

Development of Mononuclear (Arene)Ruthenium Complexes as Anticancer Agents: A Review

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Abstract

(Arene)ruthenium complexes have displayed promising activity against cancer and showed fewer side effects compared to platinum-based drugs. Activity tuning of arene complexes have been explored by varying, amines, phosphines and other N^N, N^O, N^S, N^C, S^O chelating ligands. (Arene)Ru(II) complexes of the type $[(\eta^6\text{-arene})\text{Ru}(\text{X})(\text{Y})(\text{Z})]$, $[(\eta^6\text{-arene})\text{Ru}(\text{L})(\text{X})(\text{Y})]$, $[(\eta^6\text{-arene})\text{Ru}(\text{L}^{\wedge}\text{L})\text{X}]\text{Y}$ and $[(\eta^6\text{-arene})\text{Ru}(\text{L}^{\wedge}\text{X})(\text{Y})]$, where arene = cymene (**C**), benzene (**B**), toluene (**T**), hexamethylbenzene (**H**); L = amine, phosphine; L[∧]L = en, diamine, diphosphine, (X[∧]Y) = oxalate, (L[∧]X) = acylacetonate; and (X), (Y) = halides, triflates *etc.* exhibit a high structural variety, and offer much potential in drug design. In this review, an overview of the progress in the field of mononuclear ruthenium complexes containing arenes and other co-ligands such as, PTA (1,3,5-triaza-7-phosphaadamantane), ethylenediamine (en), phosphines, thiosemicarbazone, acylthiourea and their bioactivity is presented.

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Keywords: (Arene)ruthenium complexes, Anticancer agents, metallodrugs, Cytotoxicity, Platinum complexes, Bioactivity

Introduction

Cancer is one of the leading causes of death around the world (Acharya et al., 2021), ranking second for economically developed countries, and the third for developing countries (Süss-Fink, 2010). As a consequence of the development of anticancer drugs, rates of survival for cancer in females and males have shown a steady decrease since 1970 and 1985, respectively (Haberland et al., 2010). All credits go to the scientists for introducing efficient anticancer drugs, which made a visible contribution towards treating cancers. The discovery of cisplatin (**1**) which inhibits antitumoral properties marked the beginning of a new era of metal-based anticancer research. Platinum-based complexes like, carboplatin (**2**), oxaliplatin (**3**) (Figure 1) were also discovered later, which had significant influence on the field of metal based anticancer drugs.

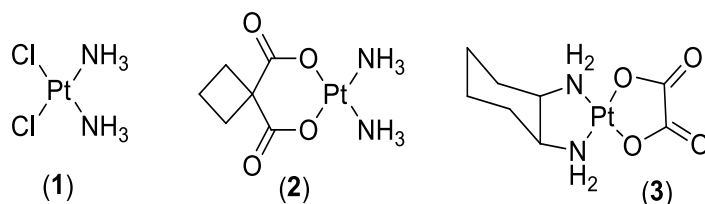


Figure 1. First examples of Pt(II) complexes approved for clinical use in cancer treatment

Evolution of metal-based anticancer drugs

In the investigation on anticancer drugs, in 1931, Collier and Krauss studied the effect of inorganic metal salts and complexes on anticancer activity (Collier & Krauss, 1931). About 40 years later, in 1969, Rosenberg claimed platinum-based complexes as a new class of potent antitumor agents because cisplatin, [PtCl₂(en)], *cis*-[PtCl₄(NH₃)₂] and [PtCl₄(en)] demonstrated antineoplastic effects (Rosenberg, 1973). In 1978, cisplatin was clinically approved as an anticancer drug after Pascoe and Roberts confirmed that the cellular target of cisplatin is DNA (Pascoe & Roberts, 1974). Cisplatin presented an immense potential as an anticancer drug by demonstrating its antitumor activity for several tumour types. But it showed severe side effects

such as neurotoxicity (nerve damage), alopecia (hair loss), vomiting, nephrotoxicity (kidney damage), drug resistance, bone marrow suppression, ototoxicity (loss of high frequency hearing) and vomiting when it was combined with chemotherapy (Prestayko, 1979; Lazarević et al., 2017; Allardyce et al., 2016; Zhao et al., 2019).

Generations of platinum anticancer drugs

Cisplatin, $[\text{PtCl}_2(\text{en})]$, *cis*- $[\text{PtCl}_4(\text{NH}_3)_2]$ and $[\text{PtCl}_4(\text{en})]$ belong to the first generation of anticancer drugs, which are platinum complexes containing chloride ligands; the binding of these platinum complexes takes place replacing chloride ligands. In the second generation of anticancer drugs, the chloride ligand was replaced by different ligands as in carboplatin (**2**) and $[\text{Pt}(\text{C}_2\text{O}_4)(\text{NH}_3)_2]$. In 1992, carboplatin (**2**) was introduced to the market and it showed less side effects than cisplatin due to its reduced neurotoxicity and nephrotoxicity (Lokich & Anderson, 1998). Though cisplatin showed low cytotoxicity in colorectal and breast tumors (Keppler et al., 1990), the third generation Pt(II) complex, oxaliplatin (**3**), was able to treat colon cancer liver metastases (Ono et al., 2012).

Ruthenium complexes with anticancer properties

In the search of anticancer agents containing metals other than platinum, the most promising one was found to be ruthenium. Ruthenium and osmium metallodrugs were originally designed to mimic the action of platinum in which, DNA was considered to be the primary target (Pragti et al., 2021). However, this perspective changed considerably during the last decade, because it was experimentally proven that ruthenium based anticancer drugs showed high potential as cytotoxic and cytostatic drugs which followed novel action mechanisms. One of the crucial factors that affects the anticancer activity of metal complexes is the ligand exchange kinetics in aqueous solutions. It varies in different metal cations (rates in the range of 10^{-6} to 10^8 s^{-1}). It was found that the rates of ligand exchange in ruthenium and platinum complexes are in the same range of 10^{-3} to 10^{-2} s^{-1} (Ranade, 2007). Therefore, ruthenium is considered to be a desirable alternative to platinum, as it mimics iron, which plays an active role in the physiological functions of the human body.

