Tetra-substituted pyridinylimidazoles as dual inhibitors of p38α mitogen-activated protein kinase and c-Jun *N*-terminal kinase 3 for potential treatment of neurodegenerative diseases.

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General information

All reagents and (anhydrous) solvents are commercially available and were used without further purification. (*E*)-*N*-(4-(2-(4-Fluorophenyl)-2-(hydroxyimino)acetyl)pyridin-2-yl)acetamide **3a** [1] and (*E*)-2-(4-Fluorophenyl)-1-(2-fluoropyridin-4-yl)-2-(hydroxyimino)ethan-1-one **3b** [2] were synthesized according to literature.

NMR:
^{1}H- and ^{13}C-NMR spectra were obtained with Bruker Avance 200 or with Bruker 400 Avance. The spectra were obtained in the indicated solvent and calibrated against the residual proton peak of the deuterated solvent. Chemical shifts (δ) are reported in parts per million.

Mass Spectrometry:
Mass spectra (FAB-MS, ESI-HRMS and FT-ICR-MS) were obtained from the Mass Spectrometry Department, Institute of Organic Chemistry, Eberhard Karls Universität Tübingen or from the Institute of Sciences, Department of Pharmaceutical Analytics and Bioanalytics. GC/MS analyses were carried out on a Hewlett Packard HP 6890 series GC-system equipped with a HP-5MS capillary column (0.25 µm film thickness, 30 m x 250 µm) and a HP 5973 mass selective detector (EI ionization). Helium was used as carrier gas in the following temperature program: start at 100 °C and hold for 1 min, then increase to 160 °C and hold for 5 min, then increase to 250 °C and hold for 8 min.

TLC:
Analyses were performed on fluorescent silica gel 60 F_{254} plfates (Merck) and visualized under UV illumination at 254 nm and 366 nm.

Column chromatography:
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.

HPLC:
The purity of all tested compounds is > 95 % and was determined via reverse phase high performance liquid chromatography on 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 gradient of the used method was (Flow: 1.5 mL/min): 0.01 M KH_2PO_4, pH 2.3 (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.

Microwave:
The microwave reaction was performed on a CEM Discover system.

Docking:
The docking studies were carried out using AutoDock Vina 1.1.2.[3] The presented docking results were the best ranked ones. For visualization and generation of pharmacophore models PyMOL Molecular Graphics System, Version 1.3 Schrödinger, LLC was used.

Experimental procedures

General procedures:

General procedure I: synthesis of thiones 5a-m

A solution of oxime **3a** or **3b** (1 eq) and the respective 1,3,5-trialkyl-[1,3,5]triazinane (1 eq) in absolute ethanol (~ 6 mL / 1 mmol oxime) was heated under reflux until complete consumption of the oxime was detected by TLC. The reaction mixture was allowed to cool to room temperature and evaporated under reduced pressure. The resulting brown resin was triturated with Et_2O resulting in the intermediate *N*-Oxide which was sulfurized without further characterization or purification. A solution of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (1.1 eq) was added dropwise to a suspension of the corresponding *N*-oxide (1 eq) in DCM (~ 17 mL / 1 mmol *N*-oxide). The mixture was stirred at room temperature until complete conversion was detected. After evaporation of the solvent the residual yellow-red solid was triturated with Et_2O resulting in the desired imidazole-thione as a off-white solid which was used for the next reaction step without further purification.[4]

General procedure II: synthesis of compounds 6g-p, 14c-f, 14h-i

A solution of propiolic acid or ethyl propiolate (1.05 eq) and corresponding thione (1 eq) in absolute methanol (80 mL / mmol thione) was refluxed for 2 h until complete conversion. The solvent was removed under reduced pressure and the residue was purified by silica flash-chromatography.[5]

General procedure IIIa: synthesis of compounds 6a-h

A suspension of N-(4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide in dry THF (10 mL /mmol) was treated with K_2CO_3 (1.25 eq), the corresponding alkyl halide (1.2 eq) and vigorously stirred at room temperature for 24 h. The volatiles were evaporated and the crude mixture purified via flash chromatography or dilution with a suitable solvent and filtration of the crystalline products.

General procedure IIIb: synthesis of compounds 6q-t

To a solution of the corresponding thione derivative in dry THF (60 mL / 1 mmol thione) potassium *tert*-butoxide (4 eq) and the corresponding alkyl halide were added under ice cooling. The mixture was allowed to warm to room temperature, hereafter heated to 80 °C and stirred for 4 h. After cooling to room temperature the mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate three times. The organic layers were combined, dried over sodium sulfate and evaporated to dryness under reduced pressure to be purified by silica flash-chromatography.

General procedure IV: synthesis of compounds 6u-w, 14k

DABCO (2 eq) and ethyl (*E*)-3-iodoacrylate (1 eq) were dissolved in dry DMF (8 mL / mmol ethyl (*E*)-3-iodoacrylate) and stirred under argon atmosphere for 10 minutes. The respective thione (1.1 eq) was dissolved in dry DMF (3 mL / mmol ethyl (*E*)-3-iodoacrylate) and added dropwise to the solution. After 3 h of stirring at room temperature the reaction mixture was evaporated to dryness and purified by silica flash-chromatography.[6]

General procedure V: synthesis of intermediates 17a-d

To a stirred suspension of the carboxylic acid derivative (1 eq) in DCM (2 mL / mmol carboxylic acid), TBTU (1.1 eq) and *N*,*N*-diisopropylethylamine (2 eq) were added, followed by the corresponding amine (1 eq). The clear solution was stirred at room temperature until either TLC or HPLC confirmed complete conversion. The occurring precipitate was collected by filtration, washed with DCM and purified by silica flash-chromatography.

General procedure VI: synthesis of compounds 16a-k

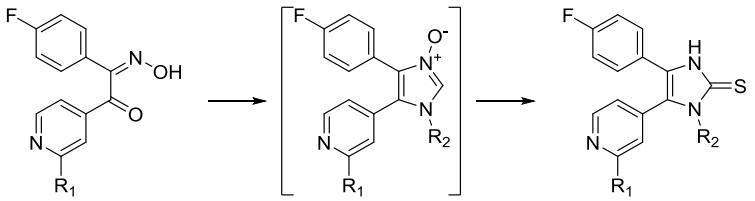
BrettPhos precatalyst (2.5 mol %) was added to dry dioxane (2.6 mL / mmol amine) in an argon flushed Schlenk-flask. 4-(4-(4-fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-amine **15** (1 eq) was dissolved in a mixture of 3:1 dioxane and *tert*-butanol (7 mL / mmol amine) and added to the reaction mixture followed by cesium carbonate (4 eq) and the respective aryl bromide (1.1 eq). The reaction mixture was heated to 110 °C and stirred for 2 h until either TLC or HPLC confirmed complete conversion. All volatiles were removed under reduced pressure and the residue was purified by silica flash-chromatography.

General procedure VII: synthesis of intermediates 13a-e

GP-VII-a (if the amine is aniline): To the corresponding 2-fluoropyridin-4-yl imidazole (1 eq), 1-methylpyrrolidin-2-one and concentrated aqueous hydrochloric acid (4 eq) was added and heated to 200 °C for 30 minutes. After adding the aniline (10 eq), the reaction mixture was stirred at 200 °C for further 30 minutes, to obtain complete conversion (monitored by HPLC). The reaction mixture was allowed to cool to room temperature and added dropwise to a vigorously stirred ice cooled saturated ammonium chloride solution causing the precipitation of a white to pale yellow solid. The suspension was filtered and the filter cake was washed with saturated ammonium chloride solution.

GP-VII-b (if the amine is an aliphatic amine): The respective 2-fluoropyridin-4-yl imidazole (1 eq) and the corresponding amine (11 eq) were mixed in a sealed tube and heated to 100 °C for 14 h (in case of liquid amines) or treated with 200 µl PEG 400 and heated to 120 °C for 6 h (in case of solid amines).

Synthesis of intermediates: Imidazole-2-thiones 5a-n



3 4 5

***N*-(4-(5-(4-Fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5a)**

According to the general procedure I, **3a** and 1,3,5-trimethyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 65 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.96 (s, 1H), 10.69 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.04 (s, 1H), 7.42 – 7.26 (m, 2H), 7.25 – 7.07 (m, 3H), 2.14 – 2.01 (m, 3H). **ESI-MS** (m/z): 343,1 $[M+H]^+$.

***N*-(4-(3-Cyclopropyl-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5b)**

According to the general procedure I, **3a** and 1,3,5-tricyclopropyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 61 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.82 (s, 1H), 10.61 (s, 1H), 8.35 (d, *J* = 5.0 Hz, 1H), 8.05 (s, 1H), 7.38 – 7.07 (m, 5H), 3.02 (s, 1H), 2.06 (s, 3H), 0.90 – 0.75 (m, 2H), 0.59 (s, 2H). **ESI-HRMS**: $[M+H]^+$ calculated: 369.1180, found: 369.1178.

***N*-(4-(3-Cyclobutyl-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5c)**

According to the general procedure I, **3a** and 1,3,5-tricyclobutyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2h and afforded 62 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.87 (s, 1H), 10.72 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.08 (s, 1H), 7.40 – 6.99 (m, 5H), 4.87 – 4.51 (m, 1H), 2.38 – 2.16 (m, 1H), 2.09 (s, 5H), 1.49 (s, 1H), 1.23 (s, 2H). **ESI-MS** (m/z): 383 $[M+H]^+$.

***N*-(4-(3-Cyclopentyl-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5d)**

According to the general procedure I, **3a** and 1,3,5-tricyclopentyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 65 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.87 (s, 1H), 10.70 (s, 1H), 8.38 (d, *J* = 5.1 Hz, 1H), 8.08 (s, 1H), 7.26 – 7.09 (m, 5H), 4.72 – 4.50 (m, 1H), 2.42 – 2.34 (m, 1H), 2.09 (s, 3H), 1.84 – 1.60 (m, 5H), 1.46 – 1.34 (m, 2H). **ESI-MS** (m/z): 397 $[M+H]^+$.

***N*-(4-(3-Cyclohexyl-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5e)**

According to the general procedure for I, **3a** and 1,3,5-tricyclohexyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h afforded 53 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.89 (s, 1H), 10.70 (s, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.10 (s, 1H), 7.31 – 7.03 (m, 5H), 2.07 (s, 3H), 1.83 – 1.40 (m, 6H), 1.28 – 0.72 (m, 5H). **FAB-MS** (m/z): 411 $[M+H]^+$.

***N*-(4-(3-(Cyclopropylmethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5f)**

According to the general procedure I, **3a** and 1,3,5-tris(cyclopropylmethyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 81 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.97 (s, 1H), 10.69 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.07 (s, 1H), 7.37 – 7.24 (m, 2H), 7.22 – 7.06 (m, 3H), 3.88 (d, J = 6.9 Hz, 2H), 2.07 (s, 3H), 0.91 – 0.83 (m, 1H), 0.37 – 0.23 (m, 2H), 0.15 – 0.00 (m, 2H). **ESI-MS** (m/z): 383 $[M+H]^+$.

***N*-(4-(3-(Cyclohexylmethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5g)**

According to the general procedure I, **3a** and 1,3,5-tris(cyclohexylmethyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 60 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.95 (s, 1H), 10.68 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.03 (s, 1H), 7.35 – 7.05 (m, 5H), 3.86 (d, *J* = 7.1 Hz, 2H), 2.08 (s, 3H), 1.63 – 1.22 (m, 9H), 1.04 – 0.71 (m, 7H). **ESI-MS** (m/z): 425,1 $[M+H]^+$.

***N*-(4-(5-(4-Fluorophenyl)-3-((tetrahydrofuran-2-yl)methyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5h)**

According to the general procedure I **3a** and 1,3,5-tris((tetrahydrofuran-2-yl)methyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 54 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.99 (s, 1H), 10.66 (s, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.05 (s, 1H), 7.41 – 7.03 (m, 6H), 4.16 (s, 1H), 3.92 – 3.62 (m, 2H), 2.08 (s, 3H), 1.92 – 1.40 (m, 6H). **ESI-HRMS**: $[M+H]^+$ calculated: 407.1550, found: 407.1527.

***N*-(4-(3-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5i)**

According to the general procedure I, **3a** and 1,3,5-tris(2,2-dimethoxyethyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 73 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 13.00 (s, 1H), 10.65 (s, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.03 (s, 1H), 7.32 – 7.06 (m, 5H), 4.69 (t, *J* = 5.2 Hz, 1H), 3.97 (d, *J* = 5.2 Hz, 2H), 3.14 (d, *J* = 4.2 Hz, 6H), 2.07 (s, 3H). **ESI-HRMS**: $[M+H]^+$ calculated: 417.1391, found: 417,1390.

***N*-(4-(3-(2,3-Dihydroxypropyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (5j)**

According to the general procedure I, **3a** and 3,3',3''-(1,3,5-triazinane-1,3,5-triyl)tris(propane-1,2-diol) were refluxed overnight. The sulfurization was stirred for 2 h and afforded 26 % of the title compound. **^{1}H NMR** (200 MHz, DMSO) δ 10.63 (s, 1H), 8.37 (d, J = 5.1 Hz, 1H), 8.04 (s, 1H), 7.33 – 7.07 (m, 5H), 4.14 – 4.04 (m, 1H), 3.96 – 3.88 (m, 1H), 3.79 – 3.70 (m, 1H), 2.06 (s, 3H). NH proton of the imidazole and both hydroxyl-group protons were not detected; water signal is shifted downfield. **ESI-HRMS**: $[M+H]^+$ calculated: 402.1162,found: 402.1173.

1-(2,2-Dimethoxyethyl)-4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (5k)

According to the general procedure I, **3b** and 1,3,5-tris(2,2-dimethoxyethyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 36 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.29 (d, *J* = 5.1 Hz, 1H), 7.31 – 7.15 (m, 3H), 7.09 – 6.90 (m, 3H), 5.03 (t, *J* = 5.4 Hz, 1H), 4.05 (d, *J* = 5.4 Hz, 2H), 3.40 (s, 6H). **ESI-MS** (m/z): 378 $[M+H]^+$.

1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (5l)

According to the general procedure I, **3b** and 1,3,5-tris(cyclopropylmethyl)-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 40 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 13.04 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 2H), 7.36 – 7.10 (m, 4H), 3.96 (d, *J* = 7.0 Hz, 2H), 0.79 (d, *J* = 7.7 Hz, 1H), 0.35 – 0.25 (m, 2H), 0.10 – -0.01 (m, 2H). **ESI-HRMS**: $[M+H]^+$ calculated: 344.1028, found: 344.1016.

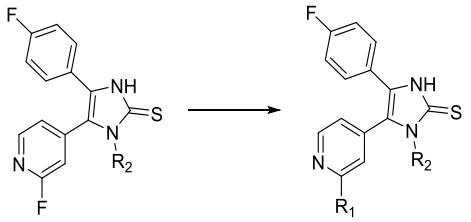
4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1-methyl-1,3-dihydro-2*H*-imidazole-2-thione (5m)

According to the general procedure I, **3b** and 1,3,5-trimethyl-1,3,5-triazinane were refluxed overnight. The sulfurization was stirred for 2 h and afforded 53 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 13.01 (s, 1H), 8.31 (d, *J* = 4.5 Hz, 1H), 7.46 – 7.04 (m, 6H), 3.41 (s, 3H). **ESI-HRMS**: $[M+H]^+$ calculated: 304.0715, found: 304.0717. Analytical data in accordance literature.[7]

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (5n)

4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione was synthesized according to literature[2] and identity was confirmed analytically. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.82 (s, 2H), 8.11 (s, 1H), 7.56 – 7.03 (m, 6H). **FAB-MS** (m/z): 290 $[M+H]^+$.

