Review Article

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Gold complexes: a new frontier in the battle against lung cancer

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Abstract: Lung cancer is the second leading cause of the mortality related to the cancer. So, it is very necessary to explore the novel strategies to eradicate it. Currently, gold based medicinal compounds have emerged as remarkable anticancer agents and expressed strong potential against the lung cancer cell lines. This review provides a comprehensive overview of the history, advancements, and recent state of gold complexes in the treatment of the lung cancer. We discuss the biological evaluation in relation with the chemical structures of numerous gold complexes, including those featuring thiosemicarbazone, *N*-heterocyclic imine, *N*-heterocyclic carbenes, steroidyl NHC, CAACs, carbamates, and diphosphanes as ligands. Gold complexes' cytotoxicity has been assessed and contrasted with that of standard drugs such as auranofin and cisplatin, with a special focus on IC_{50} values for evaluating potency. This review targets to deliver a detailed understanding of the potential of the gold complexes in lung cancer therapies, paving way for the future research and clinical applications.

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1 Introduction

Life on Earth, including the proliferation of bacteria and cancer cells, depends on metal ions such as iron, copper, and zinc.[1,2] Trace metals, which make up roughly 0.3 % of body weight, are essential for enzyme function. On the other hand, excessive metal contamination resulting from industrial processes can be harmful and cause cancer.[3,4] Many biological systems depend on chelators, which bind these ions. The process of coordinating a metal ion with a polydentate ligand for the formation of a cyclic complex known as a chelate is known as chelation.[5,6] The metal may precipitate from this complex, or it may result in a stable, soluble chemical. Unwanted metal ions can be selectively removed using chelating agents.[7,8] Numerous metal complexes exhibit anticancer action, most likely through the deactivation of carcinogenic metals or the inhibition of enzymes necessary for the fast proliferation of both malignant and healthy cells.[9] Chelating agents can stop the growth of bacteria and cancerous cells by targeting their metal ion needs.[10] Instead of preventing the growth of bacteria and cancer, several chelators and drugs may unintentionally increase the availability of metals.[11–13] Chelating therapies are used as primary, alternative for a wide range of diseases, such as those requiring antioxidant support, metal detoxification, chemotherapy for cancer, infection control, or modification of protein activities or pathways.[14–17]

Lung cancer is a formidable foe, ranking as one of the prominent cause of deaths related to cancer worldwide.[18] It is a malignant type of tumour which originates from the bronchial mucosa or from the lung glands with very high rate of mortality and morbidity.[19,20] Lung cancer ranked as the second most prevalent cause of cancer death globally in 2018 and the third most common disease among women.[21] Micronesia/Polynesia, Eastern Asia, and Europe have high incidence rates; rates exceeding 40 per 100,000 are reported

in China, Japan, and South Korea.[22,23] More than 80 % of instances are related to cigarette smoking, while 53 % of women and 15 % of males do not smoke.[24,25] According to GLOBOCON 2020 predictions, lung cancer is becoming more common in Pakistan, accounting for 10,538 new cases annually, and ranking third overall and second among men. Age-standardized incidence rates (ASIRs) differ by area; Punjab has lower rates than Karachi.[26,27] Most cases of lung cancer occur in older persons (65 years of age or older; around 65 % of diagnosis). In Pakistan, the average age at which lung cancer reveals itself is 68.5 years for women and 63 years for men.[28] This indicates a lower life expectancy than the global average of 70 years.[29] Lung cancer survival rates range from 7 % to 18 % worldwide, and there are no data specifically for Pakistan.[30] With 5.7 % of women and 32.4 % of men smoking, tobacco use is correlated with an increase in lung cancer incidence in Pakistan.[31] The absence of a centralized cancer registry in Pakistan makes it difficult to acquire reliable data. In order to manage the rising lung cancer burden, quit smoking initiatives and a national cancer registry are crucial.[30]

Lung cancer is subdivided into two categories: a) non-small cell lung cancer (NSCLC) and b) small lung cancer (SCLC) on the basis of diagnosis and treatments.[32] First type of lung cancer is more lethal; 85 % of all the cases lie in this category and are cited as the leading cause of lung cancer. It is, in most cases, diagnosed at the last stage, has least option of treatment and drug resistance usually occurred. Some of the current treatments for NSCLC are, surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy.[33–35] Targeted therapies and immunotherapies have developed advance procedures and give effective results.[36] Chemotherapy is basic component of the NSCLC but its effectiveness is reduced due to the drug resistance.[37] The urgency in the treatments and therapies cannot be over-elaborated. Despite the advancement in cancer research area, the current resources of treatments which includes, surgery, chemotherapy, and radiotherapy often falls short to compete this aggressive disease. The limitations in the orthodox ways of cancer treatments have glimmered a zealous quest for inventive methods, and in the recent years gold complexes have arisen as a novel frontier in the battle against lung cancer.[38] Since ancient time it has been observed that metals and inorganic compounds have been used in medicinal applications.[39–41] In the early 20th century[42–46] with the enhancement in the modern discoveries in synthetic organic chemistry many anticancer and antibiotic agents were prepared.[47–49] It reduced the interest to use the metal in medicinal drugs due to systematic toxicity. In 1978 when cisplatin was approved by FDA, the metal-based interest in medicinal field renewed. Alongside their extensive research in cytotoxicity and anticancer potential, metal-based drugs are commonly used for cancer immune interface and have capability to realm the pivotal characteristics of immune elusion. Platinum based drugs were first generation anticancer drugs established efficiently for head, neck and reproductive cancer.[38,50–52]

