Supporting Information

Discovery of AZD6642, an inhibitor of 5-Lipoxygenase Activating Protein (FLAP) for the treatment of inflammatory diseases

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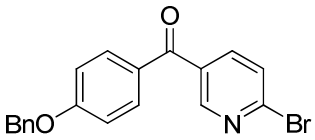
Chemistry Section

General Chemistry

All solvents and reagents were obtained from commercially available sources and used without further purification. The microwave syntheses were performed in a Biotage initiator with an external surface IR probe. Flash column chromatography was carried out on prepacked silica gel columns supplied by Biotage and using Biotage automated flash systems with UV detection. Analytical HPLC/MS was conducted on a QTOF mass spectrometer using a UV detector monitoring either at (a) 210 nm with a BEH C18 column (2.1 × 100 mm, 1.7 μm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium carbonate buffer pH 10) to 98% v/v CH_3CN in H_2O or at (b) 230 nm with an HSS C18 column (2.1 × 100 mm, 1.8 μm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium formate buffer pH 3) to 98% v/v CH_3CN in H_2O. All tested compounds were determined to be ≥95% pure using the analytical method (a) or (b) described above based on the peak area percentage. Preparative HPLC was performed by either a Waters Fraction Lynx with ZQ MS detector on either a Waters Xbridge C18 OBD 5 μm column (19 × 150 mm, flow rate 30 mL/min, or 30 × 150 mm, flow rate 60 mL/min) using a varying gradient of MeCN with 0.2% NH_3 at pH 10 or a Waters SunFire C18 OBD 5 μm column (19 × 150 mm, flow rate 30 mL/min, or 30 × 150 mm, flow rate 60 mL/min) using a varying gradient of MeCN with 0.1 M HCO_2H or on a Gilson Preparative HPLC with a UV/VIS detector 155 on a Kromasil C8 10 μm column (20 × 250 mm, flow rate 19 mL/min, or 50 × 250 mm, flow rate 100 mL/min) using a varying gradient of MeCN with 0.1 M HCO_2H or 0.1 M acetic acid. ^1H NMR and ^{13}C spectra were recorded on a Bruker Avance II or III spectrometer at a proton frequency of 300, 400, 500, or 600 MHz at 25 °C. Chemical shifts (δ) are given in parts per million (ppm), with the residual solvent signal used as a reference. Coupling constants (J) are reported as Hz. NMR abbreviations are used as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

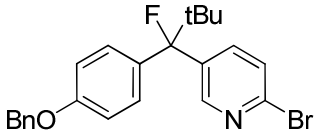
Experimental Section



[4-(Benzyloxy)phenyl](6-bromopyridin-3-yl)methanone (1).

Step 1: 6-Bromopyridine-3-carboxylic acid (354 g, 1.75 mol) was suspended in 2-Me-THF (2.5 L) at rt and CDI (284 g, 1.75 mol) was added in portions. After 1.5 h DIPEA (460 mL, 2.63 mol) was added followed by *N,O*-dimethylhydroxylamine hydrochloride (171 g, 1.75 mol, finely grounded). The resulting reaction mixture was stirred overnight. The reaction mixture was washed with 10% citric acid solution (2 x 1 L, until pH ~3) 10% aqueous Na_2CO_3 solution (375 mL) and finally water. The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give 6-bromo-*N*-methoxy-*N*-methylpyridine-3-carboxamide as an oil (289 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.70 (m, 1H), 7.85 (dd, *J* = 2.4, 8.3 Hz, 1H), 7.50 (dd, *J* = 0.7, 8.3 Hz, 1H), 3.50 (s, 3H), 3.32 (s, 3H); MS *m/z* 245 $(M+H)^+$.

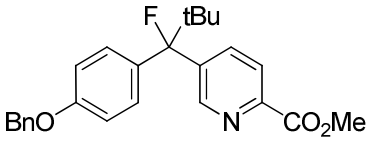
Step 2: 1-(Benzyloxy)-4-bromobenzene (202 g, 769 mmol), 20% solution in THF, was heated with magnesium scrapings (26 g, 1.11 mol) to 60 °C for 2 h to produce a Grignard reagent. 6-Bromo-N-methoxy-N-methylpyridine-3-carboxamide (173 g, 769 mmol), prepared as described above, was dissolved in THF (850 mL). The Grignard solution was added to the 6-bromo-N-methoxy-N-methylpyridine-3-carboxamide solution at 20-30 °C over a period of 1.75 h. After completion the resulting mixture was cooled to 0 °C and left overnight. The reaction mixture was worked up using CH_2Cl_2, washed with 2x1.5 L citric acid, saturated $NaHCO_3$ (aq), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give compound **1** (234 g, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.2 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.46 (m, 4H), 7.33 – 7.38 (m, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 2H); MS *m/z* 368 $(M+H)^+$.



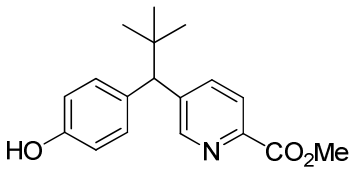
5-{1-[4-(Benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}-2-bromopyridine (2).

Step 1*:* tert-Butylmagnesium chloride (274 mL, 274 mmol) was added dropwise at rt to a solution of (4-(benzyloxy)phenyl)(6-bromopyridin-3-yl)methanone (43 g, 117 mmol) in THF (860 mL) via a syringe pump (73 mL/h). The reaction was quenched with saturated NH_4Cl (aq) (400 mL). The mixture was diluted with CH_2Cl_2, filtrated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was recrystallised from toluene to give 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-2,2-dimethylpropan-1-ol as a yellow/white solid (21g, 41 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.1 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.4 Hz, 1H), 7.31 – 7.46 (m, 8H), 6.87 – 6.92 (m, 2H), 5.04 (s, 2H), 1.14 (s, 9H); MS *m/z* 426.0 (M+H)+.

Step 2*:* DAST (83 g, 0.51 mol) was added dropwise to a stirred solution of 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-2,2-dimethylpropan-1-ol (80 g, 0.19 mol) in CH_2Cl_2 (1 L) and $CHCl_3$ (120 mL) at 0 °C. The resulting mixture was stirred at rt for 4 h, then quenched by the addition of water. The combined organic layer was washed with saturated $NaHCO_3$ (aq) and brine, dried, filtered and concentrated. The residue was recrystallised from EtOH to give compound **2** as a solid (65 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.5 Hz, 1H), 7.68 (dd, *J* = 2.6, 8.4 Hz, 1H), 7.30 – 7.47 (m, 8H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.05 (s, 2H), 1.13 (s, 9H); MS *m/z* 430.0 (M+H)+.



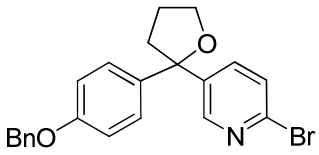
Methyl 5-{1-[4-(benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}pyridine-2-carboxylate (3). CO (g) was bubbled to a solution of compound **2** (65 g, 0.15 mol) in DMF-MeOH-Et_3N (5:5:1, 880 mL) for 10 min. Pd(dppf)Cl_2 (12 g, 0.015 mol) was added and the mixture was heated at 70 °C under CO-atmosphere (30 PSI) for 3 h. The solvents were evaporated and the residue was partitioned between CH_2Cl_2 and water. The organic phase was separated, dried and concentrated. The crude product was purified by flash column chromatography (10→33% EtOAc in petroleum ether) to give compound **3** (60 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.04 (dd, *J* = 7.4, 40.8 Hz, 2H), 7.28 – 7.51 (m, 7H), 6.94 (d, *J* = 7.6 Hz, 2H), 5.05 (s, 2H), 4.00 (s, 3H), 1.12 (s, 9H); MS *m/z* 408.6 (M+H)+.



Methyl 5-(*R* and *S*)-[1-(4-hydroxyphenyl)-2,2-dimethylpropyl]pyridine-2-carboxylate [(+)-4 and (-)-4]. A solution of compound **3** (300 mg, 0.74 mmol), ammonium formate (131 mg, 2.21 mmol) and palladium hydroxide (20% on activated carbon, 100 mg) in MeOH (2 mL) and THF (2 mL) was heated at 120 °C using micro-wave irradiation for 30 min. The catalyst was then filtered off (Celite) and was washed with EtOAc, and MeOH. The filtrate was concentrated *in vacuo* and the crude product was suspended in EtOAc and 5% citric acid (aq) was added until a clear solution was obtained. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried and concentrated to give compound **4** (222 mg, 100%,). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 3.98 (s, 3H), 3.75 (s, 1H), 1.00 (s, 9H); MS *m/z* 300.3 (M+H)+.

The enantiomers of compound **4** (1.86 g, 7.57 mmol) were separated by chiral chromatography on a Kromasil AmyCoat OJ 250x30 mm, 5 μm HPLC column. 87 mg (35 mg/ml in EtOH) was injected and eluted with 15% EtOH in CO_2 at a flow rate of 130 mL/min

and detected at 254 nm. The first eluted compound was collected and evaporated to give compound (+)-**4** (850 mg, 99.8 % ee). $[\alpha]_D^{20}$: +18 (*c* 1.0, $CHCl_3$). The second eluted compound was collected and evaporated to give compound (-)-**4** (808 mg, 99.9 % ee). $[\alpha]_D^{20}$: -22 (*c* 1.0, $CHCl_3$), which was used to synthesise the most active isomer of compound **12**.

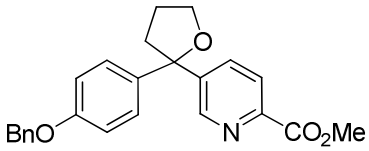


5-{2-[4-(Benzyloxy)phenyl]tetrahydrofuran-2-yl}-2-bromopyridine (5). Isopropyl magnesium chloride (2 M in THF, 70.6 mL, 141.2 mmol) was added carefully to a slurry of dry 3-chloro-*N,N*-dimethylpropan-1-amine hydrochloride (18.03 g, 114.1 mmol) in THF (135 mL). Magnesium turnings (3.7 g, 152.1 mmol), activated with iodine (1.45 g, 5.7 mmol) and gently heated with a heat gun, was added and the reaction mixture was heated at reflux for 1.5 h. The formed Grignard reagent was decanted into a mixture of compound **1** (20.0 g, 54.3 mmol) in THF (315 mL). After 1.5 h the reaction was quenched by addition of saturated NH_4Cl (aq) (~10 mL) and the mixture was concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and saturated $NaHCO_3$ (aq), and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried (phase separator/Na_2SO_4) and concentrated *in vacuo* to give crude 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-4-(dimethylamino)butan-1-ol (24.44 g, 99%), which was used without further purifications. MS *m/z* 455 $(M+H)^+$.

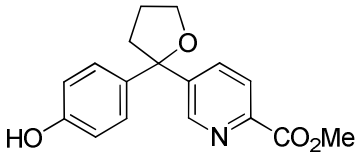
Sodium hydride in mineral oil (60% in mineral oil, 7.08 g, 177.11 mmol) was added to a solution of crude 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-4-(dimethylamino)butan-1-ol (24.44 g, 53.67 mmol), prepared as above, in *p*-xylene (350 mL). The reaction mixture was heated to reflux and kept at that temperature for 10 min, then 1-bromobutane (14.71 mL, 139.54 mmol) was added and the reaction heated at reflux for 1 h. The reaction mixture was allowed to reach rt and the reaction was then quenched by addition of 3.8 M HCl (aq) (~5 mL). The mixture was then concentrated *in vacuo*. The residue was partitioned between EtOAc and saturated NaCl (aq) with a pH adjusted to ~5 using 3.8 M HCl (aq). The organic phase was washed with saturated NH_4Cl (aq) and saturated NaCl (aq), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (0→20% EtOAc in heptane) to give compound **5** (16.42 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 – 8.45 (m, 1H), 7.57 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.36 – 7.44 (m, 5H), 7.28 – 7.35 (m, 3H), 6.9 – 6.96 (m, 2H), 5.04 (s, 2H), 4.04 (t, *J* = 7.1 Hz, 2H), 2.55 – 2.65 (m, 1H), 2.39 – 2.48 (m, 1H), 1.89 – 2.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 147.8, 141.7, 140.3, 137.1, 136.9, 136.5, 128.6, 128.0, 127.5, 127.4, 126.9, 114.7, 86.0, 70.0, 67.6, 38.6, 25.4; MS *m/z* 410 $(M+H)^+$.

5-{(2*R* and *S*)-2-[4-(Benzyloxy)phenyl]tetrahydrofuran-2-yl}-2-bromopyridine [(−)-5 and (+)-5]. The enantiomers of compound **5** (2.90 g, 7.08 mmol) were separated by chiral

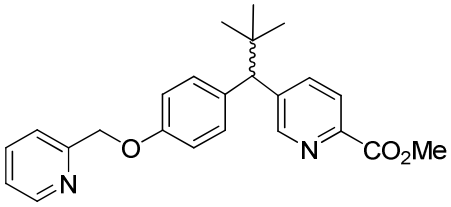
chromatography on a Lux C2 250x30 mm, 5 µm SFC column. 300 mg (150 mg/ml in CH_2Cl_2:EtOH 1:3) was injected and eluted with 25% EtOH in CO_2, 120 bar at 40 °C, a flow rate of 80 mL/min and detected at 260 nm. The first eluted compound was collected and evaporated to give compound (−)-**5** (1.30 g, 99.9% ee). $[\alpha]_D^{20}$: −12 (*c* 1.0, $CHCl_3$). The second eluted compound was collected and evaporated to give compound (+)-**5** (1.40 g, 97.2% ee). $[\alpha]_D^{20}$: +12 (*c* 1.0, $CHCl_3$).



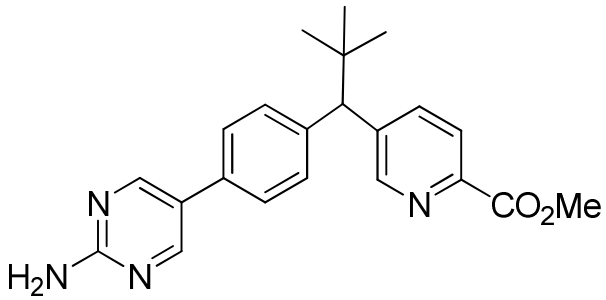
Methyl 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylate (6). CO(g) was bubbled through a stirred solution of compound **5** (7.00 g, 17.06 mmol) in DMF (100 mL), MeOH (100 mL) and Et_3N (20 mL) at rt for 10 min. $PdCl_2$(dppf) (1.75 g, 2.17 mmol) (complex with CH_2Cl_2 1:1) was then added and the mixture was heated at 70 °C under CO-atmosphere (balloon) overnight. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 and saturated NaCl (aq). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was dried (phase separator) and concentrated *in vacuo*. The residue was purified by flash column chromatography (0→30% EtOAc in toluene) to give compound **6** (4.71 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.34 – 7.42 (m, 4H), 7.28 – 7.33 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 2H), 4.04 (t, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 2.59 – 2.69 (m, 1H), 2.42 – 2.51 (m, 1H), 1.88 – 2.06 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 158.0, 147.6, 146.1, 146.0, 136.9, 136.8, 134.3, 128.9, 128.6, 128.0, 127.4, 127.0, 124.7, 114.7, 114.6, 86.2, 70.0, 67.6, 52.8, 38.6, 25.4; MS m/z 390 $(M+H)^+$.



Methyl 5-[2-(4-hydroxyphenyl)tetrahydrofuran-2-yl]pyridine-2-carboxylate (7). Ammonium formate (1.02 g, 16.18 mmol) and $Pd(OH)_2$ (20% on activated carbon, 0.38 g, 0.54 mmol) were added to a solution of compound **6** (1.05 g, 2.70 mmol) in MeOH (60 mL) and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc) to give compound **7** (0.69 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.01 – 4.09 (m, 2H), 3.97 (s, 3H), 2.59 – 2.70 (m, 1H), 2.38 – 2.49 (m, 1H), 1.94 (dd, *J* = 6.3, 13.2 Hz, 2H); MS *m/z* 300 $[M+H]^+$.



Methyl 5-{(1*R* or 1*S*)-2,2-dimethyl-1-[4-(pyridin-2-ylmethoxy)phenyl]propyl}pyridine-2-carboxylate (8). 2-(Chloromethyl)pyridine hydrochloride (1.12 g, 6.81 mmol) and potassium iodide (0.63 g, 3.78 mmol) were added to a solution of compound **(−)-4** (1.13 g, 3.78 mmol) in DMF (40 mL). After stirring for 18 h, the reaction mixture was partioned between water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layer was filtered through a phase separator and evaporated. The residue was purified by flash column chromatography (50→80% EtOAc in heptane) to give compound **8** (1.12 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.64 (d, *J* = 4.7 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.26 (s, 2H), 4.03 (s, 3H), 3.81 (s, 1H), 1.05 (s, 9H); MS m/z 391.5 $(M+H)^+$.

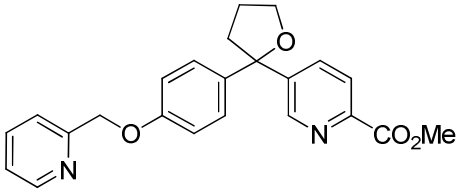


Methyl 5-{1-[4-(2-aminopyrimidin-5-yl)phenyl]-2,2-dimethylpropyl}pyridine-2-carboxylate (9). Trifluoromethanesulfonic anhydride (0.084 mL, 0.50 mmol) was added to a solution of compound **4** (100 mg, 0.33 mmol) in CH_2Cl_2 (8 mL) and pyridine (0.057 mL, 0.67 mmol) at 0 °C. The resulting mixture was stirred at rt. The reaction mixture was diluted with Et_2O and washed with $NaHCO_3$ (aq) and brine, filtered through a phase separator and concentrated to give crude methyl 5-[2,2-dimethyl-1-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propyl]pyridine-2-carboxylate (142 mg, 99%). MS m/z 432.4 $(M+H)^+$

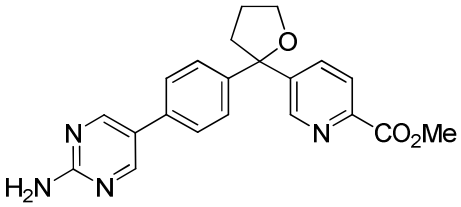
To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (131 mg, 0.59 mmol) and crude methyl 5-[2,2-dimethyl-1-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propyl]pyridine-2-carboxylate (142 mg, 0.33 mmol) in DME (1 mL), EtOH (0.5 mL) and water (0.5 mL) was added potassium phosphate (126 mg, 0.59 mmol) and $PdCl_2$(dppf) (17 mg, 0.02 mmol). The resulting mixture was heated in a microwave reactor for 25 min at 135 °C. The catalyst was then filtered off and the filtrate was concentrated *in vacuo* and the crude product was purified by preparative HPLC (Kromasil C8, 15→70% CH_3CN in 0.2% HCO_2H (aq)) to give compound **9** (17 mg, 14%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.51 (s, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.56 (m, 4H), 3.99 (s, 3H), 3.86 (s, 1H), 1.06 (s, 9H); MS m/z 377.4 $(M+H)^+$,

as well as **5-{1-[4-(2-Aminopyrimidin-5-yl)phenyl]-2,2-dimethylpropyl}pyridine-2-carboxylic acid** (53 mg, 44%). ^1H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.53 (s, 2H), 8.13 – 8.23 (m, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.54 (s, 4H), 6.72 (s, 2H), 4.04 (s, 1H), 0.98 (s, 9H).); MS m/z 363.4 $(M+H)^+$.

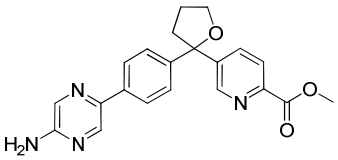


Methyl 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylate (10). Potassium iodide (0.80 g, 4.84 mmol) was added to a suspension of compound **7** (1.45 g, 4.84 mmol), 2-(chloromethyl)pyridine hydrochloride (1.43 g, 8.72 mmol), and potassium carbonate (2.14 g, 15.50 mmol) in DMF (45 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was diluted with water and the solution was extracted with EtOAc (x3). The combined organic phase was washed with brine (x3) and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (0→10% of EtOH in EtOAc) to give compound **10** (1.30 g, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.7 Hz, 1H), 8.58 (d, *J* = 4.2 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.70 (ddd, *J* = 1.7, 7.7, 7.7 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.33 (m, 2H), 7.19 – 7.24 (m, 1H), 6.89 – 6.94 (m, 2H), 5.18 (s, 2H), 4.04 (t, *J* = 7.1, 7.1 Hz, 2H), 3.97 (s, 3H), 2.64 (dt, *J* = 7.4, 7.4, 12.4 Hz, 1H), 2.43 – 2.51 (m, 1H), 1.87 – 2.06 (m, 2H); MS *m/z* 391 $[M+H]^+$.

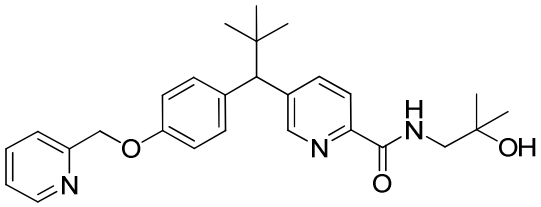


Methyl 5-{2-[4-(2-aminopyrimidin-5-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylate (11a) Trifluoromethanesulfonic anhydride (1.28 mL, 7.60 mmol) was slowly added to a solution of compound **7** (1.75 g, 5.85 mmol) and DMAP (3.57 g, 29.23 mmol) in CH_2Cl_2 (60 mL) at -78°C. The reaction mixture was stirred at -78 °C for 5 h and then added to a solution of saturated $NaHCO_3$ (aq) (200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic phase was dried by passing through a phase-separator and then evaporated *in vacuo*. The residue was purified by flash column chromatography (20→80% EtOAc in heptane) to give methyl 5-[2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)tetrahydrofuran-2-yl]pyridine-2-carboxylate (2.0 g, 79%). MS *m/z* 433 $(M+H)^+$.

Potassium phosphate (171 mg, 0.81 mmol) dissolved in water (1.7 mL) and Pd(dppf)Cl_2 (66 mg, 0.08 mmol) were added to a solution of methyl 5-[2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)tetrahydrofuran-2-yl]pyridine-2-carboxylate (175 mg, 0.41 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (103 mg, 0.46 mmol) in a mixture of DME (5.1 mL) and EtOH (1.70 mL). The mixture was heated in a microwave reactor at 140 °C for 10 min. The mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 and brine. The organic phase was dried by passing through a phase-separator and concentrated *in vacuo*. The residue was purified by preparative HPLC (Kromasil C8, 15→55% CH_3CN in 0.2% HCO_2H (aq)) to give compound **11a** (63 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.48 (s, 2H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.90 (dd, *J* = 6.4 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 5.29 (s, 2H), 4.09 (t, *J* = 7.0, 7.0 Hz, 2H), 3.98 (s, 3H), 2.64 – 2.74 (m, 1H), 2.52 – 2.61 (m, 1H), 1.91 – 2.08 (m, 2H); MS *m/z* 377 $(M+H)^+$.



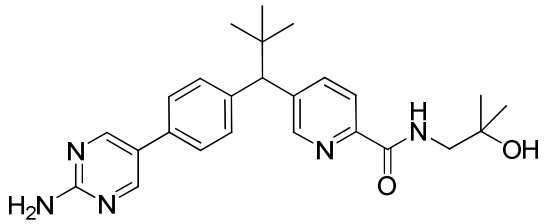
Methyl 5-{2-[4-(5-aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylate (**11b**). Compound **11b** was prepared according to the procedure described for compound **15b** starting from compound **7**. (280 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 – 8.89 (m, 1H), 8.33 – 8.39 (m, 1H), 8.11 (s, 1H), 8.03 – 8.08 (m, 1H), 7.90 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.78 – 7.84 (m, 2H), 7.46 – 7.54 (m, 2H), 4.11 – 4.17 (m, 2H), 3.98 (s, 3H), 2.48 – 2.76 (m, 2H), 1.90 – 2.04 (m, 2H); MS *m/z* 377.3 $(M+H)^+$.



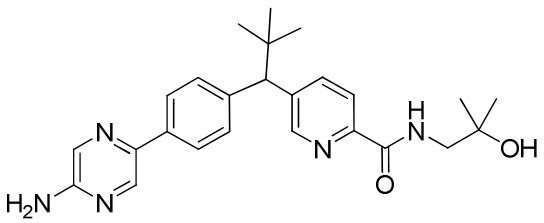
5-{(1*R* or 1*S*)-2,2-Dimethyl-1-[4-(pyridin-2-ylmethoxy)phenyl]propyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (12). A solution of lithium hydroxide (0.026 g, 1.10 mmol) in water (1.2 mL) was added to a solution of compound **8** (0.36 g, 0.92 mmol) in THF (3 mL) and MeOH (3 mL). The reaction mixture was stirred at room temperature overnight (~14 h) and at 40 °C for 1.5 h. Additional lithium hydroxide (9 mg, 0.37 mmol) was added and the reaction mixture was stirred at 40 °C for 1h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between EtOAc and 5% citric acid (aq). The aqueous phase was extracted with EtOAc (x3) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give crude 5-{2,2-dimethyl-1-[4-(pyridin-2-ylmethoxy)phenyl]propyl}pyridine-2-carboxylic acid (0.35 g, 100%). MS *m/z* 377.1 $(M+H)^+$.

