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Ionic Sal-SG Schiff bases as new synergetic chemotherapeutic candidates: Synthesis, metalation with Pd(II) and *in vitro* pharmacological evaluation.

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Abstract

A series of novel N-(salicylidene)-sulfaguanidines (Sal-SG) bearing ionic liquids (ILs) terminals (ILSSGH, **4a-f**) have been synthesized by Schiff base condensation of ILs-functionalized salicylaldehydes (ILSal, **3a-g**) and sulfaguanidine (SG). Metalation trials of these ionic Schiff bases with palladium(II) chloride affords the corresponding Pd(II) complexes, [Pd(II)(ILSSG)Cl(H_2O)] (**5a-g**). Further, the antimicrobial profiles of new compounds against a set of common pathogens have been described. Zone of inhibitions (ZOIs) and minimal inhibitory concentration (MIC) values revealed that most of the new compounds exhibited significant antibacterial and potential inhibitory activity against Staphylococcus aureus (*S. aureus*), and this activity is modulated by substituents attached to the ionic liquid core as well as the counter-ion.

Introduction

Sulfonamides (SAs), such as sulfaguanidine (SG), become an increasingly important class of compounds for medicinal chemists due to their cost-effectiveness, low-toxicity coupled with their assorted pharmacological effects.[1] As well, arylsulfonamide motifs act as the active pharmaceutically ingredients (APIs) in a large number of pharmaceutical drugs which are prescribed to control bacterial infections, diabetes mellitus, oedema, hypertension and gout.[2] However, antibiotic resistance genes (ARGs), encoding resistance to sulfonamide[3,4], remains a major impediment for their large-scale use. Moreover, the progression of drug-resistant strains has contributed to the inefficiency of the straight antimicrobial therapy. Thus, there is an urgent call for the identification of novel targets and development of novel antimicrobial drugs with divergent and unique structures for the treatment of infectious diseases. Several approaches to negate antibiotic resistance are currently being investigated, including inactivation of enzymes in essential metabolic pathways and inhibiting signal transduction systems.[5,6] These approaches involve development of new antimicrobial agents with unique modes of action that circumvent

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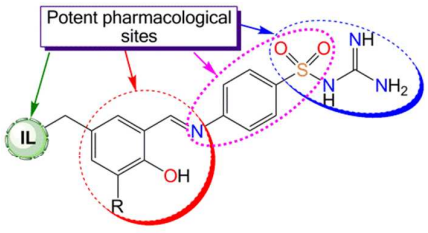
current resistance mechanisms.[7,8]

In this context, designing of the metal based drugs with synergizing beneficial effect of the ligands and metals to produce a complex with enhanced activity have been promising and present focal theme of the contemporary biomedical research. Consequently, selection of organic ligand and metal ion plays an essential role. As well, Schiff bases have been shown to exhibit a wide range of pharmacological activities such as antibacterial, antifungal, antimalarial, antitubercular, antiproliferative, anti-inflammatory and antiviral. It has been suggested that the remarkable biological activity of Schiff bases are essentially attributed to the presence of azomethine linkage.[9]

Recently, ionic liquids (ILs) have become attractive candidates for biomedical applications due to their tunable properties and the ability to generate biological responses upon binding to several biological targets. They have been recognized as bactericidal,[10] fungicidal,[10] acetylcholinesterase (AChE) inhibitor,[11] delivery of anti-inflammatory drugs,[12] local anesthetic,[10] anti-nociceptive, anticholinergic and anticancer drugs.[10b,13]

Despite extensive work done on Schiff's bases ligands, little attention has been paid to the sulfaguanidine (SG)-salicylaldimine (Sal) Schiff bases. To the best of our knowledge, there is no reports about the fabrication of ionic liquids-based N-(salicylidene)sulfaguanidine IL-Sal-SG Schiff bases (ILSSGH).

With an objective of exploring the role of Schiff base metal complexes as antimicrobial agents and in continuation of our ongoing programs directed toward the development of novel materials for magnetic[14] or biological application,[10a-c,15,16] we now report a concise, practical synthetic route and *in vitro* antimicrobial assessment of novel ILSSGH Schiff bases (Scheme 1) and their Pd(II) complexes which may allow us to develop a new promising therapeutic strategy to combat antibiotic resistance.



Nr.	R	IL
4a	H	Pic^+Cl^-
4b	H	Qn^+Cl^-
4c	H	$1,2\text{-}(CH_3)_2Im^+Cl^-$
4d	H	$1\text{-}(^nBu)Im^+Cl^-$
4e	^{i}Pr	$1,2\text{-}(CH_3)_2Im^+Cl^-$
4f	^{i}Pr	$1,2\text{-}(CH_3)_2Im^+BF_4^-$
4g	^{i}Pr	$1,2\text{-}(CH_3)_2Im^+PF_6^-$

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Scheme 1 significant pharmacological sites in IL-Sal-SG Schiff bases (ILSSGH, **4a–g**) that used in this work

Experimental

Instrumentation, materials and the preparation details of a series of ionic liquids-based salicylaldehydes can be found in electronic supplementary information.

Synthesis of the ionic Sal-SG Schiff bases (4a-g)

Generally, an ethanolic solution (10 mL) contain (0.214 g, 1 mmol) of sulfaguanidine (SG) and (1 mmol) of IL-salicylaldehyde salts IL-sal (**3a-f**) into a 50 mL RB flask was refluxed for 6 h. Then the supernatant was partially removed, and the yellow-orange products of **4a-g** were collected by filtration, washed with ethanol (3 x 3 mL), ether (3 x 3 mL), dried and then crystallized from ethanol. Samples of the isolated solids were characterized as follows;

N-(5-(*2-methylpyridinium chloride)-salicylidene*) *sulfaguanidine (**4a**)*: Yellow crystals, Yield (0.336 g, 73%), mp: 230-232 °C. FTIR (KBr, cm^{-1}): 3425 (m, br, $\nu_{(O-H)}$), 3356, 3324 (m, sh, $\nu_{(NH_2)}$), 3185 (m, br, $\nu_{(N-H)}$), 1617 (vs, sh, $\nu_{(C=N)Azomethine}$), 1326 (s, sh, $\nu_{(SO_2)}$), 1263 (m, sh, $\nu_{(Ar-O)}$), 1162 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Py). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.71 (s, 1H, OH), 11.16 (s, 1H, SO_2NH), 10.67 (s, 1H, NH), 10.30-10.22 (m, 1H, Py-H), 9.06 (ddd, *J* = 10.7, 6.7, 1.5 Hz, 1H, Py-H), 8.95 (d, *J* = 3.9 Hz, 1H, H-C=N), 8.73 (dd, *J* = 5.7, 0.9 Hz, 1H, Py-H), 8.59-8.50 (m, 1H, Py-H), 8.37 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-H), 8.13-7.99 (m, 1H, Ar-H), 7.86 -7.74 (m, 1H, Ar-H), 7.67 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.61 (dd, *J* = 4.3, 2.4 Hz, 1H, Ar-H), 7.54-7.37 (m, 1H, Ar-H), 7.11 (dd, *J* = 13.3, 8.6 Hz, 1H, Ar-H), 7.03-6.95 (m, 1H, Ar-H), 6.78 (d, *J* = 9.8 Hz, 2H, NH_2), 5.84 (d, *J* = 14.0 Hz, 2H, CH_2-Ar), 2.81 (d, *J* = 11.1 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 190.66, 161.70, 160.30, 158.13, 156.03, 151.15, 146.11, 136.61, 132.12, 130.72, 128.83, 127.77, 127.47, 126.35, 124.31, 121.97, 118.90, 113.17, 111.45, 59.88, 39.58 and 20.51. EI-MS, (*m*/*z*, Int.%): (459.0, 5.46) $[M]^+$. Anal. Calcd. for $C_{30}H_{36}Cl_2N_6O_2$ (M = 459.95): C, 54.84; H, 4.82; N, 15.23; S, 6.97; Found: C, 55.01; H, 4.63; N, 15.51; S, 7.11. Conductivity = 28.8 μS/cm.

