Electronic supplementary information (ESI) for

An optimized and versatile synthesis to pyridinylimidazole-type p38α mitogen activated protein kinase inhibitors

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General information and Instrumentation:

All reagents and solvents were of commercial quality and utilized without further purification.

The purity of all final compounds are > 95% as determined via reverse phase high performance liquid chromatography (HPLC) on a Hewlett Packard HP 1090 Series II LC equipped with a UV diode array detector (DAD, detection at 230 nm and 254 nm). The chromatographic separation was performed on a Phenomenex Luna 5u C8 column (150 mm x 4.6 mm, 5 μm) at 35 °C oven temperature. The injection volume was 5 μL and the flow 1.5 mL / min using the following gradient: 0.01 M KH₂PO₄, pH 2.30 (Solvent A), Methanol (Solvent B), 40% B to 85% B in 8 min; 85% B for 5 min; 85% to 40% B in 1 min; 40% B for 2 min; stop time 16 min.

TLC reaction controls were performed for all reactions using fluorescent silica gel 60 F₂₅₄ plates (Merck) and visualized under natural light and UV illumination at 254 and 365 nm.

Column chromatography was performed on Davisil LC60A 20-45 micron silica from Grace Davison and Geduran Si60 63-200 micron silica from Merck for the pre-column using an Interchim PuriFlash 430 automated flash chromatography system.

NMR spectra were measured on a Bruker Avance NMR spectrometer at 250 MHz in the Organic Chemistry Institute, Eberhard Karls Universität Tübingen, Germany, on a Bruker Avance 200 NMR spectrometer or Bruker Avance 400 NMR spectrometer in Institute of Pharmaceutical Sciences, Eberhard Karls Universität Tübingen, Germany. Chemical shifts are reported in parts per million relative to TMS. All spectra were calibrated against the (residual proton) peak of the deuterated solvent that has been used. Mass spectra were obtained from the mass spectrometry department, Eberhard Karls Universität Tübingen, Germany.

The optical rotation data were obtained on a Perkin-Elmer polarimeter model 241 (589 nm).
Schemes S1-S7:

**Scheme S1:** Synthesis of 4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12).

Reagents and conditions: (i) NaHMDS, ethyl 4-fluorobenzoate, THF, 0 °C – r.t.; (ii) NaNO₂, acetic acid, 10 °C – r.t.; (iii) Pd/C 10%, IsOH/HCl, H₂, atmospheric pressure, r.t.; (iv) KSCN, MeOH, reflux temperature, 1.5 h.

**Scheme S2:** Synthesis of (R)-2-((4-(4-fluorophenyl)-5-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S2).

Reagents and conditions: (i) (R)-(−)-3-methyl-2-butylamine 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.

**Scheme S3:** Synthesis of (S)-2-((4-(4-fluorophenyl)-5-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S4).

Reagents and conditions: (i) (S)-(−)-3-methyl-2-butylamine, 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.
**Scheme S4:** Synthesis of 2-((4-(4-Fluorophenyl)-5-(2-(((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S6).

Reagents and conditions: (i) 1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 1.25 M HCl/EtOH, 3 h, r.t.

**Scheme S5:** Synthesis of 3-((4-(4-Fluorophenyl)-5-(2-(((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)propane-1,2-diol (S8).

Reagents and conditions: (i) 1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.

**Scheme S6:** Synthesis of (R)-3-((4-(4-Fluorophenyl)-5-(2-(((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)propane-1,2-diol (S10).

Reagents and conditions: (i) (R)-(+)1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.
**Scheme S7:** Synthesis of (S)-3-((4-(4-Fluorophenyl)-5-((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)propane-1,2-diol (S12).

Reagents and conditions: (i) (S)-(-)-1-phenyl-ethylamine, 160 °C, 16 h, sealed tube; (ii) 2 M aq HCl, 3 h, r.t.
General procedure for the introduction of an amino moiety at the pyridine C²-position via nucleophilic aromatic substitution (General Procedure A)

The 2-fluoropyridinyl-containing compound and the corresponding amine were stirred in a 10 cm³ pressure glass tube for 16 h at 160 °C. After cooling to r.t., the solvent was removed and the residue was purified by flash chromatography (SiO₂, dichloromethane-ethanol 95-5) to afford a light brown solid of the pure product.

General procedure for the cleavage of the THP-protecting group or the acetal protecting group (General Procedure B)

In a round flask the THP or acetal-protected alcohol (0.07 – 0.34 mmol) was dissolved in 4 mL of 1.25 M HCl/ethanol or 2 M aq. HCl. The reaction mixture was stirred for 3 h at r.t. The solvent was removed and the residue was purified by flash chromatography (SiO₂, dichloromethane-ethanol 99-1 to 9-1).

1-(4-Fluorophenyl)-2-(fluoropyridin-4-yl)ethanone (S13)

2-Fluoro-4-methylpyridine (4.40 g, 40 mmol) and ethyl 4-florobenzoate (6.73 g, 40 mmol) were treated with THF (10 ml) and cooled to 0 °C. NaHMDS (40.0 mL, 80 mmol, 2 M in THF) was added dropwise and the reaction mixture was stirred for 2 h at 0 °C and 1 h at r.t. Ethyl acetate followed by 10% aq. HCl were added. The organic layer was washed twice with 10% aq. HCl. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford 8.81 g (94%) of S13 as a colorless solid.

Spectroscopic data were in agreement with those in the literature.¹,²

1-(4-Fluorophenyl)-2-(fluoropyridin-4-yl)ethan-1,2-dion-2-oxime (S14)

A solution of ethanone S13 (1.35 g, 5.8 mmol) in glacial acetic acid was cooled to 10 °C and a solution of NaNO₂ (1.21 g, 17.5 mmol) in water (7 mL) was added dropwise. The reaction was stirred for 30 min at 10 °C and warmed to r.t. while the product precipitates as a colorless solid. Water (80 mL) was added, the precipitate was filtered and dried in vacuo.