TBTU (384 mg, 1.20 mmol) was added to a solution of crude 5-{2,2-dimethyl-1-[4-

(pyridin-2-ylmethoxy)phenyl]propyl}pyridine-2-carboxylic acid (346 mg, 0.92 mmol), 1-amino-2-methylpropan-2-ol (246 mg, 2.76 mmol) and 4-methylmorpholine (202 μL, 1.84 mmol) in DMF (7 mL) and CH_2Cl_2 (7 mL). The reaction mixture was stirred at rt for 3 h. Additional 4-methylmorpholine (101 μL, 0.92 mmol), 1-amino-2-methylpropan-2-ol (123 mg, 1.38 mmol) and TBTU (177 mg, 0.55 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction mixture was then partially evaporated and the residue was partitioned between EtOAc and saturated NH_4Cl (aq). The organic phase was washed with saturated $NaHCO_3$ (aq), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (XBridge C18, 35→100% CH_3CN in 0.2% NH3(aq)) to give compound **12** (256 mg, 62 %, 99.9%ee). $[\alpha]_D^{20}$: +1 (*c* 8.3, CH_3CN); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.7 Hz, 1H), 8.55 (d, *J* = 1.7 Hz, 1H), 8.33 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.19 – 7.24 (m, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.18 (s, 2H), 3.74 (s, 1H), 3.41 – 3.50 (m, 3H), 2.50 (s, 1H), 1.27 (s, 6H), 1.00 (s, 9H); MS m/z 448.4.4 $(M+H)^+$.



5-{1-[4-(2-Aminopyrimidin-5-yl)phenyl]-2,2-dimethylpropyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (13a). TBTU (26 mg, 0.08 mmol) was added to a solution of 5-{1-[4-(2-aminopyrimidin-5-yl)phenyl]-2,2-dimethylpropyl}pyridine-2-carboxylic acid (isolated as a by-product in the preparation of compound **9**) (25 mg, 0.07 mmol), 1-amino-2-methylpropan-2-ol (12 mg, 0.14 mmol) and 4-methylmorpholine (0.015 mL, 0.14 mmol) in DMF (2 mL). The reaction mixture was stirred at rt overnight, concentrated *in vacuo* and the crude product was purified by preparative (XBridge C18, 15→65% CH_3CN in 0.2% NH_3 (aq)) to give compound **13a** (16 mg, 54 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.51 (s, 2H), 8.35 (s, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.54 (m, 4H), 5.09 (s, 2H), 3.85 (s, 1H), 3.47 (d, *J* = 4.0 Hz, 2H), 2.49 (s, 1H), 1.28 (s, 6H), 1.07 (s, 9H); MS m/z 434.4 $(M+H)^+$.



5-{(2*R* and *S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (13b and 13b′). 1,1,1-Trifluoro-*N*-phenyl-*N*-

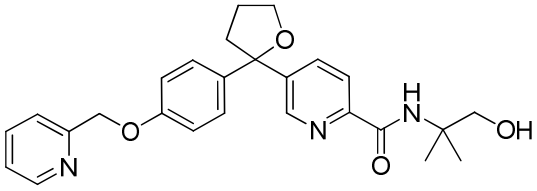
[(trifluoromethyl)sulfonyl]methanesulfonamide (11 g, 0.03 mol) was added to a solution of compound **16** (8.0 g, 0.023 mol), Et_3N (4.0 g, 0.04 mol) and DMAP (0.30 g, 2.4 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The resulting mixture was warmed up to rt gradually and stirred for 4 h, then quenched with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$ (aq) and brine, filtered and concentrated. The residue was purified by flash column chromatography (10:1→2:1, petroleum ether:EtOAc) to give 4-(1-{6-[(2-hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}-2,2-dimethylpropyl)phenyl trifluoromethanesulfonate (8.0 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.9 Hz, 1H), 8.27 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 1H), 3.40 (d, *J* = 6.4 Hz, 2H), 2.38 (s, 1H), 1.21 (s, 6H), 0.96 (s, 9H).

Potassium acetate (10 g, 0.1 mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.0 g, 0.03 mol) and $PdCl_2$(dppf) (4.0 g, 4.9 mmol) were added to a solution of 4-(1-{6-[(2-hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}-2,2-dimethylpropyl)phenyl trifluoromethanesulfonate (8.0 g, 0.02 mol) in degassed dioxane (200 mL) under N_2. The reaction mixture was heated at reflux for 3 h and was then partitioned between EtOAc and H_2O, filtered (Celite).The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried and concentrated to give 5-{2,2-dimethyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (11.5g) which was used in the next step without futher purification.

A solution of potassium carbonate (6.8g, 49.2 mmol) in degassed water (60 mL) was added to a solution of a 5-{2,2-dimethyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (0.02 mol), bromopyrazin-2-amine (5.0 g, 0.03 mol) and $PdCl_2$(dppf) (2.0 g, 2.5 mmol) in dioxane (150 mL). The reaction mixture was heated at reflux for 3 h and the reaction mixture was then partitioned between EtOAc and H_2O then filtered (Celite). The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phase was dried and concentrated and the residue was purified by flash column chromatography (10:1→1:1, petroleum ether:EtOAc) to give the racemate of the title compounds as a yellow solid (3.28 g, 43 %).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.9 Hz, 1H), 8.43 (d, *J* = 1.5 Hz, 1H), 8.36 (t, *J* = 6.25 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 1.5 Hz, 1H), 7.99 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.61 (s, 2H), 3.86 (s, 1H), 3.41 – 3.54 (m, 2H), 2.56 (s, 1H), 1.29 (s, 6H), 1.07 (s, 9H); MS *m/z* 433.2476 $(M+H)^+$.

The enantiomers (3.28 g, 7.57 mmol) were separated by chiral chromatography on a Chiralpak OJ 250x50 mm, 20 μm HPLC column. 245 mg (70 mg/ml in EtOH/MeOH 1/1) was injected and eluted with EtOH/MeOH/Et_3N 50/50/0.1 at a flow rate of 110 mL/min and detected at 320 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (**13b´**) (1.60 g, 99 % ee). $[\alpha]_D^{20}$: −33 (*c* 1.0, CH_3OH); HRMS (ESI) *m/z* calcd for $C_{25}H_{31}N_5O_2$ $[M + H]^+$ 434.2556; found 434.2575. The second eluted compound was collected and evaporated to give the most active enantiomer (**13b**) (1.60 g, 99 % ee). $[\alpha]_D^{20}$:

+34 (*c* 1.0, CH_3OH). HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_5O_2$ $[M + H]^+$ 434.2551; found 434.2549.

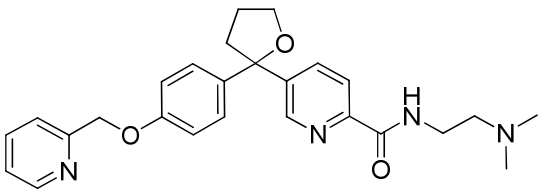


***N*-(1-Hydroxy-2-methylpropan-2-yl)-5-{(2*S* and *R*) 2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (14a).**

Step 1: A solution of LiOH (4.0 mL, 4.00 mmol) in water (4.8 mL) was added to a solution of compound **10** (1.3 g, 3.33 mmol) in a mixture of MeOH (12 mL) and THF (12 mL) and the resulting solution was stirred at rt for 4 h. The pH was adjusted to pH 8 by addition of 6M HCl (aq) and the reaction mixture was concentrated to give 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid as an orange solid (1.25 g, 100%). MS *m/z* 375 $[M-H]^-$.

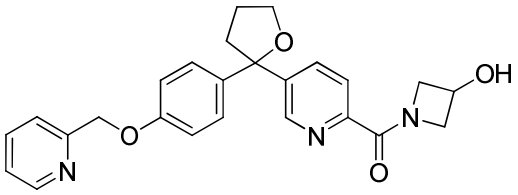
Step 2: A solution of 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (100 mg, 0.27 mmol), 2-amino-2-methylpropan-1-ol (47 mg, 0.53 mmol), TBTU (154 mg, 0.48 mmol) and DIPEA (0.14 mL, 0.80 mmol) in DMF (1 mL) was stirred at rt overnight. The reaction mixture was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq). The phases were separated by passage through a phase-separator. The organic layer was concentrated *in vacuo* and purified by preparative HPLC (Sunfire Prep C18, 5-95% ACN in a 0.1 M HCO_2H (aq)) to give the racemate of the title compounds (37 mg, 29%).

The enantiomers were separated by chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 μm HPLC column. 15 mg (15 mg/ml in EtOH) was injected and eluted with Heptane/EtOH/Et_3N 60/40/0.1 at a flow rate of 18 mL/min and detected at 265 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (12.6 mg, 99.9%ee). HRMS (ESI) *m/z* calcd for $C_{26}H_{29}N_3O_4$ $[M + H]^+$ 448.2236; found 448.2272. The second eluted compound was collected and evaporated to give the least active enantiomer (15 mg, 99.6%ee). ^1H NMR (600 MHz, $(CD_3)SO$) δ 8.66 (d, *J* = 2.1 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.17 (s, 1H), 7.97 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.81 (ddd, *J* = 1.8, 7.7, 7.7 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.33 (dd, *J* = 4.9, 6.6 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 5.13 (s, 2H), 3.94 (t, *J* = 7.5 Hz, 2H), 3.41 – 3.44 (m, 2H), 2.54 – 2.63 (m, 2H), 1.79 – 1.93 (m, 2H), 1.31 (s, 6H).



***N*-[2-(Dimethylamino)ethyl]-5-{(2*S* and *R*) *2*-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (14b).** A solution of 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (85 mg, 0.23 mmol) (prepared as described in **Step 1** of compound **14a**), N',N'-dimethylethane-1,2-diamine (60 mg, 0.68 mmol), TBTU (80 mg, 0.25 mmol) and 4-methylmorpholine (0.050 mL, 0.45 mmol) in DMF (1.5 mL) was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (XBridge C18, 16-65% CH_3CN in 0.2% NH_3 (aq)) to give the racemate of the title compounds (74 mg, 73%).

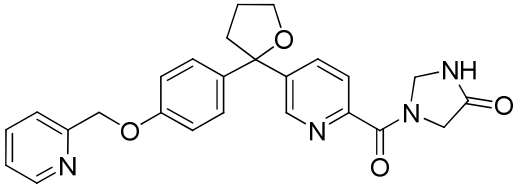
The enantiomers were separated by chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 μm HPLC column. 8 mg (20 mg/ml in IPA) was injected and eluted with Heptane/IPA/Et_3N 80/20/0.1 at a flow rate of 18 mL/min and detected at 254 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (43 mg, 99.9%ee). HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_4O_3$ $[M + H]^+$ 447.2396; found 447.2393. The second eluted compound was collected and evaporated to give the least active enantiomer (37 mg, 99.6%ee). ^1H NMR (500 MHz, CD_3OD) δ 8.69 (s, 1H), 8.61 (d, *J* = 4.1 Hz, 1H), 8.06 (t, *J* = 7.7 Hz, 1H), 7.96 – 8.04 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.58 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 2H), 3.96 – 4.1 (m, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 3.40 (t, *J* = 5.6 Hz, 2H), 2.97 (s, 6H), 2.69 (dt, *J* = 7.0, 13.2 Hz, 1H), 2.52 (dt, *J* = 7.3, 13.0 Hz, 1H), 1.91 – 2.02 (m, 2H).



(3-Hydroxyazetidin-1-yl)(5-{(2*S* and *R*) 2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)methanone (14c). A solution of 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (100 mg, 0.27 mmol) (prepared as described in **Step 1** of compound **14a**), azetidine-3-ol (39 mg, 0.53 mmol), TBTU (154 mg, 0.48 mmol) and DIPEA (0.14 mL, 0.80 mmol) in DMF (1 mL) was stirred at rt overnight. The reaction mixture was dissolved in CH_2Cl_2 and washed with a solution of saturated $NaHCO_3$ (aq). The phases were separated by passage through a phase-separator. The organic layer was concentrated *in vacuo* and purified by preparative HPLC (Sunfire Prep C18, 5-95% ACN in 0.1 M HCO_2H (aq)), to give the racemate of the title compounds (33 mg, 29%).

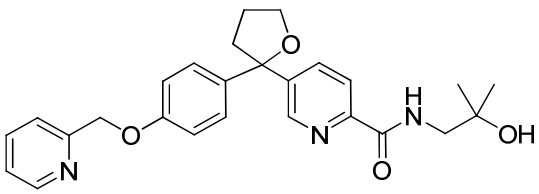
The enantiomers were separated by chiral chromatography on a Chiralpak AS 250 mm x 20 mm, 5 μm HPLC column. 20 mg (16 mg/ml in EtOH) was injected and eluted with MeOH/Et_3N 100/0.1 at a flow rate of 18 mL/min and detected at 260 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (10 mg, 99.9%ee). The second eluted compound was collected and evaporated to give the most active enantiomer (11 mg, 98%ee). HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_3O_4$ $[M + H]^+$ 432.1923;

found 432.1924. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.64 – 8.66 (m, 1H), 8.56 (d, *J* = 4.3 Hz, 1H), 7.94 (ddd, *J* = 1.8, 1.8, 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.81 (ddd, *J* = 1.7, 7.7, 7.7 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.33 (dd, *J* = 5.1, 7.3 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.68 – 5.73 (m, 1H), 5.13 (s, 2H), 4.71-4.65 (m, 1H), 4.47-4.41 (m, 1H), 4.19 – 4.28 (m, 2H), 3.88 – 3.99 (m, 2H), 3.74 – 3.78 (m, 1H), 2.57 – 2.63 (m, 1H), 1.81 – 1.9 (m, 2H).



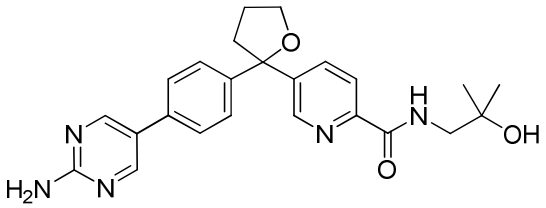
1-[(5-{(2*S* and *R*) 2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)carbonyl]imidazolidin-4-one (14d). A solution of 5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (600 mg, 1.59 mmol), (prepared as described in **Step 1** of compound **14a**), imidazolidin-4-one (412 mg, 4.78 mmol), TBTU (921 mg, 2.87 mmol) and DIPEA (0.84 mL, 4.78 mmol) in DMF (15 mL) was stirred at rt overnight. The mixture was dissolved into EtOAc and washed with a solution of saturated $NaHCO_3$, brine, a solution of saturated NH_4Cl and finally brine. The organic layer was concentrated *in vacuo* and the residue was purified by preparative HPLC (XBridge C18, 5-50% CH_3CN in 0.2% NH_3 (aq)) buffer system as mobile phase, over 30 min, with a flow of 100 mL/min, to give the racemate of the title compounds (275 mg, 39%).

The enantiomers were separated by chiral chromatography on a Chiralpak AD 250 mm x 20 mm, 5 μm HPLC column. 20 mg (50 mg/ml in IPA) was injected and eluted with Heptane/IPA 40/60 at a flow rate of 12 mL/min and detected at 262 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (103 mg, 98.7%ee). $[\alpha]_D^{20}$: +10 (*c* 1.0, CH_3CN). The second eluted compound was collected and evaporated to give the most active enantiomer (102 mg, 97.9%ee). $[\alpha]_D^{20}$: −9 (*c* 1.0, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 2.1, 15.6 Hz, 1H), 8.58 (d, *J* = 4.6 Hz, 1H), 8.01 (dd, *J* = 8.2, 20.7 Hz, 1H), 7.86 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.71 (ddd, *J* = 1.5, 7.7, 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 2.7, 8.9 Hz, 2H), 7.19 – 7.25 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 23.3 Hz, 1H), 5.51 (s, 1H), 5.18 (s, 2H), 5.12 (s, 1H), 4.62 (s, 1H), 4.23 (s, 1H), 4.01 – 4.1 (m, 2H), 2.6 – 2.7 (m, 1H), 2.41 – 2.52 (m, 1H), 1.91 – 2.07 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{25}H_{24}N_4O_4$ $[M + H]^+$ 445.1876; found 445.1905.



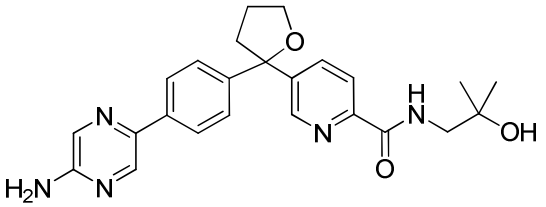
***N*-((2*R* and *S*)-2-Hydroxy-2-methylpropyl)-5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (14e).** Potassium iodide (2.58 g, 15.57 mmol) was added to a mixture of compound **17a** (5.55 g, 15.57 mmol), 2-(chloromethyl)pyridine hydrochloride (4.60 g, 28.03 mmol) and cesium carbonate (16.24 g, 49.83 mmol) in DMF (200 mL) and the reaction mixture was stirred vigorously at rt overnight. The reaction mixture was then partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with saturated NaCl (aq), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (80→100% EtOAc in heptane). The crude product was partitioned between EtOAc and water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the racemate of the title compounds (5.74 g, 82 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 0.7, 2.2 Hz, 1H), 8.59 (ddd, *J* = 0.9, 1.6, 4.8 Hz, 1H), 8.37 (t, *J* = 6.2 Hz, 1H), 8.11 (dd, *J* = 0.7, 8.2 Hz, 1H), 7.88 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.68 – 7.75 (m, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.36 (m, 2H), 7.20 – 7.25 (m, 1H), 6.91 – 6.98 (m, 2H), 5.19 (s, 2H), 4.03 – 4.09 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.61 – 2.69 (m, 1H), 2.52 (s, 1H), 2.44 – 2.51 (m, 1H), 1.89 – 2.07 (m, 2H), 1.28 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_4$ $[M + H]^+$ 448.2236; found 448.2254.

The enantiomers (5.72 g, 12.8 mmol) were separated by chiral chromatography on a Chiralcel OJ 250 mm × 50 mm, 20 μm HPLC column. 500 mg (100 mg/mL in heptane/IPA 1/5) was injected and eluted with heptane/IPA 60/40 at a flow rate of 120 mL/min and detected at 290 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (2.92 g, 99.0% ee). $[\alpha]_D^{20}$: −4 (*c* 1.0, CH_3CN); HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_4$ $[M + H]^+$ 448.2236; found 448.2252. The second eluted compound was collected and evaporated to give the least active enantiomer (2.62 g, 98.8% ee). $[\alpha]_D^{20}$: +4 (*c* 1.0, CH_3CN); HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_4$ $[M + H]^+$ 448.2236; found 448.2215.



5-{2-[4-(2-Aminopyrimidin-5-yl)phenyl]tetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (15a). A solution of lithium hydroxide (5 mg, 0.20 mmol) in water (0.25 mL) was added to compound **11a** (63 mg, 0.17 mmol) dissolved in THF (2 mL). The resulting mixture was stirred at rt for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (Kromasil C8, 5-45% CH_3CN in 0.2% HCO_2H (aq)) to give 5-{2-[4-(2-aminopyrimidin-5-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (38 mg, 63%). MS *m/z* 363 $(M+H)^+$.

TBTU (33 mg, 0.10 mmol) was added to a solution of 5-{2-[4-(2-aminopyrimidin-5-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (32 mg, 0.090 mmol), 1-amino-2-methylpropan-2-ol (22 mg, 0.25 mmol), and DIPEA (0.031 mL, 0.18 mmol) in a mixture of CH_2Cl_2 (1 mL) and DMF (1 mL). The resulting mixture was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (XBridge C18, 15-55% CH_3CN in 0.2% NH_3 (aq)) to give compound **15a** (25 mg, 65%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 2.0 Hz, 1H), 8.51 (s, 2H), 8.31 – 8.40 (m, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.92 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.10 (t, *J* = 7.1 Hz, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.64 – 2.73 (m, 1H), 2.53 – 2.62 (m, 1H), 1.95 – 2.08 (m, 2H), 1.27 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2199.



5-{(2*R* and *S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (15b and 15b′)

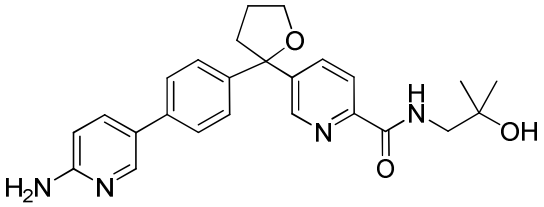
Step 1*:* Trifluoromethanesulfonic anhydride (1.7 mL, 10.41 mmol) was slowly added to a solution of compound **17a** (2.9 g, 8.01 mmol) and DMAP (4.9 g, 40.05 mmol) at -78 °C in CH_2Cl_2 (130 mL). The reaction mixture was stirred at -78 °C for 7 h and the reaction mixture was then added to saturated $NaHCO_3$ (aq) (200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried (phase separator) and concentrated *in vacuo*. The residue was purified by flash column chromatography (70→100% EtOAc in heptane) to give 4-(2-{6-[(2-hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}tetrahydrofuran-2-yl)phenyl trifluoromethanesulfonate

(3.53 g, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1H), 8.35 (t, *J* = 6.3 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.48 – 7.55 (m, 2H), 7.2 – 7.24 (m, 2H), 4.02 – 4.12 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 1H), 1.92 – 2.09 (m, 2H), 1.28 (s, 6H); MS *m/z* 489 $(M+H)^+$.

Step 2: Potassium acetate (3.55 g, 36.1 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.39 g, 9.4 mmol) and $PdCl_2$(dppf) (1.05 g, 1.44 mmol) were added to a solution of 4-(2-{6-[(2-hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}tetrahydrofuran-2-yl)phenyl trifluoromethanesulfonate (3.53 g, 7.2 mmol) in degassed dioxane (30 mL) under Ar(g). The reaction mixture was heated at reflux for 50 min and was then partitioned between EtOAc and water and the aqueous phase was extracted with EtOAc (x2). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. CH_2Cl_2 was added to the residue and the mixture was filtered (Celite) and the filtrate was concentrated *in vacuo* to give crude *N*-(2-hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide. MS *m/z* 467 $(M+H)^+$.

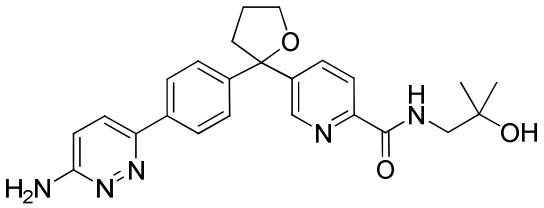
Step 3: A solution of potassium carbonate (2.0 g, 14.44 mmol) in degassed water (60 mL) was added to solution of crude *N*-(2-hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (7.2 mmol), 5-bromopyrazin-2-amine (1.51 g, 8.7 mmol) and $PdCl_2$(dppf) (0.52 g, 0.72 mmol) in dioxane (60 mL). The reaction mixture was heated at reflux for 50 min and the reaction mixture was then diluted with EtOAc and filtered (Celite) and the filtrate was washed with saturated NaCl (aq). The aqueous phase was extracted with EtOAc and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (0→10% EtOH in EtOAc) and then by preparative HPLC (XBridge C18, 20→80% CH_3CN in 0.2% NH_3 (aq)) to give the racemate of the title compounds (2.45 g, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, *J* = 1.8 Hz, 1H), 8.46 (s, 1H), 8.41 (t, *J* = 6.1 Hz, 1H), 8.06 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 1.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.55 (s, 2H), 4.68 (s, 1H), 4.00 (t, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 6.1 Hz, 2H), 2.58 – 2.72 (m, 2H), 1.84 – 2 (m, 2H), 1.09 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.3, 154.9, 148.2, 145.9, 144.7, 144.2, 138.8, 138.6, 135.9, 134.7, 131.4, 125.7, 124.7, 121.4, 86.1, 69.1, 67.0, 49.6, 37.8, 27.2, 24.9. HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2177.

The enantiomers (2.45 g, 5.7 mmol) were separated by chiral chromatography on a Chiralcel OJ 250x50 mm, 20 μm HPLC column. 125 mg (25 mg/ml in MeOH/CH_3CN/HCO_2H 12/6/1) was injected and eluted with EtOH at a flow rate of 120 mL/min and detected at 323 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (**15b**) (1.18 g, 98.1% ee). $[\alpha]_D^{20}$: −23 (*c* 1.0, CH_3OH); HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2211. The second eluted compound was collected and evaporated to give the least active enantiomer (**15b′**) (1.10 g, 99.7% ee). $[\alpha]_D^{20}$: +23 (*c* 1.0, CH_3OH); HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2207.



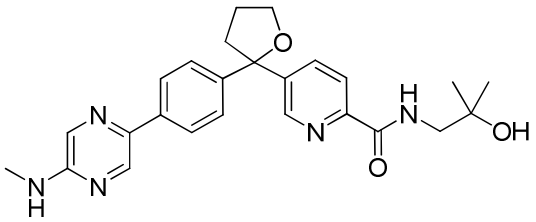
5-{(2*R* and *S*)-2-[4-(6-Aminopyridin-3-yl)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (15c). Compound **15c** was prepared as described in Step 3 of compound **15b** from crude *N*-(2-hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (5.18 mmol) (prepared as described in step 2 of compound **15b**) and 5-bromopyridin-2-amine (1.08 g, 6.22 mmol). The crude product was purified by preparative HPLC (XBridge C18, 20→95% CH_3CN in 0.2% NH_3(aq)) to give the racemate of the title compounds (1.23 g, 55 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (d, *J* = 2.0 Hz, 1H), 8.38 (t, *J* = 6.1 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.47 (s, 4H), 6.46 (d, *J* = 8.6 Hz, 1H), 6.01 (s, 2H), 4.66 (s, 1H), 3.96 (t, *J* = 7.2 Hz, 2H), 3.23 (d, *J* = 6.2 Hz, 2H), 2.54 – 2.68 (m, 2H), 1.81 – 1.93 (m, 2H), 1.05 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_4O_3$ $[M + H]^+$ 433.2240; found 433.2217.

The enantiomers (1.22 g, 2.82 mmol) were separated by chiral chromatography on a Chiralcel OJ 250x50 mm, 20 μm HPLC column. 300 mg (200 mg/ml in EtOH) was injected and eluted with EtOH/Et_3N 100/0.1 at a flow rate of 120 mL/min and detected at 330 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (623 mg, >99.9% ee). $[\alpha]_D^{20}$: −30 (*c* 1.0, EtOH); HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_4O_3$ $[M + H]^+$ 433.2240; found 433.2254. The second eluted compound was collected and evaporated to give the least active enantiomer (609 mg, 99.2% ee). $[\alpha]_D^{20}$: +24 (*c* 1.0, EtOH); HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_4O_3$ $[M + H]^+$ 433.2240; found 433.2237.



