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Novel ammonium ionic liquids as scavengers for aromatic and heterocyclic amines: Conversion into new pharmacological agents

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ABSTRACT

The aim of our protocol is to develop new simple, economic and efficient scavengers for primary amines, due to their substantial adverse impacts on environment and human health. In this endeavor, we have designed, successfully synthesized and structurally characterized new salicylaldehyde-tri-^{n}butylammonium ionic liquids which were investigated as scavengers for diverse aromatic and heterocyclic primary amines in the synthesis of new pharmacologically relevant candidates, imines scavenging product, via Schiff-base-scavenging reaction. The new scavengers exhibited good capture efficiency and can be easily regenerated and reused. The advantages of our scavengers over polymer-supported scavengers are the simplicity, shorter reaction time and real-time monitoring of a model reaction. The biocidal and antitumor activities of the scavenging products revealed a moderate to excellent broad-spectrum antibacterial efficacy, low activity or inactivity as fungicides and different levels of cytotoxicity (weak to excellent) against human breast carcinoma (MCF-7) cells.

1. Introduction

Aromatic and heterocyclic amines, notorious environmental pollutants, are often released into the environment as industrial effluents from epoxy and polyurethane polymers [1], textile, leather and dyestuffs, plastics, pesticides, photographic and pharmaceutical industries [2] or as the breakdown products of herbicides [3]. Skin contact, ingestion and inhalation exposure to aromatic amines even at very low doses is suspected to result in carcinogenicity [4]. Moreover, aromatic amines become a source of serious social and hygienic problems as notorious environmental pollutants [5]. Therefore, the scavenging of aromatic amines from industrial effluents for both healthcare reasons and reducing their emissions into the environment is a topic of great concern.

Scavengers are designed materials that can effectively sweep or quench particular undesirable substances or byproducts form the reaction mixture and industrial effluents. Polymer-supported materials are the most commonly used scavengers due to simplicity and ease of their removing from scavenging area by simple filtration process to obtain pure product, thus avoiding tedious chromatography purification [6]. However, these traditional polymer-supported scavengers suffer from several drawbacks, including; (i) using excessive amount of scavenger due to its lower functional groups (responsible for scavenging) to the polymer ratio. (ii) Carrying out the polymer-based scavenging protocol in a biphasic system which diminishes the rate of scavenging process, due to imine formation on solid phase, as compared to that performed in a monophasic system. (iii) Depletion excessive amount of a suitable solvent as a scavenging medium to fulfill the swelling requirement of polymer-based scavengers. These obstacles limit the wide applications of traditional polymer-supported scavengers. Thus, various alternatives such as PEG-anchored [7], silica-based [8], fluorous-phase [9,10] and aqueous-phase [11] scavengers have been developed to replace them.

The unrivaled physicochemical features of ionic liquids (ILs) such as low melting point (mp < 100 °C) which give them a wide liquid range, negligible vapor pressure, nonflammability, excellent thermal and chemical stability, wide electrochemical window, high dual solubility in both polar and nonpolar solvents [12], have attracted the attention of many analytical chemists. These peculiar properties endow ILs several analytical applications like separation process, MALDI-MS matrix, quartz crystal microbalance sensors and designer solvent in liquid/liquid extractions, purification processes, and synthetic organic chemistry as well as electroanalysis [13]. Recently, amine- [14] and pH-sensing applications [15] of ILs-based architectures have been addressed.

However, to the best of our knowledge, scavengers based on salicylaldehyde ionic liquids (Sal-ILs) with amine-dependent morphological response have not yet been reported.

In the last two decades, a great attention has been paid to the development of new Schiff bases due to their facile synthesis, marvelous structural and electronic features and they have been well documented as smart materials for potential applications in many fields including

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pharmaceutical [16], magnetism [17], luminescence [18], optical [19] and catalysis [20]. Interestingly, based on our previous work, Schiff bases bearing ionic liquids compartments exhibited significant antimicrobial [21], anticancer [21c,22] and antibiofouling [23] efficacies so that they may offer promising pharmacological candidates. Moreover, ionic *o*-aminothiophenol-based Schiff base demonstrated a remarkable fluorescence sensing of Ca(II) ions [24].

Inspired by this literature survey, we aimed herein to investigate the efficacy of new Sal-ILs probes (see Fig. 1) in hope that we develop new promising simple and efficient amine scavengers smart materials. The preference of our proposed salicylaldehyde ammonium ionic liquid-based scavenger over other imidazolium and pyridinium ionic liquid-functionalized scavengers stems also from an economic point of view, as ammonium-based ionic liquids (AILs) are less expensive than imidazolium and pyridinium ones. Furthermore, the dual function of *o*-hydroxy group in: (i) Stabilization of imines scavenging products via intramolecular hydrogen bonding, as a result of which enhancement of scavenging efficacy. (ii) Promoting the hydrolysis of scavenging products under either acidic or basic conditions to regenerate the parent scavenger, and thus ease of scavenger recovery.

2. Experimental

2.1. Materials

Chemicals were obtained from the following suppliers and used without further purification: 3-chlorosalicylaldehyde (ClSal), tri-*n*-butylamine ($^{n}Bu_3N$), hexafluoro-phosphoric acid aqueous solution ~55 wt.% (HPF_6) 3-methyl-2-aminopyridine (**AP**), 2-aminothiophenol (**ATP**), *p*-toluidine (***p*-Tol**), anthranilic acid (**Anth**) and 2 6-diisopropylaniline (**DIPA**) (Sigma–Aldrich), paraformaldehyde ($(CH_2O)_n$) (Roth)) and anhydrous zinc chloride ($ZnCl_2$) (Grüssing GmbH).

2.2. Instrumentation

Melting points were measured using a BÜCHI Melting point B-540 apparatus; all melting points were measured in open glass capillaries and are uncorrected. FT-IR spectra were recorded on a BRUKER Tensor-37 FT-IR spectrophotometer in the range 400–4000 cm^{-1} as KBr disc in the 4000–550 cm^{-1} region with 2 cm^{-1} resolution. For signal intensities the following abbreviations were used: br (broad), sh (sharp), w (weak), m (medium), s (strong), vs (very strong). NMR-spectra were obtained with a Bruker Avance DRX200 (200 MHz for ^{1}H) or Bruker AvanceDRX500 (125, 202 and 470 MHz for ^{13}C, ^{31}P and ^{19}F respectively) spectrometer with calibration to the residual proton solvent signal in DMSO-d_6 (^{1}H NMR: 2.52 ppm, ^{13}C NMR: 39.5 ppm), $CDCl_3$ (^{1}H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm) against TMS ($\delta = 0.00$ ppm) for ^{1}H and ^{13}C, 85% phosphoric acid ($\delta = 0.00$ ppm) for ^{31}P and $CFCl_3$ ($\delta = 0.00$ ppm) for ^{19}F NMR. Multiplicities of the signals were specified as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The mass spectra of the synthesized Sal-ILs were acquired in the linear mode for positive ions on UHR-QTOF maXis 4G (Bruker Daltonics) and Bruker Ultraflex MALDI-TOF instrument equipped with a 337 nm nitrogen laser pulsing at a repetition rate of 10 Hz. The 2+ charge assignment of ions in ESI-MS was confirmed by the $m/z = 0.5$ difference between the isotope peaks (x, x + 1, x + 2). Peaks with chlorine showed the isotope ratio $^{35/37}Cl = 75.8{:}24.2$. For the mass spectral assignment: Peaks are based on ^{12}C with 12.0000 Da, ^{35}Cl with 34.968 Da. All instruments are available in the lab of Prof. Dr. Christoph Janiak, Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine Universität Düsseldorf.

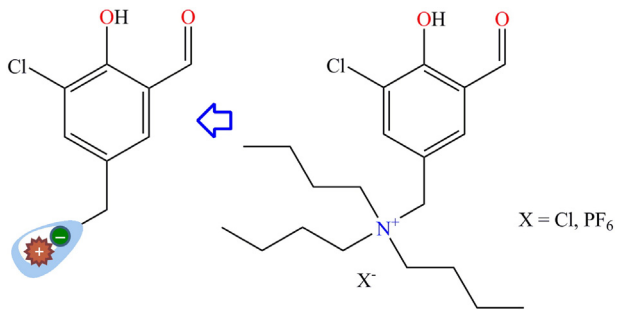


Fig. 1. Chlorosalicylaldehyde ionic liquids ClSal-($^{n}Bu_3N^{+}X^{-}$) (**2**a,b) used in this work.

2.3. Synthesis of 5-chloromethyl-3-chloro-2-hydroxybenzaldehyde (CM(Cl)Sal, 1)

Compound **1** was synthesized from the corresponding ClSal according to the modified chloromethylation procedure [21a]. It was isolated as white needles (65% yield). FTIR (ATR, cm^{-1}): 3240 (m, br, $\nu_{(O-H)}$), 3120 (m, br, $\nu_{(C-H)asym}$, Ar), 3050 (m, br, $\nu_{(C-H)sym}$, Ar), 2876 (m, sh, $\nu_{(CH2)}$), 1659 (vs, sh, $\nu_{(C=O)}$), 1578, 1489, 1437 (s, sh, $\nu_{(C=CAr+\ C\text{-}Hbend)}$), 1252 (s, sh, $\nu_{(C-Cl)}$, CH_2Cl), 1150 (s, sh, $\nu_{(HC=C)}$, Ar), 770 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 11.07 (s, 1H) 9.90 (s, 1H), 7.65 (s, H), 7.38 (s, 1H), 4.63 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 193.58, 161.32, 137.14, 134.26, 131.48, 129.47, 126.58 and 47.77.

