Design, Synthesis of New Imidazolium-1,2,3-triazole Hybrid Derivatives as Antimicrobial Agents

Ameer Salem Muttaleb[1], Nardeen Adnan Berto[2], Sahar Adeeb Mamoori[1], Zaman Abdalhussein Ibadi Alaridhee[3], Ehab Kareem Obaid[1], and Ali Jabbar Radhi[4*]

[1]*Faculty of Agriculture, Al-Qasim Green University, Babylon 51001, Iraq*

[2]*Department of Engineering of Polymers and Petrochemicals Industries, University of Babylon, Babylon 51001, Iraq*

[3]*Department of Medical Laboratory Techniques, College of Health and Medical Techniques, University of Alkafeel, Najaf 54001, Iraq*

[4]*College of Pharmacy, University of Al-Kafeel, Najaf 54001, Iraq*

* ***Corresponding author:***

email: alijebar56@gmail.com

Received: June 14, 2023
Accepted: December 28, 2023

DOI: 10.22146/ijc.85704

Abstract: *New imidazolium salts with 1,2,3-triazole rings (rm1-rm5) were prepared in the current work using a design-driven synthetic procedure scheme. By using analytical techniques such as NMR, IR and spectral information, the chemical structures of target synthesized products were identified using results that were discovered in perfect accord with their assigned structures. The microorganism used in the current study were bacterial strains of* Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Bacillus subtilis *and* Micrococcus luteus, *as well as the fungal strains of* Aspergillus niger *and* Candida albicans. *All the end products were estimated for their antibacterial activity. The values for the minimum inhibitory concentration (MIC) were confirmed by comparison to the widely used antibiotics fluconazole and ciprofloxacin as control drugs. Particularly, the compounds (rm5) and (rm4) showed observable antibacterial activity. These compounds might offer a brand-new place to start when looking for new antibacterial medications.*

Keywords: *imidazole; 1,2,3-triazole ring; imidazolium salts; antifungal activity; antibacterial activity*

■ INTRODUCTION

Developing new medications by molecular modification has been the primary goal of medicinal chemists in recent years, along with improving the efficacy and duration of existing treatments while lowering their toxicities and side effects [1]. The drug development process has continued to be a priority for the biopharmaceutical industry and a medicinal chemist. The natural or artificial origin of organic therapeutic compounds is up for debate. The structures of natural pharmaceuticals are modified to create synthetic drugs, or they are created entirely from scratch [2]. A significant global public health concern now is the gradual rise in infectious illness occurrences brought on by rising microbial antibiotic resistance [3]. This big problem has encouraged chemists and researchers to prepare and improve new antimicrobial drugs and medications that will be more active and effective, less dangerous, and more targeted in combating medication-resistant bacteria [4]. Nitrogen atoms that contain heterocyclic compounds such as, 1,2,3-triazole have a high biocompatibility and a variety of pharmacological actions, including antihypertensive, anticonvulsant [5], antiallergic, analgesic [6], antimalarial [7], CNS depressant [8], antitubercular [9], antifungal [10], antiviral [11], antibacterial [12], the usage of heterocyclic molecules contain triazole ring, attractive linkages that led to collection two or more pharmacophores to create novel functional medications, has increased in significance [13-15]. Aromatic

heterocycles, in particular the imidazole ring, have been used in recent years to synthesize a variety of active molecules with antiviral, antidiabetic, antifungal, antitumor, antibacterial, and other actions [16]. Finding new, potent therapeutic molecules made from imidazole is an active area of medicinal chemistry research [17]. Furthermore, improvements in medicinal chemistry research, regulation, and manufacturing are hastening the development or preparation of solid active components that are taken as tablets or powders; nonetheless, many solid medications that function well *in vitro* are still too insoluble to be absorbed by the body [18]. Ionic liquids are a promising class of therapeutic options from this standpoint, and their physicochemical and pharmacological characteristics can be easily changed [19-20]. Salts make up the majority of bioactive compounds that are sold to the food or pharmaceutical industries [21]. In the current study, the prepared imidazolium salt can be used to produce ionic molecules with extremely effective pharmacological effects [22]. Results have been obtained that imidazolium salt derivatives are used as a new antibacterial substance [23]. Regarding this, the literature has described mono-imidazolium salts based on amino acids as having good bacterial toxicity [24].

■ EXPERIMENTAL SECTION

Materials

The materials used in this study were Imidazole ($C_3H_4N_2$) (99% purity, Sigma Aldrich (USA), Series from Alkyl Bromide ($C_nH_{2n+1}Br$) where n = 10, (99% purity, Sigma Aldrich (USA), Propargyl bromide (~80% purity, Sigma Aldrich (USA)). High-quality absolute Diethyl ether, Dioxan, DMF, DMSO and Sodium azide (NaN_3), Sodium hydroxide (NaOH) (99% purity Fluka & Merck, Germany).

Instrumentation

The instrumentations used in this study were Fourier transformation infrared (Bruker ALPHA FTIR, Germany) (KBr plate) at the University of Kufa, Faculty of Science. NMR spectra in DMSO-d_6 at the Iranian Shahid Beheshti University (75 MHz for ^{13}C-NMR and 300 MHz for ^{1}H-NMR, Bruker spectrometer, Germany). The melting points were recorded using the (Electro Thermal Melting Point Apparatus, United Kingdom).

Procedure

Synthesis of N-*Substituted imidazole (m1-m5) [25]*

KOH (29.4 mmol) was added directly to a new solution of starting material imidazole (15 mmol) in 20 mL DMSO. After 2 h of continuous stirring at 90 °C, alkyl bromide (15 mmol) was added slowly dropwise at room temperature to the reaction solution with constant stirred. Following complete addition, the mixture of reaction was agitated for the remainder of the reaction's 1.5 h duration at 40 °C. The reactant solution was then added to 250 mL of water and separated with chloroform (3 × 30 mL). After the solvent had evaporated, the residue was obtained. Acetonitrile was used to recrystallize the final product.

