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Synthesis of Naamidine A and Selective Access to N^2-Acyl-2-aminoimidazole Analogues

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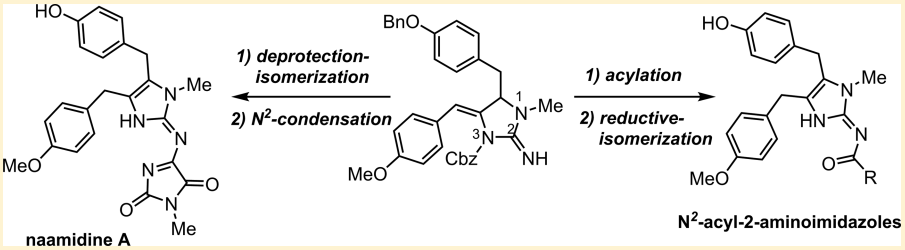
Supporting Information



ABSTRACT: A short and scalable 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 monoprotected 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, *Cryptococcus neoformas* (MIC = 6.25 μg/mL). *N*,*N*-Dimethylnaamine D (**2**) was active against an antimicrobial panel consisting of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans*.[3] Kealiinine B (**3**) was recently reported to show antiproliferative activity (IC_{50} ~ 10 μM) against the breast cancer cell line T47D, while other kealiinine analogues have displayed modest activity against MCF-7 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 co-workers 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

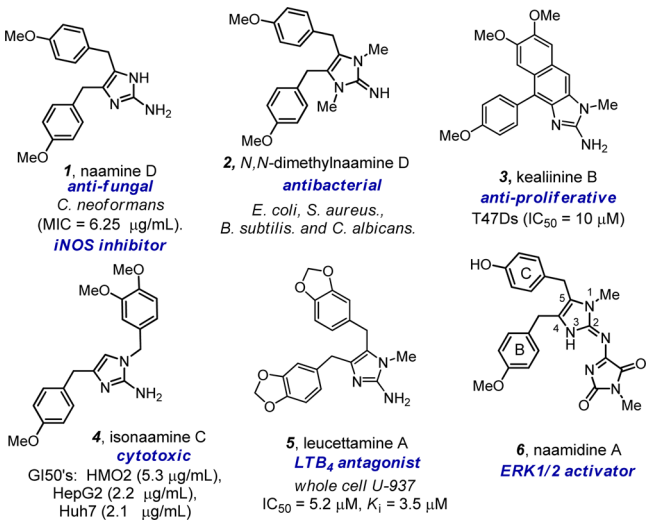


Figure 1. Representative *Leucetta* alkaloids.

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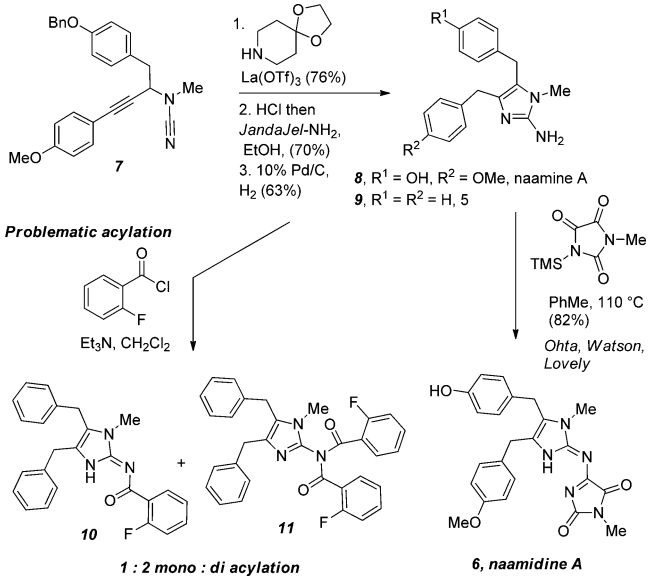
ERK1/2.[9] This sustained increase in MAPK activity has been shown to be a result of naamidine A-induced expression of p21, leading to inhibition of cyclin-dependent kinase activity and activation of caspases 3, 8, and 9.[10] Since the EGFR signaling pathway is overexpressed in many human tumors, the 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.

