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Chiral metallic anticancer drugs: A brief-review

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REVIEW ARTICLE

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ABSTRACT

Chiral metallic drugs are becoming the hottest point of discussion in the field of medicinal chemistry. As we know that more than 80% drugs are chiral in nature, and prescribed in the racemic form. The main problem with chiral drugs is the different biological activities of different enantiomers. This is because the human body has a chiral environment, as there is the presence of protein, carbohydrates, enzymes, and other chiral macromolecules. Hence, if a chiral anticancer drug is being prescribed to the patient in the racemic form, it means two or more drugs are being prescribed. Therefore, the chiral separation and analysis of chiral anticancer drugs are important for improving the quality of chiral drug medication. Many metal complexes are used as anticancer drugs, but the conditions become more critical if they have chirality or a chiral moiety, because of which they exist in two or more forms. Because of the presence of chirality or chiral moiety, the complex of metals is termed a chiral metallic complex. Of course, the enantioseparation of the chiral metallic complexes must be done before their prescription. Enantioseparation of the chiral metallic complex will not only provide a pharmaceutically active form to the patient but also reduce the side effects caused by the racemic mixture. Hence, the accessible article reviews the chiral metallic complexes having ruthenium, osmium, palladium, gold, silver, and platinum, *etc*. as central metal atoms. Besides, the future perspectives regarding the chiral metallic anticancer drugs and the role of their enantioseparation are also discussed.

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1. Introduction

Cancer is a very dangerous disease for which a large number of drugs are available in the market. Many of them are lab synthesized [1,2], while some of them are plant isolated [3-5]. A class of drugs that has attracted many scientists involves chirality, due to which they exist in more than one enantiomeric form [6]. Chirality is found in those drugs which have at least one chiral center because of which they exist in more than one form. The most interesting point regarding chiral drugs is the different biological activities of different enantiomers of such drugs [7,8]. Hence, it becomes a great challenge for researchers to find the most biologically active enantiomer of a chiral drug. Not only the removal of the side effect causing enantiomers but also the prescription of the biologically active enantiomer of a chiral drug makes the treatment of cancer improved and superior. Hence, the enantiomeric separation of chiral drugs is very important. It was Louis Pasteur, a French chemist and biologist who laid the foundation of chiral chemistry in 1848 by handpicking the separation of a mixture of two isomers of sodium ammonium tartrate [9,10]. Unfortunately, it took about 100 years to come under this new phenomenon of chirality that plays a pro vital role in plant and animal life along with agricultural, pharmaceutical, and other chemical industries. Amino acids, enzymes, proteins, nucleosides, carbohydrates, hormones, and numerous alkaloids are almost chiral. Hence, the human body environment is chiral due to which stereoselective binding of different enantiomers of chiral drugs takes place differently. Approximately 80% of the drugs available on the market are chiral in nature [11-26]. Therefore, enantiomeric forms of a chiral drug show differences in pharmacology, metabolism, pharmacokinetics and toxicology, *etc*. The type of biological environment is directly related to the mechanism of chiral drugs.

Chirality is one of the significant and inevitable topics in the world of research as well as in pharmaceutical companies. One of its pieces of evidence is the 2001 Nobel Prize in chemistry given to three scientists Dr. William S. Knowles, Pr. K. Barry Sharpless from USA and Pr. Ryori Nyori from Japan for their development of asymmetric synthesis using chiral catalysts in the production of a single enantiomer of chiral drugs or chemicals [27]. Chiral separation of compounds with an extensive range of new technologies has US Food and Drug Administration (FDA) endorsed for the evaluation of each enantiomer of racemic drugs *in vivo*. It also encourages the synthesis and development of new chiral drugs of a single enantiomer [28-30]. Today, one-third of total drugs are chiral, including hydroxylated enones [31], the next generation of platinum drugs [32], asymmetrically synthesized 1,2,4-trioxane [33], *etc*. Worldwide sales of single-enantiomeric formulations from 2001 to 2005 are given in Table 1.

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Table 1. Worldwide sales of final formulation of single-enantiomer pharmaceutical products.

