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Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

POLYNUCLEAR GOLD (III) COMPOUNDS AS ANTICANCER AGENTS

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ABSTRACT

From extensive *in vitro* (cell-based) and *in vivo* (animal based) studies it is observed that different gold complexes reveal unique biological and medicinal properties. Particularly, gold(III) compounds have attracted special interest as efficient cytotoxic and antitumor agents because of their structural similarity with the most extensively used anti-cancer drug, cisplatin. Recently, new classes of polynuclear gold(III) compounds were synthesized and characterized that showed improved stability profiles with significant anti-cancer activities and majority of them are also capable to overcome cisplatin resistance. The implementation of appropriate ligand selection strategies plays the vital role in this connection as metal-ligand coordination improves the efficiency of these compounds against the selective cancer cell lines with reduction of unwanted side effects. The primary aim of this review is to sum up the chemistry and biological activities of some novel representative polynuclear anticancer gold(III) compounds that making themselves efficient for further pharmacological evaluation. The correlation of their stability and cytotoxicity with the nature of the corresponding ligands is outlined here. The importance of multinuclearity in modulating and enhancing the biological actions of anticancer gold(III) drugs compare to their mononuclear analogue is also discussed.

Keywords: Polynuclear Gold(III) Compound, Ligand Effects, Chemistry, Antitumor Activity.

1. INTRODUCTION

Cancer is a disease which is originated from the mutation of genes. It causes a sequence of alterations in cellular activity with persistent or uncontrolled inflammation in the tumour micro location that leads to the spread of cancer [1, 2]. In the 1960s, a new period of metal-based drugs started by the discovery of cisplatin which is still effectively used as anti-cancer chemotherapeutic drugs by inhibiting cancer cell activities through the formation of DNA-platinum adducts [3]. This non-selective DNA-targeted mechanism creates numerous toxic side effects like cardiotoxicity, nephrotoxicity and neurotoxicity [4, 5]. The clinical success of anticancer platinum(II) compounds suggests that other metal-based compounds may similarly serve as antitumor drugs hopefully by displaying different patterns of selectivities and activities.

Since ancient times, gold compounds have been used effectively to treat inflammation, infection and tuberculosis in traditional Chinese, Egyptian and Indian medicines [6, 7]. From 1980's, a few investigations have been done on different gold compounds in +3 or +1 oxidation states. It is reported that gold compounds perform their bioactivities through a "DNA-independent mechanism" [8] and hence they were considered soon as possible antiproliferative agents after the discovery of cisplatin. Though gold(I) compounds are found to be quite active *in vitro* [9-11] but almost ineffective *in vivo* due to their extensive binding to serum proteins and inactivation. On the other hand, gold(III) compounds attract special interest in cancer treatment as gold(III) ions are isoelectronic and isostructural to platinum(II) complexes and adopt square planar geometry like cisplatin. Hence they may exhibit similar biological actions like cisplatin. Consequently, a major effort has been dedicated to use gold(III) species in the treatment of cancer and many other diseases [12]. In spite of showing high *in vitro* cytotoxicity, the use of gold(III) compounds as experimental anticancer agents is limited due to its poor chemical stability under physiological conditions with possible quickly reduction to the more labile gold(I) and rather pronounced systemic toxicity [13] in animal models. In order to inhibit reduction and stabilize the apparently more active Au(III) oxidation state, a number of organic ligands containing different

substituents along with various auxiliary ligands have been used. With suitable organic ligands, gold(III) ions through metal-ligand coordination can form stable lipophilic cations having diverse functionalities and promising anti-cancer activities targeting to mitochondria. From literature survey it is found that the maximum cytotoxic gold compounds may induce apoptosis in treated human tumor cells possibly through profoundly distinct DNA-independent processes [8] with a far lower affinity for DNA than that of cisplatin and thus overcome resistance to cisplatin. Moreover, a large number of reported cytotoxic gold(III) compounds with modified ligands are found to reduce their relevant systemic toxicity by affecting just the cell cycle of tested cells [14].

