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Enantioselective synthesis and selective functionalization of 4-aminotetrahydroquinolines as novel GLP-1 secretagogues

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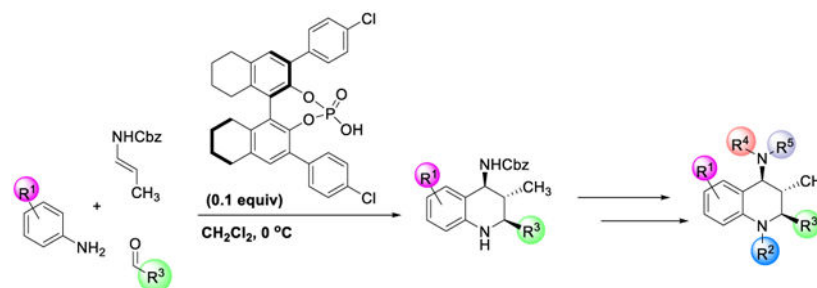
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Abstract

Polysubstituted tetrahydroquinolines were obtained in moderate to high yields (28% to 92%) and enantiomeric ratios (er 89:11 to 99:1) by a three-component Povarov reaction using a chiral phosphoric acid catalyst. Significantly, post-Povarov functional group interconversions allowed a rapid access to a library of 36 enantioenriched 4-aminotetrahydroquinoline derivatives featuring five points of diversity. Selected analogs were assayed for their ability to function as glucagon-like peptide-1 (GLP-1) secretagogues.

Graphical Abstract



Keywords

Povarov reaction; 4-aminotetrahydroquinoline; asymmetric catalysis; chiral phosphoric acid; diversity-oriented synthesis; GLP-1 secretagogues

INTRODUCTION

The chemistry of tetrahydroquinolines has attracted substantial attention in recent years due to the activity profile of this privileged scaffold in biological assays,^{3–5} and various organocatalytic⁶ and metal-catalyzed^{7–10} synthesis methods have been reported. In particular, the 4-aminotetrahydroquinoline (4-ATQ) motif is present in a large number of natural products and pharmaceutical agents, such as martinellid acid, martinelline,

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I-BET726, and compound 4D (Figure 1). The martinella alkaloids display antibacterial activity and act as bradykinin receptor antagonists.¹¹⁻¹² I-BET726 (GSK1324726A) is a lead structure for the development of a class of selective tetrahydroquinoline-based BET bromodomain inhibitors.¹³ Compound 4D serves as an example for a short-acting, high-potency μ -opioid receptor (MOR) agonist/ δ -opioid receptor (DOR) antagonist with antinociceptive activity *in vivo*.¹⁴ Furthermore, various 4-ATQ-containing molecules possess estrogenic, anti-inflammatory, antiviral, antiallergenic, and androgen receptor activity.³ The best-known synthetic tetrahydroquinolines are oxamniquine, which is used as a schistosomicide, nicainoprol, which is used as an antiarrhythmic drug, and virantmycin, which is used as an antibiotic. Furthermore, L-689,560 is a very potent N-methyl-D-aspartate (NMDA) antagonist.¹¹

Enantiopure tetrahydroquinoline derivatives are also of considerable interest as synthetic building blocks. Kang and Kim obtained α,β -unsaturated ketone-containing tetrahydroquinoline derivatives in high diastereoselectivity and enantioselectivity, using the Povarov reaction.²² Muthukrishnan and co-workers reported that phosphoric acid-catalysis is effective in the Povarov reaction and Shi and co-workers used a chiral phosphoric acid to synthesize indolyl-substituted spiroquinolines in high yield, high diastereoselectivity (>95:5 dr), and enantioselectivity (89:11 er).²³

The Povarov reaction is a formal inverse electron-demand aza-Diels-Alder reaction between 2-azadienes and electron-rich olefins that is usually catalyzed by Lewis or Brønsted acids.¹⁵ Masson and Zhu coworkers previously developed a convenient three-component variant of the Povarov reaction capable of accessing the 4-ATQ scaffold in an asymmetric fashion from an aniline, an aldehyde, and an *N*-vinylcarbamate.¹⁶⁻¹⁸ Herein, we utilize this reaction to access novel, biologically relevant molecules with high diastereo- and enantioselectivity. Significantly, late stage functionalization of the 4-ATQ scaffold provides a structurally diverse library of biological screening samples.

MATERIALS AND METHODS

General

All glassware was flame-dried and cooled under dry N₂ or Ar prior to use. All moisture-sensitive reactions were performed under an atmosphere of dry N₂. THF and Et₂O were distilled from sodium/benzophenone ketyl; CH₂Cl₂ and toluene were distilled from CaH. Anhydrous DMF was used as available from a commercial supplier. Triethyl amine was purified by distillation from KOH.

Melting points were determined using a Laboratory Devices Mel-Temp II in open capillary tubes. Infrared spectra were determined as neat solids or oils on a Smiths Detection IdentifyIR FT-IR spectrophotometer. Mass spectra were obtained on a Waters QtoF API US or Thermo Scientific Exactive Orbitrap LC-MS. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 300 MHz, 400 MHz, or 500 MHz instruments. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ ¹H / ¹³C (Solvent); 7.27 / 77.0 (CDCl₃); 2.05 / 29.84 (acetone-d₆); 5.32 / 53.5 (CD₂Cl₂); 2.54 / 40.45 (DMSO); 3.34 / 49.86 (MeOD) and are tabulated as follows:

chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 100 MHz or 125 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. CDCl_3 was filtered through dried basic alumina prior to sample preparation. Visualization was accomplished with a 254 nm UV light and by staining with a phosphomolybdic acid (PMA) solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH) or a KMnO_4 solution (1.5 g of KMnO_4 and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). The enantiomeric ratio was determined by SFC (Chiralpak IB and IA, CO_2/MeOH) on Mettler Toledo-MiniGram instrument, Berger ALS-3100/50 Autosampler, Berger FCM-1100/1200 Fluid Control Module (Column Length: 250 mm; Column Diameter: 10.0 mm; Column Particle Size: 6.0 μm ; Pore Size: 60 Å; Pressure: 100 bar; Flow Rate: 9.0 mL/min; Mobile Phase: 8.0 % MeOH / 92.0% CO_2), Berger KNR-2501 Detector Module (Wavelength: 220 nm), Berger TCM-2250 Heater Control (Column Temperature: 35 °C), Berger PDM-1250 Peak Detector Module. Compounds **5a**,¹⁷ **5c**,¹⁷ and **5d**¹⁰ are known in the literature.

Experimental Procedures

General procedure A for the three-component Povarov reaction: To a solution of benzaldehyde (0.10 mmol) in dried CH_2Cl_2 (0.5 mL) at room temperature was added aniline (0.10 mmol). After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C and phosphoric acid catalyst (diphenylphosphinic acid for a racemic synthesis) (0.01 mmol) and a CH_2Cl_2 (0.5 mL) solution of ene-carbamate (0.11 mmol) were added. The reaction mixture was stirred under an Ar atmosphere at 0 °C for 17 h. Solvents were removed in vacuo and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 95:5) to afford pure product.

Benzyl ((2R,3R,4S)-2-isopropyl-6-methoxy-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (5b): According to general procedure A, 4-methoxyaniline (0.13 g, 1.05 mmol), (*E*)-benzyl prop-1-enylcarbamate (0.22 g, 1.15 mmol), 2-methylpropanal (0.096 mL, 1.05 mmol) and phosphoric acid catalyst (0.06 g, 0.10 mmol) provided **5b** (0.21 g, 55 %) as a yellow solid: R_f 0.4 (EtOAc/hexanes, 1:4); $[\alpha]_D^{25} -19$ (c 1.05, CH_2Cl_2); m.p. 136 °C; ATR-IR (cm^{-1}) 3371, 2959, 1699, 1502, 1450, 1230, 1028; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.31 (m, 5 H), 6.70 (d, J = 2.7 Hz, 1 H), 6.65 (dd, J = 2.7, 8.6 Hz, 1 H), 6.47 (d, J = 8.6 Hz, 1 H), 5.20 (s, 2 H), 4.95 (d, J = 9.8 Hz, 1 H), 4.65 (t, J = 9.8 Hz, 1 H), 3.67 (s, 3 H), 3.52 (br s, 1 H), 2.93 (d, J = 6.7 Hz, 1 H), 2.07-1.98 (m, 1 H), 1.77-1.69 (m, 1 H), 1.04 (d, J = 4.4 Hz, 3 H), 1.03 (d, J = 4.8 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 152.1, 139.1, 136.7, 128.5, 128.0 (2 peaks), 122.9, 115.4, 114.8, 112.9, 66.7, 61.5, 55.8, 54.7, 37.3, 28.4, 20.0, 14.7, 14.5; HRMS (ES+) m/z calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_3$ ($[\text{M}+\text{H}]^+$) 369.2178, found 369.2166. SFC (Chiralpak IA, CO_2/MeOH 90:10, 254 nm) er = 89:11 (flow rate = 2.0 mL/min) major isomer: t_R = 22.84 min; minor isomer: t_R = 19.30 min.

Benzyl tert-butyl ((2R,3R,4S)-2-ethyl-3-methyl-1,2,3,4-tetrahydroquinoline-4,6-diyl)dicarbamate (5e): According to general procedure A, *tert*-butyl (4-aminophenyl)carbamate (0.02 g, 0.11 mmol), (*E*)-benzyl prop-1-enylcarbamate (0.02 g, 0.11 mmol), propionaldehyde (7 μL , 0.10 mmol) and phosphoric acid catalyst (0.006 g, 0.010

mmol) provided **5e** (0.253 g, 60 %) as a light yellow solid: R_f 0.15 (EtOAc/hexanes, 1:4); $[\alpha]_D^{25} -12$ (c 1.1, CH_2Cl_2); m.p. 141 °C; ATR-IR (cm^{-1}) 3330, 2974, 1696, 1509, 1450, 1233, 1161; ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.32 (m, 5 H), 7.21 (brs, 1 H), 6.83 (s, 1 H), 6.46 (d, J = 8.4 Hz, 1 H), 6.17 (brs, 1 H), 5.20 (s, 2 H), 4.82 (d, J = 9.6 Hz, 1 H), 4.61 (t, J = 9.6 Hz, 1 H), 3.69 (s, 1 H), 3.04-3.02 (m, 1 H), 1.75-1.60 (m, 3 H), 1.55-1.46 (m, 10 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.1, 153.4, 141.1, 136.7, 128.7, 128.5, 128.1, 122.1, 120.9, 119.5, 114.5, 79.9, 66.7, 57.4, 54.3, 38.3, 28.4, 26.0, 14.8, 8.8; HRMS (ES+) m/z calcd for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}_4$ ($[\text{M}+\text{H}]^+$) 440.2549, found 440.2540. SFC (Chiralpak IB, CO_2/MeOH 85:15, 254 nm) er = 93:7 (flow rate = 2.0 mL/min) major isomer: t_R = 8.98 min; minor isomer: t_R = 11.96 min.

