Supporting information

Discovery and optimisation of potent and highly subtype selective $Na_V1.8$ inhibitors with reduced cardiovascular liabilities

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Biology experimental.

Cell culture of sodium channel stable cell lines

Human embryonic kidney (HEK) 293 cells stably expressing human Nav subtypes were commercially sourced (Merck Millipore, Billerica, MA, USA). Cells were maintained using minimum essential medium (MEM) with Earle's salts supplemented with 10% foetal calf serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 1x non-essential amino acids and 0.4mg/ml geneticin (G-418) and kept at 37 ˚C in a humidified atmosphere of 5 % CO2. All cell culture reagents were from Invitrogen (Life Technologies, Gent, Belgium).

Isolation of rat and cynomolgus monkey DRG neurons for voltage-clamp recordings

Rat and cynomolgus monkey DRG neuronal cultures were prepared as described in Passmore, 2005. Notable differences were the absence of NGF in the growth medium and cells were plated on pre-coated coverslips (poly-D-lysine/laminin; BD Biosciences, San Jose, CA, USA). Healthy DRG neurons had a visible nucleolus 2-3 hours after isolation and were patched within 12-24 hours of isolation.

Manual patch electrophysiological recordings

Coverslips containing either HEK293 cells expressing sodium channels or DRG neurons from rat or cynomolgus monkey were placed in a recording chamber and perfused (approximately 1 ml min^{-1}) with an extracellular solution containing (in mM): 132 NaCl, 5.4 KCl, 10 HEPES, 5 Glucose, 1.8 $CaCl_2$ and 0.8 $MgCl_2$, pH 7.4 with NaOH for $hNa_V1.1$, $hNa_V1.2$, $hNa_V1.4$, $hNa_V1.6$, $hNa_V1.7$ and $hNa_V1.8$. For $hNa_V1.5$, sodium concentration was reduced by substituting 102 mM Choline Cl. For whole-cell voltage-clamp recordings of tetrodotoxin-resistant (TTX-R) currents from human DRG neurons, ECS contained (in mM): 20 mM NaCl,

112 mM Choline Cl, 5.4 KCl, 10 HEPES, 5 Glucose, 1.8 $CaCl_2$, 0.8 $MgCl_2$, 0.05 $CdCl_2$ and 0.2 TTX, pH 7.4 with NaOH. Patch pipettes were filled with an intracellular solution containing (in mM): 110 CsF, 35 CsCl, 5 NaCl, 10 HEPES and 10 EGTA, pH 7.3 with NaOH, and had a resistance of 1 to 2 MΩ. All recordings were made at room temperature (22-24°C) using Axopatch 200B or Multiclamp 700B amplifiers and PCLAMP software (Molecular Devices, Sunnyvale, CA, USA). All compounds were dissolved in dimethyl sulfoxide (DMSO). The final maximal concentration of DMSO used (<0.3%) was found to have no significant effect on sodium currents. Solutions containing compound or DMSO control were applied using a perfusion system (MSC-200, Bio-Logic SAS, Claix, France).

PatchXpress automated electrophysiological recordings

All assay solutions were identical to those used in conventional whole-cell voltage-clamp experiments described above. HEK293 cells constitutively expressing Nav1.5 and Nav1.7 were grown (as described above) to 50–80% confluency and harvested by trypsinization. Trypsinized cells were washed and resuspended in extracellular buffer at a concentration of 106 cells/ml. The onboard liquid handling facility of the PatchXpress was used for dispensing cells and application of test compounds. A detailed rationale and description of the development of the PatchXpress protocol has been previously disclosed (Castle et al., 2009).

Electrophysiological protocols

A conditioning prepulse was applied at the specific half inactivation voltage for each sodium channel subtype to assess pharmacological block. Cells were depolarized from a holding potential of -120 mV (or -150 mV for $Na_V1.5$) to a membrane potential that inactivated half of the available channels for 8 seconds followed by a 2 or 20 ms recovery at -120 mV and a 20 ms test pulse to 0 mV.

Data analysis

Concentration response data was analyzed using nonlinear least squares fit of the Logistic Equation (GraphPad Prism 5, San Diego, CA, USA) to provide half maximal inhibitory (IC_{50}) concentration.

References

Castle N, Printzenhoff D, Zellmer S, Antonio B, Wickenden A, Silvia C, Sodium channel inhibitor drug discovery using automated high throughput electrophysiology platforms. *Comb. Che. High Throughput Screen*. 2009, **12**, 107

Passmore, GM Dorsal root ganglion neurones in culture: a model system for identifying novel analgesic targets? *J. Pharmacol. Toxicol. Methods*, 2005, **51**, 201.

Creation of a homology model of hNav1.8

The sequences of human, rat and mouse Nav channels were split into the four domains (D1, D2, D3, and D4) and these fragmented sequences were aligned to the sequences of NavAb, NavAe and NavMs separately. The alignments were carried out by the program MAFFT (Multiple Alignment using Fast Fourier Transform). The four alignments were merged to provide a total sequence alignment (D1-D4). The crystal structures of NavAb (3RVY, 3RVZ and 3RW0), NavAe (4LTO, 4LTP, 4LTQ and 4LTR) and NavMs (3ZJZ and 4P30) were used as templates for homology modelling of the hNav1.8. Structure models of the hNav1.8 were

generated with the program Modeller. A total of 150 models were created, which differed in dihedral angles and positions of residues in the fenestration site so that binding site flexibility in the hNav1.8-ligand interaction was taken into account. The models were subjected to the protein preparation module (Schrodinger Suite) in order to make them compatible with docking calculations by Glide (Schrodinger Suite).

References

Katoh, K.; Misawa, K.; Kuma, K.; Miyata, T. MAFFT: a novel method for rapid multiple sequence alignment based on fast Fourier transform. *Nucleic Acids Res.* 2002, **30**, 3059.
Sali, A.; Blundell, T. L. Comparative protein modelling by satisfaction of spatial restraints. *J Mol. Biol.* 1993, **234**, 779.

Molecular docking study of hNav1.8

Grid files of the 150 models were generated by Glide. The grids were located in the center of the fenestration site. The 3D structures of the ligands were created by the LigPrep module (Schrodinger Suite) and they were docked to the 150 homology models (with the XP precision) with docking calculation of each pair of a hNav1.8 model and a ligand providing 50 docking poses (Glide). As a result, at most 7500 docking poses were generated. Confidence of docking poses was evaluated based on an RMSD analysis for the extent to which 50 top docking poses were consistent. If more than half of the 50 docking poses were within RMSD distance of 2Å, the cluster of the poses were regarded as a potential binding mode and the best docking pose in the cluster was used for subsequent discussion.

References

Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* 2004, **47**, 1739.

Chemistry experimental.

Analytical methods.

^{1}H nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million, downfield from tetramethylsilane, using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations and chemical formulae have been used for NMR solvents: $CDCl_3$, deuterochloroform; DMSO-d_6, deuterodimethylsulphoxide; CD_3OD, deuteromethanol. Mass spectra (MS) were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). LCMS indicates liquid chromatography mass spectrometry (t = retention time). Two different methods were used for LCMS. Unless indicated, all LCMS data were obtained using conditions A.

LCMS conditions A

A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile

Column: C18 phase Phenomenex Gemini 50 × 4.6 mm, 5 µm particle size
Gradient: 95–5% A over 3 min, 1 min hold, 1 mL/min
UV: 210–450 nm DAD
Temperature: 75 °C

LCMS conditions B

A: 0.1 % methanesulfonic acid in water
B: acetonitrile
Column: Waters BEH RP C18 2.1 x 100 mm 1.7 µm
Gradient: 95%–0% A over 8.2 min, 0.5 min hold, 0.5 mL/min
UV: 210 nm
Temperature: 45 °C

Certain examples were purified using automated preparative high-performance liquid chromatography (HPLC):

Reverse-phase HPLC conditions were on FractionLynx systems. Samples were submitted dissolved in 1 mL of DMSO. Depending on the nature of the compounds and the results of pre-analysis, purification was performed under either acidic or basic conditions at ambient temperature. Acidic runs were carried out on a Sunfire Prep C18 OBD column (19 × 50 mm, 5 µm). Basic runs were carried out on an Xterra Prep MS C18 (19 × 50 mm, 5 µm), both from Waters. A flow rate of 18 mL/min was used with mobile phase: A, water + 0.1 % modifier (v/v); B, acetonitrile + 0.1 % modifier (v/v). For acidic runs, the modifier was formic acid; for basic runs, the modifier was diethylamine. A Waters 2525 binary LC pump supplied a mobile phase with a composition of 5% B for 1 min then ran from 5% to 98% B over 6 min, followed by a 2 min hold at 98% B. Detection was achieved using a Waters 2487 dual-wavelength absorbance detector set at 225 nm followed, in series, by a Polymer Labs PL-ELS 2100 detector and a Waters ZQ 2000 4-way MUX mass spectrometer in parallel. The PL 2100 ELSD was set at 30 °C with 1.6 L/min supply of nitrogen. The Waters ZQ MS was tuned with the following parameters:

ES+ Cone voltage: 30 v; Capillary: 3.20 kv

ES- Cone voltage: -30 v; Capillary: -3.00 kv

Desolvation gas: 600 L/h

Source Temp: 120 °C

Scan range: 150–900 Da

The fraction collection was triggered by both MS and ELSD.

