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Review article

Gold (III) Complexes as Breast Cancer Drug

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ABSTRACT
Transition metals represent the d block element which includes groups 3-12 on the periodic table. Their d shells are in a process of filling. This property of these kinds of metals realized the foundation of co-ordination structures. Some of new gold (III) compounds have been prepared that are enough consistent under physiological conditions and are promising contender for pharmacological testing as cytotoxic and antitumor administrators. *In vitro* pharmacological studies point out that some of these novel gold (III) structures are astoundingly cytotoxic toward refined human tumor cell lines. Preliminary results on legitimate to DNA *in vitro* were exhibited, raising that the affiliations were generally slight. A few of Au (III) mixes with multi-dentate ligands such asen (ethylendiamine), dien (diethylendiamine) and sticky (N-benzyl-N, N-dimethylamine) have been seen to be dynamic against human tumor cell lines.

Key words: Gold (III) complex, Breast cancer drug, Anti-proliferative, Multi-dentate ligand, Antitumor, Auranofin.

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INTRODUCTION

Gold Complexes

Metallic gold is understood as entirely inert, not responding with oxygen or sulfur at any temperature; henceforth, it is thought to be the most honorable among of the considerable number of metals. It has the most insignificant oxidation ability in contrast and whatever other metals; in this way, the arranging of positive oxidation state gold complex requires a modestly solid oxidizing agent (e.g. Fe (III)) and a decent legend for gold (e.g. Cl-). Notwithstanding the low reactivity of metallic gold, an expansive number of gold complex have been adequately organized.[1]

History of Gold as a Therapeutic Agent

The most punctual recorded therapeutic use of gold was by the Chinese around 2500 BC. In 1890, Robert Koch reported that potassium aurocyanide, $KAu(CN)_2$, impeded the advancement of tubercle bacillus, the living being responsible for tuberculosis, which around then was generally called the 'white plague'. This gave the biological premise for gold treatment and stimulated various studies. Potassium aurocyanide was excessively unsafe for clinical use, which is not bewildering for a compound of cyanide, yet rather all through the accompanying thirty years, a couple gold (I) thiolates were exhibited for the treatment of tuberculosis; the period from 1925-1935 has been known as the "gold decade" in tuberculosis treatment. In the late 1920s, Dr. K. Landé and Dr. J. Forestier, by virtue of a conviction that rheumatoid joint pain is chronic infection disease like tuberculosis, uninhibitedly displayed gold (I) structures for the treatment of joint pain.[1]

As of late new gold containing drugs have been masterminded and inspected as antineoplastic specialists. A progression of square planer gold (III) complexes have been developed by Calamai *et. al.* containing not less than two gold chloride bonds in cis position and their activity were examined *in vitro* cytotoxicity on a panel of established human tumor cell line.[2]

Gold (III)

This is basic consistent and generally stable oxidation state for gold. Gold (III) complexes are diamagnetic and most have 4-coordinate square–planar stereo science with low turn_5d8 electron arrangements. The most generally perceived case of gold (III) complex, $[AuCl_4]$-, is successfully orchestrated by dissolving gold metal in water regional, and is the trailblazer of most other gold structures. Five coordinate gold (III) structure are uncommon, however when they are found, they have a square pyramidal or a twisted square pyramidal geometry. The fair-minded AuF3 is rare example of gold (III) compound in which the gold molecules are 6-coordinate in its precious crystal formula. There are two criteria which can be taken after to offset Au (III) complexes. These are (i) the ligand should have more than one atom giver (multi-dentate) and (ii) contain two nitrogen atoms. These two criteria were at that point offered an explanation to redesign the stability of Au (III) complexes under physiological conditions.[3]

Overview of Gold Drugs

The chemical formulae of different gold thiol compounds, which are currently being implemented or have been utilized for medicinal purposes, are shown in (Figure 1). Each of these are gold (I) type with the exception of aurol sulfide, for which the ordinarily represented in stoichiometry that demonstrates (a+III) oxidation state for gold, however, it is not well characterized.[1]

Messori *et. al.* (2013) and Buckley *et. al.* (1996)_utilized en, dien and sticky as multi-dentate nitrogen-containing ligands to frame gold (III) complex, which were seen to be alterable against human tumor cells.[4,5] Moreover a later *in vitro* cytotoxicity study demonstrated promising activity of two gold(III) complexes with bipyridyl ligands, (dihydroxy (2,2'- bipyridyl) gold (III) ion) [Au(bipy)- (OH)2] PF6 and [Au(bipy-H) (OH)]PF6 (see Figure 2 and 3).

