Supplementary Material (ESI) for Chemical Communications

Supporting materials

Facile, solvent and ligand free iron catalyzed direct functionalization of N-protected tetrahydroisoquinolines and isochroman

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Experimental details and characterization data for all new compounds

Abbreviations

Abbreviation	Full name
Et_2O	Diethyl ether
EtOH	Ethanol
EtOAc	Ethyl acetate
equiv.	Equivalent
J	Coupling constant
PE	Petrol ether
MeOH	Methanol
M.p.	Melting point
MPLC	Medium pressure liquid chromatography
rf	Reflux
rt	Room temperature
tBHP	Tert-butyl hydroperoxide
TLC	Thin layer chromatography

General

Caution

Mixing a metal salt and peroxide can cause explosion. See: Jones, A. K.; Wilson, T. E.; Nikam, S. S. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed.; John Wiley & Sons, Inc. 1995, 2, 880. In our cases, such a problem was not observed, even if the reactions were scaled up to 5.0 mmol.

General Notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification.

Iron(III)-nitrate specifications

Typical Analysis

Material: Iron (III) nitrate nonahydrate(99.999%-Fe) PURATREM
Catalog Number: 93-2672
Color and Form: green-yellow solid
Elemental analysis:

Al	3ppm
Ca	3ppm
Mn	1ppm
Si	1ppm
Cu	<1ppm
Mg	<1ppm
Au	<1ppm

Quality Control Manager

October 26, 2009

Chromatography

Flash chromatography

Flash column chromatography was performed on silica gel 60 from Merck (40-63µm) whereas separations were carried out using a Büchi Sepacore™ MPLC system. For thin layer chromatography (TLC) aluminum coated silica gel was used and signals were visualized with UV light (254nm).

GC-MS

GC-MS runs were performed on a Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30m x 0.32 mm ID) and applying one of the following standardized temperature profiles:

- STD 80 - 280°C method
  2 minutes at 80°C 80°C, 10°C/min until 280°C, 15 minutes at 280°C
- STD 110 – 280°C method
  2 minutes at 110°C, 10°C/min until 280°C, 15 minutes at 280°C

HR-MS

HR-MS was carried out by E. Rosenberg at the Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method

All samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+H]^+$), and further data or information were not taken into consideration.

Instrumental parameters

Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient Pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A).

MS System: Shimadzu IT-TOF-MS with electrospray interface.

Chromatography (parameters: Short_Col_PI_NI_MS2):

Column: Phenomenex Prodigy ODS(3), 30 mm x 4.6 mm, 3 µm particles, operated at 40°C; Gradient: 0 min: 70% A, 30% B (1 min); linear gradient to 5 min to 10% A, 90% B (hold 4 min); at 9.01 min back to 70% A, 30% B, hold until 10.0 min);. A: acetonitrile+0.1% formic acid, B: H_2O + 0.1% formic acid. Column flow: 0.5 mL/min; injection volume: 2 µl.

MS Parameters:

MS parameters as in autotune. Data recorded with detector voltage at autotune value.

Scan range: 100-600 amu for both, MS and MS/MS (PI) detection. ES ionization.

Preparative HPLC

Preparative HPLC was performed on a Shimadzu LC-8A device with an SIL-10AP autosampler, SPD-20A dectector and FRC-10A fraction collector. For seperation the following conditions were used: column: Phenomenex Luna 10 µm RP18(2) 100A, 250 x 21.20 mm; Eluent: MeOH:Water:70:30 – 90:10 (linear gradient), 40 minutes; Injection volume: 3 mL, Flow: 20 mL/min; Detection wavelength: 254 nm.

Lyophilizer Compounds purified by preparative HPLC, were directly lyophilized using a LABCONCO FreeZone 2.5 lyophilizing system.

Microwave Reactions were performed on a BIOTAGE Initiator^{TM} sixty microwave unit.

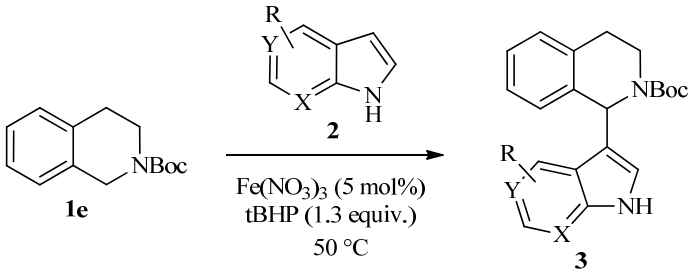
Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

NMR-spectroscopy

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 200 (200 MHz) or on a Bruker Advance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported as ppm downfield from TMS (tetramethylsilane) as internal standard with multiplicity, number of protons, allocation, and coupling constant(s) in Hertz.

General procedures

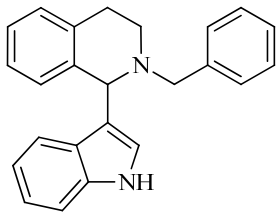
Indolation of N-Boc-protected THIQ



A mixture of 2-(tertbutyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline **1e** (200 mg, 0.857 mmol, 1.0 equiv.), iron(III)-nitrate nonahydrate (17.3 mg, 42.9 µmol, 0.05 equiv.), and indole (1.03 mmol, 1.2 equiv.) was placed into a 5 mL glass vial. TBHP (203 µL, 5.5 M in decane, 1.3 equiv.) was added dropwise at 0°C under air and the reaction mixture stirred for 10 minutes at 0°C. The neat mixture was then smoothly heated up to 50°C and stirred for 15 hours in a heating block. The reaction was monitored by TLC and/or GC-MS. The dark brown slurry was diluted with DCM (3 mL) and directly subjected to flash chromatography. The desired, pure product was obtained after MPLC where the solvent mixture used for TLC was also used for column chromatography (100 g SiO_2).

Compounds **3b, 3c, 3d** were synthesized according to the same procedure as mentioned above.

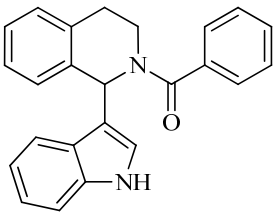
2-Phenylmethyl-1-(1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (3b)



$C_{24}H_{22}N_2$
MW: 338.44

Yield: 7 % (20 mg, 0.059 mmol); pale yellow solid; **M.p.:** 55-60°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.97 (bs, 1H), 7.60 (d, 1H, ^{3}J= 7.8Hz), 7.33- 6.85 (m, 13H), 4.96 (s, 1H), 3.91 (d, 1H, ^{2}J=13.5Hz), 3.33 (d, 1H, ^{2}J=13.5), 3.22-2.94 (m, 2H), 2.83 (td, 1H, ^{3}J=9.1Hz, ^{3}J=5.8Hz), 2.64-2.44 (m, 1 H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 139.9 (s), 138.6 (s), 136.6 (s), 134.7 (s), 128.9 (2C, d), 128.3 (d), 128.0 (2C, d), 126.8 (s), 126.6 (d), 125.8 (d), 125.5 (d), 124.3 (d), 122.0 (d), 120.7 (d), 119.3 (d), 118.6 (s), 110.9 (d), 61.0 (d), 58.8 (t), 47.0 (t), 28.7 (t); **MS (EI+):** m/z (rel. Intensity): 338 (M^{+},75), 337 (56), 247 (32), 245 (16), 231 (22), 219 (50), 218 (100), 217 (35), 130 (11), 106 (15), 91 (31); **HRMS (ESI^{+}):** exact mass calculated for $C_{24}H_{22}N_2$: 339.1856. Found: 339.1852

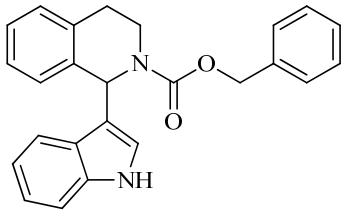
(1-(1H-Indol-3-yl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (3c)



