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One pot synthesis of 1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*] imidazoles in ionic liquids: Evaluation of antioxidant and antimicrobial activities

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ABSTRACT

In view of pharmacological importance of benzimidazole and 1,2,3-triazole nuclei, we made an effort to synthesize the bi-functional mimic 1,2,3-triazolyl-benzimidazoles through the copper catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction in ionic liquids. The synthesized compounds were characterized by NMR, IR and Mass spectral analysis. The synthesized compounds were screened for antimicrobial and antioxidant activities. A good number of the compounds found to possess potent antioxidant and antimicrobial activities.

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1. Introduction

Benzimidazole and 1,2,3-triazole nuclei are valuable functionalities in the field of medicinal chemistry due to their important pharmacological properties. The benzimidazole has been an important pharmacophore and privileged structure, encompassing a diverse range of their biological properties [1,2]. Benzimidazoles have been reported as antimicrobial [3-10], antiviral [11-14], antioxidant [15], anti-inflammatory [16,17], antitumor [18] and anticancer agents [19-21]. 1,2,3-Triazoles due to their exclusive chemical and structural properties, have acknowledged a lot of awareness over the past decades and found extensive applications in medicinal chemistry [22-25], biological activities such as anti-HIV [27] and antimicrobial [27,28]. Several methods for the synthesis of 1,2,3-triazoles have been reported in the literature [29,30]. Among them, the most common method is the "click chemistry" copper-catalyzed cycloaddition of azides to alkyne [31]. During the investigation of highly efficient and environmentally benign processes ionic liquids have been emerged as sustainable solvents. They were employed in many reactions including, in the synthesis of azides [32], in the *N*-alkylation of amines [33-35], and in copper catalyzed cycloaddition of azides to alkyne [36,37]. Further, one pot synthetic procedure [38,39] has been become an attractive option in click chemistry in which azides generated *in situ,* followed by azide-alkyne cycloaddition to avoid the isolation of the azide intermediates since the organic azides tend to be explosive and are difficult to handle.

In view of the above considerations and in continuation of our effort to design the new bifunctional mimic heterocyclic compounds consisting the 1,2,3-triazole, here in, we report a highly efficient multi component one pot method for the synthesis of 1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazoles using *N*-propargylbenzimidazole, aniline and sodium azide in ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] and their antioxidant and antimicrobial activities.

2. Experimental

2.1. Materials and methods

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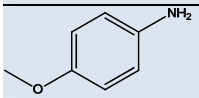
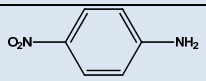
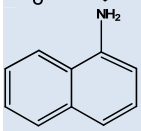
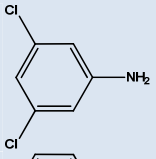
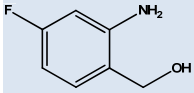
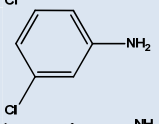
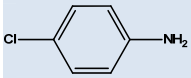
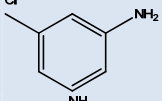
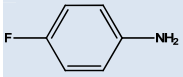
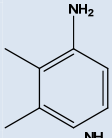
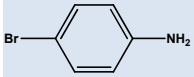
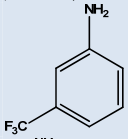
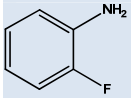
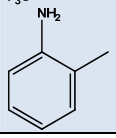
Table 1. Synthesized 1,4-di-substituted 1,2,3-triazole derivatives of benzimidazole (**A-N**).

Ar-NH_2	Product	Time (hr)	Yield (%)	Ar-NH_2	Product	Time (hr)	Yield (%)
	A	8.0	95		H	8.5	88
	B	9.0	90		I	9.5	75
	C	10.0	88		J	9	80
	D	8.5	91		K	8	92
	E	8.5	90		L	8	90
	F	8.5	92		M	9	86
	G	9.0	85		N	9.5	85

All reactions were carried out in a round bottom flask under room temperature. Copper (I) iodide, benzimidazole, propargyl bromide, [BMIM][PF_6] and aromatic amines were purchased from Aldrich chemical company. All the reagents and solvents were purchased from S.D. Fine chemicals limited and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60F_{254} precoated plates (0.25 mm) and silica gel (particle size 60-120 mesh) was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz instrument. ^{1}H NMR spectra were reported relative to Me_4Si (δ, 0.00 ppm) and residual $CDCl_3$ (δ, 7.26 ppm). ^{13}C NMR was reported relative to $CDCl_3$ (δ, 77.16 ppm). FT-IR spectra were recorded on a Bruker spectrometer and are reported on the frequency of absorption (cm^{-1}). Mass spectra were recorded on ESI-MS.