Mechanism of Gold Complexes

The mechanism of anti-proliferative gold complex activity had been under inquiry for quite a while. However reports that auranofin and other gold (I) compound strongly inhibited the thioredoxin reductase enzyme (TrxR) have most probably tended to the question on the biological principle of gold compleses. Auranofin restrained TrxR with high intensity and around 1000 fold selectivity conversely with other related enzymes

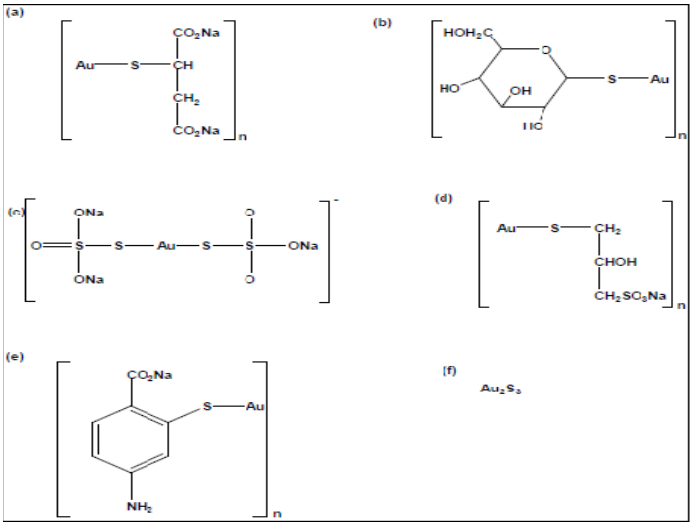

Figure 1: Some representative gold (I) thiol complexes of medicinal interest: (a) gold sodium thiomalate (GST;Myochrysine; Marketed in Britain, the united states (USA) and Canada) ; (b) gold B-D thioglucose (Solganal;marketed in the USA) ; (C) gold sodium thiosulfate (Sanochrysine; marketed in Europe) ; (d) gold Sodium 3- thio –2- propanol –1-Sulfonate (Allochrysine; Marketed in Europe) ; (e) gold Sodium 4- amino –2- Mercapto benzoate (Krysolgan; not currently used in medicine) ; (F) gold sulfide (Aurol Sulfide; not currently used in medicine).

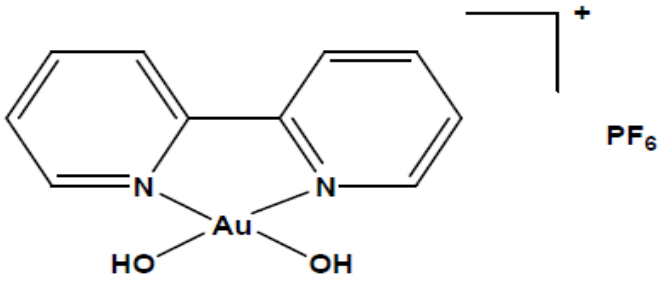

Figure 2: The structure of (dihydroxy (dihydroxy(2,2′-bipyridyl) gold (III) ion) [Au(bipy) (OH)2]PF6.

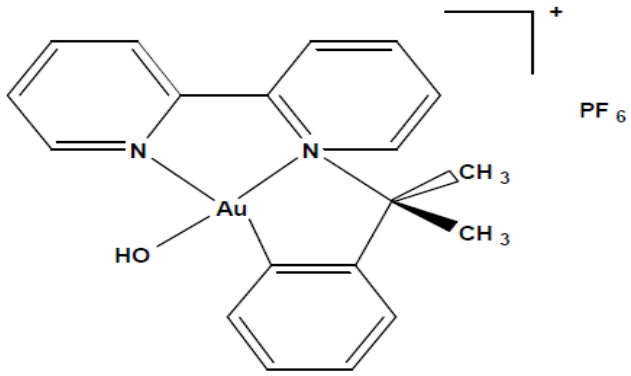

Figure 3: The structure of [Au(bipy-H)(OH)]PF6.

(glutathione reductase and glutathione peroxidase). Based on the distinctive ligand structures of the various gold formulas are pointed in (Figure 4) for which cell growth restraining properties have been observed. An exceptional model of the agent activity is not liable to exist but rather a growing number of reports on gold complexes with immense TrxR inhibitory properties emphasize the congruity of this enzyme in the pharmacology of gold metallodrugs. However, the limitation of TrxR has been accounted for different gold (I) formulas and additionally for various gold (III) complexes.[6]

