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Silver Complexes of N-Heterocyclic Carbenes as Anticancer Agents: A Review

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Abstract: This review covers the explanation of all the biological efficiencies of the N-Heterocyclic Carbenes (NHCs). Most of the reviews of NHCs focused on its chemical and physical applications, we have noted the properties, types and applications of metal complexes of NHCS. Our principle aim is to throw a light on the biological applications of the complexes. N heterocyclic carbenes (NHC) have been discovered in the 90's and have been marking an important place in organic chemistry. NHCs contain divalent carbon atoms. It is bound to at least one nitrogen atom. Presence of heteroatoms imparts them a wide range of electronic behavior. They create stable bonds and compounds making them excellent ligands in coordination chemistry. Silver metal complexes of organic ligands had been an interesting research area for the pharmaceutical researchers. Because of the electron donating ability of NHCs, the formation of Ag metal complexes had been pursued by many inorganic chemists and they were evaluated for various biological activities. Thus, in this review we have listed out the Ag-NHCs which have anticancer potential and its use as cytotoxic therapeutic agents. This article concludes with the basic concept that, how to design efficient Ag-NHCs in order to develop efficient, biologically active metal complex derivatives.

Keywords: Silver Metal Complexes, N-Heterocyclic Carbenes, Antimicrobial Agents, Anticancer Agents

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1. INTRODUCTION

Carbenes are characterized by the presence of unpaired electrons and they have inherent nucleophilic ability. They act as lewis base and attach to the metals efficiently. The stability of the carbenes is notable compared to the phosphine complexes. They are highly stable kinetically. The lipophilic property and chargeless ability makes them an efficient active lead molecule. There are different types of carbenes such as there is a large number of NHC frameworks known in the literature, ranging from five-membered to seven-membered rings including, imidazolium, imidazolinium, triazolium,oxazolium, thiazolium, pyrrolidinium, benzimidazolium, bisoxazoline, quinoxaline, naphtha annulated imidazolium, diazaphosphetidin amine, pyrimidine, perimidine, dibenzo(1,3)diazepine, imidazopyridine, 2,2-bipyridine derived imidazolium, bis-imidazolium with arene backbone The anticancer activity of metal-N-heterocyclic carbenes (Ag(I), Au(I), Pd(II), and Cu(I)-NHCs) have previously been reviewed[1-3]. SCCs derived from cyclophanes and silver oxide were synthesized, and display greater antitumor activity than cisplatin in several ancer cell lines, including a cisplatin-resistant cell line. The silver cyclophane complexes were less active than the corresponding gold derivatives but also less toxic in the human hepatocyte cell line (LO2) I NHCs are readily available compounds. These ligands act as sigma donors, and to a lesser degree in π-back-donation, capable of forming a wide variety of metal-NHC complexes with almost any metal in the periodic table The first report of successful isolation of free carbene was achieved by deprotonation using NaH and catalytic DMSO. The carbenes are the neutral compounds having divalent C atoms with six e-valence shells which enhances their reactivity by many folds. The first report of stable carbene was followed by the extensive study of electronic and steric stabilization of NHCs. Electronic stabilization is influenced by π-donation by electron rich N-C=C-N system to out-of-plane p orbital of carbene and -electronegativity effects of N atoms. These effects work by the electron withdrawal by N which is more electronegative compared to Carbene C. The substituents attached to imidazolium ring awards the kinetic stability to the carbenes. NHC are π -donors which can bind with both hard as well as soft metals. This formation of carbene-metal bond works through π -interaction as well as π- interaction. π -Interaction works through π -donation from NHC to metal center while π- interaction further have two significant interactions such as π donation from NHC to metal center and π back-donation from metal center to NHC-C.

1.1 Types of NHC Complexes

1.2 Monodentate NHC complexes

Many mono-dentate NHC–metal complexes reported with four-, five-, six- and seven-membered NHCS. Four-membered ring system. However, the five-membered ring system is undoubtedly the most well-known. These ligands have shown that, bulky substituents on the NHC are not only beneficial for the stability of the ligands, but also for catalytic activities of the resulting complexes in the case of several reaction types

1.3 Bi-Multi dentate NHCs

Bi- and multi-dentate NHCs tend to make very stable chelate complexes, which can be especially useful for reactions with oxidizing conditions at elevated temperatures [4]. Mono dentate NHCs are highly susceptible to the reductive elimination process. This may result from the conformational rigidity imposed by the chelate ring that prevents the NHC from adopting the correct conformation for reductive elimination.