2.2. Synthesis

2.2.1. Synthesis of N-propargylbenzimidazole

N-Propargylation was carried out by the addition of propargyl bromide (1.2 mmol) to a mixture of benzimidazole (1 mmol), Cs_2CO_3 (1 mmol) in 1 mL of [BMIM][PF_6] and 3 mL of H_2O and stirred at room temperature for 12 hours. The reaction was stopped by addition of H_2O and the product was extracted with ethylacetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford *N*-propargylbenzimidazole. The residue ionic liquid was washed with water and reused for the cycloaddition reaction. Color: Pale yellow solid. Yield: 90%. M.p.: 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.978 (s, 1H, N-*CH*=N), 7.820 (d, 1H, *J* = 8.4 Hz, Ar), 7.515 (m, 2H, Ar), 7.310 (m, 1H, *J* = 4 Hz, Ar), 4.762 (s, 2H, N-CH_2), 2.489 (s, 1H, CH-alkyne). MS (EI, *m/z* (%)): 157 (M+H, 100).

2.2.2. General procedure for 1-{[1-(aryl)-1H-1, 2, 3-triazol-4-yl] methyl}-1H-benzimidazoles (A-N)

Aryl amines (0.8 mmol) were homogenized by mixing solid *p*-TsOH hydrate (2.4mmol) and 0.2 mL of water into a round-bottom flask and cooled to 0 °C in an icebath. To this stirred mixture $NaNO_2$ (1.6 mmol) was added, followed by the solution of NaN_3 (2.2 mmol) in [BMIM][PF_6] (14 mmol, 2.64 mL) and 5 mL of H_2O drop wise and thoroughly stirred at room temperature for 3 h. *N*-Propargylbenzimidazole (0.9 mmol) and CuI (15 mol %) were then added and the reaction was stirred for 8 hours at room temperature. The reaction proceeds smoothly and rapidly to afford 1,2,3-triazoles in excellent yields (Figure 1). The product was extracted with ethyl acetate (65-85% extraction yields) and the results are presented in Table 1.

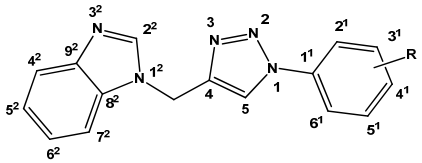


Figure 1. Numbering of carbon atoms in 1,4-disubstituted 1,2,3-triazoles (A-N).

1-{[1-(4-Methoxyphenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**A**): Color: White solid. Yield: 95%. M.p.: 152-

154 °C. FT-IR (KBr, cm^{-1}): 3135 (triazole-H), 1593 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) : 8.070 (s, 1H, N-*CH*=N), 7.820 (d, 1H, *J* = 8.4 Hz, Ar), 7.641 (s, 1H, triazole-H), 7.515 (m, 3H, Ar), 7.310 (t, 2H, *J* = 4 Hz, Ar), 6.977 (d, 2H, *J* = 8.8 Hz, Ar), 5.582 (s, 2H, N-CH_2), 3.843 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) : 159.8 (1C, C-4^1), 145.8 (1C, C-4), 143.0 (1C, C-2^2), 138.7 (1C, C-9^2), 135.6 (1C, C-1^1), 134.1 (1C, C-8^2), 130.2 (2C, C-2^1 & C-6^1), 125.3 (1C, C-5^2), 124.9 (1C, C-6^2), 122.3 (2C, C-3^1 & C-5^1), 119.1 (1C, C-4^2), 115.5 (1C,C-7^2), 114.7 (1C, C-5), 57.3 (1C, N-CH_2), 55.6 (1C, O-CH_3). MS (EI, *m/z* (%)): 306 (M^+, 100).

1-{[1-(Naphthalen-1-yl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**B**): Color: Pale red solid. Yield: 90%. M.p.: 169-171 °C. FT-IR (KBr, cm^{-1}): 3144 (triazole-H), 1594 (C=C, triazole), 1518 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.933 (s, 1H, N-*CH*=N), 7.847 (d, 2H, *J* = 5.2 Hz, Ar), 7.710 (s, 1H, triazole), 7.540 (m, 5H, Ar), 7.324 (m, 4H, Ar), 5.676 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) : 145.0 (1C, C-4, triazole), 142.9 (1C, C-2^2), 139.5 (1C, C-9^2), 138.7 (1C, C-9^1), 135.6 (1C, C-1^1), 134.4 (1C, C-8^2), 133.4 (1C, C-10^1), 132.1 (1C, C-2^1), 130.5 (1C, C-4^1), 128.3 (1C, C-5^1), 128.2 (1C, C-8^1), 127.0 (1C, C-3^1), 126.4 (1C, C-6^1), 124.4 (1C, C-5^2), 124.1 (1C, C-6^2), 123.5 (1C, C-7^1), 120.1 (1C, C-4^2), 116.5 (1C, C-7^2), 115.5 (1C, C-5), 57.6 (1C, N-CH_2). MS (EI, *m/z* (%)): 326 (M^+, 100).

