Supporting information for the manuscript entitled:

Determination of the active stereoisomer of the MEP pathway-targeting antimalarial agent MMV008138, and initial structure-activity studies.

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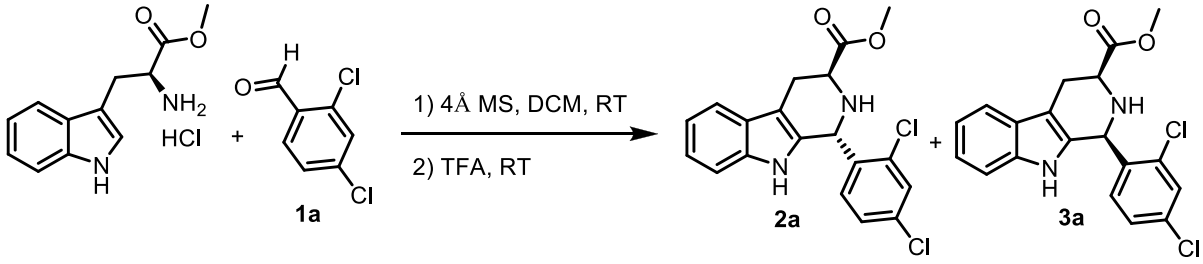
A. Synthesis and analytical characterization of tested compounds

General

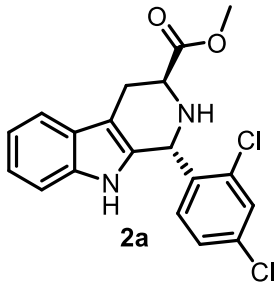
Compounds were purchased from Sigma-Aldrich and were used without purification, unless otherwise noted. ^{1}H NMR spectra were recorded at 400 or 500 MHz; the corresponding ^{13}C NMR resonant frequencies were 101 and 126 MHz respectively; the corresponding ^{19}F NMR resonant frequencies were 376 and 470 MHz.

(1*R*,3*S*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) and (1*S*,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3a**)



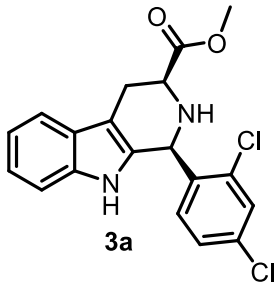
All of the tetrahydro-β-carboline derivatives were synthesized by a modified literature procedure[1] of Pictet-Spengler reaction. To a suspension of L-Tryptophan methyl ester hydrochloride (2.55 g, 10.0 mmol) and 4Å molecular sieve (5 g, powder form) in DCM (30 mL) was added 2,4-dichlorobenzaldehyde (**1a**) (1.75 g, 10.0 mmol, in 5 mL DCM). The resulting reaction mixture

was stirred for 20 hours at room temperature. TFA (1.53 mL, 20.0 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 44 hours. An aqueous solution of $NaHCO_3$ (2.40 g, 30.0 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **2a** (1.30 g, 35 % yield) and **3a** (1.88 g, 50 % yield).



2a

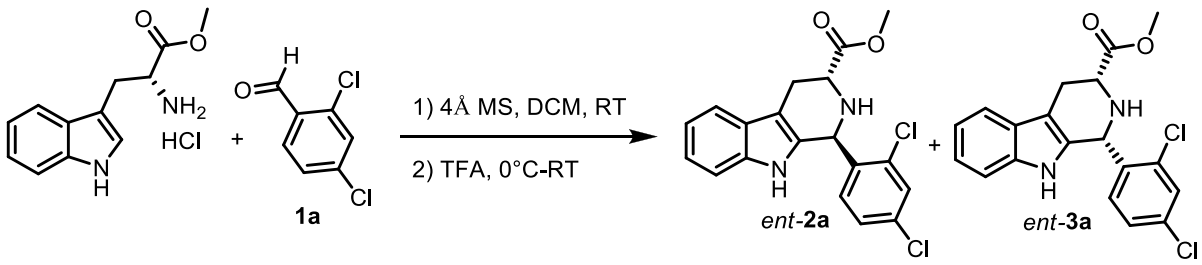
(1*R*,3*S*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) $[\alpha]_D^{21.0}$ = -17.9° (c = 1.30, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.52 (dd, J = 7.2 and 2.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.12 (m, 3H), 7.04 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.73 (s, 1H), 3.76 (dd, *J* = 8.0 and 4.8 Hz, 1H), 3.68 (s, 3H), 3.20 (ddd, *J* = 15.2, 4.8 and 0.8 Hz, 1H), 3.01 (ddd, *J* = 15.2, 8.0 and 0.8 Hz, 1H), 2.73 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.6, 136.2, 134.2, 131.3,130.8, 129.6, 127.0, 126.6, 122.1, 119.5, 118.2, 111.0, 109.5, 52.1, 51.9, 51.1, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2O_2$: 375.0662. Found: 375.0650.



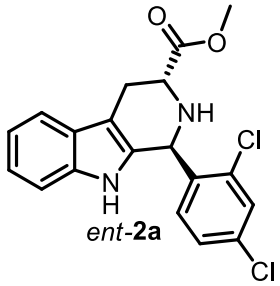
3a

(1*S*,3*S*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3a**) $[\alpha]_D^{21.0}$ = -33.0° (c = 2.08, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.49 (dd, *J* = 3.6 and 2.8 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.11 (m, 4H), 5.72 (s, 1H), 3.91 (dd, *J* = 10.8 and 4.0 Hz, 1H), 3.77 (s, 3H), 3.19 (ddd, *J* = 15.2, 4.0 and 2.4 Hz, 1H), 2.97 (ddd, *J* = 15.2, 10.8 and 2.4 Hz, 1H), 2.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.2, 136.1, 134.4, 134.0, 133.0, 131.3, 129.2, 127.8, 126.7, 122.0, 119.6, 118.1, 110.9, 109.2, 56.4, 53.7, 52.2, 25.3. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2O_2$: 375.0662. Found: 375.0655.

(1*S*,3*R*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-2a) and (1*R*,3*R*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-3a)

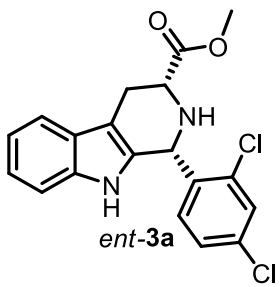


To a suspension of D-Tryptophan methyl ester hydrochloride (2.55 g, 10.0 mmol) and 4Å molecular sieve (5 mg, powder form) in DCM (30 mL) was added 2,4-dichlorobenzaldehyde (**1a**) (1.75 g, 10.0 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 23 hours at room temperature. TFA (1.6 mL, 20.0 mmol) was then added dropwise. The reaction mixture was further stirred for 42 hours. An aqueous solution of $NaHCO_3$ (3.0 g, 35.0 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give *ent*-**2a** (0.96 mg, 26 % yield) and *ent*-**3a (**2.41 g, 64 % yield).



(1*S*,3*R*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-**2a**)

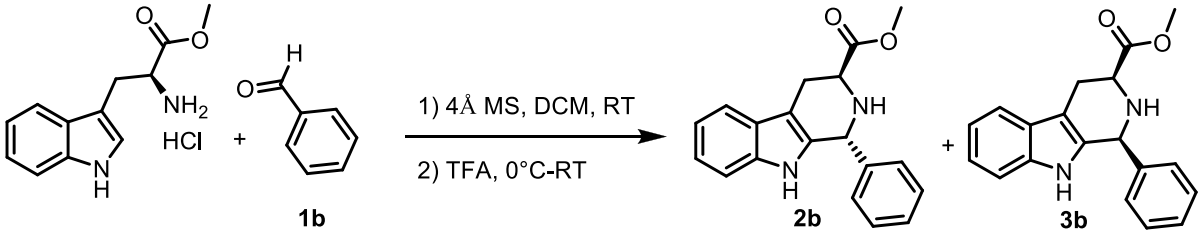
$[\alpha]_D^{21.0}$ = +19.5° (c = 1.29, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.13 (m, 2H), 7.07 (dd, *J* = 8.5 and 2.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 5.78 (s, 1H), 3.79 (dd, *J* = 8.0 and 5.0 Hz, 1H), 3.70 (s, 3H), 3.22 (ddd, *J* = 15.0, 5.0 and 1.0 Hz, 1H), 3.05 (ddd, *J* = 15.0, 8.0 and 1.0 Hz, 1H), 2.75 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 137.7, 136.2, 134.3, 134.2, 131.4, 130.8, 129.7, 127.1, 126.7, 122.2, 119.6, 118.3, 111.0, 109.6, 52.2, 52.0, 51.1, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2O_2$: 375.0662. Found: 375.0672.



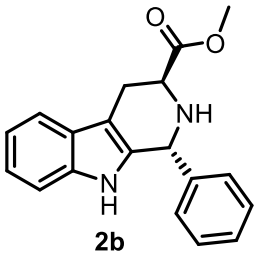
(1*R*,3*R*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-**3a**)

$[\alpha]_D^{21.0}$ = +28.4° (c = 1.92, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.53 (dd, *J* = 7.5 and 1.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.15 (m, 4H), 5.78 (s, 1H), 3.98 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.82 (s, 3H), 3.23 (ddd, *J* = 15.0, 4.0 and 2.0 Hz, 1H), 3.00 (ddd, *J* = 15.0, 11.0 and 2.0 Hz, 1H), 2.62 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 137.3, 136.2, 134.6, 134.1, 133.1, 131.4, 129.4, 128.0, 126.8, 122.2, 119.8, 118.2, 110.9, 109.4, 56.6, 53.8, 52.3, 25.4. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2O_2$: 375.0662. Found: 375.0668.

(1*R*,3*S*)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2b**) and (1*S*,3*S*)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3b**)



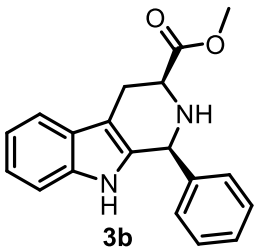
To a suspension of L-Tryptophan methyl ester hydrochloride (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (5 mL) was added benzaldehyde (**1b**) (336 μL, 3.3 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 23 hours at room temperature. The reaction mixture was cooled to 0 °C, and TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **2b** (130 mg, 14 % yield) and **3b (**612 mg, 67 % yield).



(1*R*,3*S*)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2b**)

$[\alpha]_D^{21.0}$ = -34.1° (c = 1.45, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.51 (dd, *J* = 6.4 and 2.0 Hz, 1H), 7.25 (m, 3H), 7.11 (m, 5H), 5.23 (s, 1H), 3.86 (dd, *J* = 7.2 and 6.0 Hz, 1H), 3.64 (s, 3H), 3.20 (ddd, *J* = 15.2, 5.2 and 1.2 Hz, 1H), 3.04 (ddd, *J* = 15.2, 7.2 and 1.2 Hz, 1H), 2.38 (br s, 1H).

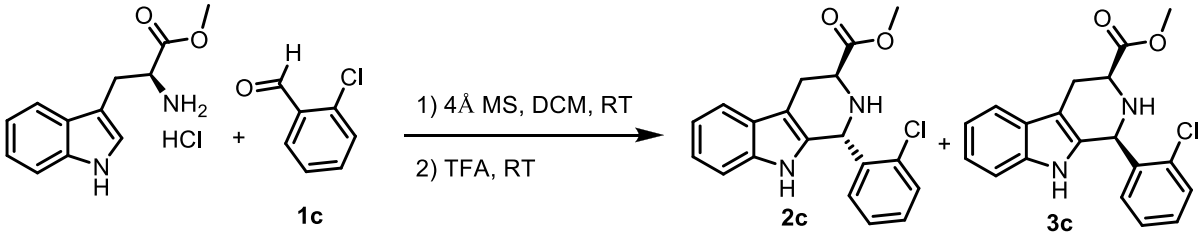
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 141.9, 136.1, 133.1, 128.6, 128.3, 127.9, 126.8, 121.8, 119.3, 118.1, 110.9, 108.3, 54.8, 52.2, 52.0, 24.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_2$: 307.1441. Found: 307.1428.



3b

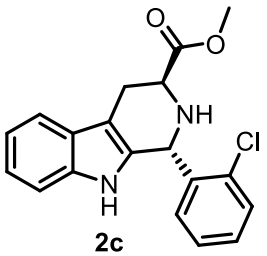
(1*S*,3*S*)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3b**)
$[\alpha]_D^{21.0}$ = -57.0° (c = 0.17, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.4 and 2.4 Hz, 1H), 7.44 (br s, 1H), 7.36 (m, 5H), 7.13 (m, 3H), 5.22 (s, 1H), 3.96 (dd, *J* = 11.2 and 4.0 Hz, 1H), 3.80 (s, 3H), 3.22 (ddd, *J* = 14.8, 4.0 and 2.4 Hz, 1H), 3.00 (ddd, *J* = 14.8, 11.2 and 2.4 Hz, 1H), 2.40 (br s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.7, 136.1, 134.7, 128.9, 128.6, 128.5, 127.1, 121.9, 119.6, 118.2, 110.9, 108.9, 58.7, 56.9, 52.2, 25.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_2$: 307.1441. Found: 307.1443.

(1*R*,3*S*)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2c**) and (1*S*,3*S*)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3c**)



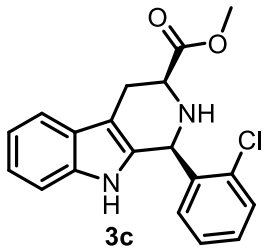
1c **2c** **3c**

To a suspension of L-Tryptophan methyl ester hydrochloride (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2-chlorobenzaldehyde (**1c**) (370 μL, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 :5 : 1 hexane / DCM / EtOAc) to give **2c** (183 mg, 18 % yield) and **3c (**601 mg, 59 % yield).



