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1-((1-Aryl-1H-1,2,3-triazol-4-yl)-Methyl)-1H-indole: Synthesis, characterization and antibacterial activity

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ABSTRACT

A facile and highly efficient method for regioselective synthesis of 1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole in good to excellent yields from in-situ-generated alkyne and azides by Cu(I)-catalyzed 1,3 dipolar cycloaddition (the so-called click reaction), is described. The reaction proceeds smoothly in a mixture of [BMIM][PF_6] and water at room temperature without any additive. The method is a convenient means of preparation of a wide range of triazoles in a one-pot operation via a three-component reaction. The final 1, 2, 3-triazoles screened for anti bacterial activity majority of compounds shows good to excellent activity.

Keywords: Click chemistry; indole; [BMIM][PF_6]; 1,2,3-Triazoles; Anti bacterialactivity

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INTRODUCTION

Though there are many of active compounds developed for functionalized indole. Still there is scope for synthesis of new compounds to built indole ring system and it found to be among the most efficient for achieving useful transformations in to indole backbone and their derivatives later on. Nitrogen containing heterocyclic compounds like indole and substituted indole are very important building blocks in medicinal chemistry [1] field. So the indole derivatives are extensively very essential in the drug discovery research, which stimulate research activity in the field of the broad spectrum of biological activity study. After the literature survey that many indole derivative molecule are shows very good biological activity in different therapeutic areas **Figure 1.**

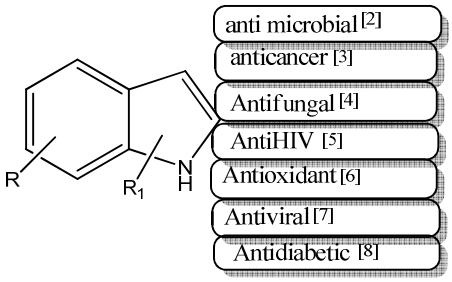


Figure 1. Potential applications based on the indole

1,4-Disubstituted 1,2,3-triazoles have emerged as an important class of heterocyclic compounds, displaying a vast spectrum of properties and are widely used as pharmaceuticals[9-12]. Many 1,2,3-triazoles have found medicinal applications, such as HIV protease inhibitors[13], anticancer drugs[14], antituberculosis drugs[15], antifungal agents[16], antibacterial drugs[17], histone deacetylase inhibitors, and bioorthogonal probes, and are also used as corrosion inhibitors, lubricants, dyes, and photostabilizers (**Figure 2**).

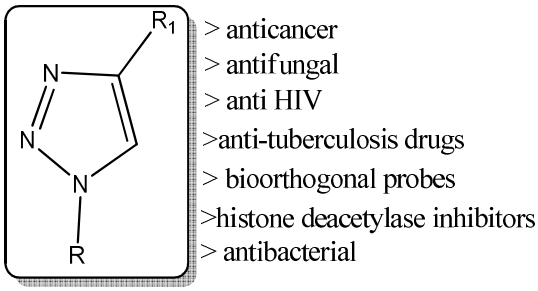


Figure 2. Potential applications based on the 1,2,3-triazoles

For all the above consideration, biological importance of triazoles and indole, we design the new bi-functional mimic heterocyclic compounds consisting the 1,2,3- Triazoles, here we present a highly efficient one pot synthetic method for the synthesis of the new bi-functional mimic heterocyclic compounds containing indole and 1,2,3-Triazoles from indole, propargyl bromide and aryl azides in ionic liquid 1-Butyl-3-methylimidazolium hexafluorophosphate [bmim][PF6] and the new molecules were screened for their anti-bacterial activity.

MATERIALS AND METHODS

Chemistry

All chemicals were purchased from Aldrich Chemical Co. and solvents were used without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualisation of the developed chromatogram was performed by UV light (254 nm). Column chromatography was performed on silica gel 60–120 mesh. Melting points were determined using a Cintex apparatus. Elemental analysis were measured by means of Perkin Elmer 2400 CHN elemental analyzer. ^{1}H nuclear magnetic resonance (NMR) (400 MHz) and ^{13}C NMR (**Compound 2a, 2b**) (100 MHz) spectra were obtained using Bruker DRX-500 Avance at ambient temperature, using tetramethylsilane (TMS) as internal standard. Coupling constant (J) values are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Fourier-transform infrared (FT-IR) spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were recorded by using ESI–MS.

Synthesis of 1,4-disubstituted 1,2,3-triazoles.

