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A synthesis of naamidine A and selective access to N^2-acyl-2-aminoimidazole analogues.

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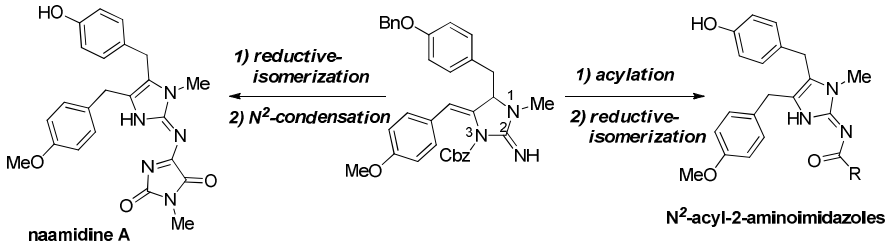
Abstract: A short and scaleable synthesis of naamidine A, a marine alkaloid with a selective ability to inhibit epidermal growth factor receptor (EGFR) dependent cellular proliferation, has been achieved. A key achievement in this synthesis was the development of a regioselective hydroamination of a mono-protected propargylguanidine to deliver N^3-protected cyclic ene-guanidines. This permits the extension of this methodology to prepare N^2-acyl analogues in a fashion that obviates the troublesome acylation of the free 2-aminoimidazoles which typically yields mixtures of N^2- and N^2,N^2-diacylated products.

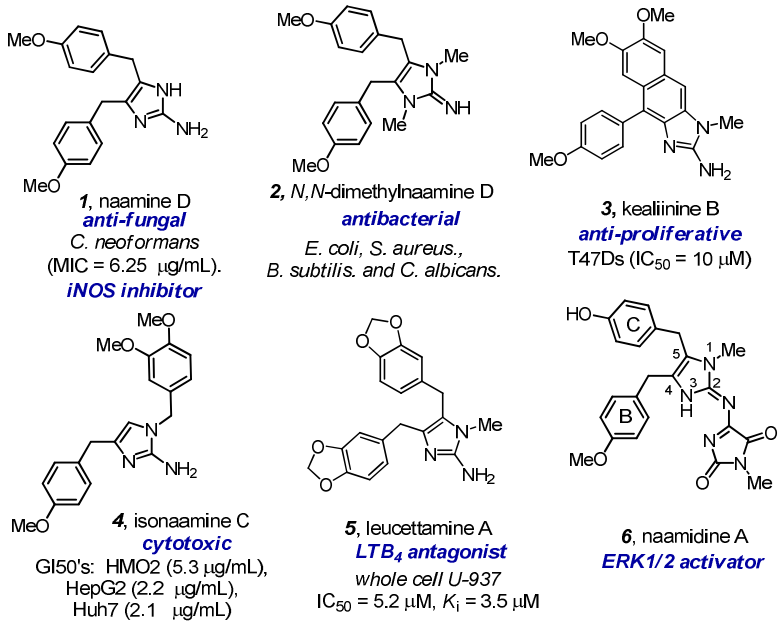


Introduction: Marine sponges from the *Leucetta* family have produced a wealth of natural products comprising highly functionalized 2-aminoimidazoles (2-AIs).[1] This family of alkaloids effects a number of diverse biological activities (Figure 1). Naamine D (**1**), for example, has been shown to be a moderate inhibitor of iNOS, an isozyme scrutinized for its involvement in a number of diseases.[2] Naamine D was also shown to be active against the opportunistic pathogen in AIDS patients, *C. neoformas* (MIC = 6.25 μg/mL). *N,N*-Dimethylnaamine D (**2**), was active against an antimicrobial panel consisting of *E. coli*, *S. aureus*., *B. subtilis.* and *C. albicans*.[3] Kealiinine B (**3**) was recently reported to show anti-proliferative activity (IC_{50} ~ 10 μM) against the breast cancer cell line T47D while other kealiinine analogues have displayed modest activity against MCF7 proliferation.[4,5] Isonaamine C (**4**) was found to be cytotoxic to a variety of cell lines[6] while leucettamine A was found to be a leukotriene B4

(LTB_4) antagonist.[7] These examples clearly demonstrate that the 2-aminoimidazole, bearing a variety of substitution patterns, serves as an important heterocyclic scaffold for small molecule drug discovery.

Our interest in this family stems from the selective cytotoxicity of naamidine A (**6**). Studies by Ireland and coworkers determined **6** to be a selective inhibitor for EGF-mediated growth in epidermal growth factor receptor (EGFR) transfected NIH3T3 cells (IC_{50} = 11.3 μM), yet displayed a 21-fold decrease in potency against insulin-mediated growth (IC_{50} = 242 μM).[8] This particular selectivity prompted *in vivo* studies, where nude mice xenografts of EGF-overexpressing A431 epidermal carcinoma displayed 87.4% tumor growth inhibition when treated with **6** at 25 mg/kg. Although many compounds affect EGFR signaling, **6** is the first known example to stimulate phosphotransferase activity of extracellular regulated kinases ERK1/2.[9] This sustained increase in MAPK activity has been shown to be a result of naamidine A-induced expression of p21, leading to inhibition of cyclin-dependent kinase activity and activation of caspases 3, 8, and 9.[10] Since EGFR signaling pathway is overexpressed in many human tumors, the ability to selectively inhibit EGFR-mediated proliferation represents an important strategy for new chemotherapeutics. Herein, we report the synthesis of **6**, as well as related analogues via regioselective construction of cyclic ene-guanidines.

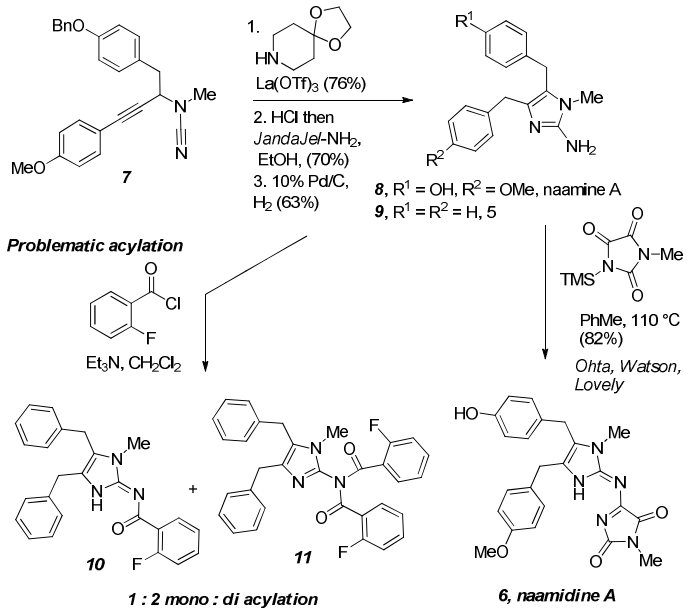
Figure 1. Representative *Leucetta* alkaloids.



Results and Discussion: The structural novelty of **6** and other highly substituted 2-AI scaffolds has generated interest in several synthetic laboratories.[11-16] We previously reported the synthesis of naamine A (**8**) via an

addition-hydroamination-isomerization sequence utilizing the propargylcyanamide **7** (Scheme 1).[17] Analogous to the syntheses of **6** by Ohta and Watson, we were able to add the *N*-Me-dehydrohydantoin selectively to N^2 via silylated N-methylparabanic acid (Scheme 1).[11,12] However, the transamination reaction of the piperidinone to the free 2-aminoimidazole proved problematic on larger scales. We had also simultaneously discovered the tandem addition – hydroamination sequence that was reported by Van der Eycken employing *N,N*-diboc guanidines. Removal of the Boc groups with TFA in this sequence presented problems, as cleavage of electron rich groups at N^1 was quite facile under acidic conditions (e.g. those needed for the synthesis of isonaamine C). Furthermore, while trying to access simplified naamidine A analogues, exemplified by the reaction of **9** with 2-fluorobenzoyl chloride, an unfavorable 1:2 mixture of mono-acylated and diacylated N^2 products (**10**:**11**) was obtained. A recent report by Jiang and coworkers identified the same problem, requiring forcing conditions or extra protecting group manipulations to obtain the mono-acyl-2-aminoimidazoles in low to moderate yields, reinforcing the need for a high yielding and selective strategy to access mono-substituted 2-aminoimidazoles.[18]

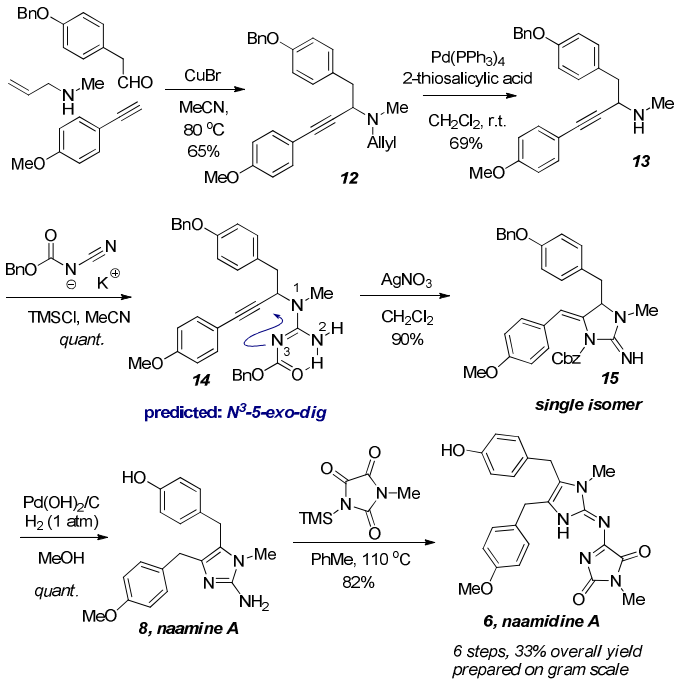
Scheme 1. First generation synthesis of naamidine A and analogues.



