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Anticancer activities of polynuclear gold(I) complexes: A critical survey

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ABSTRACT
The development of transition metal based anticancer drugs is currently a very active field in Medicinal Inorganic Chemistry. The most remarkable success in this field is the effective use of platinum(II) based complexes against cancer. Several scientists make efforts to discover new inorganic agents for use in chemotherapy with improved specificity and decreased toxic side effects than the most common anticancer drug cisplatin. Nowadays, gold(I) compounds are potentially attractive as anticancer agents due to the unique chemical properties of the gold(I) center. Recently, a number of gold(I) compounds reveal outstanding antiproliferative properties without undesirable side effects and are also able to overcome cisplatin resistance. Polynuclear anticancer gold(I) compounds are a comparatively new and successful approach in respect. Extensive effort has been put to elucidate their mechanisms of action and to optimize their bioactivity through structural modification. In this review, the development of some novel polynuclear gold(I) anticancer drugs are discussed on the basis of the available experimental evidences.
Keywords: Polynuclear Gold(I) Compounds, Anticancer Activities.

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INTRODUCTION

After cardiovascular diseases, cancer is considered as the second most fatal disease [1] that originates from the mutation of genes. The spread of cancer occurs through a sequence of alterations in cellular activity with continual or uncontrolled inflammation in the tumor micro location [2]. A new period of metal-based drugs initiated by the discovery of one of the leading platinum-based drugs 'Cisplatin' which is still successfully used in chemotherapy by inhibiting cancer cell activities through DNA-platinum adducts formation [3]. Inspite of having powerful anticancer activity, cisplatin causes some undesirable side effects like cardiotoxicity, nephrotoxicity and neurotoxicity due to its non-selective DNA-targeted mechanism [4]. Moreover, it is effective against only a few kinds of cancers. Therefore, research in this field has been extended to include new non-platinum based antitumor drugs with an improved spectrum of efficiency and lower toxicity. Complexes of coinage metals (copper, silver and gold) are prospective candidates to fulfill this requirement. In this regard, gold(I) compounds acquire special attention because of their long and traditional uses in medicine [5] as antiarthritic agent. Extensive research on gold(I)-based antitumor agents was initiated when commercially used anti-arthritic gold(I) drugs showed potent cell growth inhibiting effects *in vitro* and some experimental *in vivo* models [6-9]. Moreover, a large number of anticancer gold(I) complexes have better activity than cisplatin and they effectively overcome the cisplatin resistance [10] tumor cell probably through different mechanisms from cisplatin. Consequently, they may be selected as effective antiproliferative agents after the discovery of cisplatin. Gold(I) compounds are quite active *in vitro,* but not so effective *in vivo* due to their extensive binding to serum proteins [7] In addition, some of the gold(I) create distinct systemic toxicity in animal models. In order to minimize the systemic toxicity and to enhance the anti-cancer activities, a number of stable coordination compounds of gold(I) are prepared using suitable organic ligands with different substituents. Some of these complexes with modified ligands show promising anti-cancer activities targeting to mitochondria as well as reduce relevant systemic toxicity by affecting just the cell cycle of tested cells [11].

Generally, polynuclear anticancer gold compounds are obtained by the "fusion" of two or more mononuclear units. Here, the activity of each gold center is controlled by the molecular framework as well as its interactions with the nearby gold center(s). Notably, addition of two or more metal centers in an extended molecular frame work may considerably influence its specific biological activity compare to its

mononuclear analogues [1,12-14]. Generally, the polynuclear compounds are shown to be effective inhibitors of cancer cells proliferation with a considerable improvement than that of their mononuclear parent complexes [15,16].

This review highlights the current developments in the design of polynuclear gold(I) complexes that may be used clinically as effective anticancer drugs after more investigation. The aim of this review is to show the emerging importance of structure-activity relationship methods in the study of anticancer metal complexes. The correlations of the nature of the ligand and nuclearity of the resulting complexes with their anticancer activities are briefly discussed here.

CHEMISTRY OF GOLD(I) COMPOUNDS

The chemistry of gold(I) compounds includes the following distinct characteristics:

(a) Compounds containing gold(I) with $5d^{10}$ closed-shell configuration can adopt three types of coordination environments: (i) two-coordinated linear (the most important), (ii) three-coordinated trigonal planar and (iii)four-coordinated tetrahedral environments.

(b) As gold(I) ion is a soft cation, it prefers to bind with a soft ligand. It can form stable AuX_2^- ions with soft anionic (X^-) ligands like cyanide, thiolate, iodide etc. Simultaneously, it can also easily form a variety of cationic complexes of the type AuL_2^+ and AuL_4^+ with neutral (L) ligands, e.g. phosphines, arsines etc.

SOME NOVEL POLYNUCLEAR GOLD(I)-BASED ANTICANCER AGENTS:

The potential anticancer activities of polynuclear compounds are discussed briefly in this review into three major groups along with different sub groups.

A. Dinuclear organometallic compounds of gold(I):

(i) With only C-donor ligands:

The main compounds **1-8** of this sub group are shown in **Scheme 1**.

A series of dinuclear gold(I) complexes **1-7** containing bidentate N-heterocyclic carbene ligands exhibited potential new antimitochondrial antitumour activity [17,18]. These complexes were tested for their capacity to induce mitochondrial membrane permeability (MMP) in isolated rat liver mitochondria. Compounds **2-7** induced Ca^{2+}-sensitive MMP at micro molar concentrations as evidenced by mitochondrial swelling but they were either inactive or their activity was considerably decreased in absence of exogenous Ca^{2+} in low concentrations. In addition, their activity was completely lost by the addition of the well-established inhibitor cyclosporine A. There were only slight differences in the activities of compounds **2-7** in the swelling assays. Here, compound **2** was the most active species in the mitochondrial swelling assays. On the other hand, compound **1** was structurally dissimilar to the other six complexes. Although compound **1** caused greater level of mitochondrial swelling compare to that which occurred in the control, it was least active than the other six compounds.

Using fluorescence confocal microscopy, the cellular uptake and distribution of dinuclear gold(I) complex **8** [18,19] containing bidentate NHC ligands was tested in RAW264.7 cells (mouse macrophage cancer cell line) [20]. Moreover, colocalization studies indicated the localization of gold complexes in lysosomes rather than mitochondria [19]. Remarkably, this compound showed only modest cytotoxicity in the above cell line. From preliminary studies, it was observed that this compound also revealed significant potency against human promyelocytic leukaemia cell line, HL [21,22].

