



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Piperidine and octahydropyrano[3,4-c] pyridine scaffolds for drug-like molecular libraries of the European Lead Factory

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ARTICLE INFO

Article history:

Received 28 April 2017

Revised 6 July 2017

Accepted 7 July 2017

Available online xxxxx

Keywords:

Nitrogen heterocycles

Compound libraries

Quinine

1,3-Amino alcohols

Non-racemic scaffolds

ABSTRACT

We report short and efficient scalable syntheses of enantiomerically pure (3*R*,4*S*)-3-(hydroxymethyl)-4-(hydroxyethyl)-piperidine and 1-hydroxymethyl-octahydro-1*H*-pyrano[3,4-*c*]pyridine scaffolds. The alkaloid core was readily synthesized from naturally occurring quinine and can serve as a valued starting point for drug-discovery. Cleavage of a terminal 1,2-diol and acid catalysed epoxide opening cyclization are the key steps involved. A number of members of a projected small-molecular library is synthesized for each scaffold.

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1. Introduction

Despite numerous advances in the field of therapeutics our ability to treat diseases remains limited. On the one hand, the development of new drug candidates is hampered by the high cost and low rate of target-lead discovery.¹ On the other hand, structural diversity in small molecular libraries is essential to populate new chemical space and to uncover bioactive molecules with potential pharmacological properties. Until recently the chemical library designs for high throughput screening (HTS) was mostly limited to flat molecules with high *sp*²-carbon content. With increase in medicinal chemists' ability to track physical properties of molecules has rightly highlighted the need of more three dimensional *sp*³-carbon rich molecular scaffolds for improving therapeutic efficiency.³

The joint European compound library (JECL) is an unique asset developed by European Lead Factory (ELF), which is a public-private initiative of European Union aimed to accelerate drug development. The aim here is to offer novel three-dimensional lead compounds to probe novel drug targets, including the emerging ones such as protein-protein interactions. This is expected that JECL will enable the medicinal chemistry community to discover

true potential of *sp*³-carbon rich heterocyclic scaffolds in biologically-relevant chemical space.^{4,5}

Functionalized piperidines are frequently studied aza-heterocycles, as they are found in many natural products and synthetic drugs.⁶ (–)Epimyrthine **A**, (–) pinidinol **B** and (+)Alkaloid 241D **C** are representative examples of bioactive piperidines (Fig. 1).⁷ Owing to their pharmacological properties a number of routes for the synthesis of multifunctional piperidines, including enantioselective syntheses are reported. Frequently used protocols involve cycloaddition reactions, reductive cyclization, ring closing metathesis, metal catalysed reactions, hydroamination, multicomponent reactions and hydrogenation of pyridines.⁸ Taking into account their compact structure and interesting properties, it is remarkable that synthetic *cis*-3,4-disubstituted piperidines are seldom evaluated for bioactivity.⁹ Octahydropyrano[3,4-*c*]pyridines are part of many alkaloid natural products including (–)Ajmalicine **D** and (–)Tetrahydroalstonine **E** among others (Fig. 1).¹⁰ Octahydropyrano[3,4-*c*]pyridines, perhaps due to a relatively complex synthetic access to these, remain rarely studied heterocycles in synthetic and medicinal chemistry despite having an 1,3-amino alcohol and a piperidine moieties that are present in many natural products.¹¹

In this paper, we will present a synthesis route to obtain novel molecular libraries of *sp*³-rich molecules and natural product-like scaffolds to enrich the JECL. These libraries will be screened at

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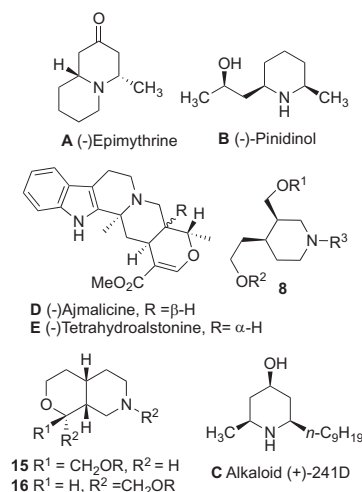


Fig. 1. Bio-active piperidines (**A–E**) and scaffolds for library synthesis (**8–16**).

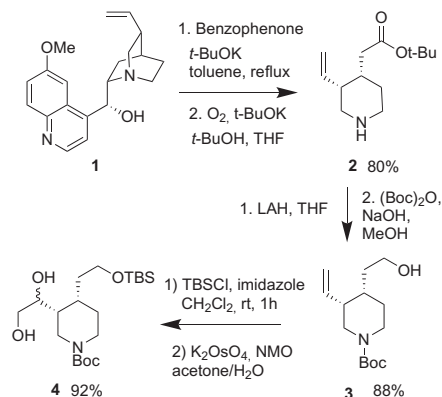
the European Screening Center to furnish novel starting points for drug discovery programs. Here, we discuss the use of quinine as a readily available chiral starting compound for the development of two molecular libraries, namely (3*R*,4*S*)-3-(hydroxymethyl)-4-(hydroxyethyl)-piperidine **8** and 1-hydroxymethyl-octahydro-1*H*-pyrano[3,4-*c*]pyridines **15**, **16** respectively.

2. Results and discussion

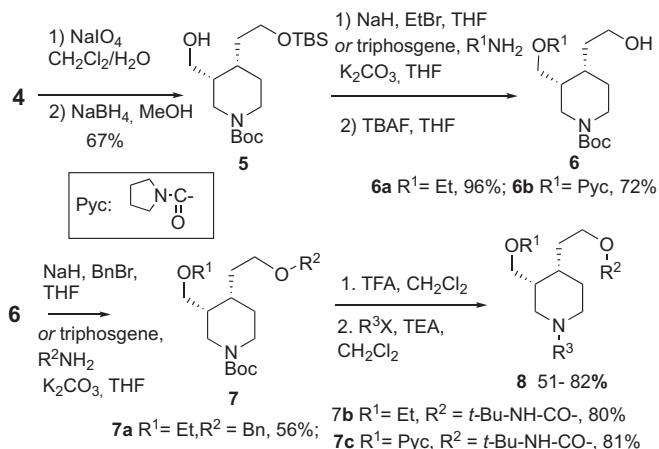
Key intermediate **4** that was required for the preparation of both scaffolds was efficiently synthesized from naturally occurring cinchona alkaloid quinine (**1**) using literature protocols.^{12,13} Oppenauer–Woodward oxidation of quinine **1** was followed by oxidative degradation to yield piperidine core **2** in 80% yield. LiAlH₄ reduction of the ester function followed by protection of the secondary amine with Boc-group yielded alcohol **3**. Subsequently, the alcohol was protected by treatment with TBS-Cl in presence of imidazole. Next, the hydroxylation of **3** with potassium osmate/*N*-methylmorpholine-*N*-oxide in aqueous acetone yielded key intermediate **4** in 92% yield as 1:1 mixture of diastereomeric diols (Scheme 1).

2.1. Synthesis and diversification of piperidine scaffold

The mixture of diols **4** was treated overnight with sodium periodate in dichloromethane water (1:1.5) and the crude aldehyde,



Scheme 1. Synthesis of key diol intermediate **4**.

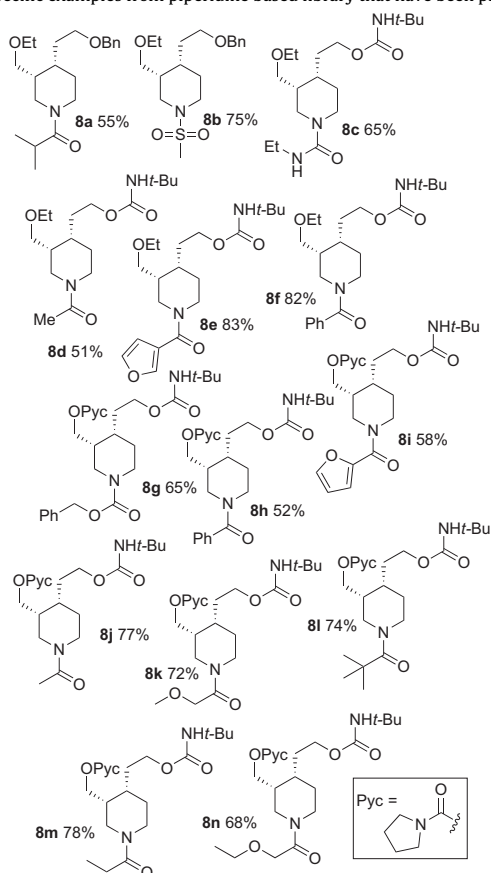


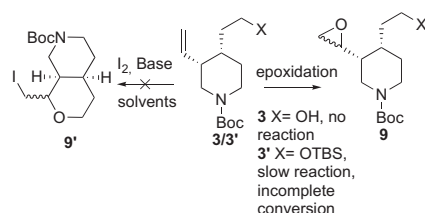
Scheme 2. Synthesis of piperidine scaffolds. (Substituent R³ stands for acyl, oxycarbonyl, carbamoyl or sulfonyl, see Table 1.)

thus obtained, was reduced with sodium borohydride to produce alcohol **5** in good yield (Scheme 2). The free hydroxyl group in **5** was then used as first diversification point and was either converted into an ether by treatment with ethyl bromide or transformed into a carbamate by sequential treatment with triphosgene and pyrrolidine. Upon cleavage of the silyl ether (TBS) alcohols **6a** and **6b** were obtained. The free hydroxyl group in **6** was converted into either benzyl ether or *t*-butyl carbamate (**7**) by treatment either with benzyl bromide and sodium hydride or with *t*-butyl isocyanate under basic conditions. The Boc-protection

Table 1

Specific examples from piperidine based library that have been prepared in this study.





Scheme 3. Attempted iodocyclization and epoxidation reactions. Base: NaHCO_3 , K_2CO_3 , NaOH ; Solvents: CH_2Cl_2 , CH_3CN , DMF .

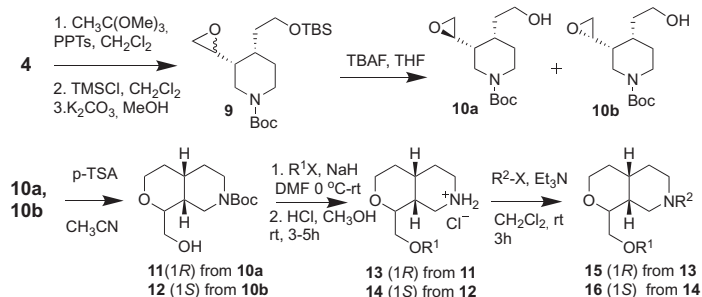
in **7** was removed by stirring with trifluoroacetic acid (TFA) for overnight and the free amine as a second diversification point was converted into diverse array of functional groups such as an amide (**8a**, **8d**, **8e**, **8f**, **8h–8n**), an urea (**8c**) carbamate (**8g**) and sulfone amide (**8b**) by reaction with an acid chloride, isocyanate, chloroformate and sulfonyl chloride respectively in 51–82% isolated yields. A number of acid chlorides including with functionalized aliphatic (**8h**, **8k**) and heteroaromatic (**8e**, **8i**) substitution reacted to deliver the amide products. (Table 1).

