Supporting Information

Synthesis and SAR of 1,2,3,4-Tetrahydroisoquinoline Based CXCR4 Antagonists

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General Procedures: Unless otherwise indicated, all reactions were conducted in oven (150°C) or flame-dried glassware using distilled and degassed solvents under positive pressure of dry argon with standard Schlenk techniques. Stainless steel syringes or cannulae that had been oven-dried (150°C) and cooled under an argon atmosphere or in a desiccator were used to transfer air- and moisture-sensitive liquids. Yields refer to chromatographically (LC-MS (ESI-API, 254 nm) MeOH in H_2O (0.1% HCO_2H), C18 (Agilent Zorbax XDB-18, 50 mm x 4.6 mm, 3.5 μm), *m/z* and spectroscopically (^{1}H NMR) homogeneous (≥95% purity by LC-MS) materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on pre-coated glass plates of silica gel (0.25 mm) 60 F_{254} using the indicated solvent system. Visualization was accomplished with ultraviolet light (UV 254 nm), or by shaking the plate in a sealed jar containing silica gel and Iodine. Alternatively, plates were treated with one of the following solutions (this was accomplished by holding the edge of the TLC plate with forceps or tweezers and immersing the plate into a wide-mouth jar containing the desired staining solution) and carefully heating with a hot-air gun (450°C) for approximately 1-2 min (NOTE: excess stain was removed by resting the TLC on a paper towel prior to heating): 10% phosphomolybdic acid in ethanol, 1% potassium permanganate/7% potassium carbonate/0.5% sodium hydroxide aqueous solution, and/or anisaldehyde in ethanol with 10% sulfuric acid. Flash column chromatography was performed using Silica Flash® P60 silica gel (40-63 μm) from Silicycle, or Teledyne Isco Combiflash. All the key compounds were isolated using the same eluents with the same protocol on a Teledyne Isco combiflash. Dichloromethane was used as the non-polar eluent (A) and the polar eluent (B) was a mixture (80:20:3) DCM:MeOH:NH_4OH, (DCM, 5 min, 10%B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min). All work-up and purification procedures were carried out with reagent grade solvents in air.

NMR Integration of exchangeable protons: Some compounds when analyzed showed the exchangeable amine protons visible within the noise but did not integrate well due to overlap. For instance, the NH protons overlap with the butyl protons and residual water (1.8-1.4 ppm) resulting in an inaccurate integration. These protons were excluded from the reported data for compounds **16c**, **20a**, **20b** and **20k**

CXCR4 and Muscarinic Receptors Calcium Flux Assays:

Exemplary compounds were tested for their ability to induce or inhibit calcium flux in CCRF-CEM cells. The experimental procedure and results are provided below. The exemplified biological assays, which follow, have been carried out with all compounds. Human T lymphoblast cells (CCRF-CEM) expressing endogenous CXCR4 receptors and musarinic acetycholine receptors were grown in suspension culture and plated in clear bottom 384-well microplates (Greiner bio-one Cat# 789146) in assay buffer [Hank's Buffered Saline Solution (Gibco Cat# 14025-092) supplemented with 20 mM HEPES (Gibco Cat# 15630-080) and 0.1% fatty-acid free BSA (Sigma Cat# A9205)] at 40,000 cells per well. The cells were loaded with equal volume of calcium indicator dye (AAT Bioquest Inc, Cat# 34601) for 30 minutes at 37°C. The cells were then equilibrated to room temperature for 15 minutes before assay. Test compounds solubilized and serially diluted in DMSO were transferred to 384 well plates (Matrix Cat# 4307). The serially diluted compounds were diluted to working concentrations with the same assay buffer to 0.5% DMSO. They were added to the cells by FDSS6000 (Hamamatsu) at final concentrations ranging from 25,000 nM to 0.423 nM. Activity of the compounds to induce calcium flux was monitored by FDSS in the "agonist mode" for 90 sec. For "antagonist mode" assessment, the cells are subsequently incubated for 25 minutes at room temperature. SDF-1α (R&D System Cat# 350-NS/CF) or acetylcholine was then added at a final concentration of 5 nM and 2,000 nM, respectively, to stimulate the cells. Inhibition of SDF-1α and acetylcholine-induced calcium flux was monitored by FDSS6000 for 90 seconds.

Activation data for the test compound over a range of concentrations was plotted as percentage activation of the test compound (100% = maximum response triggered by a saturating concentration of SDF-1α, i.e., 160 nM). After correcting for background, EC_{50} values were determined. The EC_{50} is defined as the concentration of test compound, which produces 50% of the maximal response and was quantified using the 4-parameter logistic equation to fit the data. Inhibition data for the test compound over a range of concentrations was plotted as percentage inhibition of the test compound as compared to an internal control compound. The IC_{50} is defined as the concentration of test compound, which inhibits 50% of the maximal response and was quantified using the 4-parameter logistic equation to fit the data.

None of the compounds tested demonstrated agonist activity in the calcium flux assay. All compounds demonstrated EC_{50} values >30 μM. In contrast, compounds demonstrated a range of potencies in inhibiting SDF-1 α -induced calcium flux.

PAMPA Assay:

Compounds and controls are utilized as 10 mM stocks in 100% DMSO. Compounds are diluted 1:100 in pH 7.4 or pH 5.5 donor well buffer (pION CAT # 110151) providing a 100 µM assay solution in 1% DMSO. Compound diluted in donor well buffer is transferred to a Whatman Unifilter plate and filtered prior to dispensing 200 µl into the donor well of the assay plate (pION CAT #110163). The PAMPA membrane is formed by pipetting 4 µl of the lipid solution (pION CAT #110169) onto the filter plate (VWR CAT #13503). The membrane is then covered with 200 µl of acceptor well buffer at pH 7.4 (pION CAT #110139). The PAMPA assay plate (donor side and acceptor side) is combined and allowed to incubate at room temperature for 4 hours. The plate is then disassembled and spectrophotometer plates (VWR CAT #655801) are filled (150 µl/well). The donor, acceptor, reference, and blank plates are read in the SpectraMax UV plate reader. Data is captured by the pION software which analyzes the spectra and generates Pc values.

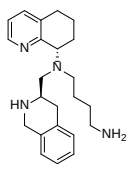
Recombinant CYP2D6 Inhibition Assay:

The CYP2D6 inhibition assay utilizes microsomes from the insect cells expressing human recombinant CYP2D6 enzyme and fluorogenic probe (AMMC, 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin) that produces fluorescent metabolite; both reagents were obtrained from Thermo Fisher Scientific/Discovery Labware (Woburn, MA). Assay was performed in 1536-well microplates in a total volume of 5 µl. Automated liquid handling equipment (Thermo Multidrop Combi, LabCyte ECHO 550) was used in all steps of compound preparation and for assay reagent additions. Each compound was tested in duplicate at 7 concentrations ranging from 1 nM to 20 µM; final concentration of DMSO in reactions was 0.2%. Positive controls were included in each experiment/run. Test compounds (10 nL/well) were first pre-incubated at 37°C for 30 min with 2.5 µL of prewarmed 2-fold-concentrated mixture of AMMC fluorogenic substrate (3 µM) and 12.5 nM rCYP2D6 enzyme in 100 mM potassium phosphate assay buffer pH 7.4. At the end of preincubation, the reactions were initiated by the addition of 2.5 µL of prewarmed 2-fold-concentrated NADPH-regenerating system (16.2 nM NADP) in the same assay buffer. Assay plates were then incubated at 37°C for 45 min. Following incubation, reactions were terminated by the addition of 3 µL of quench buffer (80% acetonitrile, 20% 0.5 M TRIS-base). Fluorescence intensity was measured using the Envision fluorescence plate reader (Perkin Elmer) at excitation and emission wavelengths of 405 and 460 nm, respectively, using a 430-nm cut-off filter. The end-point fluorescence readout was normalized to the fluorescence intensity of the reaction performed in the absence of the test substance (totals, 0% inhibition) and the mixture of reaction components in the presence of "Inhibitor Cocktail" (background, 100% inhibition). The IC_{50} value for each compound is derived from the fitted 20-point curve using a four-parameter logistic regression model.

For Metabolic Stability experimental see[1] (Kieltyka, K.; *et al. Rapid Commun. Mass Spectrom.* **2009,** *23* (11), 1579-1591.)

For Metabolite ID assay see[2] (Paiva, A. A.; *et al. Bioanalysis* **2017,** *9* (7), 541-552.)

Table 1:



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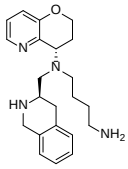

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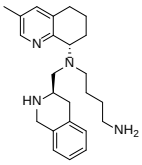

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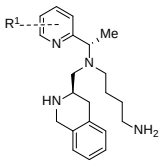
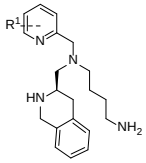


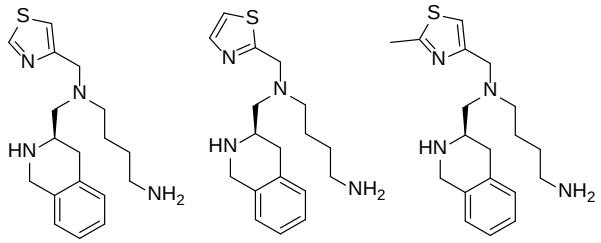
16a-c

Compound	R^1	CXCR4 Ca^{+2} Flux (IC_{50}) *n*M	SD N=2	mAChR Ca^{+2} Flux (IC_{50}) *u*M	LM % (H/R/M)	CYP450 2D6 (IC_{50}) *n*M	Pampa (pH 7.4/5.5)
	TIQ-15	6.5		30	77/37/17	320	0/6
	8	6.2		16.7	91/3/39	93	25/42
	13	10.7	0	16.7	84/7/2	27	ND/17
16a	H	61.99	12.22	28.5	97/77/79	322	-
16b	3-Me	1709.64	882.55	33	100/22/11	1300	-
16c	5-Me	24.35	2.17	6.1	79/1/5	654	-

Table 2:

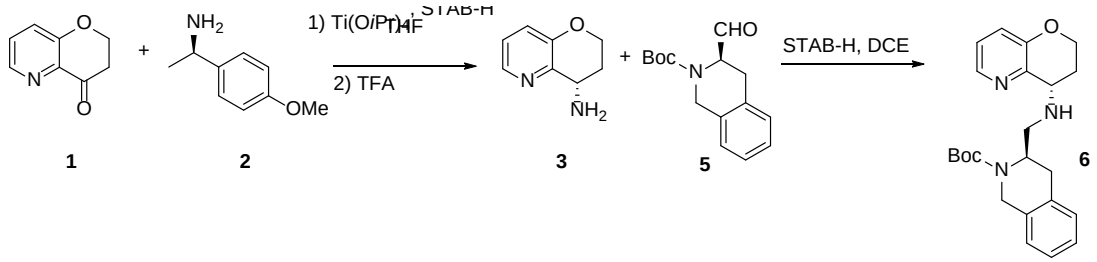


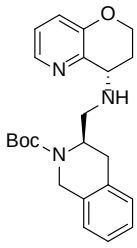
Entry	R^1	CXCR4 Ca^{+2} Flux (IC_{50}) nM	SD N=2	mAChR Ca^{+2} Flux (IC_{50}) uM	LM % (H/R/M)	CYP450 2D6 (IC_{50}) nM	PAMPA (pH7.4/5.5)
20a	H	230.5	135.27	11.5	100/33/77	87	0
20b	2-quin	13647	N=1	16.7	88/8/35	27	134/ND
20c	1-isoquin	8721	N=1	4.35	88/5/62	172	16/0
20d	3-isoquin	3307.08	2868.83	16.7	100/31/45	84	0/ND
20e	6-Me	2902.11	28.62	10.7	100/34/ND	55	0
20f	5-Me	71.02	29.86	23.2	100/3/67	121	0
20g	4-Me	697.84	135.86	3.0	87/30/74	115	0
20h	3-Me	20.91	4.93	5.9	86/33/64	459	0
20i	5-Cl	33K	-	16.7	89/5/56	552	ND/ND
20j	4-Cl	631.07	486.43	33	89/31/ND	93	ND/ND
20k	3-Cl	1855.00	1357.9	16.7	100/14/43	211	ND/ND
20l	5-F	260.19	220.77	33	88/10/76	238	21/ND
20m	3-F	2115.59	2105.09	16.7	83/9/64	178	0
20n	5-OMe	7590.56	N=1	27	92/13/69	240	6/0
20o	3-OMe	2290.39	533.43	33	100/38/99	98	4/0
20p	5-CF_3	33K	-	21	98/8/85	37	0
20q	3-CF_3	405.51	299.71	33	100/66/82	633	ND/ND
20r	3-*c*Pr	162.78	80.52	16.7	90/29/56	36	ND/74
20s	3-vinyl	484.16	N=1	16.7	86/4/44	199	18/ND
20t	3,5-Me	69.18	34.58	33	100/39/79	744	10/9
20u	3-Me-5-F	126.56	78.25	33	100/36/91	1270	20/0
20v	5-Me-3-F	322.62	45.14	11.63	86/18/51	191	116/35



Entry	R	Z	CXCR4 Ca^{+2} Flux (IC_{50}) *n*M	SD N=2	mAChR Ca^{+2} Flux (IC_{50}) *u*M	LM % (H/R/M)	CYP450 2D6 (IC_{50}) *n*M	PAMPA pH (7.4/5.5)
1	H	4-S	16558.92	2931.89	33	100/16/80	249	ND/562
2	H	2-S	33333	0	33	ND/23/96	134	ND/ND
3	Me	4-S	33333	0	18	89/42/46	134	6/0

Experimental for Pyran 8:



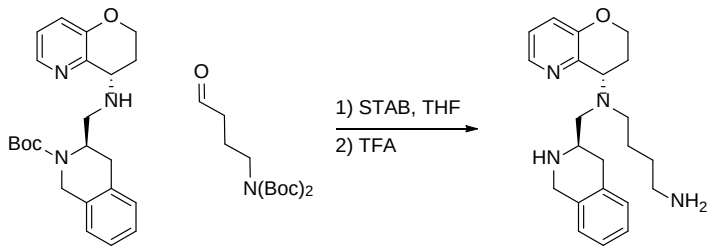


Compound 6: Procedure adapted from literature protocol.[3] The 2H-pyrano[3,2-b]pyridin-4(3H)-one (**1,** 1.0 g, 6.70 mmol) was dissolved in anhydrous THF and added titanium isopropoxide (3.93 mL, 13.41 mmol) and (*S*)-1-(4-methoxyphenyl)ethanamine (**2,** 1.093 mL, 7.38 mmol) at room temperature. The reaction was stirred at room temperature for 8 hours. Then added sodium triacetoxyborohydride (4.39 g, 20.11 mmol) and 5 mL anhydrous MeOH. It was stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc. The organic phase was washed with water and brine; dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* column chromatography (combiflash) starting with DCM and increased the polarity with DCM:MeOH NH_4OH (9:1:01) to 25-50% in DCM slowly to provide **S1** (0.676 g, 35%) as a brown oil.

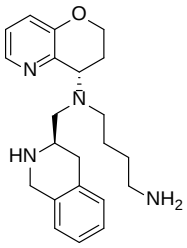
^{1}H NMR (400 MHz, Chloroform-d) δ = 8.16 (dd, *J* = 3.6, 2.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.09 - 7.06 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.19 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 4.10 - 3.96 (m, 2H), 3.90 (dd, *J* = 6.3, 4.9 Hz, 1H), 3.80 (s, 3H), 1.78 - 1.58 (m, 3H), 1.44 (d, *J* = 6.6 Hz, 3H).

The brown oil **S1** (0.676 g, 2.377 mmol) was dissolved in TFA (3.66 mL, 47.5 mmol) and stirred at room temperature overnight. After all the starting material was consumed 10 mL water and 10 mL EtOAc was added and stirred for 1 hour at room temperature. The EtOAc was washed with water 4 times. The combined aqueous phase was cooled in an ice bath and 1M NaOH was added until pH > 10-12 was achieved. The basic phase was extracted with DCM several times. The combined organic layer was dried over anhydrous $MgSO_4$; filtered and concentrated *in vacuo* to afford an oil **3** (0.300 g, 85%) which was used without purification. The oil (**3,** 0.3 g, 1.998 mmol) was dissolved in 1,2-DCE and added sodium triacetoxyborohydride (0.714 g, 3.27 mmol) stirred for few minutes and then added the aldehyde (R)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate[4] (**5,** 0.475 g, 1.816 mmol) at room temperature and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution then extracted with DCM 3 times. The combined organic layer was washed with water then brine; dried over anhydrous $MgSO_4$; filtered and concentrated *in vacuo*. The crude material was purified *via* column chromatography (combiflash) starting with DCM and increased the polarity with DCM:MeOH:NH_4OH (9:1:01.) to 50% in DCM to provide **6** (0.556 g,77%) as a yellow oil.

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.10 (s, 1H), 7.21 - 6.98 (m, 6H), 4.83 - 4.36 (m, 2H), 4.32 - 4.22 (m, 2H), 4.15 - 4.05 (m, 1H), 3.78 - 3.70 (m, 1H), 3.01 - 2.88 (m, 1H), 2.82 (dd, *J* = 11.7, 6.4 Hz, 1H), 2.53 (s, 1H), 1.95 (s, 1H), 1.78 (s, 2H), 1.48 (s, 9H).



6 7 8



Compound 8**:** Compound **6** (0.556 g, 1.406 mmol) and aldehyde **7** (0.606 g, 2.109 mmol) were dissolved in 1,2-DCE and stirred for few minutes. Then STAB-H (0.614 g, 2.81 mmol) was added and allowed to stir overnight. The reaction was quenched with saturated $NaHCO_3$ solution then extracted with DCM. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$; filtered and concentrated *in vacuo*. The crude material was purified *via* column chromatography starting with DCM and increased the polarity with DCM:MeOH:NH_4OH (9:1:0.1) to 50% in DCM (0.473 g, 51%).

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.12 - 7.97 (m, 1H), 7.12 - 7.08 (m, 2H), 7.05 - 6.95 (m, 4H), 4.62 (d, *J* = 16.3 Hz, 1H), 4.30 (dt, *J* = 10.7, 4.9 Hz, 1H), 4.03 (d, *J* = 31.0 Hz, 2H), 3.65 - 3.50 (m, 2H), 3.51 - 3.36 (m, 3H), 2.90 (td, *J* = 51.6, 50.6, 16.0 Hz, 2H), 2.63 - 2.37 (m, 3H), 1.49-1.47 (m, 5H), 1.48 - 1.46 (m, 27H).

The residue (0.473 g, 0.709 mmol) was dissolved in DCM and TFA (2.0 mL, 26.0 mmol) was added. The reaction was allowed to stir at room temperature overnight. The reaction was quenched with 1M NaOH. The phases were separated and the aqueous phase was extracted with DCM (3X) . The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified *via* column chromatography starting with DCM and increased the polarity with DCM:MeOH:NH_4OH (8:2:0.3) to 100% DCM: MeOH: NH_4OH (8:2:0.3) slowly to provide **8** (100 mg, 39%)

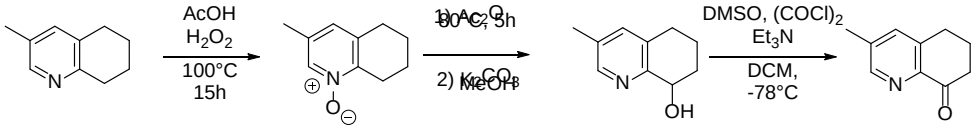
^{1}H NMR (400 MHz, Chloroform-d) δ = 8.19 (t, *J* = 3.0 Hz, 1H), 7.14 - 7.03 (m, 7H), 4.36 - 4.31 (m, 1H), 4.18 - 4.12 (m, 2H), 4.06 (d, *J* = 15.4 Hz, 1H), 3.90 (d, *J* = 15.4 Hz, 1H), 2.98 (dd, *J* = 13.3, 3.5 Hz, 2H), 2.92 - 2.80 (m, 1H), 2.74 (q, *J* = 6.7 Hz, 2H), 2.66 - 2.54 (m, 3H), 2.51 - 2.41 (m, 3H), 2.25 (tt, *J* = 9.8, 3.8 Hz, 1H), 2.15 - 2.07 (m, 1H), 1.58 - 1.50 (m, 4H);

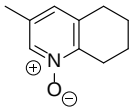
^{13}C NMR (100 MHz, Chloroform-d) δ = 152.7, 145.1, 141.2, 135.3, 134.3, 129.1, 126.3, 125.9, 125.6, 124.1, 123.2, 65.6, 58.1, 57.8, 57.4, 53.7, 52.3, 48.3, 41.5, 33.6, 30.3, 26.9;

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.80 at 254 nM, MS (+) 367.2

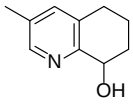
Anal. Calcd. For $C_{22}H_{30}N_4O \bullet 2.1H_2O$; C=65.35, H=8.52, N=13.86; Found C=65.20, H=8.58, N=13.54

Experimental For Compound 13:





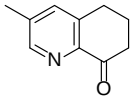
Coumpound S2: To a 500 mL RBF was added 3-methyl-5,6,7,8-tetrahydroquinoline **9** (25 g, 170 mmol), AcOH (170 mL) and hydrogen peroxide (30% in water, 60 mL, 509 mmol). The mixture was heated to 100 °C for 18h, then cooled to 0 °C and neutralized (pH 6-7) with 4M NaOH. The aqueous phase was extracted with DCM (3 x 50 mL) dried with $MgSO_4$, filtered and concentrated to an oil which was used without further purification.



