Expanding the Medicinal Chemist Toolbox: Comparing Seven C(sp²)-C(sp³) Cross-Coupling Methods by Library Synthesis

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General Information

All reagents that were used in this publication were purchased from commercial vendors (such as Sigma-Aldrich, Enamine, Combi-Blocks, etc.) and used as-is, unless indicated otherwise. Reagents or substrates that were not commercially available were prepared as described in this supporting document or prepared according to published procedures. Anhydrous solvents were purchased from Sigma-Aldrich in sealed bottles (Sure/Seal™) and were either degassed before use or moved to a nitrogen atmosphere glove box to be dispensed. Test reactions and libraries were run in 1-dram pressure relief vials (4 mL, part number CG-4912-01) and set up either in a glove box under an N2 atmosphere or in the hood using sparged reagents/solvents.

For coupling methods requiring heating, controlled reaction heating and stirring was achieved using IKA RCT stir plates equipped with circular top reaction blocks. Reaction times ranged from overnight to 72 h. Ambient temperature photoredox coupling reactions were run HepatoChem Photoredox Duo parallel photoreactors (HCK1006-01-023) using 18W CREE XPE 450 nm blue LED lamps (HepatoChem, HCK1012-01-002) and 4 mL vial inserts with fan cooling. IKA RCT stir plates were placed under the HepatoChem photoreactors for stirring. Reaction times ranged from overnight to 72 h.

Isolation of products from reaction mixtures was accomplished by preparative-scale reverse-phase HPLC on 2-coupled C8 5 um 100Å columns (30mm × 75mm each). When possible, an ammonium acetate purification method was used: a gradient of acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 50 mL/min (0-0.5 min 5% A, 0.5-8.5 min linear gradient 05-100% A, 8.7-10.7 min 100% A, 10.7-11 min linear gradient 100-0.5% A). The following TFA purification method was used for samples which were not compatible with the analytical ammonium acetate method: a gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/min (0-0.5 min 5% A, 0.5-8.5 min linear gradient 0.5-100% A, 8.7-10.7 min 100% A, 10.7-11 min linear gradient 100-0.5% A). Samples were injected in 2 mL of DMSO:MeOH (1:1). An Agilent 1100 Series Purification system was used, consisting of the following modules: Agilent 1100 Series LC/MSD SL mass spectrometer with API-electrospray source; two Agilent 1100 Series preparative pumps; Agilent 1100 Series isocratic pump; Agilent 1100 Series diode array detector with preparative (0.3 mm) flow cell; Agilent active-splitter, IFC-PAL fraction collector/autosampler. The make-up pump for the mass spectrometer used 3:1 methanol:water with 0.1% formic acid at a flow rate of 1 mL/min. Fraction collection was automatically triggered when the extracted ion chromatogram (EIC) for the target mass exceeded the threshold specified in the method. The system was controlled using Agilent Chemstation (Rev B.10.03), Agilent A2Prep, and Leap FractPal software, with custom Chemstation macros for data export.

Library analytical crude reaction monitoring and final product purity checks were performed on a Waters Acquity UPLC system equipped with in-line photodiode array detector (PDA) and SQD mass spectrometer, running MassLynx 4.1 and Openlynx 4.1 software (Waters Corporation, Milford, MA, USA). The SQD mass spectrometer was operated under positive ESI ionization conditions. The column used was a Waters BEH C8, 1.7μm (2.1mm × 30mm) at a temperature of 55°C. The following ammonium acetate analytical method was used: a gradient of 10-100% acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 1.0 mL/min (0-0.1 min 10% A, 0.1-1.1 min 10-100% A, 1.1-1.3 min 100% A, 1.3-1.4 min 100-10% A). NMR
spectra were acquired on various spectrometers (Varian or Bruker) equipped with sample changers. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane and referenced to solvent (e.g. DMSO-$d_6$). NMR data are represented as follows: chemical shift, multiplicity ($s =$ singlet, $br s =$ broad singlet, $d =$ doublet, $dd =$ doublet of doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet, etc.), coupling constant, and integration. Coupling constants ($J$) are given in Hertz (Hz). High-resolution mass spectrometry characterization was acquired using Thermo Scientific™ Orbitrap Elite™ Hybrid Ion Trap-Orbitrap Mass Spectrometer.
Substrate Synthesis

1 and 3 were purchased from commercial suppliers.

(R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (2)

Prepared according to published procedures. Spectral data was in agreement with literature values.¹

7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (4)

Prepared according to published procedures. Spectral data was in agreement with literature values.²
General Procedures

General Procedure A – Suzuki Coupling with Potassium Alkyltrifluoroborate Salts (used in Figure 2 and 3)

The alkyl reagent (1.3 equiv, 0.13 mmol) and CataCXium A Pd G3 (5 mol%, 3.6 mg, 4.9 x 10^{-3} mmol) were weighed into a 4 mL vial and purged with nitrogen. A solution of the aryl halide (1 equiv, 0.10 mmol) in 0.45 mL of toluene was added. A nitrogen sparged Cs$_2$CO$_3$ solution (3 equiv, 7 M in H$_2$O, 43 µL) was added, and the reaction was stirred at 100 °C for 72 h. Upon completion, the reaction was concentrated, taken up in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC. This procedure was used for all Suzuki couplings with BF$_3$K salts.

General Procedure B – Suzuki Coupling with MIDA Boronate Reagents (used in Figure 2)

The alkyl reagent (1.2 equiv, 0.12 mmol) and SPhos Pd G3 (5 mol%, 3.9 mg, 5.3 x 10^{-3} mmol) were weighed into a vial and purged with nitrogen. The aryl halide (1 equiv, 0.10 mmol) dissolved in dioxane (0.5 M, 0.20 mL) was added, and the solution was stirred at room temperature for 10 minutes. A nitrogen sparged K$_3$PO$_4$ solution (7.5 equiv, 3.0 M in H$_2$O, 0.25 mL) was added, and the reaction was stirred at 60 °C for 6 h. Upon completion, the reaction was concentrated, taken up in 1:1 MeOH/DMSO and filtered through Celite. The product was purified using reverse phase HPLC. This procedure was used for all Suzuki couplings with MIDA boronates.

General Procedure C – Nickel/Photoredox Decarboxylative Coupling – activated/stabilized carboxylic acids (used in Figure 2, 3 and 4b)

Heteroaryl$\text{-Br}$ $\xrightarrow{2 \text{ mol } \% \text{ Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)}PF_6}$ $\text{R}_1$ $\xrightarrow{5 \text{ mol } \% \text{ NiCl$_2$(dtbbpy)}}$ $\text{R}_1$ $\xrightarrow{1.5 \text{ equiv Cs$_2$CO$_3$}}$ $\text{R}_1$ $\xrightarrow{0.1 \text{ M DMA, rt}}$ $\text{R}_1$ $\xrightarrow{450 \text{ nm LEDs}}$ $\text{R}_1$ $= \text{H or alkyl}$ $\text{R}_2$ $= \text{aryl, O–R, N(PG)–R}$
The alkyl reagent (carboxylic acid, 1.5 equiv, 0.19 mmol, if solid) and Cs$_2$CO$_3$ (1.5 equiv, 0.19 mmol) were weighed into a 4 mL vial equipped with a stir bar. The vial was moved to a nitrogen-atmosphere dry box. There a solution of the aryl halide core (1 equiv, 0.13 mmol) in 0.65 mL DMA was added to the vial followed by the photocatalyst, Ir(df(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2 mol%, 2.5 µmol), in 0.30 mL DMA and the nickel catalyst, NiCl$_2$(dtbbpy)$_2$ (5 mol%, 6.3 µmol), in 0.30 mL DMA. Liquid alkyl acid building blocks were dispensed to the vessels at this stage. The vial was capped, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction was diluted with 1:1 MeOH/DMSO to 2 mL and filtered. The product was purified by reverse phase HPLC.

General Procedure D - Nickel/Photoredox Decarboxylative Coupling – alpha-alkyl carboxylic acids (used in Figure 2 and 3)

The alkyl reagent (carboxylic acid, 1.5 equiv, 0.19 mmol) was weighed into a 4 mL vial equipped with a stir bar. The vial was moved to a nitrogen-atmosphere dry box. There a solution of the aryl halide core (1 equiv, 0.13 mmol) in 0.65 mL DMSO was added to the vial followed by the photocatalyst, Ir(df(CH$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2 mol%, 2.5 µmol) in 0.30 mL DMSO and the nickel catalyst, NiCl$_2$(dtbbpy) (5 mol%, 6.3 µmol) in 0.30 mL DMSO. Finally, 2-tert-butyl-1,1,3,3-tetramethylguanidine (1.5 equiv, 0.19 mmol) was added to the vial. The vial was capped, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction was diluted with 1:1 MeOH/DMSO to 2 mL and filtered. The product was purified by reverse phase HPLC.

General Procedure E - Nickel/Photoredox Potassium Alkyltrifluoroborate Salt Coupling (used in Figure 2 and 3)

The potassium alkyltrifluoroborate salt reagent (1.3 equiv, 0.16 mmol) was weighed into a 4 mL vial equipped with a stir bar. The vial was moved to a nitrogen-atmosphere dry box. There a stock solution of the aryl halide core (1 equiv, 0.13 mmol), photocatalyst Ir(df(CF$_3$)ppy)$_2$(bpy)PF$_6$ (2 mol%, 2.5 µmol), and nickel catalyst NiCl$_2$(dtbbpy) (5 mol%, 6.3 µmol) in 0.30 mL DMSO. Finally, 2,6-lutidine (2 equiv, 4:1 dioxane/DMA, rt) was added to the reaction vial. The vial was capped, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction was diluted with 1:1 MeOH/DMSO to 2 mL and filtered. The product was purified by reverse phase HPLC.
lutidine (2.0 equiv, 0.50 mmol) was added to the vial using a pipette. The vial was capped, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction was concentrated to remove dioxane, diluted with 1:1 MeOH/DMSO to 2 mL, and filtered. The product was purified by reverse phase HPLC.

**General Procedure F – Nickel/Photoredox Potassium Alkyltrifluoroborate Salt Coupling – tertiary BF$_3$K salt examples (used in Figure 2)**

The potassium alkyltrifluoroborate salt reagent (2 equiv, 0.25 mmol), was weighed into a 4 mL vial equipped with a stir bar. The photocatalyst, Ir(dF(CF$_3$)ppy)$_2$(bpy)PF$_6$ (1 mol%, 1.3 µmol), the nickel catalyst, Ni(TMHD)$_2$ (10 mol%, 13 µmol), ZnBr$_2$ (10 mol%, 13 µmol), and K$_2$HPO$_4$ (2 equiv, 0.25 mmol) were then dispensed into the vial. The vial was moved to a nitrogen-atmosphere dry box. There a stock solution of the aryl halide core (1 equiv, 0.13 mmol) in 1.25 mL DMA was added to the vial. The vial was sealed, removed from the dry box, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction diluted with 1:1 MeOH/DMSO to 2 mL and filtered. The product was purified by reverse phase HPLC.

**General Procedure G – Nickel/Photoredox Cross-Electrophile Coupling (used in Figure 2, 3 and 4a)**

The alkyl bromide (1.5 equiv, 0.19 mmol) was weighed into a 4 mL vial equipped with a stir bar. The vial was moved to a nitrogen-atmosphere dry box. There a solution of the aryl halide core (1 equiv, 0.13 mmol), NiCl$_2$(dtbbpy) (0.5 mol%, 0.70 µmol), and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (1.0 mol%, 1.3 µmol) were added in 1.0 mL DME followed by 2,6-lutidine (2 equiv, 0.26 mmol) and tris(trimethylsilyl)silane (1.2 equiv, 0.15 mmol). The vial was sealed with a teflon cap, placed in the HepatoChem photoreactor, and irradiated for 48 h using 450 nm blue LEDs. Upon completion, the reaction diluted with 1:1 MeOH/DMSO to 2 mL and filtered. The product was purified by reverse phase HPLC. This procedure was used for all nickel/photoredox cross-electrophile couplings.
General Procedure H – Nickel-Catalyzed Cross-Electrophile Coupling (used in Figure 2, 3 and 4a)

\[
\text{Heteroaryl}^\text{Br} \quad X \quad R_1 \quad R_2
\]

\[
\text{Heteroaryl} \quad R_1 \quad R_2
\]

\(X = \text{Br, Cl}\)

A 4 mL scintillation vial was charged with a stir bar, NiCl\(_2\) glyme (7.0 \(\mu\)mol, 7 mol%), NaI (0.25 mmol, 25 mol%), ligand (1, 10, or 13) (7.0 \(\mu\)mol, 7 mol %), and Zn Flake (0.20 mmol, 2 equiv). The vial was moved to a nitrogen atmosphere dry box, and 100 \(\mu\)L of a stock solution of the alkyl halide in DMA (0.20 mmol, 2 equiv) was added. To this, 300 \(\mu\)L of a stock solution of the aryl bromide core (0.10 mmol, 1 equiv) in DMA was added followed by the addition of trifluoroacetic acid (0.01 mmol, 10 mol%). The vial was capped using a septa cap and placed to heat at 60°C for 18 hours. Upon completion the crude material was diluted with additional DMA to 2mL and filtered. The product was purified using reverse phase HPLC. This procedure was used for all nickel catalyzed cross-electrophile couplings.

General Procedure J – Negishi Coupling with Commercial Organozincs (used in Figure 2)

\[
\text{Heteroaryl}^\text{Br} \quad X \quad Zn \quad R_1 \quad R_2
\]

\[
\text{Heteroaryl} \quad R_1 \quad R_2
\]

\(X = \text{Cl, Br, I}\)

In a 4 mL vial containing a stir bar was added aryl bromide (0.10 mmol, 1.0 equiv.) in THF (0.5 mL). Pd-PEPPSI-IPent\(^\text{Cl}\) (0.025 M in THF, 200 \(\mu\)L, 5.0 \(\mu\)mol, 0.05 equiv) was added. The vial was purged with nitrogen and capped. Alkyl zinc (0.20 mmol, 2.0 equiv) was added and the reaction was stirred overnight at room temperature. Upon completion, the reaction was filtered through a syringe filter and the product was purified via reverse phase HPLC.

General Procedure K – Negishi Coupling with \textit{in situ} Formed Organozincs (used in Figure 3)

\[
\text{Heteroaryl}^\text{Br} \quad X \quad Zn \quad R_1 \quad R_2
\]

\[
\text{Heteroaryl} \quad R_1 \quad R_2
\]

\(X = \text{Cl, Br, I}\)

In a 4 mL vial containing a stir bar was added aryl bromide (0.10 mmol, 1.0 equiv) in dimethyl acetamide (0.3 mL). SPhos Pd G4 (0.025 M in DMA, 200 \(\mu\)L, 5.0 \(\mu\)mol, 0.05 equiv) was added. The vial was purged with nitrogen...
and capped. Alkyl zinc (0.20 mmol, 2.0 equiv) was added, and the reaction was stirred overnight at 50 °C. Upon completion, the reaction was filtered through a syringe filter, and the product was purified via reverse phase HPLC.

**General Procedure for in situ Organozinc Formation (used with General Procedure K and in Figure 3)**

\[
\begin{array}{c}
R_1 \\
\text{X = I, Br} \\
\end{array} \xrightarrow{\text{Zn cartridge in flow}} \begin{array}{c}
R_1 \\
XZn \\
\text{X = I, Br} \\
\end{array}
\]

Organozinc reagents were prepared using the method described by Alcazar and coworkers.\(^4\) Substrates were passed through a 12 g packed bed of granular zinc at a flow rate of 0.5 mL/min, collected under nitrogen, titrated and used without further modification.

| Starting material                      | Solvent                  | Temperature | Final Titre |
|----------------------------------------|--------------------------|-------------|-------------|
| t-butyl 2-bromoacetate                 | 0.54 M in THF            | 40 °C       | 0.28 M      |
| t-butyl 3-iodoazetidine-1-carboxylate  | 0.56 M in 0.5 M LiCl in THF | 40 °C     | 0.20 M      |
| t-butyl 3-iodopyrrolidine-1-carboxylate| 0.48 M in 0.5 M LiCl in THF | 60 °C     | 0.05 M      |
| t-butyl 4-iodopiperidine-1-carboxylate | 0.50 M in 0.5 M LiCl in THF | 60 °C     | 0.15 M      |
| 4-iodotetrahydro-2H-pyran              | 0.52 M in 0.5 M LiCl in THF | 60 °C     | 0.28 M      |
Supplementary Table 1. Success rates by method and building block class.$^1$

| Method          | Reactions | Success rate (%) | 1° Success rate (%) | 1° Reactions run (#) | 2° Success rate (%) | 2° Reactions run (#) | 3° Success rate (%) | 3° Reactions run (#) |
|-----------------|-----------|------------------|---------------------|----------------------|---------------------|---------------------|---------------------|---------------------|
| Negishi         | 74        | 86               | 83                  | 29                   | 96                  | 45                  | -                   | 0                   |
| Suzuki-MIDA     | 48        | 21               | 40                  | 20                   | 7                   | 28                  | -                   | 0                   |
| Suzuki-BF$_3$K | 104       | 44               | 73                  | 40                   | 28                  | 60                  | 38$^2$              | 8$^2$               |
| Photoredox-BF$_3$K | 104     | 63               | 50                  | 40                   | 75                  | 60                  | 10                  | 4                   |
| Photoredox-COOH | 132       | 22               | 11                  | 40                   | 22                  | 88                  | 0                   | 4                   |
| Photoredox CEC  | 104       | 72               | 80                  | 44                   | 71                  | 56                  | 0                   | 4                   |
| Reductive CEC   | 92        | 47               | 45                  | 40                   | 52                  | 48                  | 0                   | 4                   |
| Total           | 658       | 50               | 55                  | 229                  | 50                  | 385                 | 13                  | 20                  |

$^1$Success is defined as ≥10% yield. This dataset includes the four cores and all monomers shown in the manuscript. $^2$A tert-butyl group could not be incorporated using any method in this study. However, one tertiary group was able to be incorporated by the BF$_3$K Suzuki coupling using potassium trifluoro-(1-methylcyclopropyl) boranuide in 39% yield (see SI page 21, compound 53). Unfortunately, this building block was not available for other methods and does not appear in our comparison in the manuscript.
Characterization Data

Figure 2:
1-(4-cyclopropylbenzyl)-4-methylpiperazine (5).