2.2. Synthesis and diversification of octahydropyrano[3,4-c]pyridine scaffolds

Next, we decided to use readily available intermediate **3** to synthesize octahydro-pyrano[3,4-c]pyridine core by iodine mediated cyclization (Scheme 3). However, all reactions we tried using various bases such as anhydrous or aqueous NaHCO_3 , K_2CO_3 , NaOH and solvents CH_2Cl_2 , CH_3CN , EtOAc , DMF resulted in complex reaction mixtures. This led us to switch to epoxide

opening reaction to generate the octahydro-1H-pyrano[3,4-c]pyridine core (Scheme 3).

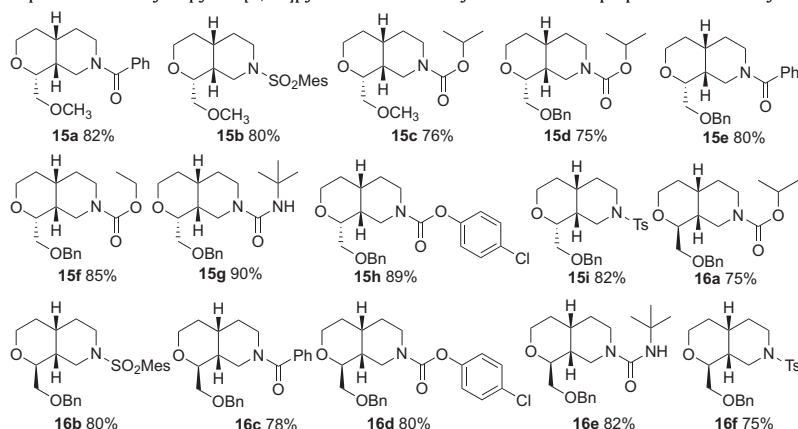
Nevertheless, free alcohol **3** failed to react with various epoxidizing reagents such as *m*-CPBA, *m*-CPBA/ NaHCO_3 , trifluoroacetic acid and trifluoromethyl(methyl)dioxirane in dichloromethane. The silyl ether **3'** (OTBS) reacted slowly and only 50% conversion to epoxide **9** was observed when treated with 4 eq. *m*-CPBA for 72 h. Use of additives such as NaHCO_3 resulted in a sluggish reaction (Scheme 3). To overcome these problems, we decided to use diol **4** for synthesis of epoxide **9**. The diol **4** was treated with trimethylorthoacetate/PPTs and the orthoester intermediate was opened using chlorotrimethylsilane. Treatment with base gave mixture (1:1) of epoxides **9** that were separated using column chromatography. Alternatively, the silyl protection can be removed using TBAF, followed by separation of the free epoxy alcohols **10a** and **10b** by column chromatography. The absolute stereochemistry of the newly formed chiral center in epoxides **10a** and **10b** was assigned using the “mnemonic device” for Sharpless dihydroxylation.¹⁴ The reaction of **3'** with AD-mix β favored epoxide **10a** over **10b** (dr 3:1). Thus newly generated chiral center in **10a** was assigned to be of *R*-configuration and that in **10b** to be *S*. The epoxy-alcohols **10a/10b** were then separated and treated with *p*-toluenesulfonic acid in acetonitrile leading to an efficient formation of 1-hydroxymethyl-octahydropyrano[3,4-c]pyridine **11** and **12** in 73% and 70% yields, respectively. It is noteworthy that side-products, containing a seven-membered oxepane ring **11'**/**12'** were formed in 10% and 15% yields during the acid catalysed cyclization reaction of epoxides **10a/10b**, respectively.¹⁵ The free hydroxyl group in **11/12** was converted into alkyl ether by treatment with an alkyl halide under basic conditions. In next step the Boc protection was removed under acidic conditions to get amines **13/14**. The reaction works best when performed using methanolic HCl (4.0 M) and yields amines quantitatively as their hydrochloride salts. A



Scheme 4. Synthesis of octahydropyrano[3,4-c]pyridine scaffolds.

Table 2

Examples from octahydropyrano[3,4-c]pyridine based library that have been prepared in this study.



diverse library was generated by treatment of hydrochloride salts **13/14** with several acid chlorides, chloroformates, sulfonyl chlorides and isocyanates (Scheme 4). All the reactions worked well to yield corresponding amides (**15a**, **15e**, **16c**), carbamates (**15c**, **15d**, **15f**, **15h**, **16a**, **16d**), sulfonamides (**15b**, **15i**, **16b**, **16f**) or ureas (**15g**, **16e**) in 75–90% yields (Table 2).

3. Conclusions

In conclusion, we have successfully developed an efficient synthesis of the sp^3 -rich scaffolds 3,4-disubstituted chiral piperidines and octahydropyrano[3,4-*c*]pyridines for the development of focused compound libraries for drug discovery. Use of quinine, a readily available starting compound, and robust chemistry involved should make this protocol attractive for large library synthesis for development of new leads and drug candidates.

4. Experimental section

4.1. General information

Commercially available reagents were used throughout without further purification unless otherwise stated. Dichloromethane (DCM), di-methylformamide (DMF) tetrahydrofuran (THF) and acetonitrile (ACN) were stored over 4 Å molecular sieves. All reactions were carried out under nitrogen or argon atmosphere unless mentioned otherwise. Thin layer chromatography was carried out using aluminum backed plates coated with silica gel. The plates were visualized under UV light at 254 nm and/or by sulphuric acid in methanol or potassium permanganate stains. Flash column chromatography was carried out using silica gel (0.040–0.063 mm) with eluents specified. Purification by reverse phase column chromatography was performed using Reveleris, 12 g acidic columns. ^1H and ^{13}C NMR spectra were recorded on Bruker DMX-400 and AV-400 instruments (^1H frequencies 400 MHz, corresponding ^{13}C frequencies are 101 MHz respectively). Chemical shifts are quoted in parts per million (ppm). Coupling constants (*J*) values are recorded in Hz. The spectral data of known compounds are in accordance with literature data. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution *R* = 60,000 at *m/z* 400 (mass range *m/z* = 150–2000) and dioctylphthalate (*m/z* = 391.2842) as a “lock mass”. The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

4.2. Synthetic procedures

4.2.1. *tert*-Butyl 2-((3*R*,4*S*)-3-vinylpiperidin-4-yl)acetate (**2**)

Quinine (**1**) (67 g, 206 mmol) was dissolved in 400 mL of dry toluene. To this mixture benzophenone (75 g, 412 mmol) and *KOt*-Bu (58 g, 517 mmol) were added and the resulting mixture was refluxed overnight. The reaction mixture was cooled down to room temperature and quenched with 2 M HCl (275 mL) solution. The organic layer was extracted with 2 M HCl (100 mL) solution. The water layers were combined and the pH was adjusted to 14 by the addition of 35% NH_4OH solution. The resulting mixture was extracted three times with 300 mL of dichloromethane. The organic layers were combined, washed with brine, dried with Na_2SO_4 and the product was concentrated and directly used in the next step.

Through a solvent mixture THF/*t*-BuOH (4:1, 750 mL) oxygen was bubbled for a period of 15 min. Then *KOt*-Bu (58 g, 517 mmol) was added and the mixture was cooled to 0 °C. Purging of the mixture with oxygen was continued for another 15 min. Then crude ketone was added over a period of 10 min (this can be done by making a solution of the crude in a small volume of THF). The resulting red mixture was warmed to room temperature and purging of oxygen was continued for 1.5 h. The reaction was quenched with AcOH (60 mL) and the volatiles were removed under reduced pressure, keeping the water bath below 50 °C. The crude product was then dissolved in water (300 mL) and the pH was adjusted to 14 by the addition of 35% NH_4OH solution. The mixture was then extracted with Et_2O (4x50 mL). The organic layers were combined, washed two times with brine, dried over Na_2SO_4 and the product was concentrated to give piperidine **2** (38 g, 169 mmol, 80% over 2 steps). All analytical data was in accordance to those reported in literature.¹

4.2.2. (3*R*,4*S*)-*tert*-Butyl 4-(2-hydroxyethyl)-3-vinylpiperidine-1-carboxylate (**3**)

A mixture of lithium aluminum hydride in THF (2.4 M, 266 mmol, 111 mL) and tetrahydrofuran (dry) (150 mL) was cooled to 0 °C. A solution of *tert*-butyl 2-((3*R*, 4*S*)-3-vinylpiperidin-4-yl)acetate **2** (50 g, 222 mmol) in tetrahydrofuran (100 mL) was added dropwise. Subsequently, the temperature was raised to room temperature and the reaction mixture was stirred for 1 h. The reaction mixture was cooled using an ice/water bath. The reaction was quenched by dropwise addition of H_2O (13 mL; 1.3 mL/g LiAlH_4) followed by dropwise addition of aq. 4 M NaOH (13 mL; 1.3 mL/g LiAlH_4) and addition of H_2O (26 mL; 2.6 mL/g LiAlH_4). The resulting mixture was stirred vigorously for 15 min. Filtration was followed by washing the residue with Et_2O (3 × 100 mL). The volatiles were removed under reduced pressure to get 2-((3*R*,4*S*)-3-vinylpiperidin-4-yl)ethanol (33.34 g, 97%) as an oil.

The crude alcohol (33.2 g, 214 mmol) was dissolved in methanol (200 mL) and the solution was stirred at 0 °C. Di-*tert*-butyldicarbonate (51.3 g, 235 mmol) was added in portions followed by addition of NaOH 9.41 g, 235 mmol). The resulting mixture was stirred at room temperature overnight. The crude material was concentrated and dissolved in EtOAc (600 mL) and ice cold water (120 mL) was added. The two layers were separated and the water layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with brine and dried with Na_2SO_4 and concentrated under reduced pressure to give (3*R*,4*S*)-*tert*-butyl 4-(2-hydroxyethyl)-3-vinylpiperidine-1-carboxylate **3** (45.08 g, 91%) as a sticky colourless oil. All analytical data was in accordance to those reported in literature.²

4.2.3. (3*R*,4*S*)-*tert*-Butyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(-1,2-dihydroxyethyl) piperidine-1-carboxylate (**4**)

Alcohol **3** (45.08 g, 161 mmol) and imidazole (16.41 g, 241 mmol) were dissolved in dry dichloromethane (225 mL). The reaction mixture was stirred in a water bath at 10 °C and TBSCl (27.8 g, 185 mmol) was added in 2.0 g portions over 20 min. The reaction mixture was stirred for 1 h at this point water (150 mL) was added and the layers were separated. The water layer was extracted with dichloromethane (2 × 50 mL). The organic layers were combined and dried with Na_2SO_4 concentrated under reduced pressure and the crude product was purified by column chromatography (heptane/EtOAc, 15/1 & 9/1) to get (3*R*,4*S*)-*tert*-butyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-vinylpiperidine-1-carboxylate (54.8 g, 92%) as an oil.

