Supporting Information

Identification, Design and Biological Evaluation of Heterocyclic Quinolones Targeting Plasmodium falciparum Type II NADH: Quinone Oxidoreductase (PfNDH2)

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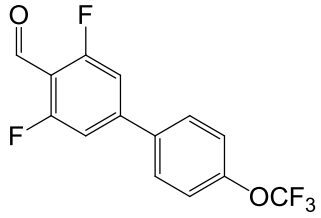
1.Experimental Section

General procedure for the preparation of aldehydes 3

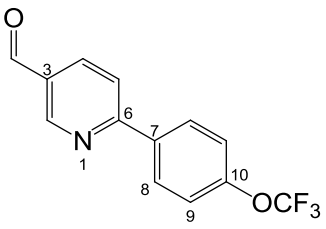
Potassium carbonate (12.2 g, 88.27 mmol) in distilled water (30 mL) was added anhydrous tetrahydrofuran (80 mL) under Nitrogen. 6-bromopyridine-3-carboxaldehyde (5.5 g, 29.57 mmol) was added followed by tetrakis(triphenylphosphine)palladium (0) (2.73 g, 2.36 mmol). The mixture was left stirring at room temperature for 5 min under N_2. 4-(Trifluoromethoxy)benzeneboronic acid (6.77 g, 32.88 mmol) was added. The resulting mixture was heated to 80^{o}C for 24 h (followed by tlc). The reaction was cooled to room temperature. It was extracted with ethyl acetate (x 3), washed with brine, dried over $MgSO_4$, filtered and concentrated to oil. The crude product was purified by column chromatography using 10% ethyl acetate in hexane to give the title compound (6.9 g, 87 %) as the white solid.

Preparation of 3,5-difluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-carbaldehyde 3a



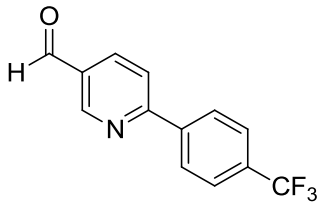
Oil (Yield 67 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H, CHO), 7.67 – 7.58 (m, 2H, H-6), 7.35 (dd, *J* = 8.9, 0.9 Hz, 2H, H-7), 7.24 – 7.14 (m, 2H, H-3); HRMS (ESI) $C_{15}H_{11}O_3F_5{}^{23}Na$ $[M+Na]^+$ requires 357.0526, found 356.0524.

Preparation of 6-(4-(trifluoromethoxy)phenyl)nicotinaldehyde 3b



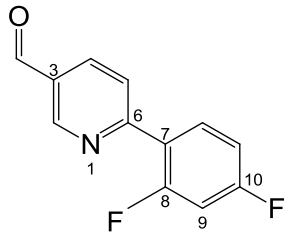
White solid (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H, C<u>H</u>O), 9.14 (d, *J* = 1.6 Hz, 1H, H-2), 8.25 (dd, *J* = 8.2, 2.2 Hz, 1H, H-4), 8.19 – 8.09 (m, 2H, H-8), 7.90 (d, *J* = 8.2 Hz, 1H, H-5), 7.36 (d, *J* = 8.1 Hz, 2H, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.73 (<u>C</u>HO), 161.06, 152.79 (C-2), 151.25, 137.15, 136.88, 130.45, 129.56 (C-8), 122.11, 121.57 (C-9), 120.88, 119.54; HRMS (ESI) $C_{13}H_9NO_2F_3$ $[M+H]^+$ requires 268.0585, found 268.0592.

Preparation of 6-(4-(trifluoromethyl)phenyl)nicotinaldehyde 3c



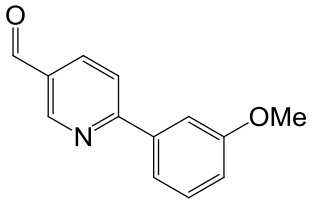
Off white powder (Yield 72%) ^{1}H NMR (400MHz, $CDCl_3$) δ_H 10.18 (s, 1H, CHO), 9.17 (s, 1H, Ar), 8.28 (d, 1H, J = 9.4 Hz, Ar), 8.21 (d, 2H, J = 8.2 Hz, Ar), 7.97 (d, 1H, J = 9.4 Hz, Ar), 7.78 (d, 2H, J = 8.2 Hz, Ar) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 189.9, 160.1, 152.0, 140.9, 136.5, 131.7, 130.1, 127.5, 125.6, 125.0, 120.6 MS (ES+), $[M + H]^+$ (100), 252.1, HRMS calculated for 252.0636 $C_{13}H_9NOF_3$, found 252.0643

Preparation of 6-(2,4-difluorophenyl)nicotinaldehyde 3d



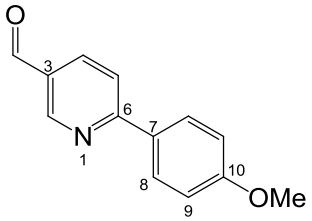
White solid (Yield 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 9.15 (d, *J* = 2.1 Hz, 1H, H-2), 8.24 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.15 (td, *J* = 8.8, 6.6 Hz, 1H, H-12), 7.97 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.11 – 7.02 (m, 1H, H-11), 6.96 (ddd, *J* = 11.3, 8.7, 2.5 Hz, 1H, H-9).

Preparation of 6-(3-methoxyphenyl)nicotinaldehyde 3e



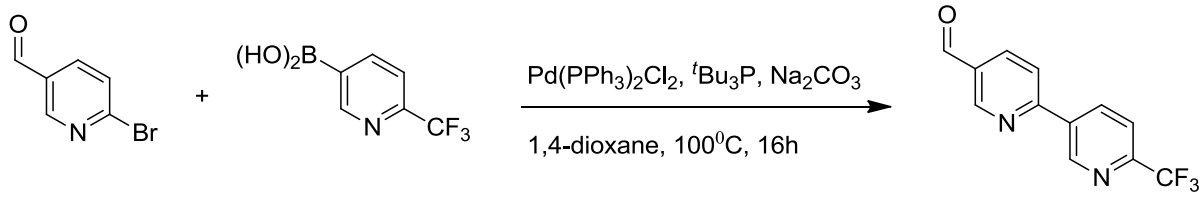
White solid (Yield 76 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 9.13 (d, *J* = 2.0 Hz, 1H, H-2), 8.24 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 7.91 (d, *J* = 8.3 Hz, 1H, H-5), 7.71 – 7.66 (m, 1H, H-8), 7.64 (d, *J* = 7.7 Hz, 1H, H-12), 7.43 (t, *J* = 8.0 Hz, 1H, H-11), 7.05 (dd, *J* = 8.2, 2.5 Hz, 1H, H-10), 3.92 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.51 (C=O), 161.98, 160.18, 152.35 (C-2), 139.40, 136.53 (C-4), 130.00 (C-11), 129.93, 120.78 (C-5), 119.89 (C-12), 116.49 (C-10), 112.57 (C-8), 55.45 (OCH_3); MS (CI) $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.

Preparation of 6-(4-methoxyphenyl)nicotinaldehyde 3f



White solid (Yield 77 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H, CHO), 9.08 (dd, *J* = 2.2, 0.8 Hz, 1H, C-2), 8.19 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 8.12 – 8.03 (m, 2H, H-8), 7.85 (d, *J* = 8.3 Hz, 1H, H-5), 7.08 – 6.98 (m, 2H, H-9), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.91(C=O), 162.23, 162.06, 153.00, 136.76, 130.89, 129.68, 129.49 (C-8), 120.08, 114.81 (C-9), 55.86.

Preparation of 6'-(trifluoromethyl)-[2,3'-bipyridine]-5-carbaldehyde 3g

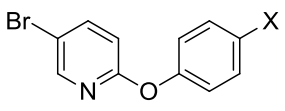


$Pd(PPh_3)_2Cl_2$ (0.15 mmol, 0.05 eq.) and $^tBu_3P$ (0.15 mmol 0.05 eq.) was added to a solution of aldehyde (2.91 mmol, 1 eq.) and boronic acid (3.20 mmol, 1.1 eq.) in dioxane (15 mL). 1M Na_2CO_3 (5.81 mmol, 2 eq.) was then added and the solution was degassed for 15 mins and then heated to 100 C for 16 hours. Palladium was removed by filtering through a pad of silica and this was washed with excess EtOAc (100 mL). The filtrate was washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil was purified by flash column chromatography (eluting with n-hexane to 30% EtOAc in n-hexane) to give the desired bipyridyl aldehyde **3g**.

Cream solid (Yield 60%); ^{1}H NMR (400 MHz, $CDCl_3$) 10.20 (s, 1H), 9.39 (s, 1H), 9.22 (s, 1H), 8.62 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.34 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.46, 158.27, 152.87, 149.70, 149.35, 149.19, 137.61, 136.78, 136.54, 131.25, 123.19, 121.50, 121.04, 121.01, 120.46; MS (ES^+) m/z 253 $(M + H)^+$ Acc Mass Found: 253.0586, calculated 253.0589 for $C_{12}H_8N_2OF_3$.

Procedures for the preparation of 3h and 3i

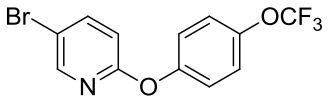
General procedure for the preparation of ether



To a solution of 4-X phenol (12 mmol 1.2 eq) in 10 ml of dry DMF was added 60% NaH (12 mmol, 1.2 eq). The reaction was stirred for a few mins under N_2 atmosphere and then a solution of 2,5-dibromopyridine (10 mmol) in 5 ml of dry DMF was added and the mixture

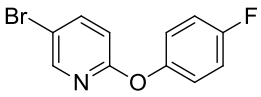
heated at 100^{o} C overnight. The reaction mixture was subsequently cooled to room temp and the solvent removed under vacuum. The residue was dissolved in EtOAc and washed with brine and dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (hexane to 20% EtOAc/hexane) to yield the pure product.

Preparation of 5-bromo-2-(4-(trifluoromethoxy)phenoxy)pyridine



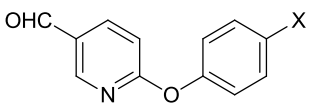
Yellow oil (Yield 78%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.25 (d, J =8.0 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H); MS (ES^+) m/z 334 $(M + H)^+$ Acc Mass Found: 333.9693, calculated 333.9690 for $C_{12}H_8NO_2F_3Br$.

Preparation of 5-bromo-2-(4-fluorophenoxy)pyridine



Yellow oil (Yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.10 (d, J =6.8 Hz, 4H), 6.84 (d, J = 8.7 Hz, 1H); MS (ES^+) m/z 268 $(M + H)^+$ Acc Mass Found: 267.9771, calculated 267.9773 for $C_{11}H_8NOFBr$.

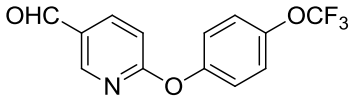
General procedure for the preparation of aldehyde



A solution of the bromo pyridine compound (1 mmol) in dry THF (4 ml) was cooled to -78 ^{0}C. A 2.5 M solution of n-BuLi (1.5 mmol, 1.5 eq) was added and stirring continued at -78^{0}C

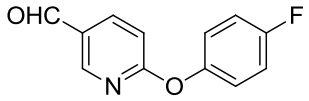
for 20 mins. To the reaction mixture was added dry DMF (1.2 mmol, 1.2 eq) and stirring continued at -78^{0}C for 1 hr followed by quenching with sat. NH_4Cl solution and extraction with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (hexane to 30% EtOAc/hexane) to give the desired compound.

Preparation of 6-(4-(trifluoromethoxy)phenoxy)nicotinaldehyde 3h



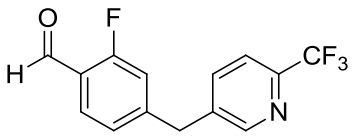
Yellow oil (Yield 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99(s, 1H), 8.62 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H).

Preparation of 6-(4-fluorophenoxy)nicotinaldehyde 3i



Yellow oil (Yield 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97(s, 1H), 8.60 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.15-7.09 (m, 4H), 7.05 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.63, 167.42, 161.64, 159.23, 152.92, 149.14, 139.16, 128.20, 123.53, 123.45, 116.96, 116.73, 112.47.

Preparation of 2-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzaldehyde 3j

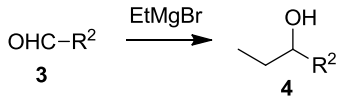


Formylphenylboronic acid (39 mmol, 1.0 eq) was added to a stirred suspension of the substituted 1-(bromomethyl)piperazine (43 mmol, 1.1 eq), tetrakis(triphenylphosphine)

palladium(0) (0.98 mmol, 0.025 eq) and potassium carbonate (130 mmol, 3.3 eq) in a solution of THF (164 mL) and H_2O (65 mL). The resulting mixture was heated under reflux for 5 hours at 80^{o}C. The reaction was quenched with HCl and extracted into EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$ and concentrated under vacuum. The removal of the solvent afforded a clear colourless oil which was purified by column chromatography (eluting with 2% EtOAc/n-Hexane increasing to 10% EtOAc) to give aldehyde **3j**.

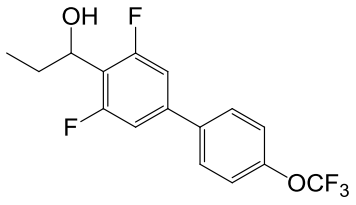
Light yellow, (Yield 68%) ^{1}H NMR (400MHz, $CDCl_3$), δ_H 10.32 (s, 1H, CHO), 8.63 (s, 1H, Ar), 7.84 (t, 1H, J = 7.6 Hz, Ar), 7.71 -7.64 (m , 2H, Ar), 7.12 (dd, 1H, J = 8.0 Hz, 1.1 Hz, Ar), 7.00 (dd, 1H, J = 11.0Hz, 1.1 Hz, Ar), MS (ES+), $[M + H]^+$ (100), 284.1, HRMS calculated for 284.0699 $C_{14}H_{10}NOF_4$, found 284.0694.

General procedure for the preparation of alcohols 4



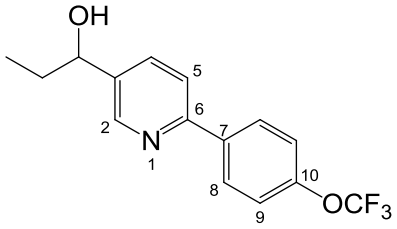
Aldehyde **3** (20 mmol, 1.0 eq) was dissolved in ether (40 mL) and cooled to 0°C under nitrogen. Ethyl magnesium bromide (24 mmol, 1.2 eq) was added dropwise and the reaction stirred at 0°C for 1 hour. The solution was then quenched with 1M HCl and extracted with EtOAc (2 x 40 mL). The organic portions were combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. Where necessary the crude product was purified by flash column chromatography (eluting with 5%-20% EtOAC in hexane) to give alcohol **4**.

Preparation of 1-(3,5-difluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)propan-1-ol 4a



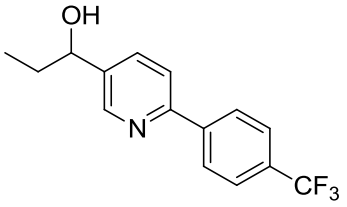
Yellow oil (Yield 82 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H, H-6), 7.31 (dd, *J* = 8.8, 0.8 Hz, 2H, H-7), 7.13 – 7.03 (m, 2H, H-3), 4.99 (dd, *J* = 16.3, 7.3 Hz, 1H, OH), 2.20 (dt, *J* = 9.0, 2.3 Hz, 1H, CH), 2.12 – 1.79 (m, 2H, CH_2), 0.99 (t, *J* = 7.4 Hz, 3H, CH_3); HRMS (CI) $C_{16}H_{13}F_5O_2$ $[M]^+$ requires 332.0830, found 332.0822; $C_{16}H_{12}F_5O_2$ $[M\text{-}H]^+$ requires 331.0752, found 331.0743.

Preparation of 1-(6-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)propan-1-ol 4b



Colourless oil (Yield 73 %); (Rf = 0.38, 50% Ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.1 Hz, 1H, H-2), 8.06 – 7.95 (m, 2H, H-8), 7.76 (dd, *J* = 8.2, 2.2 Hz, 1H, H-4), 7.67 (d, *J* = 8.2 Hz, 1H, H-5), 7.30 (d, *J* = 8.1 Hz, 2H, H-9), 4.68 (t, *J* = 6.5 Hz, 1H, C<u>H</u>OH), 2.56 (s, 1H, OH), 1.96 – 1.71 (m, 2H, CH_2), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.66, 150.24, 148.30 (C-2), 138.99, 138.10, 135.04, 128.72 (C-8), 121.46 (C-9), 120.88 (d, J = 257 Hz, OCF_3), 120.65, 73.76 (<u>C</u>HOH), 32.29 (CH_2), 10.30 (CH_3); HRMS (ESI) $C_{15}H_{15}NO_2F_3$ $[M+H]^+$ requires 298.1055, found 298.1043; Anal. $C_{15}H_{14}NO_2F_3$ requires C 60.06%, H 4.75%, N 4.71%, found C 60.41%, H 4.81%, N 4.77%.

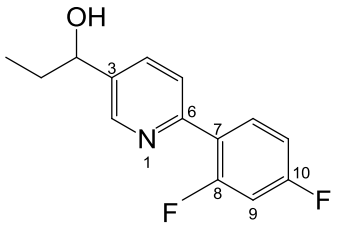
Preparation of 1-(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)propan-1-ol 4c



Colourless oil (Yield, 68%); ^{1}H NMR (400MHz, $CDCl_3$) δ_H 8.74 (s, 1H, Ar), 8.11 (d, 2H, J = 8.2 Hz, Ar), 7.95 (dd, 1H, J = 8.2 Hz, 2.2 Hz, Ar), 7.80 (d, 1H, J = 8.2 Hz, Ar), 7.75 (d, 2H, J

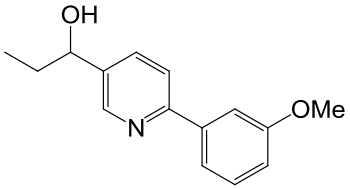
= 8.2 Hz, Ar), 5.10 (bs, 1H, OH), 4.78 (t, 1H, J = 6.5 Hz, CH), 1.95-1.76 (m, 2H, CH_2), 0.97 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 154.1, 146.7, 141.1, 140.6, 137.3, 128.0, 126.3, 122.1, 73.2, 32.2, 10.3; MS (ES+), $[M + H]^+$ (100), 282.1, HRMS calculated for 282.1106 $C_{15}H_{15}NOF_3$, found 282.1107.

