Supporting Information

Incorporation of fluorinated pyridine in the side chain of 4-aminoquinolines: Synthesis, characterization and antibacterial activity

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General information

All the solvents and starting materials were obtained commercially (Merck). \(^1\)H NMR spectra were recorded at 300 MHz. \(^1^\)C NMR spectra were recorded at 75 MHz. \(^1^\)H NMR spectra were recorded at 282 MHz. IR spectra were recorded on a SHIMADZU-IR460 spectrometer in a KBr matrix. All melting points were obtained by Stuart Scientific apparatus. TLC monitored all reactions and all yields refer to overall isolated ones. TLC analysis was performed on silica gel TLC plates (Merck). Preparative Thin Layer Chromatography (Prep TLC) with plate dimensions: 20 cm x 20 cm, 2.5 mm SiO\(_2\) thickness was carried out with mixed solvents (EtOH/ethyl acetate).

General procedure for Reaction of perfluoropyrines with amino- and hydroxy-functionalized quinolines.

A mixture of perfluoropyrine (1 mmol) and hydroxy- or amine-functionalized quinoline (1 mmol) in the presence of K\(_2\)CO\(_3\) (3 mmol) at CH\(_3\)CN (10 mL) were stirred at room temperature for the indicated time. After completion reaction, the reaction mixture was poured into 10 ml of water. In cases that precipitate formed, it filtered off and dried. In other cases, the mixture was extracted with CH\(_2\)Cl\(_2\) (3\(\times\)10 ml), dried over MgSO\(_4\) and solvent evaporated. The crude product was obtained after purification with prep chromatography (EtOH/EtOAc) or recrystallization with EtOH.

7-chloro-N-(2-((perfluoropyridin-4-yl)oxy)ethyl)quinolin-4-amine (10a). This compound was obtained as white solid after 24 h reaction time and purification with plate chromatography (EtOH/EtOAc, 1:4); 0.30 g (81%); mp 179-182 °C; IR (KBr): \(\nu\)max 3250 (NH) cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\), 300 MHz): \(\delta\) 8.41 (d, 1H, J = 4.9 Hz, Ar-H), 8.19 (d, 1H, J = 9.1 Hz, Ar-H), 7.78 (s, 1H, Ar-H), 7.49 (s, 1H, NH), 7.45 (d, 1H, J = 9.0 Hz, Ar-H), 6.60 (d, 1H, J = 5.4 Hz, Ar-H), 4.80 (m, 2H, CH\(_2\)), 3.73 (m, 2H, CH\(_2\)); \(^1^\)C NMR (DMSO-d\(_6\), 75 MHz): \(\delta\) 151.8 (Ar-C), 149.8 (Ar-CH), 148.9 (Ar-C), 147.1 (m, C-4 py), 143.5 (dm, J = 236.3}
Hz, C-2,6 py), 134.5 (dm, J = 253.0 Hz, C-3,5 py), 133.5 (Ar-CH), 127.5 (Ar-CH), 124.3 (Ar-C), 123.8 (Ar-C), 117.4 (Ar-CH), 99.0 (Ar-CH), 72.1 (CH₂), 42.2 (CH₂); ¹⁹F NMR (DMSO-d₆, 282 MHz): δ -92.8 (m, 2F, F-2,6), -158.4 (m, 2F, F-3,5).

N¹-(7-chloroquinolin-4-yl)-N²-(perfluoropyridin-4-yl)ethane-1,2-diamine (10b). This compound was obtained as white solid after 12 h reaction time and recrystallization with EtOH; 0.32 g (86%); mp 237-240 °C; IR (KBr): ν max 3315, 3249 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 8.39 (d, 1H, J = 5.4 Hz, Ar-H), 8.15 (d, 1H, J = 9.0 Hz, Ar-H), 7.77 (s, 1H, Ar-H), 7.43 (d, 1H, J = 8.9 Hz, Ar-H), 7.40 (s, 2H, NH), 6.55 (d, 1H, J = 5.5 Hz, Ar-H), 3.67 (m, 2H, CH₂), 3.52 (m, 2H, CH₂); ¹³C NMR (DMSO-d₆, 75 MHz): δ 151.8 (Ar-C), 149.9 (Ar-Ch), 149.0 (Ar-C), 138.2 (m, C-py), 133.4 (Ar-CH), 127.5 (Ar-CH), 124.1 (Ar-C), 123.8 (Ar-C), 117.4 (Ar-CH), 98.6 (Ar-CH), 42.7 (CH₂), 42.1 (CH₂); ¹⁹F NMR (DMSO-d₆, 282 MHz): δ -96.8 (m, 2F, F-2,6), -163.2 (m, 2F, F-3,5).

