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Platinum-based anticancer agents: structure-activity relationship and action mechanism. Research on how to overcome cancer cells resistance

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Als meus pares i el meu germà, ja que sempre m'han donat aquest impuls quan em feia més falta.

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Als meus companys de Fuchs, ja que des del principi m'han mostrat un suport i interès constant i m'han animat en els moments més estressants.

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REPORT

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1. SUMMARY

Platinum complexes are drugs that are usually used in chemotherapy to try to kill cancerous cells of all kinds and different types of cancers.

Even though there are several platinum drugs approved by the FDA (Food and Drug Administration) and in clinical use, there are still thousands of studies trying to develop new platinum complexes. This is due to the existent resistant mechanisms produced by cancerous cells that inhibit these drugs, and for the several side effects that produce towards the human body.

The goal of this study is to recollect all the novel platinum complexes developed over the last ten years and organize then depending on their properties.

Keywords: Platinum complexes, Cancer

2. RESUM

Els complexos de platí són medicaments que s'utilitzen habitualment en quimioteràpia per intentar matar cèl·lules canceroses de tota mena i de diversos tipus de càncers.

Tot i que existeixen uns quants complexos de platí aprovats per la FDA (Food and Drug Administration) i que s'utilitzen actualment a la clínica, hi ha encara milers d'estudis que intenten desenvolupar nous complexos de platí. Això és pel fet que els complexos de platí utilitzats en la clínica tenen diversos mecanismes de resistència, produïts per les cèl·lules canceroses i que inhibeixen el medicament i també pels diversos efectes secundaris que produeix.

L'objectiu d'aquest treball és recopilar tots els nous complexos de platí desenvolupats Durant els últims deu anys i organitzar-los segons les seves propietats.

Paraules clau: Complexos de platí, càncer

3. INTRODUCTION

Cancer is a disease, which is responsible for one in eight deaths around the world.[1] It is a complex disease with common features including uncontrolled cell growth, reduction of apoptosis and loss of cell cycle regulation.[2]

Cancer cells are known as the basis of cancer disease. These cells initiate tumors by carrying mutations in oncogenes and tumor suppressor genes. Some of the hallmarks of cancer cell are sustained proliferation, evasion growth of suppressors, the activation of metastasis and invasion through the inhibition of cell-cell contact and cell-matrix contact, induction of angiogenesis, uncontrolled replicative potential and immortality. [3]

The anticancer activity of cisplatin, the firs drug of this type, was discovered several decades ago. It was discovered that cisplatin showed antitumor activity against sarcoma 180 and leukemia L1210 cells. Cisplatin was the first member of platinum (II) based complexes approved by FDA in USA (Food and Drug Administration) in 1978.[4,5] Carboplatin, nedaplatin and oxaliplatin are also platinum complexes, which are actually used in clinical anticancer therapies.

Despite the fact that a few platinum (II) drugs are currently being used, with efficiency, in chemotherapy, thousands of studies are being made in order to develop new platinum anticancer drugs that may overcome cancer cells resistance mechanisms, which disable the action of these drugs against cancerous cells.[6] Another disadvantage of the use of these complexes are the adverse side effects such as nephrotoxicity, myelosuppression, neurotoxicity, ototoxicity, nausea, vomiting, and other adverse effects.[7]

When searching on Scifinder about this research field it is possible to find more than 42.000 references that contain the concept of anticancer platinum complexes. This fact reflects the general interest in the research and development of these compounds.

4. OBJECTIVES

The purpose of this study was to evaluate the advances of the research in anticancer platinum-based drugs in the last decade.

To try to delimit the 42.316 references found, related to platinum complexes and cancer, a criteria was stablished.

First of all, Scifinder was selected as the scientific database of references and only the articles published in the last ten years (2009-2019) were selected.

The topic "platinum complexes and anticancer agents" was the first combination of closely related keywords to delimit the articles of interest having a total of 7198 references. When the period of time was selected, this number of articles decreased to 3768. Finally, the search was filtered to the ones written in English and that were books, journals, patents or reviews having a final number of 3243 articles in the global search.

Once a global search was made, several searches were made individually to delimit more specific topics. These topics will be the sections of the results and discussion of the present work.

The topics searched and further analysed were:

- New action mechanisms
- New target
- New cell-death mechanism
- SAR- Structure-Activity Relationship
- Multitarget platinum drugs
- Decrease of toxicity by design
- New clinical applications of platinum-based drugs

5. RESULTS AND DISCUSSION

5.1. NEW ACTION MECHANISMS

In pharmacology, the term mechanism of action is used to describe the process by which a molecule functions to produce a pharmacological effect. In terms of platinum complexes, the most common mechanism of action is that of cisplatin that binds to DNA and forms covalent cross-links.[8] However, despite being the most common, this mechanism of action produces several adverse side effects and has developed resistance for some kind of cancers.

That is the reason why there is the need to synthesize new platinum drugs that present different mechanisms of action to improve their efficiency and to decrease the side effects and resistance, preferably if they interact with specific molecular targets other than DNA.[9]

5.1.1. Affection of the mitochondrial apoptotic signalling

The platinum (IV) complex, illustrated in Figure 1, has been tested along with an apoptosis inducing ligand named TRAIL to try to decipher its mechanism of action.

It has been demonstrated that this complex is able to enhance the sensitivity of human prostate cancer cell lines to TRAIL-induced cell death by mitochondrial apoptosis pathway and this way it is more effective compared to the individual action of the platinum drugs alone. [10]

This Pt(IV) complex was also tested against colon cancer cells and a novel molecular mechanism responsible for cooperative action of Pt(IV) drug and TRAIL was uncovered, demonstrating that this complex was able to lower the threshold for triggering mitochondrial apoptotic signaling.[11]

It is also known that the evaluated Pt(IV) complex disrupts cellular proliferation regardless of the p53 status in the cells, but the potency of the drug is enhanced by the presence of functional p53, which indicates several mechanisms of action. The interaction with molecular chaperone Hsp90 was also studied and it was found that Pt(IV) complex induced degradation of other Hsp90 client proteins such as Cyclin D1 and estrogen receptor. Thus, new platinum-based drug proved to be more efficient in comparison with cisplatin. These results open opportunities to design new anticancer drugs that combine DNA damaging and Hsp90 inhibitory effects.[12]

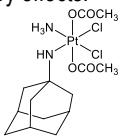


Figure 1. Chemical structure of platinum (IV) L-12 complex.

5.1.2. Inhibition of COH-2: Trans-Dichlorido[(rac)-2-(5-(dimethylamino)naphthalene-1-sulfonamido) cyclohexylamino] (dimethylsulfoxide) platinum(II)

This complex was synthesized to compare its cytotoxic effects with that of cisplatin and against two human melanoma cells that differed in their TP53 status.

It was discovered that, while combined, both cell lines where inhibited and that the new complex presented in vitro antitumor activity against melanoma cell lines with a different mechanism of action from that of cisplatin.

It has been proven that the complex induces cell cycle G1 arrest mediated by CDKN1A and CDKN1B that bind to CDK2 after the trans-sulphonamide complex treatment, inhibiting CDK2 activity.[13] The chemical structure of this complex is illustrated in Figure 2.

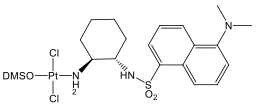


Figure 2. Chemical structure of trans-Dichloro[(rac)-2-(5-(dimethylamino) naphtalene-1-sulfonamido) cyclohexylamino] (dimethylsulfozide) platinum (II).

5.1.3. Interference of the catalytic activity of topoisomerase II: trans-[PtCl2(PPh3) {NH(Bu)(CH2Ph)}]
When this complex was first synthesized, it was assumed that it had the same mechanism of action as cisplatin. However, when the cytotoxic effects were tested it was confirmed that this complex was able to overcome the resistance of A2780cis, which are cisplatin-resistant ovarian cancer cells, and was able to induce apoptotic pathway in a dose-dependent manner, which suggested a different mechanism of action with respect to cisplatin. This complex is also able to interfere with the catalytic activity of topoisomerase II.[14] The mentioned complex is illustrated in Figure 3.

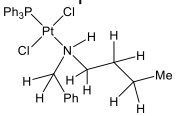


Figure 3. Chemical structure of trans-[PtCl2(PPh3) {NH(Bu)(CH2Ph)}].

5.1.4 Anticancer Potency of Platinum (II) Complexes Containing Both Chloride Anion and Chelated Carboxylate as Leaving Groups
Three platinum complexes bearing both a chloride anion and a chelated carboxylate as leaving groups where synthesized and spectrally characterized. The three compounds showed good cytotoxicity against the cell lines tested and produced death of tumor cells through an apoptotic pathway. The mechanism of action was slightly clarified when the kinetics studies were made. In those, it was concluded that the chloride anion departed from the Pt atom quickly, whereas the five or six-membered ring formed by coordination of N, O donors and the metal ion was opened a little more slowly by the rupture of the Pt-O bond.[15] The three compounds are illustrated in Figure 4.

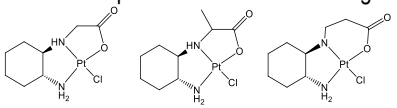


Figure 4. Chemical structure of platinum complexes containing chloride anion and chelated carboxylates as leaving groups.

5.1.5 Diazido Mixed-Amine platinum (IV) complexes
Several diazido mixed-amine platinum (IV) were synthesized. Four of these synthesized complexes, which are illustrated in Figure 5, presented evidences that showed that they function through a different mechanism of action as the one of cisplatin. One of those tests was high mobility group protein B1 with a gel mobility shift assay. This high mobility group B1 exhibited no detectable binding to the complexes synthesized while it was strongly binded to cisplatin. This result indicated that these complexes present different mechanisms of action that of cisplatin.[16]

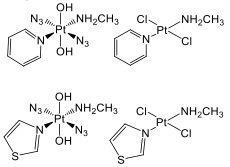


Figure 5. Chemical structures of the diazido-amine platinum (IV) complexes tested.

5.1.6 β-aminoethylferrocenes heterometallic-platinum (II) complexes

Some heterometallic compounds bearing ferrocenyl and platinum (II) were synthesized. Its cytotoxic effect was tested, and the complex illustrated in Figure 6 presented the best results in antiproliferative activity and it showed a superior activity profile in one of the most drug resistant cell lines compared to cisplatin.

To try and investigate the effects that this new compound produced on tumor cell lines, some cell cycle studies were made. In those, the results of this compound compared to cisplatin were different, indicating that the mechanism of antiproliferative activity of this compound is not affecting the cell cycle. Although it is known that the mechanism of action of this new compound is not the same as the one of cisplatin, the exact biological target is still not clear. Further studies will reveal the specific mechanism of action of this new anticancer drug. [17]

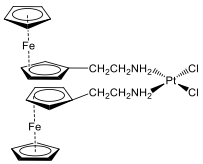


Figure 6. Chemical structure of cis-dichlorobis[1-b-aminoethylferrocene] platinum (II).