(ii) With P/S/Cl-donor ligands:

Some important compounds (**9-13**) of this sub group are given in **Scheme 2**.

Complexes **9a** and **9b** [6,23] inhibited TrxR effectively with IC_{50} values in the low micromolar range. They were also used as starting materials for further preparation of dinuclear gold(I) alkynyl anticancer agents. Complexes **9a** and **9b** inhibited both Glutathione reductase (GR) and TrxR. Complex **9a** with shorter bridging ligands was more active than complex **9b.** It indicates that the carbon-carbon chain length of ligands has an important role in the anticancer activity of the corresponding complexes. Due to being highly active, complex **9a** was preferred for more detailed studies on its uptake into HT-29 cells.

Using the MTT assay, the cytotoxicity of 1,4-bis-(hydroxyl)-anthraquinone derivative and its corresponding complex **10** [6,24] was evaluated with breast adenocarcinoma (MCF7), lung adenocarcinoma (A549), prostate adenocarcinoma (PC3) and colon adenocarcinoma (LOVO) cell lines. The cytotoxicity study showed that this complex revealed a broad range of activity with low IC_{50} value. This complex was considerably more toxic compare to the corresponding free ligand. So, the cytotoxicity of the complex was dominated by the gold alkynyl unit, rather than the biologically active anthraquinone unit. Moreover, this complex was remarkably more cytotoxic to MCF7s cell line (a cell line having a higher mitochondrial mass) than the other tested cell lines. This complex also showed useful room-temperature anthraquinone-based visible luminescence. Hence, it could be successfully used as fluorophores in cell imaging microscopy.

Generally, dinuclear NHC complex **11** [18,25] was interacted with DNA via non covalent interaction and created conformational changes in the structure of DNA. To differentiate between cytostatic effect and cytotoxic effect of this compound, sulphorhodamine-B (SRB) assay was used. Although this complex revealed significant cytostatic activity against MCF-7 (breast carcinoma), PC-3(prostate carcinoma) and HT29 (colon carcinoma) cell lines, it exerted a low cytotoxic effect on all cancer cell lines with a LC_{50} value in the low micromolar range.

In vivo tumor growth inhibition experiments of three dinuclear complexes **12a-12c** with mixed bridging diphosphine and bis(N-heterocyclic carbene) ligands [18] showed that complex **12a** inhibited TrxR activity with no attack by blood thiols. It exhibited cytotoxicity against breast carcinoma (MCF-7), nasopharyngeal carcinoma (SUNE-1), lung adenocarcinoma (NCI-H1975) and mouse melanoma (B16-F10) with higher IC_{50} values compare to cisplatin. Besides, under *in vivo* conditions, this complex inhibited tumor growth in mice bearing HeLa xenografts and also in highly aggressive mouse B16-F10 melanoma without notable side effects. The other two complexes **12b** and **12c** moderately inhibited tumor growth of mice bearing HeLa xenograft. After administration of **12b** and **12c** (at *dosage of* 5 mg/kg every day) considerable difference was observed with final tumor growth inhibition. Here, the counter anions exerted an important role in the *in vivo* antitumor activities [26].

The *in vitro* anticancer activities of the gold(I) pyrrolidinedithiocarbamato carbene complexes **13a** and **13b** were tested against human ovarian carcinoma (A2780 and its cisplatin-resistant variant A2780cis), human hepatocellular carcinoma (HepG2), human glioblastoma (U-87 MG) and a normal human Madin-Darby canine kidney epithelial cells (MDCK) cell line by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [27]. These complexes exhibited effective anticancer activities against the above tested cancer cell lines. Particularly against A2780 and A2780cis ovarian cell lines, they showed similar anticancer activities with quite lower resistant ratios than that of cisplatin. They revealed higher cytotoxic activities than pyrrolidinedithiocarbamate (PDTC). Between the cancerous and the normal MDCK cell lines, these two complexes generally exerted a lower cytotoxicity towards the normal cells. Between two complexes, complex **13a** exerted more than 40-fold higher anticancer activity compare to cisplatin towards A2780cis. The fluorescent microscopic experiment showed that compound **13a** could induce apoptosis towards A2780cis cancer cells. Moreover, compound **13a** could potentially be used as an antimigratory agent of cancer cells due to its ability to inhibit migration of A2780cis cells effectively [28].

B. Dinuclear metallo-organic compounds of gold(I):

(i) With P-donor ligands:

The major compounds **14-20** of this sub group are outlined in **Scheme 3**.

Homo-dimetallic complexes **14** [1,29] with bisphosphine backbones revealed strong *in vivo* and *in vitro* anticancer activity against P388 leukemia in mice with better life span increase (98%, especially for $Au^{I}Cl$) complex in compare to Au^{III} species (50%). They were also active against murine tumor models and B16 melanoma cell lines. Particularly dinuclear gold(I)complexes containing the bis(diphenylphosphine)ethane (DPPE) ligand were significantly effective while the related metal complexes of Pt(II), Ni(II), Pd(II), Rh(II) and Ag(I) were inactive [15,16]. The dinuclear Au-DPPE complexes were found to be more active *in vitro* antitumor agents than free DPPE. On the other hand, minor structural alteration from the dppe ligand reduced the anticancer activity of complex **15** due to its insufficient solubility to conduct biological assays [1,30].

