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Design and Synthesis of New 1,2,3-Triazole-pyrazole Hybrids as Antimicrobial Agents[1]

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Abstract—In the present study, a series of novel 1,2,3-triazoles derivatives (**4a–4c**) were synthesized by the 1,3-dipolar cycloaddition (click-reaction) of 1-phenyl-3-[2-(prop-2-yn-1-yloxy)phenyl substituted]-1*H*-pyrazole-4-carbaldehyade **(3a–3c**) with various aryl azides in the presence of sodium ascorbate and copper sulphate with high yields. The required precursors **3a–3c** were synthesized by the reaction of 1-(2-hydroxy phenyl substituted)ethanones (**1a–1c**) with propargyl bromide via 1-[2-(prop-2-yn-1-yloxy)phenyl substituted] ethanone (**2a–2c**)**,** followed by reaction with phenyl hydrazine. The newly synthesized 1,2,3-triazole-pyrazole derivatives were characterized by analytical and spectral data. All synthesized compounds were evaluated *in vitro* for their antibacterial and antifungal activity. The most active compounds **4a$_5$–4a$_7$** demonstrated a broad spectrum of antibacterial activity against all strains used for testing. Compounds (**4a$_4$**, **4b$_1$**, **4c$_1$**, **4c$_2$**) demonstrated significant antifungal activity at the concentration of 10 μg/mL.

Keywords: 1,2,3-triazoles, pyrazole, Knorr pyrazole synthesis, Click reaction, antimicrobial activity

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1,2,3-Triazole and its derivatives demonstrate diverse biological activities such as antitubercular [1], anti-HIV [2], antifungal [3], antibacterial [4], and anticancer [5], play significant role in organic synthesis [6], and have many other valuable properties [7–9]. Pyrazoles constitute another important pharmacophores group with diverse biological activities [10–20]. 1,2,3-Triazoles as active linker units can connect two pharmacophores to give an original bifunctional drugs [21]. Recently the strategy employing a combination of two different active fragments in one molecule has emerged [22]. According to it each drug moiety is designed to bind separately to two different biological targets.

In our earlier studies, we focused on the design and synthesis of pyrazole derivatives bearing 1,2,3-triazole scaffold as potential antimicrobial agents [23] and pyrazoline-based bis 1,2,3-triazole scaffolds [24]. Synthesized 1,2,3-triazole derivatives were tested for their antimicrobial activity [25]. In the current study we synthesized a molecular system that combined two components, 1,2,3-triazole and pyrazole, and tested its potential antibacterial and antifungal effects.

