Supporting Material

2-Oxo-tetrahydro-1,8-naphthyridine-Based Protein Farnesyltransferase Inhibitors as Antimalarials

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Synthesis of Compounds

General Methods

Unless otherwise indicated, all anhydrous solvents were commercially obtained and stored under nitrogen. Reactions were performed under an atmosphere of dry nitrogen in oven dried glassware and were monitored for completeness by thin layer chromatography (TLC) using silica gel 60 F-254 (0.25 mm) plates with detection with UV light. ^{1}H-NMR spectra were recorded on dilute solutions in $CDCl_3$ or CD_3OD at 300 or 500 MHz. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS). Coupling constants (J) are reported in Hz. Electrospray ionization mass spectra were acquired on an Bruker Esquire LC00066. Flash chromatography was carried out with silica gel (40-63 μm). Preparative reverse phase HPLC was performed on an automated Varian Prep star system using a gradient of 20% MeOH to 100% MeOH (with 0.1% trifluoroacetic acid) over 30 min using a YMC S5 ODS column (20x100 mm, Waters Inc.). All final compounds (those tested on *Pf*-PFT and on parasite cultures) were shown to be pure based on HPLC as described above.

2-Chloronicotinic acid ethyl ester (5). A solution of 2-choloronicotinic acid (1.6 g, 10 mmol) in thionyl chloride (25 mL) was stirred at reflux for 2 hours. Thionyl chloride was evaporated under vacuum, and the residue was dissolved in absolute ethanol (40 mL) at 0 ^{o}C. The reaction mixture was stirred at r.t during 12 hours. Ethanol was evaporated, and the residue was washed with a 5% aqueous K_2CO_3 solution and extracted with dichloromethane (2 x 50 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford 2-chloronicotinic acid ethyl ester **5** as a yellow oil (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 2.1 and 4.8 Hz, 1H), 8.10 (dd, *J* = 2.1 and 7.8 Hz, 1H), 7.30 (dd, *J* = 4.8 and 7.8 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

2-[(3-Methyl-3*H*-imidazol-4-ylmethyl)-amino]-nicotinic acid ethyl ester (7). A solution of (1.7 g, 15.3 mmol) Ethyl 2-chloronicotinate, (1-methyl-1*H*-imidazol-5-yl)methylamine **6** (2.83 g, 15.3 mmol, Maybridge Building Blocks) and triethyl amine (6.4 mL, 46.0 mmol) were dissolved in DMF (25 mL) was heated at 100 ^{o}C under N_2 for 18 h and then cooled to ambient temperature and added to H_2O. The mixture was extracted with EtOAc and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel with 5% MeOH in CH_2Cl_2 to give the title compound **7** (60%). ^{1}H NMR (300 MHz, methanol-d_4) δ 8.30 (dd, *J* = 2.1 and 4.8 Hz, 1H), 8.20 (dd, *J* = 2.1 and 7.8 Hz, 1H), 7.59 (s, 1H), 6.95 (s, 1H), 6.65 (dd, *J* = 4.8 and 7.7 Hz, 1H), 4.75 (d, 2H, *J* = 5.4 Hz), 4.40 (q, *J* = 6.9 Hz, 2H), 3.70 (s, 3H), 1.35 (t, *J* = 6.9 Hz, 3H).

2-[(3-Methyl-3*H*-imidazol-4-ylmethyl)-amino]-pyridine-3-carbaldehyde (8). A suspension of Ethyl nicotinate **7** (1.0 g) in dry THF (30 mL) was added slowly to a stirred suspension of lithium aluminium hydride (0.25 g) in THF (15 mL). The mixture was stirred for a further 0.5 h, and water was added. The precipitated hydroxides were filtered off and extracted with EtOAc. The solutions were combined, dried (Na_2SO_4), and evaporated to yield the alcohol. MnO_2 (4 g, 45.8 mmol) was added to a solution of alcohol (1 g, 4.58 mmol) in anhydrous methylene chloride (20 mL) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered through a pad of celite,and the filtrate was concentrated under reduced pressure to afford pure **8** (70%) as white plates. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.40 (s, 1H), 8.30 (dd, *J* = 1.5 and 4.5 Hz, 1H), 7.76 (dd, 1H, *J* = 1.8 and 7.5 Hz), 7.42 (s, 1H), 7.0 (s, 1H), 6.70 (dd, *J* = 4.8 and 7.5 Hz, 1H), 4.75 (d, 2H, *J* = 5.4 Hz), 3.62 (s, 3H).