General Procedure A was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol) as the aryl halide and potassium cyclopropyltrifluoroborate (19 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 5 (11 mg, 49% yield, >95% pure by $^1$H NMR as a clear oil. $^1$H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.17 (m, 2H), 7.08 – 6.98 (m, 2H), 3.48 (s, 2H), 2.39 (d, $J = 50.9$ Hz, 7H), 2.29 (s, 3H), 1.89 (tt, $J = 8.4$, 5.0 Hz, 1H), 1.02 – 0.89 (m, 2H), 0.75 – 0.62 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.75, 135.13, 129.21, 125.45, 62.76, 55.15, 53.05, 46.04, 15.11, 9.17. Chemical Formula of [M+H]$^+$: C$_{15}$H$_{23}$N$_2$$^+$; Exact Mass (calculated): 231.1856; HRMS (ESI$^+$) (found): 231.1859.

(R)-2-(tert-butoxy)-1-(4-(5-cyclopropylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethanone (6).

General Procedure A was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide and potassium cyclopropyltrifluoroborate (19 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. Upon completion the reaction was concentrated, taken up in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 6 (22 mg, 65% yield, >95% pure by $^1$H NMR) as a clear oil. $^1$H NMR (400 MHz, DMSO-d$_6$, 120 °C) δ 8.14 (s, 2H), 4.79 (qdd, $J = 6.7$, 4.1, 2.7 Hz, 1H), 4.34 (dt, $J = 13.5$, 3.4 Hz, 1H), 4.12 – 3.93 (m, 4H), 3.16 (ddd, $J = 13.4$, 11.4, 3.6 Hz, 2H), 3.01 (d, $J = 12.5$ Hz, 1H), 1.74 (tt, $J = 8.4$, 5.2 Hz, 1H), 1.18 (s, 9H), 1.08 (d, $J = 6.6$ Hz, 3H), 0.90 – 0.81 (m, 2H), 0.63 – 0.53 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$, rotamers present) δ 169.85, 160.05, 156.39, 124.55, 74.73, 74.69, 63.39, 63.23, 49.29, 46.87, 46.72, 46.15, 45.47, 41.93, 38.84, 38.09, 27.42, 27.37, 14.29, 14.04, 9.95, 6.93, 6.91. Chemical Formula of [M+H]$^+$: C$_{18}$H$_{29}$N$_4$O$_2$$^+$; Exact Mass (calculated): 333.2285; HRMS (ESI$^+$) (found): 333.2287.
1-(4-isopropylbenzyl)-4-methylpiperazine (7).

\[
\text{Me} \quad \text{N} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{H} \\
\text{N} \\
\text{Me} \quad \text{N} \quad \text{Me}
\]

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv.) and isopropylzinc bromide (0.11 M in THF, 1.8 mL, 2.0 equiv.) to afford the title compound 7 (21 mg, 62% yield, >95% pure by \textsuperscript{1}H NMR) as a TFA salt. \textsuperscript{1}H NMR (500 MHz, Pyridine-\textit{d}_5) \delta 7.35 – 7.29 (m, 2H), 7.29 – 7.24 (m, 2H), 3.49 (s, 2H), 3.19 – 2.97 (m, 4H), 2.91 – 2.81 (m, 1H), 2.72 (d, \textit{J} = 18.6 Hz, 7H), 1.20 (d, \textit{J} = 6.9 Hz, 6H). Chemical Formula of [M+H]+: C\textsubscript{15}H\textsubscript{25}N\textsubscript{2}+; Exact Mass (calculated): 233.2018; HRMS (ESI+) (found): 233.2015.

(R)-2-(tert-butoxy)-1-(4-(5-isopropylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (8).

\[
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\text{N} \\
\text{Me}
\]

General Procedure J was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol, 1.0 equiv.) and isopropylzinc bromide (0.11 M in THF, 1.8 mL, 2.0 equiv.) to afford the title compound 8 (24 mg, 54% yield, >95% pure by \textsuperscript{1}H NMR) as a TFA salt. \textsuperscript{1}H NMR (400 MHz, Pyridine-\textit{d}_5) \delta 8.32 (s, 2H), 5.10 – 5.01 (m, 1H), 4.64 (dt, \textit{J} = 13.5, 3.4 Hz, 1H), 4.44 – 4.09 (m, 4H), 3.39 – 3.26 (m, 1H), 3.26 – 2.94 (m, 2H), 2.67 (h, \textit{J} = 7.0 Hz, 1H), 1.23 (d, \textit{J} = 6.6 Hz, 3H), 1.20 (s, 9H), 1.14 (d, \textit{J} = 7.0, 0.8 Hz, 6H). Chemical Formula of [M+H]+: C\textsubscript{18}H\textsubscript{31}N\textsubscript{4}O\textsubscript{2}+; Exact Mass (calculated): 335.2447; HRMS (ESI+) (found): 335.2445.

1-(4-benzylbenzyl)-4-methylpiperazine (9).

\[
\text{H}_3\text{C} \quad \text{N} \\
\text{N} \\
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{Me}
\]

General Procedure A was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol) as the aryl halide and potassium benzyltrifluoroborate (26 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 9 (15 mg, 52% yield, >95% pure by \textsuperscript{1}H NMR as a yellow oil. \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \delta 7.43 – 7.08 (m, 9H),
3.99 (s, 2H), 3.50 (s, 2H), 2.42 (d, J = 37.1 Hz, 8H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz, CDCl₃) δ 141.19, 139.90, 135.85, 129.37, 128.93, 128.76, 128.46, 126.06, 62.75, 55.13, 53.05, 46.03, 41.64. Chemical Formula of [M+H]⁺: C₁₉H₂₅N₂⁺; Exact Mass (calculated): 281.2012; HRMS (ESI⁺) (found): 281.2016.

(R)-1-(4-(5-benzylpyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (10)

![Chemical structure](image)

General procedure E was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (45 mg, 0.12 mmol) as the aryl halide and potassium benzyltrifluoroborate (31 mg, 0.15 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 10 (27 mg, 58% yield, >95% pure by $^1$H NMR). $^1$H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 2H), 7.39 – 7.13 (m, 5H), 4.85 – 4.74 (m, 1H), 4.41 – 4.31 (m, 1H), 4.11 – 3.91 (m, 4H), 3.78 (s, 2H), 3.24 – 3.12 (m, 2H), 1.18 (s, 9H), 1.08 (d, J = 6.7 Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 169.33, 169.25, 160.15, 158.26, 141.34, 129.02, 128.82, 126.58, 123.12, 74.28, 62.82, 62.66, 48.78, 46.77, 46.70, 45.64, 45.05, 41.60, 38.91, 38.12, 35.04, 27.60, 27.55, 14.39. Chemical Formula of [M+H]⁺: C₂₂H₃₁N₄O₂⁺; Exact Mass (calculated): 383.2447; HRMS (ESI⁺) (found): 383.2445.

4-(4-((4-methylpiperazin-1-yl)methyl)phenyl)butanenitrile (11).

![Chemical structure](image)

General Procedure A was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol) as the aryl halide and potassium 3-cyanopropyltrifluoroborate (23 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 11 (14 mg, 54% yield, 90% pure by $^1$H NMR as a yellow oil. $^1$H NMR (400 MHz, Chloroform-d) δ 7.28 – 7.23 (m, 2H), 7.17 – 7.09 (m, 2H), 3.49 (s, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.70 – 2.35 (m, 8H), 2.32 (t, J = 7.1 Hz, 2H), 2.29 (s, 3H), 2.03 – 1.92 (m, 2H). $^{13}$C NMR (101 MHz, CDCl₃) δ 138.45, 136.38, 129.53, 128.31, 119.52, 62.64, 55.08, 52.99, 45.98, 34.04, 26.93, 16.40. Chemical Formula of [M+H]⁺: C₁₆H₂₉N₃⁺; Exact Mass (calculated): 258.1965; HRMS (ESI⁺) (found): 258.1968.
(R)-4-(2-(4-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)butanenitrile (12)

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 4-bromobutanenitrile (29 mg, 0.20 mmol) as the alkyl reagent, and ligand 13 ([2,2'-bipyridine]-6-carboximidamide hydrochloride). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 12 (18 mg, 51% yield, >90% pure by 1H NMR).

1H NMR (400 MHz, Pyridine-d5) δ 8.26 (s, 2H), 5.10 – 5.02 (m, 1H), 4.63 (dt, J = 13.6, 3.3 Hz, 1H), 4.41 – 4.26 (m, 1H), 4.20 (d, J = 1.5 Hz, 2H), 3.38 – 3.28 (m, 1H), 3.26 – 3.02 (m, 2H), 2.51 – 2.45 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.77 (p, J = 7.3 Hz, 2H), 1.23 (d, J = 6.7 Hz, 3H), 1.21 (s, 9H).

13C NMR (101 MHz, DMSO) δ 169.33, 169.26, 160.34, 158.10, 121.97, 120.83, 74.29, 62.82, 62.65, 48.79, 46.78, 46.70, 45.66, 45.06, 41.61, 38.93, 38.13, 28.15, 27.62, 27.56, 26.66, 16.18, 14.38, 14.35. Chemical Formula of [M+H]+: C19H30N5O2+; Exact Mass (Calculated): 360.2400; HRMS (ESI+) (found): 360.2399.

1-methyl-4-(4-methylbenzyl)piperazine (33).

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv.) and methylzinc chloride (1.79 M in THF, 0.11 mL, 2.0 equiv.) to afford the title compound 33 (15 mg, 47% yield, >95% pure by 1H NMR) as a TFA salt. 1H NMR (500 MHz, Pyridine-d5) δ 7.27 – 7.24 (m, 2H), 7.18 – 7.15 (m, 2H), 3.46 (s, 2H), 3.35 – 2.94 (m, 4H), 2.80 – 2.67 (m, 7H), 2.26 (s, 3H). Chemical Formula of [M+H]+: C13H21N2+; Exact Mass (calculated): 205.1705; HRMS (ESI+) (found): 205.1702.

(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-methylpyrimidin-2-yl)piperazin-1-yl)ethenone (34).

General Procedure B was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide and 2,6-dimethyl-1,3,6,2-dioxazaborocane-4,8-dione (21 mg, 0.12 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under
nucleus. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 34 (19 mg, 52% yield, >95% pure by $^1$H NMR as a white solid. $^1$H NMR (400 MHz, Pyridine-$d_5$, 90 °C) δ 8.22 (d, $J = 0.9$ Hz, 2H), 5.05 (ddd, $J = 10.4, 5.3, 3.2$ Hz, 1H), 4.65 – 4.57 (m, 1H), 4.32 (s, 2H), 4.21 (d, $J = 1.5$ Hz, 2H), 3.32 (td, $J = 13.8, 12.8, 3.7$ Hz, 1H), 3.14 (d, $J = 51.7$ Hz, 2H), 1.98 (d, $J = 0.7$ Hz, 3H), 1.24 (d, $J = 6.7$ Hz, 3H), 1.22 (s, 9H). Chemical Formula of [M+H]+: C$_{16}$H$_{27}$N$_4$O$_2$; Exact Mass (calculated): 307.2129; HRMS (ESI+) (found): 307.2132.

1-(4-butylbenzyl)-4-methylpiperazine (35).

General procedure G was followed using 1-(4-bromobenzyl)-4-methylpiperazine (35 mg, 0.13 mmol) as the aryl halide and 1-bromobutane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 35 (16 mg, 36% yield, >90% pure by $^1$H NMR) as a white solid, a TFA salt. $^1$H NMR (400 MHz, Pyridine-$d_5$) δ 7.38 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 7.9$ Hz, 2H), 3.62 (s, 2H), 3.61 (s, 3H), 3.00 – 2.94 (m, 4H), 2.83 – 2.76 (m, 4H), 2.71 – 2.65 (m, 2H), 2.61 (s, 3H), 1.72 – 1.62 (m, 2H), 1.41 (h, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H). Chemical Formula of [M+H]+: C$_{16}$H$_{27}$N$_2$; Exact Mass (calculated): 247.2174; HRMS (ESI+) (found): 247.2172.

(R)-2-(tert-butoxy)-1-(4-(5-butylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (36).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 1-bromobutane (27 mg, 0.20 mmol) as the alkyl reagent, and Ligand 13 ([2,2’-bipyridine]-6-carboximidamide hydrochloride). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 36 (17 mg, 47% yield, >90% pure by $^1$H NMR). $^1$H NMR (400 MHz, Pyridine-$d_5$) δ 8.35 (s, 2H), 5.18 – 5.10 (m, 1H), 4.71 (dt, $J = 13.2, 3.2$ Hz, 1H), 4.47 – 4.32 (m, 1H), 4.27 (d, $J = 1.5$ Hz, 3H), 3.44 – 3.34 (m, 1H), 3.33 – 3.08 (m, 2H), 2.42 (t, 2H), 1.59 – 1.48 (m, 2H), 1.39 – 1.32 (m, 2H), 1.32 – 1.29 (m, 4H), 1.28 (s, 9H), 0.92 (t, $J = 7.3$ Hz, 3H). Chemical Formula of [M+H]+: C$_{19}$H$_{33}$N$_4$O$_2$; Exact Mass (Calculated): 349.2604; HRMS (ESI+) (found): 349.2601.
1-(4-hexylbenzyl)-4-methylpiperazine (37).

![Chemical structure of 1-(4-hexylbenzyl)-4-methylpiperazine (37).](image)

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv.) and hexylzinc bromide (0.45 M in THF, 0.44 mL, 2.0 equiv.) to afford the title compound 37 (17 mg, 44% yield, >95% pure by ^1^H NMR) as a TFA salt. ^1^H NMR (500 MHz, Pyridine-^d_5) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.24 (m, 2H), 3.49 (s, 2H), 3.24 – 2.96 (m, 4H), 2.75 – 2.72 (m, 4H), 2.67 (s, 3H), 2.62 – 2.55 (m, 2H), 1.63 – 1.53 (m, 2H), 1.32 – 1.16 (m, 6H), 0.87 – 0.80 (m, 3H). Chemical Formula of [M+H]^+: C_{18}H_{31}N_{2}^+; Exact Mass (calculated): 275.2487; HRMS (ESI+) (found): 275.2486.

(R)-2-(tert-butoxy)-1-(4-(5-hexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (38).

![Chemical structure of (R)-2-(tert-butoxy)-1-(4-(5-hexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (38).](image)

General procedure J was followed using 1 (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol, 1.0 equiv.) and hexylzinc bromide (0.45 M in THF, 0.44 mL, 2.0 equiv.) to afford the title compound 38 (21 mg, 41% yield, >95% pure by ^1^H NMR) as a TFA salt. ^1^H NMR (400 MHz, Pyridine-^d_5) δ 8.30 (s, 2H), 5.13 – 5.02 (m, 1H), 4.64 (dt, J = 13.4, 3.4 Hz, 1H), 4.20 (d, J = 1.4 Hz, 4H), 3.44 – 2.94 (m, 3H), 2.37 (t, J = 7.6 Hz, 2H), 1.50 (p, J = 7.4 Hz, 2H), 1.33 – 1.18 (m, 18H), 0.87 – 0.80 (m, 3H). Chemical Formula of [M+H]^+: C_{23}H_{37}N_{4}O_{2}^+; Exact Mass (calculated): 377.2917; HRMS (ESI+) (found): 377.2914.

1-(4-(cyclobutylmethyl)benzyl)-4-methylpiperazine (39).

![Chemical structure of 1-(4-(cyclobutylmethyl)benzyl)-4-methylpiperazine (39).](image)

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv.) and cyclobutylmethylzinc bromide (0.50 M in THF, 0.40 mL, 2.0 equiv.) to afford the title compound 39 (18 mg, 47% yield, >95% pure by ^1^H NMR) as a TFA salt. ^1^H NMR (500 MHz, Pyridine-^d_5) δ 7.31 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 3.47 (s, 2H), 3.27 – 2.91 (m, 4H), 2.79 – 2.67 (m, 7H), 2.65 (d, J = 7.5 Hz, 2H), 2.58 – 2.45 (m, 1H), 2.02 – 1.85 (m, 2H), 1.82 – 1.71 (m, 2H), 1.71 – 1.61 (m, 2H). Chemical Formula of [M+H]^+: C_{17}H_{27}N_{2}^+; Exact Mass (calculated): 259.2174; HRMS (ESI+) (found): 259.2172.
(R)-2-((tert-butoxy)-1-(4-(5-(cyclobutylmethyl)pyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (40).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, (bromomethyl)cyclobutane (20 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N'2,N'6-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 40 (25 mg, 69% yield, >90% pure by ¹H NMR).

¹H NMR (400 MHz, Pyridine-d₅) δ 8.25 (s, 2H), 5.11 – 5.00 (m, 1H), 4.63 (dt, J = 13.5, 3.3 Hz, 1H), 4.39 – 4.24 (m, 1H), 3.32 (td, J = 13.7, 13.1, 3.6 Hz, 1H), 3.25 – 2.98 (m, 2H), 2.46 – 2.37 (m, 3H), 2.02 – 1.93 (m, 2H), 1.81 – 1.71 (m, 2H), 1.67 – 1.56 (m, 2H), 1.22 (d, J = 6.7 Hz, 13H), 1.20 (s, 9H).

Chemical Formula of [M+H]+: C₂₀H₃₃N₄O₂⁺; Exact Mass (calculated): 361.2604; HRMS (ESI+) (found): 361.2601.

Methyl 3-(4-(4-methylpiperazin-1-yl)methyl)phenyl)propanoate (41).

General procedure G was followed using 1-(4-bromobenzyl)-4-methylpiperazine (35 mg, 0.13 mmol) as the aryl halide and methyl 3-bromopropanoate (32 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 41 (8.7 mg, 18% yield, >90% pure by ¹H NMR) as a white solid, a TFA salt. ¹H NMR (400 MHz, Pyridine-d₅) δ 7.37 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.67 (s, 3H), 3.58 (s, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.92 – 2.84 (m, 4H), 2.78 – 2.71 (m, 6H), 2.55 (s, 3H). Chemical Formula of [M+H]+: C₁₆H₂₅N₂O₂⁺ ; Exact Mass (calculated): 277.1916; HRMS (ESI+) (found): 277.1914.

Methyl (R)-3-(2-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)propanoate (42).
General procedure G was followed using \((R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(\text{tert-butoxy})ethan-1-one\) (48 mg, 0.13 mmol) as the aryl halide and methyl 3-bromopropanoate (32 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 42 (18 mg, 36% yield, >90% pure by \(^1H\) NMR) as a yellow oil. \(^1H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.24 (s, 2H), 4.86 – 4.76 (m, 1H), 4.41 – 4.32 (m, 1H), 4.15 – 3.91 (m, 4H), 3.59 (s, 3H), 3.16 (td, \(J = 13.6, 12.5, 3.6\) Hz, 1H), 2.70 (t, \(J = 7.0\) Hz, 2H), 2.58 (td, \(J = 7.3, 1.1\) Hz, 2H), 1.18 (s, 9H), 1.08 (d, \(J = 6.7\) Hz, 3H). Chemical Formula of [M+H]^+: C\(_{19}\)H\(_{31}\)N\(_4\)O\(_4\)^+; Exact Mass (calculated): 379.2345; HRMS (ESI+) (found): 379.2343.

