Supporting Information

Discovery of TDI-10229: a potent and orally bioavailable inhibitor of soluble adenylyl cyclase (sAC, ADCY10)

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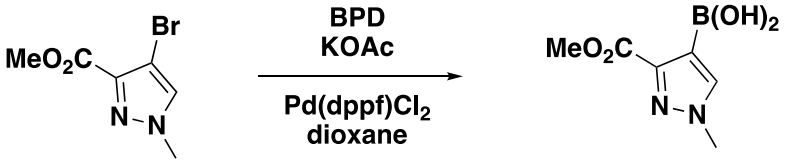
1. Synthesis and characterization for compounds 2 - 22

Preparation of **Int B**

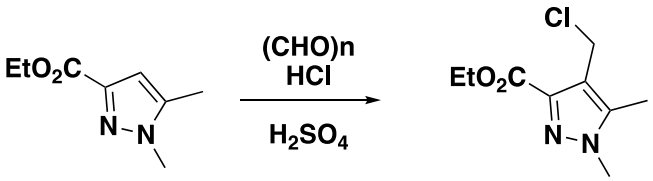


Int B

(3-methoxycarbonyl-1-methyl-pyrazol-4-yl)boronic acid (Int B)

Methyl 4-bromo-1-methyl-pyrazole-3-carboxylate (5.00 g, 22.8 mmol, 1 *eq*), BPD (6.38 g, 25.1 mmol, 1.1 *eq*), Pd(dppf)Cl_2 (835 mg, 1.14 mmol, 0.05 *eq*) and KOAc (4.48 g, 45.7 mmol, 2 *eq*) in dioxane (80 mL) was de-gassed. The mixture was heated to 100 °C for 12 h under N_2. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate gradient of 4/1 to 1/1) to furnish (3-methoxycarbonyl-1-methyl-pyrazol-4-yl)boronic acid **Int B** (4.5 g, crude) as a yellow solid.

Preparation of **Int D**

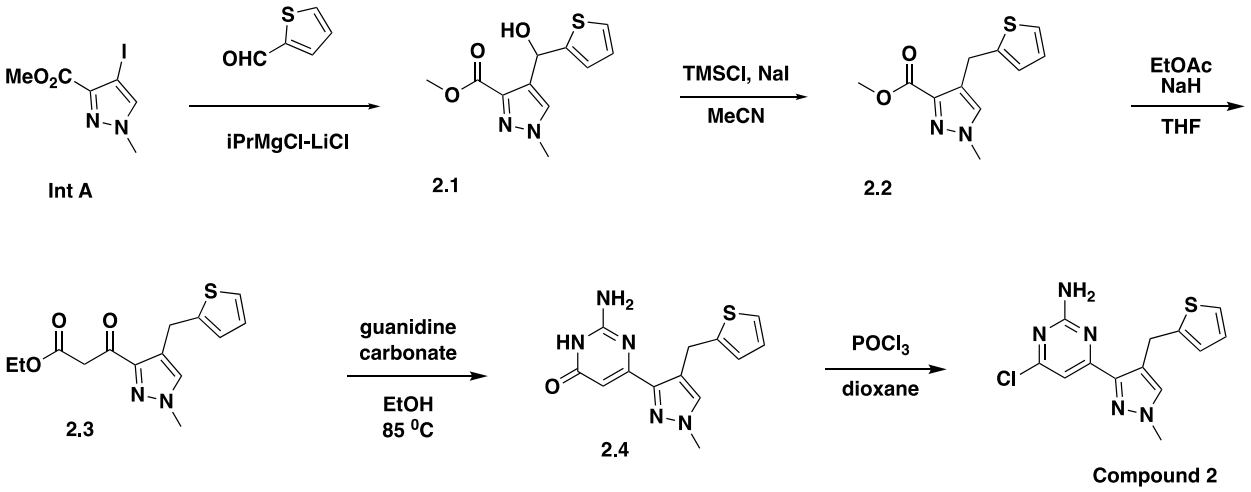


Int D

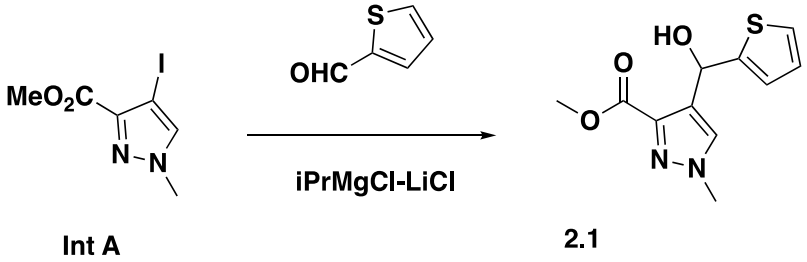
Ethyl 4-(chloromethyl)-1,5-dimethyl-pyrazole-3-carboxylate (Int D)

To a solution of ethyl 1,5-dimethylpyrazole-3-carboxylate (4.30 g, 25.6 mmol, 1 eq) and paraformaldehyde (1.54 g, 51.1 mmol, 1.41 mL, 2 eq) in dioxane (50 mL) was added HCl (12 M, 4.26 mL, 2 eq) and H_2SO_4 (256 mg, 2.56 mmol, 0.139 mL, 98% purity, 0.1 eq). The mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated under the reduced pressure to remove the solvent to furnish ethyl 4-(chloromethyl)-1,5-dimethyl-pyrazole-3-carboxylate **Int D** (6 g, crude) as a yellow solid. The material was used in the next step without further purification.

Preparation of Compound **2**



Step 1

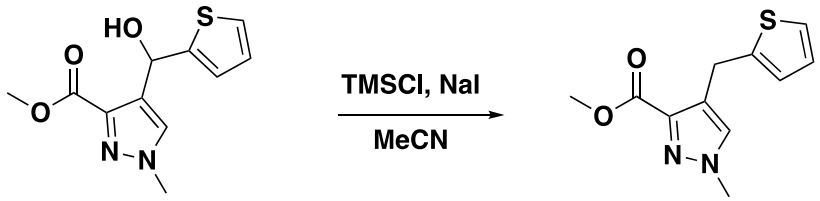


Ethyl 4-[hydroxy(2-thienyl)methyl]-1-methyl-pyrazole-3-carboxylate (2.1)

To a solution of ethyl 4-iodo-1-methyl-pyrazole-3-carboxylate **Int A** (2.20 g, 7.86 mmol, 1 *eq*) in THF (30 mL) was added isopropylmagnesium chloride-lithium chloride complex (1.3 M, 6.34 mL, 1.05 *eq*) at -15 °C under a nitrogen atmosphere. After stirring at -15 °C for 0.5 h, a solution of thiophene-2-carbaldehyde (969 mg, 8.64 mmol, 0.807 mL, 1.1 *eq*) in THF (2 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 25 °C and then stirred at that temperature for 24 h. The reaction mixture was diluted with saturated aq. NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (50 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient elution of 0 - 40% ethyl acetate/petroleum ether @ 75 mL/min) to furniish ethyl 4-[hydroxy(2-thienyl)methyl]-1-methyl-pyrazole-3-carboxylate **2.1** (1.10 g, 4.01 mmol, 51 % yield) as a light yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.20-7.16 (m, 1H), 6.92-6.84 (m, 2H), 6.17 (d, *J* = 5.7 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.39-4.33 (m, 2H), 3.86 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H)

Step 2



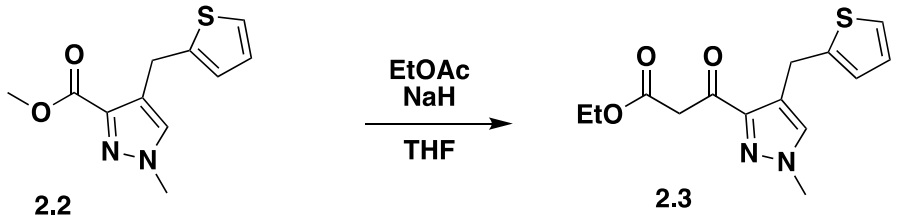
2.1 **2.2**

Ethyl 1-methyl-4-(2-thienylmethyl)pyrazole-3-carboxylate (2.2)

To a solution of NaI (3.28 g, 21.9 mmol, 6 *eq*) in MeCN (15 mL) was added TMSCl (2.37 g, 21.9 mmol, 2.77 mL, 6 *eq*) under N_2. After 1 stirring at 25 °C for 10 minutes, a solution of ethyl 4-[hydroxy(2-thienyl)methyl]-1-methyl-pyrazole-3-carboxylate **2.1** (1.00 g, 3.64 mmol, 1 *eq*) in MeCN (5 mL) was added. The mixture was stirred at 25 °C 2 h under N_2. The reaction mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with 10% aq. Na_2SO_3 solution (aq. 50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient elution of 0 - 40% ethyl acetate/petroleum ether @75 mL/min) to furnish ethyl 1-methyl-4-(2-thienylmethyl)pyrazole-3-carboxylate **2.2** (0.9 g) as light yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz)δ 7.15 (s, 1H), 7.13 (dd, *J* = 1.1, 5.0 Hz, 1H), 6.92 (dd, *J* = 3.3, 5.0 Hz, 1H), 6.86-6.83 (m, 1H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.31 (s, 2H), 3.90 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H)

Step 3



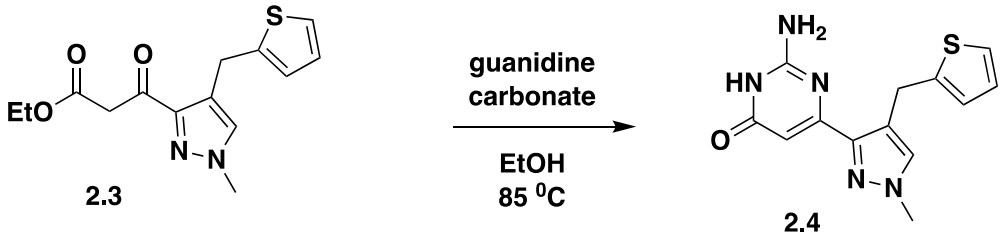
2.2 **2.3**

Ethyl 3-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate (2.3)

A mixture of ethyl 1-methyl-4-(2-thienylmethyl)pyrazole-3-carboxylate **2.2** (700 mg, 2.80 mmol, 1 *eq*) in THF (10 mL) was cooled to 0 °C. Sodium hydride (336 mg, 8.39 mmol, 60% oil dispersion, 3 *eq*) was added. After stirring for 20 min, EtOAc (1.72 g, 19.58 mmol, 1.92 mL, 7 *eq*) was added dropwise at 0 °C. The mixture was stirred at 70 °C for 2 h under N_2. The reaction mixture was poured into aq. saturated NH_4Cl (150 mL) and extracted with EtOAc (40 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient elution of 0 - 20% ethyl acetate/petroleum ether @ 75 mL/min) to furnsih ethyl 3-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate **2.3** (500 mg) as a light yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.16-7.11 (m, 2H), 6.93 (dd, *J* = 3.4, 5.1 Hz, 1H), 6.89-6.86 (m, 1H), 4.34 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 3.88 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H)

Step 4

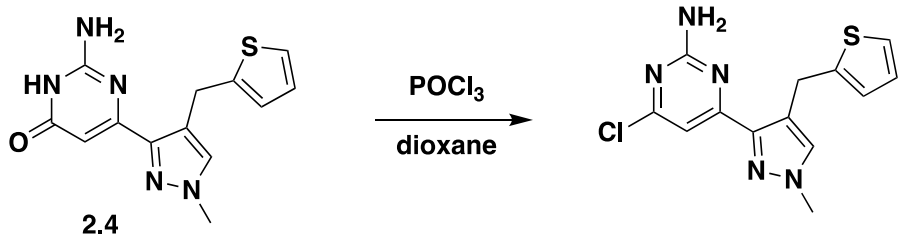


2-amino-4-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (2.4)

Ethyl 3-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate **2.3** (450 mg, 1.54 mmol, 1 *eq*) and guanidine carbonate (832 mg, 4.62 mmol, 3 *eq*) were taken up in anhydrous EtOH (10 mL). The mixture was stirred for 12 h at 85 °C under N_2. A white precipitate formed. The reaction mixture was filtered, and the filter cake was washed with EtOH (5 mL *2). The filtrate was concentrated under reduced pressure to afford 2-amino-4-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H- pyrimidin-6-one **2.4** (530 mg, crude) as light yellow solid.

LCMS: ($M+H^+$): 287.9 @ 0.337 min (30-90% ACN in H_2O, 2 min)

Step 5



4-chloro-6-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 2)

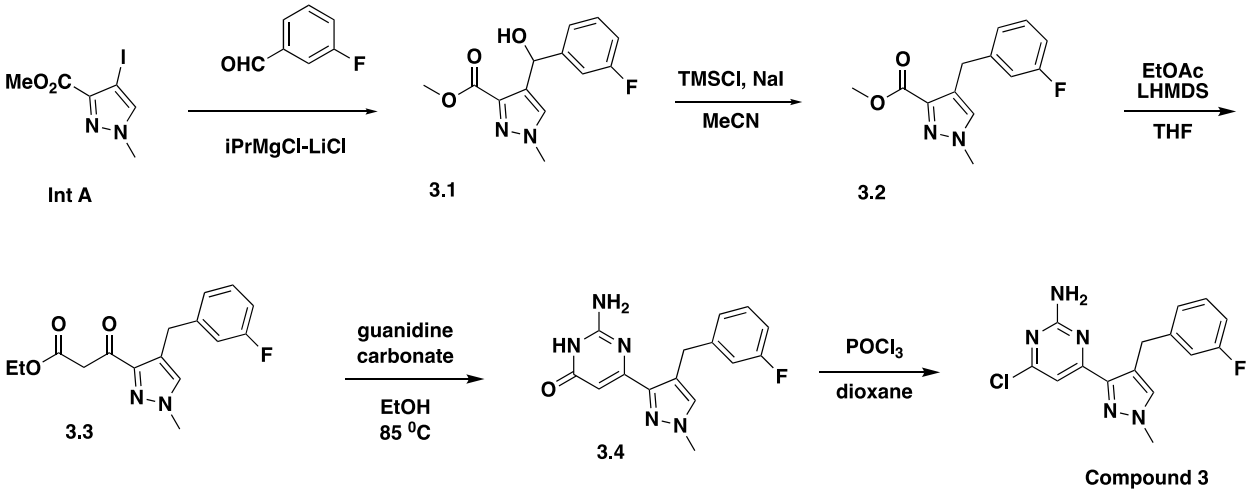
$POCl_3$ (2.74 g, 17.9 mmol, 1.66 mL, 15 eq) was added to a solution of 2-amino-4-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one **2.4** (530 mg, 1.19 mmol, 1 eq) in dioxane (10 mL) at 25 °C. The mixture was heated for 12 h at 75 °C. The reaction mixture was added slowly to aq. $NaHCO_3$ (saturated, 200 mL) to quench the excess $POCl_3$. The solution was extracted with EtOAc (70 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by neutral preparative-HPLC (column: HUAPU C8 Extreme BDS 150 * 30 5 μm; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 40%-60%,10 min) to furnish 4-chloro-6-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 2** (62 mg) as a gray solid.

LCMS: ($M+H^+$): 306.0 @ 1.831 min (5-95% ACN in H_2O, 3.0 min)

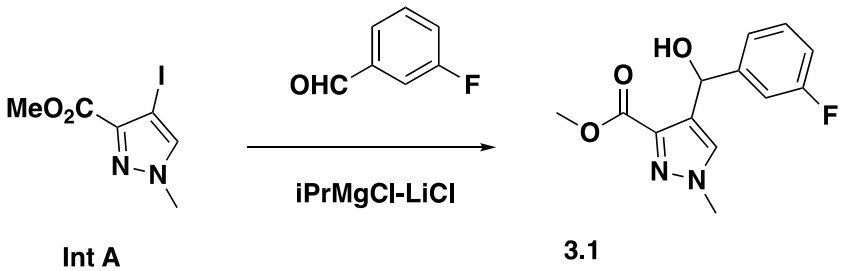
^{1}H NMR: (METHANOL-d4, 400 MHz) δ 7.42 (s, 1H), 7.18-7.10 (m, 2H), 6.91-6.83 (m, 2H), 4.49 (s, 2H), 3.89 (s, 3H)

HRMS calc'd for $C_{13}H_{12}N_5ClS$: $(M+H)^+$ 306.0575; Found: 306.0575.

Preparation of Compound **3**



Step 1

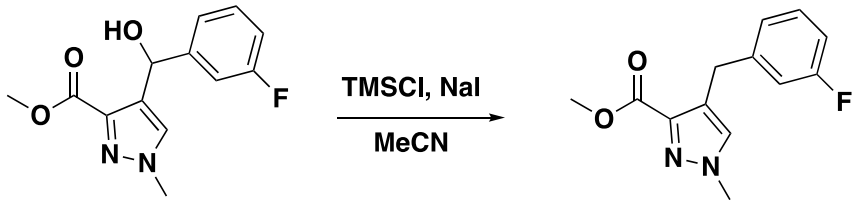


Methyl 4-[(3-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate (3.1)

To a solution of methyl 4-iodo-1-methyl-pyrazole-3-carboxylate (1.00 g, 3.76 mmol, 1 *eq*) in THF (10 mL) was added *i*-PrMgCl-LiCl (1.30 M, 2.89 mL, 1 *eq*) at -15 °C under a N_2 atmosphere. After stirring at -15 °C for 0.5 h, a solution of 3-fluorobenzaldehyde (513 mg, 4.13 mmol, 0.435 mL, 1.1 *eq*) in THF (10 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 15 °C. The reaction was stirred at room temperature for 12 h. The reaction was diluted with saturated aq. NH_4Cl solution (700 mL), and the resulting mixture was extracted with EtOAc (40 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®;12 g SepaFlash® Silica Flash Column, gradient eluent of 0 to 60% ethyl acetate/petroleum ether @ 75 mL/min) to furnish methyl 4-[(3-fluorophenyl)-hydroxy- methyl]-1-methyl-pyrazole-3-carboxylate **3.1** (800 mg, 3.03 mmol, 81 % yield) as colorless oil.

^{1}H NMR: 400MHz, CHLOROFORM-d) δ 7.37-7.30 (m, 1H), 7.22-7.15 (m, 2H), 7.00 (dt, J=2.0, 8.4 Hz, 1H), 6.93 (s, 1H), 6.02 (d, J=4.9 Hz, 1H), 4.71 (d, J=4.9 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H)

Step 2



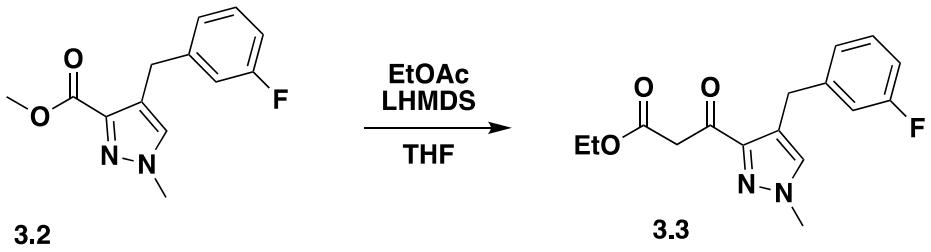
3.1 **3.2**

Methyl 4-[(3-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate (3.2)

To a solution of NaI (2.72 g, 18.2 mmol, 6 *eq*) in MeCN (12 mL) was added TMSCl (1.97 g, 18.2 mmol, 2.31 mL, 6 *eq*) under N_2. After stirring 10 minutes at 15 °C, a solution of methyl 4-[(3-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3- carboxylate **3.1** (800 mg, 3.03 mmol, 1 *eq*) in MeCN (4 mL) was added. The mixture was stirred at 15 °C under N_2 for 2 h. The reaction mixture was quenched with saturated aq. Na_2SO_3 solution (80 mL). The mixture was diluted with EtOAc (45 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (80 mL*3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®;12 g SepaFlash® silica flash column, gradient elution of 0 - 30% ethyl acetate/petroleum ether @ 45 mL/min) to furnish methyl 4-[(3-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate **3.2** (540 mg, 2.18 mmol, 72 % yield) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.17-7.08 (m, 1H), 6.93 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.82-6.74 (m, 2H), 3.99 (s, 2H), 3.78 (d, *J* = 2.4 Hz, 6H)

Step 3



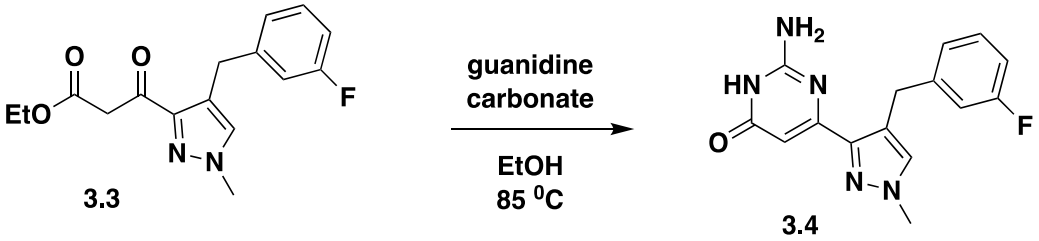
3.2 3.3

Ethyl 3-[4-[(3-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate (3.3)

To a solution of methyl 4-[(3-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate **3.2** (540 mg, 2.18 mmol, 1 *eq*) and EtOAc (1.34 g, 15.2 mmol, 1.49 mL, 7 *eq*) in THF (5 mL) was added LiHMDS (1 M, 6.53 mL, 3 *eq*) at -40 °C. The mixture was stirred at -40 °C for 1 hr under N_2. The reaction mixture was quenched with saturated NH_4Cl solution (80 mL). The mixture was extracted with EtOAc (80 mL*3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 - 20% ethyl acetate/petroleum ether @ 45 mL/min) to furnish ethyl 3-[4-[(3-fluorophenyl) methyl]-1-methyl- pyrazol-3-yl]-3-oxo-propanoate 3.3 (600 mg, 1.97 mmol, 91 % yield) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.10-7.00 (m, 1H), 6.85-6.79 (m, 2H), 6.76-6.66 (m, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 3.84 (s, 2H), 3.68 (s, 3H), 1.10-1.04 (m, 3H)

Step 4



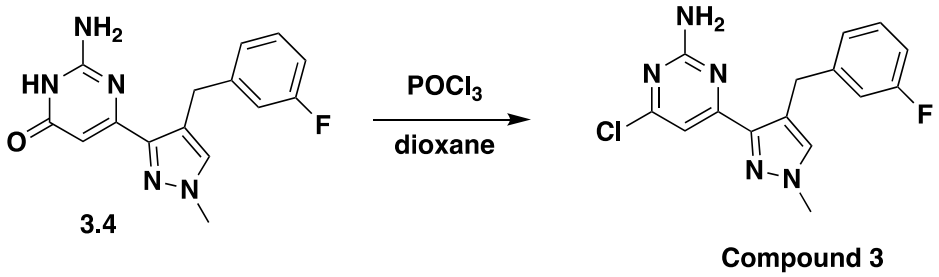
3.3 3.4

2-amino-4-[4-[(3-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one (3.4)

To a solution of ethyl 3-[4-[(3-fluorophenyl) methyl]-1-methyl-pyrazol-3-yl] -3-oxo- propanoate **3.3** (600 mg, 1.97 mmol, 1 *eq*) in EtOH (10 mL) was added guanidine carbonate (533 mg, 2.96

mmol, 1.5 *eq*). The resulting mixture was stirred for 24 h at 85 °C under N_2. The reaction mixture was diluted with water (30 mL). The mixture was concentrated under reduced pressure to remove EtOH. The pH of the solution was adjusted to 5 by addition of aq. HCl (2N). The mixture was filtered, and the filtrate was dried under reduced pressure to give 2-amino-4-[4-[(3-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **3.4** (330 mg, crude) as a white solid.

Step 5



4-chloro-6-[4-[(3-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 3)

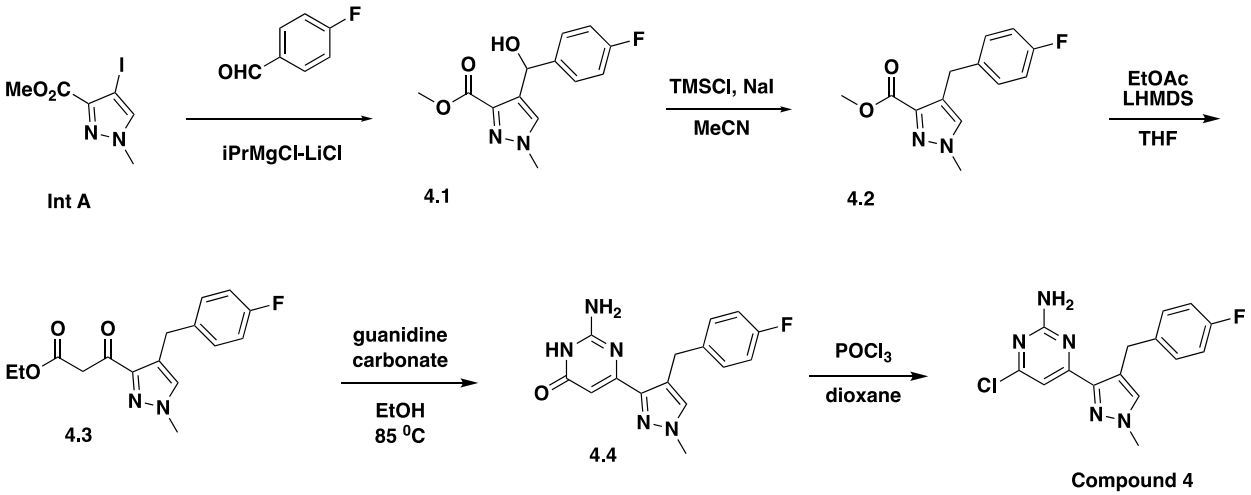
To a solution of 2-amino-4-[4-[(3-fluorophenyl) methyl]-1-methyl -pyrazol-3-yl]-1H-pyrimidin-6-one **3.4** (330 mg, 1.10 mmol, 1 *eq*) in dioxane (5 mL) was added $POCl_3$ (2.54 g, 16.5 mmol, 1.54 mL, 15 *eq*) dropwise. The reaction mixture was stirred at 75 °C for 12 hr under N_2. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (80 mL). The mixture was extracted with EtOAc (50 mL*3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative-HPLC (column: Waters Xbridge 150*25 5 mm; mobile phase: [water(10mM NH_4HCO_3)-ACN]; B%: 30%-60%,10min) to furnish 4-chloro-6-[4-[(3-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 3** (50 mg, 0.15 mmol, 14 % yield) as a white solid.

LCMS: Calc'd for $C_{15}H_{14}N_5ClF$ $(M+H^+)$ 318.1; Found: 318.2

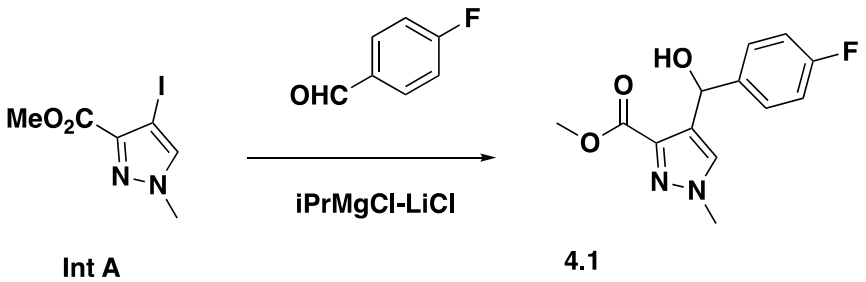
^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.32-7.23 (m, 1H), 7.10 (br s, 4H), 7.01-6.91 (m, 2H), 4.28 (s, 2H), 3.85 (s, 3H)

HRMS calc'd for $C_{15}H_{13}N_5ClF$: $(M+H)^+$ 318.0917; Found: 318.0913.