$C_{24}H_{20}N_2O$
MW: 352.43

Yield: 22 % (67 mg, 0.190 mmol); brown solid; **M.p.:** 226-228°C; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ ppm: 8.34 (bs, 1H), 7.85 (d, ^3J = 7.6 Hz, 1H), 7.54-7.18 (m, 12H), 7.13 (t, ^3J = 7.3 Hz, 1H), 6.68 (s, 1H), 3.66 (dd, ^2J = 13.2, 5.7 Hz, 1H), 3.47 (dt, ^2J = 13.4, ^3J=3.3 Hz, 1H), 3.11-2.97 (m, 1H), 2.75 (d, ^2J = 14.6 Hz, 1H); **^{13}C NMR (101 MHz, *CDCl$_3$*)** δ ppm: 169.9, 136.6, 136.4, 135.7, 133.8, 129.3, 128.9, 128.8, 128.5(2C), 126.8, 126.4 (2C), 126.1, 125.7, 122.3, 120.3, 120.0, 118.6, 111.1, 49.0, 40.6, 29.4
^{13}C NMR (101 MHz, DEPT, *CDCl$_3$*) δ ppm: 129.4 (d), 128.9 (d), 128.8 (d), 128.5 (2C, d), 126.9 (d), 126.4 (2C, d), 126.1 (d), 125.7 (d), 122.3 (d), 120.3 (d), 120.0 (d), 111.1 (d), 49.0 (d), 40.6 (t), 29.5 (t); **MS (EI+):** m/z (rel. Intensity): 352 (M^+, 40), 248 (20), 247 (100), 232 (32), 218 (21), 217 (21), 130 (18), 115 (12), 105 (56), 77 (44); **HRMS (ESI$^+$):** exact mass calculated for $C_{24}H_{20}N_2O$: 353.1648. Found: 353.1639

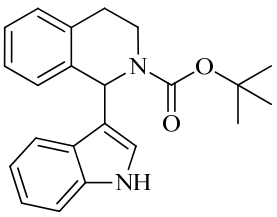
Phenylmethyl-1-(1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3d)



$C_{25}H_{22}N_2O_2$
MW: 382.45

Yield: 41 % (135 mg, 0.353 mmol); white powder; **M.p.:** 62-64°C; **^{1}H NMR (200 MHz, CDCl$_3$)** δ ppm: 8.19 (bs, 1H), 7.82-6.88 (m, 13H), 6.84-6.48, (m, 2H), 5.46-5.10 (m, 2H), 4.30-3.80(m, 1H), 3.36-2.90 (m, 2H), 2.73 (dd, ^{2}J=16.7, ^{3}J=2.7, 1H); **^{13}C NMR (50 MHz, APT, CDCl$_3$)** δ ppm: 154.9 (s), 136.7 (s), 136.3 (s), 136.0 (s), 134.6 (s), 129.0 (d), 128.5 (3C, d), 128.0 (d), 127.7 (d), 126.7 (d), 126.4 (s), 125.8 (d), 125.0 (d), 122.2 (d), 120.2 (d), 119.8 (d), 118.5 (s), 111.0 (d), 67.1 (t), 51.5 (d), 37.4 (t), 28.6 (t); **MS (EI+):** m/z (rel. Intensity): 382 (M^+,3), 292 (7), 291 (40), 248 (20), 247 (100), 218 (8), 217 (7), 130 (12), 103 (5), 91 (6); **HRMS (ESI$^+$):** exact mass calculated for $C_{25}H_{22}N_2O_2$: 383.1754. Found: 383.1722

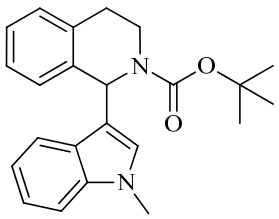
1,1-Dimethylethyl-1-(1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3e)



$C_{22}H_{24}N_2O_2$
MW: 348.44

Yield: 54 % (160 mg, 0.459 mmol); off white powder; **M.p.:** 137-139 °C; **^{1}H NMR (400 MHz, *DMSO-D$_6$*)** δ ppm: 10.95 (s, 1H), 7.72-7.44 (bs, 1H), 7.36 (d, ^3J = 8.1 Hz, 1H), 7.22 (d, ^3J = 3.1 Hz, 2H), 7.19-7.11 (bs, 2H), 7.08 (t, ^3J = 7.6 Hz, 1H), 6.96 (t, ^3J = 7.4 Hz, 1H), 6.85-6.37 (m, 2H), 4.11-3.77 (bs, 1H), 3.07 (dt, ^2J = 12.8, ^3J = 4.3 Hz, 1H), 2.96-2.84 (m, 1H), 2.77 (d, ^2J = 15.8 Hz, 1H), 1.46 (s, 9H); **^{13}C NMR (101 MHz, *DMSO-D$_6$*)** δ ppm: 153.4, 136.3, 136.1, 134.4, 128.9, 127.9, 126.5, 126.0, 125.6, 125.0, 121.2, 119.0, 118.6, 117.0, 111.5, 78.9, 50.1, 37.1, 28.1, 27.8; **^{13}C NMR (101 MHz, DEPT, *DMSO-D$_6$*)** δ ppm: 129.5 (d), 128.5 (d), 127.1 (d), 126.1 (d), 125.6 (d), 121.7 (d), 119.5 (d), 119.2 (d), 112.1 (d), 50.7 (d), 37.8 (t), 28.6 (q, 3C), 28.4 (t); **MS (EI+):** m/z (rel. Intensity): 248 (M^+-100, 46), 247 (91), 245 (100), 230 (18), 218 (53), 130 (52), 121 (46), 117 (38), 108 (50), 103 (21)

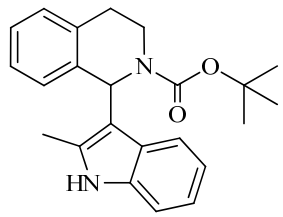
1,1-Dimethylethyl-1-(1-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3f)



$C_{23}H_{26}N_2O_2$
MW: 362.46

Yield: 65 % (203 mg, 0.560 mmol); white powder; **M.p.:** 70-72°C; **^{1}H NMR (200 MHz CDCl$_3$)** δ ppm: 7.97-7.67 (bs, 1H), 7.36-7.08 (m, 7H), 6.91-6.56 (bs, 1H), 6.49 (s, 1H), 4.32-3.88 (m, 1H), 3.70 (s, 3H), 3.30-2.96 (m, 2H), 2.88-2.68 (m, 1H), 1.58 (s, 9H); **^{13}C NMR (50 MHz, APT, CDCl$_3$)** δ ppm: 154.2 (s), 137.1 (s), 136.5 (s), 135.0 (s), 129.4 (d), 129.0 (d), 128.4 (d), 127.0 (s), 126.5 (d), 125.6 (d), 121.8 (d), 120.4 (d), 119.2 (d), 117.4 (s), 109.1 (d), 79.5 (s), 50.4 (d), 37.5 (t), 32.6 (q), 28.6 (q, 3C), 28.4 (t); **MS (EI+):** m/z (rel. Intensity): 262 (M^+-100, 48), 261 (100), 259 (33), 245 (12), 232 (22), 217 (20), 157 (6), 130 (22), 103 (7), 77 (5); **HRMS (ESI$^+$):** exact mass calculated for $C_{23}H_{26}N_2O_2$: 363.2067. Found: 363.2072.

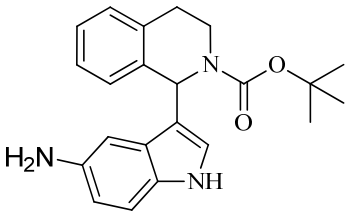
1,1-Dimethylethyl-1-(2-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3g)



$C_{23}H_{26}N_2O_2$
MW: 362.46

Yield: 23 % (71 mg, 0.196 mmol); pale yellow powder; **M.p.:** 81-84°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.91 (bs, 1H), 7.26-7.17 (m, 3H), 7.13-6.98 (m, 4H), 6.94-6.83 (m, 1H), 6.66 (s, 1H), 4.14 (dd, ^2J =11.8, ^3J= 3.5 Hz, 1H), 3.80-3.00 (m, 2H), 2.78 (dd, ^{2}J=16.7 Hz, ^{3}J=3.0 Hz, 1H), 2.24 (s, 3H), 1,49 (s, 9H); **^{13}C NMR (50 MHz, APT, CDCl$_3$)** δ ppm: 154.2 (s), 137.0 (s), 134.90 (s), 134.87 (s), 133.9 (s), 129.0 (d), 128.5 (s), 128.3 (d), 126.5(d), 126.3 (d), 120.9 (d), 119.5(d), 119.3 (d), 113,3 (s), 110.1 (d), 79.7 (s), 51.0 (d), 38.3 (t), 28.6 (t), 28.5 (q, 3C), 12.6 (q); **MS (EI+):** m/z (rel. Intensity): 262 (M^+-100, 62), 261 (100), 245 (61), 244 (37), 219 (21), 218 (44), 131 (34), 130 (85), 103 (18), 77 (20); **HRMS (ESI$^+$):** exact mass calculated for $C_{23}H_{26}N_2O_2$: 385.1886. Found: 385.1896.

