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# SYNTHESIS OF HETEROARYL-FUSED PYRAZOLES AS P38 KINASE INHIBITORS

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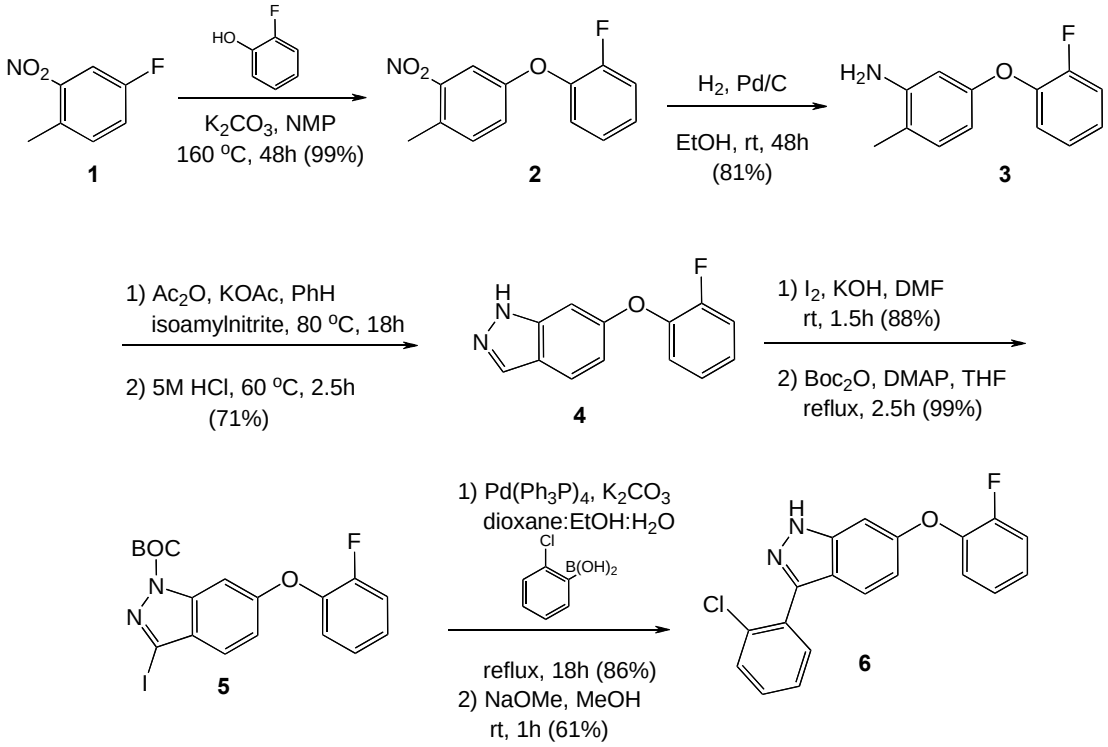
**Abstract** - The synthesis of pyrazolo-pyridine, pyrimidine, pyrazine and pyridazine heterocycles is described. In addition, we report the utilization of 2,4-difluorophenoxide as a leaving group, to facilitate formation of the desired pyrazole adducts.

## INTRODUCTION

The proinflammatory cytokines tumor necrosis factor-alpha (TNFα) and interleukin-1 beta (IL-1β) have been clinically validated as targets for the treatment of Rheumatoid Arthritis (RA).[1] p38α Mitogen Activated Protein (MAP) Kinase is an intracellular soluble threonine kinase which regulates the production and signaling of IL-1β, and TNFα.[2] Inhibiting p38 MAP kinase suppresses TNFα and IL-1β, indicating that p38 inhibitors could be effective in the treatment of RA and other inflammatory diseases.[3] Orally active small-molecule inhibitors of p38α remain attractive therapeutic agents, and several p38 inhibitors are currently in Phase II clinical trials.[4] During our investigation of fused pyrazole derivatives as p38 inhibitors, we prepared the pyrazolo-pyridine, pyrazine, pyridazine, pyrimidine and indazole systems. The syntheses of these heterocycles are described below.

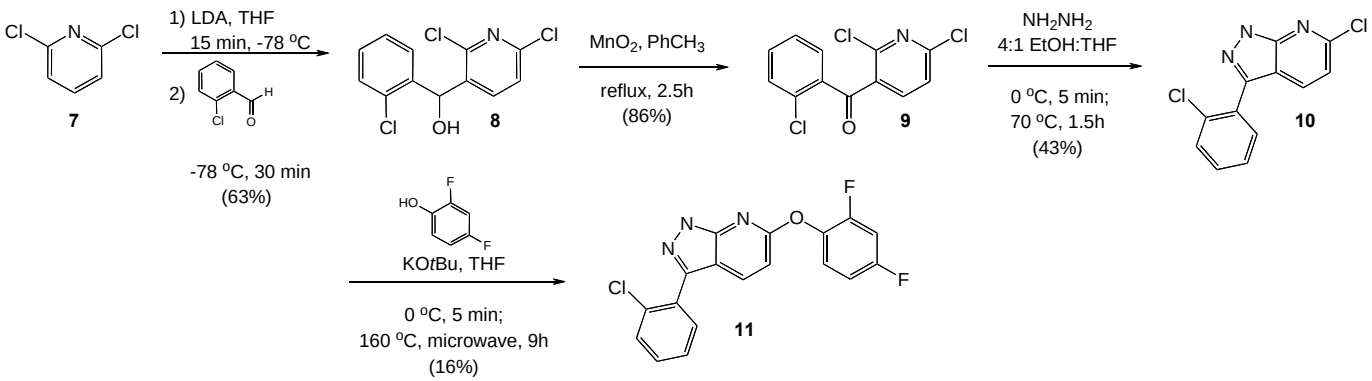
## RESULTS AND DISCUSSION

We initiated our study of fused-pyrazole derivatives with the synthesis of the indazole template, as shown in Scheme 1. The preparation of **6** began with displacement of the aryl fluoride **1** with 2-fluorophenoxide, affording intermediate **2**. Reduction of the arylnitro to the amine, followed by cyclization gave the indazole ring system **4**. Incorporation of the 2-chlorophenyl group required iodination at the 3-postion of the indazole, protection of the nitrogen, and Suzuki coupling with 2-chlorophenylboronic acid. Removal of the Boc group under basic conditions gave the desired indazole **6**.