1-Decyl-1*H*-imidazole (m1). Yield (81%), m.p. (215–217 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.86 (3H, CH_3, t, J = 7.1 Hz), 1.21–1.28 (14H, 7 x CH_2, m), 1.81 (2H, p, J = 6.9 Hz), 4.53 (2H, N-CH_2, t, J = 7.0 Hz), 7.63 (1H, imid H, s), 7.76 (1H, imid H, s), 9.79 (1H, NCHN, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 138.24 (NCHN), 121.25, 122.38 (imid-C), 46.07 (N-CH_2), 31.77, 29.89, 29.48, 29.47, 29.14, 29.01, 26.74, 22.51 (8-CH_2), 14.12 (CH_3). FTIR (KBr, cm^{-1}): 3157 (C-$_{alkene}$H), 2971 (C-$_{aliph}$H), 2858 (C-$_{aliph}$H), 1617 (C=N), and 1254 (C-N).

1-Dodecyl-1*H*-imidazole (m2). Yield (80%), m.p. (218–219 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.83 (3H, CH_3, t, J = 7.0 Hz), 1.18–1.26 (18H, 9 x CH_2, m), 1.76 (2H, p, J = 6.9 Hz), 4.54 (2H, N-CH_2, t, J = 7.0 Hz), 7.64 (imid H, 1H, s), 7.79 (imid H, 1H, s), 9.81 (1H, NCHN, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 137.81 (NCHN), 122.87, 120.54 (imid-C), 44.90 (N-CH_2), 31.97, 30.14, 29.96, 29.57, 29.37, 29.27, 29.05, 28.47, 26.47, 22.78 (10-CH_2), 13.98 (CH_3). FTIR (KBr, cm^{-1}): 3108 ($_{alkene}$C-H), 2975 ($_{aliph}$C-H), 2864 ($_{aliph}$C-H), 1618 (C=N), and 1255 (C-N).

1-Tetradecyl-1*H*-imidazole (m3). Yield (83%), m.p. (220–222 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.87 (3H, CH_3, t, J = 7.1 Hz), 1.17–1.25 (22H, 11 x CH_2,

m), 1.76 (2H, p, J = 6.9 Hz), 4.48 (2H, N-CH_2, t, J = 7.0 Hz), 7.63 (imid H, 1H, s), 7.75 (imid H, 1H, s), 9.83 (1H, NCHN, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 138.28 (NCHN), 123.41, 121.25 (imid-C), 43.78 (N-CH_2), 31.81, 29.81, 29.65, 29.59, 29.51, 29.45, 29.41, 29.33, 29.05, 28.78, 26.65, 22.52 (12-CH_2), 14.30 (CH_3). FTIR (KBr, cm^{-1}): 3141 ($_{alkene}$C-H), 2965 ($_{aliph}$C-H), 2885 ($_{aliph}$C-H), 1620 (C=N), and 1245 (C-N).

1-Hexadecyl-1*H*-imidazole (m4). Yield (75%), m.p. (227–228 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.84 (3H, CH_3, t, J = 7.1 Hz), 1.20–1.28 (26H, 13 x CH_2, m,), 1.78 (2H, p, J = 6.9 Hz), 4.49 (2H, N-CH_2, t, J = 7.0 Hz), 7.65 (imid H, 1H, s), 7.80 (imid H, 1H, s), 9.86 (1H, NCHN, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 138.54 (NCHN), 123.15, 121.12 (imid-C), 45.87 (N-CH_2), 31.98, 31.71, 29.87, 29.72, 29.51, 29.41, 29.38, 29.30, 29.07, 28.95, 28.89, 26.74, 26.88, 22.87 (14-CH_2), 14.13 (CH_3). FTIR (KBr, cm^{-1}): 3107 ($_{alkene}$), C-H2975 (C-$_{aliph}$H), 2882 ($_{aliph}$C-H), 1625 (C=N), and 1250 (C-N).

1-Octadecyl-1*H*-imidazole (m5). Yield (74%), m.p. (231–233 °C). ^{1}H-NMR (300MHz, DMSO-d_6): δ (ppm): 0.85 (3H, CH_3, t, J = 7.1 Hz), 1.18–1.25 (30H, 15 x CH_2, m), 1.74 (2H, p, J = 6.9 Hz), 4.55 (2H, N-CH_2, t, J = 7.0 Hz), 7.61 (imid H, 1H, s), 7.78 (imid H, 1H, s), 9.82 (1H, NCHN, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 137.97 (NCHN) ,123.57, 121.60 (imid-C), 45.16 (N-CH_2), 31.78, 31.78, 29.97, 29.81, 29.72, 29.55, 29.50, 29.42, 29.31, 29.20, 29.11, 28.97, 28.36, 26.54, 26.41, 22.51 (16-CH_2), 14.48 (CH_3). FTIR (KBr, cm^{-1}): 3135 ($_{alkene}$C-H), 2941 ($_{aliph}$C-H), 2874 ($_{aliph}$C-H), 1608 (C=N), and 1249 (C-N).

Synthesis of imidazolium salt (r1-r5) [25]

The 1-alkyl-1*H*-imidazole (m1-m5) (5.5 mmol) was reacted with excesses of propargyl bromide in (30 mL) of acetonitrile and refluxed for 24 h. The resulting sticky solution was separated and washed several times with diethyl ether and 1,4-dioxane, and the resulting compound was directly converted by metathesis reaction to its hexafluorophosphate counterpart anion using KPF_6 (5.00 mmol) at room temperature in methanol and water (20 mL). To get rid of any KPF_6 leftovers, the finished product was rinsed (3 × 5 mL) with distilled water. The final product was recrystallized from acetonitrile.