Preparation of 1-(6-(2,4-difluorophenyl)pyridin-3-yl)propan-1-ol 4d



Yellow oil (Yield 65 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, H-2), 8.00 (td, *J* = 8.8, 6.7 Hz, 1H, H-12), 7.77 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.74 (ddd, *J* = 8.2, 2.0, 1.0 Hz, 1H), 7.04 – 6.97 (m, 1H, H-11), 6.92 (ddd, *J* = 11.3, 8.8, 2.5 Hz, 1H, H-9), 4.72 (td, *J* = 6.6, 3.6 Hz, 1H, C<u>H</u>OH), 2.02 – 1.95 (br. s, 1H, OH), 1.95 – 1.75 (m, 2H, CH_2), 0.98 (t, *J* = 7.4 Hz, 3H, CH_3); HRMS (ESI) $C_{14}H_{14}NOF_2$ $[M+H]^+$ requires 250.1043, found 250.1049;

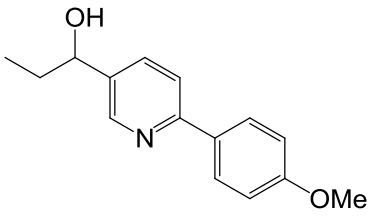
Preparation of 1-(6-(3-methoxyphenyl)pyridin-3-yl)propan-1-ol 4e



Pale yellow solid (Yield 75 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.1 Hz, 1H, H-2), 7.78 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.72 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.59 (dd, *J* = 2.4, 1.7 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 6.97 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.72 (t, *J* = 5.5 Hz, 1H), 3.90 (s, 3H), 1.94 (d, *J* = 2.8 Hz, 1H), 1.93 – 1.72 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.47, 156.98, 148.19 (C-2), 141.02, 138.57, 134.83 (C-4), 130.15 (C-11), 120.89 (C-5), 119.65 (C-12), 115.47 (C-10), 112.30 (C-8), 73.98,

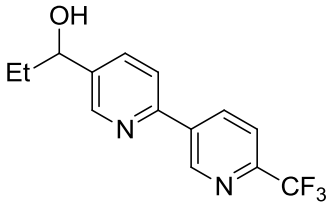
55.80, 32.31, 10.37; HRMS (CI) $C_{15}H_{18}NO_2$ $[M+H]^+$ requires 244.1332, found 244.1333; Anal. $C_{15}H_{17}NO_2$ requires C 74.05%, H 7.04%, N 5.76%, found C 73.83%, H 7.12%, N 5.49%.

Preparation of 1-(6-(4-methoxyphenyl)pyridin-3-yl)propan-1-ol 4f



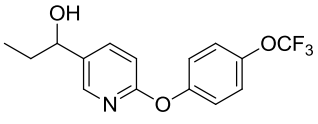
Pale yellow solid (Yield 69 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.2 Hz, 1H, H-2), 8.02 – 7.92 (m, 2H, H-8), 7.74 (dd, *J* = 8.2, 2.3 Hz, 1H, H-4), 7.67 (dd, *J* = 8.2, 0.7 Hz, 1H, H-5), 7.04 – 6.96 (m, 2H, H-9), 4.69 (td, *J* = 6.7, 3.0 Hz, 1H, OH), 3.87 (s, 3H, OCH_3), 1.93 (t, *J* = 3.8 Hz, 1H, CH), 1.91 – 1.73 (m, 2H, CH_2), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.50, 160.82, 156.92, 148.14 (C-2), 134.78, 132.19, 128.51 (C-8), 120.00, 114.53 (C-9), 74.04, 55.77, 32.25, 10.39; MS (CI) m/z 244.2 [M+H]+; Anal. $C_{15}H_{17}NO_2$ requires C 74.05%, H 7.04%, N 5.76%, found C 74.03%, H 7.16%, N 5.63%.

Preparation of 1-(6'-(trifluoromethyl)-[2,3'-bipyridin]-5-yl)propan-1-ol 4g



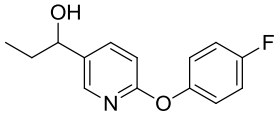
White solid (Yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) 9.28 (s, 1H), 8.71 (s, 1H), 8.51 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.86 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 4.77 (m, 1H), 2.18 (bs, 1H), 1.86 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.77, 148.93, 148.67, 140.32, 137.66, 135.96, 135.23, 121.12, 120.88, 120.86, 32.43, 10.24; MS (ES^+) m/z 283 $(M + H)^+$ Acc Mass Found: 283.1056, calculated 283.1058 for $C_{14}H_{14}N_2OF_3$.

Preparation of 1-(6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)propan-1-ol 4h



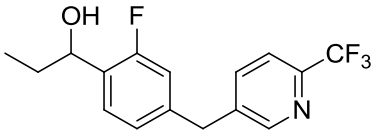
Yellow oil (Yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 4.50 (t, J = 6.6 Hz, 1H), 3.38 (brs, 1H), 1.83-1.62 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.95, 152.98, 145.78, 138.22, 135.79, 122.76, 122.45, 111.88, 73.21, 32.12, 10.27.

Preparation of 1-(6-(4-fluorophenoxy)pyridin-3-yl)propan-1-ol 4i



Yellow oil (Yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.06-7.03 (m, 4H), 6.80 (d, J = 8.2 Hz, 1H), 4.48 (t, J = 8.0 Hz, 1H), 3.75 (bs, 1H), 1.75-1.63 (m, 2H), 0.85 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.41, 161.12, 158.71, 150.33, 145.75, 138.09, 135.45, 122.97, 122.89, 116.76, 116.53, 111.41, 73.13, 32.11, 10.35; MS (ES^+) m/z 270 $(M + Na)^+$ Acc Mass Found: 270.0902, calculated 270.0906 for $C_{14}H_{14}NO_2FNa$.

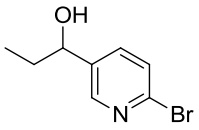
Preparation of 1-(2-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)methyl)phenyl)propan-1-ol 4j



Colorless oil (Yield 88%) ^{1}H NMR (400MHz, $CDCl_3$), δ_H 8.59 (s, 1H, Ar), 7.66-7.60 (m, 2H, Ar), 7.42 (t, 1H, 7.8 Hz, Ar), 6.97 (dd, 1H, 7.9 Hz, 1.5 Hz, Ar), 6.82 (dd, 1H, J = 11.0

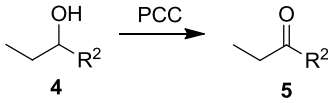
Hz, 1.5 Hz, Ar), 4.91 (t, 1H, J = 6.5 Hz, CH), 4.04 (s, 2H, $ArCH_2Ar$), 2.26 (bs, 1H, OH), 1.86-1.73 (m, 2H, CH_2), 0.94 (t, 3H, J = 7.4 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 161.6, 159.2, 150.2, 139.6, 137.9, 130.6, 128.3, 125.1, 120.8, 116.2, 115.9, 69.9, 38.6, 31.4, 10.3 MS (ES+), $[M + H]^+$ (100), 314.1, HRMS calculated for 314.1168 $C_{16}H_{16}NOF_4$, found 314.1164.

Preparation of 1-(6-bromopyridin-3-yl)propan-1-ol 4k



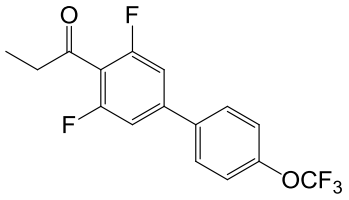
Yellow oil (Yield 68%); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 2.5 Hz, 1H), 7.58 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 4.85 – 4.51 (m, 1H), 1.91 – 1.66 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101MHz): δ 148.44, 141.35, 139.48, 136.55, 128.44, 73.25, 32.26, 10.30. MS (m/z) 216.0020 (Cl+, M+H); Anal. Calcd for $C_8H_{10}NOBr$: C, 44.47; H, 4.66; N, 6.48. Found: C, 43.56; H, 4.89; N, 6.94.

General procedure for the preparation of ketones 5



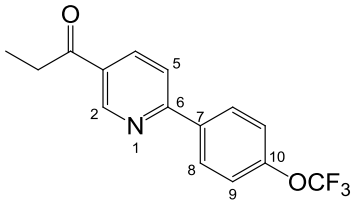
Pyridinium chlorochromate (30 mmol, 1.5 eq) was added to a solution of alcohol 2 (20 mmol, 1.0 eq) in DCM (35 mL) and the resulting mixture was stirred under nitrogen at r.t. for 1-2 hours. The reaction was then diluted with ether (500 mL) and filtered though a silica pad. The filtrate was concentrated under vacuum to give the crude product as a clear colourless oil. Where necessary purification by column chromatography (eluting with 5%-10% EtOAc in hexane) gave ketone **5**.

Preparation of 1-(3,5-difluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)propan-1-one 5a



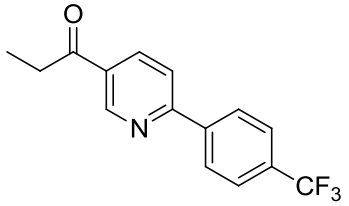
Yellow solid (Yield 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H, H-6), 7.38 – 7.30 (m, 2H, H-7), 7.19 – 7.11 (m, 2H, H-3), 2.93 (dt, *J* = 8.2, 6.8 Hz, 2H, CH_2), 1.23 (t, *J* = 7.2 Hz, 3H, CH_3).

Preparation of 1-(6-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)propan-1-one 5b



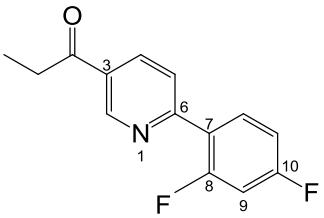
White solid. (Yield 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, *J* = 2.2 Hz, 1H, H-2), 8.32 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 8.18 – 8.04 (m, 2H, H-8), 7.83 (dd, *J* = 8.3, 0.6 Hz, 1H, H-5), 7.35 (d, *J* = 8.1 Hz, 2H, H-9), 3.07 (q, *J* = 7.2 Hz, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.55 (C=O), 159.63, 151.00, 150.15 (C-2), 137.15, 136.80, 130.98, 129.30 (C-8), 121.54 (C-9), 120.84 (q, *J* = 257 Hz, OCF_3), 120.46, 32.60 (CH_2), 8.35 (CH_3); HRMS (ESI) $C_{15}H_{13}NO_2F_3$ $[M+H]^+$ requires 296.0898, found 296.0901; Anal. $C_{15}H_{12}NO_2F_3$ requires C 61.02%, H 4.10%, N 4.74%, found C 60.42%, H 4.23%, N 4.40%.

Preparation of 1-(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)propan-1-one 5c



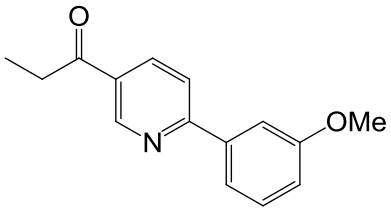
White powder (Yield, 78%) ^{1}H NMR (400MHz, $CDCl_3$) δ_H 9.23 (dd, 1H, J = 2.3 Hz, 0.7 Hz, Ar), 8.35 (dd, 1H, J = 8.3 Hz, 2.3 Hz, Ar), 8.19 (d, 2H, J = 8.2 Hz, Ar), 7.89 (dd, 1H, J = 8.3 Hz, 0.7 Hz, Ar), 7.77 (d, 2H, J = 8.2 Hz, Ar), 3.08 (q, 1H, J = 7.2 Hz, CH_2), 1.28 (t, 3H, J = 7.2 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.5, 159.5, 150.2, 141.9, 136.9, 131.4, 128.0, 126.3, 121.0, 32.7, 8.3 MS (ES+), $[M + H]^+$ (100), 280.1, HRMS calculated for 280.0949 $C_{15}H_{13}NOF_3$, found 280.0941.

Preparation of 1-(6-(2,4-difluorophenyl)pyridin-3-yl)propan-1-one 5d



Yellow solid (Yield, 70 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 1.6 Hz, 1H, H-2), 8.30 (dd, *J* = 8.3, 2.3 Hz, 1H), 8.11 (td, *J* = 8.9, 6.6 Hz, 1H, H-12), 7.89 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.09 – 7.01 (m, 1H, H-11), 6.95 (ddd, *J* = 11.3, 8.7, 2.5 Hz, 1H, H-9), 3.06 (q, *J* = 7.2 Hz, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); HRMS (ESI) $C_{14}H_{12}NOF_2[M+H]^+$ requires 248.0887, found 248.0892;

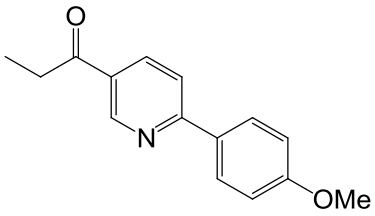
Preparation of 1-(6-(3-methoxyphenyl)pyridin-3-yl)propan-1-one 5e



Yellow solid. (Yield 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, *J* = 1.7 Hz, 1H, H-2), 8.30 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 7.84 (d, *J* = 8.3 Hz, 1H, H-5), 7.69 – 7.65 (m, 1H, H-8), 7.61 (d, *J* = 7.8 Hz, 1H, H-12), 7.41 (t, *J* = 8.0 Hz, 1H, H-11), 7.03 (ddd, *J* = 8.1, 2.5, 0.7 Hz, 1H, H-10), 3.91 (s, 3H, OCH_3), 3.06 (q, *J* = 7.2 Hz, 2H, CH_2), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3);

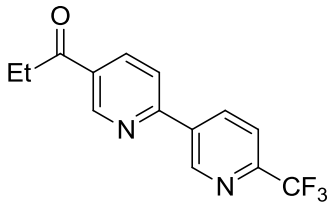
Anal. $C_{15}H_{15}NO_2$ requires C 74.67%, H 6.27%, N 5.81%, found C 74.21%, H 6.42%, N 5.70%.

Preparation of 1-(6-(4-methoxyphenyl)pyridin-3-yl)propan-1-one 5f



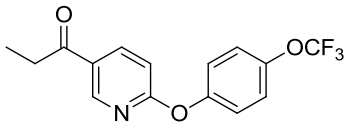
White solid (Yield 82 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 2.3, 0.8 Hz, 1H, H-2), 8.27 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 8.09 – 7.98 (m, 2H, H-8), 7.78 (dd, *J* = 8.4, 0.8 Hz, 1H, H-5), 7.14 – 6.95 (m, 2H, H-9), 3.89 (s, 3H, OCH_3), 3.05 (q, *J* = 7.2 Hz, 2H, CH_2), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.71 (C=O), 161.73, 160.77, 150.13 (C-2), 136.55 (C-4), 131.16, 130.09, 129.18 (C-8), 119.67 (C-5), 114.72 (C-9), 55.83 (OCH_3), 32.47 (CH_2), 8.44 (CH_3); MS (CI) $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.2; Anal. $C_{15}H_{15}NO_2$ requires C 74.67%, H 6.27%, N 5.81%, found C 74.44%, H 6.53%, N 5.64%.

Preparation of 1-(6'-(trifluoromethyl)-[2,3'-bipyridin]-5-yl)propan-1-one 5g



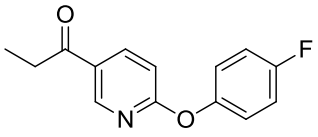
White solid (Yield 90%); ^{1}H NMR (400 MHz, $CDCl_3$) 9.37 (s, 1H), 9.30 (s, 1H), 8.59 (dd, *J* = 8.2, 1.9 Hz, 1H), 8.39 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 3.09 (q, *J* = 7.2 Hz, 2H), (t, *J* = 7.2 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.31, 156.85, 150.50, 149.41, 149.06, 137.10, 136.75, 136.52, 131.92, 121.09, 120.99, 120.96, 32.75, 8.29; MS (ES^+) m/z 281 $(M + H)^+$ Acc Mass Found: 281.0911, calculated 281.0902 for $C_{14}H_{12}N_2OF_3$.

Preparation of 1-(6-(4-(trifluoromethoxy)phenoxy)pyridin-3-yl)propan-1-one 5h



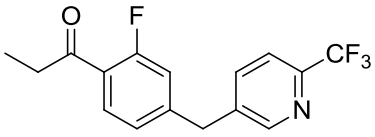
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 2.85 (q, J = 8.0 Hz, 2H), 1.13 (t, J = 8.0 Hz, 3H).

Preparation of 1-(6-(4-fluorophenoxy)pyridin-3-yl)propan-1-one 5i



Yellow oil (Yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.13-7.11 (m, 4H), 6.98 (d, J = 8.2 Hz, 1H), 2.94 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.56, 166.53, 161.57, 159.14, 149.40, 149.35, 139.63, 128.37, 123.47, 123.39, 116.93, 116.69, 111.66, 32.20, 8.42; MS (ES^+) m/z 268 $(M + Na)^+$ Acc Mass Found: 268.0753, calculated 268.0750 for $C_{14}H_{12}NO_2FNa$.

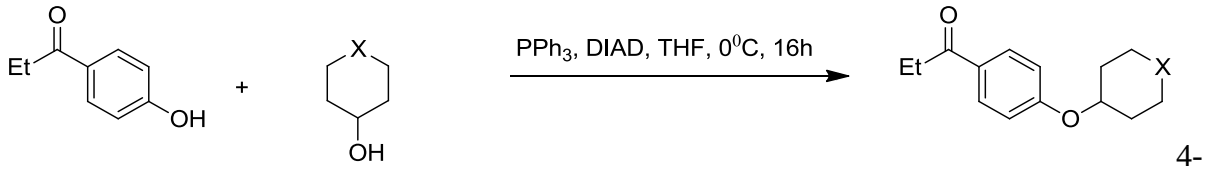
Preparation of 1-(2-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)methyl)phenyl)propan-1-one 5j



White powder (Yield 66%) ^{1}H NMR (400MHz, $CDCl_3$), δ_H 7.85 (t, 1H, J = 7.8 Hz, Ar), 7.68-7.62 (m, 2H, Ar), 7.06 (dd, 1H, J = 8.0 Hz, 1.4 Hz, Ar), 6.94 (dd, 1H, J = 11.7 Hz, 1.4 Hz, Ar), 4.11 (s, 2H, $ArCH_2Ar$), 8.62 (s, 1H, Ar), 2.98 (q, 2H, J = 7.2 Hz, CH_2CO), 1.19 (t, 3H, J

= 7.2 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.0, 163.8, 161.3, 150.7, 145.3, 138.6, 138.0, 131.7, 125.3, 124.6, 120.9, 117.5, 117.2, 37.7, 37.2, 8.4 MS (ES+), $[M + Na]^+$ (100), 334.1, HRMS calculated for 334.0831 $C_{16}H_{13}NOF_4Na$, found 334.0821.