Gold, a noble metal long admired for its value and versatility, has been surprisingly thrust into the spotlight as a potential weapon in the fight against cancer. The journey of gold complexes from mere curiosities to the capable therapeutics is evidence to the power of interdisciplinary research. Gold has extraordinary capability of aggregation to the intermetallic compounds and planer clusters so, it is widely persuaded by the chemists. Recent research suggested that gold(I) complexes may be less harmful anticancer drugs.[53,54] The d8 electronic configuration of gold(III) compounds is similar to that of platinum (II), permitting similar square planar geometries and ligand exchange processes, which is another reason for their growing interest.[55] Due to this resemblance, gold(III) presents a viable substitute for the development of metallodrugs that are modeled after cisplatin.[56,57] The Egyptians believe that healing capability of gold can cure all kinds of physical, mental and spiritual diseases. Geber wrote that Gold is the medicine conserving the body in youth.[58] It is an inert coinage metal and its stable oxidation state lies between –1 and +5, but +1 and +3 are very common.[58] With greater scientific basis, the use of gold medicines started in early 1920s when K $[Au(CN)_2]$ was tested for bacteriostatic effect through clinical trials. Auranofin (**I**), [(tetra-O-acetyl)-β-D-glucopyranosyl)-thio] (triethylphosphine)-gold(I) (**II**), and Gold(III) dithiocarbamate (**III**) evolved as second generation of the gold drugs as shown in Figure 1. The brand name of auranofin is Ridaura®. It was cited that it has the ability to inhibit the TrxR system significantly. Due to this property, it was characterized as anticancer agent.[51] A very proficient gold(III) compound **IV**,. which is made up of two gold(III) (C, N, C) fragments and also bridged through a bis(diphenylphosphino)propane ligand. Cited compound showed nanomolar *in vitro* potential against various cancer cell lines. Its tumour growth inhibition was 77 % in the mice bearing human hepatocellular carcinoma PLC cells.[59] There is a significant contribution of gold(I) compounds in the anticancer field. The structure of gold(1) complex (**V**) shown in Figure 1 is linear around the gold atom and ligand displacement occur in it as a key reaction in the biological system. The complex **V** can be modified by the change in the ancillary ligands attached with them. It can change its stability, lipophilic character and binding capability as well.[59,60]

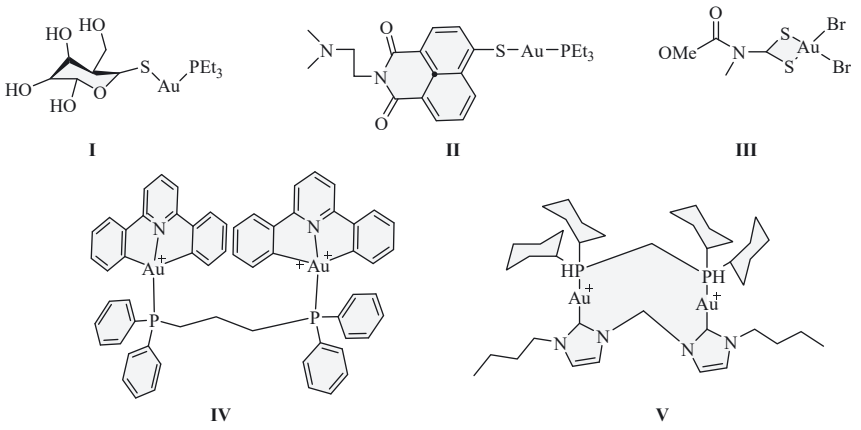

Figure 1: Represented the chemical structure of gold based biological potential drugs.

2 Gold metallodrugs for non-small cell lung cancer (NSCLC)

2.1 Thiosemicarbazone based Au(III) complexes

Under physiological circumstances, gold(I) is stable, but gold(III) is typically more volatile and unstable. In order to prevent its reduction by thiols, appropriate ligands must be designed, like cyclometalated gold(III) complexes.[61] In an effort to develop gold(III) complexes with possible anticancer qualities, researchers worked on thiosemicarbazone (TSC) ligands, which are well-known for their biological activity along with metal complex properties.[56,62–64] The complexes **C1, C2,** and **C3** were synthesized from their respective TCS ligands **L1**, **L2**, and **L3** (Figure 2).[65] Their cytotoxicity against lung cancer cells, specifically mesothelioma, was examined in relation to N^4-substituted thiosemicarbazones generated from salicylaldehyde. These complexes have an O–N–S chelating system.[66] An uncommon and severe malignancy that is resistant to traditional therapy, malignant pleural mesothelioma (MPM) is connected to asbestos exposure.[67,68] Tested on three cell lines; human lung mesothelioma H28 and H2052 and human lung cancer A549, the study assessed the efficacy of gold(III) complexes as prospective therapy alternatives. It was observed that the gold(III) complexes effectively suppressed chronic inflammation in mesothelioma cell lines H2052 and H28 by dramatically reducing Interleukin-6 (IL-6) production. The treatment may have a different effect on different cell types, as evidenced by the fact that IL-6 levels in the cells of A549 were comparable to those in untreated cells. Complexes **C1–C3** strongly suppressed the growth and viability of A549, H2052, and H28 cells, according to the results of the MTT and Trypan blue assays. The ligands **L1-L3**, and gold(III) salt did not exhibit any cytotoxic effects up to 100 μM, indicating the selectivity of the complexes' cytotoxicity in comparison to their constituent parts (Table 1). With IC_{50} values ranging from 2 to 6 μM, H28 was the cell line that responded to the gold complexes best.[65]

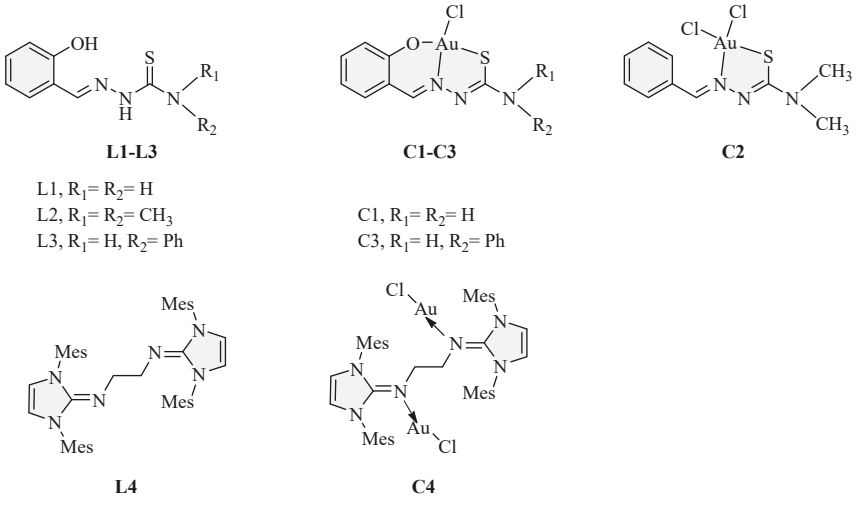

Figure 2: Thiosemicarbazone and *N*-heterocyclic imine based gold complexes for the treatment of lung cancer.

Table 1: Comparison of IC_{50} values of gold complexes (C1–C55) with their ligands and standard drugs cisplatin as well as auranofin.