Benzyl (2S,3R,4S)-6-methoxy-3-methyl-2-(pyridin-3-yl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (5f). To a solution of pyridine-3-carboxaldehyde (0.044 g, 0.402 mmol) in dry CH_2Cl_2 (1.5 mL) at room temperature was added 4-methoxyaniline (0.050 g, 0.402 mmol). After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C and phosphoric acid catalyst (0.023 g, 0.402 mmol) and a solution of ene-carbamate (0.085 g, 0.442 mmol) in CH_2Cl_2 (1.5 mL) were added. The mixture was stirred for 2 d under an argon atmosphere, concentrated in vacuo and purified by chromatography on SiO_2 (hexanes/EtOAc, 95:5) to afford **5f** (0.149 g, 92%) as a white solid: R_f 0.066 (EtOAc/hexanes, 8:2); $[\alpha]_D^{25} -53$ (c 0.42, CH_2Cl_2); m.p. 97-98 °C; ATR IR (cm^{-1}) 3315, 2975, 1629, 1420, 1340, 1215, 1094; ^1H NMR (300 MHz, DMSO) δ 8.56 (s, 1 H), 8.52 (d, J = 4.0 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.60 (d, J = 9.4 Hz, 1 H), 7.43-7.30 (m, 6 H), 6.45-6.65 (m, 3 H), 5.71 (d, J = 11.1 Hz, 1 H), 5.17 (d, J = 12.7 Hz, 1 H), 5.07 (d, J = 12.7 Hz, 1 H), 4.56 (t, J = 10.0 Hz, 1 H), 4.11 (d, J = 10.2 Hz, 1 H), 3.57 (s, 3 H), 2.02-1.88 (m, 1 H), 0.63 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO) δ 157.2, 151.1, 149.4, 148.9, 139.6, 138.0, 137.5, 135.2, 128.3, 127.7, 127.5, 123.6, 123.1, 114.9, 113.8, 112.0, 65.2, 59.7, 55.2, 54.9, 54.2, 14.8; HRMS (ES+) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 404.1974, found 404.1978. SFC (Chiralpak IB, CO_2/MeOH 85:15, 254 nm) er = 99:1 (flow rate = 2.0 mL/min) major isomer: t_R = 5.04 min; minor isomer: t_R = 9.68 min.

Benzyl ((2R,3R,4S)-2-cyclopropyl-6-methoxy-3-methyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (5g). A solution of cyclopropanecarboxaldehyde (0.016 mL, 0.201 mmol) in dry CH_2Cl_2 (1 mL) at room temperature was treated with 4-methoxyaniline (0.025 g, 0.201 mmol), stirred at room temperature for 2 h, cooled to 0 °C, and a solution of phosphoric acid catalyst (0.012 g, 0.020 mmol) in CH_2Cl_2 (0.5 mL) followed by a solution of (*E*)-ene-carbamate (0.042 g, 0.221 mmol) in CH_2Cl_2 (1.5 mL) were added sequentially. The reaction mixture was stirred at 0 °C for 19 h under an N_2 atmosphere, concentrated in vacuo and purified by chromatography on SiO_2 (hexanes/EtOAc, 17:3) to afford **5g** (0.052 g, 70%) as an off-white solid: R_f 0.26 (hexanes/EtOAc, 7:3); m.p. 140-142 °C; ATR-IR (cm^{-1}) 3319, 2966, 1692, 1530, 1504, 1460, 1245, 1233, 1020; ^1H NMR (300 MHz, CDCl_3) δ 7.37 (m, 5 H), 6.70 (d, J = 2.8 Hz, 1 H), 6.64 (dd, J = 8.6, 2.9 Hz, 1 H), 6.50 (d, J = 8.4 Hz, 1 H), 5.19 (d, J = 1.3 Hz, 2 H), 4.88 (d, J = 10.1 Hz, 1 H), 4.64 (t, J = 10.1 Hz, 1 H), 3.66 (s, 3 H), 1.78 (m, 1 H), 1.19 (d, J = 6.7 Hz, 3 H), 0.87 (m, 1 H), 0.66 (m, 1 H), 0.52 (m, 1 H), 0.38 (m, 1 H), 0.20 (m, 1 H); ^{13}C NMR (400 MHz, CDCl_3) δ 157.3, 152.5, 138.5, 136.8, 128.7, 128.3, 128.2, 123.5, 115.5, 114.9, 112.92, 67.0, 62.9, 55.9, 54.8, 41.6, 16.3, 15.3, 4.7,

1.6; HRMS (ES+) m/z calcd for $C_{22}H_{26}N_2O_3$ ($[M+H]^+$) 367.2016, found 367.2014. *er*: 96:4 HPLC (Chiralpak IB, hexanes/*i*-PrOH 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 44.57 min; minor isomer: t_R = 53.27 min.

Benzyl ((2S,3S,4S)-6-methoxy-3-methyl-2-(thiophen-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (5h).: A solution of thiophene-2-carboxaldehyde (0.019 mL, 0.201 mmol) in dry CH_2Cl_2 (1 mL) at room temperature was treated with 4-methoxyaniline (0.025 g, 0.201 mmol), stirred at room temperature for 3 h, cooled to 0 °C and treated with a solution of phosphoric acid catalyst (0.012 g, 0.020 mmol) in CH_2Cl_2 (0.5 mL) and a solution of (*E*)-ene-carbamate (0.042 g, 0.221 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred under Ar at 0 °C for 17 h, and at 21 °C for 20 h. The solution was concentrated in vacuo and purified by chromatography on SiO_2 (hexanes/EtOAc, 17:3) to afford **5h** (0.036 g, 44%) as an off-white tacky solid: R_f 0.24 (hexanes/EtOAc, 8:2); m.p. 60–63 °C; ATR-IR (cm^{-1}) 3335, 2964, 1695, 1501, 1469, 1233, 1023; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5 H), 7.16 (m, 1 H), 6.92 (dd, J = 3.6, 1.2 Hz, 1 H), 6.86 (dd, J = 5.1, 3.5 Hz, 1 H), 6.64 (dd, J = 2.8, 0.8 Hz, 1 H), 6.57 (ddd, J = 8.6, 2.9, 0.7 Hz, 1 H), 5.08 (d, J = 1.3 Hz, 2 H), 4.80 (d, J = 10.1 Hz, 1 H), 4.70 (t, J = 9.8 Hz, 1 H), 4.33 (d, J = 9.4 Hz, 1 H), 3.58 (s, 3 H), 1.89 (tq, J = 9.5, 6.8 Hz, 1H), 0.82 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.1, 152.8, 146.1, 138.1, 136.8, 128.6, 128.2, 128.1, 126.5, 125.5, 125.0, 123.1, 115.6, 115.1, 113.0, 66.9, 58.6, 55.9, 54.7, 42.8, 15.7; HRMS (ES+) m/z calcd for $C_{23}H_{24}N_2O_3S$ ($[M+H]^+$) 409.1580, found 409.1579. *er*: 98:2 HPLC (Chiralpak IB, Hexane/EtOH 85/15, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 35.16 min; minor isomer: t_R = 55.01 min.

Benzyl ((2R,3R,4S)-2-cyclobutyl-6-methoxy-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (5i).: A solution of cyclobutanecarboxaldehyde (0.016 mL, 0.201 mmol) in dry CH_2Cl_2 (1 mL) at room temperature was treated with 4-methoxyaniline (0.025 g, 0.201 mmol), stirred at room temperature for 2 h, cooled to 0 °C and treated with a solution of phosphoric acid catalyst (0.012 g, 0.020 mmol) in CH_2Cl_2 (0.5 mL) and a solution of (*E*)-ene-carbamate (0.042 g, 0.221 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred under a nitrogen atmosphere at 0 °C for 19 h, concentrated in vacuo and purified by chromatography on SiO_2 (hexanes/EtOAc, 17:3) to afford **5i** (0.022 g, 28%) as a yellowish-white solid: R_f 0.23 (hexanes/EtOAc, 8:2); m.p. 133–135 °C; ATR-IR (cm^{-1}) 3373, 3322, 2967, 1693, 1531, 1505, 1461, 1247, 1022; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5 H), 6.69 (d, J = 2.9 Hz, 1 H), 6.65 (dd, J = 8.6, 2.9 Hz, 1 H), 6.48 (d, J = 8.6 Hz, 1 H), 5.18 (s 2 H), 4.89 (d, J = 9.7 Hz, 1 H), 4.59 (t, J = 9.4 Hz, 1 H), 3.66 (s, 3 H), 2.93 (t, J = 8.3 Hz, 1 H), 2.52 (m, 1 H), 1.92 (m, 7 H), 1.63 (m, 1 H), 1.01 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.0, 152.3, 138.3, 136.7, 128.6, 128.1, 128.0, 123.0, 115.6, 115.0, 113.1, 66.8, 61.4, 55.8, 54.3, 39.6, 39.1, 26.6, 24.8, 18.2, 15.5; HRMS (ES+) m/z calcd for $C_{23}H_{28}N_2O_3$ ($[M+H]^+$) 381.2173, found 381.2169. *er*: 95:5 HPLC (Chiralpak IB, hexanes/*i*-PrOH 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 42.08 min; minor isomer: t_R = 49.59 min.

General procedure B for N-alkylation: A solution of **5a17** (0.050 mmol) in *N,N*-dimethylformamide (0.5 mL) was treated with *N*-ethyl-diisopropylamine (0.107 mmol), and

alkyl bromide (0.050 mmol). The reaction mixture was stirred for 24 h at 70 °C, and extracted with H₂O and EtOAc. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by chromatography on SiO₂ (hexanes/EtOAc, 95:5) to afford the *N*-alkylated product.

General procedure C for hydrogenation: A suspension of substrate and Pd/C (20%) in EtOH was stirred and flushed three times with H₂ gas from a balloon. The reaction mixture was stirred under H₂ gas for 5h, filtered to remove Pd/C, and concentrate in vacuo. The crude product was used for next step without purification.

General procedure D for sulfonation: To a solution of alkyl amine (1 mmol) in dichloromethane or 1,2-dichloroethane (0.1 M) was added triethylamine (2 mmol) and methanesulfonyl chloride (1.1 mmol) at 0 °C. The reaction mixture was stirred for 12 h, extracted with dichloromethane and water, dried (Na₂SO₄), and purified by chromatography on SiO₂ (hexanes/EtOAc) to afford the pure product.

General procedure E for reductive amination: A solution of alkyl amine (1 mmol), aldehyde (1.1 mmol) and acetic acid (1 mmol) in 1,2-dichloroethane (0.1 M) was stirred for 30 min, treated with sodium triacetoxyborohydride (2 mmol), and stirred for 12 h. The reaction mixture was extracted with a saturated solution of NaHCO₃ and dichloromethane, and the combined organic layers were dried (Na₂SO₄), concentrated in vacuo, and purified by chromatography on SiO₂ (hexanes/EtOAc) to afford the product.

General procedure F for amide formation: To a solution of alkyl amine (1 mmol), carboxylic acid (1.5 mmol), Et₃N (2 mmol), and HOBt (1.5 mmol) in dimethylacetamide (0.1 M) was added EDCI (2 mmol). The reaction mixture was stirred at rt for 15 h, diluted with EtOAc, washed with water, and dried (Na₂SO₄). The solvents were removed in vacuo and the residue was purified by chromatography on SiO₂ (hexanes/EtOAc) to afford the product.

General procedure G for 6f, 6g and 6h: A solution of benzyl (2*S*,3*R*,4*S*)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (1 mmol) and alkyl isocyanate (2-3.5 mmol) in dry toluene (0.1 M) was stirred for 1 d at 80 °C. After 1 day, the reaction mixture was concentrated in vacuo and purified by chromatography on SiO₂ (hexanes/EtOAc) to afford the product.

