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Functional utility of gold complexes with phosphorus donor ligands in biological systems

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ABSTRACT

Metallo-phosphines are ubiquitous in organometallic chemistry with widespread applications as catalysts in various chemical transformations, precursors for organic electronics, and chemotherapeutic agents or chemical probes. Here, we provide a comprehensive review of the exploration of the current biological applications of Au complexes bearing phosphine donor ligands. The goal is to deepen our understanding of the synthetic utility and reactivity of Au-phosphine complexes to provide insights that could lead to the design of new molecules and enhance the cross-application or repurposing of these complexes.

1. Introduction

The chemistry of Au complexes containing phosphine donor ligands has attracted interest due to their facile synthesis, unique electronic properties, diverse structural motifs, and promising applications in catalysis, material science, and chemical biology [1–7]. Au has many

Abbreviations: 5-FU, 5- fluorouracil; ACLY, ATP Citrate Lyase; ADME, Absorption, Distribution, Metabolism, and Excretion; ALDH1, Aldehyde Dehydrogenase 1; AMPK, 5′ adenosine monophosphate-activated protein kinase; AMQ, amodaquine; ATP, Adenosine triphosphate; Au, Gold; BrettPhos, 2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; CD133, Cluster of differentiation 133; CD44, Cluster of differentiation 44; COX-2, Cyclooxygenase-2 inhibitor; CQ, Chloroquine; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CRT, calreticulin; CSC, Cancer stem cell; DAPTA, 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane; Diphos, 1,2-Bis(dipyridinylphosphino)ethane; DMEM, Dulbecco's Modified Eagle Medium; DMSO, dimethylsulphoxide; DNA, Deoxyribonucleic acid; DPPBz, 1,2-bis(diphenylphosphino) benzene; DPPE, 1,2-Bis(diphenylphosphino)ethane; DPPF, 1,2-Bis(diphenylphosphino)ferrocene; DPPM, 1,2-Bis(diphenylphosphino)methane; DPPP, 1,2-Bis(diphenylphosphino)propane; DTC, Dithiocarbamate; ER, Endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase ½; ESI-MS, Electrospray ionization mass spectrometry; ESKAPE, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp; Et_3P, triethylphosphine; Et, Ethyl; FASN, Fatty acid synthase; FDA, US Food and drug Administration; GSH, Glutathione; HIV, Human Immunodeficiency virus; HPLC, High Performance Liquid Chromatography; HSP27, Heat shock protein; ICP-AES, Inductively coupled plasma atomic emission spectroscopy; JackiePhos, 2-(bis[3,5-bis(trifluoromethyl)phenyl]phosphino)-3,6-dimethoxy −2′,4′,6′-triisopropyl-1,1′-biphenyl; JNK, c-Jun NH2-Terminal Kinase; LD50, Lethal dose; LTEP, Local Tolman electronic parameter; Me, Methyl; Mes, Mesityl; MCTSs, multicellular tumor spheroids; MFF, Mitochondrial fission factor; MFN1, Mitofusin1; MLEP, Metal-ligand electronic parameter; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NHC, N-heterocyclic carbenes; NOTCH1, Neurogenic locus notch homolog protein 1; NSAIDs, non-steroidal anti-inflammatory drugs; N-XantPhos, 4,6-bis(diphenylphosphino)-10*H*-phenoxazine; OCR, Oxygen consumption rate; OPA1, optic atrophy type 1; OXPHOS, Oxidative phosphorylation; $P(t\text{-}Bu)_3$, Tri-tert-butylphosphine; PBMC, peripheral blood mononuclear cell; PBS, Phosphate buffer saline; PCR, Polymerase chain reaction; Pd, Palladium; PGE2, Prostaglandin E2; PPh_3, triphenylphosphine; Pr, propyl; PR_3, Phosphine ligands; Pt, Platinum; PTA, 1,3,5-triaza-7-phosphaadamantane; R,R-MeDuPhos, 1,2-tis[(2*R*,5*R*)-2,5-dimethylphospholano] benzene; R,R-QuinoxP®, (*R*,*R*)-2,3-bis(tert-butylmethylphosphino)quinoxaline; rac-BINAP, (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SAR, Structure activity relationship; SGlu, thioglucose; $SAcGlu_4$, thiotetraacetylated glucopyranose; SMan, thiomannose; SAcMan, thiotetraacetylated mannopyranose; SeSC, seleno thiosemicarbazonato; SI, Selectivity index; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; SREBF1, sterol regulatory element binding transcription factor 1; TEP, Tolman electronic parameter; THP, tris(hydroxymethyl)phosphane; TNBCs, triple negative breast cancer cells; TOM20, translocase of outer mitochondrial membrane 20; TPPTS, triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt; TrxR, thioredoxin reductase; TSC, thiosemicarbazonato; UPS, ubiquitin-proteasome system; V_{bur}, Buried volume; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

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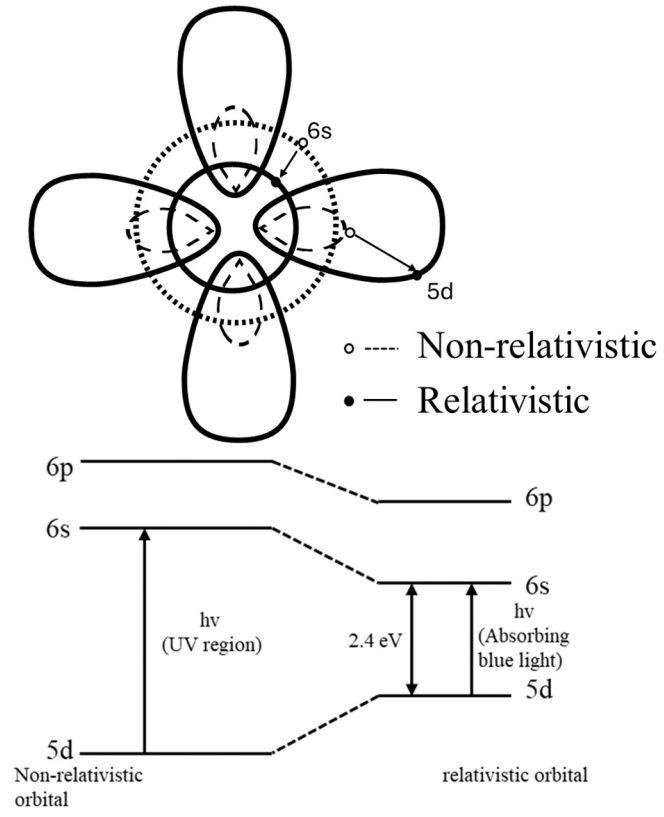


Fig. 1. A. Orbital diagram showing relativistic effect on the s and d orbitals of Au. B. Relative energy levels for Au non-relativistic (left) and relativistic (right). Modified with permission from Refs [12,21]. Copyright 2015, 2023 Elsevier.

unique properties, which can been explained by the relativistic effect [8–11]. Relativistic effect is characterized by anomalous chemical properties usually observed in heavier atoms on the periodic table [12]. According to Einstein's theory of relativity, the mass (m) of a moving particle increases with the increase of its velocity (v) compared to its rest mass (m_0) [12–14]. In heavier atoms such as Au, there is an increase in atomic nuclear charge (Z), which leads to increase in the velocity of electrons that penetrate to the nucleus (the 6s electrons) and subsequent increase in mass. This increase leads to smaller orbitals for 6s electrons and shielding of the nuclear charge from other electrons in the 5d and 4f subshell with larger orbitals (Fig. 1).

Relativistic effect of Au results in the stabilization of its 6s orbital with Au having the highest electronegativity (E.N = 2.54) among metals and situating Au complexes as thermodynamically metastable to reduction to elemental Au [10]. Furthermore, the electrochemical potential of Au is highly positive ($Au^{1+}/Au E^o$ = 1.69 V, Au^{3+}/Au^+ E^0 = 1.41 V, Au^{3+}/Au = 1.5 V) compared to other transition metals Ta^{3+}/Ta E^o = −0.6 V, W^{3+}/W = 0.1 V, Re^{3+}/Re = 0.5 V, Os^{3+}/Os = 0.9 V, Ir^{3+}/Ir = 1.0, Pt^{2+}/Pt = 1.18 V, Hg^{2+}/Hg = 0.648 V, Ag^{1+}/Ag E^o = 0.8 V, Cu^{1+}/Cu E^o = 0.52 V, Cu^{2+}/Cu^{1+} E^o = 0.34 V [15–20] this means that gold complexes in any oxidation state can be easily reduced to elemental Au when a reducing agent is present. Also, the stable electronic configuration of Au ([Xe] $6s^1 4f^{14} 5d^{10}$) with a full d orbital and half-filled s orbital limited its reactivity and Au chemistry has been under-explored until recently where different ligands have been used to tune the reactivity of Au.

1.1. Chemistry of phosphine metal complexes

Concerted ligand to metal σ-donation and metal to ligand π-back donation for transition metals also known as Dewar-Chatt-Duncanson model describes the interactions occurring between transition metal d-orbital and a donor ligand. Phosphines are neutral σ-donor ligands donating their lone pair of electrons to the empty d orbital in transition metals, they could also act as π-acceptor ligands (π-acids) depending on the nature of R-groups on the phosphine. Alkyl R-groups has the lowest π-acidity compared to alkoxy or aryl groups (Fig. 2) [22,23].

Phosphines such as triphenylphosphine (PPh_3), triethylphosphine, 1,2-bis(diphenylphosphino) benzene (DPPBz), phosphaadamantane (Fig. 3) and its derivatives exhibit strong affinity toward metal atoms, forming stable coordination complexes with distinct coordination geometries, reactivity profiles, and applications [24–26]. Moreover, the ability to tune the electronic and steric properties of phosphine ligands during its synthesis has contributed to their development as effective ligands in chemistry, while their multifaceted applications especially in coupling reactions have resulted in more diverse and complex phosphines. However, many phosphines can oxidize easily in air and are required to be handled in an inert atmosphere, yet phosphines such as triphenylphosphine (PPh_3), 1,2-Bis(diphenylphosphino)benzene (DPPBz) are air stable. Whereas primary phosphines are generally considered air sensitive, inclusion of bulkier groups, alkyl spacer groups, extended π-conjugation and heteroatoms have been proposed to confer stability on phosphines [27–30]. Also, phosphines can be categorized based on the nature of groups attached to it as homoleptic phosphines containing similar groups on the phosphorus atom (e.g PPh_3, DPPBz), heteroleptic phosphines containing different groups on the phosphorus atom (e.g 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos)), and asymmetric (P-chiral) phosphines (e.g 1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene (R,R-MeDuPhos), (*R*,*R*)-2,3-Bis(tert-butylmethylphosphino)quinoxaline (R,R-QuinoxP)®) [31]. They can also be classified as monodentate, bidentate and polydentate phosphines (Figs. 3 and 4) based on the number of phosphorus atoms and/or chelating ability of the phosphine.

Metallo-phosphines are ubiquitous in organometallic chemistry with widespread applications as catalysts in various chemical transformations, precursor for organic electronics, and as chemotherapeutic agents or probes in medicine [1,6,32–38]. The first reported synthesis of metallo-phosphines was the synthesis of Pd, Pt and Au complexes bearing tertiary phosphine ligands in the late 19th century by Cahours and Gal [39–41]. While Cahours and Gal identified bis(triethylphosphine)dichloroplatinum(II) as β and α isomers, the advent of Werners theory of coordination complexes and other spectroscopic methods ensured the complexes were given the correct nomenclature as cis (β)

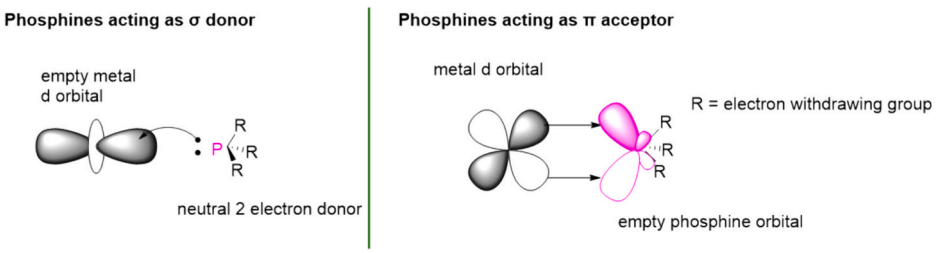


Fig. 2. Bonding in phosphines.

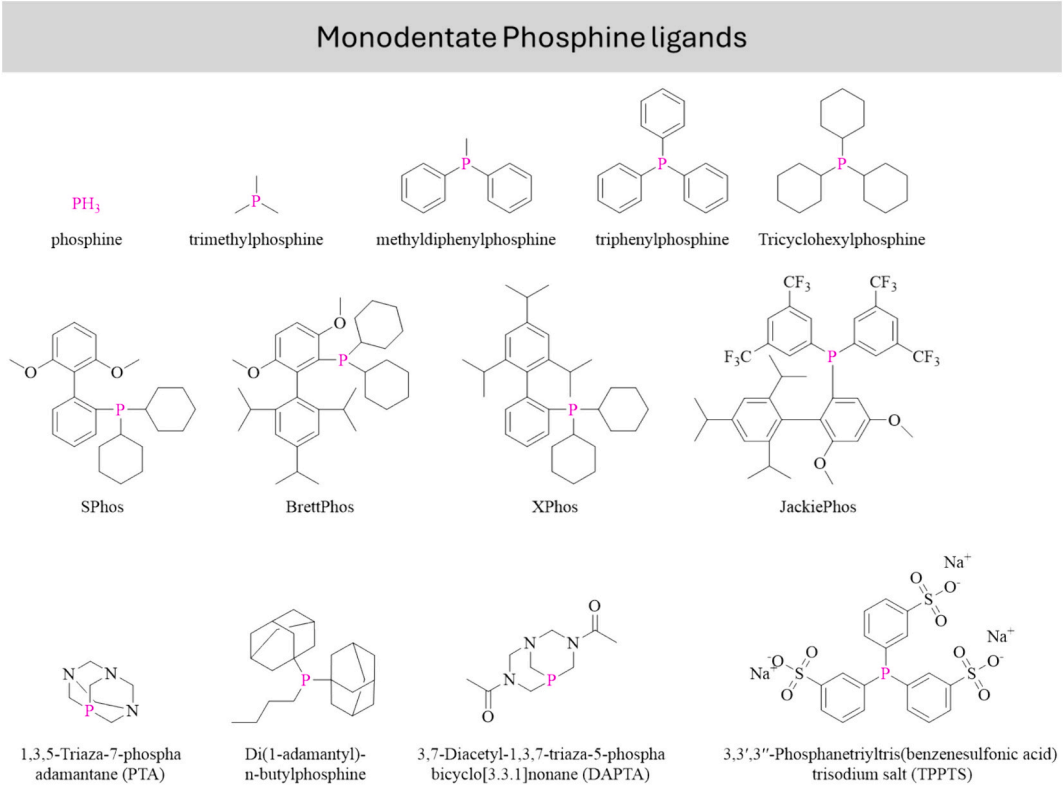


Fig. 3. Examples of monodentate phosphine ligands used in organometallic chemistry.

and trans (α) isomers. Mann et al., later reported on the synthesis of a vast number of metallo-phosphines and investigated the nature of the bond between phosphorus and the metal in the complex [42–46]. Also, research by Jensen et al., determined the dipole moments of phosphine and arsine metal complexes thereby assigning the correct cis/trans isomer to previously synthesized complexes [47,48] and Chatt who trained under Mann further synthesized a variety of tertiary metallo-phosphines and studied the importance of phosphines in bringing complex chemistry out of aqueous solutions into organic solvents [49–53]. These works further revolutionize the field with widespread applications as hydrogenation and carbonylation catalysts, alkene and alkyne functionalization reactions, stimuli responsive materials, biological probes and drugs in medicine [54,55].

1.1.1. Factors that dictate structure activity relationship (SAR) in phosphine-metal bonds

Changes in the chemical structure of phosphine ligands affect the coordination, stability and biological reactivities of the resulting Au complexes and a detailed SAR studies of phosphinogold complexes can give valuable insights into the design of phosphine ligands and hence their Au complexes for the synthesis of next generation of biologically potent Au drugs. Over the past four decades immense research has been carried out to understand the electron donor-acceptor properties of phosphorus ligands. Earlier work by Strohmeier and Müller studied some monosubstituted metal carbonyls with phosphorus ligands (PR_3) and ranked the relative π-acceptor strength of the phosphorus ligands from the changes in the valence vibration band vC-O [56]. More prominent work by Chad Tolman in the 1970s showed that electronic and steric effects can cause marked changes in the behaviour of phosphines, the electronic parameters (ν) were effectively determined by an infrared method by computing the electron donor-acceptor properties of PR_3 based on measuring the A_1 carbonyl stretching frequency of 0.05 M solution of $Ni(CO)_3L$ (L = PR_3) in CH_2Cl_2 (Fig. 5). In his experiment, Tolman proposed the substituent additivity rule for the $Ni(CO)_3PR_3$ complexes, where the A_1 of a complex was the summation of the contributions of the different R-groups (Xi) on the phosphine ligand. Tri-tert-butylphosphine ($P(t\text{-}Bu)_3$) with frequency of 2056.1 cm^{-1} was the most basic of the compounds studied with Xi = 0. The A_1 of the other complexes were determined based of the $P(t\text{-}Bu)_3$ reference from the equation below [57].

$$\nu CO\ (A_1) = 2056.1 + \sum_{i=1}^{3} Xi$$

Also, the steric parameters was determined from the cone angle (Θ) defined by angle formed by the metal atom at the base of a cone and the two farthest atoms on the ligand and this provides a measure of the steric demand of the ligand [57–59]. He and others later summarized this findings on the effect of increasing the size of substituents on phosphorus in an extensive review [58].

With advancement in computational studies, the Tolman electronic parameter (TEP) has been revisited and modified by various authors [59–63]. The key arguments are the observed mode-mode coupling between CO and M–C stretching vibrations that leads to coupling errors and the oversimplified M-L bond strength described by Tolman. This has led to authors postulating newer models such as the decoupled (local) CO stretching frequency as a local TEP (LTEP) and metal–ligand electronic parameter (MLEP) to correct these anomalies [59,61,62]. The electronic and steric parameters for metal-monophosphines have been widely studied but only few reports on bisphosphine ligands have been established. Phosphorus-Metal-Phosphorus bite angle (P-M-P) has been the ligand parameter studied for various bisphosphine ligands used in catalysis [64,65]. It should be noted that while the effect of electronic parameter have been widely studied in the field of catalysis, there are few reports that correlates the electronic parameters to biological functions of phosphine metal complexes.

The effect of phosphine substituents on gold complexes have been described both theoretically and in biological systems. Rosch and Haberlen described this effect using the scalar-relativistic version of the

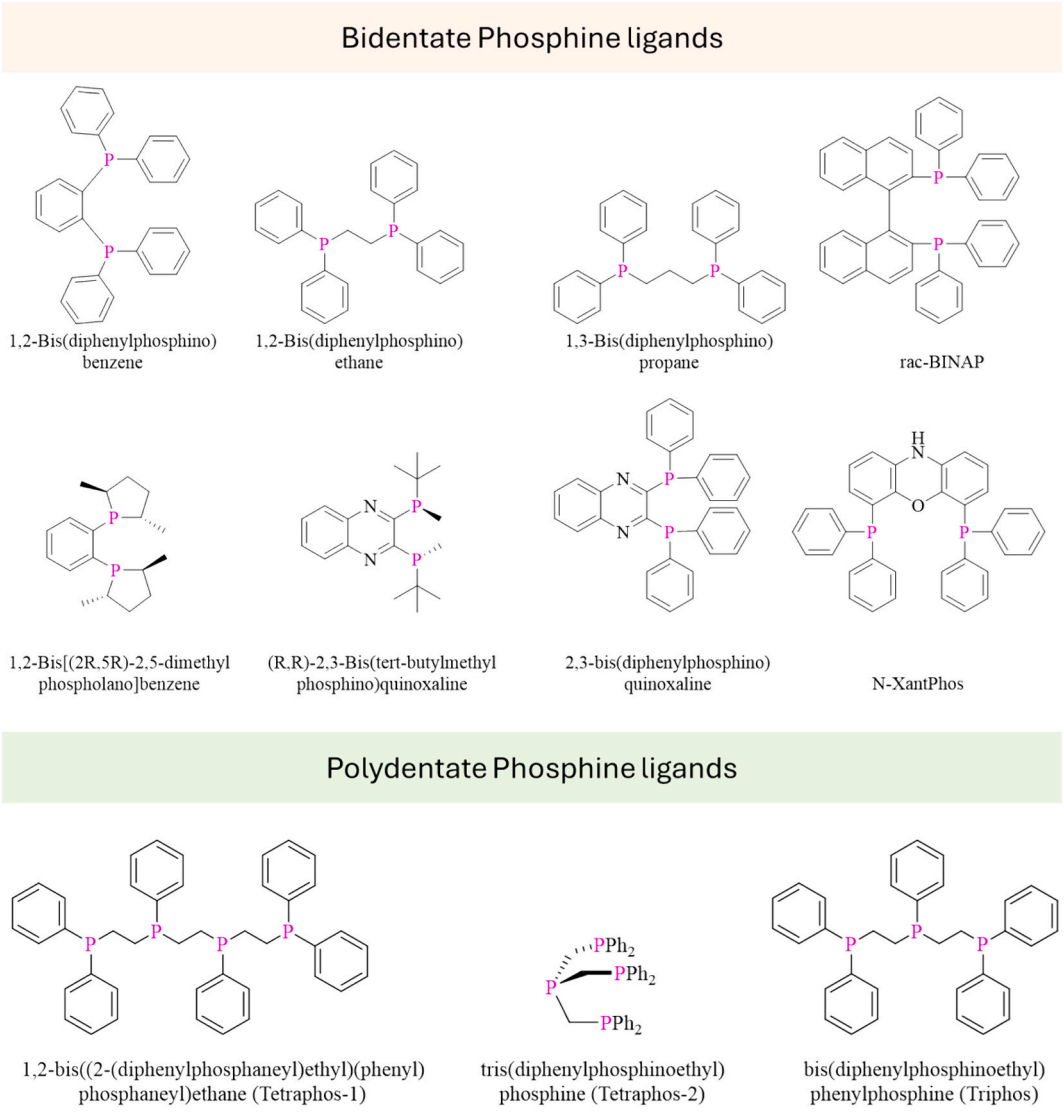


Fig. 4. Examples of bidentate and Polydentate phosphine ligands used in organometallic chemistry.

