New Transmission-Selective Antimalarial Agents through Hit-to-Lead Optimization of 2-([1,1’-Biphenyl]-4-carboxamido)benzoic Acid Derivatives

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Supporting information on compound purity and identity characterisation data

2-[(1,1′-biphenyl)-4-carboxamido]benzoic acid (5): $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.19-7.23 (t, 3H), 7.59-7.64 (t, 3H), 8.09-8.13 (m, 3H), 8.74, 8.76 (d, 1H), 8.87, 8.89 (d, 2H), 12.61 (s, 1H), 12.91 (s, 2H).

2-[(1,1′-biphenyl)-4-carboxamido]-3-methylbenzoic acid (6): $^1$H NMR (C$_2$D$_6$OS, 400 MHz) δ 2.07 (s, 3H), 7.12 (t, 1H), 7.26 (q, 1H), 7.35 (q, 3H), 7.52 (q, 1H), 7.60 (t, 2H), 7.68 (d, 2H), 9.95 (s, 1H), 12.62 (s, 1H).

2-[(1,1′-biphenyl)-4-carboxamido]-5-fluorobenzoic acid (7): $^1$H NMR (C$_2$D$_6$OS, 400 MHz) δ 7.26(t, 1H), 7.40 (m, 3H), 7.60 (m, 3H), 7.73 (d, 2H), 7.88 (d, 2H), 8.54 (q, 1H), 11.85 (s, 1H), 13.99 (s, 1H).

2-[(1,1′-biphenyl)-4-carboxamido]-3-fluorobenzoic acid (8): $^1$H NMR (CDCl$_3$, 600 MHz) δ 3.98 (d, 4H), 6.87 (q, 1H), 7.42 (t, 1H), 7.52 (q, 3H), 7.66 (m, 4H), 7.78 (t, 2H), 8.14 (q, 4H), 8.82 (q, 1H).

2-[(1,1′-biphenyl)-3-carboxamido]-3-methylbenzoic acid (10): $^1$H NMR (CDCl$_3$, 400 MHz) δ 2.27 (s, 3H), 7.14 (t, 1H), 7.23 (t, 1H), 7.34 (t, 3H), 7.46 (t, 1H), 7.54 (t, 1H), 7.61 (d, 2H), 7.72 (d, 1H), 7.78 (d, 1H), 8.15 (s, 1H), 9.90 (s, 1H), 12.69 (s, 1H).

2-[(1,1′-biphenyl)-3-carboxamido]-3-fluorobenzoic acid (11): $^1$H NMR (CDCl$_3$, 600 MHz) δ 7.41 (m, 3H), 7.58 (m, 3H), 7.81 (d, 1H), 7.88 (m, 2H), 7.94 (d, 1H), 8.00 (d, 1H), 8.11 (m, 2H), 8.37 (t, 2H), 9.88 (s, 1H).

2-[(1,1′-biphenyl)-2-carboxamido]benzoic acid (12): $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.93 (t, 1H), 7.14 (m, 3H), 7.30 (m, 4H), 7.46 (m, 2H), 7.62 (d, 1H), 7.88 (d, 1H), 8.60 (d, 1H), 10.47 (s, 1H).

2-[(1,1′-biphenyl)-2-carboxamido]-3-methylbenzoic acid (13): $^1$H NMR (CDCl$_3$, 400 MHz) δ 2.03 (s, 3H), 7.01 (d, 1H), 7.15 (d, 1H), 7.20 (t, 2H), 7.27 (t, 2H), 7.32 (d, 2H), 7.38 (t, 1H), 7.67 (t, 2H), 8.70 (s, 1H).

2-[(1,1′-biphenyl)-2-carboxamido]-5-fluorobenzoic acid (14): $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.14 (m, 4H), 7.28 (d, 1H), 7.34 (m, 2H), 7.43 (m, 1H), 7.53 (q, 1H), 7.63 (m, 1H), 8.61 (q, 1H), 10.33 (s, 1H).

2-[(1,1′-biphenyl)-2-carboxamido]-4-fluorobenzoic acid (15): $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.72 (m, 1H), 7.19 (m, 5H), 7.36 (m, 2H), 7.44 (m, 2H), 7.54 (m, 1H), 7.71 (q, 1H), 7.95 (q, 1H), 8.60 (q, 1H), 10.73 (s, 1H).