Compound	IC_{50} (μM) values against lung cancer cell lines			
	A549	H28	5 H20522	MRC-5M-5
L1	> 100	> 100	> 100	–
L2	> 100	> 100	> 100	–
L3	> 100	> 100	> 100	–
C1	14 ± 1	2.2 ± 0.5	9.5 ± 0.9	–
C2	32 ± 1	2 ± 1	14 ± 1	–
C3	19 ± 1	6.4 ± 0.8	9.3 ± 0.8	–
L4	0.9 ± 0.1	–	–	–
C4	0.4 ± 0.0	–	–	–
Cisplatin	3.4 ± 0.0	–	–	–
Auranofin	3.1 ± 0.7	–	–	–
C5	–	–	–	16.3
C6	–	–	–	22.2
C7	–	–	–	15.8
C8	–	–	–	19.7
C9	–	–	–	19.0
C10	–	–	–	16.6
C11	–	–	–	17.1
C12	–	–	–	17.4
Cisplatin	–	–	–	> 50
Auranofin	–	–	–	3.78
L5	> 100	–	–	–
C13	11.99	–	–	–
C14	6.23	–	–	–
C15	16.35	–	–	–
C16	13.10	–	–	–
C17	7.05	–	–	–
C18	11.64	–	–	–
C19	7.50	–	–	–
C20–C23	> 100	–	–	–
Cisplatin	20.26	–	–	–
C24	5.2 ± 0.3	–	–	–
C25	7.7 ± 0.1	–	–	–
C26	4.4 ± 0.2	–	–	–
C27	5.8 ± 0.2	–	–	–
Cisplatin	9 ± 1	–	–	–
C28	101.63 ± 2.3	–	–	–
C29	129.49 ± 2.09	–	–	–
C30	110.65 ± 2.68	–	–	–
C31	108.6 ± 2.44	–	–	–
C32	102.17 ± 2.57	–	–	–
C33	89.98 ± 2.41	–	–	–
C34	90.25 ± 1.78	–	–	–
C35	83.36 ± 0.71			
C36	77.90 ± 1.58	–	–	–
Cisplatin	42.2 ± 2.01	–	–	–
C37	63.3 ± 1.1	–	–	–
C37-k	17.5	–	–	–
C37-l	13.1 ± 2.8	–	–	–
C37-m	13.1 ± 4.0	–	–	–
C38	36.6 ± 4.7	–	–	–
C38-l	4.4 ± 1.2	–	–	–
C38-m	10.7 ± 0.2	–	–	–
C39	0.115 nM	–	–	–
C40	1.16 nM	–	–	–
Auranofin	4.41 nM	–	–	–
C41	10 ± 1	–	–	–
C42	20 ± 2	–	–	–
Cisplatin	38 ± 2	–	–	–
C43	7.9 ± 0.7	–	–	–
C44	10.1 ± 0.2	–	–	–
C45	25.7 ± 0.1	–	–	–
C46	10.9 ± 0.9	–	–	–
C47	>100	–	–	–
L8	76 ± 34	–	–	–
C48	0.07 ± 0.06	–	–	–
C49	4.5 ± 0.7	–	–	–
C50	6.6 ± 2.5	–	–	–
Auranofin	3.7 ± 0.6	–	–	–
C51	16 ± 2	–	–	–
C52	5.4 ± 0.7	–	–	–
$AuCl(PPh_3)$	18.6 ± 1.3	–	–	–
Cisplatin	40 ± 3	–	–	–
C53	0.22 ± 0.06	–	–	–
C54	0.26 ± 0.04	–	–	–
C55	0.13 ± 0.05	–	–	–
Cisplatin	6.21 ± 0.72	–	–	–

2.2 *N*-heterocyclic imine based Au(I) complexes

N-heterocyclic imines (NHIs) and their carbene equivalents are examples of strongly electron-donating ligands that have drawn interest for isolating electron-deficient metallic complexes.[69,70] In comparison to non-substituted NHCs, the exocyclic nitrogen at the two-position improves their σ- and π-donating abilities. Compounds belonging to the main group have recently been added to the list of documented mono- and bis-NHI transition metal complexes over the previous 20 years.[71,72] Though there have been some studies on catalysis, their biological applications remain mainly unexplored. Mihyun Park and his colleagues by using a potent *bis-N*-heterocyclic imine ligand (**L4**), a binuclear gold(I) complex (**C4**) was designed and characterized by SC-XRD (Figure 2). It showed decreased toxicity toward non-tumorigenic VERO cells while exhibiting specific antiproliferative activities *in vitro*, especially towards A549 non-small cell lung cancer cells. In comparison to existing metallodrugs such as, cisplatin, and auranofin, the efficiency of dinuclear complex **C4** against A549 lung cancer cells was assessed. With an IC_{50} of 0.4 ± 0.0 μM, **C4** has the highest potency among the standard compounds as well as ligand **L4**, according to the IC_{50} values, which are listed in Table 1.

With respect to cisplatin and auranofin, **C4** is 8–9 times more effective, demonstrating its greater efficacy in targeting these cancer cells. In addition to introducing novel bioactive ligands for controlling metallodrug behavior in biological systems, this work highlighted the potential of metal-based NHI complexes in medicine.[73]

