

An eco-friendly approach for the synthesis of 1,2,5-trisubstituted and 4-amino-1,2,5-tetrasubstituted imidazoles *via* a multi-component condensation

Hossein Mehrabi*, Farzaneh Alizadeh-Bami, Azam Meydani, and Soheila Besharat

Department of Chemistry, Vali-e-Asr University of Rafsanjan, 77176 Rafsanjan, Iran

E-mail: mehraby_h@yahoo.com

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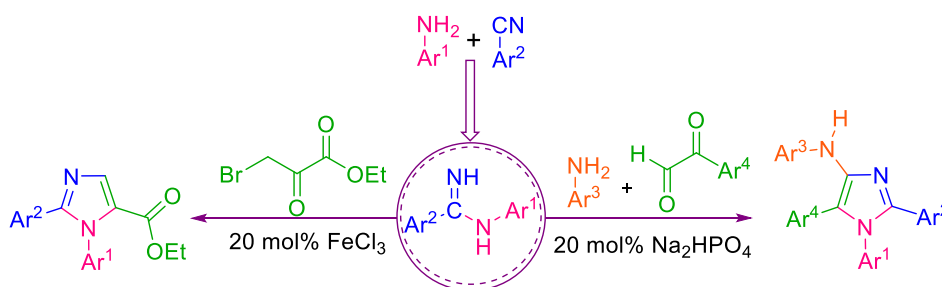
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Abstract

The synthesis of 1,2,5-trisubstituted and 4-amino-1,2,5-tetrasubstituted imidazoles was demonstrated *via* a two-step cyclo-condensation reaction of aryl amines, carbonitriles, and ethyl bromopyruvate or aryl amines and arylglyoxals in ethanol heated under reflux in the presence of iron (III) chloride (FeCl₃), and disodium phosphate (Na₂HPO₄) as catalysts, respectively. All the products were obtained in good to excellent yields and their structures were established from their spectroscopic data.



Keywords: Multi-component condensation, 1,2,5-trisubstituted imidazole, 4-amino-1,2,5-tetrasubstituted imidazole, arylglyoxal, ethyl bromopyruvate

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Introduction

Imidazoles are heterocyclic five-membered aromatic compounds with two 1,3 orientated nitrogen atoms, that have been of interest to organic chemists owing to their useful biological activities, such as, antimicrobial,¹ antitumor,² antiviral,³ antifungal,⁴ and antioxidant activity.⁵ Moreover, the imidazole moiety exists in many natural products such as histidine,⁶ histamine,⁷ and biotin.⁸ Imidazoles also appear as the core structural skeleton in many important drugs such as miconazole,⁹ clotrimazole,¹⁰ econazole,¹¹ losartan,¹² and eprosartan.¹³ Importantly, imidazoles bearing an amino group at the 4-position have attracted significant attention because they are valuable synthons for the synthesis of biologically active molecules; 4-aminoimidazoles have been used as the key intermediate for the synthesis of purine,^{14,15} and guanidine.¹⁶ Therefore, 4-aminoimidazoles exhibit various biological applications such as antibacterial agents (I),¹ anticancer agents (II),¹⁸ antidiabetic agents (III),¹⁹ kinase inhibitors (IV),^{20,21} and the treatment of Alzheimer's disease (V) (Fig. 1).²² Due to the biological importance of imidazoles, the synthesis of polysubstituted imidazoles and 4-aminoimidazoles has attracted much attention in organic synthesis.