2.4. Synthesis of formyl-chloro-hydroxybenzyl)-tri-^{n}butylammonium ionic liquids (ClSal-($^{n}Bu_3N^{+}X^{-}$), 2a,b)

A solution of CM(Cl)Sal (**1**) (4.01 g, 19.55 mmol) in dry toluene (100 mL) was added dropwise by syringe pump to a vigorously stirred solution of $^{n}Bu_3N$ (4.63 mL, 19.50 mmol) in dry toluene (25 mL) at room temperature was over 30 min under nitrogen atmosphere. Then, the resulting solution was stirred under nitrogen atmosphere at 60 °C for 24 h. After cooling, the isolated product was washed intensively with dry toluene (5 × 10 mL), several with ether (5 × 5 mL) to remove the unreacted materials, and dried under vacuum to give 3-(3-formyl-5-chloro-4-hydroxybenzyl)-tri-^{n}butylammonium chloride (**2**a) which used for the following preparations without further purification. It was obtained as a yellowish white solid, Yield (93%), mp: 66–67 °C. FTIR (KBr, cm^{-1}): 3421 (m, br, $\nu_{(O-H)}$), 2850 (m, sh, $\nu_{(C-H)}$, aldehyde), 1678 (vs, sh, $\nu_{(C=O)}$), 1612, 1444, 1373 (s, sh, $\nu_{(C=CAr+\ C\text{-}Hbend)}$), 1278 (s, sh, $\nu_{(Ar-O)}$), 772 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 10.74 (s, 1H), 10.08 (s, 1H), 7.81 (s, 1H), 7.48 (s, 1H), 4.57 (s, 2H), 3.85 (t, $J_1 = J_2 = 7.06$ Hz, 6H), 1.98–1.87 ($m_{(5)}$, 6H), 1.51–1.38 ($m_{(6)}$, 6H), 1.07 (t, $J_1 = J_2 = 6.8$ Hz, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 194.56, 162.97, 140.21, 136.32, 131.68, 129.73, 127.24, 66.11, 59.48, 24.12, 20.34 and 14.06. Positive mode ESI-MS: *m/z* calcd for $C_{20}H_{33}Cl_2NO_2$ (390.39), found 354.90, $[M - Cl^{-}]^{+}$ a.m.u.

2.5. Anion metathesis: synthesis of 3-(3-formyl-5-chloro-4-hydroxybenzyl)-tri-^{n}butylammonium hexafluorophosphates (2b)

An aqueous solution of HPF_6 (~55 wt.%, 2.7 mL, 17.62 mmol) was added portionwise to a solution of **2**a (4.59 g, 11.75 mmol) in milli-Q water (100 mL) with vigorous stirring, while the reaction mixture was cooled in an ice-bath, over 1 h. After the HPF_6 addition was completed, the reaction mixture was stirred at room temperature for 24 h. Then, the isolated solid product was filtered, washed with milli-Q water (to remove excess HPF_6 solution and any water-soluble impurities) until the washing effluent becomes neutral. The final product (**2**b) was dried under vacuum at 40 °C for 24 h. **2**b was obtained as a white solid, Yield (90%), mp: 95–97 °C. FTIR (KBr, cm^{-1}): 3427 (m, br, $\nu_{(O-H)}$), 2850 (m, sh, $\nu_{(C-H)}$, aldehyde), 1656 (vs, sh, $\nu_{(C=O)}$), 1580, 1452, 1393 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1276 (s, sh, $\nu_{(Ar-O)}$) 821 (vs, sh, $\nu_{(PF6^{-})str}$), 760 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 556 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR

(200 MHz, DMSO-d_6) δ (ppm): 10.68 (s, 1H), 10.16 (s, 1H), 7.71 (s, 2H), 7.56 (m, 1H), 7.43 (d, J = 12.9 Hz, 1H), 4.37 (s, 2H), 3.86 (t, $J_1 = J_2$ = 7.02, 6H), 1.99–1.89 ($m_{(5)}$, 6H), 1.53–1.42 ($m_{(6)}$, 6H), 1.09 (t, $J_1 = J_2$ = 6.8 Hz, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 190.23, 166.20, 157.52, 138.91, 132.16, 130.03, 128.33, 126.87, 125.45, 66.78, 59.13, 24.23, 20.02 and 14.10. ^{31}P NMR (202 MHz, DMSO-d_6): −159.41 to −117.34 ppm (septet, $^2J_{PF}$ = 711.17 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.83 to −64.80 ppm (doublet, $^1J_{PF}$ = 711.26 Hz). Positive mode ESI-MS: m/z calcd. for $C_{20}H_{33}ClF_6NO_2P$ (499.90), found 354.90, $[M\text{-}PF_6^-]^+$ a.m.u.

2.6. General procedure for scavenging of primary amine into ionic liquid-supported imines (3a–l)

Generally, a mixture of an ethanolic solution (30 mL) containing (9 mmol) of target amine and (10 mmol) of **2**a,b in the presence of catalytic amount of 0.1% acetic acid (0.5 mL) (pH = 5.78, which in the rang optimum pH for imine formation, 5.63–7.00 [25]) into a 100 mL round-bottomed (RB) flask was stirred for 5 h at 60 °C (the reaction progress was monitored by TLC). After completion of the reaction, the reaction mixture was cooled to room temperature and then allowed to stand for 30 min. Thereafter, the separated solid product was isolated by filtration, washed with ether (3 × 5 mL) and dried under vacuum. Samples of the isolated solids were recrystallized from proper solvent and characterized as follows;

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((3-methylpyridin-2-ylimino)methyl)benzyl)-ammonium chloride (3a): Yellow needles from methanol, Yield (82%), mp: 158–160 °C. FTIR (KBr, cm^{-1}): 3403 (vs, br, $\nu_{(O-H)}$), 1617 (s, sh, $\nu_{(C=N),}$ azomethine), 1568, 1443, 1398 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1277 (s, sh, $\nu_{(Ar-O)}$), 763 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.06 (s, 1H), 10.42 (s, 1H), 7.91 (s, br, 2H), 7.57 (s, 1H), 7.48 (s, 1H), 6.87–6.78 (m, 1H), 4.58 (s, 2H), 3.81 (t, $J_1 = J_2$ = 7.03 Hz, 6H), 1.87–1.79 ($m_{(5)}$, 6H), 1.49–1.38 ($m_{(6)}$, 6H), 0.98 (t, $J_1 = J_2$ = 7.0 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 162.39, 158.07, 153.55, 151.05, 146.62, 142.52, 140.65, 133.57, 130.87, 129.13, 126.92, 123.04, 114.15, 66.03, 59.13, 24.08, 19.99 and 14.11. Positive mode ESI-MS: m/z calcd for $C_{26}H_{39}Cl_2N_3O$ (480.51), found 445.00, $[M - Cl^-]^+$ a.m.u.

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((2-mercaptophenylimino)-methyl)benzyl)-ammonium chloride (3b): Brown powder from methanol, Yield (25%), mp: 188–189 °C. FTIR (KBr, cm^{-1}): 3407 (vs, br, $\nu_{(O-H)}$), 2610 (s, br, $\nu_{(S-H)}$), 1611 (s, sh, $\nu_{(C=N),}$ azomethine), 1476, 1443, 1397 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1283 (s, sh, $\nu_{(Ar-O)}$), 766 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.96 (s, 1H), 10.41 (s, 1H), 7.58–7.35 (m, 2H), 7.27 (s, 1H), 7.15–6.96 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 5.45 (s, 2H), 4.07 (s, 1H), 3.88 (t, $J_1 = J_2$ = 7.03 Hz, 6H), 1.90–1.80 ($m_{(5)}$, 6H), 1.51–1.39 ($m_{(6)}$, 6H), 1.05 (t, $J_1 = J_2$ = 7.0 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 162.97, 161.65, 158.29, 145.59, 143.38, 139.03, 134.35, 131.07, 129.58, 126.63, 122.03, 121.13, 117.99, 65.98, 59.01, 24.24, 20.04 and 13.99. Positive mode ESI-MS: m/z calcd. for $C_{26}H_{38}Cl_2N_2OS$ (497.56), found 462.10, $[M\text{-}Cl^-]^+$ a.m.u.

