C5-Alkyl-2-Methylurea- Substituted Pyridines as a New Class of Glucokinase Activators

Xiaohui Du[†*], Ronald J. Hinklin[#], Yumei Xiong[†], Paul Dransfield[†], Jaehyeon Park[†], Todd J. Kohn[†], Vatee Pattaropong[†], SuJen Lai[†], Zice Fu[†], Xianyun Jiao[†], David Chow[†], Lixia Jin[†], Jasmine Davda[†], Murielle M. Veniant[$], Deborah A. Anderson[#], Brian R. Baer[#], Josef R. Bencsik[#], Steven A. Boyd[#], Mark Joseph Chicarelli[#], Peter J. Mohr[#], Bin Wang[#], Kevin R. Condroski[#], Walter E. DeWolf[#], Marion Conn[†], Thanhvien Tran[†], Jerry Yang[†], Thomas D. Aicher[#], Julio C. Medina[†], Peter Coward[†], Jonathan B. Houze[†]

[†]Amgen San Francisco, 1120 Veterans Blvd., South San Francisco, CA 94080

[$]Amgen San Francisco, One Amgen Center Drive, Thousand Oaks, CA 91320

[#]Array BioPharma, 3200 Walnut St., Boulder, CO 80301

Supporting Information

***In Vitro* Glucokinase Assays.** The *in vitro* efficacy of glucokinase activators was assessed in three separate assays using recombinant human glucokinase: an EC_{50} assay to evaluate the potency of each compound at a fixed, physiologically relevant concentration of glucose, a variant of this assay run in the presence of 4% human serum albumin, and a V_{max} assay comprising a glucose dose-response curve at a fixed, near saturating (if possible) concentration of compound to evaluate its effect on the relative V_m for glucose. For each of these assays, glucokinase activity was estimated by monitoring the increase in absorbance at 340 nm in a coupled assay system containing NAD^+ and glucose 6-phosphate dehydrogenase (Fig. 1). Assays were conducted at 30 °C using a thermostatically controlled absorbance plate reader (Spectramax 340PC, Molecular Devices Corp.) and clear, 96-well, flat bottom, polystyrene plates (Costar 3695, Corning). Each 50-µL assay mixture contained 10 mM K^+MOPS, pH 7.2, 2 mM $MgCl_2$, 50 mM KCl, 0.01% Triton X-100, 2% DMSO, 1 mM DTT, 1 mM ATP, 1 mM NAD^+, 5 U/mL glucose 6-phosphate dehydrogenase, approximately 0.2 nM human glucokinase and (depending

on the assay) varying concentrations of glucose and test compound. The absorbance at 340 nm was monitored kinetically over a period of 5 min (10 s/cycle), and rates were estimated from the slopes of linear fits to the raw data.

Glucokinase EC_{50} Assay. For this assay, the glucose concentration was fixed at 5 mM, while the control or test compound was varied over a 10-point, 3-fold dilution series and typically ranged from a high dose of 50 µM to a low dose of approximately 2.5 nM. A standard, four-parameter logistic model (Equation 1) was fit to the raw data (rate versus concentration of compound):

$$y = A + \frac{B - A}{1 + \left[\frac{C}{x}\right]^{D}} \qquad (1)$$

where x is the concentration of compound, y is the estimated rate, A and B are the lower and upper asymptotes, respectively, C is the EC_{50} and D is the Hill slope. The EC_{50} is defined, therefore, as the midpoint or inflection point between the upper and lower asymptotes.

A variant of this assay was run in the presence of 4% human serum albumin (HSA), the concentration in normal human plasma, in order to obtain an immediate assessment of the plasma protein binding potential of the glucokinase activators (GKA's). It also served as a functional readout on activity in the presence of serum protein, given the dynamic nature of plasma protein binding. A low fold-shift in the non-treated versus 4% HSA EC_{50}'s was considered desirable, since the anticipated higher free fraction of GKA would likely translate into greater efficacy at a lower plasma GKA concentration. This parameter was calculated from the ratio of the EC_{50}'s obtained under both conditions [fold-shift = $EC_{50(4\%HSA)}/EC_{50(No\ HSA)}$].

Glucokinase $V_{max}/S_{0.5}$ Assay. For this assay, the concentration of control or test compound was fixed at or near a saturating concentration, while the glucose concentration was varied over a 10-point, 2-fold dilution series ranging from 80 to approximately 0.16 mM. The same four-parameter logistic model used for the EC_{50} assay (Equation 1) was employed to estimate the V_{max} (upper asymptote) relative to that run in the absence of GKA. In this assay, the definitions for the variables and parameters are similar except that now x represents the concentration of glucose, B is the rate at saturating glucose (V_m), C is the $S_{0.5}$ for glucose (the concentration of glucose at $V_m/2$) and D is the Hill Coefficient. The Vm for test compound is reported as a percentage relative to the estimated Vm in the absence of GKA.

Oral Glucose Tolerance Test for 12 (**AM-0822**)**:** C57Bl/6 mice were fasted beginning the night previous to the study start, so that they would be fasting for a minimum of 12 hours, not to exceed 18 hours. C57Bl/6 mice 1-8 of each group had ~0.02 ml of blood drawn directly into a glucose strip (One-touch Ultra) for immediate glucose monitoring. Blood was sampled by tail nick, allowing a drop of blood to form. Mice were randomized based upon their fasting glucose and then weighed. Then mice were dosed orally with compound **12** (**AM-0822**). 20 minutes post compound dosing, blood glucose were measured again using One-Touch Ultra (Time 0). 30 minutes post compound dosing, animals received 2g/kg glucose solution orally. Serial blood glucose monitoring began post glucose dosing at 15 min, 30 min, 45 min, 1 hour, 1.5 hour and 2 hour. Terminal plasma were collected for drug levels following 2 hour blood glucose sampling. Compound **12** was first added to 1% CMC/0.5% Tween 80 and sonicated until thoroughly wet. Then 1% CMC was added to desired final volume/dilution.

Oral Glucose Tolerance Test for 26 (**AM-9514**)**:** 8-week old male ob/ob mice (the Jackson Lab) were fasted overnight (~16 hr). In the morning following overnight fasting, animals were orally dosed with vehicle or compound **26** 30 min before an oral glucose load (2g/kg). Tail vein blood glucose levels were measured at -30, 0, 15, 30, 60, 90, and 120 min using AlphaTRAK glucose strip (Abbott Laboratories). Compound **26** was prepared as a suspension in 0.5% methylcellulose and 1% Tween 80.

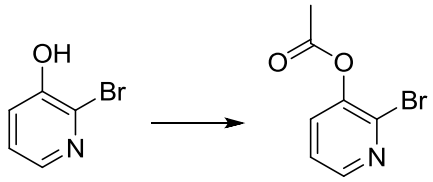
Test of compound 26 (**AM-9514**) **with no glucose bolus:** Male C57Bl/6 mice were orally dosed with vehicle or compound **26** and then food removed for 4 hr to test for hypoglycemic potential. Tail vein blood glucose levels were measured at 0, 15, 30, 60, 120, 180 and 240 min using AlphaTRAK glucose strip (Abbott Laboratories). Compound **26** was prepared as a suspension in 0.5% methylcellulose and 1% Tween 80.

General Chemistry. All reactions were conducted using a Teflon-coated magnetic stir bar at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Analytical thin layer chromatography (TLC) and flash chromatography were performed on Merck silica gel 60 (230-400 mesh). Removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a

vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Product purification by flash chromatography was performed using Teledyne-ISCO Redisep normal phase silica gel columns on a Teledyne-ISCO Companion; or by preparative reversed-phase high pressure liquid chromatography (RP-HPLC) using an Agilent SB C8 column or Phenomenex Gemini C18 column (5 micron, 100 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elution [A: H_2O with 0.1% trifluoroacetic acid (TFA); B: CH_3CN with 0.1% TFA] with UV detection at 220 nm. Low-resolution mass spectral (MS) data were determined on an Agilent 1200 series LC connected to an Agilent 6140 quadrupole MS analyzer (ESI). ^1H NMR spectra were obtained on a Bruker Avance II 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m=multiplet, quin = quintet, ttd = triplet of triplet of doublets, br=broad. All final compounds (**1**-**26**) reported in the paper have HPLC purity higher than 95%.

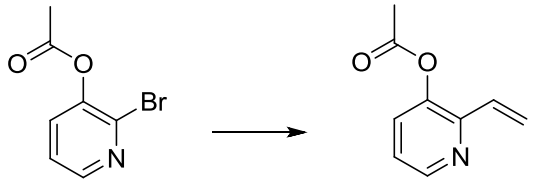
Abbreviations of the solvents and reagents: $CDCl_3$, deuterochloroform; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol; iPrOH, 2-propanol; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; Et_2O, diethyl ether; DME, 1,2-dimethoxyethane; ACN or CH_3CN, acetonitrile; DCM or CH_2Cl_2, dichloromethane; LiOH, Lithium hydroxide; $NaHCO_3$, sodium hydrogen carbonate; $MgSO_4$, magnesium sulfate; NH_4Cl: ammonium chloride; NaCl, sodium chloride; K_2CO_3, potassium carbonate; Cs_2CO_3, cesium carbonate; Pd/C: palladium on carbon; S-Phos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; $PdCl_2(PPh_3)_2$: Dichlorobis(triphenylphosphine)palladium(II), Et_3N or TEA, triethylamine; HCl, hydrochloric acid; NaOH, sodium hydroxide; $Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0); TBS: tert-butyldimethylsilyl; $CHCl_3$: chloroform; KHMDS: potassium hexamethyl disilazide; Na_2SO_3: sodium sulfite; TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl; $CDCl_3$: deuterated chloroform; CD_3OD: deuterated methanol.

Synthesis and data for individual compounds:



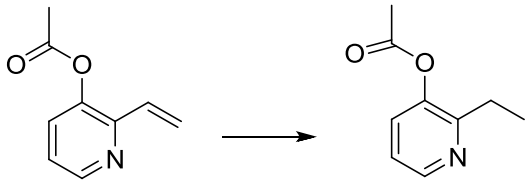
1.1

2-bromopyridin-3-yl acetate (1.1): A stirred solution of 2-bromopyridin-3-ol (80 g, 459.77 mmol) in acetic anhydride (240 mL) was heated to reflux for 3 hours and then cooled to room temperature. The reaction mixture was concentrated to one third of its volume and was poured over 100 g of ice with stirring. After 5 minutes, solid sodium bicarbonate was added portion wise until pH~7 and the mixture was diluted with ethyl acetate. The layers were separated and the aqueous phase was extracted with diethyl ether (500 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated to get the title compound (**1.1**) (99.3 g, 100% yield) that was used without any further purification. MS ESI (pos.) m/e: 215.8 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (dd, *J*=4.70, 1.56 Hz, 1 H), 7.48 (dd, *J*=8.02, 1.76 Hz, 1 H), 7.32 (dd, *J*=8.02, 4.70 Hz, 1 H), 2.40 (s, 3 H).



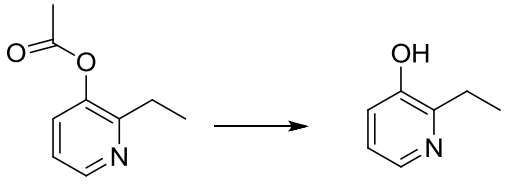
1.1 **1.2**

2-vinylpyridin-3-yl acetate (1.2): To a solution of 2-bromopyridin-3-yl acetate (**1.1**) (150 g, 694.34 mmol) in DMF (1500 mL) was added $PdCl_2(PPh_3)_2$ (16.57 g, 23.60 mmol) and tributyl(vinyl)stannane (239.97 g, 756.83 mmol). The reaction was heated at 145 ^{o}C for 3 hours. After completion, the reaction mixture was cooled to room temperature; water (2.5 liter) was added and the reaction was extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (elution: 30% EtOAc in hexanes) to yield the title compound (**1.2**) (100 g, 88.3% yield) as a brown liquid. MS ESI (pos.) m/e: 164.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.49 (dd, *J*=4.69, 1.37 Hz, 1 H), 7.44 (dd, *J*=8.22, 1.37 Hz, 1 H), 7.24 (dd, *J*=8.22, 4.50 Hz, 1 H), 6.84 - 6.95 (m, 1 H), 6.45 (dd, *J*=17.22, 1.76 Hz, 1 H), 5.56 (dd, *J*=10.86, 1.86 Hz, 1 H), 2.38 (s, 3 H).



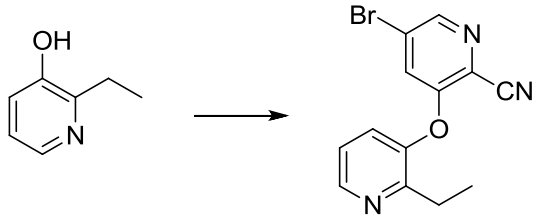
1.2 **1.3**

2-ethylpyridin-3-yl acetate (1.3): An autoclave (pressure vessel) was charged with 2-vinylpyridin-3-yl acetate (**1.2**) (100 g, 613.12 mmol) in methanol (800 mL). The mixture was degassed with argon and 10% Pd/C (18.0 g) was added slowly portion-wise under nitrogen atmosphere. The reaction mixture was stirred at 60 psi hydrogen pressure overnight and then filtered through celite. The celite bed was washed with MeOH (2 x 200 mL). The combined filtrate was concentrated under reduced pressure to afford the title compound (**1.3**) as a yellow oil (100 g, 99% yield) that was used in the next step without any further purification. MS ESI (pos.) m/e: 166.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.44 (dd, *J*=4.70, 1.56 Hz, 1 H), 7.38 (dd, *J*=8.12, 1.47 Hz, 1 H), 7.18 (dd, *J*=8.12, 4.79 Hz, 1 H), 2.77 (q, *J*=7.56 Hz, 2 H), 2.36 (s, 3 H), 1.28 (t, *J*=7.63 Hz, 3 H).



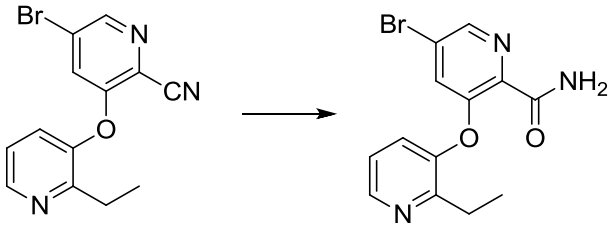
1.3 **1.4**

2-ethylpyridin-3-ol (1.4): To a solution of 2-ethylpyridin-3-yl acetate (**1.3**) (110.0 g, 665.9 mmol) in methanol (730 mL) was added sodium methoxide (53.95 g, 998.8 mmol). The reaction mixture was heated at 60 ^{o}C for 3 h. After completion, the reaction mixture was cooled to room temperature and concentrated to obtain a crude oil that was taken in ethyl acetate (1 liter) and washed with water (250 mL). The organic layer was dried and concentrated and the crude material was purified by silica gel column chromatography (eluting with 40% ethyl acetate in hexanes) to provide pure title compound (**1.4**) as an off white solid (50.0 g, 61.0% yield). MS ESI (pos.) m/e: 124.1 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.87 (dd, *J*=4.89, 1.37 Hz, 1 H), 7.14 (dd, *J*=7.82, 1.37 Hz, 1 H), 7.07 (dd, *J*=8.02, 4.69 Hz, 1 H), 2.80 (q, *J*=7.50 Hz, 2 H), 1.21 (t, *J*=7.53 Hz, 3 H).



1.4 **1.5**

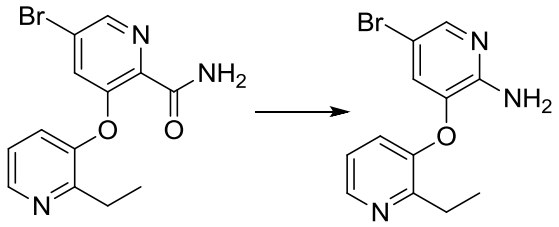
5-bromo-3-((2-ethylpyridin-3-yl)oxy)picolinonitrile (1.5): To a solution of 2-ethylpyridin-3-ol (**1.4**) (30 g, 243.60 mmol) in DMF (800 mL) was added sodium hydride (6.37 g, 265.52 mmol) at 0 ^{o}C. The reaction mixture was stirred at 10 ^{o}C for 30 min. A solution of 5-bromo-3-nitropicolinonitrile (55.5 g, 243.60 mmol) in DMF (190 mL) was added dropwise and the reaction mixture was stirred for another 30 min. at 10 ^{o}C. After completion, the reaction mixture was poured slowly to a cooled saturated aqueous NH_4Cl (200 mL) solution with vigorous stirring and then diluted with diethyl ether (500 mL). The layers were separated and organic layer was washed with water (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (eluting with 40% EtOAc in hexanes) to afford the title compound (**1.5**) (60.0 g, 81% yield) as a brownish solid. MS ESI (pos.) m/e: 304.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.57 (dd, *J*=4.60, 1.47 Hz, 1 H), 8.49 (d, *J*=1.76 Hz, 1 H), 7.35 (dd, *J*=8.22, 1.56 Hz, 1 H), 7.27 - 7.31 (m, 1 H), 7.20 (d, *J*=1.96 Hz, 1 H), 2.81 (q, *J*=7.63 Hz, 2 H), 1.31 (t, *J*=7.53 Hz, 3 H).



1.5 **1.6**

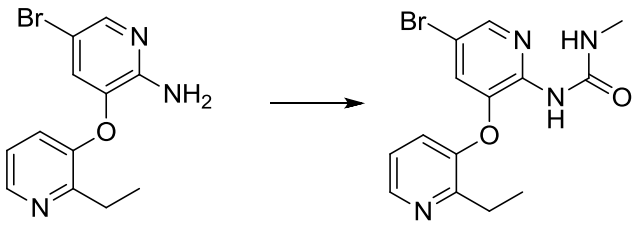
5-bromo-3-((2-ethylpyridin-3-yl)oxy)picolinamide (1.6): A mixture of 5-bromo-3-((2-ethylpyridin-3-yl)oxy)picolinonitrile (**1.5**) (60 g, 29.4 mmol) and sulfuric acid (105 mL) was stirred at ambient temperature overnight. It is important that there is no solid outside the solution to ensure completion of the reaction. The reaction mixture was cooled down in an ice bath and water was added carefully. Then the mixture was neutralized using 10 N aqueous sodium hydroxide solutions and diluted with ethyl acetate. The layers were separated. The EtOAc layer

was dried over sodium sulfate and concentrated to provide the title compound (**1.6**) as an off-white solid (51 g, 80.3% yield). MS ESI (pos.) m/e: 322.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45 (t, *J*=3.03 Hz, 1 H), 8.43 (d, *J*=1.76 Hz, 1 H), 7.54 (br. s, 1 H), 7.31 (d, *J*=1.76 Hz, 1 H), 7.19 (d, *J*=3.13 Hz, 2 H), 5.59 (br. s., 1 H), 2.87 (q, *J*=7.56 Hz, 2 H), 1.31 (t, *J*=7.53 Hz, 3 H).



