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Design, synthesis, characterization and biological studies of ruthenium and gold compounds with anticancer properties

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Citation
Garza-Ortiz, A. (2008, November 25). *Design, synthesis, characterization and biological studies of ruthenium and gold compounds with anticancer properties*. Retrieved from https://hdl.handle.net/1887/13280

Version:	Corrected Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

CHAPTER 6

Summary, General Conclusions and Further Perspectives

Abstract

The general aim of this thesis has been to develop a systematic knowledge in the search of alternative anticancer metal-based compounds with enhanced cytotoxic properties and the establishment of general structure-activity relationships. The long term goal for the mentioned research projects is to develop a systematic approach in the synthesis of gold and ruthenium based anticancer compounds capable of overcoming the inherent problems related to the *cisplatin* treatment, but also with wider application to different tumour types.

This final chapter summarizes the most important results and very specific features for each project developed in this thesis, and also general conclusions are presented. Furthermore, specific proposals for the extension of the work reported here are also described and discussed.

"Sometimes I find [mathematical problems] difficult, but my old obstinacy remains, for if I do not succeed today, I attack them again on the morrow"
Mary Somerville, mathematician (1780-1872)

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"We have a hunger of the mind which asks for knowledge of all around us; and the more we gain, the more is our desire. The more we see, the more we are capable of seeing"
Maria Mitchell, astronomer (1811-1889)

6.1 Summary of the thesis

With the aim of developing a systematic knowledge in the search of alternative anticancer metal-based compounds (particularly those of ruthenium and gold) with enhanced cytotoxic properties, this thesis describes important chemical, physical and biological properties from selected ruthenium and gold compounds. For this purpose, novel Ru(III), Ru(II) and Au(III) coordination compounds were synthesised.

Despite the remarkable success of the cisplatin chemotherapy in the treatment of cancer, several limitations in the treatment, could be described. Most importantly, cisplatin is only effective for a narrow range of cancer types. Moreover, the development of resistance to the *cisplatin* treatment and the severe side effects reduce the number of possible efficient cases treated with this metal-based drug.

The long-term goal for the research projects here started is to develop a systematic approach in the synthesis of gold- and ruthenium-based anticancer compounds capable of overcoming the inherent problems related to the *cisplatin* treatment, but also with wider application to different tumour types.

The first chapter comprises general information related to cancer and its impact in the world as well as the most important chemical and biological findings in the field of ruthenium and gold cytotoxic complexes with potential application in the treatment of cancer.

It is clear that more research is needed in the chemistry and biology of both ruthenium and gold compounds. But it is also clear that the main focus must be the development of better discriminatory procedures for the selection of the most potent cytotoxic compounds with fewer side effects. To reach this purpose, stronger collaboration among chemists, biochemists and physicians is crucial.

It is then our main duty as chemists, to provide a complete chemical study of each system that is designed and developed, with the aim to accurately predict the reactivity of these compounds under physiological conditions and more over to predict the reactivity in the biological systems. Unfortunately this is not always possible, because most of the studies are life-time experimental projects.

In fact, the knowledge of the chemical properties of a potential anticancer compound is not enough. Once the chemical properties of a system are “under control”, the high variation in the tumour response in humans, in the context of unpredictable systemic toxicities, represent the next barrier for a successful treatment with a novel compound. In order to overcome this problem, better therapy treatment selection for individual patients is needed and the participation of physicians, pharmacologist and chemists must be encouraged in order to obtain the best results. The application of combined treatments (radiation, chemotherapy or surgery) and in the particular case of chemotherapy, the administration of different cytotoxic agents must improve further the success of the chemotherapy. Certainly, all these barriers require detailed knowledge of the physical and chemical properties of potential drugs.