N-(3-((2-aminophenylthio)(hydroxy)methyl)-5-chloro-4-hydroxybenzyl)-N,N,N-triethyl-ammonium chloride (3c): Yellowish brown powder from chloroform, Yield (71%), mp: 68–69 °C. FTIR (KBr, cm^{-1}): 3476, 3433 (s, br, $\nu_{(NH2)}$), 3353 (s, br, $\nu_{(O-H)}$), 1543, 1463, 1390 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1279 (s, sh, $\nu_{(Ar-O)}$), 765 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 605 (m, sh, $\nu_{(C-S)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.21 (s, 1H), 7.24–6.93 (m, 2H), 6.73 (dd, J = 8.1, 1.3 Hz, 2H), 6.43 (ddd, J = 7.7, 7.1, 1.3 Hz, 2H), 6.28 (s, 2H), 5.65 (s, 1H), 4.04 (s, 1H), 3.76 (t, $J_1 = J_2$ = 7.01 Hz, 6H), 1.83–1.73 ($m_{(5)}$, 6H), 1.40–1.38 ($m_{(6)}$, 6H), 0.98 (t, $J_1 = J_2$ = 6.9 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 156.29, 149.19, 139.13, 132.28, 130.89, 129.45, 128.91, 128.13, 125.72, 119.78, 116.01, 114.74, 78.35, 68.03, 60.12, 23.93, 21.11 and 14.76. Positive mode ESI-MS: m/z calcd for $C_{26}H_{40}Cl_2N_2O_2S$ (515.58), found 480.10, $[M - Cl^-]^+$ a.m.u.

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((p-tolylimino)methyl)-benzyl)ammonium chloride (3d): Faint yellow needles from methanol, Yield (85%), mp: 258 °C. FTIR (KBr, cm^{-1}): 3450 (vs, br, $\nu_{(O-H)}$), 1621 (s, sh, $\nu_{(C=N),}$ azomethine), 1478, 1443, 1398 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1289 (s, sh, $\nu_{(Ar-O)}$), 767 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.08 (s, 1H), 10.65 (s, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.97–6.94 (m, 2H), 4.57 (s, 2H), 3.83 (t, $J_1 = J_2$ = 7.00 Hz, 6H), 1.91–1.83 ($m_{(5)}$, 6H), 1.50–1.40 ($m_{(6)}$, 6H), 1.01 (t, $J_1 = J_2$ = 6.9 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 160.91, 158.08, 150.23, 144.84, 137.20, 133.31, 130.56, 129.92, 127.15, 124.06, 123.13, 122.65, 119.99, 65.25, 57.73, 23.99, 20.10 and 14.03. Positive mode ESI-MS: m/z calcd for $C_{27}H_{40}Cl_2N_2O$ (479.53), found 444.07, $[M\text{-}Cl^-]^+$ a.m.u.

N-(3-((2-carboxy-5-chlorophenylimino)methyl)-4-hydroxybenzyl)-N,N,N-tri-^{n}butylammon-ium chloride (3e): Yellowish orange powder from ethanol, yield (71%), mp: 150–151 °C. FTIR (KBr, cm^{-1}): 3434 (vs, br, $\nu_{(O-H)}$), 1659 (s, sh, $\nu_{(C=O),}$ carbonyl), 1625 (s, sh, $\nu_{(C=N),}$ azomethine), 1577, 1449, 1397 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1281 (s, sh, $\nu_{(Ar-O)}$), 768 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 10.25 (s, 1H), 8.88 (s, 1H), 8.21–8.02 (m, 2H), 7.83 (dt, J = 24.8, 7.7 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.11 (s, 1H), 4.39 (s, 2H), 3.25 (t, $J_1 = J_2$ = 7.3 Hz, 6H), 1.80–1.69 ($m_{(5)}$, 6H), 1.39–1.27 ($m_{(6)}$, 6H), 0.92 (t, $J_1 = J_2$ = 7.1 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 191.02, 169.91, 159.92, 150.48, 135.26, 134.32, 133.65, 131.64, 131.09, 130.22, 128.72, 126.81, 122.12, 117.57, 67.13, 59.75, 24.98, 20.02 and 14.21. Positive mode ESI-MS: m/z calcd for $C_{27}H_{38}Cl_2N_2O_3$ (509.51), found 474.00, $[M\text{-}Cl^-]^+$ a.m.u.

N-(3-((5-chloro-2,6-diisopropylphenylimino)methyl)-4-hydroxybenzyl)-N,N,N-tri-^{n}butyl ammonium chloride (3f): Yellow crystals from ethanol, Yield (69%), mp: 270–271 °C. FTIR (KBr, cm^{-1}): 3426 (vs, br, $\nu_{(O-H)}$), 1625 (s, sh, $\nu_{(C=N),}$ azomethine), 1479, 1444, 1398 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1290 (s, sh, $\nu_{(Ar-O)}$), 768 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.75 (s, 1H), 10.01 (s, 1H), 7.66 (t, $J_1 = J_2$ = 7.1 Hz, 1H), 7.51 (s, 1H), 7.21–7.11 (m, 2H), 7.00 (s, 1H), 4.44 (s, 2H), 3.31 (t, $J_1 = J_2$ = 7.2 Hz, 6H), 2.96–2.83 ($m_{(7)}$, 6H), 1.79–1.68 ($m_{(5)}$, 6H), 1.41–1.30 ($m_{(6)}$, 6H), 1.23 (d, J = 6.8 Hz, 6H), 0.93 (t, $J_1 = J_2$ = 6.9 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 161.78, 159.83, 148.94, 136.98, 133.51, 132.23, 130.54, 128.43, 126.56, 123.74, 122.52, 67.25, 59.81, 30.01, 24.55, 23.79, 19.68 and 14.03. Positive mode ESI-MS: m/z calcd for $C_{32}H_{50}Cl_2N_2O$ (549.66), found 514.20, $[M\text{-}Cl^-]^+$ a.m.u.

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((3-methylpyridin-2-ylimino)methyl)benzyl)-ammonium hexafluorophosphate (3g): Light yellow needles from methanol, Yield (85%), mp: 112–114 °C. FTIR (KBr, cm^{-1}): 3412 (vs, br, $\nu_{(O-H)}$), 1618 (s, sh, $\nu_{(C=N),}$ azomethine), 1557, 1444, 1398 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1278 (s, sh, $\nu_{(Ar-O)}$), 826 (vs, sh, $\nu_{(PF6^-)str}$), 768 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 558 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.43 (s, 1H), 10.39 (s, 1H), 7.93 (s, br, 2H), 7.56 (s, 1H), 7.43 (s, 1H), 7.15–6.94 (m, 1H), 4.59 (s, 2H), 3.83 (t, $J_1 = J_2$ = 7.1 Hz, 6H), 1.88–1.79 ($m_{(5)}$, 6H), 1.41–1.29 ($m_{(6)}$, 6H), 0.97 (t, $J_1 = J_2$ = 6.9 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 161.89, 158.66, 153.56, 151.05, 145.92, 143.33, 140.65, 134.21, 131.12, 129.13, 125.23, 123.25, 117.13, 66.03, 59.28, 24.10, 19.76 and 13.98. ^{31}P NMR (202 MHz, DMSO-d_6): −159.42 to −117.35 ppm (septet, $^2J_{PF}$ = 711.14 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.79 to −64.75 ppm (doublet, $^1J_{PF}$ = 711.22 Hz). Positive mode ESI-MS: m/z calcd for $C_{26}H_{39}ClF_6N_3OP$ (590.02), found 445.00, $[M - PF_6^-]^+$ a.m.u.

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((2-mercaptophenylimino)methyl)benzyl)-ammonium hexafluorophosphate (3h): Canary yellow powder from ethanol, Yield (25%), mp: 260–261 °C. FTIR (KBr, cm^{-1}): 3409 (vs, br, $\nu_{(O-H)}$), 1618 (s, sh, $\nu_{(C=N),}$ azomethine), 1479, 1445, 1399 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1279 (s, sh, $\nu_{(Ar-O)}$), 823 (vs, sh, $\nu_{(PF6^-)str}$), 761 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 557 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.84 (s, 1H), 10.39 (s, 1H), 7.61–7.49 (m, 2H), 7.37 (s, 1H), 7.20 (s, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.93 (d, J = 7.1 Hz, 1H), 4.93 (s, 2H), 3.98 (s, 1H), 3.76 (t, J_1 =

J_2 = 7.1 Hz, 6H), 1.88–1.76 ($m_{(5)}$, 6H), 1.49–1.38 ($m_{(6)}$, 6H), 0.98 (t, $J_1 = J_2$ = 7.0 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 162.05, 160.21, 158.13, 145.48, 143.38, 139.00, 133.97, 131.07, 129.36, 128.10, 123.31, 121.13, 118.12, 66.78, 59.49, 24.24, 19.91 and 12.14. ^{31}P NMR (202 MHz, DMSO-d_6): −159.39 to −117.33 ppm (septet, $^2J_{PF}$ = 711.16 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.81 to −64.79 ppm (doublet, $^1J_{PF}$ = 711.25 Hz). Positive mode ESI-MS: *m/z* calcd for $C_{26}H_{38}ClF_6N_2OPS$ (507.07), found 462.10, $[M\text{-}PF_6^-]^+$ a.m.u.