These shortcomings necessitated a revised synthesis of **6** that would allow for a) reproducible and scaleable procedures, b) the presence of acid labile groups, and c) differential protection of N^2/N^3 for selective functionalization. Our attempts to address these issues are presented in the synthesis of naamidine A (Scheme 2). Cu(I)-mediated A^3-coupling of the required amine, alkyne, and aldehyde gave **12** (Scheme 2).[19] Deallylation with Pd(0) gave the secondary propargylamine (**13**) in good yield.[10] Instead of installing the di-Boc guanidine[14], we prepared the mono-acylguanidine **14** using the activated Cbz-cyanamide potassium salt guanylation conditions

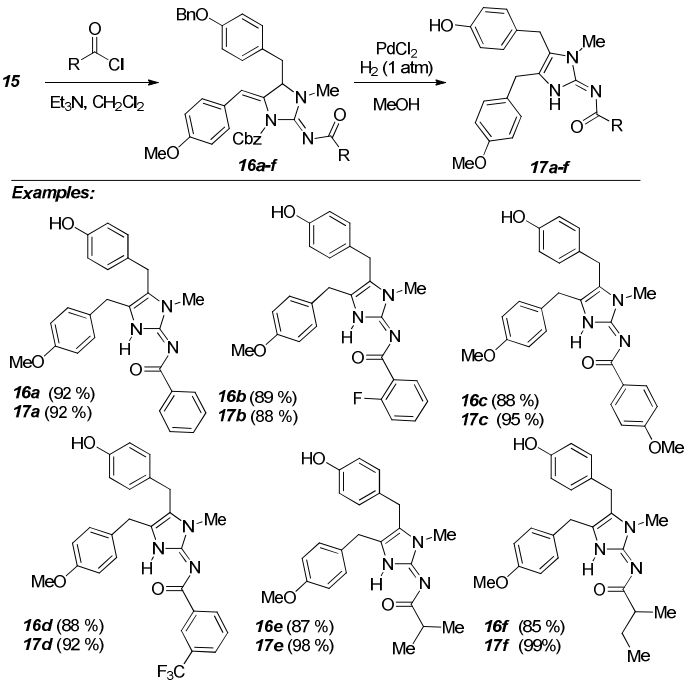
previously developed in our laboratory.[2] It is important to note that four pathways are operable in the cyclization of **14**: N^3- versus N^2- cyclization and 5-*exo*-dig versus 6-*endo* dig cyclization. We knew that mono-acylguandines prefer the tautomeric form in which the imino tautomer is directly conjugated with the acyl group and the other nitrogen forms a hydrogen bond to the carbonyl (as depicted in **10**). This would suggest that the unconjugated non-bonding lone pair on N^3- would initiate cyclization. We also knew that the Ag(I)-catalyzed cyclization proceeds preferentially in a 5-*exo*-dig fashion, however, with an electron rich alkyne substituent selectivity can be significantly diminished. For example, when unsubstituted at C5, *p*-MeOPh substituted propargylguanidines cyclize with only modest 5-exo-dig selectivity ~2:1.[14] To our delight treatment of **14** with $AgNO_3$ in CH_2Cl_2 provided a single isomer (**15**) in 87% isolated yield. The regioselectivity of this process was ultimately supported by X-ray crystallography of the intermediate **18b** (Figure 2 below). Importantly this leaves N^2- open for subsequent functionalization. The Cbz group is readily cleaved under standard hydrogenolysis conditions. Fortunately, isomerization of the exocyclic alkene provides the 2-aminoimidazole nucleus before it can be reduced. The benzyl ether is also cleaved during this step to provided naamine A in quantitative yield. Again the *N*-Me-hydantoin can be installed by Ohta's method to provide naamidine A in good yield. This sequence has proven to be robust and scalable, delivering gram quantities of naamidine A in 6 steps and 33% overall yield.

Scheme 2. Synthesis of naamdine A (**6**).



With the ability to control the regioselectivity of the mono-acylpropargylguanidine cyclization, we returned our attention to generating N^2-substituted analogues (Scheme 3). We envisioned **15** as an ideal intermediate for selective N^2-acylation as N^3- is protected and the imino-tautomer is forced $C^2{=}N^2$ and should yield only mono-acylation products. Indeed, both electron rich and electron poor aryl chlorides gave the N^2-monoacylguanidines **16a-d** in excellent yields (Table 1). Alkanoylchlorides are also reactive to give **16e-f**. Most notably, hydrogenation conditions that cleaved the Cbz group, isomerized the ene-guanidine and cleaved the phenolic benzylether in the preparation of **8** resulted in no reaction in the conversion of **16a→17a**. More forcing conditions (elevated H_2 pressures) could initiate reductive cleavage of the Cbz group and isomerization but the benzyl ether was surprisingly difficult to cleave. Ultimately, a non-supported Pd(II) catalyst was successful, providing the fully deprotected targets **17a-f** in excellent overall yields.

Scheme 3. Generation of N^2-acyl naamidine A analogues.

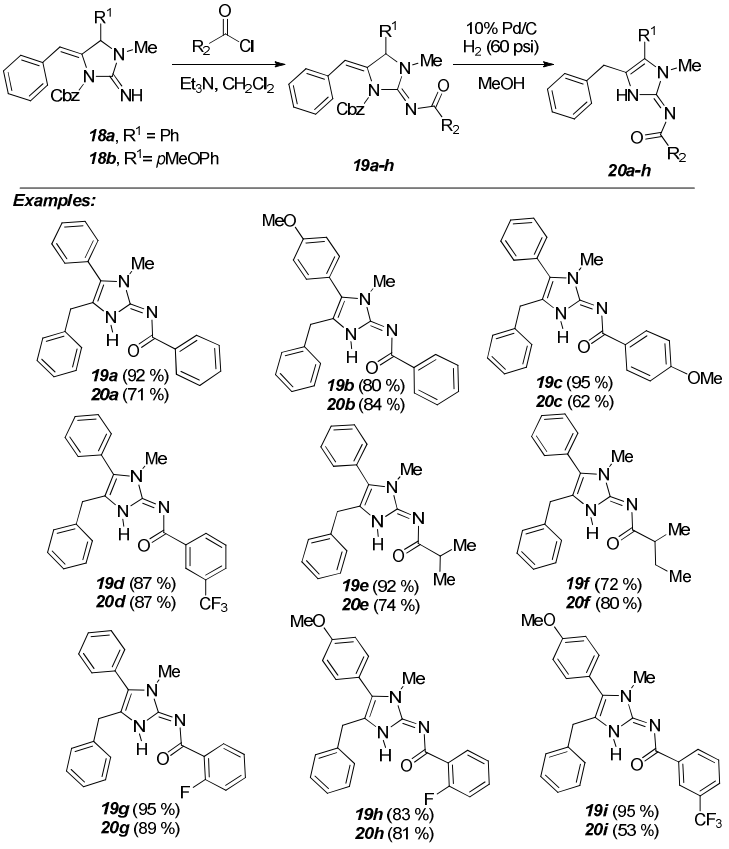


To complement our focused library, the same methodology was involved in the construction of C5-phenyl, C4-benzyl analogues (Scheme 4). The same synthetic sequence accessing **15** was also employed to prepare substrates **18a** and **18b**.[19] Acylation of these intermediates gave N^2-substituted precursors **19a-h** in excellent yields. Hydrogenation over palladium on carbon, with 60 psi H_2, was sufficient to effect the deprotection with

isomerization and deliver the 2-aminoimidazole analogues **20a-h**. Confirmation of N^2-selective acylation was confirmed by X-ray crystallography of **20h**.

Again, **18b** was characterized by X-ray crystallography confirming that the initial hydroamination proceeds to give the N^3-protected intermediates (Figure 2). The fact that the acylation / deprotection with isomerization sequence yields the mono-N^2-substituted 2-aminoimidazoles was ultimately confirmed by X-ray crystallography of product **20h**. This structure shows that even in the now aromatized aminoimidazole nucleus the exocyclic N^2-iminotautomer is preferred with H- bonding between N3 and the N^2-acyl group with a C2-N3 imino bond length of 1.33 Å.

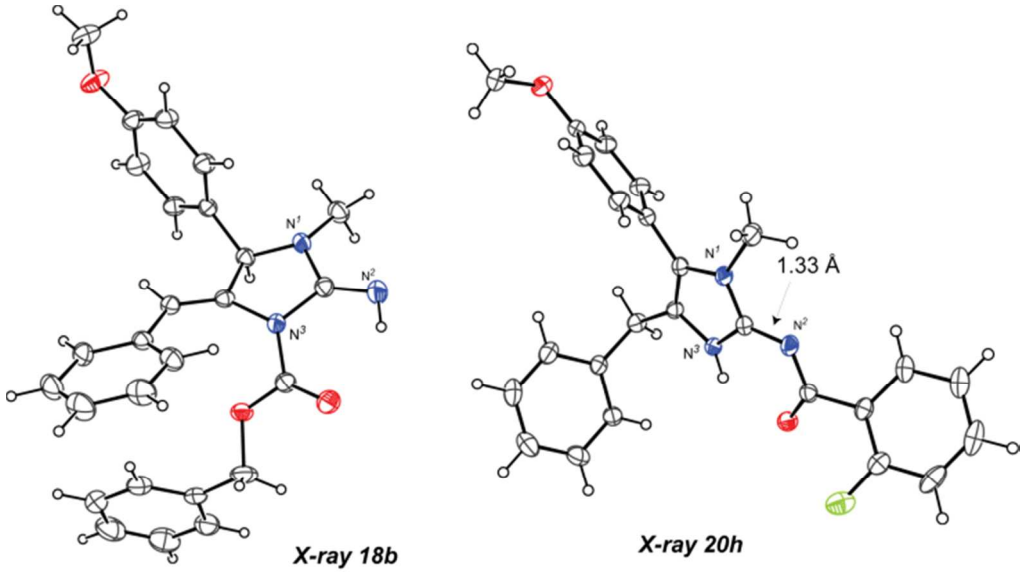
Scheme 4. Generation of N^2-acyl 2-aminoimidazoles.



Studies to evaluate the cytotoxicity of **17a-e** and **20a-i** revealed that **20h** was effective against metastatic tumor cells derived from a chemoresistant breast cancer patient (PE1007070 cells) with an EC_{50} = 8.8 μM.[22] Moreover, **20h** did not significantly affect the viability of immortalized, nontumorogenic mammary tissue (hTERT-HMEC cells), suggesting a cancer-specific mechanism of action. The effect of **20h** on cell viability was also measured in a breast cancer cell line (MCF-7) and an untransformed mammary epithelial cell line (MCF-10A) (Figure 3). As

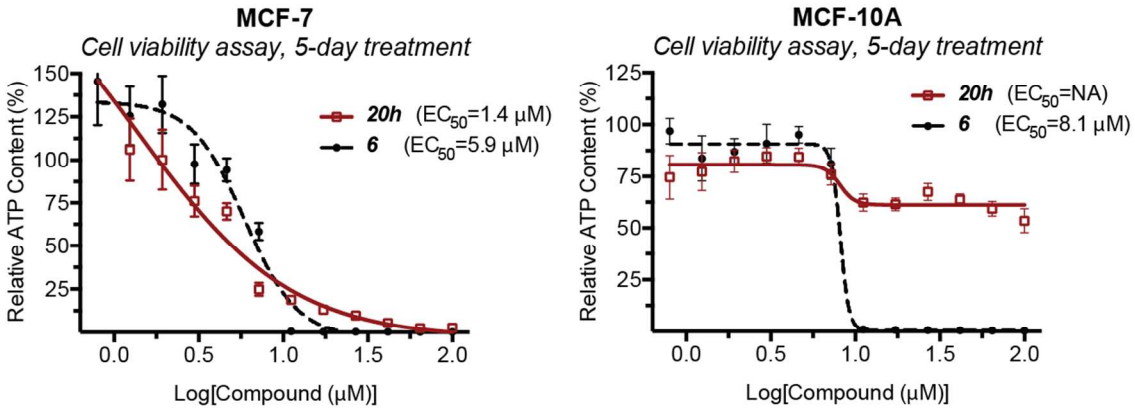
with the patient-derived cells, **20h** was found to significantly reduce the viability of MCF-7 cells (EC_{50} = 1.4 μM) while having no significant effect on the untransformed mammary cell line.

Figure 2. X-ray structures of **18b** / **20h**.



