**Supporting Information**

# Design and Optimization of Potent and Orally Bioavailable Tetrahydronaphthalene Raf Inhibitors

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**Supporting Information Contents:**

**Supporting Information Table 1.** Summary of kinase binding data for **26** and **27**.

**Ambit Binding Data: Compound 26** [a]

| Target | % INH @ 1 μM |
|---|---|
| RAF1 | 100 |
| TAOK3 | 100 |
| BRAF | 99.95 |
| DDR1 | 99.8 |
| EPHA8 | 99.7 |
| STK10 | 99.65 |
| PDGFRB | 99.55 |
| MAPK14 | 99.55 |
| EPHA6 | 99.3 |
| EPHB2 | 99.2 |
| PFB0815w | 99.2 |
| ABL2 | 98.6 |
| ABL1 | 97.8 |
| EPHA1 | 97.6 |
| MAP4K4 | 97.4 |
| ZAK | 97.2 |
| FRK | 97.1 |
| KDR | 97 |
| AKT2 | 96.1 |
| EPHB4 | 95.8 |
| EPHA5 | 95.4 |
| RET | 95 |
| CIT | 95 |
| BMX | 94.6 |
| MAPK11 | 94.6 |
| EPHA2 | 94.4 |
| LCK | 94 |
| LYN | 94 |
| TIE1 | 93.8 |
| TNNI3K | 93.6 |
| FLT4 | 92.6 |
| EPHA7 | 92.6 |
| EPHB1 | 91.8 |
| TXK | 91.2 |
| EPHA3 | 90.6 |
| CAMK1 | 90.5 |
| PDGFRA | 90.4 |
| FLT1 | 90.1 |
| TAOK1 | 90 |

| Target | % INH @ 1 μM |
|---|---|
| EPHA4 | 89 |
| TNIK | 89 |
| MINK1 | 89 |
| CSK | 88 |
| RIPK2 | 87 |
| CDC2L6 | 87 |
| CSF1R | 86 |
| CAMK1D | 86 |
| CDK8 | 85 |
| FYN | 82 |
| DDR2 | 82 |
| TAOK2 | 77 |
| EPHB3 | 75 |
| SRPK2 | 74 |
| MAP4K2 | 73 |
| FER | 73 |
| HIPK2 | 71 |
| HCK | 70 |
| FES | 69 |
| CHUK | 69 |
| MAP3K7 | 69 |
| NLK | 68 |
| BLK | 65 |
| TEK | 63 |
| SRC | 61 |
| KIT | 58 |
| ERBB4 | 57 |
| EPHB6 | 57 |
| HIPK3 | 57 |
| MAP2K5 | 57 |
| SRMS | 54 |
| BTK | 52 |
| YES1 | 52 |
| SYK | 50 |
| MAP3K11 | 50 |

## Ambit Binding Data: Compound 27[a]

| Target | % Inh @ 1 μM |
|---|---|
| RAF1 | 100 |
| BRAF | 100 |
| PDGFRB | 100 |
| RET | 100 |
| KIT | 100 |
| DDR1 | 99.9 |
| EPHA8 | 99.9 |
| ABL2 | 99.9 |
| FLT4 | 99.9 |
| TAOK3 | 99.8 |
| CIT | 99.8 |
| TAOK1 | 99.65 |
| EPHA6 | 99.5 |
| EPHA1 | 99.5 |
| MAP4K4 | 99.45 |
| FRK | 99.45 |
| MAP4K2 | 99.45 |
| EPHB2 | 99.35 |
| LCK | 99.35 |
| PDGFRA | 99.3 |
| CSK | 99.25 |
| RIPK2 | 99.15 |
| ABL1 | 99.05 |
| FLT1 | 98.8 |
| EPHA5 | 98.4 |
| BMX | 98.2 |
| CAMK1 | 98.2 |
| HCK | 98 |
| BTK | 98 |
| EPHA2 | 97.8 |
| LYN | 97.6 |
| TNNI3K | 97.6 |
| TXK | 97.6 |
| EPHB4 | 97.5 |
| EPHA7 | 97.4 |
| EPHB1 | 96.9 |

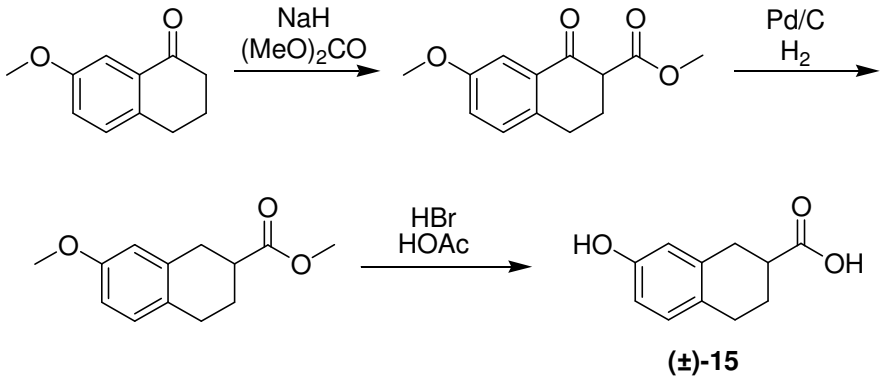
| Target | % Inh @ 1 μM |
|---|---|
| FES | 96.4 |
| FYN | 96.2 |
| BLK | 95.8 |
| ZAK | 95.4 |
| TIE1 | 95.1 |
| EPHA4 | 94.9 |
| DDR2 | 94.2 |
| EGFR | 92.6 |
| EPHA3 | 92.4 |
| TNIK | 91.7 |
| SRMS | 91.4 |
| SRC | 90 |
| CSF1R | 89 |
| FER | 89 |
| ERBB4 | 88 |
| SLK | 86 |
| AKT2 | 84 |
| CAMK1D | 84 |
| NLK | 83 |
| MAP4K5 | 82 |
| TNK1 | 82 |
| FGR | 79 |
| MYO3B | 77 |
| LTK | 74 |
| ROCK1 | 72 |
| MAST1 | 72 |
| SYK | 71 |
| MST4 | 70 |
| EPHB3 | 69 |
| PAK1 | 66 |
| CAMK1G | 64 |
| YSK4 | 64 |
| MAP4K3 | 55 |
| MAP3K2 | 51 |
| MYO3A | 50 |

[a]Compounds **26** and **27** were evaluated in a multi-kinase binding screen, KINOMEscreen™. Developed and marketed by Ambit Biosciences, KINOMEscan™ is a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand (see: http://www.kinomescan.com). **26** was screened against 379 kinases at 1 μM and showed greater than 50% inhibition of binding against 74 kinases which are listed above. **27** was

screened against 262 kinases at 1 μM and showed greater than 50% inhibition against 71 kinases which are listed above.

**Experimental Details:**

**7-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid ((±)-15).**




**(±)-15**

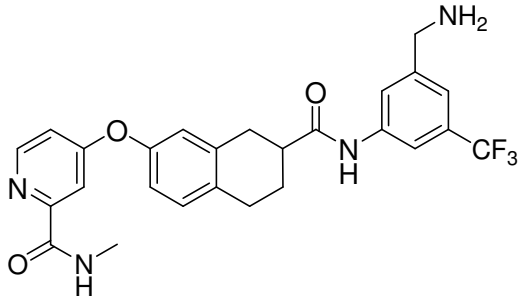
To a suspension of sodium hydride (60% in mineral oil, 9.99 g, 250 mmol) in THF (100 mL) was added dimethyl carbonate (21.0 mL, 249 mmol). The mixture was heated to 65 °C and a solution of 7-methoxy-1-tetralone (20.0 g, 114 mmol) in THF (100 mL) was added. The reaction mixture was allowed to stir vigorously at 65 °C for 2 h. After this time the reaction became very vigorous, and gas was evolved. The heating bath was removed for 10 min then heating continued for an additional 1 h. AcOH (18.0 mL, 317 mmol) was added slowly, followed by water (100 mL). The mixture was extracted with $Et_2O$ (2x) and the organic phases were combined, washed with water and saturated $NaHCO_3$ solution, dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by filtration through a pad of silica eluting with hexane then with 10% EtOAc / hexane to yield methyl 7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate as an oil. (25.2 g, 95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.44 (s, 1H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.7 Hz, 2H), 6.89

(dd, *J* = 8.3, 2.8 Hz, 1H), 3.83 (s, 6H), 3.83 (s, 3H), 3.78 (s, 3H), 3.60 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.04-2.87 (m, 2H), 2.77-2.72 (m, 2H), 2.57-2.52 (m, 2H), 2.52-2.43 (m, 1H), 2.38-2.30 (m, 1H) (1:1 mixture of keto and enol tautomers) LCMS: *m/z* 235.0 $[M+H]^+$, 233.0 $[M-H]^-$(FA).