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

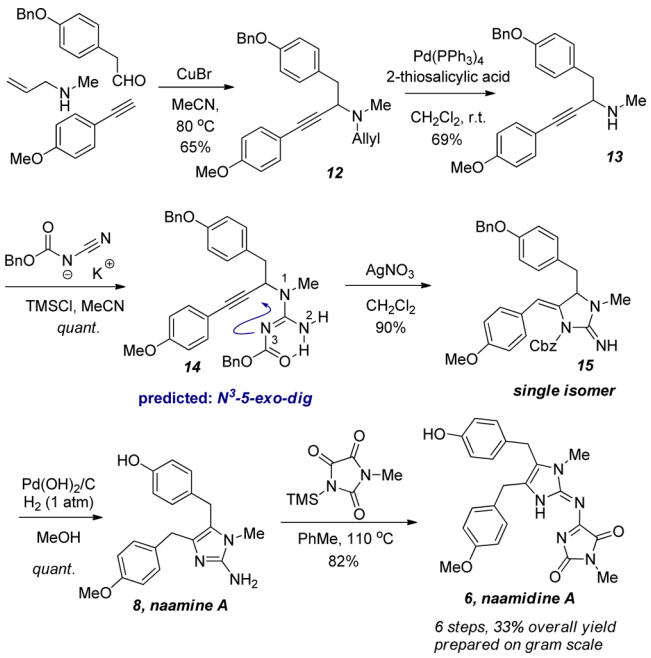
Scheme 1. First Generation Synthesis of Naamidine A and Analogues



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*-di-Boc 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, we obtained an unfavorable 1:2 mixture of monoacylated and diacylated N^2 products (**10**/**11**). A recent report by Jiang and co-workers identified the same problem, requiring forcing conditions or extra protecting group manipulations to obtain the monoacyl-2-aminoimidazoles in low to moderate yields, reinforcing the need for a high-yielding and selective strategy to access monosubstituted N^2-acyl-2-aminoimidazoles.[18]

These shortcomings necessitated a revised synthesis of **6** that would allow for (a) reproducible and scalable 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

Scheme 2. Synthesis of Naamidine A (6)



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 monoacylguanidine **14** using the activated Cbz-cyanamide potassium salt guanylation conditions previously developed in our laboratory.[20,21] 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 monoacylguandines 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 nonbonding 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 C^5, *p*-MeOPh-substituted propargylguanidines cyclize with only modest 5-*exo*-dig selectivity of ~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). 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 six steps and 33% overall yield.

With the ability to control the regioselectivity of the monoacylpropargylguanidine cyclization, we returned our attention