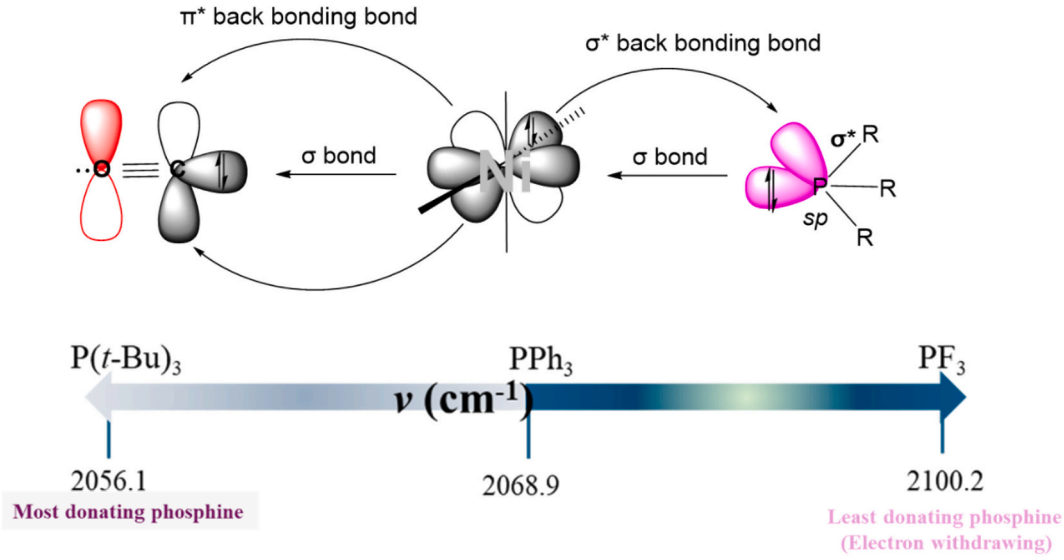
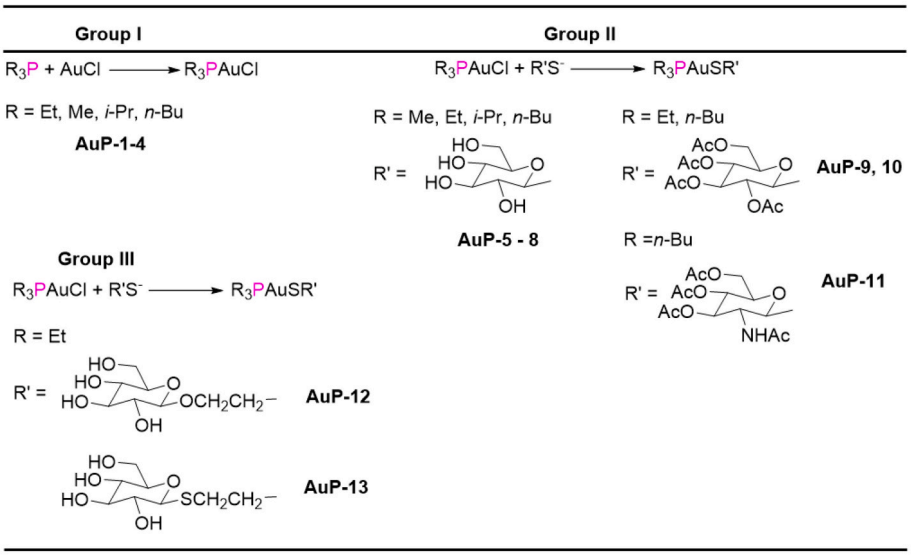


Fig. 5. Tolman electronic parameter based on changes in the valence vibration band *ν*C-O.

Table 1
Synthesis of anti-arthritic Au(I) phosphine complexes.



N.B. AuCl was prepared in situ by the reduction of $HAuCl_4 \bullet 3H_2O$ with $S(CH_2CH_2OH)_2$ (thiodiglycol).

linear combination of Gaussian-type orbitals (LCGTO) local density functional (LDF) on three Au(I) complexes $MeAuPR_3$ (R = H, Me, Ph). This model ensures the treatment of all electrons in the molecule. Results from the spectroscopic constant indicates a monotonic decrease in the ionization potential from 9.10 eV for $MeAuPMe_3$ to 8.13 eV for $MeAuPPh_3$ which aligns with the increasing electron donating activity of the ligands [66]. Furthermore, Dos Santos et al., studied the role of phosphine auxiliary ligands on the stability and redox behaviour of two classes of Au(III) complexes $[Au(C\text{-}N\text{-}C)PR_3]^+$ (C-N-C = 2,6-diphenylpyridine) and $[Au(N{-}N{-}N)PR_3]^{3+}$ (N-N-*N* = 2,2′:6′,2″-terpyridine) where PR_3 = phosphine ligand. The stability of these anticancer Au(III) complexes was influenced by the electronic properties of the phosphine ligands, complexes with strong σ-donor phosphine substituent and buried volume ($\%V_{bur}$ 32.8–41.6 %) destabilizes $[Au(C\text{-}N\text{-}C)PR_3]^+$ complexes. Furthermore, complexes with *t*-But and cyclohexyl R-groups, caused a large torsion of the N-Au-P bond angle that also contributes to facilitate the reduction of Au(III) complexes [67].

While this work will not attempt to postulate a model, we will review the biological applications of Au complexes with phosphine donor ligands as potential drugs and highlight examples where structure-activity relationships have aided their design as a general introduction to this review.

1.2. Evolution of Au phosphine in biology

The medicinal application of Au compounds can be traced back to 5000 B·C in many ancient culture like Egypt, India and China and its use was popularized during the late Middle Age and Renaissance [68–70]. The search for an improved therapy specific to treatment of rheumatoid arthritis in the 1960s to early 1970s fostered the birth of Au phosphine biology. Earlier studies have demonstrated the utility of chrysotherapy in the remission of the disease in both juvenile and adult forms with parenterally administered Au drugs aurothioglucose and aurothiomalate leading the way, yet there was the need for improved therapy with oral route of administration. Findings by researchers at Smith Kline and French Laboratories Philadelphia, Pennsylvania in 1972 on the anti-arthritic properties of 13 Au complexes with phosphine donor ligands **Table 1** [71] that led to the discovery and approval of auranofin by FDA in 1985 propelled further studies on Au complexes with phosphine donor ligands in different disease indications [72–74].

These linear 2-coordinate Au compounds showed a high degree of lipophilicity with promising anti-arthritic activity when administered orally to adjuvant arthritic rat at low therapeutic dosage. **Tables 1** and **2** shows the synthetic route and anti-arthritic activity of 13 Au phosphine compounds Class 1 compounds include compounds without a thiosugar and different phosphine alkyl groups while Class 2 and 3 includes compounds with different phosphine alkyl and thiosugar or oxosugar. The Au phosphine complexes showed significant plasma Au absorption and the degree of arthritis prevention in adjuvant arthritic rat correlate well with the degree of serum Au concentration and the nature of the phosphine ligand attached to the complex. In Class 1 compounds, the therapeutic effect and serum Au concentration decreases with increase in alkyl chain length except for AuP-1 with triethyl phosphine (Et_3P). In fact, as seen in Table 2, complexes with Et_3P (AuP-1, AuP- 6, AuP-9, AuP-12, AuP-13) showed the highest serum Au concentration and therapeutic efficacy, and the non-phosphine groups have less effect in dictating Au concentration and anti-arthritic activity. Overall, AuP-9 (auranofin) with oral LD_{50} dose of 265 (190.6–368.4) mg/kg was advanced for further clinical studies due to in vivo tolerability and it was approved by FDA in 1985 [71]. Auranofin stands out not just as an orally administered drug compared to the earlier injectable Au formulation such as sodium Au thiomalate and Au thioglucose but auranofin is also highly lipophilic with a slight net charge in solution and reacts less strongly with sulfhydryl groups [71,75].

The potent anti-inflammatory properties of auranofin have led to studies aimed at repurposing the drug with 14 clinical trials on auranofin in different diseased conditions including tuberculosis, combination regimen for rheumatoid arthritis, HIV, giardia and cancer [72,75–92]. Lorber et al., demonstrated the antitumor activity of auranofin in vitro and in vivo in HeLa cells and P388 leukemia-bearing mice [93–95], Mirabelli et al., also reported on the antitumor activities of auranofin and its analogues in both B12 melanoma cells and P388 leukemia cells [96,97].

Numerous researchers have studied the mechanism of action of auranofin in rheumatoid arthritis and other diseases [98]. Key finding involves inhibition of key enzymes such as thioredoxin reductase (TrxR) which protects cells from oxidative stress thereby maintaining intracellular ROS levels and modulation of immune cell functions (macrophages and T-cells) [99–102]. Earlier studies showed that auranofin affects polymorphonuclear cells and monocytes at lower concentrations and generally affects humoral and cell-mediated immunity [99]. In a study by Yamashita et al., where auranofin was administered to rat

Table 2
Anti-arthritic activity and plasma Au concentration of Au(I) phosphines.

		Hind-leg vol% redness from adj control[a]			
		Injected leg		Uninjected leg	
Compd	Dose, mg/kg per day, calcd as Au	Day 3	Day 16	Day 16	Au, μg/mL of serum
Class 1, R_3PAuCl					
AuP-1	10	14.38[c]	23.25[d]	36.60[c]	5.38
AuP-2	10	9.59[c]	e	e	1.66
	[b]	24.60[d]	19.47[d]	32.33	
AuP-3	10	14.73[c]	15.79[c]	33.33[c]	3.49
AuP-4	10	19.86 [d]	[e]	[e]	0.92
Class 2, R_3PAuSR`					
AuP-5	10	14.45[c]	15.96[f]	[e]	2.3
AuP-6	20	27.22[d]	22.44[d]	44.48[d]	6.92
	b	25.79[d]	23.11[d]	42.33[d]	
	10	16.88[d]	[e]	27.20[c]	4.13
	b	39.38[d]	32.82[d]	54.12[d]	
	5	11.25[f]	20.70c	34.06[d]	3.53
	b	39.38[d]	32.82[d]	54.12[d]	
AuP-7	10	18.24[d]	15.35[f]	15.76[f]	[h]
	b	35.50[d]	41.93[d]	47.23[d]	
	5	[e]	[e]	[e]	1.63
	b	23.47[d]	36.75[d]	38.60[f]	
AuP-8	20	e			[g]
	b	25.79[d]	23.11[d]	42.33[d]	
	10	28.44[d]	[e]	[e]	1.15
	b	39.38[d]	32.82[d]	54.12[d]	
	5	[e]	[e]	[e]	0.92
	b	39.38[d]	32.82[d]	54.12[d]	
AuP-9	20	33.81[d]	23.11[d]	55.21[d]	7.89
	b	25.79d	23.11[d]	42.33[d]	
	10	30.00[d]	29.74[d]	44.51[d]	4.11
	b	39.38[d]	32.82[d]	54.12[d]	
	5	30.00[d]	e	e	2.95
	b	39.38[d]	32.82[d]	54.12[d]	
AuP-10	20	26.07[d]	18.66[c]	36.20[f]	2.04
	b	25.79d	23.11[d]	42.33[d]	
	10	19.38[c]	e	e	1.25
	b	39.38[d]	32.82[d]	54.12[d]	
	5	[e]	[e]	[e]	1.24
	b	39.38[d]	32.82[d]	54.12[d]	
AuP-11	20	30.09[d]	15.11[f]	30.37[d]	1.70
	b	25.79[d]	23.11[d]	42.33[d]	
	10	21.88[d]	e	e	1.08
	b	39.38[d]	32.82[d]	54.12[d]	
	5	26.25[d]	[e]	[e]	1.15
	b	39.38[d]	32.82[d]	54.12[d]	
Class 3					
AuP-12	10	9.59[f]	27.19[d]	33.99[c]	4.8
AuP-13	10	17.47[d]	30.04[d]	44.44[d]	5.7

[a] % redn from adj control = (hind-leg vol of untreated adj control rat - hind-leg vol of treated control rat)/hind-leg vol of untreated adj control rat. Untreated non-adj-control hind-leg vol approximates a 50 % redn from that of adj control rat.
[b] Prednisolone treated, 20 mg/kg per day.
[c] $0.001 < P < 0.01$.
[d] $p < 0.001$.
[e] No significant redn in paw vol.
[f] $0.01 < p < 0.05$.
[g] All animals died by day 16.
[h] Au content not detd.

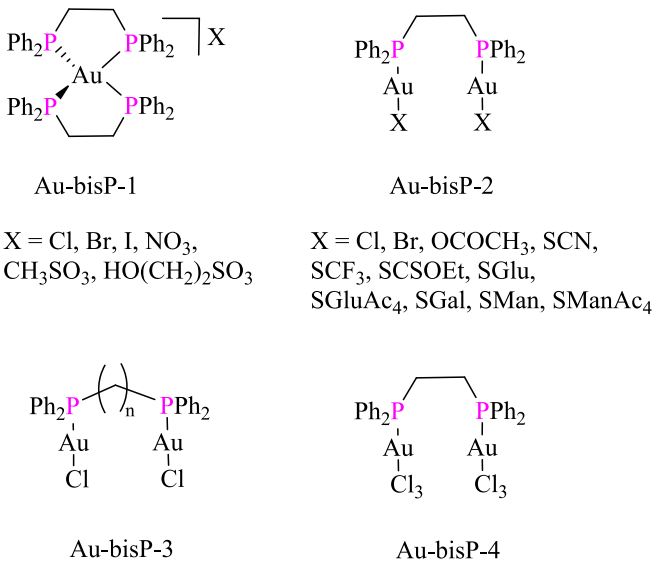


Fig. 6. Structures of bis-chelated Au(I/III) phosphine complexes.

stimulated and non-stimulated peritoneal macrophages, auranofin significantly inhibited the production of prostaglandin E2 (PGE_2) in the former while inducing the production of PGE_2 in the non-stimulated group within 4 h. Further studies in rat peritoneal macrophages showed that auranofin increased COX-1-dependent PGE_2 production, but markedly decreased COX-2-dependent PGE_2 production [101,102]. Other mechanism of action reported include inhibition of the ubiquitin-proteasome system (UPS), reduction of pro-inflammatory cytokines, inhibition of NF-κB, induction of apoptosis, and disruption of mitochondrial function [98,103–106]. These combined effects contribute to its therapeutic efficacy in treating rheumatoid arthritis and other inflammatory conditions.

Despite the notable efficacy of auranofin in the treatment of rheumatoid arthritis, some adverse effects attributed to long term use in chronic patient have limited its application. Gastrointestinal problems are the most common adverse effect with about 40 % of patient reported to have loose stools in the early months while about 5 % of patient reported watery diarrhoea. Other reported adverse effects include conjunctivitis, proteinuria, interstitial fibrosis, kidney problems, abdominal cramping and skin rashes which occur in about 20 % of patients [72,107–109].

Whereas early research into the biology of auranofin and its monophosphine derivatives were burgeoning, there were ongoing research into the antitumoral activities of Au-bisphosphine complexes. These studies were published in series of publications from Peter Sadler, Susan Berners-Price at University of London and researchers from Smith Kline and French Laboratories Philadelphia [110–114]. They synthesized various bis-chelated Au(I/III) phosphine complexes (Fig. 6) that were more active than auranofin in B16 melanoma cancer cells and P388 leukemia cancer cells. Also, these bis-chelated cytotoxic Au phosphines showed distinct mechanism of action by inhibiting mitochondria functions in cancer cells. Their SAR studies involve varying the counterions and varying the dynamics of chelate ring. The chelate ring was perturbed either by fluorination, increasing the bridge length between two P centres or by reducing the lipophilicity of the bisphosphine ligand. Although variation to the counterion did not significantly impact cytotoxicity, varying the dynamics of the chelate rings affected the cytotoxicity and selectivity of the compounds to normal and cancer cells [111].

The success recorded by auranofin in rheumatoid arthritis, followed by promising result of bisphosphine Au(I/III) provided impetus for chemist to further study the synthesis, geometry [113,115], anti-inflammatory [116], antimicrobial [90], antidiabetic [117] and

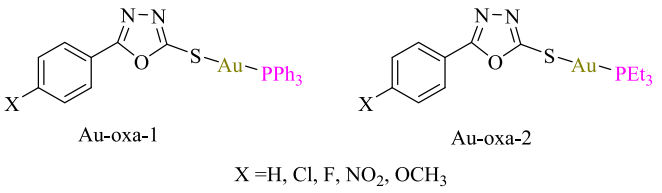


Fig. 7. Structures of Au(I) antileshmanials.

anticancer [111,112,118] activities of Au phosphines.

1.3. Therapeutic Au phosphine complexes

1.3.1. Antiparasitic

The search for novel drugs to combat parasitic infection is a major concern globally. About 3.5 billion people are affected by intestinal parasitic infection globally with over 200,000 reported deaths yearly [119]. With this rising number, there is the need for newer drug treatment regime to combat parasitic infections. The antiparasitic potential of auranofin has been investigated and the inhibition of key biological enzymes in vitro and in vivo antiparasitic studies has been demonstrated [120–122]. Leishmaniasis is a tropical parasitic disease caused by protozoans of the genus *Leishmania* and phosphinogold compounds including auranofin have been studied as a treatment option for the disease. Auranofin showed 100 % inhibition of *Leishmania infantum and Leishmania major* promastigotes at 50 μM while causing 41 % reduction of thioredoxin reductase in *Leishmania infantum* at 100 nM auranofin treatment [123,124]. de Almedia and co-workers studied the antileishmanial activities of some Au(I) complexes containing phosphine and 5-phenyl-1,3,4-oxadiazole-2-thione derivatives as ligands (Fig. 7). The complexes were potent against the promastigote (IC_{50} = 1.94–11 μM) and intracellular amastigotes forms of L. *infantum, L. braziliensis* (1 μM) and presented high selectivity index (SI) values compared to treated THP-1 macrophages [125]. These studies shows the prospect of phosphinogold compounds as antileishmanial drug.

Entamoeba histolytica is a protozoan that causes amoebiasis and it affects about 48 million people with about 54,000 deaths yearly. Stage 1 clinical studies with auranofin focusing on pharmacokinetics and safety profile in 15 healthy volunteers indicates the safety of auranofin with no significant adverse effect or death recorded at 7 days of drug administration [82,120]. Auranofin have also been studied as a treatment option for patients with toxoplasmosis. Toxoplasmosis is a tropical disease that affects immunocompromised people leading to neurological and ocular diseases. Auranofin inhibits invasion of host cell by *T. gondii's* through induction of apoptosis during the extracellular stages of the parasite [82,126].

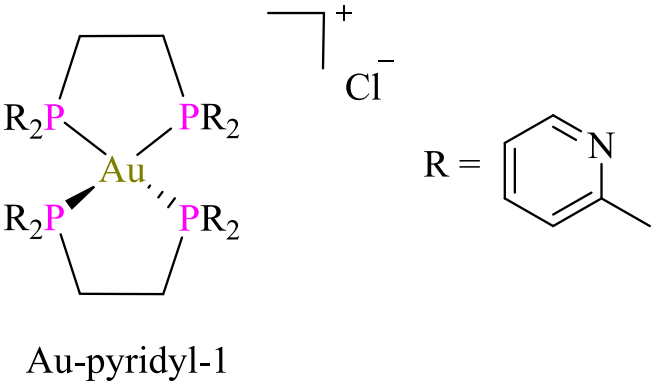


Fig. 10. Structure of bis-chelated Au(I) 2-pyridyl phosphine complex.

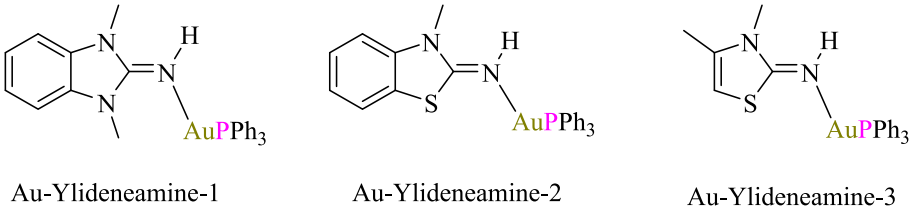


Fig. 8. Antimalarial Au(I) phosphine complexes containing ylideneamine functionalized NHC.

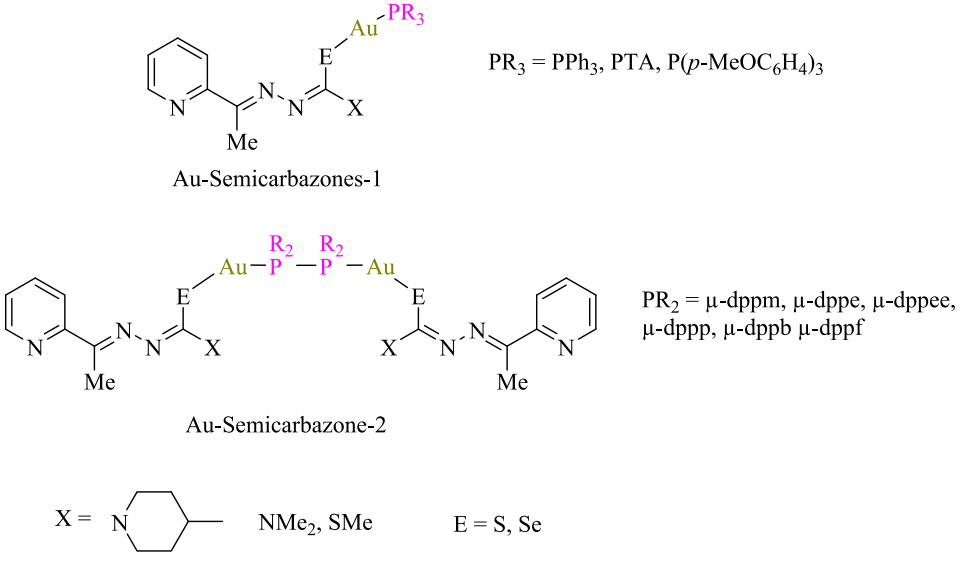
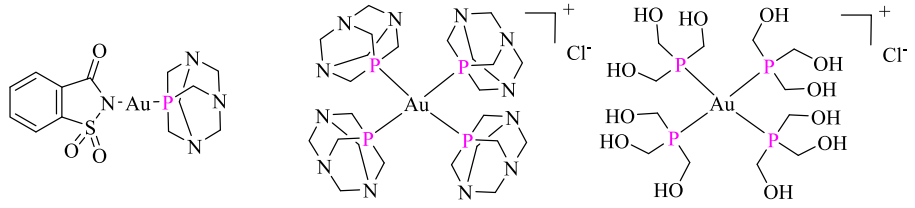


Fig. 9. Mono- and dinuclear Au(I) phosphine containing seleno- and thiosemicarbazonato ligands.

A.