Therapeutic category	2000 Scales (in $ billions)	2004 Scales (in $ billions)	2005 Scales (in $ billions)	CAGR (%) * 2000-2005
Cardiovascular	27.650	34.033	36.196	6
Antibiotic and antifungal	25.942	32.305	34.298	6
Cancer therapeutics	12.201	21.358	27.172	17
Hematology	11.989	20.119	22.439	13
Hormone and endocrinology	15.228	20.608	22.355	8
Central nervous system	9.322	17.106	18.551	15
Respiratory	6.506	12.827	14.708	18
Antiviral	5.890	11.654	14.683	20
Gastrointestinal	4.171	11.647	13.476	26
Ophthalmic	2.265	3.063	3.416	9
Dermatological	1.272	1.486	1.561	4
Vaccines	1.427	2.450	3.100	17
Other	7.128	10.400	13.268	13
Total	130.991	199.056	225.223	11

*CAGR is a compound annual growth rate. This information is from Technology Catalysts International.

Table 2. Top-selling single-enantiomer drugs worldwide in the year 2005 scales *.

Company	Brand name	Active pharmaceutical ingredient	2005 Scales (in $ billions)
Pfizer, Astellas	Lipitor	Atorvastatin	12.986
Sanoti-Aventis, Bristol-Myers Squibb	Plavix	Clopidogrel	6.345
Amgen, Johnson & Johnson	Epogen, Procrit	Epoetin alfa	5.799
Glaxo Smith Kline	Advair, Seretide	Fluticasone & Salmeterol	5.465
Genentech, Roche	Rituxan, Mab Thera	Rituximab	5.166
AstraZeneca	Nexium	Esomeprazole	4.633
Merck & Co.	Zocor	Simvastatin	4. 382
Daiichi Sankyo, Bristol-Myers Squibb	Mevalotin or Pravachol	Pravastatin	3.844
Novartis	Diovan	Valsartan	3.676
Amgen, Wyeth	Enbrel	Etanercept	3.567
Johnson & Johnson, Schering-Plough	Remicade	Infliximab	3.477
Amgen	Aranesp	Darbepoetin alfa	3.276
Pfizer	Zoloft	Sertraline	3.256
Merck & Co.	Singulair	Montelukast	2.976
Sanofi-Aventis	Lovenox	Enoxaparin	2.668
Genentech, Roche	Herceptin	Trastuzumab	2.469
Amgen	Neulasta	Pegfilgrastim	2.288
Lundbeck, Forest Laboratories	Cipralex or Lexapro	Escitalopram	2.043
Pfizer	Zithromax	Azithromycin	2.025
Sanofi-Aventis	Taxotere	Docetaxol	2.003
Sanofi-Aventis	Eloxatin	Oxaliplatin	1.947

* Sources from Technology Catalysis International and Company Information.

Additionally, the single enantiomeric forms sold globally in the year 2005 scales and the names of the companies that produced and marketed these drugs are given in Table 2.

Because of the above observation, the pharmacokinetic outlines of enantiomeric drugs administered as a racemate might diverge [34]. In the presented article, our main focus is the chirality of chiral metallic anticancer drugs and their relationship with a cancer diagnosis.

2. Chiral-based metal complexes as anticancer agents

Of course, during the drug deposition process, stereoselectivity is observed if the drug is taken in the racemic form. This is because different enantiomers of chiral drugs behave differently with chiral targets/environments such as plasma proteins [26]. Therefore, enantioselective drug deposition occurs in the case of chiral drugs. The reason behind the different enantioselective depositions is the different arrangements of atoms in chiral drugs. Thereafter, chirality becomes a remarkable tool for modern drug discovery and development. Metal-based compounds are also isomeric as their structures have the same molecular composition with different spatial arrangements [35]. The chirality of metal complexes was restricted/limited to its application in asymmetric catalysis, and chiral chemical transformation was notably a powerful approach [36]. According to Dwyer *et al*. [37], the metal complexes with chirality had an intrinsic relationship with their biological activities. A large number of scientists are associated with the development of metal-based chiral complexes and their anticancer portfolio [38]. Many metals such as platinum, ruthenium, osmium, gold, iridium, rhodium, *etc*. have been investigated in the context [39]. Their oxidation states, the stable number of ligands, and the coordination number are being studied for the chiral metallic complexes to make them perfectly chiral and more importantly stable [35-39]. Some of the metal complexes of ruthenium, osmium, palladium, gold, silver and platinum, are discussed below. These metals in complex compounds have been used as a central metal atom which are discussed briefly as follows:

2.1. Chiral complex of platinum

One of the leading examples of Pt-based chiral anticancer drugs is oxaliplatin {Pt(II)} [40]. Oxaliplatin has two chiral centers, hence, it exists in four enantiomeric forms. The most biologically active form among the four enantiomers is ((*R*,*R*)-cyclohexane-1,2-diamine), while other forms are not active. [40]. In 1970, when *cis*-platin was being tested in initial human trials, a lot of platinum complexes were synthesized side by side to study the relationship between chemical structure and anticancer activity in murine systems [40]. A great breakthrough came when carboplatin and oxaliplatin were approved by FDA [41] (Figure 1) in the years 1989 and 2002, respectively. Carboplatin has the same result as that of *cis*-platin, but the activity of oxaliplatin showed a wide variety in contrast to the former two platinum species [41]. Oxaliplatin was found effective against colorectal cancer and resistant to malignancy of cancer [41]. Also, it was not effective against squamous cell carcinomas [41]. Regionally different species of the platinum complex were used, such as lobaplatin in China, heptaplatin in Korea, and nedaplatin in Japan [42,43].

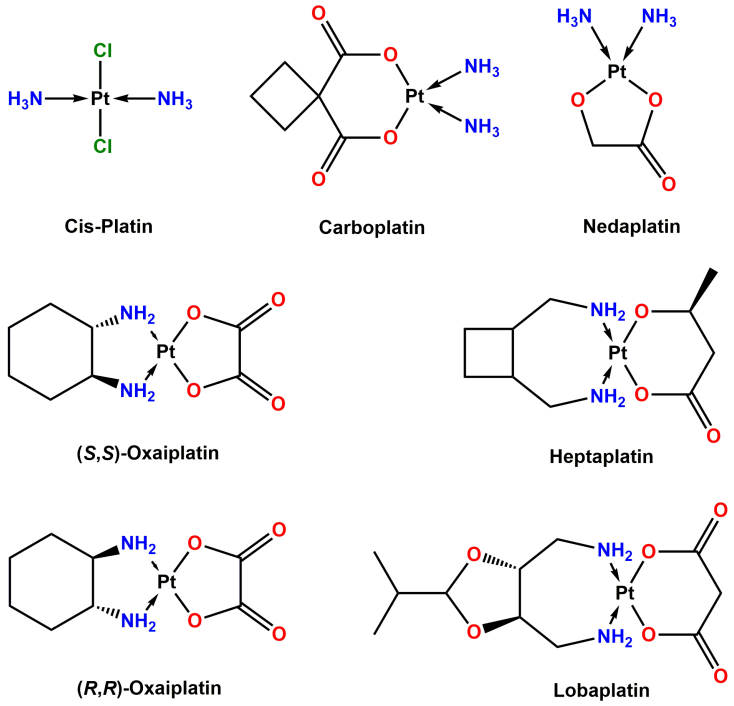

Figure 1. Platinum-based chiral anticancer drugs.