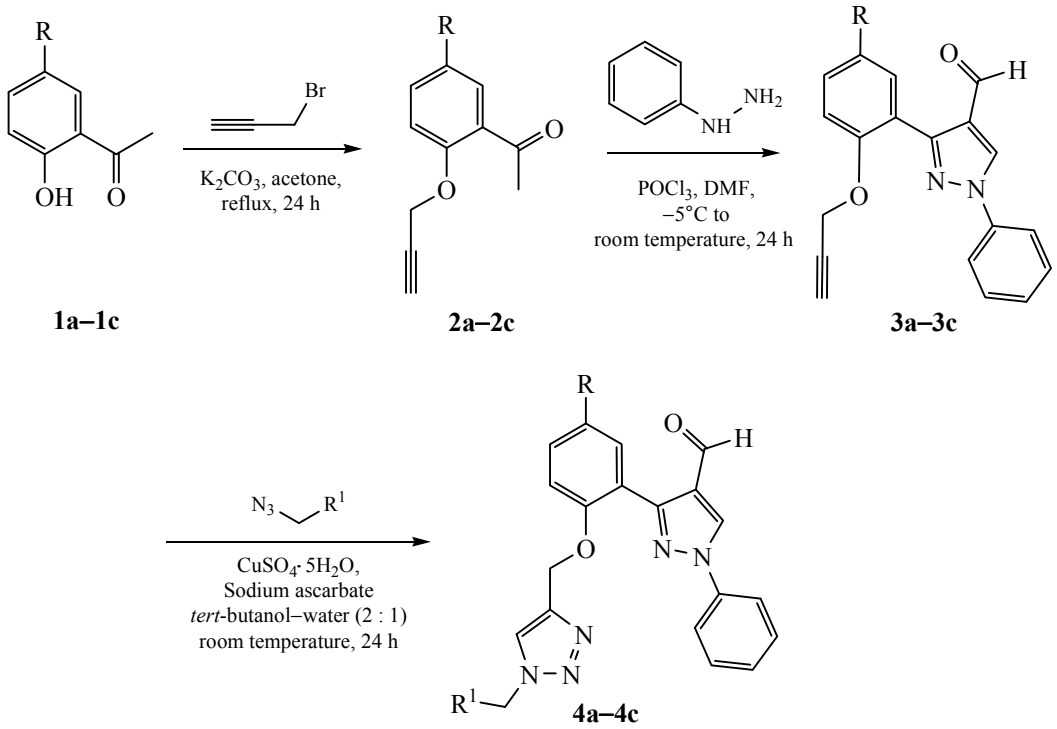
RESULTS AND DISCUSSION

Synthetic approach to the target compounds **4a–4c** is depicted in Scheme 1. Approach to 1,2,3-triazole derivatives containing pyrazole moiety was based on the Knorr pyrazole synthesis [26]. The starting compounds 1-[2-(prop-2-yn-1-yloxy)phenyl substituted] ethanone (**2a–2c**) were prepared in the nucleophilic substitution reaction of a 1-(2-hydroxyphenyl substituted) ethanone (**1a–1c**) with propargyl bromide in the presence of K_2CO_3. Reaction of **2a–2c** with phenyl hydrazine in the presence of $POCl_3$–DMF by Vilsmeier Haack reaction afforded the pyrazole moiety **3a–3c**. The compounds **4a–4c** were prepared using $CuSO_4 \cdot 5H_2O$–sodium ascorbate in the solvent system *t*-BuOH–H_2O under conventional conditions in high yields**.** In all cases, the reactions proceeded efficiently at ambient temperatures.

All analytical and spectral data accumulated for compounds **3, 4** were in accord with their structures.

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of compounds **4a$_1$-4c$_2$**.



1a–1c **2a–2c** **3a–3c** **4a–4c**

1a: R = H; **1b**: R = CH_3; **1c:** R = Cl; **2a**: R = H; **2b**: R = CH_3; **2c**: R = Cl; **3a**: R = H; **3b**: R = CH_3; **3c**: R = Cl. **4a$_1$**: R = H; R^1 = phenyl; **4a$_2$**: R = H; R^1 = 3-chlorophenyl; **4a$_3$**: R = H; R^1 = 4-bromophenyl; **4a$_4$**: R = H; R^1 = 3,5-dimethylphenyl; **4a$_5$**: R = H; R^1 = 4-methoxyphenyl; **4a$_6$**: R = H; R^1 = 4-phenylcarboxylic acid; **4a$_7$**: R = H; R^1 = CH_2OH (methyl alcohol); **4b$_1$**: R = CH_3; R^1 = phenyl; **4b$_2$**: R = CH_3; R^1 = 3-chlorophenyl; **4c$_1$**: R = Cl; R^1 = phenyl; **4c$_2$**: R = Cl; R^1 = 3-chlorophenyl.

Antibacterial activity. Antibacterial activity of compounds **4a$_1$–4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** has been assayed. The compounds in concentration range from 1 to 100 μg/mL were used against gram positive and gram negative clinically important pathogens. Zones of inhibition were determined according to the Muller–Hinton agar method. Inhibitory effects of compounds **4a$_1$–4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** are presented in Fig. 1.

The tested compounds (**4a$_1$, 4a$_2$, 4a$_5$, 4a$_6$, 4a$_7$, 4c$_2$**) demonstrated high antibacterial activity against all tested bacteria (Table 1).

Minimum inhibitory activity of bacteria stains. The minimum inhibitory concentration (MIC, μg/mL) of synthesized compounds **4a$_1$-4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** and ciprofloxacin was determined against antibiotic susceptible strains of both Gram positive and Gram negative bacteria. Among tested compounds **4a$_1$, 4a$_3$** demonstrated lower MIC values against both Gram positive and Gram negative bacteria strains.

Antifungal activity. Antifungal activity of compounds **4a$_1$–4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** was assayed *in vitro* at the concentration of 10 μg/mL in a well against *Aspergillus niger* and *Aspergillus flavus*. Inhibitory effects of compounds **4a$_1$–4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** against these organisms are presented in Fig. 2. The zones of inhibition indicated that most of compounds exhibited antifungal activity against the tested fungi. The compounds **4a$_6$, 4b$_1$, 4b$_2$, 4c$_2$** in case of *A. niger,* and **4a$_3$, 4a$_5$, 4b$_1$, 4b$_2$** in case of *A. flavus,* demonstrated substantial zones of inhibition in comparison with nystatin.

Minimum inhibitory concentration activity of fungal stains. The minimum inhibitory activity of compounds **4a$_1$–4a$_7$, 4b$_1$, 4b$_2$, 4c$_1$, 4c$_2$** was determined against *Aspergillus niger* and *Aspergillus flavus* (Table 2). The compounds **4b$_1$, 4c$_2$** exhibited the most potent antifungal activity against the tested fungi.

EXPERIMENTAL

All solvents and reagents were obtained commercially and used as received unless noted otherwise. Melting points were determined in open capillary tubes. Purity of the compounds was tested by TLC on silica gel 60

