SUPPORTING INFORMATION

Pyridinylimidazoles as GSK3β inhibitors: the impact of tautomerism on compound activity via water networks

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1. Synthetic procedures

General

All reagents and solvents were obtained from commercial sources (Merck, abcr, ChemPur, Acros, AlfaAesar or Activate Scientific) and used without further purification. Thin layer chromatography (TLC) reaction controls were performed for all reactions using fluorescent silica gel 60 F254 plates (Merck) and visualized under natural light and UV illumination at 254 and 366 nm. All tested compounds were determined to be ≥95% purity by reverse phase high-performance liquid chromatography (HPLC) (254 nm). HPLC were carried out on an Agilent 1100 series HPLC system, equipped with an UV DAD (detection at 218 nm, 254 nm, and 280 nm). The chromatographic separation was performed on a XBridge™ C18 column (150 mm x 4.6 mm, 5 µm) at 30 °C oven temperature. For Method A, the injection volume was 5 µL and the flow 1.5 mL / min using the following gradient:
0.01 M KH_2PO_4, pH 2.3 (solvent A), methanol (solvent B), 45% B to 85% B in 9 min; 85% B for 6 min; stop time 15 min. For Method B, the injection volume was 5 µL and the flow 1.5 mL / min using the following gradient: 0.01 M KH_2PO_4, pH 2.3 (solvent A), methanol (solvent B), 5% B to 95% B in 15 min; 95% B for 3 min; stop time 18 min. Flash column chromatography was performed using an Interchim PuriFlash 430 automated flash chromatography system with Davisil LC60A 20 - 45 µm silica from Grace Davison or PuriFlash SIHP 30 µm columns. Reverse-phase flash column chromatography was performed using the same system with a PuriFlash C18-HP, 15 µM 35g column. Nuclear magnetic resonance (NMR) spectra were measured on a Bruker Avance III HD NMR spectrometer at 300 MHz or a Bruker Bruker Avance III HDX at 400 MHz. The chemical shifts δ are reported in parts per million (ppm) relative to TMS. All spectra were calibrated against the (residual proton) peak of the deuterated solvent used. If a mixture of deuterated solvent was used the spectrum was calibrated against $CDCl_3$ unless otherwise stated. Mass spectra were recorded on an Advion Expression S electrospray ionization mass spectrometer (ESI-MS) with an Advion Plate Express (TLC interface).

General Procedures

General Procedure A (Radziszewski synthesis):

The corresponding diketone (1 eq.), acetaldehyde (2 eq.) and NH_4OAc (10 eq.), were dissolved in MeOH (0.2 M) and heated to reflux for 3 h. After cooling to rt, the solvent was evaporated and the crude product was taken up in a mix of EtOAc and H_2O. The organic phase was collected and the aqueous layer was extracted twice more with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure and the compound was purified by flash chromatography.

General Procedure B (Buchwald-Hartwig amidation):

The amide (1.5 eq.), $Pd_2(dba)_3$ (5 mol%), XantPhos (10 mol%), cesium carbonate (3 eq.) and the 2-chloropyridinylimidazole derivative (1 eq.) were dissolved under an atmosphere of argon in DMF (0.3 M). The reaction mixture was then stirred at 100 °C for 16 h. The reaction mixture was allowed to cool to rt and sat. aq. NH_4Cl solution was added. It was extracted with EtOAc (3x) and the combined organic layers were washed with sat. aq. NH_4Cl solution (2x) and brine. After drying over anhydrous Na_2SO_4 the solvent was removed under reduced pressure and the compound was purified by flash chromatography.

General Procedure C

The acetophenone (1 eq.) was dissolved in DMSO (0.6 M) and aq. HBr solution 48% (3 eq.) was added. The solution was stirred in an open flask at 55 °C for 18 h.[1] After cooling to rt, H_2O was added and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was immediately dissolved in MeOH (0.2 M). In a second flask, NH_4OAc (5 eq.) was also dissolved in MeOH (5 M) before ethyl glyoxylate (polymer form ~50% in toluene; 3 eq.) was added in one portion. The previously prepared solution of 2,2-dihydroxyethan-1-one derivative in MeCN was then added dropwise over 15 min. After 1.5 h, the solvent was evaporated, H_2O was added and it was extracted with EtOAc (5x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure and the compound was purified by flash chromatography.

General Procedure D (Suzuki coupling Method A)

The bromoimidazole derivative, (aryl)boronic acid (1.3 – 1.6 eq.), cesium fluoride (3 eq.), benzyltriethylammonium chloride (0.06 eq.) and Pd(dppf)Cl_2·DCM (0.06 eq.) were dissolved in a degassed 1:1 mixture of toluene/H_2O (4 mL). The mixture was heated to 100 °C under an atmosphere of argon for 18 h. The reaction mixture was allowed to cool to rt and more H_2O was added. It was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was purified by flash chromatography.

General Procedure E (SEM deprotection)

The compound was dissolved in a 1:5 mixture of trifluoroacetic acid in DCM and stirred at rt until reaction control showed full conversion (5 – 72 h). Sat. aq. $NaHCO_3$ solution was carefully added until the aqueous layer was adjusted to pH 7. The organic layer was collected and depending on the estimated polarity of the compound it was extracted with either DCM (3x) or EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure.

General Procedure F (Suzuki coupling Method B)

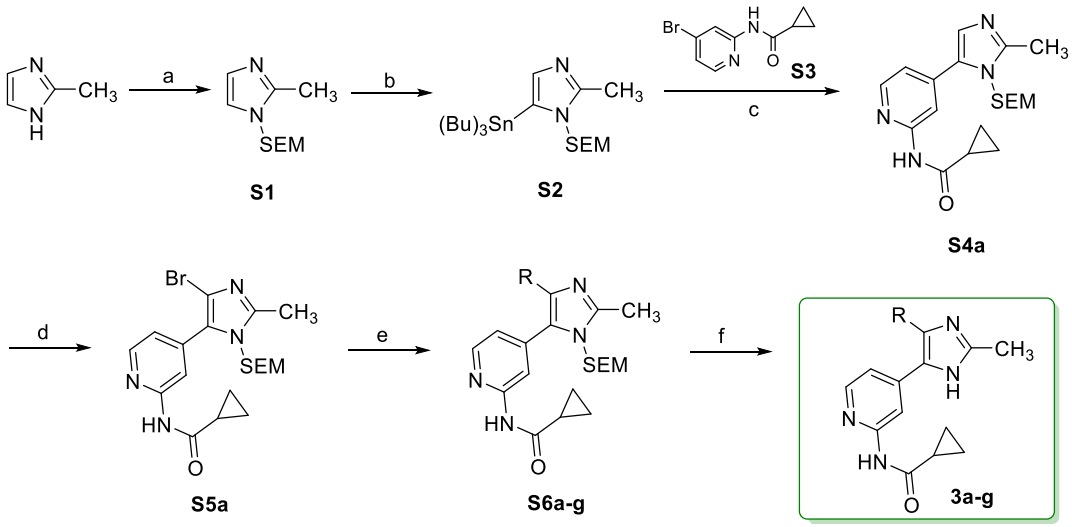
The bromoimidazole (1 eq.), (aryl)boronic acid (1.3 – 1.6 eq.), potassium carbonate (3 eq.) and Pd(dppf)Cl_2·DCM (0.06 eq.) were dissolved in degassed DMF (2.5 mL). The mixture was heated to 80 °C under an atmosphere of argon for 18 h. The reaction mixture was allowed to cool to rt and sat. aq. NH_4Cl solution was added. It was extracted with EtOAc (3x) and the combined organic layers were dried

over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was purified by flash chromatography.

General Procedure G (HATU coupling)

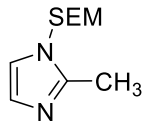
The carboxylic acid (1 eq.), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (1 eq.) and *N*,*N*-diisopropylethylamine (3 eq.) were dissolved in DCM under an atmosphere of argon. The mixture was stirred at rt for 10 min before the amine (0.7 eq.) was added and the solution was stirred for 18 h. H_2O was added to the reaction and the organic layer was collected. It was then extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was purified by flash chromatography.

Synthesis of 3a-g



Scheme S1. *Reagents and conditions:* (a) NaH, SEM-Cl, THF, 0 °C then rt, 18 h, 96%; (b) *n*-BuLi, tributyltin chloride, Et_2O, 0 °C then rt, 2 h, 26%; (c) $Pd(PPh_3)_4$, 1,4-dioxane, 105 °C, 77%; (d) NBS, MeCN, -20 °C, 20 min, 77-88%; (e) arylboronic acid, CsF, benzyltriethylammonium chloride, $Pd(dppf)Cl_2 \cdot DCM$, toluene/H_2O, 100 °C, 16 h, 53-89%; (f) trifluoroacetic acid, DCM, rt, 6 h, 25-85%.

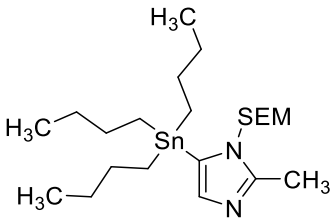
2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S1)[2]



2-Methylimidazole (925 mg, 11.27 mmol) was dissolved in THF (40 mL), cooled to 0 °C and sodium hydride 60% in mineral oil (500 mg, 12.50 mmol) was added portionwise over 5 min. After 30 min of stirring at 0 °C, 2-(trimethylsilyl)ethoxymethyl chloride (2.00 mL, 11.30 mmol) was added dropwise and

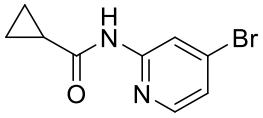
the mixture was stirred at rt for 18 h. Purification by flash chromatography (SiO_2, n-hexane/EtOAc 90:10 to 60:40) afforded **3** as a clear oil (2.30 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 9H), 0.82 - 0.95 (m, 2H), 2.43 (s, 3H), 3.39 - 3.53 (m, 2H), 5.18 (s, 2H), 6.90 (s, 2H).

2-Methyl-5-(tributylstannyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S2)[2]



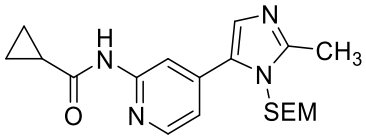
The title compound was synthesized according to the method reported by Markey and Kelly[3] to give **S2** as a clear oil (1.41 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.86 - 0.93 (m, 11H), 1.03 - 1.11 (m, 5H), 1.22 - 1.40 (m, 9H), 1.48 - 1.55 (m, 4H), 2.47 (s, 3H), 3.36 - 3.47 (m, 2H), 5.14 (s, 2H), 6.90 (s, 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{22}H_{45}N_2OSiSn$ $[M\text{-}SEM+2H]^+$ 373.2, found 373.0.

***N*-(4-Bromopyridin-2-yl)cyclopropanecarboxamide (S3)[4]**



4-Bromopyridine-2-amine (3.00 g, 17.34 mmol) was dissolved in DCM (40 mL) and pyridine (1.82 mL, 22.54 mmol) was added at 0 °C. Cyclopropylcarbonyl chloride (1.73 mL, 19.07 mmol) was added dropwise and the solution was stirred at rt for 6 h. Sat. aq. $NaHCO_3$ solution (15 mL) and H_2O (30 mL) were added and the organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and dried in vacuo to afford 3.50 g (83.7%) of a white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79 - 0.88 (m, 4 H), 1.89 - 2.12 (m, 1 H), 7.34 (dd, *J* = 5.3, 1.8 Hz, 1 H), 8.22 (dd, *J* = 5.3, 0.4 Hz, 1 H), 8.33 (dd, *J* = 1.7, 0.4 Hz, 1 H), 11.03 (s, 1 H). TLC-MS (ESI) *m*/*z*: calculated for $C_9H_9BrN_2O$ $[M\text{-}H]^-$ 239.0/241.0, found 239.0/241.0. HPLC: t_R = 4.94 min (99.3% purity).

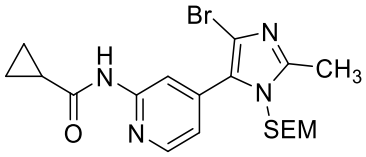
***N*-(4-(2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S4a)[2]**



Compound **S2** (462 mg, 0.92 mmol), *N*-(4-bromopyridin-2-yl)cyclopropanecarboxamide (**S3**) (222 mg, 0.92 mmol) and $Pd(PPh_3)_4$ (77 mg, 0.069 mmol) were dissolved in degassed 1,4-dioxane (9 mL) under an atmosphere of argon. The reaction mixture was heated to 105 °C for 18 h before the solution was filtered through a pad of Celite. The pad was washed with DCM (30 mL) and the solvents were removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM/EtOH 95:05) afforded 24 as an off-white solid (265 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.84 - 0.92 (m, 4H), 1.06 -

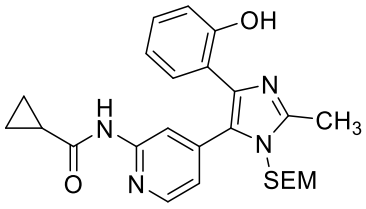
1.15 (m, 2H), 1.55 - 1.67 (m, 1H), 2.53 (s, 3H), 3.45 - 3.55 (m, 2H), 5.28 (s, 2H), 7.16 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.18 (s, 1H), 8.27 (dd, *J* = 5.2, 0.6 Hz, 1H), 8.30 (d, *J* = 0.6 Hz, 1H), 9.17 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.3, 13.7, 15.7, 17.7, 66.0, 72.7, 112.2, 118.0, 128.6, 131.3, 140.0, 148.0, 148.8, 152.2, 172.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{28}N_4O_2Si$ $[M-H]^-$ 371.2, found 371.0. HPLC: t_R = 5.99 min.

***N*-(4-(4-Bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S5a)**



Compound **S4a** (150 mg, 0.40 mmol) was dissolved in MeCN (10 mL) under an atmosphere of argon and the solution was cooled to -20 °C. *N*-Bromosuccinimide (79 mg, 0.44 mmol) was added in one portion and the mixture was stirred at -20 °C for 5 h min before it was quenched with sat. aq. Na_2SO_3 solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 160 mg (88.2%) of a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 9H), 0.80 - 0.93 (m, 4H), 1.07 - 1.14 (m, 2H), 1.58 - 1.68 (m, 1H), 2.49 (s, 3H), 3.32 - 3.43 (m, 2H), 5.20 (s, 2H), 7.21 (dd, *J* = 5.2, 1.6 Hz, 1H), 8.28 (d, *J* = 0.6 Hz, 1H), 8.34 (dd, *J* = 5.2, 0.6 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.4, 13.5, 15.7, 17.6, 66.2, 73.2, 114.4, 115.2, 120.0, 127.5, 138.9, 147.5, 147.7, 152.0, 172.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{27}BrN_4O_2Si$ $[M-H]^-$ 449.1/451.1, found 449.2/451.1. HPLC: t_R = 8.02 min.

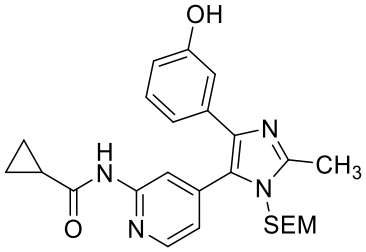
***N*-(4-(4-(2-Hydroxyphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6a)**



The title compound was synthesized according to **General Procedure D** starting from compound **S5a** (140 mg, 0.31 mmol), 2-hydroxyphenylboronic acid (68 mg, 0.50 mmol), cesium fluoride (141 mg, 0.93 mmol), benzyltriethylammonium chloride (4.2 mg, 0.019 mmol) and Pd(dppf)Cl_2·DCM (15 mg, 0.019 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 115 mg (79.8%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.74 - 0.86 (m, 2H), 0.88 - 0.96 (m, 2H), 1.06 - 1.15 (m, 2H), 1.57 - 1.68 (m, 1H), 2.55 (s, 3H), 3.34 (dd, *J* = 9.0, 7.7 Hz, 2H), 5.12 (s, 2H), 6.49 - 6.56 (m, 1H), 6.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.93 - 6.99 (m, 1H), 7.04 - 7.11 (m, 2H), 8.30 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 9.03 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.5, 13.2, 15.7, 17.7, 66.2, 72.6, 115.9, 116.6, 117.5,

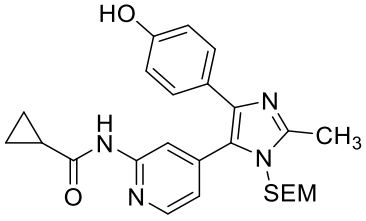
118.4, 121.9, 124.9, 126.2, 128.4, 135.8, 141.5, 144.5, 148.3, 152.4, 156.8, 172.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{32}N_4O_3Si$ $[M+H]^+$ 465.2, found 465.2. HPLC: t_R = 6.95 min.

_N_-(4-(4-(3-Hydroxyphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6b)



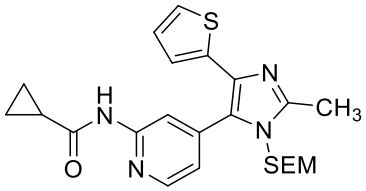
The title compound was synthesized according to **General Procedure D** starting from compound **S5a** (120 mg, 0.27 mmol), 3-hydroxyphenylboronic acid (75 mg, 0.54 mmol), cesium fluoride (171 mg, 1.12 mmol), benzyltriethylammonium chloride (5.1 mg, 0.023 mmol) and $Pd(dppf)Cl_2$·DCM (18.4 mg, 0.023 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 110 mg (89.1%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (s, 9H), 0.77 - 0.89 (m, 4H), 1.02 - 1.09 (m, 2H), 1.58 - 1.66 (m, 1H), 2.48 (s, 3H), 3.22 - 3.36 (m, 2H), 5.09 (s, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.90 - 6.99 (m, 2H), 7.01 - 7.11 (m, 2H), 8.12 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 9.24 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.5, 13.6, 15.5, 17.7, 66.1, 72.5, 114.5, 114.9, 115.6, 119.0, 121.6, 125.8, 129.5, 134.2, 137.5, 141.1, 147.0, 147.8, 151.9, 156.9, 173.0. TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{32}N_4O_3Si$ $[M+H]^+$ 465.2, found 465.5. HPLC: t_R = 6.94 min.

_N_-(4-(4-(4-Hydroxyphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6c)



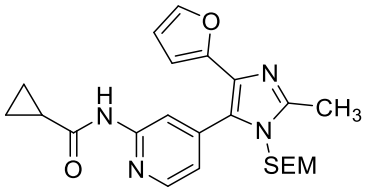
The title compound was synthesized according to **General Procedure D** (heated for 36 h) starting from compound **S5a** (160 mg, 0.35 mmol), 4-hydroxyphenylboronic acid pinacol ester (125 mg, 0.57 mmol), cesium fluoride (162 mg, 1.06 mmol), benzyltriethylammonium chloride (4.8 mg, 0.021 mmol) and $Pd(dppf)Cl_2$·DCM (17.0 mg, 0.021 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 110 mg (67.6%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 9H), 0.81 - 0.93 (m, 4H), 1.08 (br. s., 2H), 1.51 - 1.70 (m, 1H), 2.54 (s, 3H), 3.30 - 3.45 (m, 2H), 5.18 (s, 2H), 6.60 (d, *J* = 5.5 Hz, 2H), 6.95 (d, *J* = 4.1 Hz, 1H), 7.14 (d, *J* = 6.6 Hz, 2H), 8.23 (br. s., 2H), 9.29 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.4, 13.0, 15.7, 17.7, 66.1, 72.7, 115.4, 115.6, 121.6, 123.9, 124.8, 129.1, 138.2, 141.2, 146.9, 147.8, 152.1, 156.7, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{32}N_4O_3Si$ $[M+H]^+$ 465.2, found 465.5. HPLC: t_R = 6.50 min.

***N*-(4-(2-Methyl-4-(thiophen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6d)**



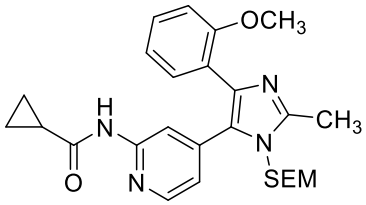
The title compound was synthesized according to **General Procedure D** starting from compound **S5a** (120 mg, 0.27 mmol), 2-thienylboronic acid (54 mg, 0.43 mmol), cesium fluoride (121 mg, 0.80 mmol), benzyltriethylammonium chloride (3.6 mg, 0.016 mmol) and Pd(dppf)Cl_2·DCM (13 mg, 0.016 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 108 mg (89.3%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 9H), 0.79 - 0.94 (m, 4H), 1.06 - 1.14 (m, 2H), 1.61 (s, 1H), 2.55 (s, 3H), 3.28 - 3.42 (m, 2H), 5.12 (s, 2H), 6.88 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.97 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.13 (dt, *J* = 5.0, 1.7 Hz, 2H), 8.28 (s, 1H), 8.34 (d, *J* = 5.0 Hz, 1H), 8.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.4, 13.4, 15.7, 17.7, 66.0, 72.8, 115.7, 121.6, 123.3, 124.0, 125.0, 127.2, 133.0, 137.0, 140.8, 146.8, 148.0, 152.2, 172.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{30}N_4O_2SSi$ $[M+H]^+$ 455.2, found 455.2. HPLC: t_R = 8.13 min.

***N*-(4-(4-(Furan-2-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6e)**



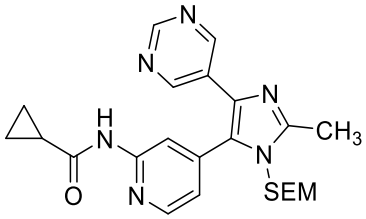
The title compound was synthesized according to **General Procedure D** starting from compound **S5a** (150 mg, 0.33 mmol), 2-furanylboronic acid (59 mg, 0.53 mmol), cesium fluoride (151 mg, 1.00 mmol), benzyltriethylammonium chloride (4.5 mg, 0.020 mmol) and Pd(dppf)Cl_2·DCM (13 mg, 0.016 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 118 mg (81.0%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.81 - 0.94 (m, 4H), 1.04 - 1.12 (m, 2H), 1.55 - 1.66 (m, 1H), 2.55 (s, 3H), 3.33 (dd, *J* = 8.9, 7.7 Hz, 2H), 5.16 (s, 2H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.44 (dd, *J* = 3.3, 0.6 Hz, 1H), 7.14 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.28 - 7.30 (m, 1H), 8.26 (s, 1H), 8.33 (d, *J* = 5.1 Hz, 1H), 8.75 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.3, 13.3, 15.4, 17.6, 66.0, 72.6, 106.1, 110.9, 115.6, 121.3, 125.5, 130.3, 140.5, 141.3, 147.3, 147.4, 148.8, 152.0, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{30}N_4O_3Si$ $[M+Na]^+$ 461.2, found 461.5. HPLC: t_R = 7.75 min.

***N*-(4-(4-(2-Methoxyphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6f)**



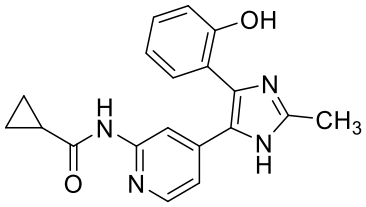
The title compound was synthesized according to **General Procedure D** starting from compound **S5a** (200 mg, 0.44 mmol), 2-methoxyphenylboronic acid (101 mg, 0.67 mmol), cesium fluoride (202 mg, 1.33 mmol), benzyltriethylammonium chloride (6 mg, 0.027 mmol) and Pd(dppf)Cl_2·DCM (22 mg, 0.027 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 113 mg (53.3%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.82 - 0.99 (m, 4H), 1.06 - 1.15 (m, 2H), 1.60 - 1.72 (m, 1H), 2.61 (s, 3H), 3.43 - 3.52 (m, 2H), 3.47 (s, 3H), 5.31 (s, 2H), 6.78 - 6.86 (m, 2H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 7.23 - 7.31 (m, 1H), 7.46 (dd, *J* = 7.5, 1.7 Hz, 1H), 8.15 (d, *J* = 5.1 Hz, 1H), 8.27 (s, 1H), 9.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.1, 13.4, 15.3, 17.6, 54.5, 65.8, 72.8, 110.7, 113.8, 119.9, 120.4, 123.2, 127.6, 128.8, 131.4, 135.9, 141.8, 146.9, 147.0, 151.9, 156.4, 172.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{26}H_{34}N_4O_3Si$ $[M+H]^+$ 479.2, found 479.3. HPLC: t_R = 7.03 min.

***N*-(4-(2-Methyl-4-(pyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6g)**



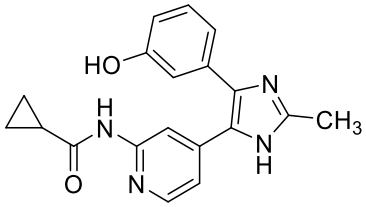
Compound **S5a** (90 mg, 0.20 mmol), pyrimidine-5-boronic acid (37 mg, 0.30 mmol), K_2CO_3 (83 mg, 0.60 mmol) and Pd(PPh_3)$_4$ (23 mg, 0.020 mmol) were dissolved in a degassed 3:1 mixture of DME/H_2O (4 mL) under an atmosphere of argon. The mixture was heated to 105 °C under an atmosphere of argon for 18 h. The reaction mixture was allowed to cool to rt and more H_2O was added. It was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the compound was purified by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) to yield 60 mg (66.7%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.81 - 0.88 (m, 2H), 0.89 - 0.95 (m, 2H), 1.03 - 1.12 (m, 2H), 1.54 - 1.66 (m, 1H), 2.58 (s, 3H), 3.32 - 3.45 (m, 2H), 5.14 (s, 2H), 6.97 (dd, *J* = 5.1, 1.3 Hz, 1H), 8.28 (s, 1H), 8.33 (d, *J* = 5.0 Hz, 1H), 8.72 (s, 1H), 8.81 (s, 2H), 9.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.4, 13.3, 15.5, 17.6, 66.2, 72.7, 115.2, 120.5, 128.0, 128.0, 131.6, 139.9, 147.8, 148.5, 152.7, 154.6, 156.4, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{30}N_6O_2Si$ $[M+Na]^+$ 473.2, found 473.5. HPLC: t_R = 7.69 min.

***N*-(4-(4-(2-Hydroxyphenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide** (**3a**)



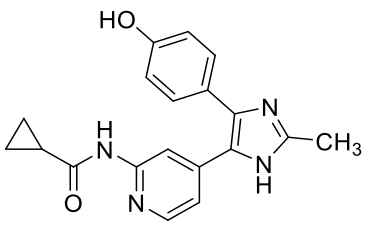
The compound was synthesized according to **General Procedure E** starting from compound **S6a** (115 mg, 0.25 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 70 mg (84.6%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 - 0.99 (m, 2H), 1.05 - 1.13 (m, 2H), 1.56 - 1.67 (m, 1H), 2.47 (s, 3H), 6.70 (td, *J* = 7.5, 1.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.13 - 7.20 (m, 1H), 7.27 - 7.30 (m, 1H), 7.37 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.18 (s, 1H), 8.18 - 8.20 (m, 1H), 8.57 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [2:1 v/v]) δ 7.3, 12.3, 14.2, 111.4, 115.7, 117.1, 117.5, 118.8, 128.9, 129.1, 142.7, 144.6, 146.7, 151.2, 154.5, 173.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{18}N_4O_2$ $[M+H]^+$ 335.2, found 335.2. HPLC: t_R = 2.14 min (99.7% purity).

***N*-(4-(4-(3-Hydroxyphenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3b)**



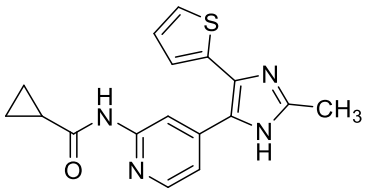
The title compound was synthesized according to **General Procedure E** starting from compound **S6b** (110 mg, 0.24 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5 to 90:10) afforded 33 mg (41.7%) of a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 - 0.82 (m, 4H), 1.95 - 2.03 (m, 1H), 2.33 (s, 3H), 6.71 - 6.90 (m, 3H), 6.98 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.17 - 7.26 (m, 1H), 8.07 (d, *J* = 4.2 Hz, 1H), 8.40 (s, 1H), 9.56 (s, 1H), 10.61 (s, 1H), 12.19 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.5, 13.7, 14.2, 110.9, 114.9, 115.0, 116.4, 118.9, 128.9, 129.8, 132.1, 132.8, 144.4, 144.7, 147.2, 152.5, 157.5, 172.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{18}N_4O_2$ $[M+H]^+$ 335.2, found 335.3. HPLC: t_R = 1.88 min (99.4% purity).

***N*-(4-(4-(4-Hydroxyphenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide** (**3c**)



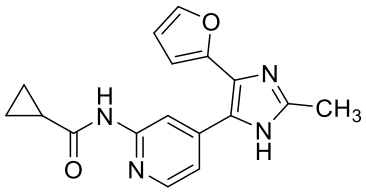
The compound was synthesized according to **General Procedure E** starting from compound **S6c** (110 mg, 0.24 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 41 mg (51.8%) of a green-yellowish solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.66 - 0.88 (m, 4H), 1.93 - 2.04 (m, 1H), 2.32 (s, 3H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.96 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 8.06 (d, *J* = 5.3 Hz, 1H), 8.36 (s, 1H), 9.64 (s, 1H), 10.60 (s, 1H), 12.09 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 13.7, 14.2, 110.5, 115.5, 116.1, 129.6, 144.2, 147.3, 152.5, 157.2, 172.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{18}N_4O_2$ $[M+H]^+$ 335.2, found 335.5. HPLC: t_R = 1.80 min (99.7% purity).

***N*-(4-(2-Methyl-4-(thiophen-2-yl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3d)**



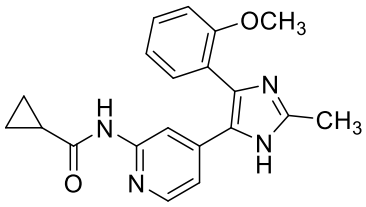
The compound was synthesized according to **General Procedure E** starting from compound **S6d** (98 mg, 0.22 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 39 mg (55.9%) of a beige solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.71 - 0.85 (m, 4H), 2.01 (quin, *J* = 6.1 Hz, 1H), 2.33 (s, 3H), 7.02 - 7.09 (m, 1H), 7.12 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.20 (d, *J* = 2.7 Hz, 1H), 7.51 (d, *J* = 4.9 Hz, 1H), 8.21 (d, *J* = 5.2 Hz, 1H), 8.35 (s, 1H), 10.74 (s, 1H), 12.37 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 13.6, 14.2, 111.0, 116.8, 125.4, 126.0, 127.6, 145.4, 147.8, 152.6, 172.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{16}N_4OS$ $[M+H]^+$ 325.1, found 325.3. HPLC: t_R = 2.33 min (99.8% purity).

***N*-(4-(4-(Furan-2-yl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3e)**



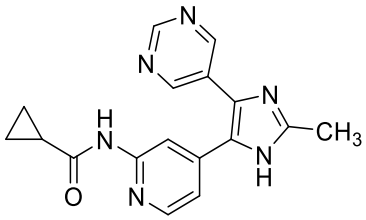
The compound was synthesized according to **General Procedure E** starting from compound **S6e** (115 mg, 0.26 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 24 mg (24.7%) of a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 - 0.93 (m, 2H), 1.00 - 1.13 (m, 2H), 1.58 - 1.68 (m, 1H), 2.40 (s, 3H), 6.42 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.71 (d, *J* = 3.3 Hz, 1H), 7.34 - 7.43 (m, 2H), 8.20 (d, *J* = 5.4 Hz, 1H), 8.41 (s, 1H), 9.04 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [2:1 v/v]) δ 8.0, 12.8, 14.9, 107.7, 111.1, 111.6, 117.8, 141.6, 146.2, 147.0, 151.2, 173.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{16}N_4O_2$ $[M+H]^+$ 309.1, found 309.2. HPLC: t_R = 2.20 min (99.2% purity).

