A Concise Silylamine Approach to 2-Amino-3-hydroxy-indoles with Potent in vivo Antimalaria Activity

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SUPPORTING INFORMATION

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General Considerations:

^{1}H NMR spectra and proton-decoupled ^{13}C NMR spectra were obtained on a Bruker 300 spectrometer (300 MHz) or a Varian Unity Inova 500 spectrometer (500 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent (CD_3SOCD_3, δ 2.50). Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br s (broad singlet) and so on. ^{13}C chemical shifts are reported relative to CD_3SOCD_3 (septet, δ 39.50). Tandem high performance liquid chromatography/mass spectral (LC/MS) analyses were performed on a Micromass Platform LCZ mass spectrometer or a Micromass Platform LCT mass spectrometer in atmospheric pressure chemical ionization (APCI) mode after separation performed on a Waters Alliance 2690 separations module. The actual separations were performed on a Waters Symmetry® C_{18} 3.5 μm, 2.1 x 50 mm column with a flow rate of 0.4 mL/min and a 12 min gradient of 15-100% CH_3CN in H_2O, with a constant 0.1% formic acid buffer using a Waters 996 photodiode array detector. The enantiomeric excess (ee) was determined using either chiral SFC OD-H column (20% MeOH, for *racemic* and chiral **3a**) or chiral SFC AD-H column (20% MeOH containing 0.5% Et_3N for *racemic* and chiral **1a**). High resolution mass spectrometry measurements were performed at the MIT Department of Chemistry Instrument Facility.

Flash column chromatography was performed using a Biotage SP4 instrument with pre-packed silica cartridges. Analytical TLC was performed on glass plates coated with 0.25 mm silica gel and visualized by ultraviolet light. Manipulations under an inert atmosphere were carried out using standard Schlenk line techniques. Microwave reactions were performed using Emrys™ Optimizer (Biotage, formerly Personal Chemistry) in a septa capped 20 mL (or 5 mL) Smith™ process vial with stirring. Unless otherwise specified, all commercially available reagents were used as received.

Experimental Section:

Preparation of TBDMS-NH_2 Reagent

Ammonia gas was bubbled (for 2-3 minutes) through a solution of TBDMSCl (5g) in 20 mL anhydrous THF at 0 °C, which immediately resulted in the precipitate formation of NH_4Cl. The cold bath was removed and the reaction mixture was then purged through an argon gas for 15-30 min to completely remove the unreacted ammonia. The reaction mixture was filtered through a syringe-less filter and thoroughly washed with THF in such a way that that the final volume of the solution containing TBDMS-NH_2 is 24 mL (concentration ~ 1 M). This solution was stored at room temperature under an argon atmosphere and used without further purification.

General Procedure for the Synthesis of 3-Aryl(alkyl)-3-hydroxyoxindoles

A solution of Grignard reagent (3-4 equiv) in THF was added to an ice-cold suspension of isatin **2** (1 equiv) in anhydrous THF under an atmosphere of N_2. The mixture was allowed to warm to room temperature and was stirred until isatin was consumed. The reaction mixture was diluted with EtOAc and then quenched with 1N HCl. The layers were separated and the aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water followed by brine and dried over $MgSO_4$. After filtration and concentration, the residue obtained was recrystallized from acetone/hexanes

or CH_2Cl_2/hexanes to afford the desired product **3** which was used without further purification.

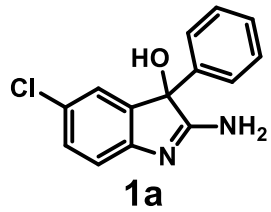
General Procedure A for the Synthesis of 3-Aryl(alkyl)-3-hydroxy-2-aminoindoles

A microwave vial was charged with **3** (0.78 mmol, 1 equiv), TBDMS-NH_2 (1 M solution in THF, 3.12 mmol, 4 equiv), and *N*-Methyl morpholine (NMM, 3.12 mmol, 4 equiv) under N_2 atmosphere. To this mixture was carefully added $SnCl_4$ (1M in CH_2Cl_2, 1.56 mmol, 2 equiv). The vial was capped and microwaved at 120 °C for 1 h. After decapping the vial, the reaction mixture was diluted with CH_2Cl_2 and quenched by adding 1M aq. NaOH solution was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2/*i*-PrOH mixture (while saturating the aq. phase with NaCl). Charcoal and $MgSO_4$ was added to the combined organic extracts and stirred for 1 h. The residue obtained after filtration (over celite) and concentration, was dissolved in minimal amount of CH_2Cl_2 and loaded directly onto the Biotage column preloaded with silica-gel (0-10% MeOH/CH_2Cl_2). The fractions containing the desired product were combined and evaporated. The white solid obtained was either triturated or recrystallized from CH_2Cl_2/hexanes to afford pure **1**.

