Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting information for

Towards the improvement of the synthesis of novel 4(5)-aryl-5(4)-heteroaryl-2-thio-substituted imidazoles and their p38 MAP kinase inhibitory activity

Stefan Laufer* and Pierre Koch

Institute of Pharmacy, Department of Pharmaceutical and Medicinal Chemistry,

Eberhard-Karls-University Tübingen,

Auf der Morgenstelle 8, 72076 Tübingen, Germany.

Fax:+49 7071 295037; Tel: +49 7071 2972459;

E-mail: stefan.laufer@uni-tuebingen.de

Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Typical synthetic procedures and selected analytical data:

All commercially available reagents and solvents are used without further purification. Melting points were determined with a Büchi melting point B-545, IR data were determined with a Perkin-Elmer Spectrum One (ATR Technique), and ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) were determined with a Bruker Advance 200 and chemical shifts are reported in ppm and relative to the residual solvent peak.

tert-Butyl 4-methylpyridin-2-ylcarbamate (3)

To a solution of freshly distilled *tert*-butanol (450 mL) and di-*tert*-butyl dicarbonate (16.81 g, 77.0 mmol) was added slowly 2-amino-4-methylpyridine (7.57 g, 70.0 mmol). The mixture was stirred at room temperature for 3 d, the solvent was removed *in vacuo* and the residue was recrystallized from 2-propanol, affording 12.30 g (84%) of a colorless solid.

$C_{11}H_{16}N_2O_2$ (M_r 208.26); ^{1}H-NMR ($CDCl_3$) δ 1.53 (s, 9H, $C(CH_3)_3$), 2.34 (s, 3H, CH_3), 6.75 – 6.78 (m, 1H, C^5-H Pyr), 7.85 (s, 1H, 1H, C^3-H Pyr), 8.17 (d, J = 5.2 Hz, 1H, C^6-H Pyr), 9.40 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 21.4 (CH_3), 28.3 ($C(\underline{C}H_3)_3$), 80.6 ($\underline{C}(CH_3)_3$), 113.0, 119.1, 146.8 (C^6-Pyr), 150.0 (C^4-Pyr), 152.7, 153.0; IR (ATR) 3178, 2975 (CH_3), 1720, 1612, 1574, 1530, 1422, 1390, 1365, 1291, 1257, 1230, 1154, 1120, 1059, 995, 866, 816, 766, 743 cm^{-1}; ESI-HRMS: calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ 209.1285, obsd. 209.1285.

General procedure for the synthesis of *N*-alkyl/phenylalkyl-*N*-boc-4-methylpyrindin-2-amines (5a-d) (General procedure A)

To a solution of *tert*-butyl 4-methylpyridin-2-ylcarbamate **3** (1.0 equiv.) in dry DMF was added under an argon-atmosphere NaH (1.25 equiv., 60% oil dispersion) at 0 °C in such a manner that the temperature was kept below 5 °C. The reaction mixture was kept at 0 °C for 20 min followed by the addition of the alkyl-/phenylalkyl halides (1.15 equiv.) at the same temperature. After additional stirring at 0 °C for 30 min the mixture was allowed to warm to room temperature within 1 h. After stirring at room temperature for 1 h, H_2O and EtOAc were added. The organic layer was washed subsequently with HCl (0.1 M), sodium bicarbonate and brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was purified by flash chromatography.

2-(*N*-Boc-*N*-ethylamino)-4-methylpyridin-2-amine (5c)

Compound **5c** was prepared according to general procedure A from **3** (4.16 g, 20.0 mmol), NaH (1.00 g, 25.0 mmol, 60% oil dispersion), ethyl bromide (2.47 g, 22.7 mmol) and DMF (60 mL).