Quality control analysis was performed using an LCMS method orthogonal to the preparative method. Acidic runs were carried out on a Sunfire C18 (4.6 × 50 mm, 5 µm); basic runs were carried out on a Xterra C18 (4.6 × 50 mm, 5 µm) - both from Waters. A flow rate of 1.5 mL/min was used with mobile phase: A, water + 0.1 % modifier (v/v); B, acetonitrile + 0.1 % modifier (v/v). For acidic runs, the modifier was formic acid; for basic runs, the modifier was diethylamine. A Waters 1525 binary LC pump ran a gradient elution

from 5% to 95% B over 3 min, followed by a 1 min hold at 95% B. Detection was achieved using a Waters MUX UV 2488 detector set at 225 nm followed, in series, by a Polymer Labs PL-ELS 2100 detector and a Waters ZQ 2000 4-way MUX mass spectrometer, in parallel. The PL 2100 ELSD was set at 30 °C with 1.6 L/min supply of nitrogen. The Waters ZQ MS was tuned with the following parameters:

ES+ Cone voltage: 25 v; Capillary: 3.30 kv

ES- Cone voltage: -30 v; Capillary: -2.50 kv

Desolvation gas: 800 L/h

Source Temp: 150 °C

Scan range: 160–900 Da

Purity criteria: Final compounds isolated as singletons >95% based on LCMS and/or ^{1}H NMR. Final compounds isolated via autopurification methods > 90% based on LCMS.

Singletons: Compounds 3, 13-21, and 25.

Library Compounds: 1a, 1b, 2a, 2b, 4-12, 22-24, and 26.

General Procedure for Amino-Imidazole formation via keto-ester and t-butylcarbamate-imidazole for singletons (GP)

Step 1

To a round bottom flask containing the acid (1 eq) and solvent mixture (DMF:THF, 2:1, 0.14M) was added 1M KOtBu in THF (1 eq) followed by the bromoketone (1 eq) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and water and the organic layer was extracted, washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated under vacuum. The keto-ester was used without further purification.

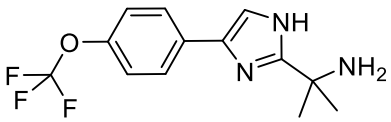
Step 2

In a sealable vial containing the crude keto-ester, anhydrous toluene (0.15M), molecular sieves (2x keto-ester weight) and ammonium acetate (15 eq) were added sequentially. The vial was sealed and heated at 110 ^{o}C for 4 hours. The reaction mixture was concentrated *in vacuo* and dissolved in DCM and 2N NaOH (aq). The organic layer was extracted, washed with brine, dried over magnesium sulfate, filtered and the filtrate was concentrated under vacuum to obtain the crude imidazole.

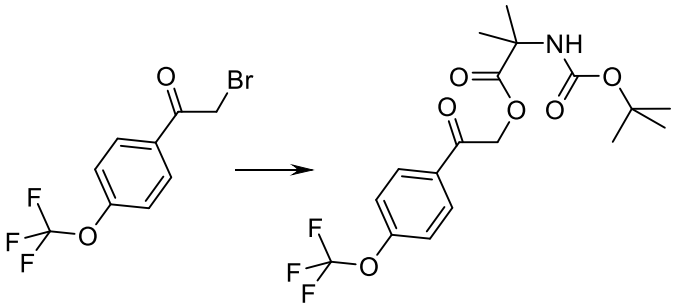
Step 3

The crude *tert*-butyl carbamate was treated with HCl in organic solvent (40-60 eq) at room temperature and stirred until the starting material had been consumed. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to obtain the pure amino-imidazole compound.

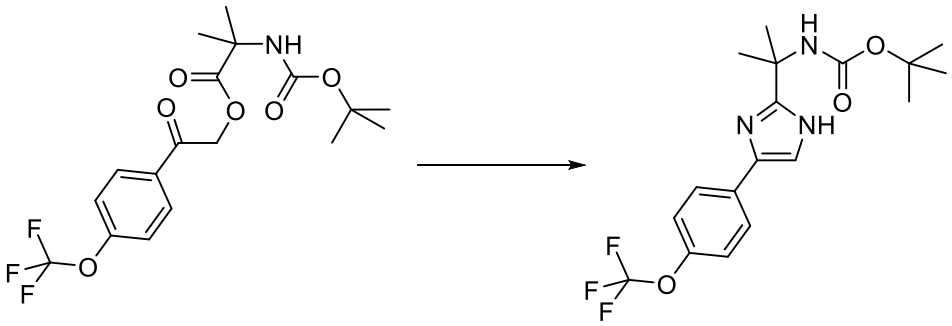
Synthetic procedures.



Compound 13
2-(4-(4-(Trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

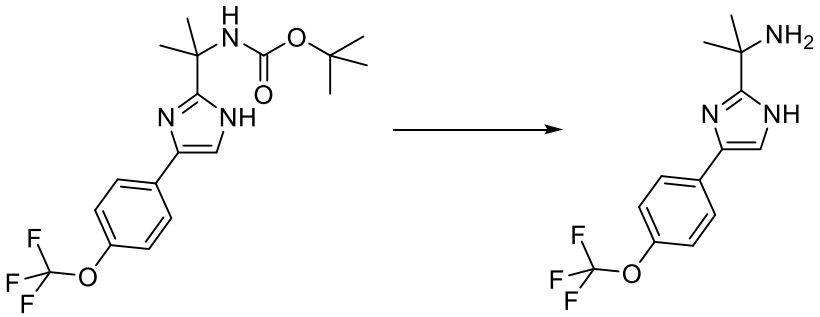


Step 1: 2-Oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate
To a stirred solution of 2-bromo-4'-trifluoromethoxy acetophenone (120.1 g, 0.424 mol) in ethyl acetate (620 mL) at room temperature was added Boc-Aib-OH (Boc-α-2-aminoisobutyric acid) (83.23 g, 0.424 mol) and triethylamine (60 mL, 0.424 mol). The resulting yellow solution was stirred at room temperature overnight. The reaction mixture was washed with 1N HCl, 5% $NaHCO_3$ aqueous solutions and brine. The aqueous layers were extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated to yield 167 g (97%) of 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoate as a white solid which was used in the next step without further purification. MS $[M+H]^+$ 405. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 5.31 (s, 2H), 1.60 (s, 6H), 0.88 (s, 9H).