N-(5-(*quinolinium chloride)-salicylidene*)*sulfaguanidine (**4b**)*: Orange powder, Yield (0.315 g, 63.5 %), mp: 223-225 °C. FTIR (KBr, cm^{-1}): 3436 (m, br, $\nu_{(O-H)}$), 3398, 3317 (m, sh, $\nu_{(NH_2)}$), 3201 (m, br, $\nu_{(N-H)}$), 1625 (vs, sh, $\nu_{(C=N)Azomethine}$), 1325 (s, sh, $\nu_{(SO_2)}$), 1272 (m, sh, $\nu_{(Ar-O)}$), 1165 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Qn). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.89 (s,

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1H, OH), 11.13 (s, 1H, SO_2NH), 10.42 (s, 1H, NH), 10.03-9.95 (m, 1H, Qn-H), 9.12 (ddd, *J* = 10.7, 6.7, 1.5 Hz, 1H, Qn-H), 8.89 (d, *J* = 3.9 Hz, 1H, H-C=N), 8.61 (dd, *J* = 5.7, 0.9 Hz, 1H, Qn -H), 8.63-8.59 (m, 1H, Qn-H), 8.56-8.49 (m, 2H, 2 x Qn-H), 8.45-8.48 (m, 1H, Qn-H), 8.31 (td, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 8.13-7.99 (m, 1H, Ar-H), 7.86-7.74 (m, 1H, Ar-H), 7.67 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.61 (dd, *J* = 4.3, 2.5 Hz, 1H, Ar-H), 7.54-7.37 (m, 1H, Ar-H), 7.11 (dd, *J* = 13.1, 8.6 Hz, 1H, Ar-H), 7.03-6.95 (m, 1H, Ar-H), 6.66 (d, *J* = 9.6 Hz, 2H, NH_2), 5.95 (d, *J* = 14.0 Hz, 2H, CH_2-Ar). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 191.03, 161.23, 160.10, 158.77, 157.35, 156.03, 150.15, 148.41, 146.11, 139.09, 136.61, 132.12, 130.72, 128.83, 127.77, 126.35, 124.31, 122.83, 121.97, 120.02, 118.92, 117.61, 115.56 and 60.88. EI- MS, (*m*/*z*, Int.%): (478.2, 6.18) $[M - H_2O]^+$. Anal. Calcd. for $C_{24}H_{22}ClN_5O_3S$ (M = 495.98): C, 58.12; H, 4.47; N, 14.12; S, 6.46; Found: C, 58.36; H, 4.73; N, 13.96; S, 6.11. Conductivity = 25.4 µS/cm.

N-(5-(1,2-dimethylimidazol-3-ium chloride)-salicylidene) *sulfaguanidine* ***(4c)***: Orange crystals, Yield (0.39 g, 84 %), mp: 246-248 °C. FTIR (KBr, cm^{-1}): 3419 (m, br, $\nu_{(O-H)}$), 3340, 3308 (m, sh, $\nu_{(NH_2)}$), 3192 (m, br, $\nu_{(N-H)}$), 1622 (vs, sh, $\nu_{(C=N)Azomethine}$), 1323 (s, sh, $\nu_{(SO_2)}$), 1267 (m, sh, $\nu_{(Ar-O)}$), 1169 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.62 (s, 1H, OH), 11.10 (s, 1H, SO_2NH), 10.29 (s, 1H, NH), 8.96 (s, 1H, H-C=N), 7.82 (d, *J* = 8.4 Hz, 2H, 2 x Ar-H), 7.75-7.70 (m, 1H, Ar-H), 7.69-7.63 (m, 2H, 2 x Ar-H), 7.57-7.50 (m, 1H, Ar-H), 7.47 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.38 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.09 (dd, *J* = 20.5, 8.5 Hz, 2H, 2 x Ar-H), 6.84 (s, 2H, NH_2), 5.38 (d, *J* = 14.3 Hz, 2H, CH_2-Ar), 3.76 (d, *J* = 6.6 Hz, 3H, CH_3), 2.62 (d, *J* = 10.1 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 190.78, 163.89, 161.49, 160.62, 144.98, 143.08, 136.51, 134.01, 131.96, 127.69, 127.49, 125.85, 121.95, 121.52, 120.11, 118.56, 117.88, 112.78, 50.45, 35.26 and 10.04. EI-MS, (*m*/*z*, Int.%): (445.0, 25.00) $[M - H_2O]^+$. Anal. Calcd. for $C_{20}H_{23}ClN_6O_3S$ (M = 462.95): C, 51.89; H, 5.01; N, 18.15; S, 6.93; Found: C, 52.13; H, 5.33; N, 18.02; S, 6.68. Conductivity = 33.0 µS/cm.

N-(5-(1- butylimidazol-3-ium chloride)-salicylidene) *sulfaguanidine* ***(4d)***: Yellow crystals, Yield (0.38 g, 77.5 %), mp: 220-222 °C. FTIR (KBr, cm^{-1}): 3419 (m, br, $\nu_{(O-H)}$), 3336, 3304 (m, sh, $\nu_{(NH_2)}$), 3200 (m, br, $\nu_{(N-H)}$), 1620 (vs, sh, $\nu_{(C=N)Azomethine}$), 1328 (s, sh, $\nu_{(SO_2)}$), 1265 (m, sh, $\nu_{(Ar-O)}$), 1137 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.55 (s, 1H, OH), 11.06 (s, 1H, SO_2NH), 9.31 (s, 1H, NH), 8.93 (s, 1H, H-C=N), 7.87-7.78 (m, 4H, 4 x Ar-H), 7.53 (dd, *J* = 8.5, 2.3 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.1 Hz, 2H, 2 x Ar-H), 7.41-7.35 (m, 2H, 2 x Ar-H), 7.07 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.79 (s, 2H, NH_2), 5.40 (s, 2H,

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CH_2-Ar), 4.18 (t, *J* = 7.4 Hz, 2H, C**H₂**-CH_2-CH_2-CH_3), 1.78 (p, *J* = 7.4 Hz, 2H, CH_2-C**H₂**-CH_2-CH_3), 1.26 (h, *J* = 7.4 Hz, 2H, CH_2-CH_2-C**H₂**-CH_3), 0.90 (t, *J* = 7.3 Hz, 3H, CH_2-CH_2-CH_2-C**H₃**). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 190.69, 161.64, 158.24, 151.83, 136.96, 136.44, 131.28, 129.15, 127.70, 127.50, 126.09, 123.25, 121.92, 112.78, 111.77, 107.31, 49.15, 40.40, 31.71, 19.27 and 13.74. EI-MS, (*m*/*z*, Int.%): (473.0, 56.46) [M – H_2O]$^+$. Anal. Calcd. for $C_{22}H_{27}ClN_6O_3S$ (M = 491.02): C, 53.82; H, 5.54; N, 17.12; S, 6.53; Found: C, 53.98; H, 5.55; N, 16.99; S, 6.23. Conductivity = 29.4 µS/cm.

N-(5-(1,2-dimethylimidazol-3-ium chloride)-3-isopropylsalicylidene)sulfaguanidine ***(4e)***: Yellow crystals, Yield (0.319 g, 63.2 %), mp: 180-182 °C. FTIR (KBr, cm^{-1}): 3476 (m, br, $\nu_{(O-H)}$), 3434, 3354 (m, sh, $\nu_{(NH_2)}$), 3236 (m, br, $\nu_{(N-H)}$), 1623 (vs, sh, $\nu_{(C=N)Azomethine}$), 1327 (s, sh, $\nu_{(SO_2)}$), 1270 (m, sh, $\nu_{(Ar-O)}$), 1137 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.62 (s, 1H, OH), 11.20 (s, 1H, SO_2NH), 10.01 (s, 1H, NH), 8.96 (s, 1H, H-C=N), 7.83 (d, *J* = 8.5 Hz, 2H, 2 x Ar-H), 7.72 (dd, *J* = 2.1, 1.1 Hz, 1H, Ar-H), 7.67-7.62 (m, 2H, 2 x Ar-H), 7.58 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.54-7.48 (m, 1H, Ar-H), 7.44-7.36 (m, 1H, Ar-H), 6.74 (s, 2H, NH_2), 5.37 (s, 2H, CH_2-Ar), 3.76 (d, *J* = 3.2 Hz, 3H, CH_3), 3.27 (dd, *J* = 13.5, 6.8 Hz, 1H, C**H**$(CH_3)_2$), 2.64 (d, *J* = 3.6 Hz, 3H, CH_3), 1.24 (d, *J* = 7.0 Hz, 6H, CH(C**H₃**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 190.69, 165.88, 155.46, 153.15, 145.01, 142.76, 137.34, 133.96, 130.71, 127.51, 123.13, 122.09, 121.45, 118.98, 115.23, 109.37, 50.73, 40.41, 35.28, 26.41, 22.63 and 9.99. EI-MS, (*m*/*z*, Int.%): (505.0, 65.00) [M]$^+$. Anal. Calcd. for $C_{23}H_{29}ClN_6O_3S$ (M = 505.03): C, 54.70; H, 5.79; N, 16.64; S, 6.35; Found: C, 54.58; H, 5.99; N, 16.48; S, 5.78. Conductivity = 34.8 µS/cm.

