Chapter

Chirality in Anticancer Agents

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Abstract

Many drugs are chiral and their therapeutic activity depends on specific recognition of chiral biomolecules. The biological activity of enantiomers can also differ drastically in terms of toxicity and pharmacokinetics. Chiral natural biological molecules, such as nucleic acids, enzymes are targeted molecules for the development of anticancer drugs. The interest in chiral agents is logically a result of the different interaction with biomolecules leading in the end consequence to improve anticancer activity and maybe to less undesirable effects. This review outlines the effects of chirality on the efficiency of anticancer metal-based agents and potential organic drugs. A variety of up-to-date examples of structurally diverse chiral agents exhibiting different mechanisms in their antitumor activity is presented.

Keywords: Chirality, anticancer, metal based, chiral complexes, drugs, organic metal agents

1. Introduction

Regardless of the origin, chirality is an integral part of biological process that derived their inherent asymmetry from the chirality of the fundamental building blocks of receptors – the L-amino acids. It would thus be expected that a receptor protein derived from the enantiomeric D-amino acids would have the same fundamental properties, but exhibit opposing chirality of interaction. In addition, the macromoleculecular structures of biopolymers also give rise to chirality as a results of helicity. Such helical structures may have either a left or righ handed turn. In the case of DNA double helix and the protein α-helix, the biopolymers have a right-handed turn. As nature has a preference in terms of its chirality, enzymes and receptor system exhibit stereochemical preferences, particularly as many of natural substrates and ligands for these system, e.g. neurotrasmitters, endogenous opioids, and hormones [1].

It is now not surprising, that stereoisomers of drugs may differ in their pharmacodynamic activity at their biological target, or in their pharmacokinetic properties (absorption, distribution, and clearance by metabolism and excretion) [2, 3]. Enantiomers may differ both quantitatively and qualitatively in their biological activities. At one extreme, one enantiomer may be devoid of any biological activity, at the other extreme, both enantiomers may have qualitatively different biological activities. These stereoselective differences may arise not only from drug interactions at the pharmacological receptors, but also from pharmacokinetic events [4, 5].

Advances in chemical technology, especially in the methodology of stereoselective syntheses and stereospecific analyzes, together with regulatory measures, have

led to an increase in the number of new authorized chirally pure drugs over the last ten years, and this trend persists [6]. In contrast to the end of the last century, when about 55% of clinically used drugs were chiral and half of them were used as racemates, the current trend in the development of new chiral drugs is mainly towards substances containing pure one enantiomeric form [7, 8]. Currently, chiral formations of small molecules are an essential part of the discovery and development of new anticancer medicines [2, 9].

2. Anticancer therapy

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably and have the potential to invade or spread to other parts of the body. Cancer cells are formed when normal cells lose the normal regulatory mechanism that controls their growth and multiplication. If the cancer cells remain localized they are said to be *benign.* If the cancer cells invade other part of the body and set up secondary tumors a process known as metastasis - the cancer is defined as *malignant* and is life threatening [10]. A major problem in treating cancer is the fact that it is not a single disease. There are more than 200 different cancers resulting from different cellular effects, and so a treatment that is effective in controling one type of cancer may be ineffective on another [11].

Cancer is the second leading cause of death globally, behind only ischemic heart disease. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women [12].

The primary treatment modalities include surgery, chemotherapy, radiation, and immunotherapy, etc. However, mainstay treatment is based on chemotherapy which is a viable alternative involving various natural and synthetic compounds that can kill or stop the unwanted proliferation of cancerous cells [13, 14].

The compounds used in the chemotherapy of cancer diseases are quite varied in structure and mechanism of action, including alkylating agents, antimetabolite analogs of folic acid, pyrimidine and purine; natural products, hormones and hormone antagonist; and a variety of agents directed at specific molecular targets. Most these of agents interacted with DNA or its precursors, inhibiting the synthesis of new genetic material and causing damage to the DNA of both normal and malignant cells. Rapidly expanding knowledge about cancer biology has led to the discovery of entirely new and more cancer specific targets (e.g. growth factor receptors, intracelluar signaling pathways, epigenic processes, tumor vascularity, DNA repairs effect, and cell death pathway [15].

3. Chiral metal-based anticancer agents

Metal-based antitumor chemotherapeutics obtained prominence after the discovery of the cytotoxic effect of cisplatin - cis-diamminedichloroplatinum (II), *cis*-[Pt $(NH_3)_2Cl_2$] – **Figure 1**. Currently, cisplatin is one of the most effective chemotherapeutic drug used for many solid malignancies [16]. The discovery of cisplatin stimulated efforts to investigate other platinum and non platinum metal-containing compounds for their potential use in the treatment of cancer. In recent years, more attention has been devoted to complexes of other transition metals (ruthenium, gold, osmium, iridium, etc.) which offer a different mechanism of action and lower systemic toxicity compared to platinum-based drugs [17, 18].

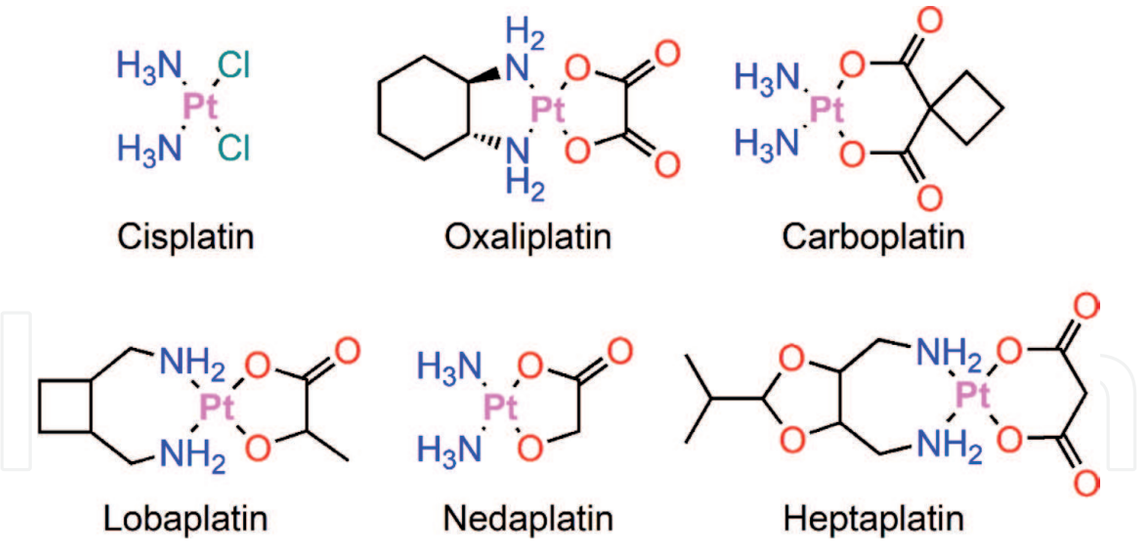


Figure 1.
The chemical structures of clinically used platinum-based anticancer drugs.

