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A REVIEW ON MONONUCLEAR GOLD(III) PORPHYRIN COMPOUNDS AS ANTICANCER AGENTS

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ABSTRACT

In the last decade gold based metallodrugs show the significant role in the progress of medicinal chemistry for therapeutic and diagnostic purpose especially in the treatment of cancer, chrysotherapy, SARS-CoV-2 virus, HIV and other diseases. Though gold compounds with +1 and +3 oxidation states are dominant in medicinal chemistry, predominantly gold(III) compounds have attracted special attention for their structural similarity with the most extensively used anticancer metallodrug cisplatin. Several mononuclear anticancer gold(III) porphyrin compounds show significant antiproliferative properties *in vitro* against certain human tumor cell lines and can overcome cisplatin resistance where the macrocyclic ligand plays a vital role in their anticancer activity. The aim of this review is to sum up the chemistry and anticancer activity of some novel mononuclear anticancer gold(III) porphyrin compounds that making themselves excellent candidates for future pharmacological evaluation. The general viewpoint on the development of these compounds as clinically effective anticancer drugs is deliberated here on the source of the existing experimental evidence.

Keywords: Gold(III) ion; porphyrin ligand; Mononuclear compounds; Chemistry and Anticancer activity

INTRODUCTION:

Cancer is a fatal disease that originates from the mutation of genes **[1-3]**. A new era of metal-based drugs initiated in the 1960s after the discovery of one of the leading metal-based drugs 'Cisplatin' **[4, 5]**. In spite of having several toxic side effects, it is yet used as chemotherapeutic drug **[6]**. Several scientists make efforts to develop non-platinum based metallodrugs with better antitumor activity and selectivity than cisplatin **[6-8]**. In this respect, gold compounds are considered as probable alternatives of cisplatin due to their unique biological and medicinal properties **[9, 10]**. Particularly, gold(III) complexes have attracted special interest **[11]** because both gold(III) and platinum(II) ions are isoelectronic and their complexes are isostructural. Consequently, several new gold(III) compounds were prepared and evaluated as experimental antitumor agents. Though some of these compounds exhibited very distinct antitumor actions *in vitro,* they were rapidly discarded due to having severe toxicity and lower *in vivo* effectiveness **[12, 13]**. To reduce the systemic toxicity and to improve the anti-cancer activities, a number of stable anticancer gold(III) based metalo-organic compounds **[14-26]** are prepared using macrocyclic porphyrin ligands with various substituents. These types of compounds are physiologically stable than other coordination complexes due to the chelate effect of the macrocyclic porphyrin ring. Moreover, the porphyrin ligand stabilizes the gold(III) ion of these complexes against demetallation upon reduction in solution. Most of the gold(III) porphyrin compounds show significant anticancer and antiangiogenic activities through different modes of action than those of cisplatin **[20, 22, 23, 27]**. Planar lipophilic Gold(III)–porphyrins cations with "tunable" lipophilicity are able to target mitochondria in cancer treatment that makes them suitable candidates **[28]** to examine the structure–bioactivity relationship. The substituents on the ligand also have an active role in determining the chemical and biological properties of the resulting complexes. The biological activities of porphyrins and metalloporphyrins are related to their overall lipophilicity parameter logP (the logarithmic ratio of the drug concentration in the organic phase to that in the aqueous phase) **[17]**. Generally the gold(III)–porphyrin complexes with more positive logP values are more cytotoxic, with least positive logP values are cytostatic and with most negative logP values

(having charged substituents at the porphyril ligand periphery) are weak cytotoxic.

The overall perspectives on the progress of mononuclear gold(III) porphyrin compounds as efficient anticancer drugs are critically discussed on the basis of their existing experimental evidence from literature. This topic is important for the syntheses of new drug-lead mononuclear gold(III) porphyrin compounds as well as for the development of further clinical studies. Therefore, the area highlighted in this review, might be beneficial for future investigation of potential anticancer drugs.