{2-[4-(1H-Benzimidazol-1-ylmethyl)-1H-1, 2, 3-triazol-1-yl]-4-fluorophenyl} methanol (**C**): Color: White solid. Yield: 88 %. M.p.: 142-144 °C. FT-IR (KBr, cm^{-1}): 3390 (-OH), 3131 (triazole-H), 1594 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.191 (s, 1H, N-*CH*=N), 7.641 (s, 1H, triazole-H), 7.498 (m, 2H, Ar), 7.424 (d, 1H, *J* = 8 Hz, Ar), 7.216 (m, 2H, Ar), 7.130 (m, 1H, Ar), 6.985 (d, Ar, *J* = 8 Hz, 1H), 5.517 (s, 2H, N-CH_2), 3.910 (s, 2H, Ar-CH_2-OH), 3.501 (br s, 1H, -OH). ^{13}C NMR (100 MHz,$CDCl_3$, δ, ppm): 160.9 (1C, C-4^1), 145.0 (1C, C-4, triazole), 143.1 (1C, C-2^2), 138.2 (1C, C-9^2), 137.7 (1C, C-9^1), 134.6 (1C, C-2^1), 128.2 (1C, C-1^1), 127.0 (1C, C-3^1), 123.2 (1C, C-5^1), 123.2 (1C, C-5^2), 122.5 (1C, C-6^2), 119.9 (1C, C-4^2), 116.5 (1C, C-7^2), 115.9 (1C, C-5) , 60.7 (1C, Ar-CH_2-OH), 57.5 (1C, N-CH_2). MS (EI, *m/z* (%)): 346 (M+Na, 100).

1-{[1-(4-Chlorophenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**D**): Color: Yellow solid. Yield: 91%. M.p.: 149-151 °C. FT-IR (KBr, cm^{-1}): 3132 (triazole-H), 1595 (C=C, triazole), 1521 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.070 (s, 1H, N-*CH*=N), 7.935 (d, 1H, *J* = 4.4 Hz, Ar), 7.641 (s, 1H, triazole-H), 7.515 (m, 3H, Ar), 7.314 (m, 2H, Ar), 7.050 (d, 2H, *J* = 4 Hz, Ar), 5.562 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 148.1 (1C, C-4^1), 144.8 (1C, C-4, triazole), 143.8 (1C, C-2^2), 138.3 (1C, C-9^2), 137.7 (1C, C-8^2), 134.8 (1C, C-1^1), 134.1 (1C, C-4^1), 128.8 (2C, C-3^1 & C-5^1), 124.5 (2C, C-2^1 & C-6^1), 120.0 (1C, C-6^2), 116.5 (1C, C-4^2), 115.5 (1C, C-5), 57.5 (1C, N-CH_2). MS (EI, *m/z* (%)): 310 (M^+, 100).

1-{[1-(4-Fluorophenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**E**): Color: Paleyellow solid. Yield: 90%. M.p.:136-138 °C. FT-IR (KBr, cm^{-1}): 3140 (triazole-H), 1593 (C=C, triazole), 1515 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.110 (s, 1H, N-*CH*=N), 7.830 (d, *J* = 8.4 Hz, 1H, Ar), 7.650 (s, 1H, triazole-H), 7.516 (m, 3H, Ar), 7.311 (m, 2H, Ar), 7.088 (d, 2H, *J* = 8 Hz, Ar), 5.518 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 155.1 (1C, C-4^1), 144.2 (1C, C-4, triazole), 143.7 (1C, C-2^2), 138.3 (1C, C-9^2), 137.7 (1C, C-8^2), 135.1 (1C, C-1^1), 134.1 (2C, C-3^1 & C-5^1), 127.5 (2C, C-2^1&C-6^1), 123.3 (1C, C-6^2), 119.9 (1C, C-4^2), 115.5 (1C, C-5), 57.3 (1C, N-CH_2). MS (EI, *m/z* (%)): 294 (M^+, 100).

1-{[1-(4-Bromophenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**F**): Color: White solid. Yield: 90%. M.p.: 141-143 °C. FT-IR (KBr, cm^{-1}): 3135 (triazole-H), 1594 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.120 (s, 1H, N-*CH*=N), 7.832 (d, 1H, *J* = 9.2 Hz, Ar), 7.621 (s, 1H, triazole-H), 7.511 (m, 2H, Ar), 7.452 (m, 1H, Ar), 7.321 (m, 2H, Ar), 6.940 (d, 2H, *J* = 9.2 Hz, Ar), 5.528 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 145.7 (1C, C-4, triazole), 143.7 (1C, C-2^2), 138.2 (1C, C-9^2), 137.5 (1C, C-8^2), 134.5 (1C, C-1^1), 132.1 (1C, C-4^1), 128.7 (2C, C-3^1 & C-5^1), 127.2 (2C, C-2^1&C-6^1), 123.2 (1C, C-6^2), 119.9 (1C, C-4^2), 115.8 (1C, C-5), 57.5 (1C, N-CH_2). MS (EI, *m/z* (%)): 355 (M^+, 100).

