Supplemental Information

Inhibition of the human proteasome by imidazoline scaffolds

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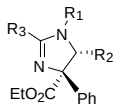
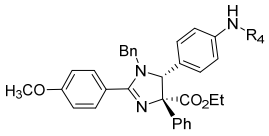
Biological Methods.

The fluorogenic substrate Suc-LLVY-AMC was used to measure CT-L proteasome activity using 1 nM purified 20S proteasome (Boston Biochem, Cambridge MA). The rate of cleavage of fluorogenic peptide substrate was determined by monitoring the fluorescence of released aminomethylcoumarin using a SpectraMax M5e multiwell plate reader at an excitation wavelength of 380 nm and emission wavelength of 460 nm. Fluorescence was measured at 37° C every minute over a 30 minute period and the maximum increase in fluorescence per minute was used to calculate specific activities of each sample. IC_{50} values and statistics were calculated using GraphPad Prism version 5.02 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.



	Trial 1	Trial2	Trial 3	IC_{50}(μM)
11	>10	Not tested	Not tested	>10
12	>10	Not tested	Not tested	>10
13	>10	Not tested	Not tested	>10
14	>10	Not tested	Not tested	>10
15	7.04	Not tested	Not tested	7.04
1	2.8	1.72	3.21	2.58 ± 0.44
16	2.12	3.34	Not tested	2.73 ± 0.61
17	2.32	4.55	4.26	3.71 ± 0.70
18	2.02	2.01	Not tested	2.02 ± 0.01
19	1.29	2.5	Not tested	1.90 ± 0.61
20	>10	Not tested	Not tested	>10
21	1.99	7.8	8.59	6.13 ± 2.08
22	4.36	7.74	8.04	6.71 ± 1.18
23	2.95	4.09	Not tested	3.52 ± 0.57
24	2.45	8.03	3.94	4.81 ± 1.67
25	2.18	1.81	2.7	2.23 ± 0.26
26	0.68	1.48	Not tested	1.08 ± 0.4
27	1.53	4.01	Not tested	2.77 ± 1.24
28	>10	Not tested	Not tested	>10
29	0.53	0.4	Not tested	0.47± 0.07
30	1.81	4.2	3.56	3.19 ± 0.71
31	1.2	1.34	Not tested	1.27 ± 0.07
32	>10	Not tested	Not tested	>10
33	>10	Not tested	Not tested	>10

Table S1. Inhibition of the chymotryptic-like activity of purified human 20S proteasome by compounds **11-33**. Each trial is the average of two technical replicates. Data are represented as means ± standard error.



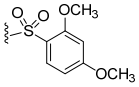
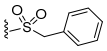
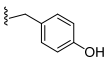
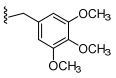
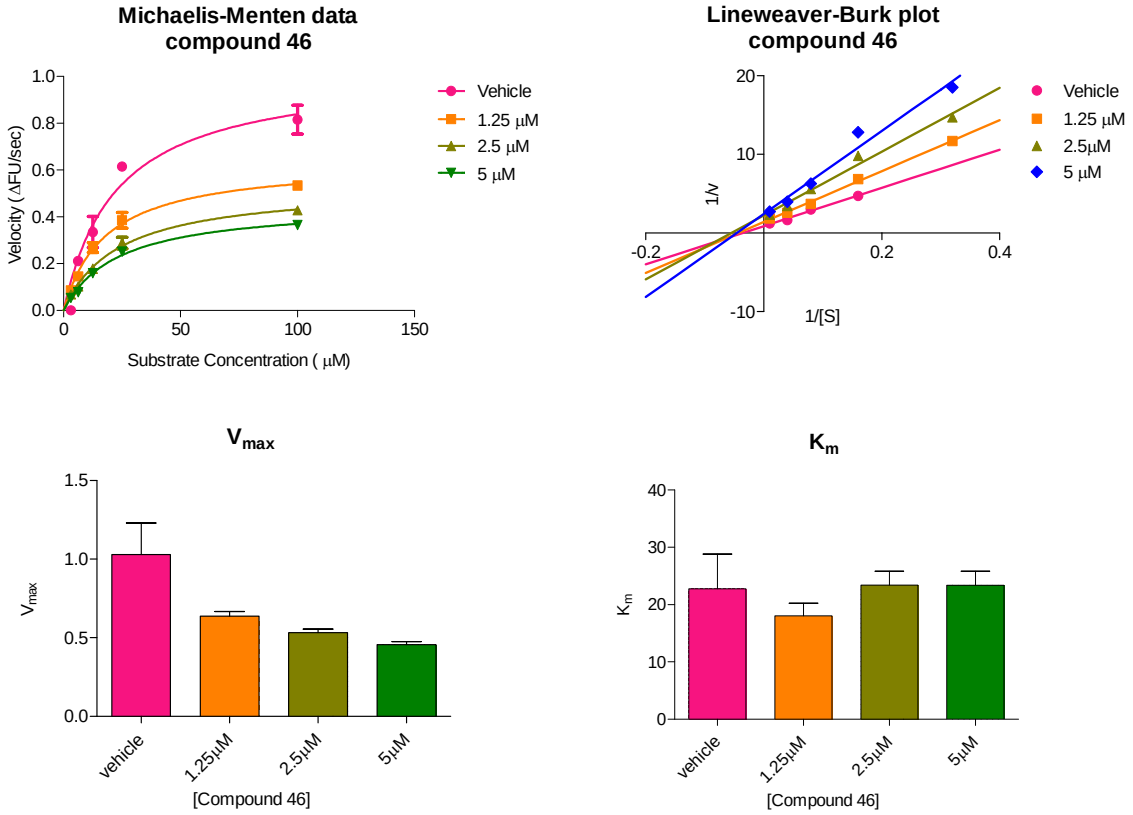
	R_4	Trial 1	Trial 2	Trial 3	Mean ± SEM
37	H	1.2	2.22	2.49	1.97 ± 0.39
38	Ac	1.67	2.07	2.78	2.17 ± 0.32
39	Bz	1.15	1.86	1.31	1.44 ± 0.21
40		0.67	0.54	0.69	0.63 ± 0.05
41		0.41	0.75	0.58	0.58 ± 0.17
42		0.37	0.60	0.63	0.53 ± 0.08
43		0.86	1.39	1.00	1.08 ± 0.16
44		0.80	1.02	No 3rd trial	0.91 ± 0.11
45		0.83	1.35	1.48	1.22 ± 0.2
46		0.29	0.3	0.3	0.30 ± 0.003
47		0.30	0.66	0.66	0.54 ± 0.12
48		0.52	0.23	0.35	0.37 ± 0.08
49		0.130	0.160	0.10	0.13 ± 0.02

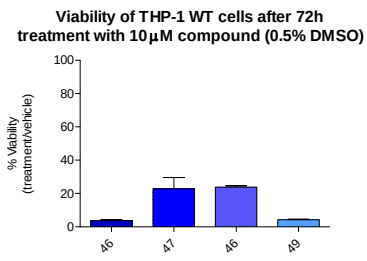
Table S2. Inhibition of the chymotryptic-like activity of purified human 20S proteasome by compounds **37-49**. Each trial is the average of two technical replicates. Data are represented as means ± standard error.

Figure S1. Kinetic analysis of CT-L activity inhibition by compound 46. Purified human 20S proteasome was treated with either vehicle, 5 µM, 2.5 µM, or 1.25 µM compound 46; and varying concentrations of Suc-LLVY-AMC substrate. Reaction velocity was monitored as specified previously. Michaelis-Menten, Lineweaver-Burk plot and statistics were calculated using GraphPad Prism version 5.02 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

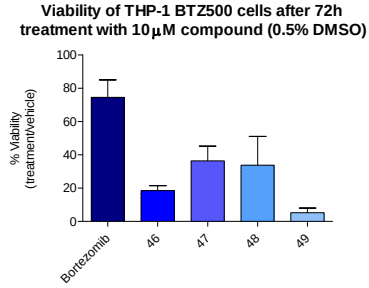


	vehicle	1.25µM	2.5µM	5µM
Michaelis-Menten				
Best-fit values				
Vmax	1.030	0.6380	0.5326	0.4564
Km	22.76	18.06	23.41	23.34
Std. Error				
Vmax	0.1077	0.02911	0.02186	0.01938
Km	6.071	2.183	2.405	2.483
95% Confidence Intervals				
Vmax	0.7752 to 1.284	0.5709 to 0.7052	0.4822 to 0.5830	0.4117 to 0.5011
Km	8.406 to 37.12	13.03 to 23.10	17.86 to 28.96	17.61 to 29.07
Goodness of Fit				
Degrees of Freedom	7	8	8	8
R square	0.9317	0.9809	0.9876	0.9871
Absolute Sum of Squares	0.04644	0.005097	0.002162	0.001707
Sy.x	0.08146	0.02524	0.01644	0.01461
Number of points				
Analyzed	9	10	10	10

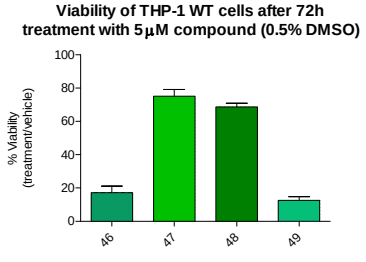
Figure S2. The human cell line THP-1 cells were a kind gift from Dr. Oerlemans of the VU University Medical Center, Amsterdam, The Netherlands. Cells were maintained in RPMI-1640 supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100 mg/mL streptomycin, 1 mM sodium pyruvate, and 0.2 mM L-glutamine. Cells were cultured at 37°C, 5% CO2. BTZ500 cells were maintained in complete media with 500nM Bortezomib and were given a 72h washout period before the cell viability assay. Drugs were dissolved in DMSO and added to cells to reach a final concentration of 10µM drug and 0.5% DMSO. Cell viability was assayed after 72h using the CellTiter 96® AQueous One Solution Cell Proliferation Assay (Promega Corporation, Madison WI) according to manufacturer specifications. The absorbance of formazan was measured at 490 nm on a SpectraMaxM5e microplate reader. Background absorbance was subtracted from each measurement and viability was calculated using the vehicle control as 100%.



