Title	NHC-Silver(I) Acetates as Bioorganometallic Anticancer and Antibacterial Drugs
Authors(s)	Patl, Siddappa; Tacke, Matthias
Publication date	2011-06-01
Publication information	Insights into Coordination, Bioinorganic and Applied Inorganic Chemistry, 10 : 555-566
Publisher	Slovak University of Technology
Item record/more information	http://hdl.handle.net/10197/10177

New Trends in Coordination, Bioinorganic and Applied Inorganic Chemistry
Edited by M. Melník, P. Segľa, M. Tatarko
Press of Slovak University of Technology, Bratislava © 2011

NHC-SILVER(I) ACETATES AS BIOORGANOMETALLIC ANTICANCER AND ANTIBACTERIAL DRUGS

Siddappa Patil and Matthias Tacke*

Conway Institute of Biomolecular and Biomedical Research, Centre for Synthesis and Chemical Biology (CSCB), UCD School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland
(e-mail: matthias.tacke@ucd.ie)

ABSTRACT

The synthesis of *N*-heterocyclic carbene (NHC) silver(I) acetate complexes with varying lipophilic benzyl-substituents at the 1 and 3 positions of the (benz)imidazole ring was achieved by reaction of silver(I) acetate with the corresponding (benz)imidazolium bromide or iodide salts. These NHC-silver(I) acetate derivatives exhibit interesting structural motifs in the solid state and proof to be soluble and stable in biological media. The preliminary antibacterial activity of all the compounds was studied against Gram-negative bacteria *Escherichia coli*, and Gram-positive bacteria *Staphylococcus aureus* using the Kirby-Bauer disk-diffusion method. Almost all the NHC-silver(I) acetate complexes have shown high antibacterial activity compared to the NHC-precursors. In addition, the NHC-silver complexes had their cytotoxicity investigated through MTT based preliminary *in vitro* testing on the human renal cancer cell line Caki-1 in order to determine their IC50 values. NHC-silver(I) acetate complexes were found to have IC50 values ranging from 1.2 to 63 μM. These values represent improved cytotoxicity against Caki-1, most notably for (1-methyl-3-(4-cyanobenzyl) benzimidazole-2-ylidene) silver(I) acetate (IC50 value = 1.2 μM), which is a three times more cytotoxic than cisplatin exhibiting an IC50 value of 3.3 μM against this cell line.

INTRODUCTION

N-Heterocyclic carbenes (NHCs) are stable singlet carbenes that can act as excellent two electron donor ligands towards almost any element in the periodic table. They coordinate strongly to late transition metals and heavy main group elements, but are also known to bind to early transition metals and the lanthanides. Öfele [1] and Wanzlick [2] successfully synthesised the first *N*-heterocyclic carbene transition metal complexes of chromium and mercury in 1968. The isolation of the first free carbene by Arduengo in 1991 set the scene for an ever-growing interest and advancement in the field of *N*-heterocyclic carbene chemistry [3]. Shortly thereafter, the use of these ligands in organometallic chemistry, particularly in catalysis dramatically increased [4, 5]. Very recently, NHCs found an application in NHC-silver complexes exhibiting antimicrobial activity, in particular for the possible treatment of cystic fibrosis (CF) and chronic lung infections [6-8] and maybe in the treatment of cancer [9].

Silver compounds have been used for medicinal applications for more than hundred years. It was targeted for water purification, wound care antiseptics and infections. Silver nitrate was commonly used as antimicrobial compound since the 17^{th} and 18^{th} century before it lost relevance with the discovery of penicillin. Only when first resistances were reported, silver compounds regained importance. Antibacterial activity of silver compounds is attributed to soluble silver ions, Ag^{+}. Elementary silver as well as insoluble silver salt precipitates, such as silver chloride, do not reveal antibacterial activity. The only side effect of long term silver treatment is the more or less unpleasant colour change to grey or blue skin of patients. The effect called Argyria occurs due to irreversible formation and deposition of silver sulfide in dermis and eyes.

The introduction of silver sulfadiazine (silvadine) as an effective antimicrobial agent was reported by Fox in 1968 [10]. High antimicrobial activity and minimal side effects of silver sulfadiazine have made it a very convenient therapy for the treatment of infections in burns over the past four decades [11-14]. Silver carbene complexes, in particular those of *N*-heterocyclic carbenes, have gained a significant amount of interest in the past few years [15,

16]. The first use of silver NHCs as antimicrobial agents was reported by Youngs *et al.* in 2004 [17]. In this report, two silver(I) complexes {silver(I)-2,6 bis(ethanolimidazolemethyl) pyridine hydroxide and silver(I)-2,6 bis(propanolimidazolemethyl) pyridine hydroxide} showed better antimicrobial activity than $AgNO_3$ against the microorganisms, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Another important contribution by the Ghosh research group led to the synthesis and antimicrobial evaluation of NHC-silver complexes derived from 1-benzyl-3-tert-butylimidazole [18]. Recently, Gürbüz and colleagues have shown that the new imidazolidin-2-ylidene silver complexes displayed effective antimicrobial activity against a series of bacteria and fungi [19].

