Supporting Information

Synthesis and Metabolic Studies of Host-Directed Inhibitors for Anti-Viral Therapy

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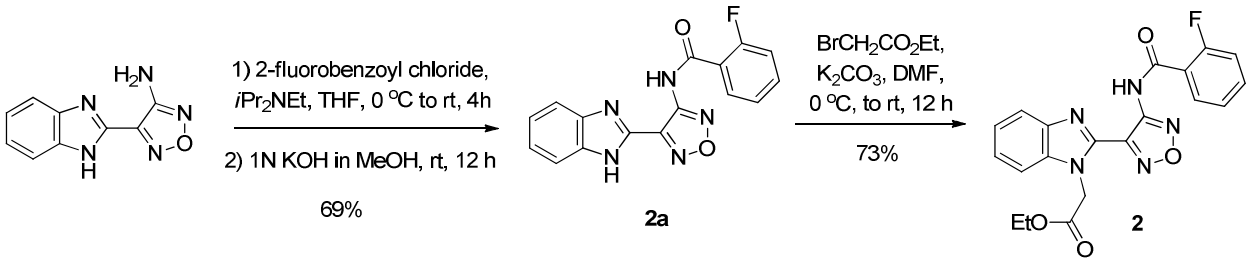
Chemistry General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and packaged under nitrogen in Sure Seal bottles. Reactions were monitored using thin-layer chromatography on 250 μm plates or using Agilent 1100 series LC/MS with UV detection at 254 nm and low resonance electrospray mode (ESI). Purification of title compounds was accomplished by flash column chromatography using silica gel 60 (particle size 0.04-0.063 mm, 230-400 mesh) or liquid chromatography on a Biotage SP4 purification system with normal phase silica gel. ^{1}H NMR spectra were recorded on a Varian spectrometer (400 MHz) at ambient temperature. Chemical shifts are reported in ppm relative to $CDCl_3$ or CD_3OD and coupling constants (J) are reported in hertz (Hz). Solvents for NMR were deuteriochloroform ($CDCl_3$) (residual shifts: δ 7.26 for ^{1}H and δ 77.7 for ^{13}C) and deuteriomethanol (CD_3OD) (residual shift: δ 3.31 for ^{1}H). The residual shifts were taken as internal references and reported in parts per million (ppm). Purity of final compounds was ≥95% based on analytical HPLC and NMR analysis.

Procedures for synthesis of compounds.

Ethyl 2-(2-(4-(2-fluorobenzamido)-1,2,5-oxadiazol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (2):



Scheme S1. Synthetic route of compound **2**

***N*-(4-(1*H*-benzo[d]imidazol-2-yl)-1,2,5-oxadiazol-3-yl)-2-fluorobenzamide (2a).**

4-(1*H*-benzo[*d*]imidazol-2-yl)-1,2,5-oxadiazol-3-amine[1] (100 mg, 0.497 mmol) in THF (3 mL) at 0 ˚C was treated with Hunig's base (175 µL, 0.994 mmol) and 2-fluorobenzoyl chloride (120 µL, 0.994 mmol). The reaction mixture was kept stirring at rt for 4h until most of the starting material disappeared according to LC-MS. Potassium hydroxide (1.2 eq, 32 mg) in methanol (1 mL) was added to the above mixture. It was kept at rt for overnight, quenched by pouring into water (5 mL), exacted with EtOAc (3 x 5 mL), dried over Na_2SO_4, and evaporated. After evaporation of the solvent a white solid was formed, which was filtered and washed with ether to provide the product **2a** (110 mg, 69%) as a white solid.

(-)-ESI-MS (*m/z*) $[M - H]^-$: = 322.0).

^{1}H NMR: (600 MHz, DMSO-d_6, δ): 14.01 (br s, 1H), 11.93 (br s, 1H), 8.08 (t, *J* = 7.8 Hz, 1H), 7.78-7.76 (m, 2H), 7.70 (br s, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.37 (br s, 2H).

Ethyl 2-(2-(4-(2-fluorobenzamido)-1,2,5-oxadiazol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (2).

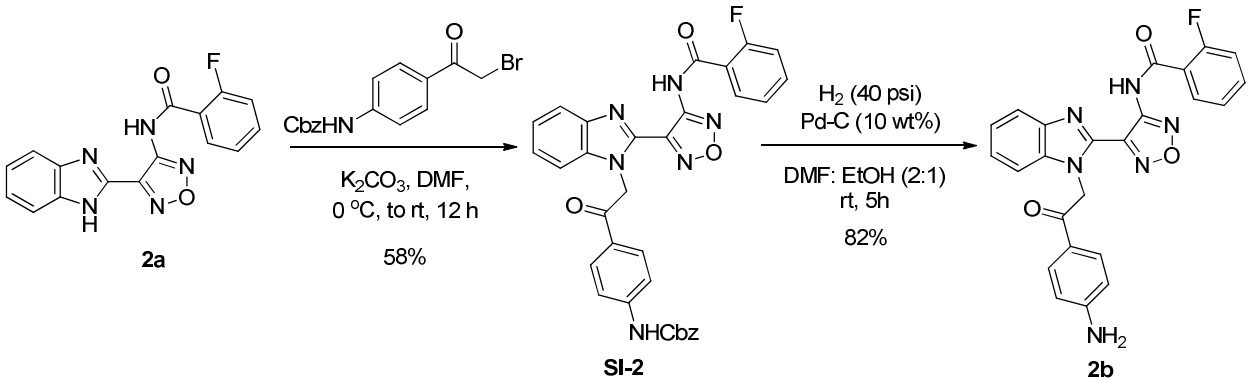
To a stirred mixture of **2a** (50 mg, 0.155 mmol) and potassium carbonate (22 mg, 0.163 mmol) in DMF (1.0 mL) at 0 °C was added ethyl 2-bromoacetate (20 µL, 0.185 mmol). After stirring at room temperature for 12 h, the mixture was diluted with EtOAc, and the organic layer was

washed with water and brine, dried over Na_2SO_4, filtered and concentrated. Chromatographic purification of the crude product using 10% Et_2O in CH_2Cl_2 provided **2** (45 mg, 73%) as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 410.1; (-)-ESI-MS (*m/z*) $[M - H]^-$: 408.0.

^{1}H NMR (300 MHz, $CDCl_3$, δ): 12.28 (d, *J* = 10.5 Hz, 1H), 8.31 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.48-7.32 (m, 5H), 5.46 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

Synthesis of *N*-(4-(1-(2-(4-aminophenyl)-2-oxoethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1,2,5-oxadiazol-3-yl)-2-fluorobenzamide (2b):



Benzyl (4-(2-(2-(4-(2-fluorobenzamido)-1,2,5-oxadiazol-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetyl)phenyl)carbamate (SI-2).

To a stirred mixture of **2a** (55 mg, 0.17 mmol) and potassium carbonate (25 mg, 0.178 mmol) in DMF (1.5 mL) at 0 °C was added benzyl (4-(2-bromoacetyl)phenyl)carbamate[1] (83 mg, 0.238 mmol). After stirring at room temperature for 12 h, the mixture was diluted with water, and a white solid was formed. The solid was filtered and washed successively with water and ether to provide the product **SI-2** (60 mg, 59%) as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: = 591.1).

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 12.17 (d, *J* = 8.4 Hz, 1H), 10.33 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 3H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.78-7.75 (m, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46-7.34 (m, 7H), 6.34 (s, 2H), 5.18 (s, 2H).

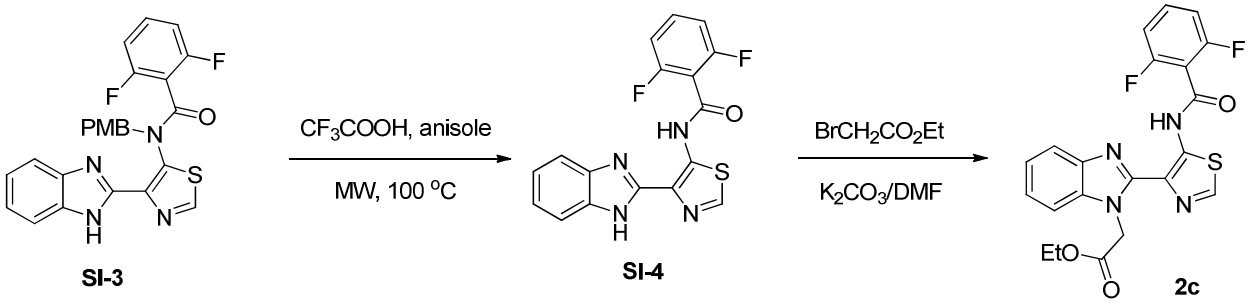
***N*-(4-(1-(2-(4-Aminophenyl)-2-oxoethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1,2,5-oxadiazol-3-yl)-2-fluorobenzamide (2b).**

10% palladium on carbon (10 mg) was added to a solution of **SI-2** (55 mg, 0.094 mmol) in DMF (4 mL) and EtOH (2 mL). The mixture was stirred under a hydrogen atmosphere for 5 h and then filtered through Celite and washed with EtOAc. The filtrate was quickly partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The crude material was triturated with Et_2O, filtered, and washed with ether to give **2b** (35 mg, 82%) as an off-white solid.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 12.21 (d, *J* = 8.4 Hz, 1H), 8.08 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.85-7.76 (m, 5H), 7.54 (dd, *J* = 8.4, 11.8 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.42-7.41 (m, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 2H), 6.18 (s, 2H).

LC-MS: 1.31 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 457.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 455.0. (>95% total peak area at 254 nm).

Synthesis of ethyl 2-(2-(5-(2,6-difluorobenzamido)thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (2c):



SI-3 **SI-4** **2c**

Scheme S2. Synthetic route of compound **2c**

***N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)thiazol-5-yl)-2,6-difluorobenzamide (SI-4).**

A solution of *N*-(4-(1*H*-benzo[*d*]imidazol-2-yl)thiazol-5-yl)-2,6-difluoro-*N*-(4-methoxybenzyl)benzamide,[2] **SI-3** (0.5 mmol, 238 mg) in trifluoroacetic acid (2 mL) and anisole (0.2mL) was heated at 100 °C (80 W) in a microwave synthesizer for 12 min. The solvent was removed. Dichloromethane was added and evaporated again to obtain a light gray crude product, which was suspended in dichloromethane. The solids were collected by filtration to give a first batch of product (135.8 mg, 90% purity). The second batch of product remained in solution, which was purified by BiotageSP4 column (Hex/EtOAc=3:1) to obtain a white solid product **SI-4** (60.1 mg).

(+)-ESI-MS (*m/z*) $[M + H]^+$: 357.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 355.0.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.49 (s, 1H), 7.62-7.52 (m, 4H), 7.32-7.28 (m, 2H), 7.12 (t, *J* = 8.4 Hz, 2H).

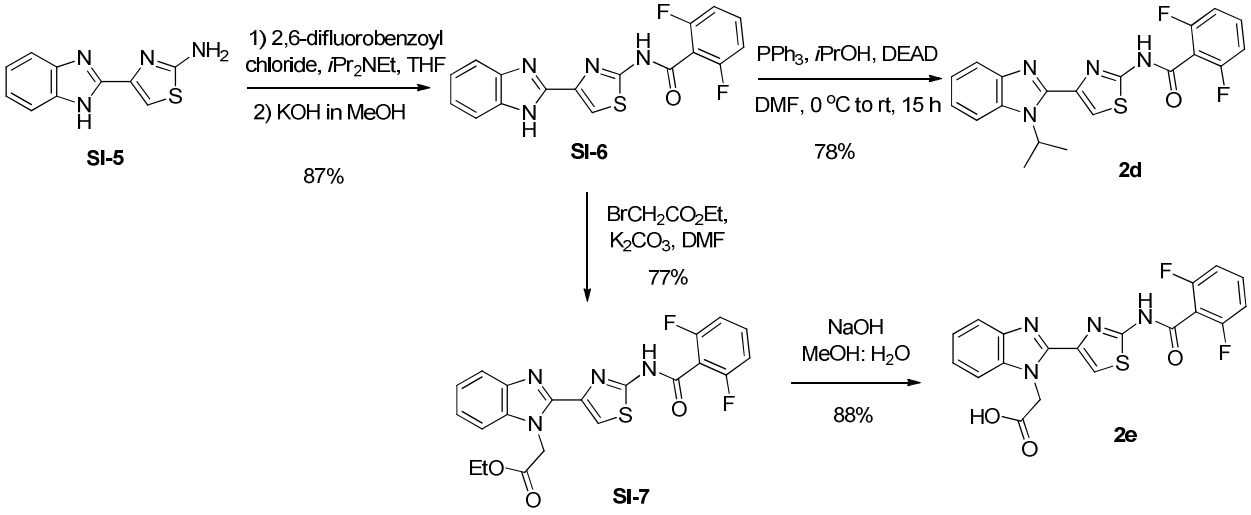
Ethyl 2-(2-(5-(2,6-difluorobenzamido)thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (2c).

Ethyl 2-bromoacetate (0.21 mmol, 23 μL) was added to a mixture of **SI-4**, (0.2 mmol, 71 mg) and K_2CO_3 (1.2 eq, 33mg) in DMF (3 mL) at rt. The reaction mixture was kept stirring at rt overnight, quenched by pouring into water, and extracted with EtOAc, dried over $MgSO_4$, and purified by BiotageSP4 chromatography (Hex:EtOAc=2:1) to obtain product **2c** as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 443.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 441.0.

^{1}H NMR (400 MHz, $CDCl_3$, δ):9.91 (s, 1H), 8.44 (s, 1H), 7.71-7.69 (m, 1H), 7.56-7.50 (m, 1H), 7.34-7.28 (m, 3H), 7.12 (t, *J* =8.4 Hz, 2H), 5.66 (s, 2H), 4.22 (q, *J* = 6.8 Hz, 2H), 1.23 (t, *J* = 6.8 Hz, 3H).