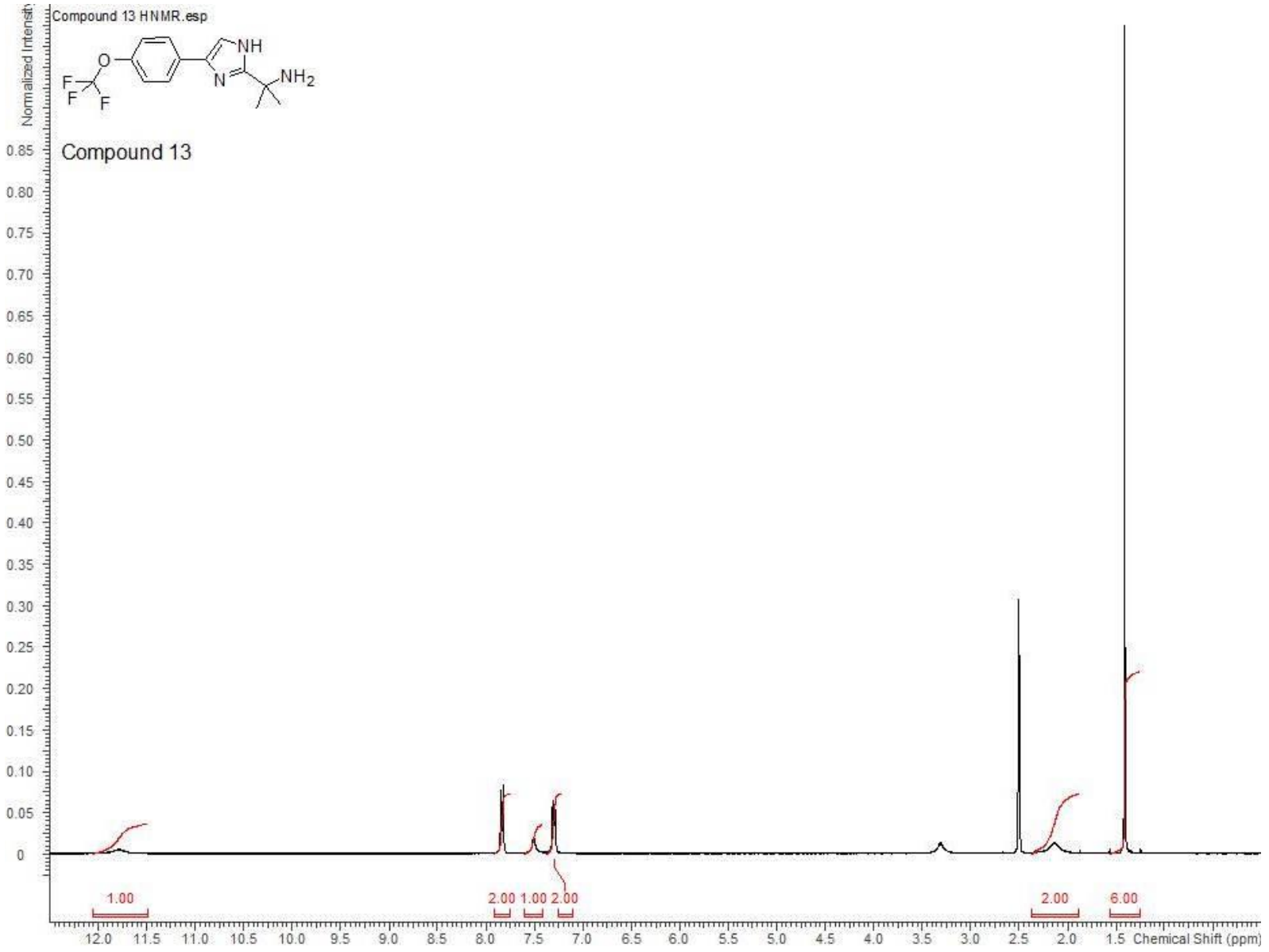
Step 2: tert-Butyl (2-(4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)propan-2-yl)carbamate
In a 500 mL round bottom flask connected to Dean-Stark apparatus (both containing molecular sieves) was placed the 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoate (5.22 g, 12.9 mmol) in toluene (100 mL) and ammonium acetate (14.9 g, 193 mmol, 15 eq). The reaction mixture was heated to reflux for 4h under argon. The reaction mixture was filtered to remove molecular sieves and concentrated. The resulting brown oil was dissolved in DCM, washed with 1N NaOH solution, water and then brine and extracted twice with DCM. The combined organic layers were dried ($MgSO_4$) and concentrated to yield a brown oil. Purification of the crude mixture

by flash chromatography (silica, hexane:EtOAc 7:3 to 1:1) yielded *tert*-butyl (2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate as a light yellow solid (4.359 g, 88%). MS $[M+H]^+$ 385. ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.48 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.97 (s, 1H), 2.46 (s, 6H), 1.51 (s, 9H).



Step 3: 2-(4-(4-(Trifluoromethoxy)phenyl)-1H-imidazol-2-yl)propan-2-amine

To a solution of *tert*-butyl (2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (34.71 g, 90.1 mmol) in THF (500 mL) was added at room temperature aqueous 4N HCl solution (1 L). The reaction mixture was stirred for 3 h then THF was evaporated. The resulting solution was washed with Et_2O. The aqueous layer was collected, basified with solid Na_2CO_3 and extracted 3 times with EtOAc. The combined organic layers were washed with 1N NaOH solution, dried ($MgSO_4$), filtered and concentrated to yield 23.79 g (92%) of 2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine as a light yellow solid. HRMS for $C_{13}H_{14}F_3N_3O$ $[M+H]^+$ calc'd: 286.1162, Found: 286.1157. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 11.80 (br. s., 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.51 (br. s., 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.13 (br. s., 2H), 1.41 (s, 6H). HRMS for $C_{13}H_{14}F_3N_3O_1$ MS m/z $[M+H]^+$: Calc'd: 286.1162, Found: 286.1157.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Normalized Intensity
Compound 13
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N
O
F
F
F
NH2
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0.80
0.75
0.70
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0.60
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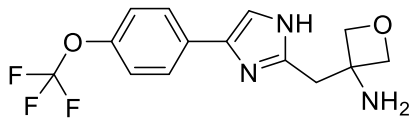
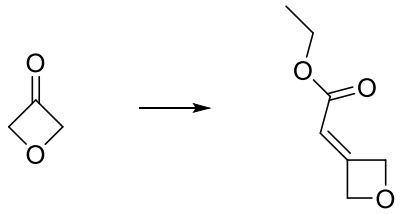
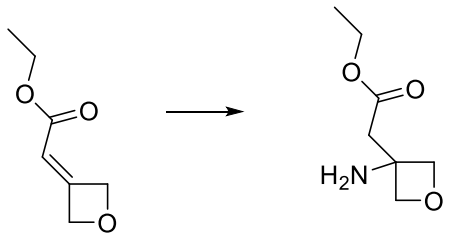
Chemical Shift (ppm)



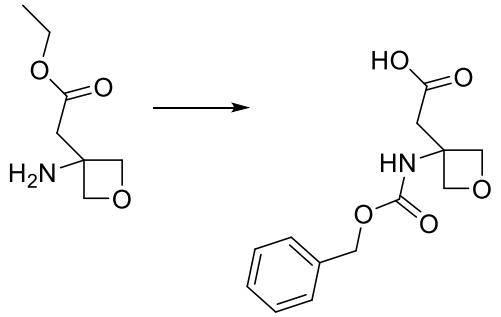
Compound 21
3-((5-(4-(Trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine



Step 1: Ethyl 2-(oxetan-3-ylidene)acetate
To a solution of (carbethoxymethylene)triphenylphosphorane (1.95 Kg, 5.61 mol) in dichloromethane (4 L) at 0 ^{o}C was added over 1 hour, a solution of 3-oxetanone (400 g, 5.55 mol) in dichloromethane (2 L) maintaining the temperature below 10 ^{o}C. The reaction was warmed gradually to room temperature and stirred for 1.5 hours. The reaction was warmed to 30 ^{o}C and dichloromethane (4 L) was removed *in vacuo*. Heptane (5 L) was added and the mixture distilled under vacuum for a further 1 hour. Further heptane (2.5 L) was added, the temperature increased to 50 ^{o}C and the reaction continued to be distilled under vacuum for a further 2 hours. The mixture was cooled to 0 ^{o}C and aged for 1 hour at atmospheric pressure. The solid was collected by filtration and washed with heptane (2 x 2.5 L). The pale yellow filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow mobile liquid (757 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (quin, *J* = 2.4 Hz, 1H), 5.45-5.55 (m, 2H), 5.30 (dt, *J* = 2.3, 3.5 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

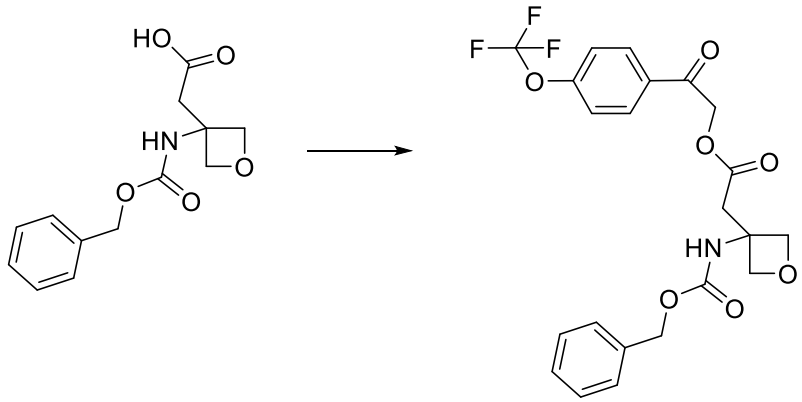


Step 2: Ethyl 2-(3-aminooxetan-3-yl)acetate
Ethyl 2-(oxetan-3-ylidene)acetate (781 g, 5.49 mol) was dissolved in 2M ammonia in ethanol (8.24 L) and heated to 100 ^{o}C in a sealed vessel for 5 hours. The reaction was concentrated *in vacuo* to afford the title compound as a mobile oil (750 g, 100% yield) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (d, *J* = 8.6 Hz, 2H), 4.5 (d, *J* = 8.6 Hz, 2H), 4.2 (q, *J* = 8.4 Hz, 2H), 2.85 (s, 2H), 2.0 (br s, 2H), 1.25 (t, *J* = 8.4 Hz, 3H).