The above prepared olefin (49.2 g, 133 mmol) was dissolved in a 1:1 mixture of acetone/water (400 mL). To this mixture *N*-methylmorpholine-*N*-oxide (18.8 g, 160 mmol) and potassium osmate dihydrate (1.47 g, 4 mmol) were added and the reaction mixture

was stirred at room temperature overnight. Next, 28 g of NaHSO₃ was added and the resulting mixture was stirred for an additional 2 h. Addition of brine (225 mL) and EtOAc (300 mL) resulted in a two-phase system with a lot of voluminous brown solid. The phases were filtered over a cotton plug and separated, the water phase was extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with brine, dried with Na₂SO₄ and the product was concentrated to give diastereomeric mixture of diols (3R,4S)-*tert*-butyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1,2-dihydroxyethyl)piperidine-1-carboxylate **4** as yellow oil quantitatively (53.7 g). ¹H NMR (400 MHz, CDCl₃) δ 3.81–3.66 (m, 4H), 3.66–3.47 (m, 10H), 3.44–3.27 (m, 3H), 3.25–2.98 (m, 3H), 2.91–2.66 (m, 2H), 2.13–2.02 (s, 1H), 1.91–1.89 (m, 1H), 1.78–1.60 (m, 4H), 1.60–1.43 (m, 8H), 1.41 (s, 9H), 1.39 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H), –0.05 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 155.3, 154.94, 79.7, 79.6, 70.9, 70.1, 64.9, 64.7, 62.6, 61.0, 43.1, 41.6, 41.4, 40.1, 29.2, 28.3, 28.3, 28.1, 25.9, 25.8, 18.3, 18.2, –5.4, –5.5. ESI-HRMS [C₂₀H₄₁NO₅Si+H]⁺: 404.28276 found, 404.28268 calculated.

4.2.4. *tert*-Butyl (3R,4S)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(hydroxymethyl) piperidine-1-carboxylate (**5**)

The diol **4** (59.7 g, 148 mmol) was dissolved in dichloromethane (150 mL) and the solution was stirred at room temperature. A solution of NaIO₄ (34.8 g, 163 mmol) in water (500 mL) was added and the mixture was stirred vigorously overnight. A solid was filtered off and discarded. The layers were separated and the water layer was extracted with dichloromethane (2 × 100 mL). The organic layers were combined, dried over Na₂SO₄ and the solvent was evaporated to give the corresponding aldehyde (50.92 g, 93%) as an oil. It was dissolved in MeOH (200 mL) and cooled to 0 °C. NaBH₄ (10.35 g, 274 mmol) was added in portions. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated and then dissolved in EtOAc (350 mL) and water (150 mL). The layers were separated. The water layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with brine, dried with Na₂SO₄ and the solvent was evaporated. The product was purified with flash column chromatography (heptane/EtOAc, 0% to 20% EtOAc) to give alcohol **5** (37.4 g, 73%) as a colourless oil.

4.2.5. *tert*-Butyl (3R,4S)-3-(ethoxymethyl)-4-(2-hydroxyethyl) piperidine-1-carboxylate (**6a**)

Alcohol **5** (5.62 g, 15.05 mmol) was dissolved in THF (dry) (55 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil) (1.204 g, 30.1 mmol, 60%) was added. After removing the cooling bath, and the mixture was allowed to warmed to room temperature. After stirring for 30 min at room temperature, iodoethane (9.39 g, 60.2 mmol, 4.81 mL) was added and the mixture was stirred overnight. The reaction mixture was quenched with saturated aqueous NH₄Cl (165 mL) and the mixture was extracted with EtOAc (3 × 165 mL). The organic layers were combined, dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure to afford the crude (3R,4S)-*tert*-butyl 4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(ethoxymethyl)piperidine-1-carboxylate.

The crude product was dissolved in THF (60 mL) and TBAF (1 M in THF) (22.58 mmol, 22.58 mL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The product was purified by column chromatography (0–70% gradient of EtOAc in heptane; TLC H/E 1:1) to afford alcohol **6** (4.15 g, Yield: 96%, 2 steps) as a light yellow oil.

4.2.6. *tert*-Butyl (3R,4S)-4-(2-hydroxyethyl)-3-(((pyrrolidine-1-carbonyl)oxy)methyl) piperidine-1-carboxylate (**6b**)

Alcohol **5** (12.80 g, 34.3 mmol), triphosgene (4.07 g, 13.70 mmol) and potassium carbonate (14.21 g, 103 mmol) were dissolved in THF (dry) (125 mL) and stirred overnight. The mixture was cooled to 0 °C and pyrrolidine (4.87 g, 68.5 mmol, 5.63 mL) was added. The mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH₄Cl (350 mL) and extracted with EtOAc (3 × 350 mL). The organic layers were combined, dried (Na₂SO₄), filtered and the solvent was evaporated under reduced pressure. The crude product (16.9 g) was used in the next step without further purification. The crude product (16.9 g) was dissolved in THF (dry) (125 mL) and TBAF (1 M in THF) (68.6 mmol, 68.6 mL) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The product was purified by flash column chromatography to get *tert*-butyl (3R,4S)-4-(2-hydroxyethyl)-3-(((pyrrolidine-1-carbonyl)oxy)methyl) piperidine-1-carboxylate (**6b**) (8.81 g, Yield: 72.1%) as a light yellow oil.

4.2.7. *tert*-Butyl (3R,4S)-4-(2-(benzyloxy)ethyl)-3-(ethoxymethyl) piperidine-1-carboxylate

Alcohol **6** (0.74 g, 2.57 mmol) was dissolved in THF (dry) (20 mL). The solution was cooled (0 °C) and NaH (60% dispersion in mineral oil) (0.257 g, 6.44 mmol, 60%) was added. The resulting mixture was stirred at room temperature for 30 min. Benzyl bromide (0.440 g, 2.57 mmol, 0.306 mL) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH₄Cl (25 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na₂SO₄), filtered and evaporated under reduced pressure to afford 1.370 g of crude product. Purification by column chromatography (Reveleris, 120 g column, acidic) followed by evaporation of the solvents under reduced pressure afforded (3R,4S)-*tert*-butyl 4-(2-(benzyloxy)ethyl)-3-(ethoxymethyl)piperidine-1-carboxylate (**7a**) (548 mg, Yield: 56.4%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.21 (m, 5H), 4.62–4.44 (m, 2H), 4.08 (bs, 2H), 3.64 (s, 1H), 3.59–3.49 (m, 2H), 3.49–3.34 (m, 3H), 3.29 (t, *J* = 9.0 Hz, 1H), 3.07–2.63 (m, 2H), 2.02–1.76 (m, 1H), 1.77–1.63 (m, 1H), 1.63–1.51 (m, 1H), 1.46 (s, 9H), 1.42–1.11 (m, 2H), 1.19 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 155.2, 138.4, 129.5, 128.3, 128.2, 128.2, 127.6, 127.5, 127.0, 126.8, 79.1, 79.1, 72.9, 68.0, 66.5, 66.4, 43.0, 38.2, 28.4, 15.2. ESI-HRMS [C₂₂H₃₅NO₄+H]⁺: 378.26404 found, 378.26389 calculated.

4.2.8. (3R,4S)-*tert*-Butyl-4-(2-((*tert*-butylcarbonyl)oxy)ethyl)-3-(ethoxymethyl)piperidine-1-carboxylate (**7b**)

Alcohol **6a** (0.74 g, 2.57 mmol) was dissolved in THF (dry) (20 mL). The solution was cooled (0 °C) and sodium hydride (60% dispersion in mineral oil) (0.257 g, 6.44 mmol, 60%) was added. The resulting mixture was stirred at room temperature for 30 min. *tert*-Butyl isocyanate (0.255 g, 2.57 mmol, 0.294 mL) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH₄Cl (25 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na₂SO₄), filtered and evaporated under reduced pressure to afford 1.157 g of crude product. Purification by reverse phase column chromatography (Reveleris, 120 g column, acidic) followed by evaporation of the solvents under reduced pressure and coevaporation using CH₂Cl₂ afforded (3R,4S)-*tert*-butyl 4-(2-((*tert*-butylcarbonyl)oxy)ethyl)-3-(ethoxymethyl)piperidine-1-carboxylate (**7b**) (0.8 g, Yield: 80%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.60 (s, 1H), 4.07 (d, *J* = 6.1 Hz, 4H), 3.44 (q, *J* = 6.9 Hz, 3H), 3.39 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.29 (t, *J* = 9.0 Hz, 1H), 2.87 (s, 2H), 1.88 (s, 1H), 1.77 (s, 1H), 1.70–1.61 (m, 2H), 1.59–1.40 (m, 11H), 1.28 (d, *J* = 24.7 Hz, 10H), 1.25–1.13 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 155.1, 79.1, 66.78, 66.5, 62.1, 50.2, 45.9, 43.0, 38.2, 34.6, 31.7, 28.9, 28.4, 27.8, 15.2. ESI-HRMS $[\text{C}_{20}\text{H}_{38}\text{N}_2\text{O}_5+\text{H}]^+$: 387.28559 found, 387.28535 calculated.

4.2.9. (3*R*,4*S*)-*tert*-Butyl 4-(2-((*tert*-butylcarbamoyl)oxy)ethyl)-3-(((pyrrolidine-1-carbonyl)oxy)methyl)piperidine-1-carboxylate

Alcohol **6b** (1.35 g, 3.79 mmol) was dissolved in THF (dry) (40 mL) and NaH (60% dispersion in mineral oil) (0.379 g, 9.47 mmol, 60%) was added. The resulting mixture was stirred at room temperature for 30 min. *tert*-Butyl isocyanate (0.375 g, 3.79 mmol, 0.433 mL) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were filtered using a phase separator and evaporated to dryness under reduced pressure to afford 2.18 g of crude product. Purification by reverse phase column chromatography (Reveleris, 120 g column, acidic) followed by evaporation of the solvents under reduced pressure and coevaporation using CH_2Cl_2 afforded (3*R*,4*S*)-*tert*-butyl 4-(2-((*tert*-butylcarbamoyl)oxy)ethyl)-3-(((pyrrolidine-1-carbonyl)oxy)methyl)piperidine-1-carboxylate (**7c**) (1.395 g, Yield: 81%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.89 (s, 1H), 4.22 (s, 1H), 4.08–3.72 (m, 5H), 3.51–3.24 (m, 4H), 2.91 (dd, $J = 13.3, 2.2$ Hz, 1H), 2.02 (s, 1H), 1.93–1.75 (m, 5H), 1.71 (dd, $J = 14.4, 6.9$ Hz, 1H), 1.65–1.54 (m, 1H), 1.54–1.36 (m, 2H), 1.44 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.0, 154.9, 79.3, 77.3, 76.68, 76.7, 62.2, 61.9, 50.1, 46.1, 45.7, 43.3, 37.1, 35.0, 31.2, 28.9, 28.3, 28.2, 27.8, 25.6, 24.9. ESI-HRMS $[\text{C}_{23}\text{H}_{41}\text{N}_3\text{O}_6+\text{H}]^+$: 456.30626 found, 456.30681 calculated.

