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Synthesis and Antimicrobial Activity of New Imidazole-Hydrazone Derivatives

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Hydrazones demonstrated significant antimicrobial activity, antitubercular activity and antitumoral activity in medicinal areas. The imidazole nucleus is well known to play an important role in living organisms since it is incorporated into the histidine molecule and many other important biological, pharmacological and therapeutic activities. Condensation of 4-phenyl-1*H*-imidazole-2-carbaldehyde (**3**) with various selected benzohydrazides (**4a-m**) resulted in imidazole-hydrazone derivatives (**5a-m**). They were evaluated for antibacterial and antifungal activity against *A. niger, C. albicans* (fungal strains), *E. coli* and *P. aeruginosa* (Gram-negative bacteria), *S. aureus* and *S. pyogenes* (Gram-positive bacteria) using griseofluvin (for fungi) and ciprofloxacin (for bacteria) as the standard drugs. In general, it is observed that most of the compounds were found to be potent against both the bacterial and fungal strains.

Keywords: Antibacterial activity, Antifungal activity, Imidazoles, Hydrazones, Synthesis.

INTRODUCTION

The imidazole nucleus is well known to play an important role in living organisms since it is incorporated into the histidine molecule and many other important biological, pharmacological and therapeutic activities[1-4]. Imidazole derivatives are the most used class of antifungal drugs[5], being active against pathogenic and non-pathogenic fungi[6]. Due to their antifungal properties imidazole-derived compounds have been used in agriculture as effective ingredients for controlling plants pests.

Hydrazones demonstrated significant antimicrobial activity[7], antitubercular activity[8] and antitumoral activity[9] in medicinal areas. On the other hand, hydrazones also exhibit good fungicidal activity against *Phytophthora infestans*[10], *Cladosporium cucumerinum* and *Colletotrichum orbiculare*[11] in the pesticides areas, some of them containing hydrazone structure have been commercialized, such as benquinox and ferimzone[12]. Hydrazones[13,14] having an azometine -NHN=CH- proton are synthesized by heating the appropriate substituted hydrazides with aldehydes in solvent. Characteristic properties of hydrazones are imprinted by the presence of the >C=N–N< structural unit, which contains two nitrogen atoms with nucleophilic character and a carbon atom which may act as either electrophile or nucleophile according to the reaction environment.

The treatment of infectious diseases still remains an important and challenging dilemma because of materialization of an increasing number of multi-drug resistant microbial pathogens. There is a realistic need for the discovery of new compounds capable with antimicrobial activity, which is distinct from the well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. Keeping in view of these observations, it was planned to synthesize some new imidazole-hydrazones (**5a-m**) by reacting 4-phenyl-1*H*-imidazole-2-carbaldehyde with various selected benzohydrazides. The synthesized compounds have been confirmed by ^{1}H NMR, mass and IR spectral analysis. The imidazole-hydrazones (**5a-m**) was tested for antibacterial and antifungal strains by disc diffusion method.

EXPERIMENTAL

Chemicals and solvents were purchased from Sigma-Aldrich and Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with a Perkin-Elmer Spectrum GX FTIR instrument and only diagnostic and/or intense peaks are reported. ^{1}H NMR spectra were recorded in DMSO-d_6 with a Varian Mercury plus 400 MHz instrument. Signals due to the residual protonated solvent (^{1}H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Mass spectra were recorded with a PE Sciex model API 3000 instrument.

General procedure for synthesis of benzohydrazide derivatives (4a-m): To a stirred solution of different benzoic acids (6.42 mmol) in ethanol (3 mL) was added H_2SO_4 (0.1 mL) and heated to reflux for 6-10 h. The reaction mixture was diluted with ethyl acetate followed by water. The organic layer was washed with saturated $NaHCO_3$ followed by water and brine solution. The organic layer was dried over sodium sulphate, filtered and evaporated to obtain the respective ethyl benzoate derivatives.

To a stirred solution of ethyl benzoate (3 mmol) derivatives in ethanol was added hydrazine-hydrate (5.44 mmol) and refluxed for 6-12 h. The reaction mixture was diluted with ethyl acetate followed by water. The organic layer was dried over sodium sulphate, filtered and evaporated to obtain the respective benzohydrazide derivatives (**4a-m**)[15,16]. The yields of the products varied from 80-85 %.