2c

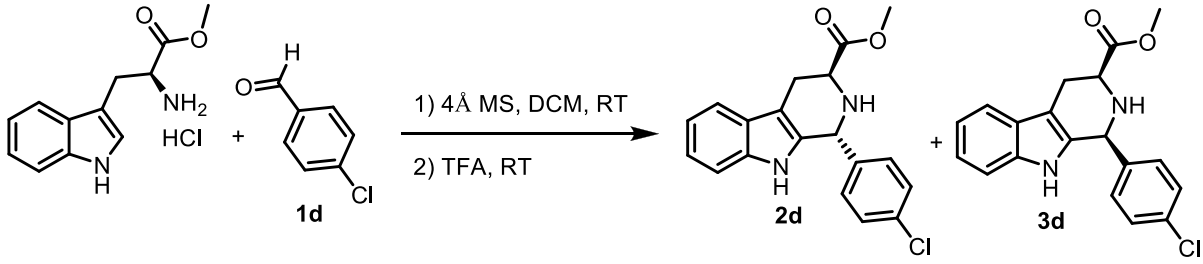
(1*R*,3*S*)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2c**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.54 (dd, *J* = 7.2 and 1.6 Hz, 1H), 7.43 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.21 (m, 2H), 7.13 (m, 3H), 6.91 (dd, *J* = 7.6 and 1.6 Hz, 1H), 5.85 (s, 1H), 3.83 (dd, *J* = 8.0 and 4.8 Hz, 1H), 3.71 (s, 3), 3.24 (ddd, *J* = 15.2, 4.8 and 1.2 Hz, 1H), 3.06 (ddd, 15.2, 8.0, and 1.2 Hz, 1H), 2.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 139.0, 136.2, 133.7, 131.9, 130.0, 129.9, 129.2, 126.8, 126.8, 122.1, 119.5, 118.2, 110.9, 109.5, 52.1, 52.1, 51.6, 24.9.



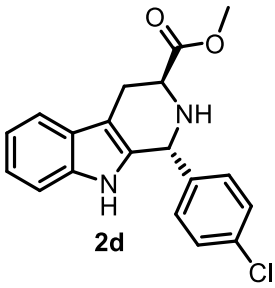
3c

(1*S*,3*S*)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3c**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br s, 1H), 7.52 (dd, *J* = 7.2 and 2.0 Hz, 1H), 7.43 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.39 (dd, *J* = 7.6 and 1.6 Hz, 1H), 7.25 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.18 (m, 2H), 7.11 (m, 2H), 5.81 (br s, 1H), 3.97 (dd, *J* = 11.2 and 4.0 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, *J* = 15.2, 4.0 and 2.0 Hz, 1H), 3.01 (ddd, *J* = 15.2, 11.2 and 2.0Hz, 1H), 2.61 (br s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 138.5, 136.1, 133.6, 133.5, 130.3, 129.6, 129.4, 127.6, 126.9, 121.9, 119.6, 118.1, 110.9, 109.1, 56.6, 54.2, 52.2, 25.5.

(1*R*,3*S*)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2d**) and (1*S*,3*S*)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3d**)

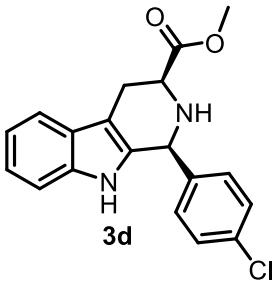


To a suspension of L-Tryptophan methyl ester hydrochloride (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 4-chlorobenzaldehyde (**1d**) (464 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **2d** (204 mg, 20 % yield) and **3d** (622 mg, 61 % yield).



2d

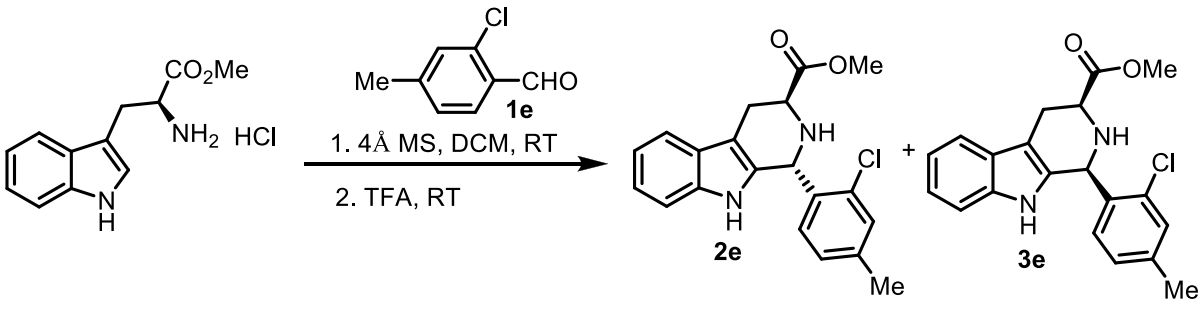
(1*R*,3*S*)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2d**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.52 (dd, *J* = 7.2 and 2.0 Hz, 1H), 7.24 (m, 2H), 7.13 (m, 5H), 5.26 (s, 1H), 3.86 (dd, *J* = 7.2 and 5.2 Hz, 1H), 3.66 (s, 3H), 3.21 (ddd, *J* = 15.6, 5.2 and 1.2 Hz, 1H), 3.06 (ddd, *J* = 15.6, 7.2 and 1.2 Hz, 1H), 2.44 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 140.4, 136.1, 133.8, 132.6, 129.7, 128.7, 126.8, 122.0, 119.5, 118.2, 110.9, 108.4, 54.1, 52.3, 52.1, 24.6.



3d

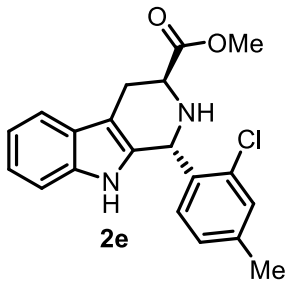
(1*S*,3*S*)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3d**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.29 (m, 4H), 7.14 (m, 3H), 5.17 (s, 1H), 3.92 (dd, *J* = 11.2 and 4.4 Hz, 1H), 3.79 (s, 3H), 3.20 (ddd, *J* = 15.2, 4.4 and 2.4 Hz, 1H), 2.98 (ddd, *J* = 15.2, 11.2 and 2.4 Hz, 1H), 2.41 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.3, 136.1, 134.3, 134.1, 129.9, 129.0, 127.0, 122.0, 119.7, 118.2, 110.9, 109.0, 58.0, 56.7, 52.2, 25.6.

(1*R*,3*S*)-methyl
1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2e**) and
(1*S*,3*S*)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3e**)



To a suspension of L-Tryptophan methyl ester hydrochloride (510 mg, 2.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2-chloro-4-methylbenzaldehyde (**1e**) (309 mg, 2.0 mmol, in 5 mL DCM), followed by an addition of TFA (100 μL, 1.3 mmol). The resulting reaction mixture was stirred for 22 hours at room temperature. TFA (250 μL, 3.3 mmol) was then added dropwise. The reaction mixture was stirred for another 21 hours. An aqueous solution of

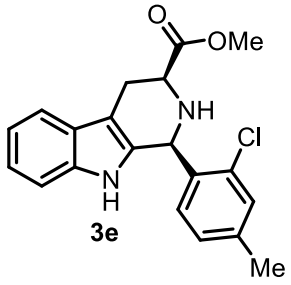
$NaHCO_3$ (840 mg, 10.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **2e** (290 mg, 40 % yield) and **3e (**457 mg, 60 % yield).



2e

(1*R*,3*S*)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2e**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.53 (dd, *J* = 7.0 and 1.0 Hz, 1H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.21 (dd, *J* = 7.0 and 1.0 Hz, 1H), 7.12 (m, 2H), 6.88 (dd, *J* = 8.0 and 0.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.78 (s, 1H), 3.81 (dd, *J* = 8.0 and 5.0 Hz, 1H), 3.70 (s, 3H), 3.22 (ddd, *J* = 15.0, 5.0 and 1.0 Hz, 1H), 3.04 (ddd, *J* = 15.0, 8.0 and 1.5 Hz, 1H), 2.75 (br s, 1H), 2.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.5, 136.2, 135.8, 133.4, 132.1, 130.3, 129.7, 127.5, 126.8, 122.0, 119.5, 118.2, 110.9, 109.4, 52.1, 52.0, 51.4, 24.9, 20.7.

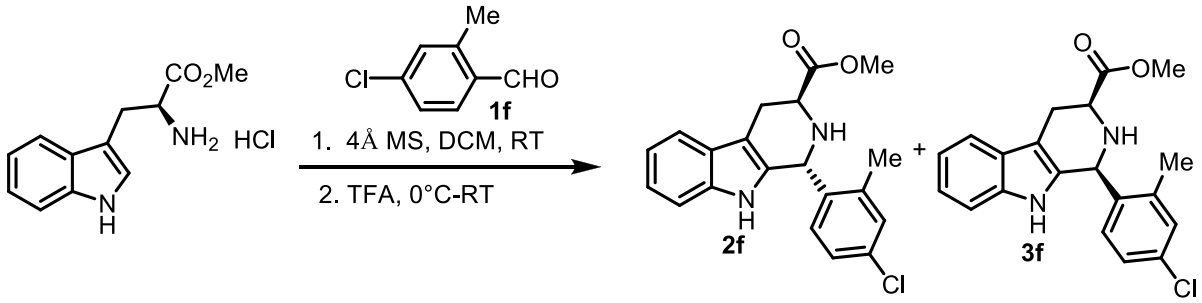


3e

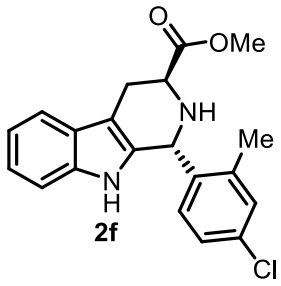
(1*S*,3*S*)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3e**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.51 (dd, *J* = 6.5 and 2.0 Hz, 1H), 7.26 (s, 1H), 7.23 (d, *J* = 6.0 Hz, 1H), 7.19 (dd, *J* = 7.0 and 2.0 Hz, 1H), 7.10 (m, 2H), 7.10 (d, *J* = 3.0 Hz, 1H), 5.77 (s, 1H), 3.96 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, *J* = 15.0, 4.0 and 2.0 Hz, 1H), 3.00 (ddd, *J* = 15.0, 11.0 and 2.5 Hz, 1H), 2.57 (br s, 1H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 139.8, 136.1, 135.3, 133.9, 133.2, 130.0, 130.0, 128.4, 126.9, 121.9, 119.6, 118.1, 110.9, 109.0, 56.7, 53.9, 52.2, 25.5, 20.8.

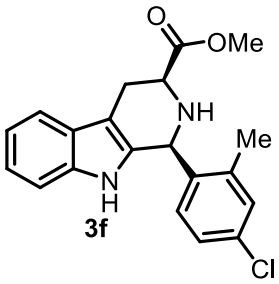
(1*R*,3*S*)-methyl
1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2f**) and (1*S*,3*S*)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3f**)



To a suspension of L-Tryptophan methyl ester hydrochloride (330 mg, 1.3 mmol) and 4Å molecular sieve (270 mg, powder form) in DCM (8 mL) was added 4-chloro-2-methylbenzaldehyde (**1f**) (200 mg, 1.3 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (200 μL, 2.6 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. An aqueous solution of $NaHCO_3$ (542 mg, 6.5 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **2f** (95 mg, 21 % yield) and **3f (**168 mg, 37 % yield).



(1*R*,3*S*)-methyl
1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2f**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.53 (dd, *J* = 7.2 and 1.6 Hz, 1H), 7.21 (m, 2H), 7.13 (m, 2H), 7.02 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.52 (s, 1H), 3.87 (dd, *J* = 7.2 and 5.2 Hz, 1H), 3.69 (s, 3H), 3.22 (ddd, *J* = 15.2, 5.2 and 1.2 Hz, 1H), 3.08 (ddd, *J* = 15.2, 7.2 and 1.6 Hz, 1H), 2.43 (s, 3H), 2.27 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 139.0, 137.8, 136.1, 133.5, 132.8, 130.8, 130.2, 126.9, 125.9, 122.0, 119.6, 118.2, 110.9, 109.0, 52.4, 52.1, 51.2, 24.8, 18.8.
HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_2$: 355.1208. Found: 355.1221.

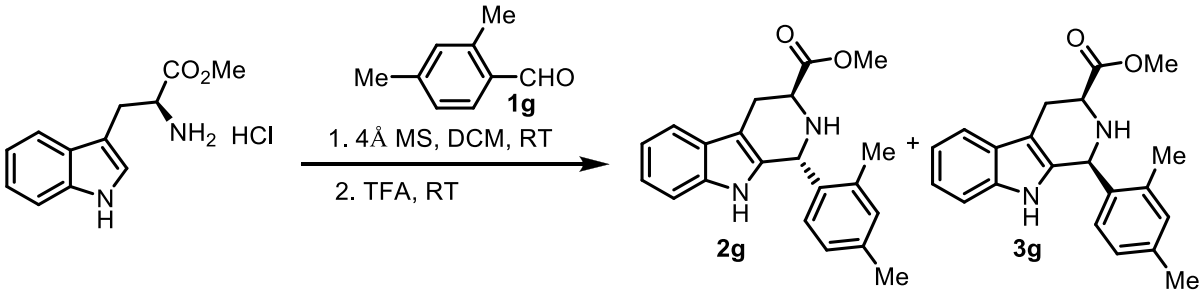


3f

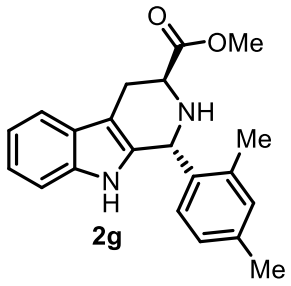
(1*S*,3*S*)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3f**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.18 (m, 2H), 7.11 (m, 4H), 7.54 (br s, 1H), 3.92 (dd, *J* = 11.2 and 4.4 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, *J* = 15.2, 4.4 and 2.0 Hz, 1H), 2.96 (ddd, *J* = 15.2, 11.2 and 2.8 Hz, 1H), 2.46 (br s, 3H), 2.22 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 136.9, 136.0, 134.1, 133.8, 130.6, 130.0, 127.0, 126.5, 121.9, 119.6, 118.1, 110.9, 56.8, 52.2, 25.7, 19.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{20}ClN_2O_2$: 355.1208. Found: 355.1218.

