IJBPAS, August, 2022, 11(8): 3679-3690

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

MONONUCLEAR ORGANOMETALLIC COMPOUNDS OF GOLD(III) AS ANTICANCER AGENTS: A CRITICAL SURVEY

SATAPATHI S

Department of Chemistry, Netaji Mahavidyalaya (Affiliated to The University of Burdwan & recognized by U.G.C.), Arambagh, Hooghly, West Bengal, PIN-712 601,

***Corresponding Author: Smita Satapathi; E Mail: smitasatapathi@gmail.com**

Received 16th Aug. 2021; Revised 20th Sept. 2021; Accepted 12th Dec. 2021; Available online 1st Aug. 2022

https://doi.org/10.31032/IJBPAS/2021/11.8.6294

ABSTRACT

Recently gold based metallodrugs with +1 and +3 oxidation states show the significant role in the progress of medicinal chemistry, especially in the treatment of cancer, HIV virus, SARS-CoV-2 virus and other diseases. Particularly, gold(III) compounds are of the extreme attention because of their structural similarity with cisplatin, one of the first metallodrugs to be widely used for cancer treatment. A large variety of anticancer gold(III) organometallics of various families are reported in literature that have significant antiproliferative properties *in vitro* against selected human tumor cell lines and majority of them are also capable to overcome cisplatin resistance. The nature of inert and labile ligands plays a vital role in the anticancer activity of these compounds. The primary goal of this review is to summarize the chemistry and activity of some novel mononuclear anticancer gold(III) organometallic compounds that making themselves promising candidates for further pharmacological evaluation. The general outlooks on the progress of these compounds as clinically efficient anticancer drugs are discussed here on the basis of the available experimental evidence.

Keywords: Gold(III) ion; Variety of ligands; Mononuclear organometallic compounds; Chemistry; and Anticancer activity

INTRODUCTION:

Cancer is considered as a lethal disease that derives from the mutation of genes **[1]**. From mid-1960s, the potential anti-cancer drug cisplatin has been widely used in chemotherapy by inhibiting the activities of cancer cells effectively through the formation of DNA-platinum adducts **[2]**. Unfortunately, for non-selective DNA-targeted mechanism, the anticancer treatment with cisplatin has a number of limitations, including resistance, inadequate range of action along with severe side effects **[3]**. So, research in this field has been extended to the development of novel non-platinum based metallodrugs as pharmaceuticals. In this regard, gold compounds have attracted special interest due to their unique biological as well as medicinal properties **[4]**. Moreover, these compounds have comparatively weaker interactions with cellular DNA through a "DNA-independent mechanism" **[5]**. Predominantly, gold(III) complexes are considered as probable alternatives **[6]** to Pt(II) complexes because both the ions are isoelectronic and their complexes are isostructural. Though a large number of gold(III) compounds showed very distinct antitumor actions *in vitro*, they have severe toxicity and lower *in vivo* effectiveness **[7]**. To minimize the systemic toxicity and to enhance the anti-cancer activities, a number of stable anticancer gold(III) based organometallics are prepared using suitable organic ligands including N-heterocyclic carbene (NHC), cyclometallated ligands and various N-donor ligands with different substituents **[8, 9]**. These types of compounds are relatively stable than other classical coordination complexes due to the formation of a strong covalent Au-C bond. In biological environments, they preferentially target proteins like Se-enzyme thioredoxin reductase (TrxR) **[10]**, Zn finger enzymes **[11]**, along with the membrane water and glycerol channel aquaglyceroporins **[12]**. The nature of the ligand coordinated to the gold(III) centre plays an active role in determining the biological properties of the resulting complexes.

The overall perspectives on the advance of mononuclear organometallic gold(III) compounds as efficient anticancer drugs are critically discussed. The purpose of this review is to show the importance of structure-activity relationship methods in the study of anticancer metal complexes. The correlations of the nature and the substituents of the ligands with their anticancer activities are briefly discussed here on the basis of their existing experimental evidence. Therefore, the area highlighted in this review, could be very useful for the syntheses of new potential gold(III) based mononuclear organometallic anticancer drugs that may be developed for future clinical studies.

CHEMISTRY OF GOLD(III) COMPOUNDS

The chemistry of gold(III) compounds includes the following distinct features:

(a) Redox chemistry of gold is related with its three most vital oxidation states: 0, +1 and +3. Frequent reduction from square planar gold(III) complex to linear gold(I) complex under physiological conditions creates inhibition to build up a variety of active gold-based anticancer drugs. To increase the redox stability of organometallic gold(III) complexes NHC, cyclometallated ligands and various N-donor ligands with different substituents may be used **[8, 9]**.

