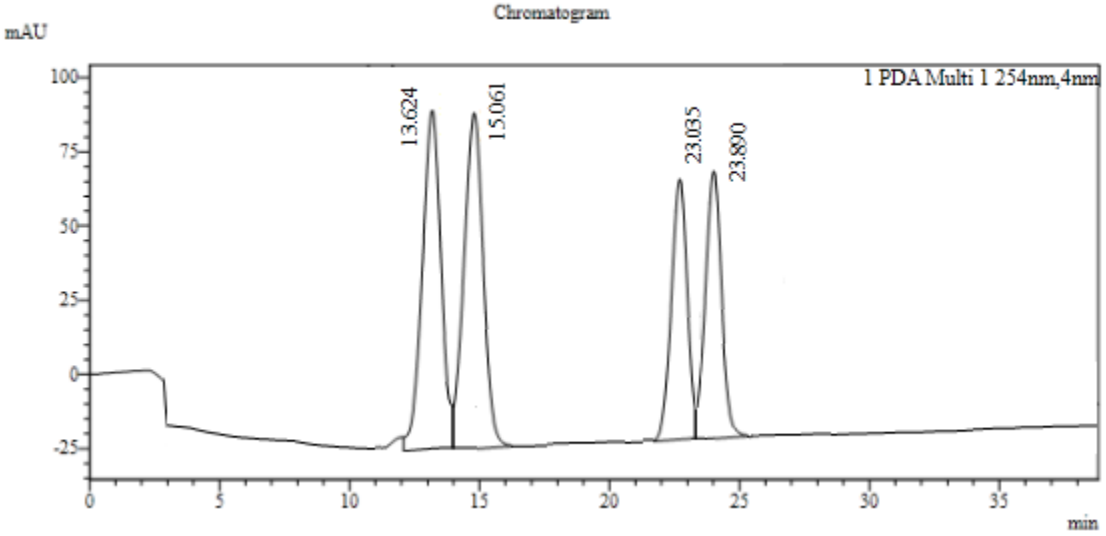


Figure S12. HPLC of crude reaction mixture at 24 h, pH 6. [2cb: R_t = 15.061 min, 1b: R_t = 23.890 min, 2cc: R_t = 13.624 min, 1c: R_t = 20.035 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2bc**) with isatin (**1b**)

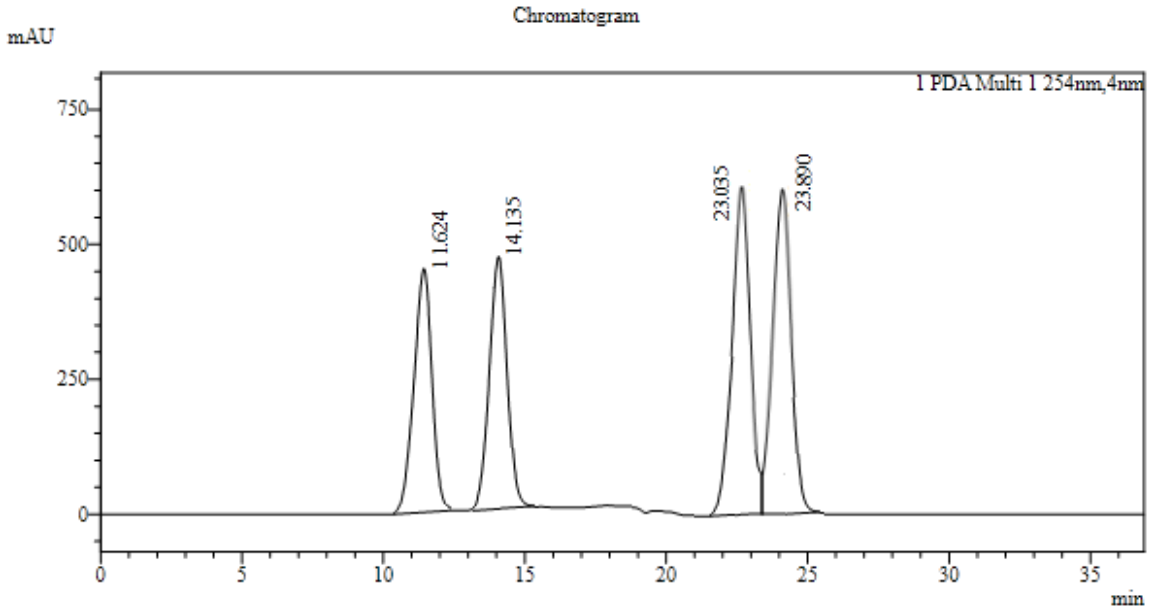


Figure S13. HPLC of crude reaction mixture at 24 h, pH 6. [2bc: R_t = 14.135 min, 1b: R_t = 23.890 min, 2bb: R_t = 11.624 min, 1c: R_t = 20.035 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2ad**) with isatin (**1b**)

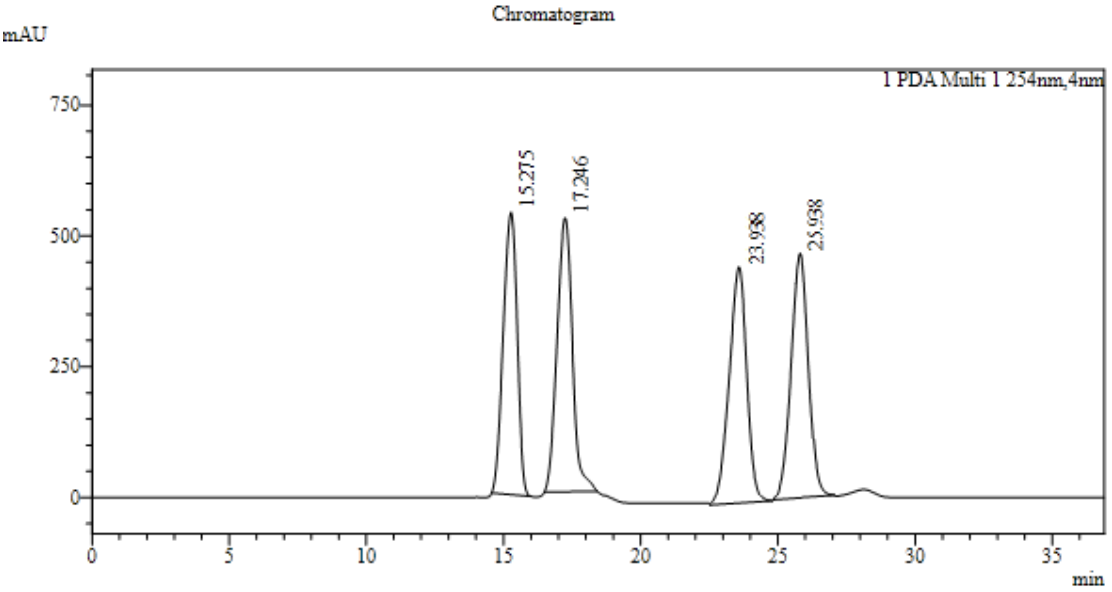


Figure S14. HPLC of crude reaction mixture at 24 h, pH 6. [2ad: R_t = 17.246 min, 1b: R_t = 23.938 min, 2ab: R_t = 15.275 min, 1d: R_t = 25.938 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2ad**) with isatin (**1a**)