Yield: 1.47 g (97%), colorless solid

Spectroscopic data were in agreement with those in the literature.¹,²
2-Amino-1-(4-fluorophenyl)-2-(4-fluoropyridin-4-yl)ethanone hydrochloride (S15)

In a three-necked flask oxime S14 (2.01 g, 77 mmol) was dissolved in isopropanol (20 mL) and saturated isopropanolic hydrogen chloride (25 mL). Pd/C 10% (0.35 g) was added. The reaction flask was evacuated and flooded with hydrogen (4-times). The suspension was agitated at r.t. under hydrogen atmosphere at atmospheric pressure for 6 h. The catalyst was filtered off and washed thoroughly with methanol. The filtrate was concentrated in vacuo to yield 2.20 g (100%) of S15 as a yellow solid.

Spectroscopic data were in agreement with those in the literature.1,2

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12)

α-Aminoketone S15 (0.43 g, 1.5 mmol) was dissolved in methanol (15 mL) and potassium thiocyanate (0.30 g, 3.1 mmol) was added. The reaction mixture was heated to reflux temperature for 1.5 h. The suspension was cooled to room temperature. The formed yellow precipitate was filtered off and washed with ethanol and acetone.

Yield: 0.27 g (62%), yellow solid

Spectroscopic data were in agreement with those in the literature.2

2-((4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1H-imidazol-2-yl)thio)ethyl acetate (16)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12) (1.07 g, 3.68 mmol) in DMF (30 mL) was placed in a round flask. Cs₂CO₃ (1.00 g, 3.07 mmol) was added followed by 2-bromoethylester (510 µL, 4.60 mmol) at 25 °C. The reaction mixture was further heated for 30 min at 55 °C. Water (10 ml) was added and the contents were extracted with ethyl acetate (3 x 15 mL). The combined organic extract was dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by flash chromatography (SiO₂, hexane-ethyl acetate 6-4) to afford 1.0 g (71%) of a white solid product.

1H NMR (400 MHz, DMSO-d₆): δ 1.97 (s, 3H, CH₃), 3.41 (t, J = 4.8 Hz, 2H, CH₂), 4.32 (t, J = 4.5 Hz, 2H, CH₂), 7.10 (s, 1H, C³-H Pyr), 7.15 – 7.40 (m, 3H, C⁵-H Pyr, C³/C⁵-H, 4-F-Phe), 7.45 – 7.60 (m, 2H, C²/C⁶-H, 4-F-Phe), 8.10 (s, 1H, C⁶-H Pyr), 12.97 (br. s, 1H, NH).

13C NMR (100 MHz, DMSO-d₆): δ 20.4 (CH₃), 31.1 (CH₂), 62.8 (CH₂), 104.7 (d, J = 40.5 Hz, C³ Pyr), 115.8 (d, J = 25.1 Hz, C³/C⁵ 4-F-Phe), 118.4 (C⁵ Pyr), 126.2 (C⁵ Imid.), 130.1 (C⁴ 4-F-Phe), 130.9 (d, J = 7.7 Hz, C²/C⁶ 4-F-Phe), 131.3 (C⁴ Imid.), 133.2 (C² Imid.), 140.8 (C⁴ Pyr), 160.1 (d, J = 248.7 Hz, C⁴ 4-F-Phe), 162.43 (d, J = 235.0 Hz, C² Pyr), 170.0 (C=O).

EI/MS, m/z (C₁₈H₁₅F₁₂N₃O₂S) calcd, 375.09 [M⁺]; found, 375.1.
4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridine-4-yl)-1,3-dihydro-2H-imidazol-2-one (15)

Compound 16 (100 mg, 0.27 mmol) and 3-methylbutyl-2-amine (614 µL, 5.33 mmol) were stirred in a pressure glass tube for 10 h at 160 °C. After cooling to r.t., the solvent was removed and the residue was purified by flash chromatography (SiO₂, dichloromethane-ethanol 95:5) to afford 55 mg (61%) of a yellow solid.

1H NMR (250 MHz, DMSO-d₆): δ 0.81 (d, J = 5.1 Hz, 3H, CH₃), 0.84 (d, J = 5.4 Hz, 3H, CH₃), 0.98 (d, J = 6.6 Hz, 3H, CH₃), 1.64 – 1.79 (m, 1H, CH), 3.53 – 3.73 (m, 1H, CH), 6.22 (d, J = 8.5 Hz, 1H, NH), 6.29 (d, J = 5.4 Hz, 1H, C⁵-H Pyr), 6.34 (s, 1H, C³-H Pyr), 7.12 – 7.28 (m, 2H, C²/C⁵-H 4-F-Phe), 7.34 – 7.47 (m, 2H, C²/C⁶-H 4-F-Phe), 7.81 (d, J = 5.13 Hz, 1H, C⁶-H Pyr), 10.56 (br. s, 1H, NH), 10.65 (br. s, 1H, NH).

13C NMR (100 MHz, DMSO-d₆): δ 16.4 (CH₃), 17.8 (CH₃), 19.3 (CH₃), 31.9 (CH), 50.8 (CH), 104.2 (C³ Pyr), 108.8 (C⁵ Pyr), 115.5 (d, J = 20.0 Hz, C³/C⁵ 4-F-Phe), 116.4 (C³ Imid.), 119.1 (C⁴ Imid.), 126.4 (d, J = 3.4 Hz, C¹ 4-F-Phe), 129.8 (d, J = 10.0 Hz, C²/C⁶ 4-F-Phe), 137.8 (C⁴ Pyr), 147.8 (C⁶ Pyr), 154.0 (C²-Pyr), 158.9 (C=O), 160.4 (d, J = 243.1 C⁴ 4-F-Phe).

EI-MS, m/z (C₁₉H₂₁FN₄O) calcd, 340.17 [M⁺]; found, 340.3.