2. Various applications of NHC metal complex

Silver complexes of NHC exhibit antimicrobial and antitumor activities, a series of NHC–silver complexes derived from 4,5-dichloro-1H-imidazole was reported. All complexes exhibited cytotoxic activity against the ovarian (OVCAR-3) and breast (MB157) cancer cells in vitro. two silver-bis(NHC) complexes ([bis(1,3-dimethylimidazol-2-ylidene)] silver(I) nitrate (37a) and [bis(4,5-dichloro-1,3-dimethylimidazol-2-ylidene)] silver(I) nitrate displayed similar antitumor efficacy against the H460 lung cancer cells. A series of saturated and unsaturated NHC–silver complexes. which have exhibited higher cytotoxic effects than cisplatin against various cell lines. The effect was found from the use of bulky N-substituents or variation of saturation between the 4- and 5- positions of the imidazole ring. 14 NHC–silver complexes with significant antimicrobial properties. Dramatic changes in the activity were observed with slight differences in the NHC ligand structures. Some complexes were efficient at low concentrations against resistant strains of Staphylococcus aureus that caused major problems to public health. In the recent past, we developed a series of NHC– silver acetate complexes which displayed antitumor activity against the Caki-1 cells (a kidney cancer cell line). Six new NHC–silver complexes were reported having screened for them in vitro antimicrobial activities against the following standard strains: Enterococcus faecalis, S. aureus, E. coli and Pseudomonas aeruginosa. These new compounds displayed effective antimicrobial activities against Gram-negative and Gram-positive bacterial strains. The NHC–gold complexes were synthesized from NHC–silver complexes by transmetalation reaction. NHC–gold complexes have been known since 1989, and they can be neutral or cationic, with the respective formulas (NHC)AuX and ([NHC]2Au) X. cationic gold(I)bis-carbene complex which has been showing very promising anticancer activity by a mitochondrial membrane permeabilization (MMP) mechanism[5] and even prepared the first carbenic auranofin mimics by substituting the phosphine ligand by different N-heterocyclic carbenes. This promotes further research toward NHC–gold complexes as anticancer agents. NHC–gold(I) complex was a better inhibitor of PTP than auranofin with an IC_{50} range from 10 to 40 μ M. NHC–gold(I) complex was a better inhibitor of PTP than auranofin with an IC_{50} range from 10 to 40 μ M. The synthesis of new NHC–gold(I) and NHC–gold(III) halide, amino acid and dipeptide complexes is also reported. Phenylalanine–NHC– gold(I) and gold(III) bromide complexes were prepared from halide exchange with LiBr 2. NHC–gold complexes of amino acid and dipeptide complexes have been prepared with good yields from the reaction of N-Boc protected cysteine methyl ester (Boc-Cys- OMe) or the dipeptide N-Boc-Leu-Cys-OMe with the NHC–gold chloride. All the NHC–gold complexes showed good antitumor activity on the human colorectal adenocarcinoma (HT-29) and HeLa, human hepatocellular carcinoma (HepG2) cancer cell lines as compared with well-known anticancer drug cisplatin.

3. Metal complex formation of NHCs

3.1 Metallation

N-Heterocyclic Carbenes (NHCs) can form metal carbene

bonds very easily due to excellent σ -donation ability. The various metal salts reported in the literature are Ag, Au, Pt, Pd, Ni, Hg, and Ru, etc. Silver complexes are of most interest amongst all because of their unique properties with respect to σ -donation and π-back donation. Ghosh and co- workers have carried out an extensive study on this concept using charge decomposition analysis (CDA). d designates the degree of NHC → metal -donation and b indicates the NHC ← metal π-back-donation. The ratio of d/b shows the extent of σ -donation and π- back-donation. The ratio d/b is 2.59 to 3.99 in the case of Pd-NHCs and 5.23 to 5.88 in Au-NHCs 7.8 to 12.68 in the case of Ag-NHCs. This pattern clearly indicates the greater back-donation ability of silver to NHC which makes them better metalation agents [6].

3.2 *Mechanism of Silver Complexation*

Silver complexes are readily prepared using various salts like Ag_2O, Ag_2CO_3 and silver acetate amongst which Ag_2O is of particular interest due to the high basicity of silver oxide and insolubility in almost all organic solvents. So, the rate of reaction depends upon the solubilization of Ag-NHC which makes the complex reaction of pseudo-first order. The high basicity of silver oxide bypasses the need to use an additional base like K_2CO_3 or NaOH for removal of NHC proton. The O atom from Ag_2O coordinates with NHC H for abstraction and this intermediate is further stabilized by the formation of Ag-Carbene bond. The intermediate AgOH causes second deprotonation, forming the stable Ag-NHC species. The widely employed method for obtaining the pure complex is the addition of a solvent or mixture of solvents for precipitation. The first deprotonation is caused by Ag_2O while the second deprotonation is favored by AgOH formed in situ[7].

