Supporting information for

**Ugi-type reactions of spirocyclic indolenines as a platform for compound library generation**

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General information

Starting materials were purchased from Sigma Aldrich, Fisher Scientific and Acros Organics and were used without purification. Unless stated otherwise, the solvents were purchased from VWR Chemicals and were used without further treatment. Celite® 512 medium was purchased from Sigma Aldrich. Column Chromatography was performed on SilicaP Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) from Silicycle. Thin Layer Chromatography (TLC) was performed using TLC plates F254 (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) or stained with basic aq. KMnO₄.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 or 500 spectrometer (at 400.13 or 500.23 MHz and 100.62 or 125.78 MHz, respectively) in the solvent indicated and with the residual solvent resonance peak used as internal standard (CHCl₃, ¹H: δ = 7.26 ppm; ¹³C: δ = 77.0; DMSO-d₆: δ = 2.50 for ¹H NMR and δ = 39.52 for ¹³C NMR). All coupling constants (J) are given in Hz and chemical shifts (δ) are reported in parts per million (ppm). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The assignment of the 1H NMR signals is based on 2D NMR techniques (COSY, NOESY, HSQC, HMBC). The APT-NMR spectra were used for the assignment of the carbons.

Electrospray Ionization (ESI) high resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Melting points were determined on a Büchi M-565 and are not corrected. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400S and wavelengths (ν) were reported in cm⁻¹.
Experimental procedure and characterization data

Synthesis of carbaldehydes 2

To a \(-60^\circ C\) solution of oxalyl chloride (120\(\mu\)L, 1.4 eq) in dry DCM (5.3 mL), a solution of DMSO (142 \(\mu\)l, 2 eq) in DCM (0.8 mL) was added dropwise. After 15 min., tetrahydrothiopyran-4-methanol (121.3 \(\mu\)l, 1.0 mmol) dissolved in 0.8 mL DCM was added. The mixture was stirred for 1 h, warming to -30\(^\circ C\). Afterwards, triethylamine (420\(\mu\)l, 3eq) was added and the mixture was allowed to warm to rt and stirred for 1 h. Next the mixture was poured into water and extracted with DCM two times. The organic layers were combined, washed with water and dried over \(\text{Na}_2\text{SO}_4\). Finally the solvent was evaporated under vacuum to achieve the expected aldehyde 2 that was used in the next reaction without further purification.

To a solution of isonipecotic acid (1.29g, 10 mmol) in a mixture of \(\text{CH}_3\text{CN}/\text{H}_2\text{O}\) (2:3, 0.1M), \(\text{NaHCO}_3\) (1.5 eq) and \(\text{Na}_2\text{CO}_3\) (1.5 eq) were added (pH~ 10-11). Once the mixture was cooled to 0 °C, Cbz-Cl (1.42 mL, 1.7 g, 10 mmol). was slowly added. The resulting solution was stirred for 2 h at rt. After completion of the reaction, the mixture was acidified by dropwise addition of a 1 N HCl aqueous solution. Then, \(\text{CH}_3\text{CN}\) was removed by evaporation, followed by the extraction with EtOAc (3x). Finally the combined organic phase was washed with brine, dried over \(\text{Na}_2\text{SO}_4\), and concentrated under reduced pressure. The crude product was obtained in quantitative yield, which was used in the next reaction without further purification.

To an ice-cooled and stirred suspension of lithium aluminum hydride (2 eq.) in THF (15 mL), a solution of the Weinreb amide (3 mmol) in THF (30 mL) was added and the reaction mixture was stirred for 1 h at 0 °C. After completion, the reaction mixture was quenched dropwise with cool water (8 eq) at 0 °C, filtered through Celite® and the cake washed with EtOAc. The filtrate was concentrated in vacuo. Next, the crude mixture was dissolved in EtOAc, washed with 1 N HClaq. solution, brine and dried over
Na₂SO₄. Finally the solvent was evaporated under vacuum to achieve the expected aldehyde 2 which was used in the Fischer indolization without further purification.

Synthesis of spiroindolenines 3

**Procedure I**

To an ice-cooled solution of carbaldehyde (1 eq.) in DCM (0.1 M), the corresponding aryl hydrazine hydrochloride (1 eq.) was slowly added. After 10 min at 0°C, TFA (2 eq.) was added dropwise. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM and water and Na₂CO₃ (3 eq.) were added. The organic phase was separated and washed with water and brine. Finally, it was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was subjected to column chromatography (SiO₂, corresponding eluent).

**Procedure II**

To a solution of PhI(OAc)₂ (1.05 eq.) and TEMPO (0.1 eq.) in DCM (0.3 M), tetrahydropyran-4-methanol (1 eq.) was added. The reaction mixture was stirred at room temperature for 4 h. Afterwards, the mixture was diluted with DCM (0.1 M) and cooled down to 0 °C, followed by the addition of the corresponding aryl hydrazine hydrochloride (1 eq.). After 10 min, TFA (2 eq.) was added dropwise. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM and water and Na₂CO₃ (3 eq.) was added. The organic phase was separated and washed with water and brine. Finally it was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was subjected to column chromatography (SiO₂, corresponding eluent).
Spiro[cyclohexane-1,3'-indole] (3a)\(^1\)

Following the procedure I with cyclohexylcarbaldehyde (336 mg, 3 mmol) and phenylhydrazine hydrochloride (435 mg, 3 mmol) the spiroindolenine (416 mg, 2.25 mmol, 75%) was obtained as a red solid. TLC (cyclohexane:EtOAc, 4:1 v/v): \(R_f = 0.28\), Mp: 45.5- 47.8 °C. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.36\) (s, 1H); 7.64 (d, \(J = 7.7\) Hz, 1H); 7.39 (d, \(J = 7.3\) Hz, 1H); 7.34 (t, \(J = 7.6\) Hz, 1H); 7.24 (t, \(J = 7.4\) Hz, 1H); 1.96 – 1.55 (m, 10H) ppm. \(^13\)C-NMR (126 MHz, CDCl\(_3\)) \(\delta = 178.26\) (CH), 154.35 (C*), 144.47 (C*), 127.57 (CH), 125.73 (CH), 121.04 (CH), 57.67 (CH), 31.58 (C*), 29.32 (CH\(_2\)), 25.44 (CH\(_2\)), 25.08 (CH\(_2\)), 23.83 (CH\(_2\)) ppm. HRMS (ESI): \(m/z\) calcd for C\(_{13}\)H\(_{15}\)N [M+H]\(^+\): 186.1277, found 186.1287.

5'-methylspiro[cyclohexane-1,3'-indole] (3b)\(^1\)

Following the procedure I with cyclohexylcarbaldehyde (112 mg, 1 mmol) and p-tolylhydrazine hydrochloride (159 mg, 1 mmol) the spiroindolenine (108 mg, 0.56 mmol, 56%) was obtained as a brownish oil. TLC (cyclohexane:EtOAc, 3:1 v/v): \(R_f = 0.65\), \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.28\) (s, 1H), 7.51 (d, \(J = 7.8\) Hz, 1H), 7.19 (s, 1H), 7.14 (d, \(J = 7.8\) Hz, 1H), 2.41 (s, 3H), 1.89 – 1.51 (m, 10H) ppm. \(^13\)C-NMR (126 MHz, CDCl\(_3\)) \(\delta = 177.56\) (CH), 152.49 (C*), 144.92 (C*), 135.80 (C*), 128.41 (CH), 123.13 (CH), 120.81 (CH), 57.70 (C*), 31.97 (CH\(_2\)), 25.73 (CH\(_2\)), 24.13 (CH\(_2\)), 21.70 (CH\(_3\)) ppm. HRMS (ESI): \(m/z\) calcd for C\(_{14}\)H\(_{17}\)N [M+H]\(^+\): 200.1434, found 200.1441.

5'-bromospiro[cyclohexane-1,3'-indole] (3c)\(^1\)

Following the procedure I with cyclohexylcarbaldehyde (112 mg, 1 mmol) and 4-bromophenylhydrazine hydrochloride (223 mg, 1 mmol) the spiroindolenine (143 mg, 0.54 mmol, 54%) was obtained as a yellow oil. TLC (cyclohexane:EtOAc, 3:1 v/v): \(R_f = 0.64\), \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.31\) (s, 1H); 7.51 – 7.45 (m, 3H); 1.95 – 1.54 (m, 10H) ppm. \(^13\)C-NMR (126 MHz, CDCl\(_3\)) \(\delta = 178.49\) (C*), 153.39 (C*), 146.64 (C*), 130.66 (CH), 125.59 (CH), 122.41 (CH), 119.71 (C*), 58.23 (CH), 31.42 (CH\(_3\)), 25.30 (CH\(_2\)), 23.72 (CH\(_2\)) ppm. HRMS (ESI): \(m/z\) calcd for C\(_{13}\)H\(_{14}\)BrN [M+H]\(^+\): 264.0382, found 264.0378.