2-Fluoro-4-(4-(4-fluorophenyl)-2-((2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)pyridine (17)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12) (500 mg, 1.73 mmol) and sodium tert-butoxide (182 mg, 1.90 mmol) were suspended in MeOH abs. (10 mL). 2-(2-Bromothoxy)-tetrahydro-2H-pyran (314 µL, 2.07 mmol) was added. The reaction mixture was heated for 30 min at 50 °C. After cooling to r.t., the solvent was removed. Water (10 mL) was added and the contents were extracted with ethyl acetate (3 x 10 mL). The combined organic extract was dried over anhydrous Na₂SO₄. The solvent was evaporated. The crude product was purified by flash chromatography (SiO₂, hexane-ethyl acetate 65:35) to afford 480 mg (67%) of a white solid product.

1H NMR (400 MHz, DMSO-d₆): δ 1.28 – 1.52 (m, 4H, 2 x CH₂), 1.53 – 1.77 (m, 2H, CH₂), 3.15 – 3.40 (m, 3H, CH₂ + CHH), 3.63 – 3.83 (m, 2H, CH₂), 3.86 – 3.99 (m, 1H, CHH), 4.62 (s, 1H, CH), 7.09 (s, 1H, C³-H Pyr), 7.14 – 7.40 (m, 3H, C⁵-H Pyr, C³/C⁵ 4-F-Phe), 7.41 – 7.62 (m, 2H, C²/C⁶-H 4-F-Phe), 8.07 (s, 1H, C⁶-H Pyr), 12.91 (s, 1H, NH).

13C NMR (100 MHz, DMSO-d₆): δ 18.9 (CH₂), 25.0 (CH₂), 30.1 (CH₃), 32.3 (CH₂), 61.3 (CH₂), 65.9 (CH₂), 97.8 (CH), 104.8 (d, J = 40.5 Hz, C³ Pyr), 115.9 (d, J = 20.6 Hz, C³/C⁵ 4-F-Phe), 118.5 (C⁵ Imid.), 131.0 (C⁴ Imid.), 141.6 (C² Imid.), 147.7 (C⁴ Pyr), 161.0 (d, J = 243.0 Hz, C⁴ 4-Fe-Phe), 162.5 (d, J = 232.6, C² Pyr).
HPLC: t = 7.82 min, purity: 99% (λ = 254 nm), t = 7.82 min, purity: 95% (λ = 230 nm).

EI-MS, m/z (C_{21}H_{21}F_{2}N_{3}O_{2}S) calcd, 417.13 [M]^+; found, 417.0.

4-(4-(4-Fluorophenyl)-2-((2-(tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(3-methylbutan-2-yl)pyridin-2-amine (18)

Compound 18 was prepared according to general procedure A starting from compound 17 (200 mg, 0.48 mmol) and 3-methylbutyl-2-amine (1.1 mL, 9.58 mmol).

Yield: 179 mg (77%) of a light brown solid.

\(^1\)H NMR (250 MHz, DMSO-\(d_6\)): δ 0.83 (t, \(J = 6.1\) Hz, 6H, 2 x CH\(_3\)), 0.99 (d, \(J = 6.6\) Hz, 3H, CH\(_3\)), 1.28 – 1.49 (m, 4H, 2 x CH\(_2\)), 1.49 – 1.84 (m, 3H, CH\(_2\) + CH), 3.24 – 3.38 (m, 3H, CH\(_2\) + C\(_5\)H), 3.59 – 3.76 (m, 3H, CH\(_2\) + CH\(_2\)), 3.77 – 3.94 (m, 1H, CH), 4.60 (br. s, 1H, CH), 6.12 – 6.33 (m, 1H, NH), 6.37 (m, 1H, C\(^{3}\)/C\(^{5}\) Pyr), 6.65 (br. s, 1H, C\(^{3}\)/C\(^{5}\) Pyr), 7.04 – 7.36 (m, 2H, C\(^{3}\)/C\(^{5}\) 4-F-Phe), 7.36 – 7.58 (m, 2H, C\(^{3}\)/C\(^{5}\) 4-F-Phe), 7.71 – 7.95 (m, 1H, C\(^{6}\) Pyr), 12.65 (br. s, 1H, NH).

\(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): δ 16.5 (CH\(_3\)), 17.8 (CH\(_3\)), 18.9 (CH\(_2\)), 19.2 (CH\(_2\)), 24.9 (CH\(_2\)), 30.1 (CH\(_2\)), 31.9 (CH), 32.4 (CH\(_2\)), 50.6 (CH), 61.2 (CH\(_2\)), 65.9 (CH\(_2\)), 97.8 (CH), 105.2 (C\(^{3}\) Pyr), 109.2, 109.6 (C\(^{5}\) Pyr), 114.9 (d, \(J = 26.9\) Hz), 115.5 (d, \(J = 30.5\) Hz, C\(^{3}\)/C\(^{5}\) 4-F-Phe), 126.7, 126.9 (C\(^{5}\) Imid.), 129.2 (d, \(J = 8.15\) Hz), 130.5 (d, \(J = 8.15\) Hz, C\(^{2}\)/C\(^{6}\) 4-F-Phe), 131.1 (C\(^{1}\) 4-F-Phe), 135.4, 137.5 (C\(^{4}\) Imid.), 140.2, 140.8, 142.3 (C\(^{2}\) Imid.), 147.0, 147.9 (C\(^{6}\) Pyr), 158.8 (C\(^{2}\) Pyr), 160.5 (d, \(J = 254.4\) Hz, C\(^{4}\) 4-F-Phe).

\(^{13}\)C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 5.13 min, purity: 100% (λ = 254 nm), t = 5.13 min, purity: 98% (λ = 230 nm).

FABMS, m/z (C\(_{26}\)H\(_{33}\)FN\(_{4}\)O\(_{2}\)S) calcd, 485.23 [M + H]^+; found, 485.3.

2-(4-(4-Fluorophenyl)-5-(2-(3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (3)

Compound 3 was prepared according to general procedure B starting from compound 18 (74 mg, 0.15 mmol) using 1.25 M HCl/ethanol.

Yield: 61 mg (100%) of a light yellow solid.