_N_-(4-(4-(2-Methoxyphenyl)-2-methyl-1_H_-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3f)



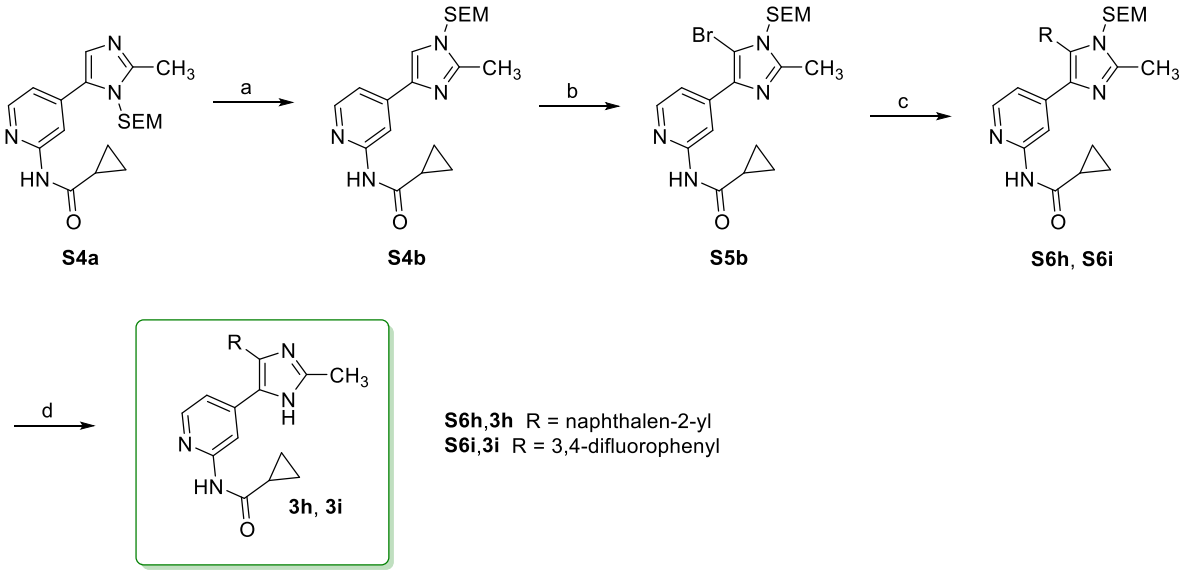
The compound was synthesized according to **General Procedure E** starting from compound **S6f** (110 mg, 0.23 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5 to 90:10) afforded 49 mg (61.2%) of a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 - 0.84 (m, 4H), 1.93 - 2.02 (m, 1H), 2.33 (s, 3H), 3.64 (s, 3H), 6.79 (dd, J = 5.3, 1.4 Hz, 1H), 7.00 (td, J = 7.4, 0.7 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.25 (dd, J = 7.5, 1.6 Hz, 1H), 7.37 - 7.45 (m, 1H), 7.99 (d, J = 5.4 Hz, 1H), 8.33 (s, 1H), 10.54 (s, 1H), 12.10 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.5, 13.7, 14.2, 55.2, 109.9, 111.7, 115.3, 120.5, 130.1, 131.2, 144.2, 147.0, 152.3, 156.8, 172.1. TLC-MS (ESI) m/z: calculated for $C_{20}H_{20}N_4O_4$ $[M+H]^+$ 349.2, found 349.3. HPLC: t_R = 2.57 min (100.0% purity).

_N_-(4-(2-Methyl-4-(pyrimidin-5-yl)-1_H_-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3g)



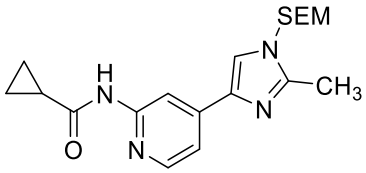
The compound was synthesized according to **General Procedure E** starting from compound **S6g** (60 mg, 0.13 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 98:2 to 90:10) afforded 26 mg (61.0%) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 - 0.84 (m, 4H), 1.90 - 2.07 (m, 1H), 2.39 (s, 3H), 7.05 (dd, J = 5.2, 1.6 Hz, 1H), 8.16 - 8.29 (m, 2H), 8.83 (s, 2H), 9.10 (s, 1H), 10.79 (s, 1H), 12.40 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.7, 13.6, 14.2, 110.6, 116.6, 146.7, 148.4, 152.7, 155.2, 156.9, 172.6. TLC-MS (ESI) m/z: calculated for $C_{17}H_{16}N_6O$ $[M+H]^+$ 321.1, found 321.3. HPLC: t_R = 1.37 min (96.9% purity).

Synthesis of 3h and 3i



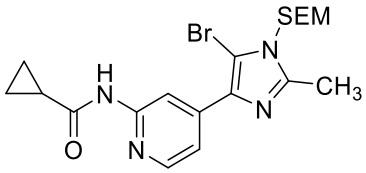
Scheme S2. *Reagents and conditions:* (a) SEM-Cl (5 mol%), MeCN, 85 °C, 18 h, 88%; (b) NBS, MeCN, -20 °C, 20 min, 77-88%; (c) arylboronic acid, CsF, benzyltriethylammonium chloride, $Pd(dppf)Cl_2 \cdot DCM$, toluene/H_2O, 100 °C, 16 h, 53-89%; (d) trifluoroacetic acid, DCM, rt, 6 h, 25-85%.

N-(4-(2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)pyridin-2-yl)cyclopropanecarboxamide (S4b)



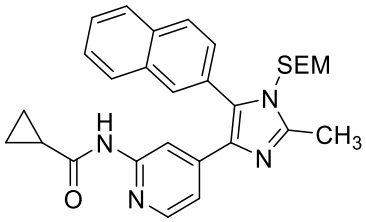
Compound **S4a** (349 mg, 0.94 mmol) was dissolved in MeCN (10 mL) and catalytic amounts of 2-(trimethylsilyl)ethoxymethyl chloride (8.31 µL, 0.047 mmol) were added. The mixture was stirred at 80 °C for 18 h to perform a "SEM switch" according to Sames an coworkers.[5] Purification by flash chromatography (SiO_2, DCM:EtOH 95:05) afforded 307 mg (88.0%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 9H), 0.78 - 0.89 (m, 4H), 0.99 - 1.12 (m, 2H), 1.68 (dq, *J* = 8.1, 3.9 Hz, 1H), 2.44 (s, 3H), 3.39 - 3.52 (m, 2H), 5.16 (s, 2H), 7.45 (s, 1H), 7.53 (dd, *J* = 5.4, 1.5 Hz, 1H), 8.18 (d, *J* = 5.4 Hz, 1H), 8.45 (s, 1H), 10.20 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.3, 12.8, 15.4, 17.6, 66.4, 75.4, 109.2, 115.2, 119.0, 136.9, 144.4, 146.4, 146.5, 151.8, 173.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{28}N_4O_2Si$ $[M-H]^-$ 371.2, found 371.0. HPLC: t_R = 7.11 min.

***N*-(4-(5-Bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)pyridin-2-yl)cyclopropanecarboxamide (S5b)**



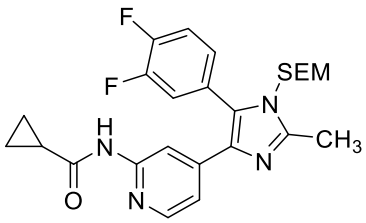
Compound **S4b** (670 mg, 1.80 mmol) was dissolved in MeCN (15 mL) under an atmosphere of argon and the solution was cooled to -20 °C. *N*-Bromosuccinimide (336 mg, 1.88 mmol) was added in one portion and the mixture was stirred at -20 °C for 20 min before it was quenched with sat. aq. Na_2SO_3 solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOAc 80:20 to 10:90) afforded 622 mg (76.6%) of a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 9H), 0.82 - 0.96 (m, 4H), 1.09 - 1.17 (m, 2H), 1.58 - 1.69 (m, 1H), 2.52 (s, 3H), 3.55 - 3.63 (m, 2H), 5.32 (s, 2H), 7.66 (dd, *J* = 5.4, 1.7 Hz, 1H), 8.27 (dd, *J* = 5.4, 0.7 Hz, 1H), 8.95 (s, 1H), 9.28 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.1, 13.8, 15.4, 17.6, 66.3, 73.2, 102.2, 110.6, 116.5, 134.0, 143.0, 146.7, 147.2, 152.0, 172.8. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{27}BrN_4O_2Si$ $[M-H]^-$ 449.1/451.1, found 449.0/450.9. HPLC: t_R = 9.13 min.

***N*-(4-(2-Methyl-5-(naphthalen-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)pyridin-2-yl)cyclopropanecarboxamide (S6h)**



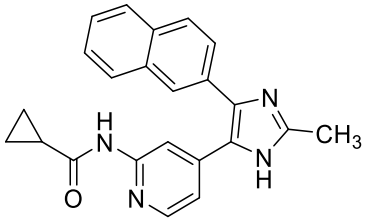
The title compound was synthesized according to **General Procedure D** starting from compound **S5b** (85 mg, 0.19 mmol), 2-napthylboronic acid (85 mg, 0.30 mmol), cesium fluoride (86 mg, 0.57 mmol), benzyltriethylammonium chloride (2.6 mg, 0.011 mmol) and $Pd(dppf)Cl_2$·DCM (9.2 mg, 0.011 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 79 mg (86.6%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.79 (dd, *J* = 7.7, 3.3 Hz, 2H), 0.83 - 0.92 (m, 2H), 0.98 - 1.06 (m, 2H), 1.51 - 1.62 (m, 1H), 2.65 (s, 3H), 3.35 - 3.45 (m, 2H), 5.14 (s, 2H), 6.94 (dd, *J* = 5.4, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.58 - 7.68 (m, 2H), 7.88 - 8.05 (m, 5H), 8.57 (s, 1H), 9.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 7.9, 13.4, 15.3, 17.7, 65.9, 72.4, 111.8, 116.7, 126.5, 126.9, 127.2, 127.7, 128.1, 128.2, 128.8, 130.6, 131.2, 133.2, 133.2, 134.3, 144.6, 146.1, 146.8, 152.1, 172.0. TLC-MS (ESI) *m*/*z*: calculated for $C_{29}H_{34}N_4O_2Si$ $[M+Na]^+$ 521.2, found 521.3. HPLC: t_R = 10.34 min.

***N*-(4-(5-(3,4-Difluorophenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)pyridin-2-yl)cyclopropanecarboxamide (S6i)**



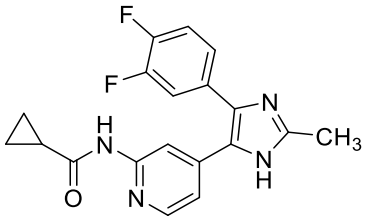
The title compound was synthesized according to **General Procedure D** starting from compound **S5b** (200 mg, 0.44 mmol), 3,4-difluorophenylboronic acid (92 mg, 0.58 mmol), cesium fluoride (202 mg, 1.33 mmol), benzyltriethylammonium chloride (6.0 mg, 0.027 mmol) and Pd(dppf)Cl_2·DCM (21.7 mg, 0.027 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20 to 20:80) afforded 172 mg (80.1%) of a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.79 (dd, *J* = 7.3, 2.9 Hz, 2H), 0.84 - 0.93 (m, 2H), 0.97 - 1.11 (m, 2H), 1.56 (d, *J* = 3.9 Hz, 1H), 2.55 (s, 3H), 3.42 (t, *J* = 8.3 Hz, 2H), 5.03 (s, 2H), 7.08 (d, *J* = 5.0 Hz, 1H), 7.17 - 7.75 (m, 3H), 8.11 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 9.71 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 8.1, 13.2, 15.4, 17.7, 66.1, 72.4, 111.6, 116.7 (d, $^2J_{CF}$ = 17.1 Hz), 118.1 (d, $^2J_{CF}$ = 17.7 Hz), 120.1, 126.4 (dd, $^3J_{CF}$ = 6.1, 4.4 Hz), 127.5 (dd, $^3J_{CF}$ = 6.4, 3.6 Hz), 129.2, 134.5, 144.1, 146.3, 146.7, 150.4, 150.9 (dd, $^1J_{CF}$ = 253.2, 15.5 Hz, 151.9 (dd, $^1J_{CF}$ = 256.0, 17.1 Hz), 172.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{30}F_2N_4O_2Si$ $[M+H]^+$ 485.2, found 485.3. HPLC: t_R = 10.05 min (100.0% purity).

***N*-(4-(2-Methyl-4-(naphthalen-2-yl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3h)**



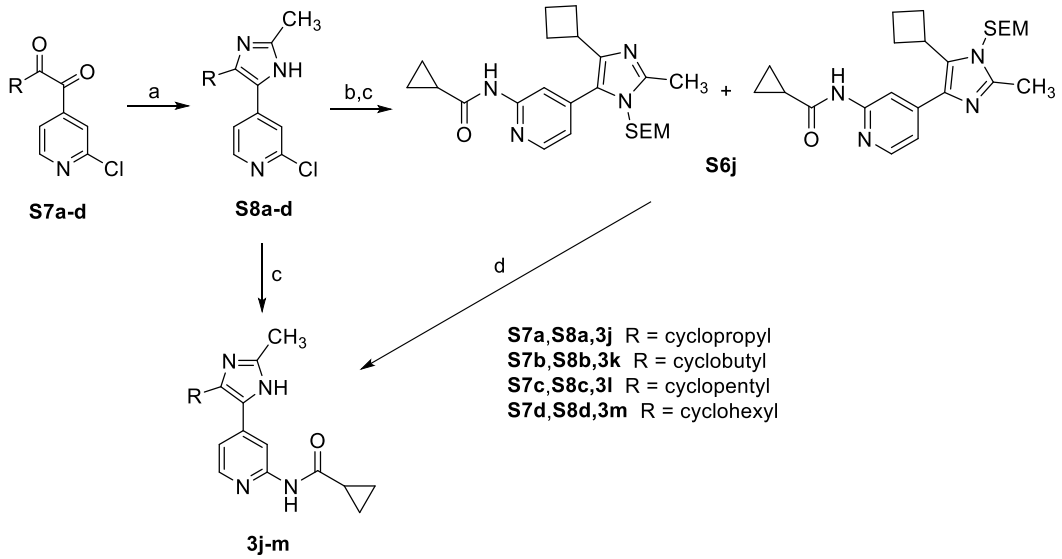
The compound was synthesized according to **General Procedure E** starting from compound **S6h** (138 mg, 0.28 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 86 mg (84.4%) of a yellowish solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.69 - 0.83 (m, 4H), 1.93 - 2.04 (m, 1H), 2.39 (s, 3H), 6.98 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.47 - 7.58 (m, 3H), 7.84 - 7.96 (m, 3H), 8.02 (s, 1H), 8.09 (d, *J* = 5.1 Hz, 1H), 8.40 (s, 1H), 10.68 (s, 1H), 12.42 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [2:1 v/v]) δ 7.7, 12.6, 14.5, 111.5, 117.4, 125.7, 125.8, 125.8, 126.6, 127.2, 127.5, 127.8, 129.3, 132.4, 133.0, 134.2, 142.7, 145.8, 146.9, 151.4, 173.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{20}N_4O$ $[M+H]^+$ 369.2, found 369.2. HPLC: t_R = 5.07 min (100.0% purity).

***N*-(4-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3i)**



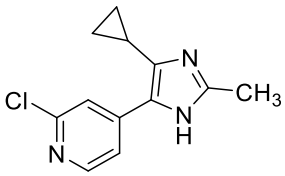
The compound was synthesized according to **General Procedure E** starting from compound **S6i** (165 mg, 0.34 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 102 mg (84.6%) of a yellowish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 - 0.95 (m, 2H), 1.02 - 1.10 (m, 2H), 1.55 - 1.69 (m, 1H), 2.44 (s, 3H), 7.02 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.07 - 7.16 (m, 1H), 7.18 - 7.25 (m, 1H), 7.27 - 7.36 (m, 1H), 8.10 (dd, *J* = 5.4, 0.5 Hz, 1H), 8.21 (d, *J* = 0.8 Hz, 1H), 8.90 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{16}F_2N_4O$ $[M+H]^+$ 355.1, found 355.2. HPLC: t_R = 3.63 min (100.0% purity).

Synthesis of 3j-m



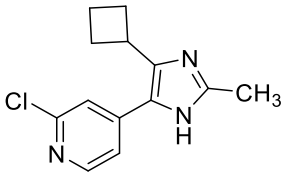
Scheme S3. *Reagents and conditions:* (a) CH_3CHO, NH_4OAc, MeOH, 65 °C, 3 h, 38-54%; (b) NaH, SEM-Cl, THF, 0 °C to rt, 18 h, 100%; (c) cyclopropanecarboxamide, Cs_2CO_3, $Pd_2(dba)_3$, XantPhos, DMF, 100 °C, 16 h, 8-77%; (d) trifluoroacetic acid, DCM, rt, 24 h, 52%.

2-Chloro-4-(4-cyclopropyl-2-methyl-1*H*-imidazol-5-yl)pyridine (S8a)



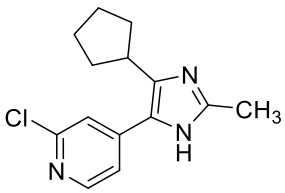
The title compound was prepared according to **General Procedure A** starting from 1-(2-chloropyridin-4-yl)-2-cyclopropylethane-1,2-dione[1] (**S7a**) (2.50 g, 11.93 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 99:1 to 90:10) afforded 1.22 g (43.59%) of a brown-orange wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 - 0.81 (m, 2H), 0.96 - 1.07 (m, 2H), 1.90 - 2.03 (m, 1H), 2.35 (s, 3H), 7.67 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.77 (d, *J* = 0.9 Hz, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 10.17 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1, 7.5, 18.3, 119.1, 120.4, 130.9, 134.1, 144.3, 144.8, 149.0, 151.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{12}ClN_3$ $[M+H]^+$ 234.1, found 233.8. HPLC: t_R = 1.57 min.

2-Chloro-4-(4-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)pyridine (S8b)



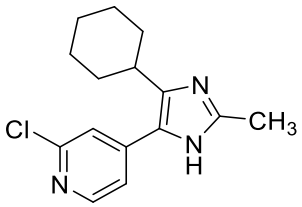
The title compound was prepared according to **General Procedure A** starting from 1-(2-chloropyridin-4-yl)-2-cyclobutylethane-1,2-dione[1] (**S7b**) (782 mg, 3.49 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 337 mg (39.0%) of a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 - 1.90 (m, 1H), 1.97 - 2.11 (m, 1H), 2.22 (quind, *J* = 9.3, 2.1 Hz, 2H), 2.31 - 2.44 (m, 2H), 2.38 (s, 3H), 3.75 - 3.84 (m, 1H), 7.38 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.48 (d, *J* = 0.9 Hz, 1H), 8.27 (d, *J* = 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.3, 29.0, 31.5, 119.6, 120.9, 129.4, 135.7, 144.7, 145.2, 149.1, 151.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{14}ClN_3$ $[M+H]^+$ 248.1, found 248.0. HPLC: t_R = 2.49 min.

2-Chloro-4-(4-cyclopentyl-2-methyl-1*H*-imidazol-5-yl)pyridine (S8c)



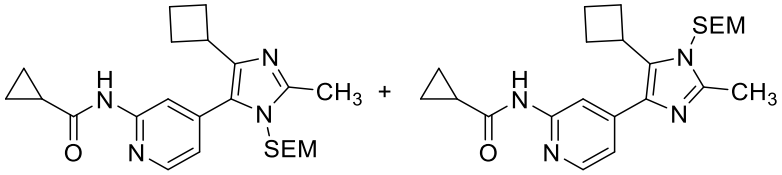
The title compound was prepared according to **General Procedure A** starting from 1-(2-chloropyridin-4-yl)-2-cyclopentylethane-1,2-dione[1] (**S7c**) (946 mg, 3.98 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 565 mg (54.2%) of a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 - 1.88 (m, 6H), 2.02 - 2.18 (m, 2H), 2.41 (s, 3H), 3.28 - 3.42 (m, 1H), 7.44 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.56 (s, 1H), 8.30 (dd, *J* = 4.9, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 25.4, 33.3, 36.5, 119.9, 121.2, 130.3, 135.8, 144.7, 145.8, 149.1, 151.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{14}H_{16}ClN_3$ $[M+H]^+$ 262.1, found 261.8. HPLC: t_R = 3.24 min (100.0% purity).

2-Chloro-4-(4-cyclohexyl-2-methyl-1*H*-imidazol-5-yl)pyridine (S7d)



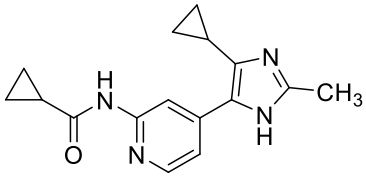
The title compound was prepared according to **General Procedure A** starting from 1-(2-chloropyridin-4-yl)-2-cyclohexylethane-1,2-dione[1] (**S7d**) (781 mg, 3.10 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 326 mg (38.1%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 - 1.28 (m, 1H), 1.29 - 1.56 (m, 4H), 1.69 - 1.99 (m, 5H), 2.38 (s, 3H), 2.83 - 3.01 (m, 1H), 7.41 (dd, *J* = 5.3, 1.4 Hz, 1H), 7.55 (s, 1H), 8.29 (d, *J* = 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 25.8, 26.4, 33.0, 35.4, 119.7, 121.2, 129.7, 137.1, 144.4, 145.8, 149.3, 151.8. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{18}ClN_3$ $[M+H]^+$ 276.1, found 275.8. HPLC: t_R = 4.39 min (100.0% purity).

***N*-(4-(4(5)-Cyclobutyl-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5(4)-yl)pyridin-2-yl)cyclopropanecarboxamide (S6j)**



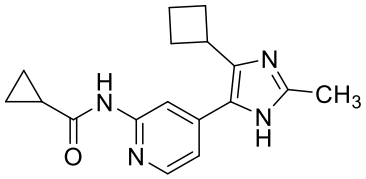
Compound **S8b** (282 mg, 1.14 mmol) was dissolved in THF (15 mL) and the solution was cooled to 0 °C. NaH 60% dispersion in mineral oil (64 mg, 1.60 mmol) was added in one portion and the resulting suspension was stirred for 30 min. Then 2-(trimethylsilyl)ethoxymethyl chloride (212 µL, 1.20 mmol) was added, the ice-bath was removed and the solution was stirred for 18 h. H_2O (25 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was dried in vacuo before it was processed according to **General Procedure B**. Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 216 mg (76.6%) of a mix of two regioisomers (ratio 2.5:1) over 2 steps. *isomer 1:* ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.07 (s, 9H), 0.77 - 0.92 (m, 4H), 1.04 - 1.13 (m, 2H), 1.56 - 1.68 (m, 1H), 1.77 - 2.02 (m, 2H), 2.16 (qt, *J* = 8.3, 2.6 Hz, 2H), 2.32 - 2.48 (m, 2H), 2.51 (s, 3H), 3.29 - 3.40 (m, 2H), 3.46 (quin, *J* = 8.8 Hz, 1H), 5.13 (s, 2H), 6.97 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.13 (s, 1H), 8.29 (d, *J* = 5.2 Hz, 1H), 9.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) -1.6, 8.3, 13.5, 15.7, 17.6, 18.4, 28.7, 32.6, 65.8, 72.6, 114.4, 120.0, 125.3, 140.7, 142.9, 146.7, 147.6, 152.0, 172.3. *isomer 2:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.75 (dd, *J* = 7.9, 3.0 Hz, 2H), 0.84 (dd, *J* = 7.7, 3.2 Hz, 2H), 1.02 - 1.12 (m, 2H), 1.42 (s, 1H), 1.59 - 2.18 (m, 4H), 2.32 - 2.48 (m, 5H), 3.44 - 3.57 (m, 2H), 3.75 - 3.93 (m, 1H), 5.13 (s, 2H), 7.27 (s, 1H), 8.05 - 8.30 (m, 2H), 9.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.1, 13.3, 15.5, 17.8, 18.6, 28.9, 31.3, 65.8, 73.0, 114.2, 119.3, 133.1, 134.0, 145.1, 146.0, 146.6, 151.3, 172.5 TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{34}N_4O_2Si$ $[M+H]^+$ 427.2, found 427.3. HPLC: t_R = 7.24 min & 8.74 min.

***N*-(4-(4-Cyclopropyl-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3j)**



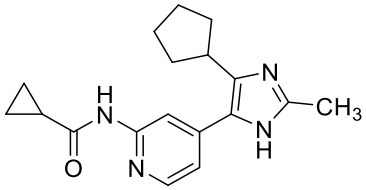
The title compound was prepared according to **General Procedure B** starting from **S8a** (238 mg, 1.02 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 51 mg (17.7%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 - 0.77 (m, 2H), 0.83 - 0.91 (m, 2H), 0.97 - 1.05 (m, 2H), 1.05 - 1.12 (m, 2H), 1.57 - 1.68 (m, 1H), 2.01 (tt, *J* = 8.3, 5.2 Hz, 1H), 2.32 (s, 3H), 7.49 (dd, *J* = 5.4, 1.4 Hz, 1H), 8.22 (d, *J* = 5.4 Hz, 1H), 8.58 (s, 1H), 9.26 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 7.6, 8.3, 13.9, 15.8, 110.4, 116.5, 130.9, 135.0, 143.4, 143.6, 147.5, 151.9, 172.7. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{18}N_4O$ $[M+H]^+$ 283.1, found 282.8. HPLC: t_R = 1.93 min (99.4% purity).

***N*-(4-(4-Cyclobutyl-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3k)**



The mix of regioisomers from **S6j** (210 mg, 0.49 mmol) was dissolved in DCM (5 mL) and trifluoroacetic acid (1 mL). The solution was stirred at rt for 24 h before additional DCM and sat. aq. $NaHCO_3$ solution was added until the aqueous phase was adjusted to pH 7. The organic layer was separated and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 76 mg (52.2%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 - 0.94 (m, 2H), 1.08 - 1.15 (m, 2H), 1.52 - 1.63 (m, 1H), 1.83 - 1.97 (m, 1H), 2.00 - 2.33 (m, 4H), 2.40 - 2.49 (m, 4H), 3.86 (quin, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 4.4 Hz, 1H), 8.14 (s, 1H), 8.18 (d, *J* = 5.2 Hz, 1H), 8.34 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 13.6, 15.7, 18.2, 28.7, 32.0, 110.5, 116.9, 127.8, 138.1, 143.0, 144.5, 147.5, 151.6, 172.9. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{20}N_4O$ $[M+H]^+$ 297.2, found 297.3. HPLC: t_R = 2.76 min (100.0% purity).

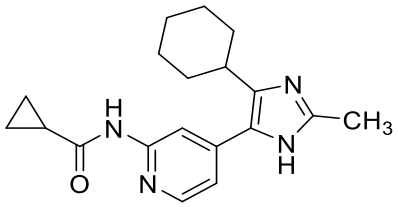
***N*-(4-(4-Cyclopentyl-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3l)**



The title compound was prepared according to **General Procedure B** starting from **S8c** (300 mg, 1.15 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 33 mg (9.3%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$/MeOD [1:1 v/v]) δ 0.81 - 0.94 (m, 2H), 1.05 - 1.14 (m, 2H), 1.56 - 1.64 (m, 1H), 1.66 - 1.86 (m, 6H), 2.05 - 2.19 (m, 2H), 2.47 (s, 3H), 3.32 - 3.44 (m, 1H), 7.31

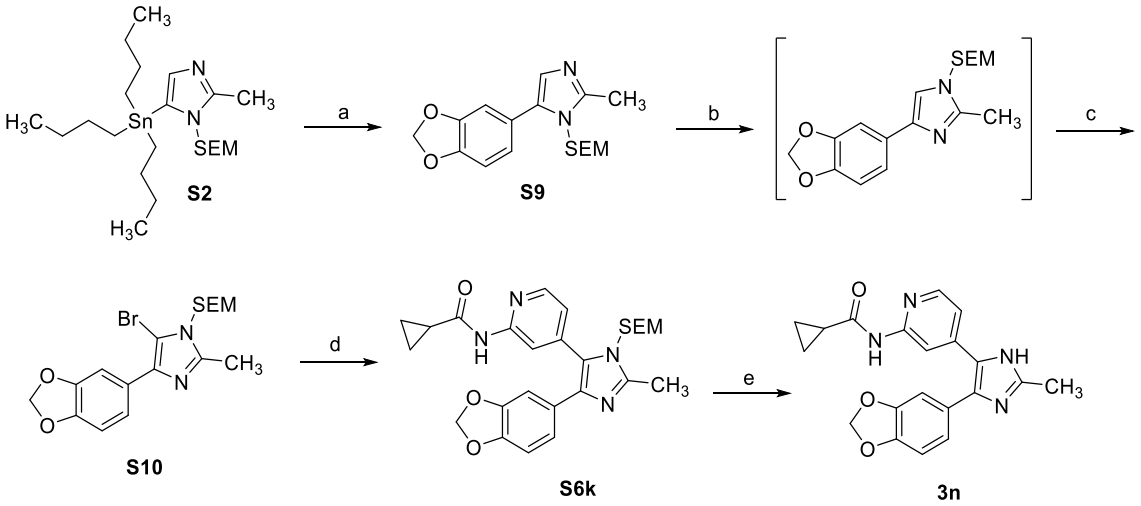
(d, *J* = 4.4 Hz, 1H), 8.22 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 8.52 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [1:1 v/v]) δ 7.2, 12.1, 14.3, 24.8, 32.5, 35.9, 111.2, 116.9, 129.5, 135.8, 143.6, 144.2, 146.8, 151.1, 173.3. TLC-MS (ESI) *m/z*: calculated for $C_{18}H_{22}N_4O$ $[M+H]^+$ 311.2, found 311.0. HPLC: t_R = 3.49 min (98.5% purity).

***N*-(4-(4-Cyclohexyl-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (3m)**



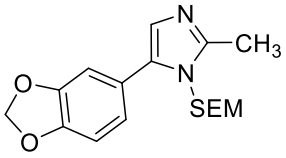
The title compound was prepared according to **General Procedure B** starting from **S8d** (250 mg, 0.91 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 22 mg (7.5%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 - 0.89 (m, 2H), 1.04 - 1.12 (m, 2H), 1.25 - 1.52 (m, 5H), 1.56 - 1.65 (m, 1H), 1.66 - 1.83 (m, 3H), 1.89 (d, *J* = 9.7 Hz, 2H), 2.34 (br. s., 3H), 2.89 - 3.05 (m, 1H), 7.27 (d, *J* = 5.1 Hz, 1H), 8.21 (d, *J* = 5.3 Hz, 1H), 8.34 (s, 1H), 9.30 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 13.8, 15.7, 25.8, 26.3, 32.9, 35.4, 111.1, 114.3, 117.1, 129.2, 138.2, 144.0, 147.5, 152.0, 172.6. TLC-MS (ESI) *m/z*: calculated for $C_{19}H_{24}N_4O$ $[M+H]^+$ 325.2, found 325.1. HPLC: t_R = 4.73 min (100.0% purity).

Synthesis of 3n



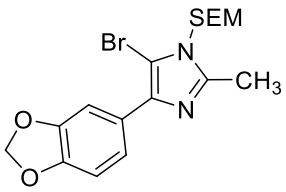
Scheme S4. *Reagents and conditions:* (a) 5-bromo-1,3-benzodioxole, $Pd(PPh_3)_4$, 1,4-dioxane, 105 °C, 18 h, 83%; (b) SEM-Cl, MeCN, 80 °C, 18 h; (c) NBS, MeCN, 0 °C, 30 min, 46% (*over 2 steps*); (d) **S11**, CsF, benzyltriethylammonium chloride, $Pd(dppf)Cl_2$·DCM, toluene/H_2O, 100 °C, 16 h, 32%; (e) trifluoroacetic acid, DCM, rt, 24 h, 50%.

5-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S9)



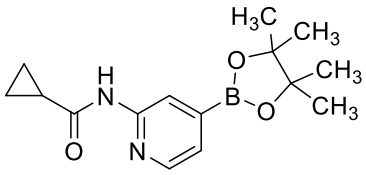
Compound **S2** (563 mg, 1.12 mmol), 5-bromo-1,3-benzodioxole (338 mg, 1.68 mmol) and $Pd(PPh_3)_4$ (97 mg, 0.084 mmol) were dissolved in degassed 1,4-dioxane (8 mL) under an atmosphere of argon. The reaction mixture was heated to 105 °C for 18 h before the solution was filtered through a pad of celite. The pad was washed with DCM (30 mL) and the solvents were removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 60:40 to 30:70) afforded 310 mg (83.1%) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.03 (s, 9H), 0.84 - 0.91 (m, 2H), 2.50 (s, 3H), 3.38 - 3.47 (m, 2H), 5.14 (s, 2H), 6.00 (s, 2H), 6.81 - 6.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 13.6, 17.7, 65.8, 72.3, 101.2, 108.5, 109.5, 122.8, 123.9, 125.7, 133.5, 146.3, 147.4, 147.8. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{24}N_2O_3Si$ $[M+H]^+$ 333.2, found 333.3. HPLC: t_R = 6.44 min.

