Supporting Information

Highly Stereoselective Synthesis of a Compound Collection based on Bicyclic Scaffolds of Natural Products

Murali Annamalai\textsuperscript{a}, Stanimira Hristeva\textsuperscript{b}, Martyna Bielska\textsuperscript{b}, Raquel Ortega\textsuperscript{b}, and Kamal Kumar\textsuperscript{*a}

\textsuperscript{a} Max-Planck-Institut für molekulare Physiologie, Otto-Hahn-Straße 11, 44227 Dortmund, Germany; \textsuperscript{b} Medicinal Chemistry, Taros Chemicals GmbH & Co. KG, Emil Figge-Str. 76a, 44227, Germany.

Email: Kamal.kumar@mpi-dortmund.mpg.de

\textbf{Table of Contents for Chemical experiments} \hspace{5cm} \textbf{Pages}

1. Materials and methods ............................................................................................................ 1
2. Experimental Procedures ........................................................................................................ 2
3. Experimental for the production phase of Elaeokanidine-A based scaffolds...........13
4. Experimental for the production phase of 8-deoxy serratine based scaffolds........35
5. Copies of NMR Spectras.......................................................................................................63

Materials and methods: Chemicals and solvents were obtained from commercial vendors and were used without further purification. All dry reactions were performed under argon atmosphere using commercial dry solvents. Column chromatography was performed on a silica column using 230–400 mesh silica gel. Thin-layer chromatography was performed on Macherey Nagel pre-coated TLC aluminum sheets with silica gel 60 UV254 (5-17 μm). Compound visualization was effected with UV lamp, Iodine, phosphomolybdic acid in ethanol and aq. KMnO4 solution. \textsuperscript{1}H NMR spectra were recorded at rt on a Bruker Avance spectrometer operating at 400 MHz. Chemical shifts are given in ppm (δ) from tetramethylsilane as an internal standard or residual solvent peak. Significant \textsuperscript{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) in hertz, number of protons. Mass spectrometry was recorded using Agilent uHPLC (1290 Infinity) equipped with a Diode Array Detector and a Quadrupole MSD using mixture gradients of formic acid/water/acetonitrile as system solvent. High-resolution electrospray ionization mass spectra (ESI-FTMS) were recorded on a Thermo LTQ Orbitrap (high-resolution mass spectrometer from Thermo Electron) coupled to an “Accela” HPLC system supplied with a “Hypersil GOLD” column (Thermo Electron).
Experimental procedures:

N-benzyl-N-(2,2-diethoxyethyl)-1,4-dioxaspiro[4.5]decan-8-amine (9): 2,2-diethoxyethan-1-amine 8 (3.63 g; 34.15 mmol) was dissolved in dry DCM (100 ml) and cooled to 0 °C, then 1,4-cyclohexanone monoethylene acetal 7 (5.0 g; 31.05 mmol) was added dropwise. After 10 min NaBH(OAc)_3 (7.89 g; 37.26 mmol) was added in one portion and stirred for 2h at room temp. The reaction mixture was diluted with DCM and saturated aq. NaHCO₃ was added slowly, and then stirred for additional 15 min at rt. The layers were separated, the DCM layer was washed couple of times with saturated aq. NaHCO₃, water, brine solution and dried over anhydrous Na₂SO₄. After concentration the crude residue was filtered through silica column to afford pure compound 9a 7.2 g (85% yield).

The amine compound 9a (7.0 g; 25.60 mmol) was re-dissolved in DCM (105 mL), benzaldehyde (2.98 g; 28.16 mmol) was added dropwise at 0 °C, after 15 min NaBH(OAc)_3 (6.5 g; 30.72 mmol) was added in one portion. Then the reaction mixture was diluted with DCM, aq. NaHCO₃ solution was added allowed to stir for 10 min. The layers were separated, and washed couple of times with saturated aq. NaHCO₃ solution, then water, brine solution and dried over anhydrous Na₂SO₄. After evaporation the crude residue was filtered through silica column to give pure compound (9) 8.7 g (93% yield); ¹H NMR (400 MHz, cdcl₃) δ 7.34 (d, J = 7.2 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 4.33 (t, J = 5.2 Hz, 1H), 3.89 (d, J = 1.1 Hz, 4H), 3.71 (s, 2H), 3.58 (dq, J = 9.1, 7.0 Hz, 2H), 3.47 – 3.38 (m, 2H), 2.68 – 2.57 (m, 3H), 1.77 (t, J = 9.9 Hz, 4H), 1.60 (ddd, J = 25.1, 12.6, 3.1 Hz, 2H), 1.52 – 1.43 (m, 2H), 1.13 (t, J = 7.1 Hz, 6H); ¹³C NMR (101 MHz, CDCll₃) δ 141.5, 128.6, 128.2, 126.7, 108.8, 103.9, 64.5, 64.4, 62.5, 59.1, 55.8, 54.0, 34.4, 25.7, 15.6.; HPLC-MS (ESI) m/z calcd. for C₂₁H₃₄NO₄ [M+H]^+ = 364.24; Found: 364.22.

TLC stain: I₂, KMnO₄
Rf: 0.6 (20% EtOAc in Pet-ether)
**2-Benzyl-6-oxo-2-azabicyclo[3.3.1]nonan-4-yl acetate (10):** The amino-acetal 9 (4.0 g; 11.0 mmol) was dissolved in a mixture of THF and 1.0 M aq. HCl (10:1; 55 mL), the resulting solution was stirred at rt. for 3 h. Then the reaction mixture was diluted with EtOAc, washed couple of times with saturated aq. NaHCO₃, water, and brine solution. After that dried over anhydrous Na₂SO₄, concentrated to give crude residue, which was carefully purified by column chromatography, using 5-10% of EtOAc in pet-ether as eluent to give the pure diastereomer 1.99g (74% yield).

TLC stain: UV, I₂, KMnO₄.

Rᵥ: 0.2 (30% EtOAc in pet-ether).

The alcohol 10a (1.0 g; 4.07 mmol) was re-dissolved in dry DCM (10 mL), and then Et₃N (0.495 g; 4.89 mmol) followed by Ac₂O (0.45 g; 4.48 mmol) and then catalytic amount of DMAP (0.05 g; 0.40 mmol) were added at 0 °C, the resulting solution was stirred 4 h. at rt. After the reaction completion, DCM was added washed couple of times with saturated aq. NaHCO₃ then water and brine solution. Then dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography using 2-5% of EtOAc in pet-ether as gradient to give the pure acetate (10) 0.77 g (66% yield). ¹H NMR (400 MHz, CD₂Cl₂): δ 7.42 – 7.23 (m, 5H), 5.11 (dt, J = 10.7, 6.1 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.70 (d, J = 13.4 Hz, 1H), 3.02 (dd, J = 11.6, 6.4 Hz, 2H), 2.92 (d, J = 2.5 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.48 – 2.39 (m, 2H), 2.21 – 2.14 (m, 1H), 2.02 (t, J = 3.3 Hz, 1H), 1.99 – 1.96 (m, 3H), 1.78 – 1.67 (m, 1H); ¹³C NMR (101 MHz, CD₂Cl₂): δ 209.9, 170.0, 137.0, 128.0, 128.8, 128.5, 127.3, 69.6, 59.3, 50.8, 49.6, 47.8, 40.1, 31.7, 23.1, 20.9.; HPLC-MS (ESI) m/z calcd. for C₁₇H₂₂NO₃ [M+H]+ = 288.15. Found: 288.11.

TLC stain: UV, I₂, KMnO₄

Rᵥ: 0.6 (30% EtOAc in pet-ether)
6-(N-(2-(1H-indol-3-yl)ethyl)acetamido)-2-benzyl-2-azabicyclo[3.3.1]nonan-4-yl acetate (11b): The bicyclic ketone 10 (0.5 g; 1.74 mmol) was added to the slurry of NaBH(OEt)₃ (1.21 g; 2.61 mmol) and MS (0.5 g) in dry DCM (5 mL) followed by tryptamine (0.31 g; 1.91 mmol) was added. Then it was allowed to stir for 24 h. at rt. After completion of reaction was confirmed by TLC, diluted with DCM and saturated aq. NaHCO₃ was added, stirred for addition 15 min at room temp. The DCM layer was washed with couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was filtered through silica column to get the mixture of diastereomers (>10:1) 0.53 g (71% yield).

TLC stain: I₂, KMnO₄; Rf: 0.4 (10% MeOH (Buffered with aq. NH₃) in DCM).

The amine (0.5 g; 1.15 mmol) in dry DCM (5 mL) was added Et₃N (0.14 g; 1.39 mmol), followed by Ac₂O (0.13 g; 1.27 mmol) dropwise at 0 °C and DMAP, and stirred for 4 h. at rt. After completion of reaction, the reaction mixture was diluted with DCM, washed with couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was purified by column chromatography using 2-5% of EtOAc in pet-ether as an eluent to give the pure acetate (11b) 0.44 g (81% yield).; ¹H NMR (500 MHz, CDCl₃) rotamers: δ 8.29 (s, 1H), 8.14 (s, 0.5H), 7.85 – 7.77 (m, 0. H), 7.59 (dd, J = 14.5, 6.2 Hz, 1H), 7.45 – 7.30 (m, 7H), 7.28 – 7.16 (m, 4H), 7.08 (dd, J = 8.9, 2.1 Hz, 1H), 5.28 (dd, J = 35.3, 28.2 Hz, 1H), 4.84 (s, 1H), 3.96 – 3.56 (m, 5H), 3.36 – 3.19 (m, 1H), 3.12 – 2.80 (m,6H), 2.75 – 2.58 (m, 2H), 2.54 – 2.32 (m, 4H), 2.23 – 2.18 (m, 5H), 2.09 – 2.04 (m, 3H), 1.95 – 1.87 (m, 6H); HPLC-MS (ESI) m/z calcd. for C₂₉H₃₄N₃O₃ [M+H]+ = 474.27; Found: 474.44. TLC stain: UV, I₂, KMnO₄

Rf: 0.5 (10% MeOH in DCM)
6-(N-(2-(1H-indol-3-yl)ethyl)acetamido)-2-(methylsulfonyl)-2-azabicyclo[3.3.1]nonan-4-yl acetate (13b): The diacetate 11b (0.3 g; 0.63 mmol) was dissolved in EtOAc and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H₂ atmosphere for overnight. After complete consumption SM, it was filtered through HPLC filter using syringe, washed couple of times with MeOH and concentrated to give pure product 210 mg (86% yield). TLC stain: UV, I₂, KMnO₄; Rf: 0.1 (10% MeOH (Buffered with aq. NH₃) in DCM).

Amine (0.05 g; 0.13 mmol) was dissolved in dry DCM was added Et₃N (0.02 g; 0.2 mmol), followed by MsCl (0.02 g; 0.012 mmol) in one portion at 0 °C, after 4h at room temp., it was then diluted with DCM, washed with couple of times with saturated aq. NaHCO₃ then water, brine solution and dried over Na₂SO₄. Then concentrated to give crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH₃) in DCM as an eluent to give the pure sulphonamide (13) 52 mg (86 % yield). ¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.11 – 7.06 (m, 1H), 6.97 (s, 1H), 5.08 – 4.97 (m, 1H), 4.79 – 4.69 (m, 1H), 3.99 – 3.91 (m, 1H), 3.85 – 3.77 (m, 1H), 3.64 – 3.55 (m, 4H), 3.44 – 3.32 (m, 1H), 3.00 – 2.79 (m, 4H), 2.60 (dd, J = 10.3, 6.5 Hz, 1H), 2.45 – 2.20 (m, 2H), 2.15 (d, J = 6.0 Hz, 3H), 2.06 – 1.96 (m, 2H), 1.92 – 1.71 (m, 5H).; ¹³C NMR (126 MHz, CDCl₃) δ 171.2, 169.3, 136.3, 127.0, 122.4, 121.9, 119.8, 118.2, 112.2, 111.6, 70.7, 55.1, 52.6, 47.6, 45.8, 39.4, 33.3, 32.4, 31.9, 27.8, 25.4, 22.3, 21.1.; HPLC-MS (ESI) m/z calcd. for C₂₃H₃₂O₅S [M+H]⁺ = 462.20; Found: 462.16.

TLC stain: UV, I₂, KMnO₄
2-Benzyl-6-(N-(3-methoxyphenethyl)acetamido)-2-azabicyclo[3.3.1]nonan-4-yl acetate (11): The ketone (1.97 g; 6.85 mmol) in dry DCM (50 mL) was added 3-methoxyphenethylamine (1.14 g; 7.54 mmol) (dilution is very important to get diastereo selectivity!!!), MS followed by NaBH(OH)₃ (5.96 g; 10.28 mmol) in one portion. Then it was allowed to stir for 24 h. at rt. After completion of reaction, diluted with DCM and saturated aq. NaHCO₃ was added, stirred for additional 15 min at rt. The DCM layer was washed couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was filtered through silica column to get the mixture of diastereomers (>10:1) 1.9 g (66% yield). ^1H NMR (400 MHz, CDCl₃) δ 7.33 – 7.17 (m, 6H), 6.82 – 6.72 (m, 3H), 5.35 – 5.28 (m, 1H), 3.79 – 3.73 (m, 4H), 3.63 (d, J = 13.4 Hz, 1H), 3.00 – 2.88 (m, 4H), 2.85 – 2.72 (m, 4H), 2.50 (dd, J = 15.3, 11.4 Hz, 2H), 2.33 – 2.25 (m, 1H), 2.18 – 2.09 (m, 1H), 1.95 – 1.87 (m, 4H), 1.67 – 1.56 (m, 2H), 1.40 (tdd, J = 14.0, 7.0, 3.7 Hz, 1H); ^13C NMR (101 MHz, CDCl₃) δ 170.2, 159.9, 141.9, 139.2, 129.7, 128.7, 128.5, 127.2, 121.2, 114.8, 111.6, 73.9, 60.7, 59.4, 55.4, 53.1, 49.8, 48.7, 37.2, 34.4, 33.4, 31.2, 25.1, 21.4; HPLC-MS (ESI) m/z calcd. for C₂₆H₃₅N₂O₃ [M+H]^+ = 423.26. Found: 423.38. TLC stain: I₂, KMnO₄

Rₓ: 0.5 (10% MeOH (Buffered with aq. NH₃) in DCM)
2-Benzyl-6-((3-methoxyphenethyl)acetamido)-2-azabicyclo[3.3.1]nonan-4-yl acetate (11a): The amine (1.8 g; 4.26 mmol) in dry DCM (23 mL) was added Et₃N (0.52 g; 5.11 mmol), followed by Ac₂O (0.48 g; 4.69 mmol) dropwise at 0 °C and DMAP (0.05 g; 0.426 mmol), and stirred for 4 h. at rt. After completion of reaction, it was diluted with DCM, washed couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was purified by column chromatography using 2-5% of EtOAc:pet-ether as an eluent to give the pure acetate 1.56 g (79% yield). HPLC-MS (ESI) m/z calcd. for C₂₈H₃₆N₂O₄ [M]⁺ = 464.27; Found: 464.37. TLC stain: UV, I₂, KMnO₄
Rᶠ: 0.7 (10% MeOH in DCM)

6-(N-(3-methoxyphenethyl)acetamido)-2-azabicyclo[3.3.1]nonan-4-yl acetate (12a): The diacetate 11a (1.6 g; 3.79 mmol) was dissolved in EtOAc and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H₂ atmosphere for overnight. After complete consumption SM, it was filtered through filter using syringe, washed couple of times with MeOH and concentrated to give pure product 12 0.95 g (67% yield). Rotamers:
$^1$H NMR (500 MHz, DMSO) $\delta$ 7.30 – 7.15 (m, 1H), 6.90 – 6.69 (m, 3H), 5.02 – 4.83 (m, 1H), 4.68 – 4.54 (m, 0.6 H), 4.18 (d, $J$ = 11.5 Hz, 0.4H), 3.94 – 3.69 (m, 3H), 3.64 – 3.43 (m, 1H), 3.25 – 3.06 (m, 6H), 2.95 – 2.69 (m, 4H), 2.56 – 2.33 (m, 5H), 2.08 – 1.66 (m, 11H);

$^{13}$C NMR (126 MHz, DMSO) $\delta$ 170.1, 169.7, 160.0, 159.9, 142.1, 140.9, 130.0, 129.9, 121.3, 121.2, 115.0, 114.7, 112.2, 111.9, 73.6, 73.4, 59.2, 55.8, 55.5, 55.3, 47.8, 46.2, 45.8, 44.6, 44.3, 37.9, 36.7, 35.9, 35.4, 35.3, 33.8, 32.4, 27.3, 26.5, 22.6, 22.1, 21.3.;

HPLC-MS (ESI) m/z calcd. for C$_{21}$H$_{31}$N$_2$O$_4$ [M+H]$^+$ = 375.22. Found: 375.27.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.1 (10% MeOH (Buffered with aq. NH$_3$) in DCM)