5-{2-[4-(6-Aminopyridazin-3-yl)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (15d). Compound **15d** was prepared as described in Step 3 of compound **15b** from crude *N*-(2-hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (0.15 mmol) (prepared as described in step 2 of compound **15b**) and 6-chloropyridazin-3-amine (23 mg, 0.18mmol). The crude product was purified by preparative HPLC (XBridge C18, 5→95% CH_3CN in 0.2% NH_3(aq)). (17 mg, 27%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, *J* = 2.1 Hz, 1H), 8.41 (t, *J* = 6.1 Hz, 1H), 8.06 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 9.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 9.3 Hz, 1H), 6.45 (s, 2H), 4.68 (s, 1H), 4.00 (t, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 6.1 Hz,

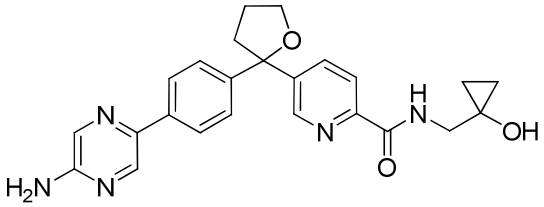
2H), 2.59 – 2.74 (m, 2H), 1.85 – 1.98 (m, 2H), 1.08 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2177.



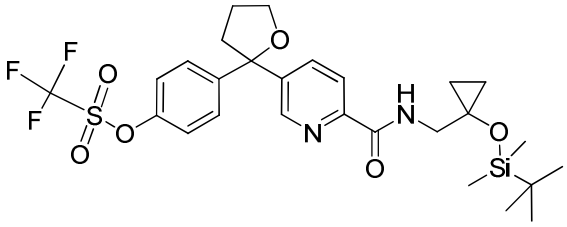
***N*-(2-hydroxy-2-methylpropyl)-5-[(2*R* and *S*)-2-{4-[5-(methylamino)pyrazin-2-yl]phenyl}tetrahydrofuran-2-yl]pyridine-2-carboxamide (15e).** 2M Methylamine in THF (7.0 ml, 14.04 mmol) was added to 2-bromo-5-iodopyrazine (200 mg, 0.70 mmol) and the reaction mixture was stirred at rt for ~48 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and saturated $NaHCO_3$ (aq). The aqueous phase was extracted with EtOAc and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (10→50%, EtOAc in heptane) to give 5-iodo-*N*-methylpyrazin-2-amine (112 mg, 68 %) contaminated with the corresponding 5-bromo-*N*-methylpyrazin-2-amine (ratio 6:1). MS *m/z* 236 $(M+H)^+$.

The racemate of the title compounds was prepared as described in step 3 of compound **15b** from crude *N*-(2-hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (0.45 mmol) (prepared as described in step 2 of compound **15b**) and crude 5-iodo-*N*-methylpyrazin-2-amine (0.45 mmol). The crude product was purified by preparative HPLC (XBridge C18, 5→95% CH_3CN in 0.2% NH_3(aq)). (108 mg, 54 %); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (d, *J* = 2.1 Hz, 1H), 8.48 (d, *J* = 1.2 Hz, 1H), 8.38 (t, *J* = 6.1 Hz, 1H), 8.02 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.92 – 7.99 (m, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.12 (q, *J* = 4.7 Hz, 1H), 4.68 (s, 1H), 3.96 (t, *J* = 7.2 Hz, 2H), 3.22 (d, *J* = 6.2 Hz, 2H), 2.79 (d, *J* = 4.8 Hz, 3H), 2.54 – 2.67 (m, 2H), 1.81 – 1.94 (m, 2H), 1.05 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{25}H_{30}N_5O_3$ $[M + H]^+$ 448.2349; found 448.2364.

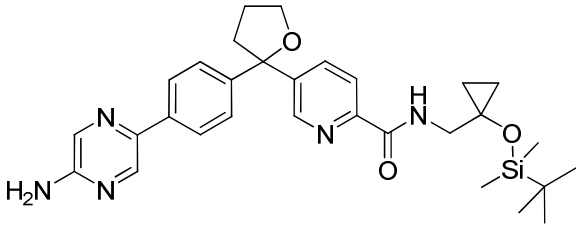
The enantiomers (104 mg, 0.23 mmol) were separated by chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 µm HPLC column. 35 mg (35 mg/mL in EtOH) was injected and eluted with EtOH/Et_3N 100/0.1 at a flow rate of 18 mL/min and detected at 265 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (38 mg, 99.9% ee). $[\alpha]_D^{20}$: −18 (c 1.0, CH_3CN); HRMS (ESI) *m/z* calcd for $C_{25}H_{30}N_5O_3$ $[M + H]^+$ 448.2349; found 448.2356. The second eluted compound was collected and evaporated to give the least active enantiomer (34 mg, 99.9% ee). $[\alpha]_D^{20}$: +20 (*c* 1.0, CH_3CN); HRMS (ESI) *m/z* calcd for $C_{25}H_{30}N_5O_3$ $[M + H]^+$ 448.2349; found 448.2364.



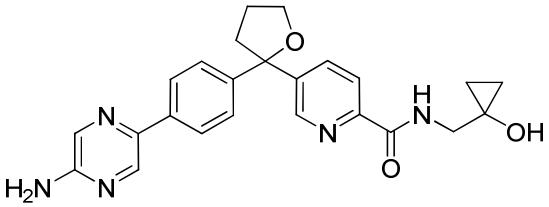
5-{(2*S* and *R*) 2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}-*N*-[(1-hydroxycyclopropyl) methyl]pyridine-2-carboxamide (15f).



Step 1: (*4-[2-(6-{[(1-{[tert-Butyl(dimethyl)silyl]oxy}cyclopropyl)methyl]carbamoyl}pyridin-3-yl)tetrahydrofuran-2-yl]phenyl trifluoromethanesulfonate):* The **Step 1** intermediate of compound **15f** was prepared as described in Step 1 for compound **15b** from compound **17b** (138 mg, 0.29 mmol). The crude product was purified by flash column chromatography (15→100%, EtOAc in heptane) to give the **Step 1** intermediate of compound **15f** as a yellow solid (141 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.63 (m, 1H), 8.32 – 8.39 (m, 1H), 8.12 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.86 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 4.08 (dd, *J* = 7.1, 7.1 Hz, 2H), 3.52 (d, *J* = 5.7 Hz, 2H), 2.60 (dd, *J* = 7.2, 7.2 Hz, 2H), 1.94 – 2.06 (m, 2H), 0.87 (s, 9H), 0.77 – 0.82 (m, 2H), 0.62 – 0.67 (m, 2H), 0.12 (s, 6H); MS *m/z* 601 $[M+H]^+$.

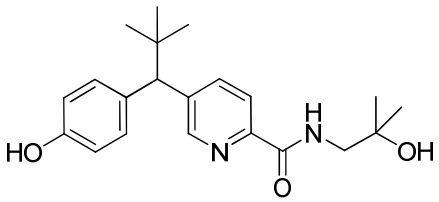


Step 2 and 3: (*5-{2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}-N-[(1-{[tert-butyl(dimethyl)silyl]oxy}cyclopropyl)methyl]pyridine-2-carboxamide)*: The **Step 2** and **Step 3** intermediates of compound **15f** were prepared as described in Step 2 and Step 3 for compound **15b** starting from the **Step 1** intermediate of compound **15f** (96 mg, 0.16 mmol). The crude product was purified by flash column chromatography (20→100%, EtOAc in heptane) to give the **Step 3** intermediate of compound **15f** 66 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.6 Hz, 1H), 8.42 (d, *J* = 1.4 Hz, 1H), 8.34 – 8.40 (m, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 1.4 Hz, 1H), 7.89 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.60 (s, 2H), 4.09 (dd, *J* = 7.2, 7.2 Hz, 2H), 3.52 (d, *J* = 5.7 Hz, 2H), 2.70 (ddd, *J* = 7.0, 7.0, 12.5 Hz, 1H), 2.54 (ddd, *J* = 7.4, 7.4, 12.4 Hz, 1H), 1.95 – 2.08 (m, 2H), 0.87 (s, 9H), 0.76 – 0.81 (m, 3H), 0.61 – 0.67 (m, 3H), 0.11 (s, 6H); MS *m/z* 546 $[M+H]^+$.



Step 4: (*5-{(2S and R) 2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}-N-[(1-hydroxycyclopropyl) methyl]pyridine-2-carboxamide):* The **Step 3** intermediate of compound **15f** (61 mg, 0.11 mmol) was dissolved in MeOH (2.5 mL) and cooled to 0 °C. Acetyl chloride (10 uL, 0.14 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. CH_2Cl_2 was added and the reaction mixture was neutralized with a solution of saturated $NaHCO_3$ (aq). The organic phase was washed with water, dried by passing through a phase-separator and concentrated *in vacuo*. The residue was purified by flash column chromatography (0→10%, EtOH in EtOAc) to give the racemate of compound **15f** (34 mg, 70%).

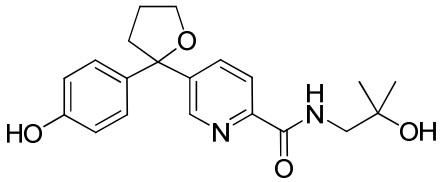
The enantiomers were separated by chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 μm HPLC column. 34 mg (17 mg/ml in EtOH) was injected and eluted with EtOH at a flow rate of 18 mL/min and detected at 280 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (14 mg, >99.9%ee). $[\alpha]_D^{20}$: −13 (*c* 1.0, CH_3CN), HRMS (ESI) *m/z* calcd for $C_{24}H_{25}N_5O_3$ $[M + H]^+$ 432.2036; found 432.2004. The second eluted compound was collected and evaporated to give the least active enantiomer (16 mg, 99.9%ee). $[\alpha]_D^{20}$: +13 (*c* 1.0, CH_3CN). ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.6 Hz, 1H), 8.37 – 8.43 (m, 2H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 1.5 Hz, 1H), 7.91 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 4.61 (s, 2H), 4.06 – 4.15 (m, 2H), 3.59 (d, *J* = 5.9 Hz, 2H), 2.70 (ddd, *J* = 7.1, 7.1, 12.5 Hz, 1H), 2.53 (ddd, *J* = 7.3, 7.3, 12.4 Hz, 1H), 1.96 – 2.04 (m, 2H), 0.81 – 0.87 (m, 2H), 0.6 – 0.69 (m, 3H).



***N*-(2-Hydroxy-2-methylpropyl)-5-[1-(4-hydroxyphenyl)-2,2-dimethylpropyl]pyridine-2-carboxamide (16).** Aqueous LiOH (30 mL, 0.18 mol) was added to a solution of compound **5** (60 g, 0.15 mol) in THF (400 mL)-MeOH (100 mL). The resulting solution was stirred at rt for 2 h before being concentrated. The residue was dissolved in EtOAc and washed with 10% citric acid (aq), dried, filtered and concentrated to give crude compound 5-{1-[4-(benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}pyridine-2-carboxylic acid (38.5 g, 68%). MS *m/z* 394.6 $(M+H)^+$.

HATU (76 g, 0.2 mol) was added to a solution of 5-{1-[4-(benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}pyridine-2-carboxylic acid (38.3 g, 0.098 mol), 1-amino-2-methylpropan-2-ol (11.3 mg, 0.13 mmol) and 4-methylmorpholine (20 g, 0.2 mmol) in DMF (400 mL). The reaction mixture was stirred at rt for 3 h, poured into ice-water and extracted with EtOAc, and the combined organic layers were washed with citric acid (aq), saturated $NaHCO_3$ (aq), brine, dried (Na_2SO_4), filtered, concentrated to give crude product. The crude product was purified by flash column chromatography (10:1→2:1, petroleum ether:EtOAc) to afford 5-{1-[4-(benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (35 g, 58 %). MS *m/z* 465.1 $(M+H)^+$.

A solution of 5-{1-[4-(benzyloxy)phenyl]-1-fluoro-2,2-dimethylpropyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (2 g, 4.3 mmol), ammonium formate (0.9 g, 14.2 mmol) and palladium hydroxide (20% on activated carbon, 0.5 g) in MeOH (10 mL) was heated at 100 °C in a micro-wave reactor for 30 min. The catalyst was then filtered off (Celite) and washed with EtOAc, and MeOH. The filtrate was concentrated *in vacuo* and the crude product was suspended in EtOAc and 5% citric acid (aq) was added until a clear solution was obtained. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried and concentrated to give compound **16** (8 g, 74.8%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.46 – 8.59 (m, 2H), 7.89 – 8.01 (m, 2H), 7.47 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 3.70 (s, 1H), 3.37 (d, *J* = 6.2 Hz, 2H), 2.72 – 2.89 (m, 1H), 1.19 (s, 6H), 0.96 (s, 9H); MS *m/z* 457.4 $(M+H)^+$.



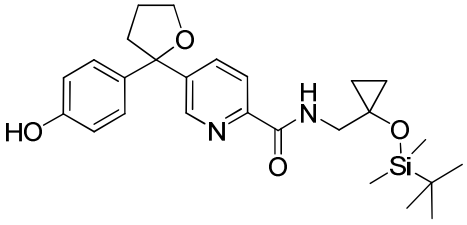
***N*-(2-Hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)tetrahydrofuran-2-yl]pyridine-2-carboxamide (17a).**

Step 1: A solution of lithium hydroxide (0.259 g, 10.83 mmol) in water (12 mL) was added to a suspension of compound **6** (3.51 g, 9.03 mmol) in THF (30.0 mL) and MeOH (30.0 mL). The reaction mixture was stirred at rt overnight (~16 h). The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between EtOAc and ~0.05 M HCl (aq). The aqueous phase was extracted with CH_2Cl_2 (x4) and the combined organic phase was dried (Na_2SO_4 and phase separator) and concentrated *in vacuo* to give crude 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid. MS *m/z* 376 $(M+H)^+$.

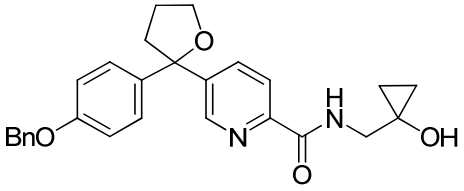
Step 2: TBTU (3.77 g, 11.74 mmol) followed by a solution of 1-amino-2-methylpropan-2-ol (2.42 g, 27.09 mmol) in CH_2Cl_2 (30 mL) were added to a solution of crude 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (3.39 g, 9.03 mmol), and 4-methylmorpholine (1.99 mL, 18.06 mmol) in DMF (75 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was then partially evaporated and the residue was partitioned between EtOAc and 0.1 M HCl (aq). The organic phase was washed with

saturated $NaHCO_3$ (aq), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOH in toluene) to give 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (4.04 g, 100%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.6 Hz, 1H), 8.36 (t, *J* = 6.2 Hz, 1H), 8.07 – 8.13 (m, 1H), 7.87 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.35 – 7.42 (m, 4H), 7.29 – 7.34 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.03 (s, 2H), 4.01 – 4.11 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.6 – 2.71 (m, 1H), 2.52 (s, 1H), 2.42 – 2.51 (m, 1H), 1.9 – 2.06 (m, 2H), 1.27 (s, 6H); MS *m/z* 447 $(M+H)^+$.

Step 3: Palladium hydroxide (5% on carbon, 317 mg, 0.45 mmol) was added to a solution of 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (4.03 g, 9.03 mmol) in MeOH (100 mL) and the reaction mixture was hydrogenated at 1 atm for 3.5 h. The catalyst was then filtered off, washed with MeOH, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC (Kromasil C8, 15→75% CH_3CN in 0.2% CH_3CO_2H (aq)). Fractions containing the desired product were partially concentrated and the aqueous mixture was extracted with CH_2Cl_2 and then EtOAc (x4). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give compound **17a** (2.86 g, 89%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (d, *J* = 1.4 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.96 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.22 – 7.30 (m, 2H), 6.68 – 6.76 (m, 2H), 3.94 – 4.11 (m, 2H), 3.40 (s, 2H), 2.60 – 2.77 (m, 1H), 2.38 – 2.57 (m, 1H), 1.86 – 2.06 (m, 2H), 1.21 (s, 6H); ^{13}C NMR (126 MHz, MeOD) δ 166.7, 157.7, 149.0, 147.7, 147.3, 137.0, 135.9, 128.1, 122.5, 116.1, 87.8, 71.4, 68.5, 50.9, 39.5, 27.2, 26.4; MS *m/z* 357 $(M+H)^+$

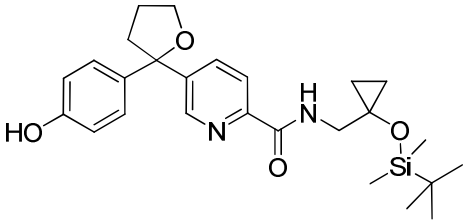


***N*-[(1-{[*tert*-Butyl(dimethyl)silyl]oxy}cyclopropyl)methyl]-5-[2-(4-hydroxyphenyl) tetrahydrofuran-2-yl]pyridine-2-carboxamide (17b).**



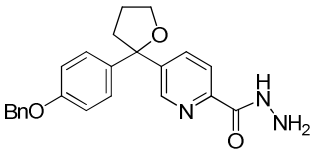
Step 1*: (5-{2-[4-(Benzyloxy)phenyl]tetrahydrofuran-2-yl}-N-[(1-hydroxycyclopropyl)methyl] pyridine-2-carboxamide):* TBTU (481 mg, 1.50 mmol) and DIPEA (0.44 mL, 2.50 mmol) were added to a solution of 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxylic acid (312 mg, 0.83 mmol) (prepared as described in Step 1 of compound **17ab**) in CH_2Cl_2 (4 mL). 1-(Aminomethyl)cyclopropanol [1] (87 mg, 1 mmol) dissolved in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was

diluted with CH_2Cl_2 and the organic phase was washed twice with saturated $NaHCO_3$ (aq), 10% NaCl (aq), and then dried by passing over a phase-separator and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOH in toluene) and then repurified by flash column chromatography (0→100%, EtOAc in heptane) to give the **Step 1** intermediate of compound **17b** (148 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 2.0 Hz, 1H), 8.40 (t, J = 5.6 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.82 – 7.88 (m, 2H), 7.28 – 7.44 (m, 7H), 6.92 (d, J = 8.8 Hz, 2H), 5.03 (s, 2H), 4.05 (dd, J = 7.1, 7.1 Hz, 2H), 3.58 (d, J = 5.9 Hz, 2H), 2.64 (ddd, J = 7.2, 7.2, 12.5 Hz, 1H), 2.40 – 2.50 (m, 1H), 1.88 – 2.06 (m, 2H), 0.81 – 0.87 (m, 2H), 0.6 – 0.67 (m, 2H); MS *m/z* 445 $(M+H)^+$.

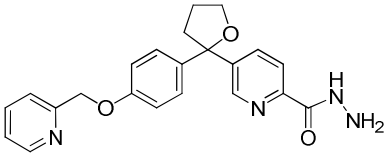


Step 2 and 3: *N-[(1-{[tert-Butyl(dimethyl)silyl]oxy}cyclopropyl)methyl]-5-[2-(4-hydroxyphenyl) tetrahydrofuran-2-yl]pyridine-2-carboxamide* **(17b):** The **Step 1** intermediate of compound **17b** (158 mg, 0.36 mmol) and imidazole (73 mg, 1.07 mmol) were dissolved in DMF (1.8 mL). *tert*-Butyldimethylsilyl chloride (107 mg, 0.71 mmol) was added and the reaction mixture was stirred at rt for 3 h. EtOAc was added dropwise followed by saturated $NaHCO_3$ (aq). The phases were separated and the organic phase was washed with 0.1M HCl (aq), saturated $NaHCO_3$ (aq), brine, and then dried over $MgSO_4$, and concentrated *in vacuo* to give crude 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}-N-[(1-{[tert-butyl(dimethyl)silyl]oxy} cyclopropyl)methyl]pyridine-2-carboxamide. MS *m/z* 559 $[M+H]^+$.

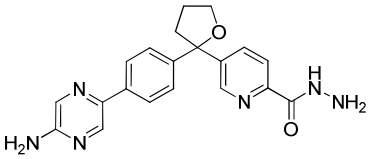
Palladium hydroxide (5% on carbon, 6 mg, 0.04 mmol) was added to a solution of crude 5-{2-[4-(benzyloxy)phenyl]tetrahydrofuran-2-yl}-*N*-[(1-{[*tert*-butyl(dimethyl)silyl]oxy} cyclopropyl)methyl]pyridine-2-carboxamide (174 mg, 0.31 mmol) in MeOH (4.5 mL) and the reaction mixture was hydrogenated at rt and 1 atm overnight. The reaction mixture was filtered through a pre-packed C18 column (1 g) and the catalyst was rinsed several times with MeOH. The collected organic phase was concentrated *in vacuo* to give compound **17b** (138 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 1.9 Hz, 1H), 8.35 – 8.43 (m, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 2.2, 8.2 Hz, 1H), 7.22 – 7.30 (m, 2H, overlapping solvent), 6.78 (d, J = 8.7 Hz, 2H), 4.00 – 4.11 (m, 2H), 3.52 (d, J = 5.7 Hz, 2H), 2.63 (ddd, J = 7.2, 7.2, 12.4 Hz, 1H), 2.46 (ddd, J = 7.3, 7.3, 12.3 Hz, 1H), 1.90 – 2.06 (m, 2H), 0.87 (s, 9H), 0.75 – 0.82 (m, 2H), 0.60 – 0.67 (m, 2H), 0.11 (s, 6H); MS *m/z* 469 $[M+H]^+$.



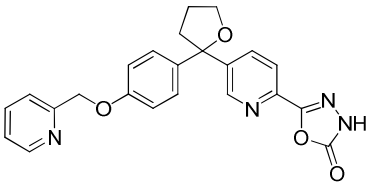
5-{2-[4-(Benzyloxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carbohydrazide (18a). Compound **18a** was prepared according to published procedure [2] starting from compound **6**. (7.55 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 2.1, 8.0 Hz, 1H), 7.28 – 7.44 (m, 7H), 6.92 (d, *J* = 8.3 Hz, 2H), 5.03 (s, 2H), 3.96 – 4.13 (m, 2H), 2.56 – 2.72 (m, 1H), 2.37 – 2.54 (m, 1H), 1.83 – 2.06 (m, 2H); MS *m/z* 390.6 $(M+H)^+$.



5-{2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridine-2-carbohydrazide (18b). Compound **18b** was prepared according to published procedure [2] starting from compound **10**. (100%, crude). MS *m/z* 391.1 $(M+H)^+$.



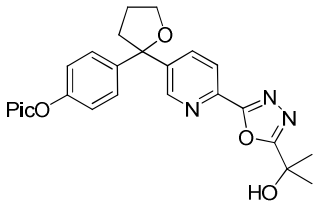
5-{2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carbohydrazide (18c). Compound **18c** was prepared according to published procedure [2] starting from compound **11b**. (280 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.61 – 8.67 (m, 1H), 8.38 – 8.45 (m, 1H), 8.02 – 8.11 (m, 2H), 7.88 – 7.96 (m, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 4.63 (s, 2H), 4.09 (t, *J* = 7.3 Hz, 2H), 2.62 – 2.79 (m, 1H), 2.42 – 2.60 (m, 1H), 1.95 – 2.07 (m, 2H); MS *m/z* 377.1 $(M+H)^+$.



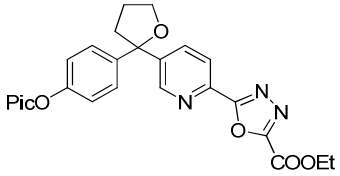
5-(5-{(2*R* and 2*S*)-2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)-1,3,4-oxadiazol-2(3*H*)-one (19). The racemate of the title compounds was prepared according to published procedure[3] starting from compound **18b**.

The enantiomers were separated by chiral chromatography on a Chiralpak AS 250 mm x 20 mm, 5 μm HPLC column. 15.5 mg, 15.5 mg/ml in EtOH, was injected and eluted with heptane/EtOH 30/70 at a flow rate of 12 mL/min and detected at 305 nm. The first eluted

compound was collected and evaporated to give the least active enantiomer (3.5 mg, 99.8%ee). The second eluted compound was collected and evaporated to give the most active enantiomer (5.9 mg, 99.8%ee). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.70 – 8.76 (m, 1H), 8.5 – 8.55 (m, 1H), 7.93 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.76 – 7.82 (m, 2H), 7.45 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.33 – 7.39 (m, 2H), 7.27 – 7.33 (m, 1H), 6.91 – 6.97 (m, 2H), 5.11 (s, 2H), 3.86 – 3.98 (m, 2H), 2.45 – 2.64 (m, 2H), 1.77 – 1.90 (m, 2H); HRMS (ESI); m/z calcd for $C_{23}H_{20}N_4O_4$ [M + H]+ 417.1563; found 417.1555.



2-[5-(5-{(2*R* and 2*S*)-2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]propan-2-ol (20)

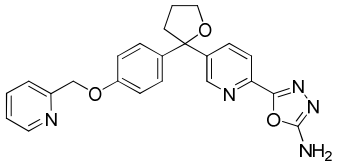


Step 1 (*Ethyl 5-(5-{2-[4-(pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)-1,3,4-oxadiazole-2-carboxylate*): Triethylamine (0.96 mL, 6.92 mmol) and ethyl 2-chloro-2-oxoacetate (0.28 mL, 2.54 mmol) were added to a solution of compound **18b** (900 mg, 2.31 mmol) in CH_2Cl_2 (40 mL) The reaction was stirred at rt for 1 h. 4-Methylbenzene-1-sulfonyl chloride (483 mg, 2.54 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction was quenched by adding saturated $NaHCO_3$ (aq) and the two phases were separated. The organic layer was dried by passage through a phase separator and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (30→100%, EtOAc in heptane) to give to give the **Step 1** intermediate of compound **20** (760 g, 70 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 2.1 Hz, 1H), 8.55 – 8.61 (m, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.94 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.66 – 7.74 (m, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.39 (m, 2H), 7.18 – 7.24 (m, 1H), 6.91 – 6.97 (m, 2H), 5.18 (s, 2H), 4.55 (q, *J* = 7.1 Hz, 2H), 4.00 – 4.15 (m, 2H), 2.63 – 2.76 (m, 1H), 2.41 – 2.55 (m, 1H), 1.89 – 2.1 (m, 2H), 1.47 (t, *J* = 7.2 Hz, 3H); MS *m/z* 473.3 $(M+H)^+$.

