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Synthesis, Characterization and Antimicrobial Activity of Novel Pyrazole Phenyl Methanamine Derivatives

Thatavarthi Padmini[1]*, Menka Surana[2], Bigala Raj Kamal[2]

[1]Research Scholar, Mewar University, Chittorgarh-312901, Rajasthan, India

[2]Research Supervisor, Mewar University, Chittorgarh-312901, Rajasthan, India.

Email :paddu2505@gmail.com

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Abstract:

In our expedition of finding newer classes of lead molecules as antimicrobial agents, a novel series of substituted pyrazole derivatives (3a-3j) were synthesized by simple and effective method in good to high yields. The compounds were characterized by IR, ^{1}HNMR and MASS spectral methods. Synthesized compounds screened for in vitro antimicrobial activity against a range of Gram-positive and Gram-negative and fungal strains using disc diffusion method were evaluated. Most of the compounds exhibited significant antimicrobial activity against bacterial strains *Bacillus subtilis* and *Staphylococcus aureus*, fungal strains *Aspergillusniger*and *Candida albican* than the standard drugs. Compound 3f and 3g displayed potent activity against all the strains.

Keywords —Pyrazole, Characterization, Schiff's base, antibacterial, antifungal.

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I. INTRODUCTION

Treatment to the microbial infections still is a challenging problem due to various factors including multi drug resistance of the pathogens. Due to inefficiency of the current antibiotics in the market, there is a need to develop new antimicrobial agents [1].

Aza-heterocyclic based drugs are acquiring significance in medicinal and natural products research by virtue of its multifarious properties and broad spectrum of applications for various ailments [2]. The extensive literature confirms that aza-heterocyclic molecules, particularly the pyrazole derivatives, are widely used. They are documented to possess anti-inflammatory [3-6], antibacterial, antifungal [7-10], antiviral [11,12], antimalarial [13,14], analgesic [15-17], antipyretic [18,19], antidepressant [20-22], anticonvulsant [23,24], antidiabetic [25,26], antiangiogenetic [27], antitubercular [28] and anticancer [29-32] activities. Pyrazoles build a crucial place in pharmaceutical industry as they constitute the fundamental structure for many commercial drugs such as celecoxib, sildenafil and rimonabant [33].

Since the inception of foremost synthetic method of pyrazole i.e. Paal-Knorr synthesis by condensation of 1,3-diketones with hydrazine which yield 1,3,5-trisubstituted pyrazoles, it is the subject of interest for researchers to synthesize the substituted pyrazoles. Due to the convenience and versatility, Paal-Knorr synthesis had been the principal synthetic method for pyrazole synthesis. There are several established methods for creating different pyrazole derivatives. There is a tonne of literature on the improvement of Paal-Knorr synthesis yields reported by researchers by substituting acetylenic and olefinic ketone [34].

Globally, efforts are now being made to rationally develop new antimicrobial agents. In a quest of this objective, our research endeavours have been focused on the direction of the rational designing of new chemical molecules that are effective as antimicrobial agents. Owing to the importance of pyrazole-based compounds, now we wish to describe simple, novel and environmentally benign approach towards the synthesis of pyrazole derivatives and *in vitro* screening results of antimicrobial agents.

II. MATERIAL AND METHODS

All chemicals and solvents used in this work were synthetic grade purchased from Sigma-Aldrich and used after purification. TLC plates were obtained from Merck-precoated aluminum sheets of silica gel 60 F254 of 0.5 thickness. For the visualization of TLC spots Iodine, U.V and Anisaldehyde. H_2SO_4 were used. The isolation and purification of the pure chemicals were done using column chromatography. With ethanol, all of the chemicals recrystallized. Remi's electrical melting point equipment was used to calculate melting points. BRUKER DRX - 400 MHz was used to record ^1H &^{13}C NMR. The splitting patterns are referred to as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m).MASS recorded on BRUKER ESI-IT MS. The bacterial and fungal strains were obtained from the Department of Microbiology, Osmania University, Hyderabad. The samples were sub cultured and preserved at 4^0 C.

