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Supporting Information

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Structurally Simple Farnesyltransferase Inhibitors Arrest the Growth of Malaria Parasites

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***Plasmodium* strains**. The *P. falciparum* strains used in this study were 3D7 (Netherlands, sensitive) provided by Dr. Pradipsinh Rathod from the University of Washington and K1 (Thailand, ChQ-R, Pyr-R) obtained from the MR4 Unit of the American Type Culture Collection (ATCC, Manassas, VA).

***P. falciparum* culture.** Strains of *P. falciparum* were sustained *in vitro* based on experimental techniques as described by Trager and Jensen.[1] Cultures were maintained in RPMI-1640 (Sigma, St. Louis, MI) with 2 mM L-glutamine, 25 mM HEPES, 33 mM $NaHCO_3$, 20 µg/ml gentamicin sulfate and 20% (v/v) heat-inactivated human plasma type A+ (RP-20P). Type A+ erythrocytes were obtained from lab donors, washed three times with RPMI, re-suspended in 50% RPMI, and stored at 4 ^oC. Parasites were grown in 10-ml of a 2% hematocrit/RP-20P (v/v) in 50-ml flasks under a 5% CO_2, 5% O_2, and 90% N_2 atmosphere.

***P. falciparum* ED_{50} determination.** One µl of PFTI dissolved in DMSO was added to each well of a 96-well plate followed by the addition of 200 µl of *P. falciparum* culture at parasitemia and hematocrit of 0.5%. Plates were flushed with 5% CO_2, 5% O_2, and 90% N_2 then incubated at 37 ^oC for 48 hr. [8-^{3}H]-hypoxanthine (0.3 µCi, 20 Ci/mmol, American Radiolabeled Chemicals) in 30 µl RP-20P was added to cultures and incubated for an additional 24 hr. Cells were harvested onto filter mats by a Multiharvester (Skatron, Sunnyvale, CA) and the radioactivity incorporated into the parasites were counted on a beta-scintillation counter. The background level detected with uninfected erythrocytes

was subtracted from the data. The ^{3}H-incorporation into infected RBCs with 1 µl DMSO vehicle alone represents 100% malaria growth. ED_{50} values were determined by linear regression analysis of the plots of ^{3}H-hypoxanthine incorporation versus concentration of compound.

PfPFT IC_{50} determination. The PFT assay used to determine the IC_{50}s of the compounds is based on a scintillation proximity assay[2]. Assays were carried out in 30 mM potassium phosphate pH 7.7, with 5 mM DTT, 0.5 mM $MgCl_2$, 20 µM $ZnCl_2$, 0.3 µCi (0.75 µM) [^{3}H]farnesyl pyrophosphate (15 µCi/mmol, American Radiolabeled Chemicals Inc.), 1 µM RAS-CVIM protein substrate in a total volume 20 µl which included 1 µl of PFTI solution in DMSO and 3 µl of partially purified PfPFT.[2] Assays in the absence of PFTI and PfPFT were included as positive and negative controls, respectively. Reaction mixtures were incubated at 30°C for 30 minutes and terminated by addition of 200 µl of 10% HCl/ethanol. After overnight incubation at room temperature, the mixtures were filtered onto a Whatman glass fiber filter (VWR, San Francisco, CA) using a 96-well vacuum manifold. After washing with 100% ethanol, the filter was cut, and individual slices were counted in a beta-scintillation counter. IC_{50} values were calculated using linear regression analysis of the plots of ^{3}H-FPP prenylation vs concentration of compounds.

Chemistry: General Methods. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker AM-400 or AM-500 MHz spectrometers. Analysis and purification by rpHPLC were performed using either Phenomenex Luna 5µ C18(2) 250 x 21 mm column run at 15 mL/minute (preparative), or a Microsorb-MV 300Å C18 250 x 4.6 mm column run at 1 mL/minute (analytical), using gradient mixtures of water:0.1% TFA (A) and 10:1 acetonitrile:water (B) with 0.1% TFA, and product fractions were always lyophilized to dryness. Inhibitor purity was confirmed by analytical rpHPLC using linear gradients from 100% A to 100% B with changing solvent composition of either: (I) 4.5% or (II) 1.5 % *per* minute after an initial 2 minutes of 100% A. Mass determinations were performed using

electrospray ionization on either a Varian MAT-C*H*-5 (HRMS) or Waters Micromass ZQ (LRMS). Solvents: DMF, THF, and DCM were dried on an Innovative Technology SPS-400 dry solvent system. Methanol, TEA and DMSO were dried over calcium hydride. Molecular sieves were activated by heating to 300°C under vacuum overnight. Flexible ligand docking was performed using GOLD,[3] with ligand minimization performed within InsightII on a SGI O2.