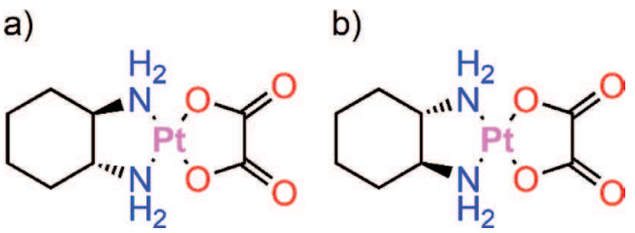


Figure 2.
The structures oxaliplatin with chiral ligands (a) 1R,2R-*cyclohexane-1,2-diamine; (b)* 1S,2S-*cyclohexane-1,2-diamine.*

Chirality is one of the important paradigms that decide the precise structure of a particular anticancer drug and its interaction with the cancer molecular target. This is valid not only for organic drugs but also for metal-based drugs which are developed for anticancer application [19, 20]. An, example is oxaliplatin, which contains the chiral ligand (*R, R*)-cyclohexane-1,2-diamine. This platinum antineoplastic compound is more biologically active in comparison with its enantiomer contaning the ligand (*S, S*)-cyclohexane-1,2-diamine **Figure 2** [20]. Interest in the development of chiral pure metal-based compounds for anticancer application is increasing.

Chiral metal-based anticancer drugs have been comprehensively reviewed in the literature [9, 21] therefore we will focus on selected examples to give the reader an overview of the most important developments. This review is limited to a variety of some recent examples of structurally diverse chiral agents exhibiting different mechanism in their anticancer effect.

Chirality in metal coordination complexes can be observed in two ways:

1. The metal centre has an asymmetric arrangement of ligands around it. This type of chirality can be observed predominantly in octahedral complexes and tetrahedral complexes,

2. The metal centre has a chiral ligand (i.e. the ligand itself has a non-superimposable mirror image).

Various methods have been used to denote the absolute configuration of optical isomers such as R or S, Λ or Δ, or C and A [22]. According to IUPAC rules the

R/S convention is applied to enantiomers with tetrahedral geometry. In the case of compounds with geometries other than tetrahedral, the same principles are followed as for the C/A convention (C for the clockwise and A for the anticlockwise priority sequence of ligands), and for bis and tris bidentate complexes the absolute configuration is designated Lambda Λ (left-handed) and Delta Δ (right-handed). Conformers with helical chirality are designated as δ (right-handed helix) and λ (left-handed helix).

3.1 Chiral Pt-based anticancer complexes

Since cisplatin was firstly approved by the US Food nd Drug Administration (FDA) in 1978, platinum complexes have become a class of important anticancer drugs [23]. Cisplatin has been widely employed to treat a variety of tumors including ovarian, cervical, head and neck, non-small cell lung carcinoma, and testicular cancers, and is commonly used in combination regimens [24]. However, the clinical application of platinum drugs has several drawback including serious toxicity and, natural and acquired drug resistance [25, 26]. Therefore, much effort has been made to overcome the side effects and improve the antitumor activity of platinum-based drugs [27–31].

To date, second and third generation platinum analogues, namely carboplatin and oxaliplatin, have been designated and approved for worldwide use. Carboplatin is effective in the treatment of ovarian carcinoma, lung, and head and neck cancers, while oxaliplatin is clinically approved for the treatment of colorectal cancer, which is resistant to cisplatin [32].

Other platinum compounds have regional approval, nedaplatin is used in Japan, lobaplatin is applied for treatment of chronic myeloid leukemia (China), heptaplatin is used for treatment of stomach cancer (in Korea). [32], though there is a little information about influence of its stereochemistry on biological effect **Figure 1** [33].

It is widely accepted that the main biochemical mechanism of action of platinum (II) drugs involves the binding of the drug to DNA in the cell nucleus and subsequent interference with normal transcription, and/or DNA replication mechanisms [34]. Cis platin becomes activated once it enters the cell. In the cytoplasm, chloride atoms on cisplatin are displaced by water molecules. This hydrolysed product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids. Cisplatin binds to the N7 reactive centre on purine residues and as such can cause deoxyribonucleic acid (DNA) damage in cancer cells, blocking cell division and resulting in apoptotic cell death [35]. Some studies, using spectroscopics techniques and crystallography, have shown an energetically favourable interaction between the chiral ligands of platinum complexes stereoisomers and the DNA structure or small nucleotides [36–38].

Platinum drugs derived from chiral 1,2-diaminecyclohexane ligand (DACH) – were the first class of compounds used to investigate the relations between spatial configuration of the ligand and the ability of the complexes to form efficient adducts with DNA [39, 40].

Each DACH stereoisomer has a particularly stable bulk structure with a nearly planar shape for (*RR*) and (*SS*)-(DACH) dichloroplatinum (II) and an L-shaped molecule for the (*RS*) stereoisomer. As a consequence of these conformations, when the RS stereoisomer forms an adduct with DNA, significant steric hindrance is expected, resulting in a slower binding of the complexes to DNA as well as a different recognition and processing of the adducts formed. This theory has been confirmed by numerous cytotoxicity tests (predominantly towards human

tumor cell lines) on DACH and their structural analogues which have, in most cases, shown the same order of activity (RR > SS > RS) [41]. From the series of platinum drugs with DACH ligands only [$PtCl_2$ (*R, R*-DACH) has been approved for clinical use [25].

Sometimes, when small modifications are made in the structure of chemically related compounds (for instance: a change in the substitution pattern of an aromatic ring or an alkyl chain) or in the conditions used to test the complexes (for instance: a change in the cell lines, a change from an *in vitro* to an *in vivo* test), a reversal of the stereoselectivity order can be detected [42, 43]. These findings suggest the possibility that interaction of platinum complexes with other biomolecules might be responsible for their stereoselectivity. These compounds are in most instances amino acids, proteins present in biological fluids and taking part in the distribution and metabolism of platinum complexes [41]. A difference in cellular accumulation between diastereoisomers was found in the platinum complex with phenyl derivative of chiral diamine ligands **Figure 3** [44]. These findings supported the hypothesis that stereoselectivity in cellular transport can also cause a different accumulation of platinum complexes in kidney and a different toxic effect of isomers [45].

The direct targeting of the G-quadruplex structure of DNA which is widely present in human telomeric DNA, transcription start sites, and promoter regions of genes responsible for cell apoptosis/growth and senescence, might play a key role in the anticancer action of chiral metal(II) complexes [46, 47]. The G-quadruplex structure is important in the control of a variety of cellular processes, including telomere maintenance, gene replication, transcription and translation [48, 49]. The induction/stabilization of quadruplex DNA is considered to be a potential target for the development of anticancer drugs [50, 51].