Remarkable features of ruthenium(II) centers are: (i) ruthenium and iron are biologically similar, (ii) they are in the Group 8, (iii) they have similar characteristics and many ruthenium complexes are not toxic, and (iv) they are quite selective of cancer cells, which is due to the ability of ruthenium to imitate iron in binding with biomolecules (Allardyce & Dyson, 2001).

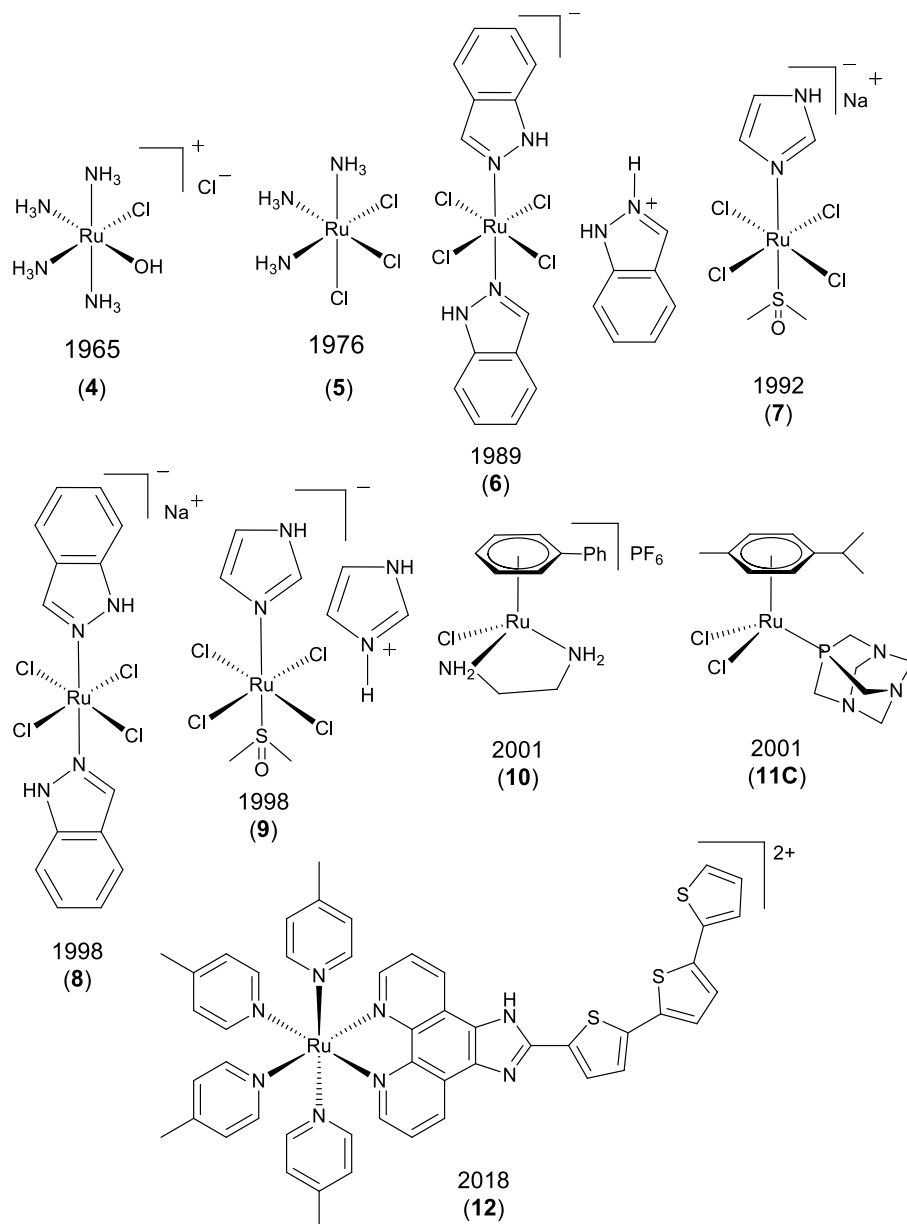


Figure 2. Timeline of discoveries of Ru-based anticancer drugs

Because of this ability, ruthenium complexes have been able to take the advantage of a human body's power to efficiently uptake and transport iron. Therefore, by imitating iron, ruthenium also has the ability to bind to transferrin and serum albumin proteins and transport within the body. Overexpression of transferrin receptors around cancer cells leads to an increased demand of iron. Hence, ruthenium based drugs can be delivered with high efficiency to the target cancer cells (Sava et al., 2011).

The ruthenium-arene unit has amphiphilic properties, because the arene unit is relatively hydrophobic, and that effect is counterbalanced by the metal centre which is relatively hydrophilic. The synthetic diversity provided by the arene ligand makes it an excellent scaffold for targeted chemotherapy (Dyson, 2007).

Evolution of ruthenium based anticancer drugs

Chloro-ammine complexes of ruthenium were the first to be studied as anticancer agents in a similar manner to well-known platinum complexes (**1**) - (**3**) (Figure 1).

In 1965, the ruthenium complex $[\text{Ru}(\text{NH}_3)_4\text{Cl}(\text{OH})]\text{Cl}$ (**4**) (Figure 2) was used in initial investigations owing to its structural resemblance to Pt(IV) analogues. *fac*- $[\text{RuCl}_3(\text{NH}_3)_3]$ (**5**) showed induced-filamentous growth in *E.coli* which resembled cisplatin (Durig et al., 1976). Inert Ru(III) complexes were activated by reduction into the labile Ru(II) species inside the cellular surrounding (Kelman, Clarke, & Edmonds, 1976). The reduction of ruthenium diminished the π -acceptor property of the metal, which lead to the increased labiality of the chloride ligand, by facilitating hydrolysis, leading to activation. After that, they reacted with DNA, which paved the path for the anticancer activity.