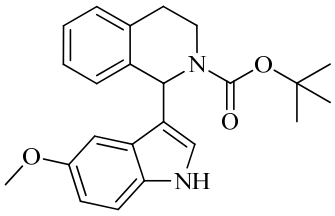
1-(5-Amino-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)- 1,1-dimethylethyl-carboxylate (3h)



$C_{22}H_{25}N_3O_2$
MW: 363.45

Yield: 16 % (50 mg, 0.138 mmol); dark brown solid; **M.p.:** 96-98°C; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ ppm: 7.86 (s, 1H), 7.24-7.19 (m, 2H), 7.14 (d, ^3J = 8.6 Hz, 2H), 7.10 (t, ^3J = 7.3 Hz, 1H), 7.03 (d, ^3J = 7.7 Hz, 1H), 6.78 (t, J = 2.7 Hz, 1H), 6.68 (d, ^3J = 8.6 Hz, 1H), 6.66 (s, 1H), 5.13 (s, 1H, 1-CH), 4.07 (dd, ^2J = 13.6, ^3J = 5.7 Hz, 1H), 3.41 (dt, ^2J = 13.3, ^3J = 3.6 Hz, 1H), 3.22-3.09 (m, 1H), 2.82 (dd, ^2J = 16.4, ^3J = 2.9 Hz, 1H), 1.48 (s, 9H); **^{13}C NMR (101 MHz, APT, *CDCl$_3$*)** δ ppm: 155.5 (s), 139.9 (s), 137.4 (s), 134.8 (s), 130.8 (s), 128.94 (d), 128.90 (d), 128.4 (s), 126.5 (d), 126.3 (d), 123.7 (d), 116.0 (s), 113.8 (d), 111.7 (d), 101.3 (d), 80.2 (s), 53.8 (d), 39.2 (t), 28.5 (t), 28.4 (q, 3C); **MS (EI+):** m/z (rel. Intensity): 263 (M^+-100, 48), 262 (30), 258 (40), 246 (75), 245 (100), 233 (13), 218 (17), 132 (23), 130 (20)

1,1-Dimethylethyl-1-(5-methoxy-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3i)

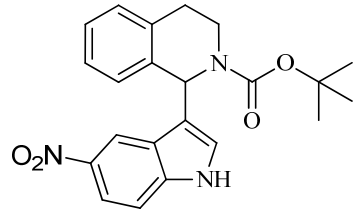


$C_{23}H_{26}N_2O_3$
MW: 378.46

Yield: 43 % (140 mg, 0.370 mmol); off white powder; **M.p.:** 69–72°C; **^{1}H NMR (400 MHz, *DMSO-D$_6$*)** δ ppm: 10.91-10.67 (bs, 1H), 7.30-7.03 (m, 6H), 6.73 (dd, ^3J=8.7 Hz, ^4J= 1.6 Hz, 1H), 6.54 (s, 1H), 6.44 (s, 1H), 4.07-3.78 (m, 1H), 3.69 (s, 3H), 3.04 (dt, ^2J=12.7 Hz, ^3J= 3.8 Hz, 1H), 2.94-2.82 (m, 1H), 2.76 (d, ^2J=15.9 Hz, 1H), 1.46 (s, 9H); **^{13}C NMR (101 MHz, APT, *DMSO-D$_6$*)** δ ppm: 153.5 (s), 153.1 (s), 136.0 (s), 134.5 (s), 131.4 (s), 128.9 (d), 128.0 (d), 126.5 (d), 126.4 (s), 126.0 (d), 116.8 (s), 112.2 (d), 111.6 (d), 100.7 (d), 78.8 (s), 54.9 (q), 50.0 (d), 37.1 (t), 28.0 (3C, s), 27.9 (t); **MS (EI+):** m/z (rel. Intensity): = 278 (M^+-100, 59), 277 (100), 261 (53), 249 (22), 248 (24), 233 (12), 218 (10), 204 (10), 132 (10), 130 (14); **HRMS (ESI$^+$)** exact mass calculated for $C_{23}H_{26}N_2O_3$: 401.1836. Found: 401.1822.

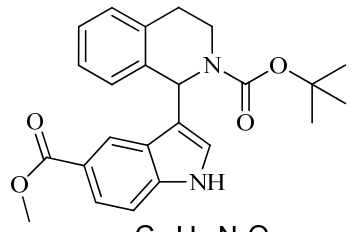
1,1-Dimethylethyl-1-(5-nitro-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3j)

Yield: 66 % (222 mg, 0.564 mmol); bright yellow solid; **M.p.:** 219–221°C; **^{1}H NMR (200 MHz, *DMSO-D$_6$*)** δ ppm: 11.86-11.50 (m, 1H), 8.73 (s, 1H), 8.02 (dd, J = 9.0, 2.2 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.29-7.09 (m, 4H), 6.80 (s, 1H), 6.62 (s, 1H), 4.09-3.76 (m, 1H), 3.07-2.63 (m, 3H), 1.50 (s, 9H); **^{13}C NMR (50 MHz, APT, *DMSO-D$_6$*)** δ ppm: 153.3 (s), 140.6 (s), 139.6 (s), 135.1 (s), 134.5 (s), 129.0 (d), 128.9 (d), 128.0 (d), 126.8 (d), 125.7 (d), 125.3 (s), 119.9 (s), 116.8 (d), 116.4 (d), 112.1 (d), 79.5 (s), 49.9 (d), 37.0 (t), 27.9 (q, 3C), 27.7 (t); **MS (EI+):** m/z (rel. Intensity): 393 (M^+-100, 43), 292 (100), 276 (10), 263 (24), 246 (34), 217 (30), 189 (8), 146 (6), 132 (6), 130 (12); **HRMS (ESI$^+$)** exact mass calculated for $C_{22}H_{23}N_3O_4$: 416.1581. Found: 416.1589.



$C_{22}H_{23}N_3O_4$
MW: 393.44

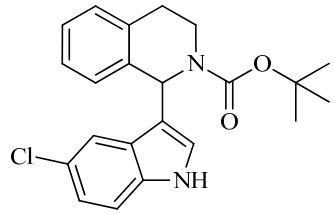
1,1-Dimethylethyl-1-(5-(methoxycarbonyl)-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3k)



$C_{24}H_{26}N_2O_4$
MW: 406.47

Yield: 5 % (18 mg, 0.820 mmol); pale yellow powder; **M.p.:** 221–224°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 8.70-8.45 (bs, 1H), 8.63 (s, 1H), 7.91 (dd, ^3J= 8.6, ^4J=1.2 Hz, 1H), 7.34 (d, ^3J=8.6 Hz, 1H), 7.24-7.08 (m, 4H), 6.89-6.61 (m, 1H), 6.58 (d, *J* = 1.9 Hz, 1H), 4.27-3.93 (m, 1H), 3.90 (s, 3H), 3.18-2.90 (m, 2H), 2.83-2.60 (m, 1H), 1.62 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 168.2 (s), 154.2 (s), 139.2 (s), 135.8 (s), 134.9 (s), 129.1 (d), 128.2 (d), 126.8 (d), 126.4 (d), 126.0 (s), 125.6 (d), 123.7 (d), 122.7 (d), 121.5 (s), 120.1 (s), 111.0 (d), 80.7 (s), 51.6 (q), 51.2 (d), 36.2 (t), 28.4 (q, 3C), 28.1 (t); **MS (EI+):** m/z (rel. Intensity): 306 (M^+-100, 45), 305 (100), 289 (12), 276 (18), 247 (8), 244 (8), 217 (15), 189 (6), 144 (8), 130 (16); **HRMS (ESI$^+$):** exact mass calculated for $C_{24}H_{26}N_2O_4$: 429.1785. Found: 429.1771.

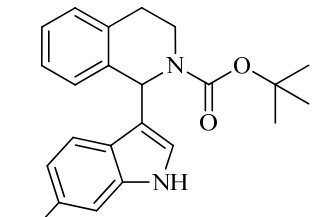
1-(5-Chloro-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-1,1-dimethylethyl-carboxylate (3l)



$C_{22}H_{23}ClN_2O_2$
MW: 382.88

Yield: 72 % (236 mg, 0.616 mmol); pale pink powder; **M.p.:** 202-204°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 8.25 (bs, 1H), 7.83 (d, ^{4}J=1.5Hz, 1H), 7.27-7.06 (m, 6H), 6.72-6.45 (bs, 1H), 6.55 (d, ^3J = 2.3 Hz, 1H), 4.20-3.90 (bs, 1H), 3.16-2.90 (m, 2H), 2.70 (dd, ^{2}J=12.2Hz, ^{3}J=1.3Hz, 1H), 1.57 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 154.2 (s). 135.8 (s), 135.0 (s), 134.7 (s), 129.2 (s), 134.7 (s), 129.1 (d), 128.3 (d), 127.5 (s), 126.8 (d), 126.1 (d), 125.7 (d), 125.5 (s), 122.6 (d),119.7 (d), 118.9 (s), 112.0 (d), 79.3 (s), 51.0 (d), 37.7 (t), 28.6 (q, 3C) 28.3 (t); **MS (EI+):** m/z (rel. Intensity): 284 (M^+-98, 13), 283 (38), 282 (M^+-100, 42) , 281 (100), 279 (14), 265 (9), 253 (21), 252 (22), 217 (30), 216 (11), 164 (8), 130 (26), 103 (9); **HRMS (ESI$^+$):** exact mass calculated for $C_{22}H_{23}N_2O_2Cl$: 405.1340. Found: 405.1350.