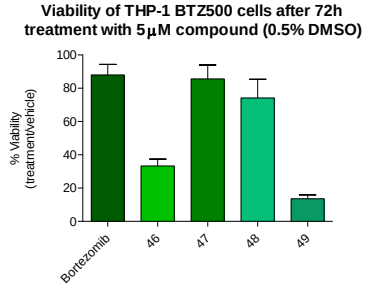
	46	47	46	49
Number of values	3	3	3	3
Minimum	3.450	10.53	22.95	3.350
25% Percentile	3.450	10.53	22.95	3.350
Median	3.510	24.00	23.78	4.450
75% Percentile	4.530	33.92	25.00	4.760
Maximum	4.530	33.92	25.00	4.760
Mean	3.830	22.82	23.91	4.187
Std. Deviation	0.6070	11.74	1.031	0.7410
Std. Error	0.3504	6.778	0.5953	0.4278
Lower 95% CI of mean	2.322	-6.347	21.35	2.346
Upper 95% CI of mean	5.338	51.98	26.47	6.027
Sum	11.49	68.45	71.73	12.56



	Bortezomib	46	47	48	49
Number of values	5	6	4	5	5
Minimum	54.32	9.850	17.13	9.040	1.050
25% Percentile	55.86	10.38	19.39	10.04	1.080
Median	60.67	20.64	38.54	11.73	1.240
75% Percentile	100.0	24.69	51.44	68.48	11.47
Maximum	100.0	25.29	51.62	100.0	15.16
Mean	74.48	18.58	36.46	33.75	5.268
Std. Deviation	23.41	7.165	17.49	38.76	6.234
Std. Error	10.47	2.925	8.747	17.34	2.788
Lower 95% CI of mean	45.42	11.06	8.620	-14.38	-2.473
Upper 95% CI of mean	103.5	26.10	64.30	81.88	13.01
Sum	372.4	111.5	145.8	168.8	26.34



	46	47	48	49
Number of values	3	3	3	3
Minimum	9.980	70.44	65.35	10.24
25% Percentile	9.980	70.44	65.35	10.24
Median	17.71	71.94	67.75	10.41
75% Percentile	23.68	83.05	72.79	17.04
Maximum	23.68	83.05	72.79	17.04
Mean	17.12	75.14	68.63	12.56
Std. Deviation	6.869	6.888	3.797	3.878
Std. Error	3.966	3.977	2.192	2.239
Lower 95% CI of mean	0.06032	58.03	59.20	2.930
Upper 95% CI of mean	34.19	92.25	78.06	22.20
Sum	51.37	225.4	205.9	37.69



	Bortezomib	46	47	48	49
Number of values	5	6	5	5	5
Minimum	65.43	21.18	54.27	42.16	5.530
25% Percentile	74.28	24.17	70.34	52.26	9.070
Median	92.93	34.23	87.00	65.94	15.33
75% Percentile	99.20	42.25	100.0	100.0	17.37
Maximum	100.0	43.90	100.0	100.0	19.16
Mean	87.98	33.40	85.54	74.09	13.64
Std. Deviation	14.23	10.01	18.70	25.33	5.097
Std. Error	6.362	4.088	8.363	11.33	2.280
Lower 95% CI of mean	70.31	22.89	62.32	42.64	7.313
Upper 95% CI of mean	105.6	43.91	108.8	105.5	19.97
Sum	439.9	200.4	427.7	370.5	68.21

EXPERIMENTAL SECTION

Solubility test. To a 3mL vial was added 1mL of a 5% dextrose in water solution and 3 µl 2 N HCl, resulting in final pH of 6.5. The compound was added 0.5 mg at a time, followed by 0.1mg at a time close to its saturation point. The vial was vortexed for 40 seconds and sonicated for an addition 30 seconds at 37.5°C. Solutions were subsequently incubated at 37.5°C for 5 minutes and checked for their solubility visually.

General Information. All commercial reagents were purchased from commercial suppliers and used without further purification. All solvents were reagent grade. THF was freshly distilled from sodium / benzophenone under nitrogen. CH_2Cl_2 was dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. Melting points were obtained using an Electrothermal® capillary melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (230-400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Unity Plus-500 spectrometer. High-resolution 70eV EI mass spectra and FAB mass spectra were obtained at the RTSF Mass Spectrometry Facility of the Michigan State University, using a JEOL AX-505H and a JEOL HX-110 double focusing mass spectrometer (JEOL USA, Peabody, MA), respectively. Combustion analysis was performed on a PerkinElmer 2400 Series II CHNS/O analyzer. Compounds are evaluated for >95% purity using HPLC analysis (acetonitrile/methanol/water) using a C18 column.

General procedure for the synthesis of compounds from Table 2
The compounds **1-10, 27** were prepared according to the methods described in previously reported literature and previously reported compounds **1-9** matched their reported data.[1] Data is provided below of all new compounds.

DL-(4*S*,5*S*)-2-hydroxyethyl 1-benzyl-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (10). The resulting crude residue was purified using silica gel (100% ethyl acetate) to afford the product as an orange solid (304 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21-3.31 (m, 2H), 3.53-3.57 (m, 1H), 3.65-3.69 (m, 1H), 3.82 (d, 1H, J = 15.6 Hz) 4.25 (br s, 1H), 4.60 (d, 1H, J = 15.6 Hz) 4.92 (s, 1H), 6.74 (d, 2H, 7.8 Hz) 7.07 (t, 2H, J = 7.4 Hz), 7.13 (t, 1H, J = 7.1 Hz), 7.28-7.31 (m, 1H), 7.35 (t, 3H, J = 7.1 Hz), 7.38-7.39 (m, 4H), 7.45-7.46 (m, 3H), 7.23-7.76 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.6, 60.2, 67.0, 73.9, 82.6, 126.5, 127.1, 127.4, 127.7, 127.9, 128.2, 128.5, 128.6, 128.67, 128.69, 128.74, 130.1, 130.6, 136.4, 137.7, 143.7, 165.7, 170.8. IR (NaCl): 3065 cm^{-1}, 1734 cm^{-1}, 1497 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{31}H_{29}N_2O_3$ [M+H], 477.2178, found 477.2178.

General procedure for the synthesis compounds from Table 3
The compounds 1**1-25, 30-32** were prepared according to the methods described in previously reported literature and previously reported compounds **11-25** matched their reported data.[1] Data is provided below of all new compounds.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2,4-diphenyl -5-(4-(phenyl sulfonamido) phenyl)-4,5- dihydro-1*H*- imidazole-4-carboxylate (26). A solution of **23** (20.0 mg, 0.042 mmol) in dichloromethane