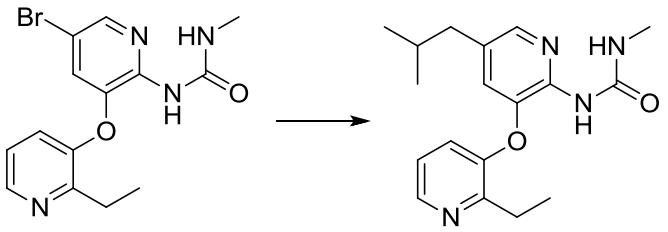
1.6 **1.7**

5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-amine (**1.7):** To a cooled solution of 5-bromo-3-((2-ethylpyridin-3-yl)oxy)picolinamide **(1.6)** (21 g, 65.21 mmol) and N-bromosuccinimide (14.97 g, 84.12 mmol) in water (22.7 mL) and MeOH (300 mL) was added a solution of 18 M potassium hydroxide (18.73 g) slowly drop-wise at 0º C. The reaction mixture was stirred at room temperature overnight. Then it was stirred at 100 ºC for 12 h and cooled to room temperature. The mixture was concentrated to provide the crude mass which was taken up in DCM (250 mL) and washed with water (100 mL). The organic layer was dried and concentrated under reduced pressure to obtain the crude material which was purified by column chromatography (neutral alumina, eluting with 50% ethyl acetate in hexane) to provide the title compound (**1.7**) as a white solid (12.0 g, 63% yield). MS ESI (pos.) m/e: 294.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 (dd, *J*=4.30, 1.96 Hz, 1 H), 7.91 (s, 1 H), 7.16 - 7.24 (m, 2 H), 6.89 (d, *J*=1.76 Hz, 1 H), 4.79 (br. s., 2 H), 2.86 (q, *J*=7.43 Hz, 2 H), 1.31 (t, *J*=7.53 Hz, 3 H).



1.7 **1.8**

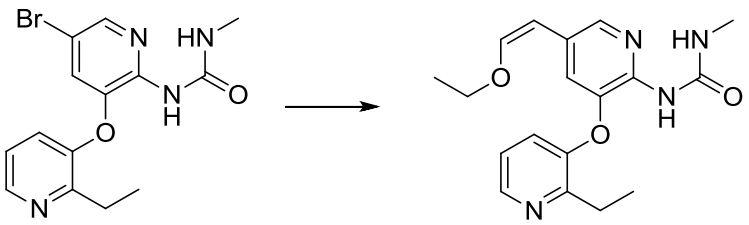
1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (1.8): To a solution of 5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-amine (**1.7)** (30 g, 102.0 mmol) in DCM (870 mL) was added anhydrous pyridine (24.20 g, 306.0 mmol) and 4-nitrophenyl carbonochloridate (32.8 g, 163.2 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 30 minutes. Triethylamine (30.96 g, 306.0 mmol) and methylamine (2.0 M solution in THF) (9.50 g, 306.0 mmol) was added. The reaction was stirred overnight. After completion, the reaction mixture was diluted with EtOAc (300 mL) and water (150 mL). The layers were separated. The organic layer was dried over sodium sulfate and concentrated to provide the crude mass that was purified by column chromatography (neutral alumina, eluting with 40% ethyl acetate in hexanes) to afford the title compound (**1.8**) (15.0 g, 41.8% yield) as a white solid. MS ESI (pos.) m/e: 351.0 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.40 (dd, *J*=4.69, 1.37 Hz, 1 H), 8.10 (d, *J*=1.96 Hz, 1 H), 7.49 (dd, *J*=8.22, 1.37 Hz, 1 H), 7.36 (dd, *J*=8.22, 4.69 Hz, 1 H), 7.14 (d, *J*=1.96 Hz, 1 H), 2.93 (s, 3 H), 2.83 (q, *J*=7.63 Hz, 2 H), 1.26 (t, *J*=7.53 Hz, 3 H).



1.8 **1**

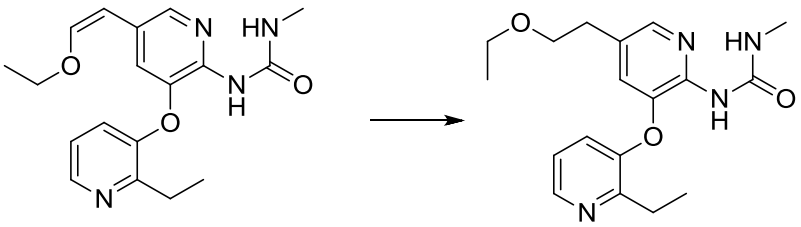
1-(3-((2-ethylpyridin-3-yl)oxy)-5-isobutylpyridin-2-yl)-3-methylurea (1): A flask was charged with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) (94 mg, 0.268 mmol), diacetoxypalladium (6.01 mg, 0.027 mmol), and S-Phos (21.98 mg, 0.054 mmol). The flask was purged with nitrogen. Argon-degassed THF (2 mL) was added followed by isobutylzinc bromide, 0.5 M solution in tetrahydrofuran (2.141 mL, 1.07 mmol). The reaction was heated to reflux overnight and quenched with saturated NH_4Cl. Then it was extracted with EtOAc. The EtOAc layer was dried, concentrated and purified on reverse phase HPLC using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 20-80% over 25 min. to provide 88 mg (34% yield) of the title compound (**1**). HRMS ESI (pos.) m/e calcd $C_{18}H_{24}N_4O_2$ 329.1972 (M+H); found 329.1966 (Δ=1.83 ppm). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.24 - 9.32 (m, 1 H), 8.37 - 8.52 (m, 1 H), 7.72 (d, *J*=1.37 Hz, 1 H), 7.38 (s, 1 H), 7.11 - 7.23 (m, 2 H), 6.62 (d, *J*=1.76

Hz, 1 H), 3.00 (d, *J*=4.69 Hz, 3 H), 2.82 (q, *J*=7.56 Hz, 2 H), 2.32 (d, *J*=7.04 Hz, 2 H), 1.64 - 1.72 (m, 1 H), 1.28 (t, *J*=7.43 Hz, 3 H), 0.85 (d, *J*=6.7 Hz, 6 H).



1.8 **2.1**

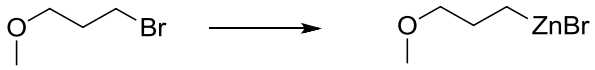
(Z)-1-(5-(2-ethoxyvinyl)-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (2.1): A mixture of 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) (0.210 g, 0.598 mmol), (Z)-tributyl(2-ethoxyvinyl)stannane (0.240 ml, 0.718 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.138 g, 0.120 mmol) in toluene (3.0 ml) was stirred at 110 °C over three days in an argon atmosphere. The reaction was cooled to room temperature then loaded onto a 12-gram Redi-Sep pre-packed silica gel column. The residue was purified by flash chromatography with 0-100% EtOAc in hexanes to afford 0.156 g (76% yield) of the title compound (**2.1**) that was used in the next step. An aliquot of the chromatographed material was purified further on reverse phase HPLC (0.1% TFA in CH_3CN/H_2O, gradient 5% to 95% over 25 minutes) for characterization purpose. MS ESI (pos.) m/e: 343.0 (M+H). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.91 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.61 (d, *J*=1.7 Hz, 1 H), 8.12 - 8.25 (m, 2 H), 7.99 (dd, *J*=8.3, 5.1 Hz, 1 H), 6.87 (d, *J*=6.8 Hz, 1 H), 5.63 (d, *J*=6.8 Hz, 1 H), 4.36 (q, *J*=7.1 Hz, 2 H), 3.38 (q, *J*=7.6 Hz, 2 H), 3.28 - 3.32 (m, 3 H), 1.72 - 1.77 (m, 3 H), 1.52 - 1.63 (m, 3 H).



2.1 **2**

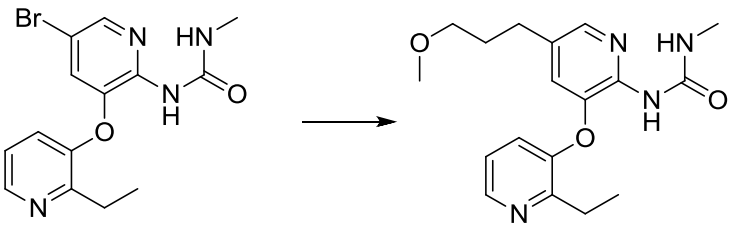
1-(5-(2-ethoxyethyl)-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (2): To a solution of (Z)-1-(5-(2-ethoxyvinyl)-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (0.034 g, 0.099 mmol) in ethanol (1.0 ml) was added 10% palladium on carbon (10.57 mg, 0.099 mmol). The reaction was stirred under H_2 atomsphere over the weekend. The reaction mixture

was filtered through a pad of celite and concentrated. The crude product was purified by reverse phase HPLC (0.1% TFA in CH_3CN/H_2O, gradient 5% to 95% over 25 minutes) to provide 0.018 g (52.6% yield) of the title compound (**2**) as a light yellow oil. MS ESI (pos.) m/e: 345.1 (M+H). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.60 - 8.69 (m, 1 H), 7.95 (s, 1 H), 7.60 (d, *J*=5.1 Hz, 2 H), 7.25 (s, 1 H), 3.60 (t, *J*=6.0 Hz, 2 H), 3.45 (q, *J*=7.1 Hz, 2 H), 3.20 (d, *J*=7.6 Hz, 2 H), 2.99 (d, *J*=4.4 Hz, 3 H), 2.83 (t, *J*=5.9 Hz, 2 H), 1.41 (t, *J*=7.6 Hz, 3 H), 1.12 (t, *J*=7.1 Hz, 3 H).



3.1

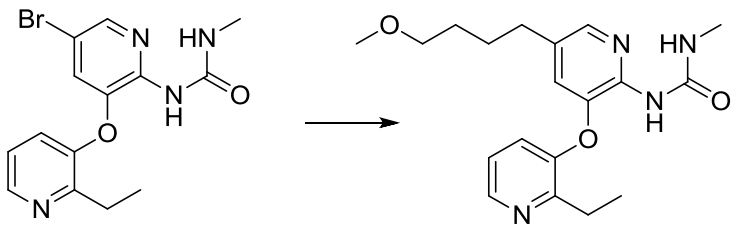
(3-methoxypropyl)zinc(II) bromide (3.1): A flask charged with lithium chloride (213 mg, 5.03 mmol) was dried on high vacuum pump at 155 ºC for 30 min. and cooled down. Zinc (362 mg, 5.54 mmol) was added and the flask was dried again on high vacuum pump for 20 min at 155 ºC. After cooling down, anhydrous THF was added (5.5 mL) under nitrogen followed by 1,2-dibromoethane (0.022 ml, 0.252 mmol). The flask was heated to 65 ºC with a heat gun and cooled down to ambient temperature. Repeat once. Chlorotrimethylsilane (6.39 µl, 0.050 mmol) was added. After stirring briefly, 5 drops of 1 M solution of iodine in THF was added followed by addition of 1-bromo-3-methoxypropane (770 mg, 5.03 mmol) in 1 mL THF. The resulting mixture was heated to 50 ºC overnight and cooled down to ambient temperature. The crude solution was used directly in next step. This procedure also serves as a general procedure for preparing other zinc bromode reagents from alkyl bromide.



1.8 **3**

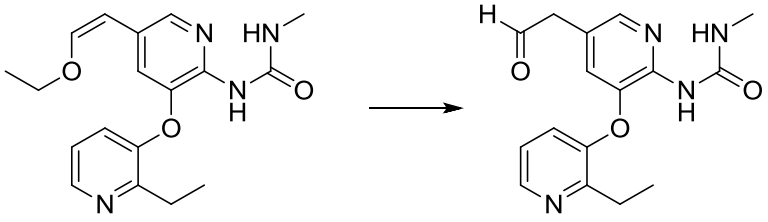
1-(3-((2-ethylpyridin-3-yl)oxy)-5-(3-methoxypropyl)pyridin-2-yl)-3-methylurea (3): The title compound (**3**) was prepared using the same procedure of preparing compound **1** (from intermediate **1.8**) by reacting (3-methoxypropyl)zinc(II) bromide (**3.1)** with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) for 7 hr.. MS ESI (pos.) m/e: 345.3

(M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.27 (d, *J*=4.11 Hz, 1 H), 8.46 (t, *J*=3.03 Hz, 1 H), 7.76 (d, *J*=1.76 Hz, 1 H), 7.40 (s, 1 H), 7.18 (d, *J*=3.13 Hz, 2 H), 6.67 (d, *J*=1.56 Hz, 1 H), 3.32 (t, *J*=6.06 Hz, 2 H), 3.29 (s, 3 H), 3.00 (d, *J*=4.70 Hz, 3 H), 2.81 (q, *J*=7.63 Hz, 2 H), 2.55 (t, *J*=7.40 Hz, 2 H), 1.70 - 1.79 (m, 2 H), 1.28 (t, *J*=7.53 Hz, 3 H).



1.8 **4**

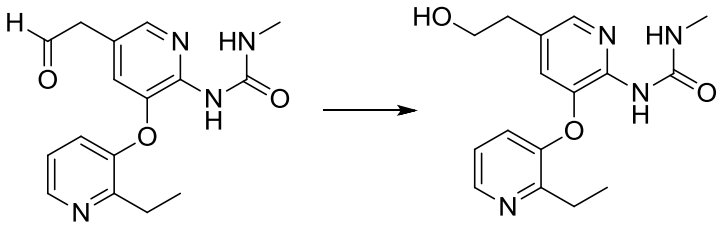
1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-methoxybutyl)pyridin-2-yl)-3-methylurea (4): The title compound (**4**) was prepared using the same procedure of preparing compound **1** by reacting (4-methoxybutyl)zinc(II) bromide (**4.1**, prepared using the same procedure as synthesizing intermediate **3.1)** with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) for 6 hr.. HRMS ESI (pos.) m/e calcd $C_{19}H_{26}N_4O_3$ 359.2078 (M+H); found 359.2063 (Δ=4.08 ppm). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.35 (dd, *J*=4.69, 1.37 Hz, 1 H), 7.88 (d, *J*=1.76 Hz, 1 H), 7.37 - 7.40 (m, 1 H), 7.30 - 7.34 (m, 1 H), 6.93 (d, *J*=1.96 Hz, 1 H), 3.36 (t, *J*=6.06 Hz, 2 H), 3.28 (s, 3 H), 2.93 (s, 3 H), 2.86 (q, *J*=7.56 Hz, 2 H), 2.54 (t, *J*=7.14 Hz, 2 H), 1.52 - 1.58 (m, 4 H), 1.27 (t, *J*=7.63 Hz, 3 H).



2.1 **5.1**

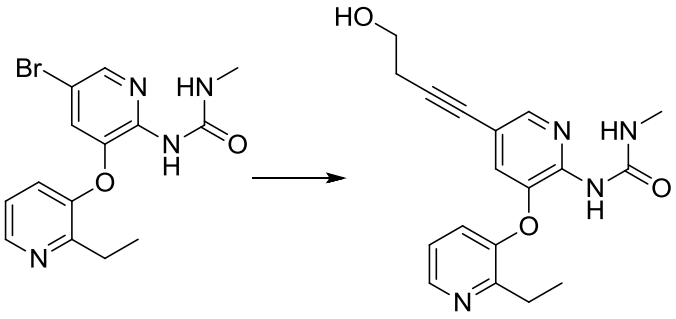
1-**(3-((2-ethylpyridin-3-yl)oxy)-5-(2-oxoethyl)pyridin-2-yl)-3-methylurea (5.1):** A solution (Z)-1-(5-(2-ethoxyvinyl)-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**2.1**) (0.111 g, 0.324 mmol) in THF (1.621 ml) and 4 N aqueous solution of HCl (0.324 ml, 1.297 mmol) was heated to reflux for 1.5 h. The reaction mixture was cooled down to ambient temperature and partitioned between saturated $NaHCO_3$ and DCM. The organic extracts were collected, dried

over $MgSO_4$ and concentrated in vacuo. The crude product 1-(3-((2-ethylpyridin-3-yl)oxy)-5-(2-oxoethyl)pyridin-2-yl)-3-methylurea (**5.1**) (0.048 g, 47.1% yield) was used in the next step without further purification.



5.1 **5**

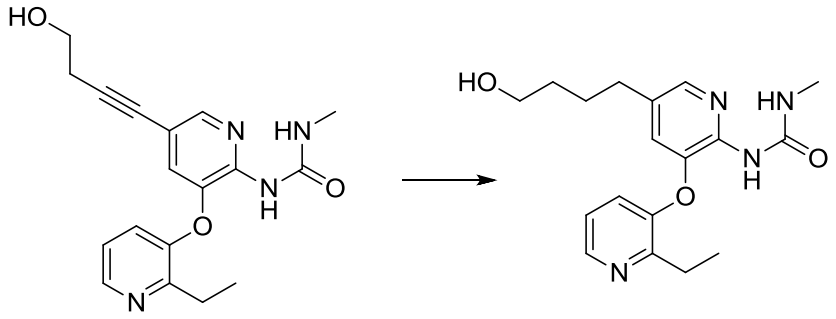
1-(3-((2-ethylpyridin-3-yl)oxy)-5-(2-hydroxyethyl)pyridin-2-yl)-3-methylurea (5): To a solution of 1-(3-((2-ethylpyridin-3-yl)oxy)-5-(2-oxoethyl)pyridin-2-yl)-3-methylurea (**5.1**) (0.048 g, 0.153 mmol) in MeOH (1.527 ml) was added sodium borohydride (0.033 ml, 0.925 mmol). The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was loaded onto a 7-gram silica gel column and purified by flash chromatography with a gradient 0 - 10% MeOH/DCM to give 0.043 g (89% yield) of the title compound (**5**) as a light yellow solid. MS ESI (pos.) m/e: 317.0 (M+H). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.34 (dd, *J*=4.8, 1.3 Hz, 1 H), 7.91 (d, *J*=2.0 Hz, 1 H), 7.40 (dd, *J*=8.3, 1.5 Hz, 1 H), 7.32 (dd, *J*=8.2, 4.8 Hz, 1 H), 7.01 (d, *J*=1.7 Hz, 1 H), 3.67 (t, *J*=6.4 Hz, 2 H), 2.93 (s, 3 H), 2.87 (q, *J*=7.6 Hz, 2 H), 2.70 (t, *J*=6.4 Hz, 2 H), 1.28 (t, *J*=7.6 Hz, 3 H).



