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Recent progress in silver(I)-, gold(I)/(III)- and palladium(II)-*N*-heterocyclic carbene complexes: A review towards biological perspectives

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ABSTRACT

N-Heterocyclic carbenes (NHCs) complexes have received a great deal of attention as new broad-spectrum antimicrobial and anticancer agents, which encourage the biological activity against numerous pathogens and human cancer cell lines. The metal-NHC complexes provide a range of versatile structural diversifications for the targeted biological applications with promising acceptable result. Most of the metal-NHC complexes are synthesized through *in situ* deprotonation or direct metalation techniques using azolium salts, and *via* transmetalation technique through initially prepared Ag(I)-NHC complexes. This review focuses on the recent reports of synthesis, structural characterization and biological applications of Ag(I)-, Au(I)/(III)-, and Pd(II)-NHC complexes with great efficacy in both *in vitro* and *in vivo* studies. Numerous reports have documented that the metal-NHC complexes are great bioactivity potential in comparable or better activity than the standard chemotherapeutic drugs. These complexes can have significant contribution in the field of bioorganometallic chemistry, and thus worthy explored as a medicinal drug in the nearer future.

Contents

1. Introduction

Starting with the first successful metalation of imidazole-2-ylidenes by Öfele and Wanzlinck in 1968 [1,2], the idea of electron-rich olifens have attracted an interest in developing the *N*-heterocyclic carbenes (NHCs) complexes [3,4]. Previously, various attempts were made to isolate the free NHC moiety, however were unsuccessful despite numerous techniques and means were introduced. Only in 1991 the first stable NHC moiety was successfully isolated which subsequently revived the significant interest of scientist community throughout the world [5–7]. Since then, the NHC began as mere laboratory curiosities and elevated to enormous scaffolds used in coordination and organometallic chemistry [8,9]. These compounds were mostly used as an excellent NHC ligand for the transition metal, due to the electronic stability, steric effects and structural diversity [10]. Additionally, the possibility of

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NHCs as a ligand for both soft and hard metal can be rationalized by their strong σ-donor capabilities as well as donation ability into σ-acceptor orbital of the metal [11,12]. The σ-donation nature of coordination bonding in metal-NHC complexes has been fully studied by different research groups and extensively reviewed by Diez-Gonzalez and Nalon [13] as well as Jacobsen and co-workers [14]. The studies have revealed that the σ-donation is the most peculiar component in metal-NHC ligand binding with the contribution of both π-back bonding and π-donation is neither significant nor considerable [15].

The attractive features of metal-NHC complexes have led to a wide range of different applications across the chemical sciences perspectives. Initially, the metal-NHC complexes were used extensively as a catalyst in organic reactions such as Suzuki-Miyaura cross-coupling [16,17], Mizoroki-Heck cross-coupling [18], transfer-hydrogenation reactions [19], hydrosilylation [20] and alkylation reactions [21]. The success of NHC spectator ligands in complexes can be attributed to the increasing catalytic activity, which consequently lowering the rates of decomposition of catalyst due to strong metal-NHC ligand bond. In addition, the distinct steric and electronic influence of NHC motif on the metal center also leads to improve the catalytic stability for better activity [22–24].

Meanwhile, despite the catalytic activities of metal-NHC complexes, various studies had revealed prominent biological activities of metal-NHC complexes. These include the discovery of new antimicrobial/anticancer compounds and instigated the evaluation of these complexes as antiproliferative agents [25,26]. Several metal-NHC complexes were employed as metallodrugs in the field of medicinal chemistry due to their remarkable biological activities with minimal side effect [27,28]. Among these novel complexes, Ag(I)-, Au(I)- and Pd(II)-NHC complexes have recently gained considerable attention due to their mode of action and their properties that perfectly fit the prerequisite for efficient drug design and fast optimization [29]. Furthermore, the aforementioned metal complexes are relatively mild or non-toxic to humans, although they can cause skin or eye irritations if the exposure is in prolonged or excessive [30]. The remarkable biological activity of Ag(I)-, Au(I)- and Pd(II)-NHC complexes against bacteria, fungi and various cancer cell lines is due to slow delivery of metal ions across the cell membrane which can finally disrupt the cell functions [31,32]. However, Eloy et al. reported that the biological activities metal-NHC complexes are not always due to the release of metal ions to the cell membrane; it is rather shows that the complexes induced apoptosis through the mitochondria apoptosis-inducing factor [33].

The successful biological activities of metal-NHC complexes explored a great structural variety ranging from linear, square pyramidal, trigonal bipyramidal, tetrahedral and octahedral geometries of Ag(I)-, Au(I)- and Pd(II)-NHC complexes [34]. The rationale behind the designing of NHC ligands is to provide controls over key kinetic properties such as hydrolysis rate of the ligands used. Furthermore, the kinetic stability of NHC ligand is usually unchanged upon coordination with Ag(I)-, Au(I)-, Pd(II) ions, due to their relatively lipophilic and low oxidation state [35]. Due to these fundamental differences compared to other classical coordination of Ag, Au and Pd-complexes, the Ag(I)-, Au(I)-, Pd(II)-NHC complexes offer ample opportunities in the design of novel classes of medicinal compounds with the new metal ions specific mode of action. The toxicity of these metals is effective against a broad range of gram-negative and gram-positive bacteria, fungi and cancer cells [36]. Noteworthy, most of the pure metals are nearly inactive, however these metal ions can show significant potential in biological activities once being ionized [37]. The bioavailability of metal-NHC complexes are also depends on delivery method, solubility and ionization of metal ions sources [38]; these could be enough to withstand the activity of metal-NHC complexes before its degradation as a result of biological molecule in the body system [39,40]. The mechanism of action for metal ions is yet to be completely discovered, but hypothesis shows that the metal ions bind to the cell surface and subsequently interact with the important cell membrane. Metal ions can also affect the cell respiration, transport and metabolism, as well as DNA, RNA and cellular organelle structure [25].

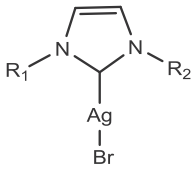
In 2009, Hindi et al. reviewed the medicinal applications of imidazolium based carbene complexes for both antimicrobial and anticancer activities [41]. Following on that, a more concise review on Ag(I)-NHC was written focusing on the biological relevant Ag(I)-NHC complexes with synthesis, structure, intramolecular interaction and applications [42]. In their recent review, Liu and Gust provide a critical assessment of the update of metal-NHC complexes that can be used as potential antitumor metallodrugs [43]. In part from that, the comparative insight into the bioactivity of mononuclear and binuclear Ag(I)-NHC complexes was also reported in order to understand the relationship between the number of metal ions and biological activity [44]. Herein, we report an analysis on the recent synthesis developments of Ag(I)-, Au(I)/(III)- and Pd(II)-NHC complexes and their biological activities. This review will focus mainly on the influence of chain lengths and substituents on the metal-NHC complexes that can effectively affecting the biological activities.

2. Silver(I)-*N*-heterocyclic carbene complexes

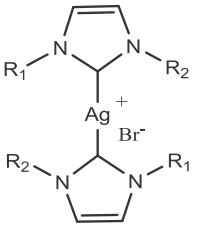
The Ag(I)-NHC complexes are observed to be very stable towards air and moisture, which can be prepared efficiently by the established protocols. These methods including the treatment of free NHCs with appropriate silver sources [45], treatment of azolium salts with basic silver sources such as Ag_2O, $AgCO_3$, and AgOAc [46], as well as with the treatment of azolium salts with silver salts in the presence of external base known as basic phase-transfer conditions [47]. Nowadays, the *in situ* deprotonation using Ag_2O as a basic silver source has become a prominent and readily available method used for the synthesis of Ag(I)-NHC complexes.

Prior to the uses of Ag(I)-NHC complexes as antimicrobial or anticancer agents, some ionic silver related drugs like silver sulfadiazine and silver nitrate are commercially available [48]. The latter aforementioned silver ion compounds have some disadvantages due to the quick release of silver ion to the target point of the cell resulting in the short-term efficacy, whereas for a good activity of silver involves the slow and sustained release of the silver ions into a cell membrane for better activity [43,49]. Furthermore, the discovery of Ag(I)-NHC complexes with different substituents are found to enhance the activity of silver drugs in antimicrobial and anticancer activities effectively. The mechanism of action for Ag(I)-NHC complexes are related to the capability of the slow and sustained release of silver ions which subsequently allow the latter to interact with the proteins involved in the cell membrane in order to disrupt the cell functions [50]. The Ag(I)-NHC complexes are found to have superior biological activity over the other silver compounds due to slow dissociation of Ag(I)-NHC complex and thus resulting continual release of silver ions over a period of time [29,51].

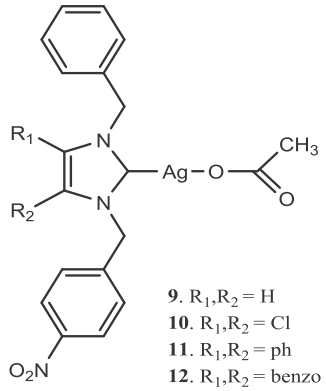
Further investigations in bioactive of Ag(I)-NHC complexes leads to different types of complexes ranging from neutral, ionic, mononuclear and binuclear complexes. Recently, Aher and coworkers have reported a new series of neutral and ionic mononuclear Ag(I)-NHC complexes, **1**–**8** (Fig. 1) [52]. The complexes were prepared from imidazolium-based novel ionic liquids (ILs) through *in situ* deprotonation method using Ag_2O at room temperature in the dark. The polarity of the solvent used in the



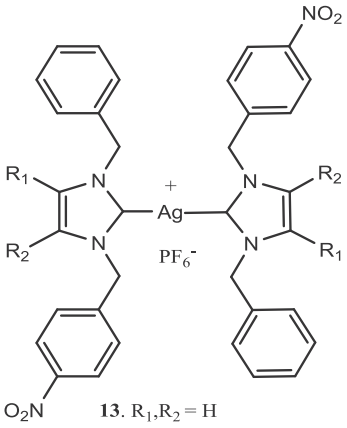
1. $R_1 = R_2$ = biphenyl carbonitrile
2. R_1 = biphenyl carbonitrile, R_2 = benzyl
3. R_1 = biphenyl carbonitrile, R_2 = butyl
4. R_1 = biphenyl carbonitrile, R_2 = methyl



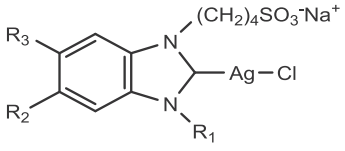
5. $R_1 = R_2$ = biphenyl carbonitrile
6. R_1 = biphenyl carbonitrile, R_2 = benzyl
7. R_1 = biphenyl carbonitrile, R_2 = butyl
8. R_1 = biphenyl carbonitrile, R_2 = methyl