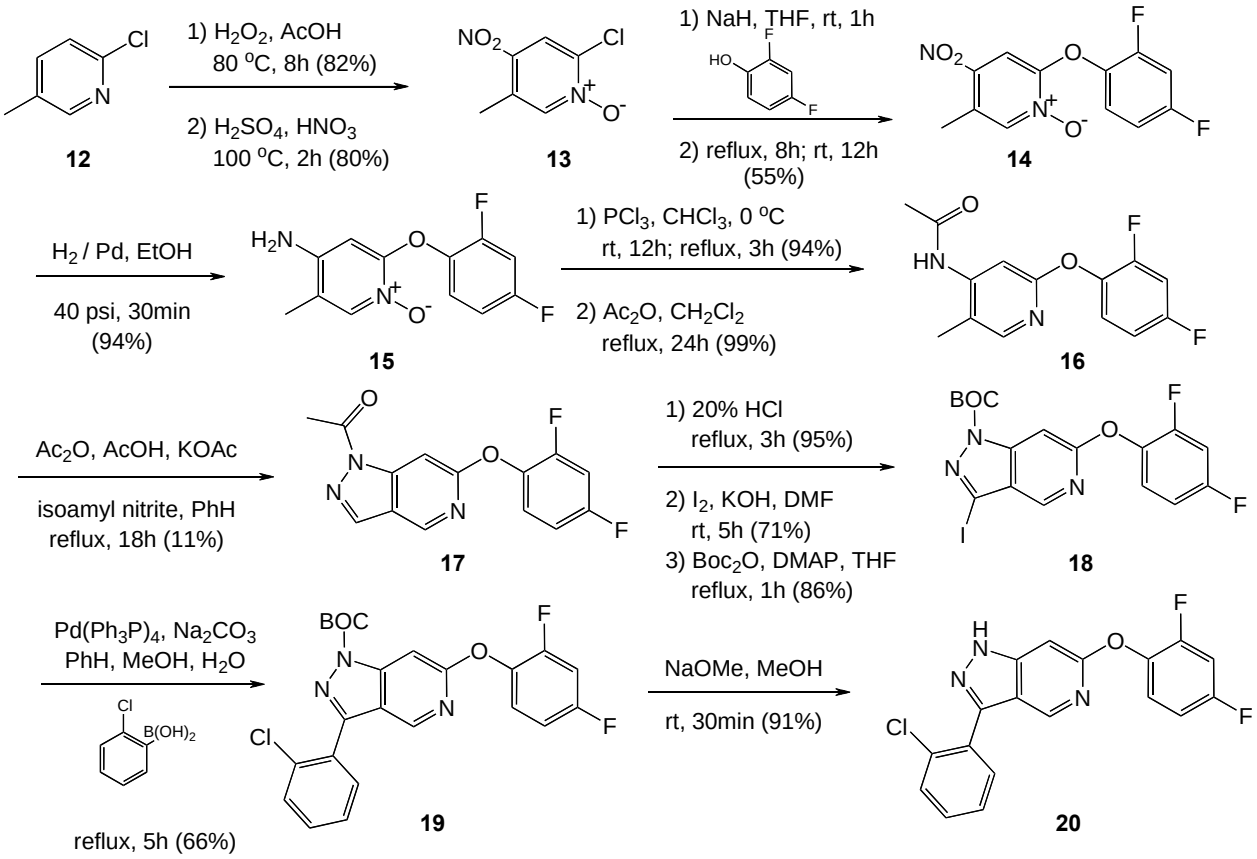

**Scheme 1**

Synthesis of the first pyrazolopyridine commenced with lithiation of 2,6-dichloropyridine (**7**), and trapping with 2-chlorobenzaldehyde, as shown in Scheme 2. Oxidation of alcohol **8** with manganese dioxide afforded the ketone **9**, then treament with hydrazine gave the desired pyrazolopyridine **10** in moderate yield. At this stage, the work done with the indazole template (Scheme 1) demonstrated that the 2,4-difluorophenyl ethers were more potent versus p38 than the 2-fluorophenyl ethers (**6**), so 2,4-DPF ethers were incorporated into the subsequent templates. Microwave heating in the presence of 2,4-difluorophenol and potassium tert-butoxide in THF, displaced the aryl chloride, completing the synthesis of the desired pyrazolo[3,4-*b*]pyridine analog **11**. We believe the 16% yield resulted from deactivation of the chloropyridine by the fused pyrazole; an improved route to **11** could utilize the cyclization protocol described in Scheme 9.



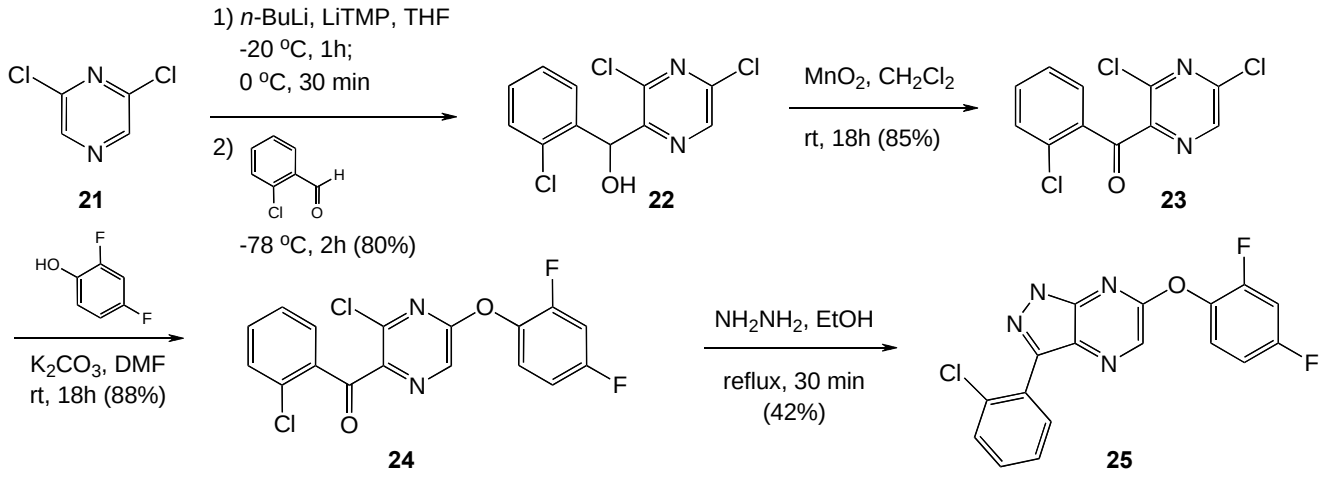

**Scheme 2**

Completion of the second pyrazolopyridine regioisomer required a longer synthetic sequence, as shown in Scheme 3. Oxidation of 2-chloro-5-methylpyridine, followed by regioselective nitration gave the N-oxide **13**; an intermediate which underwent nucleophilic displacement by 2,4-difluorophenoxide in reasonable yield. Reductions of the aryl nitro and the N-oxide, followed by mono-acylation afforded the desired cyclization substrate **16**. Treatment of the acetamide with isoamyl nitrite, in the presence of acetic anhydride and potassium acetate in benzene at reflux gave the desired pyrazolo[4,3-*c*]pyridine (**17**) in 11% yield; recovered starting material, and bis-acylated aniline accounted for most of the remaining material. Removal of the acetate, iodination and Boc protection gave Suzuki substrate **18**. Coupling of the iodide **18** with 2-chlorophenyl boronic acid, in the presence of palladium, completed the construction of the ring system (**19**). Removal of the Boc group with sodium methoxide afforded the target pyrazolo-[4,3-*c*]pyridine **20**.



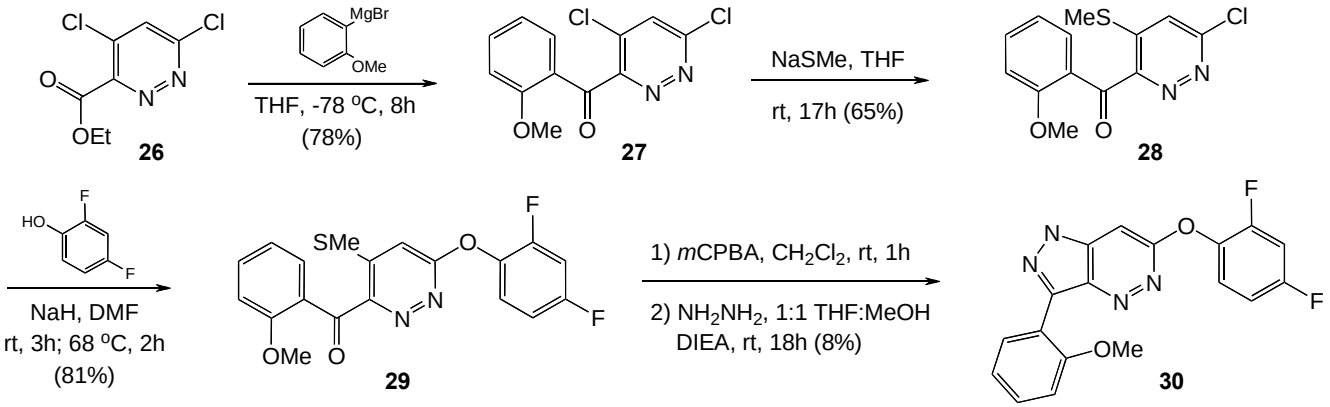

**Scheme 3**

Pyrazolo[3,4-*b*]pyrazines were synthesized using the methods developed for the pyrimidine core, as shown in Scheme 4. Treatment of 2,6-dichloropyridazine (**21**) with lithium tetramethylpiperidide (generated *in situ*), followed by trapping with 2-chlorobenzaldehyde, gave the desired alcohol **22** in excellent yield. Oxidation to the ketone **23**, followed by displacement of the less-hindered chlorine that was also *para* to the ketone by 2,4-difluorphenoxide afforded **24,** also in good yield. Finally, treament with hydrazine afforded the desired pyrazolo[3,4-*b*]pyrazines **25**.