As Au(III) and Ru(III)/Ru(II) have proved to be highly promising in the field of cancer treatment, this research project has been focussed on the design, synthesis and characterization of new Ru(III), Ru(II) and Au(III) compounds with cytotoxic properties, a goal that has been fully discussed in the final part of Chapter 1. At the same time, *in vitro* studies have helped in the establishment of general structure-activity relationships, which in turn will help in the improvement of the structural composition and the cytotoxic action of the designed compounds.

In Chapter 2, the synthesis and characterization of a novel series of Au(III) complexes, with general formula $[Au(L)Cl_2]Cl$ (where L=2-(phenylazo)pyridine (azpy), o-tolylazopyridine (tazpy), 3-methyl-2-phenylazopyridine (3-mazpy), 4-methyl-2-phenylazopyridine (4-mazpy) and 3-methyl-2-tolylazopyridine (3-mtazpy)) are described in detail. The ligands selected are derivatives of 2-(arylazo)pyridines, containing electron-donating groups, either in the pyridyl moiety, or in the phenyl one, or in both, in an attempt to tune the optimal stability and the biological *in vitro* activity. The complexes are also designed with two monodentate chloride ligands that could be hydrolyzed and thereby make 2 sites available for substitution. The compounds, stable in the solid state, were characterized by means of elemental analysis, IR, UV-Vis, conductivity measurements, ^{1}H NMR, 2D ^{1}H COSY studies, ESI-MS and ICP-OES.

Several authors have repeatedly demonstrated that Au(III) compounds have a great potential as antitumour agents, as Au(III) is isostructural and isoelectronic than Pt(II), they do not generate severe side effects and they can overcome the inhered or acquired cisplatin resistance. The major disadvantage recalls in the high tendency of Au(III) species, under physiological conditions, to form Au(I) or even Au(0) species. It has been challenging to design and synthesize, under physiological conditions, stable Au(III) compounds, especially due to the lack of knowledge in the Au(III) chemistry. As an example, Chapter 3 describes the unexpected reactivity in solution of the earlier introduced gold(III) compounds. The chemical stability of the complex cations, is analyzed by means of NMR and UV-vis. The results describe a kinetic-stability tendency, depending on the ligand coordinated to the trivalent gold ion. Half-life values were calculated based on an exponential dissociation model (one phase) from the integration values of selected ^{1}H NMR peaks from the stability studies. Tricyclic cationic organic derivatives of the original ligands (azpy, tazpy, 4mazpy and 3mtazpy) were proved to be form in solution, and subsequently isolated and characterized. The X-ray diffraction studies provide additional support to the structure proposals based on chemical evidence obtained by elemental analysis, NMR, ESI-MS and molar conductivity determinations. Moreover, a mechanistic proposal for this unexpected reactivity is described in detail and partially demonstrated through the chemical evidence obtained. The novel positively charged organic compounds obtained, represent promising starting materials for the synthesis of more elaborated organic structures. In the last part of this chapter, 2-(arylazo)pyridine ligands, Au(III) compounds and the organic cyclic cations are investigated as potential cytotoxic agents and the *in vitro* cytotoxic activity against cisplatin-sensitive and cisplatin-resistant cell lines is described. The IC_{50} values of the gold(III) compounds were found from moderate to highly cytotoxic, whereas the free 2-(arylazo)pyridine-related ligands were found to be less cytotoxic. Significant anticancer activity against the cisplatin resistant cell lines was found for one of the tricyclic salts, ruling out the occurrence of cross-resistance phenomena. Au-3mazpy showed the highest cytotoxic activity ($IC_{50=}$11 μM) and also the highest stability in solution.