1.8 **6.1**

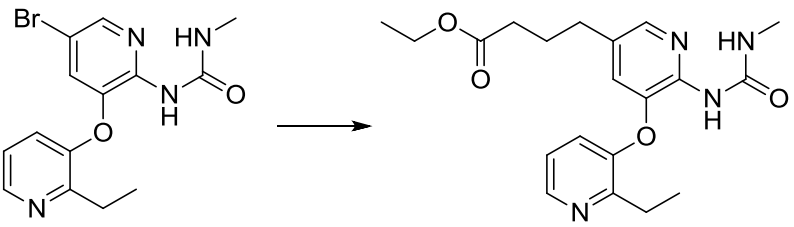
1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-hydroxybut-1-yn-1-yl)pyridin-2-yl)-3-methylurea (6.1): A flask charged with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) (0.150g, 0.427 mmol), trans-dichlorobis(triphenylphosphine)palladium (ii) (0.030 g, 0.043

mmol), triethylamine (0.048 ml, 0.342 mmol), 2-(3-butynyloxy)tetrahydro-2H-pyran (0.066 g, 0.427 mmol), and copper(i) iodide (1.447 µl, 0.043 mmol) was purged with nitrogen in the dark. Degassed THF (2.136 ml) was added. The reaction mixture was heated to reflux in the dark for 16 hours, then cooled to ambient temperature. The reaction mixture was then extracted with EtOAc, washed with saturated NaCl and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give the crude material. The crude material was purified using preparative reverse phase HPLC ($MeCN/H_2O$ containing 0.1% TFA each, 45 min from 10 to 60%) to give the title compound (**6.1**) (0.026 g, 18% yield) as a white solid. MS ESI (pos.) m/e: 341.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.12 (d, *J*=4.11 Hz, 1 H), 8.49 (dd, *J*=4.01, 2.05 Hz, 1 H), 7.97 (d, *J*=1.76 Hz, 1 H), 7.53 (s, 1 H), 7.20 - 7.24 (m, 2 H), 6.77 (d, *J*=1.76 Hz, 1 H), 3.78 (t, *J*=6.26 Hz, 2 H), 3.01 (d, *J*=4.70 Hz, 3 H), 2.79 (q, *J*=7.63 Hz, 2 H), 2.64 (t, *J*=6.26 Hz, 2 H), 1.28 (t, *J*=7.63 Hz, 3 H).



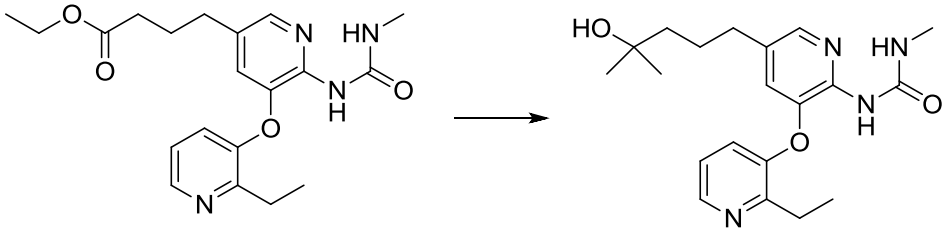
6.1 **6**

1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-hydroxybutyl)pyridin-2-yl)-3-methylurea (6): To a solution of 1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-hydroxybut-1-yn-1-yl)pyridin-2-yl)-3-methylurea (**6.1**) (0.019 g, 0.056 mmol) in MeOH (0.56 ml) and EtOAc (0.56 ml) was added 10% Pd/C (8.91 mg, 8.37 µmol) at 25 °C. The reaction mixture was stirred at 25 °C overnight under 1 atm of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, and washed with EtOAc. The filtrate was concentrated to give 1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-hydroxybutyl)pyridin-2-yl)-3-methylurea (**6**) (0.008 g, 41.6% yield). MS ESI (pos.) m/e: 345.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.34 (dd, *J*=4.69, 1.37 Hz, 1 H), 7.89 (s, 1 H), 7.36 - 7.40 (m, 1 H), 7.30 - 7.34 (m, 1 H), 6.94 (s, 1 H), 3.52 (t, *J*=6.26 Hz, 2 H), 2.92 (s, 3 H), 2.86 (q, *J*=7.50 Hz, 2 H), 2.54 (t, *J*=7.43 Hz, 2 H), 1.43 - 1.63 (m, 4 H), 1.27 (t, *J*=7.63 Hz, 3 H).



1.8 **7.1**

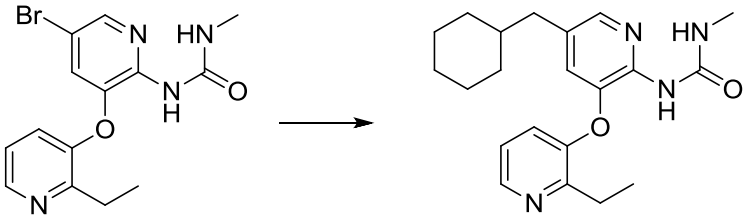
ethyl 4-(5-((2-ethylpyridin-3-yl)oxy)-6-(3-methylureido)pyridin-3-yl)butanoate (7.1): The title compound (**7.1**) was prepared using the same procedure of preparing compound **1** by reacting (4-ethoxy-4-oxobutyl)zinc(II) bromide (Aldrich**)** with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) for 7 hours. The crude material was first purified by silica gel chromatography with a gradient 0-8% MeOH/DCM and then on reverse phase HPLC. MS ESI (pos.) m/e: 387.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.22 - 9.27 (m, 1 H), 8.46 (t, *J*=3.03 Hz, 1 H), 7.76 (d, *J*=1.57 Hz, 1 H), 7.39 (s, 1 H), 7.19 (m, 2 H), 6.67 (d, *J*=1.76 Hz, 1 H), 4.11 (q, *J*=7.24 Hz, 2 H), 3.00 (d, *J*=4.70 Hz, 3 H), 2.81 (q, *J*=7.56 Hz, 2 H), 2.48 - 2.54 (m, 2 H), 2.28 (t, *J*=7.24 Hz, 2 H), 1.82 (quin, *J*=7.48 Hz, 2 H), 1.29 (t, *J*=7.53 Hz, 3 H), 1.23 (t, *J*=7.14 Hz, 3 H).



7.1 **7**

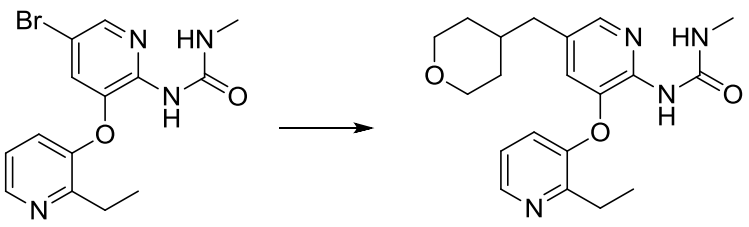
1-(3-((2-ethylpyridin-3-yl)oxy)-5-(4-hydroxy-4-methylpentyl)pyridin-2-yl)-3-methylurea (7): A flask with ethyl 4-(5-((2-ethylpyridin-3-yl)oxy)-6-(3-methylureido)pyridin-3-yl)butanoate (**7.1**) (50 mg, 0.129 mmol) was azeotroped with toluene and then purged with nitrogen. THF (2.5 mL) was added and the reaction was cooled to 0 °C. Then methyllithium (0.606 mL, 0.97 mmol) was added dropwise. After 5 minutes, the reaction was allowed to warm up to ambient temperature and stirred for one hour. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$ and combined with a second batch to purify together.

A flask with a second batch of ethyl 4-(5-((2-ethylpyridin-3-yl)oxy)-6-(3-methylureido)pyridin-3-yl)butanoate (**7.1**) (72 mg, 0.186 mmol) was azeotroped with toluene and then purged with nitrogen. THF (3.5 ml) was added and the reaction was cooled to 0 °C. Then methyllithium (0.873 ml, 1.397 mmol) was added dropwise. After 5 min., the reaction was allowed to warm up to ambient temperature and stirred for one hour. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$ and combined with the first batch and concentrated. The crude was purified on reverse phase HPLC using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 10-50% over 25 min. to provide 65 mg (56% yield) of the title compound (**7**) as a white solid. MS ESI (pos.) m/e: 373.4 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.34 (dd, *J*=4.79, 1.47 Hz, 1 H), 7.88 (d, *J*=4.97 Hz, 1 H), 7.37 - 7.41 (m, 1 H), 7.29 - 7.34 (m, 1 H), 6.93 (d, *J*=1.76 Hz, 1 H), 2.92 (s, 3 H), 2.87 (q, *J*=7.56 Hz, 2 H), 2.52 (t, *J*=7.43 Hz, 2 H), 1.54 - 1.64 (m, 2 H), 1.35 - 1.47 (m, 2 H), 1.27 (t, *J*=7.63 Hz, 3 H), 1.12 (s, 6 H).



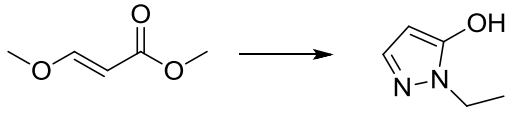
1.8 **8**

1-(5-(cyclohexylmethyl)-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (8): The title compound (**8**) was prepared using the same procedure of preparing compound **1** by reacting (cyclohexylmethyl)zinc(II) bromide with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**). The crude material was first purified by silica gel chromatography with a gradient 0-8% MeOH/DCM and then on reverse phase HPLC. MS ESI (pos.) m/e: 369.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.28 (d, *J*=3.72 Hz, 1 H), 8.43 - 8.47 (m, 1 H), 7.71 (d, *J*=1.56 Hz, 1 H), 7.37 (s, 1 H), 7.14 - 7.21 (m, 2 H), 6.62 (d, *J*=1.76 Hz, 1 H), 3.00 (d, *J*=4.89 Hz, 3 H), 2.82 (q, *J*=7.43 Hz, 2 H), 2.33 (d, *J*=7.04 Hz, 2 H), 1.55 - 1.70 (m, 5 H), 1.31 - 1.37 (m, 1 H), 1.28 (t, *J*=7.53 Hz, 3 H), 1.07 - 1.21 (m, 3 H), 0.88 (m, 2 H).



1.8 **9**

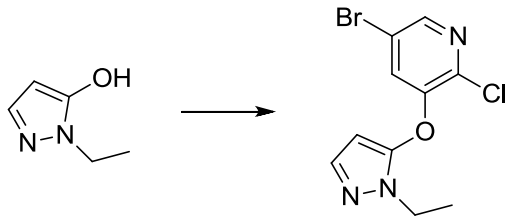
1-(3-((2-ethylpyridin-3-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (9): The title compound (**9**) was prepared using the same procedure of preparing compound **1** by reacting ((tetrahydro-2H-pyran-4-yl)methyl)zinc(II) bromide (**9.1**, prepared using the same procedure as intermediate **3.1)** with 1-(5-bromo-3-((2-ethylpyridin-3-yl)oxy)pyridin-2-yl)-3-methylurea (**1.8**) for 7 hours. The crude was first purified by silica gel chromatography with a gradient 0-8% MeOH/DCM and then on reverse phase HPLC. MS ESI (pos.) m/e: 371.4 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.35 (dd, *J*=4.69, 1.37 Hz, 1 H), 7.86 (d, *J*=1.56 Hz, 1 H), 7.37 - 7.41 (m, 1 H), 7.30 - 7.35 (m, 1 H), 6.92 (d, *J*=1.76 Hz, 1 H), 3.88 (dd, *J*=10.96, 3.72 Hz, 2 H), 3.31 (m, 2 H), 2.93 (s, 3 H), 2.86 (q, *J*=7.63 Hz, 2 H), 2.46 (d, *J*=7.04 Hz, 2 H), 1.57 - 1.72 (m, 1 H), 1.50 (d, *J*=13.30 Hz, 2 H), 1.19 - 1.30 (m, 5 H).



10.1

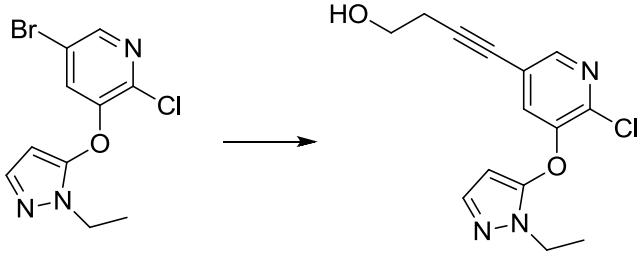
1-ethyl-1H-pyrazol-5-ol (10.1): In a 1 L glass beaker, ethylhydrazine oxalate (51.4 g, 342 mmol) was combined with water (300 ml). To the resulting slurry, 50% w/v NaOH solution was added (75.5 g) to adjust the pH to 9.5 (by pH-meter). The mixture was heated to 40 °C and methyl trans-3- methoxyacrylate (24.5 ml, 228 mmol) was added dropwise over 1 hour. The pH was adjusted periodically to about 9.0-9.5 by the addition of some 50 % w/v NaOH solution. After the completion of addition of methyl trans-3- methoxyacrylate, the mixture was agitated for additional 3 hours at 40 °C and the pH was adjusted occasionally to about 9.0-9.5. The mixture was cooled to 5 °C and filtered to remove the sodium oxalate. Then the filtrate was evaporated to about 150 ml, cooled to 5 °C and filtered again. The filtrate was acidified to pH 3-4 with 6 M HCl (45 ml) and extracted 8 times with a 3: 1 mixture of chloroform/isopropanol. The combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was

purified over silica gel (20% MeOH/EtOAc) to afford the title compound (**10.1**) (18.3 g, 71% yield) as a yellow solid. MS ESI (pos.) m/e: 112.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (br. s, 1 H), 7.09 (s, 1 H), 5.29 (d, *J*=1.76 Hz, 1 H), 3.84 (q, *J*=7.24 Hz, 2 H), 1.22 (t, *J*=7.24 Hz, 3 H).



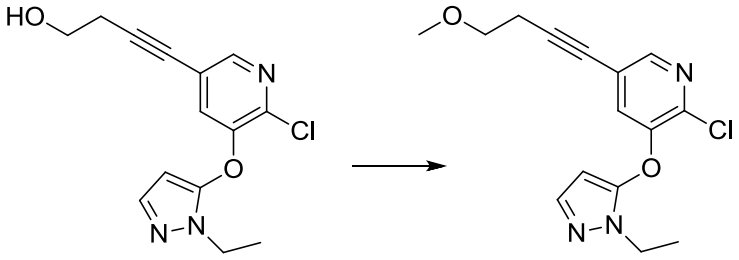
10.1 **10.2**

5-bromo-2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridine (10.2): 1-ethyl-1H-pyrazol-5-ol (**10.1**) (5.00 g, 44.6 mmol) was dissolved in DMF (49.5 ml). Cs_2CO_3 (17.43 g, 53.5 mmol) was added and the slurry was stirred for 20 minutes. To the slurry was then added 5-bromo-2-chloro-3-fluoropyridine (9.38 g, 44.6 mmol) and the slurry was stirred overnight. LCMS indicated reaction still contained pyrazole starting material. Another 9.0 g of Cs_2CO_3 (~1.8 eq total) was added and the reaction mixture was heated to 60 °C and stirred for 4.5 hours. The reaction was then diluted with water (200 mL) and this mixture was extracted with ethyl acetate (3 x 400 ml). The combined organic layers were then washed with water (1 x 300 mL), 1 N lithium chloride solution (1 x 300 mL) and brine (1 x 200 mL) and dried over magnesium sulfate. The crude product was purified by medium pressure chromagtography (silica gel, gradient 0 to 70% ethyl acetate/hexanes) to give 5-bromo-2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridine (**10.2**) (9.00 g, 29.7 mmol, 66.7 % yield). MS ESI (pos.) m/e: 303.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.48 (d, *J*=2.15 Hz, 1 H), 8.01 (d, *J*=2.15 Hz, 1 H), 7.41 (d, *J*=2.15 Hz, 1 H), 5.87 (d, *J*=2.15 Hz, 1 H), 4.05 (q, *J*=7.24 Hz, 2 H), 1.33 (t, *J*=7.24 Hz, 3 H).



10.2 **10.3**

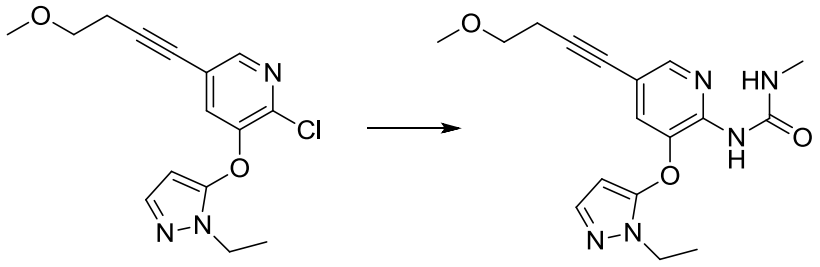
4-(6-chloro-5-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-3-yl)but-3-yn-1-ol (10.3): A flask was charged with 5-bromo-2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridine (**10.2**) (300 mg, 0.992 mmol), 3-butyn-1-ol (0.075 ml, 0.992 mmol) and triethylamine (0.553 ml, 3.97 mmol) and added DMF (1.0 ml). Copper(i) iodide (5.67 mg, 0.030 mmol) and dichlorobis(triphenylphosphine)palladium (ii) (7.79 mg, 0.030 mmol) were then added under nitrogen. The reaction mixture was heated to 80 °C and stirred for 90 minutes. The reaction mixture was then cooled and diluted with ethyl acetate (100 mL). The mixture was washed with 2 N HCl solution (1 x 35 mL), water (1 x 35 mL), 1 M lithium chloride solution (1 x 35 mL) and brine (1 x 35 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by medium pressure chromatography (silica gel, gradient 30 to 100% ethyl acetate/hexanes) to give 4-(6-chloro-5-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-3-yl)but-3-yn-1-ol (**10.3**) (144 mg, 49.8% yield). MS ESI (pos.) m/e: 292.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (d, *J*=1.96 Hz, 1 H), 7.38 (d, *J*=1.96 Hz, 1 H), 7.37 (d, *J*=1.96 Hz, 1 H), 5.62 (d, *J*=1.96 Hz, 1 H), 4.06 (q, *J*=7.24 Hz, 2 H), 3.79 (t, *J*=6.46 Hz, 2 H), 2.65 (t, *J*=6.46 Hz, 2 H), 1.40 (t, *J*=7.24 Hz, 3 H).