Step 2 *2-[5-(5-{2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]propan-2-ol* (**20**): The **Step 1** intermediate of compound **20** (375 mg, 0.79 mmol) was dissolved in THF (10 mL) followed by addition of methylmagnesium bromide (3.0 M in Et_2O, 0.56 mL, 1.67 mmol) and the reaction mixture was stirred at rt for 10 min. The reaction was quenched by addition of saturated $NaHCO_3$ (aq) and the mixture was diluted with CH_2Cl_2 and the phases were separated. The CH_2Cl_2 layer was dried using a phase-separator and evaporated leaving a slightly yellow solid. The residue was purified by flash

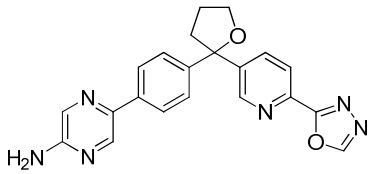
column chromatography (100% EtOAc then 0→15%, EtOH in EtOAc) to give the racemate of compound **20** as a white solid (180 mg, 49.5 %).

The enantiomers were separated by chiral chromatography on a Chiralpak AS 250 mm x 20 mm, 5 µm HPLC column. 20 mg, 50 mg/ml in EtOH, was injected and eluted with EtOH (100%) at a flow rate of 18 mL/min and detected at 254 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (78 mg, 99.9%ee). $[\alpha]_D^{20}$ +1.8 The second eluted compound was collected and evaporated to give the most active enantiomer (81 mg, 99.8%ee). $[\alpha]_D^{20}$ –2.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.2 Hz, 1H), 8.58 (d, *J* = 1.4, 4.7 Hz, 1H), 8.15 (d, 1H), 7.90 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.66 – 7.74 (m, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.36 (m, 2H), 7.17 – 7.25 (m, 1H), 6.89 – 6.96 (m, 2H), 5.18 (s, 2H), 4.00 – 4.11 (m, 2H), 2.73 (s, 1H), 2.59 – 2.73 (m, 1H), 2.42 – 2.55 (m, 1H), 1.89 – 2.09 (m, 2H), 1.77 (s, 6H); HRMS (ESI); *m/z* calcd for $C_{26}H_{26}N_4O_4$ $[M + H]^+$ 459.2032; found 459.2036.



5-(5-{(2*R* and 2*S*)-2-[4-(Pyridin-2-ylmethoxy)phenyl]tetrahydrofuran-2-yl}pyridin-2-yl)-1,3,4-oxadiazol-2-amine (21). The racemate of the title compounds was prepared according to published procedure. [4] starting from compound **18b.**

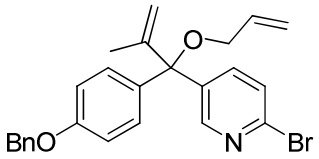
The enantiomers were separated by chiral chromatography on a Chiralpak OJ 250 mm x 20 mm, 5 µm HPLC column. 25 mg, 2.9 mg/ml in EtOH, was injected and eluted with EtOH/Et_3N 100/0.1 at a flow rate of 18 mL/min and detected at 254 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (10 mg, 99.9% ee). The second eluted compound was collected and evaporated to give the least active enantiomer of (11 mg, 98.7% ee). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.51 – 8.57 (m, 1H), 7.84 – 7.95 (m, 2H), 7.76 – 7.83 (m, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.4 (m, 3H), 7.31 (dd, *J* = 4.9, 7.5 Hz, 1H), 6.92 – 6.98 (m, 2H), 5.11 (s, 2H), 3.84 – 4.00 (m, 2H), 2.5 – 2.62 (m, 2H), 1.79 – 1.90 (m, 2H); HRMS (ESI); m/z calcd for $C_{23}H_{21}N_5O_3$ $[M + H]+$ 416.1722; found 416.1715.



5-(4-{(2*R* and 2*S*)-2-[6-(1,3,4-Oxadiazol-2-yl)pyridin-3-yl]tetrahydrofuran-2-yl}phenyl)pyrazin-2-amine (22). The racemate of the title compounds was prepared according to published procedure [2] starting from compound **18c**.

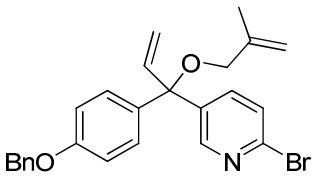
The enantiomers were separated by chiral chromatography on a Chiralpak OJ 250 mm x 20 mm, 5 µm HPLC column. 171 mg, 15 mg/ml in MeOH, was injected and eluted with

EtOH/MeOH/Et_3N 50/50/0.1 at a flow rate of 120 mL/min and detected at 280 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (73 mg, 99.9% ee). $[\alpha]_D^{20}$ –30 (*c* 0.5, CH_3OH). The second eluted compound was collected and evaporated to give the least active enantiomer (70 mg, 99.9% ee). $[\alpha]_D^{20}$ +28 (*c* 0.5, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.85 – 8.90 (m, 1H), 8.41 – 8.47 (m, 1H), 8.04 – 8.15 (m, 2H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.81 – 7.85 (m, 2H), 7.5 – 7.55 (m, 2H), 6.51 (s, 2H), 3.92 – 4.05 (m, 2H), 2.54 – 2.71 (m, 2H), 1.8 – 1.96 (m, 2H); HRMS (ESI); m/z calcd for $C_{21}H_{18}N_6O_2$ [M + H]+ 387.1569; found 387.1563.



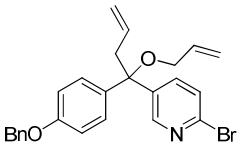
5-{1-[4-(Benzyloxy)phenyl]-2-methyl-1-(prop-2-en-1-yloxy)prop-2-en-1-yl}-2-bromopyridine (23). Prop-1-en-2-ylmagnesium bromide (0.5 M in THF, 54 mL, 27.16 mmol) was added to a refluxing solution of compound **1** (5.0 g, 13.58 mmol) in THF (75 mL). After 1 min the orange solution was quenched by adding saturated NH_4Cl (aq). The mixture was diluted with CH_2Cl_2 and the phases were separated. The organic layer was dried by passage through a phase-separator. The solvent was removed under reduced pressure to give 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-2-methylprop-2-en-1-ol as an orange oil (6.0 g, quantitative). MS *m/z* 411 $[M+H]^+$.

NaH (60% in mineral oil, 2.17 g, 54.32 mmol) was added to a suspension of crude 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)-2-methylprop-2-en-1-ol (5.57 g, 13.58 mmol) in THF (70 mL) and the solution was stirred for 10 min at rt. 3-Bromoprop-1-ene (4.70 mL, 54.32 mmol) was added in one portion and the solution was heated at 40 °C overnight. The reaction was quenched adding saturated NH_4Cl (aq). The mixture was diluted with EtOAc and the phases were separated. The organic layer was washed with saturated of $NaHCO_3$ (aq), and brine. The organic layer was dried over $NaSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (0→10%, EtOAc in heptane) to give compound **23** as a yellow oil (2.2g, 36%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.6 Hz, 1H), 7.50 (dd, *J* = 2.6, 8.4 Hz, 1H), 7.18 – 7.32 (m, 6H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.76 (ddt, *J* = 4.8, 9.8, 17.1 Hz, 2H), 5.19 – 5.26 (m, 2H), 5.09 (s, 1H), 5.02 (dd, *J* = 1.5, 10.6 Hz, 1H), 4.92 (s, 2H), 3.42 – 3.53 (m, 2H), 1.42 (s, 3H); MS *m/z* 450 $[M+H]^+$.



5-{1-[4-(Benzyloxy)phenyl]-1-[(2-methylprop-2-en-1-yl)oxy]prop-2-en-1-yl}-2-bromopyridine (24) Vinylmagnesium bromide (1.0 M in THF, 10.86 mL, 10.86 mmol) was added dropwise to a suspension of compound **1** (2.0 g, 5.43 mmol) in THF (30 mL) at rt and under an atmosphere of N_2 and the reaction mixture was stirred at rt for 15 h. The reaction mixture was quenched by addition of saturated NH_4Cl (~2 mL, aq) and then stirred for 10 min. The mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ (aq). The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried by passing through a phase separator and concentrated *in vacuo* to give crude 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)prop-2-en-1-ol as an orange oil (2.42g). MS *m/z* 394 and 396 $[M-H]^-$.

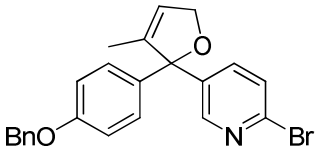
NaH (60% in mineral oil, 869 mg, 21.72 mmol) was added to a suspension of crude 1-[4-(benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)prop-2-en-1-ol (2.15 g, 5.43 mmol) in THF (27 mL) and the reaction mixture was stirred at rt for 10 min. 3-Bromo-2-methylprop-1-ene (0.82 mL, 8.15 mmol) was added in one portion and the reaction mixture was heated at 40 °C for 5 h. 3-Bromo-2-methylprop-1-ene (0.82 mL, 8.15 mmol) was added and the reaction mixture was refluxed over night. The reaction was carefully quenched with the addition of saturated NH_4Cl (3 mL, aq) and stirred for 10 min. The mixture was concentrated *in vacuo* and the crude product was suspended in CH_2Cl_2. The organic layer was washed twice with saturated $NaHCO_3$ (aq). The organic layer was dried by passing through a phase-separator and evaporated *in vacuo*. The crude product was purified by flash column chromatography (0→100%, EtOAc in heptane) to give compound **24** as a clear oil (1.76 g, 72 % over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 2.3 Hz, 1H), 7.39 (dd, J = 2.6, 8.3 Hz, 1H), 7.16 – 7.33 (m, 6H), 7.08 – 7.14 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.27 (dd, J = 10.7, 17.3 Hz, 1H), 5.28 (d, J = 10.8 Hz, 1H), 5.06 (d, J = 17.3 Hz, 1H), 4.95 (s, 1H), 4.93 (s, 2H), 4.74 (s, 1H), 3.41 – 3.61 (m, 2H), 1.58 (s, 3H); MS *m/z* 394 and 396 $[M-H]^-$.



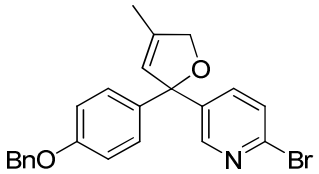
5-(1-(Allyloxy)-1-(4-(benzyloxy)phenyl)but-3-enyl)-2-bromopyridine (25).

Step 1:. Allylmagnesium bromide (109 mL, 108.6 mmol) was added to a refluxing solution of compound **1** (20 g, 54.3 mmol) in THF (300 mL). The reaction was quenched by adding saturated NH_4Cl (aq) after 20 min. The mixture was diluted with CH_2Cl_2 and the phases were separated. The organic layer was dried by passage through a phase-separator. The solvent was removed under reduced pressure leaving an orange oil. The residue was purified by flash column chromatography (10→40%, EtOAc in heptane) to give 1-(4-(benzyloxy)phenyl)-1-(6-bromopyridin-3-yl)but-3-en-1-ol (17.0 g, 76 %) as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.47 (m, 1H), 7.57 (dd, J = 2.6, 8.3 Hz, 1H), 7.28 – 7.46 (m, 8H), 6.90 – 6.99 (m, 2H), 5.58 – 5.73 (m, 1H), 5.19 – 5.29 (m, 2H), 5.05 (s, 2H), 2.88 – 3.14 (m, 2H), 2.55 (s, 1H); MS *m/z* 410.1 and 412.1 $(M+H)^+$.

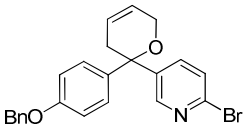
Step 2: NaH (60% in mineral oil, 2.17 g, 54.3 mmol) was added to a suspension of crude 1-(4-(benzyloxy)phenyl)-1-(6-bromopyridin-3-yl)but-3-en-1-ol (5.57 g, 13.58 mmol) in THF. The formed brown/deep-red solution was stirred for 10 min at rt. 3-Bromoprop-1-ene (4.70 mL, 54.32 mmol) was added in one portion and the solution was heated at 40 °C over night. The reaction was quenched with saturated NH_4Cl (aq). The mixture was diluted with EtOAc and the phases were separated. The organic layer was washed with saturated $NaHCO_3$ (aq.) and brine then the organic layer was dried ($NaSO_4$,). The solvent was removed under reduced pressure leaving an orange residue. The crude product was purified by flash column chromatography (0-10%, EtOAc in heptane) to give compound **25** as a colourless oil (5.0 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.36 (m, 1H), 7.49 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.29 – 7.45 (m, 6H), 7.21 – 7.29 (m, 2H), 6.89 – 6.97 (m, 2H), 5.81 – 5.94 (m, 1H), 5.53 – 5.66 (m, 1H), 5.27 – 5.37 (m, 1H), 5.1 – 5.17 (m, 1H), 4.92 – 5.08 (m, 4H), 3.63 – 3.84 (m, 2H), 3.13 – 3.23 (m, 1H), 2.91 – 3.02 (m, 1H); MS *m/z* 450.2 and 452.2 $(M+H)^+$.



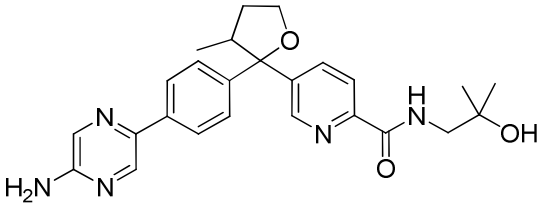
5-{2-[4-(Benzyloxy)phenyl]-3-methyl-2,5-dihydrofuran-2-yl}-2-bromopyridine (26). Grubbs^{2nd} catalyst (0.15 g, 0.18 mmol) was added to a solution of compound **23** (2.2 g, 4.88 mmol) in CH_2Cl_2 (500 mL) under an atmosphere of nitrogen at rt. The reaction mixture was stirred at rt for 16 h. The solvent was evaporated *in vacuo* and the crude residue was purified by flash column chromatography (0→20%, EtOAc in heptane) to give compound **26 (**1.92g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.2 Hz, 1H), 7.39 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.17 – 7.35 (m, 6H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.65 – 5.69 (m, 1H), 4.93 (s, 2H), 4.53 – 4.62 (m, 2H), 1.59 (d, *J* = 1.6 Hz, 3H); MS *m/z* 422 $[M+H]^+$.



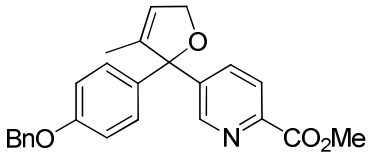
5-{2-[4-(Benzyloxy)phenyl]-4-methyl-2,5-dihydrofuran-2-yl}-2-bromopyridine (27). Grubbs^{2nd} catalyst (0.088 g, 0.10 mmol) was added to a solution of compound **24** (0.88 g, 1.95 mmol) in toluene (220 mL) and the reaction mixture was stirred at 110 °C under an atmosphere of N_2 for 2h. A second portion of Grubbs^{2nd} catalyst (0.020 g, 0.020 mmol) was added and the reaction mixture was stirred at 110 °C for 17 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (1→20%, EtOAc in heptane) to give compound **27** as a clear oil (724 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.5 Hz, 1H), 7.35 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.16 – 7.31 (m, 6H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.68 – 5.75 (m, 1H), 4.92 (s, 2H), 4.46 – 4.59 (m, 2H), 1.70 (d, *J* = 1.17 Hz, 3H); MS *m/z* 422 and 424 $[M+H]^+$.



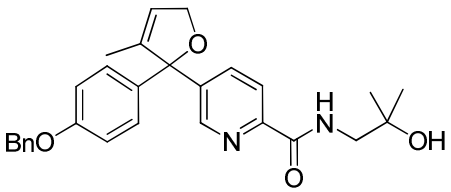
5-(2-(4-(Benzyloxy)phenyl)-3,6-dihydro-2H-pyran-2-yl)-2-bromopyridine (28) Grubbs2nd catalyst (170 mg, 0.20 mmol) was added to a solution of compound **25** (5 g, 11.10 mmol) in CH_2Cl_2 (1.2 L) under nitrogen atmosphere. The reaction mixture was stirred at rt overnight. The solvent was evaporated the residue was purified by flash column chromatography (0→20%, EtOAc in heptane) to give compound **28** (4.0 g, 85%) . ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 – 8.34 (m, 1H), 7.46 – 7.51 (m, 1H), 7.29 – 7.45 (m, 6H), 7.17 – 7.23 (m, 2H), 6.88 – 6.95 (m, 2H), 5.92 – 5.99 (m, 1H), 5.62 – 5.69 (m, 1H), 5.04 (s, 2H), 3.93 – 4.09 (m, 2H), 2.76 – 2.86 (m, 1H), 2.62 – 2.72 (m, 1H); MS *m/z* 422.1 and 424.1 $(M+H)^+$.



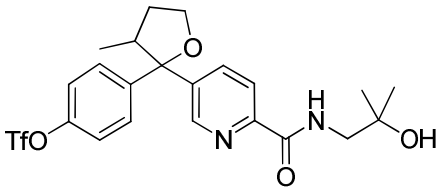
5-{(*2R,3R and 2R,3S and 2S,3R and 2S,3S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-3-methyltetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (29).



Step 1: ***(****Methyl 5-{2-[4-(benzyloxy)phenyl]-3-methyl-2,5-dihydrofuran-2-yl}pyridine-2-carboxylate****):*** The **Step 1** intermediate of compound **29** was prepared as described for compound **6** starting from compound **26** (2.2 g, 5.21 mmol). The crude product was purified flash column chromatography (0→20%, EtOAc in toulene) to give the **Step 1** intermediate of compound **29** as a colourless oil (1.87g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.16 – 7.33 (m, 5H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.69 (s, 1H), 4.93 (s, 2H), 4.61 (s, 2H), 3.88 (s, 3H), 1.60 (s, 3H); MS *m/z* 402 $[M+H]^+$.

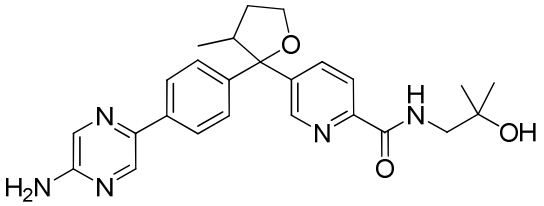


Step 2 and 3: (*5-{2-[4-(Benzyloxy)phenyl]-3-methyl-2,5-dihydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide):* The **Step 2** and **Step 3** intermediates of compound **29** were prepared as described in Step 1 and Step 2 of compound **17a** starting from the **Step 1** intermediate of compound **29** (1.74 g, 4.33 mmol). The crude product was purified by flash column chromatography (2.5% EtOH in toulene) followed by a second flash column chromatography (50%→75%, EtOAc in heptane) to give the **Step 3** intermediate of compound **29** as an orange gum (1.84 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.43 (m, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 8.31 – 8.24 (t, *J*= 5.7 Hz, 1H), 7.68 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.17 – 7.32 (m, 5H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.69 (s, 1H), 4.94 (s, 2H), 4.61 (s, 2H), 3.36 (d, *J* = 6.4 Hz, 2H), 2.40 (s, 1H), 1.16 (s, 6H); MS *m/z* 459 $[M+H]^+$.



Step 4 and 5: (*4-(2-{6-[(2-Hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}-3-methyltetrahydrofuran-2-yl)phenyl trifluoromethanesulfonate):* Palladium hydroxide (20% on carbon, 0.036 g, 0.26 mmol) was added to a solution of the **Step 3** intermediate of compound **29** (1.18 g, 2.58 mmol) in MeOH (37 mL) and the reaction mixture was hydrogenated at rt and 1 atm for 7h, after which palladium hydroxide (20% on carbon, 0.036 g, 0.26 mmol) was added and the reaction mixture was hydrogenated at rt and 1 atm over night. The reaction mixture was filtered through a pre-packed C18 column (Isolute 10g) and eluted with MeOH. The solvent was removed *in vacuo* to give *N*-(2-hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)-3-methyltetrahydrofuran-2-yl]pyridine-2-carboxamide, as a white solid (0.959 g). MS *m/z* 371 $[M+H]^+$.

Trifluoromethanesulfonic anhydride (0.59 mL, 3.51 mmol) was slowly added to a stirred solution of *N*-(2-hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)-3-methyltetrahydrofuran-2-yl]pyridine-2-carboxamide (1.0 g, 2.70 mmol) and DMAP (1.65 g, 13.50 mmol) in CH_2Cl_2 (39 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. Saturated $NaHCO_3$ (aq) and CH_2Cl_2 were added and the mixture was allowed to reach rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried by passage through a phase separator and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (50→100%, EtOAc in heptane). The resulting oil was dissolved in CH_2Cl_2 and the solvent was removed *in vacuo* to give the **Step 5** intermediate of compound **29** as a white solid (1.16g). MS *m/z* 503 $[M+H]^+$.



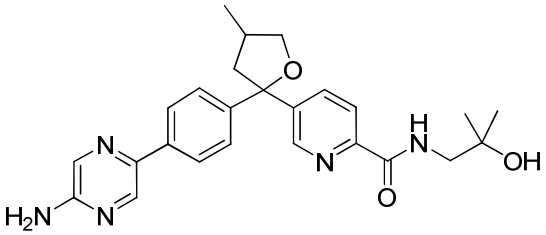
Step 6 and 7: *5-{(2R,3R and 2R,3S and 2S,3R and 2S,3S)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-3-methyltetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide* **(29).** Potassium acetate (1.61 g, 16.37 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.25 g, 4.91 mmol) and $PdCl_2$(dppf) (0.48 g, 0.65 mmol) were added to a solution of the **Step 5** intermediate of compound **29** (1.65 g, 3.27 mmol) in dioxane (22 mL). The mixture was degassed and then heated at reflux for 30 min. The reaction mixture was allowed to attain rt and was then partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. CH_2Cl_2 was added to the residue and concentrated *in vacuo* to give crude *N*-(2-hydroxy-2-methylpropyl)-5-{3-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide as a solid (1.57 g). MS *m/z* 481 $[M+H]^+$.

Potassium carbonate (0.90 g, 6.55 mmol) was added to a solution of crude *N*-(2-hydroxy-2-methylpropyl)-5-{3-methyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}pyridine-2-carboxamide (1.57 g, 3.27 mmol), 5-bromopyrazin-2-amine (0.627 g, 3.60 mmol) and $PdCl_2$(dppf) (0.24 mg, 0.33 mmol) in dioxane (30 mL) and water (30 mL). The mixture was degassed and then heated at reflux for 60 min. The mixture was partitioned between water and EtOAc and the aqueous phase was extracted once more with EtOAc. The combined organic phase was washed with saturated $NaHCO_3$ (aq), brine, saturated NH_4Cl (aq) and finally brine. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (EtOAc) to give 1.7 g of a white solid. 0.9 g of the crude residue was used and purified by preparative HPLC (XBridge C18, 10-50% CH_3CN in 0.2% NH_3 (aq))to give a stereoisomeric mixture of compound **29** as an off-white solid (0.66 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.18 – 8.3 (m, 3H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.88 – 7.92 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 3H), 4.45 (s, 2H), 4.06 – 4.15 (m, 1H), 3.65 – 3.84 (m, 1H), 3.34 (d, *J* = 6.5 Hz, 2H), 2.89 – 3.04 (m, 1H), 2.38 (s, 1H), 1.89 – 1.97 (m, 1H), 1.61 – 1.74 (m, 1H), 1.14 (s, 6H), 0.76 (d, *J* = 6.9 Hz, 3H); MS *m/z* 448 $[M+H]^+$.

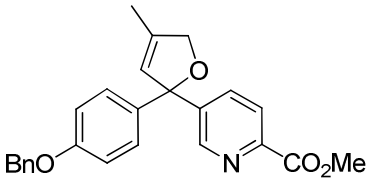
The racemate of compound **32** (0.033g) was also isolated in this step as an impurity and further used as described below.

The stereoisomers of compound **29** (665 mg, 1.49 mmol) were separated by chiral chromatography on a Cellucoat 250 mm x 50 mm, 10 µm HPLC column. 233 mg (66.5 mg/ml in EtOH) was injected and eluted with Heptane/EtOH/Et_3N, 80/20/0.1, at a flow rate of 120 mL/min and at 40°C and detected at 320 nm. The first eluted fraction was collected and evaporated to give the least active stereoisomer (293 mg, >99.8% ee). $[\alpha]_D^{20}$: −101 (*c* 1.0, CH_3CN). The second eluted fraction was collected and evaporated to give a stereoisomer

contaminated with the first eluted stereoisomer (34 mg, 82.8% ee). The third eluted fraction contained a mixture of two stereoisomers (282 mg) which was separated by a second chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 µm HPLC column. 50 mg (50 mg/ml in EtOH) was injected and eluted with Heptane/EtOH/Et_3N, 50/50/0.1 at a flow rate of 18 mL/min and detected at 320 nm. The first eluted fraction was collected and evaporated to give the most active stereoisomer (222 mg, 99.9% ee). $[\alpha]_D^{20}$: +108 (*c* 1.0, CH_3CN). ^1H NMR (400 MHz, $(CD_3)SO$) δ 8.70 (d, *J* = 1.7 Hz, 1H), 8.23 – 8.33 (m, 2H), 8.01 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.38 (s, 2H), 4.01 (q, *J* = 7.8 Hz, 1H), 3.61 – 3.71 (m, 1H), 3.11 (d, *J* = 6.2 Hz, 2H), 2.90 – 3.00 (m, 1H), 1.70 – 1.84 (m, 1H), 1.53 – 1.66 (m, 1H), 0.94 (s, 6H), 0.65 (d, *J* = 6.8 Hz, 3H); HRMS (EI/MS): *m/z* calcd for $C_{25}H_{29}N_5O_3$ [M+H]+ 448.2349, found 448.2363. The second eluted fraction was collected and evaporated to give the second most active stereoisomer (26 mg, 99.1% ee). $[\alpha]_D^{20}$: +151 (*c* 1.0, CH_3CN).