The dinuclear gold(I) complexes **16** and **17** bearing chiral and achiral bisphosphine ligands [11] respectively, exhibited effective cytotoxic effects in different cancer cell lines over normal cells by triggering apoptosis through reactive oxygen species (ROS) induction. They effectively killed the cancer cells (K562, H460, and OVCAR8 cell lines) which were 2-10 folds better compare to cisplatin with IC_{50} in the high nanomolar to low micromolar range without displaying cross-resistance. These compounds were highly stable due to the cyclometallation with their coordinated ligands. Consequently, they could reach their target avoiding any premature deactivation. Thus, they were able to reduce off-target effects. Spectrophotometric investigations**,** performed in a reaction with bovine serum albumin (BSA) under physiological conditions, indicated that these complexes could bind methionine and cysteine residues in BSA via the sulfur atoms. Though these complexes had high potency in clinically relevant tumor cells, they were slightly less potent toward the retinal pigment epithelial (RPE-Neo) cell lines. Hence, they exhibited selective toxicity for cancerous cells over healthy cells. The whole cell (OVCAR8) uptake studies and sub cellular distribution of Au(I) content for these compounds showed that the neutral complex **16** displayed the highest uptake. Here, the greater cellular uptake of compound **16** should be correlated with its high cytotoxicity, but significant correlations of uptake and cytotoxicity of this reported compound was not established. Again, the uptake for these dinuclear complexes was relatively higher than their mononuclear analogues because dinuclear gold increased lipophilicity of the agents. Both the complexes

induced significant apoptosis and showed enhanced *in vitro* potency over cisplatin. From apoptosis assay it was revealed that compound **16** induced a much higher early to late-stage apoptosis resulting mitochondria dysfunction and ER stress. Especially, complex **16** largely depolarized the mitochondria membrane and provoked major G0/G1 cell cycle arrest. When the OVCAR8 cells incubated for 48 h with this compound, caspase 3 and 9 levels were increased [31,32]. In spite of differential intracellular accumulation of complexes **16** and **17**, their cytotoxicity not varied significantly.

The hepatotoxicity along with anti-tumor activity of gold(I) phosphine complexes **18** and **19** containing ligands of type $R_2PCH_2CH_2PR_2$ (R = 3-pyridyl (**18**) and 2-pyridyl (**19**) [33] were tested against isolated rat hepatocytes [34]. The observed results displayed that both complexes, especially compound **19**, were active against the tested cancer cell lines. Moreover, compound **19** was highlighted as a potent active agent in inhibiting the *in vivo* tumor growth of colon 38 tumors [35]. These complexes exerted high hepatotoxicity and their toxicity were closely related to their lipophilicity [34].

Another type of dinuclear Au^I complex with a bis(phosphite) group **20** [1] exhibited marginal *in vitro* anticancer activity to the human cervix carcinoma HeLa cell line by inhibiting the proliferation of HeLa cells. Both this compound and the free ligand induced apoptosis in p53 nonfunctional HeLa cell line through p53 independent manner [36].

(ii) With S-donor ligands:

A novel compound **21**of this sub group is highlighted **Scheme 4**.

The dinuclear gold(I) complex **21** [33] containing dithiocarbamate derivatives exhibited potent anti-tumor activity against cisplatin-resistant cell lines. The synthesis of both DNA and RNA was inhibited by this compound. It revealed higher hemolytic properties over cisplatin [37]. Though its antiproliferative activity remains comparable or higher than that of cisplatin, it inhibited the tumor cell growth with a lesser extent compare to its gold-(III) analogues.

(ii) With N and P-donor ligands:

Two novel compounds **22** and **23** of this sub group are shown in **Scheme 5**.

The biological properties of compound **22** are promising both in terms of considerable stability under physiological-like conditions and of anticancer activities. It revealed notable *in vitro* antiproliferative effects when evaluated against the cisplatin sensitive and resistant ovarian cancer cell lines [10]. It was observed to overcome cisplatin resistance to a great extent. Though the pbiH ligand revealed some minor antiproliferative effects, the notable cytotoxicity and high antiproliferative properties observed for this compound were mainly due to the remarkable biological actions of the pbiAuPPh3 moiety.

The cytotoxic effect of dinuclear complex **23** with imidazole-based phosphane ligand was tested against nine human cancer cell lines (two leukemia cell lines and seven ovarian cancer cell lines with different sensitivity to cisplatin). The isopropyl groups in this compound improved its lipophilicity. It also exhibited only 2-fold differences in potency against all tested cell lines. [1,38]. *In vitro* anticancer activity of this compound against various tested human cancer cell lines showed IC_{50} values in the micro molar range. It showed slightly lower activity to the cisplatin-resistant variant of the A2780 cell line.

(iii)With S and P-donor ligands:

Two novel compounds **24** and **25** of this sub group are outlined in **Scheme 6**.

The dinuclear gold(I) complex **24** with bridging dithiolate ligand [1,39] showed significant *in vivo* anticancer activity on Ehrlich Ascites tumor bearing mice with increased survival rate. However a number of mice died prematurely because of the toxicity of the complex. Hence, high drug induced toxicity limited further development of this series of complexes.

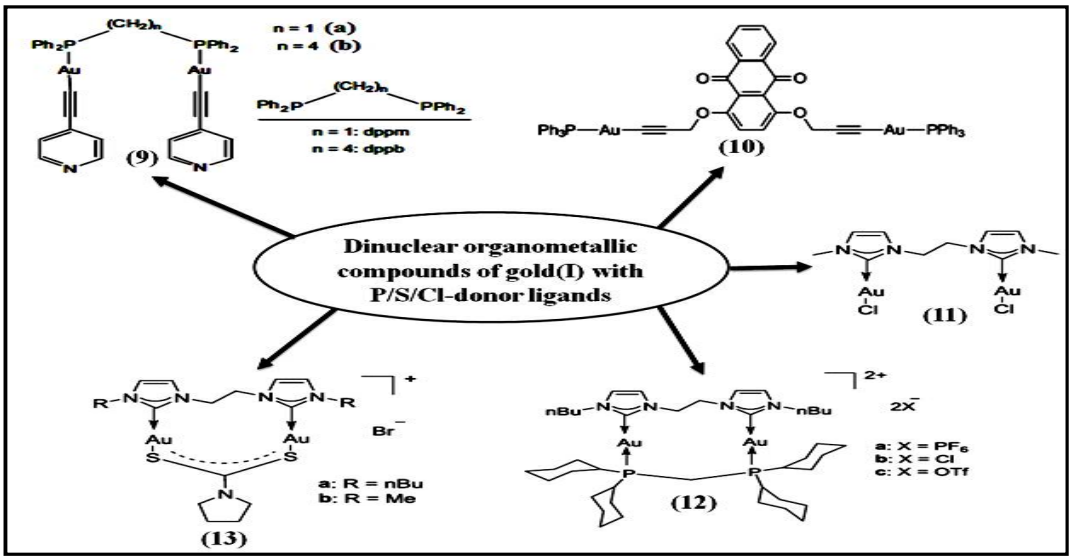
A series of compounds of type $[(AuPPh_3)_2(xspa)]$ (**25a-25j**), where xspa is a 3(aryl)-2-sulfanylpropanoato fragment, [1,40] revealed potent *in vitro* antitumor activities to the HeLa-229, A2780 and A2780cis cell lines. Majority of these compounds were particularly highly effective against the A2780cis cell line with better IC_{50} values than that of cisplatin. The deprotonation of the COOH group and the inclusion of a second $AuPPh_3$ fragment in the mononuclear $[Au(PPh_3)(Hxspa)]$ moiety not only enhanced the effectiveness of the said compounds in particular against the HeLa and A2780cis cell lines but also significantly increased their ability to get out of the cellular resistance to cisplatin [41]. Here, structural modifications improved the effectiveness of this class of dinuclear complexes.