5.2. NEW TARGETS

One of the main goals of anticancer drugs research is to find new complexes that can target not only the DNA but also other cell structures. That is why many complexes have been synthesized and tested and some of them are illustrated in the following text.

5.2.1. Telomer as a target

5.2.1.1.- 5-Bromo-oxoisoaporphine platinum (II) complexes

Two complexes with 5-bromo-oxoisoaporphine were synthesized. These two complexes were more selective towards Hep-G2 tumor cells than for normal cells and they both are telomerase inhibitors that trigger Hep-G2 cell apoptosis.

It has also been studied that these two complexes could easily target c-myc/PU27 G4 to exhibit anticancer activity and disrupt mitochondrial function and thus, inducing cell apoptosis. [18]

The chemical structure of the mentioned complexes is illustrated in Figure 7.

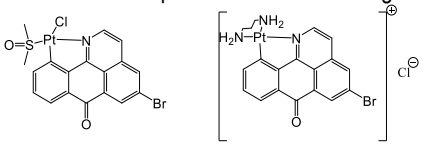


Figure 7. Chemical structure of 5-bromo-oxoisoaporphine platinum (II).

5.2.1.2.- Pt-MPQ

A platinum complex, bearing MPQ which is a G-quadruplex ligand has been synthesized. It is proven that by binding platinum to this G-quadruplex ligand the delocalization of TRF2 and TRF1 is promoted and that increases the amount of telomer damage, more than the control compound G-quadruplex ligand, thus this complex has the ability to target telomeres. [19]

The chemical structure of this complex is illustrated in Figure 8.

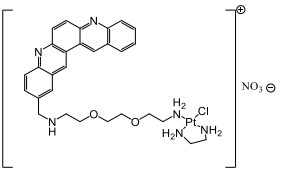


Figure 8. Chemical structure of a platinum complex bearing MPQ.

5.2.2.Luteinizing hormone releasing hormone target[20]

A platinum complex bearing a malonate linker and a luteinizing hormone releasing hormone ligand (LHRH) was synthesized in order to study its cytotoxic effect over cancer cell lines and to target the overexpression of the LHRH receptor on cancer cells relative to normal tissue.

Some early studies have shown that LHRH receptors are overexpressed in breast, prostate, endometrial and ovarian cancers in comparison to normal cells.[21]

Results indicate that this complex (Pa-Mal-LHRH) increases potency, efficacy, and selectivity towards breast cancer cells overexpressing the LHRH receptor compared to carboplatin. The complex mentioned is illustrated in Figure 9.

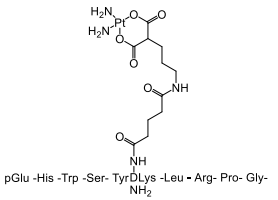


Figure 9. Chemical structure of Pt-Mal-LHRH

5.2.3. Transmembrane glycoprotein type I- mucin 1 (MUC1)

Recent studies have shown that transmembrane glycoprotein type I-mucin 1 is overexpressed in tumors of epithelial origin and especially in breast cancer. The new strategy of cancer targeting is to combine monoclonal antibodies with chemotherapeutic agents, in particular with Pt2(4-ethylpyridine)4 (berenil)2 which is illustrated in Figure 10.

Results showed that anti-MCU1 combined with this platinum (II) complex strongly induces apoptosis in breast cancer cell line. This effect was also stronger than using the platinum complex or anti-MCU1 by themselves, and the strongest DNA fragmentation was also shown while combined. [22]

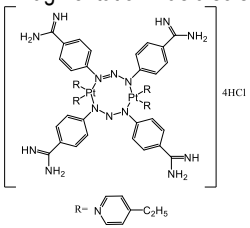


Figure 10. Chemical structure of the complex Pt2(4-ethylpyridine)4 (berenil)2.

5.2.4. Glucose Transporter target (GLUT's)[23]

5.2.4.1.Sugar conjugated (trans-R, R-cyclohexane-1, 2-diamine)-2-halo-malonato-platinum(II) complexes

A series of sugar conjugated (trans-R, R-cyclohexane-1, 2-diamine)-2-halo-malonato-platinum(II) complexes were designed and synthesized to target tumor-specifics glucose transporters.
These complexes presented a better water solubility compared to cisplatin and despite this fact these complexes presented a notable increase in cytotoxicity in six human cell lines.
Results have shown that these complexes can be recognized by the glucose recognition binding site of GLUT1 and their cell killing effect depends on the GLUT1 inhibitor.
The chemical structure of some of these platinum-sugar conjugated complexes are illustrated in Figure 11.

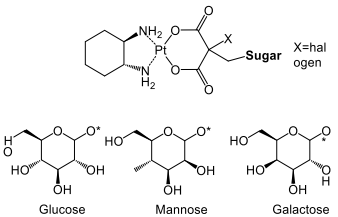


Figure 11. Chemical structure of trans-R, R-cyclohexane-1,2-diamine)-2-halo-malonato- platinum (II).

5.2.4.2.Cis-2-methlymalonato(trans-R,R-cyclohexane-1,2-diamine) platinum (II) complex[24]
The complex Cis-2-methlymalonato(trans-R,R-cyclohexane-1,2-diamine) platinum (II) was synthesized to target GLUT inhibitors. This complex presented more solubility than the common platinum drugs but despite this fact it presented more cytotoxicity in six cancer cell lines compared to cisplatin and oxaliplatin. The chemical structure of this complex is illustrated in Figure 12.

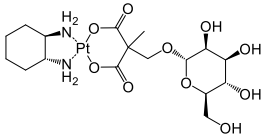


Figure 12. Chemical structure of the complex cis-2-methlymalonato (trans-R, R-cyclohexane-1,2-diamine) platinum (II).

5.2.5.Translocator protein (TSPO)[25]
Recent studies have shown that the translocator protein is overexpressed in many types of cancers and its really abundant in activated microglial cells occurring in inflammatory neurodegenerative diseases.
Several platinum complexes bearing the TSPO-selective ligand 2-(8-(2-(bis-(pyridin-2-yl methyl)amino)acetamido)-2-(4-chlorophenyl)H-imidazo[1,2-a]pyridin-3-yl)-N,N- dipropylacetamide were synthesized and when tested they showed to be able to induce apoptosis in C6 glioma cells. The chemical structure of the complex studied is illustrated in Figure 13.

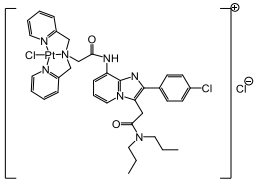


Figure 13.Chemical structure of a platinum complex bearing a TSPO-selective ligand.

5.2.6. Her 2-overexpressing SK-BR-3 cancer cells[26]

A report of a new series of Herceptin-platinum (II) complexes was made. These complexes are able to inhibit the growth of a wide panel of human cancer cell lines showing good cytotoxicity. In addition, they induce apoptosis in these cancer cell lines. An illustration of some of these complexes is shown in Figure 14.

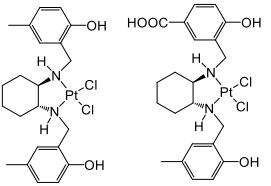


Figure 14. Chemical structure of platinum (II) complexes bearing Herceptin.

5.3. CELL DEATH MECHANISMS INDUCED BY PLATINUM-BASED ANTICANCER DRUGS

When designing an anticancer drug, it is interesting to know which cell death mechanism is inducing the drug, because it has clinical consequences. For example, a cell death mechanism by necrosis generates the degradation of all cell organelles with liberation of allergenic molecular fragments. This has as a consequence the inflammation of tissues and many other side effects. For this reason, its preferable an apoptotic mechanism of programmed and controlled cell death.

There have been discovered up to thirteen different cell death mechanisms, among of them three are the most important ones: Apoptosis, necrosis and autophagy. We present here representable examples of platinum complexes inducing cancer cell death by these three mechanisms.

5.3.1. Apoptosis

Apoptosis is a term used to describe chemical-induce cell death. The ability to modulate the life or death of a cell is recognized for its immense therapeutic potential and it is the most desirable cell death mechanism when designing an anticancer drug.[27]

5.3.1.1. Platinum (IV) prodrug containing glutathione S-transferase inhibitor ligand[28]

A platinum (IV) complex bearing a glutathione S-transferase inhibitor ligand was synthesized and an apoptosis study was made. It was stated that this complex could trigger cell death via an apoptotic pathway and arrested the cell cycle of sensitive A549 cells at G2/M phase, while mainly arrested the cell cycle of resistant A549/DDP cells at S phase. The complex could down-regulate B-cell lymphoma-2 and upregulate cleaved poly(ADP) ribose polymerase in the cisplatin resistant cells. The chemical structure of the complex studied is illustrated in Figure 15.

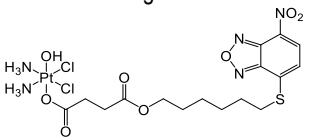


Figure 15. Chemical structure of platinum (IV) prodrug containing glutathione S-transferase inhibitor ligand.

5.3.1.2 Platinum (II) complexes having 2-[(Methylamino)methyl]pyridine ligands [29]

Other examples of complexes that induce apoptosis are Pt(II) complexes having 2-[(Methylamino)methyl]pyridine (MAMP) as a carrier ligand. The results of cell cycle analysis that were

made indicate that A549 cells are extremely susceptible to the anti-proliferative effects of the complexes studied and also induce cell death.
For some of the complexes, the G2/M phase arrest is prominently dose-dependent. The cancer cell death mechanism was evaluated by caspase 3 activity assays, which indicated that the cell death proceeds via caspase 3 activation, the major factor for apoptotic cell death pathway.
The chemical structure of the complexes studied are illustrated in Figure 16.

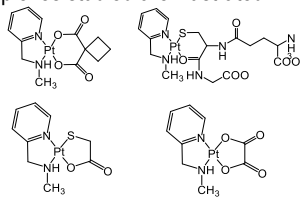


Figure 16. Platinum (II) complexes having 2-[(Methylamino)methyl]pyridine ligands.

5.3.1.3 Platinum(IV) complexes conjugated with phenstatin analogue as inhibitors of microtubule polymerization[30]

In the present example, the studied platinum complexes have a desirable target: DNA and microtubules. Platinum (IV) prodrugs bearing phenstatin analogues have shown to inhibit also microtubule polymerization. As a part of the study, the molecular mechanism showed that the complexes caused apoptotic cell death of human non-small lung cancer cell line through the mitochondrial cytochrome c, activating Apaf-1, down-regulating Bcl-2, up-regulating Bax, which in turn proteolytically activated downstream caspase 9, caspase 3, and PARP cleavage. The chemical structure of the complexes mentioned is illustrated in Figure 17.