Preparation of Compound **4**



Step 1

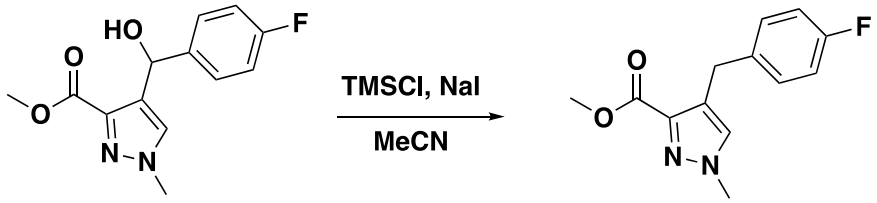


Methyl 4-[(4-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate (4.1)

A solution of methyl 4-iodo-1-methyl-pyrazole-3-carboxylate **Int A** (1.00 g, 3.76 mmol, 1 eq) in THF (10 mL) was added isopropylmagnesium chloride-lithium chloride complex (1.30 M, 3.04 mL, 1.05 eq) at -15 °C under a nitrogen atmosphere. After stirring at -15 °C for 0.5 h, a solution of 4-fluorobenzaldehyde (513 mg, 4.13 mmol, 0.435 mL, 1.1 eq) in THF (1 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 15 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with sat. NH_4Cl solution (150 mL) and extracted with EtOAc (60 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1) to furnish methyl 4-[(4-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate **4.1** (800 mg, 3.03 mmol, 81 % yield) as a colorless oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz)δ 7.33 (dd, *J* = 5.6, 8.5 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.82 (s, 1H), 5.93 (d, *J* = 4.5 Hz, 1H), 4.60 (d, *J* = 4.6 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H)

Step 2



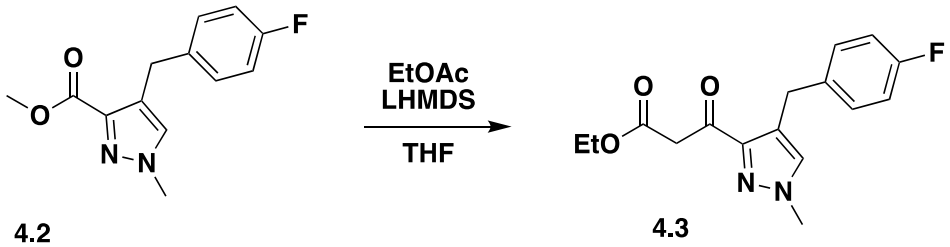
4.1 **4.2**

Methyl 4-[(4-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate (4.2)

To a solution of NaI (2.72 g, 18.2 mmol, 6 eq) in ACN (12 mL) was added TMSCl (1.97 g, 18.2 mmol, 2.31 mL, 6 eq) under N_2. After 10 min of stirring at 15 °C, a solution of methyl 4-[(4-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate **4.1** (800 mg, 3.03 mmol, 1 eq) in ACN (4mL) was added. The mixture was stirred at 15 °C under N_2 for 2 h. The reaction mixture was diluted with sat. aq Na_2SO_3 (150 mL). The solution was extracted with EtOAc (100 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/2) to furnish methyl 4-[(4-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate **4.2** (540 mg, 2.18 mmol, 72 % yield) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.21-7.15 (m, 2H), 7.02-6.93 (m, 3H), 4.08 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H)

Step 3



4.2 **4.3**

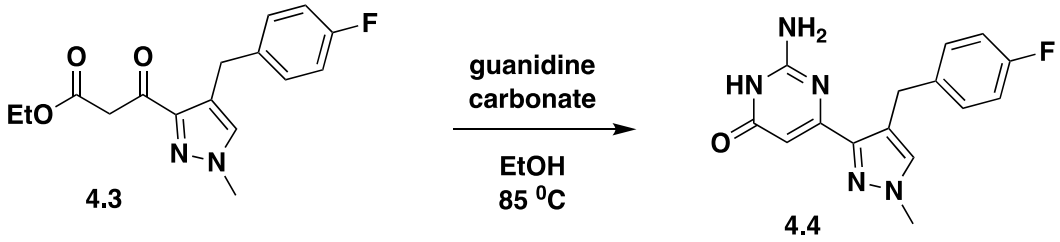
Ethyl 3-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate (4.3)

To a solution of methyl 4-[(4-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate 4.2 (540 mg, 2.18 mmol, 1 eq) and EtOAc (1.34 g, 15.2 mmol, 1.49 mL, 7 eq) in THF (10 mL) was added LiHMDS

(1 M, 6.53 mL, 3 eq) at -40 °C in one portion. The mixture was stirred at -40 °C for 1 h under N_2. The reaction mixture was diluted with sat. NH_4Cl solution (150 mL) and extracted with EtOAc (70 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 4/1) to furnsih ethyl 3-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **4.3** (580 mg, 1.91 mmol, 88 % yield) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.20-7.14 (m, 2H), 6.98-6.91 (m, 3H), 4.19 (q, *J* = 7.3 Hz, 2H), 4.06 (s, 2H), 4.01 (s, 2H), 3.84 (s, 3H), 1.28-1.23 (m, 3H)

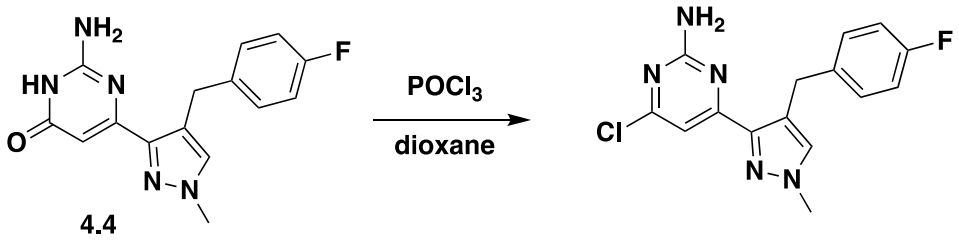
Step 4



2-amino-4-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one (4.4)

Ethyl 3-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **4.3** (580 mg, 1.91 mmol, 1 eq) and guanidine carbonate (1.03 g, 5.72 mmol, 3 eq) were taken up in anhydrous EtOH (10 mL). The mixture was stirred for 12 h at 85 °C under N_2. A white precipitate formed. The reaction mixture was diluted with water (20 mL) and concentrated under the reduced pressure to remove EtOH. The pH of the solution was adjusted to 5 by addition of aq. HCl (4N). The mixture was filtered, and the filtrate was dried under the reduced pressure to furnish 2-amino-4-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **4.4** (500 mg, 1.67 mmol, 88 % yield) as a white solid. The product was used directly in next step without further purification.

Step 5



Compound 4

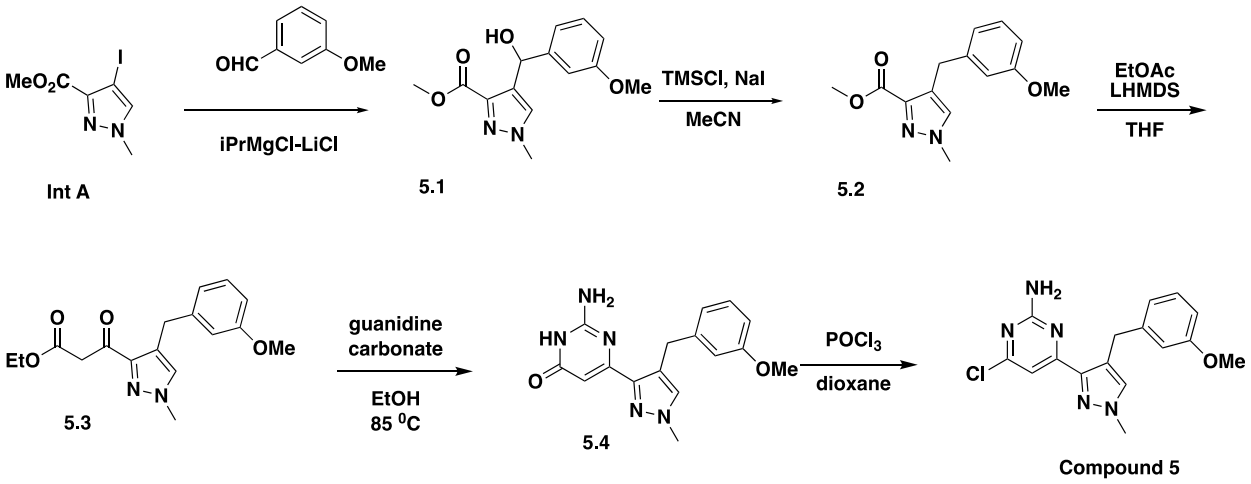
4-chloro-6-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 4)

To a solution of 2-amino-4-[4-[(4-fluorophenyl) methyl] -1-methyl -pyrazol-3-yl]-1H -pyrimidin-6-one **4.4** (330 mg, 1.10 mmol, 1 *eq*) in dioxane (5 mL) was added $POCl_3$ (2.54 g, 16.5 mmol, 1.54 mL, 15 *eq*) dropwise. The reaction mixture was stirred at 75 °C for 12 hr under N_2. The reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (80 mL). The mixture was extracted with EtOAc (50 mL*3). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative-HPLC (column: Waters Xbridge 150 * 25 5 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30% - 60%,10min) to furnish 4-chloro-6-[4-[(4-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 4** (49.9 mg, 0.155 mmol, 14 % yield) as a white solid.

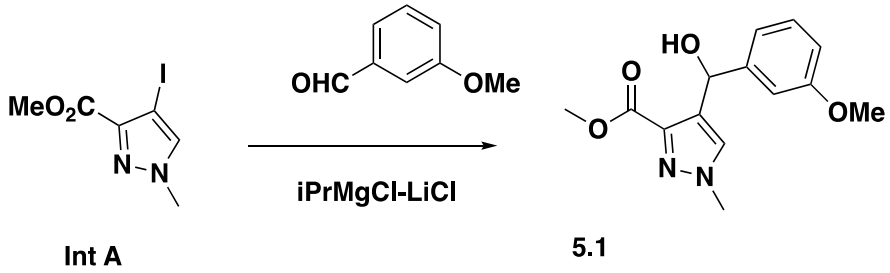
LCMS: Calc'd for $C_{15}H_{14}N_5ClF$ ($M+H^+$) 318.1; Found: 318.2

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.32-7.23 (m, 1H), 7.10 (br s, 4H), 7.01-6.91 (m, 2H), 4.28 (s, 2H), 3.85 (s, 3H)

Preparation of Compound **5**



Step 1



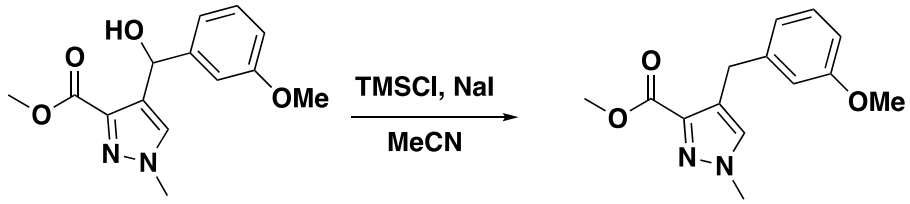
Methyl 4-[hydroxy-(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate (5.1)

To a solution of methyl 4-iodo-1-methyl-pyrazole-3-carboxylate **Int A** (1.00 g, 3.76 mmol, 1 eq) in THF (10 mL) was added isopropylmagnesium chloride-lithium chloride complex (1.3 M, 3.04 mL, 1.05 eq) at -10 °C under a N_2 atmosphere. After stirring at -10 °C for 0.5 h, a solution of 3-methoxybenzaldehyde (563 mg, 4.14 mmol, 0.502 mL, 1.1 eq) in THF (3 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 15 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with sat. aqueous NH_4Cl solution (150 mL). The resulting mixture was extracted with EtOAc (70 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2,

petroleum ether: ethyl acetate = 1:1) to furnish methyl 4-[hydroxy-(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate **5.1** (600 mg, 2.17 mmol, 58 % yield) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz)δ 7.22-7.18 (m, 1H), 6.97-6.90 (m, 2H), 6.83 (s, 1H), 6.78 (dd, *J* = 2.3, 8.1 Hz, 1H), 5.93 (s, 1H), 4.63 (br s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H)

Step 2



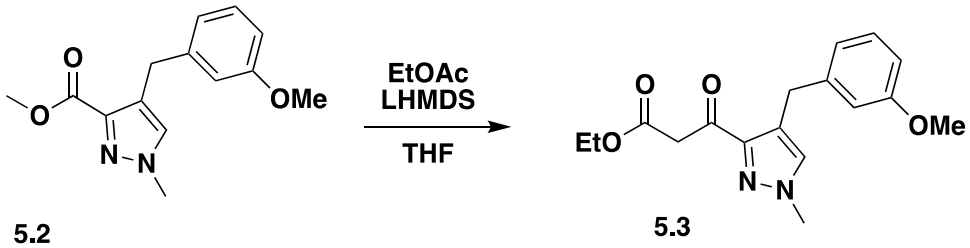
5.1 **5.2**

Methyl 4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate (5.2)

To a solution of TMSCl (1.42 g, 13.0 mmol, 1.65 mL, 6 eq) in ACN (7 mL) was added NaI (1.95 g, 13.0 mmol, 6 eq) under N_2. After 10 min of stirring at 15 °C, a solution of methyl 4-[hydroxy-(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate **5.1** (600 mg, 2.17 mmol, 1 eq) in ACN (5 mL) was added. The mixture was stirred at 15 °C under N_2 for 2 h. The reaction mixture was diluted with sat. aq Na_2SO_3 (100 mL). The solution was extracted with EtOAc (60 mL*3). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 9/1) to furnish methyl 4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate 5.2 (440 mg, 1.62 mmol, 75 % yield) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.14 (t, *J* = 7.8 Hz, 1H), 6.93 (s, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.72-6.65 (m, 2H), 4.01 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H)

Step 3



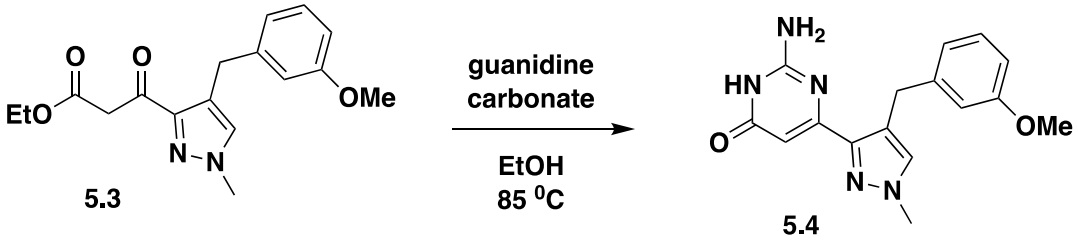
5.2 **5.3**

Ethyl 3-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate (5.3)

To a solution of methyl 4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazole-3-carboxylate **5.2** (440 mg, 1.69 mmol, 1 eq) and EtOAc (1.04 g, 11.8 mmol, 1.16 mL, 7 eq) in THF (7 mL) was added LiHMDS (1 M, 5.07 mL, 3 eq) at -40 °C in one portion. The mixture was stirred at -40 °C for 1.5 h under N_2. The reaction mixture was diluted with sat. aq NH_4Cl solution (80 mL) and extracted with EtOAc (50 mL*3). The organic layer was washed with brine (90 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 7/3) to furnish ethyl 3-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **5.3** (420 mg, 1.33 mmol, 79 % yield) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 6.75 (br d, *J* = 7.6 Hz, 1H), 6.72-6.66 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 2H), 3.96 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H)

Step 4



5.3 5.4

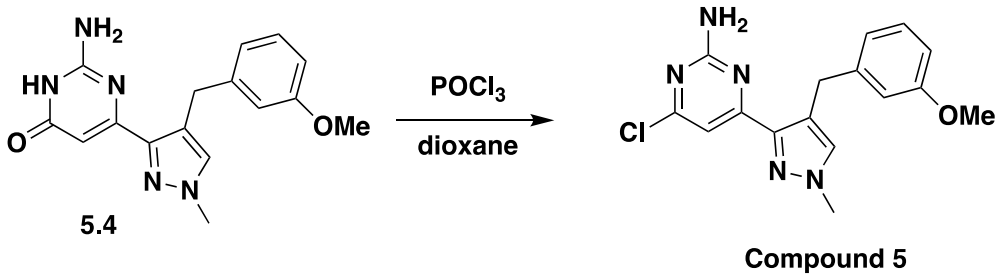
2-amino-4-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one (5.4)

Ethyl 3-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate 5.3 (420 mg, 1.33 mmol, 1 eq) and guanidine carbonate (718 mg, 3.98 mmol, 3 eq) were taken up in anhydrous EtOH (5 mL). The mixture was stirred for 12 h at 85 °C under N_2. A white precipitate formed. Additional guanidine carbonate was added (500 mg, 2.78 mmol, 2.09 eq), and the mixture was stirred and additional 12 h at 85 °C. The reaction mixture was diluted with water (10 mL) and concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 5 by addition of aqueous HCl (4N). The mixture was filtered. The residue was

concentrated under the reduced pressure to furnish 2-amino-4-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **5.4** (400 mg, crude) was obtained as a yellow solid.

^{1}H NMR: (DMSO-d6, 400 MHz)δ 7.38 (s, 1H), 7.21-6.93 (m, 2H), 6.82 (s, 1H), 6.79-6.53 (m, 4H), 5.89 (s, 1H), 4.16 (s, 2H), 3.77 (s, 3H), 3.67 (s, 3H)

Step 5



4-chloro-6-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 5)

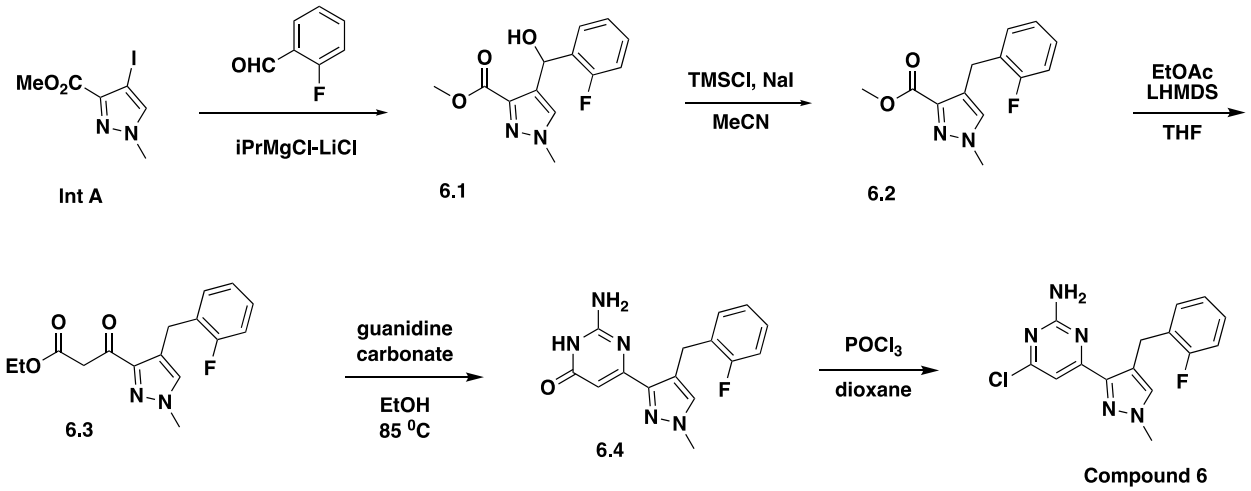
$POCl_3$ (2.66 g, 17.3 mmol, 1.61 mL, 15 eq) was added into a solution of 2-amino-4-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **5.4** (360 mg, 1.16 mmol, 1 eq) in dioxane (7 mL) at 15 °C. The mixture was heated to 75 °C and stirred at that temperature for 7 h. The reaction mixture was added slowly to aq. $NaHCO_3$ (saturated, 250 mL) to quench the excess $POCl_3$. The solution was extracted with EtOAc (70 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1). The residue was further purified by neutral preparative-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5 mm;mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 35%-

70%,8 min) to afford 4-chloro-6-[4-[(3-methoxyphenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 5** (10.4 mg) as a white solid.

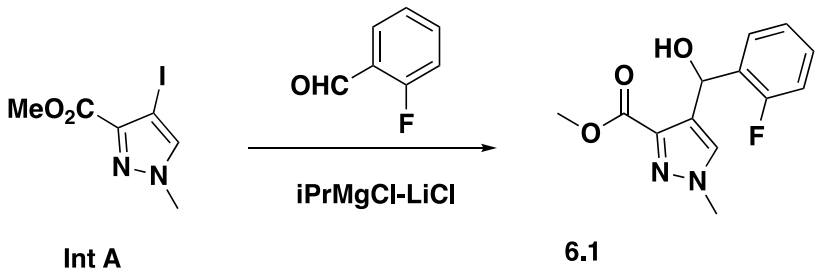
LCMS: Calc'd for $C_{16}H_{17}N_5ClO$ ($M+H^+$) 330.1; Found: 330.1

^{1}H NMR: (METHANOL-d4, 400 MHz) δ 7.30 (s, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 6.85-6.76 (m, 2H), 6.74-6.67 (m, 1H), 4.25 (s, 2H), 3.88 (s, 3H), 3.73 (s, 3H)

Preparation of Compound **6**



Step 1



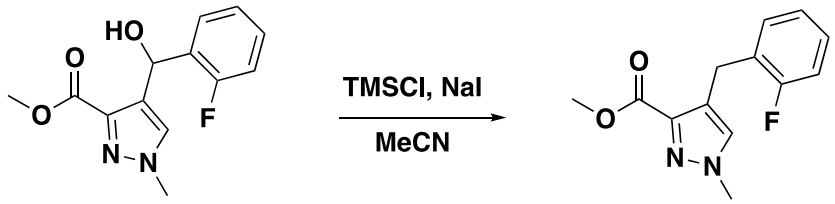
Methyl 4-[(2-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate (6.1)

To a mixture of methyl 4-iodo-1-methyl-pyrazole-3-carboxylate (**Int A**) (1.00 g, 3.76 mmol, 1 *eq*) in THF (10 mL) was added *i*-PrMgCl-LiCl (1.3 M, 3.04 mL, 1.05 *eq*) dropwise at -15 °C under a N_2 atmosphere. After the mixture was stirred for 0.5 hr at -15 °C, 2-fluorobenzaldehyde (513 mg, 4.13 mmol, 0.43 mL, 1.1 *eq*) was added to the mixture. The reaction was then allowed to warm to 20 °C and was stirred at that temperature for 12 h. The reaction mixture was diluted with sat. aq NH_4Cl solution (50 mL). The solution was extracted with EtOAc (30 mL*3). The organic layers were washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient column chromatography (SiO_2,

petroleum ether: ethyl acetate = 2:1 to 1:1) to furnish methyl 4-[(2-fluorophenyl)-hydroxy-methyl]-1-methyl-pyrazole-3-carboxylate **6.1** (600 mg, 1.93 mmol, 51.34% yield) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.64 (dt, *J* = 1.4, 7.5 Hz, 1H), 7.34-7.27 (m, 1H), 7.23-7.17 (m, 1H), 7.08-7.00 (m, 1H), 6.93 (s, 1H), 6.30 (d, *J* = 4.5 Hz, 1H), 4.97 (d, *J* = 4.9 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H)

Step 2



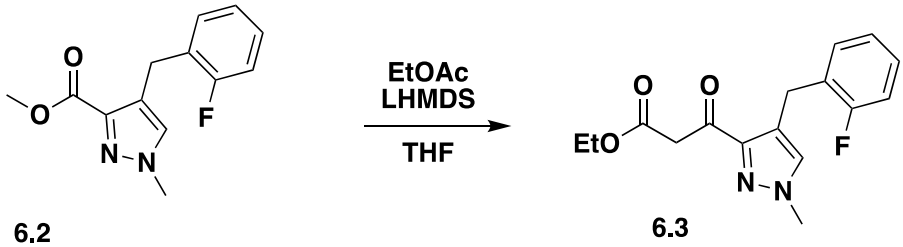
6.1 **6.2**

Methyl 4-[(2-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate (6.2)

To a mixture of NaI (2.04 g, 13.6 mmol, 6 *eq*) in MeCN (6 mL) was added TMSCl (1.48 g, 13.6 mmol, 1.73 mL, 6 *eq*) at 20 °C under a N_2 atmosphere. After stirring at 20 °C for 10 min, methyl 4-[(2-fluorophenyl)-hydroxy-methyl]-1-methylpyrazole-3-carboxylate **6.1** (600 mg, 2.27 mmol, 1 *eq*) in MeCN (4 mL) was added to the mixture. The resulting mixture was stirred at 20 °C for 2 h under N_2. The reaction mixture was diluted with sat. aq. Na_2SO_3 solution (50 mL). The solution was extracted with EtOAc (30 mL*3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient column chromatography (SiO_2, petroleum ether: ethyl acetate = 4:1 to 2:1) to furnish methyl 4-[(2-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate **6.2** (400 mg, 1.45 mmol, 64 % yield) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.31-7.18 (m, 2H), 7.12-7.01 (m, 3H), 4.16 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H)

Step 3

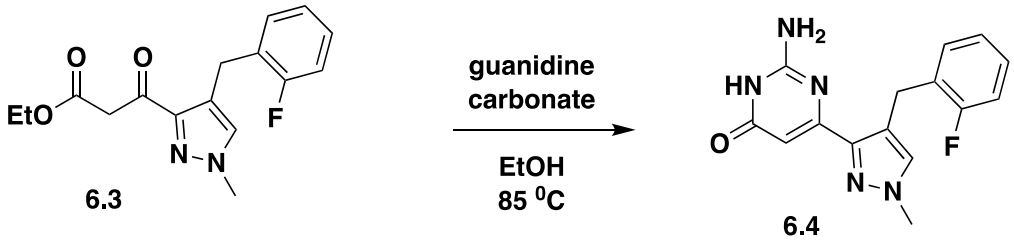


6.2 **6.3**

Ethyl 3-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate (6.3)

To a mixture of methyl 4-[(2-fluorophenyl)methyl]-1-methyl-pyrazole-3-carboxylate **6.2** (400 mg, 1.61 mmol, 1 *eq*) and EtOAc (994 mg, 11.3 mmol, 1.10 mL, 7 *eq*) in THF (4 mL) was added LiHMDS (1 M, 4.83 mL, 3 *eq*) quickly at -40 °C under N_2. The mixture was stirred at -40 °C for 1 h under N_2. The reaction mixture was diluted with sat. aq. NH_4Cl solution (50 mL). The solution was extracted with EtOAc (30 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 9:1 to 4:1) to furnish ethyl 3-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **6.3** (400 mg, 1.05 mmol, 65 % yield) as a yellow oil.