Many strategies were tested for (i) reduction of their toxicity [43], (ii) improvement in tumor targeting [44], (iii) improvement in biological targeting [45], and (iv) modification of the properties of DNA interaction [46]. The synthesis of some new platinum (II) complexes based on (Δ)- and (Λ)-1,2–bis-(1*H*-benzimidazol-2-yl)-1,2-ethanediol (Δ-H₂bie and Λ-H₂bie) enantiomers was reported [47]. Subsequently, the anticancer activities of all synthesized complexes were tested against human breast cancer cell lines (MDA-MB231) and ovarian cancer (OVCAR-8) [47]. It was found that the Δ-H₂bie complexes were showing the highest anticancer activity in the taken cell lines [47]. Oxaliplatin got publicity within all platinum species due to its intrinsic stereochemistry [41]. Due to the presence of 1,2-diaminocyclo-hexane (1,2-DACH), Pt (II) complexes also exist in more than one enantiomeric form *i.e.*; [PtCl₂(*R*,*R*-,*S*,*S*-, and *R*,*S*-DACH)]. It is because 1,2-diaminocyclo-hexane has two chiral centers. The variation in anticancer activity, as well as the cytotoxicity of four enantiomeric forms, was directly related with their stereochemical structures. The study of variation in different aspects was done by the national cancer institute (NCI)-60 cancer cell line panel [47]. NCI possesses the data of 60 human cancer lines (https://dtp. cancer.gov/discovery_development/nci-60/). This data gives us the diverse potential growth inhibitors (GI) of these three isomers. The GI_{50} value calculation shows [PtCl₂(*R*,*R*-DACH)] (1.37 μM), [PtCl₂(*S*,*S*-DACH)] (6.38 μM) and [PtCl₂(*R*,*S*-DACH)] (11.6 μM) [47]. Among these, only [PtCl₂(*R*,*R*-DACH)] is under clinical trials. As we know that proteins are chiral structures, enantiomers of chiral drugs show different anticancer activities [47].

2.2. Chiral complex of gold

Stereoselective carbenes are being developed and designed with the starting material, chiral *N*-heterocyclic ligands, for their application in organic synthesis [48]. Recently, many pharmaceutical applications of *N*-heterocyclic carbene (NHC) Au(I) complexes have been observed, including antitumor therapy [49]. Mullick *et al.* studied the *in vitro* anticancer activity of the chiral NHC dinuclear Au(I) isomer with the chiral ligand (Figure 2) [50]. The cytotoxicity of the racemic complex was confirmed against human tumor cell lines such as HeLa cervical carcinoma and NCI-H23 lung adenocarcinoma) [50]. Besides, the different enantiomeric anticancer activity of the synthesized chiral metallic complex was done on healthy cells such as human embryonic kidney cells (HEK 293) and bronchial epithelial cells (HBE 135-E6E7). [50]. The racemic mixture showed discreetly cytotoxicity against cell lines, side by side two pure enantiomers (*S*,*S*,*S*,*S*)- and (*R*,*R*,*R*,*R*)-posed questions and further investigation was required. In addition, Li *et al*. [51] studied the P-stereogenic phosphine ligand-based enantiomeric complex. The pure Au(I) enantiomers were observed (Figure 2) and it was seen that both showed good antitumor activity against adherent and suspension cancer cells [51]. The most important and notable fact regarding the synthesized drug was the least toxicity for healthy lymphocytes. They also studied pure chiral diphosphine-digold(I) complexes [51]. Interestingly, the (*R*,*R*)-cytotoxicity was found to be similar to that of the (*S*,*S*)-enantiomer [51]. The (*R*,*R*)-enantiomer was found to show more toxicity (30.1%) against healthy mammary gland cells than the (*S*,*S*)-enantiomer (3.1%) under similar conditions [51]. It was just because of the stereochemistry in the NHC gold complexes that affects its biological properties [51].

2.3. Chiral complex of ruthenium

Organometallic ruthenium is a bright star in the context of chemotherapy. Several organometallic compounds of ruthenium have been synthesized and published [52-54]. Unfortunately, a fever number of chiral Ru complexes have been reported [55]. Meggers Atilla-Gokcumen *et al.* [56] and Smalley [57] reported the bidentate staurosporine ligand-based chiral Ru complex as a protein kinase inhibitor. Two purified staurosporine-type enantiomers, DW1 and DW2 (Figure 3) were separated and the anticancer activity of each enantiomer was checked [56].