4. *Versatile biological activities of Ag-NHC*

4.1 *Ag-NHC as Anticancer agents*

The exact mode of action of cytotoxicity of silver N-Heterocyclic carbenes remains unclear; few reports have given insight into the possible mode of anticancer activity. These effects include oxidative stress, induction of MMPs and inhibition of antioxidant enzymes. These activities are supposed to be similar to Au (I), but the exact mechanism remains ambiguous. Silver complexes can induce MMP and can cause mitochondrial swelling and loss of membrane permeability. Few reports also show (Fig.1) membrane blebbing, chromatin condensation and formation of apoptotic bodies in the cytosol of cancer cells. However, this mechanism of cell death is caspases independent and mediated via MMP induction[8] .

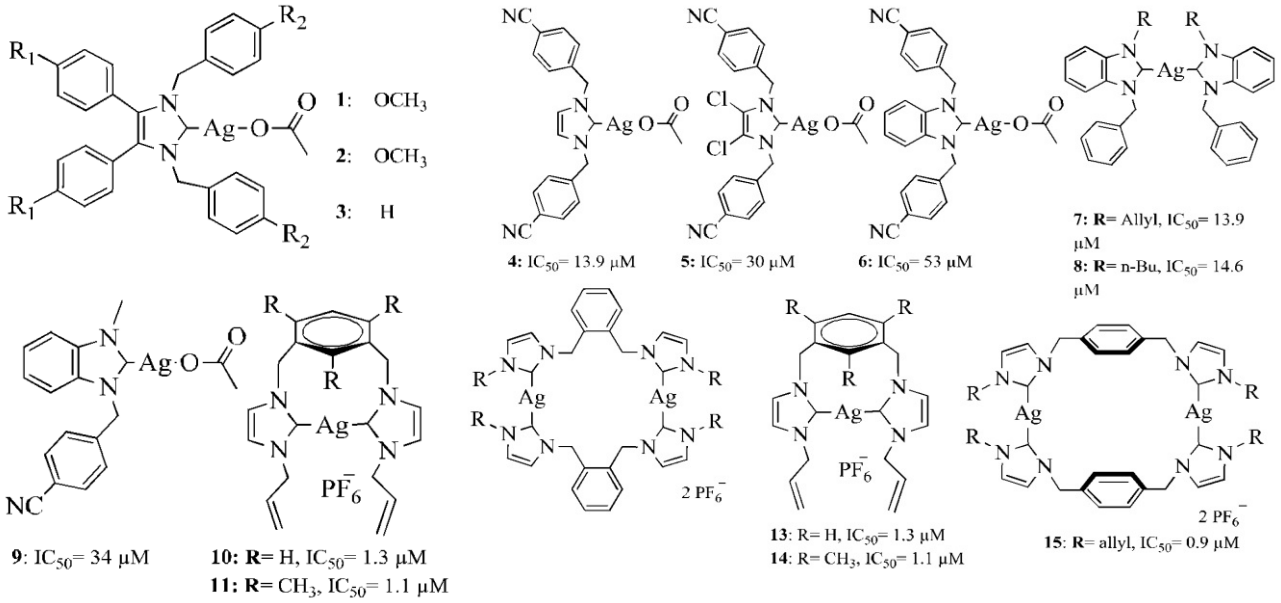

Fig 1: -Reported Ag-NHCs as anticancer agents with IC_{50} Values[8]

It was reported[9] the topology-controlled CN functionalized Ag-NHCs 16-19 assayed for cytotoxicity in HCT 116 cell lines by MTT based assay method (Fig. 2). The analyzed compounds have shown IC_{50} values in the range of 1.7-27.2 μM. At the same time, authors had evaluated the cytotoxicity of imidazolium salts and didn't find any promising data as IC_{50} for non-metal compounds was above 200 μM. Authors reported that binuclear complexes are more potent when compared with their mononuclear complexes. Additionally, authors have studied the role of adding mole equivalents of silver oxide. When silver oxide was added 1-mole equiv., the Ag Center has formed coordination with Nitrile groups (16) while the addition of 0.5 equivalents of silver oxide form complex with silver coordinated to NHC C center (17). Even changing the anion from Br^- to $PF6^-$ caused the Compound to lose its activity. In 2013, it [10] had reported p-Xylyl linked bis-Benzimidazolium Ag-NHCs 20-22 for cytotoxicity in HCT 116 cells using 5-fluorouracil as a reference standard. Binuclear silver complexes 20, 21 and 22 show IC_{50} as 0.9, 0.4, 0.01 μM and 0.7, 27, 5.6 μM in HCT 116 and HL-60 cell lines respectively. The side chain affects lipophilicity and thereby influences biological activity. Li et al. [11] had investigated antitumor and mitochondria targeting properties of Ag-NHC containing cyclophane for cytotoxicity in HeLa and MDA-MB-231 cell lines. Silver complexes 23 and 24 displayed IC_{50} as 19.1 and 12.4 μM in HeLa cell lines and 22.0 and 14.3 μM in MDA-MB-231 cell lines. Tracking the Ag complexes indicates the induction of cell death via the mitochondrial pathway and proved to be an inducer of apoptosis. Mononuclear Ag-NHC 25-27 were evaluated for cytotoxicity against several cancer cell lines such as HCT15, MCF7R, and HL60R which are resistant to chemotherapy along with sensitive cell lines such

