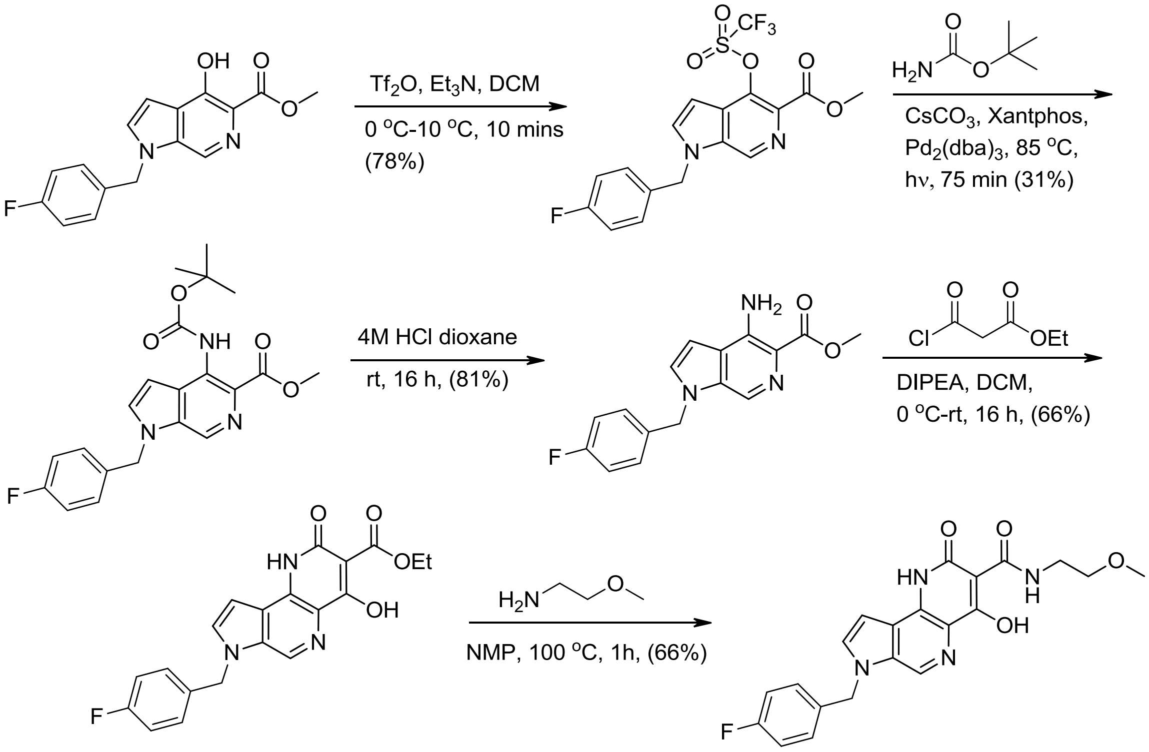
Supplementary Information

Synthetic routes to compounds **5** and **10**-**19**

Scheme 1

*Synthesis of compound **19**, and analogously compound **18***

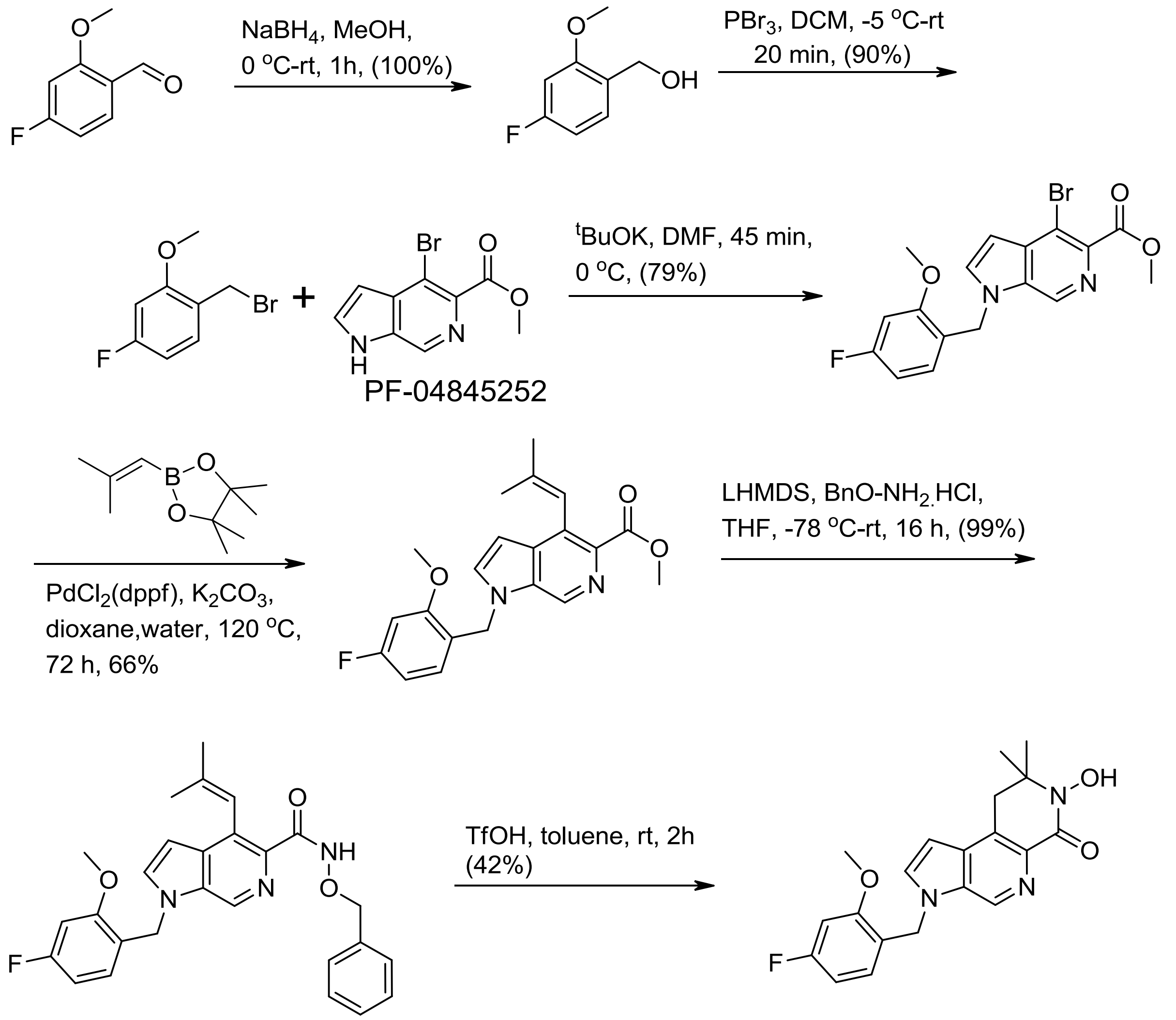


19. ^{1}HNMR (400MHz, MeOH-D4) δ ppm: 3.30 (s, 3H), 3.45-3.60 (m, 4H), 5.60 (s, 2H), 7.14 (t, 3H), 7.30-7.32 (m, 3H), 7.78 (s, 1H), 8.86 (s, 1H), 10.39 (s, 1H). LC-MS (ES+) 411 (M+H).

18. ^{1}HNMR (400MHz, MeOH-D4) δ ppm: 3.31-3.60 (m, 4H), 4.86-4.89 (m, 1H), 5.60 (s, 2H), 7.06-7.18 (m, 2H), 7.23-7.37 (m, 3H), 7.78 (s, 1H), 8.86 (s, 1H), 10.39 (s, 1H). LC-MS (ES+) 397 (M+H).

