Synthesis and Antimicrobial Activities of Novel 2-[substituted-1*H*-pyrazol-4-yl] Benzothiazoles, Benzoxazoles, and Benzimidazoles

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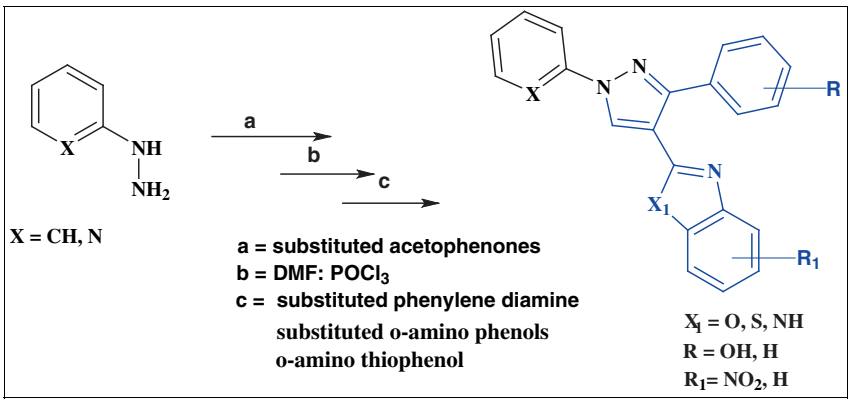


In an endeavor to find a new class of antimicrobial agents, a series of novel substituted benzimidazole, benzoxazole, and benzothiazole derivatives **6** containing pyrazole moiety have been synthesized by reaction of 3-aryl-4-formyl pyrazole **4** with substituted phenylenediamine or *o*-aminophenol or *o*-aminothiophenol **5**. Reaction of phenyl hydrazine or 2-hydrazinopyridine **1** with substituted acetophenones **2** gave the corresponding hydrazones **3**, which on Vilsmeier–Haack reaction with $POCl_3$–DMF gave substituted 3-aryl-4-formyl pyrazoles **4**. All final compounds **6a–6k** were evaluated for *in vitro* antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* strains and *in vitro* antifungal activity against *Candida albicans* and *Aspergillus niger* strains by using serial dilution method. The antimicrobial activities were expressed as the minimum inhibitory concentration in μg/mL. The compound containing benzimidazole and benzoxazole moiety gave better antibacterial and antifungal activities than benzothiazole compounds.

INTRODUCTION

Molecules with benzimidazole, benzoxazole, and benzothiazoles moieties often exhibit diverse and important biological properties. These heterocycles have shown different pharmacological activities such as antibiotic [1], antiviral [2], anticancer [3], and antimicrobial [4]. They have also been used as ligands for asymmetric transformations [5]. Benzimidazole derivatives are unique and broad-spectrum class of antirhino/enteroviral agents such as antihistaminic [6], anti-ulcerative [7], anti-allergic [8], and effective against the human cytomegalovirus [9], and are also efficient selective neuropeptide YY1 receptor antagonists [10].

Over the last decade, a variety of benzimidazole, benzoxazole, and benzothiazole derivatives has been synthesized and studied for their antibacterial activity [11–13]. Substituted benzoxazole UK-1 (**I**) and benzoxazole AJI9561 (**II**) (Fig. 1**)** are reported to possess growth inhibitory activity against murine cancer cell line P388 with IC50 value in the range of 0.3–1.6 μM [3]. Literature survey has also revealed that many hydrazone derivatives of benzimidazole, benzoxazole, and benzothiazole possesses as anticancer and antibacterial properties [14].

Moreover, pyrazoles are one of the precursors of benzimidazole, benzoxazole, and benzothiazole derivatives and are also important intermediates for the synthesis of biologically active benzofuran and coumarin systems. Although various pyrazole derivatives are reported in literature [15], antimicrobial activities of these classes of compounds have received little attention [16]. Pyrazoles and substituted pyrazoles are also reported to be potent inhibitors of many bacteria [17]. Synthesis of compounds containing benzoxazole and benzimidazole anchored with nitrogen heterocyclic ring system is known in the literature [18]. However there are no reports available describing synthesis and antibacterial activities of benzimidazole, benzoxazole, and benzothiazole with pyrazole heterocycles in a single moiety. Therefore, a series of benzimidazole, benzoxazole, and benzothiazole containing pyrazoles ring system was synthesized; their antimicrobial properties have been evaluated and compared with standard drug fluconazole and streptomycin.

RESULTS AND DISCUSSIONS

The syntheses of various hydrazones **3** were carried out by condensation of phenyl hydrazine or 2-hydrazino pyridine

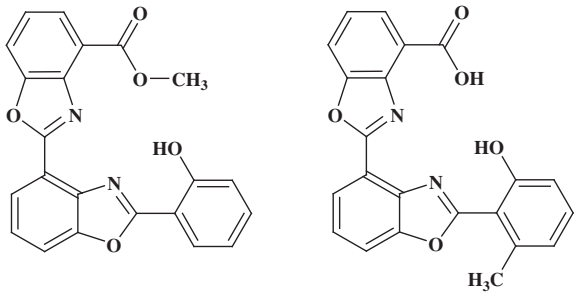


Figure 1. Structure of UK-**1** and AJI9561.