4.2.10. General procedure for Boc-removal and amidation, sulfonylation and sulfonylation (**8a–8n**)

A Boc-protected compound (**7a–7c**) was dissolved in DCM (10 mL per mmol). TFA (14 equiv) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with sat. K_2CO_3 (aq) (40 mL) and extracted three times with Et_2O (50 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was concentrated *in vacuo* to obtain free amine product that was used as such in next transformation.

In a screw cap vial (8 mL) was loaded with a solution of amine (1 equiv) in DCM (2 mL). Et_3N (1.5 equiv) then the corresponding acid chloride, sulfonyl chloride, chloroformate or isocyanate (1.2 equiv) were added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched with 2 mL of 10% Na_2CO_3 (aq) and the phases were separated. The aq. layer was extracted 2 mL of DCM. The solvent was evaporated and the crude material was purified by column chromatography.

4.2.10.1. 1-((3*R*,4*S*)-4-(2-(Benzyloxy)ethyl)-3-(ethoxymethyl)piperidin-1-yl)-2-methylpropan-1-one (**8a**). Colourless liquid, (10.3 mg, 0.030 mmol, 55%). ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.18 (m, 5H), 4.62–4.43 (m, 3H), 4.12 (d, $J = 13.4$ Hz, 1H), 3.54–3.41 (m, 3H), 3.39–3.34 (m, 2H), 3.28 (t, $J = 7.2$ Hz), 3.09–2.85 (m, 2H), 2.64 (td, $J = 12.9, 3.3$ Hz, 1H), 1.94 (s, 2H), 1.63–1.51 (m, 5H), 1.25 (d, $J = 9.1$ Hz, 1H), 1.18 (t, $J = 7.0$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 138.4, 128.4, 127.6, 73.1, 67.8, 66.6, 65.9, 46.9, 41.9, 38.3, 34.8, 32.7, 29.7, 27.6, 20.7, 19.8, 19.1, 15.2. ESI-HRMS $[\text{C}_{21}\text{H}_{33}\text{NO}_3+\text{H}]^+$: 348.25352 found, 348.25332 calculated.

4.2.10.2. (3*R*,4*S*)-4-(2-(Benzyloxy)ethyl)-3-(ethoxymethyl)-1-(methylsulfonyl)piperidine (**8b**). Colourless liquid, (14.4 mg, 0.041 mmol, 75%). ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.20 (m, 5H), 4.60–4.39 (m, 2H), 3.87–3.73 (m, 1H), 3.67 (dd, $J = 7.4, 4.1$ Hz, 1H), 3.62–3.32 (m, 6H), 2.84–2.63 (m, 2H), 2.76 (s, 3H), 2.01 (dt, $J = 8.1,$

4.0 Hz, 1H), 1.85 (tt, $J = 11.3, 4.0$ Hz, 1H), 1.75–1.33 (m, 4H), 1.18 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.3, 128.4, 127.7, 127.6, 73.0, 67.8, 66.8, 66.7, 47.8, 45.7, 37.7, 34.7, 33.7, 31.9, 27.8, 20.7, 15.2. ESI-HRMS $[\text{C}_{18}\text{H}_{29}\text{NO}_4\text{S}+\text{H}]^+$: 356.18903 found, 356.18901 calculated.

4.2.10.3. 2-((3*R*,4*S*)-3-(Ethoxymethyl)-1-(ethylcarbamoyl)piperidin-4-yl)ethyl *tert*-butylcarbamate (**8c**). Colourless liquid, (12.2 mg, 0.034 mmol, 65%). ^1H NMR (400 MHz, CDCl_3) δ 5.02 (t, $J = 4.9$ Hz, 1H), 4.60 (s, 1H), 4.40–4.30 (m, 1H), 4.05 (t, $J = 6.0$ Hz, 2H), 3.90–3.77 (m, 1H), 3.61–3.39 (m, 2H), 3.39–3.30 (m, 2H), 3.32–3.13 (m, 2H), 2.89 (dd, $J = 14.1, 2.3$ Hz, 1H), 2.67 (td, $J = 12.8, 3.2$ Hz, 1H), 2.05–1.90 (m, 1H), 1.83 (ddd, $J = 11.5, 7.8, 3.8$ Hz, 1H), 1.65–1.39 (m, 3H), 1.38–1.26 (m, 1H), 1.32 (s, 9H), 1.22 (t, $J = 7.4$ Hz, 3H), 1.13 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.0, 66.3, 65.8, 61.9, 50.3, 46.4, 43.5, 37.2, 35.6, 35.1, 32.3, 28.9, 27.8, 20.7, 15.6, 15.3. ESI-HRMS $[\text{C}_{18}\text{H}_{35}\text{N}_3\text{O}_4+\text{H}]^+$: 358.27019 found, 358.27003 calculated.

4.2.10.4. 2-((3*R*,4*S*)-1-Acetyl-3-(ethoxymethyl)piperidin-4-yl)ethyl *tert*-butylcarbamate (**8d**). Colourless liquid, (8.6 mg, 0.026 mmol, 51%). mixture of rotamers ^1H NMR (400 MHz, CDCl_3) δ 4.77–4.43 (m, 2H), 4.04 (dd, $J = 13.5, 2.3$ Hz, 3H), 3.57–3.24 (m, 4H), 3.03 (dd, $J = 13.4, 2.5$ Hz, 1H), 2.60 (td, $J = 12.8, 3.3$ Hz, 1H), 2.09 (s, 3H), 1.97 (dd, $J = 7.1, 3.4$ Hz, 1H), 1.85 (dd, $J = 7.3, 4.1$ Hz, 1H), 1.67–1.45 (m, 5H), 1.32 (s, 9H), 1.30–1.24 (m, 1H), 1.18 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 169.3, 154.9, 154.6, 62.52, 61.4, 61.0, 50.1, 47.9, 46.4, 46.1, 45.9, 45.8, 42.7, 41.6, 37.2, 36.8, 31.9, 31.1, 28.9, 28.4, 27.8, 25.8, 24.9, 24.8, 21.5, 21.2. ESI-HRMS $[\text{C}_{17}\text{H}_{32}\text{N}_2\text{O}_4+\text{H}]^+$: 329.24366 found, 329.24348 calculated.

4.2.10.5. 2-((3*R*,4*S*)-3-(Ethoxymethyl)-1-(furan-3-carbonyl)piperidin-4-yl)ethyl *tert*-butylcarbamate (**8e**). Colourless liquid, (16.3 mg, 0.043 mmol, 83%). ^1H NMR (400 MHz, CDCl_3) δ 7.81 (s, 1H), 7.40 (t, $J = 1.6$ Hz, 1H), 6.64 (s, 1H), 4.61 (s, 2H), 4.28 (dd, $J = 13.3, 1.9$ Hz, 1H), 4.08 (d, $J = 6.5$ Hz, 2H), 3.52–3.22 (m, 4H), 3.16 (dd, $J = 13.3, 3.0$ Hz, 1H), 3.01–2.68 (m, 1H), 1.97 (s, 1H), 1.89 (s, 1H), 1.77–1.49 (m, 3H), 1.48–1.24 (m, 1H), 1.39 (s, 9H), 1.13 (t, $J = 9.0$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 164.5, 154.6, 143.2, 142.6, 121.2, 110.3, 77.3, 77.1, 76.7, 62.3, 61.2, 50.2, 46.2, 35.7, 31.4, 28.9, 25.7, 24.9. ESI-HRMS $[\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_5+\text{H}]^+$: 381.23847 found, 381.23840 calculated.

4.2.10.6. 2-((3*R*,4*S*)-1-Benzoyl-3-(ethoxymethyl)piperidin-4-yl)ethyl *tert*-butylcarbamate (**8f**). Colourless liquid, (16.6 mg, 0.043 mmol, 82%). ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 5H), 4.60 (s, 2H), 4.07 (d, $J = 7.1$ Hz, 1H), 3.68–3.22 (m, 3H), 3.13 (s, 1H), 1.94 (bs, 2H), 1.65–1.55 (m, 2H), 1.52–1.38 (m, 2H), 1.31 (s, 9H), 1.30–1.14 (m, 4H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.9, 154.8, 136.3, 128.3, 127.1, 62.27, 50.2, 46.1, 35.6, 31.5, 28.9, 25.6, 24.9, 20.7. ESI-HRMS $[\text{C}_{26}\text{H}_{39}\text{N}_3\text{O}_6+\text{H}]^+$: 490.29094 found, 490.29116 calculated.

4.2.10.7. Benzyl (3*R*,4*S*)-4-(2-((*tert*-butylcarbamoyl)oxy)ethyl)-3-(((pyrrolidine-1-carbonyl)oxy)methyl)piperidine-1-carboxylate (**8g**). Colourless liquid, (20.3 mg, 0.062 mmol, 65%). ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.15 (m, 5H), 5.14 (bs, 3H), 4.36 (d, $J = 6.9$ Hz, 1H), 4.16 (dt, $J = 11.3, 8.8$ Hz, 3H), 4.01 (s, 1H), 3.87 (t, $J = 10.5$ Hz, 1H), 3.59–3.21 (m, 3H), 3.18–2.98 (m, 3H), 2.06 (s, 1H), 1.95–1.37 (m, 9H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.7, 136.8, 128.4, 127.9, 127.7, 67.1, 63.1, 62.4, 61.4, 50.2, 46.1, 45.5, 43.8, 36.9, 28.9, 27.8, 25.7, 24.8, 20.8, 20.7. ESI-HRMS $[\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_5+\text{H}]^+$: 381.23847 found, 381.23840 calculated.

4.2.10.8. ((3*R*,4*S*)-1-Benzoyl-4-(2-((*tert*-butylcarbamoyl)oxy)ethyl)piperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8h**). Colourless liquid, (15.1 mg, 0.033 mmol, 52%). major rotamer ¹H NMR (400 MHz, CDCl₃) δ 7.37 (s, 5H), 5.15–4.90 (m, 1H), 4.60 (s, 1H), 4.50–4.07 (m, 2H), 4.03 (s, 1H), 3.88 (s, 2H), 3.34 (d, *J* = 28.4 Hz, 3H), 3.23–2.96 (m, 2H), 2.71 (s, 1H), 2.51 (s, 1H), 2.04–1.41 (m, 9H), 1.31 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 154.8, 136.3, 128.3, 127.1, 62.3, 50.2, 46.1, 35.6, 31.5, 28.9, 25.6, 24.9, 20.7. ESI-HRMS [C₂₅H₃₇N₃O₅+H]⁺: 460.28046 found, 460.28060 calculated.