N-(3-((2-aminophenylthio)(hydroxy)methyl)-5-chloro-4-hydroxybenzyl)-N,N,N-triethyl ammonium hexafluorophosphate (3i): Orange powder from chloroform, Yield (74.00%), mp: 89–91 °C. FTIR (KBr, cm^{-1}): 3432, 3377 (s, br, $\nu_{(NH2)}$), 3298 (s, br, $\nu_{(O-H)}$), 1471, 1443 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1280 (s, sh, $\nu_{(Ar-O)}$), 829 (vs, sh, $\nu_{(PF6^-)str}$), 765 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 615 (m, sh, $\nu_{(C-S)}$), 556 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.36 (s, 1H), 7.42 (s, 1H), 7.31 (m, 1H), 7.23 (s, 1H), 7.14–7.01 (m, 2H), 6.83 (dd, J = 8.3, 1.4 Hz, 2H), 6.29 (s, br, 2H), 5.68 (s, 1H), 3.99 (s, 1H), 3.76 (t, $J_1 = J_2$ = 7.10 Hz, 6H), 1.85–1.73 ($m_{(5)}$, 6H), 1.41–1.30 ($m_{(6)}$, 6H), 1.11 (t, $J_1 = J_2$ = 7.2 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 157.21, 149.48, 140.17, 133.03, 130.29, 129.15, 128.45, 127.82, 125.76, 120.12, 116.31, 115.10, 77.89, 68.43, 59.49, 24.20, 19.91 and 12.14. ^{31}P NMR (202 MHz, DMSO-d_6): −159.38 to −117.33 ppm (septet, $^2J_{PF}$ = 711.16 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.83 to −64.81 ppm (doublet, $^1J_{PF}$ = 711.24 Hz). Positive mode ESI-MS: *m/z* calcd for $C_{26}H_{40}ClF_6N_2O_2PS$ (625.09), found 480.10, $[M - PF_6^-]^+$ a.m.u.

N,N,N-tri-^{n}butyl-N-(5-chloro-4-hydroxy-3-((p-tolylimino)methyl)benzyl)ammonium hexa-fluorophosphate (3j): Pale yellow powder from methanol, Yield (93%), mp: 270–271 °C. FTIR (KBr, cm^{-1}): 3449 (vs, br, $\nu_{(O-H)}$), 1623 (s, sh, $\nu_{(C=N)}$, azomethine), 1477, 1448, 1399 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1287 (s, sh, $\nu_{(Ar-O)}$), 829 (vs, sh, $\nu_{(PF6^-)str}$), 767 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 560 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.86 (s, 1H), 10.51 (s, 1H), 7.69 (s, 1H), 7.34 (s, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.08–6.97 (m, 2H), 4.56 (s, 2H), 3.85 (t, $J_1 = J_2$ = 7.00 Hz, 6H), 1.89–1.77 ($m_{(5)}$, 6H), 1.49–1.37 ($m_{(6)}$, 6H), 1.00 (t, $J_1 = J_2$ = 7.1 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 161.11, 158.23, 150.73, 145.21, 136.99, 133.42, 131.03, 129.93, 124.15, 122.91, 122.35, 120.03, 66.10, 57.75, 23.86, 19.90 and 14.01. ^{31}P NMR (202 MHz, DMSO-d_6): −159.39 to −117.32 ppm (septet, $^2J_{PF}$ = 711.15 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.83 to −64.81 ppm (doublet, $^1J_{PF}$ = 711.25 Hz). Positive mode ESI-MS: *m/z* calcd for $C_{27}H_{40}ClF_6N_2OP$ (589.04), found 444.07, $[M\text{-}PF_6^-]^+$ a.m.u.

N-(3-((2-carboxy-5-chloro-phenylimino)methyl)-4-hydroxybenzyl)-N,N,N-tri-^{n}butylamm-onium hexafluorophosphate (3k): Brownish powder from methanol, Yield (81%), mp: 168–169 °C. FTIR (KBr, cm^{-1}): 3436 (vs, br, $\nu_{(O-H)}$), 1660 (s, sh, $\nu_{(C=O)}$, carbonyl), 1625 (s, sh, $\nu_{(C=N)}$, azomethine), 1579, 1446, 1398 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1283 (s, sh, $\nu_{(Ar-O)}$), 825 (vs, sh, $\nu_{(PF6^-)str}$), 771 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 555 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.34 (s, 1H), 10.29 (s, 1H), 8.88 (s, 1H), 8.25–8.13 (m, 2H), 7.81 (d, J = 7.7 Hz, 1H), 7.73–7.63 (m, 1H), 7.55 (s, 1H), 7.25 (s, 1H), 7.11 (d, J = 8.1 Hz, 1H), 4.43 (s, 2H), 3.26 (t, $J_1 = J_2$ = 7.1 Hz, 6H), 1.80–1.69 ($m_{(5)}$, 6H), 1.40–1.28 ($m_{(6)}$, 6H), 0.96 (t, $J_1 = J_2$ = 7.0 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 190.68, 169.13, 159.90, 149.97, 135.26, 134.32, 132.89, 131.63, 131.09, 129.88, 126.74, 123.42, 119.57, 117.58 67.09, 59.77, 24.81, 20.22 and 14.23. ^{31}P NMR (202 MHz, DMSO-d_6): −159.41 to −117.34 ppm (septet, $^2J_{PF}$ = 711.17 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.83 to −64.80 ppm (doublet, $^1J_{PF}$ = 711.26 Hz). Positive mode ESI-MS: *m/z* calcd for $C_{27}H_{38}ClF_6N_2O_3P$ (619.02), found 474.00, $[M\text{-}PF_6^-]^+$ a.m.u.

N-(3-((2,6-diisopropylphenylimino)methyl)-5-chloro-4-hydroxybenzyl)-N,N,N-tri-^{n}butyl ammonium hexafluorophosphate (3l): Yellow crystals from methanol, Yield (77%), mp: 280–282 °C. FTIR (KBr, cm^{-1}): 3425 (vs, br, $\nu_{(O-H)}$), 1623 (s, sh, $\nu_{(C=N)}$, azomethine), 1479, 1446, 1397 (s, sh, $\nu_{(C=CAr\ +\ C-Hbend)}$), 1286 (s, sh, $\nu_{(Ar-O)}$), 823 (vs, sh, $\nu_{(PF6^-)str}$), 769 (vs, sh, $\nu_{(C-Cl)}$, Ar—Cl), 557 (s, sh, $\delta_{(P-F)}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 10.83 (s, 1H), 10.19 (s, 1H), 7.71 (t, $J_1 = J_2$ = 7.1 Hz, 1H), 7.56 (s, 1H), 7.28–7.18 (m, 2H), 7.01 (s, 1H), 4.45 (s, 2H), 3.33 (t, $J_1 = J_2$ = 7.2 Hz, 6H), 2.97–2.85 ($m_{(7)}$, 6H), 1.81–1.72 ($m_{(5)}$, 6H), 1.41–1.30 ($m_{(6)}$, 6H), 1.25 (d, J = 7.0 Hz, 6H), 0.96 (t, $J_1 = J_2$ = 6.9 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 161.34, 159.84, 149.11, 136.98, 134.21, 132.22, 130.89, 129.55, 125.98, 123.75, 122.31, 67.27, 59.81, 29.89, 24.54, 23.79, 19.67 and 13.99. ^{31}P NMR (202 MHz, DMSO-d_6): −159.39 to −117.32 ppm (septet, $^2J_{PF}$ = 711.16 Hz). ^{19}F NMR (470 MHz, DMSO-d_6): −67.82 to −64.79 ppm (doublet, $^1J_{PF}$ = 711.25 Hz). Positive mode ESI-MS: *m/z* calcd for $C_{32}H_{51}F_6N_2OP$ (659.17), found 514.20, $[M\text{-}PF_6^-]^+$ a.m.u.

2.7. General procedure for regeneration of Sal-($^nBu_3N^+X^-$) (2a,b) scavengers

2 N HCl (3.0 mL) was added to the ionic liquid-supported imines (**3**a–l) (100 mg) and the mixture was stirred vigorously for 4 h. While the reaction progressed, the color of the imine scavenging products solution was changed to yellowish or colorless. After a completion of the reaction, the reaction mixture was neutralized with $NaHCO_3$ and the isolated scavenger was extracted with DCM (3 × 3.0 mL). The organic layer was dried with sodium sulfate and evaporated and extracted with a hexane/ethyl acetate mixture (1:1, *v/v*) to remove amine derivative. After removal of amino component, the residue was dried under reduced pressure to yield the chlorosalicylaldehyde-functionalized ammonium ionic liquids Sal-($^nBu_3N^+X^-$) (**2**a,b) in a yield of the range (70–95%).

2.8. Antimicrobial assays

2.8.1. Reagents

Dimethylsulphoxide (DMSO), ampicillin antibiotic ($C_{16}H_{19}N_3O_4S$, 349.41 g mol^{-1}) and amphotericin B ($C_{47}H_{73}NO_{17}$, 923.49 g mol^{-1}), antifungal drug, were obtained from Sigma Chemical Co. (St. Louis, MO, USA).

2.8.2. Microbial cultures

Strains used in this study were provided by the National Organization for Drug Control and Research (NODCAR), Cairo, Egypt. The tested strains are *Staphylococcus aureus* (*S. aureus*, ATCC-25923 as a representative Gram-positive bacterial strain, *Escherichia coli* (*E. coli*, ATCC-25922) as the most important Gram-negative pathogenic bacterium as well antifungal species, *Aspergillus flavus* (*A. flavus*) and *Candida albicans* (*C. albicans*, NCIM No. 3100). Stock cultures were grown aerobically on nutrient broth (NB) agar slants (Hi-Media) at 37 °C and then maintained at 4 °C. Pre-cultures containing 10^5 CFU/mL (CFU = colony forming units), grown aerobically in Mueller Hinton (MH) liquid medium (Hi-Media) at 37 °C for 5 h, were used as inoculum for all experiments.