Chapter 4 comprises the synthetic, spectroscopic, structural and biological studies of two novel chloridobis(arylimino)pyridine-Ru(III) compounds, containing one of the tridentate ligands, 2,6-bis(2,4,6-trimethylphenyliminomethyl)pyridine and 2,6-bis(2,6-diisopropylphenyliminomethyl) pyridine. The bis(arylimino)pyridine ligands were synthesized by condensation of 2,6-pyridinedicarboxaldehyde with 2,4,6-trimethylaniline or 2,6-diisopropylaniline and further characterized in the solid state through single-crystal X-ray diffraction analysis and other standard characterization techniques. The Ru(III) compounds, with general formula $[RuCl_3(L)]\cdot x(H_2O)$, where L=L1=2,6-bis(2,4,6-trimethylphenyl-iminomethyl)pyridine, L2=2,6-bis(2,6-isopropylphenylimino methyl)pyridine and x=0 or 1, nicknamed RuL1 and RuL2, respectively, were structurally determined on the basis of analytical and spectroscopic (IR, UV-Vis, ESI-MS, EPR, 1D and 2D ^{1}H NMR) studies. Although the free ligands by themselves are moderately cytotoxic in selected cell lines (EVSA-T and MCF-7), the anticancer activity of the $[Ru(L)Cl_3]\cdot xH_2O$ compounds is significant for a broad range of cancer cell-lines tested *in vitro* (IC_{50} values = 4 ~ 17 μM). Finally, the reaction of RuL1 with the DNA model base, 9-ethylguanine (9EtGua) was found to produce in a redox reaction, the compound, *trans*-$[Ru(II)(L1)(9EtGua)_2(H_2O)](ClO_4)_2$ (RuL1-2(9EtGua)), which was fully characterized by conventional methods in solution and also in the solid state, by X-ray crystallography. The structure comprises the as yet unknown *trans*-bis(purine)Ru(II) unit. This research has led the development of a promising new generation of potential antineoplastic Ru(III) and Ru(II) compounds with bis(arylimino)pyridine ligands. The potential interest lies mainly in the facility of modifications of the ligand moiety, which could help in the tuning of the biological properties. These Ru(III) compounds also represent plausible active catalytic species in the field of metal-bis(imino)pyridine systems that have attracted significant attention in recent years.

Finally in Chapter 5, as a result of the success in the synthesis of highly cytotoxic active Ru(III)-bis(arylimino)pyridine derivatives, the synthesis and isolation of a new family of Ru(II) complexes of the type $[Ru(Lx)(Ly)Cl]^+$ (Lx=L1: 2,6-bis(2,4,6-trimethylphenyliminomethyl)pyridine or L2: 2,6-bis(2,6-diisopropylphenyliminomethyl) pyridine and Ly= azpy, bpy (2,2'dipyridyl), 3mazpy, phen (1,10-phenanthroline), pic (picolinate) and tazpy) is fully described. The characterization was performed by elemental analysis, IR, ^{1}H-NMR, ESI-MS, UV-Vis and in some cases by X-ray diffraction studies. The synthesis of this family of Ru(II) compounds was designed in an effort for further evaluation and modulation of the chemical reactivity and cytotoxicity. The complexes,

incorporating bidentate ligands with different donor nature, are also designed to contain a monodentate chloride ligand which would be easily substituted. The *in vitro* evaluation of the cytotoxic properties of these new Ru(II) complexes in comparison with the parent Ru(III)-compounds (IC_{50} values = 4 ~ 17 μM) resulted in a significant improvement in cytotoxicity (IC_{50} values =0.4 ~ 10 μM) for a broad range of cancer cell lines tested. Some of them show even higher cytotoxic effects than cisplatin. The most active family of compounds, in terms of cytotoxicity, is the one containing the tridentate ligand 2,6-bis(2,6-diisopropylphenyliminomethyl)pyridine.

6.2 General Conclusions and Further Perspectives

6.2.1 Introduction

More than a century has passed since Paul Ehrlich coined the term “magic bullet” to describe a chemotherapeutic that seeks out and kills disease-causing cells, while leaving normal ones unaffected [1]. This visionary concept remains an inspiration for many targeted drug strategies [2].