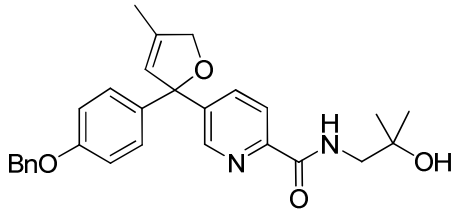


5-{(*2R,4R and 2R,4S and 2S,4R and 2S,4S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-4-methyltetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (30).

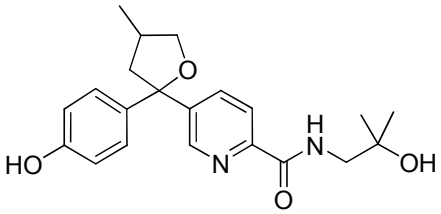


Step 1: (*Methyl 5-{2-[4-(benzyloxy)phenyl]-4-methyl-2,5-dihydrofuran-2-yl}pyridine-2-carboxylate***):**

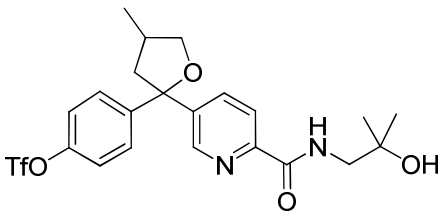
The **Step 1** intermediate of compound **30** was prepared as described for compound **6** starting from compound **27** (751 mg, 1.78 mmol). The crude product was purified by flash column chromatography (8→66%, EtOAc in toulene) to give the **Step 1** intermediate of compound **30** as a colourless oil (664 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 0.7, 2.2 Hz, 1H), 8.04 (dd, *J* = 0.7, 8.1 Hz, 1H), 7.77 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.26 – 7.41 (m, 5H), 7.12 – 7.17 (m, 2H), 6.86 – 6.91 (m, 2H), 5.87 (d, *J* = 1.6 Hz, 1H), 5.01 (s, 2H), 4.59 – 4.71 (m, 2H), 3.97 (s, 3H), 1.81 (d, *J* = 1.3 Hz, 3H); MS *m/z* 401 $[M+H]^+$.



Step 2 and 3: (*5-{2-[4-(Benzyloxy)phenyl]-4-methyl-2,5-dihydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide):* The **Step 2** and **Step** 3 intermediates of compound **30** were prepared as described in Step 1 and Step 2 of compound **17a** starting from the **Step 1** intermediate of compound **30** (664 mg, 1.65 mmol). The crude product was purified by flash column chromatography (5% EtOH in toluene) to give the **Step 3** intermediate of compound **30** as a clear oil (650 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 0.7, 2.2 Hz, 1H), 8.36 (t, *J* = 6.0 Hz, 1H), 8.10 (dd, *J* = 0.7, 8.1 Hz, 1H), 7.76 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.32 – 7.42 (m, 4H), 7.26 – 7.32 (m, 1H), 7.15 – 7.19 (m, 2H), 6.86 – 6.93 (m, 2H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.02 (s, 2H), 4.59 – 4.72 (m, 2H), 3.45 (d, *J* = 6.4 Hz, 2H), 2.51 (d, *J* = 1.6 Hz, 1H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.25 (s, 6H); MS *m/z* 459 $[M+H]^+$.

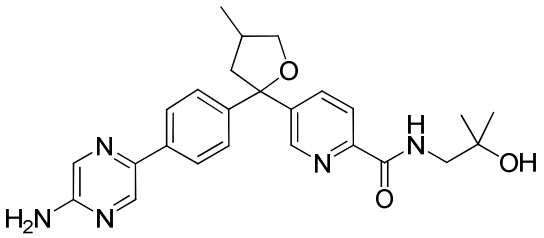


Step 4: (*N-(2Hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)-4-methyltetrahydrofuran-2-yl]pyridine-2-carboxamid).* The **Step 3** intermediate of compound **30** (440 mg, 0.96 mmol) was dissolved in EtOH (38 mL) and the solution was passed three times through an H-cube flow reactor at rt and at a presuure of 2-4 bar, and at a flow rate of 1 mL/min using a 10% Pd/C cartridge as catalyst. The solvent was evaporated *in vacuo* to give the **Step 4** intermediate of compound **30** as a clear oil (307 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.2 Hz, 2H), 8.25 (t, *J* = 6.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.71 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 3.99 – 4.11 (m, 1H), 3.45 (t, *J* = 8.6 Hz, 1H), 3.33 (d, *J* = 6.5 Hz, 2H), 2.62 (dd, *J* = 6.5, 11.9 Hz, 1H), 2.01 – 2.26 (m, 2H), 1.14 (s, 6H), 0.92 (dd, *J* = 2.5, 6.5 Hz, 3H); MS *m/z* 371 $[M+H]^+$.



Step 5: (*4-(2-{6-[(2-Hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}-4-methyltetrahydrofuran-2-yl)phenyl trifluoromethanesulfonate*): The **Step 5** intermediate was prepared as described in Step 1 of compound **15b** starting from the **Step 4** intermediate of

compound **30** (425 mg, 1.15 mmol). The crude compound was purified by flash column chromatography (15→100%, EtOAc in heptane) to give the **Step 5** intermediate of compound **30** as a clear oil (425 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.51 (m, 1H), 8.22 (t, *J* = 6.1 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.78 (m, 1H), 7.34 – 7.41 (m, 2H), 7.05 – 7.11 (m, 2H), 4.04 – 4.12 (m, 1H), 3.43 – 3.50 (m, 1H), 3.34 (d, *J* = 6.4 Hz, 2H), 2.75 (dd, *J* = 6.7, 12.3 Hz, 1H), 2.17 – 2.27 (m, 1H), 2.01 (ddd, *J* = 4.8, 10.4, 12.4 Hz, 1H), 1.14 (s, 7H), 0.94 (dd, *J* = 2.8, 6.6 Hz, 3H); MS *m/z* 503 $[M+H]^+$.



Step 6 and 7: *5-{(2R,4R and 2R,4S and 2S,4R and 2S,4S)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-4-methyltetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide* **(30)**.

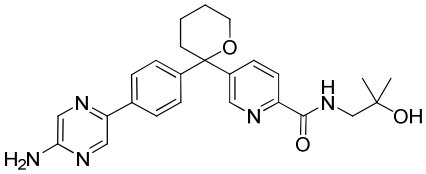
The **Step 6** and **Step 7** intermediates of compound **30** were prepared as described in Step 2 and Step 3 of compound **15b** starting from the **Step 5** intermediate of compound **30** (760 mg, 1.51 mmol). The crude product was purified by flash column chromatography (0→10%, EtOH in EtOAc) to give a stereoisomeric mixture of compound **30** as a beige foam (1.08 g, 88% over 2 steps).

The stereoisomers of compound **30** (1.63 g, 3.64 mmol) were separated by chiral chromatography on a Chiralpak IC 250x20mm, 5µm HPLC column. 50 mg (50 mg/ml in EtOAc) was injected and eluted with Heptane/EtOAc/Et_3N, 40/60/0.1 at a flow rate of 18 mL/min and at 40°C and detected at 310 nm. The first eluted fraction contained a mixture of two stereoisomers (604 mg). The second eluted fraction contained a mixture of two other stereoisomers (652 mg).

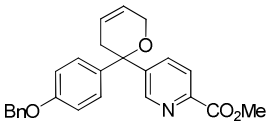
The first eluted stereoisomeric mixture was separated by a second chiral chromatography on a Chiralpak IA column 250x20mm, 5µm. 13.5 mg (45 mg/ml in THF) was injected and eluted with Heptane/THF/Et_3N, 55/45/0.1, at a flow rate of 18 mL/min and at 40°C and detected at 310 nm. The first eluted compound was collected and evaporated to give the most active stereoisomer (167mg, 99.9% ee). Final purification was made by flash column chromatography (100% EtOAc, then 0→15 %, EtOH in EtOAc) to give the most active stereoisomer (0.067 g). $[\alpha]_D^{20}$ -25 (c 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.1 Hz, 1H), 8.41 (d, *J* = 1.2 Hz, 1H), 8.33 – 8.39 (m, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 1.2 Hz, 1H), 7.90 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.59 (s, 2H), 4.23 (t, *J* = 8.0 Hz, 1H), 3.61 (t, *J* = 8.4 Hz, 1H), 3.46 (d, *J* = 6.4 Hz, 2H), 2.97 (dd, *J* = 6.8, 12.2 Hz, 1H), 2.37 – 2.49 (m, 1H), 2.05 – 2.13 (m, 1H), 1.26 (s, 6H), 1.08 (d, *J* = 6.6 Hz, 3H); HRMS (EI/MS): *m/z* calcd for $C_{25}H_{29}N_5O_3$ $[M+H]+$ 448.2349, found

448.2339. The second eluted compound was collected to give the second most active stereoisomer (643mg, 99.0% ee). Final purification was made by flash column chromatography (100% EtOAc, then 0→15 %, EtOH in EtOAc) to give the second most active stereoisomer (365mg), $[\alpha]_D^{20}$ -20 (c 1.0, $CHCl_3$).

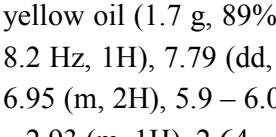
The second eluted stereoisomeric mixture obtained in the first chiral chromatography was separated by a third chiral chromatography on a Chiralpak IA column 250x20mm, 5µm HPLC column. 9 mg (45 mg/mL in THF) was injected and eluted with Heptane/THF/Et_3N, 55/45/0.1, at a flow rate of 18 mL/min and at 40°C and detected at 310 nm. The first eluted compound was collected and evaporated to give the least active stereoisomer (609 mg, 99.9% ee). Final purification was made by flash column chromatography (100% EtOAc, then 0→15 %, EtOH in EtOAc) to give the least active stereoisomer (345mg), $[\alpha]_D^{20}$ +20 (c 1.0, $CHCl_3$). The second eluted compound was collected to give a stereoisomer of compound **30** containing small impurities of the least active stereoisomer (309mg).



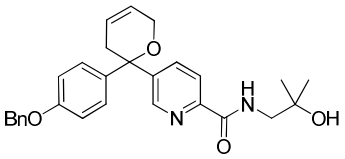
5-{(2*R* and 2*S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydro-2*H*-pyran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (31)



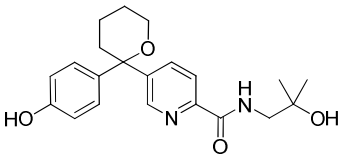
Step 1 (*Methyl 5-{2-[4-(benzyloxy)phenyl]-3,6-dihydro-2H-pyran-2-yl}pyridine-2-carboxylate*): The **Step 1** intermediate of compound **31** was prepared according to compound **6** starting from compound **28**. The residue was purified by flash column chromatography (0→20%, EtOAc in toulene) to give the **step 1** intermediate of compound **31** as a slightly yellow oil (1.7 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.71 (m, 1H), 8.05 (d, *J* = 0.8, 8.2 Hz, 1H), 7.79 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.29 – 7.47 (m, 5H), 7.18 – 7.25 (m, 2H), 6.86 – 6.95 (m, 2H), 5.9 – 6.03 (m, 1H), 5.58 – 5.71 (m, 1H), 5.03 (s, 2H), 3.91 – 4.13 (m, 5H), 2.81 – 2.93 (m, 1H), 2.64 – 2.76 (m, 1H); MS *m/z* 402.3 $(M+H)^+$.



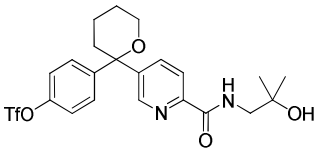
Step 2 (*5-{2-[4-(Benzyloxy)phenyl]-3,6-dihydro-2H-pyran-2-yl}pyridine-2-carboxylic acid*): The The **Step 2** intermediate of compound **31** was prepared as described in Step 1 of compound **17a** starting from the **Step 1** intermediate of compound **31** to give (1.64 g, 100%). MS *m/z* 388.3 $(M+H)^+$.



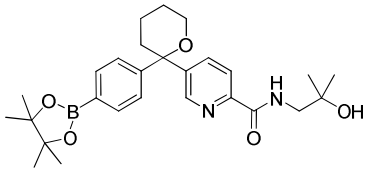
Step 3 (*5-{2-[4-(Benzyloxy)phenyl]-3,6-dihydro-2H-pyran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 3** intermediate of compound **31** was prepared according to step 2 of compound **17a**.starting from the **Step 2** intermediate of compound **31.** The residue was purified by flash column chromatography (5% EtOH in toluene) to give the **Step 3** intermediate of compound **31** as a white solid (1.60 g, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.52 (m, 1H), 8.33 – 8.41 (m, 1H), 8.11 (d, *J* = 0.8, 8.3 Hz, 1H), 7.82 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.29 – 7.45 (m, 5H), 7.19 – 7.25 (m, 2H), 6.88 – 6.95 (m, 2H), 5.93 – 6.03 (m, 1H), 5.61 – 5.71 (m, 1H), 5.04 (s, 2H), 3.94 – 4.12 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.79 – 2.93 (m, 1H), 2.65 – 2.76 (m, 1H), 2.52 (s, 1H), 1.28 (s, 6H); MS *m/z* 459.4 $(M+H)^+$.



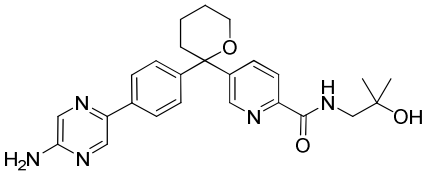
Step 4 (*N-(2-Hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)tetrahydro-2H-pyran-2-yl]pyridine-2-carboxamide*): The **Step 4** intermediate of compound **31** was prepared according to Step 3 of compound **17a** starting from the **Step 3** intermediate of compound **31.** (1.30 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 – 8.54 (m, 1H), 8.32 – 8.42 (m, 1H), 8.10 (d, *J* = 0.8, 8.2 Hz, 1H), 7.82 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.22 – 7.29 (m, 2H), 6.74 – 6.85 (m, 2H), 4.97 (s, 1H), 3.62 – 3.80 (m, 2H), 3.46 (d, *J* = 6.5 Hz, 2H), 2.54 (s, 1H), 2.35 – 2.47 (m, 1H), 2.02 – 2.20 (m, 1H), 1.57 – 1.83 (m, 4H), 1.27 (s, 6H); MS *m/z* 371.3 $(M+H)^+$.



Step 5 (*4-(2-{6-[(2-Hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}tetrahydro-2H-pyran-2-yl)phenyl trifluoromethanesulfonate*): The **Step 5** intermediate of compound **31** was prepared according to Step 1 of compound **15b** starting from the **Step 4** intermediate of compound **31**. The residue was purified by flash column chromatography (20→80%, EtOAc in heptane) to give the **Step 5** intermediate of compound **31** as a white solid. (1.50 g, 85 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.55 (m, 1H), 8.29 – 8.4 (m, 1H), 8.15 (d, *J* = 0.8, 8.3 Hz, 1H), 7.86 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.43 – 7.51 (m, 2H), 7.19 – 7.25 (m, 2H), 3.60 – 3.76 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.43 (s, 1H), 2.25 – 2.36 (m, 2H), 1.59 – 1.83 (m, 4H), 1.28 (s, 6H); MS *m/z* 503.3 $(M+H)^+$.

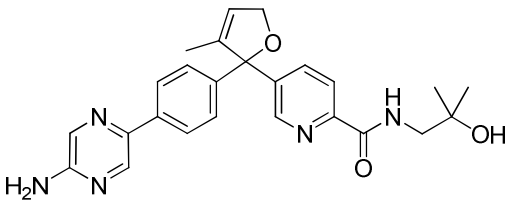


Step 6 (*N-(2-Hydroxy-2-methylpropyl)-5-{2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydro-2H-pyran-2-yl}pyridine-2-carboxamide*): The **Step 6** intermediate of compound **31** was prepared according to Step 2 of compound **15b** starting from the **Step 5** intermediate of compound **31**. (1.40 g, 100%). MS *m/z* 481.4 $(M+H)^+$.



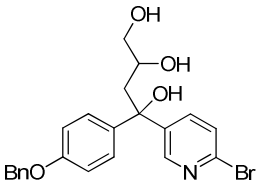
Step 7 (*5-{(2R and 2S)-2-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydro-2H-pyran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide* (**31**)): The racemate of compound **31** was prepared according to Step 3 of compound **15b** starting from the **Step 6** intermediate of compound **31**. The residue was purified by flash column chromatography (100% EtOAc. then 0→15%, EtOH in EtOAc) to give the racemate of compound **31** as a slightly yellow solid (1.16 g, 88 %).

The enantiomers were separated by chiral chromatography on a Chiralpak IC 250 mm x 20 mm, 5 μm HPLC column. 25 mg, 50 mg/ml in EtOAc, was injected and eluted with heptane/EtOAc/Et_3N 40/60/0.1 at a flow rate of 18 mL/min and detected at 360 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (278 mg, 98.2% ee). $[\alpha]_D^{20}$ –20 (*c* 1.0, $CHCl_3$). The second eluted compound was collected and evaporated to give the most active enantiomer (79 mg, 98.2% ee). $[\alpha]_D^{20}$ +21 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 1.5 Hz, 1H), 8.44 (d, *J* = 1.4 Hz, 1H), 8.34 – 8.42 (m, 1H), 8.09 – 8.15 (m, 1H), 8.06 (d, *J* = 1.5 Hz, 1H), 7.83 – 7.94 (m, 3H), 7.46 – 7.52 (m, 2H), 4.61 (s, 2H), 3.67 – 3.84 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.53 (s, 1H), 2.46 – 2.52 (m, 1H), 2.14 – 2.27 (m, 1H), 1.6 – 1.86 (m, 4H), 1.28 (s, 6H); HRMS (ESI); *m/z* calcd for $C_{25}H_{29}N_5O_3$ $[M + H]^+$ 448.2349; found 448.2355.

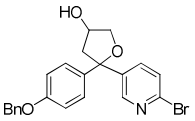


5-{(*2R and 2S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-3-methyl-2,5-dihydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (32) The racemate of compound **32** were isolated in the preparative HPLC purification, after Step 7 in the synthesis of compound **29**, as a white solid (33 mg). MS *m/z* 446 $[M+H]^+$.

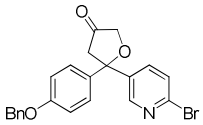
The enantiomers (33 mg, 0.074 mmol) were separated by chiral chromatography on a Chiralcel OJ 250x20mm, 5µm HPLC column. 30mg (30 mg/mL in EtOH) was injected and eluted with EtOH/Et_3N, 100/0.1, at a flow of 18mL/min and detected at 260nm. The first eluted compound was collected and evaporated to give the most active enantiomer (12mg, 99.9% ee). $[\alpha]_D^{20}$+2 (c 1.0, CH_3CN). ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.2 Hz, 1H), 8.33 (d, *J* = 1.4 Hz, 1H), 8.26 – 8.31 (m, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.69 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 5.75 (d, *J* = 1.5 Hz, 1H), 4.62 – 4.71 (m, 2H), 4.48 (s, 2H), 3.37 (d, *J* = 6.4 Hz, 2H), 1.65 (d, *J* = 1.6 Hz, 3H), 1.17 (s, 6H); HRMS (EI/MS): *m/z* calcd for $C_{25}H_{27}N_5O_3$ [M+H]+ 446.2192, found 446.2202. The second eluted compound was collected and evaporated to give the least active enantiomer (15 mg, 99.9% ee), $[\alpha]_D^{20}$–3 (c 1.0, CH_3CN).



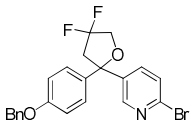
4-(4-(Benzyloxy)phenyl)-4-(6-bromopyridin-3-yl)butane-1,2,4-triol (33). Potassium osmate dihydrate (0.763 g, 2.07 mmol) and 4-methylmorpholine 4-oxide (10.44 g, 89.08 mmol) were added to a solution of the **Step 1** intermediate of compound **25** (17 g, 41.43 mmol) in a mixture of THF (240 mL), acetone (240 mL) and water (240 mL) and the reaction mixture was stirred at rt for 4 h. The reaction mixture was evaporated to half the volume and then partitioned between CH_2Cl_2 and brine. The aqueous phase was extracted into CH_2Cl_2 again and the combined organic layer was dried (phase-separator) and the solvents were removed under reduced pressure to give a mixture of diastereoisomers of compound **33** (1:1) ((18.4 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.48 (m, 1H), 7.54 – 7.69 (m, 1H), 7.26 – 7.48 (m, 8H), 6.84 – 7.01 (m, 2H), 5.04 (d, *J* = 7.6 Hz, 2H), 3.39 – 3.93 (m, 4H), 2.19 – 2.5 (m, 4H); MS *m/z* 444.1 and 446.1 $(M+H)^+$.



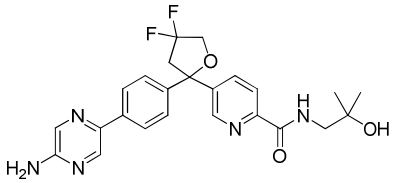
5-(4-(Benzyloxy)phenyl)-5-(6-bromopyridin-3-yl)tetrahydrofuran-3-ol (34). Compound **33** (18.4 g, 41.41 mmol) was dissolved in $CHCl_3$ (288 ml) then 4-methylbenzenesulfonic acid hydrate (1.57 g, 8.28 mmol) was added. The reaction mixture was heated at reflux for 4 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with saturated brine. The organic phase was dried (phase-separator) and the solvents were evaporated. The residue was purified by flash column chromatography (20→70%, EtOAc in heptane) to give compound **34** (15.3 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.47 (m, 1H), 7.48 – 7.68 (m, 1H), 7.26 – 7.45 (m, 8H), 6.86 – 6.99 (m, 2H), 5.03 (s, 2H), 4.5 – 4.66 (m, 1H), 4.04 – 4.2 (m, 1H), 3.9 – 4.01 (m, 1H), 2.55 – 2.95 (m, 2H), 1.59 – 1.69 (m, 1H); MS *m/z* 426.2 and 428.2 $(M+H)^+$.



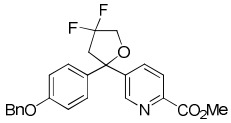
5-(4-(Benzyloxy)phenyl)-5-(6-bromopyridin-3-yl)dihydrofuran-3(2H)-one (35). Compound **34** (15.3 g, 35.89 mmol) was dissolved in CH_2Cl_2 (191 ml). Dess-Martin periodinane (15.98 g, 37.68 mmol) was added in portions and the mixture was stirred at rt over night. A solution of sodium thiosulfate (20.42 ml, 215.34 mmol) and sodium hydrogen carbonate (4.61 ml, 118.44 mmol) in water was added into the mixture and the mixture was then stirred vigorously for 2 h. The two phases were separated and the water phase was extracted with CH_2Cl_2 (100 mL). The combined organic phase was dried by passing through a phase-separator.and the solvent was evaporated to give compound **35** as a slightly yellow solid (14.90 g, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.46 (m, 1H), 7.54 – 7.62 (m, 1H), 7.24 – 7.49 (m, 8H), 6.91 – 7 (m, 2H), 5.05 (s, 2H), 3.94 – 4.18 (m, 2H), 2.95 – 3.37 (m, 2H); MS *m/z* 424.1 and 426.1 $(M+H)^+$.



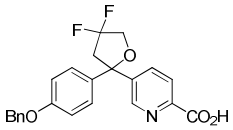
5-(2-(4-(Benzyloxy)phenyl)-4,4-difluorotetrahydrofuran-2-yl)-2-bromopyridine (36). Compound **35** (14.9 g, 35.12 mmol) and Deoxofluor (50% solution in toluene) (51.8 ml, 140.47 mmol) were dissolved into CH_2Cl_2 (651 ml) then the solution was stirred at reflux for 24 h. The organic layer was washed with saturated NH_4Cl (aq). The organic layer was dried through a phase-separator. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (0→20%, EtOAc in heptane) to give compound **36** as a colourless oil, which solidified while standing at rt over night (13.8 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.4 (m, 1H), 7.52 – 7.58 (m, 1H), 7.23 – 7.45 (m, 8H), 6.89 – 6.99 (m, 2H), 5.05 (s, 2H), 3.96 – 4.18 (m, 2H), 2.84 – 3.25 (m, 2H); MS *m/z* 446.1 and 448.1 $(M+H)^+$.



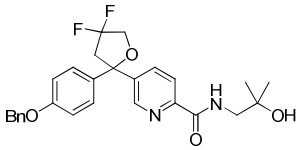
5-{(2*R* and 2*S*)-2-[4-(5-aminopyrazin-2-yl)phenyl]-4,4-difluorotetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (37)



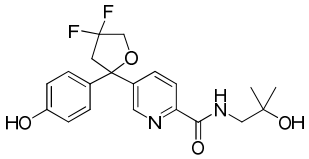
Step 1 (*Methyl 5-{2-[4-(benzyloxy)phenyl]-4,4-difluorotetrahydrofuran-2-yl}pyridine-2-carboxylate*): The **Step 1** intermediate of compound **37** was prepared according to compound **6** starting from compound **36**. (1.8 g, 80%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.81 (m, 1H), 8.07 – 8.14 (m, 1H), 7.87 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.25 – 7.47 (m, 7H), 6.93 – 7.00 (m, 2H), 5.07 (s, 2H), 4.05 – 4.22 (m, 2H), 4.02 (s, 3H), 2.95 – 3.35 (m, 2H); MS *m/z* 426.3 $(M+H)^+$.