10.3 **10.4**

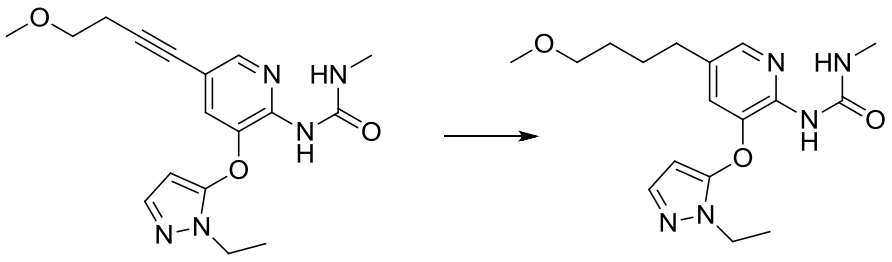
2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybut-1-yn-1-yl)pyridine (10.4): 4-(6-chloro-5-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-3-yl)but-3-yn-1-ol (**10.3**) (144 mg, 0.494 mmol) was dissolved in THF (5.0 ml). To the solution was added sodium hydride (60% dispersion) (30 mg, 0.592 mmol) and the mixture was stirred for 20 minutes. Methyl iodide (0.037 ml, 0.592 mmol) was added and the reaction mixture slowly turned dark brown over a period of two hours. The reaction was then quenched by adding water (15 mL). The mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine (1 x 25 mL) and dried over magnesium sulfate. The crude product was purified by medium pressure chromatography a couple of rounds (silica gel, gradient 45 to 60% ethyl acetate/hexanes) to give

2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybut-1-yn-1-yl)pyridine (**10.4**) (49 mg, 32.5 % yield) in good purity (95%). MS ESI (pos.) m/e: 306.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (d, *J*=1.76 Hz, 1 H), 7.43 (d, *J*=1.96 Hz, 1 H), 7.39 (d, *J*=1.96 Hz, 1 H), 5.67 (d, *J*=1.96 Hz, 1 H), 4.10 (q, *J*=7.30 Hz, 2 H), 3.58 (t, *J*=6.65 Hz, 2 H), 3.40 (s, 3 H), 2.69 (t, *J*=6.65 Hz, 2 H), 1.39 - 1.50 (m, 3 H).



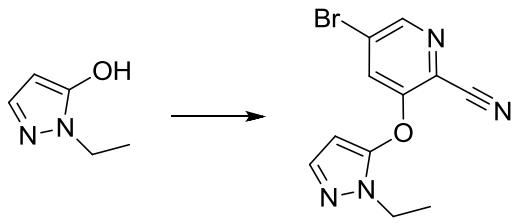
10.4 **10.5**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybut-1-yn-1-yl)pyridin-2-yl)-3-methylurea (10.5): Potassium phosphate tribasic (19.90 µl, 0.240 mmol), N-methylurea (13.79 µl, 0.224 mmol), $Pd_2(dba)_3$ (7.34 mg, 8.01 µmol) and 5-(di-tert-butylphosphino)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole (8.12 mg, 0.016 mmol) were slurried in DME (229 µl) under a blanket of argon and pre-activated at 50 °C for 45 minutes. 2-chloro-3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybut-1-yn-1-yl)pyridine (**10.4**) (49 mg, 0.160 mmol) dissolved in DME (229 µl) was then added and the resulting slurry was stirred at 85 °C overnight. The reaction mixture was cooled and concentrated under reduced pressure. The residue was purified by medium pressure chromatography (silica gel, 0 to 100% EtOAc/hexanes (hold for several minutes)) to provide the title compound (**10.5**) (12 mg, 0.035 mmol, 21.81 % yield). MS ESI (pos.) m/e: 344.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.07 (d, *J*=4.11 Hz, 1 H), 8.00 (d, *J*=1.76 Hz, 1 H), 7.40 - 7.48 (m, 2 H), 7.14 (d, *J*=1.76 Hz, 1 H), 5.74 (d, *J*=2.15 Hz, 1 H), 4.04 (q, *J*=7.37 Hz, 2 H), 3.56 (t, *J*=6.65 Hz, 2 H), 3.39 (s, 3 H), 2.99 (d, *J*=4.69 Hz, 3 H), 2.66 (t, *J*=6.65 Hz, 2 H), 1.42 (t, *J*=7.24 Hz, 3 H).



10.5 **10**

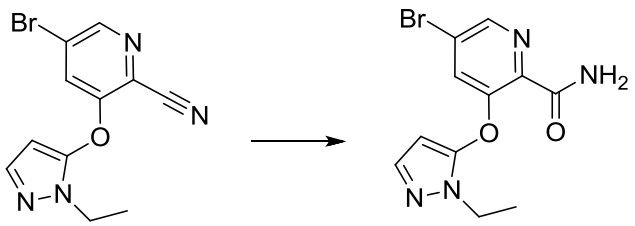
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybutyl)pyridin-2-yl)-3-methylurea (10): 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-methoxybut-1-yn-1-yl)pyridin-2-yl)-3-methylurea (**10.5**) (12 mg, 0.035 mmol) was dissolved in EtOAc (0.5 ml). To the solution was added platinum(iv) oxide (1.0 mg, 4.40 µmol). The reaction flask was flushed with hydrogen, then stirred under a hydrogen balloon for 24 hours. The slurry was filtered over a pad of celite and washed with ethyl acetate. The filtrate was concentrated to provide 11 mg of the title compound (**10**) (91 % yield). HRMS ESI (pos.) m/e calcd $C_{17}H_{25}N_5O_3$ 348.2030 (M+H); found 348.2034 (Δ=1.10 ppm). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.20 (br. d, *J*=3.9 Hz, 1 H), 7.79 (d, *J*=1.4 Hz, 1 H), 7.45 (d, *J*=2.0 Hz, 1 H), 7.27 (s, 1 H), 7.02 (br. s, 1 H), 5.68 (d, *J*=2.0 Hz, 1 H), 4.06 (q, *J*=7.2 Hz, 2 H), 3.34-3.40 (m, 2 H), 3.31 (s, 3 H), 2.99 (d, *J*=4.7 Hz, 3 H), 2.53 (t, *J*=7.1 Hz, 2 H), 1.51-1.64 (m, 4 H), 1.43 (t, *J*=7.2 Hz, 3 H).



10.1 **11.1**

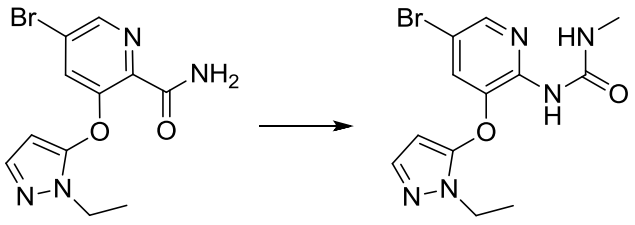
5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinonitrile (11.1): A flask was charged with 2-methylpyridin-3-ol (**10.1**) (5.0 g, 44.6 mmol) and DMF (100 mL). Sodium hydride (1.962 g, 49.1 mmol) was added and stirred for 5 minutes. 5-Bromo-3-nitropicolinonitrile (10.17 g, 44.6 mmol) was added and stirred for 30 minutes. The reaction was poured into a flask containing 300 mL saturated NH_4Cl and 300 mL water with vigorous stirring. The mixture was extracted with EtOAc. The EtOAc layer was washed with water then brine, dried, concentrated and purified by medium pressure chromatography (silica gel, 0 to 50% EtOAc/hexanes) to provide the title compound (**11.1**) (4.0 g, 31% yield). MS ESI (pos.) m/e: 293.0 (M+H). ^{1}H NMR (400 MHz,

$CDCl_3$) δ ppm 8.56 (d, *J*=3.39 Hz, 1 H), 7.66 (d, *J*=1.76 Hz, 1 H), 7.52 (d, *J*=1.96 Hz, 1 H), 5.87 (d, *J*=1.96 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 1.44 - 1.49 (m, 3 H).



11.1 **11.2**

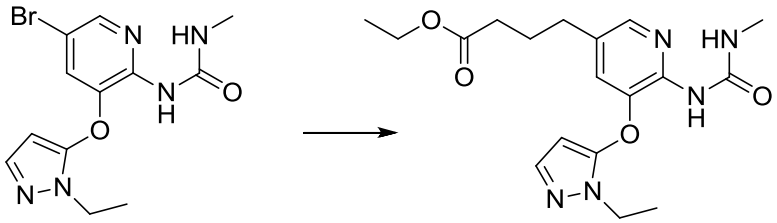
5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinamide (11.2): A flask with 5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinonitrile (**11.1**) (16.2 g, 55.3 mmol) was added concentrated sulfuric acid (32.4 ml, 608 mmol). Make sure all the solid was dissolved in sulfuric acid. The reaction was stirred overnight and cooled down in an ice bath. The reaction was diluted with water. Aqueous NaOH was added to adjust pH to around 5. Precipitates were formed. Filtered. The solids were collected. The aqueous layer was further extracted with EtOAc. The solids and the EtOAc layer were combined and all dissolved in EtOAc. The combined EtOAc layer was dried, concentrated and purified by medium pressure chromatography (silica gel, gradient 0 to 70% EtOAc/hexanes then gradient 0-8% MeOH/DCM to provide 14.74 g (86% yield) of the title compound (**11.2**). MS ESI (pos.) m/e: 311.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (d, *J*=1.96 Hz, 1 H), 7.70 (d, *J*=1.76 Hz, 1 H), 7.53 (br. s, 1 H), 7.43 (d, *J*=1.96 Hz, 1 H), 5.64 (m, 2 H), 4.15 (q, *J*=7.30 Hz, 2 H), 1.46 (t, *J*=7.34 Hz, 3 H).



11.2 **11.3**

1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (11.3): To 5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinamide (**11.2**) (20.0 g, 64.3 mmol) was added water (40.2 ml), CH_3CN (40.2 ml), and then methylamine (2 M in water, 161 ml, 321 mmol). Bis(trifluoroacetoxy)iodo benzene (30.4 g, 70.7 mmol) was added slowly to the reaction at 0°C. The reaction was stirred for 2 hours at ambient temperature. The reaction was quenched by the

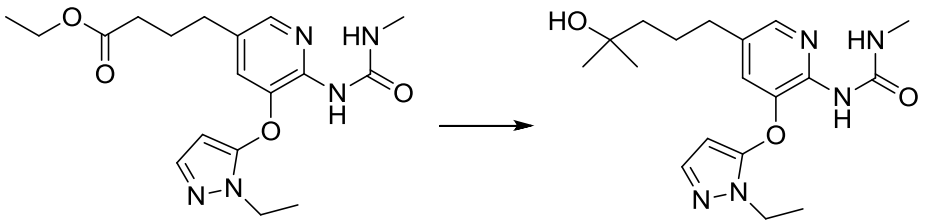
addition of saturated $NaHCO_3$ solution. The crude reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was taken in a small amount of ethyl acetate and filtered to give an off white solid 1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (20.0 g, 91% yield) which was pure and used without further purification. MS ESI (pos.) m/e: 342.0 (M+H). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.11 (s, 1 H), 8.64 - 8.66 (m, 1 H), 8.17 (d, *J*=1.96 Hz, 1 H), 7.61 (d, *J*=2.20 Hz, 1 H), 7.38 (d, *J*=2.20 Hz, 1 H), 5.78 (d, *J*=2.20 Hz, 1 H), 4.06 (d, *J*=7.09 Hz, 2 H), 2.78 (d, *J*=4.65 Hz, 3 H), 1.30 (t, *J*=7.21 Hz, 3 H).



11.3 **11.4**

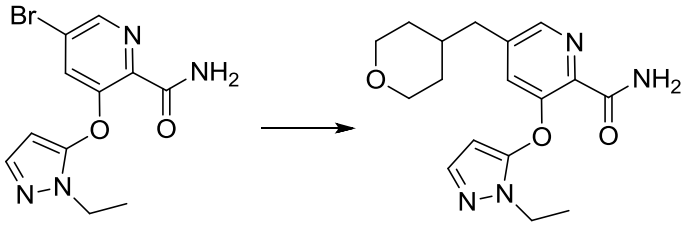
ethyl 4-(5-((1-ethyl-1H-pyrazol-5-yl)oxy)-6-(3-methylureido)pyridin-3-yl)butanoate (11.4): 1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (**11.3**) (150 mg, 0.441 mmol) was dissolved in THF (2 mL). Palladium (ii) acetate (9.90 mg, 0.044 mmol) and S-Phos (36.2 mg, 0.088 mmol) were added followed by addition of (4-ethoxy-4-oxobutyl)zinc(II) bromide, 0.5 M in THF (7.06 mL, 3.53 mmol). The reaction was refluxd for 2.5 hours and quenched by adding saturated ammonium chloride solution. The mixture was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate and the crude product was purified by medium pressure chromatography (silica, 50-100% (hold) ethyl acetate/hexanes) to give desired product contaminated with des-bromo starting material. The material was further purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 Å, 150 x 30 mm, 0.1% TFA in CH_3CN/H_2O, gradient 5% to 90% over min to provide the desired prodcuct containing a significant amount of TFA which was repurified through an SCX column eluting with 0 to 2 M ammonia in methanol to give 61 mg (36.8% yield) of the title compound (**11.4**) as an off-white solid. MS ESI (pos.) m/e: 376.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.19 (br. q, *J*=4.3 Hz, 1 H), 7.79 (d, *J*=1.8 Hz, 1 H),

7.44 (d, *J*=2.0 Hz, 1 H), 7.36 (br. s, 1 H), 7.02 (br. s, 1 H), 5.68 (d, *J*=2.0 Hz, 1 H), 4.11 (q, *J*=7.2 Hz, 2 H), 4.05 (q, *J*=7.3 Hz, 2 H), 2.97 (d, *J*=4.7 Hz, 3 H), 2.51-2.60 (m, 2 H), 2.29 (t, *J*=7.2 Hz, 2 H), (1.85 (quin, *J*=7.5 Hz, 2 H), 1.42 (t, *J*=7.2 Hz, 3 H), 1.24 (t, *J*=7.1 Hz, 3 H).



11.4 **11**

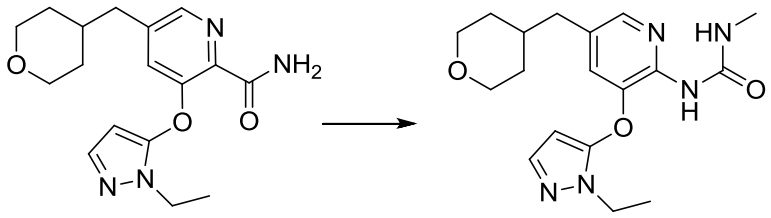
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(4-hydroxy-4-methylpentyl)pyridin-2-yl)-3-methylurea (11): ethyl 4-(5-((1-ethyl-1H-pyrazol-5-yl)oxy)-6-(3-methylureido)pyridin-3-yl)butanoate (43 mg, 0.115 mmol) (**11.4**) was dissolved in THF (1.4 ml) and cooled to 0 °C. To the solution was added methyllithium, 1.6M solution in diethyl ether (0.537 ml, 0.859 mmol) dropwise. The resulting light yellow solution was stirred for one hour. The reaction was quenched with saturated ammonium chloride solution (10 ml) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. The crude product was purified by medium pressure chromatography (silica gel, 0 to 7% MeOH/DCM) to give 30 mg (72.5% yield) of the title compound (**11**) as a light yellow tar. MS ESI (pos.) m/e: 362.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.20 (br. q, *J*=3.7 Hz, 1 H), 7.79 (d, *J*=1.0 Hz, 1 H), 7.43 (d, *J*=2.0 Hz, 1 H), 7.31 (br. s, 1 H), 7.02 (br. s, 1 H), 5.67 (d, *J*=2.0 Hz, 1 H), 4.05 (q, *J*=7.2 Hz, 2 H), 2.97 (d, *J*=4.7 Hz, 3 H), 2.51 (t, *J*=7.5 Hz, 2 H), 1.52-1.69 (m, 2 H), 1.36-1.51 (m, 5 H), 1.18 (s, 6 H).



11.2 **12.2**

3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)picolinamide (12.2): The title compound (**12.2**) was prepared using the same procedure of preparing compound **1**

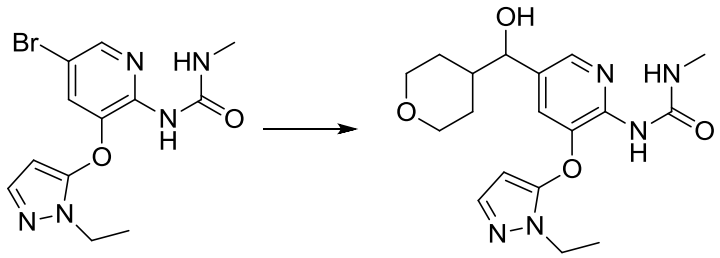
(from intermediate **1.8**) by reacting ((tetrahydro-2H-pyran-4-yl)methyl)zinc(II) bromide (**12.1**, prepared using the same procedure as synthesizing intermediate **3.1)** with 5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinamide **(11.2)** for 5.5 hr..The crude product was purified by medium pressure chromatography (silica gel, gradient 20 to 70% EtOAc/hexanes, then gradient 2 to 8% MeOH/DCM). MS ESI (pos.) m/e: 331.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.34 (d, *J*=1.76 Hz, 1 H), 7.54 (d, *J*=1.76 Hz, 1 H), 7.35 (d, *J*=2.15 Hz, 1 H), 5.46 - 5.56 (m, 1 H), 4.15 (q, *J*=7.24 Hz, 2 H), 3.91 (dd, *J*=11.05, 3.42 Hz, 2 H), 3.32 - 3.41 (m, 2 H), 2.67 (d, *J*=7.24 Hz, 2 H), 1.83 (ttd, *J*=11.35, 7.43, 3.72 Hz, 1 H), 1.49 - 1.59 (m, 2 H), 1.41 (t, *J*=7.24 Hz, 3 H), 1.27 - 1.39 (m, 2 H).



12.2 **12**

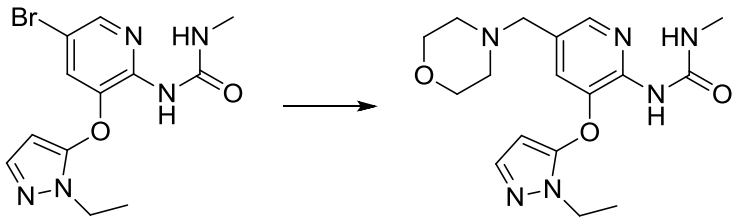
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (12): 3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)picolinamide (**12.2**) (250 mg, 0.757 mmol) was dissolvoed in ACN/H_2O 12 mL (1:1 mix). Methanamine (0.330 mL, 3.78 mmol) was added to the reaction followed by bis(trifluoroacetoxy)iodo benzene (342 mg, 0.795 mmol). The reaction was stirred at ambient temperature for 1 hour 15min.. The crude was concentrated to remove ACN. Then saturated $NaHCO_3$ was added and the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried, concentrated and purified by medium pressure chromatography (silica gel, gradient 0 to 70% EtOAc/hexanes, then 2-8% MeOH/DCM) to provide 150 mg of the title compound (**12**) with excellent purity (99%) and 90 mg of less pure title compound (**12**). The 90 mg fraction was repurified by reverse phase HPLC using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 10-60% over 25 min. to provide 50 mg of pure (99%) title compound (**12**). A total of 200 mg of the pure product (**12**) was obtained (74% yield). HRMS ESI (pos.) m/e calcd $C_{18}H_{25}N_5O_3$ 360.2030 (M+H); found 360.2045 (Δ=4.12 ppm). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.91 (d, *J*=1.96 Hz, 1 H), 7.44 (d, *J*=1.96 Hz, 1 H), 7.24 (d, *J*=1.96 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.13 (q, *J*=7.24 Hz, 2 H), 3.90 (dd, *J*=10.66, 3.62 Hz, 2 H), 3.33 - 3.39

(m, 2 H), 2.92 (s, 3 H), 2.51 (d, *J*=7.24 Hz, 2 H), 1.64 - 1.78 (m, 1 H), 1.52 (dd, *J*=13.01, 1.66 Hz, 2 H), 1.40 (t, *J*=7.24 Hz, 3 H), 1.20 - 1.35 (m, 2 H).



