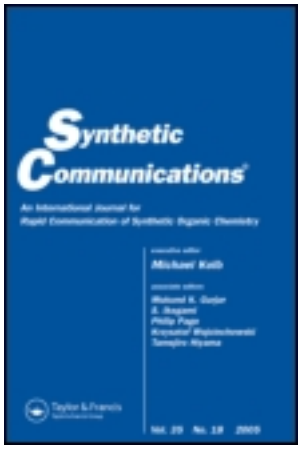

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Microwave-Assisted Synthesis of N-(1H-Imidazoline-2-yl)-1H-benzimidazol-2-amine and Its N-Functionalized Derivatives

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MICROWAVE-ASSISTED SYNTHESIS OF *N*-(1*H*-IMIDAZOLINE-2-YL)-1*H*-BENZIMIDAZOL-2-AMINE AND ITS *N*-FUNCTIONALIZED DERIVATIVES

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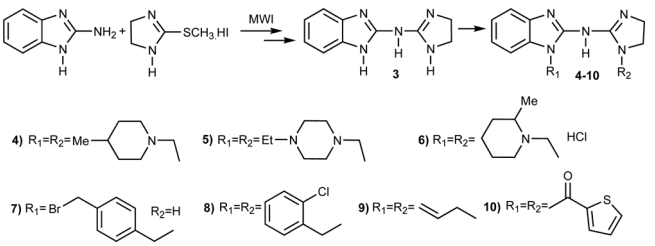
GRAPHICAL ABSTRACT



Abstract N-*(1*H-*Imidazoline-2-yl)-1*H-*benzimidazol-2-amine hydroiodide was synthesized with excellent yields, and it was converted to free base by using triethylamine under microwave irradiation (MWI) conditions. Its new Mannich, benzyl, and allyl derivatives were synthesized.*

Keywords 2-Aminobenzimidazole; guanidine; Mannich base; microwave irradiation

INTRODUCTION

The benzimidazole ring system is an important nucleus for drug discovery and represents the core structure of a number of biologically significant molecules.[1–3] 2-Aminobenzimidazoles and 2-aminoimidazolines exhibit diverse pharmacological features.[4–6] These compounds are compounds bearing guanidine functional groups. This functional group is found in numerous biologically active natural products and several drugs.[7,8] In addition to their biological roles, guanidine derivatives are widely utilized in synthetic organic chemistry as strong bases. Because of their strongly basic character, guanidines can be considered superbases, and chiral guanidines are of potential use as asymmetric reagents.[9]

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There are diverse synthetic routes to cyclic 2-aminobenzimidazoles; however, the search for a high-yielding synthesis of these useful molecules is still ongoing.[10–12] Direct synthetic approaches for the preparation of guanidine-derived products in good yields under mild conditions are of great interest in medicinal chemistry. The biological and pharmacological activities of imidazolines and the benzimidazoles prompted the development of microwave-assisted synthetic strategies for preparation of biheterocyclic dihydroimidazoles analogs.

We have previously reported the synthesis of some benzimidazole and imidazoline compounds.[13–16] This article reports the first microwave–assisted synthesis of *N*-(1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine and its Mannich bases and benzyl and allyl derivatives. These compounds have not been described in the literature until now, except for compound **8**.[17]

RESULTS AND DISCUSSION

Although 2-aminobenzimidazoles play an important role in biological and pharmaceutical areas, efficient methods for the synthesis of these molecules are limited. The classical approaches to 2-aminobenzimidazoles employ *o*-phenylenediamine as precursors. Existing methods for the solution-phase synthesis of 2-aminobenzimidazole derivatives typically involve cyclization of an *o*-phenylenediamine using cyanogen bromide or its equivalent to provide the 2-aminobenzimidazole ring system.[18] Other approaches include the aromatic nucleophilic substitution (S_NAr) reactions of 2-chlorobenzimidazoles, *N*-nucleophiles, and Pd-catalyzed coupling of 2-halobenzimidazoles with amines.[19] These methods might suffer from the limited availability of the starting materials, harsh conditions, poor yields, narrow scope, and/or expensive catalysts. Therefore, more efficient and facile routes to these useful molecules under mild conditions are needed.