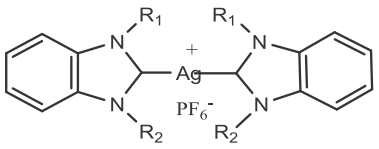
9. R_1,R_2 = H
10. R_1,R_2 = Cl
11. R_1,R_2 = ph
12. R_1,R_2 = benzo



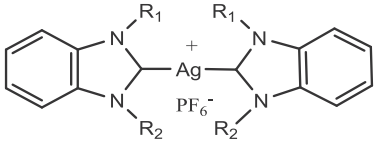
13. R_1,R_2 = H
14. R_1,R_2 = Cl
15. R_1,R_2 = ph
16. R_1,R_2 = benzo



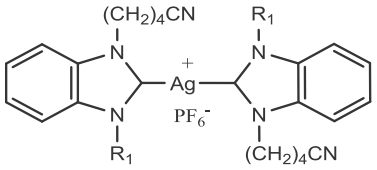
17. R_1 = 2-methylbenzyl, $R_2 = R_3$ = H
18. R_1 = 2,3,4,5,6-pentamethylbenzyl, $R_2 = R_3 = CH_3$
19. R_1 = ethylmorpholine, $R_2 = R_3$ = H
20. R_1 = 4-tert-butylbenzyl, $R_2 = R_3 = CH_3$
21. R_1 = 3,5-dimethylbenzyl, $R_2 = R_3 = CH_3$



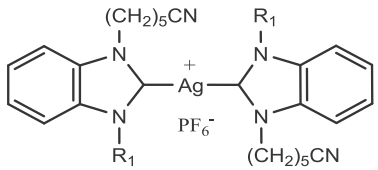
22. $R_1 = R_2$ = benzyl
23. $R_1 = R_2$ = hexyl
24. $R_1 = R_2$ = heptyl
25. $R_1 = R_2$ = octyl



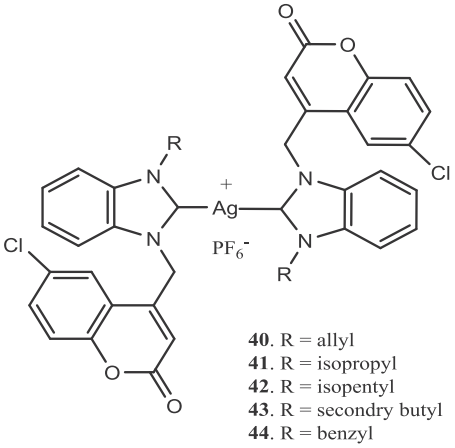
26. $R_1 = R_2$ = propyl
27. $R_1 = R_2$ = butyl
28. $R_1 = R_2$ = pentyl
29. $R_1 = R_2$ = hexyl
30. $R_1 = R_2$ = heptyl
31. $R_1 = R_2$ = octyl
32. $R_1 = R_2$ = nonyl
33. $R_1 = R_2$ = decyl



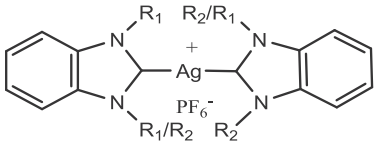
34. R = propyl
35. R = butyl
36. R = pentyl



37. R = propyl
38. R = butyl
39. R = pentyl



40. R = allyl
41. R = isopropyl
42. R = isopentyl
43. R = secondry butyl
44. R = benzyl



45. R_1 = pentyl, R_2 = cyanopropyl
46. R_1 = cyanopropyl, R_2 = cyanobenzyl
47. $R_1 = R_2$ = cyanobenzyl

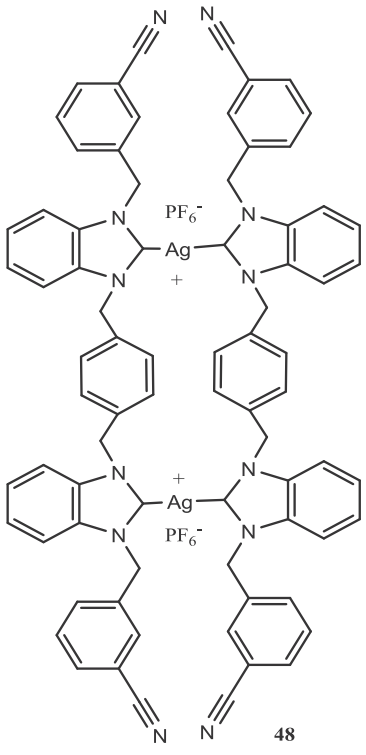


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Fig. 1. Structures of Ag(I)-NHC complexes **1**–**48**.

synthesis plays a major role in the formation of neutral or ionic complexes, in which the non-polar solvents favor the neutral complexes **1**–**4** while polar solvents stabilize ionic complexes **5**–**8**, respectively. Studies on *in vitro* antimicrobial activity of the Ag(I)-NHC complexes **1**–**8** against *S. aureus, B. cereus, E. coli* and *S. enteric*, respectively were conducted using DMSO (control) and kanamycin solution (standard). The minimum inhibitory concentrations (MICs) determination and stability studies against microbial growth have shown that all complexes inhibited the microbial growth with higher MIC values. Symmetrically substitution complexes **1** and **5** bearing biphenyl exhibited the most potent inhibition of microbial growth against *S. aureus* with the MIC value of 6.25 μM, while at the same time complex **1** also showed MIC value of 25 μM against *S. enterica* (Table 1). The better activity of these complexes was proved due to the presence of bulky group which provides an extra stability and lipophilicity of complexes in their system. The optical density measurement was used at 600 nm to assign the relative potency among the tested compounds. In addition to that, the cell morphological changes were observed with scanning electron microscope (SEM) which showed the rupture of the bacterial cell wall and thereby indicating a site action in the cell wall were resulting from the bacterial cell inhibition growth. Lipophilicity, the side chain *N*-substituted in the NHC ligands as well as metal complexes is varied in order to investigate the steric effect and hydrophobicity on antibacterial activity. The aforementioned factors contribute towards the stability of complexes which enhance the control against bacterial growth [52].

Non-symmetrically Ag(I)-NHC complexes with *p*-nitrobenzyl-substituted that were used as metallapharmaceutical agents were also recently reported [53]. The mono-NHC-Ag(I) acetate complexes **9**–**12** and bis-NHC-Ag(I) ionic complexes **13**–**16** were synthesized from their corresponding azolium salts with $Ag(OAc)_2$ and Ag_2O, via deprotonation in methanol and acetonitrile, respectively. The formation of complexes as neutral mono-NHC-Ag(I) acetate and bis-NHC-Ag(I) ionic complexes is related with the different silver sources and the polarity of the solvents used in the synthesis procedure. The structure of complex **14** was confirmed by single crystal X-ray diffraction analysis and show that the molecule is non-planar in nature with the silver center lies on the inversion center. The silver ion is coordinated to two moieties of NHC ligands in an *anti*-arrangement, representing as a linear geometry with C-Ag-C bond angle of 180°. In that work, a study of the *in vitro* antibacterial and anticancer activity of reported complexes were conducted, respectively. In the antibacterial study, the compounds were evaluated against two gram-positive bacterial strains (*S. aureus* and *B. subtilis*) and three gram-negative bacterial strains (*E. coli, S. sonnei* and *S. typhi*) with promising antibacterial activity were achieved (Table 1). The Kirby-Bauer's disc diffusion method was used to determine the MIC values of the synthesized complexes. Both mono- and bis-NHC-Ag(I) complexes exhibit moderate to high antibacterial activity with the MIC values were in the range of 8−128 μg/mL. Complex **12** exhibits high potent activity towards *S. aureus* and *E. coli*, whereas **15** was equally effective against *E. coli* with MIC value of 8 μg/mL. Furthermore, all complexes were evaluated for anticancer potential against human-derived breast adenocarcinoma cells (MCF-7) using MTT assays. Both mono- and bis-NHC-Ag(I) complexes displayed highly potential in anticancer activity with the IC_{50} values lied in the range of 10.39−59.56 μg/mL (Table 1). It was reported therein that the complex **14**, with two chlorine atoms attached to the imidazolium ring exhibited the highest anticancer potential with an IC_{50} value of 10.39 μg/mL. Generally in that study, among the synthesized complexes, the mono-NHC-Ag(I) complexes showed a pharmaceutical performance better than that of bis-NHC-Ag(I) complexes [53].

Yasar et al. reported the synthesis, characterization and biological activity of unprecedented water-soluble sulfonated-functionalized Ag(I)-NHC complexes **17**–**21** (Fig. 1) [54]. The metal complexes were prepared from their corresponding sulfonated benzimidazolium salts using Ag_2O in the presence of either NaCl or NaBr. These complexes were investigated for anticancer activity against a series of human cancer cell lines such as Hela (human cervix carcinoma), HT29 (human adenocarcinoma) and L929 (mouse fibroblast) cell lines. The IC_{50} values that lied in the range of

Table 1
Chemical shifts, structural and biological activities data of Ag(I)-NHC complexes **1**–**48**.