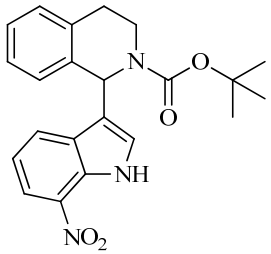
1-(6-Chloro-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-1,1-dimethylethyl-carboxylate (3m)



$C_{22}H_{23}ClN_2O_2$
MW: 382.88

Yield: 56 % (184 mg, 0.481 mmol); white powder; **M.p.:** 83-85°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 8.19 (bs, 1H), 7.68 (bs, 1H), 7.31 (d,^4J=1.7Hz, 1H), 7.23-7.10 (m, 4H), 7.05 (dd, ^3J=8.6Hz, ^4J=1.8Hz, 1H), 6.75-6.52 (m, 2H), 4.20-3.93 (bs, 1H), 3.20-2.90 (m, 2H), 2.81-2.63 (m, 1H), 1.52 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 154.4 (s), 136.8 (s), 135.9 (s), 134.9 (s), 129.1 (d), 128.3 (d), 128.2 (s), 126.7 (d), 125.7 (d), 125.4 (d), 125.1 (s), 121.2 (d), 120.5 (d), 119.2 (s), 110.9 (d), 79.8 (s), 50.5 (d), 37.5 (t), 28.5 (q, 3C), 28.4 (t); **MS (EI+):** m/z (rel. Intensity): 284 (M^+-98, 14), 283 (33), 282 (M^+-100, 40) , 281 (100), 279 (22), 265 (22), 253 (35), 252 (25), 217 (30), 216 (16), 164 (9), 130 (27), 103 (12) **HRMS (ESI$^+$):** exact mass calculated for $C_{22}H_{23}N_2O_2Cl$: 405.1340. Found: 405.1339.

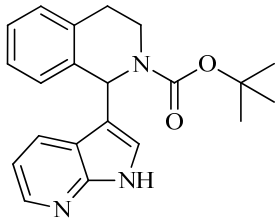
1,1-Dimethylethyl-1-(7-nitro-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3n)



$C_{22}H_{23}N_3O_4$
MW: 393.44

Yield: 70 % (235 mg, 0.597 mmol); bright yellow powder; **M.p.:** 88-91°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 9.77 (bs, 1H), 8.34-8.05 (m, 2H), 7.28-7.08 (m, 5H), 6.86-6.63 (m, 2H), 4.05 (s, 1H), 3.19-2.94 (m, 2H), 2.87-2.63 (m, 1H), 1,53 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 154.3 (s), 135.3 (s), 134.9 (s), 132.8 (s), 130.4 (s), 129.8 (s), 129.2 (d), 128.7 (d), 128.3 (d), 127.0 (d, 2C), 125.9 (d), 120.8 (s), 119.6 (d), 119.3 (d), 80.1 (s), 49.9 (d), 37.4 (t), 28.5 (q, 3C), 28.4 (t); **MS (EI+):** m/z (rel. Intensity): 293 (M^+-100, 56), 292 (100), 291 (17), 290 (38), 264 (15), 263 (24), 246 (20), 244 (16), 217 (32), 216 (20), 189 (13), 188 (10), 132 (21), 130 (27), 121 (16), 108 (26), 103 (13)

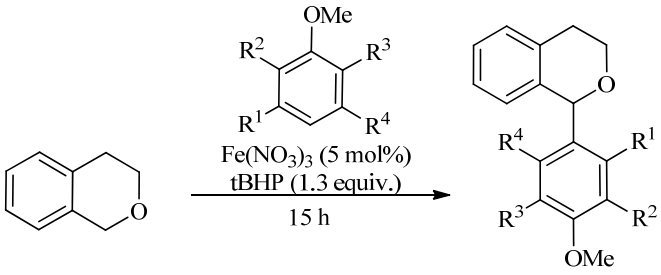
1,1-Dimethylethyl-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (3o)



$C_{21}H_{23}N_3O_2$
MW: 349.43

Yield: 42 % (126 mg, 0.361 mmol); white powder; **M.p.:** 84-86°C; **^{1}H NMR (200 MHz $CDCl_3$)** δ ppm: 12.57-11.79 (bs, 1H), 10.22-9.39 (bs, 1H), 8.64-8.09 (m, 2H), 7.32-7.05 (m, 5H), 6.90 (bs, 1H), 6.70 (bs, 1H) 4.23-3.87 (bs, 1H), 3.17-2.92 (m, 2H), 2.87-2.63 (m, H1), 1.53 (s, 9H); **^{13}C NMR (50 MHz, APT, *$CDCl_3$*)** δ ppm: 154,3 (s), 145.2 (s), 134.9 (s), 134.8 (s), 129.2 (d), 128.2 (d), 128.1 (d), 127.2 (d), 127.1 (d), 126.8 (d), 126.0 (d), 124.7 (d), 122.4 (s), 118.5 (s), 115.3 (s), 80.1 (s), 50.1 (d), 37.5 (t), 28.5 (q, 3C), 28.4 (t); **MS (EI+):** m/z (rel. Intensity): 249 (M^+-100, 56), 248 (100), 245 (36), 244 (57), 219 (50), 190 (10), 144 (14), 132 (24), 130 (28), 119 (34), 109 (27), 103 (18), 95 (16); **HRMS (ESI$^+$):** exact mass calculated for $C_{21}H_{23}N_3O_2$: 350.1863. Found: 350.1871

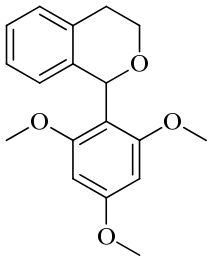
Methoxyphenylation of Isochroman



5 **6a-d**

A mixture of isochroman (200 mg, 1.49 mmol, 1.0 equiv.), iron(III)-nitrate nonahydrate (30.1 mg, 74.5 µmol, 0.05 equiv.), and methoxybenzene (1.79 mmol, 1.2 equiv.) was placed into a 5 mL glass vial. TBHP (352 µL, 5.5 M in decane, 1.3 equiv.) was added dropwise at 0°C under air and the reaction mixture stirred for 10 minutes at 0°C. The neat mixture was then smoothly heated up to 50°C and stirred for 15 hours in a heating block. Finally, the reaction temperature was raised to 80°C, and the reaction mixture stirred for another 24 hours. The reaction was monitored by TLC and/or GC-MS. The reaction mixture was diluted with DCM (3 mL) and directly subjected to flash chromatography. The desired product was obtained after MPLC where the solvent mixture used for TLC was also used for column chromatography (100 g SiO_2). If necessary, the product was finally purified by preparative HPLC, applying the conditions mentioned above.

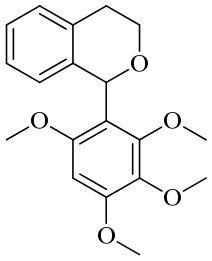
1-(2,4,6-Trimethoxyphenyl)isochroman (6a)



$C_{18}H_{20}O_4$
MW: 300.35

Yield: 55 % (246 mg, 0.820 mmol); white solid; **M.p.:** 118-120°C; **^{1}H NMR (200 MHz, *$CDCl_3$*)** δ ppm: 7.12-6.92 (m, 3H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.30 (s, 1H), 6.12 (s, 1H), 4.30 (ddd, ^2J=11.1 Hz, ^3J=5.6 Hz, ^3J=1.9 Hz, 1H), 3.93 (dt, ^2J=11.2 Hz, ^{3}J=3.1 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 6H), 3.35-3.09 (m, 1H), 2.66 (d, ^2J=15.9 Hz, 1H); **^{13}C NMR (50 MHz, APT, *$CDCl_3$*)** δ ppm: 161.2 (s), 159.9 (s, 2C), 139.7 (s), 133.8 (s), 127.8 (d), 125.5 (d), 125.1 (d), 124.2 (d), 111.7 (s), 91.4 (2C, d), 70.2 (d), 65.3 (t), 55.9 (q, 2C), 55.2 (q), 29.0 (t); **MS (EI+):** m/z (rel. Intensity): 300 (M^+, 50), 282 (22), 272 (50), 269 (100), 251 (26), 241 (98), 239 (48) 208 (23), 195 (27), 181 (35), 168 (22), 139 (28)