**Ethyl 1-benzyl-3-(3-(1,3-dioxoisindolin-2-yl)propyl)-4-oxopiperidine-3-carboxylate (17):** NaH (60% in mineral oil) (3.0 g; 75.2 mmol) was suspended in a mixture of dry THF-DMF (1:1; 200 mL), Keto-ester 15 (10.0 g; 34.2 mmol) dissolved in dry THF was added dropwise at 0 °C, the resulting solution allowed to stir for 10 min to complete deprotonation. Then bromopropyl-phthalimide 16 (11.2 g; 41.02 mmol) in dry THF was added slowly at 0 °C. Then the reaction mixture was fitted with a refluxing condenser and heated at 65 °C for overnight. The reaction completion was monitored by TLC and cooled to room temp and then the pH of the reaction mixture was adjusted to neutral with 1.0M aq. HCl. The layers were separated and aq. layer was extracted with EtOAc, combined organic layer was washed with water, brine solution dried over anhydrous Na$_2$SO$_4$. After concentration the crude residue was then purified by column chromatography using 10-15% EtOAc in pet-ether as a gradient to give pure phthalimide derivative (17) 9.5 g (64% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 – 7.79 (m, 2H), 7.72 – 7.67 (m, 2H), 7.33 – 7.22 (m, 5H), 3.71 (s, 3H), 3.65 (q, $J$ = 6.8 Hz, 2H), 3.55 (d, $J$ = 7.8 Hz, 2H), 3.33 (d, $J$ = 11.1 Hz, 1H), 2.91 (d, $J$ = 49.9 Hz, 2H), 2.37 (d, $J$ = 14.5 Hz, 2H), 2.21 (d, $J$ = 11.2 Hz, 1H), 1.89 – 1.65 (m, 2H), 1.49 (dt, $J$ = 17.4, 13.0, 5.1
Methyl 6-benzyloctahydro-1,6-naphthyridine-4a(2H)-carboxylate (18): Phthalimide (17) (7.0 g; 15.3 mmol) was dissolved in analytical grade ethanol, was added methyl amine (33% in ethanol) (4.32 g; 45.9 mmol) dropwise at room temp. The reaction mixture was fitted with a refluxing condenser and refluxed at 80 °C for 3h. The reaction completion was monitored by TLC and cooled to room temp (the by-product di-amide precipitated out). The solid di-amide separated by filtration and filtrate was concentrated and filtered through silica column to give pure product 2.99 g (63% yield). TLC stain: I₂, KMnO₄; Rf: 0.6 (10% MeOH (Buffered with aq. NH₃) in DCM. The amino-ketone (1.0 g; 3.28 mmol) was dissolved in dry DCM (dilution is very important to get diastereo selectivity!!!) was added equivalent amount of oven dried powdered MS followed by NaBH(OEh)₃ (2.29 g; 4.93 mmol) in one portion, then it was allowed to stir for 18 h. at rt. After completion of SM was confirmed by TLC, diluted with DCM and saturated aq. NaHCO₃ was added, stirred for addition 15 min at room temp. The DCM layer was washed with couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was filtered through silica column to get the mixture of diastereomers (18) (>10:1) 0.691 g (73% yield).; ¹H NMR (400 MHz, CD₂Cl₂) δ 7.23 – 7.12 (m, 5H), 3.56 (s, 3H), 3.45 (d, J = 13.4 Hz, 1H), 3.21 (d, J = 13.4 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.84 (ddt, J = 11.0, 4.4, 2.2 Hz, 1H), 2.58 (ddd, J = 12.6, 6.3, 3.6 Hz, 1H), 2.30 (dd, J = 12.1, 4.3 Hz, 1H), 2.09 (ddd, J = 18.5, 9.9, 4.4 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.77 (dd, J = 7.5, 2.9 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.45 – 1.38 (m, 1H), 1.31 – 1.20 (m, 2H).; ¹³C NMR (101 MHz, CD₂Cl₂) δ 175.2, 139.0, 128.9, 128.1, 127.1, 62.5, 61.9,
61.8, 54.6, 51.4, 47.5, 46.5, 32.5, 29.2, 23.6.; HPLC-MS (ESI) m/z calcd. for C$_{17}$H$_{35}$N$_2$O$_2$ [M+H]$^+$ = 289.18. Found: 289.24.

TLC stain: I$_2$, KMnO$_4$

R$_f$: 0.4 (10% MeOH (Buffered with aq. NH$_3$) in DCM)

Methyl 6-benzyl-1-tosyloctahydro-1,6-naphthyridine-4a(2H)-carboxylate (18a): Amine 18 (0.5 g; 1.73 mmol) was dissolved in dry DCM was added Et$_3$N (0.21 g; 2.08 mmol), followed by TsCl (0.36 g; 1.90 mmol) in one portion at 0 °C, after 4 h. at rt., it was then diluted with DCM, washed with couple of times with saturated aq. NaHCO$_3$ then water, brine solution and dried over Na$_2$SO$_4$. Then concentrated to give crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH$_3$) in DCM as an eluent to give the pure sulphonamide (18a) 674 mg (88 % yield); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.59 – 7.55 (m, 1H), 7.24 (d, $J$ = 8.0 Hz, 1H), 7.19 (ddd, $J$ = 7.4, 4.4, 1.5 Hz, 1H), 7.16 – 7.09 (m, 2H), 4.06 – 3.98 (m, 1H), 3.58 (s, 2H), 3.43 – 3.36 (m, 1H), 3.14 (d, $J$ = 13.4 Hz, 1H), 2.94 (dd, $J$ = 11.4, 2.4 Hz, 1H), 2.82 (ddt, $J$ = 11.2, 4.8, 2.5 Hz, 1H), 2.59 (ddd, $J$ = 25.3, 12.4, 4.7 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.34 (s, 2H), 2.02 (ddd, $J$ = 13.1, 7.0, 2.8 Hz, 1H), 1.87 (ddd, $J$ = 15.3, 11.7, 5.6 Hz, 1H), 1.62 – 1.39 (m, 2H), 1.03 (td, $J$ = 13.3, 4.5 Hz, 1H). $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) δ 172.68, 143.38, 138.62, 137.43, 129.72, 128.84, 128.20, 127.40, 127.16, 65.04, 62.39, 62.16, 54.25, 51.38, 50.17, 49.05, 33.62, 28.31, 23.20, 21.41.; HPLC-MS (ESI) m/z calcd. for C$_{24}$H$_{31}$N$_2$O$_4$S [M+H]$^+$ = 443.19; Found: 443.35.

TLC stain: I$_2$, KMnO$_4$

R$_f$: 0.4 (10% MeOH (Buffered with aq. NH$_3$) in DCM)
6-benzyl-1-tosyloctahydro-1,6-naphthyridin-4a(2H)-yl)methanol (19): To a suspension of LAH (0.043 g; 1.13 mmol) in dry THF was added amino-ester (0.5 g; 1.13 mmol) dissolved in dry THF at 0 °C. Then the reaction mixture was stirred for overnight at rt, after completion of reaction monitored by TLC, the excess LAH was quenched with wet Na$_2$SO$_4$!! ( Few drops of water were added to Na$_2$SO$_4$ to make paste, which used for quenching). The greyish white solid was filtered washed several times with EtOAc and the filtrate was concentrated to give pure product (19) 0.44g, (93% yield).; $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.55 – 7.50 (m, 2H), 7.26 – 7.14 (m, 7H), 4.20 (dd, $J = 10.9, 1.5$ Hz, 1H), 4.14 – 4.06 (m, 1H), 3.45 (d, $J = 10.9$ Hz, 1H), 3.37 – 3.25 (m, 2H), 2.90 – 2.76 (m, 2H), 2.56 – 2.37 (m, 3H), 2.33 (s, 3H), 1.88 – 1.76 (m, 2H), 1.70 – 1.64 (m, 2H), 1.50 – 1.35 (m, 2H), 0.85 (td, $J = 13.3, 4.4$ Hz, 1H).; $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) δ 143.4, 137.7, 137.7, 129.9, 129.1, 128.6, 127.5, 127.1, 66.4, 65.4, 62.8, 62.6, 53.5, 51.2, 38.5, 34.1, 27.5, 21.9, 21.4.; HPLC-MS (ESI) m/z calcd. for C$_{23}$H$_{31}$N$_2$O$_3$S [M+H]$^+$ = 415.20. Found: 415.41.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.3 (10% MeOH (Buffered with aq. NH$_3$) in DCM)

4a-(Methoxymethyl)-1-tosyldecahydro-1,6-naphthyridine (20): The ether 19a (2.4 g; 5.60 mmol) was dissolved in EtOAc:MeOH (1:1) and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H$_2$ atmosphere for overnight. After complete
consumption SM, it was filtered through HPLC filter using syringe, washed couple of times with MeOH and concentrated to give pure product (20) 1.6 g (84% yield).; \(^1\)H NMR (400 MHz, cdcl\(_3\)) \(\delta\) 7.60 (dd, \(J = 8.5, 1.9\) Hz, 1H), 7.31 – 7.27 (m, 1H), 4.31 – 4.23 (m, 1H), 3.92 (d, \(J = 9.6\) Hz, 1H), 3.59 (d, \(J = 9.6\) Hz, 1H), 3.37 (d, \(J = 3.8\) Hz, 1H), 3.21 – 3.06 (m, 2H), 2.75 – 2.62 (m, 1H), 2.54 (td, \(J = 12.8, 2.8\) Hz, 1H), 2.41 (s, 2H), 2.28 – 2.15 (m, 1H), 1.94 – 1.76 (m, 2H), 1.62 – 1.55 (m, 1H), 0.93 – 0.80 (m, 1H); \(^1\)C NMR (101 MHz, cdcl\(_3\)) \(\delta\) 143.3, 137.9, 129.9, 126.9, 70.4, 66.1, 59.7, 53.4, 51.4, 46.3, 38.7, 32.2, 26.8, 22.0, 21.7.; HPLC-MS (ESI) m/z calcd. for C\(_{17}\)H\(_{27}\)N\(_2\)O\(_3\)S [M+H]\(^+\) = 339.17. Found: 339.32.

TLC stain: UV, I\(_2\), KMnO\(_4\)

R\(_f\) 0.2 (10% MeOH (Buffered with aq. NH\(_3\)) in DCM)

![Chemical Formula: C\(_{20}\)H\(_{30}\)N\(_2\)O\(_4\)S](attachment)

Exact Mass: 394.19

Molecular Weight: 394.53

1-(-4a-(methoxymethyl)-1-tosyloctahydro-1,6-naphthyridin-6(2H)-yl)propan-1-one (21): Amine 20 (0.1 g; 0.29 mmol) dissolved in dry DCM was added Et\(_3\)N (0.04 g; 0.35 mmol), followed by propionyl chloride (0.03 g; 0.33 mmol) dropwise at 0 °C, and stirred for 4 h. at rt. After completion of reaction, the reaction mixture was diluted with DCM, washed couple of times with saturated aq. NaHCO\(_3\) then water and brine solution. After concentration the crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH\(_3\)) in DCM as an eluent to give the pure amide (21) 76 mg (57% yield).; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.54 (d, \(J = 8.1\) Hz, 3H), 7.24 (d, \(J = 8.0\) Hz, 3H), 4.67 (d, \(J = 13.5\) Hz, 1H), 4.23 (t, \(J = 13.5\) Hz, 1H), 3.79 (dd, \(J = 13.5, 1.8\) Hz, 1H), 3.57 (t, \(J = 8.9\) Hz, 1H), 3.25 (d, \(J = 7.0\) Hz, 4H), 2.69 – 2.58 (m, 3H), 2.39 – 2.33 (m, 5H), 2.31 – 2.21 (m, 3H), 2.00 – 1.77 (m, 7H), 1.58 (d, \(J = 14.1\) Hz, 1H), 1.39 – 1.30 (m, 1H), 1.07 – 1.00 (m, 3H), 0.81 (ddd, \(J = 16.1, 11.2, 5.1\) Hz, 2H); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.9, 143.4, 137.5, 129.9, 126.8, 67.4, 65.7, 59.1, 51.7, 51.0, 41.3, 39.7, 30.2, 29.7, 25.7, 25.6, 21.6, 21.5, 9.4.; HPLC-MS (ESI) m/z calcd. for C\(_{20}\)H\(_{31}\)N\(_2\)O\(_3\)S [M+H]\(^+\) = 395.19. Found: 395.30.

TLC stain: UV, I\(_2\), KMnO\(_4\)
Rf: 0.7(10% MeOH (Buffered with aq. NH₃) in DCM

6-Benzyl-4a-(methoxymethyl)-1-tosyldecahydro-1,6-naphthyridine (22): To a solution of amine 20 (45 mg; 0.13 mmol) in dry DCM (3 mL) was added benzaldehyde (16 µL; 0.16 mmol) dropwise at 0 °C. After 10 min NaBH(OAc)₃ (34 mg; 0.16 mmol) was added in one portion and stirred for 2 h. at rt. The reaction mixture was diluted with DCM and saturated aq. NaHCO₃ was added slowly, and then stirred for additional 15 min at rt. The layers were separated, the DCM layer was washed couple of times with saturated aq. NaHCO₃, water, brine solution and dried over anhydrous Na₂SO₄. After concentration the crude residue was filtered through silica column to afford pure compound (22) 43 mg (76% yield).; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.3 Hz, 1H), 7.33 – 7.18 (m, 4H), 4.28 – 4.21 (m, 1H), 4.00 (d, J = 8.8 Hz, 1H), 3.69 (d, J = 8.8 Hz, 1H), 3.45 – 3.29 (m, 3H), 2.90 (t, J = 13.2 Hz, 1H), 2.62 (td, J = 12.5, 2.7 Hz, 1H), 2.49 (d, J = 9.1 Hz, 1H), 2.41 (s, 2H), 2.18 (dd, J = 29.5, 14.7 Hz, 1H), 1.98 – 1.78 (m, 2H), 1.59 – 1.52 (m, 1H), 1.45 – 1.37 (m, 1H), 0.96 – 0.72 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 143.18, 137.66, 129.88, 128.81, 128.29, 127.07, 69.73, 66.28, 62.41, 60.71, 59.52, 53.67, 51.48, 39.67, 31.24, 27.11, 21.86, 21.69.; HPLC-MS (ESI) m/z calcd. for C₂₄H₃₃N₂O₃S [M+H]+ = 429.21; Found: 429.46.

TLC stain: UV, I₂, KMnO₄
Rf: 0.6 (30% EtOAc in Pet-Ether)

Experimental for the production phase of Elaeokanidine-A based scaffolds:
Methyl 1-(benzenesulfonyl)-6-benzyl-decahydro-1,6-naphthyridine-4a-carboxylate (46a): To a solution of the amine 18 (27.0 g, 94 mmol) in dry DCM (270 mL) at 0 °C was added triethylamine (28.4 g, 282 mmol) and benzenesulfonyl chloride (18.4 g, 103 mmol) and the reaction mixture was allowed to warm up to room temperature. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and saturated aq. NH₄Cl. After concentration, the crude residue was purified by column chromatography using 1-3% of MeOH, affording the sulfonamide 29.9 g (75% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.85 (d, J = 6.6 Hz, 2H), 7.57 – 7.48 (m, 3H), 7.30 – 7.25 (m, 3H), 7.21 – 7.19 (m, 2H), 4.21 (d, J = 11.9 Hz, 1H), 3.72 (s, 3H), 3.70 – 3.69 (m, 1H), 3.48 (d, J = 13.4 Hz, 1H), 3.28 (d, J = 13.4 Hz, 1H), 3.10 (dd, J = 2.2, 11.3 Hz, 1H), 2.90 (d, J = 15.2 Hz, 1H), 2.72 – 2.62 (m, 2H), 2.13 – 2.10 (m, 1H), 2.06 – 2.02 (m, 1H), 2.01 – 1.93 (m, 1H), 1.72 (d, J = 11.4 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.16 (dt, J = 4.9, 12.9 Hz, 1H), 0.91 – 0.88 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C₂₃H₂₉N₂O₄S [M]+ = 429.54. Found: 428.90. 
TLC stain: UV, I₂, KMnO₄
Rf: 0.4 (Cyclohexane/EtOAc 7:1)

Methyl 6-benzyl-1-(pyridine-3-sulfonyl)-decahydro-1,6-naphthyridine-4a-carboxylate (46b): To a solution of the amine 18 (27.0 g, 94 mmol) in dry DCM (270 mL) at 0 °C was added triethylamine (28.4 g, 282 mmol) and pyridine-3-sulfonyl chloride (18.3 g, 103 mmol) and the reaction mixture was allowed to warm up to room temperature. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and saturated aq. NH₄Cl. After concentration, the crude residue was purified by column chromatography using 10-15% ethyl acetate in cyclohexane, affording the sulfonamide 28.3 g (70% yield); ¹H NMR (300 MHz, CDCl₃): δ 8.97 (d, J = 1.9 Hz, 1H), 8.70 (d, J = 4.9 Hz, 1H), 8.07 (dd, J = 1.9, 8.0 Hz, 1H), 7.38 (dd, J = 4.9, 8.0 Hz, 1H), 7.20 – 7.08 (m, 5H), 4.13 (d, J = 12.0 Hz, 1H), 3.59 (s, 3H), 3.39 (d, J = 13.4 Hz, 1H),

14
3.17 (d, J = 13.4 Hz, 1H), 3.01 (dd, J = 1.8, 11.4 Hz, 1H), 2.81 (dd, J = 1.7, 9.6 Hz, 1H), 2.68 – 2.60 (m, 2H), 2.55 (dq, J = 4.5, 12.3 Hz, 1H), 2.04 – 1.86 (m, 3H), 1.65 – 1.42 (m, 3H), 1.10 (dt, J = 4.2, 13.3 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C₂₂H₂₈N₃O₄S [M]+ = 430.53. Found: 429.95.

TLC stain: UV, I₂, KMnO₄
Rᶠ: 0.5 (Cyclohexane/EtOAc 5:1)

**Methyl 6-benzyl-1-methanesulfonyl-decahydro-1,6-naphthyridine-4a-carboxylate (46c):**

To a solution of the amine 18 (35.0 g, 121 mmol) in dry DCM (350 mL) at 0 °C was added triethylamine (14.8 g, 146 mmol) and methanesulfonyl chloride (15.3 g, 134 mmol) and the reaction mixture was allowed to warm up to room temperature. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and saturated aq. NH₄Cl. After concentration, the crude residue was purified by column chromatography using 1-3% of MeOH, affording the sulfonamide 12.7 g (29 % yield).; ¹H NMR (300 MHz, CDCl₃); δ 7.33 – 7.21 (m, 5H), 4.13 (d, J = 12.4 Hz, 1H), 3.68 (s, 3H), 3.55 (d, J = 13.4 Hz, 1H), 3.29 (d, J = 13.4 Hz, 1H), 3.12 (dd, J = 2.3, 11.4 Hz, 1H), 3.04 (s, 3H), 3.02 – 3.01 (m, 1H), 2.85 – 2.81 (m, 2H), 2.70 (dt, J = 2.6, 12.3 Hz, 1H), 2.49 -2.40 (m, 1H), 2.16 – 2.01 (m, 2H), 1.78 (d, J = 11.4 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.53 – 1.40 (m, 1H), 1.21 (dt, J = 4.0, 13.4 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C₁₈H₂₇N₂O₄S [M]+ = 367.48. Found: 366.95.