1 with substituted acetophenones **2** in ethanol in the presence of catalytic amounts of acetic acid. Substituted hydrazones **3** were further converted into 1-phenyl-3-substituted-1*H*-pyrazole-4-carbaldehyde or 3-substituted-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde **4** derivatives by Vilsmeier–Haack reaction with $POCl_3$–DMF. Compounds **4** were condensed with *o*-substituted aromatic amines **5** in the presence of PCl_3 in ethanol to obtain corresponding 2-[substituted-1*H*-pyrazol-4-yl]-1*H*-benzimidazole, 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzoxazole, and 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzothiazole **6**. The synthetic route of the compounds is outlined in Scheme 1, and synthesized compounds are shown in Table 1. The synthesis of intermediate **4** is through Vilsmeier–Haack formylation, and its proposed mechanism is shown in Scheme 2. The purity of the compounds was confirmed by TLC using precoated silica gel as stationary phase, using appropriate solvent system as mobile phase, and visualized under UV light. Structures of the titled compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral and elemental analysis.

The strategies adopted for the synthesis of the intermediates and target compounds are depicted in Scheme 1, in which intermediate hydrazones **3** were prepared according to literature procedure [19]. Intermediate hydrazones derivatives **3** were converted into formyl pyrazole derivatives **4** using Vilsmeier–Haack reaction with $POCl_3$–DMF. Aldehyde formation was confirmed by alcoholic solution of 2,4-DNP. Aldehyde gives pink spot on TLC after dipping into 2,4-dinitrophenylhydrazine (DNP) solution. It was also confirmed by FTIR as well as ^{1}H NMR analysis. FTIR shows sharp band at 1678 cm^{-1}, and ^{1}H NMR shows signal at 9.90 δ. Title compounds **6a–6k** were confirmed by FTIR, ^{1}H NMR, and mass and elemental analysis. Compounds **6a–6k** has shown absence of absorption band at 1678 cm^{-1} confirming conversion of aldehydic functional group into corresponding benzimidazole, benzoxazole, and benzothiazole. Absence of peak at 9.90 δ ppm in ^{1}H NMR confirmed the conversion of formyl functional group into target compound. The ^{1}H NMR spectrum of **6a–6k** showed singlets at 8.9–9.6 δ ppm, which are characteristics of pyrazole ring. Mass spectra showed an accurate molecular ion for each title compounds.

Scheme 1. Synthesis of 2-[substituted-1*H*-pyrazol-4-yl]-1*H*-benzimidazole, 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzoxazole, and 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzothiazole.

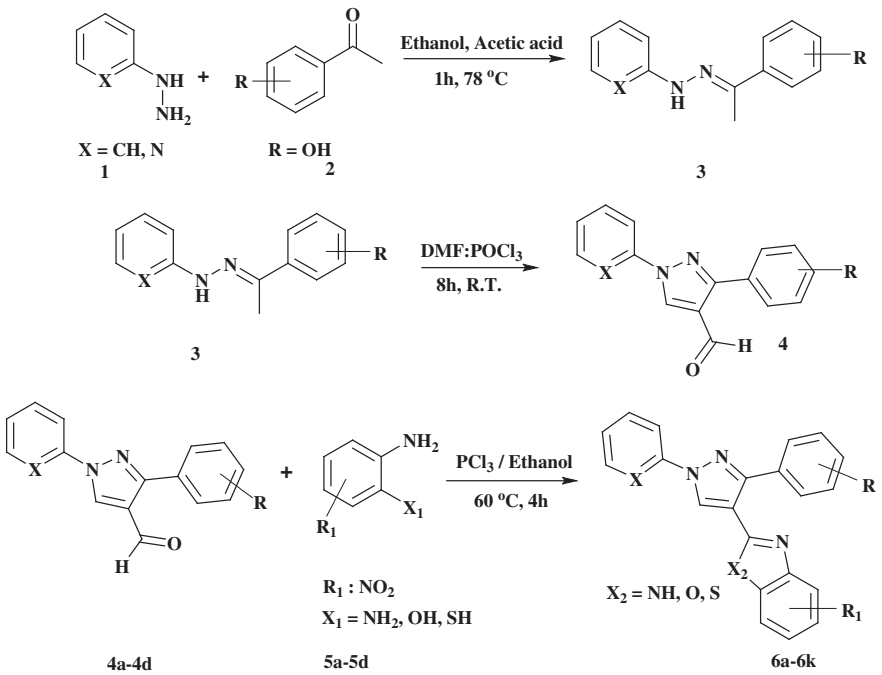
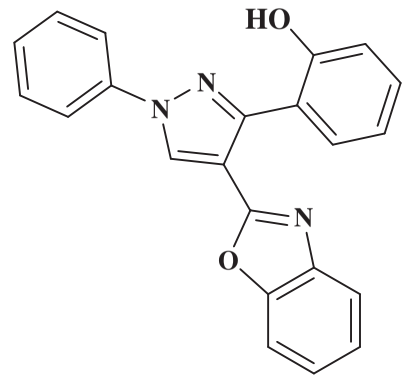
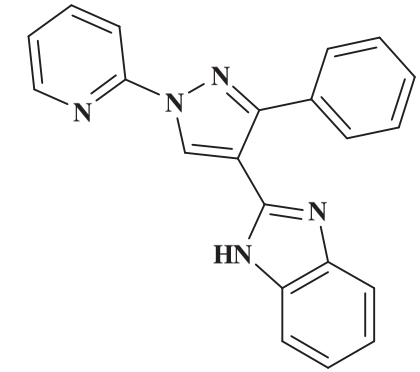
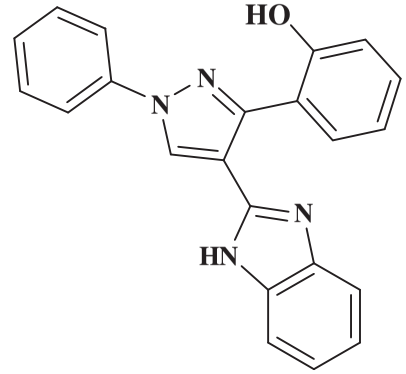
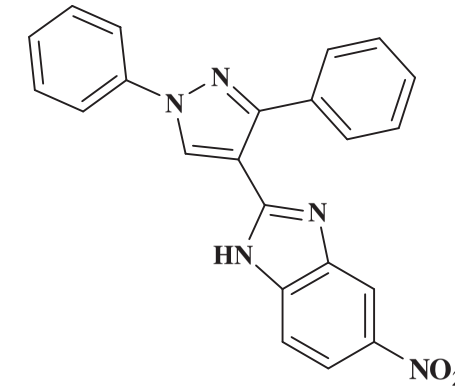