Platinum(II) complexes with chiral 4-(2,3-dihydroxypropyl)-formamide oxoaporphine R/S-(±)-FOA (1), R-(+)-FOA (2) and S-(−)-FOA ligands – **Figure 4**, showed significant antitumor activity caused by directly targeting G-quadruplex DNA [52]. Among these platinum(II) complexes, the complex with S-(−)-FOA was found to exhibit higher selectivity and telomerase inhibition via targeting telomere G4s in BEL-7404 cells, as well as inducing S phase arrest and telomeres/DNA damage, which resulted in cell senescence and apoptosis. Similar results were also found in ruthenium(II) complexes with these chiral FOA ligands. The *in vitro* anticancer activity of the Ru(II) complex with *S*-(−)-FOA was higher compare to complex with -(±)-FOA (1), *R*-(+)-FOA [53].

Apart from platinum compounds, a number of other anticancer metal complexes are currently being investigated. The main advantage of complexes containing a metal other than platinum is the different mechanism of action compared

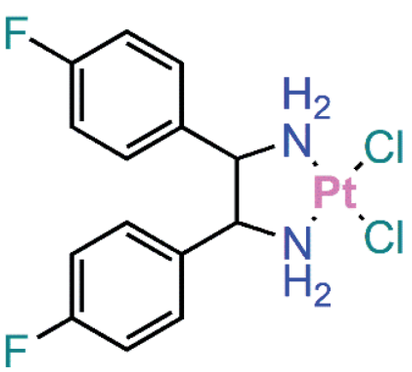


Figure 3.
Examples of Platinum(II) complexes with chiral diamines ligands where stereochemical discrimination of cytotoxic activity was SS > RR > meso.

to platinum-based chemotherapy, as well as a wider range of treated tumors, the ability to overcome resistance, and lower systemic toxicity [54, 55].

3.2 Chiral ruthenium anticancer complexes

Ruthenium complexes are promising candicates as chemotherapeutic agents because some of them have exhibited favorable *in vitro* and *in vivo* pharmacological profiles in different models including platinum-resistant cells [56, 57]. For instance, the ligand exchange kinetics of Pt(II) and Ru(II) complexes in aqueous solution, which is crucial for anticancer activity, are very similar; thus Ru is considered to be an alternative to platinum-based drugs. Many ruthenium compounds are less toxic than Pt-based drugs and some of them are quite selective for cancer cells. These facts may arise from the ability of ruthenium to mimic iron in binding to biomolecules [56, 58]. A number of ruthenium(II/III)-based anticancer agents have been developed to date, yet none of them are in clinical use as anticancer drugs. Currently, two Ru(III) complexes are in clinical studies: NAMI-A and KP1339 type ruthenium(III) coordination complexes based on N, Cl donor ligands **Figure 5** [59].

The influence of chirality on anticancer effect has been reported primarily in the group of polypyridyl and organometallic Ru complexes and [9]. Wang et al. [60] presented a series chiral polypyridyl complexes (Δ-Ru1, Λ-Ru1, Δ-Ru2, Λ-Ru2, Δ-Ru3, and Λ-Ru3) – **Figure 6** as mitochondria targeting anticancer agents. The cytotoxic activity of these ruthenium(II) complexes was tested against six selected

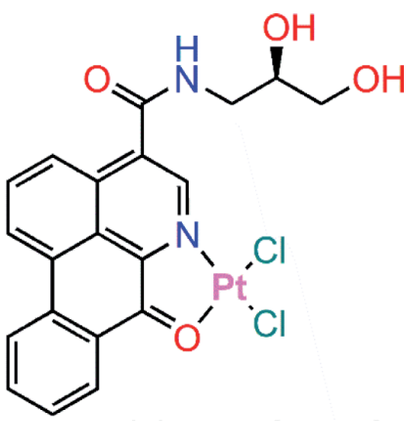


Figure 4.
The structures of chiral Platinum(II) complexes with chiral FOA ligand as G4-DNA and telomerase inhibitor.

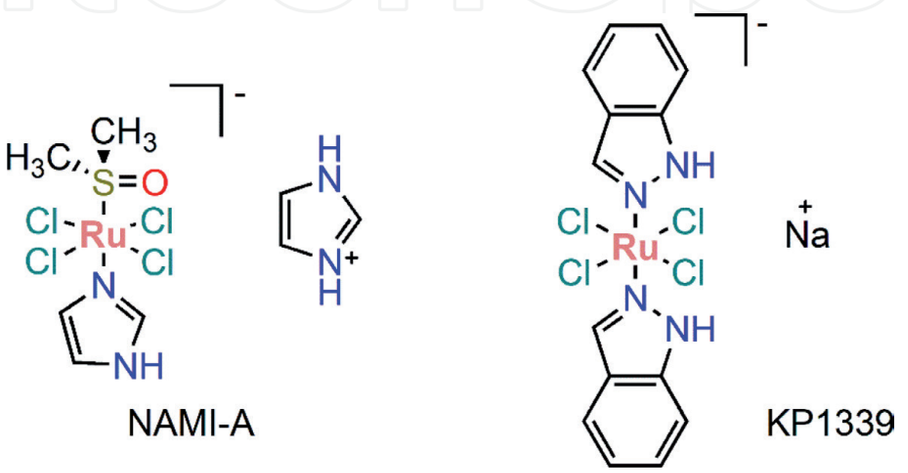


Figure 5.
The structures of ruthenium complexes in clinical studies.

