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Article

Efficient Antibacterial Dimeric Nitro Imidazolium Type of Ionic Liquids from a Simple Synthetic Approach

Pandurangan Ganapathi, Kilivelu Ganesan,* Mahendiran Dharmasivam, Mohammed Mujahid Alam, and Amanullah Mohammed

Cite This: *ACS Omega* 2022, 7, 44458−44469

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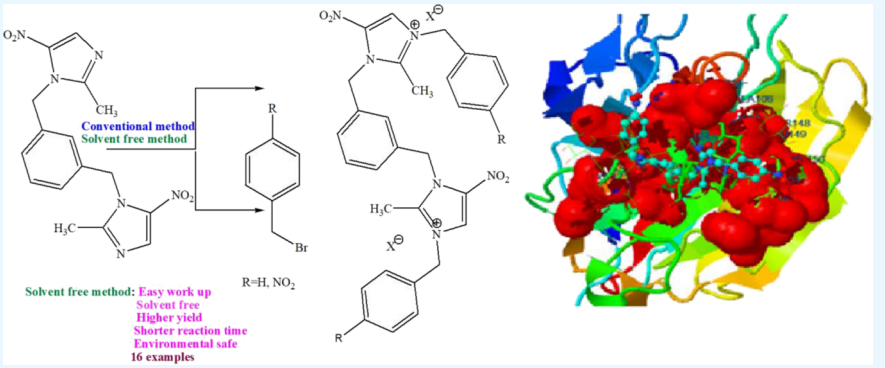


ABSTRACT: Synthesis of dimeric nitro-substituted imidazolium salts under the conventional/solvent-free method is reported. The solvent-free method is more important than the conventional one because of its shorter reaction time, higher yield from easily available starting material, environmental safety, and so forth. Counter anion exchange is carried out using inorganic salt, which is dissolved in deionized water at room temperature. In antibacterial studies, dimeric nitro-substituted imidazolium cations with bromide counter anions showed excellent inhibition against *E. coli* and *P. aeruginosa* bacteria. These experimental results were further supported by molecular docking studies. All the compounds (**3**−**6**) (**a**−**d**) showed excellent antibacterial activity than the standard drugs (gentamycin, nalidixic acid, oflaxacin, ciproflaxacin, and amikacin). Molecular docking studies showed strong hydrogen bonding, polar and hydrophobic interactions between the dimeric imidazolium salts, and *Escherichia coli*/*Pseudomonas aeruginosa*/*Proteus vulgaris*/*Staphylococcus aureus* receptors.

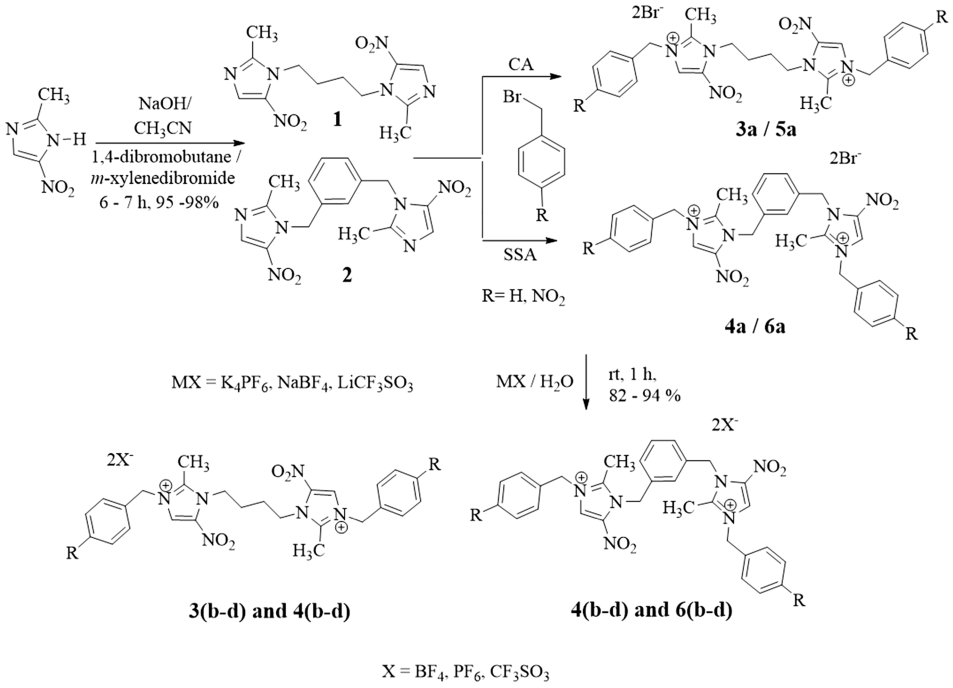
1. INTRODUCTION

Ionic liquids are potential and interesting application-oriented molecules. Ionic liquids consist of hydrophobic units, which are pharmaceutically active and a hydrophilic unit, which is easily soluble in water; hence, ionic liquids are used in pharma industries.[1] Imidazolium/pyridinium salt formation from sp^2 nitrogen of heterocyclic aromatic moieties is more useful for making ionic liquids.[2] The sp^2-hybridized nitrogen containing five-/six-membered heterocyclic components constitutes the larger segment in ionic liquid preparation. Imidazole/pyridine core-based organic cations are commonly used for the synthesis of ionic liquids.[3−5] Monomeric imidazolium/pyridinium type of ionic liquids showed moderate to excellent anti-inflammatory, anticancer, and antifungal activities.[6,7] Imidazolium/pyridinium cations with various counter anion type of ionic liquids are used in various applications such as in catalysts, corrosion inhibitors, food chemistry, and pharma industries.[8−14] Alkyl propargyl- and silyl alkyl-substituted imidazolium, piperidinium, and pyrrolidinium types of ionic liquids are prepared and their antibacterial response against Gram-positive bacteria are tested. Flexible longer alkyl chain-substituted ionic liquids showed higher cytotoxicity than the shorter alkyl-substituted imidazolium salt because of their lipophilicity behavior.[15]

Pyrrolidinium and piperidinium salts showed lesser antibacterial response than the imidazolium salts.[16] Longer alkyl-substituted imidazolium salt, 1-decyl-3-cinnamylimidazolium chloride, is easily attracted to the phospholipid bilayer than the methyl-substituted −3-cinnamylimidazolium chloride because of its longer alkyl-substituted imidazolium salts, which are more hydrophobic.[17] Pernak and co-workers reported that substituted alkoxy imidazolium salts showed an antimicrobial response against fungi rods and cocci and mentioned that

Received: October 23, 2022
Accepted: November 8, 2022
Published: November 23, 2022

Scheme 1. Synthesis of Flexible Substituted Dimeric Imidazolium Salts[a]



[a]Reagent and conditions: CA, conventional approach: CH_3CN, reflux, 10−12 h, 84−89%, SSA, silica-supported approach: muffle furnace, 100 °C, 5−6 h, 88−93%.

higher alkyl-substituted imidazolium salts showed a very active response against cocci.[18] Gram-negative and Gram-positive pathogens have negative charges in their surface, which is a phospholipid bilayer, so imidazolium/pyridinium types of ionic liquids are easily linked to the outer membrane.[19−21] Hadni and Elhallaoui reported that molecular modeling studies with substituted azaaurones derivatives showed an inhibitory response against cytochromes under two-dimensional (2D) and three-dimensional (3D)-quantitative structure-activity relationship (QSAR)analysis.[22]

The application of molecular modeling calculation is a very useful and impressive finding in the drug discovery area.[23,24] Poly(lactic-co-glycolic acid)-based chitosan-functionalized nanoparticles are prepared using the imidazolium type of ionic liquids for the drug delivery process under the emulsion solvent diffusion process.[25] Structural alterations of adenosine deaminase were obtained using alkyl and allyl group fused imidazolium chloride with the assistance of the molecular dynamics and docking model.[26,27] Hydrophobic organic cations and hydrophilic inorganic anions of imidazolium/pyridinium-based ionic liquids act as cationic surfactants in aqueous medium and also showed an antimicrobial response against Gram-positive and Gram-negative pathogens. Aljuhani *et al.* reported that 3/4 of methyl pyridinium iodide with amide linger units is prepared under conventional as well as microwave methods and its anticancer and molecular docking properties are studied.[28] Longer alkyl-substituted piperidinium salt showed excellent antimicrobial activity against human pathogenic microorganisms than the simple alkyl-substituted hydroxy piperidinium salts.[29,30]

Based on the literature report, we wish to prepare dimeric-substituted imidazolium ionic liquids under the conventional and solvent-free solid-supported method and evaluate the hydrophilic and lipophilic segments containing dimeric-substituted imidazolium salts as antibacterial agents against human pathogenic microorganisms and docking analysis.