Table 1

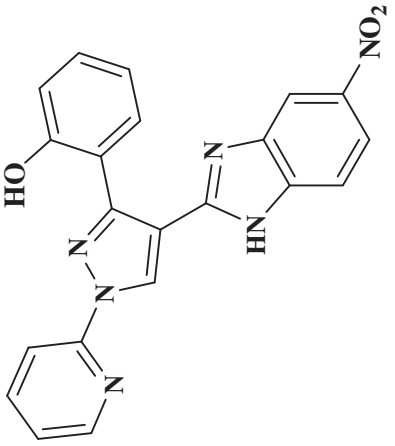
Synthesized 2-[substituted-1*H*-pyrazol-4-yl]-1*H*-benzimidazole, 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzoxazole and 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzthiazole.

Compound	Structure	Compound	Structure
6a		**6g**	
6b		**6h**	

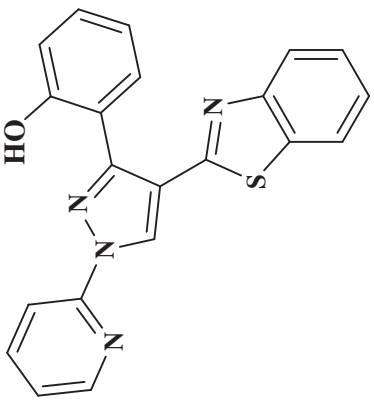
(*Continued*)

Table 1
(*Continued*)

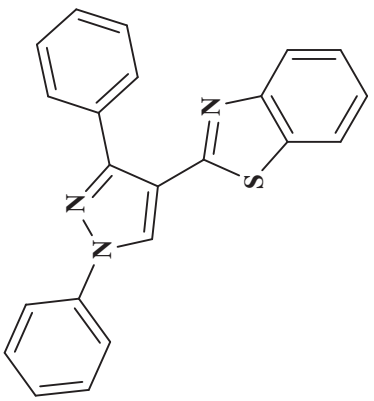
Compound	Structure	Compound	Structure
6c		**6i**	
6d		**6j**	