Scheme 2

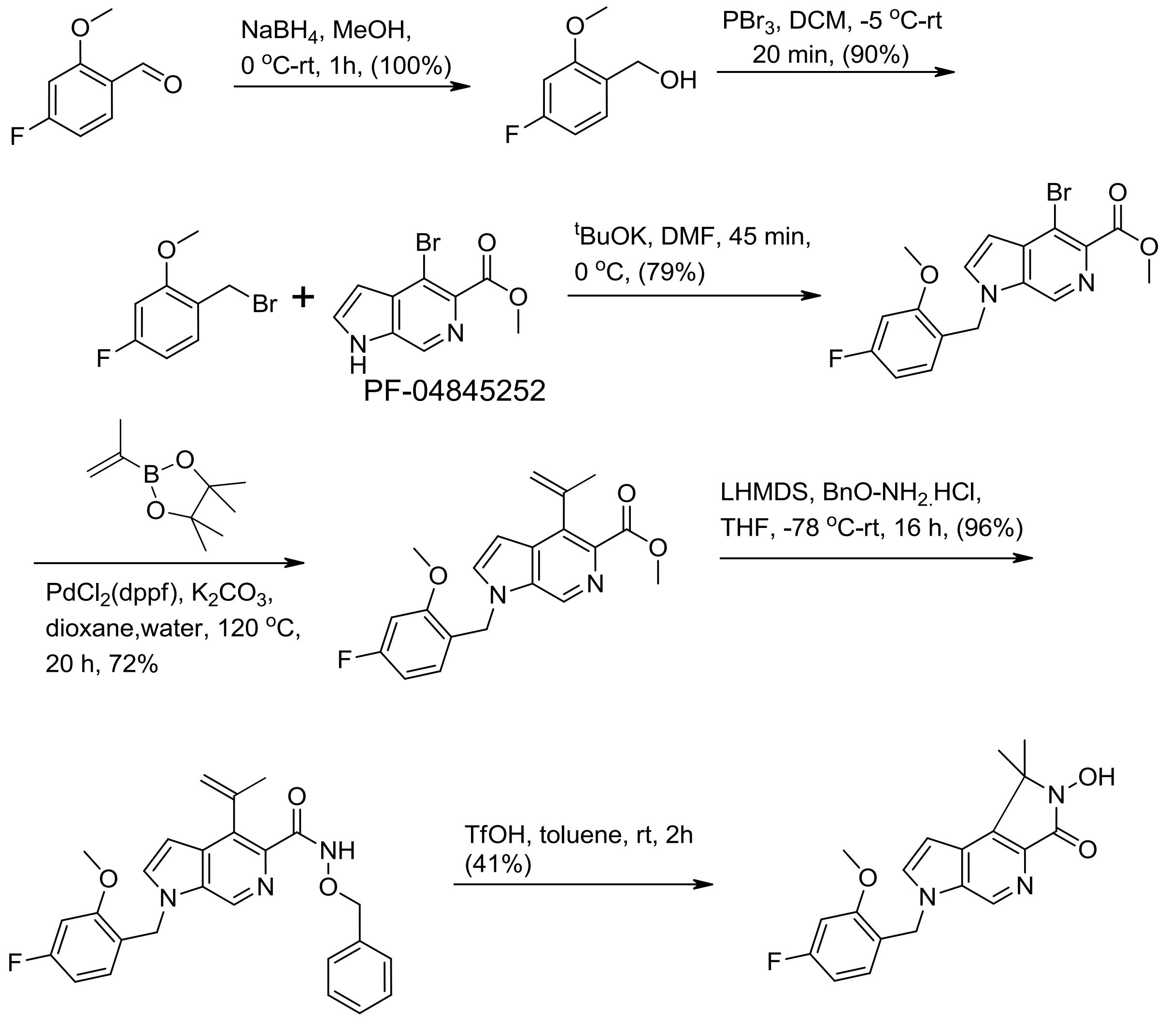
*Synthesis of compound **11***



11. ^{1}HNMR (400MHz, MeOH-D4) δ ppm: 1.45 (s, 6H), 3.20-3.38 (m, 2H), 3.82 (s, 3H), 5.35 (s, 2H), 6.50-6.63 (m, 3H), 6.92-7.03 (m, 1H), 7.34 (s, 1H), 8.87 (s, 1H). LC-MS (ES+) 370 (M+H).