TLC stain: I₂, KMnO₄
Rᶠ: 0.5 (2% MeOH (Buffered with aq. NH₃) in DCM)
Methyl 1-(benzenesulfonyl)-decahydro-1,6-naphthyridine-4a-carboxylate (47a): To a solution of the sulfonamide 46a (5.0 g, 12 mmol) in dry 1,2-dichloroethane (120 mL) was added 1-chloroethyl chloroformate (4.2 g, 30 mmol) and the reaction mixture was refluxed for 15 hours. After complete consumption of the starting material, the reaction mixture was added methanol and it was refluxed for 3 more hours. After concentration, the crude residue was purified by column chromatography using 5-10% methanol in DCM as eluent to give the pure 2.3 g (58% yield).; \(^1\)H NMR (300 MHz, MeOD-\(d_4\)): \(\delta 7.82 – 7.53 \text{ (m, 2H)}\), 7.64 – 7.53 (m, 3H), 4.25 – 4.02 (m, 1H), 3.83 (s, 3H), 3.54 – 3.43 (m, 2H), 2.97 – 2.75 (m, 4H), 2.23 – 2.11 (m, 2H), 1.69 – 1.49 (m, 2H), 1.27 – 1.24 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\(_{16}\)H\(_{22}\)N\(_2\)O\(_4\)S [M]\(^+\) = 339.42. Found: 338.9.

TLC stain: UV, I\(_2\), KMnO\(_4\)

R\(_f\) 0.3 (10% MeOH (Buffered with aq. NH\(_3\)) in DCM)

\[
\text{Methyl 1-(pyridine-3-sulfonyl)-decahydro-1,6-naphthyridine-4a-carboxylate (47b): To a solution of the sulfonamide 46b (5.0g, 12 mmol) in dry 1,2-dichloroethane (120 mL) was added 1-chloroethyl chloroformate (4.2 g, 30 mmol) and the reaction mixture was refluxed for 15 hours. After complete consumption of the starting material, the reaction mixture was added methanol and it was refluxed for 3 more hours. After concentration, the crude residue was purified by column chromatography using 5-10% methanol in DCM as eluent to give the pure 3.2 g (81% yield).;} \(^1\)H NMR (300 MHz, MeOD-\(d_4\)): \(\delta 8.86 \text{ (s, 1H)}\), 8.69 – 8.71 (m, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 4.09 (d, J = 14.8 Hz, 1H), 3.74 (s, 3H), 3.46 (t, J = 11.7Hz, 2H), 3.36 (d, J = 12.7Hz, 2H), 3.00 – 2.86 (m, 3H), 2.63 (q, J = 11.9 Hz, 1H), 2.02 (d, J = 12.9 Hz, 3H), 1.62 (d, J = 14.4 Hz, 1H), 1.41 (dt, J = 4.2, 14.4 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\(_{15}\)H\(_{22}\)N\(_3\)O\(_4\)S [M]\(^+\) = 340.41. Found: 339.95.

TLC stain: UV, I\(_2\), KMnO\(_4\)

R\(_f\) 0.3 (15% MeOH (Buffered with aq. NH\(_3\)) in DCM)
Methyl (4S,8aR)-1-methanesulfonyl-decahydro-1,6-naphthyridine-4a-carboxylate (47c): To a solution of the sulfonamide 46c (4.0 g, 11 mmol) in dry methanol (110 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 3.0 g (99% yield).; ¹H NMR (300 MHz, MeOD-d₄): δ 3.93 (d, J = 12.2 Hz, 1H), 3.71 (s, 3H), 3.21 – 3.06 (m, 3H), 2.86 (s, 3H), 2.81 (dd, J = 3.4, 12.0 Hz, 1H), 7.22 (dd, J = 3.0, 17.5 Hz, 1H), 2.65 – 2.60 (m, 1H), 2.55 (dd, J = 3.8, 11.9 Hz, 1H), 2.46 (d, J = 13.3 Hz, 1H), 2.03 (d, J = 13.3 Hz, 2H), 1.77 – 1.61 (m, 2H), 1.27 (dt, J = 4.6, 13.3 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C₁₁H₂₁N₂O₄S [M]⁺ = 277.35. Found: 277.10. TLC stain: UV, I₂, KMnO₄
Rᶠ 0.3 (15% MeOH (Buffered with aq. NH₃) in DCM)

1-(Benzenesulfonyl)-6-benzyl-decahydro-1,6-naphthyridin-4a-yl]methanol (49a): To a suspension of lithium aluminium hydride (1.7 g, 45 mmol) in dry THF (225 mL) at 0 °C was added dropwise a solution of the ester 46a (19.2 g, 45 mmol) in dry THF (225 mL) and then the reaction mixture was left at room temperature. After complete consumption of the starting material monitored by TLC, the reaction mixture was cooled down to 0 °C and was quenched with i-propanol and water. The reaction mixture was then dried with excess amount of MgSO₄ and concentrated in vacuo affording the product 13.0 g (72% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.68 (d, J = 7.5 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.21 – 7.15 (m, 5H), 4.27 (d, J = 10.9 Hz, 1H), 4.19 (d, J = 11.7 Hz, 1H), 3.52 (d, J = 10.9 Hz, 1H), 3.33 (d, J = 5.6 Hz, 2H), 2.86 (d, J = 10.6 Hz, 2H), 2.61 – 2.48 (m, 2H), 1.91 – 1.81 (m, 2H), 1.72 (d, J = 11.8 Hz, 2H), 1.61 – 1.50 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H)
1.49 – 1.41 (m, 2H), 1.20 (d, J = 8.1 Hz, 1H), 0.92 – 0.74 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C_{22}H_{29}N_{2}O_{3}S [M]^+ = 401.53. Found: 401.00.

TLC stain: UV, I_{2}, KMnO_{4}
R_f 0.3 (10% MeOH (Buffered with aq. NH_{3}) in DCM)

6-Benzyl-1-methanesulfonyl-decahydro-1,6-naphthyridin-4a-yl]methanol (49c): To a suspension of lithium aluminium hydride (0.8 g, 20 mmol) in dry THF (100 mL) at 0 °C was added dropwise a solution of the ester 46c (7.2 g, 20 mmol) in dry THF (100 mL) and then the reaction mixture was left at room temperature. After complete consumption of the starting material monitored by TLC, the reaction mixture was cooled down to 0 °C and was quenched with i-propanol and water. The reaction mixture was then dried with excess amount of MgSO_{4} and concentrated in vacuo affording the product 6.7 g (quant.). \(^1\)H NMR (300 MHz, CDCl_{3}): \(\delta\) 7.30 – 7.28 (m, 5H), 4.32 (d, J = 11.0 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.58 (d, J = 10.7 Hz, 1H), 3.46 (s, 3H), 3.06 – 2.95 (m, 2H), 2.85 – 2.76 (s, 3H; m, 1H), 2.64 (t, J = 12.3 Hz, 2H), 2.05 – 2.01 (m, 2H), 1.89 (d, J = 11.6 Hz, 1H), 1.63 – 1.50 (m, 2H), 1.02 (dt, J = 3.3, 13.3 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{17}H_{27}N_{2}O_{3}S [M]^+ = 339.47. Found: 339.05.

TLC stain: UV, I_{2}, KMnO_{4}
R_f 0.4 (5% MeOH (Buffered with aq. NH_{3}) in DCM)

[(4aS,8aR)-1-(benzenesulfonyl)-6-benzyl-decahydro-1,6-naphthyridin-4a-yl]methyl
N-[(furan-2-yl)methyl]carbamate (50a): To a solution of the alcohol 49a (6.6 g, 16 mmol)
in dry DCM (100 mL) was added triethylamine (2.5 g, 24 mmol) and furfuryl isocyanate (2.4 g, 19 mmol) and the reaction mixture was stirred at room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 15-20% of EtOAc in cyclohexane as an eluent to give the carbamate 3.7 g (43% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.68 (d, J = 7.2 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.19 – 7.09 (m, 6H), 6.22 (m, 2H), 4.64 – 4.38 (m, 2H), 4.40 (d, J = 10.6 Hz, 1H), 4.29 – 4.28 (m, 1H), 4.18 (d, 13.1 Hz, 1H), 3.43 (d, J = 13.2 Hz, 1H), 3.17 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 8.8 Hz, 1H), 2.64 – 2.50 (m, 3H), 2.10 (dq, J = 2.0, 13.1 Hz, 1H), 1.93 – 1.81 (m, 3H), 1.60 – 1.48 (m, 3H), 1.19 (t, J = 7.2 Hz, 1H), 0.78 (dt, J = 3.5, 13.2 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C₂₈H₃₄N₄O₅S [M]⁺ = 524.64. Found: 523.85.

TLC stain: UV, I₂, KMnO₄
Rᶠ: 0.4 (Cyclohexane/EtOAc 2:1)

[(4aS,8aR)-6-benzyl-1-methanesulfonyl-hexahydro-2H-1,6-naphthyridin-4a-yl]methyl N-(furan-2-ylmethyl)carbamate (50c): To a solution of the alcohol 49c (2.8 g, 8 mmol) in dry DCM (50 mL) was added triethylamine (1.2 g, 12 mmol) and furfuryl isocyanate (1.2 g, 10 mmol) and the reaction mixture was stirred at room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 2% MeOH in DCM as an eluent to give the carbamate 3.6 g (94% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.35 – 7.16 (m, 6H), 6.31 – 6.22 (m, 2H), 4.74 – 4.71 (m, 1H), 4.43 – 4.37 (m, 1H), 4.33 (d, J = 5.2 Hz, 2H), 4.04 (d, J = 11.9 Hz, 1H), 3.56 (d, J = 13.3 Hz, 1H), 3.28 (d, J = 12.9 Hz, 1H), 3.05 – 3.02 (m, 1H), 2.77 (s, 3H), 2.75 – 2.71 (m, 1H), 2.60 (dt, J = 2.8, 12.5 Hz, 1H), 2.28 (dq, J = 3.9, 12.5 Hz, 1H), 2.10 – 1.86 (m, 3H), 1.67 (d, J = 12.9 Hz, 1H), 1.56 – 1.43 (m, 2H), 1.12 (t, J = 7.1 Hz, 1H),

19
1.04 – 0.83 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{23}H_{32}N_{3}O_{5}S [M]^+ = 462.57. Found: 461.90.

TLC stain: UV, I₂, KMnO₄

R_f 0.4 (2% MeOH (Buffered with aq. NH₃) in DCM)

1-(Benzenesulfonyl)-decahydro-1,6-naphthyridin-4a-yl[methyl N-[(oxolan-2-yl)methyl]carbamate (51a): To a solution of the carbamate 50a (3.7 g, 7 mmol) in dry methanol (70 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 3.0 g (96% yield); ¹H NMR (300 MHz, CDCl₃): δ 7.71 (d, J = 7.4 Hz, 2H), 7.55 – 7.47 (m, 3H), 4.76 (t, J = 10.5 Hz, 1H), 4.27 (d, J = 11.4 Hz, 2H), 3.9 (bs, 1H), 3.82 (dd, J = 7.2, 13.9 Hz, 1H), 3.72 (dd, J = 7.2, 13.9 Hz, 1H), 3.44 – 3.88 (m, 2H), 3.18 – 3.13 (m, 2H), 2.87 – 2.66 (m, 5H), 2.53 (t, J = 12.7 Hz, 1H), 2.16 (d, J = 13.5 Hz, 1H), 2.11 – 1.80 (m, 6H), 1.73 (d, J = 13.1 Hz, 1H), 1.64 – 1.50 (m, 2H), 0.92 (t, J = 10.6 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C_{21}H_{33}N_{3}O_{5}S [M]^+ = 438.55. Found: 437.90.

TLC stain: UV, I₂, KMnO₄

R_f 0.3 (10% MeOH (Buffered with aq. NH₃) in DCM)
1-Methanesulfonyl-octahydro-1,6-naphthyridin-4a-y]methyl N-(oxolan-2-y]-methyl)carbamate (51c): To a solution of the carbamate 50c (4.4 g, 9 mmol) in dry methanol (90 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. After concentration, the crude residue was purified by column chromatography using 10% MeOH in DCM as an eluent to give the pure product 1.0 g (28% yield).; \( ^1 \)H NMR (300 MHz, MeOD-\( d_4 \)): \( \delta \) 4.43 (g, \( J = 10.0 \) Hz, 2H), 3.99 – 3.90 (m, 2H), 3.87 – 3.79 (m, 1H), 3.71 (q, \( J = 7.1 \) Hz, 1H), 3.51 – 3.45 (m, 2H), 3.41 – 3.28 (m, 2H), 3.30 – 3.28 (m, 1H), 3.21 – 3.09 (m, 3H), 2.91 (s, 3H), 2.86 – 2.81 (m, 2H), 2.41 – 2.23 (m, 2H), 1.99 – 1.79 (m, 5H), 1.68 – 1.54 (m, 2H), 1.29 – 1.27 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for \( \text{C}_{16}\text{H}_{30}\text{N}_{3}\text{O}_{5}\text{S} \) [M]+ = 376.48. Found: 376.00.

TLC stain: UV, I\(_2\), KMnO\(_4\)

R\(_f\) 0.4 (10% MeOH (Buffered with aq. NH\(_3\)) in DCM)

**General procedures for final diversification steps:**

**General procedure for the amide coupling:** Reactions were performed in parallel in 15 ml reaction tubes in a 24 position Mettler-Toledo Miniblock® equipped with a heat transfer block and inert gas manifold. Each reaction tube was loaded with TEA (5.0 eq) and a previously prepared solution of 30 mg of the corresponding intermediate in 1mL of dry THF. Then the corresponding acyl chlorides (1.5 eq) were added. The reactions were stirred at room temperature overnight. The mixtures were evaporated until dryness. The crude were rediluted in 1.0 mL of ACN, filtered and purified with preparative HPLC.

**General procedure for reductive amination:** Reactions were performed in parallel in 15 ml reaction tubes in a 24 position Mettler-Toledo Miniblock® equipped with a heat transfer block and inert gas manifold. Each reaction tube was loaded with the corresponding aldehyde
(2.0 eq), NaBH(OAc)$_3$ (2.5 eq.), acetic acid (2.0 eq) and 1.0 mL of 1,2-dichloroethene (DCE). The reaction mixture was stirred for 30 min, then a previously prepared solution of 30 mg of the corresponding intermediate in 1.0 mL DCE was added. The reactions were stirred at room temperature overnight. The mixtures were diluted with dichloromethane (2.0 mL) and washed with water (1.0 mL). The organic layers were evaporated until dryness. The crudes were rediluted in 1.0 mL of acetonitrile, filtered and purified with preparative HPLC.

**General procedure for sulfonylation:** Reactions were performed in parallel in 15 ml reaction tubes in a 24 position Mettler-Toledo Miniblock® equipped with a heat transfer block and inert gas manifold. Each reaction tube was loaded with TEA (5.0 eq) and a previously prepared solution of 30 mg of the corresponding intermediate in 1 mL of dry THF. Then the corresponding sulfonyl chlorides (1.5 eq) were added. The reactions were stirred at room temperature overnight. The mixtures were evaporated until dryness. The crudes were rediluted in 1.0 mL of ACN, filtered and purified with preparative HPLC.

**General procedure for urea formation:** Reactions were performed in parallel in 15 ml reaction tubes in a 24 position Mettler-Toledo Miniblock® equipped with a heat transfer block and inert gas manifold. Each reaction tube was loaded with TEA (5.0 eq) and a previously prepared solution of 30 mg of the corresponding intermediate in 1 mL of DCM. Then the corresponding isocyanates (1.5 eq) were added. The reactions were stirred at room temperature overnight. The mixtures were evaporated until dryness. The crudes were rediluted in 1.0 mL of ACN, filtered and purified with preparative HPLC.

![Chemical Structure](image_url)

**Methyl 6-benzyl-1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-decahydro-1,6-naphthyridine-4a-carboxylate (46d):** 10.2 mg (23% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.45 (d, $J = 1.4$ Hz, 1H), 7.39 (d, $J = 1.4$ Hz, 1H), 7.29 – 7.26 (m, 5H), 7.29 (d, $J = 1.4$ Hz, 1H), 3.42 (d, $J = 13.4$ Hz, 1H), 3.14 (d, $J = 13.4$ Hz, 1H), 3.14
(dd, J = 2.1, 11.6 Hz, 1H), 3.07 (d, J = 3.6 Hz, 1H), 2.88 (dt, J = 4.3, 12.6 Hz, 1H), 2.78 –
2.67 (m, 2H), 2.37 (dd, J = 3.1, 12.8 Hz, 1H), 2.16 (t, J = 9.9 Hz, 1H), 2.02 (d, J = 12.8 Hz,
1H), 1.92 (d, J = 11.4 Hz, 1H), 1.67 – 1.59 (m, 2H), 1.21 – 1.11 (m, 1H); UHPLC-MS
(ES+APCI) m/z calcd. for C_{21}H_{29}N_{4}O_{4}S [M]+ = 433.54. Found: 433.20.