Polynuclear anticancer gold(III) compounds are derived from the "fusion" of two or more mononuclear units where the activity of each gold(III) center is controlled not only by overall molecular framework but also by its interactions with the nearby gold(III) center(s). Remarkably, inclusion of two or more metal centers in an extended molecular network may significantly influence its specific reactivity to biomolecules than that of its mononuclear analogues [15].

This review shows the correlation of the nature of the ligand, types of substituents on the ligands and multinuclearity with biological properties of the resulting complexes. The recent development and the overall outlooks of polynuclear gold(III) compounds as effective anticancer agents against *in vitro* and *in vivo* tumor growth are briefly outlined from reported experimental evidence in literature. This topic is helpful for the syntheses of new polynuclear anticancer gold(III) compounds which after further investigation may be used clinically as effective anticancer drugs in future.

2. CHEMISTRY OF GOLD(III) COMPOUNDS

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

(a) Through ''aurophilic'' interactions gold(III) can form strong metal-metal bonds [16]. Reduction of gold(III) to gold(I) is not so easy as it is strictly associated with the change of coordination sphere from square planar to linear. But under physiological conditions, the relatively easy interchange between the oxidation states +3 and +1 in some gold(III) compounds makes them pharmacologically relevant.

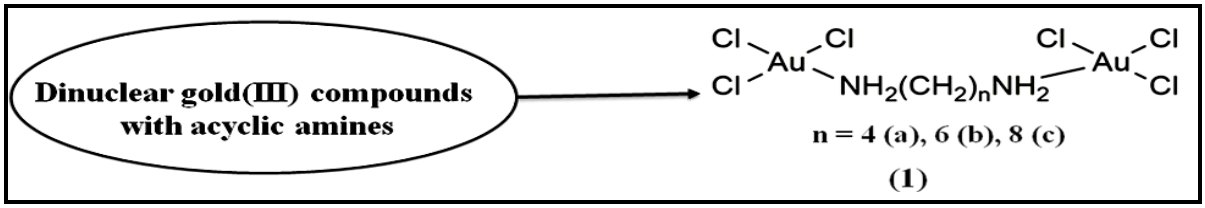
(b) As compounds of gold(III) having $5d^8$ configuration are isoelectronic and isostructural to cisplatin, they may exhibit potential anticancer activity like cisplatin. Moreover, due to borderline behavior, gold(III) cations may prefer to bind both S-donors (soft) and N/O-donors (hard) ligands. Though several gold(III) compounds with different coordination environment have been considered as potential anticancer drugs, but only the polynuclear compounds are discussed in this review. To easily understand the chemistry and anticancer activity of these compounds, they are discussed here briefly into two major groups along with different sub groups.

3. SOME NOVEL POLYNUCLEAR GOLD(III) COMPLEXES AS ANTICANCER AGENTS

3.1. Binuclear gold(III) compounds

3.1.1. With acyclic amines

The main compounds **1a-1c** of this class are shown in **Scheme 1**.



$[Au_2(dab)Cl_6]$ (dab=1,4-diaminobutane) (1a); $[Au_2(dah)Cl_6]$ (dah=1,6-diaminohexane) (1b); $[Au(dao)Cl_6]$ (dao=1,8-diaminooctane) (1c).

Scheme 1: Dinuclear gold(III) compounds with acyclic amines

In case of binuclear gold(III) complexes **1a-1c** [17-21]**,** the corresponding different nitrogen-donor inert acyclic amines, e.g. 1,4-diaminobutane (complex **1a**), 1,6-diaminohexane (complex **1b**), 1,8-diaminooctane (complex **1c**), significantly stabilized gold(III) ion and enhanced its binding affinity to primary biomolecules under physiological circumstances. The potential activity of these complexes was evaluated by 3-(4,5-