In particular, the search of metal-based anticancer compounds started with the serendipitous discovery of cisplatin, which in clinics represent nowadays, the first and best treatment option for several types of cancer among which could be mentioned testicular, ovarian, and head and neck cancers. It is estimated that 50-70% of cancer patients are nowadays treated with a cocktail containing at least a platinum drug [3].

In fact, several metal-based compounds have been used in medicine for many centuries [4], in an empirical way, with limited understanding of the molecular basis of their biological activity. This tendency has changed due to the enormous interest in the development of new metal-based compounds with better cytotoxic action, reduced side effects, better selectivity and targeting and bigger range of application.

Obviously, the purposeful design of metal-based therapeutics is not an easy task. Even more, turning a designed compound into a drug is another significant challenge, but it is clear that the design of metal-based compounds with well-defined absorption, distribution, metabolism and excretion mechanisms is an urgent task. Further challenges in the field are the development of efficient predictive methods for metal-based compounds of therapeutic interest, improvements in the methods for detection of biological activity and even improvements in the standard procedures for the selection of the most efficient drug for a particular illness. It is also of major importance to consider the expensive and highly demanding and time-consuming clinical trials if a researcher is truly serious about developing a realistically useful drug.

When talking about metal-based drug design, the choices are not easy to be made. Varying the ligand coordinated to the metal, for instance, is one obviously verifiable way of altering the endogenous distribution of metal ions in the body; however, non-specific guidelines are available to predict the effects of variations *a priori*. Tissue targeting is a highly desirable goal for metal-based therapeutics or diagnostics, but it is not always feasible and more specific targeting ligands must be found. Not only the right ligand, but also the right metal-ligand combination, is important.

The success of the clinical application of cisplatin, the aim of reducing side effects, overcome resistance and increase the types of cancer that can be treated, have promoted the search of new metal complexes with anticancer properties [5]. There is a growing interest in the study of the anticancer properties of gold(I,III), platinum(II), ruthenium(II,III), iron(II), gallium(III) and many more coordination and organometallic compounds. Certainly some of those that have been developed are waiting to start clinical trials.

Ru(II,III) and Au(I,III) complexes have shown promising cytotoxic activities, but even further chemical information is required.

6.2.2. Au(III)-2-(arylazo)pyridine compounds

In the past, many reported Au(III) compounds have shown to have a poor stability in solution, which reduces the possibilities of clinical applications. In this thesis, the design, synthesis

and isolation of a new family of Au(III) compounds was achieved through the careful selection of ligands. In order to have enough chemical evidence, a family of closely related 2-(arylazo)pyridine compounds was synthesised and coordinated to Au(III).

The compounds, fully characterized are much more stable in the solid state but a complex reactivity takes part once they are dissolved. This unexpected reactivity was studied mainly by ^{1}H NMR and a mechanistic proposal of the decomposition of the Au(III) compounds and formation of positively charged tricyclic derivatives of the 2-(arylazo)pyridine ligands used, was described and discussed based on all the chemical evidence available. This reactivity of the Au(III) complexes in solution, was studied because, even though the transformations of gold complexes in biological systems (mammals) have been proposed and some metabolites identified and studied, further research about these transformations, metabolites and Au(III) reactivity and influence in biological processes is needed for the design of more active compounds and also for the design of proper detection tests. Clearly in this Au(III) system, the synthetic possibilities are far from being explored and further chemical evidence is needed in order to predict accurately the chemical reactivity. Nevertheless, it was concluded that the better chemical stability towards cyclization is observed for Au(III)-3mazpy. 3-mazpy is considered the stronger basic ligand in the series. Worth mentioning is the fact that a sterically demanding mechanism for the cyclization could be consider as a reason for the improved stability of Au-3mazpy. The stability studies also showed that the Au(III)-2-(arylazo)pyridine compounds are reasonably stable in solution during the 48-72 h *in vitro* cytotoxic tests and therefore, the biological activity could be attributed mainly to the Au(III) compounds tested.