Scheme 3

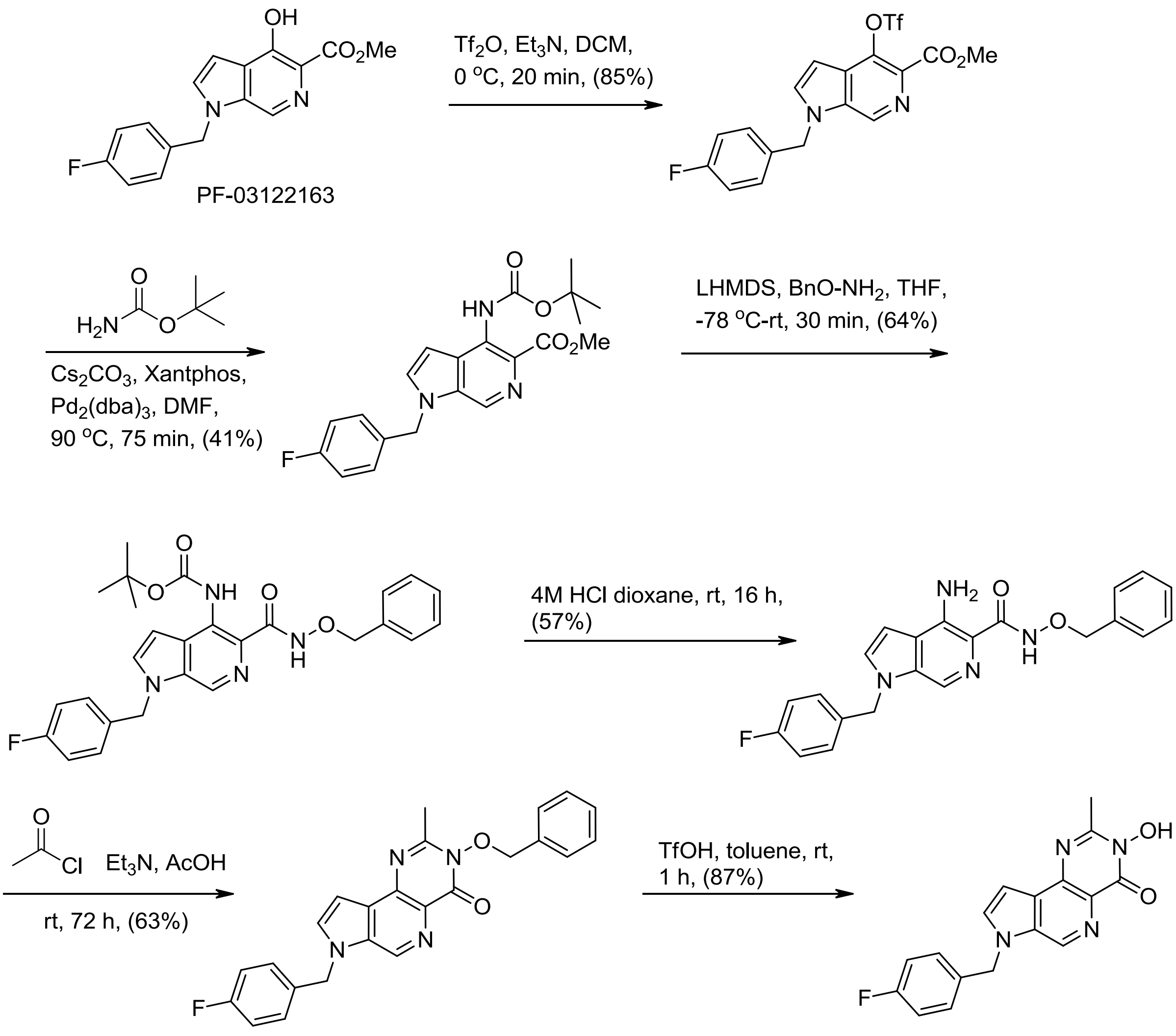
*Synthesis of compound **13***



13. ^{1}HNMR (400MHz, MeOH-D4) δ 1.77 (s, 6H), 3.84 (s, 3H), 5.40 (s, 2H), 6.38-6.69 (m, 4H), 6.99 (dd, 1H), 7.49 (s, 1H), 8.85 (s, 1H). LC-MS (ES+) 356 (M+H).

