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Review article

Metal-based compounds containing selenium: An appealing approach towards novel therapeutic drugs with anticancer and antimicrobial effects

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ABSTRACT

In recent years, both metal-based complexes and selenium-containing compounds have been widely explored for their therapeutic properties due to their roles in biological processes and modulation of diverse molecular targets. However, despite their growing interest, there is no review to date that covers the potential use of the combination of these entities to design new therapeutic derivatives. This review highlights the latest achievements in this particular field, with a focus on compounds with anticancer and/or antimicrobial properties. With this aim, the formation of coordination compounds including several metals bearing selenium either with direct interaction with the metal center or as part of the organic ligand elsewhere is covered. Besides, coordination compounds with a Se(IV) center have been assessed. The biological properties of several selenium-containing organometallic complexes have also been discussed, including metallocenes, half-sandwich complexes, and compounds with *N*-heterocyclic carbenes, CO, and π-ligands, and other σ-bonded entities. The information compiled in this review may be helpful to design and develop novel, more potent, and safer metal-based compounds for the treatment of several pathologies.

1. Introduction

The field of medicinal chemistry has been traditionally dominated by purely organic derivatives, but in recent years metals and metal-based compounds have attracted great attention in the search for new therapeutic drugs. In this context, metal ions have been proved to be indispensable for living organisms [1]. There are currently ten metal elements considered as essentials for humans that are known to be involved in multiple physiological processes, including structural roles, signal transduction and catalysis, and as part of active sites of several enzymes [2]. It is estimated that around 30–40% of proteins including metalloenzymes require metal cofactors for proper folding into an active three-dimensional (3D) structure [3]. In addition, dysregulations in metal levels due to genetic or environmental sources could lead to significant health issues and pathological disorders such as cancer [4]. Thus, in recent years metal ions have emerged as appealing building-blocks for therapeutic agents in the clinic for both diagnosis and treatment of diseases [1,5–7].

1.1. Metal-based compounds as therapeutic agents

The use of metals in medicine has been well-documented throughout the history of humankind, and many metal-containing compounds have been utilized over the centuries to treat a wide variety of disorders. For example, the use of mercury as a treatment for syphilis was a widespread, but highly toxic practice until the discovery of one of the earliest antimicrobials, the arsenic-based arsphenamine. Also known as 'salvarsan', it was used in the treatment of syphilis and trypanosomiasis [8] until its replacement with penicillin after World War II [9]. Likewise, one of the earliest treatments for psychiatric diseases was the use of lithium for bipolar disorder, and currently is still the only substance able to prevent both new depressive and manic episodes [10]. Precious metals have also been long used for a variety of medical indications [11]. For example, silver salts have been employed in the past as antibacterial agents against infections such as conjunctivitis, gastroenteritis, gonorrhea, and syphilis, but also to treat mental illness and nicotine addiction [12]. Similarly, the 'Midas touch' in therapy could be the elegant definition of the use of gold-derived compounds [13] such as auranofin. Auranofin is an orally available Au(I)

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triethylphosphine-complex introduced in clinical practice in the early 1980s for rheumatoid arthritis [13], and is indeed the most prominent example of a gold drug in widespread clinical use [14]. Undoubtedly, the milestone that marked the foundation of modern research in metal-based drugs is the platinum-derived compound cisplatin (*cis*-[$PtCl_2(NH_3)_2$]). The anticancer properties of cisplatin ('Platinol') were discovered serendipitously by Rosenberg and coworkers in the 1960s and patented by the FDA in 1978 [15]. It is still considered a standard treatment against many types of cancer, as are other Pt-based drugs such as carboplatin and oxaliplatin [9]. The unprecedented therapeutic success of these types of metal complexes in the clinic, along with the necessity of overcoming the toxicity issues and the limited activity range of Pt-based drugs [16], have prompted the design, optimization, and development of novel metal complexes also incorporating other transition metals for several therapeutic applications.

In this context, metal-based compounds offer many advantages over traditional organic compounds in the development of new therapeutic drugs. These advantages are due to the ability of the metal to coordinate ligands in a defined 3D configuration, thus allowing the tailoring of the compound to recognize and interact with certain molecular targets [17]. Metal-based complexes also offer a great variety of different chemical structures that confer a wide spectrum of coordination numbers, geometries, and kinetic properties that would not be possible with conventional carbon-based compounds [18]. Furthermore, the design of new metal-based compounds is not restricted to the set of metals naturally occurring, but it could also be applied to nonessential metals of the second- and third-row transition metals and the lanthanide elements, thus allowing to take advantage of the unique properties of these atoms [19]. The partially filled "d" orbitals of these transition metals can also provide interesting electronic and magnetic properties to the compounds [20], and additionally, the oxidation state of the metal center allows its participation in numerous biological redox chemistry processes and plays a role in the bioavailability of the drug [21,22]. The ligand attached to the metal center is also of great importance, since it can also modify the bioavailability of the metal ion and assist in targeting specific tissues or enzymes, among other biological functions [22]. The choice of suitable ligands also allows controlling important physicochemical parameters, such as the lipophilic and hydrophilic character, the reactivity or the inertness to substitutions, and the kinetics of demetallation. Besides, a synergistic effect could be obtained by designing a metal-based compound incorporating a certain ligand that is biologically active by itself [22]. Thus, metal-based compounds offer the possibility of designing molecules with multiple mechanisms of action [23].

Therefore, in recent years a plethora of studies support the use of metal-based complexes as potential drugs with a wide range of pharmacological properties, such as anticancer [24–26], antimicrobial [27–29], antiparasitic [30–32], anti-neurodegenerative [33–35], or antidiabetic [36–38] activities.

1.2. The role of selenium in the development of new therapeutic drugs

The importance of the element selenium (Se) was recognized soon after its discovery in the early 19th century, and this journey persists to the present day [39]. Se is an essential trace metalloid that plays a prominent role in human health [40]. According to the World Health Organization (WHO), the average recommended daily intake of Se is 55 μg/day for adults, with an upper limit of 400 μg/day [41]. Se participates in several physiological processes through its incorporation into selenoproteins, which contain at least one residue of the amino acid selenocysteine in their sequence [42]. This small yet crucial group comprises proteins encoded by 25 genes in humans, such as glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), iodothyronine deiodinases (DIOs), and selenoprotein P (SePP1) [42] and are involved in the thyroid metabolism [43], aging process [44], inflammation [45], immune defense, and redox state regulation [46], among other functions.

Selenoprotein-mediated biochemical mechanisms, such as the protection against oxidative stress [47,48], also play a central role in the prevention, onset, and modulation of the clinical outcome of several diseases, including cancer, cardiovascular disorders, fertility impairments, hepatopathies, neurological and mental disorders, infections, and diabetes [46,47]. Likewise, a positive relationship between Se status in the organism and a favorable prognosis of the abovementioned pathologies has been generally observed [47], while a deficiency in Se levels could be associated with the development of several diseases [41,49,50]. Additionally, Se and Se-containing compounds have been demonstrated to have a potential synergistic effect in combination with other therapeutic agents [51–53], including metal complexes [54–57]. Likewise, ionic Se species, such as sodium selenite (Na_2SO_3) [58], sodium selenate (Na_2SO_4) [59,60], and sodium selenosulfate ($NaSeSO_3$) [61] have also been reported to possess therapeutic activity [62–66] and synergistic effects, especially for cancer treatment [67–69]. Therefore, all these factors highlight the potential applicability of Se-containing compounds and ionic forms of Se for the discovery of novel therapeutic drugs.

From a chemistry point of view, an interesting aspect of the Se atom is that it has a better electron-donating ability than other chalcogen elements typically used in the formation of metal complexes, such as sulfur (S) and oxygen (O). In this context, Se is categorized as a "soft" base according to the principle of hard and soft acids and bases (HSAB) developed by Pearson [70], which is based on the polarizability of atoms. Hence, small nonpolarizable acids or bases with high charge density are classified as "hard", and large polarizable acids and bases with low charge density are classified as "soft". This designation of metal ions (Lewis acids) and their ligands (Lewis bases) serves as a useful starting point for predicting the preference of metal ions for certain ligands with several donor groups [19]. Thus, Se is more polarizable ("softer") than S and O, resulting in a stronger nucleophilic power that would allow the Se atom to readily coordinate with soft metal ions, thereby forming Se-containing metal complexes that could potentially exert pharmacological effects [39].

In this regard, some recent reviews have been published concerning the use of Se compounds such as acylselenoureas, selenosemicarbazones, and pyridyl-selenium as ligands in coordination chemistry [71–73]. Nevertheless, and to the best of our knowledge, a revision focused on the medicinal applications of metal-based compounds incorporating Se has not been yet reported to date. Thus, given the increasing interest in the use of metal-based compounds in medicinal chemistry [9,74–76] and the fact that the inclusion of Se is a valid design strategy to obtain therapeutic agents [67,77,78], we felt that it was timely to provide a summary and an update of the latest developments in this field.

With this aim, we cover the recent applications of metal coordination complexes incorporating Se for the treatment of cancer and/or infectious diseases caused by microbial agents. The formation of complexes in which the coordination is made upon an ionic center of Se(IV) is also discussed. Organometallic compounds are another wide field in medicinal inorganic chemistry, and so we encompass the description of several organometallic complexes containing Se classified according to the type of bond and ligand coordinated to the metal center. The electronic search was conducted covering all articles published from 2010 to June 2022. Searches were performed in Web of Science and Pubmed databases using the following keywords alone or in combination with the two main types of diseases involved: selenium, metal-based compound, metal complex, organometallic, selenium (IV), cancer, bacteria, fungi, antiproliferative activity, antimicrobial activity, therapeutic activity. The articles in which the chemical structure of the resulting compound was not included, along with studies lacking biological information, were excluded from this review.

2. SELENIUM-CONTAINING metal coordination complexes

Coordination complexes are characterized by the involvement of one or more coordinate (or dative) covalent bonds in which the ligand donates a lone pair of electrons to an empty orbital on the metal center. Thus, the organic molecules can act as chelating agents by incorporating a variety of heteroatoms such as "hard" nitrogen (N) and O or "soft" S and Se as donor species upon coordination with the metal ion. Increasing interest has been developed in exploring metal coordinated complexes with therapeutic potential [16,20,79] due to their unique properties, such as variable charge, strong and selective interactions with ligands, variety of coordination geometries, Lewis acid character, partially filled d-shell, and redox activity [19].

In this regard, among the strategies suggested in the design of new coordinated complexes for medicinal purposes, the inclusion of Se in a variety of organic scaffolds as coordination ligands for several transition metals has been explored, mainly as part of compounds to treat cancer or infectious diseases caused by microbial agents. Given the diversity of the metal coordination complexes, a classification based on the metal center has been made to facilitate the reading. Likewise, the formation of complexes with Se(IV) as the ionic center has also been assessed and is included in this section. An overview of all the complexes gathered in this section along with their biological activity is presented in Table 1.

2.1. Metal coordination complexes bearing selenium for cancer treatment

Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs. The disease is one of the leading causes of morbidity and mortality irrespective of the level of human development, with 19.3 million new cases according to the most recent statistics [80]. Despite striking advances in the field of molecular oncology, combating cancer remains a challenge. Since the discovery of the anticancer agent cisplatin, several metal complexes have been synthesized with appealing therapeutic properties for cancer, and some of them are either undergoing clinical trials or already in use in clinical practice for diagnosis and treatment [20].

2.1.1. Metal complexes based on Pt, Pd, Au, Ag and Cu

Since the discovery of the anticancer properties of cisplatin, a vast majority of platinum (Pt) coordination complexes have been developed for cancer treatment. Hence, the inclusion of Se has been more explored in the formation of complexes with this element than with other metals. For example, the cytotoxicity of a series of water-soluble Pt(II) complexes with dimethylpyrazole-based selenides was assessed, and complex **1** (Fig. 1) stood out with an activity comparable to cisplatin in bladder cancer cells (GI_{50} = 25.5 μM) while being not toxic to other cancer cell lines [81]. Besides, several Pt(II) complexes based on cisplatin bearing different selenone ligands were reported to have antiproliferative activity. Among them, the bis(selenone) derivatives (**2**–**5** in Fig. 1) [82–84] were found to be more effective than the tetrakis (selenone) coordinated compounds (**6**–**7** in Fig. 1) [85,86], with IC_{50} values in the low micromolar range from 0.90 to 12.27 μM. Additionally, complex **5** (Fig. 1) deactivated PI3K protein, altered the miRNA expression, and induced apoptosis in lung cancer cells [84]. Other modifications made to the cisplatin core also included the development of a small molecule assembly system based on the coordination of this complex with a selenomethionine ester. The resulting compound (**8** in Fig. 1) was found to have higher anticancer activity and lower side effects compared with cisplatin alone in a lung xenograft tumor model. Further mechanistic studies suggested that **8** consumed glutathione (GSH) in cancer cells, thus inducing reactive oxygen species (ROS) production [87].

The formation of a complex bearing a fused bicyclic selenohydantoin coordinated to a metal center of a palladium (Pd) ion led to compound **9** (Fig. 1) that was found to display greater prooxidative effect, cytotoxicity, and influence on cell migration potential than the free ligand [88]. Interestingly, in a series of metal coordination complexes synthesized with the ligand 2-amino-4-phenyl-5-selenocyanatothiazol, the compounds with Pd(II) or Pt(II) centers (**10**–**11** in Fig. 1) were able to reduce the viability of cancer cells with impressive IC_{50} values in the submicromolar range between 0.02 and 0.35 μM, showing the highest antiproliferative activity among the other metal complexes [89]. In another study, the reaction of amine-capped Pd(II) and Pt(II) compounds with 4,4′-dipyridylselenide/diselenide yielded water-soluble macrocyclic complexes that were tested for their antiproliferative activity. Remarkably, the Pt complex showed lower toxicity compared to the Pd complexes, and this behavior was attributed to the inert nature of the Pt ionic center and the higher stability of the macrocyclic ring compared to that of the Pd analog. Additionally, among the Pd complexes, the presence of the diselenide group was also determinant for the cytotoxicity (**12** in Fig. 1), since the selenide analog exhibited higher IC_{50} values [90]. In a related research, other metallo-macrocyclic complexes of Pd(II) and Pt(II) bearing wide-bite angle diphosphines were also synthesized with 4,4′-dipyridyldiselenide, and were found to induce DNA damage and form micronuclei and other nuclear distortions. In this study, the Pt(II) complex (**13** in Fig. 1) with the lesser bulky triethylphosphine exhibited the highest antiproliferative activity among all the complexes, with IC_{50} values between 4 and 13 μM [91].

Interestingly, a cobaltoceniumselenolate moiety containing a very soft anionic Se was coordinated directly through this chalcogen to a gold (Au) ion, forming water-soluble Au(I) complexes (**14**–**15** in Fig. 1). These complexes displayed potent cytotoxic activity against several cancer cell lines with IC_{50} values in the range of 3.5–12.3 μM, this effect being increased by the introduction of the Au(I) center [92]. A design based on the combination of Au(III), Se, and porphyrin yielded a complex (**16** in Fig. 1) that exerted a remarkable antiproliferative effect (IC_{50} values of 1.42–13.65 μM) on several cancer cells, which was ascribed to the synergistic effect between Se and Au moieties. Further mechanistic studies revealed that this Au(III) complex could arrest the cell cycle at the G2 phase, enhance the intracellular ROS levels, impair mitochondrial function and alter the expression of B-cell lymphoma 2 (Bcl-2) and Bax proteins, thus inducing apoptosis on the cancer cells [93]. In another study, a series of complexes bearing either adipic or sebacic acids with Au(III), Pt(IV), and silver(I) (Ag) was subjected to cytotoxicity evaluation [94]. Among the six complexes, the Ag(I) center proved to yield the most active compounds (**17**–**18** in Fig. 1), while inducing alterations in the glutathione-S-transferase (GST) activity and the levels of GSH and malondialdehyde (MDA) [94]. Interestingly, a selenosemicarbazone derivative was identified to target lysosomal integrity via its complexation with a copper (Cu) ion. The redox-active Cu(II) compounds such as **19** (Fig. 1) could generate ROS production and induce lysosomal membrane permeabilization [95]. Triapine is a thiosemicarbazone that has entered clinical trials for both solid and hematological tumors, so the complexation of its Se analog, namely Se-Triapine, was subsequently studied. Hence, the exchange of S in the thiocarbonyl moiety to Se was found to increase the solution stability of Cu(II) complexes. The coordination to a Cu(II) center (**20** in Fig. 1) also increased ROS production and displayed moderate cytotoxicity in cancer cells, with IC_{50} values between 29 and 46 μM [96]. The replacement of S with Se was also studied in a series of other selenosemicarbazone ligands coordinated to Pt(II) and Cu(II) centers. Herein, a Cu(II) complex **21** (Fig. 1) stood out with low IC_{50} values in the range of 2.74–5.11 μM in several cancer cells, along with alterations in the GSH and catalase (CAT) activities [97].

2.1.2. Metal complexes based on Ru, Fe, Co and Sn

A series of ruthenium (Ru) complexes was designed bearing different α, β-diketones and a diseleno-based ligand in which both the Se atoms were coordinated directly to the metal center. The Ru(II) complex **22** (Fig. 2) showed the best antiproliferative performance (IC_{50} = 2.81 μM in cervix cancer cells) among the complexes, and also displayed a higher cytotoxic effect compared to cisplatin (IC_{50} = 5.10 μM) [98]. A Ru(II)

Table 1
Selenium-containing coordination complexes.