General Procedure B for the Synthesis of 3-Aryl(alkyl)-3-hydroxy-2-aminoindoles

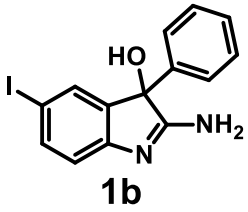
A microwave vial was charged with **3** (0.78 mmol, 1 equiv), TBDMS-NH_2 (1 M solution in THF, 3.12 mmol, 4 equiv), and *Ti(O-iPr)$_4$* (3.12 mmol, 4 equiv) under N_2 atmosphere. The vial was capped and microwaved at 120 °C for 1 h. After decapping the vial, the reaction mixture was diluted with CH_2Cl_2 and quenched by adding 1M aq. NaOH solution was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2/*i*-PrOH mixture (while saturating the aq. phase with NaCl). Charcoal and $MgSO_4$ was added to the combined organic extracts and stirred for 1 h. The residue obtained after filtration (over celite) and concentration, was dissolved in minimal amount of CH_2Cl_2 and loaded directly onto the Biotage column preloaded with silica-gel (0-10% MeOH/CH_2Cl_2). The fractions containing the desired product were combined and evaporated. The white solid obtained was either triturated or recrystallized from CH_2Cl_2/hexanes to afford pure **1**.

Spectroscopic Data:



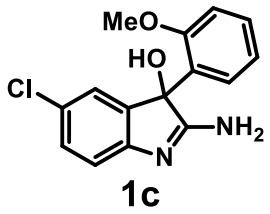
1a

Compound **1a** (Table 1, entry a): Following general procedure A, **1a** was obtained in 60% yield (121 mg), white solid. Following general procedure B, **1a** was obtained in 56% yield (113 mg). ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.33 (d, J = 4.0 Hz, 4H), 7.27 (dd, J = 8.1, 3.9 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.76 (bs, 1H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 178.3, 155.5, 142.6, 141.7, 128.6, 128.3, 127.4, 124.8, 124.3, 122.6, 116.6, 83.2. HRMS calcd for $C_{14}H_{11}ClN_2O$ (M+H) 259.0633, found 259.0637. mp: 220-222 °C.



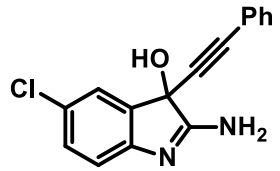
1b

Compound **1b** (Table 1, entry b): Following general procedure A, **1b** was obtained in 64% yield (175 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.42 (dd, J = 8.1, 1.7 Hz, 1H), 7.35–7.24 (m, 5H), 7.13 (d, J = 1.6 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.8, 156.6, 143.5, 141.7, 137.4, 137.3, 130.7, 127.3, 124.7, 118.0, 82.8. HRMS calcd for $C_{14}H_{11}IN_2O$ (M+H) 350.9989, found 350.9983. mp: 228-230 °C.



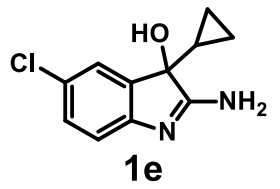
1c

Compound **1c** (Table 1, entry c): Following general procedure A, **1c** was obtained in 43% yield (97 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.84 (d, J = 7.5 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.16–6.96 (m, 2H), 6.94 – 6.80 (m, 2H), 6.67 (s, 1H), 6.47 (s, 1H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.2, 156.0, 155.1, 141.0, 129.3, 129.0, 128.3, 127.0, 123.8, 121.8, 120.3, 115.4, 111.9, 80.2, 55.6, 39.5. HRMS calcd for $C_{15}H_{13}ClN_2O_2$ (M+H) 298.0738, found 298.0736. mp: 191-193 °C.