1-Trityl-1*H*-imidazole-4-carbaldehyde (16): Dry triethylamine (12.6 mL, 90.0 mmol) was added drop wise over two hours to a slurry of (1,3)*H*-Imidazole-4-carbaldehyde (5.0 g, 52 mmol) and trityl chloride (16.0 g, 57 mmol) in acetonitrile (170 mL). After complete addition of the triethylamine, the resulting solution was stirred overnight and then hexane (16.6 mL) and water (170 mL) were added. After stirring for an additional 30 minutes, the resulting solid was collected and dried overnight under vacuum to provide the title compound as a white solid (16.8 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): d 9.81 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.29 (m, 10H), 7.04 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): d 186.9, 141.9, 141.2, 141.0, 130.0, 129.0, 128.9, 127.2, 76.7.

3-Methyl-3*H*-imidazole-4-carbaldehyde trifluoromethanesulfonate (17): Methyl triflate (10.0 g, 60.1 mmol) was added drop wise over five hours to a solution of aldehyde **16** (13.5 g, 40.0 mmol) in DCM (50 mL), and the resulting solution stirred over night at room temperature. The volume of solvent was then reduced under vacuum (~30 mL), hexane (40 mL) was added, and stirring continued for a further 30 minutes at which time the crude solid of 3-methyl-1-trityl-1*H*-imidazole-4-carbaldehyde trifluoromethanesulfonate was collected, and washed with hexane (3 x 25 mL). This solid was immediately dissolved in 2:1 acetone:water (40 mL) and stirred for four hours at room temperature. The resulting suspension was filtered, the solid washed with water (30 mL), and the supernatant concentrated under vacuum. The resulting suspension was filtered, and the supernatant lyophilized to provide the title compound as a white solid (9.7 g, 93%). ^{1}H NMR (400 MHz, d_4-

MeOH): d 8.84 (s, 1H), 7.50 (s, 1H), 5.77 (s, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, d_4-MeOH): d 188.6, 148.4, 140.8, 135.3, 30.2.

(3-Methyl-3*H*-imidazol-4-yl)-methanol (18): 3-Methyl-3*H*-imidazole-4-carbaldehyde (**17**) (2.0 g, 20 mmol) was dissolved in THF (10 mL), and the resulting solution cooled to 0°C. Lithium aluminum hydride (150 mg, 40.0 mmol) was added portion wise over 10 minutes, and the resulting suspension stirred for a further 10 minutes. Excess hydride was quenched by the addition of solid $Na_2SO_4 \cdot 10H_2O$ (~1 g) in large portions with vigorous stirring. Additional THF was added as needed to prevent solidification of the resulting slurry. The resulting suspension was stirred for a further hour, and then filtered to remove the sulfate salts, and the solvent was removed under reduced pressure to provide the title alcohol (1.8 g, 80%). ^{1}H NMR (400 MHz, d_4-MeOH): d 7.57 (s, 1H), 6.89 (s, 1H), 4.58 (s, 2H), 372 (s, 3H). ^{13}C NMR (100 MHz, d_4-MeOH): d 140.1, 132.7, 128.1, 31.9, 31.0.

5-Chloromethyl-1-methyl-1*H*-imidazole (19): DMF (1 drop) was added to a slowly stirred solution of (3-Methyl-3*H*-imidazol-4-yl)-methanol (**18**) (1.8 g, 16 mmol) dissolved in thionyl chloride (12 mL). After 30 minutes the solvent was removed under reduced pressure, and the resulting solid triturated with diethyl ether (20 mL). The resulting semi-solid was dried over night under vacuum, and used without further purification. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.98 (s, 1H), 7.63 (s, 1H), 4.85 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, d_4-MeOH): d 138.3, 132.6, 120.5, 34.5, 33.9.