as HCT116, HL60, and MCF7 cell lines. Complex 25 displayed IC_{50} of 30, 95, 55, 120, 35 and 120 in HCT 116, HCT15, MCF7, MCF7R, HL60 and HL60R cell lines respectively. Complex 26 showed IC_{50} of 28, 85, 75, 125, 58 and 125 nM where complex 27 exhibited IC_{50} of 200, 860, 375, 2480, 90 and 2990 in HCT 116, HCT15, MCF7, MCF7R, HL60 and HL60R cell lines respectively. Flow cytometry analysis revealed that these silver complexes were able to induce early apoptosis. The silver complexes were able to induce mitochondrial membrane permeabilization [12]. In 2011[13], had reported Ag-NHCs 28 and 29 containing imidazolium salts and evaluated their anticancer properties in NCL-460 lung cancer cell lines using MTT assay. The complexes have shown IC_{50} of 19 and 18 µM compared to cisplatin as a reference standard. Furthermore, these complexes were converted to gold complexes and subjected to the same studies. The complex 29 contains dichloro substitution on imidazole rings, but there is no considerable impact of replacing H by Cl.

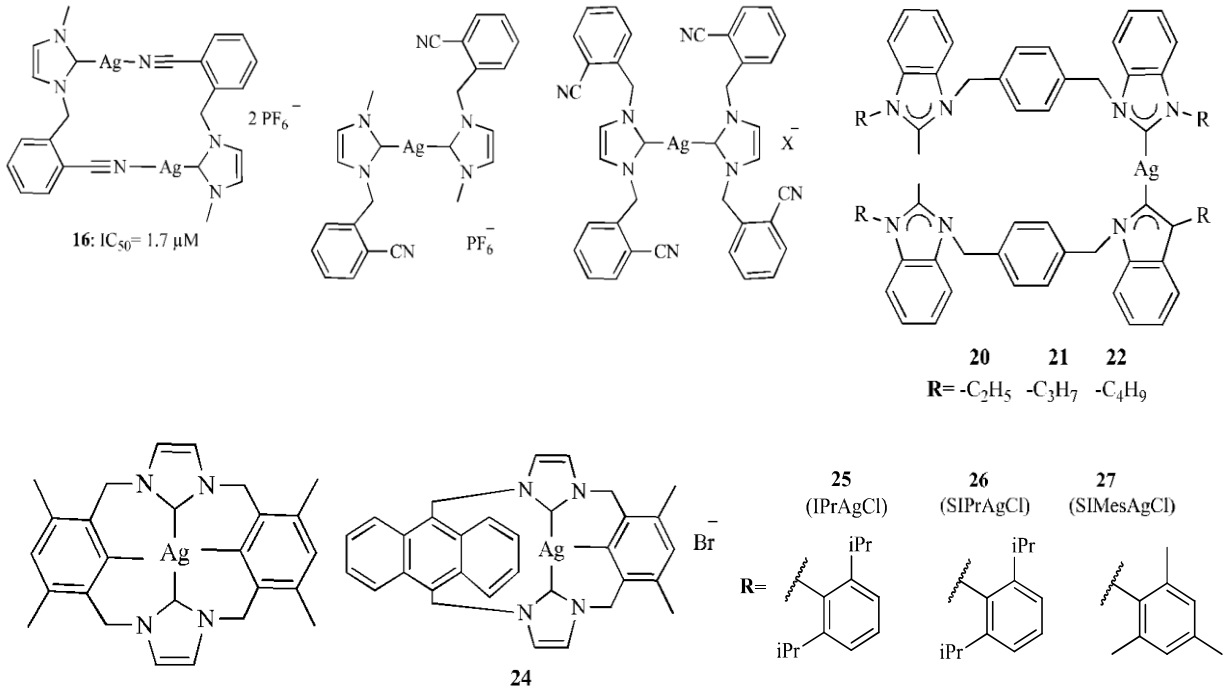

Fig 2: - Reported Ag-NHCs as anticancer agents with IC_{50} Values [13]