(40 mL), cooled to 0 °C in an ice bath, was treated with benzene sulfonyl chloride (5.8 μL, 0.045 mmol). The reaction was stirred at 0 °C for 45 minutes. The reaction was then treated with pyridine and stirred overnight while slowly warming to room temperature. The reaction was diluted with saturated $NaHCO_3$ solution and extracted with dichloromethane (3x). The combined organic extracts were dried over Na_2SO_4, concentrated, and the crude product was purified *via* silica gel chromatography (3:2 ethyl acetate:hexane) to afford the desired product as a yellow thin film (14.5 mg, 56%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (t, 3H, J = 7.1 Hz), 3.45 (dq, 1H, J_1 = 10.8 Hz, J_2 = 7.1 Hz), 3.57 (dq, 1H, J_1 = 10.8 Hz, J_2 = 7.1 Hz), 3.75 (d, 1H, J = 15.7 Hz), 4.57 (d, 1H, J = 15.7 Hz), 4.83 (s, 1H), 6.71 (d, 2H, J = 7.2 Hz), 7.06 (dd, 2H, J_1 = 10.1 Hz, J_2 = 4.7 Hz), 7.09 – 7.14 (m, 3H), 7.26 (d, 2H, J = 8.4 Hz), 7.28 – 7.35 (m, 3H), 7.44 – 7.51 (m, 5H), 7.52 – 7.57 (m, 1H), 7.67 – 7.71 (m, 2H), 7.72 – 7.76 (m, 2H), 7.81 – 7.85 (m, 2H). ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$) δ 13.5 (–**C**H$_3$), 48.8 (–**C**H$_2$), 60.9 (–**C**H$_2$), 73.1 (–**C**H), 82.7 (quaternary –**C**), 121.0 (aromatic –**C**H), 126.7 (aromatic –**C**H), 127.2 (aromatic –**C**H), 127.3 (aromatic –**C**H), 127.46 (aromatic –**C**H), 127.51 (aromatic –**C**H), 128.1 (aromatic –**C**H), 128.4 (aromatic –**C**H), 128.6 (aromatic –**C**H), 128.8 (aromatic –**C**H), 129.0 (aromatic –**C**H), 129.1 (aromatic –**C**H), 130.3 (aromatic quaternary –**C**), 130.5 (aromatic –**C**H), 133.0 (aromatic –**C**H), 134.7 (aromatic quaternary –**C**), 136.3 (aromatic quaternary –**C**), 136.6 (aromatic quaternary –**C**), 139.2 (aromatic quaternary –**C**), 143.7 (aromatic quaternary –**C**), 165.5 (quaternary –**C**), 170.6 (quaternary –**C**). IR (neat): 3248 cm^{-1}, 1732 cm^{-1}, 1232 cm^{-1}, 1159 cm^{-1}, 1093 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{37}H_{34}N_3O_4S$ [M+H], 616.2270; found, 616.2277.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-(methylthio)phenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (27). The resulting crude residue was purified using silica gel (60:39:1 ethyl acetate:hexane:dichloromethane) to afford the product as a solid (0.50 g, 23%); mp 156-158 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.1 Hz), 2.48 (s, 3H), 3.63 – 3.82 (m, 2H), 3.85 (d, 1H, J = 15.8 Hz), 4.63 (d, 1H, J = 15.8 Hz), 4.92 (s, 1H), 6.77 (d, 2H, J = 7.1 Hz), 7.05 – 7.15 (m, 3H), 7.26 – 7.31 (m, 3H), 7.33 – 7.39 (m, 4H), 7.46 – 7.50 (m, 3H), 7.77 – 7.82 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD) δ 14.0, 15.7, 49.7, 62.4, 74.5, 83.7, 127.6, 127.8, 128.6, 128.9, 129.0, 129.5, 129.8, 129.9, 130.0, 130.2, 131.3, 132.1, 135.2, 137.6, 141.2, 144.9, 167.7, 172.1. IR (neat): 1732 cm^{-1}, 1617 cm^{-1}, 1598 cm^{-1}, 1497 cm^{-1}, 1229 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{32}H_{31}N_2O_2S$ [M+H], 507.2106; found, 507.2113.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-(methylsulfonyl)phenyl)-2,4-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (28). To a solution of **27** (104 mg, 0.20 mmol) in methanol (3 mL), cooled to 0 °C in an ice bath, was added a suspension of oxone (0.76 g, 0.61 mmol) in H_2O (3 mL). The reaction was removed from the ice bath and stirred at room temperature for 3 hours. The reaction was diluted with H_2O and extracted with chloroform (3 x 30 mL). The pooled organic extracts were successively washed with H_2O and brine before being dried over Na_2SO_4 and concentrated to an oil. The crude oil was purified using silica gel (67:33 ethyl acetate:hexane) to afford the desired product as a thin film (13.8 mg, 13%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.1 Hz), 3.08 (s, 3H), 3.65 – 3.79 (m, 2H), 3.83 (d, 1H, J = 15.7 Hz), 4.62 (d, 1H, J = 15.7 Hz), 4.95 (s, 1H), 6.73 (d, 2H, J = 7.4 Hz), 7.07 (dd, 2H, J_1 = 10.3 Hz, J_2 = 4.7 Hz), 7.14 (t, 1H, J = 7.4 Hz), 7.29 – 7.38 (m, 3H), 7.50 – 7.55 (m, 3H), 7.61 (d, 2H, J = 7.8 Hz), 7.69 – 7.73 (m, 2H), 7.79 – 7.82 (m, 2H), 7.94 – 7.98 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.5, 44.4, 49.3, 61.2, 73.2, 83.2, 126.6, 127.3, 127.5, 127.66, 127.74, 128.2, 128.5, 128.8, 128.9, 129.1, 130.0, 130.7, 135.9, 140.4, 143.5, 145.0, 165.8, 170.5. IR (neat): 1734 cm^{-1}, 1309

cm^{-1}, 1236 cm^{-1}, 1151cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{32}H_{31}N_2O_4S$ [M+H], 539.2005; found, 539.2003.

DL-(4S,5S)-ethyl 1-benzyl-5-(4-(benzylamino)phenyl)-2,4-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate (29). To a flame dried flask was added **23** (90 mg, 0.19 mmol) and dichloroethane (10 mL). Then benzaldehyde (24 mg, 0.23 mmol) was added, followed by the addition of $NaBH(OAc)_3$ (121 mg, 0.57 mmol). The reaction was refluxed overnight, quenched with $NaHCO_3$, and the aqueous layer was extracted with dichloromethane. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified using TEA-neutralized silica gel (1:1 ethyl acetate:hexane) to afford the imine product as a white foam (60 mg, 56%). The unreacted imine (60 mg, 0.11 mmol) was subsequently added to a flame-dried flask along with $NaBH_4$ (10 mg, 0.26 mmol) and refluxed in ethanol (12 mL) for 12 hours to complete the reduction. The crude reaction mixture was concentrated *in vacuo* then dissolved in dichloromethane to be washed with $NaHCO_3$ (2 x 25 mL). The organic layer was dried with Na_2SO_4 and purified *via* trituration in a minimal amount of 3:2 ethyl acetate:hexanes to yield a white solid (14 mg, 13% overall yield from **23**); mp 60-64 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, J=6.9 Hz), 3.63-3.77 (m, 2H), 3.85 (d, 1H, J=15.7 Hz), 4.36 (s, 2H), 4.57 (d, 1H, J=16.1), 4.83 (s, 1H), 6.63 (d, 2H, J=8.8 Hz), 6.76 (d, 2H, J=7.3 Hz), 7.06-7.13 (m, 3H), 7.18 (d, 2H, J=7.8 Hz), 7.25-7.39 (m, 7H), 7.44-7.46 (m, 3H), 7.72-7.75 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 48.2, 48.3, 60.9, 73.6, 82.6, 112.7, 126.1, 126.9, 127.1, 127.19, 127.22, 127.3, 127.4, 127.9, 128.3, 128.5, 128.6, 128.8, 129.2, 130.1, 130.9, 137.0, 139.2, 144.3, 148.1, 165.2, 171.0. IR (NaCl): 3374 cm^{-1}, 3029 cm^{-1}, 1732 cm^{-1}, 1524 cm^{-1}, 1244 cm^{-1}. HRMS (TOF MS ES+) *m/z* calculated for $[C_{38}H_{36}N_3O_2]^+$, 566.2808; found 566.2813.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2-(4-bromophenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (30). (0.390 g, 67%); ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.1 Hz), 3.57-3.64 (m, 1H), 3.68-3.74 (m, 1H), 3.86 (d, 1H, J = 15.9 Hz), 4.57 (d, 1H, J = 15.8 Hz), 4.95 (s, 1H), 6.76 (d, 2H, J = 7.3 Hz), 7.08-7.11 (m, 2H), 7.14-7.17 (m, 1H), 7.28-7.34 (m, 1H), 7.34-7.38 (m, 3H), 7.39-7.40 (m, 4H), 7.62-7.67 (m, 4H), 7.72-7.74 (m, 2H). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 13.5, 48.7, 61.0, 73.9, 83.0, 124.7, 126.7, 127.1, 127.45, 127.47, 128.05, 128.12, 128.4, 128.48, 128.52, 129.6, 130.4, 131.9, 136.4, 137.8, 143.9, 164.5, 170.6. IR (NaCl): 3031 cm^{-1}, 1734 cm^{-1}, 1611 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{31}H_{28}N_2O_2Br$ [M+H], 539.1334; found 539.1334.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (31). (45.2 mg, 6% not optimized); mp 115-119 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, 3H, J = 7.1 Hz), 3.61 (dq, 1H, J_1 = 10.8 Hz, J_2 = 7.1 Hz), 3.70 (dq, 1H, J_1 = 10.8 Hz, J_2 = 7.1 Hz), 3.83 – 3.89 (m, 4H), 4.67 (d, 1H, J = 15.8 Hz), 4.91 (s, 1H), 6.77 (d, 2H, J = 7.2 Hz), 6.98–7.03 (m, 2H), 7.05–7.10 (m, 2H), 7.10–7.15 (m, 1H), 7.26–7.43 (m, 8H), 7.73–7.79 (m, 4H). ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.5 (–**C**H_3), 48.8 (–**C**H_2), 55.3 (–**C**H_3), 60.9 (–**C**H_2), 73.8 (–**C**H), 82.7 (quaternary –**C**), 113.9 (aromatic –**C**H), 122.7 (aromatic quaternary –**C**), 126.8 (aromatic –**C**H), 127.1 (aromatic –**C**H), 127.28 (aromatic –**C**H), 127.30 (aromatic –**C**H), 127.9 (aromatic –**C**H), 128.1 (aromatic –**C**H), 128.2 (aromatic –**C**H), 128.3 (aromatic –**C**H), 128.4 (aromatic –**C**H), 130.4 (aromatic –**C**H), 136.8 (aromatic quaternary –**C**), 138.1 (aromatic quaternary –**C**), 144.3 (aromatic quaternary –**C**), 161.2 (aromatic quaternary –**C**), 165.2