The aim of this study is to synthesize *N*-(1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine using both microwave and conventional synthetic methods, using different precursors than those previously reported.[13,14] In this work, the new derivatives of this compound were synthesized. These compound contains both imidazoline and benzimidazole rings. They are polyfunctional planar molecule with a delocalized π electronic system. Compound **3** contains five nitrogen atoms, which may act as basic centers, and it has five labile N–H bonds.[20]

2-Methylmercapto-4,5-dihydroimidazole hydroiodide **(1)** was used as the starting reagent. Synthesis of *N*-(1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine hydroiodide **(2)** was carried out from the reaction of 2-aminobenzimidazole with compound **1**. The reactions were tried using several solvents such as pyridine, methanol, ethanol, and dimethylformamide (DMF) to synthesize compound **2**. The reaction was successfully carried out by refluxing with conventional heating in pyridine for 12 h. The product was obtained as the hydroiodide salt of compound **3**. The yield of the reaction was 75% with this conventional method. Test reactions were carried out to modify the conventional method for microwave-assisted reaction conditions. These reactions were performed both atmosphere pressure (Figure 1) and 1 bar pressure under microwave irradiation conditions in a sealed tube. The product was isolated in good yields (90%) in both cases. Compound **2** was converted to

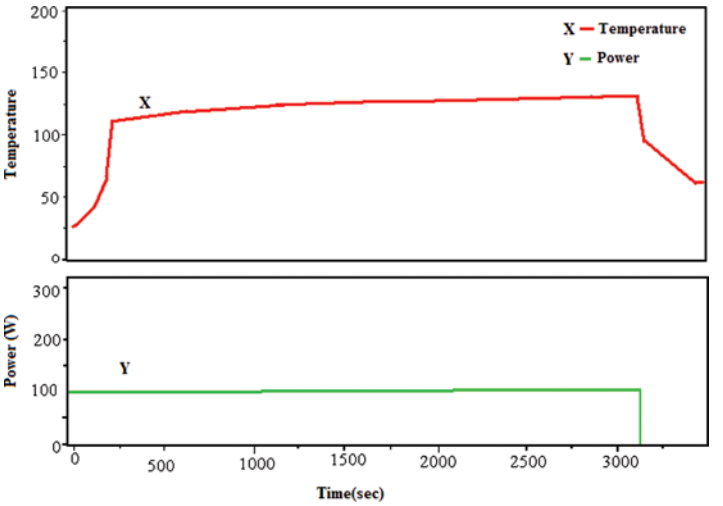
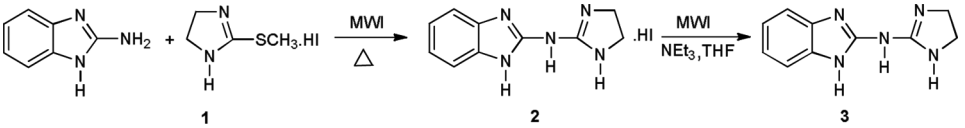


Figure 1. Profile of change in temperature under microwave irradiation by modulation of emitted power for the reaction of 2-aminobenzimidazole with compound **1** (ramp time, 4 min; and hold time, 52 min; power, 100 W). (Figure is provided in color online.)

