Solid-Phase Synthesis of 1,5-Disubstituted 2-Aryliminoimidazolidines

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Abstract: The solid-phase synthesis of 1,5-disubstituted 2-aryliminoimidazolidines, starting from resin-bound N-acylated amino acid amides, is described. Exhaustive reduction of resin-bound acylated amino acid amides with borane−THF afforded the corresponding disecondary amines. Further reaction with arylisothiocyanates in the presence of mercuric chloride ($HgCl_2$) yielded the corresponding resin-bound 1,5-disubstituted 2-aryliminoimidazolidines. Cleavage of the product from the resin using HF/anisole (95/5) for 1.5 h at 0 °C gave the desired products in good yield and purity. The preparation of a large combinatorial library of such compounds is also discussed.

Solid-phase organic synthesis is now a well-recognized approach for the rapid preparation of heterocyclic and other low molecular weight compounds for drug discovery.[1] Small heterocyclic pharmacophores, in particular, are used as rigid, highly functionalized molecular scaffolds and are known to have broad biological relevance.[2] This general structural class has received special attention in combinatorial synthesis. In addition, traditional solution-phase approaches for the preparation of heterocycles have transferred well to the solid phase, including those for benzodiazepines,[3] hydantoins,[4] pyrrolidines,[5] and bicyclic guanidines.[6] This strategy has permitted the synthesis of large numbers of heterocycles in a short time frame enabling their use in high-throughput screening.[7]

Imidazole-containing moieties are known to have useful therapeutic implications and are found in many biologically active compounds. Such compounds, based on a conformationally constrained scaffold, are common in nature with imidazole-containing natural products having been isolated encompassing a wide range of biological activities.[8] Similarly, the hydrogen-bonding acceptor and donor abilities of the guanidine group play important roles in supramolecule formation and in the active sites of various proteins, as well as in drug design in medicinal chemistry.[9] As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[10] we report here an efficient strategy for the synthesis of 1,5-disubstituted 2-aryliminoimidazolidines that contain guanidine and imidazolidine functionalities and encompass three positions of diversity.

The synthetic strategy followed is shown in Scheme 1. The reaction was carried out on the solid-phase using the "tea-bag" methodology.[1b] Starting from *p*-methylbenzhydrylamine (MBHA) resin, a Boc-L-amino acid was coupled to the resin. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resulting amine salt was neutralized, and the resulting primary amine **2** was acylated with a carboxylic acid to provide the resin-bound diamide **3**. The resin-bound diamide was treated with borane in THF, resulting in exhaustive reduction of the amides, to yield the corresponding resin-bound diamine **4**.

Several methods exist for the preparation of guanidines in solution and on the solid phase.[11] Classically, guanidines have been prepared by reacting ammonia or an amine with S-alkylthiouronium salts.[11b] Our initial efforts involved treating resin-bound diamine **4** with thiocarbonyldiimidazole in DCM overnight to afford resin-bound cyclic thiourea **5**. Formation of resin-bound S-methylthiouronium salt **6** was achieved by treatment of the resin-bound cyclic thiourea **5** with methyl iodide in DMF overnight.[12] However, all of our efforts directed toward the substitution of resin-bound S-methylthiouronium salt **6** with amines yielded poor results (Method A). The purity of product **9** in each case was low (less than 20%). Thus, the challenge was to find sufficiently activated thiouronium salts.