Benzyl(2*S*,3*S*,4*S*)-1-(3-fluorobenzyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (6a): General procedure B was used with **5a17** (0.020 g, 0.050 mmol), *N*-diisopropylethylamine (0.11 mL, 0.107 mmol) and 3-fluorobenzyl bromide (0.006 mL, 0.075 mmol) to provide **6a** (0.021 g, 83 %) as a white solid: R_f 0.30 (2:8 EtOAc/hexanes); [α]_D²⁵ -39 (*c* 1.86, CH₂Cl₂); ATR-IR (cm⁻¹) 3059, 2816, 1629, 1450, 1340, 1215, 1127; ¹H NMR (500 MHz, acetone-*d*₆) δ 7.40-7.18 (m, 11 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.98-6.89 (m, 2 H), 6.81 (d, *J* = 2.3 Hz, 1 H), 6.65 (dd, *J* = 2.7, 8.9 Hz, 1 H), 6.57 (d, *J* = 8.9 Hz, 1 H), 6.28 (d, *J* = 9.5 Hz, 1 H), 5.20-5.08 (m, 2 H), 4.69 (t, *J* = 9.7 Hz, 1 H), 4.48 (d, *J* = 16.8 Hz, 1 H), 4.27 (d, *J* = 8.6 Hz, 1 H), 3.98 (d, *J* = 16.8 Hz, 1 H), 3.64 (s, 3 H), 2.23-2.19 (m, 1 H), 0.95 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (125 MHz,

d₆-acetone) δ 163.7 (d, J = 245 Hz), 157.3, 152.8, 143.5, 143.4 (d, J = 6 Hz), 140.0, 138.4, 130.7 (d, J = 9 Hz), 129.2, 129.0, 128.5, 128.4, 128.4, 128.1, 127.5, 122.6 (d, J = 3 Hz), 114.7, 114.4 (d, J = 21 Hz), 114.0 (d, J = 21 Hz), 113.7, 112.8, 69.6, 66.4, 55.5, 54.3, 53.5, 43.5, 17.0; HRMS (ES⁺) m/z calcd for C₃₂H₃₂FN₂O₃ ([M+H]⁺), 511.2397, found 511.2393.

Benzyl (2S,3S,4S)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (6b).: According to general procedure B, **5a17** (0.040 g, 0.100 mmol), N-ethyldiisopropylamine (0.040 mL, 0.215 mmol) and 5-(bromomethyl)benzo[d][1,3]dioxole (0.032 mg, 0.150 mmol) provided **6b** (0.050 g, 94%) as a white solid: R_f 0.33 (EtOAc/hexanes, 8:2); $[\alpha]_D^{25}$ -41 (c 2.4, CH₂Cl₂); m.p. 46-47; ATR-IR (cm⁻¹) 3058, 2816, 1629, 1450, 1340, 1215, 1163, 1094; ¹H NMR (300 MHz, CD₂Cl₂) δ 7.40-7.20 (m, 8 H), 7.11 (d, J = 6.7 Hz, 2 H), 6.82 (d, J = 2.8 Hz, 1 H), 6.79-6.63 (m, 5 H), 5.92 (d, J = 1.2 Hz, 2 H), 5.01-4.98 (m, 2 H), 4.61 (t, J = 7.3 Hz, 1 H), 4.55 (s, 1 H, NH), 4.39 (d, J = 9.3 Hz, 1 H), 4.28 (d, J = 5.2 Hz, 1 H), 3.99 (d, J = 16.4 Hz, 1 H), 3.73 (s, 3 H), 2.48-2.35 (m, 1 H), 1.11 (d, J = 6.9 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 151.4, 147.8, 146.4, 142.3, 138.8, 136.6, 132.6, 128.7, 128.4, 127.9, 127.7, 127.1, 126.9, 122.9, 119.9, 114.9, 114.3, 113.0, 108.2, 107.4, 100.9, 66.4, 66.3, 55.7, 53.7, 53.0, 41.4, 18.3; HRMS (ES⁺) m/z calcd for C₃₃H₃₂N₂O₅ ([M+Na]⁺) 559.2209, found 559.2213.

Benzyl (2S,3S,4S)-6-methoxy-3-methyl-2-phenyl-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (6c).: A solution of **5a17** (0.020 g, 0.050 mmol) in *N,N*-dimethylformamide (0.5 mL) was treated with *N*-ethyldiisopropylamine (0.11 mL, 0.107 mmol) and 2-(bromomethyl)pyridine hydrobromide (0.020 mg, 0.075 mmol). The reaction mixture was stirred for 50 h at 70 °C, and quenched with H₂O and EtOAc. The organic phase was dried (Na₂SO₄), concentrated in vacuo and purified by chromatography on SiO₂ (hexanes/EtOAc, 90:10) to afford **6c** (0.020 g, 82%) as a pale yellow solid: R_f 0.066 (EtOAc/hexanes, 8:2); $[\alpha]_D^{25}$ -53 (c 0.76, CH₂Cl₂); m.p. 86.2–87.0 °C; ATR-IR (cm⁻¹) 2975, 1629, 1450, 1232, 1127, 1077. ¹H NMR (300 MHz, acetone-*d*₆) δ 8.44 (d, J = 4.4 Hz, 1 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.42-7.10 (m, 12 H), 6.80 (d, J = 2.4 Hz, 1 H), 6.63 (dd, J = 8.8, 2.7 Hz, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.26 (d, J = 9.3 Hz, 1 H), 5.25-5.07 (m, 2 H), 4.72 (t, J = 9.4 Hz, 1 H), 4.50 (d, J = 17.7 Hz, 1 H), 4.45 (d, J = 8.9 Hz, 1 H), 4.11 (d, J = 17.2 Hz, 1 H), 3.64 (s, 3 H), 2.32-2.20 (m, 1 H), 0.95 (d, J = 6.6 Hz, 1 H); ¹³C NMR (100 MHz, d₆-acetone) δ 160.3, 157.3, 152.7, 149.8, 143.6, 140.1, 138.4, 136.9, 129.6, 129.4, 129.1, 128.9, 128.6, 128.4, 128.4, 128.1, 127.3, 122.4, 122.1, 114.6, 113.7, 113.0, 70.1, 66.4, 56.2, 55.5, 54.5, 43.0, 17.0; HRMS (ES⁺) m/z calcd for C₃₁H₃₂N₃O₃ ([M+H]⁺) 494.2444, found 494.2438.

Benzyl (2S,3S,4S)-6-methoxy-3-methyl-2-phenyl-1-((1-tosyl-1H-indol-3-yl)methyl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (6d).: According to general procedure B, **5a17** (0.020 g, 0.050 mmol), N-ethyldiisopropylamine (0.020 mL, 0.107 mmol) and 3-(bromomethyl)-1-tosyl-1H-indole (0.018 mg, 0.050 mmol) provided **6d** (0.031 g, 91%), as a white solid: R_f 0.23 (EtOAc/hexanes, 8:2); $[\alpha]_D^{25}$ -8.0 (c 1.75, CH₂Cl₂); m.p. 53.4–54 °C; ATR-IR (cm⁻¹) 3029, 2919, 1717, 1497, 1446, 1340, 1215, 1094; ¹H NMR (300 MHz, CD₂Cl₂) δ 7.93 (d, J = 8.3 Hz, 1 H), 7.59 (d, J = 8.3 Hz, 2 H), 7.35-7.08 (m, 16 H), 6.8 (d, J = 2.5 Hz, 1 H), 6.69 (dd, J = 8.8, 2.6 Hz, 1 H), 6.63 (d, J = 8.8 Hz, 1 H), 5.01 (s,

2H), 4.62 (d, J = 16.4 Hz, 1 H), 4.55-4.50 (m, 1 H), 4.15-4.08 (m, 1 H), 4.75-4.00 (m, 1 H), 3.71 (s, 3 H), 2.33 (s, 3 H), 2.30-2.22 (m, 1 H), 0.91 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 156.2, 152.3, 145.6, 142.7, 139.3, 137.5, 135.9, 135.4, 130.3, 130.2, 129.4, 129.0, 128.8, 128.5, 128.3, 128.0, 127.6, 127.0, 125.6, 125.2, 124.9, 123.6, 120.5, 120.0, 114.8, 114.2, 113.9, 67.1, 66.7, 56.0, 46.1, 42.4, 21.7, 17.8; HRMS (ES+) m/z calcd for $\text{C}_{41}\text{H}_{40}\text{N}_3\text{O}_5\text{S}$ ($[\text{M}+\text{H}]^+$) 686.2689, found 686.2687.

Benzyl (2S,3S,4S)-6-bromo-3-methyl-2-phenyl-1-(phenylcarbamoyl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (6e).: According to general procedure G, **5d10** (0.018 g, 0.040 mmol) and phenyl isocyanate (4.6 μL , 0.042 mmol) provided **6e** (0.014 g, 62%) as a white solid: R_f 0.36 (EtOAc/hexanes, 8:2); $[\alpha]_{\text{D}}^{25}$ -132.8 (c 0.8, CH_2Cl_2); m.p. 100-102 °C; ATR-IR (cm^{-1}) 3320, 2934, 1709, 1629, 1523, 1498, 1232, 1028; ^1H NMR (300 MHz, CDCl_3) δ 7.52-7.45 (m, 2 H), 7.44-7.22 (m, 15 H), 6.97-6.90 (m, 1 H), 6.67 (s, 1 H), 5.13 (s, 2 H), 4.93 (d, J = 8.4 Hz, 1 H), 4.71 (d, J = 9.8 Hz, 1 H), 4.58 (t, J = 9.7 Hz, 1 H), 1.90-1.80 (m, 1 H), 1.10 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.1, 153.2, 142.6, 138.1, 137.1, 136.2, 136.1, 131.4, 129.2, 128.9, 128.8, 128.7, 128.4, 128.2, 127.8, 127.6, 127.1, 125.9, 123.5, 119.5, 118.8, 67.4, 63.6, 52.7, 47.1, 16.3; HRMS (ES+) m/z calcd for $\text{C}_{31}\text{H}_{28}\text{BrN}_3\text{O}_3$ ($[\text{M}+\text{Na}]^+$) 592.1212, found 592.1207.

Benzyl ((2S,3S,4S)-6-methoxy-1-((4-methoxyphenyl)carbamoyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (6f).: According to general procedure G, **5a** (0.25 g, 0.62 mmol) and 4-methoxyphenyl isocyanate (0.16 mL, 1.24 mmol) provided **6f** (0.027 g, 79%) as a white solid: $[\alpha]_{\text{D}}^{25}$ -126 (c 2.0, CH_2Cl_2); R_f 0.5 (EtOAc/hexanes, 2:3); m.p. 94 °C; ATR-IR (cm^{-1}) 3318, 2934, 1713, 1657, 1509, 1493, 1230; ^1H NMR (500 MHz, CDCl_3) δ 7.46-7.34 (m, 6 H), 7.18-7.30 (m, 6 H), 6.95-6.91 (m, 2 H), 6.80 (d, J = 9.0 Hz, 2 H), 6.72 (s, 1 H), 5.24 (d, J = 12.2 Hz, 1 H), 5.20 (d, J = 12.2 Hz, 1 H), 5.13 (d, J = 8.4 Hz, 1 H), 4.87-4.81 (m, 1 H), 4.66 (t, J = 10.0 Hz, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 1.96-1.88 (m, 1 H), 1.20 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.6, 156.2, 155.7, 153.8, 143.2, 137.3, 136.3, 131.5, 129.8, 128.6, 128.5, 128.3, 128.2, 127.2, 127.2, 125.5, 121.5, 114.0, 113.1, 110.2, 67.2, 63.1, 55.6, 55.4, 53.1, 47.3, 16.4; HRMS (ES+) m/z calcd for $\text{C}_{33}\text{H}_{34}\text{N}_3\text{O}_5$ ($[\text{M}+\text{H}]^+$) 552.2498, found 552.2491.