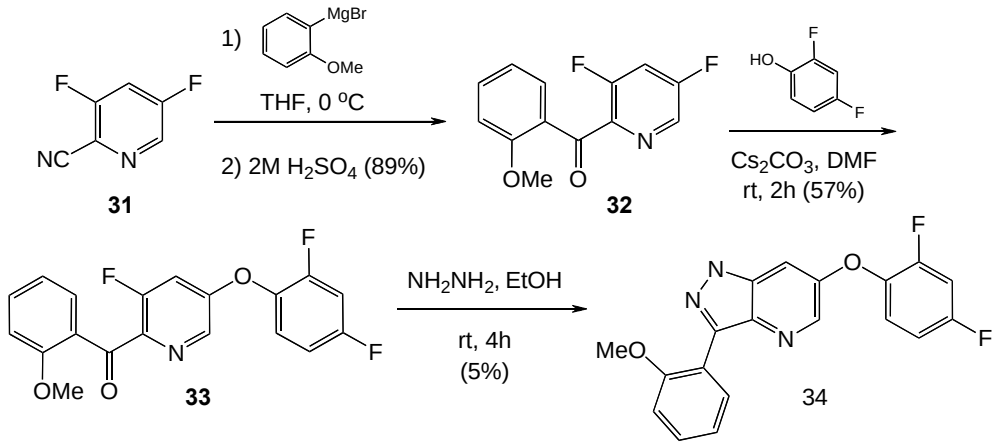

**Scheme 4**

The preparation of the pyrazolo[4,3-*c*]pyridazines (**30**) involved an aryl Grignard addition to the commercially available ethyl ester **26** for installation of the 2-methoxyphenyl group, as shown in Scheme 5. Based on literature precedent,[5] the 4-chloro substituent was displaced by thiomethoxide, and the remaining chloro group was displaced by 2,4-difluorophenoxide, affording **29**. Oxidation of the thiomethyl to the sulfone, followed by treatment with hydrazine, gave the desired pyrazolo[4,3-*c*]pyridazine **30** in low yield. This route might also be improved by utilizing 2,4-difluorophenoxide method described in Scheme 9.



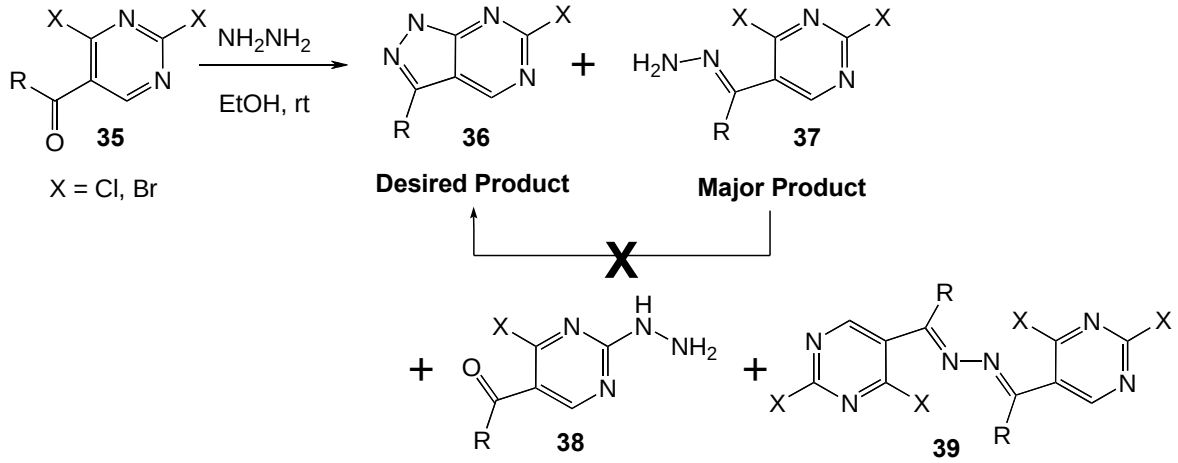

**Scheme 5**

The key to the successful preparation of the third pyrazolopyridine regioisomer was the 2,4-difluoropyridyl motif. Aryl Grignard addition to the nitrile **31**, followed by acidic aqueous workup, gave the intermediate ketone **32**. Fluoro-displacement by 2,4-difluorophenol, in the presence of cesium carbonate in DMF at rt, was regioselective and good-yielding (**33**). Treatment of the ketone with hydrazine gave the desired pyrazolo[4,3-b]pyridine **34**, in low yield (Scheme 6). The major side-product resulted from hydrazone formation, analogous to the pyrimidines shown in Scheme 7. Attempts to synthesize pyrazolo[4,3-*b*]pyridines using bromo- or chloro- intermediates did not afford the desired pyrazole; only hydrazone side products were obtained from those reactions.



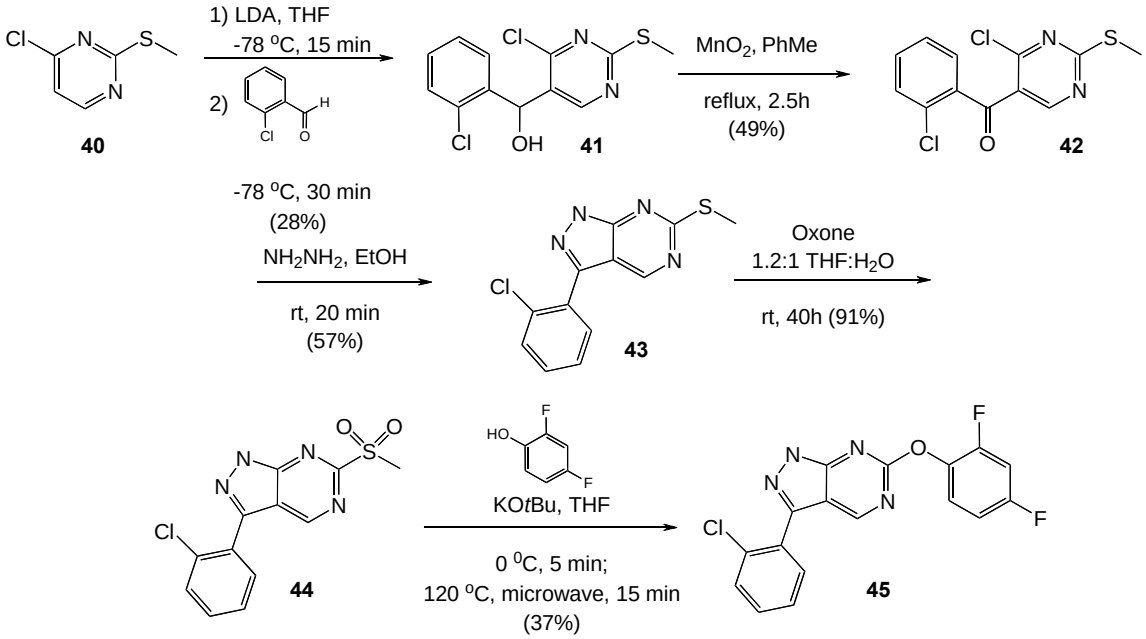

**Scheme 6**

The low yield of the desired pyrazolo[4,3-*b*]pyridine **34** is one example of the problem of un-productive hydrazone formation, which we observed throughout the syntheses of most of the pyrazolo analogs. As shown in Scheme 7, we were unable to convert the hydrazones (**37**) to their corresponding pyrazoles (**36**) despite extensive heating, strongly basic conditions, or microwave irradation. In addition, the hydrazones could also dimerize (**39**), resulting in further erosion of yield of desired pyrazoles. To avoid these side products, we ultimately biased the cyclization substrates toward formation of the desired indazole and minimized hydrazone formation; which is discussed later.