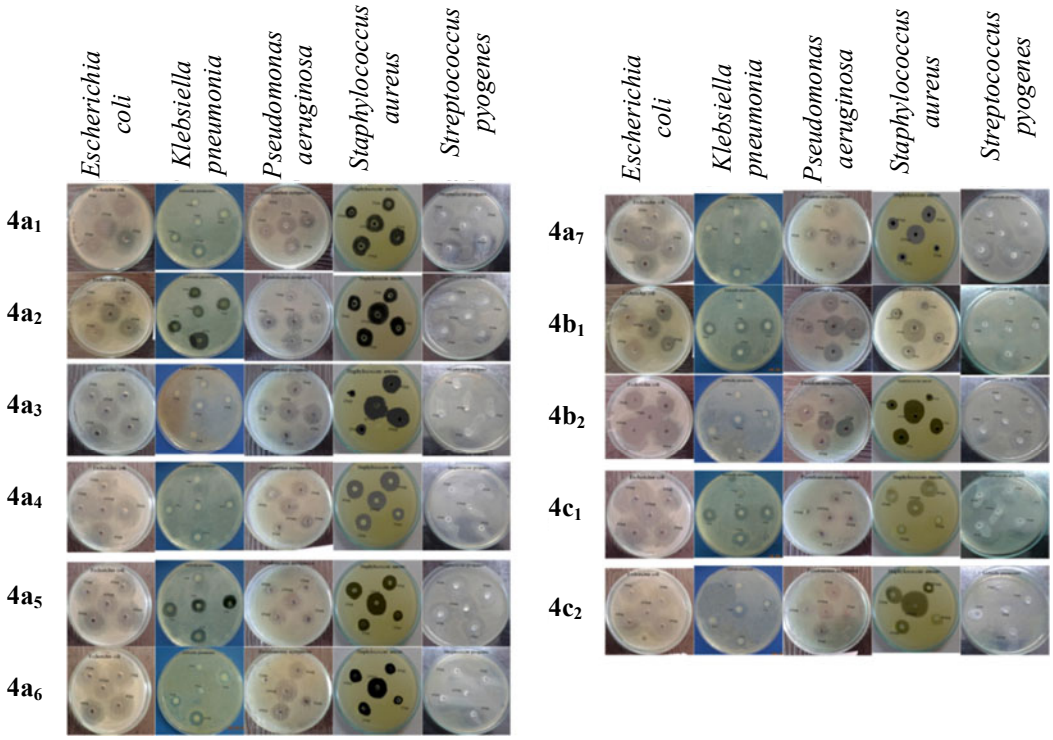


Fig. 1. Antibacterial activity of Gram positive and Gram negative starins.

F_{254} (Merck), the spots were visualized under UV light. IR spectra were recorded (KBr discs) on a Perkin-Elmer 1800 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian VNMRS-400 spectrometer in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard. Mass spectra were measured on a GCMS-QP 1000 EX mass spectrometer. All reactions were carried out under the atmosphere of Ar.

Table 1. Minimum inhibitory activity of Gram positive and Gram negative activity[a]

Compound	MIC, μg/mL				
	Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pyogenes*
4a$_1$	9.5±0.91	10.5±1.760	11.50±0.430	8.50±0.210	15.5±0.82
4a$_2$	8.5±0.32	15.5±0.720	20.50±0.270	13.50±0.710	11.5±0.58
4a$_3$	10.5±0.42	17.5±0.450	18.50±0.980	20.50±0.044	13.5±0.42
4a$_4$	11.5±0.51	19.5±0.070	10.00±0.940	8.50±0.0510	9.5±0.031
4a$_5$	6.5±0.09	10.0±0.920	10.50±0.042	7.50±0.820	9.5±0.29
4a$_6$	5.5±0.11	9.5±0.082	8.50±0.031	7.50±0.640	6.5±0.99
4a$_7$	7.5±0.33	17.5±0.210	7.50±0.068	10.50±0.036	10.5±0.32
4b$_1$	13.5±0.31	14.5±0.290	9.50±0.048	11.00±0.100	25.0±0.72
4b$_2$	20.5±1.03	13.5±0.170	11.50±0.082	10.50±0.019	22.5±0.33
4c$_1$	12.5±0.03	12.5±0.077	14.50±0.057	9.50±0.660	13.5±0.36
4c$_2$	9.5±0.16	10.5±0.310	11.00±0.073	11.50±0.710	15.0±0.61
Ciprofloxacin	8.2±4.08	4.5±1.340	8.08±0.790	8.12±0.750	9.5±0.11

[a] Micro organism were inoculated in nutrient broth with varying concentrations of synthesized compounds and incubated with *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes*.

Synthesis of 1-[2-(prop-2-yn-1-yloxy)phenyl substituted] ethanone (2a–2c). To a solution of hydroxy acetophenone (0.01 mol) in acetone was added anhydrous potassium carbonate (0.015 mol) followed by propargyl bromide (0.013 mol). The resulting mixture was refluxed at 56°C for 8–12 h (TLC), then cooled down to room temperature. Potassium carbonate was filtered off and the filtrate was distilled under reduced pressure leading to pure brown liquid product which solidified readily. The products were obtained in 90–95% of yields.

Synthesis of 1-phenyl-3-[2-(prop-2-yn-1-yloxy)-phenyl substituted]-1*H*-pyrazole-4-carbaldehyade (3a–3c). To a mixture of 1-[2-(prop-2-yn-1-yloxy)-phenyl substituted] ethanone (**2a–2c**) (0.01 mol) and phenyl hydrazine (0.01 mol) in methanol was added acetic acid (0.0005 mol) and the mixture was refluxed for 1 h. Upon completion of the reaction (TLC), the mixture was poured into water, extracted with EtOAc (twice, 40 mL) and dried over Na_2SO_4. The solvent was evaporated. Meanwhile, DMF was loaded into another round bottom flask and cooled to 0°C, then $POCl_3$ (0.02 mol) was added dropwise. The mixture was stirred for 15 minutes, then the brown syrup was added to the above reaction mass and it was stirred at room temperature for 24 h. Upon consumption of the starting compound **2a–2c** (TLC), the reaction mixture was treated with cold water, the precipitate filtered off and used in the further step without additional purification. Yield 80–85%.