6k

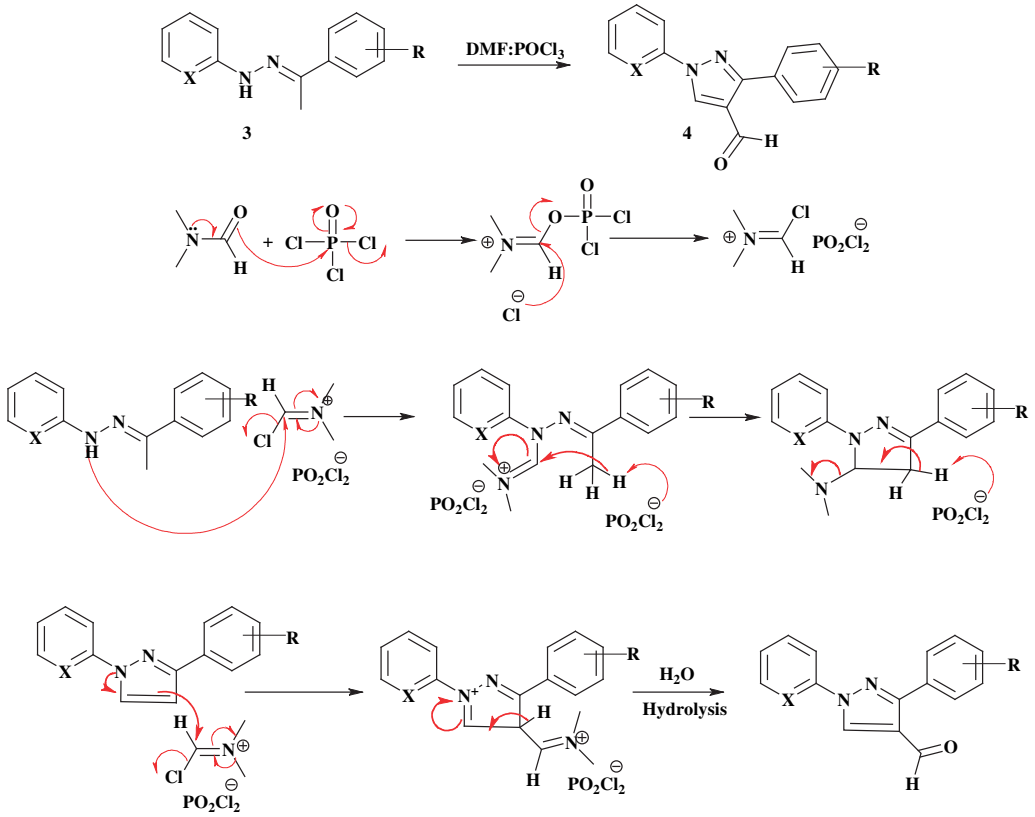


6e



6f

Scheme 2. Proposed mechanism for intermediate **4**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Biological activity. The novel compounds **6a–6k** were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* strains and *in vitro* antifungal activity against *Candida albicans* and *Aspergillus niger* strains by using serial dilution method. The minimum inhibitory concentration (MIC) measurement determined for the compounds showed significant growth inhibition zones with the use of serial dilution method. The MIC (μg/mL) values recorded in Table 2 indicate that most of the tested compounds

Table 2

Antibacterial and antifungal activities of newly synthesized compounds indicated by MIC (μg/mL) using the modified resazurin assay.

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*	*Aspergillus niger*
6a	125	62.5	125	312
6b	187.5	312	312	312
6c	62.5	62.5	312	312
6d	62.5	187.5	62.5	312
6e	312	312	312	312
6f	250	312	187.5	312
6g	187.5	62.5	312	250
6h	312	312	312	312
6i	312	187.5	62.5	312
6j	250	62.5	250	187.5
6k	125	62.5	62.5	125
Streptomycin	125	125	–	–
Fluconazole	–	–	125	125

MIC, minimal inhibitory concentration values; bacterial strain, *E. coli* and *S. aureus*; fungal strain, *C. albicans* and *A. niger*; solvent used, DMSO; standard: bacterial strain, streptomycin 125 μg/mL; fungal strains, fluconazole 125 μg/mL.

displayed variable inhibitory effects on the growth of tested against bacterial and fungal strains.

The compounds **6a**, **6c**, **6d**, **6g**, **6j**, and **6k** showed good antibacterial activity against *E. coli* and *S. aureus*, respectively. On the other hand, compounds **6b**, **6f**, and **6i** exhibited weak to moderate growth inhibitory activity against both *E. coli* and *S. aureus* as revealed from their MIC values. Among these compounds, **6e** and **6h** showed relatively poor growth inhibitory activity against both *E. coli* and *S. aureus* bacterial strains. Regarding the structure–activity relationship of the novel 2-[substituted-1*H*-pyrazol-4-yl]-1*H*-benzimidazole, 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzoxazole, and 2-[substituted-1*H*-pyrazol-4-yl]-1,3-benzothiazole derivative **6a–6k** against the tested bacteria, the results revealed that new compounds containing benzimidazole **(6b**, **6c**, **6g**, **6h**, **6i**, **6j**, and **6k)** and benzoxazole (**6a** and **6d**) exhibited broad-spectrum antibacterial profile against tested organisms as compared with benzothiazole moiety (**6e** and **6f**) in target molecules. The electron-donating and electron-withdrawing groups in target molecules **6a–6k** do not affect the growth inhibitory activity against tested bacterial strain.

Regarding the activity of benzimidazole, benzoxazole, and benzothiazole incorporating pyrazole moiety **6a–6k** against fungal strains (*C. albicans and A. niger*), the results mentioned in Table 2 showed that compounds **6d**, **6i**, and **6k** shows good inhibitory growth in case of *C. albicans* fungal strain, whereas the activity of compounds **6a** and **6k** was 50% lower inhibitory growth for *A. niger* fungal strain than *C. albicans*. Compounds **6f**, **6g**, and **6j** showed moderate antifungal activity against tested fungal strains, whereas compounds **6b**, **6c**, **6e**, and **6h** showed poor inhibitory profile against *C. albicans* as well as *A. niger* fungal strains. Electron-donating and electron-withdrawing groups on benzimidazole, benzoxazole, and benzothiazole containing pyrazole moiety does not affect the growth inhibitory activity against tested fungal strains.

In general, most of the tested compounds revealed better activity against the bacterial strain (*E. coli* and *S. aureus*) and fungal strain (*C. albicans* and *A. niger*). It would also be noticed that compounds benzimidazole and benzoxazole containing pyrazole moiety give better antibacterial and antifungal potentials than benzothiazole compounds containing pyrazole moiety. Novel compounds are very active against bacterial strain as compared with fungal strain over tested microorganisms.