Synthesis of 2,6-difluoro-*N*-(4-(1-isopropyl-1*H*-benzo[*d*]imidazol-2-yl)thiazol-2-yl)benzamide (2d) and 2-(2-(2-(2,6-difluorobenzamido)thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetic acid (2e):



Scheme S3. Synthetic route of compounds **2d** and **2e**

***N*-(4-(1*H*-Benzo[*d*]imidazol-2-yl)thiazol-2-yl)-2,6-difluorobenzamide (SI-6).**

Following the same procedure as for the preparation of **2a**, using 4-(1*H*-benzo[*d*]imidazol-2-yl)thiazol-2-amine[3] (150 mg, 0.694 mmol) and 2,6-difluorobenzoyl chloride (170 µL, 1.388 mmol) as substrates, and chromatographic purification of crude product eluting with 3-5% MeOH in CH_2Cl_2, **SI-10** (215 mg, 87%) was obtained as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$:= 357.0; (-)-ESI-MS (*m/z*) $[M - H]^-$:= 355.0.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 13.17 (s, 1H), 12.64 (s, 1H), 8.01 (s, 1H), 7.63 (t, *J* = 6.8 Hz, 2H), 7.51 (d, *J* = 5.6 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.19 (br s, 2H).

2,6-difluoro-*N*-(4-(1-isopropyl-1*H*-benzo[*d*]imidazol-2-yl)thiazol-2-yl)benzamide (2d).

To a stirred solution of **SI-10** (75 mg, 0.287 mmol) and isopropanol (27 µL, 0.359 mmol) in THF (3.0 mL) at 0 ^{o}C, was added slowly diethyl azodicarboxylate (40 wt% solution in toluene; 163 µL, 0.359 mmol). The reaction mixture was stirred at room temperature for 12 h, before water was added to quench the reaction. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatographic purification of the crude product using 30-35% EtOAc in hexanes provided **2d** (75 mg, 79%) as a white solid.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 7.65 (br s, 3H), 7.50 (dt, *J* = 1.6, 7.2 Hz, 1H), 7.28 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 2H), 5.91-5.82 (m, 1H), 1.61 (d, *J* = 6.8 Hz, 6H).

LC-MS: 1.16 min (80-95% MeOH in 0.1% ammonium formate solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 399.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 397.0. (>99% total peak area at 254 nm).

Ethyl 2-(2-(2-(2,6-difluorobenzamido)thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (SI-7).

Following the same procedure as for the preparation of **2**, using **SI-6** (50 mg, 0.14 mmol) as substrate, and chromatographic purification of the crude product eluting with 20-30% Et_2O in CH_2Cl_2, **SI-7** (48 mg, 77%) was obtained as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 443.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 441.0.

^{1}H NMR (400 MHz, $CDCl_3$); *δ* 9.87 (br s, 1 H), 8.00 (s, 1H), 7.78-7.62 (br m, 2H), 7.50 (dt, *J* = 1.6, 7.7 Hz, 1H), 7.27 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 4.87 (s, 2H), 4.10 (q, *J* = 6.8 Hz, 2H), 1.11 (t, *J* = 6.8 Hz, 3H).

2-(2-(2-(2,6-Difluorobenzamido)thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetic acid (2e).

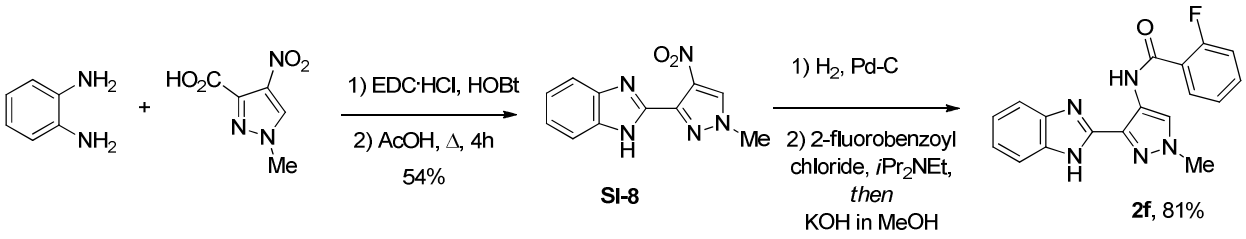
To a stirred mixture of **SI-7** (40 mg, 0.09 mmol) in MeOH: H_2O (v/v 1:1, 1.5 mL) was added sodium hydroxide (5 mg, 0.11 mmol). After stirring at room temperature for 12 h, the mixture was concentrated and neutralized with 1N HCl to pH ~4-5. Then the product was precipitated as

a white solid which was filtered and washed successively with water and ether, and dried to provide the acid **2e** (33 mg, 88%) as a white solid.

^{1}H NMR: (600 MHz, DMSO-d_6, δ): 8.11 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.58 (br s, 2H), 7.35 (t, J = 8.4 Hz, 2H), 7.20 (br s, 2H), 5.06 (br s, 2H).

LC-MS: 0.70 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 415.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 413.0. (>97% total peak area at 254 nm).

Synthesis of *N*-(3-(1*H*-benzo[*d*]imidazol-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-fluorobenzamide (2g):



Scheme S4. Synthetic route of compound **2f**

2-(1-Methyl-4-nitro-1*H*-pyrazol-3-yl)-1H-benzo[*d*]imidazole (SI-8).

To a stirred solution of 1-methyl-4-nitro-1*H*-pyrazole-3-carboxylic acid (240 mg, 1.4 mmol), benzene-1,2-diamine (165 mg, 1.54 mmol) and HOBt (210 mg, 1.54 mmol) in DMF (5 mL) at 0 ˚C was added EDCI (295 mg, 1.54 mmol). After stirring at room temperature for 24 h, the mixture was diluted with EtOAc, and washed with saturated $NaHCO_3$ solution and then brine. The organic portion was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude residue was dissolved in AcOH (4 mL) and heated at reflux for 3 h. The solvent was removed in *vacuo* and the mixture was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic portion was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to obtain **SI-8** (185 mg, 54%) as a yellow solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 244.0.

^{1}H NMR: (600 MHz, DMSO-d_6, δ): 12.89 (s, 1H), 9.01 (s, 1H), 7.68-1.66 (m, 1H), 7.56-7.54 (m, 1H), 7.25-7.22 (m, 2H), 3.99 (s, 3H).

***N*-(3-(1*H*-benzo[*d*]imidazol-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-fluorobenzamide (2f).**

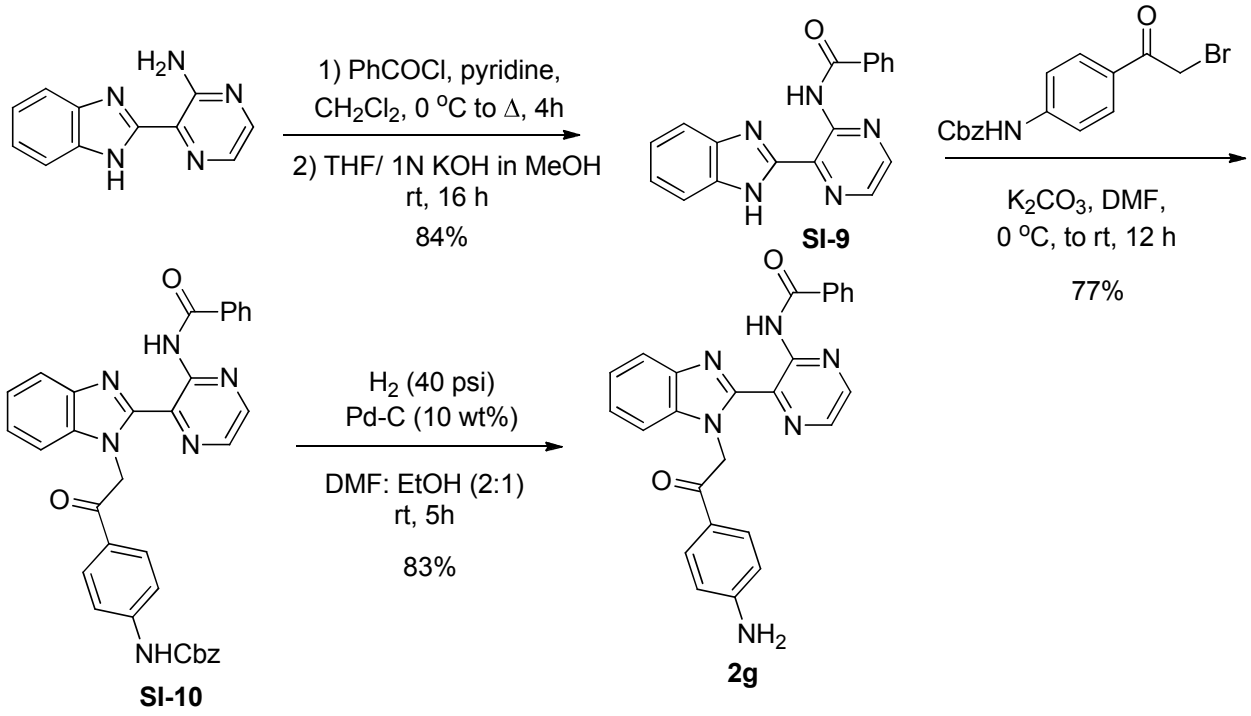
10% Pd/C (30 mg) was added to a solution of **SI-8** (125 mg, 0.51 mmol) in MeOH:EtOAc (v/v 2:1, 6 mL) and the mixture was exposed to hydrogen at 40 psi for 2 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated to give 3-(1*H*-benzo[*d*]imidazol-2-yl)-1-methyl-1*H*-pyrazol-4-amine, which was taken to the next step without further purification.

Following the same procedure as for the preparation of **2a**, using 3-(1*H*-benzo[*d*]imidazol-2-yl)-1-methyl-1*H*-pyrazol-4-amine (110 mg, 0.51 mmol) as substrate, and chromatographic purification of the crude product eluting with 3-5% MeOH in CH_2Cl_2, **2f** (140 mg, 81%) was obtained as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 336.1; (-)-ESI-MS (*m/z*) $[M - H]^-$: 334.0.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 13.08 (s, 1H), 11.57 (d, *J* = 8.8 Hz, 1H), 8.50 (s, 1H), 8.07 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.61 (m, 1H), 7.52-7.41 (m, 3H), 7.21 (dd, *J* = 1.6, 5.6 Hz, 2H), 4.0 (s, 3H).

Synthesis of *N*-(3-(1-(2-(4-aminophenyl)-2-oxoethyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrazin-2-yl)benzamide (2g):



Scheme S5. Synthetic route of compound **2g**

***N*-(3-(1*H*-benzo[*d*]imidazol-2-yl)pyrazin-2-yl)benzamide (SI-9).**

Pyridine (190 µL, 2.35 mmol) and benzoyl chloride (140 µL, 1.18 mmol) were successively added at 0 °C to a stirred solution of 3-(1*H*-benzo[*d*]imidazol-2-yl)pyrazin-2-amine[4] (50 mg, 0.237 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was heated at 40 °C for 4h, and then cooled down to room temperature. The reaction mixture was quenched with water, partitioned between CH_2Cl_2 and water, and separated. The organic layer was dried over Na_2SO_4. After evaporation of the solvent a crude mixture of amides was obtained. After the crude material was dissolved in THF (3 mL), 1.0 mL of 1 N KOH/ MeOH solution was added and the mixture stirred at room temperature for a further 16 h. The mixture was partitioned between EtOAc and water. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated. The crude material was triturated with Et_2O, filtered, and washed with ether to give **SI-9** (63 mg, 85%) as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 316.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 314.0.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 13.62 (s, 1H), 13.59 (s, 1H), 8.55 (d, *J* = 1.6 Hz, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.22-8.20 (m, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.70-7.67 (m, 3H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.35-7.29 (m, 2H).

Benzyl (4-(2-(2-(3-benzamidopyrazin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)acetyl)phenyl)carbamate (SI-10).

Following the same procedure as for the preparation of **SI-2**, using **SI-9** (60 mg, 0.19 mmol) as substrate, **SI-10** (85 mg, 77%) was obtained as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 583.1; (-)-ESI-MS (*m/z*) $[M - H]^-$: 581.0.

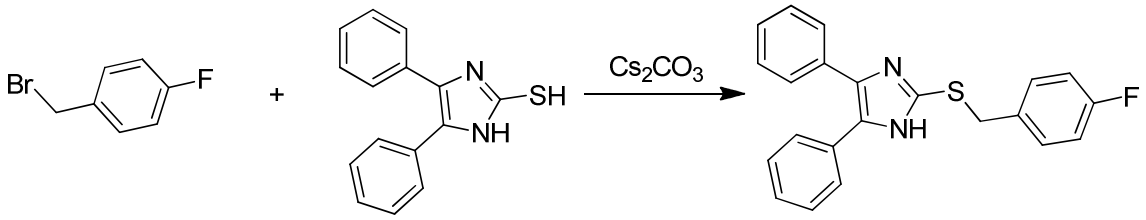
^{1}H NMR: (400 MHz, DMSO-d_6, δ): 13.83 (s, 1H), 10.28 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 8.04-7.99 (m, 3H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.70-7.65 (m, 6H), 7.41-7.33 (m, 7H), 6.32 (s, 2H), 5.17 (s, 2H).

***N*-(3-(1-(2-(4-aminophenyl)-2-oxoethyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrazin-2-yl)benzamide (2g).**

Following the same procedure as for the preparation of **2b**, using **SI-10** (55 mg, 0.094 mmol) as substrate, **2g** (35 mg, 83%) was obtained as a light yellow solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$: 449.1; (-)-ESI-MS (*m/z*) $[M - H]^-$: 447.0.

^{1}H NMR: (400 MHz, DMSO-d_6, δ): 13.88 (s, 1H), 8.41 (s, 1H), 8.16 (s, 2H), 8.09 (s, 1H), 7.83-7.81 (m, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.70-7.68 (m, 4H), 7.38-7.37 (m, 2H), 6.61 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 2H), 6.18 (s, 2H).



