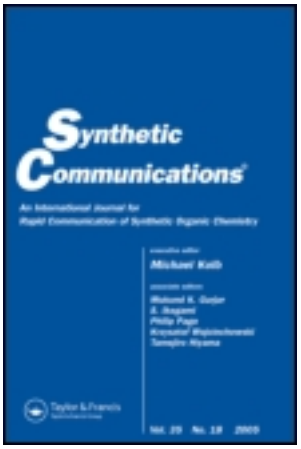

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Synthesis and Synthetic Applications of 1-Aryl-2-alkyl-4,5-dihydro-1H-imidazoles

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SYNTHESIS AND SYNTHETIC APPLICATIONS OF 1-ARYL-2-ALKYL-4,5-DIHYDRO-1*H*-IMIDAZOLES

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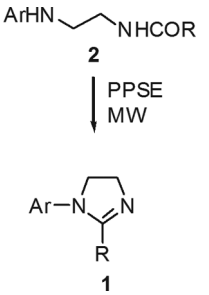
GRAPHICAL ABSTRACT



Abstract *An easy synthesis of 1-aryl-2-alkyl-4,5-dihydro-1*H*-imidazoles* ***1*** *by cyclocondensation of* N*-acyl-*N′*-arylethylenediamines* ***2*** *is described. Such precursors were synthesized by aminolysis of the corresponding* N*-(2-bromoethyl)amides* ***3****. Cyclizations were performed using trimethylsilyl polyphosphate as a mild dehydrating agent, under microwave irradiation. Chemical properties of 1-aryl-2-alkyl-4,5-dihydro-1*H*-imidazoles, typical of the amidine system, were studied. Reduction of dihydroimidazoles with sodium cyanoborohydride leads regiospecifically to* N*-alkyl-*N′*-arylethylenediamines* ***4****, and nucleophilic attack to methyl iodide leads to the corresponding 1-aryl-2-alkyl-3-methyl-4,5-dihydro-1*H*-imidazolium salts* ***5****.*

Keywords Alkylation; amidines; cyclization; 4,5-dihydro-1*H*-imidazoles; heterocycles; reductions

INTRODUCTION

4,5-Dihydro-1*H*-imidazoles **1** (2-imidazolines) are compounds of interest because of their interaction with specific imidazoline receptors, and this behavior is reflected in a multiplicity of biological functions.[1] Thus, they have been studied as antihypertensive,[2] hypoglycemic,[3] anti-inflammatory,[4] antidepressive,[5] anticancer,[6] antimicrobial,[7] antihypercholesterolemic,[8] and anticoagulant[9] agents. From a chemical point of view, the synthesis and study of such compounds

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is of interest because the compounds are synthetic intermediates,[10] auxiliaries,[11] and catalysts[12] for asymmetric synthesis. The imidazoline nucleus has also been used as a source of carbon units in transfer reactions.[13]

The classical methods for the synthesis of the imidazoline nucleus involve condensation of adequately substituted 1,2-diaminoethane with carboxylic acids[14] or derivatives as esters,[15] orthoesters,[16] and nitriles[17] at high temperatures. Some of these methods have been optimized by using alternative energy sources such as ultrasonic irradiation[18] and microwave irradiation under green synthetic conditions.[19] Besides, 2-imidazolines has been obtained via [3 + 2]-cycloaddition of aziridines with nitriles[20] as well as via multicomponent synthesis.[21] On the other hand, synthesis of imidazolines through condensation of ethylenediamines with aldehydes by means of a dehydrogenating reagent, which promotes oxidation of the N1–C2 bond in the reaction medium, has also been reported.[22]

Compounds with H or alkyl groups in N1 have been extensively studied. Nevertheless, there are few reports on the synthesis of *N*-arylimidazolines. In previous work, we developed a method for the synthesis of 1-aryl and 1,2-diarylimidazolines by ring closure of the corresponding *N*-benzoyl(or formyl)-*N*′-arylethylenediamine.[23,24] In this work, the synthesis of 1-aryl-2-alkyl-4,5-dihydro-1*H*-imidazoles **1**, which involves the ring closure of *N*-acyl-*N*′-arylethylenediamines (**2**) by trimethylsilyl polyphosphate (PPSE), employs microwave irradiation, a valuable technique that accelerates chemical reactions and minimizes thermal decomposition of the products.[25]

Some chemical properties of compounds **1** typical of the amidine system, such as reduction with a nucleophilic agent (sodium cyanoborohydride) and quaternization with methyl iodide, were also studied.

RESULTS AND DISCUSSION

The synthetic route involves the preparation of the corresponding *N*-(2-bromoethyl)amide **3** from the 2-bromoethylamine hydrobromide by Schotten–Baumann acylation with a suitable acylating agent. Reactions of compounds **3** with arylamines lead to the expected *N*-acyl-*N*′-arylethylenediamines **2a–g** (Fig. 1, Table 1) accompanied by the *N,N*-bis-(2-amidoethyl)arylamine.

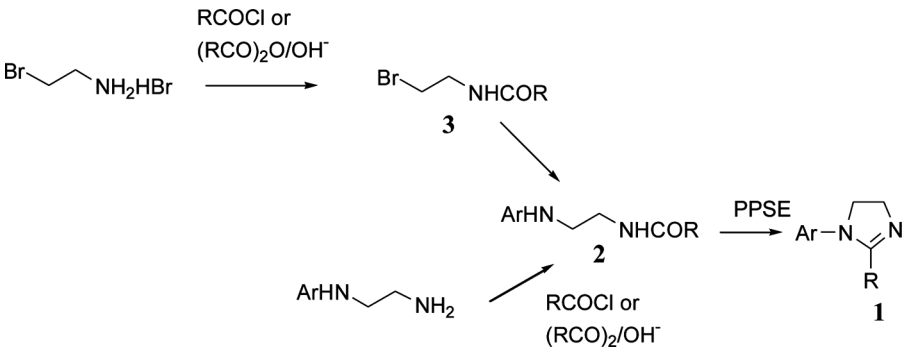


Figure 1. Synthesis of 1-aryl-2-alkyl-1*H*-4,5-dihydroimidazoles **1**.

Table 1. 4,5-Dihydro-1*H*-imidazoles **1** and ethylenediamines **2**

Compounds **1** and **2**	Ar	R
a	4-ClC_6H_4	CH_3
b	4-Cl C_6H_4	C_2H_5
c	4-Cl C_6H_4	*iso*-C_3H_7
d	4-Cl C_6H_4	*tert*-C_4H_9
e	4-Cl C_6H_4	CH_2-C_6H_5
f	4-Cl C_6H_4	CH_2-(2-ClC_6H_4)
g	4-Cl C_6H_4	CH=CHC_6H_5
h	4-$NO_2C_6H_4$	*iso*-C_3H_7
i	4-$NO_2C_6H_4$	*tert*-C_4H_9

To minimize bis derivative formation, the reaction was assayed under different conditions (in toluene, without solvent, and at different temperatures), reaching the best results when heating at 100 °C in absence of solvent. This synthetic route was not applicable to a 4-nitrophenyl derivatives because of the low nucleophilicity of the corresponding arylamine. Thus, compounds **2h** and **i** were synthesized by acylation of *N*-(4-nitrophenyl)ethylenediamine, obtained through nucleophilic displacement of 4-chloronitrobenzene (Fig. 1, Table 1).