After the discovery of the drugs featuring: (i) indazole (Ind) ligand *e.g.*, *trans*- $[\text{RuCl}_4(\text{Ind})_2][\text{IndH}]$, KP1019, (**6**); *trans*- $[\text{RuCl}_4(\text{Ind})_2]\text{Na}$, IT-139 (**8**); and (ii) imidazole (Im) ligand $[\text{RuCl}_4(\text{DMSO})(\text{Im})]\text{Na}$, NAMI (**7**); $[\text{RuCl}_4(\text{DMSO})(\text{Im})]\text{H}$, NAMI-A (**9**) (DMSO = dimethylsulfoxide) which were subjected to clinical development, a new era of ruthenium-based anticancer drugs was born (Hartinger et al., 2006; Kenny & Marmion, 2019).

The complex (**7**) has undergone active clinical development and delivered phase I data which showed distinct anticancer activity (Fuereder & Berger, 2017). In 2001 [Ru(biphenyl)Cl(en)]⁺ RM175 (**10**) was introduced by Sadler as a novel anticancer agent (Sadler et al., 2005) which was a diamine-based Ru(II) arene complex with a chloride leaving group. This agent was said to yield high efficiency against human ovarian cancer (Iida et al., 2016). The anticancer drug (**11C**) was introduced by Dyson, and was particularly investigated as an antimetastatic agent (Dyson et al., 2001; Meier-Menches et al., 2018). In 2018, a novel Ru(II) complex, TLD 1433 (**12**) (Thota et al., 2018) completed its phase I trial for bladder cancer. This complex (**12**) is undergoing phase 1 and phase 2a clinical trials for non-muscle invasive bladder cancer treatment *via* photodynamic therapy (PDT) (Thota et al., 2018; Kar et al., 2020; Smithen et al., 2017; Balaji et al., 2020; J. Liu et al., 2019). Other clinically approved ruthenium arene complexes such as [(η⁶-flu)Ru(en)Cl]⁺, (AH54, flu = fluorene) and [(η⁶-dihyphen)Ru(en)Cl]⁺, (AH63, dihyphen = 9,10-dihydrophenanthrene) are utilized in radio sensitization of human colorectal cancer cells (Moharana et al., 2021; Carter et al., 2016).

Synthesis of (arene)Ru(II) complexes

Various (arene)ruthenium(II) complexes [(η⁶-arene)Ru(L)(X)(Y)], [(η⁶-arene)Ru(L[^]L)X]Y and [(η⁶-arene)Ru(L[^]X)(Y)] are known, where arene = cymene (**C**), benzene (**B**), toluene (**T**), hexamethylbenzene (**H**); L = amine, phosphine; L[^]L = en, diamine, diphosphine, (X[^]Y) = oxalate, (L[^]X) = acylacetonate; and (X), (Y) = halides, triflate *etc.* They were prepared by using (arene)ruthenium(II) dimers such as [(η⁶-C₆H₆)RuCl(μ-Cl)]₂ (**13**), [(η⁶-cymene)RuCl(μ-Cl)]₂ (**14**) and [(η⁶-toluene)RuCl(μ-Cl)]₂ as the starting materials (Perera, 2007; Perera, 2021) (Figure 3).

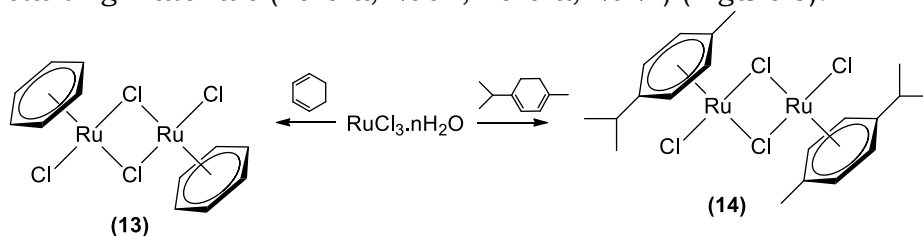


Figure 3. Synthesis of starting material [(arene)RuCl(μ-Cl)]₂

A large number of synthetic routes have been developed for (arene)Ru(II) complexes with many different monodentate, bidentate and tridentate ligands. Simple monodentate amines (NR_3) react with $[(\text{arene})\text{RuCl}_2]_2$ dimers to give neutral complexes such as $[(\text{arene})\text{RuCl}_2(\text{NR}_3)]$. For example, by using **(13)**, the neutral complex $[(\eta^6\text{-C}_6\text{H}_6)\text{RuCl}_2(\text{NH}_2\text{C}_6\text{H}_4\text{Me})]$ **(15)** and disubstituted salt **(16)** can be obtained (Figure 4) (Bates & Begley, 1990).

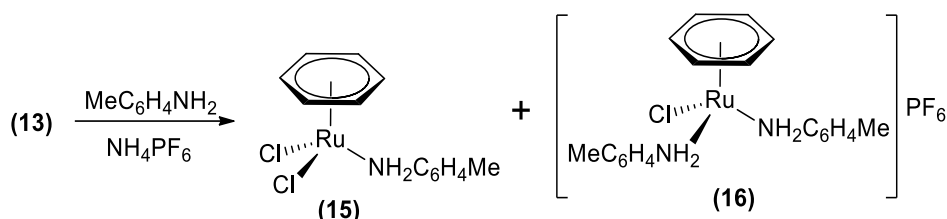


Figure 4. Preparation of (benzene)Ru(II) complexes with amines

Many phosphine complexes of the general formula $[(\eta^6\text{-arene})\text{RuCl}_2(\text{phosphine})]$ are known (Biancalana et al., 2017). For example, a series of $[(\eta^6\text{-arene})\text{RuCl}_2(\text{PTA})]$ **(11C/B/T/H)** were obtained by adding PTA ($\text{L}^1 = 1,3,5\text{-triazza-7-phosphaadamantane}$) to the corresponding precursor $[(\eta^6\text{-arene})\text{RuCl}_2]_2$, and thereby splitting the chloride bridge of the dimer (Figure 5) (Weiss et al., 2014).