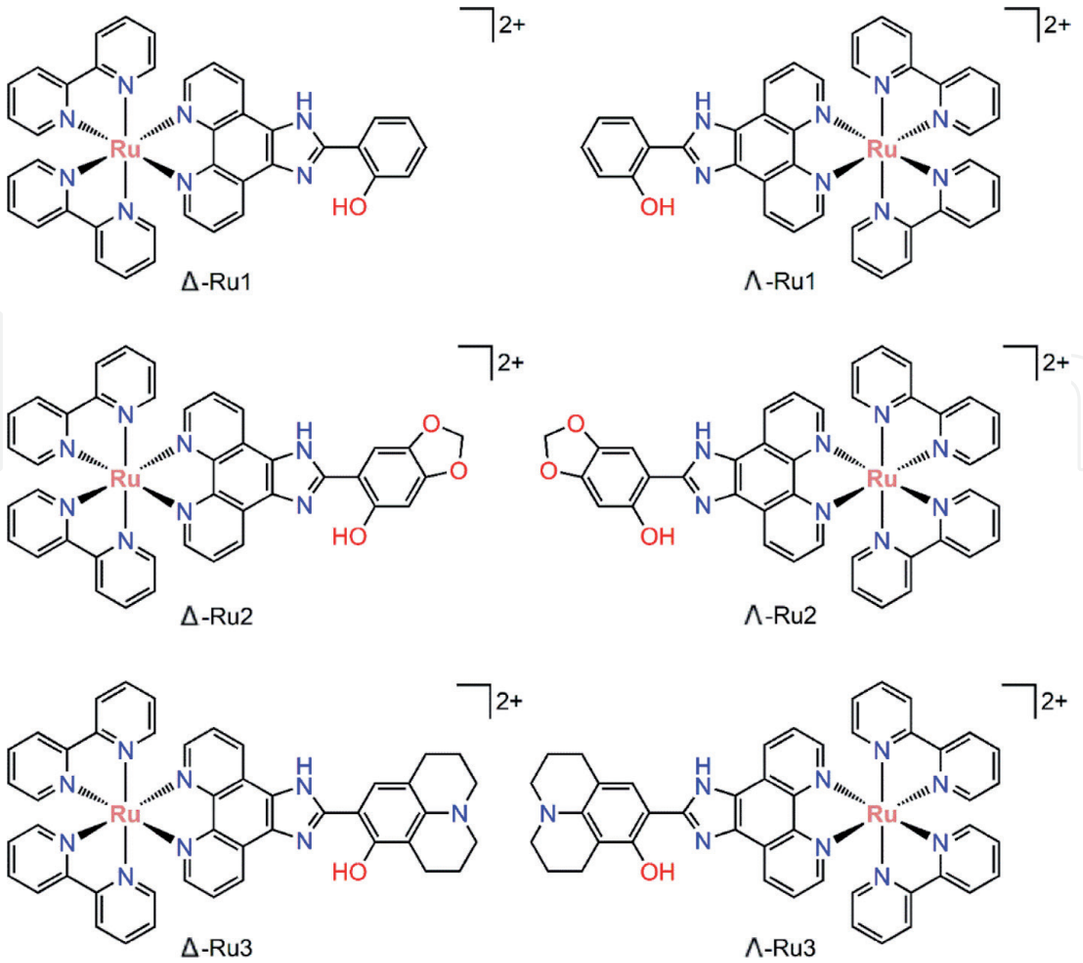


Figure 6.
The structures of chiral polypyridyl Ru(II) complexes.

human cancer cell lines, (HeLa, A549, HepG2, MCF-7, BEL-7402, and MG-63), and one cisplatin resistant cell line. Δ-Ru1 was the most active anticancer agent, exhibiting cytotoxicity similar to that of cisplatin against the six cancer cell lines. Notably, this complex inhibited the growth of the cisplatin-resistant cell line A549-CP/R, suggesting that the anticancer mechanism of Δ-Ru1 differs from that of cisplatin. Λ-Ru1 displayed slightly lower toxicity than Δ-Ru1, which also seems to be attributed to the slightly less cellular uptake of ruthenium. In HeLa cells, the same relationship was found for Δ-Ru2 and Λ-Ru2, but the opposite relationship was found for Δ-Ru3 and Λ-Ru3.

Further analysis showed that Δ-Ru1 exerts its toxicity through the intrinsic mitochondria-mediated apoptotic pathway, which is accompanied by the regulation of Bcl-2 family members and the activation of caspases [60].

Some studies have highlighted the potential of polypyridyl Ru complexes to target G4 and telomerase [61, 62]. Sun et al. [63] revealed that enatinomers of Ruthenium complexes $[Ru(phen)2(p\text{-}DMNP)]^{2+}$ – **Figure 7** possessed binding affinities and significant selectivity for human G-quadruplex DNA. The Λ–Ru complext can stabilize human telomeric G quadruplex DNA slightly more than Δ–Ru and has a strong preference for G-quadruplex over duplex DNA. The specific recognition of HepG2 cells makes Λ–Ru complex a promising class of luminescent labels for (bio) imaging agents.

Chiral organometallic ruthenium (II) complexes have been studied as protein kinase inhibitors [64, 65]. In the case of chiral complexes containing bidentate staurosporine ligand – **Figure 8** the (*R*)-enantiomer was a significantly more potent inhibitor in comparison to the (*S*)-enantiomer [65].

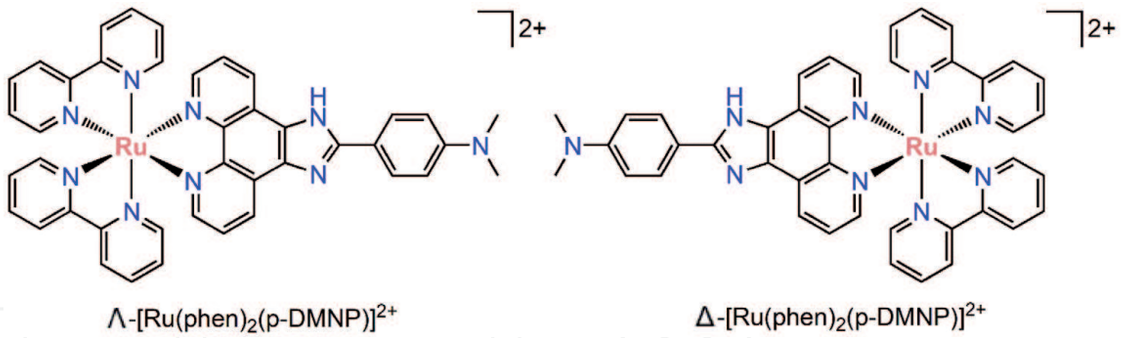


Figure 7.
Examples of chiral polypyridyl Ru(II) complexes targeting G4 and telomerase.

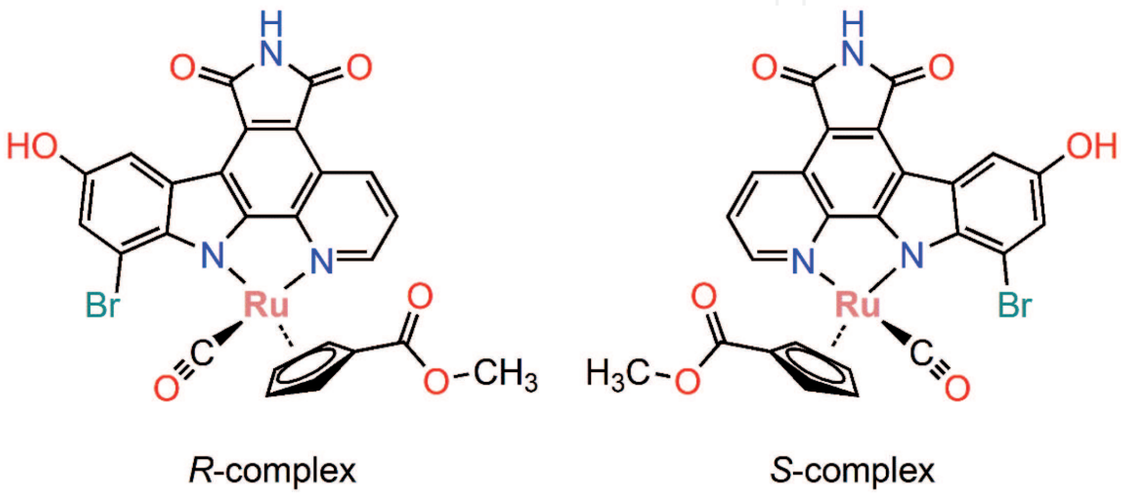


Figure 8.
The chemical structures of chiral Ru complexes with enantiomers of R- and S-staurosporine ligand.