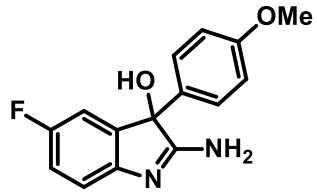
1d

Compound **1d** (Table 1, entry d): Following general procedure A, **1d** was obtained in 45% yield (99 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.44 (dd, J = 7.6, 1.7 Hz, 2H), 7.41–7.35 (m, 3H), 7.33 (d, J = 2.2 Hz, 1H), 7.19 (dd, J = 8.2, 2.2 Hz, 1H), 6.97–6.83 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 174.3, 155.4, 139.2, 131.6, 129.3, 129.1, 128.7, 124.5, 122.5, 121.4, 116.8, 88.1, 84.0, 74.3. HRMS calcd for $C_{16}H_{11}ClN_2O$ (M+H) 283.0633, found 283.0634. mp: 168-170 °C.



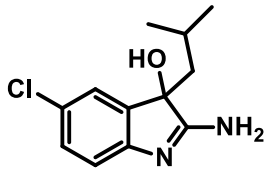
1e

Compound **1e** (Table 1, entry e): Following general procedure A, **1e** was obtained in 58% yield (101 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.14 (dd, J = 8.1, 2.1 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.93 (s, 1H), 1.04–0.95 (m, 1H), 0.73 (td, J = 9.8, 5.2 Hz, 1H), 0.42 – 0.33 (m, 1H), 0.32–0.24 (m, 1H), 0.20 (td, J = 9.6, 5.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 178.8, 139.9, 128.4, 123.5, 122.3, 116.1, 79.8, 18.1, 0.4, -0.8. HRMS calcd for $C_{11}H_{11}ClN_2O$ (M+H) 223.0633, found 223.0641. mp: 112-114 °C.



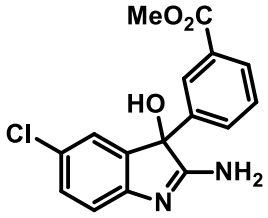
1f

Compound **1f** (Table 1, entry f): Following general procedure A, **1f** was obtained in 52% yield (110 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.19 (d, J = 8.7 Hz, 2H), 6.96–6.82 (m, 4H), 6.72 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 3.71 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.9 (d, J = 2.5 Hz), 158.6 (d, J = 2.5 Hz), 156.7, 152.3, 142.3 (d, J = 7.5 Hz), 133.8, 126.1, 115.5 (d, J = 7.5 Hz), 114.6 (d, J = 22.5 Hz), 113.6, 110.2 (d, J = 23.7 Hz), 83.0 (d, J = 2.5 Hz), 55.1. HRMS calcd for $C_{15}H_{13}FN_2O_2$ (M+H) 273.1034, found 273.1033. mp: 182-184 °C.



1g

Compound **1g** (Table 1, entry g): Following general procedure A, **1g** was obtained in 50% yield (93 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.58–6.95 (m, 4H), 6.82 (d, J = 7.7 Hz, 1H), 5.76 (s, 1H), 1.80 (qd, J = 13.3, 6.3 Hz, 2H), 1.23–1.03 (m, 1H), 0.75 (d, J = 6.4 Hz, 3H), 0.55 (d, J = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 178.2, 155.4, 140.2, 128.4, 123.8, 122.3, 116.0, 81.5, 46.3, 23.8, 23.75, 23.71. HRMS calcd for $C_{12}H_{15}ClN_2O$ (M+H) 239.0946, found 239.0949. mp: 183-185 °C.



1h

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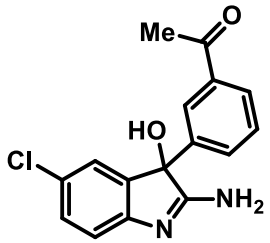
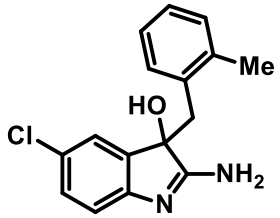
Compound **1h** (Table 1, entry h): Following general procedure A, **1h** was obtained in 38% yield (94 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.88 (s, 2H), 7.51 (d, J = 17.2 Hz, 2H), 6.95 (dd, J = 106.0, 58.8 Hz, 4H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.8, 166.1, 155.6, 155.59, 142.3, 129.7, 128.9, 128.89, 128.3, 125.3, 124.3, 122.5, 116.7, 82.9, 52.2. HRMS calcd for $C_{16}H_{13}ClN_2O_3$ (M+H) 317.0687, found 317.0683. mp: 171-173 °C.