9 **10a**

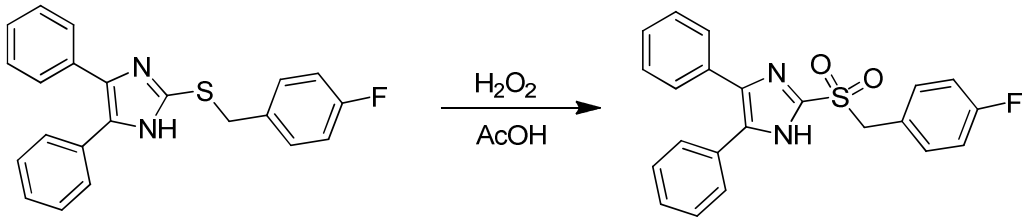
2-(4-fluorobenzylthio)-4,5-diphenyl-1*H*-imidazole (10a).

4,5-diphenyl-1H-imidazole-2-thiol (2.00 g, 7.93 mmol) was dissolved in anhydrous DMF (10 mL), and cesium carbonate (3.10 g, 9.51 mmol) was added to this solution, followed by 4-fluorobenzylbromide (1.03 mL, 8.32 mmol). The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was poured into ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was dried under high vacuum and used without further purification to give 2.84 g (99% yield) of a white solid. An analytical/biological sample was recrystallized from 80% ethanol.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.46-7.09 (m, 15H), 4.36 (2H).

LC-MS: 1.31 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 361.2; (-)-ESI-MS (*m/z*) $[M - H]^-$: 359.0. (>98% total peak area at 254 nm)

HR-ESIMS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{18}N_2F^{32}S$, 361.11693; found, 361.11748.



10a **11a**

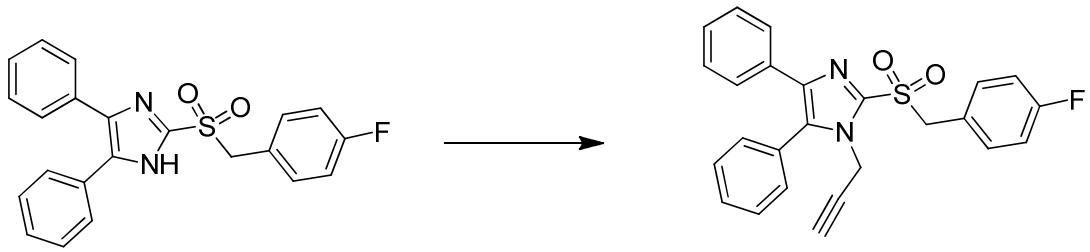
2-(4-fluorobenzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (11a).

2-(4-fluorobenzylthio)-4,5-diphenyl-1H-imidazole (1.86 g, 5.16 mmol) was dissolved in glacial AcOH (10 mL) and 30% aqueous hydrogen peroxide (7.9 mL, 77 mmol) was added to this solution. The solution was stirred at room temperature overnight, and was monitored by LC-MS. The mixture was poured into 100 mL EtOAc and then 100 mL water was added. The organic layer was separated and removed. The aqueous layer was extracted with 2 x 50 mL EtOAc, and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated to give 2.01 g (99% yield) of an off-white solid, which was used without further purification. (Adapted from Guravaiah, et al.[5])

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.46-7.12 (m, 15H), 4.85 (s, 2H).

LC-MS: 1.55 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 393.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 391.0. (93.2% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{18}FO_2N_2{}^{32}S$, 393.10675; found, 393.10754.



11a **3**

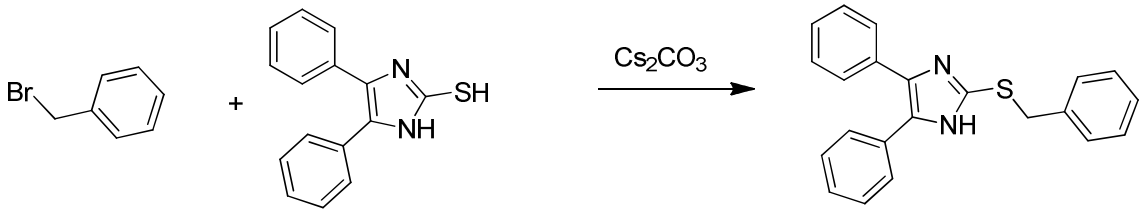
2-((4-fluorobenzyl)sulfonyl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-1*H*-imidazole (3).

In a 100 mL round-bottomed flask under Ar, 2-(4-fluorobenzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (150 mg, 0.382 mmol) was dissolved in 1 mL dry DMF, and cesium carbonate (149 mg, 0.459 mmol) was added to this solution. The reaction mixture was stirred for 5 min at room temperature, and propargyl bromide (62.5 mg, 0.420 mmol, 80 wt.% in toluene) was added. The reaction mixture was stirred for 20 hours at room temperature. The reaction mixture was then poured into 25 mL EtOAc, and washed with 25 mL water, followed by 25 mL brine. The organic layer was dried over MgSO4, filtered, and concentrated. The compound was purified by silica gel column chromatography (0 to 25% EtOAc in hexanes; 12 g column; R_f = in 25% EtOAc

= 0.36; 9 mL fractions). Evaporation of fractions 71-76 gave 50 mg (30% yield) of thin white crystals upon slow evaporation from ether.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.54-7.46 (m, 5H), 7.39-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 3H), 7.06-7.02 (m, 2H), 4.76 (s, 2H), 4.62 (d, *J* = 2.8 Hz, 2H), 2.30 (t, *J* = 2.4 Hz, 1H).

LC-MS: 1.37 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 431.1; (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak. (>98% total peak area at 254 nm)



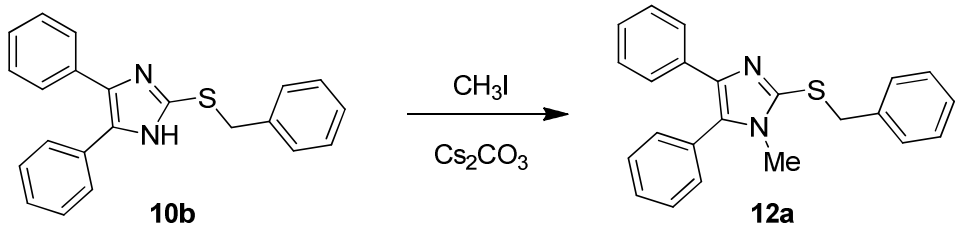
9 **10b**

2-(benzylthio)-4,5-diphenyl-1*H*-imidazole (10b).

4,5-diphenyl-1*H*-imidazole-2-thiol (2.00 g, 7.93 mmol) was dissolved in anhydrous DMF (10 mL), and cesium carbonate (3.10 g, 9.51 mmol) was added to this solution, followed by benzyl bromide (0.99 mL, 8.32 mmol). The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was poured into ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was dried under high vacuum and used without further purification to give 2.65 g (98% yield) of a white solid.

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.48-7.18 (m, 16H), 4.37 (s, 2H).

LC-MS: 1.10 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 343.2; (-)-ESI-MS (*m/z*) $[M - H]^-$: 341.2. (single peak at 254 nm)



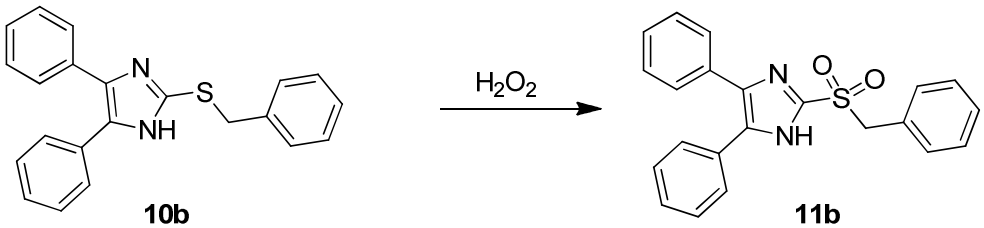
10b **12a**

2-(benzylthio)-1-methyl-4,5-diphenyl-1*H*-imidazole (12a).

2-(benzylthio)-4,5-diphenyl-1*H*-imidazole (991 mg, 2.89 mmol) was dissolved in 5 mL dry THF, and cesium carbonate (1037 mg, 3.18 mmol) was added to the solution. The mixture was allowed to stir at rt for 30 min, and iodomethane (452 mg, 3.18 mmol) was added. The mixture was stirred overnight at room temperature, and the resulting product was poured into 100 mL EtOAc, and washed once with 100 mL water and once with 50 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oil which was purified by silica gel column chromatography (0 to 25% EtOAc in hexanes; R_f = 0.60 in 50%) to give 695 mg (67%yield) of white crystals after crystallization from an ether solution.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.53-7.50 (m, 2H), 7.45-7.41 (m, 3H), 7.29-7.15 (m, 9H), 4.27 (s, 2H), 3.00 (s, 3H).

LC-MS: 2.09 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 357.2; (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak. (>98% total peak area at 254 nm)



10b **11b**

2-(benzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (11b).

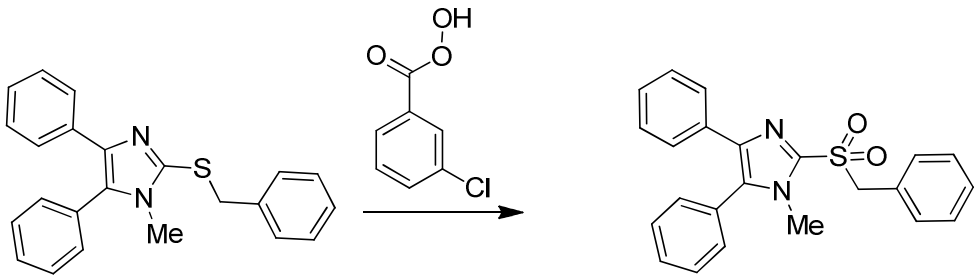
2-(benzylthio)-4,5-diphenyl-1*H*-imidazole (1.83 g, 5.34 mmol) was dissolved in glacial AcOH (10 mL) and 30% aqueous hydrogen peroxide (8.2 mL, 80 mmol) was added to this solution. The solution was stirred at room temperature for four days. The mixture was poured into 100 mL EtOAc and then 100 mL water was added. The organic layer was separated and removed. The

aqueous layer was extracted with 2 x 50 mL EtOAc, and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give 1.94 g (97% yield) of a white solid. (Adapted from Guravaiah, et al. [5])

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.41-7.30 (m, 14H), 7.24-7.20 (m, 2H), 4.84 (s, 2H).

LC-MS: 1.43 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 375.0; (-)-ESI-MS (*m/z*) $[M - H]^-$: 373.0. (98% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{19}O_2N_2{}^{32}S$, 375.11618; found, 375.11682.



12a **13b**

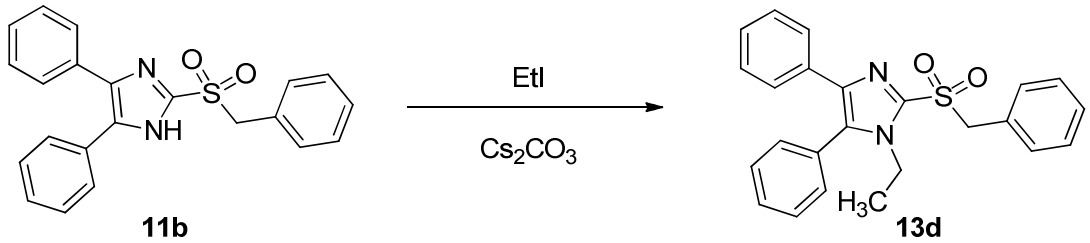
2-(benzylsulfonyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (13b).

2-(benzylthio)-1-methyl-4,5-diphenyl-1*H*-imidazole (643 mg, 1.80 mmol) was dissolved in 10 mL dry CH_2Cl_2, and the solution was cooled to 0 °C. *m*-Chloroperoxybenzoic acid (913 mg, 3.97 mmol, 75 wt.%) was added to this solution in one portion, and the cooling bath was removed. The mixture was stirred overnight at room temperature, and the reaction mixture was poured into 50 mL 15% Na_2CO_3 and 75 mL DCM. The organic layer was removed and washed with brine solution, dried over $MgSO_4$, filtered, and concentrated to give a white foam. This was further purified by column chromatography (0 to 35% EtOAc in hexanes; 25 g column; R_f = 0.56 in 50% EtOAc). Evaporation of fractions 26-30 gave 657 mg (94% yield) of white needles.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.51-7.45 (m, 5H), 7.40-7.32 (m, 3H), 7.26-7.17 (m, 7 H), 4.71 (s, 2H), 3.07 (s, 3H).

LC-MS: 1.77 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 389.0 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (>98% total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{21}O_2N_3{}^{32}S$, 389.13183; found, 389.13169.



11b **13d**

2-(benzylsulfonyl)-1-ethyl-4,5-diphenyl-1*H*-imidazole (13d).

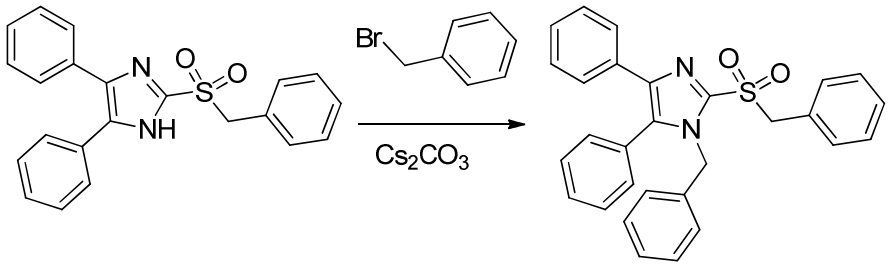
2-(benzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (150 mg, 0.401 mmol) was dissolved in *N,N*-dimethylacetamide (2 mL) in a microwave vial, and cesium carbonate (261 mg, 0.801 mmol) and iodoethane (125 mg, 0.801 mmol) were added to this solution. The vial was sealed, and the mixture was heated at 140 °C for one hour. The mixture was dissolved in 25 mL EtOAc and washed with 3 x 15 mL water and 25 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a dark residue. The residue was purified using silica gel column chromatography (0 to 40% EtOAc in hexanes, 4 g silica column, R_f = 0.37 in 25% EtOAc in hexanes). Evaporation of fractions 64-70 gave a white solid, which was further purified by recrystallization from ether/hexanes to give 84 mg (52% yield) of a white powder.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.49-7.45 (m, 5H), 7.36-7.29 (m, 3 H), 7.24-7.18 (m, 7H), 4.75 (s, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$, δ): 139.9, 139.3, 133.2, 132.8, 131.5, 131.0, 129.9, 129.6, 129.4, 129.3, 128.9, 128.5, 127.7, 127.5, 127.1, 62.4, 40.7, 16.9.