(1*R*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2g**) and (1*S*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3g**)

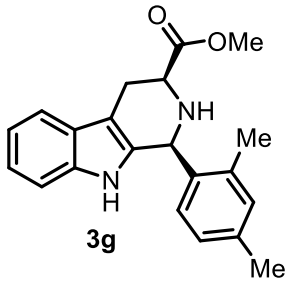


To a suspension of L-Tryptophan methyl ester hydrochloride (510 mg, 2.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2,4-dimethylbenzaldehyde (**1g**) (310 μL, 2.0 mmol, in 5 mL DCM), followed by an addition of TFA (100 μL, 1.3 mmol). The resulting reaction mixture was stirred for 23 hours at room temperature. TFA (250 μL, 3.3 mmol) was then added dropwise. The reaction mixture was stirred for another 20 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **2g** (266 mg, 40 % yield) and **3g (**346 mg, 52 % yield).



2g

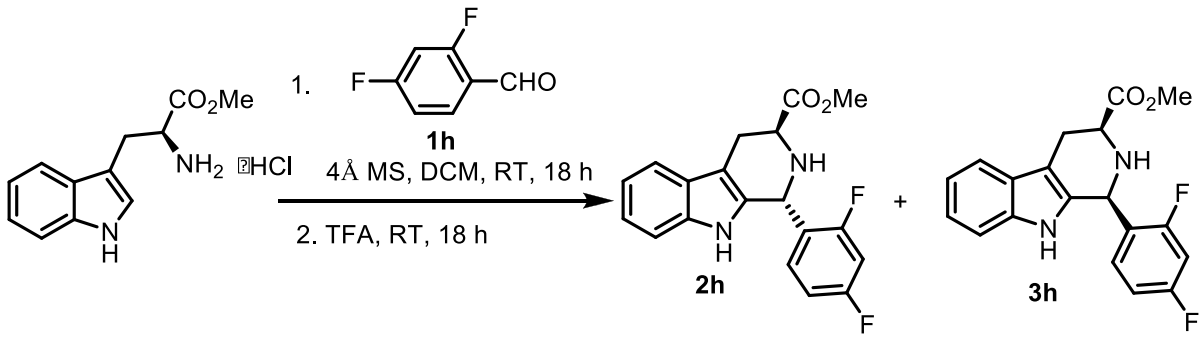
(1*R*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2g**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.53 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.19 (dd, *J* = 6.5 and 2.0 Hz, 1H), 7.12 (m, 2H), 7.03 (s, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 5.54 (s, 1H), 3.90 (dd, *J* = 7.0 and 5.0 Hz, 1H), 3.69 (s, 3H), 3.22 (ddd, *J* = 15.0, 5.0 and 1.5 Hz, 1H), 3.08 (ddd, *J* = 15.0, 7.0 and 1.5 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 2.23 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 137.6, 136.8, 136.3, 136.0, 133.6, 131.8, 128.8, 127.0, 126.5, 121.8, 119.4, 118.1, 110.8, 108.8, 52.4, 52.0, 51.4, 24.8, 20.9, 18.9.



3g

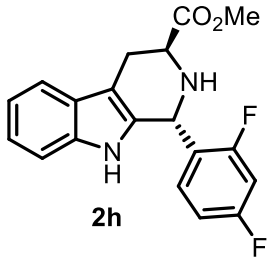
(1*S*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3g**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 6.0 and 3.0 Hz, 1H), 7.47 (s, 1H), 7.10 (m, 6H), 5.42 (br s, 1H), 3.93 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.78 (s, 3H), 3.20 (ddd, *J* = 15.0, 4.0 and 1.5 Hz, 1H), 2.97 (ddd, *J* = 15.0, 11.0 and 2.0 Hz, 1H), 2.48 (br s, 3H), 2.31 (s, 3H), 2.18 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 138.0, 136.0, 135.5, 135.0, 131.6, 129.7, 127.3, 127.1, 121.7, 119.5, 118.0, 110.8, 108.9, 57.0, 53.5, 52.1, 25.8, 21.0, 19.0.

(1*R*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2h**) and (1*S*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3h**)



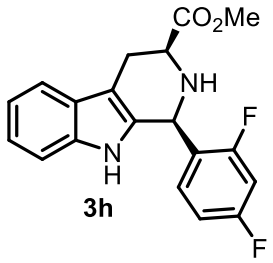
To a suspension of L-Tryptophan methyl ester hydrochloride (510 mg, 2.0 mmol) and 4Å molecular sieve (1.0 g, powder form) in DCM (10 mL) was added 2,4-difluorobenzaldehyde (**1h**) (220 μL, 2.0

mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 18 hours at room temperature. TFA (306 μL, 4.0 mmol) was then added dropwise. The reaction mixture was stirred for another 18 hours. An aqueous solution of $NaHCO_3$ (500 mg, 6.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **2h** (203 mg, 30 % yield) and **3h (**466 mg, 68 % yield).



2h

(1*R*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (2h) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.53 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.25 (ddd, *J* = 7.6, 1.6 and 0.8 Hz, 1H), 7.14 (m, 2H), 6.96 (dt, *J* = 6.4 and 8.4 Hz, 1H), 6.87 (ddd, *J* = 10.4, 8.8 and 2.4 Hz, 1H), 6.73 (ddd, *J* = 8.8, 2.4 and 0.8 Hz, 1H), 5.73 (s, 1H), 3.87 (dd, *J* = 8.0 and 4.8 Hz, 1H), 3.71 (s, 3H), 3.22 (ddd, *J* = 15.6, 4.8 and 1.2 Hz, 1H), 3.04 (ddd, *J* = 15.6, 8.0 and 1.2 Hz, 1H), 2.59 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7 (s), 162.5 (dd, *J* = 248 and 12 Hz), 160.8 (dd, *J* = 248 and 12 Hz), 136.2 (s), 131.5 (s), 130.6 (dd, *J* = 10 and 6 Hz), 126.8 (s), 125.1 (dd, *J* = 14 and 4 Hz), 122.2 (s), 119.7 (s), 118.2 (s), 111.1 (dd, *J* = 21 and 4 Hz), 110.9 (s), 109.3 (s), 104.1 (t, *J* = 25 Hz), 52.3 (s), 52.2 (s), 47.6 (d, J = 3 Hz), 24.8 (s). ^{19}F NMR (376 MHz, CDCl3) δ -110.3 (pent, *J* = 7.9 Hz), -115.2 (q, *J* = 9.0 Hz).

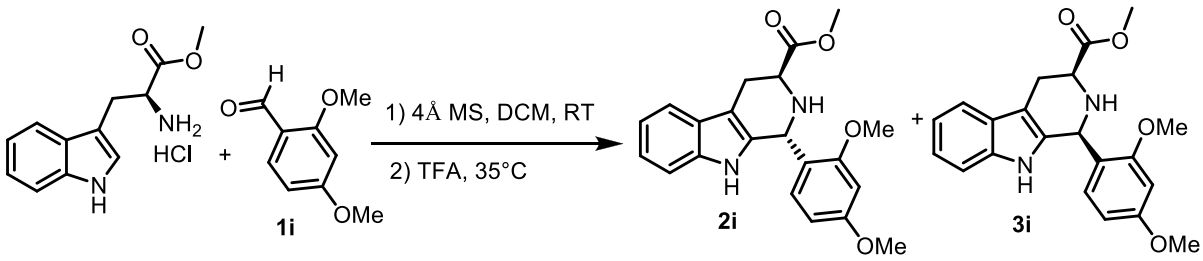


3h

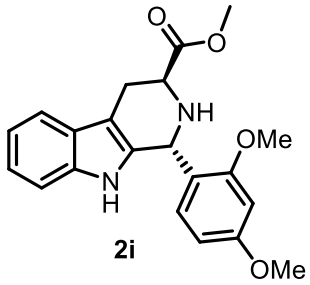
(1*S*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3h**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br s, 1H), 7.51 (dd, *J* = 6.4 and 2.0 Hz, 1H), 7.31 (dt, *J* = 6.4 and 8.4 Hz, 1H), 7.20 (dd, *J* = 6.4 and 2.0 Hz, 1H), 7.11 (m, 2H), 6.84 (m, 2H), 5.60 (s, 1H), 3.94 (dd, *J* = 11.2 and 4.0 Hz, 1H), 3.80 (s, 3H), 3.20 (ddd, *J* = 15.2, 4.0 and 2.0 Hz, 1H), 2.97 (ddd, *J* = 15.2, 11.2 and 2.0 Hz, 1H), 2.46 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (s), 162.6 (dd, *J* = 249 and 12 Hz), 160.9 (dd, *J* = 248 and 12 Hz), 136.1 (s), 133.2 (s), 131.1 (dd, *J* = 10 and 5 Hz), 126.9 (s), 123.8 (dd, *J* = 13 and 4 Hz), 122.1 (s), 119.7 (s), 118.2 (s), 112.0 (dd, *J* = 21 and 4 Hz), 110.9 (s), 109.3 (s), 103.9 (t, *J* = 26 Hz), 56.7 (s), 52.2 (s), 50.4 (d, *J* = 3 Hz), 25.5 (s). ^{19}F NMR (376 MHz, CDCl3) δ -109.6 (pent, *J* = 7.5 Hz), -116.1 (q, *J* = 8.3 Hz).

(1*R*,3*S*)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2i**)

and (1*S*,3*S*)-methyl
1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3i**)

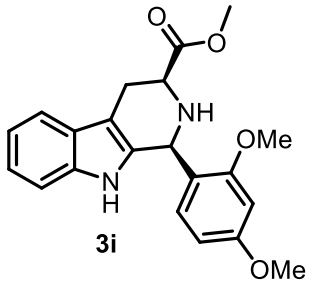


To a suspension of L-Tryptophan methyl ester hydrochloride (764 mg, 3.0 mmol) and 4Å molecular sieve (1.2 g, powder form) in DCM (20 mL) was added 2,4-dimethoxybenzaldehyde (**1i**) (548 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at 35 °C for 4 days. An aqueous solution of $NaHCO_3$ (900 mg, 10.7 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (3 : 1 DCM / EtOAc) to give **2i** (297 mg, 27 % yield) and **3i (**209 mg, 19 % yield).



(1*R*,3*S*)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2i**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.50 (dd, *J* = 6.8 and 2.0 Hz, 1H), 7.20 (dd, *J* = 6.8 and 2.0 Hz, 1H), 7.09 (m, 2H), 6.61 (dd, *J* = 8.4 and 1.2 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.21 (dt, *J* = 8.4 and 2.4 Hz, 1H), 5.63 (s, 1H), 3.82 (s, 3H), 3.75 (dd, *J* = 9.2 and 4.4 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.16 (dd, *J* = 15.2 and 4.4 Hz, 1H), 2.92 (dd, *J* = 15.2 and 9.2 Hz, 1H), 2.75 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.4, 157.9, 136.1, 133.1, 129.6, 126.8, 122.4, 121.5, 119.1, 117.9, 110.8, 108.9, 103.3, 98.6, 55.3, 55.2, 51.9, 51.7, 48.8, 25.1.

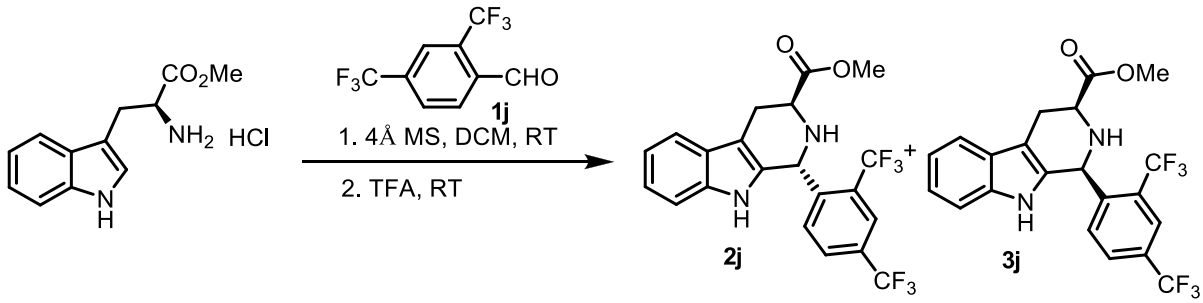


3i

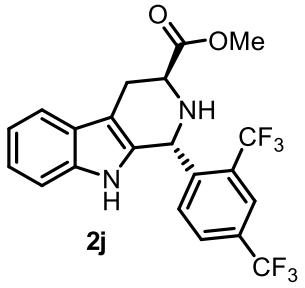
(1*S*,3*S*)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3i**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.49 (dd, *J* = 6.4 and 2.4 Hz, 1H), 7.17 (m, 2H), 7.09 (m, 2H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.4 and 2.4 Hz, 1H), 5.59 (s, 1H), 3.92 (dd, *J* = 10.8 and 4.4 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 6H), 3.17 (ddd, *J* = 15.2, 4.4 and 2.4 Hz, 1H), 2.96 (ddd, *J* = 15.2, 10.4 and 2.4 Hz, 1H), 2.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 160.6, 158.3, 135.8, 135.2, 129.8, 127.1, 121.4, 121.3, 119.3, 117.9, 110.7, 108.3, 104.7, 98.7, 56.9, 55.6, 55.3, 52.0, 51.3, 25.7.

(1*R*,3*S*)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2j**) and (1*S*,3*S*)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3j**)

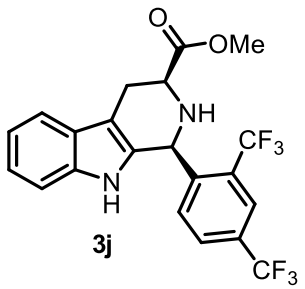


To a suspension of L-Tryptophan methyl ester hydrochloride (1.27 g, 5.0 mmol) and 4Å molecular sieve (1.0 g, powder form) in DCM (20 mL) was added 2,4-bis(trifluoromethyl)benzaldehyde (**1j**) (818 μL, 5.0 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 18 hours at room temperature. TFA (130 μL, 1.7 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. TFA (500 μL, 6.5 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. An aqueous solution of $NaHCO_3$ (1.7 g, 20.2 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **2j** (0.76 g, 39 % yield) and **3j** (1.39 g, 61 % yield).