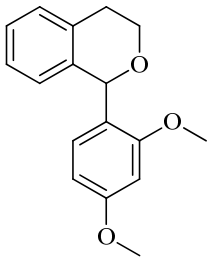
1-(2,3,4,6-Tetramethoxyphenyl)isochroman (6b)



$C_{19}H_{22}O_5$
MW: 330.37

Yield: 17 % (85 mg, 0.257 mmol); white solid; **M.p.:** 55-58°C, **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.17-6.96 (m, 3H), 6.69 (d, *J* = 7.3 Hz, 1H), 6.30 (s, 1H), 6.25 (s, 1H), 4.32 (ddd, *J* = 11.1, 5.6, and 1.7 Hz, 1H), 4.02-3.91 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 3.46 (s, 3H), 3.35-3.14 (m, 1H), 2.69 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 154.5 (s), 153.8 (s), 153.5 (s), 139.6 (s), 136.7 (s), 133.8 (s), 128.1 (d), 125.6 (d), 125.4 (d), 124.5 (d), 116.8 (s), 92.7 (d), 70.8 (d), 65.3 (t), 60.8 (q), 60.5 (q), 56.3 (q), 55.9 (q), 28.9 (t); **MS (EI+):** m/z (rel. Intensity): 330 (M^+, 100), 315 (23), 312 (14), 299 (99), 284 (10), 271 (18), 238 (16), 198 (24), 195 (16), 183 (23)

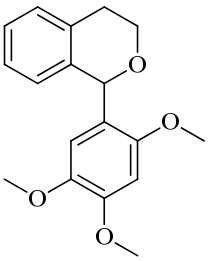
1-(2,4-Dimethoxyphenyl)isochroman (6c)



$C_{17}H_{18}O_3$
MW: 270.32

Yield: 12 % (48 mg, 0.179 mmol); colorless oil; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.21-7.03 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.22 (s, 1H), 4.18 (td, ^2J = 11.0 Hz, ^{3}J=5.0 Hz, 1H), 4.03-3.90 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.22-3.01 (m, 1H), 2.84 (td, ^2J=16.3, ^{3}J=4.4 Hz, 1H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ: ppm 160.5 (s), 158.6 (s), 137.9 (s), 134.2 (s), 130.7 (d), 128.5 (d), 126.6 (d), 126.2 (d), 125.8 (d), 123.3 (s), 104.2 (d), 98.4 (d), 72.2 (d), 63.3 (t), 55.6 (q), 55.3 (q), 28.8 (t); **MS (EI+):** m/z (rel. Intensity): 270 (M^+, 65), 255 (100), 239 (43), 225 (16), 209 (16), 194 (13), 178 (8), 165 (24), 104 (10), 77 (8)

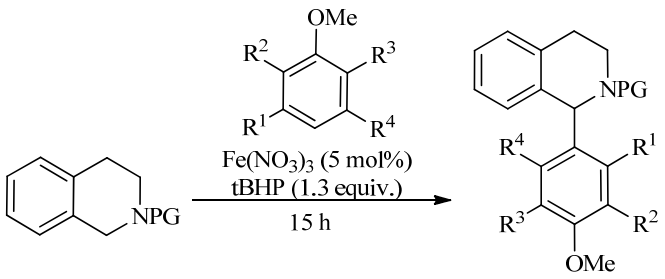
1-(2,4,5-Trimethoxyphenyl)isochroman (6d)



$C_{18}H_{20}O_4$
MW: 300.35

Yield: 15 % (67 mg, 0.223 mmol); white solid; **M.p.:** 46-48°C; **^{1}H NMR (400 MHz, *CDCl$_3$*)** δ ppm: 7.21-7.14 (m, 2H), 7.12-7.05 (m, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 4.27 (ddd, ^2J = 11.2 Hz, ^{3}J=5.6 Hz, ^{3}J=3.1 Hz, 1H), 3.99 (dt, ^2J = 11.1 Hz, ^{3}J=3.8 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.73 (s, 3H), 3.21 (ddd, ^2J = 16.0 Hz, ^{3}J=10.0 Hz, ^{3}J=5.8 Hz, 1H), 2.80 (td, ^2J = 16.2 Hz, ^{3}J=3.2, 1H); **^{13}C NMR (101 MHz, APT, *CDCl$_3$*)** δ ppm: 151.9 (s), 149.4 (s), 143.2 (s), 138.0 (s), 133.9 (s), 128.5 (d), 126.5 (d), 126.2 (d), 125.8 (d), 122.2 (s), 113.0 (d), 97.4 (d), 72.6 (d), 64.4 (t), 56.8 (q), 56.4 (q), 56.0 (q), 28.8 (t); **MS (EI+):** m/z (rel. Intensity): 300 (M^+, 100), 285 (35), 269 (39), 257 (9), 239 (26), 225 (9), 208 (12), 195 (14), 168 (25), 153 (13)

Methoxyphenylation of N-Boc-protected THIQ

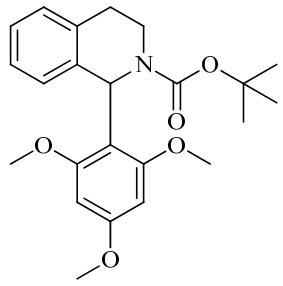


1c-e **6e-j**

A mixture of 2-protected-1,2,3,4-tetrahydroisoquinoline (0.857 mmol, 1.0 equiv.), iron(III)-nitrate nonahydrate (17.3 mg, 42.9 µmol, 0.05 equiv.), and methoxybenzene (1.03 mmol, 1.2 equiv.) was placed into a 5 mL glass vial. TBHP (203 µL, 5.5 M in decane, 1.3 equiv.) was added dropwise at 0°C under air and the reaction mixture stirred for 10 minutes at 0°C. The neat mixture was then smoothly heated up to 50°C and stirred for 15 hours in a heating block. The reaction was

monitored by TLC and/or GC-MS. The reaction mixture was diluted with DCM (3 mL) and directly subjected to flash chromatography. The desired product was obtained after MPLC where the solvent mixture used for TLC was also used for column chromatography (100 g SiO_2). If necessary, the product was finally purified by preparative HPLC, applying the conditions mentioned above.

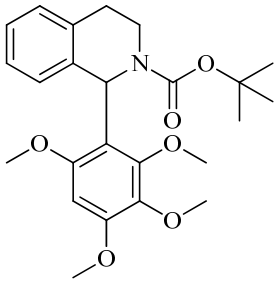
2(1H)-Isoquinolinecarboxylic acid-3,4-dihydro-1-(2,4,6-trimethoxyphenyl)-1,1-dimethylethyl ester (6e)



$C_{23}H_{29}NO_5$
MW: 399.48

Yield: 81 % (278 mg, 0.696 mmol); white solid; **M.p.:** 109-111°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.16-6.95 (m, 3H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H), 6.12 (s, 2H), 4.45-4.30 (m, 1H), 3.81 (s, 3H), 3.69 (s, 6H), 3.49 (ddd, ^2J = 12.6, ^3J = 10.6, ^3J = 4.5 Hz, 1H), 3.01-2.73 (m, 2H), 1.28 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 160.1 (s), 158.8 (2C, s), 155.4 (s), 137.2 (s), 135.2 (s), 127.9 (d), 126.3 (d), 125.8 (d), 125.4 (d), 114.0 (s), 90.5 (2C,d), 79.1 (s), 55.5 (2C, q), 55.2 (q), 49.4 (d), 39.4 (t), 30.5 (t), 28.3 (q, 3C); **MS (EI+):** m/z (rel. Intensity): 348 (M^+-51, 24), 299 (60), 298 (100), 282 (26), 268 (90), 239 (14), 180 (18), 179 (20), 151 (16), 132 (9)

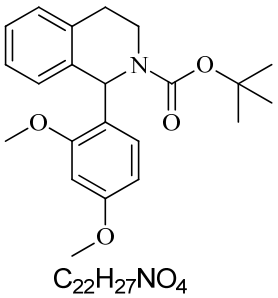
2(1H)-Isoquinolinecarboxylic acid-3,4-dihydro-1-(2,3,4,6-tetramethoxyphenyl)-1,1-dimethyl-ethyl ester (6f)