Methyl 6-benzyl-1-[(2-methoxypyridin-3-yl)methyl]-decahydro-1,6-naphthyridine-4a-carboxylate (46e): 11.5 mg (27% yield); ^1H NMR (300 MHz, CDCl_3): δ 8.14 (dd, J = 1.8, 5.0 Hz, 1H), 8.01 (dd, J = 1.7, 7.3 Hz, 1H), 7.31 – 7.20 (m, 4H), 6.96 (dd, J = 5.1, 7.3 Hz, 2H), 4.33 (d, J = 14.4 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 4.04 (s, 3H), 3.72 (s, 3H), 3.55 (d, J = 13.3 Hz, 1H), 3.32 (d, J = 13.3 Hz, 1H), 3.27 – 3.25 (m, 1H), 3.14 (dd, J = 2.2, 11.5 Hz, 1H), 3.08 (d, J = 11.5 Hz, 1H), 2.99 (dd, J = 1.6, 10.1 Hz, 2H), 2.30 – 1.45 (m, 8H); UHPLC-MS (ES+APCI) m/z calcd. for C_{24}H_{32}N_{3}O_{3} [M]+ = 410.52. Found: 410.40. (94.2%)

Methyl 6-benzyl-1-[(2E)-3-phenylprop-2-en-1-yl]-decahydro-1,6-naphthyridine-4a-carboxylate (46f): 14.3 mg (34% yield); ^1H NMR (300 MHz, CDCl_3): δ 8.48 (s, 1H), 7.42 – 7.28 (m, 7H), 7.22 – 7.20 (m, 2H), 6.71 (d, J = 15.8 Hz, 1H), 6.25 (dt, J = 7.3, 15.8 Hz, 1H), 3.90 (d, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.51 (d, J = 16.3 Hz, 2H), 3.32 (d, J = 13.3 Hz, 1H), 3.15 (dd, J = 1.9, 11.3 Hz, 1H), 3.07 (d, J = 9.4 Hz, 1H), 2.77 – 2.48 (m, 3H), 2.17 (dt, J = 3.1, 11.3 Hz, 1H), 2.06 – 1.97 (m, 2H), 1.80 (d, J = 11.3 Hz, 1H), 1.71 – 1.69 (m, 2H), 1.30 – 1.20 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{26}H_{33}N_{2}O_{2} [M]+ = 405.54. Found: 405.20.
Methyl-6-benzyl-1-[6-(morpholin-4-yl)pyridine-3-carbonyl]-decahydro-1,6-naphthyridine-4a-carboxylate (46g): 15.2 mg (31% yield).; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.22 (d, J = 1.9 Hz, 1H), 8.11 (s, 1H), 7.60 (dd, J = 2.4, 6.4 Hz, 1H), 7.25 – 7.20 (m, 4H), 6.54 (d, J = 8.8 Hz, 1H), 3.92 (dt, J = 3.3, 7.1 Hz, 1H), 3.74 (dd, J = 1.3, 5.1 Hz, 4H), 3.66 (s, 3H), 3.74 (dd, J = 1.3, 5.1 Hz, 4H), 3.42 (s, 3H), 3.19 (dt, J = 3.3, 12.0 Hz, 2H), 3.05 – 2.89 (m, 2H), 2.69 (dq, J = 4.3, 13.4 Hz, 1H), 2.37 (dd, J = 2.4, 11.7 Hz, 1H), 2.23 (dt, J = 2.4, 11.7 Hz, 1H), 1.95 (d, J = 4.2 Hz, 1H), 1.62 – 1.42 (m, 2H), 1.33 (dt, J = 5.0, 12.7 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C$_{27}$H$_{35}$N$_4$O$_4$ [M]+ = 479.58. Found: 479.20.

Methyl 6-[(2-fluorophenyl)carbamoyl]-1-methanesulfonyl-decahydro-1,6-naphthyridine-4a-carboxylate (52a): 26.2 mg (58% yield).; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.95 (dt, J = 1.8, 8.7 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.98 – 6.91 (m, 1H), 4.38 – 4.30 (m, 2H), 4.16 (dt, J = 2.4, 13.5 Hz, 1H), 3.77 (s, 3H), 3.04 (dd, J = 4.7, 11.5 Hz, 1H), 2.97 (s, 3H), 2.91 – 2.71 (m, 3H), 2.60 – 2.42 (m, 2H), 2.17 (d, J = 14.2 Hz, 1H), 2.00 (s, 2H), 1.74 – 1.69 (m, 1H), 1.39 – 1.28 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C$_{18}$H$_{25}$FN$_3$O$_5$S [M]+ = 414.46. Found: 414.20.
Methyl-6-[(2,6-dichlorophenyl)carbamoyl]-1-methanesulfonyl-decahydro-1,6-naphthyridine-4a-carboxylate (52b): 18.9 mg (37% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.33 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 7.7, 8.5 Hz, 1H), 6.69 (bs, 1H), 4.48 (dd, J = 2.6, 13.9 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.17 (dt, J = 2.7, 6.5 Hz, 1H), 3.80 (s, 3H), 3.06 (dd, J = 4.0, 12.1 Hz, 1H), 2.97 (s, 3H), 2.88 (dd, J = 3.1, 13.5 Hz, 1H), 2.88 – 2.73 (m, 2H), 2.57 (dq, J = 4.5, 12.6 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.15 (d, J = 13.5 Hz, 1H), 1.74 – 1.68 (m, 2H), 1.39 – 1.29 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\(_{18}\)H\(_{24}\)Cl\(_2\)N\(_3\)O\(_5\)S [M]+ = 465.36. Found: 465.20.

Methyl-6-(2,5-dimethylfuran-3-carbonyl)-1-(pyridine-3-sulfonyl)-decahydro-1,6-naphthyridine-4a-carboxylate (52c): 15.4 mg (38% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 9.02 (s, 1H), 8.80 (d, J = 3.9 Hz, 1H), 8.14 (d, J = 10.0 Hz, 1H), 7.50 (dd, J = 4.9, 8.0 Hz, 1H), 5.85 (s, 1H), 4.23 (d, J = 12.3 Hz, 2H), 3.65 (s, 3H), 3.03 – 2.97 (m, 1H), 2.86 – 2.77 (m, 3H), 2.60 – 2.42 (m, 1H), 2.34 – 2.29 (m, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 2.09 – 2.06 (m, 1H), 1.78 – 1.72 (m, 2H), 1.26 – 1.16 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\(_{22}\)H\(_{28}\)N\(_3\)O\(_6\)S [M]+ = 462.53. Found: 462.20.

Methyl 1-(benzenesulfonyl)-6-[(5-(hydroxymethyl)furan-2-yl)methyl]-decahydro-1,6-naphthyridine-4a-carboxylate (52d): 13.8 mg (35% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.33 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 7.7, 8.5 Hz, 1H), 6.69 (bs, 1H), 4.48 (dd, J = 2.6, 13.9 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.17 (dt, J = 2.7, 6.5 Hz, 1H), 3.80 (s, 3H), 3.06 (dd, J = 4.0, 12.1 Hz, 1H), 2.97 (s, 3H), 2.88 (dd, J = 3.1, 13.5 Hz, 1H), 2.88 – 2.73 (m, 2H), 2.57 (dq, J = 4.5, 12.6 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.15 (d, J = 13.5 Hz, 1H), 1.74 – 1.68 (m, 2H), 1.39 – 1.29 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\(_{18}\)H\(_{24}\)Cl\(_2\)N\(_3\)O\(_5\)S [M]+ = 465.36. Found: 465.20.
MHz, CDCl$_3$): $\delta$ 7.83 – 7.79 (m, 2H), 7.56 – 7.40 (m, 3H), 6.20 (d, J = 3.1 Hz, 1H), 6.11 (d, J = 3.1 Hz, 1H), 4.54 (d, J = 2.3 Hz, 2H), 4.19 (d, J = 14.7 Hz, 1H), 3.74 (s, 3H), 3.62 (d, J = 14.5 Hz, 1H), 3.43 (d, J = 14.5 Hz, 1H), 3.18 – 3.14 (m, 3H), 2.98 (d, J = 11.0 Hz, 1H), 2.70 – 2.61 (m, 3H), 2.17 – 2.12 (m, 1H), 2.09 – 2.03 (m, 1H), 1.86 (d, J = 11.6 Hz, 1H), 1.69 – 1.59 (m, 2H), 1.23 – 1.12 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{22}$H$_{29}$N$_2$O$_6$S [M]+ = 449.53; Found: 449.20.

Methyl 1-(benzenesulfonyl)-6-[(thiophen-3-yl)methyl]-decahydro-1,6-naphthyridine-4a-carboxylate (52e$^{ii}$): 12.6 mg (33% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.82 (dd, J = 1.3, 7.9 Hz, 2H), 7.58 – 7.47 (m, 3H), 7.24 (d, J = 3.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 1.3, 4.9 Hz, 1H), 4.19 (dt, J = 2.3, 11.7 Hz, 1H), 3.73 (s, 3H), 3.60 (d, J = 13.6 Hz, 1H), 3.42 (d, J = 13.6 Hz, 1H), 3.17 (dd, J = 2.3, 11.5 Hz, 1H), 3.00 (d, J = 11.5 Hz, 1H), 2.70 – 2.62 (m, 3H), 2.16 – 2.03 (m, 3H), 1.83 (d, J = 11.7 Hz, 1H), 1.68 – 1.61 (m, 2H), 1.22 – 1.11 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{21}$H$_{27}$N$_2$O$_4$S$_2$ [M]+ = 435.57. Found: 435.20.

Methyl 1-(benzenesulfonyl)-6-[(pyridin-2-yl)methyl]-decahydro-1,6-naphthyridine-4a-carboxylate (52f$^{ii}$): 14.4 mg (38% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.50 (d, J = 6.5 Hz, 1H), 7.82 – 7.79 (m, 2H), 7.69 (dt, J = 1.7, 7.7 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.38 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 5.1, 7.4 Hz, 1H), 4.21 (d, J = 11.8 Hz, 1H), 3.74 (s, 3H),
3.69 (d, J = 14.6 Hz, 1H), 3.54 (d, J = 14.6 Hz, 1H), 3.10 (d, J = 11.5 Hz, 1H), 2.94 (d, J = 13.3 Hz, 1H), 2.78 – 2.62 (m, 3H), 2.21 – 1.97 (m, 4H), 1.68 – 1.62 (m, 2H), 1.25 – 1.14 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{22}H_{26}N_{3}O_{4}S [M]+ = 430.53. Found: 430.20.

1-(Benzenesulfonyl)-6-[(pyridin-4-yl)methyl]-decahydro-1,6-naphthyridin-4a-yl]methyl N-[[(oxolan-2-yl)methyl]carbamate (52g): 10.8 mg (30% yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 8.52 (t, J = 5.3 Hz, 2H), 7.76 – 7.73 (m, 2H), 7.57 – 7.49 (m, 3H), 7.38 – 7.34 (m, 2H), 4.90 (bs, 1H), 4.81 (d, J = 10.5 Hz, 1H), 4.38 (d, J = 10.5 Hz, 1H), 4.26 (d, J = 13.3 Hz, 1H), 4.01 – 3.94 (m, 1H), 3.88 – 3.71 (m, 3H), 3.56 (d, J = 14.8 Hz, 1H), 3.33 (dd, J = 5.5, 14.8 Hz, 1H), 3.13 – 2.99 (m, 1H), 2.94 – 2.91 (m, 1H), 2.67 – 2.60 (m, 3H), 2.24 – 2.15 (m, 1H), 2.04 – 1.85 (m, 6H), 1.71 (d, J = 12.7 Hz, 1H), 1.60 – 1.47 (m, 3H), 0.86 (t, J = 11.1 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{27}H_{37}N_{4}O_{5}S [M]+ = 529.66. Found: 529.20.

1-(Benzenesulfonyl)-6-[(pyridin-3-yl)methyl]-decahydro-1,6-naphthyridin-4a-yl]methyl N-[[(oxolan-2-yl)methyl]carbamate (52h): 18.9 mg (37% yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 8.50 – 8.46 (m, 2H), 7.85 (d, J = 7.2 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.57 – 7.48 (m, 3H), 7.37 – 7.30 (m, 1H), 5.02 (bs, 1H), 4.70 (d, J = 10.9 Hz, 1H), 4.41 (d, J = 10.9 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 3.98 – 3.93 (m, 1H), 3.86 – 3.81 (m, 1H), 3.78 – 3.71 (m, 1H), 3.58 (d, J = 13.0 Hz, 1H), 3.46 – 3.33 (m, 2H), 3.16 – 2.93 (m, 2H), 2.65 (t, J = 11.7 Hz, 3H), 2.25
− 2.15 (m, 1H), 2.00 – 1.87 (m, 6H), 1.70 – 1.50 (m, 4H), 0.86 (t, J = 11.1 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{27}H_{37}N_{4}O_{5}S [M]^+ = 529.66. Found: 529.20.

Ethyl 1-(3-(1,3-dioisoindolin-2-yl)propyl)-2-oxocyclopentane-1-carboxylate (24a):
NaH (60% in mineral oil) (2.92 g; 72.1 mmol) was suspended in a mixture of dry THF-DMF (1:1; 200 mL). Keto-ester 23a (10.0 g; 60.83 mmol) dissolved in dry THF was added dropwise and 0 °C, the resulting solution allowed to stir for 10 min to complete deprotonation. Then bromopropyl-pthalimide 16 (18.3 g; 66.91 mmol) in dry THF was added slowly at 0 °C. Then the reaction mixture was fitted with a refluxing condenser and heated at 65 °C for overnight. The reaction completion was monitored by TLC and cooled to rt. and then the pH of the reaction mixture was adjusted to neutral with 1.0 M aq. HCl. The layers were separated and aq. layer was extracted with EtOAc, combined organic layer was washed with water, brine solution dried over anhydrous Na_{2}SO_{4}. After concentration the crude residue was then purified by column chromatography using 10-15% EtOAc in pet-ether as a gradient to give pure pthalimide derivative (24a) 16.7g (80% yield).; ¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.64 (m, 1H), 7.61 – 7.56 (m, 1H), 4.05 – 3.92 (m, 1H), 3.52 (q, J = 7.0 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.31 – 2.19 (m, 1H), 2.10 (dt, J = 12.8, 8.3 Hz, 1H), 1.92 – 1.70 (m, 2H), 1.69 – 1.58 (m, 1H), 1.55 – 1.42 (m, 1H), 1.12 – 1.05 (m, 1H).; ¹³C NMR (101 MHz, cdcl₃) δ 214.4, 170.8, 168.3, 134.1, 132.2, 123.3, 61.5, 60.1, 38.0, 37.9, 33.1, 30.9, 27.0, 24.2, 19.7, 14.2.; HPLC-MS (ESI) m/z calcd. for C_{19}H_{21}NO₅ [M+H]^+ = 344.14. Found: 344.08.
TLC stain: UV, KMnO₄
R₇: 0.5 (30% EtOAc in pet-ether)
Ethyl octahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (25a): Pthalimide 24a (16.0 g; 44.27 mmol) was dissolved in analytical grade ethanol, was added methyl amine (33% in ethanol) (12.5 g; 132.80 mmol) dropwise at rt. The reaction mixture was fitted with a refluxing condenser and refluxed at 80 °C for 3h. The reaction completion was monitored by TLC and cooled to rt. (the by-product di-amide precipitated out). The solid di-amide separated by filtration and filtrate was concentrated and filtered through silica column to give pure product 6.56 g (69% yield).

TLC stain: I₂, KMnO₄;
Rf: 0.6 (10% MeOH (Buffered with aq. NH₃) in DCM.

The amino-ketone (5.0 g; 23.44 mmol) was dissolved in dry DCM (230 mL; dilution is very important to get diastereo selectivity!!!) was added equivalent amount of flame dried powdered MS (5.0 g) followed by NaBH(OEh)₃ (16.33 g; 35.17 mmol) in one portion, then it was allowed to stir for 24 h. at rt. After completion of SM was confirmed by TLC, diluted with DCM and saturated aq. NaHCO₃ was added, stirred for addition 15 min at rt. The DCM layer was washed couple of times with saturated aq. NaHCO₃ then water and brine solution. After concentration the crude residue was filtered through silica column to get the mixture of diastereomers (25a) (6:1) 3.3 g (69% yield).; ¹H NMR (400 MHz, CD₃OD) δ 4.22 – 4.12 (m, 1H), 3.16 – 3.06 (m, 1H), 2.66 (td, J = 13.2, 3.5 Hz, 1H), 2.52 (dt, J = 19.9, 9.9 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.11 (ddd, J = 12.7, 8.3, 1.4 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.76 – 1.63 (m, 1H), 1.56 (dddd, J = 14.5, 12.9, 9.7, 6.1 Hz, 1H), 1.40 (dddd, J = 21.7, 17.3, 8.8, 4.0 Hz, 1H), 1.29 – 1.21 (m, 2H); ¹³C NMR (101 MHz, CD₃OD) δ 175.8, 65.6, 60.3, 50.7, 46.4, 34.2, 34.0, 26.4, 23.1, 18.6, 13.4.; HPLC-MS (ESI) m/z calcd. for C₁₁H₂₀NO₅ [M+H]⁺ = 198.14; Found: 198.09.