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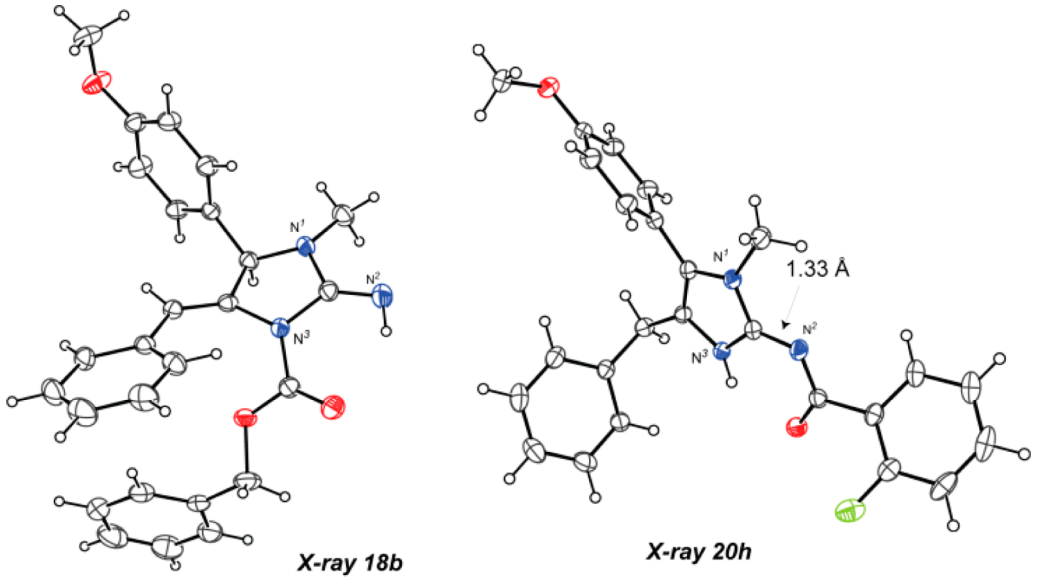
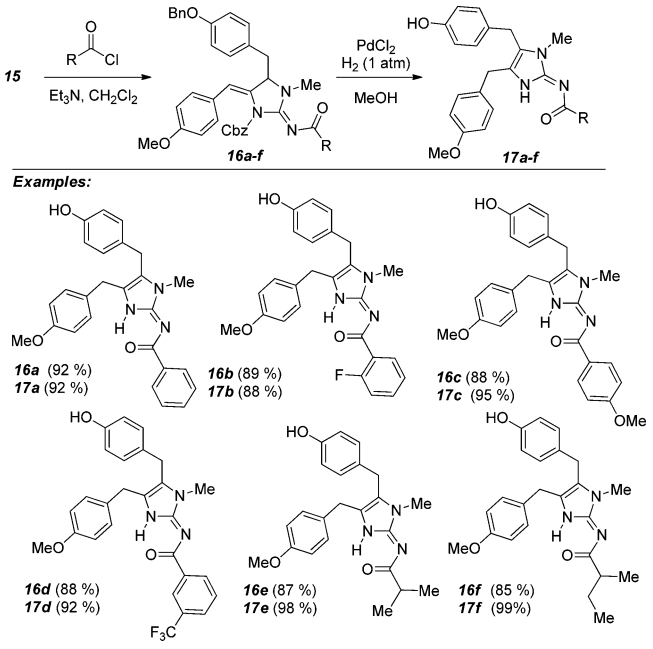
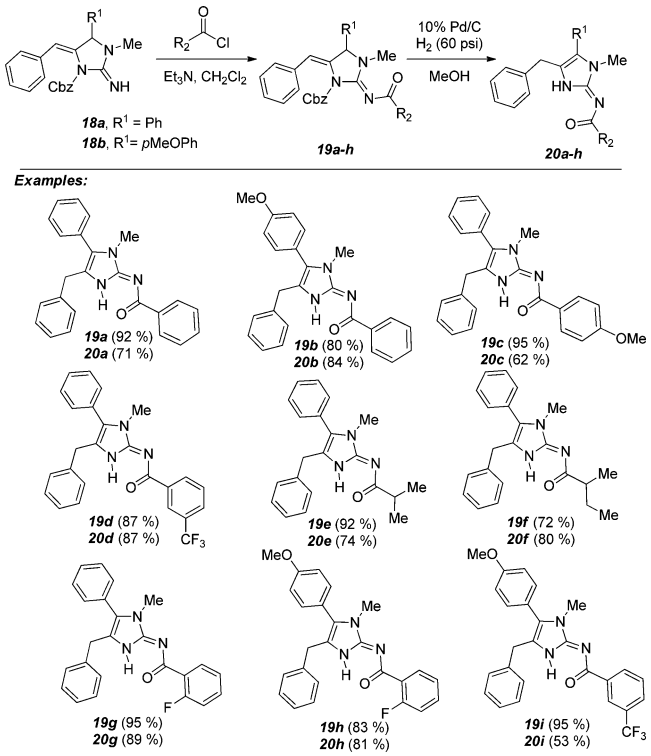


Figure 2. X-ray structures of **18b** and **20h**.

Scheme 3. Generation of N^2-Acyl Naamidine A Analogues



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



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 monoacylation products. Indeed, both electron-rich and electron-poor aryl chlorides gave the N^2-monoacylguanidines **16a–d** in excellent yields (Scheme 3). Alkanoyl chlorides 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 nonsupported Pd(II) catalyst was successful, providing the fully deprotected targets **17a–f** in excellent overall yields.