4.2.10.9. ((3*R*,4*S*)-4-(2-((*tert*-Butylcarbamoyl)oxy)ethyl)-1-(furan-2-carbonyl)piperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8i**). Colourless liquid, (16.5 mg, 0.037 mmol, 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 6.95 (d, *J* = 3.4 Hz, 1H), 6.45 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.12 (s, 1H), 4.59–4.26 (m, 3H), 4.17 (dt, *J* = 11.2, 5.6 Hz, 1H), 4.03 (s, 1H), 3.88 (t, *J* = 10.5 Hz, 1H), 3.49–2.83 (m, 5H), 2.17 (s, 1H), 2.05–1.90 (m, 1H), 1.90–1.69 (m, 5H), 1.68–1.47 (m, 4H), 1.30 (d, *J* = 13.3 Hz, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 160.0, 154.7, 148.1, 143.3, 115.7, 111.1, 62.4, 61.4, 50.2, 46.1, 45.6, 37.4, 35.8, 31.4, 28.9, 25.7, 24.9. ESI-HRMS [C₂₃H₃₅N₃O₆+H]⁺: 450.25969 found, 450.25986 calculated.

4.2.10.10. ((3*R*,4*S*)-1-Acetyl-4-(2-((*tert*-butylcarbamoyl)oxy)ethyl)piperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8j**). Colourless liquid, (19.5 mg, 0.049 mmol, 77%). Mixture of rotames ¹H NMR (400 MHz, CDCl₃) δ 5.32 (bs, 1H major), 5.10 (bs, 1H, minor), 4.74–4.40 (m, 2H), 4.04 (dd, *J* = 13.5, 2.3 Hz, 3H), 3.55–3.25 (m, 4H), 3.03 (dd, *J* = 13.4, 2.5 Hz, 1H), 2.60 (td, *J* = 12.8, 3.3 Hz, 1H), 2.09 (d, *J* = 4.4 Hz, 3H), 1.97 (dd, *J* = 7.1, 3.4 Hz, 1H), 1.85 (dd, *J* = 7.3, 4.1 Hz, 1H), 1.73–1.42 (m, 5H), 1.39–1.26 (m, 10H), 1.18 (dt, *J* = 10.8, 7.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 154.6, 62.5, 62.3, 61.4, 61.0, 47.9, 46.4, 46.1, 45.9, 45.8, 42.7, 41.6, 37.2, 36.84, 31.9, 31.1, 28.9, 27.8, 25.8, 25.7, 24.9, 24.8, 21.5, 21.2, 20.7. ESI-HRMS [C₂₀H₃₅N₃O₅+H]⁺: 398.26413 found, 398.26495 calculated.

4.2.10.11. ((3*R*,4*S*)-4-(2-((*tert*-Butylcarbamoyl)oxy)ethyl)-1-(2-methoxyacetyl)piperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8k**). Colourless liquid, (19.6 mg, 0.046 mmol, 72%). mixture of rotames ¹H NMR (400 MHz, CDCl₃) δ 5.25 (s, 1H, major), 5.13 (s, 1H, minor), 4.50 (t, *J* = 12.1 Hz, 2H), 4.18 (bs, 1 H, minor), 4.25–4.10 (m, 2H), 4.08 (d, *J* = 7.0 Hz, 1H), 4.02 (d, *J* = 12.0 Hz, 1H), 3.90 (d, *J* = 13.7 Hz, 1H), 3.85–3.69 (m, 1H), 3.54–3.24 (m, 3H), 3.41 (s, 3H), 3.09 (d, *J* = 11.5 Hz, 1H), 2.93–2.82 (m, 1H), 2.74 (s, 1H), 2.15 (s, 1H), 1.99–1.78 (m, 4H), 1.78–1.64 (m, 2H), 1.65–1.50 (m, 2H), 1.42–1.38 (m, 1H), 1.32 (s, 10H). ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 154.6, 98.4, 71.9, 71.1, 62.5, 61.2, 59.0, 50.1, 46.4, 46.1, 5.8, 44.6, 43.10, 41.9, 37.2, 36.8, 35.5, 31.7, 31.2, 28.9, 28.4, 27.7, 25.8, 24.9, 20.7, 20.6. ESI-HRMS [C₂₁H₃₇N₃O₆+H]⁺: 428.27542 found, 381.27551 calculated.

4.2.10.12. ((3*R*,4*S*)-4-(2-((*tert*-Butylcarbamoyl)oxy)ethyl)-1-pivaloylpiperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8l**). Colourless liquid, (20.7 mg, 0.047 mmol, 74%). mixture of rotames ¹H NMR (400 MHz, CDCl₃) δ 4.91 (s, 1H), 4.27 (dd, *J* = 10.7, 4.3 Hz, 1H), 4.15 (dt, *J* = 11.4, 5.4 Hz, 2H), 4.08–3.91 (m, 2H), 3.86 (t, *J* = 10.2 Hz, 1H), 3.37 (td, *J* = 6.4, 2.9 Hz, 4H), 3.26 (ddd, *J* = 13.2, 9.7, 3.4 Hz, 1H), 3.13 (d, *J* = 11.3 Hz, 1H), 2.09 (dt, *J* = 8.6, 4.5 Hz, 1H), 1.97–1.78 (m, 5H), 1.78–1.53 (m, 3H), 1.47 (ddd, *J* = 13.0, 9.2, 4.4 Hz, 1H), 1.31 (d, *J* = 3.7 Hz, 9H), 1.28 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 176.9, 154.9, 62.3, 62.2, 50.2, 46.2, 45.8, 45.5, 44.7, 38.8, 38.0, 34.8, 30.2, 28.9, 28.4, 25.8, 24.9, 20.7. ESI-HRMS [C₂₃H₄₁N₃O₅+H]⁺: 440.31168 found, 440.31190 calculated.

4.2.10.13. ((3*R*,4*S*)-4-(2-((*tert*-Butylcarbamoyl)oxy)ethyl)-1-propionylpiperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8m**). Colour-

less liquid, (20.4 mg, 0.049 mmol, 78%). mixture of rotamers ¹H NMR (400 MHz, CDCl₃) δ 5.27 (s, 1H, major), 5.07 (s, 1H, minor), 4.54 (t, *J* = 13.8 Hz, 2H), 4.38–4.25 (m, 1H, minor), 4.24–4.07 (m, 1H), 4.07–3.87 (m, 2H), 3.79 (dd, *J* = 23.4, 10.9 Hz, 1H), 3.79 (dd, *J* = 23.4, 10.9 Hz, 1H), 3.46–3.30 (m, 4H), 3.07 (dd, *J* = 18.4, 6.9 Hz, 1H), 2.98–2.81 (m, 1H, minor), 2.68 (s, 1H), 2.38 (dd, *J* = 13.3, 7.7 Hz, 2H), 2.12 (d, *J* = 5.0 Hz, 1H), 1.98–1.77 (m, 5H), 1.77–1.64 (m, 2H), 1.64–1.48 (m, 2H), 1.40–1.32 (m, 1H), 1.32 (s, 9H), 1.13 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 172.8, 154.2, 63.0, 62.5, 62.3, 61.6, 61.2, 50.11, 46.9, 46.3, 46.1, 45.7, 44.9, 42.8, 41.7, 37.3, 37.0, 36.4, 31.7, 31.0, 28.9, 28.5, 27.9, 26.7, 25.9, 25.8, 24.9, 20.7, 9.6, 9.5. ESI-HRMS [C₂₁H₃₇N₃O₅+H]⁺: 412.28036 found, 412.28060 calculated.

4.2.10.14. ((3*R*,4*S*)-4-(2-((*tert*-Butylcarbamoyl)oxy)ethyl)-1-(2-ethoxyacetyl)piperidin-3-yl)methyl pyrrolidine-1-carboxylate (**8n**). Colourless liquid, (19.0 mg, 0.043 mmol, 68%). mixture of rotames ¹H NMR (400 MHz, CDCl₃) δ 5.24–5.19 (m, 1H), 4.48 (d, *J* = 9.5 Hz, 1H), 4.41–4.30 (m, 1H), 4.30–4.08 (m, 3H), 4.09–3.91 (m, 2H), 3.87–3.74 (m, 1H), 3.55 (qd, *J* = 7.0, 4.0 Hz, 2H), 3.39–3.30 (m, 4H), 3.11 (d, *J* = 12.8 Hz, 1H), 2.76 (s, 1H), 2.14 (s, 1H), 1.94–1.87 (m, 5H), 1.78–1.66 (m, 2H), 1.69–1.67 (m, 1H), 1.57 (s, 2H), 1.50–1.36 (m, 1H), 1.32 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.4, 154.6, 70.4, 69.5, 66.8, 62.5, 62.3, 61.3, 50.1, 46.4, 46.1, 45.8, 44.8, 43.1, 41.8, 37.2, 36.9, 31.6, 31.2, 28.9, 28.4, 27.7, 25.8, 24.9, 20.7, 15.1. ESI-HRMS [C₂₂H₃₉N₃O₆+H]⁺: 442.29108 found, 442.29116 calculated.

4.2.11. Synthesis of *tert*-butyl (3*R*,4*S*)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(*oxiran-2-yl*)piperidine-1-carboxylates (**9**)

Diol **4** (1.1 g, 2.6 mmol) was dissolved in dry dichloromethane (14 mL). Trimethyl orthoacetate (1 mL, 7.8 mmol) and PPTs (65 mg, 0.2 mmol) were added and the mixture was stirred overnight. The product concentrated and dissolved in 16 mL anhydrous CH₂Cl₂. TMSCl (985 μL, 7.8 mmol) was added and stirring was continued for 4 h. The solvent was evaporated and the crude mixture was dissolved in 16 mL methanol. K₂CO₃ (1.1 g, 7.8 mmol) was added and the resultant mixture was stirred for 2 h. The reaction was quenched with saturated NH₄Cl and the mixture was extracted with dichloromethane (3x15 mL). The organic layers were combined, washed with brine and dried with MgSO₄ to get mixture of epoxides **9** (0.85 gm, 80%). The crude mixture was then purified by column chromatography to get epoxides **9a** and **9b**.

4.2.11.1. (3*R*,4*S*)-*tert*-butyl-4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**9a**). ¹H NMR (400 MHz, CDCl₃) δ 4.09 (bs, 1H), 4.00 (d, *J* = 12.8 Hz, 1H), 3.71 (dd, *J* = 12.5, 6.2 Hz, 2H), 3.04–2.90 (m, 2H), 2.83 (s, 1H), 2.74 (t, *J* = 4.4 Hz, 1H), 2.50 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.97 (dd, *J* = 6.9, 4.1 Hz, 1H), 1.78 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.67–1.52 (m, 3H), 1.45 (s, 9H), 1.35 (dd, *J* = 7.7, 3.7 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 154.5, 79.3, 60.4, 50.6, 45.1, 41.0, 35.4, 34.5, 28.3, 27.7, 25.8, 18.2, –5.7. ESI-HRMS [C₂₀H₃₉NO₄Si+H]⁺: 386.27227 found, 386.27211 calculated.