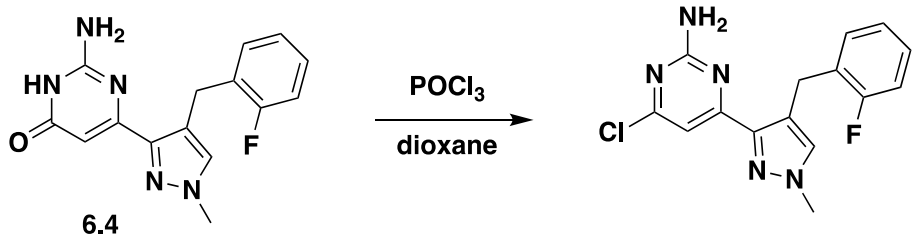
Step 4



2-amino-4-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one (6.4)

To a mixture of ethyl 3-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **6.3** (400 mg, 1.31 mmol, 1 *eq*) in EtOH (4 mL) was added guanidine carbonate (710 mg, 3.94 mmol, 3 *eq*). The mixture was stirred at 85 °C for 24 h under N_2. The reaction mixture was diluted with water (10 mL). The mixture was concentrated under reduced pressure. The residue was adjusted to pH = 5 by addition of an aq. HCl solution (1M). The mixture was then filtered, and the filter cake was washed with EtOH. The filtrate was dried under reduced pressure to furnish 2-amino-4-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **6.4** (390 mg, crude) as yellow solid. The crude product was used directly in next step.

Step 4



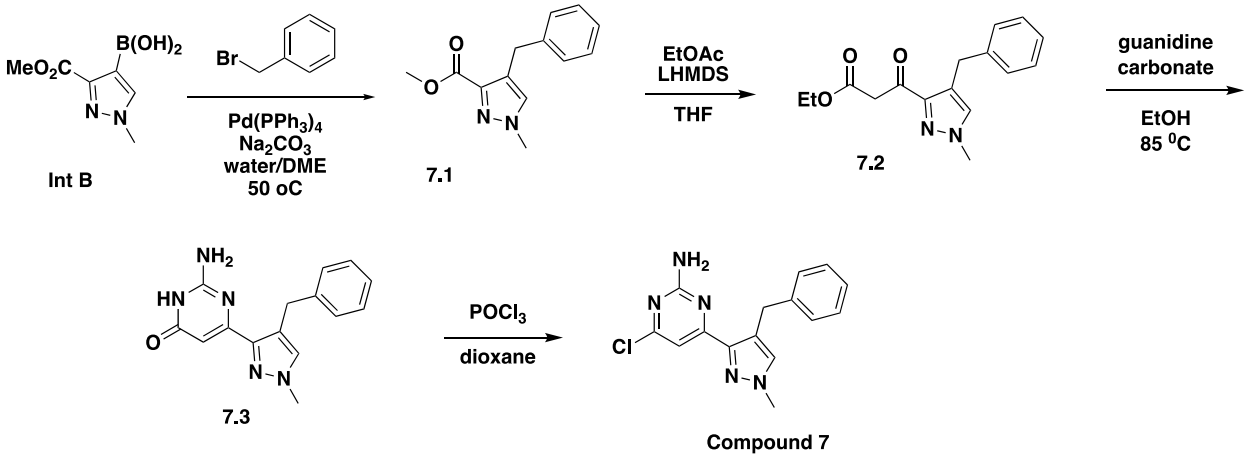
4-chloro-6-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 6)

To a mixture of 2-amino-4-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **6.4** (390 mg, 1.30 mmol, 1 *eq*) in dioxane (4 mL) was added $POCl_3$ (3.00 g, 19.6 mmol, 1.82 mL, 15 *eq*). The resulting mixture was stirred at 75 °C for 2 hr under N_2. The reaction mixture was diluted with sat. aq $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc (30 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash column chromatography (SiO_2, petroleum ether: ethyl acetate = 9:1 to 4:1). The residue was further purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5 μm; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 25%-55%, 10min) to furnish 4-chloro-6-[4-[(2-fluorophenyl)methyl]-1-methyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 6** (35 mg, 0.11 mmol, 8 % yield) as a white solid.

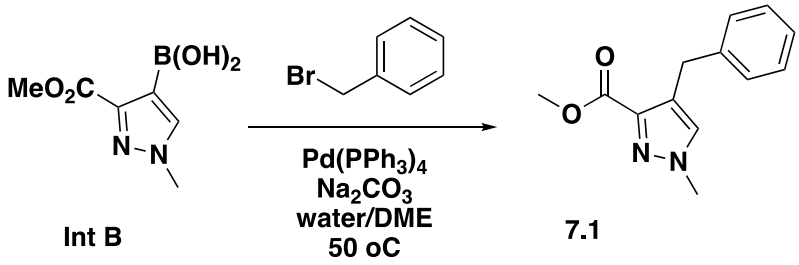
LCMS: ($M+H^+$): 318.1 @ 2.842 min (10-100% ACN in H_2O, 4.5 min)

^{1}H NMR: (400 MHz, METHANOL-d_4) δ 7.28 (s, 1H), 7.26-7.16 (m, 2H), 7.12 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.31 (s, 2H), 3.87 (s, 3H)

Preparation of Compound **7**



Step 1



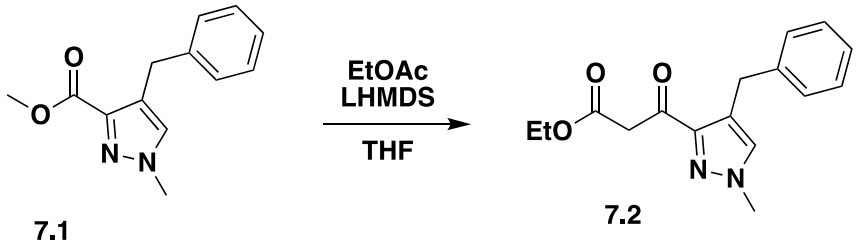
Methyl 4-benzyl-1-methyl-pyrazole-3-carboxylate (7.1)

To a solution of (3-methoxycarbonyl-1-methyl-pyrazol-4-yl)boronic acid **Int B** (3.00 g, 16.3 mmol, 1 eq) and benzyl bromide (5.58 g, 32.6 mmol, 3.87 mL, 2 eq) in 1,2-dimethoxyethane (30 mL) was added Na_2CO_3 (2 M, 42.5 mL, 5.21 eq) and $Pd(PPh_3)_4$ (3.77 g, 3.26 mmol, 0.2 eq). The mixture was stirred at 50 °C for 3 h under N_2. The reaction mixture was poured into H_2O (100 mL). The mixture was extracted with ethyl acetate (30 mL*3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate=5:1 to 2:1 gradient) to furnish methyl 4-benzyl-1-methyl-pyrazole-3-carboxylate **7.1** (1.50 g, 5.86 mmol, 36 % yield) as a yellow oil.

LCMS: ($M+H^+$): 231.3 @ 0.876min (5-95% ACN in H_2O, 2.0 min)

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.32-7.27 (m, 2H), 7.26-7.18 (m, 3H), 6.99 (s, 1H), 4.11 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H)

Step 2



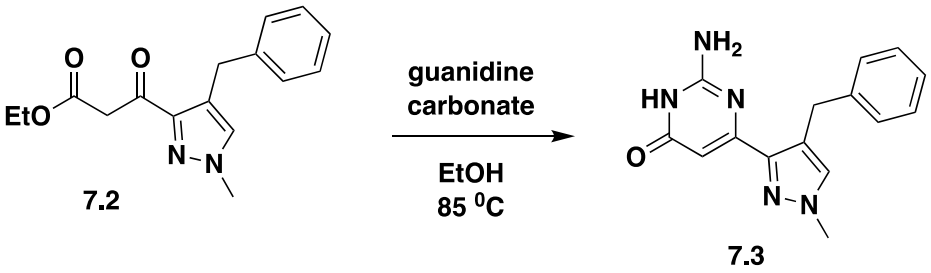
7.1 7.2

Ethyl 3-(4-benzyl-1-methyl-pyrazol-3-yl)-3-oxo-propanoate (7.2)

To a solution of methyl 4-benzyl-1-methyl-pyrazole-3-carboxylate 7.1 (1.35 g, 5.86 mmol, 1 eq) and EtOAc (3.62 g, 41.0 mmol, 4.02 mL, 7 eq) in THF (15 mL) was added LiHMDS (1 M, 17.6 mL, 3 eq) at -40 °C in one portion. The mixture was stirred at -40 °C for 2 h under N_2. The reaction mixture was added slowly to an aq. sat. NH_4Cl solution (150 mL). The solution was extracted with EtOAc (50 mL*4). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/Ethyl acetate=10:1 to 3:1 gradient) to furnish ethyl 3-(4-benzyl-1-methyl-pyrazol-3-yl)-3-oxo-propanoate **7.2** (1.3g) as a light yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.32-7.27 (m, 2H), 7.26-7.19 (m, 3H), 6.94 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 4.05-4.02 (m, 2H), 3.85 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H)

Step 3



7.2 7.3

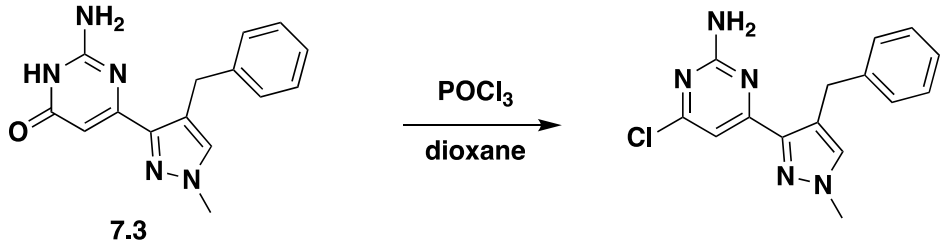
2-amino-4-(4-benzyl-1-methyl-pyrazol-3-yl)-1H-pyrimidin-6-one (7.3)

To a solution of ethyl 3-(4-benzyl-1-methyl-pyrazol-3-yl)-3-oxo-propanoate **7.2** (500 mg, 1.75 mmol, 1 eq) in EtOH (8 mL) was added guanidine carbonate (472 mg, 2.62 mmol, 1.5 eq). The mixture was stirred at 85 °C for 12 h under N_2. The reaction mixture was diluted with water (20 mL). The residue was concentrated under reduced pressure to remove the EtOH after which time a white precipitate formed. The remainder aqueous phase was adjusted to pH=5 by addition of aq. HCl solution (1 N). The white precipitate was collected by filtration and dried under reduced

pressure to furnish 2-amino-4-(4-benzyl-1-methyl-pyrazol-3-yl)-1H-pyrimidin-6-one 7.3 (0.45 g, crude) as a light yellow solid.

LCMS: ($M+H^+$): 282.2 @ 0.789min (5-95% ACN in H_2O, 2.0 min)

Step 4



4-(4-benzyl-1-methyl-pyrazol-3-yl)-6-chloro-pyrimidin-2-amine (Compound 7)

To a solution of 2-amino-4-(4-benzyl-1-methyl-pyrazol-3-yl)-1H-pyrimidin-6-one **7.3** (0.45 g, 1.60 mmol, 1 eq) in dioxane (5 mL) was added $POCl_3$ (3.68 g, 24.0 mmol, 2.23 mL, 15 eq) dropwise at 20 °C. The mixture was stirred at 75 °C for 12 h under N_2. The reaction mixture was added slowly to an aq. saturated $NaHCO_3$ solution (150 mL). The resulting solution was extracted with EtOAc (30 mL*4). The organic layer was washed with brine (80 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative-HPLC (neutral condition, column: Xtimate C18 150 * 40mm * 10 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 60%-80%, 7min) to furnish 4-(4-benzyl-1-methyl-pyrazol-3-yl)-6-chloro-pyrimidin-2-amine **Compound 7** (136 mg, 0.451 mmol, 28 % yield) as a light yellow solid.

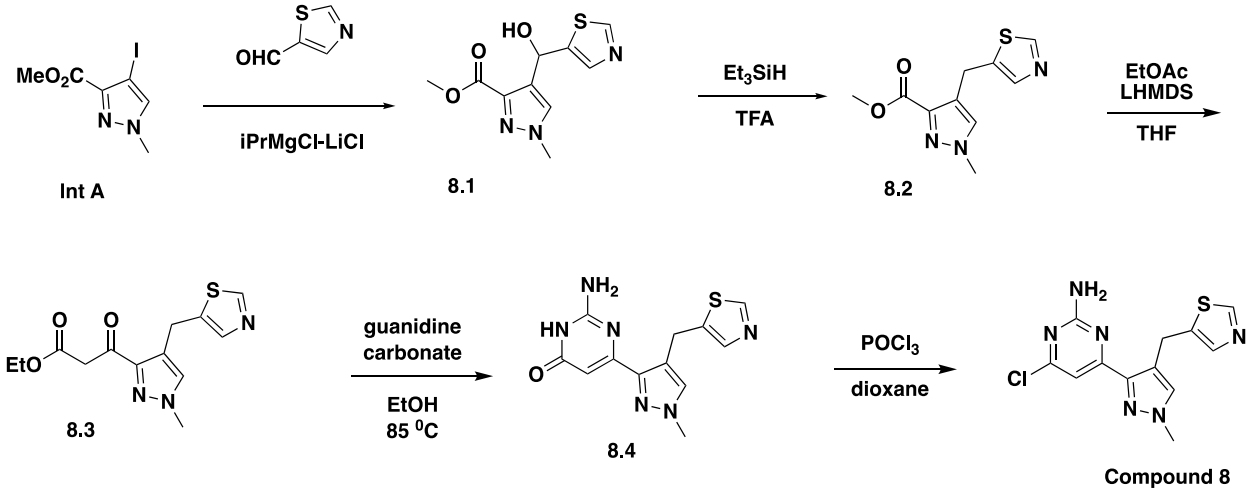
LCMS: Calc'd for $C_{15}H_{15}N_5Cl$ ($M+H^+$) 300.1; Found: 300.0

^{1}H NMR: (400 MHz, DMSO-d6) δ 7.50 (s, 1H), 7.29-7.21 (m, 4H), 7.17-7.11 (m, 1H), 7.08 (s, 2H), 6.99 (s, 1H), 4.27 (s, 2H), 3.84 (s, 3H)

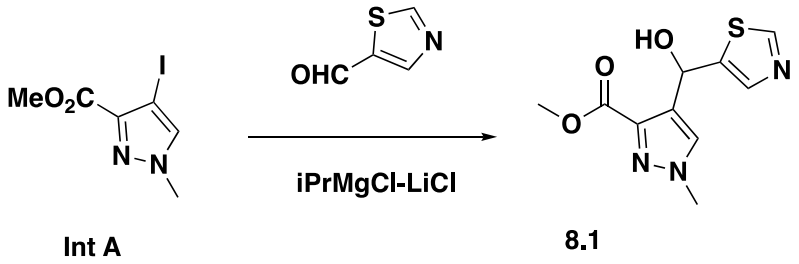
^{13}C NMR: (125 MHz, DMSO-d6) δ 163.80, 163.53, 160.43, 144.14, 142.08, 132.85, 129.16, 128.65, 126.16, 122.41, 104.45, 39.46, 30.55

HRMS calc'd for $C_{15}H_{15}N_5Cl$: $(M+H)^+$ 300.1011; Found: 300.1008.

Preparation of Compound **8**



Step 1

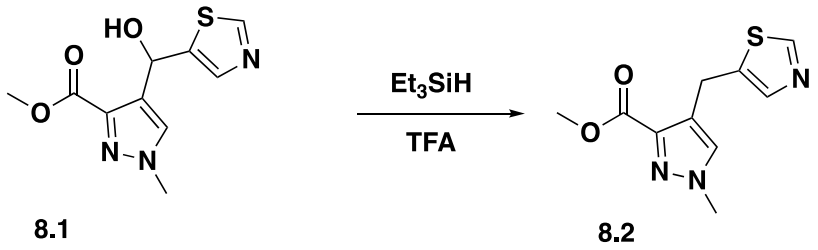


Methyl 4-[hydroxy(thiazol-5-yl)methyl]-1-methyl-pyrazole-3-carboxylate (8.1)

To a solution of methyl 4-iodo-1-methyl-pyrazole-3-carboxylate **Int A** (1 g, 3.76 mmol, 1 eq) in THF (10 mL) was added isopropylmagnesium chloride-lithium chloride complex (1.3 M, 3.04 mL, 1.05 eq) at -10 °C under a N_2 atmosphere. After stirring at -10 °C for 0.5 h, a solution of thiazole-5-carbaldehyde (468 mg, 4.13 mmol, 1.1 eq) in THF (5 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 15 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with a sat. aqueous NH_4Cl solution (100 mL). The resulting solution were extracted with EtOAc (50 mL*3). The organic layer was washed with brine (70 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/Ethyl acetate = 9/1) to furnish methyl 4-[hydroxy(thiazol-5-yl)methyl]-1-methyl-pyrazole-3-carboxylate **8.1** (650 mg) as yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 8.69 (s, 1H), 7.61 (s, 1H), 7.17 (s, 1H), 6.24 (s, 1H), 5.15 (br s, 1H), 3.89 (s, 3H), 3.88 (s, 3H)

Step 2



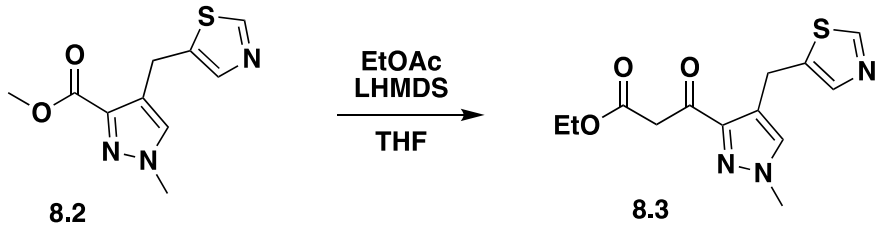
8.1 8.2

Methyl 1-methyl-4-(thiazol-5-ylmethyl)pyrazole-3-carboxylate (8.2)

Methyl 4-[hydroxy(thiazol-5-yl)methyl]-1-methyl-pyrazole-3-carboxylate **8.1** (530 mg, 2.09 mmol, 1 eq) in TFA (5.2 mL) was cooled to 0 °C. Triethyl silane (2.43 g, 20.9 mmol, 3.34 mL, 10 eq) was added. The mixture was stirred at 60 °C for 7 h. The reaction mixture was concentrated under the reduced pressure to remove the solvent. The residue was diluted with water (50 mL). The solution was extracted with EtOAc (30 mL*3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 2/3) to furnish methyl 1-methyl-4-(thiazol-5-ylmethyl)pyrazole-3-carboxylate **8.2** (440 mg) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 8.64 (br s, 1H), 7.62 (s, 1H), 7.13 (s, 1H), 4.29 (s, 2H), 3.86 (d, *J* = 1.6 Hz, 6H)

Step 3



8.2 8.3

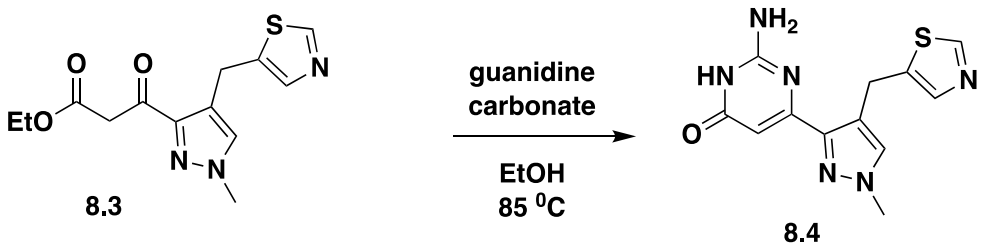
Ethyl 3-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate (8.3)

To a solution of methyl 1-methyl-4-(thiazol-5-ylmethyl)pyrazole-3-carboxylate 8.2 (400 mg, 1.69 mmol, 1 eq) and EtOAc (1.04 g, 11.8 mmol, 1.16 mL, 7 eq) in THF (1 mL) was added LiHMDS (1 M, 5.06 mL, 3 eq) at -40 °C in one portion. The mixture was stirred at -40 °C for 1.5 h under N_2. The reaction mixture was diluted with sat. aqueous NH_4Cl solution (100 mL). The mixture was

extracted with EtOAc (50 mL*3). The organic layer was washed with brine (90 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/Ethyl acetate=3/2) to furnish ethyl 3-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate **8.3** (350 mg) as a yellow solid.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) d 8.59 (s, 1H), 7.60 (s, 1H), 7.08-7.06 (m, 1H), 4.29 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 2H), 3.82 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H)

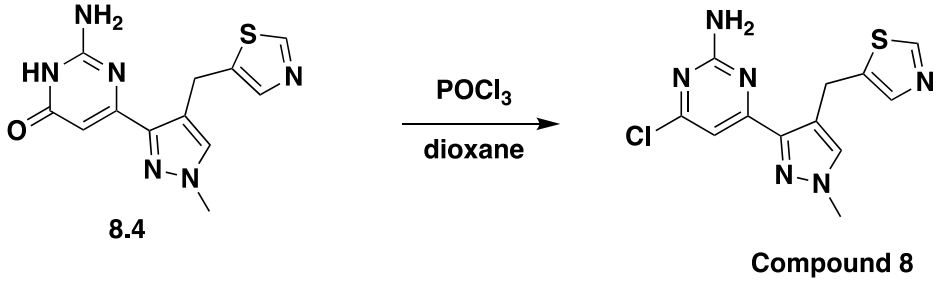
Step 4



2-amino-4-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (8.4)

Ethyl 3-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate **8.3** (320 mg, 1.09 mmol, 1 eq) and guanidine carbonate (590 mg, 3.27 mmol, 3 eq) were taken up in anhydrous EtOH (6 mL). The mixture was stirred for 24 h at 85 °C under N_2. A white precipitate formed during the reaction. The reaction mixture was diluted with water (10 mL), and the mixture was concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 5 by addition of aqueous HCl (4N). The mixture was filtered, and the residue was dried under the reduced pressure to furnish 2-amino-4-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (175 mg, crude) as a white solid. The material was used without any further purification in the next step.

Step 5



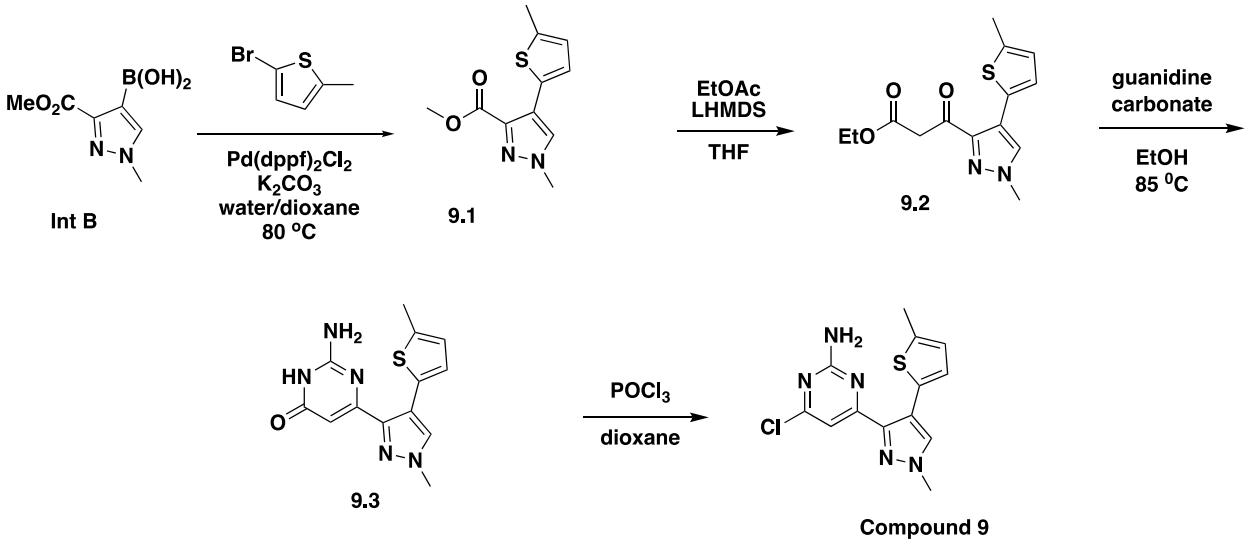
4-chloro-6-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 8)

$POCl_3$ (558 mg, 3.64 mmol, 0.338 mL, 15 eq) was added into a solution of 2-amino-4-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one **8.4** (70 mg, 0.243 mmol, 1 eq) in dioxane (3 mL). N,N-Diethylaniline (25 mg, 0.17 mmol, 0.7 eq) was added. The mixture was heated to 75 °C and stirred for 15 h. The reaction mixture was added slowly to an aq. $NaHCO_3$ solution (saturated, 200 mL) to quench the excess $POCl_3$. The solution was extracted with EtOAc (70 mL*6). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by neutral preparative-HPLC (column: Waters Xbridge BEH C18 100 * 30mm * 10 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-50%,10 min) to afford 4-chloro-6-[1-methyl-4-(thiazol-5-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 8** (19 mg) as a white solid.

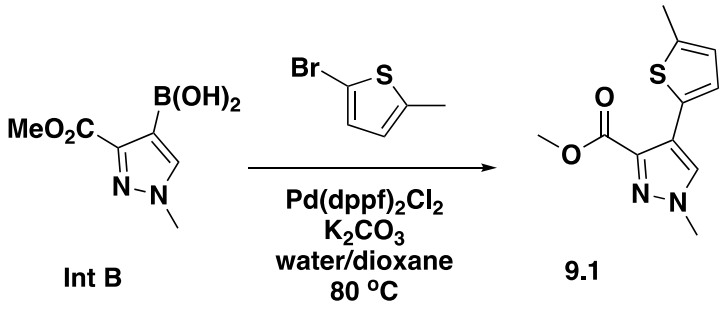
LCMS: Calc'd for $C_{12}H_{12}N_6ClS$ ($M+H^+$) 307.1; Found: 307.1

^{1}H NMR: (DMSO-d6, 400 MHz) δ 8.84 (s, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 7.12 (br s, 2H), 6.99 (s, 1H), 4.52 (s, 2H), 3.85 (s, 3H)

Preparation of Compound **9**



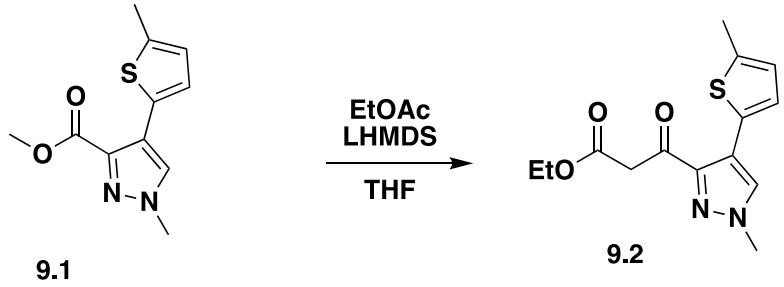
Step 1



Methyl 1-methyl-4-(5-methyl-2-thienyl)pyrazole-3-carboxylate (9.1)

A mixture of (3-methoxycarbonyl-1-methyl-pyrazol-4-yl)boronic acid **Int B** (4.70 g, 25.6 mmol, 1 *eq*), 2-bromo-5-methyl-thiophene (6.79 g, 38.3 mmol, 4.38 mL, 1.5 *eq*), $Pd(dppf)Cl_2$ (1.87 g, 2.56 mmol, 0.1 *eq*) and K_2CO_3 (7.06 g, 51.1 mmol, 2 *eq*) in dioxane (50 mL) and H_2O (10 mL) was de-gassed. The resulting mixture was heated at 80 °C for 12 h under N_2. The reaction mixture was diluted with water (200 mL). The solution was extracted with EtOAc (50 mL*4). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate= 5/1 to 2/1) to furnish methyl 1-methyl-4-(5-methyl-2-thienyl)pyrazole-3-carboxylate **9.1** (0.9 g) as a brown oil.

