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FULL PAPER

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Catechol-bearing imidazolium and benzimidazolium chlorides as promising antimicrobial agents

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Abstract

Catechol-containing imidazolium (four) and benzimidazolium chlorides (eight) were synthesized to evaluate their antimicrobial properties. All the compounds were fully characterized using ^{1}H and ^{13}C nuclear magnetic resonance, liquid chromatography–mass spectrometry, infrared spectroscopic methods, and elemental analyses. Antimicrobial activities of the compounds were tested against the bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis*, and the fungal strains *Candida albicans* and *Candida glabrata* , and promising results were achieved. The two most important benzyl-substituted benzimidazolium chlorides, **3l** and **3k**, showed comparable activity to vancomycin against MRSA.

KEYWORDS

antibacterial, antifungal, benzimidazolium, catechol, imidazolium

1 | INTRODUCTION

The emergence of microorganisms which have resistance against pharmaceutical and agrochemical antimicrobial agents forced scientists to develop more effective antimicrobial agents with low toxicity.[1] For this purpose, many classes of compounds are being investigated owing to their presence in the structure of natural products and demonstrated pharmaceutical properties, heterocyclic compounds are indispensable building blocks in drug design. Additionally, it was reported that conformationally restricted structures of heterocyclics may provide them with more bioactivity and selectivity compared with their acyclic analogues.[2] Imidazole and its benzene-fused derivative, benzimidazole, are nitrogen heterocycles that can be found in the structures of biologically important compounds. For example, imidazole is found in the structures of histidine, purine, and biotin,[3] while *N*-ribosyl-dimethylbenzimidazole acts as a ligand in the structure of vitamin B_{12}.[4] Moreover, many clinically used drugs were developed thanks to their anticancer, antimicrobial, antiulcer, and other therapeutic properties.[3]

Imidazolium and benzimidazolium salts are ionic compounds which have been mainly synthesized as *N*-heterocyclic carbene (NHC) precursors in organometallic chemistry.[5] The biological properties of imidazolium and benzimidazolium salts have been less frequently investigated compared with their neutral derivatives. As natural products, two imidazolium salts (Figure 1), which have remarkable cytotoxic effects, were isolated from the roots of *Lepidium meyenii*.[6] However, early studies in this area may be traced back to the 1980s. In 1989, Dominianni and Yen[7] reported that phenacylimidazolium salts have hypoglycemic activity.[7] In the following studies, Pernak et al.[8] and Çetinkaya et al.[9] reported that imidazolium salts have antimicrobial activity. After the pioneering study of Youngs et al. in 2004, in which silver–NHC complexes were reported as a new class of antimicrobial agents,[10] many imidazolium and benzimidazolium chlorides were synthesized to prepare their silver–NHC complexes. However, in most of these studies, imidazolium and benzimidazolium salts were not tested or reported as inactive against bacterial and fungal strains.[11–13] More recently, Schmitzer and colleagues reported that benzimidazolium salt causes electrolyte imbalance and disrupts the integrity and the potential of bacterial membranes. In addition, the same benzimidazolium

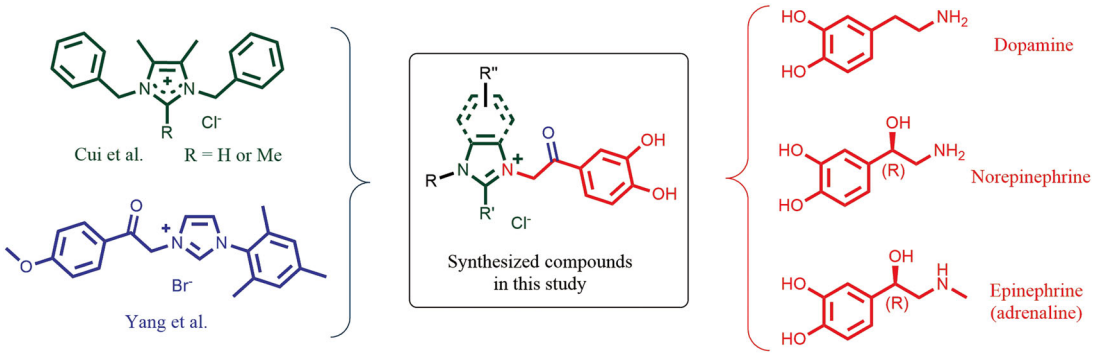


FIGURE 1 General structure of the target compounds

salt presents low toxicity to human cells in bacteriostatic range concentrations.[14] In contrast, enzyme inhibitory and anticancer properties of these compounds were also reported. Many studies showed that these compounds have a significant inhibitory effect on the activities of prolyl oligopeptidase,[15] carbonic anhydrase,[16] paraoxonase 1,[17] tyrosinase,[18] and acetylcholinesterase.[19] In 2009, Yang et al. reported that phenacyl-substituted imidazolium bromide (Figure 1) exhibits remarkable anticancer activity.[20] Later, in the following studies, they showed that attaching biologically relevant groups to the imidazolium or benzimidazolium scaffold may render these compounds as highly potent anticancer agents.[21–25]

Catechol (1,2-dihydroxybenzene) and its derivatives are ubiquitous in nature and display various chemical and physical properties.[26] For example, catecholamine derivatives dopamine, epinephrine (adrenaline), and norepinephrine (Figure 1) are hormones synthesized by adrenal glands. These compounds have well-defined biochemical roles such as raising blood pressure, sending more blood to major organs, and increasing the blood glucose level.[27] Additionally, these compounds are water soluble and bound to plasma proteins.

