Review

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Future Medicinal Chemistry

Gold(III) complexes in medicinal chemistry

A number of gold(III) compounds has been designed with the objective of overcoming the disadvantages associated with the platinum-based drugs for cancer treatment. Compounds of a remarkable structural manifold show significant antiproliferative effects *in vitro* against a number of cancer cells, including cisplatin resistant ones. The target of most of them is, unlike that of cisplatin, not the DNA. Although the mechanisms of action displayed by the gold compounds in biological media are still under investigation, many studies show evidence that the cellular targets are mitochondria-based. Recent advances in gold(III) medicinal chemistry also recommend such compounds for other pharmacological applications such as the treatment of viral or parasitic diseases. The radioactive isotopes ^{198}Au and ^{199}Au present potential in radiotherapy.

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Background

The noble character and its lustrous shine make gold perhaps to that metal, which produced most interest and attraction in the history of mankind. Despite the fact that it never had a serious practical use, it always has been desired for jewelry, religious cult objects or simply as demonstration of the wealth of its owner in almost all civilizations around the world and over the centuries. Nowadays, chemists and physicists are convinced that the element gold indeed is a matter of special importance and deserves particular attention because of many extraordinary features of its chemistry. Many of them, such as the formation of aurophilic interactions, the stabilization of gold compounds with the metal in higher oxidation states, aggregation to intermetallic compounds and planar clusters as well as some unusual photophysical properties can be ascribed to relativistic effects, which achieve a maximum with gold among the *5d* elements [1]. The energetic separation of the *d* and *s* valence shells of gold is significantly smaller than that of silver, the upper element in its group, which leads to the efficient formation of linear two-coordinate gold(I) complexes. On the other hand, the destabilization of the *5d* orbitals permits explanation for the occurrence of the oxidation state +III in gold chemistry, which is almost absent for silver. Gold frequently forms compounds with uncommon stereochemistry in oxidation states ranging from -I to +V, which have revealed singular properties like the facility to form Au–Au and Au–(other) metal bonds in clusters. Au(III) compounds are diamagnetic having a $[Xe]4f^{14}5d^{8}$ low-spin configuration, and normally have square-planar geometry [2].

All early attempts to use this fascinating metal or its compounds for medical applications were suspicious and without apparent success until a few decades ago [3]. The more serious medicinal chemistry of gold compounds started in 1890, when Robert Koch discovered some bacteriostatic effects of dicyanidoaurate(I), $[Au(CN)_2]^-$, including promising activity as antimicrobial agent against *Mycobacterium tuberculosis*, the bacteria responsible for tuberculosis [4]. This led to the use of gold compounds for tuberculosis therapy in the 1920's [5–8]. Gold therapy was then extended to the treatment of other diseases such as rheumatoid arthritis (chrysotherapy), on the mistaken belief that it was

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Key terms

Chrysotherapy: A designation for the treatment of the inflammatory disease rheumatoid arthritis with Au(I) compounds, also called 'aurotherapy'.

CD4+ T lymphocytes: White blood cells that play an essential role in the human immune system.

a bacterial infection [9]. Modern trends of medicinal coordination chemistry of gold have been summarized in a number of excellent reviews [7–13], mainly focusing on the families of well-established Au(I) pharmaceuticals, their mechanisms of activity and interesting *in vivo* chemistry. But it became also evident that Au(III) species formed by *in vivo* oxidation of Au(I) compounds may play a role in the biological distribution patterns and activity of gold compounds [10,13].

The enormous progress of our chemical knowledge about the gold(III) chemistry during the recent two decades, which is reflected by more than 2,500 papers published about this topic during this time, also draw the attention of researchers working in the field of medicinal chemistry to this oxidation state of gold. Gold(III) compounds appeared to be natural candidates as potential alternative to platinum(II). Au(III) is isoelectronic with Pt(II) and many of its complexes are isosteric with the square-planar platinum(II) compounds. Even when gold(III) complexes should be reduced rapidly by naturally occurring reductants such as thiols or disulphides, we must keep in mind that the corresponding reduction potential can be modulated by appropriate ligand systems (particularly chelators) and, thus, it is not rare that Au(III) complexes with chelating phosphinothiols are stable [14–17], while reduction is readily observed when Au(III) precursors are exposed to monodentate thiols and phosphines. Similar stabilization has been found with cysteinato and cyanido ligands [10]. Therefore, during the recent years a number of potential applications in therapeutic medicine have been identified for gold(III) compounds such as cancer treatment [18–29] or antibacterial activity [30].

Irrespective to the recent advances in medicinal chemistry on developing more effective anticancer drugs, there is an urgent necessity for new therapeutic alternatives against parasitic diseases (Chagas' disease, leishmaniasis, African tripanosomiasis, malaria and schistosomiasis), commonly referred to as "tropical diseases" or "neglected diseases". The affinity of gold-based compounds for thiol- and selenol-containing proteins that have been identified as drug targets in trypanosomes once again makes them promising candidates in this field. Additionally it is known that $[Au(CN)_2]^-$, an identified metabolite of chrysotherapy, can inhibit the proliferation of HIV in cultured T-9 cells and that the number of CD4+ T lymphocyte cells increases during treatment with gold compounds [9].

In addition to the chemical potential of gold(III), the element has two ß$^-$-emitting isotopes, which might be interesting for radiotherapeutic applications, ^{198}Au and ^{199}Au, with half-life times of 2.7 and 3.1 days and beta energies of 1.372 and 0.453 MeV, respectively [31].

This review is focused on the recent advances in the development of gold(III) complexes for medicinal chemistry as well as on the progress on describing novel targets related to their mechanisms of action. In recent years, a more rational drug design has been achieved, so that the structural trends for stabilization of gold(III) are also discussed. Finally some perspectives for future medicinal chemistry of gold(III) are noted.

Gold(III) complexes with antitumor activity

The established clinical use of gold(I) drugs for treatment of rheumatoid arthritis, made them to the first gold complexes being investigated for cytotoxicity and antitumor activity. Curiously, auranofin (**1**), see Figure 1, the most widely used drug against rheumatoid arthritis, also presented antiproliferative effects *in vitro*, however, the *in vivo* effectiveness of this compound in initial studies was poor [32]. Nevertheless, the interest in this compound is consistently renewed for the treatment of particular types of cancer.

The success of the well-established anticancer drug *cis*-diamminedichloridoplatinum(II) (cisplatin, **2**) and its second generation derivatives in the treatment of solid tumors like testicular and ovarian cancers is decidedly hindered by severe toxic side-effects and/or by the development of tumor resistance [22]. Fortunately, the arsenal of inorganic chemists provides solutions for the upcoming problems on the basis of new generations of platinum compounds such as carboplatin [33], but also with complexes of other metals such as ruthenium, gallium or gold [34].

Potassium tetrachloridoaurate, $K[AuCl_4]$, dissolves in water and undergoes a hydrolysis to form $[AuCl_3(OH)]^-$ in a similar manner to Pt(II) chlorido complexes. Nevertheless, further studies have demonstrated that the mechanism of action supposed for the Au(III) compounds is different from that of the cisplatin derivatives, which clearly attack the DNA. The "DNA independent" activity of gold(III) compounds indicate that the analogy of Au(III) and Pt(II) complexes does not extend to their interaction with cells and that the latter might be useful against cisplatin resistant tumors [20]. Inherent chemical problems such as potential *in vivo* reduction or hydrolysis of gold(III) complexes can be solved by the choice of suitable ligand systems for the coordination of the metal. Thus, strategies with multidentate ligands and organometal-

lic approaches have been chosen in order to address these points.

The Au(III) ion is a 'harder' Lewis acid than Au(I), but it is considered as a borderline 'hard-soft' metal ion, which is able to accommodate both types of Lewis bases. Thus, for its stabilization a perfect combination of hard and soft bases must be acquired. A wide spectrum of gold(III) complexes with various chelating systems has displayed promising tumor cell inhibiting properties, such as (i) nitrogen donors (amines, pyridines, phenanthrolines, Schiff bases, porphyrins and iminophosphoranes), (ii) sulfur donors (dithiocarbamates and thiosemicarbazones) and (iii) organometallic gold(III) complexes. Particularly the combination of two classes of such ligands seems to be a trend in the coordination chemistry of gold(III). Some of the recent advances involving gold(III) coordination compounds with potential as anticancer drugs are discussed below.

Nitrogen donor ligands

Nitrogen donors are the most common ligands in gold(III) coordination chemistry. Typical compounds of this class are summarized in Figure 2. Most of them are derived from diimine donors like bipyridine or phenanthroline. Simple mononuclear complexes of the type $[Au(bipy)Cl_2]^+$ (**3**) and $[Au(phen)Cl_2]^+$ (**4**), but also binuclear gold(III) oxido complexes (**5** and **6**) have demonstrated excellent antiproliferative properties *in vitro* against a wide panel of cancer cell lines. However, different mechanisms of action are suggested for these types of compounds [23,35–37].

The cytotoxicity of three gold(III) cationic complexes with bidentate *N,N*-donor ligands $[Au(bipy)Cl_2]^+$ (**3**), $[Au(DACH)Cl_2]^+$ (**7**) and $[Au(en)Cl_2]^+$ (**8**), was evaluated against a human lung carcinoma epithelial cell line. The results showed that $[Au(bipy)Cl_2]^+$ (**3**) was the most cytotoxic complex, with an activity similar to cisplatin. Flow cytometry analysis showed a high percentage of early apoptotic cells after treatment with $[Au(bipy)Cl_2]^+$ (61%) compared with cisplatin (55%), $[Au(DACH)Cl_2]^+$ (21%) and $[Au(en)Cl_2]^+$ (7%), suggesting apoptosis as the main mechanism of cell death caused by $[Au(bipy)Cl_2]^+$ [38].