2-(arylazo)pyridine ligands, Au(III) compounds and the organic tricyclic cations were investigated as potential cytotoxic agents and the *in vitro* cytotoxic activity against cisplatin-sensitive and cisplatin-resistant cell lines, was described. The IC_{50} values of the gold(III) compounds were found from moderate to highly cytotoxic, whereas the 2-(arylazo)pyridine related ligands were found to be less cytotoxic. All the Au(III)-2-(arylazo)pyridine compounds could overcome cisplatin-resistance. It was shown that the antitumor activity of this series of Au(III) compounds appears to be a function of a number of factors, such as the nature of the ligand by itself, the Au(III) compound structure, the stability of these compound an even the byproducts formed in solution, as well as the incubation times. It is strongly recommended to measure the biological activity of Au(III) compounds at different incubation times due to their now well-known instability.

Significant anticancer activity against the cisplatin resistant cell lines was found for one of the tricyclic salts, ruling out the occurrence of cross-resistance phenomena too. Au-3mazpy showed the highest cytotoxic activity ($IC_{50=}$11 μM) and - as mentioned earlier in the thesis - the highest stability in solution towards formation of positively charged cyclic compounds. This family of compounds form a class of potential antitumour drugs, since they overcome cisplatin resistance and also present promising cytotoxic activity values.

When studying the biological properties of the coordination compounds, it should be stressed the need of performing biological tests even for the free ligands. This protocol has been omitted often in the biological studies published in the specialized literature. This useful exercise could reduce or even avoid false positive results.

The application of 1D and 2D 1H NMR is of utmost importance in the understanding of the reactivity in solution and for the complete characterization of this family of coordination compounds, as shown in chapter 2 and 3.

Even though a detailed study for this family of Au(III) compounds was developed, many more questions remain to be answered. The chemical evidence strongly suggest that the synthesis of 2-(arylazo)pyridine ligands with more potent nucleophilic and electrophilic substituents in both, the phenyl and pyridine moiety and further coordination to Au(III) will help in the determination of the chemical reactivity of this family of compounds. These studies will also help in the achievement of further fine tuning of the biological properties.

Also, stability studies under closely similar physiological conditions, are extremely needed. The chemical reactivity of the Au(III) compounds need to be tested as well, in the presence of biological reducing agents as glutathione or ascorbic acid. It looks also transcendental to study the interaction of these compounds with biologically important targets, like DNA, proteins and enzymes. The cellular uptake of this set of compounds must be studied in detail as well, with

special emphasis in the identification of the storing compartments in the cell. These actions certainly would reveal important chemical information that will be translated into more specific structure-activity relationships.

With respect to the new tricyclic compounds several aspects are recommended to be studied. First of all further chemical evidence is needed in order to give more support to the mechanistic proposal of cyclization. Secondly, and apart from the potentially wide range of synthetic applications that this family of compounds could have, the cytotoxic effect developed for these compounds need to be studied in further detail as the preliminary results (pyrium) have shown even better antiproliferative effect than cisplatin. It appears that they are able to overcome the cisplatin resistance.

6.2.3. Ru(II,III)-bis(arylimino)pyridine compounds

In search of new metal-based anticancer compounds, Ru(III/II) complexes have deserved special attention, not only because of their good antitumour activity in screening studies, but also because of their cancer-cell specific targeting properties.

With respect to the field of Ru antitumour compounds, it is known that they are well suited for medical applications, due to the fact of having convenient rates of ligand exchange [5], a range of accessible oxidation states and the ability of ruthenium to mimic iron in binding to certain biological molecule [6-8]. Under aqueous conditions, three predominant oxidation states are known for Ru, i.e. Ru(II), Ru(III) and Ru(IV), all of them mostly presenting an octahedral configuration. This octahedral geometry appears to be partially responsible for the differences observed in the mechanism of action compared with cisplatin. The hypoxic environment of many tumours may favour the reduction of Ru(III) compounds (which are relatively slow to bind to most biological substrates) to Ru(II) species, which bind more rapidly [7]. Also well recognized is the fact that Ru-based drugs present reduced toxic side effects [9]. Undoubtedly, the understanding of the chemical and biological properties of Ru antitumor compounds is likely to develop rapidly [5], specially due to the progress in clinical trials of two recognized active Ru compounds, named NAMI-A and KP1019.