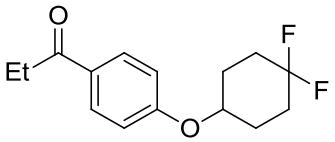
General procedure for the preparation of ketones 5k and 5l



4-

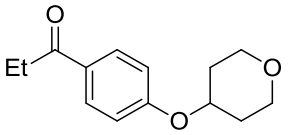
Alcohol (5.0 mmol, 1 eq.), 4-hydroxypropiophenone (5.0 mmol, 1 eq.) and PPh_3 (6.0 mmol, 1.2 eq.) was added to dry THF (20 mL) and cooled to 0°C. DIAD (6.0 mmol, 1.2 eq.) was added and allowed to stir at room temperature for 16 hours. THF removed *in vacuo* and EtOAc added (100 mL) and washed with 2M NaOH (30mL), water (30 mL) and brine (30 mL). Dried over $MgSO_4$ and concentrated *in vacuo*. The cream solid was purified by flash column chromatography (eluting with n-hexane to 30% EtOAc in n-hexane) to give the desired substituted ketone **5**.

Preparation of 1-(4-((4,4-difluorocyclohexyl)oxy)phenyl)propan-1-one 5k



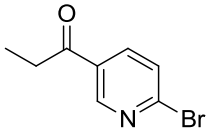
White solid (Yield 30%); ^1H NMR (400 MHz, $CDCl_3$) 7.94 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.60 (m, 1H), 2.95 (q, *J* = 7.2 Hz, 2H), 2.19-1.92 (m, 8H), 1.22 (t, *J* = 7.2 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.81, 161.33, 130.74, 123.19, 115.61, 71.14, 31.84, 30.13, 29.89, 29.64, 27.29, 27.26, 27.22, 27.19, 8.84; MS (ES^+) m/z 291 $(M + Na)^+$ Acc Mass Found: 291.1160, calculated 291.1173 for $C_{15}H_{18}O_2F_2{}^{23}Na$.

Preparation of 1-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)propan-1-one 5l



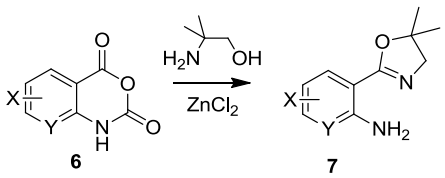
White solid (Yield 52%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.60 (tt, *J* = 7.6, 4.0 Hz, 1H), 3.99 (m, 2H), 3.61 (m, 2H), 2.95 (q, *J* = 7.3 Hz, 2H), 2.04 (m, 2H), 1.81 (m, 2H), 1.21 (t, *J* = 7.3 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.89, 161.44, 130.71, 130.44, 115.61, 70.44, 65.35, 31.98, 31.81, 8.84; MS (ES^+) m/z 235 $(M + H)^+$.

Preparation of 1-(6-bromopyridin-3-yl)propan-1-one 5k



White solid (Yield 80%); MP 101 – 103^{o}C; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.91 (d, *J* = 2.1 Hz, 1H), 8.08 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.61 (dd, *J* = 8.3, 0.6 Hz, 1H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

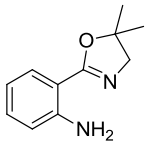
General procedure for the preparation of oxazoline 7



The appropriately substituted isobenzofuran-1,3-dione **6** (10 mmol, 1.0 eq) was suspended in chlorobenzene (25 mL) under nitrogen and stirred for 5 minutes. 2-amino-2-methylpropan-1-ol (14mmol, 1.4 eq) was added to the suspension via a syringe followed by zinc chloride (1 mmol, 0.1 eq). The mixture was heated to 140°C and was allowed to reflux for 18 hours. The solvent was removed under vacuum and the crude product extracted with EtOAc (2 x 25 mL), washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford a brown

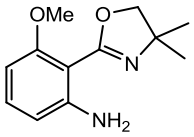
crystalline solid. Purification by column chromatography (eluting with n-hexane increasing to 10% EtOAc/n-Hexane) gave oxazoline **7**.

Preparation of 2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)aniline 7a



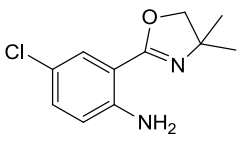
White solid (Yield 45%); M.P 103-106^{o}C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.10 (m, 1H), 6.65 (m, 2H), 6.08 (s, 2H, NH_2), 3.97 (s, 2H), 1.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.47, 148.93, 132.27, 129.88, 116.41, 116.02, 109.73, 77.75, 68.23, 29.15.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-3-methoxyaniline 7b



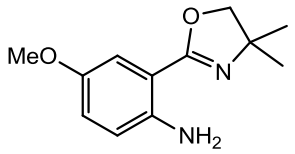
Yellow oil (1.66 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.08 (t, *J* = 8.2 Hz, 1H), 6.32 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.21 (dd, *J* = 8.2, 0.7 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 2H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.22, 159.02, 151.61, 132.21, 111.46, 105.74, 99.72, 71.39, 56.58, 56.42, 25.38.

Preparation 4-Chloro-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)aniline 7c



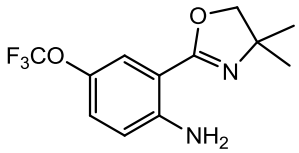
Yellow/ brown powder (0.983 mg, yield 47 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (6H, s), 3.9 (1H, s), 6.51 (1H, d), 7.10 (1H, m), 7.60 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 29.06 (2C, s), 68.44 (1C, s), 77.13 (1C, s), 110.64 (1C, s) 129.25 (1C, s), 132.12 (1C,s).

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4-methoxyaniline 7d



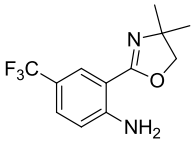
Yellow solid (1.06 g, 48.4%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 3.0 Hz, 1H), 6.86 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.76 (s, 2H), 4.00 (s, 2H), 3.76 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.22, 150.98, 143.41, 120.80, 117.60, 112.71, 109.86, 68.37, 56.32, 29.13.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4-(trifluoromethoxy)aniline 7e



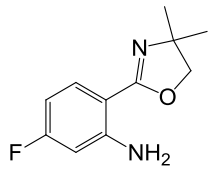
White solid (Yield 54%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.55 (s, 1H), 7.06 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.16 (bs, 2H), 4.00 (s, 2H), 1.37 (s, 6H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.49, 147.69, 139.27, 125.81, 122.70, 122.38, 119.84, 116.56, 109.64, 68.52, 29.07.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4-(trifluoromethyl)aniline 7f



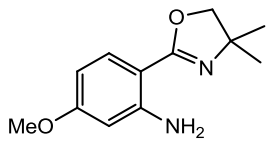
Yellow solid (Yield 51 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.31 (s, 2H, NH_2), 3.96 (s, 2H, CH_2), 1.32 (s, 6H, CH_3); HRMS (ESI) $C_{12}H_{14}N_2OF_3$ $[M+H]^+$ requires 259.1058, found 259.1054.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-5-fluoroaniline 7g



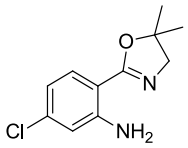
Yellow solid (Yield 60 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 9.3, 6.6 Hz, 1H, H-3), 6.38 – 6.32 (m, 2H, H-4 + H-5), 6.26 (s, 2H, NH_2), 3.98 (s, 2H, CH_2), 1.36 (s, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.59 (d, *J* = 248.3 Hz, C-F), 161.86 (C=N), 150.84, 132.05 (C-3), 106.29, 103.99, 101.77, 77.44 (OCH_2), 68.20 ($C(CH_3)_2$), 29.11 (CH_3); HRMS (CI) $C_{11}H_{14}N_2OF$ $[M+H]^+$ requires 209.1085, found 209.1084;

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-5-methoxyaniline 7h



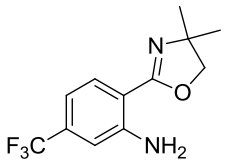
White solid (126 mg, 10.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 1H), 6.25 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H), 6.14 (s, 2H), 3.96 (s, 2H), 3.78 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.94, 162.29, 150.57, 131.39, 103.87, 103.49, 99.63, 68.02, 55.54, 29.19. ES HRMS: m/z calculated for $C_{12}H_{17}N_2O_2$ ($[M+H]^+$) 221.1285, found 221.1285.

Preparation of 5-chloro-2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)aniline 7i



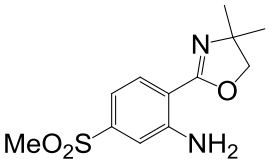
White solid (Yield 58%); M.P 84-85^{o}C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 6.13 (s, 2H, NH_2), 3.92 (s, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.87, 149.72, 137.93, 131.13, 116.65, 115.29, 108.28, 68.31, 66.28, 29.09; MS (CI m/z 225 $(M + H)^+$ Acc Mass Found: 225.0790, calculated 225.0789 for $C_{11}H_{14}N_2OCl$.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-5-(trifluoromethyl)aniline 7j



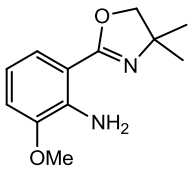
Yellow solid (Yield 56 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1H, H-3), 6.92 (s, 1H, H-6), 6.86 (d, *J* = 8.3 Hz, 1H, H-4), 6.31 (s, 2H, NH_2), 4.02 (s, 2H, CH_2), 1.38 (s, 6H, CH_3); HRMS (ESI) $C_{12}H_{14}N_2OF_3$ $[M+H]^+$ requires 259.1058, found 259.1065.

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-5-(methylsulfonyl)aniline 7k



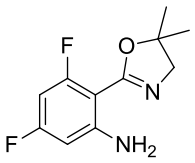
White solid (Yield 57 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 1H, H-3), 7.24 (d, *J* = 1.8 Hz, 1H, H-5), 7.13 (dd, *J* = 8.3, 1.8 Hz, 1H, H-4), 6.47 (s, 2H, NH_2), 4.04 (s, 2H, CH_2), 3.03 (s, 3H, CH_3), 1.38 (s, 6H, CH_3).

Preparation of 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-6-methoxyaniline 7l



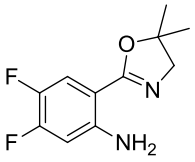
Yellow solid (740 mg, 30.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.59 (t, *J* = 8.0 Hz, 1H), 6.31 (s, 2H), 3.99 (s, 2H), 3.87 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.56, 147.16, 139.84, 121.44, 114.99, 111.91, 109.15, 68.21, 56.15, 29.17.

Preparation of 2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)-3,5-difluoroaniline 7m



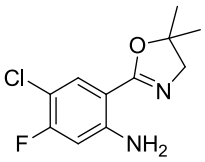
White solid (Yield 52%); ^{1}H NMR (400 MHz, $CDCl_3$) 6.44 (bs, 2H), 6.43-6.09 (m, 2H), 4.05 (s, 2H), 1.36 (s, 6H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.24, 166.07, 165.39, 165.23, 163.77, 163.60, 162.84, 160.67, 160.63, 151.82, 151.74, 151.67, 151.60, 97.92, 97.88, 97.67, 97.64, 96.08, 95.97, 93.40, 93.13, 92.86, 66.83, 29.02; MS (ES^+) m/z 227 $(M + H)^+$.

Preparation of 2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)-4,5-difluoroaniline 7n



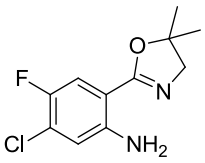
White solid (Yield 55%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 (dd, *J* = 11.5, 9.0 Hz, 1H), 6.45 (dd, *J* = 12.1, 6.7 Hz, 1H), 6.08 (bs, 2H), 4.00 (s, 2H), 1.36 (s, 6H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.16, 154.29, 151.94, 146.36, 146.26, 143.33, 140.99, 117.98, 117.96, 117.79, 117.76, 105.16, 103.79, 103.59, 68.50, 29.06.

Preparation of 4-chloro-2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)-5-fluoroaniline 7o



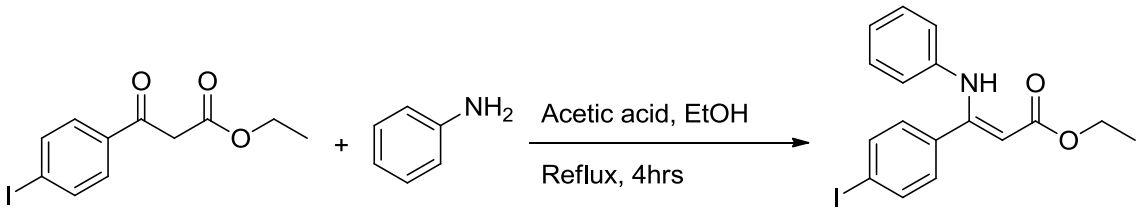
White solid (41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.35 Hz, 1H), 6.35 (d, *J* = 10.97, 1H), 6.20 (bs, 2H), 3.86 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.16, 159.55, 157.67, 147.86, 130.33, 106.46, 105.55, 101.71, 67.01, 27.60; HRMS (ESI) $C_{11}H_{13}N_2OFCl$ $[M+H]^+$ requires 243.0700, found 243.0695.

Preparation of 5-chloro-2-(5,5-dimethyl-4,5-dihydrooxazol-2-yl)-4-fluoroaniline 7p



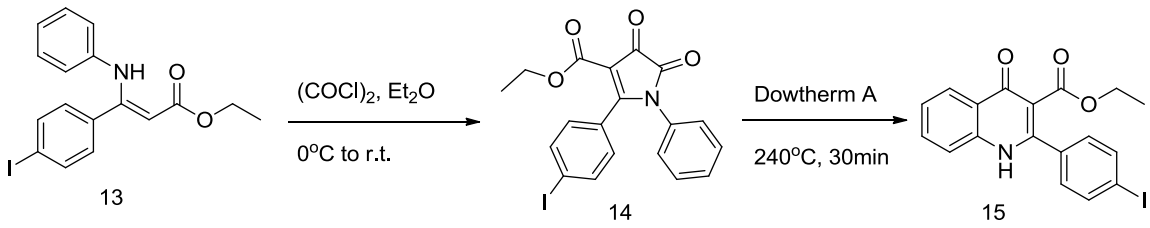
White solid (30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 10.03 Hz, 1H), 6.63 (d, *J* = 6.21, 1H), 5.95 (bs, 2H), 3.91 (s, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.72, 159.69, 149.53, 147.19, 144.23, 123.62, 115.32, 107.20, 67.17, 27.60; HRMS (ESI) $C_{11}H_{13}N_2OFCl$ $[M+H]^+$ requires 243.0700, found 243.0696.

Preparation of ethyl 3-(4-iodophenyl)-3-(phenylamino)acrylate 13



To a solution of aniline (2.93g, 2.86ml, 31.4mmol) in EtOH (10ml), acetic acid (1.89g, 1.80ml, 31.4mmol) was added, followed by the addition of a solution of ethyl (4-iodobenzoyl) acetate in EtOH (10ml). The resulting solution was heated to reflux for at least 4 hours. EtOH was removed *in vacuo,* and the residue dissolved in DCM. The DCM solution was then washed with water, 5%$HCl_{(aq.)}$ and brine, and dried with Na_2SO_4. The DCM was removed in vacuo to give the crude product as a yellow solid. The crude product was purified by column chromatography eluting with 5% EtOAc in hexane to give the title product (1.06, 86%) as a pale yellow crystalline solid. 1H NMR (400 MHz, CDCl3) δ 10.23 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.17 – 7.02 (m, 5H), 6.94 (t, J = 6.9 Hz, 1H), 6.66 (d, J = 7.5 Hz, 2H), 4.97 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H).

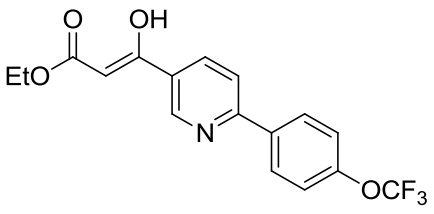
Preparation of ethyl 2-(4-iodophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 15



A solution of ethyl 3-(4-iodophenyl)-3-(phenylamino)acrylate in Et_2O was cooled to 0°C. $(COCl)_2$ was added to the solution dropwise. After the addition, 1,4-dioxane was added to the reaction mixture, and the reaction allowed to warm to room temperature. Et_2O and the HCl side product were removed *in vacuo* carefully. The precipitate formed after the evaporation was isolated by filtration to give **14**. **14** was used directly in the next step without any further purification.

A solution of **14** in Dowtherm was heat to 240°C for 30min. After cooling to room temperature, the solution was diluted with hexane. The precipitate is formed during the process was collected by filtration to give the title produce (1.0g, 91%) as an off-white solid. 1H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 8.12 (dd, J = 8.1, 1.1 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.73 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.45 – 7.34 (m, 3H), 4.00 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H).

Preparation of (Z)-ethyl 3-hydroxy-3-(6-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)acrylate 19

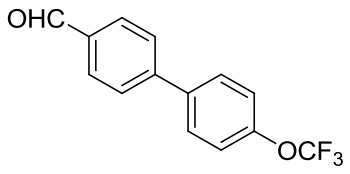


Aldehyde **18** (14 mmol, 1.0 eq) and Niobium Chloride (0.70 mmol, 5 mol %) were dissolved in DCM (140 mL) under nitrogen. Ethyl diazoacetate (15% in DCM, 16.8 mmol, 1.2 eq) was added dropwise and the reaction stirred at room temperature overnight. Water (140 mL) was

added and the layers separated. The aqueous portion was extracted with DCM (3 x 140 mL) and the combined organic portions dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting orange oil was purified by flash column chromatography (eluting with n-hexane to 80% EtOAc in n-hexane) to give the desired ketoester **19**.

White solid (Yield 50%); ^{1}H NMR (400 MHz, $CDCl_3$) 12.61 (bs, 1H), 9.05 (s, 1H), 8.15-8.07 (m, 3H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 5.75 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.24, 169.02, 158.31, 150.75, 147.92, 137.37, 134.82, 129.45, 129.05, 128.31, 121.55, 120.52, 120.27, 88.90, 61.09, 14.69; MS (ES^+) m/z 376 $(M + Na)^+$ Acc Mass Found: 376.0777, calculated 376.0773 for $C_{17}H_{14}NO_4F_3{}^{23}Na$.