Compound 10: To a 500 mL RBF was added crude **S2** and Ac_2O (150 mL) then the mixture was stirred at room temp for 1 h. The reaction vessel was heated in an 80 °C oil bath for 5 h, then the volatiles were removed *in vacuo.* The brown oil was dissolved in 100 mL DCM and washed with saturated $NaHCO_3$ then dried with $MgSO_4$, filtered and concentrated to afford a brown oil which was dissolved in 150 mL MeOH cooled to 0 °C and 70g of K_2CO_3 was added. The mixture was stirred for 4 h, then diluted with DCM, filtered through celite and rinsed with DCM. The DCM was washed with water and re-extracted with DCM (3 x 50 mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude alcohol which was recrystallized with EtOAc layered with hexanes (9.65g, 35%).

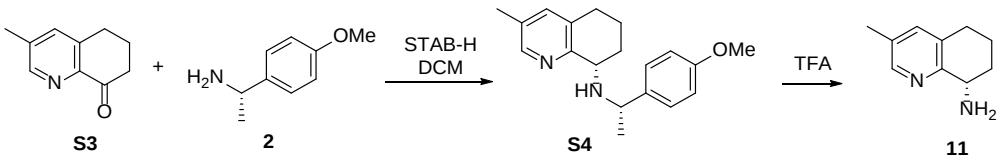
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.25 – 8.19 (m, 1H), 7.22 (dd, *J* = 2.1, 1.0 Hz, 1H), 4.69 (t, *J* = 6.6 Hz, 1H), 4.09 (d, *J* = 9.7 Hz, 1H), 2.84 – 2.67 (m, 2H), 2.29 (s, 3H), 2.27 – 2.20 (m, 1H), 2.05 – 1.93 (m, 1H), 1.87 – 1.71 (m, 3H);

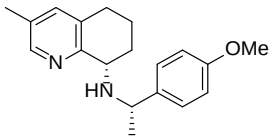
^{13}C NMR (100 MHz, Chloroform-*d*) δ = 155.15, 147.13, 137.41, 131.79, 131.09, 68.46, 30.91, 28.32, 19.32, 18.01.



Compound S3: To a 1L 3 neck RBF was added DCM (200 mL) and DMSO (18.72 mL, 264 mmol) and the mixture was cooled to -78 °C. Oxalyl chloride (11.55 mL, 132 mmol) was added dropwise via syringe and the reaction was stirred for 15 minutes followed by the dropwise addition of 3-methyl-5,6,7,8-tetrahydroquinolin-8-ol (9.57 g, 58.6 mmol) in 100 mL DCM via addition funnel (1 h). Once the addition was complete, the reaction was stirred for 15 minutes and triethyl amine (36.8 mL, 264 mmol) was added dropwise, then stirred for 30 minutes. The reaction was warmed to rt, and judged complete by TLC. The mixture was poured into 400 mL water and the organics were washed with sat. ammonium chloride, dried with $MgSO_4$, filtered and conc. *in vacuo* to afford a brown oil **S3** (7.09g 75%) which was taken directly to the next reaction.[5]

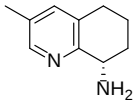
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 – 8.40 (m, 1H), 7.42 (dq, *J* = 1.8, 0.9 Hz, 1H), 2.96 (t, *J* = 6.1 Hz, 2H), 2.75 (dd, *J* = 7.3, 5.9 Hz, 2H), 2.37 (s, 3H), 2.15 (tt, *J* = 6.8, 5.6 Hz, 2H).





Compound S4: To a 200 mL RBF was added sodium triacetoxyhydroborate (15.93 g, 75 mmol), DCM (84 mL), **S3** (7.0 g, 43.4 mmol), and **2** (6.17 mL, 41.8 mmol). The reaction was stirred vigorously at room temperature for 24h. The reaction was quenched by the addition of 1N NaOH until a pH of 8 was achieved. The phases were separated and the organic layer was treated with 1N NaOH until pH 11 was observed. The DCM layer was dried with $MgSO_4$, filtered and concentrated to an oily residue which purified via column chromatography (20% EA in Hex) to afford **S4** (7.5g, 61%) as a light yellow oil.

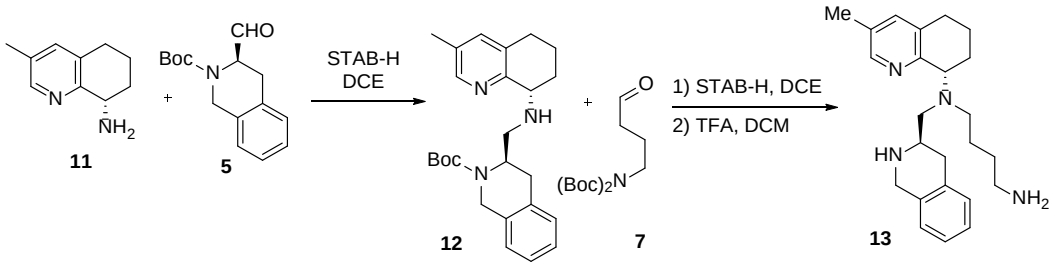
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 1.5 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 1.1 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.04 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 2.75 – 2.55 (m, 3H), 2.26 (s, 4H), 1.75 – 1.63 (m, 1H), 1.48 – 1.41 (m, 5H).

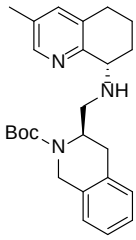


Compound 11: To a 50 mL RBF was added **S4** (3.9 g, 13.16 mmol) and TFA (Volume: 20 mL). The mixture was stirred overnight then diluted with water and extracted with ether. The ether layer was washed with water and then set aside. The aqueous layers were made basic, pH 14, with 2M NaOH then extracted with DCM. The DCM layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil. (S)-3-methyl-5,6,7,8-tetrahydroquinolin-8-amine **11** (1.98 g, 12.20 mmol, 93 % yield) was used without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.23 (s, 1H), 7.19 (s, 1H), 3.98 (dd, *J* = 7.6, 5.4 Hz, 1H), 2.74 (dtq, *J* = 16.9, 11.1, 5.9 Hz, 2H), 2.27 (s, 3H), 2.24 – 2.13 (m, 1H), 1.83 – 1.63 (m, 2H).

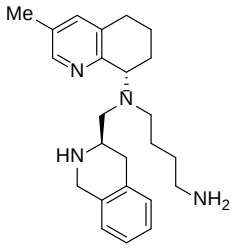
^{13}C NMR (125 MHz, Chloroform-*d*) δ = 156.71, 147.58, 137.31, 131.05, 114.29, 51.11, 32.21, 28.98, 20.01, 17.98.





Compound 12: To a 20 mL vial was added (S)-3-methyl-5,6,7,8-tetrahydroquinolin-8-amine (0.2 g, 1.233 mmol), DCE (Volume: 2.80 mL), (R)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (**5,** 0.293 g, 1.121 mmol) and STAB-H (0.428 g, 2.017 mmol) and the reaction was stirred overnight. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford an off white solid **12** (0.321 g, 0.788 mmol, 70 % yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.19 – 7.10 (m, 4H), 7.08 (s, 1H), 4.80 (d, *J* = 18.8 Hz, 1H), 4.62 (s, 1H), 4.46 (s, 1H), 4.26 (d, *J* = 17.0 Hz, 1H), 3.64 (d, *J* = 7.3 Hz, 1H), 3.01 (dd, *J* = 15.9, 5.5 Hz, 1H), 2.92 (d, *J* = 16.9 Hz, 1H), 2.81 – 2.61 (m, 3H), 2.61 – 2.46 (m, 3H), 2.23 (s, 3H), 1.94 – 1.86 (m, 2H), 1.68 – 1.53 (m, 1H), 1.48 (s, 9H).



Compound 13: To a 20 mL vial was added **12** (0.160 g, 0.393 mmol), DCE (Volume: 3.0 mL), STAB-H(0.150 g, 0.707 mmol) and butyl aldehyde **7** (0.135 g, 0.471 mmol). The reaction mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil which was dissolved in 2.5 mL DCM and 0.5 mL TFA The reaction was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes, 50% B 9 minutes). The fractions were concentrated to afford **13** (0.11 g, 0.291 mmol, 74.0 % yield) as a yellow oil

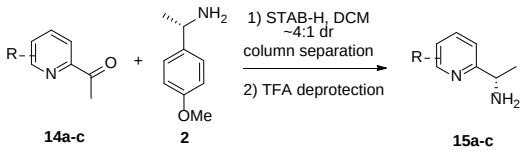
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (s, 1H), 7.11 (s, 1H), 7.07-7.05 (m, 2H), 7.02-6.98 (m, 2H), 4.03 (d, *J*= 14.6 Hz, 1H), 4.03 (overlapping s, 1H), 3.89 (d, *J*= 14.6 Hz, 1H), 3.03-2.98 (m, 1H), 2.93 (dd, *J*= 13.1, 2.6 Hz, 1H), 2.76-2.71 (m, 2H), 2.68 (t, *J*= 7.1Hz, 2H), 2.40 (dd, *J*= 15.5, 11.3 Hz, 1H), 2.33 (dd, *J*= 13.1, 10.8 Hz, 1H), 2.24 (s, 3H), 2.05-1.93 (m, 3H), 1.87 (q, *J*= 10.0 Hz, 1H), 1.66 (q, *J*= 11.0 Hz, 1H), 1.55-1.41 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 147.3, 137.0, 135.7, 134.8, 133.4, 130.6, 129.1, 126.5, 125.9, 125.5, 61.2, 57.9, 54.4, 52.4, 48.8, 42.2, 33.9, 31.6, 29.4, 29.1, 27.3, 22.0, 18.0;

HRMS (ESI) $[M+H]^+$, calcd for $C_{24}H_{35}N_4$ 379.28562, found 379.28539

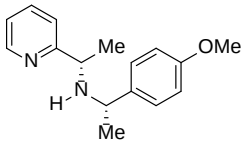
LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.578 at 254 nM, MS (+) 379.2, MS(+)/2 190.2

General Procedure C: (S)-methylaminopyridines



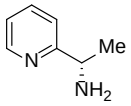
14a-c **2** **15a-c**

Following the procedure adapted from Boggs[6]



Compound S5: To a 250 mL RBF was added **2** (5.65 mL, 38.1 mmol 1.0 equiv.), 1-(pyridin-2-yl)ethanone **14a** (4.49 mL, 40 mmol, 1.05 equiv.), DCE (Volume: 38.1 mL, 1.0M) and STAB-H (16.15 g, 76 mmol, 2.0 equiv.) at rt and the reaction was stirred for 24h. The reaction was quenched by the addition of 1N NaOH until a pH of 8 was achieved. The phases were separated and the organic layer was treated with 1N NaOH until pH 11 was observed. The DCM layer was dried with $MgSO_4$, filtered and concentrated to an oily residue. The residue was purified via combiflash to separate the diastereomers (~4:1 by crude NMR, 80g column 10-30% EtOAc in hexanes over 40 min). The fractions were concentrated to a clear oil which solidified upon standing. (S)-1-(4-methoxyphenyl)-N-((S)-1-(pyridin-2-yl)ethyl)ethanamine **S5** (3.86 g, 15.06 mmol, 40 % yield)

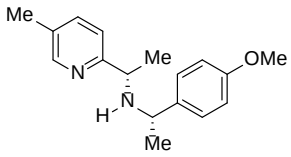
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J*= 5.2 Hz, 1H), 7.61 (dt, *J*= 7.6, 1.8 Hz, 1H), 7.21-7.12 (m, 1H), 7.13 (d, *J*= 9.2 Hz, 2H), 7.06 (d, *J*= 7.2 Hz 1H), 3.80 (s, 3H), 3.57 (q, *J*= 7.4 Hz, 1H), 3.39 (q, *J*= 6.9 Hz, 1H), 1.29 (d, *J*= 6.8 Hz, 3H), 1.26 (d, *J*= 7.3 Hz, 3H);



Compound 15a: To a 50 mL RBF was added **S5** (2 g, 7.80 mmol) and TFA (12.02 mL, 156 mmol) with stirring. The solid was slowly dissolved and the solution turned brick red and the reaction was allowed to stir overnight. The reaction was diluted with water and extracted with ether. The ether layer was washed with water and then set aside. The aqueous layers were made basic, pH 14, with 2M NaOH then extracted with DCM. The DCM layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil **15a** (0.938 g, 7.68 mmol, 98 % yield) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.55 (d, *J*= 4.5 Hz, 1H), 7.64 (dt, *J*= 7.7, 1.8 Hz, 1H), 7.29 (d, *J*= 8.2 Hz, 1H), 7.14 (ddd, *J*= 7.6, 4.9, 1.2 Hz 1H), 4.16 (q, *J*= 6.7 Hz, 1H), 1.43 (d, *J*= 6.7 Hz, 3H);

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.484 at 254 nM, MS (+) 123.2

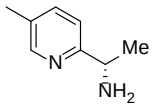


Compound S6 (RJW-1-103): To a 250 mL RBF was added **2** (6.24 mL, 42.3 mmol), 1-(5-methylpyridin-2-yl)ethanone (6.0 g, 44.4 mmol), DCM (Volume: 106 mL) and STAB-H (17.92 g, 85 mmol) at rt and the reaction was stirred for 24h. The reaction was quenched by the addition of 1N NaOH until a pH of 8 was achieved. The phases were separated and the organic layer was treated with 1N NaOH until pH 11 was observed. The DCM layer was dried with $MgSO_4$, filtered and concentrated to an oily residue. The residue was purified via combiflash to separate the diastereomers (~4:1 by crude NMR, 80g column 10-30% gradient over 40 min). The fractions were concentrated to a clear oil which was crystallized using hexanes (S)-1-(4-methoxyphenyl)-N-((S)-1-(5-methylpyridin-2-yl)ethyl)ethanamine **S6** (5.1 g, 18.86 mmol, 45 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.40 (d, *J*= 2.1 Hz, 1H), 7.39 (ddd, *J*= 7.8, 2.4, 0.8 Hz, 1H), 7.15 (d, *J*= 8.5 Hz, 2H), 6.93 (d, *J*= 8.1 Hz, 1H), 6.83 (d, *J*= 8.5 Hz, 2H), 3.78 (s, 3H), 3.53 (q, *J*= 6.8 Hz, 1H), 3.37 (q, *J*= 6.6 Hz, 1H), 1.26 (d, *J*= 6.4 Hz, 3H), 1.24 (d, *J*= 6.5 Hz, 3H);

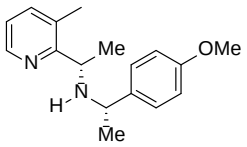
LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.480 at 254 nM, MS (+) 271.2.

XRAY- see page 50-57



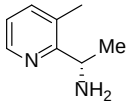
Compound 15b: To a 50 mL RBF was added **S6** (2 g, 7.40 mmol) and TFA (11.40 mL, 148 mmol) with stirring. The solid was slowly dissolved and the solution turned brick red and the reaction was allowed to stir overnight. The reaction was diluted with water and extracted with ether. The ether layer was washed with water and then set aside. The aqueous layers were made basic, pH 14, with 2M NaOH then extracted with DCM. The DCM layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil **15b** (0.76 g, 5.58 mmol, 75 % yield) which was used without further purification

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.35 (d, *J*= 2.2 Hz, 1H), 7.43 (ddd, *J*= 8.0, 2.2, 0.8 Hz, 1H), 7.17 (d, *J*= 7.8 Hz, 1H), 4.10 (q, *J*= 6.6 Hz, 1H), 1.39 (d, *J*= 6.6 Hz, 3H);



Compound S7: To a 250 mL RBF was added **2** (6.39 g, 42.3 mmol), 1-(3-methylpyridin-2-yl)ethanone (6 g, 44.4 mmol), DCM (Volume: 106 mL) and STAB-H (17.92 g, 85 mmol) at rt and the reaction was stirred for 24h. The reaction was quenched by the addition of 1N NaOH until a pH of 8 was achieved. The phases were separated and the organic layer was treated with 1N NaOH until pH 11 was observed. The DCM layer was dried with $MgSO_4$ filtered and concentrated to an oily residue. The residue was purified via combiflash to separate the diastereomers (~4:1 by crude NMR, 80g column 10-30% gradient over 40 min). The fractions were concentrated to a clear oil which solidified upon standing. (S)-1-(4-methoxyphenyl)-N-((S)-1-(3-methylpyridin-2-yl)ethyl)ethanamine **S7** (3.13 g, 27%).

