Supplementary Material (ESI) for MedChemComm
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Synthesis and Biological Activity of New Pyridone Diaryl Ether Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase

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Supporting Information

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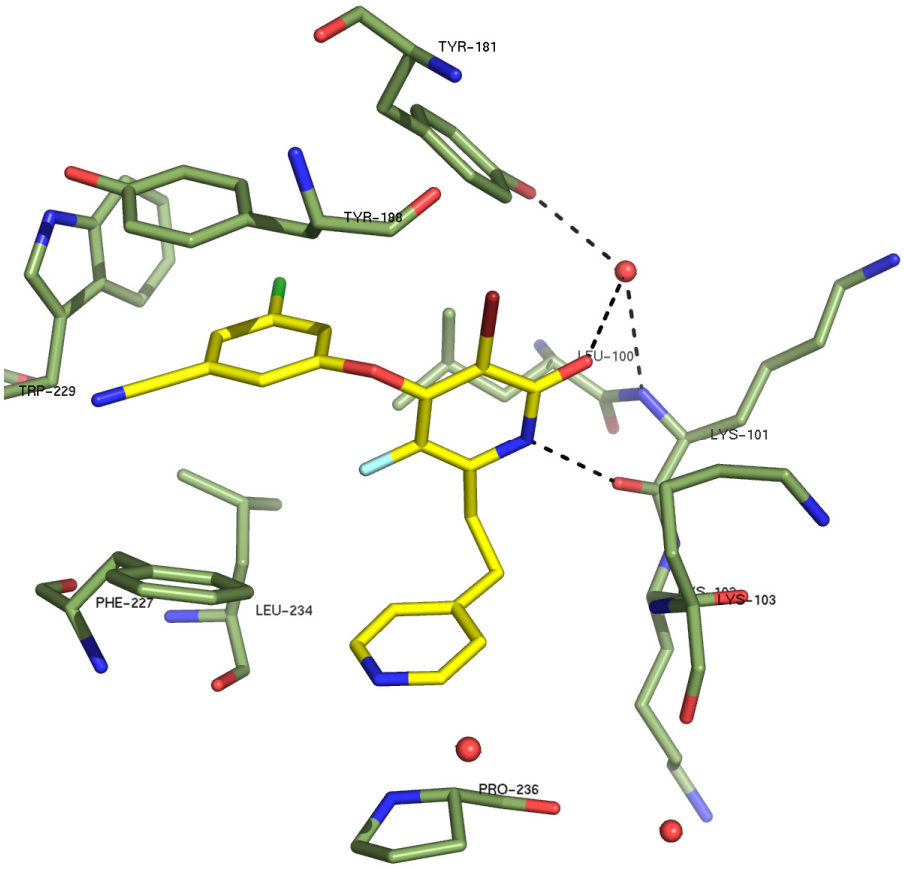
Supplemental Crystallography Data

Data set (inhibitor)	5252304
One p66/p51 heterodimer per asymmetric unit	
Spacegroup	$C222_1$
Cell dimensions *a, b, c* (Å)	117.11, 153.05, 153.10
Resolution range (Å)[a]	50-2.60 (2.69-2.60)
% Completeness [a]	74.9 (13.1)
$I/\sigma(I)$ [a]	16.4 (2.2)
Rsym (%)[a]	7.4 (29.3)
Observations [a]	1399632
Unique reflections [a]	31913 (551)
R_{cryst} [b]	23.46
R_{free} [c]	28.47
Avg B factor ($Å^2$)	
Protein (chains A/B)	83.6
Water molecules	69.7
Inhibitor	78.6
Rmsd bond length (Å)	0.006
Rmsd bond angle (º)	0.933
Ramachandran plot (% amino acids in region)	
Favored	90.4
Allowed	9.0
Generous	0.4
Disallowed	0.2

[a] numbers in parentheses are for the highest resolution shell

[b] $R_{cryst} = \Sigma_{hkl} \, | \, |F_{obs}| - |\langle F_{calc} \rangle| \, | \, / \, \Sigma_{hkl} \, |F_{obs}|$

c R_{free}, R_{cryst} with 5% of F_{obs} excluded from refinement



Model of **4f** in the NNRTI binding pocket

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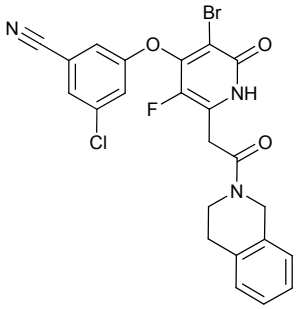
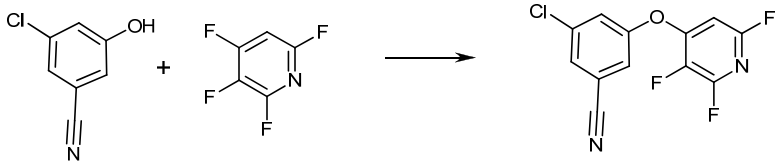
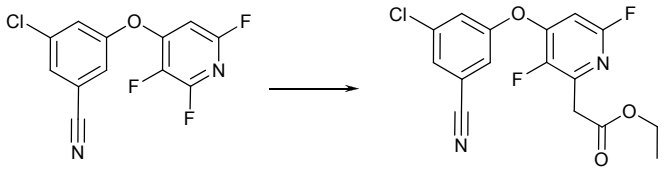
Synthetic Procedures



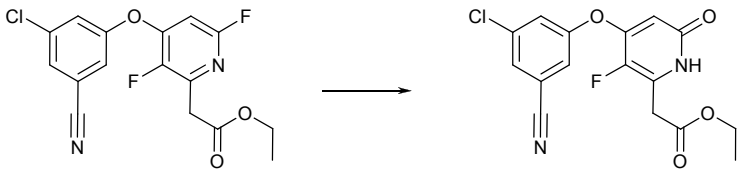
Compound 1: 3-(3-bromo-6-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-5-fluoro-2-oxo-1,2-dihydropyridin-4-yloxy)-5-chlorobenzonitrile



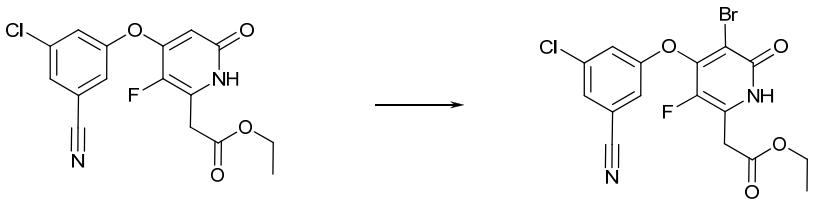
Step 1 (synthesis of compound 11): 3-chloro-5-cyanophenol (6.0 g, 20 mmol) and potassium carbonate (7.0 g, 51 mmol) were added to a solution of 2,3,4,6-tetrafluoropyridine (5.9 g, 39 mmol) in DMF (20 mL) at RT. The reaction mixture was stirred for 1h, and then partitioned between ethyl acetate and water. The organic layer was washed with brine, water, dried over sodium sulfate, and concentrated. The remaining solid was purified by flash column chromatography and eluted with 0% to 10% ethyl acetate in hexane. The product was obtained as a white solid (6.7 g, 61%).



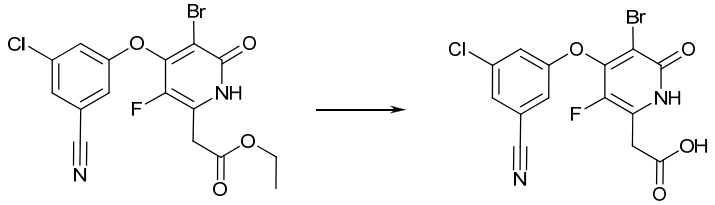
Step 2: Ethyl-tert-butylmalonate (2.06 g, 1.05 equiv) in DMF (5 mL) was added to 60% NaH (1.05 g, 2.0 equiv) in DMF (25 mL) at 0°C. The entire mixture was then warmed to RT for 20 min, after which it was recooled and the pyridyl phenyl ether (3.75 g, 13.2 mmol) in DMF (5 mL) was slowly added. The reaction mixture was then allowed to slowly warm to RT over 2 hrs. The mixture was then recooled to 0°C, quenched with saturated NH4Cl, diluted with water, and then extracted with Et_2O. The organic layers were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue obtained was redissolved in DCM (25 mL) and treated with TFA (10 mL) for 3 h. After which, the mixture was concentrated *in vacuo*, and chromatographed (SiO2, 5% to 15% EtOAc/hexanes) to provide the ester product (2.7 g, 58%).



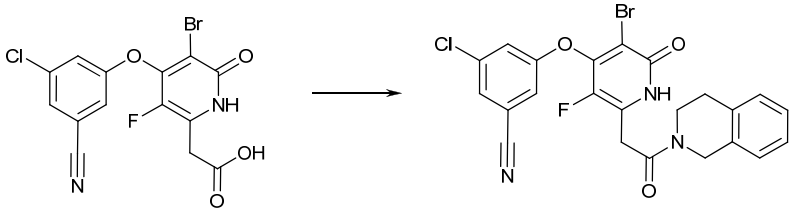
Step 3: NaOAc (1.74 g, 3 equiv) was added to the ester (1.50 g, 4.26 mmol) in AcOH (20 mL). The mixture was then heated to 115°C for 3 days, after which it was cooled, concentrated *in vacuo*, and chromatographed directly (SiO2, 1% to 10% MeOH/DCM) to provide pyridone product (580 mg, 39%).



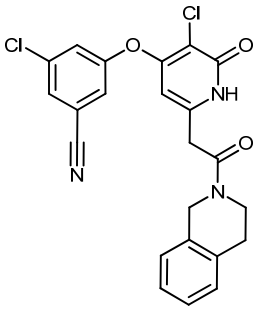
Step 4: NBS (360 mg, 3.5 equiv) was added to a solution of the pyridone (200 mg, 0.57 mmol) in acetonitrile (3.5 mL). The mixture was allowed to stir at rt for 2 h, upon which point the mixture was quenched with saturated 1 M sodium bisulfite, diluted with water, and then extracted with EtOAc. The organic layers were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue obtained was redissolved in MeOH (5 mL) and treated with 1 M sodium bisulfite (5 mL) at 45°C for 3 h. The mixture was diluted with water, and extracted with EtOAc. The organic layers were washed with brine, dried over magnesium sulfate, concentrated *in vacuo*, and chromatographed (SiO_2, 1% to 10% MeOH/DCM) to provide the bromo pyridone product (61 mg, 25%).



Step 5: $LiOH.H_2O$ (18 mg, 2.25 equiv) in H_2O (250 µL) was slowly added to a solution of the ester (80 mg, 0.19 mmol) in THF (1 mL) at 0 °C. After 7 h, 5% HCl was added, and the mixture was extracted with EtOAc. The organic layers were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Trituration of the solid with ether and hexanes provided the acid (40 mg, 54%).