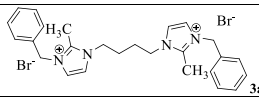
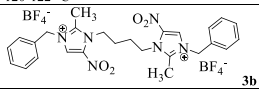
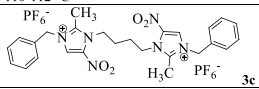
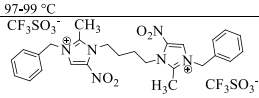
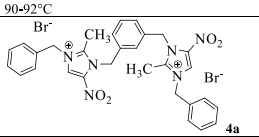
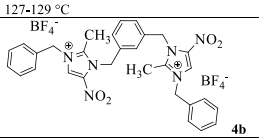
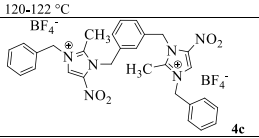
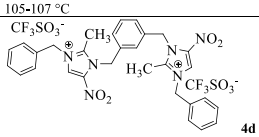
2. RESULTS AND DISCUSSION

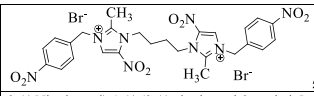
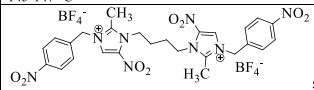
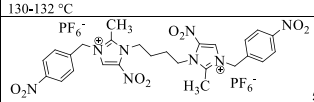
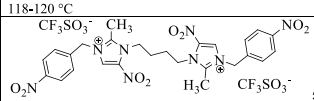
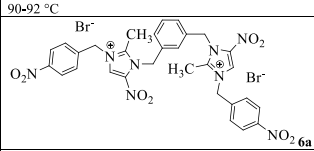
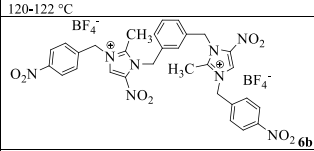
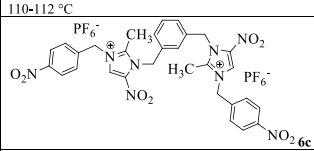
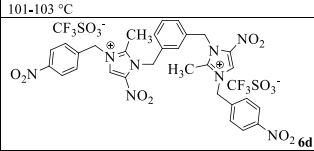
2.1. Synthesis of Flexible Substituted Dimeric Imidazolium Salts. The *N*-alkylation reaction is carried out between 1,4-dibromo butane/*m*-xylene dibromide and 2-methyl-5-nitro imidazole in the presence of one equivalence of NaOH in dry acetonitrile under refluxing conditions for 6−7 h and afforded *N*-alkylated dimeric imidazole **1** and **2** in 95% of yield after the purification process (Scheme 1). Compounds **1** and **2** are treated with benzyl/4-nitrobenzyl bromide in the presence of CH_3CN under refluxing conditions for 10 h and afforded 84% of dimeric-substituted imidazolium bromide **3a−6a** (Scheme 1). The same reaction is tried without the solvent under solid-phase silica-supported muffle furnace conditions. Fortunately, the solvent-free method is a more advantageous method than the conventional method such as easy work up, absence of organic solvents, and lesser reaction period with higher yields (Scheme 1).

When we change various counter anions in the dimeric-substituted imidazolium bromide, the physical properties are also changed. Two equivalents of inorganic salts (KPF_6, $NaBF_4$, and $LiCF_3SO_3$) and bromide counter anions containing dimeric-substituted imidazolium salt are dissolved in double-deionized water and stirred at room temperature for 1 h and it gives anion-exchanged product of compounds **3−6 (b−d)** in good yield (Scheme 1). We have used Soxhlet extraction with dry THF to remove unwanted inorganic salts (LiBr, KBr, and NaBr) and then tested with an aqueous $AgNO_3$ solution. Fortunately, we did not get any pale-yellow precipitate. All the synthesized compounds are fully characterized by various spectral and analytical methods (Table 1).

https://doi.org/10.1021/acsomega.2c06833
ACS Omega 2022, 7, 44458−44469

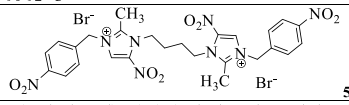
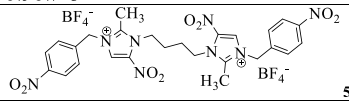
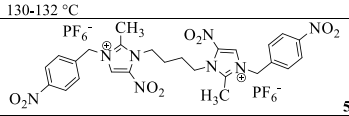
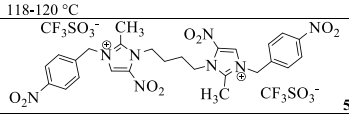
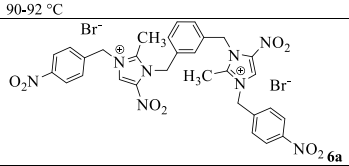
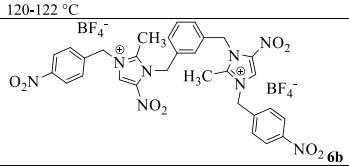
Table 1. Properties of the Synthesized Dimeric Imidazolium Salts

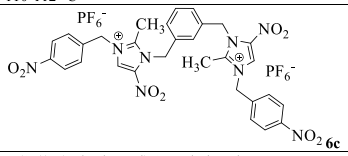
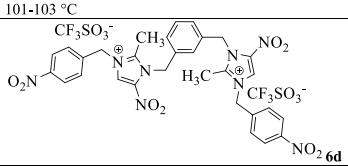
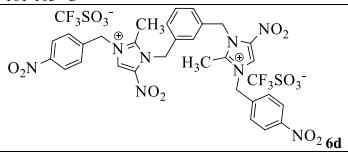
Structure of compound	 **3a**
Chemical Name	3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumbromide **3a**
Molecular Formula / Monoisotopic mass	$C_{26}H_{30}Br_2N_6O_4$ / 650
Melting point	120-122 °C
Structure of compound	 **3b**
Chemical Name	3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumtetrafluoroborate **3b**
Molecular Formula / Monoisotopic mass	$C_{26}H_{30}B_2F_8N_6O_4$ / 664
Melting point	110-112 °C
Structure of compound	 **3c**
Chemical Name	3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumhexafluorophosphate **3c**
Molecular Formula / Monoisotopic mass	$C_{26}H_{30}F_{12}N_6O_4P_2$ / 780
Melting point	97-99 °C
Structure of compound	 **3d**
Chemical Name	3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumtrifluoromethanesulfonate **3d**
Molecular Formula / Monoisotopic mass	$C_{28}H_{30}F_6N_8O_{10}S_2$ / 788
Melting point	90-92°C
Structure of compound	 **4a**
Chemical Name	1-(3-((3-Benzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide **4a**
Molecular Formula / Monoisotopic mass	$C_{30}H_{30}Br_2N_6O_4$ / 698
Melting point	127-129 °C
Structure of compound	 **4b**
Chemical Name	1-(3-((3-Benzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate **4b**
Molecular Formula / Monoisotopic mass	$C_{30}H_{30}B_2F_8N_6O_4$ / 712
Melting point	120-122 °C
Structure of compound	 **4c**
Chemical Name	1-(3-((3-Benzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate **4c**
Molecular Formula / Monoisotopic mass	$C_{30}H_{30}F_{12}N_6O_4P_2$ / 828
Melting point	105-107 °C
Structure of compound	 **4d**
Chemical Name	1-(3-((3-Benzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate **4d**
Molecular Formula / Monoisotopic mass	$C_{32}H_{30}F_6N_8O_{10}S_2$ / 836
Melting point	90-92 °C