[2-(4-Cyanophenylamino)-ethyl]-carbamic acid tert-butyl ester (20): Freshly distilled TEA (8.9 mL, 90 mmol) was added to a solution of (2-aminoethyl)-carbamic acid tert-butyl ester (5.0 g, 30 mmol) and 4-fluorobenzonitrile (3.6 g, 30 mmol) in dry DMSO (250 mL), and the resulting solution heated to 120°C for two days. A distillation head and condenser was fitted to the reaction, and the volume of solvent was reduced to ~ 20 mL under reduced pressure. The resulting solution was

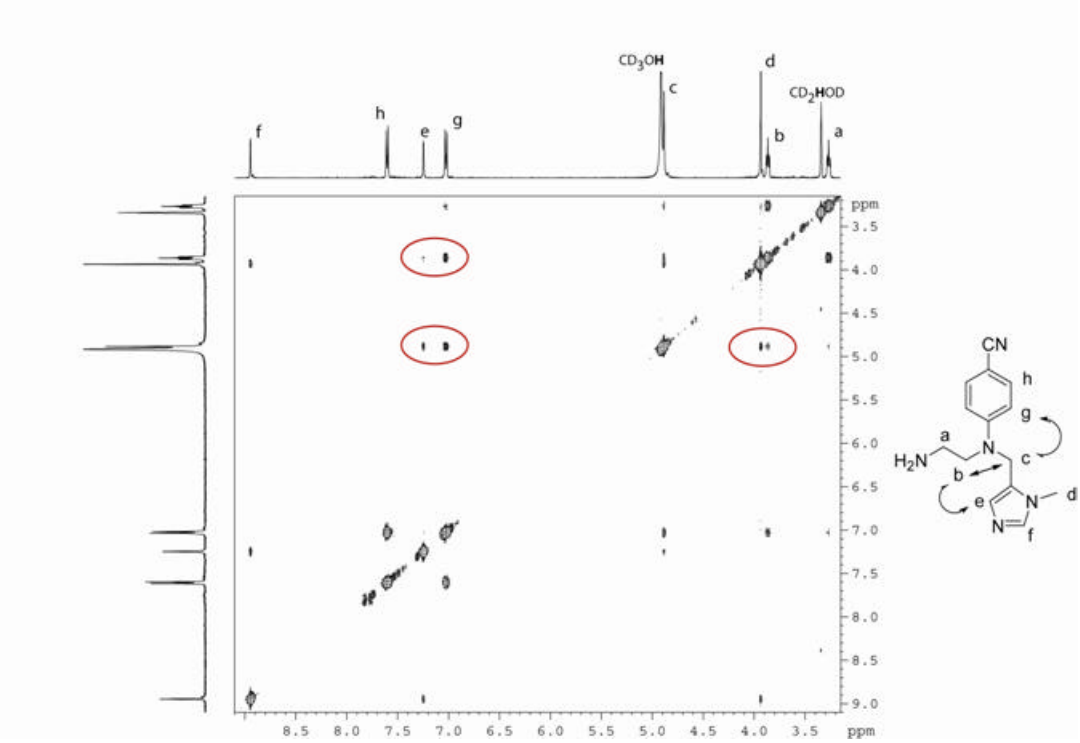
dissolved in EtOAc (300 mL) and washed consecutively with 1M aqueous HCl (1 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL), and brine (1 x 100 mL). The aqueous phase was dried over magnesium sulfate, and the solvent was removed under vacuum to provide the title compound as a yellow solid (7.0g, 89%) after FCC (1:1 EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.43 (d, *J*=8.64 Hz, 2H), 6.58 (d, *J*=8.62 Hz, 2H), 3.41 (br s, 2H), 3.29 (br t, *J*=5.67 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.3, 147.7, 134.1, 117.2, 112.5, 110.1, 79.6, 46.6, 40.5, 28.7.