Scaffold + Ligand	Coordination mode (C_M)	Experimental system[a]	Biological activity	Refs.
Metal coordination complexes for cancer treatment				
Metal complexes based on Pt, Pd, Au, Ag and Cu				
Dimethylpyrazole-based selenide Pt(II) complex [Pt(en)(L)][NO_3]$_2$, L = 3-((2-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)selanyl)propanoic acid, en = ethylenediamine (**1**)	Pt(SeN_3)	HT-29, Colo205, A2780, T24	Antiproliferative activity GI_{50} (T24) = 25.5 μM; GI_{50} (Colo205, HT-29, A2780) >100 μM	[81]
Selenone-based Pt(II) complex [Pt(1,3-diazinane-2-selenone)$_2$$Cl_2$] (**2**)	Pt(Se_2Cl_2)	MCF-7, HeLa	Antiproliferative activity IC_{50} (HeLa) = 11.33 μM; IC_{50} (MCF-7) = 12.27 μM	[82]
Selenone-based Pt(II) complexes *trans*-[Pt(NH_3)$_2$(*N*-ethylimidazolidine-2-selenone)$_2$](NO_3)$_2$ (**3**), *trans*-[Pt(NH_3)$_2$(*N*-(i-propyl)imidazolidine-2-selenone)$_2$](NO_3)$_2$ (**4**)	Pt(Se_2N_2)	MDA-MB-231, HeLa	Antiproliferative activity **Compd 3**: IC_{50} (HeLa) = 2.1 μM; IC_{50} (MDA-MB-231) = 4.4 μM **Compd 4**: IC_{50} (HeLa) = 3.1 μM; IC_{50} (MDA-MB-231) = 5.7 μM	[83]
Selenone-based Pt(II) complex *cis*-[Pt(NH_3)$_2$(1,3-imidazolidine-2-selenone)$_2$](NO_3)$_2$ (**5**)	Pt(Se_2N_2)	A549, HeLa, HCT-116	Antiproliferative activity; alteration of miRNA expression profile; deactivation of PI3K; induction of apoptosis IC_{50} (A549) = 1.20 μM; IC_{50} (HeLa) = 0.90 μM; IC_{50} (HCT-116) = 1.40 μM	[84]
Selenone-based Pt(II) complexes [Pt(*N*-propylimidazolidine-2-selenone)$_4$]Cl_2 (**6**), [Pt(*N*-isopropylimidazolidine-2-selenone)$_4$]Cl_2 (**7**)	Pt(Se_4)	MCF-7, A2780, A2780cisR, 22Rv1	Antiproliferative activity **Compd 6**: IC_{50} (A2780) = 44.7 μM; IC_{50} (22Rv1) = 46.2 μM; IC_{50} (A2780cisR, MCF-7) >50 μM **Compd 7**: IC_{50} (A2780) = 30.8 μM; IC_{50} (A2780cisR, 22Rv1, MCF-7) >50 μM	[85, 86]
Selenomethionine ester Pt(II) complex [Pt(SeMet$(CH_2)_{11}CH_3]^+$, SeMet = selenomethionine (**8**)	Pt(SeN_2Cl)	A549, HepG2	Antiproliferative activity; induction of ROS production; consumption of GSH; significant reduction of tumor growth	[87]
Bicyclic seleno-hydantoin Pd(II) complex *trans*-[Pd(Hid-Se)$_2$$Cl_2$], Hid-Se = *cis*-7a-ethyl-5-methyl-5-phenylselanylmethyl-tetrahydro-pyrrolo[1,2-*c*]imidazole-1,3-dione (**9**)	—[b]	MDA-MB-231, HCT-116	Antiproliferative activity; alteration of the redox status; alteration in the expression of the inducible nitric oxide synthase (iNOS) protein; modification of the cell migration potential IC_{50} (MDA-MB-231) = 130.7 μM; IC_{50} (HCT-116) = 81.6 μM	[88]
Selenocyanatothiazol Pd(II)/Pt(II) complexes *trans*-[Pd(PhSeCNH)$_2$$Cl_2$] (**10**), *trans*-[Pt(PhSeCNH)$_2$$Cl_2$] (**11**), PhSeCNH = 4-phenyl-5-selenocyanatothiazol-2-amine	Pd(N_2Cl_2) Pt(N_2Cl_2)	MCF-7, HeLa	Antiproliferative activity **Compd 10**: IC_{50} (HeLa) = 0.02 μM; IC_{50} (MCF-7) = 0.08 μM **Compd 11**: IC_{50} (HeLa) = 0.35 μM; IC_{50} (MCF-7) = 0.15 μM	[89]
Bis(4,4′-Dipyridyldiselenide) Pd(II) complex [Pd(tmeda)(μ_2-4,4′-py_2Se_2)]$_2$($OTf)_4$, 4,4′-py_2Se_2 = 4,4′-dipyridyldiselenide, tmda = tetramethylethylenediamine (**12**)	Pd(N_4)	A549, MCF-7	Antiproliferative activity IC_{50} (A549) = 19 μM; IC_{50} (HCT-116) = 1.7 μM	[90]
Bis(4,4′-Dipyridyldiselenide) Pt(II) complex [Pt(PEt_3)$_2$(4,4′-py_2Se_2)]$_2$($OTf)_4$, 4,4′-py_2Se_2 = 4,4′-dipyridyldiselenide, PEt_3 = triethylphosphine (**13**)	Pt(N_2P_2)	MCF-7, A549, SKOV3, U2OS Vero	Antiproliferative activity; induction of DNA damage; induction of micronuclei and other nuclear distortions IC_{50} (MCF-7) = 4 μM; IC_{50} (U2OS) = 4.8 μM; IC_{50} (A549) = 13 μM; IC_{50} (SKOV3) = 12 μM; IC_{50} (Vero) = 19.1 μM	[91]
Cobaltoceniumselenolate-based Au(I) complexes [Au(CcSe)(PPh_3)]PF_6 (**14**), [Au($CcSe)_2$]PF_6 (**15**), CcSe = cobaltoceniumselenolate	Au(SeP) Au(Se_2)	A549, MDA-MB-231, HT-29	Antiproliferative activity **Compd 14**: IC_{50} (A549) = 8.4 μM; IC_{50} (MDA-MB-231) = 3.6 μM; IC_{50} (HT-29) = 5.0 μM **Compd 15**: IC_{50} (A549) = 12.3 μM; IC_{50} (MDA-MB-231) = 3.5 μM; IC_{50} (HT-29) = 4.9 μM	[92]
Se-modified porphyrin Au(III) complex [Au(TPP-Se)]Cl, TPP-Se = 2-amino-4-(methylseleno)butanoate porphyrin (**16**)	Au(N_4)	A549, HeLa, MCF-7, K-562, HepG2, LN229	Antiproliferative activity; cell cycle arrest at G2 phase; induction of mitochondria-dependent apoptosis; up-regulation of Bax expression levels; down-regulation of the expression of Bcl-2 protein; induction of ROS production IC_{50} (HeLa) = 7.30 μM; IC_{50} (HepG2) = 1.42 μM; IC_{50} (A549) = 11.73 μM; IC_{50} (K-562) = 13.65 μM; IC_{50} (LN229) = 8.73 μM; IC_{50} (MCF-7) = 5.25 μM	[93]
Adipic and sebacic derived Ag(I) complexes [Ag_2(adip)$Se_2O_2(OH)_4Cl_2$] (**17**), [Ag_2(sebac)$Se_2O_2(OH)_4Cl_2$] (**18**), adip = adipic acid, sebac = sebacic acid	Ag(SeO)	EACC	Antiproliferative activity; increase of the GST activity and GSH levels; decrease of the MDA levels	[94]

(*continued on next page*)

Table 1 (*continued*)

Scaffold + Ligand	Coordination mode (C_M)	Experimental system[a]	Biological activity	Refs.
Dimethylselenosemicarbazone-based Cu(II) complex [Cu(Ap44mSe)(OAc)], Ap44mSe = 2-acetylpyridine 4,4-dimethyl-3-selenosemicarbazone (**19**)	$Cu(SeN_2O)$	SK-N-MC	Antiproliferative activity; induction of ROS production; prevention of methemoglobin formation; alteration of lysosome-associated membrane protein 2 (Lamp2) and cathepsin D; induction of lysosomal membrane permeabilization	[95]
Se-Triapine Cu(II) complex [Cu(Se-Triapine)(H_2O)], Se-Triapine = (*E*)-2-((3-aminopyridin-2-yl)methylene) hydrazine-1-carboselenoamide (**20**)	$Cu(SeN_2O)$	MES-SA, MES-SA/Dx5	Antiproliferative activity; higher stability compared to Triapine complexes; induction of ROS production IC_{50} (MES-SA) = 46 μM; IC_{50} (MES-SA/Dx5) = 29 μM	[96]
Selenosemicarbazone-based Cu(II) complex [Cu(L)(ONO_2)], L = benzocoumarin selenosemicarbazone (**21**)	$Cu(SeNO_2)$	MCF-7, HepG2, HCT-116 HFB-4	Antiproliferative activity; increase of the GST activity; decrease of the catalase activity IC_{50} (HepG2) = 3.13 μM; IC_{50} (HCT-116) = 2.74 μM; IC_{50} (MCF-7) = 5.11 μM; CC_{50} (HFB-4) = 3.41 μM	[97]
Metal complexes based on Ru, Fe, Co and Sn				
Diseleno-pyridyl Ru(II) complex [Ru($BP3Se_2$)(hfac)(PPh_3)]Cl·H_2O, $BP3Se_2$ = 1,9-bis(2-pyridyl)-3,7-diselenononane, hfac = hexafluoroacetylacetonate (**22**)	$Ru(Se_2NO_2P)$	HeLa	Antiproliferative activity IC_{50} (HeLa) = 2.81 μM	[98]
Phenanthrolineselenazole Ru (II) complex [Ru($phen)_2$(phenSe)]($ClO_4)_2$, phen = 1,10-phenanthroline, phenSe = 2-selenoimidazole[4,5-f] 1,10-phenanthroline (**23**)	$Ru(N_6)$	HepG2, A549, HeLa, MDA-MB-231, SW620	Antiproliferative activity; significant conversion of parallel/antiparallel G-quadruplex to antiparallel G-quadruplex; stabilization of the G-quadruplex; inhibition of telomerase activity IC_{50} (HeLa) = 21.26 μM; IC_{50} (A549) = 33.86 μM; IC_{50} (SW620) >80 μM; IC_{50} (HepG2) = 13.29 μM; IC_{50} (MDA-MB-231) = 72.04 μM	[99]
Phenanthrolineselenazole Ru (II) complex [Ru($phenSe)_2Cl_2$], phenSe = 2-selenoimidazole[4,5-f] 1,10-phenanthroline (**24**)	$Ru(N_4Cl_2)$	HeLa, A549, HepG2, MDA-MB-231, CNE HUVEC	Antiproliferative activity; stabilization of the G-quadruplex; inhibition of telomerase activity; induction of apoptosis; inhibition of tube formation; suppression of endothelial cell migration IC_{50} (HeLa) = 12.7 μM; IC_{50} (A549) = 26.5 μM; IC_{50} (CNE) = 21.6 μM; IC_{50} (HepG2) = 32.1 μM; IC_{50} (MDA-MB-231) = 33.3 μM	[100]
Phenanthrolineselenazole Ru (II) complex [Ru(phtpy)(phenSe)Cl](ClO_4) (phtpy = 4-phenyl-2,2':6',2''-terpyridine, phenSe = 2-selenoimidazole[4,5-f]1,10-phenanthroline (**25**)	$Ru(N_5Cl)$	A375 HK-2	Antiproliferative activity; low toxicity *in vitro*; enhancement of radiation-induced DNA damage; cell cycle arrest at G2/M phase; induction of apoptosis by activation of ROS-mediated pathways; up-regulation of cyclin-B; down-regulation of caspases-3, -8, and -9 expression; suppression of Bcl-xl expression; up-regulation of p53 expression; induction of mitochondrial dysfunction IC_{50} (A375) = 9.7 μM; IC_{50} (HK-2) = 110.9 μM	[101]
Phenanthrolineselenazole Ru (II) complex [Ru($PhenSe)_2$(Bioben)]($ClO_4)_2$, phenSe = 2-selenoimidazole[4,5-f]1,10-phenanthroline, Bioben = biotin-derived 2-(pyridin-2-yl)-2,3-dihydro-1λ^2-benzo[*d*]imidazole-5-carboxamide (**26**)	$Ru(N_6)$	HeLa, MDA-MB-231, MCF-7, HepG2, A549 NCM460, L02	Antiproliferative activity; up-regulation of Bax expression levels; down-regulation of the expression of Bcl-2; induction of mitochondrial dysfunction; up-regulation of caspases-3 and -9 expression levels; induction of apoptosis by ROS-mediated endoplasmic reticulum (ER) stress signal pathway; significant reduction of tumor growth with low systemic toxicity; effective accumulation in tumor tissues IC_{50} (HeLa) = 15.3 μM; IC_{50} (A549) = 17.4 μM; IC_{50} (MCF-7) = 21.0 μM; IC_{50} (MDA-MB-231) = 22.7 μM; IC_{50} (HepG2) = 34.1 μM; IC_{50} (L02) = 77.6 μM; IC_{50} (NCM460) = 68.5 μM	[102]
Phenanthrolineselenazole Ru (II) complex [Ru($PhenSe)_2$(L)]($ClO_4)_2$, phenSe = 2-selenoimidazole [4,5-f]1,10-phenanthroline, L = 2-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole (**27**)	$Ru(N_6)$	PC-3, LNCAP NK, NK-92	Synergistic potentiation of NK cell-mediated killing effect; increase of the NK cell degranulation by promoting the recognition and interaction of TRAIL-DR5 and FasL/Fas; ROS overproduction-triggered DNA damage; alteration of the downstream ATM and ATR pathways; significant reduction of tumor growth in combination with NK cells with no apparent side effects	[102, 103]

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Table 1 (*continued*)

Scaffold + Ligand	Coordination mode (C_M)	Experimental system[a]	Biological activity	Refs.
Phenanthrolineselenazole Fe (II) complex [Fe(phenSe)$_3$](ClO$_4$)$_2$ phenSe = 2-selenoimidazole[4,5-f] 1,10-phenanthroline (**28**)	Fe(N_6)	HUVEC	Antiproliferative activity; induction of apoptosis by activation of caspases-3, -8, and -9 and PARP cleavage; activation of p53-mediated mitochondrial dysfunction; up-regulation of the expression of p53 and Bad; down-regulation of the expression of Bcl-2: inhibition of VEGF expression; suppression of the transmission of the mitogenic signaling pathway by dephosphorylated AKT	[104]
		HeLa, CaSki, SiHa	Antiproliferative activity; inhibition of cellular migration and invasion; tumor spheroids damage; down-regulation of the ER stress-related selenoproteins SelS, GPX4, and SelO; sensitization of the cancer cells to TRAIL-based treatment; synergistic effect with TRAIL treatment in the induction of intracellular ROS production, cell cycle arrest, and apoptosis via the regulation of the expression levels of multiple molecules related to extrinsic and intrinsic signaling pathways 10 μM < IC_{50} (HeLa) < 20 μM; 5 μM < IC_{50} (CaSki) < 10 μM; 10 μM < IC_{50} (SiHa) < 20 μM	[105]
N-heteroaromatic selenosemicarbazone Co(III) complex [Co(8qasesc)$_2$]ClO$_4$·DMSO, 8qasesc = 8-quinolinecarboxaldehyde selenosemicarbazone (**29**)	Co(Se_2N_4)	THP-1, AsPC-1	Antiproliferative activity; induction of apoptosis and necrosis; nuclease activity on plasmid pUC19; down-regulation of CD44 expression	[106]
		A549, HeLa, MDA-MB-361, LS-174, K-562, HL-60 MRC-5	Antiproliferative activity; myeloid differentiation activity; alteration in the nuclear chromatin condensation and nuclear cytoplasmic ratios; development of numerous pseudopodia; cell cycle arrest at G2/M phase IC_{50} (HeLa) = 33.2 μM; IC_{50} (MDA-MB-361) = 36.3 μM; IC_{50} (K-562) = 31.3 μM; IC_{50} (A549, LS-174, MRC-5) >100 μM	[107]
Pyridyl functionalized selenosemicarbazonate Sn(IV) complex [Sn(L)Cl$_3$], L = pyridyl-selenosemicarbazonate (**30**)	Sn(SeN_2Cl_3)	A549, A253, DLD-1	Antiproliferative activity IC_{50} (A253) = 2.02 μM; IC_{50} (A549) = 2.53 μM; IC_{50} (DLD-1) = 0.50 μM	[108]
Metal complexes based on Ni, Zn and Cd				
2-Phenyl-4-selenazole-based Ni(II) complex, [Ni(L)(phen)$_2$]L·5H$_2$O (HL = 2-phenyl-4-selenazole carboxylic acid, phen = 1,10-phenanthroline (**31**)	Ni(N_5O)	PANC-28, HuH7	Antiproliferative activity IC_{50} (PANC-28) = 30.07 μM; IC_{50} (HuH7) = 361.25 μM	[109]
Bis(benzimidazole)selenoether-based Ni(II) complex [Ni$_2$(L)$_2$(μ-Cl)$_2$][NiCl$_4$], L = *N*,*N*-bis((1-methyl-1*H*-benzo[*d*]imidazole-2-yl)methyl)-2-(phenylselanyl) ethan-1-amine (**32**)	Ni(SeN_3Cl_2)	HeLa, SK-LU-1 HEK-293	No inhibitory effect on the growth of cancer cells IC_{50} (SK-LU-1, HeLa, HEK-293) >100 μM	[110]
Selenazoylhydrazone-based Cd(II) complexes [Cd(HLSe)$_2$](Y)$_2$, HLSe = (*E*)-4-phenyl-2-(2-(pyridin-2-ylmethylene)hydrazineyl)-1,3-selenazole derivatives, Y = ClO$_4$, NO$_3$ (**33**, **34**, **35**)	Cd(N_6)	A549, HeLa, SW1573, WiDr, T-47D HBL-100, HEK-293	Antiproliferative activity; cell cycle arrest at S phase; activation of caspases-3 and -7; induction of apoptosis; nuclease activity **Compd 33**: GI_{50} (A549) = 2.5 μM; GI_{50} (SW1573) = 1.8 μM; GI_{50} (HBL-100) = 1.6 μM; GI_{50} (HeLa) = 1.7 μM; GI_{50} (T-47D) = 1.9 μM; GI_{50} (WiDr) = 2.4 μM; GI_{50} (HEK-293) = 8.9 μM **Compd 34**: GI_{50} (A549) = 1.7 μM; GI_{50} (SW1573) = 2.5 μM; GI_{50} (HBL-100) = 1.7 μM; GI_{50} (HeLa) = 1.7 μM; GI_{50} (T-47D) = 1.7 μM; GI_{50} (WiDr) = 2.0 μM; GI_{50} (HEK-293) = 12.0 μM **Compd 35**: GI_{50} (A549) = 2.0 μM; GI_{50} (SW1573) = 2.2 μM; GI_{50} (HBL-100) = 2.2 μM; GI_{50} (HeLa) = 1.6 μM; GI_{50} (T-47D) = 1.9 μM; GI_{50} (WiDr) = 2.4 μM; GI_{50} (HEK-293) = 14.0 μM	[111
Selenosemicarbazone-based Ni(II), Zn(II) and Cd(II) complexes [CdCl$_2$(Hfpsesc)]•DMSO (**36**), [ZnCl(Hfpsesc)]•H$_2$O (**37**), [Ni(fpsesc)$_2$]•H$_2$O (**38**), Hfpsesc = (*E*)-2-benzylidenehydrazine-1-carboselenoamide	Cd(SeN_2Cl_2) Ni(Se_2N_4) Zn(SeN_2Cl)	HeLa, LS-174, U2OS, U2OScisR, MDA-MB-361, MDA-MB-453, FEMX, B16 A.hy 926, MS1	Antiproliferative activity; induction of apoptosis; alteration of MMP-9 and MMP-2 **Compd 35**: IC_{50} (MDA-MB-453) = 3.02 μM; IC_{50} (MDA-MB-361) = 6.44 μM; IC_{50} (U2OS) = 3.57 μM; IC_{50} (U2OScisR) = 2.55 μM; IC_{50} (HeLa) = 4.14 μM; IC_{50} (FEMX) = 3.74 μM; IC_{50} (B16) = 4.62 μM; IC_{50} (LS-174) = 6.51 μM; IC_{50} (A.hy 926) = 4.97 μM; IC_{50} (MS1) =	[112]

