Asian Journal of Chemistry; Vol. 34, No. 3 (2022), 614-618

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2022.23570

Synthesis, Characterization and Biological Screening of Novel Imidazolylpyrazole Scaffolds

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Received: 6 October 2021; *Accepted*: 28 November 2021; *Published online*: 14 February 2022; AJC-20693

A novel series of 3-(4-aryl)-4-(4,5-diphenyl-1*H*-imidazol-2-yl)-1-phenyl-1*H*-pyrazole was synthesized by employing the well-known Debus-Radziszewski reaction. Structures of all the newly synthesized compounds have been characterized by various spectroscopic techniques *viz*. FTIR, ^{1}H and ^{13}C NMR, LC-MS and elemental analysis. All these compounds were also screened for antimicrobial potential against bacterial strains of *S. aureus*, *K. pneumoniae* and fungal strains of *A. niger* and *T. rubrum*.

Keywords: Heterocycles, Vilsmeier-Haack reaction, Imidazolylpyrazole hybrids, Benzil, Antimicrobial activity.

INTRODUCTION

Among all the diverse heterocyclic compounds analyzed till date, nitrogen-containing heterocycles emerge as the scaffolds with unmatched applications and incessant potential to be harnessed in the fields of their chemical, agrochemical, biological and pharmacological properties. Imidazoles and pyrazoles represent two active classes of compounds that exhibit a broad spectrum of biological profiles. Pyrazole derivatives show anticancer [1,2], anti-aids [3], antitubercular, antimalarial [4], anticonvulsant [5], antidepressant [6], antitumor [7], antifungal [8], antioxidant [9], antialzheimer's [10], antihyperglycemic [11], antibacterial and anti-inflammatory [12], antiparkinsonian [13] antipyretic [14], antianxiety [15] and insecticidal properties [16]. Imidazole derivatives also encompass an extensive range [17] of applications such as antibacterial [18], antifungal [19], anti-inflammatory [20], anti-viral [21], antihistaminic [22], antiparasitic [23] anticancer [24], enzyme inhibition [25], antidiabetic [26], antirheumatic [27], antiasthmatic, α-blockers [28], antiprotozoal [29], antiaging, antimalarial and anticoagulant [30]. Studies have also revealed that clubbing these two nuclei displayed promising biological profiles, which has drawn the attention of researchers globally to explore the unrevealed potential of this structural framework.

Medicinal profile of imidazolylpyrazole derivatives include activities functioning as anticancer [31], antiviral, [32], antimicrobial [33], antifungal and antimycobacterial [34], antimalarial and antitubercular [35]. Also they have proven useful in photographic materials and processes [36]. In view of these multifaceted benefits, we aimed in this study to synthesize some novel hybrid compounds containing both pyrazole and imidazole moieties in a single molecular framework which may prove useful scaffolds to yield highly potent bioactive compounds. Pyrazole derivatives were synthesized by treating phenyl hydrazone derivatives of *p*-substituted acetophenones with Vilsmeier Haack reagent generated *in situ*. An imidazole moiety was then constructed over pyrazole nucleus by reacting the pyrazole derivatives with benzil and ammonium acetate as these two substances have shown to be very useful in building up the imidazole moiety in solvent [37] or under solvent free [38] conditions. The structures of all synthesized compounds were assigned on the basis of FTIR, NMR, mass spectroscopy and elemental analysis.

A large number of azole-based antimicrobial agents have been used in clinic in past few years which have proven their great potential as safe curative substances with lower toxicity, less side effects and especially very few resistances. Being electron rich, azole-based derivatives can easily bind with

enzymes and receptors in living beings through non-covalent interactions. This prompted us to synthesize compounds for their inhibitory effects against bacterial and fungal strains. Antimicrobial assay was carried out by the agar well diffusion method.

EXPERIMENTAL

All the chemicals used were of analytical reagent grade and procured from Sigma, Loba, Emerk and Otto. Solvents were of laboratory reagent grade and distilled before use. The chemical reactions to synthesize formyl-pyrazoles were carried out using magnetic stirrer equipped with a hot plate and hybrid imidazolylpyrazoles were synthesized by reflux on water bath.