2.3 *N*-heterocyclic carbene Au(I) complexes

The Industrial Property Office of the Czech Republic has confirmed the uniqueness and practicality of Au(I)-iPr complexes with 6-mercaptopurine derivatives. National patent CZ 307954, which deals with N-heterocyclic carbene complexes of gold with bicyclic N-donor ligands, describes this recognition. The use of these type of complexes in the development of anticancer treatment drugs is also highlighted in the patent.[74] Researchers were used sixth-mercaptopurine and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene derivatives for synthesizing eight *N*-heterocyclic carbene (NHC) gold(I) complexes (**C5–C12**) as shown in Figure 3. *In vitro* cytotoxicity tests were performed with human lung fibroblast normal cell line MRC-5 to evaluate the potential of these complexes as anticancer agents together with standard drugs auranofin and cisplatin. The results presented in Table 1, showed that all the complexes (**C5–C12**) exhibit lower toxicity towards the MRC-5 cell line with IC_{50} values in between 15.8 and 22.2 μM, as compared to cisplatin (IC_{50} = >50 μM). However, in comparison to auranofin (IC_{50} = 3.78 μM) the synthesized complexes (**C5–C12**) showed higher toxicity to normal lung cells MRC-5 as well as less effective. Moreover, the complex **C7** was more effective among the synthesized complexes as well as the ligands with an IC_{50} value of 15.8 μM. The order of effectiveness against MRC-5 cell line were the following; auranofin > C7 > C5 > C10 > C11 > C12 > C9 > C8 > C6 > cisplatin.[75] Dithiocarbamates (DTCs) have attracted a lot of attention in medicinal and organic chemistry because of their wide range of biological activity.[76] Their potential for treating cancer has been highlighted by recent studies, with ruthenium (II) and platinum/palladium (II) complexes showing particularly promising outcomes.[77] Increased anticancer activity has also been shown in Au(I) NHC-DTC complexes.[78] When alkynyl ligands are used with Au(I) complexes, stability problems can be resolved since they have potent antiproliferative effects upon ethynylation.[79–81] While the combination of Au(I) NHC with multi-active moieties offers a new approach to the development of antitumor drugs, the anticancer activity of paeonol, a derivative of flavonoids, seems promising.[82–84] New Au(I) NHC complexes were synthesized by the researchers, using alkynyl or DTC groups as additional ligands and a paeonol ligand in the side chain. The CCK8 test was used to assess the cytotoxic activity of imidazolium salt Pa-NHC (**L5**), Pa–NHC–Au-Cl (**C13**), and Au(I) N-heterocyclic carbene complexes (**C14–C19**) against A549 human lung cancer cells.[85] Cisplatin was used as the reference drug, and the IC_{50} values are shown in Table 1. The pro ligand **L5** showed insufficient cytotoxic activity (IC_{50} = >100). Au(I) complex **C13** demonstrated good cytotoxicity. Also, its cytotoxicity was higher than the standard drug cisplatin. The DTC ligands showed no activity against tumor cell line. The cytotoxicity against A549 was significantly increased by substituting DTCs in place of Cl-in Pa–NHC–Au complexes (**C14–C19**). The IC_{50} values for A549 ranged from 6.23 to 7.50 μM, indicating a 3.2-fold increase in activity against cisplatin. By comparison, DTC containing complex **C14, C17** and **C19** showed excellent cytotoxic activity among all the synthesized complexes and higher than the complex **C13**. As reported previously, adding alkynyl groups to gold(I) NHC complexes (**C20–C23**) had no effect on anticancer activity.[86] The researcher has synthesized neutral digold(I) complexes (**C24–C27**) with diNHC along with thiolato/alkynyl ligands. They treated the human lung cancer cell line A549 for 96 h with digold–thiolato and digold–alkynyl complexes, while cisplatin was used as a positive control, to examine the anticancer potential of these compounds. This method sought to assess and contrast their potency against cancerous cells. The results revealed that all the complexes **C24–C27** exhibited excellent cytotoxic activity against the A549 cell line as compared to standard drug cisplatin (IC_{50} = 9 ± 1 μM). However, complexes **C26** and **C24** outperformed among the synthesized complexes with IC_{50} values of 4.4 ± 0.2 μM and 5.2 ± 0.3 μM, respectively (Table 1). There is significant increase in anticancer activity for the complexes bearing a meta-xylene spacer (Mes). The order of increasing the cytotoxic activity of complexes were following C26 > C24 > C27 > C25 > Cisplatin.[87]

The stable Au–C bond and flexible co-ligand choices of Au(I)–NHC complexes facilitate selective gold ion release and improved drug delivery. Scholars have investigated secondary ligands such as sulfur donors and phosphines to develop potent drugs against cancer cells.[78,88] Through the reaction of Au(Ipr)Cl with various thiones (a, b, c, d), Sughra Gulzar and her coworkers designed four novel Au(I)–NHC complexes (**C28–C36**), as their structural framework shown in Figure 4. The A549 human lung cancer cell line was used to test these complexes for anticancer properties. The results showed that, although these gold NHC complexes showed some activity, they were not as cytotoxic as the standard drug cisplatin.[89] Compared to the precursor [Au(IPr)Cl] with IC_{50} values of 180 ± 2 μM, complexes **C28** and **C29** exhibited enhanced anticancer activity (Table 1). The sulfur atoms are

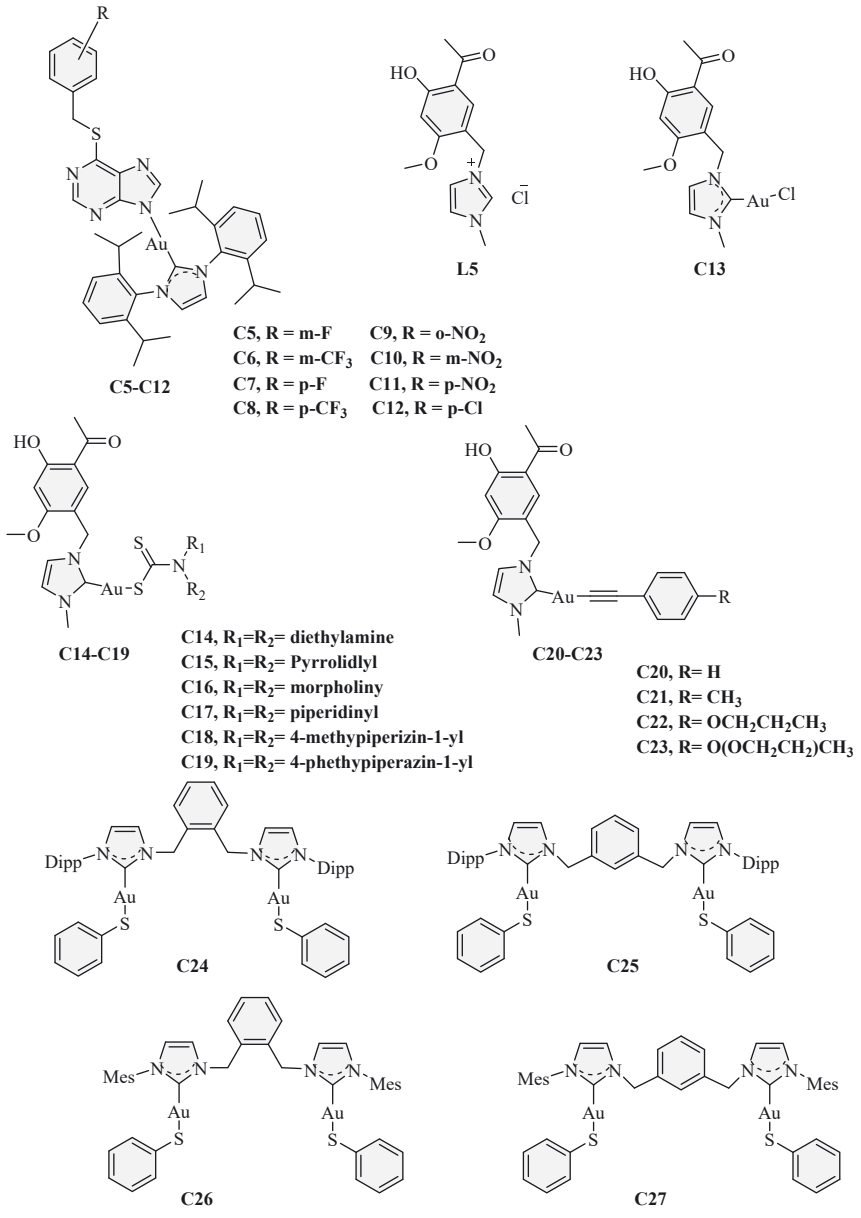

Figure 3: Structural representation of *N*-heterocyclic carbene based gold complexes.