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Following the procedure I with cyclohexylcarbaldehyde (112 mg, 1 mmol) and 2,4-difluoro-phenylhydrazine hydrochloride (180 mg, 1 mmol) the spiroindolenine (70 mg, 0.32 mmol, 32%) was obtained as a brownish solid. TLC (DCM:cyclohexane, 95:5 v/v): \( R_f = 0.8 \). Mp: 97.7–98.4 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 8.29 \) (s, 1H), 6.89 (d, \( J = 7.6 \) Hz, 1H), 6.80 (t, \( J = 9.5 \) Hz, 1H), 1.93–1.77 (m, 3H), 1.74–1.62 (m, 5H), 1.61–1.53 (m, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta = 178.3 \) (CH), 161.7 (dd, \( J = 247.9, 9.3 \) Hz, C\_*\), 154.1 (258.0, 12.7 Hz, C\_*\), 149.3 (dd, \( J_{CF} = 9.6, 4.0 \) Hz, C\_*\), 137.7 (d, \( J_{CF} = 8.6 \) Hz, C\_*\), 106.2 (dd, \( J_{CF} = 24.8, 4.1 \) Hz, CH), 103.5 (dd, \( J_{CF} = 27.2, 22.6 \) Hz, CH), 59.6 (C\_*\), 32.0 (CH\(_2\)), 25.6 (CH\(_2\)), 24.1 (CH\(_2\)) ppm. IR (neat) \( \nu_{max} = 2933.5, 2860.2, 1629.7, 1596.9, 1542.9, 1471.6, 1448.4, 1338.5, 1294.1, 1176.5, 1122.5, 1099.3, 993.3, 879.5, 787.0, 640.3, 617.2, 526.5 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{13}\)H\(_{13}\)F\(_2\)N [M+Na\(^+\)] : 244.0908, found 244.0900.

Following the procedure II with tetrahydropyran-4-methanol (125.5 µl, 116mg, 1 mmol) and phenylhydrazine hydrochloride (144 mg, 1 mmol) the spiroindolenine (77 mg, 0.41 mmol, 41%) was obtained as a yellow solid. TLC (DCM:EtOAc, 9:1 v/v): \( R_f = 0.28 \). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 8.44 \) (s, 1H); 7.67 (d, \( J = 7.6 \) Hz, 1H); 7.45 (d, \( J = 7.5 \) Hz, 1H); 7.38 (t, \( J = 7.6 \) Hz, 1H); 7.29 (t, \( J = 7.6 \) Hz, 1H); 4.15–4.09 (m, 2H); 3.95–3.88 (m, 2H); 2.01–1.92 (m, 2H); 1.66–1.61 (m, 2H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta = 176.3 \) (CH), 154.8 (C\_*\), 143.4 (C\_*\), 128.6 (CH), 126.8 (CH), 122.5 (CH), 65.9 (CH\(_2\)), 55.3 (C\_*\), 31.4 (CH\(_2\)) ppm. IR (neat) \( \nu_{max} = 2933.5, 2860.2, 1629.7, 1596.9, 1542.9, 1471.6, 1448.4, 1338.5, 1294.1, 1176.5, 1122.5, 1099.3, 993.3, 879.5, 787.0, 640.3, 617.2, 526.5 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{13}\)H\(_{15}\)NO [M+Na\(^+\)] : 244.1046, found 244.1037.

Following the procedure II with tetrahydropyran-4-methanol (125.5 µl, 116mg, 1 mmol) and 4-methyl-phenylhydrazine hydrochloride (159 mg, 1 mmol) the spiroindolenine (124 mg, 0.62 mmol, 62 %) was obtained as a dark oil. TLC (DCM): \( R_f = 0.35 \). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 8.40 \) (s, 1H), 7.56 (d, \( J = 7.9 \) Hz, 1H), 7.27 (m, 1H), 7.19 (d, \( J = 7.8 \) Hz, 1H), 4.19–4.08 (m, 2H), 3.98–3.87 (m, 2H), 2.44 (s, 3H), 2.04–1.92 (m, 2H), 1.68–1.57 (d, \( J = 14.0 \) Hz, 2H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta = 175.3 \) (CH), 152.7 (C\_*\), 143.5 (C\_*\), 136.6 (C\_*\), 129.1 (CH), 123.3 (CH), 121.3 (CH), 65.9 (CH\(_2\)), 55.0 (C\_*\), 31.5 (CH\(_2\)), 21.9 (CH\(_3\)) ppm. IR (neat) \( \nu_{max} = 2947.03, 2858.31, 1610.45, 1483.16, 1388.65, 1238.21, 1151.42, 1103.21, 1027.99, 906.48, 802.33, 725.18, 642.25, 553.53 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{13}\)H\(_{15}\)NO [M+Na\(^+\)] : 224.1046, found 224.1037.
**2',3',5',6'-tetrahydrospiro[indole-3,4'-thiopyran] (3g)**

Following the procedure I with 4-formyltetrahydrothiopyran (130 mg, 1 mmol) and phenylhydrazine hydrochloride (159 mg, 1 mmol) the spiroindolenine (57 mg, 0.28 mmol, 28%) was obtained as a brownish solid. TLC (DCM): Rf = 0.28. Mp: 75.4–76.9 °C. ¹H NMR (500 MHz, CDCl₃) δ = 8.32 (s, 1H); 7.67 (d, J = 7.5 Hz, 1H); 7.45 (d, J = 7.4 Hz, 1H); 7.38 (t, J = 7.6 Hz, 1H); 7.29 (t, J = 7.4 Hz, 1H); 3.00–2.86 (m, 4H); 2.06–1.94 (m, 2H); 1.94–1.85 (m, 2H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 176.9 (CH), 154.7 (C*), 143.7 (C*), 128.6 (CH), 126.6 (CH), 122.8 (CH), 121.9 (CH), 56.7 (C*), 32.2 (CH₂), 25.8 (CH₃) ppm. IR (neat) νmax = 3853.51, 2947.03, 2858.31, 2167.84, 1782.10, 1610.45, 1456.16, 1271.00, 1161.07, 1139.85, 1097.42, 1020.27, 906.48, 889.12, 725.18, 690.4 ppm. HRMS (ESI): m/z calcd for C₁₂H₁₃NS [M+H]⁺: 204.0841, found 204.0834.

**Benzyl spiro[indole-3,4'-piperidine]-1'-carboxylate (3h)**

Following the procedure I with benzyl 4-formylpiperidine-1-carboxylate (247 mg, 1 mmol) and phenylhydrazine hydrochloride (144 mg, 1 mmol) the spiroindolenine (173 mg, 0.54 mmol, 54%) was obtained as a yellowish oil. TLC (DCM:EtOAc, 4:1 v/v): Rf = 0.3. ¹H NMR (500 MHz, CDCl₃) δ = 8.35 (s, 1H); 7.67 (d, J = 7.9 Hz, 1H); 7.41–7.36 (m, 6H); 7.35-7.32 (m, 1H); 7.27 (t, J = 7.5 Hz, 1H); 5.20 (s, 2H); 4.09 (d, J = 6.9 Hz, 2H); 3.57 (td, J = 9.8, 3.2 Hz, 2H); 1.89–1.76 (m, 2H); 1.72–1.61 (m, 2H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 175.7 (CH), 155.3 (C*), 154.5 (C*), 142.6 (C*), 136.5 (C*), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 126.3 (CH), 122.2 (CH), 121.6 (CH), 67.3 (CH₃), 55.6 (CH₂), 41.9 (CH₃), 30.4 (C*) ppm. HRMS (ESI): m/z calcd for C₂₀H₂₁N₂O₂ [M+H]⁺: 321.1598, found 321.1580.

**Benzyl 5-methoxySpiro[indole-3,4'-piperidine]-1'-carboxylate (3i)**

Following the procedure I with benzyl 4-formylpiperidine-1-carboxylate (247 mg, 1 mmol) and 4-methoxyphenylhydrazine hydrochloride (174 mg, 1 mmol) the spiroindolenine (210 mg, 0.6 mmol, 60%) was obtained as a reddish oil. TLC (DCM:EtOAc, 4:1 v/v): Rf = 0.35. ¹H NMR (500 MHz, CDCl₃) δ = 8.24 (s, 1H); 7.56 (d, J = 8.2 Hz, 1H); 7.41–7.32 (m, 5H); 6.90-6.87 (m, 2H); 5.20 (s, 2H); 4.17–4.08 (m, 2H); 3.83 (s, 3H); 3.54–3.47 (m, 2H); 1.87–1.77 (m, 2H); 1.69–1.60 (m, 2H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 173.5 (CH), 158.7 (C*), 155.4 (C*), 148.2 (C*), 144.3 (C*), 136.5 (C*), 128.5 (CH), 128.1 (CH), 128.0 (CH), 121.9 (CH), 112.7 (CH), 56.7 (C*), 32.2 (CH₂), 25.8 (CH₃) ppm. IR (neat) νmax = 3853.51, 2947.03, 2858.31, 2167.84, 1782.10, 1610.45, 1456.16, 1271.00, 1161.07, 1139.85, 1097.42, 1020.27, 906.48, 889.12, 725.18, 690.4 ppm. HRMS (ESI): m/z calcd for C₂₀H₂₁N₂O₂ [M+H]⁺: 321.1598, found 321.1580.

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108.9 (CH), 67.4 (CH₂), 55.8 (CH₃), 55.7 (CH₃), 41.9 (CH₂), 31.0 (C*) ppm. IR (neat)νₘₐₓ = 3332.8, 2947.0, 2858.3, 1693.4, 1685.7, 1427.2, 1236.3, 729.0, 696.2 cm⁻¹. HRMS (ESI): m/z calcd for C₂₁H₂₃N₂O₃ [M+H]⁺: 351.1703, found 351.1686.