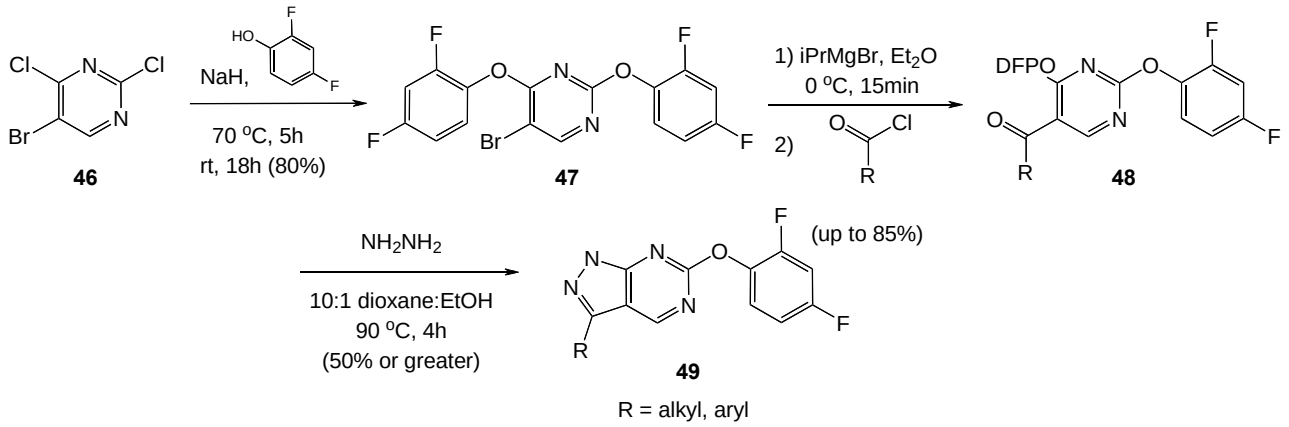

**Scheme 7**

Initially, pyrazolopyrimidines were prepared by lithiation of 5-chloro-2-thiomethylpyrimidine (**40**), followed by trapping with 2-chlorobenzaldehyde. The low yield of the desired acohol **41** resulted from dilithiation of the chloropyrimidine starting material; the regioisomeric alcohols were separated by chromatography. Oxidation of the desired regioisomer **41** to the ketone **42**, followed by treatment with hydrazine, affording the desired pyrazole (**43**) in reasonable yield. At this stage, oxidation of the thioether to the sulfone **44**, followed by displacement with the 2,4-difluorophenoxide gave the desired pyrazolo[4,3-*b*]pyrimidine (**45**). In general, the alternate route shown in Scheme 9 is preferred to this initial synthesis of pyrazolopyrimidines.




**Scheme 8**

To prevent the unproductive formation of the hydrozone, as described in Scheme 7, we found that the most effective leaving group for our syntheses was 2,4-difluorophenoxide. As shown in Scheme 9, this group improved the yield of the cyclization step (50% for the pyrazolopyrimidine), and shortened the length of the synthetic sequence. Displacement of both chlorine substituents from the starting material **46**, afforded intermediate **47**, which was converted to an aryl Grignard by halogen exchange with isopropyl magnesium bromide. Addition of an acid chloride gave ketone adducts (**48**) in excellent yield. At this stage, cyclization with hydrazine afforded the desired pyrazole adducts **49** in reasonable yields. For comparision, the original synthesis of the pyrazolopyrimidines is shown in Scheme 8.




**Scheme 9**

## CONCLUSIONS

We synthesized pyrazolo-pyridine, pyrimidine, pyrazine and pyridazine regioisomers for evaluation in the p38α kinase inhibitor program. Utilizing 2,4-difluorophenoxide as a leaving group shortened the

synthetic sequence for the pyrazolopyrimidines, and minimized the formation of the unproductive hydrazone intermediates. This method is particularly useful for the preparation of heterocyclic analogs, where neighboring nitrogens cannot promote the displacement of a leaving group. We anticipate the methods described above should provide a solid reference for synthesis of fused pyrazole analogs.

## EXPERIMENTAL

### 3-(2-Chlorophenyl)-6-(2-fluorophenoxy)-1*H*-indazole (6)

To 4-fluoro-2-nitrotoluene (**1**) (25 g, 0.016 mol) and 2-fluorophenol (15.8 mL, 0.017 mol) in NMP (350 mL) was added potassium carbonate (22.27 g, 0.016 mol) and the mixture was stirred at 160 °C for 48 h. After cooling to rt, water (350 mL) was added and the solution was extracted into EtOAc (2×150 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, concentrated and the residue was purified by flash chromatography eluting with 20:1 hexanes:EtOAc to yield 15.17 g of 4-(2-fluoro-phenoxy)-2-nitrotoluene (**2**). MS *m / z*: $ESI^+$ 248 $(M + H)^+$.

4-(2-Fluorophenoxy)-2-nitrotoluene (**2**) (15.17 g, 0,061 mol) and Pd/C (1.67 g) in EtOH (150 mL) were stirred under hydrogen atmosphere for 48 h, then the mixture was filtered through celite and the filtrate was concentrated under vacuum and purified by flash chromatography eluting with 9:1 hexanes:EtOAc to afford 10.9 g of 5-(2-fluorophenoxy)-2-methylphenylamine (**3**). MS *m / z*: $ESI^+$ 218 $(M + H)^+$.

To a suspension of 5-(2-fluorophenoxy)-2-methylphenylamine (**3**) (2.4 g, 11.04 mmol), acetic anhydride (3.36 g, 33.12 mmol) and anhydrous potassium acetate (1.10 g, 11.16 mmol) in benzene (36 mL) at 80 °C, isoamyl nitrite (2.22 mL, 16. 56 mmol) was added dropwise over 30 minutes, and the reaction mixture was stirred at this temperature overnight. After cooling to rt, the precipitate formed, was removed by filtration, and the filtrate was concentrated under vacuum. The residue was treated with 5N HCl (4.5 mL), then concentrated HCl (2.5 mL); the mixture was heated at 55 °C for 2.5 h then 60 °C for 15 min. The reaction was cooled to rt and extracted into benzene (15 mL), the aqueous layer was basified with $NH_4OH$ then extracted into EtOAc (2×25 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated and the residue was purified by flash chromatography eluting with 7:3 hexanes:EtOAc to yield 1.8 g of 6-(2-fluorophenoxy)-1*H*-indazole (**4**). MS *m / z*: $ESI^+$ 229 $(M + H)^+$.

Iodine (1.53 g, 6.02 mmol) and potassium hydroxide pellets (805 mg, 14.3 mmol) were added successively into a DMF solution of 6-(2-fluorophenoxy)-1*H*-indazole (1.35 g, 5.92 mmol) at rt under stirring. After 1.5 h, the reaction was poured into aqueous sodium bisulfite solution and extracted into EtOAc (2 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and the residue purified by flash chromatography eluting with 9:1 hexanes:EtOAc to yield 1.9 g of 6-(2-fluorophenoxy)-3-iodo-1*H*-indazole. MS *m / z*: $ESI^+$ 355 (M+H). 6-(2-Fluorophenoxy)-3-iodo-1*H*-indazole (1.9 g, 5.36 mmol), di-*tert*-butyldicarbonate (1.4 g, 6.43 mmol), and 4-dimethylaminopyridine (33 mg, 0.26 mmol) in THF (10 mL) was heated at reflux for 2.5 h. The reaction mixture was cooled to rt, concentrated under vacuum, and the residue purified by flash chromatography eluting with 9:1 hexanes:EtOAc to yield 2.4 g of 6-(2-fluorophenoxy)-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester

(**5**). MS *m / z*: ESI$^+$ 455 (M + H)$^+$.

To a solution of $(Ph_3P)_4Pd$ (36 mg, 0.03 mmol) in dioxane (4 mL) under argon, was added 6-(2-fluorophenoxy)-3-iodoindazole-1-carboxylic acid *tert*-butyl ester (**5**) (140 mg, 0.3 mmol) and the solution was stirred for 10 min, then 2-chlorophenylboronic acid (96.4 mg, 0.6 mmol) in EtOH (1.2 mL) was added. After 10 min, potassium carbonate (132 mg, 0.9 mmol) in water (0.4 mL) was added, and the mixture was stirred at 85 °C under argon for 18 h. The mixture was cooled to rt, filtered through Celite, and partitioned between water and EtOAc. The separated organic phase was dried over $Na_2SO_4$, filtered, concentrated and the residue purified by flash chromatography, eluting with 9:1 hexanes:EtOAc to yield 90 mg of 3-(2-chlorophenyl)-6-(2-fluorophenoxy)indazole-1-carboxylic acid *tert*-butyl ester. MS *m / z*: ESI$^+$ 345 (M+H). A solution of 3-(2-chlorophenyl)-6-(2-fluorophenoxy)-indazole-1-carboxylic acid *tert*-butyl ester (90 mg, 0.2 mmol) and sodium methoxide (22 mg, 0.41 mmol) in MeOH (2 mL) was stirred at room temperature for 1 h, then concentrated under vacuum. The residue was diluted with EtOAc, washed with water, dried over $Na_2SO_4$, filtered, concentrated, and the residue purified by flash chromatography eluting with 4:1 hexanes:EtOAc to yield 42 mg of 3-(2-chlorophenyl)-6-(2-fluorophenoxy)-1*H*-indazole (**6**). $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, 1H, *J* = 9 Hz), 7.57 (m, 1H), 7.51 (m, 1H), 7.36 (m, 1H), 7.19 (m, 4H), 6.99 (dd, 1H, *J* = 2. 9 Hz), 6.89 (d, 1H, *J* = 2 Hz); MS *m / z*: ESI$^+$ 339 (M + H)$^+$.