Spectroscopic data were in agreement with those in the literature.

HPLC: t = 5.13 min, purity: 100% (λ = 254 nm), t = 5.13 min, purity: 100% (λ = 230 nm).
4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(fluorophenyl)-1H-imidazol-5-yl)-2-fluoropyridine (19)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12) (500 mg, 1.73 mmol) and sodium tert-butoxide (182 mg, 1.90 mmol) were suspended in MeOH abs. (10 mL). 3-Bromo-1,2-propanediol (181.5 µL, 2.07 mmol) was added. The reaction mixture was heated for 1 h at 70 °C, the solvent was removed. Water (10 mL) was added and the contents were extracted with ethyl acetate (3 x 10 ml). The combined organic extract was dried over anhydrous Na₂SO₄. The solvent was evaporated to form compound 13b as a crude product which was used for the next step without any further purification. Compound 13b was dissolved in acetone 50 mL and p-toluenesulfonic acid monohydrate (15.71 mg, 0.08 mmol) was added. The reaction mixture was refluxed 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (SiO₂, dichloromethane-ethanol 95-5) to afford 400 mg (57%) of a white solid product.

¹H NMR (400 MHz, DMSO-δ6): δ 1.27 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 3.20 - 3.52 (m, 2H, CH₂), 3.65 - 3.85 (m, 1H, CH), 4.00 - 4.12 (m, 1H, CH₃), 4.32 - 4.43 (m, 1H, CH), 7.09 (s, 1H, C₅-H Pyr), 7.17 - 7.41 (m, 3H, C₅-H Pyr + C⁵⁻C⁵-H 4-F-Phe), 7.45 - 7.62 (m, 2H, C²/C⁶-H 4-F-Phe), 8.10 (s, 1H, C⁶-H Pyr), 12.94 (s, 1H, NH).

¹³C NMR (100 MHz, DMSO-δ6): δ 25.4 (CH₃), 26.7 (CH₃), 35.5 (CH₂), 54.8 (C(CH₃)₂), 67.7 (CH₂), 74.4 (CH), 104.9 (d, J = 40.4 Hz, C⁵-Pyr), 108.8 (C⁵ Imid.), 115.8 (d, J = 21.1 Hz, C⁵ 4-F-Phe), 118.5 (C⁶ Pyr), 128.0 (C¹ 4-F-Phe), 130.8 (d, J = 5.8 Hz, C⁵/C⁶ 4-F-Phe), 133.0 (C⁴ Imid.), 146.2 (C⁴ Pyr), 147.6 (d, J = 13.9 Hz, C⁵ Pyr), 160.9 (d, J = 249.4 Hz, C⁴ 4-F-Phe), 162.5 (d, J = 232.8 Hz, C² Pyr).

HPLC: t = 7.47 min, purity: 98% (λ = 254 nm), t = 7.47 min, purity: 98% (λ = 230 nm).

EIMS, m/z (C₂₀H₁₉F₂N₃O₂S) calcd, 403.12 [M⁺]; found, 403.1.

4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(fluorophenyl)-1H-imidazol-5-yl)-N-(3-methylbutan-2-yl)pyridin-2-amine (20)

Compound 20 was prepared according to general procedure A starting from compound 19 (100 mg, 0.25 mmol) and 3-methylbutyl-2-amine (571 µL, 4.96 mmol).

Yield: 99 mg (85%) of a light brown oily product.

¹H NMR (250 MHz, CDCl₃): δ 0.87 (d, J = 6.8 Hz, 6H, 2 x CH₃), 1.04 (d, J = 6.6 Hz, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 1.61 - 1.79 (m, 1H, CH), 3.24 (d, J = 5.6 Hz, 2H, CH₂), 3.38 (br. s, 1H, CH), 3.80 (dd, J = 8.5, 6.8 Hz, 1H, CH), 4.14 (dd, J = 8.5, 6.1 Hz, 1H, CH), 4.48 (q, J = 5.9 Hz, 1H, CH), 6.20 - 6.71 (m, 2H, C³/C⁵⁻H Pyr), 6.79 - 7.15 (m, 2H, C³/C⁵⁻H 4-F-Phe), 7.44 (br. s, 2H, C²/C⁶⁻H 4-F-Phe), 7.89 (br. s, 1H, C⁶⁻H Pyr).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 16.8 (CH$_3$), 17.6 (CH$_3$), 18.7 (CH$_3$), 25.4 (CH$_3$), 26.7 (CH$_3$), 32.5 (CH), 36.7 (CH$_2$), 52.3 (CH), 57.9 (C(CH$_3$)$_2$), 68.3 (CH$_2$), 75.6 (CH), 103.8 (C$^3$ Pyr), 109.8 (C$^5$ Imid.), 110.5 (C$^6$ Pyr.), 115.4 (d, J = 21.7 Hz, C$^3$/C$^5$ 4-F-Phe), 130.12 (d, J = 7.9 Hz, C$^2$/C$^6$ 4-F-Phe), 140.9 (C$^2$ Imid.), 147.4 (C$^4$ Pyr), 158.4 (C$^2$ Pyr), 161.1 (d, J = 21.7 Hz, C$^4$ 4-F-Phe).

HPLC: t = 6.87 min, purity: 99% (λ = 254 nm), t = 6.87 min, purity: 98% (λ = 230 nm).

FABMS, m/z (C$_{25}$H$_{31}$FN$_4$O$_2$S) calcd, 471.22 [M + H]$^+$; found, 471.3.

3-((4-(4-Fluorophenyl)-5-2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)propane-1,2-diol (4)

Compound 4 was prepared according to general procedure B starting from compound 20 (90 mg, 0.19 mmol) using 2 M aq. HCl.

Yield: 60 mg (73%) of a colorless oily product.

Spectroscopic data were in agreement with those in the literature.$^3$

HPLC: t = 5.06 min, purity: 97% (λ = 254 nm), t = 7.47 min, purity: 97% (λ = 230 nm).