In the chemotherapeutic treatment of cancer, the discovery of the cytotoxic activity of cisplatin by Rosenberg induced a new research field of organometallic complexes as drug candidates [20]. Cisplatin was accepted as drug in 1978 and proved to be especially successful against testicular and bladder cancer, where the probability of healing increased by 90% [21]. The drug did not only successfully treat 30,000 patients per year but also satisfied the pharmaceutical industry with the highest turnover for a cytotoxic drug in the US in 1983. The more advanced drug carboplatin with fewer side effects was introduced to the UK market in 1990 [22]. In a simplified mechanistic explanation, the platinum complex binds to DNA of the cancer cell mainly through N-7 of guanine and prohibits further DNA replication and therefore further tumor growth.

Soon, other transition metal complexes were considered as possible anticancer drugs. Especially treatments for cancer types that did not react on cisplatin treatment were required. Promising candidates were the titanium complexes titanocene dichloride [21] that showed *in vitro* activity against breast, lung and intestinal carcinoma but failed in clinical trials phase II [23], and also its successor budotitane [*cis*-diethoxybis(1-phenylbutane-1,3-dionato)-titanium(IV)] failed to go beyond phase I after excellent preclinical results [24]. Further substitution of the cyclopentadienyl ligand led to bis[(*p*-methoxybenzyl) cyclopentadienyl]

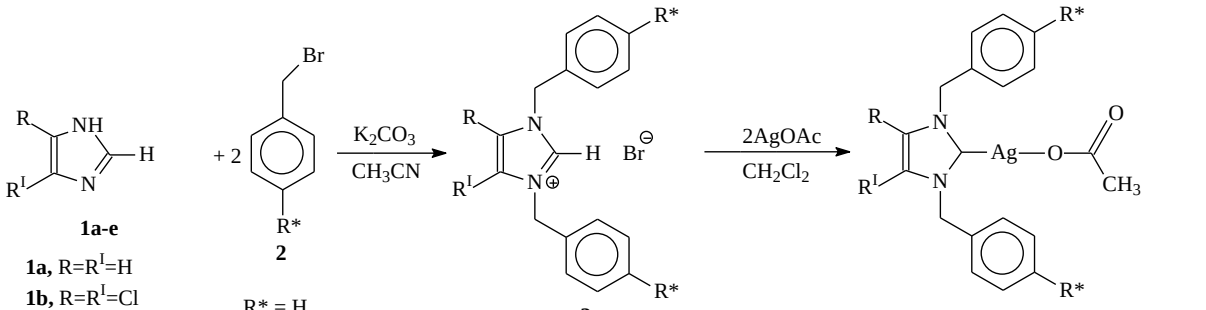
titanium(IV) dichloride (Titanocene Y), which showed to be more effective in the treatment against xenografted Caki-1 tumors in mice than that of cisplatin [25].

Recently, silver complexes have been reported to have anticancer activity *in vitro*. Egan has reported that silver complexes of coumarin derivatives possess anticancer activity against certain types of cancer [26]. Zhu has reported that silver carboxylate dimers possess anticancer activity against human carcinoma cells [27]. McKeage has shown phosphine complexes of silver to be active anticancer agents, even against cisplatin resistant cell lines [28]. Youngs and co-workers have reported anticancer activity of NHC-silver complexes derived from 4,5-dichloro-1*H*-imidazole against the human cancer cell lines OVCAR-3 (ovarian), MB157 (breast), and HeLa (cervical) [9]. These silver complexes have been shown to be very stable and can be synthesized efficiently. We have recently reported the anticancer and antibacterial activity of symmetrically and non-symmetrically *p*-methoxybenzyl-, *p*-cyanobenzyl-, *p*-nitrobenzyl or benzyl-substituted *N*-heterocyclic carbene-silver(I) acetate complexes. All the reported NHC-silver(I) acetate complexes have shown medium to high anticancer and antibacterial activity [29-33]. This encourages further research on *N*-heterocyclic carbene silver complexes as cytotoxic drug candidates.