Step 3: (3-([(Benzyloxy)carbonyl]amino)oxetan-3-yl)acetic acid

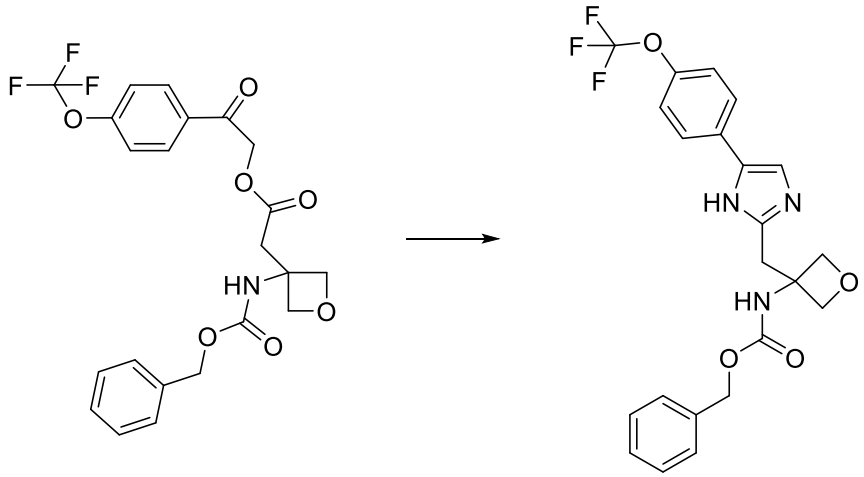
tert-Butyl methyl ether (2.5 L) and an aqueous solution of sodium carbonate (750 g in 2.2 L water, 7.07 mol) were stirred. Ethyl (3-aminooxetan-3-yl)acetate (875 g, 5.5 mol) was added to the reaction, followed by further tert-butyl methyl ether (2.5 L). The reaction was cooled to 5 °C and benzyl chloroformate (1.21 Kg, 7.09 mol) added in a controlled manner such as to maintain the temperature below 20 °C. A precipitate was observed so further water (5 L) and *tert*-butyl methyl ether (1.5 L) were added to solubilize the reaction mixture. The biphasic mixture was separated. The organic layer was basified with 2M aqueous solution of sodium hydroxide (3.5 L) and stirred vigorously for 18 hours. The aqueous layer was separated and the remaining organic layer washed with water (1.5 L). The aqueous layers were combined and cooled to 15 °C. Isopropyl acetate (5 L) was added followed by controlled addition of a 6M aqueous solution of hydrogen chloride (1.2 L), maintaining the temperature below 17 °C. The reaction was stirred for 30 minutes. Solid that crystallized out in the reactor was dissolved in a mixture of ethyl acetate and methanol (20 L). The solution was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo* to afford solid material. Ethyl acetate (5 L) was added and concentrated *in vacuo*. Further ethyl acetate (5 L) was added and the slurry heated to reflux to give an orange solution. The solution was cooled to 50 °C and heptane (2.5 L) added. A thick slurry was observed that was stirred at room temperature for 18 hours. The solid was filtered and dried on a sinter for 3 hours before drying *in vacuo* at 40 °C for 18 hours to afford the title compound as a white crystalline solid (1.07 Kg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2-7.4 (m, 5H), 5.1 (m, 2H), 4.7 (m, 2H), 4.6 (m, 2H), 3.1 (m, 2H).



Step 4: 2-Oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetate

(3-([(Benzyloxy)carbonyl]amino)oxetan-3-yl)acetic acid (1.01 Kg, 3.81 mol) was stirred in ethyl acetate (8 L). 2-Bromo-1-[4-(trifluoromethoxy)phenyl]-ethanone (1.08 Kg, 3.81 mol) was added, followed by triethylamine (585 mL, 4.19 mol). The reaction was initially fully solubilized, but a precipitate was then observed. The reaction was washed with water (2 x 4 L), then concentrated *in vacuo* to afford the title compound as a mobile orange oil (1.90 Kg, 107%, contains residual ethyl acetate) which was used as is in the next reaction.

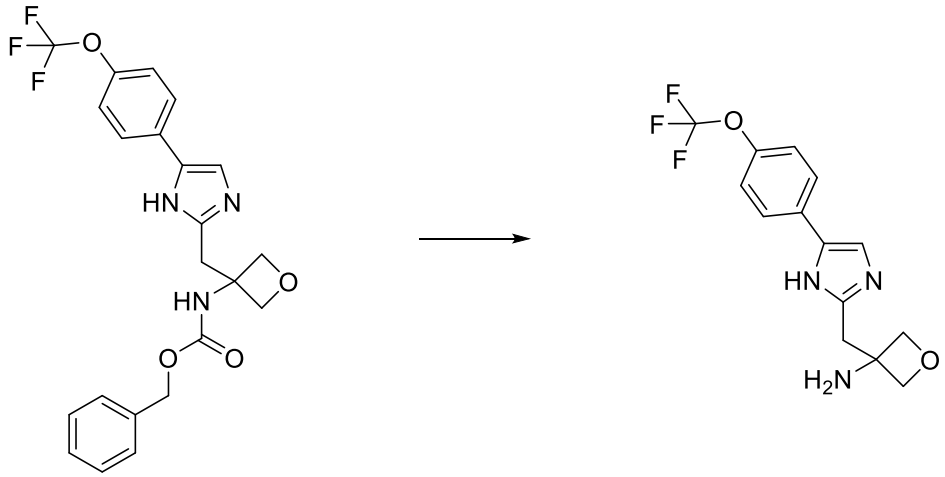
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.80 (complex m, 7H), 6.0 (s, 1H), 5.35 (s, 2H), 5.11 (s, 2H), 4.82 (d, *J* = 6.7 Hz, 2H), 4.67 (d, *J* = 6.7 Hz, 2H), 3.34 (s, 2H).



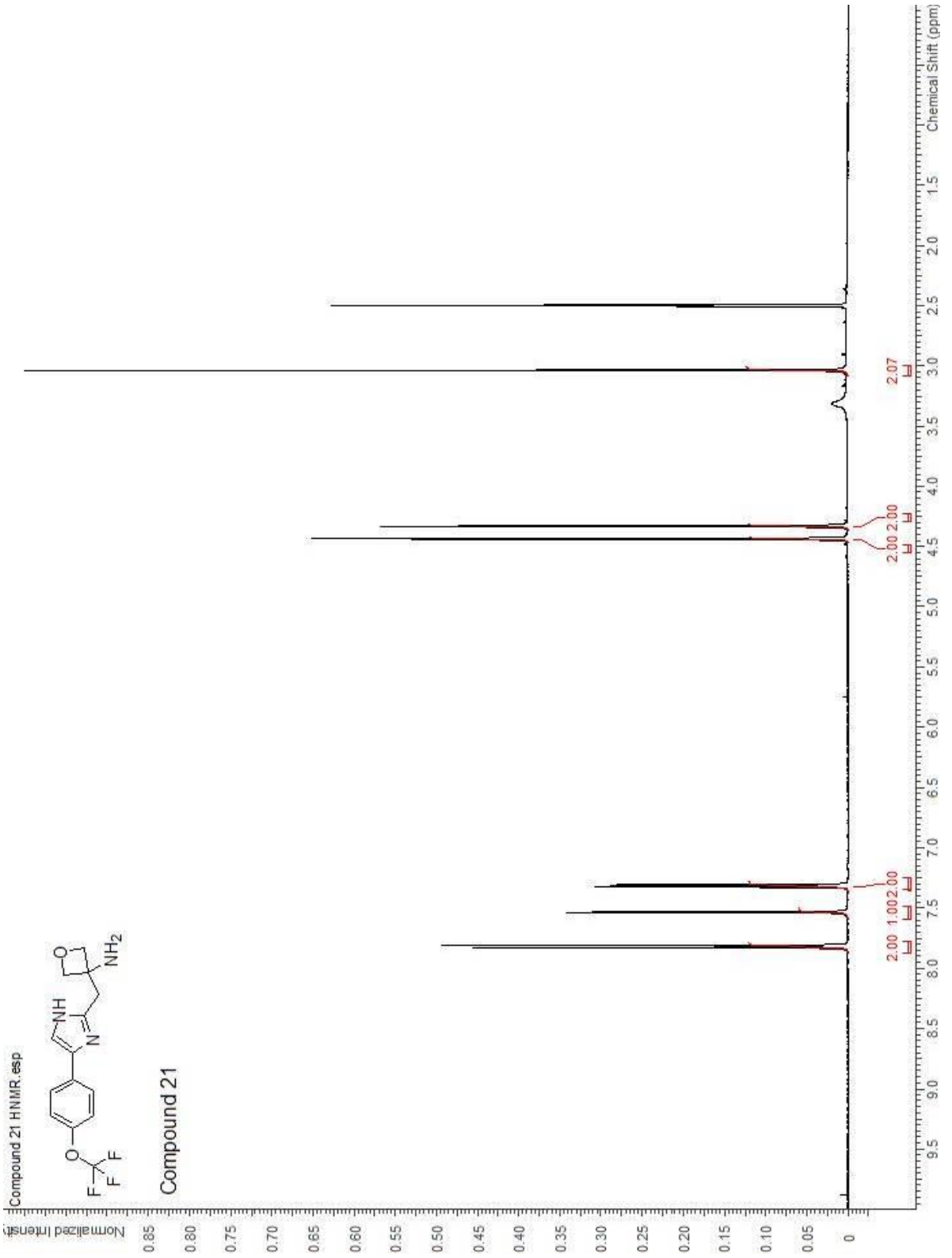
Step 5: Benzyl (3-((5-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-yl)carbamate