(R)-4-(4-(4-Fluorophenyl)-2-((tetrhydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(3-methylbutan-2-yl)pyridin-2-amine (S1)

Compound S1 was prepared according to general procedure A starting from compound 17 (100 mg, 0.24 mmol) was followed using (R)-3-methylbutyl-2-amine (557 µL, 4.79 mmol).

Yield: 65 mg (56%), as light brown solid product, which was directly used for the next step.

ESI-MS, m/z (C$_{26}$H$_{33}$FN$_4$O$_2$S) calcd, 485.23 [M + H]$^+$; found, 485.4.

(R)-2-((4-(4-Fluorophenyl)-5-2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S2)

Compound S2 was prepared according to general procedure B starting from compound S1 (65 mg, 0.13 mmol).

Yield: 53 mg (99%), as light yellow solid product.

$^1$H NMR (200 MHz, CD$_3$OD): δ 0.89 (d, J = 6.6 Hz, 3H, CH$_3$), 0.91 (d, J = 6.6 Hz, 3H, CH$_3$), 1.06 (d, J = 6.6 Hz, 3H, CH$_3$), 1.64 - 1.80 (m, 1H, CH), 3.19 (t, J = 6.2 Hz, 2H, CH$_2$), 3.48 - 3.58 (m, 1H, CH), 3.81 (t, J = 6.3 Hz, 2H, CH$_2$), 6.50 - 6.53 (m, 2H, C$^3$/C$^5$-H Pyr), 7.09 - 7.18 (m, 2H, C$^3$/C$^5$-H 4-F-Phe), 7.43 - 7.50 (m, 2H, C$^2$/C$^6$-H 4-F-Phe), 7.80 (d, J = 5.4 Hz, 1H, C$^5$-H Pyr).
$^{13}$C NMR (50 MHz, CD$_3$OD): δ 17.4 (CH$_3$), 18.5 (CH$_3$), 19.7 (CH$_3$), 34.1 (CH), 37.9 (CH$_2$), 53.2 (CH), 62.8 (CH$_2$), 107.1 (C$_3$ Pyr), 111.4 (C$_5$ Pyr), 116.6 (d, $J = 21.9$ Hz, C$_3$/C$_5$ 4-F-Phe), 131.9 (d, $J = 8.1$ Hz, C$_3$/C$_5$ 4-F-Phe), 142.8 (C$_4$ Pyr), 148.3 (C$_6$ Pyr), 160.4 (C$_2$ Pyr), 161.8 (d, $J = 245.2$ Hz, C$_4$ 4-F-Phe).

$[\alpha]_D^{b9} = -23.4^\circ$ (c 1.19 in MeOH).

HPLC: t = 5.2 min, purity: 100% (λ = 254 nm), t = 5.2 min, purity: 100% (λ = 230 nm).

ESIMS, m/z (C$_{21}$H$_{25}$FN$_3$OS) calcd, 401.17 [M + H]$^+$; found, 401.4.

(S)-4-(4-(4-Fluorophenyl)-2-((2-((tetracyclo-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(3-methylbutan-2-yl)pyridin-2-amine (S3)

Compound S3 was prepared according to general procedure A starting from compound 17 (100 mg, 0.24 mmol) and (S)-(+)-3-methylbutan-2-ylamine (670 μL, 5.99 mmol).

Yield: 77 mg (66%), as light yellow solid product.

$^1$H NMR (250 MHz, DMSO-$d_6$): δ 0.84 (t, $J = 5.86$ Hz, 6H, 2 x CH$_3$), 0.93 - 1.06 (m, 3H, CH$_3$), 1.31 - 1.51 (m, 4H, 2 x CH$_2$), 1.52 - 1.83 (m, 3H, CH$_2$ + CH), 3.25 - 3.51 (m, 3H, CH$_2$ + CH), 3.58 - 3.99 (m, 4H, 2 x CH$_2$), 4.62 (br. s, 1H, CH$_{THP}$), 6.07 - 6.78 (m, 3H, NH + C$_3$/C$_5$-H Pyr), 7.04 - 7.35 (m, 2H, C$_3$/C$_5$-H 4-F-Phe), 7.38 - 7.60 (m, 2H, C$_3$/C$_5$-H 4-F-Phe), 7.69 - 7.98 (m, 1H, C$_6$-H Pyr), 12.62 (br. s, 1H, NH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 16.5 (CH$_3$), 17.8 (CH$_3$), 18.9 (CH$_3$), 19.2 (CH$_3$), 24.9 (CH$_2$), 30.0 (CH$_2$), 31.9 (CH), 32.4 (CH$_2$), 50.5 (CH), 61.2 (CH$_2$), 65.9 (CH$_2$), 97.8 (CH), 105.1, 105.4 (C$_3$ Pyr), 109.2, 109.6 (C$_5$ Pyr), 114.9 (d, $J = 21.14$ Hz), 115.4 (d, $J = 24.67$ Hz, C$_3$/C$_5$ 4-F-Phe), 126.7, 126.9 (C$_5$ Imid.), 129.2 (d, $J = 10.57$ Hz), 130.4 (d, $J = 12.53$ Hz, C$_3$/C$_5$ 4-F-Phe), 135.4, 138.2 (C$_4$ Imid.), 140.1, 142.2 (C$_2$ Imid.), 147.2, 148.0 (C$_6$ Pyr), 158.9 (C$_2$ Pyr), 160.5 (d, $J = 243.8$ Hz, C$_4$ 4-F-Phe).

$^{13}$C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.

HPLC: t = 5.93 min, purity: 96% (λ = 254 nm), t = 5.93 min, purity: 95% (λ = 230 nm).

ESIMS, m/z (C$_{26}$H$_{33}$FN$_3$O$_2$S) calcd, 485.23 [M + H]$^+$; found, 485.4.

(S)-2-((4-(4-Fluorophenyl)-5-(2-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S4)

Compound S4 was prepared according to general procedure B starting from compound S3 (36 mg, 0.07 mmol).