Despite the reported selectivity of naamidine A (**6**) to inhibit proliferation in EGFR transfected NIH3T3 cells, no selectivity was observed in the anti-proliferative activity of MCF-7 versus MCF-10A cells (EC_{50} = 5.9 and 8.1 μM respectively). Taken together, these results suggest that the natural product inspired N^2-acyl-2-aminoimidazoles can exploit cancer selective mechanisms to cause cell death. Studies to further understand this mechanism and evaluate its therapeutic potential are underway.

Figure 3. Antiproliferative effects of naamidine A and **20h**.



Conclusion: In summary, we have shown that mono-acylguanidines preferentially adopt the *N*-acyl-imino tautomer and that this can be reliable used to predict reactivity. Thus the hydroamination of mono-acylpropargylguanidines can be effected regioselectively to generate N^3-acyl-2-aminoimidazoles and subsequently free 2-aminoimidazoles after deprotection with isomerization of the Cbz protected variants. This strategy further exploits the confined N^2-imino tautomer to allow selective N^2-acylation and deliver these analogues without contamination from the diacylated derivatives. The effectiveness of this approach was demonstrated by completing a gram-scale synthesis of both naamine A and naamidine A. The discovery of **20h** as a more selective anti-proliferative agent than naamidine A highlights the necessity to efficiently prepare mono-N^2-acyl-2-aminoimidazoles to further study this selectivity.

Experimental section

General Considerations.

All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2), and toluene (PhMe) were degassed with nitrogen and passed through activated alumina. Methanol (MeOH) and triethylamine (Et_3N) were distilled from CaH_2 immediately prior to use. Reactions were monitored to completion by TLC and visualized by a dual short/long wave UV lamp and stained with an aqueous solution of potassium permanganate and/or organic solution of phosphomolybdic acid. Flash chromatography was performed on silica gel Siliaflash P60 (40-63 μm). Infrared spectra were recorded as thin films and absorptions are reported in cm^{-1} relative to polystyrene (1601 cm^{-1}). HRMS mass spectra were determined by ESI/APCI-TOF. ^1H NMR and spectra were recorded at 500 MHz and 300 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances were reported relative to the deuterated solvent peak (7.26 ppm for $CDCl_3$, 3.31 for CD_3OD, and 2.50 ppm for DMSO-d_6) using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (*J* in Hz), integral. ^{13}C NMR spectra were recorded at 125 MHz and 75 MHz. The chemical shifts (δ) of carbon resonances were reported relative to the deuterated solvent peak (77.2 ppm for $CDCl_3$ and 39.5 for DMSO-d_6).

Procedures for the Synthesis of Naamidine A. *N-Allyl-1-(4-(benzyloxy)phenyl)-4-(4-methoxyphenyl)-N-methylbut-3-yn-2-amine* (**12**). To a 500 mL pressure flask equipped with a stir bar was added 4-

methoxyphenylacetylene (5.35 mL, 40.5 mmol), N-allylmethylamine (3.46 mL, 36.4 mmol), *p*-OBn-phenylacetaldehyde (9.2 g, 40.5 mmol), CuBr (0.52 g, 3.6 mmol), acetonitrile (140 mL) and 1 g of oven-dried 4Å molecular sieves. The flask was heated at 80 ºC for 24 hours, and then allowed to cool to room temperature. The mixture was filtered through Celite and rinsed with EtOAc (500 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (500 mL) and brine (500 mL). The organic layer was dried over Na_2SO_4. After filtration, the organic layer was concentrated and purified via flash chromatography using 4:1 hexanes/EtOAc to give **8** as a dark red oil (10.8 g, 65%). R_f = 0.35 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.27 (m, 4H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.24 (overlapped, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.78 (ddt, *J* = 6.4, 10.7, 17.1 Hz, 1H), 5.14 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.05 (dd, *J* = 2.0, 10.3 Hz, 1H), 4.95 (s, 2H), 3.72 (dd, *J* = 6.4, 8.8 Hz, 1H), 3.70 (s, 3H), 3.15 (dd, *J* = 5.9, 13.7 Hz, 1H), 3.03 (dd, *J* = 7.3, 13.5 Hz, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 157.4, 137.2, 136.0, 133.0 131.2, 130.4, 128.5, 127.8, 127.4, 117.6, 115.5, 114.5, 113.8, 88.5, 85.0, 69.9, 58.4, 58.2, 55.2, 39.5, 37.7 ppm. IR (thin film) 2954, 1606, 1508, 1454, 1420, 1381, 1289, 1243, 1173, 1106, 1026, 921, 831, 807, 791, 732, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{28}H_{30}NO_2$ *m/z* (M+H) 412.2277, Obsd. 412.2278.

1-(4-(Benzyloxy)phenyl)-4-(4-methoxyphenyl)-N-methylbut-3-yn-2-amine (**13**)**.** To a 500 mL round bottom flask equipped with a stir bar was added **12** (10.7 g, 26.0 mmol), thiosalicylic acid (8.0 g, 52 mmol), $Pd(PPh_3)_4$ (0.6 g, 0.5 mmol), and CH_2Cl_2 (260 mL). The reaction was allowed to stir at room temperature under N_2 overnight. The reaction mixture was concentrated and re-dissolved in EtOAc (200 mL). The organic layer was washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4. After filtration, the organic layer was concentrated and purified via flash chromatography using 100% EtOAc (with 0.5% Et_3N) to give **13** as an orange oil (6.6 g, 91%). R_f = 0.35 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (d, *J* = 7.3, 2H), 7.40 (t, *J* = 6.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 3H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 3.72 (t, *J* = 6.4 Hz, 1H), 2.98 (dd, *J* = 2.4, 9.4 Hz, 2H), 2.55 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 157.7, 137.2, 133.0, 130.8, 128.7, 128.0, 127.6, 115.5, 114.7, 88.7, 84.6, 70.1, 55.3, 53.9, 41.3, 34.2 ppm. IR (thin film) 2933, 1606, 1508, 1454, 1441, 1380, 1289, 1244, 1173, 1107, 1027, 831, 737, 697, 668 cm^{-1}. HRMS (ESI+) Calculated for $C_{25}H_{26}NO_2$ *m/z* (M+H) 372.1964, Obsd. 372.1966.

N-Cbz-1-(1-(4-(benzyloxy)phenyl)-4-(4-methoxyphenyl) but-3-yn-2-yl)-1-methylguanidine (**14**). To a 250 mL round bottom flask equipped with a stir bar was added TMSCl (1.65 mL, 13.0 mmol), benzyloxycarbonylcyanamide potassium salt (2.58 g, 12.0 mmol) and 50 mL acetonitrile. The reaction mixture was allowed to stir for 10 min under N_2. A solution of **13** (4.8 g, 13 mmol) in acetonitrile (15 mL) was added to the suspension, and the reaction was allowed to stir for 1 h. The reaction mixture was concentrated to approximately one-quarter of the original volume, and then diluted with EtOAc (100 mL). The organic layer was washed with aqueous solutions of saturated Na_2CO_3 (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4. After filtration, the organic layer was concentrated and purified via flash chromatography using 1:1 hexanes/EtOAc to give **14** as a yellow foam (5.9 g, 90%). R_f = 0.42 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 7.3 Hz, 4H), 7.42-7.27 (m, 8H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.02 (bs, 2H), 5.16 (d, *J* = 2.4 Hz, 2H), 5.03 (s, 2H), 3.80 (s, 3H), 3.04 (dd, *J* = 7.3, 13.2 Hz, 1H), 2.95 (dd, *J* = 6.4, 13.2 Hz, 1H), 2.90 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1, 164.0, 160.7, 159.8, 157.9, 137.8, 137.1, 133.2, 130.7, 129.1, 128.7, 128.4, 128.0, 127.9, 127.7, 114.8, 114.0, 86.1, 84.9, 70.1, 66.8, 55.4, 50.2, 39.7 ppm. IR (thin film) 2934, 1642, 1589, 1536, 1508, 1440, 1378, 1280, 1244, 1172, 1152, 1107, 1026, 909, 831, 799, 732, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{34}H_{34}N_3O_4$ *m/z* (M+H) 548.2549, Obsd. 548.2556.

Benzyl (Z)-4-(4-(benzyloxy)benzyl)-2-imino-5-(4-methoxybenzylidene)-3-methylimidazolidine-1-carboxylate (**15**). To a 25 mL round bottom flask equipped with a stir bar was added **14** (0.51 g, 0.91 mmol), $AgNO_3$ (0.02 g, 0.09 mmol) and dichloromethane (9.1 mL). The flask was wrapped with aluminum foil, and the reaction was allowed to stir at room temperature under N_2 overnight. The reaction mixture was concentrated and purified via flash chromatography using 5% MeOH in CH_2Cl_2 to give **15** as a light yellow foam (0.43 g, 87%). R_f = 0.28 (5% MeOH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46-7.20 (m, 8H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.94 - 6.87 (m, 4H), 6.74 (d, *J* = 4.3 Hz, 2H), 6.71 (d, *J* = 4.0 Hz, 2H), 5.39 (s, 1H), 4.99 (s, 2H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.08 (dd, *J* = 4.2, 6.6 Hz, 1H), 3.77 (s, 3H), 3.08 (s, 3H), 2.99 (dd, *J* = 4.2, 13.7 Hz, 1H), 2.73 (dd, *J* = 7.3, 13.7 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.7, 157.9, 154.0, 151.2, 137.1, 134.2, 131.1, 129.5, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.5, 114.8, 113.8, 113.4, 70.0, 68.6, 65.0, 55.4, 37.8 ppm. IR (thin film) 2923, 2851, 1734, 1607, 1510, 1454, 1382, 1299, 1247, 1178, 1033, 830, 738, 698 cm^{-1}. HRMS (ESI+) Calculated for $C_{34}H_{34}N_3O_4$ *m/z* (M+H) 548.2549, Obsd. 548.2555.

4-((2-Amino-4-(4-methoxybenzyl)-1-methyl-1H-imidazol-5-yl)methyl)phenol (naamine A, **8**). To a 10 mL round bottom flask equipped with a stir bar was added **15** (0.25 g, 0.46 mmol), $Pd(OH)_2$ on carbon (20% wt, 0.032 g, 0.046 mmol) and MeOH (4.6 mL). A H_2 balloon was attached, and the reaction was allowed to stir overnight. The reaction mixture was filtered through Celite and rinsed with dichloromethane. The reaction mixture was concentrated to a pale yellow solid (0.12 g, 84%, mp = 182 ºC) and used without further purification to give **8** as naamine A. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.08 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.3 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 3.76 (s, 2H), 3.72 (s, 3H), 3.69 (s, 2H), 3.08 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.5, 157.8, 156.2, 148.9, 134.5, 132.4, 130.6, 130.1, 129.5, 120.3, 115.8, 114.0, 55.6, 32.7, 29.4, 28.6 ppm. IR (thin film) 2923, 2852, 1610, 1511, 1457, 1369, 1245, 1175, 1035, 814, 773, 668, 652 cm^{-1}. HRMS (ESI+) Calculated for $C_{19}H_{22}N_3O_2$ *m/z* (M+H) 324.1712, Obsd. 324.1714.