Structure of compound	 **5a**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumbromide **5a**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}Br_2N_8O_8$ / 740
Melting point	145-147 °C
Structure of compound	 **5b**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumtetrafluoroborate **5b**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}B_2F_8N_8O_8$ / 754
Melting point	130-132 °C
Structure of compound	 **5c**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumhexafluorophosphate **5c**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}F_{12}N_8O_8P_2$ / 870
Melting point	118-120 °C
Structure of compound	 **5d**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazolium trifluoromethanesulfonate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazolium trifluoromethanesulfonate **5d**
Molecular Formula / Monoisotopic mass	$C_{28}H_{28}F_6N_8O_{14}S_2$ / 878
Melting point	90-92 °C
Structure of compound	 **6a**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide **6a**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}Br_2N_8O_8$ / 788
Melting point	120-122 °C
Structure of compound	 **6b**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate **6b**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}B_2F_8N_8O_8$ / 802
Melting point	110-112 °C
Structure of compound	 **6c**
Chemical Name	**1**-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate **6c**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}F_{12}N_8O_8P_2$ / 918
Melting point	101-103 °C
Structure of compound	 **6d**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate **6d**
Molecular Formula / Monoisotopic mass	$C_{32}H_{28}F_6N_8O_{14}S_2$ / 926
Melting point	87-89 °C

https://doi.org/10.1021/acsomega.2c06833
ACS Omega 2022, 7, 44458−44469

Table 1. continued

Chemical Name	1-(3-((3-Benzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate **4d**
Molecular Formula / Monoisotopic mass	$C_{32}H_{30}F_6N_6O_{10}S_2$ / 836
Melting point	90-92 °C
Structure of compound	 **5a**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumbromide **5a**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}Br_2N_8O_8$ / 740
Melting point	145-147 °C
Structure of compound	 **5b**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumtetrafluoroborate **5b**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}B_2F_8N_8O_8$ / 754
Melting point	130-132 °C
Structure of compound	 **5c**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazoliumhexafluorophosphate **5c**
Molecular Formula / Monoisotopic mass	$C_{26}H_{28}F_{12}N_8O_8P_2$ / 870
Melting point	118-120 °C
Structure of compound	 **5d**
Chemical Name	3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazolium trifluoromethanesulfonate-1-yl)butyl)-2-methyl-5nitro-1*H*-imidazolium trifluoromethanesulfonate **5d**
Molecular Formula / Monoisotopic mass	$C_{28}H_{28}F_6N_8O_{14}S_2$ / 878
Melting point	90-92 °C
Structure of compound	 **6a**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumbromide-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumbromide **6a**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}Br_2N_8O_8$ / 788
Melting point	120-122 °C
Structure of compound	 **6b**

Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtetrafluoroborate **6b**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}B_2F_8N_8O_8$ / 802
Melting point	110-112 °C
Structure of compound	 **6c**
Chemical Name	**1**-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate **6c**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}F_{12}N_8O_8P_2$ / 918
Melting point	101-103 °C
Structure of compound	 **6d**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate **6d**
Molecular Formula / Monoisotopic mass	$C_{32}H_{28}F_6N_8O_{14}S_2$ / 926
Melting point	87-89 °C
Chemical Name	**1**-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumhexafluorophosphate **6c**
Molecular Formula / Monoisotopic mass	$C_{30}H_{28}F_{12}N_8O_8P_2$ / 918
Melting point	101-103 °C
Structure of compound	 **6d**
Chemical Name	1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1*H*-imidazoliumtrifluoromethanesulfonate **6d**
Molecular Formula / Monoisotopic mass	$C_{32}H_{28}F_6N_8O_{14}S_2$ / 926
Melting point	87-89 °C

2.2. Antibacterial Activity. Flexible linear alkylated quinolinium salts showed antibacterial efficacy against human pathogenic bacteria.[31] Antibacterial efficacy is purely based on the length of the alkyl chain. While altering the alkyl chain length of quinolinium salts from the lower to higher alkyl group, the antibacterial activity is also changed.[32−35] We have studied the antibacterial screening of dimeric-substituted imidazolium cations with various counter anions against Gram-negative (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Proteus vulgaris*) and Gram-positive (*Staphylococcus aureus, Enterococcus faecalis*) microorganisms and it showed excellent inhibition than that available in the literature.[36] Antibacterial screening of dimeric-substituted imidazolium salts has been examined by well/disc diffusion methods using Mueller Hinton Agar (MHA).[37]

The stock solutions of samples are prepared using dimethyl sulfoxide (DMSO) as the solvent in 1 mg/mL. We have prepared various concentrations of stock solution from 25 μg/well (7.692×10^{-4} mmol/mL), 50 μg/well (1.54×10^{-3} mmol/mL), 75 μg/well (2.31×10^{-3} mmol/mL), and 100 μg/well (3.08×10^{-3} mmol/mL) in DMSO. The bacterial inoculum is adjusted to the 0.5 scale of McFarland standard.[38] The dilutions of dimeric-substituted imidazolium salts are loaded into respective wells of the MHA plate. Gentamicin (30 μg/well), nalidixic acid (30 μg/well), ofloxacin (30 μg/well), ciprofloxacin (30 μg/well), and amikacin (30 μg/well) are

https://doi.org/10.1021/acsomega.2c06833
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Table 2. Antibacterial Assay of Dimeric Imidazolium Cations with Different Counter Anions, Compounds 3−6 (a−d) against Test Bacteria Using the Microdilution Method

		Gram-negative organism								Gram-positive organism			
		E. coli		*K. pneumoniae*		*P. aeruginosa*		*P. vulgaris*		*S. aureus*		*E. faecalis*	
s. no	standard drug	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	gentamicin	10	10	20	20	10	10	10	10	10	10	20	20
2	nalidixic acid	10	10	10	10	10	10	10	10	10	10	10	10
3	oflaxacin	10	10	20	20	10	10	30	30	10	10	10	10
4	ciproflaxacin	10	10	10	10	10	10	50	50	10	10	10	10
5	amikacin	10	10	10	10	10	10	10	10	10	10	10	10
6	**3a**	20	20	30	30	20	20	40	40	20	20	50	50
7	**3b**	20	20	40	40	20	20	40	40	20	20	50	50
8	**3c**	20	20	40	40	20	20	40	40	20	20	50	50
9	**3d**	30	30	40	40	20	20	40	40	20	20	50	50
10	**4a**	20	20	30	30	20	20	40	40	20	20	50	50
11	**4b**	20	20	40	40	20	20	40	40	20	20	50	50
12	**4c**	20	20	40	40	20	20	40	40	20	20	50	50
13	**4d**	30	30	40	40	20	20	40	40	20	20	50	50
14	**5a**	20	20	30	30	20	20	30	30	20	20	50	50
15	**5b**	20	20	30	30	20	20	30	30	20	20	50	50
16	**5c**	30	30	30	30	20	20	30	30	20	20	50	50
17	**5d**	20	20	30	30	20	20	30	30	20	20	50	50
18	**6a**	20	20	20	20	20	20	20	20	20	20	50	50
19	**6b**	20	20	30	30	20	20	20	20	20	20	50	50
20	**6c**	20	20	30	30	20	20	20	20	20	20	50	50
21	**6d**	30	30	30	30	20	20	30	30	20	20	50	50

used as standard drugs for the comparison.[39] The MHA plates are incubated at 37 °C for 18−24 h. The zone of inhibition is measured in mm using a Vernier caliper and compared with the standard drug disc. Dimeric-substituted imidazolium salts showed much more bacterial efficacy than the available literature.[40,41]

2.2.1. Determination of Minimum Inhibitory Concentration. Minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) are determined using the microdilution method using Mueller Hinton broth (MHB).

2.2.2. Well Diffusion Technique. Antimicrobial activities of dimeric imidazolium salts against Gram-negative/positive microorganisms under the well diffusion technique.[42] Dimeric imidazolium salts of compound **3−6(a−d)** are screened for their microbial activities under the well diffusion method (zone of inhibition in diameters). We have prepared 16 substituted dimeric imidazolium salts; among these, nitro-substituted dimeric imidazolium salts showed excellent inhibition than the simple dimeric imidazolium salts (Table 2).

The newly synthesized compounds annoy the respiration development of the cell and thus block the synthesis of proteins that inhibit further growth of the organism.[43] Bacterial screening of more responsive nitro-substituted imidazolium salts against six different human pathogens is shown. Nitro-substituted dimeric imidazolium salts **4 (a−d)** and **6 (a−d)** showed greater antibacterial activity than others (Table 2). The observed results clearly indicate that the counter anion plays a crucial role in the antibacterial response. Bromide counter anions containing nitro-substituted dimeric imidazolium salts **4a, 6a** showed effective inhibition against *E. coli*, *P. aeruginosa*, and *S. aureus* pathogens (Figure 1). Other imidazolium salts showed good to moderate responses against human pathogens (Figure 1). All the dimeric imidazolium salts showed excellent antibacterial activity against all bacterial strains when compared to standard drugs (Table 2). The nitro-substituted dimeric imidazolium salts enhance lipophilicity, which promotes its permeation through the lipid layer of the bacterial cell membranes (Figure 2).