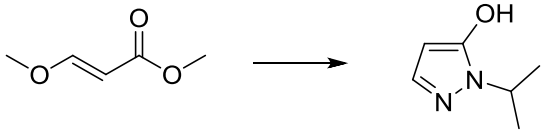
11.3 **13**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(hydroxy(tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (13): 1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (**11.3**) (71 mg, 0.209 mmol) was dissolved in THF (2087 µl) and cooled to -78 °C. Methyllithium (1.6M in diethyl ether, 457 µl, 0.731 mmol) was added dropwise and the solution was stirred for 20 minutes. Tetrahydro-2H-pyran-4-carbaldehyde (32.3 µl, 0.313 mmol) was then added at -78 °C dropwise. The resulting mixture was allowed to warm to 0 °C over 2.5 hours and then quenched with ammonium chloride solution. The mixture was extracted with ethyl acetate (3 x 30 ml) and the collected organic layers were washed with brine (1 x 20 mL) and dried over magnesium sulfate. The crude material was purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 micron, C18, 100 Å, 150 x 30 mm, 0.1% TFA in CH_3CN/H_2O, gradient 2% to 90% over 25 min to provide desired product but contaminated with some side products. A second purification using medium pressure chromatography (silica gel, 0 to 10% MeOH/DCM) was performed to provide 9.5 mg (12% yield) of the title compound (**13**). MS ESI (pos.) m/e: 376.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.19 (br. s., 1 H), 7.87 (d, *J*=1.76 Hz, 1 H), 7.45 (d, *J*=1.96 Hz, 1 H), 7.35 (s, 1 H), 7.21 (d, *J*=1.76 Hz, 1 H), 5.68 (d, *J*=2.15 Hz, 1 H), 4.35 (d, *J*=7.43 Hz, 1 H), 4.05 (q, *J*=7.24 Hz, 2 H), 3.88 - 4.02 (m, 2 H), 3.22 - 3.38 (m, 2 H), 2.98 (d, *J*=4.69 Hz, 3 H), 2.36 (br. s, 1 H), 1.78 - 1.86 (m, 1 H), 1.66 - 1.77 (m, 2 H), 1.42 (t, *J*=7.24 Hz, 3 H), 1.23 - 1.34 (m, 2 H).



11.3 **14**

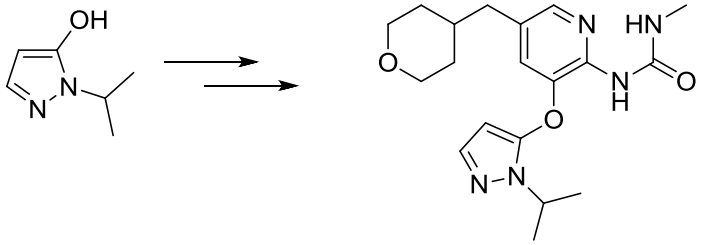
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(morpholinomethyl)pyridin-2-yl)-3-methylurea (14): To a stirred solution of dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (7.01 mg, 0.015 mmol), $Pd(OAc)_2$ (1.650 mg, 7.35 µmol), 1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (**11.3**) (0.025 g, 0.073 mmol) and potassium trifluoro(morpholinomethyl)borate (0.015 g, 0.073 mmol) in tetrahydrofuran (0.735 ml, 0.073 mmol) was added cesium carbonate (0.072 g, 0.220 mmol). The reaction mixture was heated to 80 °C overnight. The reaction was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. The organics were concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 0 to 50% ethyl acetate/ethanol (3/1) in heptanes) to afford the title compound (**14**) as a off-white film. MS ESI (pos.) m/e: 361.0 (M+H). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.99 (d, *J*=1.71 Hz, 1 H), 7.46 (d, *J*=2.20 Hz, 1 H), 7.39 (d, *J*=1.71 Hz, 1 H), 5.80 (d, *J*=2.20 Hz, 1 H), 4.12 (q, *J*=7.34 Hz, 2 H), 3.63 - 3.66 (m, 4 H), 3.46 (s, 2 H), 2.93 (s, 3 H), 2.40 - 2.45 (m, 4 H), 1.40 (s, 3 H).



17.1

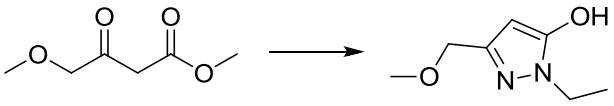
1-isopropyl-1H-pyrazol-5-ol (17.1): isopropylhydrazine hydrochloride (2.98 g, 26.9 mmol) was dissolved in water (50ml) and 50% w/v NaOH solution was added to adjust pH to 9.5 (by pH-meter). The mixture was heated to 40 °C and methyl trans-3-methoxyacrylate (2.31 ml, 21.5 mmol) was added dropwise over 20 minutes. pH was adjusted periodically by addition of 50% w/v NaOH solution to 9.0-9.5 range. After the completion of addition of methyl trans-3-methoxyacrylate, the mixture was stirred for 3 hours at 40 °C and pH was adjusted occasionally to 9.0-9.5 range. The mixture was cooled in ice bath and acidified to pH 4-5 with 6M HCl, extracted 6 times with 3:1 chloroform/isopropanol, dried over Na_2SO_4, filtered and concentrated.

The residue was purified over silica gel (10% MeOH in EtOAc) to afford 1-isopropyl-1H-pyrazol-5-ol (2.0 g, 73.6% yield) as a yellow solid. MS ESI (pos.) m/e: 127.1 (M+H).



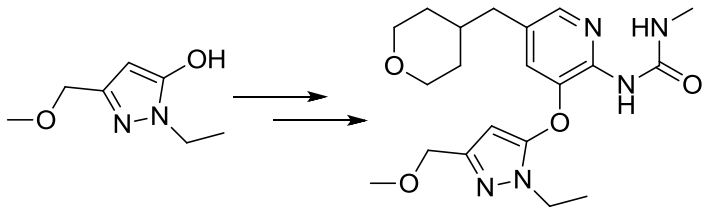
17.1 **17**

1-(3-((1-isopropyl-1H-pyrazol-5-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (17): The title compound (**17**) was prepared following the same synthetic procedure as compound **12**. MS ESI (pos.) m/e: 373.9 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J* = 1.8 Hz, 1 H), 7.47 (d, *J* = 1.8 Hz, 1 H), 7.18 (d, *J* = 1.8 Hz, 1 H), 5.76 (d, *J* = 2.2 Hz, 1 H), 4.61 (septet, *J* = 6.7 Hz, 1 H), 3.89 (dd, *J* = 10.8, 3.5 Hz, 2 H), 3.35 (dd, *J* = 11.9, 1.8 Hz, 2 H), 2.92 (s, 3 H), 2.50 (d, *J* = 7.0 Hz, 2 H), 1.70 (m, 1 H), 1.51 (m, 2 H), 1.45 (d, *J* = 6.7, 6 H), 1.27 (qd, *J* = 12.1, 4.5 Hz, 2 H).



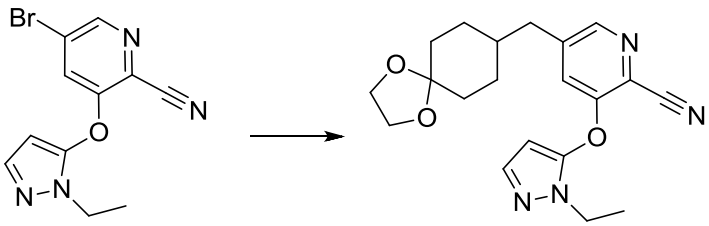
18.1

1-ethyl-3-(methoxymethyl)-1H-pyrazol-5-ol (18.1): ethylhydrazine oxalate (1.34 g, 8.90 mmol) was dissolved in MeOH (10mL). Triethylamine (1.24 ml, 8.90 mmol) was added, and stirred for 10 min, then methyl 4-methoxy-3-oxobutanoate (1.18 ml, 8.90 mmol) was added and the reaction was heated to reflux overnight. The reaction was cooled to room temperature, poured into water (30 mL), acidified to pH 4, and extracted with 5:1 CH_2Cl_2:isopropanol. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified over silica gel (3% MeOH in CH_2Cl_2) to provide 1-ethyl-3-(methoxymethyl)-1H-pyrazol-5-ol (**18.1**) (1.0 g, 72.0% yield). MS ESI (neg.) m/e: 155.1 (M-H).



18.1 **18**

1-(3-((1-ethyl-3-(methoxymethyl)-1H-pyrazol-5-yl)oxy)-5-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (18): The title compound (**18**) was prepared from **18.1** following the same synthetic procedure as compound **12**. MS ESI (pos.) m/e: 403.9 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.91 (s, 1 H), 7.27 (s, 1 H), 5.74 (s, 1 H), 4.35 (s, 2 H), 4.10 (qd, *J* = 7.2 Hz, 2 H), 3.89 (dd, *J* = 11.0, 3.3 Hz, 2 H), 3.39-3.33 (m, 5 H), 2.91 (s, 3 H), 2.51 (d, *J* = 7.2 Hz, 2 H), 1.72 (m, 1 H), 1.52 (d, *J* = 13.1 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.27 (qd, *J* = 12.5, 4.5 Hz, 2 H).

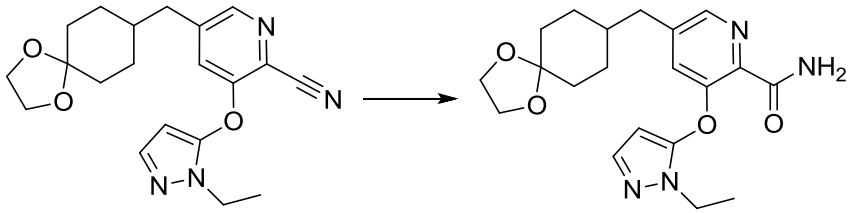


11.1 **19.1**

5-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinonitrile (19.1): 8-methylene-1,4-dioxaspiro[4.5]decane (0.087 ml, 0.563 mmol) was purged with nitrogen. Then 1 mL degassed THF was added, followed by 9-BBN, 0.5M in THF (1.126 ml, 0.563 mmol). The resulting solution was heated to reflux for 1 hour and cooled to ambient temperature. This solution was called solution A.

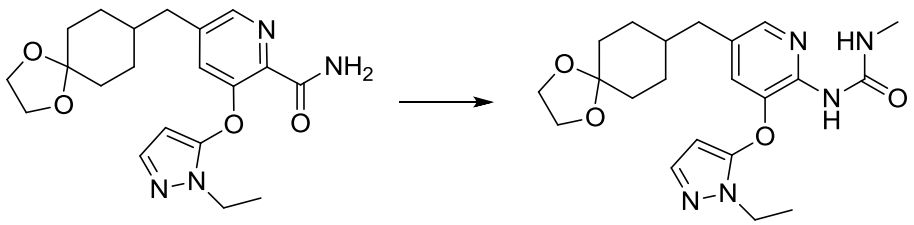
A separate flask was charged with 5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinonitrile (**11.1**) (150 mg, 0.512 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (ii) (41.8 mg, 0.051 mmol), K_2CO_3 (212 mg, 1.535 mmol), degassed DMF (2 mL), and degassed H_2O (0.14 ml, 7.77 mmol). Solution A was added at this point. The resulting mixture was heated at 80 °C for 5 hours. LCMS showed that the reaction was completed. Water was added followed by EtOAc extraction. The EtOAc layer was dried, concentrated and purified using medium pressure chromatography (silica gel, gradient 0 to 50% EtOAc/Hexanes) to provide 136 mg of the title

compound (**19.1**) with 90% purity which was used without further purification. MS ESI (pos.) m/e: 369.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (d, *J*=1.56 Hz, 1 H), 7.49 (d, *J*=1.96 Hz, 1 H), 7.24 (d, *J*=1.57 Hz, 1 H), 5.77 (d, *J*=1.96 Hz, 1 H), 4.04 - 4.20 (m, 2 H), 3.88 - 3.99 (m, 4 H), 2.59 (d, *J*=7.04 Hz, 2 H), 1.70 - 1.78 (m, 2 H), 1.48 - 1.66 (m, 5 H), 1.45 (t, *J*=7.24 Hz, 3 H), 1.23 - 1.39 (m, 2 H).



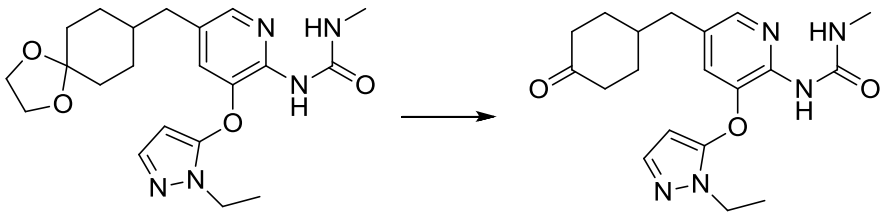
19.1 **19.2**

5-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinamide (19.2): A flask was charged with 5-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)picolinonitrile (**19.1**) (88 mg, 0.239 mmol). THF (2 mL) was added, followed by KOH (214 mg, 3.82 mmol) in 0.15 mL of water and hydrogen peroxide (0.5 mL, 5.71 mmol). A separate layer appeared. MeOH (0.5 mL) was added and stirring was continued. The reaction was stirred for 9 hours, diluted with water and extracted with EtOAc. The EtOAc layer was washed with brine, dried, concentrated and purified using medium pressure chromatography (silica gel, gradient 0 to 70% EtOAc/Hexanes first then 0 to 8% MeOH/DCM) to provide 59 mg (64% yield) of the title compound (**19.2**). MS ESI (pos.) m/e: 387.2 (M+H). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.21 (s, 1 H), 7.62 (br. s, 1 H), 7.38 - 7.40 (m, 1 H), 7.30 (d, *J*=1.56 Hz, 1 H), 5.50 - 5.52 (m, 1 H), 5.46 (br. s, 1 H), 4.17 (d, *J*=7.24 Hz, 2 H), 3.89 - 3.99 (m, 4 H), 2.59 (d, *J*=7.04 Hz, 2 H), 1.71 - 1.78 (m, 2 H), 1.49 - 1.68 (m, 5 H), 1.46 (t, *J*=7.34 Hz, 3 H), 1.28 - 1.38 (m, 2 H).



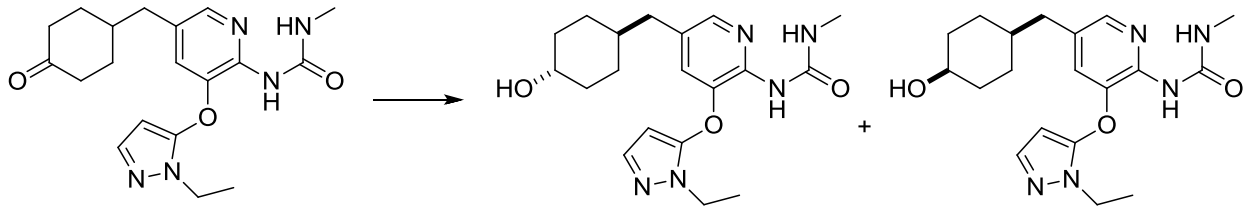
19.2 **19.3**

1-(5-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (19.3): The title compound (**19.3**) was prepared following the same procedure of preparing **12** from **12.2**. MS ESI (pos.) m/e: 416.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=2.15 Hz, 1 H), 7.44 (d, *J*=2.35 Hz, 1 H), 7.21 (d, *J*=2.15 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 3.89 (s, 4 H), 2.91 (s, 3 H), 2.48 (d, *J*=7.24 Hz, 2 H), 1.66 - 1.75 (m, 2 H) 1.56 - 1.65 (m, 2 H) 1.42 - 1.51 (m, 3 H) 1.39 (t, *J*=7.34 Hz, 3 H), 1.18 - 1.30 (m, 2 H).



19.3 **19.4**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((4-oxocyclohexyl)methyl)pyridin-2-yl)-3-methylurea (19.4): A flask with 1-(5-(1,4-dioxaspiro[4.5]decan-8-ylmethyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (**19.3**) (63 mg, 0.152 mmol) was added EtOH (4 mL) and 1 N HCl (0.455 mL, 0.455 mmol). The reaction was heated to 65 °C for 2 hours and then cooled down. The reaction was neutralized with 1 N NaOH and concentrated to remove EtOH. Then it was diluted with brine and extracted with EtOAc. The EtOAc layer was dried, concentrated and purified using medium pressure chromatography (silica gel, gradient 0 to 70% EtOAc/Hexanes first then 0 to 8% MeOH/DCM) to provide 47 mg of the title compound (**19.4**) that had some impurity and was carried to next step without further purification. MS ESI (pos.) m/e: 372.2 (M+H).