Step 2

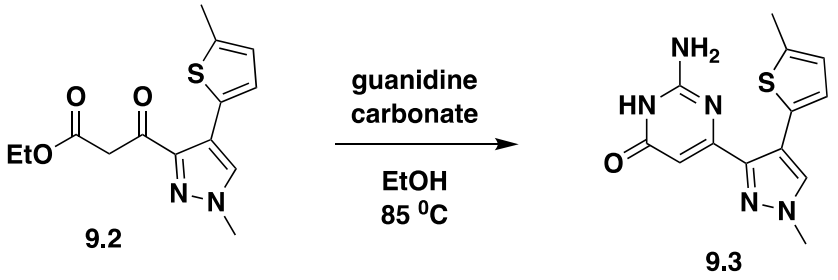


Ethyl 3-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-3-oxo-propanoate (9.2)

Methyl 1-methyl-4-(5-methyl-2-thienyl)pyrazole-3-carboxylate **9.1** (800 mg, 3.39 mmol, 1 *eq*) and EtOAc (2.09 g, 23.7 mmol, 2.32 mL, 7 *eq*) were taken up in THF (15 mL). After the solution was cooled to -40 °C, LiHMDS (1 M, 10.2 mL, 3 *eq*) was added in one portion. The mixture was stirred at -40 °C for 2 h. The reaction mixture was added slowly to an aq. sat. NH_4Cl solution (150 mL). The solution was extracted with EtOAc (30 mL*4). The organic layer was washed with brine

(40 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 6/1) to furnish ethyl 3-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-3-oxo-propanoate **9.2** (450 mg, crude) as a dark-yellow oil.

Step 3



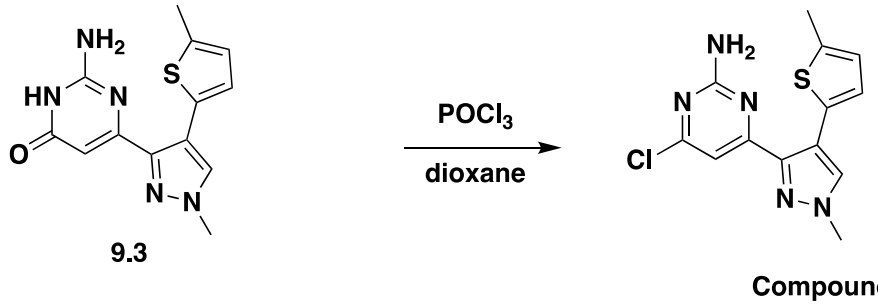
9.2 9.3

2-amino-4-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-1H-pyrimidin-6-one (9.3)

Guanidine carbonate (370 mg, 2.05 mmol, 1.5 *eq*) and ethyl 3-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-3-oxo-propanoate **9.2** (400 mg, 1.37 mmol, 1 *eq*) were taken up in EtOH (8 mL). The resulting mixture was stirred at 85 °C for 12 h under N_2. The reaction mixture was diluted with water (20 mL). The mixture was concentrated under reduced pressure to remove the EtOH at which time a white precipitate formed. The aqueous phase was adjusted to pH=5 by addition of an aq. HCl solution (1 N). The white precipitate was collected by filtration and dried under reduced pressure to furnish 2-amino-4-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-1H-pyrimidin-6-one **9.3** (200 mg) as a white solid.

LCMS: ($M+H^+$): 288.3 @ 0.311 min (5-95% ACN in H_2O, 2.0 min)

Step 4



9.3 Compound 9

4-chloro-6-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 9)

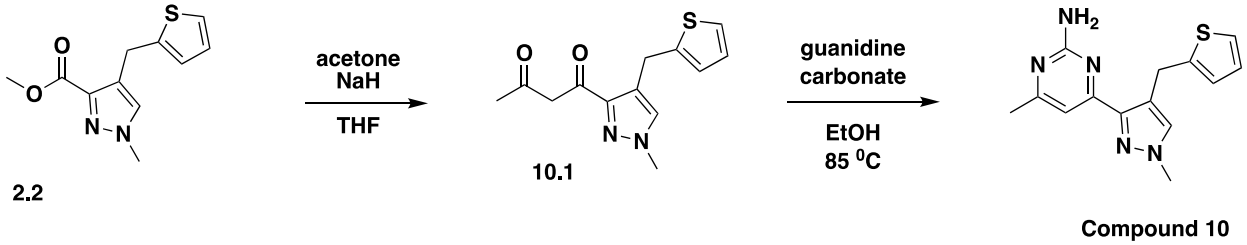
To a stirred solution of 2-amino-4-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]-1H-pyrimidin-6-one 9.3 (180 mg, 0.626 mmol, 1 *eq*) in dioxane (5 mL) was added $POCl_3$ (1.44 g, 9.40 mmol, 0.872

mL, 15 *eq*) dropwise at 25 °C. After the addition, the mixture was de-gassed and heated to 70 °C for 12 h under N_2. The reaction mixture was added slowly to an aq. saturated $NaHCO_3$ solution (150 mL). The resulting solution was extracted with EtOAc (30 mL*4). The organic layer was washed with brine (80 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative-HPLC (column: Xtimate C18 150 * 25mm * 5 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%, 10min) to furnish 4-chloro-6-[1-methyl-4-(5-methyl-2-thienyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 9** (35 mg) as a white solid.

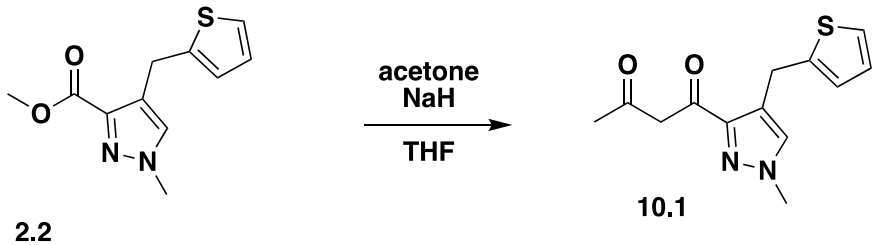
LCMS: Calc'd for $C_{13}H_{13}N_5ClS$ ($M+H^+$)306.1; Found: 306.0

^{1}H NMR: (400MHz, METHANOL-d_4) δ 7.49 (s, 1H), 6.97 (s, 1H), 6.92 (d, *J* = 3.4 Hz, 1H), 6.69 (dd, *J* = 1.0, 3.4 Hz, 1H), 5.31 (br d, *J* = 3.3 Hz, 2H), 3.99 (s, 3H), 2.49 (s, 3H)

Preparation of Compound 10



Step 1



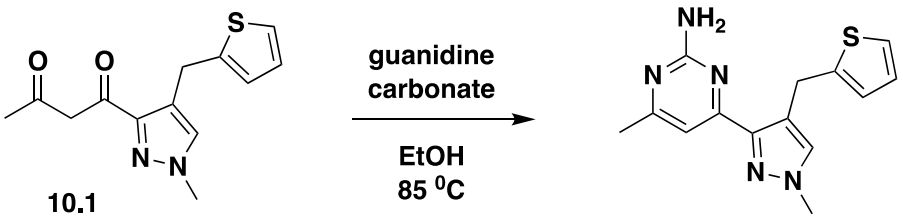
1-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]butane-1,3-dione (10.1)

To a solution of methyl 1-methyl-4-(2-thienylmethyl)pyrazole-3-carboxylate **2.2** (0.650 g, 2.75 mmol, 1 eq) in THF (10 mL) was added NaH (330 mg, 8.25 mmol, 60% dispersion in oil, 3 eq) at 20 °C. The mixture was stirred at 20 °C for 0.5 h under N_2. Acetone (160 mg, 2.75 mmol, 0.202 mL, 1 eq) was added to the mixture at 20 °C. The mixture was stirred at 20 °C for another 1.5 h under N_2. The reaction mixture was poured into aq. HCl (0.5 N, 100 mL). The mixture was extracted with ethyl acetate (30 mL*3). The organic phase was washed with brine (50 mL), dried

over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 to 15% ethyl acetate/petroleum ether) to furnsih 1-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]butane-1,3-dione **10.1** (420 mg, crude) as a light yellow oil.

^{1}H NMR: ET1 (400 MHz, CHLOROFORM-d) δ 7.15-7.12 (m, 2H), 6.93 (t, *J* = 4.2 Hz, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 4.38 (s, 2H), 3.89 (s, 3H), 3.88 (s, 2H), 2.12 (s, 3H)

Step 2



10.1

Compound 10

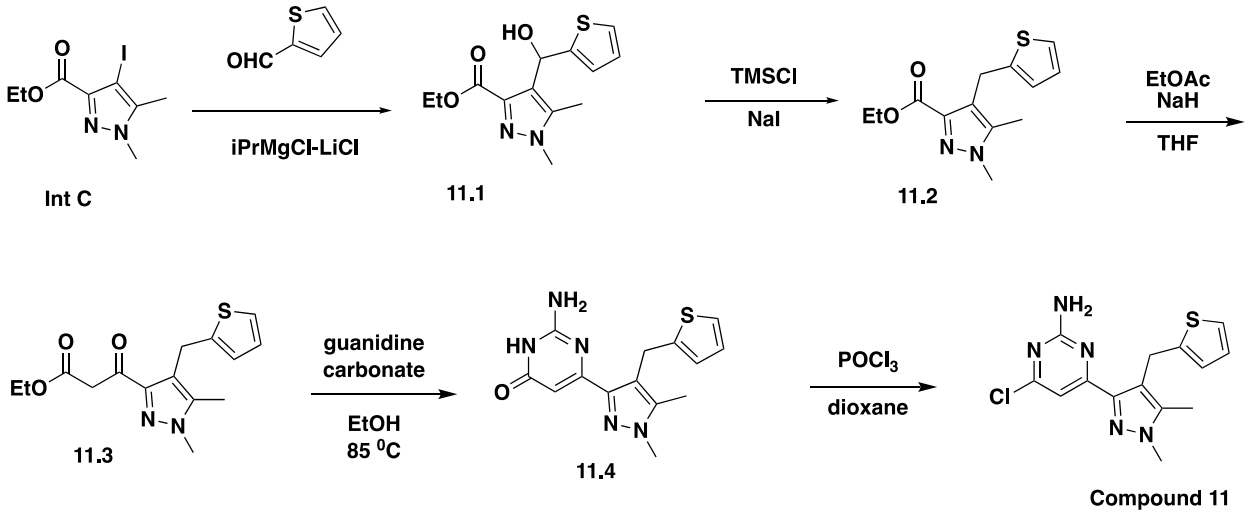
4-methyl-6-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 10)

To a solution of 1-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]butane-1,3-dione **10.1** (0.400 g, 1.52 mmol, 1 eq) in EtOH (8 mL) was added guanidine carbonate (412 mg, 2.29 mmol, 1.5 eq). The mixture was stirred at 85 °C for 12 h under N_2. The reaction mixture was poured into H_2O (100 mL). The mixture was extracted with ethyl acetate (30 mL*3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was reduced under reduced pressure. The residue was purified by preparative-HPLC (column: Waters Xbridge Prep OBD C18 150 * 30 * 10 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 20%-40%,11min) to furnish 4-methyl-6-[1-methyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 10** (111 mg) as a white solid.

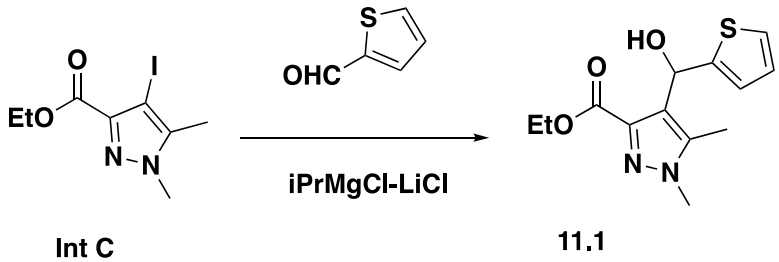
LCMS: Calc'd for $C_{14}H_{16}N_5S$ ($M+H^+$) 286.1; Found: 286.0

^{1}H NMR: (400 MHz, MeOD) δ 7.42 (s, 1H), 7.12 (dd, *J* = 1.3, 5.1 Hz, 1H), 7.01 (s, 1H), 6.88 - 6.82 (m, 2H), 4.48 (s, 2H), 3.88 (s, 3H), 2.32 (s, 3H)

Preparation of Compound 11



Step 1

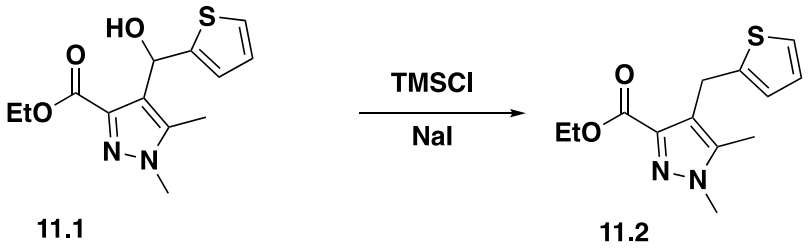


Ethyl 4-[hydroxy(2-thienyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate (11.1)

Under N_2, to a solution of ethyl 4-iodo-1,5-dimethyl-pyrazole-3-carboxylate **Int C** (0.600 g, 2.04 mmol, 1 eq) in THF (10 mL) was added isopropylmagnesium chloride-lithium chloride complex (1.3 M, 1.65 mL, 1.05 eq) at -10 °C. After stirring at -10 °C for 0.5 h, a solution of thiophene-2-carbaldehyde (252 mg, 2.24 mmol, 0.210 mL, 1.1 eq) in THF (1 mL) was added to the mixture dropwise. After the addition, the mixture was allowed to warm slowly to 15 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with sat. aqueous NH_4Cl (100 mL). The mixture was extracted with EtOAc (50 mL*3). The organic layer was washed with brine (70 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1) to furnish ethyl 4-[hydroxy(2-thienyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate **11.1** (400 mg, 1.43 mmol, 70 % yield) as a yellow solid.

^{1}H NMR: (400MHz, CHLOROFORM-d) δ 7.15-7.10 (m, 1H), 6.82 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.66-6.62 (m, 1H), 5.90 (d, *J* = 10.8 Hz, 1H), 5.72 (d, *J* = 10.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.22 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H)

Step 2

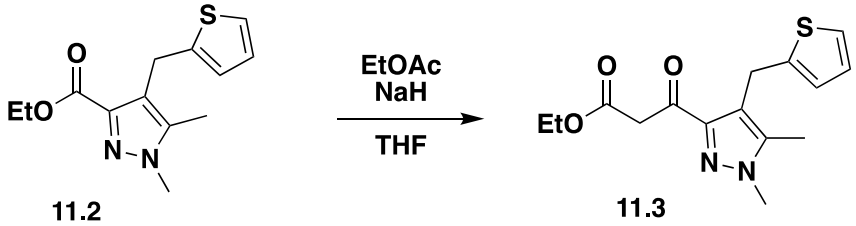


11.1 11.2

Ethyl 1,5-dimethyl-4-(2-thienylmethyl)pyrazole-3-carboxylate (11.2)

To a solution of NaI (1.28 g, 8.56 mmol, 6 eq) in ACN (6 mL) was added TMSCl (930 mg, 8.56 mmol, 1.09 mL, 6 eq) under N_2. After 10 min of stirring at 15 °C, a solution of ethyl 4-[hydroxy(2-thienyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate **11.1** (400 mg, 1.43 mmol, 1 eq) in ACN (2 mL) was added. The mixture was stirred at 15 °C under N_2 for 2 h. The reaction mixture was diluted with sat. aq Na_2SO_3 (70 mL). The solution was extracted with EtOAc (50 mL*3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate=1/1) to furnish ethyl 1,5-dimethyl-4-(2-thienylmethyl)pyrazole-3-carboxylate **11.2** (300 mg, 1.13 mmol, 80 % yield) as a yellow oil.

Step 3



11.2 11.3

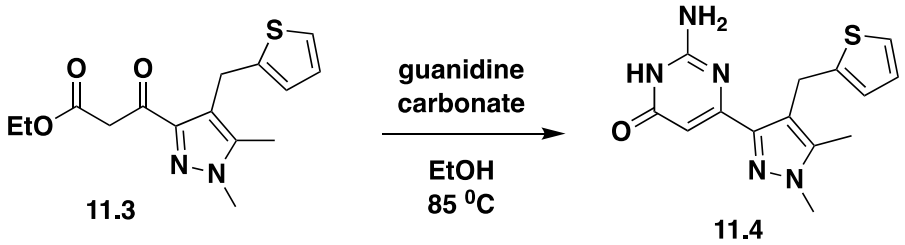
Ethyl 3-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate (11.3)

A mixture of ethyl 1,5-dimethyl-4-(2-thienylmethyl)pyrazole-3-carboxylate **11.2** (360 mg, 1.36 mmol, 1 eq) in THF (4 mL) was cooled to 0 °C. Sodium hydride (163 mg, 4.09 mmol, 60% dispersion in oil, 3 eq) was added. After stirring for 20 min, EtOAc (840 mg, 9.53 mmol, 0.93 mL,

7 eq) was added dropwise at 0 °C. The mixture was stirred at 70 °C for 2 h under N_2. The reaction mixture was poured into aq. saturated NH_4Cl (100 mL). The mixture was extracted with EtOAc (40mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1) to furnish ethyl 3-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate **11.3** (260 mg, 0.849 mmol, 62 % yield) as a light yellow oil.

^{1}H NMR: (400MHz, CHLOROFORM-d) δ 7.06-7.03 (m, 1H), 6.85 (dd, *J* = 3.5, 4.8 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 4.28 (s, 2H), 4.19 (q, *J* = 7.3 Hz, 2H), 4.00 (s, 2H), 3.81 (s, 3H), 2.22 (s, 3H), 1.28-1.23 (m, 3H)

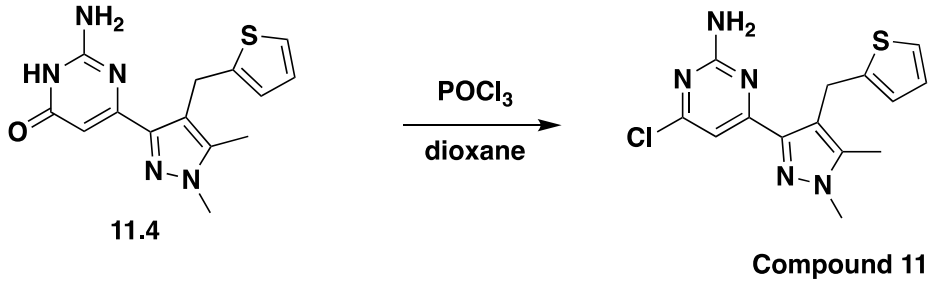
Step 4



2-amino-4-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (11.4)

Ethyl 3-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-3-oxo-propanoate **11.3** (260 mg, 0.849 mmol, 1 eq) and guanidine carbonate (459 mg, 2.55 mmol, 3 eq) were taken up in anhydrous EtOH (4 mL). The mixture was stirred for 12 h at 85 °C under N_2 at which time a white precipitate formed. The reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with water (20 mL), and the mixture was concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 5 by addition of aqueous HCl (4N). The mixture was filtered. The filter cake was dried under reduced pressure to afford 2-amino-4-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one **11.4** (240 mg, crude) as a white solid.

Step 5



4-chloro-6-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 11)

$POCl_3$ (1.83 g, 12.0 mmol, 1.11 mL, 15 eq) was added into a solution of 2-amino-4-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one **11.4** (240 mg, 0.796 mmol, 1 eq) in dioxane (4 mL) at 15 °C. The mixture was heated to 75 °C for 12 h. More $POCl_3$ (1.1 ml) was added, and the mixture was heated another 5 h at 75 °C. The reaction mixture was added slowly to aq. $NaHCO_3$ (saturated, 200 mL) to quench the excess $POCl_3$. The solution was extracted with EtOAc (70 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by neutral preparative-HPLC (column: Xtimate C18 150 * 40mm * 10 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 60%-80%,7min) to afford 4-chloro-6-[1,5-dimethyl-4-(2-thienylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 11** (54 mg, 0.16 mmol, 21 % yield,) as a white solid.

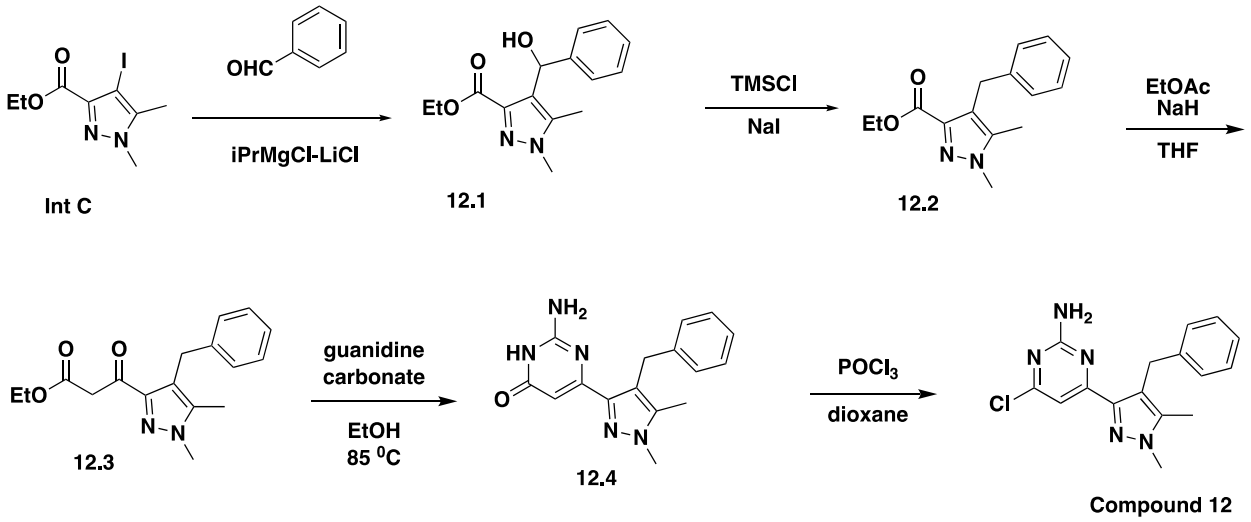
LCMS: Calc'd for $C_{14}H_{15}N_5SCl$ $(M+H^+)$ 320.1; Found: 320.0

^{1}H NMR: (400MHz, DMSO-d6) δ 7.18 (dd, *J* = 1.2, 5.0 Hz, 1H), 7.04 (br s, 2H), 6.98 (s, 1H), 6.89 - 6 .86 (m, 1H), 6.83 (dd, *J* = 3.4, 5.0 Hz, 1H), 4.49 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H)

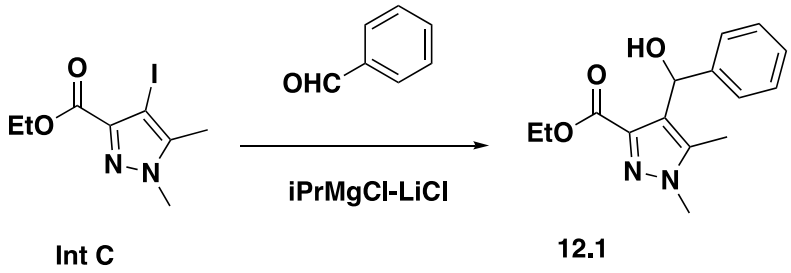
^{13}C NMR: (125MHz, DMSO-d6) δ 163.75, 163.62, 160.40, 145.64, 142.97, 139.13, 126.83, 124.76 , 124.15, 118.66, 104.29, 37.25, 24.23, 9.54

HRMS calc'd for $C_{14}H_{14}N_5SCl$: $(M+H)^+$ 320.0731; Found: 320.0729.