TrxR is a homodimeric protein has a spot with the group of glutathione reductase like enzyme. It catalyzes the NADPH subordinate diminishment of Trx disulfide and numerous other oxidized cell constituents. The active site of TrxR contains a selenocysteine (sec) which containing (Gly-Cys-Sec-Gly) motif required in the reactant technique of activity of the enzyme. Amid the enzyme catalysis are reducing reciprocals are exchanged from the NADPH substrate to thioredoxin by means for the FAD prosthetic group. Taking into account the high proclivity of the electrophilic of gold (I) center complex to the nucleophilic sulfur and selenium containing deposits a covalent interaction seemed, to be likely as medication activity mode. The favored binding of auranofin to the selenocysteine residue (deposit) was proposed based on the fact of that the agent impeded glutathione reductase, as enzyme which is fundamentally and functionally firmly related to TrxR, yet does not have the sec residue in the active site, with essentially lower affinity. The mitochondrial inhabitation type of the aforementioned enzyme TrxR by auranofin is

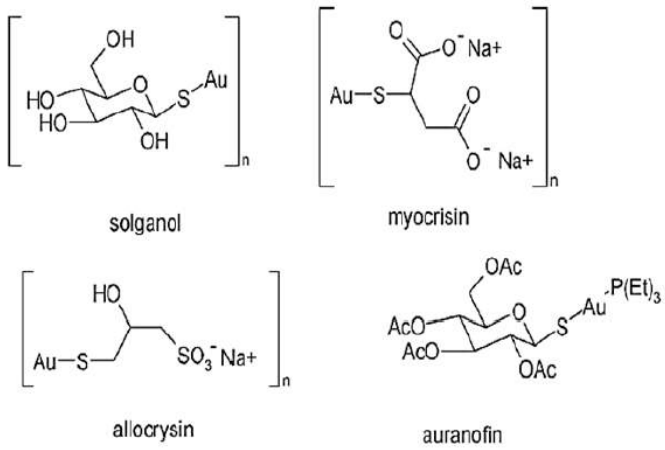

Figure 4: Gold complexes used for chemotherapy.

in incredible simultaneousness with early reports on anti-mitochondrial impacts of gold compounds in several *in vitro* considers.[7, 8]

TEP AuCl ((triethylphosphine) gold (I) chloride), is an auranofin analogue containing the triethylphosphine fragment of auranofin however a chlorine ligand as opposed to the thiocarbohydrate moiety, causing anti-mitochondrial effects. For instance, mitochondrial swelling or extended permeability of the inner membrane in isolated rat liver mitochondria. Auranofin itself incited the mitochondrial membrane vulnerability transition observed as swelling and loss of layer potential. Both events could be completely pivoted by cyclosporin, a specific inhibitor of mitochondrial permeability tranition. Cyclo-oxygenizes (COX) and lip-oxygenizes (LOX) form another class of compounds essential for the treatment of inflammation and cancer diseases.

In view of molecular modeling and mutation experiments for aurothiomalate, a particular targeting of Cys 69 in the PB1 domain of protein kinase C molecule was prescribed as a conceivable mode of action in human lung disease cells. For gold (III) complexes, the inadequate reversible inhibitation of ribonuclease A (RNase An) and deoxyribonuclease I (DNase I) has been stood. As a general result these studies recommend that other than inhibitation of TrxR, which may introduced in the most important target for most gold structures, the interaction with various biomolecules seems to be essential for the pharmacology of anti-proliferative gold complexes.[9]

Gold (III) complexes types

Taking into account their auxiliary and electronic similarity to cisplatin and cisplatin related antitumor medications gold (III) species represent

a promising sector of potential anticancer agents. Not with standing, the improvement of gold (III) complexes as therapeutic drugs has been hampered by their low solidness under physiological conditions and remains a critical parameter in the medication advancement of these species. Gold (III) complexes with different ligands have been developed and biologically examined. The majority of them are complex with Au–N bonds (in the end containing extra Au–O and Au–Cl bonds) additionally some species with Au–S or Au–C bonds and their bioactivities have been portrayed.[10]

Gold (III) complexes with Au–N bonds: Two gold chloride species with pyridine ligands (AuCl3(Hpm) and AuCl2(pm) (Figure 5) demonstrated great cytotoxic activity in Tlymphoblastoid and human ovarian cell lines, which was however practically comparable to that of $NaAuCl_4$. Binding to the DNA was attested for both complexes. Both $AuCl_3$ (Hpm) and

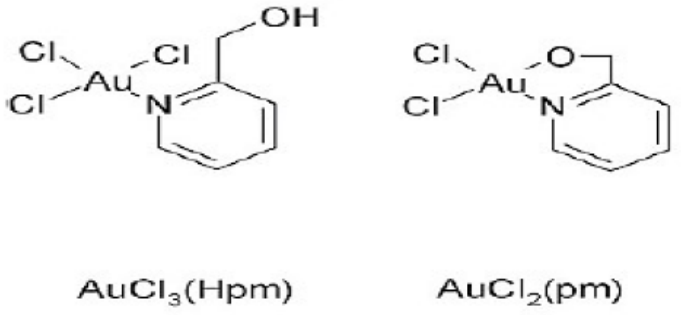

Figure 5: $AuCl_3$(Hpm) and $AuCl_2$(pm) structures.