1-Decyl-3-(prop-2-yn-1-yl)imidazolium salts (r1). Yield: (80%). m.p. (260–262 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.84 (3H, CH_3, t, J = 6.7 Hz), 1.14–1.21 (14H, 7 x CH_2, m), 1.74 (2H, p, J = 6.9 Hz,), 3.62 (1H, C≡C-H, s), 4.29 (N-CH_2, t, J = 7.0 Hz, 2H), 4.81 (2H, N-CH_2-C≡C, s), 7.18 (1H, imid H, s), 6.69 (1H, imid H, s), 8.93 (s, 1H, NCHN). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 142.41 (NCHN), 122.87, 121.15 (imid-C), 74.87 (-C≡CH), 67.74 (≡CH), 48.57 (acetylene-CH_2-N), 44.38 (N-CH_2), 32.81, 29.97, 29.81, 29.41, 29.21, 29.11, 27.10, 22.74 (8-CH_2), 14.20 (8-CH_3). FTIR (KBr, cm^{-1}): 3270 (-C≡CH), 3105 ($_{alkene}$C-H), 2950($_{aliph}$C-H), 2885($_{aliph}$C-H), 2125 (-C≡C-), 1614 (C=N), and 1265(C-N).

1-Dodecyl-3-(prop-2-yn-1-yl)imidazolium salts (r2). Yield: (75%). m.p. (277–278 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.81 (3H, CH_3, t, J = 6.7 Hz,), 1.14–1.20 (18H, 9 x CH_2, m), 1.73 (2H, p, J = 6.9 Hz), 3.61 (1H, C≡C-H, s), 4.29 (2H, N-CH_2, t, J = 7.0 Hz), 4.81 (2H, N-CH_2-C≡C, s), 7.12 (1H, imid H, s), 6.74 (1H, imid H, s), 8.93 (s, 1H, NCHN). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 142.75 (NCHN), 122.87, 121.85 (imid-C), 74.74 (-C≡CH), 67.27 (≡CH), 48.84 (acetylene-CH_2-N), 44.90 (N-CH_2), 32.71, 30.75, 29.98, 29.81, 29.60, 29.35, 29.12, 28.78, 26.21, 22.58 (10-CH_2), 14.08 (10-CH_3). FTIR (KBr, cm^{-1}): 3274 (-C≡CH), 3081 ($_{aromati}$C-H$_c$), 2975 ($_{aliph}$C-H), 2865 ($_{aliph}$C-H), 2128 (-C≡C-), 1614 (C=N), and 1260 (C-N).

1-Tetradecyl-3-(prop-2-yn-1-yl)imidazolium salts (r3). Yield: (78%). m.p. (291–292 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.86 (3H, CH_3, t, J = 6.7 Hz), 1.14–1.21 (22H, 11 x CH_2, m), 1.72 (2H, p, J = 6.9 Hz), 3.69 (1H, C≡C-H, s), 4.31 (2H, N-CH_2, t, J = 7.0 Hz), 4.84 (2H, N-CH_2-C≡C, s), 7.19 (1H, imid H,s), 6.75 (1H, imid H, s), 8.92 (s, 1H, NCHN). ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 142.91 (NCHN), 122.89, 121.21 (imid-C), 74.85(-C≡CH), 67.74(≡CH), 48.54(acetylene-CH_2-N), 44.74 (N-CH_2), 31.25, 29.88, 29.68, 29.52, 29.44, 29.35, 29.28, 29.21, 29.01, 28.54, 26.81, 22.45 (12-CH_2), 14.35 (CH_3). FTIR (KBr, cm^{-1}): 3275 (-C≡CH), 3105 ($_{alkene}$C-H), 2941 ($_{aliph}$C-H), 2885 ($_{aliph}$C-H), 2122 (-C≡C-), 15611 (C=N) and 1260 (C-N).

1-Hexadecyl-3-(prop-2-yn-1-yl)imidazolium salts (r4). Yield: (80%). m.p. (298–300 °C). ^{1}H-NMR

(300 MHz, DMSO-d_6): δ (ppm): 0.83 (3H, CH_3, t, J = 6.7 Hz), 1.16-1.23 (26H, 13 x CH_2, m), 1.71 (2H, p, J = 6.9 Hz), 3.69 (1H, C≡C-H, s), 4.32 (2H, N-CH_2, t, J = 7.0 Hz), 4.82 (2H, N-CH_2-C≡C, s), 7.22 (1H, imid H, s), 6.64 (1H, imid H, s), 8.96 (s, 1H, NCHN), ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 143.84 (NCHN), 122.78, 120.94 (imid-C), 75.15 (-C≡CH), 67.17 (≡CH), 47.87 (acetylene-CH_2-N), 45.18 (N-CH_2), 31.89, 31.80, 29.98, 29.70, 29.59, 29.50, 29.45, 29.31, 29.22, 29.11, 28.84, 26.45, 26.18, 22.41 (14-CH_2), 14.87 (CH_3). FTIR (KBr, cm^{-1}): 3287 (-C≡CH), 3105 ($_{alkene}$C-H), 2965 ($_{aliph}$C-H), 2875 ($_{aliph}$C-H), 2133 (-C≡C-), 1625 (C=N), and 1251 (C-N).

1-Octadecyl-3-(prop-2-yn-1-yl)imidazolium salts (r5). Yield: (81%). m.p. (295–297 °C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.81 (3H, CH_3, t, J = 6.7 Hz), 1.16-1.22 (30H, 15 x CH_2, m), 1.69 (2H, p, J = 6.9 Hz), 3.60 (1H, C≡C-H, s), 4.29 (2H, N-CH_2, t, J = 7.0 Hz), 4.87 (2H, N-CH_2-C≡C, s), 7.25 (1H, imid H, s), 6.74 (1H, imid H, s), 8.91 (s, 1H, NCHN), ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 143.28 (NCHN), 122.95, 121.05 (imid-C), 76.15 (-C≡CH), 67.88 (≡CH), 48.97 (acetylene-CH_2-N), 44.35 (N-CH_2), 31.97, 31.78, 30.14, 29.88, 29.61, 29.55, 29.50, 29.43, 29.32, 29.20, 29.14, 29.04, 28.97, 26.87, 26.28, 22.45 (16-CH_2), 14.70 (CH_3). FTIR (KBr, cm^{-1}): 3268 (-C≡CH), 3098 ($_{alkene}$C-H), 2985 ($_{aliph}$C-H), 2852 ($_{aliph}$C-H), 2131 (-C≡C-), 1621 (C=N), and 1254(C-N).