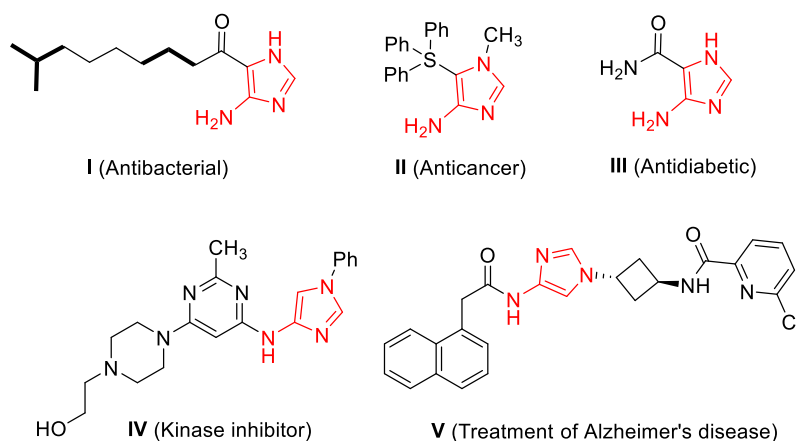


Figure 1. Selected drug molecules containing the 4-aminoimidazole moiety.

There are numerous reported syntheses of polysubstituted imidazoles and 4-aminoimidazoles, these include: (a) three or four component condensations of a 1,2-diketone, with an aldehyde, an amine or ammonium acetate by using various reagents or catalysts such as $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$,²³ *p*-toluenesulfonic acid (PTSA),²⁴ $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$,²⁵ $\text{Fe}_3\text{O}_4 @ \text{g-C}_3\text{N}_4$,²⁶ 3-*N*-morpholinopropanesulfonic acid (MOPS),²⁷ silica sulfuric acid (SSA),²⁸ ionic liquid,²⁹ Caro's acid-silica gel,³⁰ ultrasound irradiation;³¹ (b) [3+2] cycloaddition;^{32,33} (c) *via* Ugi/Passerini-reaction;³⁴ (d) aza-Wittig reaction;³⁵ and, (e) various other cyclization methods.^{36,37}

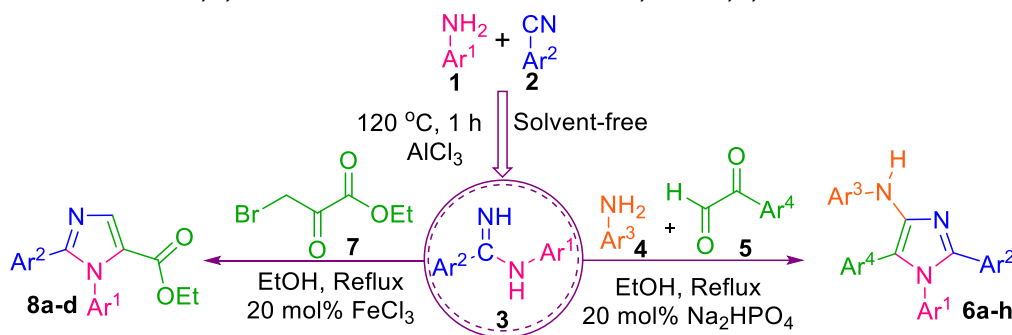
However, the above-mentioned methods suffer from drawbacks such as tedious experimental procedures, low yields, use of expensive reagents, and complex workup and purification. Therefore, the development of more general eco-friendly procedures for the synthesis of polysubstituted imidazoles and specially 4-amino-1,2,5-tetrasubstituted imidazoles from readily available starting materials remains an important task in organic chemistry.

With this in mind, and in continuation of our current studies on the development of new approaches for the synthesis of multi-substituted imidazoles,³⁸⁻⁴⁰ herein, we describe a facile and efficient protocol for the synthesis of 4-amino-1,2,5-tetrasubstituted and 1,2,5-trisubstituted imidazoles *via* a two-step, four or three-component reaction of aryl amines, carbonitriles, and aryl amines with arylglyoxals or ethyl bromopyruvate in the presence of disodium phosphate (Na_2HPO_4), and iron (III) chloride (FeCl_3) as a catalyst, respectively.

