Supporting Information

Synthesis and Structure-Activity Relationships of 4-Pyridones as Potential Antimalarials

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Contents:

A. Additional experimental and spectroscopic data

The following provides details for the synthesis of some intermediates and additional spectroscopic data.

4-(4-Chlorophenoxy)benzaldehyde (1h). 4-Chlorophenol (22.6 g, 176 mmol) was added to a stirred solution of sodium methoxide (9.5 g, 176 mmol) in MeOH (80 mL). After 30 min the solvent was evaporated and residual MeOH removed by addition of toluene and evaporation. The residue was taken up in DMF (200 mL) and 4-fluorobenzaldehyde (19.85 g, 160 mmol) added. The mixture was stirred and heated at 120 °C for 4 h, cooled, poured into water and extracted with toluene (2 x 200 mL). The combined extracts were washed with water, 2 M NaOH and brine, dried ($MgSO_4$) and the

solvent evaporated to leave a brown oil. Distillation gave the title compound (26.03 g, 64%), bp 140-50 °C/0.5 mm (lit.[1] mp 47-48.5 ^{o}C).

The following benzaldehydes were prepared from the appropriate commercially available phenols and 4-fluorobenzaldehyde in a similar manner:

4-(4-Fluorophenoxy)benzaldehyde (1g): mp 74-77 °C.

4-(3-Chlorophenoxy)benzaldehyde (1i): oil; used without further purification.

4-[3-(Trifluoromethyl)phenoxy]benzaldehyde (1k): oil; used without further purification.

4-[4-(Trifluoromethoxy)phenoxy]benzaldehyde (1l): bp 130-135 °C/0.5mm.

1-[4-(4-Chlorophenoxy)phenyl]propan-2-one (3h). A mixture of **1h** (256 g, 1.1 M) and *n*-butylamine (239 mL, 2.4 M) in toluene (1 L) was heated to reflux and the water formed removed through a Dean-Stark head. After 2 h the mixture was concentrated and the residue dissolved in acetic acid (750 mL) and nitroethane (118.5 mL, 1.65 M), heated at 100 °C for 2 h, cooled and poured into iced water. The yellow solid was filtered, dried in air and recrystallized from ethanol (750 mL) to afford 1-chloro-4-(4-(2-nitroprop-1-enyl)phenoxy)benzene (254.7 g, 80%), mp 69-71 °C. Acetic acid (115 mL, 2 M) was added over 30 min to a well stirred mixture of the 1-chloro-4-(4-(2-nitroprop-1-enyl)phenoxy)benzene (28.9 g, 100 mmol), iron powder (56 g, 1 M), water (20 mL) and MeOH (150 mL) heated to reflux. After 3 h the mixture was cooled and partitioned between water (500 mL) and CH_2Cl_2 (200 mL). The organic phase was filtered, washed with water and aq $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated to leave an oil; trituration with hexane afforded **3h** (14.6 g, 65%) as fine white crystals, mp 50-52 ^{o}C.

In a similar manner the following ketones were prepared from the corresponding substituted benzaldehydes:

1-(4-Phenoxyphenyl)propan-2-one (**3f**).

1-[4-(4-Fluorophenoxy)phenyl]propan-2-one (**3g**): mp 51-54 ^{o}C; ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.3-6.7 (7H, m), 3.64 (2H, s), 2.15 (3H, s).

1-[4-(3-Chlorophenoxy)phenyl]propan-2-one (**3i**): ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.45-6.6 (8H, m), 3.6 (2H, s), 2.1 (3H, s).

1-{4-[3-(Trifluoromethyl)phenoxy]phenyl}propan-2-one (**3k**): ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.4-6.7 (8H, m), 3.6 (2H, s), 2.1 (3H, s).

1-{4-[4-(Trifluoromethoxy)phenoxy]phenyl}propan-2-one (**3l**): mp 57-58 ^{o}C; ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.4-6.85 (8H, m), 3.7 (2H, s), 2.2 (3H, s).

1-(4′-Chlorobiphenyl-4-yl)propan-2-one (3e). To a stirred solution of 4-bromo-4'-chlorobiphenyl[2] (16 g, 59.8 mmol), isopropenyl acetate (9 g, 90 mmol) and dichlorobis(tri-*o*-tolylphosphine)palladium (0.47 g, 0.6 mmol) in dry toluene (30 mL), under nitrogen, was added tributyltin methoxide (25.9 mL, 90 mmol). The mixture was stirred and heated at 100 ^{o}C for 5 h, cooled and the solvent evaporated. The residue was chromatographed on silica gel (cyclohexane, then diethyl ether eluant) and recrystallized from cyclohexane to afford **3e** (10 g, 68%) as white crystals, mp 79-81 °C.