CHEMISTRY OF GOLD(III) COMPOUNDS

Due to having unique electronic properties of the gold(III) center, the chemistry of gold(III) ion contains the following unique characteristics:

(a) Three major oxidation states of gold are: 0, +1 and +3. Under physiological conditions, frequent reduction from square planar gold(III) complex to linear gold(I) complex **[29]** makes inhibition to produce a variety of active gold-based anticancer drug. To increase the redox stability of gold(III) complexes, the macrocyclic chelating ligands porphyrin (containing various substituents) with strong neutral or anionic σ-donor N centers may be used. The tetradentate macrocyclic porphyrin ligands **[14-26]** are not only able to block ligand-exchange reactions at the metal center but also their potent σ-donor centers can reduce the reduction potential of the gold(III) ion by transferring electron density to the metal center.

(b) Compounds of gold(III) having $5d^8$ configuration are both isoelectronic and isostructural to platinum (II) complexes.

(c) Gold(III) cations can bind hard porphyrin ligands (N-donors) due to its borderline behavior.

SOME NOVEL MONONUCLEAR METALLO ORGANIC GOLD(III) PORPHYRIN COMPOUNDS AS ANTICANCER AGENTS:

A large number of mononuclear metallo organic gold(III) compounds with diverse structural chemistry have been considered as potential anticancer drugs. Among them, only the mononuclear gold(III) porphyrin compounds are discussed in this review.

In metalloporphyrin compounds of gold(III) (**1-8)** (**Scheme 1** and **2**), the porphyrin ligand significantly stabilized the metal center **[13]** and considerably reduced its redox reactivity **[14]**. Here demetallation with the release of the gold(III) ion and reduction of gold(III) to gold(I) or elemental gold are almost impossible. The biological activity of these

compounds must be attributed for the intact molecule. The primary target for these compounds was DNA following intercalation. They also significantly affected mitochondrial activities **[15]**. The *in vitro* cytotoxicity of these compounds was evaluated by using human nasopharyngeal carcinoma (NPC), human melanoma and normal human lung fibroblast-derived cell lines. By means of MTT assay **[16]**, these compounds displayed promising anticancer activities toward a panel of human cancer cell lines.

Complex **1** (**Scheme 1)** was appreciably cytotoxic to the tested cancer cell lines **[17]**. It improved accumulation of cells in the S-phase. Treatment of cells with this compound provided significant percentages of apoptotic cells. From the flow cytometric analysis, it was observed that, this compound induced apoptosis in nasopharyngeal carcinoma (SUNE1) cells. This compound also increased caspase-3 activation following a 15-hour treatment.

Compound **2**, its metal-free ligand and compound **3 [18]** (**Scheme 1)** showed significant cytotoxicity when tested on the human ovarian cancer cell line A2780. These compounds may interact with proteasomes and thioredoxin reductase **[19]**. The planar lipophilic cationic parts of compounds **2** and **3** may act as mitochondria targeting agents **[17]**. The antiproliferative activity of compound **2** was tested on A2780 cell line. Here, the compounds revealed more favorable cytotoxic features than the constituents from which they were prepared.

A series of novel gold(III) meso-tetraarylporphyrin complexes **4a-4h** (**Scheme 1**) exhibited effective cytotoxicity to the cancer cell lines **[14, 17, 20]**. All these compounds showed outstanding *in vitro* antiproliferative effects **[21]**. Compound **4a** inhibited *in vivo* tumor growth in NPC-bearing mice and prolonged survival in hepatocellular carcinoma (HCC)-bearing rats **[22]**. It exhibited considerable *in vitro* and *in vivo* anticancer activities through different modes of action than that of cisplatin **[20]**. It exhibited about 1680-fold higher *in vitro* cytotoxicity against NPC cells lines than the clinically used cisplatin. As well as NPC cells lines, this compound also showed prominent anti-cancer activity to HCC cells lines **[23]**. By means of MTT assay **[16]**, this compound revealed effective anticancer activities against human nasopharyngeal carcinoma, hepatocellular carcinoma, promyelocytic leukemia, oral epidermoid carcinoma and cervical epithelioid carcinoma cell lines **[14, 17, 22]** with at least 10-fold higher cytotoxicity towards cancer cells than normal