2j

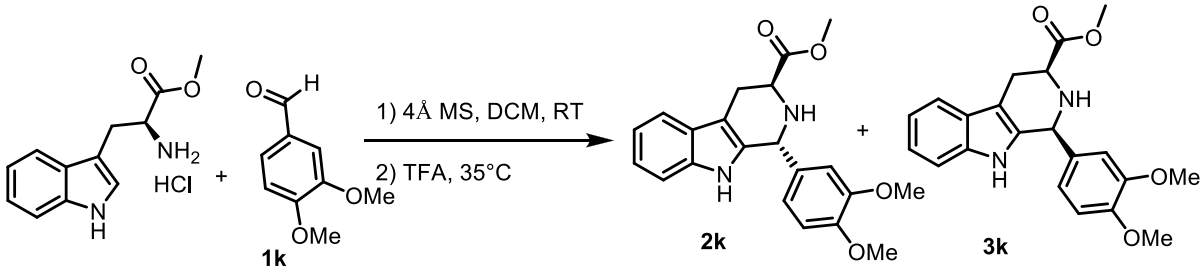
(1*R*,3*S*)-methyl
1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2j**)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.54 (dd, J = 6.5 and 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.12 (m, 3H), 5.93 (s, 1H), 4.00 (t, *J* = 5.5 Hz, 1H), 3.67 (s, 3H), 3.30 (ddd, *J* = 15.5, 5.5 and 1.5 Hz, 1H), 3.23 (ddd, *J* = 15.5, 5.5 and 1.5 Hz, 1H), 2.70 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (s), 145.0 (s), 136.3 (s), 132.1 (s), 131.5 (s), 130.4 (q, *J* = 33 Hz), 129.3 (q, *J* = 31 Hz), 128.9 (q, *J* = 3 Hz), 126.6 (s), 123.7 (q, *J* = 273 Hz), 123.2 (q, *J* = 271 Hz), 123.0 (q, *J* = 4 Hz), 122.4 (s), 119.7 (s), 118.3 (s), 110.9 (s), 109.0 (s), 53.0 (s), 52.1 (s), 49.8 (s), 24.0 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.8, -62.9.



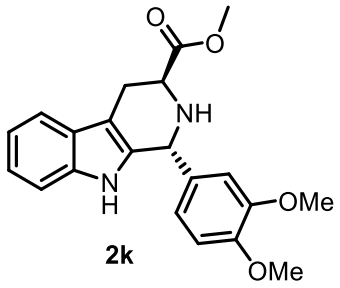
3j

(1*S*,3*S*)-methyl
1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3j**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.56 (dd, *J* = 6.4 and 2.0 Hz, 1H), 7.36 (s, 1H), 7.16 (m, 3H), 5.75 (s, 1H), 4.00 (dd, *J* = 11.1 and 4.0 Hz, 1H), 3.83 (s, 3H), 3.27 (ddd, *J* = 15.2, 4.0 and 2.0 Hz, 1H), 3.07 (ddd, *J* = 15.2, 11.2 and 2.4 Hz, 1H), 2.81 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (s), 144.6 (s), 136.4 (s), 133.0 (s), 132.9 (s), 130.7 (q, *J* = 33 Hz), 129.4 (q, *J* = 31 Hz), 139.3 (q, *J* = 3 Hz), 126.6 (s), 126.4 (q, *J* = 273 Hz), 125.9 (q, *J* = 271 Hz), 122.6 (q, *J* = 4 Hz), 122.4 (s), 119.9 (s), 118.4 (s), 111.0 (s), 109.7 (s), 56.5 (s), 53.3 (q, *J* = 2 Hz), 52.4 (s), 25.3 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.4, -62.9.

(1*R*,3*S*)-methyl 1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2k**) and (1*S*,3*S*)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3k**)

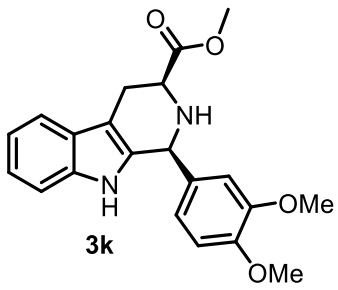


To a suspension of L-Tryptophan methyl ester hydrochloride (764 mg, 3.0 mmol) and 4Å molecular sieve (1.2 g, powder form) in DCM (20 mL) was added 3,4-dimethoxybenzaldehyde (**1k**) (548 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at 35 °C for 4 days. An aqueous solution of $NaHCO_3$ (900 mg, 10.7 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (2 : 1 DCM / EtOAc) to give **2k** (448 mg, 41 % yield) and **3k (**394 mg, 36 % yield).



(1*R*,3*S*)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2k**)

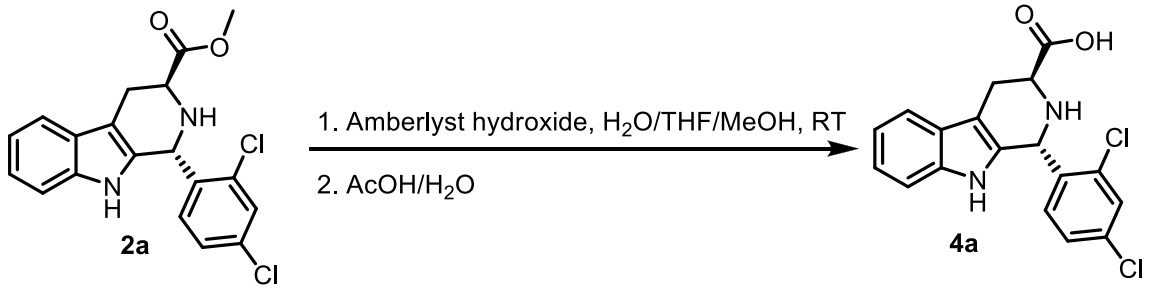
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.54 (dd, *J* = 6.8 and 2.0 Hz, 1H), 7.22 (ddd, *J* = 6.8, 2.0 and 1.6 Hz, 1H), 7.12 (m, 2H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.75 (m, 2H), 5.32 (s, 1H), 3.98 (t, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.25 (ddd, *J* = 15.2, 6.0 and 1.6 Hz, 1H), 3.13 (ddd, *J* = 15.2, 6.0 and 1.6 Hz, 1H), 2.40 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 149.2, 148.8, 136.1, 134.5, 133.5, 127.0, 121.8, 120.6, 119.3, 118.1, 111.3, 110.9, 110.8, 108.0, 55.8, 54.6, 52.8, 52.0, 24.5.



3k

(1*S*,3*S*)-methyl 1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3k**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.52 (dd, *J* = 6.4 and 2.8 Hz, 1H), 7.20 (ddd, *J* = 6.8, 2.8 and 0.8 Hz, 1H), 7.11(m, 2H), 6.88 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz), 5.14 (s, 1H), 3.94 (dd, *J* = 11.2 and 4.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.20 (ddd, *J* = 15.2, 4.4 and 2.0 Hz, 1H), 2.99 (ddd, *J* = 15.2, 11.2 and 2.8 Hz, 1H), 2.39 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 149.3, 149.0, 136.1, 134.8, 133.2, 127.1, 121.8, 120.7, 119.4, 118.0, 111.2, 111.0, 110.9, 108.6, 58.5, 56.9, 55.8, 52.1, 25.6.

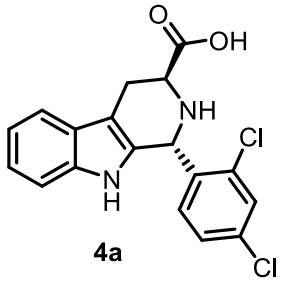
(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4a**)



2a **4a**

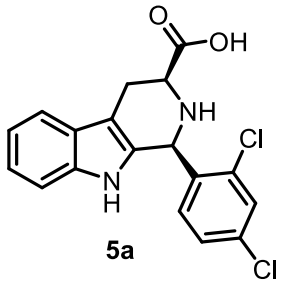
A modification of an Amberlyst resin-mediated catch and release protocol[2] was used to hydrolyze the ester to the acid. To a solution of **2a** (518 mg, 1.4 mmol) in THF / MeOH / H_2O (14 mL / 14 mL / 14 mL) was added Amberlyst hydroxide resin (4.8 g, 1.5 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred at for 21 hours, the resin was filtered and washed with MeOH and DCM alternatively (4 × 10 mL). An aqueous solution of AcOH (50%) (20 mL) was added to cleave the product from the resin, the cleaving solution was collected by filtration. The cleavage step was repeated for other 3 times. The combined cleaving solutions were condensed under vacuum. The residue was added MeOH (2 mL), followed by addition of Et_2O (20 mL) and hexane (60 mL). The mixture was stirred for 2 hours and then filtered. The solid was washed with hexane to afford (1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4a**) (443 mg, 89 % yield).

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4a**)



4a

$[\alpha]_D^{21.0}$ = -58.1° (c = 1.34, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.25 (dt, *J* = 7.6 and 1.2 Hz, 1H), 7.06 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.00 (td, *J* = 7.2 and 1.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.73 (s, 1H), 3.60 (dd, *J* = 8.4 and 4.8 Hz, 1H), 3.09 (dd, *J* = 15.2 and 4.8 Hz, 1H), 2.85 (ddd, *J* = 15.2, 8.4 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 138.7, 136.2, 134.1, 132.7, 132.3, 131.5, 129.0, 127.0, 126.4, 121.1, 118.5, 117.8, 111.1, 108.3, 51.4, 50.6, 24.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}Cl_2N_2O_2$: 361.0505. Found: 361.0514.



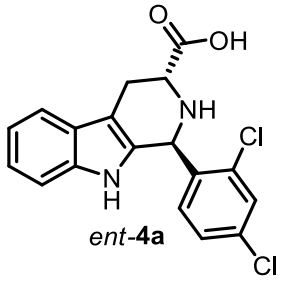
5a

(1*S*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5a**) was prepared in 75 % yield from (1*S*,3*S*)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3a**) following the procedure employed for preparation of **4a**.

(1*S*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (59)

$[\alpha]_D^{21.4}$ = -64.7° (c = 0.15, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.02 (td, *J* = 7.0 and 1.0 Hz, 1H), 6.97 (td, *J* = 8.0 and 1.0 Hz, 1H), 5.66 (s, 1H), 3.83 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.05 (ddd, *J* = 15.0, 4.0 and 2.0 Hz, 1H), 2.81 (ddd, *J* = 15.0, 11.0, and 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.7, 138.2, 136.4, 134.2, 133.8, 132.9, 132.0, 128.7, 127.6, 126.4, 120.9, 118.5, 117.7, 111.2, 108.0, 56.1, 53.6, 25.1. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0512.

(1*S*,3*R*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (*ent*-**4a**)

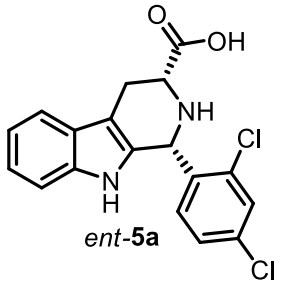


ent-**4a**

(1*S*,3*R*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (*ent*-**4a**) was prepared in 81 % yield from (1*S*,3*R*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-**2a**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.6}$ = +53.5° (c = 1.10, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 8.5 and 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 7.0 and 1.0 Hz, 1H), 6.99 (td, *J* = 8.0 and 1.0 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 5.71 (s, 1H), 3.57 (dd, *J* = 8.5 and 5.0 Hz, 1H), 3.08 (dd, *J* = 15.0 and 5.0 Hz, 1H), 2.84 (dd, *J* = 15.0 and 8.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 138.8, 136.2, 134.1, 132.7, 132.4, 131.4, 129.0, 127.0, 126.3, 121.1, 118.5, 117.8, 111.1, 108.3, 51.4, 50.6, 24.7. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0509.

(1*R*,3*R*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (*ent*-**5a**)

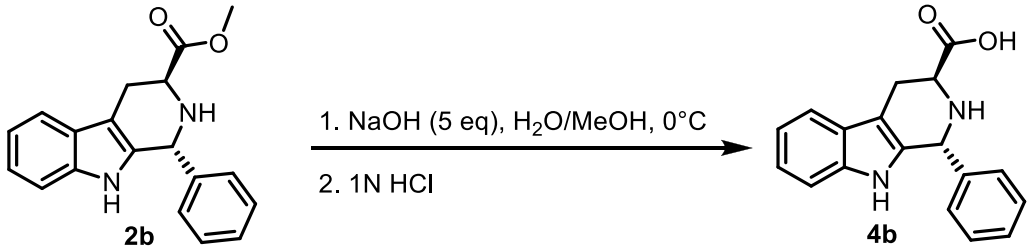


ent-**5a**

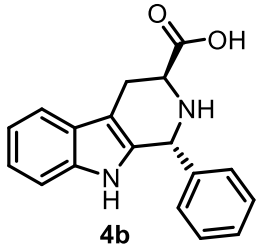
(1*R*,3*R*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (*ent*-**5a**) was prepared in 79 % yield from (*1R*,3*R*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (*ent*-**3a**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.4}$ = +64.1° (c = 0.22, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.39 (dd, *J* = 8.0 and 2.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.02 (td, *J* = 7.0 and 1.0 Hz, 1H), 6.97 (td, *J* = 8.0 and 1.0 Hz, 1H), 5.66 (s, 1H), 3.83 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.05 (ddd, *J* = 15.0, 4.0 and 2.0 Hz, 1H), 2.81 (ddd, *J* = 15.0, 11.0, and 2.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 138.2, 136.3, 134.2, 133.8, 132.9, 132.0, 128.7, 127.6, 126.4, 120.9, 118.5, 117.7, 111.2, 108.0, 56.1, 53.7, 25.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}Cl_2N_2O_2$: 361.0505. Found: 361.0511.