Cyclization of compounds **2** was initially carried out with chloroform solution of ethyl polyphosphate (PPE), which had been an appropriate agent to obtain 1,2-diarylimidazolines.[23] However, under the same conditions, cyclization of compounds **2** is not fulfilled until 15 h of heating, and the corresponding imidazolines are obtained with very poor yields in the presence of raw materials and by-products. Better results have been achieved with methylene chloride solution of trimethylsilyl polyphosphate (PPSE), an aprotic cyclizing agent.[26] The main limitation of this procedure is that long reaction times are often required (10–12 h), resulting in poor yields of the products (35–50% yields). With the aims of enhancing the reaction yields and decreasing the reaction times, the cyclization was optimized using microwave irradiation as the energy source. The reactions were carried out in a Reactor Microwave Digestion System WX-4000 at 80 °C (300 W). Results are shown in Table 2. Under these conditions, times decreased to 22–29 min with 78–98% yields. The method allowed the

Table 2. Conditions for conversion **2** → **1**

	Conventional heating		Microwave irradiation (80 °C, 300 W)	
Product	Reaction time (h)	Yield (%)	Reaction time (min)	Yield (%)
1a	10.5	42	25	83
1b	11.5	45	23	78
1c	11.0	31	28	89
1d	12.0	39	22	90
1e	11.5	47	25	89
1f	10.0	49	29	92
1g	10.5	38	28	98
1h	11.5	33	24	95
1i	10.5	49	26	94

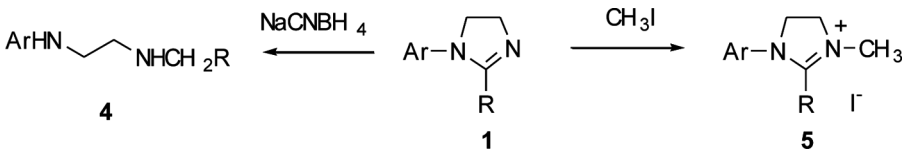


Figure 2. Chemical properties of 1-aryl-2-alkyl-4,5-dihydro-1*H*-imidazoles **1**.

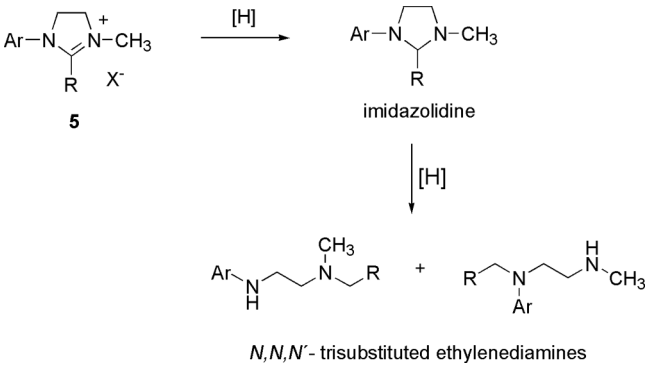
preparation of 1-arylimidazolines 2-substituted with primary (**1a** and **b**), secondary (**1c** and **h**) and tertiary (**1d** and **i**) alkyl, benzyl (**1e and f**) and substituted vinyl groups (**1-g**).

To evaluate 4,5-dihydro-1*H*-imidazoles **1** as potential precursors of cyclic and acyclic compounds carrying the ethylenediamine unit (>NCH_2CH_2N<), reactions resulting from their C2 electrophilic character (reduction) and those to N3 nucleophilic properties (quaternization) were studied (Fig. 2).

Treatment of **1a–i** with sodium cyanoborohydride in ethanol at room temperature led regiospecifically to *N,N′*-disubstituted ethylenediamines **4**. We propose for this reaction an initial hydride ion attack to the electrophilic C2, with formation of the corresponding 1-aryl-2-alkylimidazolidine in tautomeric equilibrium with the corresponding aminoimine. It is well known that N1 and/or N3 unsubstituted imidazolidines present ring (imidazolidine)-chain (aminoimine) tautomerism,[27] and usually both species can be spectroscopically identified. Thus, the selective cleavage of the C2-NAr bond may result from the direct reduction of the aminoimine or the reductive cleavage of the imidazolidine.[23]

As expected because of its nature of cyclic amidines, compounds **1** have nucleophilic character because of the N3 lone pair. Alkylation reactions with alkyl iodides led to 1,2,3-trisubstituted dihydroimidazolium ions **5,** highly stabilized by resonance. This behavior may explain the observed selectivity and the absence of *N,N*-dialkylated products.

Infrared (IR) spectra of compounds **5a–i** confirmed their ionic structure, as can be seen from the strong amidinium band at ca. 1600–1640 cm^{-1}. Mass spectrometry (MS, IE) of compounds **5** showed thermal decomposition with loss of methyl iodide before fragmentation.



Scheme 1.

Based on structural and physical features, 4,5-dihydro-1*H*-imidazolium salts **5** belong to the family of ionic liquids. They also are a potential source of imidazolidines and *N,N,N′*-trisubstituted ethylenediamines.[28]

In summary, an easy synthesis of 1-aryl-2-alkyl-4,5-dihydro-1*H*-imidazoles **1** by cyclocondensation of *N*-acyl-*N′*-arylethylenediamines **2** is described. The method has also been applied for the synthesis of 2-benzyl and 2-arylvinyl derivatives. We have also shown that microwave irradiation is essential for rapid and high-yielding reactions: the reaction times were dramatically reduced from 10–12 h (traditional heating) to 23–29 min using the microwave technique. Compounds **1** act as key intermediates for the synthesis of cyclic and acyclic compounds with the ethylenediamine structural unit.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and were uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) solutions on a Bruker MSL 300-MHz spectrometer at 25 °C. Standard concentration of the samples was 20 mg/mL. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (*J*) values are given in hertz (Hz). D_2O was employed to confirm exchangeable protons. Electron impact MS were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 70 eV. IR spectra were recorded on a Perkin-Elmer Spectrum One Fourier transform (FT)–IR spectrometer. The microwave-assisted reactions were carried out in a Reactor Microwave Digestion System WX-4000 (EU Chemical Instruments). Thin-layer chromatographic (TLC) analyses were carried out on silica-gel 60 F254 aluminum sheets. Column chromatography was performed on silica gel 60 (0.063–0.200 mesh) with typically 30–50 g of stationary phase per gram of substance.

N-(2-Bromoethyl)amides **3** were prepared by reaction of 2-bromoethylamine hydrobromide with a suitable acylating agent (acetic, propionic, or isobutyric anhydride and pivaloyl chloride) under Schotten–Baumann conditions and were used without previous purification.

N-Acyl-N′-(4-chlorophenyl)ethylenediamines 2a–g

General procedure. A mixture of the appropriate *N*-(2-bromoethyl)amide **3** (0.02 mol) and 4-chloroaniline (0.04 mol) was heated in a boiling water bath for 1 h. The crude product was treated with boiling water (3 × 20 mL) to eliminate 4-chloroaniline hydrobromide. The products were purified by column chromatography (ethyl acetate–chloroform, 8:2). Compounds **2b,c**[29] were previously described.

N-Acetyl-N′-(4-chlorophenyl)ethylenediamine (2a). Yield: 62%. It was obtained as an oil. ^{1}H NMR (DMSO-d_6) 1.90 (s, 3H CH_3), 3.25 (t, $J = 5.7$ Hz, 2H CH_2NHAr), 3.47 (q, $J = 5.7$ Hz, 2H CH_2NHCO), 3.54 (br s, 1H NHAr), 5.93 (bs, 1H NHCO), 6.54 (dd, $J = 6.9$, 2.2 Hz, 2H aromatics), 7.12 (dd, $J = 6.9$, 2.2 Hz, 2H aromatics). IR (film) 3321, 2980, 1660, 1508, 1442, 1240, 1027, 816, 731 cm^{-1}. MS: m/z 212, 214 (M^+). Anal. calcd. for $C_{10}H_{13}ClN_2O$: C, 54.47; H, 6.16; N, 13.17. Found: C, 54.51; H, 6.12; N, 13.19.

N-(4-Chlorophenyl)-N′-(2,2-dimethylpropionyl)ethylenediamine (2d). Yield: 74%. It was obtained as an oil. ^{1}H NMR (DMSO-d_6) 1.17 (s, 9H CH_3), 3.23 (t, $J = 5.7$ Hz, 2H CH_2NHAr), 3.50 (q, $J = 5.7$ Hz, 2H CH_2NHCO), 3.55 (br s, 1H NHAr), 5.96 (br s, 1H NHCO), 6.54 (dd, $J = 6.9$, 2.2 Hz, 2H aromatics), 7.11 (dd, $J = 6.9$, 2.2 Hz, 2H aromatics). IR (film) 3315, 2996, 2925 1659, 1520, 1520, 1452, 1380, 820, 740 cm^{-1}. MS: m/z 254, 256 (M^+). Anal. calcd. for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.35; H, 7.47; N, 11.13.