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Table 1 (*continued*)

Scaffold + Ligand	Coordination mode (C_M)	Experimental system[a]	Biological activity	Refs.
			3.35 μM **Compd 37**: IC_{50} (MDA-MB-453) = 5.82 μM; IC_{50} (MDA-MB-361) = 9.13 μM; IC_{50} (U2OS) = 7.03 μM; IC_{50} (U2OScisR) = 5.06 μM; IC_{50} (HeLa) = 12.11 μM; IC_{50} (FEMX) = 7.49 μM; IC_{50} (B16) = 8.26 μM; IC_{50} (LS-174) = 8.83 μM; IC_{50} (A.hy 926) = 7.71 μM; IC_{50} (MS1) >100 μM **Compd 38**: IC_{50} (MDA-MB-453) = 3.3 μM; IC_{50} (MDA-MB-361) = 20.40 μM; IC_{50} (U2OS) = 3.41 μM; IC_{50} (U2OScisR) = 4.53 μM; IC_{50} (HeLa) = 13.16 μM; IC_{50} (FEMX) = 16.28 μM; IC_{50} (B16) = 6.62 μM; IC_{50} (LS-174) = 8.10 μM; IC_{50} (A.hy 926) = 5.58 μM; IC_{50} (MS1) = 1.94 μM	
		HeLa, MDA-MB-361 A.hy 926, MS1	Inhibition of MMP-2 and -9; inhibition of cellular migration and invasion; decrease of ROS accumulation; alteration of MMP-9 and MMP-2; suppression of tubule formation; modulation of metastatic phenotype	[113]
		HeLa, MDA-MB-361 A.hy 926, MS1	Induction of apoptosis and necrosis; cell cycle arrest; up-regulation of p73, Bax, and caspase-3 expression levels; increase of phosphorylation of ERK; release of cytochrome *c*; disruption of the mitochondrial membrane potential	[114]
2-Quinolinecarboxaldehyde selenosemicarbazone Cd (II) complex [Cd(Hqasesc)(AcO)]·H_2O, Hqasesc = 2-quinolinecarboxaldehyde selenosemicarbazone (**39**)	$Cd(SeN_2O)$	H460, U-251	Antiproliferative activity; cell cycle arrest at G0/G1 phase; induction of ROS production; free-radical scavenging activity IC_{50} (H460) = 8.0 μM; IC_{50} (U-251) = 4.3 μM	[115]
2-Quinolinecarboxaldehyde selenosemicarbazone Zn (II) complex $[Zn(Hqasesc)_2](ClO_4)_2$·EtOH, Hqasesc = 2-quinolinecarboxaldehyde selenosemicarbazone (**40**)	$Zn(Se_2N_4)$	THP-1, AsPC-1	Free-radical scavenging activity; cell cycle arrest; up-regulation of caspases-8 and -9 expression levels; induction of apoptosis	[116]
Metal coordination complexes for the treatment of infections caused by bacterial and fungal pathogens				
Metal complexes based on Pt, Pd, Cu and Co				
2-(Phenylselanylmethyl)oxolane/oxane Pd(II) complexes $[PdL_2Cl_2]$, L = (2-(phenylselanylmethyl) oxolane) (**41**), (2-(phenylselanylmethyl)oxane) (**42**)	$Pd(Se_2Cl_2)$	*S. aureus*, *B. subtilis*, *B. cereus*, *P. vulgaris*, *E. coli*, *S. enteritidis*, *C. albicans*, *A. niger*	Inhibitory effect on the growth of bacterial and fungal strains	[120]
Selenated Schiff base derived from *ortho*-vanillin Pd(II) complex [Pd(L)Cl], L = (*S*,*E*)-2-(((2-(benzylselanyl)-1-phenylethyl)imino)methyl)-6-methoxyphenol (**43**)	Pd(SeNOCl)	*S. aureus*, *E. coli*, *P. desmolyticum*, *K. aerogenes*, *C. albicans*	Inhibitory effect on the growth of bacterial and fungal strains	[121]
Selenocyanatothiazol Pd(II)/Pt(II) complexes *trans*-$[Pd(PhSeCNH)_2Cl_2]$ (**10**), *trans*-$[Pt(PhSeCNH)_2Cl_2]$ (**11**), PhSeCNH = 4-phenyl-5-selenocyanatothiazol-2-amine	$Pd(N_2Cl_2)$ $Pt(N_2Cl_2)$	*E. coli*, *P. aeruginosa*, *S. aureus*	Inhibitory effect on the growth of bacterial strains	[89]
Adipic and sebacic derived Pt(IV) complexes $[Pt_2Cl_6(adip)(H_2O)_2Se_2O_2(OH)_4Cl_2]$ (**44**), $[Pt_2Cl_6(sebac)(H_2O)_2Se_2O_2(OH)_4Cl_2]$ (**45**), adip = adipic acid, sebac = sebacic acid	$Pt(SeO_2Cl_3)$	*S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *C. albicans*, *A. flavus*	Inhibitory effect on the growth of bacterial and fungal strains	[94]
Selenosemicarbazone-based Pt(II) and Cu(II) complexes $[Cu(L)(NO_3)(H_2O)]$ (**46**), $[Pt(L)Cl_2]$ (**47**), L = acetobenzylsulfonamide selenosemicarbazone	$Cu(SeNO_2)$ $Pt(SeNCl_2)$	*S. aureus*, *B. subtilis*, *S. mutants*, *P. vulgaris*, *K. pneumoniae*, S. *typhimurium*, *C. albicans*, *A. fumigatus*	Inhibitory effect on the growth of bacterial and fungal strains	[97]
Pyridylselenium Cu(II) complex $[Cu(L)Cl_2]$, L = 2,2′-bis (3-aminopyridyl)diselenide (**48**)	$Cu(N_2Cl_2)$	*M. fortuitum*, *M. massiliense*, *M. abscessus*	Inhibitory effect on the growth of bacterial strains	[122]
Pyridylselenium Cu(II) complex $[Cu(L)Br_2]$, L = 3-amine-2-((pyridin-2-ylmethyl)selanyl)pyridine (**49**)	$Cu(N_2Br_2)$	*S. aureus*, *E. coli*	Inhibitory effect on the growth of bacterial strains	[123]
(1,3-Selenazol-2-yl)hydrazone Co(III) complexes $[Co(L)_2]BF_4$, L = 1,3-selenazol-2-yl)hydrazones (**50**, **51**, **52**)	$Co(N_6)$	*P. hauseri*, *P. aeruginosa*, *E. coli*, *S. enterica*, *S. aureus*, *C. sporogenes*, *B. subtilis*, *K. rhizophila*, *A. brasiliensis*, *C. albicans*, *S. cerevisiae*, *A. salina*	Inhibitory effect on the growth of bacterial and fungal strains; free-radical scavenging activity; low toxicity *in vitro*	[124]
Diisoselenocyanate Co(II) complex [Co(btmpp)$(NCSe)_2$], btmpp = 2,6-bis(3,4,5-trimethylpyrazolyl) pyridine (**53**)	$Co(N_5)$	*B. substilis*, *P. aeruginosa*, *S. typhimurium*, *S. sonnei*, *Y. enterocolitica*	Inhibitory effect on the growth of bacterial strains; reduction of QS-regulated swarming and biofilm formation processes in bacteria	[125]
Metal complexes based on Ni, Zn, Cd and Hg				
2-Aminoselenophene-3-carbonitrile-based Ni(II) complex [Ni(SeSchCl)$(H_2O)Cl$], SeSchCl = 2-amino-5,6,7,8-tetrahydro-4H-cyclohepta[*b*]selenophene-3-carbonitrile derivative (**54**)	$Ni(NO_2Cl)$	*L. monocytogenes*, *E. coli*, *Br. abortus*, *S. epidermidis*, *M. luteus*, *S. dysenteriae*, *P. putida*, *B. cereus*, *S. aureus*, S. *typhimurium*, *C. albicans*	Inhibitory effect on the growth of bacterial strains	[126]
2-Phenyl-4-selenazole-based Ni(II) complex, $[Ni(L)(phen)_2]L·5H_2O$, HL = 2-phenyl-4-selenazole carboxylic acid, phen = 1,10-phenanthroline (**31**)	$Ni(N_5O)$	*E. coli*, *S. epidermidis*, *S. viridans*, *S. aureus*, *A. baumanii*	Inhibitory effect on the growth of bacterial strains	[109]

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Table 1 (*continued*)

Scaffold + Ligand	Coordination mode (C_M)	Experimental system[a]	Biological activity	Refs.
Selenocyanate-containing Cd(II) and Hg(II) complexes $[Cd(SeCN)_2(L)]$ (**55**), $[Hg(SeCN)_2(L)]$ (**56**), L = 2,4-dithiouracil	$Cd(Se_2NS)$ $Hg(Se_2NS)$	*S. aureus*, S. *typhimurium*, *K. pneumoniae*, *P. aeruginosa*	No inhibitory effect on the growth of bacterial strains	[127]
Selenocyanate-containing Cd(II) complexes with amino acids $[Cd(SeCN)_2(L)]$, L = histidine (**57**), glycine (**58**)	$Cd(Se_2N_2)$ $Cd(Se_2NO)$	*E. coli*, *S. aureus*, S. *typhimurium*, *K. pneumoniae*, *P. aeruginosa*	Inhibitory effect on the growth of bacterial strains	[128]
Bis(1-(ethyl) piperidine) diselenide-based Zn(II) and Cd (II) complexes $[Zn_2(L)Cl_4]$ (**59**), $[Cd_2(L)Cl_4]$ (**60**), $[Cd_2(L)Br_4]$ (**61**), L = bis(1-(ethyl)piperidine) diselenide	$Zn(SeNCl_2)$ $Cd(SeNCl_2)$ $Cd(SeNBr_2)$	*E. coli*, *E. aerogenes*, *M. racemosus*	Inhibitory effect on the growth of bacterial and fungal strains	[129]
Phenylseleno piperazine-based Zn(II), Cd(II) and Hg(II) complexes $[Zn(L)Cl_2]$ (**62**), $[Cd(L)Cl_2]$ (**63**), $[Hg(L)Cl_2]$ (**64**), L = 1-(3-chlorophenyl)-4-(3-phenylseleno propyl)piperazine	$Zn(SeNCl_2)$ $Cd(SeNCl_2)$ $Hg(SeNCl_2)$	*S. aureus*, *A. niger*	Inhibitory effect on the growth of bacterial and fungal strains	[130]
Selenosemicarbazone Schiff-base-derived Zn(II) and Cd (II) complexes $[Zn(L)_2]$ (**65**, **66**), $[Cd(L)_2]$ (**67**, **68**), L = cyclohexylidenehydrazine-1-carboselenoamide derivatives	$Zn(Se_2N_2)$ $Cd(Se_2N_2)$	*E. coli*, *S. aureus*, *B. sabtuius*, *K. pneumoniae*, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilsis*	Inhibitory effect on the growth of bacterial and fungal strains	[131]
2-Quinolinecarboxaldehyde selenosemicarbazone Cd (II) complex $[Cd(Hqasesc)(AcO)]\cdot H_2O$, Hqasesc = 2-quinolinecarboxaldehyde selenosemicarbazone (**39**)	$Cd(SeN_2O)$	*L. monocytogenes*, *E. coli*, *B. cereus*, *S. enteritidis*, *E. faecalis*, *G. stearothermophylus*, *S. sonnei*, *C. neoformans*, *S. cerevisiae*	Inhibitory effect on the growth of bacterial and fungal strains	[115]
Selenium(IV) coordination complexes with therapeutic activity				
Selenium(IV) complexes				
Quercetin-Se(IV) complex $[Se_2Quercetin_3]$ (**69**)	$Se(O_4)$	HepG2, MCF-7, A549	Antiproliferative activity; cell cycle arrest; inhibition of DNA replication; stabilization of the G-quadruplex; induction of apoptosis IC_{50} (HepG2) = 13.87 μM; 10 μM < IC_{50} (A549, MCF-7) < 20 μM	[135]
Penicillin G (Pin-G)-Se(IV) complex $[Se(Pin\text{-}G)(NH_3)(Cl)_2]\cdot Cl$ (**70**)	$Se(NO_3Cl_2)$	HepG2, MCF-7 *S. epidermidis, S. aureus, Klebsiella, E. coli*	Antiproliferative activity; inhibitory effect on the growth of bacterial strains IC_{50} (HepG2) = 0.30 μg/mL; IC_{50} (MCF-7) = 0.30 μg/mL	[136]
Aurin tricarboxylic acid-Se(IV) complex $[Se_3(C_{22}H_9O_9)(H_2O)_5Cl_7]$ (**71**)	$Se(O_4Cl_2)$ $Se(O_3Cl_3)$	HepG2, MCF-7	IC_{50} (MCF-7) = 30.3 μM; IC_{50} (HepG2) = 38.9 μM	[137]
Tri-substituted-1,3-5-triazine Se(IV) complexes $[Se(L)(Cl)_x]\cdot yCl$, x, y = 1, 2, 3, L = tri-substituted-1,3-5-triazine derivatives (**72**, **73**, **74**, **75**)	$Se(N_2Cl_2)$, $Se(N_2SCl_3)$, $Se(N_3Cl)$	A549 *S. aureus*, *E. coli*, *A. flavus*, *C. albicans*	Antiproliferative activity; inhibitory effect on the growth of bacterial and fungal strains **Compd 72**: IC_{50} = 33 μg/mL **Compd 73**: IC_{50} = 35 μg/mL **Compd 74**: IC_{50} = 68 μg/mL **Compd 75**: IC_{50} = 190 μg/mL	[138]
Gibberellic acid (GA_3)-Se(IV) complex $[Se(GA_3)(H_2O)Cl]\cdot 3H_2O$ (**76**)	$Se(O_3Cl)$	*S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*	Inhibitory effect on the growth of bacterial strains	[139]
Amygdalin-Se(IV) complex $[Se(Amygdalin)_2]Cl_2$ (**77**)	$Se(O_4)$	*S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*	Inhibitory effect on the growth of bacterial strains	[140]
Glucose-6-phosphate (G6P)–Se(IV) complex $[Se(G6P)(NH_3)_2]Cl_2$ (**78**)	$Se(N_2O_2)$	*S. aureus*, *S. epidermidis*, *E. coli*, *Klebsiella*	Inhibitory effect on the growth of bacterial strains	[141]
Sitagliptin (STG)-Se(IV) complex, $[Se(STG)_2(Cl)_2]Cl_2$ (**79**)	$Se(N_2O_2Cl_2)$	Albino diabetic rats	Enhancement of the antioxidant capacity attributed to decreasing lipid peroxidation; decrease of the glucose levels in the blood; promotion of insulin secretion	[142]
Ceftriaxone (CFX)-Se(IV) complex $[Se(CFX)(Cl)_2]\cdot 4H_2O$ (**80**)	$Se(NO_3Cl_2)$	*B. subtilis*, *S. pneumoniae*, *E. coli*, *P. aeruginosa*, *S. aureus*.	Amelioration of hepatic enzyme functions; reduction of ROS production; increase of antioxidant enzymes; inhibitory effect on the growth of bacterial strains	[143]

[a] *Malignant cell lines*: 22Rv1: prostate; A253: submandibular gland; A2780, A2780cisR: ovarian; A375: melanoma; A549: non-small cell lung; AsPC-1: pancreas; B16: murine melanoma; CaSki: cervix; CNE: nasopharyngeal; Colo205: colon; DLD-1: colon; EACC: breast; FEMX: melanoma; H460: lung; HCT-116: colon; HeLa: cervix; HepG2: hepatocellular; HL-60: leukemia; HT-29: colon; HuH7: hepatocellular; K-562: leukemia; LN229: glioblastoma; LNCAP: prostate; LS-174: colon; MCF-7; breast; MDA-MB-231: breast; MDA-MB-361: breast; MDA-MB-453: breast; MES-SA, MES-SA/Dx5: uterine; NK-92: non-Hodgkin lymphoma natural killer cell; PANC-28: pancreas; PC-3: prostate; SiHa: cervix; SK-LU-1: non-small cell lung; SK-N-MC: neuroepithelioma; SKOV3: ovarian; SW1573: lung; SW620: colon; T24: bladder; T-47D: breast; THP-1: leukemia; U-251: glioblastoma; U2OS, U2OScisR: osteosarcoma; WiDr: colon. *Nonmalignant cell lines*: A.hy 926: endothelial; HBL-100: epithelial; HEK-293: epithelial; HFB-4: melanocytes; HK-2: epithelial; HUVEC: endothelial; L02: hepatocytes; MCR-5: lung fibroblast; MS1: endothelial; NK: lymphoid natural killer cell; NMC460: epithelial; Vero: epithelial.