4-Phenyl-1*H*-imidazole-2-carbaldehyde (3): To a mixture of 4-bromo-1*H*-imidazole-2-carbaldehyde (1.0 g, 5.82 mmol), 2 M sodium carbonate (0.56 g, 5.32 mmol), $Pd(PPh_3)_4$ (0.01 mmol) in 50 % toluene:water (10 mL) was added phenyl boronic acid (0.81g, 6.62 mmol) and stirred at reflux temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with ethyl acetate and evaporated under reduced pressure to obtain the compound **3** as a pale yellow viscous liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1H), 9.96 (s, 1H), 7.84 (s, 1H), 7.76 (d, *J* = 6.4 Hz, 2H), 7.62-7.54 (m, 3H); ESI-MS: *m/z*, 173.2 $(M+H)^+$.

General procedure for the synthesis of hydrazone derivatives (5a-m): To a stirred solution of compound **3** (100 mg, 0.40 mmol) in ethanol was added corresponding benzohydrazides (**4a-m**) (1.0 mmol) and refluxed for 1 h. The reaction mass was washed with pet ether, filtered and dried under vacuum to obtain the pure hydrazone compounds. Yields of the products varied between 78 and 88 %.

(E)-N′-[(4-Phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5a): White solid; Yield: 86 %; m.p.: 112-113 °C; IR (KBr, ν_{max}, cm^{-1}): 3192, 3128, 3003, 2833, 1676, 1606, 1566, 1521, 1487, 1282, 1251, 1143, 1058, 916, 854, 813, 698; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.48 (s, 1H), 8.36 (s, 1H), 7.92-7.83 (m, 5H), 7.76 (d, *J* = 6.4 Hz, 2H), 7.62-7.54 (m, 3H), 7.14 (s, 1H); ESI-MS: *m/z*, 291.3 $(M+H)^+$.

(E)-4-Hydroxy-N′-[(4-phenyl-1*H*-imidazol-2-yl]methylene)benzohydrazide (5b): White solid; Yield: 88 %; m.p.: 120-121 °C; IR (KBr, ν_{max}, cm^{-1}): 3215, 3005, 2841, 1643, 1606, 1577, 1517, 1355, 1276, 1060, 960, 852, 694; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 10.13 (s, 1H), 8.47 (s, 1H), 8.35 (s, 1H), 7.92 (t, *J* = 6.8 Hz, 4H), 7.81 (t, *J* = 6.4 Hz, 3H), 7.14 (d, *J* = 12.0 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 307.2 $(M+H)^+$.

(E)-4-Bromo-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5c): Pale yellow solid; Yield: 85 %; m.p.: 105-106 °C; IR (KBr, ν_{max}, cm^{-1}): 3161, 3024, 1645, 1606, 1550, 1519, 1483, 1359, 1298, 1141, 1056, 823; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 7.87 (t, *J* = 6.8 Hz, 4H), 7.82 (s, 1H), 7.75 (t, *J* = 5.2 Hz, 4H), 7.14 (s, 1H); ESI-MS: *m/z*, 371.10 $(M+H)^+$.

(E)-4-Chloro-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5d): White solid; Yield: 85 %; m.p.: 109-110 °C; IR (KBr, ν_{max}, cm^{-1}): 3186, 3082, 3014, 2827, 1678, 1604, 1556, 1519, 1483, 1284, 1249, 1139, 1058, 960, 912, 846, 812, 661, 536; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.98 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 7.94 (d, *J* = 6.4 Hz, 2H), 7.86 (d, *J* = 6.4 Hz, 2H), 7.84 (s, 1H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.14 (s, 1H); ESI-MS: *m/z*, 325.0 $(M+H)^+$.

(E)-4-Fluoro-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5e): Yellow solid; Yield: 84 %; m.p.: 127-128 °C; IR (KBr, ν_{max}, cm^{-1}): 3194, 3128, 3016, 1680, 1604, 1566, 1523, 1504, 1305, 1282, 1251, 1141, 1060, 852; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.48 (s, 1H), 8.36 (s, 1H), 7.99 (d, *J* = 6.4 Hz, 2H), 7.86 (d, *J* = 6.4 Hz, 2H), 7.84 (s, 1H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.38 (t, *J* = 6.8 Hz, 2H), 7.14 (s, 1H); ESI-MS: *m/z*, 309.0 $(M+H)^+$.

(E)-4-(Methylsulfonyl)-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5f): Light brown solid; Yield: 82 %; m.p.: 134-135 °C; IR (KBr, ν_{max}, cm^{-1}): 3300, 3007, 2902, 1678, 1608, 1519, 1278, 1143, 1060, 962, 831, 783, 744; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (* 12.09, s, 1H), 8.51 (* 8.45, s, 1H), 8.37 (* 8.31, s, 1H), 8.15-8.01 (m, 4H), 7.90-7.67 (m, 5H), 7.14 (* 7.09, s, 1H); ESI-MS: *m/z*, 369.20 $(M+H)^+$.