Synthesis of 3-{2-[(1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a–4c). A round bottomed flask was loaded with 1-phenyl-3-[2-(prop-2-yn-1-yloxy)phenyl substituted]-1*H*-pyrazole-4-carbaldehyade (**3a–3c**) (0.01 mol) and azide compound (0.01 mol). A mixture of copper (II) sulfate pentahydrate (0.0005 mol) and sodium ascorbate (0.0015 mol) dissolved in *t*-BuOH–H_2O (2 : 1) was added. The reaction mixture was stirred for 15–20 h (TLC), then it was poured into ice cold water. The precipitate was filtered off as white to pale brown pure solid product.

1-[2-(Prop-2-yn-1-yloxy)phenyl] ethanone (2a). Yield 90%, mp 47–49°C. IR spectrum, ν, cm^{-1}: 3292 (C≡C–H), 2121 (C≡C), 1673 (C=O). ^1H NMR spectrum, δ, ppm: 2.52 t (1H, C≡C–H, J = 2.4 Hz), 2.61 s (3H, $COCH_3$), 4.78 d (2H, O–CH_2, J = 2.4 Hz), 7.00–7.05 m (2H, Ar-H), 7.42–7.46 m (1H, Ar-H), 7.71 d.d (1H, Ar-H, J = 1.6, 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 31.8, 56.2, 76.1, 77.9, 113.1, 121.6, 129.1, 130.4, 133.4, 156.7, 199.5. Found, %: C 75.79; H 5.74. $C_{11}H_{10}O_2$. Calculated, %: C 75.84; H 5.79.

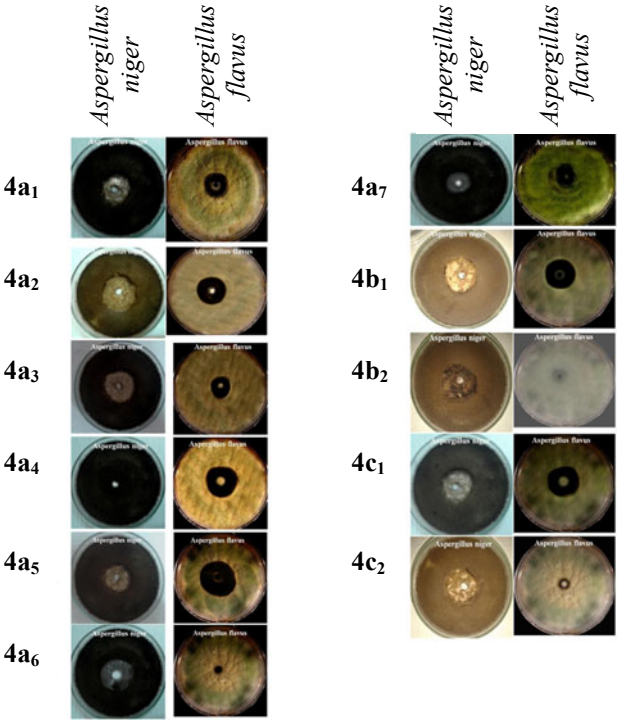


Fig. 2. Antifungal activity of *Aspergillus niger* and *Aspergillus flavus.*

Table 2. Minimum inhibitory concentration activity of synthesized compounds against *Aspergillus niger* and *Aspergillus flavus*

Compound	Concentration, μg/mL	MIC, μg/mL	
		Aspergillus niger	*Aspergillus flavus*
4a$_1$	10	15.5±0.15	11.5±0.93
4a$_2$	10	17.5±2.32	10.0±0.42
4a$_3$	10	9.5±2.18	12.5±0.22
4a$_4$	10	11.5±1.97	15.5±0.63
4a$_5$	10	8.5±0.92	9.0±0.83
4a$_6$	10	12.5±1.22	18.5±0.72
4a$_7$	10	12.0±1.03	11.0±0.52
4b$_1$	10	6.5±1.99[a]	9.5±0.91[a]
4b$_2$	10	8.5±1.42	10.5±0.89
4c$_1$	10	14.5±1.06	8.5±0.63[a]
4c$_2$	10	5.5±1.32[a]	7.5±0.82[a]
Nystatin	50	5.50±0.18	7.80±0.67

[a] Indicates statistically significant compared with Nystatin ($p \le 0.05$).

1-Phenyl-3-[2-(prop-2-yn-1-yloxy)phenyl]-1*H*-pyrazole-4-carbaldehyade (3a). Yield 85%, mp 84–86°C. IR spectrum, ν, cm^{-1}: 3297 (C≡C), 2859 (H–C=O), 2109 (C≡C), 1676 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.50 t (1H, C≡C–H, *J* = 2.4 Hz), 4.71 d (2H, O–CH_2, *J* = 2.4 Hz), 7.13–7.17 m (2H, Ar-H), 7.36 t (1H, Ar-H, *J* = 7.6 Hz), 7.44 d (1H, Ar-H, *J* = 1.6 Hz), 7.48 t (2H, Ar-H, *J* = 8 Hz), 7.63 d.d (1H, Ar-H, *J* = 1.6, 7.6 Hz), 7.77 d (2H, Ar-H, *J* = 7.6 Hz), 8.51 s (1H, $H_{pyrazole}$), 9.84 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 56, 76.1, 77.9, 112.8, 119.6, 121.1, 122, 123.3, 127.7, 129, 129.6, 130.7, 131.5, 139.1, 151.7, 154.8, 186.6. Found, %: C 75.44; H 4.63; N 9.32. $C_{19}H_{14}N_2O_2$. Calculated, %: C 75.48; H 4.67; N 9.27.