Dichloroimidazole based Ag-NHCs 30-32 were evaluated for cytotoxicity studies in OVCAR-3 (ovarian), MB157 (breast) and HeLa (cervical) cancer cell lines. These complexes showed good activity against ovarian and breast cancer cell lines but failed to show promising activity in cervical cancer cell lines. The complex 30 showed IC_{50} as 35, 30, 20 µM and 8, 20, 10 µM against ovarian and breast cancer cell lines. These complexes exhibited IC_{50} more than 200 µM in cervical cancer cell lines [14] Patil et al. [15] had prepared silver acetate based Ag-NHC 33-38 and evaluated them for anticancer activity against human renal cancer (Caki-1) cell lines using cisplatin as a reference standard. The complexes exhibited IC_{50} values ranging from 1.2- 24.2 µM where cisplatin showed IC_{50} of 3.3 µM (Fig 4).

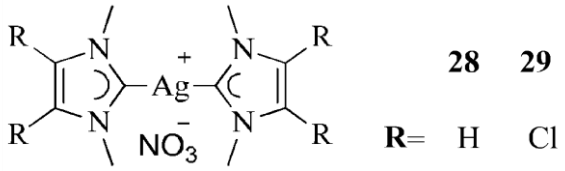

Fig 3: - Dichlorosubstituted imidazole containing Ag-NHCs [15]

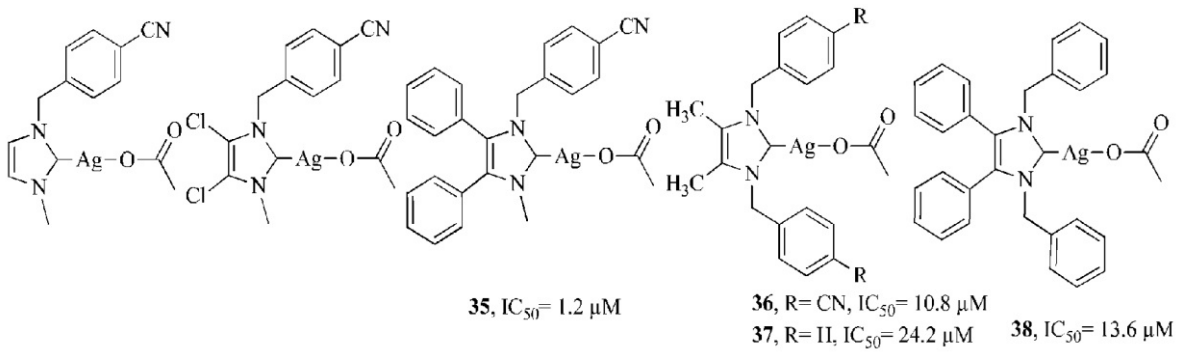

Fig 4: - Ag acetate based Ag-NHC as anticancer agents [16]

Dibenzyl based silver complexes 39-44 were reported (Table 1) for cytotoxicity in various cancer cell lines such as MCF-7 (breast cancer), MDA-MB-231(breast cancer) and T- 29 (colon carcinoma). Additionally, authors had studied the DNA binding and inhibition of cyclooxygenase-2 (COX-2). These compounds didn't show any promising activities on DNA as well as COX-2 inhibition[16]. The reports say that the scientists[17] had synthesized dicationic ligand 45 and binuclear Ag-NHC 46 for cytotoxicities against healthy cells i.e. CCD-18Co and cancer cell lines such as HCT- 116 and prostate carcinoma (PC-3) cell lines. As expected, the metal complex displayed increased activity compared to the ligand. The silver complex was able to induce apoptosis possibly via caspase pathway as revealed by FAM-FLICA assay. Compound 46 also inhibited interleukin i.e.IL-1 synthesis along with tumor necrosis factor alpha TNF-α in human macrophages (U937 cells). Additionally, it has shown strong inhibition of COX-2.