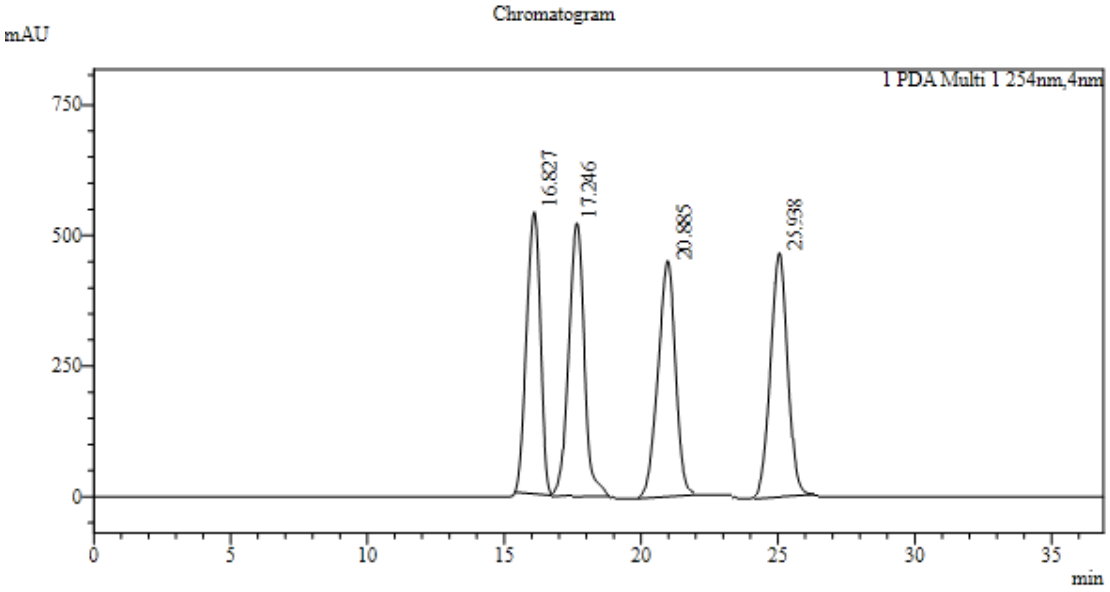


Figure S15. HPLC of crude reaction mixture at 24 h, pH 6. [2ad: R_t = 17.246 min, 1a: R_t = 20.885 min, 2aa: R_t = 16.827 min, 1d: R_t = 25.938 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2aa**) with thiazolidinedione (**3a**)

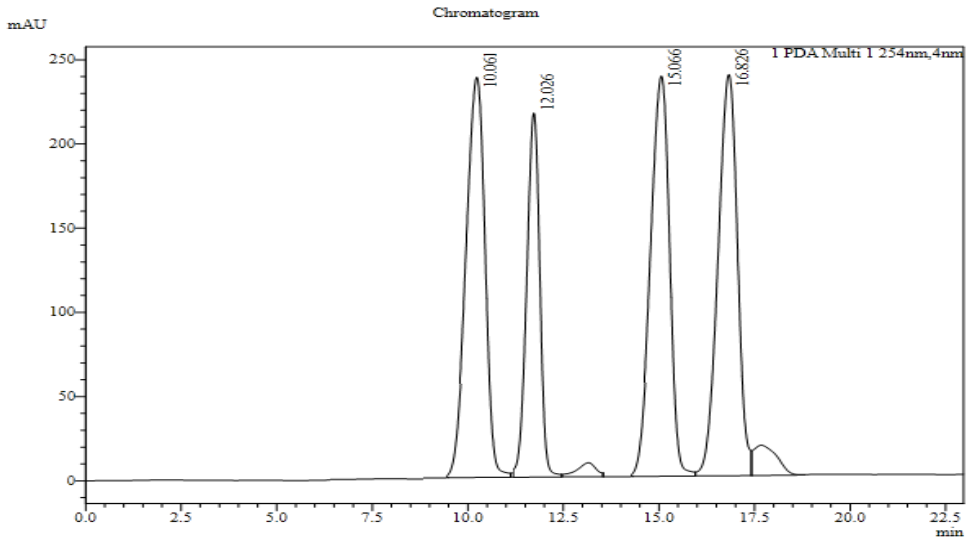


Figure S16. HPLC of crude reaction mixture at 24 h, pH 6. [2aa: R_t = 16.826 min, 3a: R_t = 10.061 min, 2cb: R_t = 15.066 min, 3b: R_t = 12.026 min]

Cross exchange reaction between oxindolyl-thiazolidinediones (**2aa** and **2ba**)

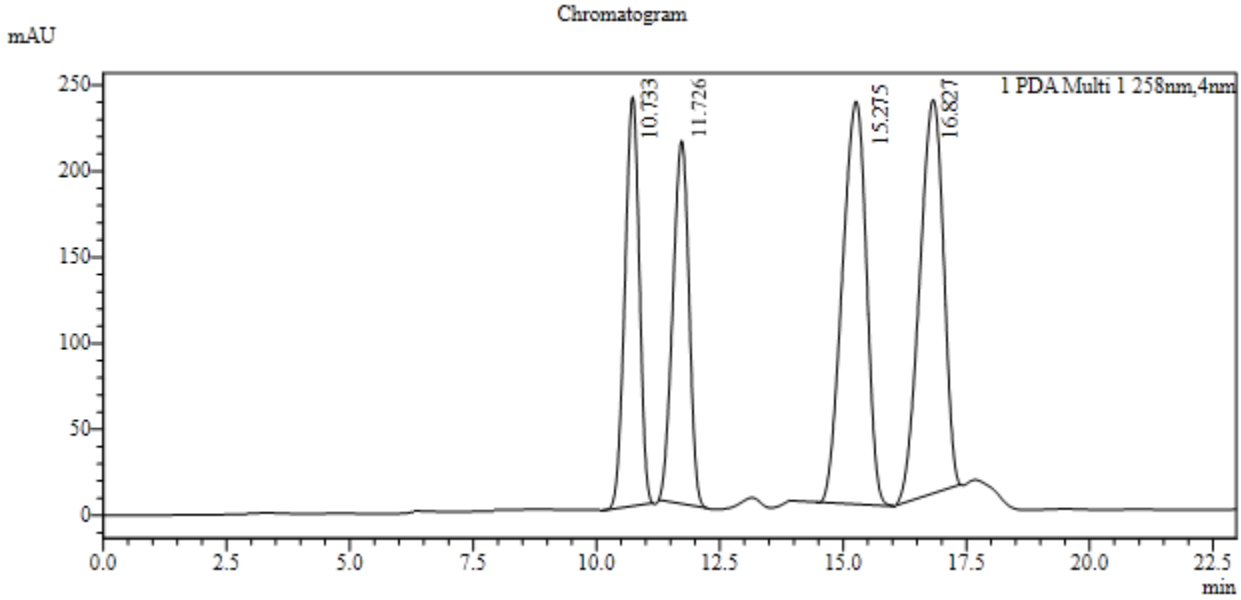


Figure S17. HPLC of crude reaction mixture at 24 h, pH 6. [2aa: R_t = 16.827 min, 2ba: R_t = 10.733 min, 2bb: R_t = 11.726 min, 2ab: R_t = 15.275 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2bb**) with oxindole (**6a**)

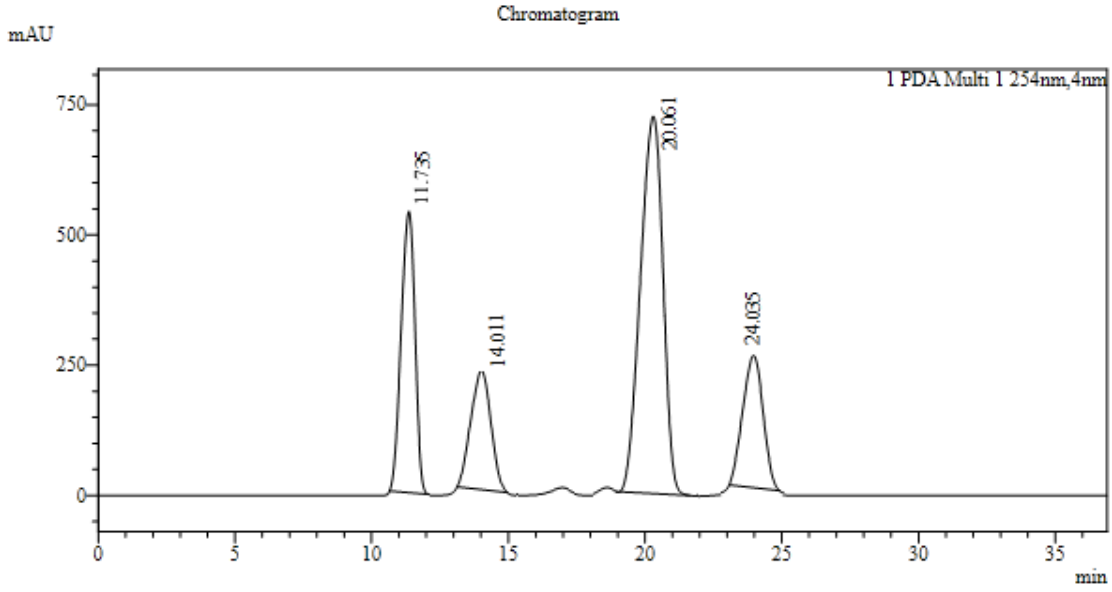


Figure S18. HPLC of crude reaction mixture at 24 h, pH 6. [2bb: R_t = 11.735 min, 6a: R_t = 20.061 min, 7aa: R_t = 14.011 min, 3d: R_t = 24.035 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2bb**) with oxindole (**6d**)