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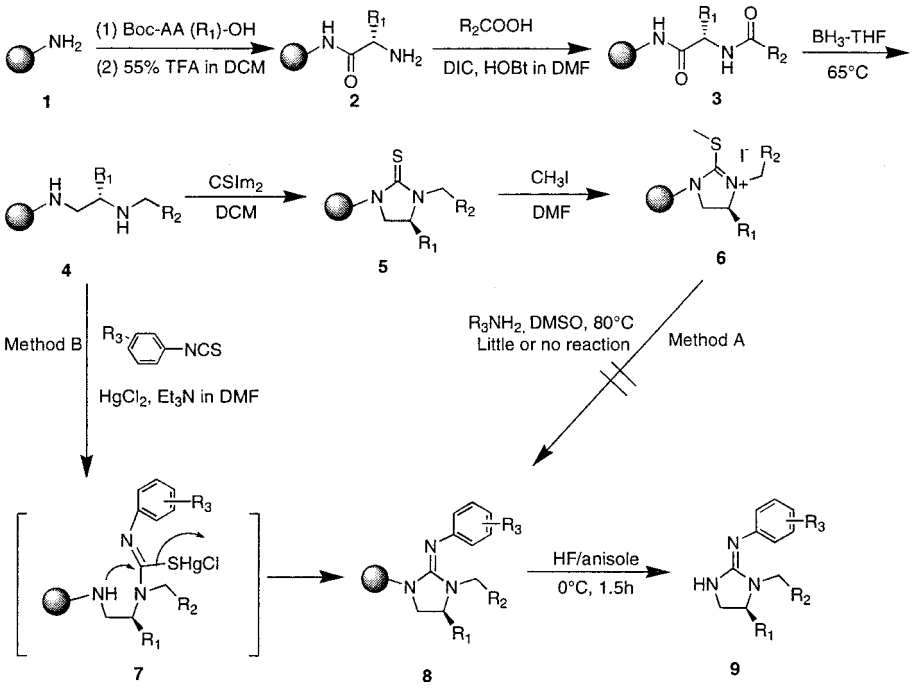
Scheme 1. Solid-Phase Synthesis of 1,5-Disubstituted 2-Aryliminoimidazolidines



Inorganic thiophiles such as mercuric chloride and mercuric oxide have been used to eliminate hydrogen sulfide from thioureas to form the intermediate carbodiimides, which then react with amines to form guanidines.[13] Ko et al. reported that $HgCl_2$-promoted guanylation is effective only with thioureas containing N-conjugated substituents. Moreover, successful thiourea substrates require one hydrogen to be present on each of the nitrogens. Trisubstituted thioureas failed to react with amines to form guanidine products under $HgCl_2$-promoted conditions.[14] However, recently it was reported that $HgCl_2$-promoted trisubstituted thiourea could be displaced by azide anion to generate an intermediate guanyl azide.[15] On the basis of previous studies, our efforts focused on the synthetic strategy of reacting a trisubstituted thiourea with an amine under $HgCl_2$-promoted conditions. We reasoned that the two different secondary amines of the resin-bound diamines **4** would react with an arylisothiocyanate to form a resin-bound thiourea, which would be immediately activated by $HgCl_2$ to form intermediate **7**. The remaining secondary amine would then displace the mercury(II)-activated sulfur via intramolecular cyclization to yield the resin-bound 1,5-disubstituted-2-iminoimidazolidines **8** (Method B). To decrease the amount of undesired dithiourea generated, we anticipated that the resin-bound diamine **4** could be reacted with arylisothiocyanates in the presence of mercuric chloride in a one-pot reaction to form resin-bound 1,5-disubstituted 2-aryliminoimidazolidines. Resin-bound diamine **4** was treated with arylisothiocyanates, $HgCl_2$, and triethylamine in DMF in a one-pot reaction at room temperature overnight to yield resin-bound 1,5-disubstituted-2-iminoimidazolidine **8**. We found resin-bound product **8** to be much more labile to acidolytic cleavage than the resin-bound diamine **4**.[6] The desired product was readily obtained following cleavage from the resin using HF/anisole (95/5) for 1.5 h at 0 °C in good yield and purity (Table 1). The product was characterized by electrospray LC-MS and ^{1}H and ^{13}C NMR. It is expected that the iminoimidazolidine ring, due to its basic character,[16] would be protonated during purification (0.05% trifluoroacetic acid). The appearance of downfield proton signals at δ 10.0−11.5 ppm in ^{1}H NMR spectra indicates that the compounds are present in the monoprotonated form. The possibility of racemization was determined as described earlier.[6,17] Negligible amounts of racemization were observed either during exhaustive reduction of amide bonds or during $HgCl_2$-promoted cyclization. A range of 2-aryliminoimidazolidines were synthesized and are listed in Table 1. The preparation of a mixture-based scanning combinatorial library,[7] containing 16 000 (40 R_1 × 20 R_2 × 20 R_3) 1,5-disubstituted 2-aryliminoimidazolidines, and its screening in different assays for the identification of highly active compounds will be reported elsewhere.