4-(Benzo[*d*][1,3]dioxol-5-yl)-5-bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S10)



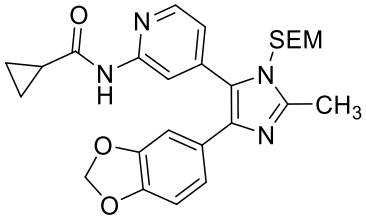
Compound **S9** (300 mg, 0.90 mmol) was dissolved in MeCN (10 mL) and catalytic amounts of 2-(trimethylsilyl)ethoxymethyl chloride (7.96 µL, 0.045 mmol) were added. The mixture was stirred at 80 °C for 18 h to perform a "SEM switch"[4]. The solvent was removed under reduced pressure and the crude product was redissolved in MeCN (15 mL). The solution was cooled to 0 °C and *N*-bromosuccinimide (160 mg, 0.90 mmol) was added in one portion. The reaction was further stirred at 0 °C for 30 min before sat. aq. Na_2SO_3 solution was added and it was extracted with EtOAc (3x). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 60:40) afforded 170 mg (45.8%) of a tangerine oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.90 - 0.99 (m, 2H), 2.53 (s, 3H), 3.57 - 3.66 (m, 2H), 5.30 (s, 2H), 5.98 (s, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.40 - 7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 13.9, 17.7, 66.1, 73.1, 98.2, 100.8, 107.3, 108.0, 120.4, 127.1, 136.7, 146.4, 146.6, 147.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{23}BrN_2O_3Si$ $[M+H]^+$ 411.1/413.1, found 411.4/413.4. HPLC: t_R = 10.39 min.

***N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)cyclopropanecarboxamide (S11)[4]**



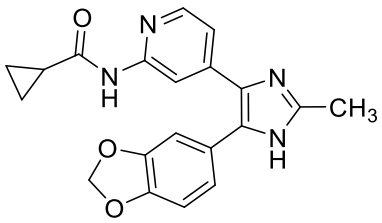
Compound **S3** (1.00 g, 4.15 mmol), Bis(pinacolato)diboron (1.26 g, 4.98 mmol), KOAc (1.43 g, 14.52 mmol) and Pd(dppf)Cl_2·DCM (136 mg, 0.166 mmol) were dissolved in degassed 1,4-dioxane (10 mL) under an atmosphere of argon. The reaction mixture was stirred at 85 °C for 18 h and after cooling to rt, EtOAc (30 mL) was added. The solution was filtered over celite and the filtrate was removed under reduced pressure and redissolved in EtOAc (50 mL). A spoon of activated charcoal was added to the solution and the resulting suspension was stirred at 85 °C for 30 min. The hot reaction mixture was filtered again over celite and the filtrate was removed under reduced pressure. The crude product was suspended in *n*-heptane and agitated for 30 min using an ultrasonic bath. The title compound was collected by filtration to yield 1.05 g (88.1%) of a beige solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.74 - 0.86 (m, 4H), 1.30 (s, 12H), 1.94 - 2.05 (m, 1H), 7.24 (dd, *J* = 4.8, 0.9 Hz, 1H), 8.33 (dd, *J* = 4.7, 0.9 Hz, 1H), 8.35 (s, 1H), 10.77 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.7, 14.2, 24.6, 84.3, 118.4, 123.5, 138.6, 147.5, 151.9, 172.6. HPLC: t_R = 1.36 min.

_N_-(4-(4-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S6k)



The title compound was synthesized according to **General Procedure D** starting from compound **S10** (165 mg, 0.40 mmol), **S11** (173 mg, 0.60 mmol), cesium fluoride (183 mg, 1.20 mmol), benzyltriethylammonium chloride (5.5 mg, 0.024 mmol) and Pd(dppf)Cl_2·DCM (19.7 mg, 0.024 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 64 mg (32.4%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 9H), 0.80 - 0.95 (m, 4H), 1.05 - 1.12 (m, 2H), 1.56 - 1.66 (m, 1H), 2.54 (s, 3H), 3.31 - 3.40 (m, 2H), 5.14 (s, 2H), 5.90 (s, 2H), 6.64 - 7.25 (m, 4H), 8.21 - 8.29 (m, 2H), 9.04 (br. s., 1H). TLC-MS (ESI) *m/z*: calculated for $C_{26}H_{32}N_4O_4Si$ $[M+H]^+$ 493.2, found 493.8. HPLC: t_R = 7.60 min.

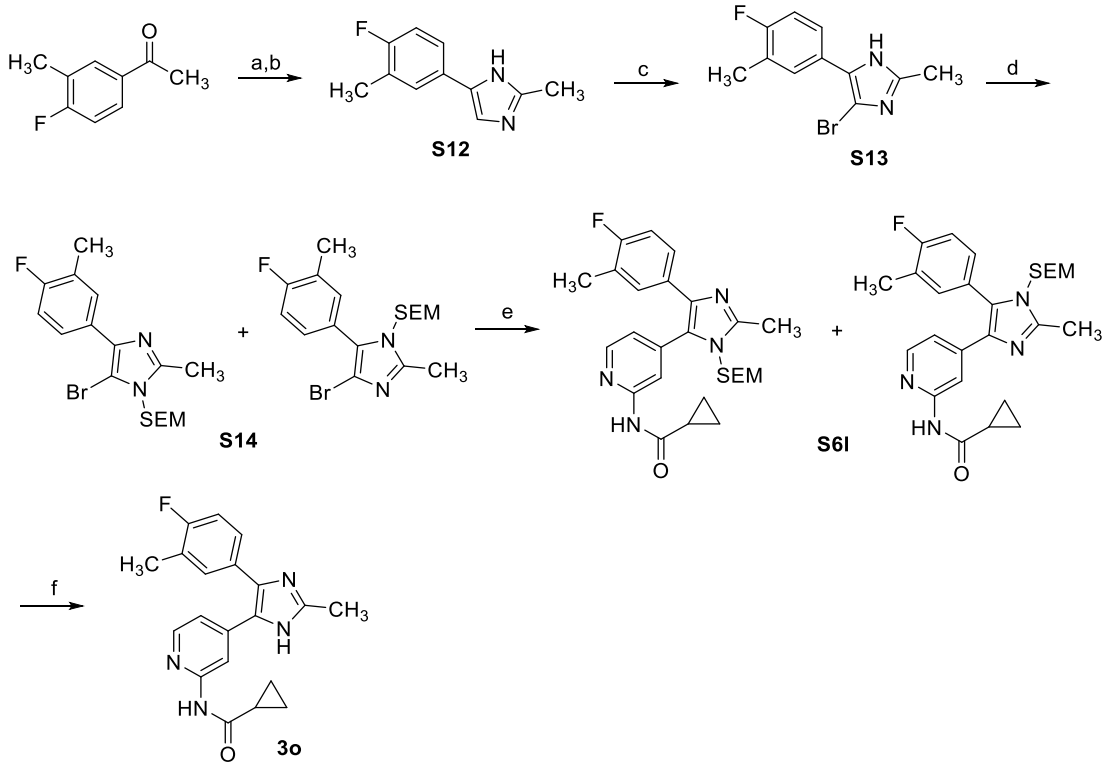
_N_-(4-(5-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1*H*-imidazol-4-yl)pyridin-2-yl)cyclopropanecarboxamide (3n)



The title compound was synthesized according to **General Procedure E** starting from **S6k** (60 mg, 0.12 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 22 mg (49.8%) of an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, *J* = 6.1 Hz, 4H), 1.89 - 2.04 (m, 1H), 2.33 (s, 3H),

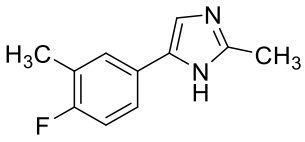
6.05 (s, 2H), 6.82 - 7.03 (m, 4H), 8.11 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 10.65 (s, 1H), 12.37 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.6, 13.6, 14.2, 101.2, 108.5, 108.6, 110.6, 116.4, 122.0, 144.5, 146.9, 147.4, 147.5, 152.5, 172.3. TLC-MS (ESI) *m/z*: calculated for $C_{20}H_{18}N_4O_3$ $[M+H]^+$ 363.1, found 363.4. HPLC: t_R = 2.70 min (98.0% purity).

Synthesis of 3o



Scheme S5. *Reagents and conditions:* (a) 48% aq. HBr/DMSO, 55 °C, 18 h; (b) ethyl glyoxylate (polymer form ~50% in toluene), NH_4OAc, MeOH/MeCN, rt, 1.5 h, 28% (*over 2 steps*); (c) NBS, MeCN, 0 °C, 1 h, 70%; (d) SEM-Cl, NaH, THF, 0 °C to rt, 18 h, 76%; (e) **S11**, CsF, benzyltriethylammonium chloride, Pd(dppf)Cl_2·DCM, toluene/H_2O, 100 °C, 18 h, 14%; (f) trifluoroacetic acid, DCM, rt, 88%.

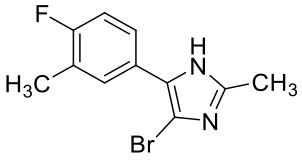
5-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole (S12)



4'-Fluoro-3'-methylacetophenone (500 mg, 3.29 mmol) was treated according to a modified **General Procedure C**. After the oxidation, the 1-(4-fluoro-3-methylphenyl)-2,2-dihydroxyethan-1-one was dissolved in MeOH (20 mL) and added dropwise to a previously prepared solution of NH_4OAc (1.27 g, 16.43 mmol) and acetaldehyde (550 µL, 9.86 mmol) in MeOH (10 mL). After 1.5 h, the solvent was

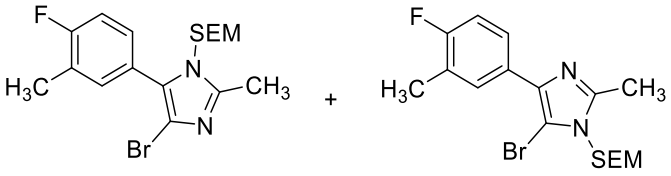
evaporated, H_2O was added and it was extracted with EtOAc (5x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure and the compound was purified by flash chromatography (SiO_2, DCM:EtOH 97:3 to 90:10) to afford 172 mg (27.5%) of a brown-red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.38 (s, 3H), 6.91 (t, J = 8.8 Hz, 1H), 7.05 (s, 1H), 7.31 - 7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.4 (d, $^3J_{CF}$ = 3.3 Hz), 114.4, 115.2 (d, $^2J_{CF}$ = 22.7 Hz), 123.7 (d, $^3J_{CF}$ = 8.3 Hz), 125.2 (d, $^2J_{CF}$ = 17.7 Hz), 127.2 (d, $^4J_{CF}$ = 3.3 Hz), 128.0 (d, $^3J_{CF}$ = 5.0 Hz), 135.8, 145.0, 160.6 (d, $^1J_{CF}$ = 245.5 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{11}H_{11}FN_2$ $[M+H]^+$ 191.1, found 191.1. HPLC: t_R = 2.52 min.

4-Bromo-5-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole (S13)



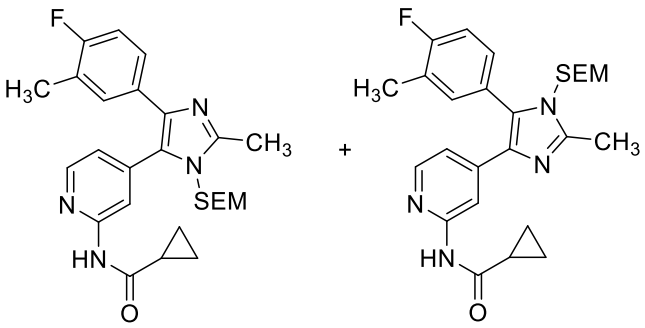
Compound **S12** (172 mg, 0.90 mmol) was dissolved in MeCN (5 mL), cooled to 0 °C and *N*-bromosuccinimide (161 mg, 0.90 mmol) was added in one portion. The mixture was stirred for 1 h at 0 °C before the reaction was quenched with sat. aq. Na_2SO_3 solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10 to 30:70) afforded 170 mg (69.8%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (d, J = 1.7 Hz, 3H), 2.29 (s, 3H), 7.16 - 7.29 (m, 1H), 7.47 - 7.64 (m, 2H), 12.44 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{11}H_{10}BrFN_2$ $[M+H]^+$ 269.1/271.1, found 269.1/271.1. HPLC: t_R = 5.93 min.

4(5)-Bromo-5(4)-(4-fluoro-3-methylphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S14)



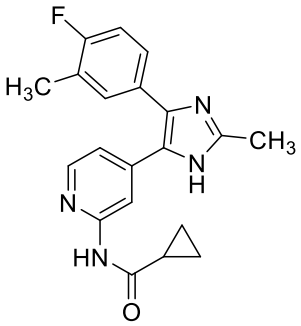
The title compound was prepared following the procedure as described for compound **S6j** starting from compound **S13** (130 mg, 0.48 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 65:35) afforded 118 mg (76.2%) of a solid as a mixture of both regioisomers. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{24}BrFN_2OSi$ $[M+H]^+$ 399.1/401.1, found 399.1/401.1. HPLC: t_R = 11.29 min & 11.69 min.

***N*-(4-(5(4)-(4-Fluoro-3-methylphenyl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4(5)-yl)pyridin-2-yl)cyclopropanecarboxamide (S6l)**



The title compound was synthesized according to **General Procedure D** starting from compound **S14** (100 mg, 0.25 mmol), **S11** (123 mg, 0.43 mmol), cesium fluoride (114 mg, 0.75 mmol), benzyltriethylammonium chloride (3.4 mg, 0.015 mmol) and $Pd(dppf)Cl_2$·DCM (12 mg, 0.015 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 65:35) afforded 17 mg (14.3%) of only one pure regioisomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (s, 9H), 0.80 - 0.93 (m, 4H), 1.04 - 1.13 (m, 2H), 1.57 - 1.65 (m, 1H), 2.20 (d, *J* = 1.7 Hz, 3H), 2.55 (s, 3H), 3.27 - 3.43 (m, 2H), 5.16 (s, 2H), 6.75 - 6.86 (m, 1H), 6.94 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.02 - 7.11 (m, 1H), 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 8.23 (dd, *J* = 5.2, 0.6 Hz, 1H), 8.27 (s, 1H), 8.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.4, 13.4, 14.4, 15.7, 17.7, 66.0, 72.7, 114.6, 115.2 , 121.4, 124.6, 125.6, 126.4, 129.6, 130.6, 137.6, 141.4, 146.9, 147.8, 152.3, 160.5 (d, $^1J_{CF}$ = 246.0 Hz), 172.4. TLC-MS (ESI) *m/z*: calculated for $C_{26}H_{33}N_4O_2Si$ $[M+H]^+$ 481.7, found 481.7. HPLC: t_R = 9.02 min.

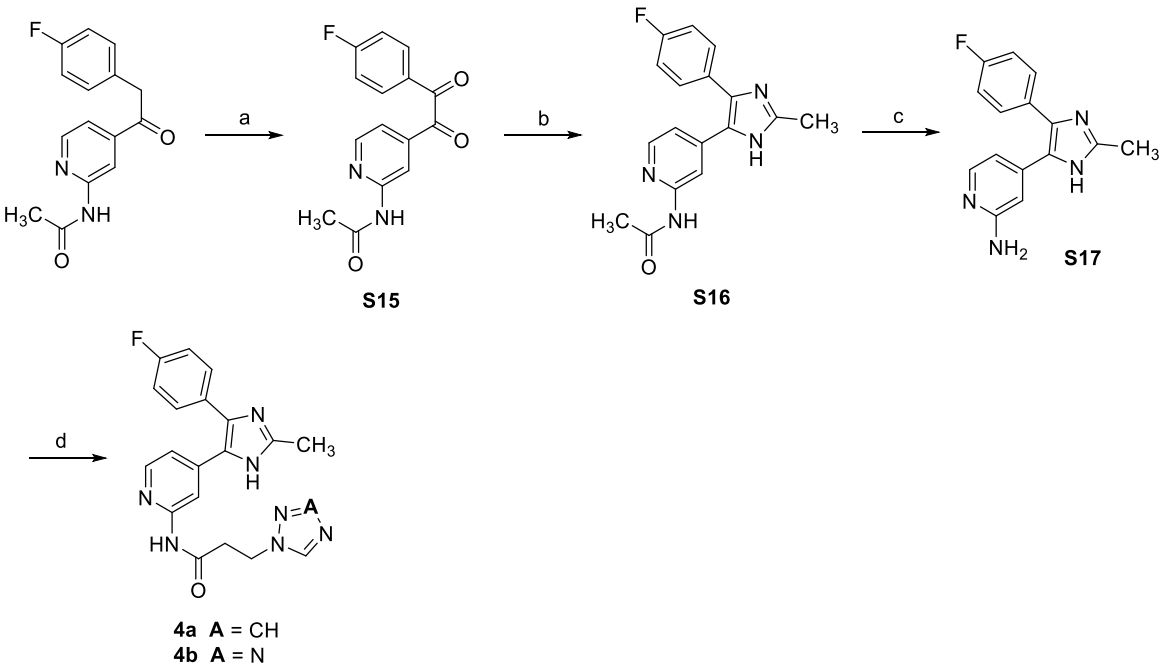
***N*-(4-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (30)**



The title compound was synthesized according to **General Procedure E** starting from one pure isomer of **S6l** (17 mg, 0.049 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 11 mg (88.4%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 - 0.91 (m, 2H), 1.02 - 1.09 (m, 2H), 1.59 - 1.68 (m, 1H), 2.24 (d, *J* = 1.7 Hz, 3H), 2.43 (s, 3H), 6.95 (t, *J* = 9.0 Hz, 1H), 7.05 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.17 - 7.24 (m, 1H), 7.32 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.03 (d, *J* = 5.3 Hz, 1H), 8.29 (s, 1H), 9.09 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 14.0, 14.4 (d, $^3J_{CF}$ = 3.3 Hz), 15.7, 110.7, 115.2 (d, $^2J_{CF}$ = 22.7 Hz), 117.2, 125.3 (d, $^2J_{CF}$ = 17.7 Hz), 127.4 (d, $^3J_{CF}$ = 8.3 Hz), 131.5 (d, $^3J_{CF}$ = 5.0 Hz), 145.6,

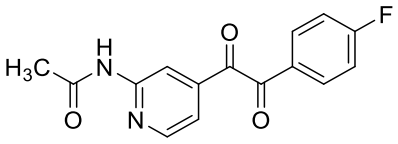
147.0, 151.8, 161.1 (d, $^{1}J_{CF}$ = 246.0 Hz), 172.9. TLC-MS (ESI) *m/z*: calculated for $C_{20}H_{17}FN_4O$ $[M+H]^+$ 351.2, found 351.5. HPLC: t_R = 4.31 min.

Synthesis of 4a and 4b



Scheme S6. *Reagents and conditions:* (a) SeO_2, acetic acid, 70 °C, 3 h, 84%; (b) acetaldehyde, NH_4OAc, MeOH, 65 °C, 3 h, 53%; (c) 10% aq. HCl, 110 °C, 18 h, 47%; (d) carboxylic acid, HATU, DIPEA, rt, 18 h, 42-56%.

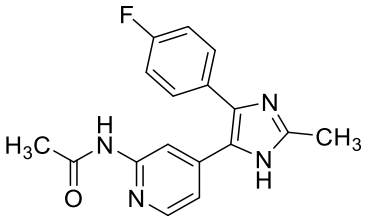
N-(4-(2-(4-Fluorophenyl)-2-oxoacetyl)pyridin-2-yl)acetamide (S15)



N-(4-(2-(4-fluorophenyl)acetyl)pyridin-2-yl)acetamide[6] (8.20 g, 30.12 mmol) was dissolved in glacial acetic acid (150 mL) and selenium dioxide (5.01 g, 45.17 mmol) was added before the mixture was heated to 70 °C for 3 h. After cooling to rt, the solution was filtered over celite and the solvent was removed in vacuo. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 60:40) afforded 7.26 g (84.2%) of a bright yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.11 (s, 3H), 7.36 - 7.57 (m, 3H), 7.95 - 8.17 (m, 2H), 8.47 - 8.69 (m, 2H), 10.87 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.9, 112.0, 116.8 (d, $^{2}J_{CF}$ = 22.7 Hz), 117.7, 128.6 (d, $^{4}J_{CF}$ = 2.8 Hz), 133.3 (d, $^{3}J_{CF}$ = 10.5 Hz), 140.1, 149.7, 153.3, 166.4 (d,

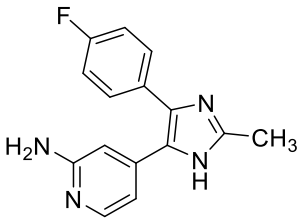
$^1J_{CF}$ = 256.6 Hz), 169.8, 191.4, 193.1. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{11}FN_2O_3$ $[M+H]^+$ 287.1, found 287.1. HPLC: t_R = 4.44 min.

_N_-(4-(5-(4-Fluorophenyl)-2-methyl-1_H_-imidazol-4-yl)pyridin-2-yl)acetamide (S16)



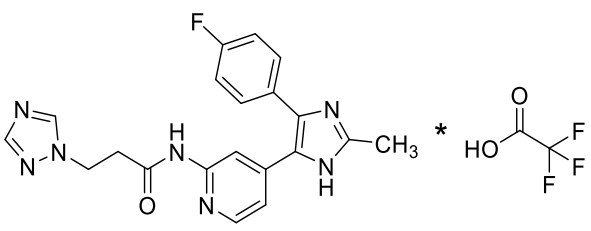
The title compound was synthesized according to **General Procedure A** starting from **S15** (7.26 g, 25.36 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:03 to 95:05) afforded 4.18 g (53.1%) of a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H), 2.34 (s, 3H), 6.97 - 7.20 (m, 2H), 7.27 (t, *J* = 8.7 Hz, 1H), 7.39 - 7.53 (m, 2H), 8.01 - 8.38 (m, 2H), 10.29 (s, 1H), 12.28 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [2:1 v/v]) δ 13.0, 23.6, 111.2, 115.3 (d, $^2J_{CF}$ = 21.6 Hz), 117.4, 129.9 (d, $^3J_{CF}$ = 8.3 Hz), 145.8, 147.2, 151.3, 162.2 (d, $^1J_{CF}$ = 245.5 Hz), 169.9. TLC-MS (ESI) *m*/*z*: calculated for $C_{17}H_{15}FN_4O$ $[M+H]^+$ 311.1, found 311.2. HPLC: t_R = 1.91 min.

4-(4-(4-Fluorophenyl)-2-methyl-1_H_-imidazol-5-yl)pyridin-2-amine (S17)



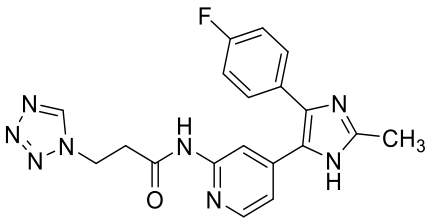
Compound **S16** (570 mg, 1.84 mmol) was dissolved in 10% aq. HCl (15 mL) and refluxed for 18 h. After cooling to rt, the solution is neutralized with 20% aq. NaOH and the forming precipitate is filtered off and dried in vacuo to give 233 mg (47.3%) of a beige-brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 5.72 (s, 1H), 5.92 (s, 1H), 6.37 - 6.70 (m, 2H), 7.14 (t, *J* = 8.9 Hz, 1H), 7.23 - 7.31 (m, 1H), 7.40 - 7.55 (m, 2H), 7.68 - 7.89 (m, 1H), 12.15 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD [2:1 v/v]) δ 12.6, 105.9, 111.4, 115.1 (d, $^2J_{CF}$ = 21.6 Hz), 129.8 (d, $^3J_{CF}$ = 7.7 Hz), 145.2, 146.2, 158.7, 162.1 (d, $^1J_{CF}$ = 247.1 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{13}FN_4$ $[M+H]^+$ 269.1, found 269.2. HPLC: t_R = 1.29 min HPLC: t_R = 4.39 min (method B).

_N_-(4-(5-(4-Fluorophenyl)-2-methyl-1_H_-imidazol-4-yl)pyridin-2-yl)-3-(1_H_-1,2,4-triazol-1-yl)propanamide TFA salt (4a)



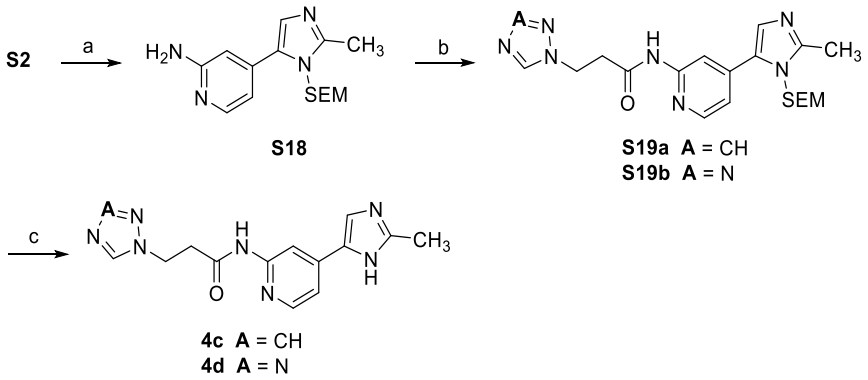
The title compound was synthesized according to **General Procedure G** (in 5 mL DMF) starting from compound **S17** (100 mg, 0.37 mmol) and 3-(1*H*-1,2,4-triazol-1-yl)propanoic acid (75 mg, 0.53 mmol). Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 90:10) and subsequent purification by RP-18 flash chromatography (MeCN:H_2O [8:2]/H_2O + 0.1% TFA) afforded 82 mg (56.3%) of the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 3H), 3.00 (t, J = 6.4 Hz, 2H), 4.45 (t, J = 6.3 Hz, 2H), 7.08 (dd, J = 5.2, 1.2 Hz, 1H), 7.29 - 7.42 (m, 2H), 7.49 - 7.61 (m, 2H), 8.20 (s, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.47 (br. s., 1H), 10.78 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 11.5, 35.7, 44.5, 111.1, 116.4 ($^2J_{CF}$ = 22.0 Hz), 117.3, 123.6 (d, $^4J_{CF}$ = 3.7 Hz), 125.3, 128.8, 131.0 (d, $^3J_{CF}$ = 8.8 Hz), 137.4, 144.2, 145.6, 148.8, 151.3, 152.5, 162.8 (d, $^1J_{CF}$ = 247.2 Hz), 169.5. ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.9 (4-F-Phe), -74.2 (CF_3). TLC-MS (ESI) m/z: calculated for $C_{20}H_{18}FN_7O$ $[M+H]^+$ 392.2, found 392.5. HPLC: t_R = 7.25 min (method B) (96.0% purity).

***N*-(4-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)pyridin-2-yl)-3-(1*H*-tetrazol-1-yl)propanamide (4b)**



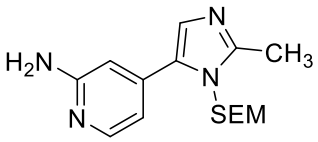
The title compound was synthesized according to **General Procedure G** starting from compound **S17** (100 mg, 0.37 mmol) and 3-(1*H*-tetrazol-1-yl)propanoic acid (75 mg, 0.53 mmol). Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 95:05 to 90:10) afforded 61 mg (42.3%) of an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.08 (t, J = 6.5 Hz, 2H), 4.72 (t, J = 6.5 Hz, 2H), 7.01 (dd, J = 5.2, 1.6 Hz, 1H), 7.23 (t, J = 8.8 Hz, 2H), 7.40 - 7.53 (m, 2H), 8.12 (d, J = 5.2 Hz, 1H), 8.25 (br. s., 1H), 9.34 (s, 1H), 10.53 (s, 1H), 12.33 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.7, 35.4, 43.6, 110.5, 115.6 (d, $^2J_{CF}$ = 21.6 Hz), 116.7, 130.2 (d, $^3J_{CF}$ = 7.2 Hz), 144.2, 145.0, 147.8, 152.1, 161.6 (d, $^1J_{CF}$ = 244.9 Hz), 168.5. TLC-MS (ESI) m/z: calculated for $C_{19}H_{17}FN_8O$ $[M+H]^+$ 393.2, found 393.6. HPLC: t_R = 7.25 min (method B) (100.0% purity).

Synthesis of 4c and 4d



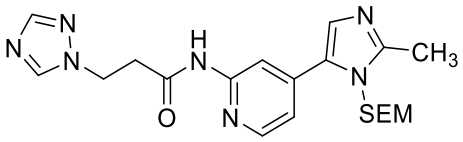
Scheme S7. *Reagents and conditions:* (a) 2-amino-4-bromopyridine, $Pd(PPh_3)_4$, 1,4-dioxane, 105 °C, 18 h, 41%; (b) carboxylic acid, HATU, DIPEA, rt, 18 h, 52-66%; (c) trifluoroacetic acid, DCM, rt, 8 h, 44-45%.

4-(2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-amine (S18)



Compound **S2** (1.00 g, 2.00 mmol), 2-amino-4-bromopyridine (282 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (170 mg, 0.15 mmol) were dissolved in degassed 1,4-dioxane (15 mL) under an atmosphere of argon. The reaction mixture was heated to 105 °C for 18 h before the solution was filtered through a pad of celite. The pad was washed with DCM (30 mL) and the solvents were removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 95:5) afforded 592 mg (41.3%) of an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.04 (s, 9H), 0.80 - 0.91 (m, 2H), 2.48 (s, 3H), 3.41 - 3.52 (m, 2H), 5.19 (s, 2H), 6.66 (s, 1H), 6.72 (dd, *J* = 5.5, 1.2 Hz, 1H), 7.05 (s, 1H), 8.00 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 13.6, 17.7, 66.0, 72.6, 107.0, 112.8, 127.8, 131.6, 139.6, 147.2, 148.2, 158.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{14}N_4OSi$ $[M+H]^+$ 305.2, found 305.3. HPLC: t_R = 2.56 min.

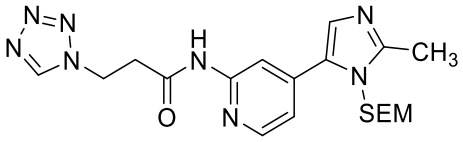
***N*-(4-(2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)pyridin-2-yl)-3-(1*H*-1,2,4-triazol-1-yl)propanamide (S19a)**



The title compound was synthesized according to **General Procedure G** starting from compound **S18** (100 mg, 0.33 mmol) and 3-(1*H*-1,2,4-triazol-1-yl)propanoic acid (67 mg, 0.47 mmol). Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 95:5) afforded 93 mg (66.3%) of a white solid.

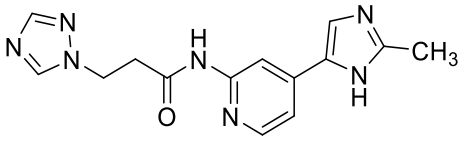
^{1}H NMR (300 MHz, $CDCl_3$) δ -0.03 (s, 9H), 0.88 - 0.98 (m, 2H), 2.53 (s, 3H), 3.03 (t, *J* = 6.1 Hz, 2H), 3.48 - 3.56 (m, 2H), 4.58 (t, *J* = 6.1 Hz, 2H), 5.26 (s, 2H), 7.17 - 7.21 (m, 2H), 7.92 (s, 1H), 8.18 (s, 1H), 8.21 - 8.30 (m, 2H), 9.39 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 13.6, 17.7, 36.5, 44.7, 66.0, 72.7, 112.4, 118.6, 128.5, 131.2, 140.1, 143.9, 148.1, 148.8, 151.7, 152.0, 168.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{20}H_{29}N_7O_2Si$ $[M+Na]^+$ 450.2, found 450.5. HPLC: t_R = 3.76 min.