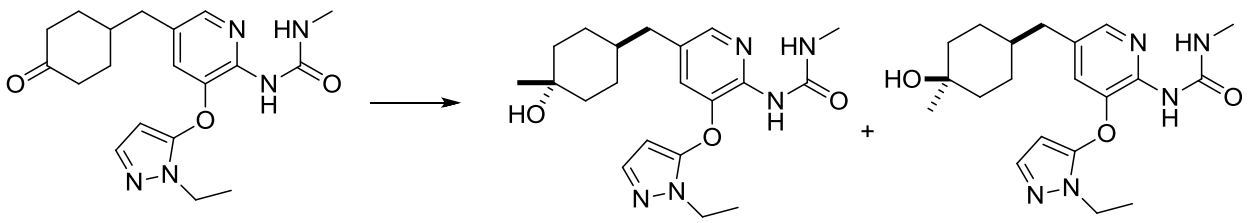


19.4 **19** **20**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1r,4r)-4-hydroxycyclohexyl)methyl)pyridin-2-yl)-3-methylurea (19): To a flask with 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((4-oxocyclohexyl)methyl)pyridin-2-yl)-3-methylurea (**19.4**) (25 mg, 0.067 mmol) was added

$NaBH_4$ (10.19 mg, 0.269 mmol) and MeOH (2 mL). The reaction was stirred for 2 hours at ambient temperature and concentrated to remove most of the MeOH. Saturated NH_4Cl was added to the crude and the crude was extracted with EtOAc. The EtOAc layer was dried, concentrated and purified by reverse phase HPLC, using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 20 to 80% over 25 min. to provide 21 mg (84% yield) of 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((4-hydroxycyclohexyl)methyl)pyridin-2-yl)-3-methylurea as a mxture of the cis and trans isomers (**19** and **20**) with a 4:1 isomer ratio. The isomer mixture was separated by supercritical fluid chromatography. Separation condition: 250mm x 21 mm AD-H column with 17.5 g/min MeOH (20mM Ammonia)+ 32.5 g/min CO_2 on Thar 80 SFC. Outlet pressure = 100 bar; Temp.= 27C; Wavelength = 296 nm. Used 0.75 mL injections of 18 mg/ 3mL (6.0 mg/mL) sample solution in MeOH i.e. 4.5 mg/injection. Run time = 5.0 min., cycle time = 3.0 min.. The title compound (**19**) was the major isomer (the later-eluting peak off chiral column) isolated from the separation and was assigned as the trans isomer based on the coupling pattern of the peaks from NMR. Also the trans isomer can take di-equatorial conformation and would be more stable which is consistent with it being the major product of the reaction. MS ESI (pos.) m/e: 374.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.88 (d, *J*=1.76 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.20 (d, *J*=1.96 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 3.45 (tt, *J*=10.93, 4.33 Hz, 1 H), 2.92 (s, 3 H), 2.45 (d, *J*=7.24 Hz, 2 H), 1.86 - 1.94 (m, 2 H), 1.62 - 1.71 (m, 2 H), 1.36 - 1.45 (m, 4 H), 1.12 - 1.24 (m, 2 H), 0.95 - 1.07 (m, 2 H).

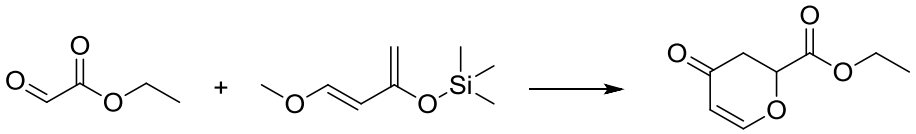
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1s,4s)-4-hydroxycyclohexyl)methyl)pyridin-2-yl)-3-methylurea (20): The title compound (**20**) is the minor isomer (the earlier-eluting peak) isolated from the above chiral separation using the same conditions to obtain compound **19**. MS ESI (pos.) m/e: 374.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.76 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.20 (d, *J*=1.96 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 3.84 - 3.90 (m, 1 H), 2.92 (s, 3 H), 2.50 (d, *J*=7.04 Hz, 2 H), 1.64 - 1.74 (m, 2 H), 1.45 - 1.58 (m, 3 H), 1.36 - 1.44 (m, 7 H).



19.4 **21** **22**

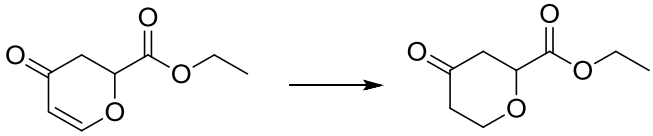
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)pyridin-2-yl)-3-methylurea (21): 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((4-oxocyclohexyl)methyl)pyridin-2-yl)-3-methylurea (**19.4**) (34.6 mg, 0.093 mmol) was azeotroped with toluene and then purged with nitrogen. The reaction was first dissolved in THF (2.5 ml) and cooled to 0 °C. To this solution was added methyllithium solution (1.6M in diethyl ether, 0.320 mL, 0.512 mmol) dropwise. After 5 min., the reaction was allowed to warm up to ambient temperature and stirred for one hour. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The EtOAc layer was dried, concentrated and purified by reverse phase HPLC, using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 20 to 80% over 25 min. to provide 9 mg of the title compound (**21**) as the less polar and later-eluting peak from HPLC. Stereochemistry was arbitrarily assigned. MS ESI (pos.) m/e: 388.3 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.76 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.20 (d, *J*=1.76 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.37 Hz, 2 H), 2.92 (s, 3 H), 2.48 (d, *J*=5.28 Hz, 2 H), 1.58 - 1.67 (m, 2 H), 1.28 - 1.45 (m, 10 H), 1.15 (s, 3 H).

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1s,4s)-4-hydroxy-4-methylcyclohexyl)methyl)pyridin-2-yl)-3-methylurea (22): The title compound (**22**), the more polar and faster-eluting peak, was isolated in 7.5 mg from the same HPLC purification that leads to **21**. Stereochemistry was arbitrarily assigned. MS ESI (pos.) m/e: 388.3 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.76 Hz, 1 H), 7.45 (d, *J*=2.15 Hz, 1 H), 7.21 (d, *J*=1.96 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 2.92 (s, 3 H), 2.49 (d, *J*=7.24 Hz, 2 H), 1.57 - 1.68 (m, 4 H), 1.35 - 1.48 (m, 6 H), 1.18 (s, 3 H), 1.05 - 1.16 (m, 2 H).



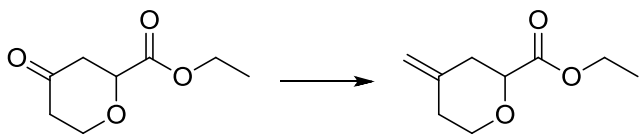
15.1

Ethyl 4-oxo-3,4-dihydro-2H-pyran-2-carboxylate (15.1): A solution of ethyl 2-oxoacetate (7.089 ml, 34.82 mmol) and (E)-(4-methoxybuta-1,3-dien-2-yloxy)trimethylsilane (6.00 g, 34.82 mmol) in toluene (50 ml) was placed under nitrogen. Zinc(II) chloride (34.82 ml, 17.41 mmol) was added and the reaction was stirred at ambient temperature overnight. The mixture was concentrated in vacuo, diluted with ethyl acetate (100 ml) and washed with 1 N hydrochloric acid (20 ml), saturated sodium bicarbonate (20 ml), and brine (20 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by silica gel chromatography using gradient ethyl acetate/hexanes (30 to 50%) as eluent to provide ethyl 4-oxo-3,4-dihydro-2H-pyran-2-carboxylate (**15.1**) (1.69 g, 22.8 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 (d, *J*= 6.06 Hz, 1 H), 5.48 (d, *J*= 6.26 Hz, 1 H), 5.01 (t, *J*= 7.83 Hz, 1 H), 4.29 (q, *J*= 7.04 Hz, 2 H), 2.86 (d, *J*= 8.02 Hz, 2 H), 1.32 (t, *J*= 7.04 Hz, 3 H).



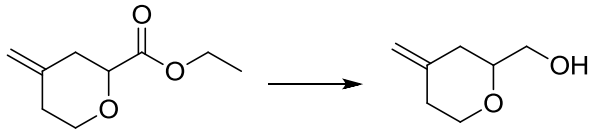
15.1 **15.2**

Ethyl 4-oxotetrahydro-2H-pyran-2-carboxylate (15.2): Ethyl 4-oxo-3,4-dihydro-2H-pyran-2-carboxylate (**15.1**) (10.0 g, 58.77 mmol) and 10% Pd/C (3.127 g, 2.938 mmol) was dissolved in EtOH (50 mL) and was placed under balloon hydrogen pressure for 18 hours. The reaction was filtered through celite and the filtrate was concentrated. The resulting residue was purified by silica gel (gradient 30-40% EtOAc/hexanes) to give ethyl 4-oxotetrahydro-2H-pyran-2-carboxylate (**15.2**) (2.36 g, 23.3% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.25 (q, *J*= 7.04 Hz, 2 H), 4.18 (d, *J*= 11.93 Hz, 1 H), 3.97 (dd, *J*= 11.15, 2.54 Hz, 1 H), 3.98 (m 1 H), 3.47 (dt, *J*= 11.93, 2.35 Hz, 1 H), 2.31 (m, 1 H), 1.92 (m, 1 H), 1.69 (m, 1 H), 1.30 (t, *J*= 7.04 Hz, 3 H).



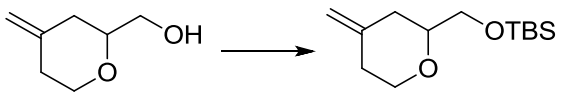
15.2 **15.3**

Ethyl 4-methylenetetrahydro-2H-pyran-2-carboxylate (15.3): Methyltriphenylphosphonium bromide (5.248 g, 14.69 mmol) was placed in THF (2 mL). KHMDS (14.69 ml, 14.69 mmol) was added and stirred at room temperature for 30 minutes. The solution was cooled to 0 ºC. A solution of ethyl 4-oxo-tetrahydro-2H-pyran-2-carboxylate (2.108 g, 12.24 mmol) in THF (20 mL) was added and the reaction was stirred at room temperature for 1 hour. Water was added and the mixture was extracted with ether (x2). The extracts were then dried, filtered and concentrated. The crude material was brought up in 1:1 pentane:ether (100 mL). Solids were filtered off and the filtrate was concentrated to give crude ethyl 4-methylenetetrahydro-2H-pyran-2-carboxylate which was used as is in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.83 (m, 2H), 4.25 (q, *J*= 7.04 Hz, 2 H), 4.18 (m, 1 H), 3.97 (dd, *J*= 10.96, 3.13 Hz, 1 H), 3.47 (dt, *J*= 11.35, 3.13 Hz, 1 H), 2.58 (m, 1 H), 2.35 (m, 2 H), 2.19 (m, 1 H), 1.31 (t, *J*= 7.04 Hz, 3 H).



15.3 **15.4**

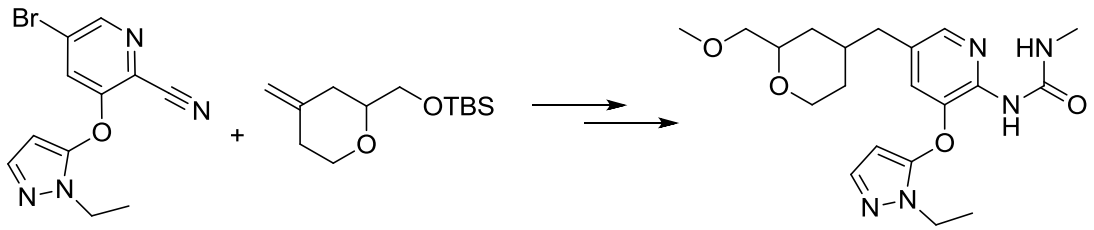
(4-methylenetetrahydro-2H-pyran-2-yl)methanol (15.4): Crude ethyl 4-methylenetetrahydro-2H-pyran-2-carboxylate (**15.3**) (2.17 g, 12.7 mmol) was dissolved in ether (10 mL). LAH (19.1 ml, 19.1 mmol) was added and the reaction was stirred for 15 minutes. The reaction was cooled in an ice-bath, quenched with slow addition of water and extracted with DCM (2 x50 mL). The organic layer was dried, filtered and concentrated. The resulting residue was purified by silica gel (40% EtOAc in hexane) to provide (4-methylenetetrahydro-2H-pyran-2-yl)methanol (**15.4**) (0.800 g, 49.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.77 (m, 2 H), 4.12 (m, 2 H), 3.64 (m, 1 H), 3.56 (m, 1 H), 3.42 (m, 1 H), 2.31 (m, 1 H), 2.20-2.07 (m, 3 H), 2.04(m, 1 H).



15.4 **15.5**

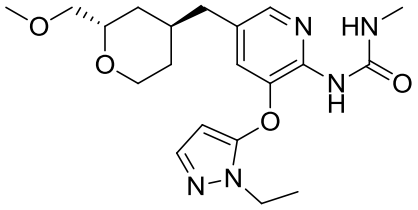
tert-butyldimethyl((4-methylenetetrahydro-2H-pyran-2-yl)methoxy)silane (15.5): To a flask of (4-methylenetetrahydro-2H-pyran-2-yl)methanol (**15.4**) (800 mg, 6.242 mmol) was

added DMF (10 mL) followed by dropwise addition of a solution of imidazole (509.9 mg, 7.490 mmol) and TBDMS-Cl (987.8 mg, 6.554 mmol) in DMF (5 mL). The reaction was stirred for 24 hours. Ether was added and the solids were filtered off. The ether layer was washed with water, brine, dried, and concentrated. The resulting residue was purified by silica gel (10% EtOAc in hexanes) to provide tert-butyldimethyl((4-methylenetetrahydro-2H-pyran-2-yl)methoxy)silane (**15.5**) (1.29 g, 85.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.74 (m, 2 H), 4.08 (m, 1 H), 3.70 (dd, *J*= 10.56, 5.28 Hz, 1 H), 3.57 (m, *J*= 10.56, 5.28 Hz, 1 H), 3.42-3.30 (m, 2 H), 2.35-2.24 (m, 2 H), 2.14 (m, 1 H), 2.01 (m, 1 H), 0.9 (s, 9 H), 0.07(m, 6 H).



11.1 **15.5** **15.6**

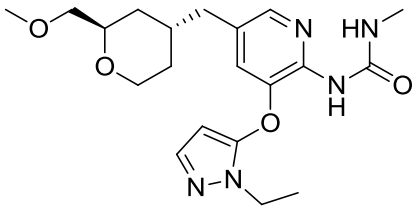
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((2-(methoxymethyl)tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (15.6): The title compound (**15.6**) was racemic and was prepared following the procedure of synthesizing compound **19**. MS (apci) m/e: 404.2 (M+H).



15

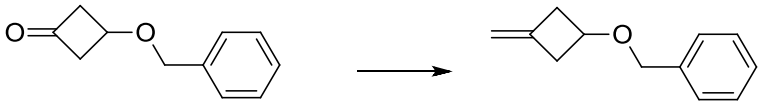
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((2S,4S)-2-(methoxymethyl)tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (15): The racemic mixture of 1-(3-(1-ethyl-1H-pyrazol-5-yloxy)-5-((2-(methoxymethyl)tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (**15.6**) (146 mg) was resolved using a Chiral Tech OD-H column (4.6mm x 250 mm, 5u) eluting with 15% ethanol:85% hexanes at a flow rate of 1 mL/min to provide the title compound (**15**) (the first peak off chiral column, 56.6 mg, 38.8% yield). Stereochemistry was arbitrarily assigned. MS (apci) m/e: 404.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.17 (m, 1 H), 7.76 (m, 1 H), 7.45 (d, *J*= 2.15 Hz, 1 H), 6.96 (d, *J*= 1.96 Hz, 1 H), 5.67 (d, *J*= 2.15 Hz, 1 H), 4.05 (m, 3 H),

3.46-3.30 (m, 7 H), 2.99 (d, *J*= 4.70 Hz, 3 H), 2.44 (m, 2 H), 1.66 (m, 1 H), 1.50 (m, 2 H), 1.42 (t, *J*= 7.24 Hz, 3 H), 1.26 (m, 1 H), 1.03 (m, 1 H).



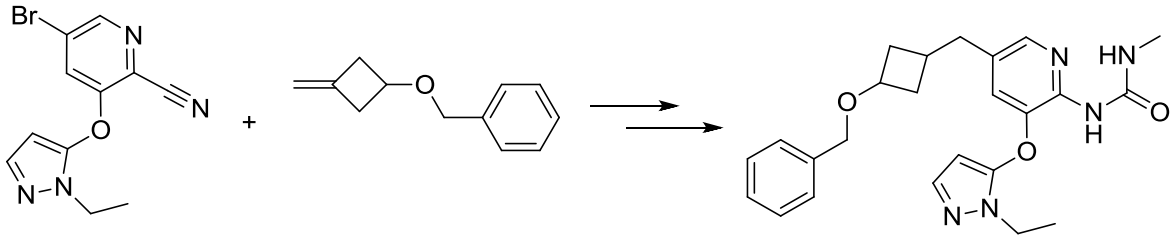
16

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((2R,4R)-2-(methoxymethyl)tetrahydro-2H-pyran-4-yl)methyl)pyridin-2-yl)-3-methylurea (16): The title compound (**16**), the fourth peak off chiral column, was prepared using the same procedure as compound **15**. Stereochemistry was arbitrarily assigned. MS (apci) m/e: 404.2 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.17 (m, 1 H), 7.76 (m, 1 H), 7.45 (d, *J*= 2.15 Hz, 1 H), 6.96 (d, *J*= 1.96 Hz, 1 H), 5.67 (d, *J*= 2.15 Hz, 1 H), 4.05 (m, 3 H), 3.45-3.30 (m, 7 H), 2.99 (d, *J*= 4.70 Hz, 3 H), 2.44 (m, 2 H), 1.66 (m, 1 H), 1.50 (m, 2 H), 1.42 (t, *J*= 7.24 Hz, 3 H), 1.26 (m, 1 H), 1.03 (m, 1 H).



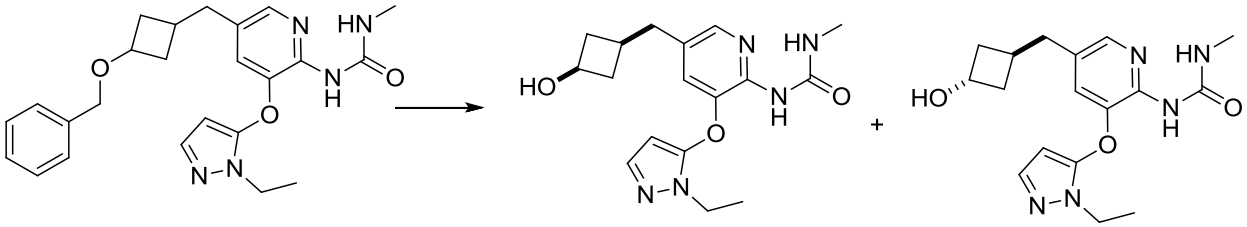
23.1

((3-methylenecyclobutoxy)methyl)benzene (23.1): To a flask with 3-(benzyloxy)cyclobutanone (0.341 mL, 2.168 mmol) was added THF (5 mL) and cooled down to 0 °C. Tebbe reagent, 0.5 M solution in toluene (4.34 mL, 2.168 mmol) was added slowly. The reaction was warmed to ambient temperature and stirred for 30 min.. Ether was added to dilute the reaction and the reaction was quenched with 0.1 M NaOH (dropwise) until gas stopped generating. The crude was filtered through celite, dried with $MgSO_4$ and concentrated. Then it was purified using medium pressure chromatography (silica gel, gradient 0 to 20% EtOAc/Hexanes) to provide 220 mg (58.2% yield) of the title compound (**23.1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 - 7.39 (m, 5 H), 4.83 - 4.89 (m, 2 H), 4.46 (s, 2 H), 4.12 (quin, *J*=6.60 Hz, 1 H), 2.83 - 2.96 (m, 2 H), 2.69 - 2.83 (m, 2 H).