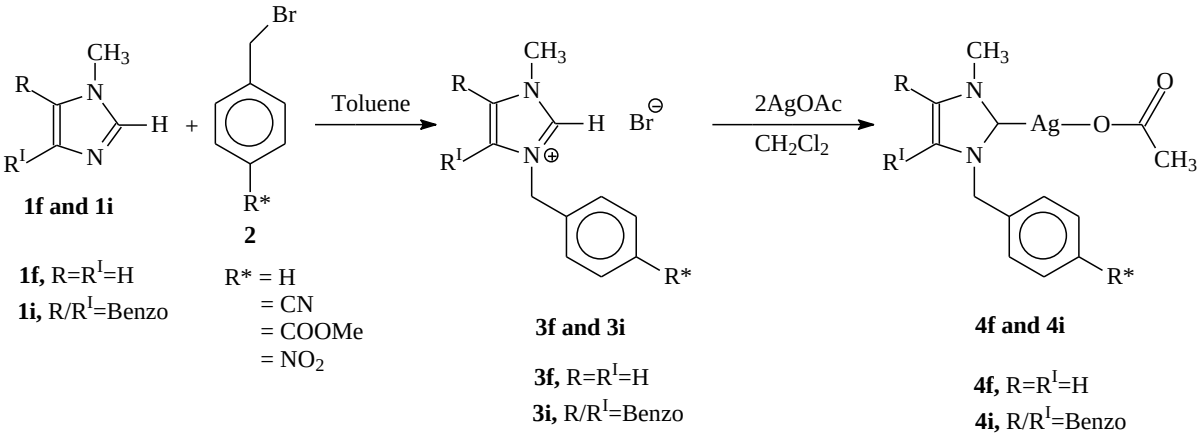
RESULTS AND DISCUSSION

Organic and inorganic syntheses follow each other in order to make NHC-precursors and its corresponding NHC-silver(I) acetate complexes. The synthetic pathway for symmetrically and non-symmetrically substituted *N*-heterocyclic carbenes as ligand precursors **(3a-h)** and their corresponding silver(I) acetate complexes **(4a-h)** described in this work is outlined in schemes 1, 2, 3 and 4 respectively. The symmetrically substituted *N*-heterocyclic carbene precursors **(3a-e)** were prepared by stirring 1H-imidazole **(1a)**, 4,5-dichloro-1H-imidazole **(1b)**, 4,5-diphenyl-1H-imidazole **(1c)**, 1H-benzimidazole **(1d)** and 5,6-dimethyl-1H-benzimidazole **(1e)** with 2 molar equivalent of alkyl halides (benzyl bromide, *p*-methoxybenzyl bromide, *p*-cyanobenzyl bromide, methyl 4-(bromomethyl)benzoate and *p*-

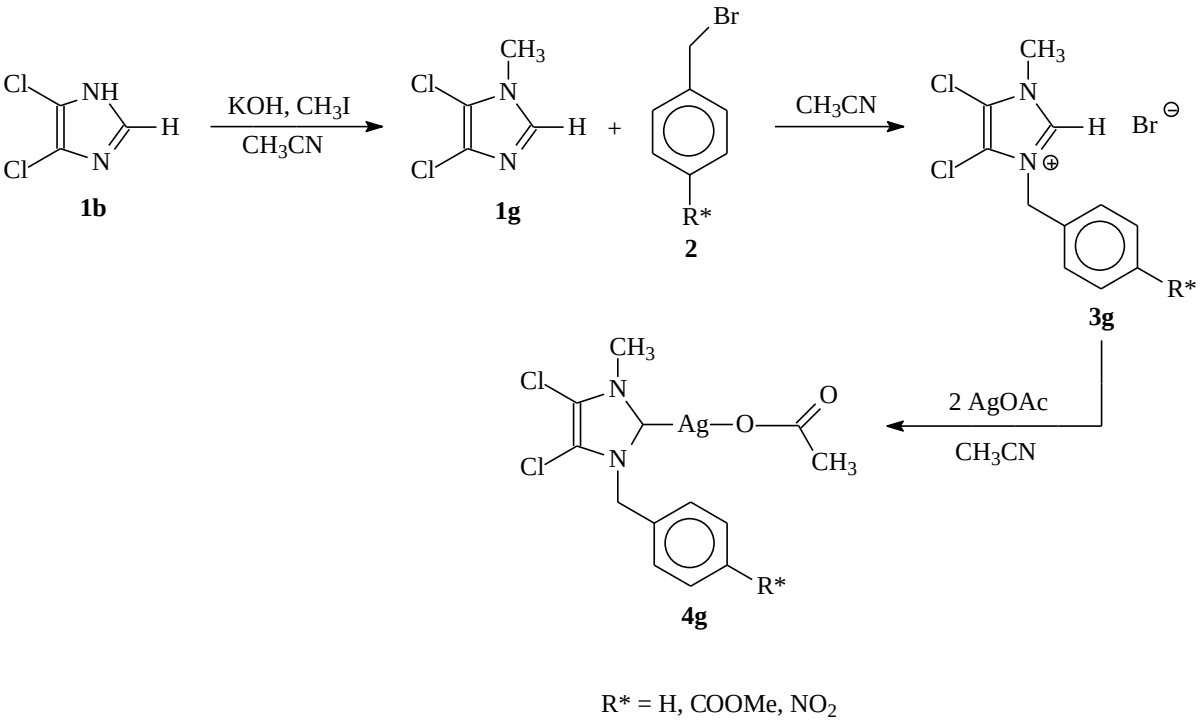
nitrobenzyl bromide) **(2)** in the presence of K_2CO_3 as a base in CH_3CN at room temperature for 2-3 days with moderate to good 40-95% yields. The non-symmetrically substituted *N*-heterocyclic carbene precursors **(3f and 3i)** were prepared by stirring 1-methylimidazole **(1f)** and 1-methylbenzimidazole **(1i)** with alkyl halides (benzyl bromide, *p*-cyanobenzyl bromide, methyl 4-(bromomethyl)benzoate and *p*-nitrobenzyl bromide) **(2)** in toluene at room temperature for 2 d with 67%-90% yields. 4,5-Dichloro-1-methylimidazole **(1g)** is formed in 97% yield from the deprotonation of 4,5-dichloroimidazole **(1b)** with potassium hydroxide and subsequent methylation with iodomethane in acetonitrile. **3g** is formed in 40% to 97% yield by the reaction of 4,5-dichloro-1-methylimidazole **(1g)** with alkyl halides (benzyl bromide, methyl 4-(bromomethyl)benzoate and *p*-nitrobenzyl bromide) **(2)** in toluene. 4,5-Dichloro-1-(4-cyanobenzyl)imidazole **(1b^{I})** is formed in 81% yield from the deprotonation of 4,5-dichloro-1H-imidazole **(1b)** with K_2CO_3 and subsequent alkylation with *p*-cyanobenzyl bromide **(2)** in acetonitrile. 4,5-Dichloro-1-(4-cyanobenzyl)-3-methylimidazolium iodide **(3h)** was prepared by heating of 4,5 dichloro-1-(4-cyanobenzyl)imidazole **(1b^{I})** with iodomethane in acetonitrile for 1d with a yield of 75%.