Half-sandwich organometallic arene complexes have also been studied for anti-cancer application, though studies of pure stereoisomers of arene complexes are limited, probably due to difficulties in their resolution [21]. Sadler et al. described the cytotoxicity of pure diastereoisomers of Ru arene complexes - **Figure 9** [9, 66]. The *R,S* or *S,R* isomers showed higher cytotoxicity against the human ovarian cancer cell line (A2780) than the *R,R* or *S,S* compounds. However, the mechanism of the different activities between the enantiomers was not reported.

Cuvea-Alique and co-workers [67] evaluated the anticancer activities of arene Ru(II) enantiomers witzzh aminooxime ligands- **Figure 10**. The oxime-containing Ru(II) compounds have shown potent anticancer activities against a broad range of different cancer cell lines, with no significant differences between the two enantiomers.

Other chiral organometallic complexes that have been studied for their anticancer properties include osmium [68, 69], iridium [70, 71], rhodium [72] and gold [73] complexes.

3.3 Chiral gold anticancer complexes

Gold complexes have emerged as a versatile and effective class of metal-based anticancer agents [74, 75]. Auranofin, (2,3,4,6- tetra-*O*-acetyl-1-(thio-*κ*S)-β-L-glucopyranosato)- (triethylphosphine) gold(I), is an orally administrated anti-arthritis drug which has also been clinically studied for its antiproliferative properties **Figure 11** [74].

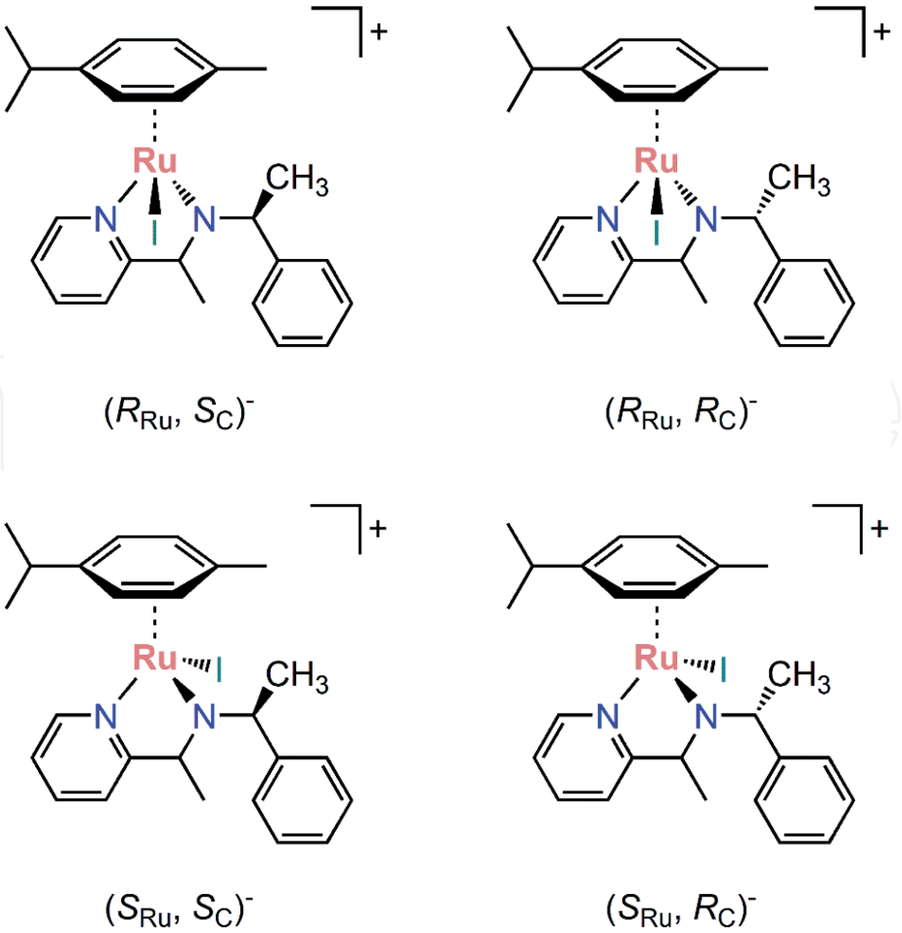


Figure 9.
The structures of diastereoisomers of organometallic arene Ru (II) complexes.

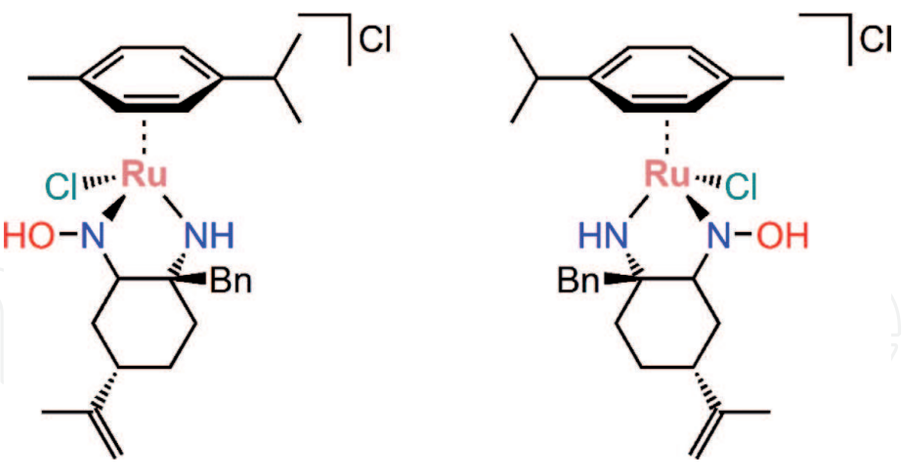


Figure 10.
The structures of chiral organometallic arene Ru (II) complexes with aminoxime ligand.

Based on these results different Au(I) complexes bearing stereogenic phosphine [76, 77], chiral N-heterocyclic carbenes ligands (NHC) [78, 79] have been synthesized and tested as potential anticancer drugs.

Enantiomeric Au(I) complexes with a phospohorus stereogenic centre - **Figure 12** has shown great toxicity against both suspended and adherent cancer cells but with marked difference s in their toxicity to healthy cells. The (*R,R*)-enantiomers were more toxic against healthy mammalian cells compare to those of the (*S,S*)-enantiomer [76, 77].