**3-(2-Chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[3,4-*b*]pyridine (11).**

2,6-Dichloropyridine (**7**) (10.0 g, 67.6 mmol) was suspended in 220 mL of dry THF and cooled to -78 °C under argon. Lithium diisopropylamide (60 mL, 118 mmol, 2M in heptane/THF/ethylbenzene) was added to the reaction mixture over 12 minutes via cannula, and the reaction mixture was stirred for 15 min at -78 °C. 2-Chlorobenzaldehyde (16 mL, 141.96 mmol) was added dropwise, and the reaction mixture was stirred for 30 minutes at -78 °C. The reaction was quenched by addition of saturated aqueous ammonium chloride (80 mL) and water (200 mL), and the mixture extracted with EtOAc (3 × 300 mL). The combined organic phase was washed with water, brine and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by chromatography using 20:1 – 4:1 hexanes:EtOAc to yield 12.2 g of (2-chlorophenyl)-(2,6-dichloropyridin-3-yl)methanol (**8**) as a yellow oil. MS *m / z*: ESI$^+$ 290 (M + H)$^+$.

(2-Chlorophenyl)-(2,6-dichloro-pyridin-3-yl)methanol (**8**) (12. 2 g, 42.3 mmol) was dissolved in 200 mL of dry toluene, and 87 g of manganese dioxide was added. The reaction mixture was refluxed for 2.5 h, and was then hot filtered through Celite. The Celite plug was washed with 80 mL of hot EtOAc (in several portions), and the organic solvents were combined. Removal of solvent under reduced pressure yielded 14.05 g of (2-chlorophenyl)-(2,6-dichloropyridin-3-yl)methanone (**9**) as a viscous yellow oil. MS *m / z*: ESI$^+$ 288 (M + H)$^+$.

(2-Chlorophenyl)-(2,6-dichloropyridin-3-yl)methanone (**9**) (3. 0 g, 10.47 mmol) was dissolved in 25 mL of 4:1 EtOH:THF and cooled to 0 $^o$C. Hunig's base (*N*,*N*-diisopropylethylamine, 1.8 mL, 10.47 mmol) was added to the reaction mixture, followed by dropwise addition of 0.36 mL (11.52 mmol) of hydrazine.

The reaction mixture was stirred at 0 °C for five minutes, then heated to 70 °C for 1.5 h. Volatiles were removed under reduced pressure, and the residue was taken up in 150 mL of EtOAc, 10 mL of THF and 10 mL of MeOH. To this mixture was added saturated aqueous ammonium chloride (20 mL) and water (110 mL). The organic phase was collected, and the aqueous phase washed with an additional 100 mL of EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and 75% of solvent was removed under reduced pressure. The product crystallized from EtOAc to yield 1.18 g of 6-chloro-3-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (**10**) as a yellow solid. MS *m / z*: $ESI^-$ 262 $(M - H)^-$.

2,4-Difluorophenol (517 mg, 4 mmol) was placed in a 10 mL microwave reactor tube under nitrogen and cooled to 0 $^oC$. Potassium *t*-butoxide (4 mL of 1.0 M solution in THF) was added dropwise, and the solution was stirred for five min at 0 °C. The reaction mixture was warmed to rt, and 6-chloro-3-(2-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (**10**) (350 mg, 1.33 mmol) was added in one portion. The reaction was then heated to 160 °C in a microwave reactor for 9 h. The reaction mixture was cooled and partitioned between water and EtOAc. The organic phase was washed with brine, followed by water, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue purified by chromatography, eluting with 1:200 MeOH:$CH_2Cl_2$. Solvent was removed, and the residue was recrystallized from $CH_2Cl_2$:hexanes to afford 78 mg of 3-(2-chlorophenyl)-6-(2,4-difluoro-phenoxy)-1*H*-pyrazolo[3,4-*b*]pyridine (**11**) as a white solid. $^1H$ NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 1H $J$ = 8 Hz), 7.57 (m, 2H), 7.38 (m, 2H), 7.24 (m, 1H), 6.98 (m, 2H), 6.89 (d, 1H, $J$ = 1 Hz). MS *m /z*: $ESI^+$ 358 $(M + H)^+$.

**3-(2-Chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[4,3-*c*] (20).**

To a solution of 2-chloro-5-methylpyridine (**12**) (10 mL) in 155 mL of glacial acetic acid was added 19 mL of 30% aqueous hydrogen peroxide. The mixture was stirred at 80 °C for 8 h. The mixture was diluted with 100 mL of water and then concentrated under reduced pressure. The residue was made strongly alkaline with anhydrous sodium carbonate and shaken with 200 mL of $CHCl_3$. The solids were removed via filtration, and the filtrate was dried over $Na_2SO_4$, filtered and concentrated to give 10.8 g of the 2-chloro-5-methylpyridine-*N*-oxide in 82% yield; MS *m /z*: $ESI^+$ 144 $(M + H)^+$. To a mixture of 165 mL of nitric acid and 209 mL of sulfuric acid was slowly added 56.4 g of 2-chloro-5-methylpyridine-1-oxide. The reaction mixture was stirred at 100 °C for 2 h, cooled to rt, and added to ice. Sodium carbonate was added to adjust the pH to about pH 2 to pH 3. The resulting yellow solid was separated by filtration and washed with ice-water. The combined filtrates were extracted with hot $CHCl_3$. The extracts were combined, dried over $Na_2SO_4$, filtered, and concentrated to give 59.1 g of 2-chloro-5-methyl-4-nitropyridine-1-oxide (**13**) in 80% yield. MS *m / z*: $ESI^+$ 189 $(M + H)^+$.

To a suspension of sodium hydride (0.47 g, 60% in mineral oil) in 50 mL of THF was added dropwise a solution of 1 mL of 2,4-difluorophenol in 10 mL of THF. The reaction mixture was stirred for 1 h, and 2-chloro-5-methyl-4-nitropyridine-1-oxide (**13**) (2.0 g) was added slowly. The resulting mixture was stirred at reflux for 8 h and at rt overnight. The solvent was removed, and the light yellow solid isolated by extraction with $CH_2Cl_2$. Purification by chromatography, eluting with 1:1 hexanes:EtOAc gave 1.65 g

of 2-(2,4-difluorophenoxy)-5-methyl-4-nitropyridine-1-oxide (**14**) in 55% yield. MS *m / z*: $ESI^+$ 283 $(M + H)^+$.

To a solution of 2-(2,4-difluorophenoxy)-5-methyl-4-nitropyridine-1-oxide (**14**) (12.0 g) in 250 mL of anhydrous EtOH was added 2.0 g of 10% Pd on carbon. The reduction was performed on a Parr hydrogenator at 40 psi for 30 minutes. The solution was filtered through a pad of Celite, dried and concentrated to give 10.1 g of 2-(2,4-difluorophenoxy)-5-methyl-1-oxypyridin-4-ylamine (**15**) in 94% yield. MS *m / z*: $ESI^+$ 254 $(M + H)^+$.

To a solution of 2-(2,4-difluorophenoxy)-5-methyl-1-oxy-pyridin-4-ylamine (**15**) (4.0 g) in 75 mL of anhydrous $CHCl_3$, a solution of phosphorus trichloride (4.1 mL) in 20 mL of $CHCl_3$ was added dropwise at 0-5 °C. The mixture was stirred for 12 h at rt, heated to reflux for 3 h, then cooled, poured into water, basified (NaOH), extracted ($CHCl_3$), and dried over $Na_2SO_4$ to give 3.5 g of 2-(2,4-difluorophenoxy)-5-methylpyridin-4ylamine in 94% yield; MS *m / z*: $ESI^+$ 238 $(M + H)^+$. To a solution of 2-(2,4-difluorophenoxy)-5-methylpyridin-4-ylamine (3.6 g) in 80 mL of $CH_2Cl_2$, was added 4.7 g of acetic anhydride. The mixture was heated for 24 h, then poured into 200 mL of 5% aqueous sodium carbonate. The aqueous solution was extracted with $CH_2Cl_2$. The organic layers were combined, dried and concentrated to give 4.2 g of *N*-[2-(2,4-difluorophenoxy)-5-methylpyridin-4-yl]acetamide (**16**) in 99% yield. MS *m / z*: $ESI^+$ 279 $(M + H)^+$.