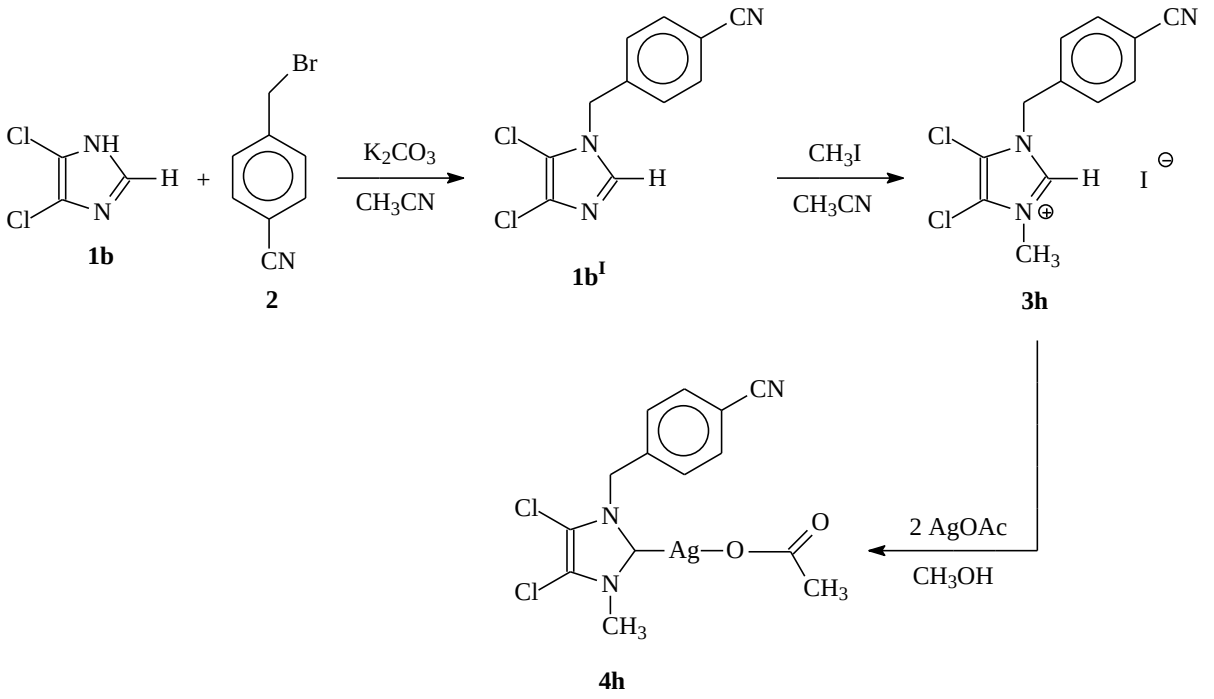
Scheme 1: General reaction scheme for the synthesis of symmetrically substituted *N*-heterocyclic carbenes **(3a-e)** and their corresponding *N*-heterocyclic carbene-silver(I) acetate complexes **(4a-e).**



Scheme 2: General reaction scheme for the synthesis of non-symmetrically substituted *N*-heterocyclic carbenes **(3f** and **3i)** and their corresponding *N*-heterocyclic carbene-silver(I) acetate complexes **(4f** and **4i)**.



Scheme 3: General reaction scheme for the synthesis of non-symmetrically substituted *N*-heterocyclic carbene **(3g)** and its *N*-heterocyclic carbene-silver(I) acetate complex **(4g).**

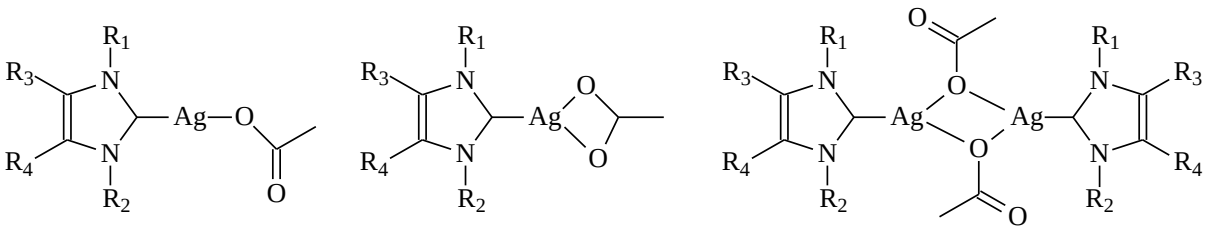


Scheme 4: General reaction scheme for the synthesis of non-symmetrically substituted *N*-heterocyclic carbene **(3h)** and its *N*-heterocyclic carbene-silver(I) acetate complex **(4h)**.