(1*R*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4b**)

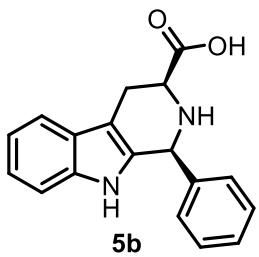


To a solution of **2b** (46 mg, 0.16 mmol) in methanol (1 mL) was added an aqueous solution of NaOH (32 mg, 0.8 mmol, in 1.5 mL H_2O) dropwise at 0 °C. The resulting reaction mixture was stirred at 0 °C for 8 hours. The reaction was adjusted with 1 N HCl aqueous solution to pH = 3. The solvents were removed under vacuum. 10 mL methanol was added to the residue. After being stirred for 30 minutes, the precipitate was filtered off. The filtrate was condensed. To the residue, 5 mL methanol and 5 mL ethyl acetate were added. After being stirred for 30 minutes, the precipitate was filtered off. The filtrate was condensed to afford (1*R*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4b**) (46 mg, 99 % yield).



(1*R*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4b**)
$[\alpha]_D^{21.0}$ = -51.4° (c = 0.14, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.42 (m, 5H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.12 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.05 (td, *J* = 7.6 and 0.8 Hz, 1H), 5.94 (s, 1H), 4.29 (dd, *J* = 7.2 and 7.0 Hz, 1H), 3.51 (dd, *J* = 16.0 and 7.0 Hz, 1H), 3.21 (dd, *J* = 16.0 and 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 136.6, 134.9, 130.3, 129.5, 128.6, 128.4, 125.5, 122.0, 119.0, 118.2, 111.5, 106.1, 54.5, 51.6, 22.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2$: 293.1285. Found: 293.1294.

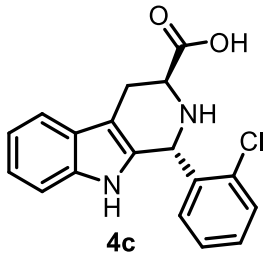
(1*S*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5b**)



(1*S*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5b**) was prepared in 95 % yield from (1S,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3b**) following the procedure employed for preparation of **4b**.
$[\alpha]_D^{21.0}$ = -49.5° (c = 2.00, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.51 (m, 6H),

7.27 (d, *J* = 8.0 Hz, 1H), 7.10 (td, *J* = 8.0 and 1.0 Hz, 1H), 7.03 (td, *J* = 8.0 and 1.0 Hz, 1H), 5.90 (s, 1H), 4.55 (dd, *J* = 11.5 and 4.0 Hz, 1H), 3.37 (dd, *J* = 15.5 and 4.0 Hz, 1H), 3.25 (ddd, *J* = 15.5, 11.5 and 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 136.8, 134.1, 130.5, 129.8, 129.1, 128.5, 125.5, 121.9, 119.1, 118.1, 111.6, 106.8, 57.6, 55.4, 22.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2$: 293.1285. Found: 293.1287.

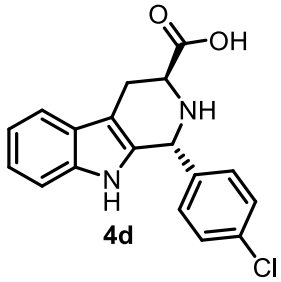
(1*R*,3*S*)-1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4c**)



4c

(1*R*,3*S*)-1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4c**) was prepared in 95 % yield from (1R,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2c**) following the procedure employed for preparation of **4b**.
$[\alpha]_D^{21.0}$ = -19.5° (c = 1.32, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.58 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.39 (td, *J* = 7.6 and 1.6 Hz, 1H), 7.25 (m, 2H), 7.08 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.01 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.92 (d, *J* = 6.8 Hz, 1H), 5.98 (s, 1H), 3.86 (br s, 1H), 3.28 (dd, *J* = 15.6 and 4.8 Hz, 1H), 2.97 (dd, *J* = 15.6 and 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 136.4, 133.7, 130.8, 130.1, 129.7, 127.1, 126.0, 121.5, 118.7, 117.9, 111.3, 107.6, 51.6, 51.0, 23.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{16}ClN_2O_2$: 327.0895. Found: 327.0898.

(1*R*,3*S*)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4d**)

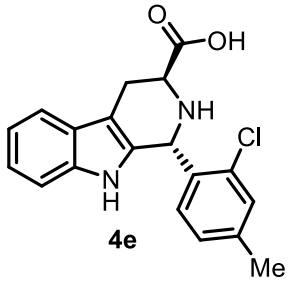


4d

(1*R*,3*S*)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4d**) was prepared in 95 % yield from (1*R*,3*S*)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2d**) following the procedure employed for preparation of **4b**.
$[\alpha]_D^{21.0}$ = -18.7° (c = 1.25, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.45 (dt, *J* = 8.4 and 2.0 Hz, 2H), 7.38 (dt, *J* = 8.4 and 2.0 Hz, 2H), 7.27 (dt, *J* = 8.0 and 1.2 Hz, 1H), 7.09 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.01 (td, *J* = 8.0 and 1.2 Hz, 1H), 5.79 (s, 1H), 4.03 (t, *J* = 6.4 Hz, 1H), 3.35 (dd, *J* = 15.6 and 5.2 Hz, 1H), 3.09 (dd, *J* = 15.6 and 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 136.5, 136.1, 133.5, 131.7, 129.8, 128.4, 125.8, 121.7, 118.8, 118.1, 111.4, 106.6, 53.5, 51.8, 22.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{16}ClN_2O_2$: 327.0895. Found:

327.0906.

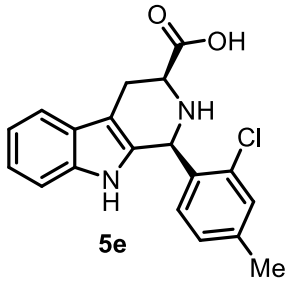
(1*R*,3*S*)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4e**)



4e

(1*R*,3*S*)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4e**) was prepared in 78 % yield from (1*R*,3*S*)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2e**) following the procedure employed for preparation of **4a**.
$[\alpha]_D^{21.0}$ = -61.9° (c = 0.70, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.01 (m, 3H), 6.64 (d, J = 7.6 Hz, 1H), 5.69 (s, 1H), 3.56 (dd, J = 8.84 and 4.8 Hz, 1H), 3.08 (dd, J = 15.2 and 4.8 Hz, 1H), 2.83 (dd, J = 15.2 and 8.8 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 139.1, 136.2, 136.2, 132.8, 132.7, 129.9, 129.9, 127.4, 126.4, 121.0, 118.4, 117.7, 111.1, 108.2, 51.2, 51.0, 24.7, 20.2. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_2$: 341.1051. Found: 341.1058.

(1*S*,3*S*)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5e**)

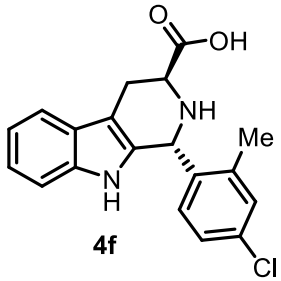


5e

(1*S*,3*S*)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5e**) was prepared in 69 % yield from (1*S*,3*S*)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3e**) following the procedure employed for preparation of **4a**.
$[\alpha]_D^{21.0}$ = -59.7° (c = 0.66, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.36 (s, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.13 (m, 2H), 7.01 (td, *J* = 7.6 and 1.2 Hz, 1H), 6.95 (td, *J* = 7.2 and 1.2 Hz, 1H), 5.66 (s, 1H), 3.82 (dd, J = 11.2 and 4.0 Hz, 1H), 3.06 (ddd, *J* = 15.2, 4.0 and 1.2 Hz, 1H), 2.82 (ddd, *J* = 15.2, 11.2 and 2.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 139.3, 136.3, 135.7, 134.1, 133.0, 130.3, 129.6, 128.1, 126.5, 120.8, 118.4, 117.6, 111.2, 107.9, 56.3, 53.9, 25.2, 20.3. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_2$: 341.1051. Found: 341.1046.

(1*R*,3*S*)-1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid

(**4f**)

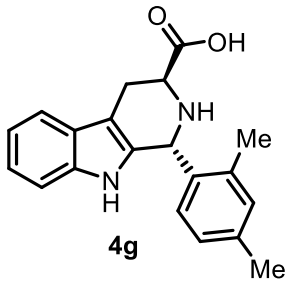


4f

(1*R*,3*S*)-1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4f**) was prepared in 56 % yield from (1*R*,3*S*)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2f**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = -16.8° (c = 0.68, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.04 (td, J = 7.6 and 1.2 Hz, 1H), 6.98 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.57 (s, 1H), 3.59 (t, *J* = 6.4 Hz, 1H), 3.06 (dd, *J* = 15.2 and 4.8 Hz, 1H), 2.88 (dd, *J* = 15.2 and 7.6 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 139.6, 138.9, 136.1, 133.3, 131.7, 130.4, 129.9, 126.5, 125.2, 120.9, 118.4, 117.7, 111.0, 107.7, 51.9, 50.3, 24.6, 18.5. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2O_2$: 341.1051. Found: 341.1057.

(1*R*,3*S*)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4g**)

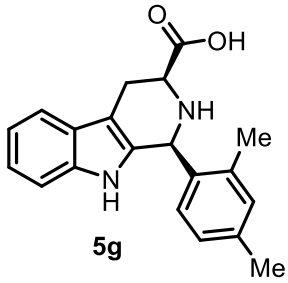


4g

(1*R*,3*S*)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4g**) was prepared in 85 % yield from (1*R*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2g**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = -20.1° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.21 (dt, *J* = 7.6 and 0.8 Hz, 1H), 7.07 (d, *J* = 0.8 Hz, 1H), 7.03 (td, *J* = 7.2 and 1.2 Hz, 1H), 6.97 (td, *J* = 7.2 and 1.2 Hz, 1H), 6.88 (dd, *J* = 7.6 and 0.8 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 5.63 (s, 1H), 3.63 (dd, *J* = 7.2 and 5.2 Hz, 1H), 3.08 (dd, *J* = 15.2 and 5.2 Hz, 1H), 2.92 (dd, *J* = 15.2 and 7.2 Hz, 1H), 2.45 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 136.9, 136.7, 136.1, 136.0, 133.3, 131.2, 128.7, 126.4, 126.0, 120.9, 118.3, 117.6, 111.0, 107.4, 52.1, 50.6, 24.3, 20.6, 18.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_2$: 321.1598. Found: 321.1596.

(1*S*,3*S*)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5g**)

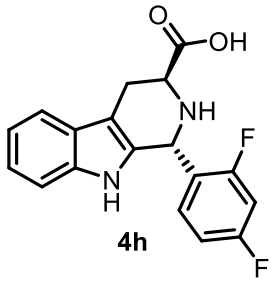


5g

(1*S*,3*S*)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5g**) was prepared in 83 % yield from (1*S*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3g**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = -73.6° (c = 0.11, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 6.98 (m, 3H), 5.54 (s, 1H), 3.81 (dd, *J* = 11.0 and 4.0 Hz, 1H), 3.11 (dd, *J* = 15.0 and 4.0 Hz, 1H), 2.86 (t, *J* = 12.5 Hz, 1H), 2.35 (br s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 137.0, 136.9, 136.4, 135.2, 134.3, 131.2, 129.2, 126.5, 126.4, 120.7, 118.4, 117.6, 111.2, 107.5, 57.1, 53.9, 24.8, 20.6, 18.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_2$: 321.1598. Found: 321.1592.

(1*R*,3*S*)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4h**)

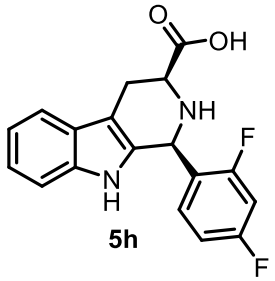


4h

(1*R*,3*S*)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid was prepared in 74 % yield from (1*R*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2h**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = -67.3° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dt, J = 8.0 and 0.8 Hz, 1H), 7.27 (dt, *J* = 8.4 and 0.8 Hz, 1H), 7.10 (m, 4H), 6.98 (td, *J* = 8.4 and 2.6 Hz, 1H), 6.28 (s, 1H), 4.02 (dd, *J* = 8.4 and 5.6 Hz, 1H), 3.49 (dd, *J* = 16.4 and 5.6 Hz, 1H), 3.26 (ddd, *J* = 16.4, 8.4 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.4 (s), 165.6 (dd, *J* = 247 and 12 Hz), 163.0 (dd, *J* = 248 and 13 Hz), 138.7 (s), 133.8 (dd, *J* = 10 and 4 Hz), 127.2 (s), 123.8 (s), 120.6 (s), 120.0 (dd, J = 14 and 4 Hz), 119.3 (s), 113.1 (dd, *J* = 22 and 4 Hz), 112.3 (s), 109.5 (s), 105.5 (t, *J* = 26 Hz), 55.1 (s), 49.1 (d, *J* = 4 Hz), 23.9 (s). ^{19}F NMR (376 MHz, CD_3OD) δ -108.6 (pent, *J* = 7.1 Hz), -113.7 (q, *J* = 9.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}F_2N_2O_2$: 329.1096. Found: 329.1094.

(1*S*,3*S*)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5h**)

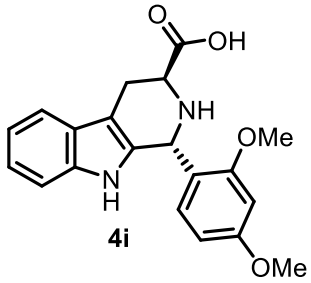


5h

(1*S*,3*S*)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**5h**) was prepared in 68 % yield from (1*S*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**3h**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = -85.5° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 (dt, *J* = 6.4 and 8.4 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.13 (m, 4H), 6.13 (s, 1H), 4.16 (dd, *J* = 12.0 and 4.8 Hz, 1H), 3.49 (dd, *J* = 16.0 and 4.8 Hz, 1H), 3.19 (ddd, *J* = 16.0, 12.0 and 2.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.3 (s), 165.5 (dd, *J* = 250 and 12 Hz), 163.4 (dd, *J* = 251 and 13 Hz), 138.7 (s), 133.7 (dd, *J* = 10 and 4 Hz), 128.9(s), 127.4 (s), 123.5 (s), 120.6 (s), 119.3 (dd, *J* = 13 and 4 Hz), 119.2 (s), 113.3 (dd, *J* = 22 and 4 Hz), 112.4 (s), 110.1 (s), 105.4 (t, J = 26 Hz), 60.5 (s), 52.1 (d, J = 5 Hz), 24.3 (s). ^{19}F NMR (376 MHz, d_6-DMSO) δ -111.1 (br s), -114.8 (br s). HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{15}F_2N_2O_2$: 329.1096. Found: 329.1103.