Ammonium acetate (1.22 Kg, 15 mol) was stirred in toluene (12 L) and heated to 100 °C for 30 minutes until the solid had melted. A solution of 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetate (700 g, 1.5 mol) in toluene (2 L) was added rapidly and the temperature increased to 130 °C and heated at vigorous reflux for 4 hours. The reaction was cooled to room temperature, water (4 L) added and the mixture stirred for 10 minutes before leaving to stand for 2 hours. The organic layer was separated and concentrated *in vacuo* to afford a thick orange oil. Dichloromethane (5 L) was added and the solution gently agitated by turning slowly on the rotary for 72 hours. A white precipitate was then observed. The solution volume was reduced *in vacuo* to 1 L and the mixture filtered through Arbocel©. The gelatinous solid was washed with dichloromethane (2 L) and the filtrate concentrated *in vacuo* to afford a dark orange mobile oil. The oil was purified by silica gel column chromatography eluting with *tert*-butyl methyl ether to afford the title compound as a light orange oil (311 g, 46% yield).

^{1}HNMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.2 Hz, 2H), 7.25 (m, 5H), 7.22 (s, 1H), 7.19 (d, *J* = 9.2 Hz, 2H), 6.10 (s, 1H), 5.07 (s, 2H), 4.83 (d, *J* = 6.4 Hz, 2H), 4.65 (d, *J* = 6.4 Hz, 2H), 3.51 (s, 2H).



Step 6: 3-((5-(4-(Trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-amine
Benzyl (3-((5-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)carbamate (311 g, 695 mmol) was dissolved in methanol (3.2 L). 5% Palladium on carbon (E105 R/W (EVONIK)) (22 g, 7wt%) was added and the reaction hydrogenated at 40 °C, 100 psi for 18 hours. Hydrogen uptake was monitored and showed the reaction to be complete after 4 hours. The mixture was cooled to room temperature and filtered over Arbocel©. The filter cake was washed with methanol (2 x 1 L) and the filtrate concentrated *in vacuo* to afford a solid. The solid was dissolved in ethyl acetate (1 L) and filtered through a carbon tablet to remove traces of palladium. The solution was warmed to 50 °C and heptane (1 L) added. The solution was cooled slowly whereupon at 40 °C crystallization was observed. The mixture was stirred at room temperature for 72 hours. The solid was collected by filtration and washed with ethyl acetate: heptane, 1:1 (250 mL). The solid was dried *in vacuo* at 40 °C for 18 hours to afford the title compound as a crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.78 - 7.87 (m, 2H), 7.54 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.44 (d, *J* = 6.2 Hz, 2H), 4.33 (d, *J* = 6.2 Hz, 2H), 3.04 (s, 2H). HRMS for $C_{14}H_{14}F_3N_3O_2$ MS m/z $[M+H]^+$: Calc'd: 314.1111, Found: 314.1114.


Compound 21 HNMR.esp
Normalized Intensity
Chemical Shift (ppm)
Compound 21
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N
O
NH2
F
F
F
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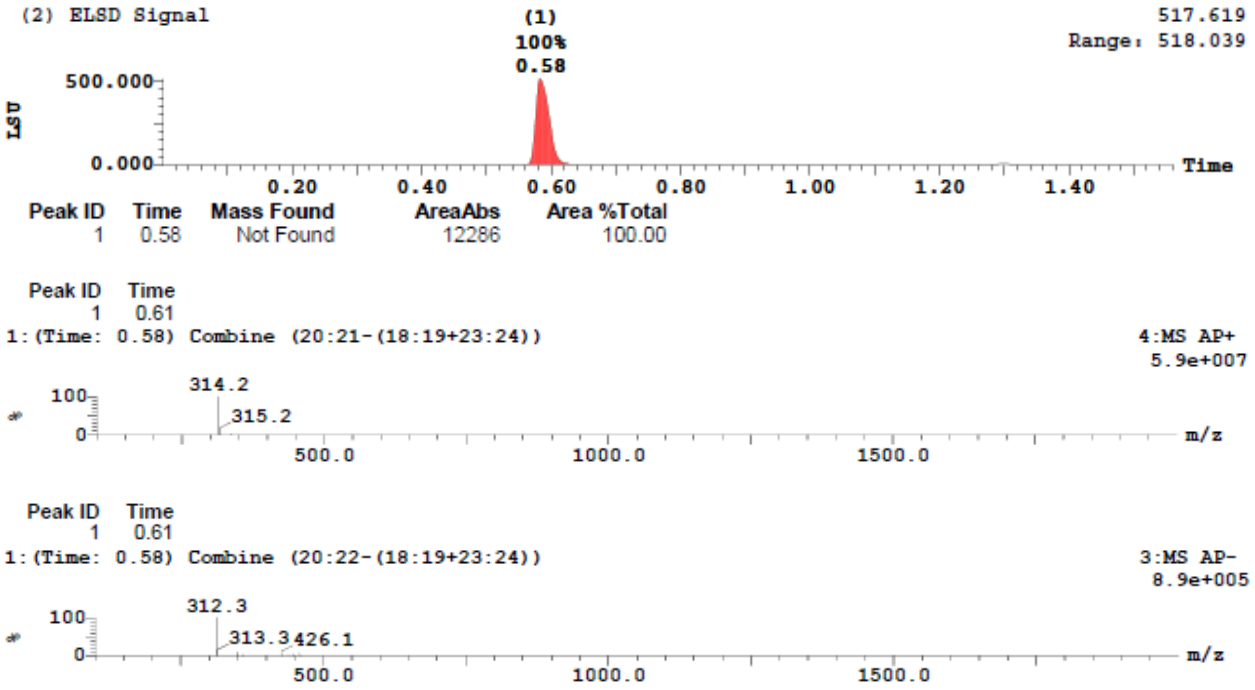
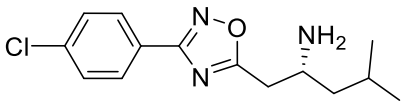
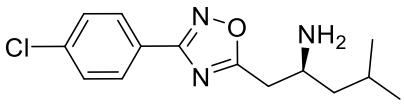




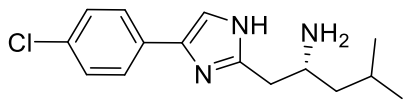
Compound 1a
(*R*)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-4-methylpentan-2-amine

(*R*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoic acid (75 umol, 1.0 eq), 4-chloro-*N*'-hydroxybenzimidamide (82.5 umol, 1.1 eq) and acetonitrile (1.0 mL) were combined in an 8 mL vial and were treated with DIEA (25 uL, 150 umol, 2.0 eq) followed by HATU (75 umol, 1.0 eq). The vial was capped and shaken at 30 °C for 6 hours and at 120 °C for 24 hours. The solvent was removed *in vacuo* and the crude material was purified using preparative HPLC. The isolate was dissolved in DCM (0.5 mL) in a 40 mL vial and treated with a solution of TFA in dichloromethane (0.5 mL, v/v = 1/4). The vial was capped and shaken at 30 °C for 2 hours. The solvent was removed *in vacuo* to obtain (*R*)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-4-methylpentan-2-amine. MS $[M+H]^+$ 280.