_N_-(4-(2-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1_H_-imidazol-5-yl)pyridin-2-yl)-3-(1_H_-tetrazol-1-yl)propanamide (S19b)



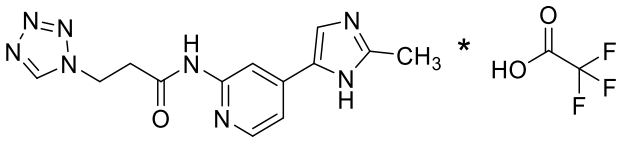
The title compound was synthesized according to **General Procedure G** starting from compound **S18** (150 mg, 0.49 mmol) and 3-(1*H*-tetrazol-1-yl)propanoic acid (100 mg, 0.70 mmol). Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 95:5) afforded 110 mg (52.4%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 9H), 0.89 - 0.99 (m, 2H), 2.56 (s, 3H), 3.15 (t, *J* = 5.8 Hz, 2H), 3.51 - 3.59 (m, 2H), 4.85 (t, *J* = 6.0 Hz, 2H), 5.28 (s, 2H), 7.20 (s, 1H), 7.23 (dd, *J* = 5.2, 1.6 Hz, 1H), 8.21 (br. s., 1H), 8.28 (dd, *J* = 5.2, 0.6 Hz, 1H), 8.86 (s, 1H), 8.90 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 13.5, 17.8, 36.2, 43.5, 66.2, 72.9, 112.4, 118.8, 127.9, 131.4, 139.9, 143.7, 148.3, 148.7, 151.4, 167.7. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{28}N_8O_2Si$ $[M+Na]^+$ 451.2, found 451.6. HPLC: t_R = 3.49 min.

_N_-(4-(2-Methyl-1_H_-imidazol-5-yl)pyridin-2-yl)-3-(1_H_-1,2,4-triazol-1-yl)propanamide (4c)



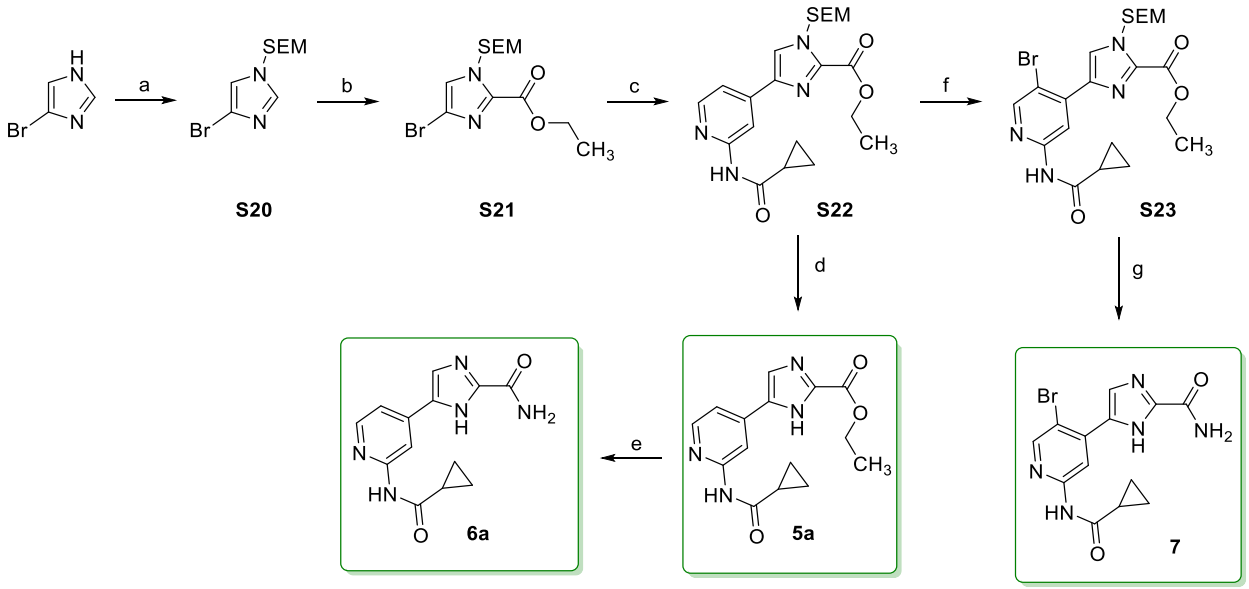
Compound **S19a** (93 mg, 0.22 mmol) was dissolved in a 1:5 mixture of trifluoroacetic acid in DCM and stirred at rt for 8 h. The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 95:5) to yield 29 mg (44.9%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.06 (t, *J* = 6.4 Hz, 2H), 4.51 (t, *J* = 6.5 Hz, 2H), 7.47 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.01 (s, 1H), 8.20 (s, 1H), 8.36 (s, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.57 (s, 1H), 10.81 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.8, 35.8, 44.6, 108.0, 114.7, 116.3, 136.6, 143.7, 144.3, 145.4, 147.8, 151.4, 152.3, 169.0. TLC-MS (ESI) *m*/*z*: calculated for $C_{14}H_{15}N_7O$ $[M+H]^+$ 298.1, found 298.2. HPLC: t_R = 1.09 min t_R = 4.14 min (method B) (95.1% purity).

_N_-(4-(2-Methyl-1_H_-imidazol-5-yl)pyridin-2-yl)-3-(1_H_-tetrazol-1-yl)propanamide TFA salt (4d)



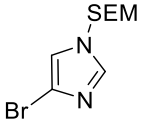
Compound **S19b** (93 mg, 0.22 mmol) was dissolved in a 1:5 mixture of trifluoroacetic acid in DCM and stirred at rt for 8 h. As the product was highly soluble in water, the solvents were evaporated and the crude product was directly purified by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 90:10). Subsequent purification by RP-18 flash chromatography (MeCN:H_2O [8:2]/H_2O + 0.1% TFA) afforded 40 mg (44.1%) of the TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.33 (s, 3H), 3.11 (t, J = 6.4 Hz, 2H), 4.64 - 4.80 (m, 2H), 7.36 (dd, J = 5.2, 1.4 Hz, 1H), 7.65 (s, 1H), 8.18 (d, J = 5.3 Hz, 1H), 8.35 (br. s., 1H), 9.40 (s, 1H), 10.51 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.7, 35.4, 43.6, 108.0, 114.8, 116.5, 136.2, 143.4, 144.3, 145.4, 147.9, 152.2, 168.6. ^{19}F NMR (282 MHz, DMSO-d_6) δ -73.4. TLC-MS (ESI) m/z: calculated for $C_{13}H_{14}N_8O$ $[M+Na]^+$ 321.1, found 321.2. HPLC: t_R = 3.77 min (method B) (97.5% purity).

Synthesis of 5a,6a and 7



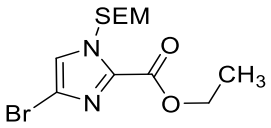
Scheme S8. *Reagents and conditions:* (a) NaH, SEM-Cl, THF, 0 °C then rt, 18 h, 91%; (b) 2.0 M LDA solution in THF/heptane/ethylbenzene, ethyl chloroformate, THF, -78 °C, 2 h, 52%; (c) **S11**, KF, XPhos, $Pd(OAc)_2$, 1,4-dioxane/H_2O, 110 °C, 18 h, 65% *or* K_2CO_3, $Pd(dppf)Cl_2$·DCM, DMF, 85 °C, 18 h, 82%; (d) trifluoroacetic acid, DCM, rt, 6 h, 94%; (e) 7 M ammonia in MeOH, 45 °C, 18 h, 66-74%.(f) NBS, MeCN, -20 °C to rt, 3 h, 70%; (g) 7 M ammonia in MeOH, 45 °C, 48 h *followed by* trifluoroacetic acid, DCM/EtOH, 45 °C, 48 h, 62% (*over 2 steps*)

4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (S20)



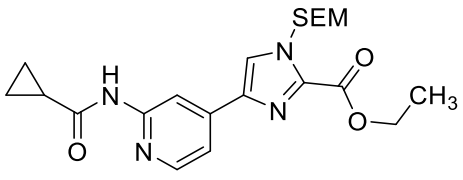
4-Bromo-1*H*-imidazole (5.00 g, 34.02 mmol) was dissolved in THF (50 mL) under an atmosphere of argon while being cooled to 0 °C. NaH 60% dispersion in mineral oil (1.77 g, 44.22 mmol) was added portionwise over 10 min and the resulting suspension was stirred for 20 more min. Then 2-(trimethylsilyl)ethoxymethyl chloride (6.37 mL, 36 mmol) was slowly added and the resulting mixture was stirred at rt for 18 h. H_2O (150 mL) was added, the organic layer was separated and the aqueous layer was further extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10) afforded 8.61 g (91.3%) of a light orange oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ -0.04 (s, 9H), 0.80 - 0.87 (m, 2H), 3.43 - 3.51 (m, 2H), 5.30 (s, 2H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ -1.4, 17.1, 65.5, 75.3, 114.3, 118.8, 138.1. TLC-MS (ESI) *m*/*z*: calculated for $C_9H_{17}BrN_2OSi$ [M+Na]$^+$ 299.0/301.0, found 299.1/301.1. HPLC: t_R = 7.93 min (*218 nm*).

Ethyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S21)



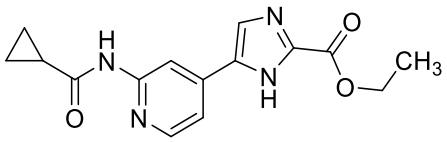
Compound **S20** (3.25 g, 11.72 mmol) was dissolved in THF (40 mL) under an atmosphere of argon and the solution was cooled to -78 °C. Lithium diisopropylamide 2.0M solution in THF/heptane/ethylbenzene (6.00 mL, 12.0 mmol) was added dropwise over 30 min. The red solution was stirred further for 30 min at -78 °C. In the meantime, a second flask was evacuated and backfilled with argon (3x). Ethyl chloroformate (3.36 mL, 35.17 mmol) and THF (5 mL) were added and then also cooled to -78 °C. Then the imidazole solution was added dropwise to the ethyl chloroformate solution and after complete addition the solution was further stirred at -78 °C for 30 min before it was quenched by the addition of H_2O (150 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10) afforded 2.14 g (52.3%) of an orange wax. ^{1}H NMR (300 MHz, DMSO-d_6) δ -0.07 (s, 9H), 0.79 - 0.87 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 3.48 - 3.57 (m, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 5.66 (s, 2H), 7.84 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ -1.5, 14.0, 17.1, 61.3, 66.1, 76.3, 114.6, 125.5, 135.6, 157.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{21}BrN_2O_3Si$ [M+Na]$^+$ 371.0/373.0, found 371.0/372.9. HPLC: t_R = 9.93 min.

Ethyl 4-(2-(cyclopropanecarboxamido)pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S22)



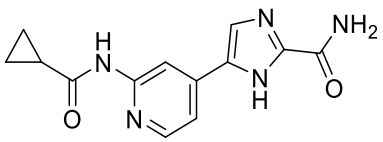
Compound **S21** (100 mg, 0.29 mmol), **S11** (148 mg, 0.52 mmol), K_2CO_3 (119 mg, 0.86 mmol) and Pd(dppf)Cl_2·DCM was dissolved in degassed DMF (3 mL) under an atmosphere of argon. The reaction mixture was heated to 85 °C for 18 h. After cooling to rt, sat. aq. NH_4Cl solution (40 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 101 mg (82.0%) of a white solid. *Alternative prep.:* Compound **S21** (500 mg, 1.43 mmol), **S22** (825 mg, 2.86 mmol), KF (333 mg, 5.73 mmol), XPhos (68 mg, 0.143 mmol) and $Pd(OAc)_2$ (16 mg, 0.072 mmol) were dissolved in a mix of degassed 1,4-dioxane (8.6 mL) and degassed H_2O (4.1 mL) under an atmosphere of argon. The reaction mixture was heated to 110 °C for 18 h. After cooling to rt, H_2O (40 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 50:50 to 30:70) afforded 401 mg (65.1%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 9H), 0.84 - 0.91 (m, 2H), 0.91 - 0.98 (m, 2H), 1.08 - 1.16 (m, 2H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.56 - 1.66 (m, 1H), 3.53 - 3.63 (m, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 5.80 (s, 2H), 7.68 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.78 (s, 1H), 8.29 (dd, *J* = 5.3, 0.6 Hz, 1H), 8.52 (d, *J* = 0.6 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.4, 14.2, 15.8, 17.8, 62.0, 67.2, 77.1, 109.6, 116.1, 122.5, 136.9, 139.7, 142.8, 148.0, 152.0, 159.0, 172.7. TLC-MS (ESI) *m*/*z*: calculated for $C_{21}H_{30}N_4O_4Si$ $[M+Na]^+$ 453.2, found 453.5. HPLC: t_R = 9.55 min.

Ethyl 5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxylate (5a)



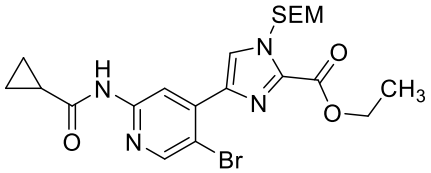
Compound **S22** (110 mg, 0.26 mmol) was treated according to **General Procedure E** and stirred at rt for 18 h. Sat. aq. $NaHCO_3$ solution was added until the aqueous phase was adjusted to pH 7. The organic phase was collected and the aqueous layer was extracted with DCM (2x). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 72 mg (93.9%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.74 - 0.90 (m, 4H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.93 - 2.09 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.49 (dd, *J* = 5.2, 1.4 Hz, 1H), 8.06 (s, 1H), 8.27 (d, *J* = 5.2 Hz, 1H), 8.54 (s, 1H), 10.74 (s, 1H), 13.65 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 14.2, 14.2, 61.0, 108.6, 115.1, 119.9, 137.9, 140.2, 142.7, 148.1, 152.8, 158.3, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{16}N_4O_3$ $[M+H]^+$ 301.1, found 301.3. HPLC: t_R = 2.20 min (100.0% purity).

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxamide (6a)



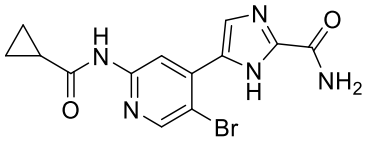
Compound **5a** (70 mg, 0.23 mmol) was dissolved in 7 M ammonia in MeOH (5 mL) and heated to 45 °C for 18 h. The solvent was removed under reduced pressure and purification by flash chromatography (SiO_2, DCM:EtOH 95:05 to 90:10) afforded 46 mg (73.5%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 - 0.95 (m, 4H), 2.02 (quin, *J* = 6.1 Hz, 1H), 7.58 (dd, *J* = 5.5, 1.3 Hz, 1H), 7.63 (br. s., 1H), 7.80 (br. s., 1H), 7.99 (s, 1H), 8.27 (d, *J* = 5.5 Hz, 1H), 8.37 (s, 1H), 11.10 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) d 8.1, 14.4, 108.8, 115.3, 120.6, 138.0, 142.4, 144.2, 146.2, 151.7, 159.9, 173.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{13}N_5O_2$ $[M+H]^+$ 271.2, found 272.2. HPLC: t_R = 1.39 min (95.3% purity).

Ethyl 4-(5-bromo-2-(cyclopropanecarboxamido)pyridin-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S23)



Compound **S22** (101 mg, 0.24 mmol) was dissolved in MeCN (2 mL) at -30 °C. *N*-Bromosuccinimide (44 mg, 0.25 mmol) was added in one portion and the solution was stirred at -30 °C. Reaction control after 10, 30 and 120 min showed no conversion so the solution was slowly brought to rt and stirred overnight. Reaction control now showed full conversion and the reaction was quenched with sat. aq. Na_2SO_3 solution and extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20 to 20:80) afforded 83 mg (69.5%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 9H), 0.84 - 0.92 (m, 2H), 0.92 - 0.99 (m, 2H), 1.11 (dd, *J* = 4.3, 3.0 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.54 - 1.65 (m, 1H), 3.57 - 3.66 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 5.83 (s, 2H), 8.06 (s, 1H), 8.38 (s, 1H), 8.70 (s, 1H), 8.78 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.4, 14.2, 15.7, 17.8, 61.9, 67.1, 77.1, 112.4, 114.6, 124.9, 136.3, 137.5, 142.7, 150.1, 150.7, 159.1, 172.1. TLC-MS (ESI) *m*/*z*: calculated for $C_{21}H_{29}BrN_4O_4Si$ $[M+Na]^+$ 531.1/533.1, found 531.0/533.0. HPLC: t_R = 11.24 min.

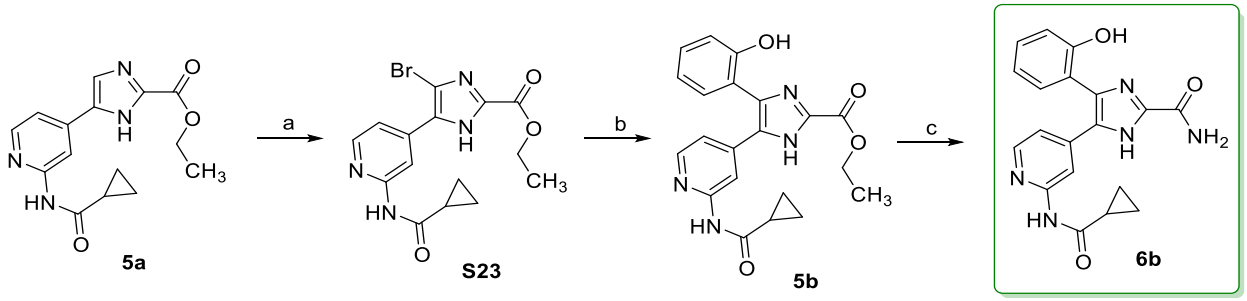
5-(5-Bromo-2-(cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxamide (7)



Compound **S23** (80 mg, 0.167 mmol) was suspended in 7 M ammonia in MeOH (3 mL) and stirred at 45 °C for 48 h. The solvent was removed under reduced pressure and the crude product was dissolved in a mix of DCM (4 mL), EtOH (2 mL) and trifluoroacetic acid (1 mL). The reaction was stirred at 45 °C for 48 h. Sat. aq. $NaHCO_3$ solution was added until the aqueous phase was adjusted to pH 7. The forming precipitate was collected by suction filtration and the aqueous phase was further extracted with EtOAc (2x) and DCM (2x). The organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The combined fractions were purified by flash chromatography (SiO_2,

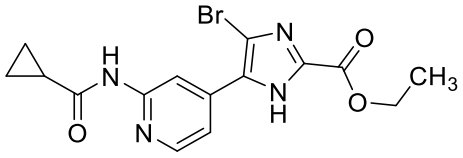
DCM:EtOH 97:3 to 90:10) to afford 36 mg (61.7%) of a yellow solid which was poorly soluble in most organic solvents (MeOH, THF, MeCN, EtOAc, DCM, *n*-hexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 - 0.89 (m, 4H), 1.95 - 2.07 (m, 1H), 7.66 (br. s., 1H), 7.73 (br. s., 1H), 8.02 (s, 1H), 8.48 (s, 1H), 8.71 (s, 1H), 10.88 (s, 1H), 13.48 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8, 14.2, 111.2, 113.4, 121.0, 136.7, 141.5, 142.6, 150.4, 151.4, 159.7, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{12}BrN_5O_2$ $[M+Na]^+$ 372.0/374.0, found 371.9/373.9. HPLC: t_R = 2.93 min (97.1% purity).

Synthesis of 6b



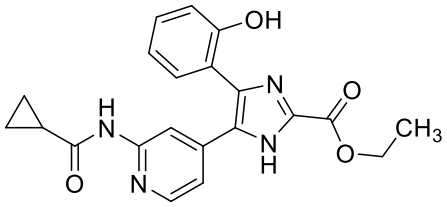
Scheme S9. *Reagents and conditions:* (a) NBS, MeCN, -20 °C, 1 h, 75%; (b) arylboronic acid, KF, $Pd(dppf)Cl_2$·DCM, 1,4-dioxane/H_2O, 85 °C, 18 h, 93%; (c) 7 M ammonia in MeOH, 45 °C, 18 h, 66-74%.

Ethyl 4-bromo-5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxylate (S23)



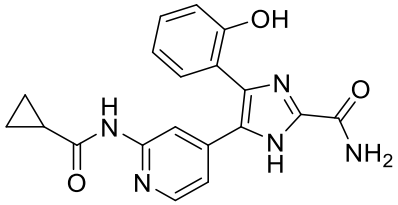
Compound **5a** (410 mg, 1.37 mmol) was dissolved in MeCN (2 mL) at -20 °C and *N*-bromosuccinimide (243 mg, 1.37 mmol) was added in one portion. The mixture was stirred at -20 °C for 1 h before it was quenched with. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 389 mg (75.1%) of a pale white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 - 0.88 (m, 4H), 1.27 - 1.37 (m, 3H), 1.97 - 2.09 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.43 - 7.56 (m, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 8.64 (s, 1H), 10.89 (s, 1H), 14.37 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.7, 14.1, 14.3, 61.4, 110.8, 116.8, 138.1, 148.3, 152.5, 157.6, 172.8. TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{15}BrN_4O_3$ $[M+Na]^+$ 401.0/403.0, found 401.0/402.9. HPLC: t_R = 4.49 min.

Ethyl 5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-4-(2-hydroxyphenyl)-1*H*-imidazole-2-carboxylate (5b)



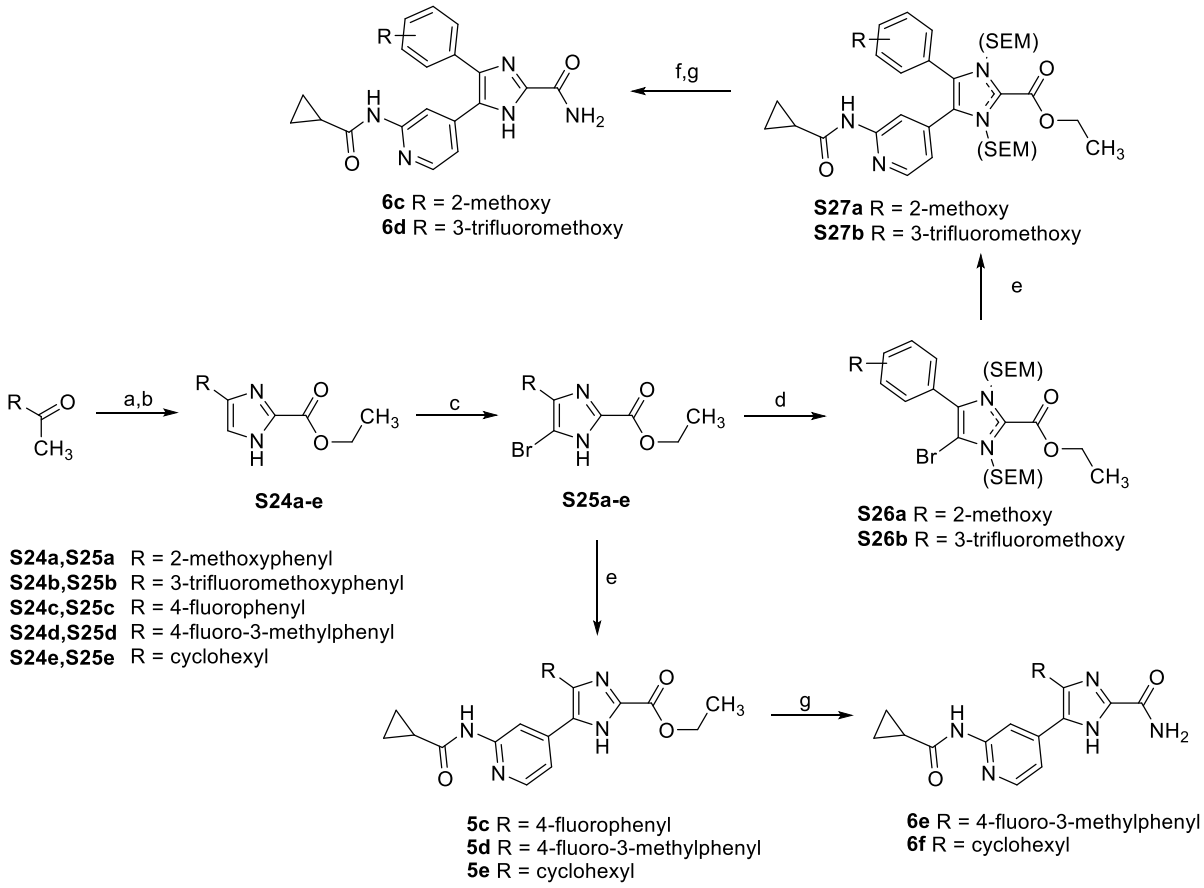
Compound **S23** (100 mg, 0.26 mmol), 2-hydroxyphenylboronic acid (73 mg, 0.53 mmol) and Pd(dppf)Cl_2·DCM were dissolved in degassed 1,4-dioxane (7 mL) under an atmosphere of argon and degassed 0.25 M aq. KF solution (3.25 mL) was added. The reaction was stirred at 90 °C for 18 h. Work-up was performed according to **General Procedure D**. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 96 mg (92.8%) of a solid. ^{1}H NMR (400 MHz, MeOD) δ 0.82 - 0.88 (m, 2H), 0.91 - 0.97 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.78 - 1.89 (m, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 4.3 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 4.3 Hz, 1H), 8.22 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{21}H_{20}N_4O_4$ $[M+H]^+$ 392.2, found 393.3. HPLC: t_R = 3.58 min.

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-(2-hydroxyphenyl)-1*H*-imidazole-2-carboxamide (6b)



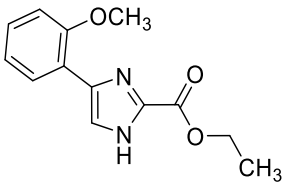
Compound **5b** (96 mg, 0.24 mmol) was dissolved in 7 M ammonia in MeOH (5 mL) and heated to 45 °C for 18 h. The solvent was removed under reduced pressure and the product was purified by flash chromatography (SiO_2, DCM:EtOH 95:5 to 90:10) to afford 59 mg (66.4%) of a beige-brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.69 - 0.84 (m, 4H), 1.83 - 2.12 (m, 1H), 6.81 - 6.91 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.55 (br. s., 1H), 7.71 (br. s., 1H), 8.06 (d, *J* = 4.9 Hz, 1H), 8.40 (s, 1H), 9.70 (s, 1H), 10.60 (br. s., 1H), 13.17 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.5, 14.2, 110.6, 115.9, 116.1, 117.2, 119.0, 129.6, 130.4, 131.5, 135.2, 140.7, 144.2, 147.2, 152.4, 155.5, 160.0, 172.2. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{17}N_5O_3$ $[M+H]^+$ 364.1, found 364.3. HPLC: t_R = 2.12 min (100.0% purity).

Synthesis of 5c and 6c-f



Scheme S10. *Reagents and conditions:* (a) 48% aq. HBr/DMSO, 55 °C, 18 h *or in case of* **S24e**: SeO_2, dioxane/H_2O (15:1), 110 °C; (b) ethyl glyoxylate (polymer form ~50% in toluene), NH_4OAc, MeOH/MeCN, rt, 1.5 h, 41-71%; (c) NBS, MeCN, 0 °C, 1 h, 53-74% *or in case of* **S25a**: Br_2, DCM/2M aq. Na_2CO_3, 0 °C to rt, 14 h, 63%; (d) SEM-Cl, K_2CO_3, DMF, 0 °C to rt, 3.5-6.5 h, 62-86%; (e) **S11**, K_2CO_3, Pd(dppf)Cl_2·DCM, DMF, 80 °C, 18 h, 71-84% *or in case of* **S26a**: **S11**, KF, Xphos, $Pd(OAc)_2$, 1,4-dioxane/H_2O (3:1), 110 °C, 18 h, 44%; (f) 7 M ammonia in MeOH, rt *or* 45 °C, 18-96 h, 59-78% (for **6c** & **6d**); (g) trifluoroacetic acid, DCM, rt, 48 h 45-70% (*over 2 steps* for **6d** and **6e**).

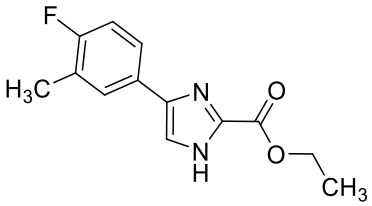
Ethyl 4-(2-methoxyphenyl)-1*H*-imidazole-2-carboxylate (S24a)



2'-Methoxyacetophenone (826 mg, 5.50 mmol) was treated according to **General Procedure C**. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 90:10) afforded 763 mg (56.3%) of a red oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.91 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.21 - 7.30 (m, 1H), 7.69 (br. s., 1H), 8.07 (br. s., 1H),

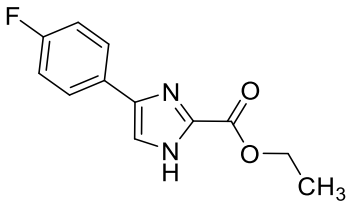
13.39 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{14}N_2O_3$ $[M+Na]^+$ 269.1, found 269.4. HPLC: t_R = 4.18 min.

Ethyl 4-(4-fluoro-3-methylphenyl)-1*H*-imidazole-2-carboxylate (S24b)



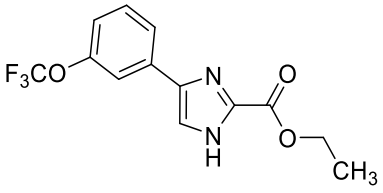
4'-Fluoro-3'-methylacetophenone (500 mg, 3.29 mmol) was treated according to **General Procedure C**. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 582 mg (71.4%) of a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.26 (d, *J* = 1.7 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 6.99 (t, *J* = 8.9 Hz, 1H), 7.45 (s, 1H), 7.48 - 7.56 (m, 1H), 7.61 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.4 (d, $^3J_{CF}$ = 3.3 Hz), 61.8, 115.2 (d, $^2J_{CF}$ = 22.7 Hz), 124.3 (d, $^3J_{CF}$ = 7.7 Hz), 125.1 (d, $^2J_{CF}$ = 17.7 Hz), 128.6 (d, $^3J_{CF}$ = 5.5 Hz), 137.8, 159.1, 160.9 (d, $^1J_{CF}$ = 246.0 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{13}FN_2O_2$ $[M+Na]^+$ 271.1, found 271.1. HPLC: t_R = 6.13 min.

Ethyl 4-(4-fluorophenyl)-1*H*-imidazole-2-carboxylate (S24c)



4'-Fluoroacetophenone (863 mg, 6.25 mmol) was treated according to **General Procedure C**. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 606 mg (41.4%) of a red oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 2H), 7.79 - 7.95 (m, 3H), 13.46 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 60.8, 115.4 (d, $^2J_{CF}$ = 22.1 Hz), 117.3, 126.6 (d, $^3J_{CF}$ = 7.7 Hz), 130.3 (d, $^4J_{CF}$ = 2.8 Hz), 137.2, 141.6, 158.4, 161.4 (d, $^1J_{CF}$ = 246.0 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{11}FN_2O_2$ $[M-H]^-$ 233.1, found 233.1. HPLC: t_R = 4.59 min.

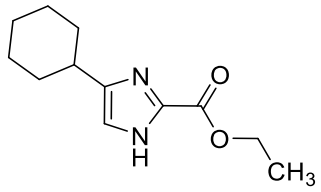
Ethyl 4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazole-2-carboxylate (S24d)



3'-(Trifluoromethoxy)acetophenone (866 mg, 3.67 mmol) was treated according to **General Procedure C**. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 70:30 to 50:50) afforded 580 mg 2(52.7%) of a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.13

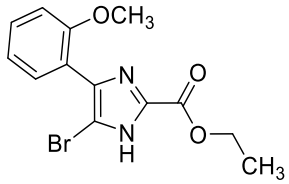
(d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.63 - 7.76 (m, 2H), 10.43 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{11}F_3N_2O_3$ $[M+H]^+$ 301.1, found 300.9. HPLC: t_R = 7.47 min.

Ethyl 4-cyclohexyl-1*H*-imidazole-2-carboxylate (S24e)



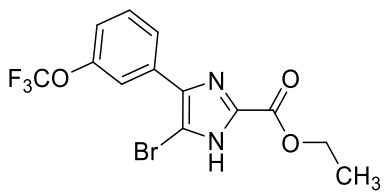
Cyclohexyl methyl ketone (500 mg, 3.96 mmol) was oxidized with selenium dioxide (484 mg, 4.36 mmol) according to a literature procedure[6] and then treated further according to **General Procedure C**. Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 385 mg (43.7%) of an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 - 1.48 (m, 8H), 1.65 - 1.85 (m, 3H), 1.98 - 2.09 (m, 2H), 2.59 - 2.72 (m, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 25.6, 25.8, 32.4, 35.7, 60.9, 121.2, 136.2, 145.0, 159.0. TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{18}N_2O_2$ $[M+H]^+$ 223.1, found 223.1. HPLC: t_R = 3.64 min.