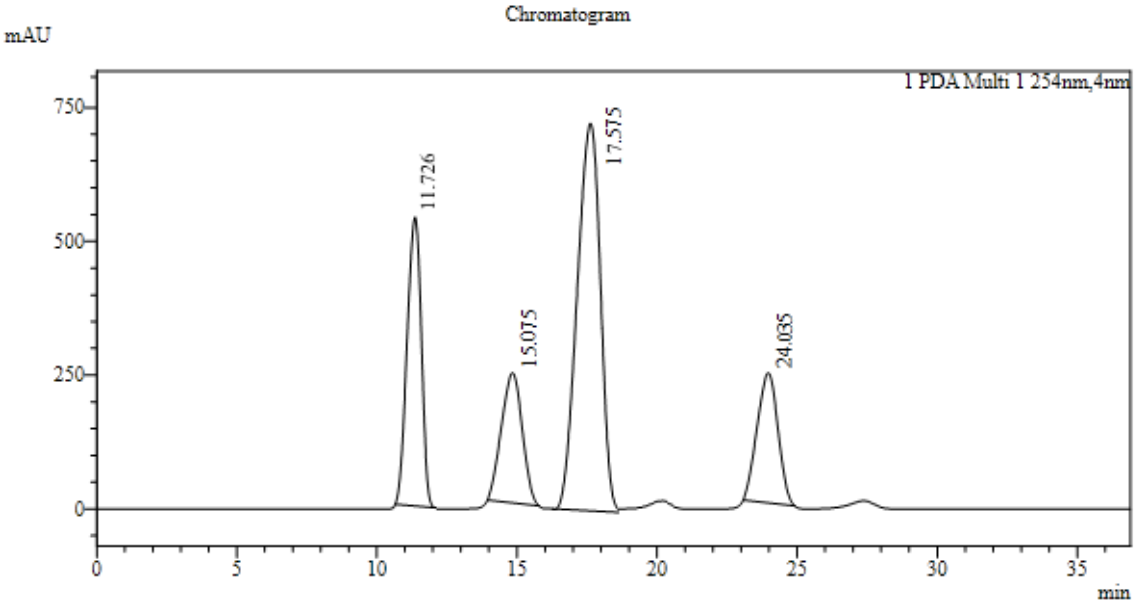


Figure S19. HPLC of crude reaction mixture at 24 h, pH 6. [2bb: R_t = 11.726 min, 6d: R_t = 15.075 min, 7da: R_t = 17.575 min, 3d: R_t = 24.035 min]

Exchange reaction between oxindolyl-thiazolidinedione (**2bc**) with oxindole (**6b**)

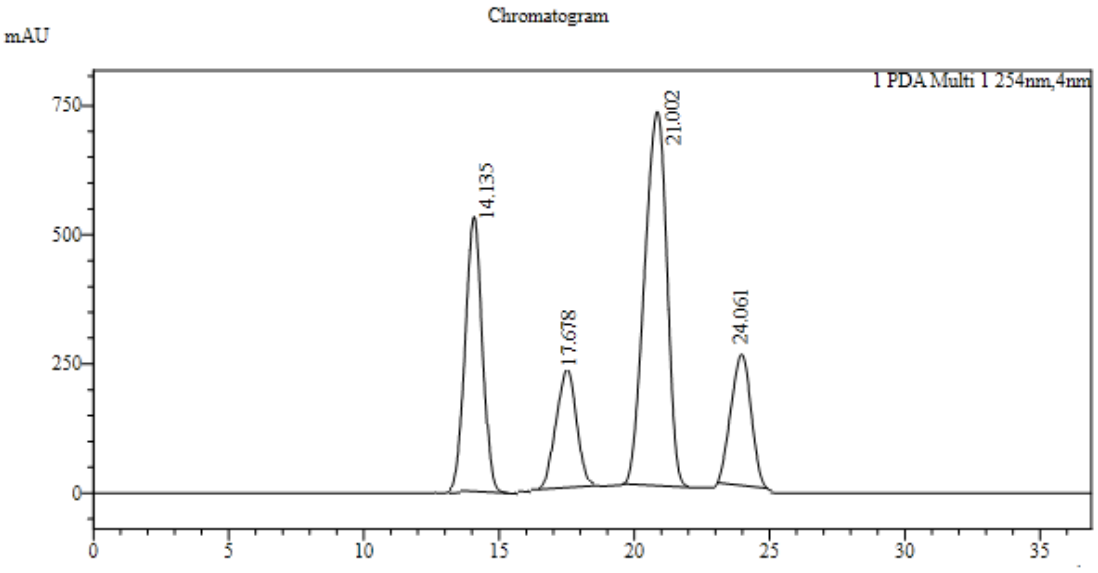


Figure S20. HPLC of crude reaction mixture at 24 h, pH 6. [2bc: R_t = 14.135 min, 6b: R_t = 17.678 min, 7bb: R_t =21.002 min, 3d: R_t = 24.061 min]

9.0 X-Ray Crystallography of 2ab and 7aa.

Crystallization of compounds **2ab** and **7aa** were carried out using vapor diffusion method. A solution of the compound was prepared in chloroform in a small glass vial and it was then placed in a larger container containing hexane and the outer vessel wall was sealed. Over time hexane evaporated and diffused over the gas phase in chloroform leading to oversaturation and finally crystallization. The crystals were then analyzed.

Intensity data was collected on a Bruker's Kappa Apex II CCD Duo diffractometer with graphite mono chromated $Mo_{K\alpha}$ radiation (0.71073 Å) at the temperature of 296 K. Scaling and multi-scan absorption correction were employed using SADABS. The structure was solved by direct methods and all the non-hydrogen atoms were refined an isotopically while the hydrogen atoms fixed in the predetermined positions by Shelxs-97 and Shelxl-97 packages respectively.

Table S3: Crystal data and structure refinement for 2ab.

Identification code	**2ab**
Empirical formula	$C_{25}H_{20}N_2O_4S$
Formula weight	444.49
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.7003(9)
b/Å	10.7468(7)
c/Å	16.0028(11)
α/°	90
β/°	105.880(2)
γ/°	90
Volume/Å^3	2100.8(2)
Z	4
ρ_{calc}g/cm^3	1.405

μ/mm^{-1}	0.191
F(000)	928.0
Crystal size/mm^3	.20 × .18 × .16
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.622 to 49.99
Index ranges	-15 ≤ h ≤ 15, -12 ≤ k ≤ 12, -19 ≤ l ≤ 19
Reflections collected	18977
Independent reflections	3670 [R_{int} = 0.0686, R_{sigma} = 0.0447]
Data/restraints/parameters	3670/0/290
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0351, wR_2 = 0.0892
Final R indexes [all data]	R_1 = 0.0409, wR_2 = 0.0958
Largest diff. peak/hole / e $Å^{-3}$	0.28/-0.28

Table S4: Bond Lengths for 2ab.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S001	C00F	1.7640(17)	C00C	C00L	1.388(2)
S001	C00H	1.8133(16)	C00C	C00D	1.391(2)
O002	C008	1.2088(19)	C00C	C00I	1.516(2)
O003	C00E	1.4129(18)	C00D	C00P	1.385(2)
O004	C00A	1.2271(19)	C00G	C00J	1.507(2)
N006	C008	1.373(2)	C00J	C00R	1.389(2)
N006	C00F	1.388(2)	C00J	C00U	1.391(2)
N006	C00G	1.477(2)	C00K	C00O	1.395(2)
N007	C00A	1.351(2)	C00L	C00N	1.394(2)
N007	C009	1.418(2)	C00M	C00Q	1.395(2)
N007	C00I	1.465(2)	C00N	C00S	1.380(3)