In summary, we have successfully synthesized 1,5-disubstituted 2-aryliminoimidazolidines from resin-bound N-acylated amino acid amides. This approach is a continuation of our efforts directed toward the synthesis of low molecular weight acyclic and heterocyclic compounds from amino acids and short peptides.

Experimental Section

MBHA resin, 1% divinylbenzene, 100−200 mesh, 1.0 mequiv/g substitution, and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex Intl. (Wood Dale, IL). Boc-amino acid derivatives and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience, Inc. (Philadelphia, PA). Trifluoroacetic acid (TFA) and HF were purchased from Halocarbon (River Edge,

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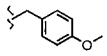
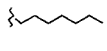
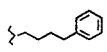
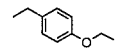
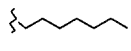
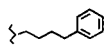
Table 1. Individual 1,5-Disubstituted 2-Aryliminoimidazolidines

entry	R_1	R_2	R_3	yield[a]	purity[b]	MW(calcd.)	MW(found)[c]
9a			4-Cl	91	86.7	355.2	356.2([M + H]$^+$)
9b			4-Cl	89	86.4	423.1	424.4([M + H]$^+$)
9c			4-Cl	82	77.4	313.1	314.3([M + H]$^+$)
9d			4-Cl	88	85.2	419.2	420.4([M + H]$^+$)
9e			4-Cl	86	91	341.2	342.4([M + H]$^+$)
9f			H	87	81	325.2	326.4([M + H]$^+$)
9g			4-Cl	85	71	417.2	418.4([M + H]$^+$)
9h			H	89	65	350.3	351.5([M + H]$^+$)
9i			2-Cl,5-CH_3	86	68	445.2	446.5([M + H]$^+$)
9j			H	86	91	369.2	370.4([M + H]$^+$)
9k			4-Cl	88	67	395.2	396.5([M + H]$^+$)
9l			2, 5-OCH_3	91	88	415.2	416.4([M + H]$^+$)
9m			4-Cl	85	81	427.2	428.5([M + H]$^+$)
9n			H	87	75	335.2	336.4([M + H]$^+$)
9o			4-Cl	86	81	355.2	356.4([M + H]$^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin. [b] Purity was estimated on the basis of the peak area of HPLC analytical traces of the crude products at $\lambda = 214$ nm. [c] Confirmed by mass spectra (ESI).

NJ) and Air Products (San Marcos, CA), respectively. All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman System Gold instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C18 column (0.46 × 25 cm). LC-MS (ESI) was recorded on a Finnigan Mat LCQ mass spectrophotometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3 × 50 mm column. NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C using DMSO as the solvent and TMS as an internal standard. Preparative RP-HPLC was performed on a Waters DeltaPrep preparative HPLC (Millipore) apparatus using a Vydac 218TP1022 C18 column (2.2 × 25 cm).

General Procedure for the Preparation of the Resin-Bound Acylated Amino Acid Amide 3. A polypropylene mesh packet was sealed with 100 mg of *p*-methylbenzhydrylamine (MBHA) resin (1.0 mequiv/g, 100−200 mesh).[18] Reactions were carried out in polypropylene bottles. The resin was washed with dichloromethane (DCM) followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM and washed with DCM. The first Boc-L-amino acid (6 equiv) was coupled using DIC and HOBt (6 equiv each) in anhydrous DMF for 2 h. Following washes with DMF (six times), Boc deprotection was performed using 55% TFA in DCM for 30 min, followed by washes with DCM (two times), 2-propanol (IPA) (two times), and DCM (two times). Following neutralization, the resin was acylated with a carboxylic acid (10 equiv, 0.1 M) in the presence of DIC and HOBt (10 equiv, 0.1 M each) in anhydrous DMF overnight to yield the resin-bound acylated amino acid amide **3**. Completeness of the coupling was verified by the ninhydrin test. The resin was washed with DMF (two times), DCM (two times), 2-propanol (IPA) (two times), and MeOH (two times) and then dried in air overnight.