$C_{24}H_{31}NO_6$
MW: 429.51

Yield: 52 % (190 mg, 0.442 mmol); pale yellow solid; **M.p.:** 116°C – 118°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.16-6.96 (m, 3H), 6.80 (d, ^3J=6.9 Hz, 1H), 6.48 (s, 1H), 6.29 (s, 1H), 4.36 (d, ^3J=12.3 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.75 (s, 3H), 3.61-3.40 (m, 4H), 3.03-2.74 (m, 2H), 1.33 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 155.1 (s), 153.6 (s), 152.7 (s), 152.6 (s), 137.3 (s), 136.5 (s), 135.1 (s), 128.1 (d), 126.5 (d), 125.7 (d), 125.6 (d), 118.9 (s), 91.7 (d), 79.2 (s), 60.7 (q), 59.8 (q), 55.9 (q), 55.7 (q), 49.8 (d), 39.4 (t), 30.2 (t), 28.3 (q, 3C); **MS (EI+):** m/z (rel. Intensity): 429 (M^+, 8), 329 (27), 328 (100), 299 (10), 298 (49), 183 (10), 132 (20), 130 (10), 57 (12)

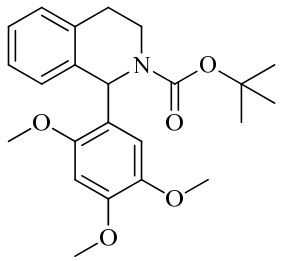
2(1H)-Isoquinolinecarboxylic acid-3,4-dihydro-1-(2,4-dimethoxyphenyl)-1,1-dimethylethyl ester (6g)



$C_{22}H_{27}NO_4$
MW: 369.45

Yield: 34 % (108 mg, 0.292 mmol); white solid; **M.p.:** 36-37°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.18-7.00 (m, 4H), 6.83 (d, ^3J = 8.3 Hz, 1H), 6.48 (s, 1H), 6.47 (s, 1H), 6.34 (dd, ^3J = 8.4, ^{4}J=2.4 Hz, 1H), 4.22-3.99 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.48-3.29 (m, 1H), 2.99 (ddd, ^2J= 15.9 Hz, ^3J=10.3 Hz, ^3J=5.6 Hz, 1H), 2.81 (td, ^2J = 16.0, ^{3}J=3.9 Hz, 1H), 1.42 (s, 9H); **^{13}C NMR (101 MHz, DEPT, *CDCl$_3$*)** δ ppm: 159.9 (s), 158.0 (s), 154.7 (s), 136.8 (s), 135.0 (s), 130.0 (d), 128.5 (d), 127.9 (d), 126.2 (d), 125.9 (d), 125.1 (s), 103.4 (d), 98.4 (d), 79.3 (s), 55.19 (q), 55.15 (q), 52.6 (d), 38.6 (t), 28.8 (t), 28.3 (q, 3C); **MS (EI+):** m/z (rel. Intensity): 269 (M^+-100, 46), 268 (100), 252 (22), 239 (12), 238 (32), 132 (15), 130 (10)

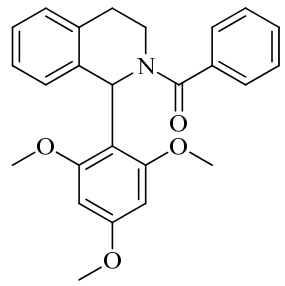
2(1H)-Isoquinolinecarboxylic acid-3,4-dihydro-1-(2,4,5-trimethoxyphenyl)-1,1-dimethylethyl ester (6h)



$C_{23}H_{29}NO_5$
MW: 399.48

Yield: 47 % (160 mg, 0.401 mmol); white solid; **M.p.:** 84-86°C; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.17-7.01 (m, 4H), 6.56 (s, 1H), 6.53 (s, 1H), 6.42 (s, 1H), 4.24-4.03 (m, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.55-3.35 (m, 1H), 3.07-2.75 (m, 2H), 1.40 (s, 9H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 154.7 (s), 151.5. (s), 148.8 (s), 142.4 (s), 136.7 (s), 134.8 (s), 128.4 (d), 127.8 (d), 126.2 (d), 125.9 (d), 124.2 (s), 113.8 (d), 97.5 (d), 79.4 (s), 56.7 (q), 56.1 (d), 56.0 (q), 53.0 (q), 39.1 (t), 29.0 (t), 28.3 (q, 3C); **MS (EI+):** m/z (rel. Intensity): 399 (M^+, 4), 343 (5), 299 (58), 298 (100), 284 (24), 268 (73), 253 (12), 239 (12), 168 (8), 132 (15)

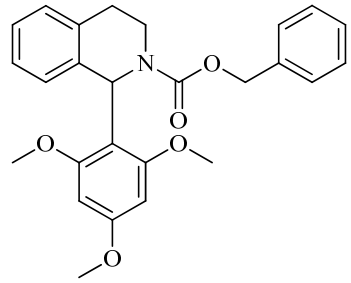
Phenyl(1-(2,4,6-trimethoxyphenyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (6i)



$C_{25}H_{25}NO_4$
MW: 403.47

Yield: 54 % (187 mg, 0.463 mmol); white solid; **M.p.:** 67-69°C; **^{1}H NMR (200 MHz, *DMSO-D$_6$*)** δ ppm: 7.59-6.93 (m, 8H), 6.86-6.49 (m, 2H), 6.38-6.04 (m, 2H), 3.93-3.47 (m, 10H), 3.37-3.29 (m, 1H), 2.98-2.70 (m, 2H); **^{13}C NMR (101 MHz, *CDCl$_3$*)** δ ppm: 172.0, 170.3, 160.6, 160.4, 159.2, 159.0, 137.5, 137.1, 135.3, 134.2, 129.2, 128.1, 127.6, 127.2, 126.2, 125.6, 112.7, 91.4, 90.2, 56.0, 55.1, 52.1, 49.0, 44.7, 38.1, 31.1, 30.1; **^{13}C NMR (101 MHz, DEPT, *CDCl$_3$*)** δ ppm: 129.3 (d), 128.2 (d), 127.7 (d), 127.4 (d), 126.3 (d), 125.7 (d), 91.5 (d), 90.3 (d), 56.1 (q), 55.3 (q), 52.3 (d), 49.1 (d), 44.8 (t), 38.3 (t), 312. (t), 30.1 (t) mixture of rotamers; **MS (EI+):** m/z (rel. Intensity): 403 (M^+, 7), 373 (26), 372 (100), 299 (4), 298 (13), 282 (6), 105 (10), 77 (9)

2(1H)-Isoquinolinecarboxylic acid-3,4-dihydro-1-(2,4,6-trimethoxyphenyl)-phenylmethyl ester (6j)

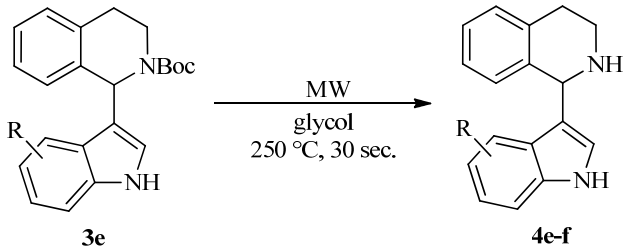


$C_{26}H_{27}NO_5$
MW: 433.50

Yield: 58 % (215 mg, 0.496 mmol); pale yellow solid; **M.p.:** 115-116°C; **^{1}H NMR (200 MHz, *DMSO-D$_6$*)** δ ppm: 7.43-6.94 (m, 8H), 6.65 (d, ^3J = 7.0 Hz, 1H), 6.41 (s, 1H), 6.19 (s, 2H), 4.97 (s, 2H), 4.27 (d, ^2J = 12.0 Hz, 1H), 3.77 (s, 3H), 3.70-3.39 (m, 7H), 2.90-2.74 (m, 2H); **^{13}C NMR (50 MHz, *CDCl$_3$*)** δ ppm: 160.2 (s, 3C), 158.9 (s), 137.04 (a), 136.98 (s), 134.7 (s), 128.2 (d, 2C), 127.9 (d, 2C), 127.8 (d), 127.5 (d), 126.2 (d), 125.9 (d), 125.5 (d), 113.3 (s), 90.8 (d, 2C), 66.8 (t), 55.4 (q, 2C), 55.2 (q), 49.3 (d), 39.9 (t), 30.4 (t); **MS (EI+):** m/z (rel. Intensity): 433 (M^+, 1), 342 (3), 299 (20), 298 (100), 283 (5), 282 (17), 90 (6)

Deprotection of the Boc-PG

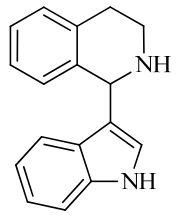
Microwave assisted deprotection



3e **4e-f**

Isoquinoline, 1,2,3,4-tetrahydro-1-(1H-indol-3-yl)- (4e)