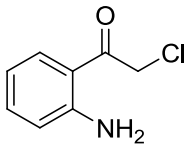
Preparation of 4'-(trifluoromethoxy)biphenyl-4-carbaldehyde 5



A suspension of the compound 1-bromo-4-(trifluoromethoxy)benzene (6.22 mmol, 1.50 g), 4-formylphenylboronic acid (9.34 mmol, 1.40 g), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (4% mol, 182 mg) and potassium phosphate tribasic (12.45 mmol, 2.64 g) in 30 mL of a mixture of toluene/water (9/1) was stirred for 5 hours under reflux. The solvent was then evaporated under reduced pressure and water was added. The aqueous layer was extracted three times with DCM. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue obtained was purified by column chromatography (DCM/Hexane: 1/9 to 3/7) to afford the product as a colorless oil (1.62 g, 98%).^{1}H NMR (400 MHz, $CDCl_3$): 10.06 (s, 1H, CHO), 7.95 (d, 2H, J = 8.5 Hz, ArH), 7.70 (d, 2H, J = 8.5 Hz, ArH), 7.64 (d, 2H, J = 8.9 Hz, ArH), 7.32 (d, 2H, J = 8.9 Hz, ArH); ^{13}C

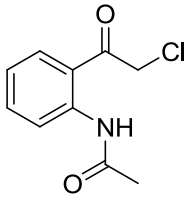
NMR ($CDCl_3$, 100MHz): 192.2, 149.9, 146.0, 130.7 (2C), 129.2 (2C), 128.0 (2C), 124.7, 122.2, 121.8 (2C), 119.6, 117.1; *m/z* (ES+) 289 ($[M+Na]^+$), found 289.0455 $C_{14}H_9F_3NaO_2$ requires 289.0452.

Preparation of 1-(2-aminophenyl)-2-chloroethanone 23



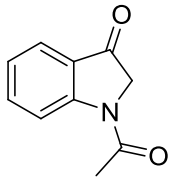
To a stirred solution of boron trichloride 1M in Hexane (60.36 mmol, 60.4 mL), a solution of aniline (54.87 mmol, 5mL) in 70 mL of dry toluene was added dropwise under ice-cooling. To the resulting mixture containing aniline boron trichloride complex, chloroacetonitrile (65.84 mmol, 4.2 mL) and aluminium trichloride (60.36 mmol, 8.05 g) were added successively. The mixture was then refluxed for 6 hours, becoming a solution of two layers. After cooling, ice 2N hydrochloric acid was added slowly and a yellow precipitate was formed. To hydrolyze the ketimine, the mixture was heated at 80°C under stirring until the precipitate had dissolved (2 hours). The cooled mixture was extracted three times with DCM. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue obtained was purified by column chromatography (DCM/Hexane: 5/5 to 8/2) to afford the product as a yellow solid (4.96 g, 54%), mp 106-108°C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (dd, 1H, J = 1.4; 8.2 Hz, ArH), 7.29 (dt, 1H, J = 1.4; 8.2 Hz, ArH), 6.68 (dd, 1H, J = 1.4; 8.5 Hz, ArH), 6.64 (dt, 1H, J = 1.4; 8.5 Hz, ArH), 6.32 (s, 2H, NH_2), 4.68 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100MHz): 192.8, 151.5, 135.7, 131.0, 118.0, 116.4, 115.5, 47.1; *m/z* (CI+) 136 ($[M+H-Cl]^+$).

Preparation of N-(2-(2-chloroacetyl)phenyl)acetamide 24



1-(2-aminophenyl)-2-chloroethanone (28.3 mmol, 4.8 g) was dissolved in 35 mL of acetic anhydride and the solution was heated at 90°C for 1 hour. After completion of the reaction, the solvent was evaporated. The residue was dissolved in DCM and passed through a silica gel layer (5 cm) to remove a polar fraction. The eluate with DCM was concentrated under reduced pressure to afford the product as a white solid (5.80 g, 97%), mp 122-124°C. ^{1}H NMR (400 MHz, $CDCl_3$): 11.36 (s, 1H, NH), 8.78 (dd, 1H, J = 1.0; 8.6 Hz, ArH), 7.82 (dd, 1H, J = 1.5; 8.1 Hz, ArH), 7.61 (dt, 1H, J = 1.0; 8.6 Hz, ArH), 7.14 (dt, 1H, J = 1.5; 8.1 Hz, ArH), 4.81 (s, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): 195.1, 170.0, 142.1, 136.6, 130.8, 122.9, 121.6, 119.4, 47.6, 26.0; *m/z* (CI+) 178 ($[M+H-Cl]^+$).

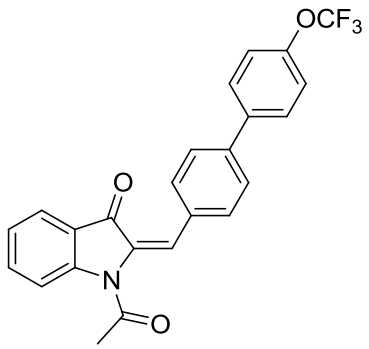
Preparation of 1-acetylindolin-3-one 25



To a stirred suspension of sodium hydride (27.79 mmol, 1.11 g) in 50 mL of monoglyme was added a solution of the compound *N*-(2-(2-chloroacetyl)phenyl)acetamide (26.46 mmol, 5.6 g) in 50 mL of monoglyme under ice-cooling. The mixture was stirred for 4 hours at 0°C. Ice and 2N hydrochloric acid were added and the mixture was extracted three times with DCM. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude obtained was purified by column chromatography (DCM + methanol 0% to 0.5%) to afford the product as a white solid (3.13 g, 61%), mp 134-136°C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (d, 1H, J = 8.4 Hz, ArH), 7.70 (d, 1H, J = 7.7 Hz, ArH), 7.64 (t, 1H,

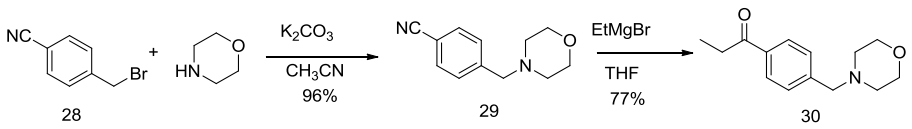
J = 8.4 Hz, ArH), 7.20 (t, 1H, J = 7.7 Hz, ArH), 4.28 (s, 2H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): 195.2, 168.6, 154.1, 137.7, 125.2, 124.6, 124.0, 118.9, 56.5, 24.6; *m/z* (CI+) 176 ($[M+H]^+$).

Preparation of 1-acetyl-2-((4'-(trifluoromethoxy)biphenyl-4-yl)methylene)indolin-3-one 26



1-acetylindolin-3-one (5.42 mmol, 0.95 g) and 4'-(trifluoromethoxy)biphenyl-4-carbaldehyde (6.50 mmol, 1.73 g) were dissolved in 60 mL of toluene. Five drops of piperidine were added and the mixture was heated at reflux for 20 hours. After completion of the reaction, the solvent was evaporated. The crude obtained was purified by column chromatography (DCM/Hexane: 7/3) to afford the product as An orange solid (2.13 g, 93%), mp 45-46°C. ^1H NMR (400 MHz, $CDCl_3$): 8.29 (d, 1H, J = 8.3 Hz, ArH), 7.87 (d, 1H, J = 7.6 Hz, ArH), 7.69 (dt, 1H, J = 1.4; 8.3 Hz, ArH), 7.64 (d, 4H, J = 8.2 Hz, ArH), 7.37 (s, 1H, CH), 7.33 (d, 2H, J = 7.5 Hz, ArH), 7.31 (d, 2H, J = 7.5 Hz, ArH), 7.26 (dt, 1H, J = 1.4; 7.6 Hz, ArH), 2.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): 186.3, 170.8, 150.6, 141.4, 138.8, 136.8, 135.5, 133.6, 131.4 (2C), 130.0, 128.9 (2C), 128.8 (2C), 128.1 (2C), 126.9, 125.5, 124.7, 124.6, 122.2, 121.8, 119.6, 118.3, 117.1, 25.6; *m/z* (ES+) 446 ($[M+Na]^+$), found 446.0988 $C_{24}H_{16}F_3NNaO_3$ requires 446.0980.

Preparation of 1-(4-(morpholinomethyl)phenyl)propan-1-ol 30



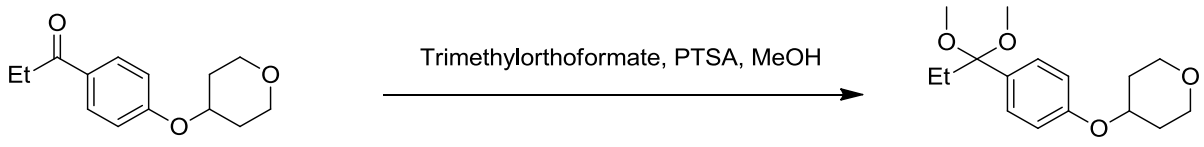
To a solution of 4-cyanobenzylbromide (2.28g, 11.6 mmol) in 25 ml of anhydrous acetonitrile was added morpholine (1.5 ml, 17.4 mmol) followed by K_2CO_3 (1.38 g, 10mmol). The reaction was stirred at rt under N_2 atm for 30 min and subsequently quenched with water and extracted with ethylacetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane - 30% EtOAc/hexane) to give **29**.

White solid (Yield 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J=7.9* Hz, 2H), 7.48 (d, *J=8.0* Hz, 2H), 3.71(s, 4H), 3.55(s, 2H), 2.44(s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.2, 132.5, 129.8, 119.2, 111.3, 67.2, 63.1, 54.1.

To a solution of cyano compound **29** (1.01 g, 5 mmol) in 5 ml of dry THF at 0 °C was added a 1M solution EtMgBr in THF (6 ml, 6 mmol) and CuI (5 mg, 0.05 mmol). The reaction mixture was allowed to warm to rt and stirred at rt overnight. The reaction was quenched with 2N HCl and extracted with EtOAc, organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography to give **30**.

White solid (Yield 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 3.78 – 3.67 (m, 4H), 3.55 (s, 2H), 3.00 (q, *J* = 7.2 Hz, 2H), 2.52 – 2.40 (m, 4H), 1.27 – 1.15 (t, *J=7.2* Hz, 3H). MS (ES^+) m/z 234 $(M + H)^+$ Acc Mass Found: 234.1502, calculated 234.1494 for $C_{14}H_{20}NO_2$

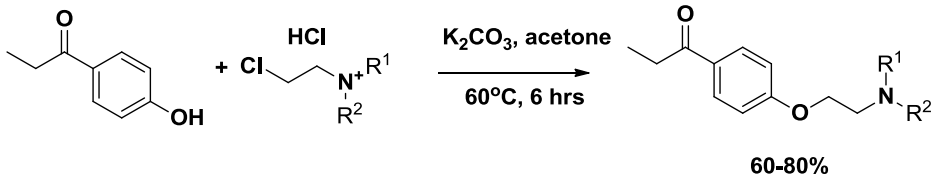
Preparation of 4-(4-(1,1-dimethoxypropyl)phenoxy)tetrahydro-2H-pyran 33



Ketone (4.5 mmol, 1.0 eq) was dissolved in methanol (40 mL) and trimethyl orthoformate (45 mmol, 10 eq) and para-toluenesulfonic acid (0.45 mmol, 0.1 eq) were added. The reaction was heated at reflux overnight and then allowed to cool. Most of the methanol was removed *in vacuo* (10 mL remained) and ether (50 mL) was added. The solution was washed with sodium bicarbonate and brine, dried over $MgSO_4$ and the solvent removed to give diacetal **33**.

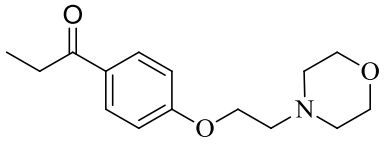
Clear oil (Yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.35 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.49 (tt, J = 7.6, 4.0 Hz, 1H), 3.99 (m, 2H), 3.60 (m, 2H), 2.97 (s, 6H), 2.02 (m, 2H), 1.88 (q, J = 7.5 Hz, 2H), 1.80 (m, 2H), 0.59 (t, J = 7.5 Hz, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.92, 133.51, 128.73, 115.58, 104.48, 71.84, 65.58, 48.92, 30.29, 8.20; MS (ES^+) m/z 303 $(M + Na)^+$ Acc Mass Found: 303.1579, calculated 303.1572 for $C_{16}H_{24}O_4{}^{23}Na$.

General procedure for the preparation of ethoxy amines 39



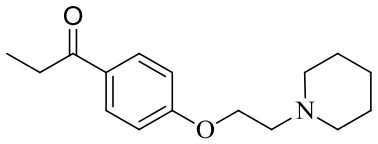
To a stirred solution of a of 4-hydroxypropiophenone (1mmol), in acetone (5mL) was added 4-(2-chloroethyl)morpholine hydrochloride (4.5mmol). To this solution was added anhydrous K_2CO_3 (5mmol) and the resulting mixture stirred at reflux for 6hrs The reaction mixture was vacuum filtered, and the residue washed with cold dry acetone and concentrate. Purification by flash column chromatography gave the respective products.

Preparation of 1-(4-(2-morpholinoethoxy)phenyl)propan-1-one 39a



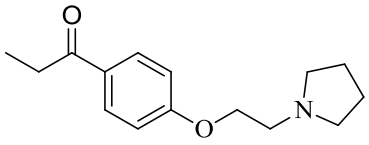
Brown oil (Yield 80%); ^{1}H NMR (400MHz, $CDCl_3$), δ_H 1.21 (t, 3H, J = 7.3 Hz, CH_3), 2.58 (t, 4H, J = 4.6 Hz, CH_2O), 2.82 (t, 2H, J = 5.7 Hz, CH_2N), 2.95(q, 2H, J = 7.3 Hz, CH_2O), 3.73 (t, 4H, J = 4.6 Hz, NCH_2), 4.17 (t, 2H, J = 5.7 Hz, OCH_2), 6.93 (d, 2H, J = 8.9 Hz, Ar), 7.94 (d, 2H, 8.9 Hz, Ar) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.9, 162.8, 130.6, 114.4, 67.4, 66.4, 57.8, 54.6, 31.9, 8.8 MS (ES+), $[M + H]^+$ (100), 264.2, HRMS calculated for 264.1600 $C_{15}H_{22}NO_3$, found 264.1601.

Preparation of 1-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one 39b



White powder (Yield 76%); ^{1}H NMR (400MHz, $CDCl_3$), δ_H 7.93 (d, 2H, J = 8.9 Hz, Ar), 6.93 (d, 2H, J = 8.9 Hz, Ar), 4.16 (t, 2H, J = 6.1 Hz, OCH_2), 2.95 (q, 2H, J = 7.3 Hz, CH_2CO), 2.79 (t, 2H, J = 6.1 Hz, CH_2N), 2.51 (bs, 4H, CH_2), 1.65-1.54 (m, 6H, CH_2), 1,21 (t, 3H, J = 7.3 Hz, CH_3), ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.8, 163.2, 131.0, 114.4, 66.4, 55.7, 31.2, 26.3, 24.7, 8.8 MS (ES+), $[M + Na]^+$ (100), 262.3.

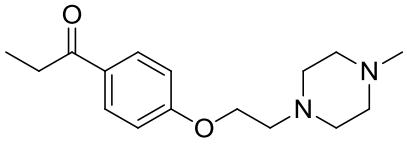
Preparation of 1-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)propan-1-one 39c



White powder (Yield 72%); ^{1}H NMR (400MHz, $CDCl_3$), δ_H 7.94 (d, 2H, J = 9.0 Hz, Ar), 6.95 (d, 2H, J = 9.0 Hz, Ar), 4.17 (t, J = 5.9Hz, OCH_2), 2.99-2.89 (m, 4H, CH_2CO/CH_2N),

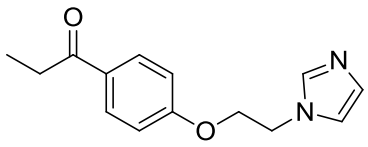
2.65-2.60 (m, 4H, CH_2), 1.84-1.77 (m, 4H, CH_2), 1.21 (t, 3H, J = 7.3 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.8, 161.8, 114.4, 67.8, 55.2, 54.5, 24.0, 8.8 MS (CI), $[M + H]^+$ (100), 248.3.

Preparation of 1-(4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)propan-1-one 39d



Brown oil (Yield 60%); ^1H NMR (400MHz, $CDCl_3$), δ_H 7.94 (d, 2H, J = 9.0Hz, Ar), 6.93 (d, 2H, J = 9.0 Hz, Ar), 4.17 (t, 2H, J = 5.8 Hz, OCH_2), 2.95 (q, 2H, J = 7.3 Hz, $COCH_2$), 2.85 (t, 2H, J = 5.8 Hz, CH_2N), 2.64 (bs, 4H, piperazinyl), 2.50 (bs, 4H, piperazinyl), 2.31 (s, 3H, NCH_3), 1.21 (t, 3H, J = 7.3 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.9, 162.2, 130.6, 114.6, 66.5, 57.4, 55.4, 53.9, 46.4, 31.8, 8.8 MS (ES+), $[M + H]^+$ (100), 277.2, HRMS calculated for 277.1916 $C_{16}H_{25}N_2O_2$, found 277.1909.