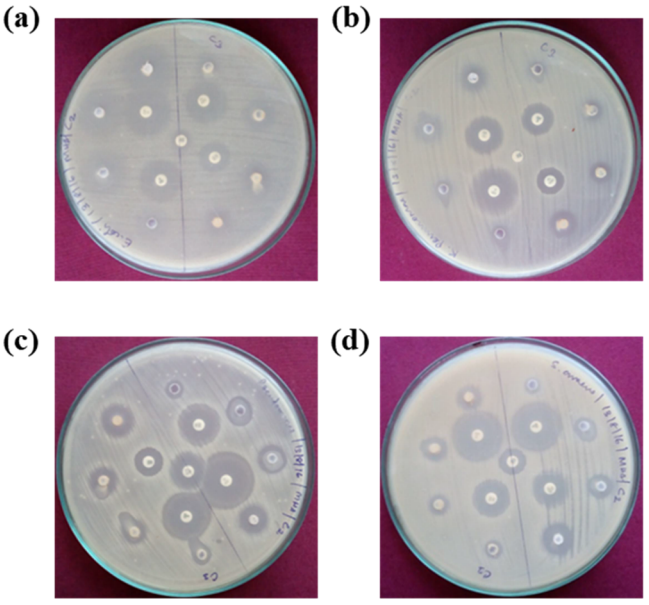

Figure 1. Antibacterial activity of dimeric imidazolium salts; (a) zone of inhibition against *E. coli* with different concentrations of compounds **3a** and **3d** (25, 50, 75, and 100 μg/well); (b) zone of inhibition against *K. pneumoniae* with different concentrations of compounds **4a** and **4b** (25, 50, 75, and 100 μg/well); (c) zone of inhibition against *P. aeruginosa* with different concentrations of compounds **5a** and **6a** (25, 50, 75, and 100 μg/well), and (d) zone of inhibition against *S. aureus* with different concentrations of compounds **5d** and **6b** (25, 50, 75, and 100 μg/well).

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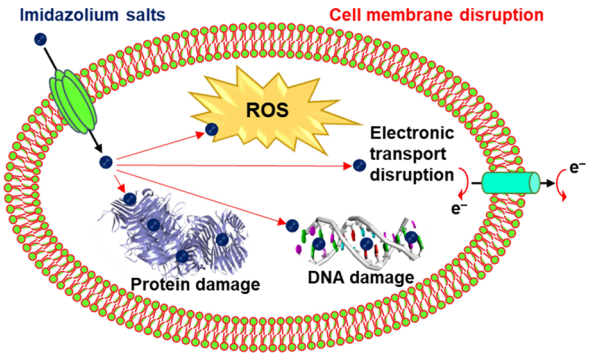

Figure 2. Proposed simple membrane disruption mechanism.

2.2.3. Microdilution Technique. MIC and MBC of synthesized imidazolium salts against Gram-negative/Gram-positive human pathogens are studied under the microdilution technique.[44] We have observed that compound **6a** shows excellent antimicrobial activity against *E. coli* and *P. vulgaris* than that against *S. aureus*; other pathogens showed good to moderate activity (Table 2).

MIC and MBC values for dimeric imidazolium salts **3−6 (a−d)** [10 μg/well (1.538×10^{-4} mmol/mL), 20 μg/well (3.07×10^{-4} mmol/mL), 30 μg/well (4.615×10^{-4} mmol/mL), 40 μg/well (6.153×10^{-4} mmol/mL), 50 μg/well (7.692×10^{-4} mmol/mL), 60 μg/well (9.230×10^{-4} mmol/mL), 70 μg/well (1.08×10^{-3} mmol/mL), and 80 μg/well (1.23×10^{-3} mmol/mL) gentamycin (8.357×10^{-4} mmol/mL), nalidixic acid (8.612×10^{-4} mmol/mL), oflaxacin (1.66×10^{-3} mmol/mL), ciproflaxacin (2.77×10^{-3} mmol/mL), and amikacin (3.415×10^{-4} mmol/mL)] concentrations against Gram-negative *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *P. vulgaris* and Gram-positive *S. aureus*, and *E. faecalis* human pathogens.

2.3. Binding Site Prediction via Docking Studies. Hydrogen bonding, ligand/nonligand bonding, and van der Waals bonding are studied using various protein sequences against synthesized dimeric imidazolium salts using computer-assisted docking studies. Figures 345 indicate how pathogens effectively bind with dimeric imidazolium salts **3−6 (a−d)** via host−gust interactions (ligand bond, hydrogen bonding etc.). We have examined effective binding between compound **6c** with *E. coli*. (Table 2). *Escherichia coli* as host for membrane protein structure determination: A comprehensive analysis of protein databases revealed using a unique membrane protein method (X-Ray diffraction), resolution (1.80 A°), crystal structure of DHFR 20% isopropanol, asymmetric-C1, monomer-A1, *R*-value free (0.253), strain K12, modeled residue count (318), total structure weight (37.17 kDa), macromolecule amount count 3020, and unique protein chain (1). PDB DOI: 10.2210/pdb5E8Q/pdb (Figure 4).

Three amino acids such as SER 49 (B), ARG 52 (B), and ARG 57 (B) showed effective binding with dimeric imidazolium nitrogen and oxygen (Figure 4b). Among these amino acids, the nitro-substituted dimeric imidazolium cation with PF_6^- anion **6c** showed effective binding interaction such as (3.24 Å), (3.06 Å), and (3.40 Å) with amino acids (Tables 3, S5−S7; Figure 3b). Two more bonding with dimeric imidazolium salt **3c** such as THR 26 (A) (3.40 Å) and HIS 228 (A) (3.18 Å) with imidazolium nitrogen and oxygen (Table 3; Figure 4a) was observed, whereas the unsubstituted dimeric imidazolium cation with the PF_6^- anion showed moderate binding with proteins with simple/nitro-substituted dimeric imidazolium salts (Tables S2−S7). Hydrogen bonding studies with nitro-substituted imidazolium bromide against various pathogens like *E. coli*., *P. aeruginosa*, *P. vulgaris*, and *S. aureus* are carried out. *Staphylococcus aureus* was used as the host for membrane protein structure determination.

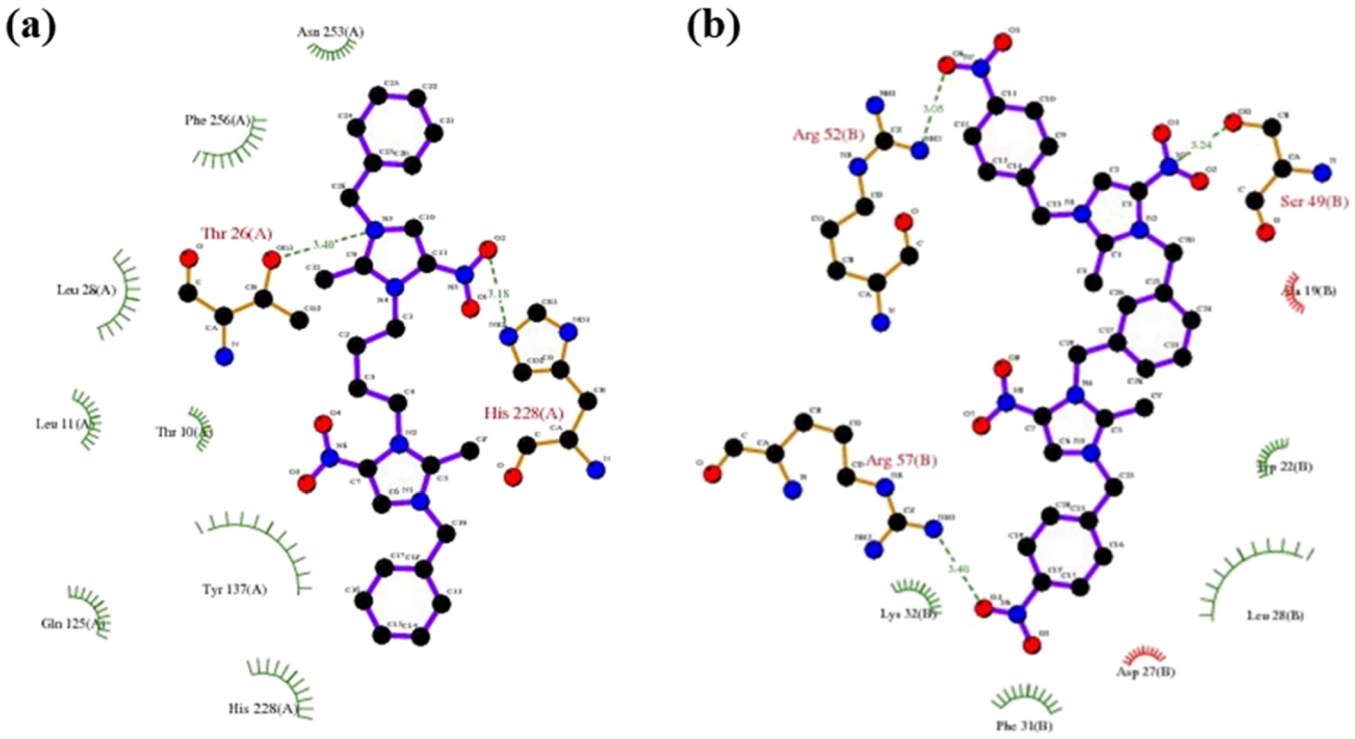

Figure 3. (a) 2D views; (a) *S. aureus* (PDB ID: 5ELZ) with compound **3c** and (b) *E. coli* (PDB ID: 5E8Q) with compound **6c**. We have used iGEMDOCK software for docking studies.