N-(4-Chlorophenyl)-N′-phenylacetylethylenediamine (2e). Yield: 79%. Mp: 119–121 °C. ^{1}H NMR (DMSO-d_6) 3.05 (t, $J = 6.5$ Hz, 2H CH_2NHAr), 3.19 (q, $J = 6.5$ Hz, 2H, CH_2NHCO), 3.39 (s, 2H CH_2CO), 5.84 (br s, 1H NHAr), 6.5 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.05 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.32–7.20 (m, 5H aromatics), 8.15 (br s, 1H HNCO). IR (film) 3341, 2975, 1649, 1434, 1252, 1137, 817, 736 cm^{-1}. MS: m/z 288, 290 (M^+). Anal. calcd. for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.59; H, 6.11; N, 9.61.

N-(2-Chlorophenylacetyl)-N′-(4-chlorophenyl)ethylenediamine (2f). Yield: 76%. It was obtained as an oil. ^{1}H NMR (DMSO-d_6) δ: 3.05 (t, $J = 6.7$ Hz, 2H CH_2NHAr), 3.21 (q, $J = 6.7$ Hz, 2H CH_2NHCO), 3.57 (s, 2H CH_2CO), 5.85 (br s, 1H HNAr), 6.5 (dd, $J = 6.7$, 2.7 Hz, 2H aromatics), 7.08 (dd, $J = 6.7$, 2.7 Hz, 2H aromatics), 7.41–7.20 (m, 4H aromatics), 8.15 (br s, 1H HNCO). IR (film) 3330, 2936, 2923, 1651, 1519, 1462, 1080, 827, 747 cm^{-1}. MS: m/z 322, 324, 326 (M^+). Anal. calcd. for $C_{16}H_{16}Cl_2N_2O$: C, 59.46; H, 4.99; N, 8.67. Found: C, 59.55; H, 4.85; N, 8.71.

N-(4-Chlorophenyl)-N′-cinnamoylethylenediamine (2g). Yield: 82%. It was obtained as an oil. ^{1}H NMR (DMSO-d_6) 3.25–3.01 (m, 4H CH_2-CH_2), 5.91 (br s, 1H NHAr), 6.50 (d, $J = 16.2$ Hz, 1H HC=), 6.59 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 6.97 (d, $J = 16.2$ Hz, 1H HC=), 7.08 (dd, aromatics, $J = 6.7$, 2.0 Hz, 2H), 7.60–7.15 (m, 5H aromatics), 8.21 (br s, 1H NHCO). IR (film) 3325, 2945, 1633, 1517, 1430, 832, 740 cm^{-1}. MS: m/z 300, 302 (M^+). Anal. calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 11.79. Found: C, 67.79; H; 5.78; N, 11.60.

N-Acyl-N′-(4-nitrophenyl)ethylenediamines 2h–i

General procedure. A mixture of *N*-(4-nitrophenyl)ethylenediamine (0.01 mol) in chloroform (50 mL), the appropiate acylating agent (0.013 mol), and triethylamine (0.016 mol) was refluxed for 1 h. After heating, the organic solution was evaporated in vacuo. The resulting residue was triturated with an aqueous solution of NaOH (5%), filtered, and washed with water, diluted HCl (5%), and water once again. The pure products were isolated by column chromatography (ethyl acetate–chloroform, 8:2) as yellow solids.

N-(4-Nitrophenyl)-N′-(2-methylpropionyl)ethylenediamine (2h). Yield: 80%. Mp: 105–107 °C. ^{1}H NMR ($CDCl_3$) 1.15 (d, $J = 7.1$ Hz, 6H CH_3), 2.40 (m, $J = 7.1$ Hz, 1H CH), 3.34 (t, $J = 5.2$ Hz, 2H CH_2NHAr), 3.56 (q, $J = 5.2$ Hz, 2H, CH_2NHCO), 5.55 (br s, 1H NH), 5.95 (br s, 1H NH), 6.50 (d, $J = 9.1$ Hz, 2H aromatics), 8.04 (d, $J = 9.1$ Hz, 2H aromatics). IR (film) 3412, 2931, 1635, 1540, 1324,

831 cm^{-1}. MS: m/z 251 (M^+). Anal. calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.45; H, 6.07; N, 16.65.

N-(4-Nitrophenyl)-N′-(2,2-dimethylpropionyl)ethylenediamine (2i). Yield: 85%. Mp: 172–174 °C. ^{1}H NMR ($CDCl_3$) 1.21 (s, 9H CH_3), 3.34 (t, $J = 5.2$ Hz, Hz, 2H CH_2NHAr), 3.58 (q, $J = 5.2$ Hz, 2H CH_2NHCO), 6.03 (br s, 1H NH), 5.56 (br s, 1H NH), 6.55 (d, $J = 9.1$ Hz, 2H artomatics), 8.08 (d, $J = 9.1$ Hz, 2H aromatics). IR (film) 3392, 2930, 2871, 1620, 1324, 835 cm^{-1}. MS: m/z 265 (M^+). Anal. calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.76; H, 7.29; N, 15.95.

2-Alkyl-1-aryl-4,5-dihydro-1H-imidazoles 1a–i

General procedure for conventional heating. A mixture of *N*-acyl-*N*′-arylethylenediamine (1 mmol) and a solution of PPSE[26] (2 mL) was refluxed and monitored by TLC using chloroform–methanol 8:2 as elution solvent until disappearance of starting diamine. The residue was cooled and extracted with water (3×2 mL). The aqueous phases were pooled, neutralized with solid sodium carbonate, and extracted with Cl_2CH_2 (3×2 mL). The organic phases were pooled and washed with water. The organic solution was dried over anhydrous sodium sulfate and evaporated in vacuo. The yellowish oily products were purified by column chromatography (chloroform-methanol, 8:2).

General procedure for microwave technique. *N*-acyl-*N*′-arylethylenediamine (1 mmol) and a solution of PPSE (2 mL) were placed in a 10-mL glass tube. The tube was closed with a septum and placed into the microwave cavity. The reaction mixture was subjected to microwave irradiation at 300 W (80 °C) for 20–29 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the reaction product **1** was isolated, as indicated in the conventional procedure.

1-(4-Chlorophenyl)-2-methyl-4,5-dihydro-1H-imidazole (1a). ^{1}H NMR ($CDCl_3$) 2.05 (s, 3H CH_3), 3.83 (s, 4H CH_2-CH_2), 7.03 (d, $J = 8.7$ Hz, 2H aromatics), 7.30 (d, $J = 8.7$ Hz, 2H aromatics). IR (film) 2959, 1615, 1491, 1083, 832, 712 cm^{-1}. MS: m/z 194, 196 (M^+). Anal. calcd. for $C_{10}H_{11}ClN_2$: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.58; H, 5.61; N, 14.46.

1-(4-Chlorophenyl)-2-ethyl-4,5-dihydro-1H-imidazol (1b). ^{1}H NMR ($CDCl_3$) 1.12 (t, $J = 7.4$ Hz, 3H CH_3), 2.27 (q, $J = 7.4$ Hz, 2H CH_2), 3.78 (s, 4H CH_2-CH_2), 7.01 (d, $J = 8.7$ Hz, 2H aromatics), 7.29 (d, $J = 8.7$, 2H aromatics). IR (film) 2950, 1616, 1483, 1061, 829, 721 cm^{-1}. MS: m/z 208, 210 (M^+). Anal. calcd. for $C_{11}H_{13}ClN_2$: C, 63.31; H, 6.28; N, 13.42. Found: C, 63.22; H, 6.39; N, 13.35.

1-(4-Chlorophenyl)-2-(1-methylethyl)-4,5-dihydro-1H-imidazole (1c). ^{1}H NMR ($CDCl_3$) 1.13 (d, $J = 6.8$ Hz, 6H CH_3), 2.60 (m, $J = 6.8$ Hz, 1H CH), 3.86–3.74 (m, 4H CH_2-CH_2), 7.05 (d, $J = 8.7$ Hz, 2H aromatics), 7.33 (d, $J = 8.7$ Hz, Hz, 2H aromatics). IR (film) 2954, 1621, 1487, 1075, 840, 730 cm^{-1}. MS: m/z 222, 224 (M^+). Anal. calcd. for $C_{12}H_{15}ClN_2$: C, 64.72; H, 6.79; N, 12.58. Found: C, 64.65; H, 6.85; N, 12.66.