(b) Compounds of gold(III) with $5d^8$ configuration are isoelectronic and isostructural to platinum(II) complexes. Though the chemistry of tetra-coordinated gold(III) complexes (square planar) are dominant, five-coordinated (square Pyramidal) and six-coordinated (octahedral) complexes are also found.

SOME NOVEL MONONUCLEAR ORGANOMETALLIC GOLD(III) COMPLEXES AS ANTICANCER AGENTS:

The anticancer activity of some novel mononuclear organometallic gold(III) compounds is discussed here briefly into five major groups.

A. With only C-donor organic ligands:

Compounds **1** and **2** of this group are outlined in **Scheme 1.**

The gold(III) complexes with NHC ligands have distinct medicinal applications **[13]**. Consequently, compound **1** **[14]** with hetero-bis(carbene) exhibited *in vitro* levels of cytotoxicity towards the non-small cell lung cancer cell line. It showed higher cytotoxicity than monocarbene/bis(carbene) analogue and cisplatin. It also considerably inhibited TrxR. It had definite anti-proliferative properties against colon carcinoma cell line **[15]**. Its selectivity against cancer cells was associated with its delocalised lipophilic cationic behavior. It was well accumulated in cancer cells due to its relatively high mitochondrial membrane potential **[16]**.

Compound **2** exerted its cytotoxic effects through direct mitochondrial damage by selective modification of the selenol active site in thioredoxin reductase **[5, 17-19]**.

B. With amines: The anti-cancer organometallic gold(III) compounds **3-5** with amines are shown in **Scheme 2**.

The organo-gold(III) compound **3** displayed cytotoxicity similar to that of cisplatin against several human tumor cell lines including human colon carcinoma **[20]**. Several novel products had been prepared from compound **3**. The compound **4** or **5** was obtained when the two chloride ligands of compound **3** were replaced by acetate or malonate anions, respectively. The resulting compounds **4** and **5** also exhibited selective cytotoxicities *in vitro* against a panel of tumoral cell lines. They also displayed *in vivo* antitumor activity in human tumor xenograft models **[20]**. These results highlights that the substitution of the chloride ligands by other anions could lead to new active gold(III) complexes.

C. With both imines-N and S donor organic ligands: New active complexes were obtained through the substitution of the chloride ligands of compound **3** by thiosemicarbazonate anions (**TSC**$^-$) as this anion itself may exhibited antineoplastic activity **[21]**. These active complexes containing bi- or tridentate **TSC**$^-$ ligands showed antitumor activity against human breast cancer cells **[22]**. Recently, much interest has grown on the antitumor activity of ferrocene derivatives typically connected with ferrocinium compounds **[23]**, because ferrocene itself has a distinct antitumor effect on tumor-bearing mice. This effect may arise from an immune-stimulatory property of the organometallic compound **[24]**. Several new active compounds **6a-6e** were obtained **[25]** by reacting a selected range of formylferrocene thiosemicarbazone ligands (HFTSC, HFMTSC, HFPTSC, HFETSC, HFMMTSC) (**Scheme 3**) with compound **3**. The low solubility of compounds **6c** and **6e** in the cell culture medium prevented their study. The IC_{50} values of the other three compounds **6a, 6b** and **6d** were around 100 times higher than that of cisplatin though their maximum cell growth inhibition was comparable to that of the platinum complex. Here, the R_1 and R_2 groups on N of the thiosemicarbazone ligand had some influence on the antitumor activity of these gold compounds. Among these five compounds, **6d** in which R_1= H and R_2 = Et was the most active antitumor compound.

D. With pyridine type ligands: Compounds **7-18** of this group of are shown in **Scheme 4**.

Compound **7** acted as effective inhibitors of the cytosolic form of the selenoenzyme TrxR and it also agitated the mitochondrial functions significantly **[5, 17-19, 26, 27]**. The large proapoptotic and cytotoxic properties of this compound were determined by direct antimitochondrial effects.