1-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2a): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (1 mmol) and 1-azido-4-methoxybenzene (1.2 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 90% yield of ***2a*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 122–124 ^{o}C; ^{1}H-NMR (400 MHz,$CDCl_3$) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.820 (d, *J=8.4 Hz*, Ar, 2H); 7.671 (s, triazole-H, 1H); 7.515 (m, Ar, 4H); 7.310 (m, Ar, 2H); 6.977 (d, *J=8.8 Hz*, Ar, 2H); 5.582 (s, N-CH_2, 2H); 3.832 (s, O-CH_3, 3H); ^{13}C-NMR(100MHz,$CDCl_3$) δ158.9 ,145.6, 136.2, 130.3, 119.1, 60.6, 56.4; IR(KBr,cm^{-1}) 3144, 1594, 1514, 1459, 1400, 1111, 835 ; EI-MS m/z (M+H)-305; Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41; found : C, 71.01; H, 5.34; N, 18.45

1-{[1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2b): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-4-methylbenzene (1.2mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 86% yield of ***2b*** as a white solid. The residue ionic

liquid was washed with water and reused for the cyclo addition reaction m.p. 118–120 ^{o}C; ^{1}H-NMR (400 MHz,$CDCl_3$) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.713 (d, *J=8 Hz*, Ar, 2H); 7.642 (s, triazole-H, 1H); 7.512 (m, Ar, 3H); 7.320 (m, Ar, 3H); 7.012 (d, *J=8.8 Hz*, Ar, 2H); 5.552 (s, N-CH_2, 2H); 2.441 (s, Ar-CH_3, 3H);^{13}C-NMR(100MHz,$CDCl_3$) δ145.6, 138.4, 136.2, 119.8, 115.2, 58.6, 25.4; IR(KBr, cm^{-1}3142, 1593,1515, 1455,1400,1110,835,EI-MS m/z (M+H)- EI-MS m/z (M+1)-289; Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43; found : C, 75.00; H, 5.55; N, 19.45

1-{[1-(3,5-dimethylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2c): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-3,5-dimethylbenzene (1.5mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 82% yield of ***2c*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction mp 129-131^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.654 (s, triazole-H, 1H); 7.541 (m, Ar, 3H); 7.512 (m, Ar, 3H); 7.311(m, Ar, 2H), 6.971(s, Ar, 1H), 5.553 (s, N-CH_2, 2H); 2.781 (s, Ar-CH_3, 6H); IR(KBr, cm^{-1}) 3142, 1594,1514, 1459,1400, 1112. EI-MS m/z (M+H)-303; Anal. Calcd for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53; found : C, 75.50; H, 6.06; N, 18.44

1-{[1-(3,5-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2d): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-3,5-dichlorobenzene (1.5 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 75% yield of ***2d*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. mp 135-137^{o}C; ^{1}H-NMR (400MHz,$CDCl_3$) δ in ppm: 7.8150 (s, Ar, 1H); 7.721 (s, Ar, 2H); 7.651 (s, triazole-H, 1H); 7.508 (m, Ar, 3H); 7.421 (m, 2H); 7.056 (d, *J= 4.8 Hz*, Ar, 1H); 5.503 (s, N-CH_2, 2H); IR(KBr, cm^{-1} 3131, 1594,1511, 1459,1398, 1110, 835, EI-MS m/z(M+H)-345; Anal. Calcd for $C_{17}H_{12}Cl_2N_4$: C, 59.49; H, 3.52; N, 16.32; found : C, 59.50; H, 3.55; N, 16.27

1-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2e): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-4-nitrobenzene (1.2mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 70% yield of ***2e*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. mp 121-123^{o}C, ^{1}H-NMR (400 MHz, CDCl3) δ in ppm: 7.730 (d, *J=8 Hz*, 2H); 7.645 (s, triazole-H, 1H); 7.520 (m, Ar, 3H); 7.310 (m, Ar, 2H); 6.971 (d, *J=8.8 Hz*, Ar, 2H); 5.582 (s, N-CH_2, 2H); IR(KBr, cm^{-1}) 3134, 1594,1514, 1459,1400, 1111, 835;EI-MS m/z(M+Na)-342; Anal. Calcd for $C_{17}H_{13}N_5O_2$ **:** C, 63.94; H, 4.10; N, 21.93; found:
C, 63.90; H, 4.13; N, 21.96.