Preparation of 1-(4-(2-(1*H*-imidazol-1-yl)ethoxy)phenyl)propan-1-one 39e

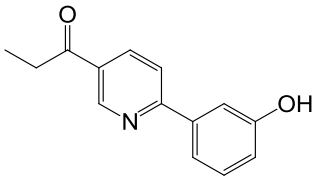


White powder (Yield 59%); ^1H NMR (400MHz, $CDCl_3$), δ_H 7.97 (d, 2H, J = 9.0 Hz, Ar), 7.60 (s, 1H, imidazolyl), 7.06 (d, 2H, J = 8.2 Hz, imidazolyl), 6.90 (d, 2H, J = 9.0 Hz, Ar), 4.28 (t, 2H, J = 6.0 Hz, OCH_2), 3.75 (t, 2H, J = 6.0 Hz, CH_2N), 2.94 (q, 2H, J = 7.3 Hz, $COCH_2$), 1.20 (t, 3H, J = 7.3 Hz, CH_3) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 199.8, 161.9, 131.1, 130.6, 130.2, 119.3, 67.7, 46.7, 31.9, 8.7 MS (CI+), $[M + H]^+$ (100),245.1, HRMS calculated for 245.1290 $C_{14}H_{17}N_2O_2$, found 245.1285

General Procedure for the preparation of alcohols 44

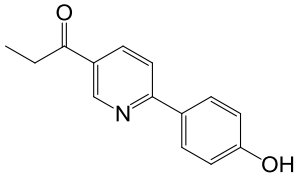
2-(diethylamino)ethanethiol hydrochloride (0.34 g, 2.0 mmol, 1.2 equiv) in anhydrous DMF (4 mL) was cooled to 0^{o}C. NaO^{t}Bu (0.40 g, 4.16 mmol, 2.52 equiv) was added. After 5 min, the ice bath was removed. The white suspension was allowed to warm to room temperature. After 15 min, **43** (0. 40 g, 1.66 mmol) was added. The resulting dark mixture was heated to reflux for 2 h (followed by tlc). The mixture was cooled to room temperature, and the flask was placed in an ice water bath. The mixture was acidified to pH 1 by 1 N HCl (aq) and diluted with water. The aqueous phase was extracted with ethyl acetate (x 3), and the combined organic extracts were washed with water (x 3) and saturated brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography using 2% methanol in dichloromethane to give the title compound

Preparation of 1-(6-(3-hydroxyphenyl)pyridin-3-yl)propan-1-one 44a



Yellow solid (Yield 60 %); ^{1}H NMR (400 MHz, MeOD) δ 9.16 (dd, *J* = 2.2, 0.7 Hz, 1H, H-2), 8.38 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 7.93 (dd, *J* = 8.4, 0.8 Hz, 1H, H-5), 7.54 – 7.41 (m, 2H, H-8 + H-12), 7.37 – 7.28 (m, 1H, H-11), 6.91 (ddd, *J* = 8.1, 2.2, 1.2 Hz, 1H, H-10), 3.11 (q, *J* = 7.2 Hz, 2H, CH_2), 1.22 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, MeOD) δ 199.81 (C=O), 160.72, 157.86, 148.95, 139.44, 136.56, 130.62, 129.65, 120.53, 118.27, 116.78, 113.83, 31.57 (CH_2), 6.83 (CH_3). HRMS (CI) $C_{14}H_{14}NO_2$ $[M+H]^+$ requires 228.1019, found 228.1023.

Preparation of 1-(6-(4-hydroxyphenyl)pyridin-3-yl)propan-1-one 44b

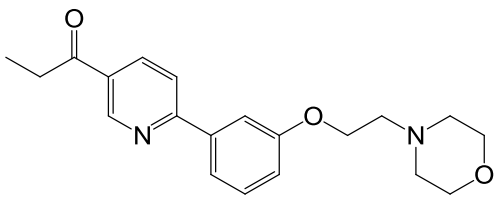


Yellow solid. (Yield 64 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 2.3, 0.8 Hz, 1H, H-2), 8.27 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 8.09 – 7.89 (m, 2H, H-8), 7.77 (dd, *J* = 8.4, 0.8 Hz, 1H, H-5), 6.93 (d, *J* = 8.9 Hz, 2H, H-9), 5.69 (s, 1H, OH), 3.04 (q, *J* = 7.2 Hz, 2H, CH_2), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.67, 160.77, 158.05, 150.02, 145.53, 136.68, 130.19, 129.48, 119.84, 116.29, 32.47, 8.43; MS (CI) $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.3; Anal. $C_{14}H_{13}NO_2$ requires C 73.99%, H 5.77%, N 6.16%, found C 73.63%, H 5.95%, N 5.95%.

General procedure for the preparation of ethoxy amine 45

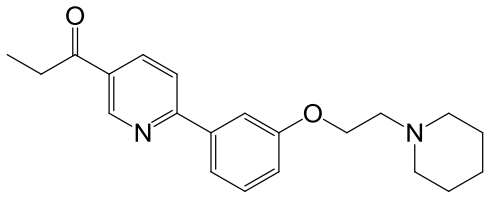
44 (0.88 mmol) in dry acetone (10 mL) was added potassium carbonate (0.49 g, 3.55 mmol, 4 equiv). The yellow mixture was stirred for 15 min. 4-(2-chloroethyl)morpholine hydrochloride (0.33 g, 1.76 mmol, 2 equiv) was added. The mixture was stirred for another 10 min, then was heated to 60 ^{o}C for 30 h (followed by tlc). The reaction was cooled, the mixture was filtered, washed with cool acetone. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate to give compound **45**.

Preparation of 1-(6-(3-(2-morpholinoethoxy)phenyl)pyridin-3-yl)propan-1-one 45a



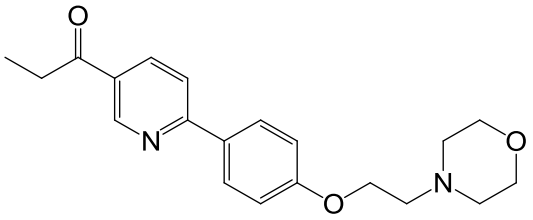
White solid (Yield 70 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 1.6 Hz, 1H, H-2), 8.30 (dd, *J* = 8.3, 2.2 Hz, 1H, H-4), 7.83 (d, *J* = 8.3 Hz, 1H, H-5), 7.68 (s, 1H, H-8), 7.61 (d, *J* = 7.8 Hz, 1H, H-12), 7.41 (t, *J* = 7.9 Hz, 1H, H-11), 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H, H-10), 4.22 (t, *J* = 5.7 Hz, 2H, OCH_2), 3.81 – 3.71 (m, 4H, OCH_2), 3.06 (d, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 2.85 (t, *J* = 5.6 Hz, 2H, NCH_2), 2.73 – 2.57 (m, 4H, NCH_2), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.09, 160.83, 150.03, 140.07, 136.62, 130.33, 120.69, 120.26, 117.73, 116.97, 113.69, 67.36, 66.36, 58.09, 54.52, 32.56, 8.39; HRMS (ESI) $C_{20}H_{25}N_2O_3$ $[M+H]^+$ requires 341.1865, found 341.1879; Anal. $C_{20}H_{24}N_2O_3$ requires C 70.56%, H 7.11%, N 8.23%, found C 70.19%, H 7.31%, N 8.09%.

Preparation of 1-(6-(3-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-3-yl)propan-1-one 45b



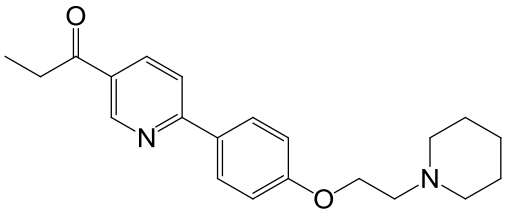
Yellow oil (Yield 69 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 1.9 Hz, 1H, H-2), 8.28 (dd, *J* = 8.3, 2.3 Hz, 1H, H-4), 7.82 (d, *J* = 8.3 Hz, 1H, H-5), 7.69 – 7.64 (m, 1H, H-8), 7.61 (d, *J* = 7.8 Hz, 1H, H-12), 7.39 (d, *J* = 7.9 Hz, 1H, H-11), 7.02 (dd, *J* = 8.1, 2.1 Hz, 1H, H-10), 4.23 (t, *J* = 5.9 Hz, 2H, OCH_2), 3.05 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 2.86 (t, *J* = 5.9 Hz, 2H, $OCH_2C\underline{H}_2$), 2.58 (s, 4H, NCH_2), 1.64 (dt, *J* = 11.2, 5.6 Hz, 4H, $NCH_2C\underline{H}_2$), 1.53 – 1.40 (m, 2H, CH_2), 1.27 (t, *J* = 5.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.64 (C=O), 160.85, 159.74, 150.00(C-2), 140.01, 136.58, 130.83, 130.29, 120.66, 120.16, 116.91, 113.72, 66.29 (OCH_2), 58.18, 55.32 (NCH_2), 32.53, 26.11 ($NCH_2\underline{C}H_2$), 24.44, 8.37 (CH_3); HRMS (ESI) $C_{21}H_{27}N_2O_2$ $[M+H]^+$ requires 339.2073, found 339.2086.

Preparation of 1-(6-(4-(2-morpholinoethoxy)phenyl)pyridin-3-yl)propan-1-one 45c



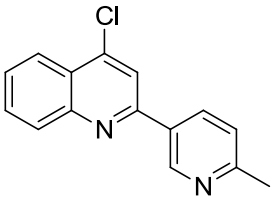
White solid (Yield 74 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 2.3, 0.7 Hz, 1H, H-2), 8.26 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 8.06 – 7.99 (m, 2H, H-8), 7.77 (dd, *J* = 8.4, 0.8 Hz, 1H, H-5), 7.05 – 6.99 (m, 2H, H-9), 4.19 (t, *J* = 5.7 Hz, 2H, $C\underline{H}_2CH_3$), 3.82 – 3.70 (m, 4H, OCH_2), 3.04 (q, *J* = 7.2 Hz, 2H, OCH_2), 2.84 (t, *J* = 5.7 Hz, 2H, NCH_2), 2.68 – 2.52 (m, 4H, NCH_2), 1.27 (t, *J* = 7.2 Hz, 3H, CH_3); HRMS (ESI) $C_{20}H_{25}N_2O_3$ $[M+H]^+$ requires 341.1865, found 341.1877; Anal. $C_{20}H_{24}N_2O_3$ requires C 70.57%, H 7.11%, N 8.23%, found C 70.47%, H 7.14%, N 8.19%.

Preparation of 1-(6-(4-(2-(piperidin-1-yl)ethoxy)phenyl)pyridin-3-yl)propan-1-one 45d



Pale yellow solid (Yield 77 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 2.2, 0.7 Hz, 1H, H-2), 8.26 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 8.10 – 7.94 (m, 2H, H-8), 7.77 (dd, *J* = 8.4, 0.7 Hz, 1H, H-5), 7.07 – 6.97 (m, 2H, H-9), 4.20 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.04 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 2.84 (t, *J* = 5.5 Hz, 2H, $OCH_2C\underline{H}_2$), 2.56 (s, 4H, NCH_2), 1.64 (dt, *J* = 11.1, 5.6 Hz, 4H, $NCH_2C\underline{H}_2$), 1.47 (dd, *J* = 11.3, 6.3 Hz, 2H, CH_2), 1.26 (dd, *J* = 8.4, 6.1 Hz, 4H, CH_3); HRMS (ESI) $C_{21}H_{27}N_2O_2$ $[M+H]^+$ requires 339.2073, found 339.2084;

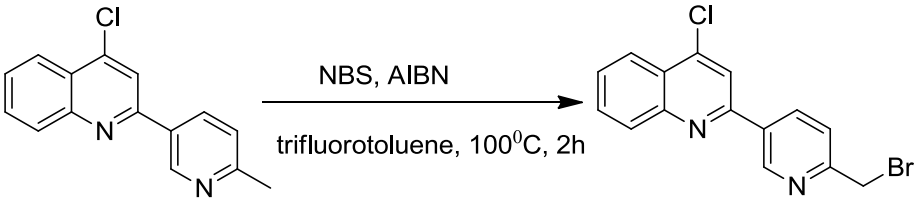
Preparation of 4-chloro-2-(6-methylpyridin-3-yl)quinoline 49



Prepared according to the procedure for the preparation of **3g.**

White solid (Yield 79%); ^{1}H NMR (400 MHz, $CDCl_3$) 9.24 (s, 1H), 8.44 (dd, *J* = 8.1, 2.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.81 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.65 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 2.69 (s, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.76, 154.70, 149.49, 147.76, 143.98, 136.20, 132.07, 131.29, 130.46, 128.07, 125.89, 124.44, 124.12, 118.82, 24.43; MS (ES^+) m/z 255 $(M + H)^+$ Acc Mass Found: 255.0687, calculated 255.0689 for $C_{15}H_{12}N_2{}^{35}Cl$.

Preparation of 2-(6-(bromomethyl)pyridin-3-yl)-4-chloroquinoline 50

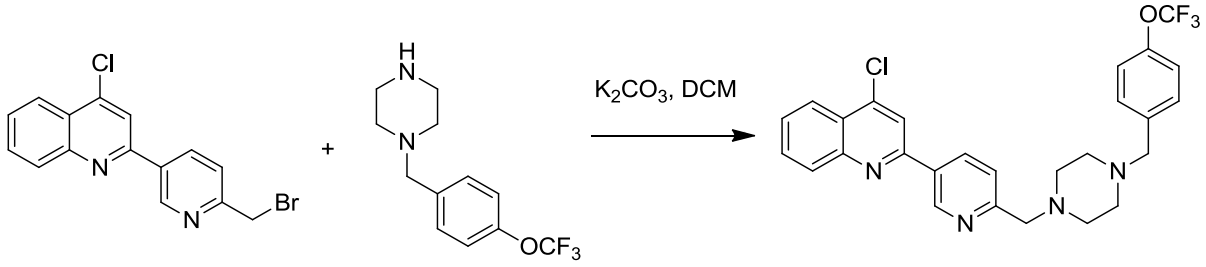


2-Pyridyl-4-chloroquinoline (1.50 mmol, 1. eq.), NBS (1.50 mmol, 1.eq.) and AIBN (0.15 mmol, 0.1 eq.) was added to trifluorotoluene (40 mL) and heated to 100C for 2 hours. After cooling, the precipitate was filtered off and DCM (50 mL) was added to the filtrate. This was washed with brine (30 mL) and then dried over $MgSO_4$. The crude solid was purified by flash column chromatography (eluting with n-hexane to 10% EtOAc in n-hexane) to give the desired compound as a white solid.

White solid (Yield 44%); ^{1}H NMR (400 MHz, $CDCl_3$) 9.29 (s, 1H), 8.51 (dd, *J* = 8.1, 2.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.82 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.67 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 4.65 (s, 2H); δ ^{13}C NMR (100

MHz, $CDCl_3$) δ 157.99, 154.01, 149.39, 148.47, 144.28, 136.84, 133.92, 131.49, 130.49, 128.41, 126.04, 124.49, 124.19, 118.94, 33.26; MS (ES^+) m/z 333 $(M + H)^+$ Acc Mass Found: 332.9788, calculated 332.9794 for $C_{15}H_{11}N_2{}^{35}Cl^{79}Br$.

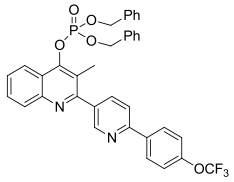
Preparation of 4-chloro-2-(6-((4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl)methyl)pyridin-3-yl)quinoline 52



Quinoline **50** (0.40 mmol, 1 eq.) was added to DCM (20 mL) with 4-OCF_3-benzylpiperazine (0.80 mmol, 2 eq.) and K_2CO_3 (0.6 mmol, 1.5 eq.). The solution was allowed to stir at room temperature overnight. The salt precipitate was filtered off and the crude solid was purified by flash column chromatography (eluting with 100% EtOAc) to give the desired compound as a white solid.

White solid (Yield 70%); ^{1}H NMR (400 MHz, MeOD) 9.28 (s, 1H), 8.56 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.86 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 2H), 3.56 (s, 2H), 2.68-2.48 (m, 8H); δ ^{13}C NMR (100 MHz, MeOD) δ 159.08, 154.32, 148.80, 148.36, 147.44, 143.50, 136.60, 135.87, 132.87, 130.94, 130.80, 129.46, 127.85, 125.33, 123.71, 123.57, 120.50, 118.63, 63.15, 61.50, 52.68, 52.43; MS (ES^+) m/z 513 $(M + H)^+$ Acc Mass Found: 513.1658, calculated 513.1669 for $C_{27}H_{25}N_4OF_3{}^{35}Cl$.

Preparation of dibenzyl (3-methyl-2-(6-(4-(trifluoromethoxy)phenyl)pyridin-3-yl)quinolin-4-yl) phosphate 54



Sodium hydride (0.57 mmol, 2.5 eq) was added at 0°C to a stirred solution of quinolone (0.23 mmol, 1.0 eq) in dry THF (10 mL). After 1 hr, tetrabenzyl pyrophosphate (0.19 mmol, 0.8 eq) was added and the stirring continued for 20 minutes. The mixture was filtered and the filtrate concentrated under vacuum at a temperature below 35°C. The residue was dissolved in DCM, washed with $NaHCO_3$ aq, dried over MgSO4 and concentrated under vacuum to give phosphonate **54**. Where necessary the product was purified by flash column chromatography (eluting with 10% ethyl acetate in n-hexane).

White solid (Yield 80%); MP 106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 2.2 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.10 (dd, *J* = 8.3, 3.5 Hz, 3H), 7.97 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.65 (m, 1H), 7.59 – 7.48 (m, 1H), 7.41 – 7.27 (m, 12H), 5.15 (dd, *J* = 9.0, 3.4 Hz, 4H), 2.44 (s, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ -5.85; ES+ HRMS: m/z found 657.1797, $[C_{36}H_{28}N_2O_5F_3P + H]^+$ requires 657.1766.

General procedure for the synthesis of quinolones 8

The appropriately substituted oxazoline **7** (4 mmol, 1 eq) was added to a solution of ketone **5** (4 mmol, 1 eq) and *para*-toluenesulfonic acid (20 mol%) in *n*-Butanol (10 mL). The reaction mixture was heated to 130°C under nitrogen and stirred for 24 hours. The solvent was removed under vacuum and water (20 mL) added. The aqueous solution was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The product

was purified by column chromatography (eluting with 20% -80% EtOAc in n-hexane) to give quinolone **8**.

8a: Yellow solid (Yield 33 %); Rf = 0.24, 40% ethyl acetate in hexane); m.p. 297 – 298 ^{o}C; ^{1}H NMR (400 MHz, MeOD) δ 8.32 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.93 – 7.81 (m, 2H), 7.71 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.48 – 7.31 (m, 3H), 2.02 (s, 3H); HRMS (ESI) $C_{23}H_{15}NO_2F_5$ $[M+H]^+$ requires 432.1023, found 432.1018. Anal. $C_{23}H_{14}NO_2F_5$ requires C 64.04%, H 3.27%, N 3.25%, found C 64.15%, H 3.16%, N 3.15%.