Complex	C-Ag (chemical shift)	*S. aureus/B. cereus*	*E. coli/S. enterica*
1	143.79	6.25	25
2	137.72	50	50
3	143.84	100	>100
4	143.88	50	>100
5	143.63	6.25	100
6	137.69	50	100

Complex	C-Ag (chemical shift)	MCF-7	*S. aureus/B. subtilis*	*E. coli/S. sonnei*	*S. typhi*
9	180.8	16.74	16/128	32/64	128
10	183.3	13.28	16/128	16/128	128
11	181.9	13.55	16/64	16/64	64
12	190.9	16.26	8/128	8/128	128
13	181.0	59.56	16/128	64/64	128
14	183.3	10.39	16/64	16/64	128
15	151.9	33.18	16/64	16/64	64
16	173.7	36.56	16/128	16/128	128

Complex	C-Ag (chemical shift)	HeLa	HT29	L929
17	188.4	30.32 ± 1.17	61.6 ± 1.20	40.0 ± 1.13
18	187.6	5.99 ± 1.32	13.87 ± 1.11	10.43 ± 1.12
19	191.6	16.64 ± 1.14	12.65 ± 1.14	23.24 ± 1.17
20	150.9	21.04 ± 1.14	49.14 ± 1.16	15.18 ± 1.17
21	190.9	15.72 ± 1.14	27.18 ± 1.10	20.42 ± 1.13

Complex	C-Ag (chemical shift)	*Ae. Albopictus*	HCT-117	MCF-7
22	187.6	3.367×10^6	–	–
23	187.5	6.982×10^5	–	–
24	188.5	8.376×10^5	–	–
25	188.5	1.223×10^6	–	–
26	187.9	–	26.8 ± 2.30	–
27	187.9	–	25.7 ± 1.27	–
28	187.6	–	13.2 ± 1.50	–
29	187.6	–	3.9 ± 0.62	–
30	187.6	–	1.1 ± 0.28	–
31	187.6	–	0.4 ± 0.05	–
32	187.5	–	0.02 ± 0.02	–
33	187.5	–	0.3 ± 0.12	–
34	188.9	–	–	12.9 ± 1.55
35	188.4	–	–	9.3 ± 0.72
36	188.8	–	–	7.3 ± 1.56
37	187.7	–	–	9.8 ± 1.36
38	187.7	–	–	9.1 ± 0.84
39	187.4	–	–	7.0 ± 1.06

Complex	C-Ag (chemical shift)	*S. aureus/B. subtilis*	*E. coli/P. aeruginosa*	*S. typhi/S. sonnei*
40	179.2	32/128	16/8	128/128
41	173.4	32/128	16/8	128/128
42	187.1	32/128	16/8	128/128
43	188.3	32/128	16/8	128/128
44	191.9	32/128	16/8	128/128

Complex	C-Ag (chemical shift)	*Ae. Albopictus* LC_{50}/LC_{90}	*E. coli*	*S. aureus*
45	188.3	33.23/116.44	50	50
46	189.2	45.35/115.61	100	100
47	190.8	56.44/165.17	100	100
48	188.9	11.68/27.735	25	12.5

5.99 ± 1.32–61.6 ± 1.20 μM of complexes were determined by proliferation BrdU enzyme-linked immunosorbent assay (ELISA) against aforementioned cancer cell lines with cisplatin as a standard drug (IC_{50} = 43.87 ± 1.14–53.15 ± 1.11 μM) (Table 1). All the new water-soluble Ag(I)-NHC complexes **17**–**21** exhibited as promising and remarkable cytotoxic potential activity against human cancer cell lines. The study showed that the complex **18**, which incorporated a bulky 2,3,4,5,6-pentamethylbenzyl moiety had a better anticancer activity with IC_{50} value was four to eight times more potent than cisplatin against Hela, HT29 and L929 cancer cell lines. This excellent cytotoxicity was correlating with structural differences and stronger electron-donating NHC-bearing the complexes that subsequently enhanced the stability of the complexes. Apoptosis study demonstrated none of the tested complexes showed DNA fragmentation potential, indicating that the antiproliferative and cytotoxicity effect of the complexes took place via different mechanisms [54].

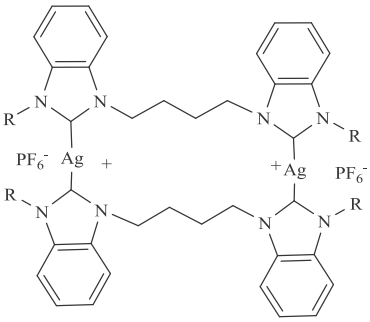
The new Ag(I)-NHC complexes **22**–**25** bearing symmetrically *N*-substituted NHC ligands were synthesized *via* deprotonation using basic Ag_2O [55]. All complexes were interacting with *Aedes albopictus* DNA through intercalation mode by a high hypochromicity of 22% and 27% and lower hypochromicity of 16% and 19%, respectively. Additionally, complexes showed efficient DNA cleavage activity through the non-oxidative mechanistic pathway, whereby the DNA activities of the tested complexes demonstrated a time and concentration-dependent activity pattern. The Ag(I)-NHC complexes showed that the DNA cleavage changed from a moderate to the highest effect (Table 1), with proportion to the increasing lipophilicity in order of complexes as **22** < **23** < **24** < **25** (1.02. 1.05, 1.78 and 2.06 for **22**–**25,** respectively). The lipophilicity order was also correlated with DNA binding ability, but with exception of complex **22**, which show higher DNA binding ability ($K_b = 3.367 \times 10^6$) than that of complexes **23**–**25** (6.982×10^5, 8.376×10^5 and 1.223×10^6, respectively) [55].

We have reported before a series of symmetrically *n*-alkyl substituted mononuclear Ag(I)-NHC complexes **26**–**33** with steady increases in *n*-alkyl chain length [56]. The structure of complex **33** that was elucidated using X-ray crystallography study showed that the structure was stabilized by interdigitating interaction of the adjacent alkyl chain. All compounds were evaluated for their *in vitro* anticancer potential against human colon cancer cell line (HCT-116) using 5-fluorouracil (5-FU) as a standard drug. It was observed that these complexes showed dose-dependent cytotoxicity against the cancer cell line with the IC_{50} values were in the range of 0.3–26.8 μM (Table 1). Furthermore, the results showed that there was an influence relationship between the increase in carbon side chain of wingtip *n*-alkyl groups and the anticancer effect. The complexes **30**–**33** with long *n*-alkyl chain length (n = 6–10) exhibited a significant anticancer activity (IC_{50} = 0.3–3.9 μM) compared to the standard drug (IC_{50} = 10.2 μM) [56]. In analogous studies, we have recently reported a series of nitrile functionalized Ag(I)-NHC complexes with varying the substituents such as with propyl, butyl and pentyl, **34**–**39** [57]. The molecular structure of **34** and **38** were elucidated using single-crystal X-ray diffraction analyses with the crystal structures showed that the complexes molecules are in asymmetric unit and Ag(I) is coordinated to two NHC ligands in a linear coordination. The synthesized complexes were evaluated for cytotoxicity effect against breast cancer cell line (MCF-7) using the MTT assay. All complexes showed a promising effect with appreciable IC_{50} values ranging from 7.0 ± 1.06 to 12.9 ± 1.55 μM, compared to the standard drug used in that study, Tamoxifen (IC_{50} = 11.2 ± 1.84) (Table 1). The study proved that the cytotoxicity of complexes were increased with the increases of carbon chain side, thus related to the lipophilicity assays which indicated that the cytotoxicity of complexes was correlated well with their lipophilicity [57].

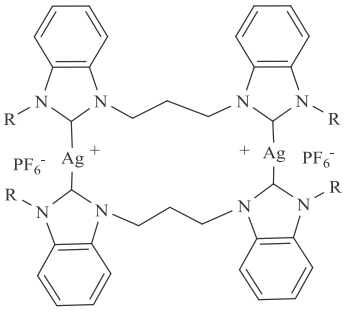
Achar and coworkers [58] had evaluated the antibacterial activities for a series of Ag(I)-NHC complexes **40**–**44**, derived from asymmetrically substituted coumarin-tethered benzimidazolium salts. Complexes were noted for pronounced antibacterial effect against two gram-positive bacterial strains (*S. aureus* and *B. subtilis*) and four gram-negative bacterial strains (*E. coli, P. aeruginosa, S. typhi* and *S. sonnei*) (Table 1). This antibacterial study was carried along with comparable MIC with that of ampicillin (internal standard drug) using disc diffusion method. The Ag(I)-NHC complexes displayed moderate to high antibacterial activity with the inhibition zone were in the range of 7±1–12 ± 1 and 7±1–25 ± 2 mm against *S. aureus* and *E. coli* respectively. The MIC values were in the range of 0.5–128 μg/mL against both strains of bacteria. Additionally, the activity of complexes against *E. coli* was in correlation with increases in alkyl substituents as well as increases in lipophilicity of the complexes. In the case of *B. subtilis*, complexes showed moderate activities which were almost two-fold lesser than that standard ampicillin (MIC = 128 μg/mL). Interestingly, the complexes activities against *P. aeruginosa* were found to be promising with the MIC value of 8 μg/mL, which was better than the standard drug. In contrast, the activities against *S. typhi* and *S sonnei* demonstrated low activity with the MIC value of 128 μg/mL [58].

More recently, we have reported a series of nitrile-functionalized Ag(I)-NHC complexes **45**–**48** which were characterized by spectroscopy techniques and molar conductivity [59]. In addition, complex **48** was structurally elucidated by single crystal X-ray diffraction technique that displayed that both Ag(I) ions are in linear fashion with the crystal packing of the molecule is dominated by the presence of π-π interactions between the aromatic rings. All compounds were screened for their *in vitro* antibacterial evaluation against two standard bacterial, gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacterial strains. The complexes displayed moderate to good antibacterial activities with MIC values of 12.5–100 μg/mL, whereby complex **48** exhibited better and promising antibacterial activity against *S. aureus* with a low MIC value of 12.5 μg/mL. Furthermore, the complexes were further investigated for effective DNA binding study, in which the results revealed that complex **48** was effectively intercalated into DNA to form 8b-DNA complex, with better binding ability for DNA ($K_b = 3.367 \times 10^6$) than the complexes **45**–**47** (2.177×10^6, 8.672×10^5 and 6.667×10^5, respectively). Furthermore, the larvicidal activity of complexes **45**–**48** was also investigated against dengue mosquito (*Ae. albopictus*) (Table 1). Complexes **45**, **46** and **48** were considered highly active (LC_{50} = 11.68–45.35 ppm and LC_{90} = 27.73–115.61 ppm) against the mosquito larvae while complex **47** was considered to be less active (LC_{50} = 50.07 ppm and LC_{90} = 165.17 ppm). Indeed, the LC_{50} value (11.68 ppm) and LC_{90} value (27.73 ppm) of complex **48** was the lowest value which approximately 3- to 5-fold and 4- to 6-fold lower respectively than that of other complexes. This indicates that complex **48**, which is a binuclear type complex was more toxic against mosquito larvae compared to the other tested complexes (mononuclear structure) that could be due to the presence of excess Ag(I) ions with the complex [59].