Synthesis of intermediates: Imidazole-2-thiones 13a-e, 18



5j-m **13**

4-(4-Fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (13a)

According to GP-VII-a, **13a** was synthesized from **5n** and aniline. Purification by recrystallization from DMF/H_2O afforded the title compound in 63 % yield. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.66 (s, 2H), 8.98 (s, 1H), 8.09 (d, *J* = 4.0 Hz, 1H), 7.56 - 7.37 (m, Hz, 4H), 7.32 – 7.15 (m, 4H), 6.86 (t, *J* = 7.2 Hz, 1H), 6.73 (s, 1H), 6.68 (d, *J* = 4 Hz, 1H). **FAB-MS** (m/z): 363 $[M+H]^+$.

1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (13b)

According to GP-VII-a, **13b** was synthesized from **5l** and aniline. Purification by silica flash-chromatography (ethyl acetate/petrol ether(70-90) 50/50) afforded the title compound in 72 % yield. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.92 (s, 1H), 9.14 (s, 1H), 8.26 (d, *J* = 5.1 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.41 – 7.07 (m, 6H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.82 – 6.69 (m, 2H), 3.91 (d, *J* = 6.7 Hz, 2H), 1.01 – 0.79 (m, 1H), 0.41 – 0.22 (m, 2H), 0.23 – 0.03 (m, 2H). **ESI-HRMS**: $[M+H]^+$ calculated: 417.1544, found: 417.1541.14b

5-(2-(Cyclopropylamino)pyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazole-2-thiol (13c)

According to GP-VII-b, **13c** was synthesized from **5k** and cyclopropanamine. The formed precipitate was diluted with DCM, treated with ultra-sonic and collected by filtration to afford the title compound in 78 % yield. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 11.48 (s, 1H), 8.07 (d, *J* = 5.9 Hz, 1H), 7.48 – 7.26 (m, 2H), 7.27 – 7.08 (m, 2H), 6.96 (s, 1H), 6.65 – 6.49 (m, 2H), 4.81 (t, *J* = 5.5 Hz, 1H), 3.99 (d, *J* = 5.4 Hz, 2H), 3.18 (s, 6H), 2.45 – 2.31 (m, 1H), 0.74 – 0.51 (m, 2H), 0.45 – 0.24 (m, 2H). **ESI-HRMS**: $[M+H]^+$ calculated: 437.1418, found: 437.1438.

5-(2-(*sec*-Butylamino)pyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1,3-dihydro-2*H*-imidazole-2-thione (13d)

According to GP-VII-b, **13d** was synthesized from **5k** and butan-2-amine. All volatiles were evaporated, the residue was diluted with cold DCM and collected by filtration to afford the title compound in 54 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.04 – 7.91 (m, 1H), 7.36 – 7.18 (m, 3H), 7.08 – 6.89 (m, 2H), 6.45 (s, 1H), 5.12 – 4.99 (m, 2H), 4.16 – 3.99 (m, 2H), 3.61 – 3.18 (m, 7H), 1.64 – 1.42 (m, J = 6.8 Hz, 1H), 1.36 – 1.06 (m, 3H), 0.99 – 0.78 (m, 3H). NH-protons were not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 431.1912, found: 431.1904.

***tert*-Butyl 4-((4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)amino)piperidine-1-carboxylate (13e)**

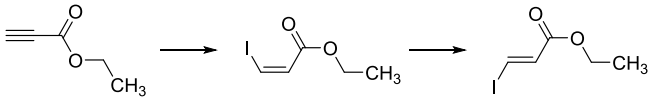
According to GP-VII-b, **13e** was synthesized from **5m** and *tert*-butyl 4-aminopiperidine-1-carboxylate at 120 °C (2.5 bar and 35 W) and 6 h in a microwave tube. The reaction mixture was diluted with EtOAc and washed with brine. The combined organic layers were dried over sodium sulfate, evaporated to dryness, and subsequently

purified by silica flash-chromatography (EtOAc/petrol ether 30/70) to afford the title compound in 54 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.07 (d, *J* = 5.3 Hz, 1H), 7.37 – 7.22 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 4.6 Hz, 1H), 6.22 (s, 1H), 4.93 (d, *J* = 7.3 Hz, 1H), 4.13 – 3.95 (m, 2H), 3.70 (s, 1H), 3.52 (s, 3H), 3.00 – 2.73 (m, 2H), 1.98 – 1.84 (m, 2H), 1.45 (s, 11H). **FAB-MS** (m/z): 482,0 $[M-H]^-$.

4-(4-Fluorophenyl)-1-methyl-5-(2-(piperidin-4-ylamino)pyridin-4-yl)-1,3-dihydro-2*H*-imidazole-2-thione (18)

13e was dissolved in DCM and (20 eq) HCl in dioxane was added to the solution and stirred for 20 minutes at room temperature until HPLC detected complete conversion. The solvent was evaporated under reduced pressure and the remaining resin was diluted with water and adjusted to a pH of 12 using a 20 % aqueous NaOH solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtred and evaporated to dryness to afford the title compound in 90 % yield. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.04 (d, *J* = 5.6 Hz, 1H), 7.41 – 7.26 (m, 2H), 7.09 (t, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 6.8 Hz, 2H), 4.02 (s, 1H), 3.52 (s, 3H), 3.44 – 3.40 (m, 1H), 3.23 – 3.05 (m, 2H), 2.28 – 2.14 (m, 2H), 1.87 – 1.66 (m, 2H), 0.90 (s, 1H). No NH signal was displayed due to the proton/deuterium exchange with deuterated methanol. **ESI-HRMS**: $[M+H]^+$ calculated: 384.1653, found: 384.1648.

Synthesis of intermediates: 8, 9



7 **8** **9**

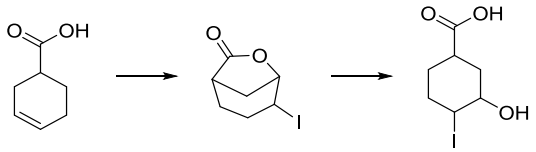
Ethyl (*Z*)-3-iodoacrylate (8)

Sodium iodide (1.5 eq) was suspended in acetic acid (0.67 mL / mmol **7**) and heated to 70 °C until the soid was completely dissolved. Ethyl propiolate (**7**) was added dropwise and the solution was stirred at 70 °C over night. The reaction was cooled to room temperature and quenched with water and diethyl ether. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with 3 M aqueous KOH to extract the acetic acid and washed subsequently with 10 % aqueous sodium thiosulfate solution and brine. After that the solution was dried over sodium sulfate and evaporated under reduced pressure to afford a yellow brown oil of the title compound in 90 % yield. Identity could be confirmed by comparison with published spectroscopic data: **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 7.71 (d, *J* = 8.9 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). **FAB-MS** (m/z): 226 $[M-H]^+$.[8]

Ethyl (*E*)-3-iodoacrylate (9)

To a solution of **8** in toluene (0.26 mL / mmol *Z*-isomere) was added hydroiodic acid (5 eq), the flask was flushed with argon and heated to 80 °C over night. The reaction was allowed to cool to room temperature, quenched with diethyl ether, washed with aqueous solution of sodium hydrogen carbonate 10 %, aqueous sodium thiosulfate solution and brine. After that the solution was dried over sodium sulfate, evaporated under reduced pressure and distilled to afford the title compound in *E*/*Z* 99:1. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 8.04 (d, *J* = 15.0 Hz, 1H), 6.94 (d, *J* = 15.0 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). **GC-MS** (m/z): 226 $[M^+]$[9]

Synthesis of intermediates: 11, 12



10 **11** **12**

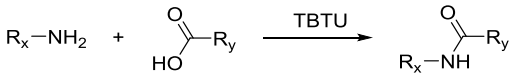
4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (11)

To a stirred solution of $NaHCO_3$ (3 eq) in water (2.5 mL / mmol **10**) 3-cyclohexene-1-carboxylic acid (**10**) (1 eq) was added dropwise at room temperature. An aqueous (2.5 mL / mmol **10**) solution of NaI (9 eq) and I_2 (1.1 eq) was added to the vigorously stirred solution. The flask was covered with aluminium foil and the reaction was allowed to stir over night at room temperature. The incurred suspension was extracted with DCM and the combined organic layers were washed with a sodium persulfate solution 10 %, sodium bicarbonate solution 10 % and brine and were dried over sodium sulfate. The solvent was evaporated under reduced pressure to yield 4-iodo-6-oxabicyclo[3.2.1]octan-7-one (89 %) as a white solid.[10] **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 4.92 – 4.82 (m, 1H), 4.67 – 4.57 (m, 1H), 2.68 – 2.53 (m, 2H), 2.46 – 2.13 (m, 2H), 2.08 – 1.91 (m, 1H), 1.88 – 1.58 (m, 2H). **ESI-MS** (m/z): 252 [M^+].

3-Hydroxy-4-iodocyclohexane-1-carboxylic acid (12)

4-iodo-6-oxabicyclo[3.2.1]octan-7-one **11** (1 eq) was dissolved in THF and water 9/1 (2.7 mL / **11**), concentrated hydrochloric acid (4 eq) was added and the mixture was heated under reflux for 1 h. The solvent was evaporated under reduced pressure to obtain 3-hydroxy-4-iodocyclohexane-1-carboxylic acid as a white solid (100 %).[11] **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 12.18 (s, 1H), 5.30 (s, 1H), 3.99 – 3.82 (m, 1H), 3.56 – 3.42 (m, 1H), 2.47 – 2.28 (m, 2H), 2.12 – 1.89 (m, 2H), 1.69 – 1.53 (m, 1H), 1.38 – 1.20 (m, 2H). **ESI-HRMS**: $[M-H]^+$ calculated: 268.9680, found: 268.9683.

Synthesis of intermediates: 17a-e



4-Bromo-*N*-cyclopropylbenzamide (17a)

17a was synthesized according to general procedure V. Eluent: ethyl acetate/*n*-hexane 80/20 → ethyl acetate/*n*-hexane 50/50 afforded 89 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (s, 4H), 1.60 – 1.36 (m, 1H), 1.15 – 1.01 (m, 2H), 0.93 – 0.76 (m, 2H). **FAB-MS** (m/z): 240/242 $[M+H]^+$.

3-Bromo-*N*-cyclopropylbenzamide (17b)

17b was synthesized according to general procedure V. Eluent: ethyl acetate/*n*-hexane 80/20 → ethyl acetate/*n*-hexane 50/50 afforded 91 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 1H), 7.70 – 7.54 (m, 2H), 7.34 – 7.20 (m, 1H), 6.42 (s, 1H), 2.96 – 2.80 (m, 1H), 0.94 – 0.77 (m, 2H), 0.70 – 0.55 (m, 2H). **FAB-MS** (m/z): 240/242 $[M+H]^+$.

***N*-(3-Bromophenyl)cyclopropanecarboxamide (17c)**

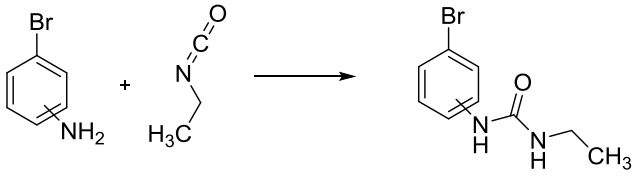
17c was synthesized according to general procedure V. Eluent: ethyl acetate/*n*-hexane 80/20 → ethyl acetate/*n*-hexane 50/50 afforded 95 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.57 (s, 1H), 7.46 –

7.31 (m, 1H), 7.25 – 7.08 (m, 2H), 1.59 – 1.40 (m, 1H), 1.16 – 1.00 (m, 2H), 0.92 – 0.75 (m, 2H). **FAB-MS** (m/z): 240/242 $[M+H]^+$.

***N*-(4-Bromophenyl)cyclopropanecarboxamide (17d)**

17e was synthesized according to general procedure V. Eluent: ethyl acetate/*n*-hexane 80/20 → ethyl acetate/*n*-hexane 50/50 afforded 92 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40 (s, 4H), 1.60 – 1.36 (m, 1H), 1.15 – 1.01 (m, 2H), 0.93 – 0.76 (m, 2H). **FAB-MS** (m/z): 240/242 $[M+H]^+$.

Synthesis of intermediates: 17f-g



1-(3-Bromophenyl)-3-ethylurea (17e)

3-Bromoaniline (1 eq) and isocyanatoethane (1.1 eq) in $DMF_{(abs)}$ (1 mL / mmol 3-bromoaniline) were heated to 100 °C over night. After TCL or HPLC detected complete conversion, all volatiles were removed under reduced pressure and the remaining resin was purified by silica flash-chromatography (EtOAc/petrol ether 20/80) afforded the title compound in 67 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.49 (s, 1H), 7.16 – 6.97 (m, 1H), 6.03 (t, *J* = 5.2 Hz, 1H), 3.28 – 3.13 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 1H). **ESI-HRMS**: $[M-H]^+$ calculated: 243.0133, found: 243.0105.

1-(4-Bromophenyl)-3-ethylurea (17f)

4-Bromoaniline (1 eq) and isocyanatoethane (1.1 eq) in $DMF_{(abs)}$ (1 mL / mmol 4-bromoaniline) were heated to 100 °C over night. After TCL or HPLC detected complete conversion all, volatiles were removed under reduced pressure and the remaining resin was purified by silica flash-chromatography (EtOAc/petrol ether 20/80) afforded the title compound in 82 % yield as a white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.49 (s, 1H), 7.16 – 6.97 (m, 3H), 6.03 (t, *J* = 5.2 Hz, 1H), 3.28 – 3.13 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H).**FAB-MS** (m/z): 234/246 $[M+H]^+$.

Synthesis of intermediates: 15, 19

4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-amine (15)

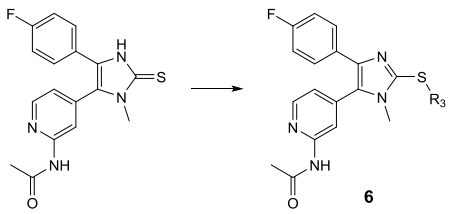
4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-amine was synthesized according to literature.[4] **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.01 (d, *J* = 5.1 Hz, 1H), 7.51 – 7.37 (m, 2H), 7.18 – 7.04 (m, 2H), 6.46 (d, *J* = 5.1 Hz, 1H), 6.37 (s, 1H), 6.09 (s, 2H), 3.37 (s, 3H), 2.63 (s, 3H). **ESI-HRMS**: $[M-H]^+$ calculated: 315.1080, found: 315.1040

Ethyl (*Z*)-3-((5-(2-((1-(ethylcarbamoyl)piperidin-4-yl)amino)pyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)acrylate (19)

14g (1 eq) was dissolved in dry DCM (50 mL / mmol **18**) and isocyanatoethane (1.5 eq) was added under argon atmosphere. The reaction mixture was stirred at room temperature for 4.5 h until TLC detected complete conversion. The reaction was quenched with water and extracted three times with DCM. The combined organic layers were dried over sodium sulfate, filtered, evaporated to dryness and the crude product was purified by silica flash-chromatography using a gradient of ethyl aceteate/*n*-hexane 50/50 → ethyl aceteate/*n*-hexane

80/20 to afford the title compound in 70 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.3 Hz, 1H), 8.03 (d, *J* = 9.9 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.01 – 6.86 (m, 2H), 6.51 (d, *J* = 4.4 Hz, 1H), 6.24 (s, 1H), 6.12 (d, *J* = 9.9 Hz, 1H), 4.63 – 4.54 (m, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.87 (d, *J* = 13.0 Hz, 2H), 3.50 (s, 3H), 3.31 – 3.18 (m, 2H), 3.00 – 2.82 (m, 2H), 1.99 (d, *J* = 11.1 Hz, 2H), 1.83 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H). **ESI-HRMS**: $[M+H]^+$ calculated: 553.2392, found: 553.2395.