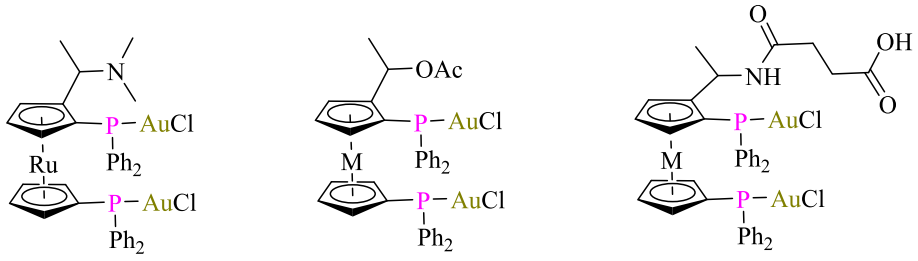


Au-PTA-1 Au-PTA-2 Au-THP-1

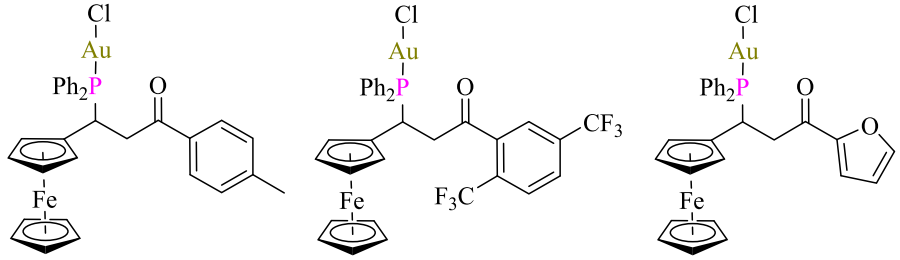
B.

	% Inhibition of Fp2	IC_{50} (μM) *P. falciparum*
Au-PTA-1	24 ± 7	5.16 ± 0.14
Auranofin	30 ± 7	0.142 ± 0.003

Fig. 11. A. Structure of Au-PTA, Au-THP, auranofin B. Au-PTA, and auranofin % inhibition of falcipain and IC_{50} (μM) in *P. falciparum.*

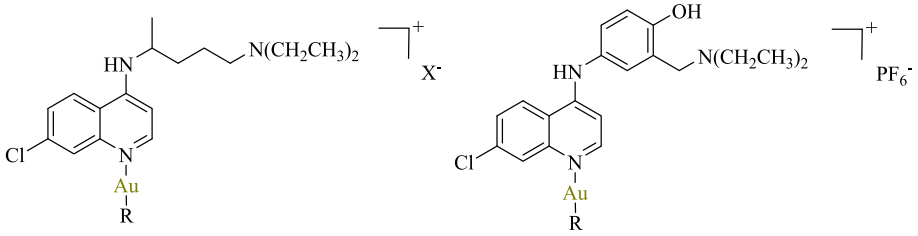


Fc-Au-P-1 M = Fe, Fc-Au-P-2 Ru, Fc-Au-P-3 M = Fe, Fc-Au-P-4 Ru, Fc-Au-P-5



Fc-Au-P-6 Fc-Au-P-7 Fc-Au-P-8

Fig. 12. Antimalarial Au-phosphine conjugated metallocenes.



CQ-Au-P AMQ-Au-P

R = PPh_3, PMe_3, PEt_3

X = PF_6, NO_3,

Fig. 13. Known antimalarials conjugated to Au phosphines.

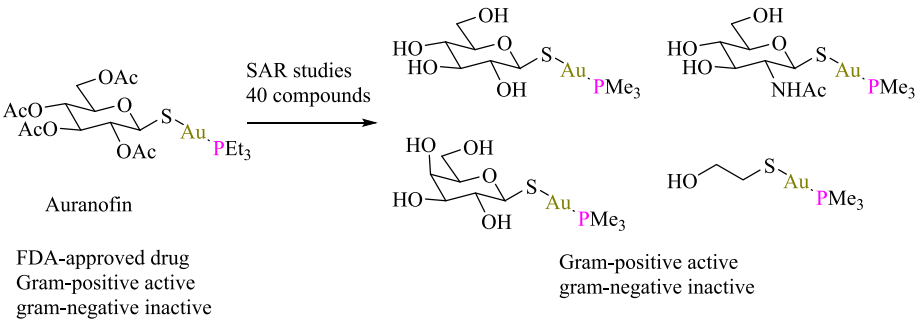


Fig. 14. Antimicrobial activity of auranofin and its derivatives against ESKAPE pathogens.

Table 3
Minimum inhibitory concentration (μg/mL) of auranofin, vancomycin and metronidazole against different strains of *C. difficile*.

C. difficile Strain	ID number	Auranofin	Vancomycin	Metronidazole
P2	NR-32883	0.5	0.25	0.06
P3	NR-32884	4	1	0.25
P4	NR-32889	1	2	0.125
P5	NR-32885	0.5	1	0.125
P6	NR-32886	2	1	0.125
P7	NR-32887	0.5	1	0.125
P8	NR-32888	1	0.5	0.125
P13	NR-32891	1	0.5	0.125
P15	NR-32892	1	0.5	0.06
P19	NR-32895	1	1	0.25
P20	NR-32896	4	1	0.25
P21	NR-32897	1	0.25	0.125
P29	NR-32903	1	0.25	0.06
P30	NR-32904	1	0.5	0.25
Isolate 1	NR-13427	1	1	0.25
Isolate 2	NR-13428	1	1	0.06
Isolate 4	NR-13430	2	0.25	0.06
Isolate 5	NR-13431	2	0.5	0.25
Isolate 6	NR-13432	1	0.5	0.125
Isolate 7	NR-13433	0.5	0.5	0.25
Isolate 9	NR-13435	0.25	0.5	0.06
Isolate 10	NR-13436	1	0.5	0.125
Isolate 11	NR-13437	2	1	0.25
Isolate 13	NR-13553	4	1	0.25
NAP07	HM-88	1	0.5	0.25
002-P50–2011	HM-746	0.25	0.25	0.125
ATCC 700057	VPI 11186	1	0.5	0.25
ATCC 43598	1470	0.5	0.5	0.25
ATCC BAA 1801	3232	1	0.5	0.125
ATCC BAA 1870	4118	0.5	1	0.25
Isolate 20,100,502	NR-49277	0.25	0.5	0.125
Isolate 20,100,207	NR-49278	0.25	0.25	1
Isolate 20,110,052	NR-49281	0.25	0.25	0.125
Isolate 20,110,868	NR-49287	0.25	0.25	0.25
Isolate 20,110,870	NR-49288	0.5	0.5	0.25
Isolate 20,110,979	NR-49285	0.25	0.25	0.25
Isolate 20,110,999	NR-49286	0.25	0.25	0.25
Isolate 20,120,013	NR-49283	0.25	0.25	0.125
Isolate 20,120,184	NR-49289	0.5	0.25	0.25
Isolate 20,120,187	NR-49290	0.5	0.5	0.25
Isolate 20,120,236	NR-49291	0.25	0.5	0.25
MIC_{50}		1	0.5	0.25
MIC_{90}		2	1	0.25

Malaria is another parasitic disease affecting millions of people. The disease is transmitted when a female anopheles mosquitoes carrying the plasmodium parasite bites a person and transmit the parasite [127]. Current antimalarial drugs include chloroquine (CQ), artesunate-amodiaquine, while patients with resistant strains are treated with artemether-lumefantrine, quinine plus clindamycin, or mefloquine [128–132]. Yet, there is a need for improvement in medication as newer plasmodium strains that are resistant to current therapy emerges. Coetzee et al., reported some ylideneamine-functionalized heterocyclic carbenes coordinated through the imine nitrogen to Au-phosphine (Fig. 8). These complexes showed lower antimalarial activity against 3D7 strain compared to chloroquine with low selectivity index, indicating the need for further structural modification for improved activity for this class of compounds [133].

Another work by Molter et al., reported mono and dinuclear Au(I) phosphine complexes containing seleno- (SeSC) and thio-semicarbazonato (TSC) ligands (Fig. 9). These complexes were characterized by NMR spectroscopy and three isomers were observed (*Z*, *E* and *EZ*), however in solid state only the *EZ* isomer was observed. The complexes showed similar to lower IC_{50} values compared to chloroquine in *P. falciparum* strains [134].

Auranofin has also been studied to be repurposed as antimalarial agents. Ssemaganda et al., reported on the antimalarial activity of auranofin and bis-chelated Au(I) 2-pyridyl phosphine complex $[Au(d2pype)_2]Cl$ (Fig. 10). Both compounds showed potent inhibition against *Plasmodium falciparum* and *P. knowlesi* and showed reduction of *P. chabaudi AS* parasite in vitro in infected mice at 2 μM. While these compounds were potent in in vitro assays, in vivo data suggests a decreased availability as auranofin and $[Au(d2pype)_2]Cl$ as there was no significant inhibition of *P. chabaudi AS* strains in vivo [135]. These results indicate that further pharmacokinetic studies need to be carried out to understand the bioavailability of these compounds after administration.

Micali et al., studied the ability of auranofin and other Au(I) complexes including compounds with 1,3,5-triaza-7-phosphaadamantane (PTA) ligand to inhibit Falcipain 2 (Fp2) an important protease of P. *falciparum* that is involved in the degradation of host haemoglobin, thereby providing the ingredients (peptides and amino acids) to sustain the growth of the parasite. Initial Fp2 inhibition assay with Au-PTA and auranofin showed mild inhibition of 24 % and 30 % respectively while the IC_{50} of *P. falciparum* growth inhibition was 5.16 ± 0.14 and 0.142 ± 0.003 μM respectively (Fig. 11) [136]. Further work by Tapanelli et al., on water soluble Au(I) phosphine of the archetype $[M(L)_4]PF_6$, where L = 1,3,5-triaza-7-phosphaadamantane (PTA) or tris(hydroxymethyl) phosphane (THP) studied the ability of these compounds to affect early sporogonic stages (ookinete) of *Plasmodium* and thus inhibit parasite establishment in the mosquito vector. The complexes demonstrate mild activity against ookinete development in the mosquito that translates to 70 % parasite growth inhibition by Au-THP at 100 μM [137].

Au-conjugated metallocenes have also being studied for their antimalarial activities. Bjelosevic et al., reported five Au(I) complexes Fc-

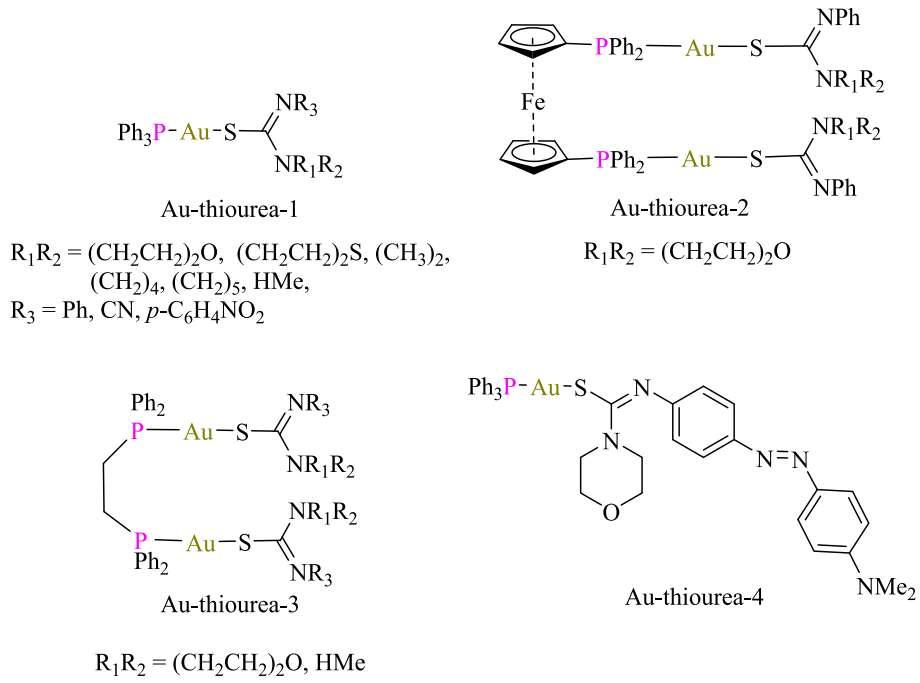


Fig. 15. Antimicrobial activity of phosphinogold(I) thiourea in *Bacillus subtilis*.

Table 4
Minimum inhibitory concentration (μg/mL) of Au complexes bearing mesityl and bisphosphine ligands.[a]

Compd	Gram-negative		Gram-positive		Yeast
	S. typhimurium	*E. coli*	*B. cereus*	*S. aureus*	*S. cerevisiae*
Au-Mes-1	ins[b]	ins[b]	10	10	ins[b]
Au-Mes-2	10	10	1	10	>100[c]
Au-Mes-3	10	10	10	10	>100[c]
Au-Mes-4	ins[b]	ins[b]	10	10	ins[b]
Au-Mes-5	>100[c]	>100[c]	>100[c]	>100[c]	>100[c]
$AgOClO_3$	100	100	10	100	100
$AgSO_3CF_3$	100	100	10	100	100
Au-Mes-6	>100[c]	>100[c]	>100[c]	>100[c]	>100[c]
Au-Mes-7	100	100	100	100	100
Au-Mes-8	100	100	100	100	100
Au-Mes-9	>100[c]	>100[c]	100	100	>100[c]
Au-Mes-10	100	100	100	100	>100[c]

[a] Compounds were dissolved in DMSO.
[b] ins—the compound was insoluble in aqueous solution above 10 $\mu g\,mL^{-1}$.
[c] Concentrations greater than 100 $\mu g\,mL^{-1}$ were not tested because the compounds would not have been soluble.

Au-P-1-5 bearing either ruthenocenyl or ferrocenyl phosphine ligand (Fig. 12). However, these complexes are not viable candidates for further studies because their antimalarial activity in CQ resistant cells lines gave lower IC_{50} compared to standard drug chloroquine [138]. In another work, Subramanian et al., synthesized three Au phosphine conjugated ferrocenes Fc-Au-P-6-8 (Fig. 12). The most active compound Fc-Au-P8 exhibited significant parasitemia reduction above 80 % at three different concentrations (100, 25, 6.25 μM) while significantly inhibiting early erythrocytic stage (ring to trophozoite), and hematin compared to the ferrocenyl phosphine derivatives studied. These results point toward Fc-Au-P6 been a great candidate for next generation antimalarial drug [139].

A few studies have also focused on conjugating existing antimalarials to Au phosphine. In an earlier study by Navarro et al., chloroquine-based Au(I) phosphine complexes CQ-Au-P Fig. 13 were synthesized, and they displayed excellent activity against two chloroquine- resistant strains of *P. falciparum*. CQ-Au(I)-P1 showed marked in vivo efficacy 84 % when compared to chloroquine diphosphate (44 %) in a *Plasmodium berghei* infected mice treated at 1 mg/kg for 4 days with no acute toxicity observed [140,141]. Buoyed by these impressive studies, Colina-Vegas et al., reported an amodiaquine (AMQ) derivative AMQ-Au-P Fig. 13. This compound showed impressive activity inhibiting multiple stages of the *Plasmodium* life cycle both in vitro and in vivo. Their result shows that AMQ-Au-P was twice as potent as amodiaquine in both chloroquine sensitive (NF54) and chloroquine resistant cell lines (W2) in overcoming chloroquine resistance with higher selectivity when compared to amodiaquine in mammalian cell lines. Also, AMQ-Au-P showed efficacy as a blood schizonticidal agent in vivo when administered to *P. berghei* infected mice with 70 % cure rate when administered at 30 μmol/kg [142].

1.3.2. Antimicrobial

Since the discovery of cephalosporins as an antibiotic with unique mechanism of action in the late 1960s [143], the search for newer antibiotics focused on derivatizing old drugs, and this has stalled the emergence of antibiotics with new mechanisms of action [144,145]. Also, the decrease in financial and labour commitment by industries made researchers to rely on old drugs for new purposes [145]. The use of Au salts for treatment of microbial infection dates to the work of Robert Koch in 1890 who demonstrated the antibacterial activity of K[Au $(CN)_2$] against *Mycobacterium tuberculosis* [146,147]. This discovery led to further research into the design of several Au-based compounds as antimicrobial agents. Auranofin has been well studied for their antimicrobial activities with studies progressing to clinical trials in bacterial and viral infections.

1.3.2.1. Antibacterial. In bacterial infections auranofin have been effective against various gram-positive bacteria strain including multidrug resistant bacteria [148–150]. The consensus is that auranofin is active in gram positive bacteria including multidrug resistant strains while inactive in gram negative strains, this is due in part to the glutathione/glutathione reductase system being able to compensate for the loss of reducing capability in the Trx–TrxR system caused by auranofin [151]. Another explanation for the inactivity of auranofin in gram

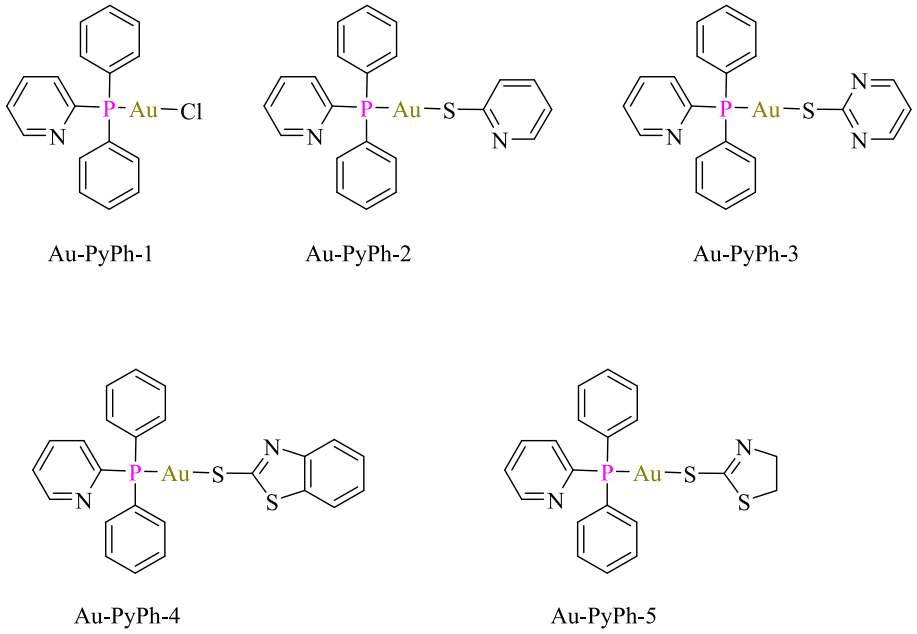


Fig. 16. Au phosphine compounds potent against gram-negative bacteria.

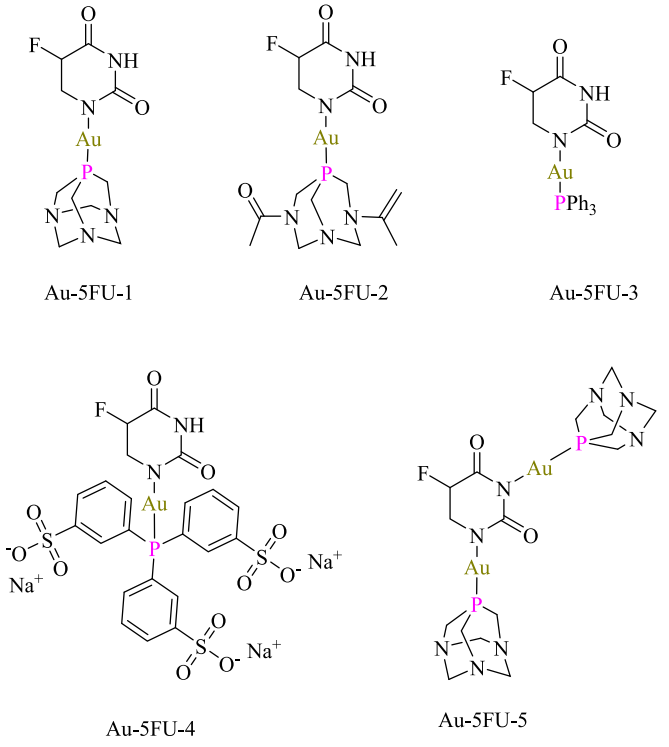


Fig. 17. Structure of phosphinogold uracil complexes.

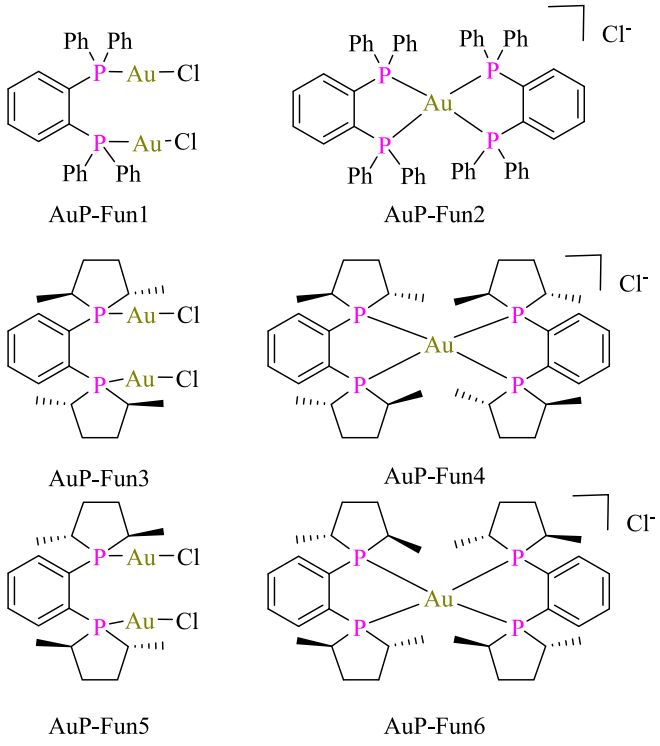


Fig. 18. Antifungal phosphinogold(I) agents.

negative bacteria is the outer membrane present in gram-negative bacteria that acts as a barrier to accumulation of auranofin [152]. Wu et al., screened 40 compounds comprising of auranofin and its analogs against ESKAPE pathogens. This in-depth SAR study indicates that auranofin is active against gram positive bacteria including multidrug resistant strain *Mycobacterium tuberculosis* but inactive against gram negative bacteria Fig. 14. To modulate the antimicrobial activity of auranofin in both bacteria strains, changes in the phosphine substituent, the sugar moiety and/or thiol groups were carried out. Their result indicates that auranofin derivative with PMe_3 substituent showed no significant difference in activity against gram positive strains compared to auranofin while derivatives with increased alkyl chain length or aryl phosphine substituent showed a reduction of antimicrobial activity in gram positive bacteria. In gram negative bacteria, complexes with PMe_3 were effective and increasing the alkyl chain led to a decrease in activity against gram negative bacteria. This shows that increase the electron donating capacity of the phosphine ligands can impart their activity against both gram positive and gram negative bacteria [153].