Step 6: EDCI (16 mg, 1.7 equiv) was added to a solution of 1,2,3,4-tetrahydroisoquinoline (9 mg, 1.3 equiv), N-methylmorpholine (6 mg, 1.2 equiv), HOBT (7 mg, 1.05 equiv), DMAP (catalytic amount), and the phenyl acetic acid (20 mg, 0.050 mmol) in DMF (250 µL) at rt. This mixture was then stirred 4 h at rt, NH_4Cl was added, and the mixture extracted with CH_2Cl_2. The organic layers were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Preparative TLC (SiO_2, 5% MeOH/ CH2Cl2) provided the desired product (10 mg, 39%).



Compound 2a: 3-chloro-5-(3-chloro-6-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-oxoethyl)-2-oxo-1,2-dihydropyridin-4-yloxy)benzonitrile

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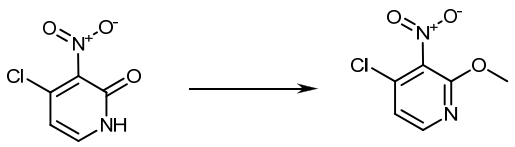
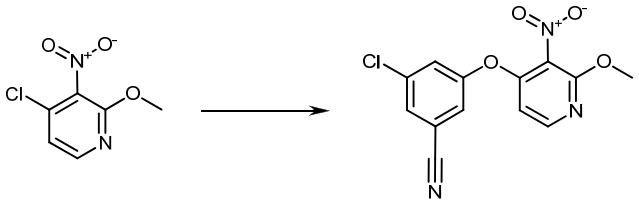
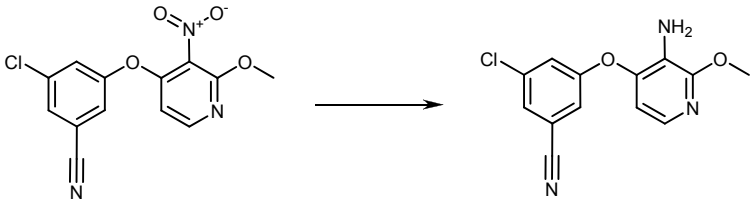


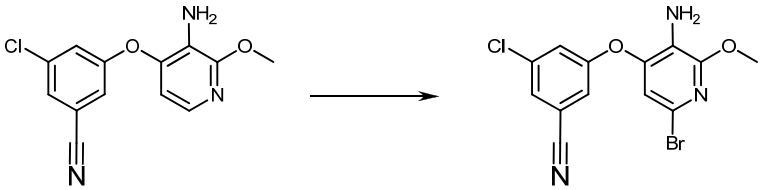
Step 1: Silver carbonate (9.50 g, 0.60 equiv) and iodomethane (18.0 mL, 5.00 equiv) were slowly added to a solution of chloro nitro pyridone (10.00 g, 56.2 mmol) in benzene (100 mL). After heating for 8 hrs at 50 ^{o}C, the reaction mixture was cooled to RT, filtered, and concentrated *in vacuo*. The crude residue was then dissolved in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo,* and chromatographed (SiO_2, 100% CH_2Cl_2) to provide the methyl ether product (5.81 g, 55%).



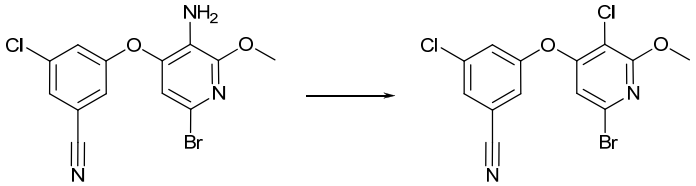
Step 2: 3-Chloro-5-cyanophenol (4.73 g, 1.00 equiv) and potassium carbonate (8.52 g, 2.00 equiv) were added to a solution of nitro compound from the previous step (5.81 g, 30.8 mmol) in DMF (90 mL). After heating for 20 hrs at 50 ^{o}C, the reaction mixture was cooled to RT, and poured into water (500 mL). The mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give material (~10 g) which was carried on to the next step.



Step 3: Ammonium chloride (6.59 g, 4.0 equiv) in water (50 mL), and Fe powder (6.88 g, 4.0 equiv) were slowly added to a solution of the nitro compound (~ 10 g, ~30.8 mmol) in EtOH (150 mL). After heating for 2 h at 100 ^{o}C, the reaction mixture was filtered, and the residual iron was washed with EtOAc. The organic layers were then washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to provide the aniline product (8.26 g, 97% over two steps).



Step 4: NBS (3.72 g, 1.05 equiv) was added in one portion to a solution of aniline compound from the previous step (5.43 mg, 19.7 mmol) in DMF (100 mL) at 0 ^{o}C. After warming the reaction mixture from 0 ^{o}C to room temperature over 2.5 hrs, the reaction mixture was poured into water. The mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give ~6.5 g aniline product that was sufficiently pure to be used in subsequent steps. Alternatively, this material can be chromatographed (SiO_2, 10% to 50% EtOAc/hexanes).



Step 5 (synthesis of compound 8): Lithium chloride (1271.76 mg, 30 mmol, 3 eq.) and Copper(II) chloride (97%, 1663.32 mg, 12 mmol, 1.2 eq.) in acetonitrile (anhydrous, 15 mL) were stirred at 60°C for a few minutes, then *tert*-Butyl nitrite (90%, 2339.2 µL, 17.7 mmol, 1.77 eq.) added, stirred for 10 min at 60°C, and eventually a solution of the aniline (3545.93 mg, 10 mmol) in acetonitrile (anhydrous, 35 mL) added. The reaction mixture was stirred at 60°C for 2 h, then cooled to 0°C and quenched with dil. Hydrochloric acid. Extracted with Ethyl acetate. The combined extracts

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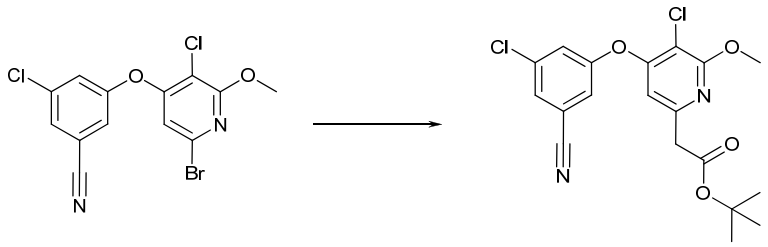
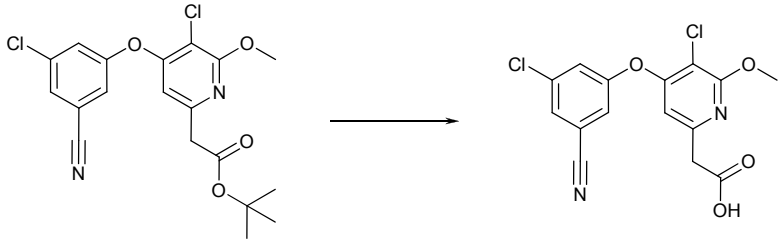
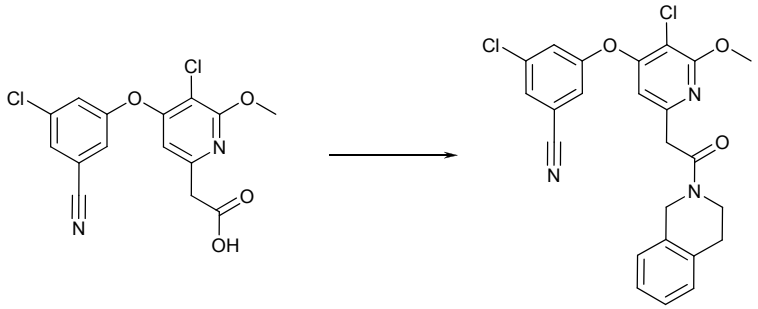
were washed with sat. aq. Sodium chloride solution, dried over Magnesium sulfate and the solvent evaporated under reduced pressure.
Purification by silica flash column chromatography (Hexane / Ethyl acetate 2 to 20%) gave 2373.6 mg (63.5%) of the chloride as a light yellow solid.



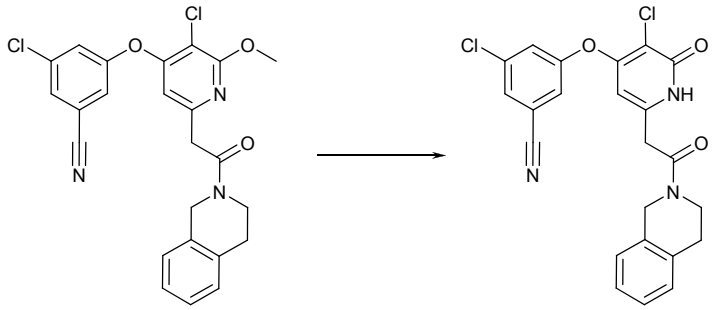
Step 6: 2-tert-Butoxy-2-oxoethylzinc chloride (6.42 mL, 0.5M, 1.2 equiv) was added to a solution of bis(tritertbutylphosphine) palladium (137 mg, 0.10 equiv) and the aryl bromide (999 mg, 2.67 mmol) in dioxane (18 mL) at RT. This solution was then stirred at RT overnight, after which the mixture was quenched with sat. NH_4Cl. The mixture was then extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (SiO_2, 5% to 25% EtOAc/hexanes) to provide the coupled product (825 mg, 75%).



Step 7 (synthesis of compound 9): TFA (2 mL) was added to a solution of the ester (800 mg, 1.96 mmol) in DCM (6 mL) at RT. This solution was stirred at rt for 4 h, and the mixture was concentrated *in vacuo*. Toluene (6 mL) was then added and the mixture was further concentrated to provide phenyl acetic acid product (690 mg, 99%).



Step 8: EDCI (54 mg, 1.7 equiv) was added to a solution of 1,2,3,4-tetrahydroisoquinoline (29 mg, 1.3 equiv), Hunig's base (26 mg, 1.2 equiv), HOBT (25 mg, 1 equiv), DMAP (20 mg, 1 equiv), and the phenyl acetic acid starting material (59 mg, 0.17 mmol) in DMF (2 mL) at RT. This mixture was then stirred at RT overnight, after which a tan precipitate had formed. This material was filtered and washed with water to provide pure amide product (77 mg, 99%).