1-{4-[4-(Trifluoromethyl)phenoxy]phenyl}propan-2-one (3j). To a solution of 4-bromophenol (86.5 g, 500 mmol) in DMSO (1.25 L) was added potassium *tert*-butoxide (56.1 g, 500 mmol) and 4-chlorobenzotrifluoride (90 g, 498 mmol). The mixture was stirred and heated at 160 °C for 3 days, cooled, poured into iced water and extracted with toluene (3 x 400 mL). The combined extracts were washed with 2 M NaOH and water, dried ($MgSO_4$) and the solvent evaporated to leave an oil; distillation afforded 1-bromo-4-[4-(trifluoromethyl)phenoxy]benzene (133.6 g, 85%), bp 94-96 °C/0.15mm. To a stirred solution of 1-bromo-4-(4-(trifluoromethyl)phenoxy)benzene (53.9 g, 170 mmol) in DMF (1 L) was added CuI (32.4 g, 170 mmol) and potassium acetylacetonate hemihydrate (125 g, 849 mmol). The mixture was stirred and heated at 100 ^{o}C for 24 h, cooled, stirred with 2 M NaOH (250 mL) for 1 h and extracted with toluene (2 x 500 mL). The combined extracts were washed with water, 1 M aq HCl and aq $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated to leave a brown oil; trituration with 1:1 diethyl ether/hexane followed by recrystallization from hexane afforded **3j** (32.l g, 64%) as white crystals, mp 88-90 ^{o}C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5-7.8 (m, 8H), 3.62 (s, 2H), 2.18 (s, 3H).

1-[*trans*-4-(4-Chlorophenyl)cyclohexyl]propan-2-one (3d). To a stirred suspension of *trans*-4-(4-chlorophenyl)cyclohexanecarboxylic acid (47.74 g, 200 mmol) in dry diethyl ether (250 mL), under nitrogen, was added dropwise borane-methyl sulphide complex (ca. 10 M soln; 8 mL, 80 mmol). After 30 min the mixture was heated to reflux and further borane-methyl sulphide (16 mL, 160 mmol) added. After 1 h the mixture was cooled to room temperature and poured into MeOH (500 mL). The solvent was

evaporated and the residue treated again with MeOH (100 mL). Evaporation of the solvent gave [*trans*-4-(4-chlorophenyl)cyclohexyl]methanol (44 g, 98%): mp 60-63 °C. A portion of this alcohol (41 g, 182 mmol) was added to 48% aq hydrobromic acid (61 g, 360 mmol) and concd sulphuric acid (20 g). The mixture was stirred and heated at 140 °C for 5.5 h, cooled and poured into iced water. The precipitate was filtered, dissolved in diethyl ether, washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent evaporated to leave a brown oil. Trituration with cold hexane gave 1-[*trans*-4-(bromomethyl)cyclohexyl]-4-chlorobenzene (44 g, 84%), mp 36-38 °C . To magnesium turnings (33.06 g, 1.36 M) in dry diethyl ether (70 mL) under nitrogen was added a crystal of iodine followed by a solution of 1-[*trans*-4-(bromomethyl)cyclohexyl]-4-chlorobenzene (19.7 g, 68.5 mmol) in diethyl ether (20 mL). The mixture was heated at reflux for 30 min, cooled to room temperature and then added dropwise to vigorously stirred acetic anhydride (32.5 mL, 343 mmol) in dry diethyl ether (70 mL) at -78 °C, at such a rate that the temperature did not exceed -70 °C. The mixture was stirred at -78 °C for a further 1 h, then allowed to warm to 0 °C and poured into saturated aq NH_4Cl (200 mL). The mixture was stirred for 30 min and the organic phase separated and washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent evaporated to leave a white solid. Recrystallization from hexane afforded **3d** (9.3 g, 54%), mp 58-60 °C; ^{1}H NMR (200 MHz , $CDC1_3$): δ 7.3-7.0 (m, 4H), 2.55-2.3 (m, 1H), 2.4-2.3 (m, 2H), 2.15 (s, 3H), 2-1.75 (m, 5H), 1.6-1.45 (m, 2H), 1.25-1.0 (m, 2H).