3-{2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-phenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde ($4a_1$). Yield 80%, mp 99–101°C. IR spectrum, ν, cm^{-1}: 2852 (H–C=O), 1672 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.24 s (2H, CH_2), 5.47 s (2H, CH_2), 7.12 t (1H, Ar-H, *J* = 7.6 Hz), 7.19–7.23 m (3H, Ar-H), 7.33–7.51 m (8H, Ar-H), 7.61 d.d (1H, Ar-H, *J* = 1.6, 7.6 Hz), 7.75 d (2H, Ar-H, *J* = 7.6 Hz), 8.42 s (1H, $H_{pyrazole}$), 9.75 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 53.4, 62.8, 112.8, 119.6, 120.9, 122.9, 123.2, 126.1, 127.7, 128, 128.9, 129.6, 130.4, 130.9, 131.4, 134.9, 136.4, 139.1, 144.3, 151.9, 155.5, 186.5. Found, %: C 71.69; H 4.83; N 16.11. $C_{26}H_{21}N_5O_2$. Calculated, %: C 71.71; H 4.86; N 16.08.

3-{2-[(1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbalde-hyde ($4a_2$). Yield 81%, mp 102–104°C. IR spectrum, ν, cm^{-1}: 2855 (H–C=O), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.25 s (2H, CH_2), 5.44 s (2H, CH_2), 7.09–7.15 m (2H, Ar-H), 7.18–7.22 m (2H, Ar-H), 7.29 d (2H, Ar-H, *J* = 7.2 Hz), 7.38 t (1H, Ar-H, *J* = 7.6 Hz), 7.44 s (1H, Ar-H), 7.45–7.52 m (3H, Ar-H), 7.62 d.d (1H, Ar-H, *J* = 1.2, 7.2 Hz), 7.75 d (2H, *J* = 7.6 Hz), 8.45 s (1H, $H_{pyrazole}$), 9.76 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 51.9, 61.5, 113, 119.1, 120.6, 121, 122.9, 124.7, 126.4, 127.4, 127.6, 128, 129.6, 130.6, 130.7, 131, 131.02, 133.2, 138.3, 138.7, 142.7, 150.7, 155.5, 185.3. Found, %: C 66.40; H 4.27; N 14.95. $C_{26}H_{20}ClN_5O_2$. Calculated, %: C 66.45; H 4.29; N 14.90.

3-{2-[(1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbalde-hyde ($4a_3$). Yield 82%, mp 144-146°C. IR spectrum, ν, cm^{-1}: 2856 (H–C=O), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.22 s (2H, CH_2), 5.45 s (2H, CH_2), 7.08–7.14 m (3H, Ar-H), 7.18 d (1H, Ar-H, *J* = 8.4 Hz), 7.35–7.51 m (7H, Ar-H), 7.61 d.d (1H, Ar-H, *J* = 1.2, 7.6 Hz), 7.75 d (2H, Ar-H, *J* = 7.6 Hz), 8.42 s (1H, $H_{pyrazole}$), 9.74 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 53.4, 62.8, 112.8, 119.6, 120.9, 121.8, 122.7, 122.8, 123.2, 127.8, 128.8, 129.6, 129.7, 131, 131.4, 132.2, 133.4, 139, 151.9, 155.5, 186.5. Found, %: C 66.69; H 3.90; N 13.65. $C_{26}H_{20}BrN_5O_2$. Calculated, %: C 60.71; H 3.92; N 13.62.

3-{2-[(1-(3,5-Dimethylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbal-dehyde ($4a_4$). Yield 77%, mp 124-126°C. IR spectrum, ν, cm^{-1}: 2852 (H–C=O), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.27 s (6H, $2CH_3$), 5.23 s (2H, CH_2), 5.37 s (2H, CH_2), 6.84 s (2H, Ar-H), 6.94 s (1H, Ar-H), 7.12 t (1H, Ar-H, *J* = 7.2 Hz), 7.20 d (1H, Ar-H, *J* = 8.0 Hz), 7.35–7.50 m (5H, Ar-H), 7.60 d (1H, *J* = 6.8 Hz), 7.74 d (2H, Ar-H, *J* = 8.0 Hz), 8.42 s (1H, $H_{pyrazole}$), 9.75 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 21.1, 54.1, 62.8, 112.9, 119.6, 120.9, 121.7, 122.8, 123.2, 125.8, 127.7, 128.8, 129.6, 130.2, 130.9, 131.4, 134.2, 138.7, 139.1, 151.9, 155.6, 186.5. Found, %: C 72.50; H 5.42; N 15.15. $C_{28}H_{25}N_5O_2$. Calculated, %: C 72.55; H 5.44; N 15.11.