Yield: 29 mg (97%), as light yellow solid product.
\[ \delta \text{ (d, } J = 6.6 \text{ Hz, } 3\text{H, } \text{CH}_3) = 0.90 \] (d, J = 6.7 Hz, 3H, CH3), 1.07 (d, J = 6.6 Hz, 3H, CH3), 1.64 - 1.82 (m, 1H, CH), 3.19 (t, J = 6.3 Hz, 2H, CH2), 3.48 - 3.57 (m, 1H, CH), 3.81 (t, J = 6.2 Hz, 2H, CH2), 6.52 - 6.56 (m, 2H, C3/C5-H Pyr), 7.10 - 7.19 (m, 2H, C3/C5-H 4-F-Phe), 7.43 - 7.50 (m, 2H, C2/C6-H 4-F-Phe), 7.79 (d, J = 5.6 Hz, 1H, C6-H Pyr).

\[ [\alpha]_D^\infty = +23.9^\circ \text{ (c 1.22 in MeOH).} \]

HPLC: t = 5.20 min, purity: 100% (λ = 254 nm), t = 5.20 min, purity: 100% (λ = 230 nm).

ESIMS, m/z \((C_{21}H_{25}FN_{4}O_{2})\) calcd, 401.17 [M + H]+; found, 401.4.

4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(1-phenylethyl)pyridin-2-amine (S5)

Compound S5 was prepared according to general procedure A starting from compound 17 (200 mg, 0.48 mmol) and 1-phenyl-ethylamine (1.22 mL, 9.58 mmol).

Yield: 100 mg (40%) of a light yellow solid.

\[ \delta \text{ (d, } J = 3.28 \text{ Hz, CH3) } = 1.30 - 1.51 \] (m, 7H, CH3 + 2 x CH2), 1.51 - 1.77 (m, 2H, CH2), 3.22 - 3.35 (m, 2H, CH2), 3.59 - 3.97 (m, 4H, 2 x CH2), 4.61 (br. s, 1H, CH), 4.80 - 5.02 (m, 1H, CH), 6.41 - 6.44 (m, 1H, NH), 6.45 - 6.73 (m, 1H, C3-H Pyr), 6.86 - 7.08 (m, 1H, C5-H Pyr), 7.08 - 7.20 (m, 2H, C3/C6-H, 4-F-Phe), 7.20 - 7.34 (m, 5H, C2/C6-H Phe), 7.34 - 7.57 (m, 2H, C3/C6-H 4-F-Phe), 7.68 - 7.95 (m, 1H, C6-H Pyr), 12.62 (br. s, 1H, NH).

\[ \delta \text{ (d, } J = 23.7 \text{ Hz, CH3) } = 115.0 \] (d, J = 28.9 Hz, C3/C6 4-F-Phe), 125.9 (C4 Phe), 126.2, 126.3 (C2/C6 Phe), 126.6, 126.9 (C5 Imid.), 128.0, 128.1 (C3/C5 Phe), 129.1 (d, J = 8.5 Hz), 130.5 (d, J = 8.2 Hz) (C2/C6 4-F-Phe), 131.0 (d, J = 4.1 Hz, C3/C5 4-F-Phe), 135.2, 137.6 (C4 Imid.), 138.3, 140.3 (C4 Pyr), 141.0, 142.3 (C2 Imid.), 145.9, 146.2 (C1 Phe), 147.2, 148.1, 158.4 (C2 Pyr), 160.0 (d, J = 248.6 Hz), 160.6 (d, J = 246.3 Hz, C4 4-F-Phe).

\[ [\alpha]_D^\infty = +23.9^\circ \text{ (c 1.22 in MeOH).} \]

HPLC: t = 7.83 min, purity: 99% (λ = 254 nm), t = 7.83 min, purity: 99% (λ = 230 nm).

FABMS, m/z \((C_{28}H_{31}FN_{4}O_{2}S)\) calcd, 519.22 [M + H]+; found, 519.3.
2-((4-(4-Fluorophenyl))-5-(2-((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S6)

Compound S6 was prepared according to general procedure B starting from compound S5 (50 mg, 0.1 mmol).

Yield: 41 mg (98%) of a light yellow solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.34 (d, 3H, \(J = 4.5\) Hz, CH\(_3\)), 1.90 - 2.00 (m, 1H, OH), 3.04 (br. s, 2H, CH\(_2\)), 3.87 (s, 2H, CH\(_2\)), 4.34 (s, 1H, CH), 6.44 (s, 1H, NH), 6.58 (d, \(J = 4.5\) Hz, 1H, C\(^3\)-H Pyr), 6.67 - 6.95 (m, 3H, C\(^2\)-H Pyr + C\(^3\)/C\(^5\)-H 4-F-Phe), 6.97 - 714 (m, 5H, C\(^2\)/C\(^5\)-H Phe), 7.15 - 7.35 (m, 2H, C\(^2\)/C\(^5\)-H 4-F-Phe), 7.54 (d, \(J = 3.6\) Hz, 1H, C\(^6\)-H Pyr).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.1 (CH\(_3\)), 36.5 (CH\(_2\)), 52.4 (CH), 63.0 (CH\(_2\)), 104.5 (C\(^3\) Pyr), 110.6 (C\(^5\) Pyr), 115.8 (d, \(J = 22.2\) Hz, C\(^3\)/C\(^5\) 4-F-Phe), 125.6 (C\(^2\)/C\(^6\) Phe), 127.1 (C\(^5\) Imid.), 127.3 (C\(^4\) Phe), 128.7 (C\(^3\)/C\(^5\) Phe), 130.3 (d, \(J = 11.1\) Hz, C\(^2\)/C\(^5\) 4-F-Phe), 135.1 (C\(^4\) Imid.), 142.1 (C\(^6\) Pyr), 143.1 (d, \(J = 9.4\) Hz, C\(^1\) 4-F-Phe), 144.5 (C\(^4\) Pyr), 145.3 (C\(^1\) Phe), 155.7 (C\(^2\) Imid.), 161.5 (d, \(J = 249.0\) Hz, C\(^2\) 4-F-Phe), 171.2 (C\(^3\) Pyr)

ESIMS, m/z (C\(_{22}\)H\(_{23}\)FN\(_2\)OS) calcd, 435.16 [M + H]\(^+\); found, 435.4.