Isab and co-workers studied the cytotoxic behavior of the two isomers of the cationic Au(III) complex with diaminocyclohexane (DACH), $[Au(DACH)Cl_2]Cl$ (**7**). Interestingly, they found that the *cis* isomer **7a** shows higher activity on prostate cancer (PC-3) and gastric carcinoma (SGC-7901) cancer cell lines than the *trans* isomers **7b** [39]. The same group also verified that diamine complexes containing labile chlorido ligands such as $[Au(diamine)Cl_2]^+$, and bis(diamine) complexes such as $[Au(diamine)_2]^{3+}$, present different selectivity for cancer cell lines. This shows that details of the molecular design of gold(III) complexes are important factors for the development of target-specific anti-cancers drugs [40].

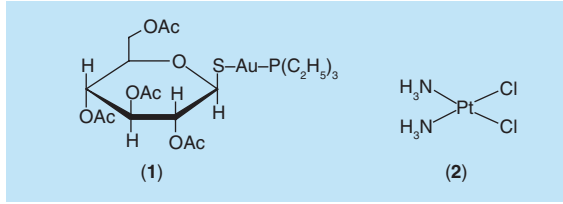

Figure 1. Auranofin (1) and cisplatin (2).

Another study demonstrated minimal renal and hepatic toxicity by a newly developed gold(III) compound, $[Au(en)Cl_2]Cl$ (**8**). In the sub-acute toxicity part of the study, this compound showed dose-dependent renal toxicity, but with an extended nephrogenic safety range. It also displayed a notably higher safe limit compared with toxicity levels of clinically established antineoplastic drugs like cisplatin and doxorubicin [41].

A new class of five-coordinate Au(III) complexes (**9**) was achieved by reactions of 2,9-dialkyl-1,10-phenanthroline with $Na[AuCl_4]$ in the presence of silver salts [42]. Two representatives were tested for cytotoxicity against different tumor cell lines. While the methyl derivative **9a** showed a limited antitumor activity, compound **9b** was found to be more cytotoxic than cisplatin against five different tumor cell lines. Figure 3 shows the molecular structure of the latter complex. Despite the promising *in vitro* results for compound **9b**, only a limited *in vivo* activity was found against xenograft tumors in mouse models [43].

Tridentate ligands have been obtained with polyamines, terpyridine and 8-aminoquinoline derivatives. These results have been reviewed in detail before [23,44].

Gold(III) complexes with 2-(2′-pyridyl)benzimidazole (**10a**) cause relevant growth inhibition of two representative ovarian carcinoma cell lines, either resistant or sensitive to cisplatin. The IC_{50} values for the investigated gold compounds fall in the nanomolar range. Similar cytotoxic properties were also observed for corresponding Au(I) complexes and the binuclear compounds of type **10b**. Highest antiproliferative activities were observed for mixed-ligand derivatives of compound **10b** with phosphines [45]. Similar ligands including the tridentate 2,6-bis(2′-benzimidazole)pyridine have been used to prepare other gold(III) complexes with relevant biological activity (**11** and **12**) [46].

Another class of compounds, which has recently aroused interest as ligands for gold(III) are the iminophosphoranes. Contel *et al.* prepared a water soluble *N,N*-chelating iminophosphorane ligand by the reaction of picolinamide with 1,3,5-triaza-7-phosphaadamantane as well as its Au(III), Pd(II) and Pt(II) complexes. While the platinum and palladium com-

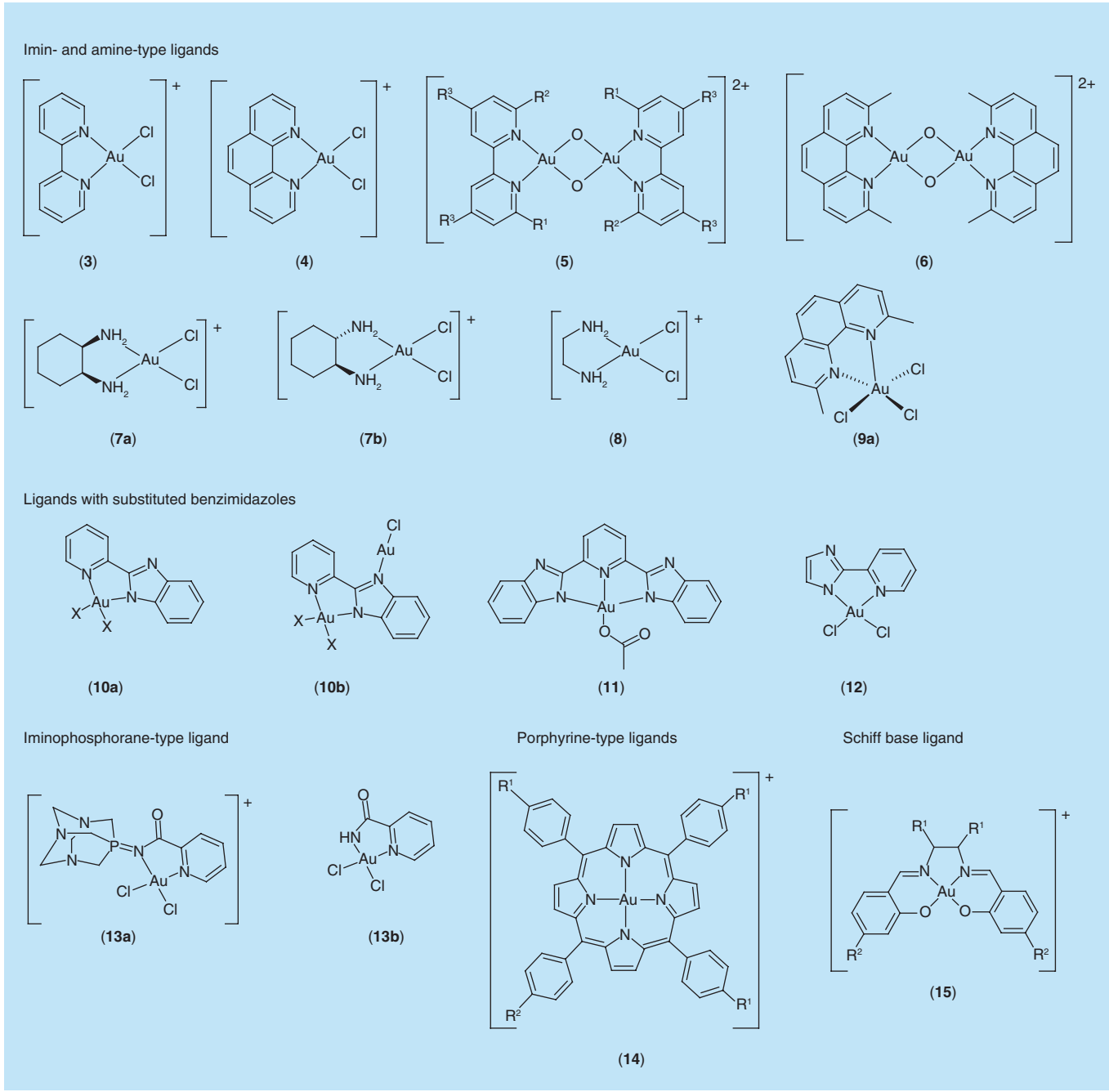

Figure 2. Typical Au(III) compounds with N-donor ligands.

plexes are stable under aqueous conditions, the Au(III) complex (**13a**) decomposes in water or other polar solvents under formation of the corresponding amide complex **13b** and phosphine oxide. More interestingly, the less stable iminophosphorane complex **13a** and its decomposition products were found to be more cytotoxic than the corresponding stable Pd(II) and Pt(II) complexes as well as cisplatin [47].

Porphyringold(III) complexes (**14**) show antiproliferative effects against a variety of carcinomas, including cisplatin-sensitive and cisplatin-resistant cells both *in vitro* and *in vivo* [48–51]. Substitutions on the phorphyrin ligands may change physicochemical properties, allowing good solubility in both water and organic solvents, and increases cytotoxic activity [52–55]. Encapsulation of the cytotoxic porphyrin complexes or some Schiff base gold(III) complexes (**15**) in gelatin-acacia microcapsules as host material showed an improved solution stability and increased *in vivo* efficacy compared with the unencapsulated complexes [56].

Sulfur donor ligands

A detailed review dealing with the chemistry and cytotoxic activity of dithiocarbamatogold(III) complexes has been written by Fregona *et al.* [57]. Some of such derivatives, e.g. the complexes of the type $[AuX_2(dtc)]$ (X = Cl, Br; dtc = various dithiocarbamato ligands; formulae **16** and **17** of Figure 4), have been designed in order to reproduce very closely the main features of cisplatin. Comparative *in vitro* cytotoxicity studies between isostructural Pt(II), Pd(II) and Au(III) derivatives on various types of cancer cells show highest activity for the gold compounds. This outstanding *in vitro* cytotoxicity holds true even toward human tumor cell lines, which are intrinsically resistant to cisplatin, and no cross-resistance to the reference platinum drug is evident [58,59]. Their chemotherapeutic properties have been confirmed *in vivo*, together with insignificant acute toxicity and almost no nephrotoxic side effects [60,61]. Attempts to increase the cytotoxicity of dithiocarbamato complexes by the design of binuclear representatives such as **16a** were not successful [62].

The chemistry of gold dithiocarbamates with medicinal relevance has now come to a new level with the development of the "second-generation" of such compounds, which comprises peptide conjugates. A series of dithiocarbamate derivatives with di- to pentapeptides, forming complexes of formula $[Au^{III}X_2(pdtc)]$ (X=Cl, Br; pdtc=oligopeptidedithiocarbamate) (**18**) has been synthesized and tested *in vitro*. The targets of the tailored peptidomimetics are two peptide transporters (PEPT1 and PEPT2), which are plasma membrane proteins responsible for the cellular uptake of di- and tripeptides and peptide-like drugs. They are upregulated in several tumor cells [63,64]. The new class of compounds shows no cross-resistance with cisplatin itself and was also active against cisplatin resistant cells, displaying antiproliferative activity against tumor cell lines by inducing either apoptosis or late apoptosis/necrosis. The favorable nephrotoxicity and acute toxicity levels of the first generation compounds was kept, but an improved selectivity toward tumor cells was observed, which might minimize undesirable side-effects [63,64]. The compounds have been characterized by means of FT-IR and mono- and multidimensional NMR spectroscopy. The compound, which was found most effective against the tested tumor cell lines, $[AuBr_2(dtc\text{-}Sar\text{-}Aib\text{-}O\text{-}(t\text{-}bu))]$(sar = sarcosine, AiB = α-aminobutyric acid)(**19**), was additionally studied by single-crystal X-ray diffraction (Figure 5A). The gold(III) complex adopts a distorted square-planar geometry achieved through the bidentate dithiocarbamate and the bromido ligands [63].