11.1 **23.1** **23.2**

1-(5-((3-(benzyloxy)cyclobutyl)methyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (23.2): The title compound (**23.2**) was prepared using the same procedure of preparing **19.3** from **11.1**. The title compound (**23.2**) existed as a pair of trans/cis isomers with a ratio about 4:1. MS ESI (pos.) m/e: 436.3 (M+H).

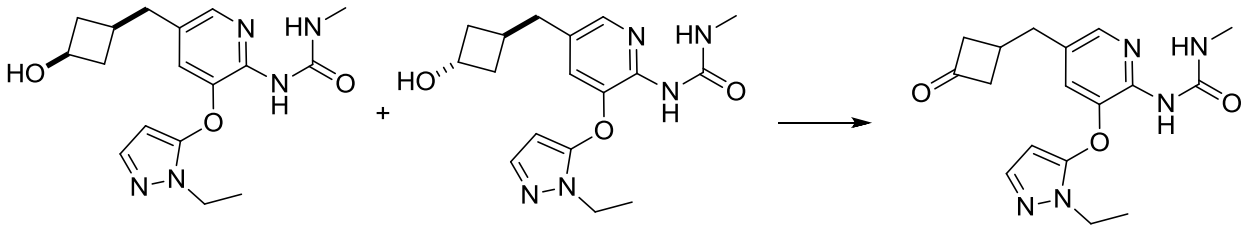


23.2 **23** **24**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1s,3r)-3-hydroxycyclobutyl)methyl)pyridin-2-yl)-3-methylurea (23): To a flask with 1-(5-((3-(benzyloxy)cyclobutyl)methyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (**23.2**) (33 mg, 0.076 mmol) was added MeOH. The flask was filled with nitrogen and 10% palladium on carbon (12.10 mg, 0.011 mmol) was added. Then it was purged with hydrogen and stirred under a double-layer hydrogen balloon for 6 hours. The reaction mixture was filtered through celite, concentrated and purifed by reverse phase HPLC using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 10-70% over 25 min. to provide **22** mg of a racemic mixture of **23** and **24**. 17 mg of the mixture was separated further by supercritical fluid chromatography. Separation condition: AD-H (2 x 15 cm) column, 15% methanol(0.1% NH_4OH)/CO_2, Outlet pressure =100 bar, 70 mL/min, Wavelength = 220 nm. inj vol.: 1 mL, 2 mg/mL methanol. The title compound (**23**), obtained in 13 mg, was the fisrt peak eluted off the chiral column and the major isomer. Stereochemistry was arbitrarily assigned. MS ESI (pos.) m/e: 346.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.76 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.19 (d, *J*=1.76 Hz, 1 H), 5.74 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz,

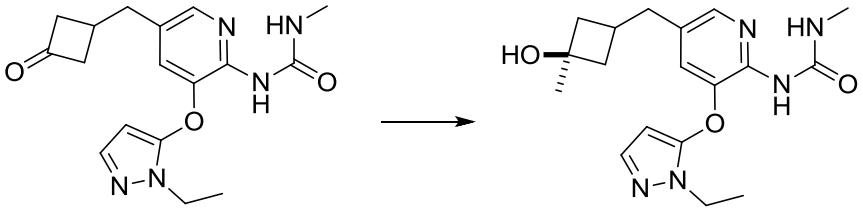
2 H), 3.96 - 4.05 (m, 1 H), 2.91 (s, 3 H), 2.64 (d, *J*=7.43 Hz, 2 H), 2.28 - 2.37 (m, 2 H), 1.85 - 1.99 (m, 1 H), 1.49 - 1.59 (m, 2 H), 1.39 (t, *J*=7.24 Hz, 3 H).

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1r,3s)-3-hydroxycyclobutyl)methyl)pyridin-2-yl)-3-methylurea (24): The title compound (**24**), obtained in 5 mg, was the second peak that eluted off the chiral column and the minor isomer. Stereochemistry was arbitrarily assigned. HRMS ESI (pos.) m/e calcd $C_{17}H_{23}N_5O_3$ 346.1874 (M+H); found 346.1857 (Δ=4.81 ppm). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.91 (d, *J*=1.76 Hz, 1 H), 7.43 - 7.45 (m, 1 H), 7.22 (d, *J*=5.63 Hz, 1 H), 5.73 (d, *J*=2.15 Hz, 1 H), 4.31 (quin, *J*=6.55 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 2.92 (s, 3 H), 2.68 (d, *J*=8.02 Hz, 2 H), 2.37 - 2.48 (m, 1 H), 1.95 - 2.09 (m, 4 H), 1.39 (t, *J*=7.24 Hz, 3 H).



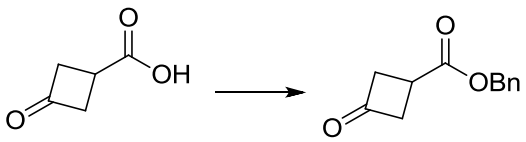
23 **24** **25.1**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((3-oxocyclobutyl)methyl)pyridin-2-yl)-3-methylurea (25.1): A flask was charged with 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((3-hydroxycyclobutyl)methyl)pyridin-2-yl)-3-methylurea (racemic mixture of **23** and **24**) (120 mg, 0.347 mmol) and dess-martin periodinane (192 mg, 0.452 mmol). DCM (6 mL) was added. The reaction was stirred at ambient temperature for 1hr 20 min and then quenched with saturated $NaHCO_3$. The crude was extracted with EtOAc. The EtOAc layer was dried, concentrated and purified using medium pressure chromatography (silica gel, gradient 0 to 8% MeOH/DCM) to provide 107 mg (69% yield) of the title compound (**25.1**). MS ESI (pos.) m/e: 344.1 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.98 (d, *J*=1.76 Hz, 1 H), 7.45 (d, *J*=2.15 Hz, 1 H), 7.33 (d, *J*=1.96 Hz, 1 H), 5.75 (d, *J*=2.15 Hz, 1 H), 4.13 (q, *J*=7.24 Hz, 2 H), 3.03 - 3.13 (m, 2 H), 2.92 (s, 3 H), 2.87 (d, *J*=7.63 Hz, 2 H), 2.71 - 2.81 (m, 2 H), 2.59 - 2.69 (m, 1 H), 1.40 (t, *J*=7.34 Hz, 3 H).



25.1 **25**

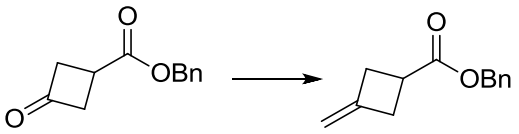
1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((3-hydroxy-3-methylcyclobutyl)methyl)pyridin-2-yl)-3-methylurea (25): A flask with 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-((3-oxocyclobutyl)methyl)pyridin-2-yl)-3-methylurea (**25.1**) (35.5 mg, 0.103 mmol) was azeotroped with toluene and purged with nitrogen. THF (2.0 mL) was added to the flask under nitrogen and the reaction was cooled down to 0 °C. Methyllithium solution (1.6 M in diethyl ether, 0.485 mL, 0.775 mmol) was added dropwise. After 5 min., the reaction was allowed to warm up to ambient temperature and stirred for one hour. Reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The EtOAc layer was dried, concentrated and purified by reverse phase HPLC, using an Agilent SB C8 column, 0.1% TFA in CH_3CN/H_2O, gradient 10-50% over 25 min. to provide 21.2 mg of a mixture of isomers (about 2:1 ratio) that contained the title compound (**25**) as the major isomer. The mixture of isomers was separated by supercritical fluid chromatography (SFC). Separation condition: 250 x 30 mm AD-H column with 33 g/min MeOH+ (20 mM NH_3) + 77 g/min CO_2 on Thar 200 SFC. Outlet pressure = 100 bar; Temp. = 26C; Wavelength = 235 nm. Used 0.3 mL injections of 58 mg/5mL MeOH/DCM(5:1) (i.e. 11.6 mg/mL and 3.4 mg/ injection), Cycle time 3.8 min, run time 7 min. The title compound (**25**) is the major isomer of the above reaction and is also the first peak to elute off the chiral column. 10 mg of compound **25** was isolated from the SFC. MS ESI (pos.) m/e: 360.2 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.76 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.19 (d, *J*=1.76 Hz, 1 H), 5.74 (d, *J*=2.15 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 2.91 (s, 3 H), 2.66 (d, *J*=7.24 Hz, 2 H), 1.94 - 2.12 (m, 3 H), 1.67 - 1.80 (m, 2 H), 1.39 (t, *J*=7.24 Hz, 3 H), 1.28 (s, 3 H).



26.1

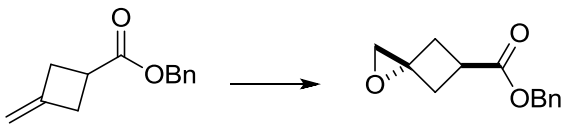
benzyl 3-oxocyclobutanecarboxylate (26.1): To a mixture of 3-oxocyclobutanecarboxylic acid (25 g, 219 mmol) and potassium carbonate (16.19 ml, 263 mmol) in anhydrous acetonitrile (400

ml, 7656 mmol) was slowly added benzyl bromide (27.8 ml, 230 mmol) under an ice/water bath. The resulting mixture was allowed to stir at ambient temperature over two and a half days. The mixture was filtered through a short column of celite and washed thoroughly with ethyl acetate. The filtrate was concentrated and the residue was divided into two portions, each portion was purified by medium pressure chromatography on a 330g silica gel column (Redi-sep) using gradient 0-80% EtOAc/hexanes as the eluent to provide 41.5 g (93% yield) of the title compound (**26.1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 - 7.42 (m, 5 H), 5.20 (s, 2 H), 3.39 - 3.50 (m, 2 H), 3.26 - 3.35 (m, 3 H).



26.1 **26.2**

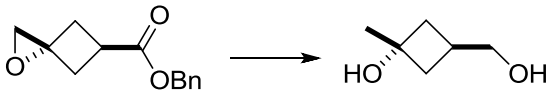
benzyl 3-methylenecyclobutanecarboxylate (26.2): To a solution of benzyl 3-oxocyclobutanecarboxylate (**26.1**) (30 g, 147 mmol) in THF (294 ml, 147 mmol) was slowly added Tebbe reagent, 0.5 M solution in toluene (308 ml, 154 mmol) under an ice bath over a period of 50 minutes. The resulting mixture was kept stirring at 0 ^{o}C for 30 minutes, and then warmed to ambient temperature for 30 minutes. 200 mL of diethyl ether was added and the mixture was again cooled down in an ice bath. Then sodium hydroxide 0.1 N (40 ml, 4.00 mmol) was added dropwise over a period of 1 hour and 10 minutes. The resulting mixture was allowed to stir at ambient temperature for 1 hour, dried with anhydrous sodium sulfate, filtered, and rinsed with diethyl ether. The filtrate was allowed to stand overnight. More solid precipitated out. The filtrate was filtered again through a pad of celite and rinsed with diethyl ether. The solution was concentrated in vacuo and the residue was purified by medium pressure chromatography on a 330g silica gel column (Redi-sep) using gradient 0-30% ethyl acetate/hexanes as the eluent to give 17.1 g (58% yield) of the title compound (**26.2**) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 - 7.41 (m, 5 H), 5.15 (s, 2 H), 4.82 (dt, *J*=4.89, 2.45 Hz, 2 H), 3.11 - 3.25 (m, 1 H), 2.99 - 3.08 (m, 2 H), 2.87 - 2.98 (m, 2 H).



26.2 **26.3**

(3r,5r)-benzyl 1-oxaspiro[2.3]hexane-5-carboxylate (26.3):

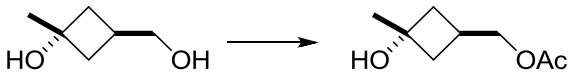
To a flask with benzyl 3-methylenecyclobutanecarboxylate (**26.2**) (14.2 g, 70.2 mmol) was added DCM (200 mL), 2,2,2-trichloroacetonitrile (14.08 mL, 140 mmol). Then in a separate vial, K_2HPO_4 (528 mg, 48 mg/mL of H_2O_2) was added into hydrogen peroxide (10.76 mL, 105 mmol) to adjust pH to 6.8. The resulting H_2O_2 solution was added to the reaction flask. The reaction was stirred at ambient temperature for 1 hour. More CCl_3CN (5.2 mL) and H_2O_2 (4 mL, with K_2HPO_4 added to adjust pH to 6.8) were added. After 2 hours, the same amount were added again. The reaction was stirred overnight. In the morning, another batch of CCl_3CN (5.2 mL) and H_2O_2 (4 mL, with K_2HPO_4 added to adjust pH to 6.8) was added and reaction was continued for another 3 hours. The reaction was diluted with 150 mL of hexanes. Some solids were generated and were filtered and rinsed with hexanes. The solids were discarded. The filtrate was concentrated to remove most of the solvents. 250 mL Et_2O was added to the concentrated filtrate and the organics was washed with water, cold 3% Na_2SO_3 (75 ml), brine and dried. Upon concentration of the organics, more solids crashed out. Filtered again and used hexanes/small amount of Et_2O to rinse. The filtrate was concentrated and purified by medium pressure chromatography on a 220g silica gel column (Redi-sep gold) using gradient 0-20% ethyl acetate/hexanes as the eluent to provide 7.34 g (48% yield) of the title compound (**26.3**) as the major isomer (less polar) in the reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 - 7.43 (m, 5 H), 5.18 (s, 2 H), 3.17 - 3.27 (m, 1 H), 2.66 - 2.79 (m, 6 H).



26.3 **26.4**

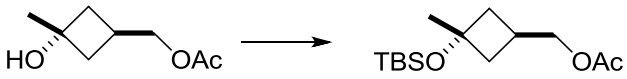
(1r,3r)-3-(hydroxymethyl)-1-methylcyclobutanol (26.4): A flask was charged with (3r,5r)-benzyl 1-oxaspiro[2.3]hexane-5-carboxylate (**26.3**) (7.34 g, 33.6 mmol) and was azeotroped with toluene. Then THF (100 ml) was added and the reaction was cooled down in an ice bath. Lithium aluminum(III) hydride (60.9 ml, 60.9 mmol) was added slowly. Reaction changed into a thick paste during the addition. The ice bath was removed and 20 mL of THF was added to make stirring easier. After stirring for 4 hours, reaction was cooled down in an ice bath again, and 2.31 mL water, 2.31 mL 15% NaOH and 6.93 mL water were added slowly and sequentially to quench the reaction. THF was added to dilute the reaction and the crude was filtered to remove

the solids. Additional THF was added to rinse the solids. The combined THF solution was concentrated and purified by medium pressure chromatography using gradient 0-70% EtOAc/Hexanes then gradient 2 to 8% MeOH/DCM as the eluent to provide 3.5 g (90% yield) of the title compound (**26.4**) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.52 (d, *J*=6.85 Hz, 2 H), 2.43 - 2.52 (m, 1 H), 2.08 - 2.15 (m, 2 H), 1.79 - 1.85 (m, 2 H), 1.28 (s, 3 H).



26.4 **26.5**

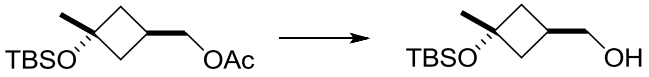
((1r,3r)-3-hydroxy-3-methylcyclobutyl)methyl acetate (26.5): A flask was charged with (1r,3r)-3-(hydroxymethyl)-1-methylcyclobutanol (**26.4**) (13.2 g, 114 mmol) and was azeotroped with toluene. DCM (400 mL) was added to the flask followed by addition of pyridine (22.98 mL, 284 mmol). Then the reaction was cooled down in an ice-bath. Acetic anhydride (12.87 mL, 136 mmol) was added. The reaction was continued stirring in ice-bath for 10 min., then raised to ambient temperature. After 4 hours, another 0.1 eq. of Ac_2O (1 mL) was added and the reaction was stirred overnight. The crude was concentrated and directly purified by medium pressure chromatography using gradient 0-50% ethyl acetate/hexanes as the eluent. The desired fractions were pooled, concentrated and azeotroped with toluene twice to get rid of the residual pyridine. 16.9 g (94% yield) of the title compound (**26.5**) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.07 (d, *J*=7.04 Hz, 2 H), 2.68 (tt, *J*=9.34, 6.90 Hz, 1 H), 2.13 - 2.28 (m, 2 H), 2.06 (s, 3 H), 1.86 - 1.94 (m, 2 H), 1.37 (s, 3 H).



26.5 **26.6**

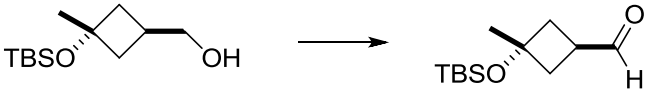
((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)methyl acetate (26.6): ((1r,3r)-3-hydroxy-3-methylcyclobutyl)methyl acetate (**26.5**) (16.9 g, 107 mmol) was azeotroped with toluene. DCM (300 mL) was added and the reaction was cooled down in an ice-bath. N-ethyl-N-isopropylpropan-2-amine (46.5 ml, 267 mmol) was added followed by tert-butyldimethylsilyl trifluoromethanesulfonate (31.9 ml, 139 mmol). The reaction was continued in the ice bath for 5min. then raised to ambient temperature and stirred overnight. Then the solvent was removed in vacuo. A mixture of DCM and hexanes were added and the crude was filtered through a plug of

celite to get rid of the salts. Then the crude was directly loaded on a 330 g silica gel column (Redi-sep gold) and purified using medium pressure chromatography with gradient 0 to 15% EtOAc/hexanes as the eluent to provide 25.2 g (87% yield) of the title compound (**26.6**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.06 (d, *J*=7.24 Hz, 2 H), 2.55 - 2.67 (m, 1 H), 2.21 - 2.30 (m, 2 H), 2.06 (s, 3 H), 1.80 - 1.89 (m, 2 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H).



26.6 **26.7**

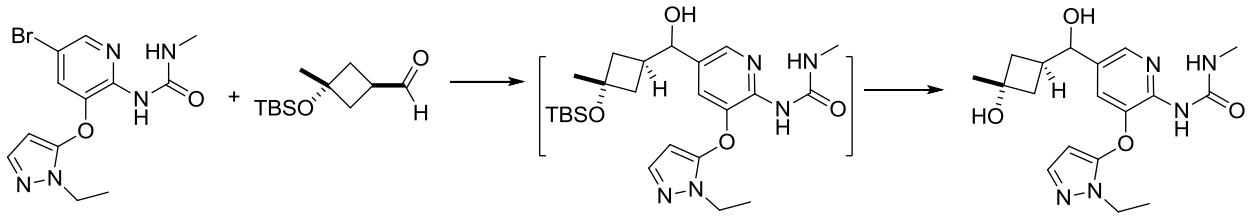
((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)methanol (26.7): A flask was charged with ((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)methyl acetate (**26.6**) (25.2 g, 92 mmol) and potassium carbonate (12.78 g, 92 mmol). MeOH (300 ml) was added. The reaction was stirred for 1 hour, filtered through a pad of celite and concentrated to remove most of the MeOH. Then the crude was redissovled in a mixture of DCM/Et_2O/EtOAc and washed with brine twice. The organics were dried, concentrated and loaded on a 220 g silica gel column (Redi-sep gold) and purified using medium pressure chromatography with gradient 0 to 30% EtOAc/hexanes as the eluent to provide 20 g (94% yield) of the title compound (**26.7**) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.63 (d, *J*=7.24 Hz, 2 H), 2.44 - 2.56 (m, 1 H), 2.24 (dd, *J*=12.62, 9.68 Hz, 2 H), 1.78 - 1.86 (m, 2 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H).