A slurry of methyl 7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (6.0 g, 26 mmol) and 10% palladium on carbon (100 mg) in AcOH (120 mL), and concentrated sulfuric acid (780 μL) was allowed to stir under 30 psi of hydrogen for 2.5 h. The reaction mixture was diluted with chloroform and filtered through Celite. The filtrate was washed with water (5x), dried over $Na_2SO_4$ and concentrated. The residue was purified by filtration through a pad of silica to give methyl 7-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylate as an oil (4.03 g, 71%). $^1$H NMR (400 MHz, d6-DMSO) δ 6.98-6.93 (m, 1H), 6.68-6.63 (m, 2H), 3.68 (s, 3H), 2.92-2.75 (m, 2H), 2.71-2.56 (m, 3H), 2.09-1.99 (m, 1H), and 1.73-1.62 (m, 1H).

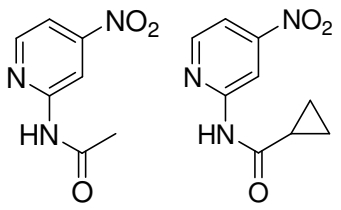
A mixture of methyl 7-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (16.85 g, 76.5 mmol) in acetic acid (28 mL) and HBr (48%, 55 mL) was heated at 100 °C overnight. The resulting red solution was cooled to rt and placed in an ice bath for 2 h. The crystals obtained were isolated by filtration, washed well with water and dried in a vacuum oven overnight to give 7-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**(±)-15**) as a white solid (12.72 g, 87% yield). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 12.22 (s, 1H), 9.01 (s, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.51-6.45 (m, 2H), 2.85-2.69 (m, 2H), 2.67-2.52 (m, 3H), 2.07-1.98 (m, 1H), and 1.73-1.58 (m, 1H).

**4-{[7-({[3-(Aminomethyl)-5-(trifluoromethyl)phenyl]amino}carbonyl)-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-*N*-methylpyridine-2-carboxamide (19)**




4-{[7-({[3-(Aminomethyl)-5-(trifluoromethyl)phenyl]amino}carbonyl)-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-*N*-methylpyridine-2-carboxamide (**19**) was prepared as described in **General procedure B1, amide bond formation** using 7-({2-[(methylamino)carbonyl]pyridine-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and 5-amino-3-cyanobenzotrifluoride followed by the Raney Ni reduction described for **18** (see main text). Compound **19** was isolated as a white solid (47% over the 2 steps). $^1$H NMR (400 MHz,$CD_3OD$, HCl salt) δ 10.36 (s, 1H), 8.61 (d, 1H, J = 6.38 Hz), 8.06 (s, 1H), 7.98 (s, 1H), 7.83 (d, 1H, J = 2.53 Hz), 7.53 (s, 1H), 7.39 (dd, 1H, J = 6.52, 2.53 Hz), 7.30 (d, 1H, J = 8.27 Hz), 7.04 (s, 1H), 7.02-6.98 (m, 1H), 4.19 (s, 2H), 3.16-2.98 (m, 3H), 2.97 (s, 3H), 2.96-2.87 (m, 2H), 2.28-2.18 (m, 1H), and 2.05-1.90 (m, 1H). LCMS: m/z 499.0 $[M+H]^+$(FA) 94% pure (DAD).

***N*-(4-Nitropyridin-2-yl)-acetamide and *N*-(4-nitropyridin-2-yl)-cyclopropane-carboxamide.**



A mixture of 2-chloro-4-nitropyridine-1-oxide (75.00 g, 0.43 mol) and 1-(4-methoxyphenyl)-methanamine (125.0 g, 0.91 mol) in ethanol (1 L) was heated at reflux for 5 h. The reaction was allowed to cool to rt and chilled in a freezer overnight. The resulting cold mixture was filtered. The solid was slurried in MeOH (100 mL) and filtered to give *N*-(4-methoxybenzyl)-4-nitropyridin-2-amine 1-oxide (51.62 g, 40 % yield) as an orange solid. $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.34 (dd, *J* = 6.5, 0.8 Hz, 1H), 8.27 (t, *J* = 6.7, 6.7 Hz, 1H), 7.39-7.34 (m, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.52 (d, *J* = 6.6 Hz, 1H), and 3.70 (s, 1H). LCMS: *m/z* 276.2 $[M+H]^+$, (FA).

A 2-L, 3-neck, round bottom flask fitted with a mechanical stirrer was charged with *N*-(4-methoxybenzyl)-4-nitropyridin-2-amine 1-oxide (38.72 g, 0.14 mol) and chloroform (580 mL). The reaction mixture was cooled to 0 °C and phosphorus trichloride (36.8 mL, 0.42 mol) was added dropwise. The reaction mixture was allowed to warm to rt and to stir overnight. The reaction mixture was filtered. The resulting solid was slurried with hexanes and filtered to afford *N*-(4-methoxybenzyl)-4-nitropyridin-2-amine (39.34 g, 102%) as a yellow solid. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.20 (d, *J* = 5.9 Hz, 1H), 7.33-7.25 (m, 1H), 7.22 (dd, *J* = 5.9, 2.0 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.51 (s, 1H), and 3.77 (s, 1H). LCMS: *m/z* 260.3 $[M+H]^+$(FA).

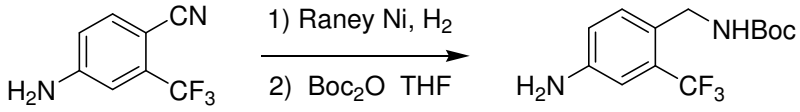
*N*-(4-Methoxybenzyl)-4-nitropyridin-2-amine (27.8 g, 0.11 mol) and anisole (13 mL, 0.12 mol) were dissolved in trifluoroacetic acid (112 mL) and heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt and concentrated. Trituration of the resulting residue with EtOAc and hexanes produced a light yellow solid that was isolated via filtration. The filtrate was allowed to stand overnight and a second crop of crystals

was obtained. The combined batches of solids were dissolved in 1N NaOH (250 mL) and extracted with EtOAc (2 x 250 mL). The combined organic solutions were dried over $MgSO_4$, filtered and concentrated to give 2-amino-4-nitropyridine as an orange solid (10.2 g, 67%). $^1$H NMR (400 MHz, $CD_3OD$) δ 8.15 (dd, *J* = 5.7, 0.6 Hz, 1H), 7.23 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.20 (dd, *J* = 5.7, 2.0 Hz, 1H). LCMS: *m/z* 140.1 $[M+H]^+$,(FA).

To a solution of 2-amino-4-nitropyridine (3.0 g, 0.018 mol) in pyridine (40 mL) was added acetic anhydride (5.2 mL 0.055 mol). The reaction mixture was allowed to stir for 30 h at rt. Water was added to the solution. The resulting solid was collected, washed with water and dried under vacuum to give *N*-(4-nitropyridin-2-yl)acetamide as a brown solid (3.3 g, 99%). $^1$H NMR (400 MHz, $CD_3OD$) δ 8.87 (d, *J* = 1.8 Hz, 1H), 8.58 (d, *J* = 5.5 Hz, 1H), 7.78 (dd, *J* = 5.5, 2.1 Hz, 1H), and 2.20 (s, 3H). LCMS: m/z 182.2 [M+H]+(FA).

*N*-(4-Nitropyridin-2-yl)-cyclopropane-carboxamide was prepared in an analogous fashion using cyclopropane carbonyl chloride (98%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 1.7 Hz, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.46 (s, 1H), 7.73 (dd, *J* = 5.4, 2.1 Hz, 1H), 1.60 (ddd, *J* = 15.7, 7.9, 4.5 Hz, 1H), 1.21 – 1.10 (m, 2H), and 1.01 – 0.90 (m, 2H). LCMS: m/z 208.3 [M+H]+ (FA).

***tert*-Butyl [4-amino-2-(trifluoromethyl)benzyl]carbamate.**

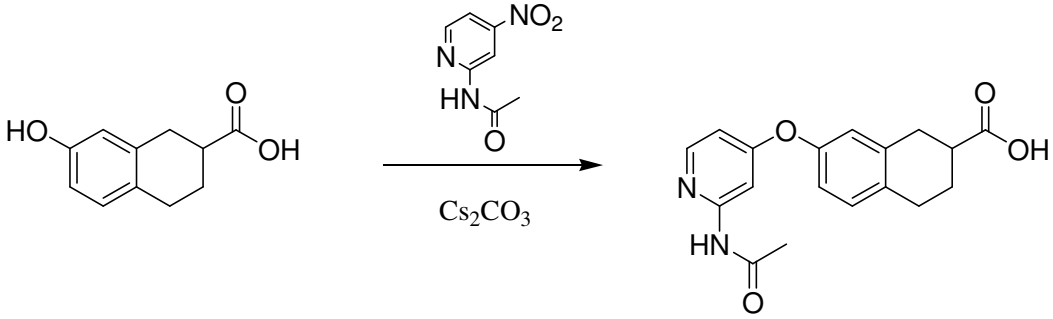



To a solution of 4-amino-2-(trifluoromethyl)benzonitrile (5.0 g, 26.7 mmol) in 7.0 M ammonia in MeOH (20.0 mL) was added Raney Nickel 2800 (50% slurry in water, 320 mg). The mixture was allowed to stir under an atmosphere of hydrogen for 18 h, then at

50 psi for 18 h. The mixture was diluted with DCM and filtered through Celite. The filtrate was evaporated and the residue was purified by column chromatography on silica to give 4-(aminomethyl)-3-(trifluoro-methyl)aniline as an orange solid (3.43 g, 67%). $^1$H NMR (400 MHz, $CD_3OD$) δ 6.89 (s, 1H), 6.83 (s, 1H), 6.82 (s, 1H), and 3.72 (s, 2H). LCMS: *m/z* 187.1 $[M+H]^+$, 185.2 $[M-H]^-$ (FA).