Synthesis

The scheme of synthesis for the designed pyrazolederivatives were depicted in Figure 1.

In a 50ml RBF 2-methyl-3-oxobutanenitrile (1mmol, 1eq) dissolved in 10ml ethanol, mixed with HCl (1mmol, 1eq). To this solution, hydrazine hydrate (1mmol, 1eq) were added and the reaction mixture refluxed for 3hrs with continuous monitoring of the reaction progress with TLC. After reaction completion the reaction mixture was worked up with sodium bicarbonate solution, extracted with two ethyl acetate, and the organic layer was washed with brine solution, dried over anhydrous sodium sulfate and the organic layer evaporated under vacuum yielded the crude product of 3,4-dimethyl-1H-pyrazol-5-amine (2). The crude product was purified with column chromatography and recrystallized with hot ethanol.

Procedure for the synthesis substituted (3,4-dimethyl-1H-pyrazol-5-yl)-1-phenylmethanimine derivatives

In a 50ml RBF 3,4-dimethyl-1H-pyrazol-5-amine (2) (1mmol, 1eq) dissolved in 10ml ethanol, mixed with acetic acid (1mmol, 1eq). To this solution, various substituted benzaldehydes (a-j) (1mmol, 1eq) were added, and the reaction mixture stirred at room temperature with continuous monitoring of the reaction progress with TLC. After reaction completion the reaction mixture was worked up with sodium bicarbonate solution, extracted with two ethyl acetate, and the organic layer was washed with brine solution, dried over anhydrous sodium sulfate and the organic layer evaporated under vacuum yielded the crude product of (3,4-dimethyl-1H-pyrazol-5-yl)-1-phenylmethanimine derivatives

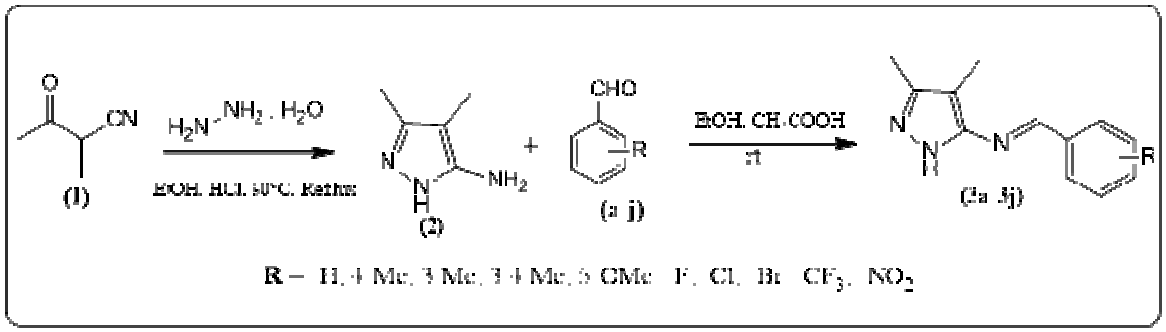

Fig. 1 Procedure for the synthesis of 3,4-dimethyl-1H-pyrazol-5-amine (2)

(3a-3j). The crude product was purified with column chromatography and recrystallized with hot ethanol.

Antimicrobial Assay

In vitro antibacterial assay

All the bacterial strains used in this experiment were obtained from the department of microbiology, Osmania University and stored at 4ºC. Synthesized compounds (3a-3j) were screened for their antimicrobial potential using disc-diffusion method against gram positive bacteria (*Staphylococcus aureus,* and *Bacillus subtilis,)* andgram-negative bacteria (*Pseudomonas aeurogonsa, Escherichia coli*). Neomycin sulphate (100µg/ml) in DMSO was used as standard antibiotic. In the pre-sterilized petri-dishes Nutrient agar medium was taken and the microorganisms were grown by inoculating 0.5 ml of spore suspension (108 spores/ml) culture broth. Using DMSO stock solutions for all the synthesized compounds (3a-3j)was prepared. The disc (6 mm in diameter) was stuffed with 200 µg/ml, 100 µg/ml and 50 µg/ml of each test solution, placed on the seeded nutrient agar medium and incubated the petri-dishes at 37˚C for 24 hr. DMSO alone was used as control at the equal preceding concentration. Each compound's zone of inhibition was measured in millimetres. Three duplicates of the experiment were performed.