Ethyl 3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)propanoate (43)

\[
\text{H}_3\text{C}-\text{N} \quad \text{O} \quad \text{O} \quad \text{CH}_3
\]

General procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv) and (3-ethoxy-3-oxopropyl)zinc) bromide (0.23 M in THF, 0.87 mL, 2.0 equiv) to afford the title compound 43 (29 mg, 70% yield, >95% pure by \(^1H\) NMR) as a TFA salt. \(^1H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.18 (d, \(J = 8.2\) Hz, 2H), 7.14 (d, \(J = 8.2\) Hz, 2H), 4.01 (q, \(J = 7.1\) Hz, 2H), 3.38 (s, 2H), 2.81 (t, \(J = 7.5\) Hz, 2H), 2.57 (t, \(J = 7.5\) Hz, 2H), 2.33 (s, 8H), 2.14 (s, 3H), 1.12 (t, \(J = 7.1\) Hz, 3H). Chemical Formula of [M+H]^+: C\(_{17}\)H\(_{27}\)N\(_2\)O\(_2^+\); Exact Mass (calculated): 291.2073; HRMS (ESI+) (found): 291.2072.

Ethyl (\(R\))-3-(2-(4-((\text{tert-butoxy})acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)propanoate (44).

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{CH}_3
\]

General procedure J was followed using (\(R\))-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(\text{tert-butoxy})ethanone (37 mg, 0.10 mmol, 1.0 equiv.) and (3-ethoxy-3-oxopropyl)zinc) bromide (0.23 M in THF, 0.87 mL, 2.0 equiv.) to afford the title compound 44 (21 mg, 41% yield, >95% pure by \(^1H\) NMR) as a TFA salt. \(^1H\) NMR (400 MHz, Pyridine-\(d_5\)) \(\delta\) 8.34 (s, 2H), 5.04 (ddd, \(J = 6.7, 4.0, 2.6\) Hz, 1H), 4.61 (dt, \(J = 13.5, 3.4\) Hz, 1H), 4.19 (d, \(J = 1.5\) Hz, 3H), 4.13 – 4.03 (m, 2H), 3.41 – 2.94 (m, 3H), 2.76 (t, \(J = 7.3\) Hz, 2H), 2.58 (td, \(J = 7.3, 0.8\) Hz, 2H), 1.20 (d, \(J = 0.8\) Hz, 12H), 1.11 (td, \(J = 7.1, 0.8\) Hz, 3H). Chemical Formula of [M+H]^+: C\(_{20}\)H\(_{39}\)N\(_4\)O\(_4^+\); Exact Mass (calculated): 393.2502; HRMS (ESI+) (found): 393.2500.
1-(4-cyclobutylbenzyl)-4-methylpiperazine (45).

![Chemical Structure](image)

General procedure E was followed using 1-(4-bromobenzyl)-4-methylpiperazine (34 mg, 0.13 mmol) as the aryl halide and potassium cyclobutyltrifluoroborate (25 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 45 (21 mg, 45% yield, >95% pure by $^1$H NMR) $^1$H NMR (400 MHz, Pyridine-$d_5$) δ 7.32 – 7.26 (m, 2H), 7.26 – 7.18 (m, 2H), 3.53 (s, 2H), 3.50 – 3.44 (m, 1H), 2.95 – 2.85 (m, 4H), 2.55 – 2.51 (m, 3H), 2.34 – 2.21 (m, 2H), 2.16 – 2.02 (m, 2H), 2.01 – 1.86 (m, 1H). Chemical Formula of [M+H]$^+$: C$_{16}$H$_{25}$N$_2$$^+$; Exact Mass (calculated): 245.2018; HRMS (ESI+) (found): 245.2014.

(R)-2-(tert-butoxy)-1-(4-(5-cyclobutylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (46).

![Chemical Structure](image)

General Procedure J was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol, 1.0 equiv.) and cyclobutylzinc bromide (0.44 M in THF, 0.45 mL, 2.0 equiv.) to afford the title compound 46 (44 mg, 95% yield, >95% pure by $^1$H NMR) as a TFA salt. $^1$H NMR (400 MHz, Pyridine-$d_5$) δ 8.32 (s, 2H), 5.12 – 5.02 (m, 1H), 4.65 (dt, J = 13.4, 3.3 Hz, 1H), 4.20 (d, J = 1.4 Hz, 4H), 3.42 – 2.89 (m, 4H), 2.29 – 2.13 (m, 2H), 2.10 – 1.69 (m, 4H), 1.24 (d, J = 6.7 Hz, 3H), 1.21 (s, 9H). Chemical Formula of [M+H]$^+$: C$_{19}$H$_{31}$N$_4$O$_2$$^+$; Exact Mass (calculated): 374.2447; HRMS (ESI+) (found): 347.2445.

1-(4-cyclopentylbenzyl)-4-methylpiperazine (47).

![Chemical Structure](image)

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv.) and cyclopentylzinc bromide (0.44 M in THF, 0.45 mL, 2.0 equiv.) to afford the title compound 47 (21 mg, 54% yield, >95% pure by $^1$H NMR) as a TFA salt. $^1$H NMR (500 MHz, Pyridine-$d_5$) δ 7.33 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 3.49 (s, 2H), 3.26 – 2.99 (m, 4H), 2.99 – 2.88 (m, 1H), 2.83 – 2.67 (m, 7H), 2.10 – 1.90 (m, 2H), 1.79 –
1.64 (m, 2H), 1.64 – 1.48 (m, 4H). Chemical Formula of [M+H]+: C_{17}H_{27}N_{2}+; Exact Mass (calculated): 259.2174; HRMS (ESI+) (found): 259.2172.

(R)-2-(tert-butoxy)-1-(4-(5-cyclopentylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (48).

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{C} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\end{align*}
\]

General procedure G was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (48 mg, 0.13 mmol) as the aryl halide and bromocyclopentane (28 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 48 (14 mg, 29% yield, >90% pure by \textsuperscript{1}H NMR) as an off-white solid. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \delta 8.25 (s, 2H), 4.80 (ddt, \textit{J} = 9.3, 6.8, 3.8 Hz, 1H), 4.44 – 4.30 (m, 1H), 4.17 – 3.89 (m, 4H), 3.15 (t, \textit{J} = 13.5, 12.5, 3.6 Hz, 1H), 2.85 (tt, \textit{J} = 9.3, 7.4 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.81 – 1.70 (m, 2H), 1.70 – 1.57 (m, 2H), 1.57 – 1.43 (m, 2H), 1.18 (s, 9H), 1.08 (d, \textit{J} = 6.7 Hz, 3H). Chemical Formula of [M+H]+: C_{20}H_{33}N_{4}O_{2}+; Exact Mass (calculated): 361.2604; HRMS (ESI+) (found): 361.2598.

1-(4-cyclohexylbenzyl)-4-methylpiperazine (49)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{H} \\
\end{align*}
\]

General procedure E was followed using 1-(4-bromobenzyl)-4-methylpiperazine (34 mg, 0.13 mmol) as the aryl halide and potassium cyclohexyltrifluoroborate (29 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 49 (26 mg, 53% yield, >95% pure by \textsuperscript{1}H NMR) \textsuperscript{1}H NMR (400 MHz, Pyridine-\textit{d}_5) \delta 7.32 – 7.28 (m, 2H), 7.25 – 7.19 (m, 2H), 3.52 (s, 2H), 2.96 – 2.85 (m, 4H), 2.73 – 2.62 (m, 4H), 2.56 – 2.51 (m, 3H), 2.51 – 2.44 (m, 1H), 1.89 – 1.81 (m, 2H), 1.79 – 1.72 (m, 2H), 1.71 – 1.61 (m, 1H), 1.47 – 1.29 (m, 4H), 1.29 – 1.12 (m, 1H). Chemical Formula of [M+H]+: C_{18}H_{29}N_{2}+; Exact Mass (calculated): 273.2331; HRMS (ESI+) (found): 273.2330.
(R)-2-(tert-butoxy)-1-(4-(5-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (50).

General Procedure J was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol, 1.0 equiv) and cyclohexylzinc bromide (0.25 M in THF, 0.80 mL, 2.0 equiv) to afford the title compound 50 (24 mg, 49% yield, >95% pure by $^1$H NMR) as a TFA salt. $^1$H NMR (400 MHz, Pyridine-$d_5$) $\delta$ 8.32 (s, 2H), 5.11 – 5.04 (m, 1H), 4.74 – 4.56 (m, 1H), 4.47 – 4.06 (m, 4H), 3.54 – 2.92 (m, 3H), 2.48 – 2.23 (m, 1H), 1.90 – 1.57 (m, 5H), 1.40 – 1.12 (m, 17H). Chemical Formula of [M+H]$^+$: C$_{21}$H$_{35}$N$_4$O$_2$ $^+$; Exact Mass (calculated): 375.2760; HRMS (ESI+) (found): 375.2757.

1-methyl-4-(4-(1-phenylethyl)benzyl)piperazine (51).

General Procedure J was followed using 1-(4-bromobenzyl)-4-methylpiperazine (27 mg, 0.10 mmol, 1.0 equiv) and $\alpha$-methylbenzylzinc bromide (0.33 M in THF, 0.61 mL, 2.0 equiv) to afford the title compound 51 (23 mg, 55% yield, >95% pure by $^1$H NMR) as a TFA salt. $^1$H NMR (500 MHz, Pyridine-$d_5$) $\delta$ 7.37 – 7.28 (m, 8H), 7.26 – 7.20 (m, 1H), 4.16 (q, J = 7.3 Hz, 1H), 3.45 (s, 2H), 3.30 – 2.89 (m, 4H), 2.70 (s, 7H), 1.60 (d, J = 7.2 Hz, 3H). Chemical Formula of [M+H]$^+$: C$_{20}$H$_{27}$N$_2$ $^+$; Exact Mass (calculated): 295.2174; HRMS (ESI+) (found): 295.2172.

2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-(1-phenylethyl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (52).

General Procedure J was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol, 1.0 equiv) and $\alpha$-methylbenzylzinc bromide (0.33 M in THF, 0.61 mL, 2.0 equiv) to afford the title compound 52 (27 mg, 52% yield, >95% pure by $^1$H NMR) as a TFA salt. $^1$H NMR (400 MHz, Pyridine-$d_5$) $\delta$ 8.35 (s, 2H), 7.32 – 7.22 (m, 4H), 7.22 – 7.15 (m, 1H), 5.08 – 5.00 (m, 1H), 4.62 (dt, J = 13.3, SI-21
3.3 Hz, 1H), 4.48 – 4.14 (m, 4H), 3.98 (d, J = 7.3 Hz, 1H), 3.37 – 3.26 (m, 1H), 3.26 – 2.94 (m, 2H), 1.55 (d, J = 7.2 Hz, 3H), 1.24 – 1.18 (m, 12H). Chemical Formula of [M+H]^+: C_{23}H_{33}N_{4}O_{2}^+; Exact Mass (calculated): 397.2604; HRMS (ESI+) (found): 397.2600.

(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-(1-methylcyclopropyl)pyrimidin-2-yl)piperazin-1-yl)ethenone (53).

General Procedure A was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide and potassium trifluoro-(1-methylcyclopropyl) boranuide (21 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. Upon completion, the reaction was concentrated, taken up in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 53 (13 mg, 39% yield, 92% pure by 1H NMR) as a white solid. 1H NMR (400 MHz, DMSO-d$_6$) δ 8.25 (s, 2H), 4.84 – 4.74 (m, 1H), 4.35 (ddd, J = 13.4, 4.1, 1.9 Hz, 1H), 4.12 – 3.92 (m, 4H), 3.19 – 3.09 (m, 2H), 2.98 (s, 1H), 1.31 (s, 3H), 1.17 (s, 9H), 1.07 (d, J = 6.7 Hz, 3H), 0.79 – 0.73 (m, 2H), 0.67 – 0.62 (m, 2H). Chemical Formula of [M+H]^+: C_{19}H_{31}N_{4}O_{2}^+; Exact Mass (calculated): 347.2447; HRMS (ESI+) (found): 347.2444.
**Figure 3:**

1-(3-(tetrahydro-2\textsubscript{H}-pyran-4-yl)phenyl)-1\textsubscript{H}-pyrazole (13)

![Chemical structure of 13](image)

General procedure E was followed using 1-(3-bromophenyl)-1\textsubscript{H}-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(tetrahydro-2\textsubscript{H}-pyran-4-yl)borate (31 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 13 (16 mg, 57% yield, >95% pure by \textsuperscript{1}H NMR).

**\textsuperscript{1}H NMR** (400 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) 8.52 (dd, \(J = 2.6, 0.6\) Hz, 1H), 7.76 – 7.71 (m, 2H), 7.70 – 7.65 (m, 1H), 7.42 (t, \(J = 7.8\) Hz, 1H), 7.23 – 7.18 (m, 1H), 6.56 – 6.52 (m, 1H), 4.00 – 3.94 (m, 2H), 3.50 – 3.40 (m, 2H), 2.90 – 2.81 (m, 1H), 1.77 – 1.68 (m, 4H).

**\textsuperscript{13}C NMR** (101 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) 148.05, 141.27, 140.32, 130.00, 128.19, 124.98, 117.21, 116.73, 108.18, 67.80, 41.14, 33.83. Chemical Formula of [M+H]\textsuperscript{+}: \(\text{C}_{14}\text{H}_{17}\text{N}_{2}\text{O}\text{;}\) Exact Mass (calculated): 229.1341; **HRMS** (ESI+) (found): 229.1337.

7-(tetrahydro-2\textsubscript{H}-pyran-4-yl)-1\textsubscript{H}-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3\textsubscript{H})-one (14)

![Chemical structure of 14](image)

General procedure G was followed using 7-bromo-1\textsubscript{H}-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3\textsubscript{H})-one (34 mg, 0.13 mmol) as the aryl halide and 4-bromotetrahydro-2\textsubscript{H}-pyran (41 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 14 (12 mg, 33% yield, >90% pure by \textsuperscript{1}H NMR) as a yellow solid.

**\textsuperscript{1}H NMR** (400 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) 8.91 – 8.88 (m, 1H), 7.81 (dd, \(J = 9.3, 0.9\) Hz, 1H), 4.98 (s, 2H), 4.31 (s, 2H), 4.02 – 3.94 (m, 2H), 3.04 – 2.93 (m, 1H), 1.82 – 1.65 (m, 4H).

**\textsuperscript{13}C NMR** (101 MHz, DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) 183.75, 157.95, 146.87, 133.63, 130.93, 124.48, 116.91, 116.65, 71.63, 67.10, 64.46, 37.53, 32.83. Chemical Formula of [M+H]\textsuperscript{+}: \(\text{C}_{15}\text{H}_{17}\text{N}_{2}\text{O}_{3}\text{;}\) Exact Mass (calculated): 273.1239; **HRMS** (ESI+) (found): 273.1237.
tert-butyl 4-(3-(1H-pyrazol-1-yl)phenyl)piperidine-1-carboxylate (15).

General Procedure K was followed using 1-(3-bromophenyl)-1H-pyrazole (22 mg, 0.10 mmol, 1.0 equiv.) and (1-(tert-butoxycarbonyl)piperidin-4-yl)zinc iodide (0.13 M in THF, 1.5 mL, 2.0 equiv.) to afford the title compound 15 (23 mg, 51% yield, 90% pure by 1H NMR) as a TFA salt. 

\[ \text{1H NMR (400 MHz, DMSO-}d_6\text{)} \delta 8.52 (d, J = 2.5 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.67 (ddd, J = 8.1, 2.3, 1.0 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.23 – 7.15 (m, 1H), 6.53 (dd, J = 2.5, 1.8 Hz, 1H), 4.14 – 4.06 (m, 2H), 2.92 – 2.70 (m, 3H), 1.84 – 1.75 (m, 2H), 1.64 – 1.48 (m, 2H), 1.42 (s, 9H). \]

\[ \text{13C NMR (101 MHz, DMSO)} \delta 154.34, 147.93, 141.27, 140.31, 130.01, 128.21, 125.09, 117.18, 116.79, 108.17, 79.07, 44.08, 42.16, 33.07, 28.59. \]

Chemical Formula of [M+H]^+: C_{19}H_{26}N_{3}O_{2}^+; Exact Mass (calculated): 328.2025; HRMS (ESI+) (found): 328.2022.

tert-butyl 4-(4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)piperidine-1-carboxylate (16).

General procedure E was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium (1-(tert-butoxycarbonyl)piperidin-4-yl)trifluoroborate (45 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 16 (16 mg, 35% yield, >95% pure by 1H NMR). 

\[ \text{1H NMR (400 MHz, DMSO-}d_6\text{)} \delta 8.91 – 8.86 (m, 1H), 7.77 – 7.70 (m, 1H), 7.68 – 7.61 (m, 1H), 4.96 (s, 2H), 4.27 (s, 2H), 4.15 – 4.05 (m, 2H), 2.95 – 2.81 (m, 3H), 1.92 – 1.82 (m, 2H), 1.62 – 1.47 (m, 2H), 1.43 (s, 9H). \]

\[ \text{13C NMR (101 MHz, DMSO)} \delta 184.16, 158.38, 154.33, 147.31, 133.93, 131.35, 125.03, 117.33, 117.07, 79.13, 72.08, 64.90, 44.07, 38.97, 32.55, 28.57. \]

Chemical Formula of [M+H]^+: C_{20}H_{26}N_{3}O_{4}^+; Exact Mass (calculated): 372.1923; HRMS (ESI+) (found): 372.1920.

1-(3-(methoxymethyl)phenyl)-1H-pyrazole (17)
General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(methoxymethyl)borate (24 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 17 (9.5 mg, 40% yield, >95% pure by $^1$H NMR). $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.50 (dd, $J = 2.5$, 0.6 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.78 – 7.69 (m, 2H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.27 – 7.22 (m, 1H), 6.58 – 6.52 (m, 1H), 4.49 (s, 2H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 141.94, 141.40, 140.50, 140.20, 129.90, 128.18, 125.54, 117.78, 108.32, 73.66, 58.11. Chemical Formula of $[\text{M+H}]^+$: $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}$; Exact Mass (calculated): 189.1028; HRMS (ESI+) (found): 189.1026.