Preparation of naamidine A (**6**)**.** To a 50 mL round bottom, 2-neck flask equipped with a stir bar and reflux condenser was added 1-methylparabanic acid (2.04 g, 15.9 mmol) and acetonitrile (14.5 mL). Bis(trimethylsilyl)acetamide (4.9 mL, 20.0 mmol) was added via syringe, and the reaction mixture was allowed to reflux for 2 hours. Without exposing reaction flask to the open atmosphere, the solvent was removed under reduced pressure. The reaction mixture was placed under N_2 and diluted with PhMe (10.5 mL). The solution was transferred via cannula to a 50 mL round bottom, 2-neck flask equipped with a stir bar and reflux condenser containing **8** (1.03 g, 3.2 mmol, mp = 188 ºC) under a N_2 atmosphere. The reaction mixture was allowed to reflux for 16 hours. The reaction was allowed to cool to room temperature, diluted with EtOAc (10 mL), then transferred to a 100 mL round bottom flash to be concentrated. The mixture was purified via flash chromatography using 85:15 PhMe/MeOH with 1% Et_3N to give **6** as a bright yellow solid (1.10 g, 76%). R_f = 0.4 (85:15 PhMe/MeOH with 1% NEt_3); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 7.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 3.87 (s, 4H), 3.77 (s, 3H), 3.40 (s, 3H), 3.17 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.3, 158.5, 157.0, 155.2, 146.7, 134.7, 131.3, 129.5, 129.3, 128.7, 127.0, 115.0, 114.3, 55.5, 32.1, 30.0, 28.8, 25.0 ppm. IR (thin film) 3335, 1789, 1736, 1665, 1612, 1569, 1512, 1486, 1445, 1392, 1303, 1247, 1174, 1153, 1035, 821, 776, 727, 606 cm^{-1}. HRMS (ESI+) Calculated for $C_{23}H_{24}N_5O_4$ *m/z* (M+H) 434.1828, Obsd. 434.1840.

General Procedure A: Acylation of 15 to give 16a-f. *Benzyl-2-(benzoylimino)-4-(4-(benzyloxy)benzyl)-5-((Z)-4-methoxybenzylidene)-3-methylimidazolidine-1-carboxylate* (**16a**)**.** To a 25 mL round bottom flask

equipped with a stir bar was added **15** (498 mg, 0.91 mmol), Et_3N (0.25 mL, 1.8 mmol, 2.0 equiv.), benzoyl chloride (0.16 mL, 1.4 mmol, 1.5 equiv.) and dichloromethane (9.1 mL). The reaction was allowed to stir for 1 hour. The reaction mixture was concentrated and purified via flash chromatography using 1:1 hexanes/EtOAc to give **16a** as a light yellow foam (545 mg, 92%). R_f = 0.43 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12 (d, *J* = 7.0 Hz, 2H), 7.51-7.11 (m, 13H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.45 (s, 1H), 5.01 (s, 2H), 4.80 (d, *J* = 19.8 Hz, 1H), 4.42 (d, *J* = 19.8 Hz, 1H), 4.08 (dd, *J* = 4.2, 6.6 Hz, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 3.03 (dd, *J* = 4.2, 13.5 Hz, 1H), 2.78 (dd, *J* = 7.6, 13.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175,6, 158.7, 157.9, 151.9, 149.1, 137.3, 137.0, 134.5, 131.4, 131.1, 129.7, 129.3, 128,7, 128.6, 128.2, 128.1, 128.0, 127.8, 127.5, 127.1, 117.4, 114.8, 113.7, 70.0, 68.7, 64.6, 55.3, 37.9, 31.0 ppm. IR (thin film) 3033, 2933, 1746, 1647, 1607, 1511, 1455, 1379, 1315, 1282, 1248, 1178, 1075, 1037, 1024, 866, 826, 739, 713, 697 cm^{-1}. HRMS (ESI+) Calculated for $C_{41}H_{37}N_3O_5Na$ *m/z* (M+Na) 674.2631, Obsd. 674.2632.

Benzyl-4-(4-(benzyloxy)benzyl)-2-((2-fluorobenzoyl)imino)-5-((Z)-4-methoxybenzylidene)-3-methylimidazolidine-1-carboxylate (**16b**). Prepared according to the general procedure A with 2-fluorobenzoyl chloride, with purification on silica gel eluting with 1:1 hexanes/EtOAc to give **16b** as a yellow oil (540 mg, 89% yield). R_f = 0.42 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (dt, *J* = 2.0, 7.8 Hz, 1H), 7.44-7.01 (m, 11H), 6.97 (d, *J* = 8.8 Hz, 4H), 6.85 (t, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 5.46 (s, 1H), 5.00 (s, 2H), 4.82 (d, *J* = 19.5 Hz, 1H), 4.33 (d, *J* = 19.5 Hz, 1H), 4.11 (dd, *J* = 3.4, 7.5 Hz, 1H), 3.76 (s, 3H), 3.15 (s, 3H), 3.00 (dd, *J* = 4.4, 13.7 Hz, 1H), 2.78 (dd, *J* = 7.5, 13.7 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 161.3 (d, J_{CF} = 253.8 Hz), 158.7, 158.0, 151.8, 149.1, 137.0, 134.4, 132.6, 132.3 (d, J_{CF} = 9.0 Hz), 131.0, 129.5, 128.7, 128.7, 128.2, 128.2, 127.7, 127.5, 127.0, 123.6 (d, J_{CF} = 3.5 Hz), 117.3, 116.4 (d, J_{CF} = 23.0 Hz), 114.9, 113.6, 70.1, 68.9, 64.6, 55.3, 37.9, 31.0 ppm. IR (thin film) 3033, 2930, 1743, 1598, 1510, 1483, 1452, 1407, 1379, 1314, 1282, 1246, 1177, 1116, 1029, 909, 862, 817, 756, 733, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{41}H_{36}N_3O_5FNa$ *m/z* (M+Na) 692.2537, Obsd. 692.2545.

Benzyl-4-(4-(benzyloxy)benzyl)-2-((4-methoxybenzoyl)imino)-5-((Z)-4-methoxybenzylidene)-3-methylimidazolidine-1-carboxylate (**16c**). Prepared according to the general procedure A with 4-methoxybenzoyl chloride, with purification on silica gel eluting with 2:1 hexanes/EtOAc to give **16c** as a yellow oil (78 mg, 88% yield). R_f = 0.48 (2:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.44-7.28 (m,

5H), 7.24-7.04 (m, 5H), 6.98 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.83-6.71 (m, 6H), 5.44 (s, 1H), 5.00 (s, 2H), 4.80 (d, J = 20.0 Hz, 1H), 4.43 (d, J = 20.0 Hz, 1H), 4.06 (dd, J = 4.1, 7.1 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.12 (s, 3H), 3.02 (dd, J = 4.1, 13.5 Hz, 1H), 2.77 (dd, J = 7.1, 13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.3, 162.5, 158.9, 158.0, 151.6, 149.3, 137.1, 134.7, 133.7, 131.8, 131.2, 130.2, 129.8, 129.5, 128.8, 128.7, 128.3, 128.2, 128.0, 127.6, 127.4, 117.4, 114.9, 113.8, 70.1, 68.6, 64.7, 55.6, 55.4, 38.1, 31.1; IR (thin film) 3033, 2933, 2837, 1743, 1598, 1509, 1454, 1378, 1281, 1236, 1176, 1163, 1110, 1074, 1027, 907, 861, 844, 826, 726, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{42}H_{39}N_3O_6Na$ *m/z* (M+Na) 704.2737, Obsd. 704.2742.

Benzyl-4-(4-(benzyloxy)benzyl)-5-((Z)-4-methoxybenzylidene)-3-methyl-2-((3-(trifluoromethyl)benzoyl)imino) imidazolidine-1-carboxylate (**16d**). Prepared according to the general procedure A with 3-trifluoromethylbenzoyl chloride, with purification on silica gel eluting with 2:1 EtOAc/hexanes to give **16d** as a yellow oil (61 mg, 94% yield). R_f = 0.66 (2:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (s, 2H), 8.35 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.42-7.29 (m, 4H), 7.22-7.11 (m, 4H), 7.00 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 5.53 (s, 1H), 5.00 (s, 2H), 4.78 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.13 (dd, J = 4.5, 7.3 Hz, 1H), 3.77 (s, 3H), 3.18 (s, 3H), 3.04 (dd, J = 4.5, 13.8 Hz, 1H), 2.84 (dd, J = 7.3, 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.9, 160.9, 158.9, 158.0, 152.9, 149.0, 138.0, 137.0, 134.2, 133.8, 132.9, 131.9 (q, J_{CF} = 33.4 Hz), 131.3 (q, J_{CF} = 3.8 Hz), 131.0, 130.4, 130.2 129.9, 129.5, 129.7 (q, J_{CF} = 3.8 Hz), 129.2, 128.7, 128.5, 128.2, 128.1 127.5, 126.8, 125.4, 124.4, 123.2, 122.3, 117.7, 114.8, 113.7, 70.0, 68.9, 64.6, 55.2, 37.8, 30.9; IR (thin film) 2935. 1797, 1743, 1606, 1511, 1455, 1379, 1332, 1313, 1300, 1275, 1249, 1226, 1167, 1124, 1070, 1033, 996, 908, 858, 818, 789, 729, 693 cm^{-1}. HRMS (ESI+) Calculated for $C_{42}H_{37}N_3O_5F_3$ *m/z* (M+H) 720.2685, Obsd. 720.2689.

Benzyl-4-(4-(benzyloxy)benzyl)-2-(isobutyrylimino)-5-((Z)-4-methoxybenzylidene)-3-methylimidazolidine-1-carboxylate (**16e**). Prepared according to the general procedure A with isobutyryl chloride, with purification on silica gel eluting with 1:1 EtOAc/hexanes to give **16e** as a yellow oil (49 mg, 87% yield). R_f = 0.32 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64-7.37 (m, 10H), 7.28 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 5.60 (s, 1H), 5.21 (s, 2H), 5.07 (d, J = 19.5 Hz, 1H), 4.71 (d, J = 19.5 Hz, 1H), 4.20 (dd, J = 4.2, 7.1 Hz, 1H), 3.97 (s, 3H), 3.24 (s, 3H), 3.18 (dd, J = 4.2, 13.5 Hz, 1H), 2.93 (dd, J = 7.1, 13.5 Hz, 1H), 2.84 (sept, J = 6.8 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.39 (d, J =

6.8 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.0, 158.7, 157.9, 150.3, 149.2, 137.0, 134.6, 131.0, 129.5, 129.4, 128.7, 128.6, 128.2, 128.0, 127.9, 127.4, 127.2, 117.0, 114.8, 113.7, 70.0, 68.6, 64.6, 55.2, 38.6, 37.9, 30.8, 20.1 ppm. IR (thin film) 3033, 2964, 2929, 1745, 1663, 1607, 1455, 1379, 1273, 1249, 1179, 1123, 1077, 1037, 923, 864, 826, 738, 697 cm^{-1}. HRMS (ESI+) calculated for $C_{38}H_{39}N_3O_5Na$ *m/z* (M+Na) 640.2787, Obsd. 640.2775.