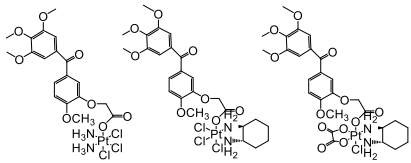


Figure 17. Chemical structure of platinum (IV) complexes conjugated with phenstatin analogues.

5.3.1.4 Binuclear platinum (II) complexes[31]
Two examples of binuclear Platinum (II) complexes, containing cis, cis-[Me2Pt (μ-N=N) (μ-dppm) PtMe2], and cis,cis-[Me2Pt(μ-N=N)(μ-dppm) Pt((CH2)4)] ligands are shown here. These complexes were tested to determine whether they were capable of inducing apoptotic death. Both complexes were able to stimulate meaningfully the activity of Caspase-3 which indicates an apoptotic cell death pathway. It was also discovered that the replacement of butylene ligand by two methyl groups proved to have a significant impact on ability of later complex to induce signaling death in the cancer cells.
The chemical structure of the complexes studied is illustrated in Figure 18.

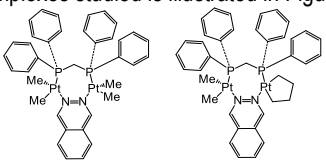


Figure 18. Chemical structure of binuclear platinum (II) complexes.

5.3.2. Autophagy

This mechanism of action plays important roles in cancer cell death via autophagosome. In most cases, cancer cells follow autophagy mediated cell death in contrast to canonical apoptotic signaling, thus activation of autophagy and autophagy mediated cellular signaling is considered important in cancer cell death.

Below an example is shown about platinum complexes that induce cancer cell death by autophagy.

5.3.2.1 ONS-donor ligand-based Pt(II) complexes[32]

The example in question are a series of platinum (II) complexes bearing ONS-donor ligands. These complexes were suspected for an autophagy cell death mechanism and thus they were tested via immunofluorescence to detect the activation of LC3B, which is an important marker of autophagy. Results showed the activation of this marker, which suggested potentials of these complexes in activation of autophagy cell death and thereby suppress the growth of cancer cells. The chemical structure of the complexes studied is illustrated in Figure 19.

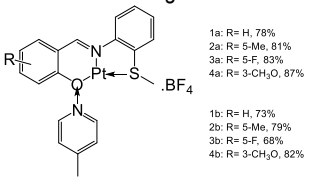


Figure 19. Chemical structure of ONS-donor ligand-based platinum (II) complex.

5.3.3. Necrosis

Necrosis is a form of cell injury, which results in the premature death of cells in living tissue by autolysis. Necrosis is caused by factors external to the cell tissue, such as infections, toxins, which results in the unregulated digestion of cell components. Cell death by necrosis makes some receptors be activated, and as a result, the loss of cell membrane integrity and uncontrolled release of products of cell death into the extracellular space. This release indicates in the surrounding tissue an inflammatory response that attracts leukocytes and nearby phagocytes, which eliminate the dead cells by phagocytosis. [33]

5.3.3.1. Platinum(II) Iodido Complexes of 7-Azaindoles[34]

An example of platinum complexes inducing cancer cell death by necrosis are a series of platinum (II) bearing iodide 7-axaindoles ligands. Several tests were made, and the treatment of this complexes led to the decrease of tumor suppressor p53 amount and increase of the levels of anti-apoptotic protein MCL-1L and active pro-apoptotic from of caspase 3, which led to think that these complexes had a different cell death mechanism than cisplatin, which is apoptosis. The microscopic observations revealed necrosis as the main cell death mechanism. The chemical structure of these complexes is illustrated in Figure 20.

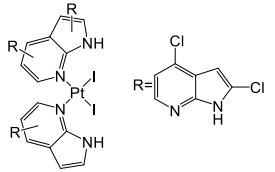


Figure 20. Chemical structure of a platinum (II) complex bearing 7-Azaindoles.

5.3.3.2. Hetero-binuclear Ir(III)-Pt(II) complex[35]

A hetero-binuclear Ir(III)-Pt(II) was developed in order to study its cell death mechanism. Some tests were made, and in vitro cytotoxicity results indicate that this complex is effective against some cisplatin-resistant tumor cells. The mechanism showed that this complex can overcome cisplatin resistance by increasing cellular uptake, target mitochondria, and inducing cell necrosis. The chemical structure of this complex is illustrated in Figure 21.

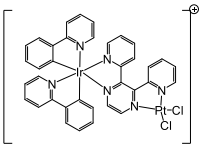


Figure 21. Chemical structure of an hetero-binuclear Ir(III)-Pt(II) complex.

5.4. STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

In order to design a drug three basics fundaments should be considered: The mechanism of action and the corresponding target biomolecules, the possible mechanisms of resistance of cancer cells and the pharmacokinetics and toxicity properties.

In general de afore mentioned mechanisms and properties depend in a great extent on the molecular structure of the active principle. The structure is then a key to a fundamental issue when thinking of a new anticancer platinum compound. A series of platinum complexes are illustrated next, discussing their structure-activity relationship. [36]

5.4.1. Tetrachlorido platinum (IV) with pyridine/bipyridine derivatives

Several platinum (IV) complexes were synthesized with different structural ligands to study its structure-activity relationship. The complexes studied are tetrachlorido platinum (IV) complexes with pyridine, 3-phenylpyridine , 2,2'-bipyridine and 4,4'-di-tert-butyl-2,2'-bipyridine.

It was discovered that octahedral platinum (IV) complexes are less reactive than platinum (II) drugs, due to their inertness. The complexes synthesized presented a reduced cytotoxic activity against some cell lines compared to cisplatin. The reason could be due to the presence of nitrogen-donor non-leaving ligands because they can improve the rate of reduction of the molecule, which is a necessary step to convert a prodrug (platinum (IV)) into a functional drug (Platinum (II) complex). Steric bulk of nitrogen ligands with branched substitution decreases the stability of the related platinum (IV) complexes and can lead to an increase in the cytotoxic activity of these complexes.

Previously [37] it was stated that bulky equatorial ligands destabilize the six-coordinated complexes synthesized and enhances the ease of reduction. The chemical structure of these complexes is illustrated in Figure 22.

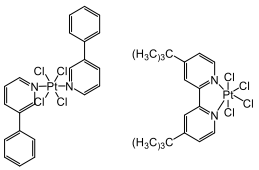


Figure 22. Tetrachlorido platinum (IV) with bipyridine/pyridine derivatives.

5.4.2. 2-Hydroxy-1-naphthaldehyde benzoyl hydrazone derivates[38]

Five platinum (II) complexes bearing 2-hydroxy-1-naphthaldehyde benzoyl hydrazone were studied to evaluate the influence of the benzohydrazine fragment in their activity. The benzohydrazine structures illustrated in Figure 23.

Its cytotoxicity was tested, and it exhibited more selective cytotoxicity than cisplatin to some tumor cells. As the main conclusion from the SAR studies of the evaluated complexes is that, the modification of aliment of the benzene ring with hydroxyl or tertiary butyl may be the responsible of the increase the antitumor activity of these complexes.

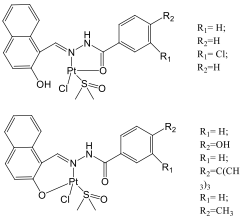


Figure 23. Chemical structure of 2-hydroxy-1-naphthaldehyde benzoyl hydrazine platinum (II) derivate.

5.4.3. Cyclometalated bipyridine platinum complexes

Some platinum compounds based on 2,2'-bipyridine were synthesized. The variation of its co-ligands on the backbone resulted in some interesting structure-activity relationship. These small modifications of the ligand scaffold affected the overall stability of the molecules and the interactions with biomolecules, but it also modified the ability of the complexes to induce distinct pathways such as DNA damage response and ER stress, etc. The chemical structure of these modifications is illustrated in Figure 24.[39]

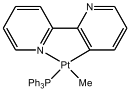


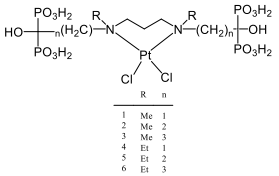
Figure 24. Chemical structure of cyclometaleted bipyridine platinum complex.

5.4.4. N,N'-bis(diphosphonate)-1,3-propanediamine-dichlorido Pt(II) complexes [40]

Some complexes bearing N,N'-bis(diphosphonate)-1,3-propanediamine-dichlorido Pt(II) complexes were evaluated for SAR studies.

Its cytotoxicity activity was tested, and it resulted to be higher than the complexes without those ligands. This fact confirms that these ligands contribute to the in vitro cytotoxicity of complexes.

It can be deduced that N, N'-dimethly substituents at the nitrogen atoms (R=H, Me) may play a role in inhibiting tumor cells and it was also stated that the preferred number of carbons in the alkyl chain between diamine moiety and the bisphosphonate group is two, based on IC50 values. An illustration of some of these complexes is shown in Figure 25. Similar studies related to long chain hydrophobic N-alkyl-diamine ligands have the same conclusions about structure-activity relationship of this kind of ligands. [41]



	R	n
1	Me	1
2	Me	2
3	Me	3
4	Et	1
5	Et	2
6	Et	3

Figure 25. Chemical structure of N,N'-bis(diphosphonate)-1,3-propanediamine-dichlorido Pt(II) complexes.

5.4.5. Platinum (IV) prodrug bearing a monoaminophosphonate ester ligand[42]

Several platinum (IV) complexes bearing monoaminophosphonate ester moiety were designed and synthesized, in order to study the structure-activity relationship, and to study the influence of the length of the carbon chain of the ligand. It was found that not only they could provide anticancer agents with bone-targeting abilities but also inhibit matrix metalloproteinases. Some of these complexes are illustrated in Figure 26.

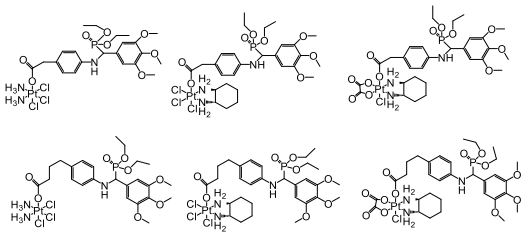


Figure 26. Chemical structure of platinum prodrugs bearing a monoaminophosphonate ester ligand.