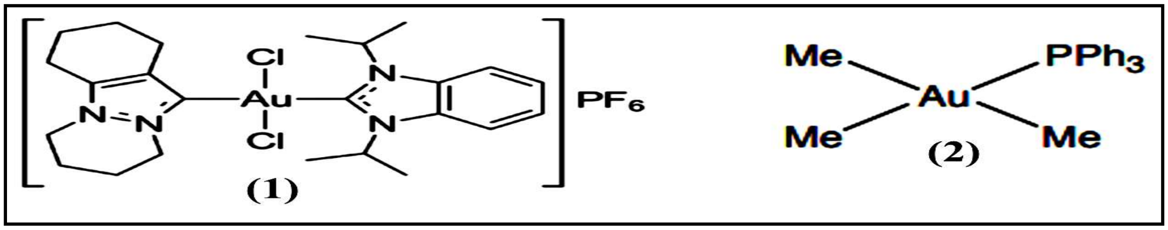
Compound **8** exerted relevant antiproliferative **[14]** effects and it was comparable with cisplatin. Here gold(III) centre has relatively lower possibility for coordination with the selenocysteine active site of TrxR as it is quite hard than Gold(I) centre **[28]**. Again, significant cross-resistance effects were observed for this compound when its resistance factors were measured in the A2780/R cell line. This compound was highly selective inhibitors **[27]** of selenoenzyme but less effective than auranofin.

The cyclometallated compound **9** containing the phosphane derivative ligand, PTA, showed enhanced *in vitro* toxicity **[28]**. Here ligand improved water-solubility and controled thio-sugar moieties to exchange with biological nucleophiles. It also revealed significant activity against the HCT116 cancer cell line over expressing tumor protein (p53). This compound also inhibited the zinc finger enzyme poly(ADP-ribose)polymerase-1 (PARP-1) **[29]**. It was tested *in vitro* in the lung, breast, colon and ovarian human cancer cell lines. The outstanding *in vitro* toxicity profile of this compound displayed p53 dependent activity in colorectal cancer HCT116 cells.

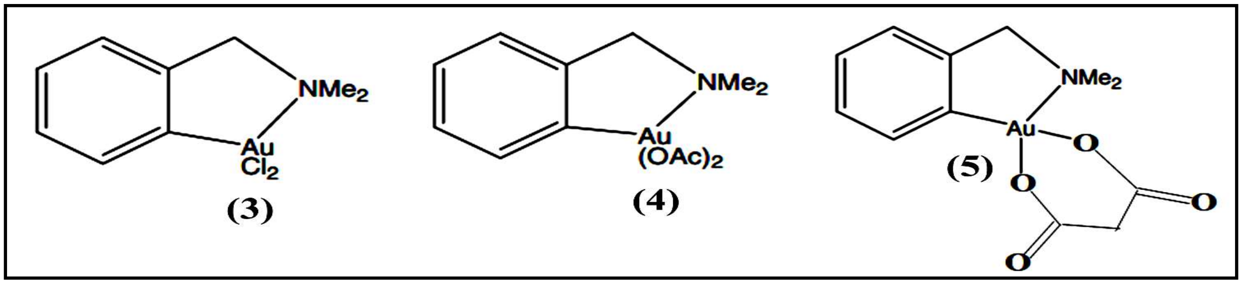
Complexes **10-18** are cyclometallated gold(III) based anticancer drugs having general formula [Au(CˆNˆC/Ph-C^N^C)L]$^{n+}$ **[26]** where L was chloride/phosphane/pyridine/ imidazole-type ligand and the abbreviations CˆNˆC/Ph-C^N^C is used for the bi-cyclometallated di-anion derived from 2,6-diphenylpyridine/2,6-dinaphthylpyridine. Cyclometallation stabilized the complexes by the formation of a strong Au-C covalent bond. These compounds possessed similar cytotoxic activities like compounds **6a-6e** **[20]**. The [Au(CˆNˆC)]$^{+}$ moiety in compound **10** stabilized the gold-phosphane ligand and acted as a carrier for biologically active phosphane molecule. It weakly interacted with calf thymus DNA (ctDNA). It also revealed cytotoxic activity towards the nasopharyngeal carcinoma (NPC) showing no significant alteration in the cell cycle of NPC cells **[30]**. Compounds **12-14** were obtained by replacing chloride from compound **11** with N-donor auxiliary ligands. All these complexes showed significant anti-cancer activity. Compound **13** appreciably reduced the tumor size in nude mice with hepatocellular carcinoma without noticeable toxic side effects. The gold(III)-induced cytotoxicity of compound **14** occurred through an apoptotic cell-death pathway. The binding of this compound to ctDNA significantly increased the stabilization of ctDNA. It also created S-phase cell arrest following incubation for 24 and 48 hours. Compounds **15** and **16** were structural analogues of **11** and **14**, respectively, with a phenyl substitution at the pyridine ring. Compounds **17**, **18a** and **18b** with extended π-conjugated Np-C^N^C motifs remained unreduced under physiological conditions and exerted anticancer potency comparable to that of cisplatin. The $[Au(Np\text{-}C\hat{}N\hat{}C)]^+$ moiety of these compounds was responsible for the observed cytotoxicity as the free N-donor ligands were relatively nontoxic.