2.8.3. Antimicrobial susceptibility

Antimicrobial susceptibility of the microbial strains was carried out by agar well diffusion method [24] for the target compounds as well as standard drugs, ampicillin and amphotericin B. The diameter of the zone of inhibition (ZOI, mm) was measured accurately as indicative of antimicrobial activity.

2.8.4. Determination of MIC_{90}

As parameters of the antibacterial efficacy, the minimum inhibitory concentration of the target compounds which inhibit the growth of 90% of tested microorganisms as compared to a control, MIC_{90}, was determined against infection isolates using the macro-dilution broth susceptibility test. Stationary–phases for tested microbial species were prepared at 37 °C and used to inoculate fresh 5.0 mL of bacterial cultures to an OD600 of 0.05. These 5.0 mL cultures were then incubated at 37 °C until an OD600 of 0.10 was achieved from which standardized bacterial suspensions were prepared with a final cell density of 6 × 10^5 CFU/mL.

Different concentrations from the tested samples (0–320 mg/mL) were prepared and mixed with 5.0 mL of the standardized bacterial suspension then added to the plates and incubated for 24 h at 37 °C. The CFU were counted for each dilution and compared to the growth of untreated controls.

2.9. In vitro anticancer (antitumor) activity

2.9.1. Reagents

Dimethylsulphoxide (DMSO), crystal violet and trypan blue dye were purchased from Sigma Chemical Co. (St. Louis, Mo, USA). Dulbecco's modified Eagle's medium (DMEM), Roswell Park Memorial Institute medium (RPMI-1640), fetal bovine serum (FBS), 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES) buffer solution, L-glutamine, gentamycin and 0.25% trypsin–EDTA were obtained from Lonza.

Crystal violet stain was prepared as 0.5% crystal violet solution by dissolving 0.5 g of crystal violet stain in 50 mL methanol, then the solution was completed to 100 mL with deionized water, filtered through Whatmann No.1 and stored at room temperature.

2.9.2. Cell cultures

Human tumor cell lines, MCF-7 (breast adenocarcinoma) was obtained from the VACSERA Tissue Culture Unit and cultured in either RPMI-1640 or DMEM media supplemented with 10% heat-inactivated FBS, 1% L-glutamine, HEPES buffer and 50 μg/mL gentamycin. All cells were maintained at 37 °C in a humidified atmosphere with 5% CO_2 and sub-cultured two times a week. Cell toxicity was monitored by determining the effect of the tested samples on cell morphology and cell viability. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

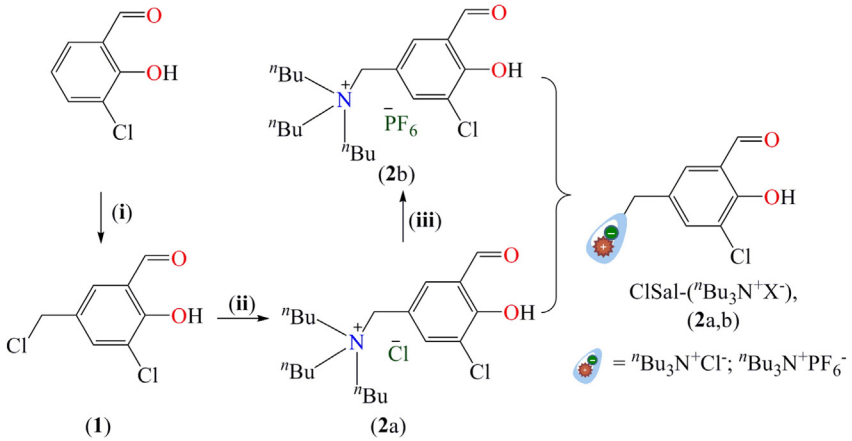
2.9.3. Antitumor assay

The in vitro antitumor activity of the most potent biocidal scavenging products was evaluated according to the procedure adopted by the Regional Center for Mycology & Biotechnology, Egypt. Briefly, MCF-7 cells were seeded in 96-well cell-culture plate at a cell concentration of (1×10^4) cells per well in 100 μL of growth medium. Fresh medium containing different concentrations of the tested sample was added after 24 h of seeding. Serial two-fold dilutions of the tested compound were added to confluent cell mono layers dispensed into 96-well, flat-bottomed microtiter plates (Falcon, NJ, USA) using a multichannel pipette. The micro-titer plates were incubated at 37 °C in a humidified incubator with 5% CO_2 for 48 h. Three wells were used for each sample concentration. A control of untreated cells was cultured in absence of tested sample. A positive control containing doxrubcine® drug was used for comparison. An infinitesimal amount of DMSO exist in the wells (maximal 0.1%) has no significant effect on the experiment. After incubation of the cells for 24 h at 37 °C, various concentrations (5–50 μg/mL) of sample were added, and the incubation was continued for further 48 h then the viable cells yield was determined by a colorimetric method. After the end of the incubation period, media were aspirated and the crystal violet solution (1%) was added to each well for at least 30 min. The stain was removed and the plates were rinsed using tap water until all excess stain was removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, and then the absorbance of the plates were measured after gently shaken on Micro plate reader (TECAN, Inc.), using a wavelength of 490 nm. All results were corrected for background absorbance detected in wells without stain. All experiments were carried out in triplicate and the average values were calculated. The number of viable cells was determined using ELISA reader as previously mentioned before and the percentage of viability was calculated as $\{(1 - (\mathbf{ODt} / \mathbf{ODc})) \times 100\}$ where **ODt** is the mean optical density of wells treated with the tested sample and **ODc** is the mean optical density of untreated cells [26]. The 50% inhibitory concentration (IC_{50}), the concentration required to cause toxic effect in 50% of intact cells, was estimated from graphic plots.

3. Results and discussion

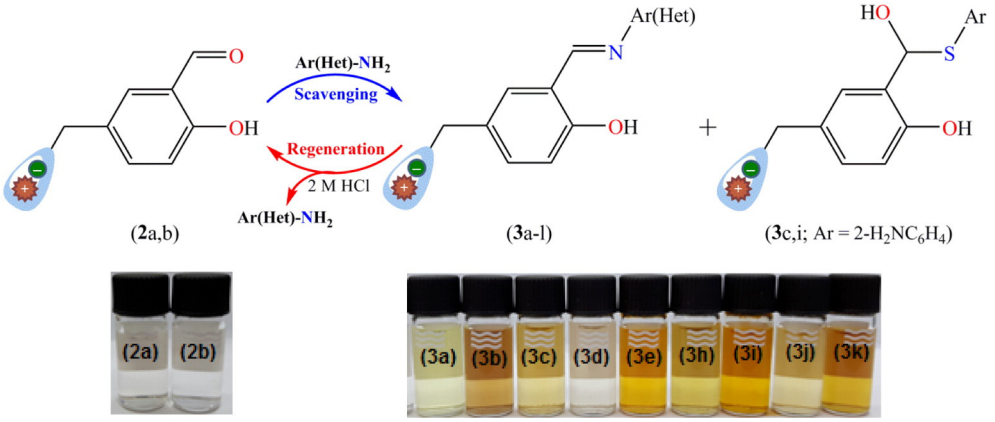
3.1. Synthesis protocol

A stepwise synthetic route for fabrication of chlorosalicylaldehyde-functionalized ammonium ionic liquids (ClSal-(^{n}Bu$_3$N$^+$X$^-$), **2**a,b) is depicted in Scheme 1. This synthetic route began with chloromethylation of ClSal, an inexpensive material, with paraformaldehyde/HCl_{aq} as co-chloromethylating agent in the presence of catalytic amount of $ZnCl_2$ under HCl_g stream to give CM(Cl)Sal (**1**) in excellent yield. Thereafter, quaternization of tri-^{n}butylamine (^{n}Bu$_3$N) using CM(Cl)Sal (**1**) as quaternizing agent afford the desired (ClSal-(^{n}Bu$_3$N$^+$Cl$^-$), **2**a) which subsequently underwent anion metathesis with $HPF_{6(aq)}$ to yield the corresponding hexafluorophosphate salt (ClSal-(^{n}Bu$_3$N$^+$PF$_6^-$), (**2**b). Noteworthy that ClSal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a) is hydrophilic and soluble in water and wide range of polar organic solvents (such as MeOH, EtOH, $CHCl_3$, … etc.) while (ClSal-(^{n}Bu$_3$N$^+$PF$_6^-$), (**2**b) is hydrophobic and insoluble in water and EtOH but soluble in MeOH.



(**i**) CH_2O, $ZnCl_2$, HCl_{aq}, HCl_g, stir, r.t. (**ii**) ^{n}Bu$_3$N, toluene, stir, 80 °C, N_2. (**iii**) 60% HPF_6, milli-Q H_2O, stir, 5 °C

Scheme 1. Schematic diagram for the synthesis of chlorosalicylaldehyde-functionalized ammonium ionic liquids (ClSal-(^{n}Bu$_3$N$^+$X$^-$), **2**a,b).



Scheme 2. Capture of aromatic and heterocyclic amines by **2**a,b.

The structures of ClSal-($^{n}Bu_3N^+X^-$) (**2**a,b) were proposed based upon spectral analysis (FTIR, NMR (^{1}H, ^{13}C, ^{19}F, ^{31}P) and ESI-MS).