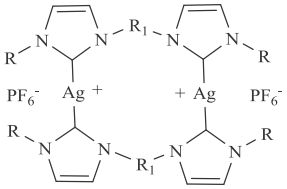
Further investigations in bioactivity for Ag(I)-NHC complexes led to the synthesis of a series of binuclear Ag(I)-NHC complexes from tetramethylenebis(*N*-n-alkylbenzimidazolium) bromide salts [60], in which the complexes **49**–**56** were reported to be prepared via deprotonation technique using corresponding bis-benzimidazolium salts (Fig. 2). The single crystal X-ray diffraction of complex **54** revealed that the complex exist as a binuclear complexes with the NHC ligand behaving as a bridging ligand connecting two units Ag(I) ions. All synthesized compounds were assessed for antiproliferative activities against human colorectal cancer cell line (HCT 116). The complexes have shown a promising



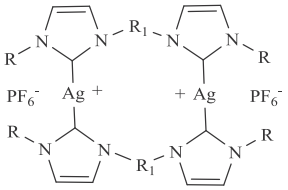
49. R = propyl **53**. R = heptyl
50. R = butyl **54**. R = octyl
51. R = pentyl **55**. R = nonyl
52. R = hexyl **56**. R = decyl



57. R = ethyl
58. R = propyl
59. R = butyl
60. R = pentyl



61. R, R_1 = CH_3, C_3H_6 **64**. R, R_1 = C_2H_5, C_4H_8
62. R, R_1 = CH_3, C_4H_8 **65**. R, R_1 = C_3H_7, C_2H_4
63. R, R_1 = C_2H_5, C_2H_4 **66**. R, R_1 = C_3H_7, C_3H_6



67. R = cyclopentane, R_1= ortho-xylyl
68. R = cyclopentane, R_1= meta-xylyl
69. R = cyclopentane, R_1= para-xylyl
70. R = cyclopentane, R_1= ethylene

Fig. 2. Structures of Ag(I)-NHC complexes **49**–**70**.

cytotoxic potential against this specific cancer cell line, with better activity compared to the standard drug 5-FU and their corresponding bis-benzimidazolium salts. Interestingly, the periodic increase of *N*-alkyl substituted chain length from $n = 3$ to 10 and tetramethylene linker reflected the increases of lipophilicity in the complexes, thus correlate to the increases of cytotoxic with IC_{50} values ranging from 0.04 to 3.5 μM (Table 2). Furthermore, the acute oral toxicity study also shown that 2 g kg^{-1} of these complexes was a safe dose and can be used for acute oral toxicity [60].

We have also reported similar series of binuclear Ag(I)-NHC complexes **57**–**60** which synthesized from the series of propylene linked bis-benzimidazolium salts with different *N*-substituents such as ethyl, propyl, butyl and pentyl [61]. All the compounds were characterized by spectroscopy techniques and crystal structure elucidation for one of the complexes, **58** has revealed that the structural arrangement of this complex is agreeable to what was proposed. All compounds were evaluated for anticancer activity against human breast cancer cell line (MCF-7) using MTT assays. The complexes showed comparable cytotoxicity activity with IC_{50} values of 7 ± 1 to 18 ± 3 μM, compared to the standard drug, Tamoxifen (IC_{50} value of 11± μM) and inactive bis-benzimidazolium salts (Table 2).

Aher et al. reported the series of symmetrically substituted binuclear Ag(I)-NHC complexes with variable linker moieties, **61**–**66** [62]. The compounds were synthesized from di-cationic ionic liquids (DCILs) which are relatively scarce. The cytotoxic behavior of these compounds was evaluated against human colorectal carcinoma cell line (HCT-116) and was used to investigate the influence of *N*-substituted on the cytotoxic activity. The complexes displayed good patterns of cytotoxicity and were found to be in correlation with an increase in the alkyl chain as well as an increase in lipophilicity. Complexes **61, 65** and **66** were reported to show 86%, 99% and 99% growth cell inhibition at the concentrations of 120, 120 and 60 μM, respectively (Table 2). The optimum complex **66** was then selected for putative mechanisms which the results displayed a significant induction of apoptosis in HCT-116 cells. Additionally, the 4,6-diamidino-2-phenylindole (DAPI) confirmed the chromatin condensation and DNA fragmentation, thus further

Table 2
Chemical shifts, structural and biological activities data of Ag(I)-NHC complexes **49**–**70**.

Complex	C-Ag (chemical shift)	HCT116[a]	MCF-7[b]
49	187.6	3.7	–
50	187.6	2.5	–
51	187.6	2.5	–
52	187.5	1.3	–
53	188.0	0.8	–
54	187.5	0.1	–
55	187.6	0.1	–
56	187.9	0.04	–
57	187.1	–	9 ± 1
58	187.7	–	7 ± 1
59	188.4	–	18 ± 3
60	187.5	–	11 ± 2
61	157.36	21.16 ± 1.9	–
62	157.36	86.12 ± 1.87	–
63	157.36	50.49 ± 0.56	–
64	157.36	63.98 ± 1.78	–
65	157.35	42.22 ± 0.47	–
66	157.35	28.54 ± 1.12	–
Complex	C-Ag (chemical shift)	*Ae. Aegypti*	*C. quinquefasciatus*
67	179.6	45.28	83.64
68	179.1	69.22	119.13
69	178.7	21.78	24.81
70	179.0	71.53	159.73

confirming the mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) formation. The HCT-116 cells was treated with complex **66** showed a higher ROS and depolarization of MMP, thus suggesting that complex **66** induced mitochondria-mediated intrinsic apoptosis in cells. Henceforth, the evaluation shows HCT-116 cells exhibited a low level of oxidant defensive protein catalase. Overall, this study suggested that the Ag(I)-NHC complexes can reduce anti-oxidative protein catalase while at the same time increase the ROS level [62].

Selvarajoo et al. synthesized and evaluated a series of binuclear Ag(I)-NHC complexes **67**–**70** (Fig. 2) with cyclopentane rings as substituent attached to the NHC moiety for their larvicidal activity [63]. Single crystal X-ray diffraction analyses were used to elucidate the molecular structure of complexes **67** and **69** which showed that each binuclear complexes is constructed by two bidentate NHC ligands, with both Ag(I) ions adopt distorted linear geometry. The larvicidal studies against *Ae. aegypti* and *Cx. quinquefasciatus* documented that the mortality rate of larvae was solely depending on the concentration of the metal complexes. Herein, the larvicidal activity showed total cause (100%) mortality at high concentration (200 ppm) in both mosquito species. The more stable complex **69** bearing *para*-xylyl linker exhibited the highest mortality with LC_{50} values of 21.78 and 24.81 ppm against *Ae. aegypti* and *Cx. Quinquefasciatus*, respectively (Table 2).

3. Gold(I)/(III)-*N*-heterocyclic carbene complexes

Gold has received an intense interest in the synthesis of metal complexes especially in the field of contemporary coordination and organometallic chemistry [64]. Recently, it has been found that gold metal exists in the formation of stable coordination complexes with NHC ligand, which their structural diversity depends on the coordination motifs of the NHC ligands used [65]. The Au(I)-NHC complexes can be prepared by various methods which have been reported before [66]. Nowadays, the synthesis of Au(I)-NHC complexes via transmetalation reaction from initially prepared Ag(I)-NHC complex, which was initiated by Wang and Lin [67] has become a preferred method used by other researchers [68,69]. This method involves the synthesis of Ag(I)-NHC complex from NHC precursor which the formed Ag(I)-NHC was subsequently reacted with the gold source [70,71]. The latter reaction then resulted in the NHC ligand primarily in Ag(I) complex being transferred to Au(I) center [72]. The developments in this synthesis support the recent resurgence of interest in Au(I)-NHC complexes for various uses, which in turn has initiated the synthesis of new complexes with diverse structure [73].

The interests in biological applications of Au-complexes are relatively increased in recent years, which are used as an active ingredient of so-called *aurum vitae* medicine [74]. Medici et al. had introduced the Au-complexes as a modern drugs therapy [32], and later Schmidt and coworkers demonstrated the antibacterial activities of gold cyanide salt [75]. Currently, Au-based complexes such as Au(I)-NHC complexes have caught an attention in inorganic medicinal chemist to be used as metallodrugs [76]. Indeed, the Au(I)-NHC complexes are known to show high potential activities against the growing cancer cell and pathogenic bacteria [77]. Moreover, Au(I)-NHC complexes offers distinct advantages over the other Au-based complexes due to their stability improvement and structural versatility of NHC ligands [78]. In previous studies, different structures of Au(I)-NHC complexes have been reported as well as investigated for their cytotoxicity potential and various biological activities such as antibacterial and anticancer activities [41,43,79].

Among them as well, a series of *N, O* and *S*-functionalized Au(I)-NHC complexes, **71**–**84** were synthesized via transmetalation reaction (Fig. 3) [80]. The complexes were evaluated for *in vitro* antiplasmodial activity against *P. falciparum* strains by determining their effectiveness which then compared to the antimalarial reference drugs (chloroquine and artemisinin). Complexes **71**–**84** showed potent antiplasmodial activity with IC_{50} values were in the range of 0.21 ± 0.04–6.6 ± 0 μM (Table 3). As expected, the potent antiplasmodial activity of Au(I)-NHC was enhanced when compared to the corresponding starting proligands which the latter were found to be less active. This result was corroborated by the presence and role of Au(I) ion in antiplasmodial activity against *P. falciparum.* The neutral complexes **72, 76** and **82** showed moderate activities while the both cationic and anionic showed higher activity. In addition, the activity of complexes was correlated with their lipophilicity in which the structure-activity relationship proved that the complex **80** that containing mesityl moiety displayed a better activity compared to the other complexes and standard drugs [80].

The interesting complexes of Au(I)/(III)-NHC based on (benz) imidazole-2-ylidene **85**–**87** that prepared by NHC ligand transfer from their corresponding Ag(I)-NHC complexes were reported from our own group [81]. The structural motif of complexes **85** and **86** and oxidation states of Au(III) in complex **85** were confirmed by single crystal X-ray diffraction method. Complexes were subjected to anticancer potential against human colon cancer (HCT 116), breast carcinoma (MCF-7), prostate cancer (PC3) and leukemia (U937) cell lines by MTT assay method. It was observed that these complexes showed dose-dependent antiproliferative activities against four aforementioned cancer cell lines with IC_{50} values were in the range of 0.05 ± 0.01–126.27 ± 1.7 μM (Table 3). However, the Au(III) complex **85** exhibited a significant antiproliferative activity ($IC_{50} = 0.05 \pm 0.01$ μM for HCT 116, 0.31 ± 0.02 μM for MCF-7, 0.34 ± 0.02 μM for PC3 and 0.19 ± 0.002 μM for U937) compared to the other Au(I) complexes and standard drug. This study revealed that the antiproliferative effect of complex **85** against four cancer cell lines was actually caused by the redox activities, which might occur at the cellular environment. Additionally, the better activity of complex **85** was also contributed due to the presence of three labile chloride ligands, which enhanced the stability of complex for remarkable activity [81].