7-(methoxymethyl)-1H-pyrano[3',4':4,5] imidazo[1,2-a]pyridin-4(3H)-one (18).

![Chemical Structure of 7-(methoxymethyl)-1H-pyrano[3',4':4,5] imidazo[1,2-a]pyridin-4(3H)-one](attachment:image.png)

General procedure E was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(methoxymethyl)borate (24 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 18 (15 mg, 54% yield, >95% pure by $^1$H NMR). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.11 – 8.91 (m, 1H), 7.87 – 7.72 (m, 1H), 7.71 – 7.54 (m, 1H), 4.99 (s, 2H), 4.63 – 4.50 (m, 2H), 4.31 (s, 2H), 3.36 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 184.29, 158.53, 147.68, 131.43, 126.94, 126.26, 117.26, 117.19, 72.08, 70.72, 64.88, 58.14. Chemical Formula of $[\text{M+H}]^+$: $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_3$; Exact Mass (calculated): 233.0926; HRMS (ESI+) (found): 233.0924.

tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidine-1-carboxylate (19).

![Chemical Structure of tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidine-1-carboxylate](attachment:image.png)

General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and boc-L-proline (40 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 19 (11 mg, 26% yield, >95% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.32 (d, $J = 2.5$ Hz, 1H), 7.68 (d, $J = 1.7$ Hz, 1H), 7.66 – 7.56 (m, 2H), 7.46 – 7.34 (m,
tert-butyl 2-(4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)pyrrolidine-1-carboxylate (20).

General procedure E was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium (1-(tert-butoxycarbonyl)pyrrolidin-2-yl)trifluoroborate (43 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 20 (9.3 mg, 21% yield, >95% pure by 1H NMR). 1H NMR (400 MHz, DMSO-d6) δ 8.89 – 8.84 (m, 1H), 7.79 – 7.72 (m, 1H), 7.61 – 7.54 (m, 1H), 4.96 (s, 2H), 4.94 – 4.86 (m, 1H), 4.28 (s, 2H), 3.53 (t, J = 6.7 Hz, 2H), 2.41 – 2.32 (m, 1H), 1.93 – 1.81 (m, 3H), 1.26 (s, 9H). Chemical Formula of [M+H]⁺: C19H24N3O4⁺; Exact Mass (calculated): 358.1767; HRMS (ESI+) (found): 358.1765.

tert-butyl 3-(3-(1H-pyrazol-1-yl)benzyl)azetidine-1-carboxylate (54).

General Procedure A was followed using 1-(3-bromophenyl)-1H-pyrazole (22 mg, 0.10 mmol) as the aryl halide and potassium (1-[(tert-butoxy)carbonyl]azetidin-3-yl)methyltrifluoroboranuïde (36 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 54 (13 mg, 42% yield, >95% pure by 1H NMR as a clear oil. 1H NMR (400 MHz, DMSO-d6) δ 8.36 – 8.29 (m, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 1.2 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.36 (td, J = 7.6, 1.1 Hz, 1H), 7.14 – 7.06 (m, 1H), 6.47 (dd, J = 2.5, 1.8 Hz, 1H), 3.89 (t, J = 8.0 Hz, 2H), 3.57 (dd, J = 8.3, 5.2 Hz, 2H), 2.94 (s, 2H), 2.91 (s, 1H), 1.35 (s, 9H). Chemical Formula of [M+H]⁺: C18H24N3O4⁺; Exact Mass (calculated): 314.1869; HRMS (ESI+) (found): 314.1866.
tert-butyl 3-((4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)methyl)azetidine-1-carboxylate (55).

General procedure G was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and tert-butyl 3-(bromomethyl)azetidine-1-carboxylate (48 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 55 (16 mg, 34% yield, >90% pure by $^1$H NMR) as a brown oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.94 (dd, $J$ = 1.8, 0.9 Hz, 1H), 7.79 (dd, $J$ = 9.1, 1.0 Hz, 1H), 7.63 (dd, $J$ = 9.2, 1.8 Hz, 1H), 4.98 (s, 2H), 4.31 (s, 2H), 3.90 – 3.83 (m, 2H), 3.64 – 3.56 (m, 2H), 3.01 (d, $J$ = 7.8 Hz, 2H), 2.93 – 2.78 (m, 1H), 1.36 (s, 9H). Chemical Formula of [M+H]$^+$: C$_{19}$H$_{24}$N$_3$O$_4$+; Exact Mass (calculated): 358.1767; HRMS (ESI+) (found): 358.1764.

1-(3-(oxetan-3-ylmethyl)phenyl)-1H-pyrazole (56).

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and 3-(bromomethyl)oxetane (29 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 56 (7.4 mg, 27% yield, 80% pure by $^1$H NMR) as a yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.48 (d, $J$ = 2.5 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.69 – 7.63 (m, 2H), 7.43 – 7.35 (m, 1H), 7.17 – 7.06 (m, 1H), 6.56 – 6.49 (m, 1H), 4.64 (dd, $J$ = 7.8, 5.8 Hz, 2H), 4.37 (t, $J$ = 6.1 Hz, 2H), 3.03 (d, $J$ = 7.9 Hz, 2H). Chemical Formula of [M+H]$^+$: C$_{13}$H$_{15}$N$_2$O$^+$; Exact Mass (calculated): 215.1184; HRMS (ESI+) (found): 215.1183.

7-(oxetan-3-ylmethyl)-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (57)
General procedure G was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and 3-(bromomethyl)oxetane (29 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 57 (4.4 mg, 13% yield, 90% pure by 1H NMR) as a brown oil. 1H NMR (400 MHz, DMSO-d6) δ 8.92 – 8.90 (m, 1H), 7.78 (dd, J = 9.1, 1.0 Hz, 1H), 7.60 (dd, J = 9.2, 1.8 Hz, 1H), 4.97 (s, 2H), 4.63 (dd, J = 7.7, 5.9 Hz, 2H), 4.37 (t, J = 6.1 Hz, 2H), 4.30 (s, 2H), 3.09 (d, J = 7.8 Hz, 2H). Chemical Formula of [M+H]+: C14H15N2O3+; Exact Mass (calculated): 259.1083; HRMS (ESI+) (found): 259.1081.

1-(3-(oxetan-3-yl)phenyl)-1H-pyrazole (58).

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and 3-bromooxetane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 58 (5.2 mg, 20% yield, >90% pure by 1H NMR) as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.54 (dd, J = 2.5, 0.6 Hz, 1H), 7.87 (t, J = 2.0 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.49 (t, J = 7.9 Hz, 1H), 7.37 – 7.30 (m, 1H), 6.55 (dd, J = 2.5, 1.7 Hz, 1H), 4.97 (dd, J = 8.4, 5.9 Hz, 2H), 4.68 (dd, J = 6.8, 5.9 Hz, 2H), 4.34 (tt, J = 8.4, 6.8 Hz, 1H). Chemical Formula of [M+H]+: C12H13N2O+; Exact Mass (calculated): 201.1028; HRMS (ESI+) (found): 201.1025.

7-(oxetan-3-yl)-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (59)

General procedure G was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and 3-bromooxetane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 59 (9.1 mg, 29% yield) as an impure mixture. Unlike other 3-bromooxetane products (58), this product unfortunately could not be purified to acceptable levels using reverse phase HPLC. Only the cross-electrophile coupling methods produced detectable amounts of this product, other methods tested failed to produce authentic product standards for characterization or comparison.
1-(3-(tetrahydrofuran-3-yl)phenyl)-1H-pyrazole (60).

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(tetrahydrofuran-3-yl)borate (28 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 60 (9.9 mg, 39% yield, >95% pure by 1H NMR). 1H NMR (500 MHz, DMSO-d6) δ 8.52 – 8.48 (m, 1H), 7.77 – 7.71 (m, 2H), 7.71 – 7.64 (m, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.25 – 7.19 (m, 1H), 6.56 – 6.52 (m, 1H), 4.10 – 4.03 (m, 1H), 4.02 – 3.94 (m, 1H), 3.86 – 3.77 (m, 1H), 3.64 – 3.58 (m, 1H), 3.51 – 3.43 (m, 1H), 2.40 – 2.30 (m, 1H), 2.04 – 1.93 (m, 1H). Chemical Formula of [M+H]+: C13H15N2O; Exact Mass (calculated): 215.1184; HRMS (ESI+) (found): 215.1182.

7-(tetrahydrofuran-3-yl)-1H-pyra[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (61).

General procedure E was followed using 7-bromo-1H-pyra[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(tetrahydrofuran-3-yl)borate (28 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 61 (9.9 mg, 31% yield, >95% pure by 1H NMR). 1H NMR (400 MHz, DMSO-d6) δ 8.96 – 8.91 (m, 1H), 7.92 – 7.75 (m, 1H), 7.75 – 7.57 (m, 1H), 4.98 (s, 2H), 4.30 (s, 2H), 4.12 – 4.02 (m, 1H), 4.02 – 3.90 (m, 1H), 3.90 – 3.75 (m, 1H), 3.72 – 3.62 (m, 1H), 3.62 – 3.50 (m, 1H), 2.42 – 2.31 (m, 1H), 2.06 – 1.92 (m, 1H). 13C NMR (101 MHz, DMSO) δ 184.21, 158.41, 147.30, 131.47, 131.35, 125.58, 117.57, 117.02, 73.75, 72.09, 68.00, 64.90, 41.49, 34.00. Chemical Formula of [M+H]+: C14H15N2O3; Exact Mass (calculated): 259.1083; HRMS (ESI+) (found): 259.1082.
**tert-butyl 3-(3-(1H-pyrazol-1-yl)phenyl)azetidine-1-carboxylate (62).**

![Chemical Structure](image)

General Procedure K was followed using 1-(3-bromophenyl)-1H-pyrazole (22 mg, 0.10 mmol, 1.0 equiv.) and (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc iodide (0.20 M in THF, 1.0 mL, 2.0 equiv.) to afford the title compound **62** (26 mg, 64% yield, >95% pure by ^1^H NMR) as a TFA salt. ^1^H NMR (400 MHz, DMSO-d$_6$) δ 8.54 (d, J = 2.5 Hz, 1H), 7.81 (t, J = 2.0 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.47 (t, J = 7.9 Hz, 1H), 7.31 – 7.24 (m, 1H), 6.55 (dd, J = 2.5, 1.8 Hz, 1H), 4.29 (d, J = 5.8 Hz, 2H), 3.95 – 3.83 (m, 3H), 1.39 (d, J = 16.3 Hz, 9H). Chemical Formula of [M+H]^+: C$_{17}$H$_{22}$N$_3$O$_2$; Exact Mass (calculated): 300.1712; HRMS (ESI+) (found): 300.1708.

**tert-butyl 3-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)azetidine-1-carboxylate (63).**

![Chemical Structure](image)

General Procedure K was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol, 1.0 equiv.) and (1-(tert-butoxycarbonyl)azetidin-3-yl)zinc iodide (0.20 M in THF, 1.0 mL, 2.0 equiv.) to afford the title compound **63** (31 mg, 66% yield, >95% pure by ^1^H NMR) as a TFA salt. ^1^H NMR (400 MHz, DMSO-d$_6$) δ 8.95 (dt, J = 1.8, 0.9 Hz, 1H), 7.79 (dd, J = 9.3, 1.0 Hz, 1H), 7.71 (dd, J = 9.3, 1.9 Hz, 1H), 4.95 (s, 2H), 4.33 – 4.24 (m, 4H), 4.03 – 3.92 (m, 1H), 3.87 (dd, J = 8.3, 6.0 Hz, 2H), 1.41 (s, 9H). Chemical Formula of [M+H]^+: C$_{18}$H$_{22}$N$_3$O$_4$; Exact Mass (calculated): 344.1610; HRMS (ESI+) (found): 344.1607.

**tert-butyl 3-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidine-1-carboxylate (64).**

![Chemical Structure](image)

General Procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium (1-(tert-butoxycarbonyl)pyrrolidin-3-yl)trifluoroborate (43 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using
ammonium acetate conditions and a focused gradient to afford the title compound 64 (8.7 mg, 22% yield, >95% pure by 1H NMR). 1H NMR (600 MHz, DMSO-d6) δ 8.52 (d, J = 2.5 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.75 – 7.73 (m, 1H), 7.72 – 7.69 (m, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 6.56 – 6.49 (m, 1H), 3.78 – 3.71 (m, 1H), 3.53 – 3.47 (m, 1H), 3.47 – 3.39 (m, 1H), 3.26 – 3.20 (m, 1H), 2.28 – 2.19 (m, 1H), 2.06 – 1.97 (m, 1H), 1.42 (d, J = 8.7 Hz, 9H). Chemical Formula of [M+H]+: C18H24N3O2+; Exact Mass (calculated): 314.1869; HRMS (ESI+) (found): 314.1866.

dert-butyl 3-(4-oxo-3,4-dihydro-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)pyrrolidine-1-carboxylate (65).

General procedure G was followed using 7-bromo-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and tert-butyl 3-bromopyrrolidine-1-carboxylate (48 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 65 (8.9 mg, 19% yield, >90% pure by 1H NMR) as a brown oil. 1H NMR (400 MHz, DMSO-d6) δ 8.93 (s, 1H), 7.82 (d, J = 9.3 Hz, 1H), 7.75 (dd, J = 9.3, 1.9 Hz, 1H), 4.98 (s, 2H), 4.30 (s, 2H), 3.75 (t, J = 9.1 Hz, 2H), 3.29 – 3.19 (m, 2H), 2.33 – 2.20 (m, 1H), 2.09 – 1.95 (m, 1H), 1.86 (s, 4H), 1.42 (s, 9H). Chemical Formula of [M+H]+: C19H24N3O4+; Exact Mass (calculated): 358.1767; HRMS (ESI+) (found): 358.1765.

dert-butyl (4-(3-(1H-pyrazol-1-yl)phenyl)cyclohexyl)carbamate (66).

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium (4-((tert-butoxycarbonyl)amino)cyclohexyl)trifluoroborate (48 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and purified through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 66 as a 3:1 mixture of inseparable trans/cis isomers (17 mg, 41% yield, >95% pure by 1H NMR). 1H NMR (500 MHz, DMSO-d6) δ 8.50 (d, J = 2.2 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.71 (dd, J = 10.4, 1.9 Hz, 2H), 7.64 (dd, J = 8.1, 2.3, 1.0 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (dt, J = 7.7, 1.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.53 (dd, J = 2.5, 1.7 Hz, 1H), 2.63 – 2.52 (m, 1H), 1.86 (ddd, J = 29.0, 10.7, 3.8 Hz, 5H), 1.71 (d, J = 12.9 Hz, 1H), 1.57 (dq, J = 16.0, 12.8, 11.8, 3.4 Hz, 4H), 1.41 (s,
tert-butyl (4-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)cyclohexyl)carbamate (67).

General procedure E was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium (4-((tert-butoxycarbonyl)amino)cyclohexyl)trifluoroborate (48 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 67 as a 2.5:1 mixture of inseparable trans/cis isomers (11 mg, 22% yield, >95% pure by $^1$H NMR). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.91 – 8.79 (m, 1H), 7.80 – 7.68 (m, 2H), 7.65 (dd, $J = 9.3, 1.8$ Hz, 1H), 6.29 (d, $J = 7.8$ Hz, 1H), 4.95 (d, $J = 2.5$ Hz, 3H), 4.27 (d, $J = 2.1$ Hz, 3H), 3.33 (ddt, $J = 11.5, 7.7, 3.9$ Hz, 1H), 2.68 – 2.59 (m, 1H), 2.01 – 1.87 (m, 5H), 1.87 – 1.72 (m, 1H), 1.72 – 1.58 (m, 2H), 1.53 (td, $J = 12.5, 3.3$ Hz, 2H), 1.41 (s, 3H), 1.40 (s, 10H), 1.38 – 1.29 (m, 1H). Chemical Formula of [M+H]$^+$: C$_{21}$H$_{28}$N$_3$O$_4$; Exact Mass (calculated): 386.2080; HRMS (ESI$^+$) (found): 386.2079.

tert-butyl 3-(1H-pyrazol-1-yl)benzylcarbamate (68).

General Procedure A was followed using 1-(3-bromophenyl)-1H-pyrazole (22 mg, 0.10 mmol) as the aryl halide and potassium ((tert-butoxycarbonylamino)methyl)trifluoroborate (31 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 68 (8.1 mg, 29% yield, >95% pure by $^1$H NMR as a clear oil. $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 8.46 (dd, $J = 2.5, 0.6$ Hz, 1H), 7.75 (dd, $J = 1.8, 0.6$ Hz, 2H), 7.69 (ddd, $J = 8.1, 2.3, 1.0$ Hz, 1H), 7.46 (dt, $J = 15.7, 7.0$ Hz, 2H), 7.18 (ddd, $J = 7.7, 1.7, 1.0$ Hz, 1H), 6.56 (dd, $J = 2.5, 1.7$ Hz, 1H), 4.21 (d, $J = 6.2$ Hz, 2H), 1.41 (s, 9H). Chemical Formula of [M+H]$^+$: C$_{15}$H$_{20}$N$_3$O$_2$; Exact Mass (calculated): 274.1556; HRMS (ESI$^+$) (found): 274.1553.
tert-butyl ((4-oxo-3,4-dihydro-1H-pyra[3',4':5,6]imidazo[1,2-a]pyridin-7-yl)methyl)carbamate (69).

General Procedure A was followed using 7-bromo-1H-pyra[3',4':5,6]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol) as the aryl halide and potassium [[[(tert-butoxycarbonyl)amino]methyl]trifluoroborate (31 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 69 (8.1 mg, 25% yield, 90% pure by 1H NMR as a yellow oil. 1H NMR (600 MHz, DMSO-d6) δ 8.93 (s, 1H), 7.82 (d, J = 9.1 Hz, 1H), 7.61 (dd, J = 9.2, 1.8 Hz, 1H), 7.57 (t, J = 6.2 Hz, 1H), 4.99 (s, 2H), 4.31 (s, 2H), 4.24 (d, J = 6.1 Hz, 2H), 1.40 (s, 9H). Chemical Formula of [M+H]+: C16H20N3O4+; Exact Mass (calculated): 318.1448; HRMS (ESI+) (found): 318.1452.

1-(3-(tetrahydro-2H-pyran-2-yl)phenyl)-1H-pyrazole (70).