N¹-(7-chloroquinolin-4-yl)-N⁴-(perfluoropyridin-4-yl)butane-1,4-diamine (10c). This compound was obtained as white solid after 15 h reaction time and recrystallization with EtOH; 0.34 g (85%); mp 170-173 °C; IR (KBr): ν max 3423, 3225 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 8.36 (d, 1H, J = 5.4 Hz, Ar-H), 8.23 (d, 1H, J = 9.0 Hz, Ar-H), 7.75 (s, 1H, Ar-H), 7.41 (d, 1H, J = 9.0 Hz, Ar-H), 7.39 (NH), 3.42 (2H, CH₂), 3.27 (2H, CH₂), 1.68 (4H, CH₂); ¹³C NMR (DMSO-d₆, 75 MHz): δ 151.9 (Ar-C), 150.0 (Ar-Ch), 149.1 (Ar-C), 133.4 (Ar-C), 127.5 (Ar-CH), 124.0 (Ar-CH), 123.9 (Ar-CH), 117.4 (Ar-C), 98.7 (Ar-CH), 43.5 (CH₂), 42.0 (CH₂), 27.7 (CH₂), 24.8 (CH₂); ¹⁹F NMR (DMSO-d₆, 282 MHz): δ -96.8 (m, 2F, F-2,6), -163.9 (m, 2F, F-3,5).

N¹-(7-chloroquinolin-4-yl)-N²-(3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-yl)ethane-1,2-diamine (11a). This compound was obtained as pale yellow solid after 12 h reaction time and purification with plate chromatography (EtOH/EtOAc, 1:10); 0.42 g (85%); mp 230-233 °C; IR (KBr): ν max 3456, 3204 (NH) cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 8.37 (d, 1H, J = 4.1 Hz, Ar-H), 8.14 (d, 1H, J = 9.0 Hz, Ar-H), 8.03 (d, 2H, J = 8.0 Hz, Ar-H), 7.85 (t, 1H, J = 7.8 Hz, Ar-H), 7.71-7.76 (4H, NH and Ar-H), 7.41 (d, 2H, J = 7.2 Hz, Ar-H), 6.60 (d, 1H, J = 5.3 Hz, Ar-H), 3.47 (m, 4H, CH₂); ¹³C NMR (DMSO-d₆, 75 MHz): δ 151.6 (Ar-C), 149.8 (Ar-Ch), 141.5 (Ar-C), 139.8 (Ar-C), 135.4 (Ar-Ch), 133.5 (Ar-CH), 130.0 (Ar-CH), 127.6 (Ar-Ch), 127.3 (Ar-CH), 124.2 (Ar-C), 124.0 (Ar-C), 41.0 (CH₂); ¹⁹F NMR (DMSO-d₆, 282 MHz): δ -91.6 (m, 1F, F-6), -137.9 (m, 1F, F-3), -161.8 (m, 1F, F-5).
N\textsuperscript{1}-(7-chloroquinolin-4-yl)-N\textsuperscript{4}-(3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-yl)butane-1,4-diamine (11b). This compound was obtained as pale yellow solid after 15 h reaction time and purification with plate chromatography (EtOH/EtOAc, 1:10); 0.42 g (81%); mp 114-117 °C; IR (KBr): v\textsubscript{max} 3383.6 (NH) cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (DMSO-d\textsubscript{6}, 300 MHz): δ 8.36 (d, 1H, J = 4.9 Hz, Ar-H), 8.26 (d, 1H, J = 9.1 Hz, Ar-H), 8.02 (d, 2H, J = 8.2 Hz, Ar-H), 7.79 (t, 1H, J = 7.7 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 7.66 (t, 2H, J = 7.4 Hz, Ar-H), 7.43 (d, 1H, J = 9.0 Hz, Ar-H), 7.34 (t, 1H, J = 5.2 Hz, NH), 6.75 (t, 1H, J = 5.3 Hz, NH), 6.46 (d, 1H, J = 5.5 Hz, Ar-H), 3.45 (m, 2H, CH\textsubscript{2}), 3.29 (m, 2H, CH\textsubscript{2}), 1.70 (4H, CH\textsubscript{2}); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 75 MHz): δ 151.8 (Ar-C), 150.0 (Ar-CH), 149.0 (Ar-C), 139.7 (Ar-C), 135.3 (Ar-), 133.4 (Ar-C), 129.9 (Ar-CH), 127.4 (Ar-CH), 124.1 (Ar-CH), 124.0 (Ar-CH), 117.4 (Ar-C), 98.7 (Ar-CH), 42.0 (CH\textsubscript{2}), 27.7 (CH\textsubscript{2}), 24.8 (CH\textsubscript{2}); \textsuperscript{19}F NMR (DMSO-d\textsubscript{6}, 282 MHz): δ -75.1 (m, 1F, F-6), -106.7 (m, 1F, F-3), -140.8 (m, 1F, F-5).