The NHC-silver(I) acetate complexes **4a-h** were synthesized by the reaction of **3a-h** with 2 equivalents of silver(I) acetate in dichloromethane/methanol. The reaction mixture was stirred for 1-3 d at room temperature or refluxed for 2-4 d to afford the NHC-silver(I) acetate complexes as white solids in 30% to 90% yield. The NHC precursors and their corresponding NHC-silver(I) acetate complexes were fully characterized by ^{1}H, ^{13}C NMR, IR, UV-visible, mass spectroscopy and elemental analysis.

Furthermore, the solid state structures of some NHC precursors and many NHC-silver(I) acetate complexes were analyzed by single crystal X-ray diffraction. Here, the NHC-silver(I) acetate derivatives are found to be typically monomeric in the solid state with the carbene ligand strongly bonded with a typical silver carbon bond of 206 pm. For the acetate group sometimes a more covalent monohapto coordination leading to an almost linear C-Ag-O arrangement with a relatively long silver oxygen bond of around 230 pm is seen. In other derivatives the acetate group is bonded in a more ionic dihapto binding mode leading to coordination number 3 at the silver atom with the two Ag-O bonds being distinctly different

with bond length in the range of 230 – 250 pm. Occasionally, the acetate group can be of bridging nature leading to a dimeric and non-symmetric complex in the solid state, which is unlikely to be the structure in solution.



These structural investigations show, that a flexible and relatively weakly bonded acetate group is a good concept for a monomeric silver complex in solution, while the strongly bonded carbene ligand stabilises the potential drug candidate and prevents decomposition of the complex and precipitation of silver halogenide in the biological medium.

All NHC-silver(I) acetate complexes were evaluated for their preliminary *in vitro* antimicrobial and anticancer activity [29-33]. Silver carbene complexes, in particular those of *N*-heterocyclic carbenes, have gained a significant amount of interest in the past few years [15, 16]. Much of this interest stems from recent studies demonstrating the exceptional antimicrobial efficacy of these complexes against a broad spectrum of both Gram-positive and Gram-negative bacteria as well as fungi [6-8, 34, 35]. Preliminary *in vitro* antibacterial activity of symmetrically and non-symmetrically substituted *N*-heterocyclic carbenes and their corresponding NHC-silver(I) acetate complexes were screened against two bacterial strains. The test organisms included *Staphylococcus aureus* (SA) (NCTC 7447) as a Gram-positive bacteria and *Escherichia coli* (E. coli) as Gram-negative bacteria. To assess the biological activity of symmetrically and non-symmetrically substituted *N*-heterocyclic carbenes and their corresponding NHC-silver(I) acetate complexes, the qualitative Kirby–Bauer disk-diffusion method was applied. All bacteria were individually cultured from a single colony in sterile LB medium overnight at 37^0C (orbital shaker incubator). All the work carried out was performed under sterile conditions.

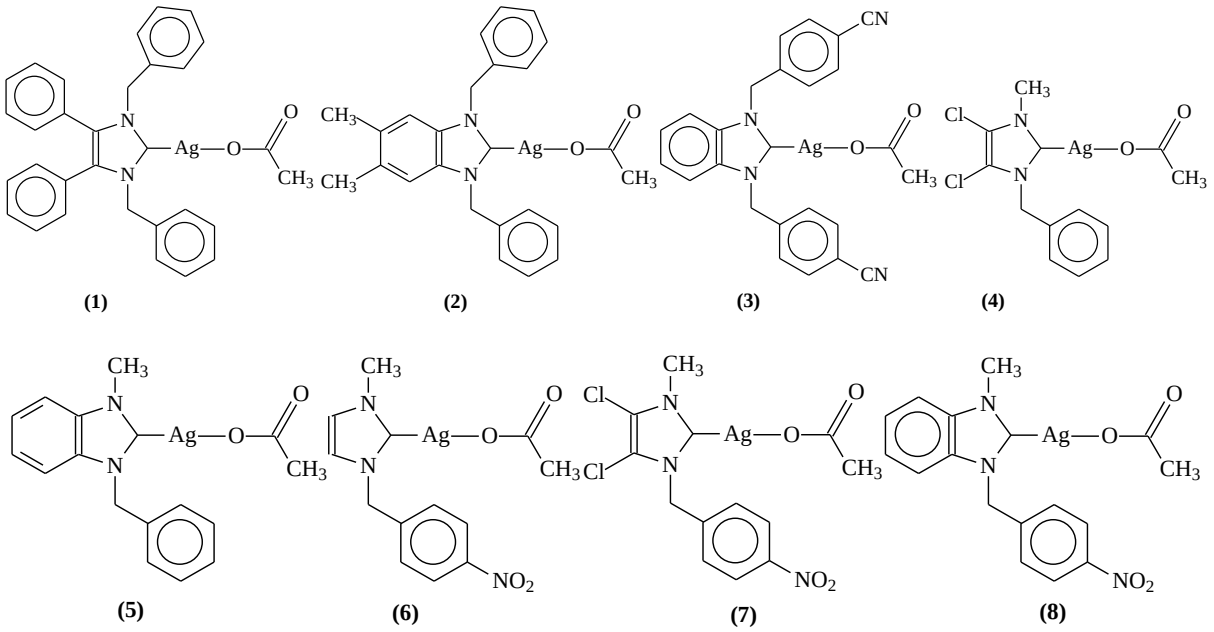


Figure 1: Symmetrically and non-symmetrically substituted NHC-silver(I) acetate complexes **1-8.**