The need of more biological and chemical evidence in the reactivity of Ru(III/II) systems has encouraged the synthetic, spectroscopic, structural and biological studies of two novel chloridobis(arylimino)pyridine Ru(III) compounds. The bis(arylimino)pyridine ligands were synthesized by condensation of 2,6-pyridinedicarboxaldehyde with 2,4,6-trimethylaniline or 2,6-diisopropylaniline and further characterized in the solid state through monocrystal X-ray diffraction analysis and other standard characterization techniques. The new Ru(III) compounds containing the tridentate ligands L1 or L2, with general formula $[RuCl_3(L)]\cdot x(H_2O)$, where L=L1=2,6-bis(2,4,6-trimethylphenyl-iminomethyl)pyridine, L2=2,6-bis(2,6-isopropylphenylimino methyl)pyridine and x=0 or 1, named RuL1 and RuL2 respectively, have been synthesised in high yields, isolated and structurally and spectroscopically characterized. ^{1}H NMR techniques for paramagnetic samples proves to be essential for a detailed characterization. The electronic effect that the ligands exerts over the metal centre are responsible for the manifested stability of the Ru(III) state. However, reduction of the compounds could be achieved under mild conditions in a mixture of ethanol and water. The planar nature of the tridentate ligands and the presence of labile chloride atoms in the coordination compounds allow relatively easy substitutions of multiple types of molecules. The major advantage of this type of Ru compounds is that the bis(imino)pyridine ligands can easily be structurally modified to tune its solubility, its cytotoxicity and also the pharmacokinetics and pharmacodynamics in the human body.

The interaction of the Ru(III) compounds with the DNA-model base, 9-ethylguanine (9EtGua), was studied and the successful coordination of this model base was demonstrated, both in the solid state and in solution for RuL1, where a peculiar trans conformation was found to be stabilized by intramolecular hydrogen bond interactions. For this compound the 9-EtGua N7 appears to be the preferred site of coordination.

Remarkable antiproliferative properties for RuL1 and RuL2 were found (IC_{50} values = 4 ~ 17 μM) for a broad range of cancer cell lines. The IC_{50} values for the ruthenium compounds are higher (up to 6 till 33 times) than the values developed for the free ligands. In some cell lines, the cytotoxic effect of these new Ru(III) compounds proves to be higher than the effect generated by

cisplatin and certainly at least one order of magnitude higher than the cytotoxic effect detected for other Ru(III) compounds reported in literature. The synthesised compounds have proven to be promising anticancer compounds as deduced from their high cytotoxic values. Even more encouraging results may be expected when structural modifications would improve the dissolution properties.

Worth mentioning is the fact that RuL2 is the most cytotoxic compound, revealing that steric and electronic factors could be determinant in the biological activity and these factors need to be further explored.

The potent cytotoxic activity observed for these families of Ru(III)-bis(arylimino)pyridine compounds stresses the need for more studies comprising the *in vitro* cytotoxic activity determination in different cell lines, the interaction with biologically relevant structures, like proteins, DNA, nucleotides and reducing agents (ascorbic acid, cysteine or glutathione), and the redox and aquation/hydrolysis properties as well. Also structural modifications that improve the solubility properties are recommended. These new Ru(III) compounds were successfully used as starting materials for the synthesis of novel mononuclear Ru(II) species by replacement of the chloride ligands. Clearly, the synthetic possibilities are almost limitless.