2,6-Dimethyl-3-octyl-4*H*-pyran-4-one (4a): ^{1}H NMR (200 MHz, $CDC1_3$): δ 5.95 (1H, s), 2.25 (3H, s), 2.2 (3H, s), 2.4-1.9 (2H, m), 1.6-0.8 (15H, m).

2,6-Dimethyl-3-phenyl-4*H*-pyran-4-one (4b). mp 70-75 ^{o}C (lit.[3] mp 78-78.5 ^{o}C).

3-(4-Chlorophenyl)-2,6-dimethyl-4*H*-pyran-4-one (4c): mp 93-95 ^{o}C; ^{1}H NMR (200 MHz, $CDC1_3$): δ 7.4-6.9 (4H, m), 6.1 (1H, s), 2.3 (3H, s), 2.2 (3H, s).

3-*trans*-[4-(4-Chlorophenyl)cyclohexyl]-2,6-dimethyl-4*H*-pyran-4-one (4d): mp 148-150 ^{o}C; ^{1}H NMR (200 MHz, $CDC1_3$): δ 7.3-7.1 (4H, m), 6.0 (1H, s), 2.8-2.5 (2H, m), 2.32 (3H, s), 2.18 (3H, s), 2-1.85 (2H, m), 1.7-1.35 (4H, m).

3-(4′-Chlorobiphenyl-4-yl)-2,6-dimethyl-4*H*-pyran-4-one (4e). mp 151-153 ^{o}C.

2,6-Dimethyl-3-(4-phenoxyphenyl)-4*H*-pyran-4-one (4f).

3-[4-(4-Fluorophenoxy)phenyl]-2,6-dimethyl-4*H*-pyran-4-one (4g): ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.3-7.1 (2H, m), 7.1-6.9 (6H, m), 6.2 (1H, s), 2.28 (3H, s), 2.2 (3H, s).

3-[4-(3-Chlorophenoxy)phenyl]-2,6-dimethyl-4*H*-pyran-4-one (4i).

2,6-Dimethyl-3-{4-[4-(trifluoromethyl)phenoxy]phenyl}-4*H*-pyran-4-one (4j): mp 86-87 ^{o}C; ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.8-6.95 (8H, m), 6.2 (1H, s0, 2.3 (3H, s), 2.2 (3H, s).

2,6-Dimethyl-3-{4-[3-(trifluoromethyl)phenoxy]phenyl}-4*H*-pyran-4-one (4k): ^{1}H NMR (200 MHz, CDC1$_3$): δ7.3-6.7 (8H, m), 6.2 (1H, s), 2.3 (3H, s), 2.25 (3H, s).

2,6-Dimethyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-4*H*-pyran-4-one (4l): ^{1}H NMR (200 MHz, CDC1$_3$): δ 7.4-6.9 (8H, m), 6.16 (1H, s), 2.24 (3H, s), 2.16 (3H, s).

3-(2-Bromophenyl)-2,6-dimethyl-4*H*-pyran-4-one (4n): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, 1H), 7.36 (t, 1H), 7.25-7.16 (m, 2H), 6.21 (s, 1H), 2.31 (s, 3H), 2.08 (s, 3H).

2,6-Dimethyl-3-{2-[4-(trifluoromethoxy)phenoxy]phenyl}-4*H*-pyran-4-one (4p): ^{1}H NMR (300 MHz, DMSO-d_6): 7.37-7.31 (m, 2H), 7.24-7.22 (m, 2H), 7.19 (dd, 1H), 7.10 (dd, 2H), 6.96 (s, 1H), 6.08 (s, 1H), 2.22 (s, 3H), 2.17 (s, 3H).

2,6-Dimethyl-3-octylpyridin-4(1*H*)-one (**5a**): mp 130-132 ^{o}C. Anal. ($C_{15}H_{25}NO$) C, H, N.

2,6-Dimethyl-3-phenylpyridin-4(1*H*)-one (5b).

3-(4-Chlorophenyl)-2,6-dimethylpyridin-4(1*H*)-one (5c): mp 316-319 ^{o}C. Anal. ($C_{13}H_{12}ClNO$) C, H, N.

3-*trans*-[4-(4-Chlorophenyl)cyclohexyl]-2,6-dimethylpyridin-4(1*H*)-one (5d): mp 334-339 ^{o}C dec. Anal. ($C_{19}H_{22}ClNO$) C, H, N.