**Benzyl 5'-chloroSpiro[piperidine-4,3'-pyrrolo[3,2-b]pyridine]-1-carboxylate (3j)**

Following the procedure I with benzyl 4-formylpiperidine-1-carboxylate (247 mg, 1 mmol), 2-chloro-5-hydrazinylpyridine (143 mg, 1 mmol) and p-TsOH (190 mg, 1 mmol) in DCE (0.1M) at 100 °C during 5h, the spiroindolenine (71 mg, 0.33 mmol, 33%) was obtained as a yellowish foam. TLC (cyclohexane:EtOAc, 1:1 v/v): Rf = 0.4. ¹H NMR (500 MHz, CDCl₃) δ = 8.32 (s, 1H); 7.86 (d, J = 8.2 Hz, 1H); 7.39-7.31 (m, 6H); 5.18 (s, 2H); 4.15-4.09 (m, 2H); 3.77-3.70 (m, 2H); 1.85-1.72 (m, 2H); 1.67-1.52 (m, 2H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 177.9 (CH), 164.0 (C*), 155.3 (C*), 148.3 (C*), 146.2 (C*), 136.6 (C*), 130.5 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 123.4 (CH), 67.3 (CH₃), 54.8 (CH₂), 40.7 (CH₂), 28.3 (C*) ppm. HRMS (ESI): m/z calcd for C₂₀H₂₂ClN₃NaO₃ [M+MeOH+Na]: 410.1241, found 410.1241.

**Synthesis of Ugi products 4**

Spiroindolenine 3 (1 eq) was dissolved in DCM (1 M) followed by the addition of the corresponding acid (1.05 eq) and isocyanide (1.05 eq). The reaction mixture was stirred for 24 h at room temperature. Afterwards, DCM was evaporated under vacuum to achieve the crude residue that was subjected to column chromatography (SiO₂, corresponding eluent).

**N-(tert-butyl)-1'-propionylspiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4a)**

reaction of spiroindolenine 3a (100 mg, 0.53 mmol), propionic acid (41 µl, 41 mg, 0.56 mmol) and tert-butylisocyanide (60 µl, 47 mg, 0.56 mmol) afforded the Ugi product (149 mg, 0.43 mmol, 82%) as a whitish solid. TLC (cyclohexane:EtOAc, 4:1 v/v): Rᵣ = 0.6. Mp: 203.6 – 204.2 °C. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.22 (s, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.09 (t, J = 7.1 Hz, 1H), 5.15 (s, 1H), 4.53 (s, 1H), 2.45 (d, J = 99.3 Hz, 2H), 1.88-1.56 (m, 10H), 1.22 (t, J = 7.3 Hz, 3H), 1.18 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ =
172.9 (C*), 168.5 (C*), 140.9 (C*), 139.7 (C*), 128.5 (CH), 124.7 (CH), 122.9 (CH), 117.2 (CH), 72.6 (CH), 51.5 (C*), 39.9 (C*), 30.5 (CH₃), 29.8 (CH₃), 29.1 (CH₂), 28.5 (CH₃), 25.6 (CH₂), 22.8 (CH₃), 9.0 (CH₃) ppm. IR (neat) νₓmax = 3315.4, 2933.5, 1676.0, 1623.9, 1542.9, 1481.2, 1456.2, 1425.3, 736.8, 650.0, 609.5, 532.3 cm⁻¹. HRMS (ESI): m/z calcd for C₂₂H₃₀N₂NaO₂ [M+Na]^+: 365.2199, found 365.2203.

N-(tert-buty)-1'-pivaloylspiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4b)

reaction of spiroindolenine 3a (100 mg, 0.54 mmol), pivalic acid (64 µl, 58 mg, 0.57 mmol) and tert-butylocyanide (64 µl, 48 mg, 0.57 mmol) afforded the Ugi product (199 mg, 0.43 mmol, 81%) as a yellowish solid. TLC (cyclohexane:EtOAc, 4:1 v/v): Rf = 0.5. Mp: 142.4 °C. ¹H NMR (500 MHz, CDCl₃) δ = 8.12 (d, J = 8.0 Hz, 1H), 7.23 (td, J = 8.1, 1.4 Hz, 1H), 7.17 (d, J = 6.4 Hz, 1H), 7.10 (td, J = 7.4, 1.0 Hz, 1H), 5.23 (s, 1H), 4.92 (s, 1H), 2.04 – 1.48 (m, 10H), 1.36 (s, 9H), 1.11 (s, 9H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 177.2 (C*), 169.0 (C*), 142.7 (C*), 140.0 (C*), 128.1 (CH), 125.1 (CH), 122.6 (CH), 119.0 (CH), 72.0 (CH), 51.28 (C*), 49.53 (C*), 40.61 (C*), 38.17 (CH₂), 30.28 (CH₂), 28.40 (CH₃), 28.0 (CH₃), 25.7 (CH₂), 23.3 (CH₂), 22.9 (CH₃) ppm. IR (neat) νₓmax = 2972.1, 2922.0, 2852.5, 1670.2, 1647.1, 1541.0, 1473.5, 1456.2, 1396.4, 1348.1, 1340.4, 1184.2, 761.8 cm⁻¹. HRMS (ESI): m/z calcd for C₂₃H₃₄N₂NaO₂ [M+Na]^+: 393.2512, found 393.2493.

1'-benzoyl-N-cyclohexylspiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4c)

reaction of spiroindolenine 3a (100 mg, 0.53 mmol), benzoic acid (68 mg, 0.56 mmol) and cyclohexylisocyanide (68 µl, 61 mg, 0.56 mmol) afforded the Ugi product (192 mg, 0.46 mmol, 87%) as a yellowish solid. TLC (cyclohexane:EtOAc, 3:1 v/v): Rf = 0.32. Mp: 172.0 – 176.1 °C. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 7.52 – 7.42 (m, 4H), 7.19 (d, J = 7.5 Hz, 1H), 7.08 (s, 2H), 5.52 (s, 2H), 4.69 (s, 2H), 3.84 – 3.65 (m, 1H), 1.85 – 1.07 (m, 20H). ¹³C NMR (126 MHz, CDCl₃) δ = 169.3 (C*), 168.0 (C*), 141.0 (C*), 133.6 (CH), 131.0 (CH), 130.3 (CH), 128.9 (CH), 128.6 (CH), 123.0 (CH), 47.9 (CH), 39.2 (C*), 32.8 (CH₃), 30.4 (CH₂), 25.6 (CH₂), 24.6 (CH₂), 23.1 (CH₂) ppm. IR (neat) νₓmax = 1676.0, 1622.0, 1544.9, 1479.3, 1450.4, 1392.5, 1226.6, 1151.4, 1028.0, 802.3, 788.7, 736.8, 709.8, 655.8, 632.6, 613.3, 559.3 cm⁻¹. HRMS (ESI): m/z calcd for C₂₇H₃₃N₂NaO₂ [M+Na]^+: 439.2356, found 439.2363.
N-(3,4-dimethoxyphenethyl)-1'-(2-oxo-2-phenylacetyl)spiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4d)

reaction of spiroindolenine 3a (125 mg, 0.67 mmol), 2-oxo-2-phenylacetic acid (107 mg, 0.71 mmol) and 4-(2-isocyanatoethyl)-1,2-dimethoxybenzene (136 mg, 0.71 mmol) afforded the Ugi product (242 mg, 0.46 mmol, 69 %) as a yellowish solid. TLC (cyclohexan:EtOAc, 3:1 v/v): Rf = 0.28. Mp: 70.1 – 77.7 °C. Rotamers were present on NMR timescale. 1H NMR (500 MHz, CDCl3) δ = 8.13 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 7.1 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.31 – 7.28 (m, 1H), 7.19 (d, J = 7.6 Hz, 2H), 6.68 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 1.8 Hz, 1H), 6.45 (dd, J = 8.1, 1.8 Hz, 1H), 5.42 (t, J = 5.5 Hz, 1H), 4.54 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.39 (dq, J = 12.7, 6.4 Hz, 1H), 3.28 (dq, J = 13.2, 7.0 Hz, 1H), 2.58 (s, 2H), 1.59 (s, 10H) ppm. 13C NMR (126 MHz, CDCl3) δ = 189.2 (C*), 167.9 (C*), 164.1 (C*), 149.0 (C*), 147.5 (C*), 140.3 (C*), 139.5 (C*), 135.0 (CH), 132.5 (C*), 130.7 (C*), 130.1 (CH), 129.0 (CH), 128.3 (CH), 126.1 (CH), 123.1 (CH), 120.4 (CH), 117.7 (CH), 111.5 (CH), 111.2 (CH), 71.3 (CH), 55.9 (CH3), 55.8 (CH3), 49.2 (C*), 40.2 (CH3), 39.3 (CH3), 34.8 (CH2), 30.2 (CH2) 25.2 (CH2), 22.6 (CH2), 22.5 (CH2) ppm. IR (neat) νmax = 1637.4, 1539.1, 1508.2, 1417.6, 1222.8, 1139.8, 1026.1, 810.0, 746.4, 661.5, 592.1 cm⁻¹. HRMS (ESI): m/z calcd for C32H34N2NaO5 [M+Na]⁺: 549.2360, found 549.2369.