2-*tert*-Butoxycarbonylamino-3-{2-[(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-pyridin-3-yl}-acrylic acid methyl ester (10). To a mixture of aldehyde **8** (0.50 g, 2.3 mmol) and (±)-Boc-α-phosphonoglycine trimethyl ester **9** (0.82 g, 2.77 mmol, Fluka) in CH_2Cl_2 (20 mL) at 10 ^oC was added N,N,N',N'-tetramethylguanidine (0.44 mL, 3.47 mmol), and the mixture was allowed to warm room temperature and stirred for 24 h. The reaction mixture was sequentially washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, and the organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography with 7% MeOH in CH_2Cl_2 to afford the compound **10** as yellow solid (65%)**.** ^{1}H NMR (300 MHz, methanol-d_4) δ 9.0 (s, 1H), 8.0 (d, 1H, *J* = 6.3 Hz), 7.90 (d,

1H, *J* = 7.5 Hz), 7.70 (s, 1H), 7.0-7.05 (m, 2H), 5.14 (s, 2H), 4.13 (s, 3H), 3.90 (s, 3H), 1.45 (s, 9H).

2-*tert*-Butoxycarbonylamino-3-{2-[(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-pyridin-3-yl}-propionic acid methyl ester (11). A mixture of **10** (0.5 g) and palladium on carbon catalyst (50 mg, 10% w/w) in ethanol (20 mL) was stirred under 1 atmosphere of hydrogen at ambient temperature for 0.5 hours. The reaction mixture was filtered through a pad of cellite and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography with 7% MeOH in CH_2Cl_2 to afford the compound **11** (50%). ^{1}H NMR (300 MHz, methanol-d_4) δ 8.98 (s, 1H), 7.95 (d, 1H, *J* = 6.0 Hz), 7.74-7.81 (m, 2H), 7.0 (t, 1H, *J* = 6.6 Hz), 4.9 (s, 2H), 4.54-4.60 (m, 1H), 3.99 (s, 3H), 3.75 (s, 3H), 3.25 (dd, 1H, *J* = 6.0 and 15.3 Hz), 2.90 (dd, 1H, *J* = 9.0 and 14.4 Hz), 1.32 (s, 9H).

3-{5-Bromo-2-[(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-pyridin-3-yl}-2-*tert*-butoxycarbonylamino-propionic acid methyl ester (12) To a stirred solution of compound **11** (0.3 g, 0.77 mmol) in HOAc (5 mL) at r. t was added bromine (0.12 g, 0.77 mmol) dropwise. A suspension formed after approximately 15 min. After the addition, the reaction mixture was stirred for an additional 1 h, and then concentrated under vacuum. The residue was taken up in 1 M Na_2CO_3 (5 mL), and the solution was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to dryness. The resulting residue was triturated with a small volume of petroleum ether, filtered, and dried under vacuum to give the title

compound **12** (65%). ^{1}H NMR (300 MHz, methanol-d_4) δ 8.92 (s, 1H), 8.10 (s, 1H), 7.65 (s, 1H), 7.50 (s, 1H), 4.90 (d, *J* = 15.9 Hz, 1H), 4.80 (d, *J* = 15.9 Hz, 1H), 4.52-4.57 (m, 1H), 4.15 (s, 3H), 3.65 (s, 3H), 3.10 (dd, *J* = 5.4 and 14.7 Hz, 1H), 2.90 (dd, *J* = 8.7 and 14.7 Hz, 1H), 1.30 (m, 9H).

[6-Cyano-1-(3-methyl-3*H*-imidazol-4-ylmethyl)-2-oxo-1,2,3,4-tetrahydro-[1,8]naphthyridin-3-yl]-carbamic acid *tert*-butyl ester(13). Bromo compound **12** (0.2 g, 0.43 mmol) was dissolved in DMF (5 mL) and then placed under high vacuum for 15 min. The solution was then purged with Ar for 15 min. while purging continued, $ZnCN_2$ (76 mg, 0.64 mmol) and the catalyst $Pd[(PPh_3)]_4$ (50 mg, 0.043 mmol) were added. The reaction mixture was heated at 100^o C under Ar for 18 h and then cooled to ambient temperature and added to H_2O. The mixture was extracted with EtOAc and dried over Na_2SO_4, filtered and concentrated. The crude residue was purified using preparative HPLC to give the cyclised cyano compound **13** as the TFA salt in 35 % yield. ^{1}H NMR (300 MHz, methanol-d_4) δ 8.85 (s, 1H), 8.65 (s, 1H), 8.03 (s, 1H), 7.55 (s, 1H), 5.40 (d, *J* = 15.9 Hz, 1H), 5.35 (d, *J* = 15.9 Hz, 1H), 4.42-4.52 (m, 1H), 4.08 (s, 3H), 3.08-3.25 (m, 2H), 1.45 (s, 9H).