3-methyl-2-(4′-methyl-[1,1′-biphenyl]-2-carboxamido)benzoic acid (16): $^1$H NMR (CDCl$_3$, 600 MHz) δ 2.355 (s, 3H), 7.19 (m, 4H), 7.37 (m, 3H), 7.45 (m, 4H), 7.54 (m, 1H), 7.81 (m, 2H), 8.93 (s, 1H).

2-(2′-methoxy-[1,1′-biphenyl]-2-carboxamido)-3-methylbenzoic acid (17): $^1$H NMR (CDCl$_3$, 400 MHz) 1.69 (s, 3H), 3.69 (s, 3H), 7.00 (t, 2H), 7.17 (m, 3H), 7.31 (m, 3H), 7.60 (m, 2H), 9.52 (s, 1H).
2-(4'-fluoro-[1,1'-biphenyl]-4-carboxamido)benzoic acid (18): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 6.99 (d, 1 H), 7.29 (d, 1 H), 7.30 (t, 1 H), 7.69 (d, 1 H), 7.74 (d, 1 H), 7.74 (d, 1 H), 7.79 (d, 1 H), 7.79 (d, 1 H), 7.98 (d, 1 H), 8.03 (d, 1 H), 8.05 (d, 1 H), 8.10 (d, 1 H), 8.66 (d, 1 H).

5-bromo-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-carboxamido)benzoic acid (19): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.76 (1H, dd), 7.84 (1H, d), 7.95 (1H, d), 7.96 (1H, d), 8.07 (1H, d), 8.12 (1H,d), 8.65 (1H, d).

2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-carboxamido)-4,5-difluorobenzoic acid (20): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 8.6164 (d,1H), 7.8523 (d, 1H), 7.9791 (d, 1H), 8.0596 (d, 1H), 8.0198 (d, 1H).

N-(4-bromo-2-(2H-tetrazol-5-yl)phenyl)-4'-(tert-butyl)-[1,1'-biphenyl]-4-carboxamide (21): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.76 (dd, 1 H), 7.81 (d, 1 H), 7.93 (d, 1 H), 7.95 (d, 1 H), 8.11 (d, 1 H), 8.18 (d, 1 H), 8.53 (d, 1 H).

2-(([1,1'-biphenyl]-4-carboxamido)nicotinic acid (22): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.41 (1H, d), 7.48 (1H, t), 7.71 (1H, d), 7.78 (1H, d), 8.00 (1H, d).

2-([1,1'-biphenyl]-3-carboxamido)nicotinic acid (23): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.48 (1H, t), 7.56 (1H, t), 7.64 (1H, d), 7.85 (1H, d), 8.08 (1H, d).

2-(3'-methyl-[1,1'-biphenyl]-4-carboxamido)nicotinic acid (24): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 4.95 (d, 2H), 7.21 (d, 1H), 7.36 (t, 1H), 7.49 (d, 1H), 7.76 (d, 2H), 7.99 (d, 2H).

2-(4'-fluoro-[1,1'-biphenyl]-4-carboxamido)nicotinic acid (25): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.31 (t, 1H), 7.76 (d, 1H), 7.77 (d, 1H), 7.99 (d, 1H).

2-(2-naphthamido)nicotinic acid (26): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.67 (d, 1H), 7.87 (d, 1H), 8.04 (d, 1H), 8.12 (t, 1H), 8.50 (d, 1H).

2-(4-cyclohexylbenzamido)-4,5-difluorobenzoic acid (27): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.32 (d, 1H), 7.44 (d, 1H), 7.83 (d, 1H), 7.85 (d, 1H), 8.01 (d, 1H), 8.61 (d, 1H), 8.62 (d, 1H).

2-(2-naphthamido)-4-fluorobenzoic acid (28): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 2.48 (d, 1H), 2.48 (d, 1H), 7.57 (d, 1H), 7.60 (d, 1H), 7.62 (t, 1H), 7.63 (d, 1H), 7.65 (d, 1H), 7.66 (d, 1H), 7.95 (d, 1H), 7.96 (d, 1H), 7.99 (d, 1H), 8.09 (d, 1H), 8.12 (d, 1H).