LC-MS: 1.63 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 403.1 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak. (93.4% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{23}O_2N_3{}^{32}S$, 403.14748; found, 403.14748.



11b **13e**

1-benzyl-2-(benzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (13e).

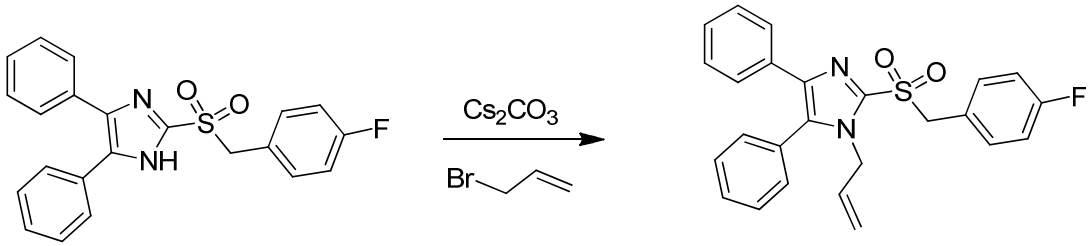
In a 100 mL RB flask under Ar, 2-(benzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (100 mg, 0.267 mmol) was dissolved in 1 mL dry DMF, and cesium carbonate (104 mg, 0.320 mmol) was added to this solution. The reaction mixture was stirred for 5 min at room temperature and benzyl bromide (31.8 µL, 0.267 mmol) was added. The reaction mixture was stirred for 20 hours at room temperature. The reaction mixture was diluted with 50 mL EtOAc and washed with 50 mL water and then 25 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The compound was purified using silica gel column chromatography (0 to 25% EtOAc in hexanes; R_f = 0.63 in 50% EtOAc). Evaporation of fractions 28-34 gave 73 mg (58% yield) of a clear colorless oil.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.51-7.48 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.43-7.31 (m, 7H), 7.26-7.19 (m, 5H), 7.16-7.08 (m, 4H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.93 (s, 2H), 4.64 (2H).

^{13}C NMR: (100 MHz, $CDCl_3$, δ): 140.7, 139.6, 136.3, 133.5, 133.1, 131.6, 131.1, 129.8, 129.4, 129.3, 129.1, 129.0, 128.7, 128.5, 127.8, 127.6, 127.4, 127.2, 126.9, 62.2, 48.8.

LC-MS: 0.68 min (95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 465.3; (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak. (>98% total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{25}O_2N_2{}^{32}S$, 465.16313; found, 465.16290.



11a **13f**

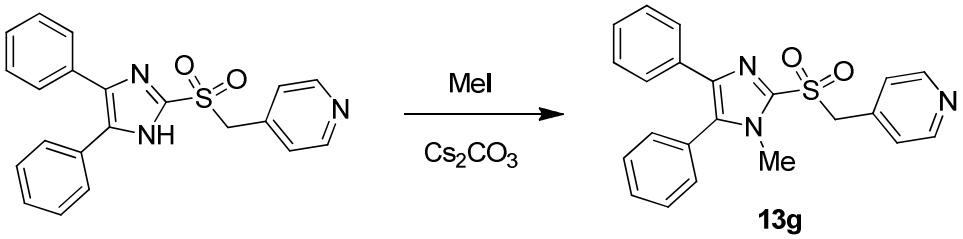
1-allyl-2-((4-fluorobenzyl)sulfonyl)-4,5-diphenyl-1*H*-imidazole (13f).

In a 100 mL round-bottomed flask under argon, 2-(4-fluorobenzylsulfonyl)-4,5-diphenyl-1*H*-imidazole (150 mg, 0.382 mmol) was dissolved in 1 mL dry DMF, followed by cesium carbonate (149 mg, 0.459 mmol). The reaction mixture was stirred for 5 min at room temperature and allyl bromide (36.4 µL, 0.420 mmol) was added and stirred for 20 hours at room temperature. The reaction mixture was poured into 25 mL EtOAc, and washed with 25 mL water and 25 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The compound was purified by silica gel column chromatography (0 to 40% EtOAc in hexanes; 4 g silica column; R_f = 0.33 in 25% EtOAc in hexanes). The oil resulting from concentration of fractions 5-13 was further purified by recrystallization from an ether/hexanes mixture to give 70 mg (42% yield) of small white needles.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.50-7.45 (m, 5H), 7.30-7.21 (m, 7H), 7.04 (t, *J* = 8.8 Hz, 2H), 5.59 (dddd, *J* = 22, 16, 10, 5.2 Hz, 1H), 5.01 (d, *J* = 10 Hz, 1H), 4.76 (s, 2H), 4.67 (d, *J* = 17 Hz, 1H), 4.39 (d, *J* = 5.2 Hz, 2H).

LC-MS: 1.71 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 433.1; (-)-ESI-MS (*m/z*) no peak. (92% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{22}O_2N_2F^{32}S$, 433.13805; found, 433.13783.



13g

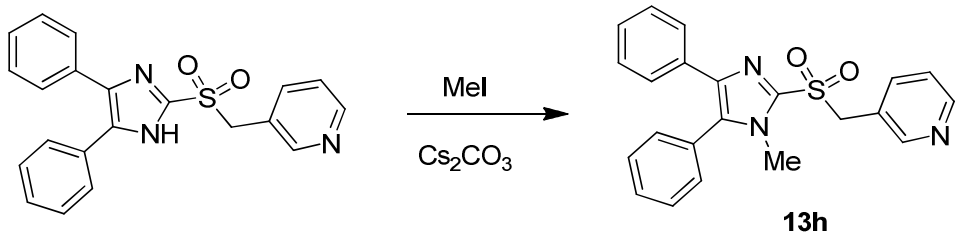
4-(((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)sulfonyl)methyl)pyridine (13g).

In a 50 mL round-bottomed flask, 4-(((4,5-diphenyl-1*H*-imidazol-2-yl)sulfonyl)methyl)pyridine (344 mg, 0.916 mmol) and cesium carbonate (328 mg, 1.00 mmol) were dissolved in 3 mL DMF, and cooled to 0 °C. Iodomethane (63 µL, 1.00 mmol) was added to this solution, and the solution was allowed to warm to room temperature. The mixture was stirred overnight at room temperature, and the resulting product was poured into 50 mL CH_2Cl_2, and washed once with 50 mL water and once with 50 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated, to give a solid. The product was purified using silica gel column chromatography (0 to 5% MeOH in CH_2Cl_2). The fractions containing product were concentrated to give an off-white foam. The compound was further purified by recrystallization from $CHCl_3$ to give 90 mg (25% yield) of thin white flakes.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.61 (dd, *J* = 4.4, 1.2 Hz, 2H), 7.59-7.55 (m, 3H), 7.49-7.45 (m, 2H), 7.43-7.38 (m, 2H), 7.34 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.27-7.21 (m, 3H), 4.93 (s, 2H), 3.35 (s, 3H).

LC-MS: 1.18 min (70-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 390.1 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (>98% total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{20}O_2N_3{}^{32}S$, 390.12707; found, 390.12698.



13h

3-(((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)sulfonyl)methyl)pyridine (13h).

In a 50 mL round-bottomed flask, 3-(((4,5-diphenyl-1*H*-imidazol-2-yl)sulfonyl)methyl)pyridine (940 mg, 2.50 mmol) and cesium carbonate (897 mg, 2.75 mmol) were dissolved in 3 mL DMF and cooled to 0 °C. Iodomethane (172 µL, 2.75 mmol) was added to this solution, and the solution was allowed to warm to room temperature. The mixture was stirred overnight at room

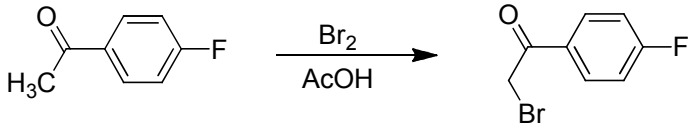
temperature, and the resulting product was poured into 50 mL CH_2Cl_2, and washed once with 50 mL water and once with 50 mL brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a solid. The compound was purified using 0 to 5% MeOH in CH_2Cl_2 (40g column). Fractions 7-11 were condensed to give 510 mg (52% yield) of the title compound as an off-white foam. The compound was further purified by recrystallization from $CHCl_3$.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.63 (d, *J* = 4.4 Hz, 1H), 8.49 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.49-7.44 (m, 5H), 7.31 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 7.26-7.19 (m, 5H), 4.80 (s, 2H), 3.30 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$, δ):151.8, 150.1, 140.1, 139.0, 138.8, 133.6, 132.8, 130.7, 129.7, 129.3, 128.6, 128.3, 127.5, 127.3, 127.0, 123.9, 123.5, 59.0, 32.5.

LC-MS: 1.21 min (70-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 390.1 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (>98% total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{20}O_2N_3{}^{32}S$, 390.12707; found, 390.12683.



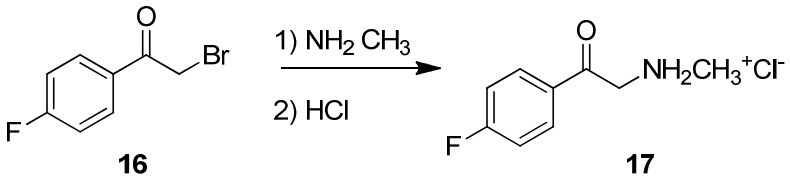
15 **16**

2-bromo-1-(4-fluorophenyl)ethanone (16).

4'-fluoroacetophenone (8.75 mL, 72.4 mmol) was dissolved in glacial acetic acid (70 mL), and bromine (3.73 mL, 72.4 mmol) was added to this solution dropwise. The solution was stirred at room temperature for 0.5 hr, and then water (5 mL) and acetone (15 mL) were added, and mixture was stirred overnight. The solvents were removed under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated $NaHCO_3$. The organic layer was concentrated, and 15.3 g (97% yield) of the compound was obtained as a yellow solid, that was ca. 90% pure by NMR. This was further recrystallized from ether/hexanes to give, after standing in the fume hood, large diamond-shape crystals. (Adapted from Ridge, et al.[6])

^{1}H NMR: (400 MHz, $CDCl_3$, δ):7.99-7.94 (m, 2H), 7.13-7.07 (m, 2H), 4.39 (s, 2H).

^{13}C NMR: (100 MHz, $CDCl_3$, δ): 190.1, 166.3 (d, $^{1}J_{CF}$ = 250 Hz), 131.9 (d, $^{3}J_{CF}$ = 9.7 Hz), 130.5 (d, $^{4}J_{CF}$ = 3.0 Hz), 116.3 (d, $^{2}J_{CF}$ = 22 Hz), 31.0.



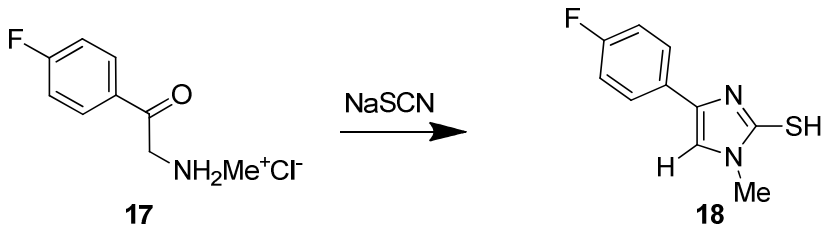
16 **17**

1-(4-fluorophenyl)-2-(methylamino)ethanone hydrochloride (17).

A solution of methylamine (1.8 M in MeOH, 37.3 mL, 67.2 mmol) was dissolved in 45 mL dry CH_2Cl_2 and cooled to 0 °C. A solution of 2-bromo-1-(4-fluorophenyl)ethanone (5.83 g, 26.9 mmol) in 45 mL dry CH_2Cl_2 was added to the stirred, cold solution over 45 minutes. The mixture was stirred at 0 °C for 90 min and poured into ice water (40 mL) and dichloromethane (50 mL). The organic phase was separated in a pre-chilled separatory funnel, and dried over Na_2SO_4 and filtered. The cold organic solution was treated with 1.25 M HCl in MeOH (30 mL). The solvent was evaporated *in vacuo* to give a viscous dark red product, which was triturated with 25 mL acetone. The product salt (3.20 g, 59% yield) was obtained as an off-white solid after filtration, washings with ether, and drying under vacuum. (Adapted from Laufer, et al.[7])

^{1}H NMR: (400 MHz, CD_3OD, δ): 8.14-8.09 (m, 2H), 7.35-7.29 (m, 2H), 4.75 (s, 2H), 2.83 (s, 3H).

LC-MS: LC-MS: 0.61 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 168.1 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (87% total peak area at 254 nm)



17 **18**

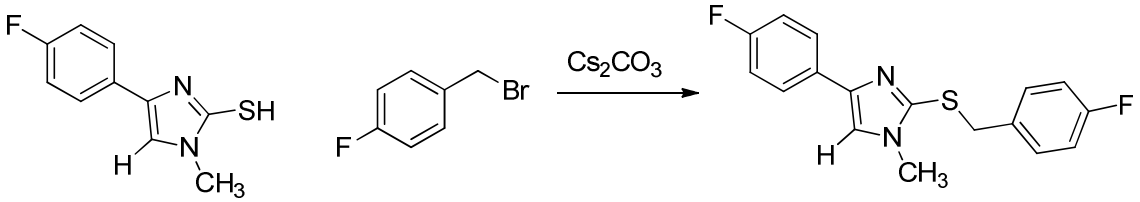
4-(4-fluorophenyl)-1-methyl-1*H*-imidazole-2-thiol (18).