Results and Discussion

To initiate our study, the arylamidine **3** was prepared *via* the reaction of aniline **1** with carbonitrile **2** in the presence of AlCl_3 at $120\text{ }^\circ\text{C}$ for 1 h under solvent-free conditions. The arylamidine compounds were identified by the comparison of their physical and spectral data with those of authentic samples.⁴¹ Then, the optimised conditions for the condensation were established, using model compounds, arylamidine **3** (1 mmol), and electrophiles such as iminone resulting from aniline **4** (1 mmol) with arylglyoxal **5** (1 mmol) or ethyl bromopyruvate (**7**) (1 mmol) in the presence of Na_2HPO_4 (20 mol%), and FeCl_3 (20 mol%) as catalysts in ethanol heated at reflux for 12 h. The optimized reaction conditions were then used to synthesize and explore the scope of this novel transformation to give two series of 4-amino-1,2,5-tetrasubstituted imidazoles **6**, and 1,2,5-trisubstituted imidazoles **8**. As can be seen from Table 1, the nature of the electrophilic component affects the type of products formed: when the electrophile is an iminone resulting from aniline **4** with arylglyoxal **5** then product **6** is formed, but when the electrophile is ethyl bromopyruvate (**7**) then product **8** is formed. Also, the catalysts affect the product yields: in the presence of both Na_2HPO_4 and FeCl_3 as catalysts, a higher yield of the products **6** and **8** were obtained, respectively. Moreover, electronic effects and the nature of substituents on the aniline, the carbonitrile, and the arylglyoxal led to products with different reaction yields. When anilines containing electron-donating groups, were reacted with carbonitriles and the arylglyoxals containing electron-withdrawing groups, higher yields were obtained (Table 1).

Table 1. Synthesis of 4-amino-1,2,5-tetrasubstituted imidazoles **6**, and 1,2,5-trisubstituted imidazoles **8**.



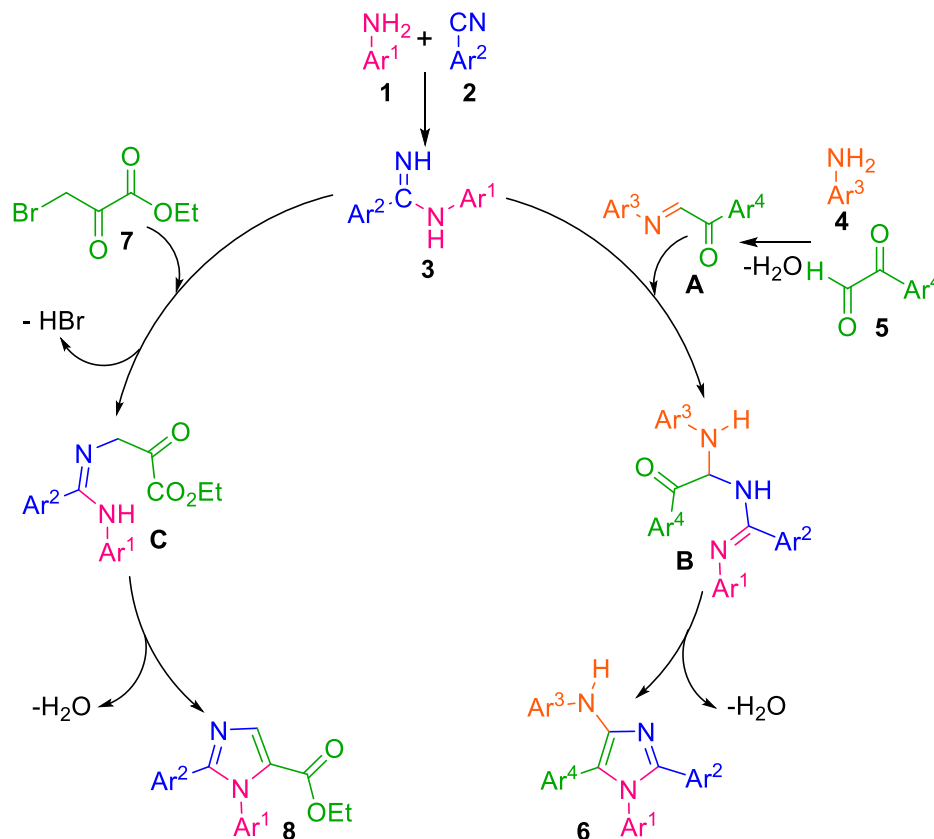
Product	Ar ¹	Ar ²	Ar ³	Ar ⁴	Catalyst	Yield (%) ^{a,b}
6a	4-MeOC ₆ H ₄	Ph	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	Na_2HPO_4	79
6b	4-BrC ₆ H ₄	2-ClC ₆ H ₄	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	Na_2HPO_4	72
6c	4-ClC ₆ H ₄	Ph	4-Tol	4-ClC ₆ H ₄	Na_2HPO_4	70
6d	4-BrC ₆ H ₄	Ph	4-Tol	4-ClC ₆ H ₄	Na_2HPO_4	68
6e	4-Tol	2-ClC ₆ H ₄	4-Tol	4-ClC ₆ H ₄	Na_2HPO_4	80
6f	4-Tol	2-ClC ₆ H ₄	3-O ₂ NC ₆ H ₄	4-ClC ₆ H ₄	Na_2HPO_4	75
6g	2,4-Me ₂ C ₆ H ₃	Ph	3-O ₂ NC ₆ H ₄	4-ClC ₆ H ₄	Na_2HPO_4	74
6h	4-Tol	2-ClC ₆ H ₄	4-MeOC ₆ H ₄	4-BrC ₆ H ₄	Na_2HPO_4	82
8a	Ph	2-ClC ₆ H ₄	-	-	FeCl_3	60
8b	4-BrC ₆ H ₄	2-ClC ₆ H ₄	-	-	FeCl_3	56
8c	4-ClC ₆ H ₄	Ph	-	-	FeCl_3	60
8d	4-Tol	Ph	-	-	FeCl_3	62