4'-methyl-N-(4-methyl-2-(2H-tetrazol-5-yl)phenyl)-[1,1'-biphenyl]-4-carboxamide (29): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.30 (d, 1H), 7.46 (d, 1H), 7.54 (d, 1H), 7.65 (d, 1H), 7.82 (d, 1H), 8.05 (d, 1H).

N-(2-(2H-tetrazol-5-yl)-4-(trifluoromethyl)phenyl)-4'-methyl-[1,1'-biphenyl]-4-carboxamide (30): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.31 (d, 1H), 7.68 (d, 1H), 7.73 (d, 1H), 7.90 (d, 1H), 8.14 (d, 1H), 8.27 (d, 1H).

2-([1,1'-biphenyl]-4-sulfonamido)benzoic acid (31): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.03 (m, 1H), 7.31 (d, 1H), 7.36 (t, 2H), 7.45 (s, 2H), 7.53 (d, 2H), 7.74 (m, 4H), 7.79 (d, 1H).

5-methyl-2-((3'-methyl-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (32): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 2.23 (s, 3H), 2.36 (s, 3H), 7.24 (d, 1H), 7.36 (t, 1H), 7.39 (d, 1H), 7.47 (d, 2H), 7.51 (br, 1H), 7.71 (d, 1H), 7.83 (d, 4H), 10.94 (br, 1H).

5-fluoro-2-((3'-methyl-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (33): \(^1H\) NMR (CDCl\(_3\), 600 MHz) \(\delta\) 2.36 (s, 3H), 6.99 (m, 1H), 7.24 (d, 1H), 7.30 (m, 1H), 7.37 (t, 1H), 7.49 (d, 1H), 7.90 (m, 1H), 7.99 (d, 4H), 7.99 (d, 1H), 11.47 (s, 1H).
4-fluoro-2-((3'-methyl-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (34): ¹H NMR (C₂D₆OS, 600 MHz): δ 2.36 (s, 3H), 6.99 (m, 1H), 7.24 (d, 1H), 7.30 (m, 1H), 7.37 (t, 1H), 7.49 (d, 1H), 7.90 (m, 1H), 7.99 (d, 4H), 7.99 (d, 1H), 11.47 (s, 1H)

4-fluoro-2-((4'-methyl-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (35): ¹H NMR (C₂D₆OS, 600 MHz): δ 2.34 (s, 3H), 6.97 (m, 1H), 7.29 (t, 1H), 7.30 (d, 2H), 7.60 (d, 2H), 7.86 (d, 2H), 7.92 (d, 2H), 7.99 (d, 2H), 11.64 (br, 1H)

2-((4'-methoxy-[1,1'-biphenyl])-4-sulfonamido)-5-(trifluoromethyl)benzoic acid (37): ¹H NMR (C₂D₆OS, 600 MHz): δ 8.15 (d, 1H), 7.94 (d, 2H), 7.92 (dd, 1H), 7.84 (d, 2H), 7.72 (d, 1H), 7.67 (d, 2H), 7.03 (d, 2H), 3.80 (s, 3H)

5-methoxy-2-((4'-methoxy-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (38): ¹H NMR (C₂D₆OS, 600 MHz): δ 3.71 (s, 3H), 3.79 (s, 3H), 7.03 (d, 2H), 7.17 (d, 1H), 7.18 (d, 1H), 7.32 (s, 1H), 7.48 (d, 2H), 7.65 (d, 2H), 7.77 (d, 2H), 10.61 (br, 1H)

5-bromo-2-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (39): ¹H NMR (C₂D₆OS, 600 MHz): δ 7.51 (d, 1H), 7.54 (d, 2H), 7.73 (d, 2H), 7.76 (d, 1H), 7.89 (d, 2H), 7.90 (d, 2H), 7.97 (d, 1H), 11.1 (s, 1H)

2-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)-5-methoxybenzoic acid (40): ¹H NMR (C₂D₆OS, 600 MHz): δ 7.17 (d, 1H), 7.17 (d, 1H), 7.31 (d, 1H), 7.48 (d, 1H), 7.50 (d, 1H), 7.69 (d, 1H), 7.78 (d, 1H)