E. With substituted bipyridine ligands: Lipophilic gold(III) cation in compounds **19** and **20 (Scheme 5)** with tridentate CˆNˆN-type ligand **[26]** showed enhanced stability under physiological conditions compare to N-donor ligands that improved its anti-cancer activity towards nucleobases. Compounds **19** exhibited two-fold higher activities than cisplatin in the A2780/R cell line **[5]**. It showed potent cytotoxic activities toward ovarian carcinoma cell line **[26]**. On the other hand, compound **20** exhibited promising cytotoxic activities toward A2780/S ovarian carcinoma cell line **[26]**. Both compounds **19** and **20** exerted apoptosis to a better extent than cisplatin and oxaliplatin with modest cell-cycle alterations. They could extensively inhibit mitochondrial thioredoxin reductase and mitochondrial respiration **[27]**. Results of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays indicated that these compounds exerted anticancer potency comparable to that of cisplatin.

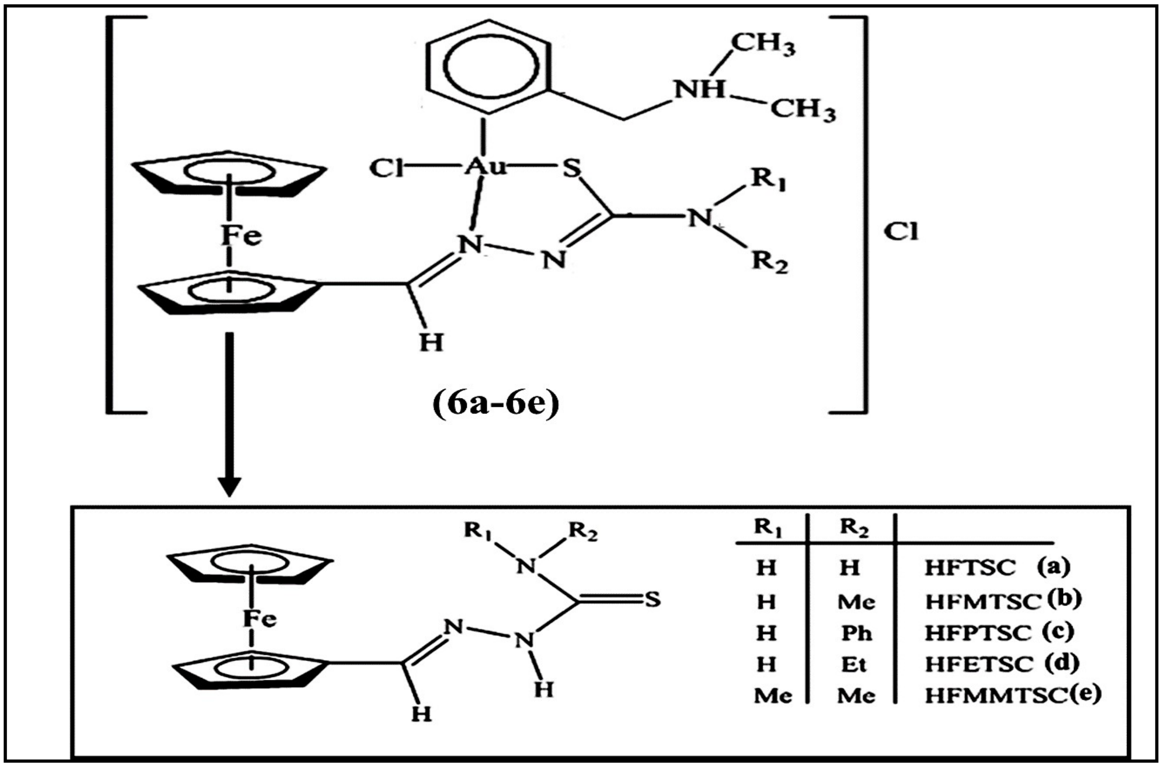
Scheme:



Scheme 1: Mononuclear organometallic compounds of gold(III) with only C-donor organic ligands: $[Au(FPyr)(iPr_2\text{-}bimy)(Cl)_2]PF_6$ (1); $[Au(Me)_3(PPh_3)]$ (2)