In vitro antifungal assay

The fungal strains were also obtained from the department of microbiology, Osmania University and preserved at 4ºC. By employing disc-diffusion method antimicrobial activity of the titled compounds (3a-3j)was evaluated against fungal strains (*Candid albicans, Aspergillusniger*). Nystatin (100µg/ml) in DMSO was used as standard antibiotic. In the pre-sterilized Petri-dishes potato dextrose agar medium was taken and the microorganisms were grown by inoculating the standard suspension of culture broth. Using DMSO stock solutions for all the synthesized compounds (3a-3j)was prepared. The disc (6 mm in diameter) was stuffed with 200 µg/ml 100 µg/ml and 50 µg/ml of each test solution, placed on the seeded potato dextrose agar medium and incubated the Petri-dishes at 28˚C for 48 hr. DMSO alone was used as control at the equal preceding concentration. Zone of inhibition of each compound was recorded in mm. The experiment was done in triplicates.

III. RESULTS AND DISCUSSION

Chemistry

All the compounds were synthesized in competitive yields. NMR spectra of the all compounds displayed the respective peak of the C-H proton of the imine at around 8.8-8.9 and the ^{13}C peak at around 160-165 determined the formation of the designed compounds. Further, the m/z values of all compounds agree with the mass values. The spectral data of the compounds given below.

Spectral characteristics of the synthesized pyrazole derivatives:

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-phenylmethanimine (3a)

^{1}H NMR: δ 2.29-2.45 (6H, 2.34 (s), 2.40 (s)), 7.36-7.51 (3H, 7.43 (dddd, *J* = 7.9, 7.4, 1.5, 0.4 Hz), 7.44 (dddd, *J* = 7.5, 7.3, 1.4, 1.3 Hz)), 8.18 (2H, dtd, *J* = 7.9, 1.4, 0.4 Hz), 8.95 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 127.3 (1C, s), 127.8 (1C, s), 128.4 (2C, s), 128.6 (2C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{12}H_{13}N_3$, m/z – 200.15.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(p-tolyl)methanimine (3b)

^{1}H NMR: δ 2.22 (3H, s), 2.28-2.43 (6H, 2.33 (s), 2.38 (s)), 7.13 (2H, ddd, *J* = 7.8, 1.2, 0.4 Hz), 7.40 (2H, ddd, *J* = 7.8, 1.7, 0.4 Hz), 8.94 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 21.3 (1C, s), 127.3 (1C, s), 128.5 (2C, s), 129.1 (2C, s), 135.6 (1C, s), 141.5 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{13}H_{15}N_3$, m/z – 214.05.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(m-tolyl)methanimine (3c)

^{1}H NMR: δ 2.21-2.44 (9H, 2.26 (s), 2.33 (s), 2.39 (s)), 7.16-7.30 (2H, 7.22 (ddd, *J* = 7.8, 1.6, 1.3 Hz), 7.23 (ddd, *J* = 7.9, 7.8, 0.4 Hz)), 7.43-7.62 (2H, 7.49 (ddd, *J* = 7.9, 1.7, 1.3 Hz), 7.56 (ddd, *J* = 1.7, 1.6, 0.4 Hz)), 8.95 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s),

17.9 (1C, s), 21.3 (1C, s), 127.3 (1C, s), 127.4 (1C, s), 128.0 (1C, s), 128.1 (1C, s), 128.6 (1C, s), 134.0 (1C, s), 134.8 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s) **ESI-MS:** $C_{13}H_{15}N_3$, m/z – 214.05.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(3,4-dimethylphenyl)methanimine (3d)