N-(5-(1,2-dimethylimidazol-3-ium tetrafluoroborate)-3-isopropylsalicylidene)sulfaguanidine ***(4f)***: Orange crystals, Yield (0.367 g, 66 %), mp: 230 °C. FTIR (KBr, cm^{-1}): 3475 (m, br, $\nu_{(O-H)}$), 3459, 3359 (m, sh, $\nu_{(NH_2)}$), 3185 (m, br, $\nu_{(N-H)}$), 1624 (vs, sh, $\nu_{(C=N)Azomethine}$), 1325 (s, sh, $\nu_{(SO_2)}$), 1270 (m, sh, $\nu_{(Ar-O)}$), 1176 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.62 (s, 1H, OH), 11.21 (s, 1H, SO_2NH), 10.01 (s, 1H, NH), 8.96 (s, 1H, H-C=N), 7.83 (d, *J* = 8.1 Hz, 2H, 2 x Ar-H), 7.71 (d, *J* = 2.1 Hz, 1H, Ar-H), 7.65 (dd, *J* = 5.1, 2.4 Hz, 1H, Ar-H), 7.59-7.49 (m, 2H, 2 x Ar-H), 7.45-7.36 (m, 2H, 2 x Ar-H), 6.74 (s, 2H, NH_2), 5.37 (s, 2H, , CH_2-Ar), 3.76 (d, *J* = 3.5 Hz, 3H, CH_3), 3.43-3.20 (m, 1H, C**H**$(CH_3)_2$), 2.64 (d, *J* = 3.6 Hz, 3H, CH_3), 1.24 (d, *J* = 6.9 Hz, 6H, CH(C**H₃**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 198, 165.38, 158.09, 149.57, 144.42, 142.79, 136.44, 133.47, 130.25, 127.00, 124.96, 124.95, 122.65, 121.58, 121.58, 120.94, 120.94, 118.29, 50.22, 34.76, 26.22,

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22.11 and 9.48. ^{19}F NMR (282 MHz, DMSO-d_6): –148.22 ppm (singlet). ^{11}B NMR (96 MHz, DMSO-d_6): –1.29 ppm (singlet). EI-MS, (*m*/*z*, Int.%): (574.1, 4.97) $[M + H_2O]^+$. Anal. Calcd. for $C_{23}H_{29}BF_4N_6O_3S$ (M = 556.38): C, 49.65; H, 5.25; N, 15.10; S, 5.76; Found: C, 49.46; H, 5.55; N, 14.98; S, 5.73. Conductivity = 30.4 µS/cm.

N-(5-(1,2-dimethylimidazol-3-ium hexafluorophosphate)-3-isopropylsalicylidene) *sulfaguanidine (**4g**)*: Yellow crystals, Yield (0.529 g, 86.1 %), mp: 150-152 °C. FTIR (KBr, cm^{-1}): 3479 (m, br, $\nu_{(O\text{-}H)}$), 3435, 3344 (m, sh, $\nu_{(NH_2)}$), 3236 (m, br, $\nu_{(N\text{-}H)}$), 1621 (vs, sh, $\nu_{(C=N)Azomethine}$), 1325 (s, sh, $\nu_{(SO_2)}$), 1273 (m, sh, $\nu_{(Ar\text{-}O)}$), 1178 (s, sh, $\nu_{(H\text{-}C=C + H\text{-}C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.62 (s, 1H, OH), 11.20 (s, 1H, SO_2NH), 10.01 (s, 1H, NH), 8.96 (s, 1H, H-C=N), 7.87-7.80 (m, 2H, 2 x Ar-H), 7.72 (dd, *J* = 2.2, 1.1 Hz, 1H, Ar-H), 7.67-7.62 (m, 2H, 2 x Ar-H), 7.54 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.53-7.48 (m, 1H, Ar-H), 7.43 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.74 (s, 4H, NH_2), 5.37 (s, 2H, CH_2-Ar), 3.76 (d, *J* = 3.2 Hz, 3H, CH_3), 3.32 – 3.25 (m, 1H, C**H**$(CH_3)_2$), 2.64 (d, *J* = 3.6 Hz, 3H, CH_3), 1.24 (d, *J* = 6.9 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 197.19, 165.88, 158.59, 150.08, 144.93, 143.31, 136.96, 130.76, 127.51, 125.46, 123.13, 122.09, 121.45, 118.81, 112.78, 50.73, 35.28, 28.20, 26.73, 22.63 and 10.00. ^{19}F NMR (282 MHz, DMSO-d_6): –70.415 ppm (doublet, $^1J_{FP}$ = 711.4 Hz). ^{31}P NMR (202 MHz, DMSO-d_6): –144.20 ppm (septet, $^2J_{PF}$ = 711.40 Hz). EI-MS, (*m*/*z*, Int.%): (614.0, 45.74) $[M]^+$. Anal. Calcd. for $C_{23}H_{29}PF_6N_6O_3S$ (M = 614.54): C, 44.95; H, 4.76; N, 13.68; S, 5.22; Found: C, 45.04; H, 4.89; N, 13.67; S, 5.10. Conductivity = 28.2 µS/cm.

Synthesis of the ionic Pd(II) Sal-SG Schiff bases complexes (5a-g)

A methanolic solution (5 mL) of palladium(II) Chloride (0.126g, 1 mmole) was added dropwise to a stirred methanolic solution (10 mL) containing ionic N-(salicylidene)sulfaguanidines (1 mmole) and 1mL of conc HCl. Then the reaction mixture was refluxed for 8 hours. After that, the solution was concentrated to leave an oily residue, which was solidified by adding of petroleum ether (40-60) and keeping in a refrigerator overnight. The isolated solids were filtered off and washed with cold methanol/ diethyl ether mixed-solvent (1:2) (3 x 3mL) to yield (**5a-g**). Samples of the isolated solids were characterized as follows;

[PdCl(4a)H$_2$O] (**5a**): Dark yellow powder, Yield (0.368 g, 68.3 %), mp: 240 °C. FTIR (KBr, cm^{-1}): 3202 (m, br, $\nu_{(N\text{-}H)}$), 3121, 1493 (m, sh, $\nu_{(NH_3^+)}$), 1627 (vs, sh, $\nu_{(C=N)Azomethine}$), 1321 (s, sh, $\nu_{(SO_2)}$), 1283 (m, sh, $\nu_{(Ar\text{-}O)}$), 1167 (s, sh, $\nu_{(H\text{-}C=C + H\text{-}C=N)bend}$, Py). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.03 (s, 1H, SO_2NH), 10.28 (s, 1H, NH), 9.09-9.00 (m, 1H, Py-H), 8.94

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(s, 1H, H-C=N), 8.54 (s, 1H, Py-H), 8.16-7.97 (m, 3H, Py-H + Ar-H), 7.94-7.79 (m, 2H, Ar-H), 7.72-7.60 (m, 2H, Ar-H), 7.54-7.44 (m, 2H, Ar-H), 7.43 (d, J = 8.7 Hz, 1H, Ar-H), 7.09 (dd, J = 8.6, 1.5 Hz, 2H, NH_2), 6.60 (d, J = 8.7 Hz, 3H, $^{+}NH_3$) 5.81 (s, 2H, CH_2-Ar), 2.79 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 193.33, 167.17, 161.79, 156.05, 151.11, 146.01, 139.59, 133.92, 133.59, 130.64, 129.01, 127.69, 126.25, 123.14, 121.60, 120.12, 119.09, 118.63, 117.54, 114.81, 56.35, and 23.95. EI-MS, (*m*/*z*, Int.%): (566.1, 90.82) $[M - H_2O]^+$. Anal. Calcd. for $C_{21}H_{23}ClN_5O_4PdS$ (M = 583.38): C, 43.24; H, 3.97; N, 12.00; S, 5.50; Found: C, 43.11; H, 4.21; N, 11.89; S, 5.24. Conductivity = 35.2 µS/cm.