Step 9: TMSCl (52 µL, 2.5 equiv) was slowly added to a solution of NaI (61 mg, 2.5 equiv) and the amide (76 mg, 0.16 mmol) in acetonitrile (10 mL). After stirring for 3 h at rt an orange precipitate had formed, to this was added

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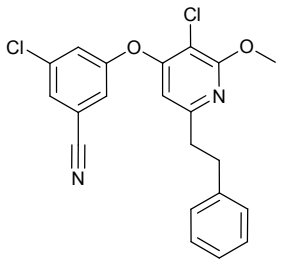
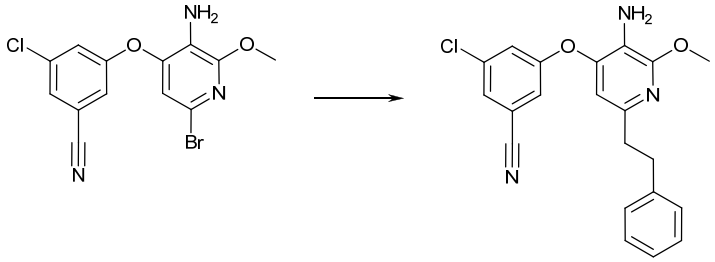
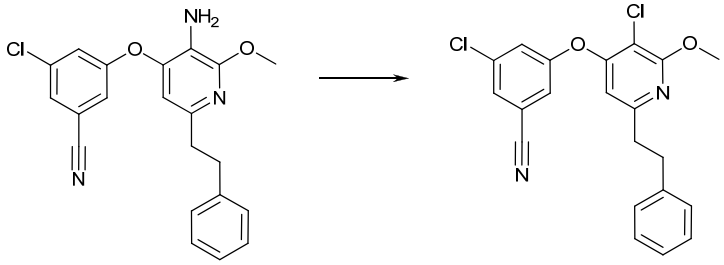
water (25 mL). The resulting mixture was filtered, washed with water and EtOAc to give to provide the resulting pyridone (34 mg, 46%).



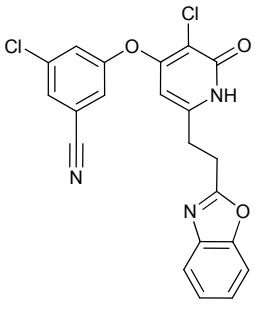
Compound 3a: 3-Chloro-5-(3-chloro-2-methoxy-6-phenethylpyridin-4-yloxy)benzonitrile



Step 1: Bis(tri-*t*-butylphosphine)palladium (0) (108 mg, 0.21 mmol, 0.15 eq.) followed by phenethylzinc bromide (Rieke, 0.5M solution in THF, 4.2 mL, 2.11 mmol, 1.5 eq.) were added to a solution of the 6-bromo-pyridine (500 mg, 1.41 mmol) in dioxane (anhydrous, 15 mL). The reaction mixture stirred under argon at room temperature overnight. Purification by silica flash column chromatography (Hexane / Ethyl acetate 5 to 40%) provided 335 mg (63%) of the desired product as a yellow oil.



Step 2: The Sandmeyer reaction to produce **3a** was performed analogously to that for **2a** (step 5, see above). The product was isolated as a white solid 65 mg (56.2%).



Compound 3b: 3-(6-(2-(Benzo[d]oxazol-2-yl)ethyl)-3-chloro-2-oxo-1,2-dihydropyridin-4-yloxy)-5-chlorobenzonitrile

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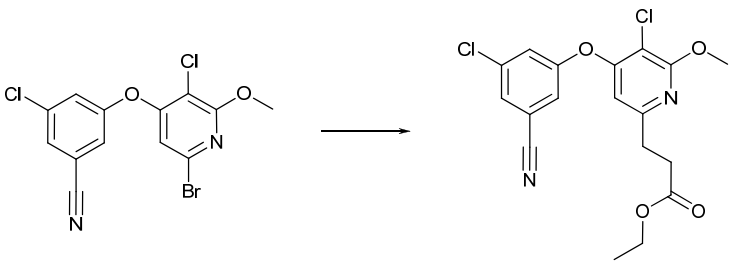
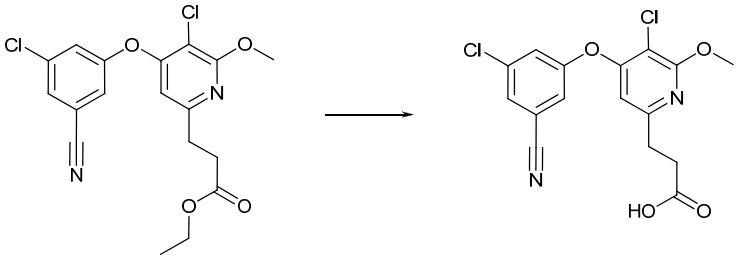
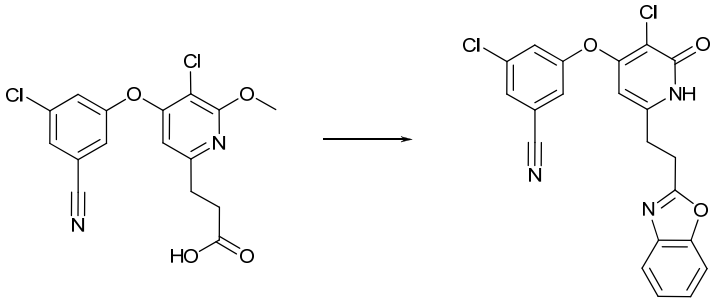


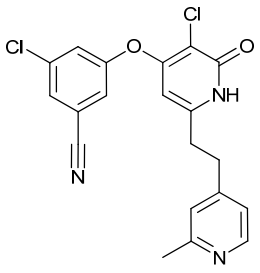
Step 1: To a solution of 6-bromo-pyridine (561 mg, 1.5 mmol) in dioxane (anhydrous, 24 mL) was added bis(tri-*t*-butylphosphine)palladium (0) (117 mg, 0.22 mmol, 0.15 eq.) followed by 3-ethoxy-3-oxopropylzinc bromide (Rieke, 0.5M solution in THF, 4.5 mL, 2.25 mmol, 1.5 eq.) and the reaction mixture stirred under Argon at room temperature overnight. The reaction mixture was concentrated under reduced pressure. Purification by silica flash column chromatography (Hexane / Ethyl acetate 2 to 20%, 2nd run 1 to 10%) provided 430 mg (72.5%) of the ester as a white solid.



Step 2: To a solution of the ester (428 mg, 1.08 mmol) in THF (17 mL) was added a solution of lithium hydroxide (264 mg, 10.8 mmol, 10 eq.) in water (4.2 mL) and the reaction mixture stirred at room temperature for 8 h. The reaction mixture was then diluted with water and ethyl acetate, acidified with 1M hydrochloric acid, the org. phase was washed with sat. aq. sodium chloride solution, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Purification by silica flash column chromatography (dichloromethane / methanol 1 to 8%, 2nd run 0.5 to 5%) gave 216 mg (54%) of the acid as a white solid.



Step 3: To a suspension of the acid (36 mg, 0.1 mmol) in acetonitrile (anhydrous, 1.5 mL) was added 2-aminophenol (99%, 11 mg, 0.1 mmol, 1 eq.), polymer supported triphenylphosphine (Polymer Laboratories PL-TPP Resin, loading 1.5 mmol/g, 200 mg, 0.3 mmol, 3 eq.) and trichloroacetonitrile (98%, 20.5 µL, 0.2 mmol, 2 eq.) sequentially. The reaction mixture was heated in the microwave (Personal Chemistry Emrys Optimizer EXP) to 150°C for 15 min. After cooling the resin was filtered off and washed with dichloromethane / methanol (8:2) and methanol. The combined filtrates were concentrated under reduced pressure. The crude material thus obtained was triturated with warm (60°C) acetonitrile. Purification of the residue by prep. HPLC provided 7 mg (15.0%) of the benzoxazole as a white solid.



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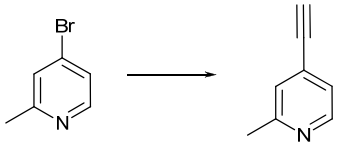
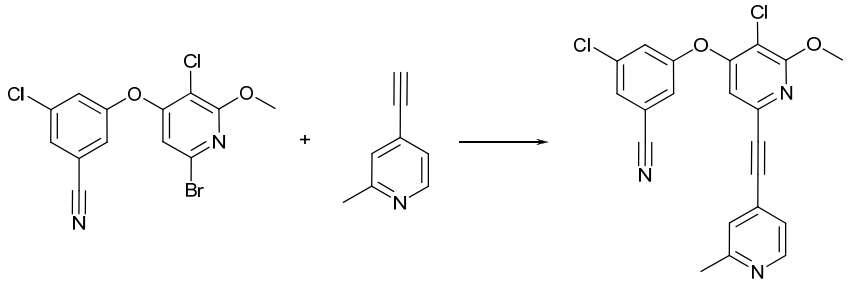
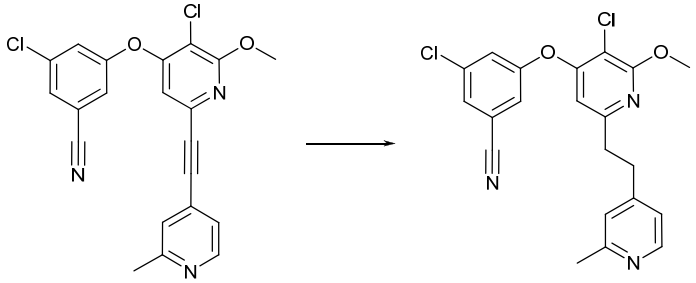
Compound 3a: 3-Chloro-5-(3-chloro-6-(2-(2-methylpyridin-4-yl)ethyl)-2-oxo-1,2-dihydropyridin-4-yloxy)benzonitrile



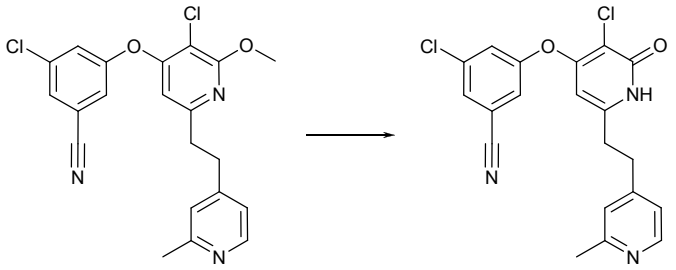
Step 1: To 4-bromo-2-methylpyridine (500 mg, 2.90 mmol), copper(I) iodide (55 mg, 0.29 mmol, 0.1 eq.) and trans-dichlorobis(triphenylphosphine)palladium(II) (Strem, 99%, 206 mg, 0.29 mmol. 0.1 eq.) in triethylamine (10.5 mL) was added trimethylsilylacetylene (98%, 503 µL, 3.4 mmol, 1.2 eq.), and the reaction mixture stirred under nitrogen at room temperature overnight. Aqueous sodium chloride solution was added to the reaction mixture, and the organic material was extracted with ethyl acetate. The combined extracts were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. The residue thus obtained was taken up in THF (35 mL), the solution cooled to 0°C, and tetrabutylammonium fluoride (3.2 ml of a 1.0M solution in THF, approx. 1.1 eq.) added. After stirring 15 min at 0°C, sat. aq. sodium chloride solution was added and the mixture extracted with ethyl acetate. The combined org. extracts were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Purification by silica flash column chromatography (Hexane / Ethyl acetate 12 to 100%) gave 184 mg (43%) of the alkyne as a brown solid.