3-(4′-Chlorobiphenyl-4-yl)-2,6-dimethylpyridin-4(1*H*)-one (5e): mp >300 ^{o}C dec; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.75-7.55 (4H, m), 7.55-7.45 (2H, m), 7.3-7.2 (2H, m), 5.95 (1H, s), 2.2 (3H, s), 2.1 (3H, s). Anal. ($C_{19}H_{16}ClNO$) C, H, N.

2,6-Dimethyl-3-(4-phenoxyphenyl)pyridin-4(1*H*)-one (5f): mp >300 ^{o}C dec. Anal. ($C_{19}H_{17}NO_2$) C, H, N.

3-[4-(4-Fluorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (5g): mp 293-296 ^{o}C. Anal. ($C_{19}H_{16}FNO_2$) C, H, N.

3-[4-(4-Chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (5h): mp 271-273 ^{o}C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.42 (2H, m), 7.18 (2H, m), 7.1-6.95 (4H, m), 5.95 (1H, s), 2.2 (3H, s), 2.1 (3H, s). Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

3-[4-(3-Chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (5i): mp 232-234 ^{o}C. Anal. ($C_{19}H_{16}ClNO_2$) C, H, N.

2,6-Dimethyl-3-{4-[4-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (5j): ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.70 (2H, dd, *J* = 5, 0.5 Hz), 7.3-7.0 (6H, m), 5.97 (1H, s), 2.2 (3H, s), 2.1 (3H, s). Anal. ($C_{20}H_{16}F_3NO_2$) C, H, N.

2,6-Dimethyl-3-{4-[3-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (5k): mp 261-263 ^{o}C. Anal. ($C_{20}H_{16}F_3NO_2$) C, H, N.

2,6-Dimethyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (5l): mp 244-248 ^{o}C. Anal. ($C_{20}H_{16}F_3NO_3$) C, H, N.

2,6-Dimethyl-3-{3-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (5o). The pyrone **4o** (82 mg, 0.22mmol) in a mixture of 30% aq ammonia (75 mL, ca. 1.2 M) and EtOH (25 mL) was heated at 140 ºC in a Parr pressure reactor for 8 h. After cooling, the solvent was evaporated and the residue chromatographed on silica gel (10:1 CH_2Cl_2/MeOH eluant) to give **5o** (56 mg, 68%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.10 (s, 1H), 7.41-7.35 (m, 3H), 7.11 (d, 2H), 6.99-6.93 (m, 2H), 6.85 (t, 1H), 5.91 (s,1H), 2.17 (s, 3H), 2.06 (s, 3H).

2,6-dimethyl-3-{2-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (5p): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.05 (s, 1H), 7.23 (d, 2H), 7.18-7.16 (m, 2H), 6.98-6.93 (m, 4H), 5.79 (s, 1H), 2.35 (s, 3H), 2.01 (s, 3H).

3-Chloro-2,6-dimethyl-5-octylpyridin-4(1*H*)-one (6a): mp 222-224 ^{o}C. Anal. ($C_{15}H_{24}ClNO$) C, H, N.

3-Chloro-2,6-dimethyl-5-phenylpyridin-4(1*H*)-one (6b): mp 338-340 ^{o}C. Anal. ($C_{13}H_{12}ClNO$) C, H, N.

3-Chloro-2,6-dimethyl-5-(4-chlorophenylpyridin-4(1*H*)-one (6c): mp >330 ^{o}C dec. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.4 (2H, d, J = 5 Hz), 7.1 (2H, d, J = 5 Hz), 2.4 (3H, s), 2.15 (3H, s).

3-Chloro-5-*trans*-[4-(4-chlorophenyl)cyclohexyl]-2,6-dimethylpyridin-4(1*H*)-one (6d): mp 358-360 ^{o}C. Anal. ($C_{19}H_{21}Cl_2NO$) C, H, N.

3-Chloro-5-(4′-Chlorobiphenyl-4-yl)-2,6-dimethylpyridin-4(1*H*)-one (6e): mp >350 ^{o}C dec. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.8-7.6 (4H, m), 7.55-7.45 (2H, m), 7.35-7.22 (2H, m), 2.4 (3H, s), 2.15 (3H, s). Anal. ($C_{19}H_{15}Cl_2NO$) C, H, N.