Key term

Peptidomimetics: Organic molecules with small protein-like chains, which are able to mimic some properties of natural peptides.

Thiosemicarbazones are compounds of considerable significance with respect to their biological and pharmaceutical properties and many of their metal complexes show remarkable structural features and biological properties [65]. Surprisingly, the first gold(III)-thiosemicarbazone compounds were published only in 1998 (**20** and **21**) [66,67]. The two compounds, however, belong to the class of damp$^-$ (2-dimethylaminomethylphenyl) derivatives, which possess a gold-carbon bond, therefore, belong to the group of organometallic gold compounds and will be treated in Chapter 2.3. Since then, a few complexes of this type have been published [68–70]. Some of them have shown interesting cytotoxic activity, sometimes higher than that of cisplatin, depending on the tested cell line [71–73]. Examples are the series of complexes **22**, which are more active against HeLa than against A549 cell lines [71]. An interesting comparison has been presented recently by Beraldo and co-workers, who showed that a series of gold(III) thiosemicarbazone complexes is more active against glioma cell lines U-87 and T-98 than cisplatin, auranofin and also the platinum(II) and platinum(IV) complexes with the same ligands [74].

In general, the Au(III) thiosemicarbazone complexes without the stabilizing support of a gold-carbon bond (as in the corresponding damp$^-$ complexes **20** and **21**) are reported to be instable and a number of decom-

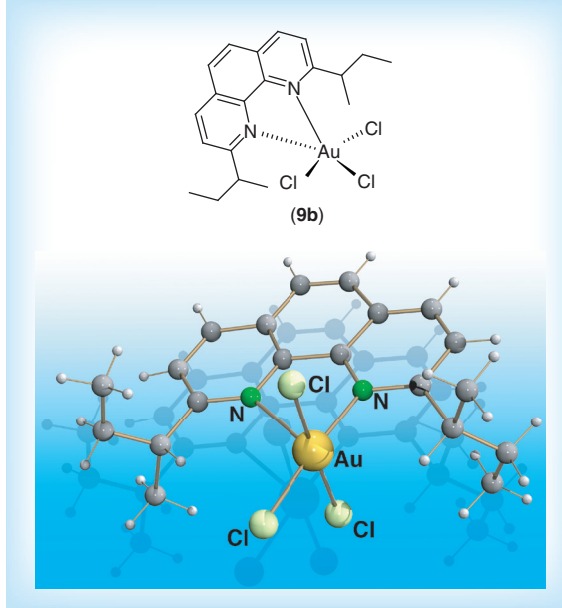

Figure 3. Molecular structure of compound 9b as a rare example of a biologically active five-coordinate Au(III) complex.

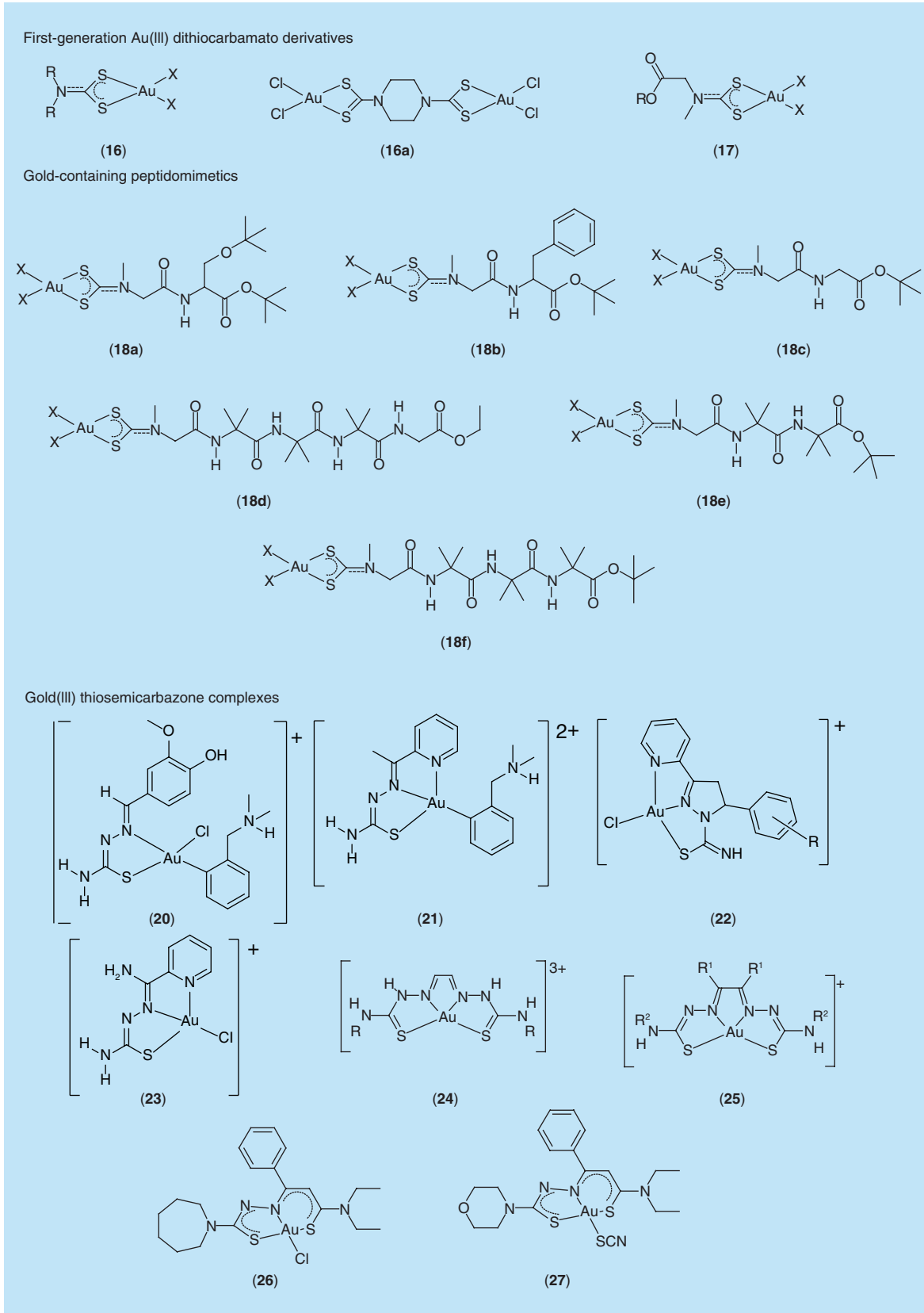

Figure 4. Typical Au(III) complexes with S-donor ligands.

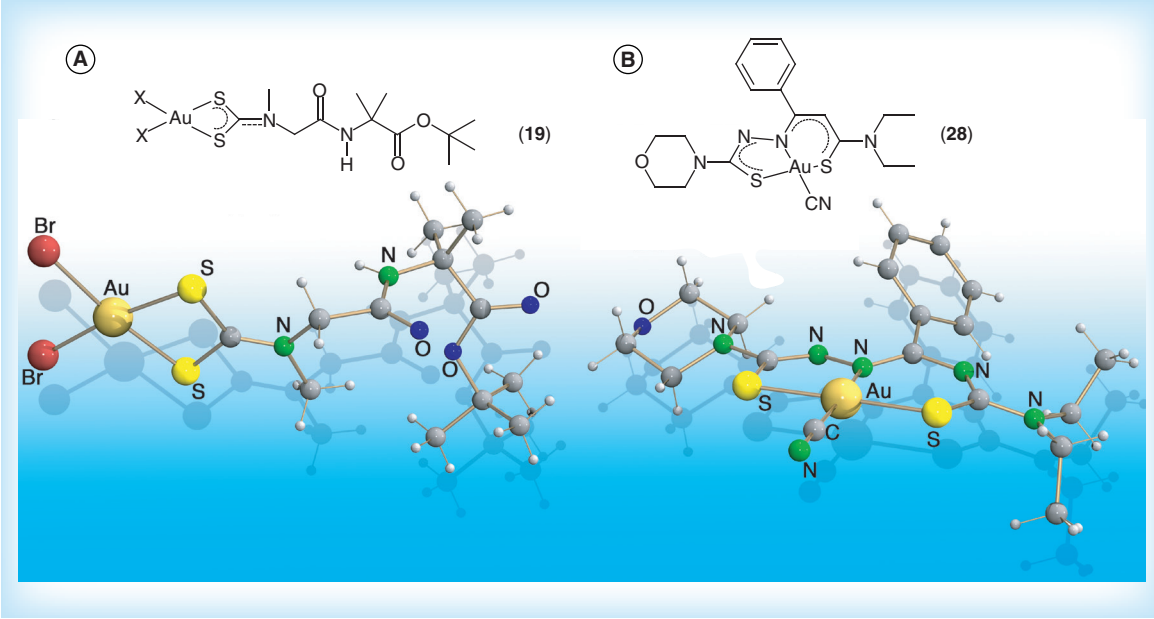

Figure 5. Molecular structures of (A) compound 19 as an example of a Au(III) biomimetic complex and (B) a stable neutral gold(III) complex with a binegative thiosemicarbazone ligand (28).

position or reduction products has been isolated and characterized [68,69,74]. Such a behavior, of course, also limits applications in tumor therapy. Indeed, only few complexes without damp$^-$ ligand have been structurally characterized and all of them were cationic (**23–25**) [68,69,75]. A new type of tridentate *SNS* thiosemicarbazonato ligands, which allows double deprotonation, thus, the stabilization of neutral gold(III) complexes of the type [AuCl(L)] (**26**), was recently developed. The chlorido ligands in the [AuCl(L)] complexes can readily be replaced by other monoanionic ligands such as SCN^- or CN^- giving [Au(SCN)(L)] (**27**) or [Au(CN)(L)] (**28**) complexes. The antiproliferative effects of these [AuX(L1)] complexes on human MCF-7 breast cancer cells display better IC_{50} values than cisplatin with a maximum cytotoxicity at lower incubation times. The exchange of the chlorido ligand of **26** by thiocyanate shows no significant changes in the antiproliferative effects, while the substitution by a cyanido ligand decreases the IC_{50} to a value of about 0.02 µMol [76]. The molecular structure of compound **28** has been determined by X-ray structure and is shown in Figure 5B