(1*R*,3*S*)-1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4i**)

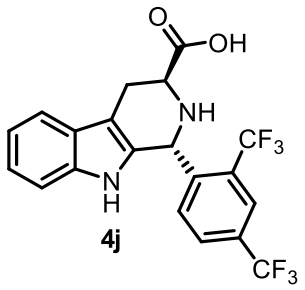


4i

(1*R*,3*S*)-1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4i**) was prepared in 90 % yield from (1*R*,3*S*)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2i**) following the procedure employed for preparation of **4a**.

$[\alpha]_D^{21.0}$ = +32.0° (c = 0.10, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.50 (dd, *J* = 8.5 and 2.0 Hz, 1H), 6.22 (s, 1H), 3.98 (s, 3H), 3.88 (br s, 1H), 3.80 (s, 3H), 3.46 (dd, *J* = 15.5 and 4.5 Hz, 1H), 3.18 (dd, *J* = 15.5 and 4.5 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 164.2, 160.1, 138.6, 132.6, 128.2, 127.3, 123.5, 120.5, 119.2, 115.9, 112.3, 109.3, 106.1, 99.7, 56.4, 56.0, 54.9, 51.3, 24.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_4$: 353.1496. Found: 353.1489.

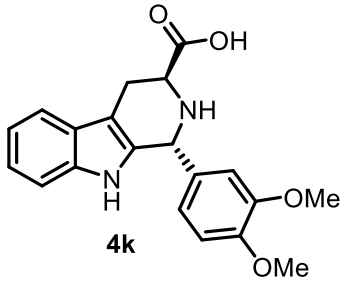
(1*R*,3*S*)-1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4j**)



4j

(1*R*,3*S*)-1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4j**) was prepared in 84 % yield from (1*R*,3*S*)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2j**) following the procedure employed for preparation of **4a**.
$[\alpha]_D^{21.0}$ = -70.6° (c = 2.04, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5 (s, 1H), 8.08 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.05 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.99 (td, *J* = 8.0 and 1.2 Hz, 1H), 5.87 (s, 1H), 3.86 (t, *J* = 5.6 Hz, 1H), 3.15 (dd, *J* = 15.2 and 4.8 Hz, 1H), 3.03 (dd, *J* = 15.2 and 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.9 (s), 146.4 (s), 136.4 (s), 132.6 (s), 132.5 (s), 129.2 (q, J = 2 Hz), 128.5 (q, *J* = 31 Hz), 128.4 (q, *J* = 33 Hz), 126.3 (s), 123.7 (q, *J* = 274 Hz), 123.5 (q, *J* = 271 Hz), 122.5 (q, *J* = 2 Hz), 121.2 (s), 118.6 (s), 117.9 (s), 111.2 (s), 107.7 (s), 52.2 (s), 49.4 (d, J = 2 Hz), 24.1 (s). ^{19}F NMR (470 MHz, DMSO-d_6) δ -56.6, -61.3. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{15}F_6N_2O_2$: 429.1032. Found: 429.1019.

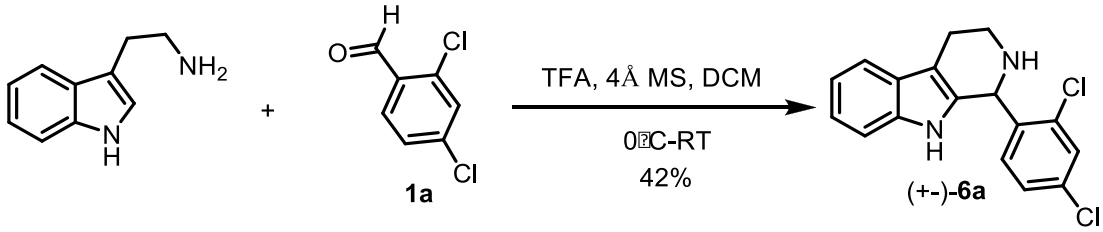
(1*R*,3*S*)-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4k**)



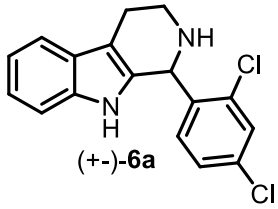
4k

(1*R*,3*S*)-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**4k**) was prepared in 86 % yield from (1*R*,3*S*)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2k**) following the procedure employed for preparation of **4a**.
$[\alpha]_D^{21.0}$ = -56.9° (c = 1.43, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.25 (dt, *J* = 8.0 and 1.2 Hz, 1H), 7.05 (m, 2H), 6.98 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4 and 2.0 Hz, 1H), 5.48 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.66 (dd, *J* = 8.0 and 5.2 Hz, 1H), 3.11 (dd, *J* = 15.2 and 5.2 Hz, 1H), 2.93 (dd, *J* = 15.2 and 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 148.6, 148.6, 136.3, 132.5, 132.4, 126.3, 121.1, 120.9, 118.4, 117.8, 112.8, 111.3, 111.1, 107.2, 55.5, 55.5, 54.0, 52.1, 23.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_4$: 353.1496. Found: 353.1500.

1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (±)-**6a**)



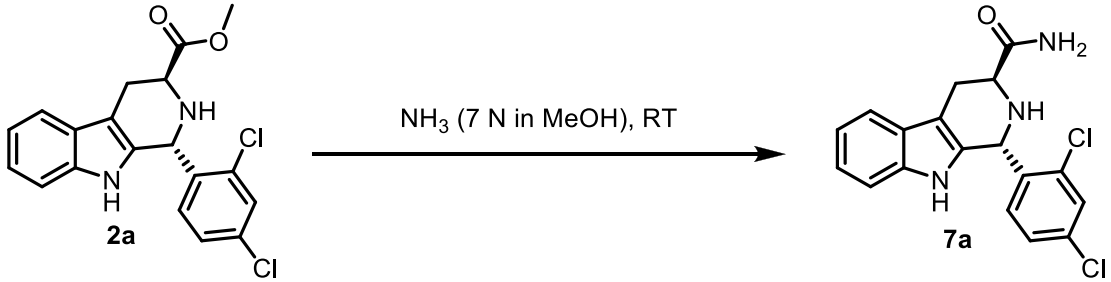
To a 50-mL flask charging with 4Å molecular sieve (500 mg, powder form) was added tryptamine (320 mg, 2.0 mmol, in 5 mL DCM), and 2,4-dichlorobenzaldehyde (**1a**) (420 mg, 2.4 mmol, in 5 mL DCM). 2 drops of TFA was added at 0 °C. The resulting reaction mixture was stirred for 17 hours at room temperature. The reaction was cooled to 0 °C and TFA (310 μL, 4.0 mmol) was added dropwise. The reaction mixture was further stirred for 7 hours at room temperature. Then the reaction was cooled to 0 °C again. An aqueous solution of $NaHCO_3$ (420 mg, 5.0 mmol, in 10 mL H_2O) was added dropwise, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOH) to give 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (±)-**6a**) **(**264 mg, 42 % yield).



1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (±)-**6a**)

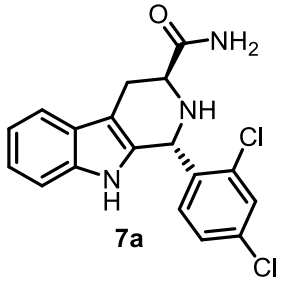
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.54 (dd, J = 7.6 and 1.6 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.22 (ddd, J = 7.6, 1.6 and 0.8 Hz, 1H), 7.14 (m, 3H), 7.02 (d, J = 8.4 Hz, 1H), 5.66 (s, 1H), 3.16 (m, 2H), 2.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 135.9, 134.5, 132.0, 131.2, 129.6, 127.3, 127.0, 122.1, 119.6, 118.3, 111.0, 110.9, 53.1, 41.4, 22.1. HRMS (ESI) $[M+H]^+$ calculated for $C_{17}H_{15}Cl_2N_2$: 317.0607. Found: 317.0628.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**7a**)



To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (16.5 mg, 0.044 mmol) and ammonia solution in methanol (1.5 mL, 7 N, 10.5 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 24 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / MeOH) to give **7a (**15.5 mg, 98 %

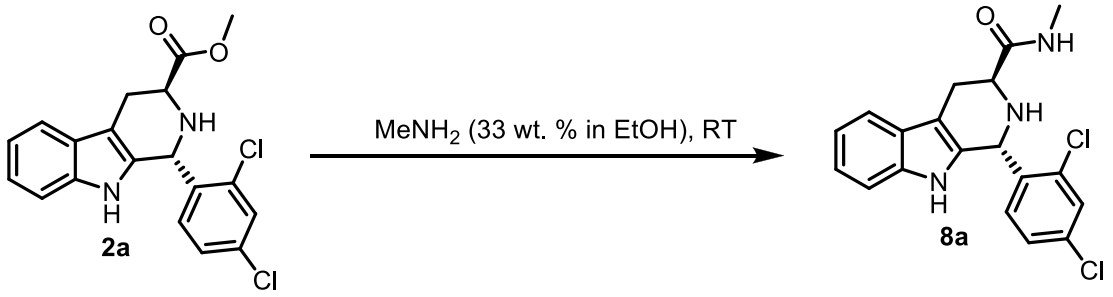
yield).



7a

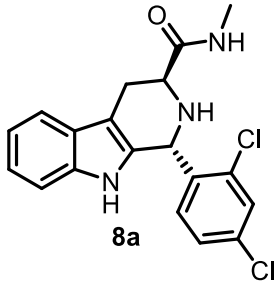
(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**7a**) $[\alpha]_D^{21.0}$ = -25.7° (c = 0.32, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 8.4 and 2.0 Hz, 1H), 7.26 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 7.06 (td, *J* = 8.4 and 1.6 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.57 (s, 1H), 3.34 (br s, 1H), 3.08 (br s, 1H), 3.03 (dd, J = 15.2 and 4.8 Hz, 1H), 2.70 (ddd, *J* = 15.2, 10.0 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 138.9, 136.1, 134.4, 132.6, 132.5, 131.2, 129.0, 126.8, 126.5, 121.1, 118.4, 117.7, 111.1, 109.1, 51.3, 50.7, 25.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{18}H_{16}Cl_2N_3O$: 360.0665. Found: 360.0672.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8a**)



2a **8a**

To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (36.0 mg, 0.096 mmol) and methylamine solution (2.0 mL, 33 wt. % in absolute ethanol, 16.1 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 16 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **8a (**35.5 mg, 99 % yield).

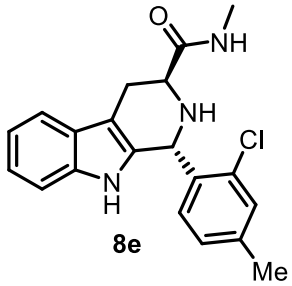


8a

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8a**)

$[\alpha]_D^{21.0}$ = -41.4° (c = 0.63, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 7.0 and 1.0 Hz, 1H), 7.14 (td, *J* = 7.5 and 1.0 Hz, 1H), 7.05 (dd, *J* = 8.0 and 2.0 Hz, 1H), 6.89 (d, *J* = 4.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 3.49 (dd, *J* = 10.0 and 5.0 Hz, 1H), 3.31 (dd, *J* = 15.5 and 4.5 Hz, 1H), 2.84 (ddd, *J* = 15.5, 10.0 and 1.0 Hz, 1H), 2.77 (d, *J* = 4.5 Hz, 3H), 2.05 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 136.8, 136.3, 135.0, 134.6, 131.4, 131.1, 129.9, 126.8, 122.5, 119.8, 118.5, 111.4, 111.0, 52.3, 51.9, 25.9, 24.8. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}Cl_2N_3O$: 374.0821. Found: 374.0830.

(1*R*,3*S*)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxa mide (**8e**)

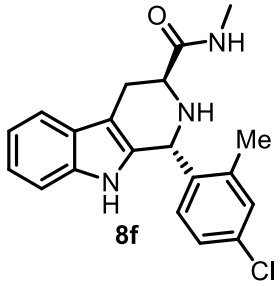


8e

(1*R*,3*S*)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxa mide (**8e**) was prepared in 99 % yield from (1R,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2e**) following the procedure employed for preparation of **8a**.

$[\alpha]_D^{21.0}$ = -39.0° (c = 0.68, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.17 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.12 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.96 (d, *J* = 4.8 Hz, 1H), 6.86 (dd, *J* = 7.6 and 0.8 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.57 (s, 1H), 3.54 (dd, *J* = 10.0 and 4.8 Hz, 1H), 3.28 (dd, *J* = 15.6 and 4.8 Hz, 1H), 2.85 (ddd, *J* = 15.6, 10.0 and 1.2 Hz, 1H), 2.75 (d, *J* = 4.8 Hz, 3H), 2.29 (s, 3H), 2.01 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 139.6, 136.2, 135.1, 133.9, 132.2, 130.4, 130.0, 127.3, 126.9, 122.1, 119.5, 118.4, 110.9, 110.8, 52.3, 51.9, 25.8, 24.7, 20.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}ClN_3O$: 354.1368. Found: 354.1383.