3-Chloro-5-[4-(3-Chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (6i): mp 268-272 ^{o}C. Anal. ($C_{19}H_{15}Cl_2NO_2$) C, H, N.

3-Chloro-2,6-dimethyl-5-{4-[4-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (6j): mp 267-270 ^{o}C. Anal. ($C_{20}H_{15}ClF_3NO_2$) C, H, N.

3-Chloro-2,6-dimethyl-5-{4-[3-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (6k): mp 265-268 ^{o}C. Anal. ($C_{20}H_{15}ClF_3NO_2$) C, H, N.

3-Chloro-2,6-dimethyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (6l): mp 271-274 ^{o}C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.5-7.35 (2H, m), 7.3-7.1 (4H, m), 7.1-7.0 (2H, m), 2.38 (3H, s), 2.1 (3H, s). Anal. ($C_{20}H_{15}ClF_3NO_3$) C, H, N.

3-Bromo-2,6-dimethyl-5-(4-phenoxyphenyl)pyridin-4(1*H*)-one (7f): mp 291-293 ^{o}C. Anal. ($C_{19}H_{16}BrNO_2$) C, H, N.

3-Bromo-5-[4-(4-fluorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (7g): mp 291-293 ^{o}C. Anal. ($C_{19}H_{15}BrFNO_2$) C, H, N.

3-Bromo-5-[4-(3-chlorophenoxy)phenyl]-2,6-dimethylpyridin-4(1*H*)-one (7i): mp 286-290 ^{o}C. Anal. ($C_{19}H_{15}BrClNO_2$) C, H, N.

3-Bromo-2,6-dimethyl-5-{4-[4-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (7j): mp 304-305 ^{o}C. Anal. ($C_{20}H_{15}BrF_3NO_2$) C, H, N.

3-Bromo-2,6-dimethyl-5-{4-[3-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (7k): mp 299-300 ^{o}C. Anal. ($C_{20}H_{15}BrF_3NO_2$) C, H, N.

3-Bromo-2,6-dimethyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (7l): mp 284-286 ^{o}C. Anal. ($C_{20}H_{15}BrF_3NO_3$) C, H, N.

3-Bromo-2,6-dimethyl-5-{2-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (7p): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.59 (s, 1H), 7.26(d, 2H), 7.20-7.18 (m, 2H), 7.00-6.93 (m, 4H), 2.35 (s, 3H), 2.01 (s, 3H).

3-Iodo-2,6-dimethyl-5-{4-[3-(trifluoromethyl)phenoxy]phenyl}pyridin-4(1*H*)-one (**10k**): ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.62 (bs, 1H), 7.63 (m, 1H), 7.49 (m, 1H), 7.32 (m, 2H), 7.23 (m, 2H), 7.07 (m, 2H), 2.49 (m, 3H + DMSO-d_6), 2.09 (s, 3H).

1-Bromo-4-[4-(trifluoromethoxy)phenoxy]benzene (16). To a solution of 4-bromophenol (0.173 g, 1 mmol) in *N*-methylpyrrolidine (4 mL) under an argon atmosphere was added 4-(trifluoromethoxy)iodobenzene (0.313 mL, 2 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (0.046 mL, 0.22 mmol) and cesium carbonate (0.652 g, 2 mmol). The slurry was degassed by bubbling argon for 15 min and CuCl (0.099 g, 1 mmol) added. The reaction mixture was again degassed and then warmed to 100º C for 5 h under argon. After cooling to room temperature, *tert*-butyl methyl ether (30 mL) was added dropwise. The resulting slurry was filtered and the solid washed with *tert*-butyl methyl ether (3 x 20 mL). The combined filtrates were washed with 1 M NaOH (50 mL), water (50 mL), 1 M aq HCl (50 mL), water (50 mL) and saturated brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane eluant) to afford **16** (0.15 g, 45%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.20 (m 2H), 6.99 (m 2H), 6.90 (m 2H).