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(tetrahydro-2H-pyran-2-yl)borate (31 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 70 (11 mg, 39% yield, >95% pure by 1H NMR). 1H NMR (500 MHz, DMSO-d6) δ 8.51 – 8.47 (m, 1H), 7.82 – 7.78 (m, 1H), 7.75 – 7.72 (m, 1H), 7.72 – 7.68 (m, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.56 – 6.51 (m, 1H), 4.42 – 4.36 (m, 1H), 4.09 – 4.01 (m, 1H), 3.60 – 3.51 (m, 1H), 1.92 – 1.82 (m, 2H), 1.74 – 1.53 (m, 3H), 1.53 – 1.37 (m, 1H). Chemical Formula of [M+H]+: C14H17N2O+; Exact Mass (calculated): 229.1341; HRMS (ESI+) (found): 229.1337.

7-(tetrahydro-2H-pyran-2-yl)-1H-pyra[3',4':5,6]imidazo[1,2-a]pyridin-4(3H)-one (71).
General procedure E was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(tetrahydro-2H-pyran-2-yl)borate (31 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 71 (7.5 mg, 22% yield, >95% pure by 1H NMR). 1H NMR (400 MHz, DMSO-\textit{d}_6) \delta 9.00 (d, J = 1.6 Hz, 1H), 7.74 (dd, J = 9.3, 1.0 Hz, 1H), 7.64 (dd, J = 9.2, 1.8 Hz, 1H), 4.96 (s, 2H), 4.51 (dd, J = 11.3, 2.2 Hz, 1H), 4.28 (s, 2H), 4.08 (ddt, J = 11.3, 4.0, 2.1 Hz, 1H), 3.65 – 3.57 (m, 1H), 1.99 – 1.88 (m, 2H), 1.72 – 1.44 (m, 4H). Chemical Formula of [M+H]^+ : C_{19}H_{24}N_{3}O_{4}^+; Exact Mass (calculated): 273.1239; HRMS (ESI+) (found): 273.1238.
1-(3-butylphenyl)-1H-pyrazole (72)

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium butyltrifluoroborate (26 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 72 (6.4 mg, 26% yield, >95% pure by 1H NMR). 1H NMR (600 MHz, DMSO-d$_6$) $\delta$ 8.48 (dd, $J$ = 2.5, 0.6 Hz, 1H), 7.73 – 7.72 (m, 1H), 7.69 – 7.67 (m, 1H), 7.65 – 7.62 (m, 1H), 7.38 (t, $J$ = 7.8 Hz, 1H), 7.15 – 7.11 (m, 1H), 6.55 – 6.51 (m, 1H), 2.68 – 2.62 (m, 2H), 1.64 – 1.56 (m, 2H), 1.37 – 1.28 (m, 2H), 0.91 (t, $J$ = 7.4 Hz, 3H). Chemical Formula of [M+H]$^+$: C$_{13}$H$_{17}$N$_2^+$; Exact Mass (calculated): 201.1392 HRMS (ESI+) (found): 201.1390.

7-butyl-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (73).

General procedure G was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and 1-bromobutane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 73 (9.2 mg, 29% yield, >90% pure by 1H NMR) as a brown oil. 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.88 (dd, $J$ = 1.9, 1.0 Hz, 1H), 7.78 (dd, $J$ = 9.2, 1.0 Hz, 1H), 7.63 (dd, $J$ = 9.2, 1.8 Hz, 1H), 4.98 (s, 2H), 4.30 (s, 2H), 2.71 (t, $J$ = 7.6 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.33 (h, $J$ = 7.3 Hz, 2H), 0.91 (t, $J$ = 7.3 Hz, 3H). Chemical Formula of [M+H]$^+$: C$_{14}$H$_{17}$N$_2$O$_2^+$; Exact Mass (calculated): 245.1290; HRMS (ESI+) (found): 245.1288.

1-(3-(cyclobutylmethyl)phenyl)-1H-pyrazole (74).
General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium (cyclobutylmethyl)trifluoroborate (27 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 74 (7.5 mg, 28% yield, >95% pure by 1H NMR). 1H NMR (600 MHz, DMSO-d6) δ 8.47 (dd, J = 2.5, 0.6 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.66 – 7.61 (m, 2H), 7.39 – 7.35 (m, 1H), 7.11 – 7.07 (m, 1H), 6.55 – 6.52 (m, 1H), 2.74 (d, J = 7.6 Hz, 2H), 2.62 – 2.55 (m, 1H), 2.03 – 1.93 (m, 2H), 1.86 – 1.79 (m, 2H), 1.75 – 1.68 (m, 2H). Chemical Formula of [M+H]+: C_{14}H_{17}N_{2}+; Exact Mass (calculated): 213.1392; HRMS (ESI+) (found): 213.1390.

7-(cyclobutylmethyl)-1H-pyrano[3’,4’:4,5]imidazo[1,2-a]pyridin-4(3H)-one (75).

General procedure H was followed using 7-bromo-1H-pyrano[3’,4’:4,5]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol) as the aryl halide, (bromomethyl)cyclobutane (31 mg, 0.20 mmol) as the alkyl reagent, and ligand 13 ([2,2’-bipyridine]-6-carboximidamide hydrochloride). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 75 (11 mg, 44% yield, >95% pure by 1H NMR). 1H NMR (400 MHz, DMSO-d6) δ 8.84 (dd, J = 2.0, 0.9 Hz, 1H), 7.70 (dd, J = 9.2, 1.0 Hz, 1H), 7.53 (dd, J = 9.2, 1.8 Hz, 1H), 4.95 (s, 2H), 4.27 (s, 2H), 2.81 (d, J = 7.5 Hz, 2H), 2.62 (dq, J = 15.4, 7.8 Hz, 1H), 2.13 – 1.98 (m, 2H), 1.91 – 1.81 (m, 2H), 1.79 – 1.68 (m, 2H). Chemical Formula of [M+H]+: C_{15}H_{17}N_{2}O_{2}+; Exact Mass (Calculated): 257.1290; HRMS (ESI+) (found): 257.1291.

(R)-tert-butyl-3-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)methyl)azetidine-1-carboxylate. (76).

General Procedure A was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide and potassium ((1-[(tert-butoxy)carbonyl]azetidin-3-yl)methyl)trifluoroboranuide (36 mg, 0.13 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 76 (24 mg, 52% yield, 90% pure by 1H NMR as a white solid. 1H NMR (400 MHz, Pyridine-d5, 90 °C) δ 8.27 (s, 2H), 5.06 (ddd, J =
6.7, 4.2, 2.6 Hz, 1H), 4.64 (dt, $J = 13.6, 3.4$ Hz, 1H), 4.33 (s, 1H), 4.29 – 4.13 (m, 3H), 4.00 (t, $J = 8.0$ Hz, 2H), 3.72 – 3.61 (m, 2H), 3.40 – 3.28 (m, 1H), 3.27 – 3.00 (m, 2H), 2.71 – 2.53 (m, 3H), 1.51 (s, 9H), 1.24 (d, $J = 6.7$ Hz, 3H), 1.22 (d, $J = 0.7$ Hz, 9H). Chemical Formula of [M+H]$^+$: $C_{24}H_{40}N_5O_4^+$; Exact Mass (calculated): 462.3075; HRMS (ESI$^+$) (found): 462.3078.

(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-oxetan-3-ylmethyl)pyrimidin-2-yl)piperazin-1-yl)ethenone (77).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 3-(bromomethyl)oxetane (31 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N'2,N'6-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 77 (18 mg, 49% yield, >90% pure by $^1$H NMR).

$^1$H NMR (400 MHz, Pyridine-$d_5$) $\delta$ 8.23 (d, $J = 0.6$ Hz, 2H), 5.04 (ddd, $J = 6.7, 4.0, 2.5$ Hz, 1H), 4.68 (dd, $J = 7.6, 5.9$ Hz, 2H), 4.62 (dt, $J = 13.5, 3.4$ Hz, 1H), 4.36 (t, $J = 6.0$ Hz, 3H), 4.19 (d, $J = 1.5$ Hz, 3H), 3.32 (td, $J = 13.6, 12.9, 3.6$ Hz, 1H), 3.10 (pt, $J = 7.5, 6.1$ Hz, 2H), 2.69 (d, $J = 7.7$ Hz, 2H), 2.07 (s, 1H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.20 (s, 9H). Chemical Formula of [M+H]$^+$: $C_{20}H_{33}N_4O_2^+$; Exact Mass (calculated): 361.2604; HRMS (ESI$^+$) (found): 361.2601.

1-(3-(2-methoxyethyl)phenyl)-1H-pyrazole (78).

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and 1-bromo-2-methoxyethane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 78 (11 mg, 38% yield, >90% pure by $^1$H NMR) as a yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.47 (d, $J = 2.7$ Hz, 1H), 7.76 – 7.69 (m, 2H), 7.70 – 7.63 (m, 1H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.21 – 7.14 (m, 1H), 6.53 (dd, $J = 2.5, 1.7$ Hz, 1H), 3.59 (t, $J = 6.8$ Hz, 2H), 3.25 (s, 3H), 2.88 (t, $J = 6.8$ Hz, 2H). Chemical Formula of [M+H]$^+$: $C_{12}H_{15}N_2O^+$; Exact Mass (calculated): 203.1184; HRMS (ESI$^+$) (found): 203.1181.
(R)-2-(tert-butoxy)-1-(4-(5-(2-methoxyethyl)pyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (79).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 1-bromo-2-methoxyethane (28 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N'2,N'6-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 79 (16 mg, 45% yield, >90% pure by $^1$H NMR). $^1$H NMR (400 MHz, Pyridine-$d_5$) δ 8.34 (d, $J$ = 0.7 Hz, 2H), 5.05 (ddd, $J$ = 10.2, 5.2, 3.1 Hz, 1H), 4.62 (ddd, $J$ = 13.5, 3.8, 2.8 Hz, 1H), 4.39 – 4.26 (m, 1H), 4.19 (d, $J$ = 1.4 Hz, 3H), 3.46 (t, $J$ = 6.4 Hz, 2H), 3.22 (s, 3H), 3.04 (s, 1H), 2.63 (t, $J$ = 6.4 Hz, 2H), 1.21 (d, $J$ = 6.7 Hz, 3H), 1.20 (s, 9H). Chemical Formula of [M+H]$^+$: C$_{18}$H$_{31}$N$_4$O$_3$; Exact Mass (Calculated): 351.2396; HRMS (ESI+) (found): 351.2394.

7-(2-methoxyethyl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (80).

General procedure G was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and 1-bromo-2-methoxyethane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 80 (5.6 mg, 17% yield, 90% pure by $^1$H NMR) as a brown oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.94 (dd, $J$ = 1.8, 1.0 Hz, 1H), 7.78 (dd, $J$ = 9.2, 1.0 Hz, 1H), 7.65 (dd, $J$ = 9.2, 1.8 Hz, 1H), 4.98 (s, 2H), 4.30 (s, 2H), 3.60 (t, $J$ = 6.3 Hz, 2H), 3.25 (s, 3H), 2.95 (t, $J$ = 6.2 Hz, 2H). Chemical Formula of [M+H]$^+$: C$_{13}$H$_{15}$N$_2$O$_3$; Exact Mass (calculated): 247.1083; HRMS (ESI+) (found): 247.1080.

4-(3-(1H-pyrazol-1-yl)phenyl)butanenitrile (81).

General Procedure A was followed using 1-(3-bromophenyl)-1H-pyrazole (22 mg, 0.10 mmol) as the aryl halide and potassium 3-cyanopropytrifluoroborate (23 mg, 0.13 mmol) as the alkyl reagent. After the reaction was
complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 81 (8.3 mg, 39% yield, >95% pure by $^1$H NMR as a yellow oil. 

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.50 (dd, $J$ = 2.5, 0.6 Hz, 1H), 7.73 (dd, $J$ = 1.8, 0.6 Hz, 1H), 7.72 (td, $J$ = 1.7, 0.8 Hz, 1H), 7.68 (ddd, $J$ = 8.1, 2.3, 1.0 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.22 – 7.11 (m, 1H), 6.54 (dd, $J$ = 2.5, 1.7 Hz, 1H), 2.80 – 2.70 (m, 2H), 2.52 (d, $J$ = 7.2 Hz, 2H), 2.01 – 1.86 (m, 2H).

Chemical Formula of [M+H]$^+$: C$_{13}$H$_{14}$N$_3$; Exact Mass (calculated): 212.1182; HRMS (ESI$^+$) (found): 212.1184.

4-(4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)butanenitrile (82).

General procedure H was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol) as the aryl halide, 4-bromobutanenitrile (21 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N$'2$,N$'6$-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 82 (9.1 mg, 24% yield, >90% pure by $^1$H NMR). 

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.92 (d, $J$ = 1.6 Hz, 1H), 7.74 (dd, $J$ = 9.1, 1.0 Hz, 1H), 7.60 (dd, $J$ = 9.2, 1.8 Hz, 1H), 4.96 (s, 2H), 4.28 (s, 2H), 2.85 – 2.79 (m, 2H), 2.51 (t, $J$ = 7.1 Hz, 2H), 1.96 (p, $J$ = 7.2 Hz, 2H).

Chemical Formula of [M+H]$^+$: C$_{14}$H$_{14}$N$_3$O$_2$; Exact Mass (calculated): 256.1086; HRMS (ESI$^+$) (found): 256.1085.

3-(3-(1H-pyrazol-1-yl)phenyl)-N,N-dimethylpropanamide (83).

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and 3-bromo-N,N-dimethylpropanamide (34 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 83 (12 mg, 37% yield, 90% pure by $^1$H NMR) as a brown oil. 

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.46 (d, $J$ = 2.5 Hz, 1H), 7.72 (t, $J$ = 2.3 Hz, 2H), 7.64 (ddd, $J$ = 8.1, 2.4, 1.0 Hz, 1H), 7.38 (t, $J$ = 7.8 Hz, 1H), 7.18 (dt, $J$ = 7.7, 1.3 Hz, 1H), 6.53 (dd, $J$ = 2.5, 1.8 Hz, 1H), 2.94 (s, 3H), 2.87 (dd, $J$ = 8.6, 6.9 Hz, 2H), 2.82 (s, 3H), 2.66 (dd, $J$ = 8.5, 6.9 Hz, 2H).

Chemical Formula of [M+H]$^+$: C$_{14}$H$_{18}$N$_3$O; Exact Mass (calculated): 244.1450; HRMS (ESI$^+$) (found): 244.1449.
(R)-3-{2-[(4-(3-tert-butoxy)acyl)-2-methylpiperaz-1-yl]pyrimidin-5-yl}-N,N-dimethylpropanamide (84).

General Procedure B was followed using (R)-1-{4-(5-bromopyrimidin-2-yl)-3-methylpiperaz-1-yl}-2-(3-tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide and N,N-dimethyl-3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)propanamide (31 mg, 0.12 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC to afford the title compound 84 (26 mg, 67% yield, >95% pure by 1H NMR as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.23 (s, 2H), 4.78 (td, J = 9.6, 8.1, 5.0 Hz, 1H), 4.39 – 4.30 (m, 1H), 4.12 – 3.82 (m, 4H), 3.17 – 3.08 (m, 2H), 2.67 – 2.61 (m, 2H), 2.53 (td, J = 7.1, 1.2 Hz, 2H), 1.17 (s, 9H), 1.06 (d, J = 6.6 Hz, 3H). Chemical Formula of [M+H]+: C20H34N5O3+; Exact Mass (calculated): 392.2662; HRMS (ESI+) (found): 392.2660.

N,N-dimethyl-3-{4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl}propenamide (85).

General procedure H was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol) as the aryl halide, 3-bromo-N,N-dimethylpropanamide (36 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N',N'-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 85 (9.2 mg, 23% yield, 93% pure by 1H NMR). 1H NMR (400 MHz, DMSO-d6) δ 8.93 – 8.90 (m, 1H), 7.70 (dd, J = 9.2, 1.0 Hz, 1H), 7.62 (dd, J = 9.2, 1.8 Hz, 1H), 4.95 (s, 2H), 4.27 (d, J = 0.8 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.88 (s, 6H), 2.68 (t, J = 7.2 Hz, 2H). Chemical Formula of [M+H]+: C15H18N3O3+; Exact Mass (calculated): 288.1348; HRMS (ESI+) (found): 288.1348.
1-(3-isopropylphenyl)-1H-pyrazole (86).

![Chemical structure of 1-(3-isopropylphenyl)-1H-pyrazole](image)

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium trifluoro(isopropyl)borate (23 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound **86** (8.3 mg, 36% yield, >95% pure by ¹H NMR). ¹H NMR (600 MHz, DMSO-d₆) δ 8.51 – 8.48 (m, 1H), 7.76 – 7.68 (m, 2H), 7.66 – 7.61 (m, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.21 – 7.16 (m, 1H), 6.56 – 6.51 (m, 1H), 2.97 (hept, J = 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H). Chemical Formula of [M+H]+: C₁₂H₁₅N₂⁺; Exact Mass (calculated): 187.1235; HRMS (ESI+) (found): 187.1231.

7-isopropyl-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (87).

![Chemical structure of 7-isopropyl-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one](image)

General procedure G was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and tert-butyl 2-bromopropane (23 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound **87** (5.4 mg, 18% yield, >90% pure by ¹H NMR) as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.91 – 8.86 (m, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.72 (dd, J = 9.2, 1.9 Hz, 1H), 4.98 (s, 2H), 4.30 (s, 2H), 3.09 (hept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 6H). Chemical Formula of [M+H]+: C₁₃H₁₅N₂O₂⁺; Exact Mass (calculated): 231.1134; HRMS (ESI+) (found): 231.1131.

1-(3-cyclopropylphenyl)-1H-pyrazole (88).

![Chemical structure of 1-(3-cyclopropylphenyl)-1H-pyrazole](image)

General Procedure J was followed using 1-(3-bromophenyl)-1H-pyrazole (21 mg, 0.09 mmol, 1.0 equiv.) and cyclopropylzinc bromide (0.23 M in THF, 0.78 mL, 2.0 equiv.) to afford the title compound **88** (17 mg, 61% yield,
7-cyclopropyl-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (89).

General Procedure J was followed using 7-bromo-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (27 mg, 0.10 mmol, 1.0 equiv.) and cyclopropylzinc bromide (0.23 M in THF, 0.87 mL, 2.0 equiv.) to afford the title compound 89 (22 mg, 64% yield, 87% pure by 1H NMR) as a TFA salt. 1H NMR (400 MHz, Pyridine-d5) δ 8.93 – 8.85 (m, 1H), 7.65 – 7.57 (m, 1H), 7.18 (dd, J = 9.3, 1.9 Hz, 1H), 5.02 (s, 2H), 4.36 (s, 2H), 1.88 – 1.76 (m, 1H), 0.93 – 0.80 (m, 2H), 0.74 – 0.55 (m, 2H). Chemical Formula of [M+H]+: C13H15N2O2+; Exact Mass (calculated): 229.0977; HRMS (ESI+) (found): 229.0974.