Based on the above information, with the aim of enhancing the biological properties of imidazolium and benzimidazolium salts with biologically relevant molecules, we synthesized catechol bearing four imidazolium and eight benzimidazolium chlorides (Figure 1). The antimicrobial properties of the compounds were evaluated against four Gram-negative and three Gram-positive bacteria, and two fungal strains.

2 | RESULTS AND DISCUSSION

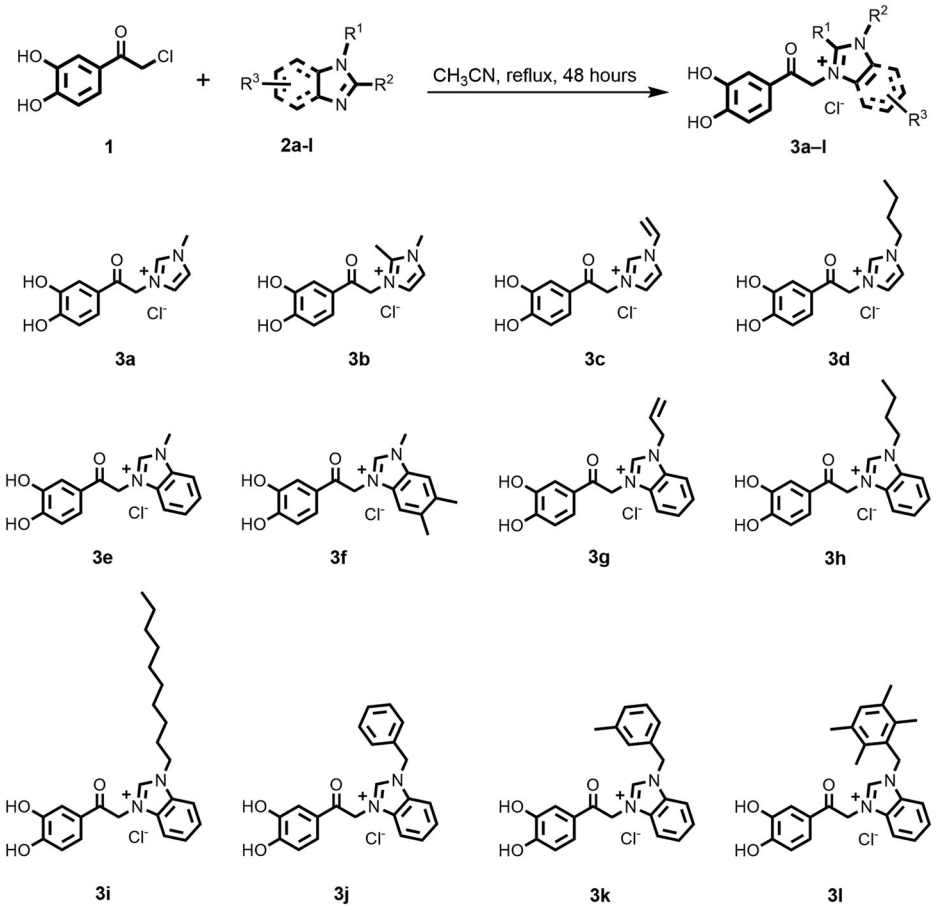
2.1 | Synthesis and spectral characterization

The target compounds were synthesized by a reaction between 2-chloro-3′,4′-dihydroxyacetophenone (**1**) and *N*-alkylimidazole or *N*-alkylbenzimidazole derivatives (**2a–l**). The reaction was carried out in acetonitrile under open-air conditions and target compounds were obtained in good yields between 58% and 91%. After completion of the reaction, the precipitation of target compounds facilitated the purification step. The synthesis and structures of compounds are given in Scheme 1 and some physical and spectral data of compounds are given in Table 1. Additionally, *N*-butyl-*N*-benzylbenzimidazolium chloride (**4**) was synthesized according to the literature[28,29] (Figure 2) to compare its antimicrobial activity with catechol-substituted analogues.

The compounds were fully characterized by a combination of ^{1}H and ^{13}C nuclear magnetic resonance (NMR), liquid chromatography–mass spectrometry (LC–MS) and infrared (IR) spectra and elemental analyses (see Supporting Information for all spectra). In ^{1}H NMR spectra of compounds, the signals of acidic –NCHN– hydrogens were observed in the range 9.09–9.97 ppm except for **3b** which has a methyl group instead of hydrogen at 2-position of the imidazole ring. Signals of hydroxy hydrogens were observed as broad signals as expected. Other signals were observed in accordance with the expected integral values and coupling patterns. In ^{13}C NMR spectra of compounds, signals of carbonyl carbons were observed in the range 189.4–189.8 ppm. The signals of –NCHN– imino carbons were observed in the range 137.2–138.2 ppm for imidazolium chlorides and 142.8–144.3 ppm for benzimidazolium chlorides. The signal for –NC(CH_3)N– imino carbon of **3b** was observed at 146.2 ppm. Other signals were observed in accordance with the proposed structures. In LC–MS spectra of compounds, maximal peak intensities were attributed to the cationic part of salts (see characterization data). In IR spectra, the broad signals of hydroxy groups and sharp signals of carbonyl groups were observed as expected. Additionally, elemental analyses also support the proposed structures.