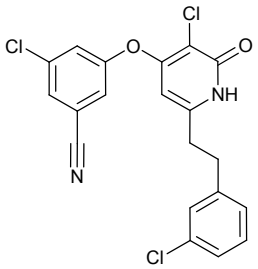
Step 2: To the bromide (50 mg, 0.13 mmol), copper(I) iodide (2.55 mg, 0.01 mmol, 0.1 eq.) and *trans*-Dichlorobis(triphenylphosphine)palladium(II) (Strem, 99%, 9.48 mg, 0.01 mmol. 0.1 eq.) in triethylamine (0.5 mL) was added the acetylene (23.49 mg, 0.16 mmol, 1.2 eq.) and the reaction mixture was stirred under nitrogen at room temperature overnight. Aqueous sodium chloride was added to the reaction mixture, and the organic material was extracted with ethyl acetate. The combined extracts were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Purification by silica flash column chromatography (Hexane / Ethyl acetate 10 to 80%) gave 23 mg (43%) of the diaryl alkyne.



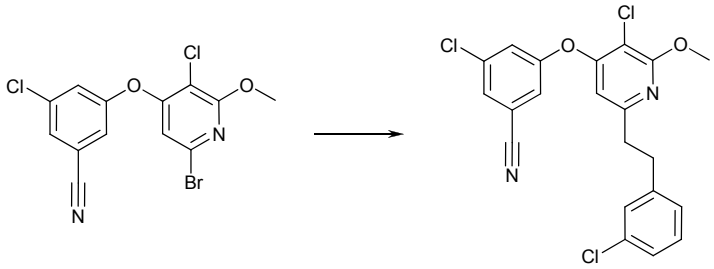
Step 3: A solution of the diaryl alkyne (23 mg, 0.05 mmol) in THF (2.7 mL) with palladium on carbon (10 wt. %, 7.6 mg) was stirred under a hydrogen atmosphere at room temperature until LC/MS analysis indicated virtually complete conversion (60 min). The catalyst was removed by filtering the solution through a membrane filter. Evaporation of the solvent under reduced pressure and purification by silica flash column chromatography (Hexane / Ethyl acetate 12 to 100%) gave 14 mg (63.3%) of the pyridine.



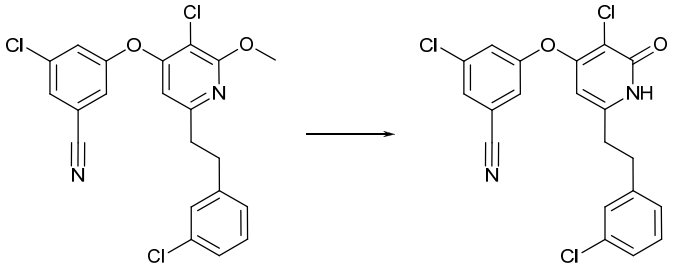
Step 4: To a solution of the pyridine (23 mg, 0.05 mmol) in acetonitrile (anhydrous, 3.0 mL) was added sodium iodide (21 mg, 0.14 mmol, 2.5 eq.) followed by a solution of chlorotrimethylsilane (99%, 18 µL, 0.14 mmol, 2.5 eq.) in acetonitrile (anhydrous, 0.5 mL). The mixture was stirred at room temperature for 3 h. A mixture of sat. aq. sodium chloride solution (2 mL) and sat. aq. sodium hydrogencarbonate (1.0 mL) solution was added, and the organic materials were extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Purification by prep. TLC (dichloromethane / methanol 5%) provided 14 mg (40.6%) of the pyridone product as a white solid.



Compound 3f: 3-Chloro-5-(3-chloro-6-(3-chlorophenethyl)-2-oxo-1,2-dihydropyridin-4-yloxy)benzonitrile



Step 1 (synthesis of compound 10f): To a solution of 6-bromo-pyridine (112 mg, 0.3 mmol) in 1,4-dioxane (anhydrous, 4.8 mL) was added bis(tri-*t*-butylphosphine)palladium (0) (Strem, 23 mg, 0.045 mmol, 0.15 eq.) followed by 3-chlorophenethylzinc bromide (Rieke, 0.5M solution in THF, 900 µL, 0.45 mmol, 1.5 eq.), and the reaction mixture stirred under Argon at room temperature overnight. The reaction mixture was concentrated under reduced pressure. Purification by silica flash column chromatography (hexane / ethyl acetate 2 to 20%) gave 74 mg (57.0%) of the product as a white solid.



Step 2: To a solution of the ether (74 mg, 0.17 mmol) in acetonitrile (anhydrous, 9.7 mL) was added sodium iodide (64 mg, 0.43 mmol, 2.5 eq.) followed by a solution of chlorotrimethylsilane (99%, 54.6 µL, 0.43 mmol, 2.5 eq.) in acetonitrile (anhydrous, 1.1 mL). The reaction mixture was stirred at room temperature for 2 h. A mixture of sat. aq.

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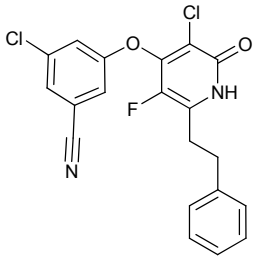
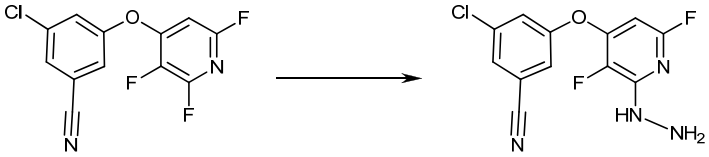
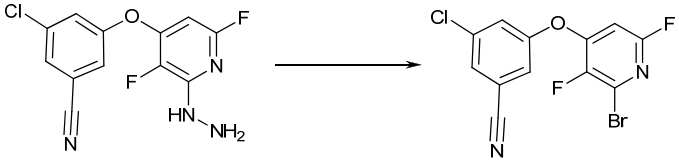
sodium chloride solution and sat. aq. sodium hydrogencarbonate solution was added, and the organics were extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and the solvent evaporated under reduced pressure. The residue thus obtained was triturated with methanol and warm (60°C) acetonitrile to give 26 mg (36%) of the pyridone compound as a white solid.



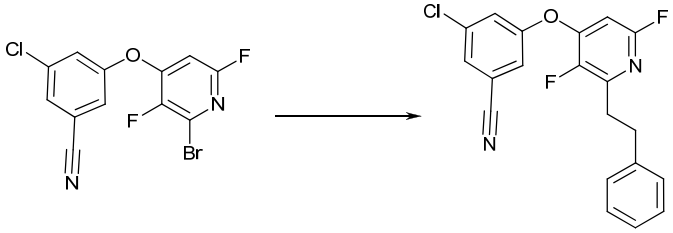
Compound 4a: 3-Chloro-5-(3-chloro-5-fluoro-2-oxo-6-phenethyl-1,2-dihydropyridin-4-yloxy)benzonitrile



Step 1: Hydrazine (1.5 mL, 47.3 mmol) was added to 3-chloro-5-(2, 3, 6-trifluoro pyridin-4-yloxy)benzonitrile (6.7 g, 23.6 mmol) in 24 mL of THF at RT,. White precipitate appeared after 1h. The solvent was removed and the white residue triturated with hexane to obtain the product as a white solid (7.0 g, 100%).



Step 2 (synthesis of compound 12): To 3-chloro-5-(3,6-difluoro-2-hydrazino-pyridin-4-yloxy)-benzonotrile (7.0 g, 23.6 mmol) suspended in 50 mL of chloroform, was added bromine (2.44 mL, 47.2 mmol) dropwise. The reaction mixture became an orange suspension, which was heated to 60^0C for 6 h. The mixture was diluted with DCM, washed with saturated sodium sulfite, water, dried over sodium sulfate, and concentrated. Purification by flash column chromatography and elution with 0% to 10% ethyl acetate in hexane, provided the product as a white solid (3.1g, yield 38%).



Step 3 (synthesis of compound 13a): To 3-(2-bromo-3,6-difluoro-pyridin-4-yloxy)-5-chloro benzonitrile(1.5 g, 4.35 mmol) in 40 mL of dioxane, was added bis-(tri-tertbutyl phosphine)palladium(0), followed by 0.5 M phenethyzinc bromide (13 mL, 6.5 mmol) in THF. After stirring at RT for 2 h, the reaction mixture was partitioned between ethyl acetate and brine, the organic layer dried over sodium sulfate, and the mixture was concentrated. Purification by flash column chromatography, eluting with 0% to 10% ethyl acetate in hexane, provided the product as a colorless oil (1.1g, 68%).

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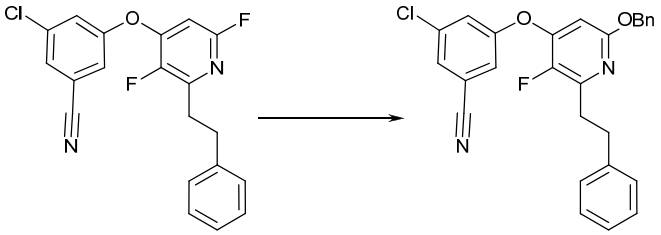
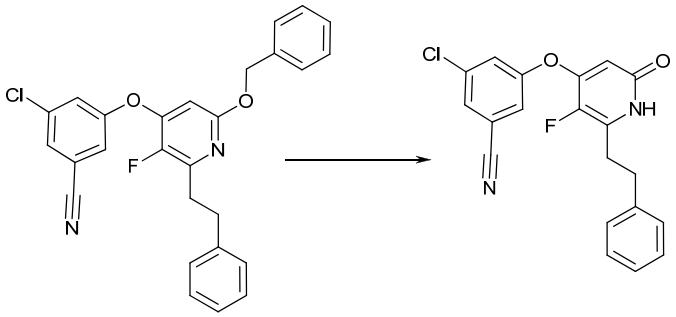
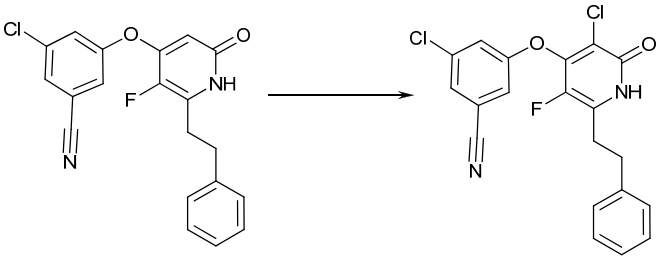


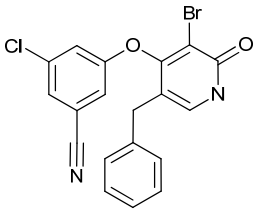
Step 4: Benzyl alcohol (460 µL, 4.45 mmol) was added to a mixture of sodium hydride (178 mg, 4.45 mmol) suspended in THF (20 ml) at RT. After stirring for 10 min, a THF (20 mL) solution of 3-chloro-5-(3,6-difluoro-2-phenethyl-pyridin-4-yloxy)-benzonotrile (1.1 g, 4.45 mmol) was added. After 1h, the reaction was quenched with saturated aqoues ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and concentrated. Purification by flash column, eluting with 0% to 10% ethyl acetate in hexane, provided the desired ether as a colorless oil (0.71g, 58%).