The results indicate that all the NHC-precursors show a weak antibacterial activity against the both Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* with an area of clearance of 1 to 6 mm at the highest amount used [29-33]. Medium to high antibacterial activity was observed for all NHC-silver(I) acetate complexes against both Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* with areas of clearance 5 to 15 mm at the highest amount used [29-33]. Based on the above discussion it can be stated that, compared to the NHC-precursors the NHC-silver complexes exhibited enhanced antibacterial activity, which is due to the synergistic effect of the increased lipophilicity of the complexes. Chelation decreases the polarity of the metal ion, which further leads to the enhanced lipophilicity of the complex. Since the bacterial cell wall is surrounded by a lipid membrane, increased lipophilicity of complexes allows for the penetration into and through the membrane leading to deactivation of active enzyme sites of the microorganisms [36]. The structures of some best NHC-silver(I) acetate complexes are given in figure 1. High antibacterial activity was observed for the compounds **1-8** against Gram-positive bacteria *Staphylococcus aureus* with areas of

clearance 7 to 15 mm while medium activity was observed towards Gram-negative bacteria *Escherichia coli* with areas of clearance 5 to 12 mm at the highest amount used (see Table 1). From the above discussion, it can be concluded that the antibacterial activity of NHC-silver(I) acetate complexes **1-8** was generally better against Gram-positive bacteria *Staphylococcus aureus* compared to Gram-negative bacteria *Escherichia coli.* Hence these compounds should now be tested against Gram-positive bacteria *Staphylococcus aureus* and MRSA in order to measure MIC values for a precise evaluation.

Table 1. Area of clearance for compounds **1-8** in mm

Compounds	*Staphylococcus aureus* (Gram + ve)	*Escherichia coli* (Gram – ve)
1	15	7
2	12	7
3	10	10
4	9	6
5	9	12
6	7	5
7	7	5
8	7	5

In addition, all NHC-silver(I) acetate complexes were investigated as possible anticancer drugs. Therefore, the anticancer activity of symmetrically and non-symmetrically substituted NHC-silver(I) acetate complexes were measured against Caki-1 cancer cells in order to predict the potential against solid tumors [29-33]. The preliminary *in vitro* cytotoxicity of symmetrically and non-symmetrically substituted NHC-silver(I) acetate complexes was evaluated by MTT-based assays on this human renal cancer cell line Caki-1. This test involves a 48 h drug exposure period, followed by a 24 h recovery time.