[2-(4-Bromophenylamino)-ethyl]-carbamic acid tert-butyl ester (21): A solution of 4-bromoaniline (6.5 g, 37.2 mmol), (2-oxoethyl)-carbamic acid tert-butyl ester (2.0 g, 12.4 mmol) and acetic acid (790 µL, 12.4 mmol) in dry methanol (20 mL) with dry 3 ? molecular sieves (1 g) was stirred under nitrogen for 20 minutes. Sodium cyanoborohydride (790 mg, 12.4 mmol) was added in one portion, and the resulting solution stirred for a further hour under nitrogen, at which time EtOAc (300 mL) was added, and the organic phase washed consecutively with 1M aqueous HCl (1 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL), and brine (1 x 100 mL). The aqueous phase was dried over magnesium sulfate, and the solvent was removed under vacuum to provide the title compound as a viscous yellow oil (3.1 g, 79%) after FCC (1:4 EtOAc/Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.14 (d, *J*=8.88 Hz, 2H), 6.38 (d, *J*=8.89 Hz, 2H), 4.88 (br s, 1H), 3.26 (br s, 2H), 3.09 (br t, *J*=5.94 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): d 157.0, 147.5, 132.6, 114.6, 109.2, 80.1, 44.5, 40.3, 29.0.

{2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-carbamic acid tert-butyl ester (22): Lithium diisopropylamide (2.0 M, 3.8 mL, 7.6 mmol) was added dropwise to a solution of **20** (1.0 g, 3.8 mmol) in dry THF (50 mL) at -78°C and the resulting orange solution was stirred for 1 hour at -78°C under nitrogen. In a separate flask sodium hydride (230 mg, 5.7 mmol) was added to a solution of 5-chloromethyl-1-methyl-1*H*-imidazole·HCl (630 mg, 3.8 mmol) in dry THF (20 mL) at

0°C. The suspension of sodium chloride and imidazole was the immediately added to the dianion of **20** *via* cannula under nitrogen, and the resulting solution stirred overnight while warming slowly to room temperature. The reaction was quenched by addition of brine (1 mL), diluted with EtOAc (200 mL) and washed consecutively with 1M aqueous HCl (1 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL), and brine (1 x 100 mL). The aqueous phase was dried over magnesium sulfate, and the solvent was removed under vacuum. Purification by FCC (1:10 MeOH/DCM) provided the title compound as a white solid (330 mg, 59% b.r.s.m) after FCC (1:4 EtOAc/Hexane). ^{1}H NMR (500 MHz, d_4-MeOH): d 8.82 (s, 1H), 7.42 (d, *J*=8.97 Hz, 2H), 7.15 (s, 1H), 6.88 (d, *J*=9.00 Hz, 2H), 4.70 (s, 2H), 3.82 (s, 3H), 3.51 (t, *J*=6.69 Hz, 2H), 3.20 (obscured t, *J*= 6.70 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$): d 156.5, 151.4, 139.4, 134.0, 129.1, 127.2, 120.5, 112.9, 99.4, 80.0, 49.5, 44.9, 38.1, 32.1, 28.7.

2D NOESY of deprotected **22** identifies close spatial arrangement of protons about the imidazole and aniline.



{2-[(4-Bromophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-carbamic acid tert-butyl ester (23): The title compound was prepared as described for **22** and purified by FCC (1:10 MeOH/DCM, 62 % b.r.s.m). ^{1}H NMR (400 MHz, d_4-MeOH): d 8.78 (s, 1H), 7.22 (d, *J*=9.01, Hz, 2H), 7.17 (s, 1H), 6.74 (d, *J*=9.14 Hz, 2H), 4.58 (s, 2H), 3.79 (s, 3H), 3.40 (t, *J*=6.87 Hz, 2H), 3.14 (t, *J*= 6.70 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): d 158.9, 148.5, 137.9, 134.0, 133.6, 119.6, 118.5, 111.5, 80.6, 51.9, 46.7, 39.1, 34.6, 29.1.