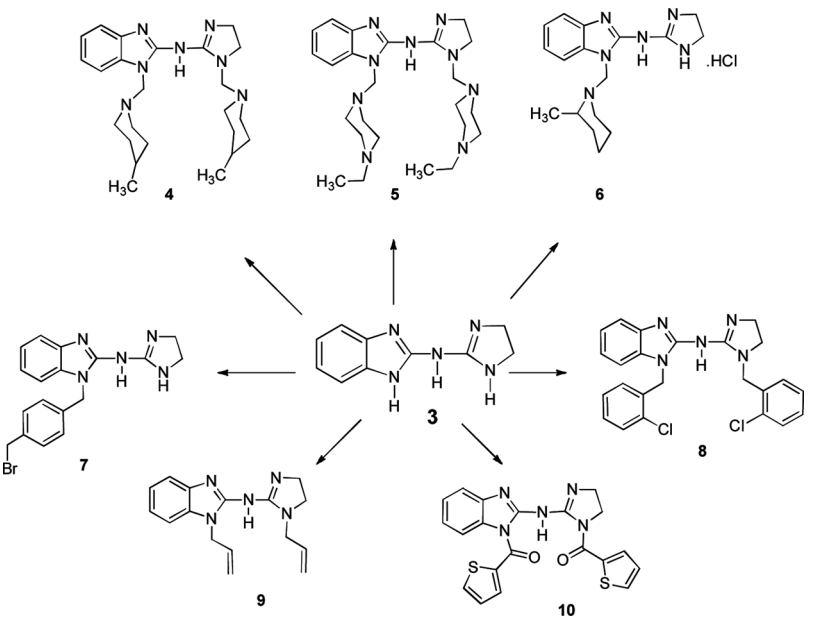
the free base by refluxing with triethylamine for 10 min under microwave irradiation conditions (Scheme 1).

In the light of the available literature and as a continuation of our previous studies on benzimidazole- and imidazoline-derived compounds, we aimed to synthesize some new benzimidazole derivatives as potential biologic active compounds. Because benzimidazole derivatives including piperidine and the piperazine core are widely used in medicine and pharmacology, we aimed to design and synthesize some new 4-methylpiperidine and 2-methyl piperazine derivatives of compound **3**.

Compound **3** has three appropriate NH functional groups on which to perform nucleophilic substitution and aminomethylation (Mannich bases) reactions. These reactions were carried out on NH functional groups with four different types of reactivities in different reaction conditions. In spite of similar compounds have been synthesized in the literature previously,[21,22] these derivatives were first synthesized by treatment of compound **3** with 4-methylpiperidine, N-ethyl piperazine, or 2-methlypiperidine and formaldehyde. In Mannich reactions, different molar ratios of formaldehyde and various saturated cyclic secondary amines were used to synthesize the compounds **4–6**. In the case of excessive use of 4-methyl piperazine or 4-ethyl piperazine, the compounds **4** or **5** were only isolated in these reactions. Synthesis of



Scheme 1. Synthetic pathway for the synthesis of compound **3**.



Scheme 2. Synthesis of Mannich bases, benzyl and allyl derivatives of **3**.

compound **6** was performed with acid catalysis, and the product was isolated as the HCl salt[23] The synthesis of this compound failed without acid catalysis. *N*-Benzyl derivatives of **3** (compounds **7** and **8**) have been synthesized by using 1,4-bis(bromomethyl)benzene and 1-chloro-2-(chloromethyl) benzene in dimethylsulfoxide (DMSO) and basic medium. The structure of **8** was characterized by infrared (IR) and ^{1}H NMR spectroscopy and single-crystal x-ray diffraction.[17] The synthesis of *N*-allyl derivative of **3** (compound **9**) was carried out by the reaction of **3** with allyl bromide. Compound **10** was obtained by reacting **3** with thiophene-2-carbonyl chloride in tetrahydrofuran (THF) and basic medium. (Scheme 2) IR and ^{1}H NMR spectra clearly indicated the formation of these products.

CONCLUSION

In summary, an efficient strategy for the synthesis of *N*-(1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine was developed. The reaction time was reduced from hours to minutes. The compound that might possess biological and pharmaceutical activities was easily synthesized in good yields via a microwave-assisted method. Mannich, benzyl, and allyl derivatives of this new guanidine compound were first synthesized by aminomethylation and nucleophilic substitution reactions.