^a Isolated yields.

^b Reaction time was 13 h.

To the best of our knowledge, all the synthesized compounds were new, as such, they were characterized by ¹H and ¹³C NMR, IR, CHN analysis and melting points. For instance, the ¹H NMR spectrum of the compound **6a** consisted of two singlets at δ_{H} 3.59 and 3.73 for the methoxy groups in the product. The aromatic protons resonated in the region δ_{H} 6.45-7.91 and a broad singlet signal at δ_{H} 7.44 for the proton of the nitrogen group were also observed. The ¹³C NMR spectrum of compound **6a** exhibited 21 distinct signals in agreement with the proposed structure. In the IR spectrum, the NH and C=N groups absorption were observed at 3409 and 1608 cm⁻¹. Partial assignments of these resonances for the other products are given in the experimental section.

A proposed mechanism for the formation of 4-amino-1,2,5-tetrasubstituted imidazoles **6** and 1,2,5-trisubstituted imidazoles **8** is described in Scheme 1. The nature of the electrophile was different, so that: 4-amino-1,2,5-tetrasubstituted imidazoles **6** formed *via* four steps; at first, based on the result in the current study and our previous report,⁴⁰ arylamidine **3** is formed by the addition of the aniline **1** to the carbonitrile **2** at 120 °C for 1 h under solvent-free conditions. Also, iminone **A** is formed through Knoevenagel condensation of the aniline **4** to the arylglyoxal **5**, in agreement with our previous report.⁴² Then, on addition of arylamidine **3**, the formation of intermediate **B** occurred *via* intermolecular nucleophilic addition of the nitrogen at the imine carbon atom of **A**, which subsequently undergoes intramolecular nucleophilic addition the second nitrogen to the carbonyl group and elimination of H₂O affording the 4-amino-1,2,5-tetrasubstituted imidazole **6**. 1,2,5-Trisubstituted imidazole **8** is formed, according to the mechanism of the previous works.⁴³⁻⁴⁵ Firstly, arylamidine **3** is formed by the addition of the aniline **1** to the carbonitrile **2** at 120 °C for 1 h under solvent-free conditions. Then, on addition of arylamidine **3**, the formation of intermediate **C** occurred *via* a nucleophilic addition reaction of the nitrogen to methylene group in ethyl bromopyruvate (**7**) followed by the elimination of HBr. In the last step, intermediate **C** undergoes intramolecular nucleophilic addition the second nitrogen to the carbonyl group and elimination of H₂O to form the 1,2,5-trisubstituted imidazole **8**.