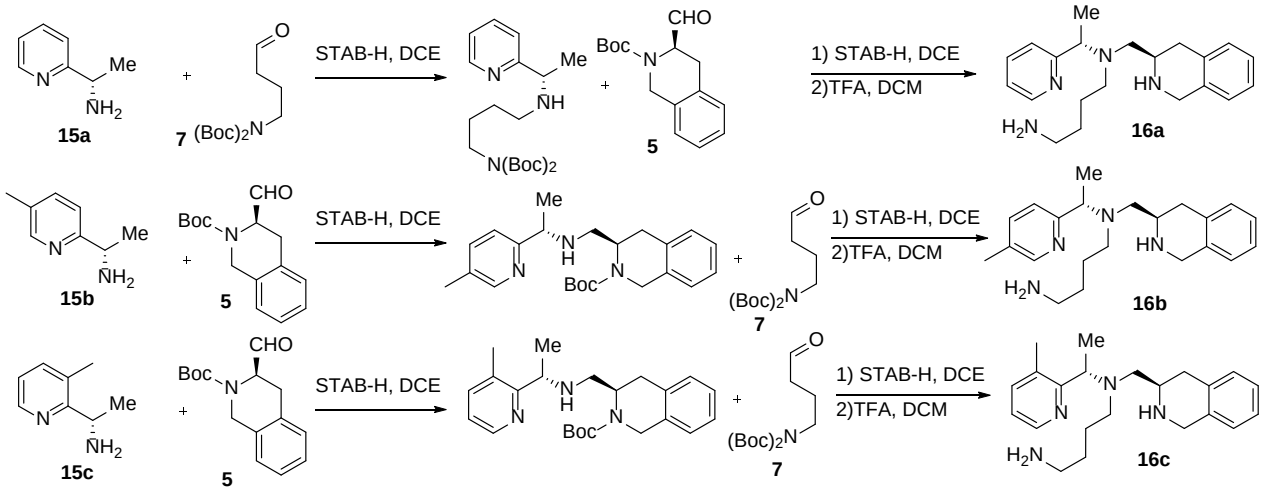
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.45 (d, *J*= 4.8 Hz, 1H), 7.34 (d, *J*= 7.6 Hz, 1H), 7.13 (d, *J*= 8.5 Hz, 2H), 7.04 (dd, *J*= 7.8, 4.6 Hz, 1H), 6.82 (d, *J*= 9.2 Hz, 2H), 3.79 (s, 3H), 3.74 (q, *J*= 6.0 Hz, 1H), 3.27 (q, *J*= 5.9 Hz, 1H), 1.24 (d, *J*= 6.3 Hz, 3H), 1.20 (d, *J*= 6.3 Hz, 3H);

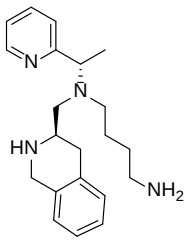


Compound 15c: To a 50 mL RBF was added **S7** (2.26 g, 8.36 mmol) and TFA (12.88 mL, 167 mmol) with stirring. The solid was slowly dissolved and the solution turned brick red and the reaction was allowed to stir overnight. The reaction was diluted with water and extracted with ether. The ether layer was washed with water and then set aside. The aqueous layers were made basic, pH 14, with 2M NaOH then extracted with DCM. The DCM layer was dried with MgSO4, filtered and concentrated to a yellow oil **15c** (0.56 g, 4.11 mmol, 49.2 % yield) which was used without further purification

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.39 (d, *J*= 4.0 Hz, 1H), 7.38 (d, *J*= 7.8 Hz, 1H), 7.03 (dd, *J*= 7.6, 4.7 Hz, 1H), 4.27 (q, *J*= 6.2 Hz, 1H), 1.33 (d, *J*= 6.6 Hz, 3H);

Procedure for 16a-c





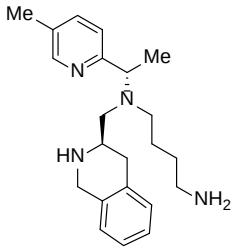
Compound 16a: To a 20 mL vial was added **15a** (0.3 g, 2.456 mmol), DCE (Volume: 5.85 mL), butyl-aldehyde **7** (0.672 g, 2.339 mmol) and STAB-H (0.744 g, 3.51 mmol) and the reaction was allowed to stir overnight. The reaction was stirred for 16h then quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a semisolid. The crude material was purified via combiflash (DCM 2 minutes, 10%B (B= 80:20:3 DCM:MeOH:NH_4OH) 7 minutes, 50%B 8 minutes) to afford secondary amine **S8** (0.733 g, 1.863 mmol, 80 % yield). To a 20 mL vial was added **5** (0.203 g, 0.777 mmol), DCE (Volume: 1.943 mL), secondary amine **S8** (0.312 g, 0.793 mmol) and STAB-H (0.247 g, 1.166 mmol). The reaction was stirred overnight for 14 h. The reaction was diluted with DCM, washed with 2M NaOH, dried with $MgSO_4$, filtered and concentrated to a yellow oil. The oil was dissolved in 10 mL DCM and allowed to stir with TFA (1 mL) for 12 h. The reaction was diluted with DCM and made basic with 1M NaOH. The layers were separated and the aqueous was extracted with DCM (2 x10 mL). The organics were dried with Na_2SO_4, filtered and concentrated to a brown oil which was purified via combiflash (DCM 2 minutes, 10%B (B= 80:20:3 DCM:MeOH:NH_4OH) 7 minutes, 50%B 8 minutes) to afford **16a** (0.097 g, 0.287 mmol, 37 % yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (dd, *J*= 4.8, 0.8 Hz, 1H), 7.61 (dt, *J*= 7.6, 1.8 Hz, 1H), 7.31 (d, *J*= 7.8 Hz, 1H), 7.11 (ddd, *J*= 7.4, 5.0, 0.8 Hz, 1H), 7.08-6.96 (m, 4H), 4.03 (d, *J*= 14.6 Hz, 1H), 4.03 (q, *J*= 6.9 Hz, 1H), 3.96 (d, *J*= 14.9 Hz, 1H), 2.85-2.80 (m, 1H), 2.62 (t, *J*= 6.9 Hz, 2H), 2.59-2.53 (m, 3H), 2.52 (dd, *J*= 13.1, 4.2 Hz, 1H), 2.45 (dd, *J*= 13.8, 7.1 Hz, 1H), 2.39 (dd, *J*= 15.4, 10.5 Hz, 1H), 1.80 (bs, 3NH), 1.49-1.41 (m,2H), 1.43 (d, *J*= 6.9 Hz, 3H), 1.41-1.32 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5, 148.7, 136.0, 135.6, 134.6, 129.1, 126.4, 125.9, 125.5, 122.6, 121.9, 60.1, 56.6, 52.2, 51.3, 48.7, 42.1, 33.9, 31.5, 25.7, 16.2;

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{31}N_4$ 339.25432, found 339.25409

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.763 at 254 nM, MS (+) 339.2, MS(+)/2 170.2



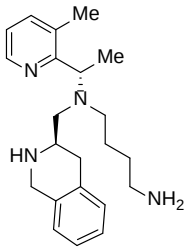
Compound 16b: To a 50mL RBF was added **15b** (0.45 g, 3.30 mmol), DCE (Volume: 16.52 mL), **5** (0.907 g, 3.47 mmol) and STAB-H (1.260 g, 5.95 mmol). The reaction was stirred for 16 h then quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a semisolid. The crude material was purified via combiflash (DCM 5 min, 10% B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford secondary amine **S9** (1.01 g, 2.65 mmol, 80 % yield) which was taken directly to the next step. To a 20 mL vial was added secondary amine **S9** (0.5 g, 1.311 mmol), DCE (Volume: 4.37 mL) and butyl aldehyde **7** followed by STAB-H (0.500 g, 2.359 mmol) and the reaction was stirred overnight. The reaction was quenched by the addition of 2M NaOH and extracted with DCM. The organic phase was dried with $MgSO_4$, filtered and concentrated to a yellow oil. The crude oil was dissolved in 3 mL DCM then TFA (1 mL) was added and the mixture was allowed to stir overnight. The reaction was quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a yellow oil. The oil was purified via combiflash (DCM 5 min, 10% B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford **16b** (0.167 g, 0.474 mmol, 36 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 7.44 (d, *J*= 8.6 Hz, 1H), 7.22 (d, *J*= 8.4 Hz, 1H), 7.10-7.08 (m, 2H), 7.05-7.00 (m, 2H), 4.06 (d, *J*= 15.4 Hz, 1H), 4.01 (q, *J*= 7.0 Hz, 1H), 4.00 (d, *J*= 14.8 Hz, 1H), 2.89-2.83 (m, 1H), 2.67-2.38 (m, 9H), 2.30 (s, 3H), 1.52-1.35 (m,6H), 1.43 (d, *J*= 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 149.4, 136.5, 135.6, 134.6, 131.1, 129.0, 126.3, 125.8, 125.4, 122.0, 60.7, 56.5, 52.1, 51.2, 48.7, 42.1, 33.89, 31.51, 25.6, 18.0, 16.5;

HRMS (ESI) $[M+H]^+$, calcd for $C_{22}H_{33}N_4$ 353.26997, found 353.26950

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.781 at 254 nM, MS (+) 353.2, MS(+)/2 177.2



Compound 16c: To a 50mL RBF was added **15c** (0.45 g, 3.30 mmol), DCE (Volume: 16.52 mL), **5** (0.907 g, 3.47 mmol) and STAB-H (1.260 g, 5.95 mmol). The reaction was stirred for 16 h then quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a semisolid. The crude material was purified via combiflash (DCM 5 min, 10%B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford secondary amine **S10** (0.85 g, 2.228 mmol, 67.4 % yield). To a 20 mL vial was added secondary amine **S10** (0.5 g, 1.311 mmol), DCE (Volume: 4.37 mL) and aldehyde **7** followed by STAB-H (0.500 g, 2.359 mmol) and the reaction was stirred overnight. The reaction was quenched by the addition of 2M NaOH and extracted with DCM. The organic phase was dried with $MgSO_4$, filtered and concentrated to a yellow oil. The crude oil was dissolved in 3 mL DCM and TFA (1 mL) was added and the mixture was allowed to stir overnight. The reaction was quenched with 2M NaOH extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a yellow oil. The oil was purified via combiflash (DCM 5 min, 10%B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford **16c** (0.281 g, 0.797 mmol, 61 % yield)

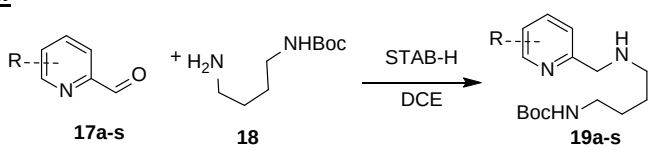
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J*= 4.7 Hz, 1H), 7.42 (d, *J*= 7.6 Hz, 1H), 7.08-7.04 (m, 3H), 6.99-6.96 (m, 2H), 4.27 (q, *J*= 6.6 Hz, 1H), 3.99 (d, *J*= 15.2 Hz, 1H), 3.87 (d, *J*= 15.2 Hz, 1H), 2.81 (dd, *J*= 11.4, 2.8 Hz, 1H), 2.71-2.65 (m, 1H), 2.60-2.49 (m, 6H), 2.46 (s, 3H), 2.22 (dd, *J*= 16.6, 10.4 Hz, 1H), 1.43 (d, *J*= 6.6 Hz, 3H), 1.32-1.24 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 145.8, 137.7, 135.5, 134.6, 132.3, 129.1, 126.2, 125.8, 125.4, 121.9, 58.4, 57.8, 52.7, 52.0, 48.6, 42.0, 33.8, 31.6, 26.8, 18.7, 11.8;

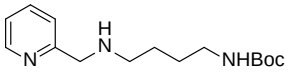
HRMS (ESI) $[M+H]^+$, calcd for $C_{22}H_{33}N_4$ 353.26997, found 353.26955

LC/MS 85% MeOH in H_2O over 3 minutes, r_t = 0.689 at 254 nM, MS (+) 353.2, MS(+)/2 177.2

GENERAL PROCEDURE A:



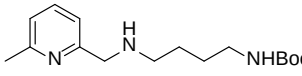
tert-butyl (4-aminobutyl)carbamate **18** (1.05-1.1 equiv.), DCE (0.5M) and substituted aldehyde **17a-s** (1.0 equiv.) were stirred at room temperature followed by the addition of STAB-H (1.5-1.8 equiv.) in three portions. The reaction was stirred at RT over-night (12-18h) then diluted with DCM and washed with 1.0M NaOH. The organics were separated, dried with Na_2SO_4, filtered and concentrated. The residue was purified via silica gel chromatography (combiflash, DCM:Mixture B(80:20:3, DCM:MeOH:NH_4OH), 0%B for 5 minutes, 10% B for 8 minutes, 50% B for 8 minutes). All purifications were conducted using this standard mixture unless otherwise noted. To afford **19a-s**



Compound 19a: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.933 g, 10.27 mmol), DCE (Volume: 20 mL) and picolinaldehyde (0.888 mL, 9.34 mmol) followed by STAB-H (2.97 g, 14.00 mmol) were combined and stirred overnight. Purification via combiflash yielded tert-butyl (4-((pyridin-2-ylmethyl)amino)butyl)carbamate **19a** (1.8 g, 6.44 mmol, 69 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, *J*= 5.0, 1.2 Hz, 1H), 7.63 (dt, *J*= 7.6, 1.8 Hz, 1H), 7.29 (d, *J*= 7.8 Hz, 1H), 7.15 (dd, *J*= 7.5, 5.0 Hz, 1H), 4.76 (s, 1H), 3.90 (s, 2H), 3.12 (q, *J*= 4.1 Hz, 2H), 2.67 (t, *J*= 6.6 Hz, 2H), 1.60-1.50 (m, 4H), 1.43 (s, 9H);

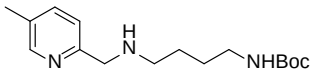
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.527 at 254 nM, MS (+) 280.2



Compound 19b: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.658 mL, 8.67 mmol), DCE (Volume: 16.51 mL), 6-methylpicolinaldehyde (1 g, 8.26 mmol) and STAB-H(2.62 g, 12.38 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((6-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19b** (0.7 g, 2.386 mmol, 29 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (t, *J*= 7.6 Hz, 1H), 7.09 (d, *J*= 7.6 Hz, 1H), 7.00 (d, *J*= 7.6 Hz, 1H),4.77 (s, 1H), 3.84 (s, 2H), 3.12 (q, *J*= 6.4 Hz, 2H), 2.66 (t, *J*= 6.3 Hz, 2H), 1.59-1.47 (m, 4H), 1.43 (s, 9H);

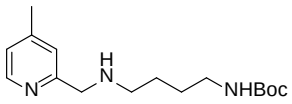
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.503 at 254 nM, MS (+) 294.2



Compound 19c: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.658 mL, 8.67 mmol), DCE (Volume: 16.51 mL), 5-methylpicolinaldehyde (1 g, 8.26 mmol) and STAB-H (2.62 g, 12.38 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((5-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19c** (0.82 g, 2.79 mmol, 34 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, *J*= 2.4, 1.0 Hz 1H), 7.44 (dd, *J*= 7.9, 2.3 Hz, 1H), 7.18 (d, *J*= 7.8 Hz, 1H), 4.77 (s, 1H), 3.84 (s, 2H), 3.12 (q, *J*= 6.0 Hz, 2H), 2.64 (t, *J*= 6.0 Hz, 2H), 1.58-1.53 (m, 4H), 1.43 (s, 9H);

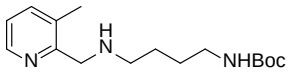
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.501 at 254 nM, MS (+) 294.2



Compound 19d: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18**(1.597 mL, 8.35 mmol), DCE (Volume: 15.90 mL), 4-methylpicolinaldehyde (0.963 g, 7.95 mmol) and STAB-H (2.53 g, 11.92 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((4-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19d** (1.87 g, 6.37 mmol, 80 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J*= 4.8 Hz, 1H), 7.09 (d, *J*= 4.1 Hz, 1H), 6.96 (d, *J*= 6.0 Hz, 1H), 4.73 (s, 1H), 3.82 (s, 2H), 3.09 (br s, 2H), 2.63 (t, *J*= 5.6 Hz, 2H), 2.32 (s, 3H), 1.53-1.50 (m, 4H), 1.43 (s, 9H);

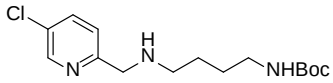
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.505 at 254 nM, MS (+) 294.2



Compound 19e: Following general procedure A, tert-butyl (4-aminobutyl)carbamate **18** (2.1g, 11.15 mmol), DCE (Volume: 40 mL) and 3-methylpicolinaldehyde (0.98g, 8.1 mmol) followed by STAB-H (3.25g, 15.3 mmol) were combined and stirred overnight. Purification via combiflash yielded tert-butyl (4-((3-methylpyridin-2-ylmethyl)amino)butyl)carbamate **19e** (1.98 g, 6.72 mmol, 83 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J*= 4.7 Hz, 1H), 7.42 (dq, *J*= 7.6, 0.8 Hz, 1H), 7.07 (dd, *J*= 7.6, 4.8 Hz, 1H), 4.76 (s, 1H), 3.87 (s, 2H), 3.13 (q, *J*= 7.2 Hz, 2H), 2.72 (t, *J*= 6.4 Hz, 2H), 1.61-1.56 (m, 4H), 1.43 (s, 9H);

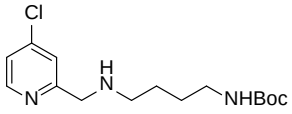
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.488 at 254 nM, MS (+) 292.2



Compound 19f: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.596 g, 8.48 mmol), DCE (Volume: 17.66 mL), 5-chloropicolinaldehyde (1 g, 7.06 mmol) and STAB-H(2.70 g, 12.72 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((5-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19f** (1.24 g, 3.95 mmol, 56 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.50 (dd, *J*= 2.5, 0.7 Hz, 1H), 7.61 (dd, *J*= 8.3, 2.5 Hz, 1H), 7.27 (d, *J*= 8.8 Hz, 1H), 4.72 (s, 1H), 3.87 (s, 2H), 3.12 (q, *J*= 6.4 Hz, 2H), 2.65 (t, *J*= 6.7 Hz, 2H), 1.56-1.53 (m, 4H), 1.43 (s, 9H);

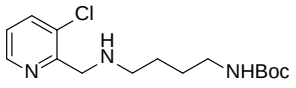
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.483 at 254 nM, MS (+) 314.0



Compound 19g: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.596 g, 8.48 mmol), DCE (Volume: 14.13 mL), 4-chloropicolinaldehyde (1 g, 7.06 mmol) and STAB-H (2.70 g, 12.72 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((4-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19g** (1.45 g, 4.62 mmol, 65 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.44 (d, *J*= 5.4 Hz, 1H), 7.35 (d, *J*= 2.0 Hz, 1H), 7.17 (dd, *J*= 5.2, 2.0 Hz, 1H), 4.71 (s, 1H), 3.88 (s, 2H), 3.12 (q, *J*= 5.0 Hz, 2H), 2.65 (t, *J*= 6.8 Hz, 2H), 1.56-1.53 (m, 4H), 1.43 (s, 9H);

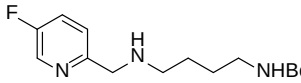
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.480 at 254 nM, MS (+) 314.0



Compound 19h: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.798 g, 4.24 mmol), DCE (Volume: 8.83 mL), 3-chloropicolinaldehyde (0.5 g, 3.53 mmol) and STAB-H(1.348 g, 6.36 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19h** (0.81 g, 2.58 mmol, 73 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.46 (dd, *J*= 4.6, 1.5 Hz, 1H), 7.64 (dd, *J*= 8.0, 1.5 Hz, 1H), 7.14 (dd, *J*= 8.0, 4.6 Hz, 1H), 4.74 (s, 1H), 4.02 (s, 2H), 3.12 (q, *J*= 6.0 Hz, 2H), 2.69 (t, *J*= 6.7 Hz, 2H), 1.60-1.53 (m, 4H), 1.43 (s, 9H);

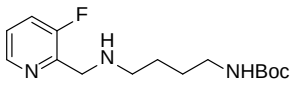
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.488 at 254 nM, MS (+) 314.0



Compound 19i: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.655 g, 8.79 mmol), DCE (Volume: 15.99 mL), 5-fluoropicolinaldehyde (1 g, 7.99 mmol) and STAB-H(2.54 g, 11.99 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((5-fluoropyridin-2-yl)methyl)amino)butyl)carbamate **19i** (1.64 g, 5.52 mmol, 69 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.40 (d, *J*= 2.7 Hz, 1H), 7.35 (dd, *J*= 8.5, 2.8 Hz, 1H), 7.32 (dd, *J*= 8.6, 4.7 Hz, 1H), 4.73 (s, 1H), 3.89 (s, 2H), 3.12 (q, *J*= 6.0 Hz, 2H), 2.67 (t, *J*= 6.6 Hz, 2H), 1.58-1.54 (m, 4H), 1.43 (s, 9H);

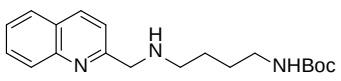
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.498 at 254 nM, MS (+) 298.2



Compound 19j: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.655 g, 8.79 mmol), DCE (Volume: 15.99 mL), 3-fluoropicolinaldehyde (1 g, 7.99 mmol) and STAB-H (2.54 g, 11.99 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-fluoropyridin-2-yl)methyl)amino)butyl)carbamate **19j** (1.44 g, 4.84 mmol, 61 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.38 (dt, *J*= 4.7, 1.5 Hz, 1H), 7.35 (ddd, *J*= 9.6, 8.3, 1.4 Hz, 1H), 7.20 (ddd, *J*= 8.3, 4.7, 4.2 Hz, 1H), 4.72 (s, 1H), 3.98 (s, 2H), 3.12 (q, *J*= 4.4 Hz, 2H), 2.68 (t, *J*= 6.8 Hz, 2H), 1.61-1.54 (m, 4H), 1.43 (s, 9H);

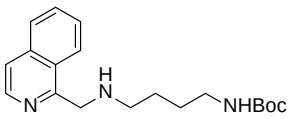
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.484 at 254 nM, MS (+) 298.2



Compound 19k: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.318 g, 7.00 mmol), DCE (Volume: 15.91 mL), quinoline-2-carbaldehyde (1.0 g, 6.36 mmol) and STAB-H (2.023 g, 9.54 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-((quinolin-2-ylmethyl)amino)butyl)carbamate **19k** (1.1 g, 3.34 mmol, 53 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J*= 8.5 Hz, 1H), 8.05 (d, *J*= 8.5 Hz, 1H), 7.80 (d, *J*= 8.4 Hz, 1H), 7.70 (dt, *J*= 8.4, 1.2 Hz, 1H), 7.52 (dt, *J*= 8.4, 1.2 Hz, 1H), 7.45 (d, *J*= 8.5 Hz, 1H), 4.76 (s, 1H), 4.12 (s, 2H), 3.14 (q, *J*= 6.6 Hz, 2H), 2.77 (t, *J*= 6.4 Hz, 2H), 1.63-1.57 (m, 4H), 1.42 (s, 9H);