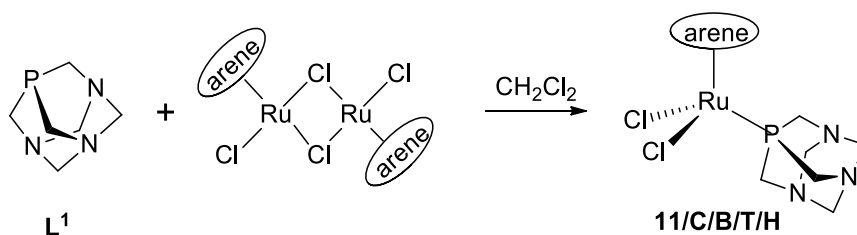


Figure 5. Synthesis of $[(\eta^6\text{-arene})\text{RuCl}_2(\text{PTA})]$ **(11C/B/T/H)**
 {arene = *p*-cymene (**C**), benzene (**B**), toluene (**T**) or hexamethylbenzene (**H**)}

A mixture consisting of starting materials $[(\eta^6\text{-arene})\text{RuCl}_2]_2$ and ($\text{L}^2\text{-L}^4$) was allowed to react at room temperature to produce neutral (arene)Ru(II) benzhydrazone complexes **(17)** containing anionic chelating ligand (N^-O^-) (Figure 6) (Subarkhan & Ramesh, 2016).

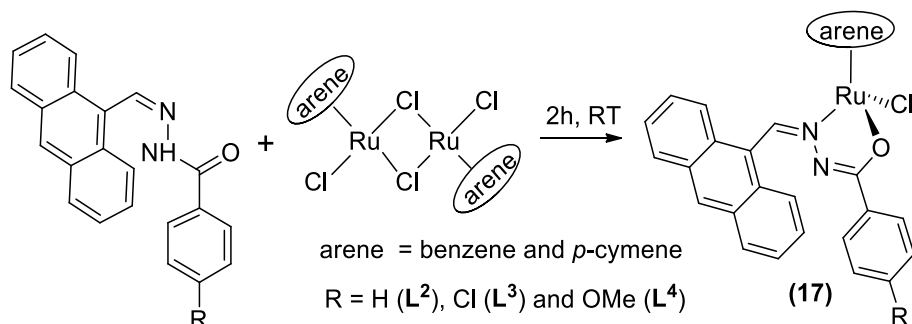


Figure 6. Synthesis of (arene)Ru(II) benzhydrazone complexes

The neutral Ru(II) complex $[\text{Ru}(\eta^6\text{-toluene})(\text{dppz})\text{Cl}]\text{PF}_6$ (**18**) containing a N^{^N} bidentate ligand was obtained by adding a solution of dipyridophenazine (dppz) (**L⁵**) to a suspension of $[(\eta^6\text{-toluene})\text{RuCl}_2]_2$ and NH_4PF_6 in methanol (Nikolić et al., 2019) (Figure 7).

As shown in Figure 7, (arene)Ru(II) complexes of the type $[(\text{arene})\text{Ru}(\text{N}^{\wedge}\text{N})\text{X}]\text{Y}$, $[(\text{arene})\text{Ru}(\text{N}^{\wedge}\text{O})\text{X}]\text{Y}$, $[(\text{arene})\text{Ru}(\text{N}^{\wedge}\text{S})\text{X}]\text{Y}$, $[(\text{arene})\text{Ru}(\text{N}^{\wedge}\text{P})\text{X}]\text{Y}$ and $[(\text{arene})\text{Ru}(\text{O}^{\wedge}\text{O})\text{X}]$ have been prepared (Suss-Fink G, 2010).

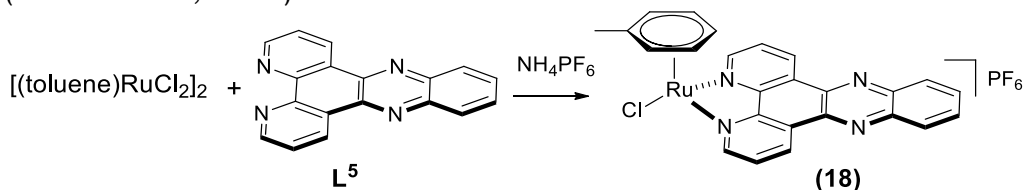


Figure 7. Synthesis of $[(\eta^6\text{-toluene})\text{Ru}(\text{dppz})\text{Cl}]\text{PF}_6$ (**18**)

Cytotoxicity of Ruthenium Complexes

Among the most investigated and advanced non-platinum anticancer metallodrugs are, ruthenium-based anticancer drugs, which have undergone considerable advances over the past two decades. Two representatives of ruthenium-based anticancer drugs are currently undergoing clinical trials, due to its high cytotoxic activity.

Indazole-based KP1019, KP1339 and IT-139 as anticancer agents

Ruthenium(III) complex, *trans*-[RuCl₄(Ind)₂][IndH] KP1019 (**6**) (Figure 2) was investigated for its activity using freshly explanted human tumour cells *in-vitro* (Depenbrock et al., 1997). Based on experimental data, the tumour specific activity and its mode of action were found to be controlled by the mechanism of substantial binding to serum proteins in blood (Clarke, 1989). When appropriate plasma levels were reached, (**6**) was able to achieve clinical activity against various tumour types. The sodium salt of (**6**), which is KP1339 is also under clinical trials (Sonkar et al., 2021). The ruthenium(III) complex, IT-139 (**8**) (Figure 2) has been used to treat cancer cells by targeting metastatic development in cancer patients (Lizardo et al., 2016), which was very effective in combination treatments and also as a single agent for carcinoid neuroendocrine tumours and colorectal cancer (Trondl et al., 2014).