5.4.6. Platinum (IV) anticancer agents with bicyclic 1,4-diamine ligands[43]

Fourteen platinum (IV) drugs were prepared in order to study the effect that some ligands had over its cytotoxic activity. The complexes were designed to improve the oral bioavailability, to compare lipophilicity, to improve solubility, among others properties.

After all tests were assayed, it was concluded that the insertion of an oxygen bridge or an acetylic function on the non-labile carrier ligand produces a noteworthy decrease in the cytotoxic activity due to stereo-electronic factors. Another fact is that when a chloride ligand is substituted by a hydroxide ligand, an important reduction of cytotoxicity is induced due to the modification of the reduction potential of platinum. The exchange by bidentated malonate ligands improve the desired activity and it's probably because of the improvement of water solubility and bioavailability. An increase in the cytotoxicity was reported in those complexes having an DMF labile ligand, probably because of its higher water solubility, because of their polar character and better quality as leaving group of the N,N-dimethyl-O-formamidate ligand, which promotes the formation of aquo-complexes.

The chemical structure of the complexes studied are illustrated in Figure 27.

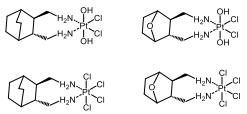


Figure 27. Chemical structure of platinum (IV) complexes havig a bicyclic 1,4-diamino ligand.

5.4.7. Platinum complexes bearing bis(carboxylate)dichloride ligands

Several platinum (IV) complexes bearing bis (carboxylate)dichloride ligands were synthesized to perform SAR studies. [44]

The first batch of complexes, derived from satraplatin, which are illustrated in Figure 28, presented high cytotoxicity activity in vitro and it could be enhanced by increasing the lipophilicity of their axial ligands. The second kind of complexes, derived from carboplatin and nedaplatin and illustrated in Figure 28, were far less potent, regardless of their lipophilicity. This fact could be due the much lower rate of activation for tri- and tetracaboxylato-platinum (IV), compared to their analogues.

Some other theoretical structure-activity relationship studies have been made regarding bis- and tetra-carboxylates.

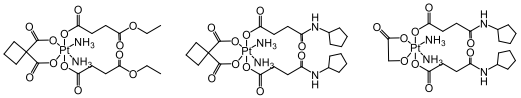


Figure 28. Chemical structure of platinum (IV) complexes bearing bis(carboxylate) dichloride ligands.

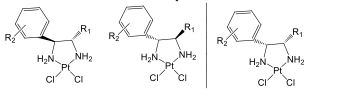
5.4.8. Chiral 1,2-diaminophenylalkane platinum(II) complexes[45]

Some structure-activity tests were made on the chiral molecule 1,2-diaminophenylalkane platinum(II), focusing on their interactions with DNA, the acid-base properties of the activated species and on DFT computed structural features.

The binding modes of the complexes to a G4 structure were found similar to cisplatin, but no effects were observed which was unexpected. The ability to bind DNA faster is not correlated to any increase of the antiproliferative effect.

It was also stated that the most basic diastereoisomer was the less cytotoxic. DFT calculations revealed that the most effective diastereoisomer possess a low energy conformer for which the platinum atom is not hindered by the ethylenediamine substituent.

The chemical structure of before mentioned complexes is illustrated in Figure 29.



1a= R_2= p-F, R_1= ^{i}Pr (1S, 2S)
1a= R_2= p-F, R_1= ^{i}Pr (1R, 2R)
1a= R_2= p-F, R_1= Me (1R, 2R)
1a= R_2= p-H, R_1= Me (1R, 2R)

2a= R_2= p-F, R_1= ^{i}Pr (1R, 2S)

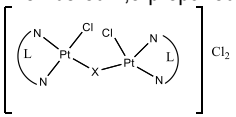
Figure 29. Chemical structure of chiral 1,2-diaminophenylalkane platinum(II) complexes.

5.4.9. Pyrazine bridged dinuclear platinum (II) complexes[46]

Some complexes bearing derivatives of pyrazine were synthesized. After being tested it was discovered that diazine-bridged dinuclear platinum (II) complexes, illustrated in Figure 9, generally appear to be less cytotoxic in comparison to cisplatin and azine-bridged complexes which are illustrated in Figure 30.

Some of the complexes presented desirable 3- to 5-fold lower activity against fibroblasts in comparison to carcinoma cell lines, which can be correlated with steric hindrance.

It was also discovered that complexes with five-membered ethylenediamine rings showed lower IC50 values in comparison to those with six-membered 1,3-propanediamine rings.



L= en, 1,2-pd, ibn, 2,2-diMe-1,3-pd
X= pz or pydz

Figure 30. Chemical structure of dinuclear bridged platinum (II) complexes.

5.4.10. 1,2-Bis(aminomethyl)cyclohexane platinum(II) complexes[47]

Several 1,2-bis(aminomethyl) cyclohexane platinum(II) complexes were synthesized. Studies showed several structure-activity relationships.

Firstly, the compounds having a carrier ligand with a saturated cyclohexane and a protected oxygenated function (OMe) are more active than those having a cyclohexane framework but bearing a free OH. Hence oxygen seems to improve the activity when acting as a hydrogen-bond acceptor but decreases the activity when acting as a hydrogen-bond donor.

Also introducing, a C=C double bond on the carbocycle of carrier ligand decreases the activity.

The complexes having a saturated cyclohexane framework the presence of an oxygenated function increases the cytotoxic activity and also the relative stereochemistry of the oxygenated function may have an influence on activity. The compounds studied are illustrated in Figure 31.

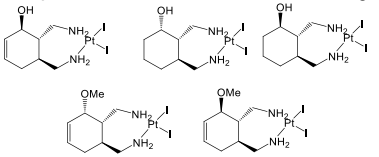


Figure 31. Chemical structure of 1,2-bis(aminomethyl) cyclohexane platinum(II) complexes.

5.4.11. Diester diiodido Platinum(II) complexes

Several complexes, whith the general structure illustrated in Figure 32, were synthesized to test their cytotoxic activity and to study their structure-activity relationship. Variations in the cytotoxicity of the complexes have been reported in relation to the lipophilic parameters, influenced by the alkyl ester chain in the carrier ligands. Also, there was an increase of the intracellular accumulation and DNA platination of the tested complexes in relation of length and branching of the ester chain.[48]

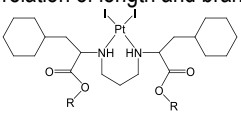
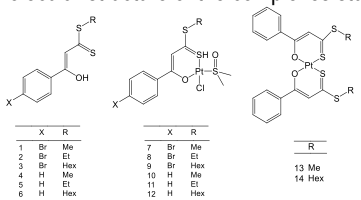


Figure 32. Chemical structure of platinum (II) iodide complexes.

5.4.12. β-hydroxydithiocinnamic ester platinum (II) derivatives[49]

A series of platinum complexes bearing a β-hydroxydithiocinnamic ester were synthesized and the structure-activity was studied. As a result, some SAR facts were found. Thus, it was observed that the elongation of the alkylic chain from methyl to hexyl seems to increase the cytotoxic effect of the drug. Substitution ant the aromatic site, does not alter the solution behavior or binding of the ligands towards the platinum center. The length of the polar alkyl chain does influence the solution behavior in aqueous solutions. The hexyl chains increase the molecule lipophilicity and it may have an advantage in cell proliferation. An image of the molecular structure of the complexes studied is illustrated in Figure 33.



	X	R
1	Br	Me
2	Br	Et
3	Br	Hex
4	H	Me
5	H	Et
6	H	Hex

	X	R
7	Br	Me
8	Br	Et
9	Br	Hex
10	H	Me
11	H	Et
12	H	Hex

	R
13	Me
14	Hex

Figure 33. Chemical structure of β-hydroxydithiocinnamic ester platinum (II) derivatives.

5.4.13. Platinum(II) complexes conjugated at position 7α of 17β-acetyltestosterone

Some platinum complexes were synthesized, containing 7α of 17β-acetyltestosterones as ligands.[50] Structure-activity studies were made and some of the conclusions made are that the stereochemistry of the amino acids used has minor effects on the cytocidal activity. Moreover, L- and D-2-pyridylalanine and L-4-thiazolylalanine platinum (II) complexes exhibited the most potent antiproliferative activity and are unaffected by the overexpression of P-glycoprotein.

It was stated that the strategic location of the platinum (II) moiety and the efficient chemical transformations of testosterone represent an attractive strategy to develop anticancer drugs. The chemical structure of some of the complexes studied are illustrated in Figure 34.

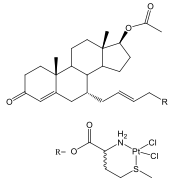


Figure 34. Chemical structure of platinum (II) complexes bearing 7α of 17β-acetyltestosterone ligands.

5.4.14. Transplatinum complexes containing sulfonamide ligands[51]

A series of trans platinum complexes bearing sulfonamide ligands were synthesized. Regarding structure-activity relationship it was stated that complexes with aromatic rings such as quinoleyl groups have a bad biological activity, whereas complexes with tolyl rings and electron-donating groups show a better antiproliferative activity, in some cases, better than cisplatin. It was also observed that chloride complexes show more cytotoxic activity than iodide complexes.

The chemical structure of the complexes studied is illustrated in Figure 35.

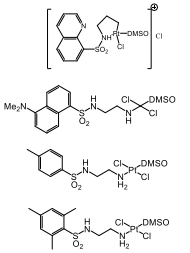


Figure 35. Chemical structure of platinum (II) complexes bearing trans-sulfonamide ligands.

5.4.15. Platinum(II/IV) complexes containing N,N'-bis(2-propionate ester)-ethylenediamine ligands[52]

Some platinum complexes containing N,N'-bis(2-propionate ester)-ethylenediamine ligands were synthesized. Some structure-activity relationships were stablished. An improvement in cytotoxicity has been observed by coordination of ligands to the dichloroplatinum(II) moiety. It was observed that the cytotoxicity increases when the platinum (II) complexes have more lipophilic ester part (increasing, isopropyl, isobutyl, cyclopentyl…).

Furthermore, when platinum (II) is substituted with a platinum (IV) ion, higher cytotoxicity activity is achieved. The exchange of alaninato to β-alaninato moiety has no effect in improving the antitumoral activity. It was also observed that the ligands with more hydrophobic alkyl side chain improve apparently the activity of the complexes. These results are in accordance with previous studies. [53]The chemical structure of some of the complexes studied are illustrated in Figure 36.

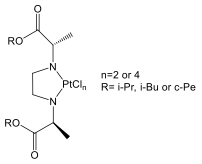


Figure 36. Chemical structure of platinum(II/IV) complexes containing ethylenediamine-N,N0 -di-2/3-propionate ester ligands.