Synthesis of compounds 6a-h



***N*-(4-(4-(4-Fluorophenyl)-1-methyl-2-((2-oxopropyl)thio)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide (6a)**

According to the general procedure IIIa, N-(4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide, K_2CO_3 and 2-chloroacetone were suspended and stirred at room temperature overnight. The crude product was suspended in diethyl ether, filtrated and exhaustively washed wit petrol ether and water. Yield 92 % **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 2.07 (s, 3H), 2.29 (s, 3H), 3.41 (s, 3H), 4.18 (s, 2H), 7.06-7.13 (m, 3H), 7.32-7.34 (m, 2H), 8.03 (s, 1H), 8.39 (d, J=5,5Hz, 1H), 10.66 (s, 1H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 24.3, 29.2, 31.0, 114.5, 115.6 (d, 2J= 21,5Hz), 120.6, 128.5 (d, 3J =8,0Hz), 130.5, 130.6, 137.4, 140.1, 142.6, 153.2, 169.9, 202.9. **ESI-HRMS**: $[M+H]^+$ calculated: 399.128551, found: 399.128181.

***N*-(4-(4-(4-Fluorophenyl)-2-((3-methoxy-2-oxopropyl)thio)-1-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide (6b)**

According to the general procedure IIIa, N-(4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide, K_2CO_3 and methyl 2-bromoacetate were suspended and stirred at room temperature overnight. The crude product was suspended in diethyl ether, filtrated and exhaustively washed with petrol ether and water. Yield 82 % **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 2.07 (s, 3H), 3.32 (s, 3H), 3.41 (s, 3H), 4.06 (s, 2H), 7.08-7.36 (m, 5H), 8.03 (s, 1H), 8.41-8.60 (m, 1H), 10.65 (s, 1H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 24.2, 32.2, 35.2, 52.7, 114.5, 115.6 (d, 2J= 21.2 Hz), 120.6, 128.5 (d, 3J= 8.4Hz), 140.1, 142.1, 149.2, 153.2, 169.6, 169.9. **ESI-HRMS**: $[M+H]^+$ calculated: 415.123466, found: 415.123775.

2-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)-*N*,*N*-dimethylacetamide (6c)

According to the general procedure IIIa, N-(4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide, K_2CO_3 and 2-chloro-*N*,*N*-dimethylacetamide were suspended and stirred at room temperature overnight. The crude product was suspended in diethyl ether, filtrated and exhaustively washed with diethyl ether and water. Yield 67 % **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 2.07 (s, 3H), 2.84 (s, 3H), 3.03 (s, 3H), 3.44 (s, 3H), 4.17 (s, 2H), 7.04-7.12 (m, 3H), 7.34-7.41 (m, 2H), 8.04 (s, 1H), 8.38-8.41 (d, J=4.5 Hz, 1H), 10.65 (s, 1H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 24.2, 32.3, 35.7, 37.2), 37.5, 114.5, 115.5 (d, 2J = 21.3 Hz), 120.3, 128.7 (d, 3J= 8.2Hz), 129.3, 140.2, 149.2, 153.2, 162.8, 167.5, 169.9. **ESI-HRMS**: $[M+H]^+$ calculated: 428.155100, found: 428.155190.

2-((5-(2-acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1H-imidazol-2-yl)thio)acetic acid (6d)

According to the general procedure IIIa, N-(4-(5-(4-fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide, K_2CO_3 and 2-bromoacetic acid were suspended and stirred at room temperature overnight. The crude product was taken up in water and acidified with hydrochloric acid. The solid was collected by filtration and washed with water and petrol ether. Yield 68 % **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.53 (s, 3H), 3.86 (s, 2H), 6.92-7.01 (m, 3H), 7.30-7.37 (m, 2H), 8.3 (d, J= 5.3 Hz), 8.45 (s, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 24.6, 32.4, 114.6, 115.6 (d, 2J= 21.6 Hz), 128.7 (d, 3J= 8.2Hz), 139.6, 148.5, 152.1, 168.9, 169.9. **ESI-HRMS**: $[M+H]^+$ calculated: 401.107816, found: 401.107978.

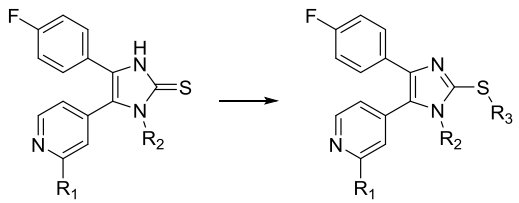
3-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)propionic acid (6e)

N-(4-(5-(4-Fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)pyridin-2-yl)acetamide (1 eq), acrylic acid (0.67 eq) and iodine (0.14 eq) were transferred into a screw cap vial and stirred at room temperature for 24 h. Water was added to the mixture and the product was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated in vacuum. The resulting crude product mixture was suspended in diethyl ether and stirred for 15 minutes. The pure product was collected by filtration. Yield 48 % **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 2.07 (s, 3H), 2.75 (t, J= 6.5Hz), 3.27-3.38 (m, 5H), 7.05-7.14 (m, 3H), 7.35-7.42 (m, 2H), 8.04 (s, 1H), 8.40 (d, J=5.5Hz), 10.65 (s, 1H)**. ^{13}C NMR** (50 MHz, DMSO-*d6*) δ 172.78, 169.54, 161.18 (d, J = 243.9 Hz), 152.77, 148.74, 142.46, 139.75, 137.01, 130.02 (d, J = 2.9 Hz), 128.42 (d, J = 8.1 Hz), 128.17, 120.35, 115.26 (d, J = 21.5 Hz), 114.25, 34.35, 31.86, 28.41, 23.92. **ESI-HRMS**: $[M+H]^+$ calculated: 415.123466, found: 415.123747.[12]

3-((5-(2-Acetamidopyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)propanoic acid (6f)

N-(4-(3-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)pyridin-2-yl)acetamide (1 eq), acrylic acid (0.67 eq) and iodine (0.13 eq) were transferred into a screw cap vial and stirred at room temperature for 24 h. Water was added to the mixture and the product was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product mixture was dissolved in 4M NaOH and acidified with hydrochloric acid (pH = 5). The resulting precipitation was collected by filtration and washed with petrol ether. Yield 11 %. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 2.16 (s, 3H), 2.76 (t, J= 6.7Hz, 2H), 3.23 (s, 6H), 4.15 (d, J= 5.1Hz), 4.37 (t, J= 4.5 Hz), 6.94-7.09 (m, 3H), 7.34-7.41 (m, 2H), 8.12 (s, 1H), 8.36 (d, J= 5.1Hz). C^3-H propyl was overlaid by solvent peak. **^{13}C NMR** (50 MHz, methanol-*d4*) δ 22.5, 29.7, 34.1, 47.5, 54.2, 102.9, 114.6 (d, J=21.8 Hz), 115.8, 121.3, 129.0 (d, J= 8.1 Hz), 129.3, 138.7, 140.6, 143.2, 148.4, 152.2, 165.0 (d, J= 240,5 Hz), 170.8, 173.7. **ESI-HRMS**: $[M+H]^+$ calculated: 489.160245, found: 489.160211.[12]

Synthesis of compounds 6g-p and 14a-f, 14i-j



6, 14

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)acrylic acid (6g)

6g was synthesized from **5a** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 62 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 10.69 (s, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 8.08 (s, 1H), 7.97 (d, *J* = 9.9 Hz, 1H), 7.52 – 7.31 (m, 2H), 7.20 – 7.04 (m, 3H), 6.16 (d, *J* = 9.7 Hz, 1H), 3.45 (s, 3H), 2.08 (s, 3H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 170.38, 168.16, 161.98 (d, *J* = 243.9 Hz), 153.57, 149.62, 144.33, 142.25, 140.23, 137.95, 130.63 (d, *J* = 3.1 Hz), 129.37, 128.96 (d, *J* = 8.1 Hz), 120.93, 116.31, 115.77 (d, *J* = 21.5 Hz), 114.78, 31.94, 23.81. **ESI-HRMS**: $[M+H]^+$ calculated: 413,10782, found: 413,10794.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6h)

6h was synthesized from **5i** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 58 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.70 (s, 1H), 10.71 (s, 1H), 8.45 (d, *J* = 5.0 Hz, 1H), 8.10 (s, 1H), 7.92 (d, *J* = 9.8 Hz, 1H), 7.53 – 7.35 (m, 2H), 7.22 – 7.02 (m, 3H), 6.14 (d, *J* = 9.8 Hz, 1H), 4.29 (s, 1H), 3.98 (s,

2H), 3.14 (s, 6H), 2.09 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*d6*) δ 170.49, 168.14, 162.02 (d, *J* = 244.1 Hz), 153.54, 149.67, 145.31, 143.42, 140.56, 137.97, 130.47 (d, *J* = 3.0 Hz), 129.24, 128.91 (d, *J* = 8.1 Hz), 121.49, 116.22, 115.78 (d, *J* = 21.5 Hz), 115.49, 102.97, 55.00, 46.68, 23.82. **ESI-HRMS**: $[M+H]^+$ calculated: 487.14460, found: 487.14465.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6i)

6i was synthesized from **5b** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/ AcOH 99/1 → DCM/*i*PrOH/ AcOH 89/10/1 as eluent afforded 71 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.71 (s, 1H), 10.61 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 10.0 Hz, 1H), 7.47 – 7.34 (m, 2H), 7.22 – 7.00 (m, 3H), 6.18 (d, *J* = 9.9 Hz, 1H), 2.06 (s, 3H), 0.88 (d, *J* = 6.3 Hz, 2H), 0.62 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-*d6*) δ 170.22, 168.16, 162.01 (d, *J* = 244.1 Hz), 153.21, 148.99, 144.64, 142.92, 140.54, 137.47, 130.63 (d, *J* = 2.8 Hz), 130.23, 129.28 (d, *J* = 8.1 Hz), 120.95, 116.04, 115.70 (d, *J* = 21.5 Hz), 114.81, 26.00, 23.76, 8.47. **ESI-HRMS**: $[M+H]^+$ calculated: 439.12347, found: 439.12353.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-cyclobutyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6j)

6j was synthesized from **5c** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 29 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 10.78 – 10.64 (m, 1H), 8.42 (d, *J* = 4.2 Hz, 1H), 8.22 – 8.03 (m, 2H), 7.45 – 7.28 (m, 2H), 7.22 – 7.01 (m, 3H), 6.16 (d, *J* = 9.9 Hz, 1H), 4.77 – 4.56 (m, 1H), 2.48 – 2.35 (m, 2H), 2.30 – 2.03 (m, 4H), 1.80 – 1.54 (m, 2H), 1.23 (s, 1H), carboxylic acid proton was not detected. **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 170.47, 153.37, 149.49, 143.77, 141.84, 140.89, 137.47, 130.53 (d, *J* = 3.1 Hz), 129.17, 129.15, 128.98 (d, *J* = 7.9 Hz), 121.58, 116.24, 115.66 (d, *J* = 21.8 Hz), 115.42, 50.40, 30.32, 23.83, 14.41, C1 of 4-fluorophenyl was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 453.13912, found: 453.13931.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-cyclopentyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6k)

6k was synthesized from **5d** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 55 % of the title compound. **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 12.68 (s, 1H), 10.72 (s, 1H), 8.43 (s, 1H), 8.21 – 8.07 (m, 2H), 7.37 (s, 2H), 7.18 – 7.04 (m, 3H), 6.17 (d, *J* = 9.4 Hz, 1H), 4.49 – 4.31 (m, 1H), 2.17 – 1.92 (m, 7H), 1.76 (s, 2H), 1.52 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-*d6*) δ 170.46, 168.02, 161.89 (d, *J* = 244.0 Hz), 153.48, 149.66, 143.77, 140.87, 140.74, 137.47, 130.53 (d, *J* = 2.8 Hz), 129.58, 128.85 (d, *J* = 8.1 Hz), 121.54, 116.12, 115.60 (d, *J* = 21.4 Hz), 115.41, 56.97, 31.34, 24.37, 23.75. **ESI-HRMS**: $[M+H]^+$ calculated: 467.15477, found: 467.15489.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-cyclohexyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6l)

6l was synthesized from **5e** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 68 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.72 (s, 1H), 10.73 (s, 1H), 8.55 – 8.35 (m, 1H), 8.26 – 8.03 (m, 2H), 7.50 – 7.21 (m, 2H), 7.20 – 6.98 (m, 3H), 6.15 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 1H), 2.10 (s, 3H), 1.87 (s, 6H), 1.65 – 1.44 (m, 1H), 1.24 – 1.01 (m, 3H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 169.66, 167.27, 161.11 (d, *J* = 244.0 Hz) , 152.77, 149.00, 143.45, 140.32, 140.23, 136.97,129.96 (d, *J* = 3.0 Hz), 128.49, 128.29 (d, *J* = 8.1 Hz), 121.13, 115.60, 115.18 (d, *J* = 21.3 Hz), 56.99, 31.64, 25.48, 24.60, 23.92. **ESI-HRMS**: $[M+H]^+$ calculated: 481.17042, found: 481.17067.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6m)

6m was synthesized from **5f** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 63 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.76 (s, 1H), 10.72 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.11 (s, 1H), 8.01 (d, *J* = 9.7 Hz, 1H), 7.50 – 7.34 (m, 2H), 7.20 – 7.02 (m, 3H), 6.17 (d, *J* = 9.8 Hz, 1H), 3.78 (d, *J* = 6.7 Hz, 2H), 2.09 (s, 3H), 0.96 – 0.74 (m, 1H), 0.47 – 0.31 (m, 2H), 0.14 – -0.02 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-*d6*) δ

170.46, 168.02, 161.89 (d, *J* = 244.0 Hz), 153.48, 149.66, 143.77, 140.87, 140.74, 137.47, 130.53 (d, *J* = 2.8 Hz), 129.58, 128.85 (d, *J* = 8.1 Hz), 121.54, 116.12, 115.60 (d, *J* = 21.4 Hz), 115.41, 56.97, 31.34, 24.37, 23.75. **ESI-HRMS**: $[M+H]^+$ calculated: 453.139116, found: 453.139122.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-(cyclohexylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6n)

6n was synthesized from **5g** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 47 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.73 (s, 1H), 10.68 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 8.07 (s, 1H), 8.00 (d, *J* = 9.8 Hz, 1H), 7.51 – 7.32 (m, 2H), 7.17 – 7.01 (m, 3H), 6.16 (d, *J* = 9.8 Hz, 1H), 3.76 (d, *J* = 6.6 Hz, 2H), 2.08 (s, 3H), 1.62 – 1.42 (m, 3H), 1.44 – 1.21 (m, 3H), 1.12 – 0.57 (m, 5H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 169.59, 167.28, 152.81, 149.02, 143.50, 141.90, 139.98, 137.50, 129.92 (d, *J* = 3.1 Hz), 128.44, 128.36 (d, *J* = 8.0 Hz), 120.70, 115.87, 115.23 (d, *J* = 21.4 Hz), 114.56, 50.19, 38.07, 29.83, 25.51, 25.04, 23.92. **ESI-HRMS**: $[M+H]^+$ calculated: 495.18607, found: 495.18672.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6o)

6o was synthesized from **5h** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 46 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.41 (s, 1H), 8.18 (d, *J* = 5.2 Hz, 1H), 8.06 (d, *J* = 9.9 Hz, 1H), 7.49 – 7.32 (m, 2H), 7.03 – 6.88 (m, 3H), 6.17 (d, *J* = 9.9 Hz, 1H), 4.17 – 3.92 (m, 3H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.31 (s, 3H), 2.01 – 1.73 (m, 3H), 1.55 – 1.37 (m, 1H), carboxylic acid proton was not detected. **^{13}C NMR** (50 MHz, $CDCl_3$) δ 171.70, 170.59, 162.87 (d, *J* = 246.8 Hz), 153.05, 147.47, 147.12, 144.10, 143.03, 140.49, 129.88 (d, *J* = 3.4 Hz), 129.74 (d, *J* = 8.1 Hz), 128.17, 121.99, 116.00, 115.69 (d, *J* = 21.6 Hz), 115.40, 77.44, 68.04, 49.05, 28.95, 25.36, 24.17. **ESI-HRMS**: $[M+H]^+$ calculated: 483.14968, found: 483.14985.