[PdCl(4b)H_2O] (**5b**): Pale brown powder, Yield (0.385 g, 62.1 %), mp: 236 °C. FTIR (KBr, cm^{-1}): 3188 (m, br, $\nu_{(N-H)}$), 3115, 1492 (m, sh, $\nu_{(NH_3^+)}$), 1647 (vs, sh, $\nu_{(C=N)Azomethine}$), 1321 (s, sh, $\nu_{(SO_2)}$), 1283 (m, sh, $\nu_{(Ar-O)}$), 1166 (s, sh, $\nu_{(H-C=C\ +\ H-C=N)bend}$, Qn). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.09 (s, 1H, SO_2NH), 10.36 (s, 1H, NH), 9.9-9.95 (m, 1H, Qn-H), 9.13 (dd, J = 6.3, 1.7 Hz, 1H, Qn-H), 9.11 (d, J = 3.9 Hz, 1H, H-C=N), 8.58 (dd, J = 5.8, 0.9 Hz, 1H, Qn-H), 8.61-8.58 (m, 1H, Qn-H), 8.56-8.49 (m, 2H, 2 x Qn-H), 8.45-8.48 (m, 1H, Qn-H), 8.31 (td, J = 7.5, 1.7 Hz, 1H, Ar-H), 8.12-7.97 (m, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.67 (d, J = 2.2 Hz, 1H, Ar-H), 7.61 (dd, J = 4.3, 2.5 Hz, 1H, Ar-H), 7.54-7.37 (m, 1H, Ar-H), 7.11 (d, J = 8.6 Hz, 1H, Ar-H), 7.03-6.95 (m, 1H, Ar-H), 6.66 (d, J = 9.6 Hz, 2H, NH_2), 5.61 (s, 2H, CH_2-Ar). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 192.24, 161.23, 160.09, 158.65, 157.35, 156.43, 150.15, 148.41, 146.11, 139.09, 136.61, 132.12, 130.72, 128.83, 127.56, 126.31, 124.31, 123.83, 122.97, 121.13, 119.87, 118.63, 117.56 and 58.55. EI- MS, (*m*/*z*, Int.%): (566.1, 16.32) $[M - H_2O - Cl]^+$. Anal. Calcd. for $C_{24}H_{23}ClN_5O_4PdS$ (M = 619.41): C, 46.54; H, 3.74; N, 11.31; S, 5.18; Found: C, 46.36; H, 3.96; N, 11.03; S, 4.86. Conductivity = 28.6 µS/cm.

[PdCl(4c)H_2O] (**5c**): Deep orange crystals, Yield (0.387 g, 62.3 %), mp: 200-202 °C. FTIR (KBr, cm^{-1}):: 3200 (m, br, $\nu_{(N-H)}$), 3119, 1494 (m, sh, $\nu_{(NH_3^+)}$), 1649 (vs, sh, $\nu_{(C=N)Azomethine}$), 1323 (s, sh, $\nu_{(SO_2)}$), 1282 (m, sh, $\nu_{(Ar-O)}$), 1168 (s, sh, $\nu_{(H-C=C\ +\ H-C=N)bend}$, Im). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.05 (s, 1H, SO_2NH), 10.28 (s, 1H, NH), 8.98 (s, 1H, H-C=N), 7.82 (d, J = 2.0 Hz, 1H, Ar-H), 7.70-7.64 (m, 2H, Ar-H), 7.62 (s, 2H, Ar-H), 7.55-7.46 (m, 2H, Ar-H), 7.13-7.07 (m, 1H, Ar-H), 7.05 (d, J = 8.5 Hz, 1H, Ar-H), 6.93 (d, J = 8.4 Hz, 2H, NH_2), 5.36 (s, 2H, CH_2-Ar), 3.76 (s, 3H, CH_3), 2.62 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 191.02, 163.98, 161.27, 158.48, 156.90, 144.87, 136.42, 128.84, 128.32, 127.41, 125.77, 123.04, 122.82, 121.89, 121.42, 121.36, 118.46, 117.80, 116.49, 50.45, 35.23 and 10.03. EI-MS, (*m*/*z*, Int.%): (569.0, 16.77) $[M - H_2O - Cl]^+$. Anal. Calcd. for

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$C_{20}H_{24}Cl_2N_6O_4PdS$ (M = 621.83): C, 38.63; H, 3.89; N, 13.51; S, 5.16; Found: C, 38.42; H, 4.01; N, 13.37; S, 4.99. Conductivity = 31.3 µS/cm.

[PdCl(4d)H_2O] (**5d**): Pale brown powder, Yield (0.386 g, 59.4 %), mp: 168-170 °C. FTIR (KBr, cm^{-1}): 3199 (m, br, $\nu_{(N-H)}$), 3111, 1494 (m, sh, $\nu_{(NH_3^+)}$), 1649 (vs, sh, $\nu_{(C=N)Azomethine}$), 1323 (s, sh, $\nu_{(SO_2)}$), 1282 (m, sh, $\nu_{(Ar-O)}$), 1135 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.06 (s, 1H, SO_2NH), 10.30 (s, 1H, NH), 9.30 (s, 1H, d, J = 10.5 Hz, H-C=N), 8.94 (s, 1H, Ar-H), 7.85-7.79 (m, 3H, Ar-H), 7.75 (d, J = 2.4 Hz, 1H, Ar-H), 7.60 (dd, J = 8.7, 2.4 Hz, 1H, Ar-H), 7.47 (d, J = 8.5 Hz, 1H, Ar-H), 7.38 (d, J = 8.7 Hz, 2H, Ar-H), 7.08 (dd, J = 17.0, 8.6 Hz, 1H, Ar-H), 6.54 (d, J = 8.7 Hz, NH_2, 2H), 5.36 (s, 2H, CH_2-Ar), 4.17 (t, J = 7.0 Hz, 2H, C**H$_2$**-CH_2-CH_2-CH_3), 1.81-1.73 (m, 2H, CH_2-C**H$_2$**-CH_2-CH_3), 1.30-1.21 (m, 2H, CH_2-CH_2-C**H$_2$**-CH_3), 0.90 (td, J = 7.3, 2.3 Hz, 3H, CH_2-CH_2-CH_2-C**H$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 192.45, 161.73, 157.36, 151.80, 136.85, 135.78, 131.64, 130.68, 129.15, 127.75, 126.11, 123.25, 121.92, 112.78, 111.80, 107.31, 49.32, 40.58, 31.71, 20.08 and 14.68. EI-MS, (*m*/*z*, Int.%): (650.0, 65.32) $[M]^+$. Anal. Calcd. for $C_{22}H_{28}C_{l2}N_6O_4PdS$ (M = 649.89): C, 40.66; H, 4.34; N, 12.93; S, 4.93; Found: C, 40.43; H, 4.61; N, 12.76; S, 4.56. Conductivity = 26.4 µS/cm.