flash chromatography: SiO_2, petroleum ether/EtOAc 5:1

yield: 3.60 g (76%) of a colorless oil

$C_{13}H_{20}N_2O_2$ (M_r 236.31); ^{1}H-NMR ($CDCl_3$) δ ppm 1.03 (t, J = 7.0 Hz, 3H, CH_3), 1.33 (s, 9H, $C(CH_3)_3$), 2.11 (s, 3H, CH_3, Pyr), 3.78 (q, J = 7.0 Hz, 2H, CH_2), 6.59 – 6.62 (m, 1H, C^5-H Pyr), 7.28 (s, 1H, C^3-H Pyr), 8.01 – 8.03 (m, 1H, C^6-H Pyr); ^{13}C-NMR ($CDCl_3$) δ ppm 13.7 (CH_3), 20.5 (CH_3), 27.7 ($C(\underline{C}H_3)_3$), 41.4 (CH_2), 79.9 ($\underline{C}(CH_3)_3$), 119.6, 120.0, 146.6, 147.3, 153.5, 154.1; IR (ATR) 2976 (CH_3), 2932, 1702, 1603, 1564, 1477, 1448 (CH_3), 1411, 1387, 1366, 1316, 1272, 1252, 1178, 1143, 1118, 1104, 1084, 990, 875, 815, 771, 747 cm^{-1}; ESI-HRMS: calcd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237.1598, obsd. 237.1596.

General procedure for the synthesis of 2-(*N*-alkyl-*N*-boc-amino)-4-methylpyridine *via* Buchwald-Hartwig-reaction and Boc-protection (5e-h) (General procedure B)

2-Bromo-4-methylpyridine (1.0 equiv.), amine (1.2 equiv.) or corresponding hydrochlorides (1.2 equiv.), *t*-BuONa (1.4 equiv., or in case of hydrochlorides 2.4 equiv.), $Pd_2(dba)_3$ (0.02 equiv.), BINAP (0.04 equiv.) were dissolved in dry toluene under argon atmosphere. The mixture was heated to 70 °C or to reflux temperature until the disappearance of the starting material 2-bromo-4-methylpyridine (TLC-control: *n*-hexane/EtOAc 3:1 or 1:1). The mixture was allowed to cool to room temperature before *n*-hexane was added. The formed precipitate was filtered off and the filtrate concentrated to dryness. Once again, *n*-hexane was added to the residue and the precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford the crude product which was dissolved in dry DCM and subsequently treated with di-*tert*-butyl dicarbonate (2.5 equiv.) and DMAP (catalytic amounts). The reaction mixture was stirred for 16 h at room temperature and the solvent was removed *in vacuo*. *n*-Hexane was added to the residue, the precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography.

2-(*N*-Boc-*N*-isopropylamino)-4-methylpyridine (5g)

Compound **5g** was prepared according to general procedure B from 2-bromo-4-methylpyridine (2.00 g, 11.6 mmol), isopropylamine (0.83 g, 13.9 mmol), *t*-BuONa (1.56 g, 16.2 mmol), $Pd_2(dba)_3$ (0.20 g, 0.23 mmol), BINAP (0.29 g, 0.47 mmol), toluene (40 mL), di-*tert*-butyl dicarbonate (3.98 g, 18.2 mmol) and DCM (100 mL)

flash chromatography: SiO_2, from *n*-hexane/EtOAc 4:1 to *n*-hexane/EtOAc 2:1

yield: 0.84 g (29%, covering two steps) of a colourless solid

$C_{14}H_{22}N_2O_2$ (M_r 250.34); mp. 56.2 °C; ^{1}H-NMR ($CDCl_3$) δ 1.25 (dd, J_1 = 6.8 Hz, J_2 = 2.4, 6H, 2x CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 2.36 (s, 3H, CH_3, Pyr) 4.41 – 4.55 (m, 1H, CH), 6.97 – 7.02 (m, 2H, C^3-/ C^5-H Pyr), 8.34 (d, J = 5.1 Hz, 1H, C^6-H Pyr) ^{13}C-NMR ($CDCl_3$) δ 20.9 (CH_3), 21.3 (2x CH_3), 28.3 ($C(\underline{C}H_3)_3$), 49.5 (CH), 80.3 ($\underline{C}(CH_3)_3$), 122.6 (C^3-Pyr), 124.5 (C^5-Pyr), 147.6 (C^6-Pyr), 148.8 (C^4-Pyr), 153.8, 154.2; IR (ATR) 2975 (CH_3), 1684, 1597, 1555, 1477, 1422, 1388, 1367, 1337, 1282, 1257, 1169, 1091, 988, 904, 850, 767, 747 cm^{-1}; ESI-HRMS: calcd for $C_{14}H_{23}N_2O_2$ $[M+H]^+$ 251.1754, obsd 251.1754.