Syntheses of bis-1,2,3-triazoleimidazolium salt (rm1-rm5) [26]

The following ingredients were dissolved in 30 mL DMF and agitated for 30 min: imidazolium salt (rm1-rm5; 3.4 mmol), sodium ascorbate (1.18 mmol), and copper(II) sulfate pentahydrate (1.16 mmol). The mixture was then supplemented with sodium azide (1.7 mmol), while stirring at 50 °C. The reactant solution for the target product was then allowed to stir slowly at room temperature while the TLC plate technique used with a constant volume of mixed solvents (methanol: dichloromethane; 1:9 ratio), and the end point of the chemical reaction were all used to confirm it. The organic solvents were then evaporated using a vacuum, and the leftover material was dissolved in 50 mL of dichloromethane before being cleaned three times with 50 mL of water. The organic solvent was dried over anhydrous Na_2SO_4 before being eliminated.

3-((1*H*-1,2,3-triazol-4-yl)methyl)-1-decyl-imidazolium salts (rm1). Yield (82%), ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.89 (3H, CH_3, t, J = 6.7 Hz), 1.17–1.25 (14H, 7 x CH_2, m), 1.70 (2H, p, J = 6.9 Hz), 4.31 (2H, N-CH_2, t, J = 7.0 Hz), 5.35 (2H, N-$CH_{2\text{-triazole ring}}$, s), 6.68 (1H, imid H, s), 7.70 (1H, imid H, s), 7.82 (s, 1H, H-triazole ring), 9.82 (s, 1H, NCHN), ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 143.21 (NCHN), 142.14 (triazole-C4), 122.98 (triazole-C5), 122.04, 121.12 (imid-C), 47.84 (-CH_2-N), 42.18 (N-CH_2-triazole ring), 32.01, 30.18, 29.97, 29.81, 29.35, 29.22, 26.98, 22.78 (8-CH_2), 14.20(CH_3). FTIR (KBr, cm^{-1}): 3108 ($_{triazole}$C-H), 2968 ($_{aliph}$C-H), 2852 ($_{aliph}$C-H), 1612 (C=N), and 1254 (C-N).

3-((1*H*-1,2,3-triazol-4-yl)methyl)-1-dodecyl-benzimidazolium salts (rm2). Yield (80%), ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.86 (3H, CH_3, t, J = 6.7 Hz), 1.14–1.21 (18H, 9 x CH_2, m,), 1.68 (2H, p, J = 6.9 Hz), 4.35 (2H, N-CH_2, t, J = 7.0 Hz), 5.32 (2H, N-$CH_{2\text{-triazole ring}}$, s), 6.67 (1H, imid H, s), 7.75 (1H, imid H, s), 7.84 (s, 1H, H-triazole ring), 9.80(s, 1H, NCHN), ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm): 143.75 (NCHN), 142.11 (triazole-C4), 122.91 (triazole-C5), 122.11, 120.78 (imid-C), 48.14 (-CH_2-N), 43.21 (N-$\underline{C}H_2$-triazole ring), 32.11, 31.42, 30.97, 30.15, 29.99, 29.78, 29.45, 29.08, 26.87, 22.55 (8-CH_2), 14.25(CH_3). FTIR (KBr, cm^{-1}): 3122 ($_{triazole}$C-H), 2945 ($_{aliph}$C-H), 2835 ($_{aliph}$C-H), 1632 (C=N), and 1251 (C-N).

3-((1H-1,2,3-triazol-4-yl)methyl)-1-tetradecyl-imidazolium salts (rm3). Yield (74%). (300 MHz, DMSO-d_6): δ (ppm): 0.85 (3H, CH_3, t, J = 6.7 Hz), 1.15–1.22 (22H, 11 x CH_2, m), 1.73 (2H, p, J = 6.9 Hz), 4.35 (2H, N-CH_2, t, J = 7.0 Hz), 5.31 (2H, N-$CH_{2\text{-triazole ring}}$, s), 6.65 (1H, imid H, s), 7.76 (1H, imid H, s), 7.83 (s, 1H, H-triazole ring), 9.80 (s, 1H, NCHN), ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm):143.44 (NCHN), 141.94 (triazole-C4), 122.78 (triazole-C5), 122.14, 121.02 (imid-C), 47.94 (-CH_2-N), 43.15(N-CH_2-triazole ring), 32.21, 31.54, 30.79, 30.32, 29.87, 29.77, 29.71, 29.38, 29.20, 28.38, 26.54, 22.65 (CH_2), 14.28 (CH_3). FTIR (KBr, cm^{-1}): 3111 ($_{triazole}$C-H), 2975 ($_{aliph}$C-H), 2850 ($_{aliph}$C-H), 1625 (C=N), and 1265 (C-N).

3-((1*H*-1,2,3-triazol-4-yl)methyl)-1-hexadecyl-imidazolium salts (rm4). Yield (78%), ^{1}H-NMR

(300 MHz, DMSO-d_6): δ (ppm): 0.83 (3H, CH_3, t, J = 6.7 Hz), 1.17–1.24 (26H, 13 x CH_2, m), 1.71 (2H, p, J = 6.9 Hz), 4.33 (2H, N-CH_2, t, J = 7.0 Hz), 5.38 (2H, N-$CH_{2\text{-triazole ring}}$, s), 6.72 (1H, imid H, s), 7.74 (1H, imid H, s), 7.84 (s, 1H, H-triazole ring), 9.85(s, 1H, NCHN), ^{13}C-NMR (300 MHz, DMSO-d_6): δ (ppm): 143.65 (NCHN), 142.47 (triazole-C4), 122.87 (triazole-C5), 122.58, 121.05 (imid-C), 47.75 (-CH_2-N), 42.73 (N-CH_2-triazole ring), 32.54, 31.87, 30.98, 30.25, 30.11, 29.95, 29.80, 29.54, 29.30, 29.20, 29.04, 28.41, 26.85, 22.24 (8-CH_2), 14.26 (CH_3). FTIR (KBr, cm^{-1}): 3122 ($_{triazole}$C-H), 2987 ($_{aliph}$C-H), 2874 ($_{aliph}$C-H), 1635 (C=N), and 1239 (C-N).