Benzyl-4-(4-(benzyloxy)benzyl)-5-((Z)-4-methoxybenzylidene)-3-methyl-2-((2-methylbutanoyl)imino) imidazolidine-1-carboxylate (**16f**). Prepared according to the general procedure A with 2-methylbutyryl chloride, with purification on silica gel eluting with 1:1 EtOAc/hexanes to give **16f** as a yellow oil (28 mg, 85% yield). R_f = 0.44 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.17 (m, 8H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 7.3 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.39 (d, *J* = 5.8 Hz, 1H), 5.00 (s, 2H), 4.88 (dd , *J* = 4.0 Hz, 20.5 Hz, 1H), 4.51 (dd , *J* = 4.0 Hz, 20.5 Hz, 1H), 3.99 (p, *J* = 3.7, 1H), 3.75 (s, 3H), 3.03 (s, 3H), 2.97 (dd, *J* = 4.4, 13.5 Hz, 1H), 2.72 (m, 1H), 2.46 (ddq, *J* = 6.9, 5.6, 7.0 Hz, 1H), 1.83 (m, 1H), 1.51 (m, 1H), 1.18 (dd, *J* = 6.9, 7.0, 3H), 0.97 (dt, *J* = 4.0, 7.6 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 187.5, 158.9, 158.0, 151.1, 150.7, 149.4, 137.2, 134.7, 131.2, 129.7, 128.8, 128.7, 128.4, 128.2, 128.0, 127.6, 127.4, 127.3, 117.2, 114.9, 113.8, 70.1, 68.8, 64.8, 55.4, 45.9, 45.5, 38.1, 31.1, 27.7, 27.5, 17.2, 16.4, 12.2, 12.0. IR (thin film) 2963, 2931, 2873, 1746, 1653, 1607, 1511, 1456, 1378, 1249, 1179, 1119, 1077, 1039, 827, 741, 696 cm^{-1}. HRMS (ESI+) calculated for $C_{39}H_{41}N_3O_5Na$ *m/z* (M+Na) 654.2944, Obsd. 654.2941.

General Procedure B: deprotection with isomerization of 16 to 17. *N-(5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)benzamide* (**17a**). To a 5 mL round bottom flask equipped with a stir bar was added **16a** (52 mg, 0.08 mmol), $PdCl_2$ (25 mg, 0.18 mmol) and methanol (0.9 mL). The reaction was allowed to stir until completion under an H_2 atmosphere balloon. The reaction mixture was filtered through 0.45 μM PTFE syringe filter and rinsed with additional methanol and CH_2Cl_2. The solvent was removed and the product was triturated with diethyl ether. The solid was isolated to give **17a** as an off-white solid (34 mg, 92%, mp = 135 ºC). R_f = 0.40 (5% MeOH in CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.41 (s, 1H), 8.10 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.33 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H) 6.86 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 6.4 Hz, 2H) 4.03 (s, 2H), 4.00 (s, 2H), 3.69 (s, 3H), 3.15 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.5, 156.7, 133.3, 130.4, 130.0, 129.5, 129.0, 128.9, 127.0, 116.0, 114.4, 55.6, 49.0, 31.7, 28.7, 27.4 ppm. IR (thin film) 3926, 2932, 1688 1612, 1510, 1474, 1453, 1408, 1363,

1301, 1246, 1174, 1104, 1033, 908, 818, 731, 706 cm^{-1}. HRMS (ESI+) calculated for $C_{26}H_{26}N_3O_3$ *m/z* (M+H) 428.1974, Obsd. 428.1973.

2-Fluoro-N-(5-(4-hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)benzamide (**17b**). Prepared according to the general procedure B with **16b,** with purification *via* trituration with diethyl ether to give **17b** as a waxy solid (23 mg, 88% yield). R_f = 0.30 (1:1 hexanes/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.29 (s, 1H), 7.80 (s, 1H), 7.43 (s, 1H), 7.19 (d, *J* = 8.1 Hz, 4H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 4H), 3.71 (s, 3H), 3.20 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 157.8, 155.9, 131.3, 129.9, 129.7, 129.4, 128.3, 116.7 (d, J_{CF} = 22.8 Hz), 115.8, 114.2, 55.4, 29.5, 27.7 ppm. IR (thin film) 1686, 1581, 1512, 1478, 1441, 1305, 1247, 1173, 1156, 1105, 904 cm^{-1}. HRMS (ESI+) calculated for $C_{26}H_{24}N_3O_3FNa$ *m/z* (M+Na) 468.1699, Obsd. 468.1700.

N-(5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)-4-methoxybenzamide (**17c**). Prepared according to the general procedure B with **16c,** with purification *via* trituration with diethyl ether to give **17c** as an off-white solid (50 mg, 95% yield, mp = 178 ºC). R_f = 0.30 (1:1 hexanes/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.44 (s, 1H), 8.07 (d, *J* = 9.3 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 4.06 (s, 2H), 4.01 (s, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.43 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.8, 157.8, 155.9, 130.4, 129.6, 129.2, 128.8, 126.2, 115.2, 113.7, 64.6, 55.3, 54.8, 31.5, 27.8, 26.6, 14.9 ppm. IR (thin film) 2929, 1605, 1585, 1569, 1510, 1465, 1367, 1303, 1248, 1166, 1101, 1030, 906, 843, 815, 770, 728, 692, 668 cm^{-1}. HRMS (ESI+) calculated for $C_{27}H_{28}N_3O_4$ *m/z* (M+H) 458.2080, Obsd. 458.2083.

N-(5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)-3-(trifluoromethyl)benzamide (**17d**). Prepared according to the general procedure B with **16d**, with purification via trituration with diethyl ether to give **17d** as an off-white solid (58 mg, 92% yield, mp = 237 ºC). R_f = 0.40 (2:1 EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.32 (s, 2H), 8.38 (s, 2H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 4H), 3.71 (s, 3H), 3.29 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 157.8, 155.9, 132.2, 129.5, 129.0, 124.5, 115.4, 113.9, 55.1, 28.9, 27.1 ppm. IR (thin film) 1564, 1532, 1512, 1483, 1383, 1322, 1277, 1248, 1170, 1153, 1113, 916 cm^{-1}. HRMS (ESI+) calculated for $C_{27}H_{25}N_3O_3F_3$ *m/z* (M+H) 496.1848, Obsd. 496.1850.

N-(5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)isobutyramide (**17e**). Prepared according to the general procedure B with **16e**, with purification *via* trituration with diethyl ether to give **17e** as an off-white solid (20 mg, 98% yield, mp = 196 ºC). R_f = 0.17 (1:1 hexanes/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 2H), 3.80 (s, 2H), 3.72 (s, 3H), 3.16 (s, 3H), 2.63 (sep, *J* = 6.8 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 176.3, 157.6, 155.8, 136.3, 130.0, 129.1, 128.7, 126.3, 125.5, 115.1, 113.5, 54.7, 33.5, 31.0, 28.0, 26.5, 18.6, ppm. IR (thin film) 3274, 2968, 2472, 1670, 1611, 1510, 1465, 1404, 1301, 1244, 1174, 1102, 1032, 973, 816 cm^{-1}. HRMS (ESI+) calculated for $C_{23}H_{28}N_3O_3$ *m/z* (M+H) 394.2147, Obsd. 394.2138.

N-(5-(4-Hydroxybenzyl)-4-(4-methoxybenzyl)-1-methyl-1,3-dihydro-2H-imidazol-2-ylidene)-2-methylbutanamide (**17f**). Prepared according to the general procedure B with **16f**, with purification *via* trituration with diethyl ether to give **17f** as an off-white solid (16 mg, 99%, mp = 102 ºC). R_f = 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.40 (s, 1H), 7.17 (d, *J* = 8.7 Hz), 6.87 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.98 (s, 2H), 3.94 (s, 2H), 3.71 (s, 3H), 3.36 (s, 3H), 2.89 (sextet, *J* = 6.6 Hz, 1H), 1.61 (m, *J* = 7.4 Hz, 1H), 1.43 (m, *J* = 6.8 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 176.1, 157.9, 156.1, 136.7, 130.5, 129.5, 129.1, 126.8, 125.9, 115.4, 113.9, 55.1, 31.3, 28.5, 26.9, 26.4, 16.9, 11.5 ppm. IR (thin film) 3357, 2965, 2483, 2076, 1670, 1653, 1635, 1612, 1558, 1510, 1458, 1405, 1301, 1245, 1175, 1118, 1033, 971, 816 cm^{-1}. HRMS (ESI+) calculated for $C_{24}H_{30}N_3O_3$ *m/z* (M+H) 408.2303, Obsd. 408.2286.

Preparation of Compound 18a. *N-(1,3-diphenylprop-2-yn-1-yl)-N-methylprop-2-en-1-amine* (**S1a**). In a 250 mL high pressure flask containing a magnetic stir bar were added benzaldehyde (3.1 g, 29.0 mmol), phenylacetylene (2.95 g, 28.9 mmol), *N*-allylmethylamine (1.88 g, 26.3 mmol), oven dried molecular sieves (Grade 564, 3 Å, 8-12 mesh) (*ca.* 2 g) and acetonitrile (200 mL). The flask was sealed and placed in a preheated 80˚C oil bath for 24 h. The reaction flask was removed from the oil bath and allowed to cool to room temperature. CuBr (0.38 g, 2.6 mmol) was added and the flask was sealed and returned to the preheated 80 ˚C oil bath for 48 h. The reaction tube was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through Celite and rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure.

The crude product was purified via flash chromatography, eluting with 9:1 hexanes/EtOAc to give **S1a** as a dark orange oil (5.3 g, 88%). R_f = 0.78 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, *J* = 6.9 Hz, 2H), 7.56-7.53 (m, 2H), 7.40-7.26 (m, 6H), 5.93 (ddt, *J* = 6.6 Hz, 10.4 Hz, 17.1 Hz, 1H), 5.32 (dd, *J* = 17.1 Hz, 1.5 Hz, 1H), 5.18 (dd, *J* = 10.4 Hz, 1.2 Hz, 1H), 4.99 (s, 1H), 3.89 (s, 3H), 3.19 (d, *J* = 5.1 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 136.3, 131.9, 128.5, 128.4, 128.3, 127.7, 123.4, 117.8, 88.5, 84.9, 59.8, 57.9 ppm. IR (thin film): 3061, 3030, 2978, 2945, 2844, 2788, 1598, 1489, 1448, 1324, 1273, 1196, 1155, 1127, 1070, 1023, 994, 963, 917, 754, 726, 689 cm^{-1}. HRMS (ESI+) Calculated for $C_{19}H_{19}N$ *m/z* 262.1590 (M+H), Obsd. 262.1572.

N-methyl-1,3-diphenylprop-2-yn-1-amine (**S2a**). In a 250 mL round bottom flask containing a magnetic stir bar were added $Pd(PPh_3)_4$ (1.3 g, 1.1 mmol), thiosalicylic acid (7.0 g, 45.0 mmol) and CH_2Cl_2 (100 mL). A solution of **S1a** (5.3 g, 22.7 mmol) in 15 mL in CH_2Cl_2 was added, and the reaction mixture was allowed to stir at room temperature under N_2 for 12 h. The solvent was then removed under reduced pressure and the crude product was re-dissolved in Et_2O (10 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (50 mL) and brine (50mL), then dried and filtered over Na_2SO_4. The crude product was purified via flash chromatography, eluting with 4:1 hexanes/EtOAc to give **S2a** as a dark orange oil (3.1 g, 73%). R_f = 0.22 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61-7.31 (m, 10H), 4.76 (s, 1H), 2.57 (s, 3H), 1.47 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.3, 131.8, 128.6, 128.4, 128.2, 127.9, 127.7, 123.2, 89.1, 85.7, 56.4, 33.9 ppm. IR (thin film) 3060, 3029, 2933, 2850, 2793, 1653, 1598, 1559, 1540, 1489, 1473, 1449, 1306, 1214, 1177, 1098, 1071, 1027, 915, 755, 691 cm^{-1}. HRMS (ESI+) Calculated for $C_{16}H_{16}N$ *m/z* 222.1259 (M+H), Obsd. 222.1288.