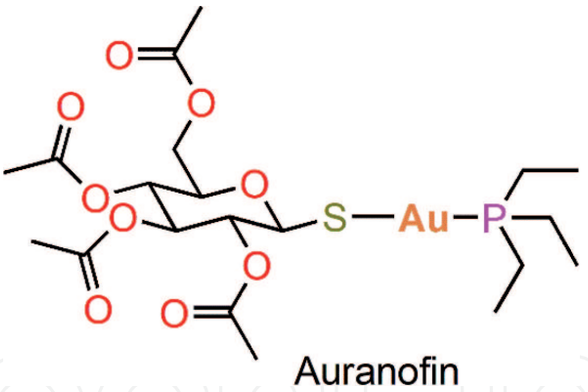


Figure 11.
The structure of gold complex, which is under clinical investigation for treatment cancer.

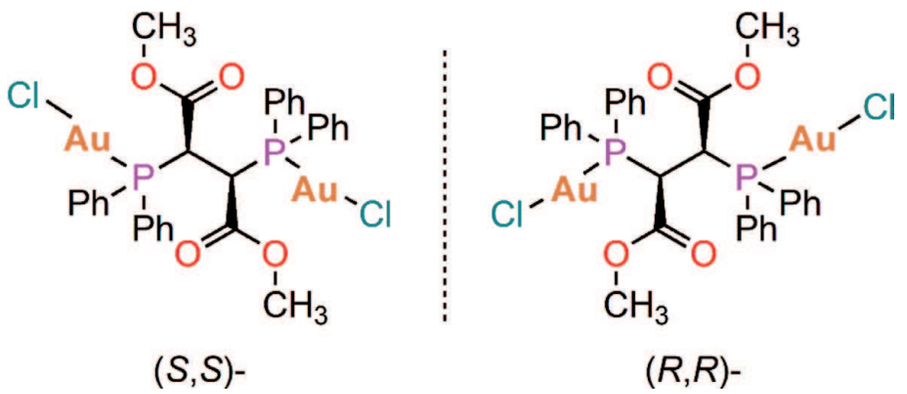


Figure 12.
Examples of enantiomeric phosphine-Au(I) complexes.

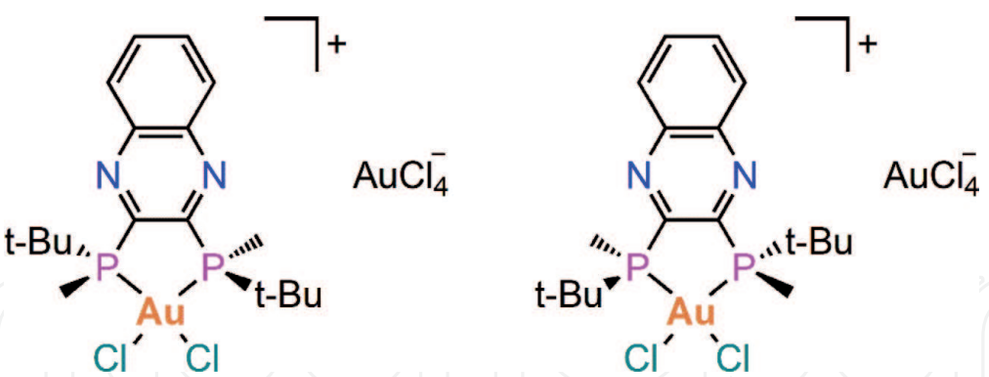


Figure 13.
Chemical structures of the enantiomeric phosphine-Au(III) complexes.

The mechanism of action of Au(I) complexes is thought to trigger apoptosis *via* inhibition of selenium- and sulfur-containing enzymes such as thioredoxin reductase (TrxR), glutathione peroxidase, cysteine protease or glutathione-S-transferase [80].

The novel chiral Au(III) complexes containing chiral P stereogenic phosphine ligand: *R,R* and *S,S*- QuinoxP* (2,3-bis(tert-butylmethylphoshino)quinoxaline) were prepared **Figure 13** [81]. The antiproliferative activities of the two compound were evaluated against panel of cell lines and exhibited cytotoxicity slightly higher than that of cisplatin and auranofin. However, no diffrence was found in the cytotoxic effect between the two enantiomers.

4. Chiral organic anticancer agents

The search for novel natural and synthetic compounds with potential antitumor activity is a major goal of many research groups. The tests involve known compounds with proven biological activity that have not been previously used in oncology as well as newly synthesized molecules that are structural analogues of biologically active substances already used in the treatment of cancer [82].

4.1 Alkylating agents

Alkylating agents were among the first group of chemicals determined to be useful in cancer chemotherapy, and the largest drug group among conventional cytotoxic chemotherapeutics. They are so named because of their ability to add alkyl groups to negatively charged groups on biological molecules such as DNA and proteins [83]. Classical alkylating agents include nitrogen mustards, nitroso ureas, aziridines, and alkyl sulfonates. Nonclassical alkylating agents include hydrazine, triazene, and altretamines. In addition, the alkylating-like agent group, which similarly to alkylating agents functions by crosslinking with DNA, includes platinum compounds. The high clinical efficacy of one of the main classes of alkylating agents, nitrogen mustards, makes them the current choice for the first-line treatment of different tumor types. However, severe side effects limit the therapeutic value of such compounds, and new effective compounds are required [84].

The group of bifunctional chloropiperidine derivatives has been revealed to possess novel efficient DNA-alkylating properties, leading to direct strand cleavage at guanine nucleotides and indirect effects on the human topoisomerase II enzyme [85, 86].

4.1.1 Chiral chloropiperidines

Carraro et al. [87] investigated series of racemic and enantiomerically pure monofunctional chloropiperidines – **Figure 14**. Derivatives of chloropiperidines demonstrated the ability to alkylate DNA *in vitro*. On a panel of carcinoma cell lines, M-CePs exhibited low nanomolar cytotoxicity indexes, which showed their remarkable activity against pancreatic cancer cells and in all cases performed strikingly better than the chlorambucil control. Interestingly, stereochemistry modulated the activity of the chloropiperidines.

An analysis of the cytotoxicity of enantiomers *N*-butyl derivatives of chloropiperidines D-1 and L-1 in three cancer cell lines revealed that D-1 was the most

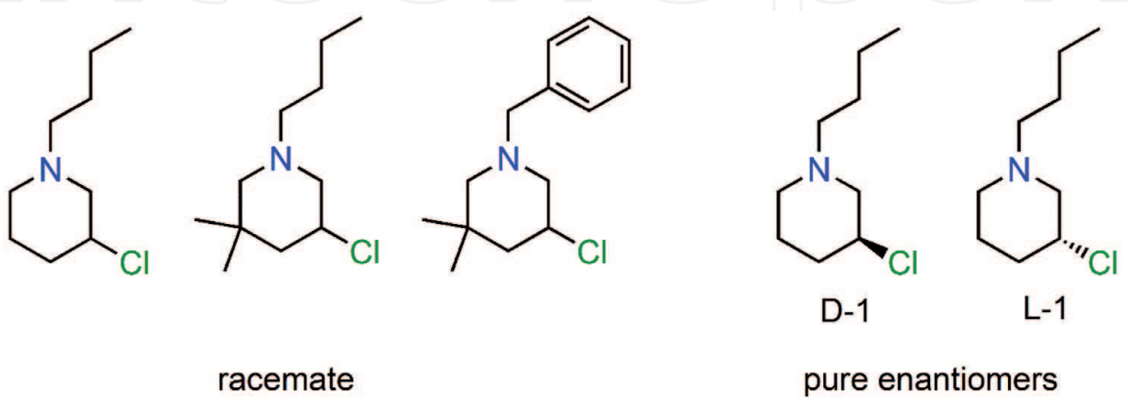


Figure 14.
Chemical structure of racemic chloropiperidines and enatiomerically pure compounds.

active compound, again with a clear tropism for pancreatic cancer cells, while its enantiomer, L-1 enantiomer was less cytotoxic, with an eudismic ratio of ~40 in the case of BxPC-3 cells. The direct damage observed to isolated DNA was not sufficient to explain their nanomolar cytotoxicity, especially when considering the enantiomeric couple.