Scheme 4

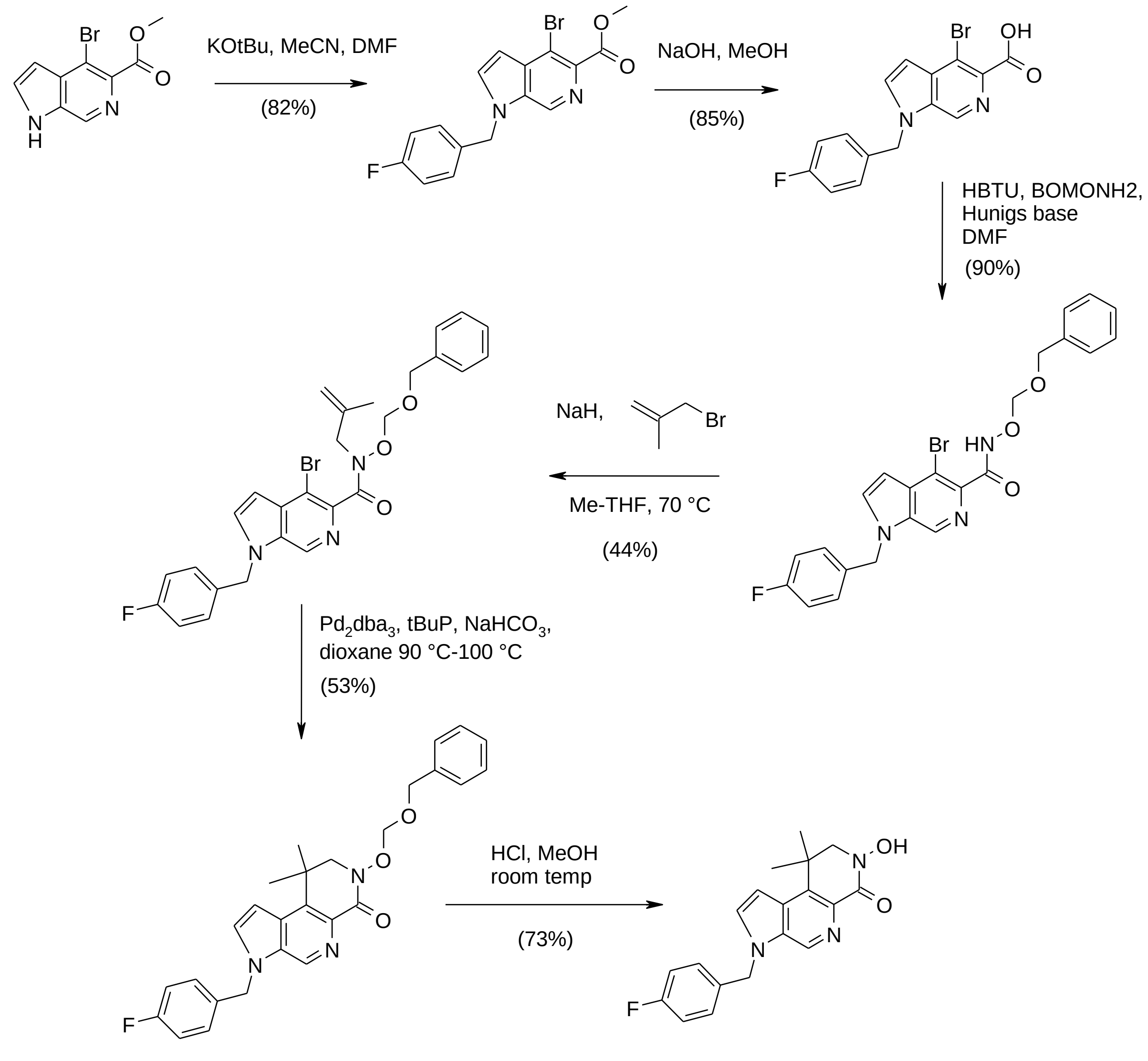
Synthesis of compound ***12***



12. ^{1}HNMR (400MHz, MeOH-D4) δ 1.94 (s, 3H), 5.58 (s, 2H), 6.99-7.05 (m, 2H), 7.18-7.25 (m, 3H), 7.62-7.65 (m, 1H), 8.71-8.84 (m, 1H). LC-MS (ES+) 325 (M+H).