Benzyl (Z)-5-benzylidene-2-imino-3-methyl-4-phenylimidazolidine-1-carboxylate (**S3a**). In a 100 mL round bottom flask containing a magnetic stir bar were added potassium benzyloxycarbonylcyanamide (0.65 g, 3.0 mmol), TMSCl (0.34 g, 3.1 mmol) and acetonitrile (15 mL). The solution was stirred at room temperature for 10 minutes. A solution of **S2a** (0.46 g, 2.4 mmol) in acetonitrile (3.5 mL) was then added, and the reaction mixture was allowed to stir at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was dissolved in EtOAc (150 mL). The organic layer was washed aqueous solutions of saturated $NaHCO_3$ (50 mL) and brine (50 mL), then dried and filtered over Na_2SO_4. The crude product was purified via flash chromatography, eluting with 1:1 hexanes/EtOAc to give **S3a** as a dark brown oil (0.75 g, 85%). R_f = 0.48

(1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58-7.23 (m, 15H), 5.18 (s, 2H), 2.83 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.3, 161.3, 158.0, 137.2, 132.1, 128.9, 128,8, 128.6, 128.3, 128.2, 127.9, 127.6, 122.7, 87.0, 85.1, 67.1, 51.4, 30.1 ppm. IR (thin film) 3331, 3031, 2939, 1736, 1646, 1596, 1534, 1491, 1450, 1379, 1153, 1050, 1028, 801, 757, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{25}H_{24}N_3O_2$ *m/z* 398.1869 (M+H), Obsd. 398.1877.

(Z)-Benzyl 5-benzylidene-2-imino-3-methyl-4-phenylimidazolidine-1-carboxylate (**18a**). In a 50 mL foil-wrapped round bottom flask containing a magnetic stir bar were added **S3a** (0.75, 2.0 mmol), $AgNO_3$ (35 mg, 0.20 mmol), and CH_2Cl_2 (20 mL). The solution was stirred at room temperature for 6 h. The solvent was then removed under reduced pressure and the crude product was re-dissolved in EtOAc (50 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (15 mL) and brine (15 mL), then dried and filtered over Na_2SO_4. The crude product was purified via flash chromatography, eluting with 1:1 hexanes/EtOAc to give **18a** as a dark brown oil (0.53 g, 71%). R_f = 0.31 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43-7.12 (m, 11H), 7.08 (d, *J* = 7.0 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 5.52 (d, *J* = 3.0 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H), 4.79 (d , *J* = 19.5 Hz, 1H), 4.37 (d, *J* = 19.5 Hz, 1H), 2.81 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1, 151.4, 137.6, 136.3, 34.4, 129.2, 129.1, 128.7, 128.5, 128.4, 128.2, 127.4, 127.1, 113.4, 68.4, 67.6, 30.2 ppm. IR (thin film) 3346, 3031, 1734, 1684, 1652, 1495, 1426, 1386, 1303, 1249, 1197, 1161, 1047, 1026, 957, 797, 696 cm^{-1}. HRMS (ESI+) Calculated for $C_{25}H_{24}N_3O_2$ *m/z* 398.1869 (M+H), Obsd. 398.1876.

Preparation of compound 18b. *N-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)-N-methylprop-2-en-1-amine* (**S1b**). Prepared according to the A^3-coupling procedure of **S1a** using *p*-anisaldehyde, *n*-allylmethylamine, and phenylacetylene with purification on silica gel eluting with 2:1 hexanes/EtOAc to give a dark orange oil (12.7 g, 65%). R_f = 0.78 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59-7.53 (m, 4H), 7.37-7.26 (m, 3H), 6.49 (d, *J* = 8.7 Hz, 2H), 5.92 (ddt, *J* = 6.6 Hz, 10.5 Hz, 17.4 Hz, 1H), 5.33 (dd, *J* = 17.4 Hz, 2.0 Hz, 1H), 5.19 (dd, *J* = 9.3 Hz, 2.0 Hz, 1H), 4.94 (s, 1H), 3.83 (s, 3H), 3.19 (d, *J* = 6.6 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 136.3, 131.9, 131.1, 129.7, 128.4, 128.2, 123.4, 117.7, 113.6, 88.3, 85.3, 59.3, 57.8, 55.4, 37.8 ppm. IR (thin film) 2948, 2834, 2786, 1642, 1609, 1583, 1507, 1488, 1441, 1301, 1244, 1169, 1126, 1107, 1033, 994, 962, 916, 850, 807, 778, 754, 689, 583, 524 cm^{-1}. HRMS (ESI+) Calculated for $C_{20}H_{21}NO$ *m/z* 292.1701 (M+H), Obsd. 292.1699.

1-(4-Methoxyphenyl)-N-methyl-3-phenylprop-2-yn-1-amine (**S2b**). Prepared according to the Pd(0)-deallylation procedure with **S1b**, with purification on silica gel eluting with 2:1 hexanes/EtOAc to give **S2b** a dark orange oil (2.1 g, 44%). R_f = 0.22 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54-7.48 (m, 4H), 7.33-7.31 (m, 3H), 6.9 (d, *J* = 8.7 Hz, 2H), 5.18 (s, 1H), 3.81 (s, 3H), 2.56 (s, 3H), 1.81 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 132.4, 131.7, 128.8, 128.3, 128.1, 123.1, 113.8, 89.2, 85.5, 55.6, 55.3, 33.7 ppm. IR (thin film) 2953, 2834, 2790, 1609, 1584, 1508, 1488, 1462, 1440, 1301, 1243, 1171, 1095, 1031, 956, 913, 829, 754, 727, 703, 689, 573, 547, 524 cm^{-1}. HRMS (ESI+) Calculated for $C_{17}H_{17}NONa$ *m/z* 274.1208 (M+Na), Obsd. 274.1213.

Benzyl (Z)-5-benzylidene-2-imino-4-(4-methoxyphenyl)-3-methylimidazolidine-1-carboxylate (**S3b**). Prepared according to the guanylation procedure of **S2b,** with purification on silica gel eluting with 1:1 hexanes/EtOAc to give a dark orange oil (2.97 g, 82%). R_f = 0.48 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51-7.43 (m, 6H), 7.36-7.25 (m, 7H), 6.9 (d, *J* = 6.3 Hz, 2H), 5.18 (s, 2H), 3.80 (s, 3H), 2.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.1, 160.9, 159.4, 137.6, 131.9, 129.0, 128.7, 128.6, 128.4, 128.0, 127.7, 122.2, 113.9, 86.6, 85.2, 66.9, 55.3, 50.6, 29.7 ppm. IR (thin film) 3403, 2932, 1646, 1584, 1532, 1508, 1488, 1440, 1376, 1273, 1246, 1121, 1150, 1110, 1027, 908, 845, 799, 775, 755, 729, 690, 647, 586, 552 cm^{-1}. HRMS (ESI+) Calculated for $C_{26}H_{26}N_3O_3$ *m/z* 428.1974 (M+Na), Obsd. 428.1979.

(Z)-Benzyl 5-benzylidene-2-imino-4-(4-methoxyphenyl)-3-methylimidazolidine-1-carboxylate (**18b**). Prepared according to the Ag(I)-cyclization procedure, with purification by silica gel eluting with 1:1 hexanes/EtOAc to give a dark brown oil (1.2 g, 87%). R_f = 0.18 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28-7.16 (m, 9H), 7.10-7.08 (m, 2H), 6.92-6.88 (m, 4H), 5.47 (d, *J* = 2.1 Hz, 1H), 4.92 (d, *J* = 2.1 Hz, 1H), 4.82 (d, *J* = 19.5 Hz, 2H), 4.33 (d, *J* = 19.5 Hz, 2H), 3.81 (s, 3H), 2.75 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 106.1, 153.5, 151.4, 136.5, 135.1, 134.4, 129.7, 129.6, 128.7, 128.4, 127.4, 127.0, 114.5, 113.0, 62.2, 67.0, 55.4, 30.1 ppm. IR (thin film) 3404, 2932, 1646, 1548, 1532, 1508, 1488, 1440, 1376, 1273, 1246, 1171, 1150, 1110, 1027, 908, 845, 799, 779, 755, 728, 690, 647, 586, 552 cm^{-1}. HRMS (ESI+) Calculated for $C_{26}H_{26}N_3O_3$ *m/z* 428.1974 (M+Na), Obsd. 428.1979.

General Procedure C: Acylation of 18 to give 19. *Benzyl-2-(benzoylimino)-5-((Z)-benzylidene)-3-methyl-4-phenylimidazolidine-1- carboxylate* (**19a**). In a 10 mL round-bottomed flask containing a magnetic stir

bar were added **18a** (73 mg, 0.18 mmol), benzoyl chloride (0.032 mL, 0.28 mmol, 1.5 equiv.), triethylamine (0.051 mL, 0.37 mmol, 2.0 equiv.), and dichloromethane (2 mL) under N_2. The reaction was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the crude material was dissolved in EtOAc (20 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, and the resulting material was purified via flash chromatography (3:2 hexanes/EtOAc) to yield **19a** as a light brown foam (86 mg, 93%). R_f = 0.22 (3:2 hexanes/EtOAc) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21-8.18 (m, 2H), 7.51-7.32 (m, 8H), 7.25-7.11 (m, 8H), 6.8-6.78 (m, 2H), 5.77 (d *J* = 2.0 Hz, 1H), 5.16 (d , *J* = 2.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 2.93 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.8, 151.8, 149.3, 137.1, 136.8, 135.4, 134.5, 133.9, 131.6, 129.7, 129.4, 129.3, 127.8, 127.5, 116.9, 68.8, 67.0, 30.6 ppm. IR (thin film) 3060, 3029, 1744, 1557, 1494, 1448, 1404, 1377, 1315, 1277, 1226, 1173, 1144, 1080, 1036, 1020, 976, 909, 856, 794, 752, 727, 696, 668 cm^{-1}. HRMS (ESI+) calculated for $C_{32}H_{27}N_3NaO_3$ *m/z* (M+Na) 524.1950, Obsd. 524.1963.