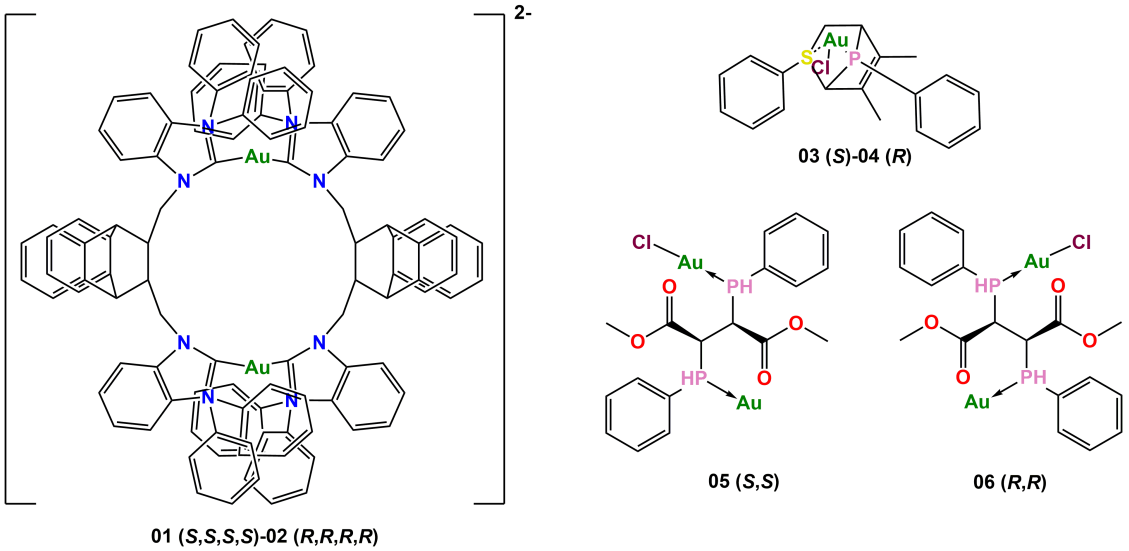

Figure 2. Gold-based chiral anticancer drugs.

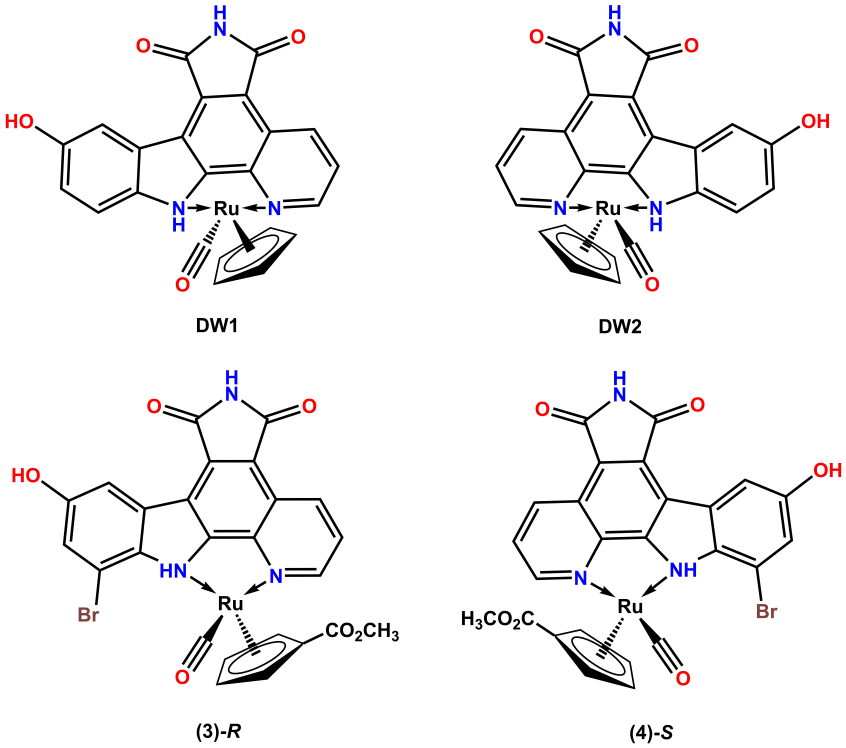

Figure 3. Ruthenium-based chiral anticancer drugs.