Scheme 5

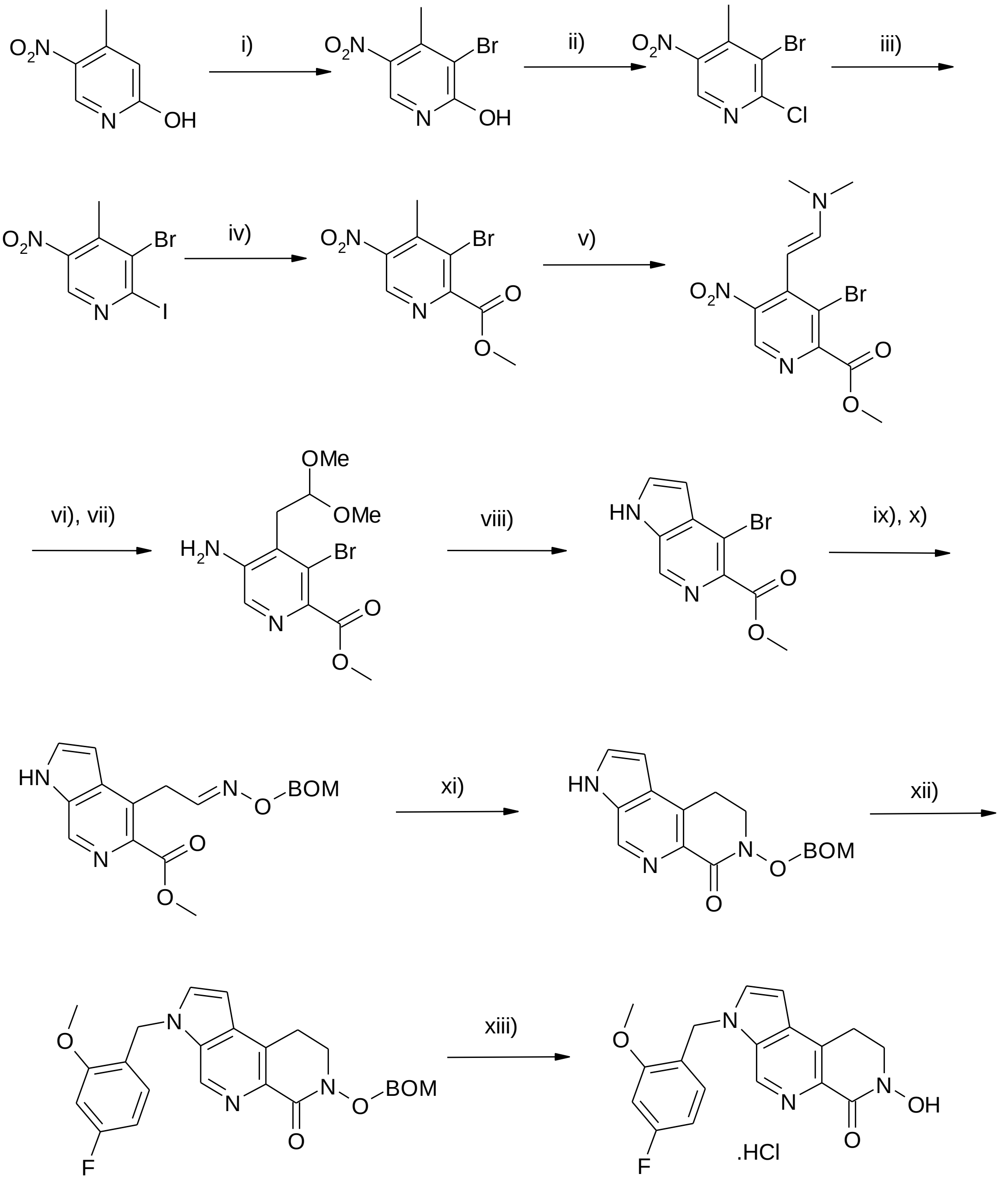
*Synthesis of compound **14***



14. ^{1}HNMR (400 MHz, DMSO-D6) δ ppm 1.56 (s,6H) 3.78 (s, 2H) 5.80 (s, 2H) 7.18 (t, 2H) 7.40 (m, 3H) 8.52 (d, 1H) 9.34 (s, 1H). LC-MS (ES+) 340 (M+H).