Exhaustive Reduction of Amide 3 by BH_3−THF. Exhaustive reduction of the N-acylated amino acid amide **3** was carried out in 50 mL glass conical tubes under nitrogen. To each tube was added the resin packet (0.1 mequiv of resin, 100 mg of starting resin, 0.20 mequiv of carbonyl) and boric acid (12 equiv, 163 mg). Trimethyl borate (12 equiv, 0.27 mL) was added followed by addition of borane−THF complex (40 equiv, 1 M, 8 mL). After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h in a heating block followed by decantation of the reaction solution and quenching with MeOH. The resin packet was then washed with DMF and methanol (MeOH) (four times). The resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[6] Following decantation of the piperidine−borane solution, the resin packet was washed with DMF (four times), DCM (four times), and MeOH (two times) and dried in air overnight.

General Procedure for the Preparation of 1,5-Disubstituted 2-Aryliminoimidazolidines 9. The resin-bound diamine **4** was reacted with arylisothiocyanate (5 equiv, 0.1 M) in the presence of $HgCl_2$ (5 equiv, 0.1 M) and Et_3N (5 equiv, 0.1 M) in anhydrous DMF at room temperature overnight to afford the corresponding resin-bound guanidines **8**. Following washes with DMF (three times), MeOH (three times), and DCM (three times), the resin was cleaved by anhydrous HF in the presence of anisole at 0 °C for 1.5 h.[19] The product was extracted with 95% acetic acid in H_2O and lyophilized. Following purification by RP-HPLC, the identity of the products **9** were confirmed by LC-MS, ^{1}H NMR, and ^{13}C NMR.

4-Chloro-*N*-[(2*Z*,5*S*)-5-[(1*S*)-1-methylpropyl]-1-(2-phenylethyl)imidazolidin-2-ylidene]aniline (9a). MS (ESI) *m/z*: 356.2 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85−0.91 (m, 6H), 1.13−1.21 (m, 2H), 1.75 (m, 1H), 2.79 (t, $J = 6.2$ Hz, 2H),

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3.17−3.22 (m, 1H), 3.32−3.35 (m, 1H), 3.41 (t, J = 10 Hz, 1H), 3.66−3.70 (m, 1H), 3.72−3.77 (m, 1H), 7.04−7.10 (dd, J = 8.4, 16.7 Hz, 14H), 7.23−7.29 (m, 5H), 8.50 (brs, 1H), 11.08 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.9, 12.2, 25.4, 33.5, 35.4, 41.8, 45.4, 63.7, 125.7, 127.5, 128.8, 129.2, 130.0, 132.8, 134.3, 137.2, 157.4.

4-Chloro-*N*-[(2*E*,5*S*)-5-(4-chlorobenzyl)-1-(2-phenylethyl)imidazolidin-2-ylidene]aniline (9b). MS (ESI) m/z: 424.4 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70−2.78 (m, 3H), 2.92−2.96 (dd, J = 5.5, 8.2 Hz, 1H), 3.07−3.13 (m, 1H), 3.28−3.31 (dd, J = 5, 5.4 Hz, 1H), 3.39 (t, J = 9.8 Hz, 1H), 3.63−3.68 (m, 1H), 3.73−3.78 (m, 1H), 7.01−7.07 (m, 6H), 7.24−7.31 (m, 7H), 8.70 (brs, 1H), 11.48 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.9, 38.6, 46.2, 46.3, 61.5, 125.5, 127.6, 128.8, 129.3, 129.5, 130.1, 130.6, 132.9, 133.6, 133.9, 134.2, 137.2, 157.3.

4-Chloro-*N*-[(2*E*,5*S*)-5-methyl-1-(2-phenylethyl)imidazolidin-2-ylidene]aniline (9c). MS (ESI) m/z: 314.3 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (d, J = 6.2 Hz, 3H), 2.74−2.80 (m, 2H), 3.18−3.21 (dd, J = 3.2, 6.8 Hz, 1H), 3.24−3.29 (m, 1H), 3.62−3.67 (m, 2H), 3.80−3.85 (m, 1H), 7.05−7.09 (m, 4H), 7.22−7.32 (m, 5H), 8.81 (brs, 1H), 11.38 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8, 33.7, 45.4, 48.4, 56.5, 125.7, 127.4, 128.9, 129.2, 130.0, 132.8, 134.4, 137.1, 157.0.