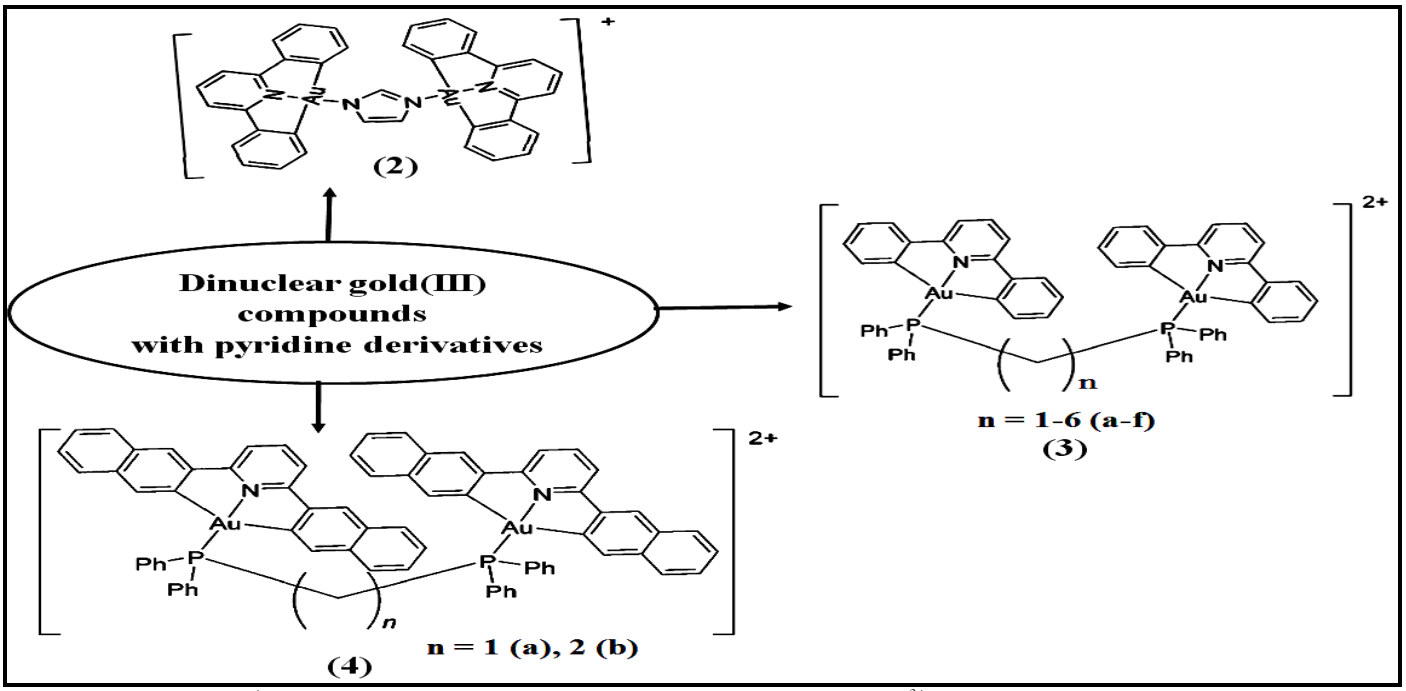
dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test on different cell lines (MDA-MB-231, HCT-116, MRC-5). They exhibited significant cytotoxic effect than $K[AuCl_4]$ after 1 day treatment. From docking analysis it was observed that these complexes were fitted in the minor groove on DNA where the length of diamine permitted enhanced interaction with DNA. Docking results also revealed that these complexes could be bound to BSA to sub domain IIA (site I) via hydrogen bonds where hydrophobic and electrostatic interactions had the pivot role on binding [17].

3.1.2. With pyridine derivatives

This class of compounds (**2**-**4**) is given in **Scheme 2**.