4'-chloro-N-(5-methoxy-2-(2H-tetrazol-5-yl)phenyl)-[1,1'-biphenyl]-4-sulfonamide (41): ¹H NMR (C₂D₆OS, 600 MHz): δ 3.77 (s, 3H), 6.90 (d, 1H), 7.06 (d, 1H), 7.52 (d, 2H), 7.70 (d, 2H), 7.80 (d, 1H)

2-((4'-chloro-[1,1'-biphenyl])-4-sulfonamido)-5-methylbenzoic acid (42): ¹H NMR (C₂D₆OS, 600 MHz): δ 3.6 (s, 3H), 7.44 (d, 1H), 7.52 (d, 1H), 7.71 (d, 1H)

5-fluoro-2-((4'-fluoro-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (43): ¹H NMR (C₂D₆OS, 600 MHz): δ 7.30 (t, 1H), 7.30 (d, 1H), 7.43 (d, 1H), 7.45 (dd, 1H), 7.55 (dd, 1H), 7.60 (d, 1H), 7.60 (d, 1H), 7.74 (d, 1H), 7.74 (d, 1H), 7.74 (d, 1H), 7.81 (d, 1H), 7.81 (d, 1H)

2-((4-cyclohexyl)sulfonamido)-5-(trifluoromethyl)benzoic acid (44): ¹H NMR (C₂D₆OS, 600 MHz): δ 1.21 (m, 1H), 1.35 (m, 4H), 1.67 (m, 1H), 1.75 (m, 4H), 2.58 (m, 1H), 7.44 (d, 2H), 7.66 (d, 1H), 7.82 (d, 2H), 7.87 (dd, 1H), 8.14 (d, 1H), 12.19 (br, 1H)

2-((4-cyclohexyl)sulfonamido)-5-fluorobenzoic acid (45): ¹H NMR (C₂D₆OS, 600 MHz): δ 1.21 (m, 1H), 1.33 (m, 4H), 1.67 (m, 1H), 1.73 (m, 4H), 2.55 (t, 1H), 7.40 (d, 2H), 7.45 (m, 1H), 7.45 (m, 1H), 7.54 (m, 1H), 7.61 (d, 1H), 7.61 (d, 1H), 7.68 (d, 2H), 10.94 (br, 1H)

5-fluoro-2-((4'-(trifluoromethyl)-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (46): ¹H NMR (C₂D₆OS, 600 MHz): δ 6.74 (dd, 1H), 7.12 (d, 1H), 7.12 (d, 1H), 7.34 (d, 1H), 7.36 (d, 1H), 7.44 (d, 1H), 7.46 (d, 1H), 7.47 (d, 1H), 7.55 (d, 1H), 7.56 (d, 1H), 7.59 (d, 1H), 7.61 (d, 1H), 7.69 (d, 1H), 7.78 (d, 1H), 7.84 (d, 2H)

4-fluoro-2-((4'-(trifluoromethyl)-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (47): ¹H NMR (C₂D₆OS, 600 MHz): 7.75 (d, 1H), 7.82 (d, 1H), 7.76 (1H, dd), 7.82 (1H, d), 7.90 (1H, d), 7.94 (1H, d), 8.10 (1H, d), 8.24 (1H, d), 8.61 (1H, d)

5-methyl-2-((4'-(trifluoromethyl)-[1,1'-biphenyl])-4-sulfonamido)benzoic acid (48): ¹H NMR (C₂D₆OS, 600 MHz): δ 7.36 (dd, 3H), 7.46 (d, 3H), 7.69 (d, 3H), 7.80 (d, 1H), 7.88 (d, 1H)
5-methoxy-2-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-sulfonamido)benzoic acid (49): $^1$H NMR (C$_2$D$_6$O, 600 MHz): δ 7.17 (d, 1 H), 7.17 (d, 1 H), 7.31 (d, 1 H), 7.48 (d, 1 H), 7.80 (d, 1 H), 7.88 (d, 1 H)

4-methyl-2-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-sulfonamido)benzoic acid (50): $^1$H NMR (C$_2$D$_6$O, 600 MHz): 5.11 (t, 1 H), 7.75 (d, 1 H), 7.80 (d, 1 H) 7.88 (d, 1 H), 8.10 (1H, d), 8.14 (1H, d), 8.68 (1H, d)