During the *in vitro* assay, it was found that DWI showed IC_{50} 2 and 2.5 nM for GSK-3α and GSK-3β (protein kinase inhibitors), respectively [57]. Similarly, DW2 showed IC_{50} 9 and 15 nM for the same protein kinase inhibitors at 100 μM ATP [56]. The *R*-complex (3) (Figure 3) showed not only an inhibitory effect against GSK-3β with IC_{50} = 0.35 nM but also anticancer activity at a concentration of 100 μM ATP. It was 257 times higher compared to the *S*-enantiomer (4) (Figure 3) with IC_{50} = 90 nM at 100 μM ATP [56]. Additionally, the 1205Lu melanoma cells were used to test anticancer activity for 72 h. After this study, DW1 was found to be more potent than DW2 against protein kinase inhibitors [57]. A series of new chiral Ru(II) polypyridyl complexes (1-5) with the general formula {Δ/Λ-[Ru(bpy)$_2$(X,Y-sal)]BF_4} (bpy = 2,2′-Bipyridyl; X,Y-sal = 5-bromosalicyl aldehyde (1), 3,5-dibromosalicylaldehyde (2), 5-chlorosalicyl aldehyde (3), 3,5-dichlorosalicylaldehyde (4) and 3-bromo-5-chlorosalicylaldehy (5) were also synthesized [58]. Subsequently, the anticancer activities of all synthesized complexes were tested against human lung cell lines (A549). Among all synthesized compounds, only three complex compounds (1, 2 and 5) were found as active drugs because they were showing the highest anticancer activity against the taken cell lines [58].

2.4. Chiral complex of osmium

Although scanty data was found about the osmium metallic complexes, they have shown anticancer activity, hence, they have been considered as potential anti-cancer drugs. [59,60].

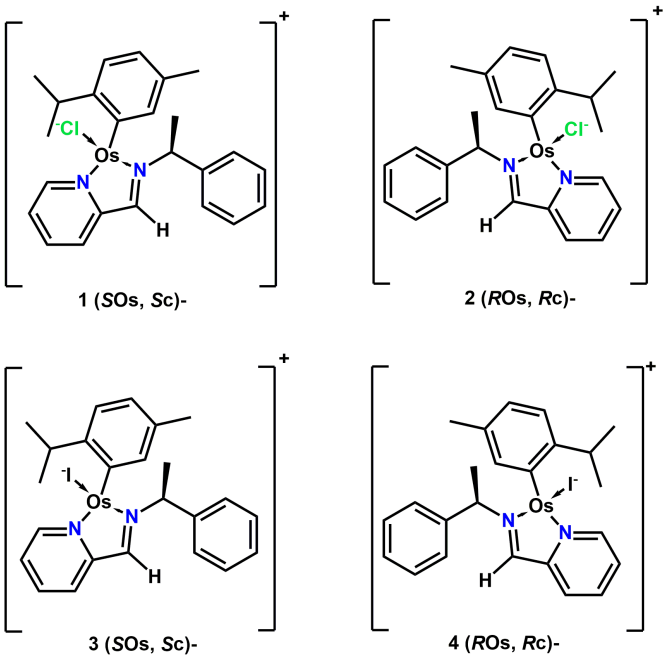

Figure 4. Osmium-based chiral anticancer drugs.

Sadler *et al.* [60] reported chiral Os(II) arene iminopyridine complexes, the derivative of two unsymmetric *R*- and *S*-ImpyMe ligands, (*R*/*S*-ImpyMe = *N*-(2-pyridylmethylene)-*R*/*S*-1-phenylethylamine). The bidentate chelating chiral ligand is utilized for the pure diastereomeric separation with configuration (*R*Os, *R*C)- or (*S*Os, *S*C)-osmium complexes by fractional crystallization (Figure 4) [60]. The osmium iodide complex (Figure 4) treatment on A2780 human ovarian tumor cells depicted its strong potential cytotoxicity as compared to the osmium chloride complex (Figure 4) which showed moderate antitumor activity [60]. The anticancer activity of the *R*-enantiomeric form of Os complex was found higher as compared to its *S*-enantiomeric form. The correct reason for it, is not known yet.