HPLC: \(t = 5.45\) min, purity: 98% (\(\lambda = 254\) nm), \(t = 5.45\) min, purity: 95% (\(\lambda = 230\) nm).

4-(2-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-4-(4-fluorophenyl)-1H-imidazol-5-yl)-N-(1-phenylethyl)pyridin-2-amine (S7)

Compound S7 was prepared according to general procedure A starting from compound 19 (100 mg, 0.25 mmol) and 1-phenyl-ethylamine (631.5 \(\mu\)L, 4.96 mmol).

Yield: 88 mg (70%) of a light yellow solid.

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 1.27 (s, 3H, CH\(_3\)), 1.30 - 1.47 (m, 6H, 2 x CH\(_3\)), 3.17 - 3.40 (m, 2H, CH\(_2\)), 3.65 - 3.82 (m, 1H, CH), 3.97 - 4.14 (m, 1H, CH\(_H\)), 4.26 - 4.44 (m, 1H, CH\(_H\)), 4.92 (br. s, 1H, CH), 6.43 (br. s, 1H, NH), 6.48 - 6.71 (m, 1H, C\(^3\)-H Pyr), 6.90 - 7.09 (m, 1H, C\(^5\)-H Pyr), 7.12 - 7.20 (m, 2H, C\(^3\)/C\(^5\)-H 4-F-Phe), 7.21 - 7.36 (m, 5H, C\(^2\)/C\(^6\)-H, Phe), 7.38 - 7.57 (m, 2H, C\(^2\)/C\(^6\)-H 4-F-Phe), 7.67 - 7.95 (m, 1H, C\(^6\)-H Pyr), 12.68 (s, 1H, NH).

\(^13\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 23.5, 23.6 (CH\(_3\)), 25.4 (CH\(_3\)), 26.7 (CH\(_3\)), 35.7 (CH\(_2\)), 49.8 (CH), 56.0 (C(CH\(_3\))\(_3\)), 67.7 (CH\(_2\)), 74.5 (CH), 105.1, 105.5 (C\(^3\) Pyr), 108.7 (C\(^5\) Imid.), 109.8, 110.2 (C\(^5\) Pyr), 115.0 (d, \(J = 21.7\) Hz), 115.5 (d, \(J = 22.3\) Hz, C\(^3\)/C\(^5\) 4-F-Phe), 125.9 (C\(^2\)/C\(^6\) Phe), 126.1, 126.2 (C\(^4\) Phe), 126.4 (d, \(J = 12.1\) Hz), 126.69 (d, \(J = 13.4\) Hz, C\(^1\) 4-F-Phe), 128.0 (C\(^3\)/C\(^5\) Phe), 129.3 (d, \(J = 9.6\) Hz), 130.6 (d, \(J = 7.6\) Hz, C\(^2\)/C\(^6\) 4-F-Phe), 135.3, 137.7 (C\(^4\) Imid.), 138.3, 139.9 (C\(^4\) Pyr), 140.6, 142.2 (C\(^2\) Imid.), 145.0 (d, \(J = 19.4\) Hz), 147.3, 148.0 (C\(^6\) Pyr), 158.4 (C\(^2\) Pyr), 160.0 (d, \(J = 246.5\) Hz), 160.6 (d, \(J = 245.3\) Hz, C\(^4\) 4-F-Phe).

\(^13\)C NMR of this compound is highlighted by complex signals due to diastereomeric mixture.
HPLC: $t = 7.44$ min, purity: 99% ($\lambda = 254$ nm), $t = 7.44$ min, purity: 99% ($\lambda = 230$ nm).

FABMS, m/z (C$_{29}$H$_{29}$FN$_4$O$_2$S) calcd, 505.2 [M + H]$^+$; found, 505.3.

3-((4-(4-Fluorophenyl)-5-((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)propane-1,2-diol (S8)

Compound S8 was prepared according to general procedure B starting from compound S7 (61 mg, 0.12 mmol) using 2 M aq HCl.

Yield: 40 mg (71%) of a light yellow solid.

Spectroscopic data were in agreement with those in the literature.

HPLC: $t = 4.51$ min, purity: 97% ($\lambda = 254$ nm), $t = 4.51$ min, purity: 97% ($\lambda = 230$ nm).

(R)-4-((4-(4-Fluorophenyl)-2-((2-(tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(1-phenylethyl)pyridin-2-amine (S9)

Compound S9 was prepared according to general procedure A starting from compound 17 (157 mg, 0.12 mmol) and (R)-(−)-1-phenyl-ethylamine (967 µL, 7.52 mmol).

Yield: 133 mg (68%), white semisolid of S9 which will use for the next step.

ESIMS, m/z (C$_{29}$H$_{31}$FN$_4$O$_2$S) calcd, 519.22 [M + H]$^+$; found, 519.5.

(R)-2-((4-(4-Fluorophenyl)-5-((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S10)

Compound S10 was prepared according to general procedure B starting from compound S9 (133 mg, 0.26 mmol) 2 M aq HCl.

Yield: 90 mg (81%) as a white solid product.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.38 (d, $J = 6.57$ Hz, 3H, CH$_3$), 3.19 (t, $J = 6.32$ Hz, 2H, CH$_2$), 3.67 (t, $J = 6.06$ Hz, 2H, CH$_2$), 4.90 (br. s, 1H, CH), 5.09 (br. s, 1H, OH), 6.41 (d, $J = 4.80$ Hz, 1H, NH), 6.67 (br. s, 1H, C$_3$-H Pyr), 6.87 - 7.06 (m, 1H, C$_5$-H Pyr), 7.07 - 7.18 (m, 2H, C$_3$/C$_6$-H Pyr), 7.64 - 7.96 (m, 1H, C$_6$-H Pyr), 12.62 (br. s, 1H, NH).