(quaternary –**C**), 170.8 (quaternary –**C**). IR (neat): 1729 cm^{-1}, 1617 cm^{-1}, 1252 cm^{-1}, 1074 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{32}H_{31}N_2O_3$ [M+H], 491.2335; found, 491.2346.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-cyanophenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (32). The resulting residue was purified using silica gel (1:1 ethyl acetate:hexane) to afford the desired product as a white solid (108 mg, 32% yield); mp 228-232 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, 3H, J = 7.2 Hz) 3.54-3.59 (m, 1H) 3.63-3.68 (m, 1H), 3.77 (d, 1H, J = 15.8 Hz), 3.79 (s, 3H), 4.56 (d, 1H, J = 15.5 Hz), 4.80 (s, 1H), 6.65 (d, 2H, J = 7.3 Hz), 6.94 (d, 2H, J = 8.8 Hz), 6.97 (t, 2H, J = 7.8 Hz), 7.04 (t, 1H, J = 7.3), 7.19-7.23 (m, 1H), 7.26 (t, 2H, J = 6.9 Hz), 7.42 (d, 2H, J = 7.9 Hz), 7.58 (d, 2H, J = 8.8 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.68 (d, 2H, J = 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 49.6, 55.3, 61.1, 73.3, 83.0, 111.8, 114.0, 118.5, 122.1, 126.5, 127.2, 127.51, 127.54, 128.1, 128.4, 128.8, 130.4, 132.1, 136.0, 143.6, 144.2, 161.4, 165.5, 170.4. IR (NaCl): 2228 cm^{-1}, 1734 cm^{-1}, 1617 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{33}H_{30}N_3O_3$ [M+H], 516.2287; found 516.2277.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-carbamoylphenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (33). To a flask containing **32** (208 mg. 0.390 mmol) and THF (10 mL) was added concentrated ammonium hydroxide (3 mL) and 30% hydrogen peroxide solution (3 mL). The reaction was allowed to stir at room temperature for 12 hours. The reaction was diluted with water (15 mL), extracted with dichloromethane (25 mL), and dried over Na_2SO_4. The organic layer was concentrated *in vacuo* and the crude product was recrystallized from ethanol to afford the desired product as a white solid (60 mg, 28%); mp 189-191 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (t, 3H, J = 7.2 Hz), 3.48-3.54 (m, 1H), 3.57-3.620 (m, 1H), 3.71 (d, 1H, J = 15.8 Hz) 3.76 (s, 3H), 4.55 (d, 1H, J = 15.8 Hz), 4.83 (s, 1H), 5.92 (br s, 1H), 6.65 (d, 2H, J = 7.3 Hz), 6.87 (br s, 1H), 6.90 (d, 2H, J = 8.8 Hz), 6.98 (t, 2H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.3 Hz), 7.19-7.22 (m, 1H), 7.26 (t, 2H, J = 7.5) 7.37 (d, 2H, J = 7.4 Hz) 7.62-7.63 (m, 4H), 7.88 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 49.1, 55.3, 61.1, 73.1, 82.7, 114.0, 122.2, 126.5, 127.2, 127.46, 127.54, 127.8 (2 signals observed by HMQC), 128.1, 128.4, 130.3, 133.3, 136.3, 142.3, 143.8, 161.3, 165.4, 168.8, 170.8. IR (NaCl): 3177 cm^{-1}, 1740 cm^{-1}, 1680 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{33}H_{32}N_3O_4$ [M+H], 534.2393; found 534.2402.

Procedures for the synthesis of compounds from Table 4.

2-(4-methoxybenzamido)-2-phenylacetic acid (34). DL-α-phenylglycine (7.0 g, 46.3 mmol) was added to a 0.6 M Na_2CO_3 solution (262 mL) in 1,4-dioxane (93 mL). Thereafter, 4-methoxybenzoyl chloride (6.9 mL, 50.9 mmol) was added and the reaction was allowed to stir for 1 hour at room temperature. The reaction was then diluted with H_2O (100 mL) and the 1,4-dioxane was extracted with dichloromethane (100 mL). The aqueous layer was acidified with concentrated HCl until a precipitate crashed out of the solution. The precipitate was filtered and washed with diethyl ether (3 x 15 mL). Crude precipitate was then dissolved in ethyl acetate (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the desired product as a white solid (11.2 g, 85%); mp 186-188 °C. ^{1}H NMR (500 MHz, d6-DMSO) δ 3.80 (s, 3H), 5.58 (d, 1H, J = 7.5 Hz), 6.97-7.00 (m, 2H), 7.30-7.39 (m, 3H), 7.47-7.49 (m, 2H), 7.89-7.92 (m, 2H), 8.83 (d, 1H, J = 7.5 Hz), 12.85 (br s, 1H). ^{13}C NMR (125 MHz, d6-DMSO) δ 55.3, 56.7, 113.3, 125.9, 127.8, 128.1, 128.3, 129.5, 137.3, 161.7, 165.6, 172.0.

The acylated amino acid (4 g, 14.0 mmol) was subsequently added to a flame dried round bottom flask and was dissolved in dry dichloromethane (50 mL). Thereafter, trifluoroacetic

anhydride (2.14 mL, 15.4 mmol) was added dropwise at room temperature. After 18 hours the reaction was quenched with $NaHCO_3$ (1 x 50 mL). The organic layer was separated, and the remaining aqueous layer was extracted with additional dichloromethane (2 x 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford the desired product **34** as a yellow solid (3.30 g, 88%); mp 113-116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.49 (s, 1H), 7.00-7.02 (m, 2H), 7.35-7.46 (m, 5H), 8.03-8.05 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 68.3, 114.5, 118.1, 127.0, 128.8, 129.1, 130.2, 134.0, 162.4, 163.6, 176.6.