Benzyl ((2S,3S,4S)-1-(isopropylcarbamoyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (6g).: According to general procedure G, **5a** (0.25 g, 0.62 mmol) and isopropyl isocyanate (0.22 mL, 2.17 mmol) provided **6g** (0.028 g, 94%) as a yellow solid: R_f 0.07 (EtOAc/hexanes, 1:4); $[\alpha]_{\text{D}}^{25}$ -55 (c 2.0, CH_2Cl_2); m.p. 85 °C; ATR-IR (cm^{-1}) 3303, 2975, 1715, 1642, 1493, 1450, 1247; ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.30 (m, 5 H), 7.29-7.12 (m, 6 H), 6.90-6.83 (m, 2 H), 5.22 (d, J = 12.3 Hz, 1 H), 5.17 (d, J = 12.3 Hz, 1 H), 5.06 (d, J = 8.1 Hz, 1 H), 4.77 (d, J = 9.8 Hz, 1 H), 4.70 (d, J = 7.8 Hz, 1 H), 4.58 (t, J = 9.8 Hz, 1 H), 4.00-3.89 (m, 1 H), 3.80 (s, 3 H), 1.93-1.84 (m, 1 H), 1.15 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.3 Hz, 3 H), 1.05 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.0, 156.2, 155.6, 143.7, 136.7, 136.4, 130.4, 128.6, 128.4, 128.3, 128.2, 127.2, 127.0, 125.4, 113.1, 110.2, 67.1, 62.7, 55.5, 53.1, 47.1, 42.6, 23.3, 23.0, 16.4; HRMS (ES+) m/z calcd for $\text{C}_{29}\text{H}_{34}\text{N}_3\text{O}_4$ ($[\text{M}+\text{H}]^+$) 488.2549, found 488.2544.

Benzyl ((2S,3S,4S)-6-methoxy-3-methyl-2-phenyl-1-((4-(trifluoromethyl)phenyl)carbamoyl)-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (6h):

According to general procedure G, **5a** (0.20 g, 0.50 mmol) and 4-(trifluoromethyl)phenyl isocyanate (0.15 mL, 1.04 mmol) provided **6h** (0.24 g, 82%) as a white solid: R_f 0.2 (EtOAc/hexanes, 1:4); $[\alpha]_D^{25}$ -142 (c 1.32, CH₂Cl₂); m.p. 101 °C; ATR-IR (cm⁻¹) 3409, 2933, 1664, 1522, 1493, 1317, 1232, 1110; ¹H NMR (300 MHz, CDCl₃) δ 7.50-7.19 (m, 14 H), 7.00 (s, 1 H), 6.96-6.20 (m, 2 H), 5.26-5.15 (m, 2 H), 5.07 (d, J = 8.7 Hz, 1 H), 4.84 (d, J = 9.9 Hz, 1 H), 4.70 (t, J = 10.5 Hz, 1 H), 3.83 (m, 3 H), 1.93-1.83 (m, 1 H), 1.19 (d, J = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.0, 156.3, 152.9, 142.9, 141.7, 137.8, 136.2, 129.2, 128.6, 128.4, 128.2, 127.4, 127.2, 126.1, 126.0, 125.5, 124.7 (q, J = 32 Hz), 124.2 (q, J = 270 Hz), 118.6, 113.2, 110.3, 67.3, 63.4, 55.6, 53.2, 47.4, 16.3; HRMS (ES⁺) m/z calcd for C₃₃H₃₁F₃N₃O₄ ([M+H]⁺) 590.2267, found 590.2266.

(2S,3S,4S)-4-(((1H-Imidazol-4-yl)methyl)amino)-6-methoxy-N-(4-methoxyphenyl)-3-methyl-2-phenyl-3,4-dihydroquinoline-1(2H)-carboxamide (8a):

According to general procedure C, **6f** (0.25 g, 0.46 mmol), Pd/C (0.05 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, the crude intermediate (40 mg, 0.10 mol), imidazole-4-carboxaldehyde (9.4 mg, 0.10 mmol), acetic acid (4 μ L, 0.10 mmol) and sodium triacetoxyborohydride (41 mg, 0.20 mmol) provided **8a** (0.024 g, 50%) as a white solid: R_f 0.6 (EtOAc/hexanes, 7:3); $[\alpha]_D^{25}$ -168 (c 1.52, CH₂Cl₂); m.p. 113 °C; ATR-IR (cm⁻¹) 3413, 2934, 1655, 1629, 1509, 1491, 1450, 1419, 1267; ¹H NMR (300 MHz, d₆-DMSO) δ 7.61 (s, 1 H), 7.30-7.09 (m, 9 H), 7.63 (s, 1 H), 6.88 (dd, J = 8.7, 3.0 Hz, 1 H), 6.76 (d, J = 2.1 Hz, 1 H), 6.74 (d, J = 2.1 Hz, 1 H), 4.83 (d, J = 7.8 Hz, 1 H), 3.90 (d, J = 13.8 Hz, 1 H), 3.80 (s, 3 H), 3.77 (d, J = 12.3 Hz, 1 H), 3.66 (s, 3 H), 3.34 (d, J = 10.2 Hz, 1 H), 1.83 (d, J = 4.2 Hz, 1 H), 1.77-1.68 (m, 1 H), 1.15 (d, J = 6.6 Hz, 3 H); ¹³C NMR (125 MHz, d₆-DMSO) δ 156.4, 154.5, 153.9, 153.8, 144.5, 138.9, 134.8, 132.9, 132.8, 130.6, 128.0, 126.8, 126.4, 125.3, 121.2, 121.1, 113.4, 112.2, 110.5, 63.0, 58.0, 55.2, 55.1, 46.7, 43.8, 17.1; HRMS (ES⁺) m/z calcd for C₂₉H₃₂N₅O₃ ([M+H]⁺) 498.2505, found 498.2494.

(2S,3S,4S)-6-Methoxy-N-(4-methoxyphenyl)-3-methyl-4-(5-methylthiophene-2-carboxamido)-2-phenyl-3,4-dihydroquinoline-1(2H)-carboxamide (8b):

According to general procedure C, **6f** (0.25 g, 0.46 mmol), Pd/C (0.05 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure F, this intermediate (40 mg, 0.10 mol), 5-methyl-2-thiophenecarboxylic acid (0.021 g, 0.14 mmol), Et₃N (0.027 mL, 0.20 mmol), HOBt (0.020 g, 0.140 mmol) and EDCI (0.037 mg, 0.20 mmol) provided **8b** (0.04 g, 77%) as a yellow solid: R_f 0.7 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -155 (c 3.14, CH₂Cl₂); m.p. 186 °C; ATR-IR (cm⁻¹) 3416, 3304, 2933, 2816, 1638, 1511, 1493, 1450, 1232; ¹H NMR (300 MHz, CDCl₃) δ 7.43 (d, J = 9.6 Hz, 1 H), 7.37-7.23 (m, 6 H), 7.13 (d, J = 3.6 Hz, 1 H), 7.00-6.92 (m, 2 H), 6.89-6.78 (m, 3 H), 6.73 (d, J = 3.0 Hz, 1 H), 5.97 (d, J = 9.0 Hz, 1 H), 5.32 (d, J = 6.9 Hz, 1 H), 5.09 (t, J = 8.7 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.53 (s, 3 H), 2.30-2.23 (m, 1 H), 1.22 (d, J = 6.6 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 161.4, 157.2, 155.8, 154.2, 145.8, 142.6, 135.5, 135.2, 131.4, 129.8,

128.6, 128.6, 127.1×2, 126.0, 125.0, 121.5, 114.0, 113.6, 111.9, 62.0, 55.5, 55.4, 50.8, 45.4, 17.0, 15.6; HRMS (ES+) m/z calcd for $C_{31}H_{32}N_3O_4S$ ($[M+H]^+$) 542.2109, found 542.2114.

(2S,3S,4S)-6-Methoxy-N-(4-methoxyphenyl)-3-methyl-4-((5-methylfuran-2-yl)methyl)amino)-2-phenyl-3,4-dihydroquinoline-1(2H)-carboxamide (8c).: According to general procedure C, **6f** (0.25 g, 0.46 mmol), Pd/C (0.05 g, cat.) and H_2 provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, this intermediate (40 mg, 0.10 mol), 5-methylfurfural (10 μ L, 0.11 mmol), acetic acid (4 μ L, 0.10 mmol) and sodium triacetoxyborohydride (41 mg, 0.20 mmol) provided **8c** (0.03 g, 61%) as a light yellow solid: R_f 0.1 (EtOAc/hexanes, 1:4); $[\alpha]_D^{25}$ -187 (c 2.2, CH_2Cl_2); m.p. 120 °C; ATR-IR (cm^{-1}) 3058, 2933, 1661, 1509, 1450, 1219, 1028; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 8 H), 6.91 (dd, J = 8.8 Hz, J = 2.4 Hz, 1 H), 6.80-6.77 (m, 3 H), 6.12 (d, J = 1.6 Hz, 1 H), 5.94-5.90 (m, 1 H), 5.01 (d, J = 8.8 Hz, 1 H), 4.02 (d, J = 14.4 Hz, 1 H), 3.93 (s, 3 H), 3.87 (d, J = 14.4 Hz, 1 H), 3.75 (s, 3 H), 3.44 (d, J = 10.4 Hz, 1 H), 2.31 (s, 3 H), 1.90-1.81 (m, 1 H), 1.18 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 155.6, 153.8, 151.6, 143.6, 131.8, 130.1, 129.0, 128.4, 128.2, 127.4, 127.1, 125.4, 125.3, 121.2, 114.0, 113.0, 110.6, 106.1, 63.8, 58.5, 55.6, 55.5, 47.0, 44.8, 16.3, 13.6; HRMS (ES+) m/z calcd for $C_{31}H_{34}N_3O_4$ ($[M+H]^+$) 512.2538, found 512.2549.

(2S,3S,4S)-N-Isopropyl-6-methoxy-3-methyl-2-phenyl-4-((thiazol-2-ylmethyl)amino)-3,4-dihydroquinoline-1(2H)-carboxamide (8d).: According to general procedure C, **6g** (0.26 g, 0.54 mmol), Pd/C (0.05 g, cat.) and H_2 provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, this intermediate (50 mg, 0.14 mol), 2-thiazolecarboxaldehyde (12 μ L, 0.14 mmol), acetic acid (5 μ L, 0.14 mmol) and sodium triacetoxyborohydride (61 mg, 0.27 mmol) provided **8d** (0.046 g, 75%) as a yellow solid: R_f 0.2 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -100 (c 3.6, CH_2Cl_2); m.p. 161 °C; ATR-IR (cm^{-1}) 3470, 2974, 2933, 1647, 1491, 1453, 1260; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 3.3 Hz, 1 H), 7.30 (d, J = 3.3 Hz, 1 H), 7.27-7.22 (m, 5 H), 7.14-7.20 (m, 3 H), 6.87 (dd, J = 8.6, 2.9 Hz, 1 H), 4.99 (d, J = 8.6 Hz, 1 H), 4.72 (d, J = 7.6 Hz, 1 H), 4.41 (d, J = 15.7 Hz, 1 H), 4.32 (d, J = 15.7 Hz, 1 H), 3.96-3.88 (m, 1 H), 3.87 (s, 3 H), 3.45 (d, J = 10 Hz, 1 H), 1.94-1.85 (m, 1 H), 1.23 (d, J = 6.6 Hz, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 157.2, 155.6, 143.8, 142.7, 139.0, 130.6, 128.3, 127.2, 126.8, 125.3, 119.0, 112.7, 110.5, 63.3, 59.3, 55.5, 49.5, 47.2, 42.5, 23.3, 23.0, 16.6; HRMS (ES+) m/z calcd for $C_{25}H_{31}N_4O_2S$ ($[M+H]^+$) 451.2167, found 451.2153.