General procedure for the synthesis of the 2-(2-(boc(alkyl/phenylalkyl)amino)pyridin-4-yl)-1-(4-fluorophenyl)ethanones (6a-h) (General procedure C)

2-(*N*-alkyl/phenylalkyl-*N*-boc-amino)-4-methylpyridine (1.0 equiv.) and ethyl 4-fluorobenzoate (1.0 or 1.1 equiv.) were dissolved in dry THF under argon atmosphere. The solution was cooled to 0 °C and NaHMDS (2.0 equiv., 2 M in THF) was added dropwise. The mixture was allowed to stir at this temperature for 1 h and additional 2.5 h at room temperature. The reaction was quenched with saturated NH_4Cl solution, EtOAc was added and the mixture was extracted twice with water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography.

2-(2-(Boc(isopropyl)amino)pyridin-4-yl)-1-(4-fluorophenyl)ethanone (6g)

Compound **6g** was prepared according to general procedure C from **5g** (0.80 g, 3.2 mmol), ethyl 4-fluorobenzoate (0.54 g, 3.2 mmol), NaHMDS-solution (3.2 mL, 6.4 mmol), and THF (10 mL).

flash chromatography: SiO_2, from *n*-hexane/EtOAc 4:1 to *n*-hexane/EtOAc 7:3

yield: 0.82 g (69%) of a colorless solid.

$C_{21}H_{25}FN_2O_3$ (M_r 372.43); mp. 82.7 °C; ^{1}H-NMR ($CDCl_3$) δ 1.09 (d, J = 6.8 Hz, 6H, 2x CH_3), 1.24 (s, 9H, $C(CH_3)_3$), 4.12 (s, 2H, CH_2), 4.31 – 4.44 (m, 1H, CH), 6.88 – 7.01 (m, 4H, C^3/ C^5-H Pyr + C^3-/C^5-H 4-F-Ph), 7.83 – 7.90 (m, 2H, C^2-/C^6-H 4-F-Ph), 8.23 (d, J = 5.1 Hz, 1H, C^6-H Pyr); ^{13}C-NMR ($CDCl_3$) δ 20.9 (2x CH_3), 27.8 ($C(\underline{C}H_3)_3$), 43.9 (CH_2), 49.0 (CH), 79.8 ($\underline{C}(CH_3)_3$), 115.6 (d, J = 21.9 Hz, C^3-/ C^5-4-F-Ph), 122.1 (C^3-Pyr), 124.3 (C^5-Pyr), 130.7 (d, J = 9.4 Hz, C^2/ C^6 4-F-Ph), 132.2 (d, J = 3.1 Hz, C^1 4-F-Ph), 144.1, 147.8 (C^6-Pyr), 153.7, 154.1, 165.5 (d, J = 254.1 Hz, C^4 4-F-Ph), 193.7 (CO); IR (ATR)

2976 (CH_3), 1689, 1672 (CO), 1602, 1558, 1507, 1421, 1389, 1368, 1335, 1280, 1215, 1156, 1090, 998, 909, 847, 770 cm^{-1}; ESI-HRMS: calcd for $C_{21}H_{26}FN_2O_3$ $[M+H]^+$ 373.1922, obsd. 373.1921.