3-((1*H*-1,2,3-triazol-4-yl)methyl)-1-octadecyl-imidazolium salts (rm5). Yield (75%), ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm): 0.86 (3H, CH_3, t, J = 6.7 Hz), 1.15–1.22 (30H, 15 x CH_2, m), 1.73 (2H, p, J = 6.9 Hz), 4.28 (2H, N-CH_2, t, J = 7.0 Hz), 5.33 (2H, N-$CH_{2\text{-triazole ring}}$, s), 6.68 (1H, imid H, s), 7.70 (1H, imid H, s), 7.82 (s, 1H, H-triazole ring), 9.81 (s, 1H, NCHN), ^{13}C-NMR(75 MHz, DMSO-d_6): δ (ppm): 143.78 (NCHN), 142.78 (triazole-C4), 122.90 (triazole-C5), 122.24, 121.08 (imid-C), 47.78 (-CH_2-N), 42.38 (N-$\underline{C}H_2$-triazole ring), 32.21, 31.87, 31.61, 30.98, 30.64, 30.47, 30.21, 29.95, 29.86, 29.56, 29.33, 29.24, 29.14, 28.74, 26.93, 22.97 (8-CH_2), 14.09 (CH_3). FTIR (KBr, cm^{-1}): 3132 ($_{triazole}$C-H), 2987 ($_{aliph}$C-H), 2880 ($_{aliph}$C-H), 1621 (C=N), and 1242 (C-N).

Antibacterial activity

The biological activity (antibacterial activity) of target products was studied *in vitro* under controlled conditions with Muller Hinton Agar medium using the disc diffusion technique. The test organisms that are used in this study were first grown in nutrient broth and cultured at 37 °C for 24 h before being moved onto the Muller Hinton agar dishes in a laminar flow cabinet. The newly prepared compounds were first dissolved in DMSO and then soaked onto sterile dishes of filter paper number 1 with (6 mm diameter). The prepared discs were then placed carefully on top of the previously arranged contaminated plates and incubated at a fixed place. After one day of incubating materials at 37 °C, the mm-sized zone of the inhibition zone for each substance was determined. The DMSO-impregnated disc was used as a negative control. Ciprofloxacin, a popular antibiotic, was used as a positive control drug in the comparison of the effectiveness [27]. Each test was performed three times, with the average serving as the final reading. Compounds with a good zone of inhibition were chosen to calculate the minimum inhibitory concentration (MIC).

Antifungal activity

Using potato dextrose agar medium and using a classic technique, the disc diffusion method, the newly synthesized molecules *in vitro* antifungal activity was estimated. The bacteria under study were injected onto the outer surface of a used agar plate. The surface of the plate was next covered with new sterile discs of filter paper no. 1 (6 mm in diameter) having precise doses of the antifungal medication fluconazole as control (100 mg for the end products). The used plates were incubated at 28 °C for 72 h to test the antifungal activity. A paper disc that had been dipped in DMSO was employed as a checkpoint. The nutritional agar medium was made, autoclaved for 20 min at 15 lbs. of pressure, and then placed into petri plates to set. Using a sterile cotton swab, a microbial suspension was applied to the surface of the media. Using a previously sterilized cork borer, cups were created by boring into the surface of the agar and scooping up the agar that had been punched. In four cavities or cups that had been carved out of the medium, various amounts of the test chemicals and the reference drug as control fluconazole were placed. After being kept at ambient temperature for 1 h, the plates were incubated at 37 °C for 1 d. The diameter of the inhibition zone that had developed around the cavities (cups) was determined after 1 d incubation period, and the compound's percentage of inhibition was determined. A solvent control was also used to ascertain the blank's activity.

Determination of MIC

In this work, the agar streak dilution technique was utilized to measure the substance's MIC. From a stock solution of the prepared chemical products (100 g/mL in DMSO), graded amounts of the test compounds were added to a specified amount of molten sterile agar (Muller Hinton agar). A predefined volume of the compound-containing medium at (45 °C) was added to

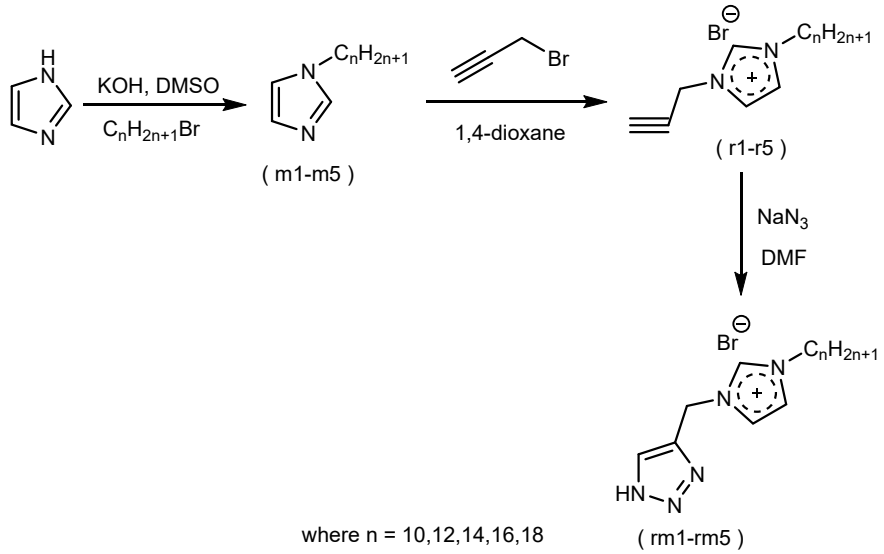
a Petri dish that was used with a depth of 3–4 mm, and then the prepared compound was allowed to crystallize. The microorganism was created as a suspension with an approximate concentration of 105 cfu/mL, added to test plates containing chemicals that were serially diluted in DMSO, and then incubated at 37 °C. Following the incubation period, MIC values were determined. Each determination was made in three copies, with the average serving as the final reading. DMSO was working as a negative control, while the common antibiotic ciprofloxacin medication was used as a reference (100 g/mL). MIC was defined as the lowest concentration of the test substance where there was no appreciable growth of bacteria or fungi on the lamina [28].