To a solution of 4-(aminomethyl)-3-(trifluoromethyl)aniline (3.42 g, 18.0 mmol) in THF (90 mL) was added BOC anhydride (4.33 g, 19.8 mmol). The reaction was allowed to stir for 18 h. The solvents were evaporated and the residue was purified by column chromatography on silica to give *tert*-butyl [4-amino-2-(trifluoromethyl)benzyl]carbamate as yellow solid. (4.43 g, 85%). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.81 (s, 1H), 6.78 (s, 1H), 4.89 (s, 1H), 4.26 (d, *J* = 5.7 Hz, 1H), and 1.46 (s, 9H). LCMS: *m/z* 291.4 $[M+H]^+$, (FA).

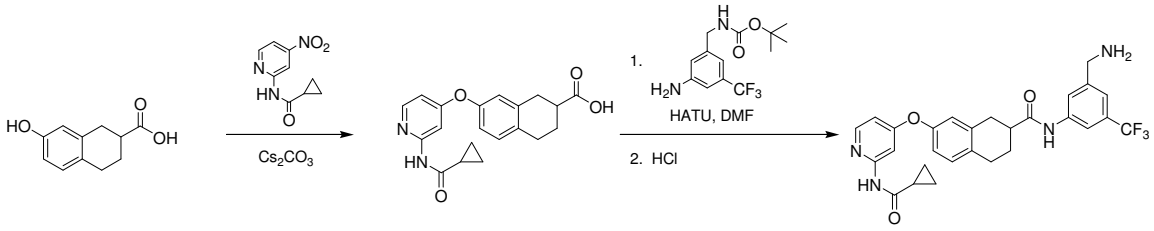
**7-(2-Acetamidopyridin-4-yloxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid**




**7-(2-Acetamidopyridin-4-yloxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid** was prepared as described in **General procedure A1, biaryl ether bond formation** using *N*-(4-nitropyridin-2-yl)acetamide and 7-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**(±)-15**) in 90% yield. $^1$H NMR (400 MHz, $d_6$-DMSO) δ 10.51 (s, 1H), 8.15 (d, *J* = 5.7 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* =

8.3 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.60 (dd, *J* = 5.7, 2.4 Hz, 1H), 2.95 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.89-2.75 (m, 3H), 2.66 (ddt, *J* = 10.0, 10.0, 5.5, 3.2 Hz, 1H), 2.11 (ddd, *J* = 12.3, 8.1, 4.1 Hz, 1H), 2.04 (s, 1H), and 1.80-1.67 (m, 1H).

***N*-[3-(Aminomethyl)-5-(trifluoromethyl)phenyl]-7-({2-[(cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxamide (6).**



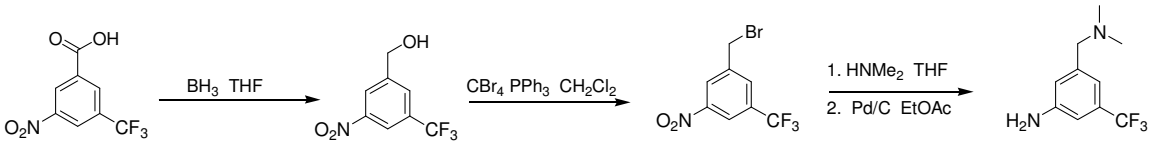

*N*-(4-Nitropyridin-2-yl)-cyclopropanecarboxamide (2.75 g, 13.3 mmol) and 7-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**(±)-15**), 2.55 g, 13.3 mmol) were combined as described in **General procedure A1, biaryl ether bond formation** to provide 7-({2-[(cyclopropylcarbonyl)-amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (4.08 g, 87.2 %) as a beige solid. $^1$H NMR (400 MHz, $d_6$-DMSO) δ 11.27 (s, 1H), 8.19 (d, *J* = 6.1 Hz, 1H), 7.42 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.92 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.76 (dd, *J* = 5.9, 2.1 Hz, 1H), 3.01-2.75 (m, 4H), 2.71-2.61 (m, 1H), 2.15-2.05 (m, 1H), 2.00-1.87 (m, 1H), 1.81-1.64 (m, 1H), and 0.86-0.77 (m, 4H). LCMS: *m/z* 353.2 $[M+H]^+$, 351.3 $[M-H]^-$ (FA).

7-({2-[(Cyclopropylcarbonyl)-amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and *tert*-butyl [4-amino-2-(trifluoromethyl)benzyl]carbamate were combined as described in **General procedures B2 (amide bond formation)** and **C (*tert*-butyl carbamate deprotection)** to give **6** as the HCl salt (51% yield over both steps). $^1$H

NMR (400 MHz, $d_6$-DMSO) δ 11.66 (s, 1H), 10.78 (s, 1H), 8.44 (s, 1H), 8.22 (d, *J* = 6.3 Hz, 1H), 8.07 (s, 1H), 8.03 (s, 1H), 7.60 (s, 1H), 7.34 (s, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.86 (dd, *J* = 6.3, 2.4 Hz, 1H), 4.08 (q, *J* = 5.6, 5.6, 5.3 Hz, 2H), 3.00-2.77 (m, 5H), 2.18-2.06 (m, 1H), 2.01-1.90 (m, 1H), 1.88-1.72 (m, 1H), and 0.93-0.76 (m, 4H).

**6** was separated into 2 enantiomers by chiral HPLC using the following conditions: Chirobiotic T 250 x 21.2 mm column eluting with MeOH / 0.1% FA (pH4), flow rate 10mL / min. Peak 1 RT 34.5 min (98.6% ee) ((2*S*)-*N*-[3-(aminomethyl)-5-(trifluoromethyl)phenyl]-7-({2-[(cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxamide, **20**), peak 2 RT 38.9 min (97.6% ee) ((2*R*)-*N*-[3-(aminomethyl)-5-(trifluoromethyl)phenyl]-7-({2-[(cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxamide, **21**).[1]

**3-[(Dimethylamino)methyl]-5-(trifluoromethyl)aniline.**




3-Nitro-5-(trifluoromethyl)benzoic acid (25.3 g, 108 mmol) was dissolved in THF (300 mL), and this solution was cooled to 0 °C. A solution of borane in THF (1.00 M, 215 mL, 215 mmol) was added dropwise. After 3 h at 0 °C, the reaction mixture was allowed to warm to rt, stirred overnight and then quenched by the slow addition of saturated $NaHCO_3$ solution. EtOAc was added and the phases were separated. The aqueous phase was extracted with EtOAc, and combined organic phases were washed

with water and brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give [3-nitro-5-(trifluoromethyl)phenyl]methanol as a yellow oil (27 g, 95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.39 (s, 1H), 7.98 (s, 1H), 4.90 (s, 2H), 2.44 (s, 1H).

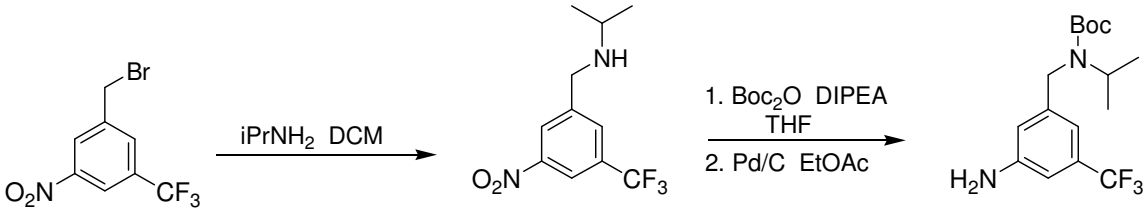
A solution of [3-nitro-5-(trifluoromethyl)phenyl]methanol (13.3 g, 60.1 mmol) in DCM (200 mL) was cooled to 0 °C and $PPh_3$ (18.9 g, 72.2 mmol) and $CBr_4$ (21.9 g, 66.2 mmol) were added.[2] The reaction mixture was stirred at rt overnight. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (elution with 0-20% EtOAc in hexane) to give 1-(bromomethyl)-3-nitro-5-(trifluoromethyl)benzene as a pale yellow oil (12.7 g, 76%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 4.59 (s, 2H).

1-(Bromomethyl)-3-nitro-5-(trifluoromethyl)benzene (50.6 g, 160 mmol) was dissolved in THF (300 mL) and a solution of dimethylamine in THF ( 2.00 M, 802 mL, 1,600 mmol) was added dropwise. A white/yellow precipitate formed. The reaction mixture was stirred at rt for 2 days, concentrated *in vacuo* and suspended in EtOAc (800 mL). This suspension was washed with water; the aqueous phase was separated and extracted with EtOAc. The combined organic phases were washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated to give *N,N*-dimethyl-1-[3-nitro-5-(trifluoromethyl)phenyl]methanamine as a yellow oil (44.6 g, 100%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 3.57 (s, 2H), and 2.27 (s, 6H).