2.2 | Antimicrobial studies

In drug design, solubility and bioconjugation of compounds are highly important parameters. Therefore, solubilities of all compounds were tested in physiological saline solution (containing 2.5% ethanol and 2.5% Tween-80) according to the literature.[30] As seen in Table 1, 9 of 12 compounds are soluble in physiological saline solution at room temperature, while 1 compound (**3k**) is soluble at 37°C and 2 compounds (**3j,l**) are not soluble even at 37°C. In addition, the



SCHEME 1 Synthesis and structures of the imidazolium and benzimidazolium chlorides

synthesized salts have structural similarity with catecholamines such as dopamine, epinephrine, and norepinephrine which are biologically synthesized and water-soluble hormones.[27]

Minimal inhibitory concentrations (MICs) of all compounds were determined against four Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*) and three Gram-positive (*Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Enterococcus faecalis*) bacteria and two fungal (*Candida albicans*, *Candida glabrata*) strains. The results are listed in Table 2. Ampicillin, amikacin, vancomycin, and fluconazole were used as standard drugs for comparison.

As seen in Table 2, all compounds inhibited the growth of all bacterial and fungal strains. If we evaluate the results, first, we must point out that benzimidazolium salts exhibited stronger inhibitory effect than imidazolium salts against all bacterial and fungal strains. If we compare the benzimidazolium salts, it can be said that methyl- (**3e**,**f**) and benzyl- (**3j**–**l**) containing salts are more active than allyl- (**3g**), butyl- (**3h**) and decyl- (**3i**) containing derivatives. Especially, the activities of benzyl-containing derivatives are comparable with standard drugs. For example, compounds **3j** and **3l** exhibited the same activity as fluconazole against *C. albicans*. In contrast, all compounds exhibited lower or equal inhibitory effect against Gram-negative bacterial strains compared with Gram-positive and fungal strains. This result can be attributed to the outer membrane of Gram-negative bacteria that render them more resistant against antimicrobial agents.[31]

The antimicrobial properties of 2-chloro-3′,4′-dihydroxyacetophenone (**1**), *N*-benzylbenzimidazole (**2j**), and *N*-butyl-*N*-benzylbenzimidazolium chloride (**4**) were also tested against the same bacterial and fungal strains to control whether a combination of catechol and imidazolium scaffolds confer an advantage. These results are also listed in Table 2. As shown in Table 2, **3j** exhibited much stronger activity than its starting materials (**1** and **2j**). Moreover, the activity of benzimidazolium salt without catechol (**4**) can be compared with **3h** and **3j** which contain the same groups except catechol. As seen from the results, benzimidazolium salts containing catechol displayed stronger activity against all bacterial and fungal strains than their noncatechol analogue. This result clearly revealed that introducing the catechol group into the imidazolium scaffold increased the antimicrobial activity significantly.

Vancomycin is one of the most widely used antibiotics against methicillin-resistant *S. aureus* (MRSA); however, emergence of vancomycin-resistant *S. aureus* necessitated the development of new antibiotics.[32] In recent years, it was shown that cationic small molecules have a different mechanism of action such as depolarizing and disturbing the bacterial membrane.[33] Schmitzer

TABLE 1 Some physical and spectral data of the compounds

Compound	Yield (%)	Melting point (°C)	Solubility[a]	^{1}H NMR (ppm)		^{13}C NMR (ppm)	
				–OH	–NCHN–	–C=O	–NCHN–
3a	89	250–251	+	10.39, 9.73	9.15	189.8	138.2
3b[c]	78	245–247	+	9.92 (2 × OH)	–[c]	189.6	146.2[c]
3c	71	220–222	+	10.46, 9.73	9.60	189.4	137.2
3d	90	166–168	+	10.42, 9.76	9.27	189.7	137.9
3e	75	252–253	+	10.48, 9.71	9.80	189.7	144.3
3f	69	290–292	+	10.48, 9.71	9.64	189.7	143.0
3g	64	177–178	+	10.41, 9.65	9.80	189.6	144.1
3h	83	250–252	+	10.47, 9.71	9.90	189.6	143.9
3i	58	169–172	+	10.48, 9.71	9.91	189.6	143.9
3j	91	276–277	–	9.00–11.00 (2 × OH)	9.97	189.6	144.2
3k	83	227–230	+[b]	10.48, 9.74	9.74	189.7	144.3
3l	80	248–249	–	10.46, 9.72	9.09	189.7	142.8

Abbreviations: +, completely dissolved; –, not all dissolved.
[a]One milligram of compound dissolved in 1.0 ml of physiological saline (containing 2.5% ethanol and 2.5% Tween-80) at room temperature.
[b]Completely dissolved at 37°C.
[c]Compound has a methyl group instead of hydrogen at 2-position.

et al. showed that benzimidazolium salts also follow a similar mechanism of action.[14] Therefore, quaternization of currently used antimicrobial drugs is one of the new strategies. For example, excellent antibacterial activity was obtained against some drug-resistant bacterial strains by the lipophilic quaternization of vancomycin. Additionally, it was also reported that permanent positive charge instead of secondary amines is essential for activity.[34] Therefore, among the results obtained in this study, the most promising ones are the comparable inhibitory effects of **3k** and **3l** with vancomycin against MRSA. Although detailed mechanistic studies are necessary, in light of the above information, we think that the compounds exhibit their antimicrobial activity by disturbing the bacterial membrane.