responsible for the complexes' increased solubility in aqueous conditions through ionic interactions, which contributes to their higher efficiency. Their enhanced solubility is a contributing factor to their higher inhibitory efficacy against cancerous cells.[90] On the other hand, mostly due to the large IPr ligand and the large ring size of the thione ligands (a-j), the Au(I) complexes (**C28–C36**) showed less anticancer activity when compared to cisplatin.[91] Au(I)–NHC-thione complexes' large carbene ligands may prevent the Au(I) ion from interacting with cancer cells, which would reduce efficacy and increase IC_{50} values.[92,93] Although, five membered rings containing complex **C36, C35,** and **C33** demonstrated better cytotoxic activity in comparison to six and seven membered rings containing thionic complexes **C29** and **C30**.[89,94] It seems that the thione co-ligand is a factor in the overall stability and effectiveness of these gold(I) complexes in the fight against cancer.

Transition metal-mediated bioorthogonal activation is a method that uses regulated chemical stimulants to change inactive prodrugs, profluorophores, or caged proteins into their active versions.[95,96] This comprises reactions including cycloaddition, uncaging, and cross coupling.[97–100] The scope of bioorthogonal reactions in biological systems is still growing, despite the effectiveness of these techniques. Crucial for cross coupling, organometallic transmetallation is the process of moving groups such as aryl or alkynyl to metal catalysts (like Pd) in order to break strong metal-carbon bonds and form labile metal-ligand species.[101–103]

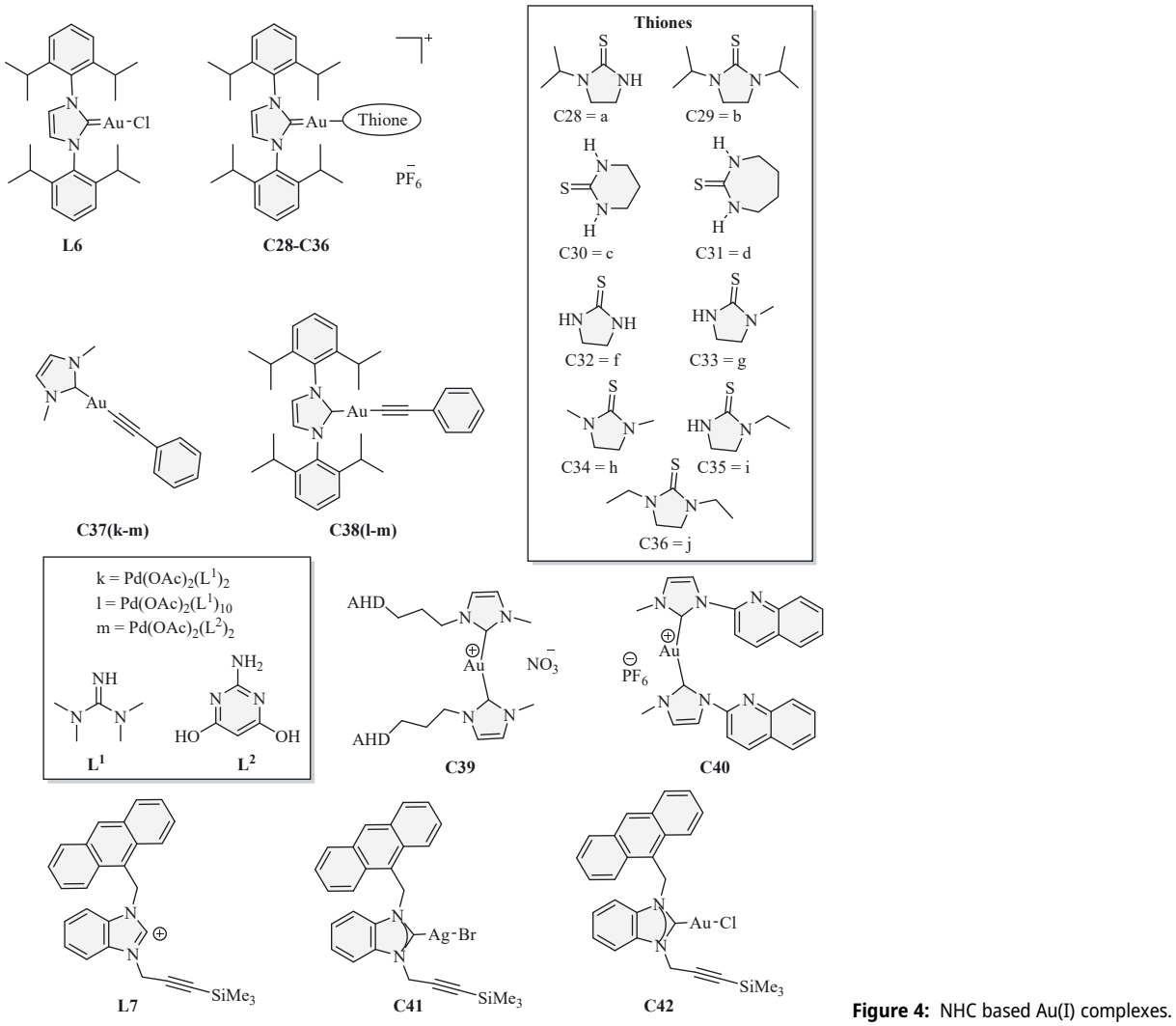

Figure 4: NHC based Au(I) complexes.