(2S,3S,4S)-N-isopropyl-6-methoxy-3-methyl-2-phenyl-4-((pyridin-2-ylmethyl)amino)-3,4-dihydroquinoline-1(2H)-carboxamide (8e).: According to general procedure C, **6g** (0.26 g, 0.54 mmol), Pd/C (0.05 g, cat.) and H_2 provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, this intermediate (50 mg, 0.14 mol), 2-pyridinecarboxaldehyde (13 μ L, 0.14 mmol), acetic acid (5 μ L, 0.14 mmol) and sodium triacetoxyborohydride (61 mg, 0.27 mmol) provided **8e** (0.04 g, 66%) as a yellow solid: R_f 0.2 (EtOAc/hexanes, 1:3); $[\alpha]_D^{25}$ -73 (c 2.08, CH_2Cl_2); m.p. 106 °C; ATR-IR (cm^{-1}) 3427, 2961, 2933, 1647, 1491, 1453, 1258; ^1H

NMR (500 MHz, CDCl₃) δ 8.6 (d, *J* = 4.7 Hz, 1 H), 7.69 (dt, *J* = 7.7, 1.7 Hz, 1 H), 7.41 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 2.6 Hz, 1 H), 7.27-7.16 (m, 7 H), 6.88 (dd, *J* = 8.6, 2.8 Hz, 1 H), 4.95 (d, *J* = 8.8 Hz, 1 H), 4.73 (d, *J* = 7.7 Hz, 1 H), 4.24 (d, *J* = 14.5 Hz, 1 H), 4.09 (d, *J* = 14.5 Hz, 1 H), 3.97-3.90 (m, 1 H), 3.87 (s, 3 H), 3.44 (d, *J* = 10.4 Hz, 1 H), 1.95-1.85 (m, 1 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 6.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 157.3, 155.6, 149.2, 144.0, 136.5, 130.7, 128.3, 127.4, 126.8, 125.3, 122.1, 112.6, 110.5, 63.6, 59.2, 55.5, 53.0, 47.1, 42.4, 29.7, 23.3, 23.0, 16.5; HRMS (ES⁺) *m/z* calcd for C₂₇H₃₃N₄O₂ ([M+H]⁺) 445.2604, found 445.2589.

N-((2S,3S,4S)-1-(Isopropylcarbamoyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-3,5-dimethylisoxazole-4-carboxamide (8f).: According to general procedure C, **6g** (0.26 g, 0.54 mmol), Pd/C (0.05 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure F, this intermediate (0.05 g, 0.14 mmol), 3,5-dimethylisoxazole-4-carboxylic acid (0.03 g, 0.20 mmol), Et₃N (0.04 mL, 0.27 mmol), HOBt (0.028 g, 0.20 mmol) and EDCI (0.052 mg, 0.27 mmol) provided **8f** (0.057 g, 88%) as a white solid: R_f 0.16 (EtOAc/hexanes, 2:3); [α]_D²⁵ -75 (c 2.9, CH₂Cl₂); m.p. 105 °C; ATR-IR (cm⁻¹) 3058, 2974, 2933, 1630, 1491, 1453, 1163; ¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, *J* = 8.7 Hz, 1 H), 7.26-7.11 (m, 5 H), 6.90 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.79 (d, *J* = 2.7 Hz, 1 H), 5.57 (d, *J* = 8.7 Hz, 1 H), 5.30 (d, *J* = 6.3 Hz, 1 H), 5.00 (t, *J* = 6.9 Hz, 1 H), 4.86 (d, *J* = 7.5 Hz, 1 H), 3.95-3.86 (m, 1 H), 3.77 (s, 3 H), 2.43 (s, 3 H), 2.35-2.28 (m, 1 H), 2.16 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 6.3 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 161.4, 157.4, 156.6, 155.9, 142.4, 133.3, 130.2, 128.5, 126.9, 126.9, 125.0, 113.9, 112.0, 111.5, 60.8, 55.4, 50.3, 44.3, 42.7, 23.1, 22.8, 17.3, 12.7, 11.4; HRMS (ES⁺) *m/z* calcd for C₂₇H₃₃N₄O₄ ([M+H]⁺) 447.2502, found 447.2494.

(2S,3R,4S)-6-Methoxy-3-methyl-4-(methylsulfonamido)-2-phenyl-N-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinoline-1(2H)-carboxamide (8g).: According to general procedure C, **6h** (0.20 g, 0.34 mmol), 5% Pd/C (0.06 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure D, this intermediate (0.055 g, 0.12 mmol), Et₃N (0.034 mL, 0.058 mmol) and methanesulfonyl chloride (0.01 mL, 0.13 mmol) provided **8g** (0.055 g, 85%) as a white solid: R_f 0.3 (EtOAc/hexanes, 2:3); [α]_D²⁵ -186 (c 4.4, CH₂Cl₂); m.p. 160 °C; ATR-IR (cm⁻¹) 3058, 2974, 1664, 1619, 1524, 1493, 1317, 1235, 1112; ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 8.7 Hz, 2 H), 7.38-7.25 (m, 5 H), 7.20-7.16 (m, 3 H), 7.04 (s, 1 H), 6.96 (dd, *J* = 8.6, 2.8 Hz, 1 H), 5.03 (t, *J* = 9.2 Hz, 2 H), 4.32 (t, *J* = 10.4 Hz, 1 H), 3.88 (s, 3 H), 3.08 (s, 3 H), 1.90-1.80 (m, 1 H), 1.26 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 152.9, 142.7, 141.6, 138.0, 129.1, 128.6, 127.6, 127.2, 126.0, 125.6, 124.7 (q, *J* = 32 Hz), 124.2 (q, *J* = 270 Hz), 118.5, 113.1, 110.9, 63.5, 55.9, 55.6, 47.9, 41.9, 16.6; HRMS (ES⁺) *m/z* calcd for C₂₆H₂₇F₃N₃O₄S ([M+H]⁺) 534.1674, found 534.1665.

(2S,3S,4S)-4-(Ethylamino)-6-methoxy-3-methyl-2-phenyl-N-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinoline-1(2H)-carboxamide (8h).: According to general procedure C, **6h** (0.20 g, 0.34 mmol), 5% Pd/C (0.06 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification.

According to general procedure E, this intermediate (55 mg, 0.12 mol), acetaldehyde (7.5 uL, 0.13 mmol), acetic acid (5 uL, 0.12 mmol) and sodium triacetoxyborohydride (51 mg, 0.24 mmol) provided **8h** (0.03 g, 51%) as a white solid: R_f 0.05 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ -167 (c 2.2, CH₂Cl₂); m.p. 72 °C; ATR-IR (cm⁻¹) 3409, 2933, 1670, 1610, 1491, 1315, 1235, 1112; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, J = 8.9 Hz, 2 H), 7.43 (d, J = 8.9 Hz, 2 H), 7.30-7.17 (m, 6 H), 7.05 (s, 1 H), 6.92 (dd, J = 8.5, 2.9 Hz, 1 H), 5.02 (d, J = 9.0 Hz, 1 H), 3.92 (s, 3 H), 3.37 (d, J = 10.8 Hz, 1 H), 2.96-2.89 (m, 1 H), 2.86-2.79 (m, 1 H), 1.85-1.76 (m, 1 H), 1.29-1.14 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 158.2, 153.0, 143.3, 141.9, 141.2, 129.5, 128.5, 127.4, 127.3, 126.1, 125.3, 125.2, 124.7 (q, J = 32 Hz), 124.2 (q, J = 270 Hz), 118.4, 112.5, 111.1, 64.2, 59.5, 55.6, 47.2, 42.6, 16.3, 15.8; HRMS (ES⁺) m/z calcd for C₂₇H₂₉F₃N₃O₂ ([M+H]⁺) 484.2212, found 484.2199.

(2S,3S,4S)-4-Acetamido-6-methoxy-3-methyl-2-phenyl-N-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinoline-1(2H)-carboxamide (8i).: According to general procedure C, **6h** (0.20 g, 0.34 mmol), 5% Pd/C (0.06 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure F, this intermediate (0.055 g, 0.12 mmol), acetic acid (0.024 mL, 0.18 mmol), Et₃N (0.034 mL, 0.24 mmol), HOBt (0.025 g, 0.180 mmol) and EDCI (0.046 mg, 0.24 mmol) provided **8i** (0.052 g, 87%) as a white solid: R_f 0.07 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -161 (c 3.7, CH₂Cl₂); m.p. 140 °C; ATR-IR (cm⁻¹) 3420, 3026, 1655, 1619, 1524, 1493, 1317, 1243, 1163; ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.34-7.18 (m, 5 H), 7.09 (s, 1 H), 6.93 (d, J = 8.8 Hz, 1 H), 6.88 (s, 1 H), 5.61 (d, J = 9.2 Hz, 1 H), 5.10 (d, J = 8.0 Hz, 1 H), 4.89 (t, J = 9.6 Hz, 1 H), 3.87 (s, 3 H), 2.08 (s, 3 H), 2.00-1.94 (m, 1 H), 1.14 (d, J = 6.4 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.0, 157.7, 153.1, 142.7, 141.6, 136.6, 129.4, 128.6, 127.3, 127.1, 126.0, 125.3, 124.7 (q, J = 32 Hz), 124.2 (q, J = 270 Hz), 118.6, 112.8, 111.4, 62.9, 55.6, 50.9, 46.2, 23.2, 16.5; HRMS (ES⁺) m/z calcd for C₂₇H₂₇F₃N₃O₃ ([M+H]⁺) 498.2004, found 498.1994.

N-((2S,3S,4S)-1-(3-Fluorobenzyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-3,5-dimethylisoxazole-4-carboxamide (8j).: According to general procedure C, **6a** (0.15 g, 0.29 mmol), Pd/C (0.03 g) and H₂ provided intermediate **7** which was used for next step without further purification. According to general procedure F, **7** (0.070 g, 0.19 mmol), 3,5-dimethylisoxazole-4-carboxylic acid (0.040 g, 0.280 mmol), Et₃N (0.052 mL, 0.372 mmol), HOBt (0.039 g, 0.280 mmol) and EDCI (0.071 mg, 0.372 mmol) provided **8j** (0.046 g, 50%) as a yellow solid: R_f 0.16 (EtOAc/hexanes, 2:8); $[\alpha]_D^{25}$ -54 (c 2.9, CH₂Cl₂); m.p. 82 °C; ATR-IR (cm⁻¹) 3282, 3027, 2933, 1653, 1629, 1498, 1489, 1450, 1420, 1340, 1163; ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.23 (m, 3 H), 7.18-7.18 (m, 3 H), 7.06 (d, J = 7.7 Hz, 1 H), 6.99 (d, J = 9.8 Hz, 1 H), 6.93 (td, J = 8.4, 2.3 Hz, 1 H), 6.85 (d, J = 2.9 Hz, 1 H), 6.79 (dd, J = 9.0, 3.0 Hz, 1 H), 6.61 (d, J = 9.0 Hz, 1 H), 5.16 (d, J = 8.8 Hz, 1 H), 5.05 (dd, J = 8.8, 2.7 Hz, 1 H), 4.71 (d, J = 17.0 Hz, 1 H), 4.43 (d, J = 3.3 Hz, 1 H), 4.17 (d, J = 17.0 Hz, 1 H), 3.73 (s, 3 H), 2.73-2.67 (m, 1 H), 2.29 (s, 3 H), 2.05 (s, 3 H), 1.30 (d, J = 7.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 163.2 (d, J = 245 Hz), 157.5, 151.6, 142.3, 141.7 (d, J = 6 Hz), 138.3, 130.1 (d, J = 9 Hz), 129.1, 127.3, 126.7, 122.1 (d, J = 3 Hz), 121.2, 115.6 (2 C),

113.9 (d, $J = 21$ Hz), 113.5 (d, $J = 21$ Hz), 112.5, 111.5, 66.1, 55.7, 54.3, 50.6, 40.6, 19.5, 12.6, 11.2; HRMS (ES⁺) m/z calcd for C₃₀H₃₁FN₃O₃ ([M+H]⁺) 500.2349, found 500.2341.