CONCLUSION

In conclusion, we have designed and synthesized a series of novel benzimidazole, benzoxazole, and benzothiazole derivatives containing pyrazole moiety. These novel compounds were evaluated for *in vitro* antibacterial activity against *E. coli* and *S. aureus* as well as for antifungal activity against *C. albicans* and *A.niger* with the use of serial dilution technique. Benzimidazole and benzoxazole incorporating pyrazole moiety gives excellent results than benzothiazole contains pyrazole moiety. All synthesized compounds are confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and mass and elemental analysis. We believe that the insights gained in this study would be useful for the development of potential drug candidates derived from benzimidazole, benzoxazole, and benzothiazole incorporating pyrazole moiety in the development of novel anti-infective agent.

EXPERIMENTAL

All commercial reagents and solvents were procured from S.D. Fine Chemicals (India) and were used without purification. The reaction was monitored by TLC using on 0.25-mm E-Merck silica gel 60 F_{254} (Merck Millipore, Darmstadt, Germany) precoated plates, which were visualized with UV light. The FTIR spectra were recorded on PerkinElmer 257 spectrometer (UK) using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian MR 400 MHz (Palo Alto, CA, USA) instrument using TMS as an internal standard. Mass spectra were recorded on Finnigan mass spectrometer (San Jose, CA).

General. Incubator at 35 and 37°C; pipettes of various sizes (Gilson, Middleton, WI); sterile tips, 100, 200, 500, and 1000 μL; sterile normal saline; sterile isosensitest agar (Southern Group Laboratory, Corby, UK); antibiotic solutions (Sigma-Aldrich, St. Louis, MO); sterile solution of 10% (v/v) DMSO in water (Sigma-Aldrich).

Medium. Isosensitest medium was used throughout the assay, as it is pH buffered. Although the National Committee for Clinical Laboratory Standards recommends the use of Mueller Hinton medium for susceptibility testing, the isosensitest medium had comparable results for most of the tested bacterial strains.

Preparation of the plates. Plates were prepared under aseptic conditions. A sterile 96-well plate was labeled. A volume of 100 μL of test material in 10% (v/v) DMSO (usually a stock concentration of 4 mg/mL) was pipetted into the first row of the plate. To all other wells, 50 μL of nutrient broth was added. Serial dilutions were performed using a multichannel pipette. Tips were discarded after use such that each well had 50 μL of the test material in serially descending concentrations. To each well, 10 μL of resazurin indicator solution was added. With the use of a pipette, 30 μL of 3.3× strength isosensitised broth was added to each well to ensure that the final volume was single strength of the nutrient broth. Finally, 10 μL of bacterial suspension (5×10^6 cfu/mL) was added to each well to achieve a concentration of 5×10^5 cfu/mL. Each plate was wrapped loosely with cling film to ensure that bacteria did not become dehydrated. Each plate had a set of controls: a column with a broad-spectrum antibiotic as positive control, a column with all solutions with the exception of the test compound, and a column with all solutions with the exception of the bacterial solution, adding 10 μL of nutrient broth instead. The plates were prepared in triplicate and placed in an incubator set at 37°C for 18–24 h. The color change was then assessed visually. Any color changes from purple to pink or colorless were recorded as positive. The lowest concentration at which color change occurred was taken as the MIC value. The

average of three values was calculated, and that was the MIC for the test material and bacterial or fungal strain [20].

General procedure for the synthesis of substituted-2-(1-phenylethylidene) hydrazine or substituted-2-(1-phenylethylidene) hydrazinyl]pyridine 3. A mixture of phenyl hydrazine or 2-hydrazinopyridine **1** (0.01 mol) and appropriate acetophenones **2** (0.01 mol) in ethanol (20 mL) containing 0.05 mL of glacial acetic acid was refluxed for 1 h. The solid that separated out on cooling was filtered and recrystallized from ethanol to afford **3**.

General procedure for synthesis of 1-phenyl-3-substituted-1H-pyrazole-4-carbaldehyde or 3-substituted-1-(pyridin-2-yl)-1H-pyrazole-4-carbaldehyde 4. To the Vilsmeier–Haack reaction, the reagent prepared from DMF (10 mL) and $POCl_3$ (1.1 mL, 0.012 mol), intermediates **3** (0.01 mol) was added and the reaction mixture stirred at room temperature for 8 h. and poured into ice-cold water. The solid that separated on neutralization with $NaHCO_3$ was filtered, washed with water, and recrystallized from ethanol to give **4**.

General procedure for synthesis of 2-[substituted-1H-pyrazol-4-yl]-1H-benzimidazole or 2-[substituted-1H-pyrazol-4-yl]-1,3-benzoxazole or 2-[substituted-1H-pyrazol-4-yl]-1,3-benzothiazole 6. Phosphorus trichloride (0.33 mol) was added dropwise to a solution of the 1-phenyl-3-substituted-1*H*-pyrazole-4-carbaldehyde or 3-substituted-1-(pyridin-2-yl)-1*H*-pyrazole-4-carbaldehyde (0.33 mol) and substituted phenylenediamine or aminophenol or thiophenol (0.33 mol) in ethanol (50 mL), maintaining the temperature at 40–45°C. The mixture was heated at 60°C for 4 h, after completion of reaction (checked by TLC) cooled the reaction mass at room temperature and made alkaline to pH 8 with 20% aqueous sodium bicarbonate solution. Separated solid was collected by filtration and crystallized from isopropyl alcohol.