Scheme 1. Proposed mechanism for the synthesis of 4-amino-1,2,5-tetrasubstituted imidazoles **6**, and 1,2,5-trisubstituted imidazoles **8**.

Conclusions

In summary, we have successfully described a convenient and efficient protocol for the synthesis of two series of 4-amino-1,2,5-tetrasubstituted and 1,2,5-trisubstituted imidazoles *via* a two-step, four or three-component reaction of aryl amines, carbonitriles, and aryl amines with arylglyoxals or ethyl bromopyruvate in the presence of disodium phosphate, and iron (III) chloride as catalyst, respectively. The catalysts are readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. The notable features offered by this method are the environmentally friendly procedure, readily available starting materials, easy workup, and good to high product yields.

Experimental Section

General. All chemicals were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All melting points were obtained by Barnstead Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by TLC and all yields refer to isolated products. NMR spectra were obtained on a Varian 500 MHz spectrometer (¹H NMR at 500 MHz, ¹³C NMR at 125 MHz) using TMS as an internal standard; coupling constants are measured in Hz. Infrared spectra were recorded on a Bruker FT-IR Equinox-55 spectrophotometer in KBr with absorption in cm⁻¹. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

General procedure for the synthesis of arylamidine (3). The mixture of aryl amine **1** (1.2 mmol), carbonitrile **2** (1.0 mmol), and AlCl₃ (1.0 mmol) was charged to a round bottom flask. The mixture was stirred at 120 °C for 1 h, then ice water (20 mL) was added to round bottom flask heat mixture, after 10% sodium hydroxide solution was added with a mixture of reaction to obtain pH = 14, and the precipitate was extracted with CHCl₃ (3 × 7 mL), dried (MgSO₄), and the solvent evaporated. The colorless crude product was crystallized from toluene.

General procedure for the synthesis of compounds 6a-h. A mixture of arylamine **4** (1.0 mmol) and arylglyoxal **5** (1.0 mmol) was stirred in EtOH (15 mL) heated at reflux for 2 h to give iminone. Then, arylamidine **3** (1.0 mmol) was added in the presence of disodium phosphate (20 mol%) under reflux conditions for 10 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and the resulting crude product was purified by washing with EtOH to give the pure compounds **6a-h** (68–82%).

General procedure for the synthesis of compounds 8a-d. A mixture of arylamidine **3** (1.0 mmol) and ethyl bromopyruvate (**7**) (1.0 mmol) was stirred in EtOH (15 mL) in the presence of iron (III) chloride (20 mol%) heated at reflux for 12 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and the viscous residue was purified by plate chromatography (20 × 20 cm) using *n*-hexane/EtOAc (25:75) as eluent to give the pure compounds **8a-d** (56–62%).

5-(4-Chlorophenyl)-*N*,1-bis(4-methoxyphenyl)-2-phenyl-1*H*-imidazol-4-amine (6a). Colorless solid; mp: 118–120 °C. IR ν/cm^{-1} (KBr): 3409 (NH), 1608 (C=N) cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆): δ 3.59 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 6.45 (d, *J* 9.0, 2H, ArH), 6.64 (d, *J* 9.0, 2H, ArH), 6.91 (d, *J* 9.0, 2H, ArH), 7.13–7.38 (m, 9H, ArH), 7.44 (bs, 1H, NH), 7.91 (d, *J* 9.0, 2H, ArH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ _c 55.5, 55.7, 114.7, 115.1, 127.1, 128.3, 128.6, 128.6, 128.6, 128.7, 129.3, 129.5, 129.9, 131.0, 131.1, 140.4, 144.2, 152.3, 156.7, 159.5, 161.1. Anal. Calcd for C₂₉H₂₄ClN₃O₂ (481.98): C, 72.27; H, 5.02; N, 8.72. Found: C, 72.53; H, 5.07; N, 8.65.