[PdCl(4e)H_2O] (**5e**): Dark yellow powder, Yield (0.453 g, 68.3 %), mp: 240 °C. FTIR (KBr, cm^{-1}): 3195 (m, br, $\nu_{(N-H)}$), 3116, 1493 (m, sh, $\nu_{(NH_3^+)}$), 1645 (vs, sh, $\nu_{(C=N)Azomethine}$), 1318 (s, sh, $\nu_{(SO_2)}$), 1284 (m, sh, $\nu_{(Ar-O)}$), 1173 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.21 (s, 1H, SO_2NH), 10.02 (s, 1H, NH), 8.98 (s, 1H, H-C=N), 7.88-7.78 (m, 1H, Ar-H), 7.73 (dd, J = 2.2, 1.4 Hz, 1H, Ar-H), 7.70-7.62 (m, 1H, Ar-H), 7.59 (d, J = 2.3 Hz, 1H, Ar-H), 7.55 (d, J = 2.3 Hz, 1H, Ar-H), 7.54-7.49 (m, 1H, Ar-H), 7.49-7.33 (m, 1H, Ar-H), 7.02 (d, J = 13.6 Hz, H, Ar-H), 6.83 (d, J = 8.5 Hz, 2H, NH_2), 5.38 (s, 2H, CH_2-Ar), 3.54 (dd, J = 17.3, 11.1 Hz, 3H, CH_3), 3.31 (tq, J = 13.6, 6.9 Hz, 1H, C**H**$(CH_3)_2$), 2.65 (d, J = 4.0 Hz, 3H, CH_3), 1.23 (d, J = 6.9 Hz, 6H, $CH(C\mathbf{H_3})_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 196.72, 172.03, 158.07, 149.58, 145.39, 144.50, 142.69, 137.19, 136.41, 133.48, 130.23, 127.02, 125.91, 124.96, 122.66, 121.61, 120.90, 118.29, 109.59, 50.22, 34.81, 25.90, 22.12 and 9.55. EI-MS, (*m*/*z*, Int.%): (611.2, 27.76) $[M - H_2O - Cl]^+$. ESI-MS (*m*/*z*): (319.2, 100) $[C_{10}H_{12}ClNO_2Pd]^+$. Anal. Calcd. for $C_{23}H_{30}Cl_2N_6O_4PdS$ (M = 663.91): C, 41.61; H, 4.55; N, 12.66; S, 4.83; Found: C, 41.28; H, 4.76; N, 12.46; S, 4.49. Conductivity = 29.6 µS/cm.

[PdCl(4f)H_2O] (**5f**): Dark yellow powder, Yield (0.476 g, 66.6 %), mp: 90-92 °C. FTIR

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(KBr, cm^{-1}): 3201 (m, br, $\nu_{(N-H)}$), 3116, 1494 (m, sh, $\nu_{(NH_3^+)}$), 1644 (vs, sh, $\nu_{(C=N)Azomethine}$), 1320 (s, sh, $\nu_{(SO_2)}$), 1287 (m, sh, $\nu_{(Ar-O)}$), 1171 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.20 (s, 1H, SO_2NH), 10.02 (s, 1H, NH), 8.96 (d, J = 5.0 Hz, 1H, H-C=N), 7.97-7.91 (m, 1H, Ar-H), 7.87-7.80 (m, 1H, Ar-H), 7.78 (d, J = 2.5 Hz, 1H, Ar-H), 7.77-7.73 (m, 1H, Ar-H), 7.72 (dd, J = 2.1, 1.3 Hz, 1H, Ar-H), 7.65 (td, J = 3.4, 2.1 Hz, 1H, Ar-H), 7.58 (d, J = 2.3 Hz, 1H, Ar-H), 7.50-7.49 (m, 1H, Ar-H), 6.78 (s, 2H, NH_2), 5.38 (s, 2H, CH_2-Ar), 3.55 (dd, J = 17.7, 11.1 Hz, 3H, CH_3), 3.31 (tq, J = 13.7, 6.9, 6.2 Hz, 1H, C**H**$(CH_3)_2$), 2.67 – 2.62 (m, 3H, CH_3), 1.22 (dd, J = 9.8, 6.9 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 196.13, 174.88, 167.26, 161.86, 157.87, 152.63, 147.05, 144.01, 141.97, 140.28, 133.46, 127.00, 124.96, 120.90, 116.06, 107.51, 107.00, 56.38, 52.14, 34.79, 26.22, 22.09 and 9.53. ^{19}F NMR (282 MHz, DMSO-d_6): –148.28 ppm (singlet). ^{11}B NMR (96 MHz, DMSO-d_6): –1.30 ppm (singlet). EI-MS, (*m*/*z*, Int.%): (662.2, 21.65) [M – H_2O – Cl]$^+$. ESI-MS (*m*/*z*): (319.2, 100) $[C_{10}H_{12}ClNO_2Pd]^+$. Anal. Calcd. for $C_{23}H_{30}BClF_4N_6O_4PdS$ (M = 715.26): C, 38.62; H, 4.23; N, 11.75; S, 4.48; Found: C, 38.38; H, 4.51; N, 11.77; S, 4.25. Conductivity = 28.5 µS/cm.

[PdCl(4g)H_2O] (**5g**): Orang powder, Yield (0.491 g, 63.5 %), mp: 121-123 °C. FTIR (KBr, cm^{-1}): 3185 (m, br, $\nu_{(N-H)}$), 3117, 1493 (m, sh, $\nu_{(NH_3^+)}$), 1650 (vs, sh, $\nu_{(C=N)Azomethine}$), 1323 (s, sh, $\nu_{(SO_2)}$), 1280 (m, sh, $\nu_{(Ar-O)}$), 1173 (s, sh, $\nu_{(H-C=C + H-C=N)bend}$, Im). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.21 (s, 1H, SO_2NH), 10.02 (s, 1H, NH), 8.98 (s, 1H, H-C=N), 7.88-7.79 (m, 1H, Ar-H), 7.73 (t, J = 1.8 Hz, 1H, Ar-H), 7.70 – 7.62 (m, H, Ar-H), 7.59 (d, J = 2.4 Hz, 1H, Ar-H), 7.54 (d, J = 2.0 Hz, 1H, Ar-H), 7.52 (d, J = 1.8 Hz, 1H, Ar-H), 7.50 (d, J = 2.2 Hz, 1H, Ar-H), 7.49-7.35 (m, 1H, Ar-H), 7.02 (s, 1H, Ar-H), 6.81 (s, 2H, NH_2), 5.38 (s, 2H, CH_2-Ar), 3.54 (dd, J = 17.2, 11.1 Hz, 3H, CH_3), 3.30 (dp, J = 13.6, 6.8 Hz, 1H, C**H**$(CH_3)_2$), 2.65 (d, J = 4.0 Hz, 3H, CH_3), 1.22 (dd, J = 9.8, 6.9 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 196.72, 165.44, 158.10, 149.60, 144.50, 142.71, 137.21, 133.48, 130.22, 127.02, 125.93, 124.97, 122.66, 121.61, 120.91, 118.30, 53.06, 50.21, 34.80, 26.22, 22.12 and 9.56. ^{19}F NMR (282 MHz, DMSO-d_6): –70.417 ppm (doublet, $^1J_{FP}$ = 711.5 Hz). ^{31}P NMR (202 MHz, DMSO-d_6): –144.21 ppm (septet, $^2J_{PF}$ = 711.40 Hz). EI-MS (*m*/*z*, Int.%): (721.2, 19.24) [M – H_2O – Cl]$^+$. ESI-MS (*m*/*z*): (319.2, 100) $[C_{10}H_{12}ClNO_2Pd]^+$. Anal. Calcd. for $C_{23}H_{30}ClF_6N_6O_4PPdS$ (M = 773.42): C, 35.72; H, 3.91; N, 10.87; S, 4.15; Found: C, 35.38; H, 4.03; N, 10.67; S, 4.00. Conductivity = 27.3 µS/cm.

Microbiological screening

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Antibacterial survey

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

Bacterial cultures: strains used in this study from National Organization for Drug Control and Research (NODCAR), Cairo, Egypt. The different strains are Staphylococcus aureus (*S. aureus*, ATCC-25923 as representatives for the Gram-positive bacteria and Escherichia coli (*E. coli*, ATCC-25922) as the most important Gram-negative pathogenic bacteria. Antifungal species, Aspergillus flavus (*A. flavus*) and Candida albicans (*C. albicans*, NCIM No. 3100). Stock cultures grown aerobically on nutrient broth (NB) agar slants (Hi-Media) at 37°C were maintained at 4°C. Pre-cultures containing 10^5 CFU/ml, grown aerobically in Mueller Hinton (MH) liquid medium (Hi-Media) at 37°C for 5 h, were used as inoculum for all experiments.

Antimicrobial susceptibility: Antimicrobial susceptibility of the bacterial strains was carried out by agar well diffusion method[17] (see supplementary information) for the target compounds as well as standard drugs, Ampicillin. The diameter of the zones of inhibition (ZOI, mm) was measured accurately as indicative of antimicrobial activity.

Determination of MIC; As parameters of the antibacterial efficacy, the minimal inhibitory concentration (MIC) of the new compounds against infection isolates were determined using the macro-dilution broth susceptibility test. Freshly prepared Mueller-Hinton (MH) broth was used as diluent in the macro-dilution method. A serial dilution of each compound was prepared within a desired range (0.25 mM to 20.00 mM). One mL of the stock cultures was then inoculated and tubes were incubated at 37 °C for 24 h, control tubes were assayed simultaneously. MIC was examined visually, by checking the turbidity of the tubes.