1-(4-Chlorophenyl)-2-(1,1-dimethylethyl)-4,5-dihydro-1H-imidazole (1d). ^{1}H NMR ($CDCl_3$) 1.30 (s, 9H CH_3), 4.16 (s, 4H CH_2-CH_2), 7.28 (d, $J = 8.5$ Hz, 2H aromatics), 7.49 (d, $J = 8.5$ Hz, 2H aromatics. IR (film) 2900, 1629, 1490, 1090, 811, 710 cm^{-1}. MS: m/z 236, 238 (M^+). Anal. calcd. for $C_{13}H_{17}ClN_2$: C, 65.95; H, 7.24; N, 11.83. Found: C, 65.88; H, 7.33; N, 11.76.

2-Benzyl-1-(4-chlorophenyl)-4,5-dihydro-1H-imidazole (1e). ^{1}H NMR ($CDCl_3$) 3.61 (s, 2H CH_2), 3.87–3.78 (m, 4H CH_2-CH_2), 6.93 (d, $J = 8.8$ Hz, 2H aromatics), 7.12 (d, $J = 8.8$ Hz, 2H aromatics), 7.23–7.20 (m, 5H aromatics). IR (film) 2935, 1620, 1480, 1079, 823, 715 cm^{-1}. MS: m/z 270, 272 (M^+). Anal. calcd. for $C_{16}H_{15}ClN_2$: C, 70.98; H, 5.58; N, 10.35. Found: C, 70.87; H, 5.66; N, 10.24.

2-(2-Chlorobenzyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-imidazole (1f). ^{1}H NMR ($CDCl_3$) 3.67 (s, 2H CH_2), 3.89 (s, 4H CH_2-CH_2), 6.94 (d, $J = 8.8$, 2 H aromatics), 7.30–7.10 (m, 6H aromatics). IR (film) 2956, 1615, 1483, 1065, 833, 731 cm^{-1}. MS: m/z 304, 306, 308 (M^+). Anal. calcd. for $C_{16}H_{14}Cl_2N_2$: C, 62.97; H, 4.62; N, 9.18. Found: C, 62.79; H, 4.70; N, 9.26.

1-(4-Chlorophenyl)-2-(2-phenylvinyl)-4,5-dihydro-1H-imidazole (1g). ^{1}H NMR ($CDCl_3$) 4.05–3.81 (m, 4H CH_2-CH_2), 6.52 (d, $J = 15.9$, 1H CH=), 7.03 (d, $J = 8.7$, 2H aromatics), 7.50–7.15 (m, aromatics, 7H), 7.52 (d, $J = 15.9$, 1H CH=). IR (film) 2943, 1612, 1480, 1072, 836, 720 cm^{-1}. MS: m/z 282, 284 (M^+). Anal. calcd. for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.38; H, 5.39; N, 9.82.

2-(1-Methylethyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-imidazole (1h). ^{1}H NMR ($CDCl_3$) 1.29 (d, $J = 7.1$, 6H CH_3), 2.85 (m, CH, $J = 7.1$, 1H), 3.95–3.80 (m, CH_2-CH_2, 4 H), 7.15 (d, aromatics, $J = 9.1$, 2H), 8.20 (d, $J = 9.1$, 2H aromatics). IR (film) 2947, 1611, 1491, 1378, 1061, 835 cm^{-1}. MS: m/z 233 (M^+). Anal. calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.62; H, 6.55; N, 18.15.

2-(1,1-Dimethylethyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-imidazole (1i). ^{1}H NMR ($CDCl_3$) 1.10 (s, 9H CH_3), 3.90–3.70 (m, 4H CH_2-CH_2), 7.35 (d, $J = 9.1$, 2H aromatics), 8.25 (d, $J = 9.1$, 2H aromatics). IR (film) 2900, 1639, 1502, 1353, 111, 847 cm^{-1}. MS: m/z 247 (M^+). Anal. calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.23; H, 6.05; N, 16.83.

N-Alkyl-N′-arylethylenediamines 4a–i

General procedure. Sodium cyanoborohydride (0.05 mol) was added for 5 min to a solution of the appropriate 1*H*-4,5-dihydroimidazole **1** (0.01 mol) in ethanol (20 mL) keeping the mixture at rt. When total transformation had occurred (ca. 30 min for compounds **4a–g** and 50 min for compounds **4 h–i**, the suspension was extracted with chloroform (3 × 15 mL). The organic layers were pooled, washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo affording dark oily compounds **4a-i** which were purified by column chromatography (chloroform/methanol, 1:1).

N-(4-Chlorophenyl)-N′-ethylethylenediamine (4a). Yield: 67%. ^{1}H NMR ($CDCl_3$) 1.10 (t, $J = 7.1$ Hz, 3H CH_3), 1.90 (br s, 1H NHR), 2.65 (q, $J = 7.1$ Hz, 2H CH_2-CH_3), 2.85 (t, $J = 5.5$ Hz, 2H CH_2-NHR), 3.15 (t, $J = 5.5$ Hz, 2H

CH_2-NHAr), 4.22 (br s, 1H NHAr), 6.55 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.10 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics). IR (film) 3378, 2930, 1601, 1502, 1457, 812, 756 cm^{-1}. MS: m/z: 198, 200 (M^+). Anal. calcd. for $C_{10}H_{15}ClN_2$: C, 60.45; H, 7.61; N, 14.10. Found: C, 60.41; H, 7.67; N, 14.06.

N-(4-Chlorophenyl)-N′-propylethylenediamine (4b). Yield: 72%. ^{1}H NMR ($CDCl_3$) 0.90 (t, $J = 7.4$ Hz, 3H CH_3), 1.25 (br s, 1H NHR), 1.55 (m, 2H CH_2CH$_3$), 2.60 (t, $J = 6.9$ Hz, 2H CH$_2$CH_2CH$_3$), 2.90 (t, $J = 5.4$ Hz, 2H CH$_2$NR), 3.25 (t, $J = 5.4$ Hz, 2H CH$_2$NAr), 4.75 (s, 1H NHAr), 6.55 (dd, $J = 6.7$, 2.1 Hz, 2H aromatics), 7.05 (dd, $J = 6.7$, 2.1 Hz, 2H aromatics). IR (film) 3359, 2920, 1599, 1502, 1445, 816, 721 cm^{-1}. MS: m/z: 212, 214 (M^+). Anal. calcd. for $C_{11}H_{17}ClN_2$: C, 62.11; H, 8.06; N, 13.17. Found: C, 62.20; H, 8.01; N, 13.20.

N-(4-Chlorophenyl)-N′-(2-methylpropyl)ethylenediamine (4c). Yield: 69%. ^{1}H NMR ($CDCl_3$) 0.95 (d, $J = 6.6$ Hz, 6H CH$_3$), 1.55 (br s, 1H NHR), 1.70 (m, 1H, CH), 2.40 (d, $J = 6.6$ Hz, 2H CH_2-CH), 2.85 (t, $J = 5.4$ Hz, 2H CH_2NHR), 3.15 (t, $J = 5.48$ Hz, 2H CH_2NHAr), 4.22 (br s, 1H NHAr), 6.55 (dd, $J = 6.6$, 2.1, 2H aromatics), 7.10 (dd, $J = 6.6$, 2.1 Hz, 2H aromatics). IR (film) 3381, 2931, 1602, 1512, 1420, 811, 714 cm^{-1}. MS: m/z: 226, 228 (M^+). Anal. calcd. for $C_{12}H_{19}ClN_2$: C, 63.56; H, 8.45; N, 12.35. Found: C, 63.50; H, 8.49; N, 12.31.

N-(4-Chlorophenyl)-N′-(2,2-dimethylpropyl)ethylenediamine (4d). Yield: 74%. ^{1}H NMR ($CDCl_3$) 0.98 (s, 9H, CH$_3$), 1.65 (br s, 1H, NHR), 2.48 (s, 2H, CH$_2$-C), 3.05 (t, $J = 5.5$ Hz, 2H CH_2NR), 3.30 (t, $J = 5.5$ Hz, 2H CH$_2$NAr), 4.35 (br s, 1H NHAr), 6.55 (dd, $J = 6.7$, 2.0, Hz, 2H aromatics), 7.10 (dd, $J = 6.7$, 2.0 Hz, 2H, aromatics). IR (film) 3380, 2926, 1601, 1504, 1410, 822, 799 cm^{-1}. MS: m/z: 240, 242 (M^+). Anal. calcd. for $C_{13}H_{21}ClN_2$: C, 64.85; H, 8.79; N, 11.63. Found: C, 64.89; H,8.72; N, 11.58.