***N*-{(2*E*,5*S*)-5-Benzyl-1-[2-(4-methoxyphenyl)ethyl]imidazolidin-2-ylidene}-4-chloroaniline (9d).** MS (ESI) m/z: 420.4 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.69 (t, J = 6.4 Hz, 2H), 2.78−2.82 (dd, J = 6.0, 7.7 Hz, 1H), 2.97−3.01 (dd, J = 5.6, 8.0 Hz, 1H), 3.03−3.07 (dd, J = 7.6, 7.6 Hz, 1H), 3.36−3.39 (dd, J = 5, 5.4 Hz, 1H), 3.45 (t, J = 9.8 Hz, 1H), 3.50−3.54 (m, 1H), 3.76 (s, 3H), 3.82−3.88 (s, 1H), 6.56−7.12 (m, 7H), 7.19−7.36 (m, 6H), 8.95 (brs, 1H), 11.40 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.9, 36.5, 46.2, 46.5, 55.4, 61.8, 120.1, 125.4, 127.9, 129.3, 129.4, 130.1, 130.3, 132.8, 134.3, 135.1, 138.6, 157.4, 160.2.

4-Chloro-*N*-[(2*E*,5*S*)-5-isopropyl-1-(2-phenylethyl)imidazolidin-2-ylidene]aniline (9e). MS (ESI) m/z: 342.4 (M + H$^+$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (d, J = 6.5 Hz, 3H), δ 0.92 (d, J = 6.5 Hz, 3H), 1.98−2.03 (m, 1H), 2.72−2.75 (t, J = 7.2 Hz, 2H), 3.14−3.18 (m, 1H), 3.36−3.44 (m, 2H), 3.50−3.56 (m, 2H), 7.02−7.09 (m, 4H), 7.23−7.35 (m, 5H), 9.50 (brs, 1H), 11.78 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8, 18.1, 30.0, 33.8, 42.5, 47.2, 65.9, 125.4, 127.6, 128.8, 129.2, 130.1, 132.6, 134.6, 136.9, 157.9.

***N*-(4-Chlorophenyl)-*N*-{(2*E*,5*S*)-1-[2-(4-fluorophenyl)ethyl]-5-isopropylimidazolidin-2-ylidene}amine (9f).** MS (ESI) m/z: 326.4 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 0.82 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 2.20−2.23 (m, 1H), 2.91−3.02 (m, 2H), 3.32−3.35 (m, 1H), 3.46−3.54 (m, 2H), 3.98−4.02 (m, 1H), 4.09−4.13 (m, 1H), 7.02−7.45 (m, 9H), 8.25 (brs, 1H), 10.14 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 14.1, 17.4, 27.1, 31.8, 41.2, 42.7, 61.9, 124.5, 125.2, 126.9, 129.6, 130.2, 130.3, 135.5, 140.9, 156.2.

***N*-[(2*E*,5*S*)-5-Benzyl-1-(3-phenylbutyl)imidazolidin-2-ylidene]-4-chloroaniline (9g).** MS (ESI) m/z: 418.4 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 1.20 (d, J = 6.5 Hz, 3H), 1.91−2.02 (m, 2H), 2.75−2.89 (m, 2H), 3.08−3.10 (m, 1H), 3.20−3.25 (m, 1H), 3.31−3.37 (m, 1H), 3.46 (t, J = 10, 1H), 3.56−3.64 (m, 1H), 4.23−4.32 (m, 1H), 7.20−7.49 (m, 14H), 8.17 (brs, 1H), 10.14 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 24.3, 36.0, 38.9, 41.2, 42.9, 47.3, 60.5, 128.2, 128.4, 128.7, 130.5, 131.3, 131.6, 133.2, 133.5, 136.1, 136.6, 137.8, 148.2, 157.6.