Ethyl 5-bromo-4-(2-methoxyphenyl)-1*H*-imidazole-2-carboxylate (S25a)



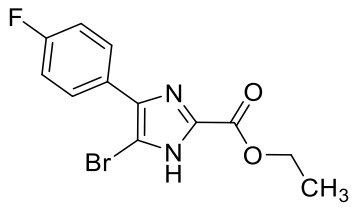
Compound **S24a** (400 mg, 1.62 mmol) was dissolved in DCM (5 mL) and 2M aq. Na_2CO_3 solution (5 mL). The mixture was cooled to 0 °C and bromine (100 µL, 1.95 mmol) was added dropwise. The reaction was further stirred at rt overnight before sat. aq. NaS_2O_3 solution was added and it was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 60:40) afforded 333 mg (63.1%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.2 Hz, 3H), 3.92 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.08 (td, *J* = 7.6, 1.0 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.6 Hz, 1H), 11.15 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 55.8, 62.0, 111.3, 115.6, 115.9, 121.0, 128.4, 129.2, 130.4, 135.5, 155.7, 158.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{13}BrN_2O_3$ $[M+Na]^+$ 247.0/249.0, found 347.2/349.2. HPLC: t_R = 5.89 min.

Ethyl 5-bromo-4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazole-2-carboxylate (S25b)



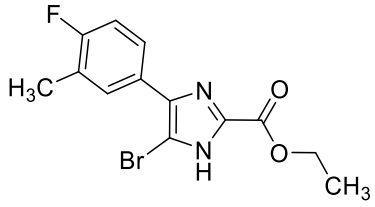
Compound **S24b** (580 mg, 1.93 mmol) was dissolved in MeCN, cooled to 0 °C and *N*-bromosuccinimide (344 mg, 1.93 mmol) was added in one portion. The mixture was stirred for 1 h at 0 °C before the reaction was quenched with sat. aq. Na_2SO_3 solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10) afforded 541 mg (73.9%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.22 - 7.28 (m, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 12.11 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 62.6, 119.9, 120.4 (d, $^1J_{OCF3}$ = 258.2 Hz), 121.0, 125.6, 130.2, 137.1, 149.4, 158.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{10}BrF_3N_2O_3$ $[M+Na]^+$ 401.0/403.0, found 400.8/402.7. HPLC: t_R = 9.61 min.

Ethyl 5-bromo-4-(4-fluorophenyl)-1*H*-imidazole-2-carboxylate (S25c)



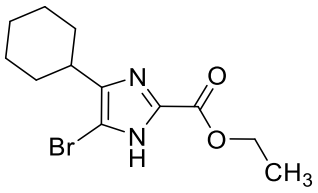
The title compound was prepared following the procedure as described for compound **S25b** starting from compound **S24c** (540 mg, 2.31 mmol) and *N*-bromosuccinimide (410 mg, 2.31 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20) afforded 430 mg (59.4%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 7.71 - 7.83 (m, 2H), 12.02 (br. s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 62.4, 115.8 (d, $^2J_{CF}$ = 21.6 Hz), 129.4 (d, $^3J_{CF}$ = 8.8 Hz), 136.6, 158.7, 162.8 (d, $^1J_{CF}$ = 246.0 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{10}BrFN_2O_2$ $[M+Na]^+$ 335.0/337.0, found 335.2/337.2. HPLC: t_R = 6.84 min.

Ethyl 5-bromo-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole-2-carboxylate (S25d)



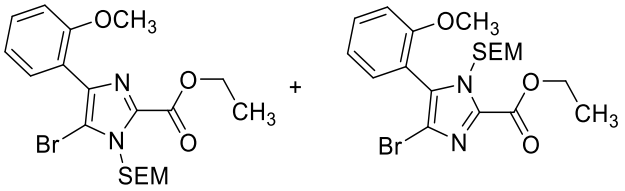
The title compound was prepared following the procedure as described for compound **S25b** starting from compound **S24d** (470 mg, 1.89 mmol) and *N*-bromosuccinimide (337 mg, 1.89 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20) afforded 384 mg (52.8%) of a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 7.06 (t, *J* = 8.8 Hz, 1H), 7.48 - 7.66 (m, 2H), 11.71 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.6 (d, $^3J_{CF}$ = 3.3 Hz), 62.3, 115.4 (d, $^2J_{CF}$ = 23.2 Hz), 125.5 (d, $^2J_{CF}$ = 17.7 Hz), 126.7 (d, $^3J_{CF}$ = 8.3 Hz), 130.7 (d, $^3J_{CF}$ = 5.5 Hz), 136.5, 158.6, 161.5 (d, $^1J_{CF}$ = 249.3 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{12}BrFN_2O_2$ $[M+Na]^+$ 349.0/351.0, found 349.2/351.2. HPLC: t_R = 8.14 min.

Ethyl 4-cyclohexyl-1*H*-imidazole-2-carboxylate (S25e)



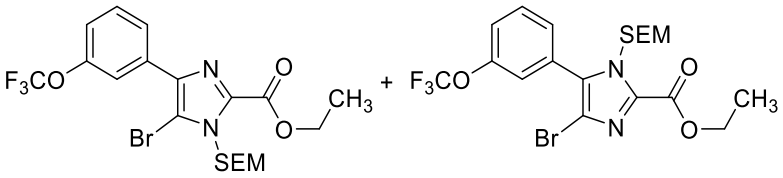
The title compound was prepared following the procedure as described for compound **S25b** starting from compound **S24e** (380 mg, 1.71 mmol) and *N*-bromosuccinimide (304 mg, 1.71 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20) afforded 299 mg (58.1%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 - 1.59 (m, 5H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.71 - 1.97 (m, 5H), 2.78 (tt, *J* = 11.8, 3.3 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 10.98 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 25.4, 26.0, 31.3, 34.9, 61.5, 114.0, 135.3, 138.2, 158.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{12}H_{17}BrN_2O_2$ $[M+Na]^+$ 323.0/325.0, found 323.2/325.2. HPLC: t_R = 8.31 min.

Ethyl 5(4)-bromo-4(5)-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S26a)



Compound **S25a** (326 mg, 1.00 mmol) was dissolved in DMF (3 mL) and cooled to 0 °C before K_2CO_3 (180 mg, 1.10 mmol) was added. After stirring for 30 min, SEM-Cl (195 µL, 1.30 mmol) was added and the reaction was further stirred at rt for 3 h. H_2O (35 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10 to 50:50) afforded 280 mg (61.5%) of a clear oil, containing both regioisomers. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{27}N_2O_4Si$ $[M+Na]^+$ 477.1/479.1, found 476.8/478.8.

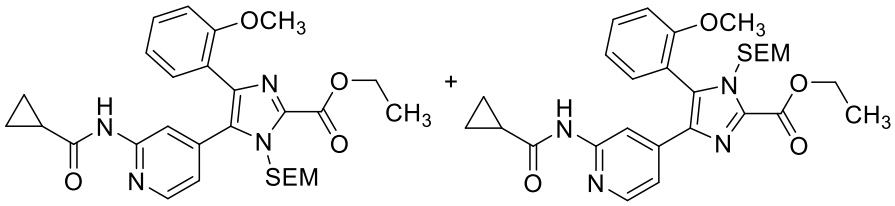
Ethyl 4(5)-bromo-5(4)-(3-(trifluoromethoxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S26b)



Compound **S25b** (490 mg, 1.30 mmol) was dissolved in DMF (3 mL) and cooled to 0 °C before K_2CO_3 (215 mg, 1.56 mmol) was added. After stirring for 30 min, SEM-Cl (259 µL, 1.57 mmol) was added and the reaction was further stirred at rt for 6 h. H_2O (35 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 95:05 to 85:05)

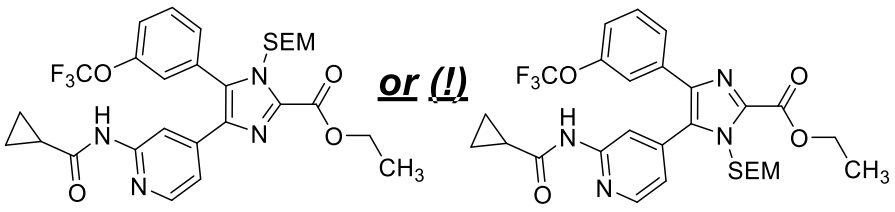
afforded 565 mg (85.6%) of a mix of regioisomers (ratio 4.3:1). *isomer 1:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.83 - 1.05 (m, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 3.66 (dd, *J* = 8.7, 7.7 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 5.96 (s, 2H), 7.21 (ddt, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.94 (dt, *J* = 7.8, 1.2 Hz, 1H). *isomer 2:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.86 - 0.94 (m, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 3.54 - 3.62 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 5.66 (s, 2H), 7.35 (dd, *J* = 6.7, 1.0 Hz, 1H), 7.47 - 7.56 (m, 3H). TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{24}BrF_3N_2O_4Si$ $[M+Na]^+$ 531.1/533.1, found 530.8/532.9. HPLC: t_R = 12.55 min & 14.27 min.

Ethyl 5(4)-(2-(cyclopropanecarboxamido)pyridin-4-yl)-4(5)-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S27a)



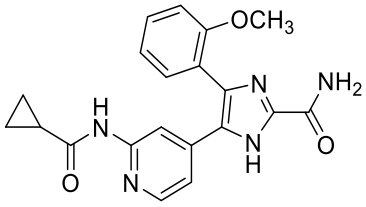
Compound **S26a** (265 mg, 0.70 mmol), **S11** (406 mg, 1.41 mmol), KF (164 mg, 2.82 mmol), XPhos (34 mg, 0.070 mmol) and $Pd(OAc)_2$ (8 mg, 0.035 mmol) were dissolved in a mix of degassed 1,4-dioxane (6 mL) and degassed H_2O (2 mL) under an atmosphere of argon. The reaction mixture was heated to 110 °C for 18 h. After cooling to rt, H_2O (40 mL) was added and it was extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 70:30 to 50:50) afforded 165 mg (43.7%) of a mix of regioisomers which could not be separated completely by column chromatograpy. *example NMR for one pure isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.11 (s, 9H), 0.68 - 0.80 (m, 4H), 0.95 - 1.03 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.49 - 1.57 (m, 1H), 3.26 - 3.37 (m, 2H), 3.70 (s, 3H), 4.46 (q, *J* = 7.1 Hz, 2H), 5.22 (d, *J* = 10.2 Hz, 1H), 5.88 (d, *J* = 10.3 Hz, 1H), 6.98 - 7.09 (m, 3H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 5.3 Hz, 1H), 8.29 (s, 1H), 9.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.6, 7.9, 14.2, 15.4, 17.7, 55.4, 61.6, 66.1, 73.8, 111.5, 111.8, 117.1, 117.2, 121.0, 131.6, 132.6, 132.7, 136.8, 136.9, 143.8, 146.8, 151.9, 157.7, 159.2, 171.8. TLC-MS (ESI) *m*/*z*: calculated for $C_{28}H_{36}N_4O_5Si$ $[M+H]^+$ 537.3, found 537.3.

Ethyl 4-(2-(cyclopropanecarboxamido)pyridin-4-yl)-5-(3-(trifluoromethoxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate or ethyl 5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-4-(3-(trifluoromethoxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S27b)



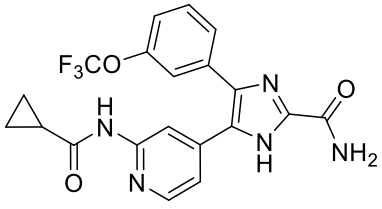
The title compound was synthesized according to **General Procedure F** starting from one (*not closer characterized*) pure regioisomer of **S26b** (250 mg, 0.49 mmol), **S11** (219 mg, 0.76 mmol), potassium carbonate (203 mg, 1.47 mmol) and Pd(dppf)Cl_2·DCM (40 mg, 0.049 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 70:30) afforded 213 mg (73.5%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.02 (s, 9H), 0.84 - 0.97 (m, 4H), 1.07 - 1.16 (m, 2H), 1.50 (t, *J* = 7.1 Hz, 3H), 1.58 - 1.68 (m, 1H), 3.47 - 3.59 (m, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 5.74 (s, 2H), 7.04 - 7.13 (m, 2H), 7.28 - 7.35 (m, 2H), 7.49 (dt, *J* = 7.9, 1.2 Hz, 1H), 8.34 - 8.41 (m, 2H), 8.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 8.5, 14.3, 15.7, 17.7, 62.1, 66.4, 73.7, 115.4, 120.3, 120.0, 120.2 (d, $^1J_{OCF3}$ = 257.1 Hz), 121.2, 126.1, 129.7, 131.7, 134.7, 137.3, 138.7, 139.6, 148.3, 149.1, 152.4, 159.1, 172.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{28}H_{33}F_3N_4O_5Si$ $[M+Na]^+$ 613.2, found 613.0.

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-(2-methoxyphenyl)-1*H*-imidazole-2-carboxamide (6c)



Compound **S27a** (160 mg, 0.30 mmol) was dissolved in 7 M ammonia in MeOH (5 mL) and stirred at 45 °C for 48 h. The solvent was removed under reduced pressure and the crude product was redissolved in DCM (3 mL) and trifluoroacetic acid (3 mL). The solution was stirred at rt for 48 h and work-up was performed according to **General Procedure E**. Purification by flash chromatography (SiO_2, DCM:EtOH 99:1 to 95:5) afforded 51 mg (45.3%) of a tan white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.70 - 0.88 (m, 4H), 1.97 (quin, *J* = 6.2 Hz, 1H), 3.60 (s, 3H), 6.89 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.39 - 7.48 (m, 1H), 7.57 (br. s., 1H), 7.75 (br. s., 1H), 8.07 (d, *J* = 5.3 Hz, 1H), 8.29 (s, 1H), 10.66 (s, 1H), 13.27 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 14.2, 55.2, 110.5, 111.7, 116.1, 120.4, 130.6, 131.4, 141.0, 147.0, 152.2, 157.0, 160.0, 172.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{20}H_{19}N_5O_3$ $[M+Na]^+$ 400.1, found 400.0. HPLC: t_R = 2.08 min (98.5%).

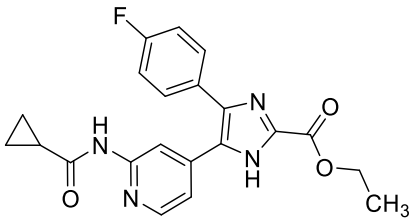
5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazole-2-carboxamide (6d)



Compound **S27b** (213 mg, 0.36 mmol) was dissolved in 7 M ammonia in MeOH (4 mL) and stirred at rt for 96 h. The solvent was removed under reduced pressure and the crude product was redissolved in DCM (3 mL) and trifluoroacetic acid (3 mL). The solution was stirred at rt for 48 h and work-up was performed according to **General Procedure E**. Purification by flash chromatography (SiO_2, DCM:EtOH

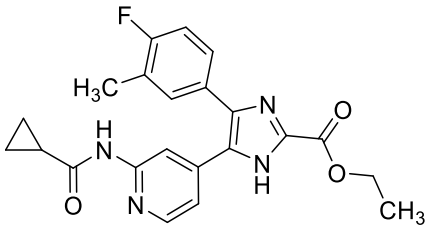
95:5) afforded 109 mg (70.1%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.70 - 0.85 (m, 4H), 1.91 - 2.06 (m, 1H), 6.97 - 7.43 (m, 3H), 7.52 (br. s., 2H), 7.64 (s, 1H), 7.89 (br. s., 1H), 8.12 - 8.37 (m, 2H), 10.57 - 10.96 (m, 1H), 13.71 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 14.1, 111.6, 117.5, 119.7, 120.0 (d, $^{1}J_{OCF3}$ = 256.5 Hz), 120.9, 127.8, 130.6, 141.9, 143.5, 147.8, 148.3, 152.6, 159.8, 172.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{20}H_{16}F_3N_5O_3$ $[M-H]^-$ 430.1, found 429.8. HPLC: t_R = 6.30 min (100.0%).

Ethyl 5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-4-(4-fluorophenyl)-1*H*-imidazole-2-carboxylate (5c)



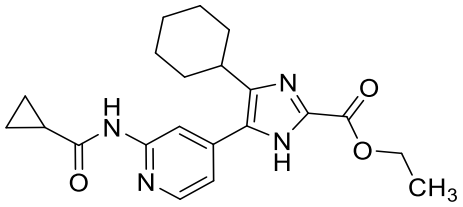
The title compound was synthesized according to **General Procedure F** starting from compound **S25c** (200 mg, 0.64 mmol), **S11** (239 mg, 0.83 mmol), potassium carbonate (265 mg, 1.92 mmol) and Pd(dppf)Cl_2·DCM (31 mg, 0.038 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 198 mg (78.7%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 - 0.92 (m, 2H), 0.99 - 1.09 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.53 - 1.71 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 7.05 (t, *J* = 8.4 Hz, 3H), 7.36 - 7.54 (m, 2H), 7.91 (d, *J* = 5.1 Hz, 1H), 8.36 (s, 1H), 9.14 (br. s., 1H), 12.25 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 14.2, 15.6, 62.2, 112.2, 115.9, 118.0, 130.6, 137.8, 147.3, 151.9, 159.4, 163.0, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{21}H_{19}FN_4O_3$ $[M+Na]^+$ 417.1, found 417.4. HPLC: t_R = 4.85 min (97.6% purity).

Ethyl 5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole-2-carboxylate (5d)



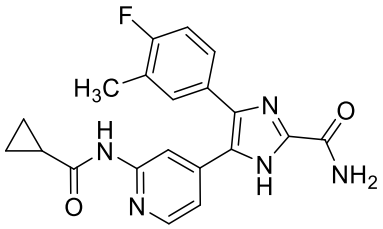
The title compound was synthesized according to **General Procedure F** starting from compound **S25d** (200 mg, 0.61 mmol), **S11** (229 mg, 0.79 mmol), potassium carbonate (265 mg, 1.83 mmol) and Pd(dppf)Cl_2·DCM (30 mg, 0.037 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 208 mg (83.5%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, *J* = 3.7 Hz, 2H), 1.03 (br. s., 2H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.63 (br. s., 1H), 2.21 (s, 3H), 4.42 (q, *J* = 6.9 Hz, 2H), 6.95 (t, *J* = 8.6 Hz, 1H), 7.03 - 7.24 (m, 2H), 7.33 (br. s., 1H), 7.91 (d, *J* = 3.3 Hz, 1H), 8.38 (s, 1H), 9.23 (br. s., 1H), 12.39 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{22}H_{21}FN_4O_3$ $[M+Na]^+$ 431.2, found 431.4. HPLC: t_R = 6.49 min.

Ethyl 4-cyclohexyl-5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxylate (5e)



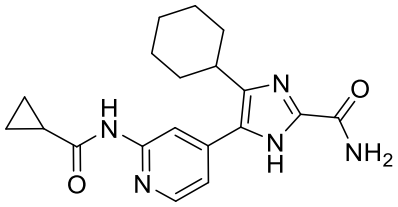
The title compound was synthesized according to **General Procedure F** starting from compound **S25e** (200 mg, 0.66 mmol), **S11** (287 mg, 1.00 mmol), potassium carbonate (277 mg, 2.00 mmol) and Pd(dppf)Cl_2·DCM (43 mg, 0.053 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:05) afforded 179 mg (70.5%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 - 0.89 (m, 2H), 1.03 - 1.12 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.41 - 1.58 (m, 3H), 1.60 - 1.66 (m, 1H), 1.69 - 2.05 (m, 5H), 2.60 (br. s., 2H), 3.09 (br. s., 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.44 (dd, *J* = 5.1, 1.7 Hz, 1H), 8.24 (d, *J* = 5.2 Hz, 1H), 8.43 (s, 1H), 9.27 (br. s., 1H), 11.15 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{21}H_{26}N_4O_3$ $[M+Na]^+$ 405.2, found 405.6. HPLC: t_R = 6.93 min.

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole-2-carboxamide (6e)



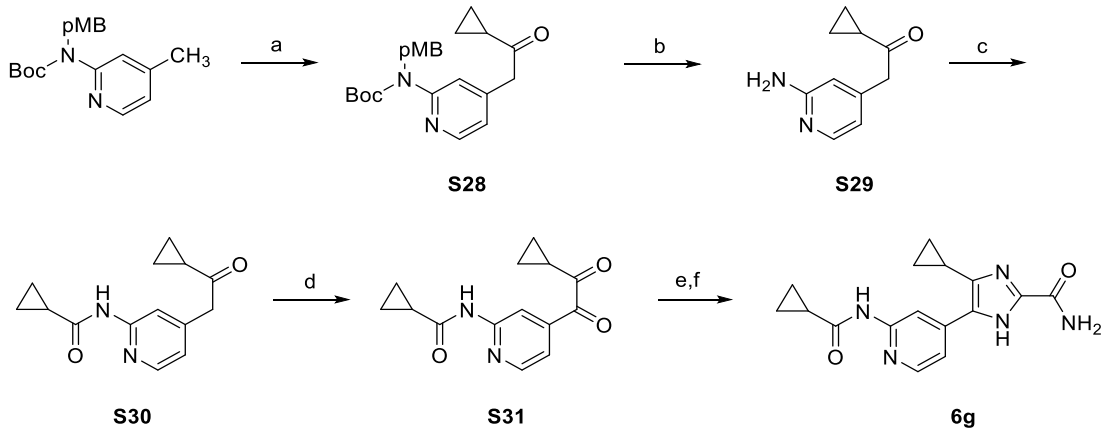
Compound **5d** (190 mg, 0.47 mmol) was dissolved in 7 M ammonia in MeOH (4 mL) and stirred at rt for 18 h. The solvent was removed under reduced pressure and purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 104 mg (58.9%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.66 - 0.87 (m, 4H), 1.88 - 2.08 (m, 1H), 2.22 (s, 3H), 7.05 (d, *J* = 5.0 Hz, 1H), 7.12 - 7.31 (m, 2H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.79 (br. s., 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 10.68 (s, 1H), 13.45 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 14.1 (d, $^3J_{CF}$ = 3.3 Hz), 14.2, 111.2, 115.2 (d, $^2J_{CF}$ = 22.1 Hz), 117.2, 124.6, 125.6, 128.5, 131.4, 132.3, 134.7, 141.2, 143.8, 147.6, 152.5, 159.9, 160.7 (d, $^1J_{CF}$ = 246.2 Hz), 172.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{20}H_{18}FN_5O_2$ $[M+Na]^+$ 402.1, found 402.3. HPLC: t_R = 4.85 min (99.0%).

4-Cyclohexyl-5-(2-(cyclopropanecarboxamido)pyridin-4-yl)-1*H*-imidazole-2-carboxamide (6f)



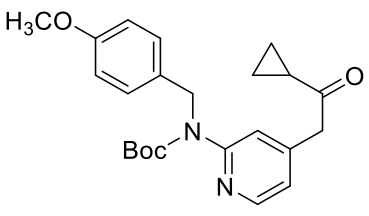
Compound **5e** (170 mg, 0.44 mmol) was dissolved in 7 M ammonia in MeOH (4 mL) and stirred at rt for 18 h. The solvent was removed under reduced pressure and purification by flash chromatography (SiO_2, DCM:EtOH 95:5 to 90:10) afforded 123 mg (78.3%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 - 0.86 (m, 4H), 1.14 - 1.43 (m, 3H), 1.62 - 1.86 (m, 7H), 1.97 - 2.07 (m, 1H), 2.90 - 3.03 (m, 1H), 7.30 (dd, J = 5.2, 1.5 Hz, 1H), 7.47 (br. s., 1H), 7.68 (br. s., 1H), 8.29 (d, J = 5.2 Hz, 1H), 8.33 (s, 1H), 10.74 (s, 1H), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 14.3, 25.2, 26.1, 31.5, 34.8, 111.0, 117.2, 133.6, 138.5, 140.3, 144.0, 147.9, 152.4, 160.1, 172.6. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{23}N_5O_2$ $[M+H]^+$ 354.2, found 354.5. HPLC: t_R = 5.19 min (99.5% purity).

Synthesis of 6g



Scheme S11. *Reagents and conditions:* (a) 2.0M NaHMDS in THF, ethyl cyclopropanecarboxylate, THF, 0 °C then rt, 2 h, 68%; (b) trifluoroacetic acid, DCM, 55 °C, 48 h, 78%; (c) cyclopropanecarbonyl chloride, pyridine, DCM, 0 °C then rt, 18 h, 85%; (d) SeO_2, acetic acid, 70 °C, 3 h, 38%; (e) ethyl glyoxylate (polymer form ~50% in toluene), NH_4OAc, THF/MeOH, rt, 18 h, 38%; (f) 7 M ammonia in MeOH, 45 °C, 72 h, 65%.

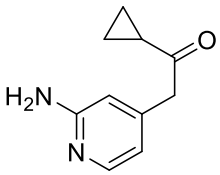
tert-Butyl (4-(2-cyclopropyl-2-oxoethyl)pyridin-2-yl)(4-methoxybenzyl)carbamate (S28)



tert-Butyl (4-methoxybenzyl)(4-methylpyridin-2-yl)carbamate (1500 mg, 4.66 mmol) was dissolved in THF (60 mL) under an atmosphere of argon. The solution was cooled to 0 °C before 2M sodium bis(trimethylsilyl)amide in THF (4.75 mL, 9.50 mmol) was added via syringe over 10 min and the resulting mixture was stirred for 45 min while still being cooled to 0 °C. Then ethyl

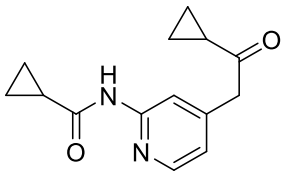
cyclopropanecarboxylate (783 mg, 6.88 mmol) dissolved in THF (5 mL) was added in one portion and the reaction was further stirred for 2 h at rt. H_2O (150 mL) was added, the organic layer was separated, and it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 75:25) afforded 1.23 g (67.8%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 - 0.94 (m, 2H), 1.01 - 1.11 (m, 2H), 1.42 (s, 9H), 1.89 - 2.00 (m, 1H), 3.77 (s, 3H), 3.82 (s, 2H), 5.12 (s, 2H), 6.75 - 6.83 (m, 2H), 6.88 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.18 - 7.25 (m, 2H), 7.57 (s, 1H), 8.33 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 20.4, 28.2, 49.4, 49.8, 55.2, 81.3, 113.5, 120.4, 120.6, 128.7, 131.5, 144.2, 147.5, 154.2, 154.8, 158.4, 206.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{28}N_2O_3$ $[M+Na]^+$ 419.2, found 419.3. HPLC: t_R = 8.28 min.

2-(2-Aminopyridin-4-yl)-1-cyclopropylethan-1-one (S29)



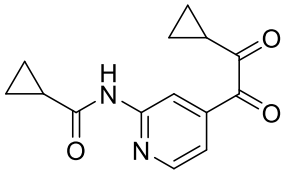
Compound **S28** (1.23 g, 3.16 mmol) was dissolved in DCM (2 mL) and trifluoroacetic acid (2 mL) and heated to 55 °C for 48 h. The solvent was evaporated and the product was redissolved in EtOAc and then washed with sat. aq. $NaHCO_3$ solution (2x). The organic layer was removed under reduced pressure to afford 435 mg (78.1%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 - 0.93 (m, 2H), 1.00 - 1.11 (m, 2H), 1.95 (tt, *J* = 7.8, 4.5 Hz, 1H), 3.70 (s, 2H), 4.34 (br. s., 2H), 6.37 (d, *J* = 0.6 Hz, 1H), 6.52 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.00 (dd, *J* = 5.3, 0.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 20.3, 49.8, 109.2, 115.3, 144.9, 148.2, 158.7, 206.9. TLC-MS (ESI) *m*/*z*: calculated for $C_{10}H_{12}N_2O$ $[M+H]^+$ 177.1, found 177.1. HPLC: t_R = 1.13 min.

***N*-(4-(2-Cyclopropyl-2-oxoethyl)pyridin-2-yl)cyclopropanecarboxamide (S30)**



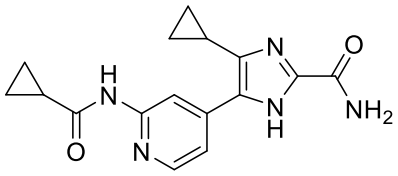
Compound **S29** (435 mg, 2.36 mmol) was dissolved in DCM (10 mL), cooled to 0 °C and pyridine (242 µL, 2.94 mmol) was added slowly. After 5 min, cyclopropanecarbonyl chloride (195 µL, 2.60 mmol) was added dropwise and the resulting solution was stirred at rt for 18 h. The solvents were removed under reduced pressure and purification by flash chromatography (SiO_2, DCM:EtOH 97:3) afforded 490 mg (85.0%) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 - 0.92 (m, 4H), 0.99 - 1.13 (m, 4H), 1.54 - 1.68 (m, 1H), 1.96 (tt, *J* = 7.8, 4.6 Hz, 1H), 3.83 (s, 2H), 6.88 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.15 (s, 1H), 8.19 (d, *J* = 5.1 Hz, 1H), 9.83 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 11.5, 15.4, 20.5, 49.8, 115.4, 120.6, 145.9, 147.2, 152.2, 172.7, 206.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{14}H_{16}N_2O_2$ $[M+Na]^+$ 267.1, found 267.1. HPLC: t_R = 1.67 min.

***N*-(4-(2-Cyclopropyl-2-oxoacetyl)pyridin-2-yl)cyclopropanecarboxamide (S31)**



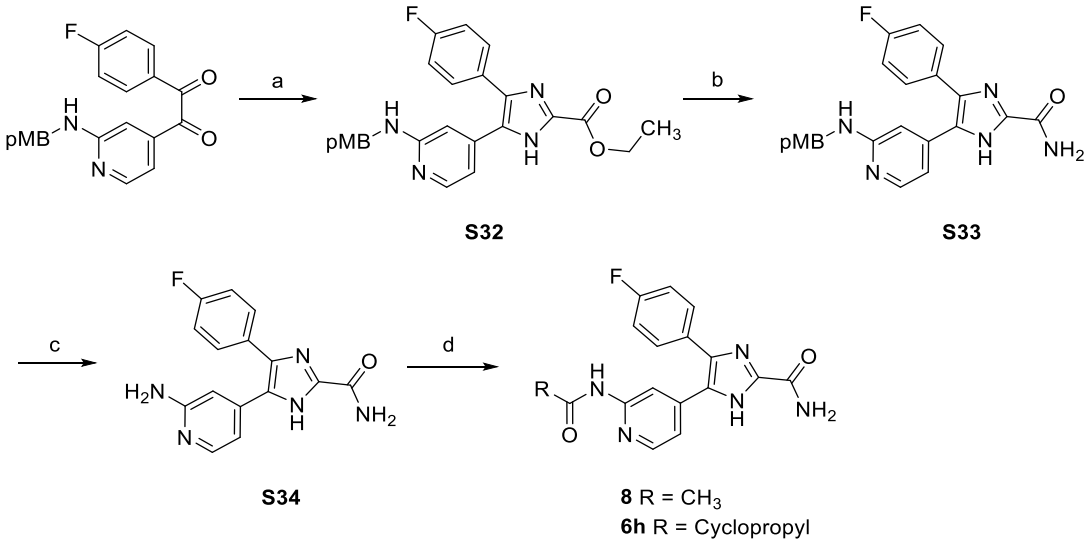
Compound **S30** (450 mg, 1.84 mmol) was dissolved in glacial acetic acid (10 mL) and selenium dioxide (232 mg, 2.09 mmol) was added. The mixture was heated to 70 °C for 3 h. After cooling to rt, the solution was filtered over celite, the solvent was removed in vacuo and redissolved in DCM. The organic phase was washed with sat. aq. $NaHCO_3$ solution (2x) and then removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 60:40) afforded 180 mg (37.8%) of a yellow-orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 - 0.99 (m, 4H), 1.07 - 1.18 (m, 4H), 1.61 - 1.70 (m, 1H), 2.64 (tt, *J* = 7.8, 4.6 Hz, 1H), 7.52 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.40 (dd, *J* = 5.2, 0.7 Hz, 1H), 8.73 (s, 1H), 9.27 (br. s., 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 13.9, 15.7, 18.0, 114.4, 118.3, 141.3, 148.1, 152.7, 172.8, 190.0, 200.1. TLC-MS (ESI) *m*/*z*: calculated for $C_{14}H_{14}N_2O_3$ $[M-H]^-$ 257.1, found 257.1. HPLC: t_R = 2.60 min.