Scheme 6

*Synthesis of compound **10**, and analogously compounds **5**, **15**, **16** and **17***



i) **3-bromo-4-methyl-5-nitropyridin-2-ol**

4-Methyl-5-nitropyridin-2-ol 1 (104.5 g, 0.68 mol) was suspended in AcOH (1000 mL) and bromine (208 mL, 6 eq) was added dropwise in 1.5 h. The mixture was stirred for 5 min, the poured into ice-water (2000 mL) and stirred for 1 h. The resulting suspension was filtered and the residue was washed with water (3× 100 mL), dried in vacuo and then stripped with toluene (2× 500 mL) and CH3CN (500 mL). This afforded the title compound as a yellow solid (143.8 g, 91%).

ii) **3-bromo-2-chloro-4-methyl-5-nitropyridine**

The compound from preparation 1 (133.1 g, 0.57 mol) was suspended in CH_3CN (800 mL) and $POCl_3$ (85.2 mL, 1.6 eq) was added dropwise. Subsequently, the reaction mixture was heated at 75 ºC for 19 h. The mixture was allowed to cool and poured into 3000 mL of ice-water. The precipitate was isolated by filtration and the residue was washed with water (2× 250 mL), dried *in vacuo*, then stripped with toluene (2× 500 mL) and propionitrile (200 mL) at 60 ºC. The resulting brown oil, rapidly solidified upon cooling to yield the title compound (126.6 g, 88%).

iii) **3-bromo-2-iodo-4-methyl-5-nitropyridine**

The compound from preparation 2 (126.6 g, 0.50 mol) was dissolved in propionitrile (1500 mL) and NaI (226.4 g, 3 eq) was added followed by addition of TMSCl (67.5 mL, 1.05 eq). The reaction mixture was heated at 80 ºC for 1 h, then allowed to cool overnight. The resulting suspension was poured into brine (3000 mL) and extracted with EtOAc (3× 500 mL). The combined organic layers were washed with 10% $Na_2S_2O_3$ (500 mL) during which the color changed from brown to yellow, then dried on Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was washed with pentane (200 mL), crushed, and washed again with pentane (200 mL). The residue was dried *in vacuo*, affording the title compound as a green crystalline solid (141.5 g, 82%).

iv) **Methyl-3-bromo-4-methyl-5-nitropicolinate**

The compound from preparation 3 (129.0 g, 0.38 mol) and $(Ph_3P)_2PdCl_2$ (7.92 g, 3 mol%) were suspended in CH_3CN (1300 mL) and MeOH (430 mL) and Et_3N (79.3 mL, 1.5 eq) was added. The mixture was transferred to a steel 5000 mL pressure vessel, 4 bar of CO pressure was applied and the reaction mixture was slowly heated to 80 ºC. Subsequently, it was stirred for 5 h at this temperature, then allowed to cool overnight. The volatiles were removed *in vacuo*, the residue was stirred in EtOAc (1000 mL) and filtered. The residue was extracted with EtOAc (2× 250 mL) and the combined filtrates were washed with brine (1000 mL) and dried on Na_2SO_4. The volatiles were removed *in vacuo*, affording 120 g of a brown oil. This was coated on 120 g of silicagel and purified by column chromatography (3500 g of silica gel, EtOAc/heptane 1:3, $KMnO_4$ staining). The appropriate fractions were combined and concentrated to give the title compound as a beige solid (63.5 g, 61%).

v) **Methyl-3-bromo-4-(2-dimethylaminovinyl)-5-nitropicolinate**

The compound from preparation 4 (3.62 Kg, 13.16 mol) was slurried in 2-butanol (36.2 L) and DMFDMA (6.28 Kg, 52.6 mol) was added. The mixture was heated at 70°C for 18 hours, then the solvent was distilled and replaced *in vacuo* with fresh 2-butanol until all traces of DMFDMA had been removed. The solution was cooled and granulated for 4 hours. The solid was collected by filtration and washed with 2-butanol to afford the title compound as a dark solid (3.26Kg, 75%). ^1H NMR (400 MHz, $CDCl_3$): δ= 8.51 (s, 1H), 7.10-7.13 (d, 1H), 5.30-5.33 (d, 1H), 3.98 (s, 3H), 3.01 (s, 6H).