^{1}H NMR: δ 2.15-2.25 (6H, 2.19 (s), 2.20 (s)), 2.32 (3H, s), 2.42 (3H, s), 6.91 (1H, dd, *J* = 8.0, 0.5 Hz), 7.14 (1H, dd, *J* = 8.0, 1.8 Hz), 7.39 (1H, dd, *J* = 1.8, 0.5 Hz), 8.95 (1H, s).**^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 19.9-20.1 (2C, 20.0 (s), 20.0 (s)), 127.3 (1C, s), 127.4 (1C, s), 128.5 (1C, s), 128.9 (1C, s), 133.4 (1C, s), 134.0 (1C, s), 134.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{14}H_{17}N_3$, m/z – 228.20.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(4-methoxyphenyl)methanimine (3e)

^{1}H NMR: δ 2.22-2.35 (6H, 2.27 (s), 2.30 (s)), 3.82 (3H, s), 7.14 (2H, ddd, *J* = 8.8, 1.2, 0.5 Hz), 7.53 (2H, ddd, *J* = 8.8, 1.6, 0.5 Hz), 8.90 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 56.0 (1C, s), 114.3 (2C, s), 127.3 (1C, s), 130.1 (2C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 159.8 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{13}H_{15}N_3O$, m/z – 230.25.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(4-fluorophenyl)methanimine (3f)

^{1}H NMR: δ 2.27-2.43 (6H, 2.32 (s), 2.38 (s)), 7.31 (2H, ddd, *J* = 8.4, 1.2, 0.5 Hz), 7.59 (2H, ddd, *J* = 8.4, 1.5, 0.5 Hz), 8.92 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 115.4 (2C, s), 127.3 (1C, s), 130.1 (2C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s), 162.5 (1C, s).**ESI-MS:** $C_{12}H_{12}FN_3$, m/z – 218.15.

(E)-1-(4-chlorophenyl)-N-(3,4-dimethyl-1H-pyrazol-5-yl)methanimine (3g)

^{1}H NMR: δ 2.28-2.44 (6H, 2.33 (s), 2.39 (s)), 7.37 (2H, ddd, *J* = 8.5, 1.5, 0.5 Hz), 7.59 (2H, ddd, *J* = 8.5, 1.4, 0.5 Hz), 8.94 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 127.3 (1C, s), 128.7 (2C, s), 129.2 (2C, s), 133.7 (1C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s).**ESI-MS:** $C_{12}H_{12}ClN_3$, m/z – 234.60.

(E)-1-(4-bromophenyl)-N-(3,4-dimethyl-1H-pyrazol-5-yl)methanimine (3h)

^{1}H NMR: δ 2.28-2.45 (6H, 2.33 (s), 2.40 (s)), 7.38-7.61 (4H, 7.45 (ddd, *J* = 8.5, 1.7, 0.5 Hz), 7.55 (ddd, *J* = 8.5, 1.4, 0.5 Hz)), 8.92 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 122.3 (1C, s), 127.3 (1C, s), 127.5 (2C, s), 131.7 (2C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{12}H_{12}BrN_3$, m/z – 279.05.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(4-(trifluoromethyl)phenyl)methanimine (3i)

^{1}H NMR: δ 2.30-2.46 (6H, 2.35 (s), 2.41 (s)), 7.47 (2H, ddd, *J* = 8.2, 1.8, 0.5 Hz), 7.70 (2H, ddd, *J* = 8.2, 1.7, 0.5 Hz), 8.96 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 123.8 (1C, s), 125.7 (2C, s), 127.3 (1C, s), 128.5 (2C, s), 130.3 (1C, s), 135.6 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s).**ESI-MS:** $C_{13}H_{12}F_3N_3$, m/z – 268.15.