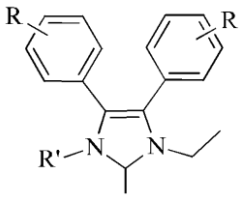

Fig 5: - Dibenzyl Ag- NHC derivatives [17]

Table - 1: IC_{50} Value of dibenzyl NHC derivatives

Compound	R	R'	X	IC_{50}(uM)		
				MCF-7	MDA-MB-231	HT-29
39	2-F	Et	Br	3.4	3.6	7.5
40	3-F	Et	Br	3.5	4.1	7.4
41	4-F	Et	Br	3.9	3.5	4.4
42	2-MeO	Et	Br	3.7	8.5	9.9
43	4-OH	Et	Br	9.2	12.8	16.2
44	4-F	PhCH2	Cl	3.6	3.4	6.8

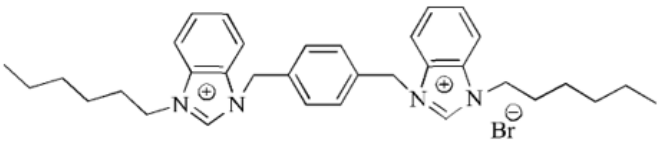

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Fig 6A: - Dicationic ligand based AG-NHCs [18]

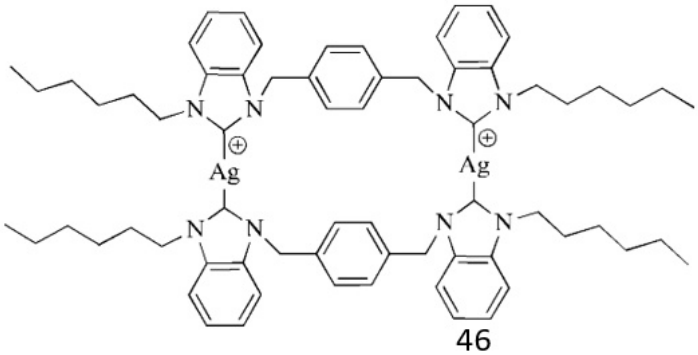

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Fig. 6B: - Dicationic ligand based AG-NHCs [18]

Haque et al. [18] had prepared binuclear Ag-NHC 47-50 with different aromatic spacers with substitutions on aromatic moiety and evaluated for anticancer activity in HCT 116 cell lines. IC_{50} values were assessed and found to be in the range of 3.4-18.1 µM and compared against 5-Fluorouracil for which IC_{50} was 5.2 µM. These metal complexes were active against bacteria like E. coli and S. aureus. Sulfonate and ester functionalized Ag-NHC 51-53 were evaluated for cytotoxicity studies in cisplatin-resistant cancer cell lines such as HCT-15, A549, MCF-7, A431 and A375 with IC_{50} ranging from 8-15 µM. Along with the cytotoxicity, authors also studied the effect of silver complexes on inhibition of a selenoenzyme TrxR (Thioredoxin Reductase). The inhibition of antioxidant TrxR leads to induction of oxidative stress, an imbalance in thiols redox state which ultimately leads to cancer cell death[19].