In case of compound **2** [22], gold(III) centre of $[Au(C^N^C)]^+$ (**Scheme 2**) moiety was stabilized by cyclometalated dianionic tridentate pyridine derivatives and two gold(III) centres of two $[Au(C^N^C)]^+$ units were further coordinated by N donors of the bidentate imidazolato ligand. It exerted effective cytotoxic activity to a panel of cancer cell lines, together with a cisplatin-resistant variant. $[Au(C^ N^C)]^+$ moiety in compound **2** exhibited instrumental $[Au(C^N^C)]^+$ cytotoxicity [22] where nontoxic N-donor auxiliary ligand considerably influenced the biological activities as well as the mechanism of cytotoxicity and DNA binding affinity. Moreover, this compound could act as metallo intercalators and potential telomerase inhibitors through coordination of nontoxic imidazolato ligand. It not only induced apoptosis in cancer cells but also induced cell-cycle arrest in the S phase.

Dianionic tridentate pyridine derivatives along with neutral auxiliary bidentate bis-(diphenylphosphine)C_n ligands (in which C_n is a saturated hydrocarbon linker with n = 1-6) stabilized gold(III) ions forming lipophilic binuclear complexes $[Au_2^{III}(C^N^C)_2$(1,2-bis-(diphenyl phosphine)C_n)$]^{2+}$ (**3a**-**3f**), each of which contains two $[Au^{III}(C^N^C)]^+$ cations [22,23] (**Scheme 2**). The cytotoxicity of these binuclear complexes was significantly higher than that of mononuclear $[Au^{III}(C^N^C)(PPh_3)]^+$ complex. Among complexes **3a**-**3f**, complex **3c**, revealed the most potent cytotoxicity against human cervical epithelial carcinoma and nasopharyngeal carcinoma cell lines. Complex **3c** also showed effective *in vivo* anti-cancer activity on rats bearing HCC orthografts [24].



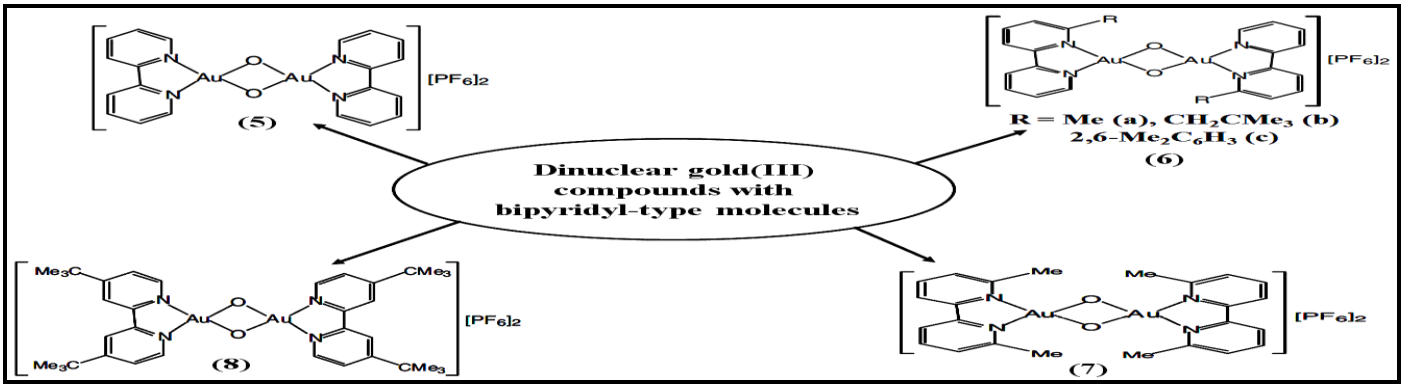
$[Au_2(C^N^C)_2$(imidazole)$]^+$ (HC^N^CH=2,6-diphenylpyridine) (2); $[Au_2(C^N^C)_2(\mu$-dppm$)_2]^{2+}$ {μ-dppm=1,2-bis(diphenylphosphino) methane} (3a), $[Au_2(C^N^C)_2(\mu$-dppe$)_2]^{2+}$ {μ-dppe=1,2-bis(diphenylphosphino)ethane}(3b), $[Au_2(C^N^C)_2(\mu$-dppp$)_2]^{2+}$ {μ-dppp=1,2-bis (diphenylphosphino)propane}(3c), $[Au_2(C^N^C)_2(\mu$-dppb$)_2]^{2+}$ {μ-dppb = 1,2-bis(diphenylphosphino)butane}(3d), $[Au_2(C^N^C)_2(\mu$-dpppe$)_2]^{2+}$ {μ-dpppe = 1,2-bis(diphenylphosphino)pentane}(3e), $[Au_2(C^N^C)_2(\mu$-dpph$)_2]^{2+}$ {μ-dpph = 1,2-bis(diphenylphosphino)hexane}(3f); $[Au_2$(Np-$C^N^C)_2(\mu$-dppm$)_2]^{2+}$ (Np-C^N^C = 2,6-dinaphthylpyridine) (4a), $[Au$(Np-$C^N^C)(\mu$-dppe$)]^+$ (4b).