Another related works are the studies on the synthesis and biological evaluation of both Au(I)-pseudohalides and Au(I)-thiolates–NHC complexes, **88**–**93** which were reported by Dada and co-workers [82]. The two series of complexes have been synthesized by two separate developed procedures; the pseudohalides complexes were synthesized using a biphasic medium while the thiolates complexes required a higher temperature in the synthesis procedure. All complexes **88**–**93** were fully characterized and the crystal structure of complexes **89, 91** and **92** was developed by single crystal X-ray diffraction analyses. The structural studies showed that the bond angles of C-Au-S and C-Au-N are almost in linear geometry, leading to pseudo-carbene symmetry for the molecules. The Au(I)-NHC complexes were tested for cytotoxicity potential on the National cancer Institute's 60 (NCI 60) human cancer tumor cell lines (Table 3), in which complexes **88, 89** and **92** showed medium to low activity while complexes **90, 91** and **93** showed a promising activity on NCI 60 cancer cell panel. Furthermore, complexes **90** and **93** showed similar average growth inhibition 50% (GI_{50}) values of 1.78 μM and 1.95 μM respectively, while complex **91** showed superior activity with an average GI_{50} value of 0.47 μM [82].

A recent study on the synthesis of Au(I)-NHC complexes including their antibacterial activity bearing a steroid derivative (ethinylestradiol and ethisterone), **94**–**99** have been reported by Velle et al. [83]. In this work, the structure of complex **97** was merely determined by single-crystal X-ray diffraction analyses. The

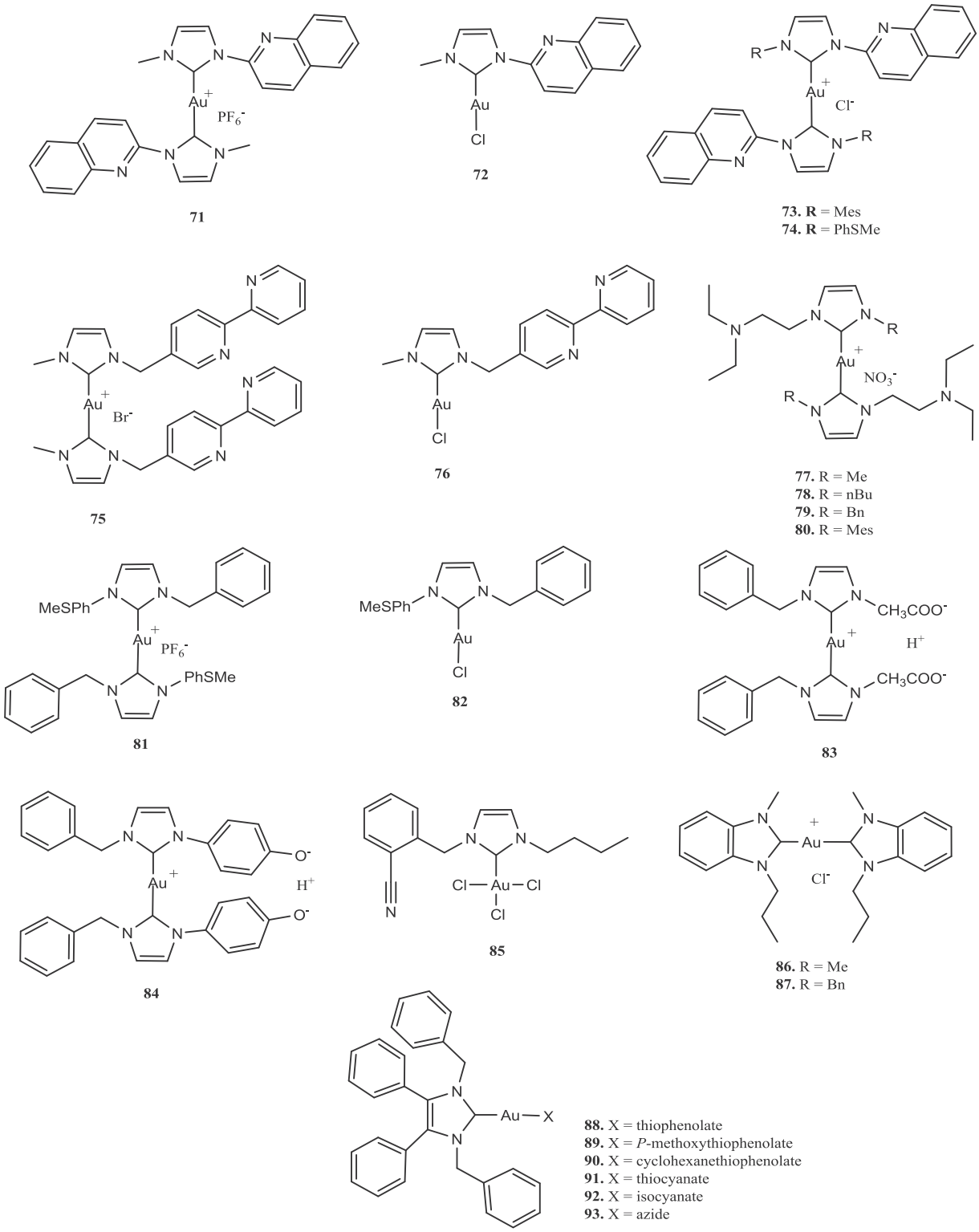


Fig. 3. Structures of Au(I)/(II)-NHC complexes **71**–**93**.

crystal structure studies showed that the Au(I) ion is coordinated to one NHC ligand and alkynyl fragment with the C-Au-C angle show a minimal distortion in molecular structure. The biological studies revealed a noteworthy antibacterial activity against both gram-positive and gram-negative bacterial strains, *S. aureus* and *E. coli*, respectively (Table 3). Complexes **94** and **95** bearing 1,3-dimethyl and 1-methoxyethyl-3-methyl moieties, respectively, were the most active among the other synthesized Au(I)-NHC complexes screened in both *S. aureus* and *E. coli* bacterial strain, with very low MIC_{50} value (average $MIC_{50} = 4.1$ and 5.85 μM for **94** and **95** respectively). The presence of estrogens seemed to slightly lower the antibacterial activity with respect to complexes **94** and **95**. In

Table 3
Chemical shifts and selected biological activities data of Au(I)/(III)-NHC complexes **85**–**107**.

Complex	C-Au (chemical shift)	*P. falciparum*
71	182.9	1.1 ± 0.1
72	170.10	5.2 ± 2.0
73	181.41	1.1 ± 0.2
74	180.82	0.47 ± 0.1
75	183.21	0.33 ± 0.03
76	171.99	6.6 ± 0
77	184.01	2.2 ± 3.8
78	182.81	2.1 ± 0.3
79	183.80	0.48 ± 0.06
80	183.90	0.21 ± 0.04
81	181.57	0.32 ± 0.08
82	168.90	4.1 ± 0.4
83	184.51	5.6 ± 0.8
84	181.55	3.7 ± 0.7

Complex	C-Au (chemical shift)	HCT116	MCF-7	PC3	U937
85	171.3	0.05 ± 0.01	0.31 ± 0.02	0.34 ± 0.02	0.05 ± 0.02
86	184.9	49.9 ± 2.4	7.62 ± 0.4	126.27 ± 1.7	4.7 ± 0.4
87	178.3	23.4 ± 1.8	7.32 ± 0.8	5.58 ± 0.6	1.7 ± 0.06

Complex	C-Au (chemical shift)	MCF-7	SN12C	K-562	NCI/COLO205
88	182.8	1.32	1.86	0.60	3.47/2.04
89	156.3	1.55	2.24	1.62	5.25/2.00
90	166.0	1.55	1.82	2.24	2.95/1.95
91	175.5	0.47	0.37	0.40	1.95/0.29
92	165.6	–	–	–	–
93	169.6	1.74	1.38	1.74	4.57/1.74

Complex	C-Au (chemical shift)	*S. aureus*	*E. coli*
94	172.2	7.02 ± 0.9	1.17 ± 0.3
95	171.2	7.02 ± 0.7	4.68 ± 0.5
96	188.2	14.1 ± 1.8	2.34 ± 0.4
97	187.5	75 ± 3.8	4.68 ± 0.6
98	188.3	115 ± 6.6	75 ± 4.3
99	199.9	129 ± 7.8	9.37 ± 0.7

Complex	C-Au (chemical shift)	HT-29	MCF-7	MDA-MB-231	RC124
100	181.2	11.15 ± 0.71	6.68 ± 0.82	9.18 ± 0.50	5.07 ± 0.14
101	178.9	11.59 ± 0.51	9.05 ± 1.88	10.89 ± 0.15	8.84 ± 0.33
102	178.9	11.71 ± 0.41	7.19 ± 0.83	9.00 ± 0.69	11.48 ± 0.45
103	169.8	16.97 ± 0.25	11.25 ± 1.09	11.58 ± 0.09	10.58 ± 0.69
104	171.8	12.05 ± 0.72	6.52 ± 0.72	8.22 ± 0.37	5.49 ± 0.32
105	170.3	6.80 ± 0.98	4.76 ± 0.21	8.13 ± 0.60	4.46 ± 0.04
106	170.5	6.14 ± 0.75	5.05 ± 0.67	5.54 ± 0.25	4.62 ± 0.25
107	170.9	6.23 ± 0.57	4.73 ± 0.65	7.20 ± 0.45	4.91 ± 0.73

addition, complexes **96** and **97** bearing an estradiol derivative were much better active than their counterpart complexes **98** and **99** bearing a testosterone moiety (average $MIC_{50} = 8.2$ μM and 39.4 μM for **96** and **97**, and 95.0 μM and 69.2 μM for **98** and **99**, respectively). This activity could be correlated with higher stability and solubility of complexes bearing estradiol than complexes with testosterone derivative. In further studies, the most active complexes **94**–**97** were further investigated for *in vivo* toxicity against *G. mellonella* insect larvae using three different concentrations of complexes. Complexes **94** and **95** showed the highest activity without any significant increases in larvae survival, while complexes **96** and **97** bearing estradiol demonstrated an opposite activity compared with the former [83].