C008	C00H	1.517(2)	C00O	C00Q	1.384(2)
C009	C00K	1.381(2)	C00P	C00S	1.389(3)
C009	C00B	1.393(2)	C00R	C00W	1.389(3)
C00A	C00E	1.554(2)	C00T	C00U	1.382(2)
C00B	C00M	1.388(2)	C00T	C00V	1.388(3)
C00B	C00E	1.510(2)	C00V	C00W	1.381(3)

Table S5: Bond Angles for 2ab.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C00F	S001	C00H	92.69(7)	C00B	C00E	C00A	109.68(12)
C008	N006	C00F	117.01(13)	C00H	C00E	C00A	124.45(15)
C008	N006	C00G	121.78(13)	O005	C00F	N006	124.54(13)
C00F	N006	C00G	121.21(13)	O005	C00F	S001	111.01(12)
C00A	N007	C009	110.96(13)	N006	C00F	S001	111.00(13)
C00A	N007	C00I	124.76(13)	N006	C00G	C00J	112.51(12)
C009	N007	C00I	124.28(13)	C008	C00H	C00E	106.71(11)
O002	C008	N006	124.12(14)	C008	C00H	S001	111.23(10)
O002	C008	C00H	123.53(14)	C00E	C00H	S001	111.86(13)
N006	C008	C00H	112.35(13)	N007	C00I	C00C	118.96(16)
C00K	C009	C00B	122.41(15)	C00R	C00J	C00U	121.02(15)
C00K	C009	N007	127.56(15)	C00R	C00J	C00G	117.28(15)
C00B	C009	N007	110.00(13)	C00U	C00J	C00G	120.32(16)
O004	C00A	N007	125.90(15)	C009	C00K	C00O	117.28(15)
O004	C00A	C00E	125.41(14)	C00C	C00L	C00N	120.32(16)
N007	C00A	C00E	108.63(12)	C00B	C00M	C00Q	118.48(15)
C00M	C00B	C009	119.72(14)	C00S	C00N	C00L	120.24(16)
C00M	C00B	C00E	131.62(14)	C00Q	C00O	C00K	121.16(15)
C009	C00B	C00E	108.62(13)	C00D	C00P	C00S	120.00(16)

C00L	C00C	C00D	119.02(15)	C00O	C00Q	C00M	120.93(16)
C00L	C00C	C00I	121.48(14)	C00J	C00R	C00W	120.64(17)
C00D	C00C	C00I	119.50(14)	C00N	C00S	C00P	119.73(15)
C00P	C00D	C00C	120.66(15)	C00U	C00T	C00V	120.16(17)
O003	C00E	C00B	110.60(12)	C00T	C00U	C00J	120.49(16)
O003	C00E	C00H	109.16(12)	C00W	C00V	C00T	119.85(17)
C00B	C00E	C00H	115.29(13)	C00V	C00W	C00R	119.89(17)
O003	C00E	C00A	110.10(12)				

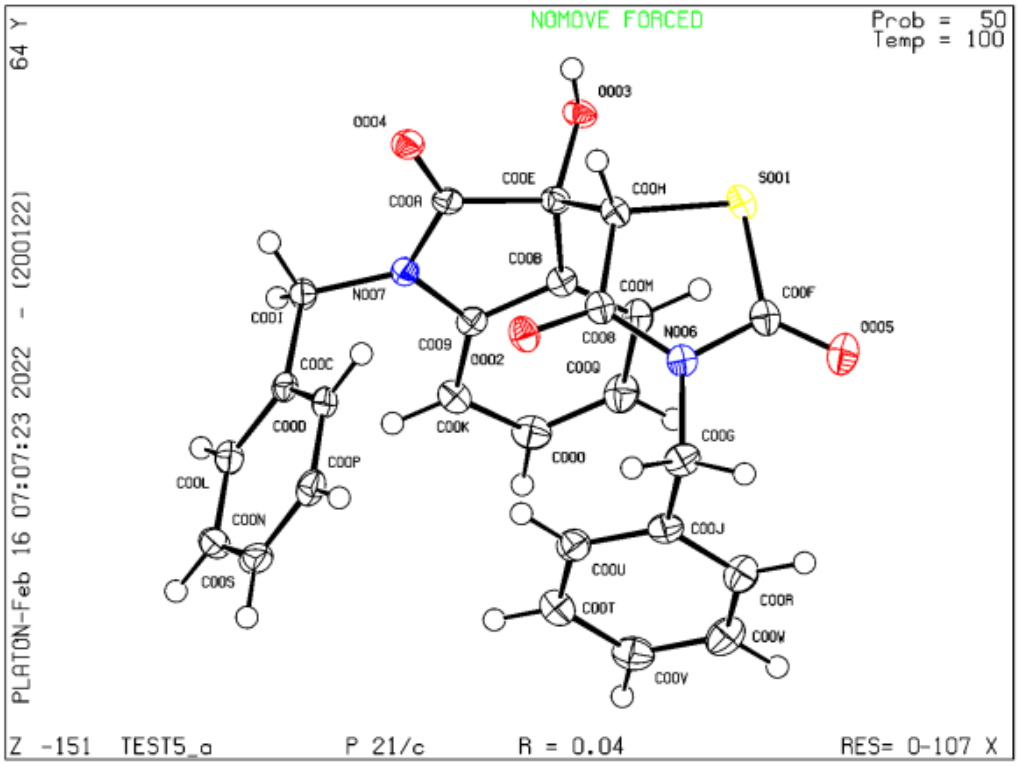


Figure S21. The ORTEP diagram of *anti*-**2ab** showing 50% probability thermal ellipsoid. (CCDC 2170211)

Table S6: Crystal data and structure refinement for 7aa.

Identification code	**7aa**
Empirical formula	$C_{18}H_{16}N_2O_3$

Formula weight	308.33
Temperature/K	111(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.9951(3)
b/Å	8.5493(2)
c/Å	15.5588(4)
α/°	90
β/°	109.0350(10)
γ/°	90
Volume/Å^3	1508.30(7)
Z	4
ρ_{calc}g/cm^3	1.358
μ/mm^{-1}	0.094
F(000)	648.0
Crystal size/mm^3	.20 × .16 × .14
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.056 to 50
Index ranges	$-14 \le h \le 14$, $-10 \le k \le 10$, $-17 \le l \le 18$
Reflections collected	12703
Independent reflections	2637 [R_{int} = 0.0359, R_{sigma} = 0.0275]
Data/restraints/parameters	2637/0/211
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0372, wR_2 = 0.0881
Final R indexes [all data]	R_1 = 0.0447, wR_2 = 0.0947
Largest diff. peak/hole / e Å^{-3}	0.30/-0.20

Table S7: Bond Lengths for 7aa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C00F	1.4126(18)	C008	C00H	1.385(2)
O002	C007	1.2152(18)	C008	C00A	1.393(2)
O003	C00D	1.2240(18)	C009	C00A	1.508(2)
N004	C007	1.364(2)	C009	C00F	1.550(2)
N004	C008	1.4074(19)	C00A	C00E	1.391(2)
N004	C00N	1.454(2)	C00B	C00K	1.381(2)
N005	C00D	1.357(2)	C00C	C00I	1.393(2)
N005	C00B	1.4108(19)	C00D	C00F	1.549(2)
N005	C00M	1.454(2)	C00E	C00L	1.398(2)
C006	C00C	1.381(2)	C00G	C00H	1.377(2)
C006	C00B	1.394(2)	C00G	C00L	1.391(2)
C006	C00F	1.509(2)	C00I	C00J	1.391(2)
C007	C009	1.532(2)	C00J	C00K	1.395(2)

Table S8: Bond Angles for 7aa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C007	N004	C008	111.43(12)	C00K	C00B	C006	122.45(14)
C007	N004	C00N	123.17(13)	C00K	C00B	N005	127.54(14)
C008	N004	C00N	125.37(13)	C006	C00B	N005	110.01(13)
C00D	N005	C00B	110.96(12)	C006	C00C	C00I	118.84(14)
C00D	N005	C00M	124.07(13)	O003	C00D	N005	125.12(14)
C00B	N005	C00M	124.94(13)	O003	C00D	C00F	126.23(14)
C00C	C006	C00B	119.80(14)	N005	C00D	C00F	108.54(12)
C00C	C006	C00F	131.56(14)	C00A	C00E	C00L	118.08(15)