Scheme 2: Binuclear gold (III) compounds with pyridine derivatives

Compounds **4a** and **4b** (**Scheme 2**) exhibited inherent cytotoxicity. Hence, they may be used as potential anticancer agents [22]. In spite of having possibility of $[Au(Np\text{-}C\text{^}N\text{^}C)]^{+}$ moiety in these compounds to carry phosphine ligands in biological systems, their clinical development as anticancer agents is hindered due to their instability in physiological circumstances and nonspecific binding affinities to different biomolecules.

3.1.3. With bipyridyl-type molecules

A series of structurally related oxo-bridged dinuclear $[Au^{III}_2(\mu\text{-}O)_2(N\text{^}N)_2](PF_6)_2$ compounds (**5**-**8**), where N^N was 2,2′-bipyridine or a substituted 2,2′-bipyridine (**Scheme 3**), contained a common Au_2O_2 "diamond core" that were further coordinated to two bipyridyl type ligands forming nearly square planar geometry. Definitely very small structural changes were appeared in these complexes due to the introduction of a variety of substituents on the bipyridine ligand which created significant differences in their solution behavior, overall reactivity, biological activity and pharmacological properties. They displayed favorable stability profiles both in buffered aqueous solutions and in physiological like conditions. They revealed significant *in vitro* antiproliferative effects against selected human tumor cell lines [e.g. the A2780 ovarian carcinoma human cell line either sensitive (A2780/S) or resistant (A2780/R) to cisplatin] [16,25] and used as potential cytotoxic and anticancer agents. Here, compounds **5** and **6a**-**6c** exhibited almost similar biological activities and noticeable antiproliferative properties without any relevant cross resistance effects with cisplatin. On the contrary, compound **7** was more active on both cell lines-sensitive line and the resistant one and also 5 times more active than cisplatin on the CDDP resistant line. While other compounds **5, 6a**-**6c** and **8** exhibited moderate cytotoxic properties, compound **7** was driven out to be about 5-15 times more active against both cell lines. When the interactions of compounds **5** and **7** with a few model proteins (viz. serum albumin, cytochrome *c*, ubiquitin) and with calf thymus DNA were analyzed in detail by various spectroscopic methods it was found that both the compounds showed noticeably high and unusual reactivity toward the above mentioned model proteins. Moreover they revealed particular differences in their reactivity with DNA. Compound **7** with 6,6′-dimethyl-2,2′-bipyridine derivative exhibited major structural deviations with respect to the model compound **5.** Interestingly, compound **7** had also the highest oxidizing power, least thermal stability, greatest cytotoxic activity, greatest reactivity with model proteins and strongest antiproliferative properties compare to the other compounds **5, 6a**-**6c** and **8** of this series. Hence, there was a positive correlation between the oxidizing power of these complexes to their antiproliferative activities. Such correlations might be very important to design new more-active gold-based anticancer drugs. Unlike classical platinum metallodrugs, the cytotoxic effects induced by these dinuclear gold(III) compounds were not a effect of direct DNA binding and damaging but resulted from alteration of mitochondrial processes by potent inhibition of the selenoenzyme thioredoxin reductase [25]. Interestingly, due to the occurrence of redox processes, a very high reactivity of compound **7** with proteins like serum albumin and cytochrome *c* was detected 25].