Compound 1b
(*S*)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-4-methylpentan-2-amine
The procedure used to generate **Compound 1a** [(*R*)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-4-methylpentan-2-amine] was followed using (*S*)-3-((*tert*-butoxycarbonyl)amino)-5-

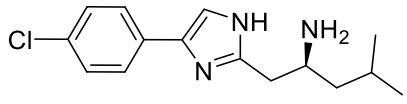
methylhexanoic acid to produce (*S*)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-4-methylpentan-2-amine. MS $[M+H]^+$ 280.



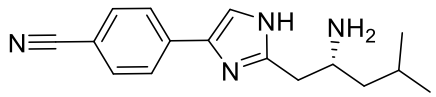
Compound 2a
(*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine
To a 0.5M solution of (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoic acid in THF/DMF (1:1) (250 uL, 125 umol, 1.0 eq) in an 8 mL vial was added DMF (375 uL) followed by 1.0M KOtBu in THF (125 uL, 125 umol, 1.0 eq). The mixture was shaken to achieve a homogenous solution and then 0.5M solution of 2-bromo-1-(4-chlorophenyl)ethan-1-one in THF (250 uL, 125 umol, 1.0 eq) was added. The vial was capped and shaken at 30 °C for 4 hours. The solvent was removed *in vacuo* and the crude product was used directly without purification.

To the intermediate ester was added freshly prepared 4.0M ammonium acetate in MeOH (470uL, 1.88 mmol, 15 eq) and toluene (625 uL). The vial was capped and shaken at 100 °C for 4 hours followed by concentration *in vacuo*. The crude material was diluted with DCM (1.9 mL), 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) and 2.0M NaCl (aq) (470 uL). The vial was capped and shaken. Upon settling, the top aqueous layer was removed and discarded. 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) was again added and the vial capped and shaken. Upon settling, the top aqueous layer was removed and discarded. Water (780 uL) was added and the vial capped and shaken. The bottom organic layer was removed and put in a 8 mL collection vial. To the water layer was added DCM (1.25 mL) and the vial capped and shaken. The bottom organic layer was removed and combined with the previous extract in the collection vial. The solvent was removed *in vacuo*. The crude material was purified using preparative HPLC to obtain pure Boc-protected aminoimidazole intermediate, which was used directly.

The Boc-protected amine in a reaction vial was diluted with DCM (1.5 mL) and treated with TFA (300 uL, 3.9 mmol). The vial was capped and shaken at 30 °C for 6 hours. The solvent was removed *in vacuo* to obtain (*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine. MS $[M+H]^+$ 278.



Compound 2b
(*S*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine
The procedure used to generate (*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine was followed using (*S*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoic acid and 2-bromo-1-(4-chlorophenyl)ethan-1-one to produce (*S*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine. MS $[M+H]^+$ 278.

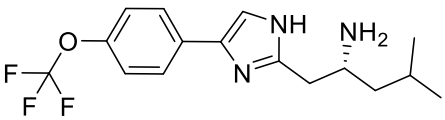


Compound 3
(*R*)-4-(2-(2-amino-4-methylpentyl)-1*H*-imidazol-4-yl)benzonitrile
Step 1: 2-(4-bromophenyl)-2-oxoethyl (R)-3-((tert-butoxycarbonyl)amino)-5-methylhexanoate
Following GP, Step 1, (*R*)-3-((tert-butoxycarbonyl)amino)-5-methylhexanoic acid (1.00 g, 4.08 mmol) and 2-bromo-1-(4-bromophenyl)ethan-1-one (1.13 g, 4.08 mmol) were used to generate 2-(4-bromophenyl)-2-oxoethyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoate, which was used crude in the cyclization. MS $[M+Na]^+$ 464.

Step 2: tert-butyl (R)-(1-(4-(4-bromophenyl)-1H-imidazol-2-yl)-4-methylpentan-2-yl)carbamate
Following a modified GP, Step 2, 2-(4-bromophenyl)-2-oxoethyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoate (240 mg, 0.54 mmol) was cyclized in a round bottom flask equipped with a Dean-Stark trap at reflux and worked up according to GP1 to generate *tert*-butyl (*R*)-(1-(4-(4-bromophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-yl)carbamate, which was used crude in the cyanation. MS $[M+H]^+$ 422.

Step 3: tert-butyl (R)-(1-(4-(4-cyanophenyl)-1H-imidazol-2-yl)-4-methylpentan-2-yl)carbamate
To a mixture of $Zn(CN)_2$ (12 mg, 0.10 mmol), dppf (18 mg, 0.032 mmol), $Pd(dba)_2$ (5 mg, 0.008 mmol) and *tert*-butyl (*R*)-(1-(4-(4-bromophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-yl)carbamate (70 mg, 0.17 mmol) was added 4 mL of degassed DMF containing four drops of water. The reaction mixture was flushed with nitrogen and the mixture heated at 120 ^oC for 2 hours. The solvent was evaporated under reduced pressure and the crude partitioned between 1M NaOH (2 mL) and dichloromethane (2 mL). The DCM layer was extracted using a phase separator cartridge and the aqueous was back-extracted with DCM (2 x 2 mL) through the phase separator cartridge. The combined organics were concentrated *in vacuo* and the crude *tert*-butyl (*R*)-(1-(4-(4-cyanophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-yl)carbamate was used directly in the next step. MS $[M+H]^+$ 369.

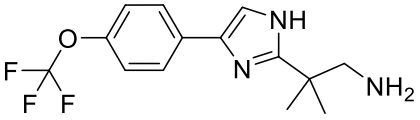
Step 4: (R)-4-(2-(2-amino-4-methylpentyl)-1H-imidazol-4-yl)benzonitrile
3M HCl in EtOAc (10 mL, 30 mmol) was added to a flask containing *tert*-butyl (*R*)-(1-(4-(4-cyanophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-yl)carbamate (80 mg, 0.22 mmol) and stirred at room temperature for 30 min. The mixture was concentrated under vacuum and purified by HPLC to obtain the title compound. MS $[M+H]^+$ 269.2.



Compound 4

(*R*)-4-methyl-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)pentan-2-amine

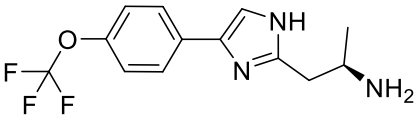
The procedure used to generate **Compound 2a** [(*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine] was followed using (*R*)-3-((*tert*-butoxycarbonyl)amino)-5-methylhexanoic acid and 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one to produce (*R*)-4-methyl-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)pentan-2-amine. MS $[M+H]^+$ 328.



Compound 5

2-methyl-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-1-amine

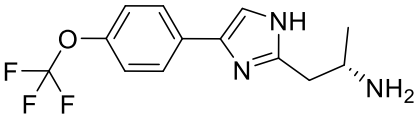
The procedure used to generate **Compound 2a** [(*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine] was followed using 3-((*tert*-butoxycarbonyl)amino)-2,2-dimethylpropanoic acid and 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one to produce 2-methyl-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-1-amine. MS $[M+H]^+$ 300.



Compound 6

(*R*)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

The procedure used to **Compound 2a** [(*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine] was followed using (*R*)-3-((*tert*-butoxycarbonyl)amino)butanoic acid and 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one to produce (*R*)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 286.

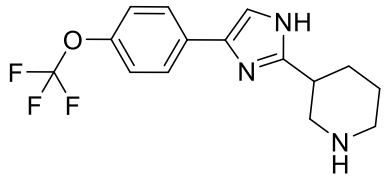


Compound 7

(*S*)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

The procedure used to generate **Compound 2a** [(*R*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine] was followed using (*S*)-3-((*tert*-butoxycarbonyl)amino)butanoic

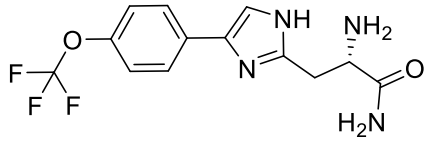
acid and 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one to produce (*S*)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 286.



Compound 8
3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)piperidine
To a 0.5M solution of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid in THF/DMF (1:1) (250 uL, 125 umol, 1.0 eq) in an 8 mL vial was added DMF (320 uL) followed by 1.0M KOtBu in THF (125 uL, 125 umol, 1.0 eq). A 0.5M solution of 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one in THF (250 uL, 125 umol, 1.0 eq) was added. The vial was capped and shaken at 30 °C for 4 hours. The solvent was removed *in vacuo* and the crude product was used directly without purification.