N-((2S,3R,4S)-1-(3-Fluorobenzyl)-6-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)methanesulfonamide (8k).: According to general procedure C, **6a** (0.15 g, 0.29 mmol), Pd/C (0.03 g, cat.) and H₂ provided intermediate **7** which was used for next step without further purification. According to general procedure D, **7** (0.070 g, 0.19 mmol), Et₃N (0.05 mL, 0.37 mmol) and methanesulfonyl chloride (0.016 mL, 0.20 mmol) provided **8k** (0.050 g, 59%) as a yellow solid: R_f 0.2 (2:8 EtOAc/hexanes); $[\alpha]_D^{25} -15$ (c 3.1, CH₂Cl₂); m.p. 75 °C; ATR-IR (cm⁻¹) 3300, 2933, 1588, 1497, 1450, 1420, 1321, 1148; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.23 (m, 4 H), 7.13 (d, $J = 7.0$, 2 H), 7.01 (d, $J = 7.6$, 1 H), 6.95-6.90 (m, 3 H), 6.78 (dd, $J = 8.9$, 3.0 Hz, 1 H), 6.59 (d, $J = 9.0$ Hz, 1 H), 4.63 (d, $J = 16.8$ Hz, 1 H), 4.38 (dd, $J = 9.1$, 4.6 Hz, 1 H), 4.35 (d, $J = 4.3$ Hz, 1 H), 4.11 (d, $J = 16.8$ Hz, 1 H), 3.97-3.92 (m, 1 H), 3.76 (s, 3 H), 2.80 (s, 3 H), 2.52-2.45 (m, 1 H), 1.22 (d, $J = 7.0$ Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 163.1 (d, $J = 245$ Hz), 151.7, 142.0, 141.5 (d, $J = 6$ Hz), 138.3, 130.1 (d, $J = 9$ Hz), 129.0, 127.7, 126.9, 122.3 (d, $J = 3$ Hz), 122.0, 115.3, 114.9, 113.9 (d, $J = 21$ Hz), 113.6 (d, $J = 21$ Hz), 112.8, 66.5, 55.7, 55.6, 53.5, 42.4, 42.2, 19.0; HRMS (ES⁺) m/z calcd for C₂₅H₂₈FN₂O₃S ([M+H]⁺) 455.1805, found 455.1795.

N-((2R,3R,4S)-2-Ethyl-6-methoxy-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methanesulfonamide (8l).: According to general procedure C, **5c** (0.018 g, 0.51 mmol), Pd/C (0.036 g, cat.) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure D, this intermediate (0.055 g, 0.25 mmol), Et₃N (0.07 mL, 0.50 mmol) and methanesulfonyl chloride (0.022 mL, 0.27 mmol) provided **8l** (0.058 g, 78%) as a light yellow solid: R_f 0.6 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25} -25$ (c 1.14, CH₂Cl₂); m.p. 176 °C; ATR-IR (cm⁻¹) 3384, 3302, 2933, 1504, 1420, 1297, 1278, 1215, 1150; ¹H NMR (500 MHz, CDCl₃) δ 6.93 (d, $J = 2.7$ Hz, 1 H), 6.68 (dd, $J = 8.6$, 2.7 Hz, 1 H), 6.49 (d, $J = 8.6$ Hz, 1 H), 4.67 (d, $J = 9.4$ Hz, 1 H), 4.31 (t, $J = 9.0$ Hz, 1 H), 3.74 (s, 3 H), 3.06 (s, 3 H), 2.97 (td, $J = 7.9$, 3.6 Hz, 1 H), 1.83-1.75 (m, 1 H), 1.74-1.66 (m, 1 H), 1.59-1.49 (m, 1 H), 1.10 (d, $J = 6.7$ Hz, 3 H), 0.99 (t, $J = 7.4$ Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 152.3, 138.7, 122.9, 115.6, 115.1, 113.3, 58.2, 58.0, 55.7, 42.4, 39.2, 26.8, 16.1, 9.1.

(2R,3R,4S)-2-Ethyl-6-methoxy-3-methyl-N-(thiazol-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-amine (8n).: According to general procedure C, **5c** (0.018 g, 0.51 mmol), Pd/C (0.036 g) and H₂ provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, this intermediate (55 mg, 0.25 mol), 2-thiazolecarboxaldehyde (32 mg, 0.27 mmol), acetic acid (17 uL, 0.30 mmol) and sodium triacetoxyborohydride (111 mg, 0.50 mmol) provided **8n** (0.05 g, 63%) as a yellow solid: R_f 0.5 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25} -31$ (c 4.5, CH₂Cl₂); ATR-IR (cm⁻¹) 3334, 2957, 1500, 1457, 1232, 1219; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, $J = 3.3$ Hz, 1 H), 7.26 (d, $J = 3.3$ Hz, 1 H), 7.11 (d, $J = 2.5$ Hz, 1 H), 6.66 (dd, $J = 8.6$, 2.5 Hz, 1 H), 6.50 (d, $J = 8.6$ Hz, 1 H), 4.09 (d, $J = 15.4$ Hz, 1 H), 3.89 (d, $J = 15.4$ Hz, 1 H), 3.74 (s, 3 H), 3.71-3.65 (m, 1H) 2.96-2.91 (m, 1 H), 1.96-1.88 (m, 1 H), 1.79-1.70 (m, 1 H), 1.62-1.53 (m, 1 H), 1.08 (d, $J = 6.7$ Hz, 3 H), 1.00 (t, $J = 7.4$ Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃)

δ 173.1, 152.3, 142.4, 139.7, 123.7, 118.7, 115.4, 114.4, 112.8, 60.7, 58.2, 55.8, 45.7, 35.7, 26.7, 15.7, 9.2; HRMS (ES+) m/z calcd for $C_{17}H_{23}N_3OS$ ($[M]^+$) 317.1562, found 317.1542.

N-((2R,3R,4S)-2-Isopropyl-6-methoxy-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methanesulfonamide (8m).: According to general procedure

C, **5b** (0.18 g, 0.51 mmol), Pd/C (0.036 g) and H_2 provided an intermediate heterocycle which was used for next step without further purification. According to general procedure D, this intermediate (0.050 g, 0.21 mmol), Et_3N (0.06 mL, 0.43 mmol) and methanesulfonyl chloride (0.02 mL, 0.23 mmol) provided **8m** (0.05 g, 75%) as a light brown solid: R_f 0.8 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -36 (c 1.3, $CHCl_3$); ATR-IR (cm^{-1}) 3384, 3323, 2974, 2933, 1504, 1420, 1358, 1317, 1297, 1217, 1058; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, J = 2.7 Hz, 1 H), 6.70 (dd, J = 8.6, 2.7 Hz, 1 H), 6.52 (d, J = 8.6 Hz, 1 H), 4.65 (d, J = 9.4 Hz, 1 H), 4.31 (t, J = 8.6 Hz, 1 H), 3.75 (s, 3 H), 3.57 (brs, 1 H), 3.03 (s, 3 H), 2.83 (dd, J = 7.8, 4.5 Hz, 1 H), 2.05-1.93 (m, 1 H), 1.09 (d, J = 4.5 Hz, 3 H), 1.05 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 139.1, 123.2, 115.7, 115.0, 113.3, 62.7, 58.1, 55.8, 42.3, 37.9, 29.7, 19.8, 16.7, 15.7.

(2R,3R,4S)-2-Isopropyl-6-methoxy-3-methyl-N-(thiazol-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-amine (8o) and (2R,3R,4S)-2-Isopropyl-6-methoxy-3-methyl-N,N-bis(thiazol-2-ylmethyl)-1,2,3,4-tetrahydroquinolin-4-amine (8p).:

According to general procedure C **5b** (0.018 g, 0.51 mmol), Pd/C (0.036 g) and H_2 provided an intermediate heterocycle which was used for next step without further purification. According to general procedure E, this intermediate (50 mg, 0.21 mol), 2-thiazolecarboxaldehyde (27 mg, 0.23 mmol), acetic acid (15 μ L, 0.26 mmol) and sodium triacetoxyborohydride (95 mg, 0.43 mmol) provided **8o** (0.04 g, 57%) as a yellow liquid, and **8p** (0.018 g, 20%) as a light yellow solid. **8o**: R_f 0.6 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -33 (c 3.3, $CHCl_3$); ATR-IR (cm^{-1}) 3315, 2928, 1500, 1465, 1358, 1232, 1215; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 3.3 Hz, 1 H), 7.26 (d, J = 3.3 Hz, 1 H), 7.08 (d, J = 2.7 Hz, 1 H), 6.66 (dd, J = 8.6, 2.9 Hz, 1 H), 6.51 (d, J = 8.6 Hz, 1 H), 4.10 (d, J = 15.4 Hz, 1 H), 3.90 (d, J = 15.4 Hz, 1 H), 3.74 (s, 3 H), 3.69 (d, J = 8.1 Hz, 1 H), 2.83 (dd, J = 8.3, 3.9 Hz, 1 H), 2.12-2.02 (m, 2 H), 1.06 (d, J = 5.3 Hz, 3 H), 1.05 (d, J = 5.6 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 152.2, 142.4, 139.9, 123.8, 118.7, 115.4, 114.4, 112.9, 62.4, 60.9, 55.8, 46.0, 34.2, 29.2, 20.1, 15.9, 15.3; HRMS (ES+) m/z calcd for $C_{18}H_{26}N_3OSNa$ ($[M+Na]^+$) 354.1616, found 354.1598. **8p**: R_f 0.5 (EtOAc/hexanes, 2:3); $[\alpha]_D^{25}$ -68 (c 1.7, $CHCl_3$); m.p. 212 $^{\circ}C$; ATR-IR (cm^{-1}) 3330, 3058, 2963, 1496, 1463, 1351, 1215, 1146; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 3.3 Hz, 2 H), 7.30 (d, J = 3.3 Hz, 2 H), 7.21 (d, J = 2.7 Hz, 1 H), 6.67 (dd, J = 8.5, 2.8 Hz, 1 H), 6.50 (d, J = 8.6 Hz, 1 H), 4.35 (d, J = 15.4 Hz, 2 H), 4.16 (d, J = 15.4 Hz, 2 H), 3.81 (s, 4 H), 2.76 (dd, J = 9.7, 2.5 Hz, 1 H), 2.15-2.06 (m, 1 H), 2.04-1.98 (m, 1 H), 1.15 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 152.3, 142.2, 141.5, 123.7, 119.6, 115.6, 114.7, 113.7, 63.7, 63.2, 55.9, 52.9, 35.7, 28.2, 20.4, 17.2, 14.4; HRMS (ES+) m/z calcd for $C_{22}H_{28}N_4OS_2Na$ ($[M+Na]^+$) 451.1602, found 451.1586.

N-((2R,3R,4S)-2-Ethyl-3-methyl-4-(methylsulfonamido)-1,2,3,4-tetrahydroquinolin-6-yl)acetamide (8q).: According to general procedure C, **8r** (0.02 g, 0.05

mmol), Pd/C (0.004 g, cat.) and H₂ provided an intermediate amine which was used for next step without further purification. According to general procedure E, this amine (0.015 g), Et₃N (15 μ L, 0.10 mmol) and methanesulfonyl chloride (5 μ L, 0.06 mmol) to give **8q** (0.008 g, 50%) as a light brown solid: *R*_f 0.7 (EtOAc/hexanes, 7:3); [α]_D²⁵ -11 (*c* 0.5, MeOH); ATR-IR (cm⁻¹) 3356, 2974, 1655, 1506, 1420, 1310, 1140; ¹H NMR (300 MHz, MeOD) δ 7.47 (d, *J* = 1.8 Hz, 1 H), 7.06 (dd, *J* = 8.6, 2.4 Hz, 1 H), 6.52 (d, *J* = 8.6 Hz, 1 H), 4.20 (d, *J* = 9.3 Hz, 1 H), 3.12 (s, 3 H), 3.08-3.02 (m, 1 H), 2.06 (s, 3 H), 1.78-1.70 (m, 2 H), 1.68-1.57 (m, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H); HRMS (ES+) *m/z* calcd for C₁₅H₂₄N₃O₃S ([M+H]⁺) 326.1538, found 326.1531.