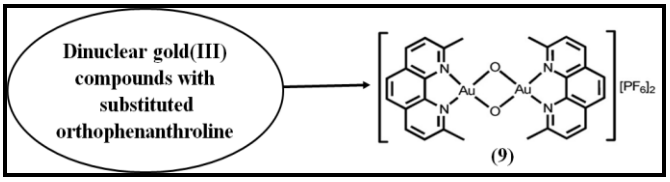


$[Au_2(\mu\text{-}O)_2(bipy)_2](PF_6)_2$ (bipy= 2,2′-bipyridine) (5) cis-$[Au_2(\mu\text{-}O)_2(6\text{-}Mebipy)_2](PF_6)_2$ (6-Mebipy = 6-methyl-2,2′-bipyridine) (6a), trans-$[Au_2(\mu\text{-}O)_2(6\text{-}neoPenbipy)_2](PF_6)_2$ (6-neoPenbipy = 6-neopentyl- 2,2′-bipyridine) (6b), trans-$[Au_2(\mu\text{-}O)_2(6\text{-}oXylbipy)_2](PF_6)_2$ (6-oXylbipy = 6-(2,6-dimethylphenyl)-2,2′-bipyridine) (6c) $[Au_2(\mu\text{-}O)_2(6,6'\text{-}Me_2bipy)_2](PF_6)_2$ (6,6′-Me_2bipy = 6,6′-dimethyl-2,2′-bipyridine) (7), $[Au_2(\mu\text{-}O)_2(4,4'\text{-}tBubipy)_2](PF_6)_2$ (4,4′-tBubipy = 4,4′-di-tert-butyl-2,2′-bipyridine) (8).

Scheme 3: Dinuclear gold(III) compounds with bipyridyl-type molecules

3.1.4. With substituted orthophenanthroline

In the novel dinuclear compound **9** (**Scheme 4**) bearing two 2,9-dimethylphenanthroline ligands, both gold atoms showed a usual square-planar coordination with a small square pyramidal distortion. This compound revealed potential *in vitro* anti-proliferative activity to a representative panel containing 36 different human tumor cell lines [23, 26]. Although this compound was predominantly active against a selected lung cancer line (1121 L), a few prostate cancer lines (22RV1, LNCAP, DU145 and PC3M) and an ovarian cancer line (1619 L), but it was less efficient against a few renal cancer cell lines. Compound **9** was noticed to be 10 times more effective antiproliferative agent than Auphen with a significantly different cytotoxicity profile [27]. However, compound **9** was better than compound **7** both in average cytotoxic activity and tumor selectivity.



$[Au^{III}_2(\mu\text{-}O)_2\text{-}(phen^{2Me})_2]^{2+}$ (wherein $phen^{2Me}$ = 2,9-dimethyl-1,10-phenanthroline) (9).

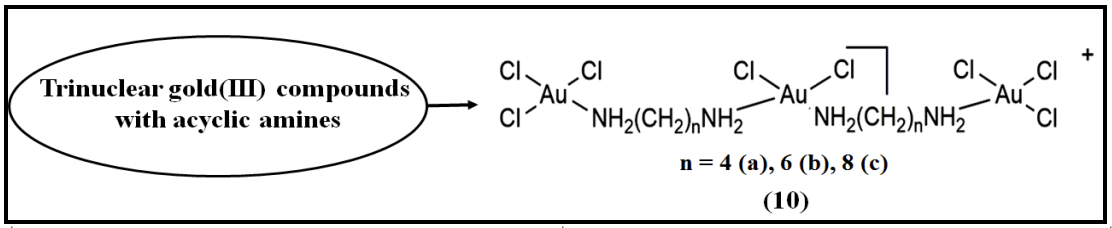
Scheme 4: Dinuclear gold(III) compound with substituted orthophenanthroline

By COMPARE algorithm analysis, it was suggested that the mode of induced cytotoxic action of this compound strictly resembled to compound **7** and might involve histone deacetylase (HDAC) inhibition. Upon interaction with a model protein superoxide dismutase (SOD), break down of dioxo bridge of this dimetallic compound occurred with reduction of two gold(III) ions to gold(I) ions which were eventually found to associate to SOD by releasing the free $phen^{2Me}$ ligands. Furthermore, like several related cytotoxic gold(III) compounds, this compound may behave as a classical prodrug. This novel compound is considered as the most favorable candidate for further pharmacological testing due to its favorable biological activity and particular tumor selectivity.