1'-benzoyl-N-(6-bromopyridin-2-yl)spiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4e)

reaction of spiroindolenine 3a (97 mg, 0.52 mmol), benzoic acid (67 mg, 0.55 mmol) and 2-bromo-6-isocyanopyridine (100 mg, 0.55 mmol) afforded the Ugi product (127 mg, 0.26 mmol, 50 %) as an orange solid. TLC: (cyclohexane:EtOAc, 4:1 v/v): Rf = 0.85. Mp: 120.1 – 148.6 °C. Rotamers were present on NMR timescale. 1H NMR (500 MHz, CDCl3) δ = 8.15 (d, J = 7.5 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.03 (s, 2H), 6.18 (s, 2H), 4.91 (s, 1H), 1.94 – 1.31 (m, 10H) ppm. 13C NMR (126 MHz, CDCl3) δ = 171.0 (C*), 168.4 (C*), 151.1 (C*), 141.0 (C*), 140.8 (CH), 139.0 (C*), 133.7 (CH), 130.2 (CH), 129.3 (C*), 129.1 (CH), 128.7 (CH), 128.5 (CH), 123.9 (CH), 123.0 (CH), 112.8 (CH), 39.5 (C*), 31.0 (CH), 30.4 (CH2), 29.7 (CH2), 25.3 (CH2), 23.1 (CH3), 22.7 (CH3) ppm. IR (neat) νmax = 2922.0, 2852.5, 1685.7, 1566.1, 1479.3, 1427.2, 1388.7, 1292.2, 1153.3, 1126.3, 786.9, 746.4, 705.9 cm⁻¹. HRMS (ESI): m/z calcd for C26H24BrN3NaO2 [M+Na]⁺: 514.0944, found 519.0922.
5'-bromo-N-(tert-butyl)-1'-pivaloylspiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4f)

reaction of spiroindolenine 3c (100 mg, 0.37 mmol), pivalic acid (40 mg, 0.39 mmol) and tert-butylisocyanide (44 µl, 33 mg, 0.39 mmol) afforded the Ugi product (92 mg, 0.2 mmol, 54%) as an orange solid. TLC (cyclohexane:EtOAc, 3:1 v/v): Rf = 0.77. Mp: 172.3 – 176.6 °C. 1H NMR (500 MHz, CDCl3) δ = 8.04 (d, J = 8.6 Hz, 1H), 7.37 (d, J = 10.0 Hz, 1H), 7.29 (s, 1H), 5.22 (s, 1H), 1.89 – 1.53 (m, 10H), 1.36 (s, 9H), 1.17 (s, 9H) ppm. 13C NMR (126 MHz, CDCl3) δ = 177.3 (C*), 168.5 (C*), 142.3 (C*), 141.9 (C*), 131.0 (CH), 125.9 (CH), 120.3 (CH), 117.7 (C*), 71.9 (CH), 51.5 (C*), 49.6 (C*), 40.7 (C*), 38.2 (CH2), 30.1 (CH3), 28.4 (CH3), 27.9 (CH3), 25.5 (CH3), 23.1 (CH3), 22.8 (CH2) ppm. IR (neat) νmax = 2922.0, 1670.2, 1654.8, 1456.2, 1334.6, 1180.3, 887.2, 823.5 cm⁻¹. HRMS (ESI): m/z calcd for C23H32BrN2O2 [M+Na]⁺: 473.1597, found 473.1586.

1'-benzoyl-N-(tert-butyl)-5'-methylspirop[cyclohexane-1,3'-indoline]-2'-carboxamide (4g)

reaction of spiroindolenine 3b (100 mg, 0.5 mmol), benzoic acid (64 mg, 0.52 mmol) and tert-butylisocyanide (59 µl, 0.52 mmol) afforded the Ugi product (145 mg, 42 mg, 72%) as a white solid. TLC (cyclohexane:EtOAc, 1:1 v/v): Rf = 0.56. Mp: 208.8 – 209.9 °C. Rotamers were present on NMR timescale. 1H NMR (500 MHz, CDCl3) δ = 7.45 (dt, J = 34.6, 7.3 Hz, 5H), 6.96 (s, 1H), 6.71 – 5.94 (m, 2H), 4.77 (s, 1H), 2.29 (s, 3H), 1.85 – 1.34 (m, 10H), 1.28 (s, 9H) ppm. 13C NMR (126 MHz, CDCl3) δ = 168.2 (C*), 138.8 (C*), 130.8 (CH), 128.6(CH), 127.5 (CH), 123.3 (CH), 122.6 (CH), 121.3 (CH), 60.4 (C*), 51.5 (C*), 39.1 (CH3), 31.0 (CH), 30.0 (CH2), 28.6 (CH3), 25.5 (CH3), 23.1 (CH3), 21.2 (CH3) ppm. IR (neat) νmax = 2929.7, 1685.7, 1621.4, 1535.2, 1488.9, 1448.4, 1390.6, 1355.9, 1247.86,1228.57, 1201.6, 825.5, 711.7, 690.5, 640.3, 580.5 cm⁻¹. HRMS (ESI): m/z calcd for C26H32N2O2 [M+H]⁺: 405.2537, found 405.2551.

1'-acetyl-N-(tert-butyl)-5',7'-difluorospiro[cyclohexane-1,3'-indoline]-2'-carboxamide (4h)

reaction of 3d (82 mg, 0.37 mmol), acetic acid (23 µl, 23 mg, 0.39 mmol) and tert-butylisocyanide (44 µl, 33 mg, 0.39 mmol) afforded the Ugi product (106 mg, 0.29 mmol, 79%) as a yellowish solid. TLC (DCM): Rf = 0.54. Mp: 184.4 – 185.6 °C. Rotamers were present on NMR timescale. 1H NMR (500 MHz, CDCl3) δ = 6.75 – 6.67 (m, 2H), 6.31 (s, 1H), 4.99 (s, 1H), 2.27 (d, J = 5.0 Hz, 3H), 2.05 – 1.96 (m, 1H), 1.84 – 1.57 (m, 7H), 1.58 – 1.49 (m, 1H), 1.36 – 1.31 (m, 1H), 1.28 (s, 9H) ppm. 13C NMR (126 MHz, CDCl3) δ = 170.3 (C*), 167.7 (C*), 160.5 (dd, JCF = 246.8, 10.6 Hz, C*), 150.4 (dd, JCF = 255.6, 12.7 Hz, C*), 148.3 (dd, JCF =
12.7, 2.7 Hz, C*), 124.5 (d, J = 9.0 Hz, C*), 106.7 (dd, J_CF = 24.5, 2.7 Hz, CH), 103.9 (t, J_CF = 26.0 Hz, CH), 72.4 (CH), 51.8 (C*), 48.8 (C*), 37.8 (CH2), 30.2 (CH2), 28.8 (CH3), 25.8 (CH2), 23.5 (CH2), 23.3 (CH3), 22.8 (CH3) ppm. IR (neat) _ν_max_ = 3321.2, 2935.5, 2358.8, 2237.3, 1674.1, 1625.9, 1548.7, 1485.1, 1456.2, 1404.8, 1386.7, 1336.6, 1120.6, 918.0, 846.7, 727.1, 644.2, 574.7 cm⁻¹. HRMS (ESI): m/z calcd for C_20H_26F_2N_2NaO_3 [M+Na]^+ : 387.1855, found 387.1865.

**N-cyclohexyl-1-pivaloyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-carboxamide (4i)**

reaction of spiroindolenine 3e (64 mg, 0.34 mmol), pivalic acid (37 mg, 0.36 mmol) and cyclohexylisocyanide (45 μL, 40 mg, 0.36 mmol) afforded the Ugi product (65 mg, 0.16 mmol, 48 %) as a white solid. TLC (DCM): _R_f = 0.28. Mp: 177.2–177.9 °C. ¹H NMR (500 MHz, CDCl₃) δ = 8.14 (d, J = 7.8 Hz, 1H), 7.30 – 7.25 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 5.39 (d, J = 7.8 Hz, 1H), 5.15 (s, 1H), 4.08 (t, J = 11.4 Hz, 1H), 4.02–3.96 (m, 1H), 3.95–3.88 (m, 1H), 3.83–3.73 (m, 1H), 3.70–3.59 (m, 1H), 2.29–2.18 (m, 1H), 1.79 – 1.70 (m, 1H), 1.70 – 1.60 (m, 3H), 1.53 – 1.41 (m, 3H), 1.34 (s, 9H), 1.33 – 1.14 (m, 3H), 1.09 – 0.93 (m, 2H), 0.82 – 0.72 (m, 1H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 177.3 (C*), 138.6 (C*), 142.9 (C*), 143.8 (C*), 126.9 (CH), 125.6 (CH), 122.7 (CH), 119.2 (CH), 70.9 (CH), 65.7 (CH₂), 64.7 (CH₂), 47.9 (CH), 47.5 (C*), 40.9 (C*), 33.7 (CH₂), 32.7 (CH₂), 30.6 (CH₂), 28.1 (CH₃), 25.5 (CH₂), 24.4 (CH₃) ppm. IR (neat) _ν_max_ = 3853.5, 3423.4, 2935.5, 1672.2, 1508.2, 1471.6, 1456.2, 1348.1, 1186.1, 1186.1, 1105.1, 1028.0, 937.3, 767.6 cm⁻¹. HRMS (ESI): m/z calcd for C₂₄H₃₆F₂NaO₃ [M+Na]^+ : 421.2462, found 421.2477.