1-{[1-(2-Fluorophenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**G**): Color: Pale yellow solid. Yield: 85%. M.p.: 137-139 °C. FT-IR (KBr, cm^{-1}): 3140 (triazole-H), 1594 (C=C, triazole), 1515 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.154 (s, 1H, N-*CH*=N), 7.948 (m, 1H, Ar), 7.927 (s, 1H, triazole-H), 7.452 (m, 2H, Ar), 7.290 (m, 5H, Ar), 5.393 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 160.6 (1C, C-2^1), 145.5 (1C, C-4, triazole), 143.1 (1C, C-2^2), 138.6 (1C, C-1^1), 137.5 (1C, C-9^2), 136.7 (1C, C-8^2), 134.6 (1C, C-3^1), 133.6 (1C, C-5^1), 128.2 (1C, C-4^1), 127.0 (1C, C-6^1), 123.2 (1C, C-6^2), 121.6 (1C, C-4^2), 116.5 (1C, C-5), 57.5 (1C, N-CH_2). MS (EI, *m/z* (%)): 294 (M^+, 100).

1-{[1-(4-Nitrophenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**H**): Color: White solid. Yield: 88%. M.p.: 161-163 °C. FT-IR (KBr, cm^{-1}): 3135 (triazole-H), 1593 (C=C, triazole), 1502 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.140 (s, 1H, N-CH=N), 7.830 (d, 1H, *J* = 8 Hz, Ar), 7.645 (s, 1H, triazole-H), 7.520 (m, 3H, Ar), 7.310 (m, 2H, Ar), 6.971 (d, 2H, *J* = 8.8 Hz, Ar), 5.582 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 147.3 (1C, C-4^1), 145.5 (1C, C-4, triazole), 143.7 (1C, C-2^2), 138.5 (1C, C-1^1), 137.7 (1C, C-9^2), 135.5 (1C, C-8^2), 134.1 (2C , C-3^1 & C-5^1), 128.2 (2C, C-2^1 & C-6^1), 123.0 (1C, C-6^2), 120.2 (1C, C-4^2), 116.9 (1C, C-5), 56.2 (1C, N-CH_2). MS (EI, *m/z* (%)): 321 (M^+, 100).

1-{[1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl]methyl}-1H-benzimidazole (**I**): Color: White solid. Yield: 75%. M.p.: 169-171 °C. FT-IR (KBr, cm^{-1}): 3133 (triazole-H), 1594 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.210 (s, 1H, N-*CH*=N), 7.830 (d, 1H, *J* = 8.4 Hz, Ar), 7.651 (s, 1H, triazole-H), 7.530 (s, 1H, Ar), 7.421 (m, 3H, Ar), 7.056 (d, 2H, *J* = 4.8 Hz, Ar), 5.503 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 145.1 (1C, C-4, triazole), 143.5 (1C, C-2^2), 137.7 (1C, C-9^2), 135.8 (2C, C-3^1 & C-5^1), 135.5 (1C, C-8^2), 131.8 (1C, C-1^1), 128.8 (1C, C-4^1), 123.4 (2C, C-2^1 & C-6^1), 123.7 (1C, C-6^2), 120.1 (1C, C-4^2), 115.6 (1C, C-5), 57.5 (1C, N-CH_2). MS (EI, *m/z* (%)): 345 (M^+, 100).

1-{[1-(3-Chlorophenyl)-1H-1, 2, 3-triazol-4-yl] methyl}-1H-benzimidazole (**J**): Color: Yellow solid. Yield: 80%. M.p.:150-152 °C. FT-IR (KBr, cm^{-1}): 3139 (triazole-H), 1596 (C=C, triazole), 1515 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.116 (s, 1H, N-*CH*=N), 7.840 (s, 1H, triazole-H), 7.630 (d, 2H, *J* = 8.4 Hz, Ar), 7.517 (m, 2H, Ar), 7.291 (m, 2H, Ar), 6.994 (d, 2H, *J* = 5.3 Hz, Ar), 5.512 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 145.5 (1C, C-4, triazole), 143.1 (1C, C-2^2), 138.6 (1C, C-9^2), 137.6 (1C, C-8^2), 134.6 (1C, C-3^1), 133.6 (1C, C-2^1), 131.6 (1C, C-1^1), 128.2 (1C, C-4^1), 127.0 (1C, C-5^1), 126.2 (1C, C-6^1), 122.2 (1C, C-6^2), 121.6 (1C, C-4^2), 116.5 (1C, C-5), 57.5 (1C, N-CH_2). MS (EI, m/z (%)): 332 (M+Na, 100).