DL-(4*S*,5*S*)-1-benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic acid hydrochloride (35). A solution of benzyl amine (3.1 mL, 28.0 mmol) and 4-nitrobenzaldehyde (4.2 g, 28.0 mmol) in dry benzene (275 mL) was refluxed under N_2 for 3 hours and then concentrated *in vacuo*. The resulting residue was redissolved in dry dichloromethane (200 mL) at room temperature. Then **34** (12.8 g, 53.4 mmol) and chlorotrimethylsilane (6.8 mL, 53.4 mmol) were added and the reaction mixture was refluxed under N_2 for 22 hours. The solution was then concentrated *in vacuo* and the resulting yellow/orange reside was suspended in ethyl acetate (300 mL) and allowed to stir for several hours. The resulting white precipitate was isolated *via* filtration to afford the desired product as a white solid (8.23 g, 34%); mp 190-192 °C. ^{1}H NMR (500 MHz, d6-DMSO) δ 3.91 (s, 3H), 4.30 (d, 1H, J = 16.0 Hz), 4.95 (d, 1H, J = 16.0 Hz), 5.77 (s, 1H), 6.74 (d, 2H, J = 7.3 Hz), 7.08 (t, 2H, J = 7.7 Hz), 7.17 (t, 1H, J = 7.4 Hz), 7.27 (d, 2H, J = 8.8 Hz), 7.44-7.56 (m, 3H) 7.77 (d, 2H, J = 7.2 Hz), 7.88 (d, 2H, J = 8.8 Hz), 8.01-8.06 (m, 2H), 8.33 (d, 2H, J = 8.7 Hz), 12.70 (br s, 1H). ^{13}C NMR (125 MHz, d6-DMSO) δ 49.3, 55.9, 72.4, 75.7, 112.7, 115.0, 123.8, 125.7, 127.3, 128.3, 128.6, 128.9, 129.1, 130.1, 132.1, 133.2, 138.9, 140.6, 148.2, 164.0, 165.6, 167.5. IR (NaCl): 2637 cm^{-1}, 1719 cm^{-1}, 1610 cm^{-1}. HRMS (ESI) m/z calculated for $C_{30}H_{26}N_3O_5$ [M+H], 508.1872; found 508.1886.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (36). To a flame dried flask under N_2, was added **35** (3.12 g, 5.74 mmol) and dry dichloromethane (30 mL). Thereafter, EDCI.HCl (1.7 g, 8.6 mmol), dimethylaminopyridine (2.1 g, 17.2 mmol), and ethanol (30 mL) were added and the mixture was allowed to stir at room temperature overnight. The reaction mixture was then diluted with 5% HCl (2 x 50 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude residue. The crude residue was then dissolved in ethyl acetate (20 mL) and hexane was added until a white precipitate was observed. The precipitate was isolated by filtration to afford the desired product as a white solid (2.63 g, 86%); mp 154-156 °C. ^{1}H NMR (500 MHz, d6-DMSO) δ 0.70 (t, 3H, J = 7.1 Hz), 3.42-3.53 (m, 2H), 3.83 (s, 3H), 3.91 (d, 1H, J = 16.2 Hz), 4.56 (d, 1H, J = 16.2 Hz), 5.06 (s, 1H), 6.74 (d, 2H, J = 7.2 Hz), 7.01 (t, 2H, J = 7.4 Hz), 7.06-7.14 (m, 3H), 7.28-7.30 (m, 1H), 7.34-7.37 (m, 2H), 7.66 (t, 4H, J=7.4 Hz), 7.75-7.77 (m, 2H), 8.23-8.25 (m, 2H). ^{13}C NMR (125 MHz, d6-DMSO) δ 13.2, 49.0, 55.3, 60.5, 72.6, 83.0, 114.1, 122.0, 123.3, 126.6, 127.0, 127.2, 127.4, 128.0, 128.2, 129.3, 130.3, 136.4, 143.8, 146.3, 147.2, 161.0, 164.6, 170.0. IR (NaCl): 1734 cm^{-1}, 1608 cm^{-1}, 1520 cm^{-1}. HRMS (ESI): m/z calculated for $C_{32}H_{30}N_3O_5$ [M+H], 536.2185; found 536.2187.

DL-(4*S*,5*S*)-ethyl 5-(4-aminophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (37). To a flame-dried flask under N_2, **36** (190 mg, 0.35 mmol)

was dissolved in glacial acetic acid at room temperature. Subsequently, zinc dust (0.85 g, 13.1 mmol) was added. After 30 minutes the mixture was filtered and the filtrate was neutralized with saturated $NaHCO_3$ (40 mL plus additional $NaHCO_3$ (s) until pH = 6). The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organics were concentrated *in vacuo.* The resulting brown oil was dissolved in dichloromethane (20 mL) and stirred in saturated $NaHCO_3$ (20 mL) for 10 minutes to remove excess acetic acid. The organic layer was separated, dried with Na_2SO_4, and concentrated *in vacuo* to afford the desired product **37** as a yellow foam (166 mg, 93%); mp 149-151 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.1 Hz), 3.67-3.82 (m, 2H), 3.85 (s, 3H), 3.88 (d, 1H, J = 16.0 Hz), 4.64 (d, 1H, J = 15.8 Hz), 4.84 (s, 1H), 6.67 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 7.1 Hz), 6.99-7.02 (m, 2H), 7.07-7.19 (m, 5H), 7.26-7.30 (m, 1H), 7.32-7.36 (m, 2H), 7.71-7.80 (m, 4H). ^{13}C NMR + **DEPT** (150 MHz) ($CDCl_3$): δ 13.4 (–**C**H_3), 48.2 (–**C**H_2), 55.0 (–**C**H_3), 60.6 (–**C**H_2), 73.3 (–**C**H), 82.2 (quaternary –**C**), 113.6 (aromatic –**C**H), 114.5 (aromatic –**C**H), 122.8 (aromatic quaternary –**C**), 126.6 (aromatic –**C**H), 126.7 (aromatic quaternary –C), 126.85 (aromatic –**C**H), 126.92 (aromatic –**C**H), 126.93 (aromatic –**C**H), 127.6 (aromatic –**C**H), 128.1 (aromatic –**C**H), 128.9 (aromatic –**C**H), 130.1 (aromatic –**C**H), 136.8 (aromatic quaternary –**C**), 144.2 (aromatic quaternary –**C**), 146.5 (aromatic quaternary –**C**), 160.8 (quaternary –**C**), 164.8 (quaternary –**C**), 170.9 (quaternary –**C**). IR (neat): 3462 cm^{-1}, 3370 cm^{-1}, 3218 cm^{-1}, 1737 cm^{-1}, 1617 cm^{-1}, 1252 cm^{-1}. HRMS (FAB): *m/z* calcd for $C_{32}H_{32}N_3O_3$ [M+H], 506.2444; found, 506.2449.

DL-(4*S*,5*S*)-ethyl 5-(4-acetamidophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (38). To a flame-dried flask was added **37** (100 mg, 0.198 mmol) and pyridine (2 mL) under N_2. This was allowed to stir briefly then acetic anhydride (0.056 mL, 0.593 mmol) was added dropwise for 5 min. The reaction was left to stir for 12 hours. The crude reaction mixture was concentrated under vacuum then dissolved in dichloromethane to be washed with $NaHCO_3$ (2 x 10 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified *via* TEA-neutralized silica (9:1 ethyl acetate:hexanes) to afford a white solid (49.2 mg, 46%); mp 93-102 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.1 Hz), 2.10 (s, 3H),), 3.58-3.73 (m, 2H), 3.79 (d, 1H, J = 15.5 Hz), 3.82 (s, 3H), 4.60 (d, 1H, J = 15.6 Hz), 4.84 (s, 1H), 6.71 (d, 2H, J = 7.1Hz), 6.95 (d, 2H, J = 8.8 Hz), 6.99 (t, 2H, J = 7.6 Hz), 7.04-7.07 (m, 1H), 7.19-7.27 (m, 5H), 7.51 (d, 2H, J = 8.5 Hz), 7.59-7.62 (m, 4H) 8.58 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 24.5, 48.7, 55.4, 61.2, 73.1, 82.1, 114.1, 119.8, 121.9, 126.6, 127.3, 127.5, 127.6, 128.1, 128.5, 128.6, 130.4, 132.6, 136.4, 138.9, 143.7, 161.5, 165.3, 169.0, 170.8. IR (NaCl): 3854 cm^{-1}, 2928 cm^{-1}, 2361 cm^{-1}, 1514 cm^{-1}, 1254 cm^{-1}. HRMS (TOF MS ES+) *m/z* calculated for $C_{34}H_{34}N_3O_4$ [M+H], 548.2549; found 548.2530.

DL-(4*S*,5*S*)-ethyl 5-(4-benzamidophenyl)-1-benzyl-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (39). To a flame-dried flask containing **37** (100 mg, 0.198 mmol) in dichloroethane (10 mL) was added benzoyl chloride (0.025 mL, 0.218 mmol) and 4-(N,N-dimethylamino)pyridine (36.3 mg, 0.297 mmol). The reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was diluted with dichloromethane (20 mL) and washed with a 5% HCl solution (2 x 30 mL). Then the organic layer was washed with $NaHCO_3$ (2 x 30 mL), and dried over Na_2SO_4. The organic layer was concentrated *in vacuo*, and the crude product was purified by column chromatography in TEA-neutralized silica (7:3 ethyl acetate:hexanes) to afford the desired product as a white solid (38 mg, 31%). ^{1}H NMR: (500