■ RESULTS AND DISCUSSION

Synthesis

Using commercially available imidazole as the starting material, the desired 1,2,3-triazole hybrids (rm1-rm5) were synthesized, as shown in Scheme 1. To remove acidic hydrogen from nitrogen for 2 h, the secondary amine of imidazole ring at 1-position was first alkylated with alkyl halide having chain of carbon atoms such as (10, 12, 14, 16 and 18 carbon atom) in the presence of potassium hydroxide as a basic catalyst. Then, the next step is a nucleophile attack in the imidazole ring on the carbon atom bonded bromide refluxing in DMSO for 1.5 h to produce the desired *N*-alkyl imidazole (Scheme 1).

Based on their spectral data, molecules (m1-m5) had their structures determined. Based on the elimination of hydrogen (NH) absorption band at 3390 cm^{-1} in the secondary amine of the imidazole ring, the IR spectrum proved that (m1-m5) had been monoalkylated. The spectra also showed the presence of two distinct bands associated with the alkene hydrogen (=C-H) at 3157 and 3107 cm^{-1}. Alkyl chains are substituted in 1-alkyl-1*H*-imidazoles (m1-m5), which have absorptions of the (-C-H) aliphatic stretching at 2840–2980 cm^{-1}. According to the removal of one exchangeable hydrogen in secondary amine NH of imidazole ring in the downfield, the ^{1}H-NMR study clearly demonstrated that an alkyl chain had been inserted at the nitrogen atom of imidazole. Alkyl chain substitutes that show in the high field are present in the substituted imidazoles (m1-m5). The N-CH_2 protons exist in the region δ 4.55–4.48 ppm, whereas methylene protons are present in the range δ 1.28–1.18 ppm, and methyl protons(-CH_3) are present at δ 0.87–0.83 ppm. Through the emergence of diagnostic carbon signals in the range of δ C 45–14 ppm, which were attributed to the methylene carbons, the ^{13}C-NMR study verified the incorporation of an alkyl residue. In the next step, the resulting *N*-alkyl imidazole derivatives were dissolved in acetonitrile solvent and refluxed with an additional



Scheme 1. Synthesis new 1,2,3-triazole compounds based on imidazole

amount of propargyl bromide. At a high temperature of about 90 °C, the free pair of nitrogen electrons in imidazole coupled with the electrophilic site of alkyl bromide to form imidazolium salts (r1-r5). The IR spectrum verified the presence of two strong bands in the range of 3287–2268 cm^{-1} and 2133–2122 cm^{-1}, which are connected to the acetylenic proton (C-H) and triple bond, respectively, in the disubstituted imidazolium salt (r1-r5).

Evaluation of Anti-microbial Screening

In this work, two types of bacteria (gram-positive and gram-negative) and a synthetic substance of fungus, were tested *in vitro* whereas the functional groups essential for anti-microbial activity were preserved. The synthetic compounds were shown to be more effective against gram-positive bacteria than the other bacteria. The molecule's strong lipophilicity is estimated to play a key role in delivering the antibacterial action. A fundamental factor governing how drugs interact with biological systems is a compound's lipophilicity (hydrophobicity), a critical physical property affecting membrane permeability, solubility rate and bioavailability. The log P representation of a compound's lipophilicity is regarded to be a crucial predictor of potential antibacterial action. The octanol/water partition index log is used to express the ratio of hydrophobicity to lipid susceptibility. Moreover, it plays an important role in regulating passive membrane partition permeability (i.e., increased log P enhances permeability). Hydrophobic pharmaceuticals (high partitioning coefficients) are preferentially transported to the lipophilic compartments, such as the fat cell bilayers, while hydrophilic drugs (low partitioning coefficients) are preferentially located in the hydrophilic compartments, such as serum. The findings of Swiss ADME, which are shown in Table 1, were utilized to calculate the values of log P. Swiss ADME [29] was also used to compute molar refractivity (MR), a measure of molecular mass, polarizability, and steric facto, to clarify the activity performance of created molecules. The end results are shown in Table 1. Molar refractivity is produced by adjusting the molar volume for the refractive index. The connection of the antimicrobial information with the values of molar refractivity and log P led to the conclusion that the compounds with higher molar refractivity and log P values had greater antibacterial activity. Bacterial membrane permeability is necessary to measure antibiotic activity. The antibacterial effect of the compounds may be related to the formation of bacterial cell walls. This is plausible given that many bacteria rely on their cell walls to survive and that some antibiotics can kill bacteria by obstructing a process necessary to produce peptidoglycans. The relatively thin cell walls of gram-negative bacteria, which consist of a few layers of peptidoglycan, are surrounded by a second lipid membrane with lipopolysaccharides and lipoproteins. In the other hand, gram-positive bacteria have thick cell walls consisting of several layers of peptidoglycan and teichoic acids. Some drugs active against gram-positive bacteria have been found to be ineffective against gram-negative bacteria due to these changes in cell wall composition [30].

Table 1. Substituted (-R), compounds symbol, molar refractivity and log P of prepared products (rm1-rm5)

No Comp.	Subs. R	Molar refractivity	Log P
rm1	$C_{10}H_{21}$	97.2	3.22
rm2	$C_{12}H_{25}$	105.5	4.01
rm3	$C_{14}H_{29}$	115.3	4.83
rm4	$C_{16}H_{33}$	124.7	5.65
rm5	$C_{18}H_{37}$	135.5	5.76

Anti-bacterial activity

Table 2 displays the anti-bacterial screening findings for all synthesized compounds. Compound (rm5) showed substantial efficacy against all tested bacteria. At the same time, some displayed good activity, some of the produced compounds displayed just moderate activity. It was found that the effect against bacteria increases with the increase in the number of carbon atoms in the tail of the alkyl chain. The results of the antibacterial activity research are presented in Table 2 at a single concentration of 100 µg/mL.