3-{2-[(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-car-baldehyde ($4a_5$). Yield 82%, mp 149–151°C. IR spectrum, ν, cm^{-1}: 2853 (H–C=O), 1682 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.72 s (3H, O–CH_3), 5.18 s (2H, CH_2), 5.48 s (2H, CH_2), 6.90 d (2H, Ar-H, *J* = 8.8 Hz), 7.11 t (1H, Ar-H, *J* = 7.6 Hz), 7.24 d (2H, Ar-H, *J* = 8.8 Hz), 7.36–7.42 m (2H, Ar-H), 7.48 d (2H, Ar-H, *J* = 7.6 Hz), 7.54 d (2H, Ar-H, *J* = 7.6 Hz), 7.95 d (2H, Ar-H, *J* = 7.6 Hz), 8.02 s (1H, Ar-H), 9.11 s (1H, $H_{pyrazole}$), 9.71 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 52.3, 55.1, 61.6, 112.9, 114, 119.1, 120.6, 120.9, 122.9, 124.1, 127.4, 127.7, 129.4, 129.6, 130.7, 130.9, 131, 138.7, 142.5, 150.7, 155.6, 159, 185.3. Found, %: C 69.63; H 4.97; N 15.08. $C_{27}H_{23}N_5O_3$. Calculated, %: C 69.66; H 4.98; N 15.04.

4-{[4-([2-(4-Formyl-1-phenyl-1*H*-pyrazol-3-yl)-phenoxy]methyl)-1*H*-1,2,3-triazol-1-yl]methyl}benzoic acid ($4a_6$). Yield 81%, mp 139–141°C. IR spectrum, ν, cm^{-1}: 2852 (H–C=O), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.20 s (2H, CH_2), 5.66 s (2H, CH_2), 7.11 t (1H, Ar-H, *J* = 7.2 Hz), 7.37–7.39 m (4H, Ar-H), 7.48–7.54 m (4H, Ar-H), 7.94 d (4H, Ar-H, *J* = 7.2 Hz), 8.14 s (1H, Ar-H), 9.11 s (1H, $H_{pyrazole}$), 9.70 s (1H, H–C=O), 12.96 s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm:

52.2, 61.4, 112.9, 119, 120.5, 120.9, 122.8, 124.8, 127.3, 128.1, 129.5, 130.6, 130.9, 131.3, 133.2, 138.6, 140.5, 142.8, 150.6, 155.4, 169.1 185.2. Found, %: C 67.60; H 4.37; N 14.62. $C_{27}H_{21}N_5O_3$. Calculated, %: C 67.63; H 4.41; N 14.61.

3-{2-[(1-(2-Hydroxyethyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a$_7$). Yield 79%, mp 125–127°C. IR spectrum, ν, cm^{-1}: 3390 (OH), 2853 (H–C=O), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.73 q (2H, O–CH_2 *J* = 5.6 Hz), 4.36 t (2H, N–CH_2, *J* = 5.6 Hz), 4.99 t (1H, OH, *J* = 5.6 Hz), 5.19 s (2H, O–CH_2), 7.11 t (1H, Ar-H, *J* = 7.6 Hz), 7.38 s (1H, Ar-H), 7.41 d (1H, Ar-H, *J* = 7.6 Hz), 7.48–7.56 m (4H, Ar-H), 7.95 d (2H, Ar-H, *J* = 8.4 Hz), 8.01 s (1H, Ar-H), 9.12 s (1H, $H_{pyrazole}$), 9.73 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 52.1, 59.8, 61.6, 113, 119.1, 120.6, 121, 123, 124.8, 127.5, 129.6, 130.8, 131.1, 131.2, 138.7, 142.1, 150.8, 155.6, 185.5. Found, %: C 64.75; H 4.90; N 17.99. $C_{21}H_{19}N_5O_3$. Calculated, %: C 64.77; H 4.92; N 17.98.

1-[5-Methyl-2-(prop-2-yn-1-yloxy)phenyl]ethanone (2b). Yield 93%, mp 49–51°C. IR spectrum, ν, cm^{-1}: 3259 (C≡C–H), 2130 (C≡C), 1652 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, Ar–CH_3), 2.52 s (3H, $COCH_3$), 3.60 t (1H, C≡C–H, *J* = 2.4), 4.90 d (2H, O-CH_2 *J* = 2.4 Hz), 7.12 d (1H, Ar-H, *J* = 8.4 Hz), 7.34 d.d (1H, Ar-H, *J* = 2.4, 8.4 Hz), 7.37 d (1H, Ar-H, *J* = 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.8, 31.5, 56.2, 78.4, 78.8, 113.9, 128.3, 129.6, 130.2, 133.8, 154.3, 198.6. Found, %: C 76.55; H 6.40. $C_{12}H_{12}O_2$. Calculated, %: C 76.57; H 6.43.