The D-1 enantiomer turned out to be the most cytotoxic compound of the entire series, although it was inactive in the DNA cleavage assay. In contrast, its mirror image, L-1, found to efficiently nick and fragment the plasmid *in vitro*, happened to be much less cytotoxic.

The enantiomers also differed in permeation through an artificial membrane, that simulates passive diffusion. Because D-1 was the most cytotoxic but least permeable enantiomer, the permeation analysis of the chiral compounds suggests the involvement of active mechanisms of uptake into cells.

4.2 Inhibitors of topoisomerases

4.2.1 Chiral epoxy-substituted chromones

Human DNA topoisomerases (Top) have been recognized as a good target molecule for the development of anticancer drugs because they play an important role in solving DNA topological problems caused by DNA strand separation during replication and transcription [88].

Jo et al. [89] designed and synthesized novel chiral epoxy-substituted chromone analogues -**Figure 15** that exhibit an anticancer effect by inhibiting the DNA synthesis of cancer cells. Their ability to alkylate DNA and inhibit topo enzymes and cancer cell growth was evaluated.

In the brief structure–activity relationship analysis, no clear correlation was seen between stereochemistry and topos inhibitory and cytotoxic activity. However, compounds **6**, **10** and **11** were more potent than the others in both Top I and IIα inhibitory activity.

The 5(*R*),7(*S*)-bisepoxy-substituted compound **11** showed the most potent cell antiproliferative activity against all tested cancer cell lines with particularly strong inhibition of K562 myelogenous leukemia cancer cell proliferation.

4.2.2 Chiral hydroxyanthraquinone analogs

Natural and synthetic analogs of hydroxyanthraquinones (e.g., anthracyclines, mitoxantrone and emodin) are additional prototypes for the design of anticancer drug candidates with the ability to bind double-stranded DNA and inhibit topoisomerases 1 and 2 mediated relaxation of supercoiled DNA [90, 91].

Derivatives of (4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione) were identified as a promising scaffold for the search of agents active against resistant tumor cells [92]. Shchekotikhin et al. [93] explored new TopI and TopII antagonists based on a 4,11-dihydroxy naphtho[2,3-*f*]indole-5,10-dione scaffold bearing the cyclic chiral diamine in the side chain - **Figure 16**.

Potent cytotoxicity (at submicromolar to low micromolar concentrations) against a panel of wild type mammalian tumor cells and isogenic drug resistant sublinies was observed for all novel derivatives of naphtho[2,3-*f*]indole-5,10-diones. Only isomer **7** induced the formation of specific DNA cleavage products similar for classical Top1 inhibitors camptothecin and indenoisoquinoline MJ-III-65. Importantly, the derivative of (*R*)- aminopyrrolidine **7** increased the life span of mice bearing P388 leukemia while its enantiomer **6** was inactive.

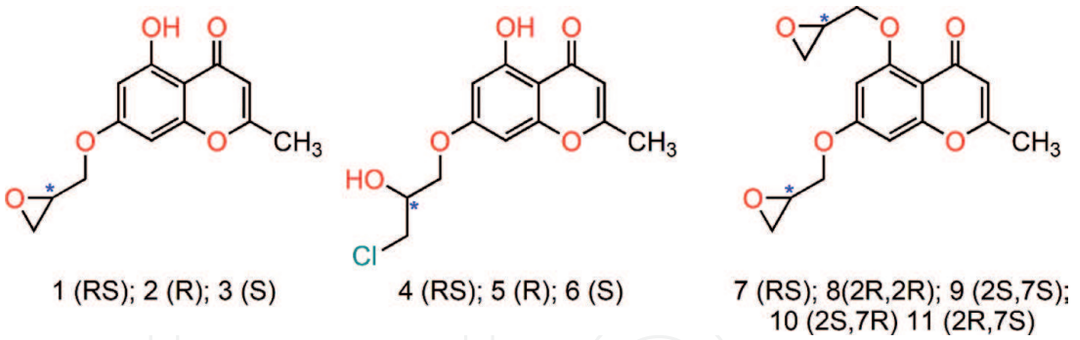


Figure 15.
The structures of prepared chiral chromane analogs.