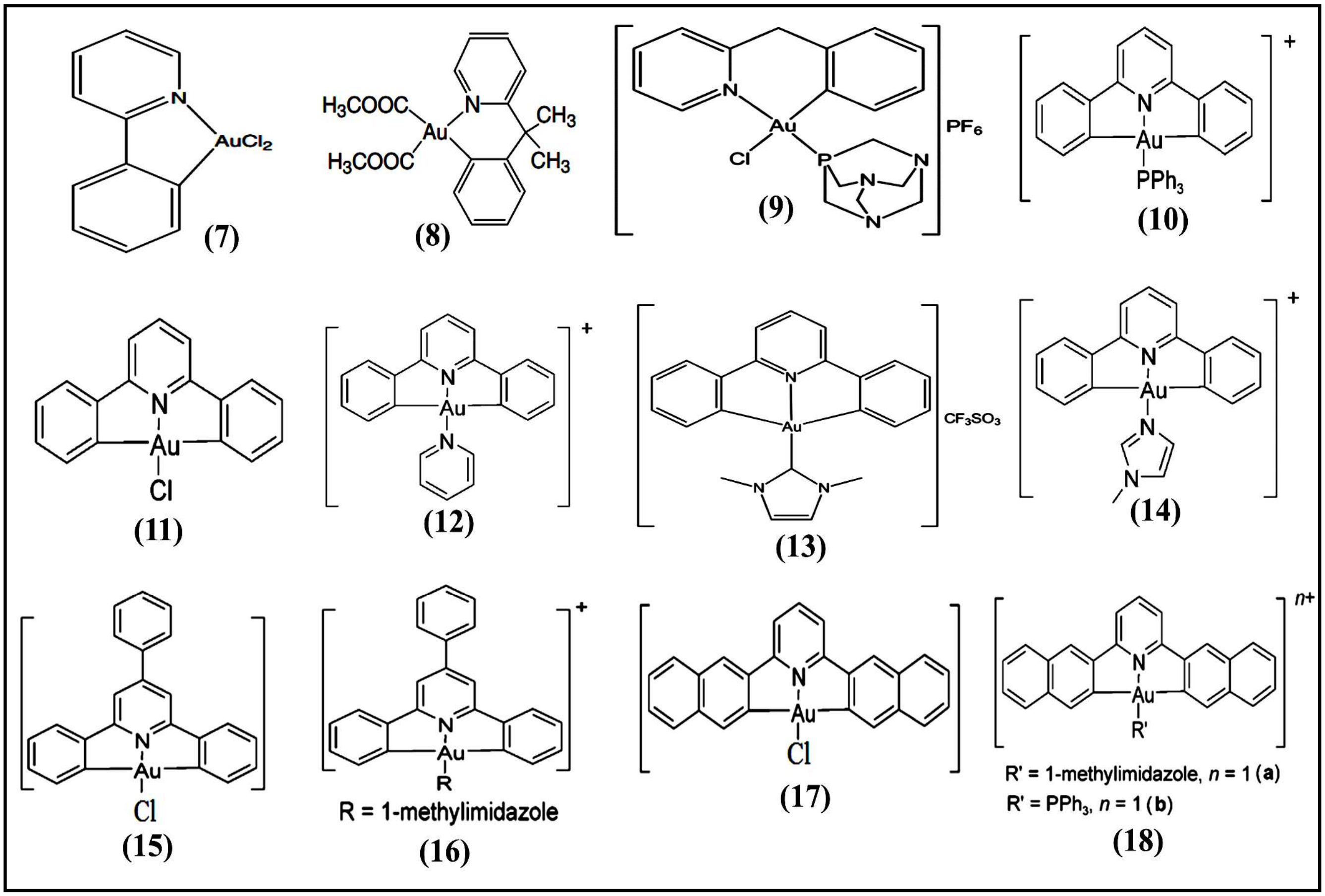


Scheme 2: Mononuclear organometallic compounds of gold(III) with amines: [Au(damp-C^1; N)Cl$_2$] (3), [Au(damp-C^1;N)(OAc)$_2$] (4), [Au(damp-C^1; N)(malonate)] (5)