1-{[1-(3-Methylphenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**K**): Color: White solid. Yield: 92%. M.p.: 134-136 °C. FT-IR (KBr, cm-1): 3135 (triazole-H), 1593 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.120 (s, 1H, N-*CH*=N), 7.830 (d, 1H, *J* = 8 Hz, Ar), 7.643 (s, 1H, triazole-H), 7.515 (m, 3H, Ar), 7.310 (m, 2H, Ar), 6.977 (d, 2H, *J* = 8.8 Hz, Ar), 5.582 (s, 2H, N-CH_2), 2.41 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) : 144.1 (1C, C-4, triazole), 143.1 (1C, C-2^2), 138.6 (1C, C-9^2), 138.0 (1C, C-8^2), 134.3 (1C, C-1^1), 128.2 (1C, C-3^1), 127.1 (1C, C-2^1), 126.2 (1C, C-6^1) 123.3 (1C, C-5^1), 122.8 (1C, C-6^2), 119.3 (1C, C-4^2), 115.6 (1C, C-5), 57.1 (1C, N-CH_2), 21.1 (1C, Ar-CH_3). MS (EI, *m/z* (%)): 290 (M^+, 100).

1-{[1-(2,3-Dimethylphenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**L**): Color: White solid. Yield: 90%. M.p.: 139-141 °C. FT-IR (KBr, cm^{-1}): 3141 (triazole-H), 1594 (C=C, triazole), 1515 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.100 (s, 1H, N-*CH*=N), 7.654 (s, 1H, triazole-H), 7.531

Table 2. Antibacterial activity of 1,4-di-substituted 1,2,3-triazole derivatives of benzimidazole (**A-N**).

Compound	MIC, µg/mL			
	E. coli	*S. aureus*	*B. subtilis*	*P. vulgaris*
A	46	48	50	66
B	80	46	58	78
C	NA	64	62	48
D	NA	62	46	NA
E	NA	78	64	80
F	74	48	NA	68
G	58	45	NA	78
H	45	60	44	NA
I	54	54	40	64
J	58	52	NA	70
K	62	36	NA	NA
L	58	40	42	72
M	40	44	42	54
N	40	40	40	44
Streptomycin sulphate	10	12	16	14

Table 3. Antifungal activity of 1,4-di-substituted 1,2,3-triazole derivatives of benzimidazole (**A-N**).

Compound	MIC, µg/mL	
	Aspergillus sp	*Penicillium sp*
A	25	34
C	32	-
E	38	-
F	50	28
G	52	48
I	26	26
K	42	42
N	44	-
Ampothericin-B	25	25

(m, 3H, Ar), 7.311 (m, 2H, Ar), 6.971 (d, 2H, *J* = 8.8 Hz, Ar), 5.553 (s, 2H, N-CH_2), 2.781 (s, 3H, Ar-CH_3), 2.401 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 144.5 (1C, C-4, triazole), 143.4 (1C, C-2^2), 138.0 (1C, C-9^2), 137.4 (1C, C-8^2), 136.3 (1C, C-1^1), 134.6 (1C, C-2^1), 133.5 (1C, C-3^1), 128.2 (1C, C-6^1), 127.1 (1C, C-5^1), 123.3 (1C, C-4^1), 122.2 (1C, C-6^2), 119.3 (1C, C-4^2), 115.5 (1C, C-5), 56.6 (1C, N-CH_2), 24.5 (1C, Ar-CH_3), 22.1 (1C, Ar-CH_3). MS (EI, *m/z* (%)): 304 (M^+, 100).

1-({1-[3-(Trifluoromethyl)phenyl]-1H-1, 2, 3-triazol-4-yl} methyl)-1H-benzimidazole (**M**): Color: Orange solid. Yield: 86%. M.p.: 165-167 °C. FT-IR (KBr, cm^{-1}): 3135 (triazole-H), 1593 (C=C, triazole), 1516 (N=N, triazole). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.110 (s, 1H, N-*CH*=N), 7.844 (s, 1H, triazole-H), 7.631 (d, 2H, *J* = 8.4 Hz, Ar), 7.514 (m, 2H, Ar), 7.295 (m, 2H, Ar), 6.992 (d, 2H, *J* = 5.3 Hz, Ar), 5.515 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 144.5 (1C, C-4, triazole), 143.2 (1C, C-2^2), 138.1 (1C, C-9^2), 137.2 (1C, C-8^2), 134.8 (1C, C-3^1), 133.3 (1C, C-2^1), 131.4 (1C, C-1^1), 128.1 (1C, C-4^1), 127.2 (1C, C-5^1), 126.8 (1C, C-6^1), 123.3 (1C, *CF*$_3$) 122.4 (1C, C-6^2), 121.2 (1C, C-4^2), 116.8 (1C, C-5), 57.7 (1C, N-CH_2). MS (EI, *m/z* (%)): 344 (M^+, 100).