4-[4-(Trifluoromethoxy)phenyoxy]phenylboronic acid (17). To a solution of the bromo derivative **16** (4.53 g, 13.6 mmol) and triisopropyl borate (4.1 mL, 17.8 mmol) in dry THF (100 mL) at -75 ºC was added dropwise a 1.47 M solution of *n*-butyllithium in hexane (11.1 mL, 16.3 mmol). The mixture was stirred for 3 h at -75 ºC, then quenched by addition of 6 M HCl (12 mL) and stirred for 18 h at room temperature. The mixture was partitioned between ethyl acetate (200 mL) and water (200 mL), the organic phase separated and washed with water (200 mL) and saturated brine (200 mL), dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure. The residual solid was treated with 2 M NaOH (60 mL), stirred for 15 min, then diluted with water (250 mL) and stirred until the solids were dissolved. The solution was filtered and the filtrate washed with pentane (2 x 200 mL). The aqueous layer was acidified to pH 1.5 with 6 M aq HCl and the resulting precipitate filtered, washed with water and dried in vacuo to give a pale yellow solid (3.23 g, ca. 79%), consisting of **17** and its anhydride, used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (bs, 2H), 7.85-7.78 (m, 2H), 7.43-7.33 (m, 2H), 7.15-7.07 (m, 2H), 7.02-6.94 (m, 2H).

2-Methyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (26l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.51 (br s, 1H), 7.68-7.75 (m, 3H), 7.35-7.41 (m, 2H), 7.01-7.12 (m, 4H), 6.04 (s, 1H), 2.19 (s, 3H). ESIMS m/z: 362.1 (MH^+).

3-Bromo-2-methyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (29l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.11 (d, 1H, J = 5.9 Hz), 7.83 (d, 1H, J = 5.9 Hz), 7.67-7.71 (m, 2H), 7.36-7.42 (m, 2H), 7.04-7.14 (m, 4H), 2.42 (s, 3H). ESIMS m/z: 440.0 (MH^+).

3-Bromo-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-2-(trifluoromethyl)pyridin-4(1*H*)-one (30l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.55 (br s, 1H), 8.27 (br s, 1H), 7.61-7.66 (m, 2H), 7.39-7.45 (m, 2H), 7.12-7.20 (m, 4H). ESIMS m/z: 493.9 (MH^+).

2-Methyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-6-(trifluoromethyl)pyridin-4(1*H*)-one (28l): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.29 (m, 4H), 7.09-7.19 (m, 5H), 2.38 (s, 3H). ESIMS m/z: 430.1 (MH^+).

3-Bromo-6-methyl-5-{4-[4-(trifluoromethoxy)phenoxy]phenyl}-2-(trifluoromethyl)pyridin-4(1*H*)-one (31l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.39-7.49 (m, 2H), 7.31-7.36 (m, 2H), 7.12-7.22 (m, 4H), 2.19 (s, 3H). ESIMS m/z: 508.0 (MH^+).

2-Methyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (34l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.36 (br s, 1H), 7.61-7.02 (m, 9H), 6.08 (d, 1H, J = 5.9 Hz), 2.08 (s, 3H). ESIMS: m/z 362.1 (MH^+).

5-Bromo-2-methyl-3-{4-[4-(trifluoromethoxy)phenoxy]phenyl}pyridin-4(1*H*)-one (35l): ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.86 (s, 1H), 8.14 (s, 1H), 7.41-7.03 (m, 8H), 2.07 (s, 3H). ESIMS: m/z 437.90 (MH^-).

B. Elemental Analysis.

Table S1. Microanalysis of Selected Compounds

Compound	Formula	% Calculated (Found)		
		C	H	N
5a	$C_{15}H_{25}NO$	76.55 (76.60)	10.71 (10.72)	5.95 (5.975)
5c	$C_{13}H_{12}ClNO$	66.80 (67.15)	5.17 (5.16)	5.99 5.72)
5d	$C_{19}H_{22}ClNO$	72.24 (72.45)	7.02 (7.35)	4.43 (4.80)
5e	$C_{19}H_{16}ClNO$	73.66 (73.83)	5.20 (5.17)	4.52 (4.57)
5f	$C_{19}H_{17}NO_2$	78.33 (78.08)	5.88 (5.89)	4.81 (5.11)
5g	$C_{19}H_{16}FNO_2$	73.77 (73.31)	5.21 (5.17)	4.53 (4.35)
5h	$C_{19}H_{16}ClNO_2$	70.05 (69.80)	4.95 (4.98)	4.30 (4.46)
5i	$C_{19}H_{16}ClNO_2$	70.4 (69.70)	4.95 (5.00)	4.30 (4.41)
5j	$C_{20}H_{16}F_3NO_2$	66.85 (66.63)	4.49 (4.45)	3.90 (3.85)
5k	$C_{20}H_{16}F_3NO_2$	66.85 (66.58)	4.49 (4.47)	3.90 (3.84)
5l	$C_{20}H_{16}F_3NO_3$	64.00 (63.60)	4.30 (4.24)	3.73 (3.71)
6a	$C_{15}H_{24}ClNO$	66.77 (66.62)	8.97 (8.95)	5.19 (5.05)
6b	$C_{13}H_{12}ClNO$	66.81 (66.63)	5.18 (5.20)	5.99 (5.99)
6d	$C_{19}H_{21}Cl_2NO$	65.15 (65.32)	6.04 (6.17)	4.00 (3.91)
6e	$C_{19}H_{15}Cl_2NO$	66.21 (65.880	4.39 (4.51)	4.07 (4.35)
6h	$C_{19}H_{15}Cl_2NO_2$	63.35 (63.48)	4.2 (4.10)	3.89 (3.91)
6i	$C_{19}H_{15}Cl_2NO_2$	63.35 (63.03)	4.16 (4.24)	3.89 (4.00)
6j	$C_{20}H_{15}ClF_3NO_2$	61.00 (60.81)	3.84 (3.87)	3.56 (3.57)