5.4.16. Transplatinum complexes: methylamine, dimethylamine and isopropylamine ligands

Platinum (II) complexes bearing the aliphatic amines methylamine, dimethylamine and isopropylamine, which are illustrated in Figure 37, were synthesized in order to stablish some structure-activity relationships.[54]

Regarding the aquation kinetics, it was found that the monoaquation takes places rapidly as expected for trans geometry, but such aquation favors the dichloro species, being markedly slower than in other trans complexes. It was observed that the fastest aquation is for complex trans-Pt2(methylamine)(dimethylamine) and it seems to be due steric effects, because this complex beats the smaller aliphatic amines.

In conclusion, kinetic studies revealed that the complex with the smaller aliphatic amines are the least aquated in the equilibrium, with the higher aquation rate.

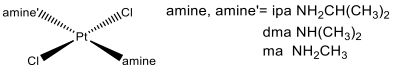


Figure 37. Chemical structure of trans-PtCl2(Amine)(Amine').

5.4.17. Tetraazolato-bridged dinuclear platinum (II) complex

Chromatin DNA is known to have various cellular functions and it is copied for the next cell division. Thus, this molecule is an interesting target. An azolato-bridged dinuclear platinum (II) complex, which is illustrated in Figure 38, is capable to inhibit DNA replication and also RNA transcription, arresting cells in the S/H2 phase, and hence due to its structure its capable to improve its cytotoxic activity towards cancerous cells.[55]

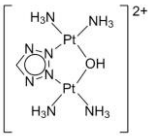
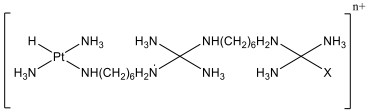


Figure 38. Chemical structure of tetraazolato-bridged dinuclear platinum (II) complex.

5.4.18.Triplatin

Triplatin is a highly positively charged, substitution-inert derivate of a phase II clinical anticancer drug. Due to its structure, it has a rapid cellular entry mechanism via interaction with cell surface glycosaminoglycans. Studies show that in human colon carcinoma cells, the production rate of 47S rRNA precursor transcripts is dramatically reduced after drug treatment and that transcriptional inhibition of rRNA was followed by a robust G1 arrest, and activation of apoptotic proteins caspase and PARP-1 in a p53-independent manner. The chemical structure of triplatin is illustrated in Figure 39. [56]



X=Cl n=4
X=NH(CH2)6H2N n=8

Figure 39. Chemical structure of triplatin.

5.4.19. Transplatinum complexes tethered to 1-adamantylamine

The lipophilic complexes trans,trans,trans-[PtCl2(CH3COO)2(NH3)(1-adamantylamine)] [trans-adamplatin(IV)] and its reduced analogue trans-[PtCl2(NH3)(1-adamantylamine)] [trans-adamplatin(II)] were examined and are illustrated in Figure 40. An important factor discovered was that these complexes have a remarkable circumvention of both acquired and intrinsic cisplatin resistance. Trans-adamplatin (IV) was considerably less mutagenic than cisplatin. Trans-adamplatin attacks better the DNA than cisplatin due to the unwinding angle of this complex.[57]

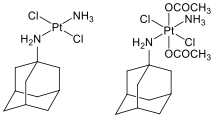


Figure 40. Chemical structure of trans-platinum complexes tethered to 1-adamantylamine.

5.5. MULTI-TARGET PLATINUM (II) DRUGS

It is thought of multitarget anticancer drugs as the future in drug development, because cancer is known to be a disease, which can involve multiple genes, and multitarget drugs can enhance efficacy and lower drug resistance.[58]

The concept of multitarget is used to describe complexes, which present more than one bifunctional moiety. Examples are cytotoxic complexes that are capable of binding DNA and can also incorporate tumor targeting vectors and/or ligands with distinct, but synergistic, biological functions. Also, these complexes are designed to limit the side effects of the drug towards the human body and to circumvent resistance while enhancing therapeutic efficacy.

It is possible to classify these types of platinum-based drugs according to the different targets of the molecule.[59]

5.5.1. Multitargeting Cell Receptors by Platinum (II) Drugs

5.5.1.1. Glucose Receptor Targeting

Cancer cells require large amounts of glucose to survive. Due to their hypoxic environment, ATP is generated via anaerobic glycolysis. It is known that anaerobic glycolysis is energetically inefficient compared to aerobic oxidation of the pyruvate.[60] This leads to an over-reliance on anaerobic glycolysis which leads to an over expression of glucose transporter (GLUT) membrane proteins on these cells. Therefore, a glucose transporter associated to a platinum (II) complex, is a possible drug target to inhibit anaerobic glycolysis to take place.[61]

Some examples of platinum-based drugs linked to GLUT inhibitors are illustrated in Figure 41[62,63]

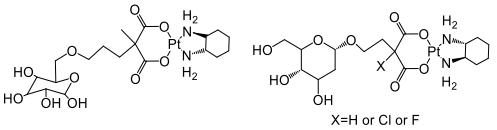


Figure 41. Platinum-based drugs for GLUT inhibition.

5.5.1.2. Hormone Receptor Targeting

It is known that sex hormones play a role in the cancer progression of hormone-sensitive tissues.[64] For example, breast cancer is a hormone-dependent cancer because estrogen receptor (ER) is overexpressed[65]. Disrupting the biological function of estrogens receptors has become a possible strategy to design anticancer agents and, therefore, estrogen receptors are potential targets. Over the years, some testosterone-linked platinum (II) conjugates where designed and tested as possible anticancer drugs. [66]

Some examples of these drugs are quoted in Figure 42.

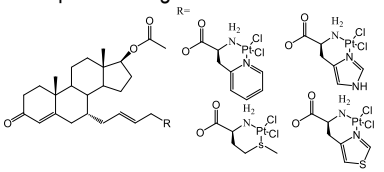


Figure 42. Platinum-based analogues for estrogen receptors inhibition.

5.5.1.3. Integrin Receptor Targeting

Cancerous cells as it has been said can overexpress certain receptors. Receptors such as growth factor and integrins are an option to try to selectively deliver a cytotoxic agent to tumor cells.[67]

Integrins are heterodimeric transmembrane cell adhesion glycoproteins which play a role in enhancing migration, invasion, proliferation of cancerous cells and recently linked to tumor angiogenesis, thus, they are an attractive target.[68]

An example of their approach is the design of the following structure, illustrated in Figure 43.[69]

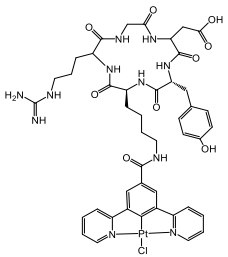


Figure 43. Platinum (II)-peptide conjugate structure for integrin-targeted photodynamic therapy.

5.5.1.4. Biotin Receptor Targeting

Biotin, which is known as vitamin H, is also overexpressed on the cell surface by cancerous cells. Hence, this molecule is used as a selective drug transporter and some studies have shown that biotin conjugated with classical chemotherapeutics has positive effects as anticancer drug.[70]

Some of the biotinylated conjugated platinum structures are illustrated in Figure 44[71,72].

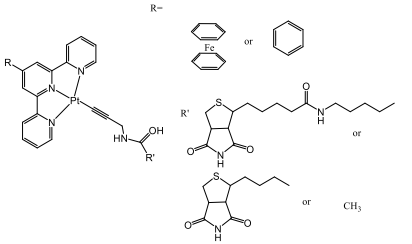


Figure 44. Biotinylated conjugated platinum (II) complexes.

5.5.2. Platinum (II) Drugs Targeting Enzymes

One of the targets for these drugs are enzymes. The inhibition of some enzymes can provoke that some major physiological cell processes could be inhibited, inducing, thus, the death of the cancerous cells. Next several platinum(II) complexes acting on a wide range of enzymes are discussed.

5.5.2.1. Histone Deacetylases as targets

These enzymes play a major role, as an epigenetic regulator of gene expression, so inhibiting these kinds of enzymes would avoid transcription to take place.[73]

The first histone deacetylase inhibitor used in clinics was suberoylanilide hydroxamic acid known as SAHA and it's illustrated in Figure 45.

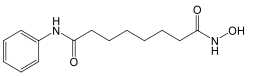


Figure 45. SAHA structure.

5.5.2.2. Pyruvate Dehydrogenase Kinases as targets

Dichloroacetate (DCA) is known to be a structural analogue of pyruvate which by inhibiting pyruvate dehydrogenase kinases leads to an influx of pyruvate in the mitochondria promoting the oxidation of glucose instead of glycolysis, which leads to the suppression of tumor cell growth.[74]

Two mixed-ammine/ amine platinum (II) complexes were originally developed in which DCA was attached to the complex through an ester bond. Though, those complexes where found to be insoluble in water.[75] An example of these compounds is shown in Figure 46.

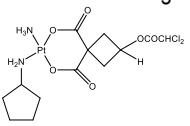


Figure 46. First Platinum (II) complex bearing DCA derivative.

Trying to improve these properties, similar complexes were developed. At the end, one analogue was chosen as the most effective compound against cancerous cells. This analogue can release the DCA moiety via hydrolysis of the ester bond, under physiological conditions, and was more soluble in water than the other analogues previously synthetized. [76]The following structure is shown in Figure 47.

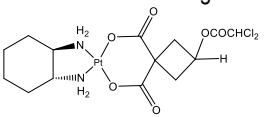


Figure 47. Platinum (II) complex bearing DCA derivative.

5.5.2.3. Cyclin-Dependent Kinases as targets

Cyclin-dependent kinases (CDK's) play a regulatory role in the cell cycle and in transcription, mRNA processing and cell differentiation[77,78]. In cancerous cells, these kinases are known to be overactive. Therefore, these enzymes are promising anticancer targets and multiple drugs are being developed for this purpose. Some analogues of platinum (II) complexes incorporating CDK inhibitors were synthesized to test its inhibition power.[79] An example is quoted in Figure 48.

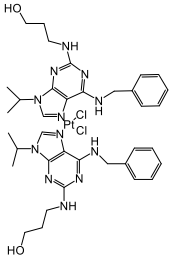


Figure 48. Platinum (II) complex bearing CDK inhibitor ligands.

5.5.2.4. Glutathione Peroxidase and Thioredoxin Reductases as targets

Some drugs containing imidazoles and pyrazoles where designed to inhibit these enzymes resulting in being weak inhibitors.[80,81]

Some cisplatin and transplatin analogues, bearing these inhibitor ligands, were developed, having been theorized that these new complexes were going to result in irreversible inhibition and to target DNA. However, the complexes failed to inhibit these enzymes. At the end, any analogue had Glutathione Peroxidase inhibitory properties, but they had promising in vitro cytotoxicity with a mechanism of action distinct to the most common platinum drugs.[82] Some examples of these platinum (II) complexes are illustrated in Figure 49.