C. Polynuclear metallo-organic compounds of gold(I) with S-donor ligands:

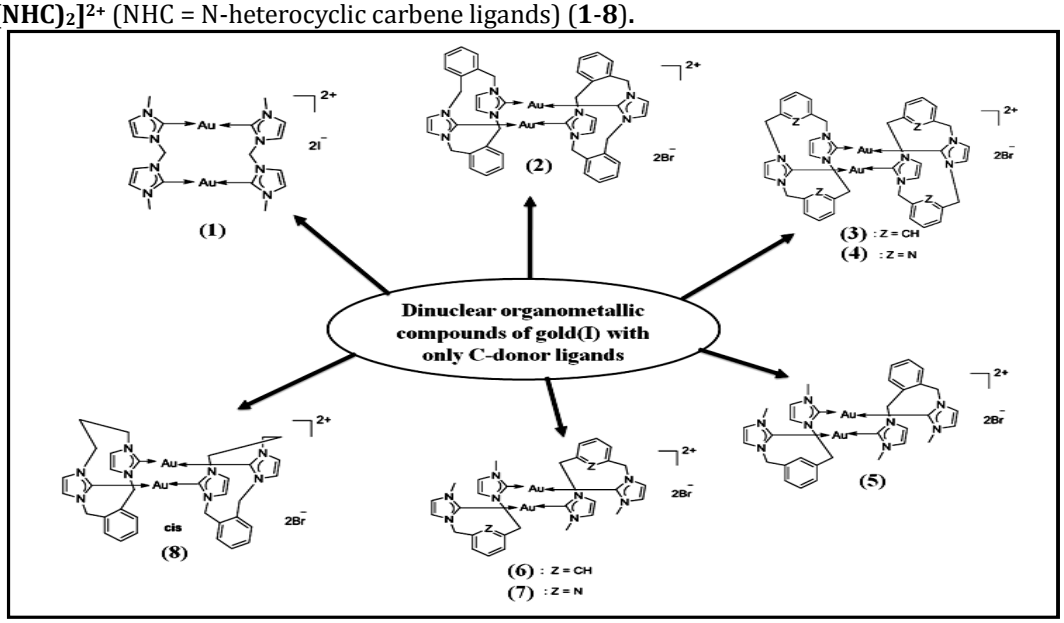
The compounds **26-28** of this group are highlighted in **Scheme 7**.

Polynuclear gold(I) thiolates compounds **26**-**28**, [6,7] previously used in the treatment of rheumatoid arthritis, are proved to possess anticancer properties. They are the traditional examples of "drug repositioning" [42,43] where a drug used for the treatment of a specific disease (rheumatoid arthritis) is investigated for other (cancer) therapies. Both the charged species **26** and the neutral species **28** inhibited primary tumor growth in mice bearing Lewis carcinoma and also reduced lung metastases [8]. Another polymeric charged compound aurothiopropanol sulphonate (**allocrysin**) (**27**) was also found to

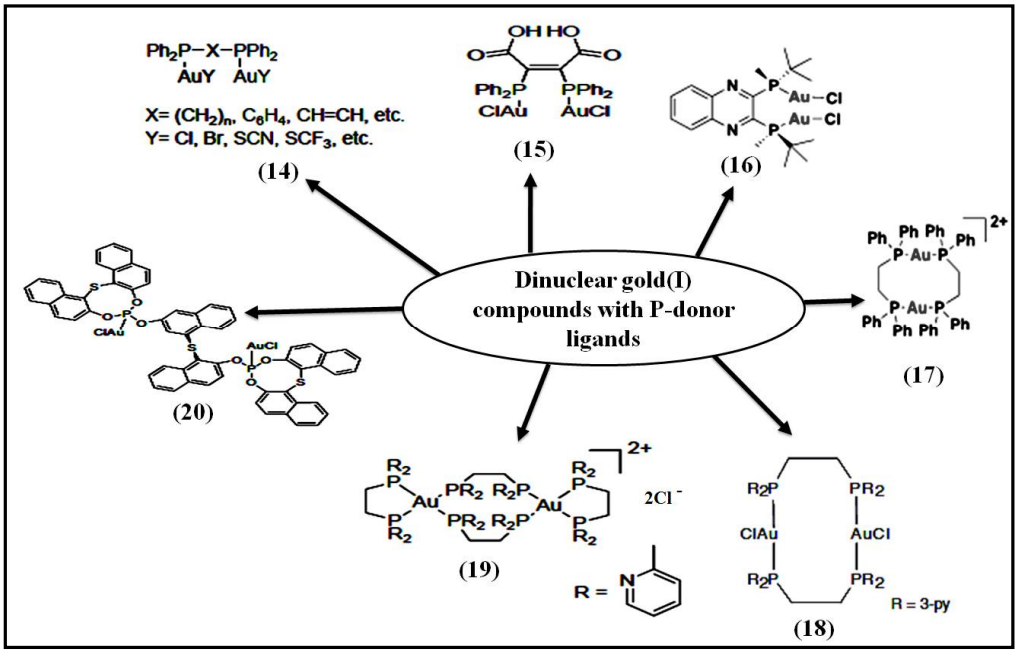
exhibit anticancer activities [9]. Moreover, among the above three compounds, compound **26** inhibited the growth of HCT-15, AGS and Meth/A cells *in vitro* [44]. Although compound **26** was less effective than cisplatin, it showed a wider range of dose effectiveness without significant toxicity. It could induce apoptosis of aggressive prostate cancer cells by activation of extracellular signal-regulated kinases in a dose-dependent manner [45]. In future, it may act as a promising drug for the treatment of advanced prostate cancer without affecting the normal epithelial prostate cells.