General Procedure, Alkyl carbamates: Sodium hydride (60% dispersion, 1.5 *eq*) was added in one portion to a solution of the carbamate (1 *eq*) dissolved in DMF (2 mL/mmol) at 0°C. The resulting suspension was stirred for 5 minutes before addition of the alkyl halide (1.1 *eq*), and stirring was then continued for a further 10 minutes. The resulting solution was diluted with EtOAc (20 mL/mmol) and washed consecutively with equal portions of 1M aqueous HCl, saturated $NaHCO_3$, and brine. The aqueous phase was dried over magnesium sulfate, and the solvent was removed under vacuum. The crude reaction product was generally deprotected immediately by dissolving the crude material in TFA (1 mL/mmol) and stirring for 10 minutes. After removing the TFA under reduced pressure, the resulting oil was purified by rpHPLC to provide the product amine as the TFA salt.

***N*'-Benzyl-*N*-(4-bromophenyl)-N-(3-methyl-3*H*-imidazol-4-ylmethyl)-ethane-1,2-diamine (24, X=Br, R^1=Benzyl, R^3=Me):** Yield 73%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.75 (s, 1H), 7.35 (s, 5H), 7.26 (d, *J*=9.02 Hz, 2H), 7.12 (s, 1H), 6.75 (d, *J*=9.06 Hz, 2H), 4.57 (s, 2H), 4.14 (s, 2H), 3.74 (s, 3H), 3.60 (t, *J*=7.11 Hz, 2H), 3.17 (t, *J*=7.20 Hz, 2H). ^{13}C NMR (100 MHz, d_4-MeOH): d 147.5, 138.2, 133.9, 133.3, 132.7, 131.4, 131.2, 130.8, 119.8, 118.5, 113.5, 53.0, 48.5, 46.6, 45.3, 34.6.

4-[(2-Benzylaminoethyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-benzonitrile (25, X=CN, R^1=Benzyl, R^3=Me): Yield 65%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.88 (s, 1H), 7.55 (d, *J*=8.73 Hz,

2H), 7.45 (s, 5H), 7.19 (s, 1H), 6.95 (d, *J*=8.87 Hz, 2H), 4.82 (s, 2H), 4.20 (s, 2H), 3.87 (s, 3H), 3.34 (br s, 2H), 3.24 (br s, 2H). ^{13}C NMR (100 MHz, d_4-MeOH): d. 151.7, 138.2, 134.2, 133.4, 132.5, 131.3, 131.1, 130.8, 122.0, 116.2, 114.6, 102.0, 53.2, 47.9, 46.0, 45.2, 34.7.

4-[[2-(Cyclohexylmethyl-amino)-ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-benzonitrile (26, X=CN, R^1=Cylohexylmethyl, R^3=Me): Yield 59%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.84 (s, 1H), 7.48 (d, *J*=9.09 Hz, 2H), 7.14 (s, 1H), 6.91 (d, *J*=9.13 Hz, 2H), 4.76 (s, 2H), 3.82 (s, 3H), 3.78 (t, *J*=7.45 Hz, 2H), 3.19 (obscured), 2.84 (d, *J*= 6.96 Hz, 2H), 1.68 (m, 6H), 1.22 (m, 3H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, d_4-MeOH): d 151.7, 138.4, 135.4, 133.1, 121.0, 119.2, 114.6, 101.8, 55.8, 47.7, 46.0, 37.0, 34.6, 31.8, 27.4, 26.9.

***N*-*tert*-Butyl-2-{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethylamino}-acetamide (27, X=CN, R^1 = *N*-*tert*-Butylacetamido, R^3=Me):** Yield 52%. ^{1}H NMR (400 MHz, d_4-MeOH): *d* 8.98 (s, 1H), 7.56 (d, *J*=9.01 Hz, 2H), 7.28 (s, 1H), 7.01 (d, *J*=9.01 Hz, 2H), 4.86 (s, 2H), 4.83 (s, 2H), 3.91 (s, 3H), 3.83 (t, *J*=7.13 Hz, 2H), 3.23 (t, *J* =7.13 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, d_4-MeOH): *d* 165.6, 151.3, 140.2, 135.0, 132.7, 122.7, 120.6, 114.3, 101.3, 52.7, 52.2, 45.6, 37.4, 34.5, 29.1, 28.8.