Imidazole-based NAMI, NAMI-A and KP418 as anticancer agents

In 1975, [RuCl₂(DMSO)₄] was explored for induced filamentous growth in E.coli and was found to possess similar properties as cisplatin (Monti Bragadin et al., 1975). However, *trans*-[Ru^{II}Cl₄(DMSO)₂] displayed only a slight effect on primary tumors, but a significant reduction was shown in the volume of lung metastases (Pacor et al., 1991). The *trans*-[Ru^{III}Cl₄(DMSO)₂] complex was unstable in aqueous solution during hydrolysis, immediately liberating DMSO. Investigation of Ru(III) complexes with imidazole ligands lead to the discovery of Na[RuCl₄(DMSO)(HIm)] NAMI, (**7**) (Figure 2). The complex (**7**) containing both N and S donor ligands was found to be an anti-tumor metastasis inhibitor (Mestroni et al., 1993) due to : (i) the effective inhibition of spontaneous metastasis formation (ii) good solubility and (iii) higher stability. Additionally, the S donor displayed a strong kinetic *trans*-effect, resulting in an increment of lability of the ligands of (**7**) in biological media. The reduction of the metal occurred before the hydrolysis of (**7**), which could be catalysed by biological reductants (Mestroni et al., 1993). NAMI (**7**) was also investigated for its antitumor activity (Meier-Menches et al., 2018). *trans*-[RuCl₄(DMSO)(Im)][HIm] (NAMI-A (**9**) (Figure 2) displayed increased stability in air compared to (**7**), but both showed similar pharmacological effects (Pillozzi et al., 2014). Phase I studies of complex (**9**) was completed in 2004, and it was the first ruthenium based anticancer agent to enter clinical trials (Rademaker-Lakhai et al., 2004).

KP418, *i.e.* $trans$ -[RuCl₄(Im)₂ImH], and **(6)** were shown to induce apoptosis through the mitochondrial pathway in the cell lines of SW480 (colorectal carcinoma) (Kapitza *et al.*, 2005). KP418, showed therapeutic activity against B16 melanoma and P388 leukaemia (Trondl *et al.*, 2014).

Cytotoxicity of (arene)ruthenium(II) complexes

The activity of arene ruthenium complexes can be identified based on many properties, but the main focus regarding the activity would be the cytotoxicity of these complexes, involving their antitumoral and antimetastatic properties. Cytotoxicity of ruthenium complexes with phosphines, amines, and other N[^]N, N[^]O, N[^]S, N[^]C, S[^]O chelating ligands are presented below.

PTA as a P donor ligand

Among the monodentate ligands used in (arene)ruthenium complexes, the PTA ligand (L¹) is one of the most widely employed. The anticancer activity of [(η⁶-arene)Ru(PTA)(X)(Y)] was studied by Dyson *et al.* by varying the arene, X and Y, where arene = cymene (**C**), benzene (**B**), toluene (**T**), hexamethylbenzene (**H**); X,Y = oxalate, acylacetate and halides *etc.* The complexes [(η⁶-arene)Ru(PTA)Cl₂] (**11**) (Figure 8) demonstrate very specific interactions with proteins compared to cisplatin (Scolaro *et al.*, 2005).

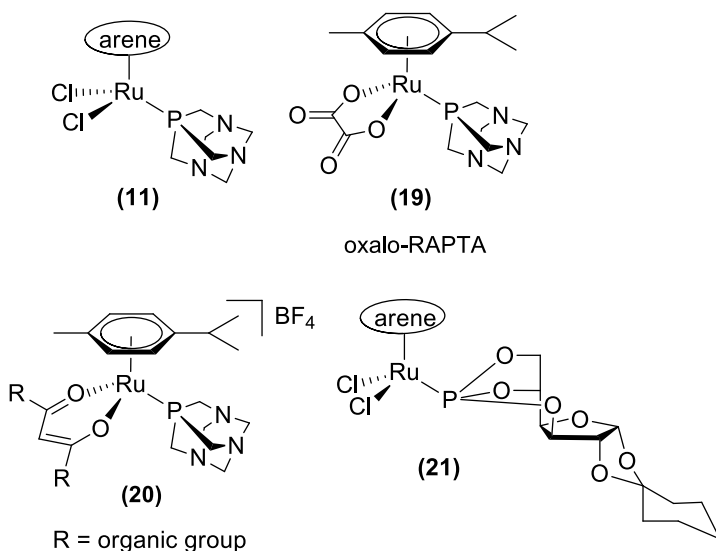


Figure 8. (Arene)Ru(II) complexes with P-donor ligands {arene = *p*-cymene (**C**), benzene (**B**), toluene (**T**) or hexamethylbenzene (**H**)}

Both RAPTA-C (**11C**) and RAPTA-B (**11B**) inhibited metastasis growth, and RAPTA-T (**11T**) and RAPTA-H (**11H**) displayed cytotoxicity (Nowak-Sliwinska et al., 2011). Two mechanisms were proposed to explain the effective hindrance of metastatic formation by (**11T**): (i) by the inhibition of detachment from the primary tumor and (ii) by the inhibition of re-adhesion to a new substrate. Both the above mechanisms were prominent in the MDA-MB-231 breast cancer model. Complexes (**11T**) and (**11C**) displayed anti-angiogenic properties as well (Portoghese, 1990). Variation of the anionic ligands of (**11C**) by replacing the chloro ligand with iodo, bromo and isocyanato ligands paved the way to new complexes which were able to show antimicrobial activity, but in contrast, antiviral activity was not seen (Allardyce et al., 2003). The second generation oxalo-RAPTA complex [(cymene)Ru(PTA)(O,O-C₂O₄)] (**19**) and the dikenato complex [(cymene)Ru(PTA)(O,O-R₂acac)]⁺ (**20**) (Figure 8) showed an increase of cytotoxicity due to the replacement of chloride ligands by the oxalate ligand (Wee et al., 2006).

The aquation of (**11C**) in water has been studied using NMR and UV-Vis spectroscopy (Scolaro et al., 2008), and it was determined that the activation step in the cytotoxicity is aquation. Suppression of hydrolysis was observed in the blood plasma, because of the high chloride concentration in blood plasma, approximately around 100 mM, but once the compound penetrated the cell cytoplasm, aquation was activated due to the sudden drop of chloride concentrations in the cell cytoplasm, allowing the labile aqua ligand to undergo substitution by biomolecules (Dyson, 2007).