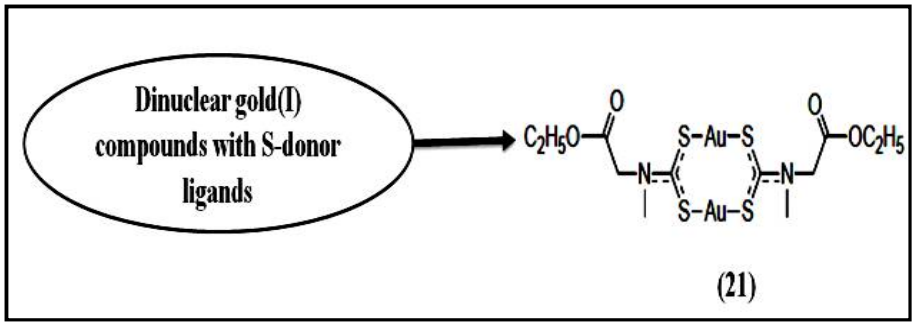
Scheme 1. Dinuclear organometallic compounds of gold(I) with only C-donor ligands: $[Au^{I}_2(NHC)_2]^{2+}$ (NHC = N-heterocyclic carbene ligands) (**1**-**8**)**.**



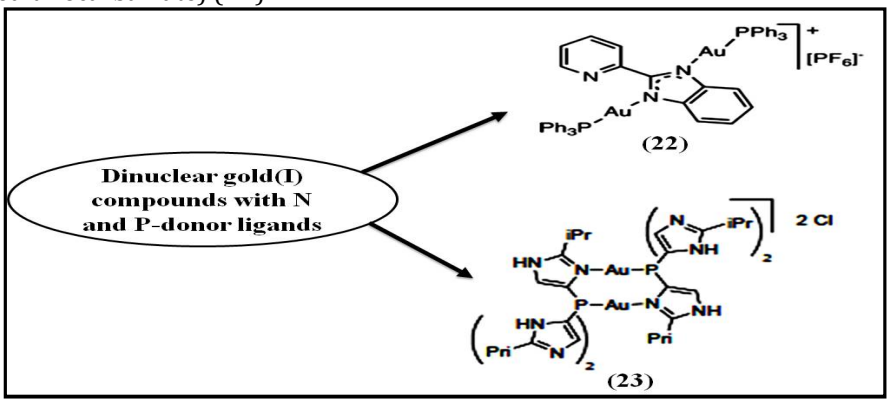
Scheme 2. Dinuclear organometallic compounds of gold(I) with P/S/Cl-donor ligands: [(dppm){Au-C≡C-(4-pyr)}$_2$] {dppm =bis(diphenylphosphino)methane} (**9a**), **[(dppb){Au-C≡C-(4-pyr)}$_2$]** {dppb =1,4-bis(diphenylphosphino)butane} (**9b**); **[(dpoa)(Au-PPh$_3$)$_2$]** {dpoa = di-anion of 1,4-bis(prop-2-yn-1-yloxy)anthraquinone} **(10); [Au$_2$Cl$_2$(NHC)]** {NHC = bis(N-heterocyclic carbene diphosphine} (**11**)**; [Au$_2$(bdp)(NHC)]$_2$X** {bdp = bridging diphosphine}, [X= PF_6 (**12a**), Cl (**12b**) and OT_f (**12c**)]; **[Au$_2$(pdc)(NHC-R)]Br** (Hpdc = pyrrolidinedithiocarbamate) [R = nBu (**13a**) and Me (**13b**)].



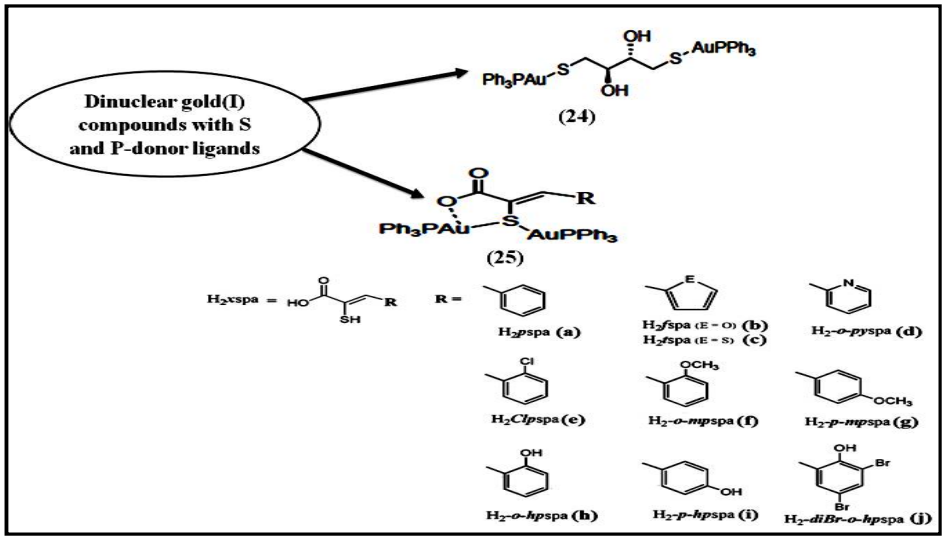
Scheme 3. Dinuclear gold(I) compounds with P-donor ligands: **$[(AuY)_2(PPh_2\text{-}X\text{-}PPh_2)]$** {X = $(CH_2)_n$, C_6H_4, C_2H_2, etc. and Y = Cl, Br, SCN, SCF_3, etc.} **(14)**; **$[(AuCl)_2(dpmaa)].2thf$** {dpmaa = 2,3-bis(diphenylphosphino)2,3-bis(diphenylphosphino)maleic acid **(15); $[Au_2(btbmpq)(Cl)_2]$** {btbmpq=(R,R)-(-)-2,3-bis(t-butylmethylphosphino)quinoxaline}(**16**); **$[Au_2(dppe)(Cl)_2][ClO_4)_2]$** {**dppe =**1,2-Bis(diphenylphosphino)ethane}(**17**); **$[Au_2(R_2PCH_2CH_2PR_2)_2)(Cl)_2]$** (R = 3-pyridyl (**18**) and 2-pyridyl (**19**); **[ClAu(P∧P)AuCl]** [(P∧P) = large-bite bis(phosphite) ligand: *{*(–$OC_{10}H_6$(μ-S)$C_{10}H_6O$–)P*{*μ-(–$OC_{10}H_6$(μ-S)$C_{10}H_6O$–)*}*-P(–$OC_{10}H_6$(μ-S)$C_{10}H_6O$–)*}*] (**20**)