N-(4-Chlorophenyl)-N′-(2-phenylethyl)ethylenediamine (4e). Yield: 70%. ^{1}H NMR ($CDCl_3$) 2.00 (br s, 1H NHR), 2.94–2.84 (m, 6H CH$_2$NR and CH_2-CH_2C$_6$H$_5$), 3.20 (t, $J = 5.6$ Hz, 2H CH$_2$NAr), 4.15 (br s, 1H NHAr), 6.55 (dd, $J = 6.6$, 2.0 Hz, 2H aromatics), 7.05 (dd, $J = 6.6$, 2.0 Hz, 2H aromatics), 7.40–7.15 (m, 5H aromatics). IR (film) 3365, 2921, 1599, 1502, 1420, 821, 720 cm^{-1}. MS: m/z: 274, 276 (M+). Anal. calcd. for $C_{16}H_{19}ClN_2$: C, 69.93; H, 6.97; N, 10.19. Found: C, 69.98; H, 7.05; N, 10.13.

N-(4-Chlorophenyl)-N′-[2(2-chlorophenyl)ethyl]ethylenediamine (4f). Yield: 73%. ^{1}H NMR ($CDCl_3$) 2.10 (br s, 1H NHR), 2.96-2.92 (m, 6H CH$_2$NR and CH$_2$-CH$_2$), 3.20 (t, $J = 5.4$ Hz, 2H CH$_2$NAr), 4.20 (br s, 1H N*H*Ar), 6.53 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.09 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.21–7.15 (m, 3H aromatics), 7.36–7.33 (m, 1H aromatic). IR (film) 3371, 2927, 1600, 1504, 1412, 816, 715 cm^{-1}. MS: m/z: 308, 310, 312 (M^+). Anal. calcd. for $C_{16}H_{18}Cl_2N_2$: C, 62.14; H, 5.87; N, 9.06. Found: C, 62.06; H, 5.95; N, 9.12.

N-(4-Chlorophenyl)-N′-(3-phenylallyl)ethylenediamine (4g). Yield: 67%. ^{1}H NMR ($CDCl_3$) 2.11 (br s, 1H NHR), 2.96–2.92 (m, 4H, CH$_2$NR and CH$_2$-CH=), 3.20 (t, $J = 5.4$ Hz, 2H CH$_2$NAr), 4.25 (br s, 1H NHAr), 6.50 (d, $J = 15.9$, 1H CH=), 6.60 (dd, $J = 6.7$, 2.0 Hz, 2H aromatics), 7.25 (d, $J = 15.9$, 1H CH=), 7.35–6.90 (m, 7H aromatics). IR (film) 3385, 2920, 1597, 1499, 1401, 811,

721 cm^{-1}. MS: m/z: 286, 288 (M^+). Anal. calcd. for $C_{17}H_{19}ClN_2$: C, 71.19; H, 6.68; N, 9.77. Found: C, 71.25; H, 6.75; N, 9.70.

N-(2-Methylpropyl)-N′-(4-nitrophenyl)ethylenediamine (4h). Yield: 75%. ^1H NMR ($CDCl_3$) 0.93 (d, $J = 6.7$ Hz, 6H CH_3), 1.81–1.75 (m, 2H NHR and CH), 2.46 (d, $J = 6.7$ Hz, 2H CH_2CH), 2.94 (t, $J = 5.4$ Hz, 2H CH_2NHR), 3.27 (dt, $J = 5.47$, 4.9 Hz, 2H CH_2NAr), 6.53 (d, $J = 9.1$, Hz, 2H aromatics), 5.35 (br s,1H NHAr), 8.08 (d, $J = 9.1$ Hz, 2H aromatics). IR (film) 3410, 2921, 1602, 1505, 1406, 1324, 831 cm^{-1}. MS: m/z: 237 (M^+). Anal. calcd. for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.79; H, 8.15; N, 17.65.

N-(2,2-dimethylpropyl)-N′-(4-nitrophenyl)ethylenediamine (4i). Yield: 74%. ^1H NMR ($CDCl_3$) 0.91 (s, 9H CH_3), 1.35 (br s, 1H NHR), 2.35 (s, 2H CH_2C), 2.92 (t, $J = 5.6$ Hz, 2H CH_2NHR), 3.24 (dt, $J = 5.6$, 4.8 Hz, 2H CH_2NHAr), 5.37 (br s, 1H NHAr), 6.51 (d, $J = 9.2$ Hz, 2H aromatics), 8.08 (d, $J = 9.2$ Hz, 2H aromatics). IR (film) 3415, 2920, 1601, 1510, 1412, 1320, 835 cm^{-1}. MS: m/z: 251 (M^+). Anal. calcd. for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.05; H, 8.48; N, 16.79.

2-Alkyl-1-aryl-3-methyl-4,5-dihydro-1H-imidazolium Iodides 5a–g

General procedure. A solution of the appropriate compound **1** (3 mmol) and methyl iodide (4 mmol) in methylene chloride (20 mL) was refluxed, and the mixture was monitored by TLC (benzene:methanol, 9:1) until disappearance of the starting material. The solution was concentrated in vacuo affording a hygroscopic oil that could not be crystallized. The products **5a–i** were purified by column chromatography (chloroform/methanol, 1:1).

1-(4-Chlorophenyl)-2,3-dimethyl-4,5-dihydro-1H-imidazolium Iodide (5a). Yield: 85%. ^1H NMR ($CDCl_3$) 2.70 (s, 3H C-CH_3), 3.30 (s, 3H N-CH_3), 4.37–4.16 (ms, 4H CH_2-CH_2), 7.40 (dd, $J = 6.7$, 2.0, 2H aromatics), 7.62 (dd, $J = 6.7$, 2.0, 2H aromatics). IR (film) 2901, 1635, 1497, 1250, 821, 691 cm^{-1}. MS: m/z: 194, 196 (M-ICH$_3$)+. Anal. calcd. for $C_{11}H_{14}ClIN_2$: C, 39.25; H, 4.19; N, 8.32. Found: C, 39.13; H, 4.28; N, 8.43.

1-(4-Chlorophenyl)-2-ethyl-3-methyl-4,5-dihydro-1H-imidazolium iodide (5b). Yield: 88%. ^1H NMR ($CDCl_3$) 1.12 (t, $J = 7.8$, 3H CH_3), 2.50 (q, $J = 7.8$, 2H CH_2), 3.26 (s, 3H NCH_3), 4.33–4.16 (ms, 4H CH_2-CH_2), 7.40 (dd, $J = 6.7$, 2.0, 2H aromatics), 7.61 (dd, $J = 6.7$, 2.0, 2 H aromatics). IR (film) 2917, 1615, 1500, 1249, 820, 699 cm^{-1}. MS: m/z: 208, 210 (M-ICH$_3$)+. Anal. calcd. for $C_{12}H_{16}ClIN_2$: C, 41.11; H, 4.60; N, 7.99. Found: C, 41.19; H, 4.54; N, 8.23.

1-(4-Chlorophenyl)-3-methyl-2-(1-methylethyl)-4,5-dihydro-1H-imidazolium iodide (5c). Yield: 85%. ^1H NMR ($CDCl_3$) 1.32 (d, $J = 7.2$, 6H CH_3), 2.93-2.75 (sept., $J = 7.2$, 1H CH), 3.34 (s, 3H N-CH_3), 4.40–4.20 (m, 4H CH_2-CH_2), 7.40 (dd, $J = 6.7$, 2.0, 2H aromatics.), 7.45 (dd, $J = 6.7$, 2.0, 2H aromatics). IR (film) 2930, 1630, 1505, 1249, 819, 702 cm^{-1}. MS: m/z: 222, 224 (M-ICH$_3$)+. Anal. calcd. for $C_{13}H_{18}ClIN_2$: C, 42.82; H, 4.98; N, 7.68. Found: C, 44.75; H, 4.82; N, 7.76.