(*Z*)-3-((5-(2-Acetamidopyridin-4-yl)-1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6p)

6p was synthesized from **5j** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM → DCM/*i*PrOH 90/10 as eluent afforded 76 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.70 (s, 1H), 10.66 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 7.97 (d, *J* = 9.9 Hz, 1H), 7.49 – 7.32 (m, 2H), 7.21 – 7.01 (m, 3H), 6.12 (d, *J* = 10.0 Hz, 1H), 5.12 (s, 1H), 4.65 (s, 1H), 4.11 – 3.94 (m, 1H), 3.88 – 3.68 (m, 1H), 3.19 (s, 2H), 2.08 (s, 3H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 169.48, 167.30, 161.12 (d, *J* = 242.9 Hz), 152.74, 148.80, 145.04, 142.71, 140.08, 137.27, 130.16 (d, *J* = 2.8 Hz), 128.48, 128.27 (d, *J* = 7.7 Hz), 120.93, 115.43, 115.22 (d, *J* = 21.6 Hz), 114.80, 70.05, 63.65, 48.25, 23.93. **ESI-HRMS**: $[M+H]^+$ calculated: 473.12895, found: 473.12912.

2-((1-(2,2-Dimethoxyethyl)-4-(4-fluorophenyl)-5-(2-fluoropyridin-4-yl)-1*H*-imidazol-2-yl)thio)acetonitrile (14a)

5i (1 eq), 2-chloroacetonitrile (1,1 eq) and potassium carbonate (3 eq) were suspended in dry THF (20 mL/ mmol **5i**) and refluxed for 3,5 h until complete conversion was detected. The residue was diluted with EtOAc and water and several times extracted with EtOAc. The organic layers were filtered, evaporated to dryness and purified by silica flash-chromatography (ethyl acetate/ petrol ether 30/70 → 60/40) to afford the title compound in 78 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.9 Hz, 1H), 7.41 – 7.25 (m, 2H), 7.15 (d, *J* = 4.7 Hz, 1H), 7.03 – 6.87 (m, 3H), 4.43 (t, *J* = 4.7 Hz, 1H), 4.20 – 4.03 (m, 4H), 3.41 (s, 6H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 148.77 (d, *J* = 15.5 Hz), 144.02, 140.60 (d, *J* = 16.8 Hz), 129.18 (d, *J* = 8.1 Hz), 129.09, 123.39 (d, *J* = 4.4 Hz), 116.40, 115.60 (d, *J* = 21.6 Hz), 111.53 (d, *J* = 37.8 Hz), 103.10, 55.69, 47.27, 20.02. C1 of p-fluorophenyl was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 417.11913, found: 417.11957.

2-((5-(2-(Cyclopropylamino)pyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acetonitrile (14b)

13c (1 eq), 2-chloroacetonitrile (1.1 eq) and potassium carbonate (3 eq) were suspended in dry THF (20 mL / mmol **13c**) and refluxed for 3.5 h until complete conversion was detected. The residue was diluted with EtOAc and water and several times extracted with EtOAc. The organic layers were filtered, evaporated to dryness and purified by silica flash-chromatography (ethyl acetate / petrol ether (50/50 → 80/20) to afford the title compound in 75 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.1 Hz, 1H), 7.56 – 7.41 (m, 2H), 7.01 – 6.87 (m, 2H), 6.72 (s, 1H), 6.62 (dd, *J* = 5.1, 1.4 Hz, 1H), 5.31 – 5.22 (m, 1H), 4.33 (t, *J* = 5.3 Hz, 1H), 4.08 (d, *J* = 5.3 Hz, 2H), 3.99 (s, 2H), 3.28 (s, 6H), 2.51 – 2.36 (m, 1H), 0.79 – 0.66 (m, 2H), 0.55 – 0.43 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.20 (d, *J* = 246.5 Hz), 160.55, 149.57, 140.04, 139.69, 139.30, 129.70 (d, *J* = 3.2 Hz), 129.63 (d, *J* = 0.9 Hz), 128.85 (d, *J* = 8.0 Hz), 116.57, 115.30 (d, *J* = 21.6 Hz), 115.08, 107.77, 103.26, 55.48, 47.24, 24.05, 20.21, 7.82. **ESI-HRMS**: $[M+H]^+$ calculated: 454.17075, found: 454.17086.

(*Z*)-3-((5-(2-(Cyclopropylamino)pyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (14c)

14c was synthesized from **13c** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/*i*PrOH/AcOH 89/10/1 as eluent afforded 72 % of the title compound. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.05 (d, *J* = 5.3 Hz, 1H), 7.62 (d, *J* = 9.8 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.10 – 6.97 (m, 2H), 6.76 (s, 1H), 6.71 – 6.63 (m, 1H), 6.11 (d, *J* = 9.8 Hz, 1H), 4.40 (t, *J* = 5.0 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.26 (s, 6H), 2.55 – 2.42 (m, 1H), 0.80 – 0.67 (m, 2H), 0.52 – 0.41 (m, 2H). NH- and carboxylic acid-protons were not detected due to a proton/deuterium exchange with deuterated methanol. **^{13}C NMR** (50 MHz, methanol—*d4*) δ 170.17, 163.60 (d, *J* = 245.7 Hz), 161.26, 148.37, 145.80, 144.99, 141.81, 140.18, 130.94 (d, *J* = 3.3 Hz), 130.78 (d, *J* = 0.7 Hz), 130.48 (d, *J* = 8.1 Hz), 117.42, 116.13 (d, *J* = 21.8 Hz), 115.48, 111.00, 104.37, 55.76, 24.59, 7.82. **ESI-HRMS**: $[M+H]^+$ calculated: 485.16533, found: 485.16549.

(*Z*)-3-((5-(2-(*sec*-Butylamino)pyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (14d)

14d was synthesized from **13d** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM/AcOH 99/1 → DCM/ethanol/AcOH 89/10/1 as eluent afforded 43 % of the title compound. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.01 (d, *J* = 5.9 Hz, 1H), 7.53 – 7.35 (m, 3H), 7.06 – 6.94 (m, 2H), 6.56 – 6.47 (m, 2H), 6.09 (d, *J* = 9.6 Hz, 1H), 4.39 (t, *J* = 4.9 Hz, 1H), 4.16 (d, *J* = 5.1 Hz, 2H), 3.25 (s, 6H), 1.59 – 1.44 (m, 2H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). NH- and carboxylic acid-protons were not detected due to a proton/deuterium exchange with deuterated methanol. **^{13}C NMR** (50 MHz, methanol-*d4*) δ 163.52 (d, *J* = 245.3 Hz), 160.31, 148.72, 145.30, 143.51, 141.27, 139.78, 131.01 (d, *J* = 3.3 Hz), 130.78 (d, *J* = 0.7 Hz), 130.35 (d, *J* = 8.0 Hz), 119.50, 116.06 (d, *J* = 21.8 Hz), 114.20, 111.88, 104.37, 55.68, 49.29, 30.51, 20.52, 10.79. **ESI-HRMS**: $[M+H]^+$ calculated: 501.19663, found: 501.19724.

(*Z*)-3-((5-(2-((1-(ethylcarbamoyl)piperidin-4-yl)amino)pyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)acrylic acid (14e)

19 (1 eq) was dissolved in THF (9,5 mL / mmol **19**), KOH 10 % (19 mL / 1mmol **19**) was added and the reaction mixture was heated to 95 °C for 2 h until TLC and HPLC detected complete conversion. THF was evaporated under reduced pressure and to the aqueous layer was added a saturated solution of ammonium chloride to adjust the pH of the solution to 5. The aqueous layer was extracted with DCM .The combined organic layers where dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. Silica flash-chromatography (DCM / 1 % AcOH → DCM / 10 % MeOH / 1 % AcOH) gave 19 % of the title compound. **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 8.09 (s, 1H), 7.91 (d, *J* = 9.3 Hz, 1H), 7.82 (d, *J* = 15.5 Hz, 1H), 7.47 (s, 2H), 7.21 – 7.06 (m, 2H), 6.72 – 6.62 (m, 1H), 6.53 – 6.36 (m, 3H), 6.15 (d, J = 9.5 Hz, 1H), 5.77 (d, J = 15.2 Hz, 1H), 3.91 – 3.79 (m, 2H), 3.49 – 3.37 (m, 3H), 3.08 – 2.97 (m, 2H), 2.87 – 2.69 (m, 2H), 1.93 – 1.76 (m, 2H), 1.31 – 1.13 (m, 3H), 1.05 – 0.91 (m, 3H). Carboxylic acid proton was not detected. **^{13}C NMR** (100 MHz, DMSO-*d6*) δ 158.57, 157.21, 148.60, 142.68, 141.10, 138.21, 136.63, 130.33, 129.45, 128.17 (d, *J* = 8.2 Hz), 115.29, 115.10 (d, *J* = 21.2 Hz), 112.36, 109.14, 47.41, 42.42, 34.81, 31.75, 31.54, 15.57. C1 and C4 of *p*-fluorophenyl residue were not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 525.20786, found: 525.20800.

(*Z*)-3-((1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)acrylic acid (14f)

14f was synthesized from **13b** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of DCM 99 → DCM/*i*PrOH 90/10 as eluent afforded 19 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.7 Hz, 1H), 7.81 (d, *J* = 9.8 Hz, 1H), 7.48 – 7.28 (m, 2H), 7.26 – 6.87 (m, 7H), 6.76 (s, 1H), 6.67 (d, *J* = 5.3 Hz, 1H), 6.10 (d, *J* = 9.8 Hz, 1H), 3.81 (d, *J* = 6.6 Hz, 2H), 0.93 – 0.74 (m, 1H), 0.51 – 0.31 (m, 2H), 0.21 – 0.08 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.01 (d, *J* = 246.6 Hz), 159.65, 156.57, 148.32, 144.43, 142.17, 140.66, 139.34 (d, *J* = 1.6 Hz), 129.33 (d, *J* = 3.2 Hz), 129.21, 129.02 (d, *J* = 8.0 Hz), 128.11, 123.55, 120.73, 115.54, 115.47, 115.16 (d, *J* = 21.5 Hz), 109.68, 49.64, 11.72, 4.14. **ESI-HRMS**: $[M+H]^+$ calculated: 487.15985, found: 487.16018.

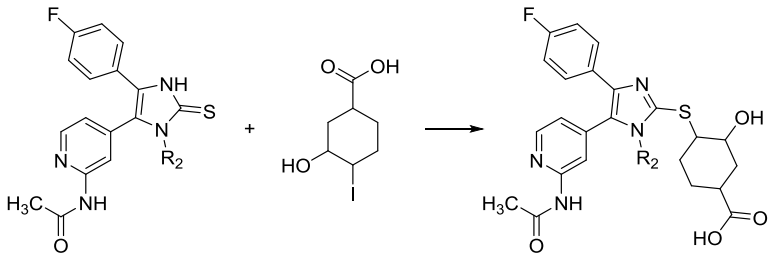
Ethyl (*Z*)-3-((4-(4-fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)acrylate (14i)

14i was synthesized from **13a** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of ethyl acetate/petrol ether (70-90) 70/30 → ethyl acetate as eluent afforded 52 % of the title compound. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.01 (d, *J* = 5.5 Hz, 1H), 7.71 (d, *J* = 9.9 Hz, 1H), 7.58 – 7.40 (m, 2H), 7.36 – 7.05 (m, 6H), 7.03 – 6.74 (m, 3H), 6.08 (d, *J* = 9.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 4H). NH protons were not detected due to a proton/deuterium exchange with deuterated methanol **^{13}C NMR** (50 MHz, methanol-*d4*) δ 164.22 (d, *J* = 247.5 Hz), 161.76, 157.99, 148.86, 146.28, 142.11, 142.01, 131.79 (d, *J* = 8.3 Hz), 129.93, 123.20, 120.98, 116.89 (d, *J* = 22.1 Hz), 115.59, 113.96, 108.33, 61.68, 14.61. **ESI-HRMS**: $[M+H]^+$ calculated: 461.14420, found: 461.14472.

Ethyl (*Z*)-3-((4-(4-fluorophenyl)-1-methyl-5-(2-(piperidin-4-ylamino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)acrylate (14j)

14j was synthesized from **18** according to general procedure II. The crude product was purified by silica flash-chromatography using a gradient of ethyl acetate/petrol ether (70-90) 70/30 → ethyl acetate as eluent afforded 69 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.10 – 7.91 (m, 2H), 7.52 – 7.38 (m, 2H), 7.04 – 6.88 (m, 2H), 6.79 (s, 1H), 6.47 (d, *J* = 5.9 Hz, 1H), 6.11 (d, *J* = 9.8 Hz, 1H), 4.33 – 4.14 (m, 3H), 3.64 – 3.46 (m, 5H), 3.24 – 3.06 (m, 2H), 2.27 (m, 2H), 2.04 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 4H). **ESI-HRMS**: $[M+H]^+$ calculated: 482.2021, found: 482.2019.

Synthesis of compounds 6q-t



4-((5-(2-Acetamidopyridin-4-yl)-1-cyclohexyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)-3-hydroxycyclohexane-1-carboxylic acid (6q)

According to general procedure IIIb, **6q** was synthesized from **5e** and **12**. Purification by silica flash-chromatography using a gradient of DCM → DCM/*i*PrOH 90/10 as eluent afforded 16 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.34 (s, 1H), 8.17 (d, *J* = 5.1 Hz, 1H), 7.36 – 7.16 (m, 2H), 7.02 – 6.85 (m, 3H), 4.02 – 3.71 (m, 2H), 3.54 – 3.27 (m, 1H), 2.53 (s, 1H), 1.86 (d, *J* = 7.1 Hz, 4H), 1.64 (d, *J* = 4.3 Hz, 5H), 1.39 – 1.07 (m, *J* = 10.2 Hz, 7H), 1.01 – 0.71 (m, 3H). Proton of carboxylic acid was not detected. **^{13}C NMR** (50 MHz, $CDCl_3$) δ 179.59, 169.88, 162.15 (d, *J* = 246.7 Hz), 152.56, 146.85, 143.11, 142.67, 137.84, 129.07 (d, *J* = 3.3 Hz),

128.91 (d, *J* = 8.0 Hz), 127.32, 121.66, 116.45, 115.45 (d, *J* = 21.6 Hz), 77.79, 77.16, 76.52, 75.51, 57.96, 54.46, 41.64, 38.37, 35.54, 32.56, 31.99, 31.33, 31.16, 29.80, 28.96, 26.54, 26.44, 26.27, 26.05, 25.01, 24.54, 23.01, 22.79. Carbon atoms of cyclohexyl give two signals presumably due to restricted rotatability or diastereomerism. **ESI-HRMS**: $[M+H]^+$ calculated: 553.22793, found: 553.22844.