To complement our focused library, the same methodology was involved in the construction of C^5-phenyl and C^4-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

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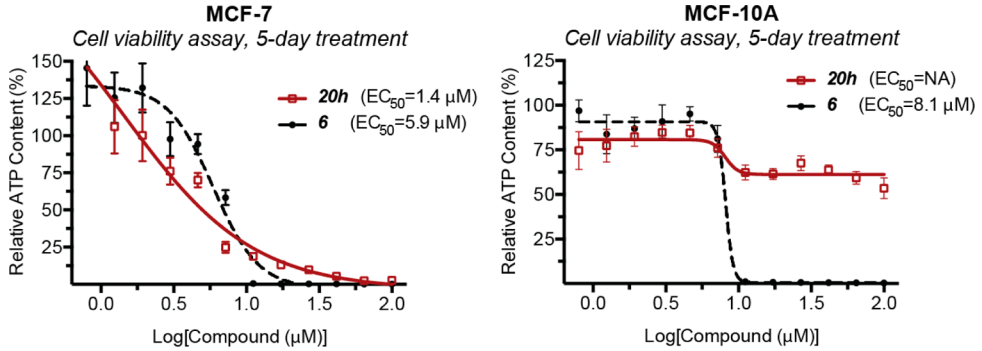

Figure 3. Antiproliferative effects of naamidine A and **20h**.

confirmed by X-ray crystallography of product **20h**. This structure shows that even in the now aromatized aminoimidazole nucleus, the exocyclic N^2-imino tautomer is preferred with H bonding between N^3 and the N^2-acyl group with a C^2-N^3 imino bond length of 1.33 Å.

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.

Despite the reported selectivity of naamidine A (**6**) to inhibit proliferation in EGFR transfected NIH3T3 cells, no selectivity was observed in the antiproliferative 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.

■ CONCLUSION

In summary, we have shown that monoacylguanidines preferentially adopt the *N*-acylimino tautomer, and that this can be reliably used to predict reactivity. Thus, the hydroamination of monoacylpropargylguanidines 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 antiproliferative 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 on 500 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 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 were 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 4 Å molecular sieves. The flask was heated at 80 °C for 24 h 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); ^1H 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+) calcd for $C_{28}H_{30}NO_2$ *m*/*z* (M + H) 412.2277, found 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 were 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 redissolved 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

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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+) calcd for $C_{25}H_{26}NO_2$ m/z (M + H) 372.1964, found 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 were added TMSCl (1.65 mL, 13.0 mmol), benzyloxycarbonylcyanamide potassium salt (2.58 g, 12.0 mmol) and 50 mL of 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 (br s, 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+) calcd for $C_{34}H_{34}N_3O_4$ m/z (M + H) 548.2549, found 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 were 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+) calcd for $C_{34}H_{34}N_3O_4$ m/z (M + H) 548.2549, found 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 were 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 °C) 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+) calcd for $C_{19}H_{22}N_3O_2$ m/z (M + H) 324.1712, found 324.1714.

*Preparation of Naamidine A (**6**).* To a 50 mL round-bottom, two-neck flask equipped with a stir bar and reflux condenser were 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 h. Without exposing the 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, two-neck flask equipped with a stir bar and reflux condenser containing **8** (1.03 g, 3.2 mmol, mp = 188 °C) under a N_2 atmosphere. The reaction mixture was allowed to reflux for 16 h. The reaction was allowed to cool to room temperature, diluted with EtOAc (10 mL), then transferred to a 100 mL round-bottom flask 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+) calcd for $C_{23}H_{24}N_5O_4$ m/z (M + H) 434.1828, found 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 were 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 h. 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+) calcd for $C_{41}H_{37}N_3O_5Na$ m/z (M + Na) 674.2631, found 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+) calcd for $C_{41}H_{36}N_3O_5FNa$ m/z (M + Na) 692.2537, found 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

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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+) calcd for $C_{42}H_{39}N_3O_6Na$ m/z (M + Na) 704.2737, found 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+) calcd for $C_{42}H_{37}N_3O_5F_3$ m/z (M + H) 720.2685, found 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+) calcd for $C_{38}H_{39}N_3O_5Na$ m/z (M + Na) 640.2787, found 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+) calcd for $C_{39}H_{41}N_3O_5Na$ m/z (M + Na) 654.2944, found 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 were 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 a 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 °C): 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+) calcd for $C_{26}H_{26}N_3O_3$ m/z (M + H) 428.1974, found 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+) calcd for $C_{26}H_{24}N_3O_3FNa$ m/z (M + Na) 468.1699, found 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 °C): 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+) calcd for $C_{27}H_{28}N_3O_4$ m/z (M + H) 458.2080, found 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 °C): 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+) calcd for $C_{27}H_{25}N_3O_3F_3$ m/z (M + H) 496.1848, found 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 °C): 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),