4-[[2-(2-Methyl-benzylamino)-ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-benzonitrile (28, X = CN, R^1 = *o*-Methylbenzyl, R^3=Me): Yield 62%. ^{1}H NMR (400 MHz, d_4-MeOH): *d* 8.91 (s, 1H), 7.56 (d, *J*=8.67 Hz, 2H), 7.45 (d, *J*=7.43 Hz, 2H), 7.34–7.26 (m, 3H), 7.20 (s, 1H), 7.00 (d, *J*=8.67 Hz, 2H), 4.86 (s, 2H), 4.32 (s, 2H), 3.93–3.89 (m, 5H), 3.43 (t, *J*=7.53 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, d_4-MeOH): *d* 151.3, 138.8, 138.0, 135.0, 132.7, 132.2, 131.3, 130.9, 130.8, 127.8, 120.6, 118.8, 114.3, 101.4, 50.0, 47.4, 45.6, 45.2, 34.2, 19.2.

General Procedure, Sulfonamides: The required sulfonyl chloride (1.2 *eq*) was added in one portion to a solution of the amine (1.0 *eq*) and dry TEA (5.0 *eq*) in DMF (2 mL/mmol) at 0°C. The reaction was stirred for 10 minutes, diluted with acetonitrile and purified directly by rpHPLC to provide the desired sulfonamide as the TFA salt.

1-Methyl-1*H*-imidazole-4-sulfonic acid benzyl-{2-[(3*H*-imidazol-4-ylmethyl)-phenyl-amino]-ethyl}-amide (8, X=H, R^1=Benzyl, R^2= 4-methyl-1*H*-imidazole, R^3=H): Yield 62%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.74 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.28 (m, 5H), 7.22 (s, 1H), 7.04 (t, *J*=7.40 Hz, 2H), 6.64 (t, *J*=7.30 Hz, 1H), 6.45 (d, *J*=8.02 Hz, 2H), 4.40 (s, 2H), 4.22(s, 2H), 3.73 (m, 5H), 3.30 (obscured). ^{13}C NMR (100 MHz, d_4-MeOH): d 148.6, 141.8, 138.3, 135.7, 133.5, 131.4, 130.7, 130.6, 130.2, 129.6, 127.0, 119.6, 118.4, 114.8, 55.2, 52.3, 46.8, 46.6, 34.7. HRMS Calculated for $C_{23}H_{26}N_6O_2SH^+$ 451.1910, found 451.1916. Retention time for analytical rpHPLC: condition (I) 16.46, (II) 30.06 minutes.

1-Methyl-1*H*-imidazole-4-sulfonic acid benzyl-{2-[(4-bromo-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-amide (9, X=Br, R^1=Benzyl, R^2=4-Methyl-1*H*-imidazole, R^3=Methyl): Yield 65%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.71 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 7.23 (m, 5H), 7.17 (s, 1H), 7.07 (d, *J*=9.10 Hz, 2H), 6.30 (d, *J*= 9.15 Hz, 2H), 4.33 (s, 2H), 4.16 (s, 2H), 3.69 (s, 3H), 3.21 (obscured, 4H). ^{13}C NMR (100 MHz, d_4-MeOH): d 147.8, 141.9, 139.6, 138.2, 135.9, 133.4, 133.0, 130.6, 130.2, 129.7, 127.1, 118.5, 116.4, 111.2, 55.3, 52.7, 46.7, 46.6, 34.7. HRMS Calculated for $C_{24}H_{27}BrN_6O_2SH^+$ 543.1178, found 543.1186. Retention time for analytical rpHPLC: condition (I) 14.26, (II) 29.12 minutes.

1-Methyl-1*H*-imidazole-4-sulfonic acid {2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-cyclohexylmethyl-amide (12, X=CN, R^1=Cylohexylmethyl, R^2=4-Methyl-1*H*-imidazole, R^3=Methyl): Yield 75%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.82 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.47 (d, *J*= 9.04 Hz, 2H), 7.21 (s, 1H), 6.91 (d, *J*=9.14 Hz, 2H), 4.78 (s, 2H), 3.82 (s, 3H), 3.69 (m, 5H), 3.30 (m, 2H), 2.82 (d, *J*=7.32 Hz, 2H), 1.57 (m, 5H), 1.34(m, 1H), 1.05(m, 3H), 0.76 (m, 2H). ^{13}C NMR (100 MHz, d_4-MeOH): d 152.2, 141.7, 139.5, 138.3, 135.3, 133.4, 127.0, 121.2, 119-61 114.3, 100.8, 58.6, 51.61 48.4, 45.8, 38.4, 34.7, 32.3, 27.9, 27.3. HRMS Calculated for $C_{25}H_{34}N_7O_2S^+$: 496.2495, found 496.2497. Retention time for analytical rpHPLC: condition (I) 14.92, (II) 27.55 minutes.