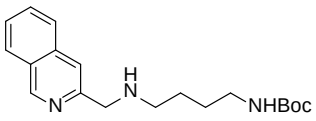
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.509 at 254 nM, MS (+) 330.2



Compound 19l: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.659 g, 3.50 mmol), DCE (Volume: 7.95 mL), isoquinoline-1-carbaldehyde (0.5 g, 3.18 mmol) and sodium triacetoxyborohydride (1.011 g, 4.77 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-((isoquinolin-1-ylmethyl)amino)butyl)carbamate **19l** (.779 g, 2.365 mmol, 74 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.45 (d, *J*= 5.7 Hz, 1H), 8.17 (dq, *J*= 8.4, 0.9 Hz, 1H), 7.82 (d, *J*= 8.0 Hz, 1H), 7.68 (ddd, *J*= 8.1, 6.8, 1.3 Hz, 1H), 7.60 (ddd, *J*= 8.3, 6.8, 1.4 Hz, 1H), 7.55 (d, *J*= 5.8 Hz, 1H), 4.74 (s, 1H), 4.41 (s, 2H), 3.14 (q, *J*= 6.4 Hz, 2H), 2.80 (t, *J*= 6.8 Hz, 2H), 1.67-1.52 (m, 4H), 1.43 (s, 9H);

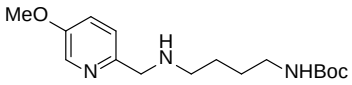
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.518 at 254 nM, MS (+) 330.2



Compound 19m: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.320 mL, 1.670 mmol), DCE (Volume: 3.18 mL), isoquinoline-3-carbaldehyde (0.25 g, 1.591 mmol) and STAB-H (0.506 g, 2.386 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-((isoquinolin-3-ylmethyl)amino)butyl)carbamate **19m** (0.41 g, 1.245 mmol, 78 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 1H), 7.95 (d, *J*= 8.2 Hz, 1H), 7.79 (d, *J*= 8.2 Hz, 1H), 7.68 (dt, *J*= 6.8, 1.3 Hz, 1H), 7.63 (s, 1H), 7.57 (dt, *J*= 8.2, 1.2 Hz, 1H), 4.75 (s, 1H), 4.04 (s, 2H), 3.13 (q, *J*= 6.0 Hz, 2H), 2.70 (t, *J*= 6.0 Hz, 2H), 1.60-1.51 (m, 4H), 1.43 (s, 9H);

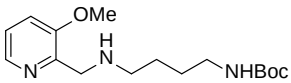
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.508 at 254 nM, MS (+) 330.2



Compound 19n: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.755 g, 4.01 mmol), DCE (Volume: 7.29 mL), 5-methoxypicolinaldehyde (0.5 g, 3.65 mmol) and STAB-H (1.159 g, 5.47 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((5-methoxypyridin-2-yl)methyl)amino)butyl)carbamate **19n** (.91 g, 2.94 mmol, 81 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.24 (d, *J*= 2.8 Hz, 1H), 7.21 (d, *J*= 8.4 Hz, 1H), 7.15 (dd, *J*= 8.4, 2.8 Hz, 1H), 4.77 (s, 1H), 3.84 (s, 3H), 3.82 (s, 2H), 3.11 (q, *J*= 6.4 Hz, 2H), 2.66 4(t, *J*= 7.8 Hz, 2H), 1.58-1.47 (m, 4H), 1.43 (s, 9H);

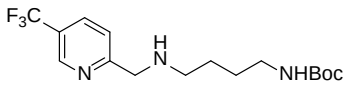
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.487 at 254 nM, MS (+) 310.2



Compound 19o: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18**(0.755 g, 4.01 mmol), DCE (Volume: 7.29 mL), 3-methoxypicolinaldehyde (0.5 g, 3.65 mmol) and STAB-H (1.159 g, 5.47 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-methoxypyridin-2-yl)methyl)amino)butyl)carbamate **19o** (0.77 g, 2.489 mmol, 68 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.13 (d, *J*= 4.5, 1.6 Hz, 1H), 7.15 (dd, *J*= 8.4, 4.2 Hz, 1H), 7.11 (dd, *J*= 8.4, 1.6 Hz, 1H), 4.76 (s, 1H), 3.93 (s, 2H), 3.84 (s, 3H), 3.12 (q, *J*= 6.8 Hz, 2H), 2.66 (t, *J*= 7.4 Hz, 2H), 1.57-1.51 (m, 4H), 1.43 (s, 9H);

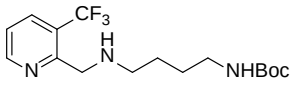
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.498 at 254 nM, MS (+) 310.2



Compound 19p: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.591 g, 3.14 mmol), DCE (Volume: 5.71 mL), 5-(trifluoromethyl)picolinaldehyde (0.5 g, 2.86 mmol) and STAB-H(0.908 g, 4.28 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)butyl)carbamate **19p** (.716 g, 2.061 mmol, 72 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.81 (s, 1H), 7.88 (dd, *J*= 8.3, 2.4 Hz, 1H), 7.46 (d, *J*= 8.1 Hz, 1H), 4.71 (s, 1H), 3.97 (s, 2H), 3.13 (q, *J*= 6.2 Hz, 2H), 2.66 (t, *J*= 6.5 Hz, 2H), 1.59-1.53 (m, 4H), 1.43 (s, 9H);

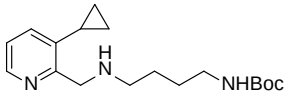
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.497 at 254 nM, MS (+) 348.2



Compound 19q: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (1.075 g, 5.71 mmol), 3-(trifluoromethyl)picolinaldehyde (0.5 g, 2.86 mmol), DCE (Volume: 5.71 mL) and STAB-H(0.908 g, 4.28 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)butyl)carbamate **19q** (0.660 g, 1.900 mmol, 67 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.73 (d, *J*= 5.0 Hz, 1H), 7.92 (d, *J*= 8.0 Hz, 1H), 7.30 (dd, *J*= 8.5, 5.0 Hz, 1H), 4.73 (s, 1H), 4.05 (s, 2H), 3.12 (q, *J*= 6.1 Hz, 2H), 2.65 (t, *J*= 7.4 Hz, 2H), 1.59-1.51 (m, 4H), 1.43 (s, 9H);

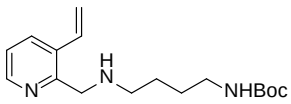
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.503 at 254 nM, MS (+) 348.2



Compound 19r: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.352 g, 1.869 mmol), DCE (Volume: 5.66 mL), 3-cyclopropylpicolinaldehyde (0.25 g, 1.699 mmol) and STAB-H(0.648 g, 3.06 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-cyclopropylpyridin-2-yl)methyl)amino)butyl)carbamate **19r** (0.405 g, 1.268 mmol, 75 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.36 (dd, *J*= 5.5, 0.6 Hz, 1H), 7.33 (d, *J*= 7.6 Hz, 1H), 7.14 (dd, *J*= 7.9, 5.0 Hz, 1H), 4.79 (s, 1H), 4.25 (s, 2H), 3.15 (q, *J*= 6.2 Hz, 2H), 2.90 (t, *J*= 7.2 Hz, 2H), 1.89-1.82 (m, 1H), 1.79-1.53 (m, 4H), 1.43 (s, 9H), 1.03-0.98 (m, 2H), 0.67-0.63 (m, 2H);

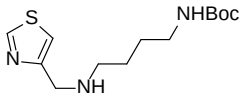
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.498 at 254 nM, MS (+) 320.2



Compound 19s: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.296 g, 1.570 mmol), DCE (Volume: 3.57 mL), 3-vinylpicolinaldehyde (.190 g, 1.427 mmol) and STAB-H (0.544 g, 2.57 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((3-vinylpyridin-2-yl)methyl)amino)butyl)carbamate **19s** (0.31 g, 1.015 mmol, 71 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.45 (dd, *J*= 4.8, 1.8 Hz, 1H), 7.76 (dd, *J*= 7.8, 1.8 Hz, 1H), 7.19 (dd, *J*= 7.8, 4.8 Hz, 1H), 6.91 (dd, *J*= 17.4, 11.0 Hz, 1H), 5.69 (d, *J*= 17.4 Hz, 1H), 5.44 (d, *J*= 11.0 Hz, 1H), 4.74 (s, 1H), 4.02 (s, 2H), 3.13 (q, *J*= 6.4 Hz, 2H), 2.76 (t, *J*= 6.7 Hz, 2H), 1.67-1.52 (m, 4H), 1.43 (s, 9H);

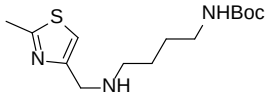
LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.497 at 254 nM, MS (+) 306.2



Compound S11: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.998 g, 5.30 mmol), DCE (Volume: 8.84 mL), thiazole-4-carbaldehyde (0.4 g, 3.54 mmol) and STAB-H(1.349 g, 6.36 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-((thiazol-4-ylmethyl)amino)butyl)carbamate **S11** (0.653 g, 2.288 mmol, 65 % yield)

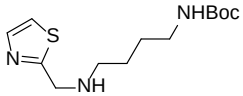
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.77 (d, *J*= 1.6 Hz, 1H), 7.16 (d, *J*= 1.6 Hz, 1H), 4.75 (s, 1H), 3.95 (s, 2H), 3.12 (q, *J*= 5.0 Hz, 2H), 2.65 (t, *J*= 5.9 Hz, 2H), 1.58-1.50 (m, 4H), 1.43 (s, 9H);

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.491 at 254 nM, MS (+) 286.0



Compound S12: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.666 g, 3.54 mmol), DCE (Volume: 5.90 mL), 2-methylthiazole-4-carbaldehyde (0.3 g, 2.359 mmol) and STAB-H(0.750 g, 3.54 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-(((2-methylthiazol-4-yl)methyl)amino)butyl)carbamate **S12** (0.21 g, 0.701 mmol, 30 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.89 (s, 1H), 4.81 (s, 1H), 3.80 (s, 2H), 3.07 (q, *J*= 6.4 Hz, 2H), 2.64 (s, 3H), 2.60 (t, *J*= 7.0 Hz, 2H), 1.50-1.47 (m, 4H), 1.38 (s, 9H);



Compound S13: Following general procedure A; tert-butyl (4-aminobutyl)carbamate **18** (0.915 g, 4.86 mmol), DCE (Volume: 8.84 mL), thiazole-2-carbaldehyde (0.5 g, 4.42 mmol) and STAB-H(1.405 g, 6.63 mmol) were stirred overnight. Purification via combiflash yielded tert-butyl (4-((thiazol-2-ylmethyl)amino)butyl)carbamate **S13** (1.01 g, 3.54 mmol, 80 % yield)

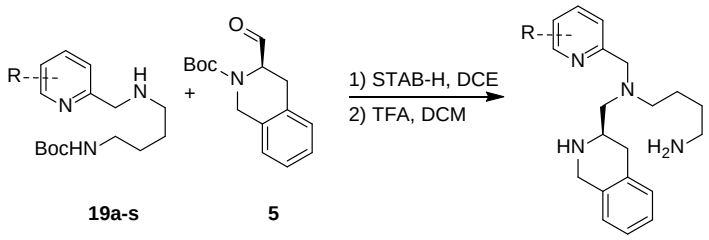
^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.71 (d, *J*= 3.3 Hz, 1H), 7.26 (d, *J*= 4.8 Hz, 1H), 4.64 (s, 1H), 4.12 (s, 2H), 3.12 (q, *J*= 5.1 Hz, 2H), 2.71 (t, *J*= 6.6 Hz, 2H), 1.57-1.53 (m, 4H), 1.43 (s, 9H);

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.485 at 254 nM, MS (+) 286.2

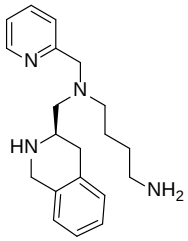
GENERAL PROCEDURE B:

To a 20 mL vial was added aminopyridine (**19a-s**, 1.0 equiv.), DCE (0.4M), **5** (1.1 equiv.) and STAB-H (1.5 equiv.). The reaction was allowed to stir overnight (12-24h) then diluted with DCM and quenched with 1.0M NaOH. The organic layer was dried with $MgSO_4$, filtered, concentrated and purified via silica gel chromatography (combiflash, DCM:Mixture B(80:20:3, DCM:MeOH:NH_4OH), 0%B for 5 minutes, 10% B for 8 minutes, 50% B for 8 minutes). All purifications were conducted using this standard mixture unless otherwise noted. The intermediate material was dissolved in DCM (0.1M) and TFA (ratio DCM:TFA, 5:1) and allowed to stir overnight (12-24h). The reaction was diluted with DCM and quenched with 1.0M NaOH. The organics were dried with $MgSO_4$, filtered, concentrated and purified via combiflash to afford final compounds **20a-s**

Two Step Procedure



19a-s **5** **20a-s**



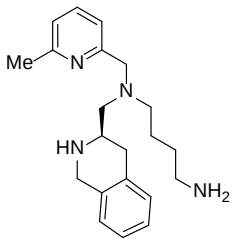
Compound 20a: Following general procedure B; **19a** (0.515 g, 1.843 mmol), DCE (Volume: 4.61 mL), **5** (0.530 g, 2.028 mmol) and STAB-H (0.586 g, 2.77 mmol) were stirred overnight. Purification via combiflash provided intermediate (**Carbamate 1** 0.7 g, 1.334 mmol, 72 % yield) as a yellow semi solid. **Carbamate 1**(0.46 g, 0.877 mmol), DCM (Volume: 8.77 mL) and TFA (1.351 mL, 17.53 mmol) were stirred overnight. Purification via combiflash yielded **20a** (0.241 g, 0.743 mmol, 85 % yield) as a yellow-brown oil. (79% over two steps)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J*= 4.8, 1.0 Hz, 1H), 7.66 (dt, *J*= 7.7, 1.8 Hz, 1H), 7.45 (d, *J*= 7.8 Hz, 1H), 7.15 (t, *J= 5.0* Hz, 1H), 7.09-7.05 (m, 3H), 7.00-6.98 (m, 1H), 4.01(d, *J*= 15.2 Hz, 1H), 3.93 (d, *J*= 15.0 Hz, 1H), 3.47 (d, *J*= 14.6 Hz, 1H), 3.71 (d, *J*= 14.4 Hz, 1H), 2.90-2.86 (m, 1H), 2.68-2.60 (m, 6H), 2.58-2.52 (m, 1H), 2.46 (dd, *J*= 16.5, 11.5 Hz, 1H), 1.59-1.52 (m,2H), 1.49-1.36 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 149.1, 136.4, 135.6, 134.5, 129.1, 126.4, 126.0, 125.6, 122.8, 122.0, 61.6, 60.7, 55.5, 51.8, 48.6, 42.1, 33.9, 31.6, 24.7;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{29}N_4$ 325.23867, found 325.23840

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.816 at 254 nM, MS (+) 325.2, MS(+)/2 163.2; purity (>95%) 10-95% MeOH in H_2O over 10 minutes, r_t = 6.356 at 254 nM, MS (+) 325.2, MS(+)/2 163.2



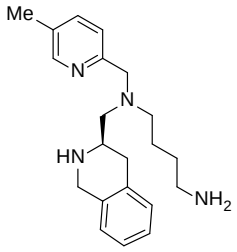
Compound 20b: Following general procedure B; **19b** (0.486 g, 1.656 mmol) DCE (Volume: 4.14 mL), **5** (0.476 g, 1.822 mmol) and STAB-H (0.527 g, 2.485 mmol) were stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford **Carbamate 2** (0.780 g, 1.448 mmol, 87 % yield). To a 20 mL vial was added **Carbamate 2**(0.379 g, 0.704 mmol) and DCM (Volume: 5.86 mL, Ratio: 5) followed by TFA (Volume: 1.173 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM/MeOH/NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20b** (0.124 g, 0.366 mmol, 52 % yield) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (t, *J*= 7.0 Hz, 1H), 7.28 (d, *J*= 8.7 Hz, 1H), 7.10-7.03 (m, 3H), 7.01-6.99 (m, 2H), 4.03 (d, *J*= 15.1 Hz, 1H), 3.94 (d, *J*= 15.3 Hz, 1H), 3.82 (d, *J*= 14.7 Hz, 1H), 3.67 (d, *J*= 14.7 Hz, 1H), 2.93-2.87 (m, 1H), 2.69-2.57 (m, 7H), 2.52 (s, 3H), 2.50-2.48 (m, 1H), 1.59-1.51 (m,2H), 1.49-1.37 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 157.4, 136.5, 135.4, 129.0, 126.2, 125.8, 125.4, 121.2, 119.3, 61.5, 60.5, 55.4, 51.6, 48.4, 41.9, 33.7, 31.3, 24.5, 24.3;

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{31}N_4$ 339.25432, found 339.25410

LC/MS 55% MeOH in H_2O over 3 minutes, r_t = 0.822 at 254 nM, MS (+) 339.2, MS(+)/2 170.2



Compound 20c: To a 20 mL scintillation vial was added tert-butyl (4-(((5-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19c** (0.519 g, 1.767 mmol) and **5** (0.508 g, 1.944 mmol) in DCE (Volume: 4.42 mL) followed by STAB-H (0.562 g, 2.65 mmol) and the reaction was stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford(R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((5-methylpyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 3** (0.762 g, 1.414 mmol, 80 % yield). **Racemic Carbamate 3** was synthesized using *racemic* **5** and analyzed by Chiral HPLC, (254 nm) 5% *i*PrOH in hexanes, isocratic, 30 minutes, 1.0 mL/min, AD-H (daicel, chiralpak, 150 mm, 4.6 mm, 5 *u*m), t_1= 13.820, t_2= 14.888, *er*= 52:48. **Carbamate 3** was analyzed by Chiral HPLC, (254 nm) 5% *i*PrOH in hexanes, isocratic, 30 minutes, 1.0 mL/min, AD-H (daicel, chiralpak, 150 mm, 4.6 mm, 5 *u*m), t_1= 13.892, t_2= 14.977, *er*= 98.5:1.5.