Tetrahydro-2-terbutyloxycarbonyllisoquinoline **3e** (150 mg, 0.430 mmol) was suspended in 20 mL ethylene glycol and microwaved at 250°C for 30 seconds (holdup time). The reaction mixture was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed twice with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified by flash chromatography (100g SiO_2, PE:EtOAc=100:0 → 0:100 (30 min), EtOAc:EtOH=95:5→ 60:40 (30min))

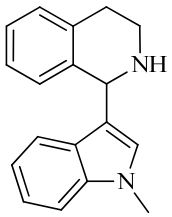


$C_{17}H_{16}N_2$
MW: 248.32

Yield: 89 % (95 mg, 0.383 mmol); brown solid; **M.p.:** 44-46°C, **^{1}H NMR (200 MHz, *DMSO-D$_6$*)** δ ppm: 11.04 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.20-6.75 (m, 1H), 5.36 (s, 1H), 4.25 (s, 1H), 3.28-2.66 (m, 4H), **^{13}C NMR (50 MHz, APT, *DMSO-D$_6$*)** δ ppm: 138.8 (s), 136.5 (s), 134.8 (s), 128.6 (d), 127.1 (d), 126.1 (s), 125.7 (d), 125.2 (d), 124.5 (d), 120.8 (d), 119.7 (d), 118.2 (d), 117.6 (s), 111.4 (d), 53.6 (s), 41.7 (t), 29.0 (t), **MS (EI+):** m/z (rel. Intensity): 248 (M^+, 38), 247 (100), 231 (15), 219 (22), 218 (32), 217 (19), 130 (20)

Isoquinoline, 1,2,3,4-tetrahydro-1-(1-methyl-1H-indol-3-yl)- (4f)

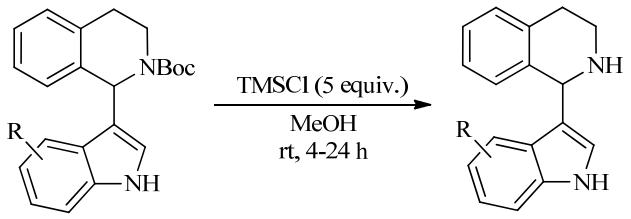
1-(N-Methylindolyl)-N-boc-tetrahydroisoquinoline **3f** (50 mg, 0.138 mmol) was suspended in 10 mL ethylene glycol and microwaved at 250°C for 30 seconds (holdup time). The reaction mixture was diluted with water, chilled down with liquid nitrogen and lyophilized to afford the desired product as pale brown solid.



$C_{18}H_{18}N_2$
MW: 262.35

Yield: 97 % (35 mg, 0.133 mmol); brown solid; **^{1}H NMR (200 MHz, *CDCl$_3$*)** δ ppm: 7.51 (d, *J* = 7.9 Hz, 1H), 7.36-6.97 (m, 7H), 6.79 (s, 1H), 5.52 (s, 1H), 3.73 (s, 3H), 3.35-3.19 (m, 1H), 3.17-2.83 (m, 3H), 2.52 (s, 1H); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 138.3 (s), 137.2 (s), 135.2 (s), 128.9 (d), 128.5 (d), 127.9 (d), 126.9 (s), 126.1 (d), 125.6 (d), 121.7 (d), 119.4 (d), 119.1 (d), 118.1 (s), 109.3 (d), 53.6 (d), 41.5 (t), 32.7 (q), 29.7 (t); **MS (EI+):** m/z (rel. Intensity): 262 (M^+, 60), 261 (100), 245 (6), 233 (14), 232 (24), 217 (12), 131 (22), 130 (29), 115 (11), 108 (14)

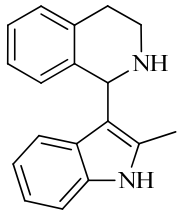
TMSCl promoted Boc-deprotection



3e **4g-o**

To an argon degassed solution of the corresponding Boc-protected amine (0.5 mmol, 1.0 equiv.) in dry MeOH (4 mL) was added TMSCl (272 mg, 2.50 mmol, 5.0 equiv.) dropwise at room temperature and the reaction mixture stirred for 4 to 24 hours under argon. The reaction mixture was cooled down to 0 °C and poured into ice cold 2N aqueous NaOH. The suspension was extracted three times with EtOAc and washed once with 2 N NaOH. The combined organic layers were dried over sodium sulfate, filtered, and evaporated to afford the desired product in quantitative yields.

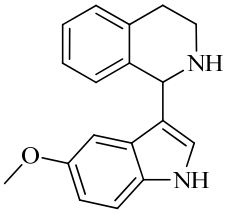
Isoquinoline, 1,2,3,4-tetrahydro-1-(2-methyl-1H-indol-3-yl)- (4g)



$C_{18}H_{18}N_2$
M = 262.35

Yield: 100 % (131 mg, 0.499 mmol); brown solid; reaction time: 4h; **M.p.:** 68-70°C; **TLC:** R_f (EtOAc:EtOH=10:1) = 0.14; **^{1}H NMR (200 MHz *CDCl$_3$*)** δ ppm: 8.22 (s, 1H, NH), 7.14-6.70 (m, 8H, H_{Ar}), 5.34 (s, 1H, 1-CH), 3.37-3.19 (m, 1H, 3-CH_2), 3.18-2.94 (m, 2H, 3-CH_2 & 4-CH_2), 2.90-2.70 (m, 1H, 4-CH_2), 2.58 (s, 1H, 2-NH), 2.18 (s, 3H, CH_3); **^{13}C APT NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 138.5 (s), 135.4 (s), 134.9 (s), 133.3 (s), 128.8 (d), 127.4 (d), 127.3 (s), 126.0 (d), 125.9 (d), 120.8 (d), 119.2 (d), 118.8 (d), 113.6 (s), 110.2 (d), 53.6 (d), 43.3 (t), 29.8 (t), 11.9 (q); **GC/MS (EI+):** m/z (rel. Intensity): 262 (M^+, 86), 261 (100), 247 (24), 245 (60), 244 (37), 233 (22), 230 (21), 218 (38), 217 (41), 130 (46); **HRMS (ESI$^+$):** exact mass calculated for $C_{18}H_{18}N_2$: 263.1543. Found: 263.1548.

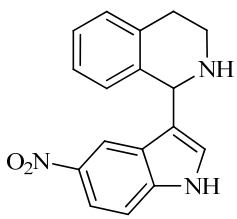
Isoquinoline, 1,2,3,4-tetrahydro-1-(5-methoxy-1H-indol-3-yl)- (4i)



$C_{18}H_{18}N_2O$
M = 278.35

Yield: 99 % (137 mg, 0.492 mmol); light brown solid; reaction time: 7h; **M.p.:** 144-147°C; **TLC:** R_f (EtOAc:EtOH=5:1) = 0.11; **^{1}H NMR (200 MHz *CDCl$_3$*)** δ ppm: 9.65-9.00 (bs, 1H, NH), 7.20-6.67 (m, 6H, H_{Ar}), 6.47-5.68 (bs, 2H, H_{Ar}), 5.52 (s, 1H, 1-CH), 3.59 (s, 3H, OCH_3), 3.35-2.70 (m, 4H, 3-CH_2 & 4-CH_2), 1.66 (s, 1H, 2-NH); **^{13}C NMR (50 MHz, APT, *CDCl$_3$*)** δ ppm: 153.8 (s), 135.8 (s), 133.6 (s), 131.5 (s), 128.7 (d), 128.1 (d), 126.8 (d), 126.6 (s), 126.2 (d), 126.1 (d), 115.0 (s), 112.2 (d), 112.1 (d), 100.8 (d), 55.6 (q), 52.9 (d), 40.5 (t), 27.8 (t); **GC/MS (EI+): m/z (rel. Intensity):** 278 (M^+, 62), 277 (100), 261 (49), 249 (26), 248 (26), 234 (10), 233 (8), 217 (7), 132 (9), 130 (12); **HRMS (ESI+):** exact mass calculated for $C_{18}H_{18}N_2O$: 278.1419. Found [m/z]: 279.1499 $(M+H)^+$

Isoquinoline, 1,2,3,4-tetrahydro-1-(5-nitro-1H-indol-3-yl)- (4j)