A mixture of *N*-[2-(2,4-difluorophenoxy)-5-methylpyridin-4-yl]acetamide (**16**) (2.3 g), acetic anhydride (2.6 g), acetic acid (2.7 mL) and potassium acetate (1.7 g) in 40 mL of benzene was heated to reflux. A solution of isoamyl nitrite (1.5 mL) in 10 mL of benzene was added to the refluxing solution over a period of 2 h, and heating at reflux was continued for another 18 h. The reaction mixture was cooled and stirred with 50 mL of 5% aqueous sodium carbonate solution for 3 h. The organic layer was separated, dried, concentrated and purified by chromatography, using 15:1 hexanes:EtOAc as eluent to give 0.27 g of 1-[6-(2,4-difluorophenoxy)pyrazolo[4,3-*c*]pyridine-1-yl]ethanone (**17**) in 11% yield. MS *m / z*: $ESI^+$ 290 $(M + H)^+$.

A mixture of 1-[6-(2,4-difluorophenoxy)pyrazolo[4,3-*c*] pyridine-1-yl]ethanone (**17**) (0.26 g) in 15 mL of 20% aqueous hydrochloric acid was heated for 3 hours, cooled, neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$ to give 0.21 g of 6-(2,4-difluorophenoxy)-1*H*-pyrazolo[4,3-*c*]pyridine in 95% yield. MS *m /z*: $ESI^+$ 248 $(M + H)^+$. To a rt solution of 6-(2,4-difluorophenoxy)-1*H*-pyrazolo[4,3-*c*]-pyridine (0.10 g) in DMF was added 0.11 g of iodine and 0.049 g of potassium hydroxide. After 5 h, an additional 10% of iodine was added, and the reaction mixture was stirred for an additional hour. The mixture was quenched with 1M sodium bisulfite (50 mL) solution and extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give 0.11 g of 6-(2,4-difluorophenoxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine in 71% yield; MS *m /z*: $ESI^+$ 374 $(M + H)^+$. To a solution of 6-(2,4-difluorophenoxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (0.10 g) in THF was added 0.15 g of di-*tert*-butyl dicarbonate and 1.6 mg of 4-(dimethylamino)pyridine. The resulting solution was heated at reflux for 1 h

under a nitrogen atmosphere, cooled, concentrated under vacuum, and purified by chromatography, using 9:1 hexanes:EtOAc as eluent, to afford 0.11 g of the *N*-Boc derivative of 6-(2,4-difluorophenoxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (**18**) in 86% yield. MS *m / z*: $ESI^+$ 474 $(M + H)^+$.

A solution of 1-Boc-6-(2,4-difluorophenoxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridine (**18**) (0.071 g) and 2-chlorophenylboronic acid in 5 mL of benzene and 1 mL of MeOH was stirred at rt for 15 min. To this solution was added *tetrakis*(triphenylphosphine)palladium (52 mg), and 0.3 mL of 1M sodium carbonate. The resulting mixture was heated to reflux for 5 h, cooled, filtered, and the organic layer was separated. The organic layer was washed, dried and concentrated. The residue was purified by chromatography using 20:1 hexanes:EtOAc as eluent to afford 45 mg of 3-(2-chlorophenyl)-6-(2,4-difluorophenoxy)pyrazolo[4,3-*c*]pyridine-1-carboxylic acid, *tert*-butyl ester (**19**) in 66% yield. MS *m / z*: $ESI^+$ 458 $(M + H)^+$.

A mixture of 3-(2-chlorophenyl)-6-(2,4-difluorophenoxy)pyrazolo[4,3-*c*]pyridine-1-carboxylic acid, *tert*-butyl ester (**19**) (14.0 mg) in 3 mL of 0.5 M sodium methoxide solution in MeOH was stirred for 30 minutes at rt. The resulting solution was concentrated and the residue was extracted with EtOAc, washed, dried and concentrated to give 10.0 mg of 3-(2-chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[4,3-*c*]pyridine (**20**) in 91% yield. $^1H$ NMR ($CDCl_3$, 300 MHz) δ 11.28 (s, 1H), 8.67 (s, 1H), 7.61 (m, 2H), 7.42 (m, 2H), 7.19 (m, 1H), 6.92 (m, 2H), 6.74 (s, 1H); MS *m / z*: $ESI^+$ 356 $(M + H)^+$.

**3-(2-Chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[3,4-*b*]pyrazine (25).**

To a -20 °C solution of *n*-butyllithium (2.5M in hexane, Aldrich, 26.5 mmol) in dry THF (200 mL), under argon, was added 2,2,6,6-tetramethylpiperidine (Aldrich, 11.5 mL, 66.5 mmol, 1.22 eq). The resulting solution was warmed to 0 °C over 0.5 hour period. The solution was then cooled to -78 °C, and a solution of 2,6-dichloropyrazine (**21**, Aldrich, 8.24 g, 55.3 mmol, 1.0 eq) in THF was slowly added via syringe. After addition was complete, the resulting mixture was stirred at -78 °C for an additional 1 h, then 2-chlorobenzaldehyde (Aldrich, 9.3 mL, 83 mmole, 1.5 eq) was added dropwise via syringe. The reaction mixture was stirred for another hour, then quenched with hydrochloric acid (18 mL, 220 mmol, 4 eq)/EtOH (75 mL)/THF (90 mL) mixture, and warmed to rt. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution and extracted with $Et_2O$. The organic layer was separated and washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to give a crude oil which was purified via chromatography, using 1:1 $CH_2Cl_2$:hexanes as the eluent, to give (2-chlorophenyl)-(3,5-dichloropyrazin-2-yl)methanol (**23**) (12.8 g, 44 mmol, 80% yield). MS *m / z*: $ESI^+$ 290 $(M + H)^+$.

To a $CH_2Cl_2$ solution of (2-chlorophenyl)(3,5-dichloropyrazin-2-yl)methanol (7.1 g, 24.5 mmol) was added solid manganese (IV) oxide (25 g, 245 mmol) in portions. The resulting mixture was stirred at rt overnight. The reaction mixture was filtered, and the filtrate was concentrated to give (2-chlorophenyl)-(3,5-dichloropyrazin-2-yl)methanone (**23**) (6.02 g, 21 mmol, 85% yield). MS *m / z*: $ESI^+$ 288 $(M + H)^+$.

To a solution of (2-chlorophenyl)-(3,5-dichloropyrazin-2-yl)methanone (**23**) (2.1 g, 7.3 mmol, 1.0 eq) in

25 mL DMF, under nitrogen, was added 2,4-difluorophenol (0.7 mL, 7.3 mmol, 1.0 eq) and potassium carbonate (1.21 g, 8.76 mmol, 1.2 eq). The resulting mixture was stirred overnight at rt and then concentrated. The residue was dissolved in $CH_2Cl_2$ and washed with water and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under vacuum to give a crude oil which was purified by chromatography, using 1:1 $CH_2Cl_2$/hexanes as the eluent, to give [3-chloro-5-(2,4-difluorophenoxyl)-pyrazin-2-yl](2-chlorophenyl)methanone (**24**) (2.46 g, 6.45 mmol, 88% yield). MS *m / z*: $ESI^+$ 382 $(M + H)^+$.

To a solution of [3-chloro-5-(2,4-difluorophenoxyl)pyrazin-2-yl](2-chlorophenyl)methanone (**24**) (0.73 g, 1.9 mmol, 1.0 eq) in EtOH, was added hydrazine hydrate (0.19 mL, 3.8 mmol, 2.0 eq). The resulting mixture was refluxed under nitrogen for 0.5 h. The reaction mixture was cooled and filtered to give 3-(2-chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[3,4-*b*]pyrazine (**25**) (0.285 g, 0.8 mmol, 42% yield) as a solid. mp 240.5-241.5 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 14.06 (s, 1H), 8.66 (s, 1H), 7.78 (m, 1H), 7.57 (m, 4H), 7.25 (m, 2H); MS *m / z*: $ESI^+$ 359 $(M + H)^+$.