Reports has also shown auranofin to be effective against *Clostridium difficile* [154]. Infections due to *C. difficile* are deadly with the emergence

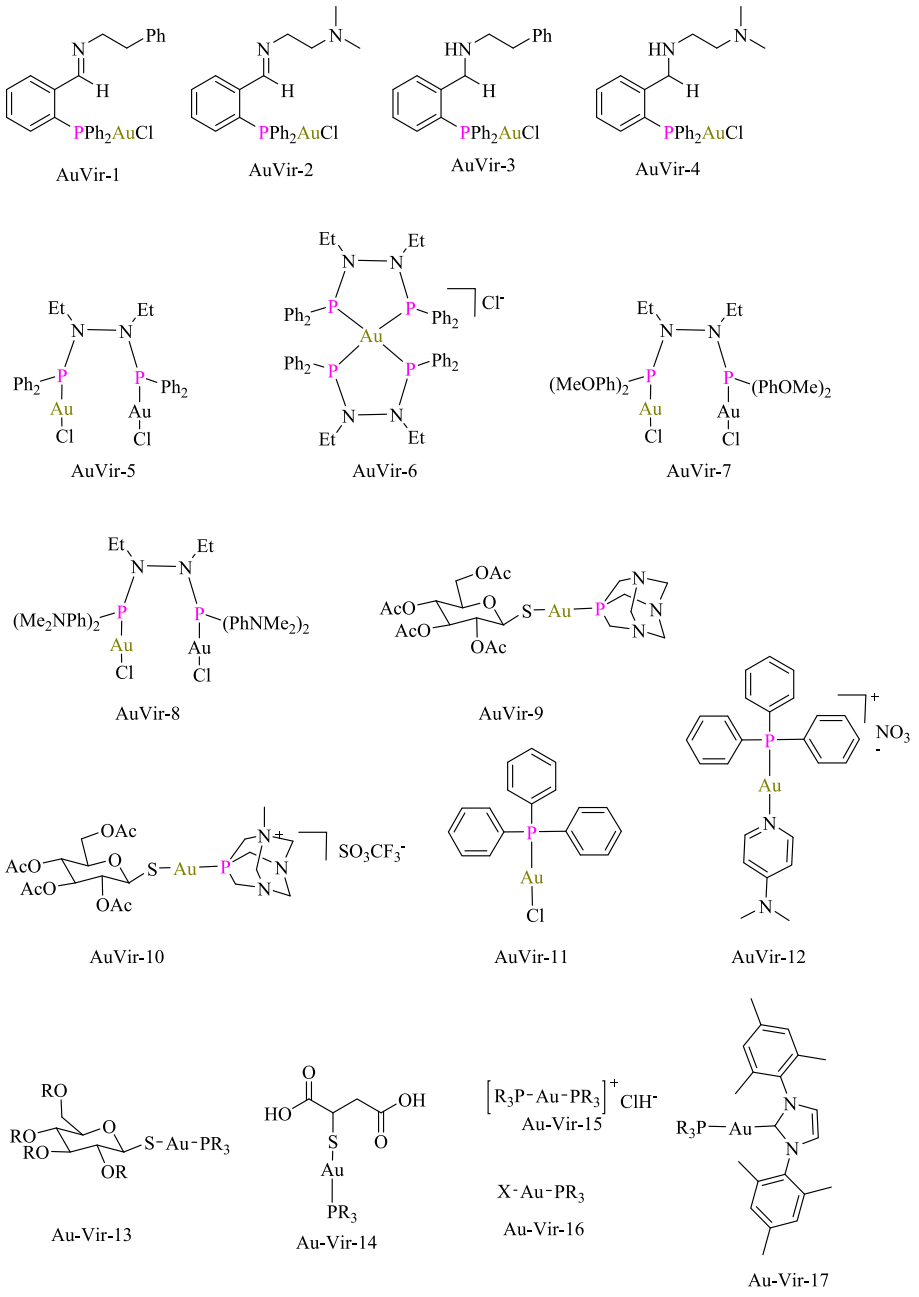


Fig. 19. Antiviral phosphinogold(I) compounds. R = trimethyl, triethyl, tripropyl, triisopropyl, tributyl, triisobutyl, phenyl, tolyl or trifluoro methyl phenyl.

of hypervirulent mutants with increased capability to produce toxins and spores accounting for about 500,000 cases yearly [155,156]. The standard drugs used to treat *C. difficile* are vancomycin, metronidazole and fidaxomicin and these drugs have shown limited efficacy and high recurrence rates, hence the need for newer drugs [155]. Auranofin inhibit the growth of 41 *C. difficile* strains with concentrations ranging from 0.25 to 4 μg/mL. Table 3. Auranofin also inhibits toxin production and spore formation in hypervirulent, toxigenic strain of ATCC BAA—1870*C. difficile* [154].

Henderson et al., reported moderate antibacterial activity of 14 phosphine Au(I) thiourea complexes Fig. 15 against *Bacillus subtilis* [157]. Ortego et al., described some aminophosphane Au(I) complexes that were active in gram positive bacteria but inactive toward gram negative bacteria. These complexes showed a bacteriostatic activity at the lower minimum inhibitory concentration (MIC) [158].

Organo-heterometallic complexes containing mesityl and bisphosphane bridging ligands of the general formular $[Au_2(\mu\text{-mes})_2(\mu\text{-LL})]$ (Au-Mes-1 - 5) and $[Au_2M(\mu\text{-mes})_2(\mu\text{-LL})][A]$ (Au-Mes-6–10) have been reported. These luminescent complexes were shown to have promising antimicrobial activities. The dinuclear Au complexes with dppe ligands Au-Mes-1 were insoluble, while their heteronuclear complexes counterpart Au-Mes-2 and Au-Mes-3 were soluble and displayed the lowest inhibition concentration in both gram positive and negative bacteria Table 4. Also, Au-Mes-2 and Au-Mes-3 showed strong bactericidal activity in *E. coli* and *S. aureus*. The luminescence properties of these complexes can be exploited to track their interactions with various cells and organelles via fluorescence microscopy [159].

Phosphinogold complexes bearing diphenyl pyridine have also been reported in literature. These complexes were reported to be active against both gram-negative bacteria at low concentration with Au-PyPh-3 Fig. 16 inhibiting *P. aeruginosa* at 3.89 μg/mL and *E. coli* at 3.15 μg/mL, while auranofin was inactive [160].

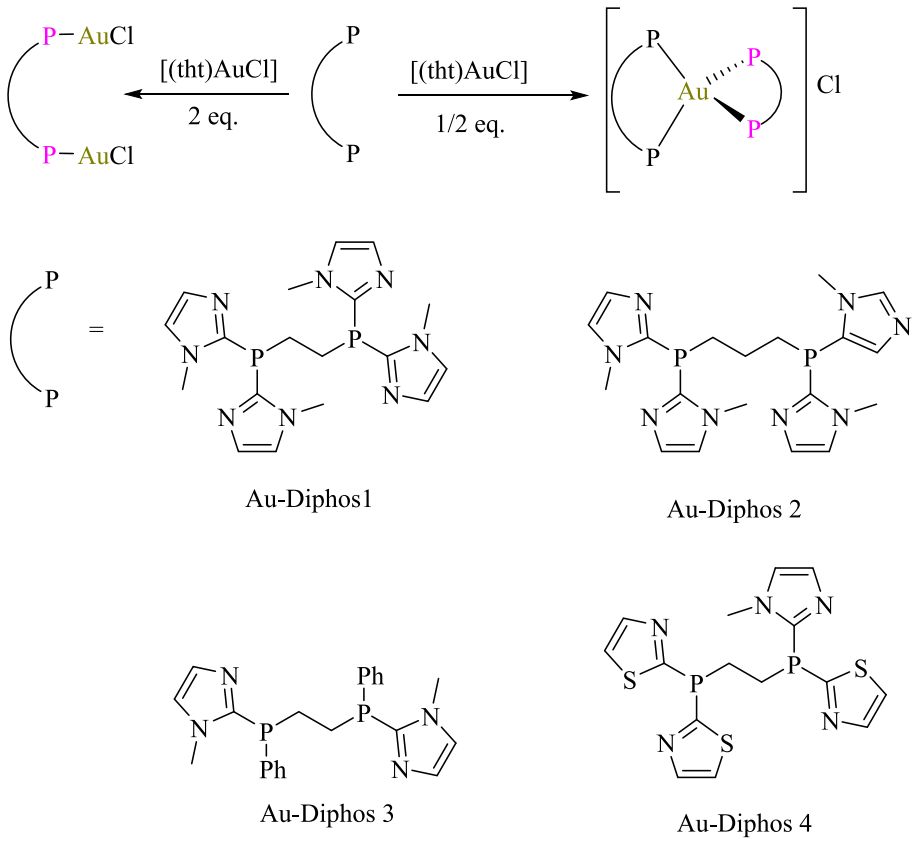


Fig. 20. Anticancer Au(I) complexes containing water soluble diphos ligand.

Table 5
IC_{50} (μM) for inhibition of TrxR 1 and TrxR2 by water soluble Au phosphines.

Compound	TrxR1	TrxR2
auranofin	0.74 ± 0.20	2.45 ± 0.32
Au-PTA-1	1.61 ± 0.21	4.12 ± 0.28
Au-PTA-2	1.92 ± 0.15	6.73 ± 0.25
Au-DAPTA-3	1.54 ± 0.17	6.20 ± 0.35
Au-PTA-4	0.96 ± 0.08	4.06 ± 0.41
Au-DAPTA-5	1.55 ± 0.16	5.86 ± 0.32
Au-TPPTS-6	0.62 ± 0.04	6.95 ± 0.14
Au-TPPTS-7	1.67 ± 0.05	6.82 ± 0.25

Coordination of an anticancer drug 5-fluorouracil (5-FU) with Au phosphine (Fig. 17) represents another class of compounds that has shown antibacterial activity against *E. coli* and *B. subtilis*. Gram-positive and gram-negative bacterial strains have previously been demonstrated to be susceptible to 5-fluorouracil with its primary mode of action being the regulation of virulence genes and behaviors, quenching of quorum sensing in bacteria or inhibiting the growth of biofilms [161–163]. When 5-FU is coordinated to Au-phosphine, the activity of the complex is improved greater than 5 times the drug alone. The improved activity was also observed in treated biofilms viewed under scanning electron microscope, with the images showing changes in the morphology and damages to the outer membrane of biofilms treated with Au-phosphine-uracil construct compared to biofilms treated with 5-FU only [164].

1.3.2.2. Antifungal. Despite notable advancement in management of mycosis (fungal infection) in the last three decades, common invasive mycosis such as *Cryptococcus neoformans, Candida albicans*, *Candida auris,* and *Aspergillus fumigatus*, still have a high mortality rate [165]. To determine the effective treatment regime for fungal infections, there is the need to identify the class of infection based on 3 main criteria. 1) Determine the site of infection and extent of the infection as either systemic or local. 2) Determine if the route of acquiring the infection is through an exogenous process or endogenous process and 3) determine the nature or virulence of the causative organism either as a primary infection or opportunistic infection [166,167]. To combat the growing threat of resistance of fungi infections to currently approved antifungal drugs, there is an urgent need for new antifungal agents with novel mechanism of action. Awuah and Garneau-Tsodikova's lab reported six Au-phosphine complexes (Fig. 18) and tested their potency against panel of 21 fungal strains including invasive mycosis such as *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., and *Fusarium* spp. The phosphinogold complexes showed potent activity against fungal strains and biofilms including the multidrug resistant *Candida auris* [168].

1.3.2.3. Antiviral. There is a pressing need for novel antiviral drugs with newer mechanism of action as fatalities due to viral infection keeps increasing worldwide. Unlike antibiotics, antivirals do not destroy the pathogen but rather inhibit the development of the pathogen. Au complexes have been shown to have antiviral properties with auranofin entered into clinical trial as a potential antiviral agent for treatment of HIV [88,169–171]. In the multi intervention study, the impact of auranofin, maraviroc and dolutegravir on proviral HIV-1 DNA was examined on subjects undergoing antiretroviral therapy. In the study, auranofin was well tolerated with no major side effect, and it impacted the viral DNA dynamics by decreasing the total viral DNA in peripheral blood mononuclear cell (PBMCs) significantly compared to treatment groups without auranofin [169]. Also, Au(III) salts have been reported to interact with nucleocapsid protein of HIV-1 [172], therefore changes in viral DNA dynamics were further quantified by measuring the integrated viral DNA using Alu PCR techniques and observed significant decrease of the integrated HIV-1 DNA over time in groups that included auranofin in the treatment regime [169]. Earlier report by Fonteh and Meyer reports on the ability of Au(I) phosphine complexes AuVir-1 –

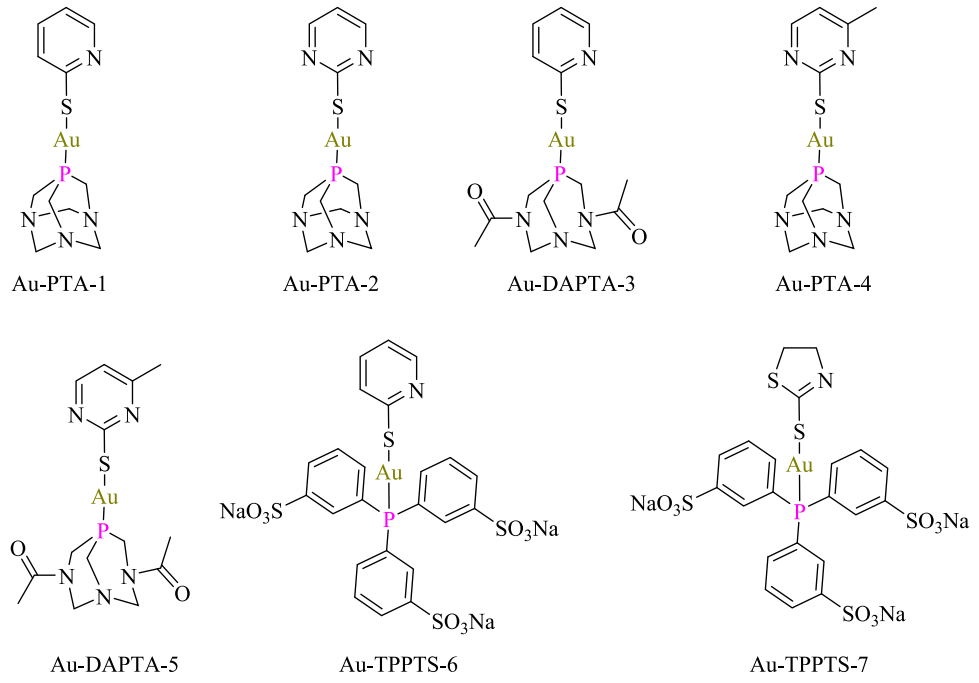


Fig. 21. Anticancer Au(I) complexes containing water soluble adamantane ligand.

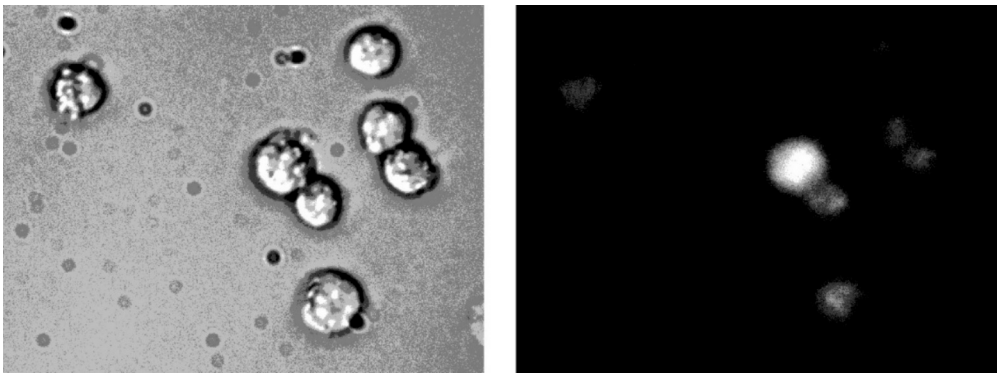


Fig. 22. Cellular distribution of trinuclear $N[Au(C \equiv CCH_2)(PTA)]_3$ in A2780 cancer cells after 6 h incubation at 37 °C. Reproduced from ref. [204] Copyright 2010 American Chemical Society.

AuVir-10 and auranofin Fig. 19 to inhibit HIV enzymes. In the report, all the compounds tested were non-toxic to PBMCs and was taken efficiently as quantified by ICP-AES. Also, the compounds inhibit either reverse transcriptase activity or protease activity while AuVir-3 inhibited both reverse transcriptase activity and protease activity, and auranofin did not inhibit transcriptase nor protease activity. This points to the fact that these compounds exhibit their antiviral activity through a mechanism different from auranofin [173].

Chikungunya fever is a viral infection caused by the RNA virus Chikungunya that affects people across the Mediterranean countries and North America. Currently there are no drugs to treat this condition hence the need to develop new drugs [174,175]. Aires et al., synthesized a series of Au complexes containing phosphine and 1,3-bis(mesityl)imidazole-2-ylidene ligands. Complexes with phosphine ligand AuVir-11 and AuVir-12 (Fig. 19) inhibited CHIKV replication in BHK-21 infected cells and showed higher cellular uptake compared to complexes with 1,3-bis (mesityl)imidazole-2-ylidene [176].

Trichomoniasis is the most common non-sexually transmitted viral infection caused by *Trichomonas vaginalis* with about 200 million people infected worldwide [177]. Reported cases of resistance to approved medications (metronidazole and tinidazole) has necessitated the need for newer drugs to combat drug resistance [178]. Drugs that target Trx-dependent antioxidant defense systems can help circumvent drug resistance as Trx and Trx peroxidase is upregulated in *T. vaginalis*. Auranofin has been demonstrated to target TrxR in microbial infections [179–182], therefore it is worthy to study the effect of auranofin and other Au phosphines on the treatment of *T. vaginalis*. Wrischnik et al., studied the effect of auranofin on the growth of *T. vaginalis* and *T. foetus* and they observed that auranofin suppresses the growth of the virus by targeting TrxR which encodes for a functional reductase in *T. vaginalis* trophozoites [183]. Following up on this study, Eckman et al., reported SAR studies of some Au phosphines to improve drug selectivity. Their study showed that trimethyl, triethyl, tripropyl, and triisopropyl, mono- and bisphosphine ligands showed excellent trichomonacidal activity with great selectivity compared to tributyl and triisobutyl phosphine ligands and replacement of the alkyl chain with phenyl, tolyl or trifluoromethyl phenyl groups compromised the activity and selectivity toward *T. vaginalis*. Also, the active compounds inhibited the two most abundant isoforms of TrxR and significantly reduced the infection in BALB/c mice model [184].

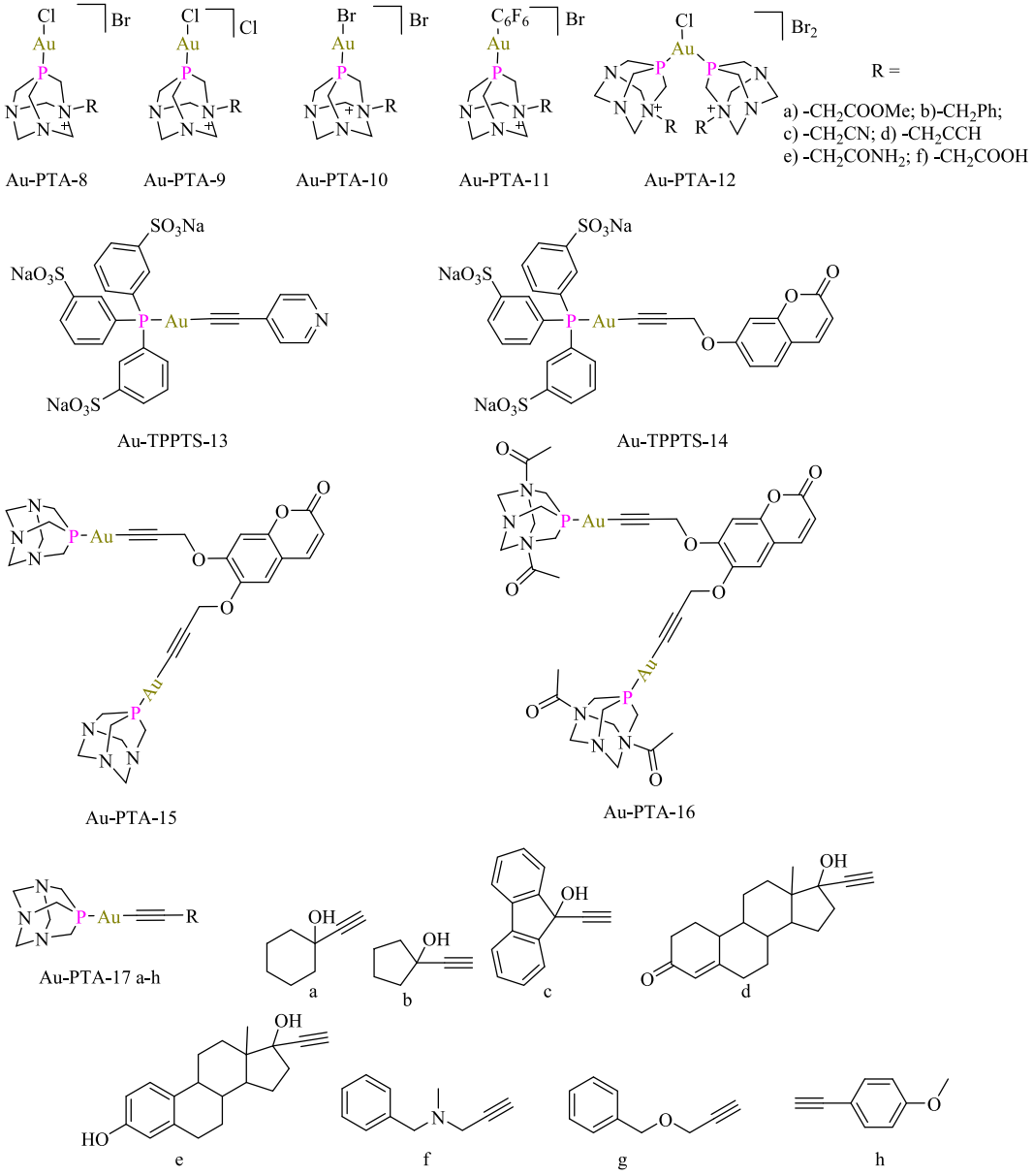


Fig. 23. Mononuclear and dinuclear Au(I) phosphaadamantane complexes.