8b: White solid (Yield 69 %); m.p. 277-278 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.76 (s, 1H), 8.90 (d, *J* = 2.1 Hz, 1H), 8.37 – 8.31 (m, 2H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.17 (dd, *J* = 8.2, 2.2 Hz, 1H), 8.15 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.65 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.33 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 176.98, 155.52, 149.75, 144.79, 139.95, 138.49, 137.46, 131.83, 130.30, 129.34, 129.17 (C-8'), 125.37, 123.50, 123.22, 121.70, 120.35, 119.18, 118.51, 115.59, 12.39; HRMS (ESI) $C_{22}H_{16}N_2O_2F_3$ $[M+H]^+$ requires 397.1164, found 397.1173. Anal. $C_{22}H_{15}N_2O_2F_3$ requires C 66.67%, H 3.81%, N 7.07%, found C 66.77%, H 3.73%, N 6.98%.

8c: light brown powder (Yield 4%); 1H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 8.86 (s, 1H), 8.33 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.1 Hz, 1H), 8.12 (dd, J = 8.1, 2.1 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 3.82 (s, 3H), 1.86 (s, 3H). HRMS(ESI) $C_{23}H_{18}N_2O_3F_3$ ([M+H]+) requires 427.1270, found 427.1271

8d: White solid (Yield 34%); m.p. >300 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.96 (bs, 1H), 8.90 (s, 1H), 8.34 (d, *J* = 8.7 Hz, 2H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.08 (s, 1H), 7.65 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 175.84, 155.66, 149.73, 145.23, 138.51, 137.41, 132.03, 130.00, 129.19, 127.81, 124.38,

124.24, 121.71, 121.06, 120.38, 119.18, 116.13, 12.40; HRMS (ESI) $C_{22}H_{15}N_2O_2F_3{}^{35}Cl$ $[M+H]^+$ requires 431.0774, found 431.0755.

8e: White solid (Yield 32%); m.p. 312-314 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.77 (bs, 1H), 8.89 (s, 1H), 8.34 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.16 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.56 (m, 4H), 7.31 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.86 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 176.24, 155.70, 155.44, 149.77, 149.70, 143.99, 138.52, 137.47, 134.71, 130.37, 129.16, 124.43, 122.59, 121.73, 120.34, 114.45, 104.26, 55.69, 12.54; HRMS (ESI) $C_{23}H_{18}N_2O_3F_3$ $[M+H]^+$ requires 427.1270, found 427.1248.

8f: White solid (Yield 33%); m.p. >300 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 12.07 (bs, 1H), 8.91 (s, 1H), 8.34 (d, *J* = 8.9 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.99 (s,1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.69 (dd, *J* = 9.2, 2.4 Hz , 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 176.21, 155.70, 149.74, 145.47, 138.59, 138.51, 137.40, 129.95, 129.20, 125.68, 123.85, 121.71, 121.37, 120.39, 116.33, 115.87, 12.36; HRMS (ESI) $C_{23}H_{15}N_2O_3F_6$ $[M+H]^+$ requires 481.0987, found 481.0988.

8g: White solid (Yield 33%); m.p >300 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.96 (bs, 1H), 8.94 (s, 1H), 8.43 (s, 1H), 8.35 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 8.7 Hz , 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 176.56, 155.76, 149.76, 145.70, 141.93, 138.52, 137.37, 129.80, 129.20, 127.76, 126.05, 123.63, 123.30, 123.14, 122.52, 121.70, 120.39, 120.23, 117.16, 12.34; HRMS (ESI) $C_{23}H_{14}N_2O_2F_6{}^{23}Na$ $[M+Na]^+$ requires 487.0857, found 487.0858.

8h: Pale yellow solid (Yield 30 %); m.p. 317 – 319 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.83 (s, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 8.39 – 8.31 (m, 2H), 8.24 (t, *J* = 8.7 Hz, 1H), 8.22 – 8.11 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.30 (dd, *J* = 10.1, 2.4 Hz, 1H), 7.20 (td, *J* = 8.8, 2.5 Hz, 1H), 1.95 (s, 3H); HRMS (ESI) $C_{22}H_{14}N_2O_2F_4{}^{23}Na$ $[M+Na]^+$ requires 437.0889, found 437.0905.

8i: White solid (Yield 23 %); m.p. 324 – 325 ^{o}C. ^{1}H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.88 (d, *J* = 2.1 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.3 Hz, 1H), 8.15 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.93 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.84 (s, 3H), 1.93 (s, 3H); HRMS (ESI) $C_{23}H_{18}N_2O_3F_3$ $[M+H]^+$ requires 427.1270, found 427.1280. Anal. $C_{23}H_{17}N_2O_3F_3$ requires C 64.79%, H 4.02%, N 6.57%, found C 64.65%, H 3.88%, N 6.47%.

8j: White solid (Yield 30 %); m.p. 317 – 318 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.82 (s, 1H, N-H), 8.91 (s, 1H), 8.34 (d, *J* = 8.7 Hz, 2H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.21 – 8.05 (m, 2H), 7.61 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.35 (dd, *J* = 8.7, 1.5 Hz, 2H), 1.95 (s, 3H, CH_3); HRMS (ESI) $C_{22}H_{15}N_2O_2F_3{}^{35}Cl$ $[M+H]^+$ requires 431.0774, found 431.076 (100 %), $C_{22}H_{15}N_2O_2F_3{}^{37}Cl$ $[M+H]^+$ requires 433.0745, found 433.0757 (32 %).

8k: White solid (Yield 10%); m.p. 322 – 324 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 12.07 (s, 1H, N-H), 8.94 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 8.7 Hz, 3H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.20 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.96 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 1.99 (s, 3H, CH_3); HRMS (ESI) $C_{23}H_{15}N_2O_2F_6$ $[M+H]^+$ requires 465.1038, found 465.1039. Anal. $C_{23}H_{14}N_2O_2F_6$ requires C 59.49%, H 3.04%, N 6.03%; found C 59.58%, H, 2.89%, N 5.95%.

8l: White solid (Yield 40 %); m.p. 334 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 12.17 (s, 1H), 8.93 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 8.37 – 8.32 (m, 2H), 8.27 (dd, *J* = 8.3, 0.6 Hz, 1H), 8.23 – 8.17 (m, 2H), 7.81 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 3.31 (s, 3H), 2.00 (s, 3H); HRMS (ESI) $C_{23}H_{18}N_2O_4F_3S$ $[M+H]^+$ requires 475.0939, found 475.0922.

8m: Pale yellow solid (Yield 25%); m.p. 182-185 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.11 (s, 1H), 8.78 (d, *J* = 1.6 Hz, 1H), 8.33 (d, *J* = 8.9 Hz, 2H), 8.18 (dd, *J* = 8.2, 0.5 Hz, 1H), 8.05 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.27 (t, *J* =

7.8 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.94 (s, 3H), 1.89 (s, 3H). HRMS(ESI) $C_{23}H_{18}N_2O_3F_3$ ($[M+H]^+$) requires 427.1270, found 427.1268

8n: White solid (Yield 33%); m.p. 288-290 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.85 (bs, 1H), 8.89 (s, 1H), 8.33 (d, *J* = 8.7 Hz, 2H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.15 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.14 – 7.07 (m, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 175.25, 155.72, 149.69, 144.27, 138.45, 137.39, 129.70, 129.20, 121.70, 120.42, 117.69, 99.53, 12.15; HRMS (ESI) $C_{22}H_{14}N_2O_2F_5$ $[M+H]^+$ requires 433.0975, found 433.0967.

8o: White solid (Yield 41%); m.p. 288-290 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.96 (bs, 1H), 8.90 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.16 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.99 (dd, *J* = 10.7, 9.1 Hz, 1H), 7.54 (m, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 175.73, 155.73, 149.69, 145.42, 138.51, 137.38, 136.96, 136.86, 129.91, 129.20, 121.71, 120.42, 115.55, 112.56, 112.38, 106.55, 106.38, 12.29; HRMS (ESI) $C_{22}H_{14}N_2O_2F_5[M+H]^+$ requires 433.0975, found 433.0967.

8p: Yellow solid (Yield 40 %); m.p. 340 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 8.85 (dd, *J* = 2.1, 1.1 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.29 – 8.18 (m, 2H), 8.16 – 8.04 (m, 2H), 7.45 (dd, *J* = 8.8, 0.8 Hz, 2H,), 7.43 (d, *J* = 9.8 Hz, 1H), 2.09 (s, 3H); HRMS (ESI) $C_{22}H_{14}N_2O_2F_4{}^{35}Cl$ $[M+H]^+$ requires 449.0680, found 449.0677 (100 %), $C_{22}H_{14}N_2O_2F_4{}^{37}Cl$ $[M+H]^+$ requires 451.0650, found 451.0661 (35 %); Anal. $C_{22}H_{13}N_2O_2F_4Cl$ requires C 58.88%, H 2.92%, N 6.24%, found C 58.99%, H 2.80%, N 6.15%.

8q: Yellow solid (Yield 50 %); m.p. 350 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.91 (d, *J* = 2.2 Hz, 1H), 8.39 – 8.29 (m, 2H), 8.26 (d, *J* = 8.2 Hz, 1H), 8.17 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.96 (d, *J* = 9.6 Hz, 1H), 7.77 (d, *J* = 6.3 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 1.95 (s, 3H); HRMS (ESI) $C_{22}H_{14}N_2O_2F_4{}^{35}Cl$ $[M+H]^+$ requires 449.0680, found 449.0671 (100 %), $C_{22}H_{14}N_2O_2F_4{}^{37}Cl$ $[M+H]^+$ requires 451.0650, found 451.0654 (35 %). Anal.

$C_{22}H_{13}N_2O_2F_4Cl$ requires C 58.88%, H 2.92%, N 6.24%, found C 58.76%, H 2.85%, N 6.34%.

8r: White powder (Yield 48%); m.p. 238-240 ^oC; ^1H NMR (400MHz, MeOD) δ_H 8.86 (d, 1H, J = 1.4 Hz, Ar), 8.31 (d, 2H, J = 8.2 Hz, Ar), 8.28 (d, 1H, J = 1.2 Hz, Ar), 8.18 (dd, 1H, J = 8.2 Hz, 0.7 Hz, Ar), 8.12 (dd, 1H, J = 8.2 Hz, 2.2 Hz, Ar), 7.83 (d, 2H, J = 8.2 Hz, Ar), 7.69 (ddd, 1H, J = 8.4 Hz, 6.9 Hz, 1.4 Hz, Ar), 7.60 (d, 1H, J = 8.2 Hz, Ar), 7.40 (ddd, 1H, J = 8.2 Hz, 6.9 Hz, 1.0 Hz, Ar), 2.08 (s, 3H, CH_3); ^{13}C NMR (100MHz, MeOD), δ_C 177.0, 155.3, 149.9, 144.7, 142.1, 140.0, 138.6, 131.9, 130.8, 127.9, 126.2, 125.4, 123.5, 120.9, 118.5, 115.6, 12.4; HRMS (ESI) $C_{22}H_{16}N_2OF_3$ $[M+H]^+$ requires 381.1215, found 381.1216.

8s: White solid (Yield 20%); m.p. 308-309 ^0C; ^1H NMR (400 MHz, MeOD) δ 8.88 (d, *J* = 1.6 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.13 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.10 – 7.96 (m, 2H), 7.71 (t, *J* = 7.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 9.2 Hz, 2H), 2.11 (m, 4H); HRMS (ESI) $C_{21}H_{15}N_2OF_2$ $[M+H]^+$ requires 349.1152, found 349.1153.

8t: White solid (Yield 58 %); m.p. 239 – 240 ^oC; ^1H NMR (400 MHz, DMSO) δ 11.76 (s, 1H), 8.88 (d, *J* = 1.7 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.14 (m, 2H), 7.77 (m, 2H), 7.64 (m, 2H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.08 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.87 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 202.11, 176.96, 160.16, 156.69, 149.58, 144.92, 139.94, 139.75, 138.27, 131.83, 130.42, 130.06, 125.37, 123.22, 120.31, 119.44, 118.52, 115.82, 115.54, 112.21, 55.58, 12.42; HRMS (ESI) $C_{22}H_{19}N_2O_2$ $[M+H]^+$ requires 343.1447, found 343.1451.

8u: White solid (Yield 52 %); m.p. 288 ^oC; ^1H NMR (400 MHz, MeOD) δ 8.76 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.31 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.09 – 7.95 (m, 4H), 7.70 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.15 – 7.05 (m, 2H), 3.89 (s, 3H), 2.11 (s, 3H); HRMS (ESI) $C_{22}H_{19}N_2O_2$ $[M+H]^+$ requires 343.1447, found 343.1450.

8v: White solid (Yield 52%); m.p. 293-295^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.80 (bs, 1H), 9.57 (s, 1H), 8.99 (s, 1H), 8.85 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.2, 2.0 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.67 (m, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H) 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.97, 153.22, 150.20, 148.86, 147.27, 144.51, 139.96, 138.78, 136.92, 136.69, 131.89, 131.89, 131.40, 125.39, 123.52, 123.28, 121.50, 121.38, 120.70, 118.53, 115.68; HRMS (ESI) $C_{21}H_{15}N_3OF_3$ $[M+H]^+$ requires 382.1167, found 382.1164.

8w: White solid (Yield 25%); m.p. 264-268 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.33-7.19 (m, 5H), 7.12 (d, *J* = 8.6 Hz, 1H, 1.97 (s, 3H); HRMS (ESI) $C_{22}H_{16}N_2O_3F_3$ $[M+H]^+$ requires 413.1113, found 413.1115.

8x: White solid (Yield 28%); m.p. 275-278^{0}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.24-7.19 (m, 5H), 2.06 (s, 3H); HRMS (ESI) $C_{21}H_{16}N_2O_2F$ $[M+H]^+$ requires 347.1196, found 347.1211.

8y: White powder (Yield 52%); m.p. 236-238 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$), δ_H 12.26 (s, 1H, NH), 8.46 (s, 1H, Ar), 8.09 (d, 1H, J = 8.3 Hz, Ar), 7.94 (d, 1H, J = 8.3Hz, Ar), 7.60 (t, 1H, J = 7.6 Hz, Ar), 7.53 (s, 2H, Ar), 7.22 (t, 2H, J = 7.6 Hz, Ar), 6.68 (d, 1H, J = 7.9 Hz, Ar), 6.68 (d, 1H, J = 10.3 Hz, Ar), 3.88 (s, 2H, $ArCH_2Ar$), 1.85 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 182.2, 164.8, 161.8, 153.6, 145.6, 143.1, 146.6, 141.7, 135.3, 134.8, 129.0, 128.4, 127.1, 124.3, 121.4, 120.1, 41.8, 15.6; HRMS (ESI) $C_{23}H_{17}N_2OF_4$ $[M+H]^+$ requires 413.1277, found 413.1283.

8z: White solid (Yield 39%): m.p. >310 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.52 (bs, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.60 (m, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.29 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 4.74 (m, 1H), 2.05-1.90 (m, 8H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ

177.04, 157.99, 147.84, 139.84, 131.50, 130.89, 127.98, 125.27, 123.97, 123.36, 122.90, 118.48, 116.07, 114.65, 71.13, 30.23, 29.99, 29.74, 27.14, 12.65; HRMS (ESI) $C_{22}H_{22}NO_2F_2$ $[M+H]^+$ requires 370.1619, found 370.1622.

9a: White solid (Yield 33%); m.p. 304-306 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.51 (bs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.60 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.29 (ddd, *J* = 5.9, 5.9, 3.8 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.71 (m, 1H), 3.88 (m, 2H), 3.52 (m, 2H), 2.01 (m, 2H), 1.91 (s, 3H), 1.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 177.04, 157.99, 147.85, 139.81, 131.51, 130.86, 127.72, 125.27, 123.35, 122.91, 118.46, 115.95, 114.64, 71.76, 64.88, 32.04, 12.66; HRMS (ESI) $C_{21}H_{22}NO_3$ $[M+H]^+$ requires 336.1600, found 336.1594.

9b: White solid (Yield 30%); m.p. 251 – 253 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.68 – 7.46 (m, 4H), 7.31 (t, *J* = 7.1 Hz, 1H), 1.88 (s, 3H); HRMS (ESI) $C_{15}H_{11}N_2OBr$ $[M+H]^+$ requires 315.0133, found 315.0130; C, 61.17; H, 3.85; N, 4.46. Found: C, 61.04; H, 4.00; N, 4.84.

9c: White solid (Yield 30%); m.p. 283 – 284 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.74 (s, 1H), 8.64 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 8.02 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 1.89 (s, 3H); HRMS (ESI) $C_{16}H_{13}NOBr$ $[M+H]^+$ requires 314.0181, found 314.0180.

General procedure for the synthesis of quinolones 10a-c

Quinolone **8** (0.04 mmol) in anhydrous toluene (10 mL) was cooled to 0^{o}C. Boron tribromide 1.0 M in dichloromethane (0.13 mL, 0.12 mmol, 3 equiv) was added. The mixture was stirred at room temperature for ½ h then was heated to reflux for 18 h. The mixture was cooled to 0^{o}C and methanol was added. The solution was evaporated and the residue triturated with diethyl ether. The crude product was purified by column chromatography using 10% methanol in dichloromethane to give the desired hydroxyl quinolone **10**.

10a: White solid (Yield 49%); m.p. decomposed at 250 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.66 (bs, 1H), 9.67 (s, OH), 8.88 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 2H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.14 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.47(m, 2H), 7.17 (dd, *J* = 8.9, 2.8 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 176.24, 155.37, 153.73, 149.75, 149.69, 143.82, 138.47, 137.49, 133.68, 129.14, 122.33, 121.70, 120.31, 120.08, 113.75, 107.51, 12.48; HRMS (ESI) $C_{22}H_{16}N_2O_3F_3$ $[M+H]^+$ requires 413.1122, found 413.1113.

10b: White solid (Yield 68 %); ^{1}H NMR (400 MHz, MeOD) δ 8.81 (dd, *J* = 2.2, 1.0 Hz, 1H), 8.33 – 8.20 (m, 3H), 8.17 – 8.13 (m, 1H), 8.11 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.08 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.45 (dd, *J* = 8.9, 0.9 Hz, 2H), 6.92 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.89 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 199.27, 178.62, 161.39, 156.56, 155.27, 150.26, 149.03, 145.49, 141.82, 137.97, 137.26, 130.10, 128.66, 126.87, 120.95, 120.26, 117.19, 115.18, 114.82, 112.86, 100.31, 11.01; HRMS (ESI) $C_{22}H_{16}N_2O_3F_3$ $[M+H]^+$ requires 413.1113, found 413.1102.