A solution of *N,N*-dimethyl-1-[3-nitro-5-(trifluoromethyl)phenyl]methanamine (20.54 g, 82.76 mmol) in EtOAc (400 mL) was degassed and then placed under an atmosphere of nitrogen gas. Pd (10% on carbon, 2.00 g) was added and the reaction mixture was placed under an atmosphere of hydrogen. The reaction mixture was stirred at rt for 24 h,

and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and purified by column chromatography ($SiO_2$, elution with 5-10% MeOH in DCM) to give 3-[(dimethylamino)methyl]-5-(trifluoromethyl)aniline (17.55 g, 92% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 3.53 (s, 1H), and 2.37 (s, 1H).

***tert*-Butyl [3-amino-5-(trifluoromethyl)benzyl]isopropylcarbamate.**

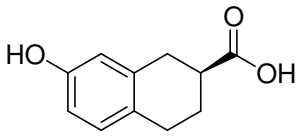



A solution of 2-propanamine (12.8 mL, 150 mmol) in DCM (170 mL) was cooled to 0 °C. A solution of 1-(bromomethyl)-3-nitro-5-(trifluoromethyl)benzene (14.22 g, 50.1 mmol) in DCM (100 mL) was added dropwise to the cooled solution over 70 minutes. The solution was allowed to warm to rt and then stirred overnight. Additional 2-propanamine (5 mL, 58.6 mmol) was added as reaction was not complete. The mixture was stirred for another 24 h, and then poured into water (100 mL). DCM (200 mL) was added and the 2 phases were separated. The organic phase was washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography ($SiO_2$, elution with 5-10% MeOH in DCM) provided *N*-[3-nitro-5-(trifluoromethyl)benzyl]propan-2-amine (11.58 g, 86%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.36 (s, 1H), 7.98 (s, 1H), 3.96 (s, 2H), 2.87 (septet, $J$ = 6.3 Hz, 1H), and 1.12 (d, $J$ = 6.3 Hz, 6H).

A solution of *N*-[3-nitro-5-(trifluoromethyl)benzyl]propan-2-amine (11.10 g, 42.33 mmol) and DIPEA (14.7 mL, 84.6 mmol) in THF (170 mL) was cooled in an ice-water bath. A solution of $(Boc)_2O$ (10.2 g, 46.6 mmol) in THF (50 mL) was added dropwise to the cooled reaction mixture. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The resulting mixture was washed with water, aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give *tert*-butyl isopropyl[3-nitro-5-(trifluoromethyl)benzyl]carbamate (17.32 g, 100% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.30 (s, 1H), 7.83 (s, 1H), 4.64-4.32 (m, 3H), 1.64-1.29 (m, 9H), and 1.13 (d, *J* = 6.8 Hz, 6H).

The reduction of *tert*-butyl isopropyl[3-nitro-5-(trifluoromethyl)benzyl]carbamate to *tert*-butyl [3-amino-5-(trifluoromethyl)benzyl]isopropylcarbamate was accomplished with Pd and hydrogen as described in the synthesis of 3-[(dimethylamino)methyl]-5-(trifluoromethyl)aniline. Purification by column chromatography ($SiO_2$, elution with 20% EtOAc in hexane) provided t*ert*-butyl [3-amino-5-(trifluoromethyl)benzyl]isopropylcarbamate as a white solid (12.79 g, 83%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 6.67 (s, 1H), 6.65 (s, 1H), 6.61 (s, 1H), 5.54 (s, 2H), 4.36-4.08 (m, 3H), 1.52-1.17 (m, 9H), and 1.04 (d, *J* = 6.8 Hz, 6H).

**(2*S*)-7-Hydroxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ((*S*)-15).**




**(*S*)-15**

To a stirred solution of 3-(3-methoxyphenyl) propionic acid (20 g, 111 mmol) in toluene (69.2 mL) was added thionyl chloride (14.4 mL) dropwise at rt. The resulting mixture was heated to reflux (60 °C) for 2 h, after which excess thionyl chloride and the solvent were removed under reduced pressure. Meanwhile, a solution of (*S*)-4-benzyl-2-oxazolidinone (16.4 g, 92 mmol) in anhydrous THF (232 mL) at –78 °C was treated with a solution of *n*-butyl lithium (63.2 mL, 1.6 M in hexanes), dropwise. This mixture was stirred for 1 h at –78 °C and then the acid chloride was added as a solution in THF (6 mL). This mixture was maintained at –78 °C for 3 h. A saturated aqueous solution of $NH_4Cl$ was added and the mixture was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The yellow residue obtained was triturated a twice with hexane to give a white powder which was dried under high vacuum to give (*S*)-4-benzyl-3-(3-phenyl-propionyl)-oxazolidin-2-one (28.2 g, 89%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.33–7.17 (m, 4 H), 7.16–7.12 (m, 2 H), 6.84–6.81 (m, 3 H), 4.64 (ddd, *J* = 10.8, 7.7, 2.9 Hz, 1 H), 4.30 (t, *J* = 8.5, 8.5 Hz, 1 H), 4.17 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.72 (s, 3 H), 3.17 (ddd, *J* = 16.1, 8.9, 7.1 Hz, 1 H), 3.05 (ddd, *J* = 14.8, 8.4, 6.5 Hz, 1 H), and 2.98 (dd, *J* = 13.5, 3.2 Hz, 1 H).

To a stirred solution of (*S*)-4-benzyl-3-(3-phenyl-propionyl)-oxazolidin-2-one (5.2 g, 15 mmol) in anhydrous THF (27.5 mL) cooled to –78 °C was added NaHMDS (1 M in THF, 19.4 mL, 19.4 mmol) dropwise over a period of 15 min. The resulting mixture was stirred for 1 h following which *tert*-butyl bromoacetate (2.9 mL) was added dropwise. The reaction mixture was stirred for another 4 h at –78 °C (Note: After about an hour of adding the bromide, the reaction mixture becomes very viscous and strong stirring is necessary in order to drive the reaction to completion). Saturated $NH_4Cl$ solution was

added and the resulting mixture was extracted with EtOAc. The combined organic phases were washed with water and brine, dried ($Na_2SO_4$), filtered and concentrated. The semi-solid residue was triturated several times with hexane so as to rid it of the excess bromide. The white solid thus obtained was dried to yield 3-benzyl-4-((*S*)-4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxo-butyric acid *tert*-butyl ester (5.5 g, 79 %). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.37–7.12 (m, 6 H), 6.83–6.75 (m, 3 H), 4.64–4.51 (m, 1 H), 4.28–4.18 (m, 2 H), 4.14 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.71 (s, 3 H), 3.04–2.80 (m, 3 H), 2.68 (dd, *J* = 16.8, 10.9 Hz, 1 H), 2.55–2.50 (m, 1 H), 2.24 (dd, *J* = 16.8, 3.9 Hz, 1 H), and 1.35 (s, 9 H).

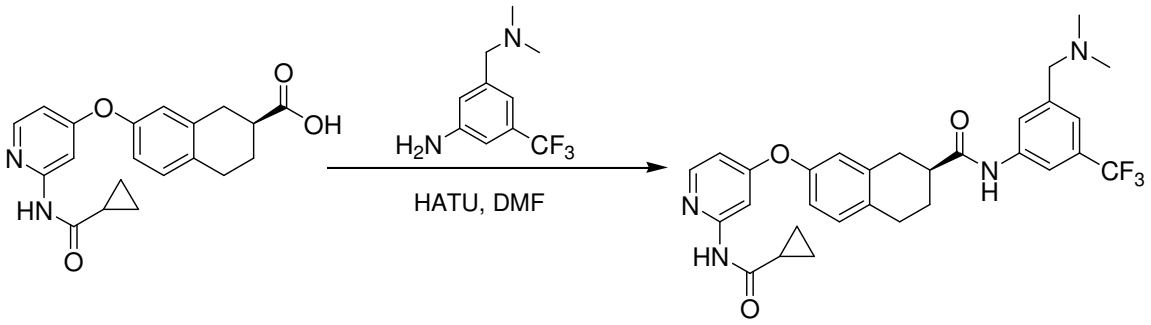
To a solution of 3-benzyl-4-((*S*)-4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxo-butyric acid *tert*-butyl ester (35 g, 77 mmol) in benzene (42 mL) was added triflic acid (21 mL, 238 mmol). The reaction mixture was heated at reflux overnight and then concentrated under reduced pressure. THF (140 mL) and water (35 mL) were added. The mixture was cooled to 0 °C and hydrogen peroxide (30%, 35 mL) and lithium hydroxide (20 g) were added (the reaction mixture pH 10). The reaction mixture was stirred for 1 h and then an excess of sodium sulfite solution (10% w/v) was added. The mixture was allowed to warm to rt and a saturated solution of $NaHCO_3$ (150 mL) was added. This was then washed with DCM and the aqueous phase was acidified with HCl (pH 2-3). The resulting off-white precipitate was isolated by filtration, washed with cold water and dried to give (2*S*)-7-methoxy-4-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (12 g, 70 %). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 12.51 (s, 1 H), 7.79 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 2.3 Hz, 1 H), 6.89 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.82 (s, 1 H), 3.24–3.04 (m, 3 H), and 2.73–2.66 (m, 2 H).