1-(4-Bromophenyl)-2-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(4-methoxyphenyl)-1*H*-imidazol-4-amine (6b). Colorless solid; mp: 116–118 °C. IR ν/cm^{-1} (KBr): 3340 (NH), 1614 (C=N) cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆): δ _H 3.81 (s, 3H, OCH₃), 6.53–6.58 (m, 3H, ArH), 6.91 (d, 8.5, 2H, ArH), 7.06 (d, *J* 8.5, 2H, ArH), 7.51–7.64 (m, 7H, ArH), 8.20 (d, *J* 8.5, 2H, ArH), 8.47 (bs, 1H, NH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ _c 55.9, 115.1, 124.4, 125.7, 127.0, 127.9, 128.3, 128.6, 129.0, 129.3, 130.0, 130.6, 131.1, 131.4, 131.7, 132.5, 134.5, 138.8, 140.9, 141.5, 154.8, 160.6. Anal. Calcd for C₂₈H₂₀BrCl₂N₃O (565.29): C, 59.49; H, 3.57; N, 7.43. Found: C, 59.81; H, 3.61; N, 7.26.

1,5-Bis(4-chlorophenyl)-2-phenyl-*N*-(*p*-tolyl)-1*H*-imidazol-4-amine (6c). Colorless solid; mp: 122–124 °C. IR ν/cm^{-1} (KBr): 3409 (NH), 1617 (C=N) cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆): δ _H 2.28 (s, 3H, CH₃), 6.33 (d, *J* 8.5, 1H, ArH), 6.43 (d, *J* 8.5, 2H, ArH), 6.75 (d, *J* 8.5, 2H, ArH), 6.83 (d, *J* 8.5, 2H, ArH), 7.01 (d, *J* 8.5, 2H, ArH), 7.15–7.22 (m, 4H, ArH), 7.53 (d, *J* 8.5, 2H, ArH), 7.70 (bs, 1H, NH), 7.92 (d, *J* 8.5, 2H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ _c 21.4, 113.4, 122.2, 125.7, 127.3, 127.8, 128.4, 128.5, 128.6, 128.7, 128.7, 129.1, 129.2, 129.3, 129.6, 130.1, 140.5, 144.1, 144.3, 162.9. Anal. Calcd for C₂₈H₂₁Cl₂N₃ (470.40): C, 71.49; H, 4.50; N, 8.93. Found: C, 71.13; H, 4.46; N, 8.86.

1-(4-Bromophenyl)-5-(4-chlorophenyl)-2-phenyl-*N*-(*p*-tolyl)-1*H*-imidazol-4-amine (6d). Colorless solid; mp: 127–129 °C. IR ν/cm^{-1} (KBr): 3412 (NH), 1617 (C=N) cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆): δ _H 2.29 (s, 3H, CH₃), 6.43 (d, *J* 8.5, 2H, ArH), 6.84 (d, *J* 8.5, 2H, ArH), 7.15–7.39 (m, 9H, ArH), 7.59 (d, *J* 9.0, 2H, ArH), 7.70 (bs, 1H, NH), 7.91 (d, *J* 9.0, 2H, ArH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ _c 20.5, 113.3, 122.2, 125.7, 127.3, 128.4, 128.6, 128.6, 128.7, 128.8, 128.9, 129.1, 129.3, 130.1, 130.4, 132.5, 140.3, 144.1, 144.3, 158.4. Anal. Calcd for C₂₈H₂₁BrClN₃ (514.85): C, 65.32; H, 4.11; N, 8.16. Found: C, 65.50; H, 4.15; N, 8.03.