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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+) calcd for $C_{23}H_{28}N_3O_3$ m/z (M + H) 394.2147, found 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 °C): 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+) calcd for $C_{24}H_{30}N_3O_3$ m/z (M + H) 408.2303, found 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+) calcd for $C_{19}H_{19}N$ m/z 262.1590 (M + H), found 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 of 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 redissolved in Et_2O (10 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (50 mL) and brine (50 mL) and 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+) calcd for $C_{16}H_{16}N$ m/z 222.1259 (M + H), found 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 min. 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 with aqueous solutions of saturated $NaHCO_3$ (50 mL) and brine (50 mL) and 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+) calcd for $C_{25}H_{24}N_3O_2$ m/z 398.1869 (M + H), found 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 redissolved in EtOAc (50 mL). The organic layer was washed with aqueous solutions of saturated $NaHCO_3$ (15 mL) and brine (15 mL) and 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+) calcd for $C_{25}H_{24}N_3O_2$ m/z 398.1869 (M + H), found 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+) calcd for $C_{20}H_{21}NO$ m/z 292.1701 (M + H), found 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+) calcd for $C_{17}H_{17}NONa$ m/z 274.1208 (M + Na), found 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,

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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+) calcd for $C_{26}H_{26}N_3O_3$ m/z 428.1974 (M + Na), found 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+) calcd for $C_{26}H_{26}N_3O_3$ m/z 428.1974 (M + Na), found 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+) calcd for $C_{32}H_{27}N_3NaO_3$ m/z (M + Na) 524.1950, found 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+) calcd for $C_{33}H_{29}N_3NaO_4$ m/z (M + Na) 554.2056, found 554.2066.

*Benzyl 5-((Z)-Benzylidene)-2-((4-methoxybenzoyl)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+) calcd for $C_{33}H_{29}N_3NaO_4$ m/z (M + Na) 554.2056, found 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+) calcd for $C_{33}H_{26}F_3N_3NaO_3$ m/z (M + Na) 592.1824, found 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+) calcd for $C_{29}H_{29}N_3NaO_3$ m/z (M + Na) 490.2107, found 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 (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+) calcd for $C_{30}H_{31}N_3NaO_3$ m/z (M + Na) 504.2263, found 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+) calcd for $C_{32}H_{26}FN_3NaO_3$ m/z (M + Na) 542.1856, found 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,

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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+) calcd for $C_{33}H_{28}FN_3NaO_4$ m/z (M + Na) 572.1962, found 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+) calcd for $C_{34}H_{28}F_3N_3NaO_4$ m/z (M + Na) 622.1930, found 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 nonpolar 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+) calcd for $C_{24}H_{22}N_3O$ m/z (M + H) 368.1763, found 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+) calcd for $C_{25}H_{23}N_3NaO_2$ m/z (M + Na) 420.1688, found 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+) calcd for $C_{25}H_{23}N_3NaO_2$ m/z (M + Na) 420.1688, found 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+) calcd for $C_{25}H_{21}N_3OF_3$ m/z (M + H) 436.1637, found 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+) calcd for $C_{21}H_{23}N_3O$ m/z (M + Na) 356.1739, found 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+) calcd for $C_{22}H_{25}N_3O$ m/z (M + H) 348.2076, found 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+) calcd for $C_{24}H_{21}FN_3O$ m/z (M + H) 386.1669, found 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,

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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+) calcd for $C_{25}H_{22}FN_3NaO_2$ m/z (M + Na) 438.1594, found 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+) calcd for $C_{26}H_{22}F_3N_3NaO_2$ m/z (M + Na) 488.1562, found 488.1559.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01703.

X-ray data for **18b** (CIF)
X-ray data for **20h** (CIF)
X-ray crystallography data for compounds **18b** and **20h**.
^{1}H and ^{13}C NMR spectra for all compounds (PDF)
Elemental composition report (PDF)

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Notes

The authors declare no competing financial interest.

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