The synthesis and biological evaluation for a series of halogen-containing complexes, NHC-Au(I)-Cl, **100**–**107** were reported by Schmidt et al. (Fig. 4) [78]. The synthesized complexes exhibited good cytotoxic potential activity against HT-29 carcinoma cells as well as MCF-7 and MDA-MB-231 breast cancer cell lines. These anticancer results were also supported by previously established results which showed that the complexes can triggered the IC_{50} values in the range of 4–17 μM (Table 3). A certain trend for higher cytotoxicity was observed for complexes **105**–**107**, thus indicated the strong antiproliferative effect against all mentioned cancer cell lines. Complexes **105**–**107** were selected for evaluation of their protein binding and cellular uptake due to their high activity against tested cancer cell lines. The studies revealed that the cytotoxic activity of complexes was strongly influenced by the stability and efficiency to accumulate in the cells. Additionally, the cellular bioavailability of complexes was also affected by binding to albumin with afforded values of greater than 80%. The effective inhibition of mammalian and bacterial thioredoxin (TrxR) was confirmed for all complexes. Overall, the *in vitro* antibacterial efficiencies against gram-positive bacterial strains (*E. faecium* and *S. aureus*) and gram-negative bacterial strains (*A. baumannu, E. cloacae, E. coli, K. pneumonie* and *P. aeruginosa*) resulted the inhibition using low concentration of the compounds. Complex **103** displayed moderate activity against *E. coli, E. cloacae* and *K. pneumonie* with the MIC values were in the range of 37–42 μM (Table 3). The most potent analogue complex was **104** which inhibited the proliferation of *E. faecium* and two Methicillin-resistant *staphylococcus aureus* (MRSA) strains with MIC values of 3.12, 0.64 and 0.64 μM, respectively. The latter was more active compared to complex **103** could be due to the present of bromide moiety attached to the imidadolium ring (Fig. 4).

Another important contribution of Au(I)-NHC complexes is by Karaca et al. which led to the synthesis and biological evaluation of a series of mononuclear and binuclear Au(I)-NHC complexes **108**–**114** (Fig. 4) [84]. The reported complexes bearing sulfonated bis-NHC ligands, **108**–**111** and hydroxylated mono-NHC ligand, **112**–**114** were examined against the 2008 human ovarian cancer cells line by MTT assays. Cell viability assay proved the strong antiproliferative activity of the hydroxylated Au(I)-NHC complexes **112**–**114** against human ovarian cancer cells ($IC_{50} = 13.2 \pm 3.5$–24.5 ± 4.2 μM), while complexes **108**–**111** were found to be inactive (Table 4). The complexes have been comparatively evaluated *in vitro* on purified seleno-enzyme thioredoxin reductase (TrxR), glutathione reductase (GR) and on cell lysates to observe their inhibitory effect. In contrast, the complexes were selectively considered in targeting the TrxR over GR. The two techniques, BIAM assays and mass spectrometric studies were used to suggest the binding affinity of complexes toward selenols and thiols. Notably, the activity order of the complexes was observed similar to the inhibition order of TrxR in 2008 cell lysates, thus indicating a possible correlation between the protein binding and the cytotoxic effect.

Moreover, Rendon-Nava and coworkers have reported the synthesis of chrysin-functionalized Au(I)-NHC complexes, **115**–**118** [85]. The crystal structure of complexes **116** and **117** were elucidated from single crystal X-ray diffraction data. The molecular structures display a monomeric unit with Au(I) ion center in linear geometry. The mesityl ring is located orthogonal to the Au(I) ion center while chrysin fragment pointed outwards the core structure. Complexes were tested to observe the biological effect against nematode caenorhabditis elegans using egg-laying assays. The study had shown that the complexes **115** and **117** inhibited the rate of egg-laying and consequently the progeny of worms, while the complexes **116** and **118** did not elicit any apparent effect. The effect of compounds was not observed on the cell division rate of embryos and larvae development [85]. Another series of new mononuclear neutral Au(I)-NHC complexes **119**–**127** [86] was synthesized and fully characterized by a spectroscopic method. The structure from single crystal X-ray diffraction analyses of complexes **120**–**123** were presented to prove the formation of the synthesized complexes. The crystal structures show that the C-Au-C angles are nearly perfect linear coordination with classical geometry for the

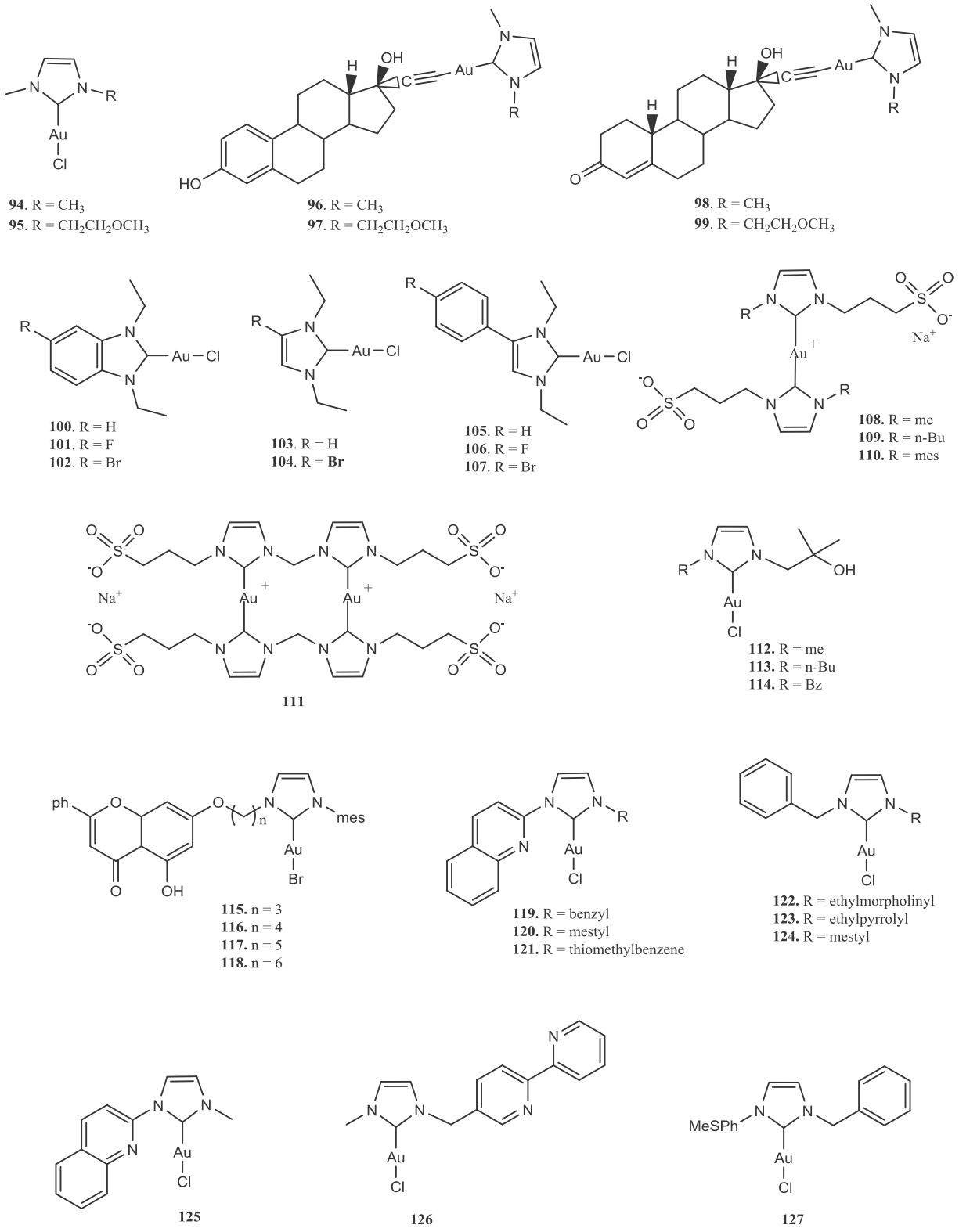


Fig. 4. Structures of Au(I)/(II)-NHC complexes **94**–**127**.

Au in oxidation state +1. The significant Au···Au separations known as aurophilic interaction are observed between the adjacent molecules. All complexes were evaluated for *in vitro* anti-leishmanial potency against both promastigotes and axenic amastigote stages of *leishmanial infantum*, by determining their cytotoxic effect ($IC_{50} = 0.19 \pm 0.04$–$57.03 \pm 0.46\ \mu M$) and compared to anti-leishmanial reference drugs (Table 4). From the study, complexes, particularly those bearing simple mesityl and benzyl substituents, presented a promising metallodrug activity against the pathological relevant form of *L. infantum*.

Table 4
Chemical shifts and selected biological activities data of Au(I)/(III)-NHC complexes **108**–**127**.

Complex	C-Au (chemical shift)	Ovarian 2008	*C. elegans*	*L. infantum promastigotes*	*L. infantum amastigote*
108	184.43	Inactive	–	–	–
109	185.55	Inactive	–	–	–
110	185.56	Inactive	–	–	
111	184.54	Inactive	–	–	–
112	172.04	13.2 ± 3.5	–	–	–
113	171.41	17.5 ± 1.5	–	–	–
114	172.15	24.5 ± 4.2	–	–	–
115	182.5	–	$p > 0.01$	–	–
116	182.5	–	No effect	–	–
117	182.5	–	$p > 0.001$	–	
118	182.4	–	No effect	–	–
119	170.20	–	–	11.16 ± 0.15	1.17 ± 0.21
120	170.49	–	–	4.68 ± 0.61	0.68 ± 0.02
121	168.86	–	–	8.27 ± 0.15	0.73 ± 0.09
122	170.51	–	–	57.63 ± 0.46	11.07 ± 1.04
123	170.74	–	–	10.32 ± 1.29	2.17 ± 0.14
124	170.32	–	–	2.52 ± 0.51	0.19 ± 0.04
125	170.53	–	–	6.76 ± 0.72	0.88 ± 0.30

4. Palladium(II)-*N*-heterocyclic carbene complexes

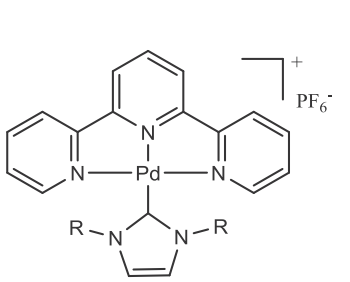
The Pd(II)-NHC complexes were first reported by Hermann and coworkers in 1998 [87,88]. Nowadays, the complex is among the focused metal-NHC complexes, with the development of newly designed NHC ligand system to ensure the improvement in their efficiency, scope and applicability in catalysis [89,90] and biological activity [88,91]. Mostly, the Pd(II)-NHC complexes were synthesized via transmetalation reaction of Ag(I)-NHC complexes using palladium sources such as $Pd(MeCN)Cl_2$, $Pd(MeCN)Br_2$ and $Pd(COD)Cl_2$ [92]. In addition, other methods such as free carbene method and *in situ* deprotonation method are also known, however are relatively scarce [93]. The Pd(II)-NHC complexes can exist in various structural motifs with geometries of tetrahedral or square-planer are known [94]. The substituents of NHC such as alkyl, aryl and functionalized substituents are also affecting the electronic and steric properties of the complexes [11]. The Pd(II)-NHC complexes exhibit in ionic or neutral complexes with one or more NHC ligand, which can generate a strong linear coordination between Pd(II) ion and carbene carbon [95]. Additionally, Pd(II)-NHC compounds can exhibit as a pincer complexes whereby the donor atoms such as O, S, N and P are connected or chelated to the Pd-metal [96–99]. The Pd(II)-NHC complexes bearing pincer ligand offer a unique, highly protective in metal resident and stability opportunities for a long period of time in their applications [95,100–102].