$AuCl_2$(pm) were moderately steady in organic solvents but experienced hydrolysis of the chloride ligand in buffer media, a truth which may constrain their commonsense application.[11]

Gold (III) complexes with Au–S bonds

Gold(III) dithiocarbamate complexes (see Figure 6 for some relevant examples) showed better cytotoxic impacts in compared to cis-platin, were likewise dynamic in resistant cells and actuated apoptosis. The compounds indicated great stability under physiological conditions, bound promptly to the DNA, synthesis and induced fast DNA lesions Experiments on red blood cells indicated that hemolytic properties might

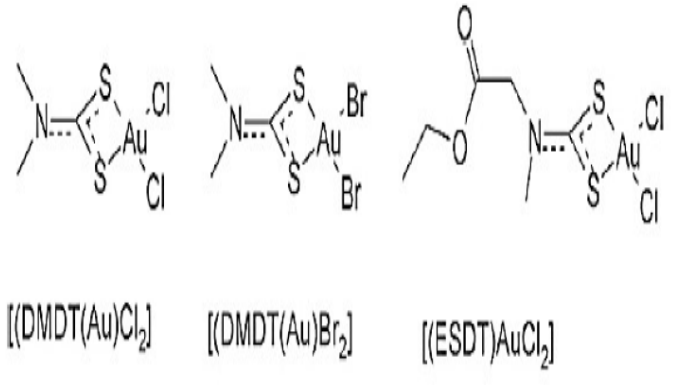

Figure 6: Some example of Gold (III) dithiocarbamate complexes.

contribute significantly to the bioactivity of the agents. The complexes triggered cancer cell death via apoptotic and non-apoptotic pathways, affected mitochondrial functions, generated free radicals, increased ERK1/2 phosphorylation and inhibited TrxR.[12]

Gold (III) complexes containing Au–C bonds

The TrxR inhibiting and antiproliferative properties of a series of gold(III) complexes including many species with gold–carbon bonds was studied. The complex depicted in (Figure 1-7) top left showed the best cytotoxicity results and inhibited TrxR activity.

However, the extent of TrxR inhibition did not correlate with the antiproliferative properties Gold (III) complexes with 2-[(dimethylamino) methyl]phenyl ligands were active *in vitro* and in *in vivo*. More detailed investigations on [Au(acetato)2(damp)] showed that the compound did not cause DNA interstrand crosslinks and induced only minor cell cycle alterations. Solution studies on the gold–carbon complexes AuTol, AuXyl and AuPyAcO revealed that the complexes underwent hydrolysis of the labile ligands while the gold carbon bond and the oxidation state

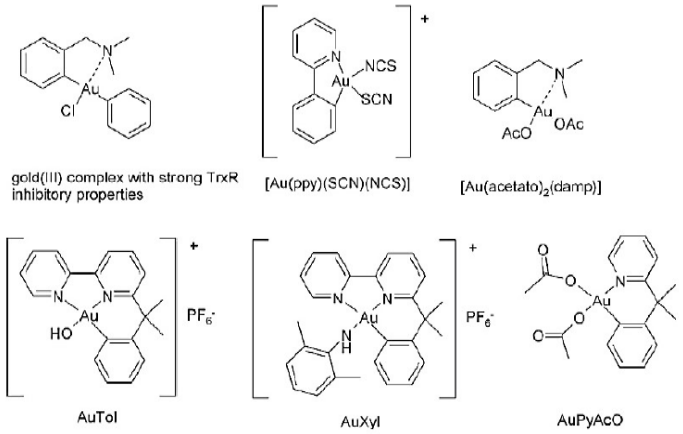

Figure 7: Gold (III) complexes with Au-C bond.

remained intact. In cytotoxicity experiments IC_{50} values in the low micro molar range were determined. The agents also induced anti-apoptotic effects. Interestingly, this was accompanied by only modest perturbations of the cell cycle.[13, 14]

CONCLUSION

The gold (III) complex and its ligand demonstrate strong cell-growth inhibition against MCF7 with MTT assay implying that they complex-induced apoptosis in breast cancer cells. gold (III) complex may cause cell death in MCF7 cells by inducing the mitochondrial membrane permeability change which leads to cytochrome c release which leads to apoptotic cell death.

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