EXPERIMENTAL

All reagents were of commercial quality, and solvents were used without further purification. IR spectra were determined on a Perkin-Elmer Spectrum One

Fourier transform–infrared (FT-IR) spectrometer. Thin-layer chromatography (TLC) was carried out on aluminum sheets (105) precoated with silica gel 60 F254 (Merck). Column chromatography was carried out on silica gel 60 (40–63 *m*M). Melting points (uncorrected) were determined with an Electrothermal IA 9100 apparatus. NMR spectra were recorded on Bruker 300-MHz and 400-MHz spectrometers. Chemical shifts δ are reported in parts per million (ppm) relative to $CHCl_3$ (^{1}H NMR 7.27), $CDCl_3$ (^{13}C NMR 77.0), and dimethylsulfoxide (DMSO) (^{1}H NMR 2.51 and 3.36 for water present in DMSO), DMSO-d_6(^{13}C NMR 39.51), and tetramethylsilane (TMS) as internal standard. The microwave-assisted reactions were performed with a single-mode CEM Discover Labmate instrument (producing continuous irradiation at 2450 MHz), which has an in situ magnetic stirrer, irradiation monitored by PC computer, IR measurement, and continuous feedback temperature control.

Compound 2

Conventional synthesis of compound 2. 2-Aminobenzimidazole (22.5 mmol) and 2-methylmercapto-4,5-dihydroimidazole hydroiodide (22.5 mmol) were dissolved in pyridine (30 mL), and the mixture was refluxed for 12 h. *Caution:* The noxious gas CH_3SH evolves during the synthesis, and it should be trapped with a concentrated aqueous solution of NaOH and then destroyed with sodium hypochlorite. After the reaction completed, pyridine was evaporated under vacuum. The crude product was dissolved in ethanol (2 mL) and then diethyl ether (30 mL) was added. The precipitate was filtered off and dried in vacuum. The products were purified by crystallization from ethanol.

Microwave-irradiation synthesis of compound 2. 2-Aminobenzimidazole (22.5 mmol) and 2-methylmercapto-4,5-dihydroimidazole hydroiodide (22.5 mmol) was dissolved in pyridine (30 mL), and the mixture was irradiated in the microwave oven at 100 W for 52 min at 125 °C. The next process is as described in the conventional synthesis method.

***N*-(1*H*-Imidazoline-2-yl)-1*H*-benzimidazol-2-amine hydroiodide (compound 2).** Yield 90%, white powder, mp 239–242 °C (ethanol); IR (KBr) υ_{max}: 3465 (benzimidazole N-H stretching), 3383 ($^+$N-H stretching), 3176 (N-H stretching), 2892 (aliphatic C-H stretching), 1634 (C=N$^+$ stretching), 1591 (C=C stretching), 1535 (N-H bending). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.65 (s, 4H, imidazoline CH_2), 7.19–7.37 (m, 4H, Ar-H), 8.38 (s, 2H, HI and endo NH), 12.43 (s, 2H, benzimidazole NH and exo NH). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 44.54, 111.83, 123.34, 130.72, 152.50, and 160.93, Anal. calcd. for $C_{10}H_{12}N_5I$ (329,14): C, 36.49; H, 3.67; N, 21.28. Found: C, 36.56; H, 3.89; N, 21.85.

Compound 3

Synthesis of compound 3. A solution of **2** (22.5 mmol) in 100 mL (THF) and 9.3 mL triethylamine (67.6 mmol) was added. The mixture was refluxed for 10 min under microwave irradiation conditions (ramp time, 2 min; hold time, 10 min; power, 100 W). The solution was then evaporated under vacuum, and the resulting oil was

washed with water and dried. The crude product was purified by column chromatography on silica gel using 1:1 chloroform/methanol as eluent to give compound **3** in 60% yield.

***N*-(1*H*-Imidazoline-2-yl)-1*H*-benzimidazol-2-amine (compound 3).** White powder, mp 249–252 °C (ethanol); IR (KBr) υ_{max}: 3398 (benzimidazole N-H stretching), 3238 (N-H stretching), 3141 (imidazoline N-H stretching), 2856 (aliphatic C-H stretching), 1645 (C=N stretching), 1615 (C=C stretching), 1536 (N-H bending). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.55 (s, 4H, imidazoline CH_2), 6.86–7.16 (m, 4H, Ar-H), 7.83 (broad peak, 2H, imidazoline NH), 11.09 (s, 1H, benzimidazole NH); it was made D_2O exchange. ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 43.51, 113.48, 121.96, 139.51, 160.58, and 164.17. Anal. calcd. for $C_{10}H_{11}N_5$ (201.23): C, 59.69; H, 5.51; N, 34.80, Found: C, 59.83; H, 5.75; N, 34.91.