(E)-3-Nitro-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]-benzohydrazide (5g): Yellow solid; Yield: 88 %; m.p.: 99-100 °C; IR (KBr, ν_{max}, cm^{-1}): 3439, 3207, 3030, 1678, 1610, 1523, 1348, 1300, 1261, 1062, 721; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H), 8.77 (s, 1H), 8.52 (s, 1H), 8.45 (d, *J* = 6.4 Hz, 1H), 8.37 (d, *J* = 6.0 Hz, 2H), 7.90 (d, *J* = 6.4 Hz, 2H), 7.92 (d, *J* = 6.4 Hz, 2H), 7.86 (t, *J* = 6.8 Hz, 2H), 7.15 (s, 1H); ESI-MS: *m/z*, 335.0 $(M+H)^+$.

(E)-3-Chloro-N′-[(4-phenyl-1*H*-imidazol-2-yl)-methylene]benzohydrazide (5h): Pale Yellow solid; Yield: 80 %; m.p.: 117-118 °C; IR (KBr, ν_{max}, cm^{-1}): 3439, 3207, 1678, 1610, 1523, 1348, 1300, 1261, 1062, 721; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.37 (s, 1H), 7.97 (s, 1H), 7.87 (d, *J* = 6.0 Hz, 2H), 7.84 (s, 1H), 7.81 (d, *J* = 6.0 Hz, 2H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.58 (d, *J* = 6.4 Hz, 2H), 7.15 (s, 1H); ESI-MS: *m/z*, 325.0 $(M+H)^+$.

(E)-2-Bromo-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]benzohydrazide (5i): Yellow solid; Yield: 78 %; m.p.: 124-125 °C; IR (KBr, ν_{max}, cm^{-1}): 3132, 2978, 2798, 1674, 1606, 1587, 1519, 1485, 1301, 1255, 1153, 1058, 956, 738; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (* 12.05, s, 1H), 8.37 (* 8.27, s, 1H), 8.31 (* 8.09, s, 1H), 7.86 (t, *J* = 6.4 Hz, 2H), 7.79-7.64 (m, 4H), 7.56-7.34 (m, 3H), 7.14 (s, 1H); ESI-MS: *m/z*, 370.20 $(M+H)^+$.

(E)-2-Iodo-N′-[(4-phenyl-1*H*-imidazol-2-yl)methylene]-benzohydrazide (5j): Pale yellow solid; Yield: 86 %; m.p.: 129-130 °C; IR (KBr, ν_{max}, cm^{-1}): 3433, 3130, 2980, 2818, 1681, 1606, 1519, 1487, 1301, 1255, 1153, 1058, 848; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.91 (* 12.02, s, 1H), 8.36 (* 8.27, s, 1H), 8.30 (* 8.09, s, 1H), 8.06-7.85 (m, 3H), 7.79-7.74 (m, 2H), 7.50-7.49 (m, 2H), 7.26-7.20 (m, 2H), 7.13 (* 7.09, s, 1H); ESI-MS: *m/z*, 417.10 $(M+H)^+$.

(E)-2,5-Difluoro-N′-[(4-phenyl-1*H*-imidazol-2-yl)-methylene]benzohydrazide (5k): White solid; Yield: 88 %;

m.p.: 98-99 °C; IR (KBr, ν_{max}, cm^{-1}): 3230, 3057, 1664, 1608, 1573, 1521, 1487, 1427, 1305, 1257, 1186, 1130, 1056, 962, 831, 655, 536; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.99 (* 12.15, s, 1H), 8.36 (* 8.29, s, 1H), 8.36 (* 8.11, s, 1H), 7.87 (t, *J* = 6.0 Hz, 2H), 7.77 (d, *J* = 6.0 Hz, 2H), 7.67 (* 7.54, d, *J* = 6.4 Hz, 2H), 7.45 (* 7.41, d, *J* = 6.2 Hz, 2H), 7.14 (* 7.10, s, 1H); ESI-MS: *m/z*, 327.20 $(M+1)^+$.

(E)-3,5-Dichloro-N′-[(4-phenyl-1*H*-imidazol-2-yl)-methylene]benzohydrazide (5l): White solid; Yield: 84 %; m.p.: 136-1375 °C; IR (KBr, ν_{max}, cm^{-1}): 3213, 3070, 2989, 1670, 1606, 1566, 1521, 1489, 1357, 1282, 1112, 1064, 960, 866, 829, 806; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 7.95-7.79 (m, 8H), 7.14 (s, 1H); ESI-MS: *m/z*, 359.0 $(M+H)^+$.