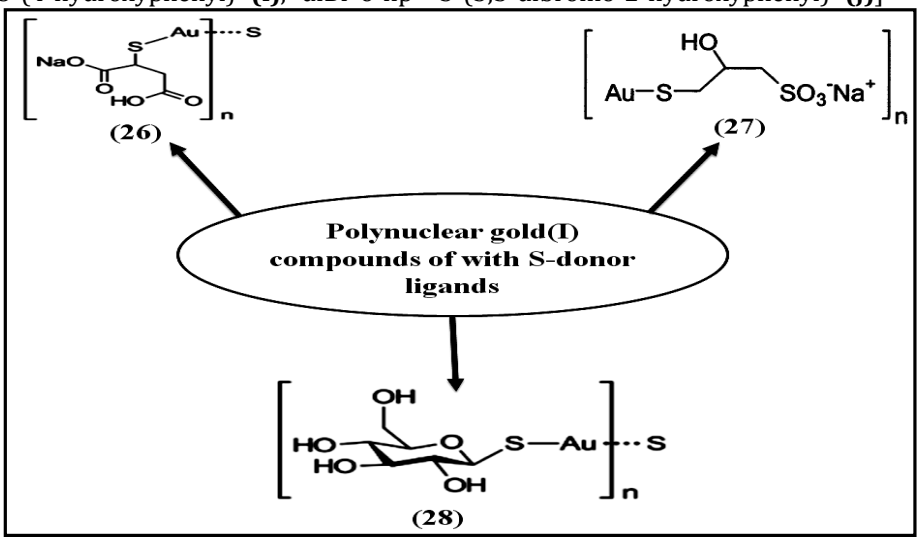
Scheme 4. Dinuclear gold(I) compounds with S-donor ligands: $[(ESDT)Au]_2$ (ESDT = ethylsarcosinedithiocarbamate) (**21**).



Scheme 5. Dinuclear gold(I) compounds with N and P-donor ligands: $[(PPh_3)_2Au_2(\mu\text{-pbi})][PF_6]$ {pbiH = 2-(2′-pyridyl)benzimidazole} (**22**); **$[\{(4\text{-}TIP^{iPr})Au\}_2]Cl_2$** {4-$TIP^{iPr}$ = tris(2-isopropylimidazol-4(5)yl)phosphane}(**23**).



Scheme 6. Dinuclear gold(I) compounds with S and P-donor ligands: [$(Ph_3PAu)_2(\mu\text{-DTE})$] ($H_2$DTE = dithioerylthritol) (**24**); [$(AuPPh_3)_2$(xspa)] (**25a-25j**) [xspa = 3(aryl)-2-sulfanylpropanoato; x: p = 3-phenyl- **(a)**, f = 3-(2-furyl)- **(b)**, t = 3-(2-thienyl)- **(c)**, -o-py = 3-(2-pyridyl)- **(d)**, Clp = 3-(2-chlorophenyl)- **(e)**, -o-mp = 3-(2-methoxyphenyl)- **(f)**, -p-mp = 3-(4-methoxyphenyl)- **(g)**,-o-hp = 3-(2-hydroxyphenyl)- **(h)**, -p-hp = 3-(4-hydroxyphenyl)- **(i)**, -diBr-o-hp = 3-(3,5-dibromo-2-hydroxyphenyl)- **(j)**]



Scheme 7. Polynuclear gold(I) compounds of with S-donor ligands: Sodium aurothiomalate , aurothiomalate (**myocrisin**) (**26);** Aurothiopropanol sulphonate (**allocrysin**) (**27**) and aurothioglucose (**solganol) (28).**

CONCLUSION

Although cisplatin is successfully used as anticancer agent in chemotherapy, it has undesirable side effects and is not effective against all types of cancers. Therefore, new active anticancer drugs with a better usefulness and lower toxicity against cisplatin-resistant cell lines are required. The design of an effective anticancer agent depends not only on the drug's inherent inhibitory properties but also on its delivery, dosage, and *in vivo* residence time. Under physiological condition, the stable polynuclear gold(I) complexes overcome some of these challenges by forming strong covalent attachments to targets. Hence, polynuclear gold(I) compounds may be considered as possible alternatives to Pt-based anticancer drugs. They show similar cytotoxicity against the cisplatin-sensitive and -resistant cell lines with no cross resistance since they induce cytotoxicity through different mechanisms than cisplatin. Unlike cisplatin, these compounds have better selectivity and effectiveness to cancer cells than normal cells due to their weaker DNA-binding activity. However, in spite of having pronounced anticancer activity, gold(I) compounds also exhibit some toxic side effects. The selection of suitable non-toxic ligands for the design of anticancer gold(I) complexes is an important matter to enhance the effectiveness of these drugs and to minimize their unwanted side-effects. In this regard, more research works along with experimental trials are essential. Furthermore, the polynuclear gold(I) compounds considerably increase their specific

activity to cancer cell lines than that of their mononuclear analogues. So, there is an amazing opportunity of polynuclear gold(I) based compounds for future upgrading as anticancer drugs.

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CONFLICT OF INTEREST
There is no conflict of interest.