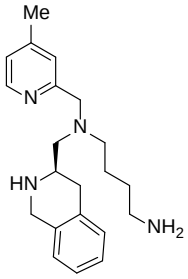
To a 20 mL vial was added **Carbamate 3** (0.305 g, 0.566 mmol) and DCM (Volume: 4.72 mL, Ratio: 5) followed by TFA (Volume: 0.944 mL, Ratio: 1.000) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM/MeOH/NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20c** (0.091 g, 0.269 mmol, 48 % yield) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 7.43 (d, *J*= 7.8 Hz, 1H), 7.28 (d, *J*= 7.8 Hz, 1H), 7.04-6.99 (m, 3H), 6.95-6.94 (m, 1H), 3.99 (d, *J*= 15.0 Hz, 1H), 3.88 (d, *J*= 15.0 Hz, 1H), 3.78 (d, *J*= 14.3 Hz, 1H), 3.63 (d, *J*= 14.3 Hz, 1H), 2.89-2.82 (m, 1H), 2.63-2.53 (m, 6H), 2.49-2.39 (m, 2H), 2.25 (s, 3H), 1.85 (bs, 3NH), 1.54-1.47 (m,2H), 1.37-1.32 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 149.3, 137.1, 135.4, 131.3, 129.1, 126.3, 125.9, 125.5, 122.4, 61.1, 60.4, 55.3, 51.6, 48.4, 41.8, 33.7, 31.2, 24.6, 18.1;

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{30}N_4$ 339.25432, found 339.25411

LC/MS 55% MeOH in H_2O over 3 minutes, r_t = 0.810 at 254 nM, MS (+) 339.2, MS(+)/2 170.2



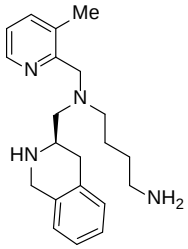
Compound 20d: To a 20 mL scintillation vial was added tert-butyl (4-(((4-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19d** (0.519 g, 1.767 mmol) and **5** (0.508 g, 1.944 mmol) in DCE (Volume: 4.42 mL) followed by STAB-H (0.562 g, 2.65 mmol) and the reaction was stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((4-methylpyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 4** (0.72 g, 1.336 mmol, 76 % yield) To a 20 mL scintillation vial was added **Carbamate 4** (0.293 g, 0.544 mmol) and DCM (Volume: 4.53 mL, Ratio: 5) followed by TFA (Volume: 0.906 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM/MeOH/NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20d** (0.064 g, 0.189 mmol, 35 % yield) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J*= 5.2 Hz, 1H), 7.20 (s, 1H), 7.06-7.01 (m, 3H), 6.97-6.92 (m, 2H), 3.98 (d, *J*= 15.1 Hz, 1H), 3.89 (d, *J*= 15.5 Hz, 1H), 3.77 (d, *J*= 14.2 Hz, 1H), 3.65 (d, *J*= 14.2 Hz, 1H), 2.88-2.81 (m, 1H), 2.65-2.61 (m, 3H), 2.57-2.56 (m, 3H), 2.52-2.40 (m, 2H), 2.32 (s, 3H), 1.56-1.49 (m,2H), 1.47-1.33 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 148.8, 147.5, 135.6, 134.5, 129.1, 126.4, 126.0, 125.6, 123.7, 123.1, 61.5, 60.7, 55.6, 51.8, 48.4, 42.0, 33.8, 31.4, 24.7, 21.2;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4$ 339.25432, found 339.25415

LC/MS 65% MeOH in H_2O over 3 minutes r_t = 1.069 at 254 nM, MS (+) 339.2, MS(+)/2 170.2



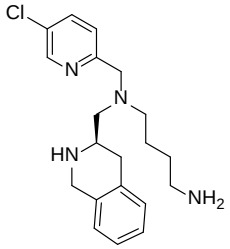
Compound 20e: To a 50 mL RBF was added tert-butyl (4-(((3-methylpyridin-2-yl)methyl)amino)butyl)carbamate **19e**(0.206 g, 0.702 mmol), DCE (Volume: 10 mL), **5** (0.202 g, 0.772 mmol) and STAB-H (0.223 g, 1.053 mmol) then the reaction was stirred overnight. The reaction was quenched by the addition of 1M NaOH and the aqueous layer was extracted with DCM (3 x 15 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo.* The crude oil was purified via combiflash (12g column, DCM for 4 minutes then 5 minute gradient to 20% B solvent mixture 80:20:3 DCM:MeOH:NH_4OH). Fractions were concentrated to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((3-methylpyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 5** (0.289 g, 0.536 mmol, 76 % yield). To a 20 mL scintillation vial was added **Carbamate 5** and 3 mL DCM. The solution was stirred and TFA was added dropwise at RT. The reaction was stirred overnight then diluted with 10 mL DCM and quenched with 1M NaOH. The aqueous layer was extracted with DCM (1x 5mL), dried with $MgSO_4$ filtered and concentrated. The crude oil was purified via combiflash eluted with DCM for 4 min followed by 20% solvent B (80:20:3, DCM:MeOH:NH_4OH) for 8 minutes and finally 50% B for 8 minutes. The fractions were concentrated to afford **20e** (0.042 g, 0.124 mmol, 42 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (dd, *J*= 4.8, 1.2 Hz, 1H), 7.42 (dd, *J*= 7.6, 0.8 Hz, 1H), 7.10-7.06 (m, 3H), 7.03 (dd, *J*= 9.0, 5.4 Hz, 1H), 6.97 (dd, *J*= 5.4, 3.2 Hz, 1H), 3.97 (d, *J*= 15.0 Hz, 1H), 3.89 (d, *J*= 15.0 Hz, 1H), 3.87 (d, *J*= 12.4 Hz, 1H), 3.67 (d, *J*= 12.6 Hz, 1H), 2.89-2.87 (m, 1H), 2.63-2.55 (m, 6H), 2.50 (dd, *J*= 8.4, 5.6 Hz, 1H), 2.43 (s, 3H), 1.55-1.46 (m,2H), 1.41-1.30 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 146.3, 138.1, 135.5, 134.5, 132.8, 129.2, 126.4, 126.0, 125.6, 122.5, 60.8, 60.7, 55.4, 51.8, 48.6, 42.0, 33.9, 31.6, 24.2, 18.4;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4$ 339.25432, found 339.25418

LC/MS 50-95% MeOH in H_2O over 3 minutes, r_t = 0.797 at 254 nM, MS (+) 339.2, MS(+)/2 170.2



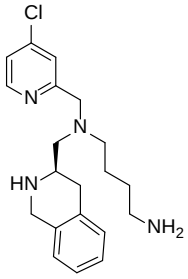
Compound 20f: To a 20 mL vial was added tert-butyl (4-(((5-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19f** (0.5 g, 1.593 mmol), DCE (Volume: 3.79 mL), **5** (0.397 g, 1.517 mmol) and STAB-H (0.579 g, 2.73 mmol). The reaction was allowed to stir for 16h then diluted with DCM, washed with 2M NaOH, dried with Na_2SO_4, filtered and concentrated to a yellow semi solid which was purified via silica gel chromatography (combiflash, DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((5-chloropyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 6** (0.666 g, 1.191 mmol, 78 % yield). To a 20 mL vial was added **Carbamate 6** (0.335 g, 0.599 mmol) and DCM (Volume: 1 mL, Ratio: 2) followed by TFA (Volume: 0.5 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM/MeOH/NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20f** (0.154 g, 0.429 mmol, 72 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J*= 1.8 Hz, 1H), 7.59 (dd, *J*= 8.2, 1.8 Hz, 1H), 7.37 (d, *J*= 8.2 Hz, 1H), 7.05-7.00 (m, 3H), 6.96-6.95 (m, 1H), 3.98 (d, *J*= 15.0 Hz, 1H), 3.92 (d, *J*= 15.0 Hz, 1H), 3.78 (d, *J*= 14.6 Hz, 1H), 3.64 (d, *J*= 14.6 Hz, 1H), 2.91-2.85 (m, 1H), 2.62 (t, *J*= 6.6 Hz, 3H), 2.58-2.51 (m, 3H), 2.49-2.41 (m, 2H), 1.68 (s, 3H), 1.54-1.47 (m,2H), 1.42-1.33 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3, 147.8, 136.2, 135.4, 134.3, 130.2, 129.1, 126.3, 125.9, 125.6, 123.5, 60.7, 60.4, 51.6, 48.5, 42.0, 33.8, 31.5, 24.5;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4Cl$ 359.19970, found 359.19966

LC/MS 10-95% MeOH in H_2O over 10 minutes, r_t = 7.900 at 254 nM, MS (+) 359.4, MS(+)/2 180.3



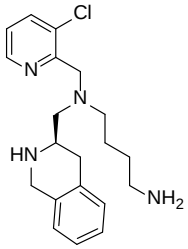
Compound 20g: To a 20 mL vial was added tert-butyl (4-(((4-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19g** (0.430 g, 1.370 mmol), DCE (Volume: 3.26 mL), **5** (0.341 g, 1.305 mmol) and STAB-H (0.498 g, 2.349 mmol). The reaction was allowed to stir for 16h then diluted with DCM, washed with 2M NaOH, dried with Na_2SO_4, filtered and concentrated to a yellow semi solid which was purified via silica gel chromatography (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((4-chloropyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 7**(0.616 g, 1.102 mmol, 84 % yield). To a 20 mL vial was added **Carbamate 7** (0.319 g, 0.571 mmol) and DCM (Volume: 1 mL, Ratio: 2) followed by TFA (Volume: 0.5 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM:MeOH:NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20g** (0.162 g, 0.451 mmol, 79 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J*= 5.4 Hz, 1H), 7.44 (d, *J*= 1.8 Hz, 1H), 7.13 (dd, *J*= 5.4, 1.8 Hz, 1H), 7.09-7.03 (m, 3H), 6.99-6.97 (m, 1H), 4.02 (d, *J*= 15.3 Hz, 1H), 3.93 (d, *J*= 15.3 Hz, 1H), 3.81 (d, *J*= 15.3 Hz, 1H), 3.70 (d, *J*= 15.3 Hz, 1H), 2.89-2.83 (m, 1H), 2.66-2.65 (m, 3H), 2.64-2.54 (m, 3H), 2.52-2.43 (m, 2H), 1.72 (s, 3H), 1.54-1.50 (m,2H), 1.45-1.34 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1, 149.9, 144.5, 135.5, 134.3, 129.1, 126.3, 125.9, 125.6, 122.9, 122.4, 61.1, 60.7, 55.5, 51.7, 48.4, 42.0, 33.8, 31.5, 24.5;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4Cl$ 359.19970, found 359.19973

LC/MS 10-95% MeOH in H_2O over 10 minutes, r_t = 7.804 at 254 nM, MS (+) 359.4, MS(+)/2 180.3



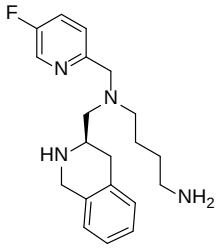
Compound 20h: To a 20 mL vial was added tert-butyl (4-(((3-chloropyridin-2-yl)methyl)amino)butyl)carbamate **19h** (0.491 g, 1.565 mmol), DCE (Volume: 3.73 mL), **5** (0.389 g, 1.490 mmol), and STAB-H (0.568 g, 2.68 mmol). The reaction was allowed to stir for 16h then diluted with DCM, washed with 2M NaOH, dried with Na_2SO_4, filtered and concentrated to a yellow semi solid which was purified via silica gel chromatography (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((3-chloropyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 8** (0.592 g, 1.058 mmol, 71 % yield). To a 20 mL vial was added **Carbamate 8** (0.331 g, 0.592 mmol) and DCM (Volume: 1 mL, Ratio: 2) followed by TFA (Volume: 0.5 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM:MeOH:NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20h** (0.157 g, 0.437 mmol, 74 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (dd, *J*= 4.5, 1.4 Hz, 1H), 7.67 (dd, *J*= 8.0, 1.4 Hz, 1H), 7.16 (dd, *J*= 8.0, 4.5 Hz, 1H), 7.09-7.04 (m, 3H), 7.01-6.99 (m, 1H), 4.03 (d, *J*= 13.0 Hz, 1H), 4.00 (d, *J*= 14.9 Hz, 1H), 3.94 (d, *J*= 14.9 Hz, 1H), 3.74 (d, *J*= 13.0 Hz, 1H), 2.95-2.89 (m, 1H), 2.70-2.60 (m,6H), 2.58-2.50 (m, 1H), 2.46 (dd, *J*= 15.9, 10.9 Hz, 1H), 1.62 (s, 3H), 1.55-1.46 (m,2H), 1.44-1.30 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 146.9, 137.4, 135.6, 134.4, 132.1, 129.1, 126.4, 125.9, 125.5, 123.4, 60.4, 58.6, 55.1, 51.5, 48.5, 41.9, 33.7, 31.4, 24.7;

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4Cl$ 359.19970, found 359.19972

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.783 at 254 nM, MS (+) 359.2, MS(+)/2 180.2



Compound 20i: To a 20 mL vial was added tert-butyl (4-(((5-fluoropyridin-2-yl)methyl)amino)butyl)carbamate **19i** (0.379 g, 1.276 mmol),DCE (Volume: 3.19 mL), **5** (0.35 g, 1.339 mmol) and STAB-H (0.406 g, 1.913 mmol) at RT. The reaction was stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((5-fluoropyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 9** (0.621 g, 1.144 mmol, 90 % yield). To a 20mL vial was added **Carbamate 9** (0.275 g, 0.507 mmol), DCM (Volume: 2.5 mL, Ratio: 3) and TFA (Volume: 0.833 mL, Ratio: 1.000). The reaction was stirred for 24h then diluted with DCM, quenched with 1M NaOH and extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM:MeOH:NH_4OH, 0% 4 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20i** (0.141 g, 0.412 mmol, 81 % yield)

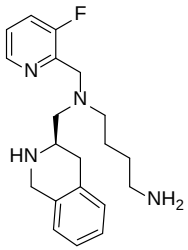
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J*= 2.2 Hz, 1H), 7.42 (dd, *J*= 8.5, 4.5 Hz, 1H), 7.34 (dd, *J*= 8.3, 2.6 Hz, 1H), 7.07-6.96 (m, 4H), 3.99 (d, *J*= 15.1 Hz, 1H), 3.92 (d, *J*= 15.1 Hz, 1H), 3.79 (d, *J*= 14.4 Hz, 1H), 3.66 (d, *J*= 14.4 Hz, 1H), 2.87-2.85 (m, 1H), 2.65-2.41 (m, 10H), 1.55-1.32 (m,4H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, C-F *J*= 252.8 Hz), 156.0 (d, C-F *J*= 4.0 Hz), 137.0 (dd, C-F *J*= 23.2, 2.3 Hz), 135.4, 134.3, 129.1, 126.3, 125.9, 125.6, 123.6 (d, C-F *J*= 3.9 Hz), 123.3 (d, C-F *J*= 18.3 Hz), 60.6, 60.4, 55.2, 51.6, 48.5, 42.0, 33.8, 31.4, 24.5;

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -129.7 (dd, *J*= 7.7, 4.6 Hz)

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4F$ 343.22925, found 343.22913

LC/MS 50-95% MeOH in H_2O over 3 minutes, r_t = 0.778 at 254 nM, MS (+) 343.2, MS(+)/2 172.2



Compound 20j: To a 20 mL vial was added tert-butyl (4-(((3-fluoropyridin-2-yl)methyl)amino)butyl)carbamate **19j** (0.270 g, 0.908 mmol), DCE (Volume: 2.270 mL), **5** (0.249 g, 0.953 mmol) and STAB-H (0.289 g, 1.362 mmol) at RT. The reaction was stirred overnight then diluted with DCM and washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((3-fluoropyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 10** (0.388 g, 0.715 mmol, 79 % yield). To a 20mL vial was added **Carbamate 10** (0.210 g, 0.387 mmol), DCM (Volume: 2.5 mL, Ratio: 3) and TFA (Volume: 0.833 mL, Ratio: 1.000). The reaction was stirred for 24h then diluted with DCM, quenched with 1M NaOH and extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (12g column, DCM and B mix 80:20:3 DCM:MeOH:NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20j** (0.121 g, 0.353 mmol, 91 % yield)

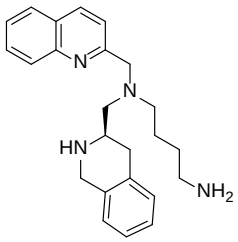
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J*= 4.8 Hz, 1H), 7.38 (ddd, *J*= 9.7, 8.3, 1.3 Hz, 1H), 7.23 (dd, *J*= 8.5, 4.3 Hz, 1H), 7.11-7.00 (m, 4H), 4.04 (d, *J*= 15.2 Hz, 1H), 3.99 (d, *J*= 15.2 Hz, 1H), 3.98 (dd, *J*= 13.2, 2.0 Hz, 1H), 3.73 (dd, *J*= 13.4, 1.6 Hz, 1H), 3.03-2.96 (m, 1H), 2.69-2.45 (m, 10H), 1.60-1.34 (m,4H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, C-F *J*= 258.2 Hz), 147.5 (d, C-F *J*= 14.4 Hz), 144.7 (dd, C-F *J*= 5.2, 2.0 Hz), 135.6, 134.5, 129.1, 126.4, 125.9, 125.5, 123.7 (d, C-F *J*= 3.9 Hz), 123.0 (d, C-F *J*= 19.5 Hz), 60.1, 54.9, 54.8, 51.6, 48.5, 41.9, 33.7, 31.3, 24.4;

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -124.4 (d, *J*= 8.3 Hz)

HRMS (ESI) $[M+H]^+$, calcd for $C_{20}H_{28}N_4F$ 343.22925, found 343.22927

LC/MS 50-95% MeOH in H_2O over 3 minutes, r_t = 0.778 at 254 nM, MS (+) 343.2, MS(+)/2 172.2



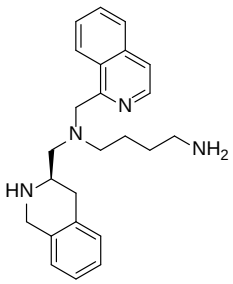
Compound 20k: To a 20 mL vial was added tert-butyl (4-((quinolin-2-ylmethyl)amino)butyl)carbamate **19k** (0.390 g, 1.184 mmol), DCE (Volume: 2.96 mL), **5** (0.340 g, 1.302 mmol) and STAB-H (0.376 g, 1.776 mmol) then the reaction was stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)(quinolin-2-ylmethyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 11** (0.59 g, 1.027 mmol, 87 % yield). To a 25 mL rbf was added **Carbamate 11** (0.34 g, 0.592 mmol) and DCM (Volume: 5.92 mL) followed by TFA (0.912 mL, 11.83 mmol) dropwise. The reaction was diluted with 10 mL DCM then quenched with 1M NaOH. The aqueous layer was extracted with DCM (2x 5mL), dried with $MgSO_4$, filtered and concentrated. The crude oil was purified via combiflash eluted with DCM for 4 min followed by 20% solvent B (80:20:3, DCM:MeOH:NH_4OH) for 8 minutes and finally 50% B for 8 minutes. The fractions were concentrated and placed on high-vac for 48h to afford **20k** (0.187 g, 0.499 mmol, 84 % yield) as a yellow-brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J*= 8.3 Hz, 1H), 8.03 (d, *J*= 8.6 Hz, 1H), 7.80 (d, *J*= 8.0 Hz, 1H), 7.69 (dt, *J*= 8.3, 1.2 Hz, 1H), 7.63 (d, *J*= 8.5 Hz, 1H), 7.51 (dt, *J*= 7.9 , 0.8 Hz, 1H), 7.09-7.03 (m, 3H), 6.99-6.97 (m, 1H), 4.03 (d, *J*= 14.2 Hz, 2H), 3.94 (d, *J*= 15.1 Hz, 1H), 3.88 (d, *J*= 14.6 Hz, 1H), 2.99-2.93 (m, 1H), 2.71-2.63 (m, 6H), 2.61-2.53 (m, 1H), 2.47 (dd, *J*= 15.0, 10.4 Hz, 1H), 1.62-1.54 (m,2H), 1.51-1.36 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 147.6, 136.4, 135.6, 134.5, 129.5, 129.2, 129.0, 127.6, 127.4, 126.4, 125.6, 120.8, 62.5, 60.9, 55.6, 51.8, 48.6, 42.1, 33.9, 31.6, 24.7;

HRMS (ESI) $[M+H]^+$, calcd for $C_{24}H_{31}N_4$ 375.25432, found 375.25391

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.689 at 254 nM, MS (+) 375.2, MS(+)/2 188.2



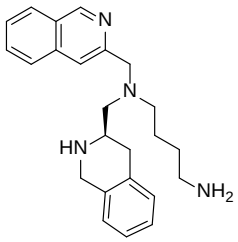
Compound 20l: To a 20 mL vial was added tert-butyl (4-((isoquinolin-1-ylmethyl)amino)butyl)carbamate **19l** (0.358 g, 1.087 mmol), **5** (0.284 g, 1.087 mmol), DCE (Volume: 2.72 mL) and STAB-H (0.345 g, 1.630 mmol). The reaction was allowed to stir for 16h then diluted with DCM, washed with 2M NaOH, dried with Na_2SO_4, filtered and concentrated to a yellow semi solid which was purified via silica gel chromatography (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)(isoquinolin-1-ylmethyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 12** (0.494 g, 0.859 mmol, 79 % yield) as an off white solid. To a 20 mL vial was added **Carbamate 12** (0.264 g, 0.459 mmol), DCM (Volume: 5 mL, Ratio: 5) andTFA (Volume: 1.000 mL, Ratio: 1). The reaction was allowed to stir over night then diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil which was purified via silica gel chromatography (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes) to afford **20l** (0.13 g, 0.347 mmol, 76 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J*= 8.4 Hz, 1H), 8.39 (d, *J*= 5.7 Hz, 1H), 7.78 (d, *J*= 8.1 Hz, 1H), 7.67 (ddd, *J*= 8.2, 6.8, 1.0 Hz, 1H), 7.60 (ddd, *J*= 8.2, 6.8, 1.0 Hz, 1H), 7.54 (d, *J*= 5.7 Hz, 1H), 7.04-7.02 (m, 2H), 6.97-6.90 (m, 2H), 4.30 (d, *J*= 12.5 Hz, 1H), 4.18 (d, *J*= 12.5 Hz, 1H), 3.82 (d, *J*= 15.0 Hz, 1H), 3.61 (d, *J*= 15.0 Hz, 1H), 2.71-2.60 (m, 5H), 2.58 (t, *J*= 6.9 Hz, 3H), 2.34 (dd, *J= 16.0, 9.3* Hz, 1H), 1.80 (bs, 3NH), 1.59-1.49 (m,2H), 1.41-1.27 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ =158.8, 141.5, 136.4, 135.4, 134.3, 130.0, 129.1, 127.6, 127.3, 126.8, 126.3, 125.9, 125.5, 120.7, 61.3, 60.8, 55.9, 51.8, 48.3, 41.9, 33.8, 31.5, 24.1;