N-(1*H*-Imidazoline-2-yl)-1*H*-benzimidazol-2-amine Derivatives: (Compounds 4–10)

General procedure for synthesis of Mannich derivatives (compounds 4 and 5). A solution of compound **3** (0.995 mmol) in methanol (20 mL) was stirred at room temperature for 2 h with aqueous formaldehyde (37%, 2.98 mmol) and 1.99 mmol secondary amine such as 2-methyl piperazine, 1-ethylpiperazine (d: 0.899 g cm^{-3}), and 4-methylpiperidine (d: 0.838 g cm^{-3}). The solvent was removed on a rotary evaporator. The residue was mixed with methanol, and the precipitate formed was filtered and then recrystallized from ethanol.

1-{(4-Methylpiperidin-1-yl)methyl}-*N*-[1-(4-methylpiperidin-1-yl)methyl}-1*H*-imidazoline-2-yl]-1*H*-benzimidazol-2-amine (4). Yield 83%, yellow powder, mp 162–164 °C (ethanol); IR (KBr) υ_{max}: 3224 (N-H stretching), 3047–3034 (C=C-H stretching), 2943–2784 (aliphatic C-H stretching), 1610 (C=N stretching), 1597 (C=C stretching), 1499 (N-H bending). ^{1}H NMR ($CHCl_3$-d, 300 MHz) δ: 0.86 (d, 3H, $J = 4$ Hz), 0.93 (d, 3H, $J = 4$ Hz), 1.20 (m, 5H), 1.57 (m, 5H), 2.17–2.26 (m, 4H), 2.92 (d, 2H, $J = 12$ Hz), 3.11(d, 2H, $J = 12$ Hz), 3.61–3.69 (m, 4H), 4.17 (s, 2H), 4.96 (s, 2H), 7.04–7.42 (m, 4H, Ar-H), 8.98 (broad peak 1H), ^{13}C NMR ($CHCl_3$-d, 75 MHz), δ: 21.96, 30.04, 30.78, 31.41, 34.29, 46.8, 51.50, 51.70, 63.91, 67.31, 109.09, 115.93, 119.67, 120.60, 134.86, 141.71, 158.84, 160.58, Anal. calcd. for $C_{24}H_{37}N_7$ (423,60): C, 68.05; H, 8.80; N, 23.15. Found: C, 68.23; H, 8.93; N, 23.76.

1-{(4-Ethylpiperazin-1-yl)methyl}-*N*-[1-{(4-ethylpiperazin-1-yl)methyl}-1*H*-imidazoline-2-yl]-1*H*-benzimidazol-2-amine (5). Yield 75%, oil; IR (KBr) υ_{max}: 3250 (N H stretching), 3051 (C=C-H stretching), 2969–2850 (aliphatic C-H stretching), 1618 (C=C stretching), 1504 (N-H bending). ^{1}H NMR ($CHCl_3$-d, 300 MHz) δ: 1.09–1.19 (m, 6H, CH_3), 2.13–2.29 (m, 20 H piperazine CH_2 and piperazin ring-N-CH_2) 3.57–3.74 (m, 4H, imidazoline CH_2), 4.18 (s, 2H imidazoline ring-N-CH_2-N) 4.91 (s, 2H benzimidazole ring -N-CH_2-N) 6.98–7.44 (m, 4H, Ar-H), 8.96 (broad peak 1H, NH), Anal. calcd. for $C_{24}H_{39}N_9$ (453.63): C, 63.54; H, 8.67; N, 27.79 Found: C, 63.60; H, 8.83; N, 27.96.