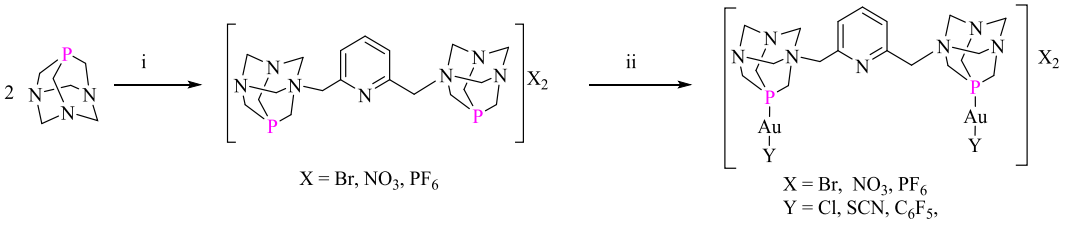


Fig. 24. Synthesis of Dinuclear Au(I) phosphaadamantane complexes i) 2,6-(CH_2Br-py-CH_2Br), *ii*) [AuCl(tht)], [Au(SCN)(tht)] or [Au(C_6F_5)(tht)]).

1.3.3. Anticancer activity

Despite numerous interventions and intensive research into cancer treatment, cancer remains the second leading cause of death worldwide and it is not surprising that research into the anticancer properties of Au phosphine complexes exceed other medicinal applications. In this section, the focus will be on the structure and mechanism of anticancer Au phosphine complexes studied within the past two decades. Auranofin and its derivatives have been extensively studied by different research groups for their anticancer activities in different cancer models. The anticancer properties of auranofin and Au(I) phosphines have been attributed primarily to inhibition of thioredoxin reductase in the mitochondria and cytosol leading to disruption in intracellular redox homeostasis, induction of oxidative stress and anticancer activity in vitro [185–187]. Aside targeting thioredoxin reductase, other targets have been suggested for Au phosphines. Mitochondria is the powerhouse of the cell where ATP is generated through oxidative phosphorylation

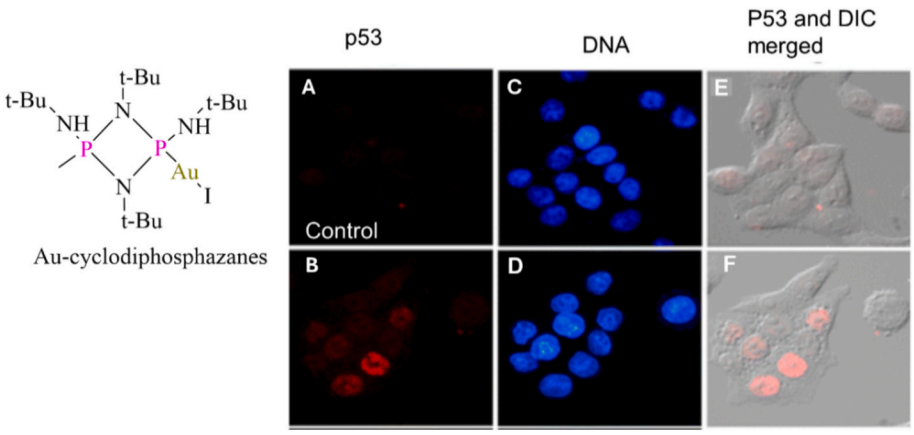


Fig. 25. Effects of Au-cyclodiphosphazanes complex (20 μM) on the nuclear accumulation of the p53 protein in HCT-116 cells after treatment for 24 h. Reproduced from ref. [211] Copyright 2008 The Royal Society of Chemistry.

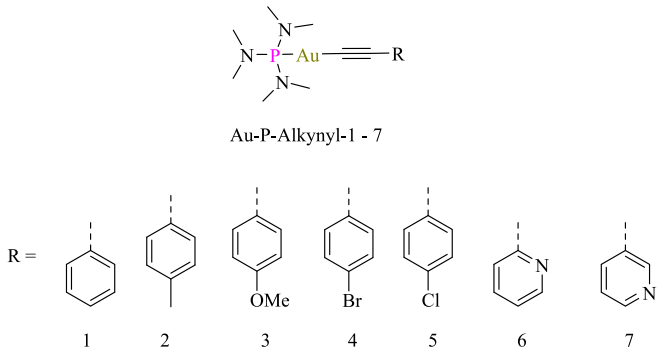


Fig. 26. Water soluble Au(*I*)phosphine complexes.

(OXPHOS). Also, mitochondria play a pivotal role in regulating many cellular processes including maintaining homeostasis, providing intermediates for construction of biomolecules, regulating proteins in the apoptosis pathway, and a primary source for cellular ROS generation [188–190]. Therefore, various gold phosphine compounds have been studied as mitochondria targeting anticancer agents [189,191–193].

1.3.3.1. Water soluble Au-phosphine complexes. Oral drug intake is the most common route of drug administration because of its ease of administration, minimal sterility restrictions, good patient compliance, economical to produce and purchase, and dose form design flexibility [194–196]. Low oral bioavailability of a drug can be attributed to poor solubility in aqueous media and low permeability, therefore oral bioavailability is an important factor to consider in drug design. As discussed above, earlier Au phosphine drug design focused on either auranofin derivatives or compounds with delocalized lipophilic cations compounds such as *Au*-bis-*P*-1-4 Fig. 6. This class of compounds, though cytotoxic, has numerous side effects due to the nonspecific binding to biomolecules hence the need for hydrophilic Au compounds [112,197,198]. On the other hand, highly hydrophilic Au compounds can also be excreted easily out of the body because of low protein binding. Therefore, there is a need for a balance between the lipophilic and hydrophilic character of metallodrugs to ensure potent anticancer activity [199].

Diphos ligand is a water-soluble variant of the dppe class of ligand with the phenyl ring replaced by pyridinyl ring resulting in improved selectivity and reduced side effects. Some hydrophilic Au(I) complexes bearing DiPhos ligand (Fig. 20) have been reported with log$D_{7.4}$ between −1.73 and + 0.79. These complexes with moderate lipophilicity exhibited promising IC_{50} values ranging from 0.4 to 40 μM in A2780 cisplatin sensitive and resistant cells [200].

Adamantane-like phosphanes is another class of hydrophilic ligand that has gathered much attention due to similar reactivity to other alkylphosphanes ligands, its resistance to oxidation and greater stability in air [201,202]. These properties confer the complexes with the ability to overcome the challenges of complicated drug formulations for in vitro and in vivo testing. Vergara et al., reported on some neutral hydrophilic Au phosphine complexes that inhibit TrxR1 and TrxR2 Table 5. These complexes contains water soluble PTA, DAPTA and TPPTS ligands ((Fig. 21) and they displayed good cytotoxicity especially in cisplatin resistant cell lines (A2780R) with IC_{50} between 4 and 16 μM [203].

The same group later reported on some mono, di and trinuclear Au(I) alkynyl complexes bearing phosphaadamantane ligands. The mononuclear [Au(C ≡ CPh)(DAPTA)], [Au(C ≡ C-3-SC_4H_3)(PR_3)], [Au(C ≡ CCH_2OH)(PR_3)] and trinuclear N[Au(C≡CCH_2)(PR_3)]$_3$ (PR_3 = PTA or DAPTA) complexes showed potent antiproliferative activity in both cisplatin-sensitive (A2780) and cisplatin-resistant (A2780cisR) human ovarian cancer cells. The compounds also displayed intracellular accumulation when A2780 treated cells were incubated for 6 h at 37 °C and viewed under an epifluorescence microscopy (Fig. 22). The images showed an efficient uptake of the compound into cancer cells. Further subcellular accumulation studies could not be ascertained due to the relatively low level of fluorescence observed [204].

Santini et al., later reported on monocationic complexes [Au(L)$_4$]PF_6 (L: thp = tris(hydroxymethyl)phosphine, PTA = 1,3,5-triaza-7-phosphaadamantane, or thpp = tris(hydroxypropyl)phosphine). The complexes were synthesized from metathesis reactions of [Au(L)$_4$]Cl and $TlPF_6$ at room temperature and displayed low cytotoxicity compared to their Cu(I) counterparts [205]. Mariano Laguna's group also synthesized Au(I) phosphaadamantanes by the reaction of [AuCl(tht)] with [PTA–R]Br (R = –CH_2C ≡ CH, –CH_2CONH_2, –CH_2COOH) to give [AuCl(PTA–R)]Br complexes (Fig. 23). These complexes displayed potent activity against A2780 and cisplatin resistant A2780cisR cell lines better than cisplatin [206]. They further reported some Au(I) thiolates bearing alkylated PTA ligands that showed strong antiproliferative activity in CaCo-2 cancer cells and apoptosis induced cell death for all 16 compounds tested [207]. Also Wei et al., recently explored the influence of different alkynyl substituent on the cytotoxicity of luminescent Au phosphines complexes. They observed that the complexes showed strong emissive characteristics at the range of 477–613 nm with microsecond range of luminescent lifetime (0.40–14.0 μs) in solid states at 298 K and 77 K while showing potent anticancer activity in MCF-7 cancer cells [208].

Later, they reported some mono and dinuclear Au(I) phosphaadamantane complexes (Fig. 24). The dinuclear water soluble complexes were obtained by treating [AuY(tht)] (Y = Cl, SCN, C_6F_5;) with bis-PTA

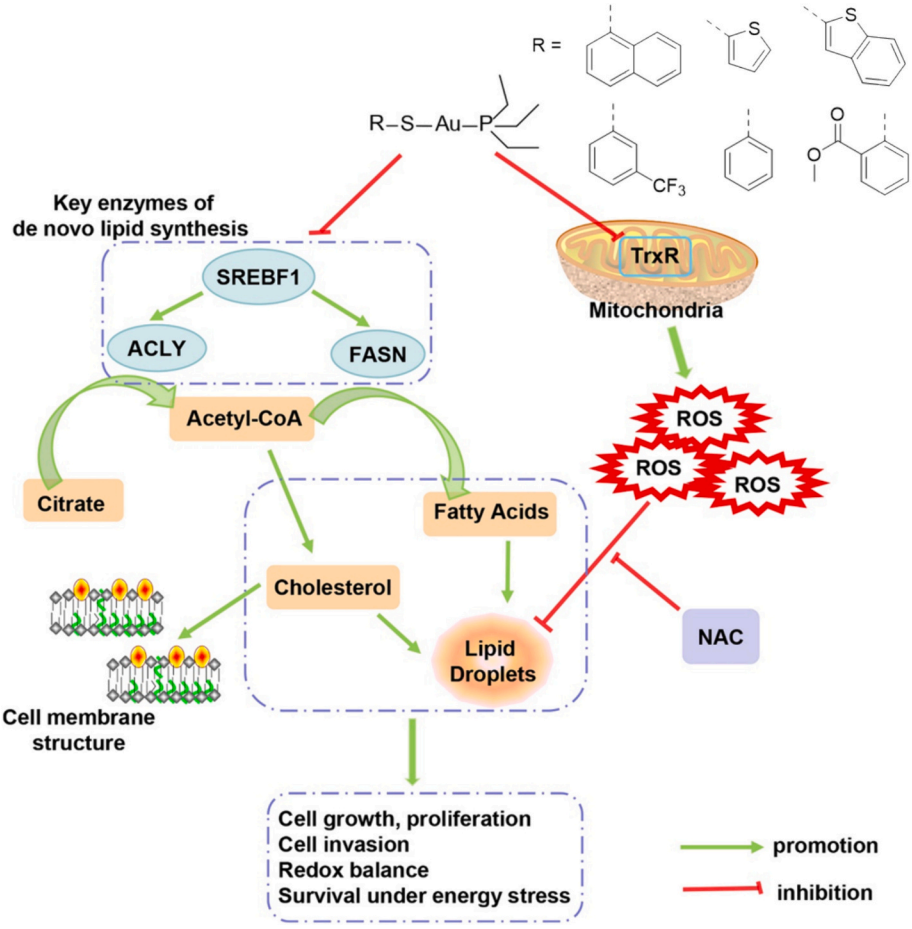


Fig. 27. Proposed mechanism of action of Au(I) thiolates to inhibit de novo lipid synthsis and storage. Reproduced from ref. [226] Copyright 2014 Elsevier.

phosphanes ligands. The complexes displayed increased cytotoxicity against colon cancer cells (Caco-2/PD7 and Caco-2/TC7 clones, isolated from late and early passage) compared to cisplatin. Also, the dinuclear complexes displayed similar potency when compared to the mononuclear complexes indicating that increasing the metallic centers from one to two does not affect the cytotoxicity in Caco-2 cells [209]. Rodriguez and co-workers reported on some luminescent Au phosphines with water soluble phosphines and 4-pyridylethynyl Au-TPPTS-13 or propargyloxycoumarin chromophoric unit Au-TPPTS-14, Au-PTA-15, and Au-DAPTA-16 Fig. 23. The complexes showed low cytotoxicity in MDA-MB-231 and HT-29 cancer cells but strong inhibitory TrxR inhibition. The low cytotoxicity of the complexes was attributed to the poor bioavailability of the compounds in the cell lines tested [210].

Cyclodiphosphazanes is a class of phosphorus containing compound that has gained prominence due to their synthetic utility in forming macrocycles, however their catalytic and biological applications have been underexplored. Suresh et al., reported on the synthesis of water soluble cyclodiphosphazanes ligands and their coordination with [(Me_2S)AuCl] to afford both mono and binuclear Au(I) complexes. These complexes showed potent antiproliferative activity against HeLa cells and causes induction of apoptosis by inhibiting p53 protein (Fig. 25) [211].

Laguna et al., explored some water-soluble heteroleptic Au(*I*)complexes bearing phosphane HMPT and an ethynylphenyl or ethynylpyridine moiety Fig. 26 and their absorption, distribution, metabolism, and excretion (ADME) properties evaluated. These cytotoxic complexes induce apoptosis and causes cell cycle in the G2/M (Au-P-Alkynyl-4 - 5 and 7) or S phase (Au-P-Alkyne-6) in Caco-2/TC7 cells [212].

1.3.3.2. Lipophilic cationic Au complexes. Research into the use of lipophilic agents as drugs has a long history. This is because the lipophilicity of the compound is a crucial consideration in the development of efficacious anticancer agent as they affect the compound's pharmacokinetic properties, biodistribution, and cellular uptake. Earlier works have shown that lipophilic cationic compounds such as bisquaternary derivatives of terephthalanilides, quinolinium dibromide, rhodamine 123, dequalinium, ditercalinium, and pyronine Y accumulate in the mitochondria to perturb cellular functions [213–221]. These compounds exhibited great potency in vitro and in vivo but the high level of toxicity during clinical trials has stalled their development.

$[Au(dppe)_2]^+$ is a lipophilic cationic Au(I) phosphine compound that displayed potent antitumor activity in vitro and in vivo in several cancer models [114,197]. Earlier studies has shown that $[Au(dppe)_2]^+$ perturbs mitochondria activities as a mode of action but further research was abandoned due to toxicity to normal cells and tissues, this was attributed to alterations in mitochondria function [198,222,223].

1.3.3.3. Heteroleptic Au-phosphines. The design of anticancer agents as heteroleptic complex is an attractive option in coordination chemistry. The central metal is surrounded by more than one type of ligand thereby improving ligand tuning, variability, and the antiproliferative activities displayed. In this section, we shall discuss the anticancer properties of heteroleptic Au complexes containing a phosphine and one other ligand (halides, thiolates, dithiocarbamates, thiosemicarbazones, thiocarbohydrates and N-heterocyclic carbenes).

Phosphinogold(I) thiolates have been extensively studied due to the repurposing of auranofin [106,224,225]. Previous studies have shown that auranofin can perturb internal redox homeostasis by elevating ROS

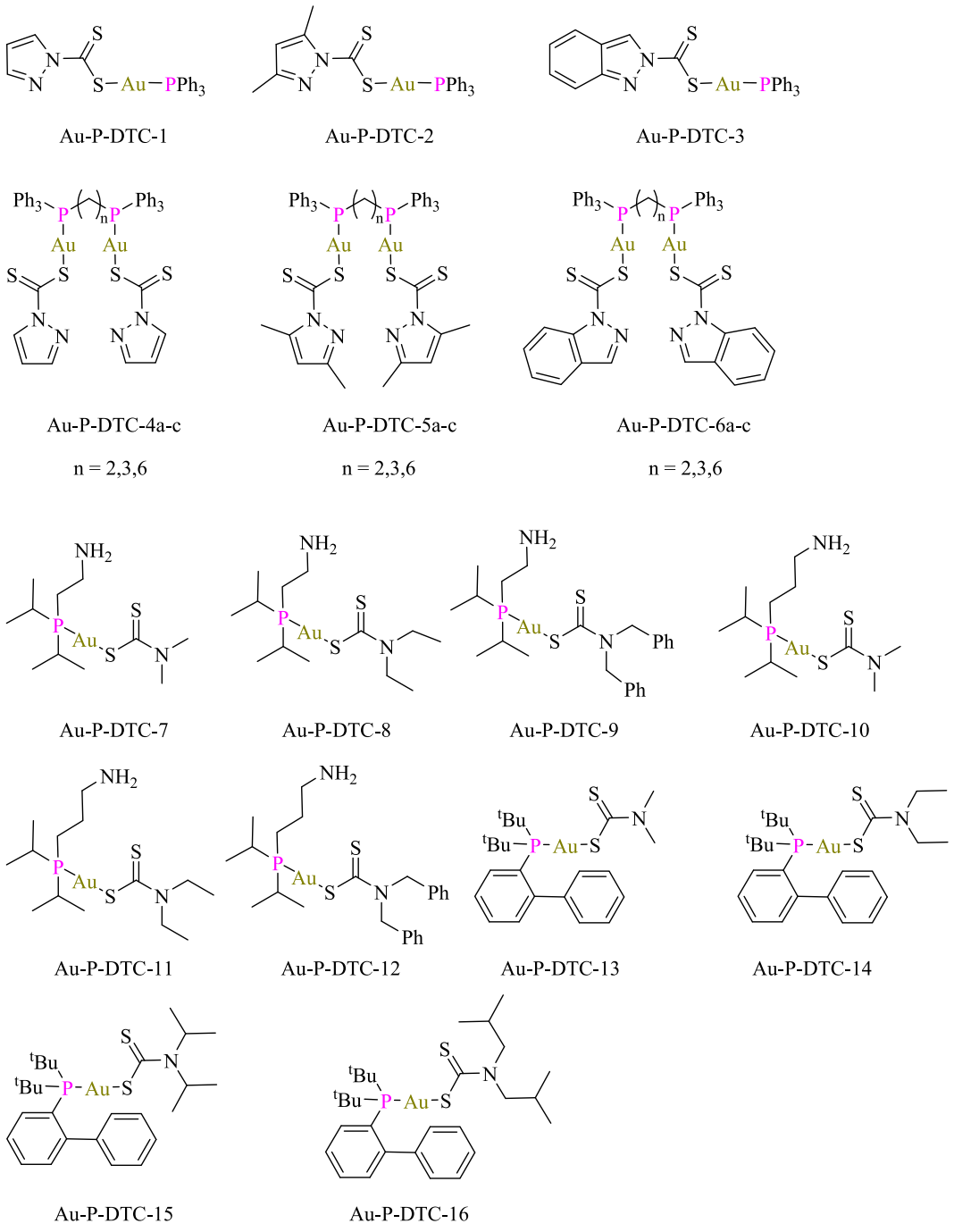


Fig. 28. Anticancer phosphinogold complexes bearing dithiocarbamate ligands.

levels to inhibit tumor cell growth and promote apoptosis [106,187]. SAR studies have focused on different phosphine derivatives and/or substituting the sugar moiety with an aliphatic or aromatic group. To further understand the mechanism of auranofin, Luo et al., studied the effect of auranofin and its analogs (where the sugar was replaced by different R-groups) on the regulation of lipid metabolism in lung cancer cells. Results from their study suggest inhibition of the key enzymes (SREBF1, FASN, and ACLY) that are involved in de novo lipid synthesis. This inhibition led to the reduction of endogenous fatty acid and phospholipid synthesis, thereby interfering with physiological functions of tumor cells to proliferation, invasion, redox balance and resisting energy stress (Fig. 27) [226]. Also, other studies have explored the use of different saccharide thiols, a bi-gold system and different phosphine ligands to understand the mechanism of action of auranofin and other Au phosphines. In recent studies, Wen et al., evaluated some novel glycosylated bi-Au mitocans in lung cancer and cancer stem cells. These complexes accumulate preferentially in the mitochondria nearly 40-fold higher than auranofin, inhibited oxygen consumption rate (OCR) produced mitochondria ROS significantly and depolarized mitochondria membrane [227,228]. Other studies have shown the anticancer properties of auranofin and its derivatives acting alone or in synergy with other biologically active agents in a broad spectrum of cancer cells such as colorectal cancer [229–231], ovarian cancer [232,233], lung cancer [234–236], cervical cancer [237], prostate cancer [238–240] liver cancer [241,242] and breast cancer [243–246],

Keter et al., reported on novel mono- and diphosphinogold(I) dithiocarbamate bearing triphenylphosphine, diphenylphosphinoalkyl ligands Au-P-DTC-1–6 Fig. 28. Attempts to grow crystals of the

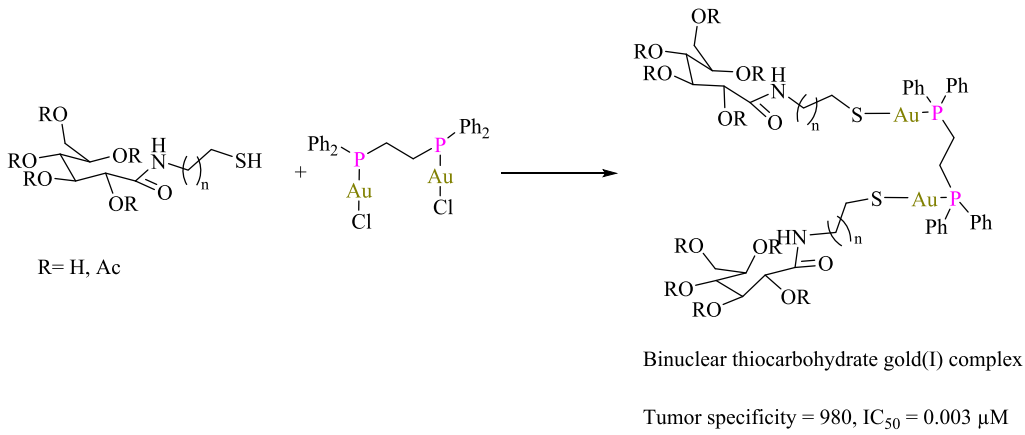


Fig. 29. Phosphinogold(I) complexes containing thiocarbohydrates.