1-{[1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2f): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-3-chlorobenzene (1.2mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 80% yield of ***2f*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 118–120 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.632 (s, 1H .triazole-*H*); 7.052 -7.655(m,10H); 5.521 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3131, 1590,1514, 1449,1405, 1110, 835, EI-MS m/z(M+1)-309; Anal. Calcd for $C_{17}H_{13}ClN_4$:C, 66.13; H, 4.24; N, 18.15; found: C, 66.08; H, 4.23; N, 18.17

1-{[1-(4-butylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2g): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-4-butylbenzene (1.5 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 70% yield of ***2g*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 125–127 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.878 (s, 1H .triazole-*H*); 6.987-7.654 (m,10H); 5.523 (s, 2H . N-CH_2); 2.701(t, *J*= 6 Hz ,2H),1.3-

1.654(m,4H),0.961(t, *J*=8 Hz,3H); IR(KBr, cm^{-1}) 3134, 1593,1511, 1459,1400, 1111, 835 ;EI-MS m/z (M+Na)-331; Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96; found: C, 76.39; H, 6.70; N, 16.91

1-({1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}methyl)-1*H*-indole(2h): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-3-(trifluoromethyl)benzene (1.5 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 65% yield of ***2h*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 136–138 ^oC, ^1H-NMR (400 MHz, $CDCl_3$) δ 7.780 (s, 1H .triazole-*H*); 7.032-7.698 (m,10H); 5.523 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3144, 1593,1511, 1449, 1390, 1114; EI-MS m/z (M+1)-343; Anal. Calcd for $C_{18}H_{13}F_3N_4$: C, 63.16; H, 3.83; N, 16.37; found: C, 63.18; H, 3.85; N, 16.33

{1-{[1-(naphthalen-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2i): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azidonaphthalene (1.2mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 85% yield of ***2i*** as a pale red solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction . m.p. 144–146 ^oC, ^1H-NMR (400 MHz, $CDCl_3$) δ 7.874 (s, 1H .triazole-*H*); 7.782(m,4H); 7.132-7.608 (m,10H) 5.548 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3134, 1593,1511, 1450,1409, 1115: EI-MS m/z(M+1)-325; Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27; found: C, 77.68; H, 4.99; N, 17.33

1-{[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2j): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-4-bromobenzene (1.2 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 80% yield of ***2j*** as a yellow solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction . m.p. 134–136 ^oC, ^1H-NMR (400 MHz, $CDCl_3$) δ 7.742 (d, *J=8 Hz*, Ar, 2H); 7.632 (s, triazole-H, 1H); 7.523 (m, Ar, 3H); 7.120 (m, Ar, 3H); 7.002 (d, *J=8.8 Hz*, Ar, 2H); 5.535 (s, N-CH_2, 2H); IR(KBr, cm^{-1}) 3141, 1593,1511, 1449, 1411 , 1109;EI-MS m/z(M+1)-354; Anal. Calcd for $C_{17}H_{13}BrN_4$: C, 57.81; H, 3.71; N, 15.86;found: C, 57.76; H, 3.73; N, 15.88

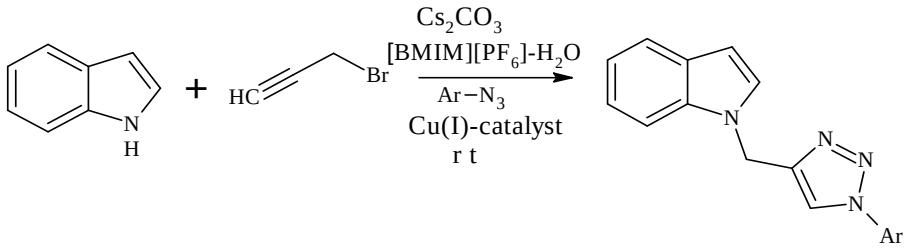
Antibacterial activity

The newly synthesized compounds **(2a-j)** were evaluated for in-vitro antibacterial against various Gram-positive and Gram-negative bacteria [18]. The results are shown in **Tables 2** . Penicillin were used as standard drugs for comparison. The minimum inhibitory concentrations (MIC) of synthesized compounds (**2a-j)** were tested against three representative Gram-positive organisms such as *E.coli***(MTCC 443)**, *B.subtiles* **(MTCC 441)**, *S.aureus* **(*MTCC 96),*** *and K.pneumoniae* **(MTCC 618**) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards. The Standard antibacterial agent Penicillin also screened under identical conditions for comparison.The standard pathogenic microbial cultures were procured from the Microbial Type Culture Collection (MTCC), Chandigarh, India and were incubated on sterile nutrient agar at room temperature and inoculated into the fresh nutrient broth of 10 mL, in order to yield bacterial suspension of about 10–100 colony forming units (CFU) per mL. The inoculums size of approximately 106 CFU per plate was spread plated over the surface of the nutrient agar by diluting the initial microbial suspension 10 times with distilled water. 30 mL of Antibacterial suspension of 100 µg mL^{-1} concentration was transferred into the 6 mm diameter well made by the sterile cork borer and incubated for about 24 h at 37 ^oC. Antibacterial screenings were conducted in triplicates by wellplate method in Mueller- Hinton Agar at 100 µg mL^{-1}concentration for the synthesized compounds **(2a-j)** with respect to positive control streptomycin at 30 µg mL^{-1}. Minimum inhibitory concentration (MIC) forthe tested compounds, as well as standards was measured in µg $mL^{-1}$by micro dilution method. DMSO used as a solvent control and the results are depicted in **Table 2**.