5-fluoro-2-((5,6,7,8-tetrahydronaphthalene)-2-sulfonamido)benzoic acid (51): $^1$H NMR (C$_2$D$_6$O, 600 MHz): δ 2.70 (d, 1 H), 7.19 (d, 1 H), 7.43 (dd, 1 H), 7.44 (d, 1 H), 7.50 (d, 1 H), 7.52 (d, 1 H), 7.59 (d, 1 H), 7.60 (d, 1 H)

5-fluoro-2-(naphthalene-2-sulfonamido)benzoic acid (52): $^1$H NMR (C$_2$D$_6$O, 600 MHz): 7.35 (1H, t), 7.49 (1H, d), 7.49 (1H, d), 7.54 (1H, d), 7.55 (1H, d), 7.61 (2H, d), 7.94 (1H, d), 8.03 (2H, dd)

4-fluoro-2-(naphthalene-2-sulfonamido)benzoic acid (53): $^1$H NMR (C$_2$D$_6$O, 600 MHz): 1.14 (t, 1 H), 4.23 (d, 1 H), 4.25 (d, 1 H), 4.26 (d, 1 H), 6.97 (d, 1 H), 7.09 (d, 1 H), 7.23 (d, 1 H), 7.25 (d, 1 H), 7.26 (d, 1 H), 7.52 (d, 1 H), 7.88 (d, 1 H), 8.88 (d, 1 H)

5-methyl-2-(naphthalene-2-sulfonamido)benzoic acid (54): $^1$H NMR (C$_2$D$_6$O, 600 MHz): 7.30 (dd, 1 H), 7.47 (d, 1 H), 7.65 (d, 1 H), 7.70 (dd, 1 H), 7.96 (d, 1 H), 8.04 (d, 1 H), 8.12 (d, 1 H)

2-((2,3-dihydrobenzo[b][1,4]dioxine)-6-sulfonamido)benzoic acid (55): $^1$H NMR (C$_2$D$_6$O, 600 MHz): 1.14 (t, 1 H), 4.23 (d, 1 H), 4.25 (d, 1 H), 4.26 (d, 1 H), 6.97 (d, 1 H), 7.09 (t, 1 H), 7.23 (d, 1 H), 7.25 (d, 1 H), 7.26 (d, 1 H), 7.52 (d, 1 H), 7.88 (d, 1 H), 8.88 (d, 1 H)

2-((2,3-dihydrobenzo[b][1,4]dioxine)-6-sulfonamido)-5-fluorobenzoic acid (56): $^1$H NMR (C$_2$D$_6$O, 600 MHz): δ 4.26 (d, 1 H), 4.26 (dd, 1 H), 6.97 (d, 1 H), 6.97 (d, 1 H), 7.45 (d, 1 H), 7.45 (d, 1 H), 7.50 (d, 1 H), 7.52 (d, 1 H), 7.60 (d, 1 H), 7.70 (d, 1 H)

2-((2,3-dihydrobenzo[b][1,4]dioxine)-6-sulfonamido)-5-fluorobenzoic acid (57): $^1$H NMR (C$_2$D$_6$O, 600 MHz): δ 4.26 (d, 1 H), 4.26 (d, 1 H), 6.95 (d, 1 H), 7.00 (d, 1 H), 7.22 (d, 1 H), 7.24 (d, 1 H), 7.29 (d, 1 H), 7.31 (d, 1 H), 7.31 (d, 1 H), 7.97 (d, 1 H), 7.97 (d, 1 H)

2-((2,3-dihydrobenzo[b][1,4]dioxine)-6-sulfonamido)-5-methylbenzoic acid (58): $^1$H NMR (C$_2$D$_6$O, 600 MHz): δ 4.22 (d, 1 H), 4.24 (d, 1 H), 4.25 (d, 1 H), 6.63 (d, 1 H), 6.95 (d, 1 H), 7.20 (d, 1 H), 7.22 (d, 1 H), 7.30 (dd, 1 H), 7.40 (d, 1 H), 7.47 (d, 1 H), 7.69 (d, 1 H)