(E)-N-(3,4-dimethyl-1H-pyrazol-5-yl)-1-(4-nitrophenyl)methanimine (3j)

^{1}H NMR: δ 2.31-2.45 (6H, 2.36 (s), 2.40 (s)), 7.74 (2H, ddd, *J* = 8.7, 1.9, 0.5 Hz), 8.29 (2H, ddd, *J* = 8.7, 1.8, 0.5 Hz), 9.25 (1H, s). **^{13}C NMR:** δ 13.7 (1C, s), 17.9 (1C, s), 123.8 (2C, s), 127.3 (1C, s), 129.4 (2C, s), 135.6 (1C, s), 147.3 (1C, s), 148.1 (1C, s), 154.4 (1C, s), 161.7 (1C, s). **ESI-MS:** $C_{12}H_{12}N_4O_2$, m/z – 245.10.

Antimicrobial activity

Antibacterial activity

In the present study total 10 synthesized novel imidazolineacetamide derivatives (3a-3j) were screened for their antimicrobial potential against two gram-positive (*Bacillus subtilis,* and *Staphylococcus aureus*) and two gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). The results of antibacterial assay in terms of zone of inhibition (mm) of all tested compounds against gram-positive and gram-negative strains were illustrated in Table 2 and Table 3 respectively. *Invitro*antibacterial assay revealed the antibacterial potential of the all-tested compounds with difference in magnitude of inhibition of microbial growth. All the values of inhibition of microbial growth were compared

against the standard drug (Neomycin sulphate at 100µg/ml) zone of inhibition.

TABLE 1
Zone of inhibition (mm) of the compounds against gram positive bacteria

Compound	Gram positive bacteria					
	Bacillus subtilis			Staphylococcus aureus		
	50 µg/ml	100 µg/ml	200 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml
3a	18.4	23.6	26.2	17.1	22.3	24.9
3b	18.4	22.3	24.9	18.4	22.3	26.2
3c	15.8	18.4	22.3	15.8	19.7	23.6
3d	14.5	19.7	23.6	15.8	18.4	22.3
3e	15.8	19.7	22.3	14.5	21	24.9
3f	24.9	31.4	37.9	23.6	32.7	36.6
3g	18.4	23.6	28.8	18.4	22.3	26.2
3h	17.1	22.3	26.2	15.8	21	26.2
3i	19.7	24.9	28.8	19.7	23.6	27.5
3j	22.3	28.8	34	24.9	31.4	32.7
DMSO	3.4			2.6		
Neomycin sulphate 100µg/ml	32.4			34.1		

TABLE 2
Zone of inhibition (mm) of the compounds against gram negative bacteria

Compound	Gram negative bacteria					
	Escherichia coli			Pseudomonas aeruginosa		
	50 µg/ml	100 µg/ml	200 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml
3a	23.4	24.9	27.5	17.1	19.7	23.6
3b	17.1	21	26.2	14.5	18.4	22.3
3c	15.8	22.3	26.2	15.8	17.1	22.3
3d	17.1	22.3	27.5	18.4	23.6	27.5
3e	14.5	19.7	24.9	15.8	19.7	24.9
3f	27.5	36.6	41.8	23.6	27.5	34
3g	24.9	34	39.2	21	24.9	32.7
3h	19.7	26.2	30.1	18.4	22.3	26.2
3i	18.4	23.6	27.5	15.8	21	24.9
3j	24.9	28.8	35.3	19.7	23.6	32.7
DMSO	3.9			3.1		
Neomycin sulphate 100µg/ml	36.3			28.2		

With respect to gram positive bacteria growth inhibition, the compounds 3a, 3b, 3f, 3g, 3h, 3i and 3j displayed relatively significant inhibition at a dose of 100µg/ml and 200 µg/ml than the remaining compounds against both *Bacillus subtilis* and*Staphylococcus aureus*. Compound 3f and 3i is sensitive towards both gram-positive bacterial strains at all concentrations. Compound 3f is exhibiting better activity at a dose 200 µg/ml than the standard Neomycin sulphate at a dose of 100µg/ml.