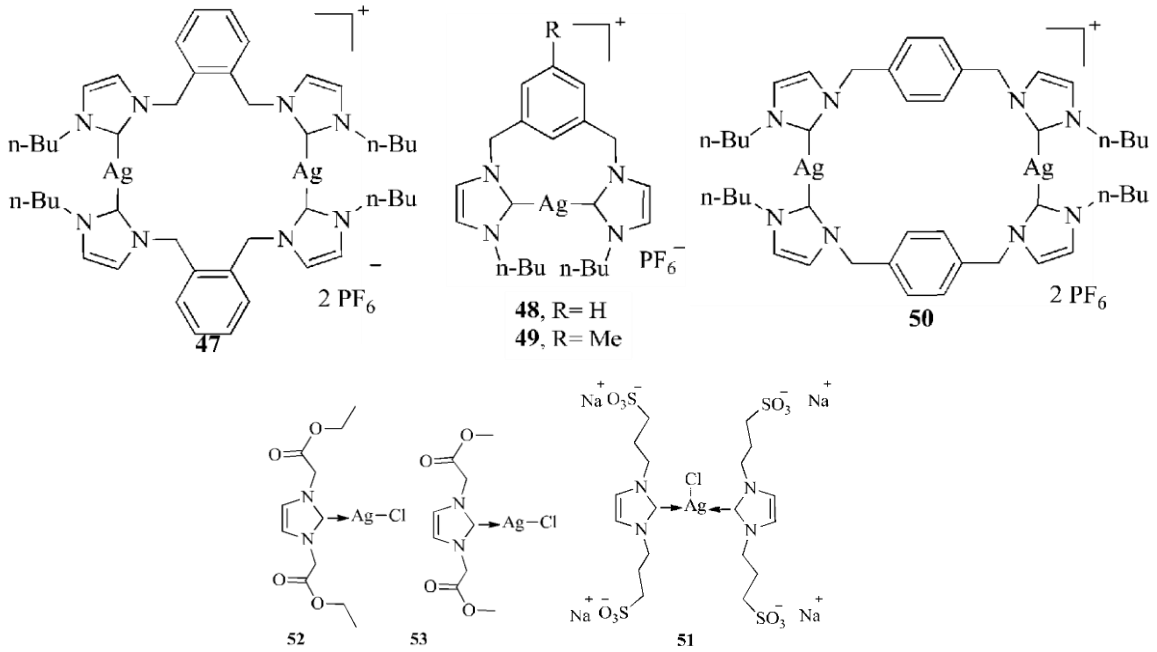

Fig 7: Alkyl substituted and Sulfonate Ag NHCs [19]

A series of NHC–silver complexes derived from 4,5-dichloro-1*H*-imidazole complexes exhibited cytotoxic activity against the ovarian (OVCAR-3) and breast (MB157) cancer cells *in vitro*. However, they had little effects on the cervical (HeLa) cancer cells. It was also reported a low cytotoxic NHC– silver complex on HeLa cells. Additionally, *in vivo* studies demonstrated that the NHC–silver complex was active against the ovarian cancer cells of mice.

5. CONCLUSION

Ag-NHCs have been explored for their wide range of anticancer activities. Various structural analogues have been prepared and have shown specific IC_{50} against the cancer cell lines. It was observed that the Ag-NHCs with presence of dibenzyl aromatic rings were having effective IC_{50} values in the range of 3-10 uM whereas the Ag-NHCs having Acetate derivatives exhibited IC_{50} values in the range of 1024 uM. The presence of imidazole substitutions enhanced the electronic behavior of the NHCs developing into an electronically rich entity to interact with cancer cell lines. Thus, a substitution of a high electron density group enhances the potential of biological activity of the Ag-NHCs. The change in the substitution on the NHCs or change in the transition metals connecting to the NHCs may lead to variable biological activities. Thus, according to IC_{50} values reported, we can design specific metal centered NHCs, as an efficient and less toxic drug discovery.

6. ACKNOWELDGEMENT

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7. AUTHOR CONTRIBUTION STATEMENT

Sainath B. Aher has worked on Ag-NHCs through his experimental work. Poonam R. Inamdar and Mrunalini Kulkarni have written the manuscript. Srushti Parekh and Vasudev Bendre have removed the plagiarism and formatted the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

1. Arduengo AJ, Harlow RL, Kline MA. A stable crystalline carbene. J Am Chem Soc. 1991a;113(1):361-3. doi: 10.1021/ja00001a054.
2. Bertrand B, Stefan L, Pirrotta M, Monchaud D, Bodio E, Richard P et al. Caffeine-based gold(I) N-heterocyclic carbenes as possible anticancer agents: synthesis and biological properties. Inorg Chem. 2014;53(4):2296-303. doi: 10.1021/ic403011h, PMID 24499428.
3. Arduengo AJ, Dias HVR, Harlow RL, Kline M. Electronic stabilization of nucleophilic carbenes. J Am Chem Soc. 1992;114(14):5530-4. doi: 10.1021/ja00040a007.
4. Patil SA, Patil SA, Patil R, Keri RS, Budagumpi S, Balakrishna GR et al. N-heterocyclic carbene metal complexes as bio-organometallic antimicrobial and anticancer drugs. Future Med Chem. 2015;7(10):1305-33. doi: 10.4155/fmc.15.61, PMID 26144266.
5. Arduengo AJ, Dias HVR, Dixon DA, Harlow RL, Klooster WT, Koetzle TF. Electron distribution in a stable carbene. J Am Chem Soc. 1994;116(15):6812-22. doi: 10.1021/ja00094a040.
6. Samantaray MK, Katiyar V, Roy D, Pang K, Nanavati H, Stephen R et al. A cationic (N-heterocyclic carbene) silver complex as catalyst for bulk ring-opening polymerization of L-lactides. Eur J Inorg