Benzyl ((2*R*,3*R*,4*S*)-6-acetamido-2-ethyl-3-methyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamate (8r).: To a cold (0 °C) solution of **5e** (0.210 g, 0.480 mmol) in CH₂Cl₂ (1.5 mL) was added TFA (1.4 mL). The reaction mixture was stirred for 5 h at 0 °C, concentrated in vacuo, and the residue was used for the next reaction without further purification. According to general procedure F, this residue (0.075 g, 0.22 mmol), acetic acid (0.018 mL, 0.33 mmol), Et₃N (0.062 mL, 0.44 mmol), HOBT (0.046 g, 0.33 mmol) and EDCI (0.085 mg, 0.44 mmol) provided **8r** (0.025 g, 30%) as a white solid: *R*_f 0.07 (EtOAc/hexanes, 2:3); m.p. 212 °C; ATR-IR (cm⁻¹) 3308, 2974, 1688, 1647, 1535, 1506, 1450, 1246; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.28 (m, 5 H), 7.15 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.09 (brs, 1 H), 6.53 (d, *J* = 8.6 Hz, 1 H), 5.19 (d, *J* = 12.6 Hz, 1 H), 5.11 (d, *J* = 12.6 Hz, 1 H), 4.45 (d, *J* = 10.2 Hz, 1 H), 3.06-2.99 (m, 1 H), 2.04 (s, 3 H), 1.78-1.63 (m, 2 H), 1.62-1.50 (m, 1 H), 1.10-0.95 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3, 158.7, 143.6, 138.5, 129.5, 128.9, 128.8, 128.7, 123.4, 122.7, 121.5, 115.4, 67.5, 58.8, 55.6, 38.1, 26.6, 23.4, 15.0, 8.6; HRMS (ES+) *m/z* calcd for C₂₂H₂₈N₃O₃ ([M+H]⁺) 382.2130, found 382.2111.

Benzyl (2*S*,3*R*,4*S*)-3-methyl-2,6-diphenyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (9).: A flame-dried Schlenk flask was charged with **5d** (0.075 g, 0.166 mmol), PhB(OH)₂ (0.017 g, 0.216 mmol) and P(*o*-Tol)₃ (0.004 g, 0.012 mmol), placed under vacuum, purged with Ar, and treated with toluene (0.720 mL), EtOH (0.320 mL) and 2 M aq. K₂CO₃ (0.200 mL). The reaction mixture was degassed with Ar, heated to 60 °C, treated with Pd(OAc)₂ (0.003 g, 0.013 mmol), and the temperature was further increased to 80 °C. After 10 h, the conversion was found to be complete by ¹H NMR analysis of an aliquot, and the reaction mixture was filtered through a pad of celite (Et₂O), concentrated, and purified by chromatography on SiO₂ (EtOAc/hexanes, 5:95) to provide **9** (0.070 g, 94%) as a brownish foamy solid: *R*_f 0.46 (8:2 EtOAc/hexanes); [α]_D²⁵ -21 (*c* 0.8, CH₂Cl₂); m.p. 101-102 °C; ATR-IR (cm⁻¹) 3338, 3027, 1707, 1614, 1513, 1340, 1230; ¹H NMR (400 MHz, CD₂Cl₂) δ 7.50 (d, *J* = 7.6 Hz, 2 H), 7.42-7.24 (m, 15 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 5.18 (d, *J* = 12.8 Hz, 1 H), 5.13 (d, *J* = 12.8 Hz, 1 H), 4.92 (d, *J* = 10.0 Hz, 1 H), 4.84 (t, *J* = 10 Hz, 1 H), 4.23 (d, *J* = 9.6 Hz, 2 H), 2.11-2.03 (m, 1 H), 0.85 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 157.3, 144.7, 142.5, 141.5, 137.5, 130.7, 129.0, 129.0, 128.8, 128.4, 128.3, 128.0, 128.0, 127.4, 126.5, 126.4, 122.5, 114.6, 66.9, 62.9, 54.9, 41.1, 30.1, 15.6; HRMS (ES+) *m/z* calcd for C₃₀H₂₉N₂O₂ ([M+H]⁺) 449.2229, found 449.2226.

RESULTS AND DISCUSSION

As a part of our research efforts directed towards the synthesis of screening libraries of heterocycles,¹⁹⁻²¹ we decided to explore the viability of a late-stage diversification of 4-ATQ scaffolds obtained by Zhu and Masson's version of the asymmetric Povarov reaction. The chiral phosphoric acid catalyst **1** generated the desired 4-ATQ products in high enantiomeric ratios of up to 99:1 and in >90% yield (Table 1). While the 4-ATQs **5a**¹⁷, **5c**¹⁷ and **5d**¹⁰ are known in the literature, six new 4-ATQ scaffolds were successfully synthesized with aniline, benzyl (*E*)-prop-1-en-1-yl carbamate, the appropriate aldehydes, and a chiral Brønsted acid catalyst. Importantly, the methodology proved to be robust, allowing for the synthesis of 4-ATQs on >1 g scale with efficient recovery of the chiral catalyst (Table 1).

For the diversification of the enantioenriched 4-ATQ derivatives, we first attempted amide couplings, sulfonylations and reductive aminations for selective derivatization of the endocyclic nitrogen. In order to perform a reductive amination at the ring nitrogen, compound **5a** was treated with various aliphatic and aromatic aldehydes in the presence of Ti(O-*i*Pr)₄ and AcOH. However, despite our attempts, we did not observe any formation of intermediate iminium ion or enamine. Sulfonylation was also attempted at this position, but the starting material was recovered. Since the tetrahydroquinoline nitrogen demonstrated a low nucleophilicity, we then used more reactive electrophiles such as isocyanates. 4-ATQ derivatives were reacted with phenyl isocyanate at 80 °C overnight, and functionalization of the tetrahydroquinoline nitrogen was achieved. Four isocyanates, i.e. 4-methoxy-, 4-trifluoromethyl-, phenyl-, and isopropylisocyanate, were used for diversification at this position, and high yields (62 to 94%) of *N*-substituted-dihydroquinoline-1(2*H*)-carboxamides were obtained in this fashion (Table 2).

Other methods to functionalize the endocyclic nitrogen also included an alkylation with alkyl bromides. The use of 3-fluorobenzylbromide and Hünig's base provided the desired compound **6a** at 70 °C overnight in high yield (83%). The conversion with four additional alkyl bromide derivatives was also high-yielding (Table 2; 82 to 94%). However, this reaction failed with MeI, *n*-butyl bromide, and 1-bromo-2,2-dimethylpropane (Table 2).

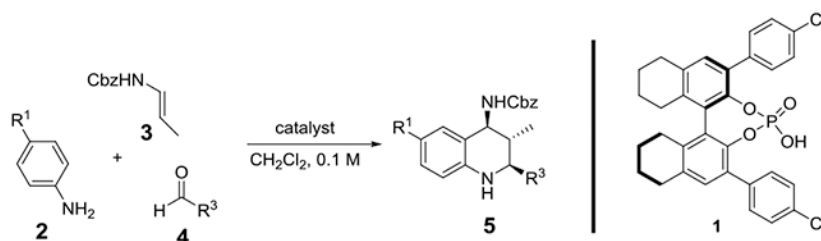


TABLE 1

Reagents and conditions for enantioselective synthesis of 4-ATQs: aldehyde **4** (1 equiv.), amine **2** (1 equiv.), *N*-vinylcarbamate **3** (1.1 equiv.), and catalyst **1** (0.1 equiv.) in CH₂Cl₂ (0.1 M).

Entry	Product	R ¹	R ³	Yield [%]	er ^a
1	5a	MeO-		87	98:2
2	5b	MeO-		55	89:11
3	5c	MeO-		54	95:5
4	5d	Br-		77	98:2
5	5e	BocNH-		60	93:7
6	5f	MeO-		92	99:1
7	5g	MeO-		70	96:4
8	5h	MeO-		44	98:2
9	5i	MeO-		28	95:5

^aEnantiomeric ratio (er) was determined by SFC or HPLC.

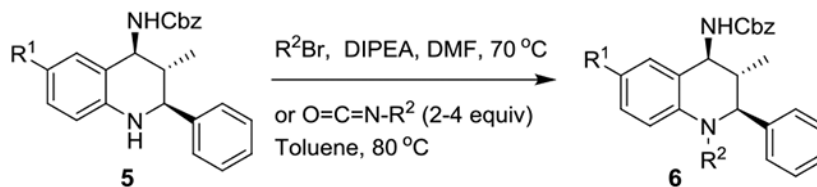
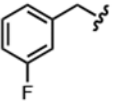
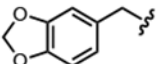
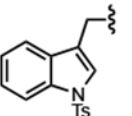
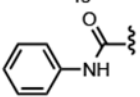
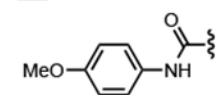
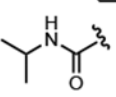
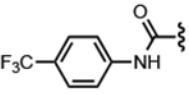


TABLE 2

Reagents and conditions to functionalize the aniline nitrogen in 4-ATQs: (i) 4-ATQ derivatives (1 equiv.), *N*-ethyldiisopropylamine (2 equiv.), alkylbromide (1 equiv.), *N,N*-dimethylformamide, 70 °C, 24h; (ii) 4-ATQ derivatives (1 equiv.), alkyl isocyanate (2-3.5 equiv.), toluene (0.1 M), 80 °C, 1 day.

Entry	R ¹	R ²	Product	Yield [%]
1	MeO-		6a	83
2	MeO-		6b	94
3	MeO-		6c	82
4	MeO-		6d	91
5	Br-		6e	62
6	MeO-		6f	79
7	MeO-		6g	94
8	MeO-		6h	82

After successful functionalization of the endocyclic nitrogen, we explored methods for selective removal of the Cbz-protecting group at the exocyclic nitrogen atom. After several unsuccessful trials, we discovered that the Cbz group could be removed either via hydrogenation with 10% Pd/C (cat. 20% loading) at r.t. for 5 h in EtOH, or with 33% HBr solution in AcOH. The products **7** were used for the next step without further purification. Late-stage functionalization reactions included amide couplings, sulfonylations, and reductive aminations. Acylated derivatives were accomplished by amide coupling conditions with carboxylic acids, EDCI/HOBt and Et₃N, in high yields of up to 88%. Both aromatic and aliphatic carboxylic acids could be used without incident. The sulfonylation reactions of five different primary amine scaffolds **7** were accomplished in moderate to high yields (50 to 85%) with methane sulfonyl chloride, Et₃N in CH₂Cl₂ after overnight reaction. Finally, eight different reductive aminations with aldehydes and acetic acid/sodium triacetoxyborohydride in 1,2-dichloroethane proceeded in 50 to 75% yield. When the aldehyde component was used in >1 equiv., a double reductive amination resulted (Table 3).