4.2.11.2. (3*R*,4*S*)-*tert*-butyl-4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-((*S*)-oxiran-2-yl)piperidine-1-carboxylate (**9b**). ¹H NMR (400 MHz, CDCl₃) δ 4.19 (d, *J* = 12.5 Hz, 3H), 3.84–3.51 (m, 4H), 3.04–2.68 (m, 7H), 2.59 (d, *J* = 2.5 Hz, 2H), 1.88 (ddd, *J* = 16.9, 9.1, 4.7 Hz, 2H), 1.80–1.36 (m, 26H), 1.35–1.12 (m, 3H), 0.89 (d, *J* = 9.3 Hz, 17H), 0.04 (s, 11H). ¹³C NMR (101 MHz, CDCl₃) δ 155.12, 79.52, 77.20, 60.73, 50.01, 48.40, 46.95, 43.25, 42.01, 35.90, 34.63, 28.33, 28.33, 27.71, 25.92, 25.92, 18.31, –5.35. ESI-HRMS [C₂₀H₃₉NO₄Si+H]⁺: 386.27212 found, 386.27211 calculated.

4.2.12. Synthesis of *tert*-butyl (3*R*,4*S*)-4-(2-hydroxyethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**10a**)

The epoxide **9a** (0.4 g, 1.03 mmol) was dissolved in THF (15 mL) and TBAF (1.5 mL, 1 M in THF, 1.5 mmol) was drop wise added. The mixture was stirred for 2 h and then the crude material was concentrated. The product was purified by column chromatography (PE/EtOAc 1:1) to get epoxy alcohol *tert*-butyl (3*R*,4*S*)-4-(2-hydroxyethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**10a**) (270 mg). ¹H NMR (400 MHz, CDCl₃) δ 4.38–3.92 (m, 2H), 3.83–3.60 (m, 2H), 3.13–2.98 (m, 2H), 2.94 (d, *J* = 12.0 Hz, 1H), 2.88–2.73 (m, 3H), 2.53 (dd, *J* = 4.8, 2.7 Hz, 1H), 1.95 (dt, *J* = 11.8, 7.5 Hz, 1H), 1.83 (td, *J* = 13.8, 7.1 Hz, 1H), 1.72–1.51 (m, 3H), 1.47 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 154.5, 79.4, 60.3, 50.7, 47.2, 45.3, 44.2, 43.4, 40.9, 40.7, 35.5, 35.4, 28.2, 27.9. ESI-HRMS [C₁₄H₂₅NO₄+H]⁺: 272.18565 found, 272.18563 calculated.

4.2.13. Synthesis of *tert*-butyl (1*R*,4*aS*,8*aR*)-1-(hydroxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**11**)

tert-Butyl (3*R*,4*S*)-4-(2-hydroxyethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**10a**) (260 mg, 0.96 mmol) and PPTs (65 mg, 0.26 mmol) were dissolved in 15 mL of dry acetonitrile and the resulting mixture was stirred overnight at 75 °C. The crude material was concentrated and directly purified with flash column chromatography (PE/EtOAc 1:1) to get cyclic ether **11** (190 mg, 73%) and **11'** (26 mg, 10%) as colourless oil.

4.2.13.1 (**11**). ¹H NMR (400 MHz, DMSO) δ 4.33 (s, 1H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.78 (t, *J* = 12.8 Hz, 2H), 3.52–3.24 (m, 4H), 2.84 (t, *J* = 11.7 Hz, 2H), 1.96 (d, *J* = 15.3 Hz, 2H), 1.79–1.57 (m, 2H), 1.41 (s, 10H), 1.19 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (101 MHz, DMSO) δ 153.9, 79.8, 78.0, 67.1, 61.3, 38.5, 38.3, 35.2, 31.5, 30.0, 27.8, 24.2.

4.2.13.2. *tert*-Butyl (4*aS*,9*R*,9*aR*)-9-hydroxyoctahydrooxepino[4,5-*c*]pyridine-2(1*H*)-carboxylate (**11'**). ¹H NMR (400 MHz, DMSO) δ 4.34 (s, 1H), 3.82 (dd, *J* = 12.8, 4.9 Hz, 1H), 3.74–3.52 (m, 4H), 3.52–3.31 (m, 3H), 3.12 (d, *J* = 13.2 Hz, 1H), 3.01 (t, *J* = 9.1 Hz, 1H), 2.06 (d, *J* = 20.6 Hz, 1H), 1.76 (dd, *J* = 16.8, 10.5 Hz, 2H), 1.59 (d, *J* = 19.0 Hz, 2H), 1.47–1.38 (m, 2H), 1.43 (s, 9H), 1.08 (t, *J* = 6.9 Hz, 1H). ¹³C NMR (101 MHz, DMSO) δ 154.1, 78.0, 70.6, 69.3, 66.1, 55.8, 45.1, 44.9, 42.4, 34.0, 31.3, 27.9, 27.8, 18.1.

4.2.14. Synthesis of *tert*-butyl (1*R*,4*aS*,8*aR*)-1-((methoxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**13a**)

To a suspension of sodium hydride (60% suspension in mineral oil) (0.035 g, 0.85 mmol) in dry DMF (5.0 mL) under argon atmosphere at 0 °C was added alcohol **11** (190 mg, 0.7 mmol) as DMF solution. The reaction mixture was stirred at 0 °C for 15 min and methyl iodide (82 μL, 1.32 mmol) was added and stirred at ambient temperatures for 5 h. After completion, the reaction mixture was cooled at 0 °C and quenched with water and extracted with diethyl ether (2 × 15 mL). All organic layers were combined, washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue obtained was subjected to column chromatography to get pure *tert*-butyl (1*R*,4*aS*,8*aR*)-1-((methoxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**13a-Boc**). ¹H NMR (400 MHz, CDCl₃) δ 4.09 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.97–3.73 (m, 2H), 3.99–3.71 (m, 2H), 3.67–3.22 (m, 4H), 3.37 (s, 3H), 3.02–2.66 (m, 2H), 2.11–1.89 (m, 2H), 1.81–1.63 (m, 2H), 1.52–1.36 (s, 1H), 1.47 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 154.9, 79.3, 78.6, 73.9, 78.7, 74.3, 72.7, 68.3, 67.8, 67.5, 63.0, 59.1, 40.8, 40.57, 39.2, 36.4, 32.2, 32.0, 30.6, 29.6, 28.4, 28.3, 24.6. ESI-HRMS [C₁₅H₂₇NO₄+H]⁺: 286.20127 found, 286.20128 calculated.

To this compound methanolic HCl (4.0 M, 2.0 mL) was added and the reaction mixture was stirred at room temperature for 5 h. The reaction was monitored by TLC and after consumption of all starting material; the reaction mixture was concentrated to

dryness. The residue obtained was co-evaporated with toluene to remove traces of water. The crude compound was washed with diethyl ether (3 × 15 mL) to get amine as hydrochloride salt (1*R*,4*aS*,8*aR*)-1-((methoxy)methyl)octahydro-1*H*-pyrano[3,4-*c*]pyridin-7-ium chloride (**13a**) (108 mg, 70% yields over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ 9.15 (s, 1H), 8.76 (s, 1H), δ 4.13 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.61 (d, *J* = 13.8 Hz, 1H), 3.79 (bs, 2H), 3.52 (t, *J* = 11.8 Hz, 1H), 3.46–3.23 (m, 3H), 3.39 (s, 3H), 3.17 (dd, *J* = 23.9, 11.9 Hz, 1H), 3.02 (dd, *J* = 23.9, 12.5 Hz, 1H), 2.29–2.23 (m, 2H), 2.13 (d, *J* = 14.8 Hz, 1H), 2.04–1.87 (m, 1H), 1.71 (d, *J* = 14.3 Hz, 1H), 1.35 (d, *J* = 13.7 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 77.5, 72.8, 68.1, 59.3, 39.5, 39.2, 33.8, 30.6, 27.3, 24.3. ESI-HRMS [C₁₀H₁₉NO₂+H]⁺: 186.14873 found, 186.14885 calculated.

4.2.15. Synthesis of (1*R*,4*aS*,8*aR*)-1-((benzyloxy)methyl)octahydro-1*H*-pyrano[3,4-*c*]pyridin-7-ium chloride (**13b**)

To a suspension of sodium hydride (60% suspension in mineral oil) (0.050 g, 1.2 mmol) in dry DMF (5.0 mL) under argon atmosphere at 0 °C was added alcohol **11** (272 mg, 1.0 mmol) as DMF solution. The reaction mixture was stirred at 0 °C for 15 min and an alkyl halide (1.32 mmol) was added and stirred at ambient temperatures for 5 h. After completion, the reaction mixture was cooled at 0 °C and quenched with water and extracted with diethyl ether (2 × 15 mL). All organic layers were combined, washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue obtained was subjected to column chromatography to get pure product *tert*-butyl (1*S*,4*aS*,8*aR*)-1-((methoxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**13b-Boc**).

To this compound methanolic HCl (4.0 M, 3.0 mL) was added and the reaction mixture was stirred at room temperature for overnight. The reaction was monitored by TLC and after consumption of all starting material; the reaction mixture was concentrated to dryness. The residue obtained was co-evaporated with toluene to remove traces of water. The crude compound was washed with diethyl ether (3 × 15 mL) to get amine as hydrochloride salt **13b** (238 mg, 80% yields over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.16 (m, 5H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.18–4.04 (m, 1H), 3.85 (s, 2H), 3.71–3.59 (m, 1H), 3.57–3.32 (m, 3H), 2.92–2.84 (m, 2H), 2.01 (t, *J* = 9.3 Hz, 2H), 1.75 (d, *J* = 9.7 Hz, 2H), 1.46–1.42 (m, 1H), 1.43 (s, 9H), 1.22 (d, *J* = 10.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 155.0, 137.9, 128.3, 127.8, 127.6, 79.3, 78.7, 73.5, 71.02, 68.3, 39.0, 36.3, 32.2, 30.6, 28.4, 24.6. ESI-HRMS [C₁₆H₂₃NO₂+H]⁺: 262.18013 found, 262.18016 calculated.

4.2.16. *tert*-Butyl (3*S*,4*S*)-4-(2-hydroxyethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**10b**)

The epoxide **9b** (0.4 gm, 1.03 mmol) was dissolved in 15 mL of THF and TBAF (1.5 mL, 1 M in THF, 1.5 mmol) was drop wise added. The mixture was stirred for 2 h and then the crude material was concentrated. The products were purified by column chromatography (PE/EtOAc 1:1) to get *tert*-butyl (3*S*,4*S*)-4-(2-hydroxyethyl)-3-((*R*)-oxiran-2-yl)piperidine-1-carboxylate (**10b**) (270 mg).

¹H NMR (400 MHz, CDCl₃) δ 4.33–3.95 (m, 2H), 3.71 (td, *J* = 10.7, 3.9 Hz, 2H), 3.04–2.68 (m, 4H), 2.61 (s, 1H), 2.15–1.83 (m, 2H), 1.83–1.51 (m, 4H), 1.50–1.40 (m, 1H), 1.47 (s, 9H), 1.35–1.25 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 155.1, 79.6, 77.3, 77.0, 76.7, 60.0, 49.8, 48.3, 46.9, 43.2, 41.8, 35.7, 34.4, 29.6, 28.3, 28.2, 27.6. ESI-HRMS [C₁₄H₂₅NO₄+H]⁺: 272.18564 found, 272.18563 calculated.