3.2. Characterizations of ClSal-($^{n}Bu_3N^+X^-$) (2a,b)

The collected spectral data reveals a success of our protocol in achieving the synthesis of new ClSal-functionalized ammonium ionic liquids ClSal-($^{n}Bu_3N^+X^-$) (**2**a,b). Where the FTIR spectroscopic signatures of ClSal-($^{n}Bu_3N^+X^-$) (**2**a,b) highlighted the following markers; (i) an intense broad absorption band with a maxima at the range of 3424 ± 7 cm^{-1} is characteristic for the stretching vibration of phenolic hydroxyl (Ar-OH) involved into an intramolecular hydrogen bonding. (ii) An extremely sharp band around 1667 cm^{-1} coupled with a medium peak around 2850 cm^{-1} are assignable to the carbonyl (C═O) and aldehydic proton stretching vibrations of salicylaldehyde fragment. (iii) A set of versatile peaks around 3000, 2980 cm^{-1}, due to aliphatic chain; 950, 750 cm^{-1} which are characteristic for antisymmetric and symmetric vibration of quaternary nitrogen (R_4N^+) coupled with PF_6^- vibration bands noticed at 821 and 556 cm^{-1} are typical for tri-^{n}butylammonium ionic liquid terminals.

^{1}H/^{13}C NMR spectra of Sal-$^{n}Bu_3N^+X^-$ (**2**a,b) are dominated by common spectral peculiarities represented in; (i) The two low-field singlets, around 10.70 and 10.16 ppm, are attributable to an intramolecular hydrogen-bonded phenolic proton (this further confirmed by notice of a maxima of $(C—O)_{phenol}$ resonance peak in ^{13}C NMR at ca. 160 ppm) and the aldehydic proton (which in agreement with observation of ^{13}C NMR carbonyl peak at ~190 ppm). (ii) A set of peaks at the ranges of δ 7.81–7.02 and δ 3.86–1.00 ppm are originating from the resonances of aromatic and ^{n}butyl protons, respectively, which confirm the successful quaternization of $^{n}Bu_3N$ with CM(Cl)Sal. (iii) ^{31}P/^{19}F NMR spectra of ClSal-($^{n}Bu_3N^+$ PF_6^-) (**2**b) provide an evidence for the success of chloride metathesis with hexafluorophosphate as revealed from a septet centered at −142.28 ppm ($^2J_{PF}$ = 711.17 Hz) and doublet centered at −66.32 ppm ($^1J_{PF}$ = 711.26 Hz) those observed in its ^{31}P and ^{19}F NMR spectra, respectively.

3.3. Primary amines scavenging with ClSal-($^{n}Bu_3N^+X^-$) (2a,b) scavengers

The primary amine scavenging efficiency of newly synthesized chlorosalicylaldehyde-tri-^{n}butylammonium ionic liquids (**2**a,b) was investigated by reacting them, initially, with *p*-toluidine under different conditions for determination of the optimum scavenging conditions. Only 58% and 63% of *p*-toluidine was captured from its ethanolic solution by **2**a and **2**b, respectively, under reflux conditions for 6 h. Whilst, an addition of a catalytic amount of acetic acid to the reaction mixture provides synergistic effects that dramatically increases the *p*-toluidine scavenging efficiency of **2**a and **2**b up to 85% and 93%, respectively, and accelerates the scavenging process even at ambient temperature. Schiff-base-scavenging reaction of five different aromatic and heterocyclic amines by scavengers (**2**a,b) to yield the corresponding scavenging products, ionic liquid-supported imines (**3**a–l), was depicted in Scheme 2. Interestingly that the reaction between 2-aminothiophenol (ATP) and scavengers (**2**a,b), under the scavenging conditions, has been found to yield not only the expected imines (**3**b,h) as scavenging products but also hemimercaptals (**3**c,i) as co-scavenging products. These scavenging products were dismissed from the homogeneous solution as ethanol-insoluble products which removed by filtration. Thus, simple filtration and washing with appropriate solvents is the stepwise protocol followed to remove imine scavenging products.

Changes in the physicochemical properties of the scavenging products in comparison to reaction entries (such as color, solubility and melting points; check experimental section) coupled with the structural characterization of these products based on spectral analysis (FTIR, ^{1}H NMR and ^{13}C NMR) give very strong evidences for the successful Schiff-base-scavenging strategy.

FTIR spectra of all scavenging products (**3**a–l) evinced; demise of two stretches around 3300 and 3400 cm^{-1}, characteristic for NH_2 stretching modes, and the aldehyde carbonyl stretch in ClSal-($^{n}Bu_3N^+X^-$) (**2**a,b) at the range of 1678 ± 11 cm^{-1} along with the emergence of two new peaks at the range of 1618 ± 7 cm^{-1} and 1283 ± 7 cm^{-1} assignable to the stretching vibrations of azomethine (HC═N) and aryl-oxygen (Ar—O), respectively, belonging to salicylidene core [21]. These FTIR spectral data provide a significant preliminary evidence for a successful Schiff-base-scavenging process and formation of ionic liquid-functionalized imines as scavenging products. Moreover, FTIR

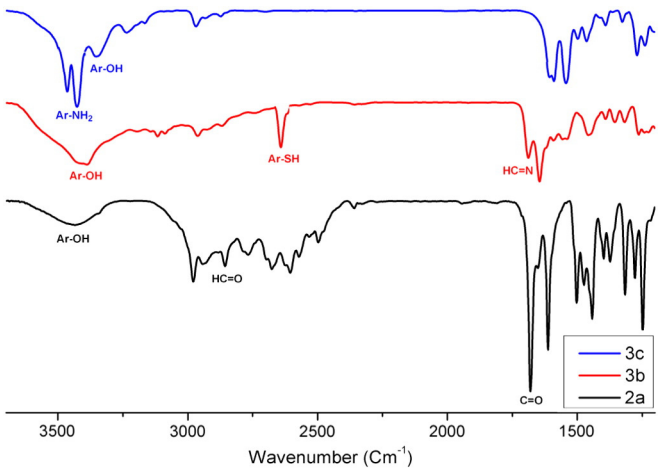


Fig. 2. FTIR segment for comparison of the stretching vibrations and splitting patterns of ATP-based scavenging products (**3**b,c) with scavengers (**2**a).

Table 1
Scavenging of primary amines into ionic liquid-based imines.

Entry	Sal-(^{n}Bu$_3$N$^+$X$^-$)	Ar/Het (abbrev.)	Imines	Conversion %
1	Sal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a)	3-$CH_3C_5H_3N$ (**AP**)	**3**a	82
2	Sal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a)	2-HSC_6H_4(**ATP**)	(**3**b + c)[a]	**95**
3	Sal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a)	4-$CH_3C_6H_4$ (***p*-Tol**)	**3**d	85 (58)[b]
4	Sal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a)	2-$COOHC_6H_4$ (**Anth**)	**3**e	71
5	Sal-(^{n}Bu$_3$N$^+$Cl$^-$) (**2**a)	2,6-(^{iso}Pr)$_2C_6H_3$ (**DIPA**)	**3**f	69
6	Sal-(^{n}Bu$_3$N$^+$PF$_6^-$) (**2**b)	3-$CH_3C_5H_3N$ (**AP**)	**3** g	85
7	Sal-(^{n}Bu$_3$N$^+$PF$_6^-$) (**2**b)	2-HSC_6H_4 (**ATP**)	(**3** h + i)[a]	**99**
8	Sal-(^{n}Bu$_3$N$^+$PF$_6^-$) (**2**b)	2-$CH_3C_6H_4$ (***o*-Tol**)	**3**j	93 (63)[b]
9	Sal-(^{n}Bu$_3$N$^+$PF$_6^-$) (**2**b)	2-$COOHC_6H_4$ (**Anth**)	**3** k	81
10	Sal-(^{n}Bu$_3$N$^+$PF$_6^-$) (**2**b)	2,6-(^{iso}Pr)$_2C_6H_3$ (**DIPA**)	**3** l	77

[a] Co-scavenging products, imines and hemimercaptals.
[b] Isolated yield in the absence of acetic acid.

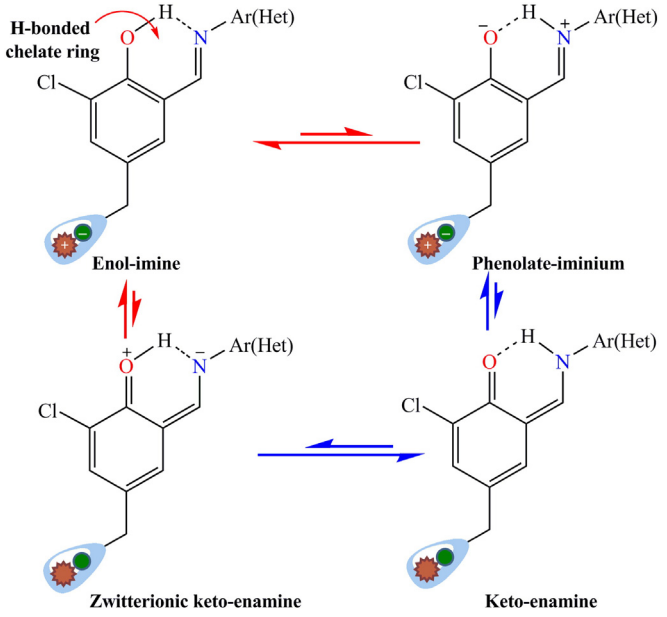
spectroscopic markers (Fig. 2) may provide a powerful tool for validation of mixed-scavenging products in the case of capture of 2-aminothiophenol with scavengers (**2**a,b). Whereas, notice of an intense sharp stretches around 2610 and 1623 cm^{-1}, in the FTIR spectra of **3**b,h, attributable to the stretching vibrations of azomethine (HC═N) and aryl-thiol (Ar—SH) moieties, respectively, confirms the formation of imines (**3**b,h), as aminothiophenol scavenging product, via Schiff-base-scavenging reaction. On the other hand, observation of two strong peaks around 3400 cm^{-1}, characteristic for NH_2 stretching vibrations, coupled with the absence of vibration bands assignable to HC═N and Ar—SH fragments proves the formation of hemimercaptals (**3**c,i)), as aminothiophenol co-scavenging product, through nucleophilic-addition-scavenging pathway.