Benzyl (2-(benzoylimino)-5-((Z)-benzylidene)-4-(4-methoxyphenyl)-3-methylimidazolidine- 1-carboxylate (**19b**). Prepared according to general procedure C using **18b** and benzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19b** as a light brown foam (96 mg, 80%). R_f = 0.22 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, *J* = 8.0 Hz, 2H), δ 7.50-7.21 (m, 14H), δ 6.91 (d, *J* = 8.5 Hz, 2H), δ 6.80 (d, *J* = 7.0 Hz, 2H), δ 5.74 (d, *J* = 1.8 Hz, 1H), δ 5.13 (d, *J* = 1.8 Hz, 1H), δ 4.72 (d, *J* = 12.0 Hz, 1H), δ 4.24 (d, *J* = 12.0 Hz, 1H), δ 3.82 (s, 3H), δ 2.90 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.2, 160.5, 151.9, 149.4, 137.3, 135.6, 134.7, 134.6, 134.4, 131.7, 129.8, 129.4, 128.7, 128.5, 128.4, 128.3, 128.2, 127.6, 116.8, 114.9, 69.0, 66.8, 55.6, 30.7 ppm. IR (thin film) 3404, 2932, 1646, 1548, 1532, 1508, 1488, 1440, 1376, 1273, 1246, 1171, 1150, 1110, 1027, 908, 845, 799, 779, 755, 728, 690 cm^{-1}. HRMS (ESI+) calculated for $C_{33}H_{29}N_3NaO_4$ *m/z* (M+Na) 554.2056, Obsd. 554.2066.

Benzyl 5-((Z)-benzylidene)-2-((4-methoxy benzoyl)imino)-3-methyl-4- phenylimidazolidine-1-carboxylate (**19c**). Prepared according to general procedure C using **18a** and 4-methoxybenzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19c** as a light brown foam (0.12 g, 95%). R_f = 0.19 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16 (d, *J* = 9.0 Hz, 2H), 7.41-7.37 (m, 3H), 7.33-7.30 (m, 2H), 7.26-7.12 (m, 8H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 5.72 (d, *J* = 2.0 Hz, 1H), 5.13 (s, 1H), 4.71 (d , *J* = 12.3 Hz), 4.65 (d , *J* = 12.3 Hz), 3.86 (s, 3H), 2.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.0,

162.6, 151.5, 149.5, 137.1, 135.6, 134.8, 134.2, 131.8, 130.1, 129.5, 129.4, 1283, 127.9, 127.6, 116.9, 113.4, 68.9, 67.2, 55.6, 30.8 ppm. IR (thin film) 3058, 2951, 1745, 1652, 1597, 1507, 1456, 1427, 1249, 1227, 1177, 1162, 1022, 974, 863, 843, 731, 693 cm^{-1}. HRMS (ESI+) calculated for $C_{33}H_{29}N_3NaO_4$ *m/z* (M+Na) 554.2056, Obsd. 554.2061.

Benzyl-5-((Z)-benzylidene)-3-methyl-4-phenyl-2-((3-(trifluoromethyl)benzoyl)imino)imidazolidine-1-carboxylate (**19d**). Prepared according to general procedure C using **18a** and 3-trifluoromethylbenzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19d** as a light brown foam (0.12 g, 87%). R_f = 0.31 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47 (s, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.42 (m, 4H), 7.34 (m, 2H), 7.26 (m, 3H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 7.0 Hz, 2H), 5.80 (s, 1H), 5.20 (s, 1H), 4.69 (d , *J* = 11.8 Hz), 4.64 (d , *J* = 11.8 Hz), 2.95 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 155.1, 144.3, 138.1, 136.7, 135.4, 134.4, 133.9, 133.1, 130.6 (q, J_{CF} = 32.4 Hz), 128.8, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2 (q, J_{CF} = 2.8 Hz), 128.0, 127.7, 126.8 (q, J_{CF} = 3.6 Hz), 124.3 (q, J_{CF} = 270.5 Hz), 117.4, 69.2, 67.3, 30.8 ppm. IR (thin film) 1699, 1652, 1616, 1325, 1259, 1166, 1121, 1070, 998, 920, 855, 817, 758, 692 cm^{-1}. HRMS (ESI+) calculated for $C_{33}H_{26}F_3N_3NaO_3$ *m/z* (M+Na) 592.1824, Obsd. 592.1821.

Benzyl 5-((Z)-benzylidene)-2-(isobutyrylimino)-3-methyl-4-phenylimidazolidine-1- carboxylate (**19e**). Prepared according to general procedure C using **18a** and isobutyryl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19e** as a light brown foam (38 mg, 92%). R_f = 0.34 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.35 (m, 3H), 7.29- 7.15 (m, 10H), 6.86 (d, *J* = 7.0 Hz, 2H), 5.72 (d, *J* = 2.0 Hz, 1H), 5.07 (d, *J* = 2.0 Hz, 1H), 4.74 (d , *J* = 12.3 Hz), 4.69 (d , *J* = 12.3 Hz), 2.81 (s, 3H), 2.71 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 187.6, 150.2, 149.5, 137.1, 135.6, 134.7, 134.1, 129.5, 128.6, 128.4, 128.3, 127.8, 127.6, 116.6, 68.8, 67.1, 38.8, 30.6, 20.0 ppm. IR (thin film) 3030, 2966, 2360, 2340, 1743, 1653, 1598, 1494, 1455, 1403, 1378, 1345, 1261, 1175, 1121, 1080, 1023, 977, 919, 847, 820, 752, 730, 695, 668, 634, 598, 557 cm^{-1}. HRMS (ESI+) calculated for $C_{29}H_{29}N_3NaO_3$ *m/z* (M+Na) 490.2107, Obsd. 490.2103 (M+Na).

Benzyl-5-((Z)-benzylidene)-3-methyl-2-((2-methylbutanoyl)imino)-4- phenylimidazolidine-1-carboxylate (**19f**). Prepared according to general procedure C using **18a** and 2-methylbutyryl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19f** as a light brown foam Light brown foam (57 mg, 70%). R_f=

0.39 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.12 (m, 13H), δ 6.86 (d, *J* = 7.5 Hz, 2H), 5.72 (d, *J* = 2.0 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.77-4.66 (m, 2H), 2.81 (s, 3H), 2.53 (m, 1H), 1.87 (m, 1H), 1.55 (m, 1H), 1.23 (d, *J* = 7 Hz, 3H), 1.01 (t, *J* = 6.5 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 186.8, 150.6, 149.6, 137.3, 137.1, 135.6, 134.7, 134.3, 134.1, 129.5, 129.4, 128.5, 128.4, 128.3, 127.9, 127.8, 127.5, 116.4, 68.8, 45.8, 30.7, 27.6, 16.8, 12.1 ppm. IR (thin film) 3031, 2963, 2931, 2873, 1744, 1653, 1597, 1494, 1456, 1403, 1375, 1264, 1175, 1113, 1080, 1039, 978, 908, 752, 730, 695, 668, 633, 588 cm^{-1}. HRMS (ESI+) calculated for $C_{30}H_{31}N_3NaO_3$ *m/z* (M+Na) 504.2263, Obsd. 504.2275.

Benzyl-5-((Z)-benzylidene)-2-((2-fluorobenzoyl)imino)-3-methyl-4-phenylimidazolidine- 1-carboxylate (**19g**). Prepared according to general procedure C using **18a** and 2-fluorobenzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19g** as a light brown foam (120 mg, 95%). R_f = 0.28 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (t, *J* = 8.0 Hz, 1H), 7.50-7.34 (m, 4H), 7.34-7.29 (m, 2H), 7.21-7.07 (m, 8H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 7.0 Hz) 5.71 (d, *J* = 2.0 Hz, 1H), 5.17 (d, *J* = 2.0 Hz, 1H), 4.75 (d , *J* = 11.8 Hz), 4.54 (d , *J* = 11.8 Hz), 2.93 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 161.3 (d, J_{CF} = 423.0 Hz), 151.5, 149.3, 136.7, 135.2, 134.4, 133.9, 132.6, 132.5, 134.4, 129.4, 128.7, 128.4, 128.3, 128.0, 127.9, 127.5, 125.9 (d, J_{CF} = 16.6 Hz), 123.8 (d, J_{CF} = 6.6 Hz), 117.2, 116.5 (d, J_{CF} = 38.4 Hz), 69.0, 67.9, 30.5 ppm. IR (thin film) 3031, 1745, 1596, 1483, 1404, 1378, 1316, 1280, 1263, 1223, 1179, 1157, 1111, 1081, 1023, 974, 909, 866, 782, 755, 732, 696, 655 cm^{-1}. HRMS (ESI+) calculated for $C_{32}H_{26}FN_3NaO_3$ *m/z* (M+Na) 542.1856, Obsd. 542.1865.

Benzyl-5-((Z)-benzylidene)-2-((2-fluorobenzoyl)imino)-4-(4-methoxyphenyl)-3- methylimidazolidine-1-carboxylate (**19h**). Prepared according to general procedure C using **18b** and 2-fluorobenzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19h** a light brown foam (0.98 g, 83%). R_f = 0.25 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (t, *J* = 6 Hz, 1H), 7.44 (m, 1H), 7.24-7.05 (m, 10H), 6.99-6.83 (m, 5H) 5.69 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 1.8 Hz, 1H), 4.77 (d *J* = 19.8 Hz), 4.64 (d , *J* = 19.8 Hz), 3.82 (s, 3H), 2.89 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.3 (d, J_{CF} = 253.4 Hz), 160.4, 151.5, 149.4, 135.3, 134.4, 134.3, 132.7, 132.6, 129.4, 128.8, 128.4, 128.3, 128.0, 127.5, 123.8 (d, J_{CF} = 4.0 Hz), 117.1, 116.5 (d, J_{CF} = 23.0 Hz), 114.8, 69.0, 66.6, 55.4, 30.4 ppm. IR (thin film) 2933, 2834, 2790, 109, 1584, 1508, 1488, 1462, 1440, 1301, 1243, 1171, 1095, 1031, 956, 913, 829, 783, 754, 727, 689, 660, 634, 618, 573, 547, 524 cm^{-1}. HRMS (ESI+) calculated for $C_{33}H_{28}FN_3NaO_4$ *m/z* (M+Na) 572.1962, Obsd. 572.1980.

Benzyl-5((Z)-benzylidene)-4-(4-methoxyphenyl)-3-methyl-2-((3-(trifluoromethyl)benzoyl)imino)imidazolidine-1-carboxylate (**19i**). Prepared according to general procedure C using **18b** and 3-trifluoromethylbenzoyl chloride, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **19i** as a light brown foam (95%). R_f = 0.25 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 1 MHz): δ 8.46 (s, 1H), 8.36 (d, *J* = 9.5 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.55 (t, *J* = 10.0 Hz, 1H), 7.27-7.10 (m, 10), 6.93 (d, *J* = 10.5 Hz, 2H), 6.78 (d, *J* = 9.5 Hz, 2H), 5.77 (s, 1H), 5.18 (s, 1H), 4.70 (d , *J* = 14.5 Hz), 4.62 (d , *J* = 14.5 Hz), 3.89 (s, 3H), 2.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 160.4, 152.8, 149.1, 137.9, 135.3, 134.0, 132.8, 130.3 (q, J_{CF} = 24.7 Hz), 129.3, 128.5, 128.3, 128.3, 128.2, 128.1, 127.9, 127.5, 126.5 (q, J_{CF} = 2.9 Hz), 124.2 (q, J_{CF} = 203.2 Hz), 117.0, 114.7, 68.9, 66.7, 55.4, 30.4 ppm. IR (thin film) 1775, 1739, 1670, 1608, 1514, 1383, 1323, 1252, 1172, 1127, 1072, 1030, 770 cm^{-1}. HRMS (ESI+) calculated for $C_{34}H_{28}F_3N_3NaO_4$ *m/z* (M+Na) 622.1930, Obsd. 622.1927.