3 | CONCLUSION

In conclusion, catechol containing four imidazolium and eight benzimidazolium salts were synthesized and fully characterized by appropriate spectroscopic and physical techniques. Antimicrobial activities of all compounds were evaluated against four Gram-negative and three Gram-positive bacteria and two fungal strains. Especially, some of the benzimidazolium salts exhibited remarkable inhibitory activity against the growth of bacterial and fungal strains. We believe that some of the reported compounds deserve further mechanistic and clinical investigation due to their advantages such as facile synthesis, low cost, and high solubility in addition to remarkable antimicrobial activity.

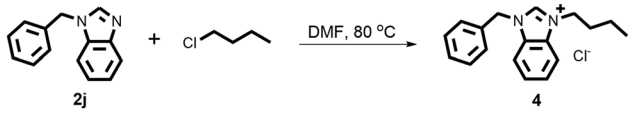


FIGURE 2 Structure of *N*-butyl-*N*-benzylbenzimidazolium chloride. DMF, dimethylformamide

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

The synthesis of imidazolium and benzimidazolium chlorides were carried out under open-air conditions. 1-Alkylbenzimidazole derivatives were synthesized according to the literature.[35] Alkyl chlorides, benzyl chloride derivatives, 1-methylimidazole, 1, 2-dimethylimidazole, 1-vinylimidazole, 1-butylimidazole, 2-chloro-3′, 4′-dihydroxyacetophenone, and solvents were commercially provided by Sigma-Aldrich (Istanbul, Turkey) and used without further purification. Melting points were determined in open capillary tubes by Electrothermal 9200 melting point apparatus. IR spectra were recorded in attenuated total reflection sampling accessory with PerkinElmer Spectrum 100 spectrophotometer. The C, H, and N elemental analyses were determined by LECO CHNS-932 elemental analyzer. LC–MS spectra were recorded in an Agilent 1100 LC/MSD SL mass spectrometer equipped with an electrospray ion source. ^{1}H and ^{13}C NMR spectra were recorded using Bruker Ascend™ 400 Avance III HD operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). NMR

TABLE 2 Minimal inhibitory concentrations (μg/ml) of compounds

Compound	Bacteria							Fungi	
	Gram negative				Gram positive				
	Escherichia coli	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Staphylococcus aureus* (MRSA)	*Enterococcus faecalis*	*Candida albicans*	*Candida glabrata*
1	200	400	400	200	200	200	200	200	100
2j	200	400	400	200	400	400	400	200	100
3a	200	200	100	100	100	25	100	50	50
3b	200	200	100	100	100	50	100	100	100
3c	100	100	100	100	50	50	50	50	50
3d	100	100	100	100	50	50	25	50	50
3e	25	50	25	12.5	12.5	25	12.5	12.5	6.25
3f	25	25	25	25	25	25	12.5	12.5	12.5
3g	50	100	100	50	50	50	50	50	50
3h	50	100	100	50	50	50	50	50	50
3i	100	100	100	100	50	50	25	50	50
3j	25	25	25	25	6.25	25	6.25	6.25	6.25
3k	50	50	25	25	12.5	12.5	12.5	12.5	12.5
3l	25	25	25	25	6.25	12.5	6.25	6.25	6.25
4	200	200	200	100	200	200	100	100	100
Ampicillin	3.12	–	–	1.56	1.56	–	1.56	–	–
Amikacin	–	1.56	3.12	1.56	–	–	–	–	–
Vancomycin	–	–	–	–	–	3.12	–	–	–
Fluconazole	–	–	–	–	–	–	–	6.25	3.12

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

multiplicities were abbreviated as follows: br, broad; s, singlet; d, doublet; t, triplet; quin, quintet; sex, sextet; m, multiplet.

The original spectra of the investigated compounds are provided as Supporting Information, as are their InChI keys together with some biological activity data.

4.1.2 | General procedure for the synthesis of the imidazolium and benzimidazolium chlorides 3a–l

A solution of 2-chloro-3′,4′-acetophenone (5 mmol) and corresponding *N*-alkylimidazole or *N*-alkylbenzimidazole (5 mmol) in 10 ml of CH_3CN was stirred at 82°C for 48 hr. After this period of time, the mixture was allowed to cool to ambient temperature and the precipitated crude product was collected by filtration, washed with diethyl ether (3 × 10 ml), and dried under vacuum.

*1-Methyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}imidazolium chloride (**3a**)*

White solid, yield: 1.2 g (89%), m.p.: 250–251°C. Elemental analysis, calculated for $C_{12}H_{13}ClN_2O_3$: C: 53.64, H: 4.88, N: 10.43; found: C: 53.93, H: 5.09, N: 10.17. LC–MS, calculated for cationic part, $C_{12}H_{13}N_2O_3$, *m/z*: 233.1; found: 233.1. IR (υ_{max}, cm^{-1}): 3,322 (O–H), 3,080 (Ar–H), 1,678 (C=O), 1,524 (C=N). ^{1}H NMR (400 MHz, dimethyl sulfoxide (DMSO)-d_6, 298 K): δ 10.39 (br, 1H, –O**H**), 9.73 (br, 1H, –O**H**), 9.15 (s, 1H, –NC**H** N–), 7.78 (s, 1H, Ar**H**), 7.72 (s, 1H, Ar**H**), 7.47 (m, 2H, Ar**H** and $\mathbf{H}_{imidazole}$), 7.01–6.99 (m, 1H, $\mathbf{H}_{imidazole}$), 5.96 (s, 2H, –NC$\mathbf{H}_2$CO–), 3.95 (s, 3H, –NC$\mathbf{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.8 (**C**=O), 152.6, 146.1, 138.2 (–N**C**HN–), 125.8, 124.4, 123.6, 122.1, 116.0, 115.4, 55.2 (–N**C**H_2CO–), 36.4 (–N**C**H_3).