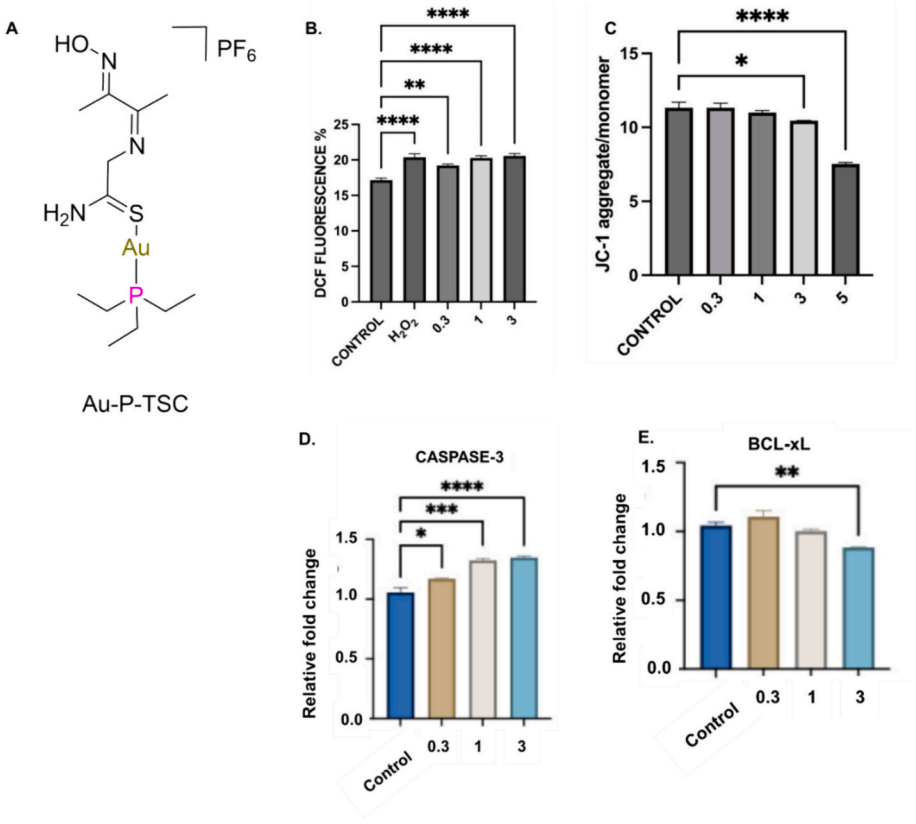


Fig. 30. A) Structure of cytotoxic Au-P-TSC B) Impact of Au-P-TSC on ROS levels in MDA-MB-231 cells. C) Effect of Au-P-TSC on mitochondria membrane in MDA-MB-231 cell line. D) Relative fold change of caspase-3 gene expression levels in MDA-MB-231 cells after treatment with Au-P-TSC E) Relative fold change of BCL-xL gene expression levels in MDA-MB-231 cells after treatment with Au-P-TSC. Reproduced from ref. [251] Copyright 2020 Elsevier.

compounds showed that complexes with diphenylphosphinoethane were unstable transforming to a Au18 cluster and longer chain phosphines produced stable Au complexes in solution. Cytotoxicity of the stable phosphinogold(I) complexes showed activity against HeLa cells with complexes with hexyl chain length the most active and selective class of compound [247]. Sulaiman et al., also reported on phoshinogold (I) dithiocarbamate complexes Au-P-DTC-7–12. These complexes showed little to moderate cytotoxicity (IC_{50} = 3.45 - > 100) in A549, HeLa and HepG2 cancer cells examined [248]. Van Le et al., reported on some cytotoxic phosphinogold dithiocarbamate complexes Au-P-DTC-13 - 16 (Fig. 28**)** that induces severe ER stress in ovarian cancer cell models and causes a concentration dependent increase in calreticulin (CRT) expressing cells which can trigger anticancer immunogenic response [249].

Biofriendly thiocarbohydrates have also been used as ligands in the synthesis of mononuclear and binuclear phosphinogold(I) complexes because of their biocompatibility, water solubility and reduced toxicity. Cytotoxicity studies of these complexes indicate that the compounds show a broad spectrum of activity against MCF-7 (breast cancer), HCT116 (colon cancer) and PC3 (prostate cancer) cells with the nature of phosphine ligand influencing cytotoxicity. Also two of the dinuclear complexes showed great tumor specificity between PC3 cancerous and W-I-38 normal cells demonstrating the efficacy of these complexes in colon cancer (Fig. 29) [250].

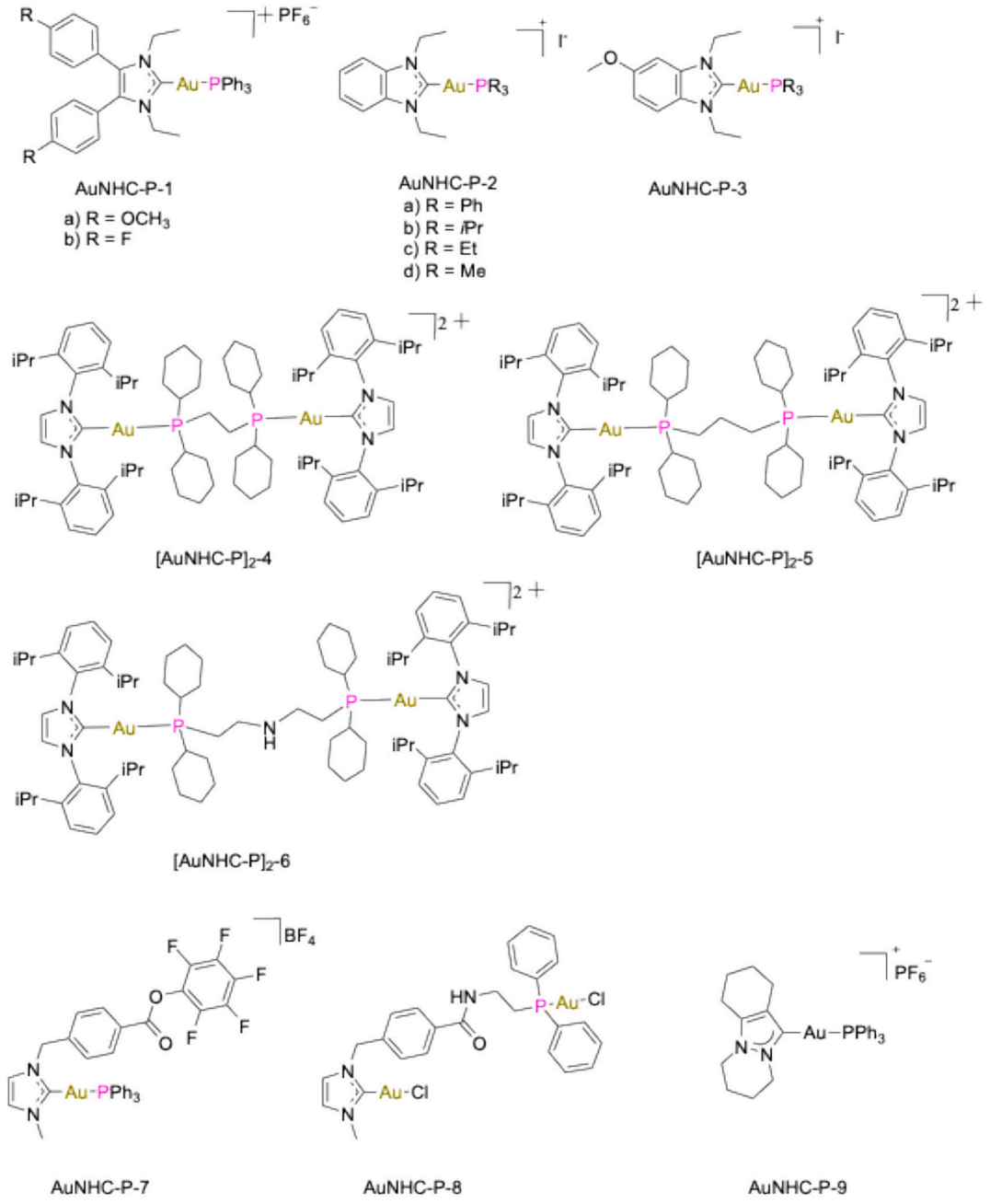


Fig. 31. Heteroleptic mononuclear and dinuclear Au(*I*)phosphine complexes containing N-heterocyclic carbenes.

Zarewa et al., synthesized four phosphanegold(I) thiosemicarbazone complexes (Au-P-TSCs) with high solution stability in DMSO and H_2O: Ethanol (1:1). These complexes showed potent anticancer activity in HCT116 (human colon cancer), MDA-MB-231 (human breast cancer), and B16 (murine skin cancer) cancer cells. Further studies on the mechanism of cell death shows that Au-P-TSC acts as potent apoptosis-inducing agent in breast cancer MDA-MB-231 cells, with upregulation of caspase-3, downregulation of BCL-xL, and depolarization of mitochondrial membrane potential in a concentration dependent manner (Fig. 30) [251]. Diversifying the route for the synthesis of metal complexes can help in the synthesis of a wider range of complexes. In this regard, Gonzalez-Barcia and co-workers synthesized cytotoxic neutral phosphinogold(I) thiosemicarbazones via electrochemical synthesis and cationic phosphinogold(I) thiosemicarbazones complexes via traditional chemical synthesis. The electrochemistry approach affords access to synthesize a wide range of Au-based complexes without the need for bases, ligands and counterions [252].

There is an increase in the use of N-heterocyclic carbenes (NHC) as ligands in bioinorganic chemistry. This may be related to the enhanced stability displayed by NHC in biological conditions because of strong σ-donation of NHCs and the ability to tune the lipophilicity of Au-NHC complexes by modulating the substituent groups on the heterocyclic ring [253–255]. In a SAR study of Au complexes containing 1,3-diethyl-4,5-diarylimidazol-2-ylidene ligands, and other ligands including triphenyl phosphine (Fig. 31), Liu et al., showed that incorporating a phosphine ligand to Au(I) 1,3-diethyl-4,5-diarylimidazol-2-ylidene complexes (AuNHC-P1) resulted in a 5-fold decrease in IC_{50} compared to the parent compound AuNHC-Br and higher cellular and nuclear uptake in MCF-7 and HT-29 cancer cells [256]. Ingo Ott and co-workers reported on the potent antiproliferative activities of AuNHC-P-2 in MCF-7 and HT-29 cancer cells. AuNHC-P-2 inhibits TrxR significantly, binds to bovine serum albumin, and accumulates significantly intracellularly and in the

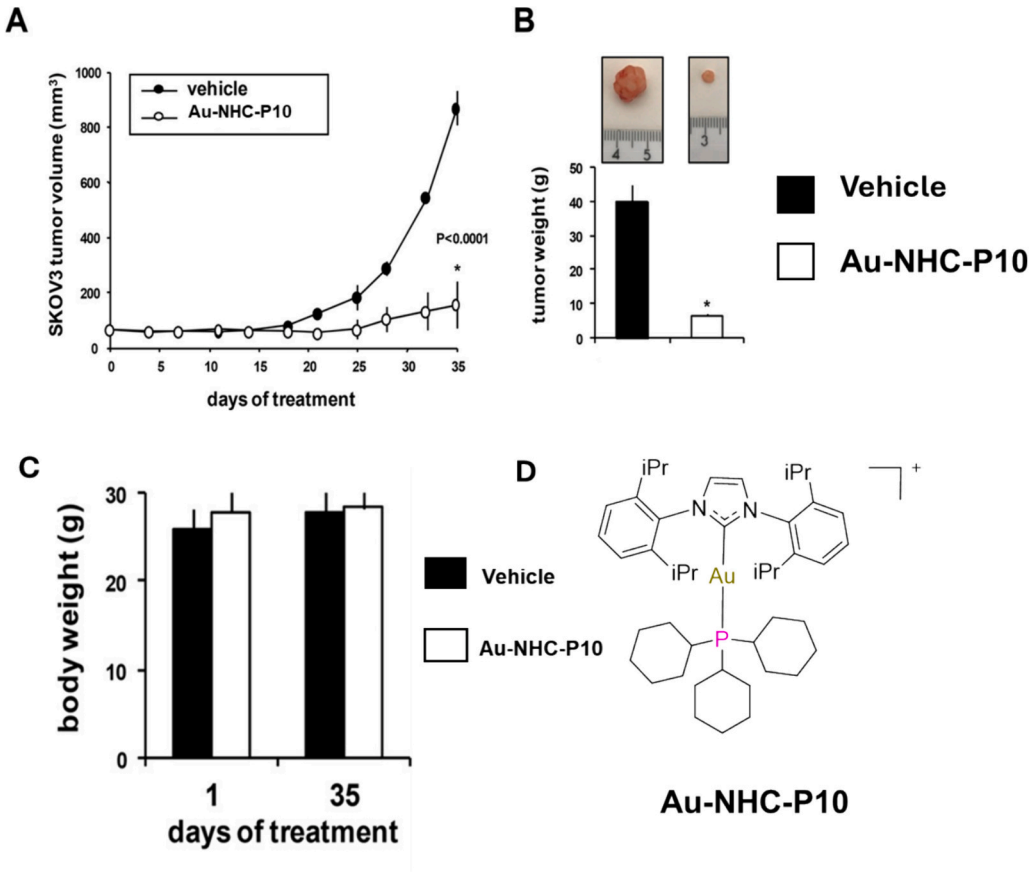


Fig. 32. In vivo Anticancer studies of Au-NHC-P10. Reproduced from ref. [261] Copyright 2022 American Chemical Society.

mitochondria compared to other carbenes. On the mode of cytotoxic action, AuNHC-P-2 induces cell death via apoptosis and accumulation of ROS [257]. To unravel the molecular mechanisms underlying the cytotoxic activity of Au(*I*)NHC phosphines, Ott and co-worker further examined the effect of AuNHC-P-3 (Fig. 31) phosphines to modulate redox homeostasis. Apoptotic cell death was observed as a result of irreversible loss of mitochondrial respiration that was triggered by imbalance in redox homeostasis. Furthermore, upregulation of pro-apoptotic proteins (p38 and JNK) and down regulation of thioredoxin was observed pointing to the role of thioredoxin reductase as a target for this class of Au-NHC phosphines [258]. This group later showed by ESI-MS that thioredoxin reductase is a realistic target of Au(*I*)NHC phosphines when incubated with C-terminal dodecapeptide of hTrxR containing selenocysteine at position 498 [259]. Furthermore they reported SAR studies of this class of Au complexes by substituting the triphenylphosphine with different alkyl phosphines AuNHC-P-2 (Fig. 31). Results from the antiproliferative uptake studies shows that alkyl substituted AuNHC-P-2 (Fig. 31) shows a decrease in potency and cellular uptake in MCF-7 and HT-29 cancer cells which could be attributed to the higher lipophilicity of the triphenylphosphine compared to the alkylated phosphines [260].

A series of seven complexes containing NHC and phosphine mixed ligands were described by Sulaiman and coworkers. The antiproliferative activity of all seven complexes were higher than cisplatin in ovarian cancer cells A2780 and A2780cis with a fold resistance (FR) ranging from 0.86 to 1.78, thus excluding cross-resistance to cisplatin in these cell lines. Au-NHC-P-10 the only member of the series with fold resistance <1 was chosen for further studies. Au-NHC-P-10 induced cell death through apoptosis, mitochondrial ROS, and DNA damage while causing G1 phase cell cycle arrest. Au-NHC-P-10 also inhibited 20S proteasome activity, and cell migration and significantly inhibits OvCa murine xenografts (Fig. 32) [261].

Further work by this lab on three dinuclear Au(I) complexes containing NHC and phosphine ligands ($[AuNHC\text{-}P]_2$ 4–6) (Fig. 31) showed that the novel dinuclear Au complexes showed a distinct mechanism of action inhibiting 20S proteasome activity and NF-kB in A549, while the enzymatic activity of TrxR was not affected. Furthermore, the dinuclear Au phosphine complexes reduced the expression levels of certain lung cancer stem cell biomarkers (ALDH1, CD133, CD44 and NOTCH1 receptor) in A549 lung cancer cell, and was more cytotoxic than cisplatin in A549-2D cell culture. The complexes also inhibited viability of A549 in 3D-multicellular tumor spheroids (3D-MCTSs) with an IC_{50} of 0.95 μM compared to cisplatin IC_{50} = 44 μM. These interesting results demonstrates the utility of Au phosphine complexes as next generation anticancer agents [262].

Casini et al., also synthesized cytotoxic Au(*I*)NHC phosphine containing an activatable ester moiety (AuNHC-P-7 & 8) (Fig. 31). These complexes showed 2-fold selectivity in A2780 ovarian cancer cells compared to non-tumorigenic HEK-293 T cells [263], while Sivarem et al., described a heteroleptic Au(*I*)phenylphosphine complex bearing a pyrazole-based ligand (AuNHC-P-9) (Fig. 31**)** that showed similar cytotoxicity to cisplatin in NCI-H1666 non-small cell lung cancer cell line [264].

Horvath et al., reported on the synthesis and anticancer properties of 25 phosphinogold(I) complexes bearing N-donor molecules such as imidazole, pyrazole, pyrrole, 1,2,3-triazole, 1,2,4-triazole, 9*H*-purine and adenine Au-P-N-1 – Au-P-N-4 (Fig. 33). The cytotoxicity of these dinuclear complexes is determined by the length of the alkyl chain between the phosphorus donor atoms with complexes with 5 or 6 bridging carbons presenting lower IC_{50}. Also, these complexes induces cell death by apoptosis but their effect in mitochondria processes was not prominent [265]. Maneiro reported two benzimidazole gold(I) phosphines Au-

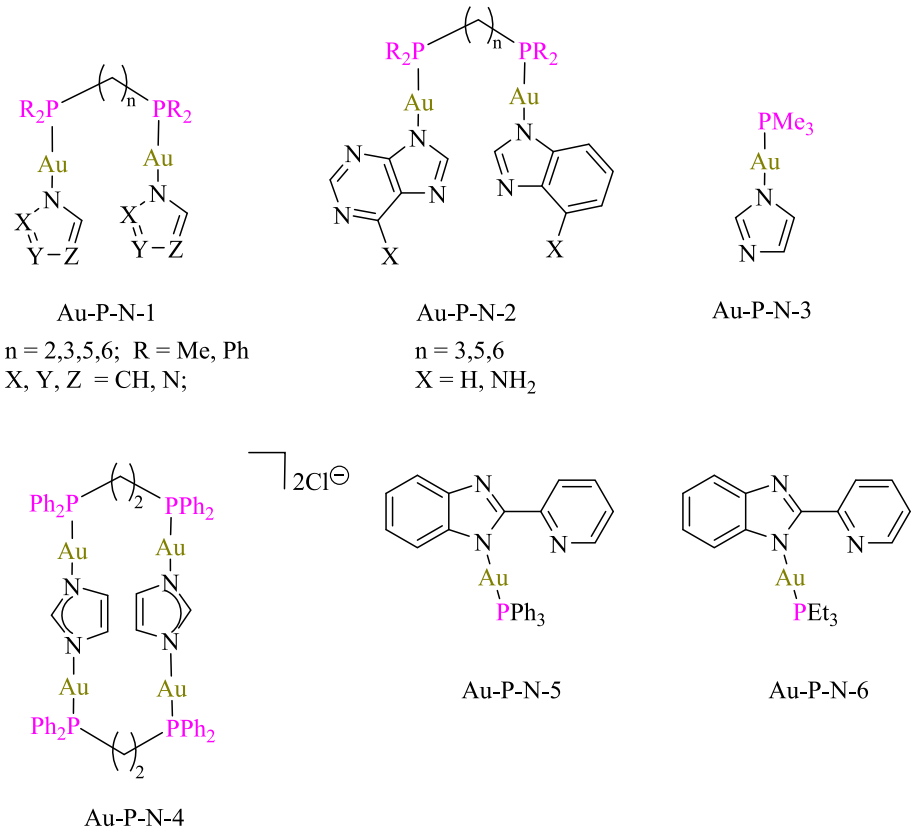


Fig. 33. Phosphinogold(I) complexes with N-donor ligands.

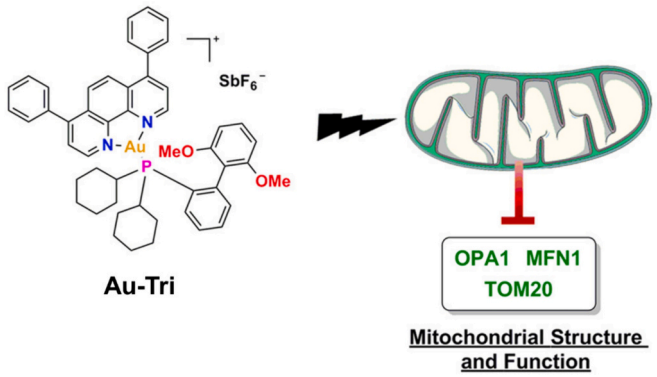


Fig. 34. Tricoordinate Au(I) phosphine perturbs mitochondria structure and function in MDA-MB-231 cancer cells. Reproduced from ref. [267] Copyright 2021 American Chemical Society.

P-N-5 or Au-P-N-6 Fig. 33 that exhibited potent anticancer activity in SH-SY5Y neuroblastoma cancer cell. In vitro analysis of these compounds indicate that they induce apoptosis and induce cell death through caspase dependent and caspase independent mechanism [266].

Furthermore, Awuah et al., reported SAR studies on tricoordinate phosphino Au(I) and arsino Au(I) complexes bearing N, N-bidentate ligands. The tricoordinate geometry of these Au(I) complexes seems to play an important role in anticancer activity, with IC_{50} values in the low micromolar range in MDA-MB-231 triple negative breast cancer cell (TNBC) and displayed high selectivity (>35 times) toward TNBC's over normal lung fibroblasts. This class of Au(I) phosphine complexes were found to fragment and perturb the mitochondria structure in MDA-MB-231 by significantly increasing the maximal cristae width in comparison to the vehicle control, downregulating OPA1, MFN1, MFF and TOM20, key proteins that are involved in mitochondrial structure homeostasis (Fig. 34). Further studies shows the Au-Tri depolarizes mitochondria membrane and showed in vivo tolerability in mice [267].