To the intermediate ester was added freshly prepared 4.0M ammonium acetate in MeOH (470uL, 1.88 mmol, 15 eq) and toluene (625 uL). The vial was capped and shaken at 100 °C for 4 hours followed by concentration *in vacuo*. The crude material was diluted with DCM (1.9 mL), 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) and 2.0M NaCl (aq) (470 uL). The vial was capped, shaken and centrifuged to separate the two layers. The top aqueous layer was removed and discarded. 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) was again added and the vial capped, shaken and centrifuged. The top aqueous layer was removed and discarded. Water (780 uL) was added and the vial was again capped, shaken and centrifuged. The bottom organic layer was removed and put in an 8 mL collection vial. To the water layer was added DCM (1.25 mL) and the vial was capped, shaken and centrifuged. The bottom organic layer was removed and combined with the previous extract in the collection vial and concentrated *in vacuo*. The crude material was purified using preparative HPLC to obtain pure Boc-protected aminoimidazole intermediate, which was used directly.

The Boc-protected amine in a reaction vial was diluted with DCM (0.8 mL) and treated with TFA (115 uL, 1.50 mmol). The vial was capped and shaken for 2 hours. The solvent was removed *in vacuo* to obtain 3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)piperidine. MS $[M+H]^+$ 312.

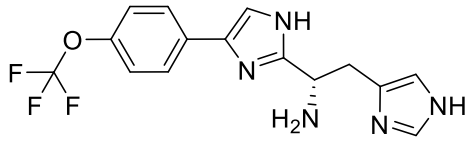


Compound 9
(*S*)-2-amino-3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propanamide
In an 8 mL vial was combined (*S*)-4-amino-3-((tert-butoxycarbonyl)amino)-4-oxobutanoic acid (200 umol, 1.0 eq), a mixture of DMF/THF (400 uL, v/v = 1/1) and DMF (600 uL)

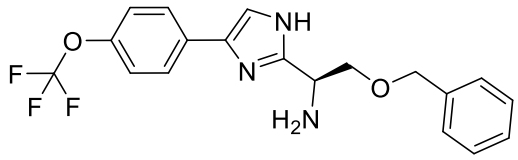
followed by 1.0M KOtBu in THF (200 uL, 200 umol, 1.0 eq). A 0.5M solution of 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one in THF (400 uL, 200 umol, 1.0 eq) was added. The vial was capped and shaken at 30 °C for 4 hours. The solvent was removed *in vacuo* and the crude product was used directly without purification.

To the intermediate ester was added freshly prepared 4.0M ammonium acetate in MeOH (750 uL, 3.00 mmol, 15 eq) and toluene (1000 uL). The vial was capped and shaken at 100 °C for 4 hours followed by concentration *in vacuo*. The residue was purified using preparative HPLC to obtain pure Boc-protected aminoimidazole intermediate, which was used directly.

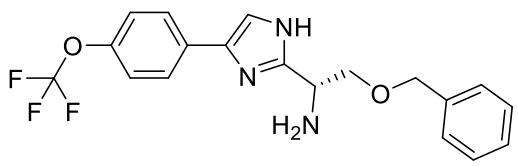
The Boc-protected amine in a reaction vial was diluted with DCM (1000 uL) and treated with TFA (200 uL, 2.61 mmol). The vial was capped and shaken at 30 °C for 16 hours. The solvent was removed *in vacuo* to obtain (*S*)-2-amino-3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propanamide. MS $[M+H]^+$ 315.



Compound 10
(S)-2-(1*H*-imidazol-4-yl)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine
The procedure used to generate **Compound 8** [3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)piperidine] was followed using (tert-butoxycarbonyl)-L-histidine to produce (*S*)-2-(1*H*-imidazol-4-yl)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine. MS $[M+H]^+$ 338.



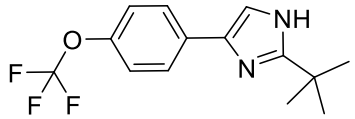
Compound 11
(*S*)-2-(benzyloxy)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine
The procedure used to generate **Compound 8** [3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)piperidine] was followed using *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-D-serine to produce (*S*)-2-(benzyloxy)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine. MS $[M+H]^+$ 378.



Compound 12

(*R*)-2-(benzyloxy)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine

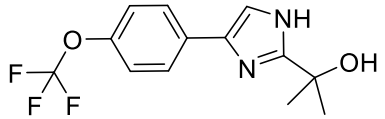
The procedure used to generate **Compound 8** [3-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)piperidine] was followed using *O*-benzyl-*N*-(tert-butoxycarbonyl)-L-serine to produce (*R*)-2-(benzyloxy)-1-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)ethan-1-amine. MS $[M+H]^+$ 378.



Compound 14

2-(tert-butyl)-4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole

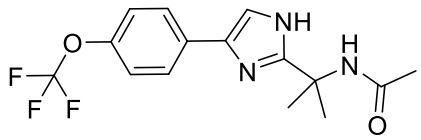
To a vial containing 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl pivalate (200 mg, 0.66 mmol) was added ammonium acetate (760 mg, 9.86 mmol), molecular sieves (400 mg) and anhydrous toluene (4 mL). The vial was sealed and heated at 110 °C for 4 hours. The reaction mixture was concentrated under vacuum and DCM (4 mL) and 2M NaOH (4 mL) were added. The mixture was passed through a phase separator cartridge and the organic filtrate was washed with brine (3 x 3 mL) and passed through another phase separator. The organic filtrate was concentrated to dryness under vacuum and a portion was purified by preparative HPLC to obtain the title compound. MS $[M+H]^+$ 285.1.



Compound 15

2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-ol

To a vial containing 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-hydroxy-2-methylpropanoate (200 mg, 0.65 mmol) was added ammonium acetate (755 mg, 9.80 mmol), molecular sieves (400 mg) and anhydrous toluene (4 mL). The vial was sealed and heated at 110 °C for 4 hours. The reaction mixture was concentrated under vacuum and DCM (3 mL) and 2M NaOH (3 mL) were added. The biphasic suspension was passed through a phase separator cartridge and the organic filtrate was washed with brine. A precipitate developed during the brine wash. The mixture was filtered and the collected solid was then dissolved in 2M HCl and DCM. The organic layer was extracted and discarded. The aqueous layer was extracted and made basic using 2M NaOH, causing a white precipitate to form. The mixture was filtered and the solid washed with DCM and water. The organics of the filtrate were separated from the aqueous using a phase separator cartridge and concentrated to dryness under vacuum to obtain the title compound as a white solid (8 mg, 4%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.78 (d, *J* = 9.0 Hz, 2H), 7.31 (s, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 1.61 (s, 6H). MS $[M+H]^+$ 287.



Compound 16

***N*-(2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)acetamide**

Step 1: 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate

Following GP1, Step 1, 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid (500 mg, 2.46 mmol) and 2-bromo-1-(4-(trifluoromethoxy)phenyl)ethan-1-one (697 mg, 2.46 mmol) were used to generate 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate (850 mg, 85% yield), which was used crude in the cyclization. MS $[M+Na]^+$ 428.

Step 2: tert-butyl (2-(4-(3-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)propan-2-yl)carbamate

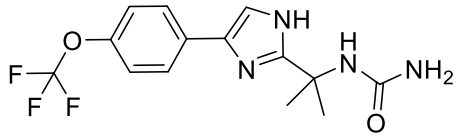
Following GP1, Step 2, 2-oxo-2-(4-(trifluoromethoxy)phenyl)ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate (120 mg, 0.30 mmol) was cyclized to give *tert*-butyl (2-(4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (75 mg, 66% yield), which was used crude in the deprotection. MS $[M+H]^+$ 386.

Step 3: 2-(4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)propan-2-amine

Following GP1, Step 3, *tert*-butyl (2-(4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (100 mg, 0.30 mmol) was treated with 3M HCl in EtOAc (5 mL, 15 mmol) and stirred for 30 minutes. After HPLC purification, 2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine was isolated cleanly. MS $[M+H]^+$ 286.1.

Step 4: N-(2-(4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)propan-2-yl)acetamide

To a solution of 2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine (50 mg, 0.18 mmol) in acetonitrile (2 mL) was added 2,6-lutidine (61 uL, 0.53 mmol) followed by acetic anhydride (33 uL, 0.35 mmol), dropwise. The mixture was stirred at room temperature for 1 hour and quenched with saturated aqueous $NaHCO_3$ (2mL) and diluted with EtOAc (2mL). The organic layer was extracted, concentrated *in vacuo* and the residue re-dissolved in water (2 mL) and DCM (2 mL). The biphasic mixture was passed through a phase-separator cartridge, the organic filtrate concentrated to dryness and the residue purified by preparative HPLC to obtain the title compound. MS $[M+H]^+$ 328.1.