**1-acetyl-N-(2,6-dimethylphenyl)-5-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-carboxamide (4j)**

reaction of 3f (74 mg, 0.37 mmol), acetic acid (23 μL, 23 mg, 0.39 mmol), 2,6-dimethylphenyl isocyanide (51 mg, 0.39 mmol) afforded the Ugi product (139 mg, 0.35 mmol, 96%) as an orange solid. TLC (DCM): _R_f = 0.33. Mp: 98.5–101.3 °C. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.11 (d, J = 8.26 Hz, 1H), 7.15–6.96 (m, 5H), 6.88 (s, 1H), 4.95 (s, 1H), 4.02–3.87 (m, 3H), 3.88–3.78 (m, 1H), 2.41–2.27 (m, 1H), 2.37 (s, 6H), 1.93 (s, 3H), 1.89–1.58 (m, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 168.9 (C*), 167.5 (C*), 138.4 (C*), 138.3 (C*), 135.7 (C*), 134.6 (C*), 132.7 (C*), 129.8 (CH), 128.7 (CH), 128.0 (CH), 123.6 (CH₂), 117.7 (CH), 72.4 (CH), 65.4 (CH₂), 64.6 (CH₃), 47.1 (C*), 38.9 (CH₃), 30.7 (CH₂), 24.4 (CH₃), 21.6 (CH₃), 18.7 (CH₃) ppm. IR (neat) _ν_max_ = 3259.5, 2954.7, 2925.8, 1647.1, 1488.9, 1436.9, 1386.7, 1350.1, 1265.2, 1164.9, 1103.2, 1033.8, 908.4, 727.1, 713.6, 646.1 cm⁻¹. HRMS (ESI): m/z calcd for C₂₄H₃₈N₂NaO₃ [M+Na]^+ : 415.1992, found 415.1981.
N-pentyl-1-pivaloyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-thiopyran]-2-carboxamide (4k)

Reaction of 3g (69 mg, 0.34 mmol), pivalic acid (37 mg, 0.36 mmol), 1-pentyl isocyanide (32 µl, 35 mg, 0.36 mmol) afforded the Ugi product (66 mg, 0.16 mmol, 48%) as a yellowish solid. TLC (DCM): Rf = 0.91. Mp: 127.8–129.0°C. 1H NMR (500 MHz, CDCl3) δ = 8.16 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 5.59–5.40 (m, 1H), 5.06 (s, 1H), 3.52–3.40 (m, J = 13.2 Hz, 1H), 3.16–3.07 (m, 1H), 3.07–2.99 (m, 1H), 2.99–2.92 (d, J = 13.2 Hz, 1H), 2.63 (d, J = 14.0 Hz, 1H), 2.56 (d, J = 14.0 Hz, 1H), 2.36–2.24 (m, 1H), 2.04–1.94 (m, 2H), 1.78–1.68 (m, 1H), 1.35 (s, 9H), 1.29–1.19 (m, 2H), 1.18–1.09 (m, 2H), 1.01–0.89 (m, 2H), 0.77 (t, J = 7.5 Hz, 3H) ppm. 13C NMR (126 MHz, CDCl3) δ = 177.4 (C*), 169.5 (C*), 142.7 (C*), 138.9 (C*), 128.9 (CH), 125.6 (CH), 122.9 (CH), 119.4 (CH), 71.1 (CH), 49.0 (C*), 40.9 (C*), 39.5 (CH2), 38.4 (CH3), 32.1 (CH2), 29.0 (CH2), 28.9 (CH3), 28.2 (CH3), 25.3 (CH3), 22.4 (CH2), 14.2 (CH3) ppm. IR (neat) νmax = 3853.5, 3423.4, 2947.0, 2858.3, 2167.8, 1782.1, 1610.4, 1596.9, 1471.6, 1458.1, 1388.6, 1344.3, 1294.1, 1271.0, 1263.3, 1238.2, 1207.4, 1139.8, 1097.4, 1020.3, 908.4, 889.1, 729.0, 692.4, 642.2 cm−1. HRMS (ESI): m/z calcd for C23H34N2O2S [M+H]+: 425.2233, found 425.2221.

Benzyl 1-acetyl-2-(tert-butylcarbamoyl)spiro[indoline-3,4'-piperidine]-1'-carboxylate (4l)

Reaction of spiroindolenine 3h (120 mg, 0.37 mmol), acetic acid (23 µl, 23 mg, 0.39 mmol) and tert-butylisocyanide (44 µl, 33 mg, 0.39 mmol) afforded the Ugi product (134 mg, 0.28 mmol, 77%) as a pinkish solid. TLC (DCM:EtOAc, 4:1 v/v): Rf = 0.4. Mp: 233.2-234.9 °C. Rotamers were present on NMR timescale. 1H NMR (500 MHz, CDCl3) δ = 8.21 (s, 1H), 7.37–7.33 (m, 5H); 7.28–7.25 (m, 1H); 7.16–7.09 (m, 2H); 5.25 (s, 1H); 5.15 (s, 2H); 4.55 (s, 1H); 4.25–4.00 (m, 2H); 3.52–3.47 (m, 1H); 3.24–3.18 (m, 1H); 2.24 (s, 3H); 2.14–1.95 (m, 1H); 1.88–1.75 (m, 1H); 1.72–1.49 (m, 2H); 1.20 (s, 9H) ppm. 13C NMR (126 MHz, CDCl3) δ = 169.3 (C*), 167.8 (C*), 155.2 (C*), 140.5 (C*), 137.4 (C*), 129.0 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 125.0 (CH), 122.7 (CH), 117.1 (CH), 72.3 (CH2), 67.2 (CH2), 51.6 (C*), 46.9 (C*), 41.2 (CH2), 40.6 (CH3), 38.5 (CH2), 29.9 (CH2), 28.3 (CH3), 24.0 (CH3) ppm. IR (neat)νmax = 3332.8, 2947.0, 1618.2, 1610.5, 1400.2, 1481.23, 1272.9, 1217.0, 756.0, 746.4, 667.3 cm−1. HRMS (ESI): m/z calcd for C23H34N2O4 [M+H]+: 464.2544, found 464.2551.
Benzyl 2-(cyclohexylcarbamoyl)-1-propionylspiro[indoline-3,4′-piperidine]-1′-carboxylate (4m)

reaction of spiroidolenine 3h (110 mg, 0.34 mmol), propionic acid (27 μl, 26 mg, 0.36 mmol) and cyclohexylisocyanide (45 μl, 40 mg, 0.36 mmol) afforded the Ugi product (138mg, 0.27 mmol, 80 %) as a withuish foam. TLC: (DCM:EtOAc, 4:1 v/v): Rf = 0.5. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.24 (s, 1H), 7.37- 7.30 (m, 6H); 7.15- 7.08 (m, 2H); 5.32 (s, 1H); 5.15 (s, 2H); 4.69 (s, 1H); 4.24-4.00 (m, 2H); 3.77- 3.63 (m, 1H); 3.61- 3.37 (m, 1H); 3.31- 3.14 (m, 1H); 2.61- 2.47 (m, 1H); 2.39- 2.33 (m, 1H); 2.13- 1.98 (m, 1H); 1.86- 1.36 (m, 8H); 1.35- 1.16 (m, 5H); 1.11- 0.93 (m, 2H); 0.93- 0.79 (m, 1H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 172.6 (C*), 167.7 (C*), 155.2 (C*), 140.7 (C*), 137.4 (C*), 136.7 (C*), 129.0 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 125.0 (CH), 122.7 (CH), 117.1 (CH), 70.7 (CH), 67.2 (CH₃), 48.0 (CH), 46.9 (C*), 41.3 (CH₂), 40.6 (CH₂), 38.3 (CH₂), 32.5 (CH₂), 30.2 (CH₂), 29.9 (CH₂), 25.2 (CH₂), 24.3 (CH₂), 8.8 (CH₃) ppm. IR (neat) νmax = 3332.8, 2947.0, 2858.3, 1693.4, 1610.4, 1429.1, 1260.7, 696.2 cm⁻¹.