MHz, $CDCl_3$) δ 0.78 (t, 3H, J = 7.4 Hz), 3.49-3.71 (m, 2H), 3.79 (s, 3H), 4.05 (d, 1H, J = 15.1 Hz), 4.88 (d, 1H, J = 15.1 Hz), 5.19 (s, 1H), 6.70 (d, 2H, J = 7.4 Hz), 6.93 (d, 2H, J = 8.8 Hz), 7.18 (t, 2H, J = 7.8 Hz), 7.26-7.30 (m, 3H), 7.38-7.54 (m, 6H), 7.85-7.96 (m, 4H), 8.34-8.41 (m, 4H), 10.43 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 49.2, 55.6, 62.5, 73.4, 76.2, 106.8, 112.5, 114.8, 122.0, 126.2, 126.6, 127.4, 128.2, 128.5, 128.9, 129.0, 129.1, 129.2, 131.6, 132.1, 132.3, 134.0, 138.7, 141.7, 164.2, 165.2, 166.2, 166.5. IR (NaCl): 3301 cm^{-1}, 1732 cm^{-1}, 1514 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{39}H_{36}N_3O_4$ [M+H], 610.2706; found 610.2718.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-guanidinophenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (40). To a flame-dried flask containing compound **37** (100 mg. 0.198 mmol) in dichloroethane (4 mL) was added N,N'-bis(t-butoxycarbonyl)thiourea, (55 mg, 0.20 mmol), ethyl diisopropyl amine (26.0 μL, 0.15 mmol), and EDCI.HCl (57 mg, 0.30 mmol). The reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and then dichloromethane (20 mL) was added. The reaction mixture was washed with $NaHCO_3$ (2 x 30 mL), dried over Na_2SO_4, and concentrated *in vacuo.* The crude product was purified by column chromatography using TEA- neutralized silica (1:1 ethyl acetate:hexanes) to afford the desired product as a white solid (68 mg, 46%); mp 87-91 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3H, J = 7.2 Hz), 1.45 (s, 9H), 1.47 (s, 9H), 3.54-3.60 (m, 1H), 3.63-3.70 (m, 1H), 3.74-3.77 (m, 4H, contains overlapping s, 3.768, 3H) 4.56 (d, 1H, J = 15.9 Hz), 4.76 (s, 1H), 6.67 (d, 2H, J = 7.0 Hz), 6.91 (d, 2H, J = 8.8 Hz), 6.98 (t, 2H, J = 7.2 Hz), 7.02-7.07 (m, 1H), 7.18-7.19 (m, 2H), 7.23 (t, 1H, J = 7.5 Hz), 7.27 (d, 2H, J = 8.1 Hz) 7.57 (d, 2H, J = 8.8 Hz), 7.63-7.66 (m, 4H), 10.31 (s, 1H), 11.56 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 28.0, 28.1, 48.6, 55.3, 61.0, 73.3, 79.6, 82.6, 83.8, 113.9, 121.8, 122.8, 126.8, 127.1, 127.22, 127.23, 127.9, 128.3, 128.7, 130.4, 134.3, 136.8, 136.9, 144.2, 153.28, 153.34, 161.1, 163.4, 165.1, 170.8. IR (NaCl): 2980 cm^{-1}, 2934 cm^{-1}, 1719 cm^{-1}, 1559 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{43}H_{50}N_5O_7$ [M+H], 748.3710; found 748.3712.

Deprotection: To a flame-dried flask was added the Boc-protected guanidine (156 mg, 0.21 mmol) and a 1:1 mixture of trifluoroacetic acid: dichloromethane (5 mL: 5 mL). The reaction was allowed to stir at room temperature for 5 hours. The reaction mixture was concentrated *in vacuo* to yield the crude product as a TFA salt. The crude product was dissolved in dichloromethane (20 mL) and washed with a saturated solution of K_2CO_3, (2 x 30 mL) and then dried over Na_2SO_4. The organic layer was concentrated *in vacuo* to afford the desired product as a white sticky solid (38 mg, 68%). ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, 3H, J = 7.1 Hz), 3.52-3.58 (m, 1H), 3.66-3.73 (m, 1H), 3.84 (s, 3H), 3.85 (d, 1H, J = 15.6 Hz), 4.60 (d, 1H, J = 15.6 Hz), 4.91 (s, 1H), 6.24 (br s, 4H), 6.75 (d, 2H, J = 7.4 Hz), 7.01 (d, 4H, J = 8.8 Hz), 7.08 (t, 2H, J = 7.4 Hz), 7.13 (t, 1H, J = 7.1 Hz), 7.26-7.33 (m, 5H), 7.59 (d, 2H, J = 7.3 Hz), 7.65 (d, 2H, J = 8.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 48.9, 55.4, 61.4, 72.6, 82.6, 114.3, 121.8, 124.1, 126.4, 127.3, 127.6, 127.7, 128.3, 128.5, 129.4, 130.2, 134.5, 136.3, 140.6, 143.4, 154.9, 161.6, 165.8, 171.7. IR (NaCl): 2930 cm^{-1}, 1734 cm^{-1} 1684 cm^{-1}. HRMS (TOF MS ES+) m/z calculated for $C_{33}H_{34}N_5O_3$ [M+H], 548.2662; found 548.2664

General procedure for the sulfonation of imidazoline 37

A solution of **37** in dichloromethane, cooled to 0 °C in an ice bath, was treated with the desired sulfonyl chloride (1.1 eq), and the reaction stirred at 0 °C for 45 minutes. The reaction was then treated with pyridine and stirred overnight while slowly warming to room temperature. The reaction was diluted with saturated $NaHCO_3$ solution and extracted with dichloromethane (x3).

The pooled organic extracts were dried (Na_2SO_4) and concentrated, and the crude product was purified *via* silica gel chromatography to yield the desired sulfonamide.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-(phenylsulfonamido)phenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (41). Following the general procedure for sulfonylation, a solution of **37** (50.7 mg, 0.10 mmol) in dichloromethane (3.0 mL) was treated with $PhSO_2Cl$ (13.0 μL, 0.10 mmol) and pyridine (0.02 mL, 0.2 mmol). The crude product was purified *via* silica gel chromatography (67:33 ethyl acetate:hexanes) to afford the desired product as a yellow solid (58.9 mg, 91%); mp 134-138 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.68 (t, 3H J = 6.9 Hz), 3.33-3.59 (m, 2H), 3.75 (d, 1H, J = 15.8 Hz), 3.84 (s, 3H), 4.59 (d, 1H, J = 15.6 Hz), 4.79 (s, 1H), 6.69 (d, 2H, J = 7.2 Hz), 6.97 (d, 2H, J = 7.4 Hz), 7.04 (t, 2H, J = 7.1 Hz), 7.09 (d, 3H, J = 7.7 Hz), 7.19–7.34 (m, 5H), 7.43 (t, 2H, J = 7.3 Hz), 7.52 (t, 1H, J = 7.3 Hz), 7.68 (t, 4H, J = 7.9 Hz), 7.81 (d, 2H, J = 7.9 Hz). ^{13}C NMR + **DEPT** (150 MHz, $CDCl_3$) δ 13.5 (–**C**H$_3$), 48.9 (–**C**H$_2$), 55.4 (–**C**H$_3$), 60.8 (–**C**H$_2$), 73.1 (–**C**H), 82.6 (quaternary –**C**), 114.0 (aromatic –**C**H), 120.8 (aromatic –**C**H), 122.5 (aromatic quaternary –**C**), 126.7 (aromatic –**C**H), 127.1 (aromatic –**C**H), 127.3 (aromatic –**C**H), 127.37 (aromatic –**C**H), 127.41 (aromatic –**C**H), 128.0 (aromatic –**C**H), 128.4 (aromatic –**C**H), 129.0 (aromatic –**C**H), 129.1 (aromatic –**C**H), 130.4 (aromatic –**C**H), 132.9 (aromatic –**C**H), 134.8 (aromatic quaternary –**C**), 136.5 (aromatic quaternary –**C**), 136.6 (aromatic quaternary –**C**), 139.3 (aromatic quaternary –**C**), 143.9 (aromatic quaternary –**C**), 161.3 (quaternary –**C**), 165.3 (quaternary –**C**), 170.7 (quaternary –**C**). IR (neat): 3245 cm^{-1}, 1737 cm^{-1}, 1612 cm^{-1}, 1512 cm^{-1}, 1254 cm^{-1}, 1163 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{38}H_{36}N_3O_5S$ [M+H], 646.2376; found 646.2384.

DL-(4S,5S)-ethyl 1-benzyl-5-(4-(2,4-dimethoxyphenylsulfonamido)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (42). Following the general procedure for sulfonylation, a solution of **37** (51.6 mg, 0.102 mmol) in dichloromethane (3.5 mL) was treated with 2,4-dimethoxylbenzene sulfonyl chloride (25.5 mg, 0.107 mmol) and pyridine (20 μL, 0.2 mmol). The crude residue was purified *via* silica gel chromatography (1:24 ethanol:dichloromethane) to afford the desired product as a light yellow solid (59.4 mg, 83%); mp 106-110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.63 (t, 3H, J = 7.1 Hz), 3.26 (dq, 1H, J_1 = 10.8, J_2 = 7.1 Hz), 3.41 (dq, 1H, J_1 = 10.8, J_2 = 7.1 Hz), 3.74 (d, 1H, J = 15.7 Hz), 3.79 (s, 3H), 3.85 (s, 3H), 4.01 (s, 3H), 4.58 (d, 1H, J = 15.6 Hz), 4.78 (s, 1H), 6.45 – 6.50 (m, 2H), 6.68 (d, 2H, J = 7.5 Hz), 7.96–7.00 (m, 2H), 7.03 (t, 2H, J = 7.6 Hz), 7.09 (d, 3H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.24–7.33 (m, 4H), 7.64–7.71 (m, 4H), 7.79 (dd, 1H, J_1 = 8.1, J_2 = 0.9 Hz). ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 13.4 (–**C**H$_3$), 48.9 (–**C**H$_2$), 55.3 (–**C**H$_3$), 55.6 (–**C**H$_3$), 56.3 (–**C**H$_3$), 60.7 (–**C**H$_2$), 73.0 (–**C**H), 82.6 (quaternary –**C**), 99.3 (aromatic –**C**H), 104.4 (aromatic –**C**H), 113.9 (aromatic –**C**H), 118.5 (aromatic quaternary –**C**), 120.6 (aromatic –**C**H), 122.5 (aromatic quaternary –**C**), 126.7 (aromatic –**C**H), 127.1 (aromatic –**C**H), 127.31 (aromatic –**C**H), 127.33 (aromatic –**C**H), 127.9 (aromatic –**C**H), 128.3 (aromatic –**C**H), 128.9 (aromatic –**C**H), 130.4 (aromatic –**C**H), 132.8 (aromatic –**C**H), 134.6 (aromatic quaternary –**C**), 136.5 (aromatic quaternary –**C**), 137.0 (aromatic quaternary –**C**)143.9 (aromatic quaternary –**C**), 157.7 (aromatic quaternary –**C**), 161.2 (quaternary –**C**), 165.0 (quaternary –**C**), 165.1 (quaternary –**C**), 170.6 (quaternary –**C**). IR (neat): 3262 cm^{-1}, 1734 cm^{-1}, 1598 cm^{-1}, 1252 cm^{-1}, 1225 cm^{-1}, 1164 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{40}H_{40}N_3O_7S$ [M+H], 706.2587; found 706.2587.