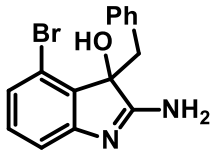
1i

Compound **1i** (Table 1, entry i): Following general procedure B, **1i** was obtained in 30% yield (70 mg), white solid. ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.95–7.84 (m, 2H), 7.45 (dt, J = 15.3, 7.8 Hz, 2H), 7.15 (dd, J = 8.2, 2.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.81 (s, 1H), 2.57 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 197.8, 177.8, 155.6, 142.3, 142.26, 136.8, 129.6, 128.84, 128.8, 127.7, 124.3, 124.0, 122.5, 116.7, 82.9, 26.7. HRMS calcd for $C_{16}H_{13}ClN_2O_2$ (M+H) 301.0738, found 301.0738. mp: 163-165 °C.



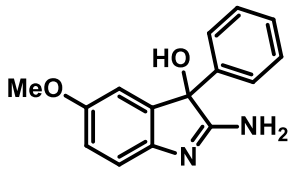
1j

Compound **1j** (Table 1, entry j): Following general procedure A, **1j** was obtained in 53% yield (118 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.53–6.95 (m, 7H), 6.76 (d, J = 8.1 Hz, 1H), 6.25 (s, 1H), 5.98 (s, 1H), 3.22 (d, J = 13.8 Hz, 1H), 2.73 (d, J = 13.8 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 178.4, 154.7, 138.7, 137.0, 134.1, 129.6, 125.0, 123.2, 123.1, 123.0, 115.9, 81.6, 19.52, 19.50. HRMS calcd for $C_{16}H_{15}ClN_2O$ (M+H) 287.0946, found 287.0953. mp: 188-190 °C.



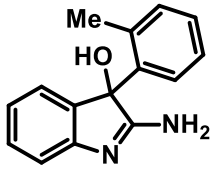
1k

Compound **1k** (Table 1, entry k): Following general procedure A, **1k** was obtained in 51% yield (126 mg), white solid. ^{1}H NMR (300 MHz, DMSO-d^6) δ 10.21 (s, 1H), 7.21-6.95 (m, 5H), 6.87 (s, 2H), 6.51 (d, J = 7.4 Hz, 1H), 6.24 (s, 1H), 3.63 (d, J = 12.4 Hz, 1H), 3.06 (d, J = 12.4 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 177.7, 144.0, 134.5, 130.9, 129.3, 128.4, 127.7, 126.5, 125.4, 119.2, 108.7, 78.6, 40.3. HRMS calcd for $C_{15}H_{13}BrN_2O$ (M+H) 317.0284, found 317.0292. mp: 283-285 °C.



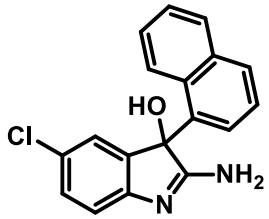
1l

Compound **1l** (Table 1, entry l): Following general procedure A, **1l** was obtained in 49% yield (97 mg), white solid. Following general procedure B, **1l** was obtained in 48% yield (95 mg). ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.53–7.14 (m, 6H), 6.87 (d, J = 8.3 Hz, 1H), 6.69 (dd, J = 8.3, 2.6 Hz, 1H), 6.54 (d, J = 2.5 Hz, 2H), 3.62 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 176.4, 154.5, 148.8, 142.3, 141.5, 128.2, 127.2, 124.8, 115.3, 113.2, 109.8, 83.3, 55.4. HRMS calcd for $C_{15}H_{14}N_2O_2$ (M+H) 255.1128, found 255.1132. mp: 179-181 °C.