Organometallic gold(III) complexes

Recent reviews, which go into details of the biological activity of candidates for future organometallic drugs have been presented by Ott, Casini and Ruiz [77–79]. Typical representatives of the first generation of organometallic gold compounds, which have been regarded as anticancer agents are shown in Figure 6. They contain the orthometallated *N,N*-dimethylaminomethylphenyl (damp$^-$) ligands and follow structurally the **'cisplatin concept'**. The parent compounds have a composition of [Au(damp)X_2] (**29**; X = Cl, SCN, acetate; $X_2 = C_2O_4$, $CO_2CH_2CO_2$). They are active against several tumor cell lines and the acetate and malonate complexes show activity similar to cisplatin *in vivo*, but it became also evident that the mode of action of such compounds is different [80]. Based on these results, novel complexes have been prepared by substitution of the monodentate ligands in [Au(damp)-X_2] [81]. Depending on the incoming ligands, which include monodentate or chelating thiones, thiols or mercaptopurine (**30–32**), the amine part of the organometallic unit remains coordinated or underlies a Au-N bond cleavage with subsequent protonation of the dimethylamino group. Since the presence of the organometallic damp$^-$ ligand effectively prevents the Au(III) ion from reduction by thiols, also a number of stable thiosemicarbazonato complexes has been prepared. Besides a series of bi- and tridentate thiosemicarbazones (for examples see formulae **20** and **21**) [67,82], also representatives with *SNS*-donating thiosemicarbazone hybrid ligands have been synthesized (**33**). The cytotoxicity of the latter compounds has been tested against MCF7 cell lines showing values comparable with those of cisplatin.

Key term

'Cisplatin concept': Square planar complexes that present one of the following structural systems: i) two pairs of equal monodentate ligands in cis position to each other; ii) a bidentate ligand and two monodentate ones; or iii) two bidentate ligands.

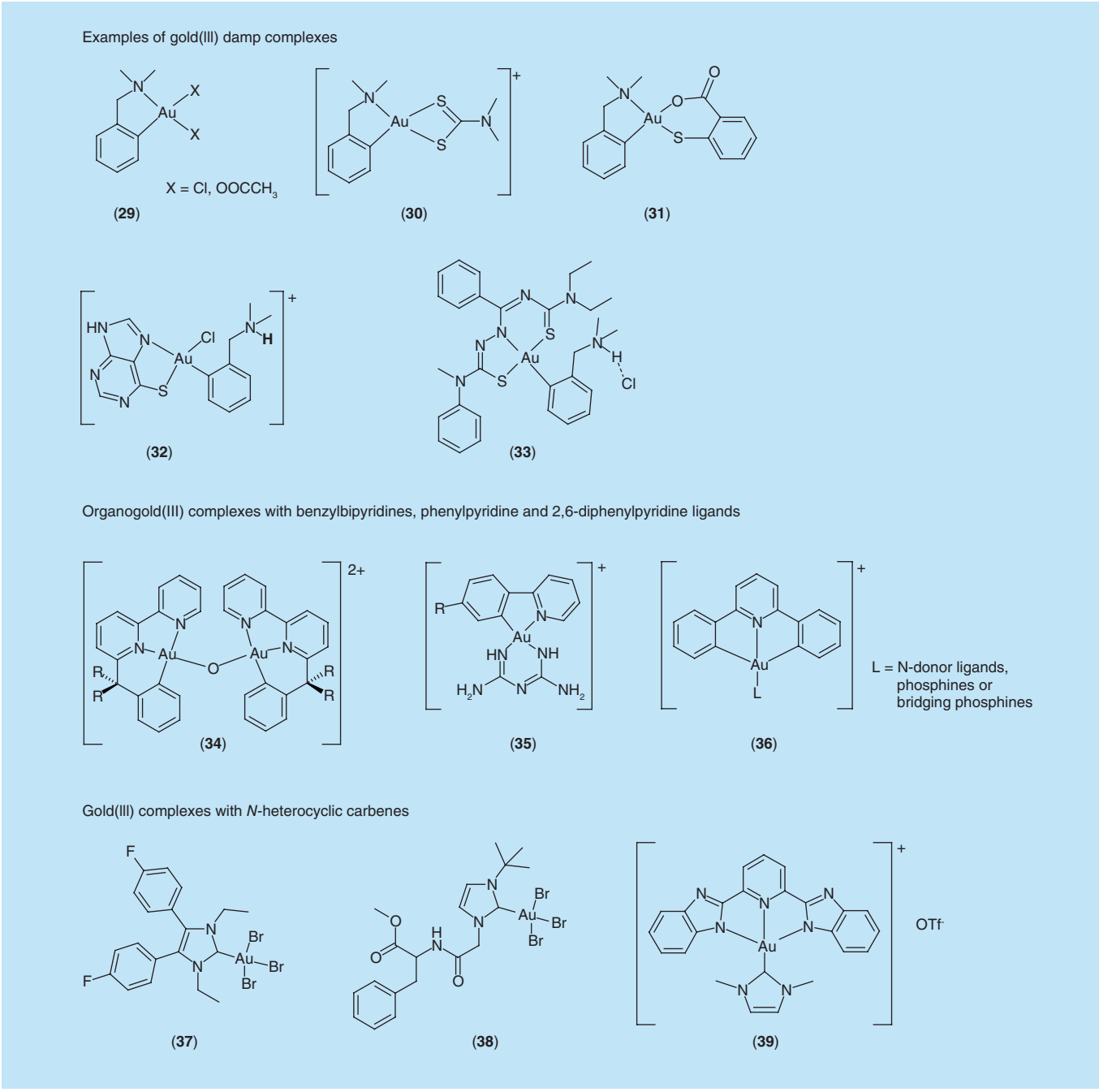

Figure 6. Typical representatives of first-generation organometallic gold(III) compounds.

Similar complexes have been obtained by the formation of cycloaurated iminophosphorane compounds [83, 84]. Interestingly, it was observed that the replacement of the chlorido ligands by dianionic chelating ligands enhances antitumor activity [85].

Messori and co-workers reported the synthesis of two dinuclear oxo-bridged organogold(III) compounds derived from benzyl-2,2'-bipyridines (**34**). Notably, these compounds reveal high redox stability even in the presence of effective biological reducing agents such as ascorbic acid and glutathione. In spite of the apparent stability of their oxidation state +III, these compounds still manifest appreciable cytotoxic properties when challenged against a representative panel of 12 human tumor cell lines [86].

A stimulating work on this field was recently developed by reactions of 2-phenylpyridine derivatives of gold(III) with biguanide or biuret, giving raise to water-soluble complexes of the type [Au(R-phenylpyridyl)(biguanide)]$^+$ (**35**) or [Au(R-phenylpyridyl)(biu-

ret)], where R= H or n-butyl. The complexes with the *n*-butyl group are remarkably more cytotoxic than cisplatin. Besides [Au(butylphenylpyridyl)(biguanide)] Cl displays cytotoxicity through *S*-phase cell cycle arrest and endoplasmic reticulum damage in HeLa cells, it shows a promising anti-angiogenic effect at sub-cytotoxic concentrations. A mechanism of action is also proposed [87]. A whole series of cyclometallated gold(III) complexes contains 2,6-diphenylpyridine as core-ligand [88]. The compounds can be mononuclear, as shown in formulae **36**, or can contain two Au(III) units, which are linked by bisphosphines or *bis-N*-heterocyclic carbenes. Both types of compounds exert considerable anticancer potency. Those of the mononuclear complexes are similar to the activity of cisplatin, but they do not show cross-resistance with cisplatin. The dinuclear complexes show a higher activity, which is comparable with that of the uncoordinated phosphines. This leads to the conclusion that the gold complexes most probably act as vehicles for membrane penetration. Corresponding *in vivo* tests identify the binuclear representatives as promising future anticancer drugs [89].

A relatively new, but fast-growing area of medicinal chemistry of metal complexes uses *N*-heterocyclic carbenes (NHC) as ligands. For many metals, such as platinum, palladium, copper, silver, ruthenium or nickel, there exist NHC complexes showing cytotoxic effects comparable with cisplatin and for corresponding Ag(I), Pt(II) and Ru(II) derivatives *in vivo* data confirm their efficacy [90]. The corresponding gold chemistry is dominated by Au(I) compounds, but during the recent years also Au(III) complexes entered the focus of interest. Such complexes are readily obtained by oxidation of the related gold(I) complexes, as has been demonstrated for compounds **37** and **38** [91,92], or by substitution reactions [93,94]. The Au(III) complex **37** shows cytotoxicity, which is in the range of its Au(I) congener for several cell lines and only for HT-29 cells it was less active [91]. Similar effects were observed for Au(I) complexes of the type $[Au(NHC)_2]^+$ and their gold(III) derivatives $[Au(NHC)_2X_2]^+$ (NHC = *N*-heterocyclic carbene of **37** and its -OCH_3 derivative, X = Br, I). They show growth inhibitory effects against MCF-7, MDA-MB 231 and HT-29 cells, which is more than 10-fold higher than that of cisplatin. The effects were independent of the oxidation state of the metal [95]. As can be seen from formula **38**, NHC ligands have successfully been used for the design of bioconjugates. Both the shown gold(III) complex and similar derivatives with cysteine-modified NHC ligands show similar biological activity as their Au(I) congeners [92]. A whole family of redox-inert Au(III) complexes has already been introduced

Key term

Bioconjugate: The product formed by a covalent orthogonal binding between a chemical compound and a bioactive molecule.

with the compounds represented by formula **36**. The 2,6-diphenylpyridyl core stabilizes Au(III) and one of the well-studied representatives, which exhibits prominent antitumor activity is the cationic complex with 1,3-dimethylimidazol-2-ylidene, **40**. Figure 7 shows its molecular structure. The compound shows high antitumor activity *in vitro* and *in vivo*. Its cytotoxicity is more than a magnitude higher than that of cisplatin and it induces DNA strand disruptions and subsequent cell death [96]. In addition, complex **40** and some similar ones have shown interesting photoinduced cytotoxic properties, displaying higher cytotoxicity when exposed to visible light [97], or display luminescent properties and good cytotoxicities [98].