The complexes (**19** and **20**) were resistant to hydrolysis, but also cytotoxic, presumably activated using a different mechanism which involved the slippage of the arene ring (Vock et al., 2008). RNA or DNA are generally considered as the drug targets inside the cancer cells, but serum proteins can also act as targets. RAPTA compounds are strong inhibitors of cathepsin B, and can slightly inhibit thioredoxin reductase as well (Ang et al., 2011). The complex (**11C**) has the ability to slow down cell division in cancer cells, and also to induce apoptosis. The primary target of

(**11C**) is presumed to be proteins instead DNA as proposed in platinum metallodrugs (Wu et al., 2008).

With Carbohydrate phosphine ligands

In order to tune and enhance the biological behaviour of drugs, a bioactive molecule can be incorporated to a metal complex. To perform that, various bioactive fragments within phosphine ligands have been used in the arene ruthenium frame (Biancalana et al., 2017). The cancer cell selectivity is provided by the carbohydrate fragment in the arene ruthenium complex against several cancer cell lines (Patra et al., 2016). The complexes (**21**) containing a carbohydrate-based ligand (Figure 8) showed intermediate anticancer activities, but they demonstrated lower cytotoxicity against nontumorigenic cells, which showed that it has cancer cell selectivity (Berger et al., 2008; Pelletier et al., 2010). By enhancing the lipophilicity of the carbohydrate moiety, the performance of this complex could be improved (Berger et al., 2008).

With monodentate phosphine ligands

Phosphine Complexes containing silicon-side groups with the general formula $[\text{Ru}(\text{cymene})\text{Cl}_2(\text{phosphine})]$ showed IC_{50} values which were in the same range as of cisplatin in human leukemia cancer cells (HL-60) (Aznar et al., 2013). Similarly, complexes with aminomethylphosphanes (**22**) $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}_2(\text{PPh}_2\text{R})]$ (Figure 9) showed cytotoxic activities close to cisplatin against the MCF7 (human breast adenocarcinoma) and A549 (human lung adenocarcinoma) cell lines.

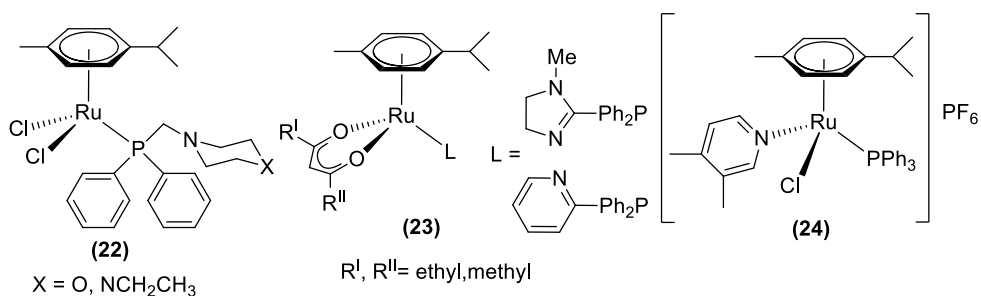


Figure 9. (Arene)Ru(II) complexes with P-donor ligands
Hydrophobicity enhancement of the ruthenium arene complex was observed with the introduction of a triphenylphosphine

ligand, which lead to increased cytotoxicity. Aminophosphine complexes with the general formula of $[\text{Ru}(\text{cymene})(\text{O},\text{O-acac})(\text{L})]$ in which (L = 2-pyridyl or imidazolyl phosphines) (**23**) showed better cytotoxicity *in vitro* against pancreatic cancer cell line (CAPAN-1) and breast cancer cell line (MCF-7) (Biancalana et al., 2017).

Cationic (arene)ruthenium complex (**24**) with both PPh_3 and 3,4-dimethylpyridine (Me_2py) ligands, $[\text{Ru}(\text{cymene})(\text{Me}_2\text{py})\text{Cl}(\text{PPh}_3)]^+$, demonstrated cytotoxicity comparable to that of cisplatin, against the human leukaemia tumour cell line (Biancalana et al., 2017). Ruthenium arene complexes with triphenylphosphine ligands showed enhanced ability to bind with DNA and changed its secondary and tertiary structures, in contrast to neutral complexes in which the PPh_3 ligand was absent, that could bind to DNA solely in a covalent manner (Sáez et al., 2014).

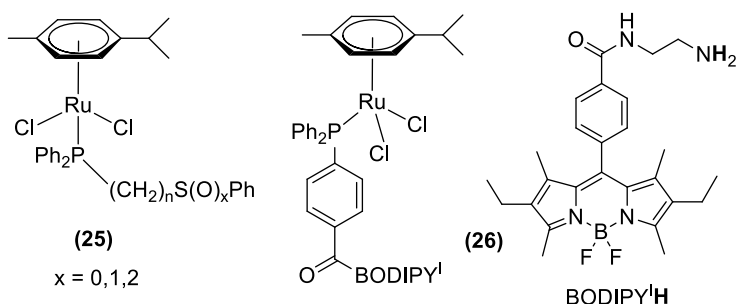


Figure 10. (Arene)Ru(II) complexes with bulky P-donor ligands

(Arene)ruthenium complexes with S-functionalized phosphine ligands (**25**) (Figure 10) showed cytotoxicity in the cancer cell lines 8505C, SW480, 518A2, MCF-7 and A253 (Biancalana et al., 2017).

The R group of PPh_2R ligands has a variety of roles which includes its employment as a scaffold for tethering specific functionalities to the ruthenium center. The (arene)ruthenium complex tethered to BODIPY to the phosphino moiety *via* an amide bond (**26**) is highly florescent (Bertrand et al., 2018).

With monodentate N donor ligands

(Arene)ruthenium complexes of the type **(27)** had the ability to induce cell death through inhibition of DNA synthesis. In comparison to the free anthracene-based ligand, the uptake and the accumulation of the complex in the cells was accelerated (Vock et al., 2007).