Scientists have shown that Pd(II) can effectively initiate transmetallation and activate organogold(I) complexes within biological systems. In living cells and zebrafish, this activation generates active gold(I) species that can accelerate π-bond activation events and have anti-cancer properties. When Pd(II) compounds (**k-m**) were tested to increase the cytotoxicity of gold complexes (**C37–C38**), compound **k** caused the IC_{50} of **C37** in A549 cells to increase from 63.3 μM to 17.5 μM. The cytotoxicity of **C37** was enhanced by non-toxic Pd(II) compounds **l** and **m**, which also decreased its IC_{50} to 13.1 μM. The cytotoxicity of complex **C38** was greatly enhanced by **l** and **m** activating agents; under f co-treatment, the IC_{50} dropped from 36.6 μM to 4.4 μM. According to these findings, Pd(II) compounds (**k-m**) have the ability to boost the thiol-reactivity and cytotoxicity of organogold(I) complexes **C37** and **C38** in cancer cells, suggesting that they may be more successful in treating cancer (Table 1).[104] The antimalarial properties of artemisinin and its derivatives are well known, but there is growing interest in the potential of these compounds to treat cancer and viral disorders.[105–107] Reactive oxygen species (ROS) are produced when iron activates free heme, which mostly happens in mitochondria, and this is one way in which they have anticancer properties.[108,109] Artemisinin derivatives that specifically target mitochondria have a greater anticancer impact. Similarly, N-heterocyclic carbene (NHC) gold(I) complexes with cationic properties have demonstrated potential for use in cancer treatment.[110,111] Most recent work has been devoted to the anticancer optimization of these NHC gold(I) complexes. They developed a novel class of hybrid complexes (**C39–C40**) by fusing cationic bis(NHC)Au(I) units with derivatives of artemisinin. Interestingly, one compound, **C39**, outperformed conventional therapies in its substantial anticancer effectiveness against human lung A549 and liver HepG2 carcinoma cells. Compound **C39** showed higher cytotoxic activity for cancer cell line A549 compared to

HepG2 cell line. Even the cytotoxic potential of complex C**39** (IC_{50} = 0.115 nM) was higher than the complex **C40** (IC_{50} = 1.16 nM) as well as standard drug auranofin (IC_{50} = 4.41 nM) against A549 cell line. In comparison with control molecule, hybrid complex **C39** also demonstrated noticeably higher efficacy against difficult HepG2 hepatocellular carcinoma type comparedwith the standard, which is difficult to treat by chemotherapeutic drugs.[112] This indicates that hybrids of gold(I) and artemisinin may be viable candidates for new anticancer treatments.[113] Researchers used a luminous benzimidazole ligand (**L7**) functionalized with anthracenyl to produce and evaluate two new gold(I) and silver(I) complexes, **C41** and **C42** respectively. In comparison to cisplatin, these complexes (**C41–C42**) showed stronger antiproliferative effects and notable cytotoxicity in the micromolar range against a variety of tumor cell lines, such as SW480 (colon), A549 (lung), and HepG2 (liver). The main objective was to assess the gold complexes' cytotoxic effects on A549 lung cancer cells in particular. The results indicated that these Au(I) complex **C42** exhibit potential efficacy beyond that of cisplatin, making them attractive candidates for the development of novel treatments for lung cancer. Au(I) complex **C42** has the higher cytotoxic potential than the standard drug cisplatin with an IC_{50} value of 20 ± 2 μM. While complex **C42** does not have the same cytotoxic capacity as complex **C41**, it is still a more effective treatment for lung cancer cells than cisplatin.[114]

Based on literature,[115] in order to facilitate concerted-metallation-deprotonation (CMD) between [Au(NHC)Cl] and ethisterone, researchers synthesized Au-steroidyl complexes (**C43–C47**) with a variety of saturated and unsaturated NHC ligands using the weak base K_2CO_3 (Figure 5). There was no complicated work-up for this process, which runs under air. A thorough investigation of these complexes' antiproliferative effects on A549 lung cancer cells showed promise for their ability to target the disease. Among the gold-steroidyl complexes evaluated, compound **C43** was shown to be the most effective anticancer agent by the study. Its IC_{50} value against A549 lung cancer cells was 7.9 ± 0.7 μM (Table 1). The inadequate solubility of complex **C47** in the stock solutions and cell culture media may have contributed to its inactive nature. The cytotoxic potential of complexes **C44** and **C46** was comparable. An intriguing discovery from the structure-activity relationship (SAR) analysis was the significant reduction in activity that resulted from replacing the imidazole-derived NHC ligand in **C43** with an imidazoline-based NHC in **C45**. This finding highlighted, how important ligand structure is to these gold complexes' anticancer properties and shows the importance of precise ligand selection in the development of successful treatments.[116]

2.4 Cyclic (alkyl) (amino) carbene based Au(I) complexes

The special steric and electrical properties of cyclic (alkyl) (amino) carbenes, or CAACs, have made them useful tools in chemistry.[117–119] Having a quaternary carbon instead of a

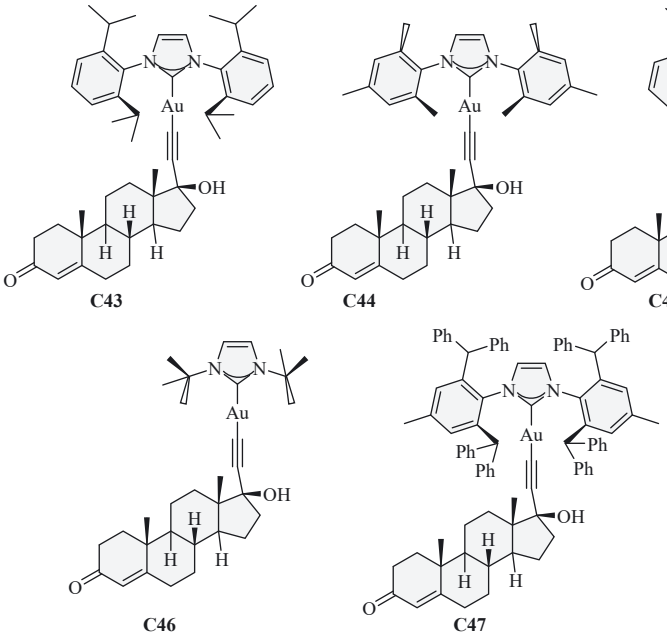

Figure 5: Structural representation of Au-steroidyl NHC complexes.