Au phosphine-alkyne is another class of heteroleptic Au complexes investigated for their antiproliferative effect in several cancer cell lines. This is due to their stable coordinative bond (strong Au—C σ-bond) that enhances stability in physiological conditions. Ott and coworkers synthesized some phosphinogold(I) alkynyl complexes P-Au-C ≡ CRa-f (Fig. 35) that showed selective inhibition of thioredoxin reductase over glutathione reductase. These complexes inhibited mitochondrial respiration and triggered significant anti-angiogenic effect in zebrafish embryos [268]. Later, they reported some bridged dinuclear phosphinogold (I) alkynyl complexes $[Py\text{-}C \equiv C\text{-}Au\text{-}PR_2]_2(CH_2)_n$ a-d Fig. 35 that inhibits TrxR mildly in MCF-7 breast cancer cells coupled with potent anticancer activity (0.7–2.8 μM) in MCF-7 breast cancer and HT-29 colon carcinoma cells for the active TrxR inhibitors [269]. Motivated by this interesting results, Ott and coworkers further studied the SAR of phosphinogold(I) alkynyl of the type PR_3-Au-C ≡ C a-f Fig. 35 by varying the phosphine ligands and evaluated their cytotoxic effects on cellular signaling and in vivo anticancer potency. While the cytotoxicity of the complexes was independent of the phosphino groups attached to the Au central atom, groups with alkyl or phenyl phosphines inhibited TrxR preferentially to complexes studied. [PPh_3-Au-C ≡ C-] was observed to significantly induce ERK1/2 phosphorylation and HSP27 phosphorylation as the signaling pathway. Initial difficulty in drug formulation for in vivo studies was overcome by nano formulation of [PPh_3-Au-C ≡ C] in a peanut oil nano emulsion prior to injection in mice however the treatment condition was not effective to inhibit tumor growth [270]. Recently, Wang et al., reported some Au(I) phosphines PR_3-Au-C ≡ C-2 - PR_3-Au-C ≡ C-7 Fig. 35 that exhibited in vitro cytotoxicity in PC3 prostate cancer cells and showed significant reduction of tumor weigh and in vivo tolerability in PC3 injected nude mice compared to auranofin and cisplatin [271].

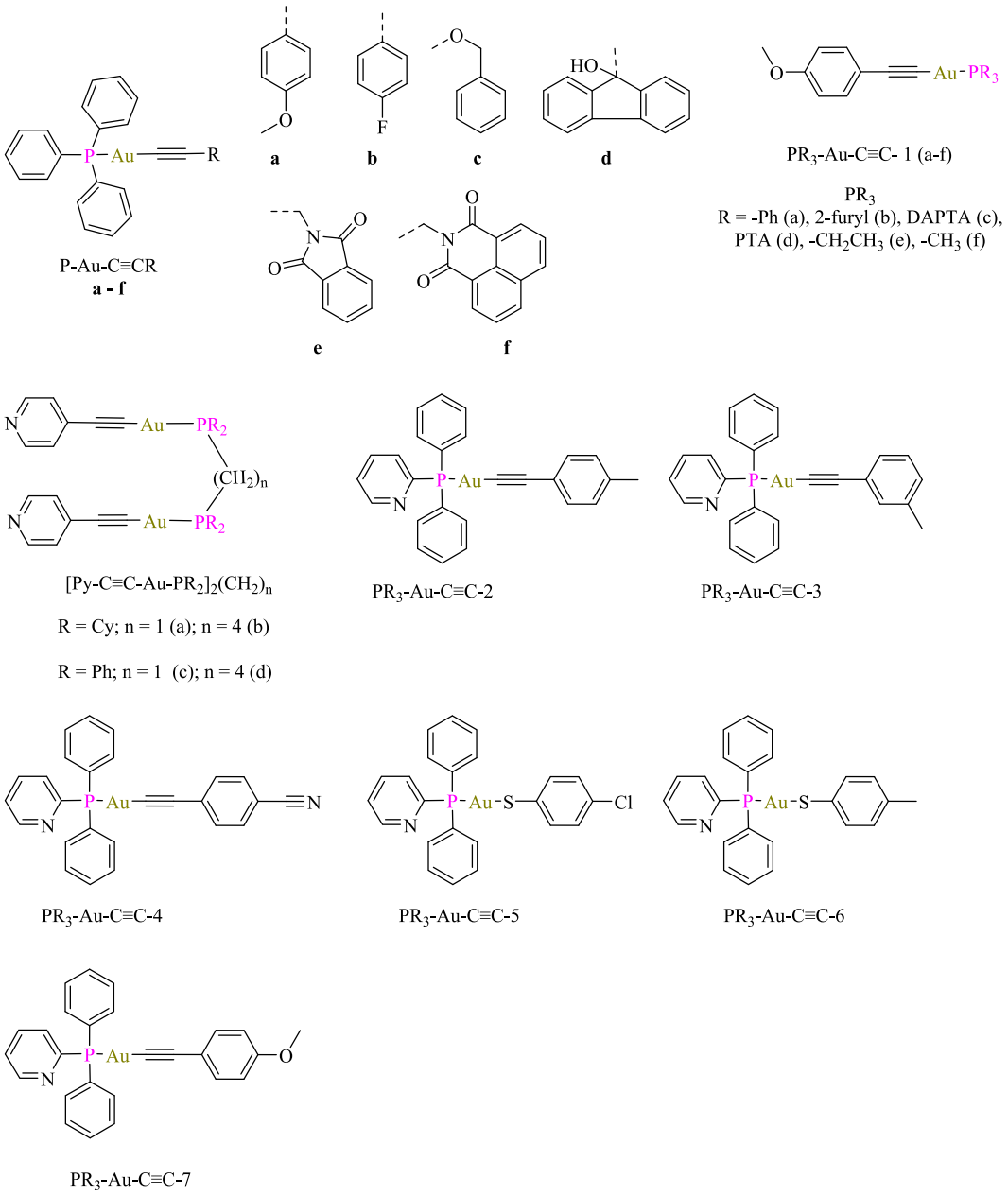


Fig. 35. Chemical structures of Au phosphine-alkynes.

Balasingham et al., reported on some luminescent Au phosphine-alkyne that showed cytotoxicity in MCF-7 breast cancer cells compared to the free ligand. Further live cell imaging with confocal microscopy showed localization of the Au phosphine-alkyne in the cytoplasm Fig. 36 [272].

Complexation of metal complexes with biologically active molecules such as non-steroidal anti-inflammatory drugs (NSAIDs), flavonoids, chloroquine and cinnamide have been shown to improve the anticancer properties of the metal complexes [273,274]. Tabrizi and Romanova synthesized phosphinogold(I) alkynyl complexes bearing ibuprofen, a NSAID, IBU-C ≡ C-Au-PPh_3 (Fig. 37**)**. This compound showed solution stability in DMSO/PBS solution (1:99 *v*/v) and potent anticancer activity with 4.2, 3.7, and 1.7-fold more cytotoxic than cisplatin in HT-29, MDA-MB-231, MCF-7 cancer cell lines respectively [275]. The role of dietary flavonoids in cancer management has been widely discussed and the anticancer activity of their phosphinogold alkynyl complex was studied in PC-2 (human prostate cancer) cell line. The study showed that FL-C ≡ C-Au-PPh_3 (Fig. 37) has an improved bioactivity compared to the free compound. Further studies are required to elucidate whether the cytotoxicity observed was a result of synergistic effect of the flavone and Au (PPh_3) fragments [276]. Au(I) complexes containing propagylated cinnamides and lipophilic (PPh_3) or water soluble (PTA) ligands have also been explored for their anticancer activities [CNA-C ≡ C-Au-PPh_3] or [CNA-C ≡ C-Au-PTA] (Fig. 37**)**. These complexes showed good stability in a buffer solution containing 50 mM Tris, 4 mM NaCl, pH 7.4 over 72 h using UV–vis spectroscopy. The complexes containing lipophilic PPh_3 ligands were more potent compared to the complexes with hydrophilic ligands in A549 (lung), D24 (melanoma), and HT1080 (fibrosarcoma) cancer cells. Also [CNA-C ≡ C-Au-PPh_3 -c] inhibit TrxR, induces mitochondrial-mediated apoptosis and showed significant anti-angiogenic effects in zebrafish embryos, in contrast to cisplatin, which is almost inactive [277].

Suntharalingam, Awuah and coworkers reported on the anti-breast cancer stem cell (CSC) properties of some linear Au(I) phosphines

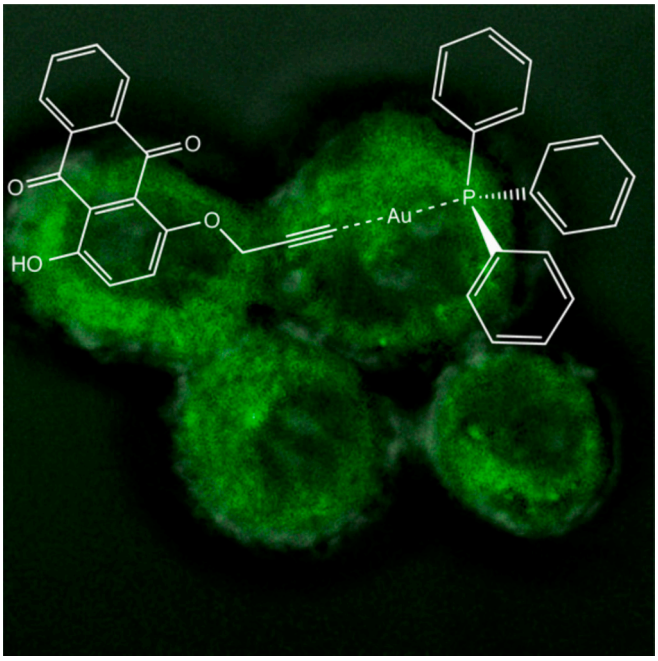


Fig. 36. Figure showing luminescent Au(I) phosphine alkyne localizing in the cytoplasm. Reproduced from ref. [272] Copyright 2012 American Chemical Society.

bearing non-steroidal anti-inflammatory drugs (NSAIDs) Fig. 37 by inhibiting cyclooxygenase-2 (COX-2) – an enzyme responsible for inflammation and pain. The cytotoxicity of Au-NSAIDs1–3 was examined against a panel of human, murine bulk breast cancer cells (MDA-MB-231, MDA-MB-468, HMLER, and 4 T1) and breast CSC-enriched cells (HMLER-shEcad) complexes and they showed potency with IC_{50} in the lower micromolar range. Interestingly, Au-NSAIDs-1 showed greater potency at inhibiting breast CSC than clinically approved breast cancer drugs such as 5-fluorouracil, capecitabine, cisplatin, and carboplatin while showing selectivity for breast cancer cells against non-tumorigenic HEK 293 cells. Further mechanistic studies showed that the inhibitory activity of Au-NSAID-1 is related to its ability to inhibit COX-2 activity, promotes apoptosis and increase intracellular ROS [278].

To understand whether Au-phosphine complexes act as prodrug or the Au atom remains attached to the phosphine in biological systems, Bodio et al., studied structurally similar Au phosphine complexes bearing coumarin ligands Au-P-Cl-1, Au-P-Cl-2, Au-P-SAcGlu and its non-Au phosphonium counterpart Fig. 38 [279,280], and track their activity through fluorescence microscopy. Despite the similarity in the structure of these compounds, they show different cytotoxic activity, subcellular localization, and biodistribution in the zebrafish larval model. While the Au-phosphine complexes accumulate in lipid raft with no ROS accumulation, the phosphonium compound accumulated in the cytoplasm [279]. Further they showed that potency of Au phosphine complexes can be increased by combining them with a phosphonium ligand Au-P-Br-4 – Au-P-Br-9 Fig. 38. This is due to the lipophilic cationic character of the complex that could facilitates entry into the cells to elicit anticancer activity [281]. Later, they reported on Au-P-Br-3 with structural capability for in vitro tracking through two photon imaging and improved anticancer activity due to the presence of coumarin

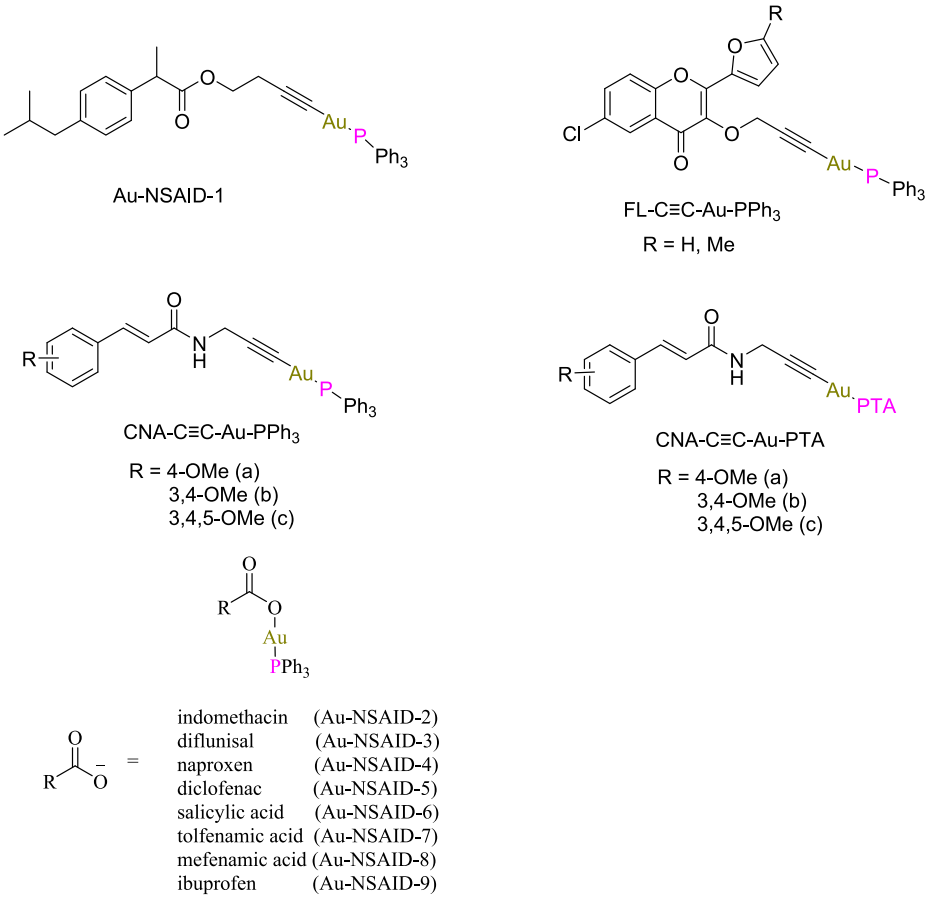


Fig. 37. Chemical structures of anticancer phosphinogold alkynyl complexes biologically active molecules.

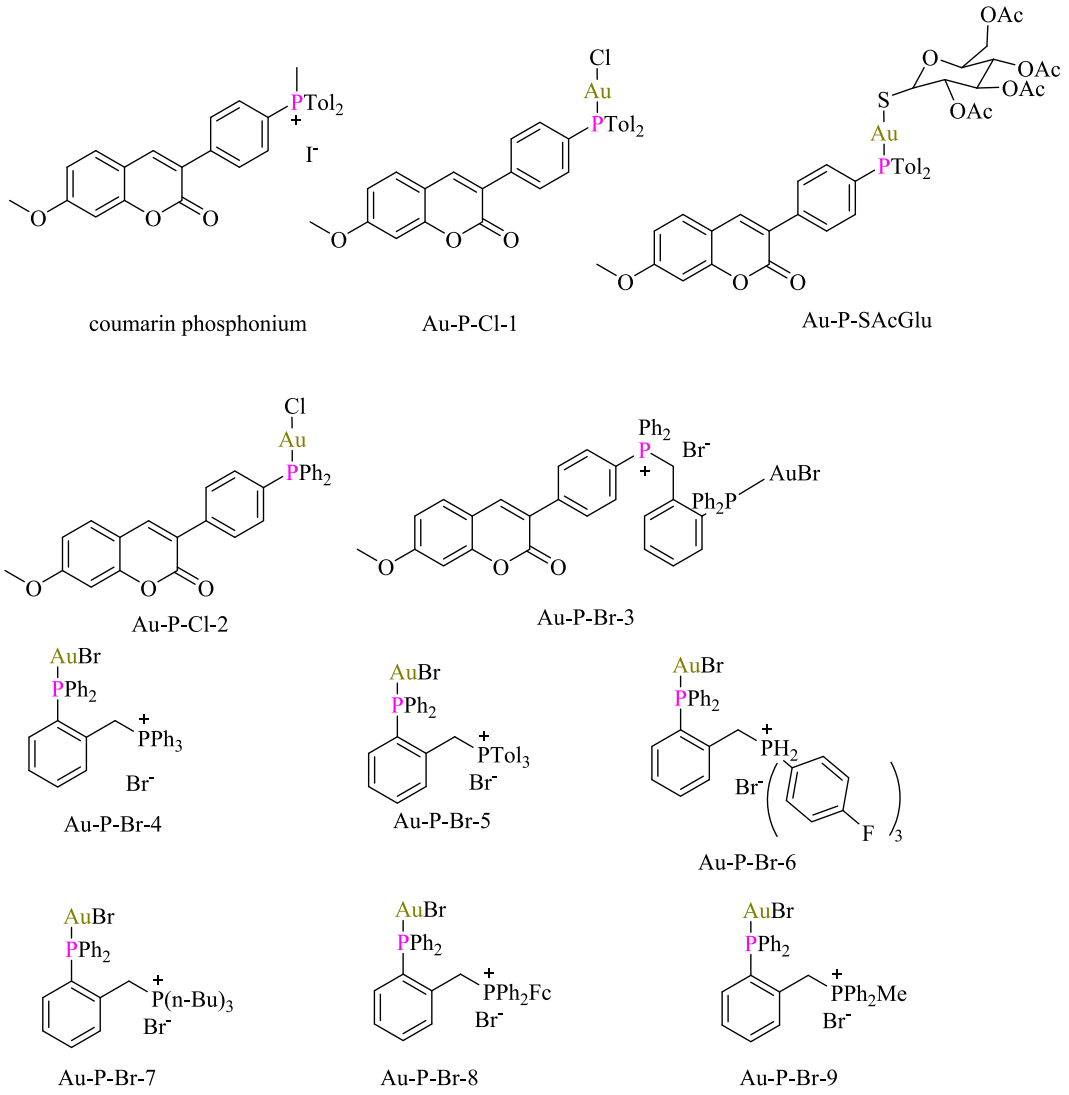


Fig. 38. Figure showing Au complexes bearing coumarinphosphine ligands.

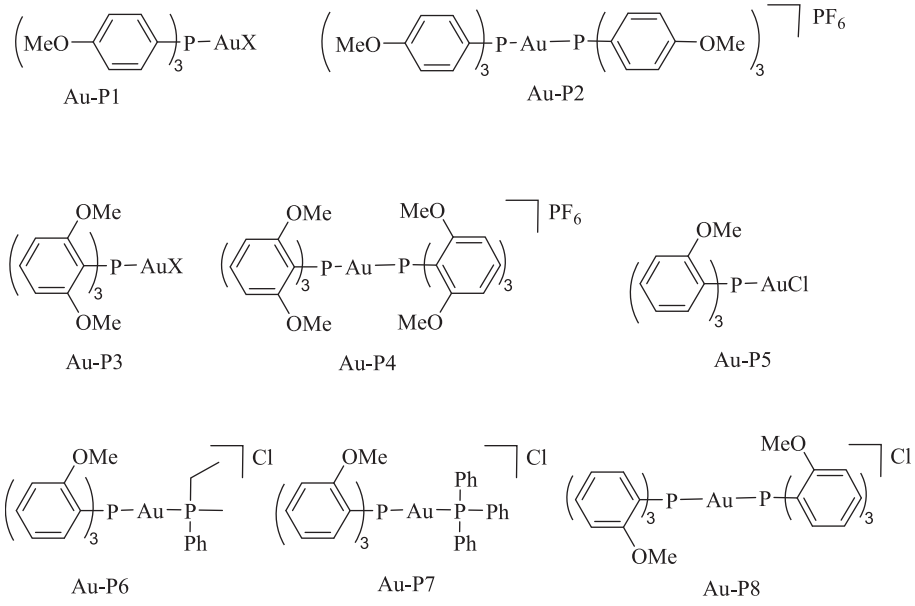


Fig. 39. Structures of Au (I) complexes bearing methoxyphenyl phosphine ligand. X═Cl, Br, I, Cl_3.

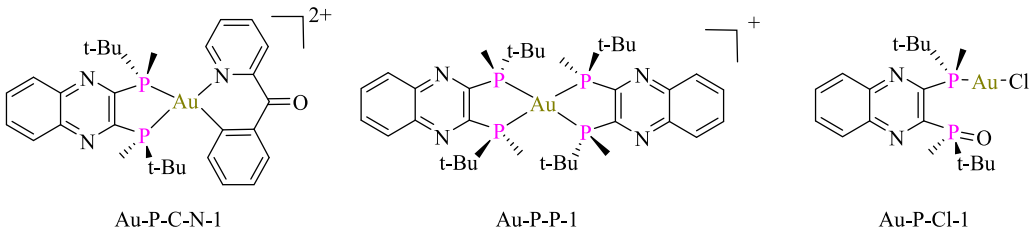


Fig. 40. Au(III) and Au(I) complexes with QuinoxP* ligands.

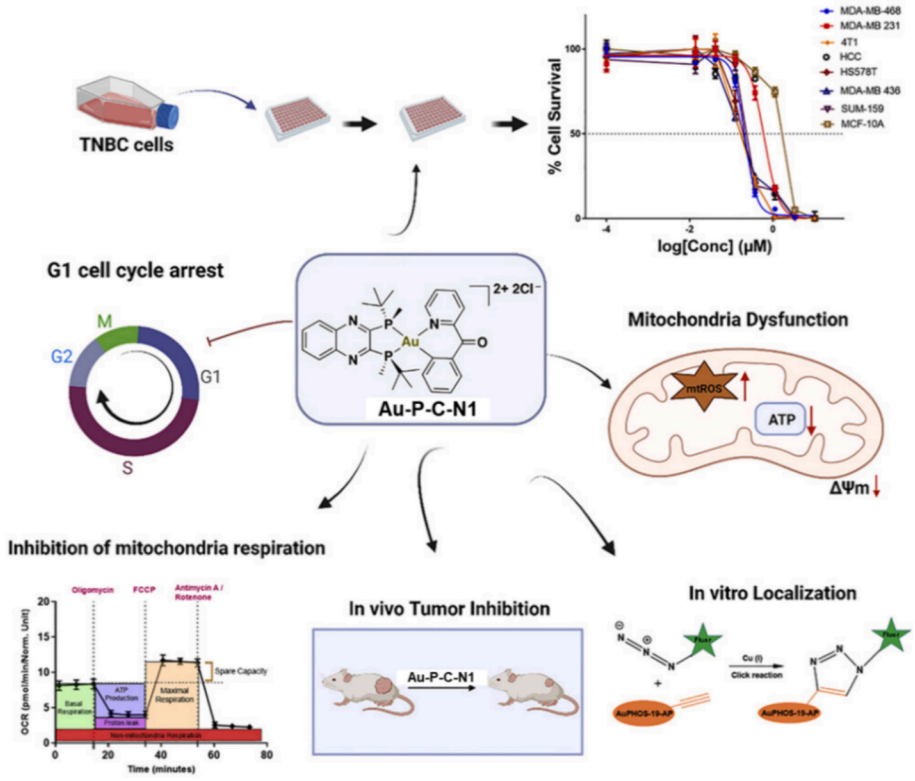


Fig. 41. Diagram showing the cytotoxicity of Au-P-C-N1 in different TNBCs in vitro and in vivo, and the mechanism of action in TNBCs. Reproduced from ref. [287] Copyright 2022 Elsevier.

and phosphonium ligands. This complex shows good in vitro anticancer activity in A549, MDA-MB-231 and SW480 cancer cells. Further they demonstrate in vivo potency in CT26 tumor bearing BALB/c mice [282].