REFERRENCES
1. Hartinger, C.G.; Phillips, A.D., & Nazarov, A.A. (2011). Polynuclear Ruthenium, Osmium and Gold Complexes. The Quest for Innovative Anticancer Chemotherapeutics. Curr. Top. Med. Chem., 11:2688-2702.
2. Balkwill, F.R., & Mantovani, A. *(*2012). Cancer-related inflammation: Common themes and therapeutic opportunities. *Semin. Cancer Biol.*, 22:33-40.
3. Kelland, L. (2007). The resurgence of platinum-based cancer chemotherapy**.** Nat. Rev. Cancer., 7:573-584.
4. Wang, X., & Gou, Z. (2013). Targeting and delivery of platinum-based anticancer drugs. Chem. Soc. Rev., 42:202**-**224.
5. Fricker, S.P. (1996). Medical uses of gold compounds**:** Past, present and future**.** *Gold Bull.*, 29:53-60.
6. Yeo, C.I., Ooi, K.K., & Tiekink, E.R.T. (2018). Gold-Based Medicine: A Paradigm Shift in Anti-Cancer Therapy?. Molecules, 23:1410.
7. Tiekink, E.R.T. (2002). Gold derivatives for the treatment of cancer. Crit. Rev. Oncol. Hematol., 42:225-248.
8. Giraldi, T., Sava, G., Perissin, L., & Zorbet, S. (1984). Primary tumor growth and formation of spontaneous lung metastases in mice bearing Lewis carcinoma treated with proteinase inhibitors. Anticancer Res., 4:221-224.
9. Bindoli, A., Rigobello, M.P., Scutari, G., Gabbiani, C., Casini, A., & Messoric L. (2009). Thioredoxin reductase: A target for gold compounds acting as potential anticancer drugs. Coord. Chem. Rev., 253:1692-1707.
10. Serratrice, M., Cinellu, M.A., Maiore, L., Pilo, M., Zucca, A., Gabbiani, C., Guerri, A., Landini, I., Nobili, S., Mini, E., & Messori, L. (2012). Synthesis, Structural Characterization, Solution Behavior, and in Vitro Antiproliferative Properties of a Series of Gold Complexes with 2-(2′-Pyridyl)benzimidazole as Ligand: Comparisons of Gold(III) versus Gold(I) and Mononuclear versus Binuclear Derivatives. Inorg. Chem., 51:3161-3171.
11. Kim, J.H., Reeder, E., Parkin, S., & Awuah, S.G. (2019). Gold(I/III)-Phosphine Complexes as Potent Antiproliferative Agents. Sci. Rep., 9:12335.
12. Mendoza-Ferri, M.G., Hartinger, C.G., Mendoza, M.A., Groessl, M., Egger, A.E., Eichinger, R.E., Mangrum, J.B., Farrell, N.P., Maruszak, M., Bednarski, P.J., Klein, F., Jakupec, M.A., Nazarov, A.A., Severin, K., & Keppler, B.K. (2009). Transferring the Concept of Multinuclearity to Ruthenium Complexes for Improvement of Anticancer Activity. J. Med. Chem., 52(4):916-925.
13. Tian, S., Siu, F.M., Kui, S.C.F., Lok, C.N., & Che, C.M. (2011). Anticancer gold(i)–phosphine complexes as potent autophagy-inducing agents. Chem. Commun., 47:9318-9320.
14. Serratrice, M., Edafe, F., Mendes, F., Scopelliti, R., Zakeeruddin, S.M., Gratzel, M., Santos, I., Cinellu, M.A., & Casini, A. (2012). Cytotoxic gold compounds: synthesis, biological characterization and investigation of their inhibition properties of the zinc finger protein PARP-1. Dalton Trans., 41:3287-3293.
15. Snyder, R.M., Mirabelli, C.K., Johnson, R.K., Sung, C.M., Faucette, L.F., McCabe, F.L., Zimmerman, J.P., Whitman M., Hempel J.C., & Crooke, S.T. (1986). Modulation of the Antitumor and Biochemical Properties of Bis(diphenylphosphine)ethane with Metals. Cancer Res., 46:5054-5060.
16. Mirabelli, C.K., Hill, D.T., Faucette, L.F., McCabe, F.L., Girard, G.R., Bryan, D.B., Sutton, B.M., Barus, J.O.L., Crooke, S.T., & Johnson, R.K. (1987). Antitumor activity of bis(diphenylphosphino)alkanes, their gold(I) coordination complexes, and related compounds. J. Med. Chem., 30:2181-2190.
17. Barnard, P.J., Baker, M.V., Berners-Price S.J., & Day, D.A. *(*2004). Mitochondrial permeability transition induced by dinuclear gold(I)–carbene complexes: potential new antimitochondrial antitumour agents. J. Inorg. Biochem., *98* (10):1642-1647.
18. Zhang, C. (2018). Metal-NHC complexes for anti-cancer applications : gold(I) for antimitochondrial activity and iridium(III) for photodynamic therapy. Coordination chemistry. Université Paul Sabatier -Toulouse III. English. NNT : 2018TOU30129.tel-02146373,1-97.
19. Barnard, P.J., Wedlock, L.E., Baker, M.V., Berners Price S.J., Joyce, D.A., Skelton, B.W., & Steer, J.H. (2006). Luminescence Studies of the Intracellular Distribution of a Dinuclear Gold(I) N-Heterocyclic Carbene Complex. Angew. Chem. Int. Ed., 45 (36):5966-5970.
20. Ralph, P., & Nakoinz, I. (1977). Antibody-Dependent Killing of Erythrocyte and Tumor Targets by Macrophage-Related Cell Lines: Enhancement by PPD and LPS. J. Immunol., 119:950-954.
21. Gallagher R., Collins, S., Trujillo, J., McCredie, K., Ahearn, M., Tsai, S., Metzgar, R., Aulakh, G., Ting, R., Ruscetti, F., & Gallo, R. (1979). Characterization of the continuous, differentiating myeloid cell line (HL-60) from a patient with acute promyelocytic leukemia. Blood, 54(3):713-733.
22. Collins, S.J., Gallo, R.C., Gallagher, & R.E. (1977). Continuous growth and differentiation of human myeloid leukaemic cells in suspension culture. Nature, 270:347-349.