26.7 **26.8**

(1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutanecarbaldehyde (26.8): ((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)methanol (**26.7**) (10.0 g, 43.4 mmol) was azeotroped with toluene. DCM (140 mL) was added followed by iodobenzene diacetate (14.68 g, 45.6 mmol). Then TEMPO (0.339 g, 2.170 mmol) was added and the mixture was stirred for 2.5 hours at ambient temperature. TLC showed reaction not complete. More iodobenzene diacetate (3 g, 0.20 eq.) and TEMPO (68 mg. 0.2eq.) were added and the reaction was continued stirring for 2 hours. Another batch of the same scale was run using the same procedure. Then the crude of both batches were combined and concentrated to remove most of DCM, directly loaded on a 220 g silica gel column (Redi-sep gold) and purified by medium pressure chromatography with

gradient 0 to 15% EtOAc/hexanes as the eluent to provide 16.9 g (85% yield) of the title compound (**26.8**) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.80 (s, 1 H), 3.02 - 3.14 (m, 1 H), 2.29 - 2.40 (m, 4 H), 1.29 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 6 H).

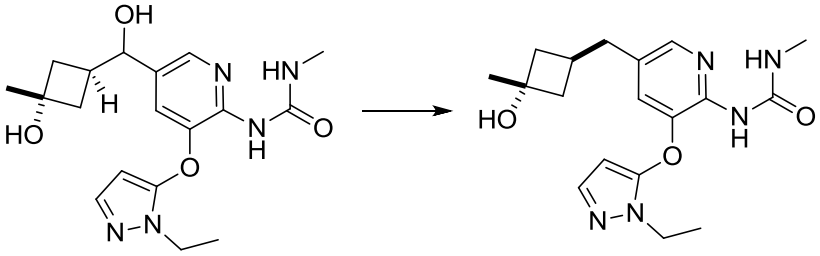


11.3 **26.8** **intermediate** **26.9**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(hydroxy((1r,3r)-3-hydroxy-3-methylcyclobutyl)methyl)pyridin-2-yl)-3-methylurea (26.9): 1st Stage: A flask with 1-(5-bromo-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea (11.2 g, 32.9 mmol) (**11.3**) was azeotroped with toluene. THF (400mL) was added and the reaction was cooled down in dry ice acetone bath. Methyllithium (41.2 mL, 65.8 mmol) was added and reaction was stirred for 8 min.. Butyllithium (15.80 mL, 39.5 mmol) was then added dropwise while with vigorous stirring. After 30 min., (1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutanecarbaldehyde (**26.8**) (8.05 g, 35.2 mmol) in 5 mL of THF was added rapidly. The reaction was continued stirring at the same bath temperature for 2 hr 40min. then the bath was removed. After 30 min., the reaction was quenched with saturated NH_4Cl and extracted with EtOAc. Another batch of the same scale was run using the same procedure. Then the crude of both batches were combined and concentrated. The combined crude material was purified using medium pressure chromatography with gradient 0 to 70% EtOAc/hexanes then gradient 2 to 8% MeOH/DCM as the eluents to provide 17.6 g of the intermediate (1-(5-(((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)(hydroxy)methyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea) mixed with some side products and was carried to next stage without further purification. MS ESI (pos.) m/e: 490.1 (M+H).

2nd Stage: A flask with the above intermediate (1-(5-(((1r,3r)-3-((tert-butyldimethylsilyl)oxy)-3-methylcyclobutyl)(hydroxy)methyl)-3-((1-ethyl-1H-pyrazol-5-yl)oxy)pyridin-2-yl)-3-methylurea) (17.6 g, 35.9 mmol) was added MeOH (260 mL), and methanesulfonic acid (13 mL, 200 mmol). The reaction was stirred overnight. Then aqueous NaOH was added to adjust the

reaction pH to about 7. The reaction was concentrated to remove MeOH and then EtOAc/water was added. The crude was extracted with EtOAc. The EtOAc layer was dried, concentrated and purified using medium pressure silica gel chromatography with gradient 0 to 70% EtOAc/Hexanes then gradient 2 to 10% MeOH/DCM as the eluent to provide 14 g (57% yield for two stages) of the title compound (**26.9**) as a white solid. MS ESI (pos.) m/e: 376.1 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.00 (d, *J*=1.56 Hz, 1 H), 7.46 (d, *J*=2.15 Hz, 1 H), 7.33 (d, *J*=1.76 Hz, 1 H), 5.78 (d, *J*=1.96 Hz, 1 H), 4.49 (d, *J*=8.22 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 2.91 - 2.94 (m, 3 H), 2.50 - 2.63 (m, 1 H), 1.98 - 2.12 (m, 2 H), 1.78 - 1.91 (m, 2 H), 1.39 (t, *J*=7.24 Hz, 3 H), 1.28 (s, 3 H).

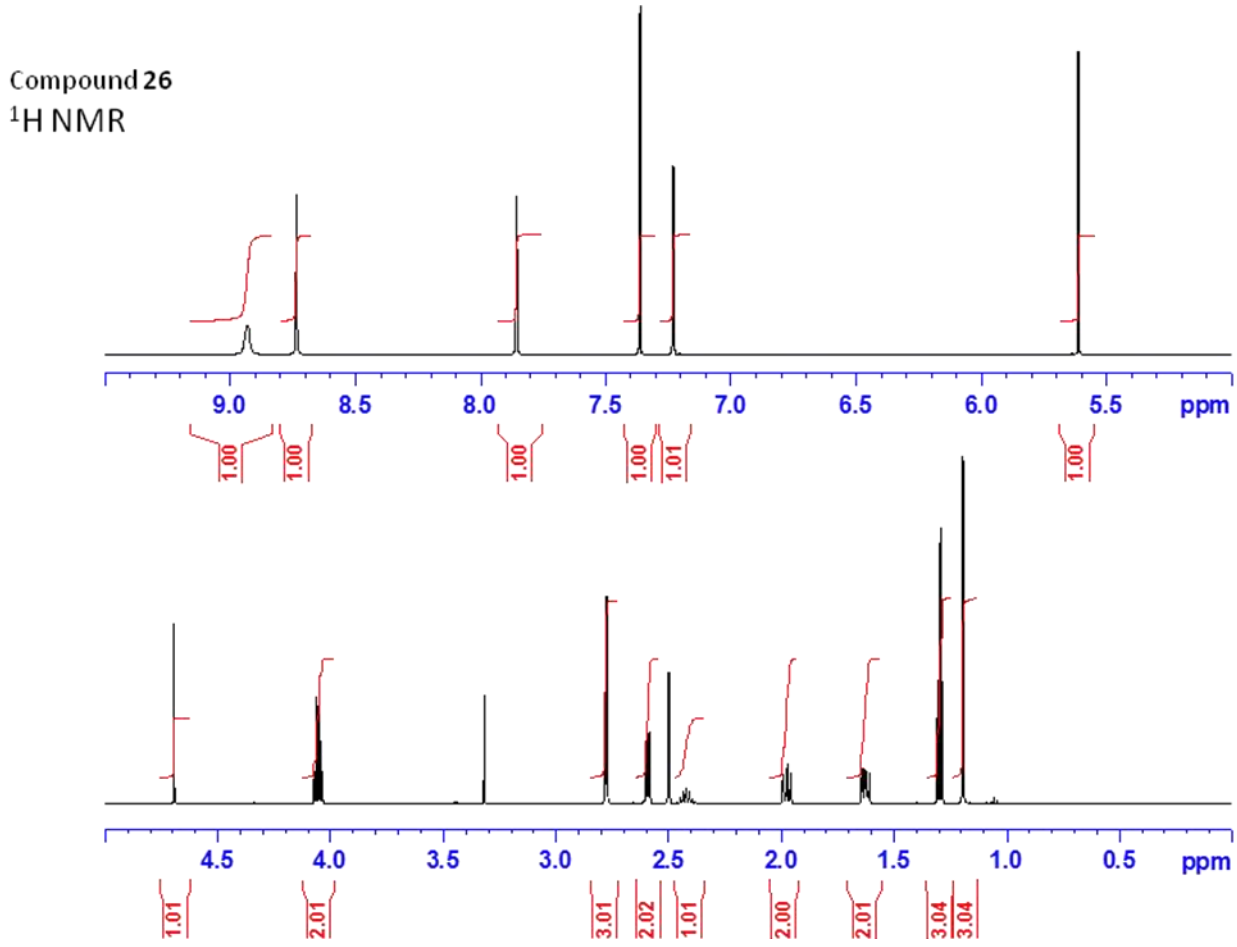


26.9 **26**

1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(((1r,3s)-3-hydroxy-3-methylcyclobutyl)methyl)pyridin-2-yl)-3-methylurea (26):

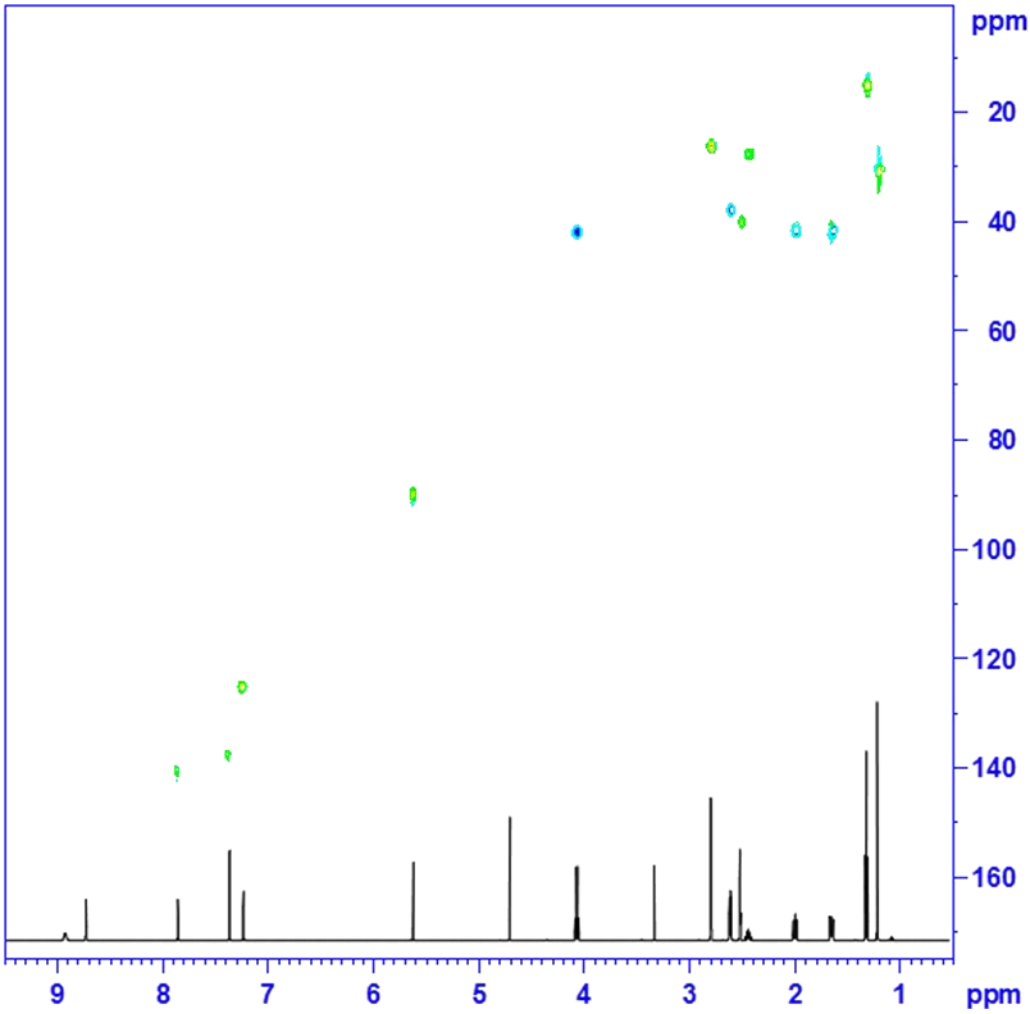
A flask with 1-(3-((1-ethyl-1H-pyrazol-5-yl)oxy)-5-(hydroxy((1r,3r)-3-hydroxy-3-methylcyclobutyl)methyl)pyridin-2-yl)-3-methylurea (**26.9**) (14 g, 37.3 mmol) was added MeOH (200 mL), and methanesulfonic acid (20 mL, 308 mmol). It was purged with nitrogen. Then 10% palladium on carbon (7.94 g, 746 mmol) was added and the reaction was purged with hydrogen and stirred under a double-layer hydrogen balloon overnight (The reaction was refreshed with fresh balloons of hydrogen once in between). LCMS showed the presence of starting material. The reaction was purged with nitrogen, 1 g of palladium on carbon was added and then reaction was purged with hydrogen and continued hydrogenation under hydrogen atomsphere. After 7 hr., the process was repeated with the addition of 0.5 g of palladium on carbon and the reaction was continued overnight. The crude was purged with nitrogen and filtered through celite. Aqueous NaOH was added to adjust the reaction pH to about 7. The reaction was concentrated to remove MeOH and then water was added. The crude was extracted with EtOAc. Some precipitates were generated that were product. Filtered. However, the precipitates had impurity and were combined

with the rest of the EtOAc layer and purified using medium pressure silica gel chromatography with gradient 0 to 70% EtOAc/Hexanes then gradient 2 to 10% MeOH/DCM as the eluent to provide 7.95 g (59% yield) of the title compound (**26**) as a white solid. HRMS ESI (pos.) m/e calcd $C_{18}H_{25}N_5O_3$ 360.2030 (M+H); found 360.2045 (Δ=4.12 ppm). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, *J*=1.96 Hz, 1 H), 7.44 (d, *J*=2.15 Hz, 1 H), 7.20 (d, *J*=1.76 Hz, 1 H), 5.73 (d, *J*=1.96 Hz, 1 H), 4.12 (q, *J*=7.24 Hz, 2 H), 2.91 (s, 3 H), 2.66 (d, *J*=8.02 Hz, 2 H), 2.47 - 2.62 (m, 1 H), 2.06 - 2.14 (m, 2 H), 1.69 - 1.81 (m, 2 H), 1.39 (t, *J*=7.24 Hz, 3 H), 1.29 (s, 3 H). ^{13}C NMR (600 MHz, DMSO): δ ppm 154.8, 148.9, 142.7, 140.6, 139.2, 137.6, 130.4, 124.9, 89.9, 69.5, 69.4, 41.8, 41.5, 37.7, 30.4, 27.4, 26.1, 14.8. The stereochemistry assignment of compound **26** was confirmed by HSQC and NOESY data (see the following pages).



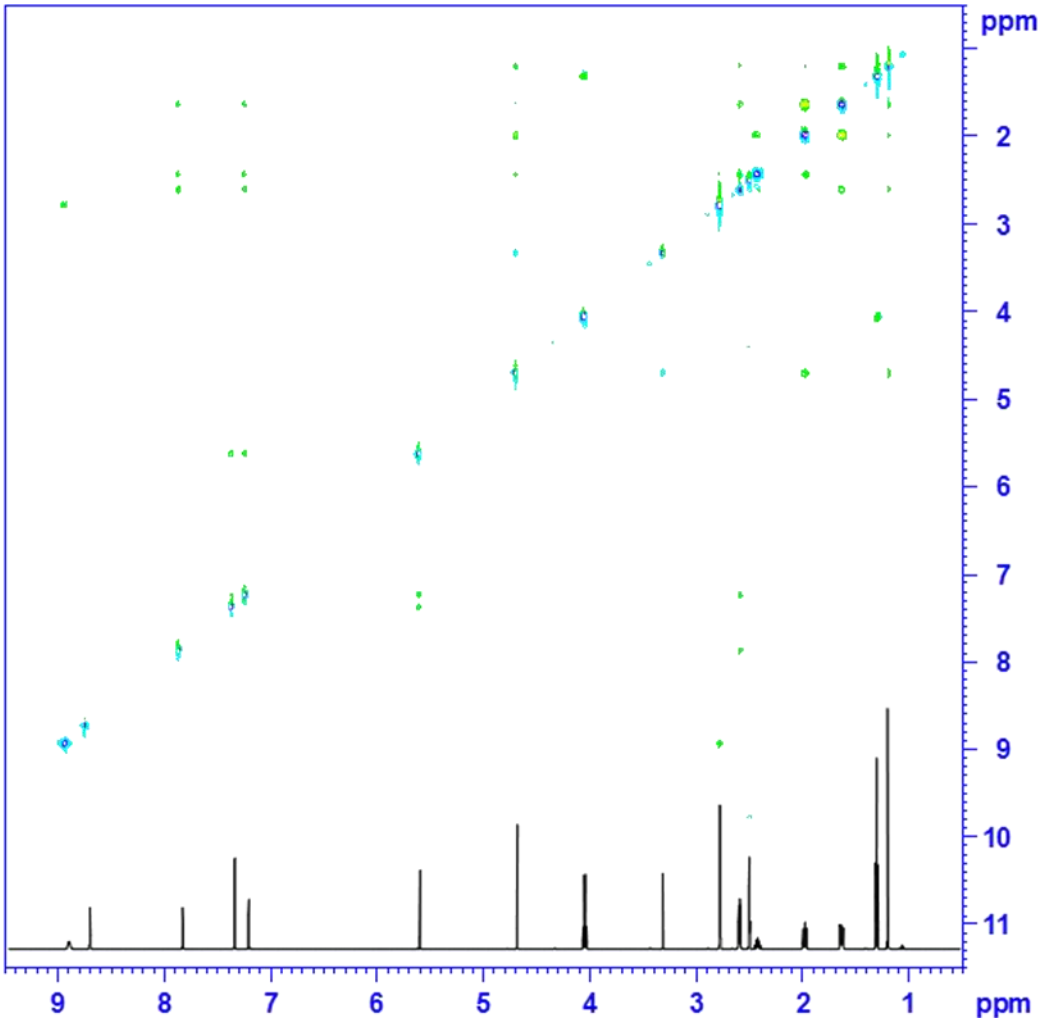
Compound **26**

HSQC



Compound **26**

NOESY



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