4-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl)thio)-3-hydroxycyclohexane-1-carboxylic acid (6r)

According to general procedure IIIb, **6r** was synthesized from **5a** and **12**. Purified by silica flash-chromatography using a gradient of DCM → DCM/*i*PrOH 90/10 as eluent afforded 28 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 12.13 (s, 1H), 10.67 (s, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.04 (s, 1H), 7.46 – 7.27 (m, 2H), 7.20 – 6.95 (m, 3H), 5.31 (s, 1H), 3.47 (s, 3H), 3.23 – 3.03 (m, 1H), 2.43 – 2.22 (m, 1H), 2.22 – 1.94 (m, 5H), 1.83 (d, *J* = 13.0 Hz, 1H), 1.65 – 1.10 (m, 3H). **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 175.90, 169.87, 161.44 (d, *J* = 243.8 Hz), 153.13, 149.19, 141.82, 140.43, 137.59, 130.59 (d, *J* = 3.1 Hz), 128.64 (d, *J* = 8.0 Hz), 120.72, 115.58 (d, *J* = 21.5 Hz), 114.55, 71.74, 54.75, 32.69, 31.62, 28.57, 24.25. **ESI-HRMS**: $[M+H]^+$ calculated: 485.16533, found: 485.16508.

4-((5-(2-Acetamidopyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)-3-hydroxycyclohexane-1-carboxylic acid (6s)

According to general procedure IIIb, **6s** was synthesized from **5i** and **12,** and purified by silica flash-chromatography using a gradient of DCM → DCM/*i*PrOH 90/10 as eluent afforded 19 % of the title compound. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.36 (d, *J* = 4.9 Hz, 1H), 8.14 (s, 1H), 7.45 – 7.30 (m, 2H), 7.13 – 6.90 (m, 3H), 4.44 – 4.32 (m, 1H), 4.28 – 4.14 (m, 2H), 3.80 – 3.48 (m, 2H), 3.23 (s, 6H), 2.72 (s, 1H), 2.53 – 2.32 (m, 1H), 2.17 (s, 3H), 2.08 – 1.25 (m, 5H). Polar Protons were not detected due to a proton/deuterium exchange with methanol-*d4*. **^{13}C NMR** (50 MHz, methanol-*d4*) δ 178.21, 172.25, 163.56 (d, *J* = 245.4 Hz), 153.82, 149.92, 144.02, 142.06, 140.01, 130.84 (d, *J* = 3.0 Hz), 130.46 (d, *J* = 8.2 Hz), 130.17, 122.74, 117.26, 116.11 (d, *J* = 21.8 Hz), 104.54, 72.49, 55.75, 55.66, 53.40, 40.26, 32.49, 31.48, 25.59, 23.98. **ESI-HRMS**: $[M+H]^+$ calculated: 559.20211, found: 559.20258.

4-((5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-2-yl)thio)-3-hydroxycyclohexane-1-carboxylic acid (6t)

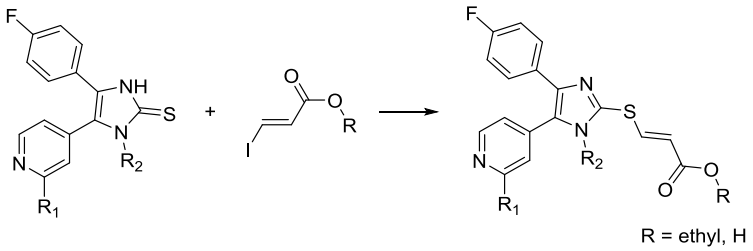
According to general procedure IIIb, **6t** was synthesized from **5h** and **12** and purified by silica flash-chromatography using a gradient of DCM → DCM/*i*PrOH 90/10 as eluent afforded 17 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.36 (s, 1H), 8.14 (d, *J* = 5.1 Hz, 1H), 7.41 – 7.22 (m, 2H), 7.03 – 6.79 (m, 3H), 4.17 – 3.73 (m, 4H), 3.71 – 3.50 (m, 2H), 3.23 (s, 1H), 2.61 – 2.40 (m, 2H), 2.33 – 2.02 (m, 5H), 1.95 – 1.38 (m, 7H). Carboxylic proton was not detected. **^{13}C NMR** (50 MHz, $CDCl_3$) δ 180.20, 180.19, 170.55, 162.80 (d, *J* = 246.8 Hz), 153.06, 153.03, 145.13, 144.63, 142.96 (d, *J* = 3.2 Hz), 139.07 (d, *J* = 1.4 Hz), 129.41 (d, *J* = 8.0 Hz), 127.70, 127.67, 127.29, 127.28, 122.08, 121.97, 116.10, 116.02, 115.71 (d, *J* = 21.6 Hz), 77.60, 77.47, 75.25, 75.11, 68.08, 67.97, 54.68, 49.23, 49.03, 41.41, 37.77, 28.80, 25.30, 25.21, 24.22. The ^{13}C spectra shows rotamers resulting in multiple signals for one carbon atom. **ESI-HRMS**: $[M+H]^+$ calculated: 555.20720, found: 555.20736.

***N*-(4-(1-Cyclohexyl-4-(4-fluorophenyl)-2-((6-iodopyridin-2-yl)thio)-1*H*-imidazol-5-yl)pyridin-2-yl)acetamide (6y)**

In an oven dried Schlenk flask potassium *tert*-butanolate (2 eq), **5e** (1 eq), Cu_2O (0.005 eq) and 2,6-diiodopyridine (1 eq) were combined under argon atmosphere and dry dioxane (4 mL / 1mmol **5e**) was added. The resulting suspension was heated to 110 °C and stirred over night. The reaction mixture was allowed to cool to room temperature and was then diluted with ethyl acetate, filtered through a pad of Celite and washed with ethyl acetate. The solvents were evaporated under reduced pressure and the crude product was purified by silica flash-chromatography using a gradient of ethyl acetate/*n*-hexane 50/50 → ethyl acetate/*n*-hexane 80/30 to afford the title compound (60 % yield).[13] **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 10.73 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.14 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.24 (m, 3H), 7.20 – 6.99 (m, 4H), 4.05 (s, 1H), 2.09 (s, 3H), 1.84 (s,

3H), 1.76 – 0.71 (m, 7H). .**^{13}C NMR** (50 MHz, DMSO-*d6*) δ 170.03, 160.20, 153.08, 149.33, 140.84, 139.98, 139.07, 134.22, 132.16, 130.17 (d, *J* = 3.0 Hz), 130.05, 128.63 (d, *J* = 8.1 Hz), 121.67, 120.84, 118.26, 115.57 (d, *J* = 21.5 Hz), 115.56, 65.25, 58.84, 32.43, 26.00, 24.90, 24.28, 15.51. **ESI-HRMS**: $[M+H]^+$ calculated: 614.08813 found: 614.08792.

Synthesis of compounds: 6u-x and 14g-h, 14k



R = ethyl, H

Ethyl (*E*)-3-((5-(2-acetamidopyridin-4-yl)-1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylate (6u)

According to the general procedure IV, **6u** was synthesized from **5b** and **9**. Purification by silica flash-chromatography using a gradient of: ethyl acetate/petrol ether (70-90) 80/20 afforded 74 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.36 (s, 1H), 8.29 – 8.09 (m, 2H), 7.53 – 7.32 (m, 2H), 7.04 – 6.82 (m, 3H), 6.09 (d, *J* = 15.6 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.31 – 3.11 (m, 1H), 2.21 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.08 – 0.89 (m, 2H), 0.75 – 0.60 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.86, 164.68, 162.13 (d, *J* = 246.7 Hz), 151.87, 147.82, 141.50, 140.81, 140.53, 139.62, 129.51, 129.36 (d, *J* = 3.3 Hz), 129.34 (d, *J* = 8.0 Hz), 120.52, 118.20, 115.16 (d, *J* = 21.5 Hz), 115.08, 60.51, 26.83, 24.60, 14.18, 9.36. **ESI-HRMS**: $[M+H]^+$ calculated: 467.15477, found: 467.15489.

Ethyl (*E*)-3-((5-(2-acetamidopyridin-4-yl)-1-(2,2-dimethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylate (6v):

According to the general procedure IV, **6v** was synthesized from **5i** and **9**. Purification by silica flash-chromatography using a gradient of: ethyl acetate/petrol ether(70-90) 80/20 afforded 42 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.38 – 8.23 (m, 2H), 7.85 (d, *J* = 15.4 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.02 – 6.83 (m, 3H), 5.96 (d, *J* = 15.4 Hz, 1H), 4.36 (t, *J* = 5.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 5.2 Hz, 2H), 3.25 (s, 6H), 2.21 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 169.00, 164.81, 162.26 (d, *J* = 246.8 Hz), 152.44, 148.61, 143.29, 141.07, 140.16, 138.28, 129.30 (d, *J* = 3.2 Hz), 129.09 (d, *J* = 8.0 Hz), 129.09, 121.79, 118.33, 115.55, 115.33 (d, *J* = 21.7 Hz), 103.12, 60.70, 55.49, 47.38, 24.81, 14.38. **ESI-HRMS**: $[M+H]^+$ calculated: 515.17590, found: 515.17587.

Ethyl (*E*)-3-((5-(2-acetamidopyridin-4-yl)-1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylate (6w)

According to the general procedure IV, **6w** was synthesized from **5f** and **9**. Purification by silica flash-chromatography using a gradient of: ethyl acetate/petrol ether(70-90) 80/20 afforded 67 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.45 (d, *J* = 5.1 Hz, 1H), 8.11 (s, 1H), 7.95 (d, *J* = 15.3 Hz, 1H), 7.48 – 7.32 (m, 2H), 7.22 – 7.02 (m, 3H), 6.00 (d, *J* = 15.3 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.79 (d, *J* = 6.8 Hz, 2H), 2.08 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 2H), 0.43 – 0.28 (m, 2H), 0.13 – -0.01 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 169.56, 165.36, 152.84, 149.26, 143.33, 141.77, 140.93, 137.12, 129.77 (d, *J* = 3.2 Hz), 129.46 (d, *J* = 8.0 Hz), 129.00, 122.04, 118.66, 115.62 (d, *J* = 21.5 Hz), 115.38, 77.80, 77.16, 76.52, 60.66, 49.77, 24.57, 14.01, 11.72, 4.04. C1-signal of p-fluorophenyl residue was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 481,17042, found: 481,17071.

(*E*)-3-((5-(2-Acetamidopyridin-4-yl)-1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)thio)acrylic acid (6x)

6w (1 eq) was dissolved in THF (9.5 mL / mmol **6w**), KOH 10 % (19 mL / 1mmol **6w**) was added and the mixture stirred at room temperature overnight. TLC and HPLC detected complete conversion. The THF was evaporated under reduced pressure and to the aqueous layer was added a saturated solution of ammonium chloride to adjust the pH of the solution to 5. The aqueous layer was extracted three times with DCM. The combined

organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. Silica flash-chromatography (DCM / 1 % AcOH → DCM/ 4 % MeOH/1 % AcOH) gave 58 % of the title compound. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.19 (s, 1H) , 8.42 (s, 1H), 8.21 (d, *J* = 5.2 Hz, 1H), 7.92 (d, *J* = 15.0 Hz, 1H), 7.52 – 7.32 (m, 2H), 7.08 – 6.83 (m, 3H), 5.97 (d, *J* = 15.0 Hz, 1H), 3.88 (d, *J* = 5.9 Hz, 2H), 2.25 (s, 3H), 1.01 – 0.73 (m, 1H) , 0.56 – 0.28 (m, 2H), 0.18 – -0.04 (m, 2H). Carboxylic acid proton was not detected. **^{13}C NMR** 13C NMR (50 MHz, $CDCl_3$) δ 170.05, 169.21, 162.37 (d, *J* = 247.3 Hz), 152.72, 147.07, 143.99, 142.33, 140.78, 137.20, 129.28 (d, *J* = 8.1 Hz), 129.24, 128.41, 121.39, 118.94, 115.73, 115.47 (d, *J* = 21.7 Hz), 50.03, 24.61, 12.14, 4.55. **ESI-HRMS**: $[M+H]^+$ calculated: 453.13912, found: 453.13929.

(*E*)-3-((1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)acrylic acid (14g)

14k (1 eq) was dissolved in THF (9.5 mL / mmol **14k**), KOH 10 % (19 mL / mmol **14k**) was added and was heated to 95 °C for 2 h until TLC and HPLC detected complete conversion. THF was evaporated under reduced pressure and to the aqueous layer was added a saturated solution of ammonium chloride to adjust the pH of the solution to 5. The aqueous layer was extracted three times with DCM .The combined organic layers where dried over sodium sulfate and the solvent was removed under reduced pressure. Silica flash-chromatography (DCM / 1 % AcOH → DCM / 4 % MeOH / 1 % AcOH) gave 63 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 9.19 (s, 1H), 8.30 (d, *J* = 4.9 Hz, 1H), 7.86 (d, *J* = 15.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.38 (m, 2H), 7.33 – 7.07 (m, 4H), 6.95 – 6.77 (m, 3H), 5.87 (d, *J* = 15.2 Hz, 1H), 3.81 (d, *J* = 6.7 Hz, 2H), 0.97 – 0.86 (m, 1H), 0.47 – 0.33 (m, 2H), 0.12 (d, *J* = 5.0 Hz, 2H). Carboxylic acid proton was not detected. **^{13}C NMR** (50 MHz, DMSO-*d6*) δ 162.19 (d, *J* = 246.0 Hz), 156.89, 148.25, 142.93, 140.52, 139.65, 139.59, 135.88, 129.81, 129.17 (d, *J* = 3.2 Hz), 128.99 (d, *J* = 8.2 Hz), 128.40, 121.77, 119.22, 118.19, 115.12, 114.97, 114.75 (d, *J* = 21.9 Hz), 111.39, 49.58, 21.56, 11.39, 3.21. **ESI-HRMS**: $[M+H]^+$ calculated: 487.15985, found: 487.15997.

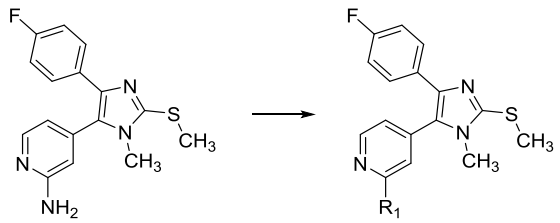
(Z)-3-((4-(4-Fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1H-imidazol-2-yl)thio)acrylic acid (14h)

14i (1 eq) was dissolved in THF (9.5 mL / mmol **14i**), KOH 10 % (19 mL / mmol **14i**) was added and was heated to 95 °C for 2 h until TLC and HPLC detected complete conversion. THF was evaporated under reduced pressure and to the aqueous layer was added a saturated solution of ammonium chloride to adjust the pH of the solution to 5. The aqueous layer was extracted three times with DCM .The combined organic layers where dried over sodium sulfate and the solvent was removed under reduced pressure. Silica flash-chromatography (DCM → DCM / 46 % MeOH) gave 23 % of the title compound. **^{1}H NMR** (200 MHz, DMSO-*d6*) δ 13.09 (s, 1H), 12.67 (s, 1H), 9.04 (s, 1H), 8.21 – 7.89 (m, 2H), 7.58 (d, *J* = 8.1 Hz, 4H), 7.40 – 7.01 (m, 5H), 6.95 – 6.65 (m, 2H), 6.13 (d, *J* = 9.7 Hz, 1H). **^{13}C NMR** (50 MHz, DMSO) δ 167.38, 156.23, 147.21, 143.77, 142.63, 141.65, 140.09, 135.06, 130.81 (d, J = 8.1 Hz), 130.49, 128.57, 126.50, 120.42, 118.17, 115.90 (d, J = 22.6 Hz), 115.21, 112.01, 107.40. C1 of p-fluorophenyl residue was not detected. C4 of p-fluorophenyl residue did not appear as a doublet. Signals are broadened due to inter and/or intramolecular salt bridges. **ESI-HRMS**: $[M+H]^+$ calculated: 433.1129, found: 433.1132.