The ready reduction of gold(III) compounds inside the cells to the corresponding Au(I) complexes gives access to applications in fluorescence microscopy. The Au(III) complex **39** contains a ligand, whose fluorescence abilities are quenched as a result of the coordination to the Au(III) ion. After reduction of the complex inside the cells by thiols, however, it is released and can be detected by a strong emission in

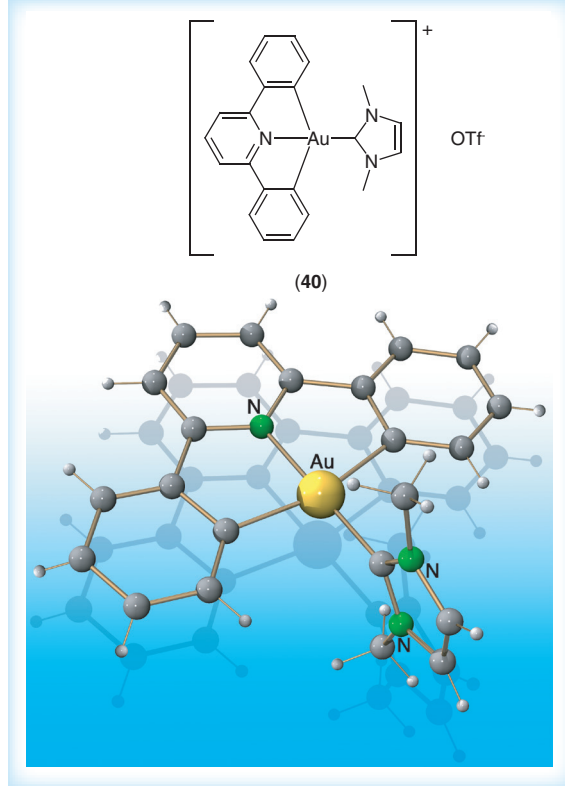

Figure 7. Molecular structure of an antitumor gold(III) compound with an N-heterocyclic carbene.

the blue range of the visible spectrum, which might be used for cell imaging [99]. A more general overview about this point is given in a review by Bronner and Wenger [100].

Gold(III) complexes with antibacterial & antiviral properties

The incidence of resistance to antibiotics has increased at alarming rates, bringing with it the consensus of the necessity of development of new antibacterial drugs, particularly against *Mycobacterium tuberculosis*, the pathogen responsible for tuberculosis. Based on this fact, gold(III) complexes appear once more as promising agents, however the advances on this field have hitherto not been the same as in cancer chemotherapy. Some compounds of interest for this field are summarized in Figure 8.

Since Robert Koch's discovery of the bacteriostatic effects of dicyanidoaurate(I), $[Au(CN)_2]^-$ [4], no other gold drug has been used in clinical therapy of tuberculosis [6]. Nowadays it is well known that microorganisms such as archaea, bacteria, fungi and yeasts are able to solubilize and precipitate gold and play an important role in the biogeochemical gold cycle [101]. Complexes such as sodium bis(thiosulfato-*S*)aurate(I), sanocrysin (**41**), have come into clinical trial in the 1920's. However, the high systemic toxicity and the low antitubercular effect at tolerable doses resulted in the abandonment of these agents [6].

The antimicrobial activity of gold complexes derived from a tripodal bis(imidazole) thioether (**42**) was evaluated against Gram-positive and Gram-negative bacteria. The gold(III) complex showed selective antimicrobial activity towards the Gram-positive bacteria (*Bacillus cereus* and *Staphyloccocus aureus*) being more toxic than its Au(I) analogue, while the free ligand is totally inactive [102].

The application of auranofin to an AIDS patient against arthritis lead to the finding that the number of his +T lymphocytes increased, which is unusual for AIDS patients who normally suffer on an irreversible decline of these cells. Finally, it was found that dicyanidoaurate(I), $[Au(CN)_2]^-$, a common metabolite in patients of chrysotherapy, was responsible for the anti-HIV activity. Most probably it inhibits reverse transcriptase, the key enzyme involved in the conversion of viral RNA to DNA, which is crucial for arresting the replication of HIV [9].

The literature information on the use of gold(III) complexes as anti-HIV agents is scarce and only recently a few reports have been published. The $(3,5\text{-}Me_2bpzaH_2)Cl[AuCl_4]$(**43**) was found to be an inhibitor of the two very important HIV-1 enzymes, reverse transcriptase and protease [103]. More recently, some bis(thiosemicarbazonate)gold(III) complexes (**44**) were synthesized and evaluated as anti-HIV agents. One of the complexes (R^1 = Me, R^2 = Me, **44a**) inhibited viral infection of TZM-bl cells by 98% (IC_{50}=6.8±0.6 μM) at a non-toxic concentration, while the complex **44** (R^1 = Me, R^2 = Et) was able to do the same at cytostatic concentrations. None of the uncoordinated ligands demonstrated anti-viral activity, supporting the importance of metal complexation in these potential drugs [70].

Gold(III) complexes against parasitic diseases

The main parasitic diseases, also called tropical diseases, such as malaria, leishmaniasis, trypanosomiasis orschistosomiasis afflict millions of people in developing countries. Malaria is a potentially deadly disease caused by the parasite *Plasmodium falciparum*, which is transferred to humans through the bite of female anopheles mosquitos. This disease affects more than 500 million people annually, causing approximately one death every 30 s [104]. Schistosomiasis ranks as the second parasitic disease behind malaria and finally, american trypanosomiasis or "Chagas disease" is endemic in Latin America, caused by *Trypanosoma cruzi*, a hemoflagellate protozoan, which affects 18 million people and causes 50,000 deaths per year [105]. Although there is urgent need for new anti-parasitic drugs, research progress is slow. The advances of gold compounds in this area have been reviewed

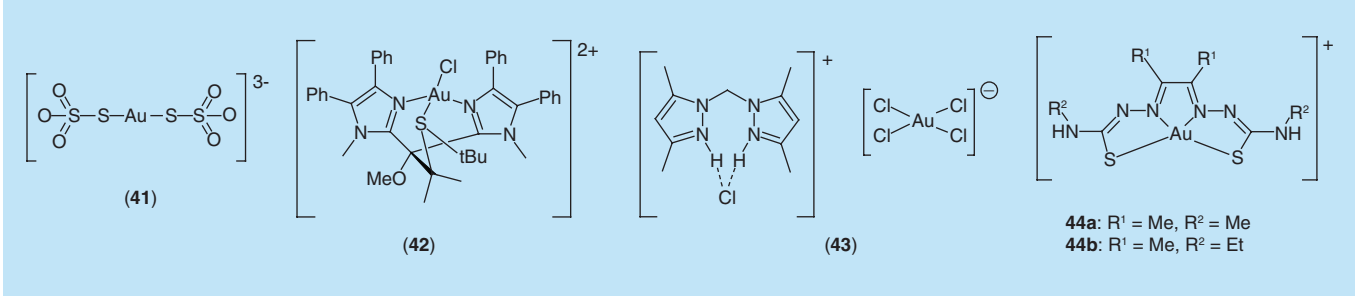

Figure 8. Gold complexes with antibacterial and antiviral activity.

before [106]. Many of the compounds have the widely used anti-malaria drug chloroquine as lead structure. Chloroquine itself was used as efficient and low-cost anti-malaria drug for decades. The appearance of chloroquine-resistant parasites, however, requires the development of novel agents. A couple of gold(I) complexes, but also the gold(III) derivatives of Figure 9, were tested for their activity against *Plasmodium falciparum*. They are metal complexes with chloroquine ligands (**45** and **46**) [107].

Recently, some gold(III) thiosemicarbazone complexes (**47**) derived from [Au(damp-C^1,N)Cl_2](compound **29** with X = Cl)) were studied for their antibacterial activity [108]. Although the coordination of the thiosemicarbazones to the gold(III) damp units did not enhance antitubercular activity of the uncoordinated thiosemicarbazones against the *Mycobacterium tuberculosis* virulent strain H_{37}Rv, their efficacy against the malaria parasite *Plasmodium falciparum* was significantly improved. Similarly, some complexes of the type **33**, which are cytotoxic against MCF-7 cells, present *in vitro* antiproliferative activity on *T. cruzi* trypomastigotes being higher than that of the standard drug used for Chagas' disease treatment, benznidazole.