10c: Light brown solid (Yield 40%); m.p.154-156 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 10.53 (s, 1H), 8.79 (d, *J* = 1.8 Hz, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.06 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.4 Hz, 1H), 1.89 (s, 3H). HRMS (ESI) $C_{22}H_{16}N_2O_3F_3$ ($[M+H]^+$) requires 413.1113, found 413.1109

General procedure for the synthesis of quinolones 11a-b

Quinolone **8** (0.35 mmol) in anhydrous dichloromethane (20 mL) was cooled to -10^{o}C. Boron tribromide, 1.0 M in dichloromethane (1.00 mL, 1 mmol) was added slowly. The mixture was stirred at -10^{o}C for 2 h, then stirred at room temperature overnight (followed by tlc). The reaction was quenched by ice-water and was further diluted by dichloromethane. The solid was filtered and washed with water followed by ethyl acetate to give the desired hydroxy quinolone **11**.

11a: White solid (Yield 91 %); Rf = 0.28, ethyl acetate); ^{1}H NMR (400 MHz, MeOD) δ 8.87 – 8.78 (m, 1H), 8.33 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.12 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.73 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.46 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.40 – 7.30 (m, 1H), 6.99 – 6.87 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 195.17, 174.53, 172.79, 158.37, 148.54, 143.73, 139.65, 139.40, 138.12, 132.08, 129.73, 129.47, 124.79, 123.92, 120.57, 118.09, 117.91, 116.57, 116.17, 113.67, 11.20; HRMS (ESI) $C_{21}H_{17}N_2O_2$ $[M+H]^+$ requires 329.1290, found 329.1291.

11b: Pale yellow solid (Yield 81%); MP 283 – 284 ^{o}C. ^{1}H NMR (400 MHz, Acetone) δ 8.74 (dd, J = 2.2, 0.9 Hz, 1H), 8.35 – 8.26 (m, 1H), 8.03 (dd, J = 8.3, 2.3 Hz, 1H), 7.99 (dd, J = 8.3, 0.9 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.70 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.62 (ddd, J = 8.5, 1.1, 0.6 Hz, 1H), 7.42 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 6.97 – 6.88 (m, 2H), 2.12 (s, 3H); HRMS (ESI) $C_{21}H_{17}N_2O_2$ [M+H]+ requires 329.1290, found 329.1284.

General procedure for the synthesis of quinolones 12a-f

Quinolone **9** (1 mmol, 1.0 eq), $PdCl_2$(dppf) (5 mol%) and potassium carbonate (3 mmol, 3 equiv) in anhydrous 1,4-dioxane (10 mL) were stirred for 5 min under N_2. Boronic acid (2 mmol, 2 equiv) was added. The reaction was evacuated and backfilled with N_2 (this sequence was carried out three times). The reaction mixture was heated to 100^{o}C for 1 day. The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a pad of $MgSO_4$-silica. The silica pad was further washed with ethyl acetate. The filtrate was evaporated and the crude material was purified by flash chromatography on silica gel to give the desired quinolone **12**.

12a: Pink solid (Yield 60%); MP 295 – 296 ^{o}C; ^{1}H NMR (400 MHz, MeOD-d4) δ 8.32 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.91 – 7.80 (m, 4H), 7.77 – 7.61 (m, 4H), 7.42 (m, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, MeOD-d4) δ 142.30, 133.00, 130.76, 129.85, 128.54, 126.29, 126.22,

124.90, 124.58, 122.71, 122.59, 90.67, 66.81, 49.42, 49.21, 49.00, 48.79, 48.57, 15.50; ES+ HRMS: m/z found 396.1198, $[C_{23}H_{16}NO_2F_3 + H]^+$ requires 396.1211.

12b: Pale pink solid (Yield 50%); m.p. 270 – 271 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 8.1, 0.7 Hz, 1H), 8.22 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.46 (m, 6H), 7.42 – 7.29 (m, 4H), 2.14 (s, 3H); HRMS (ESI) $C_{23}H_{17}NOF_3$ $[M+H]^+$ requires 380.1262, found 380.1262.

12c: Brown solid (Yield 65%); m.p. >315 ^oC; ^1H NMR (400 MHz, DMSO) δ 11.66 (s, 1H, N-H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.71 – 7.65 (m, 3H), 7.65 – 7.60 (m, 2H), 7.49 – 7.40 (m, 1H), 7.34 – 7.29 (m, 1H), 7.29 – 7.22 (m, 1H), 1.95 (s, 3H, CH_3);HRMS (ESI) $C_{22}H_{16}NOF_2$ $[M+H]^+$ requires 348.1200, found 348.1183.

12d: Brown solid (Yield 69 %); m.p. 320 – 322 ^oC; ^1H NMR (400 MHz, MeOD) δ 8.31 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.72 – 7.65 (m, 3H), 7.64 – 7.56 (m, 2H), 7.62 – 7.38 (m, 2H), 7.32 (td, *J* = 7.5, 1.2 Hz, 1H), 7.25 (ddd, *J* = 11.0, 8.2, 1.1 Hz, 1H), 2.11 (s, 3H); HRMS (ESI) $C_{22}H_{17}NOF$ $[M+H]^+$ requires 330.1294, found 330.1297.

12e: Pink solid (Yield 70%); m.p. 279 – 280 ^oC; ^1H NMR (400 MHz, MeOD) δ 8.84 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.31 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.83 – 7.68 (m, 4H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 2.10 (s, 3H); HRMS (ESI) $C_{22}H_{16}N_2OF_3$ $[M+H]^+$ requires 381.1215, found 381.1197.

12f: Pale brown solid (Yield 65 %); m.p. 269 – 270 ^oC. ^1H NMR (400 MHz, MeOD) δ 8.88 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.32 (ddd, *J* = 8.3, 1.4, 0.5 Hz, 1H), 8.14 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.04 (ddd, *J* = 8.2, 2.0, 0.9 Hz, 1H), 8.00 (td, *J* = 7.8, 1.8 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.57 – 7.49 (m, 1H), 7.43 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (ddd, *J* = 11.4, 8.3, 1.0 Hz, 1H), 2.12 (s, 3H); HRMS (ESI) $C_{21}H_{16}N_2OF$ $[M+H]^+$ requires 331.1247, found 331.1239.

General procedure for the synthesis of quinolones 16a-b

To a suspension of ethyl 2-(4-iodophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (210mg, 0.5mmol) in DMF (10ml) were added x-boronic acid (1.0mmol), $PdCl_2$(dppf) (37mg, 0.05mmol) and K_2CO_3 (207mg, 1.5mmol). The reaction mixture was degassed and kept stirring at 120^{o}C for 1 day.

The DMF was then removed *in vacuo*. The residue redissolved in 20% MeOH in DCM, and filtered through a pad of silica. The silica pad was washed further with 20% MeOH in DCM (100ml). All solvents in the filtrate were removed *in vacuo* to give the crude product. The crude product was purified by flash column chromatograph eluting with 5% MeOH in DCM to give the desired quinolone **16**.

16a: White solid (Yield 53%); m.p. 241-243 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.94 – 7.87 (m, 4H), 7.78 – 7.67 (m, 3H), 7.52 (d, J = 8.0 Hz, 2H), 7.42 (ddd, J = 8.1, 6.5, 1.7 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 174.32, 166.63, 149.35, 140.82, 139.92, 138.71, 136.53, 133.49, 132.90, 129.33, 129.18, 127.33, 125.33, 122.04, 120.04, 119.18, 115.84, 107.49, 106.43, 60.64, 14.01; HRMS (ESI) $C_{25}H_{19}NO_4F_3$ $[M+H]^+$ requires 454.1266, found 454.1263.

16b: White solid (Yield 75%); m.p. 228-230 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 4H), 7.58 (d, J = 8.6 Hz, 2H), 7.42 (ddd, J = 8.1, 6.4, 1.7 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 166.65, 158.47, 149.33, 149.23, 148.87, 140.94, 139.94, 138.18, 133.44, 132.88, 129.46, 129.32, 128.99, 127.13, 125.32, 125.02, 124.47, 119.19, 60.64, 14.03; HRMS (ESI) $C_{24}H_{18}NO_3NaCl$ $[M+Na]^+$ requires 426.0873 and 428.0843, found 426.0856 and 428.0850.

Procedure for the synthesis of quinolones 17

To a suspension of quinolone **16a** (25mg, 0.055mmol) in toluene, a solution of $LiBH_4$ in THF (2M, 28ul, 0.055mmol) was added. The resulting mixture was heated to 100^oC and kept stirring for 2 hours. The reaction mixture was cooled to room temperature and a few drops of water are used to quench the reaction. The crude material was isolated by removing all solvents *in vacuo* and purified by flash column chromatograph eluting with 5% MeOH in DCM to give quinolone **17**.

White solid (Yield 66%); ^{1}H NMR (400 MHz, Acetone) δ 10.80 (s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.94 – 7.87 (m, 4H), 7.82 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.39 (ddd, J = 8.1, 5.8, 2.3 Hz, 1H), 4.49 (s, 2H); 13C NMR (101 MHz, Acetone) δ 169.04, 145.41, 141.82, 140.98, 140.05, 137.01, 132.87, 132.15, 130.65, 129.75, 128.01, 126.13, 124.16, 122.48, 120.63, 120.49, 119.02, 118.95, 59.15; HRMS (ESI) $C_{23}H_{16}NO_3F_3Na$ $[M+Na]^+$ requires 434.0980, found 434.0961.

Procedure for the synthesis of quinolones 21

β-amine-ester **20** (2.0 mmol, 1 eq.) was added to DMF (15 mL) and NaH (2.0 mmol, 1 eq.) The flask was flushed with nitrogen and stirred at room temperature for 15 minutes. Isatoic anhydride (2.0 mmol, 1 eq.) was added in DMF (5 mL) and heated to reflux for 16 hours. DMF removed *in vacuo* and EtOAc (100 mL) was added to dissolve the residue. This was washed with water (30 mL), brine (30 mL) and then dried over $MgSO_4$. The brown solid was purified by flash column chromatography (eluting with EtOAc to 5% MeOH in EtOAc) to give the desired 3-ester quinolone **21.**

21: White solid (Yield 28%); m.p. decomposed at 250 ^{0}C; ^{1}H NMR (400 MHz, DMSO) δ 12.31 (bs, 1H), 8.88 (s, 1H), 8.33 (d, *J* = 8.9 Hz, 2H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.14 (m, 2H), 7.76 (dd, *J* = 8.2, 8.0 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.44 (dd, *J*= 7.0, 7.0 Hz, 1H), 4.02 (q, *J* = 7.1, 2H), 0.94 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (100 MHz, DMSO) δ 173.90, 166.31, 156.24, 149.83, 148.94, 147.13, 139.91, 137.77, 137.21, 133.06,

129.24, 129.16, 125.42, 125.20, 124.71, 121.76, 120.30, 119.19, 116.06, 60.71, 14.08; HRMS (ESI) $C_{24}H_{17}N_2O_4F_3{}^{23}Na$ $[M+Na]^+$ requires 477.1038, found 477.1022.

Procedure for the synthesis of quinolones 22

3-Ester quinolone **21** (0.25 mmol, 1 eq.) was added to dry THF (30 mL) and cooled to 0^0C. $LiAlH_4$ (0.50 mmol, 2 eq.) was added and the solution was allowed to stir at room temperature for 2 hours. EtOAc (5mL) was added and the solvent was removed *in vacuo*. The cream solid was purified by flash column chromatography (eluting with EtOAc to 5% MeOH in EtOAc) to give the desired 3-methyl-hydroxy-quinolone **22**.

22: White solid (Yield 40%); m.p 288-290 ^{0}C; ^{1}H NMR (400 MHz, MeOD) δ 9.01 (s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 8.28 (d, *J* = 8.9 Hz, 3H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 8.0 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.49 (m, 3H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, MeOD) δ 178.50, 157.03, 149.03, 148.56, 140.05, 138.06, 137.18, 132.43, 129.03, 128.72, 125.09, 124.52, 124.02, 120.97, 120.14, 118.84, 118.05, 55.78; HRMS (ESI) $C_{22}H_{15}N_2O_3F_3{}^{23}Na$ $[M+Na]^+$ requires 435.0932, found 435.0942.

Procedure for the preparation of 3-methoxy quinolone 27

To a solution of 1-acetyl-2-((4'-(trifluoromethoxy)biphenyl-4-yl)methylene)indolin-3-one (1.417 mmol, 600 mg) in 40 mL of dry DCM was added bromine (1.56 mmol, 80 µL). The mixture was stirred for 2 hours at room temperature. After completion of the reaction, the solvent was evaporated.

To a solution of the crude obtained in 15 mL of dry dioxane was added a solution of sodium methoxide (2.74 mmol, 148 mg) in 15 mL of dry methanol. The mixture was stirred for 24 hours under reflux. After completion of the reaction (monitored by TLC), 10 mL of concentrated hydrochloric acid was added and the reaction was stirred under reflux for 48 hours. The solvent was then evaporated under reduced pressure. The acidic layer was neutralized with ammonia and then extracted three times with DCM. The combined organic

layers was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude obtained was purified by column chromatography (DCM with methanol 0 to 2.5%) to afford the quinolone **27**.

27: Beige solid (35 mg, 6%); m.p. 281-283°C. ^{1}H NMR (400 MHz, $CDCl_3$): 11.71 (s, 1H, NH), 8.17 (d, 1H, J = 7.9 Hz, ArH), 7.92 (d, 1H, J = 8.8 Hz, ArH), 7.91 (d, 1H, J = 8.4 Hz, ArH), 7.80 (d, 2H, J = 8.8 Hz, ArH), 7.69 (d, 1H, J = 7.9 Hz, ArH), 7.65 (dt, 1H, J = 1.0; 8.1 Hz, ArH), 7.52 (d, 2H, J = 8.4 Hz, ArH), 7.32 (dt, 1H, J = 1.3; 8.1 Hz, ArH), 3.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100MHz): 170.1, 146.1, 139.8, 137.8, 137.1, 136.7, 136.6, 129.7, 129.2, 127.8 (2C), 126.7 (2C), 124.7 (2C), 123.5, 122.7, 121.9, 120.4, 119.5 (2C), 119.3, 116.8, 116.3, 112.9, 57.3; HRMS (ESI) $C_{23}H_{15}F_3NNaO_3$ $[M+Na]^+$ requires 434.0980, found 434.0987.

General procedure for the preparation of quinolone 31a-b

The appropriately substituted oxazoline **7** (4 mmol, 1 eq) was added to a solution of ketone **30** (4 mmol, 1 eq) and triflic acid (20 mol%) in n-butanol (10 mL). The reaction mixture was heated to 130°C under nitrogen and stirred for 24 hours. The solvent was removed under vacuum and water (20 mL) added. The aqueous solution was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated under vacuum. The product was purified by column chromatography (eluting with 20% -80% EtOAc in n-hexane) to give quinolone **31a-b**.

31a: White powder (Yield 30%); m.p. 305-307^{0}C; ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, J = 8.8 Hz, 1H), 7.64-7.54 (m, 5H), 7.38 (d, J = 8.8 Hz, 1H), 3.74 (t, J = 4.7 Hz, 4H) 3.66 (s, 2H), 2.54 (t, J = 4.6 Hz, 4H), 2.05 (s, 3H); HRMS (ESI) $C_{21}H_{22}N_2O_2Cl$ $[M+H]^+$ requires 369.1370, found 369.1366.

31b: White powder (Yield 32%); m.p. 230-232^{0}C; ^{1}H NMR (400 MHz, MeOD) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 8.3 Hz, 1H), 7.61 – 7.48 (m, 5H), 7.39 (t, *J* = 8.1 Hz, 1H), 3.71 (t,

J = 4.6 Hz, 4H), 3.63 (s, 2H), 2.51 (t, *J* = 4.6 Hz, 4H), 2.04 (s, 3H); HRMS (ESI) $C_{21}H_{23}N_2O_2$ $[M+H]^+$ requires 335.1760, found 335.1753.

Procedure for the synthesis of quinolone 35

Diacetal **33** (3.26 mmol, 1.0 eq) and the appropriately substituted acid **34** (3.26 mmol, 1.0 eq) in Dowtherm A (4 mL) were heated at 240°C overnight. The reaction was allowed to cool and hexane added. The resulting dark brown precipitate was filtered off and washed with hexane. Purification by flash column chromatography (eluting with EtOAc) gave the required quinolone **35**.

35: White solid (Yield 32%): m.p. 222-223 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (bs, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 4.6, 1.9 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.10 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 4.62 (m, 1H), 4.04 (m, 2H), 3.64 (m, 2H), 2.12 (m, 2H), 2.08 (s, 3H), 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.12, 158.77, 152.24, 150.27, 148.41, 136.86, 130.75, 128.08, 119.47, 118.94, 118.13, 116.56, 72.17, 65.45, 32.08, 12.74; HRMS (ESI) $C_{20}H_{20}N_2O_3{}^{23}Na$ $[M+Na]^+$ requires 359.1372, found 359.1369.

General procedure for the synthesis of quinolone 36

Quinolone **9** (1 mmol, 1.0 eq), $PdCl_2$(dppf) (5 mol%) and potassium carbonate (3 mmol, 3 equiv) in 1,4-dioxane and water (10 mL, ratio 9:1) were stirred for 5 min under N_2. Boronic ester (2 mmol, 2 equiv) was added. The reaction was evacuated and backfilled with N_2 (this sequence was carried out three times). The reaction mixture was heated to 100^{o}C for 1 day. The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a pad of $MgSO_4$-silica. The silica pad was further washed with ethyl acetate. The filtrate was evaporated and the crude material was purified by flash chromatography on silica gel to give the desired quinolone **36**.

36a: Brown solid (Yield 61 %); m.p. 258 – 260 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.84 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.62 (m, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.31 (ddd, *J* = 8.1, 4.9, 3.1 Hz, 1H), 3.69 – 3.58 (m, 4H), 3.53 (s, 2H), 2.39 (m, 4H), 1.95 (s, 3H); 13C; HRMS (ESI) $C_{27}H_{27}N_2O_2$ $[M+H]^+$ requires 411.2073, found 411.2071; Anal. $C_{27}H_{26}N_2O_2$ requires C 79.00%, H 6.38%, N 6.82%, found C 78.80%, H 6.38%, N 6.82%.