23. Meyer, A., Gutiérrez, A., Ott, I., & Rodríguez, L. (2013). Phosphine-bridged dinuclear gold(I) alkynyl complexes: Thioredoxin reductase inhibition and cytotoxicity. Inorg. Chim. Acta, 398:72-76.
24. Balasingham, R.G., Williams, C.F., Mottram, H.J., Coogan, M.P., & Pope, S.J.A. (2012). Gold(I) Complexes Derived from Alkynyloxy-Substituted Anthraquinones: Syntheses, Luminescence, Preliminary Cytotoxicity, and Cell Imaging Studies. Organometallics, 31:5835-5843.
25. Sanchez, O., González, S., Fernández, M., Higuera-Padilla, A.R., Leon, Y., Coll, D., Vidal, A., Taylor, P., Urdanibia, I., Goite, M.C. (2015). Novel silver(I)– and gold(I)–N-heterocyclic carbene complexes. Synthesis, characterization and evaluation of biological activity against tumor cells. Inorg. Chim. Acta, 437:143-151.
26. Zou, T., Lum, C.T., Lok, C.N., To, W.P., Low, K.H., & Che, C.M. (2014). A binuclear gold(I) complex with mixed bridging diphosphine and bis(N-heterocyclic carbene) ligands shows favorable thiol reactivity and inhibits tumor growth and angiogenesis in vivo. Angew. Chem. Int. Ed. Engl., 53 (23):5810-5814.
27. Mosmann, T. (1983). Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. J. Immunol. Methods. 65:55-63.
28. Sun, R.W.Y., Zhang, M., Li, D., Zhang, Z.F., Cai, H., Li, M., Xian, Y.J., Ng, S.W., & Wong, A.S.T. (2015). Dinuclear Gold(I) Pyrrolidinedithiocarbamato Complex: Cytotoxic and Antimigratory Activities on Cancer Cells and the Use of Metal-Organic Framework. *Chem.Eur. J., 21* (51):18534-18538.
29. Wenzel, M., de Almeida, A., Bigaeva, E., Kavanagh, P., Picquet, M., Le Gendre, P., Bodio, E., & Casin, A. (2016). New Luminescent Polynuclear Metal Complexes with Anticancer Properties: Toward Structure–Activity Relationships. Inorg. Chem., 55(5):2544-2557.
30. Berners-Price, S.J., Bowen, R.J., Fernandes, M.A., Layh, M., Lesueur, W.J., Mahepal, S., Mtotywa, M.M., Sue, R.E., & van Rensburg, C.E.J. (2005). Gold(I) and silver(I) complexes of 2,3-bis(diphenylphosphino) maleic acid: Structural studies and antitumour activity. Inorg. Chim. Acta, *358*:4237-4246.
31. Rackham, O., Nichols, S.J., Leedman, P.J., Berners-Price, S.J., & Filipovska, A.A. (2007). Gold(I) phosphine complex selectively induces apoptosis in breast cancer cells: Implications for anticancer therapeutics targeted to mitochondria. Biochem. Pharmacol., 74: 992-1002.
32. Barnard, P.J., & Berners-Price, S.J. (2007). Targeting the mitochondrial cell death pathway with gold compounds. Coord. Chem. Rev., 251:1889-1902.
33. Tan, S.J., Yan, Y.K., Lee, P.P.F., & Lim, K.H. (2010). Copper, gold and silver compounds as potential new anti-tumor metallodrugs. Future Med. Chem., 2(10):1591-1608.
34. Liu, J.J., Galettis, P., Farr. A., Maharaj, L., Samarasinha, H., McGechan, A.C., Baguley, B.C., Bowen, R.J., Berners-Price, S.J., & McKeage M.J. (2008). In vitro antitumour and hepatotoxicity profiles of Au(I) and Ag(I) bidentate pyridyl phosphine complexes and relationships to cellular uptake. J. Inorg. Biochem., 102(2):303-310.
35. McKeage, M.J., Berners-Price, S.J., Galettis, P., Bowen, R.J., Brouwer, W., Ding, L., Zhuang, L., Baguley, B.C. (2000). Role of lipophilicity in determining cellular uptake and antitumour activity of gold phosphine complexes. Cancer Chemother. Pharmacol., 46:343-350.
36. Suresh, D., Balakrishna, M.S., Rathinasamy, K., Panda, D., Mague, J.T. (2008). Large-bite bis(phosphite) ligand containing mesocyclic thioether moieties: synthesis, reactivity, group 11 (Cu-I, Au-I) metal complexes and anticancer activity studies on a human cervical cancer (HeLa) cell line. Dalton Trans., 2285-2292.
37. Ronconi, L., Giovagnini, L., Marzano, C., Bettìo, F., Graziani, R., Pilloni, G., & Fregona, D. (2005). Gold dithiocarbamate derivatives as potential antineoplastic agents: design, spectroscopic properties, and in vitro antitumor activity. Inorg. Chem., 44:1867-1881.
38. Kunz, P.C., Kassack, M.U., Hamacher, A., & Spingler, B. (2009). Imidazole-based phosphane gold(I) complexes as potential agents for cancer treatment: Synthesis, structural studies and antitumour activity. Dalton Trans, 7741-7747.
39. Shaw III, C.F., Beery, A., & Stocco, G.C. (1986). Antitumor activity of two binuclear gold(I) complexes with bridging dithiolate ligands. Inorg. Chim. Acta, 123:213-216.
40. Barreiro, E., Casas, J.S., Couce, M.D., Sanchez, A., Sanchez-Gonzalez, A., Sordo, J., Varela, J.M., & Vázquez Lopez, E.M. (2010). Dinuclear triphenylphosphinegold(I) sulfanylcarboxylates: Synthesis, structure and cytotoxic activity against cancer cell lines. J. Inorg. Biochem., 104:551-559.
41. Barreiro, E., Casas, J.S., Couce, M.D., Sánchez, A., Sánchez-González, A., Sordo, J., Varela, J.M., & Vázquez-López, E.M. (2009). Synthesis, structure and cytotoxicity studies of diisopropylammonium and triethylammonium salts of triphenylphosphinegold(I) sulfanylcarboxylates. J. Inorg. Biochem., 103:1023-1032.
42. Elder, D.P., Holm, R., & Lopez de Diego, H. (2013). Use of pharmaceutical salts and cocrystals to address the issue of poor solubility. Int. J. Pharm., 453:88-100.
43. Tilborg, A., Norberg, B., & Wouters, J. (2014). Pharmaceutical salts and cocrystals involving amino acids: A brief structural overview of the state-of-art. Eur. J. Med. Chem., 74:411-426.
44. Koide T., Kojima T., & Kamei H. (1998). Antitumor effect of gold as revealed by growth suppression of cultured cancer cells. Cancer Biother Radiopharm; 13:189-192.
45. Trani, M., Sorrentino, A., Busch, C., & Landstrom, M. (2009). Proapoptotic effect of aurothiomalate in prostate cancer cells, Cell Cycle, 8(2):306-313.

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