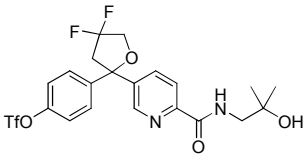
Step 2 (*5-{2-[4-(Benzyloxy)phenyl]-4,4-difluorotetrahydrofuran-2-yl}pyridine-2-carboxylic acid*): The **Step 2** intermediate of compound **37** was prepared according to Step 1 of compound **17a** starting from the **Step 1** intermediate of compound **37**. (1.74 g, 100%). MS *m/z* 412.2 $(M+H)^+$.



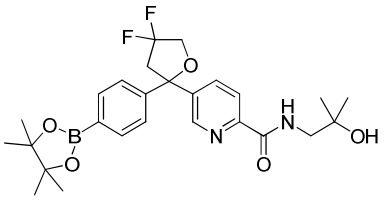
Step 3 (*5-{2-[4-(Benzyloxy)phenyl]-4,4-difluorotetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 3** intermediate of compound **37** was prepared according to Step 2 of compound **17a** starting from the **Step 2** intermediate of compound **37** (1.95 g, 96%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.61 (m, 1H), 8.31 – 8.40 (m, 1H), 8.15 (d, 1H), 7.85 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.26 – 7.46 (m, 7H), 7.13 – 7.21 (m, 1H), 6.9 – 7.01 (m, 2H), 5.05 (s, 2H), 3.97 – 4.23 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.95 – 3.33 (m, 2H), 1.28 (s, 6H); MS *m/z* 483.3 $(M+H)^+$.



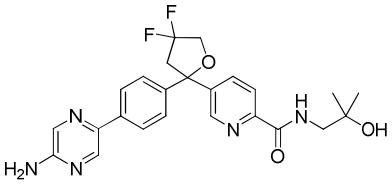
Step 4 (*5-[4,4-Difluoro-2-(4-hydroxyphenyl)tetrahydrofuran-2-yl]-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 4** intermediate of compound **37** was prepared according to Step 3 of compound **17a** starting from the **Step 3** intermediate of compound **37** (1.50 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.62 (m, 1H), 8.32 – 8.42 (m, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.23 – 7.27 (m, 2H), 6.79 – 6.86 (m, 2H), 5.14 (s, 1H), 4.03 – 4.20 (m, 2H), 3.49 (d, *J* = 6.4 Hz, 2H), 2.94 – 3.32 (m, 2H), 2.41 (s, 1H), 1.29 (s, 6H); MS *m/z* 393.3 $(M+H)^+$.



Step 5 (*4-(4,4-Difluoro-2-{6-[(2-hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}tetrahydrofuran-2-yl)phenyl trifluoromethanesulfonate*): The **Step 5** intermediate of compound **37** was prepared according to Step 1 of compound **15b** starting from the **Step 4** intermediate of compound **37** (1.62 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 – 8.63 (m, 1H), 8.29 – 8.37 (m, 1H), 8.19 (d, *J* = 0.8, 8.2 Hz, 1H), 7.88 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.47 – 7.53 (m, 2H), 7.27 – 7.32 (m, 2H), 4.06 – 4.25 (m, 2H), 3.48 (d, *J* = 6.4 Hz, 2H), 3.1 – 3.22 (m, 2H), 2.29 (s, 1H), 1.28 (s, 6H); MS *m/z* 525.0 $(M+H)^+$.



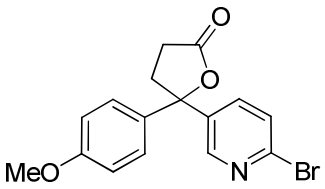
Step 6 (*5-{4,4-Difluoro-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 6** intermediate of compound **37** was prepared according to Step 2 of compound **15b** starting from the **Step 5** intermediate of compound **37** (1.55 g, 100%). MS *m/z* 503.3 $(M+H)^+$.



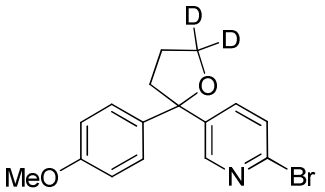
Step 7 (*5-{(2R and 2S)-2-[4-(5-aminopyrazin-2-yl)phenyl]-4,4-difluorotetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide* (**37**)): The racemate of compound **37** was prepared according to Step 3 of compound **15b** starting from the **Step 6** intermediate of compound **37.**

The enantiomers were separated by chiral chromatography on a Chiralpak IA 250 mm x 20 mm, 20 μm HPLC column. 100 mg (100 mg/ml in THF) was injected and eluted with Heptane/THF/ HCO_2H 30/70/0.1 at a flow rate of 120 mL/min and detected at 315 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (130 mg, 99.9% ee). $[\alpha]_D^{20}$ +12 (*c* 1.0, CH_3CN). The second eluted compound was collected and evaporated to give the most active enantiomer (170 mg, 99.9% ee). $[\alpha]_D^{20}$ –11 (*c* 1.0, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.66 (m, 1H), 8.4 – 8.45 (m, 1H), 8.31 – 8.39 (m, 1H), 8.16 (d, *J* = 0.8, 8.2 Hz, 1H), 8.05 (d, *J* = 1.5 Hz, 1H), 7.84 – 7.92 (m, 3H), 7.45 – 7.51 (m, 2H), 4.63 (s, 2H), 4.07 – 4.25 (m, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 3.02 – 3.36 (m, 2H), 2.39 (s,

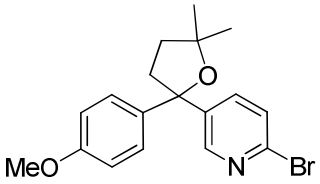
1H), 1.27 (s, 6H); HRMS (ESI); *m/z* calcd for $C_{24}H_{25}F_2N_5O_3$ $[M + H]^+$ 470.2003; found 470.1998.



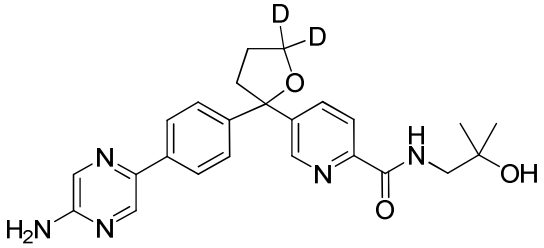
5-(6-Bromopyridin-3-yl)-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (38). 2 M Isopropyl magnesium chloride (3.17 mL, 6.35 mmol) in THF was added to a solution of 2-bromo-5-iodopyridine (1.56 g, 5.50 mmol) in THF (10 mL) and the reaction mixture was stirred at rt for 5 min. The reaction mixture was then slowly added to a solution of ethyl 4-(4-methoxyphenyl)-4-oxobutanoate [5] (1.00 g, 4.23 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was then partitioned between CH_2Cl_2 and saturated $NaHCO_3$ (aq) and the organic phase was dried (phase separator) and concentrated *in vacuo*. The residue was purified by flash column chromatography (20→60%, EtOAc in heptane, then 50%, EtOAc in heptane) to give compound **38** (0.643 g, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 2.7, 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.32 (m, 2H), 6.87 – 6.93 (m, 2H), 3.80 (s, 3H), 2.92 – 3.01 (m, 1H), 2.73 – 2.83 (m, 1H), 2.58 – 2.64 (m, 2H); MS *m/z* 350 $(M+H)^+$.



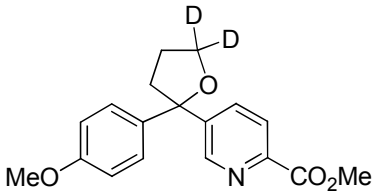
2-Bromo-5-[2-(4-methoxyphenyl)(5,5-$^2H_2$)tetrahydrofuran-2-yl]pyridine (39). Lithium aluminum deuteride (0.247 g, 5.89 mmol) was added to a solution of compound **38** (2.03 g, 5.83 mmol) in THF (50 mL). The reaction mixture was stirred at 0 °C for 50 min and the reaction was then quenched by addition of excess $Na_2SO_4x10H_2O$/Celite (1:1) at 0°C. The mixture was stirred at rt for 1 h and then filtered. The solid material was washed with THF and the combined filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (2 mL) and 4-methylbenzenesulfonic acid hydrate (0.222 g, 1.17 mmol) was added. The reaction mixture was heated at reflux for 7 h. The reaction mixture was diluted with CH_2Cl_2 and the organic phase was washed with saturated $NaHCO_3$ (aq). The organic phase was dried (phase separator) and concentrated *in vacuo* and the residue was purified by flash column chromatography (10→40%, EtOAc in heptane) to give compound **39** (1.444 g, 74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 2.55 – 2.64 (m, 1H), 2.38 – 2.46 (m, 1H), 1.88 – 2.02 (m, 2H); MS *m/z* 338 $(M+H)^+$.



2-Bromo-5-[2-(4-methoxyphenyl)-5,5-dimethyltetrahydrofuran-2-yl]pyridine (40). Compound **38** (3.6 g, 10.34 mmol) was dissolved in THF (100 mL) and methyl magnesium bromide (16.25 mL, 22.75 mmol, 1.4 M in toluene:THF 75:25) was added. The reaction mixture was stirred at rt for 3 h. Saturated $NaHCO_3$ (aq) and CH_2Cl_2 were added and the two phases were separated. The organic layer was dried (phase separator) and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (100 mL), 4-methylbenzenesulfonic acid hydrate (0.590 g, 3.10 mmol) was added and the reaction mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to rt before saturated $NaHCO_3$ (aq) was added, and the two phases were separated. The organic layer was dried (phase separator) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (5→60%, EtOAc in heptane) to give compound **40** (1.00 g, 27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.33 (m, 2H), 6.79 – 6.85 (m, 2H), 3.78 (s, 3H), 2.64 – 2.76 (m, 1H), 2.49 – 2.63 (m, 1H), 1.73 – 1.93 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H); MS *m/z* 364 $(M+H)^+$.

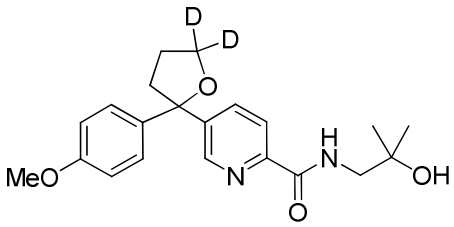


5-{(2*R* and *S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl](5,5-$^2H_2$)tetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (41)

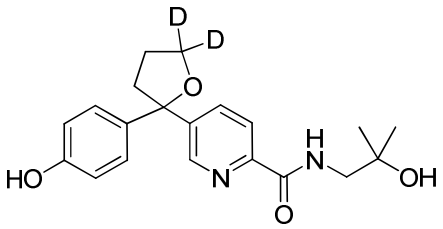


Step 1 (*Methyl 5-[2-(4-methoxyphenyl)(5,5-$^2H_2$)tetrahydrofuran-2-yl]pyridine-2-carboxylate):* The **Step 1** intermediate of compound **41** was prepared from compound **39** in manner analogous to compound **3**. The crude product was purified by flash column chromatography (30→80%, EtOAc in heptane). (0.82 g, 57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 – 8.83 (m, 1H), 8.04 (dd, *J* = 0.6, 8.2 Hz, 1H), 7.86 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.29 – 7.35

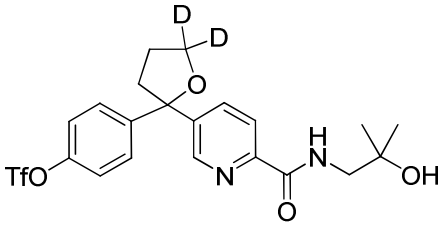
(m, 2H), 6.82 – 6.87 (m, 2H), 3.98 (s, 3H), 3.78 (s, 3H), 2.61 – 2.7 (m, 1H), 2.43 – 2.53 (m, 1H), 1.89 – 2.06 (m, 2H); MS *m/z* 316 $(M+H)^+$.



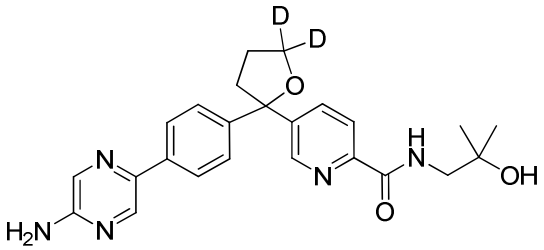
Step 2 and 3 (*N-(2-Hydroxy-2-methylpropyl)-5-[2-(4-methoxyphenyl)(5,5-$^2H_2$)tetrahydrofuran-2-yl]pyridine-2-carboxamide*): The **Step 2 and Step 3** intermediates of compound **41** were prepared from the **Step 1** intermediate of compound **41** according to Step 1 and Step 2 of compound **17a**. The crude product was purified by flash column chromatography (60→100%, EtOAc in heptane) to give the **Step 3** intermediate of compound **41**. (0.845 g, 91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.6 Hz, 1H), 8.36 (t, *J* = 5.7 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.87 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.30 – 7.35 (m, 2H), 6.82 – 6.88 (m, 2H), 3.78 (s, 3H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.6 – 2.71 (m, 1H), 2.50 (s, 1H), 2.43 – 2.5 (m, 1H), 1.88 – 2.04 (m, 2H), 1.27 (s, 6H); MS *m/z* 373 $(M+H)^+$.



Step 4 (*N-(2-Hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)(5,5-$^2H_2$)tetrahydrofuran-2-yl]pyridine-2-carboxamide*): The **Step 3** intermediate of compound **41** (0.83 g, 2.24 mmol) was dissolved DMF (16 mL). Sodium methanethiolate (1.23 g, 17.91 mmol) was then added and the reaction mixture was heated in a microwave reactor at 120°C for 2 h. Acetic acid (~3 mL) was added and the reaction mixture was then partitioned between with EtOAc and water. The organic phase was washed with water and saturated NaCl (aq), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (70→100%, EtOAc in heptane) and then by preparative HPLC (Kromasil C8, 15→75% CH_3CN in 0.2% CH_3CO_2H (aq)) to give the **Step 4** intermediate of compound **41** (0.48 g, 60%); ^{1}H NMR (600 MHz,CD_3OD) δ 8.65 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.95 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 3.39 (s, 2H), 2.59 – 2.72 (m, 1H), 2.37 – 2.54 (m, 1H), 1.88 – 2.01 (m, 2H), 1.20 (s, 6H); MS *m/z* 359 $(M+H)^+$.

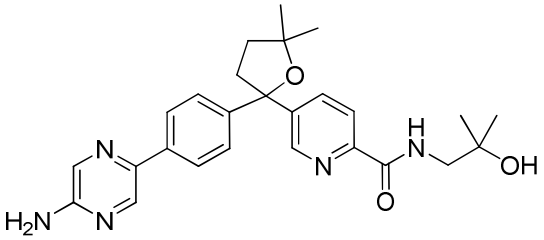


Step 5 (*4-[2-{6-[(2-Hydroxy-2-methylpropyl)carbamoyl]pyridin-3-yl}(5,5-$^2H_2$)tetrahydrofuran-2-yl]phenyl trifluoromethanesulfonate*): The **Step 5** intermediate of compound **41** was prepared from the **Step 4** intermediate of compound **41** according to Step 1 of compound **15b**. (0.62 g, 96%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1H), 8.35 (t, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 3.47 (d, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.38 (s, 1H), 1.94 – 2.04 (m, 2H), 1.28 (s, 6H): MS *m/z* 535 $(M+H)^+$.

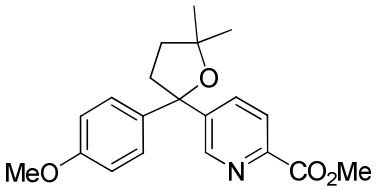


Step 6 and 7 (*5-{2-[4-(5-Aminopyrazin-2-yl)phenyl](5,5-$^2H_2$)tetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The racemate of compound **41** was prepared from the **Step 5** intermediate of compound **41** according to Step 2 and Step 3 of compound **15b**. (0.33 g, 61%); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, *J* = 1.5 Hz, 1H), 8.46 (d, *J* = 1.3 Hz, 1H), 8.40 (t, *J* = 6.1 Hz, 1H), 8.05 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 1.3 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 6.54 (s, 2H), 4.68 (s, 1H), 3.26 (d, *J* = 6.2 Hz, 2H), 2.56 – 2.71 (m, 2H), 1.82 – 1.96 (m, 2H), 1.08 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{24}H_{28}D_2N_5O_3$ $[M + H]^+$ 436.2318; found 436.2320.

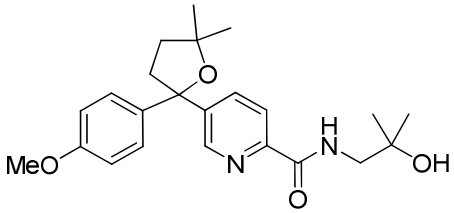
The enantiomers (32 mg, 0.74 mmol) were separated by chiral chromatography on a Chiralcel OJ 250 mm x 20 mm, 5 μm HPLC column. 150 mg (50 mg/ml EtOH/MeOH 1/1) was injected and eluted with MeOH/EtOH/Et_3N 50/50/0.1 at a flow rate of 18 mL/min and detected at 310 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (160 mg, 99.9% ee). $[\alpha]_D^{20}$: −15 (c 1.0 g, CH_3CN). HRMS (ESI) *m/z* calcd for $C_{24}H_{28}D_2N_5O_3$ $[M + H]^+$ 436.2318; found 436.2311. The second eluted compound was collected and evaporated to give the least active enantiomer (156 mg, 99.9% ee). $[\alpha]_D^{20}$: +16 (*c* 1.0, CH_3CN). HRMS (ESI) *m/z* calcd for $C_{24}H_{28}D_2N_5O_3$ $[M + H]^+$ 436.2318; found 436.2327.



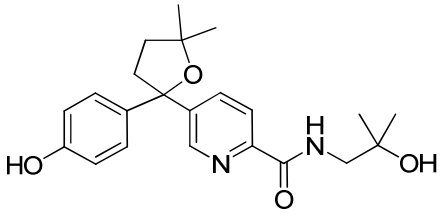
5-{(2*R* and *S*)-2-[4-(5-Aminopyrazin-2-yl)phenyl]-5,5-dimethyltetrahydrofuran-2-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (42)



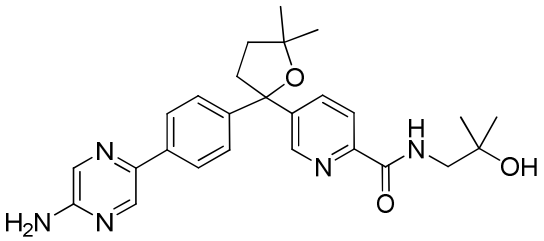
Step 1 (*Methyl 5-[2-(4-methoxyphenyl)-5,5-dimethyltetrahydrofuran-2-yl]pyridine-2-carboxylate*): The **Step 1** intermediate of compound **42** was prepared from compound **40** according to compound **3**. The crude product was purified by flash column chromatography (0→20%, EtOAc in heptane). (1.15 g, 76 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 1.7 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.86 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.28 – 7.36 (m, 2H), 6.79 – 6.86 (m, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 2.69 – 2.81 (m, 1H), 2.54 – 2.67 (m, 1H), 1.73 – 1.94 (m, 2H), 1.32 (s, 3H), 1.31 (s, 3H); MS *m/z* 342 $(M+H)^+$.



Step 2 and 3 (*N-(2-Hydroxy-2-methylpropyl)-5-[2-(4-methoxyphenyl)-5,5-dimethyltetrahydrofuran-2-yl]pyridine-2-carboxamide*): The **Step 2** and **Step 3** intermediates of compound **42** were prepared from the **Step 1** intermediate of compound **42** according to Step 1 and Step 2 of compound **17a**. The crude product was purified by flash column chromatography (30→100%, EtOAc in heptane) to give the **Step 3** intermediate of compound **42**. (1.10 g, 82 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.6 Hz, 1H), 8.36 (t, *J* = 5.9 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.30 – 7.36 (m, 2H), 6.8 – 6.86 (m, 2H), 3.77 (s, 3H), 3.46 (d, *J* = 6.4 Hz, 2H), 2.70 – 2.80 (m, 1H), 2.55 – 2.65 (m, 1H), 2.51 (s, 1H), 1.75 – 1.94 (m, 2H), 1.32 (s, 6H), 1.27 (s, 6H); MS *m/z* 399 $(M+H)^+$.



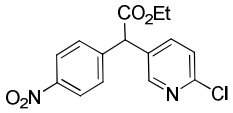
Step 4 (*N-(2-Hydroxy-2-methylpropyl)-5-[2-(4-hydroxyphenyl)-5,5-dimethyltetrahydrofuran-2-yl]pyridine-2-carboxamide*): The **Step 3** intermediate of compound **42** (1.00 g, 2.51 mmol) was dissolved in DMF (20 mL) and the mixture was added to a reaction tube containing sodium methanethiolate (1.07 g, 15.1 mmol). The reaction mixture was heated to 120 °C for 5 h and was then partitioned between EtOAc and water. A small volume of 10% citric acid (aq) was added to the aqueous phase and the aqueous phase was extracted with EtOAc**.** The combined organic phase was dried (phase separator) and concentrated under reduced pressure. The residue was purified by flash column chromatography (40→100%, EtOAc in heptane). To remove residual DMF the product was dissolved in EtOAc and the organic layer was washed twice with slightly acidic water. The organic phase was dried and concentrated *in vacuo* to give the **Step 4** intermediate of compound **42** (0.80 g, 83 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 6H), 1.32 (s, 6H), 1.75 – 1.93 (m, 2H), 2.52 – 2.62 (m, 1H), 2.69 – 2.78 (m, 1H), 3.46 (d, 2H), 6.75 – 6.82 (m, 2H), 7.22 – 7.25 (m, 2H), 7.87 (dd, 1H), 8.07 (d, 1H), 8.33 – 8.41 (m, 1H), 8.63 (d, 1H); MS *m/z* 385 $(M+H)^+$.



Step 5, 6 and 7 (*5-{2-[4-(5-Aminopyrazin-2-yl)phenyl]-5,5-dimethyltetrahydrofuran-2-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The racemate of compound **42** was prepared starting from the **Step 4** intermediate of compound **42** according to Step 1, Step 2 and Step 3 of compound **15b**. The crude product was purified by flash column chromatography (0→25%, MeOH in EtOAc) to give the racemate of compound **42** (0.37 g, 42%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.77 (d, *J* = 1.7 Hz, 1H), 8.45 (d, *J* = 1.4 Hz, 1H), 8.41 (t, *J* = 6.2 Hz, 1H), 8.05 (dd, *J* = 2.2, 8.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 1.4 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 6.53 (s, 2H), 4.68 (s, 1H), 3.25 (d, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 1.72 – 1.86 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H), 1.08 (s, 6H); HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_5O_3$ $[M + H]^+$ 462.2505; found 462.2507.

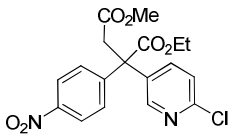
The enantiomers (370 mg, 0.80 mmol) were separated by chiral chromatography on a Chiralpak IA 250mm x 20 mm, 5 μm HPLC column. 100 mg (50 mg/ml in MeOH/EtOH 1/1) was injected and eluted with MeOH/EtOH/Et_3N 50/50/0.1 at a flow rate of 18 mL/min and detected at 275 nm. The first eluted compound was collected and evaporated to give the least active enantiomer (160 mg, 98.1% ee). $[\alpha]_D^{20}$: +15 (c 1.0 g, CH_3CN). HRMS (ESI) *m/z* calcd

for $C_{26}H_{32}N_5O_3$ $[M + H]^+$ 462.2505; found 462.2502. The second eluted compound was collected and evaporated to give the most active enantiomer (155 mg, 99.7% ee). $[\alpha]_D^{20}$: −14 (c 1.0 g, CH_3OH). HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_5O_3$ $[M + H]^+$ 462.2505; found 462.2504.

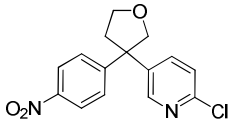


Ethyl 2-(6-chloropyridin-3-yl)-2-(4-nitrophenyl)acetate (43). H_2SO_4 (5 mL) was added to a solution of 2-(6-chloropyridin-3-yl)acetic acid (40 g, 0.23 mmol) in EtOH (800 mL) and the reaction mixture was stirred at reflux for 10 h. The mixture was concentrated *in vacuo* and then partitioned between EtOAc (500 mL) and saturated $NaHCO_3$ (aq, 200 mL). The organic layer was washed with brine and water, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (6% EtOAc in petroleum ether) to give ethyl 2-(6-chloropyridin-3-yl)acetate as a colourless oil (42 g, 91%).

Ethyl 2-(6-chloropyridin-3-yl)acetate (42 g, 0.21 mol) was dissolved into DMF (300 mL) and kept under nitrogen atmosphere. NaH (60% in mineral oil, 10.1 g, 0.25 mol) was added at 0°C and the mixture was stirred at 0°C for 30 min. 1-Fluoro-4-nitrobenzene (44.4 g, 0.32 mol) was dissolved into DMF (200 mL) and added dropwise to the first mixture at 0°C. This reaction mixture was stirred at 0°C for 2 h. The reaction was quenched with water and extracted into EtOAc. The organic layer was washed with brine and water, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (9% EtOAc in petroleum ether) to give compound **43** (45 g, 67%). MS *m/z* 321 $(M+H)^+$.



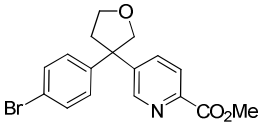
1-Ethyl 4-methyl 2-(6-chloropyridin-3-yl)-2-(4-nitrophenyl)succinate (44). Compound **43** (20 g, 62.5 mmol) was dissolved into DMF (200 mL) and kept under nitrogen atmosphere. NaH (5 g, 125 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min. Methyl 2-bromoacetate (24 g, 156 mmol) was dissolved into DMF (25 mL) and added dropwise to the first mixture at 0°C. This mixture was stirred at rt for 2 h. The reaction was quenched with water and extracted into EtOAc. The organic layer was washed with brine and water, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (9% EtOAc in petroleum ether) to give compound **44** (25 g, 100%). MS *m/z* 393 $(M+H)^+$.