Ethyl (*E*)-3-((1-(cyclopropylmethyl)-4-(4-fluorophenyl)-5-(2-(phenylamino)pyridin-4-yl)-1*H*-imidazol-2-yl)thio)acrylate (14k)

According to the general procedure IV, **14k** was synthesized from **13a** and **9**. Purification by silica flash-chromatography using a gradient of: ethyl acetate/petrol ether (70-90) 70/30 afforded 79 % of the title compound. **^{1}H NMR** (200 MHz, methanol-*d4*) δ 8.28 – 8.18 (m, 1H), 7.81 (d, *J* = 15.2 Hz, 1H), 7.53 – 7.39 (m, 4H), 7.24 (t, *J* = 7.9 Hz, 2H), 7.12 – 6.90 (m, 3H), 6.81 – 6.71 (m, 2H), 5.82 (d, *J* = 15.2 Hz, 1H), 4.31 – 4.10 (m, 2H), 4.02 – 3.90 (m, 2H), 1.36 – 1.19 (m, 3H), 1.04 – 0.84 (m, 1H), 0.52 – 0.37 (m, 2H), 0.21 – 0.12 (m, 2H). NH Proton was not detected due to a proton/deuterium exchange with deutrated methanol. **ESI-HRMS**: $[M+H]^+$ calculated: 515.1912, found: 515.1904.

Synthesis of compounds 16a-k



4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-(3-methoxyphenyl)pyridin-2-amine (16a)
According to general procedure VI, **16a** was synthesized from **15** and 1-bromo-3-methoxybenzene. Eluent: ethyl acetate/*n*-hexane 10/90 → ethyl acetate/*n*-hexane 40/60 afforded 70 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.38 (m, 2H), 7.14 (t, *J* = 8.2 Hz, 1H), 7.03 – 6.87 (m, 3H), 6.82 (s, 1H), 6.79 – 6.52 (m, 4H), 3.72 (s, 3H), 3.46 (s, 3H), 2.69 (s, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.11 (d, *J* = 246.1 Hz), 160.69, 156.75, 149.42, 144.79, 141.22, 140.43, 138.82, 130.28 (d, *J* = 3.3 Hz), 130.19, 129.04 (d, *J* = 8.0 Hz), 128.25, 116.11, 115.35 (d, *J* = 21.5 Hz), 112.87, 109.51, 108.64, 106.69, 77.79, 77.16, 76.52, 55.32, 31.96, 16.16. **ESI-HRMS**: $[M+H]^+$ calculated: 421.14929, found: 421.14949.

4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-(4-methoxyphenyl)pyridin-2-amine (16b)
According to general procedure VI, **16b** was synthesized from **15** and 1-bromo-4-methoxybenzene. Eluent: ethyl acetate/*n*-hexane 10/90 → ethyl acetate/*n*-hexane 40/60 afforded 49 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.0 Hz, 1H), 7.54 – 7.36 (m, 2H), 7.14 – 6.89 (m, 4H), 6.87 – 6.75 (m, 2H), 6.70 (s, 1H), 6.65 – 6.56 (m, 1H), 6.51 (s, 1H), 3.78 (s, 3H), 3.45 (s, 3H), 2.67 (s, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 158.10, 156.71, 149.40, 144.69, 140.22, 138.84, 132.60, 130.39 (d, *J* = 3.3 Hz), 129.17 (d, *J* = 7.9 Hz), 128.48, 124.38, 115.28 (d, *J* = 21.4 Hz), 115.19, 114.78, 108.30, 55.63, 31.97, 16.16. C1 of p-fluorophenyl residue was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 421.14929, found: 421.14954.

4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-(4-morpholinophenyl)pyridin-2-amine (16c)
According to general procedure VI, **16c** was synthesized from **15** and 4-(4-bromophenyl)morpholine. Eluent: ethyl acetate/*n*-hexane 40/60 → ethyl acetate/*n*-hexane 60/40 afforded 82 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.22, 8.20, 7.49, 7.46, 7.44, 7.42, 7.26, 7.08, 7.03, 7.01, 6.96, 6.92, 6.82, 6.78, 6.68, 6.61, 6.58, 6.53, 3.88, 3.86, 3.83, 3.45, 3.12, 3.10, 3.07, 2.68. **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.07 (d, *J* = 245.7 Hz), 158.02, 149.41, 148.40, 144.67, 140.20, 138.77, 132.16, 130.40 (d, *J* = 3.1 Hz), 129.15 (d, *J* = 7.9 Hz), 128.48, 123.86, 116.80, 115.27 (d, *J* = 21.4 Hz), 115.16, 108.41, 67.03, 49.82, 31.98, 16.16. **ESI-HRMS**: $[M+H]^+$ calculated: 476.19149, found: 476.19147.

4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)-*N*-(2-methoxyphenyl)pyridin-2-amine (16d)
According to general procedure VI, **16d** was synthesized from **15** and 1-bromo-2-methoxybenzene. Eluent: ethyl acetate/*n*-hexane 10/90 → ethyl acetate/*n*-hexane 40/60 afforded 90 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.2 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.56 – 7.41 (m, 2H), 7.07 – 6.80 (m, 6H), 6.74 (s, 1H), 6.70 – 6.61 (m, 1H), 3.86 (s, 3H), 3.47 (s, 3H), 2.70 (s, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 156.43, 149.28, 149.02, 144.63, 140.20, 138.70, 130.34 (d, *J* = 3.1 Hz), 129.72, 129.00 (d, *J* = 8.0 Hz), 128.30, 122.37, 120.98, 118.63, 116.01, 115.35 (d, *J* = 21.4 Hz), 110.58, 110.45, 55.77, 31.95, 16.18. **ESI-HRMS**: $[M+H]^+$ calculated: 421.14929, found: 421.14973.

***N*-(2,4-Dimethoxyphenyl)-4-(4-(4-fluorophenyl)-1-methyl-2-(methylthio)-1H-imidazol-5-yl)pyridin-2-amine (16e)**

According to general procedure VI, **16e** was synthesized from **15** and 1-bromo-2,4-dimethoxybenzene. Eluent: ethyl acetate/*n*-hexane 10/90 → ethyl acetate/*n*-hexane 40/60 afforded 43 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.30 – 8.19 (m, 1H), 7.57 – 7.40 (m, 3H), 7.04 – 6.87 (m, 2H), 6.70 – 6.54 (m, 3H), 6.54 – 6.45 (m, 1H), 6.40 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.80 (d, *J* = 2.0 Hz, 6H), 3.46 (s, 3H), 2.69 (s, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.03 (d, *J* = 245.7 Hz), 157.49, 156.55, 151.77, 149.25, 144.46, 140.10, 138.55, 130.39 (d, *J* = 3.1 Hz), 128.97 (d, *J* = 7.9 Hz), 128.46, 122.58, 122.03, 115.36, 115.26 (d, *J* = 21.4 Hz), 109.30, 103.96, 99.35, 55.76, 55.70, 31.91, 16.19. **ESI-HRMS**: $[M+H]^+$ calculated: 451.15985, found: 451.16023.

_N_-(3-((4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1H-imidazol-5-yl)pyridin-2-yl)amino)phenyl)cyclopropanecarboxamide (16f)

According to general procedure VI, **16f** was synthesized from **15** and **17c**. Eluent: ethyl acetate/*n*-hexane 10/90 → ethyl acetate/*n*-hexane 40/60 afforded 79 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.2 Hz, 1H), 7.68 – 7.39 (m, 4H), 7.22 – 6.85 (m, 6H), 6.73 (s, 1H), 6.65 (d, *J* = 5.1 Hz, 1H), 3.47 (s, 3H), 2.68 (s, 3H), 1.58 – 1.40 (m, 1H), 1.12 – 0.98 (m, 2H), 0.91 – 0.75 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 172.15, 162.01 (d, *J* = 246.1 Hz), 156.59, 149.33, 144.76, 140.74, 140.35, 139.27, 138.75, 130.35 (d, *J* = 3.2 Hz), 129.83, 129.11 (d, *J* = 7.9 Hz), 128.32, 116.17, 115.80, 115.32 (d, *J* = 21.4 Hz), 114.29, 111.63, 109.68, 32.02, 16.20, 15.81, 8.16. **ESI-HRMS**: $[M+H]^+$ calculated: 474.17584, found: 474.17616.

_N_-(4-((4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1_H_-imidazol-5-yl)pyridin-2-yl)amino)phenyl)cyclopropanecarboxamide (16g)

According to general procedure VI, **16g** was synthesized from **15** and **17d**. Eluent: ethyl acetate/*n*-hexane 30/70 → ethyl acetate/*n*-hexane 60/40 afforded 79 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.4 Hz, 1H), 7.58 – 7.33 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.84 (s, 1H), 6.68 – 6.57 (m, 2H), 3.46 (s, 3H), 2.67 (s, 3H), 1.57 – 1.41 (m, 1H), 1.11 – 1.01 (m, 2H), 0.91 – 0.76 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.63 (d, *J* = 246.0 Hz), 157.61, 149.77, 145.24, 140.73, 139.29, 136.30, 134.46, 130.66 (d, *J* = 3.2 Hz), 129.51 (d, *J* = 8.0 Hz), 128.67, 128.66, 122.10, 121.31, 115.58 (d, *J* = 21.4 Hz), 115.36, 109.24, 31.72, 15.83, 15.35, 7.60. **ESI-HRMS**: $[M+H]^+$ calculated: 474.17584, found: 474.17598.

_N_-Cyclopropyl-4-((4-(4-(4-fluorophenyl)-1-methyl-2-(methylthio)-1_H_-imidazol-5-yl)pyridin-2-yl)amino)benzamide (16h)

According to general procedure VI, **16h** was synthesized from **15** and **17a**. Eluent: ethyl acetate/*n*-hexane 30/70 → ethyl acetate/*n*-hexane 60/40 afforded 72 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.33 (d, *J* = 5.4 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.39 (m, 2H), 7.37 – 7.27 (m, 2H), 6.98 (t, *J* = 8.9 Hz, 2H), 6.85 (s, 1H), 6.79 – 6.70 (m, 2H), 6.14 (s, 1H), 3.49 (s, 3H), 2.98 – 2.82 (m, 1H), 2.71 (s, 3H), 0.93 – 0.81 (m, 2H), 0.62 (s, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.48, 155.74, 149.23, 145.06, 143.52, 140.38, 138.98, 130.25 (d, *J* = 3.4 Hz), 129.15 (d, *J* = 7.9 Hz), 128.30, 128.00, 127.79, 118.30, 116.79, 115.41 (d, *J* = 21.5 Hz), 110.99, 32.00, 23.24, 16.10, 6.95. C1 of *p*-fluorophenyl was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 474,17584, found: 474,17636.

_N_-Cyclopropyl-3-((4-(4-(4-fluorophenyl)-1-methyl-2-(methylthio)-1_H_-imidazol-5-yl)pyridin-2-yl)amino)benzamide (16i)

According to general procedure VI, **16i** was synthesized from **15** and **17b**. Eluent: ethyl acetate/*n*-hexane 30/70 → ethyl acetate/*n*-hexane 60/40 afforded 86 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.2 Hz, 1H), 7.79 (s, 1H), 7.55 – 7.37 (m, 3H), 7.24 – 7.13 (m, 2H), 7.02 – 6.85 (m, 2H), 6.75 – 6.61 (m, 2H), 6.34 (s, 1H), 3.47 (s, 3H), 2.91 – 2.77 (m, 1H), 2.68 (s, 3H), 0.87 – 0.78 (m, 2H), 0.65 – 0.52 (m, 2H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.85, 162.06 (d, *J* = 246.0 Hz), 156.31, 149.17, 144.89, 140.91, 140.41, 138.80, 135.69, 130.26 (d, *J* = 3.2 Hz), 129.44, 129.02 (d, *J* = 8.0 Hz), 128.09, 122.52, 120.37, 118.86, 116.51, 115.35 (d, *J* = 21.4 Hz), 110.34, 32.02, 23.29, 16.16, 6.92. **ESI-HRMS**: $[M+H]^+$ calculated: 474,17584, found: 474,17576.

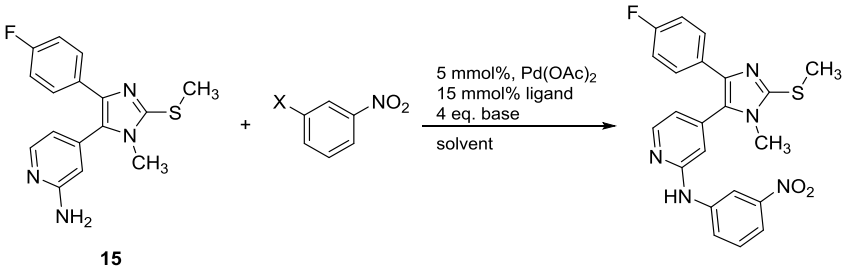
1-Ethyl-3-(3-((4-(4-(4-fluorophenyl)-1-methyl-2-(methylthio)-1_H_-imidazol-5-yl)pyridin-2-yl)amino)phenyl)urea (16j)

According to general procedure VI, **16j** was synthesized from **15** and **17e**. Eluent: ethyl acetate/*n*-hexane 30/70 → ethyl acetate/*n*-hexane 60/40 afforded 73 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.10 (d, J = 5.2 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.10 – 6.78 (m, 5H), 6.68 (s, 1H), 6.55 (d, J = 5.3 Hz, 1H), 3.46 (s, 3H), 3.16 (q, J = 7.3 Hz, 2H), 2.58 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H). No NH-proton was detected due to the deuterated methanol. **^{13}C NMR** (50 MHz, $CDCl_3$) δ 156.49, 156.11, 148.38, 144.53, 140.38, 140.17, 139.83, 138.58, 129.58 (d, J = 3.2 Hz), 129.31, 129.04 (d, J = 8.0 Hz), 128.19, 115.39, 115.04 (d, J = 21.5 Hz), 113.95, 113.65, 111.10, 109.94, 34.45, 31.92, 16.15, 14.97. The C1 of the *p*-fluorophenyl residue was not detected. **ESI-HRMS**: $[M+H]^+$ calculated: 477,18674, found: 477,18707.

1-Ethyl-3-(4-((4-(4-(4-Fluorophenyl)-1-methyl-2-(methylthio)-1*H*-imidazol-5-yl)pyridin-2-yl)amino)phenyl)urea (16k)

According to general procedure VI, **16k** was synthesized from **15** and **17f**. Eluent: ethyl acetate/*n*-hexane 30/70 → ethyl acetate/*n*-hexane 60/40 afforded 70 % yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.3 Hz, 1H), 7.51 – 7.36 (m, 2H), 7.20 – 7.02 (m, 4H), 7.01 – 6.86 (m, 3H), 6.77 (s, 1H), 6.69 – 6.58 (m, 2H), 4.98 (s, 1H), 3.46 (s, 3H), 3.36 – 3.14 (m, 2H), 2.67 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 162.12 (d, *J* = 246.1 Hz), 156.96, 156.29, 148.93, 144.99, 140.48, 139.05, 135.79, 134.44, 130.26 (d, *J* = 3.2 Hz), 129.24 (d, *J* = 8.0 Hz), 128.29, 122.83, 122.17, 115.70, 115.37 (d, *J* = 21.4 Hz), 109.34, 35.31, 32.07, 16.25, 15.55. **ESI-HRMS**: $[M+H]^+$ calculated: 477.18674, found: 477.18703.