Synthesis of compound 6. A solution of 2-methylpiperidine (d: 0.844 g cm^{-3}, 1.99 mmol), aqueous formaldehyde, and concentrated hydrochloric acid (0.5 mL HCl, 5 mL ethanol) in methanol (10 mL) was added to a solution of N-(1*H*-Benzimidazole-2-yl)-N-(4,5-dihydro-1*H*-imidazol-2-yl) amine (0.995 mmol) in ethanol (10 mL). The resulting solution was stirred at room temperature for 2 h. The solvent was removed on a rotary evaporator. The residue was mixed with methanol, and the precipitate formed was filtered and then recrystallized from ethanol.

***N*-(1*H*-imidazoline-2-yl)-1-{(2-methylpiperidin-1-yl)methyl}-1*H*-benzimidazol-2-amine hydrochloride (6).** Yield 86%, white powder, mp 163–165 °C (ethanol), IR (KBr) υ_{max}: 3465 ($^{+}$N-H stretching), 3241–3163 (N-H stretching), 3073 (C=C-H stretching), 2948–2750 (aliphatic C-H stretching), 1634 (C=N^{+} stretching), 1597 (C=C stretching), 1507 (N-H bending). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.23 (d, 3H, CH_3, $J = 6.6$ Hz), 1.32–1.76 (m, 6H) 2.83–3.19 (m, 3H), 3.62–3.85 (m, 4H, imidazoline CH_2), 5.76 (s, 2H, N-CH_2-N), 7.26–7.29 (m, 2H, Ar-H), 7.37–7.41(m, 2H, Ar-H), 8.62 (s, 1H, HCl), 8.71 (broad peak 1H, endocyclic NH), 9.11 (broad peak 1H, exocyclic NH). Anal. calcd. for $C_{17}H_{25}ClN_6$ (348,87): C, 58.53; H, 7.22; N, 24.09, Found: C, 58.74; H, 7.44; N, 24.26.

Synthesis of compound 7. 1,4-Bis(bromomethyl) benzene (0.995 mmol) was added dropwise to a mixture of *N*-(1*H*-benzimidazol-2-yl)-*N*-(4,5-dihydro-1*H*-imidazol-2-yl) amine (0.2 g, 0.995 mmol) and finely powdered NaOH (0.004 g, 0.1 mmol) in DMSO (5 mL). The resulting solution was stirred at 35–40 °C for 2 h. Then water was added to the reaction mixture, and the solid that precipitated was collected and crystallized from ethanol.

1-{4-(Bromomethyl)benzyl}-*N*-(1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine (7). Yield 78%, white powder, mp 175–177 °C (ethanol); IR (KBr) υ_{max}: 3292–3275 (N-H stretching), 3051–3025 (C=C-H stretching), 2922–2875 (aliphatic C-H stretching), 1617 (C=C stretching), 1501 (N-H bending). ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.52 (s, 4H, imidazoline CH_2), 4.48 (m, 2H, CH_2Br), 5.34 (m, 2H), 6.78–7.36 (m, 8H, Ar-H), 7.96 (s 1H, endocyclic NH), 8.74 (s 1H, exocyclic NH). Anal. calcd. for $C_{18}H_{18}BrN_5$ (384.27): C, 56.26; H, 4.72; N, 18.22. Found: C, 56.49; H, 4.63; N, 18.37.

Syntheses of compounds 8 and 9. 2-Chloro benzyl chloride (or allyl bromide) (1.9 mmol) was added dropwise to a mixture of N-(1*H*-benzimidazol-2-yl)-N-(4,5-dihydro-1*H*-imidazol-2-yl) amine (0.2 g, 0.995 mmol) and finely powdered NaOH (0.158 g, 3.96 mmol) in DMSO (5 mL). The resulting solution was stirred at 35–40 °C for 1 h. Then water was added to the reaction mixture, and the solid that precipitated was collected and recrystallized from ethanol.