4.2.17. *tert*-Butyl (1*S*,4*aS*,8*aR*)-1-(hydroxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**12**)

This epoxide (260 mg, 0.96 mmol) and PTSA (65 mg, 0.26 mmol) were dissolved in 15 mL of dry acetonitrile and the

resulting mixture was stirred overnight at 75 °C. The crude material was concentrated and directly purified with flash column chromatography (PE/EtOAc 1:1) to get cyclic ether **12** (182 mg, 70%) and *tert*-butyl (4*a*S,9*S*,9*a*R)-9-hydroxyoctahydrooxepino[4,5-*c*]pyridine-2(1*H*)-carboxylate (**12'**) (40 mg, 15%) as colourless oil.

¹H NMR (400 MHz, DMSO) δ 4.11 (s, 1H), 3.93 (d, *J* = 13.5 Hz, 2H), 3.72–3.46 (m, 4H), 3.44–3.26 (m, 1H), 3.10 (s, 1H), 2.80 (d, *J* = 13.2 Hz, 2H), 1.97 (s, 1H), 1.92–1.69 (m, 3H), 1.42–1.36 (m, 1H) 1.39 (s, 9H). ¹³C NMR (101 MHz, DMSO) δ 153.5, 78.2, 74.0, 62.1, 61.5, 44.6, 42.9, 39.9, 39.7, 39.5, 39.3, 39.1, 34.8, 30.7, 30.08, 27.8, 25.2, 20.0.

4.2.18. *tert*-Butyl (4*a*S,9*S*,9*a*R)-9-hydroxyoctahydrooxepino[4,5-*c*]pyridine-2(1*H*)-carboxylate (**12'**)

¹H NMR (400 MHz, CDCl₃) δ 4.06 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.97–3.87 (m, 1H), 3.87–3.77 (m, 1H), 3.75–3.64 (m, 2H), 3.60–3.49 (m, 2H), 3.38 (dd, *J* = 13.4, 9.5 Hz, 1H), 3.28 (s, 1H), 2.71 (s, 1H), 2.19–1.84 (m, 3H), 1.79–1.54 (m, 3H), 1.49 (d, *J* = 23.8 Hz, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 155.3, 79.4, 72.6, 70.6, 68.5, 43.6, 42.3, 34.7, 32.5, 31.4, 28.4, 20.7.

4.2.19. Synthesis of (1*S*,4*a*S,8*a*R)-1-((benzyloxy)methyl)octahydro-1*H*-pyrano[3,4-*c*]pyridine-7-ium chloride (**14**)

To a suspension of sodium hydride (60% suspension in mineral oil) (50 mg, 1.2 mmol) in dry DMF (5.0 mL) under argon atmosphere at 0 °C was added alcohol **6a** (0.7 mmol) as DMF solution. The reaction mixture was stirred at 0 °C for 15 min and an alkyl halide (1.32 mmol) was added and stirred at ambient temperatures for 5 h. After completion, the reaction mixture was cooled at 0 °C and quenched with water and extracted with diethyl ether (2 × 15 mL). All organic layers were combined, washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue obtained was subjected to column chromatography to get pure *tert*-butyl (1*S*,4*a*S,8*a*R)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate **14-Boc**: ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.19 (m, 5H), 4.79–4.41 (m, 2H), 4.30–3.88 (m, 3H), 3.88–3.54 (m, 5H), 2.75 (bd, *J* = 14.0 Hz, 2H), 2.01–1.98 (m, 4H), 1.60–1.21 (m, 3H), 1.37 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 154.3, 138.3, 128.2, 127.5, 79.4, 73.5, 72.98, 70.9, 63.0, 45.8, 43.4, 35.3, 31.8, 30.9, 28.3, 25.3. ESI-HRMS [C₂₁H₃₁NO₄+H]⁺: 362.23263 found, 362.23258 calculated. To above compound, methanolic HCl (4.0 M, 2.0 mL) was added and the reaction mixture was stirred at room temperature for overnight. The reaction was monitored by TLC and after consumption of all starting material; the reaction mixture was concentrated to dryness. The residue obtained was co-evaporated with toluene to remove traces of water. The crude compound was washed with diethyl ether (3 × 15 mL) to get free amine as hydrochloride salt **14** (232 mg, 78% yields over 2 steps).

¹H NMR (400 MHz, CDCl₃) δ 9.38 (s, 1H), 9.12 (s, 1H), 7.39–7.20 (m, 5H), 5.69 (s, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.03 (s, 1H), 3.87–3.52 (m, 4H), 3.31 (s, 2H), 2.93 (s, 2H), 2.28 (s, 1H), 2.06 (s, 2H), 1.90–1.61 (m, 2H), 1.52 (d, *J* = 11.7 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 137.9, 128.3, 127.6, 127.5, 73.3, 72.4, 69.7, 62.4, 43.8, 42.6, 32.7, 28.9, 23.1. ESI-HRMS [C₁₆H₂₃NO₂+H]⁺: 262.18011 found, 262.18016 calculated.

4.2.20. General procedure for Synthesis of library molecules **15**, **16**

To the solution of amine hydrochloride **13a-b/14** (20 mg; 1 equiv) in dichloromethane (2.0 mL), triethylamine (3.0 eq) and DMAP (catalytic amount) followed by respective reagent (1.2 equiv) was added. The reaction mixture was stirred at room temperature for 3 h (alternatively can be left overnight). After completion, the reaction mixture was diluted with water and extracted with dichloromethane; the organic layers were combined, washed with brine, dried over MgSO₄, and concentrated in

vacuo. The crude product was purified by column chromatography to get pure title compounds (75–90%).

4.2.20.1. ((1*R*,4*a*S,8*a*R)-1-(methoxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*i*)-yl)(phenyl) methanone (**15a**). Colourless liquid (21 mg, 82%), ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 5H), 4.54 (bd, *J* = 11.7 Hz, 1H), 4.11 (bd, *J* = 10.1 Hz, 1H), 3.70–3.42 (m, 3H), 3.43 (s, 3H), 3.31–2.73 (m, 4H), 2.09 (s, 4H), 1.99–1.53 (m, 3H), 1.48–1.19 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 136.2, 129.4, 128.4, 128.3, 126.7, 78.8, 77.4, 74.0, 72.25, 68.3, 59.3, 59.0, 43.1, 37.5, 37.3, 37.2, 36.6, 32.3, 31.5, 30.5, 24.8, 24.7. ESI-HRMS [C₁₇H₂₃NO₃+H]⁺: 290.17499 found, 290.17507 calculated.

4.2.20.2. (1*R*,4*a*S,8*a*R)-7-(Mesitylsulfonyl)-1-(methoxymethyl)octahydro-1*H*-pyrano[3,4-*c*]pyridine (**15b**). Colourless liquid (26.5 mg, 80%), ¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 2H), 4.08 (d, *J* = 9.5 Hz, 1H), 3.56 (d, *J* = 4.1 Hz, 1H), 3.52–3.23 (m, 5H), 3.32 (s, 3H), 3.04 (t, *J* = 12.4 Hz, 1H), 2.90 (t, *J* = 12.9 Hz, 1H), 2.61 (s, 6H), 2.30 (s, 3H), 2.01 (d, *J* = 11.8 Hz, 2H), 1.86 (dd, *J* = 17.8, 13.5 Hz, 2H), 1.51 (d, *J* = 13.6 Hz, 1H), 1.27–1.16 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 142.3, 140.2, 131.8, 131.7, 81.1, 78.1, 73.3, 68.3, 67.53, 67.3, 59.1, 57.1, 40.2, 40.0, 39.9, 39.5, 39.1, 36.1, 32.7, 32.2, 31.9, 30.13, 24.4, 22.8, 22.7, 20.9. ESI-HRMS [C₁₉H₂₉NO₄S+H]⁺: 368.18891 found, 368.18901 calculated.

4.2.20.3. Isopropyl (1*R*,4*a*S,8*a*R)-1-(methoxymethyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**15c**). Colourless liquid (18.6 mg, 76%), ¹H NMR (400 MHz, CDCl₃) δ 4.92 (sept, *J* = 6.4 Hz, 1H), 4.12 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.04–3.73 (m, 2H), 3.65–3.29 (m, 4H), 3.41 (s, 3H), 3.00 (t, *J* = 12.8 Hz, 1H), 2.88 (t, *J* = 12.8 Hz, 1H), 2.21–1.92 (m, 2H), 1.87–1.65 (m, 3H), 1.47 (d, *J* = 13.3 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 155.4, 78.6, 77.4, 77.1, 76.7, 68.5, 68.4, 67.9, 67.6, 59.3, 39.0, 38.9, 36.5, 32.3, 32.1, 30.6, 24.7, 22.3, 22.2. ESI-HRMS [C₁₄H₂₅NO₄+H]⁺: 272.18571 found, 272.18563 calculated.

4.2.20.4. Isopropyl (1*R*,4*a*S,8*a*R)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**15d**). Colourless liquid (18.2 mg, 75%), ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.22 (m, 5H), 4.90 (dt, *J* = 12.5, 6.3 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.11 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.90 (d, *J* = 11.1 Hz, 2H), 3.73–3.35 (m, 4H), 2.99 (t, *J* = 12.4 Hz, 1H), 2.87 (t, *J* = 12.9 Hz, 1H), 2.14–1.93 (m, 2H), 1.84–1.67 (m, 1H), 1.52–1.41 (m, 1H), 1.34–1.14 (m, 8H). ¹³C NMR (101 MHz, CDCl₃) δ 155.4, 137.8, 128.4, 127.6, 78.8, 73.6, 70.9, 68.4, 39.0, 36.5, 32.4, 30.6, 24.49, 22.2, 21.8, 21.6. ESI-HRMS [C₂₀H₂₉NO₄+H]⁺: 348.21697 found, 348.21693 calculated.

4.2.20.5. ((1*R*,4*a*S,8*a*R)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-yl)(phenyl) methanone (**15e**). Colourless liquid, (19.6 mg, 80%), ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.19 (m, 9H), 7.15 (s, 1H), 4.68–4.48 (m, 2H), 4.27 (dd, *J* = 24.6, 11.4 Hz, 1H), 4.11 (dd, *J* = 24.1, 9.9 Hz, 1H), 3.67–3.57 (m, 4H), 3.27–2.80 (m, 3H), 2.06 (bs, 2H), 1.90 (d, *J* = 11.7 Hz, 1H), 1.78–1.53 (m, 1H), 1.33–1.16 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.5, 137.9, 136.3, 129.4, 128.4, 127.9, 127.7, 126.7, 78.9, 77.6, 73.6, 73.3, 71.2, 69.7, 68.31, 43.0, 37.3, 36.5, 32.3, 31.5, 30.5, 24.8. ESI-HRMS [C₂₃H₂₇NO₃+H]⁺: 366.20660 found, 366.20637 calculated.