Metallodrugs persist to ever grown in medicinal inorganic chemistry despite all the difficulties in synthesis, bioavailability, drug interactions, efficacy and their safety [103]. Platinum-based complexes like cisplatin and carboplatin exhibited a promising cytotoxicity in various cancer therapies. The palladium-based complexes are naturally competent as anticancer agents due to structural preferences similar to those of platinum-based complexes [104,105]. Interestingly, Pd(II) complexes bearing NHC ligands moiety are also favorable and potentially act as promising agents in both biological and catalytic activities [106]. The Pd(II)-NHC complexes are foremost and grown as catalytic agents in various organic synthesis reactions [16,17]. Moreover, despite their catalytic activities, Pd(II)-NHC complexes showed potential cytotoxicity effect against different human cancer cell lines which are presumed to be the same as platinum-based drugs employed for cancer treatment [107]. However, only limited number of Pd(II)-NHC complexes have been reported and their results were found to be stronger than their counter platinum-based drugs [31,41].

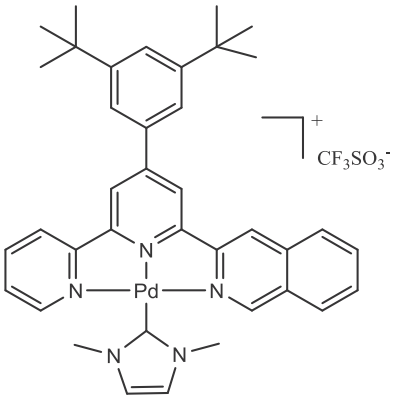
Further investigations of biologically active Pd(II)-NHC complexes led to the development of series of studies by numerous research groups. The Pd(II)-NHC complexes were given attention and explored as potential chemotherapeutic agents against human cancer cell lines [105,108]. Ray and coworkers were the first to evaluate the cytotoxicity effect of Pd(II)-NHC complexes against the human cancer cell lines. These complexes were found to have significant activity against HeLa, HCT-116 and MCF-7 cancer cell lines with better activity than that of cisplatin cancer drugs [104].

Aforementioned, to investigate the effect of Pd(II)-NHC complexes in biological activities, Fong et al. reported a new series of Pd(II)-NHC complexes **128**–**133** (Fig. 5) that are stable in the presence of biological thiols [91]. All complexes were characterized by elemental analyses, FAB-MS spectrometry and NMR spectroscopy. The structure of complexes **128** and **130** were elucidated using X-ray diffraction method. The structures exist as cyclometalated complexes which are further stabilized by coordination bonds with nitrogen to adopt tetrahedral geometry. Compounds were tested as anticancer agents for potent *in vitro* cytotoxicity and *in vivo* tumor growth suppression. The *in vitro* cytotoxicities of complexes toward various human cancer cell lines, including a cervical epithelial cancer (HeLa), lung cancer (NCI-H1650 and NCI-H460), breast cancer (MDA-MB-231) and ovarian cancer (A2780) were evaluated. All complexes displayed promising antiproliferative activity toward cancer cell lines ($IC_{50} = 0.09–2.5\ \mu M$) (Table 5), which were up to 172-fold more toxic than the cisplatin drug. The *in vivo* anticancer activity of complex **131** was examined toward tumor xenograft in nude mice, with no observable toxicity. The mechanism of anticancer activity of complexes was investigated using proteomics analysis and biochemical assays, which involved the mitochondrial dysfunction and inhibition of EGFR signaling induction of apoptotic cell death of cancer cells [91].

A new Pd(II)-NHC complex **134**, which bearing the bis-NHC units was also reported for antiproliferative activity [88]. Single crystal X-ray diffraction study showed that the Pd(II) ion adopts a square planar geometry from two bis-NHC units. Complex **134** showed cytotoxicity with IC_{50} values of $2.5 \pm 0.2\ \mu M$, which was close to the standard drug used in the test (Tamoxifen, $IC_{50} = 2.4 \pm 0.1\ \mu M$). The unsymmetrically substituted sterically tuned Pd(II)-NHC complexes **135**–**137** were also reported through transmetalation reaction from their corresponding Ag(I)-NHC complexes [109]. The crystal structure of complexes **135** and **137** showed that the Pd(II) ion adopts a *trans*-arrangement while Pd(II) in complex **136** adopts a *cis*-arrangement of the NHC ligands. The antibacterial studies of complexes were evaluated against gram-



128. R = CH_3
129. R = CH_2CH_3
130. R = $CH_2CH_2CH_3$
131. R = $CH_2CH_2CH_2CH_3$



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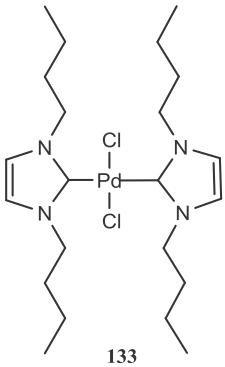

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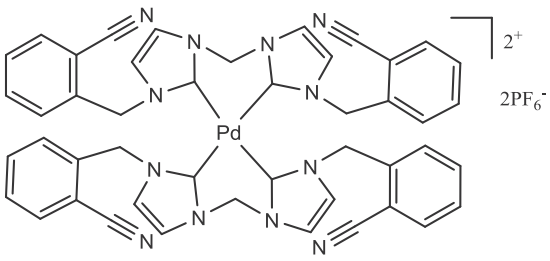

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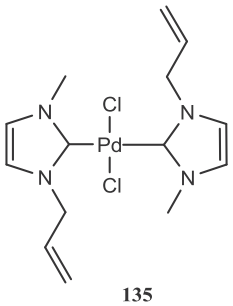

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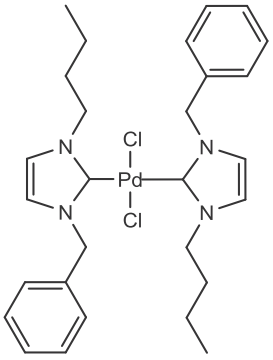

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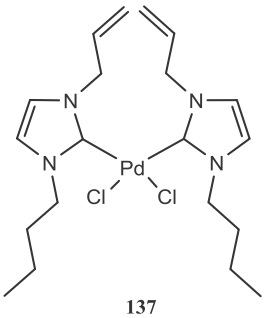

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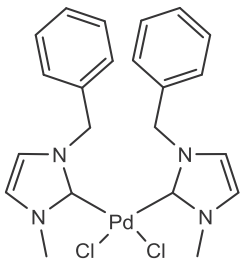

138

Fig. 5. Structures of Pd(II)-NHC complexes **128**–**138.**

negative (*E. coli*) and gram-positive (*S. aureus*) bacteria strains using different concentrations with ampicillin were used as the reference standard (Table 5). In general, all complexes showed an activity against mentioned bacteria with the antibacterial activity of complex **135** against *S. aureus* was significantly higher than that of other complexes, **136** and **137**. In comparison, the antimicrobial activities complexes are more pronounced against *S. aureus* than that of *E. coli* bacterial strain. Furthermore, all complexes were screened for their anticancer activity against HCT 116 cancer cell line with 5-FU was used as an internal standard by MTT assays method. The *trans*-complex **137** displayed significant anticancer activity with an IC_{50} value of 6.6 μM while the *cis*-complex **136** displayed less activity ($IC_{50} = 26.5$ μM) despite the structural mimics with most active anticancer drug, cisplatin. Surprisingly, complex **135** absolutely inactive against tested cancer cell line despite the significant antimicrobial activities against bacterial strains [109]. In another related work [110], the synthesized complex **138** that exists in a *cis*-conformation also showed a weak anticancer potential against HCT 116 cancer cell line based on the MTT assay despite sharing a similar confirmation with cisplatin analogues.

Lamia et al. investigated the biological activity of a series of Pd(II)-NHC complexes **139**–**144** (Fig. 6), derived directly from symmetrically substituted benzimidazolium salts with the presence of K_2CO_3 [111]. The antibacterial activity of bis-NHC-Pd(II) complexes, **139**–**141** and PEPPSI-types NHC-Pd(II) complexes, **142**–**144** was evaluated against gram positive and gram negative

Table 5
Chemical shifts, structural and biological activities data of Pd(II)-NHC complexes **128**–**161**.

Complex	C-Pd (chemical shift)	NCI-H1650	NCI-H460	HeLa	A2780
128	Not reported	2.5 ± 0.2	2.1 ± 0.2	0.9 ± 0.05	1.7 ± 0.2
129	Not reported	1.2 ± 0.09	1.1 ± 0.1	1.4 ± 0.2	1.5 ± 0.2
130	Not reported	0.5 ± 0.03	0.4 ± 0.05	0.5 ± 0.05	1.6 ± 0.1
131	Not reported	0.09 ± 0.01	0.08 ± 0.01	0.1 ± 0.01	0.2 ± 0.03
132	Not reported	0.9 ± 0.1	1.1 ± 0.09	0.4 ± 0.03	1.3 ± 0.2
133	Not reported	>100	>100	>100	>100

Complex	C-Pd (chemical shift)	MCF-7
134	169.7	2.5 ± 0.2

Complex	C-Pd (chemical shift)	*E. coli*	*S. aureus*	HCT 116
135	169.8	10 ± 1	10 ± 1	–
136	170.0	8 ± 1	11 ± 1	26.5
137	170.2	8 ± 1	14 ± 1	6.6
138	170.1	–	–	>200

Complex	C-Pd (chemical shift)	LB14110	ATCC19117	ATCC14028	HCT116
139	180.89	0.039	1.25	2.5	–
140	181.34	0.0197	0.078	1.25	–
141	181.94	0.025	1.25	2.5	–
142	161.91	0.3125	2.5	2.5	–
143	163.36	0.039	0.3125	2.5	–
144	162.84	0.625	1.25	5	–
145	180.2	–	–	–	51.5 ± 4.1
146	168.3	–	–	–	102.3 ± 3.9
147	175.4	–	–	–	16.3 ± 2.0
148	181.7	–	–	–	21.5 ± 2.1
149	175.1	–	–	–	117.9 ± 3.3
150	177.8	–	–	–	42.1 ± 1.8
151	178.8	-	-	-	16.3 ± 0.9
152	168.7	–	–	–	1.3 ± 0.2
153	169.9	–	–	–	5.8 ± 0.8
154	172.5	0.042	1.23	2.3	–
155	174.1	0.0186	0.076	1.32	–
156	173.2	0.024	1.35	2.3	–
157	172.6	0.323	2.4	2.4	–
158	172.6	0.049	0.42	2.2	–
159	174.5	0.425	1.34	5	–
160	172.7	0.525	1.20	3	–
161	172.6	0.723	1.34	1.4	–

bacterial strains using disc diffusion method. Complexes **139, 141** and **142**–**144** exhibited potential antibacterial activity against four bacterial species among the five that were used, while complex **140** inhibited the growth of all the five tested bacteria (inhibition zone = 12 ± 0.1–30 ± 0.5 mm and MICs = 0.0197–5.0 mg/mL for all complexes) (Table 5). Additionally, the antioxidant activity determination of all complexes using DPPH as a reagent indicated that the complexes **139**–**141** and **143** possess DPPH antiradical activity. Complex **140** has a higher antioxidant activity with radical scavenging activity comparable to that of two positive controls used. The anti-acetylcholinesterase activity of complexes was investigated; the study showed that complexes **140, 142** and **143** exhibited moderate activities at 100 μg/mL.