Chem. 2006;2006(15):2975-84. doi: 10.1002/ejic.200600209.
7. Samantaray MK, Roy D, Patra A, Stephen R, Saikh M, Sunoj RB et al. Experimental and theoretical studies of a silver complex of O-functionalized N-heterocyclic carbene. J Organomet Chem. 2006b;691(18):3797-805. doi: 10.1016/j.jorganchem.2006.05.037.
8. Lee M, Hu CH. Density functional study of N-heterocyclic and diaminocarbene complexes: comparison with phosphines. Organometallics. 2004;23(5):976-83. doi: 10.1021/om0341451.
9. Hayes JM, Viciano M, Peris E, Ujaque G, Lledós A. Mechanism of formation of silver N-heterocyclic carbenes using silver oxide: a theoretical study. Organometallics. 2007;26(25):6170-83. doi: 10.1021/om700898d.
10. Budagumpi S, Haque RA, Endud S, Rehman GU, Salman AW. Biologically relevant silver(I)-N-heterocyclic carbene complexes: synthesis, structure, intramolecular interactions, and applications. Eur J Inorg Chem. 2013;2013(25):4367-88. doi: 10.1002/ejic.201300483.
11. Zetty Zulikha H, Haque RA, Budagumpi S, Abdul Majid AMS. Topology control in nitrile-functionalized silver(I)–N-heterocyclic carbene complexes: Synthesis, molecular structures, and in vitro anticancer studies. Inorganica Chimica Acta. 2014;411:40-7. doi: 10.1016/j.ica.2013.11.011.
12. Iqbal MA, Haque RA, Ahamed MBK, Majid AMSA, Al-Rawi SS. Synthesis and anticancer activity of para-xylyl linked bis-benzimidazolium salts and respective Ag(I) N-heterocyclic carbene complexes. Med Chem Res. 2013;22(5):2455-66. doi: 10.1007/S00044-012-0240-6.
13. Li Y, Liu GF, Tan CP, Ji LN, Mao ZW. Antitumor properties and mechanisms of mitochondria-targeted Ag(I) and Au(I) complexes containing N- heterocyclic carbenes derived from cyclophanes. Metallomics. 2014;6(8):1460-8. doi: 10.1039/c4mt00046c, PMID 24788133.
14. Eloy L, Jarrousse AS, Teyssot ML, Gautier A, Morel L, Jolivalt C et al. Anticancer activity of silver-N-heterocyclic carbene complexes: caspase-independent induction of apoptosis via mitochondrial apoptosis-inducing factor (AIF). ChemMedChem. 2012;7(5):805-14. doi: 10.1002/cmdc.201200055, PMID 22383263.
15. Siciliano TJ, Deblock MC, Hindi KM, Durmus S, Panzner MJ, Tessier CA et al. Synthesis and anticancer properties of gold(I) and silver(I) N-heterocyclic carbene complexes. J Organomet Chem. 2011;696(5):1066-71. doi: 10.1016/j.jorganchem.2010.10.054.
16. Medvetz DA, Hindi KM, Panzner MJ, Ditto AJ, Yun YH, Youngs WJ. Anticancer activity of Ag(I) N-heterocyclic carbene complexes derived from 4,5-dichloro-1H-imidazole. Met Based Drugs. 2008;2008:384010. doi: 10.1155/2008/384010, PMID 18615197.
17. Patil S, Deally A, Gleeson B, Müller-Bunz HM, Paradisi F, Tacke M. Novel benzyl-substituted N-heterocyclic carbene–silver acetate complexes: synthesis, cytotoxicity and antibacterial studies. Metallomics. 2011;3(1):74-88. doi: 10.1039/c0mt00034e, PMID 21135954.
18. Liu C, Liu Z, Li M, Li X, Wong YS, Ngai SM et al. Enhancement of auranofin-induced apoptosis in mcf-7 human breast cells by selenocystine, a synergistic inhibitor of thioredoxin reductase. PLOS ONE. 2013;8(1):e53945. doi: 10.1371/journal.pone.0053945, PMID 23342042.
19. Iqbal MA, Umar MI, Haque RA, Khadeer Ahamed MBK, Asmawi MZ, Majid AMSA. Macrophage and colon tumor cells as targets for a binuclear silver(I) N-heterocyclic carbene complex, an anti-inflammatory and apoptosis mediator. J Inorg Biochem. 2015;146:1-13. doi: 10.1016/j.jinorgbio.2015.02.001, PMID 25699476.
20. Haque RA, Salman AW, Budagumpi S, Abdullah AA, Majid AMSA. Sterically tuned Ag(I)- and Pd(II)-N-heterocyclic carbene complexes of imidazol-2-ylidenes: synthesis, crystal structures, and in vitro antibacterial and anticancer studies. Metallomics. 2013;5(6):760-9. doi: 10.1039/c3mt00051f, PMID 23645390.
21. Gandin V, Pellei M, Marinelli M, Marzano C, Dolmella A, Giorgetti M et al. Synthesis and in vitro antitumor activity of water soluble sulfonate- and ester-functionalized silver(I) N-heterocyclic carbene complexes. J Inorg Biochem. 2013;129:135-44. doi: 10.1016/j.jinorgbio.2013.09.011, PMID 24121303.