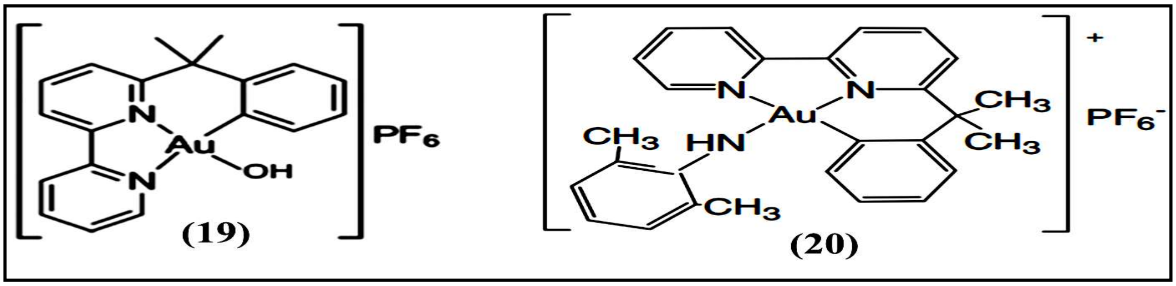


R_1	R_2	
H	H	HFTSC (a)
H	Me	HFMTSC (b)
H	Ph	HFPTSC (c)
H	Et	HFETSC (d)
Me	Me	HFMMTSC (e)

Scheme 3: Mononuclear organometallic compounds of gold (III) with both imines-N and S donor organic ligands: [Au(Hdamp-C^1)Cl(FTSC)]Cl.(CH$_3$)$_2$CO (6a), [Au(Hdamp-C^1)Cl(FMTSC)]Cl (6b), [Au(Hdamp-C^1)Cl(FPTSC)]Cl (6c), [Au(Hdamp-C^1)Cl(FETSC)]Cl (6d), [Au(Hdamp-C^1)Cl(FMMTSC)]Cl (6e).



Scheme 4: Mononuclear organometallic compounds of gold(III) with pyridine type ligands: [Au(phpy)(Cl)$_2$] (7); [Au(py^{dmb}-H)(CH$_3$COO)$_2$] (8); [Au(py^{b}-H)(PTA)Cl][PF$_6$] (9); [Au(C^N^C)(PPh$_3$)]$^+$ (10); [Au(C^N^C)Cl] (11); [Au(C^N^C)Py]ClO$_4$ (12); [Au(C^N^C)(IMe)][CF$_3$SO$_3$] (13); [Au(C^N^C)(1-methylimidazole)]$^+$ (14); [Au(Ph-C^N^C)]Cl (15); [Au(Ph-C^N^C)(meim-1)]ClO$_4$ (16); [Au(Np-C^N^C)(Cl)]$^+$ (17); [Au(Np-C^N^C)(1-methylimidazole)]$^+$ (18a); [Au(Np-C^N^C)(PPh$_3$)]$^+$ (18b)



Scheme 5: Mononuclear organometallic compounds og gold(III) with substituted bipyridine ligands: [Au(bipydmb-H)(OH)][PF$_6$] (19); [Au^{III}(bipydmb–H)(2,6-xylidine–H)]$^+$ (20)

CONCLUSION:

Mononuclear organometallic gold(III) compounds may be considered as probable alternatives to Pt-based drugs and may be used as efficient therapeutic agents due to their stability in physiological conditions. They have better selectivity and effectiveness towards cancer cells than normal cells in compare to cisplatin. Few of them display significant anticancer activity through inhibition of thioredoxin reductase. Further research works based on experimental trials are required to improve the efficiency of these compounds against the selective cancer cells. The pharmacokinetic profiles of these compounds greatly depend on the nature of the coordinated ligands. There is a huge possibility of development of new effective gold(III) based organometallic anticancer drugs through the modification of the ligands. Further preclinical investigations are required to recognize these compounds as suitable candidates for clinical trials. So, it is an emerging area of research for the rational design of organometallic gold(III) based anticancer materials and there remain wonderful opportunities for further development.

ABBRIVIATION OF LIGANDS:

FPyr = 1,3-diisopropylbenzimidazolin-2-ylidene; **iPr_2-bimy** = 1,2,3,4,6,7,8,9-octahydropyridazino[1,2-a]indazolin-11-ylidene; **damp** = 2-[(dimethylamino)methyl]phenyl; **phpy** = 2-phenylpyridine; **py^{dmb}-H** = cyclometallated anion derived from 6-(1,1-dimethylbenzyl)-2,2′-bipyridine; **py^{b}-H** = C^N cyclometallated 2-benzylpyridine; **PTA** = 1,3,5-triazaphosphaadamantane; **HC^N^CH** = 2,6-diphenylpyridine; **PPh_3** = triphenylphosphine; **Py** = Pyridine; **IMe** = N,N′-dimethylimidazolium; **Ph-C^N^C** = 2,6-diphenyl(4-phenylpyridine); **meim-1** = 1-methylimidazole; **Np-C^N^C** = 2,6-dinaphthylpyridine; **bipydmb** = 6-(1,1-dimethyl-benzyl)-2,2′-bipyridine.