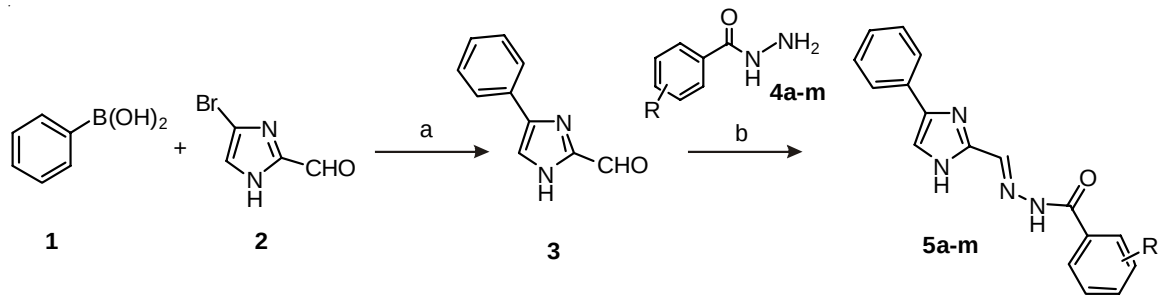
(E)-2,4-Dichloro-N′-[(4-phenyl-1*H*-imidazol-2-yl)-methylene]benzohydrazide (5m): White solid; Yield: 88 %; m.p.: 130-131 °C; IR (KBr, ν_{max}, cm^{-1}): 3109, 2985, 2821, 1683, 1604, 1519, 1483, 1301, 1251, 1151, 1058, 914, 844, 542; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (* 12.15, s, 1H), 8.37 (* 8.28, s, 1H), 8.31 (* 8.10, s, 1H), 7.87 (t, *J* = 6.4 Hz, 2H), 7.80-7.76 (m, 3H), 7.68-7.51 (m, 3H), 7.14 (* 7.11, s, 1H); ESI-MS: *m/z*, 359.0 $(M+H)^+$.

Antimicrobial and antifungal bioassay: The synthesized compounds **5a-m** was tested for antimicrobial and antifungal activity by disc diffusion method[17]. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi and nutrient agar for bacteria medium. The filter paper disks prepared by only DMSO (as a negative control) and with solution of 250 µg/mL concentrations of test compounds **5a-m** as well as standard compounds (ciprofloxacin and griseofluvin as positive control) were carefully placed over the spread cultures and incubated at 37 °C for 24 h for bacteria and at 28-30 °C for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter for the zones of inhibition was measured including the diameter of disk also. All determinations were made in triplicate for each of the compounds and the average value was taken. The antibacterial and antifungal activity was evaluated against *A. niger, C. albicans* (fungal strains), *E. coli* and *P. aeruginosa* (Gram-negative bacteria), *S. aureus* and *S. pyogenes* (Gram-positive bacteria) using griseofluvin (for fungi) and ciprofloxacin (for bacteria) as the standard drugs.

RESULTS AND DISCUSSION

The reaction scheme for the synthesis of imidazole-hydrazone derivatives (**5a-m**) is given in **Scheme-I**. Suzuki reaction of phenyl boronic acid (**1**) with 4-bromo-1*H*-imidazole-2-carbaldehyde (**2**) resulted in the formation of 4-phenyl-1*H*-imidazole-2-carbaldehyde (**3**). Condensation of aldehyde (**3**) with various hydrazides (**4a-m**) gave rise to imidazole hydrazone derivatives (**5a-m**). They were characterized by ^{1}H NMR, Mass and IR spectral data. As a general representative example, the ^{1}H NMR data of compound **5c** is interpreted as follows, the imidazole –NH proton appeared as a singlet at 11.70 ppm and the protons resonating at 8.45 ppm, 8.35 ppm as a singlet corresponds to -**CO**-**N*H***-N- proton and -N=**C*H***- groups respectively. The proton resonating at 7.14 ppm as a singlet represents the imidazole ring proton. All the other aliphatic and aromatic protons were observed at expected regions. The mass spectra of compounds showed (M+1) peaks, in agreement with their molecular formula. In the IR spectra, some significant stretching bands due to N–H, C=O, C=C and C=N were observed in the range 3444-3161, 1674-1640 and 1614-1504 cm^{-1} respectively. Because hydrazones exist as couple of diastereo-isomers E/Z[18], -N-H, imidazole -NH- and-CH=N-N protons were observed as couples[19] of peaks in varying ratios at respective regions respectively. As an example in the present discussions, imidazole hydrazone derivatives *viz.,* compounds **5i** (R = 2-Br), **5j** (R = 2-I), **5k** (R = -2,5-difluoro), **5l** (R = 3,5-dichloro), **5m** (R = 2,5-dichloro) appeared as a couple of diastereomers.