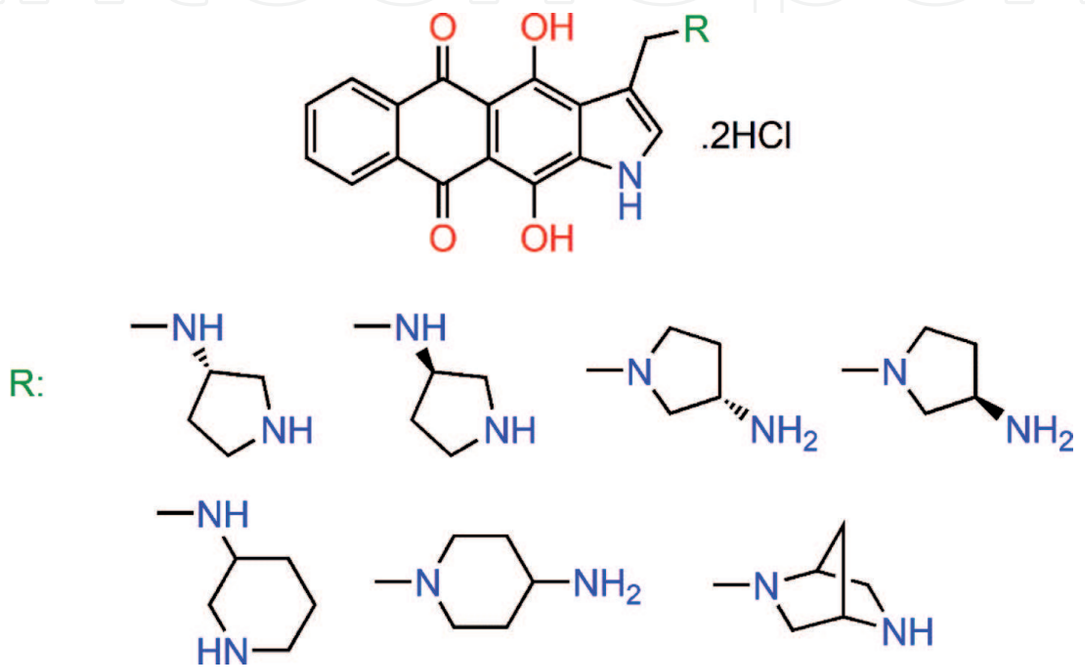
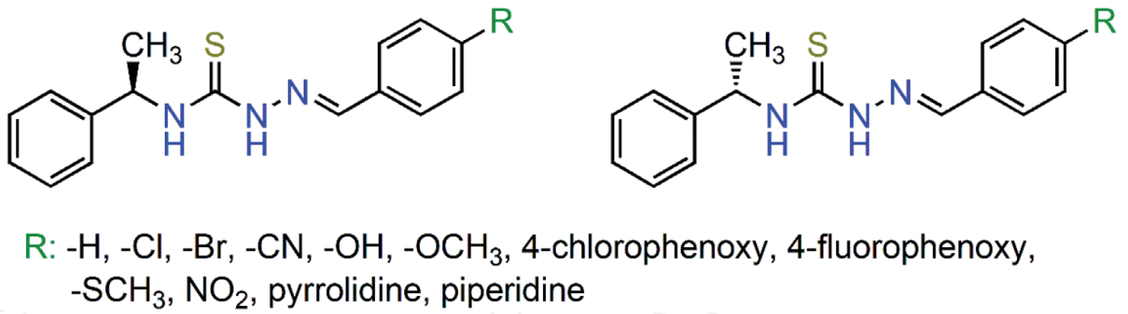


Figure 16.
The chemical structures of naphthoindolediones with some chiral substituents.

4.3 Chiral thiosemicarbazones

Another group of potent anticancer agents is made up from chiral thiosemicarbazones derived from homochiral amines **Figure 17** [94]. Their antiproliferative activity was evaluated against several panels of cancel cell lines (A549 (human alveolar adenocarcinoma), MCF-7 (human breast adenocarcinoma), HeLa (human cervical adenocarcinoma), and HGC-27 (human stomach carcinoma) cell lines. Some of the compounds, especialy thiosemicarbazones with substituted hydroxyl group, 4-chlorophenoxy, 4-fluorophenoxy showed inhibitory activities on the growth of cancer cell lines. Compounds with substituted piperidine ring exhibited higher activity against HCG-27 than taxol, which was uses as the standard. In every active thiosemicarbazone derivatives the (*S*)-enantiomer was more active than (*R*)-enantiomer. The most active compounds the (*S*)-isomers of the thiosemicarbazone derivative with substituted piperidine group, also showed the best fit for the generated pharmacophore hypothesis. In the pharmacophore model, the (*S*)-enantiomer was better matched than the (*R*)-enantiomer. This showed that the configuration of isomers greatly influenced their activity.



R: -H, -Cl, -Br, -CN, -OH, $-OCH_3$, 4-chlorophenoxy, 4-fluorophenoxy, $-SCH_3$, NO_2, pyrrolidine, piperidine

Figure 17.
The chemical structures of chiral thiosemicarbazones.

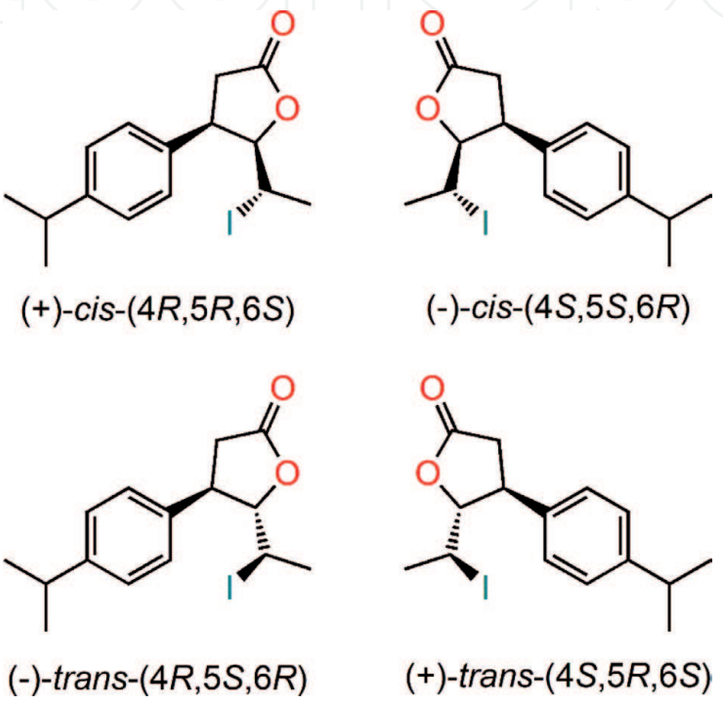


Figure 18.
The structure of stereoisomers δ-iodo-γ-lactones with p-isopropylphenyl substituent.

4.4 Chiral δ-iodo-γ-lactones

Compounds with both a lactone function and an aromatic ring in their structure are promising as potential anticancer agents [95, 96]. Four stereoisomers of δ-iodo-γ-lactones with a 4-isopropylphenyl substituent at the β-position - **Figure 18** were tested against a broad panel of canine cancer cell lines representing hematopoietic and mammary gland cancers. The investigated isomers exerted higher activity against canine lymphoma/leukemia cell lines than against mammary tumors, whereas the configuration of stereogenic centres of the examined compounds affected their activity.

Stereoisomers with the 4*S* configuration shown to be were more active, with the cis-(4*S*,5*S*,6*R*) isomer as the most potent. The investigated δ-iodo-γ-lactones act as an anticancer agent by the induction of apoptosis of canine cancer cells via a mitochondrial-mediated, caspase-dependent pathway [97].

5. Conclusions

Chirality has become a major task for the synthesis and development of drugs. One enantiomer of a chiral drug may be a medicine for particular disease

whereas; another enantiomer of the molecule may be not only inactive but can even be toxic. The pharmacological activity of chiral drugs depends mainly on the drug's interaction with chiral biological molecules such as proteins, nucleic acids and bio membranes. This is valid not only for organic drugs, but also for metal-based drugs which are developed for anticancer application. This review outlines the effect of chirality on the efficiency of anticancer metal-based drugs and interesting potential organic chiral drug molecules. The influence of stereoselectivity on anticancer activity can hardly be generalized, it is manifested specifically for each individual chiral compound and depend on the type of cellular targets. However, knowledge of the stereochemistry of anticancer compounds can influence some critical processes underlying their toxicity towards cancer cells and provide a rational basis for the design of new antitumor drugs.

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Conflict of interest

The authors declare no conflict of interest.

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