Spectral Data of compounds 6a–6k. ***2-[4-(1,3-Benzoxazol-2-yl)-1-phenyl-1H-pyrazol-3-yl]phenol (6a)***. Yield: 78%; recrystallized from ethyl alcohol. FTIR (KBr): 3197, 2874 (OH), 1574, 1546, 1500, 1473 (C=C), 1168, 770 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.21 (s, 1H, OH), 8.92 (s, 1H, pyrazole H), 7.93–7.96 (d, 2H, *J* = 8.2, 2.0 Hz, Ar–H), 7.54–7.57 (d, 2H, *J* = 8.0, 2.4 Hz, Ar–H), 7.33–7.38–7.39 (d, 2H, *J* = 7.8,1.8 Hz, Ar–H), 7.21 (t, 1H, Ar–H), 6.98 (d, 4H, *J* = 6.8, 2.0 Hz, Ar–H), 6.87 (d, 2H, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 160.1, 159.8, 155.9, 148.3, 141.0, 140.5, 132.6, 130.7 (s), 128.3, 127.8, 124.7, 122.4, 122.0, 121.1 (s), 120.5, 119.3, 118.1, 115.2, 113.0, 112.6. HRMS (*m/z*): 353.371 (M + 1: 48%), 261.232 (10%), 250.291 (35%), 235.198 (100%), 122.024 (53%). *Anal*. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.76; H, 4.26; N, 11.90.

2-[4-(1H-Benzimidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl]phenol (6b). Yield: 66%; recrystallized from ethyl alcohol. FTIR (KBr): 3391, 3206, 2872 (OH), 1578, 1536, 1500, 1480 (C=N, C=C), 756, 743 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.45 (s, 1H, OH), 9.25 (s, 1H, NH) 8.93 (s, 1H, pyrazole H), 8.54–8.57 (d, 2H, *J* = 8.0,1.8 Hz, Ar–H), 7.81–7.85 (d, 2H, *J* = 8.0, 2.4 Hz, Ar–H), 7.46–7.52 (d, 2H, *J* = 7.4,1.8 Hz, Ar–H), 7.24 (t, 1H, Ar–H), 7.17–7.21 (d, 4H, *J* = 7.0, 6.4 Hz, Ar–H), 6.86–6.90 (d, 2H, *J* = 6.8 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 161.0, 151.5, 142.0, 140.0, 138.0, 135.7, 132.6, 130.3 (s), 127.7, 127.4, 125.6, 123.0, 122.1, 119.6 (s), 118.3 (s), 117.5, 116.8, 113.6, 104.3. HRMS (*m/z*): 352.376 (M + 1: 27%), 352.378 (22%), 236.259 (100%), 119.001 (49%). *Anal*. Calcd. for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 74.75; H, 4.25; N, 15.88.

2-[4-(1H-Benzimidazol-2-yl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl] phenol (6c). Yield: 84%; recrystallized from ethyl alcohol. FTIR (KBr): 3382, 3210, 2872 (OH), 1574, 1538, 1499, 1472 (C=N, C=C), 762, 740 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.50 (s, 1H, OH), 9.21 (s, 1H, NH), 8.92 (s, 1H, pyrazole H), 8.45–8.49 (d, 1H, *J* = 8.0, 2.4 Hz, Ar–H), 7.86–8.07 (d, 4H, *J* = 8.2, 6.8, 2.0 Hz, Ar–H), 6.89–7.45 (d, 5H, *J* = 8.0, 6.8, 1.8 Hz, Ar–H), 6.84 (d, 2H, *J* = 7.0 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 160.9, 152.2, 148.0, 147.6, 142.0, 139.7, 138.3, 135.9, 133.0, 128.9, 123.8, 123.0, 122.2, 120.4, 118.7, 118.5, 117.9, 116.9, 113.8, 112.0, 100.0. HRMS (*m/z*): 353.371 (M + 1: 17%), 350.234 (78%), 260.020 (15%), 258.234 (100%), 118.451 (49%). *Anal*. Calcd. for $C_{21}H_{15}N_5O$: C, 71.38; H, 4.28; N, 19.82. Found: C, 71.37; H, 4.26; N, 19.85.

2-[4-(1,3-Benzoxazol-2-yl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl] phenol (6d). Yield: 73%; recrystallized from ethyl alcohol. FTIR (KBr): 3199, 2870 (OH), 1576, 1546, 1500, 1471 (C=N, C=C), 1168, 770, 739 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.45 (s, 1H, OH), 8.90 (s, 1H, pyrazole H), 8.36 (d, 1H, *J* = 8.2, 2.0 Hz, Ar–H), 7.70–7.98 (d, 4H, *J* = 7.8, 2.4 Hz, Ar–H), 6.78–7.32 (d,5H, *J* = 8.0, 6.8, 1.8 Hz, Ar–H), 6.71 (d, 2H, *J* = 6.8 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 161.3, 159.9, 156.8, 148.3, 148.0 (s), 142.3, 139.8, 133.0, 129.5, 126.6, 124.8, 122.3, 120.9, 120.7 (s), 119.3, 118.0, 114.8, 113.4, 112.9. HRMS (*m/z*): 354.373 (M + 1: 45%), 262.452 (23%), 165.879 (100%), 120.017 (69%). *Anal*. Calcd. for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.16; H, 3.98; N, 15.78.