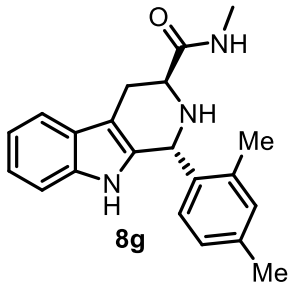
(1*R*,3*S*)-1-(4-chloro-2-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8f**)



8f

(1*R*,3*S*)-1-(4-chloro-2-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8f**) was prepared in 64 % yield from (1R,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2f**) following the procedure employed for preparation of **8f**.
$[\alpha]_D^{21.0}$ = -47.9° (c = 0.63, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.27 (dt, *J* = 7.6 and 1.2 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.19 (td, *J* = 8.0 and 1.6 Hz, 1H), 7.14 (td, *J* = 7.2 and 1.2 Hz, 1H), 6.95 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.80 (d, *J* = 4.8 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 3.49 (dd, *J* = 10.0 and 4.8 Hz, 1H), 3.33 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.82 (ddd, *J* = 16.0, 10.0 and 1.2 Hz, 1H), 2.76 (d, *J* = 4.8 Hz, 3H), 2.53 (s, 3H), 1.92 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 139.1, 137.0, 136.2, 133.5, 132.8, 130.7, 130.2, 126.9, 125.6, 122.3, 119.7, 118.4, 111.1, 110.9, 52.1, 52.0, 25.9, 24.7, 19.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{21}ClN_3O$: 354.1368. Found: 354.1373.

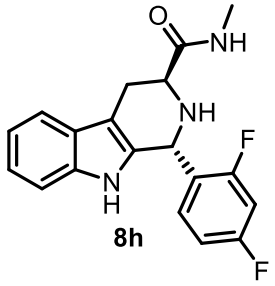
(1*R*,3*S*)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8g**)



8g

(1*R*,3*S*)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8g**) was prepared in 99 % yield from (1*R*,3*S*)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2g**) following the procedure employed for preparation of **8a**.
$[\alpha]_D^{21.0}$ = -46.5° (c = 0.99, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.24 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.16 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.12 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.05 (s, 1H), 6.87 (q, *J* = 5.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 3.53 (dd, *J* = 10.0 and 4.8 Hz, 1H), 3.31 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.82 (ddd, *J* = 16.0, 10.0 and 1.2 Hz, 1H), 2.73 (d, *J* = 5.2 Hz, 3H), 2.50 (s, 3H), 2.26 (s, 3H), 1.91 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 137.7, 136.9, 136.2, 135.5, 133.6, 131.6, 128.9, 127.0, 126.2, 122.0, 119.5, 118.3, 110.8, 110.7, 52.1, 52.0, 25.8, 24.6, 20.9, 19.0. HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{24}N_3O$: 334.1914. Found: 334.1898.

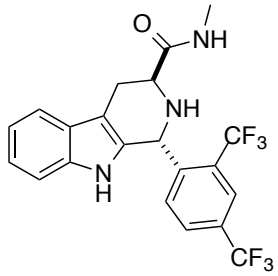
(1*R*,3*S*)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8h**)



8h

(1*R*,3*S*)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8h**) was prepared in 99 % yield from (1*R*,3*S*)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2h**) following the procedure employed for preparation of **8a**.
$[\alpha]_D^{21.0}$ = -70.4° (c = 0.75, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.76 (q, *J* = 4.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.29 (ddd, *J* = 10.4, 9.6 and 2.8 Hz, 1H), 7.25 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.06 (td, *J* = 7.2 and 1.2 Hz, 1H), 6.99 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.94 (td, *J* = 8.4 and 2.4 Hz, 1H), 6.75 (dt, *J* = 6.8 and 8.4 Hz, 1H), 5.54 (s, 1H), 3.42 (br s, 1H), 3.11 (br s, 1H), 3.01 (dd, *J* = 15.2 and 4.8 Hz, 1H), 2.69 (ddd, *J* = 15.2, 10.0 and 0.8 Hz, 1H), 2.60 (d, *J* = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (s), 161.6 (dd, *J* = 244 and 12 Hz), 160.4 (dd, *J* = 248 and 12), 136.1 (s), 132.7 (s), 131.0 (dd, *J* = 10 and 6 Hz), 126.6 (s), 126.4 (dd, *J* = 14 and 4 Hz), 121.0 (s), 118.4 (s), 117.7 (s), 111.1 (s), 110.5 (dd, *J* = 21 and 4 Hz), 109.0 (s), 103.9 (t, *J* = 26 Hz), 51.6 (s), 47.3 (d, *J* = 2 Hz), 25.4 (s), 25.1 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.8 (pent, *J* = 7.8 Hz), -114.2 (q, *J* = 9.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{18}F_2N_3O$: 342.1412. Found: 342.1429.

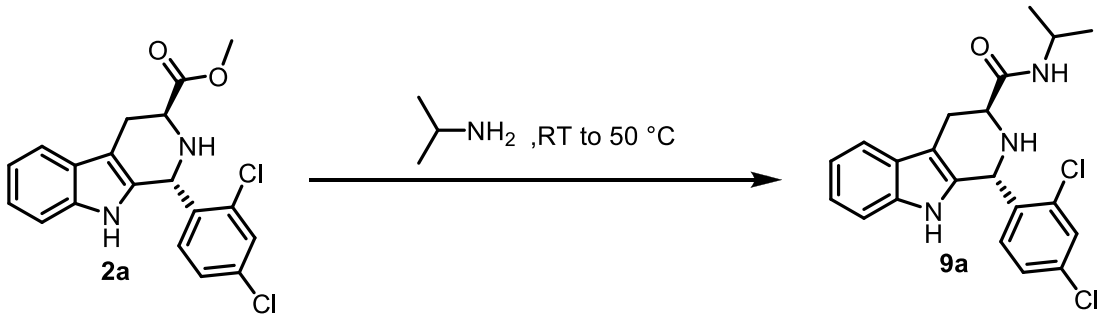
(1*R*,3*S*)-1-(2,4-bis(trifluoromethyl)phenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8j**)



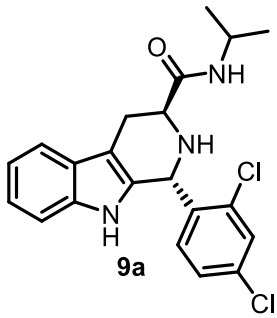
(1*R*,3*S*)-1-(2,4-bis(trifluoromethyl)phenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**8j**) was prepared in 77 % yield from (1*R*,3*S*)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**4j**) following the procedure employed for preparation of **8a**.
$[\alpha]_D^{21.0}$ = -57.9° (c = 0.71, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.28 (dt, *J* = 7.6 and 0.8 Hz, 1H), 7.21 (td, *J* = 7.6 and 1.2 Hz, 2H), 7.17 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.83 (d, *J* = 5.2 Hz, 1H), 5.74 (s, 1H), 3.61 (dd, *J* = 13.2 and 8.8 Hz, 1H), 3.35 (dd, *J* = 16.0 and 5.2 Hz, 1H), 2.96 (ddd, *J* = 16.0, 9.2 and 1.6 Hz, 1H), 2.78 (d, *J* = 5.2 Hz, 3H), 2.18 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (s), 143.5 (s), 136.4 (s), 131.3 (s), 130.9 (q, J = 33 Hz), 130.8 (s), 129.7 (q, J = 31 Hz), 128.7 (q, J = 4 Hz), 126.8 (s), 124.2 (q, J = 4 Hz), 123.9 (q, J = 267 Hz), 123.1 (q, J = 266 Hz), 122.8 (s), 120.0 (s), 118.7 (s), 111.5 (s), 111.0 (s), 52.4

(s), 50.8 (s), 26.0 (s), 24.4 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -58.4, -62.9. HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{18}F_6N_3O$: 442.1349. Found: 442.1356.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N-isopropyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamid e (**9a**)



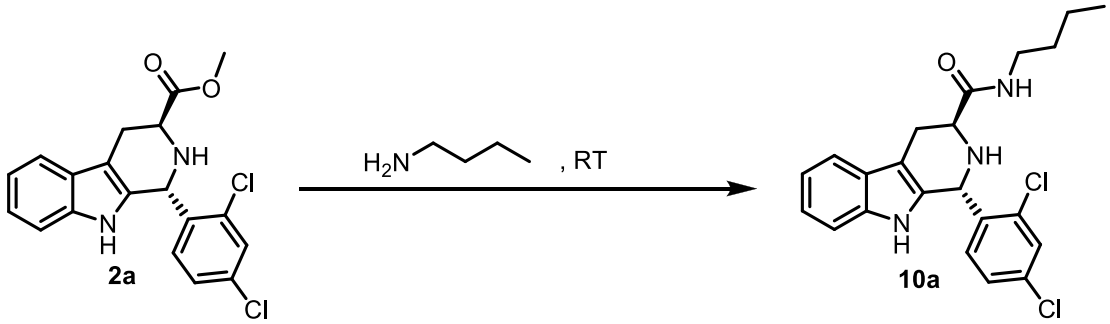
To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (76.0 mg, 0.2 mmol) and isopropylamine (1.0 mL, 58.8 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 24 hours and then at 50 °C for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **9a (**37.0 mg, 47 % isolated yield) and the starting material **2a** (29.2 mg, 38 % yield).



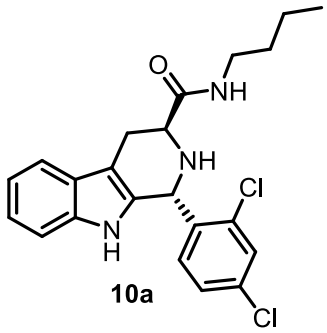
(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N-isopropyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamid e (**9a**)

$[\alpha]_D^{21.0}$ = -33.8° (c = 0.77, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.18 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.12 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.06 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.53 (s, 1H), 3.96 (m, 1H), 3.47 (dd, *J* = 9.2 and 4.8 Hz, 1H), 3.23 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, *J* = 16.0, 9.2 and 1.6 Hz, 1H), 1.91 (br s, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.9, 136.3, 134.9, 134.5, 131.3, 131.0, 129.9, 126.9, 126.8, 122.4, 119.7, 118.5, 111.0, 110.9, 52.4, 51.6, 41.1, 24.6, 22.7, 22.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{21}H_{22}Cl_2N_3O$: 402.1134. Found: 402.1155.

(1*R*,3*S*)-N-butyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**10a**)



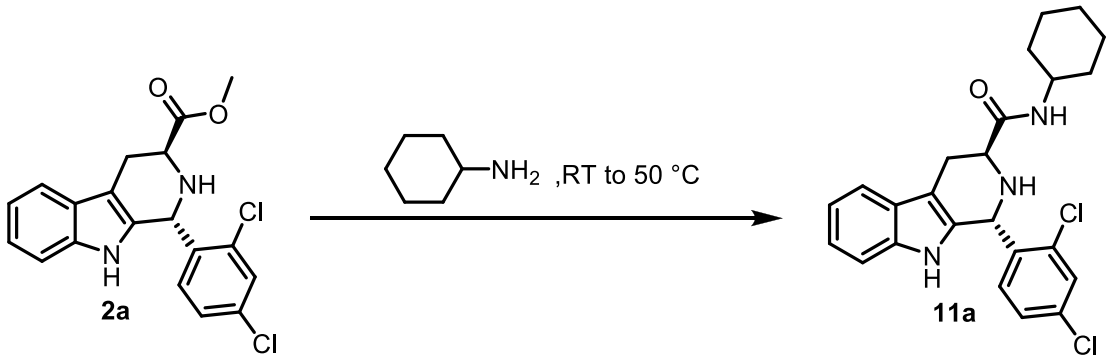
To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (76.0 mg, 0.2 mmol) and n-butylamine (1.0 mL, 10.1 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **10a (**80.0 mg, 96 % yield).



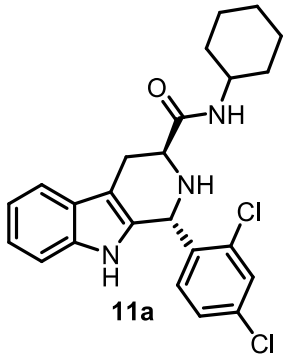
(1*R*,3*S*)-N-butyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**10a**)

$[\alpha]_D^{21.0}$ = -35.0° (c = 0.96, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.27 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.18 (td, *J* = 6.8 and 1.2 Hz, 1H), 7.11 (td, *J* = 7.6 and 1.2 Hz, 1H), 7.03 (dd, *J* = 8.0 and 2.0 Hz, 1H), 6.91 (t, *J* = 6.0 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.51 (s, 1H), 3.45 (dd, *J* = 10.0 and 4.8 Hz, 1H), 3.25 (dd, *J* = 16.0 and 4.8 Hz, 1H), 3.16 (m, 2H), 2.84 (ddd, *J* = 16, 10.0 and 1.2 Hz, 1H), 1.93 (br s, 1H), 1.45 (m, 2H), 1.30 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 136.9, 136.3, 134.9, 134.4, 131.4, 131.0, 129.8, 126.8, 122.3, 119.6, 118.5, 111.1, 111.0, 52.4, 51.7, 38.9, 31.5, 24.7, 20.1, 13.7. HRMS (ESI) $[M+H]^+$ calculated for $C_{22}H_{24}Cl_2N_3O$: 416.1291. Found: 416.1275.

(1*R*,3*S*)-N-cyclohexyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**11a**)



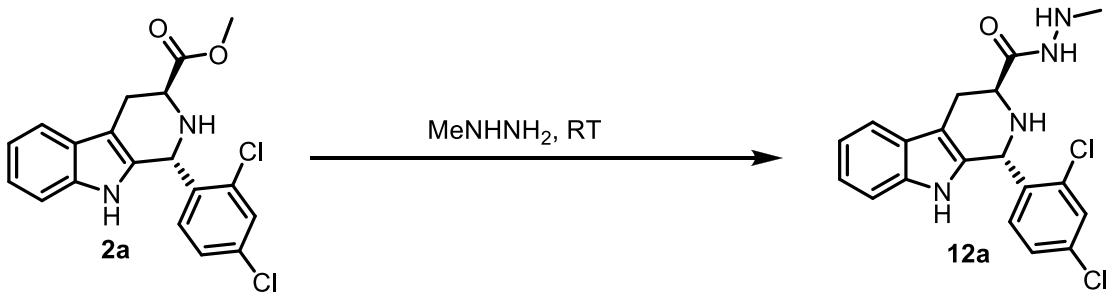
To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (76.0 mg, 0.2 mmol) and cyclohexylamine (1.0 mL, 43.7 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 24 hours and then at 50 °C for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **11a (**53.0 mg, 60 % isolated yield) and the starting material **2a** (29.0 mg, 38 % yield).