nitrogen, CAACs have a lower LUMO and a higher HOMO than *N*-heterocyclic carbenes (NHCs).[120] CAACs are extremely basic and π-acidic due to their structure.[121] CAACs are extremely basic due to their strong electron-donating properties and π-acidic due to their ability to accept electron pairs through π-bonding.[122] Developing strong pre-catalysts, producing compounds with peculiar shapes or oxidation states, and successfully isolating active catalytic intermediates are some of its advantages.[123,124] NHC analogs lack the stronger metal-carbene bonds found in CAAC-bound metal complexes, such as those containing copper, silver, and gold. This could result in less side effects and more targeted medication interactions. According to certain metal-dependent pathways, recent investigations demonstrate their efficacy as cytotoxic agents.[125] As shown in Figure 6, Gold(I) complexes (**C48–C50**) with CAAC accessory ligands were examined in detail for their potential antitumor effects *in vitro*. Considerable antitumor activity was found in complexes that were evaluated, supporting their potential as therapeutic agents. The cytotoxicity of the CAACEtH$^+$TfO$^-$ salt (**L8**) and the gold(I) complexes **C48–C50** against the human cancer cell lines HeLa, A549, HT1080, and Caov-3 was investigated. All cell lines exhibited significant antitumoral activity, with the main focus on strong effects against lung cancer cell line A549. Complex **C48** outperformed **C49**, **C50**, and the medication auranofin in terms of cytotoxicity against the A549 cell line. C48 > > C49 > Auranofin > C50 > L8 was the sequence in which the cytotoxic activity against A549 increased. The tendency for Au(I) complexes that has been seen has to do with their capacity to pass through hydrophobic barriers and mitochondrial membranes.[126] Compared to the complex **C50**, auranofin had somewhat higher activity. This suggested that, out of all the complexes studied and the reference drug, **C48** (IC_{50} = 0.07 ± 0.06 μM) is the most effective and results for their IC_{50} values enlisted in Table 1.[127] The significance of the gold core in antitumor activity is highlighted by the reduced cytotoxicity of **L8**. Because bulkier CAAC-ligands are less active than CAACEt-ligand-containing gold complexes, it is clear that hydrophilic/lipophilic balance and steric interactions are important considerations.[128]

2.5 Carbamate based Au(I) complexes

Monoanionic carbamato ligands exhibit tunable properties, exhibiting bridging, chelating, or monodentate behavior in response to their surroundings. Oxides and hydroxides of metals are formed when they combine with protic species such as water, resulting in their breakdown into amine and CO_2. Exploration of biological applications of these metals has been limited due to their quick disintegration, particularly with high-valent, oxophilic metals, which has forced handling under inert circumstances.[129,130] Because of their significant water stability and cytotoxicity, Pt (IV) complexes with axial carbamato ligands have been investigated recently as possible treatments for cancer.[131] When these complexes are activated within the cells, they release bioactive amines that are more effective than their carboxylato counterparts.[132] These results, along with the potential medical benefits of carbamates, are driving efforts to assess their antiproliferative properties and being appropriate for biological applications.[133] The compounds [Ag(O_2CNEt$_2$)] (**C51**) and [Au(O_2CNMe$_2$) (PPh_3)] (**C52**) shown in Figure 6, exhibited notable stability in aqueous solutions and noteworthy cytotoxicity *in vitro* when tested against the A549 lung cancer cell line.[134] Two reference compounds were utilized: cisplatin (CDDP) and [Au(Cl)PPh_3]. Compared to other vanadocene compounds with bidentate nitrogen ligands, vanadocene bis-carbamate exhibited a lower IC_{50} value against A549 cells, indicating a moderate level of cytotoxicity.[135] The results indicated that the complex **C40** was more effective compared to the standard drug and **C51** Pt complex. The potential of **C52** (IC_{50} = 5.4 ± 0.7 μM) as a strong anticancer agent was highlighted by the fact that its cytotoxicity was either equal to or greater than that of

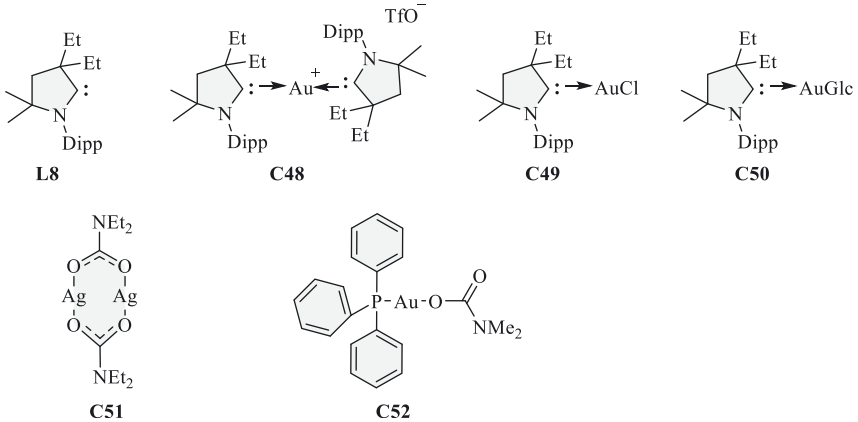

Figure 6: CAAC and carbamates-based Au(I) complexes.

other reported Au(I) triphenylphosphine complexes including chloro (triphenylphosphine)Au(I) (Table 1).[136,137]

2.6 Diphosphane based Au(I) complexes

Motivated by encouraging results from previous investigations on Au(I)-diphosphane complexes,[138,139] scientists have explored three novel gold(I)-carbene complexes (**C53–C55**) with diphosphane co-ligands (Figure 7). Based on their proven antitumor efficaciousness and their function in stabilizing gold(I) complexes, diphosphanes were selected.[140,141] By adding diphosphane ligands, these complexes become more lipophilic and stable, which improves their cellular uptake and bioavailability. Their anticancer activity is greatly enhanced, by this enhanced stability, in