1-{[1-(2-Methylphenyl)-1H-1, 2, 3-triazol-4-yl]methyl}-1H-benzimidazole (**N**): Color: White solid. Yield: 85%. M.p.: 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.115 (s, 1H, N-*CH*=N), 7.834 (d, 1H, *J* = 8 Hz, Ar), 7.642 (s, 1H, triazole-H), 7.516 (m, 3H, Ar), 7.320 (m, 2H, Ar), 6.978 (d, 2H, *J* = 8.8 Hz, Ar), 5.552 (s, 2H, N-CH_2), 2.441 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 144.2 (1C, C-4, triazole), 143.3 (1C, C-2^2), 138.4 (1C, C-9^2), 138.2 (1C, C-8^2), 134.3 (1C, C-1^1), 130.1 (1C, C-2^1), 128.4 (1C, C-3^1), 127.6 (1C, C-4^1), 126.8 (1C, C-6^1), 123.4 (1C, C-5^1), 122.9 (1C, C-6^2), 119.3 (1C, C-4^2), 115.6(1C, C-5), 57.1(1C, N-CH_2), 22.4(1C, Ar-CH_3). IR (KBr, cm^{-1}): 3141 (triazole-H), 1595 (C=C, triazole), 1504 (N=N, triazole). MS (EI, *m/z* (%)): 290 (M^+, 100).

2.4. Biological activity

2.4.1. Antimicrobial activity

A broad panel of bacterial and fungal strains was used for testing the antimicrobial properties of the synthesized molecules. The molecules were screened against both Gram positive (*S. aureus* and *B. Subtilis*) and Gram negative (*E. coli* and *P. vulgaris*) organisms. The samples were tested by standard protocols, Agar well diffusion method [40,41] for antibacterial activity (Table 2) and Agar plug method for antifungal activity (Table 3). For all the derivatives, minimum inhibitory concentration was determined by using microtiter plate technique and resazurin as bio-indicator. Streptomycin sulphate was used as a standard drug for antibacterial activity and ampothericin-B was used as a standard for antifungal activity and they were also screened under identical conditions for comparison. All the culture used in this present study was obtained by Agricultural Research Service-United States Department of Agriculture (ARS-USDA) on request and their help in this regard is duly acknowledged.

2.4.2. Antioxidant activity

The synthesized compounds (**A-N**) were investigated for *in vitro* antioxidant activity in terms of hydrogen donating or radical scavenging ability by rapid and convenient technique, *i.e.* 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay [42,43] using trolax and ascorbic acid as standard drugs. Methanol (95%), DPPH solution and standard drugs were used as blank, control, and reference, respectively. Absorbance was calculated at 517 nm (at an absorption maximum of DPPH) after keeping the mixture of 100 µL of synthesized compounds of concentration 10 µg/mL (dissolved in DMSO) and 900 µL of DPPH radical solution (0.004% *w:v* of DPPH in methanol) in a dark place for 30 min incubation period. Antioxidant activity was evaluated in IC_{50} in µM (the effective concentration at which 50% of the radicals were scavenged) and depicted in Table 4.

3. Results and discussion

3.1. Chemistry

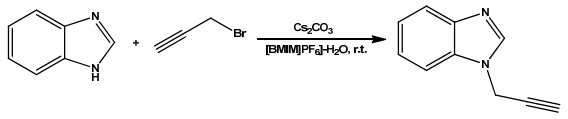
In the present work, we report an efficient *N*-propargylation of benzimidazole in the presence of Cs_2CO_3 and one pot multi-component synthesis of 1,2,3-triazoles using

Table 4. Antioxidant activity of 1,4-di-substituted 1,2,3-triazole derivatives of benzimidazole (**A**-**N**) by DPPH method .

Compound	IC_{50}
A	50.37±1.35
B	15.64±1.32
C	25.93±1.19
D	22.49±1.42
E	87.02±1.23
F	58.05±1.25
G	26.34±1.26
H	51.85±1.10
I	6.308±1.35
J	38.31±1.40
K	94.20±1.52
L	101.62±1.35
M	8.51±1.18
N	134.20±1.32
Trolox	14.80±1.43
Ascorbic acid	3.0±1.34

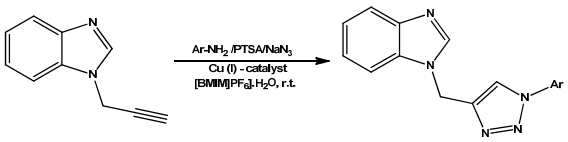
N-propargylbenzimidazole, anilines, sodium nitrite and sodium azide in ionic liquid [BMIM][PF_6]·H_2O at room temperature.