Preparation of Compound 12 (TDI-10229)



Step 1

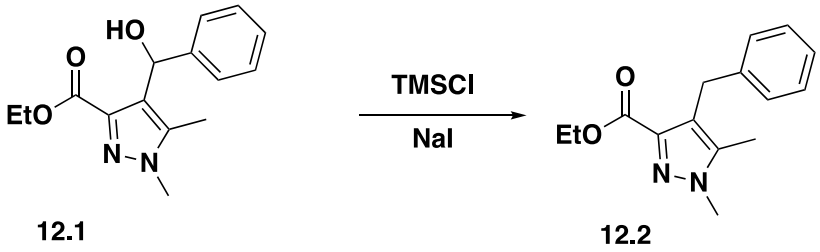


Ethyl 4-[hydroxy(phenyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate (12.1)

To a solution of **Int C** (245 g, 833 mmol, 1.00 *eq*) in THF (500 mL) was added i-PrMgCl-LiCl (1.3 M, 705 mL, 1.10 *eq*) dropwise at -15 °C under N_2. After the mixture was stirred at -15 °C for 0.5 h, benzaldehyde (97.3 g, 916 mmol, 92.6 mL, 1.10 *eq*) was added dropwise at -15 °C. The mixture was stirred at 25 °C for 12 h under N_2. TLC (Petroleum ether/Ethyl acetate = 2/1) showed the compound **2** (R_f = 0.7) was consumed and a new main spot (R_f = 0.6) was detected. The reaction was poured into sat. aqueous NH_4Cl (2.00 L) and extracted with ethyl acetate (2.00 L * 2). The combined organic layer was washed with brine (1.00 L), dried over Na_2SO_4, filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 10/1 to 1/1, R_f = 0.6) to furnish **12.1** (330 g, 974 mmol, 59 % yield) as a yellow solid.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.24 - 7.19 (m, 4H), 7.17 - 7.11 (m, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 5.25 (d, *J* = 10.0 Hz, 1H), 4.32 - 4.25 (m, 2H), 3.81 (s, 3H), 2.18 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H)

Step 2



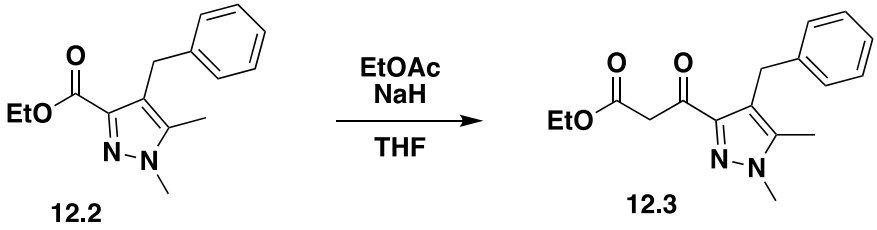
12.1 12.2

Ethyl 4-benzyl-1,5-dimethyl-pyrazole-3-carboxylate (12.2)

(2 batches were performed in parallel) To a solution of NaI (292 g, 1.95 mol, 6.00 *eq*) in MeCN (2.00 L) was added TMSCl (212 g, 1.95 mol, 247 mL, 6.00 *eq*) under N_2. After 30 mins of stirring at 15 °C, a solution of compound **12.1** (110 g, 325 mmol, 1.00 *eq*) in MeCN (1.00 L) was added. The mixture was stirred at 25 °C under N_2 for 4 h. TLC (Petroleum ether/Ethyl acetate =2/1) indicated the compound **12.2** (R_f = 0.3) was consumed, and a new spot (R_f = 0.4) was detected. The reaction was poured into sat. aqueous Na_2SO_3 (4.00 L) and extracted with ethyl acetate (2.00 L * 2). The combined organic layer was washed with brine (2.00 L), dried over Na_2SO_4, and filtered. The filtrate was concentrated to furnish **12.2** (193 g, crude) as a yellow oil. The residue was used next step directly without further purification.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.26 - 7.20 (m, 2H), 7.18 - 7.12 (m, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 3.85 (s, 3H), 2.17 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H)

Step 3



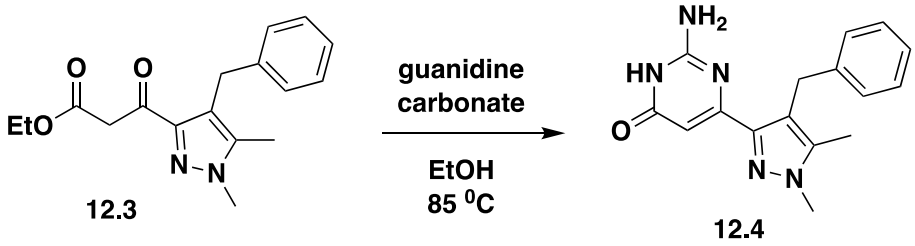
12.2 12.3

Ethyl 3-(4-benzyl-1,5-dimethyl-pyrazol-3-yl)-3-oxo-propanoate (12.3)

A mixture of ethyl acetate (346 g, 3.93 mol, 385 mL, 7.00 *eq*) in THF (1.40 L) was cooled to 0 °C and then NaH (67.4 g, 1.68 mol, 60% wt dispersion in oil, 3.00 *eq*) was added. After stirring for 0.2 h, a solution of compound **12.2** (145 g, 561 mmol, 1.00 *eq*) in THF (800 mL) was added drop-wise at 0 °C. The mixture was stirred at 70 °C for 2 h under N_2. TLC (petroleum ether/ethyl acetate = 2/1) indicated the compound **12.2** (R_f = 0.4) was consumed, and a new spot (R_f = 0.6) was detected. The reaction was quenched with sat. aqueous NH_4Cl (5.00 L). The mixture was extracted with ethyl acetate (5.00 L * 2). Combine organic layer was washed with brine (5.00 L), dried over Na_2SO_4, and filtered. The residue was concentrated to furnish **12.3** (207 g, 543 mmol) as a yellow oil. The residue was used next step directly without further purification.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.21 - 7.12 (m, 5H), 4.17 (s, 2H), 4.10 (s, 2H), 4.00 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H), 1.23 - 1.21 (m, 3H)

Step 4



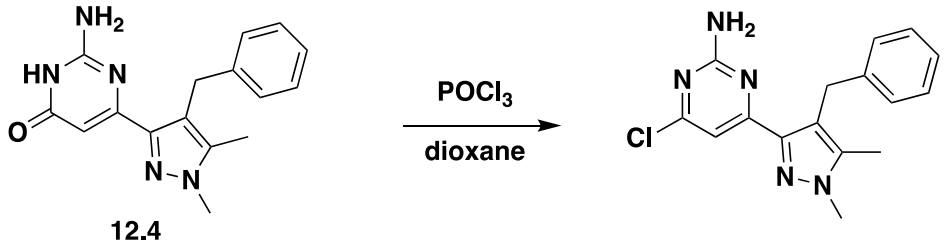
2-amino-4-(4-benzyl-1,5-dimethyl-pyrazol-3-yl)-1H-pyrimidin-6-one (12.4)

To a solution of compound **12.3** (264 g, 692 mmol, 1.00 *eq*) in EtOH (2.60 L) was added guanidine carbonate (374 g, 2.07 mol, 3.00 *eq*). The mixture was stirred at 95 °C for 18 h. The reaction was cooled to 25 °C and concentrated under reduce pressure to removed EtOH. The residue was diluted with water (2.50 L) and adjusted to pH = 5 by addition of aqueous 4N HCl. The precipitate was filtered, and the filter cake was triturated with EtOH (400 mL). The cake was washed with

petroleum ether/ethyl acetate = 5/1 (200 mL) and then dried under vacuum to furnish compound **12.4** (98.3 g, 333 mmol, 48 % yield) as an off-white solid.

^{1}HNMR: (400 MHz, DMSO-*d6*) δ 10.67 (br s, 1H), 7.19 - 7.16 (m, 4H), 7.14 - 7.08 (m, 1H), 6.44 (br s, 2H), 5.93 (s, 1H), 4.25 (s, 2H), 3.73 (s, 3H), 2.14 (s, 3H)

Step 5



4-chloro-6-[4-benzyl-1,5-dimethyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 12)

To a solution of compound **12.4** (47.0 g, 159 mmol, 1.00 *eq*) in dioxane (750 mL) was added $POCl_3$ (366 g, 2.39 mol, 222 mL, 15.0 *eq*) under N_2. The mixture was heated and stirred at 75 °C for 12 h. TLC (petroleum ether/ethyl acetate = 2/1) indicated the formation of **12** (R_f = 0.7). The reaction was cooled to 25 °C and then concentrated under reduced pressure to remove most of the $POCl_3$. The residue was poured into ice-water (2.00 L) and the pH was adjusted to 7 by addition of aqueous 1N NaOH and sat. $NaHCO_3$. The solution was extracted with ethyl acetate (3.00 L * 2). The combined organic layer was washed with brine (500 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 50/1 to 3/1). The crude product (20.0 g) was triturated with ethyl acetate (40.0 mL) at 25 °C for 30 mins. The mixture was filtered and concentrated under vacuum to give **12** (11.7 g, 37.0 mmol, 23 % yield) as a yellow solid Then Compound **12** (11.7 g, 37.03 mmol, 1.00 eq) was further purified by preparative-HPLC (TFA condition; column: Phenomenex luna C18 250 * 80mm * 10 mm; mobile phase: [water (0.1%TFA)-MeCN]; B%: 40%-70%, 25 min) to furnish **Compound 12** (7.01 g, 22.3 mmol) as an off-white solid.

LCMS: Calc'd for $C_{16}H_{17}N_5Cl$ ($M+H^+$) 314.1; Found: 314.1

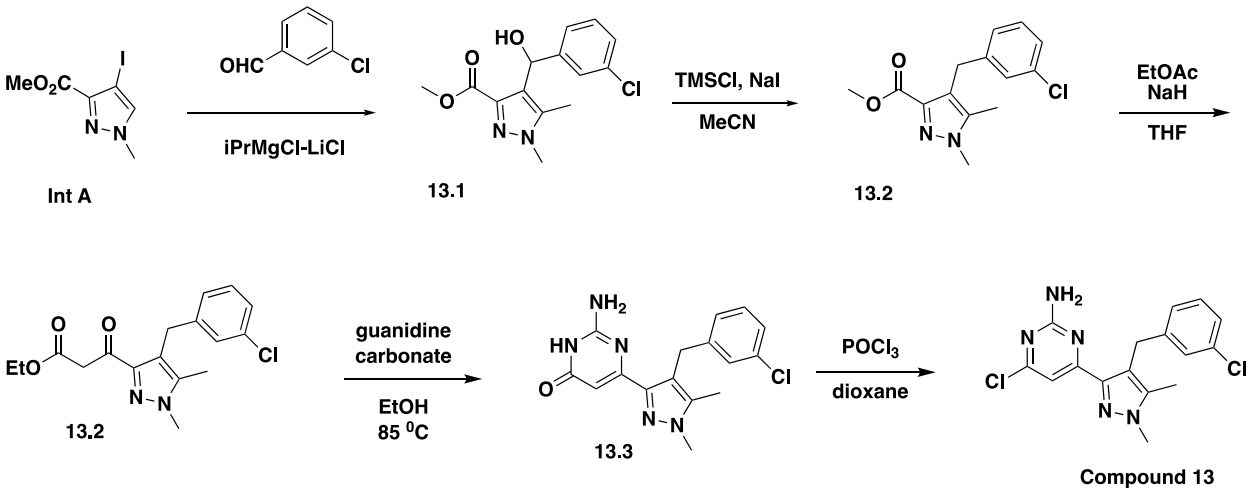
^{1}H NMR: (400 MHz, DMSO-*d6*) δ 7.18 (d, *J* = 4.4 Hz, 4H), 7.12 - 7.05 (m, 1H), 7.02 (br s, 2H), 6.98 (s, 1H), 4.31 (s, 2H), 3.78 (s, 3H), 2.20 (s, 3H)

^{13}C NMR: (125 MHz, DMSO-*d6*) δ 163.85, 163.77, 160.34, 143.32, 142.37, 139.26, 128.79, 128.52, 125.90, 118.63, 104.46, 37.26, 29.32, 9.69

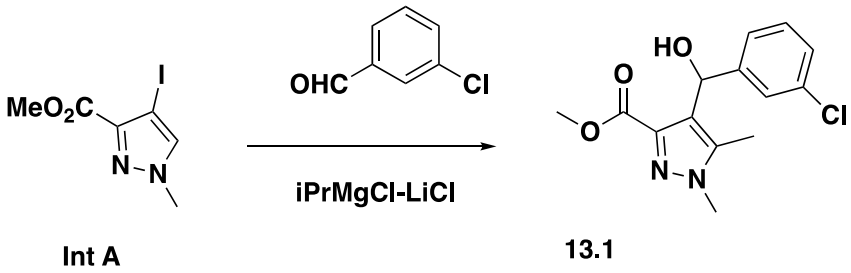
Anal. Calc'd for $C_{16}H_{16}N_5Cl$: C: 61.24; H: 5.14; N: 22.32. Found: C: 61.27; H: 5. 08; N: 22.52

HRMS Calc'd for $C_{16}H_{17}N_5Cl$: $(M+H)^+$ 314.1167; Found: 314.1163.

Preparation of Compound 13



Step 1



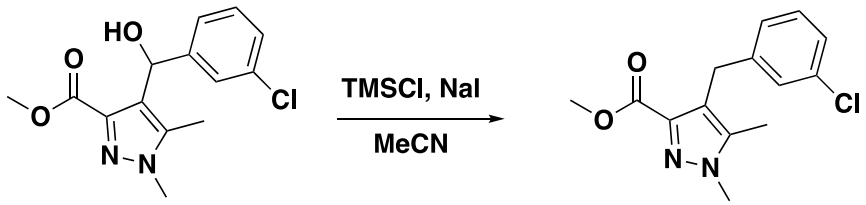
Ethyl 4-[(3-chlorophenyl)-hydroxy-methyl]-1,5-dimethyl-pyrazole-3-carboxylate (13.1)

To a mixture of ethyl 4-iodo-1,5-dimethyl-pyrazole-3-carboxylate **Int A** (1.50 g, 5.10 mmol, 1 eq) in THF (20 mL) was added i-PrMgCl-LiCl (1.30 M, 4.32 mL, 1.1 eq) dropwise at -15 °C under N_2. After stirring for 30 min at -15° C, 3-chlorobenzaldehyde (789 mg, 5.61 mmol, 0.636 mL, 1.1 eq) was added to the mixture at -15 °C. The reaction mixture was stirred at 15 °C for 12 h under N_2. The reaction mixture was quenched with saturated aqueous NH_4Cl (80 ml). The mixture was extracted with EtOAc (80 mL*3). The combined organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 to 25% ethyl acetate/petroleum ether @ 75 mL/min) to

furnish ethyl 4-[(3-chlorophenyl) -hydroxy-methyl]-1,5-dimethyl-pyrazole-3-carboxylate **13.1** (1.50 g, 4.86 mmol) was obtained as a white solid.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.26-7.23 (m, 1H), 7.22-7.16 (m, 3H), 5.80 (br d, *J* = 4.6 Hz, 1H), 5.36 – 5.28 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 2.26 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H)

Step 2

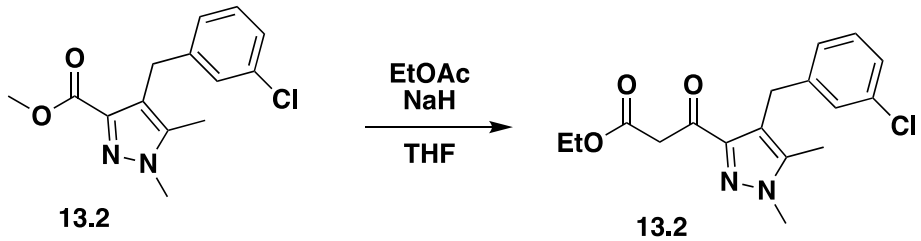


13.1 **13.2**

Ethyl 4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate (13.2)

To a solution of NaI (4.08 g, 27.2 mmol, 6 eq) in MeCN (15 mL) was added TMSCl (2.96 g, 27.2 mmol, 3.45 mL, 6 eq) under N_2. The mixture was stirred at 20 °C for 10 min. A solution of ethyl 4-[(3-chlorophenyl)-hydroxy-methyl]-1,5-dimethyl -pyrazole-3-carboxylate **13.1** (1.40 g, 4.53 mmol, 1 eq) in MeCN (10 mL) was added dropwise to the mixture. The reaction was stirred at 20 °C for another 2 h under N_2. The reaction mixture was diluted with EtOAc (100 mL). The organic layer was washed with 10% aqueous Na_2SO_3 solution (aq. 50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient elution of 0 to 50% ethyl acetate/petroleum ether @ 75 mL/min) to furnish ethyl 4-[(3-chlorophenyl) methyl]-1,5-dimethyl-pyrazole-3-carboxylate **13.2** (1.20 g, 4.10 mmol, 90 % yield) as a colorless oil.

Step 3



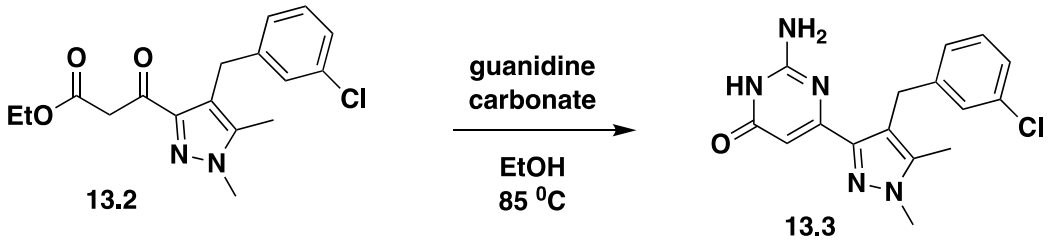
13.2 **13.2**

Ethyl 3-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-3-oxo-propaneate (13.2)

To a solution of EtOAc (2.53 g, 28.7 mmol, 2.81 mL, 7 eq) in THF (5 mL) was added NaH (492 mg, 12.3 mmol, 60 % wt dispersion in oil, 3 eq) at 0 °C. The mixture was stirred at 0 °C for 5 min. Ethyl 4-[(3-chlorophenyl)methyl]-1,5-dimethyl –pyrazole-3-carboxylate **13.2** (1.20 g, 4.10 mmol, 1 eq) in THF (8 mL) was added to the mixture at 0 °C. The mixture was stirred at 60 °C for another 35 min under N_2. The reaction mixture was poured into saturated ammonium chloride solution (150 mL). The mixture was extracted with ethyl acetate (50 mL*3). The organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 to 20% ethyl acetate/petroleum ether @ 72 mL/min) to furnish ethyl 3-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-3- oxo-propanoate **13.2** (0.90 g, 2.69 mmol, 66 % yield) was obtained as a light yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.18-7.04 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.09 (s, 2H), 4.01 (s, 2H), 3.82 (s, 3H), 2.17 (s, 3H), 1.27-1.23 (m, 3H)

Step 4

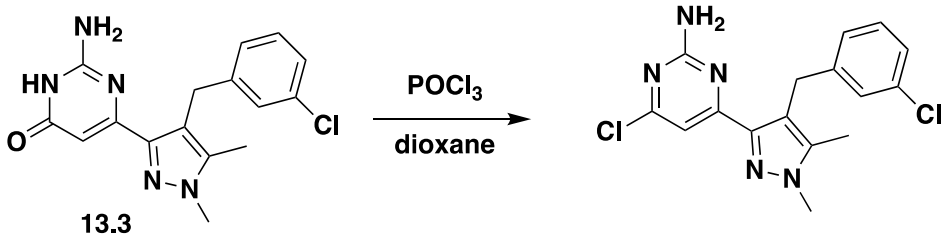


2-amino-4-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-1H-pyrimidin-6-one (13.3)

To a solution of ethyl 3-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl] -3-oxo-propanoate **13.2** (500 mg, 1.49 mmol, 1 eq) in EtOH (10 mL) was added guanidine carbonate (807 mg, 4.48 mmol, 3 eq). The mixture was stirred at 85 °C for 12 h under N_2. The reaction mixture was diluted with water (10 mL). The mixture was concentrated under reduced pressure to remove the EtOH at which time a white precipitate formed. The pH of the mixture was adjusted to 5 by addition of aq. HCl solution (1 N). The white precipitate was collected by filtration and dried under reduced pressure to furnish 2-amino-4-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-

pyrazol-3-yl]-1H-pyri midin-6-one **13.3** (0.45 g, crude) as a white solid. The crude product will be used directly in next step without further purification.

Step 5



Compound 13

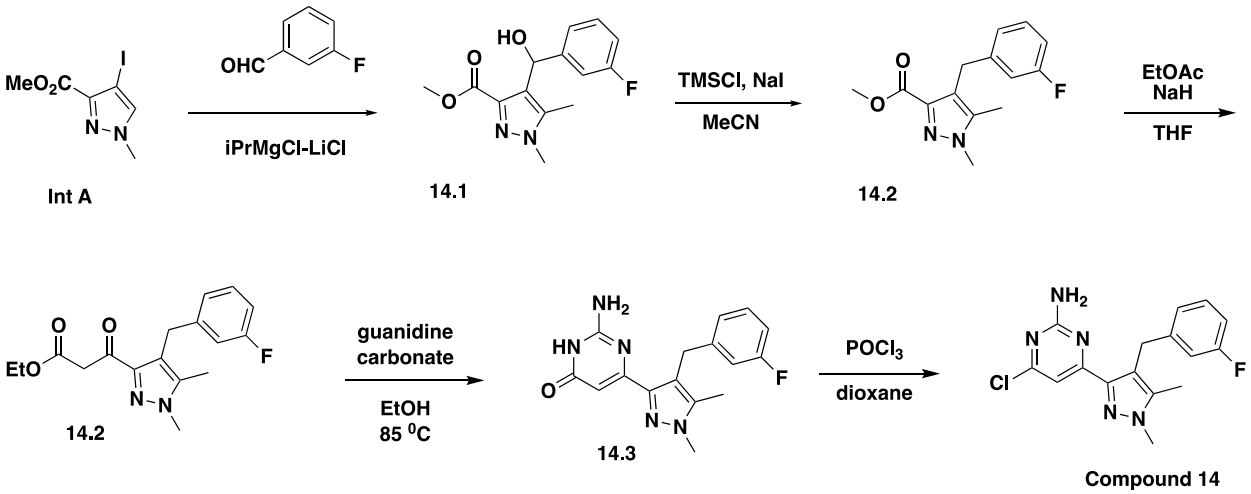
4-chloro-6-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]pyrimidin-2-amine (Comound 13)

To a solution of 2-amino-4-[4-[(3-chlorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]- 1H-pyrimidin-6-one **13.3** (0.45 g, 1.36 mmol, 1 eq) in dioxane (7 mL) was added $POCl_3$ (3.14 g, 20.5 mmol, 1.90 mL, 15 eq). The mixture was stirred at 75 °C for 1.5 h under N_2. The reaction mixture was poured into saturated sodium bicarbonate (80 mL). The mixture was extracted with ethyl acetate (30 mL*3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to furnish a residue (400 mg). The residue was purified by gradient flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, gradient elution of 0 to 20% ethyl acetate/petroleum ether @ 75 mL/min) to furnish **Compound 13** (130 mg, crude). The compound was purified by preparative-HPLC (column: Welch Xtimate C18 150 * 25mm * 5 mm; mobile phase: [water(10mM NH_4HCO_3) -ACN];B%: 50%-70% ,9min) to give 4-chloro-6-[4-[(3-chlorophenyl)methyl]-1,5- dimethyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 13** (68 mg, 0.19 mmol, 14 % yield) as a white solid.

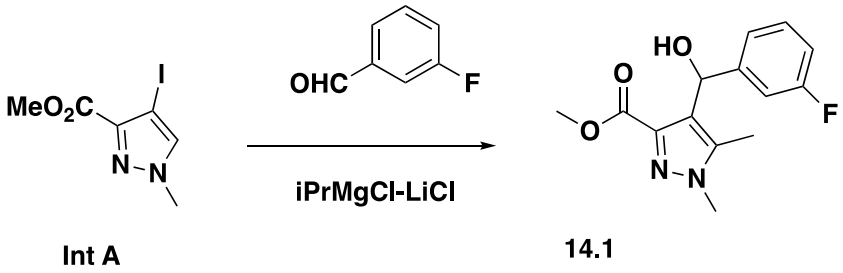
LCMS: Calc'd for $C_{16}H_{16}N_5Cl_2$ ($M+H^+$) 348.1; Found: 348.0

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.27-7.24 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.17-7.13 (m, 2H), 7.05 (s, 2H), 6.99 (s, 1H), 4.32 (s, 2H), 3.80 (s, 3H), 2.23 (s, 3H)

Preparation of Compound 14



Step 1

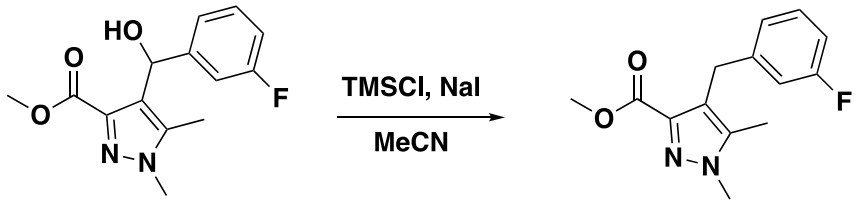


Ethyl 1,5-dimethylpyrazole-3-carboxylate (14.1)

To a stirred mixture of ethyl 5-methyl-1H-pyrazole-3-carboxylate **Int A** (5.00 g, 32.4 mmol, 1 *eq*) in DMF (50 mL) was added Cs_2CO_3 (12.7 g, 38.9 mmol, 1.2 *eq*). Methyl iodide (5.52 g, 38.9 mmol, 2.42 mL, 1.2 *eq*) was added dropwise to the reaction. The mixture was stirred at 15 °C for 12 hr under N_2. The reaction mixture was diluted with water (100 mL) and $NH_3.H_2O$ (25%, 2.0 mL). The solution was extracted with EtOAc (80 mL*3). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient eluent of 0 to 20% ethyl acetate/petroleum ether gradient @ 75 mL/min) to furnish ethyl 1,5- dimethylpyrazole-3-carboxylate **14.1** (2.00 g, 11.9 mmol, 37 % yield) as a colorless oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 6.56 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.29 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H)

Step 2



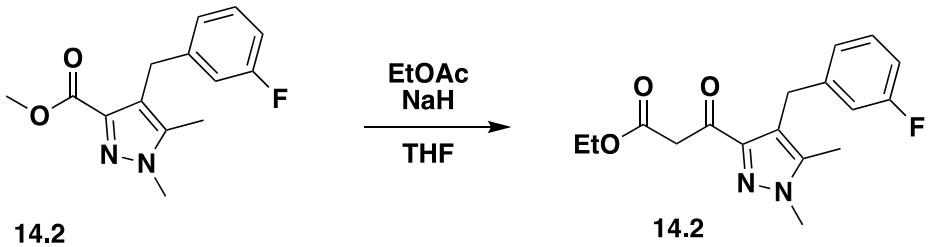
14.1 14.2

Ethyl 4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate (14.2)

To a solution of NaI (3.69 g, 24.6 mmol, 6 *eq*) in MeCN (30 mL) was added TMSCl (2.68 g, 24.6 mmol, 3.13 mL, 6 *eq*) under N_2. After 10 min of stirring at 15 °C, a solution of ethyl 4- [(3-fluorophenyl) -hydroxy-methyl]-1,5-dimethyl - pyrazole -3 -carboxylate **14.1** (1.20 g, 4.11 mmol, 1 *eq*) in MeCN (10 mL) was added. The mixture was stirred at 15 °C under N_2 for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 (100 mL). The mixture was extracted with EtOAc (80 mL*3). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, gradient elution of 0 to 30% ethyl acetate/petroleum ether @ 75 mL/min) to furnish ethyl 4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazole-3 -carboxylate **14.2** (1.00 g, 3.62 mmol, 88 % yield) as a slightly yellow oil.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.32-7.23 (m, 1H), 7.02-6.88 (m, 3H), 4.24-4.17 (m, 2H), 4.03 (s, 2H), 3.82-3.78 (m, 3H), 2.20 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H)

Step 3



14.2 14.2

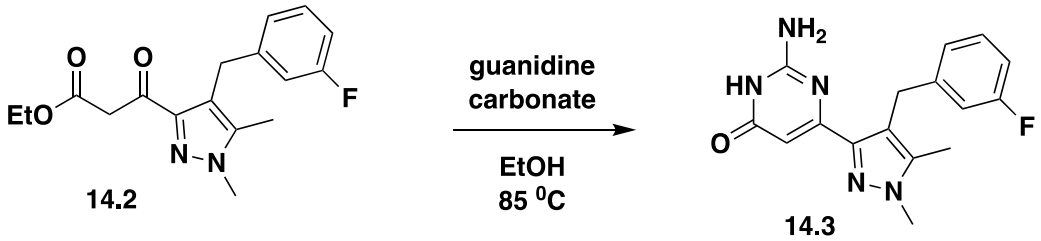
Ethyl 3-[4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-3-oxo-propanoate (14.3)

A mixture of EtOAc (2.23 g, 25.3 mmol, 2.48 mL, 7 *eq*) in THF (10 mL) was cooled to 0 °C. Sodium hydride (434 mg, 10.86 mmol, 60 wt % dispersion in oil, 3 *eq*) was added. After stirring for 2 min, ethyl 4-[(3-fluorophenyl) methyl]-1,5-dimethyl-pyrazole-3- carboxylate **14.2** (1.00 g, 3.62 mmol,

1 *eq*) in THF (5 mL) was added dropwise at 0 °C. The mixture was stirred at 70 °C for 2 h under N_2. The reaction mixture was quenched with saturated aqueous NH_4Cl (80 mL). The mixture was extracted with EtOAc (80 mL*3). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 to 15% ethyl acetate/petroleum ether @ 75 mL/min) to furnsih ethyl 3-[4-[(3-fluorophenyl) methyl]-1,5- dimethyl- pyrazol-3-yl]-3-oxo-propanoate **14.2** (800 mg, 2.51 mmol, 69 % yield) as a yellow oil.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.31-7.23 (m, 1H), 7.02-6.88 (m, 3H), 4.12-4.03 (m, 4H), 3.96 (s, 2H), 3.83 (s, 3H), 2.21 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H)

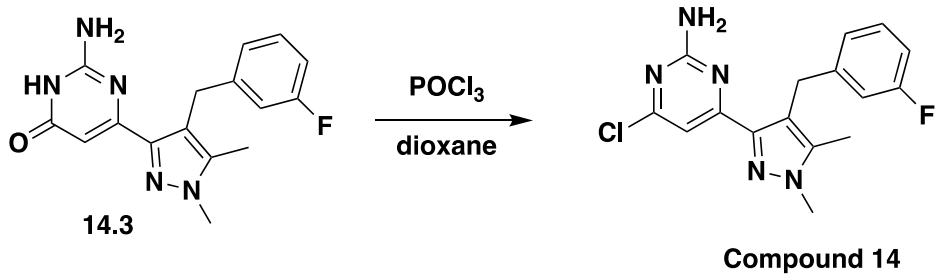
Step 4



2-amino-4-[4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-1H-pyrimidin-6-one (14.3)

To a solution of ethyl 3-[4-[(3-fluorophenyl) methyl] -1,5-dimethyl-pyrazol-3-yl] -3-oxo-propanoate **14.2** (800 mg, 2.51 mmol, 1 *eq*) in EtOH (10 mL) was added guanidine carbonate (1.36 g, 7.54 mmol, 3 *eq*). The mixture was stirred at 85 °C for 18 hr under N_2. The reaction mixture was diluted with water (10 mL) and then concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 5 with HCl (4N). The mixture was filtered, and the filter cake was dried under reduced pressure to furnish 2-amino-4-[4-[(3-fluorophenyl) methyl]-1,5-dimethyl-pyrazol-3-yl]-1H-pyrimidin-6-one **14.3** (700 mg, crude) as a white solid.