Step 5: 3-(6-Benzyloxy-3-fluoro-2-phenethyl-pyridin-4-yloxyl)-5-chloro-benzonitrile (0.71 g) in 20 mL of TFA, was heated to 50^0C for 5 h. Most of the volatile materials were removed, and the residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate. The extracts were dried over sodium sulfate and concentrated. Purification by flash column chromatography, eluting with 0% to 5% methanol in dichloromethane, provided the desired pyridone as an offwhite solid (0.26g, 46%).



Step 6: 3-Chloro-5-(5-fluoro-2-oxo-6-phenethyl-1,2-dihydro-pyridin-4-yloxy)-benzonitrile (37 mg, 0.1 mmol) was suspended in CH_3CN (1 mL) and isopropanol(1 mL). NCS (13.4 mg, 0.1 mmol) was added at RT, and the reaction mixture was heated to 60^0C for 2 h. Removal of the volatile materials and purification by preparative HPLC provided the product as white solid (8mg, 20%). Compound **4b** was prepared analogously using NBS.



Compound 5a: 3-(5-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yloxy)-5-chlorobenzonitrile

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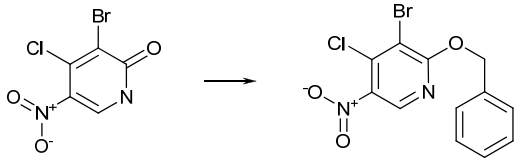
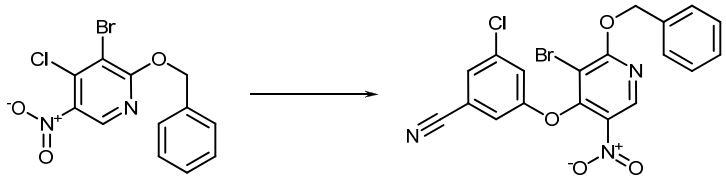
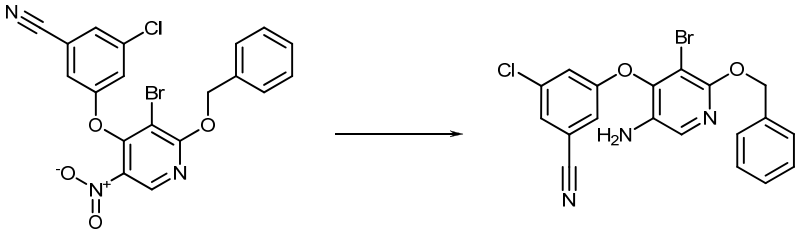


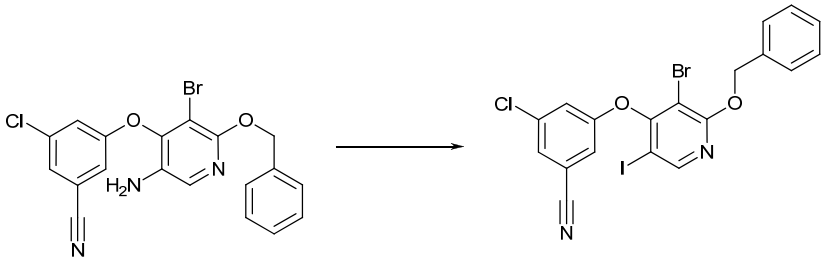
Step 1 (synthesis of compound 15): Silver carbonate (4.73 g, 0.51 equiv) and benzyl bromide (4.00 mL, 1.05 equiv) were slowly added to a solution of bromopyridone (8.5 g, 33.6 mmol) in benzene (120 mL). After heating for 18 hrs at 60 ^{o}C, the reaction mixture was cooled to RT, filtered, washed with EtOAc, and concentrated *in vacuo*. The resulting material was chromatographed directly (SiO_2, 3% to 15% EtOAc/hexanes) to provide the benzyloxypyridine product (5.1 g, 44%).



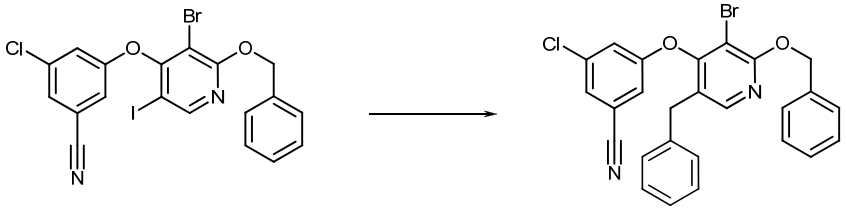
Step 2: 3-chloro-5-cyanophenol (2.23 g, 1.00 equiv) and potassium carbonate (3.50 g, 1.75 equiv) were added to a solution of the nitro compound from the previous step (5.00 g, 14.55 mmol) in THF (50 mL). After heating for 20 h at 60 ^{o}C, the reaction mixture was cooled to RT and poured into water (200 mL). The mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude diaryl ether (~7 g) which was carried on to the next step.



Step 3: To a solution of diaryl ether (6.5 g, 14.1 mmol) in EtOH (50 mL) and EtOAc (10 mL) containing ammonium chloride (2.70 g, 3.5 equiv) and H_2O (15 mL) was added electrolytic Fe powder (2.60, 3.5 equiv) with rapid stirring at 50^{o}C. The temperature of the reaction was then raised to 100^{o}C. After 3 h, the reaction was filtered hot and EtOAc were added. Concentration *in vacuo* gave a residue (~4.8 g) that was sufficiently pure to carry on to the next step.



Step 4 (synthesis of compound 16): t-BuONO (3.1 mL, 2.2 equiv) was slowly added to a suspension of the aniline (4.6 g, 10.7 mmol) in diiodomethane (17.3 mL, 20 equiv), and the mixture was heated to 60^{o}C. After 30 min, the mixture was cooled and chromatographed directly (SiO_2, 1% to 10% EtOAc/hexanes) to provide the desired iodide (2.75 g, 48%).



Step 5: Benzylzinc bromide (450 µL, 0.5M, 1.2 equiv) was added to a solution of bis(tritertbutylphosphine) palladium (5 mg, 0.05 equiv) and the iodide (100 mg, 0.19 mmol) in dioxane (1 mL) at rt. This solution was then stirred at room

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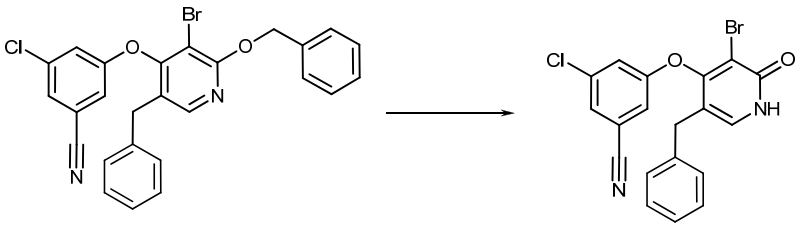
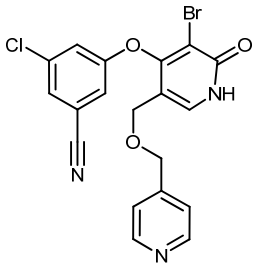
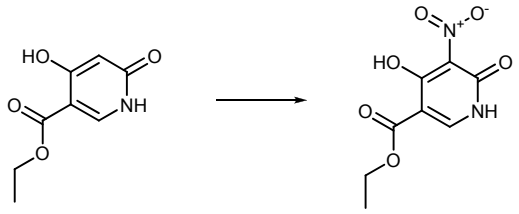
temperature until deemed complete by LC/MS (~ 4 h). Upon quenching with saturated NH_4Cl, the mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (SiO_2, 10% to 33% EtOAc/hexanes) to provide the coupled product (46 mg, 50%).



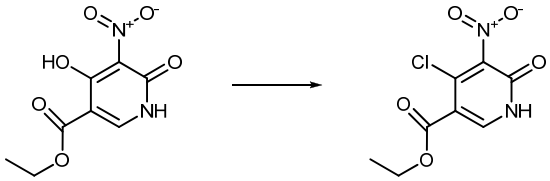
Step 6: TFA (1 mL) was added to a solution of the ether (45 mg, 0.092 mmol) in DCM (2 mL) at rt. This solution was stirred at rt for 2 h, after which the mixture was concentrated *in vacuo,* and chromatographed (SiO_2, 2% to 10% MeOH/DCM) to provide pyridone product (18 mg, 47%).



Compound 5d: 3-(3-Bromo-2-oxo-5-((pyridin-4-ylmethoxy)methyl)-1,2-dihydropyridin-4-yloxy)-5-chlorobenzonitrile



Step 1: To a cold (ice bath) solution of 4-hydroxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid ethyl ester (9.1g, 49.7 mmol) in concentrated sulfuric acid (75 mL) was added nitric acid (2.9 mL, 64.6 mmol) dropwise. The mixture was stirred for 1 h and then the cooling bath was removed. After 15 min, the mixture was poured into a beaker containing a 500 mL of ice. The material was stirred for 10 min, and the precipitated product was collected by filtration. The precipitate was washed well with greater than 1 L of water. The solid was dried in a vacuum oven, providing the desired product as a light yellow white solid (6.8 g).



Step 2: To a mixture of 4-hydroxy-5-nitro-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid ethyl ester (6.8 g, 29.8 mmol) and benzyltriethylammonium chloride (27.15 g, 119 mmol) in dry acetonitrile (115 mL) was added phosphoryl chloride (12 mL, 131 mmol) via drop-wise addition. The material was heated to 40 ^oC (oil bath) for 30 min and then heated to reflux for 1 hour. The mixture was cooled to ambient temperature, and the solvent and volatiles were removed on the rotary evaporator. Water (115 mL) was added and the mixture was stirred for 3 h. The precipitated product was collected by filtration. The solid is washed well with water and dried in the vacuum oven, providing an off-white crystalline product (6.21 g).