N-Propargylation was carried out by the addition of propargyl bromide, under stirring, to the [BMIM][PF_6] and H_2O mixture containing benzimidazole and Cs_2CO_3 at room temperature for 12 hours (Scheme 1). The ionic liquid was recycled and used for the cycloaddition reaction.



Scheme 1

In a typical reaction (Scheme 2), aryl amines were homogenized by mixing a wet solid *p*-TsOH hydrate followed by addition of $NaNO_2$ and NaN_3 in [BMIM][PF_6]·H_2O stirred at room temperature for 3 h. *N*-Propargylbenzimidazole and CuI were then added and the reaction was stirred for 8-10 hrs at room temperature. The reaction proceeds smoothly and rapidly to afford 1,2,3-triazoles in excellent yields. The results are presented in Table 1. The residue ionic liquid was washed with water and reused.



Scheme 2

3.2. Antimicrobial activity

All the new compounds were screened for their antibacterial and antifungal activities using standard protocols and the minimum inhibitory concentration (MIC) values were recorded (Table 2 and 3). Among the compounds tested, compound-**B** and **D** exhibited excellent antibacterial activities against gram negative bacteria *E.coli* and *P.vulgaris* while the compound **F** exhibited appreciable activity against *S. aureus* and *B. Subtilis*. The compounds **A** and **C** are more potent against *Aspergillus* and compounds **F** and **I** exhibited moderate activity.

3.3. Antioxidant activity

Evaluation of antioxidant activity revealed that the most of the tested compounds exhibited moderate to strong DPPH radical scavenging ability compared with the positive controls trolox and ascorbic acid. Among them, the compounds 3,5-dichloro phenyl and 3-(trifluoromethyl) phenyl on the triazole ring that is I and M were found to be more effective and potent DPPH radical scavenging ability when compared with positive control drug Trolax. Remaining all the compounds have shown good to moderate radical scavenging activity with IC_{50} values in the range of 15.64±1.32 and 134.20±1.32 μM. It was noticed that, the compounds with electrons attracting groups on the phenyl ring were found to be good radical scavenging ability (Table 4).

4. Conclusion

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

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References

[1]. Kamal, S.; Sumit, C.; Sushant K. S.; Pradeep, M. *Med. Chem. Res.* **2013**, *22*, 5077-5104.
[2]. Balasubramanian, N.; Deepika, S.; Pradeep, K. *Med. Chem. Res.* **2012**, *21*, 269-283.
[3]. Shivakumar, R.; Pradeepchandran, R. V.; Narasimha, J. K. *Eur. J. Chem.* **2011**, *2*, 558-560.
[4]. Love Kumar, S.; Narsinghani, T.; Anand, S. *Med. Chem. Res.* **2012**, *21*, 4330-4334.
[5]. Tuncbilek, M.; Kiper, T.; Altanlar, N. *Eur. J. Med. Chem.* **2009**, *44*, 1024-1033.
[6]. Desai, N. C.; Pandya, D. D.; Joshi, V. V.; Rajpara, K. M.; Vaghani, H. V.; Satodiya, H. M. *Med. Chem. Res.* **2012**, *21*, 4463-4472.
[7]. Deepkumar, J.; Kalpesh, P. *Med. Chem. Res.* **2014**, *23*, 1290-1299.
[8]. Afaf, H. E. M.; Fahmy, H. H.; Ali Abdelwahed, S. H. *Molecules* **2000**, *5*, 1429-1438.
[9]. Ravishankara, D. K.; Chandrashekara, P. G. *Eur. J. Chem.* **2012**, *3*, 363-366.
[10]. Guruswamy, B.; Arul, R. K.; Chaitanya, M. V. S. R. K.; Darsi, S. S. P. K. *Eur. J. Chem.* **2013**, *4*, 329-335.
[11]. Tonelli, M.; Matteo, S.; Bruno, T.; Federica, N.; Giuseppina, S.; Fabio, S.; Giuseppe, P.; Sabrina, P.; Vito, B.; Gabriele, G.; Sylvain, B.; Cristina, I.; Roberta, L.; Paolo, L. C. *Bioorg. Med. Chem.* **2010**, *18*, 2937-2953.
[12]. Angela, R.; Alba, C.; Erik, D. C.; Anna, M. M.; Pietro, M.; Christophe, P.; Maria, Z. *Il Farmaco* **2002**, *57*, 819-823.
[13]. Ruiming, Z.; Kevin, R.; Ayres, J. C.; Drach, L. B.; Townsend. *J. Med. Chem*. **1996**, *39*, 3477-3482.
[14]. Garuti, L.; Roberti, M.; G. Gentilomi, G. *Il Farmaco* **2000**, *55*, 35-39.