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-cyclopropyl-1*H*-imidazole-2-carboxamide (6g)



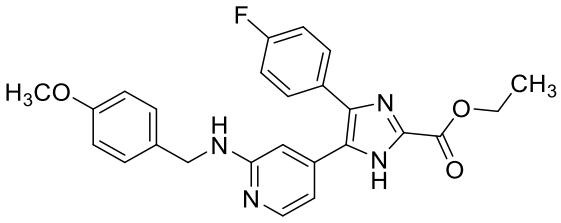
Compound **S31** (180 mg, 0.70 mmol) was dissolved in THF (5 mL) and ethyl glyoxylate (polymer form ~50% in toluene; 428 µL, 2.10 mmol) was added in one portion. A previously prepared solution of NH_4OAc (540 mg, 7.00 mmol) in MeOH (3 mL) was now added and the solution was stirred at rt for 18 h. The solvent was removed under reduced pressure and H_2O (40 mL) was added before it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was dissolved in 7 M ammonia in MeOH (4 mL) and the mixture was heated to 45 °C for 18 h. The solvent was removed under reduced pressure and purification by flash chromatography (SiO_2, DCM:EtOH 90:10) afforded 17 mg (7.8%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 - 0.84 (m, 4H), 0.87 - 0.92 (m, 2H), 0.98 - 1.06 (m, 2H), 1.99 - 2.07 (m, 2H), 7.48 (br. s., 1H), 7.55 (dd, *J* = 5.3, 1.5 Hz, 1H), 7.66 (br. s., 1H), 8.28 (dd, *J* = 5.3, 0.5 Hz, 1H), 8.64 (s, 1H), 10.71 (s, 1H), 12.84 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 7.1, 7.6, 7.8, 14.3, 110.2, 116.4, 135.2, 135.4, 139.4, 143.7, 147.7, 152.4, 160.0, 172.5. TLC-MS (ESI) *m*/*z*: calculated for $C_{16}H_{17}N_5O_2$ $[M+Na]^+$ 334.1, found 334.4. HPLC: t_R = 1.95 min (98.8% purity).

Synthesis of 8 and 6h



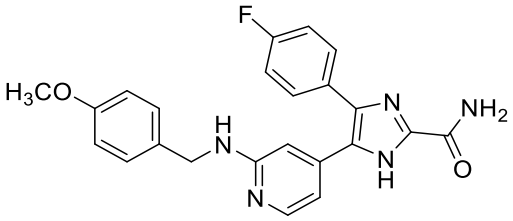
Scheme S12. *Reagents and conditions:* (a) ethyl glyoxylate (polymer form ~50% in toluene), NH_4OAc, MeOH, rt, 18 h, 38%; (b) 7 M ammonia in MeOH, 45 °C, 72 h, 65%; (c) trifluoroacetic acid, DCM, 55 °C, 6 h, 91%; (d) cyclopropanecarbonyl chloride *or* acetyl chloride, pyridine, 0 °C then rt, 18 h, 39-49%.

Ethyl 4-(4-fluorophenyl)-5-(2-((4-methoxybenzyl)amino)pyridin-4-yl)-1*H*-imidazole-2-carboxylate (S32)



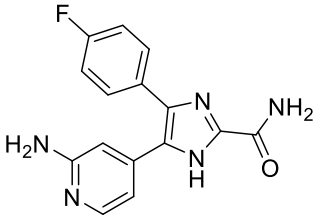
1-(4-Fluorophenyl)-2-(2-((4-methoxybenzyl)amino)pyridin-4-yl)ethane-1,2-dione[2] (500 mg, 1.37 mmol) was dissolved in THF (7 mL) and ethyl glyoxylate (polymer form ~50% in toluene; 841 µL, 4.12 mmol) was added in one portion. A previously prepared solution of NH_4OAc (1.06 g, 13.72 mmol) in MeOH (5 mL) was now added and the solution was stirred at rt for 18 h. The solvent was removed under reduced pressure and H_2O (40 mL) was added before it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 50:50 to 0:100) afforded 230 mg (37.6%) of a yellow resin. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H), 3.76 (s, 3H), 4.22 (s, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 5.81 (br. s, 1H), 6.57 (br. s., 1H), 6.65 (d, *J* = 5.4 Hz, 1H), 6.77 - 6.82 (m, 2H), 6.96 - 7.04 (m, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.41 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.80 (d, *J* = 5.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 45.6, 55.2, 62.1, 104.7, 111.5, 113.9, 115.7 (d, $^2J_{CF}$ = 21.6 Hz), 128.4, 130.4, 130.6 (d, $^3J_{CF}$ = 8.3 Hz), 137.5, 147.0, 158.6, 158.8, 159.2, 162.8 (d, $^1J_{CF}$ = 249.3 Hz). TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{23}FN_4O_3$ $[M+H]^+$ 447.2, found 447.0. HPLC: t_R = 6.38 min.

4-(4-Fluorophenyl)-5-(2-((4-methoxybenzyl)amino)pyridin-4-yl)-1*H*-imidazole-2-carboxamide (S33)



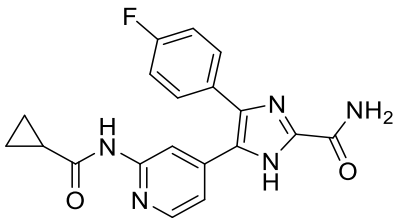
Compound **S32** (330 mg, 0.74 mmol) was dissolved in 7 M ammonia in MeOH (4 mL) and the mixture was heated to 45 °C for 72 h. The solvent was evaporated and H_2O (10 mL) was added before it was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure to yield 200 mg (64.8%) of a cream-colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (s, 3H), 4.28 - 4.39 (m, 2H), 6.48 - 6.66 (m, 2H), 6.86 (dd, *J* = 8.6, 3.5 Hz, 2H), 7.13 - 7.31 (m, 4H), 7.44 - 7.60 (m, 3H), 7.66 - 8.03 (m, 3H), 13.43 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{23}H_{20}FN_5O_2$ $[M+H]^+$ 418.2, found 418.1. HPLC: t_R = 4.60 min.

5-(2-Aminopyridin-4-yl)-4-(4-fluorophenyl)-1*H*-imidazole-2-carboxamide (S34)



Compound **S33** (190 mg, 0.46 mmol) was dissolved in DCM (3 mL) and trifluoroacetic acid (3 mL). The solution was heated to 55 °C for 6 h before the reaction was quenched with sat. aq. $NaHCO_3$ solution and it was extracted with DCM (3x). Purification by flash chromatography (SiO_2, DCM:EtOH 97:3 to 95:5) afforded 124 mg (90.5%) of an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.89 (br. s., 2H), 6.50 (dd, *J* = 5.3, 1.5 Hz, 1H), 6.57 (s, 1H), 7.25 (t, *J* = 8.7 Hz, 2H), 7.47 - 7.55 (m, 2H), 7.57 (br. s., 1H), 7.80 (br. s., 1H), 7.84 (d, *J* = 5.2 Hz, 1H), 12.28 (br. s., 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{15}H_{12}FN_5O$ $[M+H]^+$ 298.1, found 298.0. HPLC: t_R = 2.19 min.

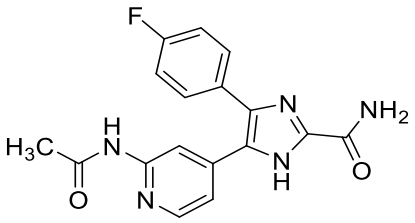
5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-(4-fluorophenyl)-1*H*-imidazole-2-carboxamide (6h)



Compound **S34** (35 mg, 0.12 mmol) was dissolved in pyridine (4 mL) and cooled to 0 °C. Cyclopropanecarbonyl chloride (11.75 µL, 0.13 mmol) was added and the mixture was stirred at rt for

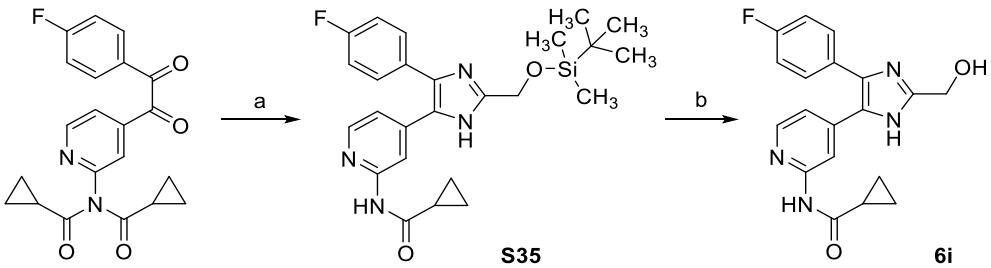
18 h. The solvent was removed in vacuo and purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 21 mg (48.8%) of a sand-colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 - 0.84 (m, 4H), 1.91 - 2.04 (m, 1H), 7.04 (dd, J = 5.2, 1.6 Hz, 1H), 7.24 (t, J = 8.9 Hz, 2H), 7.49 (dd, J = 8.9, 5.5 Hz, 2H), 7.60 (br. s, 1H), 7.84 (br. s., 1H), 8.20 (d, J = 5.2 Hz, 1H), 8.25 (s, 1H), 10.77 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.8, 14.3, 111.7, 115.6 (d, $^2J_{CF}$ = 21.6 Hz), 117.6, 130.9 (d, $^3J_{CF}$ = 8.3 Hz), 141.5, 147.6, 152.4, 160.0, 162.1 (d, $^1J_{CF}$ = 246.5 Hz), 172.6. TLC-MS (ESI) *m/z*: calculated for $C_{19}H_{16}FN_5O_2$ $[M+Na]^+$ 388.1, found 388.1. HPLC: t_R = 3.95 min (96.8% purity).

5-(2-Acetamidopyridin-4-yl)-4-(4-fluorophenyl)-1*H*-imidazole-2-carboxamide (8)



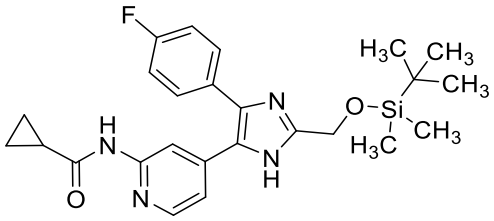
The title compound was prepared following the procedure as described for compound **6h** starting from compound **S34** (150 mg, 0.50 mmol) and acetyl chloride (47 µL, 0.66 mmol). Purification by flash chromatography (SiO_2, DCM:EtOH 95:5 to 90:10) afforded 64 mg (37.4%) of an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 3H), 7.10 (dd, J = 5.2, 1.6 Hz, 1H), 7.23 (t, J = 8.8 Hz, 2H), 7.50 (dd, J = 8.8, 5.5 Hz, 2H), 7.61 (s, 1H), 7.85 (s, 1H), 8.20 (d, J = 5.3 Hz, 1H), 8.23 (s, 1H), 10.42 (s, 1H), 13.51 (br. s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.9, 111.4, 115.6 (d, $^2J_{CF}$ = 22.1 Hz), 117.6, 130.8 (d, $^3J_{CF}$ = 8.3 Hz), 141.4, 147.8, 152.4, 159.9, 162.0 (d, $^1J_{CF}$ = 246.6 Hz), 169.1. TLC-MS (ESI) *m/z*: calculated for $C_{17}H_{14}FN_5O_2$ $[M+Na]^+$ 362.1, found 362.2. HPLC: t_R = 2.14 min (98.1% purity).

Synthesis of 6i



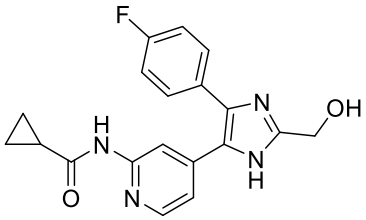
Scheme S13. *Reagents and conditions:* (a) (*tert*-butyldimethylsilyloxy)acetaldehyde, NH_4OAc, MeOH, 80 °C, 4 h, 20%; (b) Tetrabutylammonium fluoride in THF, rt, 5 h, 46%.

***N*-(4-(2-(((tert-Butyldimethylsilyl)oxy)methyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (S35)**



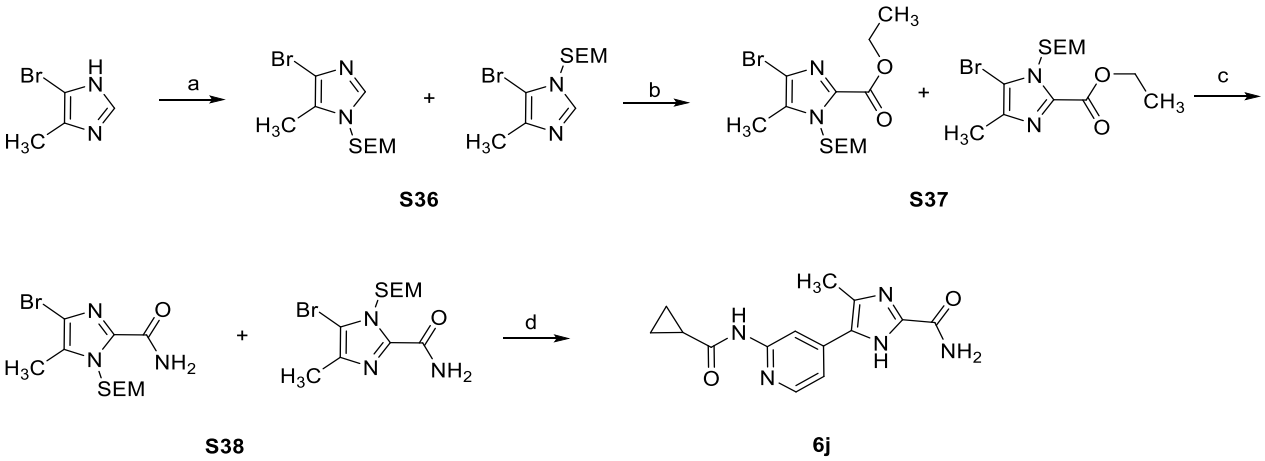
N-(Cyclopropanecarbonyl)-*N*-(4-(2-(4-fluorophenyl)-2-oxoacetyl)pyridin-2-yl)cyclo-propanecarbox-amide[2] (313 mg, 0.82 mmol), 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (251 µL, 1.32 mmol) and NH_4OAc (1.27 g, 16.46 mmol) were dissolved in MeOH (8 mL). The reaction mixture was heated to 80 °C for 4 h. Work-up was performed according to **General Procedure A**. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 80:20 to 0:100) afforded 78 mg (20.3%) of a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.81 - 0.88 (m, 2H), 0.94 (s, 9H), 1.01 - 1.10 (m, 2H), 1.50 - 1.65 (m, 1H), 4.86 (s, 2H), 6.96 - 7.11 (m, 3H), 7.39 - 7.49 (m, 2H), 8.07 (d, *J* = 5.4 Hz, 1H), 8.33 (br. s, 1H), 9.10 (s, 1H). TLC-MS (ESI) *m*/*z*: calculated for $C_{25}H_{31}FN_4O_2Si$ $[M+H]^+$ 467.2, found 467.7. HPLC: t_R = 9.95 min.

***N*-(4-(4-(4-Fluorophenyl)-2-(hydroxymethyl)-1*H*-imidazol-5-yl)pyridin-2-yl)cyclopropanecarboxamide (6i)**



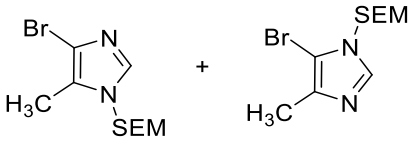
Compound **S35** (78 mg, 0.67 mmol) was dissolved in 1.0M TBAF in THF (5 mL) and stirred at rt for 5 h. Purification by flash chromatography (SiO_2, DCM:EtOH 95:5) afforded 27 mg (45.8%) of a yellow-orange solid. ^{1}H NMR (300 MHz, MeOD) δ 0.14 (s, 6H), 0.81 - 0.88 (m, 2H), 0.94 (s, 9H), 1.01 - 1.10 (m, 2H), 1.50 - 1.65 (m, 1H), 4.86 (s, 2H), 6.96 - 7.11 (m, 3H), 7.39 - 7.49 (m, 2H), 8.07 (d, *J* = 5.4 Hz, 1H), 8.33 (br. s, 1H), 9.10 (s, 1H). ^{13}C NMR (75 MHz, MeOD) δ 8.6, 15.7, 58.3, 113.6, 116.8 (d, $^2J_{CF}$ = 22.1 Hz), 119.1, 129.5 (d, $^4J_{CF}$ = 3.3 Hz), 131.8 (d, $^3J_{CF}$ = 8.3 Hz), 144.5, 149.1, 150.6, 153.6, 164.2 (d, $^1J_{CF}$ = 246.6 Hz), 175.3. TLC-MS (ESI) *m*/*z*: calculated for $C_{19}H_{17}FN_4O_2$ $[M+H]^+$ 353.1, found 353.4. HPLC: t_R = 2.78 min (95.9% purity).

Synthesis of 6j



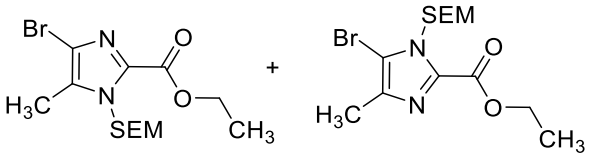
Scheme S14. *Reagents and conditions:* (a) NaH, SEM-Cl, THF, 0 °C then rt, 18 h, 98%; (b) 2.0 M Lithium diisopropylamide solution in THF/heptane/ethylbenzene, ethyl chloroformate, THF, -78 °C, 2 h, 32%; (c) 7 M ammonia in MeOH, rt, 18 h, 88%; (d) **S11**, Na_2CO_3, cataCXium® A, $Pd(OAc)_2$, DME/H2O, 90 °C, 18 h, 40%.

Ethyl 4(5)-bromo-5(4)-methyl-1*H*-imidazole-2-carboxylate (S36)



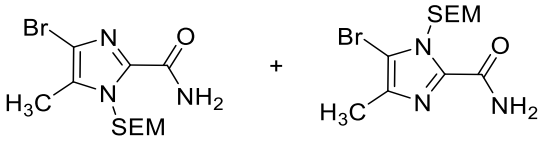
The title compound was prepared following the procedure as described for compound **S20** starting from 4-bromo-5-methyl-1*H*-imidazole (820 mg, 5.09 mmol), NaH 60% dispersion in mineral oil (305 mg, 7.64 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (991 µL, 5.60 mmol). Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10 to 60:40) afforded 1.46 g (98.3%) of a clear oil (mix of both regioisomers). ^{1}H NMR (300 MHz, DMSO-d_6) δ -0.03 (s, 18H, *2x (CH₃)₃ of SEM*), 0.74 - 0.91 (m, 4H, *2x CH₂ of SEM*), 2.06 (s, 3H, *CH₃[1]*), 2.15 (s, 3H, *CH₃[2]*), 3.39 - 3.51 (m, 4H, *2x CH₂ of SEM*), 5.24 (s, 2H, *CH₂ of SEM[1]*), 5.29 (s, 2H, *CH₂ of SEM[2]*), 7.75 (s, 1H, *Imid.-CH[1]*), 7.90 (s, 1H, *Imid.-CH[2]*). TLC-MS (ESI) *m/z*: calculated for $C_{10}H_{19}BrN_2OSi$ $[M+H]^+$ 291.0/293.0, found 291.0/293.1. HPLC: t_R = 7.57 min + 8.90 min.

Ethyl 4(5)-bromo-5(4)-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-2-carboxylate (S37)



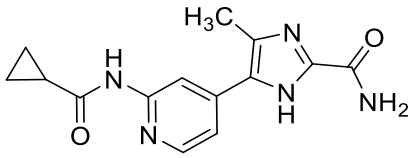
The title compound was prepared following the procedure as described for compound **S21** starting from **S36** (550 mg, 1.88 mmol), lithium diisopropylamide 2.0M solution in THF/heptane/ethylbenzene (944 µL, 1.88 mmol) and ethyl chloroformate (550 µL, 5.76 mmol). Work-up was performed according to the synthesis of **S21**. Purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 90:10 to 50:50) afforded 220 mg (32.1%) of a mix of regioisomers which could not be separated completely by column chromatograpy. *example NMR for one pure isomer:* ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 9H), 0.85 - 0.94 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 3.51 - 3.61 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 5.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.5, 9.6, 14.2, 17.7, 61.8, 66.3, 74.0, 116.3, 132.5, 135.3, 158.4. TLC-MS (ESI) *m*/*z*: calculated for $C_{13}H_{23}BrN_2O_3Si$ $[M+Na]^+$ 385.1/387.1, found 385.2/387.2. HPLC: t_R = 10.14 min & 10.37 min.

4(5)-Bromo-5(4)-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carboxamide (S38)



A mixture of regioisomers **S37** (220 mg, 0.61 mmol) was dissolved in 7 M ammonia in MeOH (5 mL) and stirred at rt for 18 h. The solvent was evaporated and purification by flash chromatography (SiO_2, *n*-hexane:EtOAc 50:50 to 0:100) afforded 178 mg (87.9%) of a mix of regioisomers which could not be separated by column chromatography. TLC-MS (ESI) *m*/*z*: calculated for $C_{11}H_{20}BrN_3O_2Si$ $[M+H]^+$ 334.1/336.1, found 334.4/336.4. HPLC: t_R = 9.14 min.

5-(2-(Cyclopropanecarboxamido)pyridin-4-yl)-4-methyl-1*H*-imidazole-2-carboxamide (6j)



Compound **S38** (60 mg, 0.18 mmol), **S11** (78 mg, 0.27 mmol), Na_2CO_3 (57 mg, 0.54 mmol), cataCXium® A (13 mg, 0.036 mmol) and $Pd(OAc)_2$ (6 mg, 0.027 mmol) were dissolved in a degassed 3:1 mixture of DME/H_2O (4 mL) under an atmosphere of argon. The mixture was heated to 90 °C under an atmosphere of argon for 18 h. The reaction mixture was allowed to cool to rt and more H_2O was added. It was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was dissolved in DCM (4 mL) and trifluoroacetic acid (4 mL). After stirring for 24 h, the solution was neutralized with sat. aq. $NaHCO_3$ to pH 7. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2, DCM/2M ammonia in MeOH 99:1 to 95:5) afforded 20 mg (40.0%) of a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 - 0.89 (m, 4H), 1.96 - 2.08 (m, 1H), 2.46 (s, 3H), 7.43 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.49 (br. s., 1H), 7.67 (br. s., 1H), 8.27 (d, *J* = 5.2 Hz, 1H), 8.44 (s, 1H), 10.73 (s, 1H), 13.11 (br. s., 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 11.4,

14.2, 109.6, 116.0, 129.4, 134.1, 139.5, 143.8, 147.8, 152.5, 160.0, 172.6 TLC-MS (ESI) *m*/*z*: calculated for $C_{14}H_{15}N_5O_2$ $[M+H]^+$ 286.1, found 286.2. HPLC: t_R = 6.31 min (method B) (100.0% purity).

2. ESI-QTOF assay

We followed the method reported in our previous paper.[7]

Materials: GSK3β enzyme and synthetic peptide GSM were purchased from Merck Millipore (Darmstadt, Germany). Adenosine triphosphate (ATP) disodium salt hydrate, ammonium acetate, ammonium hydroxide, dimethyl sulfoxide (DMSO), magnesium acetate tetrahydrate, formic acid, were purchased from Sigma–Aldrich (St. Louis, MO, USA). All other reagents were of analytical grade and filtered by nylon membrane filters 0.40 µm from Merck Millipore (Darmstadt, Germany). Ultrapure water was obtained on a Purite LTD water purification system (Thame, UK). Stock solutions of ATP (1 mM) were prepared in pH 7.4, 6 mM ammonium acetate and 1.6 mM magnesium acetate buffer. Stock solutions of GSM (1 mM) and 100 ng/L GSK3β were prepared in the same buffer and stored in aliquots at −80 °C. Further dilutions were prepared with fresh buffer before carrying out the assay. The inhibitors stock solutions (10 mM) were diluted with DMSO to achieve the concentration of 1 mM and then they were further diluted to the desired concentration with buffer. The percentage of DMSO was kept below 1%.

Inhibition assay by ESI-QTOF: The inhibition studies were performed by setting the assay solutions composed of 2.5 ng/L GSK3β, 62.5 µM GSM substrate, 250 µM ATP and inhibitors. Enzymatic reactions were carried out in the Eppendorf ThermoMixer (Hamburg, Germany) at 37 °C for 30 min. The sample solutions were analyzed by flow injection into the electrospray ionization (ESI) source at a 10 µL/min flow rate in positive ion mode (+ESI) with Micromass QTOF Ultima Global (Manchester, UK) equipped with an ESI source, and operating with a QTOF mass analyzer. Instrument control, data acquisition and processing were performed with Waters MassLynx 4.1 software (Manchester, UK). The ESI-QTOF source temperature was set at 80 °C, the capillary voltage at 3.0 kV and the cone voltage at 80 V. The scan time was set at 1 s, the inter scan time at 0.1 s and the desolvation gas was 200 L/h. Mass chromatograms were recorded in total ion current (TIC) mode in the mass range 100–1200 m/z. The spectra (m/z 370–815) deconvolution was carried out onto a true mass scale using the maximum entropy (MaxEnt1)-based software supplied with MassLynx 4.1 software. Output parameters were set as follows: mass range 2000–5000 Da; resolution 0.50 Da/channel. The uniform Gaussian model was used with 0.75 Da width at half height. The abundance of phosporylated muscle glycogen synthase P-GSM, as ion product of enzymatic reaction, was expressed as the ratio between the intensity of its diphosphorylated ion form and the amount of both the intensities of diphosphorylated and monophosphorilated GSM most abundant ion form, expressed as percentage. The applied formula is reported in Eq. (1). Data were analyzed by Microsoft Excel software.

Eq. (1) $$\frac{\mathrm{P-GSM}}{(\mathrm{P-GSM+GSM})}\cdot 100$$

The % of inhibition at different inhibitors concentrations, was calculated by the following formula reported in Eq. (2).

Eq. (2) $$100-(\frac{\mathrm{Ai}}{\mathrm{A0}}\cdot 100)$$

A_i is the intensity percent obtained in the presence of inhibitor and A_0 is the intensity percent obtained in the absence of inhibitor. Inhibition curves were obtained for compound **3a** by plotting the % inhibition versus the logarithm of inhibitor concentrations in the assay solution. The linear regression parameters were determined and an IC_{50} value of 0.034 µM was extrapolated (GraphPad Prism 4.0, GraphPad Software Inc.).

Compounds **3i**, **6a** and **6h** were tested at single concentration corresponding to their IC_{50} previously determined by luminometric assay. Compound **1** was tested at 0.7 µM. The obtained percentages of inhibition are reported in Table 1.

Table S1. Comparison of ESI-QTOF and ADO-Glo™ results.

	ESI-QTOF assay results	ADP-Glo™ assay results
Cpd	**% inhibition**	**IC_{50} ± SEM [µM]**
1	0% @ 0.700 µM	1.684 ± 0.120
3i	27.85% @ 0.059 µM	0.059 ± 0.007
6a	29.80% @ 0.047 µM	0.047 ± 0.020
6h	25.41% @ 0.039 µM	0.039 ± 0.017

For these compounds, the IC_{50} values were derived by applying the Eq. (3) reported by Kornacker and coworkers,[8] where [I] is the concentration of the tested inhibitor and "% inhibition" is the observed inhibition percentage. The derived IC_{50} values are reported in Table S2.

Eq. (3) $$IC_{50} = [I] \cdot \frac{100}{(\%\ \text{inhibition} - 1)}$$

Table S2. Comparison of ESI-QTOF and ADO-Glo™ IC_{50} values.

	ESI-QTOF assay results	ADP-Glo™ assay results
Cpd	**IC_{50}[µM][a]**	**IC_{50} ± SEM [µM]**
1	> 0.700	1.684 ± 0.120
3a	0.034	0.011 ± 0.001
3i	0.220	0.059 ± 0.007
6a	0.163	0.047 ± 0.020
6h	0.159	0.039 ± 0.017

[a]mean value of two independent experiments. RSD below 5%

The IC_{50} values obtained by both ADP-Glo™ method and by ESI-QTOF method are in good agreement as shown by the following correlation graph.

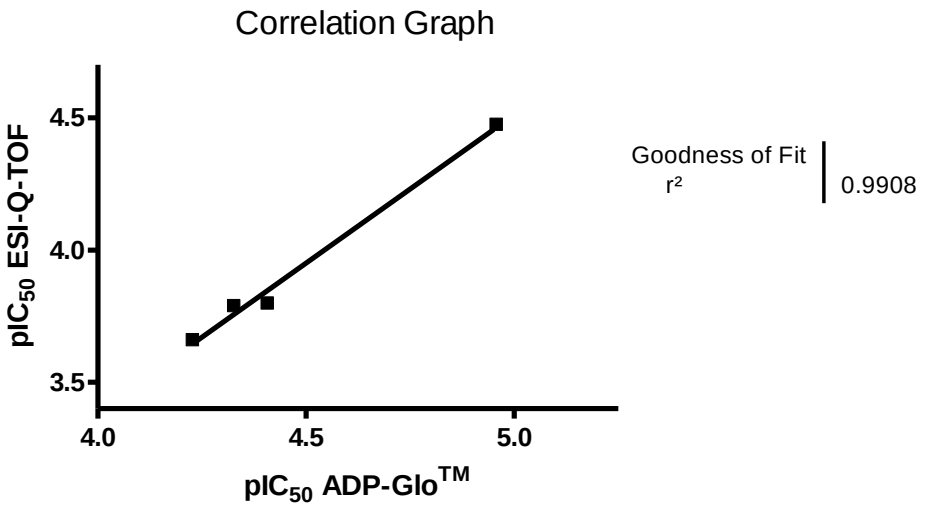


Figure S1. Correlation plot for inhibitory potency (pIC_{50}) of tested inhibitors obtained by ESI-QTOF assay and the ADP-Glo™ assay.

3. Molecular modeling, QM calculations and MD simulations

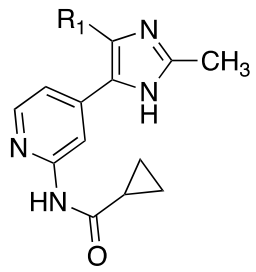
All the modeling was conducted with Maestro Small-Molecule Drug Discovery Suite 2018-4 (Schrödinger, LLC) with OPLS3e force field,[9-10] unless otherwise stated. The figures were prepared with PyMOL 2.2.3 (Schrödinger, LLC).

QM Conformer & Tautomer Prediction

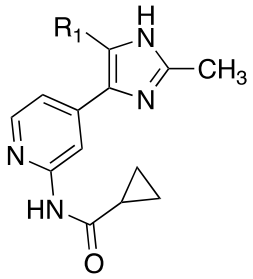
For the tautomer prediction, we used the QM Conformer & Tautomer Predictor tool of Maestro (Schrödinger, LLC, New York, NY, 2018) that utilizes Jaguar[11] in the QM calculations. In brief, the workflow is the following:

The proton donor and acceptor atoms are identified, and protons are redistributed among these to form a list of tautomers (protons can also be added to or subtracted from the input molecule). The generated tautomers were next ranked by their semiempirical PM3 heat of formation, and the high-energy tautomers were then discarded. For the surviving tautomers, a set of conformers were generated with MacroModel and the high-energy structures were eliminated by their semiempirical PM3 heat of formation. Subsequently, DFT geometry optimizations were performed on the surviving structures, using the B3LYP-D3/LACVP** level of theory. Finally, the structures were ranked using single-point energies at the M06-2X/cc-pVTZ(-f) calculated at the optimal geometries from the previous step. The Boltzmann populations were calculated based on the Solution phase energy at the temperature of 298.15 K.

Table S3 Results of QM Conformer & Tautomer Prediction



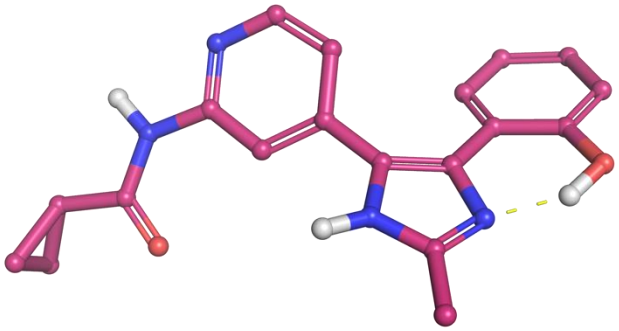
Tautomer A ("acceptor")



Tautomer B ("donor")

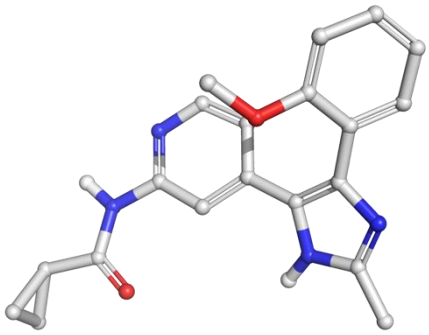
Note: The conformations highlighted with yellow (e.g. **3a-I**) are shown on the right.