3.2. Trinuclear gold(III) compounds

3.2.1. With acyclic amines

Gold(III) ions in trinuclear complexes **10a**-**10c** (**Scheme 5**) were greatly stabilized by structurally diverse nitrogen-donor acyclic amines, viz. 1,4-diaminobutane (complex **10a**), 1,6-diaminohexane (complex **10b**), 1,8-diaminooctane (complex **10c**), [17-21] that enhanced their interaction and binding affinity with primary biomolecules. Their potential activity was estimated by MTT test on MDA-MB-231, HCT-116 and MRC-5 cell lines. Generally, complexes **10a**-**10c** exhibited better cytotoxicity than dinuclear compounds **1a**-**1c**.Consequently, the chain length and the number of diamines enhanced the hydrophobic properties of the trinuclear gold(III) complexes giving them appropriate flexibility to enter in the cells. The highest activity of these complexes was noticed for colorectal cancer cells (HCT-116). Docking analysis showed that trinuclear compounds **10a**-**10c** were fitted well in the minor groove on DNA similar to dinuclear analogues where the longer diamine chain increased their interaction with DNA. Docking results also showed that depending on electrostatic and hydrophobic interactions, these compounds could be bound to BSA to sub domain IIA (site I) through hydrogen bonding [17].



$[Au_3(dab)_2Cl_8]^+$ (dab = 1,4-diaminobutane) (10a); $[Au_3(dah)_2Cl_8]^+$ (dah = 1,6-diaminohexane) (10b); $[Au_3(dao)_2Cl_8]^+$ (dao = 1,8-diaminooctane) (10c).

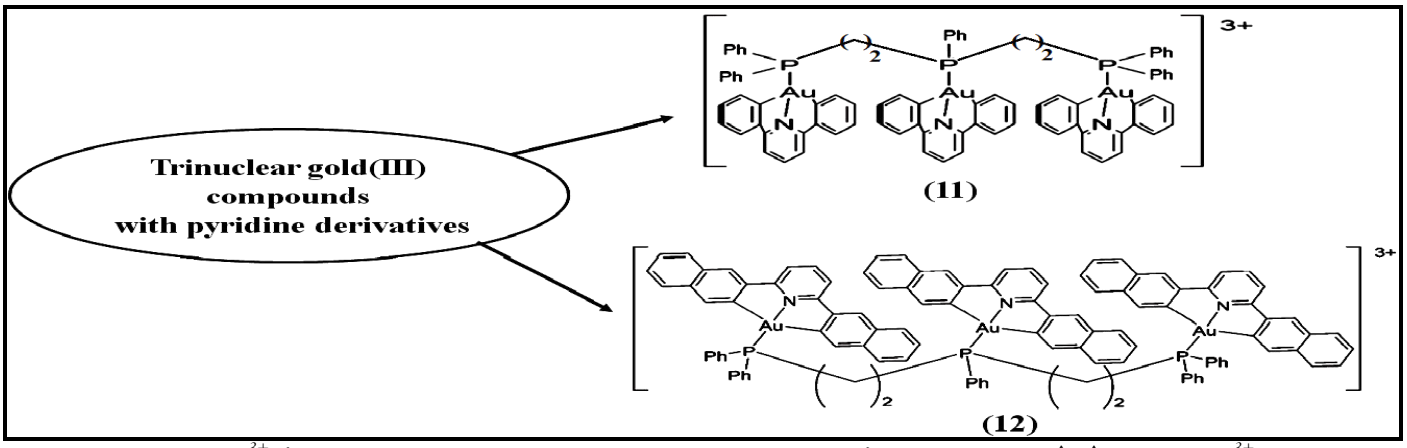
Scheme 5: Trinuclear gold(III) compounds with acyclic amines