1-(2-Chlorobenzyl)-*N*-(1-(2-chlorobenzyl)-1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine (8). Yield 90%, yellow powder, mp: 159–161 °C (ethanol); IR (KBr) υ_{max}: 3224 (N-H stretching), 3060–3024 (C=C-H stretching), 2935–2862 (aliphatic C-H stretching), 1608 (C=N stretching), 1591 (C=C stretching), 1499 (N-H bending). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.52 (m, 2H, imidazoline CH_2), 3.73 (m, 2H, imidazoline CH_2), 4.70 (s, 2H imidazoline ring-N-CH_2-N), 5.50 (s, 2H benzimidazole ring -N-CH_2-N), 6.82–7.53 (m, 12H, Ar-H), 8.93 (broad peak 1H, NH).

Anal. calcd. for $C_{24}H_{21}Cl_2N_5$ (450.36): C, 64.01; H, 4.70; N, 15.55, Found: C, 64.31; H, 4.54; N, 15.78.

1-Allyl-*N*-(1-allyl-1*H*-imidazoline-2-yl)-1*H*-benzimidazol-2-amine (9). Yield 76%, yellow powder, mp: 60–62 °C ($CHCl_3$), IR (KBr) υ_{max}: 3243 (N-H stretching), 3076–3041 (C=C-H stretching), 2917–2881 (aliphatic C-H stretching), 1619 (C=N stretching), 1601 (C=C stretching), 1498 (N-H bending). ^{1}H NMR ($CHCl_3$-d, 300 MHz) δ: 3.45 (t, 2H, imidazoline CH_2, $J = 8.4$ Hz), 3.65 (t, 2H, imidazoline CH_2, $J = 7.2$ Hz), 4.072 (d, 2H imidazoline ring-N-CH_2, $J = 5.7$ Hz), 4.81 (d, 2H benzimidazole ring -N-CH_2, $J = 6.0$ Hz), 5.19 (m, 4H, allyl C=CH_2), 5.93 (m, 2H, allyl C=CH), 7.03–7.55 (m, 4H, Ar-H), 8.88 (broad peak 1H, NH); it was confirmed by D_2O exchange. Anal. calcd. for $C_{16}H_{19}N_5$ (281.36): C, 68.30; H, 6.81; N, 24.89. Found: C, 68.95; H, 7.13; N, 24.96.

Synthesis of Compound 10. N-(1*H*-Benzimidazol-2-yl)-N-(4,5-dihydro-1*H*-imidazol-2-yl) amine (0.2 g, 0.995 mmol) was dissolved in 30 mL THF, and 0.28 mL triethylamine (1.99 mmol) was added. The reaction mixture was stirred on an ice bath for 0.5 h. thiophene-2-carbonyl chloride (1.99 mmol) was added dropwise over a period of 10 min to the mixture, and the mixture was refluxed for 2 h. The solution was then evaporated under vacuum to half its volume and poured into ice water, resulting in a precipitate. The residue was filtered off and recrystallized from ethanol.

Thiophen-2-yl-[2-{1-(thiophene-2-carbonyl)-1*H*-benzimidazol-2-ylamino}-1*H*-imidazoline-1-yl] methanone (10). Yield 73%, white powder, mp: 211–213 °C (ethanol); IR (KBr) υ_{max}: 3193 (N-H stretching), 3025 (C=C-H stretching), 2978–2857 (aliphatic C-H stretching), 1666 (C=O stretching broader band), 1619 (C=N stretching), 1595 (C=C stretching), 1520 (N-H bending). ^{1}H NMR ($CHCl_3$-d, 300 MHz) δ: 3.85 (t, 2H, imidazoline CH_2, $J = 7.2$ Hz), 4.20 (t, 2H, imidazoline CH_2, $J = 7.5$ Hz), 7.08–7.11 (m, 2H), 7.13–7.17 (m, 2H, Ar-H), 7.44–7.46 (m, 3H, Ar-H), 7.62 (d, 2H, $J = 4.8$ Hz, Ar-H), 7.93 (d, 2H, $J = 3.3$ Hz, Ar-H). Anal. calcd. for $C_{20}H_{15}N_5O_2S_2$ (421.50): C, 56.99; H, 3.59; N, 16.62; S, 15.21. Found: C, 57.12; H, 3.72; N, 16.29; S, 15.65.

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