1-(3-cyclobutylphenyl)-1H-pyrazole (90).

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and bromocyclobutane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 90 (5.0 mg, 19% yield, >90% pure by 1H NMR) as a yellow oil. 1H NMR (400 MHz, DMSO-d6) δ 8.50 (dd, J = 2.5, 0.6 Hz, 1H), 7.77 – 7.60 (m, 3H), 7.40 (t, J = 7.8 Hz, 1H), 7.22 – 7.13 (m, 1H), 6.53 (dd, J = 2.5, 1.8 Hz, 1H), 3.59 (p, J = 8.8 Hz, 1H), 2.39 – 2.26 (m, 2H), 2.22 – 2.08 (m, 2H), 2.07 – 1.92 (m, 1H), 1.91 – 1.77 (m, 1H). Chemical Formula of [M+H]+: C13H15N2+; Exact Mass (calculated): 199.1235; HRMS (ESI+) (found): 199.1232.
7-cyclobutyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (91).

General procedure G was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and bromocyclobutane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 91 (8.6 mg, 27% yield, >90% pure by \textsuperscript{1}H NMR) as a brown oil. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) δ 8.85 – 8.80 (m, 1H), 7.80 (dd, \(J = 9.2, 1.0\) Hz, 1H), 7.69 (dd, \(J = 9.3, 1.9\) Hz, 1H), 4.97 (s, 2H), 4.30 (s, 2H), 3.75 – 3.62 (m, 1H), 2.42 – 2.29 (m, 2H), 2.22 – 1.94 (m, 3H), 1.93 – 1.80 (m, 1H). Chemical Formula of [M+H]+: \(\text{C}_{14}\text{H}_{15}\text{N}_{2}\text{O}_{2}\); Exact Mass (calculated): 243.1134; HRMS (ESI+) (found): 243.1131.

1-(3-cyclopentylphenyl)-1H-pyrazole (92).

General procedure E was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and potassium cyclopentyltrifluoroborate (27 mg, 0.16 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 92 (11 mg, 40% yield, >95% pure by \textsuperscript{1}H NMR). \textsuperscript{1}H NMR (600 MHz, DMSO-\textit{d}_6) δ 8.49 (dd, \(J = 2.5, 0.6\) Hz, 1H), 7.74 – 7.72 (m, 1H), 7.72 – 7.70 (m, 1H), 7.65 – 7.62 (m, 1H), 7.39 (t, \(J = 7.8\) Hz, 1H), 7.21 – 7.17 (m, 1H), 6.56 – 6.51 (m, 1H), 3.09 – 3.00 (m, 1H), 2.10 – 2.00 (m, 2H), 1.84 – 1.74 (m, 2H), 1.72 – 1.63 (m, 2H), 1.63 – 1.53 (m, 2H). Chemical Formula of [M+H]+: \(\text{C}_{14}\text{H}_{17}\text{N}_{2}\); Exact Mass (calculated): 213.1392; HRMS (ESI+) (found): 213.1390.

7-cyclopentyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (93).

General procedure E was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and potassium cyclopentyltrifluoroborate (27 mg, 0.16 mmol) as the alkyl reagent.
After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 MeOH/DMSO and filtered through Celite. The product was purified by reverse phase HPLC using ammonium acetate conditions and a focused gradient to afford the title compound 93 (9.2 mg, 29% yield, >95% pure by $^1$H NMR). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.91 – 8.86 (m, 1H), 7.76 – 7.69 (m, 1H), 7.66 – 7.59 (m, 1H), 4.95 (s, 2H), 4.27 (s, 2H), 3.22 – 3.12 (m, 1H), 2.17 – 2.04 (m, 2H), 1.88 – 1.76 (m, 2H), 1.76 – 1.65 (m, 2H), 1.65 – 1.53 (m, 2H). Chemical Formula of [M+H]$^+$: C$_{15}$H$_{17}$N$_2$O$_2^+$; Exact Mass (calculated): 257.1290; HRMS (ESI+) (found): 257.1289.

1-(3-cyclohexylphenyl)-1H-pyrazole (94).

![1-(3-cyclohexylphenyl)-1H-pyrazole](image)

General procedure G was followed using 1-(3-bromophenyl)-1H-pyrazole (29 mg, 0.13 mmol) as the aryl halide and bromocyclohexane (31 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 94 (9.7 mg, 33% yield, >90% pure by $^1$H NMR) as a yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.49 (dd, $J = 2.5$, 0.6 Hz, 1H), 7.74 – 7.59 (m, 3H), 7.38 (t, $J = 7.8$ Hz, 1H), 7.16 (dt, $J = 7.7$, 1.5 Hz, 1H), 6.52 (dd, $J = 2.5$, 1.7 Hz, 1H), 2.58 (tt, $J = 11.7$, 3.2 Hz, 1H), 1.92 – 1.64 (m, 5H), 1.54 – 1.18 (m, 5H). Chemical Formula of [M+H]$^+$: C$_{15}$H$_{19}$N$_2^+$; Exact Mass (calculated): 227.1548; HRMS (ESI+) (found): 227.1546.

7-cyclohexyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (95).

![7-cyclohexyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one](image)

General procedure G was followed using 7-bromo-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and bromocyclohexane (31 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 95 (5.3 mg, 15% yield, >90% pure by $^1$H NMR) as a yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.89 – 8.84 (m, 1H), 7.79 (dd, $J = 9.2$, 1.0 Hz, 1H), 7.69 (dd, $J = 9.2$, 1.9 Hz, 1H), 4.97 (s, 2H), 4.30 (s, 2H), 2.75 – 2.66 (m, 1H), 1.91 – 1.78 (m, 4H), 1.76 – 1.68 (m, 1H), 1.52 – 1.33 (m, 4H), 1.33 – 1.20 (m, 1H). Chemical Formula of [M+H]$^+$: C$_{16}$H$_{19}$N$_2$O$_2^+$; Exact Mass (calculated): 271.1447; HRMS (ESI+) (found): 271.1445.
(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-oxetan-3-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (96).

General procedure G was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (48 mg, 0.13 mmol) as the aryl halide and 3-bromooxetane (26 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 96 (11 mg, 22% yield, >90% pure by 1H NMR) as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 2H), 4.92 – 4.78 (m, 3H), 4.59 (ddd, J = 6.8, 5.9, 2.0 Hz, 2H), 4.40 (dt, J = 13.6, 3.4 Hz, 1H), 4.18 – 3.91 (m, 5H), 3.24 – 3.13 (m, 1H), 1.19 (s, 9H), 1.10 (d, J = 6.6 Hz, 3H). Chemical Formula of [M+H]+: C18H29N4O3+; Exact Mass (calculated): 349.2240; HRMS (ESI+) (found): 349.2237.

2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-tetrahydrofuran-3-yl)pyrimidin-2-yl)piperazin-1-yl)ethenone (97).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 3-bromotetrahydrofuran (31 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N2,N6-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 97 (18 mg, 51% yield, >90% pure by 1H NMR). 1H NMR (400 MHz, Pyridine-d5) δ 8.34 (s, 2H), 5.10 – 5.01 (m, 1H), 4.62 (t, J = 3.3 Hz, 1H), 4.40 – 4.25 (m, 1H), 4.20 (d, J = 1.4 Hz, 3H), 4.01 (dd, J = 8.4, 7.2 Hz, 1H), 3.95 (td, J = 8.3, 4.9 Hz, 1H), 3.81 (dt, J = 8.4, 7.4 Hz, 1H), 3.64 (dd, J = 8.4, 6.8 Hz, 1H), 3.37 – 3.29 (m, 1H), 3.14 (p, J = 7.3 Hz, 2H), 2.17 (ddt, J = 12.6, 7.9, 4.9 Hz, 1H), 1.82 (dq, J = 12.3, 7.6 Hz, 1H), 1.24 (d, J = 6.7 Hz, 3H), 1.21 (s, 9H). Chemical Formula of [M+H]+: C19H31N4O3+; Exact Mass (calculated): 363.2396; HRMS (ESI+) (found): 363.2394.

(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-tetrahydro-2H-pyran-4-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (98).
General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (37 mg, 0.10 mmol) as the aryl halide, 4-bromotetrahydro-2H-pyran (33 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-N\textsuperscript{2},N\textsuperscript{6}-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 98 (31 mg, 83% yield, >90% pure by \textsuperscript{1}H NMR).

\textsuperscript{1}H NMR (400 MHz, Pyridine-\textit{d}_5) δ 8.33 (s, 2H), 5.07 (ddd, \textit{J} = 6.7, 4.1, 2.5 Hz, 1H), 4.65 (dt, \textit{J} = 13.5, 3.3 Hz, 1H), 4.40 – 4.26 (m, 1H), 4.20 (d, \textit{J} = 1.5 Hz, 2H), 4.03 – 3.97 (m, 2H), 3.41 (td, \textit{J} = 11.5, 2.5 Hz, 2H), 3.30 (ddd, \textit{J} = 24.8, 11.5, 8.8 Hz, 2H), 3.15 – 3.01 (m, 1H), 2.55 (tt, \textit{J} = 11.7, 4.2 Hz, 1H), 1.69 (ddt, \textit{J} = 13.3, 11.6, 4.4 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.24 (d, \textit{J} = 6.6 Hz, 3H), 1.21 (s, 9H). Chemical Formula of [M+H]\textsuperscript{+}: C\textsubscript{20}H\textsubscript{33}N\textsubscript{4}O\textsubscript{3}; Exact Mass (calculated): 377.2553; HRMS (ESI+) (found): 377.2550.

\textit{(R)-tert-butyl 3-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)azetidine-1-carboxylate (99).}

\textsuperscript{1}H NMR (400 MHz, Pyridine-\textit{d}_5) δ 8.38 (d, \textit{J} = 0.5 Hz, 2H), 5.10 – 5.02 (m, 1H), 4.64 (dt, \textit{J} = 13.5, 3.4 Hz, 1H), 4.48 – 4.45 (m, 1H), 4.29 (t, \textit{J} = 8.5 Hz, 3H), 4.20 (d, \textit{J} = 1.5 Hz, 3H), 3.97 (ddd, \textit{J} = 8.4, 6.1, 1.2 Hz, 2H), 3.56 – 3.47 (m, 1H), 3.33 (td, \textit{J} = 14.1, 13.3, 3.6 Hz, 1H), 3.26 – 3.01 (m, 2H), 1.51 (s, 9H), 1.24 (d, \textit{J} = 6.7 Hz, 12H), 1.21 (s, 9H). Chemical Formula of [M+H]\textsuperscript{+}: C\textsubscript{23}H\textsubscript{38}N\textsubscript{5}O\textsubscript{4}; Exact Mass (calculated): 448.2924; HRMS (ESI+) (found): 448.2921.

te\textit{r}-butyl 3-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)pyrrolidine-1-carboxylate (100).
General procedure G was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-\((\text{tert}-\text{butoxy})\)ethan-1-one (48 mg, 0.13 mmol) as the aryl halide and \(\text{tert}\)-butyl 3-bromopyrrolidine-1-carboxylate (48 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 100 (21 mg, 34% yield, >90% pure by \(^1\)H NMR) as an off-white solid. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.30 (s, 2H), 4.83 (ddd, \(J = 6.7, 4.1, 2.6\) Hz, 1H), 4.40 (dt, \(J = 13.5, 3.4\) Hz, 1H), 4.16 – 3.91 (m, 4H), 3.71 – 3.64 (m, 1H), 3.47 (ddd, \(J = 11.2, 8.3, 3.2\) Hz, 1H), 3.36 – 3.12 (m, 5H), 2.25 – 2.11 (m, 1H), 1.43 (s, 9H), 1.20 (s, 9H), 1.11 (d, \(J = 6.7\) Hz, 3H). Chemical Formula of [M+H]\(^+\): \(\text{C}_{24}\text{H}_{40}\text{N}_5\text{O}_4^+\); Exact Mass (calculated): 462.3080; HRMS (ESI+) (found): 462.3078.

\((\text{R})\)-\(\text{tert}\)-butyl 4-(2-(4-(2-(\(\text{tert}\)-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)piperidine-1-carboxylate (101).

General procedure H was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-\((\text{tert}-\text{butoxy})\)ethanone (37 mg, 0.10 mmol) as the aryl halide, \(\text{tert}\)-butyl 4-bromopiperidine-1-carboxylate (53 mg, 0.20 mmol) as the alkyl reagent, and ligand 1 ((2Z,6Z)-\(N'\),2,\(N'\),6-dicyanopyridine-2,6-bis(carboximidamide) (2.6 mg, 0.01 mmol). After the reaction was complete, the reaction was concentrated under nitrogen. The crude residue was dissolved in DMA and filtered through Celite. The product was purified by reverse phase HPLC using trifluoroacetic acid conditions and a focused gradient to afford the title compound 101 (31 mg, 65% yield, >90% pure by \(^1\)H NMR). \(^1\)H NMR (400 MHz, Pyridine-\(d_5\)) \(\delta\) 8.31 (s, 2H), 5.10 – 5.03 (m, 1H), 4.64 (dt, \(J = 13.5, 3.3\) Hz, 1H), 4.39 – 4.26 (m, 3H), 4.20 (dd, \(J = 2.9, 1.5\) Hz, 3H), 3.33 (td, \(J = 13.8, 12.9, 3.6\) Hz, 1H), 3.13 (td, \(J = 12.8, 3.1\) Hz, 1H), 2.77 (ddd, \(J = 13.2, 12.0, 2.8\) Hz, 2H), 2.47 (tt, \(J = 12.9, 4.2\) Hz, 1H), 1.69 (dt, \(J = 13.3, 2.7\) Hz, 2H), 1.57 (dd, \(J = 12.4, 4.1\) Hz, 1H), 1.52 (s, 9H), 1.23 (d, \(J = 6.7\) Hz, 4H), 1.21 (s, 9H). Chemical Formula of [M+H]\(^+\): \(\text{C}_{25}\text{H}_{42}\text{N}_5\text{O}_4^+\); Exact Mass (calculated): 476.3237; HRMS (ESI+) (found): 476.3235.

\(\text{tert}\)-butyl (R)-4-(2-(4-(2-(\(\text{tert}-\text{butoxy})\)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)cyclohexylcarbamate (102).

General procedure G was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-\((\text{tert}-\text{butoxy})\)ethan-1-one (48 mg, 0.13 mmol) as the aryl halide and \(\text{tert}\)-butyl (4-bromocyclohexyl)carbamate (52 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was concentrated under...
nitrogen. The crude residue was dissolved in 1:1 DMSO/MeOH and purified via reverse phase HPLC to afford the title compound 102 (17 mg, 27% yield, >90% pure by $^1$H NMR) as an inseparable mixture of 2.7:1 trans/cis stereoisomers. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.32 (s, 1H), 8.27 (s, 2H), 6.44 (s, 1H), 6.26 (d, $J$ = 7.8 Hz, 1H), 4.92 – 4.76 (m, 1H), 4.47 – 4.30 (m, 2H), 4.15 – 3.86 (m, 6H), 3.71 (dd, $J$ = 7.8, 4.1 Hz, 1H), 3.32 (ddt, $J$ = 19.2, 11.5, 7.6, 3.8 Hz, 2H), 3.24 – 3.12 (m, 3H), 2.36 (tt, $J$ = 12.1, 3.5 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.97 – 1.86 (m, 3H), 1.86 – 1.76 (m, 3H), 1.76 – 1.61 (m, 3H), 1.61 – 1.51 (m, 2H), 1.48 (dd, $J$ = 12.5, 3.2 Hz, 2H), 1.42 (s, 4H), 1.41 – 1.39 (m, 13H), 1.39 – 1.23 (m, 3H), 1.23 – 1.18 (m, 13H), 1.10 (dd, $J$ = 6.7, 2.5 Hz, 4H). Chemical Formula of [M+H]$^+$: C$_{26}$H$_{45}$N$_5$O$_4$; Exact Mass (calculated): 490.3393; HRMS (ESI+) (found): 490.3391.
Figure 4b:

**tert-butyl (1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)carbamate (22).**

![Chemical Structure of 22](image)

General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and boc-L-alanine (35 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound **22** (9.1 mg, 24% yield, >90% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.45 (dd, $J = 2.5, 0.6$ Hz, 1H), 7.80 (t, $J = 2.0$ Hz, 1H), 7.74 (dd, $J = 1.7, 0.6$ Hz, 1H), 7.66 (ddd, $J = 8.1, 2.3, 1.0$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.42 (t, $J = 7.9$ Hz, 1H), 7.26 – 7.12 (m, 1H), 6.54 (dd, $J = 2.5, 1.7$ Hz, 1H), 4.77 – 4.62 (m, 1H), 1.37 (s, 9H), 1.34 (d, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 155.31, 147.72, 141.29, 140.16, 129.81, 128.09, 124.12, 116.99, 116.58, 108.24, 78.27, 50.07, 28.72, 23.36. Chemical Formula of [M+H]$^+$: C$_{16}$H$_{22}$N$_3$O$_2$; Exact Mass (calculated): 288.1712; HRMS (ESI+) (found): 288.1708.

**tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)azetidine-1-carboxylate (23).**

![Chemical Structure of 23](image)

General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (38 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound **23** (12 mg, 32% yield, 90% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.35 (d, $J = 2.5$ Hz, 1H), 7.79 (t, $J = 2.0$ Hz, 1H), 7.75 – 7.66 (m, 2H), 7.46 (t, $J = 7.9$ Hz, 1H), 7.28 (ddd, $J = 7.8, 1.8, 0.9$ Hz, 1H), 6.50 (dd, $J = 2.6, 1.7$ Hz, 1H), 5.22 (dd, $J = 8.8, 6.3$ Hz, 1H), 3.97 – 3.88 (m, 2H), 2.65 (ddt, $J = 11.1, 8.8, 7.2$ Hz, 1H), 2.10 (dt, $J = 11.2, 7.9, 6.2$ Hz, 1H), 1.29 (s, 9H). $^{13}$C NMR (101 MHz, DMSO) δ 155.99, 144.82, 141.38, 140.26, 129.95, 128.17, 124.15, 117.60, 116.51, 108.29, 79.11, 63.87, 28.71, 28.41, 25.23. Chemical Formula of [M+H]$^+$: C$_{17}$H$_{22}$N$_3$O$_2$; Exact Mass (calculated): 300.1712; HRMS (ESI+) (found): 300.1708.
4-(3-(1H-pyrazol-1-yl)phenyl)azetidin-2-one (24).