https://doi.org/10.1021/acsomega.2c06833
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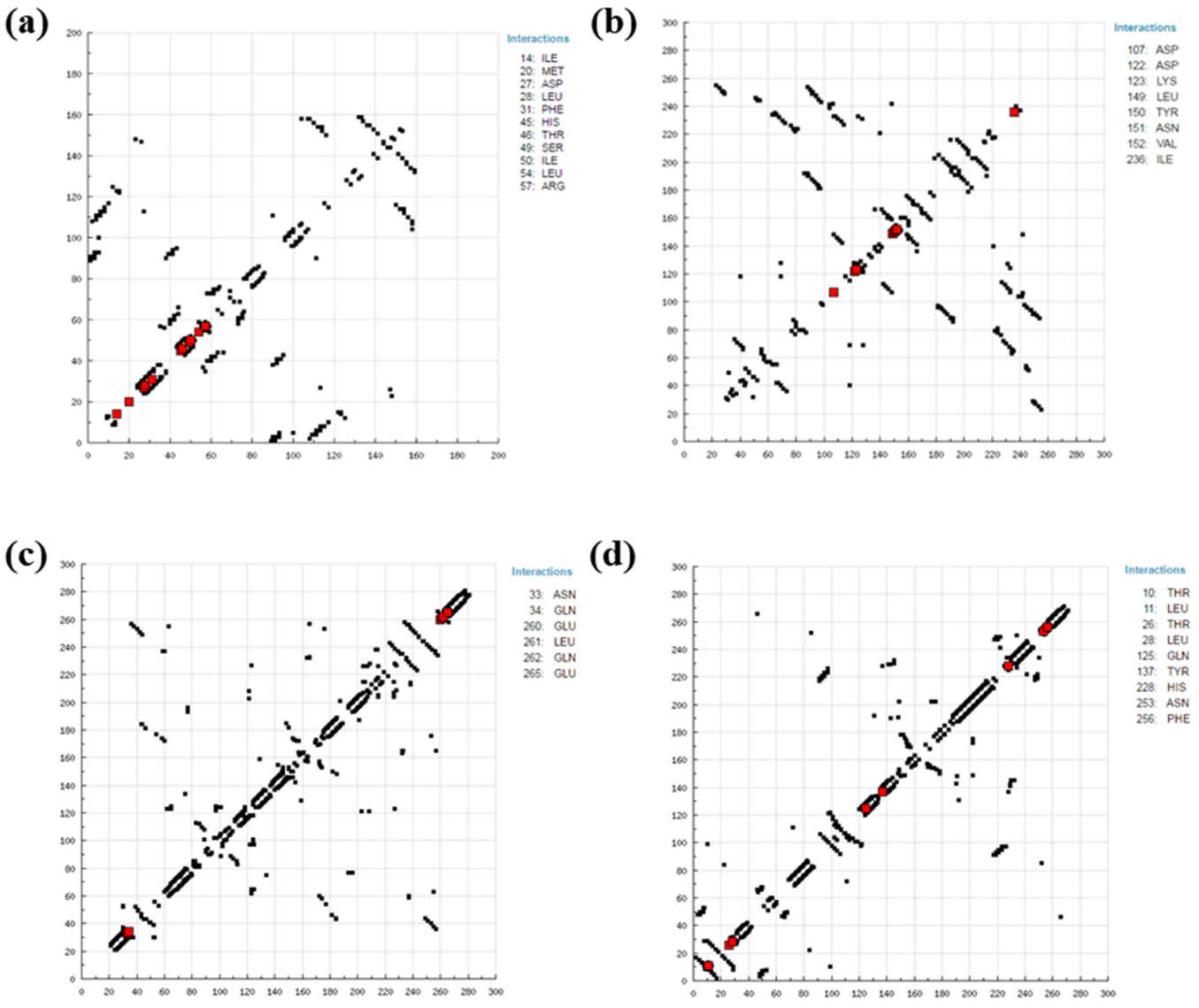

Figure 4. HB plots of (a) *E. coli* interacts with compound **3a**; (b) *P. vulgaris* interacts with compound **3b**; (c) *P. aeruginosa* interacts with compound **3b**, and (d) *S. aureus* interacts with compound **3c**.

A comprehensive analysis of protein databases through the unique membrane protein method (X-ray diffraction) revealed resolution (1.80 A°) cyclic-C2, H, Homo2-mer-A2, *R*-Value free (0.207), strain NCTC 8325/PS47, modeled residue count (272), total structure weight (30.84 kDa), macromolecule amount count 2468, and unique protein chain (1). PDB DOI: 10.2210/pdb5ELZ/pdb. (Figure 5) Among these pathogens (Figures 345), the nitro-substituted dimeric imidazolium salts **4 (a−d)** showed the highest intermolecular binding in the order *E. coli* > *P. aeruginosa* > *P. vulgaris* > *S. aureus* based on the number of hydrogen bonding, intermolecular energy, residues, and other physical parameters (Tables 2 and 3, S2−S7). Other dimeric imidazolium salts **3 (a−d)** and **5 (a−d)** have shown good to moderate values. HB plots give additional evidence for effective binding between various pathogenic microorganisms against dimeric imidazolium salts. HB plots of microorganisms of *E. coli* (5E8Q), *P. aeruginosa* (5EOE), *P. vulgaris* (5AVA), and *S. aureus* (5ELZ) for compounds **3a**, **3b**, and **3c**, respectively (Figure 4), are given.

Molecular docking analysis suggested that significant binding affinity toward *E. coli* with compound **3b** showed hydrogen bonding, hydrophobicity, and van der Waals bonding with different peptides (Tables 4, S5−S7; Figure 5a). Molecular docking studies are extended to *P. aeruginosa* with compound **3c** which showed hydrogen bonding with nearly six different amino acids (Tables 3, S5−S7; Figure 5b). Interesting observations are made based on docking results which showed effective binding with *P. vulgaris* and *S. aureus* against compound **5a** and **6a**, respectively (Tables 2 and 3, S2−S7; Figure 5c,d). We conclude that the dimeric imidazolium salts showed effective antibacterial activity, hydrogen bonding, hydrophobicity, van der Waals bonding based on antibacterial and molecular docking studies.

3. CONCLUSIONS

Dimeric-substituted imidazolium salts are prepared using benzyl/4-nitro benzyl bromide under the conventional/solvent-free method. We observed that the solvent-free method is more advantageous than the conventional one because of its shorter reaction time, higher yield, environmentally safe and easy work procedure, and so forth. The counter anion exchange is carried out using inorganic salt which is dissolved