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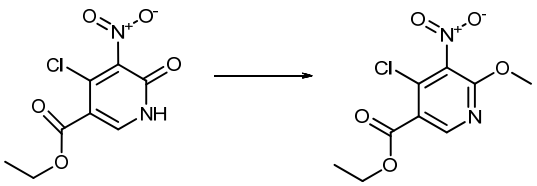
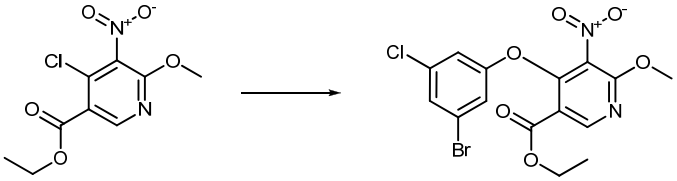
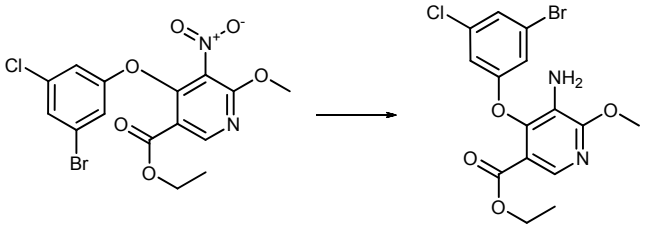


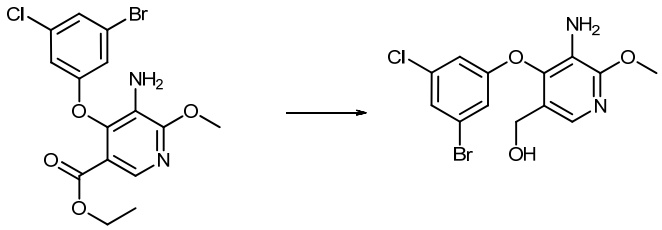
Step 3: To a solution of 4-chloro-5-nitro-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid ethyl ester (7.5 g, 30.4 mmol) in dry dichloromethane (100 ml) was added trimethyloxonium tetrafluoroborate (4.59 g, 30.4 mmol) and the mixture was heated to reflux overnight. Additional trimethyloxonium tetrafluoroborate (2.3 g, 15.2 mmol) was added, and heating was continued for 4 hours. The solution was cooled to RT and water (50 ml) was added with stirring. The solution was extracted with CH_2Cl_2 and dried over magnesium sulfate. Chromatography (SiO_2, 20 % EtOAc/Hexanes) gave the desired compound as a white crystalline solid (6 g).



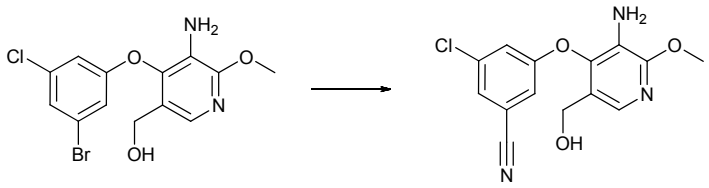
Step 4: To a solution of 4-chloro-6-methoxy-5-nitro-nicotinic acid ethyl ester pyridine (1.61 g, 6.18 mmol) in dry DMF (14 mL) was added powdered potassium carbonate (1.71 g, 13.6 mmol) followed by 3-bromo-5-chloro-phenol (1.41 g, 6.8 mmol). The mixture was heated to 50 ^oC for 6 h and then at 80 ^oC for 5 h. Additional 3-bromo-5-chloro-phenol (220 mg) was added as well as K_2CO_3 (270 mg) and heating at 80 ^oC was continued for 4 h. The material was cooled to RT and concentrated (rotary evaporator/high vacuum pump). The remainder was taken up in ethyl acetate (60 ml) and water (60 ml). The organic phase was separated and dried over magnesium sulfate. Chromatography (SiO_2, 2 - 14 % EtOAc/Hexanes) gave the title compound as a light yellow-brown solid (1.92 g).



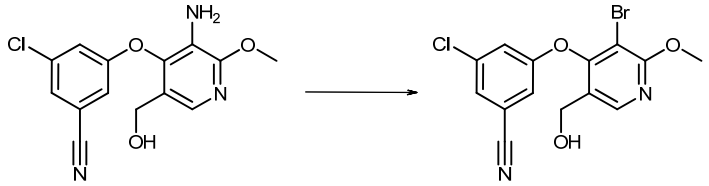
Step 5: To a solution of 4-(3-bromo-5-chloro-phenoxy)-6-methoxy-5-nitro-nicotinic acid ethyl ester (1.91 g, 4.43 mmol) in ethanol (10 mL) and water (6 ml) was added electrolytic iron (1 g, 17.7 mmol) and ammonium chloride (957 mg, 17.7 mmol). The mixture was heated to 100 ^oC for 4 hours. The material was filtered (hot) and rinsed well with hot EtOAc (about 100 ml). The filtrite was washed with an equal volume of brine and extracted with EtOAc (2 x 50 ml). The title compound was obtained as a light yellow-brown solid (1.54 g).



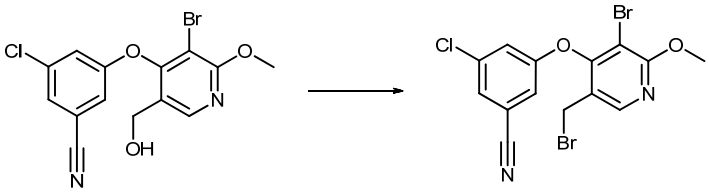
Step 6: A solution of 5-amino-4-(3-bromo-5-chloro-phenoxy)-6-methoxy-nicotinic acid ethyl ester (1.53 g, 3.82 mmol) in dry THF (45 mL) was cooled to -78 ^oC (acetone / dry ice bath) under a N_2 atmosphere. A solution of diisobutylaluminum hydride in CH_2Cl_2 (15 ml, 1.4 M) was added via drop-wise addition. The mixture was stirred for 5 min and then warmed to 0 ^oC. An aqueous solution of 10% Rochelle's salt (75 ml) was added and the mixture was stirred for 1.5 hours. The material was transferred to a separatory funnel and water (40 ml) was added with EtOAc (about 100 ml). The material was agitated and the EtOAc phase collected and washed with brine (100 ml). The aqueous phase was back extracted with EtOAc (2 x 75 ml). The combined organic phases were dried (MgSO4), filtered, and concentrated on the rotovap. Purification by preparative TLC (50% EtOAc / Hexanes) provided the final product as a light yellow-brown solid (900 mg).



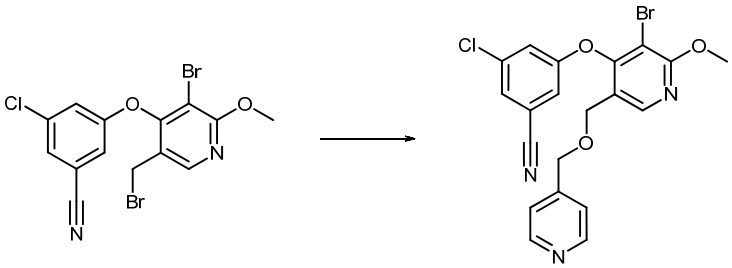
Step 7: A mixture of [5-amino-4-(3-bromo-5-chloro-phenoxy)-6-methoxy-pyridin-3-yl]-methanol (847 mg, 2.36 mmol), $Zn(CN)_2$ (277 mg, 2.36 mmol) and $Pd(PPh_3)_4$ (278 mg, 0.24 mmol) in dry DMF (20 mL) was degassed (5 vacuum / argon cycles). The material was heated to 80 ^oC for 8 hours under argon balloon. The material was cooled to RT and concentrated (rotary evaporator/high vacuum pump). The remainder was taken up in ethyl acetate (50 ml) and water (50 ml). Extraction with EtOAc, drying over magnesium sulfate, and chromatography (SiO_2, 20 - 60 % EtOAc/Hexanes) gave the title compound as a off-white solid (648 mg).



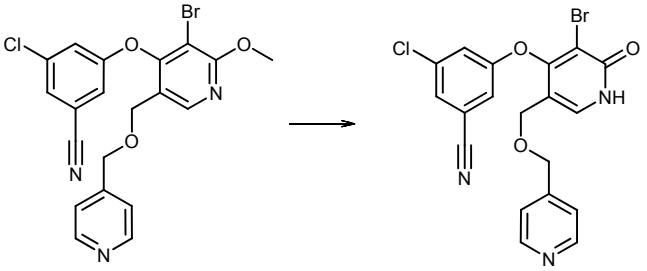
Step 8: A mixture of $Cu(II)Br_2$ (366 mg, 1.64 mmol) and LiBr (357 mg, 4.11 mmol) in dry acetonitrile (5 mL) was heated to 60 ^oC. Tert-butylnitrite (0.31 ml, 2.4 mmol) was added dropwise and the material was stirred for 25 minutes. A solution of 3-(3-amino-5-hydroxymethyl-2-methoxy-pyridin-4-yloxy)-5-chloro-benzonitrile (418 mg, 1.37 mmol) in acetonitrile (4 mL) was added dropwise, and the mixture was stirred at 60 ^oC for 3 h. The material was cooled to RT and poured into a mixture of 10% aqueous HBr (35 mL) and ethyl acetate (40 mL). The mixture was agitated and washed with equal volumes of water and brine. Extraction with EtOAc (2 x 40 ml), combination of the organic phases and drying over magnesium sulfate followed by chromatography (preparative TLC, 47% EtOAc/Hexanes) gave the title compound as a yellow-brown solid (259 mg).



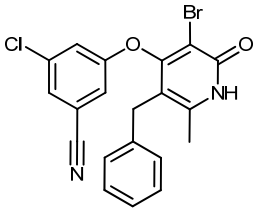
Step 9: An oven dried flask was charged with bromine (68 mg, 0.42 mmol) and taken up in CH_2Cl_2 (4ml). Imidazole (29 mg, 0.42 mmol) and 4-diphenylphosphino polystyrene resin (140 mg, 3 mmol/g) were added and the mixture was stirred for 5 minutes. A solution of 3-(3-bromo-5-hydroxymethyl-2-methoxy-pyridin-4-yloxy)-5-chloro-benzonitrile (118 mg, 0.38 mmol) in CH_2Cl_2 (2 ml) was added dropwise. The mixture was stirred for 15 min and then filtered. The CH_2Cl_2 filtrate was transferred to a separatory funnel and washed consecutively with equal volumes of 5% aqueous sodium thiosulfate and then brine. Extraction with CH_2Cl_2 (2 X 40 ml), drying (MgSO4), filtration, evaporation provided the title compound as a light yellow oil (131 mg).



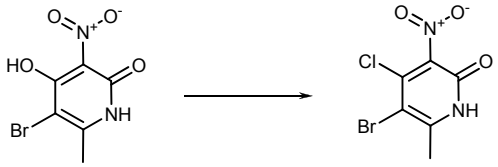
Step 10: A solution of pyridine-4-methanol (73 mg, 0.67 mmol) in dry THF (3 mL) was cooled to 0 ^oC (ice bath) under a N_2 atmosphere. Powdered NaH (29 mg, 0.7 mmol, 60% in oil) was added, and the mixture stirred for 10 min. After 20 min a solution of 3-(3-bromo-5-bromomethyl-2-methoxy-pyridin-4-yloxy)-5-chloro-benzonitrile (131 mg, 0.30 mmol) in dry THF (2.5 ml) was added. The mixture was stirred for 3 h and then quenched with a saturated solution of aqueous NH_4Cl (5 ml), water (30 ml) and EtOAc (30 ml). The material was shaken in a separatory funnel, and the EtOAc phase was collected and washed with brine (30 ml). Extraction with EtOAc (2 X 30 ml), drying ($MgSO_4$), filtration and evaporation provided an oil. Chromatography (preparative TLC, 4% MeOH/CH_2Cl_2) gave the title compound as a light yellow semi -solid (34 mg).