Further evidences confirm successful anchoring of aromatic and heterocyclic amines onto the salicylaldehyde-tri-^{n}butylammonium ionic liquids (**2**a,b) scaffolds are the common features of the $^1H/^{13}C$ NMR spectra which are dominated by common peculiarities represented in: (i) A low-field singlet in the region of δ 14.00–11.00 ppm assignable to the resonance of phenolic proton involved in internal hydrogen-bonded environment (which agree with a notice of maxima for $(C—O)_{phenol}$ resonance peak in ^{13}C NMR around 159 ppm). (ii) Moreover, a deshielded singlet due to azomethine proton signal was observed around 10.50 ppm (which is consistent with the ^{13}C NMR imine peak in the region of 169–161 ppm).

3.4. Scavenging efficiency of ClSal-($^nBu_3N^+X^-$) (2a,b) scavengers

The Schiff-base-scavenging efficiency of primary amine with ClSal-($^nBu_3N^+X^-$) (**2**a,b) is demonstrated by the rate of capture of amine and yield conversion of entries in Scheme 2 into imines scavenging products. Generally, Schiff-base scavenging efficiency of aromatic and heterocyclic amines depends on the structural features and substitution pattern of scavenger, amino component and scavenging products. The essential requirement for effective Schiff-base scavenging is an enhancement of the nucleophile-electrophile interaction between a nucleophilic nitrogen atom from amino component and electrophilic carbonyl group of a scavenger. Nature of the substituents on scavenger and aromatic or heterocyclic amine play crucial roles in refinement this interaction. Data from scavenging experiment is collected in Table 1 and depicted in Fig. 3. These data revealed that the presence of ortho or para electron-donating group (EDG) in aniline derivatives such SH and CH_3 was significantly increased the nucleophilicity of amino group and promoted the ClSal-($^nBu_3N^+X^-$) scrubbing for amine capture. However, ortho or para electron-withdrawing group (EWG) such as COOH in entries **4** and **9** (Table 1, Fig. 2) reduces the nucleophilicity of amino group and amine capture accordingly.

Noteworthy, an ortho bulky substituent, isopropyl group, entries **5** and **10** (Table 1, Fig. 3) hinders nucleophile-electrophile interaction and amine-imine conversion leading to a drop in the scavenging efficiency. Interestingly, as shown in Fig. 3, hexafluorophosphate salt (**2**b) in more efficient than the corresponding chloride salt (**2**a) for Schiff-base scavenging of aromatic and heterocyclic amines from ethanolic media.



Scheme 3. schematic representation for possible tautomeric forms and H-bonded six-membered chelate ring in ionic imine scavenging products (**3**a–l).

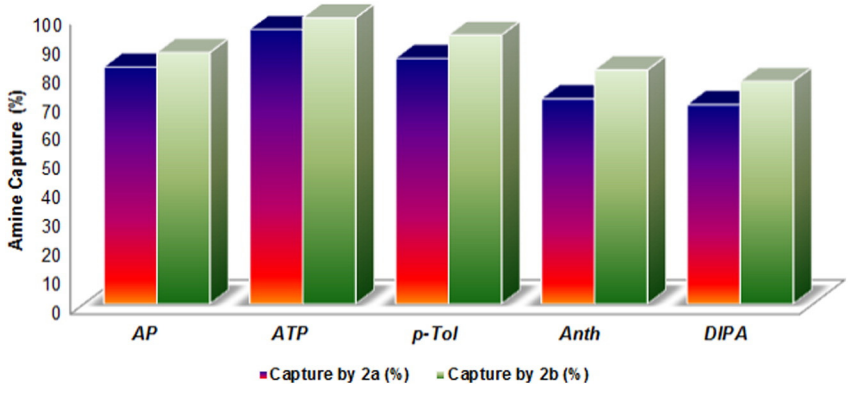


Fig. 3. ClSal-($^nBu_3N^+X^-$) (**2**a,b) scrubbing for primary amine capture.

Table 2
Scavenging of p-toluidine by our scavengers in comparison to literature ones.

1° Amine	Scavenger	Scavenging protocol	Imine yield (%)	Ref.
4- $CH_3C_6H_4$ (***p*-Tol**)	ClSal-($^nBu_3N^+Cl^-$) (**2**a)	EtOH/60 °C/5 h	85	This work
	ClSal-($^nBu_3N^+PF_6^-$) (**2**b)	EtOH/60 °C/5 h	93	This work
	Wang aldehyde resin	DCM/reflux/24 h	59	[27]
	Polyacrolein aldehyde resin	DCM/r.t/24 h	84	[28]
	IL-based aldehyde	EtOH/60 °C/6 h	82	[29]

Furthermore, the strong electron-withdrawing nature cationic terminal and chloro group of scavenger enhances the electrophilicity of carbonyl moiety and the reactivity of scavenger, accordingly, for Schiff-base condensations with primary amines. Moreover, stabilization of imines scavenging products via formation H-bonded six-membered chelate ring, through intramolecular hydrogen bonding interaction between *o*-hydroxy group of salicyl fragment and azomethine group (see Scheme 3), leads to an enhancement of the scavenging efficacy.

Shorter reaction time and real-time monitoring are the major preferable advantages for our proposed scavengers over polymer-supported scavenger for amine. For example, in previous work [27] (see Table 2), using of Wang aldehyde resin as scavenger for a series of primary amines revealed scavenging efficacies, using reflux/ 24 h as a scavenging protocol, of the value in the range of 59–82%. On the other hand, our ionic liquid scavengers exhibited scavenging efficacies of 69–99% using shorter scavenging protocol, stirring at 60 °C/5 h. Moreover, alterations of the physical properties of the scavenging products in comparison to reaction entries open window for real-time monitoring of scavenging process.

3.5. Recovery of ClSal-($^nBu3N^+X^-$) (2a,b) scavengers

Schiff-base hydrolysis is the followed protocol for recovering of ClSal-($^nBu_3N^+X^-$) (**2**a,b) scavengers from imines scavenging products (**3**a–l). This hydrolysis is carried out in water–alcohol mixtures and has established the susceptibility to readily precede under acid catalysis conditions. The proposed mechanism for this acid catalysis Schiff-base hydrolysis involves the addition of water to the azomethine (HC═N) moiety to form the carbinolamine intermediate which underwent further hydrolysis to regenerate the desired ClSal-($^nBu_3N^+X^-$) (**2**a,b) scavengers (see Scheme 4) in excellent yield and pure state.

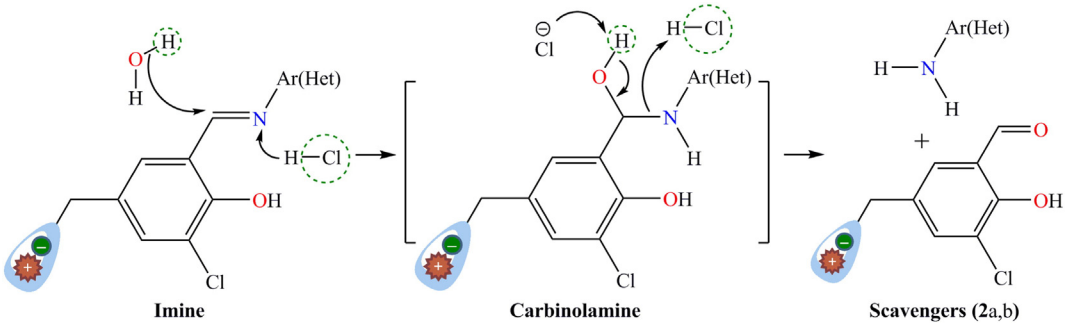
4. Pharmacology of imine scavenging products

Many trials to explore new pharmacologically active ingredient (PAI) ended in failure because of its low efficacy associated with its limited bioavailability or solubility. Anchoring of this PAI to ionic liquid terminals may offer synergistic effects of improving its water solubility and enhancing the pharmacological action.