Conform.	Solution phase energy	Tautomer	Boltzmann population
3a-I	-1104.296602	A	44.472
3a-II	-1104.296234	A	30.106
3a-III	-1104.295322	B	11.457
3a-IV	-1104.294701	A	5.934
3a-V	-1104.294536	A	4.982
3a-VI	-1104.293568	B	1.788
3a-VII	-1104.293228	B	1.248
3a-VIII	-1104.288470	A	0.008
3a-IX	-1104.287568	A	0.003
3a-X	-1104.287402	A	0.003



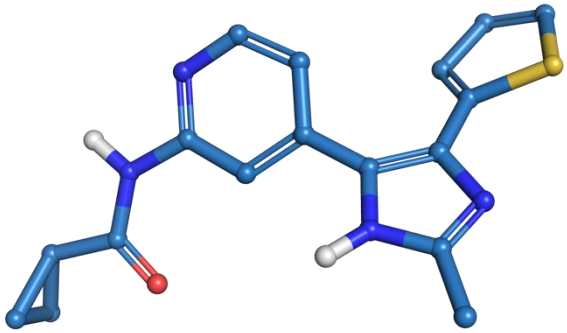
GSK3β: IC_{50} ± SEM [μM]= **0.011 ± 0.001**
Tautomer A total pop: 85.508%

Conform.	Solution phase energy	Tautomer	Boltzmann population
3f-I	-1143.578678	B	38.173
3f-II	-1143.578454	B	30.113
3f-III	-1143.578256	A*	24.408
3f-IV	-1143.577047	A*	6.782
3f-V	-1143.573711	B	0.198
3f-VI	-1143.573631	B	0.182
3f-VII	-1143.573149	B	0.109
3f-VIII	-1143.572068	B	0.035



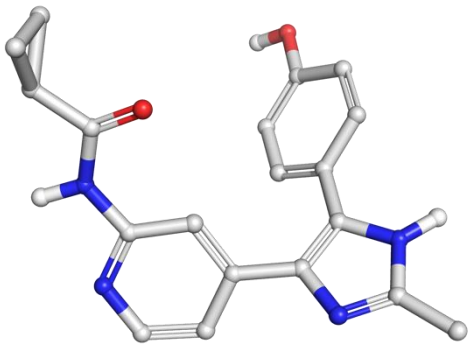
GSK3β: IC_{50} ± SEM [μM] = **> 10 μM**
Tautomer A total pop: 31.19%
*Tautomer A appears only in a conformation where the methoxy-group folds on top of the pyridinyl ring (non-binding conformation)

Conform.	Solution phase energy	Tautomer	Boltzmann population
3d-I	-1349.830260	A	33.202
3d-II	-1349.830196	A	31.018
3d-III	-1349.829072	B	9.433
3d-IV	-1349.829046	B	9.178
3d-V	-1349.828982	A	8.575
3d-VI	-1349.828974	A	8.503
3d-VII	-1349.823891	B	0.039
3d-VIII	-1349.823712	B	0.032
3d-IX	-1349.822647	A	0.010
3d-X	-1349.822568	A	0.010



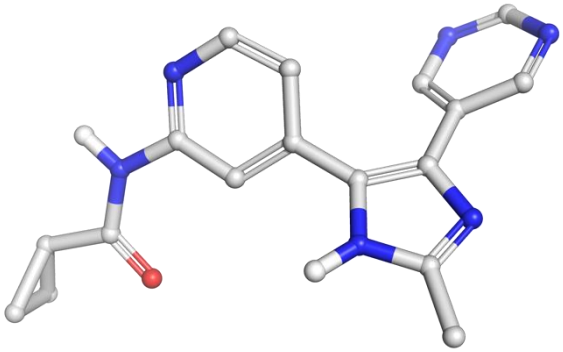
GSK3β: IC_{50} ± SEM [μM] = **0.069 ± 0.000**
Tautomer A total pop: 81.318%

Conform.	Solution phase energy	Tautomer	Boltzmann population
3c-I	-1104.295629	B	35.763
3c-II	-1104.295420	B	28.660
3c-III	-1104.295204	B	22.803
3c-IV	-1104.293884	A	5.631
3c-V	-1104.293827	A	5.302
3c-VI	-1104.292269	A	1.019
3c-VII	-1104.291961	A	0.735
3c-VIII	-1104.288925	B	0.029
3c-IX	-1104.288924	B	0.029
3c-X	-1104.288892	B	0.028



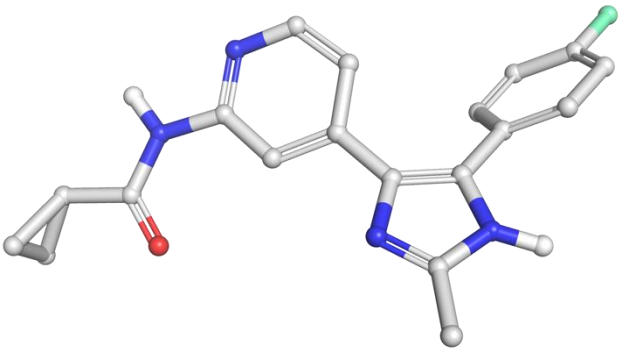
GSK3β: IC_{50} ± SEM [μM] = **0.893 ± 0.001**
Tautomer A total pop: 12.687%

Conform.	Solution phase energy	Tautomer	Boltzmann population
3g-I	-1061.148029	A	21.208
3g-II	-1061.147961	A	19.717
3g-III	-1061.147922	A	18.917
3g-IV	-1061.147245	A	9.244
3g-V	-1061.147183	A	8.652
3g-VI	-1061.147127	A	8.154
3g-VII	-1061.146353	B	3.593
3g-VIII	-1061.146340	B	3.543
3g-IX	-1061.146333	B	3.515
3g-X	-1061.146317	B	3.457



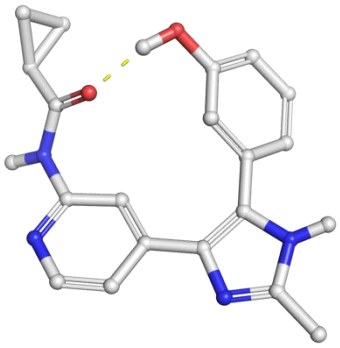
GSK3β: IC_{50} ± SEM [μM] **> 10 μM**
Tautomer A total pop: 85.892%
Note: Pyrimidine is unsuitable for hydrophobic pocket.

Conform.	Solution phase energy	Tautomer	Boltzmann population
1-I	-1128.306260	B	24.865
1-II	-1128.306193	B	23.180
1-III	-1128.305582	A	12.136
1-IV	-1128.305315	A	9.144
1-V	-1128.305114	B	7.389
1-VI	-1128.305110	B	7.360
1-VII	-1128.304984	B	6.437
1-VIII	-1128.304611	A	4.337
1-IX	-1128.304478	A	3.769
1-X	-1128.303533	B	1.385



GSK3β: IC_{50} ± SEM [μM] = **0.053 ± 0.012**[a]
Tautomer A total pop: 29.386%

Conform.	Solution phase energy	Tautomer	Boltzmann population	Boltzmann population[a]
3b-I	-1104.297522	B*	96.981	-
3b-II	-1104.293541	A	1.431	47.390
3b-III	-1104.293523	A	1.403	46.495
3b-IV	-1104.290784	B	0.077	2.556
3b-V	-1104.290191	B	0.041	1.364
3b-VI	-1104.289543	B	0.021	0.686
3b-VII	-1104.289482	B	0.019	0.644
3b-VIII	-1104.289403	B	0.018	0.592
3b-IX	-1104.288674	B	0.008	0.273
3b-X	-1104.283337	B	0.000	0.001



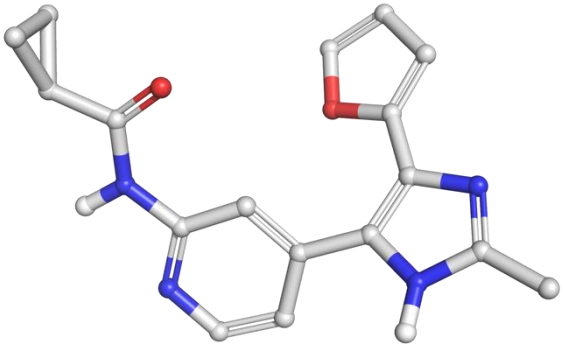
GSK3β: IC_{50} ± SEM [μM] = **0.043 ± 0.005**

Tautomer A total pop: 2.834% (93.885% when intramolecular H-bond conformation **16-I** is excluded)

*intramolecular H-bond

[a] population distribution excluding the intramolecular bond conformation

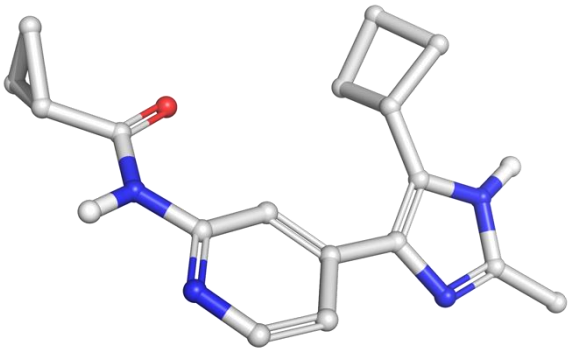
Conform.	Solution phase energy	Tautomer	Boltzmann population
3e-I	-1026.847726	A	27.085
3e-II	-1026.847633	A	24.544
3e-III	-1026.847341	B	18.016
3e-IV	-1026.846808	B	10.237
3e-V	-1026.846805	A	10.210
3e-VI	-1026.846746	A	9.590
3e-VII	-1026.842545	B	0.112
3e-VIII	-1026.842530	B	0.110
3e-IX	-1026.841911	B	0.057
3e-X	-1026.841532	A	0.038



GSK3β: IC_{50} ± SEM [μM] = **0.099 ± 0.033**

Tautomer A total pop: 71.467%

Conform.	Solution phase energy	Tautomer	Boltzmann population
3k-I	-954.022095	B	28.389
3k-II	-954.022069	B	27.632
3k-III	-954.021732	B	19.337
3k-IV	-954.021454	B	14.403
3k-V	-954.020006	A	3.106
3k-VI	-954.019877	A	2.710
3k-VII	-954.019871	A	2.693
3k-VIII	-954.019448	A	1.720
3k-IX	-954.014328	B	0.008
3k-X	-954.013155	B	0.002

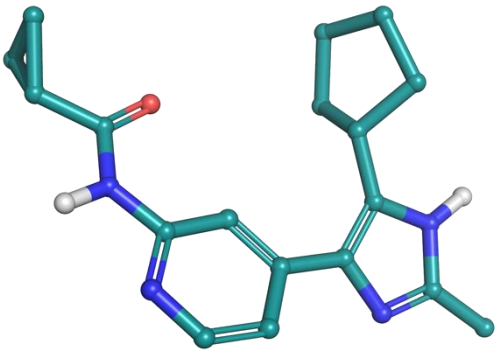


GSK3β: IC_{50} ± SEM [μM] = **4.114 ± 0.191**

Tautomer A total pop: 10.229%

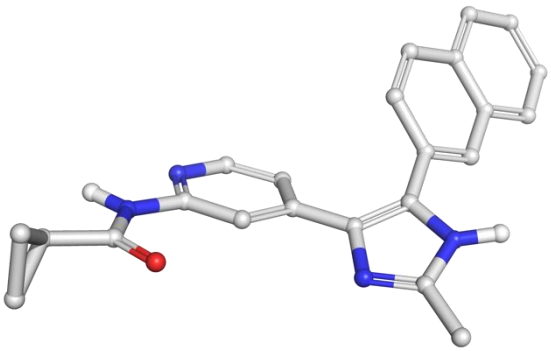
Conform.	Solution phase energy	Tautomer	Boltzmann population
3l-I	-993.357257	B	28.091
3l-II	-993.357103	B	23.843
3l-III	-993.356732	B	16.095
3l-IV	-993.356680	B	15.237
3l-V	-993.355688	A	5.329
3l-VI	-993.355552	A	4.612
3l-VII	-993.355282	A	3.467
3l-VIII	-993.355232	A	3.286
3l-IX	-993.351037	A	0.039
3l-X	-993.347911	A	0.001

GSK3β: IC_{50} ± SEM [μM] = **5.456 ± 0.006**
Tautomer A total pop: 16.734%



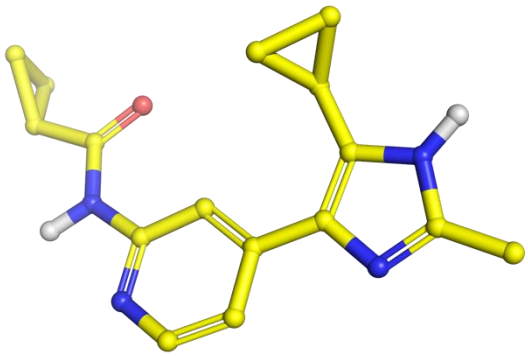
Conform.	Solution phase energy	Tautomer	Boltzmann population
3h-I	-1182.687499	B	51.856
3h-II	-1182.686104	B	11.833
3h-III	-1182.685564	B	6.681
3h-IV	-1182.685365	A	5.411
3h-V	-1182.685277	A	4.931
3h-VI	-1182.685252	B	4.802
3h-VII	-1182.685199	B	4.539
3h-VIII	-1182.684985	A	3.617
3h-IX	-1182.684886	A	3.257
3h-X	-1182.684831	A	3.073

GSK3β: IC_{50} ± SEM [μM] = **> 10 μM**
Tautomer A total pop: 20.289%

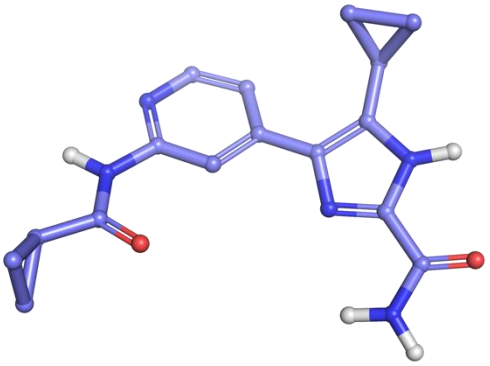


Conform.	Solution phase energy	Tautomer	Boltzmann population
3j-I	-914.716713	B	20.118
3j-II	-914.716682	B	19.469
3j-III	-914.716653	B	18.864
3j-IV	-914.716572	B	17.327
3j-V	-914.716067	B	10.144
3j-VI	-914.715850	B	8.063
3j-VII	-914.714501	A	1.932
3j-VIII	-914.714341	A	1.630
3j-IX	-914.714283	A	1.534
3j-X	-914.713799	A	0.918

GSK3β: IC_{50} ± SEM [μM] = **3.085 ± 0.304**
Tautomer A total pop: 6.014%

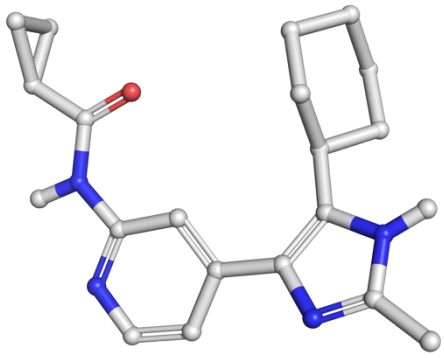


Conform.	Solution phase energy	Tautomer	Boltzmann population
6g-I	-1044.125829	B	21.528
6g-II	-1044.125800	B	20.867
6g-III	-1044.125748	B	19.762
6g-IV	-1044.125613	B	17.132
6g-V	-1044.125424	B	14.023
6g-VI	-1044.124012	A	3.142
6g-VII	-1044.123911	A	2.823
6g-VIII	-1044.121999	A	0.372
6g-IX	-1044.121940	A	0.350
6g-X	-1044.115771	A	0.001



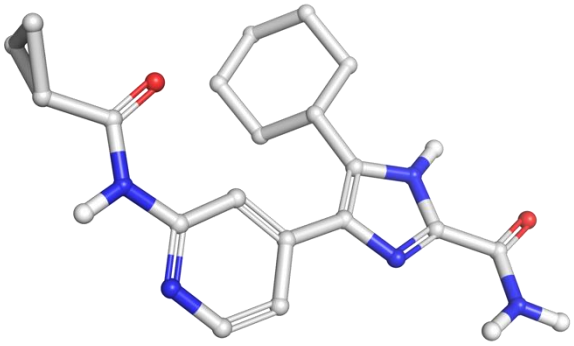
GSK3β: IC_{50} ± SEM [μM] = **0.003 ± 0.000**
Tautomer A total pop: 6.688%

Conform.	Solution phase energy	Tautomer	Boltzmann population
3m-I	-1032.674226	B	38.531
3m-II	-1032.673584	B	19.524
3m-III	-1032.673014	B	10.676
3m-IV	-1032.672765	B	8.199
3m-V	-1032.672547	B	6.511
3m-VI	-1032.672202	A	4.514
3m-VII	-1032.672180	A	4.414
3m-VIII	-1032.672106	A	4.078
3m-IX	-1032.671974	A	3.546
3m-X	-1032.666049	B	0.007



GSK3β: IC_{50} ± SEM [μM] = **4.644 ± 1.159**
Tautomer A total pop: 16.552%

Conform.	Solution phase energy	Tautomer	Boltzmann population
6f-I	-1162.082426	B	29.067
6f-II	-1162.082186	B	22.549
6f-III	-1162.082042	B	19.362
6f-IV	-1162.081962	B	17.784
6f-V	-1162.080625	A	4.317
6f-VI	-1162.080347	A	3.216
6f-VII	-1162.080159	A	2.634
6f-VIII	-1162.079229	A	0.984
6f-IX	-1162.076626	B	0.062
6f-X	-1162.075806	B	0.026



GSK3β: IC_{50} ± SEM [μM] = **0.003 ± 0.000**
Tautomer A total pop: 11.151%

MD simulations

For the MD simulations we used the structures 6GN1[12] and 4PTC[4] (for the additional simulations of **3a**, **3j**, **6b** and **6g**), which were prepared with Protein Preparation Wizard (default settings).[13] The initial coordinates for the ligand-protein complexes were obtained by Induced Fit Docking (IFD),[14-16] using default settings, except the Glide redocking was conducted with XP.[17] The grid box was defined by the co-crystalized ligand. Before the docking, the small-molecules were prepared with LipPrep (default settings) using Epik.[18-19] The tautomeric state of a compound used in the simulations was chosen based on the QM Conformer & Tautomer Predictor results. The MD simulations were conducted with Desmond.[20]

For the compounds **3a**, **3j**, **6b** and **6g**, the systems were solvated in a cubic box (edges 14 Å from the protein) and neutralized with counterions (Cl^-) with 0.15M NaCl salt. The water was described with TIP3P water model.[21] The final 6GN1 systems consisted of 65,545; 65,405; 65,561 and 65,460 atoms. The 4PTC systems consisted of 74,622; 74,642; 74,632 and 74,631 atoms. The default relaxation protocol of Desmond was used before the 1,000 ns production simulations, which were conducted in NPT ensemble (310 K, thermostat: Nosé-Hoover chain; 1.01325 bar, barostat: Martyna-Tobias-Klein). The default timestep of 2 fs and cutoff radius of 9.0 Å for Coulombic interactions were used. The total simulation time was 8 μs (4 x 2 x 1,000 ns).

The compounds **4a** and **4b** were solvated in an orthorhombic box (edges 13 Å from the protein) with counterions (Cl^-) without salt, resulting in systems of 56,176 and 56,445 atoms. After the default relaxation protocol, the systems were simulated for 200 ns with the above-mentioned settings.

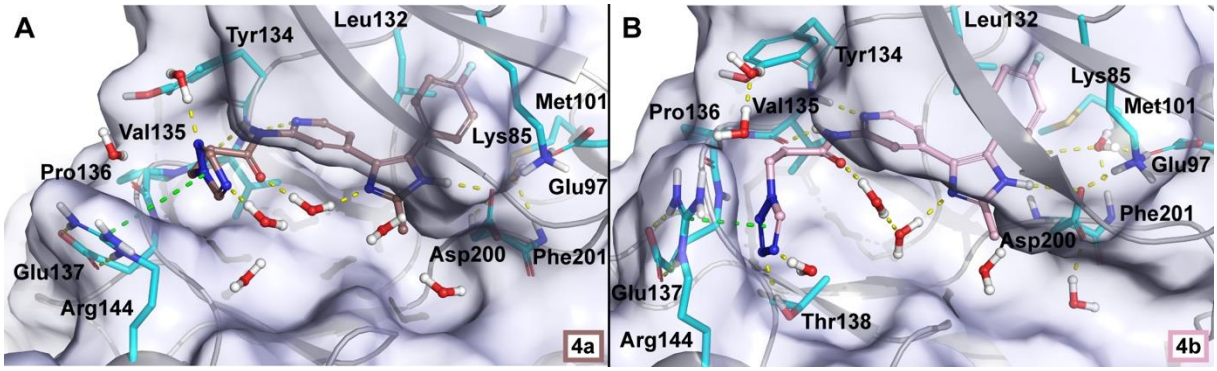


Figure S2. The output conformations of compounds **4a** (**A**) and **4b** (**B**) after 200 ns MD simulations. The most important interacting residues and the closest water molecules are shown. The H-bonds are displayed with yellow and the cation-π interaction with green dashed line.

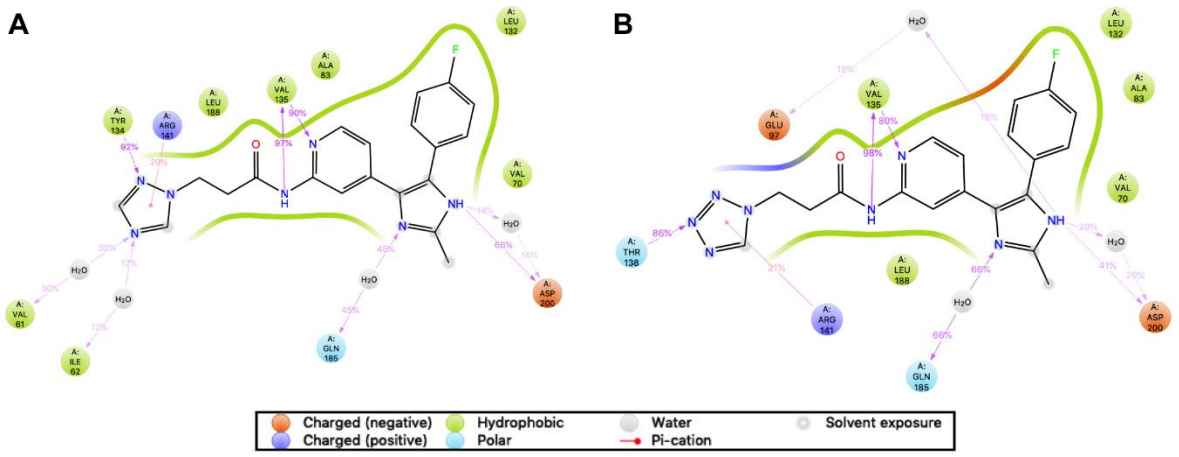


Figure S3. The simulation interactions of compound **4a** (**A**) and **4b** (**B**). In the solvent exposed area near the HR II, compound **4a** displays interaction to Tyr134, π-cation interaction to Arg141 and water mediated interactions, whereas **4b** interacts with Thr138 and Arg141. Interactions that appear >10% frequency in the simulation are shown.

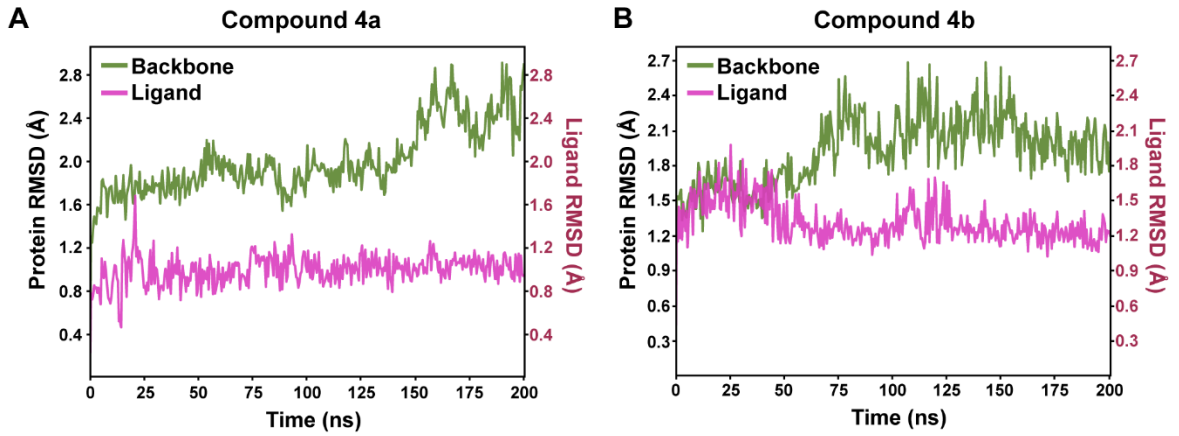


Figure S4. The RMSD of protein backbone and ligand in the simulations of compound **4a** (**A**) and **4b** (**B**).

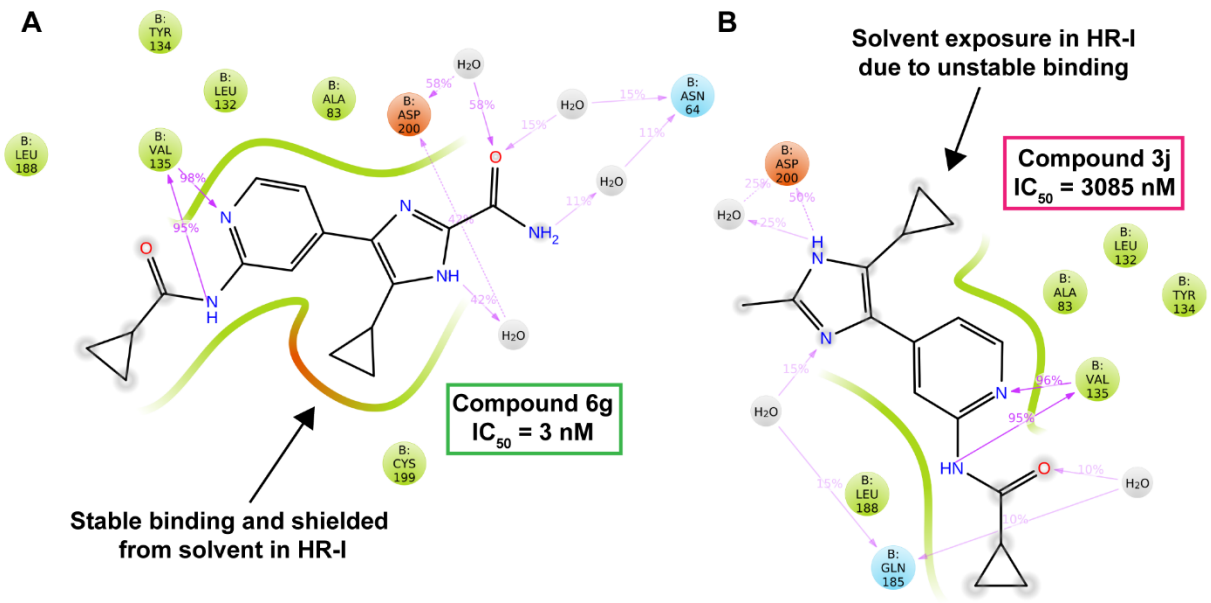


Figure S5. The simulation interactions of compound **6g** (**A**) and **3j** (**B**) in 6GN1 simulations. The instability of compound **3j** binding can be observed from the solvent exposure of the cyclopropyl moiety in the HR-I region. The amide residue (compound **6g**) stabilizes the solvent interaction networks and shields HR-I from solvent enabling stable binding. Interactions that appear >10% frequency in the simulation are shown. See interaction legend from **Figure S3.**

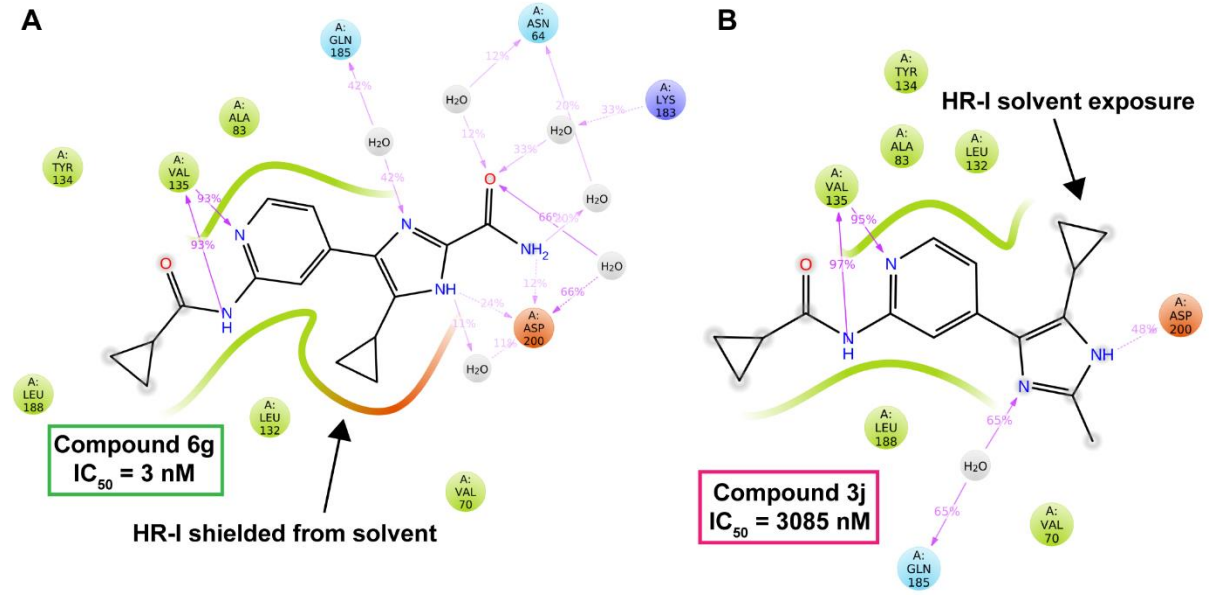


Figure S6. The simulation interactions of compound **6g** (**A**) and **3j** (**B**) in 4PTC simulations. Identical interactions are observed as in **Figure S5**, with the solvent exposure of the cyclopropyl with compound **3j** (**B**). Interactions that appear >10% frequency in the simulation are shown. See interaction legend from **Figure S3.**

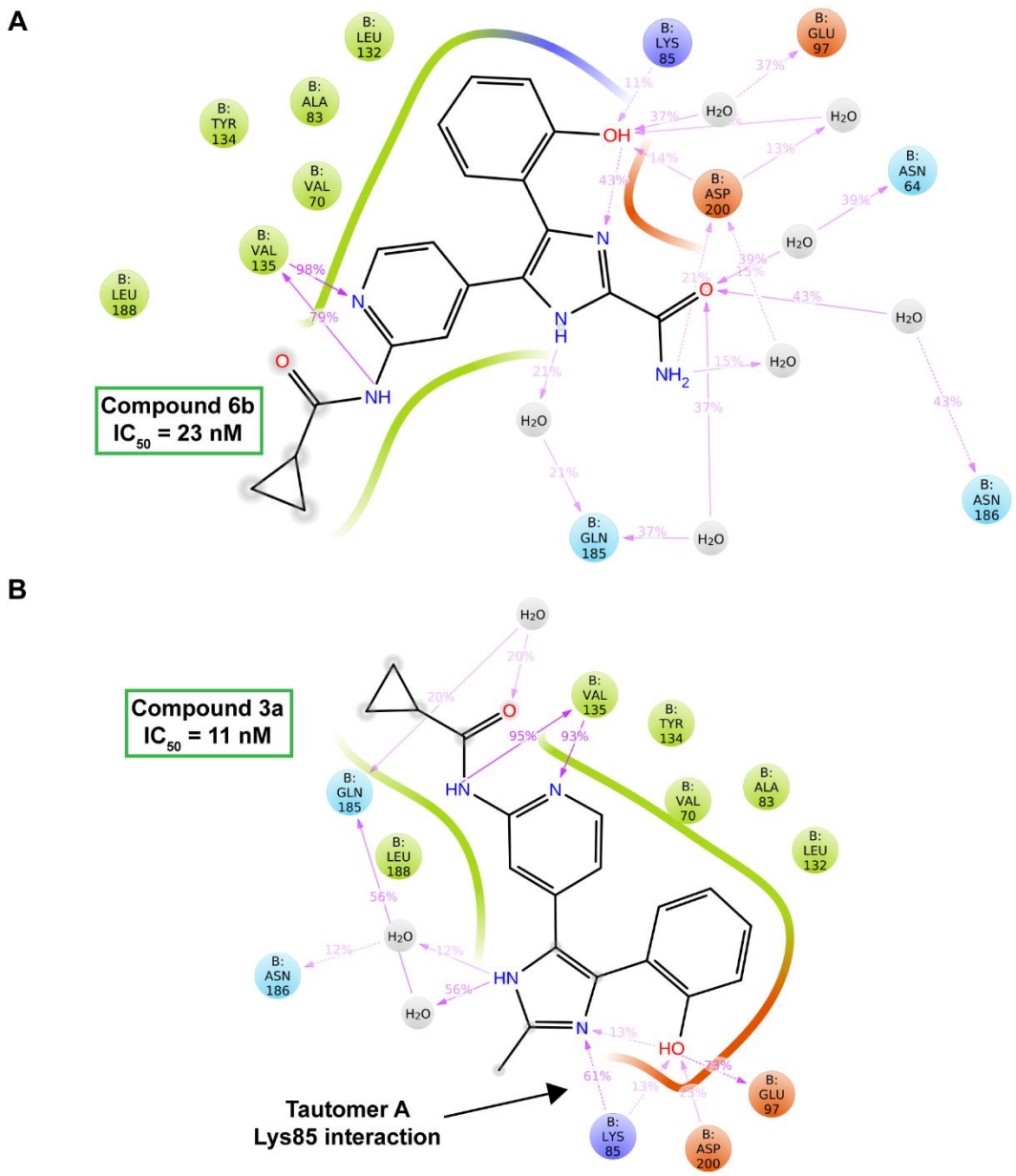


Figure S7. The simulation interactions of compound **6b** (**A**) and **3a** (**B**) in 6GN1 simulations. The tautomer A with the methyl derivative (compound **15**) forms a direct interaction to the Lys85 (61%). Interactions that appear >10% frequency in the simulation are shown. See interaction legend from **Figure S3**.