cells. Treatment with this compound not only reduced the mitochondrial membrane potential **[15]** rapidly but also suppressed BCL-2 expression shortly. Extended incubation of this compound enhanced the synthesis-phase (S-phase) cell-cycle arrest, reduced the cells portions at the growth 1 (G1) and growth 2 (G2)-mitotic (M) phases and improved the percentage of apoptotic cells, that was found as the sub-G1 population. Notably, this compound was 61 to 152 times more active against all the cancer cell lines than cisplatin under the alike circumstances. The other compounds **4b-4h** also exhibited effective cytotoxicity to the tested cancer cell lines. By comparing their corresponding IC_{50} values it was found that among these compounds, the para-substituent of the *meso*-phenyl rings had minute effect on the cytotoxicity **[14]**.

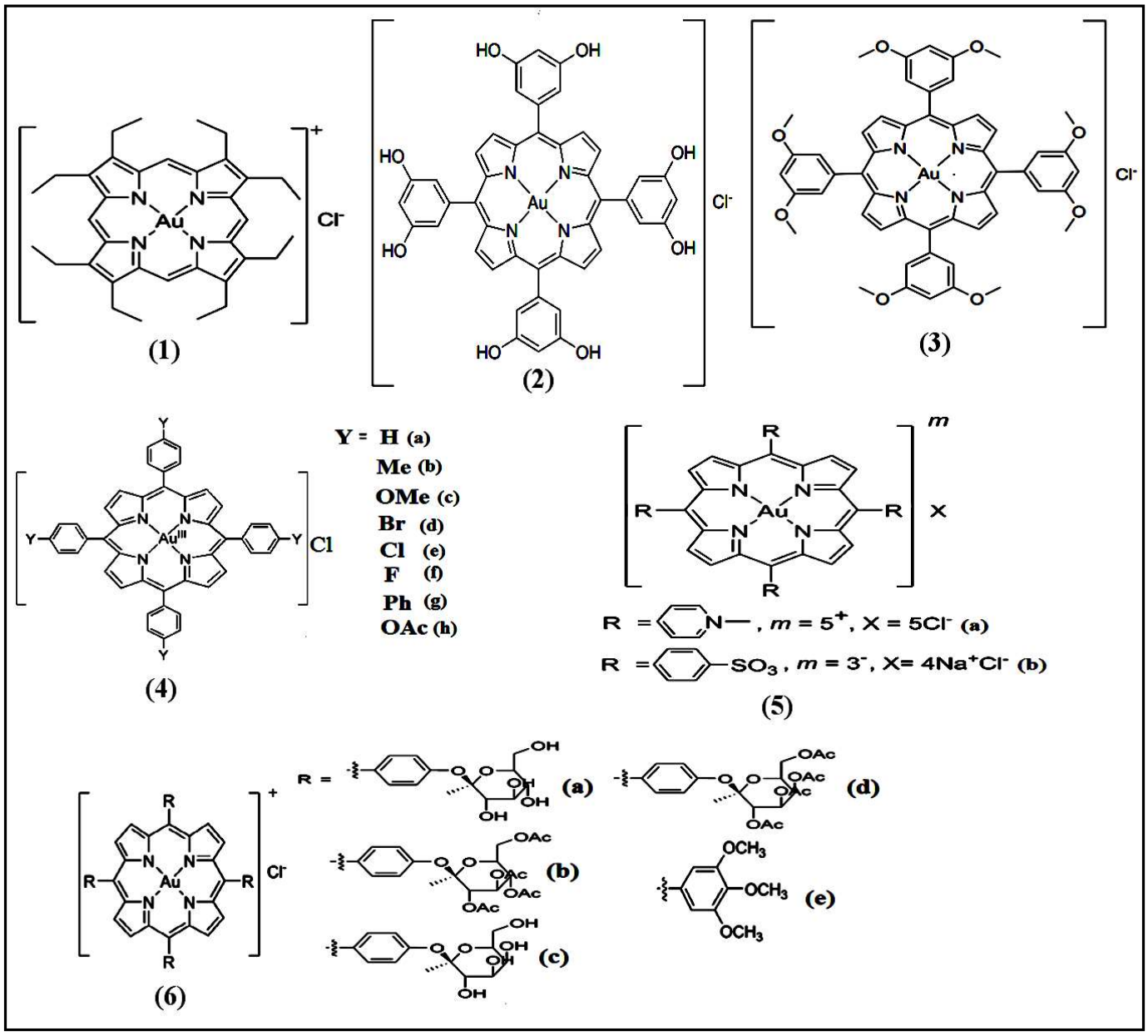
Gel mobility shift assay (GMSA) and viscosity measurement indicated that complex **5a** interacted with DNA similarly like DNA intercalator ethidium bromide. Compound **5a,** in a polymerase chain reaction stop assay, can inhibit the amplification of a DNA substrate containing G-quadruplex structure. Compounds **5a** and **5b [17]** (**Scheme 1)** with charged substituents at the porphyrin ligand periphery had the most negative lipophilicity parameter and were relatively less toxic to all of the tested cancer cell lines. Treatment of the cells with the relatively nontoxic compound **5a** displayed no apparent increase in apoptotic cell death. This compound did not induce cancer cell death or activate caspase-3.