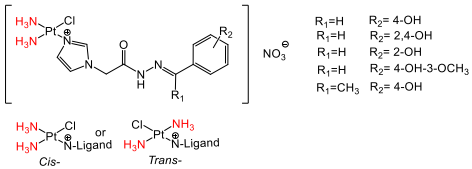


Figure 49. cis- and transplatinum(II) complexes bearing imidazoles and pirazoles.

5.5.2.5. Farnesyl Pyrophosphate Synthases

Bisphosphonates which are compounds commonly used in diseases such as osteoporosis, tumor-induced hypercalcemia or bone metastases combined with platinum (II) complexes, have been used to develop new and effective bone-related cancer chemotherapies.[83]

Some examples of such complexes are illustrated in Figure 50.

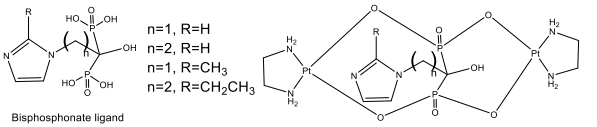


Figure 50.Chemical structures of platinum (II)-bisphosphonate complexes.

5.5.2.6. Matrix Metalloproteinases as targets

Matrix metalloproteinases are known to be zinc-containing proteolytic enzymes, which play a major role in healthy tissue remodeling and degradation of the extracellular matrix. When these enzymes have an abnormal expression, it can result in the breakdown of the extracellular matrix, inducing tumor metastases.[84]

Bisphosphonates are known to be matrix metalloproteinases and by hence multiple platinum (II) complexes bearing these compounds were designed to inhibit them. Some examples of these complexes are illustrated in Figure 51.[85]

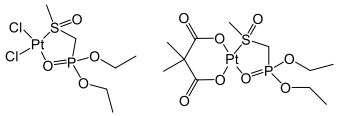


Figure 51. Chemical structures of platinum (II)-phosphonate complexes.

5.5.3. Cell Proteins, different from enzymes, as targets

Recent studies show that developments in proteomics will identify new protein targets for therapeutic clinical use. [86]

Multiple platinum (II) complexes have been designed to interact with key protein targets that are involved in cancer progression or metastases.

5.5.3.1. STAT3 protein as a target

STAT3 which is the acronym for signal transducer and activator of transcription 3 is a transcription factor that plays an important regulatory role in gene expression related to the cell cycle, cell survival, and immune response linked with cancer progression.

STAT3 induces the cancerous cell to apoptosis but it has no effect over healthy cells which makes this protein an attractive target.[87]

Multiple platinum (II) complexes bearing oxadiazoles where designed to inhibit this protein. Some examples of the aforementioned compounds are illustrated in Figure 52.[88]

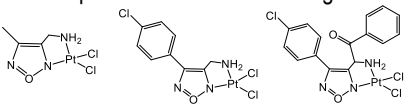


Figure 52. Chemical structures of platinum (II)-oxadiazoles complexes with STAT3 inhibitory proprieties.

5.5.3.2. Tubulin as a target

There have been designed complexes that inhibit tubulin polymerization at the same time that make cross-links among DNA strands. An example is the complex platinum (II)-combrestatin A-4, which is known to be a dual targeting agent due to its capacity to bind DNA, be specifically cytotoxic to cancer cell lines and provide cytoselectivity.[89] Such a structure is illustrated in Figure 53.

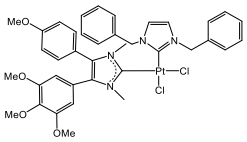


Figure 53. Chemical structure of platinum (II)-combrestatin A-4 derivative.

5.5.4. Mitochondrial DNA as a target

Some non-covalent complexes were developed as an alternative to the typical irreversible DNA binders. Bipyridines and phenanthrolines when coordinated to platinum can intercalate DNA, causing it to unwind. [90]

The platinum (II) complex bearing a monoanionic tetradentate β-diketiminate ligand, which is shown in Figure 54, is a promising complex because it not showed the common platinum drugs effects, but it also showed photophysical properties, and it is able to damage genomic mitochondrial DNA and induce mitochondrial-meditated apoptosis. Thus, the mitochondria is an interesting target to attack.[91,92]

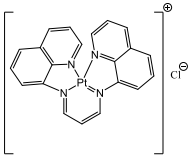


Figure 54. Chemical structure of planinum (II) complex bearing a monoanionic tetradentate β-diketinimate ligand.

5.5.5. Platinum complexes having natural products as bioactive ligands with diverse cell targets

An example of this kind of bioactive natural products acting as ligands is Curcumin, which is widely used in traditional medicine due to its important antiflammatory properties. Thus, it is able to inhibit proinflammatory transcription factors and has anticancer capabilities.

Platinum (II) complexes bearing curcumin ligands have shown to be photoactivable dual-action anticancer agents.[93] Some of these complexes are illustrated in Figure 55.

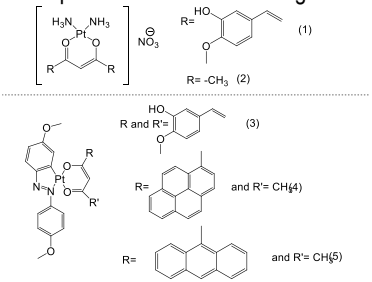


Figure 55.Chemical structures of Platicur (1), a platinum-acetylacetone derivate (2), and photoactivatable organometallic platinum (II) complexes bearing β-diketonates (3-5).

5.6. MULTITARGET PLATINUM (IV) PRODRUGS

The concept prodrug is used to describe molecules that after being administrated are metabolized into a pharmacologically active drug. In the case of platinum complexes, platinum (IV) is metabolized into platinum (II) which is the active drug.

Platinum (IV) prodrugs offer multiple therapeutic advantages over their platinum (II) derivatives. Platinum (IV) complexes are octahedral geometry compounds due to platinum (IV) being a low spin d6

and are therefore coordinately saturated. As a result, platinum (IV) complexes are more resistant to ligand substitution. This reduces unwanted side reactions and hence lower toxic side effects.
On the other hand, the two additional axial ligands can be functionalized to enhance tumor cell targeting. As a result, it is possible to generate new complexes with a different mechanism of action, and by doing so lower resistance.[94,95,96]
There are three known platinum (IV) complexes that have undergone clinical trials but despite those, none have made it into the clinics yet. These complexes are ormaplatin, iproplatin and satraplatin and these are illustrated in Figure 56. [97]

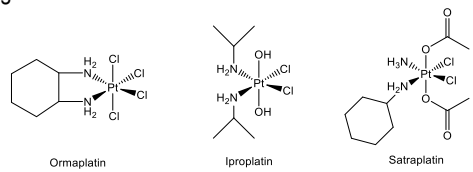


Figure 56. Chemical structures of Ormaplatin, Iproplatin and Satraplatin.

5.6.1. Glucose receptor as a target

As previously mentioned, cancerous cells rely on anaerobic glycolysis for production of ATP. This factor leads to an overexpression of GLUT membrane proteins on the surface of the cell. Thus, some platinum (IV) complexes have been designed to inhibit GLUT.
An example of these platinum (IV) complexes is illustrated in Figure 57.

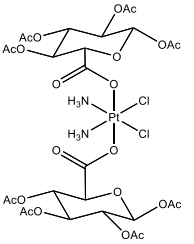


Figure 57. Chemical structure of glycosylated platinum (IV) complex.

5.6.2. CD44 glycoprotein as a target

CD44 is a cell surface glycoprotein receptor that is highly expressed in many types of cancers and plays a regulatory role in metastasis.[98] CD44 can promote the migration and invasion processes associated with metastasis when linked to ligands such as hyaluronic acid.[99]
A complex based on platinum (IV) and linked to ethylenediamine and hyaluronic acid via a succinate linker was developed and it showed to have anticancer effects and a lower toxicity than common platinum drugs. [100]The chemical structure of said complex is illustrated in Figure 58.

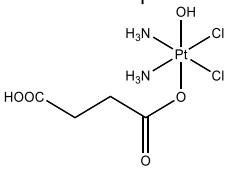


Figure 58. Chemical structure of platinum (IV) for CD44 targeting.

5.6.3. Hormone receptor as a target

As it is known, sex hormones play a major role in cancer progression in hormone-sensitive tissues.[101] A strategy used to develop anticancer agents is to use steroids as carriers or as agents in order to be able to disrupt the biological function of hormone membrane receptors.
Some platinum (IV) prodrugs linked to estrogen where developed and showed cytotoxic proprieties towards cancerous cells particularly in breast and ovarian cancers.[102]
A platinum (IV) prodrug linked with estrogen is illustrated in Figure 59.

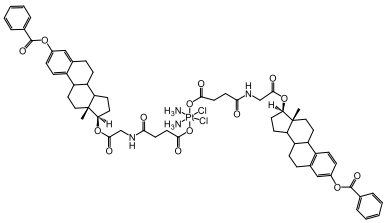


Figure 59. Chemical structure of an estrogen-tethered platinum (IV) complex.

5.6.4. Epidermal growth factor receptor as a target
The epidermal growth factor receptors are transmembrane proteins that are known to regulate various cancer-related effectors and are also known to upregulate DNA repair mechanisms.[103] To inhibit these proteins some platinum (IV) prodrugs bearing epidermal growth factor receptors-targeting peptides have been designed. Those are illustrated in Figure 60. [104]

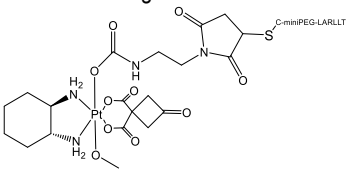


Figure 60. Chemical structure of platinum (IV) complex bearing epidermal growth factor.

5.6.5. Biotin receptor as a target
As mentioned before, biotin is rapidly taken up into tumor cells and thus some specific receptors to biotin are often overexpressed.[105] For this reason, it has been sought to design a platinum (IV) prodrug containing biotin that can be easily delivered to tumor cells. An example of these complexes developed is illustrated in Figure 61.[106]

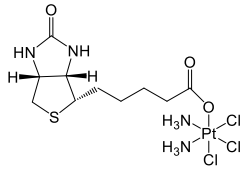


Figure 61. Chemical structure of platinum (IV) complex used in biotin receptor targeting.