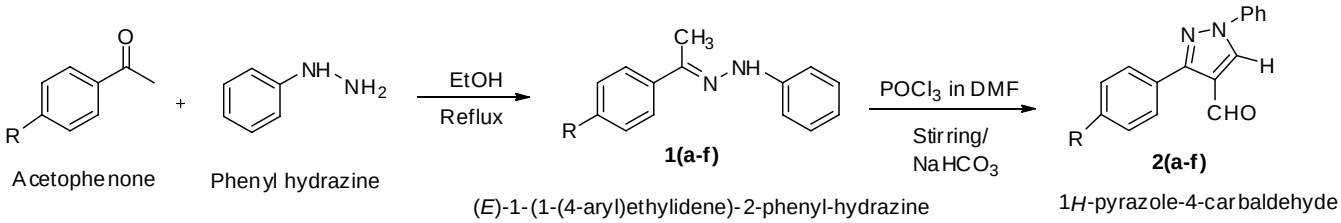
The melting points were determined using digital melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded as KBr pellets on Perkin-Elemer RX-IFTIR spectrophotometer. NMR spectra were taken down on Avance-II (Bruker) 400 MHz NMR spectrometer using DMSO as solvent and TMS as an internal standard. Mass spectra were recorded on Maldi-TOF Synapt XS HD Mass Spectrometer. Carbon, nitrogen and hydrogen content were analyzed with the help of Thermo Scientific (Flash 2000) CHN Elemental Analyzer. All spectroscopic studies were done in SAIF Punjab University, Chandigarh, India.

The synthetic approach adopted to synthesize the targeted hybrid imidazolylpyrazole compounds is summarized in **Scheme-I**. The starting material (**1a-f**) (*E*)-1-(1-(4-aryl)ethylidene)-2-phenyl hydrazine was prepared by refluxing acetophenones with phenyl hydrazine in ethanol using glacial acetic acid as the catalyst on water bath using a water condenser according to reported procedure [39,40]. The compounds (**1a-f**) were then subjected to well- known Vilsmeier-Haack reaction [41,42], which involved treating **1a-f** with Vilsmeier reagent *i.e.* chloroiminium ion generated *in situ* by treating phosphorus oxychloride with DMF on a magnetic stirrer. The formylated derivative was obtained by quenching the reaction mass on ice followed by treating with dilute sodium hydrogen carbonate solution to the neutralization point (**Scheme-I**). The products **2a-f** were obtained in pure form by recrystallization from ethanol.

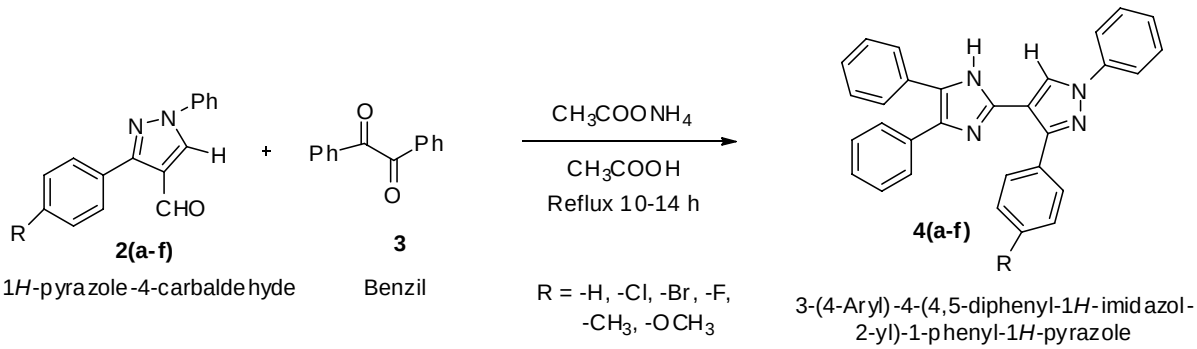
Synthesis of imidazolylpyrazole hybrid compounds: 1*H*-Pyrazole-4-carbaldehyde (**2a-f**) (1 mmol), benzil (**3**) (1 mmol) and ammonium acetate (10 mmol) were dissolved in glacial acetic acid and heated under reflux for 10-14 h on water bath using a water condenser. Progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the reaction mass was poured over crushed ice with constant stirring. A bright yellow to offwhite product was formed and washed with water several times, isolated by filtration on vacuum, dried over silica in a vacuum desiccator and recrystallized from ethanol to yield compounds (**4a-f**, **Scheme-II**). The structures of all the synthesized hybrid compounds were confirmed by spectroscopic techniques FTIR, ^{1}H and ^{13}C NMR, mass spectrometry and elemental analysis.