Ghdhayeb et al. presented the newly synthesized Pd(II)-NHC complexes **145**–**148** as anticancer agents with promising potential cytotoxic activity against human colon cancer cells line (HCT 116) [112]. All complexes were synthesized *via* transmetalation technique and characterized by various spectroscopic and analytical techniques. The *in vitro* comparative evaluation of Pd(II)-NHC complexes for their anticancer properties against HCT 116 cancer cells line indicated that these complexes were potentially active (Table 5). It is noteworthy; complexes **145** and **146** were less active compared to the other compounds with IC_{50} values of 102.3 ± 3.9 and 51.5 ± 3.1 μM, respectively. On the other hand, complexes **147** and **148** showed much better activity compared to the aforementioned complexes, which were roughly 3–6 times more effective with IC_{50} values of 16.3 ± 2.1 and 21.4 ± 2.1 μM, respectively [112]. As a continuation, a series of Pd(II)-NHC complexes **149**–**153** of both functionalized and non-functionalized NHCs were also reported with the aim to explore anticancer potential against HCT 116 cancer cells line [113]. Complexes were prepared by NHC ligand transfer technique from respective Ag(I)-NHC complexes by using palladium source as starting material. Moreover, the crystal structure of complex **152** was elucidated using single crystal X-ray diffraction method which showed that the Pd(II) ion adopts a slightly distorted square-planar geometry with the NHC and bromide ligands positioned in *cis*-conformation. The *in vitro* anticancer studies showed that complexes **152** and **153** having xylyl-linker were significantly inhibited the cancer cell growth with IC_{50} values of 5.8 ± 0.8 and 1.3 ± 0.2 μM, respectively. However, non-functionalized complex **151** displayed good cytotoxic effect with IC_{50} value of 16.3 ± 0.9 μM, while nitrile-functionalized complexes **149** and **150** displayed less cytotoxic effects with IC_{50} values of 117.9 ± 3.3 and 42.1 ± 1.8 μM, respectively (Table 5).

Recently, a novel series of Pd(II)-NHC complexes **154**–**161** bearing phosphine were reported by Boubakri and coworkers [114]. The bulky Pd(II)-NHC-PPh_3 complexes were tested against gram-positive (*Micrococcus luteus LB 14110, Staphylococcus aureus ATCC 6538* and *Listeria monocytogenes ATCC 19117*) and gram-negative (*Salmonella Typhimurium* ATCC14028 and *Pseudomonas aeruginosa ATCC 49189*) bacteria strains to investigate their biological activity by using disc diffusion method. The results showed that the

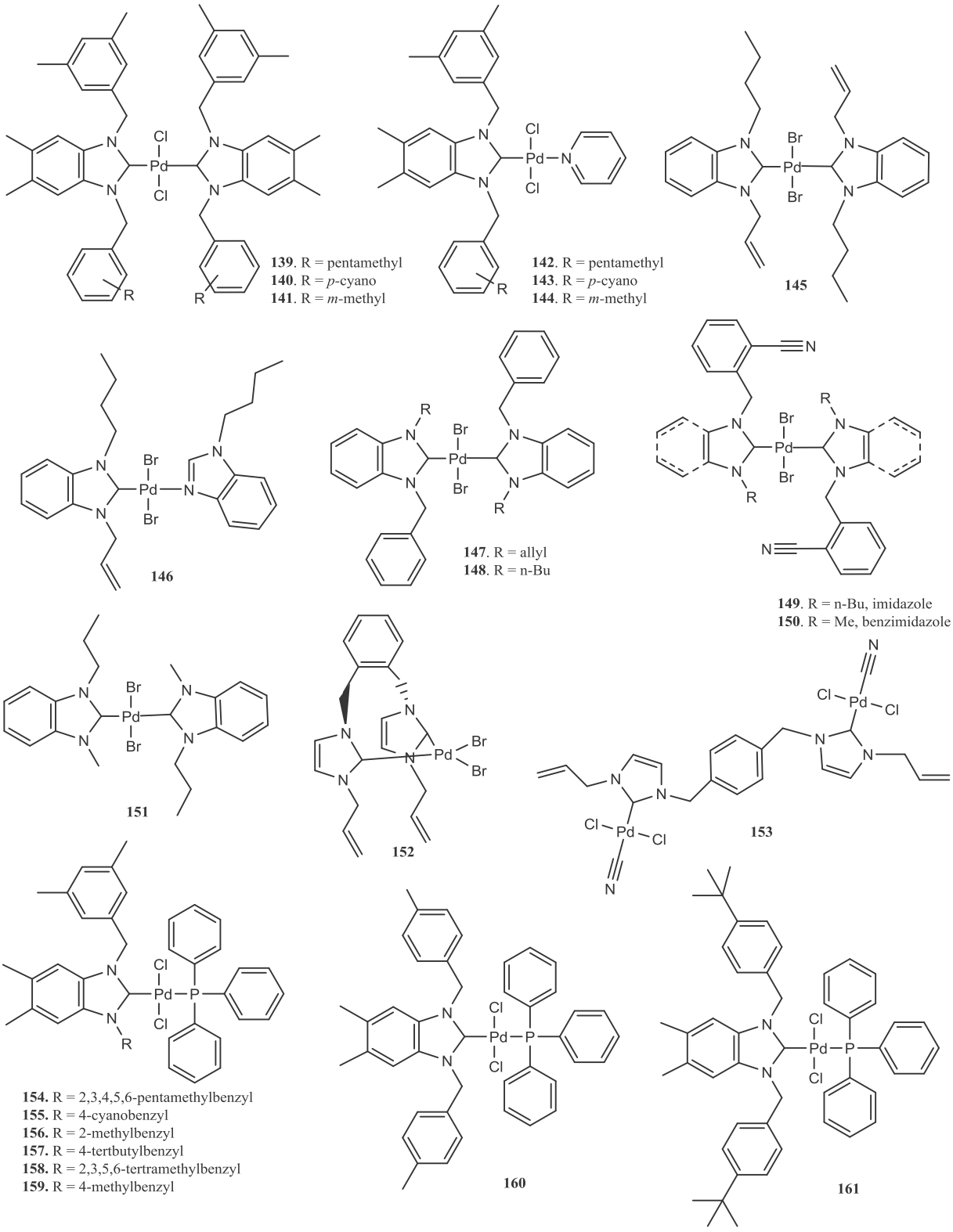

Fig. 6. Structures of Pd(II)-NHC complexes **139**–**161**.

complexes exhibited moderate to significant activities against different bacterial strains. The MIC values of complexes were in the range of 0.0197–0.625 mg/mL for *M. luteus* LB 14110, 0.078–1.25 mg/mL for *L. monocytogenes* ATCC 19117 and 1.25–5 mg/mL for *S. Typhimurium* ATCC 14028 (Table 5). Complex **155** was the most active among the synthesized complexes in that work against *M. luteus* LB 14110, ATCC 19117 and ATCC 14028 with lower MIC value (0.0186, 0.076 and 1.32 mg/mL, respectively) compared to the standard drug used (Ampicillin MIC value = 0.0195, 0.139 and 0.625 mg/mL, respectively). Additionally,

the complexes were further investigated for acetylcholinesterase enzyme inhibition (AChEI) which complexes **154**, **155** and **158** exhibited moderate AChEI activity at 100 μg/mL. In these antibacterial and antioxidant activities, complex **155** possesses the highest AChEI activity due to higher stability than the other complexes. The antimicrobial studies showed that these complexes possessed moderate to significant activities against various bacterial strains, which might be due to the presence of azomethine linkage and/or phosphor in these complexes.

5. Conclusions

In all indications, NHCs have proved and considered to be versatile compounds used in organometallic chemistry, due to their ability to bind with different types of metals in form of metal-NHC complexes. The structural diversity and multitude of chemical modification exist in metal-NHC complexes, prividesthe complexes to be attractive in many areas of scientific studies especially in biological applications. Specifically, Ag(I)-, Au(I)/(III)- and Pd(II)-NHC complexes showed coordination modes with a range of structural motifs from two linear geometry to multiple coordinate systems, indicating significant metal-metal interactions in some cases.

The biological study of Ag(I)-, Au(I)/(III)- and Pd(II)-NHC complexes have since led to the medicinal applications such as anticancer and antimicrobial activities, thus increases their interest in clinical and commercially important. Silver, gold and palladium have a long history in the promotion of human health, but their coordination with NHC ligands improved the activity with fewer side effects. Series of Ag(I)-, Au(I)/(III)- and Pd(II)-NHC complexes reported herein displayed promising pharmacological properties in various cancer cell lines and other microbial organisms tested. This thus suggested that such type of metal ions (Ag, Au and Pd ions) are vital in biological activities and NHC ligands may just facilitate the transport of metal ions to their biological targets. However, these metal-NHC complexes clearly showed superiority over other coordination metal complexes in biological activity due to strong σ-donation bond from NHC ligands.

All the three categories of metal-NHC complexes mentioned in this review demonstrate a good potential as a candidate to be used for the treatment towards the pathogens human-derived cancer cell lines. In particular, Ag(I)-NHC complexes were found to be more effective than Au(I)/(III)-NHC complexes and followed by Pd(II)-NHC complexes. Additionally, there were also observed that the increases in stability and lipophilicity of metal-NHC complexes correlate to the increases and enhancement of the biological activities of the complexes. Therefore, further research is still required to investigate the full mechanisms action of metal-NHC complexes and contribution of substituents and counterions in the context of reaching the target in an infected body area.

Acknowledgements

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