*1-Methyl-2-methyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}imidazolium chloride (**3b**)*

White solid, yield: 1.1 g (78%), m.p.: 245–247°C. Elemental analysis, calculated for $C_{13}H_{15}ClN_2O_3$: C: 55.23, H: 5.35, N: 9.91; found: C: 55.47, H: 5.51, N: 9.63. LC–MS, calculated for cationic part, $C_{13}H_{15}N_2O_3$, *m/z*: 247.1; found: 247.1. IR (υ_{max}, cm^{-1}): 3,511 (O–H), 2,953 (C–H), 1,679 (C=O), 1,520 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 9.92 (br, 2H, 2 × O**H**), 7.72 (s, 1H, Ar**H**), 7.62 (s, 1H, Ar**H**), 7.48 (m, 2H, Ar**H** and $\mathbf{H}_{imidazole}$), 7.03–7.01 (m, 1H, $\mathbf{H}_{imidazole}$), 5.97 (s, 2H, –NC$\mathbf{H}_2$CO–), 3.86 (s, 3H, –NC$\mathbf{H}_3$), 2.52 (–NC(C$\mathbf{H}_3$)N–). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.6 (**C**=O), 152.6, 146.2

(–N**C**(CH_3)N–), 146.1, 125.8, 122.8, 122.6, 122.3, 115.9, 115.7, 54.3 (–N**C**H_2CO–), 35.4 (–N**C**H_3), 9.7 (–NC(**C**H_3)N–).

*1-Vinyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}imidazolium chloride (**3c**)*

White solid, yield: 1.0 g (71%), m.p.: 220–222°C. Elemental analysis, calculated for $C_{13}H_{13}ClN_2O_3$: C: 55.62, H: 4.67, N: 9.98; found: C: 55.86, H: 4.87, N: 9.66. LC–MS, calculated for cationic part, $C_{13}H_{13}N_2O_3$, *m/z*: 245.1; found: 245.0. IR (υ_{max}, cm^{-1}): 3,337 (O–H), 2,999 (C–H), 1,677 (C═O), 1,517 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.46 (br, 1H, –O**H**), 9.73 (br, 1H, –O**H**), 9.60 (s, 1H, –NC**H**N–), 8.35 (s, 1H, Ar**H**), 7.89 (s, 1H, Ar**H**), 7.51–7.47 (m, 3H, Ar**H**, $\mathbf{H}_{imidazole}$, and –NC**H**═CH_2), 7.02–7.00 (m, 1H, $\mathbf{H}_{imidazole}$), 6.07–6.02 (m, 3H, –NC$\mathbf{H}_2$CO– and –NCH═C$\mathbf{H}_2$), 5.46 (d, 1H, *J* = 8.0 Hz, NCH═C$\mathbf{H}_2$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.4 (**C**═O), 152.7, 146.2, 137.2 (–N**C**HN–), 129.3, 125.7, 125.4, 122.1, 118.9, 116.0, 115.5, 109.4, 55.6 (–N**C**H_2CO–).

*1-Butyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}imidazolium chloride (**3d**)*

White solid, yield: 1.4 g (90%), m.p.: 166–168°C. Elemental analysis, calculated for $C_{15}H_{19}ClN_2O_3$: C: 57.97, H: 6.16, N: 9.01; found: C: 58.25, H: 6.22, N: 8.72. LC–MS, calculated for cationic part, $C_{15}H_{19}N_2O_3$, *m/z*: 275.1; found: 275.1. IR (υ_{max}, cm^{-1}): 3,295 (O–H), 2,871 (C–H), 1,677 (C═O), 1,518 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.42 (br, 1H, –O**H**), 9.76 (br, 1H, –O**H**), 9.27 (s, 1H, –NC**H**N–), 7.90 (s, 1H, Ar**H**), 7.75 (s, 1H, Ar**H**), 7.47–7.45 (m, 2H, Ar**H** and $\mathbf{H}_{imidazole}$), 7.02–7.00 (m, 1H, $\mathbf{H}_{imidazole}$), 5.96 (s, 2H, –NC$\mathbf{H}_2$CO–), 4.29 (t, 2H, *J* = 6.6 Hz, –NC$\mathbf{H}_2$$CH_2$–), 1.81 (quin, 2H, *J* = 6.9 Hz, –NCH_2C$\mathbf{H}_2$–), 1.29 (sex, 2H, *J* = 7.1 Hz, –C$\mathbf{H}_2$$CH_3$), 0.92 (t, 3H, *J* = 7.1 Hz, –$CH_2$$CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.7 (**C**═O), 152.6, 146.2, 137.9 (–N**C**HN–), 125.8, 124.6, 122.4, 122.0, 116.0, 115.5, 55.3 (–N**C**H_2CO–), 49.1 (–N**C**$H_2$$CH_2$–), 31.9 (–$NCH_2$**C**$H_2$–), 19.2 (–**C**$H_2$$CH_3$), 13.8 (–$CH_2$$CH_3$).