2-Chloro-5-(3-(4-nitrophenyl)tetrahydrofuran-3-yl)pyridine (45). $LiAlH_4$ (5.9 g, 159 mmol) was added carefully to a solution of compound **44** (25 g, 63.8 mmol) in Et_2O (300 mL)

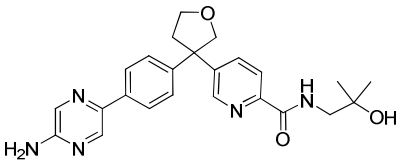
at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with brine and extracted into EtOAc. The organic layer was washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc in petroleum) to give 2-(6-chloropyridin-3-yl)-2-(4-nitrophenyl)butane-1,4-diol (5 g, 21%).

2-(6-Chloropyridin-3-yl)-2-(4-nitrophenyl)butane-1,4-diol (5 g, 15.5 mmol) was dissolved in HBr (20 mL) and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to rt and pH was adjusted to 7 by adding saturated $NaHCO_3$ (aq) in portions. The product was extracted into EtOAc. The organic layer was washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (9% EtOAc in petroleum ether) to give compound **45** (2.5 g, 52%). MS *m/z* 305 $(M+H)^+$.

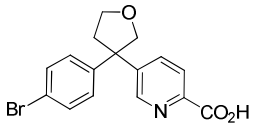


Methyl 5-[3-(4-bromophenyl)tetrahydrofuran-3-yl]pyridine-2-carboxylate (46). $Pd(dppf)Cl_2$ (1.3 g, 16 mmol) and Et_3N (11 mL, 82 mmol) were added to a solution of compound **45** (2.5 g, 8.2 mmol) in DMF (25 mL) and MeOH (25 mL) under an atmosphere of nitrogen. The reaction mixture was saturated with CO (g) and then stirred at 70 °C under CO atmosphere (5 bar) overnight. The mixture was allowed to reach rt and concentrated *in vacuo* and the residue was diluted with water and extracted into EtOAc. The organic layer was washed with brine and water, dried and finally concentrated *in vacuo*. The residue was purified by flash column chromatography (9% EtOAc in petroleum ether) to give methyl 5-(3-(4-aminophenyl)-tetrahydrofuran-3-yl)picolinate (1.6 g, 65.3%). ^1H NMR (300 MHz, MeOD-d_4) δ 8.54 (s, 1H), 7.90 – 8.09 (m, 2H), 7.00 – 7.05 (d, 2H), 6.68 – 6.72 (d, 2H), 4.15 – 4.42 (m, 2H), 3.86 – 4.04 (m, 5H), 2.59 – 2.71 (m, 2H); MS *m/z* 299.0 $(M+H)^+$.

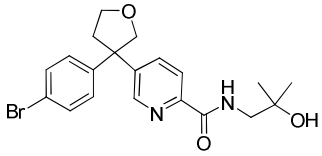
$NaNO_2$ (555 mg, 8 mmol) in H_2O (10 mL) was added dropwise to a stirred solution of methyl 5-(3-(4-aminophenyl)-tetrahydrofuran-3-yl)picolinate (1.6 g, 5.4 mmol) in HBr (5 mL) at –10°C and the reaction mixture was stirred at –10 °C for 10 min. The reaction mixture was added to a solution of CuBr (1.15 g, 8 mmol) in HBr (5 mL) at 70 °C. After the addition the reaction was quenched by adding saturated $NaHCO_3$ (aq) and the product was extracted into EtOAc. The organic layer was dried and concentrated and the crude product was purified by flash column chromatography to give compound **46** (900 mg, 46%). MS *m/z* 362, 364 $(M+H)^+$.



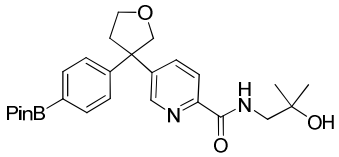
5-{(3*R* and 3*S*)-3-[4-(5-Aminopyrazin-2-yl)phenyl]tetrahydrofuran-3-yl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (47)



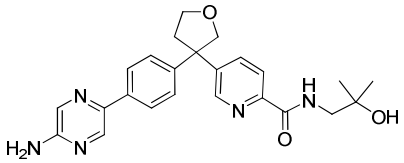
Step 1 (*5-[3-(4-Bromophenyl)tetrahydrofuran-3-yl]pyridine-2-carboxylic acid*): The **Step 1** intermediate of compound **47** was prepared from compound **46** according to Step 1 of compound **17a**. (780 mg, 100%). MS *m/z* 348 $(M+H)^+$.



Step 2 (*5-[3-(4-Bromophenyl)tetrahydrofuran-3-yl]-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 2** intermediate of compound **47** was prepared from the **Step 1** intermediate of compound **47** according to Step 2 of compound **17a**. (610 mg, 65%). MS *m/z* 419, 421 $(M+H)^+$.



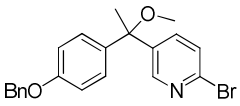
Step 3 (*N-(2-Hydroxy-2-methylpropyl)-5-{3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]tetrahydrofuran-3-yl}pyridine-2-carboxamide*): The **Step 3** intermediate of compound **47** was prepared from the **Step 2** intermediate of compound **47** according to Step 2 of compound **15b.** (50 mg, crude). MS *m/z* 467 $(M+H)^+$.



Step 4 (*5-{(3R and 3S)-3-[4-(5-aminopyrazin-2-yl)phenyl]tetrahydrofuran-3-yl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide* (**47**)): The racemate of compound **47**was prepared from the **Step 3** intermediate of compound **47** according to Step 2 and Step 3 of compound **15b.** The residue was purified by flash column chromatography (100% EtOAc, then 0→15%, EtOH in EtOAc) to give the racemate of compound **47** (12.1 mg, 26%).

The enantiomers were separated by chiral chromatography on a Chiralpak AS 250 mm x 20 mm, 5 μm HPLC column and eluted with hexane/EtOH/Et_2N 60/40/0.1 at a flow rate of 16 mL/min and detected at 254/220 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (5 mg, 99.9% ee). $[\alpha]_D^{20}$ +17 (*c* 1.0, CH_3OH). The second eluted compound was collected and evaporated to give the least active enantiomer (5 mg, 99.9% ee). $[\alpha]_D^{20}$ –18 (*c* 1.0, CH_3OH). ^1H NMR (300 MHz, acetone-d_6): δ 8.59 (m,

1H), 8.58 (m, 1H), 8.39 – 8.48 (s, 1H), 8.04 – 8.08 (m, 2H), 7.91 – 7.97 (m, 3H), 7.40 – 7.44 (m, 2H), 5.93 (s, 1H), 4.28 – 4.48 (m, 1H), 3.90 – 4.02 (m, 3H), 3.39 – 3.41 (d, 2H), 2.73 – 2.83 (m, 2H), 1.20 (s, 6H); HRMS (ESI); *m/z* calcd for $C_{24}H_{27}N_5O_3$ $[M + H]^+$ 434.2192; found 434.2190.



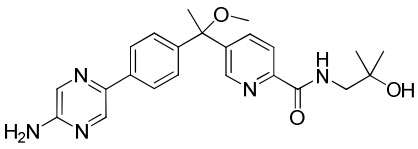
5-{1-[4-(Benzyloxy)phenyl]-1-methoxyethyl}-2-bromopyridine (48)

Step 1 (*1-[4-(Benzyloxy)phenyl]-1-(6-bromopyridin-3-yl)ethanol*):

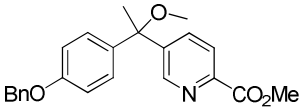
The **Step 1** intermediate of compound **48** was prepared from compound **1** according to Step 1 of compound **2,** but using methylmagnesium chloride instead of tert-butylmagnesium chloride. (2.0 g, crude). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.4 – 8.45 (m, 1H), 7.57 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.28 – 7.47 (m, 8H), 6.88 – 6.99 (m, 2H), 5.07 (s, 2H), 2.21 (s, 1H), 1.94 (s, 3H); MS *m/z* 384.3 and 386.3 $(M+H)^+$.

Step 2 *5-{1-[4-(Benzyloxy)phenyl]-1-methoxyethyl}-2-bromopyridine* **(48)**

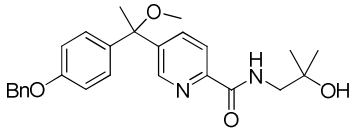
The crude **Step 1** intermediate of compound **48** (2.0 g, 5.20 mmol) was diluted with CH_2Cl_2 (40 mL) and thionyl chloride (4.56 mL, 62.46 mmol) was added. DMF (0.403 mL, 5.20 mmol) was added during stirring and the mixture was stirred at rt for 10 min. MeOH (100 mL) was added and the solution was stirred for 5 min at rt. The reaction was quenched by adding saturated $NaHCO_3$ (aq) and the product was extracted into CH_2Cl_2. The organic layer was dried and evaporated to give crude compound **48** as a yellow oil (1.05 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.39 (m, 1H), 7.3 – 7.48 (m, 7H), 7.2 – 7.25 (m, 2H), 6.93 – 7 (m, 2H), 5.10 (s, 2H), 3.14 (s, 3H), 1.83 (s, 3H); MS *m/z* 398.3 and 400.3 $(M+H)^+$.



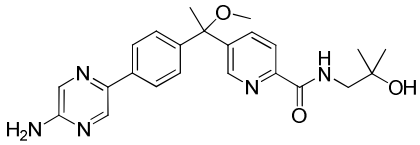
5-{(1*R* and 1*S*)-1-[4-(5-Aminopyrazin-2-yl)phenyl]-1-methoxyethyl}-*N*-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide (49)



Step 1 (*Methyl 5-{1-[4-(benzyloxy)phenyl]-1-methoxyethyl}pyridine-2-carboxylate*): The **Step 1** intermediate of compound **49** was prepared from compound **48** according to intermediate **6**. The residue was purified by flash column chromatography (0→30%, EtOAc in toulene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.78 (m, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.74 – 7.80 (m, 1H), 7.37 – 7.49 (m, 5H), 7.19 – 7.26 (m, 2H), 6.93 – 6.99 (m, 2H), 5.10 (s, 2H), 4.03 (s, 3H), 3.16 (s, 3H), 1.88 (s, 3H); MS *m/z* 378.3 $(M+H)^+$.



Step 2 and Step 3 (*5-{1-[4-(Benzyloxy)phenyl]-1-methoxyethyl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide*): The **Step 2** and **Step 3** intermediates of compound **49** were prepared from the **Step 1** intermediate of compound **49** according to Step 1 and Step 2 of compound **17a**. The residue was purified by flash column chromatography (5% EtOH in toluene) to give crude **Step 3** intermediate of compound **49**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.58 (m, 1H), 8.37 – 8.46 (m, 1H), 8.17 (d, *J* = 0.83, 8.12 Hz, 1H), 7.79 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.38 – 7.49 (m, 6H), 7.21 – 7.26 (m, 2H), 6.95 – 7 (m, 2H), 5.10 (s, 2H), 3.52 (d, *J* = 6.4 Hz, 2H), 2.81 (s, 3H), 1.60 (s, 3H), 1.31 (s, 6H); MS *m/z* 435.3 $(M+H)^+$.



Step 4, Step 5, Step 6, Step 7 (*5-{(1R and 1S)-1-[4-(5-aminopyrazin-2-yl)phenyl]-1-methoxyethyl}-N-(2-hydroxy-2-methylpropyl)pyridine-2-carboxamide)* (**49**): The racemate of compound **49** was prepared in four steps from crude **Step 3** intermediate of compound **49** as described in Step 3 of compound **17a** and in Step 1, Step 2 and Step 3 of compound **15b**. The crude product was purified by flash column chromatography (0→15%, EtOH in EtOAc) to give the racemate of compound **49** as an off-white solid (220 mg, 52%)

The enantiomers were separated by chiral chromatography on a Chiralcel OJ 250 mm x 30 mm, 5 μm HPLC column. 265 mg, 54 mg/ml in EtOH, was injected and eluted with 25% MeOH/Et_2N in CO_2 (80 bar) at a flow rate of 120 mL/min and detected at 270 nm. The first eluted compound was collected and evaporated to give the most active enantiomer (22 mg, 99.8% ee). $[\alpha]_D^{20}$ –20 (*c* 1.0, CH_3CN). The second eluted compound was collected and evaporated to give the least active enantiomer (20 mg, 96.6% ee). $[\alpha]_D^{20}$ +18 (*c* 1.0, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.58 (m, 1H), 8.44 (s, 1H), 8.34 – 8.41 (m, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.02 – 8.09 (m, 1H), 7.8 – 7.89 (m, 3H), 7.39 – 7.46 (m, 2H), 4.69 (s, 2H), 3.38 – 3.55 (m, 3H), 3.20 (s, 3H), 1.93 (s, 3H), 1.28 (s, 6H); HRMS (ESI); m/z calcd for $C_{23}H_{27}N_5O_3$ [M + H]+ 422.2192; found 422.2193.

Determination of absolute stereochemistry

Vibrational Circular Dichroism (VCD)

Summary

The structures of the two enantiomers of **5** are shown in Figure 1. The VCD spectra of the two samples in $CDCl_3$ were compared with simulated spectra of slightly truncated structures, (see Figure 2). All spectra, experimental and simulated, are presented in Figure 3.

From the comparison it was concluded that the enantiomer with negative optical rotation was determined to have (*R*)-configuration and that the enantiomer with positive optical rotation was determined to have (*S*)-configuration.

Figure 1. Full structures of the enantiomers

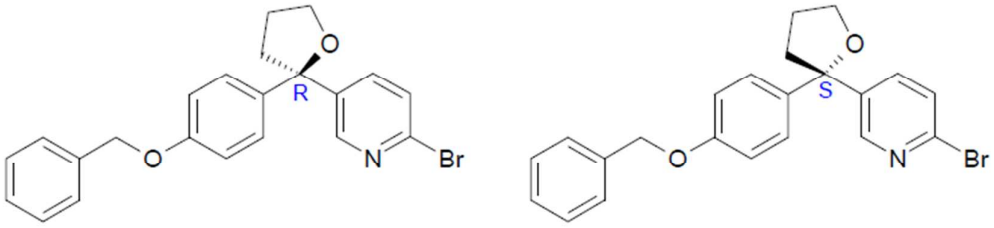


Figure 2. Truncated structures used in calculations

Experimental

Each sample was prepared by dissolving 15 mg of the solid material in 120 µl $CDCl_3$. The solutions were transferred to 0.100 mm BaF_2 cells and the VCD spectra were acquired for 7 h each in a BioTools ChiralIR instrument equipped with dual source and dual photo elastic modulator. The resolution was 4 cm^{-1}.

Computational Spectral Simulations

A Monte Carlo molecular mechanics search for low energy geometries was conducted for slightly truncated structures of the enantiomers, (*R*) and (*S*) (see Figure 2). MacroModel within the Maestro graphical interface (Schrödinger Inc.) was used to generate starting coordinates for conformers. All conformers within 5 kcal/mole of the lowest energy conformer were used as starting points for density functional theory (DFT) minimizations within Gaussian09.

Optimized structures, harmonic vibrational frequencies/intensities, VCD rotational strengths, and free energies at STP (including zero-point energies) were determined for each conformer.

In these calculations, the functional B3LYP and the basis set 6-31G* were used. Simulations of infrared and VCD spectra for each conformation were generated using an in-house built program to fit Lorentzian line shapes (12 cm^{-1} line width) to the computed spectra thereby allowing direct comparisons between simulated and experimental spectra.

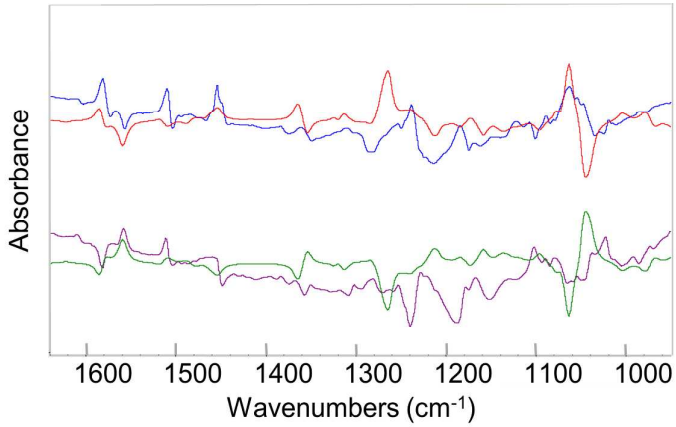
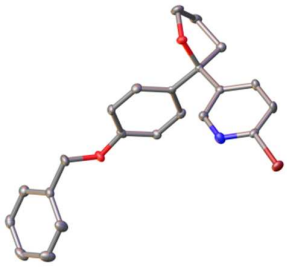


Figure 3. VCD. Blue = Experimental (–)-**5**, Purple = Experimental (+)-**5**, Red = Simulated (*R*), Green = Simulated (*S*)

X-ray Diffraction

Table 1. Crystal data and structure refinement details.

Grade: A1



Empirical formula	$C_{22}H_{20}BrNO_2$
Formula weight	410.30
Temperature	**100(2) K**
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	a = 7.0326(9) Å α = 76.140(6)°
	b = 8.8251(9) Å β = 88.225(6)°
	c = 15.0497(16) Å γ = 81.439(7)°
Volume	896.72(18) $Å^3$
Z	2 (Z'=2)
Density (calculated)	1.520 Mg / m^3
Absorption coefficient	2.308 mm^{-1}
F(000)	420
Crystal	Block; Colourless
Crystal size	0.150 × 0.080 × 0.0
θ range for data collection	2.403 – 27.523°
Index ranges	$-9 \le h \le 9$, $-11 \le k \le 11$, $-19 \le l \le 19$
Reflections collected	24132
Independent reflections	8232 [R_{int} = 0.0348]
Completeness to θ = 25.242°	99.9 %

Cell determined at **300K** on same crystal

a = 7.189(26) α = 76.39(18)
b = 8.976(18) β = 88.82(17)
c = 15.095(42) γ = 81.75(21)

Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.396
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8232 / 3 / 469
Goodness-of-fit on F^2	1.006
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0232, $wR2$ = 0.0569
R indices (all data)	$R1$ = 0.0244, $wR2$ = 0.0573
Absolute structure parameter	**–0.008(4)**
Hooft parameter	–0.013(1)
Largest diff. peak and hole	0.324 and –0.314 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100μm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst*. **A64**, 112-122). S**tructure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were located in the difference map and subsequently placed in idealised positions and refined using a riding model. The 2 molecules in the asymmetric unit are related by a pseudo centre of inversion – this is broken by the chiral centres C114/C214 – the atom types do not match across the inversion.
Chirality: C114 = R, C214 = R

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	7185(1)	–2830(1)	–5366(1)	22(1)	1
O1	6546(3)	–1931(3)	757(2)	20(1)	1
C115	12430(5)	354(5)	–2595(3)	18(1)	1
C121	7461(5)	–1278(5)	–3935(3)	20(1)	1
C101	3615(6)	–1134(4)	2505(3)	26(1)	1
C102	2144(6)	–1736(4)	3050(3)	31(1)	1
C103	871(5)	–2501(5)	2718(3)	31(1)	1
C104	1031(6)	–2657(6)	1819(3)	34(1)	1
C105	2470(6)	–2032(6)	1272(3)	30(1)	1
C106	3781(5)	–1267(5)	1604(3)	21(1)	1
C107	5316(5)	–617(4)	981(3)	22(1)	1
C108	7765(4)	–1621(4)	31(2)	14(1)	1
C109	8824(5)	–2952(4)	–192(3)	18(1)	1
C110	10060(5)	–2780(4)	–928(3)	17(1)	1
C111	10249(5)	–1292(4)	–1475(2)	16(1)	1
C112	9217(5)	24(4)	–1240(3)	16(1)	1
C113	7970(5)	–122(4)	–485(2)	17(1)	1
C114	11501(5)	–1165(4)	–2333(3)	15(1)	1
O2	13180(3)	–2365(3)	–2151(2)	18(1)	1
C116	14512(5)	–1796(4)	–1643(2)	21(1)	1
C117	14013(4)	15(4)	–1867(2)	21(1)	1
C118	10411(5)	–1470(4)	–3116(2)	15(1)	1
C119	8446(5)	–938(4)	–3241(3)	18(1)	1
C120	8518(5)	–2177(4)	–4465(3)	18(1)	1
N1	10392(4)	–2639(4)	–4407(2)	20(1)	1
C122	11315(5)	–2268(4)	–3735(3)	20(1)	1
Br2	8745(1)	4563(1)	7744(1)	21(1)	1
O3	8910(3)	3581(3)	1665(2)	19(1)	1
O4	3585(4)	1396(3)	5109(2)	17(1)	1
N2	8127(4)	3171(4)	6345(2)	21(1)	1
C201	11649(5)	2743(4)	–75(3)	21(1)	1
C202	13051(5)	3313(4)	–686(2)	23(1)	1
C203	14477(5)	4003(5)	–401(3)	27(1)	1
C204	14511(6)	4140(5)	496(3)	30(1)	1
C205	13124(6)	3565(5)	1112(3)	28(1)	1
C206	11681(5)	2860(4)	836(3)	19(1)	1
C207	10180(5)	2250(5)	1493(3)	23(1)	1
C208	7705(5)	3336(5)	2407(2)	18(1)	1
C209	6745(5)	4694(4)	2624(2)	15(1)	1
C210	5567(5)	4579(4)	3386(3)	16(1)	1
C211	5308(4)	3091(4)	3945(2)	13(1)	1
C212	6212(5)	1767(5)	3695(3)	17(1)	1

Table 2. cont.

C213	7428(5)	1856(4)	2934(2)	16(1)	1
C214	4022(5)	2990(4)	4796(2)	14(1)	1
C215	2047(4)	3966(4)	4567(2)	18(1)	1
C216	1122(5)	2940(4)	4078(2)	23(1)	1
C217	1870(5)	1287(4)	4635(3)	27(1)	1
C218	5090(5)	3342(4)	5585(2)	16(1)	1
C219	7047(5)	2862(4)	5700(2)	19(1)	1
C220	7183(5)	4006(4)	6885(2)	16(1)	1
C221	5235(5)	4525(5)	6859(3)	20(1)	1
C222	4172(5)	4162(4)	6194(3)	20(1)	1

Table 3. Bond lengths [Å] and angles [°].