[15]. Ravishankara, D. K.; Chandrashekara, P. G. *Eur. J. Chem.* **2012**, *3*, 359-362.
[16]. Kavitha, C. S. A.; Kallappa M. H.; Harisha R. S. *E. J. Med. Chem*. **2010**, *45*, 2048-2054.
[17]. Kaushik, D.; Ahmed Khan, S.; Gita C. *Med. Chem. Res*. **2012**, *21*, 459-467.
[18]. Galal, S. A.; Abdelsamie, A. S.; Rodriguez, M. L.; Kerwin, S. M. El Diwani, H. I. *Eur. J. Chem.* **2010**, *1*, 67-72.
[19]. Nofal. Z. M.; Soliman, E. A.; Abd El-Karim, S. S.; Elzahar, M. I.; Srour, A. M.; Dhavan, S. S.; Maher, T. J. *Acta P. Pharm. Drug Res*. **2011**, *68*, 519-534.
[20]. Ahmed A. E. R.; Hassan, Y. A. E. *Mini-Rev. Med. Chem.* **2013**, *13*, 399-407.
[21]. Ali, E. S.; Omer, O. A.; Sama, A. A. *Eur. J. Chem.* **2012**, *3*, 356-358.
[22]. Meldal, M.; Christian, W. T.; Christensen, C. *J. Org. Chem*. **2002**, *67*, 3057-3064.
[23]. Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem*. **2004**, *69*, 2386-2393.
[24]. Cristina, G. O.; Jagerovic, N.; Goya, P.; Alkorta, I.; Elguero, J.; Cuberes, R.; Dordal, A. *Arkivoc **2010**, 2,* 127-147.
[25]. Akhtar, T.; Hameed, S.; Khan, K. M.; Khan, A.; Choudhary, M. I. *J. Enzym Inhib. Med. Ch.* **2010**, *25*, 572-576.
[26]. Alvarez, S.; San, F.; Aquaro, S. D. C.; Perno, C, F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem*. **1994**, *37*, 4185- 4194.
[27]. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K. M. J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem*. **2000**, *43*, 953-970.
[28]. Narsimha, S.; Ranjith, K. T.; Satheesh, K. N.; Yakoob, S.; Vasudeva, R. N. *Med. Chem. Res.* **2014**, *23*, 5321-5327.
[29]. Huisgen. R. Angew. Chem. **1963**, *75*, 604-637.
[30]. David, A.; Francesco, F.; Oriana, P.; Ferdinando, P.; Ennio, Z.; Luigi, V. *J. Org. Chem.* **2005**, *70*, 6526-6529.
[31]. Sharpless, K. B.; Vsevolod, V. R.; Luke, G. G.; Valery, V. F. *Angew. Chem., Int. Ed*. **2002**, *41*, 2596-2599.
[32]. Firouzeh, N.; Ali, E. *J. Appl. Chem*. **2012**, *7*, 29-33.
[33]. Jorapur, Y. R.; Jeong, J. M.; C. hi, D. Y. *Tetrahedron Lett.* **2006**, *47*, 2435-2438.
[34]. Cinzia, C.; , Daniela, P. *Green Chem.* **2003**, *5*, 193-197
[35]. Cinzia, C.; Paolo, P.; Daniela, P. *Green Chem*. **2006**, *8*, 277-281.
[36]. Alberto, M.; Alessandra, V.; Cinzia, C.; Bernardo, M.; Alessandro, D. *J. Org. Chem.* **2008**, *73*, 2458-2461.
[37]. Ya-Bin, Z.; Ze-Yi, Y.; Yong-Min, Liang. *Tetrahedron Lett.* **2006**, *47*, 1545-1549.
[38]. Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809-1811.
[39]. Moorhouse, A. D.; Moses, J. E. *Synlett.* **2008**, *14,* 2089-2092.
[40]. Parekh, J.; Chanda, S. V. *Turk. J. Biol*. **2007**, *31*, 53-58.
[41]. Cosentino, S.; Tuberoso, C. I. G.; Pisano, B.; Satta, M.; Mascia, V.; Arzedi, E.; Palmas, F. *Lett. Appl. Microbiol*. **1999**, *29*, 130-135.
[42]. Gul, M. Z.; Farhan, A.; Anand, K. K.; Insaf, A. Q.; Irfan, A. G. *BMC Complem. Altern. Med*. **2013**, *13*, 53, 1-12.
[43]. Ramesh, G.; Janardhan, B.; Ranjith Kumar, T.; Althaf Hussain, S. K.; Rajitha, B. *RSC Adv.* **2015**, *5*, 33562-33569.