Au(I)/(III) complexes bearing methoxy substituted triphenyl phosphines have also been shown to have anticancer efficacy in 2D and 3D cancer model in the lower micromolar range (Fig. 39) [283,284]. The cationic Au(I) complexes showed improved anticancer activity compared to the neutral Au(III) complexes. Furthermore, there was an increase in ROS produced, induction of apoptosis, sub G1 cell cycle arrest and caspase-3 activation in HeLa cells [283]. Also, Au(I) complexes containing 2-$BrC_6F_4PPh_2$ have been reported to show excellent antiproliferative activity in 2D and 3D spheroids of HeLa cells. These complexes induce mitochondria damage by loss of membrane potential and increase in ROS production [285].

1.3.3.4. Cyclometalated phosphinogold(I/III) complexes. The development of novel cyclometalated phosphinoAu(I/III) complexes has been on the increase in recent years owing to the strong Au-carbon σ-bond that inhibits adverse intracellular redox processes and boost the stability of Au complexes under physiological environment. A variety of cycloaurated complexes bearing C—N, C-N-N, C-N-C and C—C ligands have been successfully synthesized with important anticancer activities and mechanism of actions. Sun et al., reported on dinuclear cyclometalated phosphinogold(III) complex that inhibits TrxR at nanomolar concentration, induces ER stress and inhibits tumor growth in animal models [286].

Awuah and coworkers reported on the SAR studies of cyclometalated Au(I/III) complexes with either QuinoxP* or dppe bisphosphine ligands. Comparing Au-P-C-N-1, a Au(III) dicationic compound with its monocationic Au(I) counterpart Au-P-P-1, Au-P-C-N-1 exhibited greater physiological stability in PBS and DMEM compared to its reductive elimination product Au-P-P1 (Fig. 40). These findings were supported by computational studies which showed that the four Au—P bonds in Au-P-P-1 are ~2.5 Å, while the two Au—P bonds in Au-P-C-N-1 show shorter bond lengths of 2.38 and 2.5 Å, respectively, which is indicative of stronger bonds [26].

Further in-depth mechanistic study on Au-P-C-N-1 by Olelewe et al., in a panel of TNBCs indicate the ability of this Au(III)-phosphine to selectively interact with oxidative phosphorylation (OXPHOS) in different TNBCs by inhibiting mitochondria respiration, depolarizing mitochondria membrane, depleting mitochondria DNA, and inducing significant AMPK activation. Furthermore, the compound causes cell cycle arrest in the G1 phase and shows in vivo tolerability in TNBCs Figure 41 [287]. Later, Kim et al., carried out a genome wide CRISPR

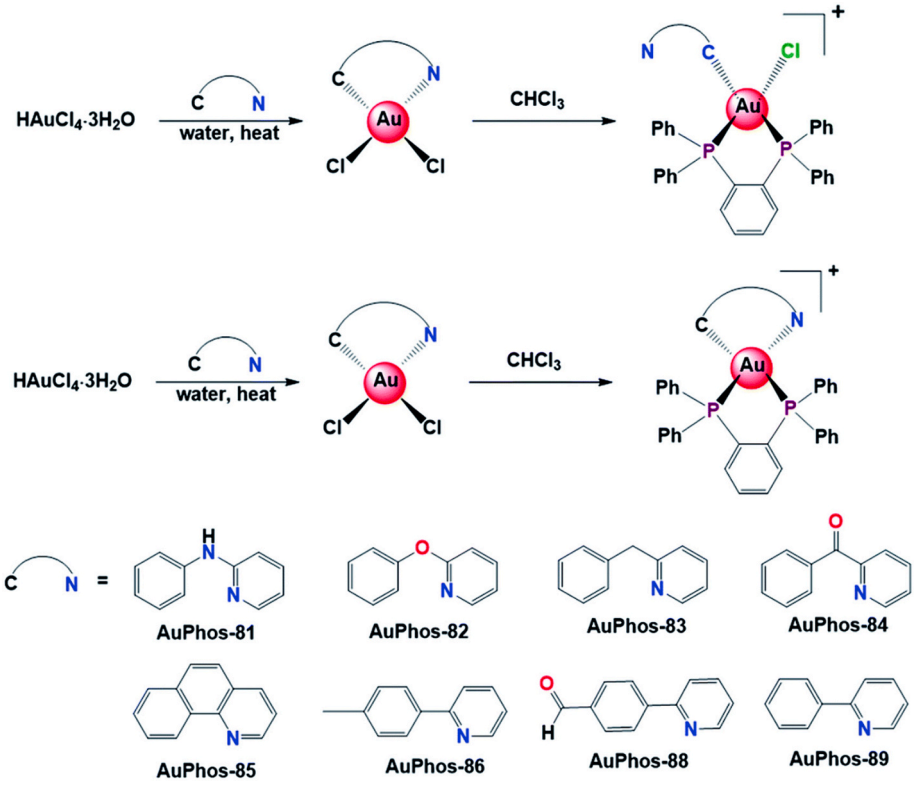


Fig. 42. Au(III) phosphines bearing C—N cyclometalated framework. Reproduced from ref. [289] Copyright 2021 The Royal Society of Chemistry.

screen to elucidate the target of Au-P-Cl-1 Fig. 40**.** Using TOXCRISPR, their study reveals proteins involved in mitochondrial carriers, mitochondrial metabolism, and oxidative phosphorylation [288].

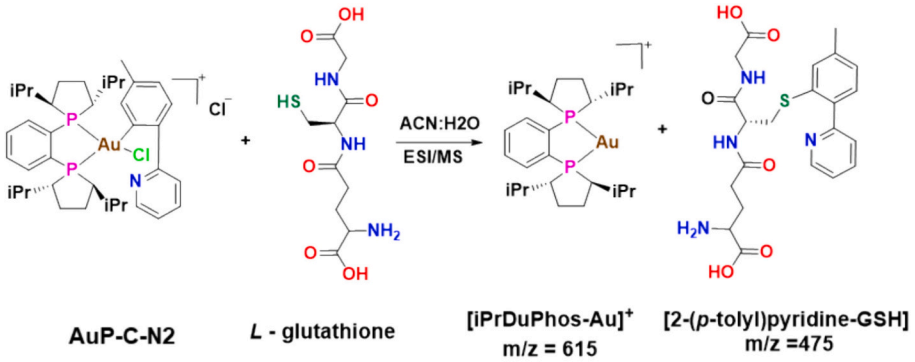
Expanding the library of C—N cyclometalated Au complexes Awuah and Sullivan lab reported on Au(III) complexes bearing DPPBz bisphosphine ligands Fig. 42. These complexes showed in vitro potency across a wide range of cancer cell lines with significant lethality in a panel of NCI-60 cell lines assessed. AuPhos89, the lead compound in the study stimulates mitochondria respiration in mouse liver and cancerous liver cells leading to oxidative stress and apoptotic cell death [289]. The novel mechanism of action of this compound has propelled advanced research into its use in other diseased conditions [290,291].

To understand the speciation of phosphinogold(III) complexes in the presence of biological reductant such as glutathione, Awuah et al., synthesized seven cytotoxic C—N cyclometalated Au(III) complexes bearing chiral MeDuPhos or iPrDuPhos ligand. AuP-C-N2 was incubated with L-glutathione (1:1) in acetonitrile/water mixture and speciation adduct formed was monitored by HPLC-MS over 4 h (Fig. 43). Products consistent with reductively eliminated C—S bond was observed immediately after incubation corresponding to peaks with reduced Au(I) adducts $[IPrDuPhos\text{-}Au]^+$ ($m/z = 615.2$) or $[IPrDuPhos\text{-}Au\text{-}ACN]^+$ ($m/z = 656.2$) and 2-(p-tolyl)pyridine-GSH ($m/z = 475$) while the parent peak was observed throughout the experiment as M^{2+} ion. Analysis of the HPLC results calculated from % area under the curve (%AUC) for each peak showed that while the peak intensity of the parent ion reduced, the peak intensity of the adducts increased over the 4 h time interval (Fig. 43). They further showed that these chiral Au(III) complexes have potent anticancer activity in vitro and in vivo cancer cell models and inhibit oxygen consumption rate (OCR) in MDA-MB-231 (triple negative breast cancer model) [292].

Structural modification to Au(III) complexes offers a path to the synthesis of stable complexes. Arojojoye et al., rationalized that stability of cyclometalated Au(III) complexes can be improved by substituting C—N with C—C cyclometalation. SAR studies was carried out to synthesize novel C—C cyclometalated Au(III) bisphosphines from the reaction of μ-chloro biphenyl Au(III) [293–295] and different bisphosphine ligands Fig. 44. The complexes demonstrate high physiological stability in GSH and blood serum showing unaltered absorbance peaks and absence of reductive elimination product for all compounds except for highly conjugated Au-P-C-5. On the mechanism of action studies, destabilization of cellular energy homeostasis through mitochondrial uncoupling is known to create vulnerability in cancer cells. Au-P-C3 depolarizes mitochondria membrane, increases oxygen consumption even at the inhibition of ATP synthase, and causes a decrease in mitochondrial ATP production leading to mild uncoupling activity in TNBCs. Further in vivo anticancer studies reveals that Au-P-C3 inhibit the growth of 4 T1 in mice [296].

Che et al., reported on C-N-C cyclometalated Au complex that induces autophagy in HeLa cancer cells [297,298]. Au-P-C-N-C-1 Fig. 45 is stable physiologically with impressive in vitro selectivity about 2.3–2.9 between normal and cancerous cell line [298]. They later reported on six dinuclear cyclometalated Au(III) complexes Au-P-C-N-C-2 Fig. 45 that showed impressive anticancer activities in PLC, HepG2 and HeLa cancer cells. This study enabled SAR studies where the cytotoxicity of the different complexes was observed based on variation of phosphines backbones (alkyl chain length elongation). The most promising candidate Au-P-C-N-C-2 containing a propyl phosphine backbone further showed promising anticancer activities in vivo and TrxR inhibition. Further mechanistic studies revealed that this compound induces ER stress [286]. Casini et al., also worked on cyclometalated Au complexes bearing water soluble PTA ligand Au-P-C-N-C-3 Fig. 45. Although the IC_{50} of Au-P-C-N-C-3 is ~50 μM in the cell lines studied, it inhibited cytosolic thioredoxin reductase in the low nanomolar range [299].

Square planar enantiomeric Au(III) complexes containing QuinoxP ligands that showed high solution stability has also been reported by Awuah et al., These complexes also showed similar anticancer activities in HCC1937, H460 and MDA-MB-468 cancer cells [300]. Furthermore, cyclic trimer and tetramers containing Au-phosphines have been ported by Barghava and co-workers Fig. 46. These complexes were stable in PBS solution at room temperature for 72 h while showing significant potency



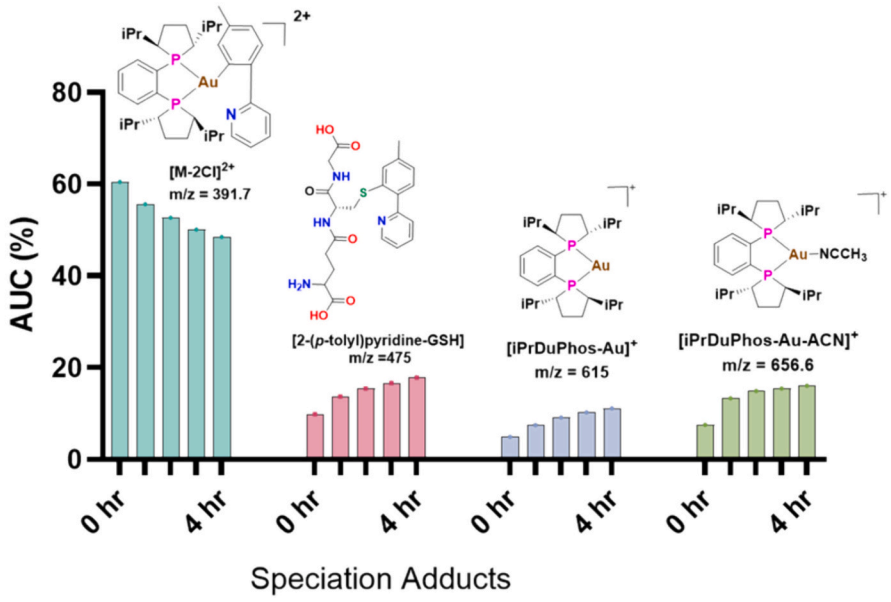


Fig. 43. Speciation studies of chiral Au(III) phosphine. AUC (area under the curve).

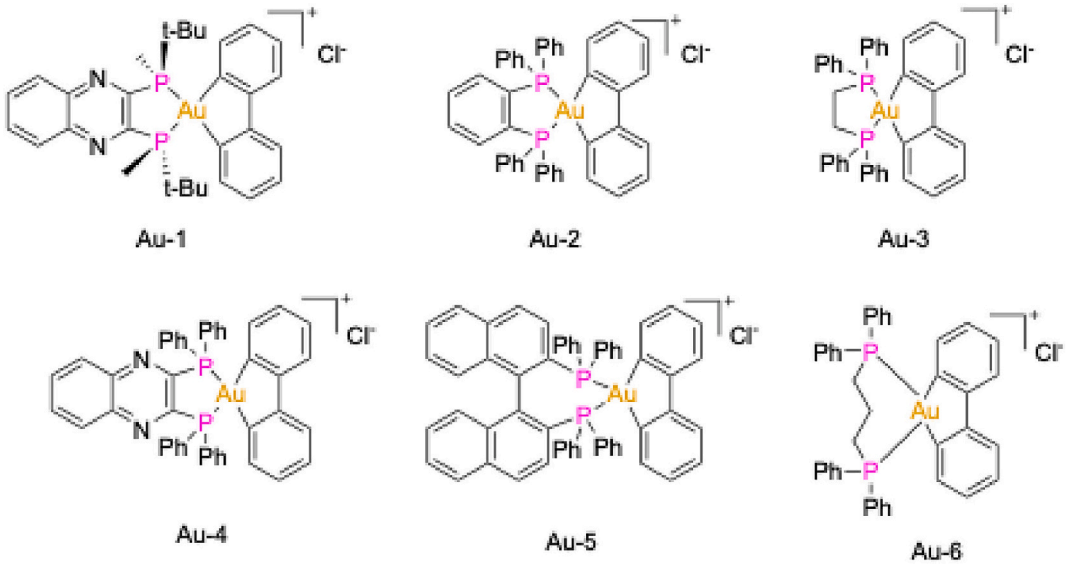


Fig. 44. Structures of Au(III)-C^C cyclometalated complexes.

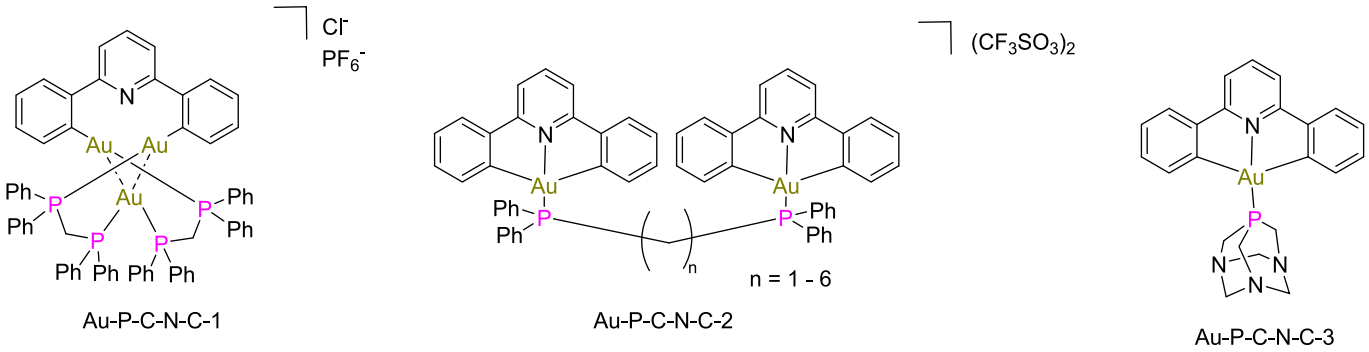


Fig. 45. Cyclometalated C-N-C- Au complexes bearing phosphine ligands.

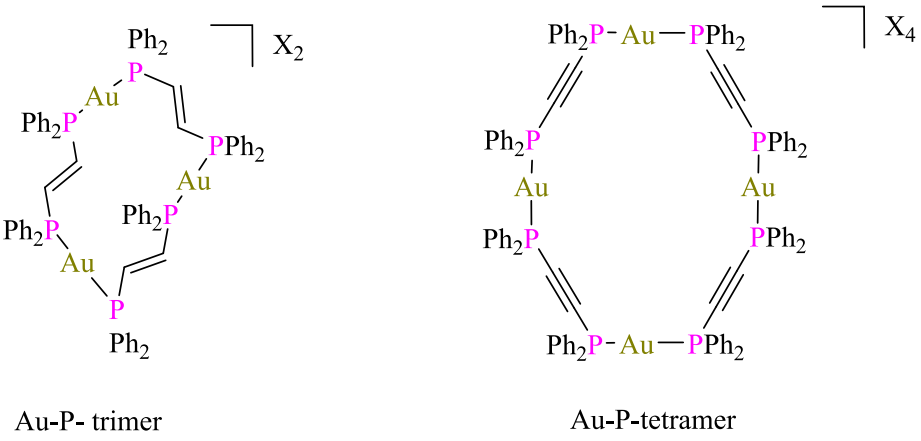


Fig. 46. Structures of Au phosphine trimers and tetramers. X = OTf and PF_6.

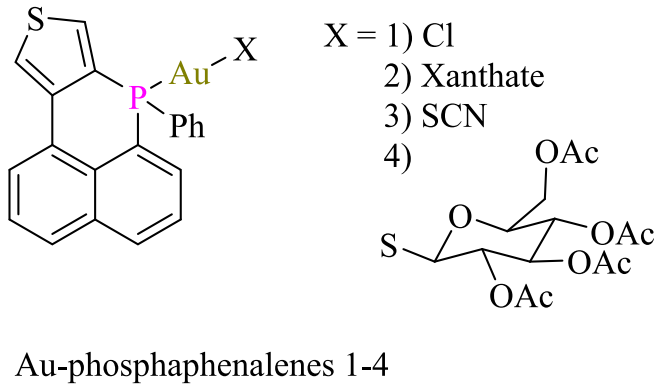


Fig. 47. Anticancer gold phosphenalenes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and selectivity toward DU 145 (prostate cancer), HeLa (cervical cancer), MDA-MB-231 breast cancer and HT1080 (fibro sarcoma cancer cells), with IC_{50} values in the range of 0.04–4.65 μM. The mechanism of cytotoxicity of these complexes were investigated in HT1080 cancer cells using wound healing assay, actin staining, flow-cytometry and Hoechst nuclear staining. Condensation of actin polymers and inhibition of migration potential was observed. Moreover, there was disruption of mitochondria function as seen in the depolarization of the mitochondria membrane, induction of apoptosis, G0/G1 cell cycle arrest and increase ROS production. These reports point to the potential of cyclic Au phosphine complexes in anticancer treatment [301].

Romero-Nieto et al., reported Au complexes bearing phosphorus heterocyclic ligands Fig. 47 that showed significant cytotoxicity in four glioma cells [302]. The use of phosphorus heterocycles in ligand design of anticancer agents is rare, this class of compounds possess distinct chemical properties from phosphines and can be utilized in synthesis of novel anticancer agent with unique mechanism of action.

1.4. Limitations and future perspectives

Despite the potential of gold-phosphines in medicine, it is critical to acknowledge that this field of research is continually evolving with many challenges, but opportunities abound for new therapeutic application for Au phosphines in the clinic. To achieve economic viability and accessibility of Au drugs, simple, robust, and reproducible synthetic methods are critical to advance the field of gold phosphines. Some of the current synthetic methods employed include reaction of the ligand with Au precursors such as $[AuCl_4]^-$, $[AuCl(SMe_2)]$, or Au salts, transmetallation reaction from Ag or Cu complexes or through electrosynthesis. These methods, though efficient, have some drawbacks which include the need for air free techniques, risk of possible contamination from other metals, long reaction times and the limited scope of ligands that can be employed hence the need for newer approach to the synthesis. For more detailed work on the synthetic approaches to synthesis of Au complexes, readers may refer to [303–306] Also, more research needs to be devoted into optimizing the pharmacodynamic properties of Au phosphines to reduce toxicity and improve drug specificity and localization. Improved drug delivery and localization can be achieved by methods such as drug encapsulation with biocompatible proteins, biodegradeable polymers which have been shown to improve drug uptake, reduce toxicity and increase clinical application [307–313].

Furthermore, the field of computational chemistry and machine learning is burgeoning, and it can be applied to aid in the design of Au

phosphines, their redox stability, and predict their reactivity and molecular interactions with protein.

1.5. Conclusion

In conclusion, it is evident that Au phosphine complexes can play an important role in the development of next generation therapeutics. While Pt and other metal-based drugs remain effective in the treatment of cancer and other diseases, there is a need for improved therapy to overcome drug resistance and toxic side effects presented by current therapies. Also, the fact that Au complexes can cause cytotoxic activity through different mechanism of action different from other metal-based drugs provides impetus for its sustained research. Au complexes with phosphine donor ligands represent an interesting class of compounds that has garnered attention in the past few decades due to their diverse structural motifs, electronic properties, and cross functional applications in chemistry and biology. As outlined, there is an enormous phosphine structural scaffold available to a chemist and this has contributed to the large body of work on Au-phosphine complexes. Additionally, Au-phosphine complexes have shown promise in chemical biology with impressive anticancer, antimicrobial, and anti-inflammatory properties. Their ability to interact with biological targets has also led to the development of potential therapeutic agents for various diseases.

In summary, Au complexes with phosphine donor ligands offer exciting opportunities for both fundamental inorganic chemistry research and practical applications not just in medicinal chemistry alone but also in catalysis, and materials science [11,25,314,315] [5,316–319].

Notes

The authors declare the following competing financial interest(s): S. G.A. has patents pending to the University of Kentucky Research Foundation. S.G.A. serves on the advisory board and is Chief Science Officer for Phronesis AI.

Declaration of competing interest

The authors declare the following competing financial interest(s): S. G.A. has patents pending to the University of Kentucky Research Foundation.

Data availability

Data will be made available on request.

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