Br1–C120	1.914(4)	C210–C211	1.413(5)	C121–C119–C118	120.1(3)
O1–C108	1.369(4)	C211–C212	1.373(5)	N1–C120–C121	125.7(4)
O1–C107	1.441(4)	C211–C214	1.538(4)	N1–C120–Br1	116.1(3)
C115–C117	1.533(5)	C212–C213	1.403(5)	C121–C120–Br1	118.2(3)
C115–C114	1.539(5)	C214–C215	1.523(4)	C120–N1–C122	116.3(3)
C121–C120	1.381(5)	C214–C218	1.540(5)	N1–C122–C118	123.9(3)
C121–C119	1.385(6)	C215–C216	1.519(5)	C208–O3–C207	118.2(3)
C101–C102	1.388(5)	C216–C217	1.523(5)	C217–O4–C214	107.9(3)
C101–C106	1.389(5)	C218–C219	1.382(5)	C220–N2–C219	115.3(3)
C102–C103	1.370(6)	C218–C222	1.387(5)	C202–C201–C206	120.4(3)
C103–C104	1.391(6)	C220–C221	1.377(5)	C203–C202–C201	120.2(3)
C104–C105	1.380(6)	C221–C222	1.391(5)	C202–C203–C204	119.9(3)
C105–C106	1.390(6)	C108–O1–C107	117.9(3)	C203–C204–C205	120.3(4)
C106–C107	1.496(5)	C117–C115–C114	101.7(3)	C206–C205–C204	120.6(4)
C108–C113	1.390(5)	C120–C121–C119	116.5(3)	C205–C206–C201	118.7(3)
C108–C109	1.399(5)	C102–C101–C106	120.1(4)	C205–C206–C207	120.8(4)
C109–C110	1.381(5)	C103–C102–C101	120.8(4)	C201–C206–C207	120.5(3)
C110–C111	1.395(5)	C102–C103–C104	119.8(4)	O3–C207–C206	108.0(3)
C111–C112	1.389(5)	C105–C104–C103	119.5(4)	O3–C208–C209	115.4(3)
C111–C114	1.532(5)	C104–C105–C106	121.2(4)	O3–C208–C213	124.5(3)
C112–C113	1.407(5)	C101–C106–C105	118.6(3)	C209–C208–C213	120.1(3)
C114–O2	1.449(4)	C101–C106–C107	122.4(4)	C210–C209–C208	120.0(3)
C114–C118	1.523(5)	C105–C106–C107	118.9(3)	C209–C210–C211	120.8(3)
O2–C116	1.443(4)	O1–C107–C106	107.5(3)	C212–C211–C210	118.1(3)
C116–C117	1.541(5)	O1–C108–C113	124.8(3)	C212–C211–C214	122.0(3)
C118–C122	1.383(5)	O1–C108–C109	115.2(3)	C210–C211–C214	120.0(3)
C118–C119	1.395(5)	C113–C108–C109	120.0(3)	C211–C212–C213	122.1(3)
C120–N1	1.319(5)	C110–C109–C108	120.1(3)	C208–C213–C212	118.9(3)
N1–C122	1.347(5)	C109–C110–C111	121.1(3)	O4–C214–C215	103.1(3)
Br2–C220	1.917(4)	C112–C111–C110	118.4(3)	O4–C214–C211	109.3(3)
O3–C208	1.375(4)	C112–C111–C114	122.3(3)	C215–C214–C211	111.7(3)
O3–C207	1.437(4)	C110–C111–C114	119.3(3)	O4–C214–C218	106.8(3)
O4–C217	1.447(4)	C111–C112–C113	121.5(3)	C215–C214–C218	115.0(3)
O4–C214	1.449(4)	C108–C113–C112	118.8(3)	C211–C214–C218	110.5(3)
N2–C220	1.324(5)	O2–C114–C118	106.8(3)	C216–C215–C214	101.0(3)
N2–C219	1.352(5)	O2–C114–C111	109.6(3)	C215–C216–C217	102.0(3)
C201–C202	1.393(5)	C118–C114–C111	110.6(3)	O4–C217–C216	107.1(3)
C201–C206	1.399(5)	O2–C114–C115	101.5(3)	C219–C218–C222	117.1(3)
C202–C203	1.377(5)	C118–C114–C115	113.7(3)	C219–C218–C214	120.3(3)
C203–C204	1.385(6)	C111–C114–C115	114.0(3)	C222–C218–C214	122.6(3)
C204–C205	1.390(6)	C116–O2–C114	106.7(2)	N2–C219–C218	124.8(3)
C205–C206	1.390(5)	O2–C116–C117	106.9(3)	N2–C220–C221	125.9(4)
C206–C207	1.494(4)	C115–C117–C116	103.1(3)	N2–C220–Br2	115.2(3)
C208–C209	1.390(5)	C122–C118–C119	117.2(3)	C221–C220–Br2	118.9(3)
C208–C213	1.394(5)	C122–C118–C114	121.9(3)	C220–C221–C222	116.9(3)
C209–C210	1.386(5)	C119–C118–C114	120.9(3)	C218–C222–C221	119.9(3)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	25(1)	25(1)	20(1)	−8(1)	−3(1)	−6(1)
O1	17(1)	19(1)	21(1)	−2(1)	6(1)	0(1)
C115	16(2)	19(2)	19(2)	−6(1)	5(1)	−6(1)
C121	18(2)	25(2)	18(2)	−7(1)	−1(1)	−2(1)
C101	34(2)	18(2)	25(2)	−8(1)	1(2)	0(1)
C102	44(2)	24(2)	20(2)	−4(1)	12(2)	6(2)
C103	20(2)	33(2)	28(2)	7(2)	7(2)	5(2)
C104	20(2)	54(3)	26(2)	3(2)	−4(2)	−12(2)
C105	24(2)	46(2)	19(2)	−4(2)	−1(1)	−10(2)
C106	17(2)	22(2)	20(2)	−1(1)	4(1)	3(1)
C107	19(2)	20(2)	27(2)	−9(1)	3(1)	1(1)
C108	12(1)	16(2)	15(2)	−4(1)	−1(1)	−1(1)
C109	15(2)	17(2)	21(2)	−2(1)	−1(1)	−3(1)
C110	13(1)	15(2)	23(2)	−7(1)	−2(1)	−1(1)
C111	13(1)	21(2)	14(1)	−4(1)	0(1)	−4(1)
C112	16(2)	12(2)	20(2)	−3(1)	0(1)	−1(1)
C113	14(2)	19(2)	20(2)	−8(1)	2(1)	0(1)
C114	10(1)	14(2)	21(2)	−4(1)	0(1)	0(1)
O2	13(1)	21(1)	22(1)	−8(1)	0(1)	0(1)
C116	13(2)	28(2)	22(2)	−6(1)	−1(1)	−2(1)
C117	14(1)	28(2)	26(2)	−12(1)	2(1)	−7(1)
C118	17(2)	15(2)	14(1)	−3(1)	2(1)	−4(1)
C119	15(2)	20(2)	19(2)	−6(1)	1(1)	1(1)
C120	16(2)	16(2)	19(2)	−1(1)	−2(1)	−4(1)
N1	20(1)	20(2)	22(2)	−8(1)	2(1)	−1(1)
C122	14(2)	22(2)	24(2)	−6(1)	−1(1)	−1(1)
Br2	23(1)	22(1)	20(1)	−6(1)	−5(1)	−6(1)
O3	16(1)	18(1)	20(1)	−2(1)	3(1)	1(1)
O4	16(1)	16(1)	18(1)	−3(1)	−1(1)	−5(1)
N2	15(1)	25(2)	23(2)	−7(1)	−2(1)	1(1)
C201	23(2)	18(2)	23(2)	−5(1)	−1(1)	−1(1)
C202	28(2)	21(2)	18(2)	−5(1)	2(1)	2(1)
C203	19(2)	31(2)	25(2)	2(2)	7(1)	−1(2)
C204	21(2)	41(2)	29(2)	−4(2)	−2(2)	−12(2)
C205	24(2)	41(2)	19(2)	−6(2)	2(1)	−8(2)
C206	18(2)	17(2)	21(2)	−5(1)	3(1)	0(1)
C207	21(2)	20(2)	27(2)	−6(1)	8(1)	−2(1)
C208	12(1)	26(2)	14(2)	−4(1)	1(1)	−4(1)
C209	13(2)	13(2)	17(2)	−1(1)	−2(1)	0(1)
C210	15(2)	17(2)	17(2)	−4(1)	0(1)	−1(1)
C211	11(1)	15(2)	14(1)	−3(1)	−2(1)	−2(1)
C212	18(2)	18(2)	16(2)	−3(1)	0(1)	−6(1)

Table 4. cont.

C213	15(2)	14(2)	20(2)	−6(1)	2(1)	0(1)
C214	14(2)	16(2)	14(1)	−4(1)	2(1)	−4(1)
C215	15(2)	20(2)	18(1)	−2(1)	−1(1)	−2(1)
C216	16(2)	36(2)	18(1)	−6(2)	0(1)	−8(1)
C217	21(2)	28(2)	35(2)	−10(2)	−1(2)	−9(1)
C218	15(2)	15(2)	16(2)	−1(1)	1(1)	−3(1)
C219	19(2)	22(2)	17(2)	−8(1)	3(1)	−2(1)
C220	21(2)	16(2)	14(2)	−4(1)	0(1)	−5(1)
C221	19(2)	23(2)	19(2)	−9(1)	−1(1)	1(1)
C222	16(2)	24(2)	23(2)	−9(1)	−1(1)	1(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H11A	12974	511	–3219	21	1
H11B	11495	1292	–2555	21	1
H121	6129	–913	–4041	24	1
H101	4508	–630	2749	31	1
H102	2018	–1616	3661	37	1
H103	–118	–2924	3100	37	1
H104	156	–3189	1585	41	1
H105	2567	–2127	656	36	1
H10A	4734	108	417	26	1
H10B	6068	–24	1288	26	1
H109	8692	–3976	165	21	1
H110	10793	–3689	–1065	20	1
H112	9355	1045	–1598	19	1
H113	7281	789	–329	21	1
H11C	15850	–2109	–1824	25	1
H11D	14382	–2241	–978	25	1
H11E	13538	387	–1319	25	1
H11F	15144	526	–2111	25	1
H119	7781	–341	–2849	22	1
H122	12669	–2573	–3683	24	1
H201	10666	2272	–277	26	1
H202	13022	3225	–1302	27	1
H203	15436	4385	–818	32	1
H204	15485	4628	692	36	1
H205	13164	3656	1727	33	1
H20A	9451	1582	1230	27	1
H20B	10790	1603	2072	27	1
H209	6896	5701	2251	18	1
H210	4925	5512	3534	20	1
H212	6007	759	4050	21	1
H213	8052	923	2779	20	1
H21A	1332	4100	5126	22	1
H21B	2142	5015	4161	22	1
H21C	1543	3092	3433	27	1
H21D	–298	3161	4098	27	1
H21E	888	888	5080	32	1
H21F	2175	556	4227	32	1
H219	7679	2272	5297	22	1
H221	4644	5103	7277	24	1
H222	2819	4476	6157	24	1

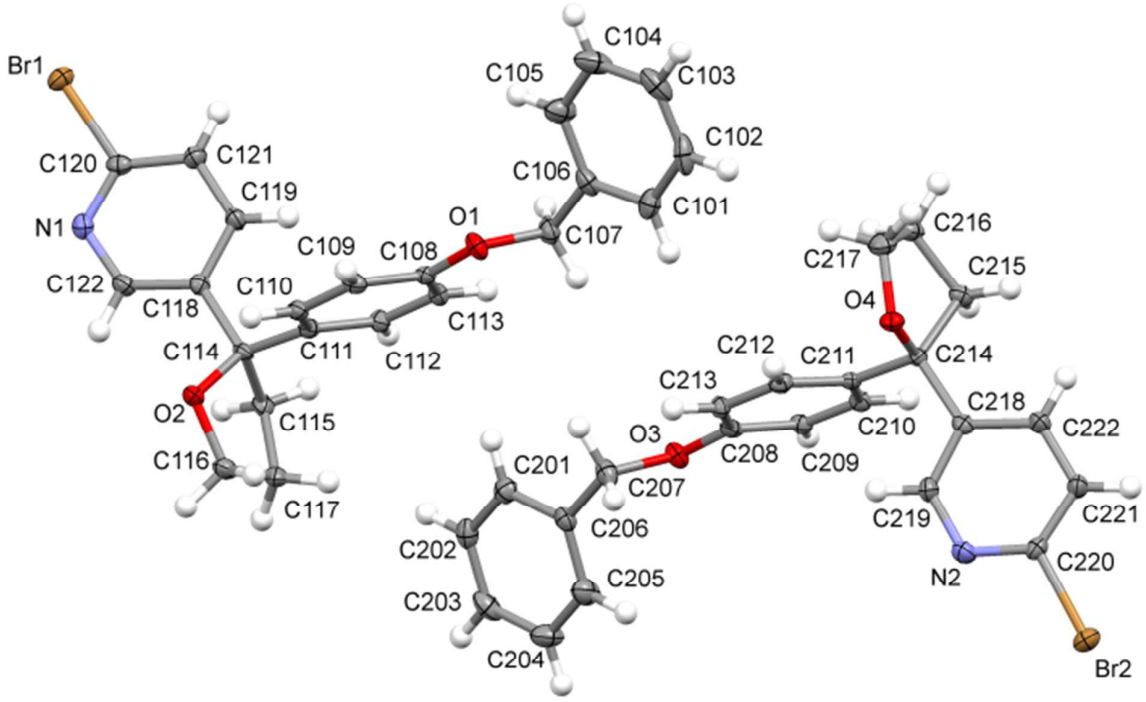


Figure 4. Thermal ellipsoids drawn at the 50% probability the PSEDUO centre of inversion is clear.

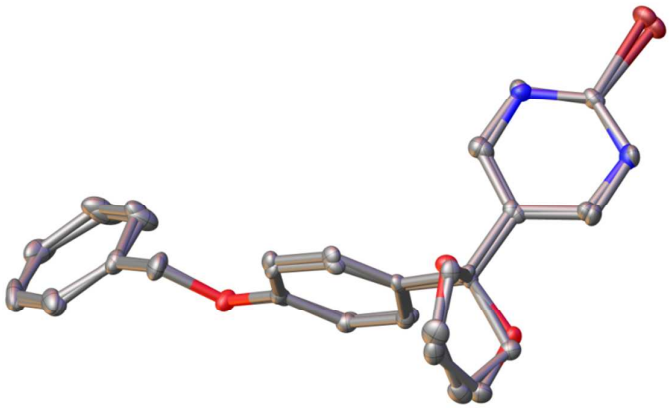


Figure 5. Overlay plot of molecule 1 and an inverted molecule 2. This shows how the basic connectivity shows a pseudo centre of inversion – but this is broken by the arrangement of the atom types at the chiral centre (chiral molecules cannot be inverted and superimposed).

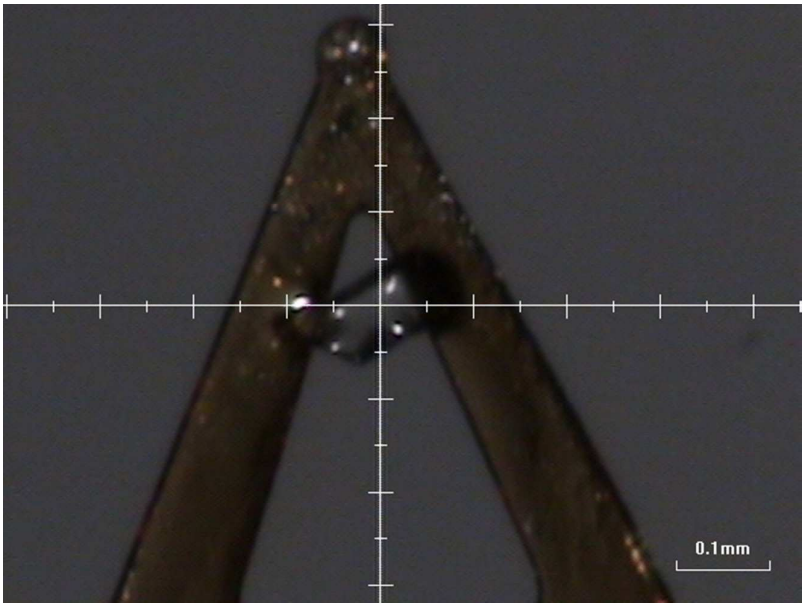


Figure 6.

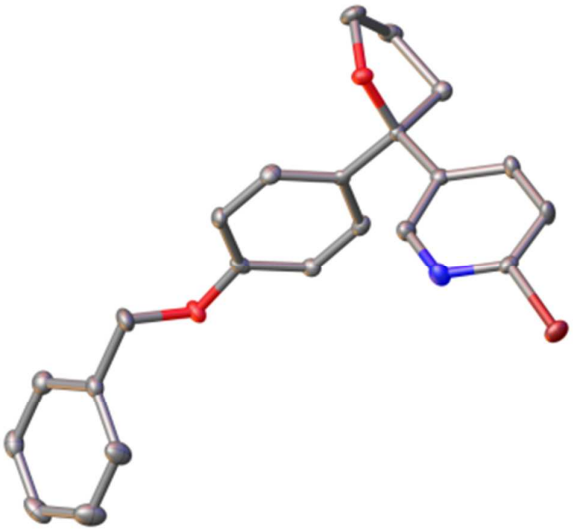


Figure 7. X-ray diffraction of (–)-(*R*)-**5**.

Biological assays

Membrane binding assay

FLAP binding was evaluated in a competition binding assay using cell membranes prepared from COS-7 cells expressing human FLAP (*ALOX5AP*) and ^{3}H-MK0591 as tracer. Compounds were tested in a 10-step, 3-fold dilution series starting from 27.5 µM. 84 µl tracer (2 nM final concentration; specific activity 955 kBq/nmol) in assay buffer (80 mM Tris, 140 mM NaCl, 2 mM EDTA, 0.5 mM DTT, 0.04% Tween-20, 5% glycerol, pH 7.5) and 1.4 µl compound dilution in DMSO were added to wells of a 96 well plate (Beckman Coulter) followed by 84 µl (2 µg) cell membrane preparation. Reactions were incubated at 25^{o}C for 60 to 80 minutes, then filtered using a harvest plate (GF/B, Whatman) and washed five times with 170 µl ice-cold wash buffer (100 mM TrisCl, 0.05% Tween-20, pH 7.5). Filters were dried at room temperature for 12 hours and 50 µl scintillation solution (Optiphase Supermix, PerkinElmer) was added followed by incubation for 30 minutes and reading on a Trilux Microbeta instrument. The average signal (CCPM) of the control wells on the plate was used as minimum (0%, no inhibition) and maximum (100%, fully inhibited target). To determine the effect of compound at a given concentration the equation %Effect=100 x ((X-Min)/(Max-Min)) was used, where X corresponds to the signal (CCPM) from the sample well.

Whole blood LTB_4 assay

To determine effect on LTB_4 production in blood, compounds were tested in dose response at 10 concentrations using a 3-fold dilution series from 30 µM to 1.5 nM. Assays were performed in triplicate using 100 µl blood and 0.5 µl compound in DMSO in 96-well plates. Heparinised whole blood obtained from consenting donors was pre-incubated with compound for 15 minutes at 37^{o}C before stimulating with 10 µM calcium ionophore (A23187, Sigma) for 20 minutes. Assays were stopped by the addition of EGTA to 10 mM and plasma was prepared by centrifugation at 2500 rpm, 4^{o}C for 10 minutes. 10 µl plasma was carefully removed and diluted in 90 µl EIA buffer. LTB_4 in the diluted plasma was quantified using a commercial EIA kit (Cayman Chemical) according to the manufacturer's instructions. Potency was defined as the molar concentration of compound required to inhibit ionophore-stimulated LTB_4 production by 50% (IC_{50}).

Whole blood COX-1 and COX-2 assays

To evaluate cross-reactivity to cyclooxygenase (COX) biosynthetic pathways, Thromboxane B_2 (TXB_2) and Prostaglandin E_2 (PGE_2) were measured as markers of COX-1 and COX-2 activity respectively. To measure TXB_2 production, assays were performed according to the protocol for whole blood LTB_4 assays except that TXB_2 was subsequently quantified in plasma supernatants using a commercial EIA kit (Cayman Chemical). To measure PGE_2 production, blood was pre-incubated with compound for 15 minutes in 96 well plates then stimulated with 1 µg/ml LPS to induce COX-2 expression (Sigma L6143). After overnight incubation at 37^{o}C, plasma supernatants were prepared by centrifugation at 2500 rpm, 4^{o}C for

10 minutes. PGE_2 was subsequently quantified in plasma using a commercial EIA kit (Cayman Chemical).

DMPK and Safety assays were performed as routine screening assays and have been described in detail elsewhere as indicated:

HPLC logD
Lipophilicity of a compound was determined using reversed-phase liquid chromatography at pH7.4. The logD value was calculated from the correlation between capacity factor and logD as determined for a set of standard compounds in the actual assay set up [6] (experimental details in eg [7])

ClogP was calculated using the Biobyte software.[8, 9]

Solubility
The thermodynamic solubility of research compound is measured in a shake-flask approach. [6] The assay is a high throughput method that has been harmonized and validated across all AstraZeneca sites: 10 mM DMSO solutions are supplied from the Compound Managements liquid store. The dried compounds are equilibrated in an aqueous phosphate buffer (pH 7.4) for 24 hours at 25 °C, the portion with the dissolved compound is then separated from the remains. The solutions are analyzed and quantified using UPLC/MS/MS. QC-samples are incorporated in each assay-run to ensure the quality of the assay.
Some solubility data was derived in the earlier solubility assay described in detail elsewhere.[7,10] The main differences are that thermodynamic solubility was measured in the presence of 1%DMSO and was tested up to 100μM.

CYP inhibition
Cytochrome P450 enzyme inhibition was performed in a semiautomated assay using human recombinant CYPs and coumarin based substrates that are biotransformed to fluorescent metabolites. The inhibitory action for each CYP was determined at five different compound concentrations and the IC50 (pIC50) value was calculated accordingly. A detailed description can be found in [10].

Hepatocyte CLint (human, rat, dog)
Metabolic stability was determined by incubating 1 μM compound solution in cryopreserved hepatocytes (1 million cells/ml), at 37°C and pH 7.4. Compound concentration at different time points (typically 2, 15, 30, 45 and 60 min) was quantified by LC-MS/MS and CLint calculated from compound disappearance.[11] Pooled human, rat (female Sprague Dawley) and dog (Beagle) hepatocyte batches were used as available for screening at the time of assay.

Caco2 Papp

An automated assay to study Caco-2 monolayer permeability in the apical to basolateral direction including a pH gradient (pH 6.5 in apical donor compartment and pH 7.4 in basolateral receiver compartment) was used.

For efflux determination two experiments were performed in a similar setup, but without pH gradient (pH 7.4 in both apical and basolateral compartment). Efflux ratios were calculated as the ratio of the apparent permeability coefficient in the apical to basolateral direction and the apparent permeability coefficient in the basolateral to apical direction:

$ER=P_{appB-A}/P_{appA-B}$

(detailed description in [10,12])

RM trapping (GSH and CH3ONH2)

Compounds were incubated in human liver microsomes in the presence of the trapping agent (glutathione or methoxylamine) and NADPH at pH7.4 and 37°C. Adducts were identified by QTOF MS analysis by use of the Waters Metabolynx software. For GSH adducts a ranking based on the 'GSH ratio' (=total integrated peak area of glutathione adducts of the test compound divided by the integrated peak area of the major glutathione adduct of the control compound clozapine) was possible.

CYP reaction profiling (CYP3A4 contribution)

Compounds were incubated with each of six CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) separately and the intrinsic clearance for each CYP determined from compound depletion at four time points. The percent contribution was then determined from the predefined Inter-system Extrapolation Factors (ISEFs) and median abundance values for each isoform as described previously (detailed description in [7]).

Plasma protein binding (human, rat, dog)

Plasma protein binding experiments were performed as reported previously[13] using blood plasma samples from humans, Sprague Dawley rats, and Beagle dogs.

***In vivo* PK experiments** in rat and dog (clearance CL, halflife $t_{1/2}$, steady state volume of distribution Vss, bioavailability F%)

Rat: pharmacokinetic properties of selected compounds were studied in female Sprague Dawley rats. Plasma pharmacokinetics were determined from 0-24h following iv or po administration, values are mean values from at least two animals. Doses were usually 2µmol/kg for iv and 8µmol/kg for po experiments (exceptions: compound **12** was dosed at 0.42µmol/kg iv and 1.68µmol/kg po and compound **21** was dosed at 1.5µmol/kg iv and 6µmol/kg po).

Dog: pharmacokinetic properties of selected compounds were studied in male and female Beagle dogs, usually 2 iv and 2 po experiments. The studies were used to estimate PD parameters as well, by *ex vivo* analysis of LTB_4 production in the blood samples. Compound tolerance was tested in an initial iv study using a low dose of 1µmol/kg iv. Doses for the three

other experiments were based on potency and PK results from this first experiment: Two dogs were dosed orally by gavage (the selected doses were 3μmol/kg for compound **12** and 1 μmol/kg for compounds **15b** and **41**) and a third dog was given the drug intravenously through up to two escalating constant rate infusion steps (the doses were 0.3 μmol/kg in one short time infusion step for compound **12** and 0.12/0.42 μmol/kg for compound **15b**). Blood samples were collected at time-points ranging from 0 to 48 hours. The samples were divided and used for determination of either plasma concentration of the drug or for measuring *ex vivo* LTB_4 production. To measure LTB_4 production, blood was first diluted 1:1 in RPMI medium (Life Technolgies) and incubated at 37°C for 30 minutes. 6 x 100 μl aliquots from each dog were then transferred to a 96 well plate and stimulated with 10 μM calcium ionophore at 37°C for 30 minutes. Assays were stopped by the addition of EGTA to 10 mM final concentration and plasma was prepared by centrifugation at 2500 rpm, 4°C for 10 minutes. 60 μl plasma was removed and transferred to a fresh plate prior to dilution in EIA buffer for quantification of LTB_4 (typically 1 to 400 dilution was used). LTB_4 in the diluted plasma was quantified using a commercial EIA kit (Cayman Chemical) according to the manufacturer's instructions.

Dose prediction equations

Equation 1 was used to calculate the allometric dose targeting an average concentraton, species differences for protein binding were considered:

$$Dose[mg] = \frac{C_{ss}\,[\mu mol/L] \times CL_{humpred}\,[ml/min/kg] \times \tau\,[min] \times MW\,[g/mol] * BW_{hum}[kg]}{F \times 1000000}$$

Where,

C_{ss} [μmol/L]: average drug concentration at steady state

$CL_{hum,pred}$ [ml/min/kg]: predicted human CL (via single species allometric scaling from rat *in vivo* CL)

$$CL_{hum,pred} = (CL_{rat} * BW_{rat}/BW_{hum} * (BW_{hum}/BW_{rat})\text{^}0.75)*fu_{hum}/fu_{rat}$$

F: bioavailability (as fraction)

τ: Dose interval; here once daily: 24*60=1440min

MW: molecular weight

BW_{hum}: human body weight: 70 kg

BW_{rat}: rat body weight: 0.25 kg

$fu_{species}$: protein binding free fraction in specified species (human or rat)

Equation 2 was used to calculate the dose targeting the trough concentration, species differences for protein binding and metabolism were considered:

$$Dose[mg] = C_{ss,min}\ [\mu mol/L] \times V_{SS,hum,pred}[L/kg] \times \frac{\left(1 - e^{-\left(\frac{CL_{humpredEHcorr}\ [ml/min/kg] \times \tau\ [min]}{V_{SS,hum,pred}\left[\frac{L}{kg}\right] \times 1000}\right)}\right)}{F \times e^{-\left(\frac{CL_{humpredEHcorr}\ [ml/min/kg] \times \tau\ [min]}{V_{SS,hum,pred}\left[\frac{L}{kg}\right] \times 1000}\right)}} \times MW\ [g/mol] \times BW_{hum}[kg] \times 0.001$$

Where,

$C_{ss,min}$ [µmol/L]: minimum drug concentration at steady state

$CL_{hum,pred,EHcorr}$ [ml/min/kg]: predicted human CL (via single species allometric scaling from rat or dog *in vivo* CL, corrected for species differences in protein binding and hepatic extraction)

$CL_{hum,pred,EHcorr} = (CL_{animal} * BW_{animal}/BW_{hum} * (BW_{hum}/BW_{animal})^{0.75}) * fu_{hum}/fu_{animal} * EH_{hum}/EH_{animal}$

$Vss_{hum,pred}$ [L/kg]: predicted human volume of distribution (animal volume of distribution corrected for species differences in protein binding)

$Vss_{hum,pred} = Vss_{animal} * fu_{hum}/fu_{animal}$

BW_{hum}: human body weight: 70 kg

BW_{animal}: animal body weight (rat: 0.25 kg; dog: 12 kg)

$fu_{species}$: protein binding free fraction in specified species (human, rat or dog)

$EH_{species}$: hepatic extraction in respective species (human, rat or dog), calculated from the *in vitro* hepatocyte CLint and scaling factors

Vss_{animal}: volume of distribution at steady state in specified species (rat or dog)

hERG inhibition

hERG inhibition was determined using the IonWorks™ instrument as was described earlier.[14]

Inhibition of other cardiac ion channels

Inhibition of four human ion channels, hNav1.5, hCav1.2, hKvLQT1/hminK (IKS) and hKv4.3-hKChIP2.2 (Ito), included in a cardiac screening panel, was determined using the IonWorks procedure as described by Davies et al.[15]

AMES

AMES activity determination was performed as described earlier.[16]

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