***N*-Benzyl-*N*-{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-benzenesulfonamide (10, X=CN, R^1= Benzyl, R^2=Phenyl, R^3=Methyl):** Yield 67%. ^{1}H NMR (500 MHz, d_4-MeOH): d 8.78 (s, 1H), 7.81 (s, 1 H), 7.80 (s, 1 H), 7.60 (t, *J*= 7.40 Hz, 1H), 7.54 (m, 2H), 7.33 (d, *J*= 9.08 Hz, 2H), 7.22 (m, 5H), 7.03 (s, 1H), 6.50 (d, *J*=9.13 Hz, 2H), 4.40 (s, 2H), 4.18 (s, 2H), 3.72 (s, 3H), 3.33 (m, 2H), 3.15 (m, 2H). ^{13}C NMR (125 MHz, d_4-MeOH): d 151.8, 140.0, 138.2, 138.0, 135.1, 134.8, 133.1, 131.0, 130.8, 130.3, 129.8, 128.9, 119.5, 114.1, 101.4, 55.7, 51.5, 46.8, 45.4, 34.6. HRMS Calculated for $C_{27}H_{27}N_5O_2SH^+$ 486.1958, found 486.1963. Retention time for analytical rpHPLC: condition (I) 13.35, (II) 26.31 minutes.

1-Methyl-1*H*-imidazole-4-sulfonic acid benzyl-{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-amide (1, X=CN, R^1=Benzyl, R^2=4-Methyl-1*H*-imidazole, R^3=Methyl): Yield 66%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.79 (s, 1H), 7.73 (s, 1H), 7.69(s, 1H), 7.32 (d, *J*=9.07 Hz, 2H), 7.25 (m, 5H), 7.06 (s, 1H), 6.48 (d, *J*=8.90 Hz, 2H), 4.44 (s, 2H), 4.17 (s, 2H), 3.73 (s,3H), 3.72 (s, 3H), 3.35 (m, 2H), 3.27 (m, 2H). ^{13}C NMR (100 MHz, d_4-MeOH): d 151.9, 141.9, 139.3, 138.2, 135.1, 133.1, 130.8, 130.2, 129.7, 127.2, 121.2, 119.5, 114.0, 100.6, 55.6, 51.5, 46.8, 45.3, 34.7,

34.6. HRMS Calculated for $C_{25}H_{28}N_7O_2S^+$: 490.2025, found 490.2028. Retention time for analytical rpHPLC: condition (I) 12.77, (II) 24.84 minutes.

5-Dimethylamino-naphthalene-1-sulfonic acid benzyl-{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-amide (11, X=CN, R^1=Benzyl, R^2=5-Dimethylamino-naphthalene, R^3=Me): Yield 64%. ^{1}H NMR (400 MHz, d_4-MeOH): d 8.78 (s, 1H), 8.58 (d, *J*= 8.54 Hz, 1H), 8.28 (d, *J*= 8.66 Hz, 1H), 8.09 (d, *J*= 7.34 Hz, 1H), 7.53 (d, *J*= 7.30 Hz, 1H), 7.49 (d, *J*= 7.16 Hz, 1H), 7.32 (d, *J*= 9.04 Hz, 2H), 7.23 (d, *J*= 7.39 Hz, 1H), 7.18 (m, 5H), 6.99 (s, 1H), 6.48 (d, *J*= 9.09 Hz, 2H), 4.41 (s, 2H), 4.37 (s, 2H), 3.71(s,3H), 3.32 (m, 4H), 2.82 (s, 6H). ^{13}C NMR (100 MHz, d_4-MeOH): d 153.5, 151.2, 138.2, 138.0, 136.1, 135.1, 133.5, 133.1, 132.2, 131.8, 131.1, 130.6, 130.2, 129.8, 129.7, 124.9, 121.2, 119.4, 117.1, 114.1, 100.9, 54.2, 50.7, 46.2, 45.7, 45.6, 34.6. HRMS Calculated for $C_{33}H_{35}N_6O_2S^+$: 579.2542, found 579.2546. Retention time for analytical rpHPLC: condition (I) 14.67, (II) 30.30 minutes.