***N*-[(2*E*,5*S*)-1-Heptyl-5-(pyridin-3-ylmethyl)imidazolidin-2-ylidene]aniline (9h).** MS (ESI) m/z: 351.5 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 0.86 (t, J = 7.5 Hz, 3H), 1.28−1.31 (m, 8H), 1.60−1.69 (m, 2H), 3.02−3.06 (dd, J = 6.5, 7.5 Hz, 1H), 3.19−3.23 (dd, J = 4.0, 10.0 Hz, 1H), 3.30−3.33 (m, 1H), 3.37−3.43 (m, 1H), 3.59 (t, J = 10.0 Hz, 1H), 3.68−3.74 (m, 1H), 4.43−4.46 (m, 1H), 7.17−7.18 (d, J = 7.5 Hz, 2H), 7.31−7.34 (t, J = 7.5 Hz, 1H), 7.43−7.46 (t, J = 7.5 Hz, 2H), 7.67−7.70 (m, 1H), 8.11−8.15 (m, 2H), 8.67−8.68 (m, 1H), 8.74 (brs, 1H), 10.25 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 13.9, 22.0, 25.9, 26.8, 28.3, 31.2, 33.8, 42.3, 45.3, 58.2, 124.6, 125.0, 127.0, 133.6, 135.5, 141.3, 144.9, 146.9, 156.0.

2-Chloro-6-methyl-*N*-[(2*E*,5*S*)-1-(4-phenylbutyl)-5-(2-phenylethyl)imidazolidin-2-ylidene]aniline (9i). MS (ESI) m/z: 446.5 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 1.54−1.64 (m, 4H), 1.80−1.84 (m, 1H), 1.06−2.09 (m, 1H), 2.13 (s, 3H), 2.54−2.59 (dd, J = 7.0, 8.0 Hz, 2H), 2.62 (t, J = 6.7 Hz, 2H), 3.30−3.38 (m, 2H), 3.35−3.59 (m, 1H), 3.69 (t, J = 9.8 Hz, 1H), 4.02−4.06 (m, 1H), 7.17−7.41 (m, 13H), 8.06 (brs, 1H), 9.85 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 16.7, 26.1, 27.6, 29.6, 32.7, 34.6, 41.5, 45.8, 58.3, 125.7, 126.0, 127.9, 128.22, 128.25, 128.29, 128.35, 128.45, 130.79, 132.6, 134.5,134.9, 140.9, 141.7, 156.2.

***N*-[(2*E*,5*S*)-5-(2-Chlorobenzyl)-1-(2-ethylbutyl)imidazolidin-2-ylidene]aniline (9j).** MS (ESI) m/z: 370.4 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 0.82−0.86 (m, 6H), 1.20−1.27 (m, 2H), 1.35−1.42 (m, 2H), 1.72−1.73 (m, 1H), 2.92−2.97 (dd, J = 5.6, 8.4 Hz, 1H), 3.13−3.17 (dd, J = 5.1, 9.8 Hz, 1H), 3.30−3.36 (m, 2H), 3.57−3.67 (m, 2H), 4.34−4.37 (m, 1H), 7.25−7.26 (m, 2H), 7.33−7.37 (m, 3H), 7.46−7.50 (m, 4H), 8.35 (brs, 1H), 10.19 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 9.9, 10.5, 22.0, 22.3, 34.7, 37.3, 45.4, 45.5, 57.2, 124.6, 127.0, 127.6, 129.1, 129.6, 129.7, 132.2, 133.3, 133.8, 135.6, 126.1.

***N*-[(2*E*,5*S*)-5-Benzyl-1-(cycloheptylmethyl)imidazolidin-2-ylidene]-4-chloroaniline (9k).** MS (ESI) m/z: 396.5 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 1.12−1.20 (m, 2H), 1.38−1.66 (m, 10H), 1.91−1.92 (m, 1H), 2.88−2.93 (dd, J = 6.4, 7.2 Hz, 1H), 3.04−3.07 (dd, J = 4.5, 9.2 Hz, 1H), 3.18−3.22 (dd, J = 6.0, 8.8 Hz, 1H), 3.29−3.32 (dd, J = 4.8, 4.9 Hz, 1H), 3.50−3.55 (dd, J = 5.1, 9.6 Hz, 1H), 3.62 (t, J = 10 Hz, 1H), 4.33−4.36 (m, 1H), 7.16−7.20 (m, 2H), 7.26−7.35 (m, 5H), 7.48−7.51 (m, 2H), 8.18 (brs, 1H), 10.13 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 25.3, 25.4, 27.8, 27.9, 30.2, 31.1, 36.4, 36.7, 45.3, 47.6, 58.8, 126.5, 126.8, 128.5, 129.4, 129.6, 131.2, 134.5, 136.0, 156.0.