DL-(4S,5S)-ethyl 1-benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-(phenylmethylsulfonamido)phenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (43). Following the general procedure for sulfonylation, a solution of **37** (51.4 mg, 0.102 mmol) in dichloromethane (1.5 mL) was treated with α-toluenesulfonyl chloride (20.7 mg, 0.109 mmol) and pyridine (0.02 mL, 0.2 mmol). The crude residue was purified *via* silica gel chromatography (7:3 ethyl acetate:hexane) to afford the desired product as a white solid (47.5 mg, 71%); mp 212-216 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84 (t, 3H, J = 7.1 Hz), 3.58–3.78 (m, 2H), 3.82–3.91 (m, 4H), 4.38 (s, 2H), 4.69 (d, 1H, J = 15.6 Hz), 4.89 (s, 1H), 6.72 (d, 2H, J = 7.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 7.08 (t, 2H, J = 7.6 Hz), 7.15 (t, 1H, J = 7.3 Hz), 7.23–7.36 (m, 12H), 7.71 (d, 2H, J = 7.6 Hz), 7.80 (d, 2H, J = 8.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 50.1, 56.1, 58.5, 62.7, 74.3, 81.3, 115.7, 120.2, 120.4, 127.3, 128.6, 129.1, 129.3, 129.56, 129.62 (2 signals by HMBC), 129.7, 130.4, 130.6, 131.8, 132.1, 132.3, 136.5, 140.6, 143.3, 164.1, 167.2, 170.7. IR (neat): 3278 cm^{-1}, 1737 cm^{-1}, 1612cm^{-1}, 1257 cm^{-1}, 1159 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{39}H_{38}N_3O_5S$ [M+H], 660.2532; found 660.2534.

DL-(4S,5S)-ethyl 1-benzyl-5-(4-(cyclopropanesulfonamido)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (44). Following the general procedure for sulfonylation, a solution of **37** (50.2 mg, 0.099 mmol) in dichloromethane (3.5 mL) was treated with cyclopropanesulfonyl chloride (11.0 μL, 0.109 mmol) and pyridine (20 μL, 0.2 mmol). The crude residue was purified *via* silica gel chromatography (9:1 ethyl acetate:hexane) to afford the desired product as an oil (53.2 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, 3H, J = 7.1 Hz), 0.95 (qd, 2H, J_1 = 5.9 Hz, J_2 = 1.6 Hz), 1.16–1.21 (m, 2H), 2.47-2.52 (m, 1H), 3.60–3.68 (m, 1H), 3.70–3.78 (m, 1H), 3.82–3.88 (m, 4H), 4.64 (d, 1H, J = 15.7 Hz), 4.87 (s, 1H), 6.75 (d, 2H, J = 7.2 Hz), 6.98–7.03 (m, 2H), 7.05–7.10 (m, 2H), 7.11–7.15 (m, 1H), 7.27–7.37 (m, 7H), 7.72–7.76 (m, 4H). ^{13}C NMR + **DEPT** (125 MHz, $CDCl_3$): δ 5.5 (–$\mathbf{C}H_2$), 13.6 (–$\mathbf{C}H_3$), 30.0 (–**C**H), 48.9 (–$\mathbf{C}H_2$), 55.3 (–$\mathbf{C}H_3$), 60.9 (–$\mathbf{C}H_2$), 73.1 (–**C**H), 82.6 (quaternary –**C**), 114.0 (aromatic –**C**H), 121.3 (aromatic –**C**H), 122.4 (aromatic quaternary –**C**), 126.7 (aromatic –**C**H), 127.1 (aromatic –**C**H), 127.36 (aromatic –**C**H), 127.43 (aromatic –**C**H), 128.0 (aromatic –**C**H), 128.4 (aromatic –**C**H), 129.1 (aromatic –**C**H), 130.4 (aromatic –**C**H), 134.7 (aromatic quaternary –**C**), 136.5 (aromatic quaternary –**C**), 137.2 (aromatic quaternary –**C**), 144.0 (aromatic quaternary –**C**), 161.3 (quaternary –**C**), 165.3 (quaternary –**C**), 170.8 (quaternary –**C**). IR (neat): 3248 cm^{-1}, 1732 cm^{-1}, 1612 cm^{-1}, 1247 cm^{-1}, 1149 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{35}H_{36}N_3O_5S$ [M+H], 610.2376; found 610.2380.

DL-(4S,5S)-ethyl 1-benzyl-5-(4-((N,N-dimethylsulfamoyl)amino)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (45). Following the general procedure for sulfonylation, a solution of **37** (50.7 mg, 0.100 mmol) in dichloromethane (3.0 mL) was treated with dimethyl sulfamoyl chloride (11.0 μL, 0.102 mmol) and pyridine (20 μL, 0.2 mmol). The crude residue was purified *via* silica gel chromatography (1:1 ethyl acetate:dichloromethane) to afford the desired product as a white solid (28.6 mg, 47%); mp 210-220 °C, (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (t, 3H, J = 7.1 Hz), 2.86 (s, 6H), 3.59-3.77 (m, 2H), 3.81–3.87 (m, 4H), 4.63 (d, 1H, J = 15.8 Hz), 4.86 (s, 1H), 6.74 (d, 2H, J = 7.4 Hz), 7.00 (d, 2H, J = 8.6 Hz), 7.06 (t, 2H, J = 7.5 Hz), 7.12 (t, 1H, J = 7.3 Hz), 7.18 (d, 2H, J = 8.6 Hz), 7.29 (d, 1H, J = 7.0 Hz), 7.33 (t, 4H, J = 7.4 Hz), 7.71–7.75 (m, 4H). ^{13}C NMR + **DEPT** (150 MHz) ($CDCl_3$): δ 13.6 (–$\mathbf{C}H_3$), 38.1 (–$\mathbf{C}H_3$), 48.9 (–$\mathbf{C}H_2$), 55.4 (–$\mathbf{C}H_3$), 61.0 (–$\mathbf{C}H_2$), 73.2 (–**C**H), 82.6 (quaternary –**C**), 114.0 (aromatic –**C**H), 119.7 (aromatic –**C**H), 122.4 (aromatic

quaternary –**C**), 126.7 (aromatic –**C**H), 127.1 (aromatic –**C**H), 127.37 (aromatic –**C**H), 127.43 (aromatic –**C**H), 128.0 (aromatic –**C**H), 128.4 (aromatic –**C**H), 129.1 (aromatic –**C**H), 130.5 (aromatic –**C**H), 134.0 (aromatic quaternary –**C**), 136.6 (aromatic quaternary –**C**), 137.5 (aromatic quaternary –**C**), 144.0 (aromatic quaternary –**C**), 161.3 (quaternary –**C**), 165.3 (quaternary –**C**)**,** 170.8 (quaternary –**C**). IR (neat): 3262 cm^{-1}, 1734 cm^{-1}, 1612 cm^{-1}, 1254 cm^{-1}, 1147 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{34}H_{37}N_4O_5S$ [M+H], 613.2485; found 613.2490.

General procedure for reductive amination of imidazoline 37

Into a flame-dried flask at room temperature was added **37** and dichloroethane. Then the appropriate aldehyde was added along with $NaBH(OAc)_3$. The contents were then allowed to reflux under N_2 for 12 hours. The reaction mixture was then concentrated *in vacuo* and dissolved in dichloromethane to be washed with $NaHCO_3$ (x2). The combined organic layers were then dried over Na_2SO_4, concentrated *in vacuo*, and purified *via* silica gel column chromatography to yield the desired secondary amine.