HPLC: $t = 4.51$ min, purity: 95% ($\lambda = 254$ nm), $t = 4.50$ min, purity: 95% ($\lambda = 230$ nm).

ESIMS, m/z (C$_{29}$H$_{23}$FN$_4$O$S$) calcd, 435.16 [M + H]$^+$; found, 435.4.

$\left[\alpha\right]_D^{20} = +41.6^\circ$ (c 0.72 in MeOH).
(S)-4-(4-(4-Fluorophenyl)-2-(((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(1-phenylethyl)pyridin-2-amine (S11)

Compound S11 was prepared according to general procedure A starting from compound 17 (200 mg, 0.48 mmol) and (S)-()-1-phenylethylamine (1.2 mL, 9.58 mmol).
Yield: 175 mg (70%) white semisolid product which will be used for the next step.
ESIMS, m/z (C$_{29}$H$_{31}$FN$_{4}$O$_{2}$S) calcd, 519.22 [M + H]$^+$; found, 519.4.

(S)-2-((4-(4-Fluorophenyl)-5-2-((1-phenylethyl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (S12)

Compound S12 was prepared according to general procedure B starting from compound S11 (175 mg, 0.34 mmol) using 2 M aq. HCl.
Yield: 94 mg (64%) as a white solid product.
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.39 (d, $J = 6.32$ Hz, 3 H, CH$_3$), 3.20 (t, $J = 6.06$ Hz, 2H, CH$_2$), 3.69 (t, $J = 5.94$ Hz, 2H, CH$_2$), 4.91 (br. s, 1H, CH), 5.10 (br. s, 1H, OH), 6.42 (d, $J = 4.80$ Hz, 1H, NH), 6.62 (br. s, 1H, C$_3$-H Pyr), 6.99 (br. s, 1H, C$_5$-H Pyr), 7.08 - 7.18 (m, 2H, C$_3$/C$_5$-H 4-F-Phe), 7.20 - 7.36 (m, 5 H, C$_2$/C$_6$-H, Phe), 7.37 - 7.61 (m, 2H, C$_2$/C$_6$-H 4-F-Phe), 7.81 (br. s, 1H, C$_6$-H Pyr), 12.61 (br. s, 1H, NH).
HPLC: $t = 4.49$ min, purity: 100% ($\lambda = 254$ nm), $t = 4.49$ min, purity: 99% ($\lambda = 230$ nm).
ESIMS, m/z (C$_{24}$H$_{23}$FN$_{4}$O$_{2}$) calcd, 435.16 [M + H]$^+$; found, 435.4.
$\left[\alpha\right]_{D}^{20} = -53.8^\circ$ (c 0.75 in MeOH).
Scale-up: synthesis of 2.3 g of inhibitor 3

2-Fluoro-4-(4-fluorophenyl)-2-((2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)pyridine (17)

In a 50 mL pressure tube, 4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (12) (3.2 g, 11.13 mmol) and sodium tert-butoxide (1.2 g, 12.24 mmol) were suspended in MeOH abs. (40 mL). 2-(2-Bromethoxy)-tetrahydro-2H-pyran (2.02 mL, 13.36 mmol) was added. The reaction mixture was heated for 1 h at 70 °C. After cooling to r.t., the solvent was removed. Water (20 mL) was added and the contents were extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over anhydrous Na₂SO₄. The solvent was evaporated. The crude product was purified by flash chromatography (SiO₂, hexane-ethyl acetate 65-35) to afford 3.2 g (69%) of a white solid product.

HPLC: t = 7.87 min, purity: 98% (λ = 254 nm), t = 7.87 min, purity: 100% (λ = 230 nm).

ESI-MS, m/z (C₂₁H₂₁F₂N₃O₂S) calcd, 440.46 [M+Na]+; found, 440.4.

4-(4-(4-Fluorophenyl)-2-((2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)thio)-1H-imidazol-5-yl)-N-(3-methylbutan-2-yl)pyridin-2-amine (18)

Compound 18 was prepared according to general procedure A starting from compound 17 (3.2 g, 7.67 mmol) and 3-methylbutyl-2-amine (17.7 mL, 153.3 mmol). The reaction was heated in a 40 mL pressure tube for 5 d at 180 °C.

Yield: 3.0 g (80%) of a light brown solid.

HPLC: t = 5.88 min, purity: 94% (λ = 254 nm), t = 5.8 min, purity: 84% (λ = 230 nm).

ESI-MS, m/z (C₂₆H₃₃FN₄O₂S) calcd, 485.64 [M+H]+; found, 485.7.

2-((4-(4-Fluorophenyl)-5-((3-methylbutan-2-yl)amino)pyridin-4-yl)-1H-imidazol-2-yl)thio)ethan-1-ol (3)

In 100 mL round flask, Compound 3 was prepared according to general procedure B starting from compound 18 (3.0 g, 6.13 mmol) using 1.25 M HCl/ethanol (40 mL).

Yield: 2.3 g (94%) of a light yellow solid.

HPLC: t = 4.27 min, purity: 100% (λ = 254 nm), t = 4.27 min, purity: 99% (λ = 230 nm).

ESI-MS, m/z (C₂₁H₂₅FN₄Oₛ) calcd, 401.5 [M + H]⁺; found, 401.6.
References

NMR spectra

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**Note:** The chemical shifts for DMSO and water are also indicated in the spectrum.
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<td>1.61</td>
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**Chemical Shift (ppm)**

| 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 163.01 | 162.47 | 160.57 | 158.40 | 148.05 | 147.27 | 146.17 | 145.92 | 142.30 | 140.27 | 135.19 | 130.53 | 125.87 | 115.72 | 115.50 | 115.18 | 109.83 | 105.52 | 105.12 | 97.80 | 65.91 | 61.21 | 49.80 | 32.41 | 30.07 | 24.93 | 23.68 | 18.88 |