Finally a series of mononuclear ruthenium complexes of the type $[Ru(Lx)(Ly)Cl]^+$ (Lx=L1: 2,6-bis(2,4,6-trimethylphenyliminomethyl)pyridine or L2: 2,6-bis(2,6-diisopropylphenyliminomethyl) pyridine and Ly= azpy, bpy, 3mazpy, phen, pic and tazpy) have been synthesised in moderate to high yields, and have been structurally and spectroscopically characterized. The complexes, incorporating bidentate ligands with different donor atoms, are also designed to contain a monodentate chloride ligand, which would be easily substituted. The fact that only one of the two possible isomers has been obtained from the synthetic procedure has been rationalized in terms of structural and electronic factors where in particular steric effects are relevant.

This project has led the development of a promising new generation of potential antineoplastic Ru(II) compounds with bis(arylimino)pyridine ligands. The potential interest lies mainly in the facility of modifications of the tridentate ligand moiety, which could help in the tuning of the biological properties with special interest in maximizing the cytotoxic activity, but also represent plausible active catalytic compounds in the field of metal-bis(imino)pyridine systems that have attracted significant attention in recent years.

The Ru(II) compounds present moderate to high cytotoxic effect and some of them show even better cytotoxic activity than cisplatin and are also comparable to the cytotoxic activity developed by α-$[Ru(azpy)_2Cl_2]$, the most cytotoxic Ru(II) compound described in literature so far. The *in vitro* evaluation of the cytotoxic properties of these new Ru(II) compounds in comparison with the parent Ru(III)-compounds led to significant improvement in cytotoxicity (IC_{50} values =0.4 ~ 10 μM) for a broad range of cancer cell lines tested. Compounds RuL1-3mazpy and RuL2-3mazpy have produced the better IC_{50} values. It appears that combination of 2,6-bis(2,6-diisopropylphenyliminomethyl)pyridine as a tridentate moiety and the azo N-donor bidentate ligand in a Ru(II) compound increases the growth inhibition of cancer cells. These encouraging results stress the need of more studies comprising structural modification in the tridentate and bidentate moiety, further *in vitro* cytotoxic activity determinations in different cell lines, studies of the interaction of these Ru(II) compounds with biologically relevant structures, like proteins, DNA, nucleotides and reducing agents (ascorbic acid, cysteine or glutathione), and the study of the redox and aquation/hydrolysis properties. These compounds, as the parental ones, have extensive synthetic possibilities. No other metallic compounds, with the possible exception of ferrocenes or ruthenocenes, show similar stability and flexibility.

Clearly, important research actions have been taken for the design, synthesis, characterization and biological activity studies of Au(III) and Ru(II,III) compounds, but many different aspects must still be explored. Moreover, it seems probable that some of these Ru(II,III) and Au(III) compounds will also exhibit pharmacological properties different from antitumor activity and they need to be explored.

As cancer represents an important health problem in our society, the governments in all countries must reconsider their health politics with the aim to increase the available funding for cancer research.

6.3. Final remarks

With respect to the human component of the fight against cancer, a more broadly based educational effort, directed towards both physicians and society as a whole, to achieve better understanding and compliance with the goals of chemoprevention and chemotherapy are needed. It is now more important than ever to convince people that absence of clinical symptoms may not guarantee health. It must be stressed that around 50–80% of human cancer is potentially preventable [10], because the factors responsible for its incidence, are largely exogenous, like cigarette smoking, occupational and environmental chemicals, radiation, dietary factors, lifestyle and socioeconomic factors, and specific viruses, bacteria, or parasites.

A major recent advance in cancer research has been through the acquisition of a new knowledge that elucidates fundamental molecular and cellular mechanisms involved in the development of malignancy and the biological action of specific drugs. On the basis of the understanding of these mechanisms, it is possible to design better drugs and even to prevent or reduce the occurrence of cancer. However, although advances in basic science have been enormous, a full understanding of the complex molecular, cellular, and chemical interactions involved in carcinogenesis is far from being complete.

6.4. References

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