5.6.6. Enzymes as targets of platinum(IV) complexes
5.6.6.1. Glutathione-S Transferases as targets

Glutathione-S Transferases are known to be a group of detoxification enzymes that play a role in phase II biotransformation in the human body and involves cancer chemotherapeutic agents.[107] Alkylating compounds are metabolically broken mainly by these compounds. [108]
Some cancer cell lines and tumors overexpress certain Glutathione-S Transferases isoenzymes and thus these enzymes are interesting targets.
To overcome this overexpression some compounds where designed. Two examples are illustrated in Figure 62.

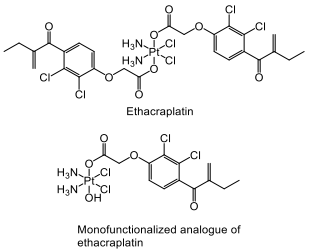


Figure 62. Chemical structure of ethacraplatin and its monofunctionalized analogue.

5.6.6.2. Histone Deacetylases as targets
As it has been said previously there are multiple platinum complexes that inhibit histone deacetylases such as SAHA, belinostat or panobinostat.[109] Despite this, few platinum (IV) prodrug complexes bearing these commonly used ligands have been reported. Nevertheless platinum (IV) prodrugs bearing valproate (derived from acid valproic) and phenylbutyrate have been designed and have good inhibitory activity against histone deacetylases.
The previously mentioned molecules are illustrated in Figure 63.[110]

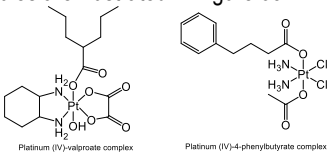


Figure 63. Chemical structure of platinum (IV) complexes bearing HDAC inhibitor valproate and phenylbutyrate ligands.

5.6.6.3. Pyruvate Dehydrogenase Kinases as targets
As previously mentioned, dichloroacetate is an oral inhibitor of pyruvate dehydrogenase kinase (PDK). The inhibition of PDK is a method to incite apoptosis in cancerous cells.[111] PDK affects the anaerobic glycolysis and therefore it is a good method to target cancerous cells while leaving normal cells unharmed.
A platinum (IV) derivative named mitaplatin was synthetized, tested in multiple cancerous cell lines and resulted in a similar cytotoxicity to cisplatin and more cytotoxic than dichloroacetate alone.[112]
This complex is illustrated in Figure 64.

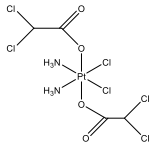


Figure 64. Chemical structure of Miaplatin.

5.6.6.4. Cyclooxygenases as targets

The body uses the enzymes cyclooxygenases to catalyze the conversion of arachidonic acid into prostaglandins, which are mediators of inflammatory and anaphylactic reactions. [113]

Some kind of cyclooxygenases have been found overexpressed in many tumor cells and also play major roles in tumor apoptosis and angiogenesis.[114] Nonsteroidal anti-inflammatory drugs are known to inhibit cyclooxygenases and some platinum (IV) complexes bearing this molecule have been synthesized. Some of these complexes are illustrated in Figure 65. [115]

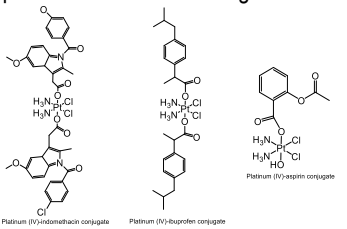


Figure 65. Chemical structures of platinum (IV)-NSAID conjugates.

5.6.6.5. Phosphatase 2A as target

Some platinum complexes have been designed based on traditional Chinese medicine using bioactive natural products as ligands, such as Cantharidin, a molecule that inhibits phosphatase 2A (a protein that is involved in cell regulation). Other ligand is Endothall a derivative of cantharidin that has been found to be less toxic than cantharidin itself.

These ligands are illustrated in Figure 66.

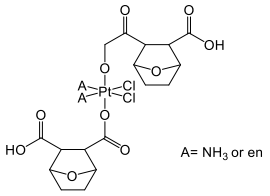


Figure 66. Chemical structure of platinum complex bearing cantharadin and/or endothall.

5.6.7. Peptide receptors as targets of platinum(IV) complexes

Peptide receptors are a valuable target because many tumor cells overexpress these receptors.[116] Below are described a few examples of theses targets and the platinum(IV) complexes inhibiting them.

5.6.7.1. Integrins and Aminopeptidase N as Targets

Cancerous cells can induce the production of angiogenesis, which leads to the formation of new blood vessels that can feed growing tumors with oxygen and nutrients. There are multiple tumor-cell surface proteins that are regulated by integrin and aminopeptidase N and thus these peptide receptors become an interesting target.[117] Some platinum (IV) complexes bearing integrin inhibitors are illustrated in Figure 67.

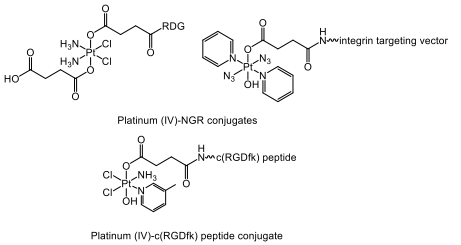


Figure 67. Chemical structure of platinum (IV) complexes bearing NGR and c(RGDfk) peptide conjugates.

5.6.7.2. Neurotensin Receptor Targeting.

Neurotensin is a well-known neurotransmitter and endocrine agent[118] that is found to be overexpressed in many cancer diseases. Few platinum (IV) complexes bearing neurotensin analogues where designed to target these molecules and are illustrated in Figure 68.[119]

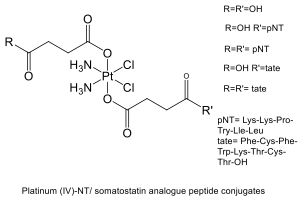


Figure 68. Chemical structure of platinum (IV)-NT/ somatostatin analogue peptide conjugates.

5.6.7.3. N-Formyl Peptide Receptor Targeting

There has been an interest in developing immunotherapies for the treatment due the knowledge that the immune system plays a major role in the regression of tumors.[120] There have been four main platinum (IV) complexes designed as immune-chemotherapeutic agents and are illustrated in Figure 69.[121]

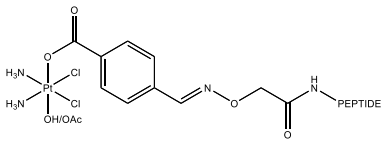


Figure 69. Chemical structure of platinum (IV)-FPR targeting conjugate.

5.6.8. Non-enzymic proteins as targets for platinum(IV) complexes

5.6.8.1. Tubulin as a target

There are few well-known tubulin inhibitors such as paclitaxel or docetaxel, which work as antimitotic agents by binding to the protein tubulin and thus disrupting the mitosis pathway. [122]

Some platinum (IV) derivatives holding this kind of ligands where developed and they exhibited enhanced cytotoxicity compared to cisplatin. An example of these complexes is illustrated in Figure 70.

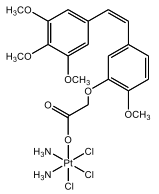


Figure 70. Chemical structure of platinum (IV)-tubulin inhibitor conjugate.

5.6.8.2. Anti-Apoptotic Proteins as targets

Some platinum (IV) complexes where designed bearing α-Tocopheryl succinate to inhibit apoptotic proteins and to give rise to mitochondria-meditated apoptotic cell death.

An example of these complexes is illustrated in Figure 71.

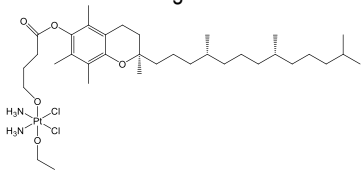


Figure 71. Chemical structure of cis,cis,trans-[Pt(NH3)2Cl2 (α -TOS)-(OEt)].

5.6.8.3. Double Minute 2 Homologue (MDM2) Protein as a target

The protein p53 is a tumor suppressor that prevents cancer cell proliferation. Double minute homologue (MDM2) protein can bind the transactivation domain of p53 and thus inhibit the action of p53. Chalcoplatin is a platinum (IV) derivative that has been designed and that is less toxic toward the body compared to other anticancer agents. The structure of chalcoplatin is illustrated in Figure 72.[123]

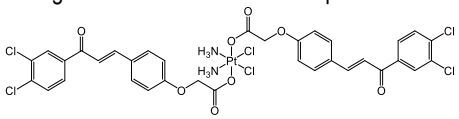


Figure 72. Chemical structure of Chalcoplatin.

5.6.9. Mitochondria as targets

Some platinum (IV) complexes have been designed to attack the mitochondria of tumor cells, and those showed more cytotoxicity and are less toxic to healthy cells than the classical drugs used in clinics. An example of these complexes is illustrated in Figure 73. [124]

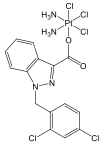


Figure 73. Chemical structure of platinum (IV) complex bearing Ionidamine.

5.7. DESIGN OF PLATINUM-BASED ANTICANCER AGENTS TO DECREASE THEIR TOXICITY

One of the most important things during the design of an antitumor drug is to ensure that it is only going to affect preferably to cancerous cells or at least is not going to produce irreversible damage to healthy cells and to be as selective as possible.

Classical platinum (II) complexes, such as cisplatin, present some serious secondary effects on healthy cells and thus the design of new drugs is required.
Over the years, several platinum complexes were synthesized and toxicity towards healthy cells was tested. Below are commented some of the investigations carried out in this field and examples of the complexes found and their respective chemical structures are illustrated.

5.7.1. DN-604 complex[125]
DN-604 is an analogue of carboplatin that has a functional dicarboxylato ligand, and it's been widely studied to explore its ability to induce apoptosis and its antitumor mechanism of action.
According to its toxicity levels, DN604 presented negligible in vivo toxic effects while having the same tumor growth-inhibition effect as cisplatin. The structure of DN604 is illustrated in Figure 74.

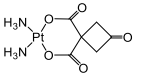


Figure 74. Chemical structure of DN-604.

5.7.2. Bispyridine-based dinuclear complexes[126]
The three dinuclear platinum-based compounds, trans-Diamminedichloroplatinum(II)-N,N'-octane-1,8-diyl)bis(isonicotinamide) (1,8 platinum), trans-Diamminedichloroplatinum(II)-N,N'-(decane-1,10-diyl)bis(isonicotinamide)(1,10 platinum) and trans-Diamminedichloroplatinum(II)-N,N'-(dodecane-1,12- diyl)bis(isonicotinamide) (1,12 platinum), that are illustrated in Figure 75, were tested to assess their potential as anticancer agents.
Regarding its toxicity, the three complexes presented slightly different toxicity than cisplatin but not enough to ensure that these complexes are safer to use than the classical platinum drugs.