2-(2-Chlorophenyl)-5-(4-chlorophenyl)-*N*,1-di-*p*-tolyl-1*H*-imidazol-4-amine (6e). Colorless solid; mp: 130–132 °C. IR ν/cm^{-1} (KBr): 3414 (NH), 1613 (C=N) cm^{-1} . ¹H NMR (500 MHz, DMSO-*d*₆): δ _H 2.06 (s, 3H, CH₃), 2.11 (s, 3H,

CH₃), 6.42 (d, *J* 9.0, 1H, ArH), 6.70-6.78 (m, 3H, ArH), 6.87-6.91 (m, 4H, ArH), 7.25 (d, *J* 9.0, 1H, ArH), 7.36-7.50 (m, 5H, ArH), 7.50 (bs, 1H, NH), 7.58 (d, *J* 8.5, 2H, ArH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 20.4, 20.8, 113.4, 113.7, 122.2, 125.7, 126.3, 127.2, 127.4, 127.8, 128.3, 129.4, 129.6, 129.9, 130.4, 131.4, 131.5, 132.3, 132.5, 144.8, 146.0, 156.8, 161.3.

2-(2-Chlorophenyl)-5-(4-chlorophenyl)-*N*-(3-nitrophenyl)-1-(*p*-tolyl)-1*H*-imidazol-4-amine (6f). Colorless solid; mp: 142-144 °C. IR ν/cm⁻¹ (KBr): 3403 (NH), 1619 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 2.10 (s, 3H, CH₃), 6.87-6.95 (m, 6H, ArH), 7.22 (d, *J* 8.5, 2H, ArH), 7.28 (bs, 1H, NH), 7.40-7.50 (m, 5H, ArH), 7.63 (d, *J* 8.5, 2H, ArH), 8.11 (d, *J* 9.0, 1H, ArH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 20.8, 112.2, 120.8, 125.8, 126.5, 127.2, 127.5, 127.9, 128.4, 129.2, 129.3, 129.5, 129.6, 130.0, 131.5, 131.6, 131.6, 132.5, 135.4, 135.5, 136.5, 141.0, 148.5, 161.4. Anal. Calcd for C₂₈H₂₀Cl₂N₄O₂ (515.39): C, 65.25; H, 3.91; N, 10.87. Found: C, 65.41; H, 3.97; N, 10.65.

5-(4-Chlorophenyl)-1-(2,4-dimethylphenyl)-*N*-(3-nitrophenyl)-2-phenyl-1*H*-imidazol-4-amine (6g). Colorless solid; mp: 146-148 °C. IR ν/cm⁻¹ (KBr): 3414 (NH), 1620 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 2.06 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 6.78-6.95 (m, 4H, ArH), 7.22-7.32 (m, 5H, ArH), 7.45-7.59 (m, 5H, ArH, NH), 7.68 (d, *J* 8.5, 2H, ArH), 8.11 (d, *J* 8.5, 1H, ArH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 20.8, 20.9, 119.6, 119.7, 120.3, 127.5, 127.7, 128.3, 128.4, 128.7, 129.0, 129.2, 129.4, 130.6, 130.8, 131.5, 131.9, 131.9, 132.5, 143.1, 148.3, 148.4, 148.7, 149.1, 162.3. Anal. Calcd for C₂₉H₂₃ClN₄O₂ (494.98): C, 70.37; H, 4.68; N, 11.32. Found: C, 70.32; H, 4.60; N, 11.19.

5-(4-Bromophenyl)-2-(2-chlorophenyl)-*N*-(4-methoxyphenyl)-1-(*p*-tolyl)-1*H*-imidazol-4-amine (6h). Colorless solid; mp: 125-127 °C. IR ν/cm⁻¹ (KBr): 3377 (NH), 1606 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 2.11 (s, 3H, CH₃), 3.56 (s, 3H, OCH₃), 6.46 (d, *J* 8.5, 2H, ArH), 6.55 (t, *J* 8.5, 2H, ArH), 6.84-6.89 (m, 4H, ArH), 7.04 (d, *J* 8.5, 1H, ArH), 7.25 (t, *J* 8.5, 1H, ArH), 7.40 (d, *J* 8.5, 2H, ArH), 7.56 (d, *J* 8.5, 2H, ArH), 7.62 (t, *J* 8.5, 1H, ArH), 8.19 (d, *J* 8.5, 1H, ArH), 8.46 (bs, 1H, NH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 20.8, 65.3, 115.1, 118.0, 121.7, 124.4, 126.3, 127.8, 128.3, 129.0, 129.3, 129.4, 129.9, 132.4, 133.4, 134.5, 135.0, 136.8, 141.1, 143.2, 146.9, 154.8, 161.2.