**6-(2,4-Difluorophenoxy)-3-(2-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]pyridazine (30).**
4,6-Dichloropyridazine-3-carboxylic acid ethyl ester (**26**) (1.03 g, 4.67 mmol, prepared as described by Xie, L. *et al*.[5]) was dissolved in 25 mL dry THF, and the reaction mixture cooled in a dry ice/acetone bath for 15 min. 2-Methoxyphenylmagnesium bromide (7 mL of 1M solution in THF, 7.00 mmol) was added, and the reaction mixture was stirred for 8 h under nitrogen at -78 °C. Silica gel (11.0 g) was added, and the reaction mixture was allowed to warm to rt. Solvent was removed under reduced pressure, and the residue was purified by chromatography, eluting with 100% hexanes – 4:1 hexanes:EtOAc, to yield (4,6-dichloropyridazin-3-yl)(2-methoxyphenyl)methanone (**27**) as a yellow solid, 1.02 g (3.65 mmol, 78% yield). MS *m / z*: $ESI^+$ 283 $(M + H)^+$.

(4,6-Dichloropyridazin-3-yl)(2-methoxyphenyl)methanone (**27**) (0.75 g, 2.66 mmol), 25 mL dry THF, and $NaSCH_3$ (0.207 g, 2.81 mmol) were stirred under nitrogen at rt for 17 h. $Et_2O$ (25 mL) was then added, and the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography, eluting with 100% hexanes – 3:1 hexanes:EtOAc, to give (6-chloro-4-methylsulfanylpyridazin-3-yl)-(2-methoxyphenyl)methanone (**28**) as a yellow solid, 0.51 g (65% yield). MS *m / z*: $ESI^+$ 296 $(M + H)^+$.

(6-Chloro-4-methylsulfanylpyridazin-3-yl)(2-methoxyphenyl)methanone (**28**) (0.101 g, 0.342 mmol, DMF (2 mL), 2,4-dinitrophenol (0.04 mL, 0.42 mmol), and sodium hydride (0.017 g, 0.42 mmol of mineral oil suspension) were stirred under nitrogen for 3 h at rt. The reaction mixture was then stirred for 2 h at 68 °C, then cooled, and 20 mL of $Et_2O$ was added. The organic layer was washed with water (2 × 20 mL), with saturated brine (20 mL), and dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography, eluting with 100% hexanes – 3:1 hexanes:EtOAc, to yield [6-(2,4-difluorophenoxy)methylsulfanylpyridazin-3-yl](2-methoxyphenyl)-methanone (**29**) as a white solid (0.107 g, 81% yield). MS *m / z*: $ESI^+$ 389 $(M + H)^+$.

[6-(2,4-Difluorophenoxy)-4-methylsulfanylpyridazin-3-yl](2-methoxyphenyl)methanone (**29**) (0.076 g, 0.196 mmol), $CH_2Cl_2$ (2 mL) , and *meta*-chloroperbenzoic acid (0.055 g of 77% *m*CPBA, 0.25 mmol) were stirred at rt for 1 h. The reaction mixture was diluted with 5 mL of $CH_2Cl_2$ and washed with saturated aqueous sodium bicarbonate (3 × 5 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in a mixture of 2 mL THF and 2 mL MeOH, hydrazine (0.0075 mL, 0.24 mmol) and diisopropylethylamine (0.045 mmol, 0.26 mmol) were added. The reaction mixture was stirred for 18 h at rt, then partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography, eluting with 100% hexanes – 3:1 hexanes:EtOAc, to yield 0.030 g of a mixture of 6-(2,4-difluorophenoxy)-3-(2-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]pyridazine and [6-(2,4-difluorophenoxy)-methylsulfonylpyridazin-3-yl]-(2-methoxyphenyl)methanone. This mixture was again treated with excess hydrazine for 18 h together with heating to 65 °C to drive the reaction to completion, followed by workup and chromatography as described above, to yield 6 mg of 6-(2,4-difluorophenoxy)-3-(2-methoxyphenyl)-1*H*-pyrazolo[4,3-*c*]pyridazine (**30**) as a pale yellow solid. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 13.65 (s, 1H), 7.72 (m, 1H), 7.57 (s, 1H), 7.51 (m, 3H), 7.12 (m, 3H), 3.76 (s, 3H); MS *m / z*: ESI$^+$ 355 $(M + H)^+$.

**6-(2,4-Difluorophenoxy)-3-(2-methoxyphenyl)-1*H*-pyrazolo[4,3-*b*]pyridine (34).**

2-Methoxyphenylmagnesium bromide (53.3 mL of 1.75 M solution in THF) was cooled to 0 °C, and 3,5-difluoronicotinonitrile (**31**) (5.0 g, 35.6 mmol) was added over 20 min to the reaction mixture at 0 °C. The reaction was quenched by addition of of 60 mL of 2M $H_2SO_4$, and the mixture was allowed to warm to rt. The reaction mixture was extracted with EtOAc (50 mL), and the aqueous phase was basified by addition of 12 mL of 5M NaOH. The aqueous phase was then extracted with EtOAc (2 × 70 mL), the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography, using 10:1 – 4:1 hexanes:EtOAc as eluent, to yield 7.9 g of (3,5-difluoro-pyridin-2-yl)-(2-methoxy-phenyl)methanone (**32**). MS *m / z*: ESI$^+$ 250 $(M + H)^+$.

Powdered cesium carbonate (1.8 g, 5.7 mmol) was suspended in 8 mL of DMF, and 2,4-difluorophenol (0.45 mL, 4.8 mmol) was added to the mixture. (3,5-Difluoropyridin-2-yl)(2-methoxyphenyl)methanone (**32**) (1.2 g, 4.8 mmol), dissoved in 7 mL of DMF was then added, and the reaction mixture was stirred for 2 h at rt. The mixture was diluted with EtOAc (60 mL), washed with water (2 × 30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified by chromatography, using 20:1 - 4:1 hexanes:EtOAc as eluent, to yield 0.37 g of [5-(2,4-difluorophenoxy)-3-fluoro-pyridin-2-yl]-(2-methoxyphenyl)methanone (**33**) as an oil. MS *m / z*: ESI$^+$ 360 $(M + H)^+$.

[5-(2,4-Difluorophenoxy)-3-fluoropyridin-2-yl]-(2-methoxyphenyl)methanone (**33**) (560 mg, 1.5 mmol) was added to 17 mL of EtOH and the reaction mixture was heated until all solids had dissolved. The

reaction mixture was cooled, and *N*,*N*-diisopropylethylamine (0.21 mL, 2.3 mmol) and hydrazine (0.1 mL, 3.1 mmol) were added. The reaction mixture was stirred for 4 h at rt, then taken up in EtOAc (60 mL), washed with water (4 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography, using 4:1 - 1:1 hexanes:EtOAc as eluent, to yield 0.03 g of 6-(2,4-difluoro-phenoxy)-3-(2-methoxy-phenyl)-1*H*-pyrazolo[4,3-*b*]pyridine (**34**). mp: 143.2-144.9 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.86 (br s, 1H), 8.57 (d, 1H, *J* = 2 Hz), 7.38 (m, 1H), 7.17 (m, 3H), 7.06 (m, 2H), 6.93 (m, 1H), 3.98 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 161.5, 158.2, 156.6, 153.1, 153.0, 141.4, 140.0, 139.3, 135.6, 134.0, 130.3, 123.6, 122.0, 118.3, 112.3, 111.6, 106.2, 77.4; MS *m / z*: ESI$^+$ 354 $(M + H)^+$; Anal. Calcd For $C_{18}H_{10}N_3O_2F_2$: C 64.58%, H 3.71%, N11.90%; found: C 64.53%, H 3.64%, N 11.84%.