Step 5



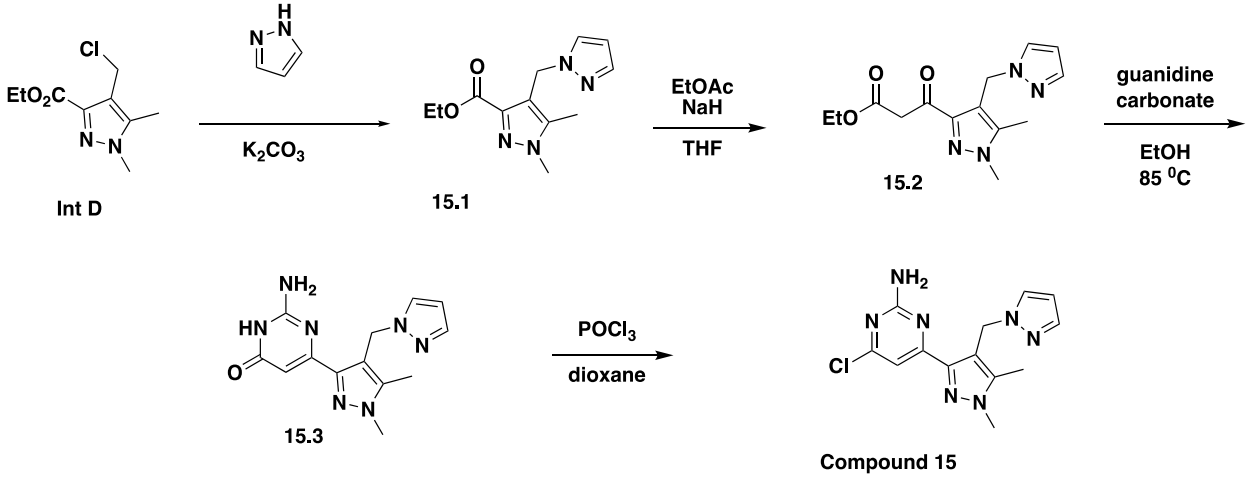
4-chloro-6-[4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]pyrimidin-2-amine (Compound 14)

$POCl_3$ (5.14 g, 33.5 mmol, 3.11 mL, 15 *eq*) was added into a solution of 2-amino-4-[4-[(3-fluorophenyl)methyl]-1,5-dimethyl-pyrazol-3-yl]-1H-pyrimidin-6-one **14.3** (700 mg, 2.23 mmol, 1 *eq*) in dioxane (10 mL). The mixture was heated to 75°C for 4.5 hours under N_2. The reaction mixture was concentrated under reduced pressure to remove $POCl_3$. The pH of the mixture was adjusted to 7 by addition of ab aqueous NaOH solution (1 N). The reaction mixture was extracted with EtOAc (40 mL*3). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, gradient elution of 0 to 20% ethyl acetate/petroleum ether @ 75 mL/min) to furnish crude **14** (300 mg). The residue was further purified by preparative-HPLC (column: Phenomenex Gemini-NX 150 * 30mm * 5 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 43%-63%) to furnish 4-chloro-6-[4-[(3-fluorophenyl) methyl] -1,5-dimethyl-pyrazol-3-yl]pyrimidin-2-amine **Compound 14** (81 mg, 0.23 mmol, 10 % yield) as a white solid.

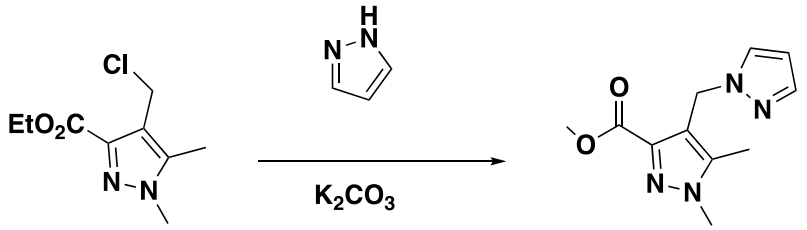
LCMS: Calc'd for $C_{16}H_{16}N_5ClF$ ($M+H^+$) 332.1; Found: 332.1

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.26-7.19 (m, 1H), 7.09-7.00 (m, 4H), 6.98 (s, 1H), 6.91 (dt, *J* = 2.1, 8.5 Hz, 1H), 4.32 (s, 2H), 3.79 (s, 3H), 2.22 (s, 3H)

Preparation of Compound 15



Step 1



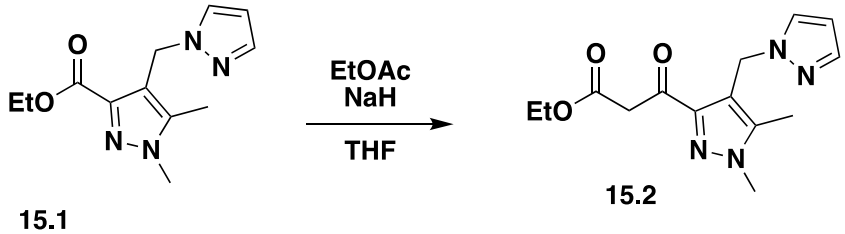
Int D 15.1

Ethyl 1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazole-3-carboxylate (15.1)

To a solution of ethyl 4-(chloromethyl)-1,5-dimethyl-pyrazole-3-carboxylate **Int D** (1.70 g, 7.85 mmol, 1 eq) and 1H-pyrazole (588 mg, 8.63 mmol, 1.1 eq) in DMF (25 mL) was added K_2CO_3 (2.71 g, 19.6 mmol, 2.5 eq). The mixture was stirred at 50 °C for 6 hr and then at 60 °C for 4 hr. The mixture was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 1/1) to furnish ethyl 1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazole-3-carboxylate 15.1 (2 g, crude) as a colorless oil.

^{1}H NMR: (METHANOL-d_4, 400 MHz) δ 7.59 (d, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 6.25 (t, *J* = 1.8 Hz, 1H), 5.45 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.31 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H)

Step 2

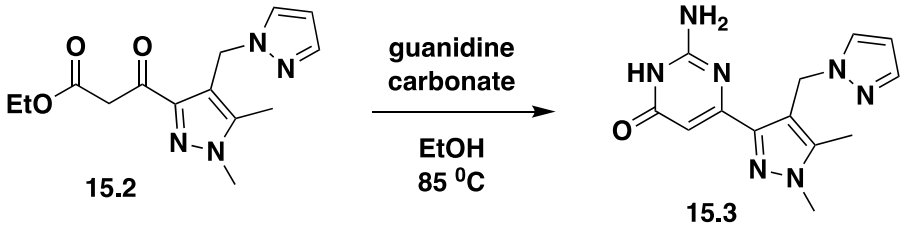


15.1 15.2

Ethyl 3-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate (15.2)

To a solution of EtOAc (4.47 g, 50.8 mmol, 4.97 mL, 7 eq) in THF (20 mL) was added NaH (870 mg, 21.8 mmol, 60 wt % dispersion in oil, 3 eq). The mixture was stirred at 15 °C for 10 min. Ethyl 1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazole-3-carboxylate **15.1** (1.80 g, 7.25 mmol, 1 eq) was added. The mixture was stirred at 15 °C for 50 min. The reaction mixture was with MeOH (20 mL). The mixture was concentrated under reduced pressure. The residue was purified by gradient flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, gradient eluention of 0 to 50% ethyl acetate/petroleum ether @ 40 mL/min) to furnish ethyl 3-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]-3-oxo- propanoate 15.2 (420 mg) as a yellow oil.

Step 3

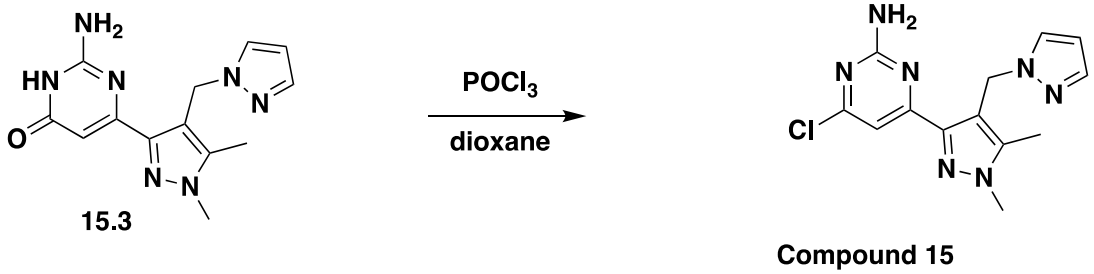


2-amino-4-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (15.3)

To a solution of ethyl 3-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate **15.2** (370 mg, 1.27 mmol, 1 eq) in EtOH (10 mL) was added guanidine carbonate (689 mg, 3.82 mmol, 3 eq). The mixture was stirred at 85 °C for 16 hr. The reaction mixture was filtered. The filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase MPLC (HCl condition, SiO_2, gradient elution of 0 to 25% H_2O/methanol) to furnish 2-amino-4-[1,5-dimethyl-4-(pyrazol-1-ylmethyl) pyrazol-3-yl]-1H-pyrimidin-6-one 15.3 (260 mg) as a white solid.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ 8.39 (br s, 2H), 7.75 (s, 1H), 7.46 (s, 1H), 6.37 (s, 1H), 6.24 (s, 1H), 5.34 (s, 2H), 3.85 (s, 3H), 2.35 (s, 3H)

Step 4



4-chloro-6-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 15)

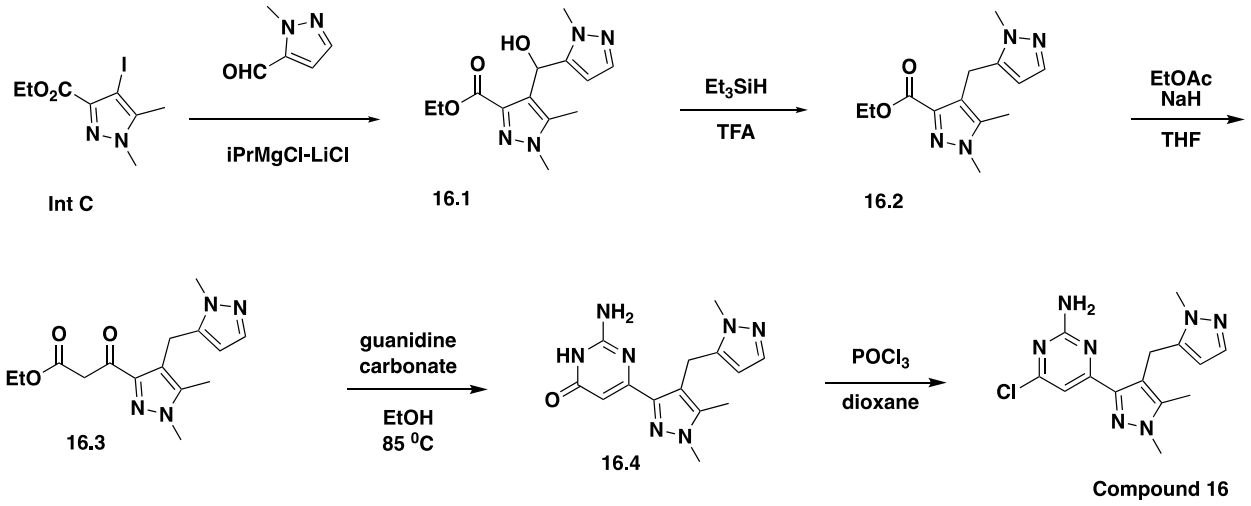
To a solution of 2-amino-4-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]-1H-pyrimidin- 6-one 15.3 (170 mg, 0.596 mmol, 1 eq) in dioxane (3 mL) was added $POCl_3$ (1.10 g, 7.15 mmol, 0.665 mL, 12 eq). The mixture was stirred at 60 °C for 10 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (30 mL). The mixture was extracted with EtOAc (30 mL x 3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue

was purified by preparative-HPLC (HCl condition, column: Phenomenex luna C18 250 * 50mm * 10 mm; mobile phase: [water (0.05%HCl)-ACN];B%: 20%-50%,10min) to furnish 4-chloro-6-[1,5-dimethyl-4-(pyrazol-1-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 15** (6.5 mg) as a white solid.

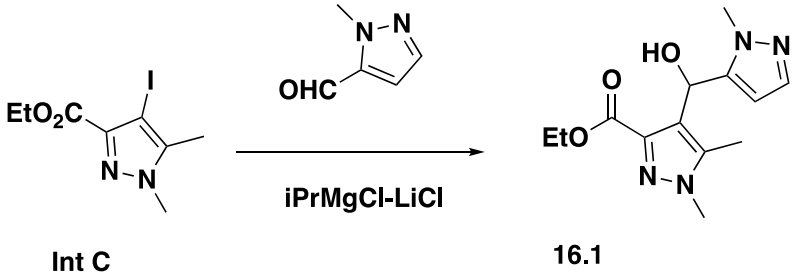
LCMS: Calc'd for $C_{13}H_{15}N_7Cl$ ($M+H^+$) 304.1; Found: 304.1

^{1}H NMR: (DMSO-d_6, 400 MHz) δ 7.81 (s, 1H), 7.34 (s, 1H), 7.00 (d, *J* = 1.6 Hz, 1H), 6.12 (br d, *J* = 1.8 Hz, 1H), 5.65 (s, 2H), 3.79 (br d, *J* = 1.3 Hz, 3H), 2.33 (s, 3H)

Preparation of Compound 16



Step 1



Ethyl 4-[hydroxy-(2-methylpyrazol-3-yl)methyl]-1,5-dimethyl-pyrazole-3-carbox

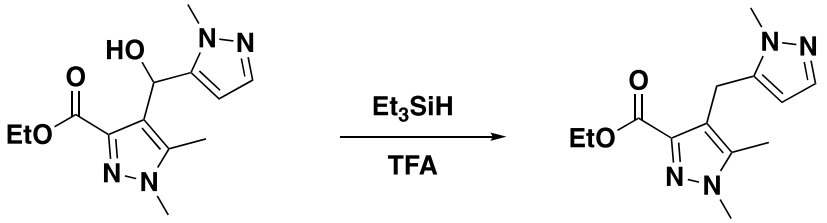
Ylate (16.1)

To a solution of ethyl 4-iodo-1,5-dimethyl-pyrazole-3-carboxylate **Int C** (900 mg, 3.06 mmol, 1 eq) in THF (15 mL) was added isopropylmagnesium chloride-lithium complex (1.30 M, 2.47 mL, 1.05 eq) at -10 °C. After stirring at -10 °C for 0.5 h, a solution of 2-methylpyrazole-3-carbaldehyde (371 mg, 3.37 mmol, 1.1 eq) in THF (3 mL) was added dropwise. After the addition, the mixture

was allowed to warm slowly to 15 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with sat. aqueous NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (50 mL*3). The organic layer was washed with brine (70 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 2:3 to 0:1) to furnish ethyl 4-[hydroxy-(2-methylpyrazol-3-yl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate **16.1** (0.9 g) as a yellow oil.

^{1}H NMR: (chloroform-d, 400 MHz) δ 5.81 (br d, *J* = 8.2 Hz, 1H), 5.64 (d, *J* = 1.3 Hz, 1H), 5.59-5.50 (m, 1H), 5.29 (s, 1H), 4.44-4.36 (m, 2H), 4.00 (s, 3H), 3.88 (s, 3H), 2.18 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H)

Step 2



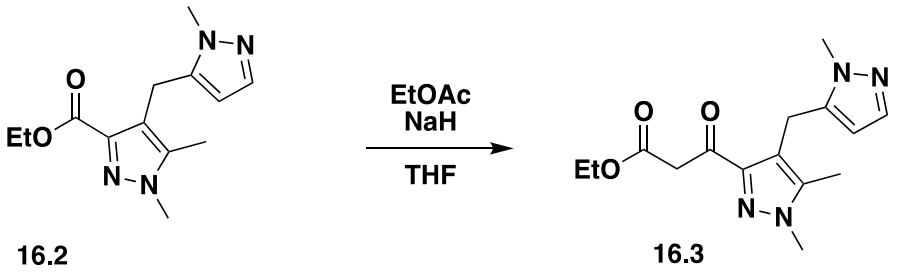
16.1 16.2

Ethyl 1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazole-3-carboxylate (16.2)

To a stirred mixture of ethyl 4-[hydroxy-(2-methylpyrazol-3-yl)methyl]-1,5-dimethyl-pyrazole-3-carboxylate **16.1** (790 mg, 2.84 mmol, 1 eq) in TFA (8 mL) was cooled to 0 °C . Triethylsilane (3.30 g, 28.4 mmol, 4.53 mL, 10 eq) was added. The mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with sat. aq $NaHCO_3$. The solution was extracted with EtOAc (30 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 7/13) to afford ethyl 1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazole-3-carboxylate **16.2** (800 mg) as yellow a oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.32 (d, *J* = 1.8 Hz, 1H), 5.75 (d, *J* = 1.6 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.14 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H)

Step 3



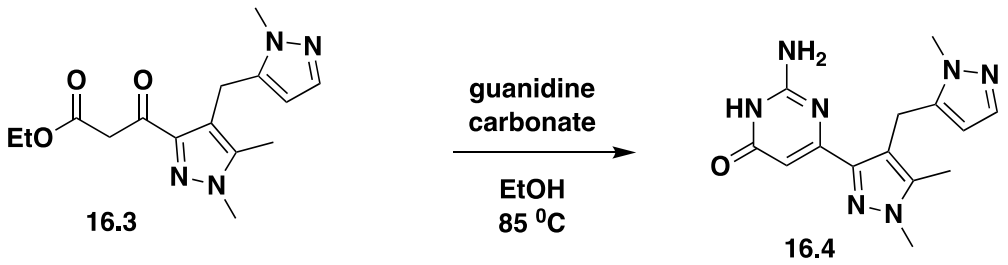
16.2 16.3

Ethyl 3-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]-3-oxo-propanoate (16.3)

To a stirrred mixture of EtOAc (1.65 g, 18.7 mmol, 1.83 mL, 7 eq) in THF (10 mL) was added NaH (320 mg, 8.01 mmol, 60 wt % dispersion in oil, 3 eq) at 0 °C. Ethyl 1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazole-3-carboxylate **16.2** (700 mg, 2.67 mmol, 1 eq) in THF (3 mL) was added into the mixture. The mixture was stirred at 70 °C for 1 h. The reaction mixture was poured into aq. saturated NH_4Cl (100 mL) and extracted with EtOAc (40mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1) to furnish ethyl 3-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]-3-oxo-propanoate **16.3** (600 mg) as yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.23 (d, *J* = 1.7 Hz, 1H), 5.71 (d, *J* = 1.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 3.93 (s, 2H), 3.75 (d, *J* = 6.2 Hz, 6H), 2.05 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H)

Step 4



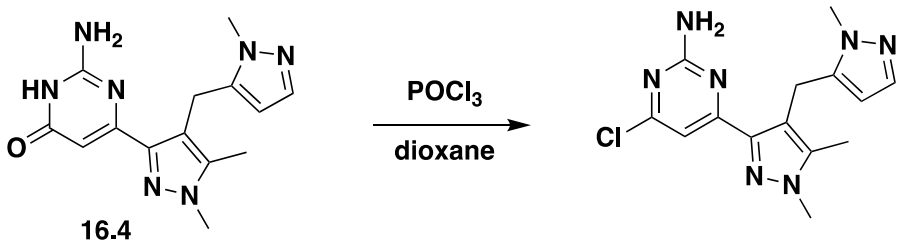
16.3 16.4

2-amino-4-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]-1H-pyrimidin-6-one (16.4)

To a stirred mixture of ethyl 3-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazo l-3-yl]-3-oxo-propanoate **16.4** (500 mg, 1.64 mmol, 1 eq) in EtOH (5 mL) was added guanidine carbonate (889 mg, 4.93 mmol, 3 eq). The mixture was stirred at 85 °C for 24 h. The reaction mixture was diluted with water (10 mL) and concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 5 by addition of aqueous HCl (4N). The mixture

was filtered, and the filter cake was dried under the reduced pressure to furnish 2-amino-4-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]-1H-pyrimidin-6-one **16.4** (400 mg, crude) as a white solid. The material was directly used in next step without purification.

Step 5



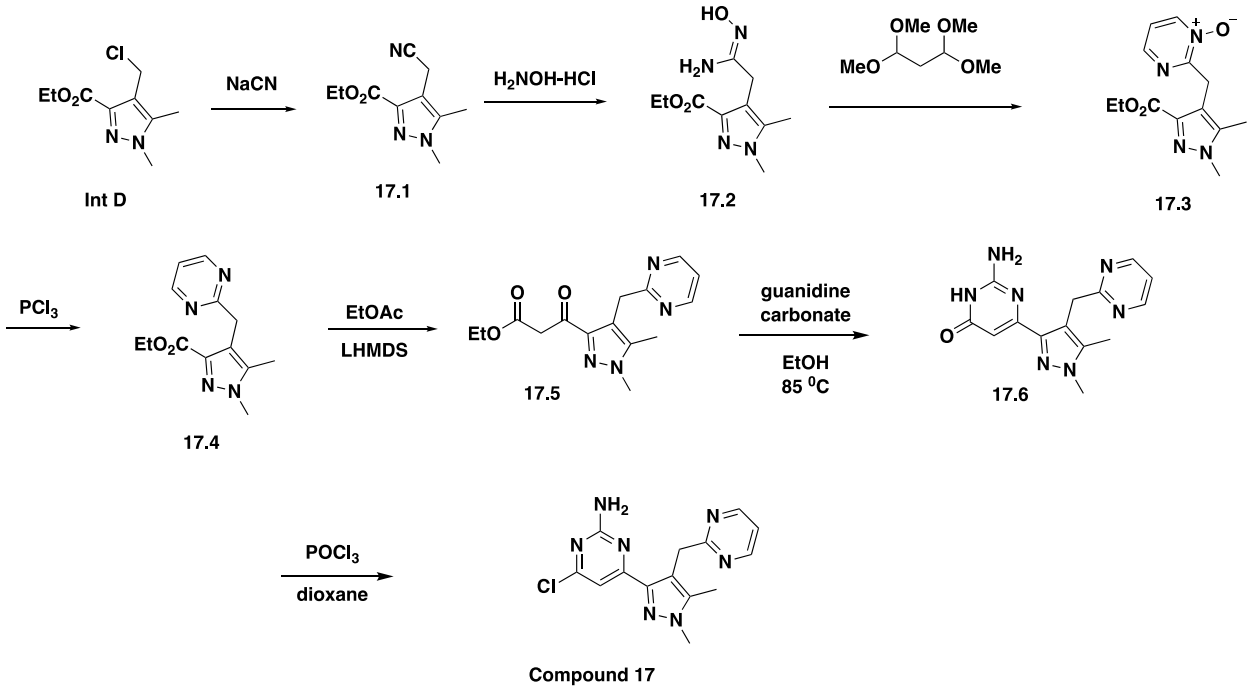
4-chloro-6-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]pyrimidin-2-amine (Compound 16)

To a solution of 2-amino-4-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]-1H-pyrimidin-6-one **16.4** (360 mg, 1.20 mmol, 1 eq) in dioxane (7 mL) was added $POCl_3$ (2.77 g, 18.0 mmol, 1.68 mL, 15 eq) dropwise. The reaction mixture was stirred at 75 °C for 1 h under N_2. The reaction mixture was added slowly to sat. aq. $NaHCO_3$ to quench the excess $POCl_3$. The solution was extracted with EtOAc (60 mL*3). The organic layer was washed with brine (80 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by neutral preparative-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40mm * 10 mm; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 15%-40%, 10min) to furnish 4-chloro-6-[1,5-dimethyl-4-[(2-methylpyrazol-3-yl)methyl]pyrazol-3-yl]pyrimidin-2-amine **Compound 16** (19 mg) as a white solid.

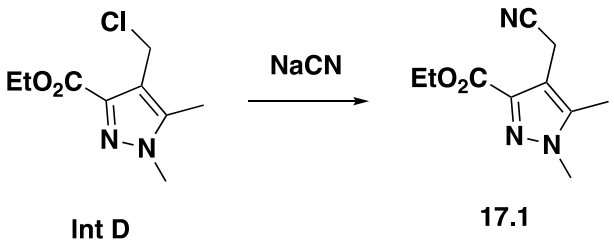
LCMS: Calc'd for $C_{14}H_{17}N_7Cl$ ($M+H^+$) 318.1; Found: 318.1

^{1}H NMR: (DMSO-d6, 400 MHz) δ 7.16 (d, *J* = 1.6 Hz, 1H), 7.04 (s, 2H), 6.99 (s, 1H), 5.73 (d, *J* = 1.5 Hz, 1H), 4.39 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 2.14 (s, 3H)

Preparation of Compound 17



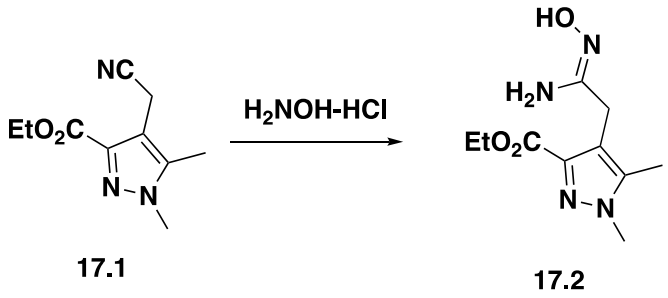
Step 1



Ethyl 4-(cyanomethyl)-1,5-dimethyl-pyrazole-3-carboxylate (17.1)

To a stirred mixture of ethyl 4-(chloromethyl)-1,5-dimethyl-pyrazole-3-carboxylate **Int D** (6.35 g, 29.3 mmol, 1 eq) in DMF (60 mL) was cooled to 0 °C. Sodium cyanide (1.72 g, 35.2 mmol, 1.2 eq). KI (5.84 g, 35.2 mmol, 1.2 eq) were added to the reaction. Then the mixture was stirred at 70 °C for 12 h. The reaction mixture was diluted with water (150 mL), and the pH was adjusted to 11 by addition of aq. NaOH (4M). The solution was extracted with DCM (60 mL*6). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/1) to furnish ethyl 4-(cyanomethyl)-1,5-dimethyl-pyrazole-3-carboxylate **17.1** (1.30 g, 5.33 mmol, 18 % yield) as a yellow solid.