4-(4,5-Diphenyl-1*H*-imidazole-2-yl)-1,3-diphenyl)-1*H*-pyrazole (4a): White crystalline solid; yield 78%; m.p.: 255-258 ºC; IR (KBr, ν_{max}, cm^{-1}): 3430 (N-H), 1501 (C=N), 1220 (C-N), ^{1}H NMR (DMSO-d_6) δ (ppm): 7.25 (s, 1H, -NH group in imidazole ring), 8.56 (s, 1H, -CH group in pyrazole ring), 7.26-7.78 (m, 20H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 150.07 (C_2 in imidazole ring), 112.81 (C_4 in pyrazole ring), 119.11-139.87 (phenyl ring); MS (relative intensity) *m/z* value $[M+1]^+$: 439.19, $[M+2]^+$: 440.19; Anal. calcd. (found) for $C_{30}H_{22}N_4$ (monoisotopic mass 438.18) (%): C, 82.17 (82.05); H, 5.06 (5.09); N, 12.78 (12.86).

4-(4,5-Diphenyl-1*H*-imidazole-2-yl)-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole (4b): Light yellow crystalline solid; yield 74%; m.p.: 267-270 ºC; IR (KBr, ν_{max}, cm^{-1}): 3421 (N-H), 1502 (C=N), 1220 (C-N); ^{1}H NMR (DMSO-d_6) δ (ppm): 12.48



Scheme-I: Synthesis of 1*H*-pyrazole-4-carbaldehyde



Scheme-II: Synthetic route for imidazolylpyrazoles

(s, 1H, -NH group in imidazole ring), 8.98 (s, 1H, -CH group in pyrazole ring), 7.21-8.11 (m, 19H, Ar-H), 2.34 (s, 3H,-CH_3 group); ^{13}C NMR (DMSO-d_6) δ (ppm): 149.86 (C_2 in imidazole ring), 112.80 (C_4 in pyrazole ring), 118.25-139.39 (phenyl ring), 21.32 (C in –CH_3 group); MS (relative intensity) *m/z* value $[M+1]^+$: 453.21, $[M+2]^+$: 454.21; Anal. calcd. (found) for $C_{31}H_{24}N_4$ (monoisotopic mass 452.20) (%): C, 82.27 (82.25); H, 5.35 (5.32); N, 12.38 (12.43).

4-(4,5-Diphenyl-1*H*-imidazole-2-yl)-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole (4c): White crystalline solid; yield 84%; m.p.: 234-237 ºC; IR (KBr, ν_{max}, cm^{-1}): 3433 (N-H), 1506 (C=N), 1222 (C-N), ^{1}H NMR (DMSO-d_6) δ (ppm): 12.52 (s, 1H, -NH group in imidazole ring), 9.00 (s, 1H, -CH group in pyrazole ring), 7.22-8.21 (m, 19H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 163.05 (C attached to -F), 148.86 (C_2 in imidazole ring), 112.64 (C_4 in pyrazole ring), 114.71-161.10 (phenyl ring); MS (relative intensity) *m/z* value $[M+1]^+$: 457.19, $[M+2]^+$: 458.19; Anal. calcd. (found) for $C_{30}H_{21}N_4F$ (monoisotopic mass 456.18) (%): C, 78.93 (78.90); H, 4.64 (4.62); N, 12.27 (12.23); F, 4.16 (4.25).

3-(4-Bromophenyl)-4-(4,5-diphenyl-1*H*-imidazole-2-yl)-1-phenyl-1*H*-pyrazole (4d): Off-white crystalline solid; yield 82 %; m.p.: 270-273 ºC; IR (KBr, ν_{max}, cm^{-1}): 3429 (N-H), 1500 (C=N), 1220 (C-N), ^{1}H NMR (DMSO-d_6) δ (ppm): 12.50 (s, 1H, -NH group in imidazole ring), 9.00 (s, 1H, -CH group in pyrazole ring), 7.20-8.15 (m, 19H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 121.52 (C attached to -Br), 148.58 (C_2 in imidazole ring), 112.84 (C_4 in pyrazole ring), 118.33-139.18 (phenyl ring); MS (relative intensity) *m/z* value $[M+1]^+$: 517.11, $[M+2]^+$: 518.11; Anal. calcd. (found) for $C_{30}H_{21}N_4Br$ (monoisotopic mass 516.09) (%): C, 69.64 (69.71); H, 4.09 (4.12); N, 10.83 (10.75); Br, 15.44 (15.42).