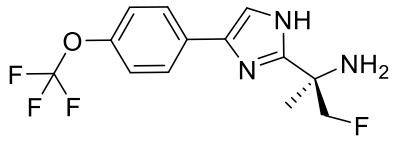


Compound 17

1-(2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)urea

To a solution of 2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine (150 mg, 0.53 mmol) [generated in the same manner as the precursor to compound **16]** in DCM (6 mL) was added 2,2,2-trichloroacetyl isocyanate (94 uL, 0.79 mmol) at room temperature. The reaction was stirred for 30 minutes, concentrated *in vacuo* and re-dissolved in methanol (3 mL). Five drops of saturated sodium carbonate solution were added and the mixture was

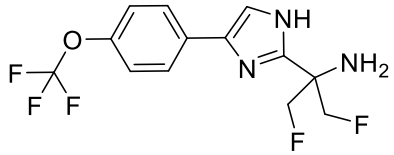
refluxed for 30 minutes. It was concentrated *in vacuo* and diluted with EtOAc and brine. The organic layer was extracted, dried over sodium sulfate, filtered and the filtrate concentrated to dryness. A portion of the crude material was purified by preparative HPLC to obtain the title compound. MS $[M+H]^+$ 329.1.



Compound 18

(*R*)-1-fluoro-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

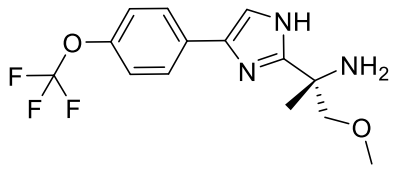
4M HCl in 1,4-dioxane (5 mL, 20 mmol) was added to a flask containing *tert*-butyl (*R*)-(1-fluoro-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (53 mg, 0.13 mmol) and stirred at room temperature for 1 hour. The mixture was concentrated under vacuum, dissolved in 10% methanol in dichloromethane (3 mL) and loaded onto a 1 g SCX cartridge. The cartridge was washed using 10 CV 10% methanol in dichloromethane and the desired material was then eluted with 4 CV of a 10% methanol in dichloromethane modified with 1% NH_3 to obtain the title compound as a pink solid (39 mg, 98% yield). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.67 - 7.75 (m, 2H), 7.17 - 7.24 (m, 3H), 4.71 (dd, *J* = 47.4, 8.6 Hz, 1H), 4.55 (dd, *J* = 47.4, 8.6 Hz, 1H), 1.59 (d, *J* = 2.0 Hz, 3H).



Compound 19

1,3-difluoro-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

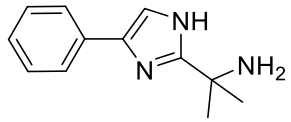
4M HCl in 1,4-dioxane (10 mL, 40 mmol) was added to a flask containing *tert*-butyl (1,3-difluoro-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (211 mg, 0.50 mmol) and stirred at room temperature for 90 minutes. The mixture was concentrated *in vacuo*, dissolved in 10% methanol in dichloromethane (3 mL) and loaded onto a 2 g SCX cartridge. The cartridge was washed using 15 CV 10% methanol in dichloromethane and the desired material was then eluted with 10 CV of 10% methanol in dichloromethane modified with 1% NH_3 to obtain the title compound as a light brown solid (145 mg, 90% yield). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.74 (d, *J* = 8.7 Hz, 2H), 7.27 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 4.74 (ddd, *J* = 47.6, 9.7, 2.9 Hz, 2H), 4.69 (ddd, *J* = 47.6, 9.7, 1.2 Hz, 2H). MS $[M+H]^+$ 322.



Compound 20

(*S*)-1-methoxy-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

1M HCl in 1,4-dioxane (5 mL, 5 mmol) was added to a flask containing *tert*-butyl (1-methoxy-2-(4-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (120 mg, 0.29 mmol) and stirred at room temperature for 10 hours. The mixture was concentrated under vacuum and a portion was subjected to preparative chiral chromatography (Chiralpak IA [250 mm x 21.2 mm]; Mobile phase: heptane to isopropanol, 95:5; Flow rate: 15 mL/min; Run time: 30 min; Detection: 225 nm; Temperature: ambient). The title compound was obtained as the second compound to elute from the preparative column. Analytical purity: 28.49 min, 96.5% ee, 99% achiral (Chiralpak IA [250 mm x 4.6 mm]; Mobile phase: heptane to isopropanol, 95:5; Flow rate: 1 mL/min; Run time: 35 min; Detection: 225 nm; Temperature: ambient). MS $[M+H]^+$ 316.



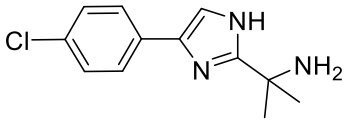
Compound 22

2-(4-phenyl-1*H*-imidazol-2-yl)propan-2-amine

To a 0.5M solution of 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid in THF/DMF (1:1) (250 uL, 125 umol, 1.0 eq) in an 8 mL vial was added DMF (375 uL) followed by 1.0M KOtBu in THF (125 uL, 125 umol, 1.0 eq). A 0.5M solution of 2-bromo-1-phenylethan-1-one in THF (250 uL, 125 umol, 1.0 eq) was added. The vial was capped and shaken at 30 ^oC for 4 hours. The solvent was removed *in vacuo* and the crude product was used directly without purification.

To the intermediate ester was added freshly prepared 4.0M ammonium acetate in MeOH (470uL, 1.88 mmol, 15 eq) and toluene (625 uL). The vial was capped and shaken at 100 ^oC for 4 hours followed by concentration *in vacuo*. The crude material was diluted with DCM (1.9 mL), 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) and 2.0M NaCl (aq) (470 uL). The vial was capped and shaken. Upon settling, the top aqueous layer was removed and discarded. 2.0M NaOH (aq) (780 uL, 1.56 mmol, 12.5 eq) was again added and the vial capped and shaken. Upon settling, the top aqueous layer was removed and discarded. Water (780 uL) was added and the vial capped and shaken. The bottom organic layer was removed and put in a 8 mL collection vial. To the water layer was added DCM (1.25 mL) and the vial capped and shaken. The bottom organic layer was removed and combined with the previous extract in the collection vial. The solvent was removed *in vacuo*. The crude material was purified using preparative HPLC to obtain pure Boc-protected aminoimidazole intermediate, which was used directly.

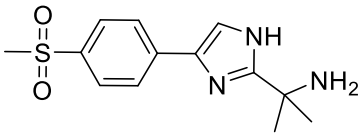
To the Boc-protected amine in a reaction vial was added a solution of DCM/TFA (v/v = 5/1) (2.0 mL). The vial was capped and shaken at 30 °C for 6 hours. The solvent was removed *in vacuo* to obtain 2-(4-phenyl-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 202.



Compound 23

(*S*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine

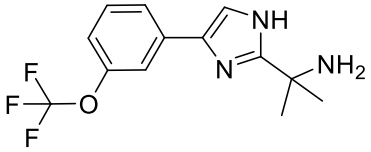
The procedure used to generate **Compound 22** [2-(4-phenyl-1*H*-imidazol-2-yl)propan-2-amine] was followed using 2-bromo-1-(4-chlorophenyl)ethan-1-one to produce (*S*)-1-(4-(4-chlorophenyl)-1*H*-imidazol-2-yl)-4-methylpentan-2-amine. MS $[M+H]^+$ 236.



Compound 24

2-(4-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

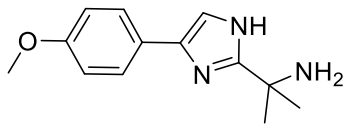
The procedure used to generate **Compound 22** [2-(4-phenyl-1*H*-imidazol-2-yl)propan-2-amine] was followed using 2-bromo-1-(4-(methylsulfonyl)phenyl)ethan-1-one to produce 2-(4-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 280.



Compound 25

2-(4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine

To *tert*-butyl (2-(4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (150 mg, 0.39 mmol) was added 1M HCl in dioxane (5 mL) and the mixture was stirred at room temperature for 10 hours. It was then concentrated *in vacuo* and the residue purified by preparative HPLC to obtain 2-(4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 286.1.



Compound 26

2-(4-(4-methoxyphenyl)-1*H*-imidazol-2-yl)propan-2-amine

The procedure used to generate **Compound 22** [2-(4-phenyl-1*H*-imidazol-2-yl)propan-2-amine] was followed using 2-chloro-1-(4-methoxyphenyl)ethan-1-one to produce 2-(4-(4-methoxyphenyl)-1*H*-imidazol-2-yl)propan-2-amine. MS $[M+H]^+$ 232.