vi) **Methyl-3-bromo-4-(2,2-dimethoxyethyl)-5-nitropicolinate**

The compound from preparation 5 (2.75 Kg, 8.33 mol) was dissolved in methanol (11 L) and p-TSA (1.9 Kg, 10.0 mol) was added. The reaction was warmed to 65°C for 75 minutes, then cooled back to ambient temperature. The reaction was partitioned between ethyl acetate (33 L) and water (22 L). The organic phase was further washed with sat. $NaHCO_3$ solution (12 L) and brine (15% w/v, 12 L). The solution was dried by distillation of ethyl acetate at constant volume to yield the title compound as a solution in ethyl acetate. The product yield was assumed to be 100% and taken directly into the subsequent reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.86 (s, 1H), 4.49-4.50 (t, 1H), 4.04 (s, 3H), 3.17-3.18 (d, 2H).

vii) **Methyl-3-bromo-4-(2,2-dimethoxyethyl)-5-aminopicolinate**

The compound from preparation 6 (2.91 Kg, 8.33 mol, assumed quantitative from prep 6) in ethyl acetate (30 L) was added to a pre-formed mixture of iron powder (1.4 Kg, 25 mol), acetic acid (6.1 L) and methanol (15 L). The mixture was stirred at 25°C for 2 hours. The mixture was basified by the addition of aqueous potassium carbonate solution (30%w/w, 30 L) and the solid residues were removed by filtration. The organic phase was washed with water (30 L) then concentrated *in vacuo* and diluted with heptanes to induce crystallisation. The solid was granulated for 3 hours and collected by filtration, to afford the title compound as a beige solid (1.83 Kg, 69% over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.92 (s, 1H), 5.85 (br s, 2H), 4.59-4.60 (t, 1H), 3.78 (s, 3H), 3.00-3.01 (d, 2H).

viii) **Methyl-4-bromo-1H-pyrrolo-[2,3]-pyridine-5-carboxylate**

The compound from preparation 7 (1.56 Kg, 4.89 mol) was slurried in methanol (3.8 L) and 4M HCl in 1,4-dioxane (1.83 L, 7.34 mol) was added. The mixture was heated at 65°C for 3 hours. The reaction was cooled and neutralised with aqueous potassium carbonate solution (15% w/w, 7.5 L), then granulated for 3 hours. The solid was collected by filtration and washed twice with water (3 L) then IPA (3 L) then dried to yield the title compound as a pale solid (1.2 Kg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ= 12.21 (br s, 1H), 8.77 (s, 1H), 7.83 (s, 1H), 6.63 (s, 1H), 3.86 (s, 3H).

ix) **Methyl-4-(2-cycohexylvinyl)-1H-pyrrolo-[2,3]-pyridine-5-carboxylate**

The compound from preparation 8 (1.2 Kg, 4.7 mol) was slurried in 2-MeTHF (9 L) and lithium chloride was added (0.6 Kg, 14.1 mol) followed by cyclohexylvinyl ether (0.65 Kg, 5.17 mol) and dicyclohexylmethylamine (1.01 Kg, 5.17 mol). The reaction vessel was inerted, and $Pd_2(dba)_3$ (0.22 Kg, 0.24 mol) was added followed by tri-(*tert*)-butylphosphine (50% w/w solution in toluene, 0.23 L, 0.47 mol). The mixture was heated at 70°C for 8 hours. The reaction was cooled and water (12 L) was added . The mixture was filtered and the phases were separated. The organics were washed sequentially with 10%w/w ammonium chloride solution (12 L), saturated sodium bicarbonate solution (12 L) and 10% w/w brine solution (12 L). The organic solvents were removed by distillation and the residue was dissolved in dichloromethane (2.5 L). The solution was filtered through a plug of silica (5 g/g) and washed with a TBME:acetone (3:2) mixture (30 L). The mother liquor was concentrated and re-dissolved in 2-MeTHF (12 L) ready for use in the next reaction without further isolation (1.13 Kg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ= 11.88 (br s, 1H), 8.56 (s, 1H), 7.68 (s, 1H), 7.24-7.20 (d, 1H), 6.80 (s, 1H), 6.53-6.49 (d, 1H), 4.05 (m, 1H), 3.82 (s, 3H), 1.99-1.90 (m, 2H), 1.76-1.67 (m, 2H), 1.54-1.20 (m, 6H).

x) **Methyl-4-(2-benzyloxymethhoxyaminovinyl)-1H-pyrrolo-[2,3]-pyridine-5-carboxylate (1:1 cis-trans mixture)**

To the compound from preparation 9 (1.13 Kg, 3.76 mol) as a solution in 2-MeTHF was added p-TSA (1.55 Kg, 9.02 mol) followed by O-benzyloxymethyl hydroxylamine (0.58 Kg, 3.8 mol). The reaction was heated at 60°C for 2 hours then cooled and washed with aqueous potassium carbonate solution (10% w/w, 11 L). The organic phase was further washed with brine (10% w/w, 11 L), and then distilled and replaced to TBME (5 L). The solid was granulated for 18 hours, collected by filtration and dried *in vacuo* to afford the title compound as a beige solid (0.99 Kg, 74%).