3-[5-Methyl-2-(prop-2-yn-1-yloxy)phenyl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3b). Yield 81%, mp 89–91°C. IR spectrum, ν, cm^{-1}: 3307 (C≡C–H), 2864 (H–C=O), 2111 (C≡C), 1677 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, Ar–CH_3), 2.48 s (1H, C≡C–H), 4.68 d (2H, O–CH_2, *J* = 1.6), 7.06 d (1H, Ar-H, *J* = 8.4 Hz), 7.26 t (1H, Ar-H, *J* = 2.4 Hz), 7.37 t (1H, Ar-H, *J* = 7.6 Hz), 7.45 s (1H, Ar-H), 7.49 d (2H, Ar-H, *J* = 8.0 Hz), 7.77 d (2H, Ar-H, *J* = 8.0 Hz), 8.50 s (1H, $H_{pyrazole}$), 9.84 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 20.4, 56.2, 75.9, 78.1, 112.9, 119.7, 120.9, 123.3, 127.7, 129, 129.6, 131.1, 131.5, 131.9, 139.2, 151.9, 152.7, 186.7. Found, %: C 75.90; H 5.09; N 8.89 $C_{20}H_{16}N_2O_2$. Calculated, %: C 75.93; H 5.10; N 8.86.

3-{2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-methylphenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4b$_1$). Yield 78%, mp 109–111°C. IR spectrum, ν, cm^{-1}: 2850 (H–C=O), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 5.19 s (2H, CH_2), 5.46 s (2H, CH_2), 7.08 d (1H, Ar-H, *J* = 8.4 Hz), 7.21–7.24 m (3H, Ar-H), 7.32–7.42 m (6H, Ar-H), 7.49 t (2H, Ar-H, *J* = 8.4), 7.74 d (2H, Ar-H, *J* = 8.0 Hz), 8.41 s (1H, $H_{pyrazole}$), 9.74 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 20.4, 54.1, 63, 113.1, 119.6, 120.6, 122.7, 123.2, 127.7, 128, 128.6, 128.8, 129, 129.6, 131.2, 131.4, 131.8, 134.5, 139.1, 144.3, 152.1, 153.5, 186.6. Found, %: C 72.10; H 5.12; N 15.62. $C_{27}H_{23}N_5O_2$. Calculated, %: C 72.14; H 5.16; N 15.58.

3-{2-[(1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy]-5-methylphenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4b$_2$). Yield 81%, mp 111–113°C. IR spectrum, ν, cm^{-1}: 2841 (H–C=O), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 5.16 s (2H, CH_2), 5.67 s (2H, CH_2), 7.12 d (1H, Ar-H, *J* = 7.2 Hz), 7.24–7.30 m (2H, Ar-H), 7.34–7.42 m (4H, Ar-H), 7.48–7.56 m (3H, Ar-H), 7.95 d (2H, Ar-H, *J* = 8.0 Hz), 8.03 s (1H, Ar-H), 9.09 s (1H, $H_{pyrazole}$), 9.69 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 19.9, 50.5, 61.7, 113, 119.1, 120.4, 122.9, 124.8, 127.4, 127.6, 129.4, 129.5, 129.8, 130.1, 130.2, 130.8, 130.9, 131.3, 132.4, 133.1, 138.6, 142.7, 150.8, 153.4, 185.3. Found, %: C 67.00; H 4.55; N 14.52. $C_{27}H_{22}ClN_5O_2$. Calculated, %: C 67.01; H 4.58; N 14.47.

1-[5-Chloro-2-(prop-2-yn-1-yloxy)phenyl]ethanone (2c). Yield 92%, mp 51–53°C. IR spectrum, ν, cm^{-1}: 3234 (C≡C–H), 2124 (C≡C), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.56 t (1H, C≡C–H, *J* = 2.8), 2.60 s (3H, O=CCH_3), 4.78 d (2H, O–CH_2 *J* = 2.8 Hz), 7.01 d (1H, Ar-H, *J* = 8.8 Hz), 7.39 d.d (1H, Ar-H, *J* = 2.8, 8.8 Hz), 7.68 d (1H, Ar-H, *J* = 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 31.8, 56.5, 76.5, 77.3, 114.7, 127, 130, 130.1, 132.9, 155.1, 198. Found, %: C 63.29; H 4.30. $C_{11}H_9ClO_2$. Calculated, %: C 63.32; H 4.35.

3-[5-Chloro-2-(prop-2-yn-1-yloxy)phenyl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3c). Yield 84%, mp 94–96°C. IR spectrum, ν, cm^{-1}: 3309 (C≡C–H), 2859 (H–C=O), 2111 (C≡C), 1684 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.51 t (1H, C≡C–H, *J* = 2.4 Hz), 4.69 d (2H, O–CH_2, *J* = 2.4), 7.10 d (1H, Ar-H, *J* = 9.2 Hz), 7.36 d (1H, Ar-H, *J* = 7.2 Hz), 7.40 d.d (1H, Ar-H, *J* = 2.8, 9.2 Hz), 7.49 t (2H, Ar-H, *J* = 7.6 Hz), 7.63 d (1H, Ar-H, *J* = 2.8 Hz), 7.76 d (2H, Ar-H, *J* = 8.0 Hz), 8.50 s (1H, $H_{pyrazole}$), 9.83 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 56.4, 76.5, 77.5, 114.2, 119.6, 122.9, 123.4, 127.1, 127.9, 129.4, 129.6, 130.2, 131.2, 139, 150.1, 153.4, 185.9. Found, %: C 67.74; H 3.88; N

8.36. $C_{19}H_{13}ClN_2O_2$. Calculated, %: C 67.76; H 3.89; N 8.32.