TLC stain: I₂, KMnO₄
Rf: 0.3 (10% MeOH (Buffered with aq. NH₃) in DCM)
Ethyl 1-benzyl[octahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (26): Mixture of diastereomers 25a (3.0 g; 14.44 mmol) were dissolved in dry DCM, was added benzaldehyde (1.84 g; 17.33 mmol) followed by NaBH(OAc)$_3$ (3.67 g; 17.33 mmol) stirred for 1h. at rt. The reaction mixture was diluted with DCM washed with saturated aq. NaHCO$_3$ and stirred for 10 min. The DCM layer washed couple of times with saturated aq. NaHCO$_3$ then water and brine solution. After concentration the crude residue was carefully purified by column chromatography using 2-10% of EtOAc in pet-ether as an eluent to give the pure diastereomer 3.7g (89% yield); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.24 (ddd, $J$ = 27.3, 17.7, 7.1 Hz, 1H), 4.21 – 4.08 (m, 1H), 3.91 (d, $J$ = 13.3 Hz, 1H), 3.09 (d, $J$ = 13.3 Hz, 1H), 2.83 – 2.68 (m, 1H), 2.39 (d, $J$ = 12.6 Hz, 1H), 2.23 – 2.09 (m, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.58 (m, 1H), 1.50 (ddd, $J$ = 15.4, 9.4, 6.5 Hz, 1H), 1.27 (t, $J$ = 7.1 Hz, 1H), 1.09 (td, $J$ = 12.9, 4.3 Hz, 1H); $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 175.6, 139.4, 128.9, 127.9, 126.6, 73.7, 60.2, 59.8, 54.6, 53.5, 48.5, 48.3, 48.1, 47.8, 47.6, 47.4, 47.2, 35.3, 34.5, 27.3, 23.7, 19.8, 13.5; HPLC-MS (ESI) m/z calcd. for C$_{18}$H$_{25}$NO$_2$ [M+H]$^+$ = 288.19. Found: 288.30.
TLC stain: UV, I$_2$, KMnO$_4$
R$_f$: 0.6 (5% MeOH (Buffered with aq. NH$_3$) in DCM)

1-Benzyl[octahydro-4aH-cyclopenta[b]pyridine-4a-yl)methanol (26a): To a suspension of LAH (3.1 g; 10.79 mmol) in dry THF (55 mL) was added amino-ester 26 (0.45 g; 11.86 mmol) dissolved in dry THF at 0 °C. Then the reaction mixture was stirred for overnight at
rt., after completion of reaction, excess LAH was quenched with moistured Na$_2$SO$_4$. The greyish white solid was filtered washed several times with EtOAc and the filtrated was concentrated to give pure product 2.48g, (94% yield); HPLC-MS (ESI) m/z calcd. for C$_{16}$H$_{23}$NO [M+H]$^+$ = 246.08. Found: 246.22.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.3 (10% MeOH (Buffered with aq. NH$_3$) in DCM)

1-Benzyl octahydro-4aH-cyclopenta[b]pyridin-4a-yl)methyl (4-methoxyphenyl) carbamate (27): The pure alcohol 26a (1.46 g; 5.65 mmol) was dissolved in dry DCM (28 mL), was added Et$_3$N (0.858 g; 8.48 mmol) followed by 4-methoxy phenyl isocyanate (0.946 g; 6.22 mmol) and stirred for 4 h. at rt. The reaction mixture was diluted with DCM, washed couple of times with saturated aq. NaHCO$_3$ then water and brine solution. After concentration the crude residue was purified by column chromatography using 2-10% of EtOAc in pet-ether as a gradient to give the pure carbamate 1.38g (62% yield); $^1$H NMR (400 MHz, CD$_3$OD) δ 7.38 – 7.15 (m, 1H), 6.85 – 6.79 (m, 1H), 4.59 (dd, $J$ = 11.1, 1.8 Hz, 1H), 4.02 (d, $J$ = 11.2 Hz, 1H), 3.83 (d, $J$ = 13.2 Hz, 1H), 2.93 (d, $J$ = 13.2 Hz, 1H), 2.80 (d, $J$ = 8.1 Hz, 1H), 2.11 (d, $J$ = 12.4 Hz, 1H), 2.02 (dd, $J$ = 12.3, 7.6 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.63 (m, 1H), 1.54 – 1.35 (m, 1H), 1.17 (tt, $J$ = 10.4, 8.0 Hz, 1H), 1.05 – 0.94 (m, 1H); $^{13}$C NMR (101 MHz, CD$_3$OD) δ 155.9, 139.6, 128.7, 127.9, 126.6, 120.6, 113.9, 72.9, 63.7, 60.4, 54.7, 54.6, 45.0, 32.9, 32.2, 26.8, 21.8, 18.3.; HPLC-MS (ESI) m/z calcd. for C$_{24}$H$_{31}$N$_2$O$_3$ [M+H]$^+$ = 395.23; Found: 395.33.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.5 (10% MeOH (Buffered with aq. NH$_3$) in DCM)
Octahydro-4aH-cyclopenta[b]pyridin-4a-yl)methyl(4-methoxyphenyl)carbamate (27a):
The carbamate 27 (0.196 g; 0.472 mmol) was dissolved in MeOH (10 mL) and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H2 atmosphere for overnight. After complete consumption SM, it was filtered through HPLC filter using syringe, washed couple of times with MeOH and concentrated to give pure product 27a 123 mg (86% yield).; HPLC-MS (ESI) m/z calcd. for C17H24N2O3 [M+H]+ = 305.18. Found: 305.22.
TLC stain: UV, I2, KMnO4
Rf: 0.2 (10% MeOH (Buffered with aq. NH3) in DCM)

1-Benzoyloctahydro-4aH-cyclopenta[b]pyridin-4a-yl)methyl 2-(4-methoxyphenyl)acetate (28a): The benzoic acid (0.05 g; 0.37 mmol) dissolved in dry DMF (5 mL), added DIPEA (0.08 g; 0.63 mmol), followed by HATU (0.136 g; 0.35 mmol) and amine 27a (0.01 g; 0.32 mmol) at rt, and the resultant solution was stirred at 50 °C for overnight. The reaction mixture was cooled to rt, water was added and extracted with EtOAc, washed with couple of times with water followed by brine solution. After concentration the crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH3) in DCM as an eluent to give the pure amide 65mg (50% yield).; 1H NMR (400
MHz, CD$_3$OD) $\delta$ 7.33 – 7.14 (m, 1H), 3.86 – 3.76 (m, 1H), 3.36 – 3.31 (m, 1H), 3.15 (dd, $J$ = 11.6, 8.2 Hz, 1H), 2.94 (dd, $J$ = 13.2, 4.3 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.09 (dt, $J$ = 8.5, 5.0 Hz, 1H), 1.99 – 1.82 (m, 1H), 1.78 – 1.59 (m, 1H), 1.49 – 1.33 (m, 1H), 1.07 (ddt, $J$ = 17.7, 10.6, 5.2 Hz, 1H), 0.96 – 0.82 (m, 1H); $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) $\delta$ 172.5, 138.3, 130.1, 129.7, 128.6, 128.5, 114.3, 67.3, 63.8, 55.6, 50.7, 45.4, 33.2, 31.8, 26.9, 22.0, 19.2.;

HPLC-MS (ESI) m/z calcd. for C$_{24}$H$_{29}$N$_2$O$_4$ [M+H]$^+$ = 409.20; Found: 409.12.

TLC stain: UV, I$_2$, KMnO$_4$

$R_f$: 0.6 (10% MeOH (Buffered with aq. NH$_3$) in DCM

![Chemical Structure](image)

**Chemical Formula:** C$_{17}$H$_{26}$NO

**Exact Mass:** 259.19

**Molecular Weight:** 259.39

1-Benzyl-4a-(methoxymethyl)octahydro-1H-cyclopenta[b]pyridine (29): NaH (0.05 g; 1.27 mmol) was suspended in a mixture of dry THF-DMF (1:1), pure alcohol 26a (0.26 g; 1.06 mmol) in dry THF (7 mL) was added dropwise and 0 °C, the resulting solution allowed to stir for 10 min to complete deprotonation. Then iodomethane (0.22 g; 1.56 mmol) in dry THF was added slowly at 0 °C. The reaction mixture was stirred for overnight at room temperature. The reaction completion was monitored by TLC, upon completion; pH of the reaction mixture was adjusted to neutral with 1.0 M aq. HCl. Extracted the reaction mixture with EtOAc and the combined organic layer were washed with water, brine solution dried over anhydrous Na$_2$SO$_4$, concentrated to give the cure product. It was then purified by column chromatography using 10-15% EtOAc in pet-ether to give pure ether (29) 200 mg (73% yield); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.37 – 7.09 (m, 30H), 3.89 – 3.77 (m, 11H), 3.34 (s, 16H), 3.15 (dd, $J$ = 11.6, 8.2 Hz, 6H), 2.94 (dd, $J$ = 13.2, 4.3 Hz, 6H), 2.85 – 2.76 (m, 6H), 2.09 (dt, $J$ = 8.5, 5.0 Hz, 6H), 2.00 – 1.84 (m, 18H), 1.80 – 1.59 (m, 26H), 1.51 – 1.34 (m, 17H), 1.16 – 1.02 (m, 8H), 0.98 – 0.84 (m, 12H); $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 139.6, 128.8, 127.9, 126.6, 73.0, 71.7, 60.5, 58.6, 54.7, 45.4, 33.0, 32.3, 26.8, 21.9, 18.5.; HPLC-MS (ESI) m/z calcd. for C$_{17}$H$_{26}$NO [M+H]$^+$ = 260.19; Found: 260.31.

TLC stain: UV, I$_2$, KMnO$_4$
Rf: 0.6 (5% MeOH (Buffered with aq. NH₃) in DCM)

4a-(Methoxymethyl)octahydro-1H-cyclopenta[b]pyridine (30a): The ether 29a (0.186 g; 0.72 mmol) was dissolved in MeOH (8 mL) and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H₂ atmosphere for overnight. After complete consumption SM, it was filtered through HPLC filter using syringe, washed couple of times with MeOH and concentrated to give pure product 118 mg (97% yield). Amine (0.03 g; 0.17 mmol) was dissolved in dry DCM (2 mL) was added Et₃N (29 µL; 0.21 mmol), followed by TsCl (0.036 g; 0.19 mmol) in one portion at 0 °C, after 4 h. at rt., it was then diluted with DCM, washed with couple of times with saturated aq. NaHCO₃ then water, brine solution and dried over Na₂SO₄. Then concentrated to give crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH₃) in DCM as an eluent to give the pure sulphonamide 30a 38 mg (66 % yield); HPLC-MS (ESI) m/z calcd. for C₁₇H₂₆NO₃S [M+H]⁺ = 324.15; Found: 324.22.

TLC stain: UV, I₂, KMnO₄
Rf: 0.4 (10% MeOH (Buffered with aq. NH₃) in DCM)

Experimental for the production phase of 8-deoxy serratinine based scaffolds:
1-Benzyl-octahydro-1H-cyclopenta[b]pyridin-4a-yl]methyl N-cyclopentyl-carbamate (27a): To a solution of the alcohol 26a (6.0 g, 25 mmol) in dry DCM (250 mL) was added triethylamine (3.7 g, 29 mmol) and cyclopentylisocyanate (3.3 g, 29 mmol) and the reaction mixture was stirred at room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 10-15% of EtOAc in cyclohexane as an eluent to give the carbamate 5.5 g (63% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.25 – 7.09 (m, 5H), 5.00 – 4.98 (m, 1H), 4.63 – 4.61 (m, 1H), 4.43 (d, J = 10.9 Hz, 1H), 3.89 (d, J = 10.0 Hz, 1H), 3.76 (d, J = 13.3 Hz, 1H), 2.83 (d, J = 13.3 Hz, 1H), 2.74 (d, J = 7.3 Hz, 1H), 1.96 – 1.75 (m, 7H), 1.63 – 1.42 (m, 9H), 1.12 – 1.02 (m, 1H), 0.92 – 0.70 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C₂₂H₃₃N₂O₂ [M⁺] = 357.51. Found: 357.05.

TLC stain: I₂, KMnO₄
Rᶠ: 0.5 (Cyclohexane/EtOAc 5:1)

1-Benzyl-octahydro-1H-cyclopenta[b]pyridin-4a-yl]methyl N-phenylcarbamate (27c): To a solution of the alcohol 26b (6.0 g, 25 mmol) in dry DCM (250 mL) was added triethylamine (5.1 g, 37 mmol) and phenylisocyanate (3.2 g, 29 mmol) and the reaction mixture was stirred at room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 10-15% of EtOAc in cyclohexane as an eluent to give the carbamate 6.0 g (67% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.35 (d, J = 7.9 Hz, 2H), 7.34 – 7.16 (m, 7H), 7.02 (t, J = 7.3 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 3.82 (d, J = 13.3 Hz, 1H), 2.90 (d, J = 13.3 Hz, 1H), 2.80 (d, J = 7.0 Hz, 1H), 2.01 (dd, J = 7.6, 12.1 Hz, 2H), 1.92 – 1.80 (m, 2H),

35
1.74 – 1.65 (m, 2H), 1.47 (dd, J = 4.8, 11.7 Hz, 1H), 1.42 – 1.36 (m, 1H), 1.23 – 1.21 (m, 1H), 1.17 – 1.07 (m, 1H), 0.97 (dt, J = 4.4, 12.8 Hz, 1H), 0.86 – 0.78 (m, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C_{23}H_{29}N_2O_2 [M]^+ = 365.48. Found: 365.00.

TLC stain: I$_2$, KMnO$_4$

R$_f$: 0.4 (Cyclohexane/EtOAc 5:1)

Octahydro-1H-cyclopenta[b]pyridin-4a-yl]methyl N-cyclopentylcarbamate (27a): To a solution of the carbamate (27a) (5.5 g, 15 mmol) in dry methanol (150 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 3.5 g (85% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.28 (d, J = 10.5 Hz, 1H), 4.15 – 3.93 (m, 1H), 3.89 (d, J = 11.0 Hz, 1H), 3.16 (dd, J = 4.5, 12.1 Hz, 1H), 2.66 (dt, J = 2.6, 12.5 Hz, 1H), 2.49 (dd, J = 7.4, 12.3 Hz, 1H), 2.07 (d, J = 12.5 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.84 – 1.54 (m, 10H), 1.45 – 1.32 (m, 3H), 1.31 – 1.23 (m, 1H), 1.08 (dt, J = 4.2, 13.1 Hz, 2H), 0.90 (t, J = 7.1 Hz, 1H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{15}$H$_{27}$N$_2$O$_2$ [M]^+ = 267.34. Found: 267.05.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.4 (15% MeOH (Buffered with aq. NH$_3$) in DCM)
Octahydro-1H-cyclopenta[b]pyridin-4a-yl]methyl N-phenylcarbamate (27c): To a solution of the carbamate (27c) (6.0 g, 16 mmol) in dry methanol (160 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 4.4 g (97% yield).; 1H NMR (300 MHz, CDCl₃): δ 7.45 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 4.33 (d, J = 11.8 Hz, 1H), 4.06 (d, J = 11.7 Hz, 1H), 3.66 (dd, J = 4.1, 12.9 Hz, 1H), 2.97 – 2.81 (m, 2H), 2.21 – 2.13 (m, 3H), 1.86 – 1.71 (m, 4H), 1.70 – 1.57 (m, 1H), 1.49 (dt, J = 3.4, 14.8 Hz, 1H), 1.29 – 1.18 (m, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C₁₆H₂₃N₂O₂ [M⁺] = 275.36. Found: 275.00.

TLC stain: UV, I₂, KMnO₄
Rᶠ: 0.3 (10% MeOH (Buffered with aq. NH₃) in DCM)

Experimental for the representative examples of final diversification:

Ethyl 1-[(1,3-thiazol-2-yl)methyl]-octahydro-1H-cyclopenta[b]pyridine-4a-carboxylate (53a) 17.5 mg (39% yield).; 1H NMR (300 MHz, CDCl₃): δ 7.67 (d, J = 3.3Hz, 1H), 7.24 (d, J = 3.3Hz, 1H), 4.21 (m, 1H), 4.12 (d, 1H, J = 15.5Hz), 3.74 (d, 1H, J = 15.3Hz), 2.45 (m, 1H), 2.97 (dd, J = 3.6Hz, J = 10.6Hz, 1H), 2.19 (s, 1H), 1.81 (m, 1H), 1.50 (s, 1H), 1.29 (s, 1H), 1.08 (dt, 1H, J=4.3Hz, J = 12.9Hz); UHPLC-MS (ES+APCI) m/z calcd. for C₁₅H₂₂N₂O₃S [M⁺] = 294.14. Found: 295.20.
Ethyl 1-[(3,4-difluorophenyl)methyl]-octahydro-1H-cyclopenta[b]pyridine-4a-carboxylate (53b\textsuperscript{iii}) 10.3 mg (21% yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.24-7.18 (m, 1H), 7.09-6.99 (dd, J = 6.9Hz, J=16.6Hz, 2H), 4.18 (c, J = 1.0Hz, J = 7.1Hz, 2H), 3.85 (d, J = 13.9Hz, 1H), 3.06 (d, J = 13.8Hz, 1H), 2.77 (dd, J = 3.0Hz, J=12.1Hz, 1H), 2.44 (d, J = 12.6Hz, 1H.), 2.18-2.07 (m, 2H), 1.98-1.87 (m, 1H), 1.85-1.61 (m, 4H), 1.57-1.43 (m, 3H), 1.29 (t, J = 7.1Hz, 3H), 1.07 (dt, J = 4.3Hz, J = 12.7Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\textsubscript{18}H\textsubscript{23}F\textsubscript{2}NO\textsubscript{2} [M]+ = 323.17. Found:324.2.

Ethyl 1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]-octahydro-1H-cyclopenta[b]pyridine-4a-carboxylate (53c\textsuperscript{iii}) 24.4 mg (47% yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.45 (dd, J = 1.3, 14.3 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.00 – 3.96 (m, 1H), 3.75 (s, 3H), 2.76 (ddd, J = 7.3, 11.9, 23.7 Hz, 1H), 2.62 (dt, J = 3.5, 12.4 Hz, 1H), 2.46 (td, J = 6.1, 12.3 Hz, 2H), 2.22 – 2.11 (m, 1H), 2.00 (ddd, J = 2.5, 9.1, 13.0 Hz, 1H), 1.82 – 1.61 (m, 4H), 1.39 – 1.33 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.07 (dt, J = 4.3, 13.1 Hz, 1H).; UHPLC-MS (ES+APCI) m/z calcd. for C\textsubscript{15}H\textsubscript{24}N\textsubscript{3}O\textsubscript{4}S [M]+ = 342.43. Found: 342.20.
1-(Propylcarbamoyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-phenylcarbamate (28a) 18 mg (46% yield).; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.34 – 7.32 (m, 2H), 7.24 (t, J = 7.5 Hz, 2H), 6.99 (t, J = 8.5 Hz, 1H), 6.84 (bs, 1H), 4.56 (t, J = 4.8 Hz, 1H), 4.23 (d, J = 12.4 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.42 (s, 2H), 3.07 (q, J = 7.1 Hz, 2H), 2.75 (dd, J = 7.1, 12.7 Hz, 1H), 2.64 (dt, J = 3.4, 12.7 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.09 – 1.94 (m, 2H), 1.80 – 1.71 (m, 2H), 1.50 – 1.36 (m, 3H), 1.09 (dt, J = 4.5, 13.6 Hz, 2H), 0.84 (t, J = 7.1 Hz, 3H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{20}$H$_{30}$N$_3$O$_3$ [M]$^+$ = 360.46. Found: 360.20.