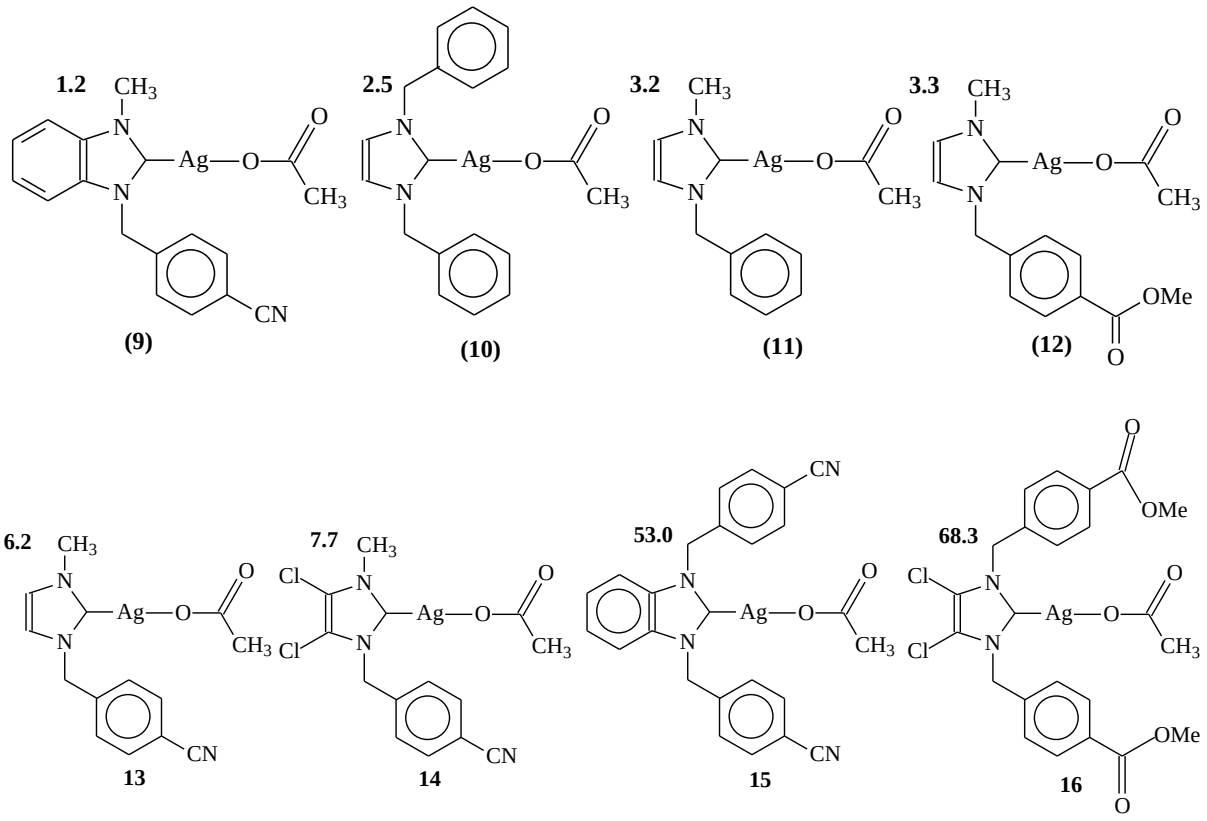


Figure 2: Symmetrically and non-symmetrically substituted NHC-silver(I) acetate complexes **9-16**; IC50 values against CAKI-1 are given in μM.

Symmetrically substituted NHC-silver(I) acetate complexes **10, 15,** and **16**, which contains 1H-imidazole, 4,5-dichloro-1H-imidazole and 1H-benzimidazole groups, has IC50 values 2.5, 53 and 63 μM respectively. Non-symmetrically substituted NHC-silver(I) acetate complexes **9, 11, 12, 13** and **14,** which also contains 1-methylimidazole, 4,5-dichloro-1-methylimidazole and 1-methylbenzimidazole groups, has IC50 values 1.2, 3.2, 3.3, 6.2 and 7.7 μM respectively. Compared to symmetrically substituted NHC-silver(I) acetate complexes **10, 15,** and **16**, the non-symmetrically substituted NHC-silver(I) acetate complexes **9, 11, 12, 13** and **14,** have shown almost high cytotoxic activity because of their solubility factor. Symmetrically substituted NHC-silver(I) acetate complexes are less soluble in DMSO solvent compared to non-symmetrically substituted NHC-silver(I) acetate complexes. The structures and IC50 values of selected symmetrically and non-symmetrically substituted NHC-silver(I) acetate

complexes are presented in figure 2. All NHC-silver(I) acetate complexes are stable in saline solution with respect to silver chloride precipitation.

CONCLUSION AND OUTLOOK

It is evident that silver-based pharmaceuticals have potential as antibiotics or anticancer drugs. There is relatively little information available about the mechanism of action of NHC-silver acetates and therefore studies need to aim at exploring the mechanistic pathways employed by these drugs. NHCs are a versatile class of ligands that can be synthesised easily; these ligands possess the ability to bind to both hard and soft metals and can be readily functionalised, which is a promising aspect in terms of designing suitably targeted pharmaceuticals. The lipophilicity of NHCs and most of their silver complexes seems to be important in contributing to both their antimicrobial and antitumor effects. Hence NHC-silver(I) acetate complexes seem to be the most efficacious in terms of their antimicrobial and anticancer activity hopefully in combination with low toxicity, which has to be proven in future *in vivo* experiments. Symmetrically and non-symmetrically substituted NHC-silver(I) acetate complexes were synthesised through the reaction of appropriately symmetrically and non-symmetrically substituted *N*-heterocyclic carbenes with silver(I) acetate. Almost all the complexes have shown high antibacterial activity compared to the precursors against both Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli*. NHC-silver(I) acetate complexes yielded antitumor IC50 values of 1.2 to 63 μM on the Caki-1 cell line. One of the compound (1-methyl-3-(4-cyanobenzyl) benzimidazole-2-ylidene)silver(I) acetate shows the highest cytotoxicity [IC50 value of 1.2 μM] up to now for the *N*-heterocyclic carbene-silver complexes synthesised in our research group, indicating the high potential as an anticancer drug. Further work is currently underway in order to improve these values by performing formulation experiments to improve solubility of these NHC-silver acetate complexes, which should allow for *in vivo* testing of (1-methyl-3-(4-cyanobenzyl) benzimidazole-2-ylidene)silver(I) acetate in the nearby future. There is still

potential to optimise the medicinal properties of the NHC ligand and the resulting Ag complex. In addition, more complexes with Au(I), Cu(II) and Pt(II) should be synthesised and biologically tested in order to find new anticancer and antifungal drugs as well as potentially resistance-breaking antibiotics.

ACKNOWLEDGEMENTS

The authors thank the Irish Research Council for Science Engineering and Technology (IRCSET) for funding through a postdoctoral fellowship for Dr. Siddappa Patil.