General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and 4-oxoazetidine-2-carboxylic acid (22 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 24 (8.7 mg, 24% yield, acetic acid salt, >90% pure by \(^1\)H NMR) as an off-white solid. \(^1\)H NMR (500 MHz, \(\text{DMSO-d}_6\)) \(\delta\) 8.52 (dd, \(J = 2.5, 0.6 \text{ Hz, 1H}\)), 8.46 (s, 1H), 7.86 (t, \(J = 2.0 \text{ Hz, 1H}\)), 7.82 – 7.67 (m, 2H), 7.50 (t, \(J = 7.9 \text{ Hz, 1H}\)), 7.30 (ddt, \(J = 7.6, 1.7, 0.8 \text{ Hz, 1H}\)), 6.55 (dd, \(J = 2.5, 1.8 \text{ Hz, 1H}\)), 4.74 (dd, \(J = 5.3, 2.5 \text{ Hz, 1H}\)), 3.47 – 3.26 (m, 1H), 2.75 (ddd, \(J = 14.6, 2.5, 0.9 \text{ Hz, 1H}\)). \(^13\)C NMR (101 MHz, \(\text{DMSO-d}_6\)) \(\delta\) 167.56, 143.77, 141.49, 140.39, 130.26, 128.27, 123.92, 117.88, 116.20, 108.40, 48.93, 47.53. Chemical Formula of [M+H]^+: C\(_{12}\)H\(_{12}\)N\(_3\)O^+; Exact Mass (calculated): 214.0980; HRMS (ESI+) (found): 214.0978.

5-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidin-2-one (25).

General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and 5-oxopyrrolidine-2-carboxylic acid (24 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 25 (7.4 mg, 25% yield, >90% pure by \(^1\)H NMR) as an off-white solid. \(^1\)H NMR (500 MHz, \(\text{DMSO-d}_6\)) \(\delta\) 8.51 (dd, \(J = 2.5, 0.7 \text{ Hz, 1H}\)), 8.15 (s, 1H), 7.81 – 7.71 (m, 3H), 7.48 (t, \(J = 7.9 \text{ Hz, 1H}\)), 7.24 (ddt, \(J = 7.7, 1.6, 0.7 \text{ Hz, 1H}\)), 6.55 (dd, \(J = 2.5, 1.7 \text{ Hz, 1H}\)), 4.75 (t, \(J = 7.1 \text{ Hz, 1H}\)), 2.57 – 2.51 (m, 1H), 2.29 – 2.21 (m, 2H), 1.86 – 1.74 (m, 1H). \(^13\)C NMR (101 MHz, \(\text{DMSO-d}_6\)) \(\delta\) 177.67, 146.08, 141.43, 140.38, 130.20, 128.23, 123.98, 117.62, 116.27, 108.35, 57.26, 31.07, 30.57. Chemical Formula of [M+H]^+: C\(_{13}\)H\(_{15}\)N\(_3\)O^+; Exact Mass (calculated): 228.1137; HRMS (ESI+) (found): 228.1134.

6-(3-(1H-pyrazol-1-yl)phenyl)piperidin-2-one (26).
General procedure C was followed using 1-(3-bromophenyl)-1H-pyrazole (28 mg, 0.13 mmol) as the aryl halide and (S)-6-oxo-2-piperidinocarboxylic acid (27 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 26 (17 mg, 55% yield, >90% pure by $^1$H NMR) as an off-white solid.

$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 8.56 – 8.44 (m, 1H), 7.82 (d, $J$ = 2.0 Hz, 1H), 7.80 – 7.67 (m, 3H), 7.47 (t, $J$ = 7.9 Hz, 1H), 7.22 (ddt, $J$ = 7.5, 1.7, 0.9 Hz, 1H), 6.55 (dd, $J$ = 2.5, 1.7 Hz, 1H), 4.59 (dd, $J$ = 7.1, 5.0, 1.7 Hz, 1H), 2.33 – 2.14 (m, 2H), 2.11 – 1.96 (m, 1H), 1.76 – 1.55 (m, 3H).

$^{13}$C NMR (101 MHz, DMSO) $\delta$ 171.34, 146.14, 141.40, 140.24, 129.94, 128.37, 124.51, 117.48, 116.81, 108.32, 56.21, 31.85, 31.76, 19.28. Chemical Formula of [M+H]$^+$: C$_{14}$H$_{16}$N$_3$O; Exact Mass (calculated): 242.1293; HRMS (ESI+) (found): 242.1291.

tert-butyl (R)-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)methyl)carbamate (27).

General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide and boc-glycine (33 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 27 (15 mg, 29% yield, >90% pure by $^1$H NMR) as an off-white solid.

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.26 (s, 2H), 6.86 (s, 1H), 4.82 (dt, $J$ = 6.7, 3.4 Hz, 1H), 4.38 (dt, $J$ = 13.4, 3.5 Hz, 1H), 4.15 – 3.99 (m, 4H), 3.96 (d, $J$ = 6.1 Hz, 2H), 3.19 (m, 3H, appears for 5H due to broad water signal), 1.38 (s, 9H), 1.18 (s, 9H), 1.09 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 169.35, 169.27, 160.56, 157.87, 156.14, 121.84, 78.41, 74.30, 62.80, 62.65, 48.76, 46.81, 46.74, 45.63, 45.04, 41.61, 39.05, 38.94, 38.15, 28.66, 27.63, 27.57, 14.45, 14.42. Chemical Formula of [M+H]$^+$: C$_{21}$H$_{36}$N$_5$O$_4$; Exact Mass (calculated): 422.2767; HRMS (ESI+) (found): 422.2766.

tert-butyl (1-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)ethyl)carbamate (28).

General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide and boc-L-alanine (35 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 28 (16 mg, 44% yield, >90% pure by $^1$H NMR) as an off-white solid.

$^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 8.55 – 8.44 (m, 1H), 7.83 (d, $J$ = 2.0 Hz, 1H), 7.81 – 7.67 (m, 3H), 7.47 (t, $J$ = 7.9 Hz, 1H), 7.21 (dd, $J$ = 7.5, 1.7 Hz, 1H), 6.56 (dd, $J$ = 2.5, 1.7 Hz, 1H), 4.59 (dd, $J$ = 7.1, 5.0, 1.7 Hz, 1H), 2.33 – 2.14 (m, 2H), 2.11 – 1.96 (m, 1H), 1.76 – 1.55 (m, 3H).

$^{13}$C NMR (101 MHz, DMSO) $\delta$ 171.34, 146.14, 141.40, 140.24, 129.94, 128.27, 124.51, 117.48, 116.81, 108.32, 56.21, 31.85, 31.76, 19.28. Chemical Formula of [M+H]$^+$: C$_{14}$H$_{16}$N$_3$O; Exact Mass (calculated): 242.1293; HRMS (ESI+) (found): 242.1291.
and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 28 (13 mg, 24% yield, >90% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.30 (s, 2H), 6.87 (d, $J = 7.8$ Hz, 1H), 4.83 (dt, $J = 6.7$, 3.4 Hz, 1H), 4.51 (p, $J = 7.2$ Hz, 1H), 4.39 (dt, $J = 13.4$, 3.5 Hz, 1H), 4.19 – 3.93 (m, 4H), 3.22 – 3.11 (m, 4H), 1.37 (s, 9H), 1.19 (s, 9H), 1.10 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 169.37, 160.49, 156.47, 155.24, 126.64, 78.35, 74.30, 62.79, 62.64, 48.78, 46.73, 45.81, 45.65, 45.05, 38.13, 28.67, 27.62, 27.56, 22.42, 22.37, 14.44. Note: doubling observed in $^{13}$C NMR spectrum due to rotamers. Chemical Formula of [M+H]$^+$: C$_{22}$H$_{38}$N$_5$O$_4$; Exact Mass (calculated): 436.2924; HRMS (ESI+) (found): 436.2922.

**tert-butyl 2-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)azetidine-1-carboxylate (29).**

![](image)

General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide and 1-[(tert-butoxy)carbonyl]azetidine-2-carboxylic acid (38 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 29 (13 mg, 24% yield, >90% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.31 (s, 2H), 6.31 (s, 1H), 4.92 – 4.78 (m, 1H), 4.49 (dd, $J = 7.5$, 5.7 Hz, 1H), 4.41 (dt, $J = 13.2$, 3.3 Hz, 1H), 4.04 (d, $J = 3.9$ Hz, 4H), 3.25 – 3.11 (m, 2H), 3.01 (td, $J = 7.0$, 5.6 Hz, 2H), 1.84 – 1.73 (m, 2H), 1.38 (s, 9H), 1.19 (s, 9H), 1.10 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 173.56, 169.35, 160.69, 156.52, 127.03, 77.90, 74.27, 66.78, 62.74, 62.58, 46.76, 45.63, 45.02, 41.60, 38.72, 37.39, 28.67, 27.57, 27.52, 23.15, 14.39. Note: doubling observed in $^{13}$C NMR spectrum due to rotamers. Chemical Formula of [M+H]$^+$: C$_{23}$H$_{38}$N$_5$O$_4$; Exact Mass (calculated): 448.2924; HRMS (ESI+) (found): 448.2922.

**tert-butyl 2-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)pyrrolidine-1-carboxylate (30).**

![](image)
General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide boc-L-proline (40 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 30 (8.7 mg, 15% yield, >90% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.21 (s, 2H), 4.82 (dt, $J$ = 6.8, 3.4 Hz, 1H), 4.64 (dd, $J$ = 7.8, 4.2 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.15 – 3.92 (m, 4H), 3.48 – 3.43 (m, 3H), 3.19 (m, appears as 4H, likely less due to water), 2.32 – 2.18 (m, 1H), 1.88 – 1.82 (m, 2H), 1.81 – 1.71 (m, 1H), 1.29 (s, 9H), 1.18 (s, 9H), 1.12 – 1.06 (m, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 169.33, 169.27, 160.67, 156.39, 153.76, 126.46, 78.84, 74.29, 62.82, 62.67, 56.84, 56.49, 48.76, 46.82, 45.63, 45.04, 41.61, 38.98, 38.18, 35.31, 34.11, 28.54, 28.39, 27.61, 27.55, 23.73, 23.42, 14.37. Chemical Formula of [M+H]: C$_{24}$H$_{40}$N$_5$O$_4$; Exact Mass (calculated): 462.3080; HRMS (ESI+) (found): 462.3079.

6-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)piperidin-2-one (31).

General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide (S)-6-oxo-2-piperidinecarboxylic acid (27 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 31 (5.3 mg, 11% yield, >95% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.29 (s, 2H), 7.27 (s, 1H), 4.84 (dt, $J$ = 6.8, 3.3 Hz, 1H), 4.51 – 4.29 (m, 2H), 4.23 – 3.84 (m, 4H), 3.24 – 3.13 (m, 2H), 2.27 – 2.14 (m, 2H), 2.01 – 1.90 (m, 1H), 1.83 – 1.57 (m, 4H), 1.19 (s, 9H), 1.10 (d, $J$ = 6.6 Hz, 3H). Chemical Formula of [M+H]: C$_{24}$H$_{32}$N$_5$O$_3$; Exact Mass (calculated): 390.2505; HRMS (ESI+) (found): 390.2503.

2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-(tetrahydrofuran-2-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (32).

General procedure C was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide and tetrahydro-2-furoic acid (22 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 31 (5.3 mg, 11% yield, >95% pure by $^1$H NMR) as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.29 (s, 2H), 7.27 (s, 1H), 4.84 (dt, $J$ = 6.8, 3.3 Hz, 1H), 4.51 – 4.29 (m, 2H), 4.23 – 3.84 (m, 4H), 3.24 – 3.13 (m, 2H), 2.27 – 2.14 (m, 2H), 2.01 – 1.90 (m, 1H), 1.83 – 1.57 (m, 4H), 1.19 (s, 9H), 1.10 (d, $J$ = 6.6 Hz, 3H). Chemical Formula of [M+H]: C$_{24}$H$_{32}$N$_5$O$_3$; Exact Mass (calculated): 390.2505; HRMS (ESI+) (found): 390.2503.
MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 32 (8.8 mg, 19% yield, >90% pure by 1H NMR) as an off-white solid. 1H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 2H), 4.91 – 4.76 (m, 1H), 4.69 (t, J = 7.1 Hz, 1H), 4.46 – 4.33 (m, 1H), 4.18 – 3.98 (m, 4H), 3.93 (dt, J = 8.1, 6.9 Hz, 1H), 3.76 (td, J = 7.8, 6.3 Hz, 1H), 3.19 (td, J = 13.6, 12.6, 3.7 Hz, 2H), 2.23 (ddddd, J = 12.2, 8.0, 6.9, 5.3 Hz, 1H), 2.05 – 1.90 (m, 2H), 1.75 (dddt, J = 12.1, 8.7, 7.5 Hz, 1H), 1.19 (s, 9H), 1.10 (d, J = 6.7 Hz, 3H). 13C NMR (101 MHz, DMSO) δ 169.25, 160.88, 156.62, 156.60, 124.51, 76.51, 74.27, 68.02, 62.76, 62.61, 48.71, 46.83, 46.74, 45.59, 44.99, 41.58, 38.92, 38.12, 33.58, 27.59, 27.54, 26.03, 14.44. Note: doubling observed in 13C NMR spectrum due to rotamers. Chemical Formula of [M+H]+: C19H31N4O3+; Exact Mass (calculated): 363.2396; HRMS (ESI+) (found): 363.2393.
Minisci Byproducts

Occasionally Minisci radical addition byproducts were observed when using alkyl radical-mediated coupling methods. Minisci addition byproducts were observed with (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (2) in the nickel/photoredox BF₃K salt coupling, nickel/photoredox decarboxylative coupling, nickel/photoredox cross-electrophile coupling, and the nickel catalyzed reductive cross-electrophile coupling. For this core, alkyl group addition occurred at the 4-position of the pyrimidine. The observed amount of the Minisci addition byproduct varied; in some reactions it made up a significant amount of the mass balance, in others this byproduct was absent. Minisci addition byproducts were observed with 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (4) under nickel/photoredox decarboxylative coupling conditions only. In these reactions, the desired coupling products were not produced at all, only regioisomeric Minisci addition (presumably) byproducts were observed. Addition occurred at the 5-position of the central imidazopyridine core rather than the desired 6-position. Two examples are shown below, the structures were confirmed by NMR analysis.

(R)-2-(tert-butoxy)-1-(4-(4-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (103).

General procedure D was followed using (R)-1-(4-(5-bromopyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethan-1-one (46 mg, 0.13 mmol) as the aryl halide and cyclohexanecarboxylic acid (24 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 103 (8.4 mg, 18% yield, >95% pure by ¹H NMR) as an off-white solid. This was the major product rather than the desired coupling at the 5-position. ¹H NMR (400 MHz, DMSO-d₆) δ 8.20 (d, J = 5.0 Hz, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.83 (ddd, J = 10.2, 5.1, 3.1 Hz, 1H), 4.47 – 4.29 (m, 1H), 4.17 – 3.79 (m, 4H), 3.21 – 3.13 (m, 1H, appears as 2H due to water signal), 2.56 – 2.32 (m, 2H), 1.83 (ddt, J = 13.0, 4.0, 2.0 Hz, 2H), 1.80 – 1.71 (m, 2H), 1.66 (dddd, J = 12.5, 5.1, 3.2, 1.5 Hz, 1H), 1.53 – 1.18 (m, 6H), 1.17 (s, 9H), 1.08 (d, J = 6.7 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 174.88, 169.27, 169.19, 161.03, 158.20, 107.98, 74.25, 62.81, 62.69, 48.74, 46.70, 46.55, 45.63, 45.51, 45.03, 41.65, 38.74, 37.88, 31.84, 31.71, 27.58, 27.51, 26.14, 26.12, 25.98, 14.45, 14.40. Chemical Formula of [M+H]⁺: C₂₁H₃₅N₄O₂⁺; Exact Mass (calculated): 375.2760; HRMS (ESI+) (found): 375.2757.
6-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (104).