(2*S*)-7-methoxy-4-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (18 g, 81 mmol), acetic acid (460 mL) and sulfuric acid (0.28 mL) were added to a Parr hydrogenation vessel. Pd/C (5.04 g, 10 wt %, wet) was added. The vessel was placed in an autoclave set at 80 °C and was heated under 20 psi of hydrogen gas for 2 h. The reaction mixture was passed though a Celite bed. The filtrate was extracted twice with DCM. The organic phases were dried ($Na_2SO_4$), filtered and concentrated. The solid residue obtained was triturated with diethyl ether and dried to yield (2*S*)-7-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (11 g, 65 %). This material was determined to be 96% ee by HPLC (*ADRH* 4.6 x 150 mm column eluting with 70% MeOH / 30% [0.1% FA in 99% $H_2O$/1%$CH_3CN$], flow rate 0.25 mL / min. Peak 1 RT 45.1 min (2*R*)-7- methoxy -1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid, peak 2 RT 62.2 min (2*S*)-7- methoxy -1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid). Optical rotation: $[\alpha]_D = -42.2^o$ (c = 1.0, MeOH).[3] $^1$H NMR (400 MHz, $d_6$-DMSO) δ 12.22 (s, 1 H), 6.95 (d, *J* = 9.2 Hz, 1 H), 6.69–6.63 (m, 2 H), 3.68 (s, 3 H), 2.88 (dd, *J* = 16.5, 5.7 Hz, 1 H), 2.80 (dd, *J* = 16.5, 9.7 Hz, 1 H), 2.71–2.55 (m, 3 H), 2.04 (ddd, *J* = 12.9, 8.3, 4.5 Hz, 1 H), and 1.68 (dtd, *J* = 12.8, 10.1, 9.9, 6.8 Hz, 1 H).

A solution of (2*S*)-7-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (31 g, 0.14 mol) in DCM (300 mL) was cooled in a dry ice/acetone bath under argon. A solution of boron tribromide in DCM (1.00 M, 280 mL, 0.28 mol) was added over 4 h. Upon completing addition, the mixture was stirred at -78 °C for 10 min then warmed to 0 °C and stirred 2 h. The mixture was cooled to – 50 °C in a dry ice/methanol bath and ice-cold water (15 mL) was added. The temperature was allowed to warm slowly to -10 °C and the cooling bath was replaced with an ice-water bath. Saturated aqueous sodium

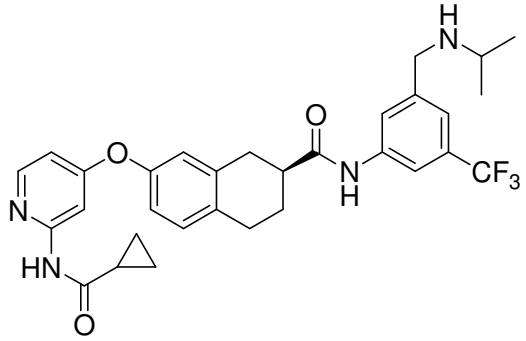
bicarbonate solution (100 mL) was added. Additional solid sodium bicarbonate was added to adjust pH to 9. The phases were separated and the aqueous phase washed twice with DCM. The pH of the aqueous phase was adjusted to 2 with concentrated HCl. The aqueous phase was then extracted with ether three times. The organic extracts were combined, washed with 1M HCl and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was suspended in a small amount of ether and filtered. The solid collected was dried *in vacuo* to afford the desired product as a white solid. The filtrate was partially concentrated and purified by silica gel chromatography (60% ether in hexanes) to afford additional product. The total combined yield of (2*S*)-7-hydroxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid was 20.3 g (74%). This material was determined to be 96% ee by HPLC (ADRH 4.6 x 150 mm column eluting with 60% MeOH / 40% [0.1% FA in 99% $H_2O$/1%$CH_3CN$], flow rate 0.25 mL / min. Peak 1 RT 25.5 min (2*R*)-7-hydroxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid, peak 2 RT 31.5 min (2*S*)-7-hydroxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid). Optical rotation: $[\alpha]_D$ = -4.4 (c = 1, MeOH). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 12.22 (s, 1 H), 9.01 (s, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 6.51–645 (m, 2 H), 2.81 (dd, *J* = 16.8, 5.9 Hz, 1 H), 2.74 (ddd, *J* = 16.4, 9.8 Hz, 1 H), 2.66–2.52 (m, 3 H), 2.03 (ddd, *J* = 12.4, 7.9, 4.6 Hz, 1 H), and 1.65 (dtd, *J* = 12.8, 9.8, 9.7, 6.9 Hz, 1 H).

**(2*S*)-7-({2-[(Cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-*N*-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydronaphthalene-2-carboxamide (22).**




(*S*)-7-({2-[(Cyclopropylcarbonyl)-amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and 3-[(dimethylamino)methyl]-5-(trifluoromethyl)aniline were combined as described in **General Procedures B2 (amide bond formation)** and **D (HCl salt formation)** to give the HCl salt of **22** (66% yield over both steps). $^1$H NMR (400 MHz, $d_6$-DMSO): δ 10.80 (s, 1H), 10.56 (s, 1H), 8.22 (d, *J* = *6.3* Hz, 1H), 8.11-8.09 (m, 2H), 7.70 (s, 1H), 7.33 (s, 1H), 7.24 (d, *J* = *8.3* Hz, 1H), 7.02-6.96 (m, 2H), 6.88-6.84 (m, 1H), 4.34 (d, *J* = *5.1* Hz, 2H), 2.97-2.84 (m, 5H), 2.73-2.68 (m, 6H), 2.16-2.09 (m, 1H), 1.99-1.91 (m, 1H), 1.86-1.73 (m, 1H) and 0.91-0.80 (m, 4H).

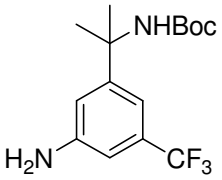
**7-({2-[(Cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-*N*-[3-[(isopropylamino)methyl]-5-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydronaphthalene-2-carboxamide (23)**.



(*S*)-7-({2-[(Cyclopropylcarbonyl)-amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and *tert*-butyl [3-amino-5-

(trifluoromethyl)benzyl]isopropylcarbamate were combined as described in **General procedure B2, amide bond formation** and the Boc group was removed as described in **General Procedure C, *tert*-butyl carbamate deprotection** to give **23** as the HCl salt (34% yield over both steps). $^1$H NMR (400 MHz, DMSO) δ 11.53 (s, 1H), 10.74 (s, 1H), 9.08 (s, 2H), 8.22 (d, J = 6.3 Hz, 1H), 8.11 (s, 1H), 8.06 (s, 1H), 7.69 (s, 1H), 7.37 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.96 (dd, J = 8.3, 2.5 Hz, 1H), 6.84 (dd, J = 6.2, 2.1 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.38 – 3.27 (m, 1H), 3.00 – 2.77 (m, 5H), 2.12 (d, J = 13.5 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.87 – 1.74 (m, 1H), 1.29 (d, J = 6.5 Hz, 6H), and 0.84 (dt, J = 7.8, 5.5 Hz, 4H). LCMS: *m/z* 597.4 $[M+H]^+$, 595.5 $[M-H]^-$ (FA).

***tert*-Butyl {2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-yl}carbamate**




A solution of 3-bromo-5-(trifluoromethyl)aniline (5.89 mL, 0.0417 mol), hexane-2,5-dione (5.03 mL, 0.0429 mol), p-toluenesulfonic acid monohydrate (160 mg, 0.00083 mol) in toluene (200 mL) was heated at reflux under Dean Stark conditions to remove the water for 2.5 h. The reaction mixture was cooled to rt and EtOAc was added. The mixture was washed with 1N HCl, a saturated $NaHCO_3$ solution and brine, dried ($Na_2SO_4$), filtered and concentrated. Purification by column chromatography ($SiO_2$, elution with 2% EtOAc in hexane) provided 1-[3-bromo-5-(trifluoromethyl)phenyl]-2,5-dimethyl-1H-pyrrole as a brown oil (12.39 g, 93%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 5.92 (s, 2H), 2.05 (s, 6H).

A solution of 1-[3-bromo-5-(trifluoromethyl)phenyl]-2,5-dimethyl-1*H*-pyrrole (50.3 g, 0.158 mol) in THF (600 mL) was cooled to -78 $^{o}$C. A solution of *n*-BuLi (2.5 M in hexane, 75.9 mL, 0.190 mol) was added dropwise to the cooled aryl bromide solution over 30 minutes and the resulting reaction mixture was stirred at -78 $^{o}$C for 30 minutes. Acetone (15.1 mL, 0.206 mol) was added dropwise and the solution was stirred at -78 $^{o}$C for 1 h. The reaction mixture was warmed to rt and a saturated solution of $NH_4Cl$ in water was added. The mixture was extracted with EtOAc twice, the combined organics were washed with brine, dried ($Na_2SO_4$), filtered and concentrated to give 2-[3-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(trifluoromethyl)phenyl]propan-2-ol as a brown oil (56 g, 80% pure by HNMR, 95% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.52 (s, 1H), 7.38 (s, 1H), 5.93 (s, 2H), 2.04 (s, 7H), 1.62 (s, 5H).