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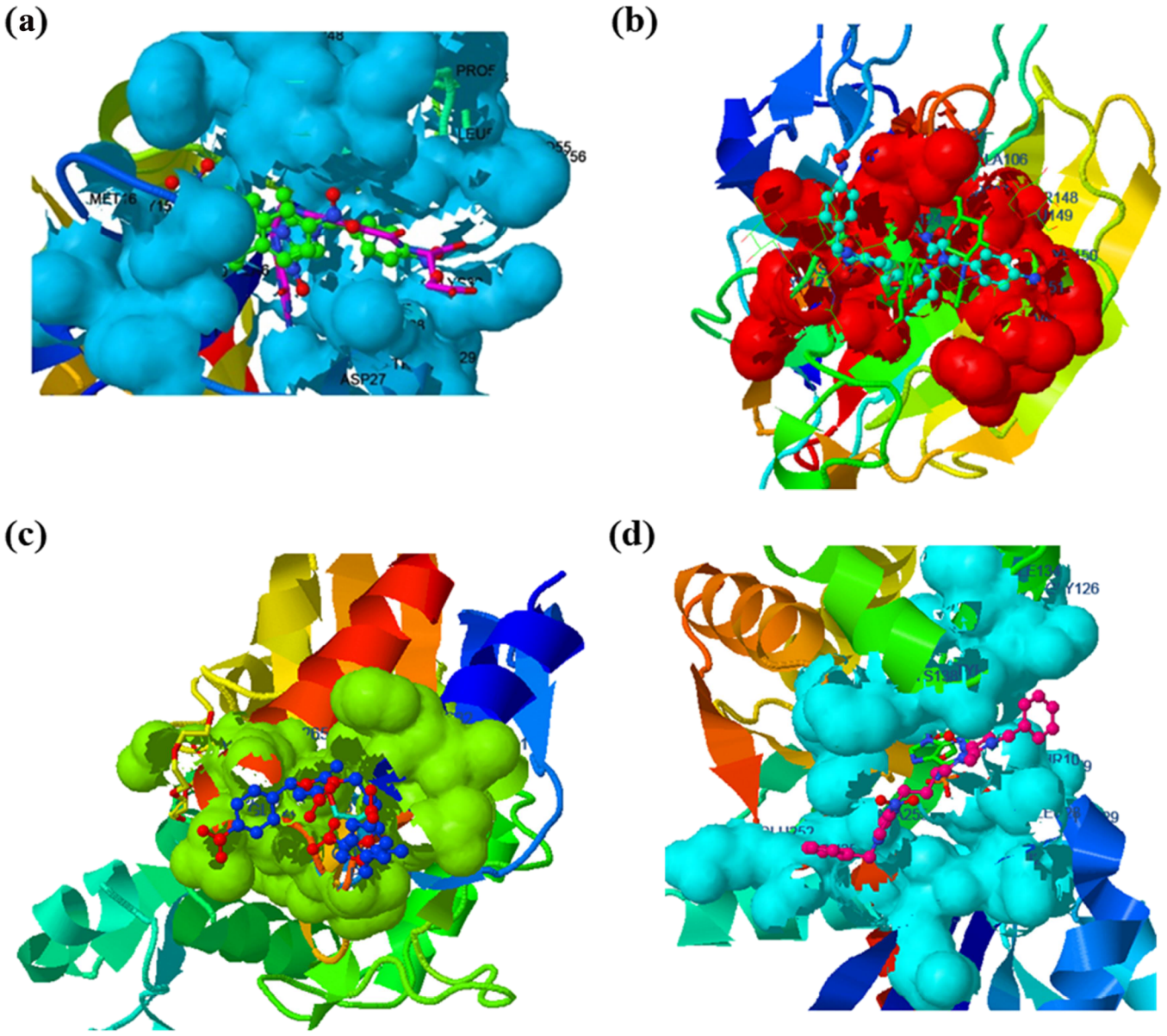

Figure 5. Molecular modeling views. (a) *E. coli* interacts with compound **3b;** (b) *P. aeruginosa* interacts with compound **3c**; (c) *P. vulgaris* interacts with compound **5a**, and (d) *S. aureus* interacts with compound **6a**.

in deionized water at room temperature. Computer-assisted docking analysis was performed for unsubstituted/nitro-substituted dimeric imidazolium salts. In docking studies, effective binding occurred between proteins and dimeric imidazolium salts **3**−**6** (**a**−**d**) via hydrogen bonding with least energy levels. Nitro-substituted imidazolium salt **4b** shows effective hydrogen bonding between SER 49 and TRP 22 with the lowest intermolecular energy at −6.68 against *E. coli*. Hydrogen bonding studies with nitro-substituted imidazolium bromide against various pathogens like *E. coli*, *P. aeruginosa*, *P. vulgaris*, and *S. aureus* are carried out. Among these pathogens, the nitro-substituted dimeric imidazolium salts **4** (**a**−**d**) showed the highest intermolecular binding in the order *E. coli* > *P. aeruginosa* > *P. vulgaris* > *S. aureus* based on the number of hydrogen bonding, intermolecular energy, residues, and other physical parameters. Other dimeric imidazolium salts **3** (**a**−**d**) and **5** (**a**−**d**) showed good to moderate values.

4. EXPERIMENTAL SECTION

4.1. General Procedure for *N*-Alkylation. 2-Methyl-5-nitroimidazole (1.573×10^{-2} mmol; 2.05 equiv) is treated with slight excess amount of 1,4-dibromobutane/1,3-bis-(bromomethyl)benzene (7.865×10^{-3} mmol; 1.0 equiv) in the presence of $NaOH/CH_3CN$ under refluxing conditions for 6−7 h to give compound **1**/**2** in a quantitative yield. We have tried the *N*-alkylation reaction between nitro-substituted dimeric imidazole **1**/**2** with benzylbromide/4-nitrobenzylbromide under a conventional route for about 10−12 h to give compounds **3a, 4a, 5a**, and **6a** in 88−93% yield.

4.2. General Procedures for Solid-Supported Solvent-Free Muffle Furnace Conditions. Required equivalents, as mentioned in the conventional method, were added in the absence of the solvent with 5 g of (80−120 mesh) silica gel followed by fine grinding using a mortar and pestle. The reaction mixture was kept in a muffle furnace at 100 °C.

https://doi.org/10.1021/acsomega.2c06833
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Table 3. Docking Results of the Compounds (3−6) (a−d) with *Escherichia coli* (PDB ID: 5e8q)

	Escherichia coli					
compounds	est. free energy of binding (kcal/mol)	est. inhibition constant, Ki (μM)	vdW + H-bond + desolv energy	electrostatic energy	total intermol energy	interact. surface
3a	−5.85	51.86	−8.20	−0.78	−8.97	1072.69
3b	−6.68	12.72	−10.14	−0.30	−10.44	1099.216
3c	−5.38	114.59	−8.15	−0.50	−8.65	934.916
3d	−5.71	65.29	−9.96	−0.61	−10.56	1086.296
4a	−4.83	289.24	−6.92	−0.79	−7.71	979.75
4b	−5.69	66.93	−8.53	−0.59	−9.12	1050.9
4c	−5.43	105.22	−7.59	−0.54	−8.13	1011.923
4d	−6.51	16.87	−8.84	−0.34	−9.18	1102.357
5a	−4.39	609.69	−8.20	−0.63	−8.83	1008.806
5b	−5.47	97.26	−7.51	−0.60	−8.11	1103.605
5c	−5.67	70.33	−7.47	−0.53	−8.00	898.619
5d	−6.22	27.60	−7.71	−0.65	−8.36	963.368
6a	−5.34	121.85	−7.88	−0.77	−8.65	1067.07
6b	−6.12	32.78	−9.94	+0.46	−9.48	1072.907
6c	−5.18	159.09	−6.87	−0.22	−7.09	959.035
6d	−5.26	140.35	−8.22	−0.29	−8.51	1058.343

Table 4. Molecular Docking Parameters of the Compounds (3−6) (a−d) with *Escherichia coli* (PDB ID: 5e8q)

	Escherichia coli		
compounds	hydrogen bond	polar	hydrophobic
3a	SER49 (−0.1668), MET20 (−1.3796)	ILE14 (−1.1923), TRP22 (−0.8356)	THR46 (−0.4967), PHE31 (−0.3694)
3b	SER49 (−1.5087), TRP22 (−1.0884)	LEU28 (−1.995), MET20 (−0.9881)	THR46 (−0.6988), ALA7 (−0.3224)
3c	SER49 (−0.7873), ARG52 (−0.7972)	PHE31 (−1.1973), TRP22 (−0.9051)	ILE50 (−0.9798), ASP27 (−0.0932)
3d	THR46 (−0.903), ILE14 (−0.6501)	ARG57 (−0.3933), ASP27 (−0.3227)	ILE50 (−1.3732), LEU28 (−1.2423)
4a	TRP22 (−0.7423), LEU28 (−1.4542)	ARG52 (−0.2138), ILE50 (−1.0608)	SER49 (−0.2088), LEU54 (−0.1187)
4b	SER49 (−0.1243), ARG52 (−0.5894)	LEU28 (−1.6218), PHE31 (−1.3547)	TRP22 (−0.999), ASN23 (−0.7346)
4c	TRP22 (−0.3554), ALA7 (−0.6851)	MET20 (−1.1017), ILE50 (−0.8928)	ARG52 (−1.1202), LEU28 (−0.8055)
4d	SER49 (−0.4847), PHE31 (−0.9907)	ARG52 (−0.668), LEU28 (−0.6818)	MET20 (−1.744), ILE50 (−1.3742)
5a	TRP22 (−0.8134), PHE31 (−1.1378)	ILE50 (−1.1792), MET20 (−1.1416)	THR46 (−0.7552), LEU54 (−0.1865)
5b	SER49 (−0.5621), ASP27 (−0.1579)	ILE14 (−0.7623), TYR100 (−0.655)	THR46 (−0.6547), TRP22 (−0.4586)
5c	MET20 (−1.214), ILE50 (−1.4158)	TRP22 (−1.284), LEU28 (−1.104)	ASN23 (−0.880), ARG52 (−0.475)
5d	ARG52 (−1.0117), ARG57 (−0.3776)	TRP22 (−0.1744), LEU28 (−2.242)	PHE31 (−0.6146), LYS32 (−0.374)
6a	ARG52 (−0.457)	ILE50 (−1.8017), LEU28 (−1.072)	PHE31 (−0.735), ASN23 (−0.572)
6b	LEU24 (−0.6434), ASP27 (−0.647)	PHE31 (−2.4713), LEU28 (−2.1923)	TRP22 (−1.0719), LYS32 (−0.9413)
6c	SER49 (−0.2458), ARG52 (−0.809)	ILE50 (−1.9295), PHE31 (−0.9942)	TRP22 (−1.0117), ARG57 (−0.9762)
6d	SER49 (−0.542), ILE94 (−0.1453)	LEU28 (−1.1261), TYR100 (−0.208)	ARG52 (−3.0979), PHE31 (−0.9811)