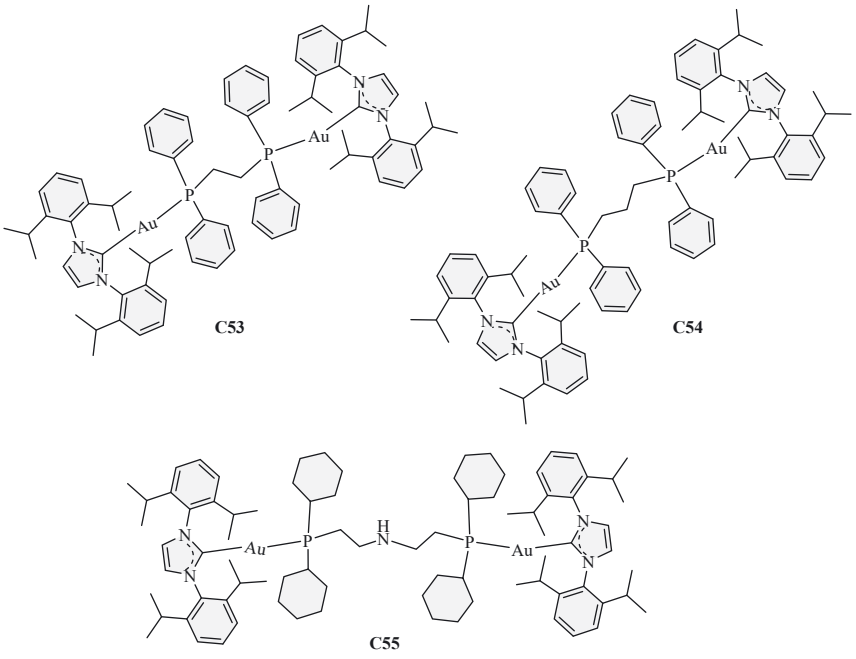

Figure 7: Structural illustration of diphosphane based Au(I) complexes.

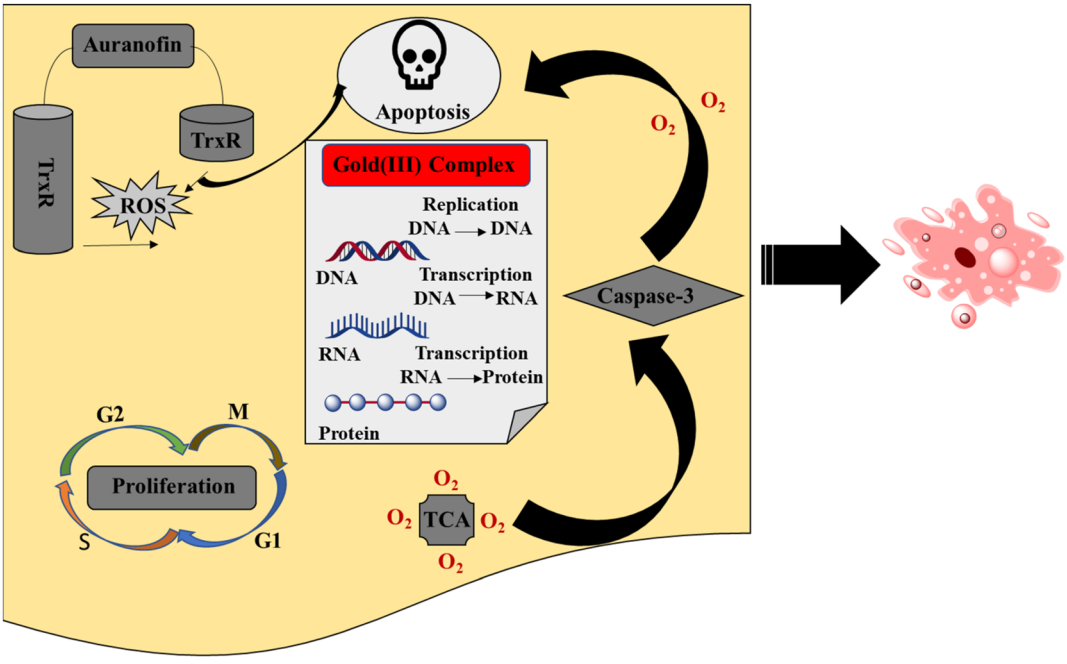

Figure 8: Schematic representation of the mechanism of action of Au(III) drug in NSCLC cells.

addition to their higher lipophilicity. The results suggested that these gold(I)-carbene-diphosphane complexes (**C53–C55**) have potential as effective cancer treatment options and demonstrate how changes in the complex's composition might affect the compounds' therapeutic potential. The cytotoxic potential of the complexes (**C53–C55**) was assessed by using cell line A549. In comparison, cisplatin used as standard with an IC_{50} value of 6.2 µM. According to IC_{50} values, all the newly synthesized complexes **C53–C55** were more potent than the standard cisplatin by possessing lower IC_{50} values in between 0.13 and 0.22 µM. However, among the complexes **C55** showed excellent cytotoxic potential than the **C53** and **C54**. The order of increasing the cytotoxic was the following; C55 > C53 > C54 > cisplatin (Table 1).[142]

3 Mechanism of action

Metal based drugs show variety of anticancer mechanisms, but their efficiency is limited due to toxicity, resistance and erratic action across cancer types. Basic mechanisms include the damage of DNA, redox modulation, inhibition of angiogenesis, and immunomodulation but optimum utilisation of these mechanisms needs deeper investigation. In NSCLC cells the visual representation of the mechanism of action of the metallodrugs is shown in the Figure 8. The protein which targets the metallodrugs such as gold(I) thiol reactive complex auranofin, an inhibitor of the selenoenzyme thioredoxin reductase (TrxR), showed cytotoxic potential by disrupting redox homeostasis during the preclinical studies. There are limitations in the clinical activity of the single agent because of the compensatory mechanism which moderate the redox effect. Efficacy of such agents can be enhanced by the addition of other stressors. For example, auranofin increased the potential of cisplatin in the lung cancer by further potentiating oxidative stress. The diverse processes like apoptosis and cell cycle arrest can also be modulated by the metallodrugs.[143]

4 Conclusions

In conclusion, the gold complexes have arisen as prominent novel frontiers in the battle to fight against lung cancer. They provide a new perspective/strategy on the treatment of this devastating disease. Limited investigations in early preclinical phases and limited *in vivo* data distinguish it as relatively recent field. Treatment efficacy of gold complexes is generally increased when different ligands are added because this increases the selectivity of compounds for cancer cells that overexpress a particular target. The potential for boosting the anticancer activity of gold(I) and gold(III) complexes has been demonstrated by the insertion of diverse ligands, including thiosemicarbazone, *N*-heterocyclic imine, *N*-heterocyclic carbenes, steroidyl NHC, carbamates, and diphosphanes. A variety of lung cancer cell lines, such as A549, H28, H2052, and MRC-5, are effectively inhibited by these modified gold complexes. The gold complexes are stabilized and their bioactivity is increased by the addition of different ligands, which makes them attractive options for targeted cancer treatment. As in this field, research continues to evolve, it is very clear that gold complexes hold marvellous potential for developing the novel, efficient therapies with the ultimate objective of translating these results into the clinical practice and enlightening patient outcomes.

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