HRMS (ESI) $[M+H]^+$, calcd for $C_{24}H_{31}N_4$ 375.25432, found 375.25423

LC/MS 10-95% MeOH in H_2O over 10 minutes, r_t = 7.624 at 254 nM, MS (+) 375.2, MS(+)/2 188.2



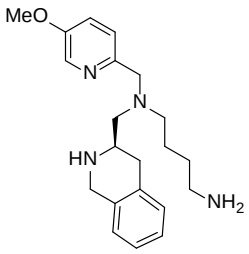
Compound 20m: To a 20 mL scintillation vial was added tert-butyl (4-((isoquinolin-3-ylmethyl)amino)butyl)carbamate **19m** (0.38 g, 1.153 mmol) and **5** (0.332 g, 1.269 mmol) in DCE (Volume: 2.88 mL) followed by STAB-H (0.367 g, 1.730 mmol) and the reaction was stirred overnight. The reaction was diluted with DCM and then washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)(isoquinolin-3-ylmethyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 13**(0.429 g, 0.746 mmol, 65 % yield) To a 20 mL vial was added **Carbamate13** (0.2 g, 0.348 mmol) and DCM (Volume: 2.90 mL, Ratio: 5) followed by TFA (Volume: 0.580 mL, Ratio: 1) and the reaction was stirred overnight. After 20 h the reaction was diluted with DCM and quenched with 1M NaOH then extracted with DCM. The organic layer was dried with $MgSO_4$, filtered and concentrated to a brown oil. The oil was purified via combiflash (24g column, DCM and B mix 80:20:3 DCM:MeOH:NH_4OH, 0% 2 minutes, 20% 7 minutes and 50% 10 minutes) to afford **20m** (0.071 g, 0.190 mmol, 55 % yield) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 7.90 (d, *J*= 7.8 Hz, 1H), 7.77 (d, *J*= 7.8 Hz, 1H), 7.69 (s, 1H), 7.63 (ddd, *J*= 8.1, 6.9, 1.2 Hz, 1H), 7.51 (ddd, *J*= 8.0, 6.9, 1.0 Hz, 1H), 7.08-6.93 (m, 4H), 4.03 (d, *J*= 15.4 Hz, 1H), 3.98 (d, *J*= 14.8 Hz, 1H), 3.90 (d, *J*= 15.4 Hz, 1H), 3.84 (d, *J*= 14.7 Hz, 1H), 2.96-2.89 (m, 1H), 2.67-2.62 (m, 6H), 2.59-2.53 (m, 1H), 2.46 (dd, *J*= 16.0, 10.8 Hz, 1H), 1.63-1.55 (m,2H), 1.48-1.35 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 152.2, 136.4, 135.7, 134.5, 130.4, 129.1, 127.7, 127.6, 126.8, 126.5, 126.4, 125.9, 125.6, 118.7, 61.2, 60.5, 55.6, 51.9, 48.6, 42.1, 33.9, 31.7, 24.7;

HRMS (ESI) $[M+H]^+$, calcd for $C_{24}H_{30}N_4$ 375.25432, found 375.25406

LC/MS 75-95% MeOH in H_2O over 3 minutes, r_t = 0.689 at 254 nM, MS (+) 375.2, MS(+)/2 188.2



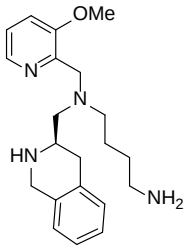
Compound 20n: To a 20 mL vial was added tert-butyl (4-(((5-methoxypyridin-2-yl)methyl)amino)butyl)carbamate **19n** (0.290 g, 0.937 mmol), DCE (Volume: 2.343 mL), **5** (0.269 g, 1.031 mmol) and STAB-H (0.298 g, 1.406 mmol) then the reaction was stirred overnight. The reaction was diluted with DCM and washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((5-methoxypyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 14**(0.448 g, 0.808 mmol, 86 % yield) . To a 20mL vial equipped with a stirbar was added **Carbamate 14** (0.206 g, 0.371 mmol) and DCM (Volume: 3 mL, Ratio: 3). To the solution was added TFA (Volume: 1.000 mL, Ratio: 1) and the reaction was stirred overnight. The reaction was quenched by the addition of 2M NaOH and extracted with DCM. The organics were dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20n** (0.088 g, 0.248 mmol, 67 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J*= 2.8 Hz, 1H), 7.30 (d, *J*= 8.7 Hz, 1H), 7.16 (dd, *J*= 8.7, 3.0 Hz, 1H), 7.07-6.96 (m, 4H), 3.99 (d, *J*= 15.4 Hz, 1H), 3.91 (d, *J*= 15.0 Hz, 1H), 3.81 (s, 3H), 3.77 (d, *J*= 14.1 Hz, 1H), 3.60 (d, *J*= 14.1 Hz, 1H), 2.90-2.83 (m, 1H), 2.65-2.59 (m, 1H), 2.64 (t, *J*= 6.9 Hz, 2H), 2.57-2.52 (m, 3H), 2.49-2.41 (m, 2H), 2.31 (bs, 3NH), 1.55-1.47 (m,2H), 1.45-1.33 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 151.8, 136.1, 135.5, 134.4, 129.1, 126.4, 126.0, 125.6, 123.3, 121.4, 60.7, 60.3, 55.6, 55.2, 51.7, 48.5, 41.9, 33.8, 31.3, 24.6;

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{31}ON_4$ 355.24924, found 355.24899

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.730 at 254 nM, MS (+) 355.2, MS(+)/2 178.2



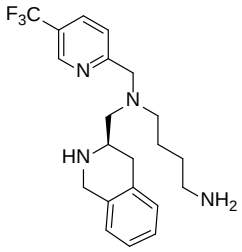
Compound 20o: To a 20 mL vial was added tert-butyl (4-(((3-methoxypyridin-2-yl)methyl)amino)butyl)carbamate **19o** (0.330 g, 1.067 mmol), DCE (Volume: 2.67 mL), **5** (0.307 g, 1.173 mmol) and STAB-H (0.339 g, 1.600 mmol) then the reaction was stirred overnight. The reaction was diluted with DCM and washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((3-methoxypyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 15** (0.446 g, 0.804 mmol, 75 % yield). To a 20mL vial equipped with a stirbar was added **Carbamate 15** (0.192 g, 0.346 mmol), DCM (Volume: 3 mL, Ratio: 3) and TFA (Volume: 1.000 mL, Ratio: 1) was added and the reaction was stirred overnight. The reaction was quenched by the addition of 2M NaOH and extracted with DCM. The organics were dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20o** (0.061 g, 0.172 mmol, 50 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J*= 4.1, 1.7 Hz, 1H), 7.25-7.11 (m, 2H), 7.07-7.01 (m, 3H), 6.99-6.97 (m, 1H), 4.01 (d, *J*= 15.0 Hz, 1H), 3.95 (d, *J*= 15.2 Hz, 1H), 3.93 (d, *J*= 13.0 Hz, 1H), 3.82 (s, 3H), 3.61 (d, *J*= 13.0 Hz, 1H), 2.99-2.92 (m, 1H), 2.66-2.56 (m, 6H), 2.50-2.42 (m, 2H), 2.37 (bs, 3NH), 1.50-1.43 (m,2H), 1.42-1.25 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 148.8, 140.3, 135.6, 134.6, 129.1, 126.4, 125.9, 125.5, 123.0, 117.3, 60.3, 55.4, 55.3, 55.0, 51.7, 48.5, 41.8, 33.7, 31.2, 24.3;

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{31}ON_4$ 355.24924, found 355.24878

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.708 at 254 nM, MS (+) 355.2, MS(+)/2 178.2



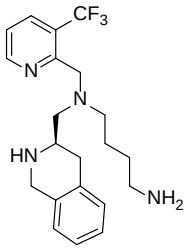
Compound 20p: To a 20 mL vial was added tert-butyl (4-(((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)butyl)carbamate **19p** (0.350 g, 1.008 mmol), DCE (Volume: 2.52 mL), **5** (0.290 g, 1.108 mmol) and STAB-H (0.320 g, 1.511 mmol) and the reaction was stirred overnight. The reaction was diluted with DCM and washed with 1M NaOH (50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (40g column, DCM then 20% B, DCM:MeOH:NH_4OH, 80:20:3) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 16** (0.525 g, 0.886 mmol, 88 % yield). To a 20mL scintillation vial equipped with a stirbar was added **Carbamate 16** (0.269 g, 0.454 mmol) and DCM. To the solution was added TFA and the reaction was stirred o/n. The reaction was quenched by the addition of 2M NaOH and extracted with DCM. The organics were dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combi-flash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20p** (0.140 g, 0.357 mmol, 79 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J*= 2.0 Hz, 1H), 7.89 (dd, *J*= 8.2, 2.2 Hz, 1H), 7.60 (d, *J*= 8.0 Hz, 1H), 7.09-6.97 (m, 4H), 4.02 (d, *J*= 15.5 Hz, 1H), 3.94 (d, *J*= 15.5 Hz, 1H), 3.91 (d, *J*= 14.9 Hz, 1H), 3.76 (d, *J*= 15.1 Hz, 1H), 2.98-2.91 (m, 1H), 2.69-2.63 (m, 1H) 2.66 (t, *J*= 7.0 Hz, 2H), 2.61-2.56 (m, 3H), 2.53 (dd, *J*= 10.2, 3.1 Hz, 1H), 2.48 (dd, *J*= 16.8, 10.8 Hz, 1H), 2.21 (bs, 3NH), 1.56-1.48 (m,2H), 1.46-1.35 (m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (q, C-F, *J*= 1.4 Hz), 145.9 (q, C-F, *J*= 4.1 Hz), 135.2, 134.1, 133.6 (q, C-F, *J*= 3.6 Hz), 129.0, 126.3, 126.0, 125.6, 125.0 (q, C-F, *J*= 33.2 Hz), 123.5 (q, C-F, *J*= 272.2 Hz), 122.3, 61.0, 60.4, 55.2, 51.6, 48.3, 41.8, 33.6, 31.0, 24.5;

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -62.25

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{28}N_4F_3$ 393.22606, found 393.22585

LC/MS 85% MeOH in H_2O over 3 minutes, r_t = 0.692 at 254 nM, MS (+) 393.2, MS(+)/2 197.2



Compound 20q: To a 20 mL vial was added tert-butyl (4-(((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)butyl)carbamate **19q** (0.318 g, 0.915 mmol), DCE (Volume: 2.266 mL), **5** (0.237 g, 0.906 mmol) and STAB-H (0.288 g, 1.360 mmol). The reaction was stirred for 6h and TLC indicated sm was consumed. The reactin was diluted with DCM and washed with 2M NaOH, dried with $MgSO_4$, filtered and concentrated to afford a yellow oil which was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 15 minutes). The fractions were concentrated to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate 17** (0.44 g, 0.742 mmol, 82 % yield). To a 20 mL vial was added **Carbamate 17** (0.44 g, 0.742 mmol), DCM (Volume: 4 mL, Ratio: 4) and TFA (Volume: 1.000 mL, Ratio: 1.000) and the reaction was stirred overnight. The reaction was diluted with DCM, washed with 2M NaOH, dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20q** (0.189 g, 0.482 mmol, 65 % yield)

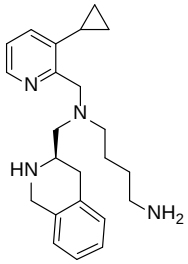
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J*= 4.3 Hz, 1H), 7.89 (d, *J*= 7.0 Hz, 1H), 7.26 (dd, *J*= 8.0, 4.8 Hz, 1H), 7.07-6.94 (m, 4H), 4.03 (d, *J*= 13.9 Hz, 1H), 3.96 (d, *J*= 15.0 Hz, 1H), 3.86 (d, *J*= 15.0 Hz, 1H), 3.85 (d, *J*= 13.9 Hz, 1H), 2.77-2.71 (m, 1H), 2.68-2.51 (m, 5H), 2.60 (t, *J*= 7.0 Hz, 2H), 2.42 (dd, *J*= 15.6, 10.9 Hz, 1H), 2.06 (bs, 3NH), 1.54-1.45 (m,2H), 1.4-1.28 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 151.7, 135.6, 134.4, 134.4 (q, C-F, *J*= 5.7 Hz), 129.0, 126.4, 125.8, 125.4, 125.1 (q, C-F, *J*= 32.0 Hz), 123.9 (q, C-F, *J*= 274.4 Hz), 121.7, 60.6, 58.4, 55.7, 51.6, 48.4, 41.9, 33.6, 31.4, 24.1;

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -59.86

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{28}N_4F_3$ 393.22606, found 393.22577

LC/MS 55% MeOH in H_2O over 3 minutes, r_t = 0.883 at 254 nM, MS (+) 393.2, MS(+)/2 197.2



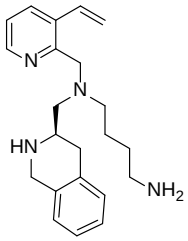
Compound 20r: To a 20 mL vial was added tert-butyl (4-(((3-cyclopropylpyridin-2-yl)methyl)amino)butyl)carbamate **19r** (0.2 g, 0.626 mmol), DCE (Volume: 1.491 mL), STAB-H(0.227 g, 1.073 mmol) and **5** (0.156 g, 0.596 mmol) then the mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil which was dissolved in 2.5 mL DCM and 0.5 mL TFA. The reaction was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20r** (0.157 g, 0.431 mmol, 72 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (dd, *J*= 4.6, 1.1 Hz, 1H), 7.14 (d, *J*= 7.2 Hz, 1H), 7.08-7.04 (m, 3H), 7.00-6.98 (m, 1H), 6.94-6.92 (m, 1H), 4.02 (d, *J*= 12.6 Hz, 1H), 3.93 (d, *J*= 15.1 Hz, 1H), 3.82 (d, *J*= 12.3 Hz, 1H), 3.77 (d, *J*= 14.8 Hz, 1H), 2.74-2.69 (m, 1H), 2.63-2.49 (m,7H), 2.58 (t, *J*= 7.0 Hz, 2H), 2.37 (dd, *J*= 15.9, 10.9 Hz, 1H), 2.30-2.25 (m, 1H) 1.82 (br s, 3NH), 1.51-1.44 (m,2H), 1.39-1.28 (m, 2H), 0.9 (dd, *J*= 8.6, 1.6 Hz, 1H), 0.69-0.62 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 145.6, 138.2, 135.4, 134.4, 132.1, 129.1, 126.3, 125.9, 125.5, 122.5, 60.6, 60.6, 55.6, 51.8, 48.5, 41.9, 33.8, 31.5, 24.2, 11.4, 8.4, 8.1;

HRMS (ESI) $[M+H]^+$, calcd for $C_{23}H_{33}N_4$ 365.26997, found 365.26970

LC/MS 10-95% MeOH in H_2O over 10 minutes, r_t = 2.723 at 254 nM, MS (+) 365.2, MS(+)/2 183.2



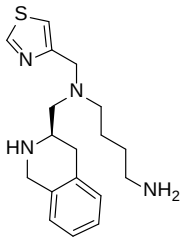
Compound 20s: To a 20 mL vial was added tert-butyl (4-(((3-vinylpyridin-2-yl)methyl)amino)butyl)carbamate **19s** (0.2 g, 0.655 mmol), DCE (Volume: 1.559 mL), STAB-H (0.238 g, 1.123 mmol) and **5** (0.163 g, 0.624 mmol) then the mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil which was dissolved in 2.5 mL DCM and 0.5 mL TFA. The reaction was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20s** (0.134 g, 0.382 mmol, 61 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (dd, *J*= 4.5, 1.0 Hz, 1H), 7.80 (d, *J*= 7.0 Hz, 1H),7.18 (dd, *J*= 7.6, 5.0 Hz, 1H), 7.15 (dd, *J*= 17.6, 11.1 Hz, 1H), 7.07-7.04 (m, 2H), 7.02-7.00 (m, 1H), 6.97-6.96 (m, 1H), 5.71 (d, *J*= 17.4 Hz, 1H), 5.40 (d, *J*= 10.8 Hz, 1H), 3.96 (d, *J*= 15.2 Hz, 1H), 3.95 (d, *J*= 12.6 Hz, 1H), 3.87 (d, *J*= 15.2 Hz, 1H), 3.74 (d, *J*= 12.6 Hz, 1H), 2.75-2.70 (m, 1H), 2.62-2.47 (m, 7H), 2.39 (dd, *J*= 15.9, 10.7 Hz, 1H), 1.86 (br s, 3NH), 1.53-1.46 (m,2H), 1.41-1.27 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1, 147.9, 135.5, 134.5, 133.4, 133.4, 133.1, 129.1, 126.4, 126.0, 125.6, 122.9, 116.4, 60.8, 60.4, 55.4, 51.8, 48.5, 42.0, 33.8, 31.6, 24.1;

HRMS (ESI) $[M+H]^+$, calcd for $C_{22}H_{31}N_4$ 351.25423, found 351.25390

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.450 at 254 nM, MS (+) 351.2, MS(+)/2 176.2



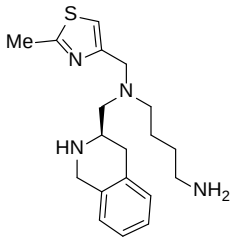
Compound S14: To a 20 mL vial was added tert-butyl (4-((thiazol-4-ylmethyl)amino)butyl)carbamate **S11** (0.4 g, 1.402 mmol), **5** (0.374 g, 1.430 mmol), DCE (Volume: 3.50 mL) and STAB-H (0.446 g, 2.102 mmol) then stirred overnight. The reaction was diluted with DCM, washed with 2M NaOH, dried with $MgSO_4$, filtered and concentrated to a yellow oil which was purified via combiflash 10% B (80:20:3, DCM:MeOH:NH_4OH) to afford (R)-tert-butyl 3-(((4-((tert-butoxycarbonyl)amino)butyl)(thiazol-4-ylmethyl)amino)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate **Carbamate S11** (0.576 g, 1.085 mmol, 77 % yield). To a 20 mL vail was added **Carbamate S11** (0.576 g, 1.085 mmol), DCM (Volume: 4.52 mL, Ratio: 5) and TFA (Volume: 0.904 mL, Ratio: 1.000). The mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford (R)-N1-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N1-(thiazol-4-ylmethyl)butane-1,4-diamine **S14** (0.211 g, 0.638 mmol, 59 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.74 (d, *J*= 2.0 Hz, 1H), 7.16 (d, *J*= 1.8 Hz, 1H), 7.07-6.97 (m, 4H), 4.01 (d, *J*= 15.1 Hz, 1H), 3.96 (d, *J*= 15.1 Hz, 1H), 3.89 (d, *J*= 14.9 Hz, 1H), 3.81 (d, *J*= 14.6 Hz, 1H), 2.95-2.89 (m, 1H), 2.65 (t, *J*= 6.9 Hz, 2H), 2.63-2.56 (m, 5H), 2.50-2.44 (m, 2H), 2.02 (bs, 3NH), 1.57-1.53 (m,2H), 1.49-1.37 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8, 152.6, 135.6, 134.4, 129.1, 126.4, 125.9, 125.6, 115.3, , 60.1, 55.0, 54.5, 51.7, 48.6, 42.0, 33.9, 31.4, 24.8;

HRMS (ESI) $[M+H]^+$, calcd for $C_{18}H_{27}N_4S$ 331.19509, found 331.19501

LC/MS 65% MeOH in H_2O over 3 minutes, r_t = 0.747 at 254 nM, MS (+) 331.2, MS(+)/2 166.2