***N*-[(2*E*,5*S*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-2,4-dimethoxyaniline (9l).** MS (ESI) m/z: 416.4 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 2.78−2.82 (dd, J = 5.6, 7.8 Hz, 1H), 2.91−2.98 (m, 2H), 3.05−3.08 (dd, J = 4.5, 9.2 Hz, 1H), 3.17−3.20 (dd, J = 3.6, 6.0 Hz, 1H), 3.36 (t, J = 9.8 Hz, 1H), 3.79 (s, 6H), 3.92−3.96 (m, 2H), 4.16−4.17 (m, 1H), 6.54−6.56 (m, 1H), 6.69−6.70 (m, 1H), 6.89−6.91 (d, J = 8.7 Hz, 1H), 7.24−7.36 (m, 10H), 7.71 (brs, 1H), 9.57 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 32.4, 37.1, 43.2, 45.4, 55.5, 55.9, 59.2, 99.6, 105.1, 115.7, 126.6, 126.7, 128.4, 128.5, 129.1, 129.2, 129.4, 136.0, 138.0, 155.7, 156.8, 160.4.

4-Chloro-*N*-[(2*E*,5*S*)-5-(4-ethoxybenzyl)-1-heptylimidazolidin-2-ylidene]aniline (9m). MS (ESI) m/z: 428.5 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 0.87 (t, J = 7.5 Hz, 3H), 1.27−1.32 (m, 13H), 1.57−1.64 (m, 2H), 2.78−2.82 (dd, J = 6.2, 7.6 Hz, 1H), 2.99−3.02 (dd, J = 4.4, 9.0 Hz, 1H), 3.25−3.34 (m, 2H), 3.54 (t, J = 10.0 Hz, 1H), 3.59−3.64 (m, 1H), 3.97−4.01 (m, 2H), 4.29−4.33 (m, 1H), 6.87−6.89 (d, J = 8.2 Hz, 2H), 7.19−7.24 (m, 4H), 7.51−7.52 (m, 2H), 8.17 (brs, 1H), 10.14 (brs, 1H). ^{13}C NMR (125 MHz, DMSO): δ 13.9, 14.6, 22.0, 25.9, 26.7, 28.3, 31.2, 36.1, 42.2, 45.4, 59.0, 62.9, 114.4, 126.5, 127.5, 129.5, 130.4, 131.2, 134.6, 155.9, 157.4.

***N*-[(2*E*,5*S*)-1-(4-Phenylbutyl)-5-propylimidazolidin-2-ylidene]aniline (9n).** MS (ESI) m/z: 335.2 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 0.91 (t, J = 7.4 Hz, 3H), 1.23−1.29 (m, 2H), 1.45−1.74 (m, 4H), 2.64 (t, J = 7.2 Hz, 2H), 3.22−3.32 (m, 2H), 3.58−3.71 (m, 4H), 3.98−4.03 (m, 1H), 7.18−7.48 (m, 10H), 8.20 (s, 1H), 10.08 (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 13.8, 16.9, 26.1, 27.6, 33.1, 34.6, 41.6, 46.0, 58.2, 124.7, 125.6, 127.0, 128.2, 129.6, 135.6, 141.8, 156.0.

***N*-[(2*E*,5*S*)-5-Benzyl-1-neopentylimidazolidin-2-ylidene]-4-chloroaniline (9o).** MS (ESI) m/z: 356.1 (M + H$^+$). ^{1}H NMR (500 MHz, DMSO): δ 1.02 (s, 9H), 2.91−3.01 (m, 2H), 3.25 (d, J = 15.5 Hz, 1H), 3.33−3.35 (m, 1H), 3.66−3.71 (m, 2H), 4.34−4.38 (m, 1H), 7.10−7.48 (m, 9H), 8.17 (s, 1H), 10.06 (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 27.4, 33.9, 35.9, 44.5, 51.6, 60.9, 126.5, 126.8, 128.5, 129.5, 129.6, 131.3, 134.5, 135.7, 155.9

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Supporting Information Available: Copies of LC-MS, HPLC, and ^{1}H and ^{13}C NMR spectra of compounds **9a**,**c**,**e**,**f**,**j**,**k**,**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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