3-(4-Chlorophenyl)-4-(4,5-diphenyl-1*H*-imidazole-2-yl)-1-phenyl-1*H*-pyrazole (4e): Bright yellow crystalline solid; yield 74%; m.p.: 266-269 ºC; IR (KBr, ν_{max}, cm^{-1}): 3429 (N-H),1501 (C=N), 1219 (C-N), ^{1}H NMR (DMSO-d_6) δ (ppm): 12.50 (s, 1H, -NH group in imidazole ring), 9.00 (s, 1H, -CH group in pyrazole ring), 7.20-8.21 (m, 19H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 134.98 (C attached to -Cl), 148.51 (C_2 in imidazole ring), 112.80 (C_4 in pyrazole ring), 118.29-139.16 (phenyl ring); MS (relative intensity) *m/z* value $[M+1]^+$: 473.16, $[M+3]^+$: 475.16; Anal. calcd. (found) for $C_{30}H_{21}N_4Cl$ (monoisotopic mass 472.15) (%): C, 76.18 (76.26); H, 4.48 (4.32); N, 11.85 (11.75); Cl, 7.50 (7.67).

4-(4,5-Diphenyl-1*H*-imidazole-2-yl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (4f): White crystalline solid; yield 85%; m.p.: 226-229 ºC; IR (KBr, ν_{max}, cm^{-1}): 3463 (N-H), 1506 (C=N), 1221 (C-N); ^{1}H NMR (DMSO-d_6) δ (ppm): 12.46 (s, 1H, -NH group in imidazole ring), 8.94 (s, 1H, -CH group in pyrazole ring), 7.01-8.09 (m, 19H, Ar-H), 3.80 (s, 3H, -OCH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 159.25 (C of Ph-group attached to -O), 149.67 (C_2 in imidazole ring), 112.40 (C_4 in pyrazole ring), 113.35-139.56 (phenyl ring), 55.06 (C of -CH_3 attached to –O); MS (relative intensity) *m/z* value $[M+1]^+$: 469.20, $[M+2]^+$: 470.20; Anal. calcd. (found) for $C_{31}H_{24}N_4O$ (monoisotopic mass 468.20) (%): C, 79.46 (79.56); H, 5.16 (5.32); N, 11.96 (11.75); O, 3.41 (3.37).

Antibacterial studies: The antibacterial activity of all newly synthesized hybrid imidazolylpyrazole compounds were studied by the agar well diffusion method [43,44] using DMSO as a solvent against two bacterial pathogenic strains *viz. Staphylococcus aureus* and *Klebsiella pneumoniae*. The stock solutions for the standard as well as for all the test compounds were prepared in DMSO. Twofold serial dilution method was adopted to inoculate the wells with varying concentrations. Sterilized petri plates were used to carry out the activity. Molten nutrient agar was spread uniformly and the plates were dried by placing in an incubator at 37 ºC for 1 h. Wells were carefully punched using a sterile cork-borer and the different doses were added into each labeled well, using different plates for different strains. The plates were then incubated at 37 ºC for 24 h. Control plate containing DMSO was also maintained along with in each trial. Neomycin was used as a reference drug and DMSO as a negative control. Experiments were performed in triplicates and standard deviation was also taken into account while computing the results reported as zone of inhibition in mm.

Antifungal studies: Antifungal studies were carried out against two fungal strains *viz. Aspergillus niger* and *Trichophyton rubrum* and performed by poisoned food technique. Potato dextrose agar medium was prepared under sterilized conditions and the plates were dried by placing in an incubator at 37 ºC for 1 h. Sterile cork-borer was used to make wells and different concentrations of the synthesized compounds prepared as mentioned above were loaded into those wells. The petri plates were prepared in triplicate and incubated at 25 ºC for 72 h. Commercial antifungal fluconazole was used as the reference drug. Activities were reported in terms of zone of inhibition.