Results and Discussion

Synthesis of the target compounds

Step-by-step route for the synthesis of ionic Sal-SG Schiff bases (IL-Sal-SG) (**4a-g**) is depicted in Schemes 2,3. Where, the key starting materials IL-functionalized salicylaldehydes (**3a-g**) were synthesized starting from salicylaldehydes (**1a,b**) *via* a literature protocol.[10a,b,c] In which, the salicylaldehydes have been chloromethylated with paraformaldehyde/ HCl_{aq}/ $ZnCl_2$ mixture and then aminated with 2-methylpyridine (α-picoline, Pic), 1,2-dimethylimidazole ($(Me)_2Im$), 1-^{n}butylimidazole (^{n}BuIm) or qunioline (Qn) to generate the

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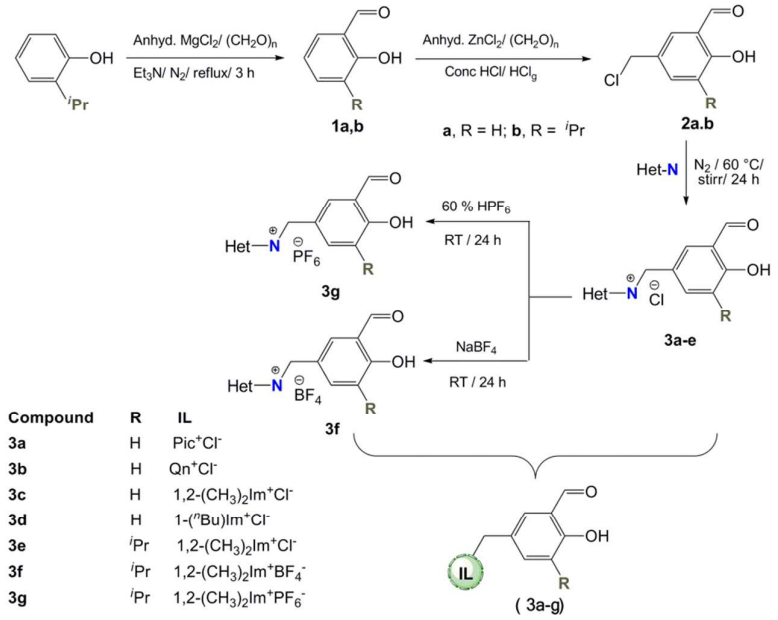
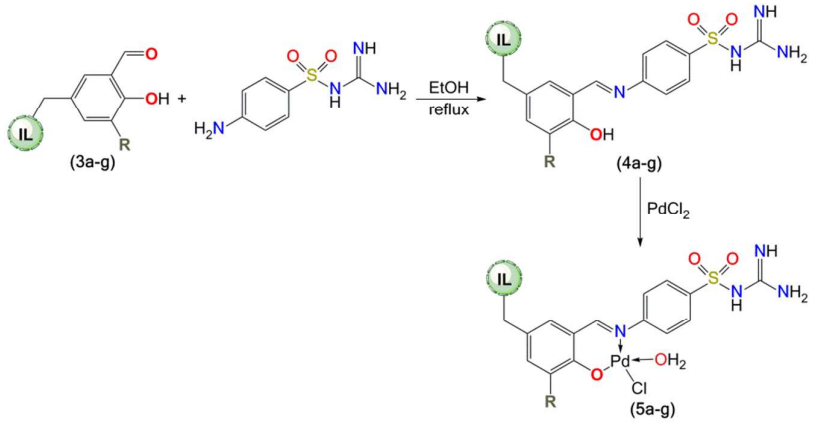
common precursors Sal-IL chlorides (**3a-e**). Anion metathesis of **3b** with hexafluorophosphoric acid ($HPF_{6(aq)}$) and sodium tetrafluoroborate afford the corresponding hexafluorophosphate and tetrafluoroborate salts (**3g,f**), respectively (see Schemes 2).



Scheme 2 Schematic diagram for the synthesis of ionic liquids-based salicylaldehydes (ILs-Sal, **3a-g**).

Eventually, the desired ILs-Sal-SG (ILSSGH) ligands (**4a-g**), were obtained simply by Schiff base condensation of ionic salicylaldehydes salts (**3a-g**) with sulfaguanidine (see Schemes 3). These ligands isolated in high to excellent yields and structurally characterized by elemental analysis, FTIR, NMR (^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{11}B), ESI-MS, as well as conductivity measurements.



Scheme 3 Synthesis of ionic sulfaguanidine-salicylaldimine Schiff base architectures (ILSSGH, **4a-f**) and their metalation by Pd(II) ion.

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Unfortunately all trials to metallate ionic sulfaguanidine Schiff bases, by refluxing a solution of the corresponding ILSSGH ligands (**4a-g**) with palladium(II) chloride in methanol, were unsuccessful. Instead, Pd(II) complexes, [Pd(II)(SGSIL)Cl(H_2O)] (**5a-g**), were obtained (*cf.* Scheme 2). The structures of Pd(II) complexes were proposed based upon elemental and spectral analysis (FTIR, NMR (^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{11}B), ESI-MS) as well as conductivity measurements and matching with the structure of previously reported Pd(II) complex analogue (Table S1, supplementary information).

Characterizations of ILSSGH ligands and their complexes

ILSSGH ligands (**4a-g**) and their Pd(II) complexes (**5a-g**) were prepared in high yields, gave satisfactory elemental analysis data which are consistent with their proposed structures (see the Experimental section). The molar conductance values of the free ligands and their Pd(II) complexes are in the range of 28.2-34.8 and 27.3-48.6 μS/cm, respectively, in accordance with their electrolytic nature.

FTIR marker bands and their assignments are given in Table S2 (supplementary information). The FTIR spectral data of ILSSGH (**4a–g**) revealed the following highlights: (i) the absorption peak appeared at the range of 3449±30 cm^{-1} attributed to the free phenolic OH stretch. (ii) Strong doublet in ranges of 3397±61 cm^{-1} and 3331±27 cm^{-1} are assignable to NH_2 vibration of guanidine moiety (NH-C(=NH)-NH_2). (iii) The N–H stretches for guanidine fragment exhibited low-energy shift, 3236-3185 cm^{-1} and 3174-3135 cm^{-1}, due to the involvement of amine protons in hydrogen bonding.[18] (iv) An intense band around 1621 cm^{-1} is due to azomethine (H–C=N) stretching vibration. (v) Three main peaks (C=N stretching vibration: 1543-1534; X^- vibration: 562-552 cm^{-1}, for Cl^-, 845 cm^{-1}, for PF_6^- and 1060 cm^{-1}, for BF_4^-; bending vibration: 773-757 cm^{-1}) which are characteristic for the ionic liquid terminals. (vi) A medium-intensity band in the range of 1268±5 cm^{-1} is attributed to $\nu_{Ar\text{-}O}$. Noteworthy, a very weak shoulder at 1578±5 cm^{-1} which could be assigned as a perturbed carbonyl stretching with the frequency lowering from a free carbonyl ascribed to conjugation and hydrogen bonding in ketoenamine forms as shown in Scheme 4. This is indicative of the central backbone is in the expected *O*-protonated enolimine tautomeric form with minor contribution of ketoenamine form in the solid state.

Comparison of the FTIR spectroscopic data collected for Pd(II) complexes with those obtained for the free ligands demonstrates marked changes in the IR signatures of ligands (see Figure 1) arising from the binding of Pd(II) ion by the donor atoms set in ligands.