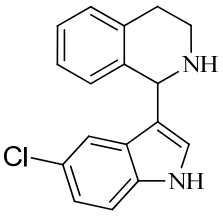


$C_{17}H_{15}N_3O_2$
M = 293.32

Yield: 100 % (146 mg, 0.498 mmol); shining dark yellow solid; reaction time: 24 h; **M.p.:** 83-85 °C; **TLC:** R_f (EtOAc:EtOH=5:1) = 0.21; **^{1}H NMR 200 MHz *CDCl$_3$*)** δ ppm: 9.13 (s, 1H, NH), 8.49 (d, ^4J = 2.1 Hz, 1H, H_{Ar}), 8.04 (dd, ^3J = 9.0 Hz, ^4J = 2.1 Hz, 1H, H_{Ar}), 7.30 (d, ^3J = 9.0 Hz, 1H, H_{Ar}), 7.22-7.15 (m, 2H, H_{Ar}), 7.09-6.98 (m, 2H, H_{Ar}), 6.91 (d, ^3J=7.6 Hz, 1H, H_{Ar}), 5.51 (s, 1H, 1-CH), 3.34-2.80 (m, 4H, 3-CH_2 & 4-CH_2), 2.50-2.05 (bs, 1H, 2-NH); **^{13}C NMR (50 MHz, DEPT, *CDCl$_3$*)** δ ppm: 141.5 (s), 139.6 (s), 137.2 (s), 135.1 (s), 129.3 (d), 127.5 (d), 127.0 (d), 126.6 (d), 125.9 (s), 125.8 (d), 121.9 (s), 117.7 (d), 117.1

(d), 111.2 (d), 53.5 (d), 41.6 (t), 29.4 (t); **GC/MS (EI+):** m/z (rel. Intensity): 293 (M^+, 43), 292 (100), 276 (12), 263 (22), 246 (31), 218 (14), 217 (27), 130 (12); **HRMS (ESI^+):** exact mass calculated for $C_{17}H_{15}N_3O_2$: 294.1237. Found: 294.1239.

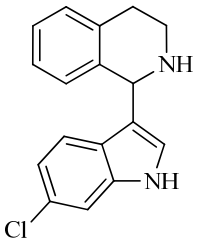
Isoquinoline, 1,2,3,4-tetrahydro-1-(5-chloro-1H-indol-3-yl)- (4l)



$C_{17}H_{15}ClN_2$
M = 282.77

Yield: 100 % (141 mg, 0.499 mmol); pale yellow solid; reaction time: 7 h; **M.p.:** 148-151 °C; **TLC:** R_f (EtOAc:Et_3N=11:1) = 0.29; **^{1}H NMR 200 MHz *$CDCl_3$*)** δ ppm: 8.45 (s, 1H, NH), 7.45 (d, *J* = 1.5 Hz, 1H, H_{Ar}), 7.26-6.87 (m, 7H, H_{Ar}), 5.43 (s, 1H, 1-CH), 3.36-2.77 (m, 4H, 3-CH_2 & 4-CH_2), 2.37 (s, 1H, NH); **^{13}C NMR (50 MHz, APT, *$CDCl_3$*)** δ ppm: 137.7 (s), 134.93 (s), 134.89 (s), 129.0 (d), 127.6 (d), 127.3 (s), 126.4 (d), 125.7 (d), 125.4 (d), 125.1 (s), 122.3 (d), 118.8 (d), 118.7 (s), 112.3 (d), 53.6 (d), 41.7 (t), 29.4 (t); **GC/MS (EI+):** m/z (rel. Intensity): 284 (19), 283 (38), 282 (M^+, 57), 281 (100), 254 (12), 253 (19), 252 (27), 217 (30), 131 (14), 130 (26), 109 (17)

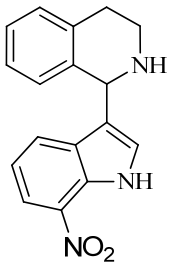
Isoquinoline, 1,2,3,4-tetrahydro-1-(6-chloro-1H-indol-3-yl)- (4m)



$C_{17}H_{15}ClN_2$
M = 282.77

Yield: 86 % (122 mg, 0.431 mmol); off white powder; reaction time: 4 h; **M.p.:** 146-148 °C **^{1}H NMR 200 MHz *$CDCl_3$*)** δ ppm: 8.61 (s, 1H, NH), 7.32 (d, ^3J = 8.5 Hz, 1H, H_{Ar}), 7.25 (d, ^4J = 1.7 Hz, 1H, H_{Ar}), 7.21-7.13 (m, 2H, H_{Ar}), 7.09-6.96 (m, 2H, H_{Ar}), 6.93 (d, ^3J = 7.6 Hz, 1H, H_{Ar}), 6.87 (s, 1H, H_{Ar}), 5.44 (s, 1H, 1-CH), 3.37-2.79 (m, 4H, 3-CH_2 & 4-CH_2), 2.23 (s, 1H. NH); **^{13}C NMR (50 MHz, APT, *DMSO-D_6*)** δ ppm: 129.5 (s), 129.1 (s), 126.4 (s), 120.3 (d), 119.4 (d), 118.8 (s), 117.9 (d), 117.2 (d), 117.1 (d), 116.6 (s), 111.7 (d), 110.8 (d), 109.7 (s), 102.6 (d), 45.1 (d), 32.8 (t), 20.3 (t); **GC/MS (EI+):** m/z (rel. Intensity): 284 (18), 283 (38), 282 (M^+, 56), 281 (100), 265 (10), 253 (22), 252 (28), 217 (29), 132 (19), 131 (19), 130 (35), 123 (13), 109 (29)

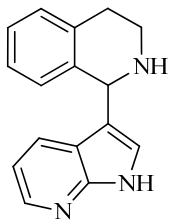
Isoquinoline, 1,2,3,4-tetrahydro-1-(7-nitro-1H-indol-3-yl)- (4n)



$C_{17}H_{15}N_3O_2$
M = 293.32

Yield: 99 % (145 mg, 0.494 mmol); shining dark yellow solid; reaction time: 6 h; **M.p.:** 58-61 °C; **TLC:** R_f (EtOAc:MeOH=11:1) = 0.35; **^{1}H NMR 200 MHz *$CDCl_3$*)** δ ppm: 9.87 (s, 1H, NH), 8.13 (d, ^3J = 8.0 Hz, 1H, H_{Ar}), 7.84 (d, ^3J = 7.8 Hz, 1H, H_{Ar}), 7.22-6.96 (m, 5H, H_{Ar}), 6.90 (d, ^3J = 7.6 Hz, 1H, H_{Ar}), 5.49 (s, 1H, 1-CH), 3.35-2.78 (m, 4H, 3-CH_2 & 4-CH_2), 2.06 (s, 1H, NH); **^{13}C NMR (50 MHz, APT, *$CDCl_3$*)** δ ppm: 137.6 (s), 135.1 (s), 132.9 (s), 130.2 (s), 130.0 (s), 129.1 (d), 128.4 (d), 127.5 (d), 126.5 (d), 126.1 (d), 125.7 (d), 121.1 (s), 119.3 (d), 119.0 (d), 53.8 (d), 42.0 (t), 29.6 (t); **GC/MS (EI+):** m/z (rel. Intensity): 293 (M^+, 57), 292 (100), 264 (15), 263 (23), 246 (18), 217 (26), 189 (10), 132 (10), 131 (8), 130 (14), 109 (11)

Isoquinoline, 1,2,3,4-tetrahydro-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)- (4o)



$C_{16}H_{15}N_3$
M = 249.31

Yield: 100 % (124 mg, 0.497 mmol); brown solid; reaction time: 8 h; **M.p.:** 172-174°C; **TLC:** R_f (EtOAc:EtOH=5:1) = 0.11; **^{1}H NMR (200 MHz DMSO-D_6)** δ ppm: 11.48 (s, 1H, NH), 8.15 (d, *J* = 3.6 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.27 (d, *J* = 1.3 Hz, 1H), 7.18-7.03 (m, 2H), 7.02-6.85 (m, 2H), 6.80 (d, *J* = 7.6 Hz, 1H), 5.30 (s, 1H, 1-CH), 3.70 (s, 1H, 2-NH), 3.24-2.63 (m, 4H, 3-CH_2 & 4-CH_2); **^{13}C NMR (50 MHz, APT, DMSO-D_6)** δ ppm: 148.9 (s), 142.3 (d), 138.5 (s), 135.0 (s), 128.7 (d), 128.0 (d), 127.0 (d), 125.8 (d), 125.2 (d), 124.8 (d), 118.4 (s), 116.8 (s), 114.8 (d), 53.9 (d), 41.7 (t), 29.0 (t); **GC/MS (EI+):** m/z (rel. Intensity): 249 (M^+, 36), 248 (100), 232 (7), 220 (18), 219 (30), 218 (11), 131 (8), 130 (10), 119 (12); **HRMS (ESI^+):** exact mass calculated for $C_{16}H_{15}N_3$: 250.1339. Found: 250.1352.