Anti-fungal activity

All the newly prepared molecule's anti-fungal screening results are reported in Table 3. Compounds (rm5 and rm4) demonstrated noticeable activity against all tested fungi. At the same time, some displayed good activity, some of the produced compounds displayed just

Table 2. Antibacterial activity of title compounds(mr1-mr5) measured by zone of inhibition against selected bacteria

No Comp.	Gram-positive		Gram-negative	
	S. aures	*B. subtilis*	*E. coli*	*K. pneumoniae*
rm1	13	15	11	8
rm2	13	17	13	8
rm3	17	20	16	14
rm4	20	21	17	15
rm5	22	24	20	18
Ciprofloxacin	29	29	28	29

Table 3. Results of antifungal activity of newly prepared compounds(rm1-rm5) measured by zone of inhibition against selected fungi

No Comp.	*A. niger*	*C. albicans*
rm1	12	11
rm2	15	13
rm3	20	18
rm4	23	20
mr5	25	22
Fluconazole	32	31

moderate activity. It was found that the effect against bacteria increases with the increase in the number of carbon atoms in the tail of the alkyl chain. The results of the antibacterial activity research are presented in Table 3 at a single concentration of 100 µg/mL.

■ CONCLUSION

Successful syntheses of the imidazole compounds rm1-rm5 have been prepared. To assess the impact of the substituent on the antibacterial and antifungal properties, a pharmacological investigation was conducted. The biological activity results showed that, in comparison to the reference medicine, all newly synthesized 1,2,3-triazole compounds with imidazole rings demonstrated better antibacterial activity than antifungal activity. The outcomes of the anti-bacterial showed that rm5, out of all the compounds, had the strongest antibacterial effect against the bacteria that were tested, but rm3 and rm4 had only mild anti-bacterial effects in comparison to ciprofloxacin. The anti-fungal screening findings demonstrated that the rm4 and rm5 demonstrated effective anti-fungal action against the investigated fungus, with effectiveness against *A. nigeer*. *A. niger* and *C. albicans* were both moderately susceptible to the rm2 and rm3.

■ ACKNOWLEDGMENTS

We would like to express our gratitude and thanks to the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Alkafeel, for constant encouragement and for providing a basic research facility.

■ CONFLICT OF INTEREST

The authors state no conflict of interest.

■ AUTHOR CONTRIBUTIONS

Ali Jabbar Radhi did the conceptualization, methodology, investigation, writing, supervision, review and editing. Ehab Kareem Obaid experimented and writing draft preparation. Zaman Abdalhussein Ibadi Alaridhee did the H-NMR and C-NMR data in Iran. Ameer Salem Muttaleb, Nardeen Adnan Berto and Sahar Adeeb Mamoori did the validation, review and editing. All authors have read and agreed to the published version of the manuscript.

■ REFERENCES

[1] Xie, S., Xia, S., Xu, Z., Li, W., Wang, E., and Wang, S., 2021, An imidazole-based fluorescent probe for cupric ion, *Synth. Met.*, 277, 116784.

[2] Jain, A.K., Ravichandran, V., Sisodiya, M., and Agrawal, R.K., 2010, Synthesis and antibacterial evaluation of 2–substituted–4,5–diphenyl–N–alkyl imidazole derivatives, *Asian Pac. J. Trop. Med.*, 3 (6), 471–474.

[3] Yoneyama, H., and Katsumata, R., 2006, Antibiotic resistance in bacteria and its future for novel antibiotic development, *Biosci., Biotechnol., Biochem.*, 70 (5), 1060–1075.

[4] Dheer, D., Singh, V., and Shankar, R., 2017, Medicinal attributes of 1,2,3-triazoles: Current developments, *Bioorg. Chem.*, 71, 30–54.

[5] Nassar, E.M., Abdelrazek, F.M., Ayyad, R.R., and El-Farargy, A.F., 2016, Synthesis and some reactions of 1-aryl-4-acetyl-5-methyl-1,2,3-triazole derivatives with anticonvulsant activity, *Mini-Rev. Med. Chem.*, 16 (11), 926–936.

[6] Rajasekaran, A., and Rajagopal, K.A., 2009, Synthesis of some novel triazole derivatives as anti-nociceptive and anti-inflammatory agents, *Acta Pharm.*, 59 (3), 355–364.

[7] Boechat, N., Ferreira, M.L.G., Pinheiro, L.C.S., Jesus, A.M.L., Leite, M.M.M., Júnior, C.C.S., Aguiar, A.C.C., de Andrade, I.M., and Krettli, A.U., 2014, New compounds hybrids 1*H*-1,2,3-triazole-quinoline against *Plasmodium falciparum*, *Chem. Biol. Drug Des.*, 84 (3), 325–332.

[8] Shukla, J.D., Md Arif Ali, K., and Deo, K., 2015, Synthesis and pharmacological evaluation of novel 1-(2,6-difuorobenzyl)-1H-1,2,3-triazole derivatives for CNS depressant and anticonvulsant profile, *Am. J. PharmTech Res.*, 5, 422–433.

[9] Zhang, S., Xu, Z., Gao, C., Ren, Q.C., Chang, L., Lv, Z.S., and Feng, L.S., 2017, Triazole derivatives and their anti-tubercular activity, *Eur. J. Med. Chem.*, 138, 501–513.

[10] Dai, Z.C., Chen, Y.F., Zhang, M., Li, S.K., Yang, T.T., Shen, L., Wang, J.X., Qian, S.S., Zhu, H.L., and Ye, Y.H., 2015, Synthesis and antifungal activity of 1,2,3-triazole phenylhydrazone derivatives, *Org. Biomol. Chem.*, 13 (2), 477–486.

[11] Jordão, A.K., Ferreira, V.F., Souza, T.M.L., de Souza Faria, G.G., Machado, V., Abrantes, J.L., de Souza, M.C.B.V., and Cunha, A.C., 2011, Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives, *Bioorg. Med. Chem.*, 19 (6), 1860–1865.