[b] Coordination to the metal center not specified.

complex containing a 1,10-phenanthrolineselenazole ligand was the first study that demonstrated the capability of metal complexes coordinated to Se heterocyclic ligands to bind to telomeric G-quadruplexes [99]. Thus, the Ru(II) complex (**23** in Fig. 2) could convert and stabilize the preformed hybrid-type G-quadruplexes structure into antiparallel G-quadruplex, and exert antiproliferative activity which was attributed to its role in telomerase inhibition. The authors ascribed these effects to the presence of planar polycyclic heteroaromatic ligands in the stabilization, and to the introduction of Se to induce the formation and stabilization of the G-quadruplex and thus exhibiting a strong inhibitory effect on telomerase activity [99]. Likewise, another Ru(II) complex formed by the coordination with the same ligand (**24** in Fig. 2) was also

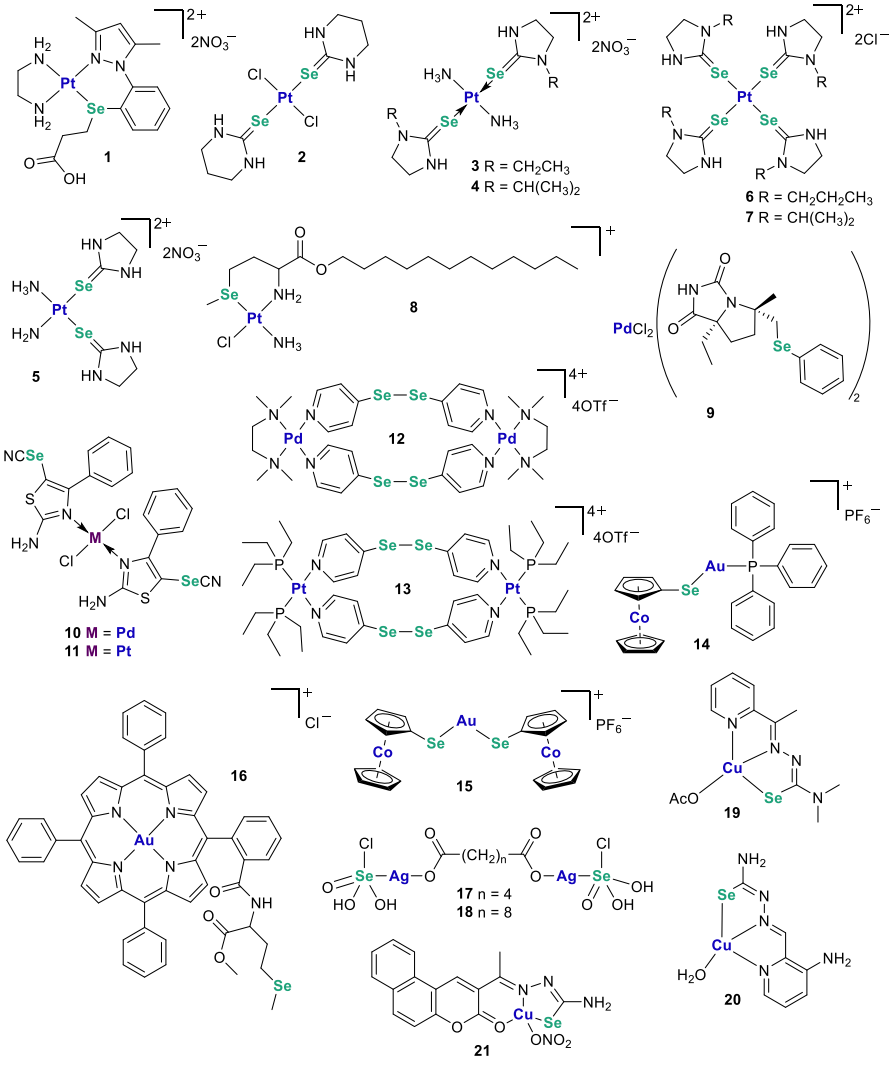

Fig. 1. Chemical structures of coordination compounds based on Pt, Pd, Au, Ag and Cu for cancer treatment.

capable of stabilizing the G-quadruplex structure and inhibiting the telomerase activity. Additionally, this complex **24** could significantly inhibit the proliferation, migration, and tube formation of endothelial cells, and was proved to induce cell death through apoptosis [100]. The improvement of the anticancer activities and radiosensitization of Ru complexes by introducing Se-based ligands was also studied in another Ru(II) complex with the 1,10-phenanthrolineselenazole moiety. This compound (**25** in Fig. 2) displayed antiproliferative and radiosensitization effects on cancer cells while being 10-fold less toxic than cisplatin. Further studies on the mechanisms of action revealed that **25** sensitized melanoma cells to radiation by triggering ROS-mediated DNA damage and downstream signaling pathways, resulting in a disruption of the cell cycle and ultimately apoptosis [101]. Likewise, a Ru(II) analog was designed by the covalent bond with a cancer-targeted molecule, forming a biotinylated conjugate complex (**26** in Fig. 2) that could selectively accumulate in tumor tissues to enhance the theranostic effects and reduce the systemic toxicity *in vivo*. It was also demonstrated that an acidic environment could alter the structure of the ligand and induce its release from the functional complex. The activated complex was located in the mitochondria, triggering oxidative stress and activating intrinsic apoptosis. Besides, the phosphorescent emission properties of **26** allowed the real-time tracking and imaging of the compound inside the biological systems [102]. These results prompted the authors to use a Se-containing Ru(II) derivative of **26** as a chemoimmunotherapeutic option in combination with immune cell therapy. Interestingly, the resulting derivative without the biotin moiety (**27** in Fig. 2) was found to increase tumor immunogenicity and synergistically enhance the immune activity of natural killer (NK) cells mediated by tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL) and FasL signaling through the stimulation of ROS overproduction-triggered DNA damage and the downstream ATM and ATR pathways. The introduction of Se was also proved to be determinant for enhancing the immune-sensitizing properties of the Ru complex. Additionally, the administration of compound **27** in combination with NK cells synergistically suppressed the tumor growth in a xenograft mouse model [103].

The design of metal complexes bearing a 1,10-phenanthrolineselenazole ligand was not limited to Ru-based compounds. In this regard, an iron (Fe) complex (**28** in Fig. 2) coordinated with this type of ligand could enhance both pro-apoptotic and anti-angiogenic activities on endothelial cells by inhibiting vascular endothelial growth factor (VEGF) and the AKT pathway in a more effective manner than the non-selenated analog [104]. Further studies with this compound revealed that **28** could also inhibit the proliferation and migration capabilities of cancer cells through the down-regulation of endoplasmic reticulum (ER) stress-related selenoproteins. In addition, Fe(II) complex **28** could efficiently damage tumor spheroids with good penetration capability, and synergize with TRAIL treatment to induce the production of ROS and

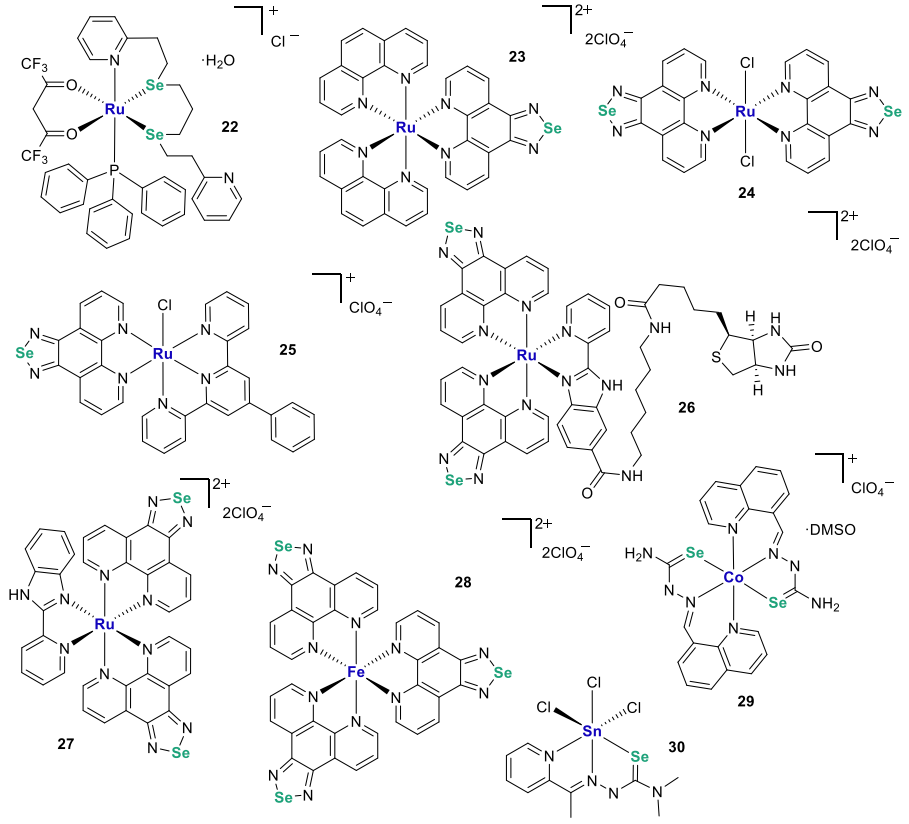

Fig. 2. Chemical structures of coordination compounds based on Ru, Fe, Co and Sn for cancer treatment.

apoptosis via the regulation of the expression levels of several proteins involved in signaling pathways, including p53, p38, JNK, PARP and caspases-3, -8 and -9 [105].

Regarding the formation of cobalt (Co) complexes with Se-based ligands, the anticancer evaluation of a Co(III) complex (**29** in Fig. 2) including an *N*-heteroaromatic selenosemicarbazone with demonstrated cytotoxic activity was reported. However, although this compound induced apoptosis in cancer cells, the complexation of the selenosemicarbazone with Co(III) did not improve the activity of the free ligand [106]. Further studies revealed that the lower induction in the differentiation of leukemia cells by this complex compared to that induced by the free ligand could be related to the Se-induced effects being suppressed by the very tight binding within the complex [107].

Additionally, given that tin (Sn) complexes bearing thiosemicarbazonato ligands had been investigated for their extensive biological activities, Molter et al. designed a series of Sn(IV) with pyridyl functionalized selenosemicarbazonates. Among them, the Sn(IV) complex **30** (Fig. 2) showed not only potent antiproliferative activity in several cancer cells with IC_{50} values in the nanomolar range (0.50–2.53 μM), but it was also more active than its S analog, proving the effectiveness of the isosteric substitution of the chalcogen atoms [108].

2.1.3. Metal complexes based on Ni, Zn and Cd

Selenazole-containing ligands were explored in the formation of a nickel (Ni) complex (**31** in Fig. 3) which exhibited only moderate antiproliferative activity against pancreatic and hepatocellular cancer cell lines [109]. Likewise, another Ni(II) complex with a selenoether-based ligand (**32** in Fig. 3) did not exert any inhibitory effect on the growth of the cancer cells tested ($IC_{50} > 100$ μM) [110].

Recently, cadmium (Cd) complexes bearing selenazoyl-hydrazones (**33**–**35** in Fig. 3) as anticancer agents were reported, along with their S analogs for comparison [111]. The complexation upon the Cd(II) center revealed approximately two-fold greater antiproliferative activity than the free ligands, and they were even more active than 5-fluoruracil and cisplatin. The Cd(II) complexes also induced cell death in breast cancer cells through apoptosis via the activation of caspases-3 and -7 [111].

Selenosemicarbazones have been explored in several studies as ligands upon coordination with Ni ions and metals of group 12 to design complexes with anticancer properties. In this context, a series of metal complexes bearing a selenosemicarbazone-based ligand synthesized as the condensation product of 2-formylpyridine and selenosemicarbazide was reported to have antiproliferative activity [112]. The Ni(II), Cd(II), and zinc(II) (Zn) complexes (**36**–**38** in Fig. 3) were proved to induce cell death through apoptosis, and also altered the activity of matrix metalloproteinases (MMPs) MMP-9 and MMP-2 [112]. Further studies on the anti-metastatic and anti-angiogenic properties of these compounds confirmed that the Ni(II) and Zn(II) complexes effectively reduced intracellular ROS levels, ultimately leading to the suppression of MMP-2/9 expression and subsequent inhibition of their invasive ability, along with the suppression of tubule formation in cancer cells. The Ni(II) complex (**38** in Fig. 3) possessed the strongest inhibitory potential on the tumor cell invasion as well as inhibition of endothelial cell migration among the other investigated metal complexes [113]. The mechanism of action of these complexes also included the perturbation of the cell cycle phase distribution, the induction of apoptosis through different signaling pathways associated with the release of cytochrome *c* into the cytosol, activation of p73, and phosphorylation of extracellular signal-regulated kinase (ERK) [114]. Likewise, some complexes with quinolinecarboxaldehyde selenosemicarbazone derivatives have also been reported. In this regard, a Cd(II) complex (**39** in Fig. 3) stood out among several compounds with different metal centers, as it displayed potent cytotoxic activity (IC_{50} in the range of 4.3–8.0 μM) comparable to cisplatin (IC_{50} values ranging from 5.4 to 14.5 μM), and was also the most efficient compound at disrupting the cell cycle via involvement of ROS production [115]. Additionally, another Zn(II) complex (**40** in

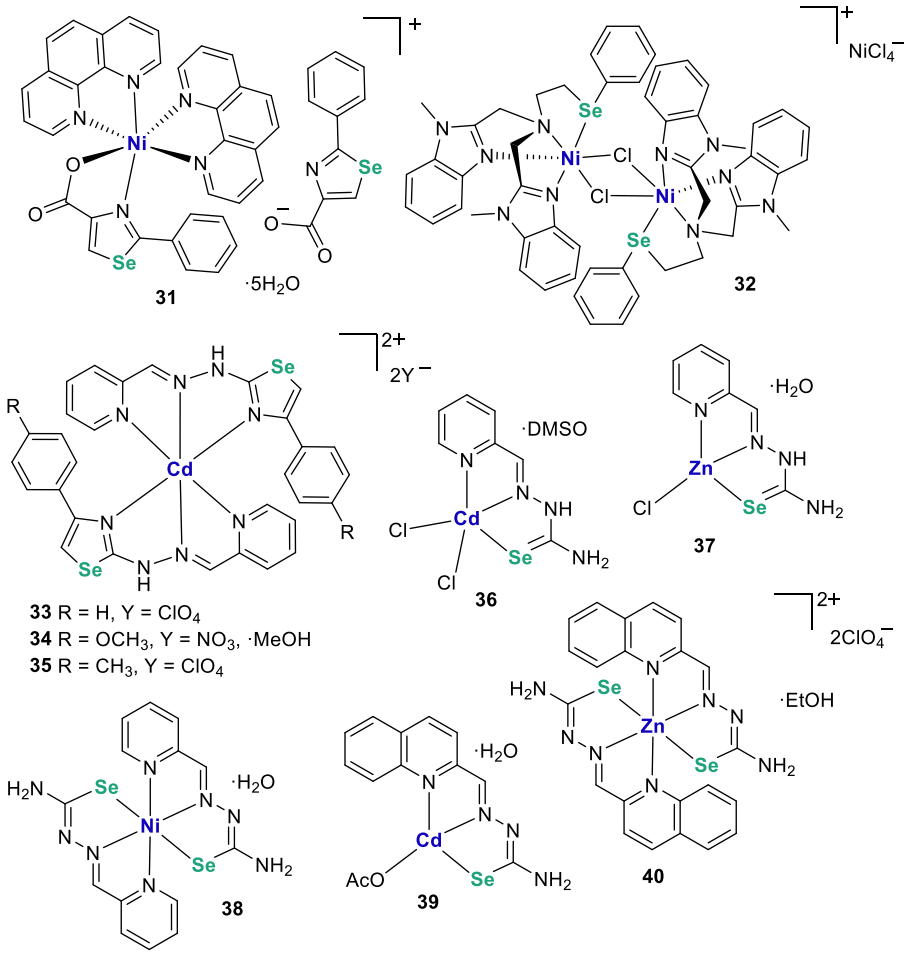

Fig. 3. Chemical structures of coordination compounds based on Ni, Zn and Cd for cancer treatment.

Fig. 3) was reported to be a strong inducer of apoptosis with a phenotype-specific activity, and was also proved to arrest the cell cycle and activate the expression of caspases-8 and -9 in pancreatic cancer cells [116].

2.2. Metal coordination complexes bearing selenium for the treatment of infections caused by bacterial and fungal pathogens

Infectious diseases are major emerging threats to public health, causing important issues in the successful prevention and treatment of diseases [117]. Furthermore, the increasing and rapid microbial resistance to current antibiotics, which is estimated to be responsible for 1.27 million deaths per year worldwide [118], have led to the urgent need to develop new targeted antimicrobial agents. In this context, metal-based antibiotics can exploit alternative mechanisms of growth inhibition and toxicity when compared with conventional approaches in the field of purely organic chemistry [119]. Thus, the use of metal-containing therapeutic drugs for treating pathogenic entities has attracted interest in recent years, and some antibacterial and antifungal coordination compounds including Se have been explored in this regard.

2.2.1. Metal complexes based on Pt, Pd, Cu and Co

The first study on the antimicrobial activity of Se-containing Pd complexes reported the synthesis of two Pd(II) compounds bearing 2-(phenylselanylmethyl)oxolane/oxane (**41**–**42** in Fig. 4) that were screened against several bacterial and fungal strains. These complexes showed moderate antimicrobial activity that was more pronounced against the fungal organisms [120]. In addition, in a very recent report, two Pd complexes coordinated to selenated Schiff bases were also evaluated for their antimicrobial activities, complex **43** (Fig. 4) derived from *ortho*-vanillin being more active in both bacterial and fungal pathogens in general [121]. On the other hand, the Pd(II) and Pt(II) metal complexes bearing a 2-amino-4-phenyl-5-selenocyanatothiazol moiety (**10**–**11** in Fig. 1) showed not only antiproliferative activity, but also demonstrated significant antibacterial activity against pathogenic bacteria compared to the free ligand [89]. Likewise, the Pt(IV) complexes derived from adipic and sebacic acids (**44**–**45** in Fig. 4) displayed efficient antimicrobial activity in all the bacterial and fungal strains tested among other derivatives containing Au(III) and Ag(I) (**17**–**18** in Fig. 1) centers [94]. Additionally, two complexes bearing either Cu(II) or Pt(II) ions (**46**–**47** in Fig. 4) exhibited potent antimicrobial activity against several pathogenic strains [97] in addition to their antiproliferative profile. The formation of metal complexes with pyridylselenium ligands was also assessed with several metal centers [122,123], the compounds with Cu(II) **48**–**49** (Fig. 4) being among the most active derivatives with antibacterial effect. Furthermore, the bacteriostatic and bactericidal activities of the complexes were higher than those of the corresponding free ligands and the metal salts used for the synthesis, thus highlighting the importance of the metal-chalcogen coordination for the biological properties [122,123].