xi) **7-benzyloxymethoxy-8,9-dihydro-3H, 7H-pyrrolo[2,3][1,7]napthyridin-6-one**

The compound from preparation 10 (310g, 0.877 mol) was slurried in methanol (2.17 L) and sodium cyanoborohydride (121 g, 1.93 mol) was added. Acetic acid (600 mL) was slowly added and stirred for 2 hours. The mixture was quenched by the addition of ammonia solution (35% w/w, 768 g), granulated for 2 hours and collected by filtration. This yielded the title compound as a pale solid (286 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6): δ= 11.98 (br s, 1H), 8.71 (s, 1H), 7.72 (s, 1H), 7.45-7.29 (m, 5H), 6.73 (s, 1H), 5.15 (s, 2H), 4.88 (s, 2H), 4.98-4.90 (m, 2H), 3.40-3.32 (m, 2H).

xii) **7-benzyloxymethoxy-3-(4-fluoro-2-methoxybenzyl)-8,9-dihydro-3H, 7H-pyrrolo[2,3][1,7]napthyridin-6-one**

The compound from preparation 11 (900 g, 2.78 mol), was slurried in acetonitrile (18 L) and potassium (*tert*)-butoxide (328 g, 2.992 mol) was added. The mixture was stirred for 1 hour, then 4-fluoro-2-methoxybenzyl bromide (609 g, 2.78 mol) was added and stirred for a further 2 hours. The solvent was distilled and the residue was partitioned with DCM (9.0 L) and water (9.0 L). The organic phase was concentrated and the residue was recrystalllised from acetone (4.5 L) to yield the title compound as a white crystalline solid (1.17 Kg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.93 (s, 1H), 7.43-7.29 (m, 6H), 7.01-6.96 (d, 1H), 6.64-6.56 (m, 3H), 5.37 (s, 2H), 5.25 (s, 2H), 4.90 (s, 2H), 4.02-3.98 (t, 2H), 3.39-3.35 (t, 2H).

xiii) **3-(4-fluoro-2-methoxybenzyl)-7-hydroxy-8,9-dihydro-3H, 7H-pyrrolo[2,3][1,7]napthyridin-6-one hydrochloride**

The compound from preparation 12 (350g, 0.758 mol) was slurried in methanol (3.5 L) and acetyl chloride (595g, 7.6 mol) was added at such a rate to keep the temperature at 40°C. The reaction was stirred for a further 2 hours at 40°C. The solvent was removed by distillation and the residue was crystallised from acetone (3.5 L) to afford the title compound as a mono-hydrochloride salt (218 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.24 (s, 1H), 8.35 (s, 1H), 7.37-7.34 (dd, 1H), 7.15 (s, 1H), 6.97-6.94 (d, 1H), 6.77-6.73 (dd, 1H), 5.67 (s, 2H), 4.00-3.96 (t, 2H), 3.51-3.47 (t, 2H).

5. ^{1}HNMR (400MHz, MeOH-D4) δ ppm: 2.72-2.85 (t, 2H), 3.09-3.16 (t, 2H), 5.44 (s, 2H), 6.53-6.61 (m, 1H), 6.98-7.17 (m, 2H), 7.16-7.23 (m, 2H), 7.60-7.67 (m, 1H), 8.31 (s, 1H). LC-MS (ES+) 312 (M+H).

15. ^{1}H NMR (400MHz, DMSO-D6), δ ppm: 1.31 (t, 3H), 3.28 (t, 2H), 3.79 (t, 2H), 4.03 (q, 2H), 5.44 (s, 2H), 6.65 (d, 1H), 6.69 (t, 1H), 6.87 (dd, 1H), 7.22 (m, 1H), 7.67 (d, 1H), 8.85 (s, 1H), 9.67 (s, OH). LC-MS (ES+) 356 (M+H).

16. ^{1}H NMR (400 MHz, MeOH-D4) δ ppm: 3.42 (t, 2H), 3.96 (t, 2H), 5.56 (s, 2H), 6.76 (d, 1H), 6.78 (s, 0.25H), 6.93 (dd, 1H), 6.97 (s, 0.5H), 7.04 (dd, 1H), 7.14 (s, 0.25H), 7.18 (dd, 1H), 7.64 (d, 1H), 8.75 (s, 1H). LC-MS (ES+) 378 (M+H).

17. 1H NMR (400MHz, DMSO-D6) δ ppm: 3.5 (t, 2H), 3.8 (s, 3H), 3.98 (t, 2H), 5.75 (s, 2H), 6.8 (m, 1H), 7.18-7.2 (m,, 2H), 7.3 (d, 1H), 8.45 (d, 1H), 9.35 (s, 1H). LC-MS (ES+) 342 (M+H).