C00B	C006	C00F	108.64(13)	O1	C00F	C006	110.10(12)
O002	C007	N004	125.94(14)	O1	C00F	C00D	109.54(12)
O002	C007	C009	126.28(14)	C006	C00F	C00D	101.84(12)
N004	C007	C009	107.74(12)	O1	C00F	C009	110.73(12)
C00H	C008	C00A	121.94(14)	C006	C00F	C009	114.37(12)
C00H	C008	N004	128.30(14)	C00D	C00F	C009	109.87(12)
C00A	C008	N004	109.76(13)	C00H	C00G	C00L	121.31(15)
C00A	C009	C007	102.90(12)	C00G	C00H	C008	117.80(15)
C00A	C009	C00F	114.34(12)	C00J	C00I	C00C	120.53(15)
C007	C009	C00F	110.13(12)	C00I	C00J	C00K	121.22(14)
C00E	C00A	C008	120.03(14)	C00B	C00K	C00J	117.16(15)
C00E	C00A	C009	131.82(14)	C00G	C00L	C00E	120.82(15)
C008	C00A	C009	108.14(13)				

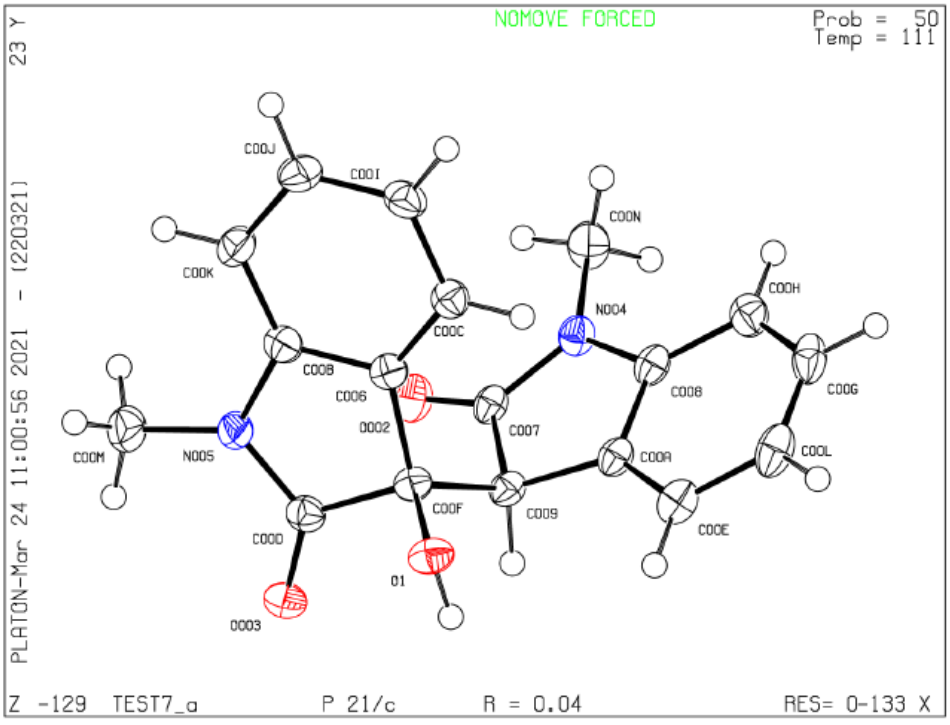
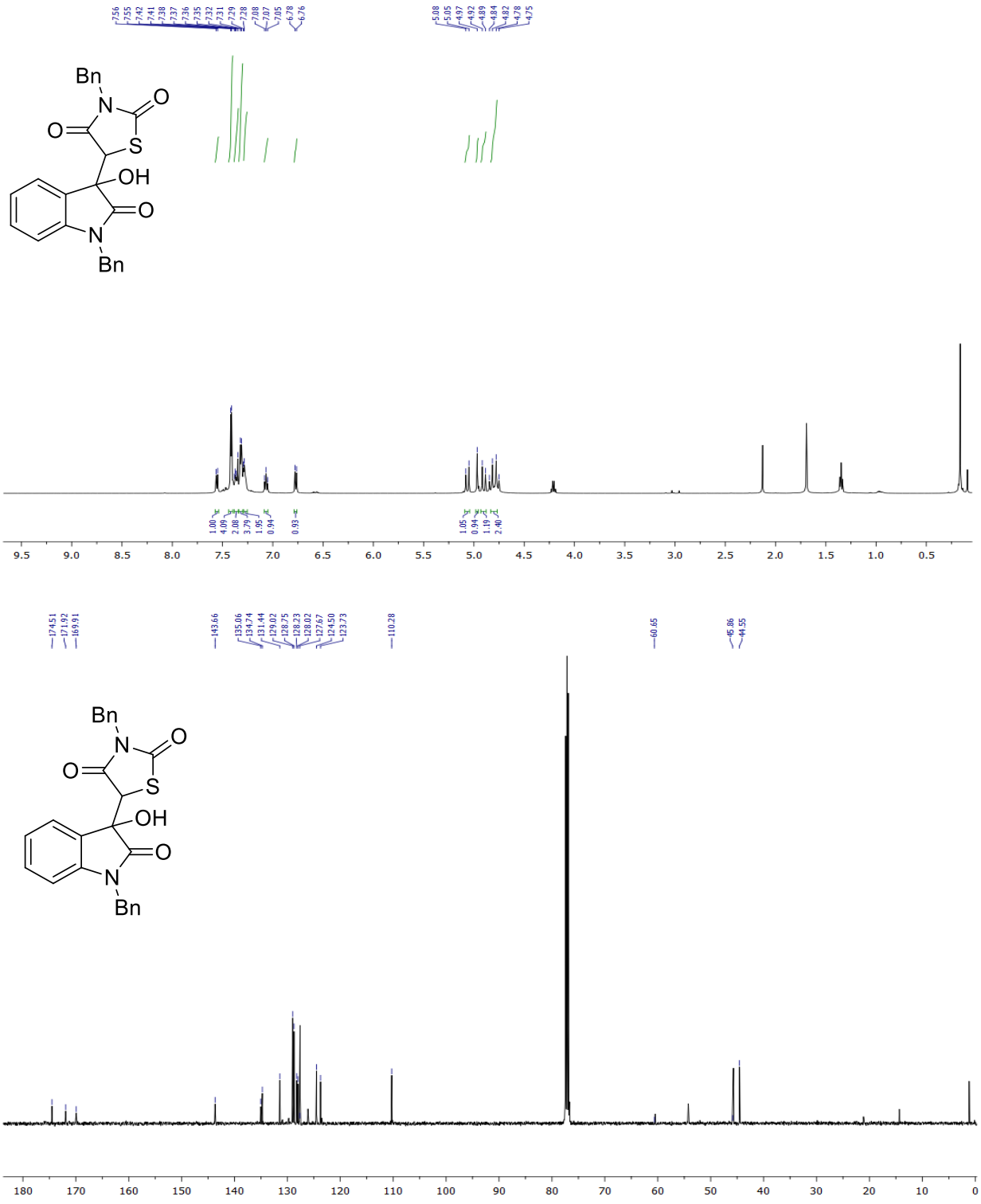