[12] Faidallah, H.M., Girgis, A.S., Tiwari, A.D., Honkanadavar, H.H., Thomas, S.J., Samir, A., Kalmouch, A., Alamry, K.A., Khan, K.A., Ibrahim, T.S., AL-Mahmoudy, A.M.M., Asiri, A.M., and Panda, S.S., 2018, Synthesis, antibacterial properties and 2D-QSAR studies of quinolone-triazole conjugates, *Eur. J. Med. Chem.*, 143, 1524–1534.

[13] Penthala, N.R., Madhukuri, L., Thakkar, S., Madadi, N.R., Lamture, G., Eof, R.L., and Crooks, P.A., 2015, Synthesis and anti-cancer screening of novel heterocyclic(2*H*)-1,2,3-triazoles as potential anti-cancer agents, *Med. Chem. Commun.*, 6 (8), 1535–1543.

[14] Gregorić, T., Sedić, M., Grbčić, P., Tomljenović Paravić, A., Kraljević Pavelić, S., Cetina, M., Vianello, R., and Raić-Malić, S., 2017, Novel pyrimidine-2,4-dione–1,2,3-triazole and furo[2,3-*d*]pyrimidine2-one-1,2,3-triazole hybrids as potential anti-cancer agents: Synthesis, computational and X-ray analysis and biological evaluation, *Eur. J. Med. Chem.*, 125, 1247–1267.

[15] Yan, X., Lv, Z., Wen, J., Zhao, S., and Xu, Z., 2018, Synthesis and *in vitro* evaluation of novel substituted isatin-propylene-1*H*-1,2,3-triazole-4-methylene-moxifoxacin hybrids for their anti-mycobacterial activities, *Eur. J. Med. Chem.,* 143, 899–904.

[16] Chen, L., Zhao, B., Fan, Z., Liu, X., Wu, Q., Li, H., and Wang, H., 2018, Synthesis of novel 3,4-chloroisothiazole-based imidazoles as fungicides and evaluation of their mode of action, *J. Agric. Food Chem.*, 66 (28), 7319–7327.

[17] Rossi, R., and Ciofalo, M., 2020, An updated review on the synthesis and antibacterial activity of molecular hybrids and conjugates bearing imidazole moiety, *Molecules*, 25 (21), 5133.

[18] Shamshina, J.L., Kelley, S.P., Gurau, G., and Rogers, R.D., 2015, Chemistry: Develop ionic liquid drugs, *Nature*, 528 (7581), 188–189.

[19] Miskiewicz, A., Ceranowicz, P., Szymczak, M., Bartuś, K., and Kowalczyk, P., 2018, The use of liquids ionic fluids as pharmaceutically active substances helpful in combating nosocomial infections induced by *Klebsiella pneumoniae* New Delhi strain, *Acinetobacter baumannii* and *Enterococcus* species, *Int. J. Mol. Sci.*, 19 (9), 2779.

[20] Cuervo-Rodríguez, R., Muñoz-Bonilla, A., López-Fabal, F., and Fernández-García, M., 2020, Hemolytic and antimicrobial activities of a series of cationic amphiphilic copolymers comprised of

same centered comonomers with thiazole moieties and polyethylene glycol derivatives, *Polymers*, 12 (4), 972.

[21] Becerril, R., Nerín, C., and Silva, F., 2020, Encapsulation systems for antimicrobial food packaging components: An update, *Molecules*, 25 (5), 1134.

[22] Wang, D., Richter, C., Rühling, A., Drücker, P., Siegmund, D., Metzler-Nolte, N., Glorius, F., and Galla, H.J., 2015, A remarkably simple class of imidazolium-based lipids and their biological properties, *Chem. - Eur. J.*, 21 (43), 15123–15126.

[23] Voloshina, A.D., Gumerova, S.K., Sapunova, A.S., Kulik, N.V., Mirgorodskaya, A.B., Kotenko, A.A., Kotenko, A.A., Prokopyeva, T.M., Mikhailov, V.A., Zakharova, L.Y., and Sinyashin, O.G., 2020, The structure–activity correlation in the family of dicationic imidazolium surfactants: Antimicrobial properties and cytotoxic effect, *Biochim. Biophys. Acta, Gen. Subj.*, 1864 (12), 129728.

[24] Kapitanov, I.V., Jordan, A., Karpichev, Y., Spulak, M., Perez, L., Kellett, A., Kümmerer, K., and Gathergood, N., 2019, Synthesis, self-assembly, bacterial and fungal toxicity, and preliminary biodegradation studies of a series of L-phenylalanine-derived surface-active ionic liquids, *Green Chem.*, 21 (7), 1777–1794.

[25] Mohsen, D.H., Radhi, A.J., Shaheed, D.Q., and Abbas, H.K., 2022, Synthesis new benzimidazole derivatives as antibacterial, *J. Pharm. Negat. Results*, 13 (3), 893–898.

[26] Radhi, A.J., Shaheed, D.Q., Heriz, M.H., and Oleiwi, Z.K., 2021, Preparation and study biological activity of polybarbiturate linked tetrazole ring, *Res. J. Pharm. Technol.*, 14 (6), 3377–3379.

[27] Minoshima, M., Chou, J.C., Lefebvre, S., Bando, T., Shinohara, K.I., Gottesfeld, J.M., and Sugiyama, H., 2010, Potent activity against K562 cells by polyamide–seco-CBI conjugates targeting histone H4 genes, *Bioorg. Med. Chem.*, 18 (1), 168–174.

[28] Mohamed, M.S., Kamel, M.M., Kassem, E.M., Abotaleb, N., Abd El-moez, S.I., and Ahmed, M.F., 2010, Novel 6,8-dibromo-4(3*H*)quinazolinone derivatives of anti-bacterial and anti-fungal activities, *Eur. J. Med. Chem.*, 45 (8), 3311–3319.

[29] Daina, A., Michielin, O., and Zoete, V., 2017, SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Sci. Rep.*, 7 (1), 42717.

[30] Smith, D.A., 1994, Design of drugs through a consideration of drug metabolism and pharmacokinetics, *Eur. J. Drug Metab. Pharmacokinet.*, 19 (3), 193–199.