1-(2-Methoxyacetyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-phenylcarbamate (28b) 15.5 mg (41% yield).; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.38 – 7.2 (m, 4H), 7.06 (t, J = 7.3 Hz, 1H), 6.74 (bs, 1H), 4.25 (dd, J = 1.6, 11.3 Hz, 1H), 4.11 – 3.97 (m, 4H), 3.43 (s, 3H), 2.91 – 2.77 (m, 2H), 2.69 – 2.55 (m, 1H), 2.42 – 2.32 (m, 1H), 2.17 (d, J = 13.3 Hz, 1H), 1.85 – 1.77 (m, 3H), 1.55 – 1.53 (m, 2H), 1.23 – 1.10 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{19}$H$_{27}$N$_2$O$_4$ [M]$^+$ = 347.42. Found: 347.20.
1-(6-(Morpholin-4-yl)pyridine-3-carbonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-phenylcarbamate (28c) 18.9 mg (37% yield); ¹H NMR (300 MHz, CDCl₃): δ 8.35 (d, J = 2.1 Hz, 1H), 7.66 (dd, J = 2.4, 8.8 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.31 (t, J = 6.1 Hz, 2H), 7.07 (t, J = 6.1 Hz, 1H), 6.81 (bs, 1H), 6.59 (d, J = 8.8 Hz, 1H), 4.40 (dm, J = 11.3 Hz, 1H), 4.07 (d, J = 11.3 Hz, 2H), 3.81 (dd, J = 1.1, 4.6 Hz, 4H), 2.57 (dd, J = 1.1, 4.6 Hz, 4H), 3.06 (dd, J = 5.4, 7.3 Hz, 1H), 2.88 (dt, J = 3.2, 13.3 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.23 – 2.08 (m, 2H), 1.94 – 1.66 (m, 4H), 1.54 (d, J = 13.3 Hz, 1H), 1.30 – 1.13 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C₂₆H₃₃N₄O₄ [M]+ = 465.56. Found: 465.20.

1-(3,5-Dimethyl-1,2-oxazole-4-carbonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-cyclopentylcarbamate (28d) 19.6 mg (45% yield); ¹H NMR (300 MHz, CDCl₃): δ 4.63 (bs, 1H), 4.27 (d, J = 11.0 Hz, 1H), 3.98 – 3.83 (m, 3H), 2.98 (t, J = 10.7 Hz, 1H), 2.87 (dt, J = 3.4, 13.3 Hz, 1H), 2.44 (s, 3H), 2.38 – 2.33 (m, 2H), 2.30 (s, 3H), 2.14 (d, J = 12.7 Hz, 1H), 1.98 – 1.76 (m, 5H), 1.71 – 1.53 (m, 6H), 1.42 – 1.35 (m, 2H), 1.19 – 1.12 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C₂₁H₃₂N₃O₄ [M]+ = 390.49. Found: 390.20.
1-(Pyridine-3-carbonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-cyclopentylcarbamate (28e)<sup>i</sup> 21.2 mg (51% yield).; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.67 – 8.62 (m, 2H), 7.76 (dt, J = 1.9, 7.8 Hz, 1H), 7.33 (ddd, J = 0.6, 4.9, 7.8 Hz, 1H), 4.71 (bs, 1H), 4.25 (d, J = 10.7 Hz, 1H), 3.98 (t, 11.7 Hz, 3H), 3.47 (s, 2H), 3.03 (dd, J = 7.4, 12.8 Hz, 1H), 2.87 (dt, J = 3.2, 13.3 Hz, 1H), 2.20 – 2.15 (m, 2H), 1.98 – 1.81 (m, 4H), 1.71 – 1.53 (m, 6H), 1.46 – 1.35 (m, 2H), 1.23 – 1.12 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C<sub>21</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> [M]<sup>+</sup> = 372.47. Found: 372.20.

1-(2H-1,3-Benzodioxole-5-carbonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-cyclopentylcarbamate (28f)<sup>i</sup> 20.8 mg (45% yield).; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.99 (dd, J = 1.6, 7.9 Hz, 1H), 6.94 (d, J = 1.6 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 5.98 (s, 2H), 4.67 (bs, 1H), 4.29 (d, J = 11.0 Hz, 1H), 4.06 – 3.92 (m, 3H), 2.96 (dd, J = 7.4, 12.8 Hz, 1H), 2.79 (dt, J = 3.2, 13.2 Hz, 1H), 2.39 – 2.35 (m, 1H), 2.18 – 2.13 (m, 2H), 2.00 – 1.81 (m, 5H), 1.69 – 1.58 (m, 5H), 1.51 – 1.37 (m, 3H), 1.20 – 1.11 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub> [M]<sup>+</sup> = 415.50. Found: 415.20.
1-(Thiophene-2-sulfonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-phenylcarbamate (28g) 21.4 mg (47% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.63 (dd, $J = 1.2, 5.0$ Hz, 1H), 7.54 (dd, $J = 1.3, 3.7$ Hz, 1H), 7.40 – 7.37 (m, 2H), 7.31 (t, $J = 7.4$ Hz, 2H), 7.15 (dd, $J = 3.8, 5.0$ Hz, 1H), 7.06 (t, $J = 7.3$ Hz, 1H), 6.62 (bs, 1H), 4.46 (dd, $J = 1.8, 11.4$ Hz, 1H), 4.11 (d, $J = 11.4$ Hz, 1H), 4.0 (dd, $J = 3.7, 11.1$ Hz, 1H), 2.3 (dt, $J = 3.2, 12.6$ Hz, 1H), 2.22 – 2.09 (m, 4H), 2.04 – 1.83 (m, 3H), 1.69 – 1.63 (m, 2H), 1.10 – 0.91 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{20}$H$_{25}$N$_2$O$_4$S$_2$ [M]$^+$ = 421.55. Found: 421.20.

1-(2,5-difluorobenzenesulfonyl)-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-cyclopentylcarbamate (28h) 19.8 mg (40% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.59 – 7.54 (m, 1H), 7.24 – 7.15 (m, 2H), 4.57 (bs, 1H), 4.19 (d, $J = 11.2$ Hz, 1H), 4.12 (dd, $J = 3.7, 12.2$ Hz, 1H), 3.95 – 3.87 (m, 2H), 2.65 (tt, $J = 3.0, 12.8$ Hz, 1H), 2.55 (t, $J = 9.9$ Hz, 1H), 2.12 – 1.76 (m, 8H), 1.68 – 1.56 (m, 6H), 1.43 – 1.37 (m, 2H), 1.04 – 0.96 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{21}$H$_{29}$F$_2$N$_2$O$_4$S [M]$^+$ = 443.52. Found: 443.20.
1-[(4-Fluorophenyl)methanesulfonyl]-hexahydro-2H-cyclopenta[b]pyridin-4a-yl)methyl N-cyclopentylcarbamate (28i) 15.3 mg (31% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.30 (dd, \(J = 5.3, 8.7\) Hz, 2H), 7.00 (t, \(J = 8.7\) Hz, 2H), 4.50 (bs, 1H), 4.13 (d, \(J = 10.9\) Hz, 1H), 4.07 (s, 2H), 3.88 – 3.77 (m, 3H), 2.56 (dd, \(J = 7.3, 12.4\) Hz, 1H), 2.42 (dt, \(J = 3.2, 12.4\) Hz, 1H), 2.05 – 2.00 (m, 2H), 1.89 – 1.71 (m, 6H), 1.60 – 1.45 (m, 6H), 1.37 – 1.25 (m, 2H), 0.87 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C\(_{22}\)H\(_{32}\)FN\(_2\)O\(_4\)S \([M]^+\) = 439.56. Found: 439.20.

Ethyl 1-(3-(1,3-dioxoisindolin-2-yl)propyl)-2-oxocyclohexane-1-carboxylate (24b): NaH (60% in mineral oil) (2.76 g; 69.09 mmol) was suspended in a mixture of dry THF-DMF (1:1; 200 mL), Keto-ester 23b (10.0 g; 57.56 mmol) dissolved in dry THF was added dropwise and 0 °C, the resulting solution allowed to stir for 10 min to complete deprotonation. Then bromopropyl-pthalimide 16 (17.3 g; 63.33 mmol) in dry THF was added slowly at 0 °C. Then the reaction mixture was fitted with a refluxing condenser and heated at 65 °C for overnight. The reaction completion was monitored by TLC and cooled to room temp and then the pH of the reaction mixture was adjusted to neutral with 1.0M aq. HCl. The layers were separated and aq. layer was extracted with EtOAc, combined organic layer was washed with water, brine solution dried over anhydrous Na\(_2\)SO\(_4\). After concentration the crude residue was then purified by column chromatography using 10-15% EtOAc in pet-ether.
as a gradient to give pure pthalimide derivative (24b) 14.8g 72% yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.76 – 7.71 (m, 2H), 7.64 (ddd, $J =$ 8.5, 4.6, 2.8 Hz, 2H), 4.15 – 4.07 (m, 2H), 3.58 (dd, $J =$ 12.7, 5.5 Hz, 2H), 2.44 – 2.27 (m, 3H), 1.95 – 1.77 (m, 2H), 1.69 – 1.46 (m, 6H), 1.41 – 1.30 (m, 2H), 1.17 (dt, $J =$ 11.1, 4.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 207.6, 171.9, 168.4, 134.0, 132.3, 123.3, 61.5, 60.6, 41.2, 38.3, 36.3, 31.9, 27.7, 27.1, 23.8, 22.7, 14.3.; HPLC-MS (ESI) m/z calcd. for C$_{20}$H$_{24}$NO$_5$ [M+H]$^+$ = 358.16. Found: 358.10.

TLC stain: UV, KMnO$_4$

R$_f$: 0.5 (30% EtOAc in pet-ether)

$\begin{align*}
\text{Chemical Formula: C}_{12}\text{H}_{22}\text{NO}_2 \\
\text{Exact Mass: 211.16} \\
\text{Molecular Weight: 211.31}
\end{align*}$

**Ethyl octahydroquinoline-4a(2H)-carboxylate (25b):** Pthalimide 24b (14.8 g; 41.41 mmol) was dissolved in analytical grade ethanol, was added methyl amine (33% in ethanol) (11.7 g; 124.23 mmol) dropwise at rt. The reaction mixture was fitted with a refluxing condenser and refluxed at 85 °C for 3h. The reaction completion was monitored by TLC and cooled to rt. (the by-product di-amide precipitated out). The solid di-amide separated by filtration and filtrate was concentrated and filtered through silica column to give pure product 6.49g (69% yield); TLC stain: I$_2$, KMnO$_4$; R$_f$: 0.6 (10% MeOH (Buffered with aq. NH$_3$) in DCM. The amino-ketone (11.7 g; 124.23 mmol) was dissolved in dry DCM (dilution is very important to get diastereo selectivity!!!) was added equivalent amount of oven dried powdered MS followed by NaBH(OEh)$_3$ (11.7 g; 124.23 mmol) in one portion, then allowed to stir for 18 h. at rt. After completion of SM was confirmed by TLC, diluted with DCM and saturated aq. NaHCO$_3$ was added, stirred for additional 15 min at rt. The DCM layer was washed with couple of times with saturated aq. NaHCO$_3$ then water and brine solution. After concentration the crude residue was filtered through silica column to get the mixture of pure diastereomers 25b (10:1) 3.91 g, 67% yield; $^1$H NMR (400 MHz, CD$_3$OD) δ 4.20 (q, $J =$ 7.1 Hz, 2H), 3.08 (ddd, $J =$ 11.8, 3.8, 1.8 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.38 (dd, $J =$ 11.6, 4.3 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.04 – 1.98 (m, 1H), 1.81 – 1.63 (m, 3H), 1.61 – 1.51 (m, 2H), 1.47 – 1.36 (m, 3H), 1.27 (t, $J =$ 7.1 Hz, 3H), 1.18 – 1.10 (m, 2H); $^{13}$C NMR (101 MHz,
CD$_3$OD) δ 175.5, 62.7, 60.2, 47.5, 46.2, 36.4, 36.1, 29.0, 25.7, 23.7, 23.2, 13.4.; HPLC-MS (ESI) m/z calcd. for C$_{13}$H$_{22}$NO$_2$ [M+H]$^+$ = 212.16. Found: 212.17.

TLC stain: I$_2$, KMnO$_4$

R$_f$: 0.2 (10% MeOH (Buffered with aq. NH$_3$) in DCM)

**Ethyl 1-benzylotahydroquinoline-4a(2H)-carboxylate (26'):** The mixture of diastereomers 25b (39.9 g; 18.46 mmol) were dissolved in dry DCM, was added benzaldehyde (2.2 g; 20.30 mmol) followed by NaBH(OAc)$_3$ (4.8 g; 22.15 mmol) stirred for 30 min at rt. The reaction mixture was diluted with DCM (184 mL) followed by saturated aq. NaHCO$_3$ and stirred for 10 min. The DCM layer was washed with couple of times with saturated aq. NaHCO$_3$ then water and brine solution. After concentration the crude residue was carefully purified by column chromatography using 2-10% of EtOAc in pet-ether as an eluent to give the pure diastereomer (26') 4.72g (85% yield).; $^1$H NMR (600 MHz, CDCl$_3$) $^1$H NMR (600 MHz, CDCl$_3$) δ 7.37 (d, $J = 7.6$ Hz, 2H), 7.31 (t, $J = 7.4$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 1H), 4.30 – 4.19 (m, 2H), 4.09 (d, $J = 13.9$ Hz, 1H), 3.23 (d, $J = 13.9$ Hz, 1H), 2.85 (d, $J = 10.8$ Hz, 1H), 2.23 (d, $J = 12.8$ Hz, 1H), 2.18 (dt, $J = 23.4$, 8.4 Hz, 2H), 2.05 (t, $J = 11.7$ Hz, 1H), 1.97 – 1.83 (m, 3H), 1.60 (qt, $J = 13.3$, 3.8 Hz, 1H), 1.51 (d, $J = 5.4$ Hz, 1H), 1.44 (d, $J = 13.4$ Hz, 1H), 1.37 – 1.29 (m, 5H), 1.29 – 1.21 (m, 1H), 1.14 (td, $J = 13.3$, 3.8 Hz, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 175.0, 141.1, 128.5, 128.0, 126.3, 69.4, 59.6, 56.6, 54.7, 48.6, 37.9, 37.4, 26.2, 25.9, 23.6, 22.2, 14.4.; HPLC-MS (ESI) m/z calcd. for C$_{19}$H$_{28}$NO$_2$ [M+H]$^+$ = 302.20; Found: 302.34.

TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.6 (5% MeOH (Buffered with aq. NH$_3$) in DCM)
1-Benzyloctahydroquinolin-4a(2H)-yl)methanol (26b): To a suspension of LAH (0.35 g; 9.12 mmol) in dry THF (40 mL) was added amino-ester 26′(2.5 g; 8.29 mmol) dissolve in dry THF at 0 °C. Then the reaction mixture was stirred for overnight, after completion of reaction monitored by TLC, the excess LAH was quenched with wet Na₂SO₄!!! (Few drops of water were added to Na₂SO₄ to make paste). The greyish white solid was filtered washed several times with EtOAc and the filtrated was concentrated to give pure product (26b) 2.02g, (94% yield).; ¹H NMR (400 MHz, CD₃OD) δ 7.42 – 7.08 (m, 5H), 4.26 (d, J = 11.1 Hz, 1H), 4.06 (t, J = 8.6 Hz, 1H), 3.63 (d, J = 11.2 Hz, 1H), 2.91 (t, J = 11.2 Hz, 1H), 2.87 – 2.80 (m, 1H), 2.23 – 2.13 (m, 1H), 2.05 – 1.84 (m, 4H), 1.76 (dd, J = 14.3, 3.0 Hz, 1H), 1.57 – 1.49 (m, 2H), 1.48 – 1.32 (m, 4H), 1.08 (td, J = 13.2, 4.7 Hz, 1H), 1.02 – 0.91 (m, 1H).; ¹³C NMR (101 MHz, CD₃OD) δ 139.8, 128.5, 128.2, 126.7, 70.9, 63.8, 56.9, 54.5, 37.9, 37.6, 35.1, 25.8, 24.9, 22.4, 20.8.; HPLC-MS (ESI) m/z calcd. for C₁₇H₂₆NO [M+H]⁺ = 260.19. Found: 260.32.
TLC stain: UV, I₂, KMnO₄
R$_f$: 0.3 (10% MeOH (Buffered with aq. NH₃) in DCM)

1-Benzyl octahydroquinolin-4a(2H)-yl)methyl (4-methoxyphenyl)carbamate (27†): The pure alcohol (1.7 g; 6.55 mmol) was dissolved in dry DCM (33 mL), was added Et₃N (0.99 g; 9.83 mmol) followed by 4-methoxy phenyl isocyanate (1.1 g; 7.21 mmol) and stirred for 4 h.
at rt. The reaction mixture was diluted with DCM, washed couple of times with saturated aq. 
NaHCO₃ then water and brine solution. After concentration the crude residue was purified by 
column chromatography using 2-10% of EtOAc in pet-ether as an eluent to give the pure 
carbamate 27. 1.61 g 62% yield); ¹H NMR (400 MHz, CD₃OD) δ 7.36 – 7.13 (m, 7H), 7.36 
– 7.13 (m, 7H), 6.88 – 6.78 (m, 2H), 6.85 – 6.80 (m, 2H), 4.76 (d, J = 11.3 Hz, 1H), 4.48 (d, J 
= 11.3 Hz, 1H), 3.95 (d, J = 13.5 Hz, 1H), 2.94 (d, J = 13.5 Hz, 1H), 2.87 – 2.74 (m, 1H), 
2.06 (dd, J = 12.0, 3.8 Hz, 1H), 1.97 – 1.77 (m, 6H), 1.65 – 1.48 (m, 1H), 1.48 – 1.31 (m, 
3H), 1.05 – 0.86 (m, 2H). ¹³C NMR (101 MHz, CD₃OD) δ 156.0, 155.8, 140.8, 132.1, 128.4, 
128.0, 126.4, 120.6, 113.9, 70.2, 57.3, 55.1, 54.7, 38.1, 34.7, 34.4, 25.8, 25.3, 21.7, 20.6.; 
HPLC-MS (ESI) m/z calcd. for C₂₅H₃₃N₂O₃ [M+H]⁺ = 409.24. Found: 409.42. 
TLC stain: UV, I₂, KMnO₄ 