Benzyl 2-(tert-butylcarbamoyl)-1-(2,4,6-trimethylbenzoyl)spiro[indoline-3,4′-piperidine]-1′-carboxylate (4n)

reaction of spiroidolenine 3h (80 mg, 0.25 mmol), 2,4,6-trimethylbenzoic acid (43 mg, 0.26 mmol) and tert-butylisocyanide (30 μl, 22 mg, 0.26 mmol) afforded the Ugi product (99 mg, 0.17 mmol, 70 %) as a withuish foam. TLC (DCM:EtOAc, 4:1 v/v): Rf = 0.45. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 7.44-7.29 (m, 5H), 7.08 (d, J = 7.5 Hz, 1H); 6.98 (s, 1H); 6.95 (t, J = 7.5 Hz, 1H); 6.88-6.81 (m, 2H); 5.87 (s, 1H); 5.64 (d, J = 8.1 Hz, 1H); 5.17 (s, 2H); 5.05 (s, 1H); 4.19- 4.11 (m, 2H); 3.41- 3.20 (m, 2H); 2.34 (s, 3H); 2.30- 2.20 (m, 2H); 2.24 (s, 3H); 2.12- 1.98 (m, 2H); 2.02 (s, 3H); 1.31 (s, 9H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 168.9 (C*), 167.4 (C*), 155.2 (C*), 139.7 (C*), 139.6 (C*), 139.3 (C*), 136.6 (C*), 134.8 (C*), 133.3 (C*), 132.9 (C*), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 124.2 (CH), 122.9 (CH), 112.7 (CH), 69.5 (CH), 67.2 (CH₂), 51.7 (C*), 44.6 (C*), 41.7 (CH₂), 40.8 (CH₂), 38.9 (CH₂), 30.3 (CH₂), 28.4 (CH₃), 21.3 (CH₃), 18.9 (CH₃), 18.8 (CH₃) ppm. HRMS (ESI): m/z calcd for C₃₅H₄₃N₃NaO₄ [M+Na]^+:590.2989, found 590.2976.
Benzyl 2-(tert-butylcarbamoyl)-5-methoxy-1-propionylspiro[indoline-3,4'-piperidine]-1'-carboxylate (4o)

reaction of spiroindolenine 3i (130 mg, 0.37 mmol), propionic acid (29 µl, 29 mg, 0.39 mmol) and tert-butylisocyanide (44 µl, 33mg, 0.39 mmol) afforded the Ugi product (168 mg, 0.33 mmol, 90%) as a purple foam. TLC (DCM:EtOAc, 4:1 v/v): Rf = 0.4. Rotamers were present on NMR timescale. 

¹H NMR (500 MHz, CDCl₃) δ = 8.15 (d, J = 7.6 Hz, 1H), 7.37- 7.27 (m, 5H); 6.77 (d, J = 7.9 Hz, 1H); 6.67 (s, 1H); 5.27 (s, 1H); 5.15 (s, 2H); 4.57 (s, 1H); 4.22- 4.02 (m, 2H); 3.79 (s, 3H); 3.60- 3.41 (m, 1H); 3.27- 3.12 (m, 1H); 2.56- 2.46 (m, 1H); 2.36- 2.23 (m, 1H); 2.09- 1.94 (m, 1H); 1.83- 1.71 (m, 2H); 1.67- 1.48 (m, 2H); 1.32-1.12 (m, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 172.0 (C*), 168.0 (C*), 157.1 (C*), 155.2 (C*), 139.1 (C*), 136.7 (C*), 134.2 (C*), 128.5 (CH), 128.0 (CH), 127.9 (CH), 117.9 (CH), 112.8 (CH), 109.3 (CH), 71.4 (CH), 67.2 (CH₂), 55.6 (CH₃), 51.6 (C*), 47.0 (C*), 41.2 (CH₃), 40.6 (CH₃), 38.5 (CH₃), 30.1 (CH₂), 28.7 (CH₃), 28.4 (CH₃), 8.8 (CH₃) ppm. IR (neat) νₘₐₓ = 3332.8, 2947.0, 2858.3, 1693.4, 1610.4, 1429.1, 1236.3, 1203.5, 812.0, 696.2 cm⁻¹. HRMS (ESI): m/z calcd for C₂₉H₃₇N₃NaO₅ [M+H⁺]^+: 530.2625, found 530.2613.

Benzyl 2'-(tert-butylcarbamoyl)-5'-chloro-1'-propionyl-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[3,2-b]pyridine]-1-carboxylate (4p)

reaction of spiroindolenine 3j (106 mg, 0.3 mmol), propionic acid (23 µl, 0.39 mmol) and tert-butylisocyanide (35 µl, 0.39 mmol) afforded the Ugi product (124 mg, 0.24 mmol, 81%) as a yellow oil. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.42 (br s, 1H), 7.42-7.27 (m, 6H); 7.22- 7.12 (m, 1H); 5.27 (s, 1H); 5.14 (s, 2H); 4.56- 4.39 (m, 1H); 4.28- 4.11 (m, 1H); 4.00- 3.82 (m, 1H); 3.72- 3.59 (m, 1H); 3.54- 3.39 (m, 1H); 2.61- 2.42 (m, 1H); 2.39- 2.17 (m, 1H); 1.94-1.73 (m, 2H); 1.72- 1.50 (m, 2H); 1.37- 1.12 (m, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 168.8 (C*), 163.1 (C*), 155.2 (C*), 145.9 (C*), 136.7 (C*), 134.6 (C*), 133.7 (C*), 128.5 (CH), 128.0 (CH), 127.9 (CH), 123.4 (CH), 118.5 (CH), 71.8 (CH), 67.2 (CH₂), 52.2 (C*), 43.4 (C*), 40.5 (CH₃), 39.7 (CH₃), 38.9 (CH₃), 30.7 (CH₂), 28.8 (CH₃), 28.4 (CH₃), 8.5 (CH₃) ppm. HRMS (ESI): m/z calcd for C₂₇H₃₃ClN₄NaO₄ [M+Na⁺]^+: 535.2083, found 535.2093.
Synthesis of Azido-Ugi products 5

To a solution of spiroindole 3 (1 eq.) in MeOH (1 M), azidotrimethylsilane (1.1 eq.) and the corresponding isocyanide (1.1 eq.) were added. The mixture was stirred for 2 hours at room temperature. Afterwards the solvent was removed and the crude product was subjected to column chromatography (SiO₂, corresponding eluents).

2'-{(1-(tert-butyl)-1H-tetrazol-5-yl)spiro[cyclohexane-1,3'-indoline]} (5a)

reaction of spiroindolenine 3a (47 mg, 0.25 mmol), azidotrimethylsilane (36 µl, 32 mg, 0.28 mmol) and tert-butylisocyanide (31 µl, 23 mg, 0.28 mmol) afforded the azido-Ugi product (52 mg, 0.17 mmol, 67 %) as a yellowish solid. TLC (cyclohexane:EtOAc, 4:1 v/v): Rₘₜₜ = 0.21, Mp: 210.4 – 213.8 °C. ¹H NMR (500 MHz, CDCl₃) δ = 7.25 (d, J = 7.3 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.85 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 5.18 (s, 1H), 1.85 (s, 9H), 2.04 – 1.44 (m, 10H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 154.68 (C*), 148.28 (C*), 136.91 (C*), 128.17 (CH), 123.67 (CH), 120.49 (CH), 110.63 (CH), 61.83 (CH), 61.63 (C*), 50.97 (C*), 39.07 (CH₂), 31.27 (CH₂), 30.10 (CH₃), 23.34 (CH₃), 23.26 (CH₂) ppm. IR (neat): νₘₚₚ (cm⁻¹) 2928.7, 1596.9, 1481.2, 1454.2, 1236.3, 1218.9, 738.7, 655.7, 628.7, 578.6, 538.1 cm⁻¹. HRMS (ESI): m/z calcd for C₁₈H₂₅N₅Na [M+Na]⁺: 334.2002, found 334.2011.

2'-{(1-cyclohexyl-1H-tetrazol-5-yl)spiro[cyclohexane-1,3'-indoline]} (5b)

reaction of spiroindolenine 3a (95 mg, 0.51 mmol), azidotrimethylsilane (72 µl, 63 mg, 0.55 mmol) and cyclohexylisocyanide (68 µl, 60 mg, 0.55 mmol) afforded the azido-Ugi product (139 mg, 42 mg, 82%) as a red solid. TLC (cyclohexane:EtOAc, 3:1 v/v): Rₘₜₜ = 0.64. Mp: 51.3 – 56.8 °C. ¹H NMR (500 MHz, CDCl₃) δ = 7.22 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.69 (d, J = 7.7 Hz, 1H), 5.37 (s, 1H), 4.18 (s, 1H), 4.05 (s, 1H)2.12 – 1.08 (m, 20H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 153.87 (C*), 148.02 (C*), 136.41 (C*), 128.28 (CH), 123.32 (CH), 119.76 (CH), 109.55 (CH), 62.38, 58.75 (C*), 50.14 (CH), 38.57 (CH), 33.97 (CH₂), 31.27 (CH₂), 30.10 (CH₃), 25.86 (CH₃), 23.34 (CH₃), 23.26 (CH₂) ppm. IR (neat): νₘₚₚ (cm⁻¹) 2928.7, 1596.9, 1481.2, 1454.2, 1236.3, 1218.9, 738.7, 655.7, 628.7, 578.6, 538.1 cm⁻¹. HRMS (ESI): m/z calcd for C₁₈H₂₅N₅Na [M+Na]⁺: 334.2002, found 334.2011.
32.21 (CH₂), 31.85 (CH₂), 25.22 (CH₂), 25.05 (CH₂), 24.61 (CH₂), 22.19 (CH₂), 21.95 (CH₂) ppm. IR (neat): \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2927.7, 2854.4, 1606.6, 1483.2, 1465.8, 1448.4, 738.7 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{20}\)H\(_{27}\)N\(_5\)Na [M+Na]\(^{+}\): 360.2159, found 360.2167.