***N*-tert-Butyl-2-[{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-(1-methyl-1*H*-imidazole-4-sulfonyl)-amino]-acetamide (13, X = CN, R^1 = *N*-*tert*-Butylacetamido, R^2 = 1-Methyl-1*H*-imidazole, R^3=Me):** Yield 83%. ^{1}H NMR (400 MHz, d_4-MeOH): *d* 8.94 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.29 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.82 (s, 4H), 3.91 (s, 3H), 3.74 (s, 3H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.21 (t, *J* = 6.2 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, d_4-MeOH): *d* 165.6, 151.7, 141.1, 140.5, 140.0, 134.8, 133.0, 125.8, 123.1, 120.8, 113.9, 100.3, 52.7, 52.2, 51.5, 46.0, 41.3, 34.5, 34.3, 28.7. HRMS Calculated for $C_{24}H_{32}N_8O_3SH^+$ 513.2396, found 513.2392. Retention time for analytical rpHPLC: condition (I) 12.14, (II) 17.82 minutes.

1-Methyl-1*H*-imidazole-4-sulfonic acid biphenyl-4-ylmethyl-{2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-amide (14, X=CN, R^1= Biphenyl-4-ylmethyl, R^2=4-Methyl-1*H*-imidazole, R^3=Me): Yield 74%. ^{1}H NMR (500 MHz, d_4-MeOH): d 8.77 (s, 1H), 7.80 (s, 1 H), 7.77 (s, 1 H), 7.58 (dd, *J*= 1.28, 8.50 Hz, 2H), 7.56 (d, *J*= 8.23 Hz, 2H), 7.44 (t, *J*= 7.47 Hz, 2H), 7.37 (d, *J*= 8.21 Hz, 2H), 7.36 (tt, *J*= 1.14, 7.38 Hz, 1H), 7.29 (d, *J*= 9.05 Hz, 2H), 7.12 (s, 1H), 6.53 (d, *J*=9.10 Hz, 2H), 4.54 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.48 (m, 2H), 3.38 (m, 2H). ^{13}C NMR (125 MHz, d_4-MeOH): d 149.1, 139.9, 139.2, 139.0, 136.5, 135.4, 134.3, 132.3, 130.4, 128.7, 127.8, 126.4, 125.8, 125.5, 124.6, 118.4, 116.7, 111.2, 97.8, 52.8, 48.8, 44.4, 42.8, 32.0, 31.8. HRMS Calculated for $C_{31}H_{32}N_7O_2S^+$: 566.2338, found 566.2358. Retention time for analytical rpHPLC: condition (I) 15.69, (II) 30.13 minutes.

1-Methyl-1*H*-imidazole-4-sulfonic acid {2-[(4-cyano-phenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]-ethyl}-(2-methyl-benzyl)-amide (15, X=CN, R^1=*o*-Methylbenzyl, R^2=4-Methyl-1*H*-imidazole, R^3 = Me): Yield 83%. ^{1}H NMR (400 MHz, d_4-MeOH): *d* 8.87 (s, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.38 (d, *J*=8.91 Hz, 2H), 7.30–7.17 (m, 4H), 7.10 (s, 1H), 6.48 (d, *J*=8.91 Hz, 2H), 4.40 (s, 2H), 4.25 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.29 (br s, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, d_4-MeOH): *d* 151.5, 141.6, 139.8, 138.2, 137.8, 134.9, 134.7, 132.6, 132.2, 132.1, 129.8, 127.2, 127.0, 120.8, 119.0, 113.5, 100.0, 54.0, 51.0, 45.6, 44.6, 34.4, 34.2, 19.3. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}N_7O_2SH^+$ 504.2182, found 504.2177. Retention time for analytical rpHPLC: condition (I) 14.68, (II) 22.48 minutes.

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