7-chloro-4-(4-(perfluoropyridin-4-yl)piperazin-1-yl)quinoline (12a). This compound was obtained as white solid after 8 h reaction time and recrystallization with EtOH; 0.36 g (91%); mp 207-210 °C; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz): δ 8.73 (d, 1H, J = 4.7 Hz, Ar-H), 8.12 (d, 1H, J = 8.9 Hz, Ar-H), 7.99 (s, 1H, Ar-H), 7.57 (d, 1H, J = 7.6 Hz, Ar-H), 7.07 (d, 1H, J = 4.8 Hz, Ar-H), 3.74 (4H, CH\textsubscript{2}), 3.31 (4H, CH\textsubscript{2}); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): δ 156.4 (Ar-C), 152.7 (Ar-CH), 150.1 (Ar-C), 134.1 (Ar-C), 128.6 (Ar-CH), 126.6 (Ar-CH), 126.4 (Ar-CH), 121.8 (Ar-C), 110.3 (Ar-CH), 52.4 (CH\textsubscript{2}), 50.1 (CH\textsubscript{2}). \textsuperscript{19}F NMR (DMSO-d\textsubscript{6}, 282 MHz): δ -94.9 (m, 2F, F-2,6), -153.8 (m, 2F, F-3,5).

7-chloro-4-(3,5,6-trifluoro-4-(phenylsulfonyl)pyridin-2-yl)piperazin-1-yl)quinoline (12b). This compound was obtained as pale yellow solid after 12 h reaction time and purification with plate chromatography (EtOH/EtOAc, 1:10); 0.45 g (87%); mp 168-171 °C; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz): δ 8.70 (d, 1H, J = 4.8 Hz, Ar-H), 8.05-8.14 (3H, Ar-H), 7.97 (s, 1H, Ar-H), 7.85 (t, 1H, J = 7.4 Hz, Ar-H), 7.73 (t, 2H, J = 7.5 Hz, Ar-H), 7.54 (d, 1H, J = 7.1 Hz, Ar-H), 7.01 (d, 1H, J = 5.0 Hz, Ar-H), 3.63 (4H, CH\textsubscript{2}), 3.26 (4H, CH\textsubscript{2}); \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 75 MHz): δ 156.0 (Ar-CH), 152.2 (Ar-C), 149.6 (Ar-C), 139.6 (Ar-C), 153.5 (Ar-C), 133.7 (Ar-CH), 130.1 (Ar-CH), 128.1 (Ar-CH), 127.7 (Ar-CH), 126.1 (Ar-CH), 125.9 (Ar-CH), 121.3 (Ar-C), 109.6 (Ar-CH), 51.2 (CH\textsubscript{2}), 47.1 (CH\textsubscript{2}); \textsuperscript{19}F NMR (DMSO-d\textsubscript{6}, 282 MHz): δ -88.6 (m, 1F, F-6), -127.8 (m, 1F, F-3), -152.2 (m, 1F, F-5).