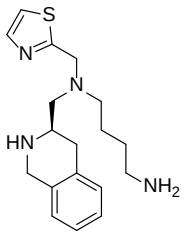
Compound S15: To a 20 mL vial was added tert-butyl (4-(((2-methylthiazol-4-yl)methyl)amino)butyl)carbamate **S12** (0.095 g, 0.317 mmol), **5** (0.087 g, 0.333 mmol), DCE (Volume: 0.793 mL) and STAB-H (0.101 g, 0.476 mmol) and the mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil which was dissolved in 5 mL DCM and 0.5 mL TFA. The mixture was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil (R)-N1-((2-methylthiazol-4-yl)methyl)-N1-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)butane-1,4-diamine **S15** (0.071 g, 0.206 mmol, 65 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09-6.99 (m, 4H), 6.94 (s, 1H), 4.03 (d, *J*= 15.2 Hz, 1H), 3.98 (d, *J*= 15.2 Hz, 1H), 3.80 (d, *J*= 14.7 Hz, 1H), 3.71 (d, *J*= 14.7 Hz, 1H), 2.95-2.89 (m, 1H), 2.70-2.67 (m, 2H), 2.68 (s, 3H), 2.64-2.60 (m, 2H), 2.58-2.57 (m, 2H), 2.53-2.45 (m, 2H), 2.03 (bs, 3NH), 1.59-1.51 (m,2H), 1.49-1.41 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 154.6, 135.5, 134.4, 129.1, 126.3, 125.9, 125.6, 114.7, 60.0, 55.2, 54.9, 51.7, 48.5, 42.0, 33.8, 31.4, 24.7, 19.2;

HRMS (ESI) $[M+H]^+$, calcd for $C_{19}H_{29}N_4S$ 345.21074, found 345.21076

LC/MS 10-95% MeOH in H_2O over 10 minutes, r_t = 7.781 at 254 nM, MS (+) 345.2, MS(+)/2 173.2



Compound S16: To 20 mL vial was added tert-butyl (4-((thiazol-2-ylmethyl)amino)butyl)carbamate **S13** (0.176 g, 0.617 mmol), **5** (0.161 g, 0.617 mmol), DCE (Volume: 3.08 mL) and STAB-H(0.196 g, 0.925 mmol). The reaction was stirred at rt for 16h then diluted with DCM and washed with 2M NaOH. The organics were dried with Na_2SO_4, filtered and concentrated to a yellow oil which was purified via silica gel chromatography (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford a yellow oil which was dissolved in 5 mL DCM and 0.5 mL TFA. The reaction was allowed to stir over night. The reaction was diluted with DCM, washed with 1M NaOH, dried with Na_2SO_4, filtered and concentrated to afford a yellow oil. The crude material was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford (R)-N1-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-N1-(thiazol-2-ylmethyl)butane-1,4-diamine **S16** (0.130 g, 0.393 mmol, 64 % yield) as a pale yellow oil

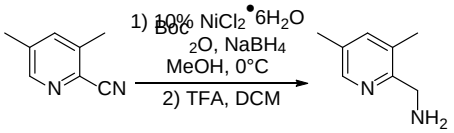
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J*= 3.3 Hz, 1H), 7.24 (d, *J*= 3.3 Hz, 1H), 7.09-7.02 (m, 3H), 7.00-6.99 (m, 1H), 4.04 (d, *J*= 15.2 Hz, 1H), 3.99 (d, *J*= 15.7 Hz, 1H), 3.98 (d, *J*= 15.2 Hz, 1H), 3.94 (d, *J*= 15.7 Hz, 1H), 2.98-2.90 (m, 1H), 2.69-2.58 (m, 6H), 2.57-2.46 (m, 2H), 1.73 (bs, 3NH), 1.59-1.50 (m,2H), 1.49-1.35 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 142.4, 135.4, 134.2, 129.1, 126.3, 125.9, 125.6, 119.2, 60.5, 56.7, 55.4, 51.8, 48.5, 42.0, 33.7, 31.4, 24.8;

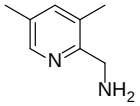
HRMS (ESI) $[M+H]^+$, calcd for $C_{18}H_{27}N_4S$ 331.19509, found 331.19607

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.757 at 254 nM, MS (+) 331.2, MS(+)/2 166.2

General Procedure C:

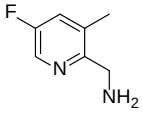


To a stirred solution of 3,5-dimethylpicolinonitrile (1 equiv.) in MeOH (0.1M) at 0 °C was added BOC-Anhydride (2 equiv) and Nickel (II) Chloride hexahydrate (0.1 equiv). To the stirred mixture was added $NaBH_4$ (7-10 equiv) in small portions over 30 minutes to prevent exothermic eruption and the reaction was allowed to stir for 3h. Additional $NaBH_4$ was added if the reaction was not complete and allowed to stir overnight. N1-(2-aminoethyl)ethane-1,2-diamine (2 equiv.) was added to complete the reaction. The mixture was concentrated to an oil, dissolved in EtOAc, washed with saturated sodium bicarbonate, brine and dried with $MgSO_4$, filtered and concentrated to afford a solid. The solid was dissolved in DCM (0.7M) and TFA (Ratio DCM:TFA, 5:1) was added and the reaction was stirred overnight. The reaction was quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to afford the pyridylamine.



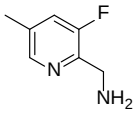
Compound S17: Following the general procedure C. 3,5-dimethylpicolinonitrile (3.67 g, 27.8 mmol) in MeOH (Volume: 214 mL) di-tert-butyl dicarbonate (12.89 mL, 55.5 mmol), Nickel (II) Chloride hexahydrate (0.660 g, 2.78 mmol), $NaBH_4$ (7.35 g, 194 mmol) An additional 2g of $NaBH_4$ was added and the reaction was allowed to stir overnight. N1-(2-aminoethyl)ethane-1,2-diamine (6.00 mL, 55.5 mmol) was added to complete the reaction. The reaction was then concentrated to an oil, diluted with EtOAc, washed with $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to a white solid. A portion of the solid (1 g, 4.23 mmol), DCM (Volume: 5 mL, Ratio: 5) and TFA (Volume: 1 mL, Ratio: 1.000) were stirred overnight then work-up and concentrated to afford (3,5-dimethylpyridin-2-yl)methanamine **S17** (0.45 g, 3.30 mmol, 78 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.19 (s, 1H), 7.27 (s, 3H), 4.36 (d, *J* = 4.4 Hz, 2H), 2.29 (s, 3H), 2.24 (s, 3H).



Compound S18: Following the general procedure C. 5-fluoro-3-methylpicolinonitrile (.672 g, 4.94 mmol), MeOH (Volume: 38.0 mL), di-tert-butyl dicarbonate (2.155 g, 9.87 mmol), Nickel (II) Chloride hexahydrate (0.117 g, 0.494 mmol) $NaBH_4$ (1.868 g, 49.4 mmol). N1-(2-aminoethyl)ethane-1,2-diamine (1.067 mL, 9.87 mmol) was added to the light brown reaction and stirred for 30 minutes (brown to pink). The reaction was then concentrated to an oil, diluted with EtOAc, washed with $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated to a yellow oil which solidified on high vac (0.9 g, 3.75 mmol, 76 % yield). The solid (0.755 g, 3.14 mmol), DCM (Volume: 5 mL, Ratio: 5) and TFA (Volume: 1 mL, Ratio: 1.000) were allowed to stir overnight. Work-up and concentrated to a yellow oil which was purified via silica gel chromatography (30% EtOAc in hexanes) to afford (5-fluoro-3-methylpyridin-2-yl)methanamine **S18** (0.18 g, 1.284 mmol, 40.9 % yield). 59% over 2 steps.

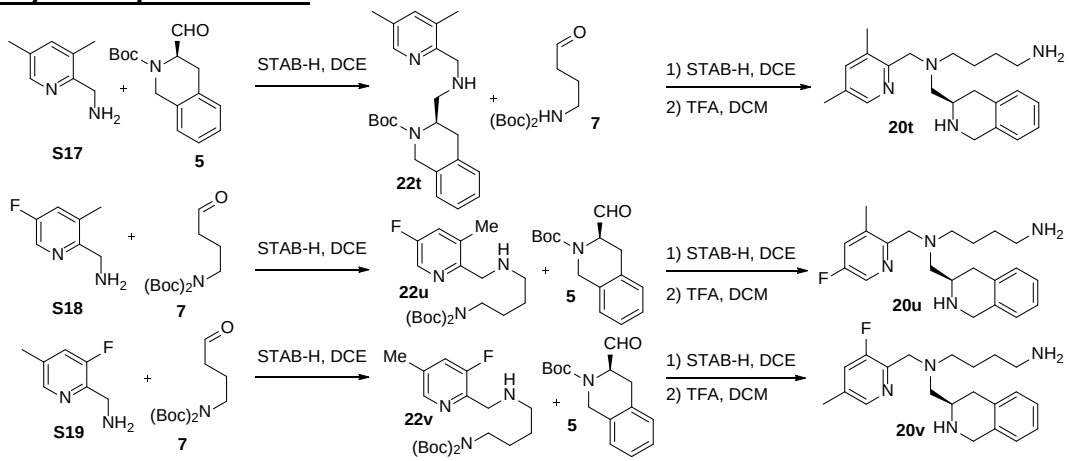
^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.26 (d, *J*= 2.7 Hz, 1H), 7.18 (dd, *J*= 9.0, 2.7 Hz, 1H), 3.92 (s, 2H), 2.30 (s, 3H);

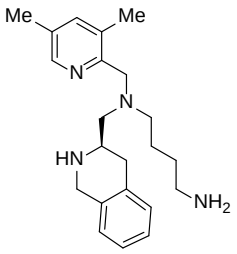


Compound S19: Following the general procedure C. 3-fluoro-5-methylpicolinonitrile (2.04 g, 14.99 mmol), MeOH (Volume: 100mL), di-tert-butyl dicarbonate (6.54 g, 30.0 mmol), Nickel (II) Chloride hexahydrate (0.355 g, 1.499 mmol), $NaBH_4$ (5.67 g, 150 mmol). N1-(2-aminoethyl)ethane-1,2-diamine (3.24 mL, 30.0 mmol) was added to the light green reaction and stirred for 30 minutes turned to pink. The reaction was then concentrated to an oil and purified via combiflash (gradient 10-30% EA in hexanes) to afford a solid (1.22 g, 5.08 mmol, 34 % yield). The solid (0.5 g, 2.081 mmol), DCM (Volume: 8.67 mL, Ratio: 5), TFA (Volume: 1.734 mL, Ratio: 1.000) were stirred overnight, work-up and concentrated to afford (3-fluoro-5-methylpyridin-2-yl)methanamine **S19** (0.220 g, 1.570 mmol, 75 % yield). 55% over 2 steps.

^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.22 (s, 1H), 7.17 (d, *J*= 8.3 Hz, 1H), 4.01 (s, 2H), 2.36 (s, 3H)

Procedure for Compounds 20t-v





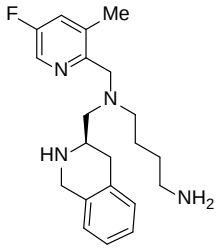
Compound 20t: To a 20 mL vial was added (3,5-dimethylpyridin-2-yl)methanamine **S17** (0.250 g, 1.836 mmol), **5** (0.504 g, 1.927 mmol), DCE (Volume: 4.59 mL) and $Na(OAc)_3BH$ (0.584 g, 2.75 mmol). The mixture was stirred vigorously for 2h then quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to an oil which was purified via combiflash (DCM 5 min, 10%B (80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford a yellow semi-solid **22t** (0.4 g, 1.048 mmol, 57 % yield). To a 20 mL vial was added **22t** (0.165 g, 0.432 mmol), DCE (2.0 mL) butyl-aldehyde **7** (0.249 g, 0.865 mmol), and STAB-H (0.137 g, 0.649 mmol). The reaction was allowed to stir overnight then quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to a yellow oil. The oil was dissolved in DCM (4 mL) and TFA (0.5 mL) was added dropwise and the mixture was allowed to stir overnight. The reaction was quenched with 2M NaOH, extracted with DCM, dried $MgSO_4$, filtered and concentrated to a yellow oil. The crude material was purified via combiflash (DCM 5 min, 10%B-(80:20:3, DCM:MeOH:NH_4OH) 7 min, 50%B 10 min) to afford **20t** (64mg, 0.182 mmol, 41 % yield) 49% over 3 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J*= 1.6 Hz, 1H), 7.24 (d, *J*= 1.6 Hz, 1H), 7.07-6.95 (m, 4H), 3.97 (d, *J*= 14.9 Hz, 1H), 3.89 (d, *J*= 15.1 Hz, 1H), 3.84 (d, *J*= 12.5 Hz, 1H), 3.59 (d, *J*= 12.5 Hz, 1H), 2.86-2.79 (m, 1H), 2.61 (t, *J*= 7.0 Hz, 1H), 2.60-2.53 (m, 3H), 2.45 (dd, *J*= 8.3, 5.3 Hz, 1H), 2.42 (dd, *J*= 11.6, 6.1 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 2.05 (bs, 3NH), 1.54-1.43 (m,2H), 1.42-1.28 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 146.4, 138.8, 135.4, 132.0, 131.8, 129.0, 126.3, 125.9, 125.5, 60.3, 60.2, 55.2, 51.7, 48.4, 41.9, 33.7, 31.4, 24.1, 18.2, 17.9;

HRMS (ESI) $[M+H]^+$, calcd for $C_{22}H_{32}N_4$ 353.26997, found 353.26968

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.779 at 254 nM, MS (+) 353.2, MS(+)/2 177.2



Compound 20u: To a 20 mL vial was added (5-fluoro-3-methylpyridin-2-yl)methanamine **S18** (.186 g, 1.327 mmol), DCE (Volume: 5 mL, Ratio: 5.00), Methanol (Volume: 1 mL, Ratio: 1.000), butyl-aldehyde **7** (0.400 g, 1.393 mmol) and STAB-H (0.506 g, 2.389 mmol). The reaction was stirred overnight and quenched with 2M NaOH, extracted with DCM, dried with $MgSO_4$, filtered and concentrated to afford **22u** (0.45 g, 1.094 mmol, 82 % yield). To a 20 mL scintillation vial was added **5** (0.254 g, 0.972 mmol), DCE (Volume: 2.430 mL), **22u** (0.4 g, 0.972 mmol) and STAB-H (0.371 g, 1.750 mmol). The reaction was stirred overnight, diluted with DCM, washed with 1m NaOH, dried with $MgSO_4$, filtered and concentrated to a yellow oil. The residue was purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated dissolved with 4 mL DCM followed by the addition of 1 mL TFA and then stirred overnight. The mixture was diluted with DCM and washed with 2M NaOH, dried with $MgSO_4$, filtered and concentrated to a yellow oil. Purified via combiflash (DCM 2 minutes, 10% B(80:20:3, DCM:MeOH:NH_4OH) 5 minutes and 50% B 9 minutes). The fractions were concentrated to afford **20u** (0.201 g, 0.564 mmol, 58 % yield). 70 % over 3 steps.

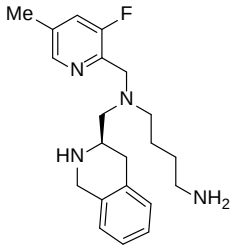
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J*= 2.8 Hz, 1H), 7.15 (dd, *J*= 9.0, 2.7 Hz, 1H), 7.07-6.94 (m, 4H), 3.95 (d, *J*= 15.2 Hz, 1H), 3.88 (d, *J*= 15.2 Hz, 1H), 3.82 (d, *J*= 12.7 Hz, 1H), 3.61 (d, *J*= 12.6 Hz, 1H), 2.84-2.77 (m, 1H), 2.59 (t, *J*= 6.8 Hz, 2H), 2.56-2.50 (m, 3H), 2.46 (dd, *J*= 8.3, 5.3 Hz, 1H), 2.41 (s, 3H), 2.38 (dd, *J*= 16.3, 10.9 Hz, 1H) 1.82 (bs, 2NH), 1.52-1.43 (m,2H), 1.39-1.27 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, C-F, *J*= 259.8 Hz), 153.1 (d, C-F, *J*= 3.9 Hz), 135.2, 134.5 (d, C-F, *J*= 3.9 Hz), 134.2, 133.8 (d, C-F, *J*= 22.4 Hz), 129.0, 126.2, 125.8, 125.4, 124.6 (d, C-F, *J*= 17.7 Hz), 60.2, 59.7 (d, C-F, *J*= 0.8 Hz), 55.0, 51.5, 48.3, 41.8, 33.6, 31.4, 23.9, 18.3 (d, C-F, *J*= 0.9 Hz);

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -130.19 (d, *J*= 9.1 Hz)

HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{30}FN_4$ 357.24490, found 357.244769

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.808 at 254 nM, MS (+) 357.2, MS(+)/2 179.2



Compound 20v: To a 20 mL vial was added (3-fluoro-5-methylpyridin-2-yl)methanamine **S19** (0.09 g, 0.642 mmol), butyl-aldehyde **7** (0.194 g, 0.674 mmol), DCM (Volume: 2.57 mL) and STAB-H (0.245 g, 1.156 mmol). The reaction was allowed to stir overnight. The reaction was diluted with DCM, washed with 2M NaOH, died with $MgSO_4$, filtered and concentrated to afford **22v** as a clear oil which was used without purification. To a 20 mL vial was added **5** (0.088 g, 0.336 mmol), **22v** (0.145 g, 0.352 mmol), DCE (Volume: 0.839 mL) and STAB-H (0.107 g, 0.503 mmol). The reaction was stirred overnight then diluted with DCM, washed with 2M NaOH, dried with Na_2SO_4, filtered and concentrated to a yellow oil. The oil was dissolved in 2mL DCM and 0.5 mL TFA was added and the mixture was stirred overnight. The reaction was diluted with DCM and quenched by the addition of 1M NaOH. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organics were dried with Na_2SO_4, filtered and concentrated to a yellow oil which was purified via silica gel chromatography (A:DCM, B:DCM:MeOH:NH_4OH; 80:20:3. 0%B 3 minutes 10%B 8 minutes 50%B 8 minutes) to afford **20v** (0.037 g, 0.104 mmol, 31 % yield) as a yellow gum. 55% over 3 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s,1H), 7.17 (d, *J*= 10.3 Hz, 1H), 7.08-6.98 (m, 4H), 3.99 (overlapping d, *J*= 15.0 Hz, 2H), 3.91 (dd, *J*= 13.3, 2.0 Hz, 1H), 3.64 (dd, *J*= 13.2, 1.8 Hz, 1H), 3.00-2.93 (m, 1H), 2.66-2.54 (m, 3H), 2.61 (t, *J*= 7.0 Hz, 2H), 2.52-2.42 (m, 2H), 2.32 (s, 3H), 2.09 (bs, 3NH), 1.57-1.45 (m,2H), 1.44-1.31 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1 (d, C-F, *J*= 323.5 Hz), 145.5 (d, C-F, *J*= 5.0 Hz), 144.6 (d, C-F, *J*= 17.4 Hz), 136.0, 134.8, 134.7 (d, C-F, *J*= 5.0 Hz), 129.4, 126.7, 126.2, 125.8, 123.7 (d, C-F, *J*= 23.8 Hz), 59.9, 54.9, 54.5 (d, C-F *J*= 3.8 Hz), 51.5, 48.4, 41.8, 33.5, 31.1, 24.3, 17.6 (d, C-F *J*= 1.3 Hz);

^{19}F NMR (375.8 MHz, $CDCl_3$): δ = -126.33 (d, *J*= 9.6 Hz)

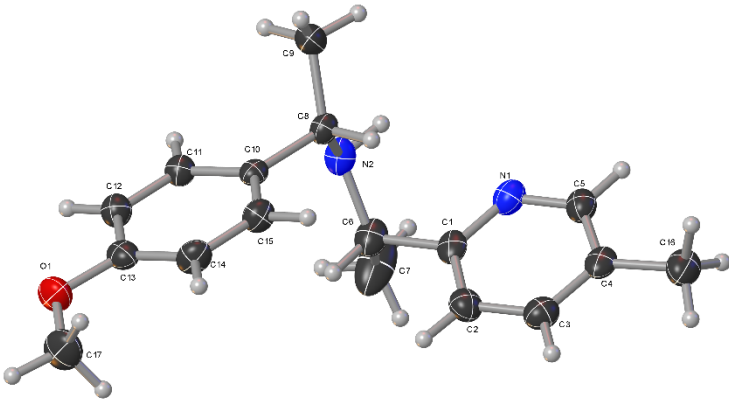
HRMS (ESI) $[M+H]^+$, calcd for $C_{21}H_{29}FN_4$ 357.24490, found 357.24496

LC/MS 75% MeOH in H_2O over 3 minutes, r_t = 0.779 at 254 nM, MS (+) 357.2, MS(+)/2 179.2

RJW-1-103

Submitted by: **Robert Wilson, Liotta Group**
Solved by: **John Bacsa**
Sample ID: **RJW-1-103**

Crystal Data and Experimental



Experimental. Single colourless block-shaped crystals of (**RJW-1-103**) were chosen from the sample as supplied.. A suitable crystal (0.35×0.32×0.22 mm^3) was selected and mounted on a loop with paratone oil on a Saxi-CrysAlisPro-abstract goniometer imported SAXI images diffractometer. The crystal was cooled to T = 100(2) K during data collection. The structure was solved with the XT (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2014/7 of **XL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{17}H_{24}N_2O_3$, M_r = 304.38, orthorhombic, $P2_12_12$ (No. 18), a = 12.490(2) Å, b = 17.074(3) Å, c = 7.8605(11) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1676.3(5) Å^3, T = 100(2) K, Z = 4, Z' = 1, $\mu(CuK_\alpha)$ = 0.669 mm^{-1}, 10859 reflections measured, 2906 unique (R_{int} = 0.0550) which were used in all calculations. The final wR_2 was 0.1621 (all data) and R_1 was 0.0593 (I > 2 σ (I)).