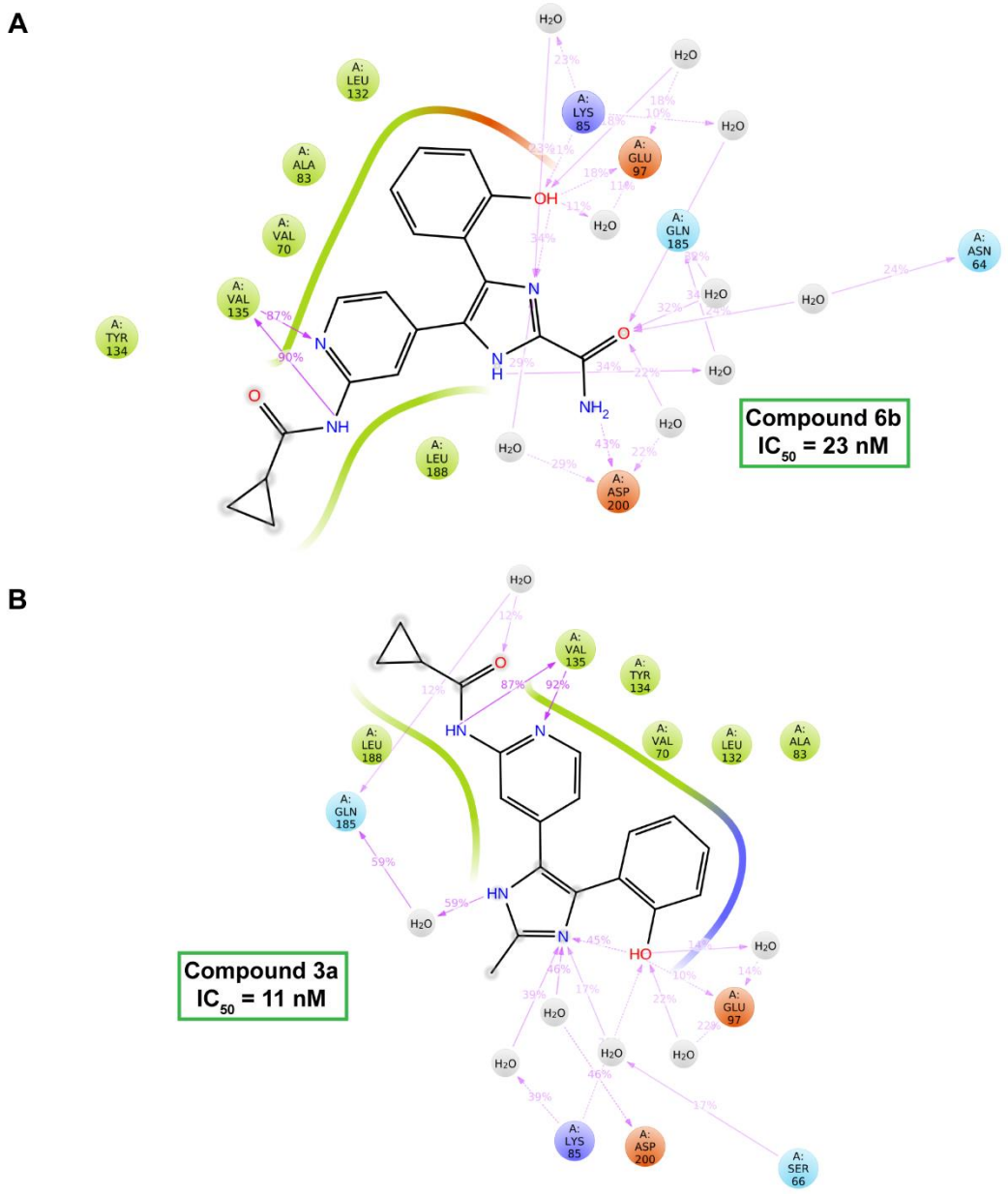


Figure S8. The simulation interactions of compound **6b** (**A**) and **3a** (**B**) in 4PTC simulations. The tautomer A with the methyl derivative (compound **3a**) forms a water mediated interactions to the Lys85 and more frequent intramolecular interaction to the hydroxyl-group compared to **Figure S7**. The lipophilic part of the 2-hydroxyphenyl is shielded from water as in **Figure S7**. Interactions that appear >10% frequency in the simulation are shown. See interaction legend from **Figure S3**.

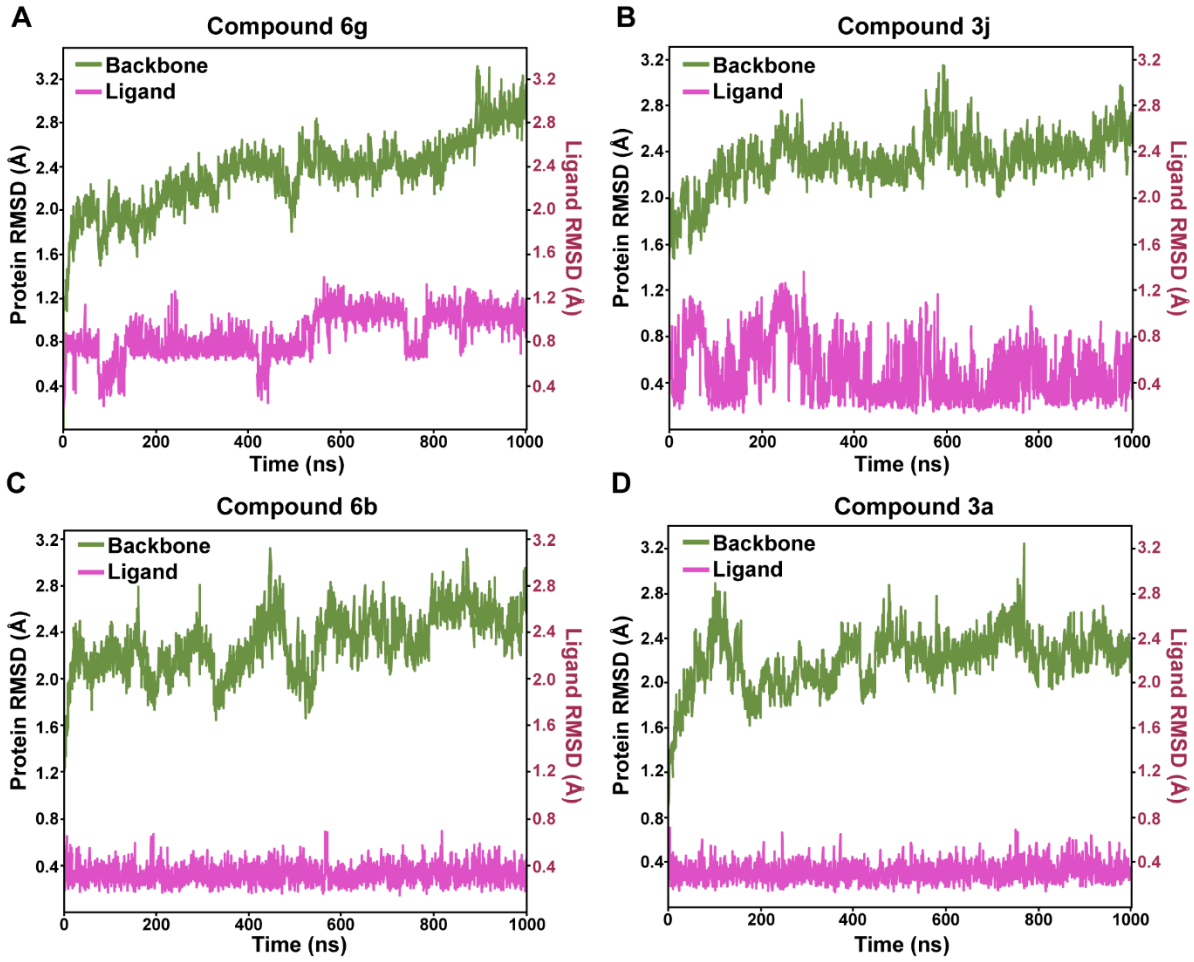


Figure S9. The RMSD of protein backbone and ligand in the 6GN1 simulations of compound **6g** (**A**), **3j** (**B**), **6b** (**C**) and **3a** (**D**).

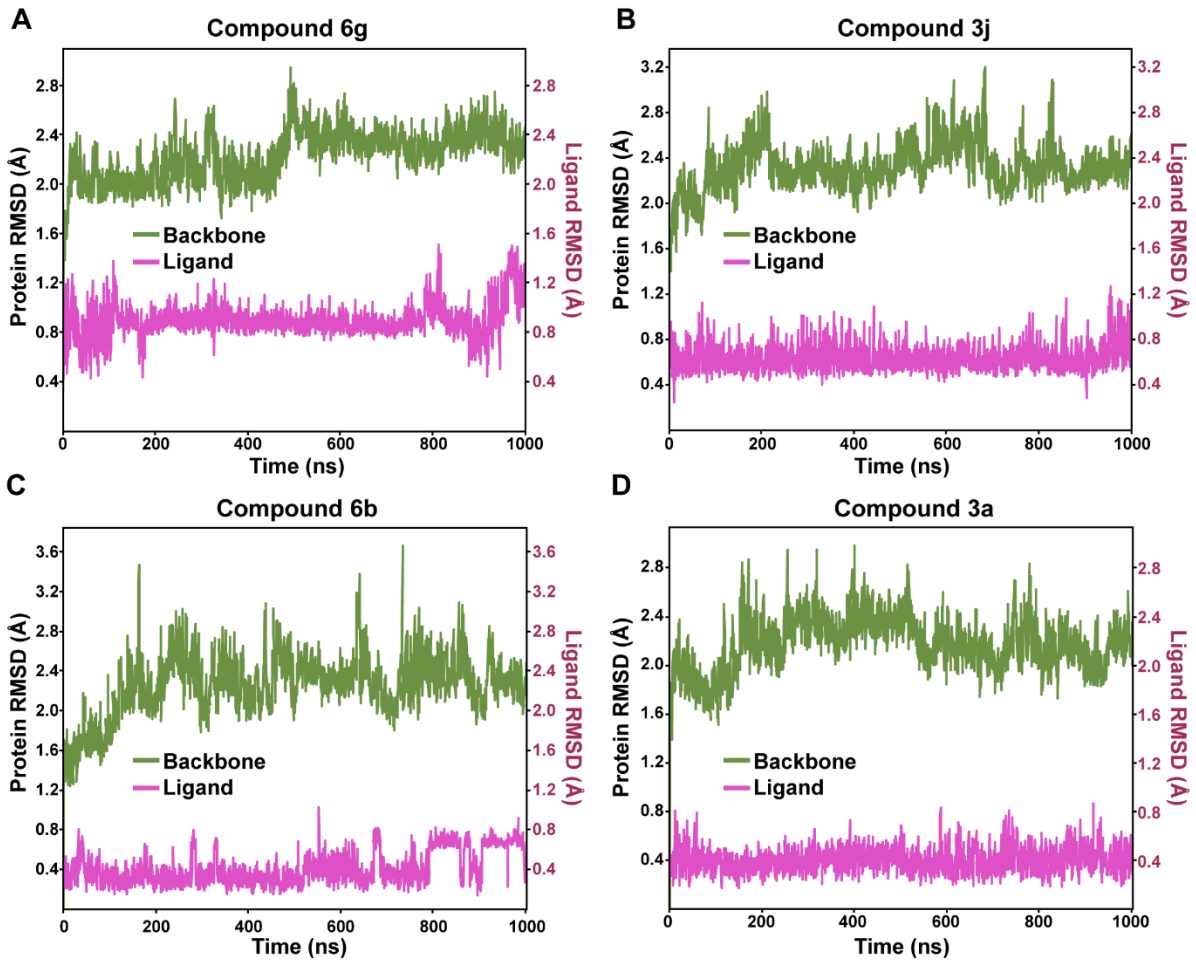


Figure S10. The RMSD of protein backbone and ligand in the 4PTC simulations of compound **6g** (**A**), **3j** (**B**), **6b** (**C**) and **3a** (**D**).

4. Metabolic stability in human liver microsomes

Microsomes from liver, pooled from human (male and female) (Lot: SLBQ7487V) were purchased from Merck (Schnelldorf, Germany). The incubations of compounds **3a** and **6g** were made in the presence of an NADPH-regenerating system (5 mM Glucose-6-phosphate, 5 U/mL Glucose-6-phosphate dehydrogenase and 1 mM $NADP^+$). The substrate (100 µM), the NADPH-regenerating system and 4 mM $MgCl_2 \cdot 6\ H_2O$ in 0.1 M Tris buffer (pH 7.4) were preincubated for 5 min at 37 °C and 750 rpm. The incubation mix was split into aliquots (50 µL) and the reaction was started by the addition of HLM. The reaction was quenched at selected time points (0, 10, 20, 30, 60, 120, 180 and 240 min) by adding 100 µL internal standard at a concentration of 22.5 µM in MeCN. The samples were vortexed for 30 s and centrifuged (19,800 relative centrifugal force/4 °C/10 min). The supernatant was directly used for LC-MS analysis (see below). All incubations were conducted in triplicates and a limit of 1% organic solvent was not exceeded. Propranolol was used as a positive control.

The metabolite formation was analyzed with an Alliance 2695 Separations Module (Waters GmbH, Eschborn). Samples were maintained at 4 °C, the column temperature was set to 40 °C and injection volume was 10 µL. The chromatographic separation for all analytes was performed on a Dr Maisch Nucleosil 100 C18 column (53 x 4.6 mm; 5 µm). The following gradient of solvent A (90% H_2O, 10% ACN, 0.1% formic acid) and solvent B (MeOH, 0.1% formic acid) at a flow rate of 400 µL/min was used:

gradient		
time [min]	**A [%]**	**B [%]**
0	90	10
2	90	10
10	0	100
12	0	100
14	90	10

The detection was performed on a Micromass Quattro micro triple quadrupole mass spectrometer (Waters GmbH, Eschborn) using the electrospray ionization in the positive-mode. Spray voltage was set to 4.5 kV. The heated capillary operated at 250 °C and the desolvation gas flow worked at 600 L/h.

Table S4 Metabolic degradation of **3a**.

time [min]	#1 [%]	#2 [%]	#3 [%]	AVERAGE [%]	SD
0	100.00	100.00	100.00	100.00	0.00
10	100.31	109.91	96.72	102.31	6.82
20	93.29	109.27	95.71	99.42	8.62
30	100.84	103.72	99.25	101.27	2.26
60	101.84	106.23	102.17	103.41	2.44
120	100.10	99.27	96.03	98.47	2.15
180	107.06	102.81	100.14	103.34	3.49
240	101.91	103.72	100.48	102.04	1.63

Table S5 Metabolic degradation of **6g**.

time [min]	#1 [%]	#2 [%]	#3 [%]	AVERAGE [%]	SD
0	100.00	100.00	100.00	100.00	0.00
10	104.45	102.45	97.33	101.41	3.67
20	99.26	103.68	95.42	99.45	4.13
30	103.95	99.37	100.85	101.39	2.33
60	99.75	102.88	101.58	101.40	1.57
120	105.62	100.03	100.14	101.93	3.20
180	94.73	97.80	105.70	99.41	5.66
240	98.49	99.30	105.62	101.14	3.90

5. Kinome selectivity screening

Compound **6g** was tested at Eurofins Cerep SA (Celle-L'Evescault, France) in enzymatic radioactive assays in a panel of 68 different kinases (including GSK3β) from diverse families.

Table S6 Kinome selectivity screening

	residual activity in % using 0.5 µM of **6g**		residual activity in % using 0.5 µM of **6g**
Abl(h)	68	MAPK2(h) (ERK2)	95
ALK(h)	85	MAP4K4(h) (HGK)	47
AMPKα1(h)	102	MAPKAP-K2(h)	33
ASK1(h)	85	MEK1(h)	102
Aurora-A(h)	38	MLK1(h)	12
CaMKI(h)	124	Mnk2(h)	65
CDK1/cyclinB(h)	36	MSK2(h)	95
CDK2/cyclinA(h)	11	MST1(h)	77
CDK6/cyclinD3(h)	98	mTOR(h)	111
CDK7/cyclinH/MAT1(h)	82	NEK2(h)	109
CDK9/cyclin T1(h)	6	p70S6K(h)	95
CHK1(h)	84	PAK2(h)	47
CK1γ1(h)	68	PDGFRβ(h)	108
CK2α2(h)	55	Pim-1(h)	79
c-RAF(h)	109	PKA(h)	111
DRAK1(h)	52	PKBα(h)	105
eEF-2K(h)	122	PKCα(h)	67
EGFR(h)	109	PKCθ(h)	98
EphA5(h)	89	PKG1α(h)	113
EphB4(h)	82	Plk3(h)	114
FGFR3(h)	87	PRAK(h)	52
Fyn(h)	74	ROCK-I(h)	105
GSK3β(h)	1	Rse(h)	116
IGF-1R(h)	108	Rsk1(h)	73
IKKα(h)	47	SAPK2a(h) (p38α)	102
IRAK4(h)	57	SAPK2b(h) (p38β)	91
JAK2(h)	77	SAPK3(h) (p38γ)	48
JNK1α1(h)	31	SAPK4(h) (p38δ)	64
JNK2α2(h)	78	SRPK1(h)	108
JNK3(h)	7	TAK1(h)	83
KDR (h) (VEGFR2)	26	PI3 Kinase (p110b/p85a)(h)	100
LOK(h)	39	PI3 Kinase (p120g)(h)	100
Lyn(h)	67	PI3 Kinase (p110d/p85a)(h)	96
MAPK1(h) (ERK1)	85	PI3 Kinase (p110a/p85a)(h)	102

6. Inhibition of CYP450 isoenzymes

CYP inhibition assays were performed by Eurofins Panlabs Inc. (St Charles, MO, USA).

CYP inhibition assay (fluorimetric detection) was performed at 10 µM inhibitor concentration in single dose duplicate mode with human recombinant CYP enzyme and the appropriate CYP substrates: CYP1A2, 3-cyano-7-ethoxycoumarin (CFC); CYP2C9, CFC; CYP2C19, 7-methoxy-4-trifluoromethyl-coumarin (MFC); CYP2D6, MFC; CYP3A4 7-benzyloxy-trifluoromethylcoumarin (BFC)

7. Investigation of cell toxicity on six different cell lines

Maintenance of cell culture

The experiments were performed in an *in vitro* model of cell cytotoxicity analyses on hepatocellular carcinoma (HepG2), human prostate cancer (LNCap), human breast adenocarcinoma (MCF7), human lung fibroblast (MRC5), chinese hamster ovary (CHO-K1) and murine macrophages (RAW 264.7). The cells lines were cultured in appropriate medium, supplemented with 10% (v/v) of fetal bovine serum (FBS) and 1 % antibiotic/antimycotic solution. For subculture, cells were dissociated with trypsin-EDTA (Cultilab), split into a 1:3 ratio and subculture into Petri dishes with 25 cm^2 growth area. Raw 264.7 cells were dissociated using a scrapper. Culture medium was replaced every 2 days until the cells reached the total confluence after 4-5 days of initial seeding. Cells were maintained in the following controlled conditions: 95% of humidified atmosphere, 5% of CO_2 and constant temperature of 37ºC.

Cytotoxicity

The assessment of cell viability was performed according to the MTT colorimetric assay on 6 different cells lines. Cells were treated with different concentrations of **6g** for 48 h. The effects were estimated by colorimetric assay based on the conversion of tetrazolium salts (MTT) after 3 h of incubation to a blue formazan product by active mitochondria. The absorbance was read at 570 nm using a Spectramax i5 microplate reader. Results were expressed as percentage of control.

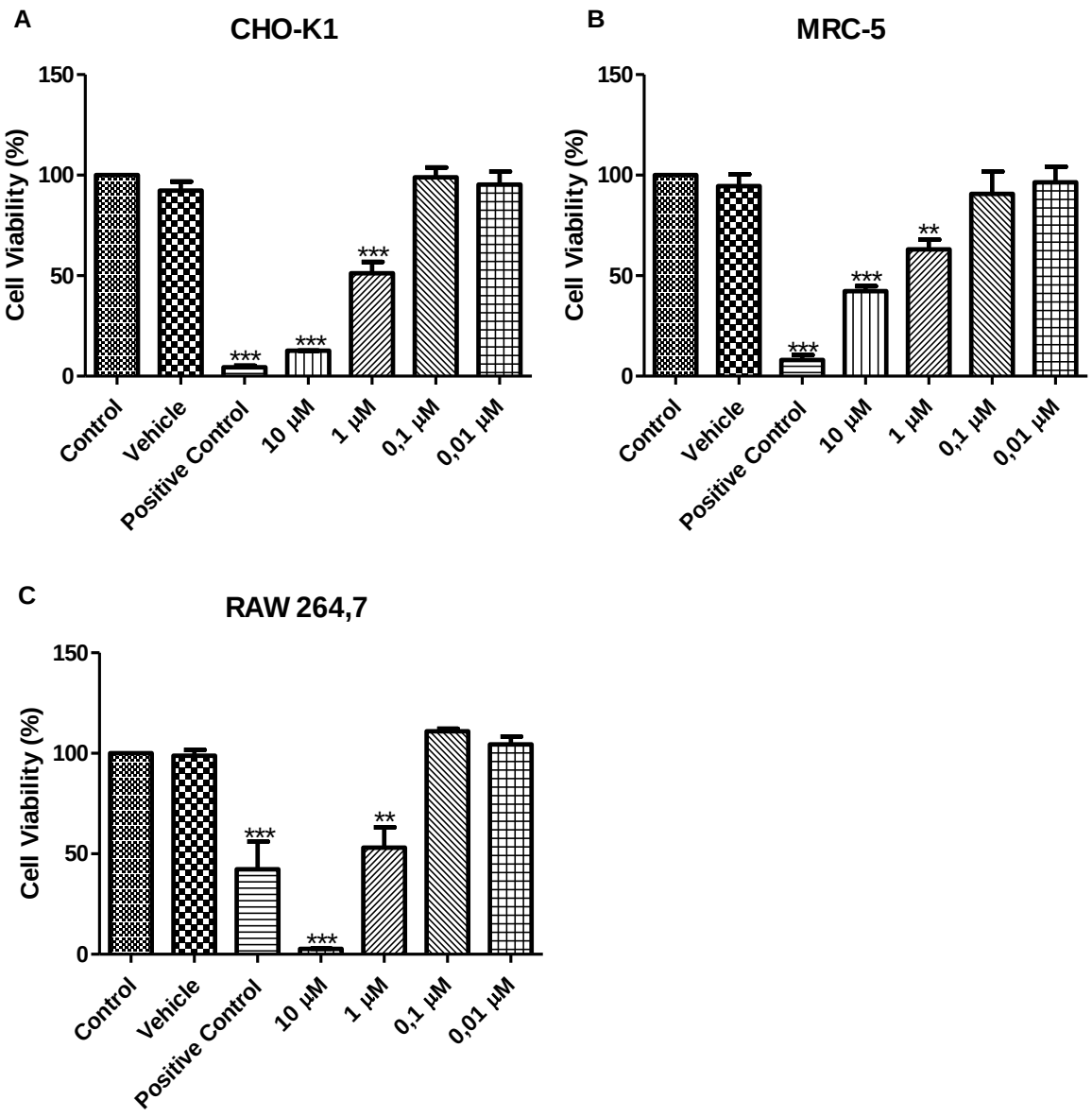


Figure S11. Evaluation of the cytotoxic potential of **6g** in non-tumorigenic cells lines. (A) Chinese hamster ovary cells CHO-K1, (B) human lung fibroblast cell line MRC-5, and (C) murine macrophages RAW 264.7.

Cell viability was evaluated by MTT assay, after 48h treatment with **6g**. Mean values ± SEM are shown. ***p<0.001 compared with control. Vehicle (DMSO); Positive Control (hydrogen peroxide).

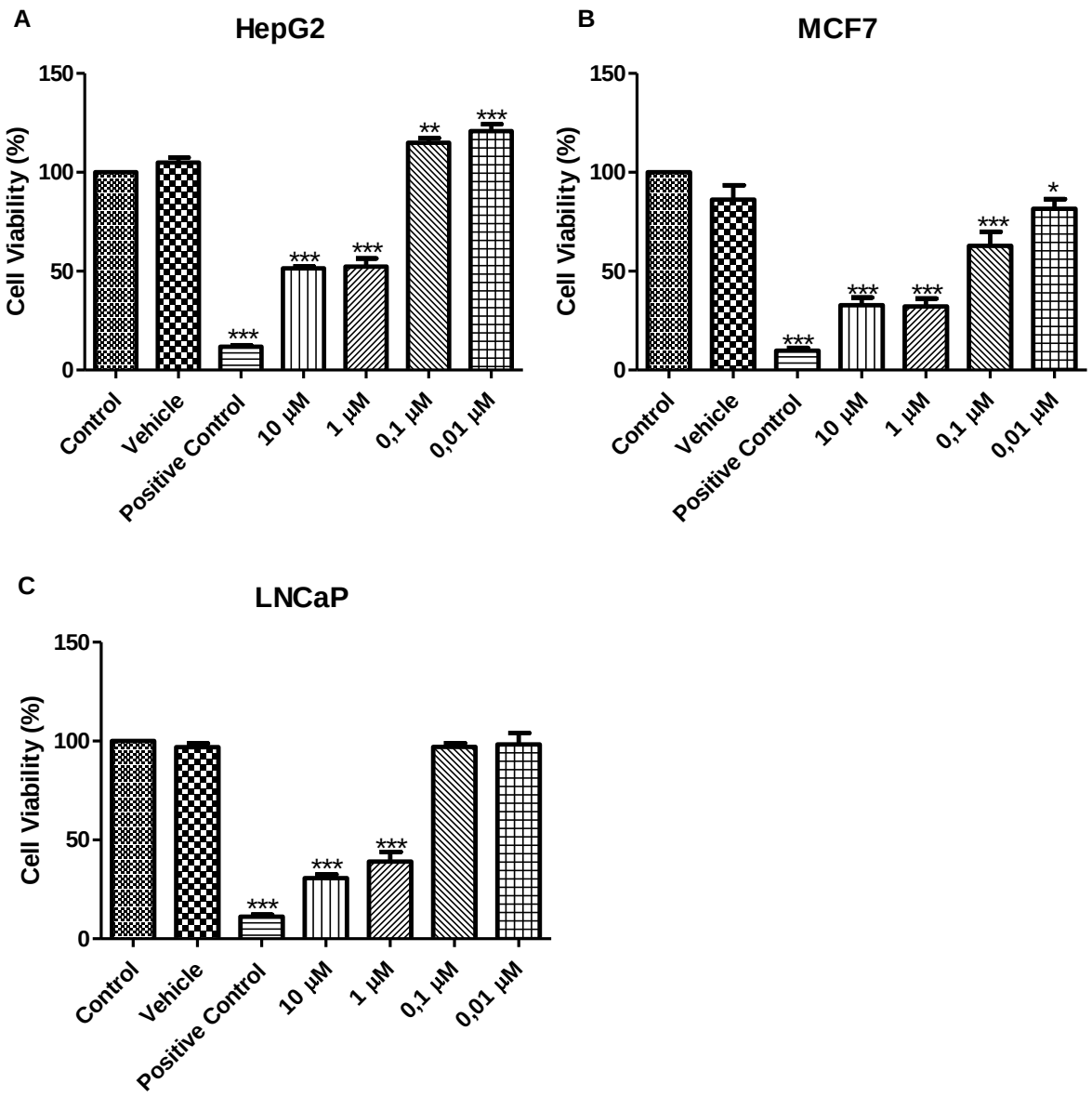


Figure S12. Evaluation of the cytotoxic potential of **6g** in tumorigenic cells lines. (A) Hepatocellular carcinoma cell line HepG2 , (B) human breast adenocarcinoma cell line MCF7, and (C) human prostate cancer cell line LNCaP.

Cell viability was evaluated by MTT assay, after 48h treatment with **6g**. Mean values ± SEM are shown. ***p<0.001 compared with control. Vehicle (DMSO); Positive Control (hydrogen peroxide).

8. Inhibition of GSK3β in SH-SY5Y cells

Material and Methods

Cell culture

Human neuronal SH-SY5Y cells were routinely grown in Dulbecco's modified Eagle's Medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 50 U/mL penicillin and 50 µg/mL streptomycin at 37°C in a humidified incubator with 5% CO_2.

Western Blotting

SH-SY5Y cells were seeded in 60 mm dishes at 2×10^6 cells/dish, incubated for 24 h and subsequently treated with compound **6g** [1 µM] for 1 h at 37°C in 5% CO_2. At the end of incubation, cells were lysed by addition of ice-cold lysis buffer containing leupeptin 2 µg/mL and PMSF 100 µg/mL. An aliquot was used for protein analysis with the Bradford assay for protein quantification. Cell lysates (50 µg per sample) were separated by SDS-polyacrylamide gels and transferred onto nitrocellulose membranes, which were probed with primary phospho-GSK3α/β (Ser21/9) (1:1000; Cell Signaling Technology, Danvers, MA, USA) and secondary antibodies. ECL reagents (Pierce, Rockford, IL, USA) were utilized to detect targeted bands. The same membrane was stripped and reprobed with total GSK3β (1:1000; Cell Signaling Technology) and β-Actin (1:1000; Sigma Aldrich, St. Louis, MO, USA) antibodies. Data were analysed by densitometry, using Quantity One software (Bio-Rad, Hercules, CA, USA). Data are expressed as ratio between phospho-GSK3α/β and total GSK3β levels normalized against β-Actin.

9. References

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