A solution of crude 2-[3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-(trifluoromethyl)phenyl]propan-2-ol (2.29 g, 7.70 mmol) in ethanol (75 mL) and water (41 mL) was treated with $NH_2OH{\cdot}HCl$ (16.06 g, 231 mmol) and KOH (8.64 g, 154 mmol) and heated at 110 $^{o}$C overnight. The mixture was cooled to rt and the solvents were removed under reduced pressure. The resulting residue was dissolved in water and extracted twice with EtOAc. The combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The resulting residue was triturated with $Et_2O$ and filtered. The filtrate was concentrated to give 2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-ol as an oil (1.70 g, ~90% pure, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.58 (s, 1H), 7.44 (s, 1H), 5.92 (s, 2H), 2.05 (s, 6H).

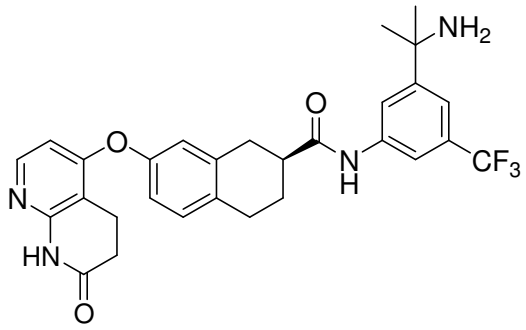
A solution of 2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-ol (4.20 g, 19.2 mmol) in acetonitrile (230 mL) was carefully treated with concentrated sulfuric acid (4.08 mL, 76.6

mmol). The reaction mixture was stirred at rt for 3 days. Water was added to the reaction mixture which was then carefully treated with saturated $NaHCO_3$ solution until a pH of 8 was achieved. The mixture was extracted with EtOAc twice and the combined organics were washed with brine, dried ($Na_2SO_4$), filtered and concentrated. The residue was triturated with DCM to afford *N*-{2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-yl}acetamide as an off-white solid (3.18 g, 64%). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.91 (s, 1H), 6.80 (s, 1H), 5.83 (s, 1H), 3.49 (s, 1H), 1.97 (s, 3H), 1.65 (s, 6H).

A mixture of *N*-{2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-yl}acetamide (3.16 g, 12.1 mmol), KOH (6.81 g, 121.4 mmol) and 1,2-ethanediol (13 mL) was heated at 160 $^o$C for 2 days. The mixuture was then cooled to rt and a 10% NaCl solution in water (200 mL) was added. The resulting mixture was extracted twice with $Et_2O$, and the combined organics were washed with brine and concentrated to give 3-(2-aminopropan-2-yl)-5-(trifluoromethyl)aniline as a brown oil (2.84 g, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 2H), 8.49 (s, 1H), 3.15 (s, 6H).

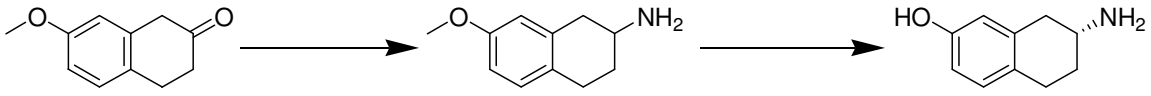
To a solution of 3-(2-aminopropan-2-yl)-5-(trifluoromethyl)aniline (1.03 g, 4.01 mmol) in DCM (20 mL) at 0 $^o$C was added a solution of $(Boc)_2O$ (1.05 g, 4.81 mmol) in DCM (10 mL). The reaction mixture was stirred at 0 $^o$C for 10 minutes and then allowed to warm to rt. After 2 days, the mixture was concentrated. Purification by column chromatography ($SiO_2$, elution with 0-30% EtOAc in hexane) provided *tert*-butyl {2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-yl}carbamate as a pink solid (1.11 g, 83%). $^1$H NMR (400 MHz, DMSO) δ 7.23 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.65 (s, 1H), 5.45 (s, 2H), 1.44 (s, 6H), 1.33 (broad s, 9H).

**(2S)-*N*-[3-(2-aminopropan-2-yl)-5-(trifluoromethyl)phenyl]-7-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)oxy]-1,2,3,4-tetrahydronaphthalene-2-carboxamide (24)**.




(2*S*)-7-[(7-Oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)oxy]-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and *tert*-butyl {2-[3-amino-5-(trifluoromethyl)phenyl]propan-2-yl}carbamate were combined as described in **General procedure B2, amide bond formation** and the Boc group was removed as described in **General Procedure C, *tert*-butyl carbamate deprotection** to give **24** as the HCl salt (36% yield over both steps). $^{1}$H NMR (400 MHz, DMSO) δ 10.67 (d, J = 30.9 Hz, 2H), 8.72 (s, 3H), 8.08 (d, J = 9.9 Hz, 2H), 7.99 (d, J = 6.0 Hz, 1H), 7.67 (s, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.91 (dd, J = 12.1, 3.9 Hz, 2H), 6.38 – 6.21 (m, 1H), 2.89 (ddd, J = 39.2, 13.4, 7.7 Hz, 7H), 2.54 (t, J = 7.7 Hz, 2H), 2.12 (d, J = 11.8 Hz, 1H), 1.88 – 1.71 (m, 1H), 1.64 (s, 6H). LCMS: m/z 539 [M+H]+, (FA).

**(7*R*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide (17).**




**16** **17**

7-Methoxy-2-tetralone (18.37 g, 104 mmol) was dissolved in DCM (400 mL) and benzylamine (11.4 mL, 104 mmol) was then added to the solution. After stirring for 15 min, sodium triacetoxyborohydride (30.9 g, 146 mmol) and AcOH (5.9 mL, 100 mmol) were added to the dark mixture. The reaction mixture was allowed to stir overnight (15 h) at rt under nitrogen. The red/brown reaction mixture was diluted with DCM (400 mL) and extracted with 1M sodium hydroxide solution (4 x 200 mL). The aqueous phases were combined and extracted with DCM (150 mL). The organic phases were combined and washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford *N*-benzyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine[4] as a brown oil (28.0 g, 100%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.02 (d, $J$ = 8.3 Hz, 1H), 6.75-6.63 (m, 2H), 3.74 (s, 3H), 3.57-3.46 (m, 1H), 3.17-3.09 (m, 1H), 2.91-2.76 (m, 3H), 2.24-2.13 (m, 1H) and 1.86-1.73 (m, 1H). LCMS: *m/z* 268 $[M+H]^+$, (AA).

*N*-Benzyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (28.0 g, 105 mmol) was dissolved in reagent ethanol (400 mL). AcOH (92 mL, 1600 mmol) was added. The dark solution was degassed under reduced pressure and backfilled with nitrogen. Palladium hydroxide (7.0 g, 20% on carbon) was added. Hydrogen gas was bubbled through the reaction for 5 minutes, then the reaction was placed under an atmosphere of hydrogen (balloon) and stirred at rt for 24 h. The reaction mixture was filtered through a Celite pad, which was subsequently washed thoroughly. The filtrate was concentrated under reduced pressure and further dried *in vacuo*. The resulting dark oil was dissolved in ether and the solution acidified by the addition of 2.0 M HCl in ether (100 mL) added in portions by pipette. A gummy precipitate formed on acidification. Thorough sonication of the gum provided 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride as a

white to light tan silty precipitate which was collected by filtration and dried *in vacuo* (22.4 g, 92 %). $^1$H NMR (300 MHz, $d_6$-DMSO) δ 6.98 (s, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 8.28 (d, *J* = 0.8 Hz, 1H), 3.69 (d, *J* = 3.4 Hz, 1H), 3.49-3.30 (m, 1H), 3.12-2.96 (m, 1H), 2.76 (dd, *J* = 3.7, 2.4 Hz, 1H), 2.19-2.01 (m, 1H), and 1.83-1.59 (m, 1H). LCMS: *m/z* 178 $[M+H]^+$, (AA).

7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride (21.7 g, 108.7 mmol) was partitioned between aqueous 1M NaOH (200 mL, 200 mmol) and ethyl acetate (200 mL). The aqueous phase was extracted with ethyl acetate (3 x 200 mL). The extracts were combined, washed with brine, dried over sodium sulfate, filtered and concentrated to afford 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine as a brown oil (17.7 g, 92%).