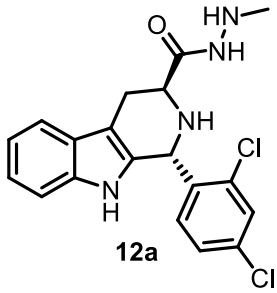
(1*R*,3*S*)-N-cyclohexyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**11a**)

$[\alpha]_D^{21.0}$ = -33.8° (c = 0.39, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.18 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.11 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.05 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 1H), 3.66 (m, 1H), 3.47 (dd, *J* = 9.2 and 4.8 Hz, 1H), 3.22 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, *J* = 16.0, 9.2 and 1.6 Hz, 1H), 1.85 (m, 3H), 1.62 (m, 3H), 1.31 (m, 2H), 1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 136.9, 136.3, 134.9, 134.5, 131.4, 131.0, 129.8, 126.9, 126.8, 122.3, 119.6, 118.5, 111.0, 110.9, 52.5, 51.6, 47.7, 32.9, 32.8, 25.5, 24.7, 24.6, 24.5. HRMS (ESI) $[M+H]^+$ calculated for $C_{24}H_{26}Cl_2N_3O$: 442.1447. Found: 442.1448.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N'-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbohydrazide (**12a**)



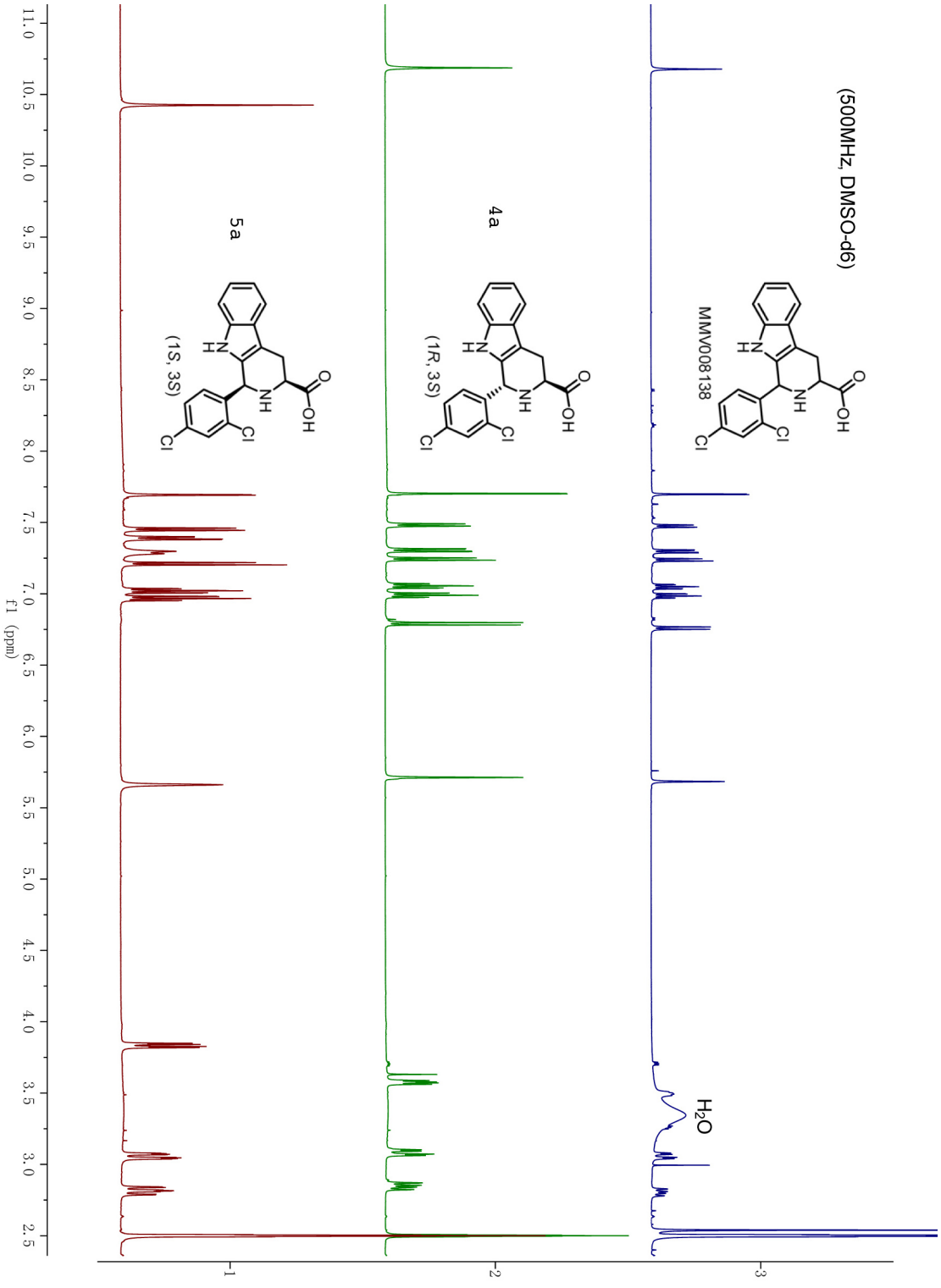
To a one-dram vial was added (1*R*,3*S*)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**2a**) (76.0 mg, 0.2 mmol) and methylhydrazine (1.0 mL, 19.0 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (20 : 1 : 1 DCM / EtOAc / EtOH) to give **12a (**61.0 mg, 78 % yield).



(1*R*,3*S*)-1-(2,4-dichlorophenyl)-N'-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbohydrazide (**12a**)

$[\alpha]_D^{21.0}$ = -29.0° (c = 1.25, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.28 (dt, *J* = 8.0 and 0.8 Hz, 1H), 7.20 (td, *J* = 7.2 and 1.2 Hz, 1H), 7.15 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.07 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.57 (s, 1H), 3.55 (dd, *J* = 9.6 and 4.8 Hz, 1H), 3.29 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, *J* = 16.0, 9.6 and 1.2 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.6, 136.2, 135.1, 134.6, 131.3, 131.0, 130.0, 126.9, 126.8, 122.5, 119.8, 118.5, 111.0, 110.9, 51.7 (2C), 39.3, 24.6. HRMS (ESI) $[M+H]^+$ calculated for $C_{19}H_{19}Cl_2N_4O$: 389.0930. Found: 389.0923.

B. Overlay of ^{1}H NMR Spectra of MMV008138, 4a, and 5a (500 MHz, d_6-DMSO)



MMV008138 and **4a** appear identical, and are easily distinguished from (1*S*,3*S*)-configured **5a** at the indole NH proton (near 10.5 ppm), at the low frequency aromatic doublet (6.75 ppm), and in the saturated ring signal near 3.6 ppm.

C. X-ray Structure Determination of 8a.

A colorless rod was cut into a prism (0.11 x 0.15 x 0.16 mm^3) and was centered on the goniometer of an Agilent Nova diffractometer operating with CuKα radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.[3] The Laue symmetry and systematic absences were consistent with the monoclinic space groups $P2_1$ and $P2_1/m$. As the sample was known to be enantiomerically pure, the chiral space group $P2_1$ was chosen. The structure was solved using SHELXS-2014[4] and refined using SHELXL-2014[4] via OLEX2.[5] The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms. A riding model was used for the aromatic and alkyl hydrogens. The H-atom positions of the N-H groups were located from the residual electron density map and refined independently. The isotropic displacement parameters of the N-H hydrogen atoms were constrained to $1.2U_{eq}$ of the attached nitrogen. The absolute configuration was established from anomalous dispersion effects [Flack x = -0.11(5);[6] Hooft P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = 0.000; P3(false) = 0.000, y = -0.013(5)].[5, 7] Olex2 was used for molecular graphics generation.[5]
CCDC 1042325 contains the supplementary crystallographic data for 8a. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre
via www.ccdc.cam.ac.uk/data_request/cif.

D. Biological Assays

Parasite Culture. *P. falciparum* Dd2 parasites (MRA-150, chloroquine-resistant (intermediate), pyrimethamine-resistant, mefloquine-resistant) were obtained from MR4 Malaria Reagent Repository (ATCC, Manassas, VA), a part of the BEI Resources Repository (NIAID, NIH). Parasites were maintained in O-positive human erythrocytes (Interstate Blood Bank Inc., Memphis, Tennessee) at 5% hematocrit in RPMI 1640 medium supplemented with 5 g/liter Albumax I (Gibco Life Technologies), 2 g/liter glucose (Sigma-Aldrich), 2.3 g/liter sodium bicarbonate (Sigma-Aldrich), 370 μM hypoxanthine (Sigma-Aldrich), 25 mM HEPES, and 20 mg/liter gentamicin (Gibco Life Technologies). The parasites were kept at 37°C under reduced-oxygen conditions (5.06% CO_2, 4.99% O_2, and 89.95% N_2).

Growth Inhibition and Rescue by Isopentenyl Diphosphate (IPP) Supplementation Assays. The effect of MMV008138 analogs was evaluated against asexual blood stages of *P. falciparum* parasites using the SYBR green assay as described previously.[8] The antimalarial activity of MMV008138 analogs was first evaluated against asexual parasites using four-point dilutions ranging from 10 μM to 1.25 μM. For active compounds, the half maximal inhibitory concentration (IC_{50}) were determined using eight- or ten-point dilutions at concentrations ranging from 20 μM to 0.02 μM in constant 0.1% DMSO (vehicle). The percentage of growth was normalized to that of untreated control parasites in the presence of 0.1% DMSO. Background determinations were made using uninfected erythrocytes. Two or more independent experiments were performed. The IC_{50} values were calculated with GraphPad Prism 6 (GraphPad Software Ltd.) using nonlinear regression curve fitting with variable slope (four parameters) and represent the average of two or more independent experiments and their standard deviation (S.D.). To assess whether compounds were specifically targeting the apicoplast,

the recovery of growth in the presence of inhibitor and IPP was performed as described previously.[8] Briefly, parasites were grown in the presence or absence of 200 μM IPP along with a serial dilution (10 μM to 0.02 μM) or single concentration (10 or 20 μM) of MMV008138 analogs. All conditions were set in 96-well half area plates using ring-stage parasite cultures (100 μl/well with 1% hematocrit and 1% parasitemia) and incubated for 72 h under normal culture conditions. Parasite growth was measured by a SYBR green assay.

***E. coli* Growth Inhibition Assays.** In order to investigate the effect of selected compounds against *E. coli*, strain BL21(DE3), an overnight culture of *E. coli* (37 °C, 200 rpm agitation) was diluted 100-fold into LB broth medium and incubated to an OD_{600} of ~0.6. The culture was then diluted 10,000-fold into LB broth medium. Then 750 μL of this *E. coli* inoculum was inoculated into a culture tube containing 750 μL of the test compounds previously diluted in LB broth medium at three concentrations (500 μM, 250 μM, and 125 μM). The final DMSO concentration was 5%. Cultures were incubated for 18 h at 37 °C and 200 rpm agitation. The following controls were performed: 100 μM fosmidomycin (FOS) treatment which targets the MEP pathway in *E. coli*, media without inoculum, 5% DMSO (vehicle of MMV008138 analogs), and control with inoculum alone (untreated). After 18h incubation, bacteria growth was measured using a cell density meter. The percentage of growth was normalized to that of untreated control bacteria and potential inhibition of growth of MMV008138 analogs was determined by comparison to the 5% DMSO control.

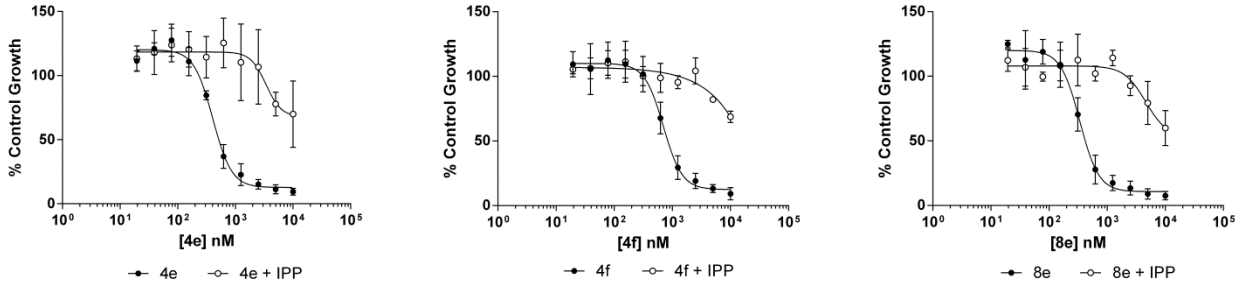


Figure S2: Dose-dependent activity (filled circles) and growth recovery of **P. falciparum** Dd2 strain parasites in the presence of 200 μM IPP (empty circles) after 72 h of incubation with each indicated analog. The data points and the error bars show the mean and S.D. of two or more independent experiments.

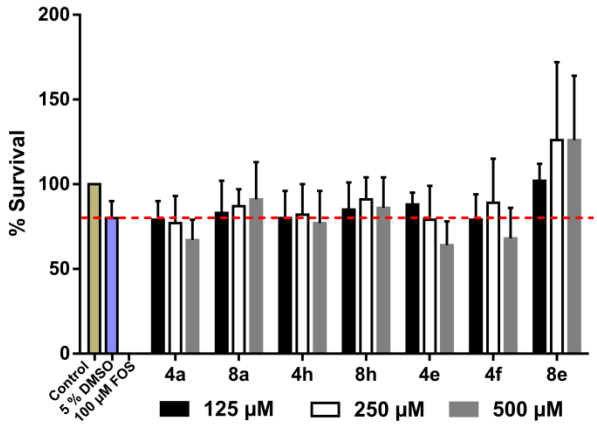


Figure S3: Dose-dependent activity of *E. coli* in the presence of MMV008138 analogs after 18 h of incubation with each indicated analog. The data represents the mean and S.D. of three independent experiments. The percentage of growth was normalized to that of untreated control bacteria and potential inhibition of growth of MMV008138 analogs was determined by comparison to the 5% DMSO control (red line).

E. References

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