General procedure for the preparation of 2-(2-(boc(alkyl/phenylalkyl)amino)pyridin-4-yl)-1-(4-fluorophenyl)ethan-1,2-dion-2-oximes (7a-h) (General procedure D)

A solution of 1-(4-fluorophenyl)-2-(2-(alkyl/phenylalkyl(boc)amino)pyridin-4-yl)ethanone (1.0 equiv.) in glacial acetic acid was cooled to 10 °C and a solution of $NaNO_2$ (3.0 equiv. in water (only as much water as necessary to obtain a clear solution)) was added dropwise. The reaction was allowed to warm to room temperature while stirring for 2.5 h. Water and EtOAc were added and the mixture was extracted with sodium bicarbonate several times. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. After drying at the oil pump the oximes were obtained as foams which were used without purification for the next reaction.

2-(2-(Boc(isopropyl)amino)pyridin-4-yl)-1-(4-fluorphenyl)ethan-1,2-dion-2-oxime (7g)

Compound **7g** was prepared according to general procedure D from **6g** (2.14 g, 5.8 mmol), $NaNO_2$ (1.19 g, 17.3 mmol in 20 mL water), and glacial acetic acid (50 mL).
yield: 1.68 g (crude product)

General procedure for the preparation of 2-amino-2-(2-(1-alkyl/phenylalkylamino)pyridin-4-yl)-1-(4-fluorophenyl)ethanone hydrochlorides (8a-h) (General procedure E)

In a three-necked flask 2-(2-(boc(alkyl/phenylalkyl)amino)pyridin-4-yl)-1-(4-fluorophenyl)ethan-1,2-dion-2-oxime was dissolved in methanol and saturated methanolic hydrogen chloride. Pd/ C 10% was added. The reaction flask was evacuated and flooded with hydrogen (4x). The suspension was stirred under hydrogen atmosphere at atmospheric pressure for 16 h. The catalyst was filtered off and washed thoroughly with methanol. The filtrate was concentrated *in vacuo*. The crude product was used without further purification for the next step.

2-Amino-1-(4-fluorophenyl)-2-(2-(isopropylamino)pyridin-4-yl)ethanone hydrochloride (8g)

Compound **8g** was prepared according to general procedure E from **7g** (1.68 g, 4.1 mmol), Pd/C 10% (0.45 g), methanol (15 mL) and saturated methanolic hydrogen chloride (25 mL).
yield: 1.90 g (crude product)

General procedure for the preparation of 5-(2-(1-alkyl/phenylalkylamino)pyridin-4-yl)-4-(4-fluorophenyl)-1,3-dihydroimidazol-2-thiones (9a-h) (General procedure F)

2-Amino-2-(2-(1-phenylalkylamino)pyridin-4-yl)-1-(4-fluorophenyl)ethanone hydrochloride (1.0 equiv.) was dissolved in absolute DMF and potassium thiocyanate (1.3 equiv.) was added. The reaction mixture was heated to reflux temperature for 3 h. The suspension was cooled to room temperature and slowly diluted with water. The yellow precipitate was filtered off and washed with water.

4-(4-Fluorophenyl)-5-(2-(isopropylamino)pyridin-4-yl)-1,3-dihydroimidazol-2-thione (9g)

Compound **9g** was prepared according to general procedure F from **8g** (1.90 g), KSCN (0.52 g, 5.4 mmol), DMF (60 mL) and water (450 mL).