DL-(4S,5S)-ethyl 1-benzyl-5-(4-(benzylamino)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (46). Following the general procedure for reductive amination, a solution of **37** (49.3 mg, 0.098 mmol) in dichloroethane (2.0 mL) was treated with benzaldehyde (10.0 μL, 0.098 mmol) and $NaBH(OAc)_3$ (31.4 mg, 0.15 mmol). The crude residue was purified *via* silica gel chromatography (3:1 ethyl acetate:hexane) to afford the desired product as an oil (50.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 7.1 Hz), 3.61–3.79 (m, 2H), 3.86 (s, 3H), 3.88 (d, 1H, J = 15.9 Hz), 4.17 (br s, 1H), 4.37 (s, 2H), 4.63 (d, 1H, J = 15.8 Hz), 4.83 (s, 1H), 6.64 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 7.1 Hz), 6.96–7.01 (m, 2H), 7.05–7.15 (m, 3H), 7.18 (d, 2H, J = 8.0 Hz), 7.25–7.41 (m, 8H), 7.69–7.78 (m, 4H). ^{13}C NMR + **DEPT** (125 MHz) ($CDCl_3$): δ 13.6 (–**C**H_3), 48.2 (–**C**H_2), 48.4 (–**C**H_2), 55.3 (–**C**H_3), 60.9 (–**C**H_2), 73.6 (–**C**H), 82.4 (quaternary –**C**), 112.6 (aromatic –**C**H), 113.8 (aromatic –**C**H), 123.1 (aromatic quaternary –**C**), 126.3 (aromatic quaternary –**C**), 126.9 (aromatic –**C**H), 127.07 (aromatic –**C**H), 127.11 (aromatic –**C**H), 127.12 (aromatic –**C**H), 127.2 (aromatic –**C**H), 127.4 (aromatic –**C**H), 127.8 (aromatic –**C**H), 128.3 (aromatic –**C**H), 128.6 (aromatic –**C**H), 129.2 (aromatic –**C**H), 130.3 (aromatic –**C**H), 137.1 (aromatic quaternary –**C**), 139.2 (aromatic quaternary –**C**), 144.5 (aromatic quaternary –**C**), 148.0 (aromatic quaternary –**C**), 161.0 (quaternary –**C**), 165.0 (quaternary –**C**), 171.1 (quaternary –**C**). IR (neat): 3394 cm^{-1}, 3282 cm^{-1}, 1732 cm^{-1}, 1252 cm^{-1}, 1176 cm^{-1}. HRMS (FAB): *m/z* calculated for $C_{39}H_{38}N_3O_3$ [M+H], 596.2913; found 596.2914.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-((4-hydroxybenzyl)amino)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (47). Following the general procedure for reductive amination, a solution of **37** (200 mg, 0.395 mmol) in dichloroethane (25 mL) was treated with 4-hydroxybenzaldehyde (48.2 mg, 0.395 mmol) and $NaBH(OAc)_3$ (251 mg, 1.187 mmol). The crude residue was purified using TEA-neutralized silica gel (6:3:1 dichloromethane:acetone:hexane) to afford the desired product as a light brown solid (38.6 mg, 16%); mp 94-104 ^{o}C. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 0.76 (t, 3H, J = 7.1 Hz), 3.47-3.62 (m, 2H), 3.81 (s, 3H), 3.86 (d, 1H, J = 15.8 Hz), 4.20 (s, 2H), 4.61 (d, 1H, J = 15.7 Hz), 4.80 (s, 1H), 6.58 (d, 2H, J = 8.8 Hz), 6.72 (t, 4H, J = 6.0 Hz), 6.92 (d, 2H, J = 8.8 Hz), 7.04 (t, 2H, J = 7.5 Hz), 7.08-7.13 (m, 4H), 7.24-7.31 (m, 4H), 7.66-7.71 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 47.8, 48.4, 55.4, 61.2, 73.6, 81.6, 112.7, 114.1, 115.9, 121.4, 125.1, 126.7, 127.2, 127.4, 127.5,

128.1, 128.5 (2C), 129.1, 129.5, 130.9, 136.5, 143.7, 148.5, 156.5, 161.5, 165.5, 170.6. IR (NaCl): 3405 cm^{-1}, 1734 cm^{-1}, 1518 cm^{-1}, 1252 cm^{-1}. HRMS (TOF MS ES+) *m/z* calculated for $C_{39}H_{38}N_3O_4$ [M+H], 612.2862; found 612.3542.

DL-(4*S*,5*S*)-ethyl 1-benzyl-2-(4-methoxyphenyl)-4-phenyl-5-(4-((3,4,5-trimethoxybenzyl)amino)phenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (48). To a flame-dried flask was added **37** (100 mg, 0.19 mmol) and toluene (12 mL). 3,4,5-trimethoxybenzaldehyde (43 mg, 0.22 mmol) was then added followed by addition of $TiCl_4$ (10 µL, 0.09 mmol). The reaction was refluxed overnight, concentrated *in vacuo*, and then dissolved in dichloromethane (25 mL) to be washed with $NaHCO_3$ (1 x 25 mL) and H_2O (1 x 25 mL). The organics were then dried using Na_2SO_4 and concentrated *in vacuo.* The crude organic components were purified by flash column chromatography using TEA-neutralized silica gel (3:2 ethyl acetate:hexanes) to afford the imine product. The imine and ethanol (5 mL) were then added to a flame-dried flask and allowed to stir for 5 minutes. $NaBH_4$ (1.1 equiv.) was added to the flask and refluxed under N_2 for 3 hours. The contents were then concentrated *in vacuo* and dissolved in dichloromethane to be washed with H_2O (1 x 25 mL) then $NaHCO_3$ (2 x 25 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to afford the desired product as a brown-orange solid (15% combined overall yield from **34**); mp 70-76 ^oC. ^1H NMR: (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.1 Hz), 3.66-3.80 (m, 2H), 3.86-3.91 (m, 13H), 4.32 (s, 2H), 4.66 (d, 1H, J = 16.2 Hz), 4.85 (s, 1H), 6.62-6.80 (m, 4H), 6.79 (d, 2H, J = 6.4 Hz), 6.97-6.99 (m, 2H), 7.06-7.09 (m, 2H), 7.11-7.15 (m, 1H), 7.18-7.19 (m, 2H), 7.25-7.27 (m, 1H), 7.30-7.33 (m, 2H), 7.72-7.78 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 48.5, 48.7, 53.4, 55.4, 56.1, 60.9, 73.6, 82.4, 104.4, 112.7, 113.9, 123.1, 126.5, 126.9, 127.11, 127.15 127.19, 127.2, 127.9, 128.4, 129.3, 130.4, 135.0, 137.1, 144.4, 148.1, 153.5, 161.1, 165.1, 171.2. IR (NaCl): 3854 cm^{-1}, 2917 cm^{-1}, 2361 cm^{-1}, 1518 cm^{-1}, 1252 cm^{-1}. HRMS (TOF MS ES+) *m/z* calculated for $C_{42}H_{44}N_3O_6$ [M+H], 686.3230; found 686.3218.

DL-(4*S*,5*S*)-ethyl 1-benzyl-5-(4-((cyclohexylmethyl)amino)phenyl)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (49). Following the general procedure for reductive amination, a solution of **37** (137.4 mg, 0.27 mmol) in dichloroethane (13 mL) was treated with cyclohexanecarboxaldehyde (48.2 mg, 0.40 mmol) and $NaBH(OAc)_3$ (173 mg, 0.82 mmol). The crude residue was purified using TEA-neutralized silica gel (3:2 ethyl acetate:hexane) to afford the desired product as a light yellow solid (70.8 mg, 43%); mp 51-62 ^oC. ^1H NMR: (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.1 Hz), 0.97-1.04 (m, 2H), 1.18-1.31 (m, 3H), 1.55-1.64 (m, 1H), 1.69-1.84 (m, 5H), 3.01 (d, 2H, J = 6.6 Hz), 3.67-3.86 (m, 2H), 3.88 (s, 3H), 3.91 (d, 1H, J = 15.6 Hz), 4.66 (d, 1H, J = 15.6 Hz), 4.85 (s, 1H), 6.62 (d, 2H, J = 8.7 Hz), 6.79-6.82 (m, 2H), 6.99-7.04 (m, 2H), 7.08-7.16 (m, 3H), 7.20 (d, 2H, J = 8.1 Hz), 7.27-7.39 (m, 3H), 7.72-7.81 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.7, 26.0, 26.6, 31.3, 37.6, 48.4, 50.6, 55.4, 60.9, 73.7, 82.4, 112.4, 113.9, 123.2, 125.6, 126.9, 127.13, 127.15, 127.16, 127.9, 128.3, 129.2, 130.4, 137.2, 144.6, 148.6, 161.0, 165.0, 171.2. IR (NaCl): 2924 cm^{-1}, 2851 cm^{-1}, 1730 cm^{-1}, 1615 cm^{-1}, 1252 cm^{-1}. HRMS (TOF MS ES+) *m/z* calculated for $C_{39}H_{44}N_3O_3$ [M+H], 602.3383; found 602.3397.

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