In order to improve the biological activity of chalcogen-containing hydrazones, the complexation upon a Co(III) center was developed with this type of organic ligands, and the isosteric replacement of S with Se was studied [124]. Hence, the free Se-ligands were found to be more active than the corresponding S-containing compounds on all bacterial and fungi strains investigated. Besides, the preparation of the

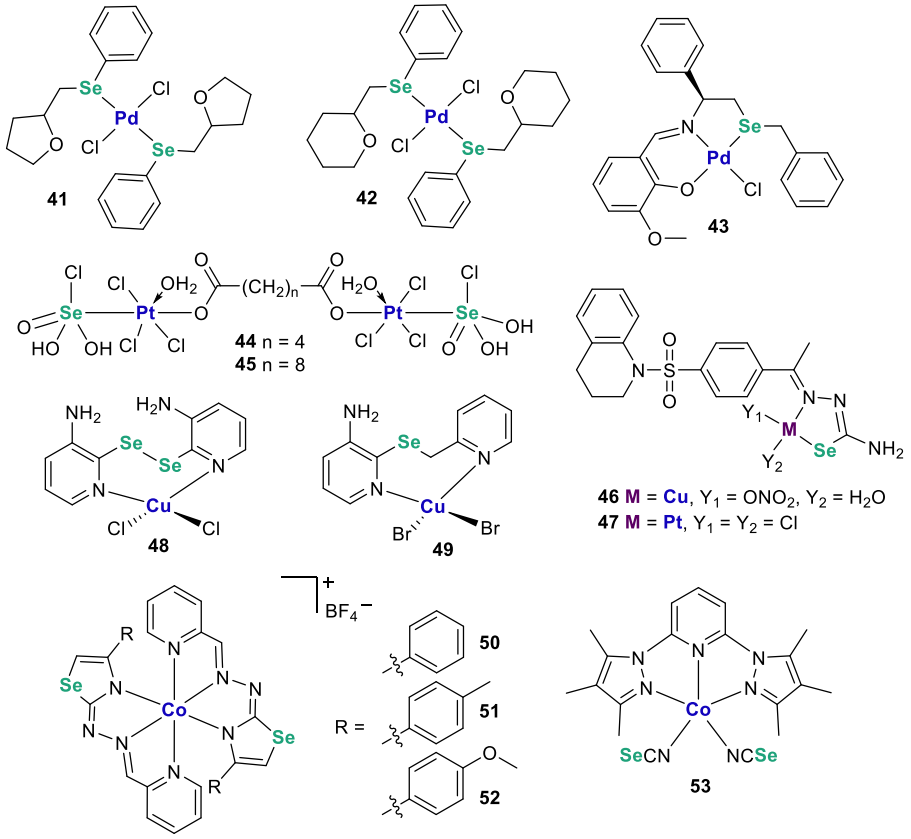

Fig. 4. Chemical structures of coordination compounds based on Pt, Pd, Cu and Co for the treatment of infections caused by bacterial and fungal pathogens.

corresponding Co(III) complexes (**50**–**52** in Fig. 4) enhanced the antibacterial activity of the ligands. Although S-based complexes reached almost the same level of antibacterial activity as their selenated analogs, significantly smaller cell toxicity of the Se-containing Co(III) complexes was observed, making them more suitable for future development [124]. Interestingly, a Co(II) complex (**53** in Fig. 4) was proved to be effective against a variety of bacterial strains and could reduce swarming and biofilm formation processes regulated by the quorum sensing (QS)

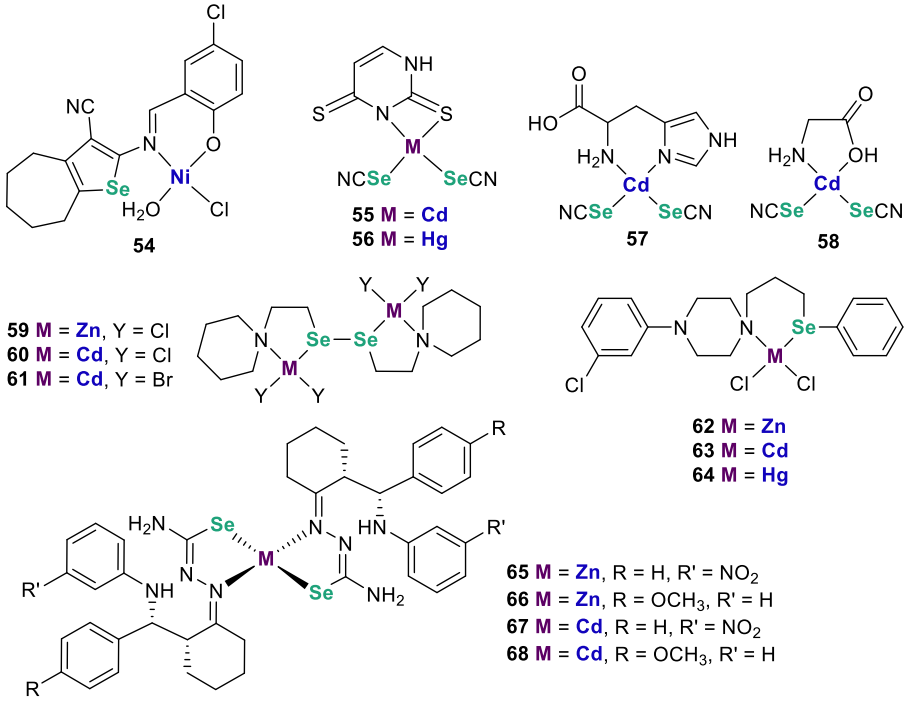

Fig. 5. Chemical structures of coordination compounds based on Ni, Zn, Cd and Hg for the treatment of infections caused by bacterial and fungal pathogens.

communication system in bacteria. The antibacterial activity of **53** was attributed to the presence of the isoselenocyanate ligands in the Co(II) complex [125].

2.2.2. Metal complexes based on Ni, Zn, Cd and Hg

A Ni(II) complex formed by the coordination to a Schiff base of a fused selenophene derivative was reported to have antibacterial activity against several strains. The activity of the complex (**54** in Fig. 5) was compared with that of five commercial antibiotics, proving to be as effective as the positive controls in some bacteria [126]. Likewise, although the Ni(II) complex **31** (Fig. 3) did not have potent antiproliferative activity on cancer cells, it exhibited stronger antibacterial activities than benzylpenicillin sodium against *E. coli*, *S. epidermidis*, *S. viridans*, and *A. baumanii* [109].

Given the tendency of soft Se to coordinate preferably with soft metals such as Cd(II) and Hg(II), some selenocyanate-containing complexes with these metal ions were reported [127,128]. The complexes (**55**–**58** in Fig. 5) were tested for their antibacterial activity in several Gram-positive and Gram-negative bacteria, but only the Cd(II) complexes including additionally amino acids as coligands (**57**–**58** in Fig. 5) were found to have an inhibitory effect on the growth of the microorganisms [128]. Likewise, in a series of Zn(II) and Cd(II) complexes bearing bis(1-(ethyl) piperidine) diselenide as a ligand (**59**–**61** in Fig. 5), it was found that although both metal centers yielded complexes that displayed significant activity against bacteria and fungi, the Cd(II) complexes were more active than the Zn(II) derivative [129]. The same research group reported later the synthesis of Zn(II), Cd(II), and Hg(II) complexes (**62**–**64** in Fig. 5) with a phenylselenopiperazine derivative along with their antimicrobial evaluation. The Zn(II) complex **62** was the most effective at inhibiting the growth of pathogens, followed by the Cd(II) derivative **63** [130]. Nevertheless, in both studies the complexation greatly enhanced the antibacterial and antifungal activity when compared to the free ligand [129,130]. Selenosemicarbazone-derived ligands were also used for the synthesis of a series of complexes including several transition metals [131]. These complexes generally displayed higher antimicrobial activity compared to the free ligands, and among them, the Zn(II) and Cd(II) complexes (**65**–**68** in Fig. 5) stood out as the most active compounds in the bacteria and fungi species tested [131]. Likewise, the formation of metal complexes by the coordination to quinolinecarboxaldehyde selenosemicarbazone also yielded

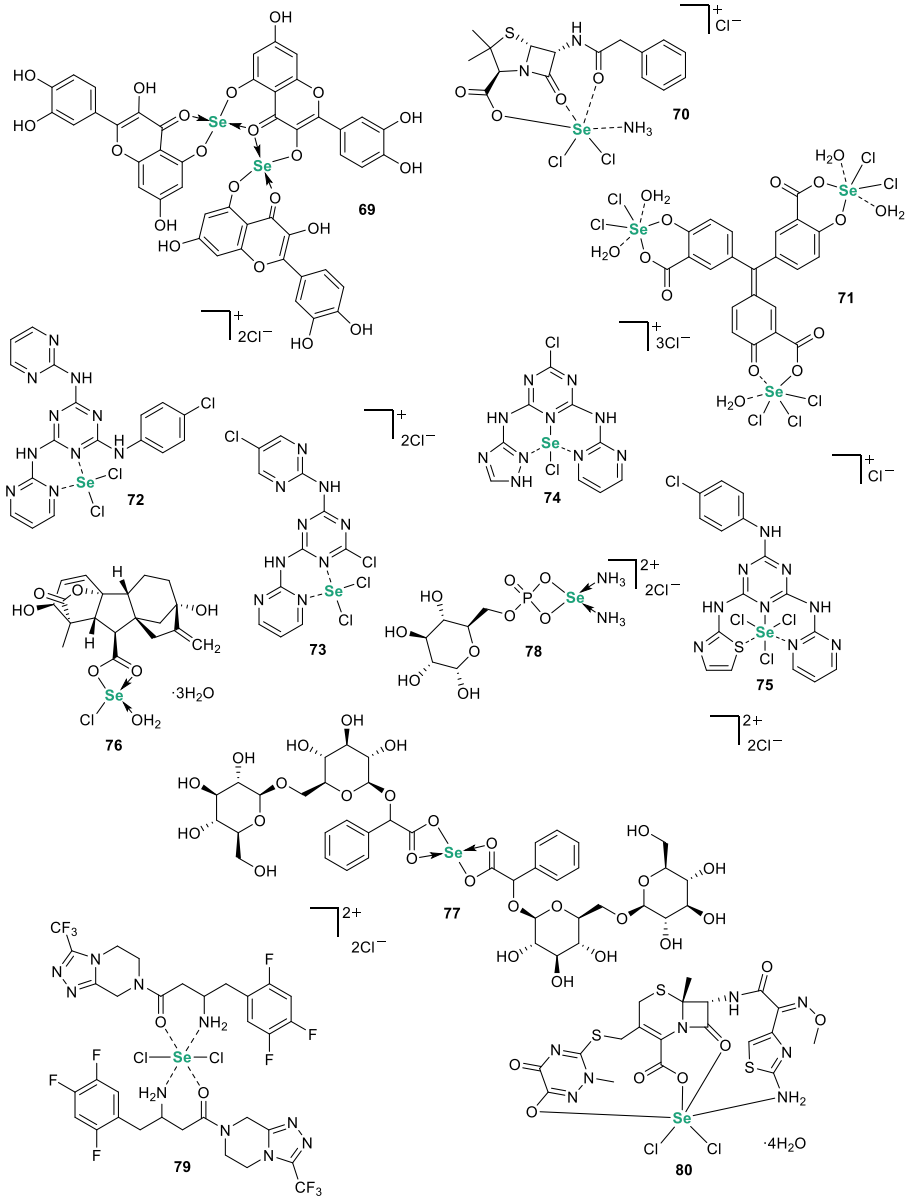

Fig. 6. Chemical structures of Se(IV) coordination compounds with therapeutic activity.

compounds with antibacterial effects even higher than those by the standard antibiotics. Cd(II) complex (**39** in Fig. 3) showed a dual activity with both antiproliferative and antimicrobial activities, given that it was also among the few compounds able to display antifungal activity in addition to its inhibitory effect on bacterial strains [115].

2.3. Se(IV) coordination complexes with therapeutic activity

The coordination compounds reported in previous sections incorporated the Se moiety into the metal complex as part of the ligand, either through direct interaction with the metal in the first coordination sphere, or integrated within the organic scaffold. However, some interesting approaches have been recently studied in which the Se atom acted as the ionic center coordinated with different ligands. Thus, Se(IV) complexes were formed as four- or six-coordinated compounds via bonds mainly with O, N, or Cl atoms. Some Se(IV) compounds were found to display antioxidant activity when attached to different organic molecules such as vitamin B6 [132], nicotinamide and riboflavin drugs [133], or gallic acid [134]. In this context, the therapeutic activity as anticancer, antimicrobial, or even antidiabetic agents of Se(IV) complexes has been reported and is included in this section.

In order to improve the antitumor effects of quercetin, this flavonoid was incorporated as a ligand coordinated to a dinuclear Se(IV) complex (**69** in Fig. 6). The resulting complex **69** was more potent than quercetin at inhibiting the growth of several cancer cell lines, intercalated with DNA, and was found to induce cell cycle arrest and apoptosis [135]. In a series of penicillate complexes bearing different ionic centers, a Se(IV) complex (**70** in Fig. 6) was proved to possess an antiproliferative activity in cancer cells comparable to cisplatin (both compounds with IC_{50} values in the range of 0.20–0.50 μg/mL), and besides, it also showed an antibacterial effect, being twice as efficient as the free ligand against *E. coli* [136]. Likewise, among the ionic centers that were used for synthesizing complexes with aurin tricarboxylic acid triammonium salt, a Se(IV) derivative (**71** in Fig. 6) displayed moderate activity against both bacteria and cancer cells [137]. A series of Se(IV) bearing different tri-substituted-1,3-5-triazine derivatives were synthesized and evaluated for their antimicrobial and anticancer potential along with the Ru (III) analogs [138]. All the Se(IV)-complexes reported by Al-Khodir et al. (**72**–**75** in Fig. 6) demonstrated to have not only a more potent inhibitory effect on the growth of fungi and bacteria compared to the other metal complexes, but also displayed greater activity against *S. aureus* and *E. coli* than the standard reference drug ampicillin. Furthermore, all the Se(IV) compounds showed antiproliferative activity, and complex **72** was found to inhibit the growth of colon cancer cells with an IC_{50} value 142-fold lower than that of the corresponding free ligand [138]. A Se (IV)-complex formed with the hormone plant gibberellic acid (GA_3) (**76** in Fig. 6) also showed an antibacterial effect against *S. aureus* and *E. coli* strains, and among all the complexes tested with other nuclei, including Pt(II), Au(III), Ru(III) and V(III), this Se(IV) complex **76** induced the highest growth inhibition against *K. pneumoniae*, also proving to be more potent than the antibiotic reference drug unasyn [139]. Likewise, another Se(IV) compound derived from a natural product, Se(IV)-amygdalin complex (**77** in Fig. 6), was also more potent than unasyn in *K. pneumoniae* among all the bacterial strains tested [140]. The Se(IV) cation chelated with the monosodium salt of glucose-6-phosphate (G6P) via both oxygen atoms of the phosphate group also formed a complex (**78** in Fig. 6) that had antibacterial activity against *S. aureus* and displayed 3-fold higher inhibitory effect in comparison to unasyn in the *E. coli* strain [141]. Interestingly, in a recent study designed to evaluate the effect of sitagliptin (STG), a commercial drug for the treatment of diabetes mellitus (DM), and STG-derived metal complexes on oxidative damage, a complex with Se(IV) acting as one of the central ions studied was reported [142]. The Se(IV)-STG complex was found to be six-coordinated, with two units of STG as bidentate chelating ligands (**79** in Fig. 6). All the STG-complexes tested were efficient and safe for the treatment of hyperglycemia and oxidative injury induced by DM and better than the STG alone, but a more antioxidant potency and insulin promotion was observed in the treatment with the Se(IV)-STG complex and its Zn analog [142]. The same research group also reported a Se(IV) complex with the antibiotic drug ceftriaxone (CFX), forming a six-coordinated compound (**80** in Fig. 6) that prevented liver injury, suppressed excessive ROS generation, and enhanced the activity of antioxidant defense enzymes *in vivo*. In addition, Se(IV)-CFX complex also showed a potent inhibitory effect on the growth of *S. aureus* and *E. coli* [143].

3. SELENIUM-CONTAINING organometallic compounds

An organometallic complex is defined as a molecule with a distinct metal-carbon (M − C) bond in its structure, and is considered as an intermediate between classical inorganic and organic derivatives [144]. Organometallic compounds have recently attracted much interest as potential anticancer, antimalarial, antimicrobial, antiviral, or diagnostic agents [14,145–147]. Such biological diversity could be explained by the specific characteristics of this class of compounds. They exhibit great structural diversity, variable oxidation states, catalytic and redox properties, the capacity to bind biological targets, and the possibility of rational ligand design in order to control the kinetic properties, like the rate of ligand exchange [144,145]. Furthermore, they are kinetically stable, usually uncharged with the metal atom in a low oxidation state, relatively lipophilic, and amenable to a host of standard chemical transformations [145]. Several approaches to obtaining organometallic compounds bearing a Se moiety as therapeutic compounds have been developed in recent years and are summarized in this section. A summary is provided in Table 2.

3.1. Metallocenes bearing selenium with therapeutic activity

Metallocenes were the first class of organometallic compounds to be systematically investigated as therapeutic agents, specifically against cancer [14]. Structurally, these compounds are typically characterized by the coordination of two cyclopentadienyl (Cp) ligands to a transition metal, where the two Cp rings are on parallel planes with equal bond lengths and strengths [148]. These two Cp rings, each having a delocalized negative charge, are coordinated to the metal center via a pentahapto (η^5) metal-carbon bond in a 'sandwich-type' configuration [144]. Undoubtedly, ferrocene stands out among this class of complexes as one of the most prominent compounds in modern organometallic chemistry, due to its low toxicity, high stability, reversible redox properties [149], and remarkable structural and mechanistic diversity [150]. Regarding medicinal chemistry, its incorporation among organic scaffolds has become a valuable toolkit for developing efficient derivatives to treat a variety of diseases [150–153], including selenocompounds. In this context, the inclusion of the Se atom via *N*-heterocyclic structures of selenazoles and selenadiazoles was explored for the development of antibacterial complexes. The novel combination of ferrocene and selenazoles/selenadiazoles was proved to be favorable for biological activity, since several compounds (**81**–**84** in Fig. 7) were found to be potent especially against *E. coli* and *P. aeruginosa*, and complex **83** even displayed a MIC value comparable to that of chloramphenicol [154]. Likewise, the contribution of a fused ferrocene ring to a selenadiazole and its comparison with its organic analog was later studied. Interestingly, compound **85** (Fig. 7) was not only more potent than the benzo-fused derivative, but it also displayed an antiproliferative effect on ovarian cancer cells similar to that produced by cisplatin [155]. Some compounds in which the Se atom and the ferrocene moiety are attached through a direct bond interaction forming a selenoether group have also been reported. In this regard, in a series of chalcogeno-triazole bridged ferrocene-carbohydrate conjugates, enhanced cytotoxic activity of the Se-containing conjugates was observed as compared to the S-counterparts. The compounds (**86**–**88** in Fig. 7) showed IC_{50} values in the low micromolar range (2.9–18.3 μM) in a variety of cancer cells, while being

Table 2
Selenium-containing organometallic compounds.