1-(4-fluorophenyl)-2-(methylamino)ethanone hydrochloride (3.0 g, 14.73 mmol) was dissolved in 12 mL dry DMF, and placed in a teflon-capped sealable flask. Sodium thiocyanate (2.508 g, 30.9 mmol) was added to this solution, and the vessel was placed under an argon atmosphere. The reaction mixture was heated to 160 °C for 45 min. The reaction mixture was cooled, and diluted with ice water. The compound did not precipitate out, so a wash was carried out using CH_2Cl_2 (150 mL) and water (3 x 50 mL). The organic extracts were evaporated, without drying or filtering (solid began to crash out of the CH_2Cl_2 layer). The crude compound was triturated with hexanes, filtered, and dried in a vacuum oven overnight to give 2.50 g of an off-white solid. The remaining filtrate was concentrated and dried under high vacuum with a magnetic stir bar. The resulting brown solid (400 mg) was recrystallized by dissolving in a small amount of dichloromethane, and then adding in hot EtOH, which boiled off the dichloromethane, causing the compound to crystallize out in the antisolvent EtOH. This give an additional 190 mg of off-white solid (total: 2.69 g: 88% yield). (Adapted from Laufer, et al.[7])

^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.63 (s, 1H), 7.66-7.62 (m, 2H), 7.53 (d, J = 1.6 Hz, 1H), 7.23-7.18 (m, 2H), 3.44 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6, δ): 162.9, 162.0 (d, $^1J_{CF}$ = 250 Hz), 127.1, 126.6 (d, $^3J_{CF}$ = 8.2 Hz), 125.4 (d, $^4J_{CF}$ = 3.0 Hz), 116.6, 116.6 (d, $^2J_{CF}$ = 22 Hz), 34.3.

LC-MS: 0.72 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 209.0 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (>98% total peak area at 254 nm)



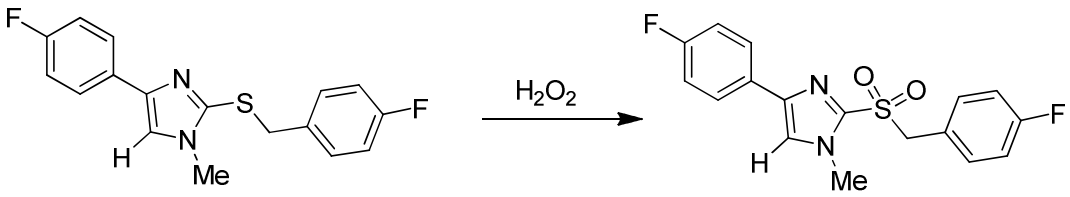
18 **19**

2-((4-fluorobenzyl)thio)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (19).

4-(4-fluorophenyl)-1-methyl-1*H*-imidazole-2-thiol (1.50 g, 7.20 mmol) was dissolved in 10 mL dry THF, and then cesium carbonate (2.347 g, 7.20 mmol) was added to the flask. This was allowed to stir for 20 minutes at room temperature. 4-Fluorobenzyl bromide (1.361 g, 7.20 mmol) was added, and the mixture was stirred at room temperature for 3 hours. The reaction was poured into water (50 mL) and EtOAc (50 mL). The layers were separated, and the organic layer was washed with 2 x 50 mL more water and 1 x 50 mL brine and dried over $MgSO_4$, filtered, and concentrated to give 2.13 g of a tan solid that was used without further purification. (Adapted from Laufer, et al.[7])

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.75-7.71 (m, 2H), 7.16-7.12 (m, 2H), 7.10-7.04 (m, 3H), 6.95-6.91 (m, 2H), 4.19 (s, 2H), 3.31 (s, 3H).

LC-MS: 1.05 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 317.0; (-)-ESI-MS (*m/z*) no peak. (>98% of total peak area at 254 nm)

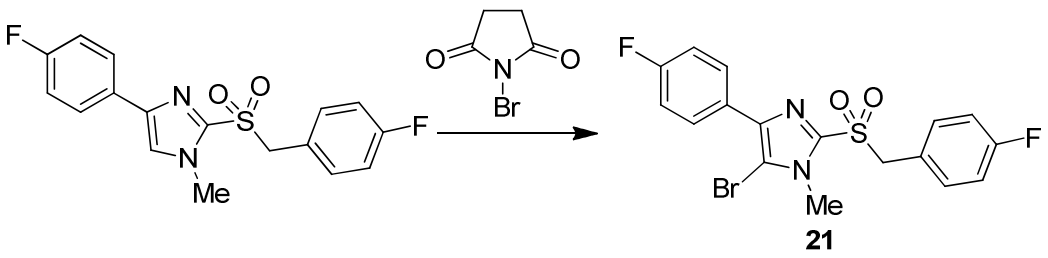


2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole.

2-((4-fluorobenzyl)thio)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (1.63 g, 5.15 mmol) was dissolved in glacial AcOH (10 mL) and 30% hydrogen peroxide solution (7.89 mL, 77 mmol) was added to this solution. The solution was stirred at room temperature overnight, and was monitored by LC-MS. After 18 hours, no sulfone was detected, so another 10 mL H_2O_2 solution was added. After six days, the mixture was filtered and dried to give 1.25 g (69% yield) of pure product.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):7.75-7.71 (m, 2H), 7.12-6.95 (m, 7 H), 4.62 (s, 2H), 3.40 (s, 3H).

LC-MS: 0.91 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 349.0; (-)-ESI-MS (*m/z*) 347.0. (>98% of total peak area at 254 nm)



21

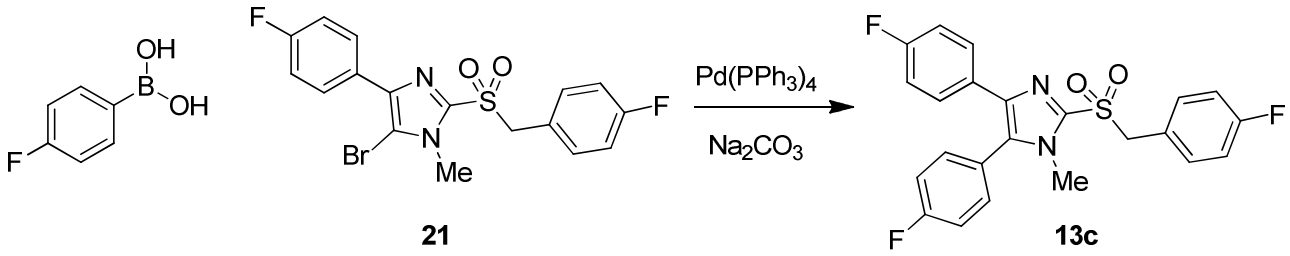
5-bromo-2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (21).

2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (1.10 g, 3.16 mmol) was dissolved in 15 mL CCl_4, and then cooled to 0 °C. Then *N*-bromosuccinimide (0.590 g, 3.32 mmol) was added, and the solution was stirred at 0 °C for 30 min, followed by stirring at RT overnight. The reaction mixture contained <5% product, so it was heated at reflux for 22 hours, at which time the reaction seemed to have stalled at ca. 80% completion (monitored by LC-MS). Another 0.12 g (0.2 eq) of NBS was added, and the reaction was allowed to stir at reflux overnight, (total time at reflux 48 hr) and then was cooled to room temperature. This gave a thick emulsion that was mostly dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated, and then triturated with EtOAc. The solid left behind (300 mg) contained mostly product, with some succinimide byproduct. The filtrate was concentrated and subjected to column chromatography (0 to 25% EtOAc in hexanes to 100% EtOAc).This gave impure product that still had substantial succinimide left with it. This material was combined with the precipitated product from earlier, dissolved in EtOAc, and washed with water. The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated. The compound was recrystallized from boling EtOH, to give 1.08 g (80% yield) of light pink crystals. (Adapted from Laufer, et al.[7])

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.96-7.91 (m, 2H), 7.19-7.09 (m, 4H), 7.04-6.99 (m, 2H), 4.64 (s, 2H), 3.48 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$, δ): 163.5 (d, $^1J_{CF}$ = 250 Hz), 162.9 (d, $^1J_{CF}$ = 250 Hz), 141.5, 139.1, 133.2 (d, $^3J_{CF}$ = 8.2 Hz), 129.2 (d, $^3J_{CF}$ = 8.2 Hz), 128.0, 122.9 (d, $^4J_{CF}$ = 2.9 Hz), 116.2 (d, $^2J_{CF}$ = 22 Hz), 115.7 (d, $^2J_{CF}$ = 22 Hz), 106.8, 61.0, 33.8.

LC-MS: 1.21 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 427.0 (-)-ESI-MS (*m/z*) $[M - H]^-$: no peak (>98% total peak area at 254 nm)



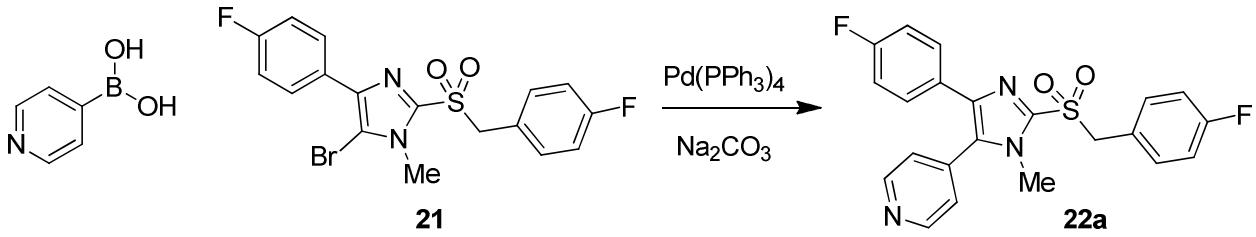
2-((4-fluorobenzyl)sulfonyl)-4,5-bis(4-fluorophenyl)-1-methyl-1*H*-imidazole (13c).

(4-fluorophenyl)boronic acid (105 mg, 0.749 mmol), 5-bromo-2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (200 mg, 0.468 mmol), and tetrakis(triphenylphosphine)palladium(0) (54.1 mg, 0.047 mmol) were added together in a microwave vial, and an atmosphere of argon was established. Toluene (4 mL) and water (0.4 mL) were added to the solids, and the mixture was bubbled with argon. Sodium carbonate (109 mg, 1.030 mmol) was added to the mixture, and the vial was sealed. The sealed vial was stirred at 120 °C for four hours. The solvents were removed under reduced pressure, with an additional co-evaporation with toluene to remove the water. The crude product was adsorbed onto 800 mg of silica gel and purified using silica gel flash column chromatography (12g column, 0 to 35% EtOAc in hexanes, R_f = 0.3 in 25% EtOAc). Evaporation of fractions 53-62 gave 170 mg (82% yield) of a white solid. (Adapted from Laufer, et al.[7])

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.42-7.38 (m, 2H), 7.25-7.20 (m, 2H), 7.18-7.15 (m, 4H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 8.4 Hz, 2H), 4.70 (s, 2H), 3.22 (s, 3H).

LC-MS: 1.35 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 443.0; (-)-ESI-MS (*m/z*) no peak. (>98% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{18}O_2N_2F_3{}^{32}S$, 443.10356; found, 443.10338.



4-(2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)pyridine (22a).

Pyridin-4-ylboronic acid (23 mg, 0.187 mmol), 5-bromo-2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1*H*-imidazole (50 mg, 0.117 mmol), and tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.012 mmol) were added together in a microwave vial, and an atmosphere of argon was established. Toluene (2 mL) and water (0.2 mL) were added to the solids, and the mixture was bubbled with argon. Sodium carbonate (27 mg, 0.257 mmol) was added to the mixture, and the vial was sealed. The sealed vial was stirred at 120 °C for four hours. An additional portion of pyridin-4-ylboronic acid (14 mg, 0.117 mmol) and 0.1tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.012 mmol) was added at this time. The reaction was again heated at 120 °C for four hours. The reaction mixture was poured into 20 mL water and extracted with 3 x 20 mL EtOAc. The organic extracts were combined and washed with brine, and dried over $MgSO_4$, filtered, and adsorbed onto 200 mg of silica gel. The product was purified using silica gel flash column chromatography. (4g silica gel column, 25 to 95% EtOAc in hexanes, R_f = 0.2 in 50% EtOAc). Evaporation of fractions 18-23 gave 20 mg (40% yield) of a white solid. (Adapted from Laufer, et al.[7])

^{1}H NMR: (400 MHz, $CDCl_3$, δ):8.74 (d, *J* = 6.0 Hz, 2H), 7.40-7.34 (m, 2H), 7.27-7.24 (m, 2H), 7.13 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.06-7.00 (m, 2H), 6.97-6.92 (m, 2H), 4.72 (s, 2H), 3.32 (s, 3H).

LC-MS: 0.89 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 426.0 (-)-ESI-MS (*m/z*) 424.0. (>98% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{18}O_2N_3F_2{}^{32}S$, 426.10823; found, 426.10822

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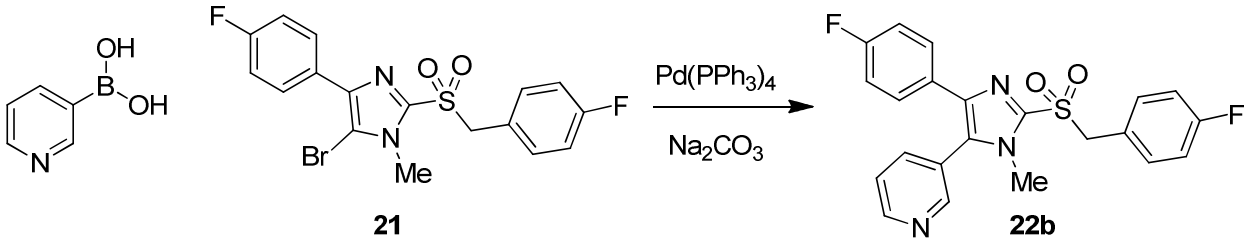


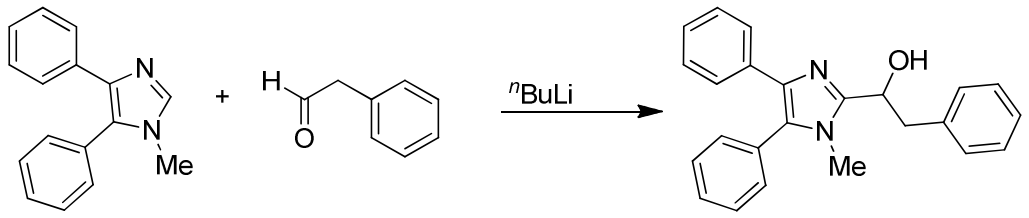
3-(2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1H-imidazol-5-yl)pyridine (22b).