3.2.2. With pyridine derivatives

The electrophilic gold(III) ions was significantly stabilized by the dianionic C^N^C ligand to form the $[Au(C^N^C)]^+$ units which were further coordinated by a tridentate bridging phosphine ligand forming the trinuclear gold(III) compound **11** (**Scheme 6**) with

tunable biological activities [22]. This compound revealed effective ligand-mediated cytotoxicity due to its higher solution stability than that of metal-free phosphine ligand. Here, the $[Au(C^N^C)]^+$ moiety of compound **11** is potentially medically important due to its possibility to carry the highly cytotoxic phosphine ligands toward cancer cells.

The trinuclear gold(III) compound **12** with three $[Au(Np\text{-}C^N^C)]^+$ moieties [22] was obtained by using appropriate bridging tridentate phosphine ligand (**Scheme 6**). Moreover, due to the formation of strong gold(III)-ligand bond, $[Au(Np\text{-}C^N^C)]^+$ moieties of this compound may be used as a pendant biological carrier of phosphine ligand through the coordination of cytotoxic phosphine ligand. Though the free phosphine ligand exhibited non-gold-mediated cytotoxicity, but its stability and aqueous solubility were improved by their coordination to the $[Au(Np\text{-}C^N^C)]^+$ moieties. This compound showed potent cytotoxicity against a panel of cancer cell lines.



$[Au_3(C^N^C)_3(\mu\text{-dpep})]^{3+}$ {μ-dpep = bis(diphenylphosphinoethyl)phenylphosphene}(11); $[Au_3(Np\text{-}C^N^C)_3(\mu\text{-dpep})]^{3+}$ (12).

Scheme 6: Trinuclear gold(III) compounds with pyridine derivatives

4. CONCLUSION

Although the use of cisplatin in chemotherapy is the last-line treatment for various types of cancer but resistance to cisplatin is also observed. So, discovery of new active anticancer drugs against cisplatin-resistant cell lines is necessary. Consequently, scientists try their best to prepare new transition metal-based anticancer drugs with enhanced activity and selectivity than cisplatin. Due to being isoelectronic and isostructural with Pt(II) complexes, gold(III) compounds are considered as possible alternatives to Pt-based drugs. Furthermore, these compounds with different coordination environments are quiet stable in physiological condition still in presence of biological reducing agents which makes them efficient antitumor drugs. These compounds are equally cytotoxic toward the cisplatin-sensitive and -resistant cell lines with lack of cross resistance which suggests that they induce cytotoxicity through different mechanisms than cisplatin. Consequently, due to their weaker DNA-binding activity, these compounds have better selectivity and effectiveness to cancer cells than normal cells compared to cisplatin. Like other anticancer drugs, gold(III) compounds also exhibit some unwanted toxic side effects and further research works including experimental trials along with molecular docking studies and *in vivo* studies are necessary to reduce these side effects. As the use of non-toxic ligands for the design of anticancer gold(III) complexes can minimize the possible side-effects, so, the selection of principal ligands with different donor atoms and substituents along with different auxiliary ligands is an important matter in this connection. Again, there is a possibility of using combination therapy by mixing organometallic gold(III) compounds with other anticancer drugs to get better result. Moreover polynuclear gold(III) compounds, obtained through "fusion" of two or more mononuclear units, significantly enhance their specific activity to cancer cell lines compare to their mononuclear analogues. So, there is a huge possibility of polynuclear gold(III) based compounds to be further used more significantly as anticancer drugs. More preclinical investigations are essential to make out these compounds as appropriate candidates for clinical trials and there remain amazing opportunities for further improvement.

5. ACKNOWLEDGEMENTS

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

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