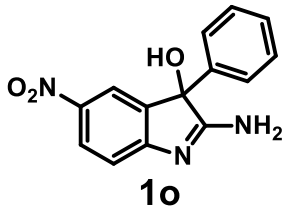
1m

Compound **1m** (Table 1, entry m): Following general procedure A, **1m** was obtained in 53% yield (98 mg), white solid. ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.99 (s, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.22–7.06 (m, 2H), 7.01 (d, J = 7.1 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.86–6.46 (m, 3H), 6.32 (s, 1H), 1.74 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 176.5, 157.4, 139.4, 138.5, 134.7, 130.9, 129.0, 127.2, 126.3, 125.4, 122.3, 120.4, 115.2, 81.7, 18.4. ES-MS calcd for $C_{15}H_{14}N_2O$ (M-H) 237.10, found 237.13. mp: 201-203 °C.



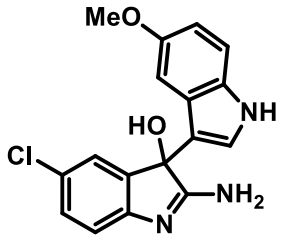
1n

Compound **1n** (Table 1, entry n): Following general procedure A, **1n** was obtained in 67% yield (161 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 8.31 (d, J = 13.2 Hz, 1H), 8.16 (s, 1H), 7.90 (d, J = 7.3 Hz, 2H), 7.76–6.89 (m, 7H), 6.60 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d^6)□□ δ 178.6, 163.3, 156.0, 142.3, 135.1, 133.4, 129.3, 129.0, 128.8, 126.0, 125.3, 124.8, 124.1, 123.0, 122.2, 117.0, 81.5. HRMS calcd for $C_{18}H_{13}ClN_2O$ (M+H) 309.0789, found 309.0787. mp: 234-236 °C.



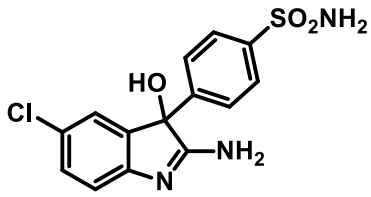
1o

Compound **1o** (Table 1, entry o): Following general procedure B, **1o** was obtained in 30% yield (63 mg), yellow solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 8.21 (s, 1H), 8.10 (d, J = 7.0 Hz, 1H), 7.67 (s, 1H), 7.56 (s, 1H), 7.33 (td, J = 14.8, 7.5 Hz, 5H), 7.07 (d, J = 8.6 Hz, 1H), 6.87 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 182.2, 164.9, 141.4, 140.9, 140.6, 128.5, 127.7, 126.9, 124.7, 117.7, 115.1, 82.3. HRMS calcd for $C_{14}H_{11}N_3O_3$ (M-H) 268.0728, found 268.0726. mp: 228-230 °C.



1p

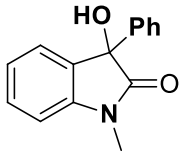
Compound **1p** (Table 1, entry p): Following general procedure B, **1p** was obtained in 40% yield (102 mg), white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.92 (d, J = 1.7 Hz, 1H), 7.29 (t, J = 8.5 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.19 – 7.12 (m, 1H), 7.04 – 6.93 (m, 2H), 6.68 (dd, J = 8.8, 2.4 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.40 (s, 1H), 3.56 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.7, 154.6, 152.8, 141.6, 131.9, 128.5, 124.5, 124.1, 123.8, 122.6, 116.2, 114.7, 112.2, 110.7, 101.3, 80.5, 55.1. HRMS calcd for $C_{17}H_{14}ClN_3O_2$ (M+H) 328.0847, found 328.0849. mp: 149-151 °C.



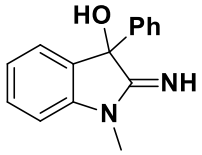
1q

Compound **1q** (Table 1, entry q): The product obtained following general procedure B was dissolved in a mixture of DCM and MeOH (2 mL, 1:1) and treated with HF/pyridine solution (0.3 mL) and stirred at room temperature for 30 minutes. The volatiles were removed *in vacuo*. The crude residue was purified by silica-gel column chromatography (0-20% MeOH/DCM) to obtain **1q** in 45% yield (118 mg) as a white solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.77 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.31 (s, 2H), 7.16 (dd, J = 8.2, 1.7 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 6.84 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d^6) δ 177.6, 155.4, 145.3, 143.1, 142.1, 129.0, 125.8, 125.3, 124.4, 122.6, 116.7, 82.9. HRMS calcd for $C_{14}H_{12}ClN_3O_3S$ (M+H) 338.0361, found 338.0373. mp: 215-217 °C.