RESULTS AND DISCUSSION

A two-step synthesis of novel hybrid imidazolylpyrazoles is reported. Initially different derivatives of 1*H*-pyrazole-4-carbaldehyde were synthesized. The Radziszewski reaction was executed by refluxing 1*H*-pyrazole-4-carbaldehyde, benzil and ammonium acetate in glacial acetic acid to procure the designed imidazolylpyrazole hybrids, which were finally purified by recrystallizing in ethanol. All the compounds were obtained in good yields. After that the spectroscopic and elemental analysis were done so as to confirm the proposed structures. The proposed structures for all synthesized compounds were confirmed on the basis of spectroscopic and elemental analysis data obtained for respective compounds.

IR studies: A sharp peak observed around 3463-3421 cm^{-1} confirms the formation of imidazole ring, is attributed to N-H stretch [38,45]. Disappearance of carbonyl bands of the pyrazole moiety clearly indicated the building up of imidazole moiety. Ar-C-H stretch at around 3059-3054 cm^{-1}, C=C stretch in the range 1636-1596 cm^{-1} are attributed to stretching vibrations of aromatic ring. Bands around 1506-1500 cm^{-1} and 1222-1219 cm^{-1} are assigned to C=N and C-N stretching vibrations of imidazole and pyrazole moiety, respectively and are in full agreement with previous reports [37].

^{1}H NMR studies: Chemical shifts at around δ 12.52-12.46 and δ 9.00-8.56 ppm confirmed the presence of -NH group in

imidazole and -CH group in the pyrazole ring structure, respectively, which are in line with previously published reports [37,39]. Also there is good accordance observed between the range as multiplet δ 7.01-8.21 ppm for aromatic protons [37].

^{13}C NMR studies: The peaks characteristic of linkage between imidazole and pyrazole rings *i.e.* the linkage between C_2 of imidazole ring and C_4 of pyrazole ring in the range; C_2 of imidazole appeared downfield around δ 148.51-150.07 ppm and C_4 of pyrazole ring shifted upfield in the range δ 112.40-112.84 ppm, these peaks are on the same track as observed in literature [45].

Mass studies: The prominent $[M+1]^+$, peak strongly supports the synthesis of novel hybrids [46]. The fragments obtained for all the derivatives are in accordance with fragmentation patterns that can be explained well by various rules. Even molecular mass, supported by prominent $[M+1]^+$ peak, confirms the presence of four nitrogen atoms in the formulae of (**4a-f**). Fragmentation pattern of compound (**4a**) is given in Fig. 1. Fragment with *m/z* 297.14 obtained after the loss of mass *m/z* 141 and fragment with *m/z* 274.27 obtained after the loss of mass *m/z* 23 further confirmed the molecular formula of $C_{30}H_{22}N_4$ for compound (**4a**).

Antimicrobial studies: The antimicrobial screening revealed that all the synthesized compounds are biologically active. All compounds were able to inhibit the growth with some variations. Compound (**4d**) has shown maximum inhibition against *S. aureus* and *K. pneumoniae*, whereas the compound (**4e**) emerged to be most active against *A. niger* and *T. rubrum*. As per previously published reports the probable reason for this may be the electronic effects of halogenated groups that favour inhibition activities [34,46]. Concentration also played an important role in deciding the degree of inhibition, maximum activity observed at 500 ppm. Previous report [47] has shown that the reason behind different inhibitions of bacterial growth seems to be based on multiple targets for the antibacterial agents that involve bacterial protein biosynthesis, bacterial cell-wall biosynthesis, bacterial cell membrane destruction, bacterial DNA replication and repair and inhibition of a metabolic pathway. Similarly, the impenetrability of the cell-wall of the fungus and the ribosomal constitution are the targets for an antifungal to work upon. Azoles, usually interfere with an enzyme that is important for creating the fungal cell membrane [48] thus making it unstable. To summarize, the novel hybrid imidazolylpyrazoles displayed moderate to good inhibition capacities against the bacterial as well as fungal strains. The details of antimicrobial and antifungal assays are summarized in Table-1. Data reported is taken as the average mean of thee values with ± 0.5 to ± 0.7 standard deviation.