Compounds **6a-6e** (**Scheme 1)** with saccharide-conjugated porphyrinato ligands **[17]** were relatively less effective than compound **4a**. The compounds that displayed more positive lipophilicity parameter (logP) values were more cytotoxic. Instead of displaying cytotoxicity, compounds **6a** and **6c** showed cytostatic activities preferentially toward cancer cell lines due to having the least positive logP values. Compound **6a** exerted cytostatic inhibition of cellular proliferation rather than cytotoxic cell-killing activity. Interaction of this compound with DNA, revealed by GMSA and viscosity measurement, was quite identical to the DNA intercalator ethidium bromide. Compound **6a** further prevented the topoisomerase-I induced relaxation of supercoiled DNA. It was less toxic to lung fibroblast cells and exerted considerable cytostatic action to cancer cells without creating cell death. Furthermore, this compound was cytostatic with at least 28-fold selectivity against different NPC cells lines over noncancerous fibroblast cells. Although the metal-free

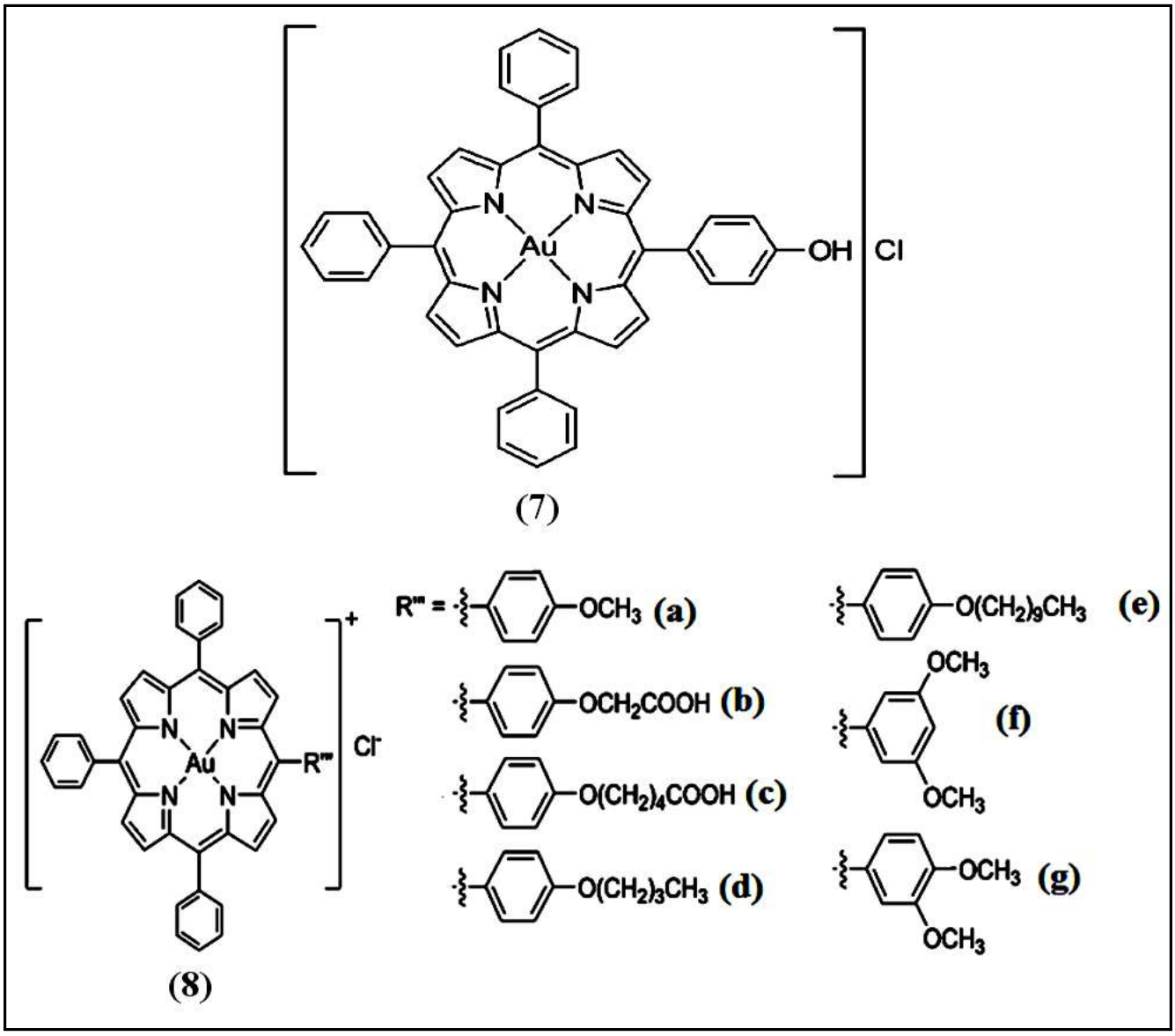
ligand showed cytostatic activity toward SUNE1 cells, its inhibitory activity was about 4.3-fold lower than its corresponding compound. Even though this compound did not show considerable inhibitory effect on telomerase but enhanced accumulation of cells in the S-phase. It did not activate caspase-3 or induce cancer cell death. Complex **6e** revealed effective cytotoxic activity to the tested cancer cell lines **[17]** and also exerted *in vitro* antiproliferative effects.