Pyridin-3-ylboronic acid (23 mg, 0.187 mmol), 5-bromo-2-((4-fluorobenzyl)sulfonyl)-4-(4-fluorophenyl)-1-methyl-1H-imidazole (50 mg, 0.117 mmol), and tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.012 mmol) were added together in a microwave vial, and an atmosphere of argon was established. Toluene (2 mL) and water (0.2 mL) were added to the solids, and the mixture was bubbled with argon. Sodium carbonate (27 mg, 0.257 mmol) was added to the mixture, and the vial was sealed. The sealed vial was stirred at 130 °C for four hours. An additional portion of pyridin-3-ylboronic acid (14 mg, 0.117 mmol) and 0.1tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.012 mmol) was added at this time. The reaction was again heated at 130 °C for four hours. The reaction mixture was poured into 20 mL water and extracted with 3 x 20 mL EtOAc. The organic extracts were combined and washed with brine, and dried over $MgSO_4$, filtered, and adsorbed onto 200 mg of silica gel. The product was purified using silica gel flash column chromatography. (4g silica gel column, 25 to 90% EtOAc in hexanes, R_f = 0.2 in 50% EtOAc). Evaporation of fractions 18-23 gave 30 mg (60% yield) of a white solid. (Adapted from Laufer, et al.[7])

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.74 (dd, *J* = 5.2, 1.6 Hz, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), 7.53 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.43 (dd, *J* = 7.6, 4.4 Hz, 1H), 7.40-7.34 (m, 2H), 7.26-7.22 (m, 2H), 7.06-7.01 (m, 2H), 6.94 (td, *J* = 7.2, 2.0 Hz, 2H), 4.71 (s, 2H), 3.27 (s, 3H).

LC-MS: 0.86 min (75-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 426.0 (-)-ESI-MS (*m/z*) 424.0. (>98% of total peak area at 254 nm)

HR-ESI-MS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{18}O_2N_3F_2{}^{32}S$, 426.10823; found, 426.10810.



29 **26**

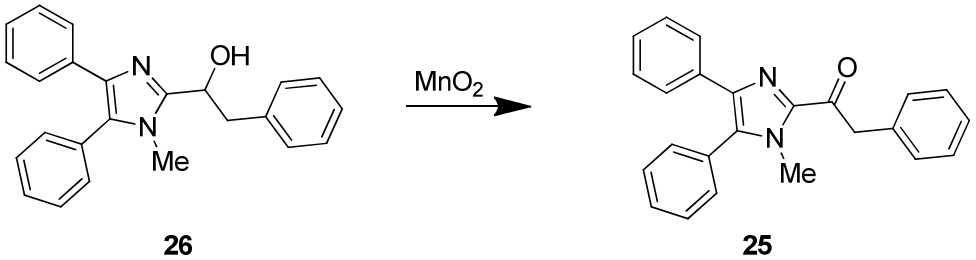
1-(1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)-2-phenylethanol (26).

1-methyl-4,5-diphenyl-1*H*-imidazole (5.0 g, 21.34 mmol) was dissolved in 40 mL dry THF and cooled to 0 °C. 1.9 M *n*-butyllithium (12.36 mL, 23.47 mmol) was added dropwise to the solution over two minutes, and the mixture was stirred for 20 min. The reaction mixture was cooled to -78 °C. 2-phenylacetaldehyde (3.08 g, 25.6 mmol), dissolved in 40 mL dry THF, was added over 20 min. The reaction mixture was stirred at -78 °C for 2 hours, allowed to come to RT, and stirred overnight. Water (30 mL) was added to the reaction mixture, and organic solvents were removed under vacuum. The precipitate was collected on a Buchner funnel, and the solids were washed with water, and then hexanes. The collected solids were added to a 500 mL round-bottomed flask, and 200 mL toluene was added. The compound was dissolved in boiling toluene, and the excess water was removed using a Dean-Stark trap. Toluene was boiled off so that the final volume was 50 mL. The hot solution was filtered through a Buchner funnel, and the filtrate was allowed to cool to room temperature, and then 0-5 °C. The first crop was collected and washed with hexanes (96% pure by LC-MS), and then the second crop (93% pure by LC-MS) was collected and added to the first. The solids were dried at 45 °C under vacuum for two hours, giving 4.63 g (61% yield) of a white solid.

^{1}H NMR: (400 MHz, DMSO-D6, δ): 7.50-7.42 (m, 3H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.31-7.23 (m, 6H), 7.16 (t, *J* = 7.2 Hz, 3H), 7.09-7.05 (m, 1H), 5.57 (d, *J* = 7.2 Hz, 1H), 4.90 (q, *J* = 6.8 Hz, 1H), 3.32 (s, 3H), 3.21-3.15 (m, 1H).

^{13}C NMR: (100 MHz, DMSO-D6, δ): 149.5, 139.7, 135.7, 135.4, 131.5, 131.4, 130.4, 130.0, 129.8, 129.3, 128.7, 128.6, 126.7, 126.5, 67.6, 42.1, 31.4.

LC-MS: 0.75 min (85% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 354.8, (-)-ESI-MS (*m/z*) no peak. (95% of total peak area at 254 nm)



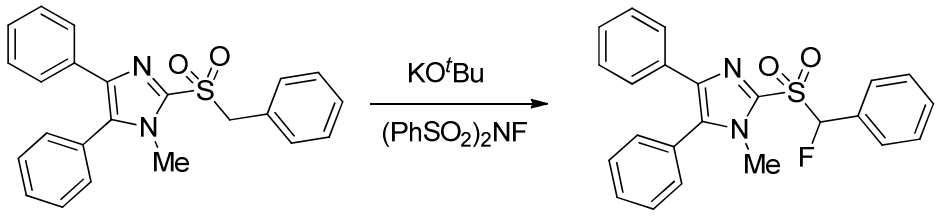
26 **25**

1-(1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)-2-phenylethanone (25).

1-(1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)-2-phenylethanol (100 mg, 0.282 mmol) was dissolved in 4 mL CH_2Cl_2 and cooled in an ice-water bath. Manganese dioxide (736 mg, 8.46 mmol) was added to this solution, and the mixture was stirred at 0-5 °C for 30 min, followed by rt for two hours. The reaction mixture was adsorbed onto silica gel and eluted using column chromatography (0 to 20% EtOAc in hexanes; 4g column; R_f = 0.6 in 25% EtOAc in hexanes) to give 50 mg of a viscous oil that solidified upon standing.

^{1}H NMR: (400 MHz, DMSO-D6, δ): 7.53-7.45 (m, 7H), 7.37-7.20 (m, 8H), 4.57 (s, 2H), 3.76 (s, 3H).

LC-MS: 2.65 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 353.1, (-)-ESI-MS (*m/z*) no peak. (>98% of total peak area at 254 nm)



13b **14a**

2-((fluoro(phenyl)methyl)sulfonyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (14a).

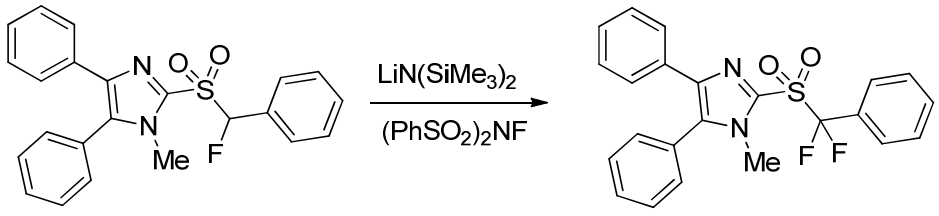
2-(benzylsulfonyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (1.0 g, 2.57 mmol) was dissolved in 10 mL dry THF, and cooled to 0 °C. Potassium *tert*-butoxide (0.289 g, 2.57 mmol) was added to this mixture, and the solution was stirred at 0 °C for 0.5 hr. *N*-Fluorobenzenesulfonimide (NFSI, 1.22 g, 3.87 mmol) dissolved in 4 mL dry THF was added to this mixture all at once, and the mixture was stirred at 0 °C for 0.5 hr. (Note: Of the methods examined, this procedure gave the

most desirable mixture of products; after 30 minutes, there was a ratio (by HPLC) of 6:18:67:8 of decomposition product : starting material : mono-fluoro product : difluoro product.) The reaction was worked up by quenching with sat. NH_4Cl, then pouring into 50 mL sat. NH_4Cl and extracting with 4 x 50 mL CH_2Cl_2. (After the first extraction, the NH_4Cl was brought to pH 8 by addition of sat. $NaHCO_3$.) The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The compound was adsorbed onto 5 g silica gel, and purified using flash column chromatography (40 g column, 0 to 20% EtOAc in hexanes).

Fractions 55-63 were concentrated and triturated with Et_2O, which removed most of the contaminating NFSI, leaving ca. 90% mono-fluorinated product and 10% di-fluorinated product. This mixture (490 mg) was taken on into the next fluorination step. The crystals that developed from fractions 63-66 crystals were collected, giving 50 mg of the title compound crystallized with 0.5 molar equivalents of EtOAc. Total yield: 540 mg (52% yield)

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.58-7.45 (m, 10H), 7.32-7.20 (m, 5H), 6.57 (d, *J* = 46 Hz, 1H), 3.57 (s, 3H) (excludes crystallized EtOAc peaks).

LC-MS: 1.54 min (80-95% MeCN in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 407.1; (-)-ESI-MS (*m/z*) no peak. (90% of total peak area at 254 nm)



14a **14b**

2-((difluoro(phenyl)methyl)sulfonyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (14b).

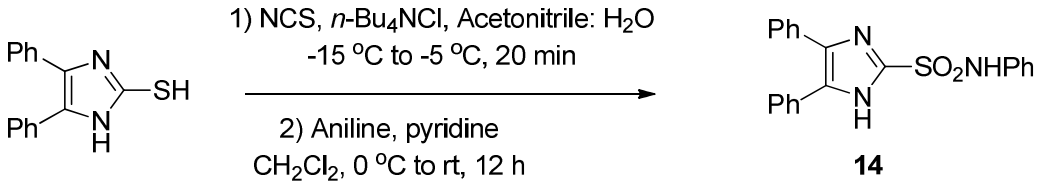
2-((fluoro(phenyl)methyl)sulfonyl)-1-methyl-4,5-diphenyl-1*H*-imidazole (50 mg, 0.123 mmol) was dissolved in 2 mL dry THF, and cooled to -78 °C. 1.0 M Lithium bis(trimethylsilyl)amide (135 µL, 0.135 mmol) was added to this mixture at -78 °C. The solution was stirred at -78 °C for 0.5 hr.

N-fluorobenzenesulfonimide (NFSI, 46.5 mg, 0.148 mmol) dissolved in 1 mL dry THF was added to this mixture all at once, and the mixture was stirred at -78 °C for 0.5 hr. The reaction mixture was adsorbed onto 0.5 g silica gel, and purified using silica gel flash column chromatography (4 g column, 0 to 20% EtOAc in hexanes). The fractions containing product were concentrated and further purified by recrystallization from ether to give 45 mg (86% yield) of thin white crystals.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.72-7.46 (m, 10H), 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H) 3.60 (s, 3H)

LC-MS: 1.85 min (80-95% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C_{18} column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) $[M + H]^+$: 425.1; (-)-ESI-MS (*m/z*) no peak. (94% of total peak area at 254 nm)

Synthesis of *N*,4,5-triphenyl-1*H*-imidazole-2-sulfonamide (23):



14

***N*,4,5-Triphenyl-1*H*-imidazole-2-sulfonamide (23).**

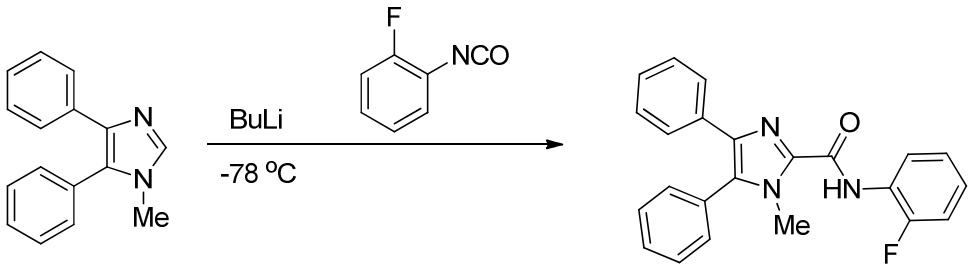
To a stirred mixture of 4,5-diphenyl-1*H*-imidazole-2-thiol (252 mg, 1.0 mmol), *n*-Bu_4NCl (1.11 g, 4.0 mmol) and water (45 µL, 2.5 mmol) in acetonitrile (5 mL) at -15 °C, *N*-chlorosuccinimide (147 mg, 1.1 mmol) was added as a solid in portions over 1-2 min. After the addition the mixture was stirred at -5-0 °C for 20 min. Then the mixture was filtered through celite and washed with CH_2Cl_2 and the filtrate was evaporated to afford the crude 4,5-diphenyl-1H-imidazole-2-sulfonyl chloride, which was taken immediately to the next step without purification.