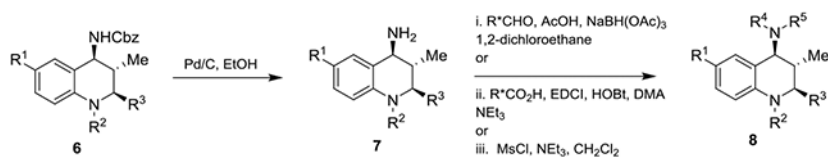


TABLE 3

Reagents and conditions to functionalize the primary amine in 4-ATQs: (i) alkyl amine (1 equiv.), aldehyde (1.1 equiv.), acetic acid (1 equiv.), 1,2-dichloroethane (0.1 M), sodium triacetoxyborohydride (2 equiv.), rt, 24 h; (ii) alkyl amine (1 equiv.), carboxylic acid (1.5 equiv.), Et₃N (2 equiv.), HOBt (1.5 equiv.), dimethylacetamide (0.1 M), EDCI (2 equiv.), rt,

15 h; (iii) alkyl amine (1 equiv.), dichloromethane or 1,2-dichloroethane (0.1 M), Et₃N (2 equiv.), alkylsulfonyl chloride (1.1 equiv.), rt, 24 h. R* = R⁴ and/or R⁵.

	R ¹	R ²	R ³	R ⁴	R ⁵	Product	Yield [%]
1	MeO-		Ph-		H-	8a	50
2	MeO-		Ph-		H-	8b	77
3	MeO-		Ph-		H-	8c	61
4	MeO-		Ph-		H-	8d	75
5	MeO-		Ph-		H-	8e	66
6	MeO-		Ph-		H-	8f	88
7	MeO-		Ph-		H-	8g	85
8	MeO-		Ph-		H-	8h	51
9	MeO-		Ph-		H-	8i	87
10	MeO-		Ph-		H-	8j	50
11	MeO-		Ph-		H-	8k	59
12	MeO-	H-			H-	8l	78
13	MeO-	H-			H-	8m	75
14	MeO-	H-			H-	8n	63
15	MeO-	H-			H-	8o	57
16	MeO-	H-				8p	20
17	AcNH-	H-			H-	8q	50
18	AcNH-	H-		Cbz-	H-	8r	30

TABLE 4

ELISA assays for selected 4-ATQs.^{25,26} Primary assays: (a) GLP-1 secretion from mouse secretin tumor (mSTC-1) intestinal enteroendocrine cells (mSTC-1 GLP1 Sec) with percent stimulation determination at 20 μ M and 2 μ M concentration of test compound. (b) Concentration–response curve (CRC) based determination of the concentration that produces a half-maximum response (EC_{50}) in GLP-1 secretion from mSTC-1 cells (mSTC-1 GLP1 Sec). (c) CRC-based determination of EC_{50} in GLP-1 release from a human cell line derived from ascites fluid of a colorectal adenocarcinoma (hNCI-H716 GLP1 Sec CRC). (d) Cytolethality counter assay measuring leakage of lactate dehydrogenase (LDH) from mSTC-1 cells (mSTC-1 LDH Sec). (e) Cytolethality counter assay measuring LDH leakage from hNCI cells (Basal hNCI LDH Sec). Secondary assay: GLP-1 secretion in a cell line derived from colonic tumors of transgenic mice expressing large T antigen under the control of the *proglucagon* promoter (GLUTag GLP1 Sec). ND = not determined.

Entry	Compound	mSTC-1 GLP1 Sec %Stim@20 μ M/2 μ M	mSTC-1 GLP1 Sec CRC EC_{50} [μ M]	hNCI-H716 GLP1 Sec CRC EC_{50} [μ M]	mSTC-1 LDH Sec EC_{50} [μ M]	Basal hNCI LDH Sec EC_{50} [μ M]	GLUTag GLP1 Sec %Stim@10 μ M
1	5a	68/2	5.3	>40	>40	>40	ND
2	5b	98/0	10.8	>40	>40	>40	ND
3	5c	53/0	17.2	>40	>40	>40	ND
4	5d	91/25	1.4	>40	>40	>40	6
5	5e	0	ND	ND	ND	ND	ND
6	5f	22/0	ND	ND	ND	ND	ND
7	6a	40/8	>40	>40	>40	>40	ND
8	6c	0	ND	ND	ND	ND	ND
9	6g	0	ND	ND	ND	ND	ND
10	8d	28/0	>40	>40	>40	>40	ND
11	8e	0	ND	ND	ND	ND	ND
12	8f	0	ND	ND	ND	ND	ND
13	8i	0	ND	ND	ND	ND	ND
14	8j	0	ND	ND	ND	ND	ND
15	8k	53/0	8.3	>40	>40	>40	ND
16	8l	0	ND	ND	ND	ND	ND
17	8m	0	ND	ND	ND	ND	ND
18	8n	49/0	26.1	>40	>40	>40	ND
19	8o	61/0	16.9	>40	>40	>40	ND
20	8p	80/0	21.9	>40	>40	>40	ND
21	8q	18/0	ND	ND	ND	ND	ND
22	9	99/82	2.2	>40	>40	>40	ND

A Suzuki coupling with compound **5d**¹⁰ was attempted with phenylboronic acid in the presence of $Pd(OAc)_2$, $P(o-Tol)_3$ and K_2CO_3 ; the desired product **9** was achieved in 94% yield (Figure 2).

Treatment options for type 2 diabetes mellitus are still limited, and small molecules that are able to regulate glucose homeostasis and stimulate the maturation of insulin-secreting β -cells without causing hypoglycemia or damage to the cardiovascular system would be highly beneficial. In particular, glucagon-like peptide-1 (GLP-1) secretagogues are currently under active early stage and clinical development.²⁴ An ELISA-based primary screen for GLP-1 secretagogue activity²⁵ was performed on our 4-ATQ library as part of the Open Innovation Drug Discovery Program (OIDD) at Eli Lilly & Co (Table 4).²⁶ Among the 22 test compounds, 13 (59%) increased the secretion of GLP-1 from mouse secretin tumor intestinal enteroendocrine cells (mSTC-1 cells) at least by 15% at 20 μ M concentration, and 2 compounds, **5d** and **9**, provided a 25% and 82% increase, respectively, even at 2 μ M. Significantly, **5d** and **9** are structurally closely related, only differing by a bromine vs phenyl substituent at the 6-position of the quinoline ring.

Determination of the EC₅₀ of the 11 most active analogs established a structure-activity relationship (SAR) in this series, confirming the remarkable activity of **5d** and **9** with EC₅₀ values of 1.4 μ M and 2.2 μ M, respectively. Two additional analogs, **5a** and **8k**, had EC₅₀ values below 10 μ M. Compound **5a** shares the structural characteristics of **5d** and **9**, whereas **8k** represents a different chemotype. While none of the hits from the mSTC-1 assay increased GLP-1 secretion in the hNCI-H716 colorectal adenocarcinoma cell line, cytotoxicity counterassays in both mSTC-1 and hNCI-H716 cells confirmed the absence of general toxicity in this compound series. Finally, a secondary GLP-1 secretion assay for the most potent analog, **5d**, in the GLUTag cell line suggested a modest 6% stimulation at 2 μ M concentration. Overall, these assays establish the 4-ATQ library as a viable platform for the discovery of bioactive lead structures and reveal for the first time the ability of this chemotype to act as a novel small molecule GLP-1 secretagogue.

CONCLUSION

We have successfully utilized a chiral phosphoric acid-catalyzed three-component Povarov reaction to prepare a series of enantioenriched 4-aminotetrahydroquinolines in up to 92% yield and in an enantiomeric ratio of up to 99:1. The heterocyclic scaffolds were subjected to further functionalizations with the goal to obtain a library of densely substituted, sterically preorganized 4-ATQ derivatives. For example, the aniline nitrogen in the 4-ATQ core was alkylated with alkyl bromides or converted to an urea with isocyanates. Amide couplings, sulfonylations, and reductive aminations were successfully utilized for derivatization of the C(4) amine moiety. Furthermore, we demonstrated the possibility to functionalize the benzene ring of 4-ATQs via a Suzuki cross coupling. The potential of the 4-ATQ scaffold to provide viable lead structures for drug discovery studies was demonstrated in a diabetes phenotype assay and cell based cytotoxicity counterassays. These biological studies established for the first time the structure-activity relationship of 4-ATQs as small molecule GLP-1 secretagogues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

REFERENCES AND NOTES

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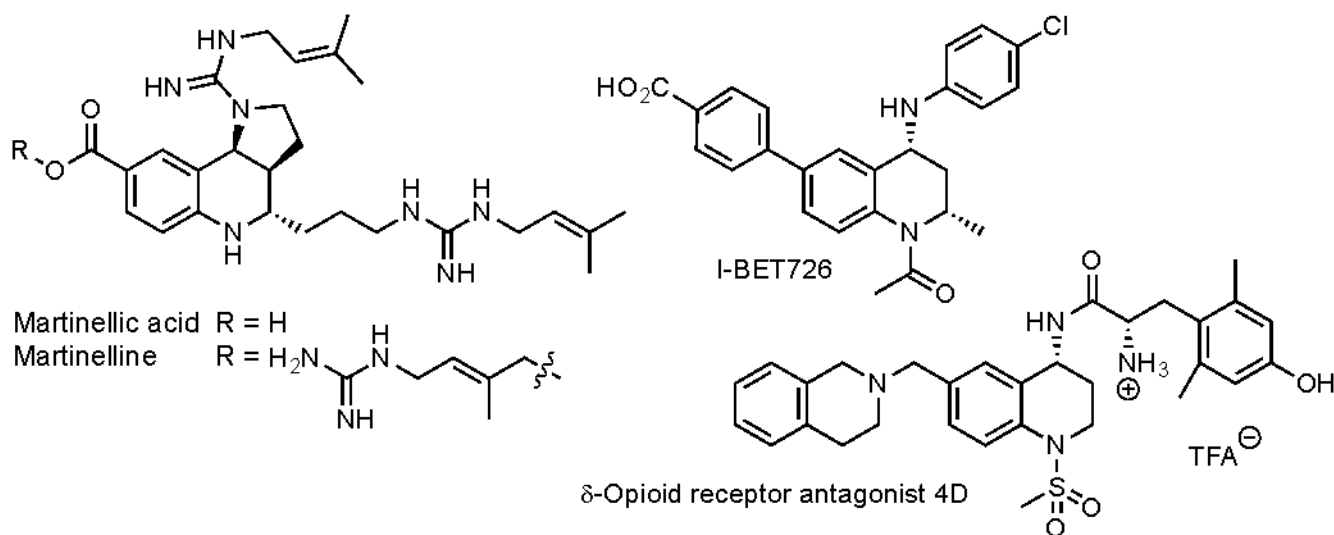
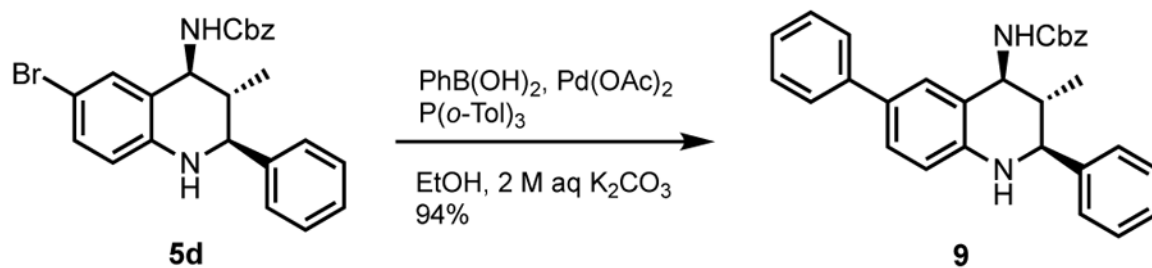


FIGURE 1.
Structures of Martinellic acid, Martinelline, I-BET726, and compound 4D

**FIGURE 2.**

Reagents and conditions to functionalize 4-ATQs with a Suzuki coupling: (i) **5d** (1 equiv.), PhB(OH)_2 (1.3 equiv.), P(o-Tol)_3 (0.01 equiv.), Pd(OAc)_2 (0.01 equiv.), 2 M aq. K_2CO_3 , toluene/EtOH, 80 °C, 10 h