Step 2



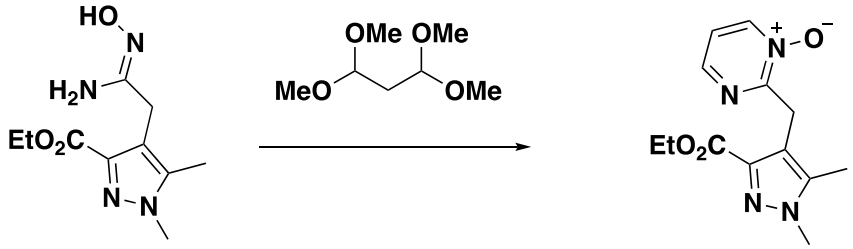
17.1 17.2

Ethyl 4-[(2Z)-2-amino-2-hydroxyimino-ethyl]-1,5-dimethyl-pyrazole-3-carboxyl Ate (17.2)

To a solution of ethyl 4-(cyanomethyl)-1,5-dimethyl-pyrazole-3-carboxylate **17.1** (800 mg, 3.86 mmol, 1 eq) in EtOH (8 mL) was added $NaHCO_3$ (341 mg, 4.05 mmol, 0.158 mL, 1.05 eq) and $NH_2OH{\cdot}HCl$ (282 mg, 4.05 mmol, 1.05 eq) at 25 °C. The mixture was stirred at 70 °C for 12 h. More $NH_2OH{\cdot}HCl$ (140 mg) and $NaHCO_3$ (150 mg) were added, and the mixture was stirred at 70 °C for 12 h. The reaction mixture was concentrated under the reduced pressure to remove the solvent. The reaction mixture was filtered, and the residue was washed with ethyl acetate (10 mL*5) and EtOH (10 mL*5). Then the filtrate was concentrated under the reduced pressure to furnish ethyl 4-[(2Z)-2-amino-2-hydroxyimino-ethyl]-1,5-dimethyl-pyrazole-3-carboxylate **17.2** (900 mg, 3.45 mmol, 89 % yield) as a yellow solid.

^{1}H NMR: (DMSO-d6, 400 MHz) δ 8.83 (s, 1H), 5.19 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 3.36 (s, 2H), 2.18 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H)

Step 3



17.2 17.3

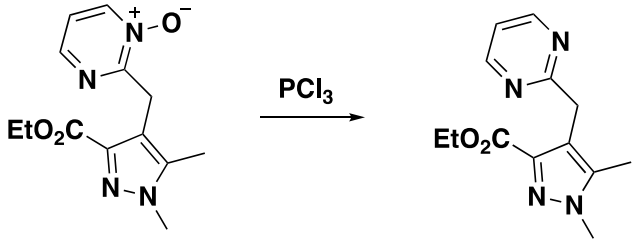
Ethyl 1,5-dimethyl-4-[(1-oxidopyrimidin-1-ium-2-yl)methyl]pyrazole-3-carboxyl Ate (17.3)

To a stirred mixture of ethyl 4-[(2Z)-2-amino-2-hydroxyimino-ethyl]-1,5-dimethyl-pyrazole-3-carboxylate **17.2** (900 mg, 3.75 mmol, 1 eq), 1,1,3,3-tetramethoxypropane (1.23 g, 7.49 mmol,

1.24 mL, 2 eq) and TFA (513 mg, 4.50 mmol, 0.333 mL, 1.2 eq) in 2-propanol (18 mL) was heated at 90 °C for 12 h. The pH of the mixture was adjusted to 7 by addition of sat. aq $NaHCO_3$. The solution was concentrated under reduced pressure. The residue was purified via preparative-HPLC (column: Welch Xtimate C18 250 * 50mm * 10 mm; mobile phase: [water(0.04% NH_3H_2O/10 mM NH_4HCO_3)-ACN];B%: 5%-30%,10min) to furnish ethyl 1,5-dimethyl-4-[(1-oxi)dopyrimidin-1-ium-2-yl)methyl]pyrazole-3-carboxylate **17.3** (400 mg, 1.45 mmol, 39 % yield) as a yellow oil.

^{1}H NMR: (DMSO-d6, 400 MHz) δ 8.62 (dd, *J* = 1.5, 6.6 Hz, 1H), 8.10 (dd, *J* = 1.4, 4.6 Hz, 1H), 7.42 (dd, *J* = 4.7, 6.4 Hz, 1H), 4.29 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.18 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H)

Step 4



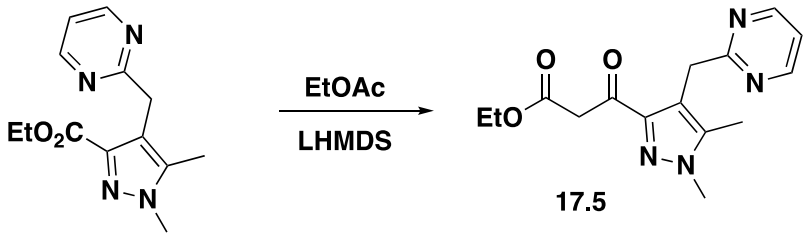
17.3 **17.4**

Ethyl 1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazole-3-carboxylate (17.4)

PCl_3 (418 mg, 3.04 mmol, 2.1 eq) was added into a solution of ethyl 1,5-dimethyl-4-[(1-oxidopyrimidin-1-ium-2-yl)methyl]pyrazole-3-carboxylate **17.3** (400 mg, 1.45 mmol, 1 eq) in chloroform (8 mL) at 25 °C. The mixture was stirred at 75 °C for 35 min. The reaction mixture was diluted with sat. aq $NaHCO_3$ (100 mL). The solution was extracted with ethyl acetate (40 mL*6) and dimethyl tetrahydrofuran (40 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 2/1 to 0/1 and then with 10% MeOH additive) to furnish ethyl 1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazole-3-carboxylate **17.4** (300 mg) as a yellow solid.

^{1}H NMR: (DMSO-d6, 400 MHz) δ 8.65 (d, *J* = 4.9 Hz, 2H), 7.28 (t, *J* = 4.9 Hz, 1H), 4.29 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.18 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H)

Step 5



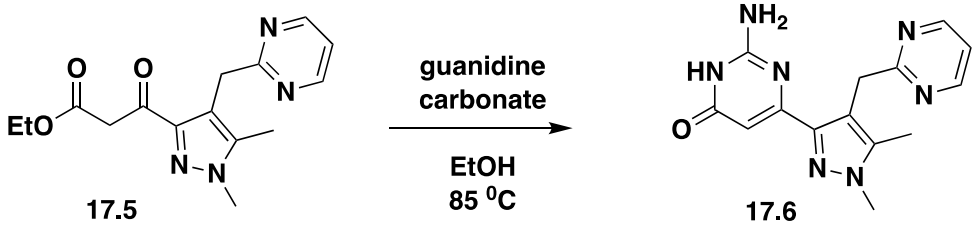
17.4 17.5

Ethyl 3-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate (17.5)

To a solution of ethyl 1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazole-3-carboxylate 17.4 (250 mg, 0.960 mmol, 1 eq) in THF (3 mL) was cooled to -40 °C. Ethyl acetate (592 mg, 6.72 mmol, 0.658 mL, 7 eq) was added to the mixture under N_2. LiHMDS (1 M, 2.88 mL, 3 eq)was added to the solution at -40 °C and stirred at that temperature for 2 h. The reaction mixture was diluted with sat. aq NH_4Cl solution (30 mL). The solution was extracted with ethyl acetate (40 mL*5). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1:0 to 24:1) to furnish ethyl 3-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate 17.5 (100 mg) as a colorless oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 8.55 (d, *J* = 5.0 Hz, 2H), 7.01 (t, *J* = 4.9 Hz, 1H), 4.39 (s, 2H), 4.13-4.07 (m, 2H), 3.92 (s, 2H), 3.77 (s, 3H), 2.13 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H)

Step 6



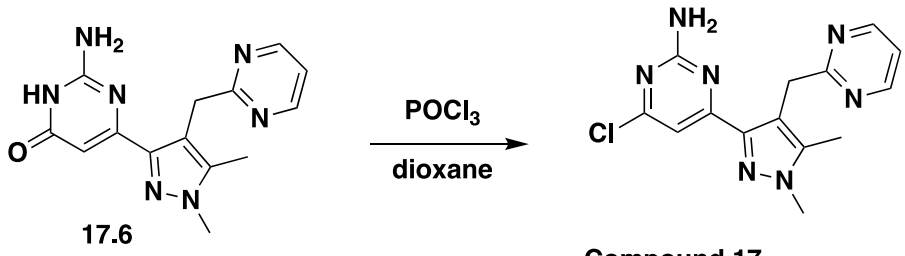
17.5 17.6

2-amino-4-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (17.6)

Ethyl 3-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-3-oxo-propanoate 17.5 (80 mg, 0.26 mmol, 1 eq) and guanidine carbonate (143 mg, 0.793 mmol, 3 eq) were taken up in anhydrous EtOH (1 mL). The mixture was stirred for 36 h at 85 °C under N_2 at which time a white precipitate formed. The reaction mixture was concentrated under the reduced pressure to remove the EtOH, and the residue was diluted with water (5 mL). The pH of the solution was adjusted to 5

by addition of aqueous HCl (1N). The mixture was filtered, and the solid was dried under the reduced pressure to furnish 2-amino-4-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one **17.6** (40 mg, crude) as a white solid.

Step 7



Compound 17

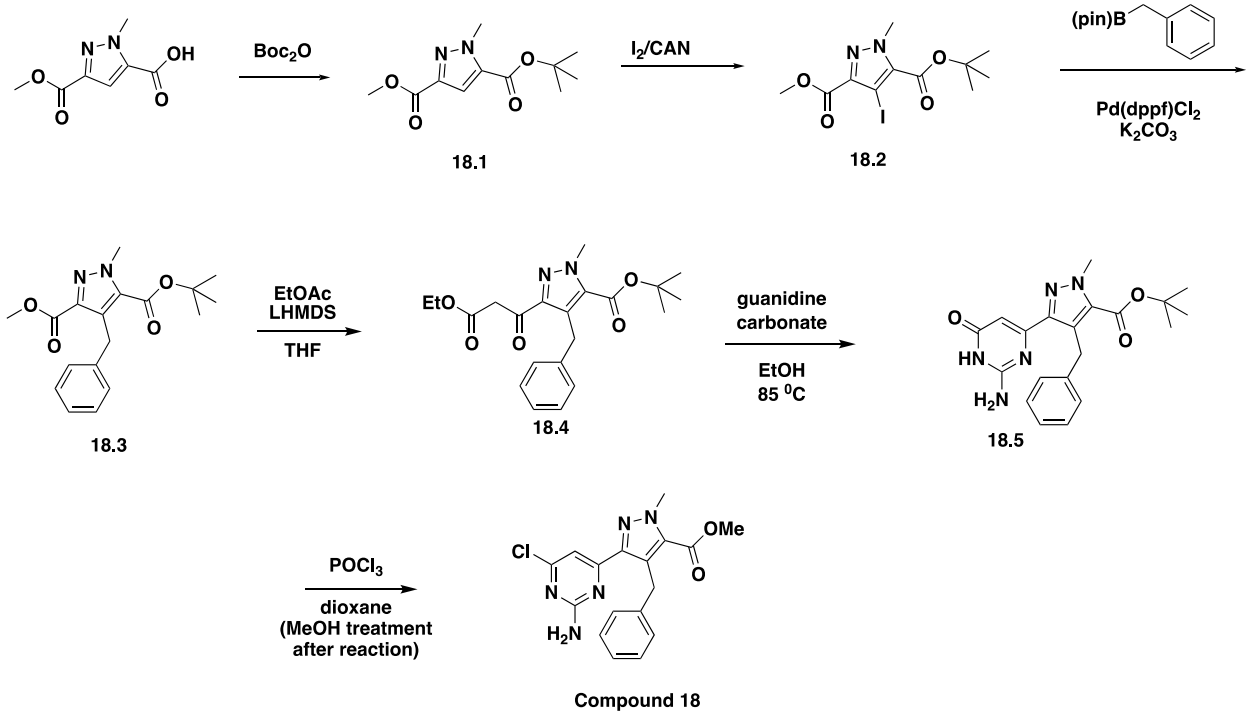
4-chloro-6-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine (Compound 17)

$POCl_3$ (193 mg, 1.26 mmol, 0.117 mL, 15 eq) was added into a solution of 2-amino-4-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]-1H-pyrimidin-6-one (25 mg, 0.084 mmol, 1 eq) and Et_3N (26 mg, 0.25 mmol, 35 uL, 3 eq) in MeCN (2 mL) at 25 °C. The mixture was heated to 75 °C and stirred for 4 h. The reaction mixturewas added slowly to aq. $NaHCO_3$ (saturated, 40 mL) to quench the excess $POCl_3$. The solution was extracted with ethyl acetate (20 mL*5). The combined organic layer was washed with brine (60 mL), dried over Na_2SO_4,and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by preparative-HPLC (column: Waters Xbridge BEH C18 100 * 30mm * 10 mm; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 15%-40%,10min) to afford 4-chloro-6-[1,5-dimethyl-4-(pyrimidin-2-ylmethyl)pyrazol-3-yl]pyrimidin-2-amine **Compound 17** (6.5 mg) as a white solid.

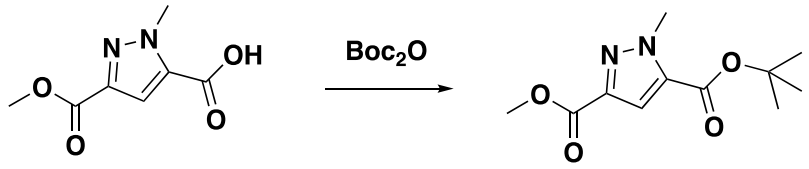
LCMS: Calc'd for $C_{14}H_{15}N_7Cl$ ($M+H^+$) 316.1; Found: 316.1

^{1}H NMR: (DMSO-d6, 400 MHz) δ 8.64 (d, *J* = 4.9 Hz, 2H), 7.26 (t, *J* = 4.8 Hz, 1H), 6.99 (s, 1H), 6.80 (br s, 2H), 4.63 (s, 2H), 3.79 (s, 3H), 2.09 (s, 3H)

Preparation of **Compound 18**



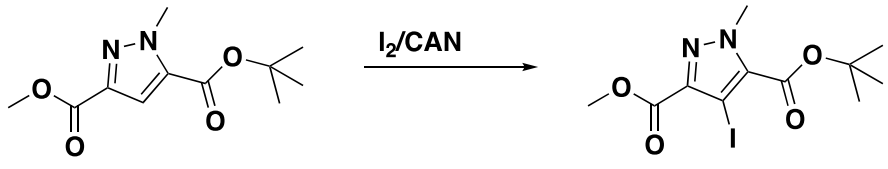
Step 1



O^5-tert-butyl-O^3-methyl-1-methylpyrazole-3,5-dicarboxylate (18.1)

To a suspension of 5-methoxycarbonyl-2-methyl-pyrazole-3-carboxylic acid (5.25 g, 28.5 mmol, 1 eq) and DMAP (697 mg, 5.70 mmol, 0.2 eq) in t-BuOH (100 mL) and THF (100 mL) at 15 °C, Boc_2O (12.44 g, 57.0 mmol, 2 eq) was added. The mixture was stirred at 15 °C for 12 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=91:9) to afford O^5-tert-butyl O^3-methyl 1-methylpyrazole-3,5-dicarboxylate **18.1** (5.00 g, 18.7 mmol, 66 % yield) as a colorless oil.

Step 2



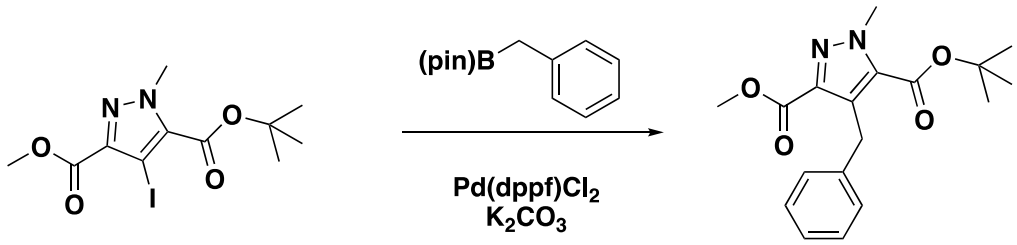
18.1 18.2

O^5-tert-butyl-O^3-methyl-4-iodo-1-methyl-pyrazole-3,5-dicarboxylate and 4-iodo-5-methoxycarbonyl-2-methyl-pyrazole-3-carboxylic acid (18.2)

To a stirred mixture of O^5-tert-butyl O^3-methyl 1-methylpyrazole-3,5-dicarboxylate (5.00 g, 20.8 mmol, 1 eq) in MeCN (100 mL) was added I_2 (3.17 g, 12.5 mmol, 2.52 mL, 0.6 eq) at 15 °C. After stirring for 10 min, CAN (6.85 g, 12.5 mmol, 6.22 mL, 0.6 eq) was added in one portion. After the addition, the mixture was stirred for 12 h 80 °C. The reaction mixture was diluted with water (70 mL) and extracted with EtOAc (40 mL*3). The combined organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether /ethyl acetate = 9/1) to furnish O^5-tert-butyl O^3-methyl-4-iodo-1-methyl-pyrazole-3,5-dicarboxylate **18.2** (1.80 g, 4.92 mmol, 24 % yield) as a colorless oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 4.17 (s, 3H), 3.88 (s, 3H), 1.61-1.55 (m, 9H)

Step 3



18.2 18.3

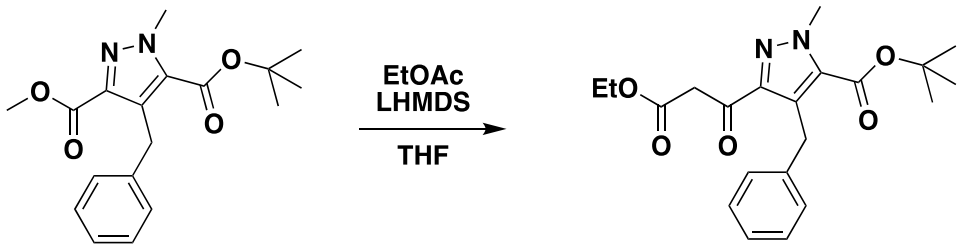
O^5-tert-butyl-O^3-methyl-4-benzyl-1-methyl-pyrazole-3,5-dicarboxylate (18.3)

To a stirred mixture of O^5-tert-butyl-O^3-methyl-4-iodo-1-methyl-pyrazole-3,5-dicarboxylate (4.06 g, 11.1 mmol, 1 eq) in H_2O (8 mL) and dioxane (40 mL) was added 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.58 g, 16.4 mmol, 1.48 eq), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (906 mg, 1.11 mmol, 0.1 eq) and K_2CO_3 (2.30 g, 16.6 mmol, 1.5 eq). The mixture was stirred at 100 °C for 12 h under N_2. The reaction mixture was diluted with water (150 mL) and extracted with EtOAc (100 mL*5). The

combined organic layer was washed with brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 22:3) to afford O^5-tert-butyl-O^3-methyl-4-benzyl-1-methyl-pyrazole-3,5-dicarboxylate 18.3 (4.4 g) as a yellow oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.24-7.19 (m, 2H), 7.16-7.10 (m, 3H), 4.46 (s, 2H), 4.22 (s, 3H), 3.87 (s, 3H), 1.46 (s, 9H)

Step 4



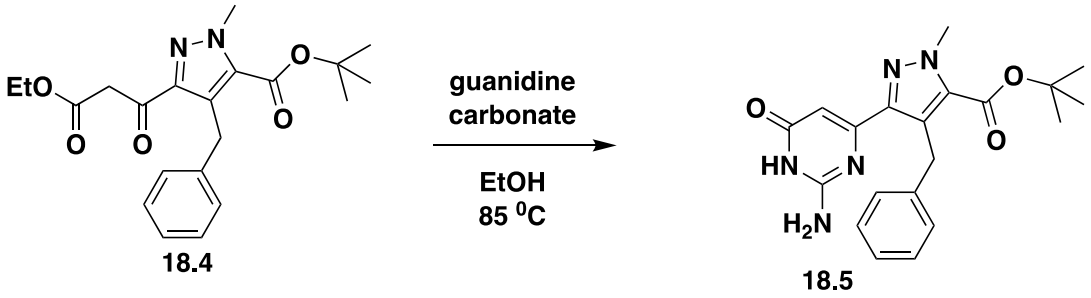
18.3 18.4

Tert-butyl 4-benzyl-5-(3-ethoxy-3-oxo-propanoyl)-2-methyl-pyrazole-3-carboxylate (18.4)

To a solution of O^5-tert-butyl-O^3-methyl-4-benzyl-1-methyl-pyrazole-3,5-dicarboxylate (4.40 g, 13.3 mmol, 1 eq) and EtOAc (8.21 g, 93.2 mmol, 9.13 mL, 7 eq) in THF (80 mL) was added LiHMDS (1 M, 40.0 mL, 3 eq) at -40 °C in one portion. The mixture was stirred at -40 °C for 1 h under N_2. The reaction mixture was diluted with sat. aqueous NH_4Cl solution (150 mL) and extracted with EtOAc (100 mL*3). The organic layer was washed with brine (150 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 19:1) to furnish tert-butyl 4-benzyl-5-(3-ethoxy-3-oxo-propanoyl)-2-methyl-pyrazole-3-carboxylate **18.4** (4.1 g, 10.6 mmol, 80 % yield) as a colorless oil.

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.12-6.98 (m, 5H), 4.35 (s, 2H), 4.08-4.02 (m, 5H), 3.89 (s, 2H), 1.37 (s, 9H), 1.14-1.09 (m, 3H)

Step 5

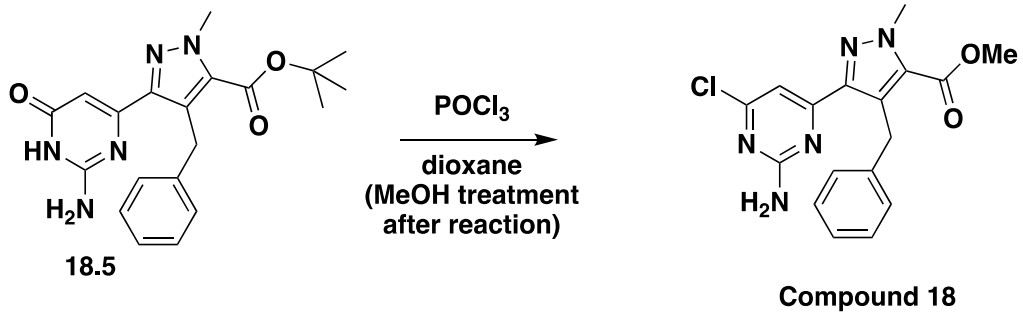


18.4 18.5

Tert-butyl 5-(2-amino-6-oxo-1H-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate (18.5)

Tert-butyl 4-benzyl-5-(3-ethoxy-3-oxo-propanoyl)-2-methyl-pyrazole-3-carboxylate **18.4** (4.1 g, 10.6 mmol, 1 eq) and guanidine carbonate (2.87 g, 15.9 mmol, 1.5 eq) were taken up in anhydrous EtOH (80 mL). The mixture was stirred for 12 h at 85 °C under N_2. The reaction mixture was diluted with water (30 mL) and then concentrated under the reduced pressure to remove the EtOH. The pH of the solution was adjusted to 4 by addition of aqueous HCl (1N). The mixture was filtered, and the residue was dried under the reduced pressure to remove H_2O. The crude product was triturated with MTBE (50 mL) at 15 °C for 20 min and filtered. The residue was washed with MTBE (10 mL*5). The solid was concentrated under reduced pressure to furnish tert-butyl 5-(2-amino-6-oxo-1H-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate (2.9 g) as a white solid. The material was used in the next step without further purification.

Step 6



18.5 Compound 18

Methyl 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate (Compound 18)

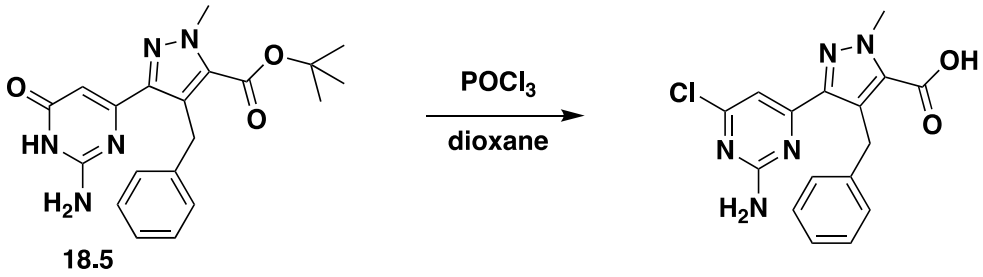
$POCl_3$ (3.01 g, 19.7 mmol, 1.83 mL, 15 eq) was added into a solution of tert-butyl 5-(2-amino-6-oxo-1H-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate **18.5** (500 mg, 1.31 mmol, 1

eq) in dioxane (10 mL) at 15 °C. Then the mixture was heated to 75 °C and stirred for 12 h. The reaction mixture was concentrated under reduced pressure. Methanol was added (15 mL), and the resulting solution was concentrated under reduced pressure. The methanol treatment/evaporation were repeated an additional three times. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 22:3) to furnish a yellow solid. A portion of yellow solid (40 mg) was purified by neutral preparative-HPLC (column: Welch Xtimate C18 150 * 25mm * 5 mm;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%:50%-70%,10min) to furnish methyl 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate **Compound 18** (8.8 mg) as a white solid.

LCMS: Calc'd for $C_{17}H_{17}N_5ClO_2$ ($M+H^+$) 358.1; Found: 358.1

^{1}H NMR: (CHLOROFORM-d, 400 MHz) δ 7.21-7.12 (m, 6H), 7.11-7.05 (m, 1H), 7.02 (s, 1H), 4.65 (s, 2H), 4.12 (s, 3H), 3.84 (s, 3H)

Preparation of **Compound 19**



18.5 Compound 19

5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylic acid (Compound 19)

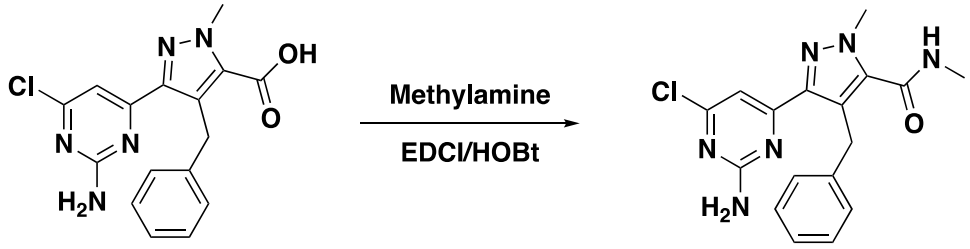
$POCl_3$ (398 mg, 2.60 mmol, 0.24 mL, 15 eq) was added into a solution of tert-butyl 5-(2-amino-6-oxo-1H-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylate **18.5** (66 mg, 0.17 mmol, 1 eq) in dioxane (2 mL) at 15 °C. The mixture was heated at 75 °C for 12 h. The reaction mixture was added slowly to aq. $NaHCO_3$ (saturated, 80 mL) to quench the excess $POCl_3$. The solution was extracted with EtOAc (30 mL*3). The pH of the water layer was adjusted to 4 by addition of aqueous HCl (1N). The water layer was extracted with EtOAc (40 mL*3). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by neutral preparative-HPLC (column: Xtimate C18

150 * 25mm * 5 mm; mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 10%-40%, 8 min) to furnish 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylic acid **Compound 19** (5.86 mg, 10 % yield) as a white solid.