2-[4-(1,3-Benzothiazol-2-yl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl] phenol (6e). Yield: 80%; recrystallized from ethyl alcohol. FTIR (KBr): 3204, 2879 (OH), 1580, 1543, 1509, 1479 (C=N, C=C), 766, 745 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.66 (s, 1H, OH), 9.21 (s, 1H, pyrazole H), 8.58–8.59 (d, 1H, Ar–H), 7.95–8.07 (d, 4H, *J* = 8.8, 8.0, 2.0 Hz, Ar–H), 7.00–7.51 (d, 5H, *J* = 8.0, 6.4, 2.0 Hz, Ar–H), 6.96–7.00 (d, 2H, *J* = 7.8, 6.4 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 181.4, 160.7, 153.8, 150.3, 148.1, 147.7, 139.7, 133.6, 132.7, 128.1, 126.0, 125.5, 125.1, 125.0, 124.8, 120.3, 118.9, 118.0, 116.9, 113.3, 113.1. HRMS: *m/z* 371.000 (M + 1: 37%), 370.035 (35%), 373.012 (10%), 161.218 (30%), 154.476 (100%), 129.203 (15%). *Anal*. Calcd. for $C_{21}H_{14}N_4OS$: C, 68.09; H, 3.81; N, 15.12; S, 8.66. Found: C, 68.07; H, 3.79; N, 15.13, S, 8.65.

2-(1,3-Diphenyl-1H-pyrazol-4-yl)-1,3-benzothiazole (6f). Yield: 87%; recrystallized from ethyl alcohol. FTIR (KBr): 1587, 1533, 1500, 1479, 1347 (C=N, C–N, C=C), 761, 738 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.35 (s, 1H, NH), 8.54 (s, 1H, pyrazole H), 8.19 (d, 1H, Ar–H), 7.95–7.98 (d, 3H, *J* = 8.2, 2.0 Hz, Ar–H), 7.81–7.849 (d, 2H, *J* = 8.0, 1.8 Hz, Ar–H), 7.60–7.63 (d, 3H, *J* = 7.8, 2.4 Hz, Ar–H), 7.39–7.45 (d, 5H, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 177.9, 153.9, 150.8, 140.0, 133.6, 133.5, 130.7 (s), 129.9, 127.9, 127.7, 127.4, 126.4, 126.0, 125.5, 125.4, 125.0, 124.6, 121.0 (s), 117.7. HRMS (*m/z*): 353.430 (M + 1: 24%), 235.023 (10%), 221.193 (36%), 135.000 (100%). *Anal*. Calcd. for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.89; S, 9.07. Found: C, 74.75; H, 4.26; N, 11.90; S, 9.05.

2-[3-Phenyl-1-(pyridin-2-yl)-1H-pyrazol-4-yl]-1H-benzimidazole (6g). Yield: 80%; recrystallized from ethyl alcohol. FTIR (KBr): 3388, 1582, 1548, 1514, 1484, 1361 (C=N, C–N, C=C), 810, 770, 748 cm^{-1}. ^1H NMR (DMSO-d_6, δ, ppm): 9.28 (s, 1H, NH), 8.64 (s, 1H, pyrazole H), 8.21 (d, 1H, Ar–H), 7.89–7.91 (d, 3H, *J* = 8.2, 2.0 Hz, Ar–H), 7.67–7.70 (d, 2H, *J* = 8.0,1.8 Hz, Ar–H), 7.54–7.57 (d, 3H, *J* = 7.8, 6.8, 2.0 Hz, Ar–H), 7.39–7.41 (d, 4H, *J* = 6.8, 7.8, 1.8 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 149.0, 148.2, 147.5, 141.9, 139.7, 136.5, 135.0, 131.1, 128.7 (s), 128.0 (s), 127.9, 123.8, 123.0, 122.1, 120.4, 118.7 (s),

112.0, 99.0. HRMS (*m/z*): 337.371 (M + 1: 38%), 262.344 (27%), 221.651 (43%), 118.901 (100%). *Anal*. Calcd. for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 74.73; H, 4.45; N, 20.77.