REFERENCES

1. K. Öfele, J. Organomet. Chem., 12 (1968) 42
2. H. W. Wanzlick and H. J. Schönberr, Angew. Chem., Int. Ed. Engl., 7 (1968) 141
3. A. J. Arduengo, R. L. Harlow and M. Kline, J. Am. Chem. Soc., 113 (1991) 361
4. W. A. Herrmann, Angew. Chem., Int. Ed. Engl., 41 (2002) 1290
5. D. Bourissou, O. Guerret, F. P. Gabbai and G. Bertrand, Chem. Rev., 100 (2000) 39
6. K. M. Hindi, T. J. Siciliano, S. Durmus, M. J. Panzner, D. A. Medvetz, D. V. Reddy, L. A. Hogue, C. E. Hovis, J. K. Hilliard, R. J. Mallet, C. A. Tessier, C. L. Cannon and W. J. Youngs, J. Med. Chem., 51 (2008) 1577
7. A. Kascatan-Nebioglu, M. J. Panzner, C. A. Tessier, C. L. Cannon and W. J. Youngs, Coord. Chem. Rev., 251 (2007) 884
8. A. Kascatan-Nebioglu, A. Melaiye, K. M. Hindi, S. Durmus, M. J. Panzner, L. A. Hogue, R. J. Mallett, C. E. Hovis, M. Coughenour, S. D. Crosby, A. Milsted, D. L. Ely, C. A. Tessier, C. L. Cannon and W. J. Youngs, J. Med. Chem., 49 (2006) 6811
9. D. A. Medvetz, K. M. Hindi, M. J. Panzner, A. J. Ditto, Y. H. Yun and W. J. Youngs, Metal-Based Drugs 2008, Article ID 384010, 7 pages http://dx.doi.org/10.1155/2008/384010
10. C. L. Fox, Arch. Surg., 96 (1968) 184
11. A. R. C. Lee, H. Leem, J. Lee and K. C. Park, Biomaterials, 26 (2005) 4670
12. H. S. Rosenkranz and H. S. Carr, Antimicrob. Agents Chemother., 2 (1972) 367
13. H. S. Carr, T. J. Wlodkowski and H. S. Rosenkranz, Antimicrob. Agents Chemother., 4 (1973) 585
14. C. L. Fox and S. M. Modak, Antimicrob. Agents Chemother., 5 (1974) 582
15. J. C. Garrison and W. J. Youngs, Chem. Rev., 105 (2005) 3978

16. I. J. B. Lin and C. S. Vasam, Coord. Chem. Rev., 251 (2007) 642
17. A. Melaiye, R. S. Simons, A. Milsted, F. Pingitore, C. Wesdemiotis, C. A. Tessier and W. J. Youngs, J. Med. Chem., 47 (2004) 973
18. S. Ray, R. Mohan, J. K. Singh, M. K. Samantaray, M. M. Shaikh, D. Panda and P. Ghosh, J. Am. Chem. Soc., 129 (2007) 15042
19. I. Özdemir, E. Ö. Özcan, S. Günal and N. Gürbüz, Molecules 15 (2010) 2499
20. D. Rosenberg, L. Van Camp, J. E. Trosko and V. H. Mansour, Nature, 222 (1969) 385
21. W. Kaim and B. Schwederski, Bioanorganische Chemie 2004, 3rd Ed., Teubner: Stuttgart, 370
22. P. Umapathy, Coord. Chem. Rev., 95 (1989) 129
23. G. Lummen, H. Sperling, H. Luboldt, T. Otto and H. Rubben, Cancer Chemother. Pharmacol., 42 (1998) 415
24. T. Schilling, B. K. Keppler, M. E. Heim, G. Niebch, H. Dietzfelbinger, J. Rastetter and A. R. Hanauske, Invest. New Drugs 13 (1995) 327
25. N. J. Sweeney, O. Mendoza, H. Müller-Bunz, C. Pampillón, F. J. K. Rehmann, K. Strohfeldt and M. Tacke, J. Organometal. Chem., 690 (2005) 4537
26. B. Thati, A. Noble, B. Creaven, M. Walsh, M. McCann, K. Kavanagh, M. Devereux and D. Egan, Cancer Lett., 248 (2007) 321
27. H. Zhu, X. Zhang, X. Liu, X. Wang, G. Liu, A. Usman and H. Fun, Inorg. Chem. Comm., 6 (2003) 1113
28. J. Liu, P. Galetis, A. Farr, L. Maharaj, H. Samarasinha, A. McGechan, B. Baguley, R. Bowen, S. Berners-Price and M. McKeage, J. Inorg. Biochem., 102 (2008) 303
29. S. Patil, J. Claffey, A. Deally, M. Hogan, B. Gleeson, L. M. Menéndez Méndez, H. Müller-Bunz, F. Paradisi and M. Tacke, Eur. J. Inorg. Chem., (2010) 1020
30. S. Patil, A. Deally, B. Gleeson, H. Müller-Bunz, F. Paradisi and M. Tacke, Appl. Organomet. Chem., 24 (2010) 781
31. S. Patil, A. Deally, B. Gleeson, H. Müller-Bunz, F. Paradisi and M. Tacke, Metallomics, 3 (2011) 74
32. S. Patil, K. Dietrich, A. Deally, B. Gleeson, H. Müller-Bunz, F. Paradisi and M. Tacke, Helv. Chim. Acta, 93 (2010) 2347
33. S. Patil, A. Deally, B. Gleeson, F. Hackenberg, H. Müller-Bunz, F. Paradisi and M. Tacke, Z. Anorg. Allg. Chem., 637 (2011) 386
34. A. Melaiye, Z. Sun, K. Hindi, A. Milsted, D. Ely, D. H. Reneker, C. A. Tessier and W. J. Youngs, J. Am. Chem. Soc.,127 (2005) 2285

35. M. J. Panzner, C. A. Tessier and W. J. Youngs in The Chemistry of Pincer Compounds (Eds.: D. Morales-Morales, C. M. Jensen), Elsevier, 2007, 1st ed., 139
36. R. Karvembu, C. Jayabalakrishnan and K. Natarajan, Trans. Met. Chem., 27 (2002) 574