Octahydroquinolin-4a(2H)-yl)methyl (4-methoxyphenyl)carbamate (27b) : The 
carbamate 27a (1.5 g; 3.49 mmol) was dissolved in MeOH (65 mL) and carefully 10% Pd/C 
was added under argon atmosphere. Then the reaction mixture was evacuated couple of times 
by applying vacuum and re-filling the hydrogen, stirred under H₂ atmosphere for overnight. 
After complete consumption SM, it was filtered through HPLC filter using syringe, washed 
couple of times with MeOH and concentrated to give pure product 130 mg (86% yield).; ¹H 
NMR (400 MHz, CD₃OD) δ 7.29 (t, J = 17.1 Hz, 2H), 6.91 – 6.79 (m, 2H), 4.55 – 4.40 (m, 
2H), 3.74 (s, 3H), 3.04 (dd, J = 12.1, 4.4 Hz, 1H), 2.79 – 2.56 (m, 1H), 2.41 (dt, J = 13.7, 6.7 
Hz, 1H), 1.83 (ddd, J = 24.5, 23.8, 13.9 Hz, 4H), 1.60 (dd, J = 14.9, 11.2 Hz, 1H), 1.51 – 1.33 
(m, 5H), 1.11 – 0.85 (m, 2H); ¹³C NMR (101 MHz, CD₃OD) δ 156.0, 155.5, 132.1, 120.6, 
113.9, 64.0, 61.4, 54.7, 37.1, 34.2, 34.2, 27.8, 25.6, 22.0, 20.9.; HPLC-MS (ESI) m/z calcd. 
for C₁₈H₂₇N₂O₃ [M+H]⁺ = 319.19. Found: 319.30. 
TLC stain: UV, I₂, KMnO₄
1-Benzoyloctahydroquinolin-4a(2H)-yl)methyl (4-methoxyphenyl)carbamate (28b): To amine 27b (0.1 g; 0.3 mmol) dissolved in dry DCM (3 mL) was added Et$_3$N (0.05 g; 0.45 mmol), followed by BzCl (0.05 g; 0.33 mmol) dropwise at 0 °C, and stirred for 4 h. at rt. After completion of reaction, it was diluted with DCM, washed with couple of times with saturated aq. NaHCO$_3$ then water and brine solution. After concentration the crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH$_3$) in DCM as an eluent to give the pure sulphonamide (28b) 78 mg 62% yield).; $^1$H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 7.38 (dddd, $J$ = 6.8, 5.7, 4.4, 2.1 Hz, 7H), 6.97 – 6.74 (m, 2H), 4.51 (d, $J$ = 11.8 Hz, 1H), 4.33 (d, $J$ = 11.7 Hz, 1H), 3.69 (s, 3H), 3.58 (d, $J$ = 12.5 Hz, 1H), 3.20 (dd, $J$ = 12.6, 3.5 Hz, 1H), 3.06 (dd, $J$ = 13.2, 10.7 Hz, 1H), 2.82 – 2.65 (m, 1H), 1.93 – 1.70 (m, 4H), 1.65 – 1.39 (m, 3H), 1.34 (d, $J$ = 12.5 Hz, 1H), 1.29 – 1.07 (m, 2H), 1.07 – 0.90 (m, 1H).; $^{13}$C NMR (101 MHz, DMSO) δ 171.6, 155.4, 154.7, 138.8, 133.0, 130.0, 129.1, 127.31, 120.4, 114.6, 67.2, 61.1, 55.9, 52.5, 35.1, 34.9, 27.2, 27.1, 23.7, 21.5.; HPLC-MS (ESI) m/z calcd. for C$_{25}$H$_{31}$N$_2$O$_4$ [M+H]$^+$ = 423.22. Found: 423.10. TLC stain: UV, I$_2$, KMnO$_4$

R$_f$: 0.3 (10% MeOH (Buffered with aq. NH$_3$) in DCM)
1-Benzyl-4a-(methoxymethyl)decahydroquinoline (29’): NaH (0.04 g; 0.88 mmol) was suspended in a mixture of dry THF-DMF (6 mL; 1:1), pure alcohol (26b) (0.2 g; 0.73 mmol) in dry THF (2 mL) was added dropwise and 0 °C, the resulting solution allowed to stir for 10 min to complete deprotonation. Then iodomethane (0.11 g; 0.81 mmol) was added slowly at 0 °C. The reaction mixture was stirred for overnight at rt. The reaction upon completion; pH of the reaction mixture was adjusted to neutral with 1.0M aq. HCl. extracted the reaction mixture with EtOAc, and the combined organic layer was washed with water, brine solution dried over anhydrous Na2SO4, concentrated to give the pure product. It was then purified by column chromatography using 10-15% EtOAc in pet-ether to give pure ether (29’) 96 mg (46% yield).; 1H NMR (600 MHz, CDCl3) δ 7.33 (d, J = 4.1 Hz, 3H), 7.27 – 7.17 (m, 1H), 3.98 (t, J = 10.1 Hz, 2H), 3.63 (d, J = 9.6 Hz, 1H), 3.42 (s, 3H), 3.01 (d, J = 13.0 Hz, 1H), 2.85 (t, J = 26.2 Hz, 1H), 2.10 – 1.73 (m, 7H), 1.60 – 1.16 (m, 5H), 0.98 – 0.83 (m, 2H); 13C NMR (151 MHz, CDCl3) δ 141.2, 128.4, 128.1, 126.4, 70.5, 70.1, 59.6, 57.5, 55.5, 38.5, 34.8, 34.7, 26.0, 25.3, 22.0, 20.8.; HPLC-MS (ESI) m/z calcd. for C18H26NO [M+H]+ = 274.21; Found: 274.29.

TLC stain: UV, I2, KMnO4

Rf 0.6 (5% MeOH (Buffered with aq. NH3) in DCM)

4a-(Methoxymethyl)decahydroquinoline (29b): The ether 29’ (0.1 g; mmol) was dissolved in MeOH (3 mL) and carefully 10% Pd/C was added under argon atmosphere. Then the reaction mixture was evacuated couple of times by applying vacuum and re-filling the hydrogen, stirred under H2 atmosphere for overnight. After complete consumption SM, it was filtered through HPLC filter using syringe, washed couple of times with MeOH and concentrated to give pure product (29b) 56 mg (crude).; HPLC-MS (ESI) m/z calcd. for C11H21NO [M+H]+ = 184.16. Found: 184.15.

TLC stain: UV, I2, KMnO4

Rf 0.2 (10% MeOH (Buffered with aq. NH3) in DCM)
4a-(Methoxymethyl)-1-tosyldecahydroquinoline (30b): Amine 29b (0.05 g; 0.25 mmol) was dissolved in dry DCM (2 mL) was added Et₃N (0.03 g; 0.27 mmol), followed by TsCl (0.05 g; 0.27 mmol) in one portion at 0 °C, after 4 h. at rt., it was diluted with DCM, washed with couple of times with saturated aq. NaHCO₃ then water, brine solution and dried over Na₂SO₄. Then concentrated to give crude residue was purified by column chromatography using 2-5% of MeOH (Buffered with aq. NH₃) in DCM as an eluent to give the pure sulphonamide (30b) 47 mg (57% yield); ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, J = 8.3 Hz, 2H), 7.26 – 7.15 (m, 2H), 4.27 – 4.17 (m, 1H), 3.63 (d, J = 9.8 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.29 (d, J = 5.7 Hz, 2H), 2.69 – 2.51 (m, 1H), 2.34 (s, 2H), 1.97 – 1.67 (m, 3H), 1.52 – 1.44 (m, 1H), 1.35 (ddd, J = 24.3, 12.5, 7.9 Hz, 1H), 1.10 – 0.95 (m, 1H), 0.78 (dtd, J = 36.0, 13.3, 4.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 142.7, 138.6, 129.7, 126.5, 68.9, 67.9, 59.6, 51.7, 38.8, 34.9, 34.6, 26.3, 26.0, 22.4, 21.5, 20.6.; HPLC-MS (ESI) m/z calcd. for C₁₈H₂₈NO₃S [M+H]+ = 338.17. Found: 338.19. 
Rᵣ = 0.4 (DCM/MeOH (9:1; MeOH : aq. NH₃) 9:1.

**Experimentals for the production phase: Intermediates prepared in large scale**

1-Benzyl-decahydroquinolin-4a-yl)methyl N-cyclopentylcarbamate (27bᵀ): To a solution of the alcohol 26b (3.0 g, 12 mmol) in dry DCM (120 mL) was added triethylamine (1.8 g, 17 mmol) and cyclopentylisocyanate (1.5 g, 14 mmol) and the reaction mixture was stirred at
room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 15-20% of EtOAc in cyclohexane as an eluent to give the carbamate 3.2 g (75% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.30 – 7.10 (m, 5H), 4.68 (d, J = 7.2 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 3.92 (d, J = 13.4 Hz, 1H), 2.87 (d, J = 13.4, 1H), 2.79 (d, J = 9.7 Hz, 1H), 2.02 – 1.69 (m, 9H), 1.64 – 1.48 (m, 6H), 1.40 – 1.16 (m, 7H), 0.95 – 0.78 (m, 2H).; UHPLC-MS (ES+APCI) m/z calcd. for C₂₃H₃₅N₂O₂ [M⁺] = 371.53. Found: 371.15.

TLC stain: I₂, KMnO₄

Rₛ: 0.5 (Cyclohexane/EtOAc 3:1)

**1-Benzyl-decahydroquinolin-4a-yl]methyl N-phenylcarbamate (27d):** To a solution of the alcohol 26b (3.0 g, 12 mmol) in dry DCM (120 mL) was added triethylamine (1.8 g, 17 mmol) and phenylisocyanate (1.6 g, 14 mmol) and the reaction mixture was stirred at room temperature for 15 hours. After the complete consumption of the starting material monitored by TLC, the reaction mixture was washed with saturated aq. NaHCO₃ and brine. After concentration, the crude residue was purified by column chromatography using 15-20% of EtOAc in cyclohexane as an eluent to give the carbamate 2.7 g (62% yield).; ¹H NMR (300 MHz, CDCl₃): δ 7.37 – 7.33 (m, 3H), 7.29 – 7.28 (m, 1H), 7.25 – 7.21 (m, 4H), 7.19 – 7.15 (m, 1H), 8.49 (t, J = 7.0 Hz, 1H), 4.77 (d, J = 11.3 Hz, 1H), 4.52 (d, J = 11.3 Hz, 1H), 3.95 (d, J = 13.6 Hz, 1H), 2.90 (d, J = 13.6 Hz, 1H), 2.81 (d, J = 10.7 Hz, 1H), 2.04 (dd, J = 3.8, 11.8 Hz, 1H), 1.90 – 1.67 (m, 6H), 1.54 – 1.18 (m, 6H), 1.00 – 0.87 (m, 2H).; UHPLC-MS (ES+APCI) m/z calcd. for C₂₄H₃₁N₂O₂ [M⁺] = 379.51. Found: 378.95.

TLC stain: I₂, KMnO₄

51
Decahydroquinolin-4a-yl]methyl N-cyclopentylcarbamate (27b): To a solution of the carbamate (27b) (3.2 g, 9 mmol) in dry methanol (90 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 2.3 g (93% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 4.40\) (q, \(J = 11.0\) Hz, 2H), \(3.95 - 3.78\) (m, 1H), \(3.42\) (s, 2H), \(3.11\) (d, \(J = 11.2\) Hz, 1H), \(2.69\) (dt, \(J = 3.4, 12.2\) Hz, 1H), \(2.41\) (dd, \(J = 4.6, 10.4\) Hz, 1H), \(2.28 - 2.18\) (m, 2H), \(1.93 - 1.85\) (m, 2H), \(1.79 - 1.72\) (m, 2H), \(1.64 - 1.51\) (m, 5H), \(1.46 - 1.32\) (m, 6H), \(1.02 - 0.82\) (m, 2H).; UHPLC-MS (ES+APCI) m/z calcd. for \(\text{C}_{16}\text{H}_{29}\text{N}_{2}\text{O}_{2}\) [M]\(^+\) = 281.40. Found: 281.10.

TLC stain: UV, I\(_2\), KMnO\(_4\)

R\(_f\): 0.5 (15% MeOH (Buffered with aq. NH\(_3\)) in DCM)

Decahydroquinolin-4a-yl]methyl N-phenylcarbamate (27d): To a solution of the carbamate (27d) (2.7 g, 7 mmol) in dry methanol (70 mL) was added palladium on charcoal (10 wt%) and the reaction mixture was stirred under hydrogen atmosphere overnight. After
complete consumption of the starting material monitored by TLC, the reaction mixture was filtered through a pad of celite. Concentration of the filtrate afforded the pure product 2.0 g (96% yield); $^1$H NMR (300 MHz, CDCl$_3$): δ 7.55 (d, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.5 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.26 (d, J = 11.9 Hz, 1H), 3.75 (d, J = 11.7 Hz, 1H), 3.40 (s, 1H), 3.02 – 2.87 (m, 2H), 2.24 – 2.15 (m, 2H), 1.87 – 1.67 (m, 4H), 1.51 – 1.10 (m, 6H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{17}$H$_{25}$N$_2$O$_2$ [M]$^+$ = 289.38. Found: 289.10.

TLC stain: I$_2$, KMnO$_4$

$R_f$: 0.5 (15% MeOH (Buffered with aq. NH$_3$) in DCM)

**Experimental for the final diversification:**

![Experimental structure](image)

**Ethyl 1-(pyridine-2-carbonyl)-octahydroquinoline-4a-carboxylate (53d)** 16.8 mg (34% yield); $^1$H NMR (300 MHz, CDCl$_3$): δ 8.51 (ddd, J = 0.9, 1.6, 4.9 Hz, 1H), 7.74 (dt, J = 1.7, 7.7 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.25 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.96 (d, J = 14.2 Hz, 1H), 3.21 (dd, J = 3.8, 12.4 Hz, 1H), 2.96 (ddd, J = 3.0, 12.1, 13.5 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.22 – 2.12 (m, 3H), 1.81 – 1.68 (m, 2H), 1.52 – 1.41 (m, 3H), 1.34 – 1.32 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 – 1.13 (m, 2H); UHPLC-MS (ES+APCI) m/z calcd. for C$_{18}$H$_{25}$N$_2$O$_3$ [M]$^+$ = 317.39. Found: 317.20.
Ethyl -1-[2-(methylsulfanyl)pyridine-3-carbonyl]-octahydroquinoline-4a-carboxylate (53e) 25.5 mg (45% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.41 (dd, \(J = 1.8, 4.9\) Hz, 1H), 7.54 – 7.52 (m, 1H), 7.01 (dd, \(J = 4.9, 7.5\) Hz, 1H), 4.23 (q, \(J = 6.9\) Hz, 2H), 3.76 – 3.74 (m, 1H), 3.21 (dd, \(J = 3.5, 12.3\) Hz, 1H), 2.96 (dt, \(J = 3.1, 11.4\) Hz, 1H), 2.55 (s, 3H), 2.31 – 2.14 (m, 3H), 1.85 – 1.47 (m, 5H), 1.36 – 1.20 (m, 7H); UHPLC-MS (ES+APCI) \(m/z\) calcd. for C\(_{19}\)H\(_{27}\)N\(_2\)O\(_3\)S [M]\(^+\) = 363.49. Found: 363.20.

2-Benzyl-6-isopropyloctahydro-4H-isindol-4-one (32a): \(N\)-(Methoxymethyl)-\(N\)-(trimethylsilylmethyl)benzylamine (10.9 g; 43.41 mmol) added to \textit{des}-methyl carvone 32 (5.0 g; 36.17 mmol) in DCM (180 mL) followed by TFA (0.83 g; 0.54 mmol) at 0 °C. After 2 h NaHCO\(_3\) was added stirred for 15 min. The layers were separated and aq. layer was extracted twice with DCM then washed with water, brine and dried over Na\(_2\)SO\(_4\). After evaporation, the crude residue was purified by silica column using 2% MeOH (9 : 1; MeOH : aq. NH\(_3\)) in DCM.; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.27 – 7.18 (m, 5H), 3.59 – 3.51 (m, 2H), 3.01 – 2.93 (m, 1H), 2.83 – 2.67 (m, 4H), 2.37 – 2.30 (m, 2H), 2.23 (t, \(J = 9.0\) Hz, 1H), 2.13 – 2.05 (m, 1H), 1.72 – 1.61 (m, 3H), 1.55 – 1.46 (m, 1H), 0.86 (dd, \(J = 6.8, 3.1\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CD\(_3\)OD) \(\delta\) 170.0, 138.4, 128.9, 128.1, 128.1, 127.1, 120.4, 60.3, 58.0, 58.0, 54.6, 54.5, 44.1, 43.9, 39.2, 39.8, 37.9, 37.9, 32.1, 28.8, 18.7, 18.5.; HR-MS (ESI) \(m/z\) calcd. for C\(_{18}\)H\(_{26}\)ON [M+H]\(^+\) = 272.2014; Found: 272.2008. 

\(R_f = 0.4\) (DCM/MeOH (9:1; MeOH : aq. NH\(_3\)) 9:1.)
2-Benzyl-6-isopropyl-N-propyloctahydro-1H-isindo1-4-amine (33b): To flam dried MS (1.0 g), added ketone 32a ((1.0 g; 3.68 mmol)) in 1,2-DCM (72 mL) followed by n-propyl amine (0.24 g; 4.05 mmol) stirred for 45 min. Then (NaBH(OEh)₃ (4.4 g; 7.37 mmol) was added and stirred for 18 h. Then saturated aq. NaHCO₃ solution (~30 mL) was added and stirred for 15 min. The DCM layer was collected and the aqueous layer was extracted twice with DCM, washed with water, brine dried over Na₂SO₄. The solvent evaporated to afford crude product, which was then purified by silica column using 10-15% MeOH/DCM (9 : 1; MeOH : aq. NH₃).; ¹H NMR (400 MHz, CD₃OD) δ 7.42 – 7.17 (m, 5H), 3.75 – 3.63 (m, 2H), 3.03 – 2.87 (m, 2H), 2.78 – 2.69 (m, 1H), 2.56 (ddd, J = 14.6, 11.8, 7.1 Hz, 4H), 2.41 (d, J = 7.1 Hz, 1H), 2.32 (dd, J = 9.7, 5.1 Hz, 1H), 1.74 – 1.29 (m, 8H), 0.90 (td, J = 7.1, 3.9 Hz, 9H); ¹³C NMR (101 MHz, CD₃OD) δ 138.4, 129.2, 128.1, 127.1, 60.8, 59.3, 52.4, 51.9, 49.0, 39.6, 37.4, 34.6, 29.8, 28.2, 28.1, 22.4, 19.7, 19.3, 10.9.; HR-MS (ESI) m/z calcd. for C₂₁H₃₅N₂ [M+H]⁺ = 315.2799. Found: 315.2794. Rf = 0.2 (DCM/MeOH (8.5 : 1.5; MeOH : aq. NH₃) 9:1.