Scaffold	Experimental system[a]	Biological activity	Refs.
Metallocene-derived drugs			
Ferrocene-based compounds			
Selenazole- and selenadiazole ferrocenes (**81**, **82**, **83**, **84**)	*E. coli*, *S. aureus*, *P. aeruginosa*	Inhibitory effect on the growth of bacterial strains	[154]
4,5-Dihydrobenzoferroceno[1,2-*d*][1,2,3]selenadiazole (**85**)	HeLa, MDA-MB-231, A2780	Antiproliferative activity	[155]
Chalcogeno-triazole bridged ferrocene-carbohydrate conjugates (**86**, **87**, **88**)	A549, MDA-MB-231, MCF-7, HeLa HEK-293T	Antiproliferative activity; low toxicity *in vitro* **Compd 86**: IC_{50} (A549) >200 μM; IC_{50} (MDA-MB-231) = 4.56 μM; IC_{50} (MCF-7) = 4.46 μM; IC_{50} (HeLa) = 10.9 μM **Compd 87**: IC_{50} (A549) = 2.9 μM; IC_{50} (MDA-MB-231) = 3.35 μM; IC_{50} (MCF-7) = 5.58 μM; IC_{50} (HeLa) = 11.6 μM **Compd 88**: IC_{50} (A549) = 3.71 μM; IC_{50} (MDA-MB-231, MCF-7) >200 μM; IC_{50} (HeLa) = 18.3 μM	[156]
1,5-Diselena [8]ferrocenophane dopamine derivative (**89**)	HepG2, AGS, MGC-803, A2780, A549, BxPC-3	Antiproliferative activity; induction of apoptosis and necrosis; activation of caspases-3 and -9; cell cycle arrest at G1 phase; activation of p53; down-regulation of the expression of Bcl-2 protein; significant reduction of tumor growth; inhibition of tubule formation; suppression of endothelial cell migration IC_{50} (AGS) = 2.4 μM; IC_{50} (A2780) = 2.3 μM; IC_{50} (A549) = 4.8 μM; IC_{50} (BxPC-3) = 5.4 μM; IC_{50} (HepG2) = 2.2 μM; IC_{50} (MGC-803) = 4.5 μM	[157]
Diferrocenylseleno-dopamine derivative (**90**)	AGS, MGC-803, A2780, HepG2 HK-2	Antiproliferative activity; induction of ROS production via the Fenton-like reaction; cell cycle arrest at S phase; induction of apoptosis through CDK-2 inactivation; significant reduction of tumor growth IC_{50} (A2780) = 13.5 μM; IC_{50} (AGS) = 6.4 μM; IC_{50} (HepG2) = 7.9 μM; IC_{50} (MGC-803) = 2.4 μM	[158]
N-(2-hydroxyethyl)ferroceneselenoamide (**91**)	U-251, HCT-15, SK-LU-1, PC-3, K-562, MCF-7	Antiproliferative activity IC_{50} (MCF-7) = 4.58 μM; IC_{50} (U-251) = 7.24 μM; IC_{50} (HCT-15) = 4.48 μM	[159]
5-Ferrocenylcarbamoylpentyl selenocyanate (Fc-SelSA) (**92**)	MDA-MB-231, MCF-7 MCF-10A, Vero	Inhibition of HDAC; antiproliferative activity; low toxicity *in vitro*; reactivation of the expression of Erα; sensitization of the cancer cells to tamoxifen; significant reduction of tumor growth with no apparent side effects CC_{50} (MCF-7) = 1.18 μM; CC_{50} (MDA-MB-231) = 0.17 μM; CC_{50} (MCF-10A, Vero) > 100 μM	[160]
1-Methoxybenzoyl-3-(4-ferrocenylphenyl)selenoureas (**93**, **94**, **95**)	*F. solani*, *H. sativum*, *E. coli*, *P. aeruginosa*	Inhibitory effect on the growth of fungal strains	[164]
Ortho-substituted ferrocenylselenoureas (**96**, **97**, **98**, **99**, **100**, **101**)	MYCN-2, SK-N-SH, Hepa-1c1c7, MCF-7, HeLa	Antiproliferative activity; inhibition of aromatase; induction of quinone reductase	[165, 166]
Vanadocene-based compounds			
Diisoselenocyanate vanadocene Y (**102**)	CAKI-1 HUVEC	Antiproliferative activity; significant reduction of tumor growth; reduction of Ki-67 expression IC_{50} (CAKI-1) = 0.25 μM; IC_{50} (HUVEC) = 37 μM	[167]
Cobaltocene-based compounds			
Cobaltoceniumdiselenide (**103**)	A549, MDA-MB-231, HT-29	Antiproliferative activity IC_{50} (A549) = 17.4 μM; IC_{50} (MDA-MB-231) = 11.5 μM; IC_{50} (HT-29) = 51.6 μM	[92]
Other organometallic-derived drugs			
Organometallic compounds based on half-sandwich scaffolds			
Tetra-iron vinyliminium complex $[Fe_2Cp_2(CO)(\mu\text{-}CO)\{\mu\text{-}\eta^1\text{:}\eta^3\text{-}C^3(Ph)C^2(Se)C^1N(Me)(Xyl)\}]_2[I]_2$, Xyl = 2,6-$C_6H_3Me_2$ (**104**)	A2780, A2780cisR HEK-293	Antiproliferative activity; induction of ROS production; catalytic activity on NADH oxidation; stability in aqueous media IC_{50} (A2780) = 1.4 μM; IC_{50} (A2780cisR) = 2.8 μM; IC_{50} (HEK-293) = 2.2 μM	[170]
Selenophene-decorated alkylidene diiron vinyliminium complexes $[Fe_2Cp_2(CO)(\mu\text{-}CO)\{\mu\text{-}k^1N\text{:}k^1C\text{:}k^1C\text{–}C^3(R')C^2(Se)C^1(NMe_2)C^4(CO_2R')C^5(CO_2R')\}]$ (R′ = Me, Pr, ^{t}Bu, Et) (**105**, **106**, **107**)	A2780, A2780cisR	Antiproliferative activity **Compd 105**: IC_{50} (A2780) = 25.9 μM; IC_{50} (A2780cisR) = 29 μM **Compd 106**: IC_{50} (A2780) = 37 μM; IC_{50} (A2780cisR) = 42 μM **Compd 107**: IC_{50} (A2780) = 39 μM; IC_{50} (A2780cisR) = 50 μM	[171, 172]
Seleno-nucleobases Ru-*p*-cymene complexes [RuCl(η^6-*p*-cymene)(seleno-nucleobases)] selenonucleobases = 6-selenopurine (**108**), 6-selenoguanine (**109**)	K-562, Jurkat, Molt-4	Antiproliferative activity; enhancement of the stability of ligand under irradiation **Compd 108**: GI_{50} (K-662) = 79.9 μM; GI_{50} (Jurkat) = 54.2 μM; GI_{50} (Molt-4) = 53.4 μM **Compd 109**: GI_{50} (K-662) = 58.5 μM; GI_{50} (Jurkat) < 0.1 μM; GI_{50} (Molt-4) = 7.4 μM	[173]
Se,O-selenopyridone-based Rh (**110**) and Ir (**111**) complexes	A549, SW480, CH1/PA-1	Antiproliferative activity; stability in aqueous media **Compd 110**: IC_{50} (A549) = 99 μM; IC_{50} (SW480) = 27 μM; IC_{50} (CH1/PA-1) = 25 μM	[174]

(*continued on next page*)

Table 2 (*continued*)

Scaffold	Experimental system[a]	Biological activity	Refs.
		Compd 111: IC_{50} (A549) = 87 μM; IC_{50} (SW480) = 17 μM; IC_{50} (CH1/PA-1) = 23 μM	
N-dibenzosuberene substituted selenourea Ru(II) (η^6-*p*-cymene) complexes (**112**, **113**, **114**)	A549, HepG2 HEK-293, Vero *B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*, *A. flavus*, *C. albicans*, *A. niger*	Antiproliferative activity; low toxicity *in vitro*; inhibitory effect on the growth of bacterial and fungal strains **Compd 112**: IC_{50} (HepG2) = 80 μM; IC_{50} (A549) = 84 μM; IC_{50} (Vero) = 149 μM; IC_{50} (HEK-293) = 123 μM **Compd 113**: IC_{50} (HepG2) = 87 μM; IC_{50} (A549) = 97 μM; IC_{50} (Vero) = 93 μM; IC_{50} (HEK-293) = 94 μM **Compd 114**: IC_{50} (HepG2) = 62 μM; IC_{50} (A549) = 78 μM; IC_{50} (Vero) = 109 μM; IC_{50} (HEK-293) = 105 μM	[175]
Aniline substituted selenourea Ru(II) (η^6-*p*-cymene) complexes (**115**, **116**, **117**)	A549, HeLa S3 IMR-90	Antiproliferative activity; low toxicity *in vitro* **Compd 115**: IC_{50} (A549) = 64 μM; IC_{50} (HeLa S3) = 24 μM; IC_{50} (IMR-90) >100 μM **Compd 116**: IC_{50} (A549) = 69 μM; IC_{50} (HeLa S3) = 26 μM; IC_{50} (IMR-90) >100 μM **Compd 117**: IC_{50} (A549) = 83 μM; IC_{50} (HeLa S3) = 56 μM; IC_{50} (IMR-90) >100 μM	[176]
Selenoureato Ru-*p*-cymene complex (**118**)	A2780, A2780cisR, SUP-B15, HL-60, K-562, MCF-7, MDA-MB-231	Antiproliferative activity; reduction of metabolic activity; induction of apoptosis; induction of ROS production IC_{50} (SUP–B15) = 2.6 μM	[177]
Dinuclear chalcogenolato-bridged Ru, Rh, Ir complexes (**119**, **120**, **121**, **122**, **123**, **124**)	A549, MCF-7, B16F10 CRL-2115, CRL-2120	Antiproliferative activity; interaction with DNA **Compd 119**: IC_{50} (CRL-2115) = 965 nM; IC_{50} (CRL-2120) = 1082 nM; IC_{50} (MCF-7) = 574 nM; IC_{50} (B16F10) = 352 nM; IC_{50} (A549) = 440 nM **Compd 120**: IC_{50} (CRL-2115) = 967 nM; IC_{50} (CRL-2120) = 1087 nM; IC_{50} (MCF-7) = 592 nM; IC_{50} (B16F10) = 342 nM; IC_{50} (A549) = 445 nM **Compd 121**: IC_{50} (CRL-2115) = 987 nM; IC_{50} (CRL-2120) = 1354 nM; IC_{50} (MCF-7) = 553 nM; IC_{50} (B16F10) = 357 nM; IC_{50} (A549) = 457 nM **Compd 122**: IC_{50} (CRL-2115) = 1037 nM; IC_{50} (CRL-2120) = 1232 nM; IC_{50} (MCF-7) = 597 nM; IC_{50} (B16F10) = 358 nM; IC_{50} (A549) = 472 nM **Compd 123**: IC_{50} (CRL-2115) = 986 nM; IC_{50} (CRL-2120) = 1089 nM; IC_{50} (MCF-7) = 557 nM; IC_{50} (B16F10) = 345 nM; IC_{50} (A549) = 446 nM **Compd 124**: IC_{50} (CRL-2115) = 1028 nM; IC_{50} (CRL-2120) = 1254 nM; IC_{50} (MCF-7) = 568 nM; IC_{50} (B16F10) = 354 nM; IC_{50} (A549) = 453 nM	[178]
Organometallic compounds as *N*-heterocyclic carbene complexes			
1,3-Imidazolidine-2-selenone Au(I) complex [Au(IPr)(ImSe)]PF_6, IPr = 1,3-bis(2,6-di-isopropylphenyl)imidazole-2-ylidene, ImSe = 1,3-imidazolidine-2-selenone (**125**)	HCT-15, A549, MCF-7	Antiproliferative activity; interaction with tryptophan and lysozyme IC_{50} (HCT-15) = 33 μM; IC_{50} (A549) = 47 μM; IC_{50} (MCF-7) = 43 μM	[183]
N-*i*-propyl-1,3-imidazolidine- (**126**) and *N*-methyl-1,3-diazinane-2- (**127**) selenones Au(I) complexes [Au(IPr)(L)]PF_6, IPr = 1,3-bis(2,6-di-isopropylphenyl)imidazole-2-ylidene, L = selenone	HCT-15, A549, MCF-7	Antiproliferative activity **Compd 126**: IC_{50} (HCT-15) = 44 μM; IC_{50} (A549) = 49 μM; IC_{50} (MCF-7) = 49 μM **Compd 127**: IC_{50} (HCT-15) = 43 μM; IC_{50} (A549) = 54 μM; IC_{50} (MCF-7) = 62 μM	[184]
Selenourea Au(I) complex [Au(IPr)(Seu)]PF_6, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene, Seu = $SeC(NH_2)_2$ (**128**)	HCT-15, A549, MCF-7	Antiproliferative activity; stability in aqueous media; interaction with glutathione and L-cysteine IC_{50} (HCT-15) = 76 μM; IC_{50} (A549) = 82 μM; IC_{50} (MCF-7) = 75 μM	[185]
Organometallic compounds with CO ligands			
Chalcogen-containing metal-carbonyl Mn complexes [$MnBr(CO)_3$(R-κ^2Se)], R = phenyl (**129**), benzyl (**130**)	HeLa, HepG2	Antiproliferative activity, release of the three CO ligands in physiological conditions **Compd 129**: IC_{50} (HeLa) = 54.7 μM; IC_{50} (HepG2) = 56.7 μM **Compd 130**: IC_{50} (HeLa) = 31.1 μM; IC_{50} (HepG2) = 47.5 μM	[189]
Re(I)-diselenoether complex [$Re(CO)_3Cl(NaO_2C–CH_2Se(CH_2)_3–SeCH_2–CO_2Na)$] (**131**)	MCF-7, HeLa, HT-29, A549S	Antiproliferative activity IC_{50} (HeLa) = 75.1 μM; IC_{50} (A549S) = 131.5 μM; IC_{50} (MCF-7) = 4.75 μM; IC_{50} (HT-29) >500 μM	[192]
	MCF-7S, MCF-7Mdr, MCF-7R, HeLa, A549S	Uptake and efflux of Re in malignant cells; Re and Se tissue distribution located mainly in the liver via an oral route	[193]
	MDA-MB-231	Antiproliferative activity; interaction with DNA through the formation of covalent mono- and bis-guanine adducts with Re; significant reduction of tumor growth without apparent signs of toxicity; significant reduction of the number of pulmonary metastases	[194, 198]
	MDA-MB-231, MCF-7, HeLa, A549, PC-3, HT-29 HEK-293	Antiproliferative activity; decrease of ROS production; decrease of VEGFA, TGF-β1, and IGF-1 levels; low toxicity *in vitro* IC_{50} (MDA-MB-231) = 48.51 μM; IC_{50} (MCF-7) = 51.36 μM;	[195, 196]

(*continued on next page*)

Table 2 (*continued*)

Scaffold	Experimental system[a]	Biological activity	Refs.
		IC_{50} (PC-3) = 59.44 μM; IC_{50} (HT-29) = 47.52 μM; IC_{50} (HeLa) = 126.40 μM; IC_{50} (A549) = 133.20 μM	
	MDA-MB-231 HEK-293	Antiproliferative activity; decrease of the expression of cathepsins B and S IC_{50} (MDA-MB-231) = 50 μM	[197]
	4T1	No significant antitumor effect; decrease of TGF-β1 and tumor necrosis factor-alpha (TNF-α) levels *in vivo*	[201]
Re(I)-diselenoether complex (**131**) + cisplatin + tetrakis(1-octanol) tris(5-aminosalicylate)Ga(III)	MCF-7	Significant decrease the tumor volume	[199]
Re(I)-diselenoether complex (**131**) + paclitaxel	MDA-MB-231	No antitumor activity after pretreatment of the mice with total body irradiation; no synergistic effect with paclitaxel	[200]
Organometallic compounds with π-ligands and other σ-bonded complexes			
Diselenobenzoquinone CP*Ir complex [Cp*Ir(η^4-$C_6H_4Se_2$] (**132**)	A2780	Antiproliferative activity IC_{50} (A2780) = 5 μM	[202]
Monoselenoquinone, diselenoquinone and selenolate π-complexes [(η^6-*p*-cymene)Ru(η^4-C_6R_4SeE)] (R = H, CH_3; E = Se, O), [(η^6-*p*-cymene)Ru(η^5-$C_6H_3R_2Se$)]SbF_6 (R = H, CH_3) (**133**, **134**, **135**, **136**, **137**)	A2780, A2780cisR	Antiproliferative activity **Compd 133**: IC_{50} (A2780) = 25 μM; IC_{50} (A2780cisR) = 51 μM **Compd 134**: IC_{50} (A2780) = 41 μM; IC_{50} (A2780cisR) = 61 μM **Compd 135**: IC_{50} (A2780) = 75 μM; IC_{50} (A2780cisR) = 74 μM **Compd 136**: IC_{50} (A2780) = 19 μM; IC_{50} (A2780cisR) = 36 μM **Compd 137**: IC_{50} (A2780) = 49 μM; IC_{50} (A2780cisR) = 240 μM	[203]
π-Cyclohexadienylselenone CP*Ir complexes [Cp*Ir(η^5-C_6H_5Se)]BF_4 (**138**), [Cp*Ir(η^5-C_6H_4MeSe)]BF_4 (**139**)	A2780, A2780cisR	Antiproliferative activity **Compd 138**: IC_{50} (A2780) = 9.7 μM; IC_{50} (A2780cisR) = 13.3 μM **Compd 139**: IC_{50} (A2780) = 26 μM; IC_{50} (A2780cisR) = 11.7 μM	[204]
Pyridocarbazole cyclooctadiene-selenocyanate Ir(III) complex (**140**)	HeLa HUVEC	Photoinduced antiproliferative activity; induction of apoptosis via activation of caspases; inhibition of VEGFR3 (FLT4) EC_{50} (HeLa, light-activated) = 0.23 μM; EC_{50} (HeLa, no light-activated) = 7.9 μM	[205]
Bis(2-(thiophen-2-yl)pyridine)-selenadiazole Ir(III) complex [Ir((2-(thiophen-2-yl)pyridine)$_2$(L)]PF_6, L = (*E*)-4′-methyl-[2,2′-bipyridine]-4-carbaldehyde *O*-(benzo[*c*][1,2,5]selenadiazol-5-ylmethyl) oxime (**141**)	HeLa, HeLacisR, SiHa Wi38, E6E7, HUVEC	Antiproliferative activity; low toxicity *in vitro*; suitable penetration ability in tumor spheroids; cell cycle arrest at S phase; down-regulation of the mitochondrial membrane potential; induction of intracellular ROS production; induction of apoptosis IC_{50} (HeLacisR) = 6.87 μM; IC_{50} (HeLa) = 0.88 μM; IC_{50} (SiHa) = 4.89 μM; IC_{50} (HUVEC) = 0.51 μM; IC_{50} (Wi38) = 4.3 μM; IC_{50} (E6E7) = 4.12 μM	[206]
2-Thienylselenoacetic acid-based carboxylate Sn(IV) complex [($SnPh_3$)$_6$($O_2CCH_2SeC_4H_3S$-*o*)$_6$] (**142**)	HeLa, MDA-MB-231	Antiproliferative activity; induction of apoptosis via ROS production and collapse of the mitochondrial membrane permeabilization IC_{50} (HeLa) = 0.03 μM; IC_{50} (MDA-MB-231) = 0.02 μM	[207]
4-Fluorophenylselenoacetic acid Sn(IV) complex [Sn(*n*-Bu)$_2$($O_2CCH_2SeC_6H_4F$-*p*)$_2$] (**143**)	MDA-MB-231	Antiproliferative activity; morphological alterations; induction of ROS production; depolarization of the mitochondrial membrane; release of cytochrome *c*; up-regulation of caspase-3 expression levels; induction of apoptosis IC_{50} = 0.40 μM	[208]
Triethylene glycol based Pt(II) complex [Pt(EG-Se)]$^+$, EG-Se = 1,3,5-tri(2,5,8-trioxa-11-selenadodecan-12-yl)benzene (**144**)	HepG2, MCF-7, A549, HT-29 L02	Antiproliferative activity; induction of ROS production; collapse of the mitochondrial membrane potential; release of cytochrome *c*; induction of apoptosis; depletion of GSH leading to ROS production; significant reduction of tumor growth with no apparent side effects	[209, 210]
	Jurkat, Molt-4	Antiproliferative activity; cell cycle arrest; induction of apoptosis; induction of ROS production; disruption of the mitochondrial membrane potential; up-regulation of Bax, cytosolic cytochrome *c*, Apaf-1, cleaved PARP, caspases-3 and -9; down-regulation of Bcl-2 and mitochondrial cytochrome *c* IC_{50} (Jurkat) = 33.75 μM; IC_{50} (Molt-4) = 24.93 μM	[211]