The activity of some gold(III) cyclometallated complexes previously tested for anti-cancer activity, **29** (X = Cl, acetate; X_2 = $CO_2CH_2CO_2$) and **48**, were also assayed against mammalian and parasitic cysteine proteases, which are involved in parasitic life cycles including *Schistosoma*, *Plasmodium*, *T. brucei*, *T. cruzi*, and *Leishmania*. All gold(III) complexes inhibited cathepsin *B*, a type of cysteine protease with IC_{50} values in the range of 0.2–1.4 μM. These preliminary results indicate that metal complexes targeted at parasite cysteine proteases may be promising for the treatment of both Chagas' disease and leishmaniasis [109]. These evidences have stimulated the evaluation of gold complexes not only against tumor

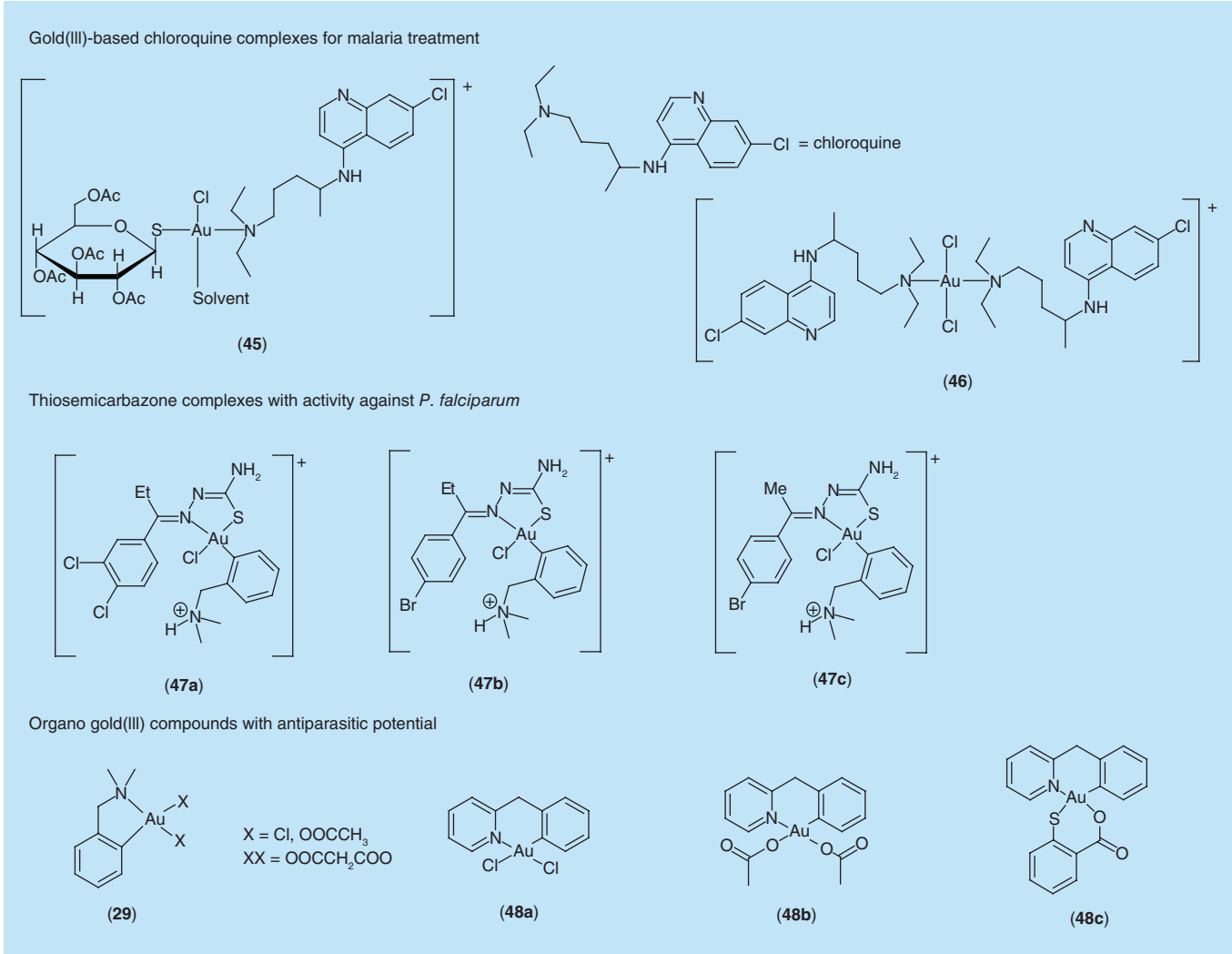

Figure 9. Gold(III) complexes with antiparasitic potential.

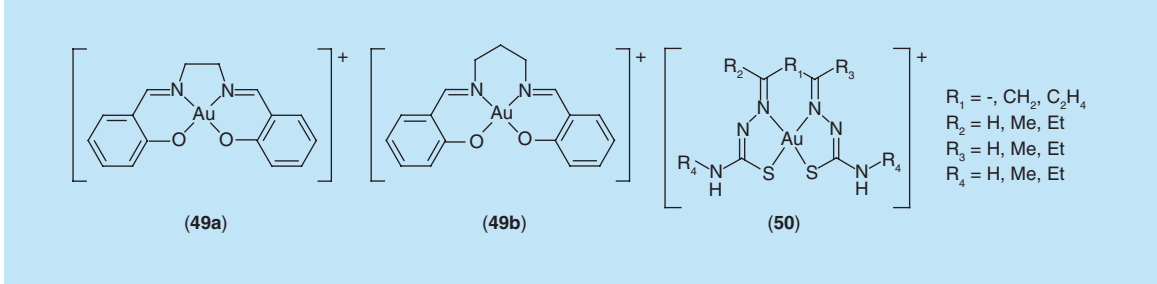

Figure 10. Schiff base and thiosemicarbazone complexes prepared and tested with ^{198}Au.

cell lines, but also against these parasitic diseases. For example, benzimidazole gold(III) complexes revealed a remarkable anti-leishmania activity in both stages of the parasite, promastigote and the intramacrophage amastigote form, while the uncoordinated ligands are inactive [110].

Gold(III) compounds as radiotherapeutic agents

Gold possesses two radioactive isotopes with nuclear properties suitable for nuclearmedical therapy: ^{198}Au and ^{199}Au. Both radionuclides are β^--emitters with gamma components, which can be used for imaging and localization in biodistribution studies. ^{199}Au has a half-life of 3.14 days and emits beta particles of E_{max} = 0.45 MeV (accompanying E_γ = 158 and 208 keV). It is potentially available in high specific activity through thermal neutron irradiation, but requires targets of isotope-enriched ^{198}Pt according to Equation 1. Another approach to ^{199}Au is double neutron capture starting from natural ^{197}Au (Equation 2). Samples with high specific activities require the more expensive isotope production from the platinum target, since samples from the second synthesis always contain ^{198}Au and a large amount of residual non-radioactive ^{197}Au. This means specific targeting with receptor-affine ligand systems such as peptides will require ^{199}Au produced from the ^{198}Pt target, from which the radioactive gold atoms can readily be separated. For research applications, however, or other ones where no high specific activities are required, radioactive gold samples prepared according to Equation 2 are sufficient, which contain normally $^{198/199}$Au isotope mixtures or ^{198}Au alone. ^{198}Au is also a β^--emitter with a half-life of 2.7 days (E_{max} = 0.96 MeV, E_γ = 412 keV).

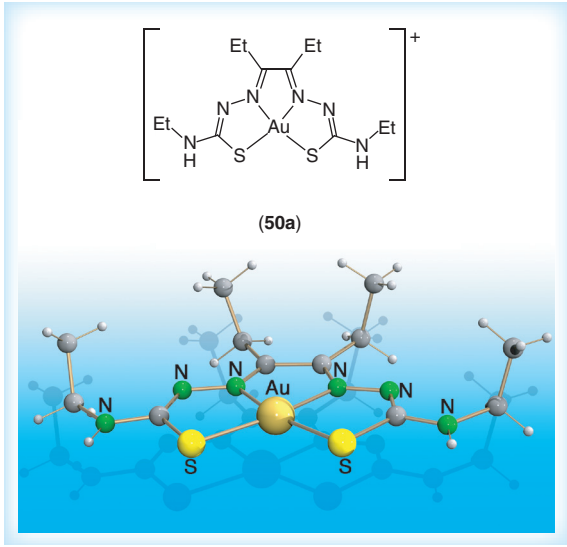

Figure 11. Molecular structure of a ^{198}Au(III) complex with a tetradentate thiosemicarbazone.

$$^{198}\text{Pt (n,}\gamma\text{) } ^{199}\text{Pt (}\beta^-\text{) } ^{199}\text{Au}$$

Equation 1

$$^{197}\text{Au (n,}\gamma\text{) } ^{198}\text{Au (n,}\gamma\text{) } ^{199}\text{Au}$$

Equation 2

Ideally, the biologically active compounds from the previous Chapters are used as radiopharmaceuticals. Then, the therapeutic effect due to the radioactivity is supported by the chemotherapy of the biologically active gold compound. In such cases, the obvious disadvantage in using ^{198}Au by a large number of accompanying "cold" gold atoms does not effectively exist, since these are then constituent of a biologically active molecule. Some restrictions arise concerning the synthesis of potential radiogold drugs: (i) it should not be time-consuming or involve complicated chemical procedures with respect to required radiation protection procedures and (ii) it should preferably start from $[AuCl_4]^-$, which can readily be prepared from the targets used for isotope production.

The radiochemistry involving Au(III) compounds was mainly developed by Jurisson and co-workers. The first ^{198}Au(III) complexes were derivatives of the tetradentate Schiff base ligands of Figure 10, sal_2en and sal_2pn (**49**). An efficient synthesis was demonstrated from $(Bu_4N)[^{198}AuCl_4]$, in the presence of NH_4PF_6 at 40 °C in a dichloromethane/ethanol solution. Radiochemical yields of 95–100% were observed for the formation of the cationic $[^{198}Au(sal_2pn)]PF_6$ complex [112]. More recently, the same group evaluated the sta-

bility of Au(III) complexes with thiosemicarbazones. Compounds of the type **50** were prepared at the macroscopic and radiotracer levels. The ^{198}Au complexes were evaluated *in vitro* at the tracer level for stability and one of them (**50a**) was selected for an *in vivo* study in mice. The molecular structure of the compound is shown in Figure 11. Although a relatively low serum stability and rapid reduction to colloidal gold is indicated, the *in vivo* distribution of the compound shows that this process does not occur immediately *in vivo*. The biodistribution of **50a** is significantly different from that of $[^{198}AuCl_4]^-$. Modifications in the backbone of the bis(thiosemicarbazone) ligand may lead to a sufficiently stable Au(III) complex for *in vivo* applications [75].

Mechanism of action of gold-based drugs

While it is widely accepted that the anticancer activity of cisplatin and related compounds exerts their activities by interacting with DNA, reactions with other molecules in biological fluids are likely to prevent significant amounts of these compounds from reaching the targeted tumor cells [32]. In spite of some works showing that gold(III) complexes may also interact with DNA, there are a plenty of barriers inside the body and the cell that may interact with the complexes before they come in contact with DNA. Earlier reports implicate gold(III) compounds to bind DNA [20], but these interactions have been shown to be weak, reversible, and mainly electrostatic in nature, suggesting that DNA is not or not always or not exclusively the primary target for the cytotoxic effects of gold(III) complexes [31].