Ethyl 2-(2-chlorophenyl)-1-phenyl-1*H*-imidazole-5-carboxylate (8a). Brown solid; mp: 158-160 °C. IR ν/cm⁻¹ (KBr): 1728 (C=O), 1598 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 1.32 (t, *J* 5.6, 3H, CH₃), 4.36 (q, *J* 5.6, 2H, CH₂), 7.23-7.48 (m, 7H, ArH), 7.59 (d, *J* 8.5, 2H, ArH), 8.33 (s, 1H, CH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 14.3, 59.8, 124.8, 127.2, 127.8, 128.9, 129.2, 129.4, 131.6, 132.5, 132.9, 133.1, 134.5, 136.4, 144.7, 162.1. Anal. Calcd for C₁₈H₁₅ClN₂O₂ (326.78): C, 66.16; H, 4.63; N, 8.57. Found: C, 66.47; H, 4.71; N, 8.54.

Ethyl 1-(4-bromophenyl)-2-(2-chlorophenyl)-1*H*-imidazole-5-carboxylate (8b). Brown solid; mp: 151-153 °C. IR ν/cm⁻¹ (KBr): 1727 (C=O), 1549 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 1.32 (t, *J* 5.6, 3H, CH₃), 4.28 (q, *J* 5.6, 2H, CH₂), 7.22 (d, *J* 8.5, 2H, ArH), 7.45-7.49 (m, 3H, ArH), 7.53 (d, *J* 8.5, 2H, ArH), 7.65 (d, *J* 9.0, 1H, ArH), 8.38 (s, 1H, CH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 14.7, 60.3, 121.9, 127.3, 127.4, 127.5, 127.7, 128.3, 129.6, 129.8, 132.2, 132.7, 133.5, 136.2, 145.1, 162.4. C₁₈H₁₄BrClN₂O₂ (405.68): C, 53.29; H, 3.48; N, 6.91. Found: C, 53.37; H, 3.52; N, 6.83.

Ethyl 1-(4-chlorophenyl)-2-phenyl-1*H*-imidazole-5-carboxylate (8c). Brown solid; mp: 163-165 °C. IR ν/cm⁻¹ (KBr): 1724 (C=O), 1563 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 1.30 (t, *J* 5.8, 3H, CH₃), 4.27 (q, *J* 5.8, 2H, CH₂), 7.21-7.44 (m, 7H, ArH), 7.63 (d, *J* 8.0, 2H, ArH), 8.31 (s, 1H, CH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ_c 15.3, 59.73, 122.6, 126.3, 127.8, 128.1, 129.4, 130.8, 132.9, 133.2, 134.5, 138.7, 146.6, 161.7. C₁₈H₁₅ClN₂O₂ (326.78): C, 66.16; H, 4.63; N, 8.57. Found: C, 66.32; H, 4.69; N, 8.48.

Ethyl 2-phenyl-1-(*p*-tolyl)-1*H*-imidazole-5-carboxylate (8d). Brown solid; mp: 148-150 °C. IR ν/cm⁻¹ (KBr): 1739 (C=O), 1592 (C=N) cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 1.29 (t, *J* 5.6, 3H, CH₃), 2.34 (s, 3H, CH₃), 4.27 (q, *J* 5.6, 2H, CH₂), 7.22 (d, *J* 8.5, 2H, ArH), 7.27 (d, *J* 8.5, 2H, ArH), 7.32-7.37 (m, 5H, ArH), 8.11 (s, 1H, CH). ¹³C

NMR (125 MHz, DMSO- d_6): δ_C 14.9, 21.1, 60.8, 122.7, 125.6, 127.8, 128.1, 129.2, 130.5, 132.3, 132.8, 134.4, 135.2, 145.8, 160.9. $C_{19}H_{18}N_2O_2$ (306.37): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.22; H, 5.83; N, 9.10.

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