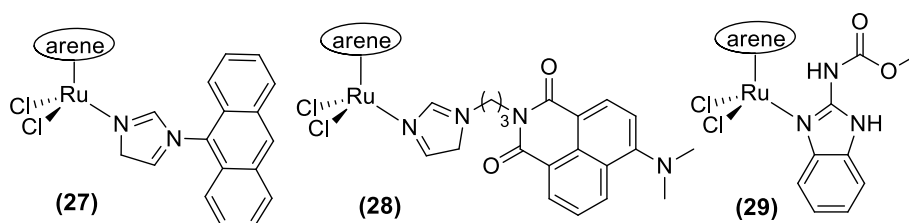


Figure 11. (Arene)Ru(II) complexes with N-donor ligands {arene = *p*-cymene (**C**), benzene (**B**), toluene (**T**) or hexamethylbenzene (**H**)}

Ruthenium arene complexes tagged with naphthalimide **(28)** showed reasonable cytotoxicity towards cancer cells and in contrast, their cytotoxicity towards model healthy cells was less (Kilpin et al., 2012). Naphthalimide-based complexes **(28)** showed higher antitumor activity than the prototype complex **(11C)**, which illustrated that the naphthalimide moiety induced higher cytotoxicity than the prototype complex **(11C)**. Ruthenium complex of mebendazole **(29)**, which was a widely known anthelmintic drug showed activity against HeLa cancer cell (Akhtar et al., 2017)

With ethylenediamine as a N^N donor ligand

Cationic (arene)Ru(II) complexes containing ethylenediamine (en) displayed elevated cytotoxicity both in *vivo* and in *vitro*. Complexes **(30A)** and **(30B)** containing the cymene ligand and the complex **(31)** containing the biphenyl (bph) ligand retarded the growth of the human ovarian cancer cell line (A2780), which had IC₅₀ values similar to carboplatin. In contrast, the complex **(32)** with the tetrahydroanthracene (tha) ligand was hydrophobic, and showed similar antiproliferative ability as cisplatin (Aird et al., 2002).

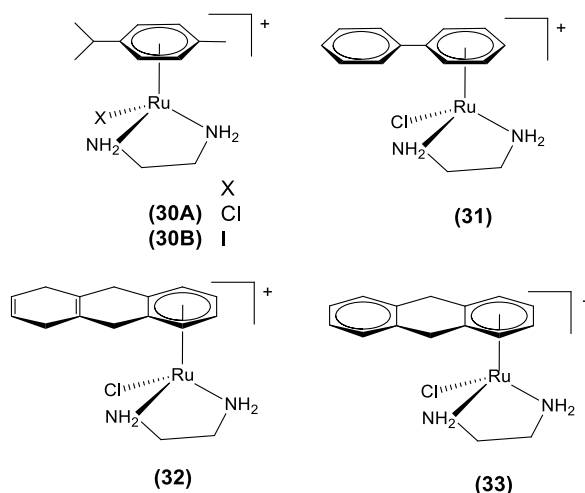


Figure 12. (Arene)Ru(II) complexes with ethylenediamine

Arene-ruthenium-ethylenediamine units showed favorable binding towards N7 of guanine in DNA (Chen et al., 2003). When two monodentate N-donor ligands were replaced by a chelating diamine ligand, the (arene)Ru(II) complexes were found to be inactive towards the A2780 cell line. In terms of structure-activity relationship, the complexes with a more hydrophobic arene ligand and a stable bidentate N^N-donor ligand along with exchangeable halide ligand showed a higher cytotoxicity (Iida et al., 2016).

The complex with the biphenyl ligand **(31)** acts as a potential DNA intercalator (Liu et al., 2006). The complex **(31)** showed powerful stereospecific hydrogen bonding between its NH group and the C6 carbonyl group in guanine in DNA, suggesting that simultaneous stereospecific hydrogen bonding, intercalation, and covalent coordination are involved in the recognition behaviour of DNA in arene-ruthenium-diamine complexes (Chen et al., 2002).

It was suggested that DNA binding of complexes containing bph **(31)**, tha **(32)** and dihydroanthracene (dha) **(33)** are due to a combination of (i) non-covalent hydrophobic interactions, (ii) covalent Ru–N (guanine N7) coordination between DNA and the arene ligand, (iii) minor groove binding, and (iv) arene intercalation. In contrast to complexes containing multiple arene rings (*e.g.*, bph, tha, dha), complexes with single arene rings such as benzene and cymene ligands were unable to interact with DNA using intercalation (Kostrhunova et al., 2008).

With guanidine as N^N and N^O donor ligands

Guanidine plays an important role in both inorganic and organic chemistry, which is found in many natural compounds. Guanidines were tested for its nuclease activity and it showed cytotoxic properties (Jeyalakshmi et al., 2019). Due to the Y-shaped CN₃ unit present in the guanidine ligand (**34** and **35**), it is an electronically and sterically flexible ligand and can be used in a wide range of biological applications, such as, antitumor, anti-inflammatory, antimalarial and urease inhibition (Murtaza et al., 2011). The donor atoms of guanidine differ as N^N and N^O, in the complexes (**34** and **35**) respectively, and it has a direct influence on the rate of hydrolysis, and thereby on cytotoxicity (Habtemariam et al., 2006).

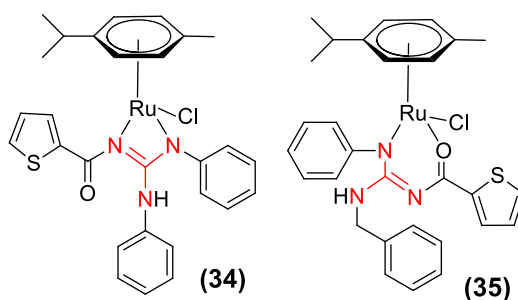


Figure 13. (Arene)Ru(II) complexes with N^N & N^O donor ligands

With dipyridophenazine as a N^N donor ligand

The (arene)Ru(II) complex (**18**) with dipyridophenazine (dppz, L⁵) as the chelating ligand (Figure 7) facilitated the transport of the complex cation across the cell membrane and contributed to DNA binding due to the high lipophilicity of the dppz ligand (Nikolić et al., 2016).

With β -ketoamine as a N^O donor ligand

Electronic and steric properties around the ruthenium ion can be fine-tuned using the β -ketoamine ligand in a (arene)Ru(II) complex (**36**) (Figure 14) by varying the arene and the properties of the R group. These complexes showed significant anticancer properties *in vitro*, and cytotoxicity against human ovarian cancer cells (Pettinari et al., 2013).