The structure of **3** (starting material) for entry r in Table 1 is

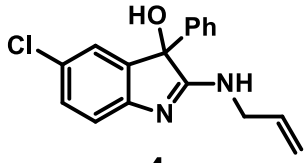


3r



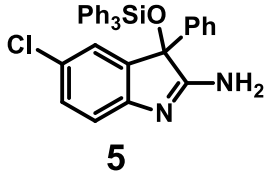
1r

Compound **1r** (Table 1, entry r): grey solid. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.31 (s, 6H), 7.07 (dd, J = 37.0, 7.0 Hz, 2H), 6.90 (dd, J = 34.2, 27.6 Hz, 2H), 3.27 (s, 3H, peak overlaps with water peak from the NMR solvent). ^{13}C NMR (125 MHz, DMSO-d^6) δ 173.5, 144.9, 142.7, 133.6, 127.6, 124.0, 121.5, 108.1, 78.6, 27.6. HRMS calcd for $C_{15}H_{14}N_2O$ (M+H) 239.1179, found 239.1182. mp: 134-136 °C.



4a

Compound **4a** (Scheme 3): A microwave vial was charged with **3a** (0.78 mmol, 1 equiv), allylamine (7.8 mmol, 10 equiv) under N_2 atmosphere. To this mixture was carefully added $SnCl_4$ (1M in CH_2Cl_2, 1.56 mmol, 2 equiv). The vial was capped and microwaved at 120 °C for 1 h. After decapping the vial, the reaction mixture was diluted with CH_2Cl_2 and quenched by adding 1M aq. NaOH solution was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2/*i*-PrOH mixture (while saturating the aq. phase with NaCl). Charcoal and $MgSO_4$ was added to the combined organic extracts and stirred for 1 h. The residue obtained after filtration (over celite) and concentration, was dissolved in minimal amount of CH_2Cl_2 and loaded directly onto the Biotage column preloaded with silica-gel (0-10% MeOH/CH_2Cl_2). The fractions containing the desired product were combined and evaporated. The white solid obtained was recrystallized from CH_2Cl_2/hexanes to afford 191 mg (82%) of **4a** as a white solid. ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.49-7.31 (m, 6H), 7.15 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.89 (s, 1H), 6.72 (s, 1H), 6.06–5.64 (m, 1H), 5.01 (dd, J = 26.2, 17.2 Hz, 2H), 3.92 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 176.7, 155.2, 142.9, 141.7, 134.8, 128.7, 128.3, 127.4, 124.6, 124.3, 122.5, 117.0, 115.1, 83.2, 44.0. HRMS calcd for $C_{17}H_{15}ClN_2O$ (M+H) 299.0946, found 299.0939. mp: 197-199 °C.

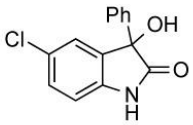


5

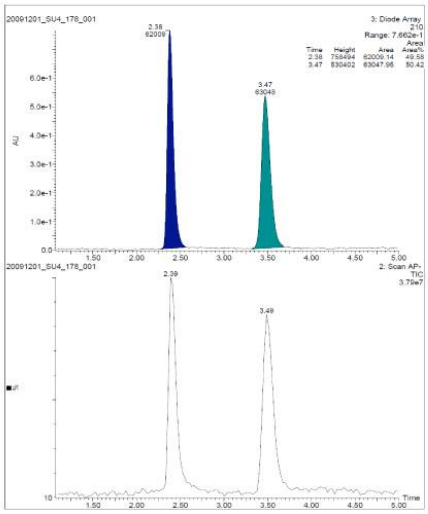
Compound **5** (Scheme 3): A microwave vial was charged with **3a** (0.78 mmol, 1 equiv), Ph_3SiNH_2 (1.56 mmol, 2 equiv), and *N*-Methyl morpholine (NMM, 3.12 mmol, 4 equiv) under N_2 atmosphere. To this mixture was carefully added $SnCl_4$ (1M in CH_2Cl_2, 1.56 mmol, 2 equiv). The vial was capped and microwaved at 120 °C for 1 h. After decapping the vial, the reaction mixture was diluted with CH_2Cl_2 and quenched by adding 1M aq. NaOH solution was added and the layers were separated. The aqueous layer was