Compound	**RJW-1-103**
Formula	$C_{17}H_{24}N_2O_3$
$D_{calc.}$/ g cm^{-3}	1.206
μ/mm^{-1}	0.669
Formula Weight	304.38
Colour	colourless
Shape	block
Size/mm^3	0.35×0.32×0.22
T/K	100(2)
Crystal System	orthorhombic
Flack Parameter	-0.01(14)
Hooft Parameter	-0.05(14)
Space Group	$P2_12_12$
a/Å	12.490(2)
b/Å	17.074(3)
c/Å	7.8605(11)
α/°	90
β/°	90
γ/°	90
V/Å^3	1676.3(5)
Z	4
Z'	1
Wavelength/Å	1.541840
Radiation type	CuK_α
Θ_{min}/°	4.386
Θ_{max}/°	67.030
Measured Refl.	10859
Independent Refl.	2906
Reflections with I > 2 σ (I)	2789
R_{int}	0.0550
Parameters	213
Restraints	7
Largest Peak	0.304
Deepest Hole	-0.474
GooF	1.056
wR_2 (all data)	0.1621
wR_2	0.1602
R_1 (all data)	0.0613
R_1	0.0593

Structure Quality Indicators

Reflections:	d min (Cu) 0.84	I/σ 19.8	Rint 5.50%	complete at 2θ=134° 97%	
Refinement:	Shift 0.001	Max Peak 0.3	Min Peak -0.5	GooF 1.056	-0.01(14)

A colourless block-shaped crystal with dimensions 0.35×0.32×0.22 mm^3 was mounted on a loop with paratone oil. Data were collected using a Bruker D8 Venture diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100(2) K.

Data were measured using ω and ϕ scans of 1.0° per frame for 1.0 s using CuK$_\alpha$ radiation (fine-focus sealed X-ray tube, 50 kV, 1 mA).The total number of runs and images was based on the strategy calculation from the program CrysAlisPro (Agilent). The maximum resolution that was achieved was Θ = 67.030°.

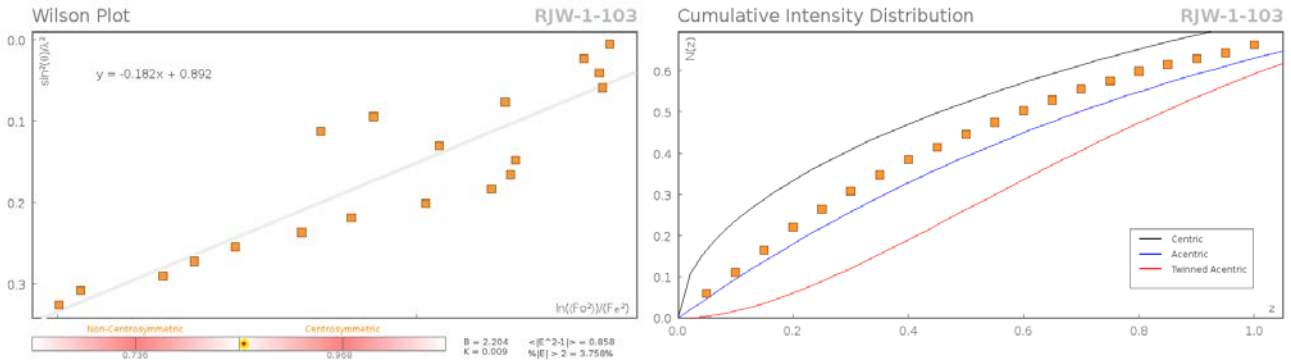
The diffraction patterns were indexed using CrysAlisPro (Agilent) and the unit cells were refined using CrysAlisPro (Agilent) on 6423 reflections, 59 % of the observed reflections. Data reduction, scaling and absorption corrections were performed using CrysAlisPro (Agilent) and CrysAlisPro 1.171.39.9g (Rigaku Oxford Diffraction, 2015)Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. software. The final completeness is 97.50 out to 67.030° in Θ. The absorption coefficient μ of this material is 0.669 at this wavelength (λ = 1.54184) and the minimum and maximum transmissions are 0.83492 and 1.00000.

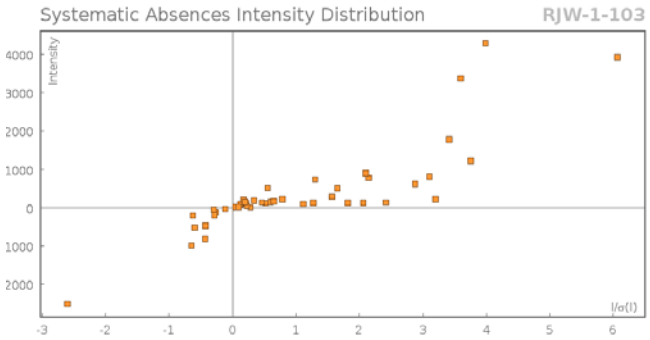
The structure was solved and the space group P2$_1$2$_1$2 (# 18) determined by the XT (Sheldrick, 2015) structure solution program using Intrinsic Phasing and refined by Least Squares using version 2014/7 of **XL** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

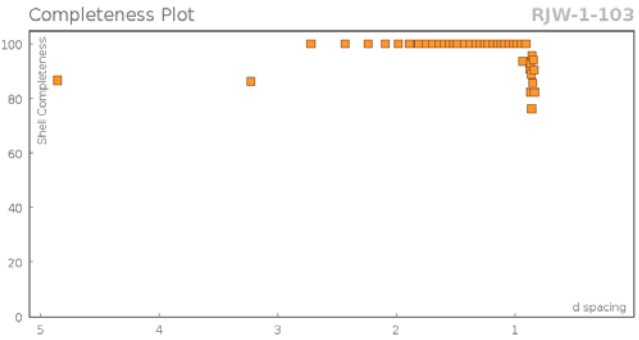
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

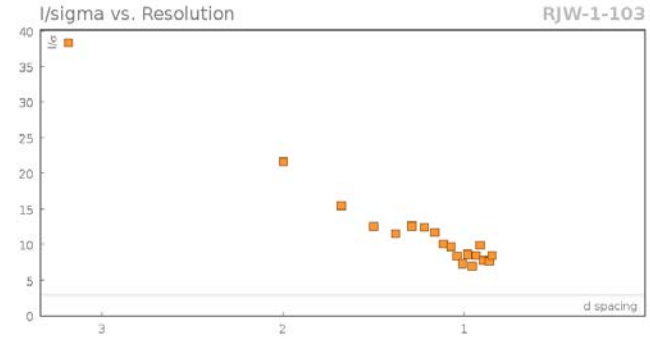
The Flack parameter was refined to -0.01(14). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.05(14). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Data Plots: Diffraction Data

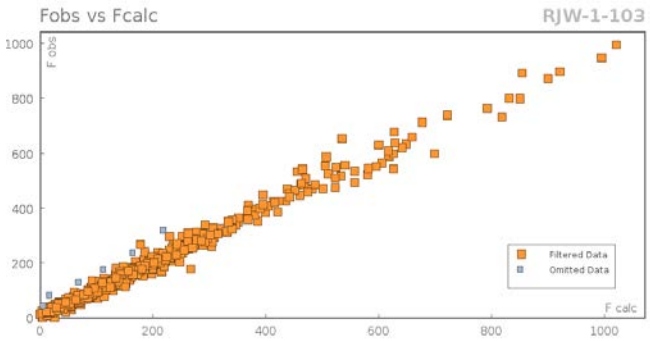


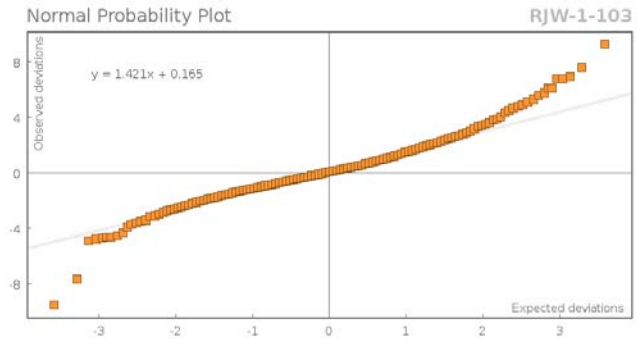






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	10936	Unique reflections	2906
Completeness	0.969	Mean I/σ	19.81
hkl_{max} collected	(14, 18, 9)	hkl_{min} collected	(-13, -20, -8)
hkl_{max} used	(14, 20, 9)	hkl_{min} used	(-14, 0, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	17.07	d_{min} used	0.84
Friedel pairs	2147	Friedel pairs merged	0
Inconsistent equivalents	29	R_{int}	0.055
R_{sigma}	0.0338	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	31
Multiplicity	(3962, 2155, 748, 100, 4)	Maximum multiplicity	10
Removed systematic absences	46	Filtered off (Shel/OMIT)	0

Images of the Crystal on the Diffractometer

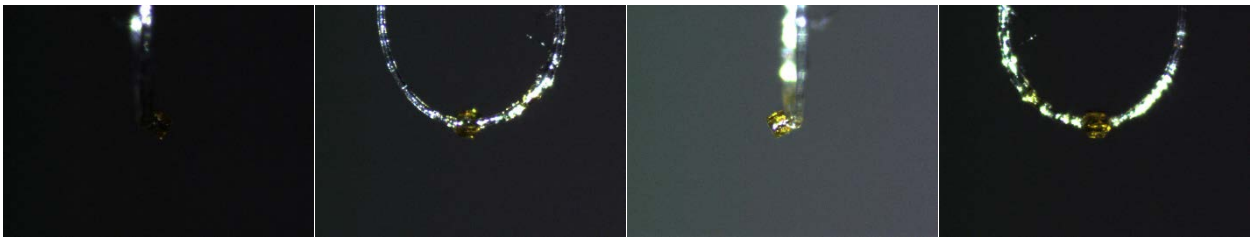


Table 1: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for **RJW-1-103**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1	2463(2)	2313.3(17)	11246(4)	39.8(7)
N1	2047(3)	4544.4(18)	1697(4)	34.1(7)
N2	3427(3)	4311.5(18)	4687(4)	32.8(7)
C1	1651(3)	4350.9(19)	3214(5)	29.2(8)
C10	3239(3)	3120.1(18)	6394(4)	22.9(7)
C11	3769(3)	3365.6(19)	7873(5)	27.3(8)
C14	2153(3)	2272(2)	8175(5)	33.7(8)
C8	3537(3)	3445.2(19)	4678(5)	26.2(7)
C12	3498(3)	3084(2)	9435(5)	30.8(8)
C15	2439(3)	2567(2)	6589(5)	30.9(8)
C5	1468(3)	4364(2)	310(5)	32.8(8)
C4	485(3)	3998(2)	345(5)	31.6(8)
C13	2680(3)	2541(2)	9605(5)	30.3(8)
C3	87(3)	3800(2)	1920(5)	35.1(9)
O1WA	4421(10)	5210(9)	7028(16)	69(3)
C2	680(3)	3971(2)	3379(5)	34.7(8)
C9	4687(3)	3249(3)	4184(5)	40.2(10)
C17	1527(4)	1856(3)	11487(6)	50.4(11)
C6	2309(3)	4572(2)	4771(5)	35.8(9)
C16	-109(3)	3819(3)	-1277(6)	41.6(9)
C7	2274(5)	5468(3)	5014(8)	69.2(17)
O2WA	5840(6)	4803(4)	10461(10)	60.8(13)
O2WB	5995(6)	4595(4)	11762(10)	60.8(13)
O1WB	5226(6)	4937(7)	6972(9)	69(3)

Table 2: Anisotropic Displacement Parameters (×10⁴) **RJW-1-103**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	38.5(14)	46.5(16)	34.6(15)	11.4(12)	5.5(12)	-2.5(12)
N1	35.4(16)	27.7(15)	39.3(19)	1.8(13)	-6.7(14)	4.2(12)
N2	39.0(16)	25.6(14)	33.8(18)	4.2(13)	-5.3(14)	-5.9(13)
C1	39.1(19)	17.5(15)	30.9(19)	-1.6(14)	-5.6(16)	12.0(14)
C10	23.2(15)	18.3(15)	27.1(17)	-3.4(12)	-0.9(13)	3.7(12)
C11	31.1(18)	20.7(15)	30(2)	-0.5(13)	-1.3(14)	0.8(13)
C14	28.3(17)	29.5(18)	43(2)	7.0(16)	-0.8(16)	-7.5(15)
C8	27.7(16)	22.1(15)	28.8(18)	-0.3(13)	-5.0(14)	0.7(13)
C12	35.4(18)	26.5(16)	31(2)	0.8(14)	-2.0(16)	1.0(14)
C15	30.9(17)	26.4(17)	35(2)	-0.8(14)	-4.2(15)	-2.9(13)
C5	38.7(18)	28.8(17)	30.9(19)	-0.3(15)	-3.7(16)	8.7(15)
C4	35.4(18)	23.7(16)	36(2)	-7.0(15)	-4.6(16)	11.6(14)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C13	32.8(18)	26.0(17)	32.2(19)	2.6(15)	3.5(15)	8.3(14)
C3	33.7(19)	30.2(18)	42(2)	-4.2(17)	-1.1(16)	2.8(15)
O1WA	72(6)	67(4)	68(2)	-3(4)	0(3)	-3(4)
C2	40(2)	32.1(19)	32(2)	-3.4(15)	1.4(16)	4.4(15)
C9	33.4(19)	58(3)	29(2)	-0.2(18)	2.2(15)	4.9(18)
C17	49(2)	56(3)	46(3)	22(2)	6(2)	-7(2)
C6	44(2)	23.7(17)	40(2)	-3.6(15)	-8.3(18)	6.5(15)
C16	46(2)	41(2)	39(2)	-9.0(18)	-5.2(18)	8.1(18)
C7	98(4)	27(2)	82(4)	-17(2)	-45(3)	16(2)
O2WA	65(3)	52(3)	65(3)	8(3)	-6(3)	-14(2)
O2WB	65(3)	52(3)	65(3)	8(3)	-6(3)	-14(2)
O1WB	72(6)	67(4)	68(2)	-3(4)	0(3)	-3(4)

Table 3: Bond Lengths in Å for **RJW-1-103**.

Atom	Atom	Length/Å
O1	C13	1.374(5)
O1	C17	1.418(5)
N1	C1	1.333(5)
N1	C5	1.344(5)
N2	C8	1.486(4)
N2	C6	1.467(5)
C1	C2	1.382(6)
C1	C6	1.521(5)
C10	C11	1.402(5)
C10	C8	1.506(5)
C10	C15	1.383(5)
C11	C12	1.361(5)
C14	C15	1.391(6)
C14	C13	1.381(5)
C8	C9	1.525(5)
C12	C13	1.387(5)
C5	C4	1.378(6)
C4	C3	1.377(6)
C4	C16	1.507(6)
C3	C2	1.397(6)
O1WA	O1WA[1]	1.62(2)
C6	C7	1.541(5)
O1WB	O1WB[1]	0.605(14)

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[1]1-X,1-Y,+Z

Table 4: Bond Angles in ° for **RJW-1-103**.

Atom	Atom	Atom	Angle/°
C13	O1	C17	116.3(3)
C1	N1	C5	118.0(3)
C6	N2	C8	113.0(3)
N1	C1	C2	121.7(3)
N1	C1	C6	117.3(3)
C2	C1	C6	121.0(3)
C11	C10	C8	121.1(3)
C15	C10	C11	116.9(3)
C15	C10	C8	122.0(3)

Atom	Atom	Atom	Angle/°
C12	C11	C10	121.7(3)
C13	C14	C15	119.1(3)
N2	C8	C10	109.9(3)
N2	C8	C9	107.9(3)
C10	C8	C9	112.4(3)
C11	C12	C13	120.4(3)
C10	C15	C14	122.1(3)
N1	C5	C4	124.5(4)
C5	C4	C16	120.9(4)

Atom	Atom	Atom	Angle/°
C3	C4	C5	116.9(3)
C3	C4	C16	122.2(3)
O1	C13	C14	125.2(3)
O1	C13	C12	115.2(3)
C14	C13	C12	119.7(3)
C4	C3	C2	119.7(4)
C1	C2	C3	119.1(4)
N2	C6	C1	113.7(3)
N2	C6	C7	109.5(4)
C1	C6	C7	109.3(3)

Table 5: Torsion Angles in ° for **RJW-1-103**.

Atom	Atom	Atom	Atom	Angle/°
N1	C1	C2	C3	-1.4(5)
N1	C1	C6	N2	-51.9(4)
N1	C1	C6	C7	70.8(5)
N1	C5	C4	C3	-0.8(5)
N1	C5	C4	C16	179.9(3)
C1	N1	C5	C4	0.6(5)
C10	C11	C12	C13	0.0(5)
C11	C10	C8	N2	-57.5(4)
C11	C10	C8	C9	62.6(4)
C11	C10	C15	C14	1.0(5)
C11	C12	C13	O1	-178.6(3)
C11	C12	C13	C14	1.4(5)
C8	N2	C6	C1	-64.8(4)
C8	N2	C6	C7	172.6(4)
C8	C10	C11	C12	179.1(3)
C8	C10	C15	C14	-179.3(3)
C15	C10	C11	C12	-1.1(5)
C15	C10	C8	N2	122.8(3)
C15	C10	C8	C9	-117.1(4)
C15	C14	C13	O1	178.5(3)
C15	C14	C13	C12	-1.5(5)
C5	N1	C1	C2	0.5(5)
C5	N1	C1	C6	-179.0(3)
C5	C4	C3	C2	-0.1(5)
C4	C3	C2	C1	1.2(5)
C13	C14	C15	C10	0.3(5)
C2	C1	C6	N2	128.6(4)
C2	C1	C6	C7	-108.7(5)
C17	O1	C13	C14	-9.6(5)
C17	O1	C13	C12	170.4(3)
C6	N2	C8	C10	-70.0(4)
C6	N2	C8	C9	167.3(3)
C6	C1	C2	C3	178.1(3)
C16	C4	C3	C2	179.1(3)

Table 6: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **RJW-1-103**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H11	4332	3738	7783	33
H14	1603	1890	8273	40
H8	3042	3223	3802	31
H12	3872	3261	10415	37
H15	2073	2383	5609	37
H5	1757	4498	-770	39
H3	-589	3547	2013	42
H2A	419	3828	4471	42
H9A	5179	3474	5023	60
H9B	4843	3469	3059	60
H9C	4778	2679	4152	60
H17A	1432	1749	12702	76
H17B	1598	1361	10867	76
H17C	904	2144	11057	76
H6	1970	4324	5789	43
H16A	215	3363	-1830	62
H16B	-69	4272	-2041	62
H16C	-860	3706	-1014	62
H7A	2674	5722	4094	104
H7B	2597	5604	6110	104
H7C	1528	5646	4991	104
H2	3680(30)	4470(20)	3630(80)	60(15)

Table 7: Atomic Occupancies for all atoms that are not fully occupied in **RJW-1-103**.

Atom	Occupancy
O1WA	0.4252
O2WA	0.5145
O2WB	0.4855
O1WB	0.5748

Citations

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