2-(1,3-Diphenyl-1H-pyrazol-4-yl)-5-nitro-1H-benzimidazole (6h). Yield: 88%; recrystallized from ethyl alcohol. FTIR (KBr): 3378, 1584, 1539, 1508, 1482, 1361 (C═N, C–N, C═C), 1528, 1330 (–NO_2), 812, 780, 732 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.45 (s, 1H, NH), 7.95 (d, 2H, Ar–H), 7.79–7.81 (d, 2H, *J* = 8.0, 2.0 Hz, Ar–H), 7.72 (d, 2H, *J* = 7.8, 1.8 Hz, Ar–H), 7.66–7.68 (t, 2H, *J* = 7.8, 2.4 Hz, Ar–H), 7.56–7.58 (d, 2H, *J* = 6.8 Hz, Ar–H), 7.50 (d, 4H, *J* = 7.8, 6.8, 1.8 Hz, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 146.3, 144.0, 142.0, 140.0, 137.6, 134.0, 130.8 (s), 128.0, 127.7, 127.5 (s), 126.6 (s), 125.3, 120.0 (s), 118.1, 117.6, 116.2, 100.0. HRMS (*m/z*): 381.383 (M + 1: 34%), 304.120 (10%), 220.185 (100%), 163.090 (38%). *Anal*. Calcd. for $C_{22}H_{15}N_5O_2$: C, 69.28; H, 3.96; N, 18.36. Found: C, 69.26; H, 3.96; N, 18.33.

5-Nitro-2-[3-phenyl-1-(pyridin-2-yl)-1H-pyrazol-4-yl]-1H-benzimidazole (6i). Yield: 68%; recrystallized from ethyl alcohol. FTIR (KBr): 3381, 1585, 1539, 1511, 1483, 1365 (C═N, C–N, C═C), 1532, 1335 (–NO_2), 814, 782, 735 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.52 (s, 1H, NH), 8.20 (d, 2H, Ar–H), 7.96–7.98 (d, 2H, *J* = 8.0, 2.0 Hz, Ar–H), 7.84–7.87 (d, 2H, *J* = 7.8, 1.8 Hz, Ar–H), 7.73–7.75 (t, 2H, *J* = 6.8, 2.4 Hz, Ar–H), 7.59–7.62 (d, 2H, *J* = 8.0, 2.0 Hz Ar–H), 7.54–7.57 (d, 3H, *J* = 7.8, 6.4, 2.2 Hz Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 148.0, 147.4, 143.8, 142.0, 140.0, 139.8, 137.8, 134.9, 128.6 (s), 128.0, 127.9, 127.6, 123.8, 120.4, 118.2, 117.6, 116.0, 112.0, 99.0. HRMS (*m/z*): 382.374 (M + 1: 46%), 221.571 (34%), 163.230 (100%). *Anal*. Calcd. for $C_{21}H_{14}N_6O_2$: C, 65.96; H, 3.69; N, 21.98. Found: C, 65.94; H, 3.68; N, 21.97.

2-[4-(5-Nitro-1H-benzimidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl]phenol (6j). Yield: 74%; recrystallized from ethyl alcohol. FTIR (KBr): 3376, 3212, 2880, 1583, 1537, 1507, 1481, 1361 (C═N, C–N, C═C), 1528, 1328 (–NO_2), 807, 782, 728 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.50 (s, 1H, OH), 9.25 (s, 1H, NH), 8.45 (d, 1H, Ar–H), 7.97 (d, 1H, Ar–H), 7.94 (d, 1H, Ar–H), 7.78 (d, 1H, Ar–H), 7.60 (d, 3H, *J* = 8.0, 2.0 Hz, Ar–H), 7.44 (d, 1H, Ar–H), 7.29 (d, 1H, Ar–H), 6.98 (d, 1H), 6.86 (d, 1H, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.1, 151.4, 144.0, 142.0, 140.0, 139.9, 137.9, 132.9, 130.9 (s), 127.9, 127.3, 125.6, 119.9 (s), 118.2, 118.0, 117.7, 116.4, 113.5, 104.2. HRMS (*m/z*): 397.388 (M + 1: 56%), 305.228 (12%), 236.089 (34%), 163.669 (100%), 94.228 (20%). *Anal*. Calcd. for $C_{22}H_{15}N_5O_3$: C, 66.49; H, 3.80; N, 17.62. Found: C, 66.48; H, 3.81; N, 17.63.

2-[4-(5-Nitro-1H-benzimidazol-2-yl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl]phenol (6k). Yield: 79%; Recrystallized from ethyl alcohol. FTIR (KBr): 3383, 3218, 2889, 1591, 1542, 1511, 1487, 1368 (C═N, C–N, C═C), 1532, 1343 (–NO_2), 814, 785, 735 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ, ppm): 9.61 (s, 1H, OH), 9.42 (s, 1H, NH), 8.97 (s, 1H, pyrazole H), 8.65 (d, 1H, Ar–H), 8.34 (d, 1H, Ar–H), 7.72–8.20 (d, 5H, *J* = 8.2, 8.0, 7.8, 6.8, 2.0 Hz, Ar–H), 7.36–7.60 (d, 2H, Ar–H), 7.20 (d, 1H, Ar–H), 7.00 (d, 1H, Ar–H). ^{13}C NMR (DMSO-d_6, δ, ppm): 161.0, 153.0, 149.0, 148.0, 144.0, 142.0, 140.1, 139.7(s), 132.9, 129.0, 124.0, 120.4, 118.2, 118.0, 117.6, 116.9, 116.2, 114.5, 112.0, 100.0. HRMS (*m/z*): 398.377 (M + 1: 65%), 237.449 (56%), 163.088 (45%), 118.032 (100%). *Anal*. Calcd. for $C_{21}H_{14}N_6O_3$: C, 63.31; H, 3.54 N, 21.10. Found: C, 63.29; H, 3.53; N, 21.13.

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