2.5. Chiral complex of silver

Silver complexes based on chirality have also shown good results in cancer treatment [61]. A research group prepared chiral silver(I) diaminocarbene complexes using imidazolium salt [62] because imidazolium and its derivatives have shown tremendous anticancer activity [1]. Besides, another research group synthesized *N*-heterocyclic carbene ligands (NHC) and their Ag(I) complexes [51]. The anticancer activity of the synthesized complexes was checked against MCF-7, MDA-MB-231 and DU-145 cancer cells [51]. After that, it was found that the Ag(I) single bond NHC complexes showed a dose and time-dependent cytotoxic activity against all cell lines. The synthesis of some new silver(I) complexes based on (Δ)- and (Λ)-1,2–bis-(1H-benzimidazol-2-yl)-1,2-ethanediol (Δ-H_2bie and Λ-H_2bie) enantiomers was reported [47]. Subsequently, the anticancer activities of all synthesized complexes were tested against human breast cancer cell lines (MDA-MB231) and ovarian cancer (OVCAR-8) [47]. It was found that the Δ-H_2bie complexes were showing the highest anticancer activity in the taken cell lines [47].

2.6 Chiral complex of palladium

The importance of Pd-complexes based on chirality can not be denied because they have a unique position in chiral complexes of transition elements [63]. Synthesis of some new palladium (II) complexes based on (Δ)- and (Λ)-1,2–bis-(1*H*-benzimidazol-2-yl)-1,2-ethanediol (Δ-H_2bie and Λ-H_2bie) enantiomers was reported [47]. Subsequently, the anticancer activities of all synthesized complexes were tested against human breast cancer (MDA-MB231) and ovarian cancer (OVCAR-8) cell lines. It was found that the Δ-H_2bie complexes were showing the highest anticancer activity in the taken cell lines [47]. Some researchers investigated the influence of chirality and halogen atoms on the anticancer activity of enantiopure palladium(ii) complexes (J1-J8) derived from chiral amino-alcohol Schiff bases and 2-picolylamine [47]. It was found that the J2 and J4 complexes showed the highest anticancer activity.

3. The chiral drug development process

One of the striking features in the introduction of chirality in a drug moiety is the increasing complexity of specific targets, which means greater diversity of compounds must be disclosed [64]. Chiral drugs have two principal circumstances for the pharmaceutical industry: first, the conversion of racemic drugs into either of the two enantiomers [65,66] and second, the fresh (de novo) development of a pharmaceutically pure enantiomer, typically called a eutomer [67]. By developing a novel moiety for not only direct entry but also drug approval and introduction in the market, we prefer an unambiguous design. New terminology has been introduced such as NCE (new chemical entity), NBE (new biological entity), NME (new molecular entity) and NAS (new active substance) by medicinal researchers and scientists for drug discovery and development with some uncertainty. A new term, NTE (new therapeutic entity) was also suggested by Branch *et al.* [68] for a new drug design. From 1994 to 2011 (as the first scenario), the chiral switching process has been a vital component in drug development portfolios. From 2001 to 2011, one-third of the chiral switch was approved such as levocetirizine, dexlansoprazole and esomeprazole. However, there is no legal authority under the FDA to test the efficiency of a single enantiomer as compared to the previously developed racemate [69].

In the case of de novo development of a pure enantiomeric drug, three ways are followed by a pharmaceutical company to access chiral products: (1) Use of natural products (chiral pool) as a starting material for pure enantiomer synthesis, (2) employment of stereoselective synthesis that includes enzymatic and biological procedures and (3) chiral resolution (a non-stereoselective synthetic protocol) for racemic separation. In all steps mentioned above, the pharmaceutical company should have comprehensive specification data for the final product to guarantee strength, identity, purity, and quality in context with stereochemistry [70]. For initial testing, the amount of enormous molecules in milligrams is required during the discovery stage. As per FDA protocol [70], both enantiomers are to be biologically tested for the new therapeutic entity, so that the development of chiral active drugs racemate can be more appropriate than stereoselective syntheses. It is not worth the time and is cost-efficient. Non-stereoselective synthesis of a single enantiomer on a large scale reduces time and cost. For the separation of enantiomeric forms, many methods are followed such as crystallization, diastereomeric salt or complex formation, and chiral chromatography [71]. This formulation has become a better protocol for drug discovery in the pharmaceutical industry and has been shown to be an accelerator in drug development [71,72]. A lot of transformations occurred significantly for the potential API (Active Pharmaceutical Ingredient) processer in the year 2015 [73]