*1-Methyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimidazolium chloride (**3e**)*

White solid, yield: 1.2 g (75%), m.p.: 252–253°C. Elemental analysis, calculated for $C_{16}H_{15}ClN_2O_3$: C: 60.29, H: 4.74, N: 8.79; found: C: 60.62, H: 4.92, N: 8.70. LC–MS, calculated for cationic part, $C_{16}H_{15}N_2O_3$, *m/z*: 283.1; found: 283.1. IR (υ_{max}, cm^{-1}): 3,152 (O–H), 3,113 (Ar–H), 1,701 (C═O), 1,513 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.48 (br, 1H, –O**H**), 9.80 (s, 1H, –NC**H**N–), 9.71 (br, 1H, –O**H**), 8.08–8.01 (m, 2H, Ar**H**), 7.73–7.65 (m, 2H, Ar**H**), 7.58–7.52 (m, 2H, Ar**H**), 7.05 (d, 1H, *J* = 8.3 Hz, Ar**H**), 6.33 (s, 2H, –NC$\mathbf{H}_2$CO–), 4.20 (s, 3H, –N**C**$\mathbf{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.7 (**C**═O), 152.7, 146.1, 144.3 (–N**C**HN–), 132.3, 131.9, 127.1, 126.9, 125.9, 122.4, 116.0, 115.7, 114.3, 114.1, 53.0 (–N**C**H_2CO–), 33.9 (–N**C**H_3).

*1-Methyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}-5,6-dimethylbenzimidazolium chloride (**3f**)*

White solid, yield: 1.2 g (69%), m.p.: 290–292°C. Elemental analysis, calculated for $C_{18}H_{19}ClN_2O_3$: C: 62.34, H: 5.52, N: 8.08; found: C: 62.57, H: 5.60, N: 7.82. LC–MS, calculated for cationic part, $C_{18}H_{19}N_2O_3$, *m/z*: 311.1; found: 311.2. IR (υ_{max}, cm^{-1}): 3,143 (O–H), 3,037 (Ar–H), 1,676 (C═O), 1,519 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.48 (br, 1H, –O**H**), 9.71 (br, 1H, –O**H**), 9.64 (s, 1H, –NC**H**N–), 7.84–7.81 (m, 2H, Ar**H**), 7.57–7.51 (m, 3H, Ar**H**), 7.06–7.03 (m, 1H, Ar**H**), 6.25 (s, 2H, –NC$\mathbf{H}_2$CO–), 4.14 (s, –N**C**$\mathbf{H}_3$), 2.44 (s, 3H, Ar**C**$\mathbf{H}_3$), 2.38 (s, 3H, Ar**C**$\mathbf{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.7 (**C**═O), 152.7, 146.1, 143.0 (–N**C**HN–), 136.8, 136.0, 130.8, 130.4, 125.9, 122.4, 116.0, 115.7, 113.7, 113.5, 52.9 (–N**C**H_2CO), 33.8 (–N**C**H_3), 20.4 (Ar**C**H_3).

*1-Allyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimidazolium chloride (**3g**)*

White solid, yield: 1.1 g (64%), m.p.: 177–178°C. Elemental analysis, calculated for $C_{18}H_{17}ClN_2O_3$: C: 62.70, H: 4.97, N: 8.12; found: C: 62.93, H: 5.19, N: 7.90. LC–MS, calculated for cationic part, $C_{18}H_{17}N_2O_3$, *m/z*: 309.1; found: 309.1. IR (υ_{max}, cm^{-1}): 3,360 (O–H), 3,064 (Ar–H), 1,669 (C═O), 1,533 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.41 (br, 1H, –O**H**), 9.80 (s, 1H, –NC**H**N–), 9.65 (br, 1H, –O**H**), 8.00–7.97 (m, 2H, Ar**H**), 7.63–7.57 (m, 2H, Ar**H**), 7.49–7.44 (m, 2H, Ar**H**), 6.98–6.95 (m, 1H, Ar**H**), 6.26 (s, 2H, –NC$\mathbf{H}_2$CO–), 6.09 (m, 1H, –NCH_2C**H**═CH_2), 5.36–5.30 (m, 2H, –NCH_2CH═C$\mathbf{H}_2$), 5.26–5.24 (m, 2H, –NC$\mathbf{H}_2$CH═CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.6 (**C**═O), 152.7, 146.1, 144.1 (–N**C**HN–), 132.6, 131.6, 131.1, 127.3, 127.1, 125.8, 122.4, 120.8, 116.0, 115.8, 114.5, 114.3, 53.1 (–N**C**H_2CO–), 49.3 (–NCH_2CH═CH_2).