[a] *Malignant cell lines*: 4T1: breast; A2780, A2780cisR: ovarian; A549, A549S: non-small cell lung; AGS: gastric; B16F10: murine melanoma; BxPC-3: pancreas; CAKI-1: renal; CH1/PA-1: ovarian; HCT-15: colon; HeLa, HeLacisR, HeLa S3: cervix; Hepa-1c1c7: hepatoma; HepG2: hepatocellular; HL-60: leukemia; HT-29: colon; Jurkat: leukemia; K-562: leukemia; MCF-7, MCF-7S, MCF-7Mdr, MCF-7R: breast; MDA-MB-231: breast; MGC-803: gastric; Molt-4: leukemia; MYCN-2: neuroblastoma; PC-3: prostate; SiHa: cervix; SK-LU-1: non-small cell lung; SK-N-SH: neuroblastoma; SUB-B15: leukemia; SW480: colon; U-251: glioblastoma. *Nonmalignant cell lines*: CRL-2115: fibroblast; CRL-2120: fibroblast; E6E7: epithelial; HEK-293: epithelial; HK-2: epithelial; HUVEC: endothelial; IMR-90: lung fibroblast; L02: hepatocytes; MCF-10A: epithelial; Vero: epithelial; Wi38: lung fibroblast.

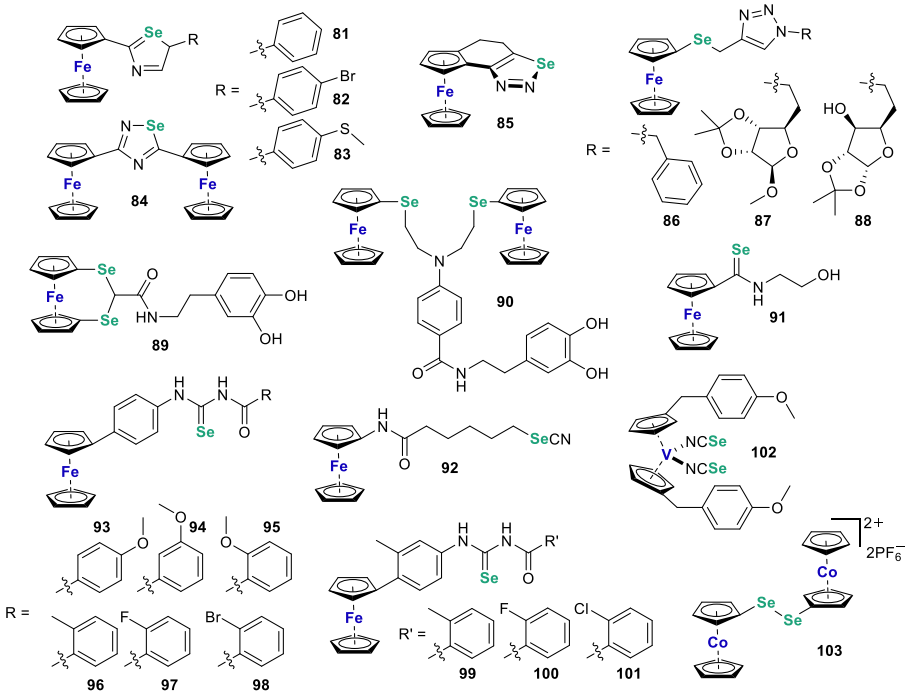

Fig. 7. Chemical structures of organometallic compounds with metallocenes.

completely inactive towards nonmalignant kidney cells [156]. In another study, the inclusion of dopamine scaffolds into the ferrocene moiety was assessed via the connection through a selenoether group [157]. Interestingly, the only ferrocenophane derivative, formed by the bridge with two Se ions (**89** in Fig. 7), stood out as the most cytotoxic compound, with IC_{50} values ranging from 2.2 to 5.4 μM. Further studies revealed that compound **89** induced cell cycle arrest at the G1 phase on hepatocellular cancer cells, triggered apoptosis with partial necrosis, and activated the expression levels of caspases-3 and -9 and the tumor suppressor p53 while down-regulating the antiapoptotic Bcl-2 protein. Additionally, it was found to suppress not only tubule formation but also endothelial cell migration, and significantly inhibited tumor growth in a xenograft mouse model. These impressive results were ascribed to the synergetic effect of the ferrocenophane, the Se moiety, and the catechol group [157]. With the aim to optimize the antitumor efficacy, the same group later reported other ferrocenylseleno-dopamine derivatives exploring different structural parameters [158]. According to the previous results, the compounds which contained two selenoether groups were demonstrated to be the most antiproliferative agents. Derivative **90** (Fig. 7) effectively generated ROS through the Fenton-like reaction possibly due to the tertiary amine that could facilitate the decomposition of hydrogen peroxide. Besides, compound **90** induced cell cycle arrest at the S phase, was proved to induce apoptosis through suppression of the expression of cyclin-dependent kinase 2 (CDK-2), and effectively inhibited the tumor growth in mice with no obvious safety issues [158]. The isosteric replacement of O with the Se atom in the carbonyl group is another useful strategy to increase the biological effect. Thus, a series of ferrocenyl-containing selenoamides were synthesized and also evaluated for their anticancer potential. Among the compounds described, derivative **91** (Fig. 7) displayed potent cytotoxicity against cancer cells with IC_{50} values in the range of 4.48–7.24 μM and lower than those of tamoxifen and cisplatin (9.5–25.8 μM). The presence of the Se atom was proved to be absolutely necessary, given that the cytotoxic activity of the S analog was almost negligible. Its antiproliferative activity was also attributed to the ferrocene moiety, the elongation of the alkyl chain, the absence of a bulky substituent, and the presence of a functional group capable of interacting through a hydrogen bond [159]. Moreover, the ferrocenyl derivative of a previously studied histone deacetylase (HDAC) inhibitor containing a selenocyanate moiety attached to the delocalized ring through an amide group was reported [160]. This modification yielded an organometallic compound (**92** in Fig. 7) that was even more potent than its organic analog in inhibiting HDAC and displaying antiproliferative activity. Further experiments with this compound revealed that **92** could sensitize breast cancer cells to conventional endocrine therapy by reactivating the estrogen receptor alpha (ERα) expression. Furthermore, the oral administration of **92** significantly inhibited the growth of triple-negative breast tumors in a xenograft mouse model with no apparent adverse effects [160]. The combination of ferrocene and Se in the chemical form of selenourea moieties has also been explored, and some ferrocene-containing selenoureas were previously assessed for their antioxidant properties [161–163]. In this context, the effect of three selenoureas including the ferrocene scaffold (**93**–**95** in Fig. 7) against bacterial and fungal strains was evaluated, but only effective antifungal activity was observed [164]. Preliminary studies were also carried out as a first approach to evaluate the anti-inflammatory and anticancer potential of this combination. Among the several selenoureas tested, the *ortho*-substituted derivatives (**95**–**101** in Fig. 7) were in general more active than the corresponding *meta*- and *para*-analogs in neuroblastoma cells [165,166].

Ferrocene was not the only metallocene to be used as a scaffold to develop new selenocompounds with therapeutic properties. Fichtner et al. reported the antitumor activity of a diisoselenocyanate-containing vanadocene (**102** in Fig. 7). This compound was able to reduce significantly the tumor growth in a xenograft renal carcinoma mouse model while being better tolerated than the dichloride analog, and was also proved to reduce the expression of the proliferation marker Ki-67 [167]. Additionally, a cobaltoceniumdiselenide (**103** in Fig. 7) was also found to exert antiproliferative activity in several cancer cell lines, especially in triple-negative breast adenocarcinoma, with an IC_{50} value of 11.5 μM [92].

3.2. Other organometallic compounds bearing selenium with therapeutic activity

The inclusion of Se into other organometallic complexes aside from metallocenes, such as half-sandwich complexes, carbenes, carbonyl (CO) and π-ligands, have also been explored comprising a variety of transition metals.

3.2.1. Organometallic compounds based on half-sandwich scaffolds

Half-sandwich (or 'piano stool') complexes are characterized by a π-bound ligand (Ar), often an arene or a Cp derivative such as η^5-pentamethylcyclopentadienyl (Cp*) [168]. Half-sandwich complexes have promptly emerged as innovative scaffolds for the design of potent anticancer agents [168,169], and several approaches to incorporate Se in the metal scaffolds have recently been reported. Recently, Fe complexes bearing S or Se obtained from diiron μ-vinyliminium precursors were synthesized and reported for their cytotoxicity [170]. Experiments suggested that this chalcogen function was associated with good stability in aqueous media, enhancing the interference of the compounds with cellular redox processes. The diselenide complex **104** (Fig. 8) was one of the most active compounds, with lower IC_{50} values (1.4–2.8 μM) than those of cisplatin (2.7–26 μM), and also displayed a moderate catalytic activity on nicotinamide adenine dinucleotide (NADH) oxidation [170]. In another study based on this diiron complex with a bridging vinyliminium ligand, a series of selenophile-decorated alkylidene complexes were reported [171]. These compounds (**105**–**107** in Fig. 8) underwent a progressive release of the alkylidene ligand as a functionalized selenophene in aqueous media, and since the released selenophenes were mainly non cytotoxic, their moderately antiproliferative activity was mostly related to the $Fe_2Cp_2(CO)_2$ core [172]. Several modifications have also been considered for Ru-based half-sandwich complexes. In this context, a series derived from the seleno-nucleobases 6-selenopurine (**108** in Fig. 8) and 6-selenoguanine (**109** in Fig. 8) acting as ligands was reported [173]. Complex **109** showed potent cytotoxicity in leukemic T cell lymphoblasts with GI_{50} values in the low micromolar range (<0.1–7.4 μM), and although the free ligand was more active, the coordination to the Ru ionic center also reduced the instability of free 6-selenoguanine under irradiation, and complex **109** was stable under similar conditions [173]. Selenopyridones were also explored as bidentate *Se,O*-chelating ligands for Ru η^6-*p*-cymene complexes, along with other transition metals. In fact, only the Rh and Ir complexes (**110**–**111** in Fig. 8) showed a slightly higher level of cytotoxicity than their Ru and Os counterparts, which was attributed to their enhanced stability [174]. Furthermore, the inclusion of selenoureas as mono- or bidentate ligands has also been assessed. In this context, the Ru η^6-*p*-cymene precursor was modified by incorporating different *N*-dibenzosuberene (**112**–**114** in Fig. 8) [175] or aniline (**115**–**117** in Fig. 8) [176] substituted-selenoureas, in which only the Se atom was coordinated to the metal center in a monodentate neutral interaction. All the compounds showed moderate cytotoxicity towards cancer cell lines while being nontoxic in nonmalignant cells. *N*-dibenzosuberene-selenourea derivatives (**112**–**114** in Fig. 8) were also evaluated for their antimicrobial potential, showing low MIC values almost comparable to those of standard drugs [175]. Likewise, a comparative study regarding a series of Au(I), Pd(II), and Ru(II) complexes featuring deprotonated thio- and seleno-ureato ligands was also reported [177]. Interestingly, not only the selenoureato derivatives proved to be more cytotoxic than their thioureato counterparts, but the half-sandwich Ru complexes stood out as the most active compounds over the coordination complexes of the other two metals. The Ru complex coordinated to selenourea as a bidentate ligand **118** (Fig. 8) also reduced the metabolic activity of acute lymphoblastic leukemia cells, while showing a proapoptotic effect and inducing oxidative stress by ROS production [177]. In contrast, the opposite tendency regarding the incorporation of S/Se was observed in a series of chalcogenolato-bridged Ru, Rh, and Ir complexes (**119**–**124** in Fig. 8). However, although the complexes with the thiolato bridges were slightly more potent than the selenolato analogs, all the compounds were highly cytotoxic with antiproliferative activity in the submicromolar range (IC_{50} values of 342–1354 nM in general) and displayed a strong interaction with DNA [178].

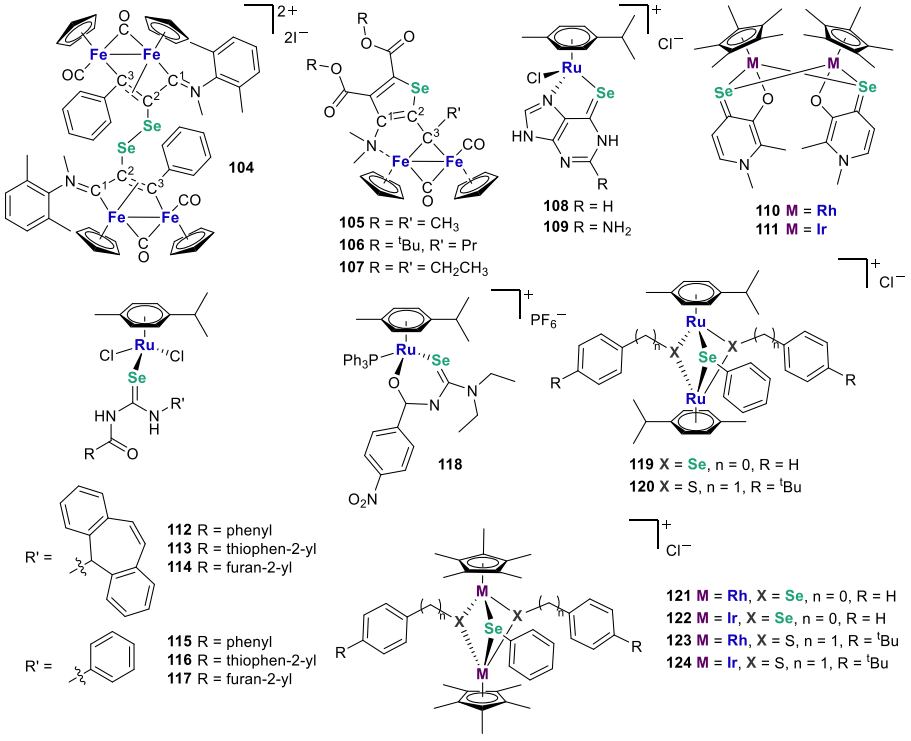

Fig. 8. Chemical structures of organometallic compounds based on half-sandwich scaffolds.

3.2.2. Organometallic compounds as N-heterocyclic carbene complexes

N-heterocyclic carbenes (NHCs) are a class of versatile ligands for organometallic complexes that typically mimic the chemical properties of phosphines [179], but they are less toxic, easier to functionalize, and can target relevant biomolecules in cancer progression [180]. Structurally, NHCs are compounds that contain a carbon atom with a lone pair of electrons. The carbene-carbon disobeys the octet rule as it only has six valence electrons, and subsequently is highly unstable and reactive [179]. Additionally, the carbene-carbon is incorporated in a nitrogen-containing heterocycle in which its empty "p" orbital acts as an acceptor for the π lone pairs of the two N atoms. NHCs bind to metal centers through σ-donation, and the π-back bonding is minimal due to the high occupancy of the formally empty π orbital of the carbene-carbon by π delocalization [181]. NHCs have been recently employed in numerous applications reflecting their structural diversity and chemical features, mainly as metal-based drug candidates with anticancer and antimicrobial properties [179,181] and in catalysis [182]. In this context, some Au(I) complexes bearing Se in the chemical forms of selenones or selenoureas have recently been reported. Seliman et al. described a series of NHC compounds including 1,3-imidazolidine-2-selenone as ligands [183]. Complexes were found to interact with tryptophan and the lysozyme protein but showed in general scarce cytotoxicity probably related to the strong binding of the ligands and their steric hindrance. The exception was derivative **125** (Fig. 9), with an activity similar to cisplatin in colon cancer cells since both compounds displayed IC_{50} values in the range of 23–47 μM. Besides, the modification of the NHC scaffold with 1,3-diazinane- and 1,3-diazepane-2-selenones also yielded complexes with less cytotoxicity than the same reference drug, and only compounds **126** and **127** (Fig. 9) showed moderate antiproliferative activity (IC_{50} values of 43–62 μM) when compared to the rest of the series included in the study. Docking studies also suggested the high binding affinity of the compounds towards DNA topoisomerase 1 [184]. Likewise, the adduct formed between the same Au(I)-carbene and a selenourea as co-ligand (**128** in Fig. 9) was synthesized by the same research group [185], but the complex was less potent as an anticancer agent than cisplatin against a panel of lung, colon, and breast cancer cell lines. Nevertheless, **128** was stable in aqueous solution and displayed a clear interaction with GSH and L-cysteine due to Au(I) soft Lewis acid property for effective S-glutathionylation [185].