4.2.20.6. Ethyl (1*R*,4*a*S,8*a*R)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**15f**). Colourless liquid (19 mg, 85%), ¹H NMR (400 MHz, CDCl₃) δ 7.46–7.21 (m, 5H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.12 (dd, *J* = 12.6, 6.2 Hz, 3H), 3.91 (bs, 2H), 3.67–3.36 (m, 4H), 3.00 (t, *J* = 12.3 Hz, 1H), 2.90 (t, *J* = 12.3 Hz, 1H), 2.15–1.92 (m, 2H), 1.78 (d, *J* = 10.4 Hz, 2H), 1.56–1.41 (m, 1H), 1.34–1.14 (m, 1H), 1.24 (t,

$J = 4.0$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.7, 138.0, 129.7, 128.4, 127.8, 127.7, 78.8, 73.6, 71.0, 68.4, 61.2, 39.0, 38.9, 36.3, 32.2, 30.6, 24.7, 14.7. ESI-HRMS $[\text{C}_{19}\text{H}_{27}\text{NO}_4 + \text{H}]^+$: 334.20103 found, 334.20128 calculated.

4.2.20.7. (1*R*,4*aS*,8*aR*)-1-((benzyloxy)methyl)-*N*-(*tert*-butyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxamide (**15g**). Colourless liquid (21.8 mg, 90%), ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.24 (m, 5H), 4.61 (d, $J = 12.2$ Hz, 1H), 4.52 (d, $J = 12.2$ Hz, 1H), 4.30 (s, 1H), 4.09 (dd, $J = 11.6$, 3.5 Hz, 1H), 3.76–3.43 (m, 6H), 3.00–2.86 (m, 2H), 2.09–1.94 (m, 2H), 1.94–1.67 (m, 2H), 1.48 (t, $J = 3.2$ Hz, 1H), 1.46–1.18 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.2, 137.9, 128.4, 127.7, 127.7, 78.5, 73.50, 70.9, 68.3, 50.62, 39.7, 38.8, 35.9, 32.1, 30.5, 29.4, 24.7. ESI-HRMS $[\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_3 + \text{H}]^+$: 361.24890 found, 361.24857 calculated.

4.2.20.8. 4-Chlorophenyl (1*R*,4*aS*,8*aR*)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**15h**). Colourless liquid (25 mg, 89%), ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, $J = 5.6$ Hz, 7H), 7.03 (d, $J = 8.9$ Hz, 2H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.11–3.99 (m, 3H), 3.67 (bs, 1H), 3.63–3.41 (m, 3H), 3.22–2.97 (m, 2H), 2.10–2.02 (m, 2H), 2.00–1.80 (m, 2H), 1.56 (d, $J = 13.7$ Hz, 1H), 1.30 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.5, 149.9, 137.8, 130.5, 129.5, 129.2, 128.37, 127.9, 127.7, 123.2, 123.1, 78.6, 78.0, 77.3, 73.6, 70.8, 70.3, 68.3, 39.8, 39.5, 36.3, 32.1, 30.8, 30.3, 24.7. ESI-HRMS $[\text{C}_{23}\text{H}_{26}\text{ClNO}_4 + \text{H}]^+$: 416.16234 found, 416.16231 calculated.

4.2.20.9. (1*R*,4*aS*,8*aR*)-1-((benzyloxy)methyl)-7-tosyloctahydro-1*H*-pyrano[3,4-*c*]pyridine (**15i**). Colourless liquid (23 mg, 82%), ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 8.2$ Hz, 2H), 7.45–7.23 (m, 7H), 4.65 (d, $J = 12.0$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 3.98 (dd, $J = 11.4$, 4.5 Hz, 1H), 3.70–3.36 (m, 6H), 2.53 (t, $J = 11.7$ Hz, 1H), 2.44 (s, 3H), 2.38 (td, $J = 12.4$, 2.5 Hz, 1H), 2.03–1.87 (m, 3H), 1.69 (dd, $J = 16.6$, 12.6, 5.0 Hz, 1H), 1.53 (d, $J = 11.8$ Hz, 1H), 1.10 (d, $J = 13.3$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.4, 137.7, 133.2, 129.7, 128.4, 127.9, 127.7, 127.5, 78.3, 73.6, 70.7, 68.3, 41.1, 36.2, 31.3, 30.0, 24.3, 21.5. ESI-HRMS $[\text{C}_{23}\text{H}_{29}\text{NO}_4\text{S} + \text{H}]^+$: 416.18888 found, 416.18901 calculated.

4.2.20.10. Isopropyl (1*S*,4*aS*,8*aR*)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**16a**). Colourless liquid, (17.5 mg, 75%), ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.20 (m, 5H), 4.97–4.80 (m, 1H), 4.73 (d, $J = 27.8$ Hz, 1H), 4.48 (s, 1H), 4.29 (s, 2H), 3.85–3.56 (m, 5H), 2.75 (dd, $J = 14.2$, 2.8 Hz, 2H), 2.01 (s, 3H), 1.41 (dd, $J = 17.6$, 7.6 Hz, 1H), 1.34–0.98 (m, 8H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.8, 128.3, 127.7, 127.6, 76.7, 73.6, 73.1, 68.4, 63.1, 45.4, 44.0, 35.2, 31.9, 31.0, 29.7, 25.5, 22.2, 22.1. ESI-HRMS $[\text{C}_{20}\text{H}_{29}\text{NO}_4 + \text{H}]^+$: 348.21699 found, 348.21693 calculated.

4.2.20.11. (1*S*,4*aS*,8*aR*)-7-(*Mesitylsulfonyl*)-1-(*phenoxymethyl*)octahydro-1*H*-pyrano[3,4-*c*]pyridine (**16b**). Colourless liquid, (22.4 mg, 80%), ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.15 (m, 5H), 6.90 (s, 2H), 4.43 (d, $J = 12.3$ Hz, 1H), 4.20 (d, $J = 12.3$ Hz, 1H), 3.89–3.72 (m, 2H), 3.71–3.49 (m, 2H), 3.27 (dd, $J = 12.9$, 1.8 Hz, 1H), 3.23–3.14 (m, 1H), 2.90–2.67 (m, 3H), 2.57 (s, 6H), 2.27 (s, 3H), 2.16–1.84 (m, 4H), 1.51 (d, $J = 12.9$ Hz, 1H), 1.39 (d, $J = 13.0$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 142.6, 140.5, 138.1, 131.8, 131.3, 128.3, 127.5, 127.5, 73.4, 73.11, 70.1, 63.2, 46.5, 43.9, 34.6, 31.5, 30.7, 24.9, 22.8, 20.9. ESI-HRMS $[\text{C}_{25}\text{H}_{33}\text{NO}_4\text{S} + \text{H}]^+$: 444.22027 found, 444.22031 calculated.

4.2.20.12. ((1*S*,4*aS*,8*aR*)-1-(*Phenoxymethyl*)hexahydro-1*H*-pyrano[3,4-*c*]pyridin-7(3*H*)-yl)(*phenyl*) methanone (**16c**). Colourless liquid, (19 mg, 78%), colourless liquid ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.08 (m, 10H), 4.66–4.15 (m, 3H), 4.05–3.39 (m, 5H), 3.30–2.79

(m, 3H), 2.34–1.68 (m, 4H), 1.48 (d, $J = 7.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 138.3, 135.9, 129.6, 128.4, 128.3, 127.7, 127.5, 126.8, 73.5, 71.2, 62.9, 47.8, 43.9, 35.5, 31.9, 30.5, 29.7, 26.4. ESI-HRMS $[\text{C}_{23}\text{H}_{27}\text{NO}_3 + \text{H}]^+$: 366.20667 found, 366.20637 calculated.

4.2.20.13. 4-Chlorophenyl (1*S*,4*aS*,8*aR*)-1-((benzyloxy)methyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxylate (**16d**). Colourless liquid, (22.4 mg, 80%), ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.13 (m, 7H), 7.03 (d, $J = 8.1$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 4.63 (t, $J = 12.4$ Hz, 1H), 4.47 (bd, $J = 12.2$ Hz, 1H), 4.26 (t, $J = 13.5$ Hz, 1H), 4.20–4.04 (m, 1H), 3.94–3.59 (m, 5H), 3.13–2.76 (m, 2H), 2.09–1.98 (m, 4H), 1.44 (d, $J = 12.3$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 149.6, 138.3, 137.9, 130.5, 129.2, 128.3, 127.85, 127.7, 127.5, 123.0, 73.6, 73.1, 71.1, 70.6, 63.1, 46.2, 45.9, 44.8, 44.5, 35.4, 35.2, 31.7, 30.8, 30.7, 25.8. ESI-HRMS $[\text{C}_{23}\text{H}_{26}\text{ClNO}_4 + \text{H}]^+$: 416.16234 found, 416.16231 calculated.

4.2.20.14. (1*S*,4*aS*,8*aR*)-1-((benzyloxy)methyl)-*N*-(*tert*-butyl)hexahydro-1*H*-pyrano[3,4-*c*]pyridine-7(3*H*)-carboxamide (**16e**). Colourless liquid, (20 mg, 82%), ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.20 (m, 5H), 4.66 (d, $J = 12.5$ Hz, 1H), 4.61–4.45 (m, 2H), 4.01 (d, $J = 12.8$ Hz, 1H), 3.89 (d, $J = 14.0$ Hz, 1H), 3.83–3.51 (m, 5H), 2.79 (dd, $J = 14.1$, 3.4 Hz, 1H), 2.71 (t, $J = 12.0$ Hz, 1H), 2.08–1.82 (m, 4H), 1.51–1.33 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.0, 138.0, 128.4, 127.7, 127.7, 73.4, 72.4, 62.8, 50.4, 46.3, 43.85, 37.3, 32.1, 30.8, 29.5, 25.7. ESI-HRMS $[\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_3 + \text{H}]^+$: 361.24899 found, 361.24857 calculated.

4.2.20.15. (1*S*,4*aS*,8*aR*)-1-((benzyloxy)methyl)-7-tosyloctahydro-1*H*-pyrano[3,4-*c*]pyridine (**16f**). Colourless liquid, (21 mg, 75%), ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.2$ Hz, 2H), 7.44–7.23 (m, 7H), 4.69 (d, $J = 12.3$ Hz, 1H), 4.49 (d, $J = 12.3$ Hz, 1H), 3.88 (dd, $J = 6.6$, 5.1 Hz, 1H), 3.84–3.72 (m, 3H), 3.70–3.63 (m, 2H), 3.53 (d, $J = 12.0$ Hz, 1H), 2.43 (s, 3H), 2.33–2.01 (m, 4H), 2.00–1.86 (m, 1H), 1.86–1.74 (m, 1H), 1.64 (d, $J = 8.4$ Hz, 1H), 1.45 (dd, $J = 17.4$, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 143.4, 138.3, 132.8, 129.6, 128.3, 127.9, 127.6, 127.5, 73.4, 73.1, 69.7, 63.3, 48.0, 46.5, 34.5, 31.1, 30.51, 25.1, 21.5. ESI-HRMS $[\text{C}_{23}\text{H}_{29}\text{NO}_4\text{S} + \text{H}]^+$: 416.18891 found, 416.18901 calculated.

Acknowledgments

The research leading to these results was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in-kind contribution.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmc.2017.07.016>.

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15. The structural assignment of **12'** was confirmed using extensive NMR analysis including ^1H , ^{13}C , COSY, HSQC, HMBC and NOESY.