4. Toxicology

It cannot be denied that different enantiomers of a chiral drug frequently have large differences in pharmacodynamics and pharmacokinetics. It may lead us to stereoselective toxicity. One of the enantiomeric forms of a chiral drug is the form of interest, whereas the other form is not. This decides the toxicity of that enantiomer which is not of interest [74]. The best example is Dopa (dihydroxy-3,4 phenylalanine) which acts as a dopamine precursor for Parkinson's disease treatment [75]. The Dopa availability in the market is in the racemic form (D,L), the D-isomer has severe toxicity causing agranulocytosis, whereas L-Dopa i.e; levorotatory acts as the therapeutic agent. One more example is tetramisole (nematocide) firstly used in racemic form. It causes many side effects such as headache, vomiting, vertigo, and abdominal pain, due to its d-isomer. In contrast, its l-isomer, namely levamisole, is used in medicine [75]. There are so many chiral drugs in the market that exhibit toxic effects [76], and are still to be enantioseparated. Many chiral anticancer drugs are cytotoxic due to their chemical reactivity [76]. It is not a surprise that many anticancer drugs have toxicities toward healthy cells [76]. Therefore, an approach to reduce stereo-selective toxicity must be exploited. One of the examples is cyclophosphamide with a chiral center at the phosphorous atom, due to which it exists in more than one enantiomeric form [76]. According to Cox *et al.* [77], the (D)-enantiomer showed two times greater therapeutic index (LD50/ID90) as compared to the (1)-enantiomer against the ADJ/PC6 cell turnover in mice. However, there was no significant therapeutic advantage gained using a single enantiomer.

5. Pharmacokinetics and metabolism

The proper procedures of absorption, distribution, elimination, and metabolism are the vital variable of drug action at the receptor site *in vivo*. The discernment potential between two enantiomers at every stage of proper procedure provides us the relevant information about stereospecific and stereo-pharmacokinetics drug assays [78]. The pharmacokinetics and metabolic profile differences in two enantiomers of chiral anticancer drugs can be demonstrated qualitatively as well as quantitatively [79-85]. According to Mehvar *et al.* [83], many racemic drugs are available such as tocainide, mexiletine, flecainide, propafenone, encainide, disopyramide *etc*. The first step of ADMET for these chiral drugs appears to be non-stereoselective. However, the other variables such as distribution, metabolism, and renal excretion respond to one enantiomer as compared to others. In distribution, blood plasma protein binding is stereoselective for most of the chiral drugs mentioned above leading to double-fold variances between two enantiomers [82,86].

6. Conclusions

In the pharmaceutical industry, the enormous availability of only a single enantiomer in the market makes it not only strong but also better tolerable for cancer treatment. Hence, before launching a chiral drug into the market, the enantiomeric forms must be separated by a pharmaceutical company. There are many cases noted where only one enantiomer has more therapeutics than the other enantiomers. Hence, the separation of enantiomeric forms of a chiral compound must be done first, so that a single biologically active form can be provided to the patient. Noticeably, it will reduce the toxicity caused by a racemic mixture. Of course, the metal-based complexes are also an active part of the chiral family because of the chiral moiety. It is a growing field of research in the discovery of anticancer drugs. The metals used are ruthenium, osmium, palladium, gold, silver, and especially platinum, which are highly active in many anticancer drugs.

7. Future perspectives

Of course, the body of all living things is suitable only for one of the more enantiomeric forms of chiral drugs. New nano-formulations of chiral anticancer drugs are required for future perspectives. In addition, new methods of enantiomeric separation are to be developed for special racemic anticancer drugs. Spirocyclic oxindoles are another promising drug that is a potent inhibitor of the p53-MDM2 interaction. Different heterocyclic substituents attached to the core of oxindoles led us to discover and develop new chiral anticancer drugs. Overall, in the pharmaceutical market, single enantiomeric drugs will grow, and their higher growth will mature the medicinal market in the case of cancer treatment in the modern era.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.

CRediT authorship contribution statement

Conceptualization: Mohammad Suhail; Writing - Review and Editing: Mohammad Suhail; Literature survey: Sofi Danish Mukhtar.

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