To a stirred solution of crude 4,5-diphenyl-1*H*-imidazole-2-sulfonyl chloride (1.0 mmol) in dichloromethane (10 mL) at 0 °C, were added successively aniline (137 µL, 1.5 mmol) and pyridine (121 µL, 1.5 mmol). After stirring at room temperature for 12 h, the mixture was washed with water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

Chromatographic purification of crude using 25-30% ethyl acetate in hexanes provided *N*,4,5-triphenyl-1*H*-imidazole-2-sulfonamide (**23**) (75 mg, 20%) as a white solid.

^{1}H NMR: (600 MHz, DMSO-d_6, δ): 13.83 (br s, 1H), 10.78 (br s, 1H), 8.28 (s, 2H), 7.37-7.26 (m, 12H), 7.05 (t, *J* = 6.6 Hz, 1H).

LC-MS: 1.39 min (85% MeOH in 0.1% formic acid solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 376.0; (-)-ESI-MS (*m/z*) [M - H]-: 374.0. (>99% total peak area at 254 nm).



29 **24a**

***N*-(2-fluorophenyl)-1-methyl-4,5-diphenyl-1H-imidazole-2-carboxamide (24a).**

To a solution of 1-methyl-4,5-diphenyl-1H-imidazole (2.0 mmol, 469 mg) in THF was slowly added *n*-BuLi (2.5 M, 2.3 mmol, 1.0 mL) at -78 °C. After stirring for 1hr, 0.225 mL of 1-fluoro-2-isocyanatobenzene (2.0 mmol, 274 mg) was added. The cooling bath was removed and the solution was kept stirring at room temperature for 2 h. The reaction mixture was poured into Na_2CO_3 (sat. aq.) and extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, concentrated, and purified by chromatography to obtain the title compound as a white solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$:=373.3.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):9.71 (s, 1H), 8.42 (t, *J* = 8.0 Hz, 1H), 7.52-7.50 (m, 4H), 7.38-7.21 (m, 6H), 3.85 (s, 3H).

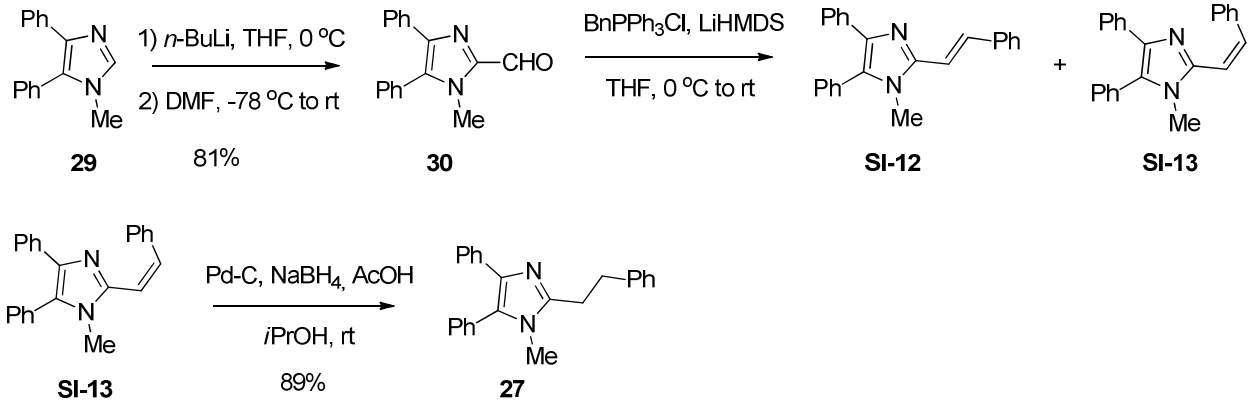
Synthesis of *N*-(2-nitrophenyl)-1-methyl-4,5-diphenyl-1H-imidazole-2-carboxamide (24b).

The same procedure as used for the synthesis of **24a** gave the title compound **24b** as a yellow solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$:=399.2.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):12.42 (s, 1H), 8.93 (d, *J* = 8.4 Hz, 1H), 8.31(d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.58 (t,*J* = 8.4 Hz, 2H), 7.52-7.51 (m, 3H), 7.38-7.20 (m, 6H), 3.86 (s, 3H).

Synthesis of 1-methyl-2-phenethyl-4,5-diphenyl-1*H*-imidazole (27):



1-Methyl-4,5-diphenyl-1*H*-imidazole-2-carboxaldehyde (30).

To a solution of 1-methyl-4,5-diphenyl-1*H*-imidazole (2.0 g, 8.54 mmol) in THF (25 mL) was added dropwise *n*-butyllithium (4.0 mL, 10.24 mmol; 2.5 M solution in hexanes) at -40 °C under nitrogen. The reaction mixture was stirred at >-20 °C for 45 min. Afterwards, the mixture was cooled to -78 °C using a dry ice-acetone bath and DMF (3.3 mL) was added into the mixture and stirred at -78 °C for 1 h, allowed to warm to room temperature and stirred overnight. Then the mixture was quenched with saturated aqueous NH_4Cl and EtOAc was added to the mixture. The organic layer was washed with water and brine and dried over Na_2SO_4 and the solvent was filtered and concentrated. Chromatographic purification of the crude product, eluting with 20-25% ethyl acetate in hexanes provided **30** (455 mg, 81%) as a yellowish solid.

(+)-ESI-MS (*m/z*) $[M + H]^+$:=263.1.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 9.93 (s, 1H), 7.51-7.46 (m, 5H), 7.35-7.33 (m, 2H), 7.26-7.22 (m, 3H), 3.84 (s, 3H).

(*E*)-1-(1-Methyl-4,5-diphenyl-2-styryl-1*H*-imidazole (SI-12) and **(*Z*)-1-(1-methyl-4,5-diphenyl-2-styryl-1*H*-imidazole (SI-13).**

To a stirred suspension of benzyltriphenyl-phosphonium chloride (445 mg, 1.14 mmol) in THF (5 mL) was added a solution of LiHMDS (1.0 m in THF, 1.14 mL, 1.14 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at 0 °C, **SI-11** solution in THF (1+1 mL) was added dropwise to the reaction mixture. The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and water and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in *vacuo*. Chromatographic purification of crude, first eluting with 15% ethyl acetate in hexanes provided **SI-12** (65 mg, 34%) as a white solid. Then, eluting with 20% ethyl acetate in hexanes provided **SI-13** (110 mg, 57%) as a white solid.

(*E*)-1-(1-Methyl-4,5-diphenyl-2-styryl-1*H*-imidazole (SI-12). ^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.76 (d, *J* = 15.6 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.48-7.45 (m, 3H), 7.40-7.34 (m, 5H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 15.6 Hz, 1H), 3.54 (s, 3H).

LC-MS: 3.16 min (60-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 5 min run); (+)-ESI-MS (*m/z*) [M + H]+: 337.2.

(*Z*)-1-(1-Methyl-4,5-diphenyl-2-styryl-1*H*-imidazole (SI-13). ^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.52 (d, *J* = 7.2 Hz, 2H), 7.45-7.41 (m, 5H), 7.34-7.27 (m, 6H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 12.0 Hz, 1H), 6.55 (d, *J* = 12.0 Hz, 1H), 3.01 (s, 3H).

LC-MS: 2.88 min (60-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 5 min run); (+)-ESI-MS (*m/z*) [M + H]+: 337.2.

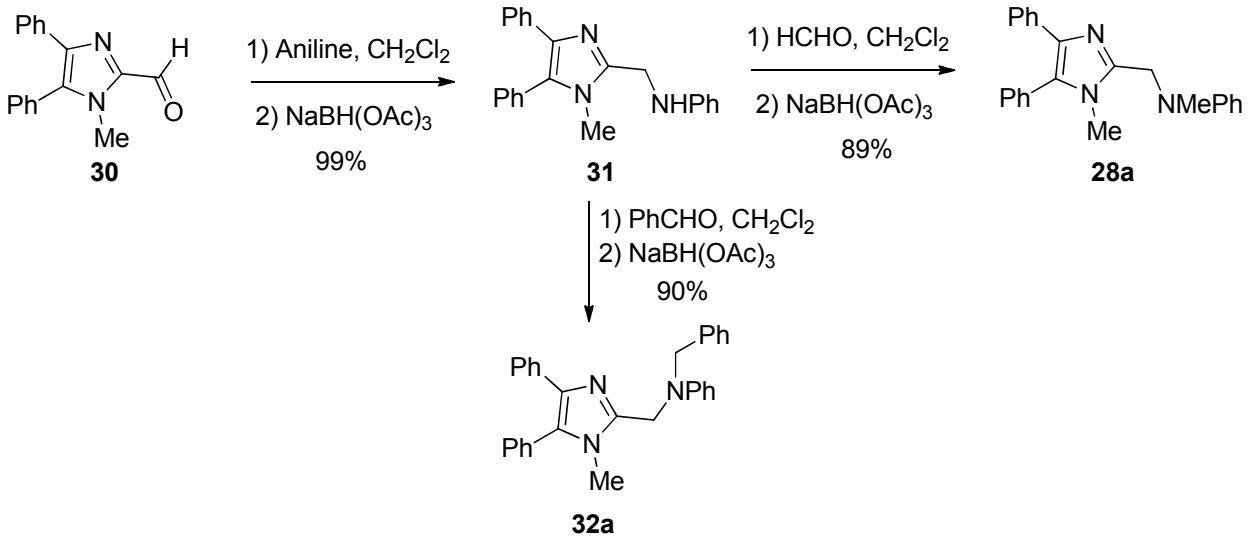
1-Methyl-2-phenethyl-4,5-diphenyl-1*H*-imidazole (27).

A 10 mL round-bottomed flask with stir bar was charged in open air with Pd/C (10 wt%; 12 mg, 0.011 mmol) catalyst, **SI-13** (75 mg, 0.223 mmol), and 1 mL of isopropyl alcohol. The flask was clamped over a mechanical stirrer, and the contents were stirred. Acetic acid (13 µL, 0.223 mmol) and powdered $NaBH_4$ (17 mg, 0.446 mmol) were added directly to the stirring heterogeneous solution. The contents of the reaction flask were left to stir in open air at room temperature for 15 min. A second portion of acetic acid (13 µL, 0.223 mmol) and powdered $NaBH_4$ (17 mg, 0.446 mmol) were added and stirred 15 for min. Similarly, a third and fourth portion of acetic acid and powdered $NaBH_4$ were added. Then, the reaction contents were filtered through Celite and washed with EtOAc. The filtrate was quickly partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Chromatographic purification of the crude product, eluting with 20-25% ethyl acetate in hexanes provided **27** (67 mg, 89%) as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.48 (d, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.32-7.19 (m, 10H), 7.14 (d, *J* = 7.2 Hz, 1H), 3.18 (t, *J* = 8.0 Hz, 2H), 3.11 (s, 3H), 3.07 (t, *J* = 7.6 Hz, 2H).

LC-MS: 1.50 min (60-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 5 min run); (+)-ESI-MS (*m/z*) [M + H]+: 339.2. (>97% total peak area at 254 nm).

Synthesis of *N*-methyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (28a):



***N*-((1-Methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (31).**

To a stirred solution of **30** (300 mg, 1.14 mmol) in CH_2Cl_2 (6 mL) was added aniline (125 µL, 1.372 mmol) and one drop of acetic acid. After stirring the mixture for 2h at room temperature, sodium triacetoxyborohydride (365 mg, 1.716 mmol) was added in to the reaction mixture. The reaction mixture was stirred at rt overnight, quenched with saturated ammonium chloride solution, and stirred for 30 min. The organic layer was separated and washed once with water, dried over Na_2SO_4, and the solvent was filtered and concentrated. Chromatographic purification of the crude product, eluting with 25-30% ethyl acetate in hexanes provided *N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline **31** (385 mg, 99%) as a very light yellow shiny solid.

LC/MS: (+)-ESI-MS (*m/z*) $[M + H]^+$:340.2; (-)-ESI-MS (*m/z*) $[M – H]^-$: 338.2.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.49-7.14 (m, 13H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.45 (s, 2H), 3.47 (s, 3H).

***N*-Methyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (28a).**

To a stirred solution of **31** (385 mg, 1.134 mmol) in CH_2Cl_2 (6 mL) was added formaldehyde (37 wt%, 120 µL, 1.475 mmol) and one drop of acetic acid. After stirring the mixture for 2h at room temperature, sodium triacetoxyborohydride (360 mg, 1.7 mmol) was added in to the reaction

mixture. The reaction mixture was stirred at rt overnight, quenched with saturated ammonium chloride solution, and stirred for 30 min. The organic layer was separated and washed once with water, dried over Na_2SO_4, filtered and concentrated. Chromatographic purification of the crude product eluting with 25-30% ethyl acetate in hexanes provided **28a** (355 mg, 89%) as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):7.49-7.42 (m, 5H), 7.33-7.30 (m, 3H), 7.27 (d *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.16-7.14 (m, 1H), 7. 02 (d, *J* = 8.4 Hz, 2H), 6.83 (t, *J* =7.2 Hz, 1H), 4.62 (s, 2H), 3.39 (s, 3H), 2.94 (s, 3H).

LC-MS: 1.58 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 5 min run); (+)-ESI-MS (*m/z*) [M + H]+: 354.1. (>99% total peak area at 254 nm).

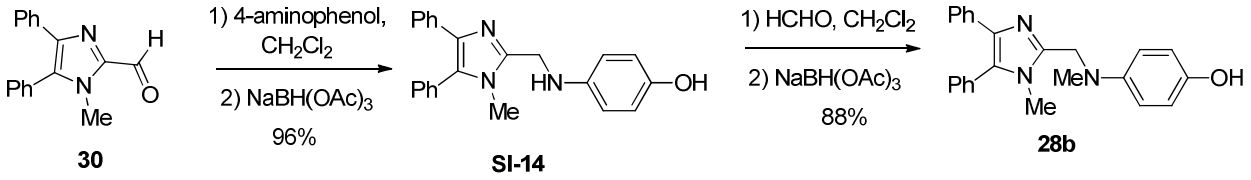
***N*-Benzyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (32a).**

Following the same procedure as for the preparation of **28a**, using **31** (75 mg, 0.221 mmol) and benzaldehyde (27 µL, 0.265 mmol) as substrates, and chromatographic purification of crude eluting with 20-25% ethyl acetate in hexanes, **32a** (95 mg, 90%) was obtained as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):7.46-7.37 (m, 5H), 7.31-7.21 (m, 9H), 7.15-7.07 (m, 5H), 6.84 (t, *J* =7.2 Hz, 1H), 4.67 (s, 2H), 4.62 (s, 2H), 3.21 (s, 3H).