Table S1. Buchwald-Hartwig cross coupling reaction optimization



Solvent	Ligand	Base	X	Conv.[a] [Yield[b]]
Toluene	Xphos	Cs_2CO_3	Cl	2%
DMF	Xphos	Cs_2CO_3	Cl	0%
Dioxane	Xphos	Cs_2CO_3	Cl	0%
Toluene/*t*-BuOH[c]	Xphos	Cs_2CO_3	Cl	15%
NMP	Xphos	Cs_2CO_3	Cl	0%
Dioxane/*t*-BuOH[d]	Xphos	Cs_2CO_3	Cl	77% [78%][e]
Dioxane/*t*-BuOH[d]	BINAP	Cs_2CO_3	Cl	0%
Dioxane/*t*-BuOH[d]	PPh_3	Cs_2CO_3	Cl	33%
Dioxane/*t*-BuOH[d]	tricyclohexylP	Cs_2CO_3	Cl	0%
Dioxane/*t*-BuOH[d]	tri-2-furylP	Cs_2CO_3	Cl	0%
Dioxane/*t*-BuOH[d]	Brettphos	Cs_2CO_3	Cl	99%[94%][f]
Dioxane/*t*-BuOH[d]	Xphos	*t*-BuOK	Cl	0%
Dioxane/t-BuOH[d]	Xphos	K_2CO_3	Cl	40%
Dioxane/*t*-BuOH[d]	Xphos	NaOH	Cl	60%
Dioxane/*t*-BuOH[d]	Brettphos	Cs_2CO_3	Br	99%[99%][g]
Dioxane/*t*-BuOH[d]	Brettphos	Cs_2CO_3	I	20%

[a]Conversion estimated via HPLC after 6h reaction time; [b]isolated yields; [c]Toluene/t-BuOH (4:1); [d]Dioxane/*t*-BuOH(4:1); [e]12h reaction time for complete conversion; [f]4h reaction time for complete conversion; [g]45 min reaction time for complete conversion.

Table S2. Screening data.

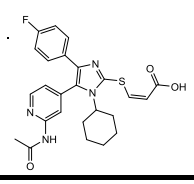
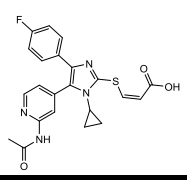
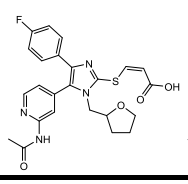
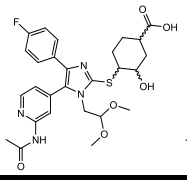
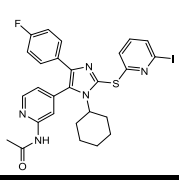
Compound	6l	6i	6o	6s	6y
					
ABL1	2.8	17.43	-3.97	0.31	-2.61
ACVR1(ALK2)	12.77	60.57	48.84	32.96	5.05
AKT1(PKBa)	0.63	0.71	-0.35	3.19	-4.42
ALK	1.85	1.27	1.17	1.37	2.24
AURKA	-0.21	2.31	2.11	5.69	0.99
BTK	1.98	-1.62	2.39	0.84	4.36
CAMK2	-1.27	-2.51	-2.15	-2.24	-1.62
CDK1B	0.7	-0.81	0.48	-0.05	0.4
CDK2	0.55	0.13	2.32	-2.3	2.61
CDK4D1	4.11	3.46	5.33	3.87	3.81
CSK	3.68	4.47	4.8	4.02	3.01
CSNK1G3(CK1)	1.16	9.54	5.19	5.73	2.9
cSRC	5.34	5.81	1.99	1.58	2.46
EGFR(HER1)	34.57	51.77	30.47	10.99	4.15
EPHB4	45.4	39.47	15.36	9.16	7.92
ERBB4(HER4)	7.01	14.85	28.02	4.32	2.01
FGFR1	0.19	3.17	4.44	3.59	4.87
FGFR2	0.55	0.22	0.81	1.27	2.05
FGFR3	-2.3	-4.77	-4.31	-1.56	-0.87
FGFR3K650E	-0.75	-2.84	-4.63	-0.9	-2.24
FGFR4	0.85	-1.91	-1.71	0.72	1.44
FLT3	0.96	0.29	-2.51	0.07	-0.66
GSK3beta	5.3	10.64	6.85	5.48	3.15
INSR	1.71	2.92	4.24	3.36	2.81
IRAK1	5.16	2.11	2.55	8.36	2.84
IRAK4	7.24	-0.39	2.87	7.32	3.75
JAK1	1.61	30.51	0.74	-2.72	1.95
JAK2	-2.94	40.38	-2.08	-5.03	-0.49
JNK1*	82.64	85.48	80.76	37.51	28.72
JNK2*	85.88	86.17	84.95	57.90	55.48
KDR	7.25	8.77	18.17	7.25	1.92
LCK	12.06	18.91	4.85	5.21	3.95
LYN	12.82	5.49	3.58	6.37	2.56
MAP3K7-TAB1	4.05	3.07	2.67	4.54	1.39
MAP3K8	0.82	-1.7	1.87	1.29	3.81
MAP4K4	46.67	36.07	30.99	12.96	-0.54
MAPK1(ERK2)	2.98	-0.69	2.21	2.13	6.03
MAPK10(JNK3)	95.05	88.65	96.71	43.35	10.46
MAPKAPK5(MK5)	28.48	28.63	28.13	26.45	18.97
MET	-0.06	-1.93	-2.19	-1.51	-0.31
MK2	-1.54	-4.81	-3.86	-1.82	-1.15
MKNK1	2.79	-1.04	-1.95	-3.75	2.68
p38a	97.54	100.36	95.57	94.89	56.45

Table S2. (continued)

Compound	6a	6d	6e	6l	6o
PAK2	1.55	-2.58	-0.33	2.3	2.3
PDGFRa	5.72	19.09	-5.55	5.98	-5.03
PRKACA(PKA)	3.73	4.58	2.01	9.73	1.15
PRKCA	5.17	-0.14	0.21	-1.2	4.46
PRKCQ	3.86	-0.11	0.88	0.7	2.33
RET	7.14	5.2	1.7	4.23	3.64
ROCK2	2.66	0.99	1.3	-0.06	0.13
S6K	2.18	0.09	2.64	-1.15	-0.61
STK17B	1.07	-0.64	-1.67	-0.98	1.07
STK4	0.32	1.95	1.06	0.02	-0.49
SYK	0.92	-4.44	-0.62	0.05	2.03
TNIK	3.54	42.19	31.15	13.08	-3.98
WNK1	6.58	-6.51	2.05	-10.04	6.07
ZAP70	-1.02	-5.65	-3.11	-2.53	1.06

* Were tested at Reaction Biology under similar conditions.

In-vitro kinase assays for selectivity profiling:

Caliper Mobility Shift Assay:

All assays were performed in 384 well microtiter plates. Each kinase was tested at a compound concentration of 5.5 µM.

Liquid handling and incubation steps were done on an Innovadyne Nanodrop Express equipped with a robotic arm (Thermo CatX, Caliper Twister II) and an incubator (Liconic STX40, Thermo Cytomat 2C450). The assay plates were prepared by addition of 50 nl per well of compound solution in 90 % DMSO. The kinase reactions were started by stepwise addition of 4.5 µl per well of peptide/ATP-solution (50 mM HEPES, pH 7.5, 1 mM DTT, 0.02 % Tween20, 0.02 % BSA, 10 mM β-glycerophosphate, and 10 µM sodium orthovanadate, Mg/Mn chloride, ATP, and peptide) and 4.5 µl per well of enzyme solution (50mM HEPES, pH 7.5, 1 mM DTT, 0.02 % Tween20, 0.02 % BSA, 10 mM beta-glycerophosphate, and 10 µM sodium orthovanadate, Mg/Mn chloride, and enzyme). Concentrations for Mg/Mn and enzyme were adjusted to the assay specific requirements. Peptides were used at 2 µM or at apparent K_m (if K_m < 2 µM). ATP concentrations were adjusted to the apparent K_m value of the specific enzyme.

Kinase reactions were incubated at 30 °C for 60 minutes and subsequently terminated by addition of 16 µl per well of stop solution (100 mM HEPES pH 7.5, 5 % DMSO, 0.1 % Caliper coating reagent, 10 mM EDTA, and 0.015 % Brij35). Plates with terminated kinase reactions were transferred to the Caliper LC3000 workstations for reading. Phosphorylated and unphosphorylated peptides were separated using the Caliper microfluidic mobility shift technology. Briefly, samples from terminated kinase reactions were applied to the chip. Analytes are transported through the chip by constant buffer flow and the migration of the substrate peptide is monitored by the fluorescence signal of its label. Phosphorylated peptide (product) and unphosphorylated peptide (substrate) are separated in an electric field by their charge/mass ratio. Kinase activities were calculated from the amounts of formed phospho-peptide.

Direct enzyme- linked immunosorbent assay (ELISA) for routine screening of p38α MAPK and JNK3 inhibitors

Being a natural substrate of both p38α MAP kinase and JNK3, activation transcription factor 2 (ATF-2) purchased from ProQinase, Freiburg, Germany (# 0594-0000-2) as full-length protein is adsorbed to the 96 well assay plates (Nunc Maxisorp®) yielding a concentration of 10 µg/mL.
Dilution rows of candidate inhibitor are prepared in a kinase buffer containing active p38α MAP kinase or activate JNK3 enzyme. The active p38α MAP kinase was obtained from Prof. Dr. J. Schultz (University of Tübingen, Germany), whereas the active JNK3 enzyme was purchased from ProQinase, Freiburg, Germany (#0900-0000-1). The ATP concentrations used in the respective kinase buffers are adjusted to twice the K_m value, depending on the kinase.
The activity of p38α MAP kinase or JNK3 kinase after one hour of incubation at 37°C with the candidate inhibitors is measured by the phosphorylation degree of ATF-2, which is directly detected by a monoclonal peroxidase-conjugated antibody purchased from Sigma Aldrich (#A6228). The phosphorylation degree achieved with the respective kinase in absence of inhibitor is taken as positive control (STIM). Pure kinase buffer without kinase serves for detection of non-specific binding (NSB). After staining with 3,3',5,5'-tetramethylbenzidine reagent (BD Biosciences Europe) and termination of colour development using 1M sulphuric acid, the optical density is read out in a n ELISA reader at 450 nm. As phosphorylation is inversely correlated with the inhibitor potency, the calculation of inhibition is carried out according to the formula.

$$Inhibition[\%] = 100 - \left(\frac{OD_{450}Sample - OD_{450}NSB}{OD_{450}STIM - OD_{450}NSB}\right) \times 100$$

Cell toxicity data:

Material and Methods

Cell Culture and Compound Treatment
U2OS cells (# HTB-96, ATCC, USA) were cultivated according to standard protocols. Briefly, growth media contained DMEM (high glucose, pyruvate, 10% fetal calf serum; PAA, Germany), supplemented with L-Glutamine and antibiotics. Cells were trypsinized for passaging and cultivated at 37 °C in a humidified chamber with a 5 % CO_2 atmosphere. To analyze the effect of tri- and tetra-substituted imidazoles on cell viability 12,500 cells U2OS cells were grown in µclear 96-well plates (Greiner, Germany). Hyperosmotic stress was induced by exchanging normal growth media with hyperosmotic media DMEM (high glucose, pyruvate, 10 % fetal calf serum, 175 mM NaCl; PAA, Germany). Immediately, compounds were added yielding a final concentration of 1 µM, 10 µM and 50 µM. Plates were mixed thoroughly and incubated for 90 min at 37 °C and 5 % CO_2 in a humidified chamber atmosphere. Subsequently cells were washed in 1x PBS and fixed using 4 % PFA/PBS in 1x PBS at pH 7.4 for 15 minutes, followed by nuclear DNA staining using 150 ng/mL DAPI in 1xPBS. Images were acquired with an Image Xpress micro XL system. Segmentation of nuclei was carried out with MetaXpress software (64 bit, 5.1.0.41) based on the nuclear staining. For each condition at least 300 cells were analyzed. Mean numbers of nuclei and standard deviation were calculated from eight technical replicates and normalized to the number of DMSO treated nuclei for each concentration.

Figure S1a. Cell toxicity data.

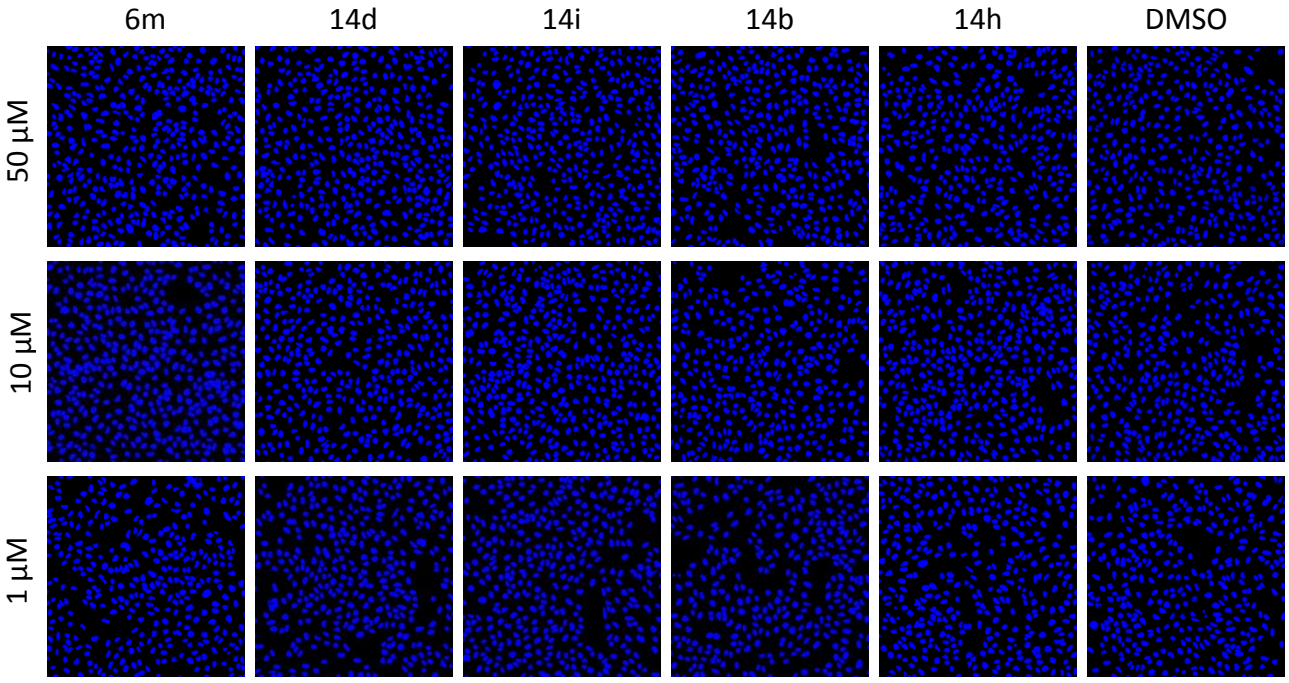
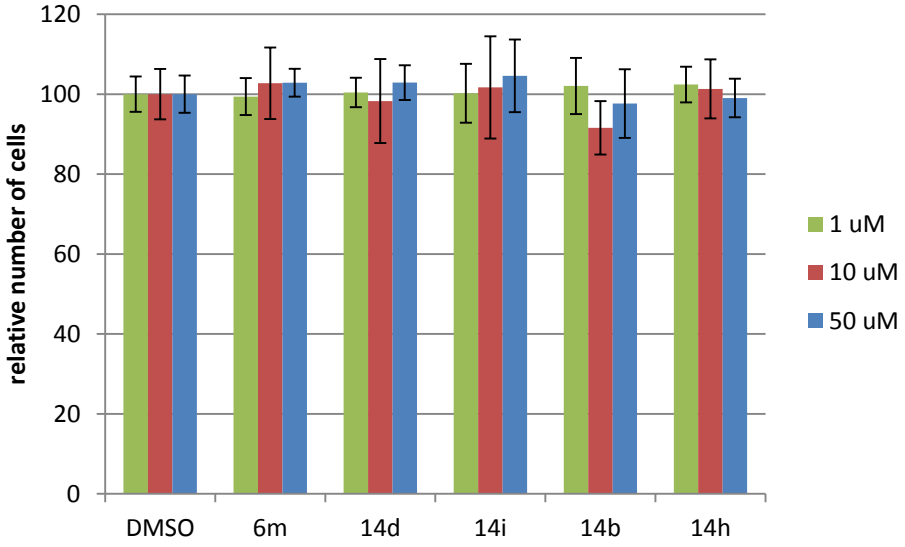


Figure S1b. Cell toxicity data.