4.1. Antimicrobial activity profile and antibacterial efficacy

The scavengers ClSal-($^nBu_3N^+X^-$) (**2**a,b) and scavenging products (**3**a–l) were in vitro assessed for their antimicrobial efficacies in comparison to standard antibiotics (antibacterial, ampicillin; antifungal, amphotericin B) against common clinically significant pathogenic microbial strains including *Staphylococcus aureus* (*S. aureus*) as a Gram-positive (G^+) bacterium, *Escherichia coli* (*E. coli*), as a Gram-negative (G^-) one, and *Aspergillus flavus* (*A. flavus*) as well *Candida albicans* (*C. albicans*, NCIM No. 3100), as fungal pathogens. Zone of inhibition (ZOI) assay (Fig. 4) demonstrates that the imine scavenging products (**3**a–l) are more effective for fighting microbial infections than the parent scavengers (**2**a,b). These antimicrobial efficacies are comparable to/ or exceed that of standard drugs. This boost in biopotency of scavenging products in comparison to scavengers may be ascribed to merging of diverse potent pharmacophores into a single molecular structure, (**3**a–l), which exerts overall additive antimicrobial effects. Primarily, hydrogen bond donor (HBD) and acceptor (HBA) pharmacophores belonging to salicylidene fragment of **3**a–l such as azomethine group (H—C═N) and phenolic OH offer significant targets for H-bonding with the active sits of the microbial cell constituents leading to an interference with their normal functions [30]. Moreover, tri-^{n}butylammonium ionic liquid terminal provide further effective pharmacophore which exert its antimicrobial action via direct electrostatic and hydrophobic interactions [31]. Whereas, the outer cellular membrane which acts as a formidable barrier especially against hydrophobic pharmacological agents can be easily attacked by biomolecules bearing cationic terminals, such as **3**a–j which bear cationic tri-^{n}butylammonium, that enable them to readily bind to their anionic targets in the cellular membrane, lipopolysaccharide (LPS) (a major constituent of G^- bacterial surface)or lipoteichoic acid (LTA) through an electrostatic interaction with the negatively charged phosphate groups of the LPS and LTA resulting in the disruption of the bacterial outer membrane and failure of its barrier function [32].

Additionally, the hydrophobic pharmacophores (butyl and isopropyl terminals) help new pharmacological agents (**3**g,l) in penetration and diffusion across the lipid bilayer of the microbial cell wall to the cell interior which may leads to a disruption of the cytoplasmic membrane, releasing of cell constituents and inducing DNA damage [33].



Scheme 4. Proposed mechanism for regeneration of ClSal-($^nBu_3N^+X^-$) (**2**a,b) scavengers.

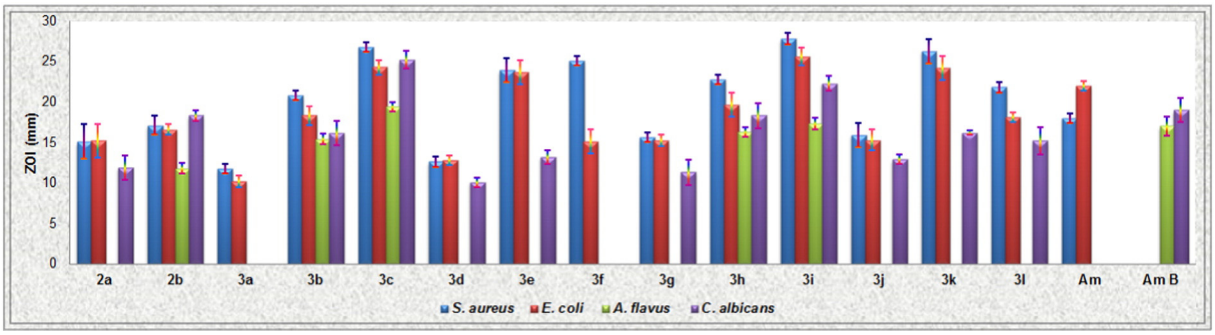


Fig. 4. Graph of zone of inhibition (ZOI, mm) for assaying compounds against different microbial species.

Noteworthy, as revealed from ZOIs data in Fig. 4, scavenging products are more effective than scavengers in inducing antibacterial effect with a slight preferable efficacy in fighting *staphylococcal* more than the *E. coli* infection.

Noticeable that, as shown in Fig. 4, imine scavenging products exhibited limited potency or inactive as fungicidal agents. This limited or lack of antifungal activities may be ascribed to either rigidity of the fungal outer-wall that composed predominately of chitin, mannan and proteins [34] which function as an impermeable barrier that limits or prevents a diffusion of pharmacological agent through it, or complexity of the mode of fungal drug-resistance which may proceeds via much more complicated mechanisms than bacterial conflict.

Among assaying compounds, thiophenol-based scavenging products, (**3**c,i) were found to exhibit excellent antibacterial action (MIC_{90} = 56.23, 34.18 μg/mL against *S. aureus*; MIC_{90} = 88.32, 101.32 μg/mL against *C. albicans*, respectively) in comparison to other scavenging products and standard drug. Thus, further structural refinement coupled with more microbiological assessments may offer new promising antibiotic candidates that play critical role in fighting *staphylococcal* and *C. albicans* infections.

4.2. Preliminary in vitro anticancer assay

The preliminary in vitro antitumor studies of representative scavenging products such as **3**b,c and **3**h,i were in vitro evaluated in relation to the standard anticancer drug doxorubicin® ($C_{27}H_{29}NO_{11}$, 543.52 g/mol) against human breast carcinoma (MCF-7). The surviving fraction assays (Fig. 5) demonstrated that all selected compounds exert pronounced inhibitory effects on proliferation of MCF-7 cell lines, with a structure-activity relationship (SAR) profile. Noteworthy, the surviving fraction assays and IC_{50} values demonstrated that the tested scavenging products exhibited different levels of cytotoxic activities (weak to excellent) against MCF-7 cells. For example, aminothiophenol-based tri-^{n}butylammonium hexafluorophosphate (**3**h) (IC_{50} = 8.03 μg/mL) was ca. 6-fold more cytotoxic than its chloride analogue (**3**b) (IC_{50} = 44.80 μg/mL). Lipophilicity and/or vulnerability to hydrolytic cleavage seem to be the key structural features leading to the observed anion-dependent cytotoxicity. Interestingly, strong hydrogen bonding interactions between hexafluorophosphate, PF_6^-, and DNA nucleobases [35] is the expected key factor for exponential efficiency of hexafluorophosphate salt, **3**h,i, over chloride analogues, **3**b,c. Furthermore, electrostatic interactions promoted association of hydrophilic cationic segments, tri-^{n}butylammonium, with terminal phosphate groups of DNA provide further reason from enhanced antitumor activity of assayed compound.

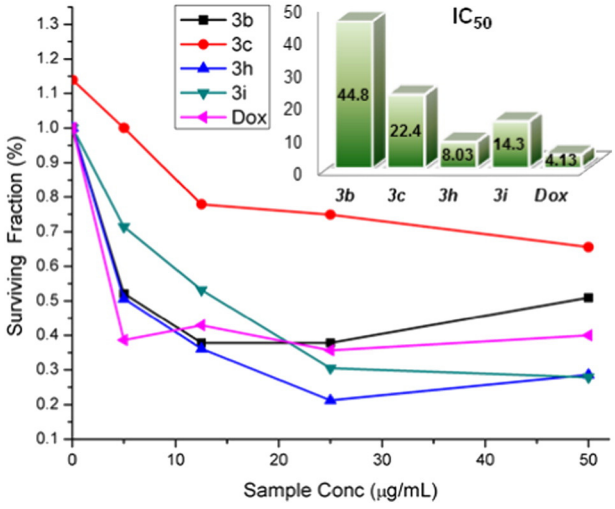


Fig. 5. Concentration-dependent antitumor efficacy assessment and IC_{50} of representative scavenging products (**3**b,c and **3**h,i) against human MCF-7 cell lines.

5. Conclusion

Novel chlorosalicylaldehyde-tri-^{n}butylammonium ionic liquids have been designed, successfully synthesized and structurally characterized. Thereafter, these ionic liquids were evaluated as scavengers for diverse aromatic and heterocyclic primary amines in the synthesis of new pharmacologically relevant candidates, imines scavenging products. The most plausible proposed mechanism for this scavenging process is a traditional simple Schiff-base condensation reaction between scavengers and target primary amines except in case of 2-aminothiophenol scavenging for which two different strategies, Schiff-base and nucleophilic addition, are involved for its capture to yield co-scavenging products, imines and hemimercaptals. The new scavengers exhibited good capture efficiency as revealed from yields of scavenging products (69–99%). The advantages of our protocol over that based on polymer-supported aldehyde scavenger are the simplicity, shorter reaction time, homogeneity of reaction medium, real-time monitoring of a model reaction, characterization of scavenging products and feasibility of regeneration and reuse of scavengers.

The biocidal and antitumor activities of the scavenging products have been investigated against common bacterial and fungal pathogens and human breast carcinoma (MCF-7) cell lines, respectively. Both the ZOIs and MIC values revealed that the designed scavenging products exhibited moderate to excellent broad-spectrum antibacterial efficacy in comparison to the parent scavengers and standard antibiotic with an ability to inhibit the growth of *A. flavus* < *C. albicans* < *E. coli* < *S. aureus*. The surviving fraction assays and IC_{50} values demonstrated that the tested scavenging products exhibited different levels of cytotoxic activities (weak to excellent) against MCF-7 cells. For example, aminothiophenol-based tri-^{n}butylammonium hexafluorophosphate (**3**h) (IC_{50} = 8.03 μg/mL) was ca. 6-fold more cytotoxic than its chloride analogue (**3**b) (IC_{50} = 44.80 μg/mL).

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