1-(4-Chlorophenyl)-3-methyl-2-(1,1-dimethylethyl)-4,5-dihydro-1H-imidazolium iodide (5d). Yield: 88%. ^{1}H NMR ($CDCl_3$) 1.28 (s, 9H CH_3), 3.40 (s, 3H NCH_3), 4.24 (s, 4H CH_2-CH_2), 7.37 (dd, $J = 6.7$, 2.2, 2H aromatics), 7.67 (dd, $J = 6.7$, 2.2, 2H aromatics). IR (film) 2920, 1640, 1510, 1250, 812, 695 cm^{-1}. MS: m/z: 236, 238 (M-ICH_3)+. Anal. Calcd for $C_{14}H_{20}ClIN_2$: C, 44.40; H, 5.32; N, 7.40. Found: C, 44.32; H, 5.44; N, 7.31.

2-Benzyl-1-(4-chlorophenyl)-3-methyl-4,5-dihydro-1H-imidazolium iodide (5e). Yield: 90%. ^{1}H NMR ($CDCl_3$) 3.20 (s, 3H NCH_3), 4.00 (s, 2H $CH_2C_6H_5$), 4.45–4.20 (m, 4H CH_2-CH_2), 7.05 (d, $J = 7.2$, 2H aromatics), 7.31 (m, 3H aromatics), 7.38 (dd, $J = 6.7$, 2.0, 2H aromatics), 7.60 (dd, $J = 6.7$, 2.0, 2H aromatics). IR (film) 2955, 1621, 1515, 1247, 815, 721 cm^{-1}. MS: m/z: 270, 272 (M-ICH_3) +. Anal. calcd. for $C_{17}H_{18}ClIN_2$: C, 49.48; H, 4.40; N, 6.79. Found: C, 49.36; H, 4.47; N, 7.13.

2-(2-Chlorobenzyl)-1-(4-chlorophenyl)-3-methyl-4,5-dihydro-1H-imidazolium iodide (5f). Yield: 87%. ^{1}H NMR ($CDCl_3$) 3.21 (s, 3H NCH_3), 4.15 (s, 2H $CH_2C_6H_5$), 4.40–4.25 (ms, 4H CH_2-CH_2), 7.24–7.02 (m, 2H aromatics), 7.26–7.25 (m, 2H aromatics), 7.32 (dd, $J = 7.6$, 2.0, 2H aromatics), 7.56 (dd, $J = 7.6$, 2.0, 2H aromatics). IR (film) 2901, 1632, 1499, 1235, 823, 712 cm^{-1}. MS: m/z: 304, 306, 308 (M-ICH_3)+. Anal. calcd. for $C_{17}H_{17}Cl_2IN_2$: C, 45.66; H, 3.83; N, 6.26. Found: C, 45.55; H, 3.87; N, 6.15.

1-(4-Chlorophenyl)-3-methyl-2-phenylvinyl-4,5-dihydro-1H-imidazolium iodide (5g). Yield: 91%. ^{1}H NMR ($CDCl_3$) 3.43 (s, 3H NCH_3), 4.45–4.30 (ms, 4H CH_2-CH_2), 6.37 (d, $J = 16.6$, 1H CH=), 7.50–7.32 (m, 7H aromatics and 1H CH=), 7.55 (dd, $J = 6.8$, 1.9, 2H aromatics). IR (film) 2933, 1643, 1505, 1493, 1260, 799, 693 cm^{-1}. Anal. calcd. for $C_{18}H_{18}ClIN_2$: C, 50.90; H, 4.27; N, 6.60. Found: C, 51.12; H, 4.36; N, 6.51. MS: m/z: 282, 284 (M-ICH_3)+.

3-Methyl-2-(1-methylethyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-imidazolium iodide (5h). Yield: 87%. ^{1}H NMR ($CDCl_3$) 1.38 (s, $J = 7.2$, 6H $(CH_3)_2CH$), 2.92–2.83 [m, 1H $CH(CH_3)_2$], 3.38 (s, 3H NCH_3), 4.50–4.28 (ms, 4H CH_2-CH_2), 7.98 (dd, $J = 8.9$, 2.0, 2H aromatics), 8.34 (dd, $J = 8.9$, 2.0, 2H aromatics). IR (film) 32967, 1637, 1496, 1324, 831 cm^{-1}. MS: m/z: 233 (M-ICH_3)+. Anal. calcd. for $C_{13}H_{18}IN_3O_2$: C, 41.61; H, 4.84; N, 11.20. Found: C, 41.56; H, 4.92; N, 11.31.

3-Methyl-2-(1,1-dimethylethyl)-1-(4-nitrophenyl)-4,5-dihydro-1H-imidazolium iodide (5i). Yield: 88%. ^{1}H NMR ($CDCl_3$) 1.36 [s, 9H $(CH_3)_3C$], 3.50 (s, 3H NCH_3), 4.34 (s, 4H CH_2-CH_2), 8.09 (dd, $J = 8.9$, 2.0, 2H aromatics), 8.33 (dd, $J = 8.9$, 2.0, 2H aromatics). IR (film) 2939, 1642, 1501, 1322, 833 cm^{-1}. MS: m/z: 247 (M-ICH_3)+. Anal. calcd for $C_{14}H_{20}IN_3O_2$: C, 43.20; H, 5.18; N, 10.80. Found: C, 43.33; H, 5.11; N, 10.72.

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REFERENCES

1. (a) Dardonville, C.; Rozas, I. Imidazoline binding sites and their ligands: An overview of the different chemical structures. *Med. Res. Rev.* **2004**, *24* (5), 639–661; (b) Szabo, B. Imidazoline antihypertensive drugs: A critical review on their mechanism of action. *Pharmacol. Therapeut.* **2002**, *93* (1), 1–35, and references cited therein.
2. (a) Touzeau, F.; Arrault, A.; Guillaument, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.; Renard, P.; Mérour, J. Y. Synthesis and biological evaluation of new 2-(4,5-dihydro-1*H*-imidazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine derivatives. *J. Med. Chem.* **2003**, *46* (10), 1962–1979; (b) Schäfer, U.; Burgdorf, C.; Engelhardt, A.; Kurz, T.; Richardt, G. Presynaptic effects of moxonidine in isolated buffer perfused rat hearts: Role of imidazoline-1 receptors and α 2-adrenoceptors. *J. Pharmacol. Exp. Ther.* **2002**, *303* (3), 1163–1170; (c) Bousquet, P.; Feldman, J. Drugs acting on imidazoline receptors: A review of their pharmacology, their use in blood pressure control, and their potential interest in cardioprotection. *Drugs* **1999**, *58* (5), 799–812.
3. (a) Wang, X.; Rondu, F.; Lamouri, A.; Dokhan, R.; Marc, S.; Touboul, E.; Pfeiffer, B.; Manechez, D.; Renard, P.; Guardiola-Lemaitre, B.; Godfroid, J.-J.; Ktorza, A.; Penicaud, L. Effect of S-21663 (PMS 812), an imidazoline derivative, on glucose tolerance and insulin secretion in a rat model of type II diabetes. *J. Pharmacol. Exp. Ther.* **1996**, *278* (1), 82–89; (b) Rondu, F.; Le Bihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, T.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. Design and synthesis of imidazoline derivatives active on glucose homeostasis in a rat model of type II diabetes, 1: Synthesis and biological activities of *N*-benzyl-*N*′-(arylalkyl)-2-(4′,5′-dihydro-1′*H*-imidazol-2-yl)piperazines. *J. Med. Chem.* **1997**, *40* (23), 3793–3803; (c) Pele-Tounian, A.; Wang, X.; Rondu, F.; Lamouri, A.; Touboul, E.; Marc, S.; Dokhan, R.; Pfeiffer, B.; Manechez, D.; Renard, P.; Guardiola-Lemaitre, B.; Gofroid, J.-J.; Penicaud, L.; Ktorza, A. The Potent antihyperglycaemic property of a new imidazoline derivative S-22068 (PMS 847) in a rat model of NIDDM. *Brit. J. Pharmacol.* **1998**, *124* (8), 1591–1596; (d) Le Bihan, G.; Rondu, F.; Pele-Tounian, A.; Wang, X.; Lidy, S.; Toubould, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J. J. Design and synthesis of imidazoline derivatives active on glucose homeostasis in a rat model of type II diabetes, 2: Synthesis and biological activities of 1,4-dialkyl-, 1,4-dibenzyl, and 1-benzyl-4-alkyl-2-(4′,5′-dihydro-1′-*H*-imidazol-2′-yl)piperazines and isosteric analogues of imidazoline. *J. Med. Chem.* **1999**, *42* (9), 1587–1603; (e) Doyle, M. E.; Egan, J. Pharmacological agents that directly modulate insulin secretion. *Pharmacol. Rev.* **2003**, *55* (1), 105–131.
4. (a) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. Effect of a novel antirheumatic drug, TA-383, on type II collagen-induced arthritis. *Int. J. Immunopharmaco.* **1995**, *17* (7), 597–599; (b) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. Highly diastereoselective multicomponent synthesis of unsymmetrical imidazolines. *Org. Lett.* **2002**, *4* (20), 3533–3535.
5. Vizi, E. S. Compounds acting on alpha$_1$- and alpha$_2$-adrenoceptors: Agonists and antagonists. *Med. Res. Rev.* **1986**, *6* (4), 431–449.
6. Chern, J. W.; Llaw, Y. C.; Chen, C. S.; Rong, J. G.; Huang, C.-L.; Chan, C.-H.; Wang, A. H.-J. Studies on 1,2,4-benzothiadiazine 1,1-dioxides VII and quinazolinones IV: Synthesis of novel built-in hydroxyguanidine tricycles as potential anticancer agents. *Heterocycles* **1993**, *36* (5), 1091–1103.
7. Servi, S.; Genc, M.; Gür, S.; Koca, M. The synthesis and antimicrobial activity of some new methyl *N*-arylthiocarbamates, dimethyl *N*-aryldithiocarbonimidates, and 2-arylamino-2-imidazolines. *Eur. J. Med. Chem.* **2005**, *40* (7), 687–693.