Treatment with tri- and tetra-substituted imidazoles has no immediate cytotoxic effect

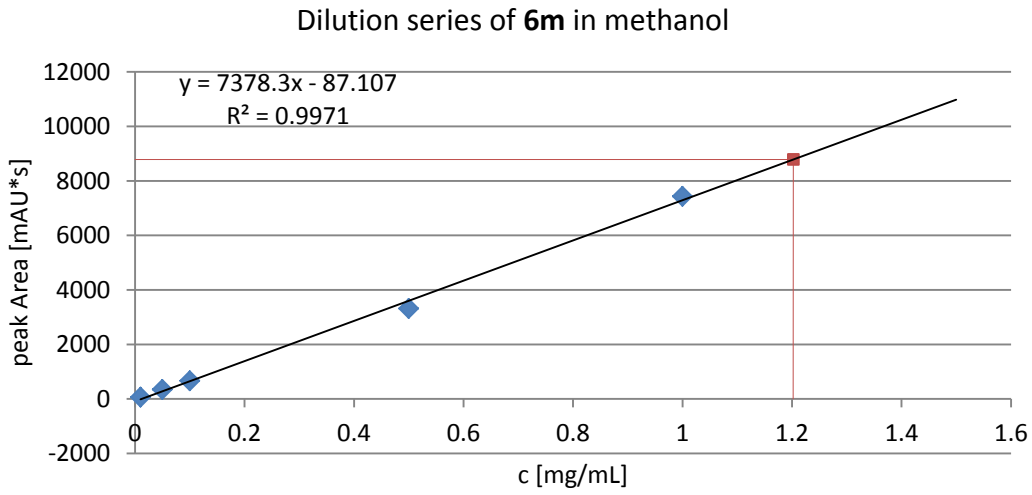
U2OS cells were treated with tri- and tetra-substituted imidazoles in three different concentrations (1 µM, 10 µM, 50 µM) or left untreated (DMSO). After 90 min cells were fixed and nuclei were stained with DAPI. (Figure S1a) Morphological analysis of the nuclei. (Figure S1b) Shown are percentages of viable cells after compound

treatment with indicated concentrations. Incubation with DMSO served as negative control and was set to 100 %. Shown is standard deviation derived from 8 technical replicates.

Solubility data:

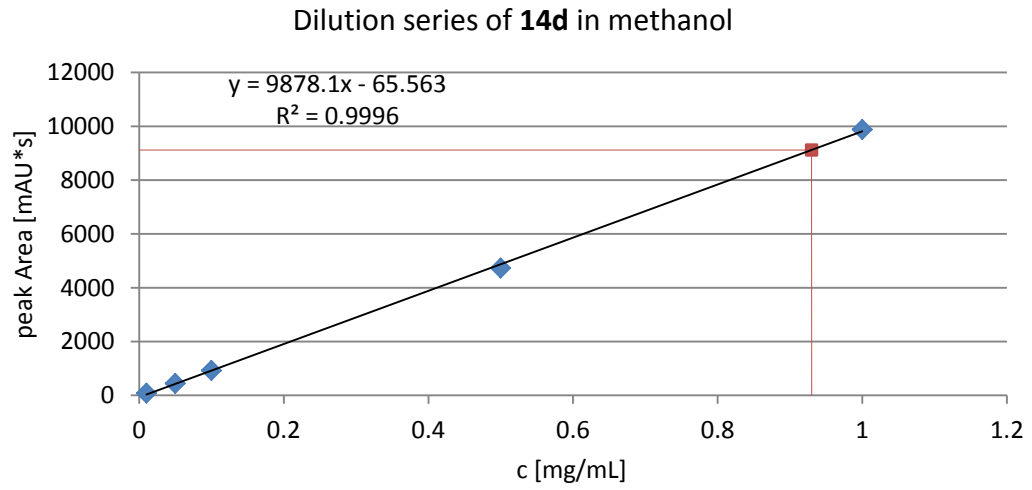
Compounds **6m** and **14d** were diluted in methanol and a dilutions series (1, 0.5, 0.1, 0.05, 0.01 mg/mL) was prepared. A saturated solution in PBS-buffer (pH = 7.4) of the corresponding compound was prepared and all samples (dilution series and saturated solution of the corresponding compound) were measured using LC-chromatography. The areas underneath the peaks were related to the concentration.

Figure S2a.



PBS-buffer [µl]	peak area [mAU*s]	c [mg/mL]	[µmol/mL]
500	8784.48	1.202	3.587

Figure S2b.



PBS-buffer [µl]	peak area [mAU*s]	c [mg/mL]	[µmol/mL]
500	9120.34	0.930	2.055

In Vitro Phase 1 Metabolism in Human Male Liver Microsomes:

In order to examine the metabolic stability of the compounds **6m** and **14d**, their biotransformation was investigated in human male liver microsomes (HLM). Although all tested substances seemed to undergo metabolic degradation (see Figure S3a), none reached its half-value time during the incubation. After 240 min compound **6m** lost about 30 % and **14d** approximate 44 %, relating to their starting concentrations.

Figure S3a. Degradation scheme of the compounds **6m** and **14d** while incubating in HLM for 240 min.

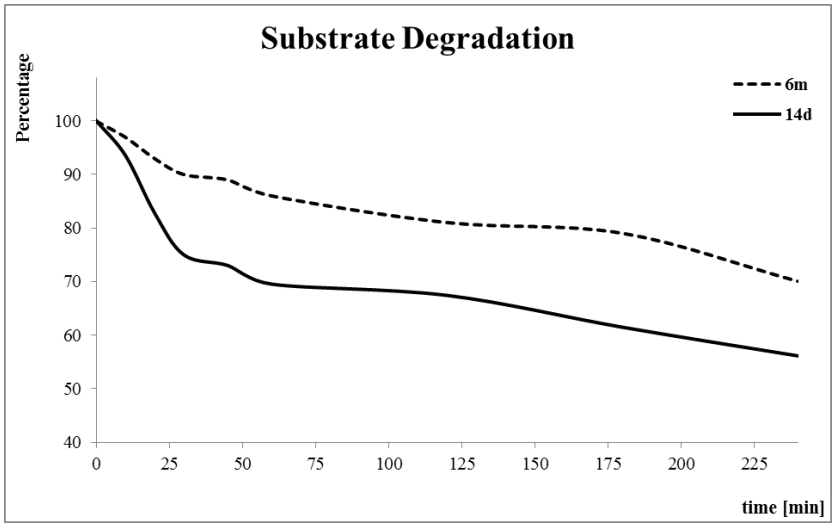
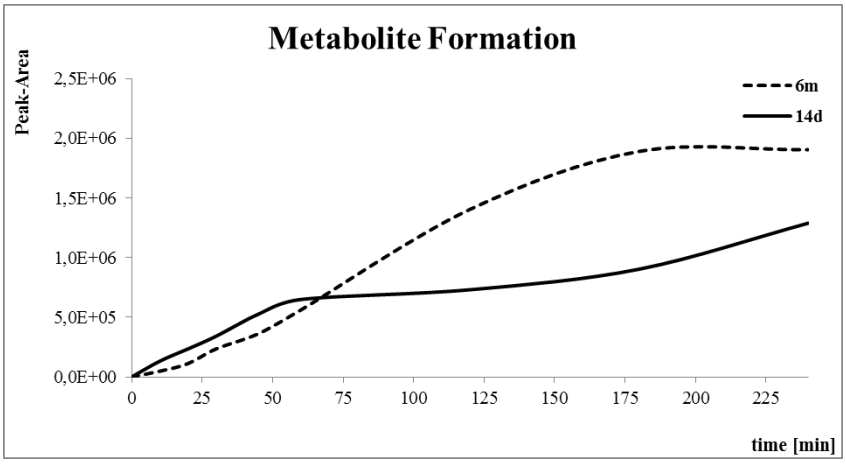


Figure S3b. Metabolite formation from compound **6m** (m/z = 333.5) and **14d** (m/z = 517.5).



As pictured in Figure S3b it was also possible to observe formation of metabolites with m/z-values of 333.5 Da from substance **6m** and 517.5 Da from **14d**.

Material and Methods

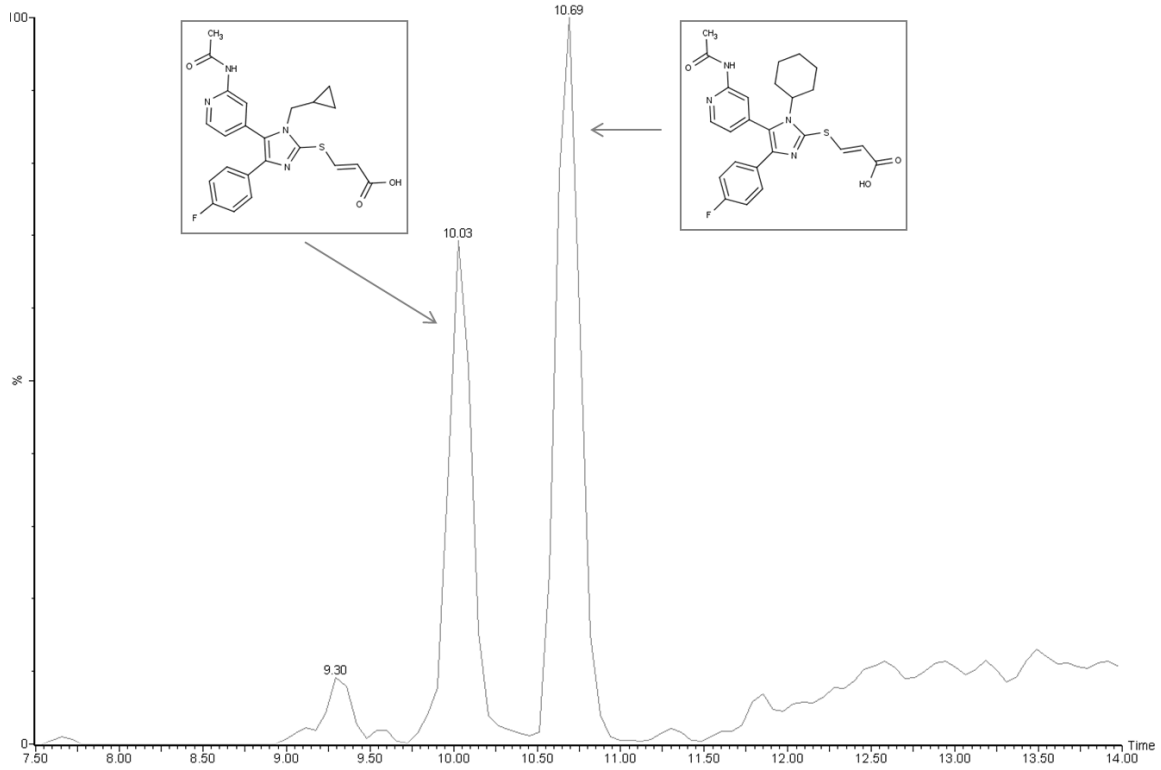
Pooled HLM were purchased from Sigma-Aldrich (Saint Louis, USA). These microsomes were characterized in protein and cytochrome P-450 content.
All incubations (final total volume 1050 µL) were made in the presence of an NADPH-regenerating system, consisting of 5 mM Glucose-6-phosphate, 5 U/mL Glucose-6-phosphate dehydrogenase and 1 mM $NADP^+$. The substrate (10 µM), the NADPH regenerating system and 3.8 mM $MgCl_2$ x 6 H2O in 0.1 M Tris buffer (pH 7.4)

were preincubated for 5 min in a shaking heating block at 37 °C and 550 rpm. The reaction was started by addition of the HLM. Thereby the microsomal protein content was standardized to 1 mg/mL. To follow the course of metabolism, 100 µL aliquots were withdrawn at different time points (0, 10, 20, 30, 45, 60, 120, 180 and 240 min) and transferred into an ice cooled vial containing 100 µL internal standard at a concentration of 100 µg/mL in acetonitrile. The samples were vortexed for 15 s and centrifuged (19800 relative centrifugal force/4°C/ 10 min). The supernatant was directly used for LC-MS analysis.[14] All incubations were conducted in triplicates; average mean values of these incubations are shown in the figures. In all incubations a limit of 1 % organic solvent was not exceeded.[15]

Screening of Metabolites by LC-MS/MS Analysis

Metabolite formation was analyzed with a Jasco (Groß-Umstadt, Germany) HPLC system, consisting of a pump (PU-1580) and an HTSPal auto sampler from CTCAnalytics (Zwingen, Switzerland). The chromatographic separation was performed on a Waters Symmetry®C18 column (150 x 4.6 mm; 5µm) with a precolumn of the same material. The injection volume was 20 µL. A binary gradient of 16 min with solvent A (H2O, 0.1 % formic acid) and solvent B (ACN, 0.1 % formic acid) at a flow rate of 500 µL/min was used. The initial composition of 25 % B was held for 1 min, followed by a linear gradient up to 100 % B in 7 min, holding for 2 min, changing to 25 % B in 1 min and reequilibrating at the end. The detection was performed on a Micromass Quattro micro triple quadrupole mass spectrometer (Waters GmbH, Eschbronn) in the electrospray ionization-positive-mode. Spray voltage was set to 3.0 kV and the heated capillary operated at 300 °C. Desolvation gas flow worked at 300 L/hr. Figure S3c shows a representative HPLC chromatogram of this metabolism assay. The retention times for the internal standard, compound **6m** and the developing metabolite were 10.69, 10.03 and 9.3 min, respectively, in a 16-min HPLC run. Substrates were quantified by internal standards as well as with calibration curves constructed from known concentrations of reference material.

Figure S3c. A representative HPLC chromatogram of in vitro phase 1 incubations showing the internal standard, substrate **6m** and its metabolite at 10.69, 10.03 and 9.3 min, respectively.



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