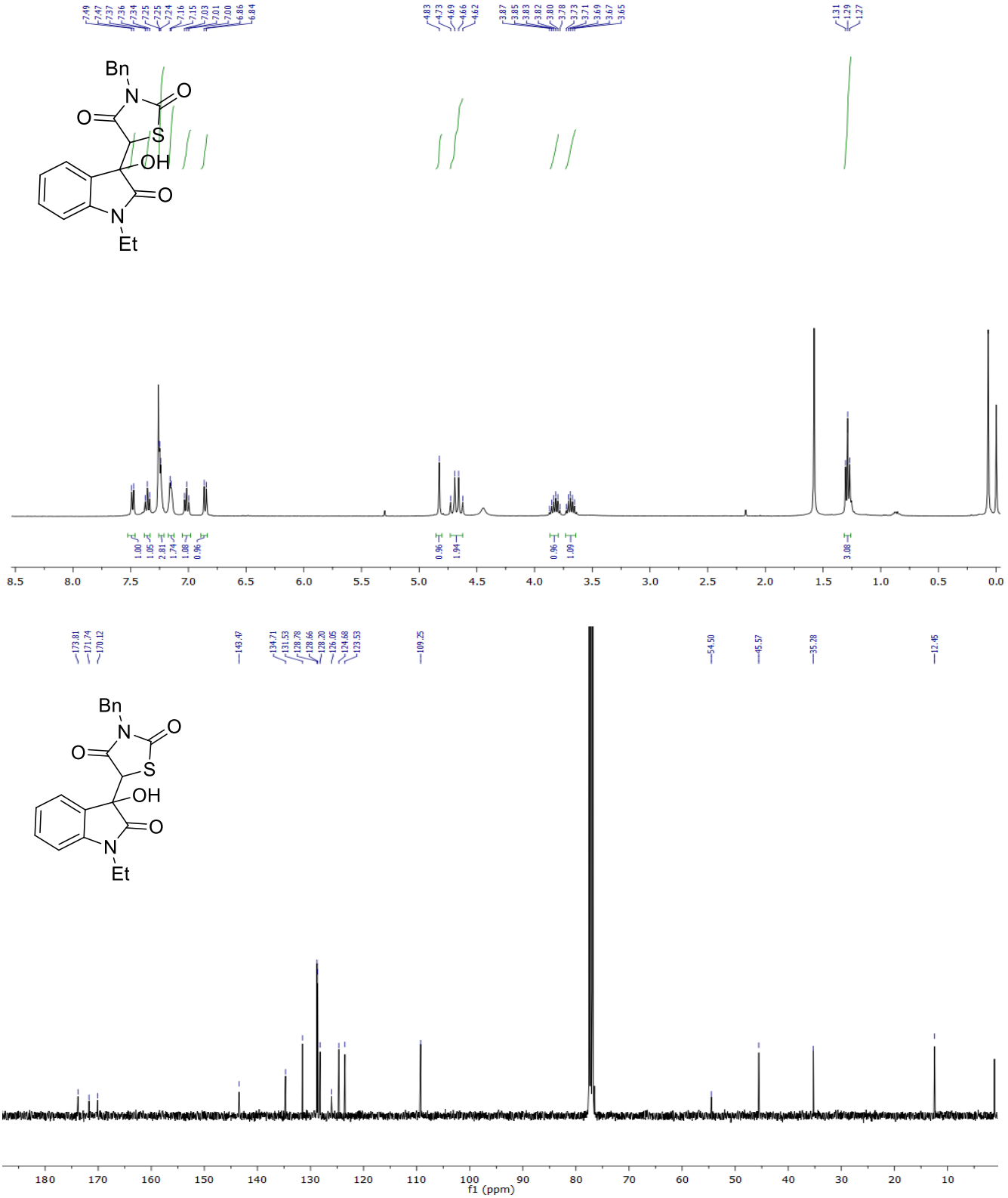
Figure S22. The ORTEP diagram of *anti*-**7aa** showing 50% probability thermal ellipsoid (CCDC 2170212).

10.0 NMR data:

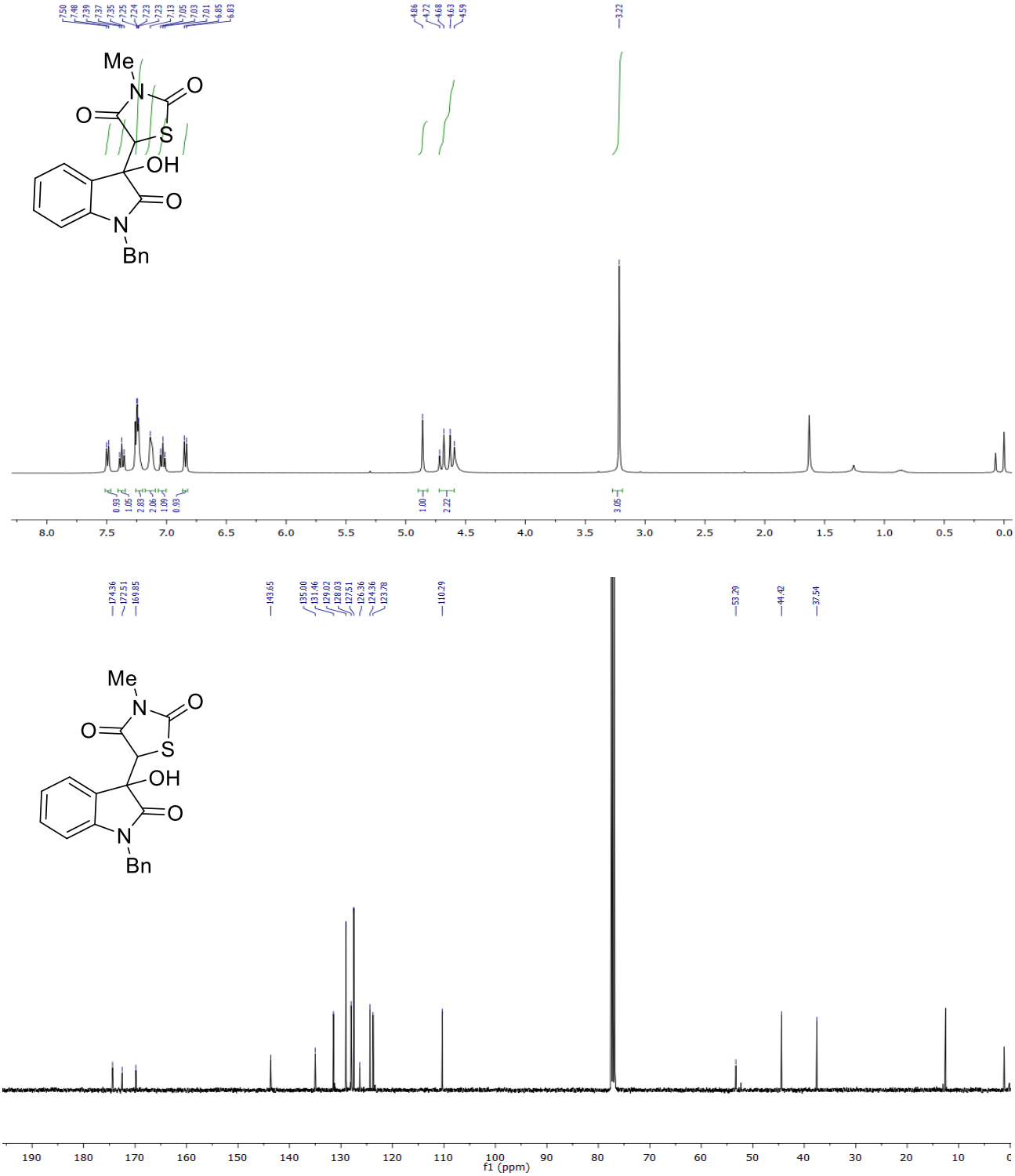
^{1}H and ^{13}C of 2ab:



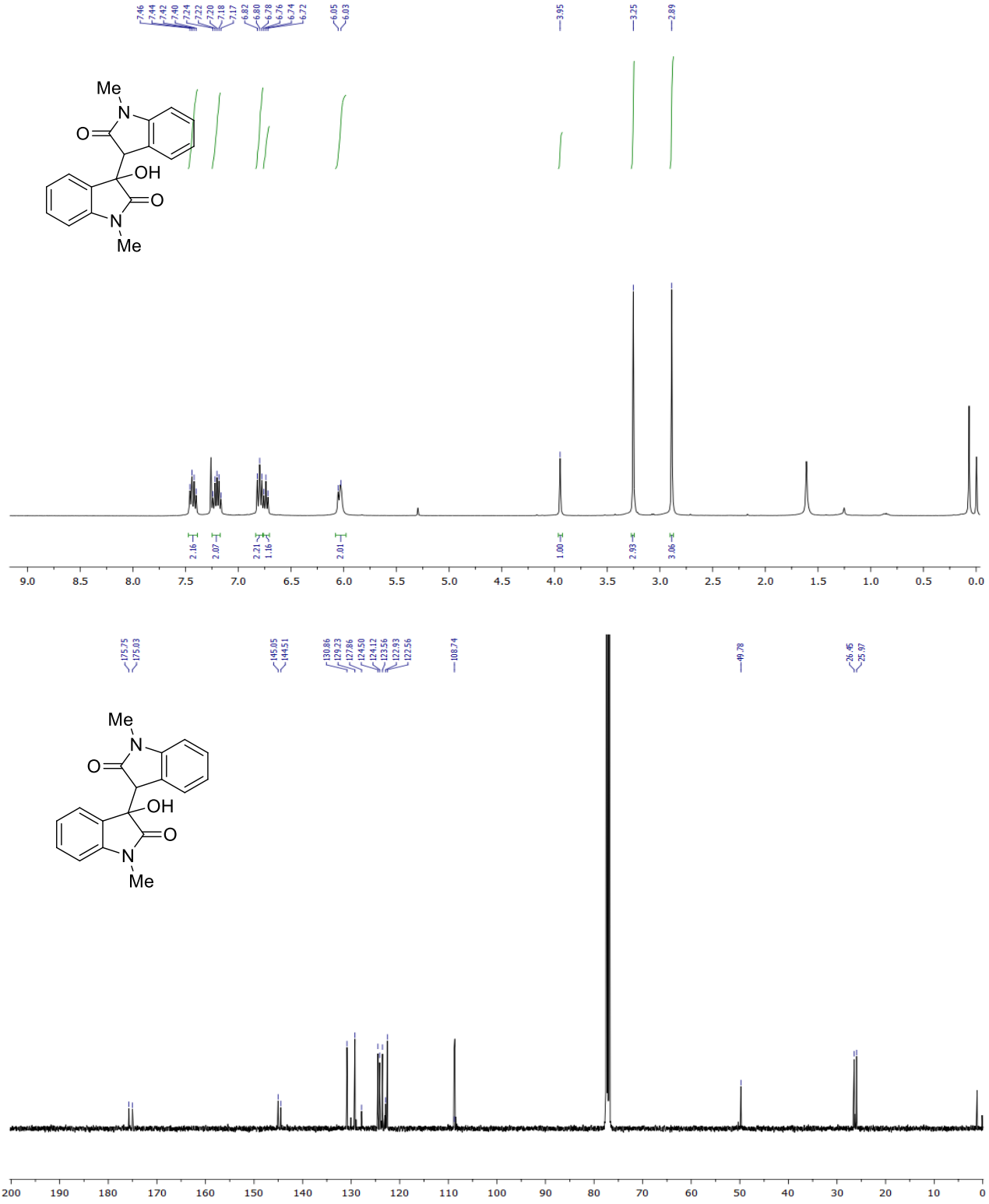
^{1}H and ^{13}C of 2ac:



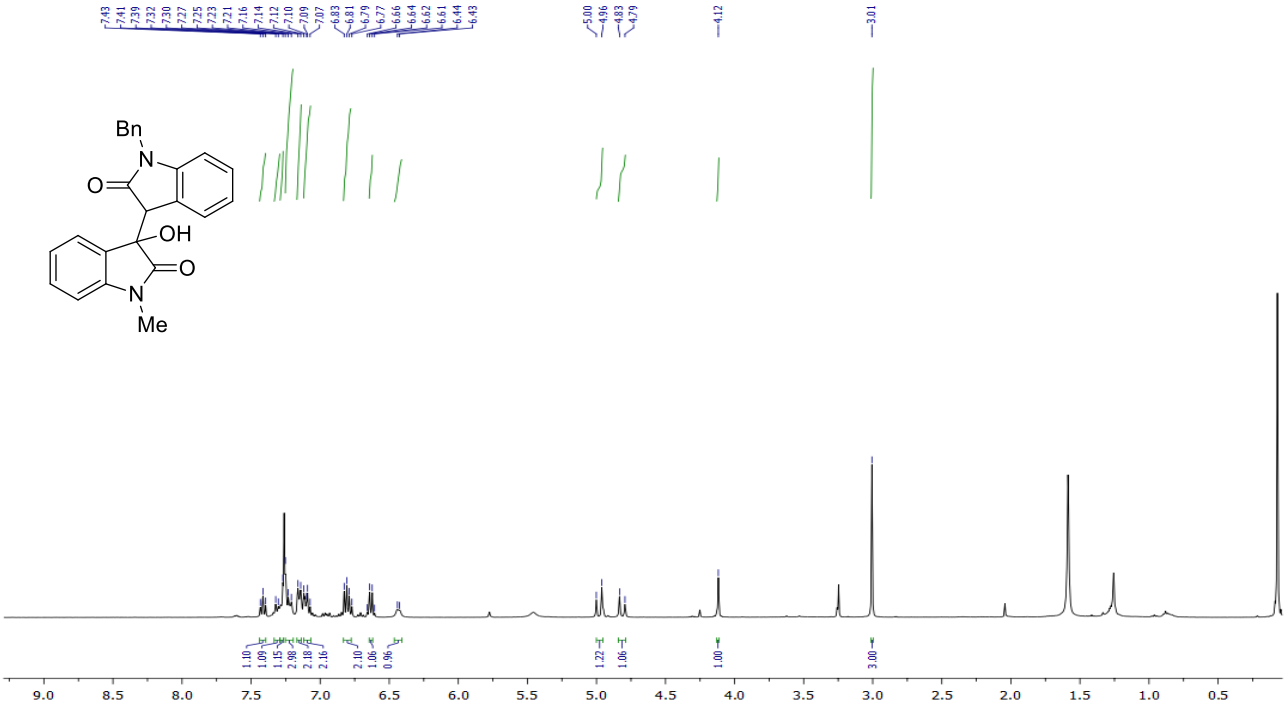
^{1}H and ^{13}C of 2ba:

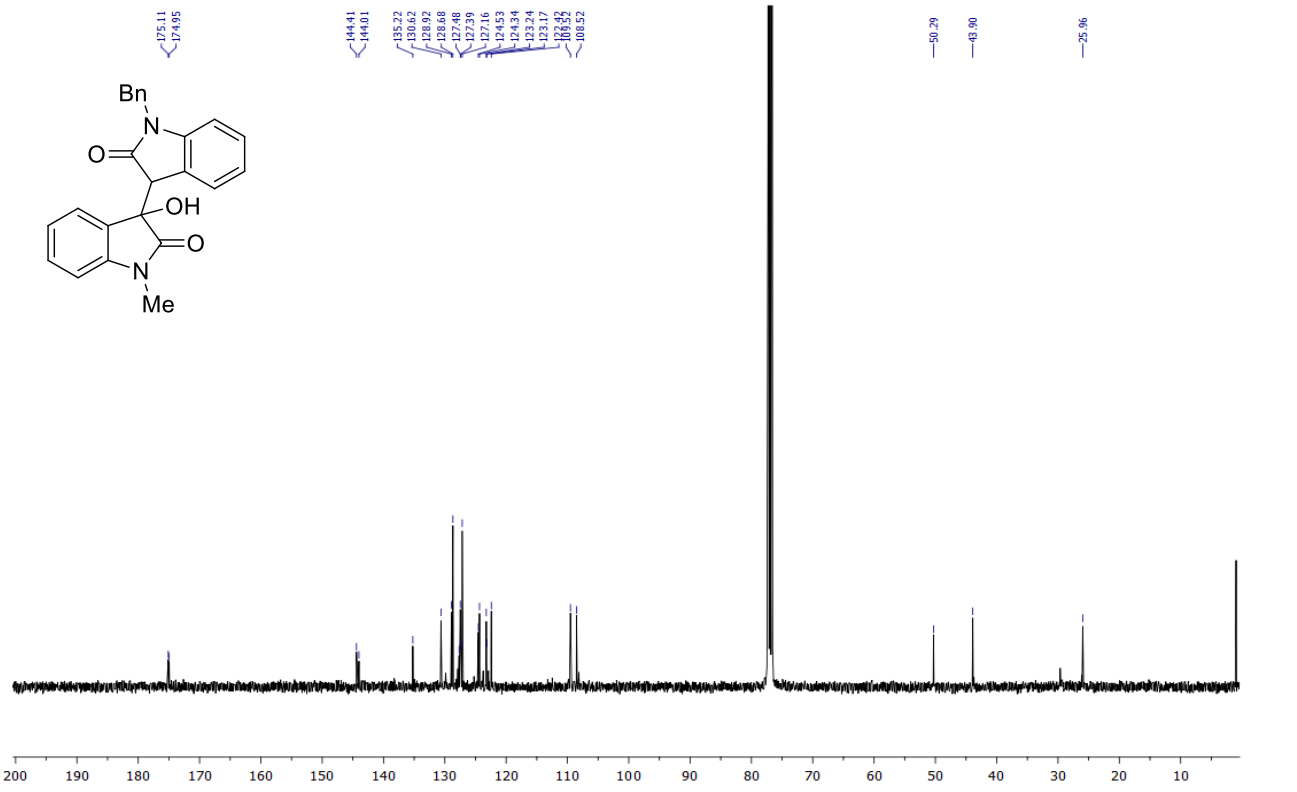


^{1}H and ^{13}C of 7aa:

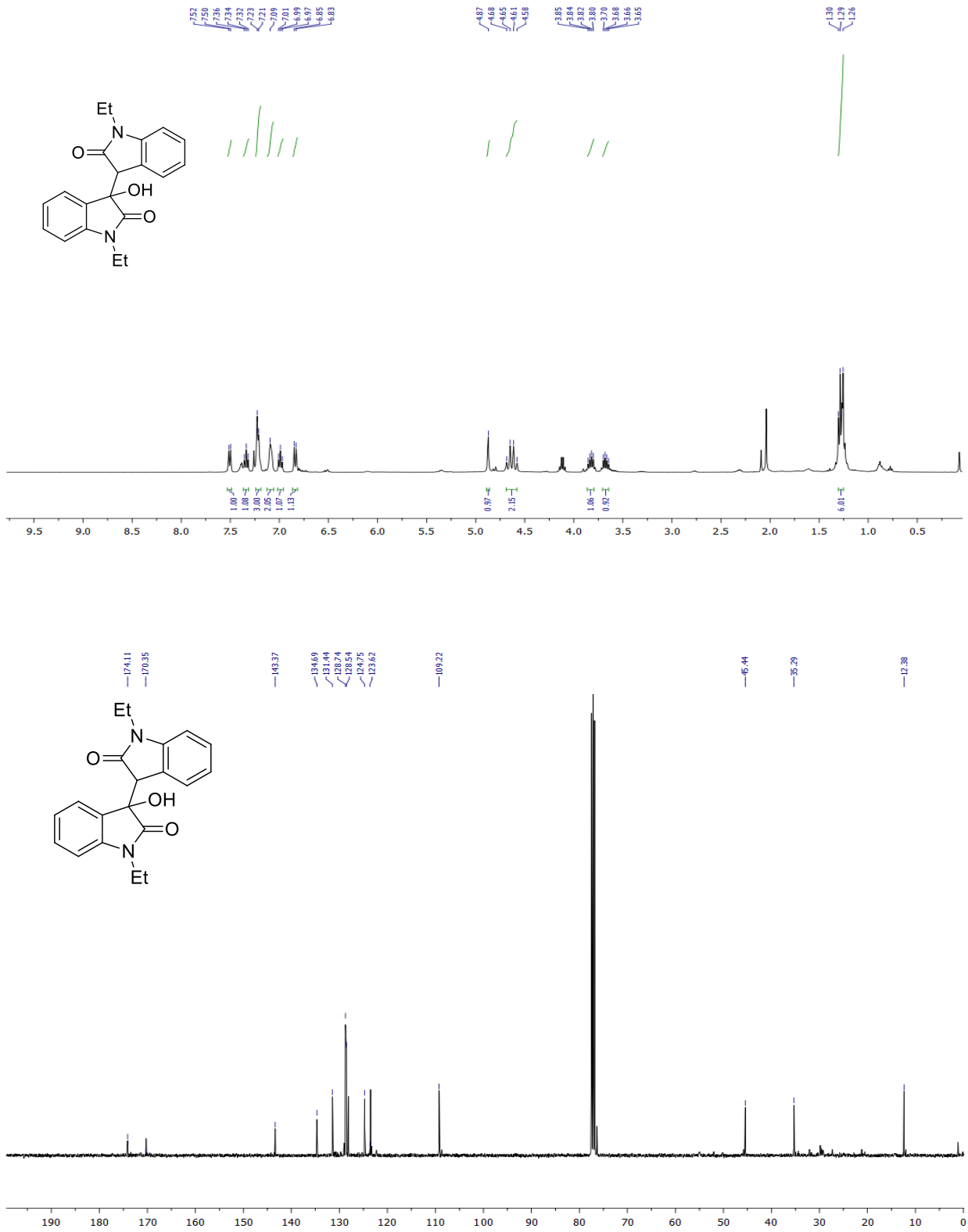


^{1}H and ^{13}C of 7da:

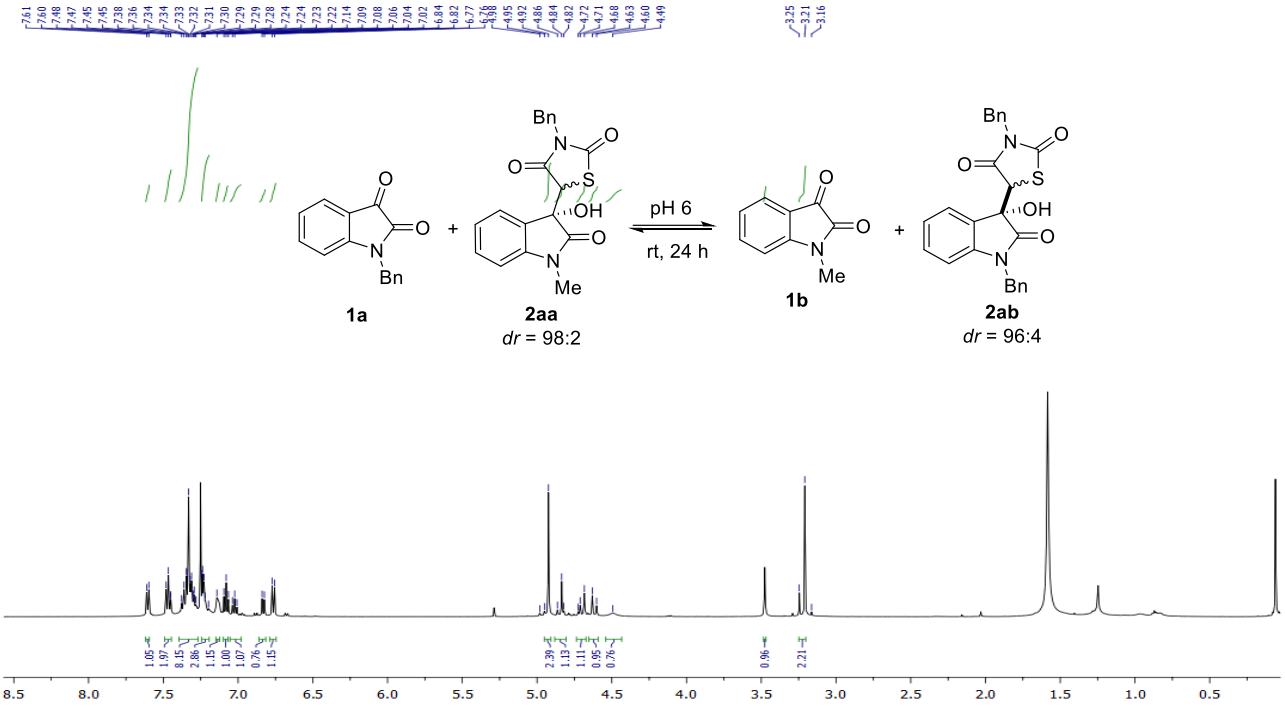




^{1}H and ^{13}C of 7bb:



^{1}H NMR of crude reaction mixture at 24 h, pH 6 (Scheme 2)



Mass spectrum of crude reaction mixture at 24 h, pH 6 (Scheme 2)