Conclusion

Synthesis of a novel series of imidazolylpyrazole compounds was reported from benzil, substituted 1*H*-pyrazole-4-

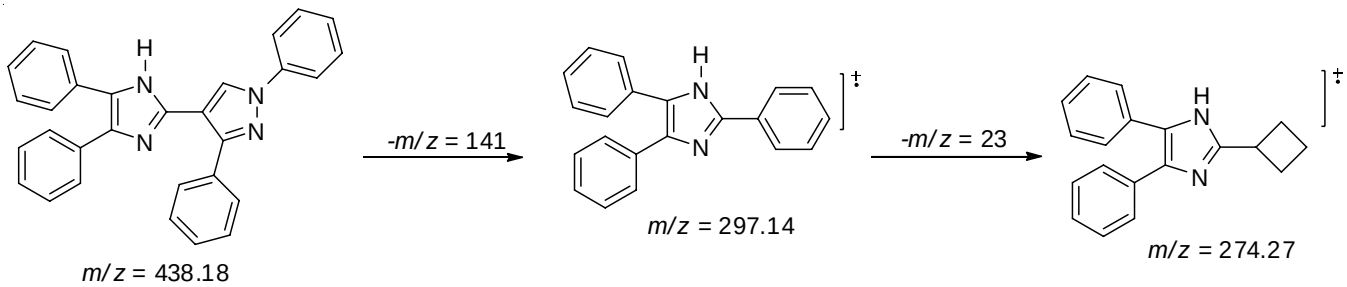


Fig. 1. Proposed mass fragmentation pattern of **4a**

TABLE-1
ANTIMICROBIAL RESULTS OF IMIDAZOLYLPYRAZOLES

Compd. No.	Zone of inhibition (mm)															
	Bacterial strains								Fungal strains							
	Staphylococcus aureus				*Klebsiella pneumoniae*				*Aspergillus niger*				*Trichophyton rubrum*			
	Dosage (ppm)				Dosage (ppm)				Dosage (ppm)				Dosage (ppm)			
	100	250	400	500	100	250	400	500	100	250	400	500	100	250	400	500
4a	7 ± 0.5	10 ± 0.6	11 ± 0.7	14 ± 0.6	8 ± 0.5	10 ± 0.5	11 ± 0.6	13 ± 0.6	6 ± 0.5	7 ± 0.5	9 ± 0.7	10 ± 0.6	7 ± 0.6	8 ± 0.5	10 ± 0.5	11 ± 0.6
4b	6 ± 0.5	8 ± 0.6	10 ± 0.6	13 ± 0.5	6 ± 0.5	7 ± 0.5	8 ± 0.5	9 ± 0.6	7 ± 0.5	9 ± 0.5	10 ± 0.6	12 ± 0.6	8 ± 0.5	10 ± 0.5	12 ± 0.6	13 ± 0.6
4c	8 ± 0.5	10 ± 0.6	12 ± 0.7	13 ± 0.5	6 ± 0.5	7 ± 0.6	9 ± 0.7	11 ± 0.7	9 ± 0.5	10 ± 0.6	11 ± 0.5	11 ± 0.6	7 ± 0.7	9 ± 0.5	10 ± 0.6	11 ± 0.5
4d	12 ± 0.6	13 ± 0.6	14 ± 0.6	16 ± 0.5	11 ± 0.6	12 ± 0.6	13 ± 0.7	14 ± 0.6	10 ± 0.5	12 ± 0.7	13 ± 0.5	14 ± 0.6	10 ± 0.7	11 ± 0.5	12 ± 0.7	13 ± 0.5
4e	10 ± 0.5	11 ± 0.4	13 ± 0.5	14 ± 0.7	9 ± 0.6	10 ± 0.4	12 ± 0.4	13 ± 0.4	12 ± 0.6	13 ± 0.5	14 ± 0.5	16 ± 0.6	11 ± 0.6	12 ± 0.5	13 ± 0.6	14 ± 0.4
4f	4 ± 0.4	6 ± 0,4	7 ± 0.6	8 ± 0.7	4 ± 0.5	7 ± 0.4	8 ± 0.5	9 ± 0.5	6 ± 0.7	7 ± 0.6	8 ± 0.6	9 ± 0.6	6 ± 0.7	7 ± 0.4	8 ± 0.4	10 ± 0.5
Standards	250 ppm 21 mm (Neomycin)				250 ppm 23 mm (Neomycin)				250 ppm 24 pmm (Fluconazole)				250 ppm 19 mm (Neomycin)			
Solvent	2 mm				3 mm				1 mm				3 mm			

carbaldehyde and ammonium acetate. All these novel compounds were characterized by advanced spectral and analytical techniques. The data fully supported the construction of imidazole moiety on the pyrazole base. The newly synthesized compounds were found to be active against the bacteria as well as the fungi. These imidazolylpyrazole scaffolds with some structural modifications may show promising pharmacological potential in future.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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