**5'-methyl-2'-(1-pentyl-1H-tetrazol-5-yl)spiro[cyclohexane-1,3'-indoline] (5c)**

The reaction of spiroindolenine 3b (80 mg, 0.4 mmol), azidotrimethylsilane (58 µl, 50 mg, 0.44 mmol) and 1-pentyl isocyanide (39 µl, 43 mg, 0.44 mmol) afforded the azido-Ugi product (79 mg, 0.23 mmol, 58 %) as a brownish solid. TLC (DCM:EtOAc, 9:1 v/v): \( R_f = 0.80 \). Mp: 94.1–95.0 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 7.05 \) (s, 1H); 6.93 (d, \( J = 7.7 \) Hz, 1H); 6.61 (d, \( J = 7.7 \) Hz, 1H); 5.24 (s, 1H); 4.17 (t, \( J = 7.6 \) Hz, 2H); 2.29 (s, 3H), 1.94–1.87 (m, 1H), 1.85–1.62 (m, 6H), 1.45 (s, 3H), 1.30–1.21 (m, 2H), 1.20–1.11 (m, 2H), 1.11–1.01 (m, 2H), 0.86 (t, \( J = 6.9 \) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta = 154.9 \) (C*), 146.0 (C*), 137.0 (C*), 129.3 (C*), 128.9 (C*), 128.4 (CH), 110.3 (CH), 63.3 (CH), 50.9 (C*), 49.0 (CH\(_3\)), 38.8 (CH\(_2\)), 32.4 (CH\(_2\)), 30.2 (CH\(_3\)), 28.8 (CH\(_2\)), 25.5 (CH\(_3\)), 22.3 (CH\(_2\)), 21.3 (CH\(_3\)), 14.1 (CH\(_3\)) ppm. IR (neat) \( \nu_{\text{max}} = 3388.5, 2929.7, 2864.1, 2360.71, 1614.3, 1490.9, 1456.2, 1298.0, 1242.1, 1176.5, 1134.1, 1101.3, 839.0, 821.6 777.3, 740.6, 624.9, 576.7 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{20}\)H\(_{29}\)N\(_5\)Na [M+Na]\(^{+}\): 362.2135, found 362.2132.

**2'-(1-(tert-butyl)-1H-tetrazol-5-yl)-5',7'-difluorospiro[cyclohexane-1,3'-indoline] (5d)**

The reaction of spiroindolenine 3d (88 mg, 0.4 mmol), azidotrimethylsilane (58 µl, 50 mg, 0.44 mmol) and tert-butyl isocyanide (49 µl, 37 mg, 0.44 mmol) afforded the azido-Ugi product (123 mg, 0.35 mmol, 89 %) as a yellowish solid. TLC (DCM:cyclohexane 4:1, 9:1 v/v): \( R_f = 0.33 \). Mp: 233.5–234.3°C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 6.80 \) (dd, \( J = 8.2, 1.7 \) Hz, 1H), 6.67–6.60 (m, 1H), 5.27 (s, 1H), 1.86 (s, 9H), 1.81–1.70 (m, 3H), 1.70–1.54 (m, 5H), 1.54–1.36 (m, 2H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta = 157.4 \) (dd, \( J_{CF} = 240.0, 8.9 \) Hz, C*), 154.0 (C*), 148.5 (dd, \( J_{CF} = 243.4, 12.7 \) Hz, C*), 141.1 (dd, \( J_{CF} = 8.4, 5.2 \) Hz, C*), 131.0 (dd, \( J_{CF} = 12.7, 1.8 \) Hz, C*), 106.7 (dd, \( J_{CF} = 24.1, 3.0 \) Hz, CH), 103.0 (dd, \( J_{CF} = 27.5, 21.4 \) Hz, CH), 62.1 (CH), 61.7 (C*), 51.8 (C*), 38.4 (CH\(_3\)), 31.0 (CH\(_3\)), 30.8 (CH\(_2\)), 25.6 (CH\(_2\)), 23.1 (CH\(_3\)) ppm. IR (neat) \( \nu_{\text{max}} = 3352.0, 2987.5, 2931.6, 2860.2, 2356.8, 1635.5, 1610.4, 1490.9, 1452.3, 1338.5, 1217.0, 1093.6, 991.3, 810.0, 655.7, 570.9 cm\(^{-1}\). HRMS (ESI): \( m/z \) calcd for C\(_{38}\)H\(_{33}\)F\(_2\)N\(_5\)Na [M+Na]\(^{+}\): 370.1814, found 370.1806.
2-(1-cyclohexyl-1H-tetrazol-5-yl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (5e)

Reaction of spiroindolenine 3e (75 mg, 0.4 mmol), azidotrimethylsilane (58 µl, 50 mg, 0.44 mmol) and cyclohexyl isocyanide (54 µl, 48 mg, 0.44 mmol) afforded the azido-Ugi product (117 mg, 0.34 mmol, 86%) as a pinkish solid. TLC (DCM:EtOAc, 9:1 v/v): Rf = 0.38. Mp: 186.1–187.0 °C. 1H NMR (500 MHz, CDCl3) δ = 7.23 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 5.40 (s, 1H), 4.67 (s, 1H), 4.05 – 3.91 (m, 2H), 3.91 – 3.83 (m, 1H), 3.72 – 3.62 (m, 1H), 3.34 (t, J = 10.5 Hz, 1H), 2.05 – 1.91 (m, 3H), 1.91 – 1.80 (m, 2H), 1.80 – 1.61 (m, 4H), 1.61 – 1.50 (m, 1H), 1.21 – 1.04 (m, 2H), 1.01 – 0.89 (m, 1H), 0.89 – 0.77 (m, 1H) ppm. 13C NMR (126 MHz, CDCl3) δ = 153.6 (C*), 148.4 (C*), 135.0 (C*), 128.8 (CH), 123.1 (CH), 119.8 (CH), 109.7 (CH), 64.0 (CH2), 63.9 (CH2), 61.9 (CH), 58.8 (CH), 47.6 (C*), 38.0 (CH2), 33.7 (CH2), 32.4 (CH2), 31.6 (CH2), 25.2 (CH2), 25.0 (CH2), 24.6 (CH2) ppm. IR (neat) νmax = 3853.5, 3332.8, 2933.5, 2852.3, 1604.7, 1485.1, 1465.8, 1448.4, 1438.8, 1388.7, 1309.6, 1238.2, 1103.2, 1095.5, 1020.3, 935.4, 894.9, 837.0, 798.5, 748.33, 642.2, 545.8 cm⁻¹. HRMS (ESI): m/z calcld for C19H25N5NaO [M+Na]+: 362.1951, found 362.1956.

2-(1-(tert-butyl)-1H-tetrazol-5-yl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-thiopyran] (5f)

Reaction of 3g (81 mg, 0.4 mmol), azidotrimethylsilane (58 µl, 50 mg, 0.44 mmol) and tert-butyl isocyanide (49 µl, 37 mg, 0.44 mmol) afforded the azido-Ugi product (78 mg, 0.23 mmol, 59%) as a yellow solid. TLC (DCM): Rf = 0.80. Mp: 219.2–219.9 °C. 1H NMR (500 MHz, CDCl3) δ = 7.29 (d, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 5.16 (s, 1H), 2.91 – 2.80 (m, 2H), 2.80 – 2.73 (m, 1H), 2.25 – 2.13 (m, 5H), 1.86 (s, 9H) ppm. 13C NMR (126 MHz, CDCl3) δ = 154.1 (C*), 148.3 (C*), 135.0 (C*), 128.7 (CH), 124.2 (CH), 120.4 (CH), 110.9 (CH), 62.1 (CH), 61.8 (C*), 49.7 (C*), 39.0 (CH2), 32.5 (CH2), 31.1 (CH2), 24.9 (CH2), 24.7 (CH2) ppm. IR (neat) νmax = 3354.0, 2918.1, 2850.6, 1604.6, 1487.0, 1460.0, 1431.1, 1396.4, 1259.4, 1234.4, 1220.9, 1122.5, 1103.2, 1047.3, 975.9, 893.0, 734.8, 669.2 cm⁻¹. HRMS (ESI): m/z calcld for C17H23N3NaS [M+Na]+: 352.1566, found 352.1573.
Final decoration of the examples of the library 7

To a round-bottomed flask charged with Pd/C (10%), MeOH (5 ml) was added under N₂ stream, followed by the addition of 4m (75 mg, 0.15 mmol, not soluble in MeOH). The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1 h. The Pd/C was removed by filtration over celite (washing with EtOAc) followed by concentration of the solvent, yielding quantitatively the unprotected product. Afterwards an ice-cooled solution of the product, acid (1 eq.) and Et₃N (2.5 eq.) in DMF (1 mL) was prepared. HOBt (1.1 eq.) and EDC.HCl (1.1 eq.) were added and the reaction mixture was stirred at rt during 15 h. After completion, the solvent was evaporated under vacuum. The residue was extracted with ethyl acetate, and the organic layers were combined and washed with 1N HCl aqueous solution, sat. solution of Na₂CO₃ and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product obtained was subjected to column chromatography (SiO₂, TLC: DCM/ EtOAc 4:1, Rf = 0.4) achieving 7a in 70% (50 mg, 0.1 mmol) yield as a white solid. Mp: 184.3-185.7 °C. Rotamers were present on NMR timescale. 