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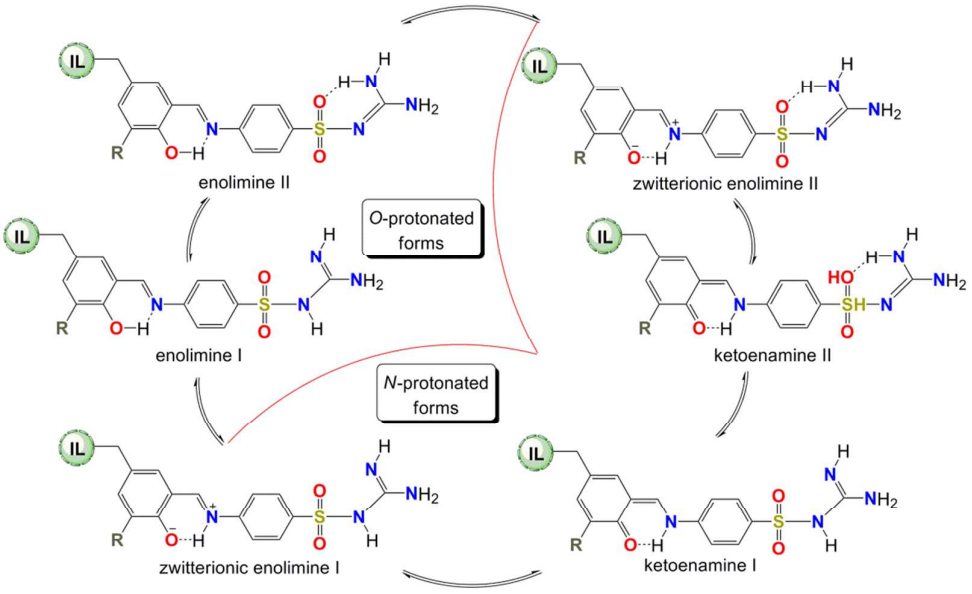

Scheme 4 Possible sulfonamide-sulfonimide and enolimine-ketoenamines tautomeric forms and H-bonding profile ionic in Sal-SD Schiff bases

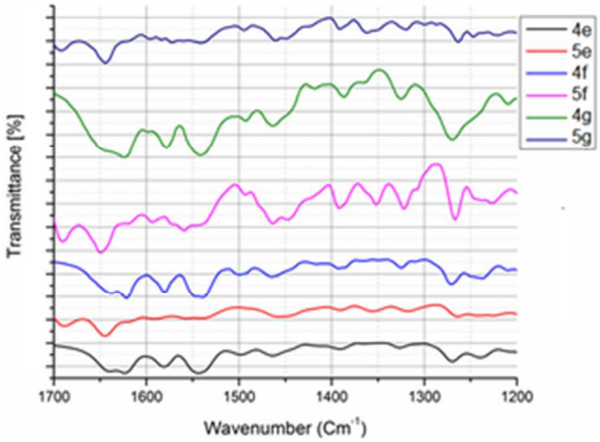

Figure 1 Selected IR region (1700-1200 cm^{-1}), for comparison of the azomethine and phenolate stretching vibrations and their splitting patterns.

The phenolic–OH stretches which have been observed in the FTIR spectra of the ILSSGH, at *ca.* 3449 cm^{-1}, were lost in the spectra of the Pd(II) complexes, indicating deprotonation of the phenolic oxygen and replacement of phenolic proton by Pd(II) ion, this further confirmed by a remarkable shift of the phenolic C–O stretch to higher frequency by 11–36 cm^{-1} in the spectra of complexes (Table 1). Interestingly, emergence of a new weak band at 1687±5 cm^{-1}, typical of a carbonyl group, coupled with a red-shift of the perturbed carbonyl stretching peak in the spectra of Pd(II) complexes confirming the participation of carbonyl oxygen of the ketoenamine tautomer in bonding with Pd(II). Moreover, the

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enolimine/ ketoenamine tautometic equilibrium is slightly shifted toward the keto-enamine tautomer upon coordination to Pd(II). Also consistent with the complex formation and the participation of azomethine nitrogen in binding with Pd(II) ion was the observation that, the strong $\nu_{C=N(azomethine)}$ stretches in the FTIR spectra of the free ligands were displaced to lower frequency, by 10–29 cm^{-1}, in complexes (*cf.* Table 1). Finally, the broad band at *ca.* 3439-3385 cm^{-1} agrees with the hydrated nature of complexes as suggested by the microanalytical data. In conclusion, infrared spectroscopic data suggested that, of ILSSGH architectures act as bidentate NO-chelating ligands.

Table 1 Comparison of FTIR structural parameters in ILSSGH ligands and their Pd(II) complexes

Nr.	$\nu_{(O-H)}$	$\nu_{(C=N)}$	$\Delta\nu_{(C=N)}$	$\nu_{(Ar-O)}$	$\Delta\nu_{(Ar-O)}$
4a	3425	1617	–	1263, 681	–
5a	–	1627	+10	1283, 706	+20, +25
4b	3419	1622	–	1267, 679	–
5b	–	1645	+23	1280, 705	+23, +26
4c	3419	1620	–	1265, 683	–
5c	–	1649	+29	1282, 707	+17, +24
4d	3476	1623	–	1270, 682	–
5d	–	1645	+22	1284, 718	+14, +36
4e	3436	1625	–	1272, 680	–
5e	–	1647	+22	1283, 715	+11, +35
4f	3475	1624	–	1270, 684	–
5f	–	1644	+20	1287, 719	+17, +35
4g	3479	1621	–	1273, 682	–
5g	–	1650	+29	1280, 716	+17, +34

^{1}H NMR spectra of ILSSGH and their Pd(II) complexes are dominated by common remarkable features: (i) The presence of deshielded resonance at δ = ~13.0 ppm, in the spectra of ILSSGH, originating from the intramolecularly H-bonded phenolic OH,[19] the disappearance of these signals in the ^{1}H NMR spectra of Pd(II) complexes (see Figure 2) corroborates the successful deprotonation and formation of phenolate precursors. This is also likely consequence of engaging the phenolate oxygen into coordination to the Pd(II) ion. (ii) The sulfonamide NH proton resonates at low field (11.14 ± 0.08 ppm in free ligand) due to intramolecular hydrogen bonding N–H···O, an amine–imine (*cf.* Scheme 4) interchange may be considered the most probable reason for broadening of this signal.[20] (iii) The immutability of guanidine N-H signal, δ 9.99 ± 0.68 ppm in free ligand, in ^{1}H NMR spectra of complexes suggested a non-participation of the C=NH moiety in coordination to Pd(II) ion. However, the NH_2 signal (δ 9.99 ± 0.68 ppm in free ligand) in the spectra of complexes is flanked by satellites due to the protonation of the amino group is with HCl to form the corresponding

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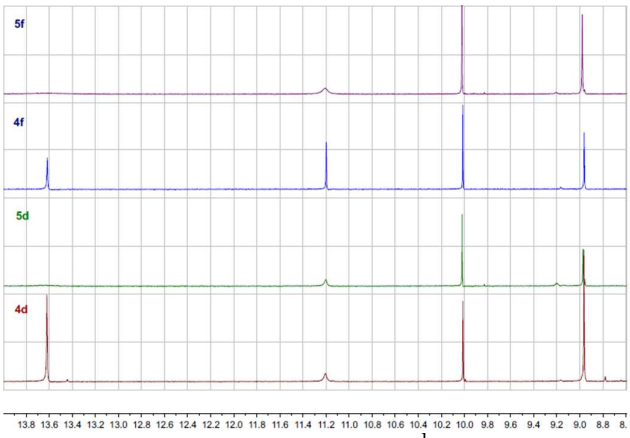
guanidinium salts. (iv) Noteworthy, consistent with the participation azomethine nitrogen in bonding to the Pd(II) ion is the observation that the splitting and a downfield shift in position



of azomethine proton signal, by 0.05-0.07 ppm, in the ^{1}H NMR spectra of complexes.

Figure 2 partial ^{1}H NMR region (8.7-14.0 ppm), for comparison of the azomethine and phenolic protons resonance and their splitting patterns in **4f** & **4d** and there Pd(II) complexes.

The common spectral peculiarities of the ^{13}C NMR spectra for ILSSGH (**4a–g**) represented in the two characteristic signals around δ 164/ 194 ppm and 158 ppm corresponding to carbon atom attached to the phenolic oxygen (C-1) and azomethine nitrogen (C-7), respectively. These peaks are shifted either downfield or upfield in all Pd(II) complexes, indicating the coordination of deprotonated Schiff base to Pd(II) *via* (O) phenolic attached to C-1 and (N) azomethine attached to C-7 as shown in Scheme 3.

Pharmacology

Many clinical trials of new active pharmaceutical ingredients (API) end in failure due to the low efficacy of the drug because of limited bioavailability or solubility. Anchoring of ionic liquid terminals to sulfaguanidine (SG) could provide a synergetic effect of improving water solubility and at the same time enhancing the pharmacological effect.