ACKNOWLEDGEMENTS

The author wants to thanks her college authority, affiliated university authority and also the persons whose works in this field inspired her.

REFERENCES:

[1] Balkwill FR, Mantovani A, Cancer-related inflammation: Common themes and therapeutic opportunities, Semin. Cancer Biol., 22, 2012, 33-40.

[2] Gielen M, Tiekink ERT, Metallotherapeutic Drugs and Metal-Based Diagnostic Agents: The Use of Metals in Medicine, John Wiley & Sons Ltd.: Chichester, UK, 2005, 1-598.

[3] Rezaee R, Momtazi AA, Monemi A, Sahebkar A, Curcumin: A potentially powerful tool to reserve cisplatin-induced toxicity, Pharmacol. Res. 117, 2017, 218-227.

[4] Rackham O, Nichols SJ, Leedman PJ, Berners-Price SJ, Filipovska A, A gold(I) phosphine complex selectively induces apoptosis in breast cancer cells: Implications for anticancer therapeutics targeted to mitochondria, Biochem. Pharmacol., 74, 2007, 992-1002.

[5] Casini A, Hartinger C, Gabbiani C, Mini E, Dyson PJ, Keppler BK, Messori L, Gold(III) compounds as anticancer agents: Relevance of gold-protein interactions for their mechanism of action, J. Inorg. Biochem., 102, 2008, 564-575.

[6] Radisavljević S, Petrović B, Gold(III) Complexes: An Overview on Their Kinetics, Interactions With DNA/BSA, Cytotoxic Activity, and Computational Calculations, Front. Chem., 8, 2020, 1-8.

[7] Wang FY, Feng HW, Liu R, Huang KB. Liu YN, Liang H, Synthesis, characterization and antitumor activity of novel gold (III) compounds with cisplatin-like structure, *Inorg.Chem. Com.* 105, 2019, 55-58.

[8] Bertrand B, Casini A, A golden future in medicinal inorganic chemistry: the promise of anticancer gold organometallic compounds, Dalton Trans., 43, 2014, 4209-4219.

[9] Bertrand B, Stefan L, Pirrotta M, Monchaud D, Bodio E, Richard P, Gendre PL, Warmerdam E, de Jager MH, Groothuis GM, Picquet M, Casini A., Caffeine-Based Gold(I) N-Heterocyclic Carbenes as Possible Anticancer Agents: Synthesis and Biological Properties, Inorg. Chem., 53(4), 2014, 2296-2303.

[10] Meyer A, Oehninger L, Geldmacher Y, Alborzinia H, Wolfl S, Sheldrick WS, Ott I, Gold(I) N-Heterocyclic Carbene Complexes with Naphthalimide Ligands as Combined Thioredoxin Reductase Inhibitors and DNA Intercalators, Chem. Med. Chem., 9(8), 2014, 1794-1800.

[11] Serratrice M, Edafe F, Mendes F, Scopelliti R, Zakeeruddin SM, Grätzel M, Santos I, Cinellu MA, Casini A, Cytotoxic gold compounds: synthesis, biological characterization and investigation of their inhibition properties of the zinc finger protein PARP-1, Dalton Trans., 41, 2012, 3287-3293.

[12] De Almeida A, Soveral G, Casini A, Gold compounds as aquaporin inhibitors: new opportunities for therapy and imaging, Med. Chem. Commun., 5, 2014, 1444-1453.

[13] Dominelli B, Correia JDG, Kühn FE, Medicinal Applications of Gold(I/III)-Based Complexes Bearing *N*-

Heterocyclic Carbene and Phosphine Ligands, J. Organomet. Chem., 866, 2018, 153-164.

[14] Yeo CI, Ooi KK, Tiekink ERT, Gold-Based Medicine: A Paradigm Shift in Anti-Cancer Therapy? Molecules, 23(6), 2018, 1410.

[15] Rubbiani R, Schuh E, Meyer A, Lemke J, Wimberg J, Metzler-Nolte N, Meyer F, Mohr F, Ott I, TrxR inhibition and antiproliferative activities of structurally diverse gold N-heterocyclic carbene complexes, Med. Chem. Comm., 4, 2013, 942-948.