Compound **7** **(Scheme 2)** was remarkably stable **[24]** under physiological conditions. It exhibited better *in vitro* cytotoxicity than cisplatin against multi-drug resistant human oral epidermoid carcinoma, cisplatin-resistant nasopharyngeal carcinoma, cisplatin-sensitive & cisplatin-resistant ovarian carcinoma, hepatocellular carcinoma, neuroblastoma and colon carcinoma cells. It also inhibited the *in vivo* tumour growth of mice bearing nasopharyngeal carcinoma (NPC) **[25]**. Before the beginning of apoptosis, compound **7** may activate the protein kinase B (PKB). Consequently, this compound may initiate the encountered resistance **[26]** which is strongly supported by the enhancement of its anti-cancer activity in neuroblastomas after the introduction of PKB signalling inhibitor.

The compounds **8a** and **8c-8g** (**Scheme 2)** exhibited effective cytotoxicity to the cancer cell lines **[17]**. Compounds **8b-8e** with peripheral $-OCH_2COOH$, $-O(CH_2)_4COOH$, $-(CH_2)_3CH_3$ and $-O(CH_2)_9CH_3$ substituent on one of the meso-phenyl rings, respectively, were at least 10-fold less cytotoxic compared to compound **4a**. On the other hand, the compounds **8f** and **8g** with two peripheral methoxy substituents at one of the meso-phenyl rings had no considerable cytotoxicity in any tested cancer cell lines. On the other hand, compounds **4a** and **8a** revealed 5.8- and 3.2-fold higher cytotoxicity, respectively, to the cancer cell lines than to noncancerous cells. Compound **8a** improved accumulation of cells in the S-phase, enhanced caspase-3 activation, induced apoptosis in SUNE1 cancer cells and displayed significant percentages of apoptotic cells detected from flow cytometric analysis. Compounds **8a**, **8f** and **8g** had similar lipophilicity with previously discussed compound **6e.** Hence all these four compounds revealed similar cytotoxic properties.