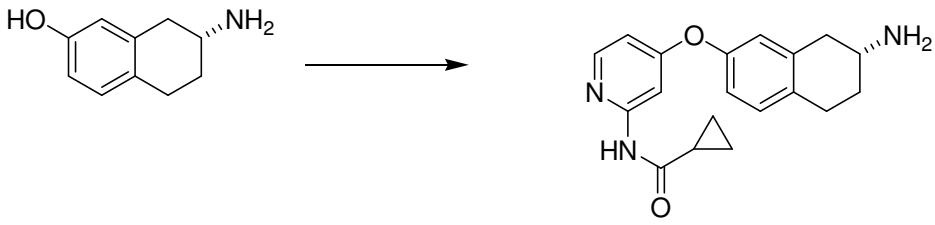
To a stirred solution of (*S*)-(+)-mandelic acid (15.4 g, 101 mmol), isopropyl alcohol (78 mL) and 80/20 methanol/water (51 mL) was added a solution of the free base of 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine in toluene (10 mL) and 80/20 methanol/water (40 mL) via a dropping funnel. After addition was completed, the mixture was stirred at reflux for 30 min. The mixture was then cooled to rt. The mixture was allowed to stand at rt over the weekend. The resulting solids (16.95 g) were isolated by filtration, washed with minimal ethyl acetate and dried *in vacuo*. The salt was then suspended in an 80/20 methanol/ water solution (55 mL) and warmed to reflux. Additional 80/20 methanol/water solution was added until the solution became homogeneous (about 10 mL). Upon complete dissolution, the solution was stirred at reflux 30 min, cooled to rt and allowed to stand undisturbed overnight. The resulting white solids which precipitated were collected by suction filtration (11.94 g) and dried *in vacuo*. The solids were recrystallized as above from 80/20 methanol/water (ca. 60 mL) to

afford 10.05 g of the (*S*)-(+)-mandelate salt ([α] = +90°, c =0.5, MeOH).[5] The salt was partitioned between 4.00 M of sodium hydroxide in water (30.0 mL) and ethyl acetate (100 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The extracts were combined, washed with brine (35 mL), dried over sodium sulfate, filtered and concentrated to afford (2*R*)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (5.39 g, 60% of theoretical) as an oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.64-6.57 (m, 1H), 3.21 (ddt, *J* = 9.8, 9.8, 5.0, 3.2 Hz, 1H), 2.99 (dd, *J* = 16.1, 4.7 Hz, 1H), 2.91-2.69 (m, 2H), 2.60 (dd, *J* = 16.1, 9.5 Hz, 1H), 2.41-2.33 (m, 2H), 2.10-1.95 (m, 1H), and 1.62 (dtd, *J* = 12.6, 10.1, 10.1, 6.7 Hz, 1H). LCMS: *m/z* 178 $[M+H]^+$, (FA).

A suspension of (2*R*)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (5.92 g, 33.7 mmol) in hydrobromic acid (48% in water, 80 mL) was warmed to reflux. After 1.75 h, the reaction solution was cooled to rt. The solvent was removed under reduced pressure. The oily residue was twice dissolved in ethanol (100 mL) and concentrated to dryness. The resulting oil was further dried *in vacuo*, affording (7*R*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide (**17**) as a brown waxy solid (9.13 g, 99% yield, ([α] = +91°, c =0.5, MeOH).[5] This material was determined to be 99% ee by HPLC (OJ 4.6 x 250 mm column eluting with 87% hexane, 13% ethanol, 0.2% $Et_2NH$, flow rate 1.0 mL / min. Peak 1 RT 14.6 min (2*R*)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine, peak 2 RT 19.0 min ((2*S*)-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.76 (s, 1H), 7.60 (s, 3H), 6.49 (d, *J* = 8.3 Hz, 1H), 6.17 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.10 (d, *J* = 2.4 Hz, 1H), 3.12-2.87 (m, 2H), 2.56 (dd, *J* = 16.1, 5.0 Hz,

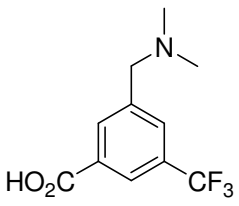
1H), 2.39-2.24 (m, 2H), 1.75-1.58 (m, 1H), and 1.29 (dq, *J* = 11.3, 11.3, 10.9, 6.6 Hz, 1H). LCMS: *m/z* 164 $[M+H]^+$, (AA).

***N*-(4-{[(7*R*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}pyridin-2-yl)cyclopropanecarboxamide**




(7*R*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide and *N*-(4-nitropyridin-2-yl)-cyclopropanecarboxamide were combined as described in **General procedure A1, biaryl ether bond formation**. *N*-(4-{[(7*R*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}pyridin-2-yl)cyclopropanecarboxamide was isolated by partitioning the concentrated reaction mixture between EtOAc and water. The organic phase was extracted with EtOAc (2x), combined organic phases were washed with brine, dried over $Na_2SO_4$, filtered, concentrated and purified by column chromatography ($SiO_2$, elution with 0.2-1% $NH_4OH$ in 10% MeOH/DCM) to give the desired product (10.26 g, 73% yield). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 10.82 (s, 1H), 8.16 (d, *J* = 5.7 Hz, 1H), 7.64 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.89-6.83 (m, 2H), 6.62 (dd, *J* = 5.7, 2.4 Hz, 1H), 3.08-2.95 (m, 1H), 2.91-2.64 (m, 3H), 2.43 (dd, *J* = 16.5, 9.2 Hz, 1H), 2.03-1.78 (m, 4H), 1.46 (dtd, *J* = 12.3, 10.5, 10.3, 5.8 Hz, 1H), and 0.80-0.72 (m, 4H).

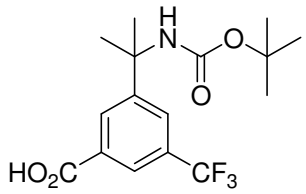
**3-[(Dimethylamino)methyl]-5-(trifluoromethyl)benzoic acid·Li salt**



To a solution of 3-bromo-5-(trifluoromethyl)benzaldehyde (30.0 g, 118.6 mmol) in DCM (150 mL) was added a solution of 2.0 M of dimethylamine in THF (118 mL) and the reaction was stirred at rt for 15 min. The reaction was cooled to 0 °C and sodium triacetoxyborohydride (37.7 g, 178 mmol) was added. The resulting mixture was warmed to rt and stirred for 3 hours. The solvents were evaporated; saturated sodium bicarbonate solution was added and the resulting mixture was extracted three times with ethyl acetate. The organic phase was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by column chromatography ($SiO_2$, elution with 10-40% ethyl acetate in hexanes) provided 1-[3-bromo-5-(trifluoromethyl)phenyl]-*N*,*N*-dimethylmethanamine as a colorless oil (24.9 g, 74% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 3.44 (s, 2H), and 2.25 (s, 6H). LCMS: *m/z* 282 $[M+H]^+$, (FA).

To a solution of 1-[3-bromo-5-(trifluoromethyl)phenyl]-*N*,*N*-dimethylmethanamine (2.0 g, 7.1 mmol) in THF (40 mL) at -78 °C was added dropwise a solution of *n*-BuLi in hexane (3.12 mL, 7.81 mmol, 2.50 M). The resulting mixture was stirred at -78 °C for 20 min. Crushed solid $CO_2$ was added and the mixture was stirred at -78 °C for another 15 min. The reaction was quenched by the addition of water (0.156 mL) and allowed to warm to rt. The solvents were evaporated and the solid was dried overnight under vacuum to give 3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoic acid·Li salt as a white solid (1.38 g, 77%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.02 (s, 2H), 7.50 (s, 1H), 3.44 (s, 2H), and 2.13 (s, 6H). LCMS: *m/z* 248 $[M+H]^+$, (FA).

**3-{1-[(*tert*-Butoxycarbonyl)amino]-1-methylethyl}-5-(trifluoromethyl)benzoic acid**.



A solution of *tert*-butyl 3-bromo-5-(trifluoromethyl)benzoate (35.0 g, 108 mmol) in THF (262 mL) was degassed with argon and cooled to -20 °C. A solution of isopropylmagnesium chloride lithium chloride complex (99.4 mL, 129 mmol, 1.3 M in THF) was added dropwise maintaining the temperature of the solution at -20 to -30 °C. When addition was complete, the mixture was stirred at this temperature for 90 min. Acetone (8.69 mL, 118 mmol) was added dropwise maintaining the temperature of the reaction mixture at -20 to -30 °C, then the mixture was stirred at this temperature for 30 min. The mixture was allowed to warm to 0 °C and stirred for 45 min. A solution of 1 M HCl (430 mL, 430 mmol) was added, and the mixture was warmed to rt and stirred for 45 min. $Et_2O$ was added and the phases were separated. The aqueous phase was extracted with further $Et_2O$ and the combined organic phases were washed with saturated $NaHCO_3$ solution, then brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, elution with 5% to 20% EtOAc / hexane) to provide *tert*-butyl 3-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)benzoate as a pale yellow oil (16.2 g, 49.3%). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 1.62 (s, 6H), and 1.61 (s, 9H). LCMS: *m/z* 287 $[M-18]^+$, (FA).