Based on the great structural variety of the used ligands and the derived complex molecules, a unique mode of action or pharmacological profile is unlikely to exist. In particular, direct DNA damage, modification of the cell cycle, mitochondrial damage including thioredoxin reductase (TrxR) inhibition, proteasome inhibition, modulation of specific kinases and other cellular processes affected by gold compounds, which eventually trigger apoptosis, seem to play a major role in the mechanism of action of gold compounds. Some interesting reviews describing different modes of action of cytotoxic gold complexes have been published [113,114].

Ontko *et al.* demonstrated that cytotoxic gold(III) polypyridyls of different size as shown in Figure 12 as **51a** to **51d**, are able to bind DNA similarly to cisplatin. However, the individual design of the ligand moiety seems to modify the DNA binding modes. In noncancer cells the cytotoxicity of the compounds is lower than that of cisplatin. The complexes most probably activate the cell death mechanism by the production of an increased amount of reactive oxygen species. The intracellular signaling cascade shows that compound **51b** disorders the tumor suppressor p53 and activates other anti-survival pathways, which finally results in cell cycle arrest and apoptosis [115].

A series of structurally similar compounds, **52**, is able to cleave DNA to circular DNA and after a higher incubation time to linear DNA. This ability is increasing in the order: **52a**<**52b**<**52d**<**52c**. Studies of the Michaelis–Menten kinetics on plasmid DNA revealed that the complexes mediate DNA cleavage in the order of 10^7 times higher than the control [116]. On the other hand, interaction studies with calf thymus DNA, as well as the results of docking studies, suggest that complex **53** is a good DNA intercalator [117].

The biological activity of gold(III) complexes with *N*-heterocyclic carbenes has been discussed above. One representative of this class of compounds, **40,** was effective in both *in vitro* and *in vivo* experiments. It was observed that the activity of this compound is related to the inhibition of topoisomerases, which are key enzymes that control the topological status of DNA through the breaking and rejoining of DNA strands. The studied gold(III) complex acts as a topoisomerase IB (Top1) inhibitor by preventing the enzyme–DNA interaction [118]. Related results were obtained by Munro *et al.* They evaluated the cytotoxic activity of amidogold(III) complexes **54**, from which only **54d** was cytotoxic enough for further experiments. A mechanistic study of the **54d** activity indicates that this complex acts in a dual mode by inhibiting both Top1 and Top2 (topoisomerase IIα), but also acts as a DNA intercalator [119]. In this context, Farrell *et al.* showed that mixed-ligand $[Au(dien)(N\text{-heterocycle})]^{3+}$ complexes possess enhanced π–π-stacking interactions when compared with their Pt(II) and Pt(II) analogs [120].

Chow and co-workers reported that the gold(III) complex derived from 5-hydroxyphenyl-10,15,20-

Key terms

Reactive Oxygen Species: Chemically reactive molecules or free radicals containing oxygen (e.g. oxygen ions, peroxides, superoxide and hydroxyl radical), which are important in cell life cycle but at increased levels may lead to substantial cell damage and apoptosis.

DNA intercalator: A compound that is able to insert into the DNA double helix by non-covalent bonds.

Topoisomerases: Topoisomerases I and II are enzymes that play a key role in the DNA topological status by controlling its replication. The type I cuts only one strand of the DNA double helix, while the type II is able to cut both strands simultaneously.

triphenylporphyrin, which has a high antiproliferative effect against breast cancer cells, selectively inhibits Wnt/β-catenin protein signaling through inhibition of class I histone deacetylase. Additionally, the gold(III) complex decreases the protein levels of β-catenin in MDA-MB-231 cells around 4 h after

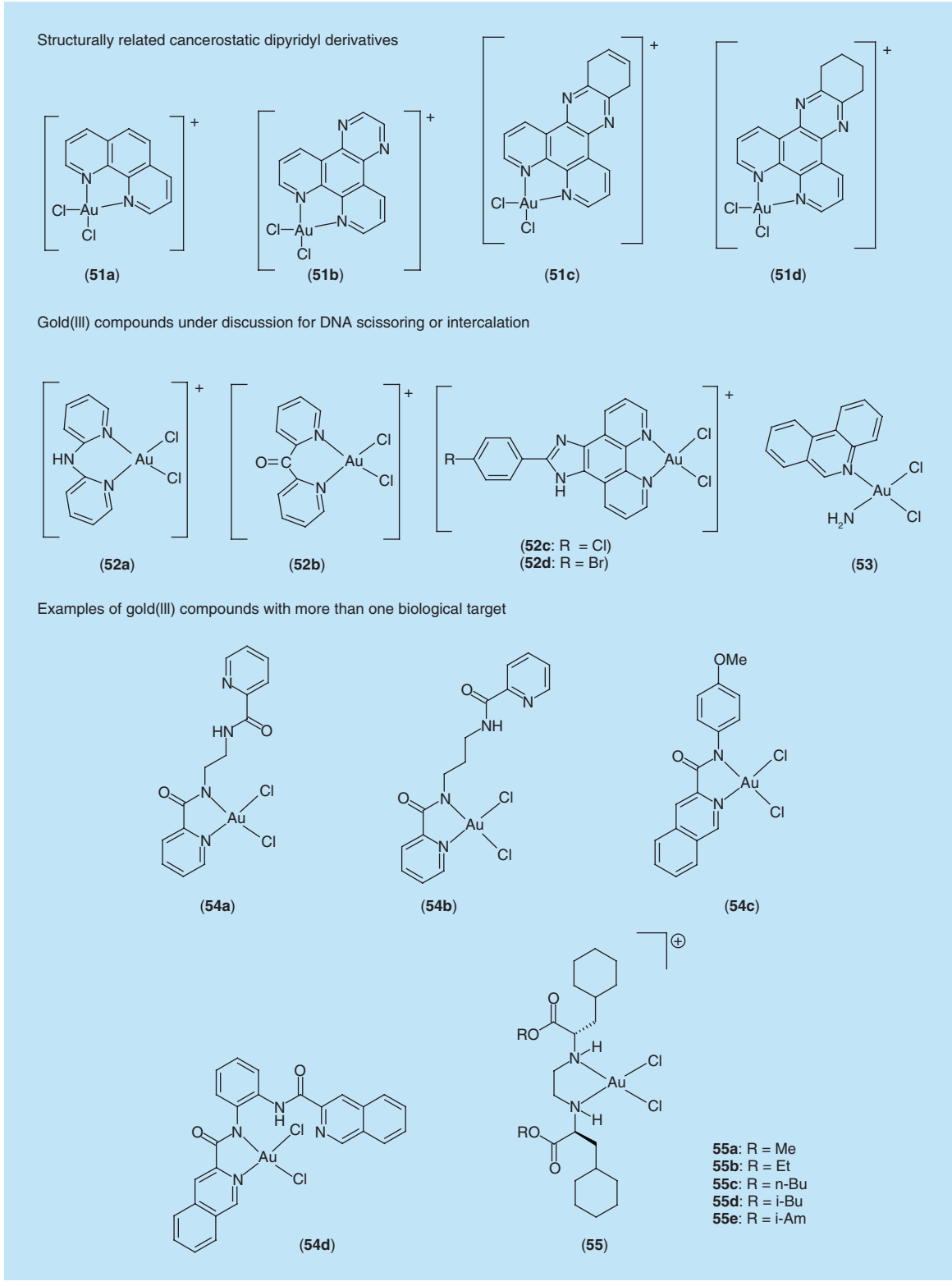

Figure 12. Examples of Au(III) complexes with known structure–activity relationships.

treatment and reduces nuclear transcriptional activities of β-catenin. Cisplatin has no influence on both the protein levels and nuclear activities of β-catenin [121]. Another gold(III) porphyrin complex was found to alter the mitochondrial trans-membrane potential, leading to cytochrome *c* release, nucleus translocation of apoptosis-inducing factor and generation of reactive oxygen species. The modulation of cell death was also investigated in relation to mitogen-activated protein kinase family proteins, which are important intermediates and convert extracellular signals into intracellular responses [122].

The gold(III) diimine and dithiocarbamato complexes **6** and **17**, which possess cytotoxic activity against human ovarian carcinoma, were examined by performing 2D-DIGE analysis in order to identify differential protein expression [123]. In both cases it was found an overexpression of ubiquitin involved in inhibiting protein degradation. The treatment with these gold(III) complexes leads to a down-regulation of proteins related to cellular distribution of the complex required for pre-mRNA splicing, and the overexpression of proteins involved in connections of cytoskeletal components to membrane.

New insights on the mechanism of gold(III) have been obtained by investigation of the cytotoxic activity of compound **35** and its biuret derivative on HeLa cells. The proposed mechanism of action involves the formation of glutathione adducts of gold, which are able to induce endoplasmic reticulum (ER) stress, ER swelling, up-regulation of ER-stress markers and partial S-phase arrest in HeLa cells, finally leading to an apoptosis- and necrosis-independent cell death [87]. Therefore it was concluded that these gold(III) complexes are able to promote cell death without getting inside the nucleus or the mitochondria. Other recent efforts to reveal the mechanism of action of gold(III) complexes include the compounds **55**. These complexes are cytotoxic against human myelogenous leukemia K562 and against human adenocarcinoma tumor cell lines, but they act in different ways depending on the type of cell line. While complexes **55b-f** induce condensation of HeLa cell nuclei leading to apoptosis, the death of K562 cells by complexes **55c-f** is caused by inhibition of cell mitosis [124].

It is well known that gold(III) complexes suffer reduction in cellular media. However, the mechanism of action of analog gold(III) and gold(I) complexes may be different. This was demonstrated by Dou and co-workers, who observed that proteasome inhibition and apoptosis induction of the gold(III) dithiocarbamate complex **17** in human breast cancer MDA-MB-231 cells are mediated through activation of reactive oxygen species, an effect which was not observed for its gold(I) analog. The observed activity can be inhibited by the addition of a reducing agent [22,125]. Similarly, a recent paper reported a gold(III) dithiocarbamate complex with a notable antioxidant activity [126].