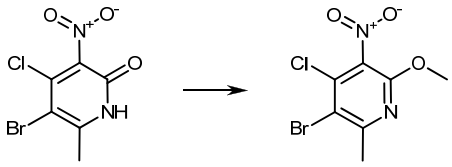
Step 11: An oven dried flask was charged with 3-[3-bromo-2-methoxy-5-(pyridin-4-ylmethoxymethyl)-pyridin-4-yloxy]-5-chloro-benzonitrile (34 mg, 0.074 mmol) and taken up in CH_3CN (5 ml). Sodium iodide (27 mg, 0.19 mmol) was added and the mixture was cooled to 0 ^oC (ice bath) under N_2 atmosphere. TMSCl (0.02 ml, 0.19 mmol) was added dropwise and the mixture was stirred for 5 min, at which point the cooling bath was removed. The mixture was stirred for 2.5 hours and then treated consecutively with 1 N HCl (0.25 ml), 5% aqueous $NaHSO_3$ (0.5 ml). The mixture was stirred vigorously for 2 min and then brine (10 ml), water (10 ml) and then EtOAc (30 ml) was added. The mixture was washed with brine (25 ml) and back extracted with EtOAc (2 X 25 mL). The organics were combined, dried (MgSO4), filtered and stripped. Chromatography (preparative TLC, 5% MeOH/CH_2Cl_2) gave the title compound as a light yellow powder (7 mg).



Compound 6a: 3-(5-Benzyl-3-bromo-6-methyl-2-oxo-1,2-dihydropyridin-4-yloxy)-5-chlorobenzonitrile



Step 1: $POCl_3$ (11.2 mL, 4.4 equiv) was added to a mixture of benzyltriethylammonium chloride (25.5 g, 4.0 equiv) and 3-nitro-4-hydroxy-5-bromo-2-pyridone (14.0 g, 56.0 mmol) in acetonitrile (100 mL). This mixture was stirred at 40^oC for 30 min, after which it was refluxed for 1 h. Upon cooling, the mixture was concentrated *in vacuo* to remove excess reagents, and then 100 mL of H_2O was added at 0^oC. After stirring overnight, 3-nitro-4-chloro-5-bromo-2-pyridone was obtained (13.9 g) as cream colored solid.



Step 2: Silver carbonate (5.25 g, 0.51 equiv) and methyl iodide (2.56 mL, 1.05 equiv) were slowly added to a solution of bromopyridone (10.0 g, 37.4 mmol) in benzene (125 mL). After heating for 18 hrs at 60 ^oC in a sealed tube, the reaction mixture was cooled to RT, filtered, washed with EtOAc, and concentrated *in vacuo*. The resulting material was chromatographed directly (SiO_2, 3% to 15% EtOAc/hexanes) to provide methoxypyridine product (6.2 g).

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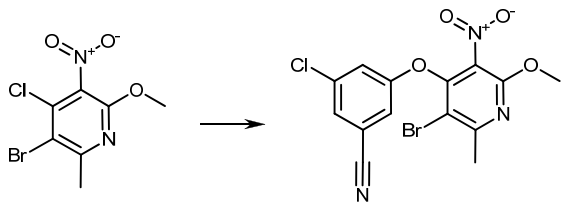
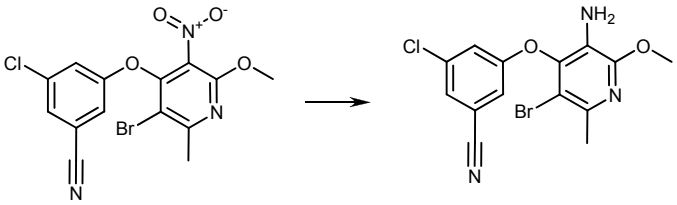
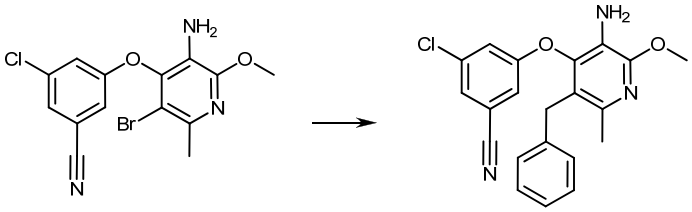


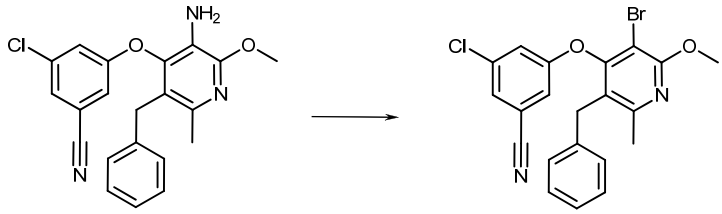
Step 3: 60% NaH (1.2 g, 1.3 equiv) was added to a solution of 3-chloro-5-cyanophenol (5.12 g, 1.4 equiv) in DMF (80 mL) at 0°C. This solution was then stirred at room temperature until all of the NaH had reacted (~30 min). After recooling to 0°C, the methoxypyridine (6.7 g, 23.8 mmol) was added and the purple colored solution was allowed to stir from 0°C to rt. After 1 h the mixture was quenched with sat. NH_4Cl, extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. This material was chromatographed (SiO_2, 15% to 33% EtOAc/hexanes) to provide slightly impure coupled product (~5 g) and recovered methoxypyridine starting material (~1 g).



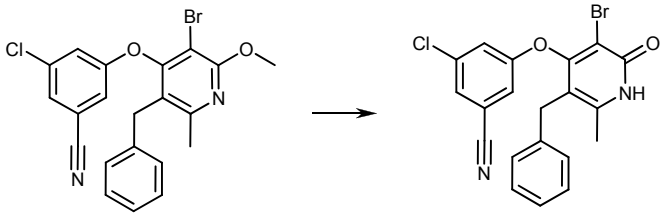
Step 4: To a solution of coupled methoxypyridine (5.0 g, 12.5 mmol) in EtOH (60 mL) containing ammonium chloride (2.68 g, 4.0 equiv) and H_2O (20 mL) was added electrolytic Fe powder (2.79, 4.0 equiv) with rapid stirring at 50°C. The temperature of the reaction was then raised to 100°C. After 1 hr the reaction was deemed complete by TLC. While still hot, celite and EtOAc were added and the entire mixture was filtered over an additional portion celite. Concentration *in vacuo* gave a residue (~4.6g) that was somewhat insoluble and difficult to purify by chromatography. This material should be recrystalized or carried on crude.



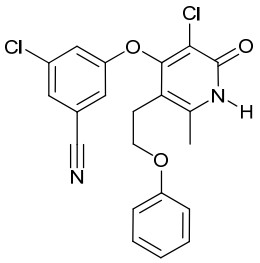
Step 5: Benzylzinc bromide (3.26 mL, 0.5M, 1.2 equiv) was added to a solution of bis(tri-tertbutylphosphine) palladium (104 mg, 0.15 equiv) and bromo-aniline (500 mg, 1.36 mmol) in dioxane (9 mL) at RT. This solution was then stirred at RT for 2 h. Upon quenching with sat. NH_4Cl, the mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (SiO_2, 10% to 33% EtOAc/hexanes) to provide the coupled product (260 mg, 51%).



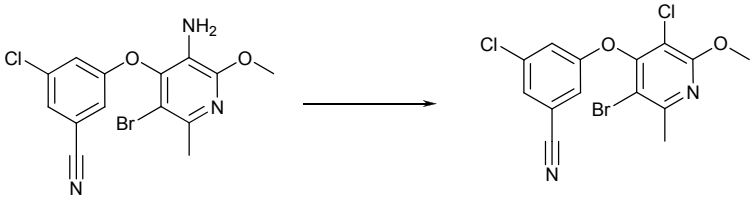
Step 6: t-BuONO (143 µL, 1.75 equiv) was slowly added to a solution of CuBr (184 mg, 1.2 equiv) and LiBr (179 mg, 3 equiv) in acetonitrile (3.5 mL) at 60°C. To this was then added the product from the previous step (260 mg, 0.69 mmol) in acetonitrile (3.5 mL) dropwise. After heating for 1 h at 60°C the reaction mixture was cooled, and quenched with 5% aq. HBr. The mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (SiO_2, 10% to 33% EtOAc/hexanes) to provide bromide (40 mg, 46%).



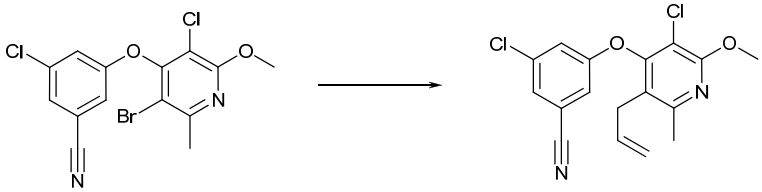
Step 7: TMSCl (87 µL, 2.5 equiv) was slowly added to a solution of NaI (103 mg, 2.5 equiv) and bromide (122 mg, 0.28 mmol) in acetonitrile (2 mL). After stirring for 3 h at rt the reaction mixture was quenched with aq. sodium thiosulfate. The resulting mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (SiO_2, 1% to 10% MeOH/DCM) to provide pyridone (50 mg, 42%).