**3-(2-Chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[3,4-*d*]pyrimidine (45).**

To a solution of 4-chloro-2-methylthiopyrimidine (Aldrich) (20 g, 124.51 mmol) in 300 mL dry THF at -78 °C under argon was slowly added a solution of 2.0 M LDA, (109 mL, 1.75 eq) in THF via cannula, slowly, over 15 min. After addition was complete, the resulting mixture was stirred at -78 °C for an additional 15 min, after which 2-chlorobenzaldehyde (Aldrich) (29.5 mL, 2.1 eq) was added dropwise via syringe. The reaction mixture was stirred for an additional 30 min at -78 °C, then quenched with saturated aqueous ammonium chloride (150 mL). EtOAc was added, the mixture was allowed to warm to rt, and the layers were partitioned and separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine. The EtOAc layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as an oil. Purification by chromatography, eluting with 20:1 – 5:1 hexanes:EtOAc gave (4-chloro-2-methylsulanyl-pyrimidin-5-yl)-(2-chloropheny) methanol (**41**), 10.8 g, as an orange-yellow semi-solid. MS *m / z*: ESI$^+$ 301 $(M + H)^+$.

To a solution of (2-chlorophenyl)-(4-chloro-2-methylsulfanylpyrimidin-5-yl)methanol (**41**) (10.8 g, 35.75 mol) in toluene (150 mL) was added manganese (IV) oxide (Aldrich) (31.2 g, 10 eq). The resulting mixture was heated to reflux with stirring for a total of 2.5 h. The reaction was then filtered hot through a 3.5 cm pad of Celite. The pad of Celite was rinsed with hot EtOAc, and the filtrate was concentrated to give a crude oil. Purification by chromatography, eluting with 50:1 – 10:1 hexanes:EtOAc, gave (2-chlorophenyl)-(4-chloro-2-methylsulfanylpyrimidin-5-yl)methanone (**42**) as a yellow viscous semi-solid, 5.3 g. MS *m / z*: ESI$^+$ 299 $(M + H)^+$.

To a solution of (2-chlorophenyl)-(4-chloro-2-methylsulfanylpyrimidin-5-yl)methanone (**42**) (5.3 g, 17.72 mmol) in EtOH (25 mL) was added anhydrous hydrazine (1.12 mL, 2 eq) dropwise with stirring. The reaction was then stirred for 20 min, after which it was cooled in an ice bath and the precipitated solid was removed by filtration. The solid was rinsed with cold EtOH. The filtrate was concentrated to provide a crude oil, which was diluted with EtOAc (80 mL), THF (10 mL), MeOH (5 mL), and water (80 mL). This mixture was partitioned and the layers separated. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated to give 3-(2-chlorophenyl)-6-methylsulfanyl-1*H*-pyrazolo[3,4-*d*]-

pyrimidine (**43**) as a yellow powder, 2.81 g. MS *m / z*: $ESI^+$ 277 $(M + H)^+$.

To a 0 °C solution of 3-(2-chlorophenyl)-6-methylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**43**) (2.8 g, 10.37 mmol) in THF (46 mL) and MeOH (28 mL) was added a solution of Oxone (Aldrich) (10. 9 g) in water (38 mL) dropwise. The mixture was stirred for 20 h at rt. The reaction was monitored by TLC. The volume of the mixture was reduced about 80% under vacuum, then EtOAc (80 mL), water (40 mL) and saturated aqueous sodium bicarbonate (15 mL) were added, then the layers were partitioned and separated. The organic layer was washed with brine (50 mL) and back extracted with EtOAc (80 mL). The EtOAc phase was dried over $MgSO_4$, filtered and concentrated to give 3-(2-chlorophenyl)-6-methanesulfonyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**44**) as a light-brown powder 2.90 g. MS *m / z*: $ESI^-$ 307 $(M - H)^-$.

To a neat sample of 2,4-difluorophenol (Aldrich) (379 mg, 3 eq) in a microwave reactor vessel, at 0 °C, was added dropwise 1M potassium *tert*-butoxide solution in THF (2.9 mL, 3.05 eq). The mixture was stirred for 5 min, then warmed to rt. Solid 3-(2-chlorophenyl)-6-methylsulfonyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (300 mg, 0. 971 mmol) was added and the reaction mixture was placed in a microwave reactor and heated at 120 °C for 15 min. The reaction mixture was diluted with EtOAc (50 mL), saturated aqueous ammonium chloride (10 mL) and water (40 mL). The mixture was partitioned and the organic layer separated. The aqueous layer was extracted with EtOAc (40 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to provide the crude compound. Purification by preparative thin layer chromatography, eluting with 50:1 MeOH:$CH_2Cl_2$, followed by crystallization from $CH_2Cl_2$:hexanes gave 3-(2-chlorophenyl)-6-(2,4-difluorophenoxy)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**45**) as a white powder, 127 mg. mp 173.4-176.4 °C; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 9.05 (s, 1H), 7.63 (m, 1H), 7.56 (m, 1H), 7.45 (m, 2H), 7.29 (M, 1H), 6.96 (M, 2H); MS *m / z*: $ESI^+$ 359 $(M + H)^+$: Anal. Calcd for $C_{17}H_{10}N_4OClF_2$: C 56.92%, H 2.53%, N 15.62%. Found: C 56.52%; H 2.37%; N 15.48%.

**6-(2,4-Difluorophenoxy)-3-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (49).**

An oven dried 1 liter flask was charged with sodium hydride (35 g, 876 mmol, 60% suspension in mineral oil) and covered with 400 mL of dry THF under argon. The flask was cooled to 0 °C and 2,4-difluorophenol (84 mL, 876 mmol) was added via slow drop-wise addition over 30 min. After complete addition, the material was stirred for 10 min at 0 °C and then warmed to rt. 5-Bromo-2,4-dichloropyrimidine (Aldrich) (50 g, 219 mmol) was added in one portion. The mixture was heated to 70 °C (oil bath) for 5 h, and then cooled to rt and stirred overnight. To the mixture was added 600 mL of EtOAc and 400 mL of 1N aqueous sodium hydroxide. The material was transferred to a separatory funnel and agitated. The organic phase was collected and washed with 1N sodium hydroxide solution (2 × 400 mL), and brine (400 mL). The aqueous phases were back extracted with EtOAc (2 × 300 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was isolated via crystallization from $Et_2O$:hexanes to afford a first crop of 55.85 g and a second crop of 17.21 g of 5-bromo-2,4-bis-(2,4-difluorophenoxy)pyrimidine (**47**) as a white solid. MS m/z: $ESI^+$ 416 $(M+H)^+$.

5-Bromo-2,4-bis-(2,4-difluorophenoxy)pyrimidine (**47**) (0.5 g, 1.2 mmol) was dissolved in 25 mL THF and cooled to 0 °C. Isopropylmagnesium chloride (0.8 mL, 1.44 mmol) was added, and the reaction mixture was stirred for 1 h at 0 °C. Isovaleryl chloride (1.47 mL, 12. 0 mmol) was then added, and the reaction mixture was stirred for another hour at 0 °C. The reaction was quenched with 35 mL of saturated aqueous sodium bicarbonate and 25 mL water. The aqueous mixture was extracted with EtOAc (3 × 25 mL), the combined organic layers washed with brine, dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure. The residue was purified by chromatography, using 5:1 hexanes:EtOAc as eluent, to yield 0.429 g (85%) of 1-[2,4-bis-(2,4-difluorophenoxy)pyrimidin-5-yl]-3-methylbutan-1-one (**48**). MS *m / z*: $ESI^+$ 421 $(M + H)^+$.

1-[2,4-Bis-(2,4-difluorophenoxy)pyrimidin-5-yl]-3-methylbutan-1-one (**48**) (0.427 g, 1.0 mmol) was dissovled in 10 mL of 10:1 dioxane:EtOH, and hydrazine (0.032 mL) was added. The reaction mixture was heated to 90 °C for 4 h, then cooled and quenched by addition of 25 mL saturated aqueous ammonium chloride and 25 mL water. The aqueous mixture was extracted with EtOAc (3 × 25 mL), the combined organic layers washed with brine, dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure. The residue was purified by chromatography, eluting with 5:1 hexanes:EtOAc, to yield 65 mg of 6-(2,4-difluorophenoxy)-3-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**49**) as an oil. $^1H$ NMR ($CDCl_3$, 300 MHz) δ 8.93 (s, 1H), 7.25 (m, 1H), 6.95 (m, 2H), 2.81 (d, 2H, *J* = 8 Hz), 2.15 (q, 1H, *J* = 8 Hz), 1.00 (d, 6H, *J* = 8 Hz); MS *m / z*: $ESI^+$ 305 $(M + H)^+$.

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