yield: 1.04 g (55% over 3 steps) as a yellow solid

$C_{17}H_{17}FN_4S$ (M_r 328.41); ^{1}H-NMR (DMSO-d_6) δ 1.09 (d, J = 6.4 Hz, 6H, 2x CH_3), 3.75 – 3.92 (m, 1H, CH), 6.31 – 6.37 (m, 3H, C^5-H Pyr + C^3-H Pyr + NH, exchangeable), 7.19 (m, 2H, C^3-/C^5-H 4-F-Ph), 7.39 – 7.47 (m, 2H, C^2-/C^6-H 4-F-Ph), 7.87 (d, J = 5.2 Hz, 1H, C^6-H Pyr), 12.57 – 12.59 (m, 2H, 2x NH, exchangeable); ^{13}C-NMR (DMSO-d_6) δ 22.5 (CH_3), 41.7 (CH), 104.8 (C^3-Pyr), 109.1 (C^5-Pyr), 115.7 (d, J = 21.7 Hz, C^3-/ C^5-4-F-Ph), 123.1 (d, J = 0,5 Hz, imid.), 124.8 (d, J = 3.1 Hz, C^1 4-F-Ph), 125.3 (imid.), 130.4 (d, J = 8.5 Hz, C^2-/ C^6-4-F-Ph), 136.2 (C^4-Pyr), 148.1 (C^6-Pyr), 158.5 (C^2-Pyr), 161.5 (C=S), 162.0 (d, J = 244.4 Hz, C^4-4-F-Ph); IR (ATR) 3393, 3050, 2970 (CH_3), 2899, 1610, 1545, 1506 (C(S)NH), 1466, 1441(CH_3), 1385 (CH_3), 1299, 1269, 1224 (C-F), 1178, 1162, 989, 840 (Ar), 813 cm^{-1}; ESI-HRMS: calcd for $C_{17}H_{18}FN_4S$ $[M+H]^+$ 329.1231, obsd 329.1232.

General procedure for the synthesis of the title compounds (General procedure G)

To a solution of 5-(2-(alkyl/phenylalkylamino)pyridin-4-yl)-4-(4-fluorphenyl)-1,3-dihydroimidazol-2 thiones (1.0 equiv.) and *t*-BuOK (1.1 or 1.2 equiv.) in dry MeOH was added under argon atmosphere the appropriate alkylhalide (1.1 or 1.2 equiv.). The solution was heated to 55 °C or reflux temperature until complete disappearance of the starting material (thiones) and cooled to room temperature. After extraction with water and EtOAc the organic phase was washed twice with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash chromatography or by crystallization.

3-(4-(4-Fluorophenyl)-5-(2-(isopropylamino)pyridin-4-yl)-1*H*-imidazol-2-ylthio)propane-1,2-diol (10g)

Compound **10g** was prepared according to general procedure G from **9g** (100 mg, 0.30 mmol), *t*-BuOK (34 mg, 0.33 mmol), 3-bromopropane-1,2-diol (52 mg, 0.33 mol) and MeOH (8 mL).

reaction time: 3.5 h at 55 °C

flash chromatography: SiO_2, from DCM/EtOH 95:5 to DCM/EtOH 75:25

yield: 70 mg (59%)

$C_{20}H_{23}FN_4O_2S$ (M_r 402.49); ^{1}H-NMR (CD_3OD) δ 1.15 (d, J = 6.3 Hz, 6H, 2x CH_3), 3.13 – 3.37 (m, CH_2 + solvent peak), 3.62 – 3.65 (m, 2H, CH_2), 3.75 – 3.91 (m, 2H, 2x CH), 6.51 – 6.53 (m, 2H, C^3-/ C^5-H Pyr), 7.10 - 7.19 (m, 2H, C^3-/ C^5-H 4-F-Ph), 7.43 – 7.50 (m, 2H, C^2-/C^6-H 4-F-Ph), 7.80 – 7.82 (m, 1H, C^6-H Pyr); ^{13}C-NMR (CD_3OD) δ 20.0 (2x CH_3), 35.2 (CH_2), 40.6 (CH), 61.1 (CH_2), 68.7 (CH), 104.1 (C^5-Pyr), 108.2 (C^3-Pyr), 113.6 (d, J = 21.7 Hz, C^3/ C^5 4-F-Ph), 128.5 (d, J = 8.2 Hz, C^2/ C^6 4-F-Ph), 140.7 (C^4-Pyr), 145.0 (C^6-Pyr), 156.9 (C^2-Pyr), 161.0 (d, J = 244.2 Hz, C^4 4-F-Ph); IR (ATR) 3340, 2974 (CH_3), 2932, 1607, 1577, 1530, 1500, 1455, 1417, 1385 (CH_3), 1221 (C-F), 1129, 1091, 1073, 999, 988, 904, 840 (Ar), 813, 735, 722, 680 cm^{-1}; ESI-HRMS: calcd for $C_{20}H_{24}FN_4O_2S$ $[M+H]^+$ 403.1599, obsd 403.1598.