TABLE 3
Zone of inhibition (mm) of the compounds against fungal strains

Compound	Fungal strains					
	Aspergillusniger			Candida albicans		
	50 µg/ml	100 µg/ml	200 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml
3a	11.6	15.5	18.1	15.5	19.4	23.3
3b	10.3	16.8	18.1	14.2	18.1	20.7
3c	9	14.2	14.2	15.5	19.4	22
3d	10.3	14.2	15.5	12.9	18.1	24.6
3e	7.7	12.9	16.8	10.3	16.8	22
3f	18.1	22	25.9	22	28.5	33.7
3g	18.1	22	27.2	23.3	25.9	33.7
3h	14.2	15.5	20.7	10.3	16.8	22
3i	15.5	16.8	22	7.7	15.5	19.4
3j	12.9	16.8	22	9	16.8	20.7
DMSO	2.8			3.4		
Nystatin (100µg/ml)	28.1			29.3		

Compound 3j displayed almost equal antibacterial activity at a dose of 200µg/ml while compared with the standard neomycin activity at a dose of 100µg/ml.

In the case of gram-negative bacteria growth inhibition, the compounds 3a, 3c, 3d, 3f, 3g, 3h, 3i and 3j displayed relatively better inhibition at a dose of 100µg/ml and 200µg/ml than the remaining compounds. Between the two gram-negative bacterial strains tested, all the compounds showed a better inhibition capacity against both *Escherichia coli* and*Pseudomonas aeruginosa.* Compound 3f possess the highest potency at doses 100µg/ml and 200µg/ml than the standard Neomycin at a dose of 100 µg/ml. Compound 3g displays better activity than standard drug at 100µg/ml and 200µg/ml against *Escherichia coli*whereas, against *Pseudomonas aeruginosa*displaying better activity at a dose 200µg/ml.

Compound 3j displayed similar antibacterial potency at a dose of 200µg/ml compared with the standard neomycin activity at a dose of 100µg/ml against *Escherichia coli*;showing better activity than Neomycin against *Pseudomonas aeruginosa*.

From the results of in vitro antibacterial assay, it can comprehend that the substituent groups on the phenyl ring system are affecting the gram-positive and gram-negative selectivity of the basic imidazolineacetamide nucleus. Most compounds that contain electron withdrawing group such as -F (3f), -Cl (3g), -NO_2 (3j) are active against the gram-positive and gram-negative bacterial strains. The antibacterial activity of the synthesized (3,4-dimethyl-1H-pyrazol-5-yl)-1-phenylmethanimine derivatives may be attributed to the pyrazole nucleus that was reported to interact with the bacterial macromolecules and the difference in selectivity, and potency to the different substituent's attached to the primary (3,4-dimethyl-1H-pyrazol-5-yl)-1-phenylmethanimine pyrazole.

Antifungal activity

Antifungal potential for the synthesized compounds was also developed against selected fungal strains (Table 3). Fascinatingly, compounds 3f, and 3g showed significant antifungal activity against *Aspergillusniger*. Compound 3a, 3d, 3f, and 3g displayed good activity against *Candida albican.*It is also noticed that *Candida albican* is more sensitive to the synthesized compounds than other strains. 3f and 3gis the most potent antifungal than the standard Nystatin and showed maximum growth inhibition with 32.5mm of zone of inhibition against *Candida albicans.* All compounds displayed less sensitivity towards *Aspergillusniger than Candida albicans.* The results suggest the antifungal potential of the imidazolineacetamide derivatives.

III. CONCLUSION

In conclusion, a novel series of pyrazol derivatives (3a-3j)were synthesized from commercially available starting materials and economically feasible method. The structure elucidation was done with the help of their physical, analytical, and spectral data. All the 10 compounds were screened for *Invitro* antimicrobial activity using both gram positive, gram negative bacterial and fungal strains using disc diffusion method. The average zone of inhibition was measured and compared with the standard drugs neomycin and nystatin, showing significant antimicrobial activities. Further studies are needed to establish the possible mechanism of antibacterial, antifungal actions can be helpful in the future development of imidazoline nucleus based acetamide derivatives as novel antimicrobial agents.

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