36b: Brown solid (Yield 50 %); m.p. 272 – 274 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.77 (s, 1H, N-H), 8.87 (d, *J* = 2.2 Hz, 1H), 8.23 – 8.07 (m, 5H), 7.71 – 7.57 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 3.63 – 3.57 (m, 4H), 3.55 (s, 2H, CH_2), 2.40 (m, 4H), 1.96 (s, 3H, CH_3); HRMS (ESI) $C_{26}H_{26}N_3O_2$ $[M+H]^+$ requires 412.2025, found 412.2043; Anal. $C_{26}H_{25}N_3O_2$ requires C 75.89%, H 6.12%, N 4.21%, found C 75.65%, H 6.23%, N 3.97%.

General procedure for the synthesis of quinolones 40a-g

Quinolones **40a-g** were prepared by the general procedure for the synthesis of quinolones **31a-b**.

40a: White powder (Yield 48%); m.p. 200-202 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$), δ_H 9.47 (s, 1H, NH), 8.28 (d, 1H, J = 7.8 Hz, Ar), 7.55 (d, 1H, J = 6.8 Hz, Ar), 7.51 (d, 1H, J = 7.8 Hz, Ar), 7.36 (d, 2H, J = 8.7 Hz, Ar), 7.29 (t, 1H, J = 6.8 Hz, Ar), 6.90 (d, 2H, J = 8.7 Hz, Ar), 4.10 (t, 2H, J = 5.6 Hz, OCH_2), 3.73 (t, 4H, J = 4.5 Hz, CH_2O), 2.82 (t, 2H, J = 5.6 Hz, CH_2N), 2.57 (t, 4H, J = 4.5 Hz, CH_2N), 2.01 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 179.1, 159.9, 147.7, 139.6, 131.9, 130.4, 128.4, 126.5, 124.1, 123.5, 117.7, 116.7, 115.0, 67.3, 66.3, 58.0, 54.5, 12.9; HRMS (ESI) $C_{22}H_{25}N_2O_3$ $[M+H]^+$ requires 365.1865, found 365.1872.

40b: Off white powder (Yield 44%); m.p. 200-202 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$), δ_H 11.76 (s, 1H, NH), 8.05 (s, 1H, Ar), 7.50 (bs, 2H, Ar), 7.36 (d, 2H, J = 8.7 Hz, Ar), 6.94 (d,

2H, J = 8.7 Hz, Ar), 4.22 (t, 2H, J = 4.7 Hz, OCH_2), 3.83 (t, 4H, J = 4.7 Hz, NCH_2), 3.01 (t, 2H, J = 4.6 Hz, CH_2N), 2.79 (t, 4H, J = 3.8 Hz, CH_2O), 2,01 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 175.9, 148.1, 138.4, 131.7, 130.9, 127.5, 124.2, 121.0, 115.9, 115.0, 57.6, 54.0, 49.5, 12.7; HRMS (ESI) $C_{22}H_{24}N_2O_3Cl$ $[M+H]^+$ requires 399.1475, found 399.1473.

40c: Off white powder (Yield 43%); m.p. 200-202 ^oC ^1H NMR (400MHz, $CDCl_3$), δ_H 11.58 (s, 1H, NH) 8.20 (d, 1H, J = 8.8 Hz, Ar), 7.52 (d, 1H, J = 1.8 Hz, Ar), 7.37 (d, 2H, J = 8.6 Hz, Ar), 7.22 (dd, 1H, J = 8.8 Hz, 1.8 Hz, Ar), 6.96 (d, 2H, J = 8.6 Hz, Ar), 4.16 (t, 2H, J = 5.5 Hz, OCH_2), 3.78 (t, 4H, J = 4.6 Hz, CH_2O), 2.89 (t, 2H, J = 5.5 Hz, CH_2N), 2.66 (t, 4H. J = 4.6 Hz, CH_2N), 2.02 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 178.7, 159.8,148.8, 140.2, 137.9, 130.5, 127.9, 124.4, 122.2, 117.2, 114.8, 67.0, 57.9, 54.4, 12.7; HRMS (ESI) $C_{22}H_{24}N_2O_3Cl$ $[M+H]^+$ requires 399.1475, found 399.1465.

40d: Off white powder (Yield 48%); m.p. 256-258 ^oC ^1H NMR (400MHz, $CDCl_3$) δ_H, 11.12 (s, 1H, NH), 8.12 (d, 1H, J = 7.9 Hz, Ar), 7.62(t, 1H, J = 6.7 Hz, Ar), 7.56 (d, 2H, J = 8.5 Hz, Ar), 7.52 (d, 1H, J = 7.9 Hz, Ar), 7.32 (t, 1H, J = 6.7 Hz, Ar), 7.20 (d, 2H, J = 8.5 Hz, Ar), 4.45 (t, 2H, J = 4.6 Hz, OCH_2), 3.35(t, 2H, J = 4.6 H, CH_2N), 1.94 (s, 3H, CH_3), 1.98-1.65 (m, 6H, CH_2) ^{13}C NMR (100MHz, $CDCl_3$), δ_C 180.1, 160.1, 147.5, 139.7, 131.4, 130.9, 128.1, 125.2, 122.8, 118.9, 115.0, 63.0, 52.8, 22.9, 21.9, 12.2; HRMS (ESI) $C_{23}H_{27}N_2O_2$ $[M+H]^+$ requires 363.2073, found 363.2067.

40e: Off white powder (Yield 42%); m.p. 248-250 ^oC ^1H NMR (400MHz, DMSO) δ_H 11.53 (s, 1H, NH), 8.12 (d, 1H, J = 7.9 Hz, Ar), 7.62 (bs, 2H, Ar), 7.55 (d, 2H, J = 8.1 Hz, Ar), 7.30 (t, 1H, J = 7.6 Hz, Ar), 7.19 (d, 2H, J = 8.1 Hz, Ar), 4.34 (bs, 2H, OCH_2), 3.37 (bs, 2H, CH_2N), 3.17 (bs 4H, CH_2), 1.91 (bs, 7H, CH_3/CH_2) ^{13}C NMR (100MHz, DMSO), δ_C 177.1, 158.9, 147.7, 139.8, 131.6, 130.9, 128.3, 125.3, 123.4, 123.0, 118.5, 114.8, 54.4, 53.6, 23.0, 12.7; HRMS (ESI) $C_{22}H_{25}N_2O_2$ $[M+H]^+$ requires 349.1916, found 349.1901.

40f: White powder (Yield 48%); m.p. 156-160 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$), δ_H 10.05 (s, 1H, NH), 8.30 (d, 1H, J = 8.0 Hz, Ar), 7.58-7.56 (m, 2H, Ar), 7.32 (d, 2H, J = 8.8 Hz, Ar), 7.29 (d, 1H, J = 8.0 Hz, Ar), 6.84 (d, 2H, J = 8.8 Hz, Ar), 4.06 (t, 2H, J = 5.6 Hz, OCH_2), 2.85 (t, 2H, J = 5.6 Hz, CH_2N), 2.60 (bs, 4H, piperazinyl), 2.45 (bs, 4H, piperazinyl), 2.30 (s, 3H, CH_3), 1.99 (s, 3H, NCH_3); ^{13}C NMR (100MHz, $CDCl_3$), δ_C 179.1, 159.8, 147.9, 139.7, 131.8, 130.5, 128.3, 126.5, 124.1, 123.5, 117.8, 116.6, 114.8, 66.1, 57.3, 55.5, 53.8, 46.4, 12.9; HRMS (ESI) $C_{23}H_{28}N_3O_2$ $[M+H]^+$ requires 378.2182, found 378.2183.

40g: White powder (Yield 44%); m.p. 248-250^{o}C; ^{1}H NMR (400MHz, DMSO), δ_H 11.50 (s, 1H, NH), 8.11 (d, 1H, J = 8.0 Hz, Ar), 7.72 (s, 1H, Ar), 7.61 (d, 2H, J = 3.3 Hz, Ar), 7.49 (d, 2H, J = 8.5 Hz, Ar), 7.31-7.26 (m, 2H, Ar), 7.12 (d, 2H, J = 8.5 Hz, Ar), 6.92 (s, 1H, indazolyl), 4.41 (t, 2H, J = 4.8 Hz, OCH_2), 4.35 (t, 2H, J = 4.8 Hz, NCH_2), 1.90 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO), δ_C 177.0, 159.1, 147.8, 139.8, 138.0, 131.5, 130.9, 128.7, 128.1, 125.3, 123.4, 122.9, 120.1, 118.5, 114.8, 67.8, 45.9, 12.6; HRMS (ESI) $C_{21}H_{20}N_3O_2$ $[M+H]^+$ requires 346.1556, found 346.1553.

General procedure for the synthesis of quinolones 42a-b

Quinolones **42a-b** were prepared by the general procedure for the synthesis of quinolones **36**.

42a: White solid (Yield 87%); m.p. 87-90 ^{0}C; ^{1}H (400 MHz, DMSO) δ 11.58 (s, 1H), 8.33 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 3.5 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.34 – 7.25 (m, 1H), 4.27 (t, J = 6.6 Hz, 2H), 3.63 – 3.50 (m, 4H), 2.76 (t, J = 6.6 Hz, 2H), 2.48 – 2.37 (m, 4H), 1.94 (s, 3H); ^{13}C (101 MHz, DMSO) δ 176.58, 147.40, 139.39, 136.22, 133.70, 132.32, 131.09, 129.46, 127.80, 124.82, 124.67, 122.93, 122.48, 120.78, 118.02, 114.19, 66.08, 57.58, 53.04, 48.78, 12.13. HRMS (ESI) $C_{25}H_{27}N_4O_2$ $[M+H]^+$ requires 415.2134, found 415.2122.

42b: White solid (Yield 92%); m.p. 128-130 ^{0}C; ^{1}H (400 MHz, DMSO) δ 11.68 (s, 1H), 8.70 (dd, J = 2.3, 0.7 Hz, 1H), 8.46 (s, 1H), 8.17 – 8.10 (m, 2H), 8.00 (dd, J = 8.2, 2.3 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.32 (ddd, J = 8.1, 6.6, 1.4 Hz, 1H), 4.30 (t, J = 6.5 Hz, 2H), 3.61 – 3.51 (m, 4H), 2.77 (t, J = 6.5 Hz, 2H), 2.47 – 2.40 (m, 4H), 1.95 (s, 3H); ^{13}C (101 MHz, DMSO) δ 176.51, 152.38, 149.04, 144.77, 139.46, 137.30, 131.28, 129.63, 127.79, 124.89, 123.00, 122.67, 121.90, 118.53, 118.01, 114.93, 66.09, 57.51, 53.03, 48.49, 11.95; HRMS (ESI) $C_{24}H_{26}N_5O_2$ $[M+H]^+$ requires 416.2087, found 416.2086.

General procedure for the synthesis of quinolones 46a-d

Quinolones **46a-d** were prepared by the general procedure for the synthesis of quinolones **31a-b**.

46a: White solid (Yield 50 %); m.p. 232 – 234 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H, N-H), 8.61 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.43 (m, 5H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.21 (m, 1H), 6.98 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.16 (t, *J* = 5.5 Hz, 2H, OCH_2), 3.73 – 3.64 (m, 4H, OCH_2), 2.80 (t, *J* = 5.5 Hz, 2H, NCH_2), 2.61 – 2.46 (m, 4H, NCH_2), 1.94 (s, 3H, CH_3); HRMS (ESI) $C_{27}H_{28}N_3O_3$ $[M+H]^+$ requires 442.2131, found 442.2138; Anal. $C_{27}H_{27}N_3O_3$ requires C 73.45%, H 6.16%, N 9.52%, found C 73.09%, H 6.26%, N 9.19%.

46b: White solid (Yield 42 %); m.p. 193 – 194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H, N-H), 8.64 (d, *J* = 1.8 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.63 – 7.48 (m, 5H), 7.44 – 7.35 (m, 1H), 7.34 – 7.28 (m, 1H), 6.99 (dd, *J* = 8.1, 1.8 Hz, 1H), 4.23 (t, *J* = 5.7 Hz, 2H, OCH_2), 2.86 (t, *J* = 5.6 Hz, 2H, $OCH_2C\underline{H_2}$), 2.64 – 2.51 (m, 4H, NCH_2), 2.02 (s, 3H, CH_3), 1.70 – 1.55 (m, 4H, $NCH_2C\underline{H_2}$), 1.47 (t, *J* = 5.8 Hz, 2H, CH_2); ; HRMS (ESI) $C_{28}H_{30}N_3O_2$ $[M+H]^+$ requires 440.2338, found 440.2341.

46c: White solid (Yield 49 %); m.p. 263 - 264 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 8.77 (dd, *J* = 2.0, 1.0 Hz, 1H), 8.31 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.10 – 8.01 (m, 4H), 7.70 (ddd, *J* = 8.4,

6.9, 1.5 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.18 – 7.07 (m, 2H), 4.25 (t, *J* = 5.5 Hz, 2H), 3.80 – 3.69 (m, 4H), 2.86 (t, *J* = 5.5 Hz, 2H), 2.69 – 2.56 (m, 4H), 2.12 (s, 3H); HRMS (ESI) $C_{27}H_{28}N_3O_3$ $[M+H]^+$ requires 442.2131, found 442.2126; Anal. $C_{27}H_{27}N_3O_3$ requires C 73.45%, H 6.16%, N 9.52%, found C 73.28%, H 6.17%, N 9.42%.

46d: Yellow solid (Yield 40 %); m.p. 234 -235 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.40 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.61 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.08 – 6.98 (m, 2H), 4.23 (t, *J* = 5.9 Hz, 2H), 2.88 (t, *J* = 5.8 Hz, 2H), 2.65 – 2.55 (m, 4H), 2.10 (s, 3H), 1.71 – 1.63 (m, 4H), 1.53 – 1.45 (m, 2H); HRMS (ESI) $C_{28}H_{30}N_3O_2$ $[M+H]^+$ requires 440.2338, found 440.2341.

Procedure for the synthesis of quinolone 53

2-Pyridyl-4-chloroquinoline (0.25 mmol, 1.0 eq) was added to DMF (10 mL) and water (1 mL). Formic acid (4 mL) was added and the solution was heated to 145 ^0C for 24 hours. The DMF was removed *in vacuo* and the solution basified (pH 12) with sat. K_2CO_3. The resultant light brown precipitate was recrystallised with chloroform to yield the desired compound.

53: White solid (Yield 70%): m.p. 223-225^0C; ^1H NMR (400 MHz, MeOD) δ 8.95 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.76 (m, 3H), 7.47 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 3.79 (s, 2H), 3.59 (s, 2H), 2.62-2.57 (m, 8H); ^{13}C NMR (100 MHz, MeOD) δ 160.12, 147.11, 136.64, 136.13, 132.20, 130.79, 124.68, 124.58, 124.09, 123.71, 120.50, 119.24, 107.43, 63.15, 61.50, 52.69, 52.43; HRMS (ESI) $C_{27}H_{26}N_4O_2F_3$ $[M+H]^+$ requires 495.2008, found 495.2007.

Procedure for the synthesis of pro-drug 55

Sodium hydride (0.57 mmol, 2.5 eq) was added at 0°C to a stirred solution of quinolone (0.23 mmol, 1.0 eq) in dry THF (10 mL). After 1 hr, tetrabenzyl pyrophosphate (0.19 mmol,

0.8 eq) was added and the stirring continued for 20 minutes. The mixture was filtered and the filtrate concentrated under vacuum at a temperature below 35°C. The residue was dissolved in DCM, washed with $NaHCO_3$ aq, dried over $MgSO_4$ and concentrated under vacuum to give phosphonate **55**. Where necessary the product was purified by flash column chromatography (eluting with 10% ethyl acetate in n-hexane).

55: Pale yellow solid (Yield 70%); MP 257 – 258 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.77 (s, 2H), 8.91 (s, 1H), 8.37 – 8.27 (m, 3H), 8.17 (dd, *J* = 6.9, 1.7 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.54 (m, 2H), 2.46 (s, 3H); ^{31}P NMR (162 MHz, DMSO) δ -1.17, -5.89.

Procedure for the synthesis of pro-drug 56

8b (124 mg, 0.31 mmol) in anhydrous THF was added ^{t}BuOK (52.7 mg, 0.47 mmol) at room temperature. The mixture was stirred for 1/2 h. 4-Morpholinecarbonyl chloride (0.05 mL, 0.41 mmol) was added. The mixture was stirred for further 2 h (followed by tlc). The reaction was quenched by brine and was extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated to an oil. The crude product was purified by column chromatography using 20% ethyl acetate in hexane to give the title compound.

56: White solid (125 mg, Yield 78 %); m.p. 150 – 151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (dd, *J* = 2.2, 0.8 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.13 – 8.10 (m, 2H), 8.08 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.91 – 7.81 (m, 2H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 3.91 (m, 2H), 3.89 (m, 2H), 3.85 (m, 2H), 3.67 (m, 2H), 2.40 (s, 3H); HRMS (ESI) $C_{27}H_{23}N_3O_4F_3$ $[M+H]^+$ requires 510.1641, found 510.1637.

2. Chemoinformatics

The chemoinformatics procedures were performed using Pipeline Pilot http://accelrys.com/products/pipeline-pilot/.) and PowerMV.[1] Full details will be published in a subsequent publication.

3. Measured Solubility Values

Compound	**Solubility (µM)**	
	pH 7.4	**pH 1.0**
Hydrocortisone	185	ND
Reserpine	<5	ND
2 (CK-2-68)	<5	<5
8h	<5	18
8h.H_3PO_4	<5	42

Table S1: Solubility values for test and control compounds in PBS at pH 7.4 and pH 1.0 (2% DMSO).

The Kinetic solubility assay was performed as described below. Using a 10 mM stock solution of each compound in 100% DMSO, dilutions were prepared to a theoretical concentration of 200 µM in phosphate buffered saline (PBS) adjusted to pH 7.4, pH 4.5 and pH 1 (2% DMSO final) and in 100% DMSO. An aliquot of the 200 µM DMSO solution was then further diluted to 10 µM and all dilutions (n=2 in 96-well plates) allowed to equilibrate at room temperature on an orbital shake for two hours. The PBS dilutions were filtered using a Multiscreen HTS solubility filter plate (Millipore) and filtrate was analysed by LC-UV and LC-MS. The concentration of compound in PBS filtrate was determined by comparing the UV absorbance peak with that of the two DMSO dilutions as calibration standards and mass

spectrometry was used to confirm the presence of the expected molecular ion in the UV peak measured.

4. References

1. Liu, K.; Feng, J.; Young, S. S. *Journal of Chemical Information and Modeling* **2005**, *45*, 515-522