*1-Butyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimidazolium chloride (**3h**)*

White solid, yield: 1.5 g (83%), m.p.: 250–252°C. Elemental analysis, calculated for $C_{19}H_{21}ClN_2O_3$: C: 63.24, H: 5.87, N: 7.76; found: C: 63.56, H: 5.97, N: 7.60. LC–MS, calculated for cationic part, $C_{19}H_{21}N_2O_3$, *m/z*: 325.2; found: 325.1. IR (υ_{max}, cm^{-1}): 3,244 (O–H), 2,934 (C–H), 1,677 (C═O), 1,521 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.47 (br, 1H, –O**H**), 9.90 (s, 1H, –NC**H**N–), 9.71 (br, 1H, –O**H**), 8.16 (d, 1H, *J* = 8.2 Hz, Ar**H**), 8.05 (d, 1H, *J* = 8.2 Hz, Ar**H**), 7.73–7.65 (m, 2H, Ar**H**), 7.58–7.52 (m, 2H, Ar**H**), 7.04 (d, 1H, *J* = 8.2 Hz, Ar**H**), 6.31 (s, 2H, –NC$\mathbf{H}_2$CO–), 4.63 (t, 2H, *J* = 7.1 Hz, –NC$\mathbf{H}_2$$CH_2$–), 1.92 (quin, 2H, *J* = 7.4 Hz, –NCH_2C$\mathbf{H}_2$–), 1.36 (sex, 2H, *J* = 7.5 Hz, –C$\mathbf{H}_2$$CH_3$), 0.94 (t, 3H, *J* = 7.3 Hz, –CH_2C$\mathbf{H}_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 298 K): δ 189.6 (**C**═O), 152.7, 146.1, 143.9 (–N**C**HN–), 132.5, 131.2, 127.2, 127.0, 125.8, 122.4, 116.0, 115.7, 114.4, 114.2, 53.0 (–N**C**H_2CO–), 47.0 (–N**C**$H_2$$CH_2$–), 31.0 (–$NCH_2$**C**$H_2$–), 19.5 (–**C**$H_2$$CH_3$), 13.8 (–$CH_2$**C**$H_3$).

*1-Decyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimidazolium chloride (**3i**)*

White solid, yield: 1.3 g (58%), m.p.: 169–172°C. Elemental analysis, calculated for $C_{25}H_{33}ClN_2O_3$: C: 67.48, H: 7.48, N: 6.30; found: C: 67.70, H: 7.66, N: 6.13. LC–MS, calculated for cationic part, $C_{25}H_{33}N_2O_3$, *m/z*: 409.2; found: 409.3. IR (υ_{max}, cm^{-1}): 3,204 (O–H), 3,061 (Ar–H), 2,920 (C–H), 1,676 (C═O), 1,520 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ 10.48 (br, 1H, –O**H**), 9.91 (s, 1H, –NC**H**N–), 9.71 (br, 1H, –O**H**),

8.16 (d, 1H, *J* = 8.0 Hz, Ar**H**), 8.05 (d, 1H, *J* = 8.0 Hz, Ar**H**), 7.72–7.65 (m, 2H, Ar**H**), 7.58–7.52 (m, 2H, Ar**H**), 7.05 (d, 1H, *J* = 8.2 Hz, Ar**H**), 6.32 (s, 2H, –NC**H**$_2$CO–), 4.62 (t, 2H, *J* = 7.0 Hz, –NC**H**$_2$–), 1.93 (m, 2H, –NCH$_2$C**H**$_2$–), 1.33–1.23 (m, 14H, –NCH$_2$CH$_2$(C**H**$_2$)$_7$–), 0.85 (t, 3H, *J* = 7.0 Hz, –N(CH$_2$)$_9$C**H**$_3$). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 298 K): *δ* 189.6 (**C**=O), 152.7, 146.2, 143.9 (–N**C**HN–), 132.5, 131.2, 127.2, 127.0, 125.8, 122.4, 116.0, 115.8, 114.4, 114.2, 53.0 (–N**C**H$_2$CO–), 10 carbons of decyl chain are as follows: 47.3, 31.8, 29.33, 29.31, 29.1, 29.0, 28.9, 26.1, 22.6, 14.4.

*1-Benzyl-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimdazolium chloride (**3j**)*

White solid, yield: 1.8 g (91%), m.p.: 276–277°C. Elemental analysis, calculated for $C_{22}H_{19}ClN_2O_3$: C: 66.92, H: 4.85, N: 7.09; found: C: 67.17, H: 5.07, N: 6.90. LC–MS, calculated for cationic part, $C_{22}H_{19}N_2O_3$, *m/z*: 359.1; found: 359.1. IR (υ_{max}, cm^{-1}): 3,198 (O–H), 3,003 (Ar–H), 1,676 (C=O), 1,520 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 298 K): *δ* 11.00–9.00 (br, 2H, 2 × O**H**), 9.97 (s, 1H, –NC**H**N–), 7.99–7.96 (m, 2H, Ar**H**), 7.59–7.55 (m, 2H, Ar**H**), 7.49–7.45 (m, 4H, Ar**H**), 7.38–7.29 (m, 3H, Ar**H**), 6.99–6.96 (m, 1H, Ar**H**), 6.27 (s, 2H, –NC**H**$_2$CO–), 5.85 (s, 2H, –NC**H**$_2$C$_6$H$_5$). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 298 K): *δ* 189.6 (**C**=O), 152.8, 146.2, 144.2 (–N**C**HN–), 134.5, 132.7, 130.4, 129.5, 129.3, 128.8, 127.3, 127.1, 125.8, 122.4, 116.0, 115.8, 114.6, 114.3, 53.2 (–N**C**H$_2$CO–), 50.4 (–N**C**H$_2$C$_6$H$_5$).