LCMS: Calc'd for $C_{16}H_{15}N_5ClO_2$ ($M+H^+$)344.1; Found: 344.1

^{1}H NMR: (DMSO-d6, 400 MHz) δ 7.23-7.20 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.09 (br s, 2H), 7.07-7.02 (m, 1H), 6.97 (s, 1H), 4.66 (s, 2H), 4.10 (s, 3H)

Preparation of **Compound 20**



Compound 19 **Compound 20**

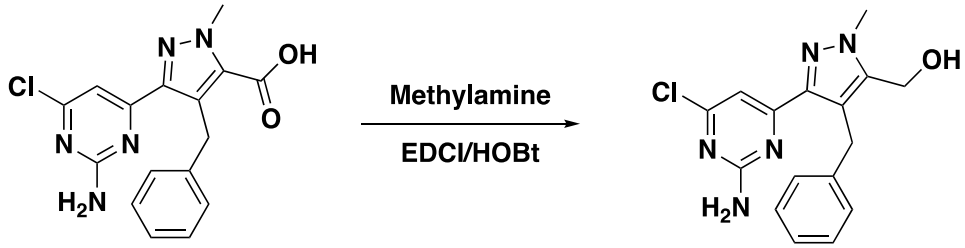
5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-N,2-dimethyl-pyrazole-3-carboxamide (Compound 20)

To a stirred mixture of 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylic acid **Compound 19** (30 mg, 0.087 mmol, 1 eq) in DMF (1 mL) was added methyl amine hydrochloride (18 mg, 0.26 mmol, 3 eq, HCl), HOBt (35 mg, 0.26 mmol, 3 eq), EDCI (50 mg, 0.26 mmol, 3 eq) and DIPEA (34 mg, 0.26 umol, 0.045 mL, 3 eq) at 15 °C. The mixture was stirred at 15 °C for 12 h. The reaction mixture was diluted with water (80 mL). The solution was extracted with EtOAc (40 mL*3). The combined organic layer was washed with brine (80 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by neutral preparative-HPLC (column: Waters Xbridge BEH C18 100 * 30mm * 10 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 25%-45%, 10min) to furnish 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-N,2-dimethyl-pyrazole-3-carboxamide **Compound 20** (18 mg) as a white solid.

LCMS: Calc'd for $C_{17}H_{18}N_6ClO$ ($M+H^+$)357.1; Found: 357.1

^{1}H NMR: (METHANOL-d4, 400 MHz) δ 7.20-7.15 (m, 2H), 7.14-7.06 (m, 4H), 4.49 (s, 2H), 3.96 (s, 3H), 2.82 (s, 3H)

Preparation of **Compound 21**



Compound 19 **Compound 21**

[5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazol-3-yl]methanol

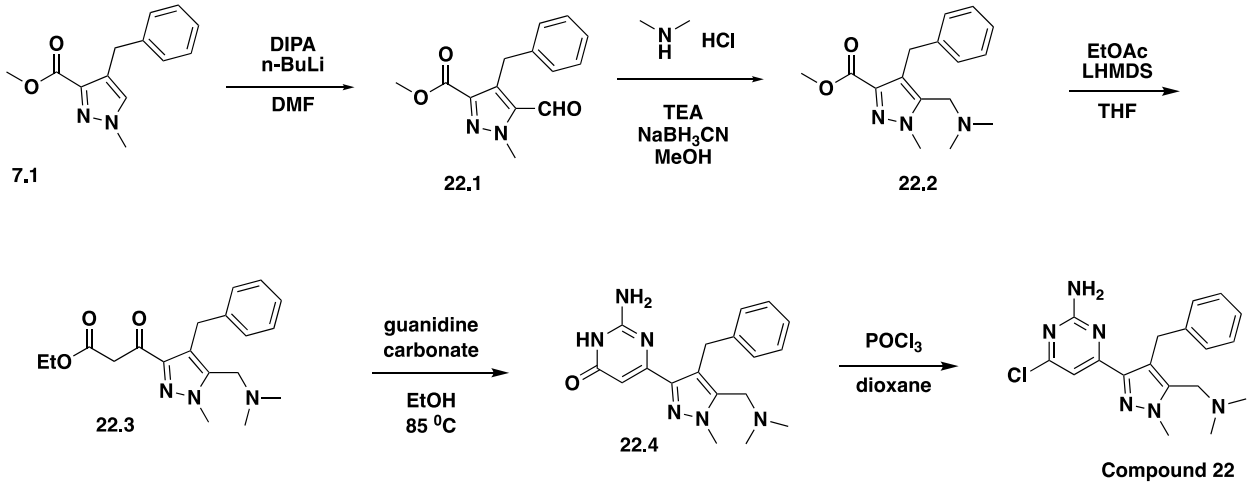
(Compound 21)

To a mixture of $LiAlH_4$ (759 mg, 20 mmol) in THF (20 mL) was added H_2SO_4 (1.10 g, 11.3 mmol, 0.6 mL, 19.4 eq) at -78 °C dropwise. The mixture was stirred at -78 °C for 2 h. The reaction was warmed to 15 °C and stirred at that temperature for 2 hours (white solid appeared). This solution (7 mL) was cooled to 0 °C, and 5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazole-3-carboxylic acid **Compound 19** (200 mg, 0.582 mmol, 1 eq) in THF (5 mL) was added dropwise at 0 °C. The mixture was stirred at 15 °C for 0.5 h. The reaction mixture was diluted with water (40 mL). The solution was extracted with EtOAc (30 mL*6). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1) to furnish a white solid. The solid was purified by neutral preparative-HPLC (column: Welch Xtimate C18 150 * 25mm * 5 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-50%, 9min) to furnish [5-(2-amino-6-chloro-pyrimidin-4-yl)-4-benzyl-2-methyl-pyrazol-3-yl]methanol **Compound 21** (4 mg) as white solid.

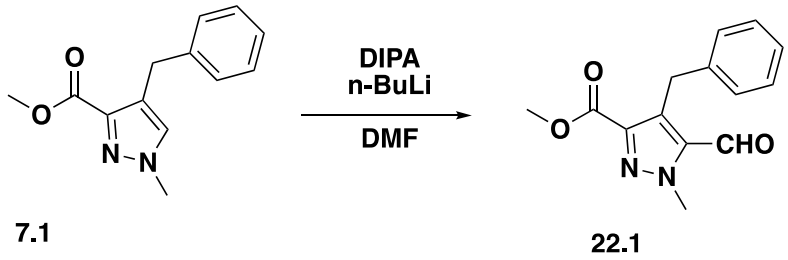
LCMS: Calc'd for $C_{16}H_{17}N_5ClO$ ($M+H^+$) 330.1; Found: 330.1

^{1}H NMR: (METHANOL-d4, 400 MHz) δ 7.20-7.15 (m, 4H), 7.11-7.05 (m, 2H), 4.60 (s, 2H), 4.37 (s, 2H), 3.97 (s, 3H)

Preparation of **Compound 22**



Step 1

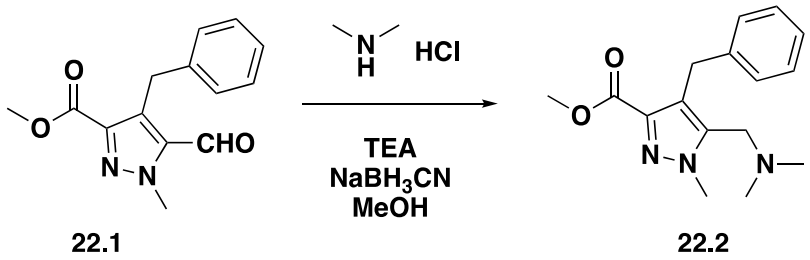


Methyl 4-benzyl-5-formyl-1-methyl-pyrazole-3-carboxylate (22.1)

To a stirred mixture of diisopropylamine (1.41 g, 13.9 mmol, 1.96 mL, 1.6 eq) in THF (40 mL) was cooled to -78 °C. n-BuLi (2.5 M, 5.21 mL, 1.5 eq) was added. The mixture was stirred at -78 °C for 0.5 h. Methyl-4-benzyl-1-methyl-pyrazole-3-carboxylate **7.1** (2.00 g, 8.69 mmol, 1 eq) was added into the mixture. DMF (952 mg, 13.0 mmol, 1.00 mL, 1.5 eq) was added directly into the mixture. The mixture was stirred at -78 °C for 0.5 h. The reaction mixture was diluted with sat. aq NH_4Cl (150 mL). The solution was extracted with EtOAc (70 mL*3). The organic layer was washed with brine (150 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under the reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 3/1) to furnish methyl 4-benzyl-5-formyl-1-methyl-pyrazole-3-carboxylate **22.1** (600 mg, 2.32 mmol, 27 %) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 9.94 (s, 1H), 7.31-7.26 (m, 2H), 7.25-7.19 (m, 3H), 4.49 (s, 2H), 4.25 (s, 3H), 3.95 (s, 3H).

Step 2



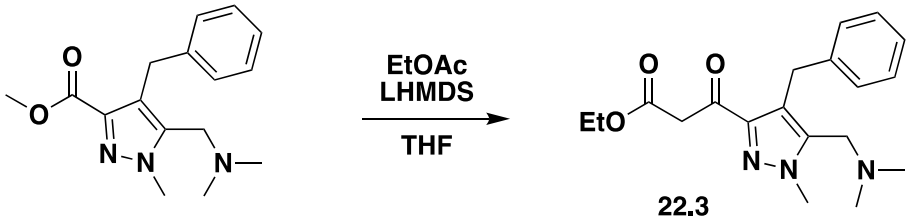
22.1 22.2

Methyl 4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazole-3-carboxylate (22.2)

To a solution of methyl 4-benzyl-5-formyl-1-methyl-pyrazole-3-carboxylate **22.1** (0.700 g, 2.71 mmol, 1 eq) in MeOH (12 mL) was added TEA (1.10 g, 10.8 mmol, 1.51 mL, 4 eq) and dimethylamine hydrochloride (884 mg, 10.8 mmol, 4 eq). The mixture was stirred at 20 °C for 12 h under N_2. $NaBH_3CN$ (341 mg, 5.42 mmol, 2 eq) was added to the mixture. The mixture was stirred at 20 °C for another 3 h under N_2. The reaction mixture was poured into H_2O (150 mL). The mixture was extracted with ethyl acetate (50 mL*3). The organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, gradient elution of 0 to 65% ethyl acetate/petroleum ether gradient @ 75 mL/min) to furnish methyl 4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazole-3-carboxylate **22.2** (400 mg, 1.39 mmol, 51 % yield) as a yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.26-7.20 (m, 2H), 7.18-7.11 (m, 3H), 4.17 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.38 (s, 2H), 2.14 (s, 6H)

Step 3



22.2 22.3

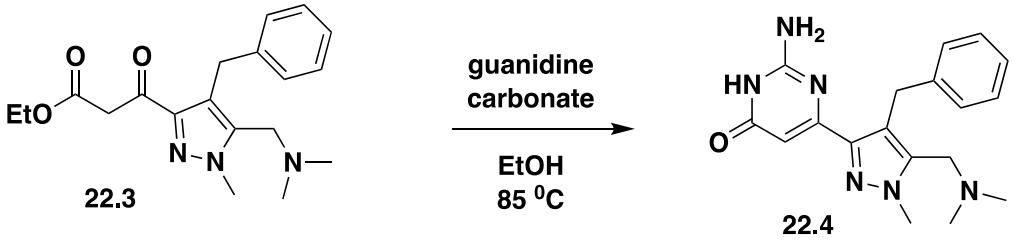
Ethyl 3-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate (22.3)

To a solution of methyl 4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazole-3-carboxylate **22.2** (540 mg, 1.88 mmol, 1 eq) and EtOAc (1.16 g, 13.2 mmol, 1.29 mL, 7 eq) in THF (8 mL) was added LiHMDS (1 M, 5.64 mL, 3 eq) in one portion at -40 °C. The mixture was stirred at -40 °C for 2 h. The reaction mixture was poured into saturated,aqueous ammonium chloride solution (100

mL). The mixture was extracted with ethyl acetate (30 mL*3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, gradient elution of 0 to 30% ethyl acetate/petroleum ether gradient @ 70 mL/min) to furnish ethyl 3-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-3-oxo-propanoate **22.3** (0.4 g) as a light yellow oil.

^{1}H NMR: (400 MHz, CHLOROFORM-d) δ 7.24-7.18 (m, 2H), 7.17-7.10 (m, 3H), 4.17 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 3.94 (s, 3H), 3.32 (s, 2H), 2.11 (s, 6H), 1.28-1.26 (m, 3H)

Step 4

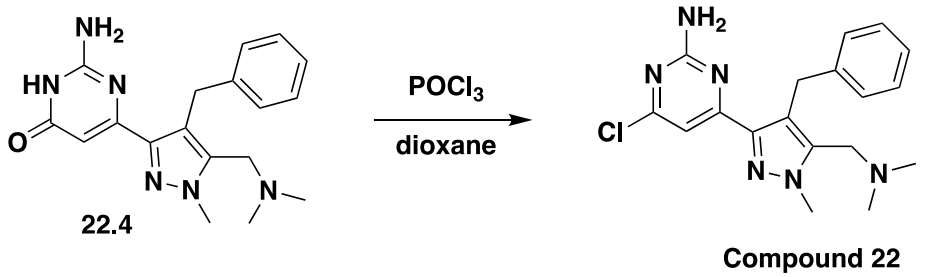


2-amino-4-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one (22.4)

To a solution of ethyl 3-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl] -3-oxo-propanoate (0.400 g, 1.16 mmol, 1 eq) in EtOH (8 mL) was added guanidine carbonate (630 mg, 3.49 mmol, 3 eq). The mixture was stirred at 85 °C for 20 h under N_2. The reaction mixture was diluted with water (10 mL). The mixture was concentrated under reduced pressure to remove the EtOH at which time a white precipitate formed. The pH of the aqueous phase was adjusted to 5 by addition of an aq. HCl solution (1 N). The mixture was filtered, and the filter cake was washed with petroleum ether/EtOAc=1:1 (5 mL*3). The white precipitate dried under reduced pressure to furnish 2-amino-4-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **22.4** (160 mg, 94%) as a white solid. The pH of the aqueous phase was adjusted to 8 by addition of a saturated, aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate (30 mL*5). The organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was further purified by preparative-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40mm * 10 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 15%-45%,8 min) to furnish

2-amino-4- [4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-1H-pyrimidin-6-one **22.4** (50 mg, 98%) as a white solid.

Step 5



4-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl-pyrazol-3-yl]-6-chloro-pyrimidin-2-amine (Compound 22)

To a solution of 2-amino-4-[4-benzyl-5-[(dimethylamino)methyl]-1-methyl- pyrazol-3-yl]-1H-pyrimidin-6-one **22.4** (10 mg, 0.030 mmol, 1 eq) in dioxane (1 mL) was added TEA (6.0 mg, 0.059 mmol, 2 eq) and $POCl_3$ (23 mg, 0.15 mmol, 5 eq) successively. The mixture was stirred at 75 °C for 1 h under N_2. The reaction mixture was poured into sat. aq $NaHCO_3$ (150 mL). The mixture was extracted with ethyl acetate (50 mL*3). The organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative-HPLC (column: Waters Xbridge BEH C18 100 * 25mm * 5 mm; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 30%-60%, 8min) to furnish 4-[4-benzyl-5-[(dimethylamino)methyl]-1- methyl-pyrazol-3-yl]-6-chloro-pyrimidin-2-amine **Compound 22** (11.1 mg, 93%) as a white solid.

LCMS: Calc'd for $C_{18}H_{22}N_6Cl$ ($M+H^+$) 357.1; Found: 357.1

^{1}H NMR: (400 MHz, METHANOL-d4) δ 7.21-7.05 (m, 6H), 4.38 (s, 2H), 3.95 (s, 3H), 3.43 (s, 2H), 2.15 (s, 6H)

2. Biology assay methods

In-Vitro Cyclase Activity Assay

Assays for sAC activity using purified protein were performed in 100 µL reactions containing 4 mM MgCl2, 2 mM CaCl2, 1 mM ATP, 40 mM NaHCO3, 50 mM Tris pH 7.5, and 3 mM DTT. Each reaction contained ~1,000,000 counts of α-32P labeled ATP. Generated cAMP was purified using sequential Dowex and Alumina chromatography as previously described (Salomon, Y., Adenylate cyclase assay. *Adv Cyclic Nucleotide Res* 1979, **10**, 35-55)

In-Vitro Cyclase Activity Assay

4-4 cells were generated and functionally authenticated in our laboratory as previously described (Zippin *et al*., (2013) CO_2/HCO_3(-)- and calcium-regulated soluble adenylyl cyclase as a physiological ATP sensor. *J Biol Chem* 2013, **288**, 33283-91) and grown in DMEM + 10% FBS. 1.25 x 10^6 4-4 cells were seeded per well of a 24 well plate and incubated for 24 hours at 37ºC, 5% CO_2. One hour before the experiment the media was aspirated and replaced with 300 µl fresh media. For 5 min, in duplicate wells, cells were preincubated with sAC inhibitor at the indicated concentrations or DMSO as control. For cAMP accumulation, cells were incubated with 500 µM IBMX for 5 min. To stop the reaction and to lyse the cells, the media was aspirated and replaced with 250 µl 0.1 M HCl. After shaking the plate for 5 min the cell lysate was transferred to a fresh tube and centrifuged at 1000 x g for 5 min. The supernatant was used for cAMP quantification using the Direct cAMP Elisa kit (Enzo) following the manufacturer's instructions

3. ADMET assay methods

LogD determination

LogD 7.4, which is a partition coefficient between 1-octanol and aqueous buffer pH 7.4, of the compounds was measured on the chromatographic procedure whose condition was developed based on a published method [Nakashima, S.; Yamamoto, K.; Arai, Y.; Ikeda, Y., Impact of physicochemical profiling for rational approach on drug discovery. Chem Pharm Bull (Tokyo) 2013, 61 (12), 1228-38.] [Masumoto, K.; Takeyasu, A.; Oizumi, K.; Kobayashi, T., [Studies of novel 1,4-dihydropyridine Ca antagonist CS-905. I. Measurement of partition coefficient (log P) by high performance liquid chromatography (HPLC)]. Yakugaku Zasshi 1995, 115 (3), 213-20.]

Parallel artificial membrane permeability assay (PAMPA)

The donor wells were filled with 200 µL of PRISMA HT buffer (pH 7.4, pION inc.) containing 10 µmol/L test compound. The filter on the bottom of each acceptor well was coated with 4 µL of a GIT-0 Lipid Solution (pION Inc.) and filled with 200 µL of Acceptor Sink Buffer (pION inc.). The acceptor filter plate was put on the donor plate and incubated for 3 hours at room temperature. After the incubation, the amount of test compound in both the donor and acceptor wells was measured by LC/MS/MS.

Kinetic solubility

Small volumes of compound solution dissolved in DMSO were added to the aqueous buffer solution. After incubation, precipitates were separated by filtration. The solubility was determined by UV absorbance of each filtrate.

Metabolic stability

Liver microsomes were purchased from Sekisui XenoTech, LLC. (Kansas City, KS). The microsomes (0.2 mg protein/mL) and the compounds (1 µM) were mixed in phosphate buffer (pH 7.4). The reactions were initiated by adding an NADPH generating system (a mixture of MgCl2, β-NADP+, glucose-6-phosphate, and glucose-6-phosphate dehydrogenase) to the mixtures before

incubation. Incubations were conducted at 37°C and terminated by adding acetonitrile. The zero-time incubations, which served as the controls, were terminated by adding acetonitrile before adding an NADPH generating system. After the samples were mixed and centrifuged, the compound concentration in the supernatant fractions were measured by LC/MS/MS.

4. Mouse pharmacokinetic studies (20 mpk IP and PO)

CD1 male mice were dosed with 20 mpk IP and PO (3 animals each arm). TDI-10229 was formulated in 100% PEG400. Blood sampling was conducted at 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 h after drug administration. The reported mean values were calculated from individual animals in each arm.

Mouse cassette dosing PK study

The compounds were administered intravenously (0.1 mg/kg) or orally (1 mg/kg) by cassette dosing to ICR male mice in the feeding conditions of ad libitum. After administration, blood samples were collected and centrifuged to obtain the plasma fraction. The plasma samples were deproteinized by mixing with acetonitrile, followed by centrifugation. The compound concentrations in the plasma were determined by LC/MS/MS.

5. Crystal structure determination

The protein construct comprising the catalytic domains of human sAC (hsAC-cat) was expressed, purified and crystallized as described {Kleinboelting, 2014 #464;Kleinboelting, 2014 #272}. In short, hsAC-cat with a C-terminal His-tag was expressed in insect cells, purified through affinity, ion exchange, and size exclusion chromatography, and crystallized in hanging drops with 0.1 M sodium acetate pH 5.0, 0.2 M trisodium citrate, 14 %(w/v) PEG 4000 and 10 % (v/v) glycerol as reservoir solution. Crystals were transferred to a drop containing 0.1 M sodium acetate pH 5.0, 0.2 M trisodium citrate, 15 %(w/v) PEG 4000, 20 % (v/v) glycerol, 10 % DMSO (v/v), soaked with 5 mM ligand for 24 h, and flash frozen in liquid nitrogen.

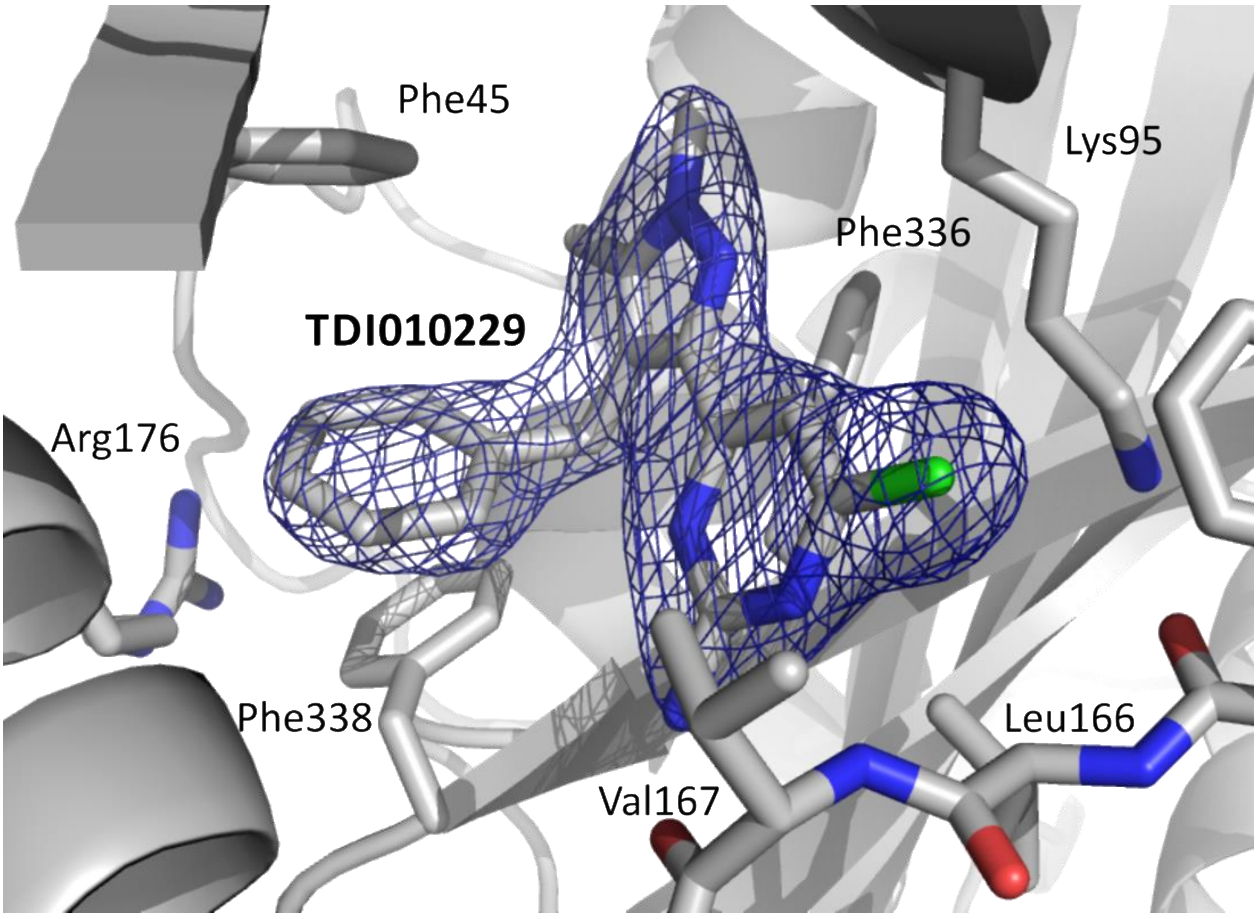
Diffraction data were collected at 100 K at BESSY beamline 14.1 operated by Helmholtz-Zentrum Berlin 1 and processed with XDSapp 2. Phases were determined through Patterson searches with Phaser 3 using hsAC apo (pdb ID 4CLL 4) as a search model. The crystallographic model was then rebuilt in Coot 5 and refined with Phenix 6.

6. Supplementary Table S1 - Diffraction and refinement statistics

	sAC/TDI010229
Diffraction data	
Resolution range [a]	44.39 - 2.20 (2.28 - 2.20)
Space group	$P6_3$
Unit cell dimensions (Å)	99.18, 99.18, 99.59
Unique reflections [a]	28295 (2795)
Multiplicity [a]	11.5 (11.5)
Completeness (%) [a]	99.48 (95.71)
Mean I/sigma(I) [a]	6.90 (0.45)
R-meas [a]	0.295 (4.084)
$CC_{1/2}$ [a]	0.995 (0.135)
Refinement	
Reflections used [a]	28159 (2677)
Reflections for test set (R-free) [a]	1409 (134)
R-work [a]	19.9 (33.6)
R-free [a]	24.3 (35.6)
Number of non-hydrogen atoms	3744
protein	3599
ligand	78
Solvent	67
Average B-factors (Å^2)	63.2
macromolecules	63.2
Ligands	71.5
Solvent	55.2
rmsd bond lengths (Å)	0.007
rmsd bond angles (°)	1.0

[a] numbers in parantheses refer to the highest resolution shell

7.Supplementary Figure S1



Crystal structure of hsAC-cat in complex with TDI-10229. The inhibitor is overlaid with 2Fo-Fc electron density contoured at 1.5 sigma.

8. Supplementary References

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