4.3. General Procedure for the Anion Exchange Reaction. The *N*-alkylated product of quaternary ammonium bromide (1.0 equiv) is treated with $NaBF_4$, KPF_6, and $LiCF_3SO_3$ (2.05 equiv) in the presence of 10 mL of deionized water at room temperature under stirring for about 1 h to afford the anion-exchanged ionic liquids. After the anion exchange reaction, we have used Soxhlet extraction to remove metal bromide from ionic liquids using 100 mL of dry THF for about 1 h refluxtion to give ionic liquids **3−6 (b−d)** in quantitative yield.

*4.3.1. 2-Methyl-1-(4-(2-methyl-5-nitro-1H-imidazol-1-yl)-butyl)-5-nitro-1H-imidazole (**1**).* Yield: 2.30 g (95%); mp: 150−152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.64−1.82 (q, 4H), 2.33 (s, 6H), 4.62−4.74 (t, 4H), 8.96 (s, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.1, 30.1, 51.8, 149.8, 150.4, 150.5. MS: *m/z*: 308; Anal. Calcd for $C_{12}H_{16}N_6O_4$: Calculated: C, 46.75; H, 5.23; N, 27.26. Found: C, 46.70; H, 5.19; N, 27.20.

*4.3.2. 1-(3-((2-Methyl-5nitro-1H-imidazol-1-yl)methyl)-benzyl)-2-methyl-5-nitro-1H-imidazole (**2**).* Yield: 2.8 g (98%);mp: 145−147 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.46 (s, 6H), 4.62 (s, 4H), 6.93−7.01 (m, 4H), 7.52 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.6, 38.3, 126.0, 127.9, 128.2, 130.5, 135.4, 140.3, 151.2. MS: *m/z*: 356; Anal. Calcd for $C_{16}H_{16}N_6O_4$: Calculated: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.89; H, 4.48; N, 23.54.

*4.3.3. 3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1H-imidazoliumbromide-1-yl)butyl)-2-methyl-5nitro-1H-imidazoliumbromide (**3a**).* Yield: 1.89 g (90%); mp: 120−122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.63−1.74 (q, 4H), 2.16 (s, 6H), 3.75−3.83 (t, 4H), 4.31 (s, 4H), 7.13−7.25 (m, 10), 7.90 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 30.0, 40.0, 53.7, 124.8, 127.8, 129.4, 135.1, 146.3, 153.4, 158.1. MS: *m/z*: 650; Anal. Calcd for $C_{26}H_{30}Br_2N_6O_4$: Calculated: C, 48.02; H, 4.65; N, 12.92. Found: C, 47.99; H, 4.60; N, 12.87.

*4.3.4. 3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate-1-yl)butyl)-2-methyl-5nitro-1H-imidazoliumtetrafluoroborate (**3b**).* Yield: 0.51 g (94%); mp: 110−112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.61−1.70 (q, 4H), 2.13 (s, 6H), 3.71−3.79 (t, 4H), 4.30 (s, 4H), 7.12−7.24 (m, 10), 7.88 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.3, 30.1, 40.2, 53.8, 124.7, 127.9, 129.3, 135.2, 146.2, 153.3, 158.0. MS: *m/z*: 664; Anal. Calcd for $C_{26}H_{30}B_2F_8N_6O_4$: Calculated: C, 47.02; H, 4.55; N, 12.65. Found: C, 46.97; H, 4.51; N, 12.59.

4.3.5. 3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate-1-yl)butyl)-2-methyl-5nitro-

https://doi.org/10.1021/acsomega.2c06833
ACS Omega 2022, 7, 44458−44469

*1H-imidazoliumhexafluorophosphate (**3c**).* Yield: 0.56 g (93%); mp: 97−99 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.60−1.71 (q, 4H), 2.14 (s, 6H), 3.70−3.81 (t, 4H), 4.32 (s, 4H), 7.10−7.23 (m, 10), 7.91 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.2, 30.2, 40.1, 53.6, 124.7, 127.7, 129.4, 135.0, 146.3, 153.2, 158.2. MS: *m/z*: 780; Anal. Calcd for $C_{26}H_{30}F_{12}N_6O_4P_2$: Calculated: C, 40.01; H, 3.87; N, 10.77. Found: C, 39.95; H, 3.83; N, 10.73.

*4.3.6. 3-Benzyl-1-(4-(3-benzyl-2-methyl-5-nitro-1H-imidazoliumtrifluoromethanesulfonate-1-yl)butyl)-2-methyl-5nitro-1H-imidazoliumtrifluoromethanesulfonate (**3d**).* Yield: 0.83 g (84%); mp: °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.60−1.71 (q, 4H), 2.15 (s, 6H), 3.74−3.80 (t, 4H), 4.33 (s, 4H), 7.14−7.24 (m, 10), 7.91 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 30.2, 40.3, 53.8, 124.6, 127.8, 129.2, 135.3, 146.1, 153.2, 158.2. MS: *m/z*: 788; Anal. Calcd for $C_{28}H_{30}F_6N_6O_{10}S_2$: Calculated: C, 42.64; H, 3.83; N, 10.66. Found: C, 42.59; H, 3.78; N, 10.60.

*4.3.7. 1-(3-((3-Benzyl-2-methyl-5-nitro-1H-imidazoliumbromide-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1H-imidazoliumbromide (**4a**).* Yield: 4.93 g (90%); mp: 127−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 6H), 4.65 (s, 4H), 5.51 (s, 4H), 7.05−7.14 (m, 4H), 7.25−7.35 (m, 10), 8.52 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.1, 45.1, 53.1, 121.1, 123.0, 124.9, 125.5, 126.7, 129.4, 132.2, 134.4, 135.9, 141.3, 152.4. MS: *m/z*: 698; Anal. Calcd for $C_{30}H_{30}Br_2N_6O_4$: Calculated: C, 51.59; H, 4.33; N, 12.03. Found: C, 51.54; H, 4.28; N, 11.92.

*4.3.8. 1-(3-((3-Benzyl-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate (**4b**).* Yield: 0.47 g (94%); mp: 120−122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 6H), 4.64 (s, 4H), 5.49 (s, 4H), 7.04−7.13 (m, 4H), 7.23−7.33 (m, 10), 8.51 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.2, 45.3, 53.0, 121.3, 123.1, 124.8, 125.4, 126.6, 129.3, 132.1, 134.3, 135.8, 141.2, 152.3. MS: *m/z*: 712; Anal. Calcd for $C_{30}H_{30}B_2F_8N_6O_4$: Calculated: C, 50.59; H, 4.25; N, 11.80. Found: C, 50.54; H, 4.21; N, 11.74.

*4.3.9. 1-(3-((3-Benzyl-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate (**4c**).* Yield: 0.50 g(86%); mp: 105−107 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 6H), 4.63 (s, 4H), 5.50 (s, 4H), 7.03−7.12 (m, 4H), 7.24−7.34 (m, 10), 8.50 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.0, 45.2, 53.2, 121.2, 123.2, 124.7, 125.3, 126.5, 129.2, 132.1, 134.2, 135.8, 141.0, 152.2. MS: *m/z*: 828; Anal. Calcd for $C_{30}H_{30}F_{12}N_6O_4P_2$: Calculated: C, 43.49; H, 3.65; N, 10.14. Found: C, 43.46; H, 3.61; N, 10.09.