General Procedure D: deprotection with isomerization of 19 to 20. *N-(4-Benzyl-1-methyl-5-phenyl-1H-imidazol-2(3H)-ylidene)benzamide* (**20a**). In a 5 mL test tube containing a magnetic stir bar were added **19a** (84 mg, 0.17 mmol), Pd/C (10% w/w, 9 mg), and distilled MeOH (2 mL) under a stream of N_2. The reaction tube was then sealed in a pressure vessel and purged with H_2 three times. The pressure vessel was then charged with H_2 at 60 psi, and the reaction was stirred at room temperature for 24 h. After releasing the H_2 from the pressure vessel, the solution was filtered with a non-polar syringe filter followed by addition of 5 mL of hot methanol to wash the filter. The filtrate was concentrated via rotary evaporation under reduced pressure, and the resulting material was purified via flash chromatography (3:2 hexanes/EtOAc) to yield **20a** as a light brown foam (44 mg, 72%). R_f = 0.47 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.28 (d, *J* = 8.5 Hz, 2H), 7.51-7.46 (m, 8H), 7.36-7.26 (m, 2H), 7.18-7.09 (m, 3H), 3.80 (s, 2H), 3.50 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 137.9, 137.2, 132.8, 132.6, 130.6, 130.2, 129.7, 129.4, 129.2, 128.9, 128.6, 128.5, 127, 34.6, 31 ppm. IR (thin film) 1695, 1653, 1601, 1560, 1494, 1472, 1452, 1379, 1314, 1269, 1025, 765, 742, 700, 658 cm^{-1}. HRMS (ESI+) calculated for $C_{24}H_{22}N_3O$ *m/z* (M+H) 368.1763, Obsd. 368.1768.

N-(4-Benzyl-5-(4-methoxyphenyl)-1-methyl-1H-imidazol-2(3H)-ylidene)benzamide (**20b**). Prepared according to general procedure D using **19b**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **20b** as a light brown foam (9.7 mg, 84%). R_f = 0.47 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (d, *J* = 7.0 Hz, 2H), 7.45-7.40 (m, 3H), 7.32-7.27 (m, 4H), 7.22 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J*

= 9.0 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 2H), 3.49 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.5, 138.7, 131.9, 130.8, 129.2, 128.9, 128.4, 128.1, 127.2, 124.5, 120.0, 114.8, 55.7, 32.4, 31.0 ppm. IR (thin film) 3061, 2933, 1675, 1636, 1566, 1541, 1494, 1464, 1453, 199, 1350, 1288, 1246, 1174, 1108, 1025, 1004, 906, 832, 718, 709, 645, 593 cm^{-1}. HRMS (ESI+) calculated for $C_{25}H_{23}N_3NaO_2$ *m/z* (M+Na) 420.1688, Obsd. 420.1698.

N-(4-Benzyl-1-methyl-5-phenyl-1,3-dihydro-2H-imidazol-2-ylidene)-4-methoxybenzamide (**20c**). Prepared according to general procedure D using **19c**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **20c** as a light brown foam (46 mg, 62%). R_f = 0.29 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.30 (d, *J* = 9.0 Hz, 2H), 7.48-7.44 (m, 3H), 7.31-7.27 (m, 2H), 7.10-7.02 (m, 3H), 7.00-6.95 (m, 4H), 3.85 (s, 3H), 3.60 (s, 2H), 3.48 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.3 137.8, 131.4, 130.5, 129.7, 129.3, 128.9, 128.4, 127.3, 126.9, 113.9, 55.7, 32.9, 30.8 ppm. IR (thin film) 2858, 1678, 1603, 1573, 1514, 1494, 1453, 1401, 1348, 1311, 1176, 1027, 846, 766 cm^{-1}. HRMS (ESI+) calculated for $C_{25}H_{23}N_3NaO_2$ *m/z* (M+Na) 420.1688, Obsd. 420.1688.

N-(4-Benzyl-1-methyl-5-phenyl-1,3-dihydro-2H-imidazol-2-ylidene)-3-(trifluoromethyl)benzamide (**20d**). Prepared according to general procedure D using **19d**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **20d** a light brown foam (123 mg, 87%). R_f = 0.76 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.55 (s, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.53-7.48 (m, 4H), 7.40-7.37 (m, 2H), 7.32-7.29 (m, 2H), 7.26-7.24 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 2H), 3.54 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 150.8, 139.5, 137.3, 132.1, 120.5, 129.5, 129.3, 129.2, 128.5, 128.4, 127.7, 127.3, 127.2 (q, J_{CF} = 3.8 Hz), 125.9 (q, J_{CF} = 3.8 Hz), 124.8, 120.6, 95.0, 30.8, 30.3 ppm. IR (thin film) 3062, 1598, 1568, 1471, 1362, 1315, 1276, 1216, 1162, 1117, 1084, 1067, 907, 795, 763, 726 cm^{-1}. HRMS (ESI+) calculated for $C_{25}H_{21}N_3OF_3$ *m/z* (M+H) 436.1637, Obsd. 436.1639.

N-(4-Benzyl-1-methyl-5-phenyl-1H-imidazol-2(3H)-ylidene)isobutyramide (**20e**). Prepared according to general procedure D using **19e**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **20e** as a light brown foam (24 mg, 74%). R_f = 0.50 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.39 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24-7.20 (m, 3H), 7.13 (d, *J* = 8.0 Hz 2H), 3.83 (s, 2H), 3.31 (s, 3H), 2.49 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.3, 130.2, 129.7, 129.0, 128.6, 128.5, 128.4, 126.2, 35.7, 32.9, 31.8, 19.8 ppm. IR (thin film) 3028, 2968, 2873, 1653, 1602, 1540, 1506, 1494, 1466, 1456,

1437, 1399, 1383, 1312, 1221, 1190, 1156, 1098, 1014, 950, 910, 867, 725, 697 cm^{-1}. HRMS (ESI+) calculated for $C_{21}H_{23}N_3O$ *m/z* (M+Na) 356.1739, Obsd. 356.1743 (M+H).

N-(4-Benzyl-1-methyl-5-phenyl-1H-imidazol-2(3H)-ylidene)-2-methylbutanamide (**20f**). Prepared according to general procedure D using **19f**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give **20f** as a light brown foam (33 mg, 80%). R_f = 0.44 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.39 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.24-7.20 (m, 3H), 7.05 (d, *J* = 8.0 Hz 2H), 3.77 (s, 2H), 3.30 (s, 3H), 2.43 (m, 1H), 1.69 (m, 1H), 1.41 (m, 1H), 1.10 (d, 7.0 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.9, 130.3, 129.1, 128.8, 128.6, 128.5, 42.8, 32.3, 27.2, 17.7, 11.1 ppm. IR (thin film) 2835, 1609, 1583, 1508, 1488, 1442, 1419, 1301, 1244, 1169, 1126, 1107, 1069, 1033, 994, 962, 917, 850, 807, 778, 754, 690, 584 cm^{-1}. HRMS (ESI+) calculated for $C_{22}H_{25}N_3O$ *m/z* (M+H) 348.2076, Obsd. 348.2082 (M+H).

N-(4-Benzyl-1-methyl-5-phenyl-1H-imidazol-2(3H)-ylidene)-2-fluorobenzamide (**20g**). Prepared according to general procedure D using **19g**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give a light brown (7.1 mg, 89%). R_f = 0.82 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.49 (m, 3H), 7.38 (m, 3H), 7.28 (m, 2H), 7.21 (m, 2H), 7.16 (m, 2H), 7.10 (m, 1H), 3.85 (s, 2H), 3.49 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.7 (d, J_{CF} = 252.4 Hz), 137.8, 132.4 (d, J_{CF} = 8.1 Hz), 131.9, 130.5, 129.4, 129.3, 129.1, 128.5, 128.0, 127.1, 125.6, 123.9 (d, J_{CF} = 3.6 Hz), 116.7 (d, J_{CF} = 23.2 Hz), 113.3, 31.2, 30.8 ppm. IR (thin film) 3029, 1683, 1560, 1494, 1452, 1350, 1286, 1259, 1222, 1135, 1127, 1075, 1054, 1030, 1014, 967, 817, 755, 725, 696, 643 cm^{-1}. HRMS (ESI+) calculated for $C_{24}H_{21}FN_3O$ *m/z* (M+H) 386.1669, Obsd. 386.1677.

N-(4-Benzyl-5-(4-methoxyphenyl)-1-methyl-1H-imidazol-2(3H)-ylidene)-2-fluorobenzamide (**20h**). Prepared according to general procedure D using **19h**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give a light brown foam (13 mg, 81%). R_f = 0.41 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (t, *J* = 8.0 Hz, 2H), 7.34 (m, 1H), 7.32-7.27 (m, 4H), 7.21 (t, *J* = 8.5 Hz, 1H), 7.19-7.16 (m, 3H), 7.08 (t, *J* = 9.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 2H), 3.44 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.8, 162.5 (d, J_{CF} = 253.4 Hz), 160.2, 148.7, 137.8, 131.8, 131.7 (d, J_{CF} = 1.9 Hz), 131.6, 128.8, 128.2, 126.8, 126.4, 124.8, 123.6 (d, J_{CF} = 3.8 Hz), 119.9, 116.5 (d, J_{CF} = 22.9 Hz), 114.5, 55.4, 31.0, 30.1 ppm. IR (thin film) 2929, 2360, 2340, 1684, 1569, 1511, 1494, 1455, 1401, 1339, 1290, 1248, 1176, 1032, 834, 815, 757, 731, 696, 667 cm^{-1}. HRMS (ESI+) calculated for $C_{25}H_{22}FN_3NaO_2$ *m/z* (M+Na) 438.1594, Obsd. 438.1601.

N-(4-Benzyl-5-(4-methoxyphenyl)-1-methyl-1H-imidazol-2(3H)-ylidene)-3- (trifluoromethyl)benzamide (**20i**). Prepared according to general procedure D using **19i**, with purification using silica gel eluting with 3:2 hexanes/EtOAc to give a light brown foam (99 mg, 53% yield). R_f = 0.76 (3:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.54 (s, 1H), 8.42 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.32-7.23 (m, 5H), 7.15 (d, *J* = 6.9 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 2H), 3.50 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 160.3, 150.5, 139.4, 137.3, 131.9, 131.6, 130.1 (q, J_{CF} = 32.2 Hz), 129.0, 128.2, 128.1, 127.0, 126.9 (q, J_{CF} = 3.8 Hz), 125.7 (q, J_{CF} = 3.8 Hz), 124.3 (q, J_{CF} = 270.4 Hz), 120.0, 119.4, 114.6, 55.4, 30.5, 29.9 ppm. IR (thin film) 1569, 1512, 1466, 1363, 1317, 1278, 1249, 1217, 1165, 1121, 1069, 1034, 906, 834, 768, 725 cm^{-1}. HRMS (ESI+) calculated for $C_{26}H_{22}F_3N_3NaO_2$ *m/z* (M+Na) 488.1562, Obsd. 488.1559.

Associated Content

Supporting Information. X-ray crystallography data for compounds **18b** and **20h**. ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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