1H NMR (500 MHz, CDCl₃) δ = 8.25 (s, 1H), 7.49- 7.33 (m, 5H); 7.33- 7.26 (m, 1H); 7.20- 7.08 (m, 2H); 5.37 (s, 1H); 4.75 (s, 1H); 4.65 (s, 1H); 3.78- 3.57 (m, 3H); 3.56- 3.36 (m, 1H); 3.35- 3.16 (m, 1H); 2.67- 2.44 (m, 1H); 2.41- 2.17 (m, 1H); 2.07- 1.94 (m, 1H); 1.88- 1.36 (m, 8H); 1.35-1.12 (m, 5H); 1.11- 0.92 (m, 2H); 0.92- 0.72 (m, 1H) ppm. 

13C NMR (126 MHz, CDCl₃) δ = 172.5 (C*), 170.3 (C*), 167.7 (C*), 140.8 (C*), 137.0 (C*), 135.7 (C*), 129.7 (CH), 129.0 (CH), 128.5 (CH), 126.9 (CH), 125.0 (CH), 122.6 (CH), 117.1 (CH), 70.7 (CH), 48.0 (CH), 47.2 (C*), 45.1 (CH₂), 39.5 (CH₂), 38.7 (CH₂), 32.5 (CH₂), 31.1 (CH₃), 29.9 (CH₃), 29.0 (CH₃), 25.1 (CH₃), 24.3 (CH₃), 8.8 (CH₃) ppm. IR (neat): νmax = 3332.8, 2947.0, 2858.3, 1693.4, 1610.4, 1508.2, 1477.4, 1388.7, 1272.9, 705.9 cm⁻¹. HRMS (ESI): m/z calcd for C₂₉H₃₆N₃O₃ [M+H]+: 474.2751, found 474.2731.

To a round-bottomed flask charged with Pd/C (10%), MeOH (5 ml) was added under N₂ stream, followed by the addition of 4l (100 mg, 0.21mmol, not soluble in MeOH). The reaction mixture was stirred at
room temperature under a hydrogen atmosphere for 1 h. The Pd/C was removed by filtration over celite (washing with EtOAc) followed by concentration of the solvent, yielding quantitatively the unprotected product. Afterwards an ice-cooled solution of the product and Et₃N (2.5 eq.) in DCM (2 mL) was prepared. Propionyl chloride (1.1 eq) was added and the reaction mixture was stirred at rt during 1 h. Then, it was diluted with DCM (2 mL) and washed with water. Finally, the organic layer was dried over anhydrous sodium sulfate and DCM was evaporated under vacuum. The crude product was purified by column chromatography (SiO₂, TLC: DCM:EtOAc, 1:1 v/v, Rᵣ = 0.3), yielding to 80% (66 mg, 0.17 mmol) of 7b as a white solid.

Mp: 191.0-191.7 °C. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.21 (s, 1H); 7.28-7.25 (m, 1H); 7.19-7.06 (m, 2H); 5.32-5.28 (m, 1H); 4.62-4.49 (m, 2H); 3.89-3.66 (m, 2H); 3.07-2.91 (m, 1H); 2.52-2.32 (m, 2H); 2.30-2.18 (m, 2H); 2.11-1.99 (m, 1H); 1.92-1.78 (m, 1H); 1.78-1.60 (m, 2H); 1.59-1.47 (m, 1H); 1.33-1.12 (m, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 172.2 (C*), 169.2 (C*), 167.9 (C*), 140.5 (C*), 137.4 (C*), 129.1 (CH), 125.2 (CH), 122.6 (CH), 117.2 (CH), 72.2 (CH), 51.8 (C*), 47.2 (C*), 42.3 (CH₂), 38.3 (CH₃), 31.0 (CH₂), 29.6 (CH₂), 28.3 (CH₃), 26.6 (CH₃), 24.0 (CH₃), 9.5 (CH₃) ppm. IR (neat): ν max (cm⁻¹) 3332.7, 2947.0, 1683.7, 1650.9, 1610.4, 1602.7, 1483.2, 1411.8, 1218.9, 981.7, 748.3 cm⁻¹. HRMS (ESI): m/z calcd for C₂₂H₃₅N₃O₃ [M+H]+:408.2258, found 408.2262.

To a round-bottomed flask charged with Pd/C (10%), MeOH (5 ml) was added under N₂ stream, followed by the addition of 4o (81 mg, 0.15 mmol, not soluble in MeOH). The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1 h. The Pd/C was removed by filtration over celite (washing with EtOAc) followed by concentration of the solvent, yielding quantitatively the unprotected product. Afterwards an ice-cooled solution of the product and Et₃N (2.5 eq.) in DCM (2 mL) was prepared. Sulfonyl chloride (1.05 eq) was added and the reaction mixture was stirred at rt 2 h. Then, it was diluted with DCM (3 mL) and washed with water, dried over anhydrous sodium sulfate concentrated under vacuum. The crude product was purified by column chromatography (SiO₂, TLC: DCM/ EtOAc 9:1, Rᵣ = 0.7), yielding to 77% (65 mg, 0.11 mmol) of 7c as a whitish solid. Mp: 206.5-208.0 °C. Rotamers were present on NMR timescale. ¹H NMR (500 MHz, CDCl₃) δ = 8.11 (d, J = 8.2 Hz, 1H); 7.67 (d, J = 8.1 Hz, 2H); 7.34 (d, J = 8.1 Hz, 2H); 6.77 (d, J = 7.9 Hz, 1H); 6.64 (d, J = 1.7 Hz, 1H); 5.24 (s, 1H); 4.32 (s, 1H); 3.83-3.69 (m, 2H); 3.78 (s, 3H); 3.00 (t, J = 11.5 Hz, 1H); 2.66-2.58 (m, 1H); 2.45 (s, 3H); 2.45-2.33 (m, 1H); 2.31-2.21 (m, 2H); 1.83-1.65 (m, 3H); 1.20-1.09 (m, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ = 171.8 (C*), 167.8 (C*), 157.2 (C*), 143.7 (C*), 138.7 (C*), 134.0 (C*), 133.7 (C*), 130.2 (CH), 127.0 (CH), 117.9 (CH), 113.2 (CH), 108.9 (CH), 71.0 (CH), 55.6 (CH₃), 51.6 (C*), 46.4 (C*), 43.6 (CH₂), 42.8 (CH₃), 37.9 (CH₂), 29.8 (CH₂), 28.6 (CH₂), 28.3 (CH₃), 21.6 (CH₃), 8.7 (CH₃) ppm. IR (neat) ν max = 3332.8, 2947.0, 2858.3,
To a round-bottomed flask charged with Pd/C (10%), MeOH (5 ml) was added under N\textsubscript{2} stream, followed by the addition of 4n (85 mg, 0.15 mmol, not soluble in MeOH). The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1 h. The Pd/C was removed by filtration over celite (washing with EtOAc) followed by concentration of the solvent, yielding quantitatively the unprotected product. Afterwards a solution of the product in DCM (2 ml) was prepared. 4-Methoxybenzyl isocyanate (1.05 eq) was added and the reaction mixture was stirred at rt during 2 h. After completion, the solvent was evaporated under vacuum and the crude product obtained was subjected to column chromatography (SiO\textsubscript{2}, TLC: DCM/ EtOAc 4:1, R\textsubscript{f} = 0.35) yielding to 70% (61 mg, 0.1 mmol) of 7d as a white solid. Mp: 228.0-230.0 °C. Rotamers were present on NMR timescale.\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta = 7.28-7.25\) (m, 2H); 7.12 (d, \(J = 7.4\) Hz, 1H); 6.99-6.95 (m, 2H); 6.89-6.84 (m, 4H); 6.44 (br s, 1H); 5.86 (br s, 1H); 5.66 (d, \(J = 8.1\) Hz, 1H); 5.08 (s, 1H); 4.09-4.03 (m, 2H); 3.78 (s, 3H); 3.51-3.45 (m, 1H); 3.39-3.29 (m, 1H); 3.35 (s, 3H); 2.30-2.23 (m, 1H); 2.26 (s, 3H); 2.15-2.11 (m, 1H); 2.03 (s, 3H); 1.73-1.64 (m, 2H); 1.70 (s, 3H); 1.31 (s, 9H) ppm. \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta = 168.9\) (C*), 167.5 (C*), 155.9 (C*), 155.4 (C*), 139.6 (C*), 139.5 (C*), 139.4 (C*), 134.8 (C*), 133.3 (C*), 132.9 (C*), 131.9 (C*), 129.0 (CH), 128.7 (CH), 128.6 (CH), 124.3 (CH), 123.0 (CH), 122.3 (CH), 114.1 (CH), 112.8 (CH), 69.6 (CH), 55.5 (CH\textsubscript{3}), 51.7 (C*), 44.8 (C*), 42.2 (CH\textsubscript{2}), 41.0 (CH\textsubscript{2}), 38.8 (CH\textsubscript{2}), 30.1 (CH\textsubscript{3}), 28.5 (CH\textsubscript{2}), 21.3 (CH\textsubscript{2}), 18.9 (CH\textsubscript{3}), 18.9 (CH\textsubscript{3}) ppm. IR (neat): \(\nu_{\text{max}} = 3332.8, 2947.0, 2858.3, 1693.4, 1610.4, 1508.2, 1477.4, 1388.7, 1236.3, 1203.5, 812.0\) cm\textsuperscript{-1}. HRMS (ESI): \(m/z\) calcd for C\textsubscript{35}H\textsubscript{43}N\textsubscript{4}O\textsubscript{4} [M+H]\textsuperscript{+}: 583.3279, found 583.3250.
Copies of NMR spectra

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