6k	$C_{20}H_{15}ClF_3NO_2$	61.00	3.84	3.56
		(60.63)	(3.81)	(3.52)
6l	$C_{20}H_{15}ClF_3NO_3$	58.61	3.69	3.40
		(58.72)	(3.69)	(3.42)
7f	$C_{19}H_{16}BrNO2$	61.64	4.36	3.78
		(61.14)	(4.33)	(3.73)
7g	$C_{19}H_{15}BrFNO_2$	58.78	3.89	3.61
		(58.47)	(3.86)	(3.48)
7h	$C_{19}H_{15}BrClNO_2$	56.39	3.74	3.46
		(56.45)	(3.76)	(3.51)
7i	$C_{19}H_{15}BrClNO_2$	56.39	3.74	3.46
		(56.26)	(3.70)	(3.50)
7j	$C_{20}H_{15}BrF_3NO_2$	54.80	3.45	3.20
		(54.29)	(3.36)	(3.08)
7k	$C_{20}H_{15}BrF_3NO_2$	54.81	3.45	3.20
		(53.97)	(3.34)	(3.12)
7l	$C_{20}H_{15}BrF_3NO_3$	52.88	3.33	3.08
		(52.59)	(3.27)	(3.07)

C. In vitro Antimalarial Assay (GSK Tres Cantos).

P. falciparum strains 3D7A (MRA-151) and FCR3-A (MRA-158) were obtained from the Malaria research and Reference Reagent Resource Centre (MR4). Chloroquine disphosphate was purchased from Sigma.

The assays were performed in 96 well flat bottom microplates.

1. Serial dilutions of the compounds (50 μL of a 5x solution/well) were dispensed in duplicate.

2. The inoculum was prepared as a suspension of parasitized red blood cells (PRBCs) at 2.5% of hematocrit and 0.5% of parasitemia (*P. falciparum* 3D7A strain) in complete medium without hypoxanthine.

3. [^{3}H]Hypoxanthine (Amersham Biosciences) was added at a concentration of 1 μCi/mL (0.25 μCi /well); 200 μL of the suspension was distributed, leading to a final volume of 250 μL, at 2% of hematocrit and 0.5% of parasitemia/well.

4. In each plate, 2 columns were reserved for control wells:

Columm 11: PRBCs with 0.2% DMSO.

Columm 12: A12-D12- Uninfected RBCs – blank control.

E12-G12- PRBCs without DMSO.

H12-Non-radioactive well. PRBCs with cold hypoxanthine.

For each assay, Chloroquine and Atovaquone were used as internal controls.

5. The plates were incubated for 48 h at 37 ºC under low oxygen atmosphere. At the end of the assay, a thin film was made with the non-radioactive sample (well H12) for a visual control of the development of the parasites. Incorporation was stopped by freezing the plates overnight at –80 ºC.

6. After thawing the plates, the content of the wells was harvested on glass fibre filters (Wallac) with a semi-automated cell-harvester (Harvester 96, Tomtec). The filters were dried and treated with a Melt-on scintillator (Meltilex® A, PerkinElmer). Incorporation of radioactivity was measured with a β-counter (Wallac Microbeta, PerkinElmer).

The assays were repeated at least three independent times.

D. Additional References

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