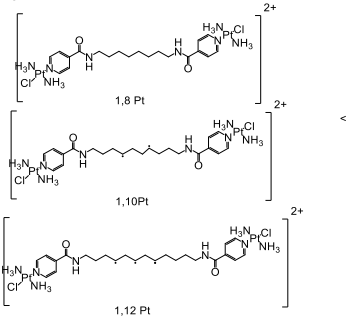


Figure 75. Chemical structure of platinum ()) bispyridine-based dinuclear complexes.

5.7.3. Oleanolic acid-NO donor-platinum (II) trihybrid molecules[127]
Some platinum (II) complexes coordinating oleanoic acid were designed and synthesized, taking advantage of its affinity to the bile acid transporter. The complex illustrated in Figure 76, after its toxicity properties were tested, presented only a very weak toxicity against healthy cells, suggesting a good safety profile drug.

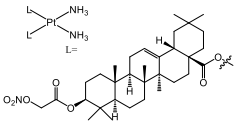


Figure 76. Chemical structure of platinum (II) complex bearing oleanolic acid.

5.7.4. Platinum (II) carboxylato complexes containing 7-azaindoles as N-donor carrier ligands[128]

Regarding platinum (II) complexes that contain 7-azaindoles, several complexes were designed. One complex in particular which is illustrated in Figure 77 presented a lower toxicity than cisplatin against healthy cells and it is believed that is due to its physicochemical properties. This complex also induces cell death by apoptosis, which is a preferable cell death mechanism rather than necrosis.

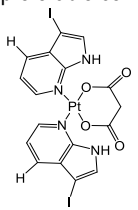


Figure 77.Chemical structure of platinum (II) carboxylated complex.

5.7.5. [Pt((1R,2R)-diaminocyclohexane) (3-carboxypredicentrinato)] [129]

[Pt((1R,2R)-diaminocyclohexane) (3-carboxypredicentrinato)] also known as boldiplatin is a non-racemic oxiplatin complex that has been synthesized in order to study its anticancer activity and its toxicity. This complex showed a significant decrease in toxicity over non-tumor cell lines compared to oxaliplatin. The chemical structure of boldiplatin is illustrated in Figure 78.

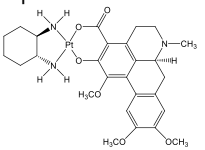


Figure 78.Chemical structure of Boldiplatin

5.8. NEW PHARMACOLOGICAL, CLINICAL OR THERAPEUTICAL APPLICATIONS

In order to improve the safety and efficiency of the anticancer platinum complexes, some improvements have been developed in different levels, especially from the pharmacological point of view and pharmacokinetics (ADME). Some of the pharmacological developments are quoted in the following text. [130]

5.8.1. Drug delivery applications: PLGA-PEG micelles encapsulation of lipophilic kiteplatin platinum (IV) prodrug

The biodegradable, PEG-coated, nanoparticles are injectable colloidal systems for the controlled and site-specific release of drugs. Some platinum (IV) complexes bearing hydrophobic carboxylic ligands at the axial positions, which are illustrated in Figure 79, were used to be encapsulated. This encapsulation resulted in a lower toxicity of the complex, a better distribution in the system and a higher cytotoxicity. [131]

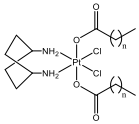


Figure 79. Chemical structure of trans,cis-[PtCl2{O2C(CH2)4CH3}2(cis-1,4- DACH)].

5.8.2. Photo-thermal therapy applications: Carbon based materials nanotubes

Carbon nanotubes have been extensively investigated as drug delivery vehicles, and some platinum (IV) prodrugs have been synthesized. The cytotoxicity and activity of the platinum prodrug complexes was enhanced when delivered with these nanotubes. The main motivation to use carbon nanoparticles as a delivery platform was the established ability of this material to absorb near-IR light and release the energy as heat, which leads this drug delivery to several photo-thermal therapy applications. [132]An example of a platinum complex encapsulated in nanotubes is illustrated in Figure 80.

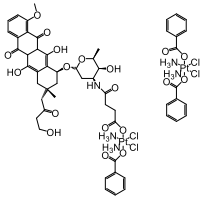


Figure 80 Chemical structures of platinum complexes encapsulated in nanotubes.

5.8.3. Photoactivated chemotherapy: Pt (IV) diazido complexes

Several platinum (IV) diazido prodrug complexes were synthesized. Some tests were made by photoactivation and these complexes resulted to be stable in the dark in the presence of cellular concentrations of reducing agents such as ascorbate, which is desirable for photoactivatable drugs.[133] This with the fact that the mechanism of action is oxygen-independent and the generally high aqueous solubility of these prodrugs, these complexes are interesting in future photoactivated chemotherapies. [134]The chemical structure of the complexes studied is illustrated in Figure 81.

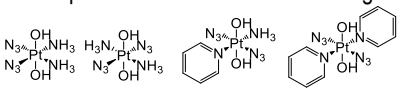


Figure 81 Chemical structure of platinum (IV) bearing diazido ligands

5.8.4. Drug delivery system by encapsulation in micelles: (1,2-Diaminocyclohexane) platinum (II) diaquo complex

The complex (1,2-Diaminocyclohexane) platinum (II), which is illustrated in Figure 82, has been encapsulated in micelles generated by poly(ethylene glycol)-b-poly(glutamic acid) and gadolinium dietylenetriaminopentaacetic acid. These micelles have been tested and it has been demonstrated that they increase the efficacy of treatment and the distribution of the drugs in the body. These micelles also present a minimal accumulation in normal tissues, which decreases the risk of undesired toxicity and side effects.[135]

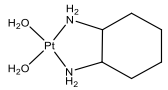


Figure 82 Chemical structure of (1,2-Diaminocyclohexane) platinum (II) diaquo complex.

5.8.5. Nanoscale Drug Delivery Platforms That Target Membrane Transporters[136]

Nanoscale drug delivery platforms are based on biodegradable, biocompatible components that are taken by endocytosis, preventing the drugs from being recognized by efflux pumps. Platinum drugs are covalently bound to these compounds, which results in a higher intracellular accumulation unaffected by transport processes.[137]

The main objective of nanoscale drug delivery platforms is to localize the therapeutic agent at its site of action for maximal effect without resulting in a toxic distribution of the agent are non-target sites. Molecules such as cisplatin itself or cis,trans,cis-[PtCl2(OH)2(NH3)2] have been encapsulated and are illustrated in Figure 83.

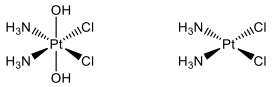


Figure 83. Chemical structure of cisplatin and cis,trans,cis-[PtCl2(OH)2(NH3)2].

5.8.6. Cancer radiosensitizers

The administration of ionizing radiation in the form of external beam radiotherapy alongside with radio-sensitizing small molecules has been a highly successful strategy for the treatment of cancer. Based on the studies it is known that the majority of radiosensitizers to date are compounds that target the DNA, but many of these agents are highly cytotoxic. Several radiosensitizers platinum (II) complexes have been tested and resulted in better radiosensitizers than cisplatin with higher cytotoxicity and lower side effects. The chemical structure of one platinum (II) radiosensitizer complex is illustrated in Figure 84.[138]

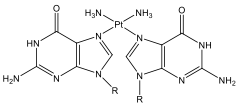


Figure 84. Chemical structure of a platinum radiosensitizer complex.

5.8.7 Photo-activated oxaliplatin (IV) complex nanoparticles[139]

It is known that the application of platinum (II) complexes in cancer treatment presents acquired resistance and severe toxic side effects towards healthy cells. To decrease this toxic side effects a photo-activated oxaliplatin complex bearing demethylcantharidin was conjugated to a polymer to form nanoparticles.

When delivered into the body the activated by UV oxiplatin, Pt(IV), is able to attack the DNA and the demethylcantharidin is able inhibit DNA repair. This complex therefore would be an interesting model as a multitarget platinum complex. The nanoparticles exhibited anticancer efficacy and also a lower toxicity compared to oxaliplatin, Pt(II). An illustration of the structure of the evaluated complex is illustrated in Figure 85.

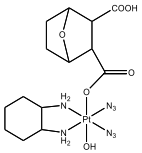


Figure 85. Chemical structure of platinum complex synthesized and transformed in nanoparticles.

5.8.8. Polymeric micelles carrying cisplatin[140]

Cisplatin is known to be a key drug in chemotherapy, but it has some several side effects such as nephrotoxicity. In order to reduce these toxicity levels some new pharmaceutical forms have been prepared such as encapsulation in polymeric micelles known as PEG (Poly(ethylene glycol)-poly(glutamic acid)

It has been discovered that if cisplatin is carried into polymeric micelles, this complex is more efficient against cancerous cells and it presents a significant lower toxicity and nephrotoxicity.

The well-known chemical structure of cisplatin is illustrated in Figure 86.

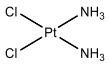


Figure 86. Chemical structure of cisplatin.

5.8.9. Liposome encapsulation of dichlorido-(N-dodecyl)-propanediamine-platinum (II) complex[141]
Dichlorido-(N-dodecyl)-propanediamine-platinum (II) complexes have been studied to try to reduce its toxicity and cellular Pt resistance.
To try so, this complex was encapsulated in pegylated liposomes and at the end, it resulted in a reduced drug toxicity and an enhanced antitumor activity compared to the non-encapsulated complex. The chemical structure of the evaluated complex is illustrated in Figure 87.

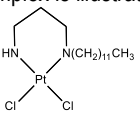


Figure 87. Chemical structure of dichloro-(N-dodecyl)-propanediamine-platinum (II) complex.

6. CONCLUSIONS

In this work, it is presented a review of the research carried out in the last ten years in the field of platinum-based anticancer drugs.

First of all, we appreciate an important effort to find new targets to kill cancerous cells.

On the other hand, it was observed that multitarget platinum complexes are of great and crescent interest due to these complexes propitiate a decrease of the acquire and cross-resistance of cancer cells. If two targets are being attacked at the same time, the probability of the cancerous cell to overcome both attacks are much lower and thus the cytotoxicity of the platinum complex increases and the multitarget drug becomes more efficient.

Also, there is a high interest in the research on the relationship between the structure and the activity of the molecule (SAR studies). If the structure of the molecule is optimized, an improvement in the cytotoxicity of the molecule can be achieved.

The design of new molecules with a new mechanism action are also a research objective of great importance, in order to improve the efficiency and to decrease the side effects of the platinum drugs.

Apoptosis is the most common cell death mechanism in the platinum complexes studied and also is the preferable one, because it induces fewer side effects among all cell death mechanisms. Necrosis and autophagy are less frequent.

Finally, new therapeutic applications have been found for platinum-based drugs, especially to improve their pharmacology and the design of new pharmaceutical forms that improve the galenic and pharmacokinetic (ADME) properties of these drugs in the clinical use.

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