Key term

Wnt/β-catenin protein signaling: Signal transduction pathways that pass signals from outside of a cell to the inside of a cell, which is responsible for the regulation of gene expression through control of β-catenin protein degradation.

Doubtlessly the peptide-dithiocarbamato derivatives **18c** and **19** are among the most advanced gold(III) complexes in medicinal chemistry. They have been evaluated on human MDA-MB-231 (resistant to cisplatin) breast cancer cells and xenografts. The *in vivo* studies showed an inhibitory effect of xenograft growth of 53% after 27 days compared with control at dose levels of 1.0 mg kg^{-1} per day. Extensive investigation has been done on evaluation of the mechanism of action of these compounds, determining the proteasome inhibition and apoptosis as main activities both *in vitro* and *in vivo* [127]. Differently from the non-peptide dithiocarbamate compounds **16** [61], cell growth inhibition was independent of the formation of reactive oxygen species (ROS). Such results identify this class of gold(III) compounds as leading candidates for Phase I clinical trials [127].

Striking evidence of the importance of the oxidation state of gold complexes has been outlined in a recent report. This study demonstrated that simple gold(III) complexes like $[AuCl_4]^-$, $[Au(DMSO)_2Cl_2]^+$ or **3** are potent Na^+/K^+ ATPase (sodium potassium adenosinetriphosphatase) inhibitors [128]. Vasić *et al.* not only demonstrated that Au(III) complexes are able to interact with the sulfhydryl groups of Na^+/K^+ ATPase, but also that redox reactions of gold(III) complexes with the cysteine residues and disulfide bonds can lead to significant functional alterations of the enzyme. Comparable results have been obtained by Fregona *et al.*, who verified that the interaction of gold(III) complexes with other simple models such as N-acetyl-$_L$-cysteine and glutathione affords the formation of disulfides and Au(I) species [129].

Another important target of gold(III) complexes is the mitochondrial thioredoxin reductase, a selenoenzyme of the thioredoxin system, which is involved in the regulation of the intracellular redox balance. In fact, various gold compounds have shown inhibition of thioredoxin reductase [21,130–133]. It is supposed that an inhibition of mitochondrial thioredoxin reductase may lead to a strong alteration of the mitochondrial membrane potential, followed by a release of cytochrome *c* and subsequent activation of apoptosis.

Table 1. Modes of action verified for some cytotoxic gold(III) complexes.

Compound	Proposed mechanism of action	Ref.
51	Enhancing of p53 expression, DNA binding and production of an increased amount of reactive oxygen species	[115]
40	Topoisomerase IB inhibitor	[118]
14	I. Inhibition of Wnt/β-catenin protein signaling through inhibition of class I histone deacetylase	[121]
	II. Alteration of mitochondrial membrane potential, release of cytochrome c and generation of reactive oxygen species	[122]
6	Overexpression of protein ubiquilin-1 leading to inhibition of protein degradation	[123]
35	Damage of endoplasmic reticulum	[87]
16,17	Proteasome inhibition, oxidative stress, inhibition of thioredoxin reductase and apoptosis	[22,114,125]
18c,19	Apoptotic cell death via proteasome inhibition	[63,127]
54d	Inhibitor of topoisomerase I and II and DNA intercalator	[119]
55	Apoptotic cell death via condensation of nuclei or inhibition of cell mitosis	[124]
5	Modification of the protein structure	[134]

Finally, a study of the interaction of gold(III) complexes with a model protein named RNase A (Bovine pancreatic ribonuclease) shall be mentioned. The oxobridged complex **5** (R = Me) forms gold-protein adducts, which were structurally characterized by X-ray crystallography. Upon reaction with RNase A, the complex **5** suffers cleavage of the bridging oxido ligands and subsequent loss of the bipy ligands. This leads to the reduction of gold(III) and the resulting Au(I) ion coordinates to two histidine residues of the protein in a nearly linear coordination geometry. Necessarily, the coordination of gold leads to modifications of the protein and inhibits its enzymatic activity [134].

Table 1 summarizes some of the recently studied gold(III) complexes with assumed mechanisms of action.

Figure 13. Space-filling model of compound 19 as a representative of biologically active gold(III) compounds together with potential fields of application in the treatment of cancer, viral and bacterial diseases as well as tropical diseases.

Conclusions & future perspectives on gold(III) medicinal chemistry

It is evident from the results discussed above that Au(III) complexes may play a vital role in future therapeutic medicine. Many compounds of various classes are presently under investigation for the treatment of diseases such as cancer, HIV, tuberculosis or tropical diseases as may be symbolized with Figure 13.

Many gold(III) complexes have shown serious cytotoxic activity against several tumor cell lines, including cisplatin resistant cells. Unfortunately, promising *in vitro* results are not always correlated with significant *in vivo* effects. It becomes obvious that the basic mechanistic ideas of the past, as simple structural analogy to cisplatin, are not sufficient to describe the more complicated biological chemistry of gold compounds, where the problems of hydrolysis and protein binding are accompanied by a more sophisticated ligand exchange behavior of the complexes and the Au(III)/Au(I) redox chemistry. More knowledge about the targets of the individual drugs and the mechanisms of their *in vivo* distribution and/or degradation may provide a rational fundament for future developments in this sector. A single mechanism of action for all gold(III) compounds is more than unlikely. Hitherto, it is known that their mechanism of action is in many cases distinct from that of cisplatin, with many evidences that mitochondria, proteins or enzymes are other targets.

In order to overcome the present disadvantages of the chemotherapy, current strategies in the development of novel gold(III) metallodrugs may focus on the development of complexes containing even more improved

organic ligands. Ligand systems with the potential to be functionalized and attached to a biomolecule may be of great interest. Techniques and strategies for the functionalization and radiolabeling of target specific biomolecules, which have been developed for ^{99m}Tc or $^{186/188}$Re radiopharmaceuticals, may also find use for future ^{199}Au therapeutic drugs. A new trend, which has also entered the pharmaceutical chemistry of gold, is the use of nanoparticles. Based on that, the biodistribution of the gold complexes may be improved by encapsulating techniques using organic nanocapsules and/or functionalization of gold nanoparticles for drug delivery [135,136].

So, it can be concluded that a high advance has been achieved in the relatively young field of gold(III) medicinal chemistry, but still a lot has to

Executive Summary

Gold(III) complexes with antitumor activity

- Gold(III) ions are isoelectronic with platinum(II) ions and many of the complexes are isosteric with the square-planar platinum(II) compounds. This makes gold(III) complexes to natural candidates as alternatives for cancer treatment. A wide spectrum of gold(III) complexes with various chelating systems and donor atom combinations has displayed promising tumor cell inhibiting properties.

Antitumor compounds with nitrogen donor ligands

- Nitrogen donors are the most common ligands in gold(III) coordination chemistry. Most of them are derived from diimine donors like bipyridine or phenanthroline. Simple mononuclear complexes with chelating diimmines or diamines, but also complexes with bi- and tridentate 2,6-bis(2′-benzimidazole)pyridine ligands have demonstrated excellent antiproliferative properties *in vitro* against a wide panel of cancer cell lines.

Antitumor compounds with sulfur donor ligands

- A number of gold(III) compounds with dialkyldithiocarbamates have been designed in order to reproduce very closely the main features of cisplatin. Comparative *in vitro* cytotoxicity studies between isostructural Pt(II), Pd(II) and Au(III) derivatives on various types of cancer cells show highest activity for the gold compounds. A "second-generation" of such compounds comprises peptide conjugates, which have successfully been synthesized and tested *in vitro* and show no cross-resistance with cisplatin itself and were also active against cisplatin resistant cells. The targets of the tailored peptidomimetics are peptide transporters. They are upregulated in several tumor cells.

Organometallic gold(III) complexes with antitumor activity

- The structural design of classical organometallic gold compounds with antitumor properties contain orthometallated *N,N*-dimethylaminomethylphenyl ligands and follow structurally the 'cisplatin concept'. They are active against several tumor cell lines and show activity similar to cisplatin *in vivo*, but it became also evident that the mode of action of such compounds is different. A relatively new, but fast-growing area of medicinal chemistry of gold complexes uses *N*-heterocyclic carbenes as ligands.

Gold(III) complexes with antibacterial and antiviral properties

- The incidence of resistance to antibiotics stimulated the development of new antibacterial drugs, particularly against *Mycobacterium tuberculosis*, the pathogen responsible for tuberculosis. Based on this fact, gold(III) complexes appear once more as promising agents, however, the advances on this field have hitherto not been the same as in cancer chemotherapy. Similarly scares is the information on the use of gold(III) complexes as anti-HIV agents and only recently a few reports have been published.

Gold(III) complexes against parasitic diseases

- Gold complexes with the anti-malaria drug chloroquine as lead structure were tested for their activity against *Plasmodium falciparum*. The activity of some gold(III) cyclometallated complexes previously tested for anti-cancer activity, were also assayed against mammalian and parasitic cysteine proteases, which are involved in parasitic life cycles including *Schistosoma*, *Plasmodium*, *T. brucei*, *T. cruzi*, and *Leishmania*.

Gold(III) compounds as radiotherapeutic agents

- Gold possesses two beta-emitting radioactive isotopes, ^{198}Au and ^{199}Au, which are potentially suitable for therapeutic applications. A number of Schiff base and thiosemicarbazonato complexes has been prepared with ^{198}Au. The products were evaluated *in vitro* at the tracer level for stability and one of them was selected for an *in vivo* study in mice.

Mechanisms of action of gold-based drugs

- Based on the great structural variety of the used ligands and the derived complex molecules, a unique mode of action or pharmacological profile for all Au(III) complexes is unlikely to exist. In particular, direct DNA damage, modification of the cell cycle, mitochondrial damage including thioredoxin reductase (TrxR) inhibition, proteasome inhibition, modulation of specific kinases and other cellular processes affected by gold compounds, which eventually trigger apoptosis, seem to play a major role in the mechanism of action of gold compounds.

be done in order to access their possible efficacy as chemotherapeutic agents.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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▪ of interest; ▪▪ of considerable interest

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