[16] Oehninger L, Rubbiani R, Ott I, N-Heterocyclic carbene metal complexes in medicinal chemistry, Dalton Trans. 42, 2013, 3269-3284.

[17] Omata Y, Folan M, Shaw M, Messer RL, Lockwood PE, Hobbs D, Bouillaguet S, Sano H, Lewis JB, Wataha JC, Sublethal concentrations of diverse gold compounds inhibit mammalian cytosolic thioredoxin reductase (TrxR1), Toxicol. In Vitro, 20(6), 2006, 882-890.

[18] Williams Jr CH, Thioredoxin-thioredoxin reductase - a system that has come of age, Eur. J. Biochem. 267, 2000, 6101-6101.

[19] Rigobello MP, Scutari G, Folda A, Bindoli A, Mitochondrial thioredoxin reductase inhibition by gold(I) compounds and concurrent stimulation of permeability transition and release of cytochrome c, Biochem.Pharmacol., 67, 2004, 689-696.

[20] Buckley RG, Elsome AM, Fricker SP, Henderson GR, Theobald BRC, Parish RV, Howe BP, Kelland LR, Antitumor properties of some 2-[(dimethylamino)methyl]phenylgold(III) complexes, J. Med. Chem., 39, 1996, 5208-5214.

[21] Pandeya SN, Dimmock JR, Recent evaluations of thiosemicarbazones and semicarbazones and related compounds for antineoplastic and anticonvulsant activities, Die Pharmazie, 48, 1993, 659-666.

[22] Abram U, Ortner K, Gust R, Sommer K, Gold complexes with thiosemicarbazones: reactions of bi- and tridentate thiosemicarbazones with dichloro[2-(dimethylamino-methyl)phenyl -C^1,N]gold(III), [Au(damp-C^1,N)Cl$_2$], J. Chem. Soc., Dalton Trans., 2000, 735-744.

[23] Osella D, Ferrali M, Zanello P, Laschi F, Fontani M, Nervi C, Cavigiolio G, On the mechanism of the antitumor activity of ferrocenium derivatives, Inorg. Chim. Acta, 306, 2000, 42-48.

[24] Kovjazin R, Eldar T, Patya M, Vanichkin A, Lander HM, Nogogrodsky A, Ferrocene-induced lymphocyte activation and antitumor activity is mediated by redox-sensitive signaling, FASEB J., 17(3), 2003, 1-16.

[25] Casas JS, Castaño MV, Cifuentes MC, García-Monteagudo JC, Sánchez A, Sordo J, Abram U, Complexes of dichloro[2-(dimethylaminomethyl)phenyl-C^1,N]gold(III), [Au(damp-C^1,N) Cl_2], with formylferrocene thiosemicarbazones: synthesis, structure and cytotoxicity, J. Inorg. Biochem. 98, 2004, 1009-1016.

[26] Che CM, Sun RWY, Therapeutic applications of gold complexes: lipophilic gold(*III*) cations and gold(*I*) complexes for anti-cancer treatment, Chem. Commun., 47, 2011, 9554-9560.

[27] Rigobello MP, Messori L, Marcon G, Cinellu MA, Bragadin M, Folda A, Scutari G, Bindoli A, Gold complexes inhibit mitochondrial thioredoxin reductase: consequences on mitochondrial functions, J. Inorg. Biochem. 98, 2004, 1634-1641.

[28] Bertrand B, Spreckelmeyer S, Bodio E, Cocco F, Picquet M, Richard P, Gendre PL, Orvig C, Cinellu MA, Casini A, Exploring the potential of gold(III) cyclometallated compounds as cytotoxic agents: variations on the C^N theme, Dalton Trans. 44, 2015, 11911-11918.

[29] Mendes F, Groessl M, Nazarov AA, Tsybin YO, Sava G, Santos I, Dyson PJ, Casini A, Metal-based inhibition of poly(ADP-ribose) polymerase--the guardian angel of DNA, J. Med. Chem., 54, 2011, 2196-2206.

[30] Li CKL, Sun RWY, Kui SCF, Zhu N, Che CM, Anticancer Cyclometalated $[Au^{III}_{m}(C\text{^}N\text{^}C)_{m}L]^{n+}$ Compounds: Synthesis and Cytotoxic Properties, Chem. Eur. J. 12, 2006, 5253-5266.