Antimicrobial activity profile

The target imidazolium/ pyridinium/ quinolinium IL-supported Sal-SG ligands, their complexes, and standards drugs were in vitro assessed separately for their capacity to inhibit the growth of a range of clinically significant pathogenic bacterial strains including *Staphylococcus aureus* (*S. aureus*) as gram-positive bacterium, *Escherichia coli* (*E. coli*), as gram-negative one, and Aspergillus flavus (*A. flavus*) as well Candida albicans (*C. albicans*, NCIM No. 3100), as fungal pathogens. In general, our data (ZOIs, Figure 3) demonstrate that

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the incorporation ionic liquid terminals exerts an overall additive effect with respect to microbiological toxicity, where ionic compartments: (i) ameliorate the water-solubility of Sal-SG and (Sal-SG)Pd(II);[21] (ii) enhance the cytotoxicity of new architectures, Sal-SG/ (Sal-SG)Pd(II), to microbial strains especially against *S. aureus*. The effectiveness of the target compounds in inducing staphylococcalcidal effect higher than E. coli-cidal action could be ascribed to their cell envelope *i.e.* membrane(s), a complex multilayered structure that serves to protect these organisms from their unpredictable and often hostile environment, structural differences. Where, *E. coli* and most gram-negative bacteria possess an outer membrane outside the peptidoglycan layer which is lacking in gram-positive organisms, *S. aureus*. The essential function of the outer membrane is to serve as a selective permeability barrier, protecting bacteria from antibacterial agents. The outer membrane of *E. coli* is predominately made of patches of Lipopolysaccharide (LPS) each containing hundreds to thousands of LPS molecules. The packing of the nearest neighbor patches is tight, and as such the LPS layer provides an effective permeability barrier for the *E. coli* bacterium.[22]

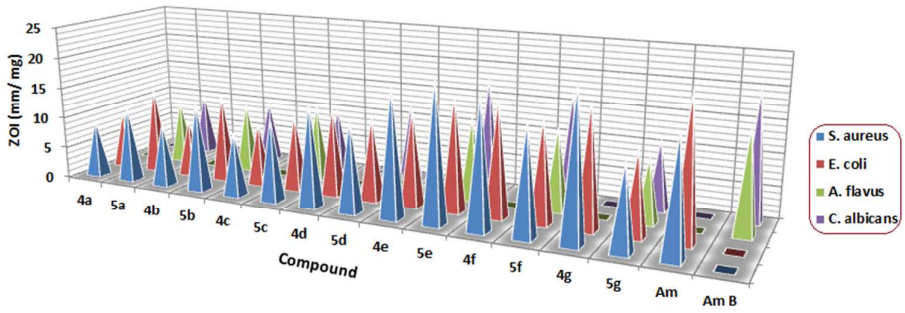
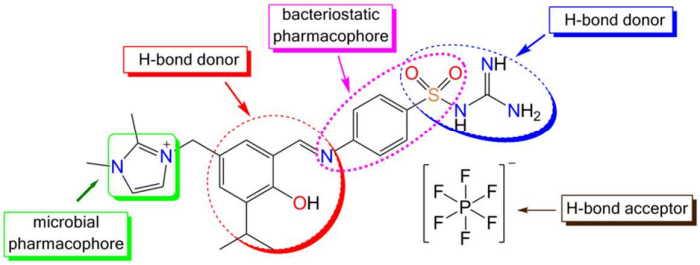


Figure 3 Graph of zone of inhibition/mm for target compounds against different microbial species.

Among all tested compounds, ligand **4g** (Scheme 5), 4-N-(5-(1,2-dimethyl-imidazolium hexafluorophosphate)-3-isopropylsalicylidene)sulfaguanidine, exhibit remarkable extra-potent bactericidal activity when compared with standard drug and can be classified as a new good candidate in fighting staphylococcalcidal infections.



Scheme 5 significant pharmacological sites in **4g**

As shown in Figure 3, all ionic Schiff bases are inactive as fungicides. This limited or

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lack of fungicidal activity could be attributed to: (i) the complex structure of fungal cell-wall that composed typically of chitin, 1,3-β- and 1,6-β-glucan, mannan and proteins[23], which function as a barrier that limits diffusion of tested compounds through. (ii) Fungal fighting that proceeds by much more complex mechanisms than bacterial conflict.

Noteworthy, Pd(II) complexes are potent than parent ligands and have moderate fungicidal efficacy compared to the standard antibiotic. The enhanced activity of the ligands upon complexation can be explained in terms of Overtone's concept of cell permeability[24] and Tweedy's Chelation theory.[25] Considering these theories, chelation considerably reduces the polarity of the Pd(II) ion because of the partial sharing of its positive charge with the donor sites and possible π–electron delocalization over the chelate ring. So the lipophilicity of Pd(II) ion increases as result of chelation, which subsequently favors the diffusion of complexes through the lipid layer of the bacterial cell membrane.[26] Moreover, complexes may also disturb the respiration process of the microbial cell and thus block the synthesis of the proteins that restricts further growth of the organism.

Antibacterial efficacy

As a parameter of antibacterial efficacy, the minimal inhibitory concentration (MIC) of the most potent compounds were determined against *S. aureus* and *E. coli* using the macro-dilution broth susceptibility test using the percentages of inhibition at five different concentration levels, 0.15-20 mM. The bacterial growth is inhibited by the target compounds in a dose-dependent profile and the activity is greatly enhanced at the higher concentration. The observed MIC values (Table 2) demonstrated the strongest biocidal action for **4g** (*cf.* Scheme 5) against *S. aureus* ($MIC_{S.\ aureus}$ = 1.18 mM) which is 8-fold lower than that against *E. coli* ($MIC_{E.\ coli}$ = 9.85 mM). Consequently, **4g** can be classified as a new promosing candidate in the fight against Staphylococcal infections. Further studies are required to explore this compound as a new antibiotic.

Table 2 MIC (mM) assay results for promising antibacterial compounds against different strains[a]

Compounds	MIC (mM)	
	S. aureus (ATCC 29737)	*E. coli* (ATCC 10536)
4e	6.56 ± 0.88	11.76 ± 0.49
5e	6.22 ± 0.53	11.39 ± 0.47
4f	7.23 ± 0.31	12.07 ± 0.30
5f	8.73 ± 0.25	13.85 ± 0.25
4g	1.18 ± 0.11	9.85 ± 0.15
Am	6.45	10.10

[a] *S. aureus* representative for G^+ Bacteria, *E. coli* as G^- Bacteria

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Am. = Ampicillin (Antibacterial drug)

Proposed mode of microbial action

Although the exact mechanism by which antimicrobial ionic Sal-SG/ (Sal-SG)Pd(II) exert microbiological toxicity has not fully elucidated, their biocidal mode of action may involve various targets in microorganisms: (i) Hydrogen-bonding interactions of the H-receptor sites in a target compound (such as guanidine, azomethine and hydroxyl fragments) with the active binding sites of components of microbial cells, resulting in interference with the normal cell process.[27] (ii) The planar geometry of these complexes might allow extra coordination of Pd(II) with electron donating centers of vital molecules of the microbial cells. Moreover, the variation in the effectiveness of the different compounds against different strains depends on the impermeability of the cells of microbes or difference in ribosome of the microbial cells.

Conclusion

The biocidal activity of newly synthesized N-(salicylidene)sulfaguanidine bearing ionic liquids compartments (ILSSGH, **4a-f**) and their Pd(II) complexes (**5a-f**) has been investigated against common bacterial and fungal pathogens. Both the ZOIs and MIC values revealed that ILSSGH have the ability to inhibit the growth of fungal strains < *E. coli* < *S. aureus*. The structure–activity relationship (SAR) study demonstrated that changes of the ionic liquids fragments exhibited different antimicrobial activities levels. Also, alkyl substituents on IL-Sal backbone play a more important role in determining the biocidal properties of ILSSGH/ Pd(II)-ILSSG architectures. Where, exchanging of H-atom on IL-Sal by ^{iso}Propyl substituent dramatically decrease the minimal inhibitory concentrations.

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Appendix A. Supplementary data

Supplementary data (experimental and spectral data) associated with this article are available with the article through the journal Web site, at doi:

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Ionic Sal-SG Schiff bases as new synergetic chemotherapeutic candidates: Synthesis, metalation with Pd(II) and *in vitro* pharmacological evaluation.

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