*1-(3-Methylbenzyl)-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}bezimidazolium chloride (**3k**)*

White solid, yield: 1.7 g (83%), m.p.: 227–230°C. Elemental analysis, calculated for $C_{23}H_{21}ClN_2O_3$: C: 67.56, H: 5.18, N: 6.85; found: C: 67.66, H: 5.30, N: 6.73. LC–MS, calculated for cationic part, $C_{23}H_{21}N_2O_3$, *m/z*: 373.2; found: 373.2. IR (υ_{max}, cm^{-1}): 3,172 (O–H), 2,909 (C–H), 1,675 (C=O), 1,520 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 298 K): *δ* 10.48 (s, 1H, –O**H**), 9.74 (s, 2H, –O**H** and –NC**H**N–), 8.11–8.08 (m, 1H, Ar**H**), 8.04–8.01 (m, 1H, Ar**H**), 7.70–7.67 (m, 2H, Ar**H**), 7.56–7.51 (m, 2H, Ar**H**), 7.35–7.24 (m, 4H, Ar**H**), 7.06–7.03 (m, 1H, Ar**H**), 6.32 (s, 2H, –NC**H**$_2$CO–), 5.92 (s, 2H, –NC**H**$_2$C$_6$H$_4$–CH$_3$), 2.37 (s, 3H, ArC**H**$_3$). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 298 K): *δ* 189.7 (**C**=O), 152.7, 146.1, 144.3 (–N**C**HN–), 137.3, 132.7, 132.2, 131.4, 131.3, 129.5, 129.1, 127.4, 127.1, 127.0, 125.8, 122.4, 116.0, 115.7, 114.6, 114.4, 53.2 (–N**C**H$_2$CO–), 49.1 (–N**C**H$_2$C$_6$H$_4$–CH$_3$), 19.2 (Ar**C**H$_3$).

*1-(2,3,5,6-Tetramethylbenzyl)-3-{[1-(3,4-dihydroxyphenyl)ethan-1-one]-2-yl}benzimidazolium chloride (**3l**)*

White solid, yield: 1.8 g (80%), m.p.: 248–249°C. Elemental analysis, calculated for $C_{26}H_{27}ClN_2O_3$: C: 69.56, H: 5.61, N: 6.24; found: C: 69.77, H: 5.83, N: 6.10. LC–MS, calculated for cationic part, $C_{26}H_{27}N_2O_3$, *m/z*: 413.2; found: 412.3. IR (υ_{max}, cm^{-1}): 3,241 (O–H), 2,948 (C–H), 1,669 (C=O), 1,518 (C=N). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 298 K): *δ* 10.46 (br, 1H, –O**H**), 9.72 (br, 1H, –O**H**), 9.09 (s, 1H, –NC**H**N–), 8.30–8.26 (m, 1H, Ar**H**), 8.08–8.06 (m, 1H, Ar**H**), 7.80–7.69 (m, 2H, Ar**H**), 7.51–7.47 (m, 2H, Ar**H**), 7.15 (s, 1H, Ar**H**), 7.04–7.01 (m, 1H, Ar**H**), 6.19 (s, 2H, –NC**H**$_2$CO–), 5.83 (s, 2H, –NC**H**$_2$C$_6$H–(CH$_3$)$_4$), 2.26 (s, 6H, ArC**H**$_3$), 2.20 (s, 6H, ArC**H**$_3$). ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 298 K): *δ* 189.7 (**C**=O), 152.6, 146.1, 142.8 (–N**C**HN–), 134.9, 134.7, 133.4, 132.9, 131.6, 128.8, 127.4, 127.1, 125.8, 122.2, 116.0, 115.7, 114.5, 114.4, 53.1 (–N**C**H$_2$CO–), 46.4 (–N**C**H$_2$C$_6$H–(CH$_3$)$_4$), 20.6 (Ar**C**H$_3$), 15.8 (Ar**C**H$_3$).

4.2 | Biological assays

4.2.1 | Determination of the antimicrobial activities of the imidazolium and benzimidazolium chlorides

All the compounds were tested at a concentration of 1,000–1.56 μg/ml against the standard culture collections of the most frequently isolated strains (listed below) among the society and hospital-acquired infectious agents depending on the suggestions of Clinical Laboratory Standards Institute (CLSI) with the method of serial dilution using sterile 96-well microplate readers (PLT microtiter plate; ESP).[36] Ten milligrams of the compound was dissolved in 1,000 μl of DMSO to obtain a stock solution. Hundred microliters of the Müller–Hinton Broth (Merck 110293) was loaded to the test wells. Hundred microliters of the stock solution of our material was taken, and starting from the 1st to 10th well, serial dilutions were performed and the last two wells were used as control groups. Ten microliters of bacterial suspensions which were prepared according to the McFarland 0.5 turbidity threshold, were distributed to all samples including the control wells.[37] Orbital shaker (PST 60HL Thermo) was used for 5 min to mix bacteria and our compounds. The lid of the microplate was closed and it was incubated at 35°C for 18–20 hr. To check bacterial growth, culture from each well was streaked on Müller–Hinton Agar plate using a sterile plastic loop and incubated under the same conditions. A predilution of the concentration in which growth was observed was determined as MIC of that substance .[38–40] Antifungal activity was determined using Sabouraud Dextrose Broth and Agar (CM0147, CM0041; Oxoid) under the same conditions.[41] In addition to this, in our study, reference drugs for each group of bacteria and fungi were tested under the same conditions in which the compounds were tested.

4.2.2 | Bacterial strains

The bacterial strains used in this study were *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. aureus* MRSA ATCC 43300, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853, *A. baumannii* ATCC 19606.

4.2.3 | Fungal strains

C. glabrata ATCC 90030 and *C. albicans* ATCC 14053 were the fungal strains used in this study.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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