6-Amino-8-(3-methyl-3*H*-imidazol-4-ylmethyl)-7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridine-3-carbonitrile (14). To a stirred solution of the cyano derivative **13** (100 mg, 0.37 mmol) in CH_2Cl_2 (5 ml) at r. t, TFA (1 ml) was added and the reaction mixture was stirred for 2 h. The solution was then concentrated under reduced pressure and the crude amine (TFA salt) **14** was carried over to the next step without further

purification. ^{1}H NMR (300 MHz, methanol-d_4) δ 8.86 (s, 1H), 8.75 (s, 1H), 8.13 (s, 1H), 7.59 (s, 1H), 5.55 (d, *J* = 15.9 Hz, 1H), 5.40 (d, *J* = 15.6 Hz, 1H), 4.45-4.55 (m, 1H), 4.08 (s, 3H), 3.08-3.25 (m, 2H).

4-{[6-Cyano-1-(3-methyl-3*H*-imidazol-4-ylmethyl)-2-oxo-1,2,3,4-tetrahydro-[1,8]-naphthyridin-3-ylamino]-methyl}-piperidine-1-carboxylic acid methyl ester (15). Compound **14** (100 mg, 0.35 mmol) and methyl 4-formylpiperdine-1-carboxylate (60 mg, 0.35 mmol) were added to MeOH (6 mL) containing 0.4 g of 4A-type molecular sieves. The solution was stirred at room temperature under nitrogen for 1 h, after which acetic acid (262 mg, 4.4 mmol) was added. After 1 h, $NaCNBH_3$ (22 mg, 0.35 mmol) was added in portions. The mixture was stirred at room temperature under nitrogen overnight. The reaction mixture was then extracted from CH_2Cl_2 and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, after which the combined organic layers were washed with brine. The organic layer was then dried with Na_2SO_4, and the solvent was removed by evaporation. The crude product was purified using preparative HPLC to give a Compound **15** as TFA salt (55%). ^{1}H NMR (300 MHz, methanol-d_4) δ 8.87 (s, 1H), 8.78 (s, 1H), 8.18 (s, 1H), 7.62 (s, 1H), 5.60 (d, 1H, *J* = 16.0 Hz), 5.42 (d, 1H, *J* = 16.0 Hz), 4.58-4.65 (m, 1H), 4.18-4.25 (m, 2H), 4.12 (s, 3H), 3.72 (s, 3H), 3.55 (dd, 1H, *J* = 6.0 and 15.0 Hz), 3.35-3.40 (m, 1H), 3.25 (dd, 1H, *J* = 6.5 and 12.5 Hz), 3.15 (dd, 1H, *J* = 7.5 and 12.5 Hz), 2.80-2.95 (m, 2H), 2.05-2.15 (m, 1H), 1.82-1.95 (m, 2H), 1.22-1.38 (m, 2H). MS *m/z* 438.4 ($M + H^+$).

4-{[[6-Cyano-1-(3-methyl-3*H*-imidazol-4-ylmethyl)-2-oxo-1,2,3,4-tetrahydro-[1,8]-naphthayridin-3-yl]-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-methyl}-piperidine-1-carboxylic acid methyl ester (20). A solution of **15** (0.1 mmol), 1-methyl-1*H*-imidazole-4-sulfonyl chloride (0.2 mmol), N, N-diisopropylethyl amine (0.3 mmol) in 5 mL of anhydrous CH_3CN was stirred at room temperature for 48 h, The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure and purified by HPLC to provide the desired sulfonamide (**20**) as the TFA salt (20%). ^{1}H-NMR (500 MHz, methanol-d_4) δ 8.83 (s, 1H), 8.68 (s, 1H), 8.03 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.53 (s, 1H), 5.45 (d, *J* = 15.5 Hz, 1H), 5.35 (d, *J* = 15.5 Hz, 1H), 4.85-4.90 (m, 1 H), 4.10-4.18 (m, 2H), 4.05 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 3.60-3.70 (m, 1H), 3.20-3.28 (m, 2H), 3.10 (dd, *J* = 8.5 and 15.0 Hz, 1H), 2.72-2.85 (m, 2H), 1.80-1.92 (m, 3H), 1.26-1.40 (m, 2H). MS m/z 582.4 ($M+H^+$).