*4.3.10. 1-(3-((3-Benzyl-2-methyl-5-nitro-1H-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3-benzyl-2-methyl-5-nitro-1H-imidazoliumtrifluoromethanesulfonate (**4d**).* Yield: 0.52 g (87%); mp: 90−92 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 6H), 4.62 (s, 4H), 5.49 (s, 4H), 7.01−7.11 (m, 4H), 7.20−7.30 (m, 10), 8.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.2, 45.0, 53.3, 121.0, 123.2, 124.6, 125.4, 126.6, 129.4, 132.3, 134.5, 135.8, 141.2, 152.5. MS: *m/z*: 836; Anal. Calcd for $C_{32}H_{30}F_6N_6O_{10}S_2$: Calculated: C, 45.93; H, 3.61; N, 10.04. Found: C, 45.89; H, 3.57; N, 10.00.

*4.3.11. 3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumbromide-1-yl)butyl))-2-methyl-5nitro-1H-imidazoliumbromide (**5a**).* Yield: 2.40 g (88%); mp: 145−147 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.80−1.95 (q, 4H), 2.28 (s, 6H), 4.04−4.11 (t, 4H), 4.65 (s, 4H), 7.23 (s, 2H), 7.59−7.61 (d, 4H), 8.19−8.22 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.9, 30.9, 42.4, 53.7, 119.1, 130.5, 139.3, 147.4, 153.3, 156.0, 157.8. MS: *m/z*: 740; Anal. Calcd for $C_{26}H_{28}Br_2N_8O_8$: Calculated: C, 42.18; H, 3.81; N, 15.14. Found: C, 42.15; H, 3.77; N, 15.10.

*4.3.12. 3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate-1-yl)butyl))-2-methyl-5nitro-1H-imidazoliumtetrafluoroborate (**5b**).* Yield: 0.53 g (85%); mp: 130−132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79−1.94 (q, 4H), 2.27 (s, 6H), 4.01−4.09 (t, 4H), 4.61 (s, 4H), 7.25 (s, 2H), 7.57−7.60 (d, 4H), 8.17−8.20 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.8, 30.7, 42.3, 53.6, 119.2, 130.4, 139.4, 147.3, 153.2, 156.1, 157.6. MS: *m/z*: 754; Anal. Calcd for $C_{26}H_{28}B_2F_8N_8O_8$: Calculated: C, 41.41; H, 3.73; N, 14.86. Found: C, 41.37; H, 3.69; N, 14.81.

*4.3.13. 3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate-1-yl)butyl))-2-methyl-5nitro-1H-imidazolium hexafluorophosphate (**5c**).* Yield: 0.65 g (89%); mp: 118−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.78−1.93 (q, 4H), 2.25 (s, 6H), 4.01−4.08 (t, 4H), 4.60 (s, 4H), 7.37 (s, 2H), 7.58−7.61 (d, 4H), 8.16−8.20 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.7, 30.8, 42.5, 53.5, 119.3, 130.3, 139.2, 147.2, 153.1, 156.2, 157.7. MS: *m/z*: 870; Anal. Calcd for $C_{26}H_{28}F_{12}N_8O_8P_2$: Calculated: C, 35.87; H, 3.24; N, 12.87. Found: C, 35.82; H, 3.20; N, 12.82.

*4.3.14. 3-(4-Nitrobenzyl)-1-(4-(3-(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazolium trifluoromethanesulfonate-1-yl)-butyl))-2-methyl-5nitro-1H-imidazolium trifluoromethanesulfonate (**5d**).* Yield: 0.63 g (90%); mp: 90−92 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.81−1.96 (q, 4H), 2.29 (s, 6H), 4.03−4.10 (t, 4H), 4.64 (s, 4H), 7.34 (s, 2H), 7.56−7.58 (d, 4H), 8.17−8.20 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.6, 30.9, 42.5, 53.5, 119.0, 130.4, 139.3, 147.5, 153.1, 156.2, 157.7. MS: *m/z*: 878; Anal. Calcd for $C_{28}H_{28}F_6N_8O_{14}S_2$: Calculated: C, 38.27; H, 3.21; N, 12.75. Found: C, 38.22; H, 3.17; N, 12.70.

*4.3.15. 1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1H-imidazoliumbromide-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumbromide (**6a**).* Yield: 5.75 g (93%); mp: 120−122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 6H), 4.04 (s, 4H), 5.36 (s, 4H), 6.93−7.05 (m, 4H), 7.22 (s, 2H), 7.78−7.82 (d, 4H), 8.19−8.22 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.7, 44.5, 52.9, 120.9, 126.4, 129.0, 130.4, 131.7, 135.1, 137.4, 139.4, 148.1, 152.8, 155.5. MS: *m/z*: 788; Anal. Calcd for $C_{30}H_{28}Br_2N_8O_8$: Calculated: C, 45.70; H, 3.58; N, 14.21. Found: C, 45.65; H, 3.54; N, 14.16.

*4.3.16. 1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumtetrafluoroborate (**6b**).* Yield: 0.45 g (89%); mp: 110−112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.20 (s, 6H), 4.03 (s, 4H), 5.33 (s, 4H), 6.91−7.03 (m, 4H), 7.21 (s, 2H), 7.76−7.80 (d, 4H), 8.18−8.21 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.6, 44.4, 52.6, 120.8, 126.2, 129.1, 130.3, 131.5, 135.2, 137.3, 139.2, 148.0, 152.7, 155.3. MS: *m/z*: 802; Anal. Calcd for $C_{30}H_{28}B_2F_8N_8O_8$: Calculated: C, 44.92; H, 3.52; N, 13.97. Found: C, 44.89; H, 3.47; N, 13.94.

*4.3.17. 1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumhexafluorophosphate (**6c**).* Yield: 0.48 g (84%); mp: 101−103 °C; ^{1}H NMR

https://doi.org/10.1021/acsomega.2c06833
ACS Omega 2022, 7, 44458−44469

(400 MHz, DMSO-d_6): δ = 2.21 (s, 6H), 4.01 (s, 4H), 5.34 (s, 4H), 6.92−7.04 (m, 4H), 7.20 (s, 2H), 7.77−7.81 (d, 4H), 8.17−8.20 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.7, 44.3, 52.7, 120.6, 126.3, 129.3, 130.2, 131.6, 135.0, 137.2, 139.3, 148.2, 152.6, 155.4. MS: *m/z*: 918; Anal. Calcd for $C_{30}H_{28}F_{12}N_8O_8P_2$: Calculated: C, 39.23; H, 3.07; N, 12.20. Found: C, 39.19; H, 3.02; N, 12.14.

*4.3.18. 1-(3-((3-(-Nitrobenzyl)-2-methyl-5-nitro-1H-imidazoliumtrifluoromethanesulfonate-1-yl)methyl)benzyl)-3(4-nitrobenzyl-2-methyl-5-nitro-1H-imidazoliumtrifluoromethanesulfonate (**6d**).* Yield: 0.48 g (82%); mp: 87−89 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 6H), 4.02 (s, 4H), 5.35 (s, 4H), 6.90−7.02 (m, 4H), 7.19 (s, 2H), 7.75−7.79 (d, 4H), 8.16−8.19 (d, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.8, 44.4, 52.8, 120.7, 126.5, 129.2, 130.1, 131.4, 135.0, 137.3, 139.0, 148.3, 152.7, 155.6. MS: *m/z*: 926; Anal. Calcd for $C_{32}H_{28}F_6N_8O_{14}S_2$: Calculated: C, 41.47; H, 3.05; N, 12.09. Found: C, 41.42; H, 3.01; N, 12.04.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06833.

Characterization data for **3a**, **4a**, **5a**, and **6a**. Antibacterial screening and docking results of the compounds (**3**−**6**) (**a**−**d**) (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.G. and P.G. thanks Dr. N. Arunagirinathan, Assistant Professor, and Dr. N. Vijaykanth, Research scholar, PG & Research Department of Biology and Biotechnology, Presidency College, Chennai-5, for microbial and docking studies. M.M.A. and M.A. thank the Deanship of Research, King Khalid University, Saudi Arabia, for Small Research Group under the grant number R. G. P. 1/339/1443.

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https://doi.org/10.1021/acsomega.2c06833
ACS Omega 2022, 7, 44458−44469