RESULTS AND DISCUSSION

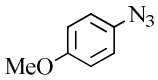
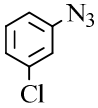
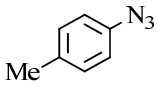
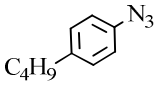
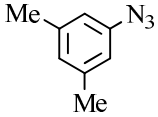
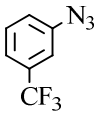
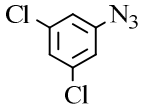
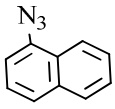
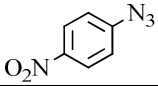
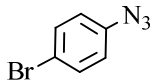
This three-component reaction proceeds via in-situ formation of an N-propargylation from an indole and propargyl bromide. The alkyne then undergoes 1, 3-dipolar cycloaddition reaction with aryl azide to give 1, 4-disubstituted

1,2,3-triazoles[19]. Here we describe a process in which copper iodide efficiently catalyzes azide–alkyne cycloaddition in the presence of [BMIM][PF_6] and H_2O mixture (**Scheme 1**). Initially, the effect of solvents on formation of the triazoles from indole, propargyl bromide, and 1-azido-4-methoxybenzene in the presence of CuI (15 mol%) as heterogeneous catalyst at room temperature was investigated. The corresponding results are listed in Table 1. Among the solvents used, CH_3CN, acetone, and THF required longer reaction times and yields were 40, 35, and 50 %, respectively (Table 1, **2a**). Reaction in water resulted in high catalytic activity and 55 % yield of the desired product. The same reaction in the presence of [BMIM][PF_6]-H_2O afforded the best yield of product, with 90 % isolated yield after 8h. The [BMIM][PF_6] effects can be explained to solvophobic interactions that generate an internal pressure, which promotes the association of the reactants in a solvent cavity during the activation process and showed an acceleration of the multi-component reactions (MCRs) in comparison to conventional solvents[20].



Scheme1. Synthetic route of 1,4-di substituted 1,2,3- triazole derived Indole

Table 1: Synthesis of 1,2,3-triazoles 2a-2j from aryl azides in the presence of [BMIM][PF_6]-H_2O

Azide	Time(h)	Product	Yield(%)	Azide	Time(h)	Product	Yield(%)
	8	2a	40[a],35[b],50[c],55[d], 90		10	2f	80
	8.5	2b	86		8.5	2g	70
	8.5	2c	82		9	2h	65
	11	2d	75		8.5	2i	85
	12	2e	70		9	2j	80

Reaction conditions: absence of IL yield of product with different solvents, a=CH_3CN; b=Acetone; c=THF; d=H_2O

Antibacterial activity:

Evaluation of antibacterial data (**Table 2**). Compounds 2d and 2e, was found to be effective against both gram positive and an gram negative bacteria and compounds 2f, 2h and 2i was also found that effective against ***K.pneumoniae*** and ***B.Subtilis***, it was also found that 2a was effective against ***S.aureus*** and ***E.coli***. A detailed report is tabulated in **Table No. 2**

Table 2: Anti-bacterial activity of 1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole (2a-2j) against tested bacteria

	MIC(*µg/mL*)			
Analog	***K.pneumoniae***	***S.aureus***	***B.Subtilis***	***E.coli***
2a	>150	4.548	>150	6.548
2b	>150	>150	>150	>150
2c	>150	>150	>150	>150
2d	1.268	1.546	1.420	1.450
2e	2.253	2.283	3.421	3.431
2f	2.150	>150	2.351	>150
2g	>150	>150	>150	>150
2h	4.251	>150	4.532	>150
2i	3.401	>150	3.441	>150
2j	>150	>150	>150	>150
Penicillin	**1.562**	**1.562**	**6.25**	**6.25**

CONCLUSION

In conclusion, the present work demonstrated an environmentally benign and a convenient method for the synthesis of biologically active 1, 2, 3-triazole hybrid compounds. The antibacterial activity indicate that the newly synthesized compounds are worthy for further pharmacological studies.

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