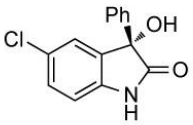
extracted twice with CH_2Cl_2/*i*-PrOH mixture (while saturating the aq. phase with NaCl). Charcoal and $MgSO_4$ was added to the combined organic extracts and stirred for 1 h. The residue obtained after filtration (over celite) and concentration, was dissolved in minimal amount of CH_2Cl_2 and loaded directly onto the Biotage column preloaded with silica-gel (0-10% MeOH/CH_2Cl_2). The fractions containing the desired product were combined and evaporated. The white solid obtained was recrystallized from CH_2Cl_2/hexanes to afford 242 mg (60%) of **5** as a white solid. ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.37 (ddd, J = 20.4, 15.6, 7.3 Hz, 22H), 6.99 (dd, J = 8.2, 2.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 6.17 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d^6) δ 176.2, 156.4, 141.2, 139.6, 135.1, 134.5, 133.9, 130.0, 129.3, 128.6, 127.7, 124.4, 124.2, 123.6, 116.7, 85.7. HRMS calcd for $C_{32}H_{25}ClN_2OSi$ (M+H) 517.1497, found 517.1507. mp: 172-174 °C.

Chiral SFC Chromatogram:

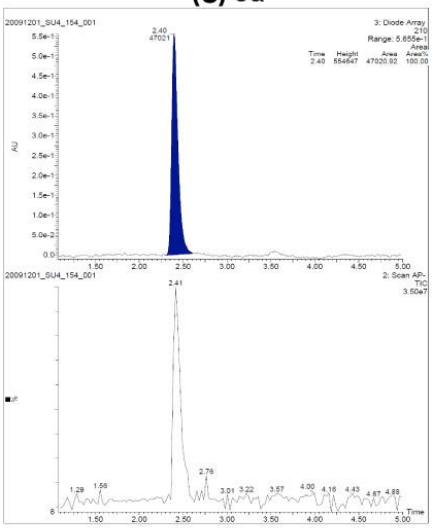


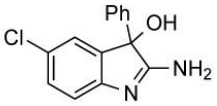
***rac*-3a**



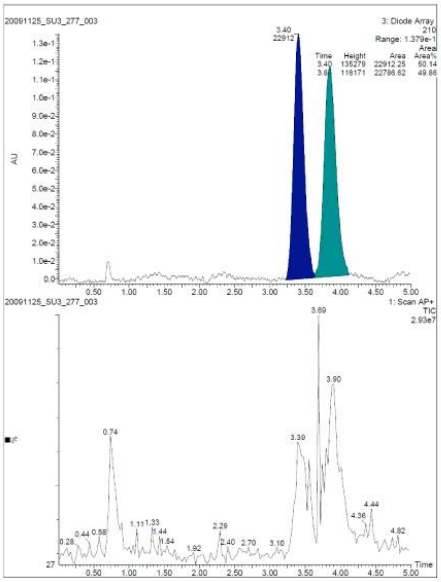


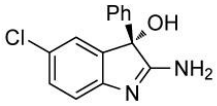
(*S*)-3a



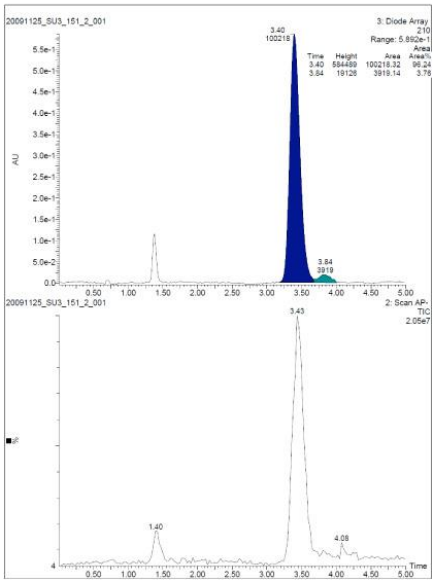


***rac*-1a**





(*S*)-1a



X-Ray Structure of 1a