Scheme 1: Mononuclear gold(III) compounds with symmetrically substituted porphyrin: [Au^{III}(OEP)]Cl (1); [Au{TPP-(3,5-OH)$_4$}]Cl (2); [Au{TPP-(3,5-OMe)$_4$}]Cl (3); [Au(TPP)]Cl (4a), [Au(TPP-Me$_4$)]Cl (4b), [Au{TPP-(OMe)$_4$}]Cl (4c), [Au(TPP-Br$_4$)]Cl (4d), [Au(TPP-Cl$_4$)]Cl (4e), [Au(TPP-F$_4$)]Cl (4f), [Au(TPP-Ph$_4$)]Cl (4g), [Au{TPP-(OAc)$_4$}]Cl (4h); [Au(TMPyP)]Cl$_5$ (5a), [Au(TSPyP)]4Na$^+$Cl$^-$ (5b); [Au(TPP-R,R-saccarideOH)]Cl (6a), [Au(TPP-R,R-saccarideOAc)]Cl (6b), [Au(TPP-R,L-saccarideOH)]Cl (6c), [Au(TPP-R,L-saccarideOAc)]Cl (6d), [Au{TPP-(3,4,5-OMe)$_4$}]Cl (6e).



Scheme 2: Mononuclear gold(III) compounds with asymmetrically substituted porphyrin: [Au(TPP-OH)]Cl (7); [Au(TPP-OMe)]Cl (8a), [Au(TPP-OCH_2COOH)]Cl (8b), [Au(TPP-$O(CH_2)_4COOH$)]Cl (8c), [Au(TPP-OBu)]Cl (8d), [Au(TPP-OOct)]Cl (8e), [Au(TPP-3,5-OMe)]Cl (8f), [Au(TPP-3,4-OMe)]Cl (8g).

CONCLUSION

Though cisplatin has been widely used in chemotherapy as anti-cancer drug, its anticancer activity has a number of limitations including resistance, inadequate range of action along with severe side effects due to its non-selective DNA-targeted mechanism. Among the non-platinum based metallodrugs, gold(III) compounds are considered as probable alternatives to Pt(II) complexes because both the ions are isoelectronic and their complexes are

isostructural. Particularly, mononuclear anticancer gold(III) compounds with N-donor macrocyclic porphyrin ligands have recently achieved increasing interest because of their better selectivity and effectiveness towards cancer cells through non-cisplatin-like mechanisms of action due to their weaker DNA-binding activity. In physiological condition, the stability of these compounds that originates from the strong chelate effect of the macrocyclic ligand, makes them efficient anticancer agents. The different substituents attached on the porphyrin ligands have an important role in their therapeutic activities. These compounds show more antiproliferative activity with reduced toxicity than cisplatin and also overcome both cisplatin acquired and intrinsic resistance. Further preclinical investigations of these compounds are required to identify them as suitable candidates for clinical trials. So, the area highlighted in this review has attractive prospects for further development of clinically active gold(III) based potential anticancer drugs.

ABBRIVIATION OF LIGANDS:

H_2OEP = octaethylporphyrin; **TPP-(3,5-OH)$_4$** = 3,5-hydroxy phenylporphyrin; **H_2TPP** = meso-tetraphenylporphyrin; **$[H_2TMPyP]^{4+}$** = meso-tetrakis(N-methylpyridinium-4-yl)porphyrin); **$[H_2TSPyP]^{4-}$** = meso-tetrakis(p-sulphophenyl)porphyrin; TPP-R,R-saccarideOH = meso-tetrakis(4-b-d-glucosylphenyl)-porphyrin); **TPP-(3,4,5-OMe)$_4$ =** meso-tetra(3,4,5-trimethoxyphenyl) –porphyrin.

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