To a solution of *tert*-butyl 3-(1-hydroxy-1-methylethyl)-5-(trifluoromethyl)benzoate (5.13 g, 16.8 mmol) in acetonitrile (160 mL), was added concentrated sulfuric acid (3.59 mL, 67.4 mmol) dropwise. The solution was stirred at rt for 3 h. EtOAc was added and the mixture was washed with water (2x). The organic phase was extracted with 1 N

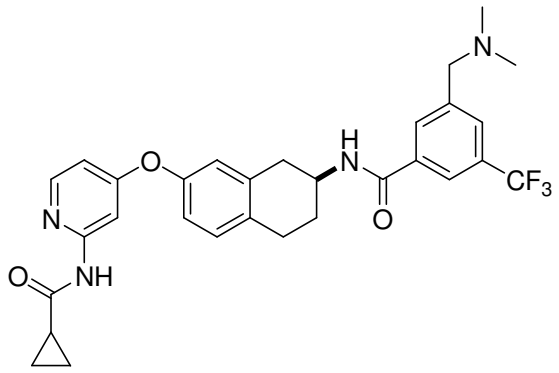
NaOH solution (3x) and the basic aqueous phases were acidified to pH 1 by the addition of 6 N HCl solution. The aqueous phase was then extracted into EtOAc (2x) and the organic phases were dried ($Na_2SO_4$), filtered, and evaporated to provide 3-[1-(acetylamino)-1-methylethyl]-5-(trifluoromethyl)benzoic acid as a white solid (4.48 g, 91.9%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.31 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.81 (s, 1H), 7.41 (s, 1H), 1.82 (s, 3H), and 1.56 (s, 6H). LCMS: *m/z* 290 $[M+H]^+$, (FA).

A mixture of 3-[1-(acetylamino)-1-methylethyl]-5-(trifluoromethyl)benzoic acid (4.48 g, 15.5 mmol), 1,2-ethanediol (20 mL) and KOH (8.69 g, 155 mmol) was heated at 150 °C for 3 days. The reaction mixture was cooled to rt and water (20 mL) was added. The mixture was washed with $Et_2O$ (2x) and the aqueous phase was acidified to pH 5 by the addition of 6 N HCl solution. The precipitate was isolated by filtration and washed with water. The solid was collected, triturated with water and dried under vacuum to provide 3-(1-amino-1-methylethyl)-5-(trifluoromethyl)benzoic acid as a white solid (3.84 g, 100%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.68 (s, 1H), 8.02 (s, 1H), 7.81 (s, 1H), and 1.64 (s, 6H). LCMS: *m/z* 248 $[M+H]^+$, (FA).

To a solution of 3-(1-amino-1-methylethyl)-5-(trifluoromethyl)benzoic acid (17.2 g, 69.5 mmol) in dioxane (180 mL), was added a solution of NaOH (208 mL, 208 mmol, 1 N) and di-*tert*-butyldicarbonate (60.7 g, 278 mmol). The reaction mixture was stirred overnight. The dioxane was evaporated and the residue was diluted with water and washed with $Et_2O$ (2x). EtOAc was added to the aqueous phase followed by addition of 6 N HCl to acidify the aqueous phase to pH 1. The mixture was extracted with EtOAc (2x). The organic phases were washed with water then brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by filtration through silica (elution with DCM, then 10% MeOH

/ 1% AcOH / DCM) followed by trituration of the product with DCM. The product was dried under vacuum to provide 3-{1-[(*tert*-butoxycarbonyl)amino]-1-methylethyl}-5-(trifluoromethyl)benzoic acid as a white solid (15.0 g, 62.2%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 13.47 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.84 (s, 1H), 7.50 (s, 1H), 1.53 (s, 6H), 1.32 (s, 7H), and 0.96 (s, 2H). LCMS: *m/z* 346 $[M-H]^-$(FA).

***N*-[(2*S*)-7-({2-[(Cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalen-2-yl]-3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzamide hydrochloride (25).**

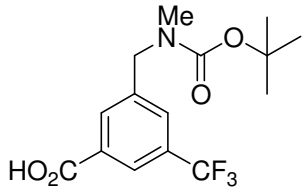



(7*S*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide was prepared from 7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine hydrochloride using the procedure described for the synthesis of (7*R*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide. (*R*)-(-)-mandelic acid was used in the place of (*S*)-(+)-mandelic acid.

*N*-(4-{[(7*S*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}pyridin-2-yl)cyclopropanecarboxamide was prepared from (7*S*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-ol hydrobromide using the procedure described for the synthesis of *N*-(4-{[(7*R*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}pyridin-2-yl)cyclopropanecarboxamide. *N*-[(2*S*)-7-({2-[(Cyclopropylcarbonyl)amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalen-2-yl]-3-[(dimethylamino)methyl]-5-

(trifluoromethyl)benzamide hydrochloride (**25**) was prepared from *N*-(4-{[(7*S*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}pyridin-2-yl)cyclopropanecarboxamide using **General procedure B3, amide bond formation** followed by **General procedure D, HCl salt formation**.

**3-{[(*tert*-Butoxycarbonyl)(methyl)amino]methyl}-5-(trifluoromethyl)benzoic acid.**



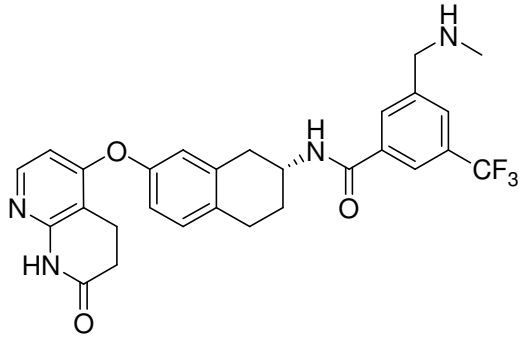

A solution of methylamine (10.0 mL, 20.0 mmol, 2.0 M in THF) was added to a solution of *tert*-butyl 3-formyl-5-(trifluoromethyl)benzoate (2.20 g, 8.02 mmol) in DCM (80 mL). This solution was stirred at rt for 15 minutes, and then sodium triacetoxyborohydride (4.25 g, 20.0 mmol) was added. The resulting solution was stirred at rt overnight. The reaction mixture was diluted with saturated sodium bicarbonate solution (50 mL) and extracted three times with methylene chloride. The organic phases were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by column chromatography ($SiO_2$, elution with 0-10% MeOH in EtOAc) provided a 1.05 g of a white solid (45% yield). $^1$H NMR (400 MHz, $CDCl_3$ δ 8.12 (s, 1H), 8.10 (s, 1H), 7.77 (s, 1H), 3.85 (s, 2H), 2.47 (s, 3H), and 1.61 (s, 9H). LCMS: *m/z* 290 $[M+H]^+$, (FA).

A solution of *tert*-butyl 3-[(methylamino)methyl]-5-(trifluoromethyl)benzoate (1.00 g, 3.46 mmol) was dissolved in DCM (6.0 mL) and trifluoroacetic acid (2.66 mL, 3.46 mmol) was added. The resulting solution was stirred at rt for 120 min, and then the solvents were removed *in vacuo*. The residue was dissolved in methylene chloride (1.0

mL) and 2.0 M of hydrochloric acid in ether (5.0 mL, 10.0 mmol) was added. The solvent was evaporated to dryness to give 895 mg of 3-[(methylamino)methyl]-5-(trifluoromethyl)benzoic acid as a white solid (96% yield). $^1$H NMR (300 MHz, d6-DMSO) δ 9.51 (br s, 2H), 8.41 (s, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 4.29 (t, *J* = 5.8 Hz, 2H), and 2.54 (t, *J* = 5.2 Hz, 3H). LCMS: *m/z* 234 $[M+H]^+$, (AA).

3-[(Methylamino)methyl]-5-(trifluoromethyl)benzoic acid·HCl (3, 0.895 g, 3.32 mmol) was dissolved in 1,4-dioxane (10 mL), water (7.0 mL) and sodium hydroxide (13.0 mL, 13.0 mmol, 1.0 M in water). Then di-*tert*-butyldicarbonate (1.45 g, 6.64 mmol) was added and the resulting solution was stirred at rt for 90 min. The dioxane was removed under reduced pressure and the pH was adjusted to 3 by the addition of 1N HCl. The aqueous phase was extracted three times with ethyl acetate. The organic phases were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Purification by column chromatography ($SiO_2$, elution with 0-15% MeOH in DCM) provided 1.01 g of 3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-5-(trifluoromethyl)benzoic acid as a white solid (91% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16 (s, 1H), 4.60-4.48 (m, 2H), 2.96-2.84 (m, 3H), and 1.56-1.43 (m, 9H). LCMS: *m/z* 332 $[M+H]^-$, (FA).

**3-[(methylamino)methyl]-*N*-{(2*R*)-7-[(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}-5-(trifluoromethyl)benzamide (28).**



Compound **28** was prepared by combining 3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-5-(trifluoromethyl)benzoic acid and 5-{[(7*R*)-7-amino-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one as described in **General procedures B1 (amide bond formation)** and **C (*tert*-butyl carbamate deprotection)**. $^{1}$H NMR (400 MHz, d6-DMSO) δ 8.86 (d, *J* = 7.2 Hz, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 8.14 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 6.96-6.91 (m, 2H), 6.36 (d, *J* = 6.0 Hz, 1H), 4.32-4.17 (m, 3H), 3.11-3.04 (m, 1H), 2.97-2.81 (m, 5H), 2.59-2.53 (m, 5H), 2.12-2.03 (m, 1H), 1.89-1.77 (m, 1H).

[1] The absolute stereochemical assignment was based on comparison (of both HPLC retention time and enzyme activity) with compound **20** prepared independently from 2(*S*)-7-({2-[(cyclopropylcarbonyl)-amino]pyridin-4-yl}oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid and *tert*-butyl [4-amino-2-(trifluoromethyl)benzyl]carbamate.

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