8. Li, H. Y.; Drummond, S.; De Lucca, I.; Boswell, G. A. Singlet oxygen oxidation of pyrroles: Synthesis and chemical transformations of novel 4,4-bis(trifluoromethyl)imidazoline analogs. *Tetrahedron* **1996**, *52* (34), 11153–11162.
9. Cho, Y.; Song, H.; Lee, D.; Baek, S.; Chae, S.; Jo, S.; Kim, Y.; Lee, H.; Park, J.; Park, T.; Woo, S.; Kim, Y. Legochem Bioscience Ltd. FXA inhibitors with cyclic amidines as P4 subunit, processes for their preparations, and pharmaceutical compositions and derivatives thereof. KR Patent WO/140220, November 20, 2008.
10. (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. Cycloaddition of homochiral imidazolinium ylides: A route to optically active pyrroloimidazoles. *Tetrahedron Lett.* **1996**, *37* (10), 1707–1710; (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. An enantioselective route to pyrrolidines: Removal of the chiral template from homochiral pyrroloimidazoles. *Tetrahedron Lett.* **1996**, *37* (10), 1711–1714; (c) Puntener, K.; Hellman, M. D.; Kuester, E.; Hegedus, L. S. Synthesis and complexation properties of poly(ethylene glycol)-linked mono- and bis-dioxocyclams. *J. Org. Chem.* **2000**, *65* (24), 8301–8306; (d) Corey, E. J.; Grogan, M. J. Enantioselective synthesis of α-amino nitriles from *N*-benzhydryl imines and HCN with a chiral bicyclic guanidine as catalyst. *Org. Lett.* **1999**, *1* (1), 157–160; (e) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. Modified guanidines as chiral superbases: The first example of asymmetric silylation of secondary alcohols. *Chem. Commun.* **2001**, *3*, 243–255; (f) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Erythro*-selective aldol-type reaction of *N*-sulfonylamidines with methyl isocyanoacetate catalyzed by gold(I). *Tetrahedron Lett.* **1996**, *37* (28), 4969–4972; (g) Hsiao, Y.; Hegedus, L. S. Synthesis of optically active imidazolines, azapenams, dioxocyclams, and bis-dioxocyclams. *J. Org. Chem.* **1997**, *62* (11), 3586–3591; (h) Jung, M. E.; Huang, A. Use of optically active cyclic *N,N*-dialkyl aminals in asymmetric induction. *Org. Lett.* **2000**, *2* (17), 2659–2661; (i) Ye, G.; Zhou, A.; Henry, W. P.; Song, Y.; Chatterjee, S.; Beard, D. J.; Pittman, Jr. C. U. Tandem reactions of 1,3-diacid chlorides with 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydropyrimidine: One-pot synthesis of 1,8-naphthyridinetetraones. *J. Org. Chem.* **2008**, *73* (13), 5170–5172.
11. (a) Dalko, P. I.; Langlois, Y. Stereoselective preparation of quaternary benzylic centres using chiral imidazolines. *Chem. Commun.* **1998**, *3*, 331–334; (b) Jones, R. C. F.; Turner, I.; Howard, K. J. A new route to homochiral piperidines. *Tetrahedron Lett.* **1993**, *34* (39), 6329–6332; (c) Langlois, Y.; Dalko, P. I. Stereoselective synthesis of quaternary benzylic carbons using C_2 symmetric imidazolines and tetrahydrofuran as electrophile. *J. Org. Chem.* **1998**, *63* (23), 8107–8117.
12. (a) Morimoto, T.; Tachibana, K.; Achiwa, K. Chiral thioimidazoline ligands for palladium-catalyzed asymmetric allylation. *Synlett* **1997**, *7*, 783–785; (b) Jones, R. C. F.; Nichols, J. R. Thiamine coenzyme models: Imidazolinium ylides and the reactions of 2-(hydroxyalkyl)imidazolines. *Tetrahedron Lett.* **1990**, *31* (12), 1771–1774; (c) Han, L.; Da-Ming, D. Recent advances in the synthesis of 2-imidazolines and their applications in homogeneous catalysis. *Adv. Synth. Catal.* **2009**, *351* (4), 489–519, and references cited therein.
13. (a) Anderson, M. W.; Jones, R. C. F.; Saunders, J. Nucleophylic addition to 4,5-dihydroimidazoles: A ketone synthesis via tetrahydrofolate coenzyme and references therein models. *J. Chem. Soc., Perkin Trans.* **1986**, *1* (11), 1995–1998, and references therein; (b) Pandit, U. K. Models of biological systems and biological processes. *Pure Appl. Chem.* **1994**, *66* (4), 759–764, and references cited therein.
14. (a) Belsky, I.; Gertner, D.; Zilkha, A. Some silicon-containing phenyl and benzyl isoquinoline derivatives, 2-aralkyl imidazolines, and *N*-substituted phenethylamines. *Can. J. Chem.* **1968**, *46* (11), 1921–1925; (b) Vorbrüggen, H.; Krolikiewicz, K. A simple synthesis of Δ^2-oxazolines, Δ^2-oxazines, Δ^2-thiazolines, and Δ^2-imidazolines. *Tetrahedron Lett.* **1981**, *22* (45), 4471–4474.
15. Neef, G.; Eder, U.; Sauer, G. One-step conversions of esters to 2-imidazolines, benzimidazoles, and benzothiazoles by aluminum organic reagents. *J. Org. Chem.* **1981**, *46* (13), 2824–2826.