General procedure D was followed using 7-bromo-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (34 mg, 0.13 mmol) as the aryl halide and tetrahydro-2H-pyran-4-carboxylic acid (24 mg, 0.19 mmol) as the alkyl reagent. After the reaction was complete, the reaction was diluted to 2 mL total volume using 1:1 MeOH/DMSO and filtered. The crude residue was purified by preparative-scale reverse-phase HPLC (mass triggered collection) using ammonium acetate conditions and a focused gradient to afford the title compound 104 (11 mg, 30% yield, >95% pure by 1H NMR) as an off-white solid. This was the major product rather than the desired coupling at the 6-position. 1H NMR (400 MHz, DMSO-d6) δ 7.73 – 7.59 (m, 2H), 7.12 (dd, J = 7.1, 1.5 Hz, 1H), 4.96 (d, J = 0.8 Hz, 2H), 4.65 (tt, J = 11.5, 3.5 Hz, 1H), 4.30 (d, J = 0.9 Hz, 2H), 4.01 – 3.92 (m, 2H), 3.56 (td, J = 11.7, 2.0 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.67 (ddt, J = 12.9, 11.6, 4.3 Hz, 2H). 13C NMR (101 MHz, DMSO) δ 181.46, 160.86, 150.94, 148.06, 132.31, 119.33, 115.65, 112.97, 73.13, 67.40, 65.60, 38.04, 32.11. Chemical Formula of [M+H]+: C15H17N2O3; Exact Mass (calculated): 273.1239; HRMS (ESI+) (found): 273.1238.
**NMR Spectra**

**Figure 2:**

1-(4-cyclopropylbenzyl)-4-methylpiperazine (5) - $^1$H NMR

![NMR Spectra](image_url)
1-(4-cyclopropylbenzyl)-4-methylpiperazine (5) $^{13}$C NMR

3750620.brk.1.fid
315002723001-401-6 in CDCL3 $\delta$05 BC2469 6.0mg s400

Acq:topspin3.6.1/s400

Chemical structure of the compound with NMR spectrum.
(R)-2-(tert-butoxy)-1-(4-(5-cyclopropylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethanone (6) - $^1$H NMR

3750865
315002723001-406-6 in DMSO $\delta$05 BC2470 9.6mg
Temp = 120 C
C18H28N4O2
m$\mu$400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}
Some doubling observed in $^{13}$C NMR spectrum due to rotamers.
1-(4-isopropylbenzyl)-4-methylpiperazine (7)
(R)-2-(tert-butoxy)-1-(4-(5-isopropylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (8)
1-(4-benzylbenzyl)-4-methylpiperazine (9) $^1$H NMR
1-(4-benzylbenzyl)-4-methylpiperazine (9)-$^{13}$C NMR
(R)-1-(4-(5-benzylpyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (10) $^1$H NMR
(R)-1-(4-(5-benzylpyrimidin-2-yl)-3-methylpiperazin-1-yl)-2-(tert-butoxy)ethanone (10) - $^{13}$C NMR
Some doubling observed in $^{13}$C NMR spectrum due to rotamers.
4-(4-((4-methylpiperazin-1-yl)methyl)phenyl)butanenitrile (11) - $^1$H NMR

3750756.brk.1.fid
315002723001-401-12 in CDCL3 $^05$ BC2472 8.6mg
Acq:topspin3.6.1/s400
4-(4-((4-methylpiperazin-1-yl)methyl)phenyl)butanenitrile (11) $^1$C NMR

3750757.brk.1.fid
315002723001-401-12 in CDCL3 405 BC2472 8.6mg 400
Acq:topspin3.6.1/400
(R)-4-(2-(4-(2-tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)butanenitrile (12) - $^1$H NMR
(R)-4-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)butanenitrile (12) - $^{13}$C NMR
1-methyl-4-(4-methylbenzyl)piperazine (33)
(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-methylpyrimidin-2-yl)piperazin-1-yl)ethenone (34) - $^1$H NMR

3700905
310603081001-992-1-1 in PYRIDINE $\delta$29 BC8193 0.5mg
Temp = 90 C
C16H26N4O2
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400

Acq: VnmrJ VERSION 3.2 REVISION A/mr400
1-(4-butylbenzyl)-4-methylpiperazine (35) - $^1$H NMR

SI-74
(R)-2-(tert-butoxy)-1-(4-(5-butylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (36)-¹HNMR

3713144
310198107001-2296-2-2 in PYRIDINE §28 BC7704 0.5mg
Temp = 90 C
C19H32N4O2
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400

\[ \text{f1 (ppm)} \]

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

-200 -100 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300 2400 2500 2600 2700 2800 2900 3000 3100 3200

\[ \text{3713144} \]
\[ \text{310198107001-2296-2-2 in PYRIDINE §28 BC7704 0.5mg} \]
\[ \text{Temp = 90 C} \]
\[ \text{C19H32N4O2} \]
\[ \text{mr400} \]

Acq: VnmrJ VERSION 3.2 REVISION A/mr400
1-(4-hexylbenzyl)-4-methylpiperazine (37)- $^1$H NMR

C$_{18}$H$_{30}$N

Acq:topspin3.6.1/av499

Av499

Pyridine

3700747.brk.1.fid
310603081001-991-3-1 in PYRIDINE $^2$9 BC0149 0.5mg

Av499

Acq:topspin3.6.1/av499

Av499

Av499

Av499
(R)-2-(tert-butoxy)-1-(4-(5-hexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (38) - $^1$H NMR

3700930
310603081001-992-3-1 in PYRIDINE $^2$9 B#195 0.5mg
Temp = 90 C
c21H36N4O2
mr=400
Acq: VnmrJ VERSION 3.2 REVISION A/mr=400

$^1$H NMR spectrum of (R)-2-(tert-butoxy)-1-(4-(5-hexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (38)
1-(4-(cyclobutylmethyl)benzyl)-4-methylpiperazine (39) - $^1$H NMR
(\(R\))-2-(tert-butoxy)-1-(4-(5-(cyclobutylmethyl)pyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (40) - \(^1\)H NMR

3709621
31019810700:2264-15-1 in PYRIDINE \$21 BC7080 0.5mg
Temp = 90 C
c20h32n4o2
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400
Methyl 3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)propanoate (41) - $^1$H NMR

$^1$H NMR

Temp = 90 C

C$_{16}$H$_{24}$N$_2$O$_2$

Acq: VnmrJ VERSION 3.2 REVISION A/mr400

3703050
315048612001-361-22-1 in PYRIDINE 405 BC8480 0.5mg.
Methyl (R)-3-(2-(4-(2-tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)propanoate (42) - $^1$H NMR

3708631
315048612001-372-22-1 in DMSO $^1$HBC9718 0.5mg
Temp = 90 C
C19H30N4O4
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400
Ethyl 3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)propanoate (43) - $^1$H NMR

- SI-82
Ethyl (R)-3-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)propanoate (44) - $^1$H NMR

- Temp = 90 C
- C20H32N4O4
- Acq: VnmrJ VERSION 3.2 REVISION A/mr400

SI-83
1-(4-cyclobutylbenzyl)-4-methylpiperazine (45) - $^1$H NMR
(R)-2-(tert-butoxy)-1-(4-(5-cyclobutylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (46) - $^1$H NMR
1-(4-cyclopentylbenzyl)-4-methylpiperazine (47) - $^1$H NMR
(R)-2-(tert-butoxy)-1-(4-(5-cyclopentylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (48) \textsuperscript{1}H NMR

$\text{C}_20H_{32}N_4O_2$
1-(4-cyclohexylbenzyl)-4-methylpiperazine (49)- $^1$H NMR

![NMR spectrum of 1-(4-cyclohexylbenzyl)-4-methylpiperazine (49)]
(R)-2-(tert-butoxy)-1-(4-(5-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (50) \( ^1H \) NMR
1-methyl-4-(4-(1-phenylethyl)benzyl)piperazine (51)- $^1$H NMR

C$_{20}$H$_{26}$N

Acq:topspin3.6.1/av499

$^1$H NMR spectrum of 1-methyl-4-(4-(1-phenylethyl)benzyl)piperazine (51) in pyridine.
2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-(1-phenylethyl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (52)- $^1$H NMR
(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-(1-methylcyclopropyl)pyrimidin-2-yl)piperazin-1-yl)ethenone (53) $^1$H NMR

3709529
315002723001-406-30-1 in DMSO $^2$0 BC7026 0.5mg
Temp = 90 C
C19H30N4O2
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400

$\text{H}_3C$
$\text{O}$
$\text{O}$
$\text{C}_3H_3$
$\text{C}_3H_3$
$\text{C}_3H_3$
$\text{C}_3H_3$

$^f_1$ (ppm)
Figure 3:

1-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazole (13) - $^1$H NMR
1-(3-(tetrahydro-2H-pyran-4-yl)phenyl)-1H-pyrazole (13)- $^{13}$C NMR
7-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (14) $^1$H NMR

3708537
315048612001-379-13-1 in DMSO $^1$H  BC9736  0.5mg
Temp = 27 C
C15H16N2O3
Acq: VnmrJ VERSION 3.2 REVISION A/mrs400
7-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (14) - $^{13}$C NMR

3751438
315045612001-379-13-1 in DMSO $\delta$06 BC2473 5mg
Temp. = 27 C
C15H16N2O3
mrs400
Acq: VnmrJ VERSION 3.2 REVISION A/mrs400

![NMR Spectrum](image-url)
tert-butyl 4-(3-(1H-pyrazol-1-yl)phenyl)piperidine-1-carboxylate (15) \-^1\text{H} NMR
tert-butyl 4-(3-(1H-pyrazol-1-yl)phenyl)piperidine-1-carboxylate (15). $^{13}$C NMR
**tert-butyl 4-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)piperidine-1-carboxylate (16)** - $^1$H NMR
tert-butyl 4-(4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)piperidine-1-carboxylate (16) $^{13}$C NMR
1-(3-(methoxymethyl)phenyl)-1H-pyrazole (17) $^1$H NMR
1-(3-(methoxymethyl)phenyl)-1H-pyrazole (17) - $^{13}$C NMR
7-(methoxymethyl)-1H-pyrano[3',4':4,5] imidazo[1,2-a]pyridin-4(3H)-one (18)- 1H NMR
7-(methoxymethyl)-1H-pyrano[3',4':4,5] imidazo[1,2-a]pyridin-4(3H)-one (18)-13C NMR
tert-butyl 2-[(1H-pyrazol-1-yl)phenyl]pyrrolidine-1-carboxylate (19) - $^1$H NMR
tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidine-1-carboxylate (19) - $^{13}$C NMR

SI-106
tert-butyl 2-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)pyrrolidine-1-carboxylate (20) - $^1$H NMR
tert-butyl 3-(3-(1H-pyrazol-1-yl)benzyl)azetidine-1-carboxylate (54) - $^1$H NMR
tert-butyl 3-((4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)methyl)azetidine-1-carboxylate (55) - $^1$H NMR
1-(3-(oxetan-3-ylmethyl)phenyl)-1H-pyrazole (56) - ¹H NMR
7-(oxetan-3-ylmethyl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (57)  1H NMR
1-(3-(oxetan-3-yl)phenyl)-1H-pyrazole (58) - $^1$H NMR
1-(3-(tetrahydrofuran-3-yl)phenyl)-1H-pyrazole (60)- $^1$H NMR
7-(tetrahydrofuran-3-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (61) - $^1$H NMR
7-(tetrahydrofuran-3-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (61) - $^{13}$C NMR
**tert-butyl 3-\{(1H-pyrazol-1-yl)phenyl\}azetidine-1-carboxylate (62)- $^1$H NMR**
tert butyl 3-(4-oxo-3,4-dihydro-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)azetidine-1-carboxylate (63) - $^1$H NMR
tert-butyl 3-((1H-pyrazol-1-yl)phenyl)pyrrolidine-1-carboxylate (64)- $^1$H NMR
tert-butyl 3-(4-oxo-3,4-dihydro-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-7-yl)pyrrolidine-1-carboxylate (65) - $^1$H NMR

SI-119
tert-butyl (4-(3-(1H-pyrazol-1-yl)phenyl)cyclohexyl)carbamate (66)- $^1$H NMR
Cis/trans stereoisomers of the product are present in $^1$H NMR spectrum.

*tert*-butyl (4-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)cyclohexyl)carbamate (67) - $^1$H NMR
Cis/trans stereoisomers of the product are present in $^1$H NMR spectrum.

tert-butyl 3-(1H-pyrazol-1-yl)benzylcarbamate (68) - $^1$H NMR
tert-butyl ((4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)methyl)carbamate (69) - $^1$H NMR
1-(3-(tetrahydro-2H-pyran-2-yl)phenyl)-1H-pyrazole (70) - ^1^H NMR
7-(tetrahydro-2H-pyran-2-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (71) - $^1$H NMR
Temp = 90°C
C15H16N2O3
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400

Figure 4a:
1-(3-butylphenyl)-1H-pyrazole (72) - $^1$H NMR

[Graph showing NMR spectrum with peaks labeled for analysis.]
7-butyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (73) - $^1$H NMR

1-(3-(cyclobutylmethyl)phenyl)-1H-pyrazole (74) - $^1$H NMR
7-(cyclobutylmethyl)-1H-pyran\[3',4':4,5\]imidazo[1,2-a]pyridin-4(3H)-one (75) - \textsuperscript{1}H NMR
(R)-tert-butyl 3-((2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)methyl)azetidine-1-carboxylate (76) - $^1$H NMR
(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-(oxetan-3-ylmethyl)pyrimidin-2-yl)piperazin-1-yl)ethenone (77) - $^1$H NMR
1-(3-(2-methoxyethyl)phenyl)-1H-pyrazole (78)- ¹H NMR
(R)-2-(tert-butoxy)-1-(4-(5-(2-methoxyethyl)pyrimidin-2-yl)-3-methylpiperazin-1-yl)ethenone (79)- ¹H NMR
3709637
310198107001-2264-18-1 in PYRIDINE $21 BC7083 0.5mg
Temp = 90 C
C18H30N4O3
mr400
Acq: VnmrJ VERSION 3.2 REVISION A/mr400
7-(2-methoxyethyl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (80) - $^1$H NMR

Acq: VnmrJ VERSION 3.2 REVISION A/mrs400
4-(3-(1H-pyrazol-1-yl)phenyl)butanenitrile (81) - $^1$H NMR

SI-136
4-(4-oxo-3,4-dihydro-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)butanenitrile (82) - $^1$H NMR
3-(3-(1H-pyrazol-1-yl)phenyl)-N,N-dimethylpropanamide (83) - $^1$H NMR

3707354
315048612001-368-21-1 in DMSO $\delta$15 8C9424 0.5mg
Temp = 27 C
C14H17N3O
Acq: VnmrJ VERSION 3.2 REVISION A/mrs400

![NMR spectrum diagram]
(R)-3-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)-N,N-dimethylpropanamide (84) - $^1$H NMR
N,N-dimethyl-3-(4-oxo-3,4-dihydro-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-7-yl)propenamide (85) - $^1$H NMR
1-(3-isopropylphenyl)-1H-pyrazole (86) - $^1$H NMR
7-isopropyl-1H-pyran[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (87)- $^1$H NMR

![NMR Spectrum](image-url)
1-(3-cyclopropylphenyl)-1H-pyrazole (88)-^1^H NMR

3686878
15037326-4B1-A in DMSO $\delta$25 BC792 2.5mg
Temp = 27 C
C12H12N2
mrs400

Acq: VnmrJ VERSION 3.2 REVISION A/mrs400
7-cyclopropyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (89)-$^1$H NMR
1-(3-cyclobutylphenyl)-1H-pyrazole (90)-1H NMR
7-cyclobutyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (91) - $^1$H NMR
1-(3-cyclopentylphenyl)-1H-pyrazole (92)- $^1$H NMR
7-cyclopentyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (93) - $^1$H NMR
1-(3-cyclohexylphenyl)-1H-pyrazole (94)- $^1$H NMR
7-cyclohexyl-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (95) - ¹H NMR
(R)-2-{tert-butoxy}-1-(3-methyl-4-(5-oxetan-3-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (96) - $^1$H NMR
2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-(tetrahydrofuran-3-yl)pyrimidin-2-yl)piperazin-1-yl)ethenone (97) - $^1$H NMR

SI-152
(R)-2-(tert-butoxy)-1-(3-methyl-4-(5-(tetrahydro-2H-pyran-4-yl)pyrimidin-2-yl)piperazin-1-yl)ethenone (98) - $^1$H NMR
(R)-tert-butyl 3-(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)azetidine-1-carboxylate (99) - $^1$H NMR
tert-butyl 3-((2-((R)-4-((tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)pyrrolidine-1-carboxylate (100) - $^1$H NMR
(R)-tert-butyl 4-(2-(4-(2-tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)piperidine-1-carboxylate (101) - $^1$HNMR
tert-butyl (R)-(4-(2-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)cyclohexyl)carbamate (102) - $^{1}H$ NMR
**tert-butyl (1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)carbamate (22)- $^1$H NMR**

SI-158
tert-butyl (1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)carbamate (22)- $^{13}$C NMR
tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)azetidine-1-carboxylate (23) \(^1\)H NMR
tert-butyl 2-(3-(1H-pyrazol-1-yl)phenyl)azetidine-1-carboxylate (23) \textsuperscript{13}C NMR
4-(3-(1H-pyrazol-1-yl)phenyl)azetidin-2-one (24) - $^1$H NMR
4-(3-(1H-pyrazol-1-yl)phenyl)azetidin-2-one (24) - $^1$H NMR spectrum generated by *in silico* removal of water and solvent signals:
4-(3-(1H-pyrazol-1-yl)phenyl)azetidin-2-one (24) - $^{13}$C NMR
5-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidin-2-one (25) - $^1$H NMR
5-(3-(1H-pyrazol-1-yl)phenyl)pyrrolidin-2-one (25)-$^{13}$C NMR
6-(3-(1H-pyrazol-1-yl)phenyl)piperidin-2-one (26) \( ^1H \) NMR
6-(3-(1H-pyrazol-1-yl)phenyl)piperidin-2-one (26) $^{13}$C NMR
tert-butyl (R)-((2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)methyl)carbamate (27)- $^1$H NMR
tert-butyl (R)-[(2-(4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)methyl]carbamate (27) \(-^13\)C NMR
tert-butyl (1-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)ethyl)carbamate (28) - $^1$H NMR
tert-butyl (1-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)ethyl)carbamate (28)- $^{13}$C NMR
tert-butyl 2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)azetidine-1-carboxylate (29). $^1$H NMR
**SI-174**

**315031524001-54-15-1 in DMSO #11 BC3192 10mg**

Temp = 90°C

C$_{23}$H$_{37}$N$_{5}$O$_{4}$ mr400

Acq: VnmrJ VERSION 3.2 REVISION A/mr400

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**tert-butyl 2-(2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)azetidine-1-carboxylate (29) - $^{13}$C NMR**
_tert-butyl 2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)pyrrolidine-1-carboxylate (30) - $^1$H NMR_
**tert-butyl 2-((R)-4-(2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)pyrrolidine-1-carboxylate (30)-^1^3C NMR**

SI-176
Rotamers present in $^{13}$C NMR spectrum.

6-((R)-2-(tert-butoxy)acetyl)-2-methylpiperazin-1-yl)pyrimidin-5-yl)piperidin-2-one (31)-$^1$H NMR
2-((tert-butoxy)-1-((3R)-3-methyl-4-(5-(tetrahydrofuran-2-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (32) - $^1$H NMR
$\text{C}19\text{H}_{30}\text{N}_4\text{O}_3$ mr400

Temp = 90 C

Acq: VnmrJ VERSION 3.2 REVISION A/mr400.

2-(tert-butoxy)-1-((3R)-3-methyl-4-(5-(tetrahydrofuran-2-yl)pyrimidin-2-yl)piperazin-1-yl)ethan-1-one (32) $^{13}$C NM
Minisci Byproducts
(R)-2-(tert-butoxy)-1-(4-(4-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (103) - 1H NMR

Acq: VnmrJ VERSION 3.2 REVISION A/mr400

3760315
315031524001-54-39-2 in DMSO $08 BC6544 7mg
Temp = 90 C
C21H34N4O2
mr400

{Chemical structure image}

(R)-2-(tert-butoxy)-1-(4-(4-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (103) - 2D NMR

SI-181
(R)-2-(tert-butoxy)-1-(4-(4-cyclohexylpyrimidin-2-yl)-3-methylpiperazin-1-yl)ethan-1-one (103) - $^{13}$C NMR
6-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (104)- $^1$H NMR
6-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3',4':4,5]imidazo[1,2-a]pyridin-4(3H)-one (104)- 2D NMR
6-(tetrahydro-2H-pyran-4-yl)-1H-pyrano[3′,4′:4,5]imidazo[1,2-a]pyridin-4(3H)-one (104) - $^{13}$C NMR
C15H16N2O
s400

Acq:topspin3.6.1/s400

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