6-Isopropyl-N-propyloctahydro-1H-isindo1-4-amine (34b): To the amine xx (0.83 g; 2.64 mmol) in MeOH (26 mL), was added Pd(OH)₂ (10 wt.%) under argon atmosphere. Then the flask was filled with H₂ using balloon and stirred for 18 h. at rt. The reaction mixture was filtered and concentrated to give pure product was taken for next step without further purification.; ¹H NMR (400 MHz, CD₃OD) δ 3.08 – 2.83 (m, 4H), 2.67 (d, J = 10.8 Hz, 1H),
2.57 (dd, J = 9.2, 6.0 Hz, 2H), 2.52 – 2.42 (m, 1H), 2.24 (td, J = 11.6, 5.8 Hz, 1H), 1.91 – 1.69 (m, 2H), 1.63 (d, J = 13.9 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.44 – 1.25 (m, 3H), 1.01 – 0.86 (m, 9H); $^{13}$C NMR (101 MHz, CD$_3$OD) δ 52.0, 51.2, 49.0, 43.0, 42.2, 40.4, 35.1, 28.4, 26.8, 22.6, 20.5, 20.8, 11.0.; HR-MS (ESI) m/z calcd. for C$_{14}$H$_{29}$N$_2$ [M+H]$^+$ = 225.2332. Found: 225.2325.

$R_f$ = 0.2 (DCM : MeOH (8.5 : 1.5; MeOH : aq. NH$_3$) 9:1.

2-(3-Chloro-4-fluorobenzyl)-6-isopropyl-N-propyloctahydro-1H-isooindol-4-amine (35):

To amine 34b (56 mg; 0.25 mmol) in DCM (5 mL) added aldehyde (42 mg g; 0.26 mmol) BzOH (152 mg; 1.24 mmol), NaBH(OAc)$_3$ (64 mg; 0.29 mmol) and stirred for 1 h. Saturated NaHCO$_3$ (~3 mL) was added for 15 min. Layers were separated and the aqueous layer was extracted twice with DCM. The combined DCM extracts were washed with water, brine, dried over anhydrous Na$_2$SO$_4$, concentrated to afford pure product 35. $^1$H NMR (400 MHz, CD$_3$OD) δ 7.49 – 7.00 (m, 3H), 3.69 (d, J = 9.0 Hz, 2H), 2.95 (d, J = 6.8 Hz, 2H), 2.78 – 2.48 (m, 5H), 2.45 – 2.23 (m, 2H), 1.84 – 1.29 (m, 8H), 0.93 (ddd, J = 17.9, 9.2, 3.7 Hz, 9H). $^{13}$C NMR (101 MHz, CD$_3$OD) δ 159.3, 156.8, 140.8, 130.3, 125.5, 118.9, 116.9, 114.6, 112.5, 59.6, 52.3, 48.9, 39.7, 37.7, 34.8, 29.5, 28.3, 22.3, 19.9, 19.4, 10.9.; HR-MS (ESI) m/z calcd. for C$_{21}$H$_{33}$N$_2$ClF [M+H]$^+$ = 367.2319; Found: 367.2310.

$R_f$ = 0.4 (DCM/MeOH (9:1; MeOH:aq. NH$_3$) 9:1.
6-Isopropyl-N-propyl-2-tosyloctahydro-1H-isoinodol-4-amine (37): To the compound 34b (50 mg; 0.22 mmol) in DCM (5 mL), added DIPEA (43 mg; 0.33 mmol) followed by TsCl (44 mg; 0.23 mmol) at rt. After 4 h., saturated NaHCO$_3$ was added followed by usual workup to give pure product (37) 84 mg (78% yield).; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.81 – 7.70 (m, 2H), 7.41 (dd, $J = 9.7$, 9.1 Hz, 2H), 3.37 – 3.23 (m, 3H), 3.13 – 3.01 (m, 2H), 2.65 – 2.55 (m, 1H), 2.44 (s, 3H), 2.24 (dt, $J = 17.8$, 5.4 Hz, 1H), 1.85 (d, $J = 13.2$ Hz, 1H), 1.68 – 1.47 (m, 5H), 1.35 – 1.19 (m, 3H), 0.96 – 0.83 (m, 11H); $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 144.0, 134.1, 129.7, 127.4, 54.3, 51.3, 45.4, 40.4, 34.2, 31.1, 29.3, 28.1, 27.2, 26.0, 24.8, 22.4, 21.8, 20.4, 20.2, 13.1, 10.8; HR-MS (ESI) m/z calcd. for C$_{21}$H$_{35}$O$_2$N$_2$S [M+H]$^+$ = 379.2422; Found: 379.2413.

R$_f$ = 0.4 (DCM : MeOH (8.5:1.5; MeOH : aq. NH$_3$) 9:1.

6-Isopropyl-4-(propylamino)octahydro-2H-isoinodol-2-yl)(phenyl)methanone (36): To benzoic acid (34 mg; 0.27 mmol) in DMF (3 mL), was added DIEPA (48 mg; 0.37 mmol), HATU (107 mg; 0.27 mmol) followed by diamine 34b (56 mg; 0.25 mmol), the resultant mixture was heated at 50 °C for 5h. Water was added to the cooled reaction mixture and extracted several times with EtOAc. The EtOAc layer was washed with water, brine and dried over anhydrous Na$_2$SO$_4$. Concentrated to give crude product, which was then purified by silica column using 10-15% MeOH:DCM (9:1; MeOH : aq. NH$_3$); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.57 – 7.43 (m, 3H), 7.16 (tt, $J = 20.1$, 7.3 Hz,1H), 3.76 – 3.58 (m, 2H), 3.55 – 3.34 (m, 2H), 3.17 (d, $J = 10.8$ Hz, 1H), 3.00 – 2.92 (m, 1H), 2.85 – 2.70 (m, 1H), 2.58 – 2.34 (m, 1H), 2.05 (dd, $J = 22.2$, 13.3 Hz,1H), 1.91 – 1.40 (m, 6H), 1.38 – 1.19 (m, 1H), 1.08 – 0.86 (m, 10H); HR-MS (ESI) m/z calcd. for C$_{21}$H$_{33}$ON$_2$ [M+H]$^+$ = 329.2596. Found: 329.2587.

R$_f$ = 0.3 (DCM : MeOH (8.5 : 1.5; MeOH : aq. NH$_3$) 9:1.
(S)-7a-methyl-2,3,7a-tetrahydrospiro[indene-1,2'-[1,3]dioxolan]-5(6H)-one (39): To the diketone 38 (4.183 g, 22.92 mmol) were added 4Å MS, dry MED (45 mL), and anhydrous ethylene glycol (45 mL). To this two phases mixture was added PTSA.H₂O (4.0 g, 20.63 mmol) at one portion. The mixture was stirred at rt. for 2 h. The reaction was monitored by GC-MS. Then, the reaction mixture was poured into the aq. solution of NaHCO₃ and the aqua layer was extracted couple of times with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, concentrated under reduced pressure and the crude product was purified through flash chromatography pet-ether: acetone (10:1) to afford colorless oil 39 in 88% yield.; ¹H NMR (400 MHz, CDCl₃) δ 5.78 (s, 1H), 3.98 – 3.87 (m, 4H), 2.67 (ddt, J = 19.4, 11.5, 2.4 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.51 – 2.46 (m, 1H), 2.40 (dd, J = 5.3, 2.1 Hz, 1H), 2.35 (dd, J = 5.3, 2.0 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.16 (ddd, J = 13.6, 11.1, 9.0 Hz, 1H), 1.90 (ddd, J = 13.6, 9.4, 2.7 Hz, 1H), 1.60 (ddd, J = 12.7, 5.3, 2.1 Hz, 1H), 1.25 (s, 3H).; GC-MS (ESI) m/z calcd. for C₁₂H₁₆O₃ [M]+ = 208.11; Found: 208.10. Rf = 0.35 in pet-ether: acetone (6:1).

7a-Methylhexahydrospiro[indene-1,2'-[1,3]dioxolan]-5(4H)-one (39a): The flask was charged with Pd/C (10% Pd/C, 425 mg) under argon. The solution of unsaturated ketone 39 (3.078 g, 14.78 mmol) in MeOH (160 mL) was added to the black suspension under argon. The mixture was filled with H₂ and stirred for 2 hours. The reaction was monitored by TLC and GC-MS. The catalyst was filtered through celite, the solvent was evaporated in vacuo to afford the desired product (39a) 3.066 g (99% yield).; ¹H NMR (400 MHz, CDCl₃) δ 3.91 – 3.82 (m, 4H), 3.10 (t, J = 7.1 Hz, 1H), 2.46 – 2.15 (m, 5H), 1.95 – 1.75 (m, 4H), 1.67 – 1.60
7a-Methyloctahydrospiro[indene-1,2'-[1,3]dioxolan]-5-ol: The solution of L-Selectride (1M in THF, 18 mL, 18 mmol) was cooled to 0 °C. The solution of ketone 39a (3.0 g, 14.33 mmol) in anhydrous THF (60 mL) was added at 0 °C, stirred for 1 hour. The reaction process was monitored by TLC and GC-MS. The reaction was quenched with water, and 20% KOH solution (10 mL), 30% H2O2 solution (10 mL) were added (exothermic) at rt. The mixture was stirred at rt. for additional 1 h and extracted with diethyl ether couple of tims, the combined organic layers were washed with brine and dried over MgSO4, concentrated in vacuo. The product was purified through column chromatography using pet-ether-EtOAc (2:1) as a gradient to afford colorless oil (40) 2.652g (87% yield); 1H NMR (400 MHz, CDCl3) δ 3.89 – 3.68 (m, 5H), 1.92 – 1.48 (m, 10H), 1.20 – 1.10 (m, 1H), 0.87 (s, 3H); GC-MS (ESI) m/z calcd. for C12H20O3 [M]+ = 212.14. Found: 212.12. Rf = 0.34 in pet-ether: EtOAc (1.5:1)

7a-Methyloctahydrospiro[indene-1,2'-[1,3]dioxolan]-5-yl (4-methoxyphenyl)carbamate (40a): To a solution of alcohol 40 (1.0 g, 4.71 mmol) in anhydrous THF (30 mL) were added p-methoxyphenyl isocyanate (1.065g, 7.07 mmol) and Et3N (1.43 g, 14.13 mmol). The mixture was stirred at rt. for overnight and the reaction was monitored by TLC and LC-MS. The solvent was removed in vacuo and crude product was dissolved in DCM for flash
chromatography. The product was purified through flash chromatography (pet-ether: EtOAc = 5:1) to afford light brown oil (40a) 1.2g (70% yield).; \( ^1\)H NMR (400 MHz, CDCl₃) δ 7.26 (s, 2H), 6.88 – 6.79 (m,2H), 6.44 (s, 1H), 3.95 – 3.85 (m, 4H), 3.77 (s, 3H), 1.90 – 1.71 (m, 10H), 1.33 – 1.18 (m, 2H), 0.95 (s, 3H); HPLC-MS (ESI) m/z calcd. for C\(_{20}\)H\(_{28}\)NO\(_5\) [M+H]\(^{+}\) = 362.19; Found: 362.21. 
\( R_f = 0.42 \) in pet-ether: EtOAc (3:1)

![Chemical Structure](image1)

Chemical Formula: C\(_{18}\)H\(_{23}\)NO\(_4\)
Exact Mass: 317.1627
Molecular Weight: 317.3850

7a-Methyl-1-oxooctahydro-1H-inden-5-yl (4-methoxyphenyl)carbamate (41): The Ketal 40a (1.2 g, 3.38 mmol) was dissolved in acetone-water (15:1, 32 mL), and then PPTS (283 mg, 1.13 mmol) was added. The resulting mixture was refluxed for 3 h. and the reaction was monitored by TLC and LC-MS. Upon completion the solvent acetone was removed in vacuo and the residue was dissolved in EtOAc, washed with aq. NaHCO₃ solution, brine, dried over MgSO₄, concentrated to give brown foamy solid. The crude product was purified by column chromatography using pet-ether: EtOAc (5:1) to afford the yellowish foamy solid (41) 945 mg (90% yield); HPLC-MS (ESI) m/z calcd. for C\(_{18}\)H\(_{24}\)NO\(_5\) [M+H]\(^{+}\) = 318.16. Found: 318.11. 
\( R_f = 0.41 \) in pet-ether: EtOAc (3:1).

![Chemical Structure](image2)

Chemical Formula: C\(_{25}\)H\(_{32}\)N\(_2\)O\(_3\)
Exact Mass: 408.2413
Molecular Weight: 408.5420

1-(Benzylamino)-7a-methyloctahydro-1H-inden-5-yl (4-methoxyphenyl)carbamate (43): To NaBH(OEh)₃ (0.424 g, 0.91 mmol) were added the solution of ketone 41 (145 mg, 0.46 mmol) in dry DCM followed by benzyl amine (73 mg, 0.68 mmol) and molecular sieves (50 mg). The mixture was stirred at rt. for 3 days. The reaction was monitored by TLC and LC-
MS. Then aq. NaHCO$_3$ solution was added and stirred for 15 min, washed the DCM layer couple of times with aq. NaHCO$_3$, brine dried over MgSO$_4$, concentrated to afford crude product, which was then purified by column chromatography using DCM: MeOH: Et$_3$N 100:2:0.5 as a gradient to give 131 mg of colorless oil 43 (70% yield).; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 – 7.25 (m, 7H), 6.88 – 6.78 (m, 2H), 6.61 (s, 1H), 5.02 (s, 1H), 3.77 (d, $J$ = 12.9 Hz, 3H), 2.71 (s, 1H), 2.23 (d, $J$ = 5.3 Hz, 1H), 1.99 – 1.40 (m, 9H), 1.24 (dd, $J$ = 27.1, 15.1 Hz, 3H), 1.04 (s, 3H), 0.90 (ddd, $J$ = 12.5, 7.2, 5.8 Hz, 2H).; HPLC-MS (ESI) m/z calcd. for C$_{25}$H$_{33}$N$_2$O$_3$ [M+H]$^+$ = 409.24. Found: 409.22. 

R$_f$ = 0.26 in DCM : MeOH (10:1)

7a-Methyloctahydrospiro[indene-1,2’-[1,3]dioxolan]-5-yl (4-nitrophenyl)carbamate (40a): To the solution of alcohol 40 (536 mg, 2.52 mmol) in anhydrous THF (16 mL) were added $p$-nitrophenyl isocyanate (0.640 g, 3.78 mmol) and Et$_3$N (383 mg, 3.78 mmol). The mixture was stirred at rt. overnight. The reaction was monitored by TLC and LC-MS. The solvent was removed under vacuo and the crude product was purified through flash chromatography using pet-ether: acetone (6:1) as a gradient to afford 775 mg as brown oil 40a (82% yield).; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.16 – 8.09 (m, 2H), 7.49 (d, $J$ = 9.2 Hz, 2H), 6.88 (s, 1H), 4.92 – 4.75 (m, 1H), 3.93 – 3.74 (m, 4H), 1.93 – 1.65 (m, 9H), 1.56 (dd, $J$ = 9.3, 4.6 Hz, 1H), 1.24 (dd, $J$ = 9.4, 7.4 Hz, 1H), 0.91 (d, $J$ = 6.2 Hz, 3H).; HPLC-MS (ESI) m/z calcd. for C$_{19}$H$_{25}$N$_2$O$_6$ [M+H]$^+$ = 377.16; Found: 377.08. 

R$_f$ = 0.36 pet-ether: acetone (5:1)
5-Methoxy-7a-methyloctahydrospiro[indene-1,2’-[1,3]dioxolane] (44a): NaH (60% in oil, 29 mg, 0.73 mmol) was suspended in anhydrous THF (3 mL) under argon. The solution of alcohol 40 (104 mg, 0.5 mmol) in anhydrous THF (2 mL) was added to the suspension at 0 °C. The mixture was heated to 40 °C and stirred for 0.5 hour. After cooling to 0 °C, iodomethane was added to the mixture and stirred at rt. for overnight. The reaction was monitored by TLC and GC-MS. The reaction was quenched with water and Na$_2$S$_2$O$_3$ solution, the aqueous layer was extracted couple of times with EtOAc and the combined layers were washed with brine, dried over MgSO$_4$, concentrated in vacuo. The product was purified through flash chromatography using pet-ether: EtOAc (20:1) to give the colorless liquid (44a) 46 mg (40% yield).; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.91 – 3.85 (m, 4H), 3.31 – 3.26 (m, 4H), 1.83 – 1.54 (m, 10H), 1.24 – 1.11 (m, 1H), 0.93 (s, 3H).; HPLC-MS (ESI) m/z calcd. for C$_{13}$H$_{22}$O$_3$ [M]$^+$ = 226.15. Found: 226.21. 
$R_f$ = 0.49 in pet-ether: EtOAc (8:1)

![Chemical formula of 44a]

5-Butoxy-7a-methyloctahydrospiro[indene-1,2’-[1,3]dioxolane] (44b): NaH (60% in oil, 166 mg, 4.14 mmol) was suspended in anhydrous THF (2 mL) under argon. The solution of alcohol 40 (587 mg, 2.76 mmol) in anhydrous THF (2 mL) was added to the suspension at 0 °C. The mixture was heated to 40 °C and stirred for 0.5 hour. After cooling to rt., 1-iodobutane was added to the reaction mixture and stirred at rt. for 18 h. The reaction was monitored by TLC and GC-MS. The reaction was quenched with water and Na$_2$S$_2$O$_3$ solution, the aqueous layer was extracted couple of times with EtOAc and the combined layers were washed with brine, dried over MgSO$_4$, concentrated in vacuo. The product was purified through flash chromatography using pet-ether: acetone (100:2) to give the colorless liquid (44b) 387 mg (52% yield).; GC-MS (ESI) m/z calcd. for C$_{16}$H$_{28}$O$_3$ [M]$^+$ = 268.20; Found: 268.15. 
$R_f$ = 0.52 in pet-ether: acetone (20:1)
Copy of $^1$H and $^{13}$C NMR spectra's:
Chemical Formula: C_{26}H_{34}N_{2}O_{3}
Exact Mass: 422.26
Molecular Weight: 422.57