16. (a) Hill, A. J.; Johnston, J. V. Amidines derived from ethylenediamine, II: Imidazolines. *J. Am. Chem. Soc.* **1954**, *76* (3), 922–923; (b) Bessel, M.; Rominger, F.; Straub, B. F. Modular trimethylene-linked Bisimidazol(in)ium salts. *Synthesis* **2010**, *9*, 1459–1466.
17. (a) Levesque, G.; Gressier, J. C.; Proust, M. 4,5-Dihydroimidazoles from dithiocarboxylic esters, thiocarboxamides, or nitriles. *Synthesis* **1981**, *12*, 963–964; (b) Korshin, E. E.; Sabirova, L. I.; Akhmadullin, A. G.; Levin, Y. A. Aminoamidines, 7: 2-(Arylaminomethyl)imidazolines and their acylated derivatives. *Russ. Chem. Bull.* **1994**, *43* (3), 431–438; (c) Crane, L. J.; Anastassiadou, M.; Stigliani, J.-L.; Baziard-Mouysset, G.; Payard, M. Reactions of some *ortho* and *para* halogenated aromatic nitriles with ethylenediamine: Selective synthesis of imidazolines. *Tetrahedron* **2004**, *60* (25), 5325–5330, and references cited therein; (d) Nasr-Esfahani, M.; Montazerozohori, M.; Moghadam, M.; Akhlaghi, P. Efficient catalytic synthesis of 2-imidazolines and bis-imidazolines with silica supported tungstosilicic acid. *Arkivoc* **2010**, *2*, 97–109, and references cited therein.
18. Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Kargar, H. Rapid and efficient synthesis of 2-imidazolines and bis-imidazolines under ultrasonic irradiation. *Tetrahedron Lett.* **2006**, *47* (13), 2129–2132.
19. (a) de la Hoz, A.; Díaz-Ortiz, A.; Mateo, M. C.; Moral, M.; Moreno, A.; Elguero, J.; Foces-Foces, C.; Rodríguez, M.; Sánchez-Migallón, A. Microwave-assisted synthesis and crystal structures of 2-imidazolines and imidazoles. *Tetrahedron* **2006**, *62* (25), 5868–5874; (b) Mohammadpoor-Baltork, I.; Abdollahi-Alibeik, M. Microwave-assisted facile and convenient synthesis of imidazolines. *Bull. Korean Chem. Soc.* **2003**, *24* (9), 1354–1356; (c) Pathan, M. Y.; Paike, V. V.; Pachmase, P. R.; More, S. P.; Ardhapure, S. S.; Pawar, R. P. Microwave-assisted facile synthesis of 2-substituted 2-imidazolines. *Arkivoc* **2006**, *15*, 205–210; (d) García, M. B.; Torres, R.; Orelli, L. R. Microwave-enhanced synthesis of cyclic amidines. *Tetrahedron Lett.* **2006**, *47* (28), 4857–4859.
20. (a) Wu, J.; Sun, X.; Xia, H. $Sc(OTf)_3$-catalized [3 + 2]-cycloaddition of aziridines with nitriles under solvent-free conditions. *Tetrahedron Lett.* **2006**, *47* (10), 1509–1512; (b) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. An efficient route to regioselective opening of *N*-tosylaziridines with zinc(II) halides. *Tetrahedron Lett.* **2005**, *46* (23), 4103–4106; (c) Cancellón, J. M.; Riego, E.; Suárez, J. R.; Garcia-Granda, S.; Díaz, M. R. Synthesis of enantiopure imidazolines through a Ritter reaction of 2-(1-aminoalkyl)aziridines with nitriles. *Org. Lett.* **2004**, *6* (24), 4499–4501; (d) Papa, C.; Tomasini, C. Synthesis and ring opening of methyl 2-alkyl-3-(alkyl/aryl)-1-benzoylaziridine-2-carboxylates: Synthesis of polysubstituted amino acids. *Eur. J. Org. Chem.* **2000**, *8*, 1569–1576; (e) Dai, L.; Lin, Y.; Hou, X.; Zhou, Y. Stereoselective reactions with imines. *Pure Appl. Chem.* **1999**, *71* (6), 1033–1040.
21. (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. Novel multicomponent reaction for the combinatorial synthesis of 2-imidazolines. *Org. Lett.* **2003**, *5* (20), 3759–3762; (b) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. Highly diastereoselective multicomponent synthesis of unsymmetrical Imidazolines. *Org. Lett.* **2002**, *4* (20), 3533–3535; (c) Han, Y.; Xie, Y.-X.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. Synthesis of highly substituted 2-imidazolines through a three-component coupling reaction. *Synthesis* **2008**, *1*, 87–93.
22. (a) Murai, K.; Takaichi, N.; Takahara, Y.; Fukushima, S.; Fujioka, H. One-pot condensation-oxidation of glyoxamide with 1,2-diamines providing imidazolines and benzimidazoles. *Synthesis* **2010**, *3*, 520–523, and references cited therein; (b) Gogoi, P.; Konwar, D. An efficient and one-pot synthesis of imidazolines and benzimidazoles via anaerobic oxidation of carbon–nitrogen bonds in water. *Tetrahedron Lett.* **2006**, *47* (1), 79–82; (c) Ishihara, M.; Togo, H. An efficient preparation of 2-imidazolines and imidazoles from aldehydes with molecular iodide and (diacetoxyiodo)bencene. *Synlett* **2006**, *2*, 227–230; (d) Ishihara, M.; Togo, H. Facile preparation of 2-imidazolines from aldehydes with

tert-butyl hypochlorite. *Synthesis* **2007**, *13*, 1939–1942; (e) Paliakov, E.; Elleboe, T.; Boykin, D. W. New synthons for the preparation of arylimidazolines and tetrahydropyrimidine analogues. *Synthesis* **2007**, *10*, 1475–1480.

23. (a) Perillo, I. A.; Lamdan, S. J. Synthesis of 1,2-diaryl-2-imidazolines. *J. Heterocyclic Chem.* **1970**, *7* (4), 791–798; (b) Perillo, I. A.; Caterina, M. C.; Lopez, J.; Salerno, A. Synthesis and study of 1-aryl-1*H*-4,5-dihydroimidazoles. *Synthesis* **2004**, *6*, 851–856; (c) Fernández, B. M.; Reverdito, A. M.; Paolucci, G. A.; Perillo, I. A. Synthesis and hydrolysis of substituted imidazolinium salts. Behaviour of the degradation products on varying pH. *J. Heterocyclic Chem.* **1987**, *24* (6), 1717–1724.
24. Recently, the synthesis of trisubstituted imidazolines by ciclyzation of the corresponding aminoamides with phosphorous oxychloride was reported: Lakner, F. J.; Parker, M. A.; Rogovoy, B.; Khvat, A.; Ivachtchenko, A. Synthesis of novel trisubstituted imidazolines. *Synthesis* **2009**, *12*, 1987–1990.
25. For reviews on microwave chemistry, see: (a) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH Ed.: Weinheim, Germany, 2002; (b) Kappe, C. O.; Dallinger, D. The impact of microwave synthesis on drug discovery. *Nat. Rev. Drug Discovery* **2006**, *5*(1), 51–63; (c) Roberts, B. A.; Strauss, C. R. Toward rapid, "Green", predictable microwave-assisted synthesis. *Acc. Chem. Res.* **2005**, *38* (8), 653–661; (d) Kappe, C. O. Controlled microwave heating in modern organic synthesis. *Angew. Chem. Int. Ed.* **2004**, *43* (46), 6250–6284.
26. (a) Yokoyama, M.; Yoshida, S.; Imamoto, T. Organic reactions using trimethylsilyl polyphosphate (PPSE): A convenient synthesis of nitriles from carboxamides. *Synthesis* **1982**, *7*, 591–592; (b) Hedrera, M.; Perillo, I. Polyphosphoric acid trimethylsilyl ester (PPSE) in the synthesis of heterocycles. *Trends Heterocycl. Chem.* **2002**, *8* (9), 105–111.
27. Göblyös, A.; Lázár, L.; Evanics, F.; Fülöp, F. Substituent effects in the ring-chain tautomerism of 1,2-diarylimidazolidines. *Heterocycles* **1999**, *51* (10), 2431–2438 and references cited therein.
28. (a) Salerno, A.; Ceriani, V.; Perillo, I. A. Reduction of substituted 1*H*-4,5-dihydroimidazolium salts. *J. Heterocyclic Chem.* **1992**, *29* (7), 1725–1733 and references cited therein; (b) Salerno, A.; Ceriani, V.; Perillo, I. A. Nucleophilic addition to substituted 1*H*-4,5-dihydroimidazolium salts. *J. Heterocyclic Chem.* **1997**, *34* (3), 709–716, and references cited therein.
29. Caterina, M. C.; Corona, M. V.; Perillo, I.; Salerno, A. An efficient synthesis of 1-acyl-3-arylimidazolidines catalyzed by Montmorillonite K-10 clay under microwave irradiation. *Heterocycles* **2009**, *78* (3), 771–781.