LC-MS: 2.32 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 430.2. (>98% total peak area at 254 nm).

Synthesis of 4-(Methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)phenol (28b):



4-(((1-Methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)phenol (SI-14).

Following the same procedure as for the preparation of **31**, using **30** (100 mg, 0.381 mmol) and 4-aminophenol (50 mg, 0.457 mmol) as substrates, and chromatographic purification of the crude product eluting with 2-3% MeOH in CH_2Cl_2, **SI-14** (140 mg, 96%) was obtained as a white solid.

^{1}H NMR: (400 MHz, DMSO-d_6, δ):8.45 (s, 1H), 7.49-7.46 (m, 3H), 7.34 (t, *J* = 7.2 Hz, 4H), 7.17 (t, *J* = 7.2 Hz, 2H), 7. 09 (d, *J* = 7.2 Hz, 1H), 6.64 (d, *J* =8.4 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 5.45 (br s, 1H), 4.27 (s, 2H), 3.40 (s, 3H).

LC-MS: 0.82 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 356.1. (>98% total peak area at 254 nm).

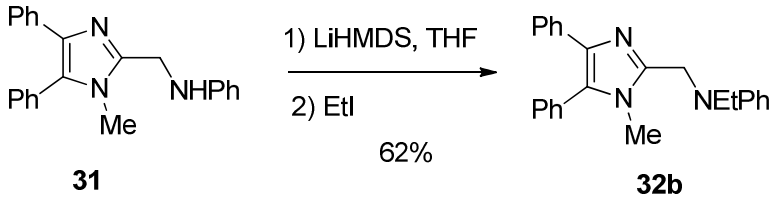
4-(Methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)phenol (28b).

Following the same procedure as for the preparation of **28a**, using **SI-14** (130 mg, 0.366 mmol) as substrate, and chromatographic purification of crude eluting with 2-3% MeOH in CH_2Cl_2, **28b** (120 mg, 88%) was obtained as a white solid.

^{1}H NMR: (400 MHz, DMSO-d_6, δ):8.73 (s, 1H), 7.49-7.46 (m, 3H), 7.33 (d, *J* = 7.2 Hz, 4H), 7.16 (t, *J* = 7.2 Hz, 2H), 7. 08 (d, *J* = 7.2 Hz, 1H), 6.87 (d, *J* =8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 2H), 3.55 (s, 3H), 2.76 (s, 3H).

LC-MS: 1.05 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 370.1. (>99% total peak area at 254 nm).

Synthesis of *N*-ethyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (32b):



31 **32b**

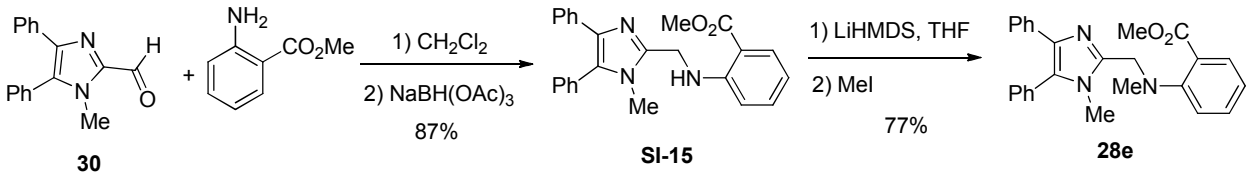
***N*-Ethyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)aniline (32b).**

To a solution of **31** (40 mg, 0.118 mmol) in THF (2 mL) at 0 °C was added lithium bis(trimethylsilyl)amide-solution 1M in THF (240 µL, 0.24 mmol); the reaction mixture was stirred for 30 min. Ethyl iodide (28 µL, 0.354 mmol) was added into the mixture and stirred at ambient temperature for 1 h. Then the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatographic purification of crude using 20-25% ethyl acetate in hexanes provided **32b** (27 mg, 62%) as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ):7.49-7.42 (m, 5H), 7.32-7.26 (m, 4H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.81 (t, *J* =7.2 Hz, 1H), 4.60 (s, 2H), 3.42 (q, *J* = 6.8 Hz, 2H), 3.36 (s, 3H), 1.09 (t, *J* = 6.8 Hz, 3H).

LC-MS: 1.83 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 368.2. (>98% total peak area at 254 nm).

Synthesis of methyl 2-(methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoate (32d):



30 **SI-15** **28e**

Methyl 2-(((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoate (SI-15).

Following the same procedure as for the preparation of **31**, using **30** (200 mg, 0.762 mmol) and methyl 2-aminobenzoate (140 mg, 0.915 mmol) as substrates, and chromatographic purification of the crude product eluting with 25-30% ethyl acetate in hexanes, **SI-15** (265 mg, 87%) was obtained as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.20 (t, *J* = 4.8 Hz, 1H), 7.94 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.49-7.40 (m, 6H), 7.34-7.32 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.67 (t, *J* =7.2 Hz, 1H), 4.62 (d, *J* = 4.8 Hz, 2H), 3.87 (s, 3H), 3.48 (s, 3H).

LC-MS: 1.84 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 5 min run); (+)-ESI-MS (*m/z*) [M + H]+: 398.1. (>98% total peak area at 254 nm).

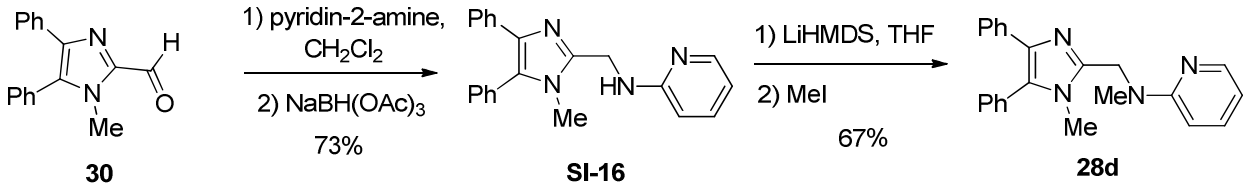
Methyl 2-(methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoate (28e).

Following the same procedure as for the preparation of **32b**, using **SI-15** (225 mg, 0.566 mmol) and methyl iodide (106 µL, 1.7 mmol) as substrates, and chromatographic purification of crude eluting with 25% ethyl acetate in hexanes, **28e** (180 mg, 77%) was obtained as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 7.69 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.46-7.41 (m, 6H), 7.32-7.29 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 4.50 (s, 2H), 3.87 (s, 3H), 3.40 (s, 3H), 2.80 (s, 3H).

LC-MS: 1.41 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 412.1. (>99% total peak area at 254 nm).

Synthesis of *N*-methyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)pyridin-2-amine (28d):



***N*-((1-Methyl-4,5-diphenyl-1H-imidazol-2-yl)methyl)pyridin-2-amine (SI-16).**

Following the same procedure as for the preparation of **31**, using **30** (100 mg, 0.381 mmol) and pyridine-2-amine (43 mg, 0.457 mmol) as substrates, and chromatographic purification of the crude product eluting with 3-5% MeOH in CH_2Cl_2, **SI-16** (95 mg, 73%) was obtained as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.14 (dd, *J* = 0.8, 4.0 Hz, 1H), 7.48-7.41 (m, 6H), 7.34-7.31 (m, 2H), 7.21 (t, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.63-6.60 (m, 2H), 5.43 (br s, 1H), 4.72 (d, *J* = 4.8 Hz, 2H), 3.48 (s, 3H).

LC-MS: 0.91 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 341.1. (>99% total peak area at 254 nm).

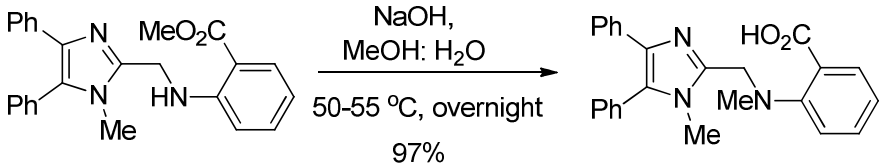
***N*-Methyl-*N*-((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)pyridin-2-amine (28d)**.

Following the same procedure as for the preparation of **32b**, using **SI-16** (50 mg, 0.147 mmol) and methyl iodide (28 µL, 0.44 mmol) as substrates, and chromatographic purification of the crude product eluting with 30% ethyl acetate in hexanes, **28d** (35 mg, 67%) was obtained as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.19 (dd, *J* = 1.2, 4.0 Hz, 1H), 7.50-7.47 (m, 3H), 7.43-7.41 (m, 3H), 7.32-7.30 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.62-6.59 (m, 2H), 5.13 (s, 2H), 3.42 (s, 3H), 3.05 (s, 3H).

LC-MS: 1.41 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 412.1. (>99% total peak area at 254 nm).

Synthesis of 2-(methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoic acid (28c):



28e **28c**

2-(Methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoic acid (28c).

A mixture of methyl 2-(methyl((1-methyl-4,5-diphenyl-1*H*-imidazol-2-yl)methyl)amino)benzoate (80 mg, 0.194 mmol) and NaOH (10 mg, 0.233) in MeOH: H_2O (1:1 v/v, 3 mL) was stirred overnight at 50-55 °C. The mixture was cooled to rt and acidified with HCl (aq, 10%, pH ~ 4-5), and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatographic purification of the crude product using 3% MeOH in CH_2Cl_2 provided **28c** (75 mg, 97%) as a white solid.

^{1}H NMR: (400 MHz, $CDCl_3$, δ): 8.20 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.54 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.38-7.33 (m, 7H), 7.22-7.19 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 4.27 (s, 2H), 3.18 (s, 3H), 2.92 (s, 3H).

LC-MS: 0.92 min (80-95% MeOH in 10mM ammonium acetate solution (aq.); Agilent Zorbax 50 mm C18 column; 1 mL/min; 3 min run); (+)-ESI-MS (*m/z*) [M + H]+: 398.1. (>99% total peak area at 254 nm).

Biological Assays:

Cells and viruses

All cell lines were maintained at 37 °C and 5% CO_2 in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. Vero (African green monkey kidney epithelial) cells

(ATCC CCL-81) stably expressing human signaling lymphocytic activation molecule (CD150w/SLAM), called in this study Vero-SLAM cells[8] were incubated at every third passage in the presence of G-418 (Geneticin) at a concentration of 100 μg/ml. Virus strains used in this study were recombinant MeV-Edmonston (recMeV)[9], recombinant RSV A2 (recRSV)[10], and influenza A virus strains IAV/New York/55/2004 (H3N2) (IAV-New York), IAV/Aichi/2/1968 (H3N2) (IAV-Aichi), IAV/Mexico/INDRE4489/2009 (H1N1) (IAV-Mexico), IAV/WSN/1933 (H1N1) (IAV-WSN), and IAV/Texas/15/2009 (H1N1) (IAV-Texas). MeV stocks were grown and titered through $TCID_{50}$ titration on Vero-SLAM cells. RSV was grown and immunoplaque assay titered on HEp-2 cells (ATCC HB-8065) as described. IAV strains were grown and plaque assay titered on Madin-Darby canine kidney (MDCK) cells, or grown on MDCK cells and titered by TaqMan real time PCR-based quantification of progeny genome copy numbers as described[11]. recMeV-ren and recRSV-ren stocks were dialyzed prior to storage (100K molecular weight cut-off) to reduce contamination of stocks with free luciferase protein synthesized during virus amplification.

Generation of luciferase reporter systems

Basis for the generation of recMeV-ren was a plasmid harboring a complete cDNA copy of the recMeV-eGFP genome[12], which contains an eGFP open reading frame in pre-MeV N position. The generation and recovery of the equivalently designed recRSV-ren recombinant is outlined in reference 10. For construction of the IAV firefly luciferase minireplicon reporter plasmid under the control of the RNA-Pol*I* promoter, the firefly luciferase gene was amplified with appropriate primers and transferred into the pHH21 vector, restoring non-coding flanking regions of IAV gene segment 5 as specified[13], with the exception of an A to G exchange at position 8 in the 5'-non coding region.

Virus-driven luciferase reporter assays

Luciferase enzymatic activity was measured to quantify reporter protein expression. Unless otherwise specified, 293T cells were transfected with 1 μg of IAV-firefly minigenome reporter plasmid/10^5 cells and cryo-preserved 28 hours post-transfection. Thawed cells were seeded at a density of $3x10^4$ cells/well in 96-well plate and infected with TPCK-treated trypsin-actviated IAV strains (MOI 0.1 pfu/cell), recMeV-ren (MOI 0.2 $TCID_{50}$/cell), and/or recRSV-ren (MOI 0.2 pfu/cell) after a 20-hour incubation unless otherwise stated for individual experiments. For experiments involving recRSV-ren, HEp-2 cells were seeded at a density of $1.5x10^4$ cells/well.

Twenty-eight hours post-infection, Bright-Glo, Renilla-Glo, or Dual-Glo substrates (all Promega) were added as specified according to the manufacturer's instructions and bioluminescence intensities determined using an Envision Multilabel microplate reader (Perkin Elmer).

Minireplicon reporter assay

293T cells were transfected with plasmid DNA encoding the IAV (0.5 μg) or MeV (1 μg)[14] luciferase minigenome reporters and plasmids encoding the RdRp components MeV-L (1.1 μg), MeV-N (0.4 μg) and MeV-P (0.3 μg) for MeV replicon assays, or IAV-NP, -PA, -PB1, and -PB2 (0.5 μg each) for IAV replicon assays.

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