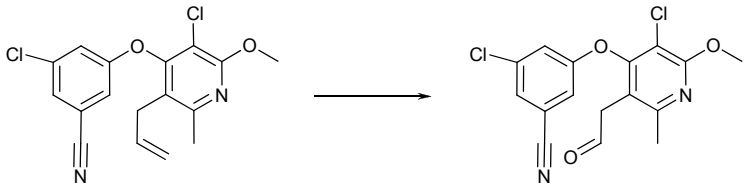
Compound 6b: 3-Chloro-5-(3-chloro-6-methyl-2-oxo-5-(2-phenoxyethyl)-1,2-dihydropyridin-4-yloxy)benzonitrile



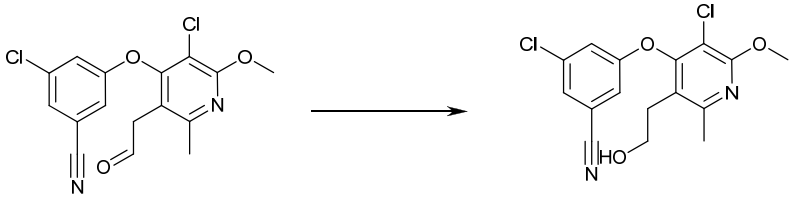
Step 1: To a solution of copper chloride (0.878g, 6.53mmol) and lithium chloride (0.481g, 11.4mmol) in acetonitrile (20mL) at 60ºC was added tert-butyl nitrite (1.31mL, 9.94mmol, 1.75 eq. 90 %) dropwise. After 25 min at 60ºC, the pyridinyl compound was added. After 3 h at room temperature, the reaction mixture was poured into saturated ammonium chloride (15mL). Organic layer was washed with saturated ammonium chloride (15mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a foamy, brown oily residue, which was flashed on silica (SiO_2, 5 % EtOAc/Hexanes) to give the product as a white solid. (1.49 g, 68%)



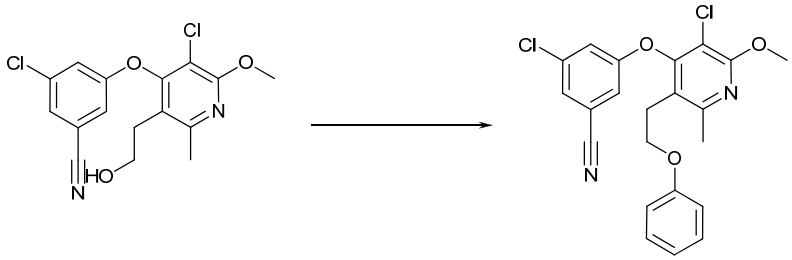
Step 3: To a suspension of the pyridine (1.37g, 3.53mmol) and $Pd(PPh_3)_4$ (0.408g, 0.353mmol) in toluene (10mL) was added tributyl allyl tin (1.23mL, 3.88mmol, 1.1eq. 97%). The yellow reaction mixture was heated at 120ºC. After 16 h, the reaction mixture was cooled to RT and concentrated *in vacuo* to give a green oil, which was taken up in ether (20mL) and washed with brine (20mL), dried (MgSO4), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (SiO_2, 5 % EtOAc/Hexanes) gave the product as a oil (0.850g, 69 %).



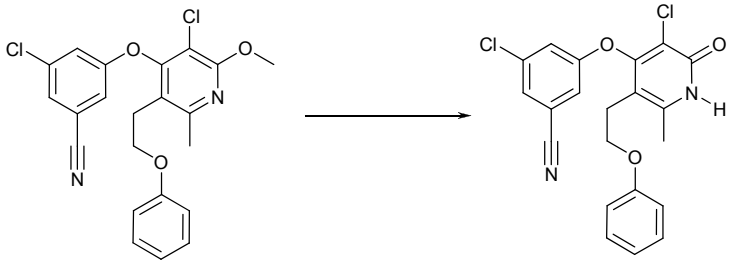
Step 4: To a solution of the allylarene (0.814g, 2.33mmol) in THF (11mL) and H_2O (2.4mL) was added osmium tetraoxide (47mg, 0.183mmol), followed by N-methyl morpholine N-oxide (0.630g, 4.58g) at 0ºC. The reaction mixture was warmed to room temperature over 1 h and stirred for 12h, To the brown reaction mixture was added 10 % $Na_2S_2O_3$ in an aqueous solution (800mg in 8mL H_2O) and the reaction mixture was stirred. After 30 min., the reaction mixture was extracted with EtOAc(2x10mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and the volume of the solvent was reduced to 3 mL and filtered through a short plug of silica with EtOAc. The solvent was removed to give a foamy, white solid, which was taken up in MeOH (6 mL) and H_2O (6 mL) and stirred with sodium periodate (0.748 g, 1.5 eq.). After stirring the white slurry for 1.5 h, the reaction mixture was filtered to rid of the salt and diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the product as a white foamy solid (0.792 g, 97 %).



Step 5: To a solution of aldehyde (0.792g, 2.26mmol) in methanol (16mL) was added sodium borohydride (94 mg, 2.48 mmol) at 0ºC. Bubbling occurred and the color turned pink orange and a solid started to precipitate out of solution with further stirring. After 20 min. at 0ºC, the reaction mixture was partitioned between H_2O (15mL) and EtOAc (15mL). The organic layer was washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give an orange solid, which was purified by chromatography (SiO_2, 40 % EtOAc in Hexanes) to give the product as a white solid (0.591g, 74 %).



Step 6: To a solution of the alcohol (0.250g, 0.708mmol) in THF (3mL) was added PPh_3 (0.371g, 1.42mmol), phenol (0.067g, 0.708mmol) and diisopropylazodiacetate (0.151mL, 0.779mmol) dropwise at 0ºC. The reaction mixture was gradually warmed to room temperature and stirred for 12h. The solvent was removed under reduced pressure to give an oil, which was flashed (SiO_2, 0%-100% 60/10/1 CH_2Cl_2/MeOH/NH_4OH in CH_2Cl_2 to give the product (23mg, 8%).



Step 7: To a solution of the pyridinyl compound in acetonitrile (1 mL) was added sodium iodide (20mg, 0.134 mmol), followed by a dropwise addition of trimethylsilylchloride (0.017 mL, 0.134 mmol) at 0ºC. After 20 min, the ice bath was removed and the reaction mixture was stirred at RT. After 3 h, the reaction mixture was diluted with EtOAc (5mL) and poured into a mixture of saturated aqueous sodium bicarbonate (3 mL) and H_2O (3 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellow oil, which was purified by preparative TLC (50 % 60/10/1 CH_2Cl_2/MeOH/NH_4OH in CH_2Cl_2) to give an off-white solid (4mg, 18 %).

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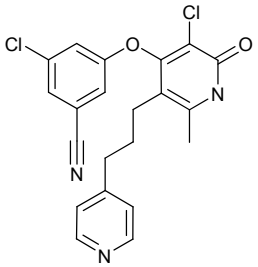
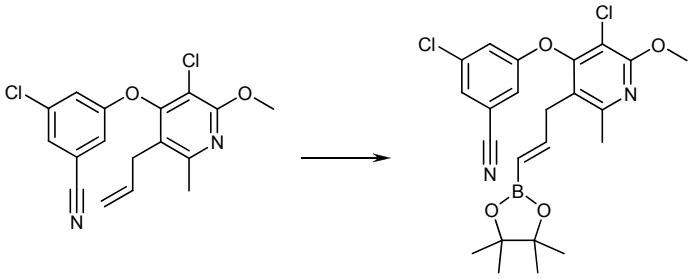
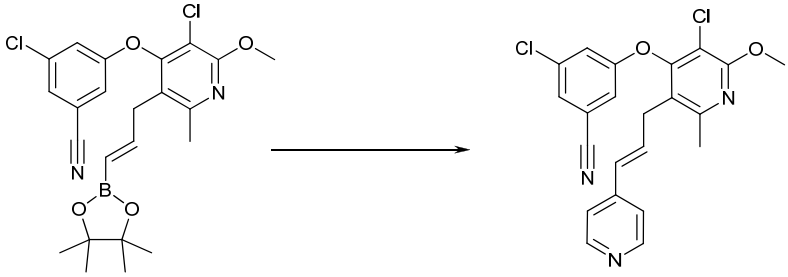


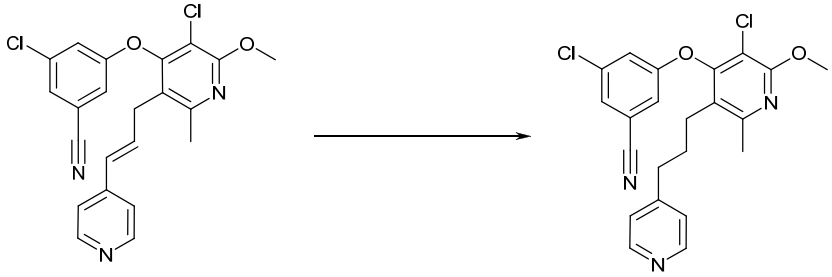
Compound 6c: 3-Chloro-5-(3-chloro-6-methyl-2-oxo-5-(3-(pyridin-4-yl)propyl)-1,2-dihydropyridin-4-yloxy)benzonitrile



Step 1: In a 50 ml Schlenck flask was placed 1.78 g (5.09 mmole) of the allyl-pyridine 0.216 g (0.25 mmole, 5%) of Grubb's catalyst (second generation), 1.71 g (10.2 mmole, 2 equivalent) of propenyl boronic acid pinacol ester, and 32 ml of dichloromethane. The mixture was evacuated, back filled with argon, and refluxed at 50 ^{o}C for 8 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with 0 to 10% ethyl acetate/hexane. The product was obtained as a light brown solid (1.44 g, 59%).



Step 2: In a 25 ml Schlenk flask was placed 0.200 g (0.42 mmole) of boronic ester in 4 ml of 1,2-dimethoxyethane, 0.104 g of 4-iodopyridine, 24 mg (0.021 mmole) of tetrakis(triphenylphosphine)palladium, and 0.145 g (1.05 mmole) of potassium carbonate in 0.5 ml of water. The mixture was stirred, evacuated, and back filled with argon. The mixture was stirred and heated at 90^{o}C for 18 h. The solvent was evaporated, triturated the residue with 30 mL of 50% ethyl acetate/dichloromethane, and the crude product was purified by flash chromatography on silica gel eluting with 0 to 25% ethyl acetate / dichloromethane. The product (0.145 g, 81%) was obtained as a pink solid.



Step 3: In a roundbottom flask was placed 0.129 g (0.30 mmole) of the alkene dissolved in 13 mL of THF. Platinum oxide (26 mg) was added. The mixture was stirred under a balloon of hydrogen gas for 12 h, filtered through a pad of Celite, evaporated, and purified by chromatography on silica eluting with 0 to 25% ethyl acetate/dichloromethane. The product was obtained as a white solid (81 mg, 62%).

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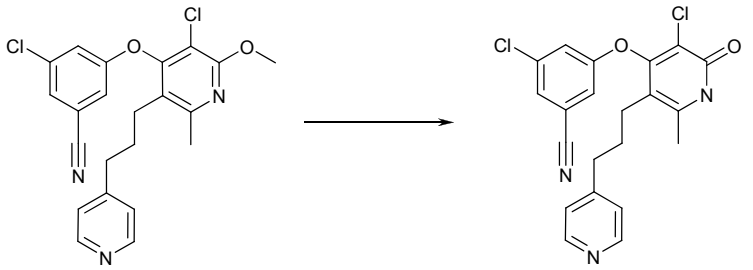

Step 4: In a flask was placed 75 mg (0.175 mmole) of the pyridine dissolved in 4 mL of acetonitrile and 66 mg (0.437 mmole) of sodium iodide and 48 mg (0.437 mmole) of chorotrimethylsilane were added. The cloudy mixture was stirred at RT under a nitrogen atmosphere for 1 h. The mixture was poured into 100 ml of ethyl acetate, washed with 10 mL of saturated sodium bicarbonate solution, 10 mL of 10% sodium bisulfite solution, 10 mL of brine, dried over magnesium sulfate, evaporated, and the residue purified by chromatography on silica gel eluting with 0 to 10% methanol/dichloromethane. The pyridone was obtained as a white solid (56 mg of the pyridone, 77%).