3.2.3. Organometallic compounds with CO ligands

Another common ligand used in organometallic chemistry is the carbon monoxide or carbonyl (CO) molecule. CO is a stable, naturally occurring compound in which the carbon is found in the rare +2 oxidation state [186]. As a ligand, CO donates its electron pair to an empty orbital of the metal ion forming a σ bond, and simultaneously acts as a π acceptor, forming a bonding interaction in which metal d electrons are back-donated to an empty anti-bonding orbital of the CO ligand [186]. Additionally, CO can coordinate terminally to a metal center but also act as a μ^2-and even μ^3-ligand [187], bridging two or three metal centers as could be observed in compounds described in other sections of this review (**104**–**107** in Fig. 8) [170,172]. Biologically, CO has important signaling, antiapoptotic and anti-inflammatory effects [188], and it is believed that its physiological and therapeutic targets are transition metals contained in enzymes [186]. In this context, several organometallic compounds have been developed containing this type of ligand as delivery systems [187]. With the aim to modify the CO dissociation by the enhancement of the spin-orbit coupling (SOC) with heavy atoms such as S and Se and therefore potentially changing the photoexcitation behavior of the resulting compound, the inclusion of chalcogens was considered in the design of two Se-containing manganese (Mn) complexes (**129**–**130** in Fig. 9). The results revealed an effective release of the three CO ligands even in physiological conditions, this increase in the CO release rate being related to the presence of heavier atoms in the first coordination sphere and the dissociative populated excited states [189]. A CO-dependent inhibition of cell viability was also observed, and among the compounds, complex **130** was the most cytotoxic derivative in cervix and liver cancer cells (IC_{50} values of 31.1 and 47.5 μM, respectively), probably due to its ability to release CO faster than the other Mn complexes [189]. On the other hand, the tri- and di-carbonyl complexes of rhenium (Re) have also attracted great attention due to their relative ease of preparation, stability, and unique photophysical and luminescent properties that allow the combination of diagnostic and therapeutic purposes mainly for anticancer and antibiotic applications [190]. Interestingly, a Re(I) disodium salt containing a diselenoether moiety (**131** in Fig. 9) is one of the Re complexes which is at a more advanced stage of biological evaluation for cancer treatment, with defined targets at the cellular level [191]. Complex **131** has the advantage of being soluble in water and lipophilic with a good diffusion of both Re and Se into the tissues after oral administration [191]. The synthesis of the Re(I)-diselenoeter compound **131** was first reported by Kermagoret et al., and was initially found to have an antiproliferative effect against breast cancer cells with an IC_{50} value in the low micromolar range of 4.75 μM [192]. Additionally, complex **131** was also proved to deliver both Re and Se to the organism mainly in liver tissues with a prolonged oral administration. Likewise, the uptake and efflux of Re in the nucleus of malignant cells exposed to complex **131** were also demonstrated [193]. Re complex **131** formed mono- and bis-adducts with methylguanine [194], and besides, it was shown to significantly decrease the production of ROS, the expression levels of transforming growth factor-beta 1 (TGF-β1), vascular endothelial growth factor A (VEGFA) and insulin-like growth factor 1 (IGF-1) [195,196], and the expression of cathepsins B and S [197]. The antitumor effect *in vivo* of complex **131** (Fig. 9) has also been assessed. A significant tumor growth inhibition could be observed with the single treatment with **131** at a dose of 10 mg/kg in a triple-negative breast cancer model with oral [194] or intraperitoneal [198] administration, along with a significant reduction of the number of pulmonary

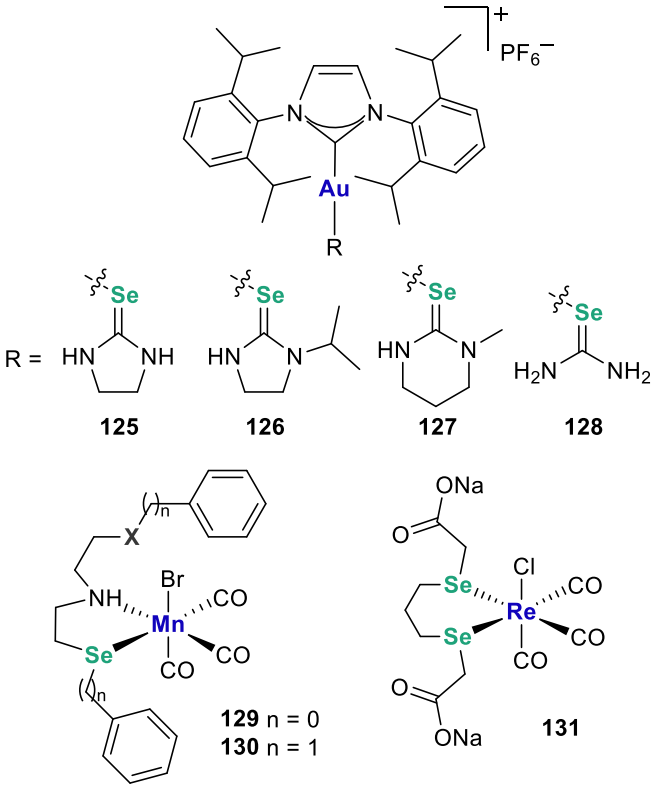

Fig. 9. Chemical structures of organometallic compounds as *N*-heterocyclic carbene complexes or with CO ligands.

metastases [194]. The triple combinatory therapy with cisplatin and a gallium (Ga) complex also induced a significant decrease of 50% of the tumor volume [199]. In contrast, in another study the expected tumor regression was not observed, and no synergistic effect was determined along with paclitaxel. The authors ascribed this effect to the pretreatment with total body irradiation in order to increase the tumor growth in the mice for the experiment [200]. Currently, complex **131** is also under evaluation in other experimental mouse models [201].

3.2.4. *Organometallic compounds with π-ligands and other σ-bonded complexes*

Interestingly, the first successful isolation of selenoquinone was achieved using a Cp*Ir moiety as a stabilizing entity. The resulting organometallic compound (**132** in Fig. 10) was the most cytotoxic agent among other related quinone and thioquinone metal analogs and even exhibited comparable potency to cisplatin in ovarian cells, with an IC_{50} value of 5 μM [202]. Based on these results, a Ru η^6-*p*-cymene moiety was later reported to stabilize selenolate, diselenobenzoquinone, and monoselenoquinone entities through π-bonding interactions (**133**–**137** in Fig. 10). The selenoarene ring would be expected to dissociate eventually inside the cells and induce a cytotoxic effect, since the presumably solvated Ru η^6-*p*-cymene byproduct is known to exert negligible cytotoxicity. Nevertheless, the new series displayed only moderate antiproliferative activity in cancer cells [203]. Likewise, the selenocyclohexadienyl unit was also isolated for the first time by π-coordination to a Cp*Ir moiety. The complexes (**138**–**139** in Fig. 10) displayed antiproliferative activity and were more potent than cisplatin in cisplatin-resistant ovarian cells with IC_{50} values of 13.3 and 11.7 μM, respectively [204].

Interestingly, an Ir(III) pyridocarbazole cyclooctadiene complex containing a selenocyanate moiety (**140** in Fig. 10) [205] was the first example of an Ir complex with visible-light-induced anticancer activity triggering cellular apoptosis in cancer cells. Further experiments of the mechanism for photoinduced cytotoxicity revealed that irradiation of the complex **140** induced the substitution of the selenocyanate group by chloride, rather than favoring the cleavage of the Ir–CH_3 bond homolytically. Additionally, complex **140** was also a potent inhibitor of the vascular endothelial growth factor receptor kinases (VEGFR), inhibiting VEGFR3 (FLT4) and showing complementary antiangiogenic properties [205]. The introduction of a non-conjugated aromatic selenocompound into the side arm of the ligand led to a significant improvement in the lipid-water distribution coefficient of a fluorescent Ir(III) complex (**141** in Fig. 10) in comparison with the S analog. The suitable lipophilicity of the complex not only reduced the toxicity on normal cells, but also effectively increased the anticancer activity by enhancing the penetration and retention in malignant cells, thus overcoming cisplatin resistance in cervix cancer cells. Moreover, mechanistic studies showed that complex **141** entered cancer cells through endocytosis, and triggered apoptosis via the down-regulation of the mitochondrial membrane potential and excessive production of ROS [206].

Another strategy for developing organometallic derivatives was the introduction of Se into carboxylates to form Se-containing carboxylic acids as bridging ligands between Sn ions. Hence, it was proved that the anticancer properties of organotin complexes were enhanced by the inclusion of Se in the form of 2-thienylselenoacetic acid-based carboxylate ligands [207]. The Sn(IV) complex **142** (Fig. 10) exhibited remarkable anticancer activity by interfering in the redox signaling pathways to induce mitochondria-mediated and ROS-dependent apoptosis in triple-negative breast cancer cells [207]. Additionally, another series based on 4-fluorophenylselenoacetic acid yielded Sn(IV) derivatives which also possessed antiproliferative activity. Among them, the Sn(IV) complex **143** (Fig. 10) was found to inhibit cell growth by

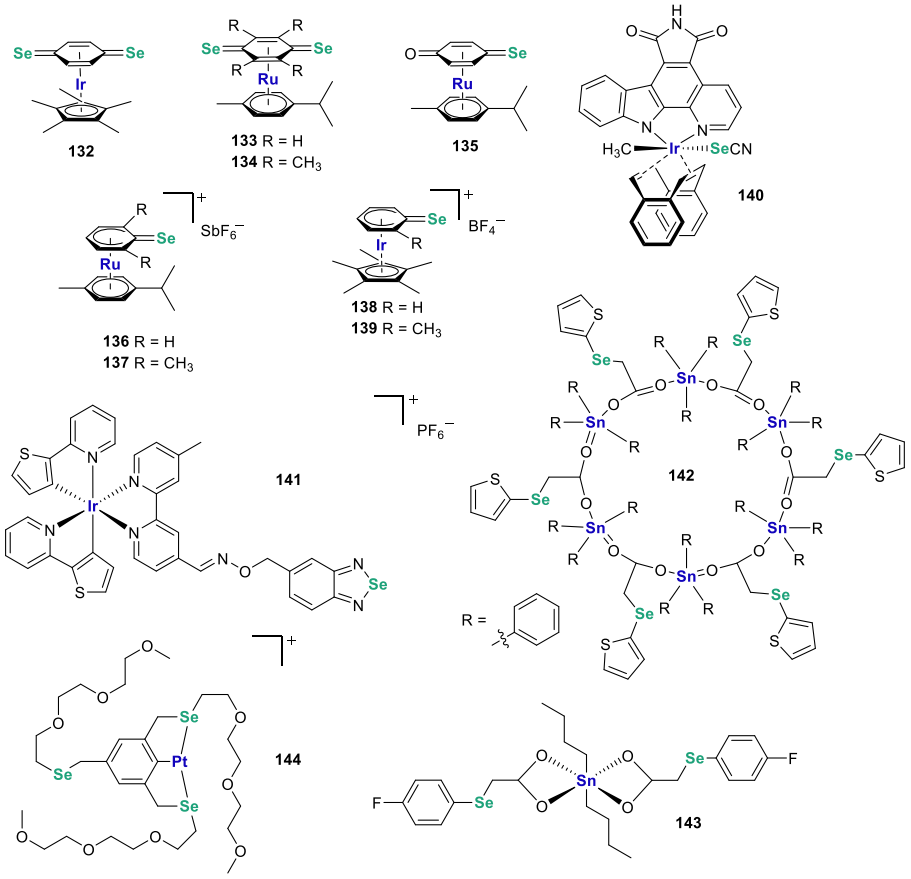

Fig. 10. Chemical structures of organometallic compounds with π-ligands and other σ-bonded complexes.

targeting the intracellular redox system and contributed to the collapse of the mitochondrial membrane potential and the release of cytochrome *c* from the outer membrane of the mitochondria, activating caspase-3 and ultimately leading to apoptosis in the cancer cells [208].

Interestingly, the coordination of Pt(II) and Se through a triethylene glycol-based ligand yielded an amphiphilic compound (**144** in Fig. 10) that could self-aggregate into nano-assemblies. The Pt(II) complex **144** demonstrated high selective cytotoxicity that was closely related to the GSH antioxidant defense system through depletion of GSH in both reduced and oxidized (GSSG) states [209]. Besides, **144** was found to lead to apoptosis by inducing the excessive production of ROS, and effectively inhibited the tumor growth in hepatocellular cancer xenograft mouse models [209,210]. Additional studies with this compound revealed its anticancer properties for the treatment of T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) by inducing cell cycle arrest and ROS-mediated apoptosis through the mitochondrial signaling pathway [211].

4. Summary and perspectives

In a field traditionally dominated by pure organic chemistry, metal-based compounds have been attracting great attention for developing new therapeutic drugs, and several approaches have been made in recent years to design more potent compounds with fewer negative outcomes. In this context, both Se and metal ions play essential roles in human health and are involved in several physiological processes. Thus, the incorporation of Se into the structure of metal-based compounds is an appealing design approach that has been widely explored. This review provides a compendium of the most recent literature on both coordination complexes and organometallic compounds bearing Se for medicinal purposes. We have focused on reported compounds that were evaluated for cancer and/or bacterial and fungal pathogens, as Se-containing metal-based compounds have been mainly assessed in these pathologies. In general, the synthesized metal complexes often outperformed the free ligands in exhibiting therapeutical activity.

Se-containing metal-based compounds have demonstrated numerous advantages over traditional organic molecules. Hence, the binding geometry in space of pure organic entities is dictated by the principles of hybridization (sp-linear, sp^2-trigonal planar, and sp^3-tetrahedrical) as they rely on carbon, whereas for metal-based compounds the growing number of substituents around the metal center allows stereochemical flexibility that opens a huge diversity in 3D structures, as shown in this review. In addition to this structural diversity, different active ligands can also be attached to modulate the biological properties. In this context, Se confers an additional diversification, as it could be incorporated in several chemical forms including selenoethers, diselenides, selenocyanates, selenoureas, selenoheterocycles, and selenosemicarbazones, among others. As summarized in this review, the versatility of Se could also be implied in its involvement with the metal-based compound via the direct coordination with the metal center, or by being part of the organic ligand attached to it. Furthermore, the polarizability ("softness") of this chalcogen atom makes Se a suitable donor center for the coordination with soft and borderline acids offering numerous bonding possibilities, as shown in this review. Thus, the direct coordination to Se could be observed in compounds mainly bearing Pt(II), Pd(II), Au(I), Ag(I), Cu(II), Co(II), Ni(II), Zn(II) and Cd(II). The formation of coordination complexes containing a Se(IV) center with therapeutic activity has also been discussed herein. Se(IV) is an ionic center suitable for the coordination with ligands via interactions with O, N, and Cl atoms, allowing the combination of this entity with other biological molecules with appealing properties in a unique form that would not be possible in traditional organic chemistry. Another interesting aspect of introducing Se into metal-based drugs is that Se-containing compounds could be characterized and monitored easily by ^{77}Se NMR spectroscopy, since a minor change in its electronic environment induces drastic changes in the chemical shifts of the signals. Thus, several studies included in this review have relied on this complementary technique for the characterization of the metal complex.

Nevertheless, some major challenges are still ongoing. A detailed understanding of the biological processes that affect the metal-based complex once the drug has entered the organism is essential to fully exploit the potential of these types of compounds. Besides, some of the limitations in the use of Se-containing molecules in medicine are their toxicity and poor solubility. To overcome these problems, it would be of great interest to design new metal-based compounds that could increase the solubility in water and the life-time in blood circulation, and improve the selectivity of the biological effect. In this regard, we also consider the use of carrier delivery systems to improve the efficacy in targeted-drug delivery and consequently decrease toxicity by providing a controlled release of the drug.

In conclusion, the design of metal-based compounds including Se in the structure has been demonstrated to be a valid approach to obtaining potent therapeutic drugs with several applications by acting on different targets and/or through different mechanisms. The inclusion of Se has been considered in both coordination complexes and organometallic compounds allowing a huge structural diversity, with impressive results overall. Taken together, metal-based compounds containing Se could have the potential to make a difference in the search for next-generation therapeutics for the treatment of several pathologies.

Author contribution

S. R.-I.: Bibliographical research, Writing - original draft preparation. C. S. and D. P.: Supervision, Writing – Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviations

Bcl-2	B-cell lymphoma 2
CAT	catalase
CDK-2	cyclin-dependent kinase 2
CFX	ceftriaxone
Cp*	η^5-pentamethylcyclopentadienyl
Cp	cyclopentadienyl
DIOs	iodothyronine deiodinases
DM	diabetes mellitus
ER	endoplasmic reticulum
Erα	estrogen receptor alpha
ERK	extracellular signal-regulated kinase
G6P	glucose-6-phosphate
GA_3	gibberellic acid
GPxs	glutathione peroxidases
GSH	glutathione
GSSG	oxidized glutathione
GST	glutathione S-transferase
HDAC	histone deacetylase
HSAB	hard and soft acids and bases theory

IGF-1	insulin-like growth factor 1
iNOS	inducible nitric oxide synthase
Lamp2	lysosome-associated membrane protein 2
MDA	malondialdehyde
MMPs	matrix metalloproteinases
NADH	reduced nicotinamide adenine dinucleotide
NHCs	*N*-heterocyclic carbenes
NK	natural killer
Pin-G	penicillin G
QS	quorum sensing
ROS	reactive oxygen species
SePP1	selenoprotein P
SOC	spin-orbit coupling
STG	sitagliptin
T-ALL/LBL	T-cell acute lymphoblastic leukemia/lymphoma
TGF-β1	transforming growth factor-beta 1
TNF- α	tumor necrosis factor-alpha
TRAIL	TNF-related apoptosis inducing ligand
TrxRs	thioredoxin reductases
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
VEGFR	vascular endothelial growth factor receptor kinases

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