Antibacterial activity and antifungal activity: The results of antibacterial and antifungal activities of compounds **5a-m** are presented in Table-1. The newly synthesized hydraide-hydrazone derivatives (**5a-m**) displayed excellent to nil antibacterial and antifungal activities; In case of Gram-negative bacteria *viz., E. coli* and *P. aeruginosa,* compounds **5f** (R = -4-SO_2CH_3) showed excellent activity (zone of inhibition = 30 mm), while compounds **5b** (R = OH), compound **5k** (R = 2,5-fifluoro) displayed equipotent activity (zone of inhibition



Scheme-I: Synthesis of novel hydrazone derivatives (**5a-m**)

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF COMPOUNDS **5a-m** (ZONE OF INHIBITION IN mm)

Compound No.	Gram-negative bacteria		Gram-positive bacteria		Fungi	
	E. coli MTCC 443	*P. aeruginosa* MTCC 424	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*A. niger* MTCC 282	*C. albicans* MTCC 227
5a	26	24	18	17	26	22
5b	28	27	24	25	30	26
5c	15	13	–	–	22	18
5d	14	12	–	–	21	17
5e	25	23	25	23	28	24
5f	30	30	26	25	31	27
5g	25	24	18	19	28	24
5h	14	12	–	–	21	18
5i	13	13	–	–	20	16
5j	15	14	–	–	18	16
5k	28	27	20	20	30	26
5l	15	15	–	–	17	15
5m	14	13	–	–	16	15
Ciprofloxacin	28	27	22	22	–	–
Griseofluvin	–	–	–	–	28	24

Ciprofloxacin (conc. 250 µg/mL) was used as a standard drug for antibacterial activity; Greseofulvin (conc. 250 µg/mL) was used as a standard drug for antifungal activity.

= 27-28 mm) and compounds **5a** (R = H), **5e** (R = 4-F), **5g** (R = 3-NO_2) displayed good activity (zone of inhibition = 23-26 mm), with respect to ciprofloxacin. The remaining compounds **5c** (R = 4-Br), **5d** (4-Cl), **5h** (R = 3-Cl), **5i** (R = 2-Br), **5j** (R = 2-I), **5l** (R = 3,5-Cl) and **5m** (R= 2,4-Cl) exhibited weak activity (zone of inhibition = 12-15 mm).

In case of Gram-positive bacteria *viz.,* S.*aureus* and *S.pyogenes,* compounds **5b** (R = 4-OH), **5e** (R = 4-F) and **5f** (R = -4-SO_2CH_3) exhibited excellent activity (zone of inhibition = 24-26 mm). Compounds **5a** (R = H), **5g** (3-NO_2) and **5k** (R = 2,5-F) showed good activity and remaining compounds in the series did not show any activity.

The results of antifungal activity against *A. niger* and *C. albicans* with respect to standard drug griseofluvin is as follows: Compounds **5b** (R = 4-OH), **5f** (R = 4-SO_2CH_3) and **5k** (R = 2,5-F) indicated excellent activity (zone of inhibition = 26-31 mm) while compounds **5e** (R = 4-F), **5g** (R = 3-NO_2) showed equipotent activity and compounds **5c** (R = 4-Br), **5d** (R = 4-Cl), **5h** (R = 3-Cl), **5i** (R = 2-Br) and **5j** (R = 2-I) showed good activity (zone of inhibition = 16-18 mm). The remaining compounds **5l** (R = 3,5-Cl) and **5m** (R = 2,4-Cl) showed weak activity.

Conclusion

We have synthesized and characterized new imidazole-hydrazone derivatives (**5a-m**). They were effectively tested against selected bacterial and fungal strains. Most of the compounds showed significant antibacterial and antifungal activity. Against fungal strains, compounds **5b** (R = 4-OH), **5f** (R = 4-SO_2CH_3) and **5k** (R = 2,5-F) indicated excellent activity. Against, S. *aureus* and *S. pyogenes,* compounds **5b** (R = 4-OH), **5e** (R = 4-F) and **5f** (R = -4-SO_2CH_3) exhibited excellent activity (zone of inhibition = 24-26 mm) while compounds **5f** (R = -4-SO_2CH_3) showed excellent activity (zone of inhibition = 30 mm) against *E. coli* and *P. aeruginosa*.

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