3-{2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-chlorophenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde ($4c_1$). Yield 82%, mp 114–116°C. IR spectrum, ν, cm^{-1}: 2847 (H–C=O), 1673 (C=O). ^1H NMR spectrum, δ, ppm: 5.23 s (2H, CH_2), 5.46 s (2H, CH_2), 7.15 d (1H, Ar-H, J = 8.8 Hz), 7.24–7.26 m (2H, Ar-H), 7.34–7.40 m (6H, Ar-H), 7.50 t (2H, Ar-H, J = 7.2 Hz), 7.60 s (1H, Ar-H), 7.74 d (2H, Ar-H, J = 7.6 Hz), 8.41 s (1H, $H_{pyrazole}$), 9.74 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 54.2, 63, 114.3, 119.6, 122.6, 122.9, 123.2, 126.8, 127.9, 128.1, 128.7, 129.1, 129.2, 129.7, 130.5, 131.1, 134.4, 139, 143.6, 150.4, 154.2, 185.9. Found, %: C 66.44; H 4.26; N 14.95. $C_{26}H_{20}ClN_5O_2$**.** Calculated, %: C 66.45; H 4.29; N 14.90.

3-{5-Chloro-2-[(1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-phenyl-1*H*-pyrazole-4-carbaldehyde ($4c_2$). Yield 79%, mp 119–121°C. IR spectrum, ν, cm^{-1}: 2854 (H–C=O), 1673 (C=O). ^1H NMR spectrum, δ, ppm: 5.22 s (2H, CH_2), 5.68 s (2H, CH_2), 7.12 d (1H, Ar-H, J = 6.8 Hz), 7.35–7.43 m (4H, Ar-H), 7.50–7.55 m (5H, Ar-H), 7.96 d (2H, Ar-H, J = 7.6 Hz), 8.09 s (1H, Ar-H), 9.16 s (1H, $H_{pyrazole}$), 9.72 s (1H, H–C=O). ^{13}C NMR spectrum, δ_C, ppm: 50.6, 61.9, 114.9, 119.2, 122.6, 123, 124.7, 125.2, 127.6, 127.7, 129.6, 129.7, 130.2, 130.3, 131.6, 132.5, 133.2, 138.6, 142.3, 149.1, 154.5, 185.2. Found, %: C 61.89; H 3.79; N 13.93. $C_{26}H_{19}Cl_2N_5O_2$**.** Calculated, %: C 61.91; H 3.80; N 13.89.

Antibacterial activity. Synthesized compounds have been assayed for their antimicrobial activity against different bacteria. The entire organisms were collected from Department of Microbiology, Osmania University, Hyderabad. Seven bacterial strains *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 15380, *Pseudomonas aeruginosa* ATCC 12454, *Staphylococcus aureus* ATCC 25923, and *Streptococcus pyogenes* ATCC 35552 were used in the study. Microbial cultures were stored at –20°C in microcentrifuge tubes having 40% sterile glycerol. Synthesized compounds inhibitory activity was tested according to the "well plate or disc diffusion method" [27, 28]. The wells were created in Mueller Hinton solid agar medium with well puncture10, Trypton soy agar or Nutrient agar. The media was preinoculated with test organisms. The standard inoculum size was of $(1–2)\times10^8$ CFU/mL of bacteria for inoculating diffusion plates13 which was equal to McFarland 0.5 turbidity standard. After that all tested compounds were inoculated into the wells and the plates were incubated at 37°C for 24 h. Each test was carried out in triplicate with controls. Microbial growth was determined by measuring the diameter of inhibition zone. The minimum inhibitory concentration was determined using the tube dilution techniques [27, 28]. Various concentrations of each compound were prepared using single dilution method. The least concentration of each compound that did not permit any visible growth or turbidity of the inoculated test organisms in broth culture was taken as the minimum inhibitory concentration in each case. Control experiments with each compound and a tube with no compound were also performed.

Antifungal activity. Antifungal activity was studied by the well plate or disc diffusion method [29, 30]. Fungal suspension (2×10^5) was streaked on the potato dextrose agar (PDA) medium. Then, wells were loaded with different concentrations of synthesized compounds. Similarly, each plate was loaded with a sterile disc and tetracycline as a positive control. All plates were incubated at 28°C for 24–48 h. The zones of growth inhibition were measured after 48 h. Sensitivity of the fungal species to each compound was determined by measuring the sizes of inhibition zones. The MIC was determined by the broth micro dilution method using 96-well micro-plates [29, 30]. Each sample (1.0 mg) was dissolved in DMSO (1 mL) to obtain 1000 μg/mL stock solution. Nystatin was used as a positive control. Plates were incubated at 37°C for 24 h.

CONCLUSIONS

Herein, we present the synthesis of a new series of 1,2,3-triazole-pyrazole hybrids **$4a_1$–$4a_7$, $4b_1$, $4b_2$, $4c_1$,** and **$4c_2$** using a two step synthetic route in which a substituted 1,2,3-triazole ring was constructed in the final step via the click reaction protocol. All target compounds were characterized by IR, ^1H and ^{13}C NMR, and MS spectral data and elemental analysis. The *in vitro* antibacterial and antifungal activity screening data accumulated for the synthesized compounds demonstrated promising antibacterial and antifungal activity.

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