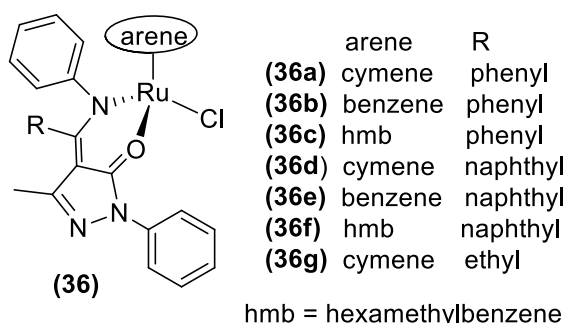


Figure 14. (Arene)Ru(II) complexes with N⁺O donor ligands

With picolinate as a N⁺O donor ligand

The (arene)Ru(II) complex [(cymene)RuCl(picolinate)] (**37**) bound efficiently to DNA and showed antimetastatic activity and anti-proliferative activity, despite its low level of genotoxicity and cytotoxicity (Sonkar et al., 2021).

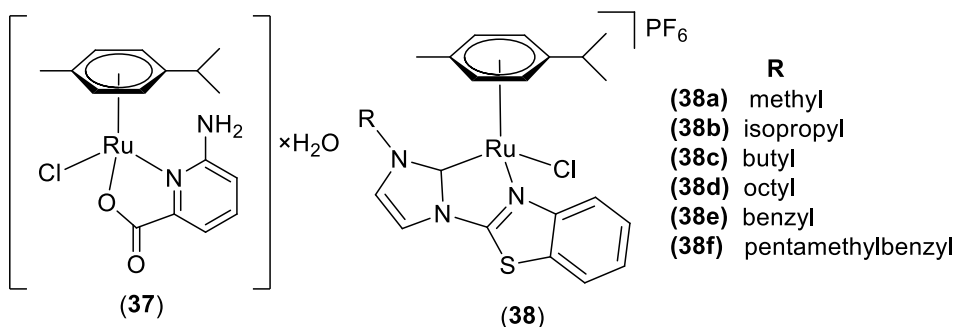


Figure 15. (Arene)Ru(II) complexes with N⁺O & N⁺C donor ligands

With NHC as a N⁺C donor ligand

Cationic (arene)Ru(II) complexes (**38a-f**) (Figure 15) with benzothiazole-functionalized NHC ligand (NHC = nitrogenheterocarbene) were studied for their cytotoxic activity. Their *invitro* cytotoxicity was evaluated using six cancer cell lines, A549, HT-29, HeLa, A2780, LoVo and HCT-116 (colon cancer) (Chen et al., 2020). The complexes (**38a**) and (**38b**) were found to be inactive against these cell lines, and (**38d**) demonstrated significant cytotoxicity against the cell lines A2780 and HT-29,

which occurred due to the increase in the length of the alkyl substituent.

With acylthiourea as a S^ΛO donor ligand

(Arene)Ru(II) complexes (**39**) with the formula [Ru(cymene)(PPh₃)(S^ΛO)]PF₆ having acylthiourea were evaluated for the cytotoxic activity on five cell lines, MCF-10A, DU145, A549, MRC-5 and MDA-MB-231 (Cunha et al., 2020). These complexes showed high selectivity towards breast cancer cells compared to cisplatin, and they were cytotoxic against the A549 and DU145 cell lines. The complex (**39a**) with thienyl as R¹ was cytotoxic to all the above cell lines. The cytotoxicity was enhanced by the increase of the chain length of R², because the increase of chain length amplified the lipophilicity of the complexes, thereby increasing the cellular uptake of these agents.

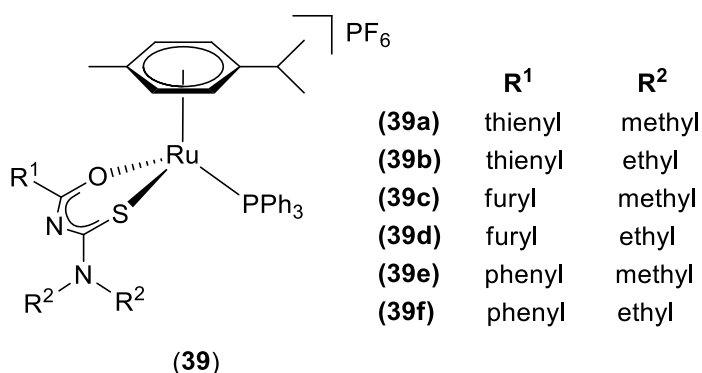


Figure 16. (Arene)Ru(II) complexes with S^ΛO donor ligands

Activity tuning of (arene)ruthenium complexes

The cytotoxicity of these (arene)ruthenium complexes were determined using various assays such as, tube formation assay (Yamamoto et al., 2003), adhesion assay (Gurgul et al., 2020), migration and invasion assay (Chambers et al., 2002), wound healing assay (Zamora et al., 2015), colony formation assay (Chen et al., 2021), RT-PCR, and western blotting.

Various (arene)Ru(II) complexes [(η⁶-arene)Ru(L)(X)(Y)], [(η⁶-arene)Ru(L^ΛL)X]Y and [(η⁶-arene)Ru(L^ΛX)(Y)] where arene = cymene (**C**), benzene (**B**), toluene (**T**), hexamethylbenzene (**H**); L =

amine, phosphine; L^L = en, diamine, diphosphine, (X^Y) = oxalate, (L^X) = acylacetate; and (X), (Y) = halides, triflates *etc.* can be tuned using various ligands.

(i) Fine tuning of the bidentate ligand (L^L , L^X and X^Y) is used as one such method. Chelate ligands generally exhibit higher resistance towards substitution, and as a result the aquation is controlled by the suitable choice of the other ligands in the molecule. The toxicity of these complexes can be changed by the appropriate choice of the X ligand (Aird et al., 2002). One such example is, the change of the bidentate ligand from en to acac. Apart from increasing the pK_a of the aqua complex significantly (Fernández et al., 2004), acac influenced the recognition of the complex by DNA and other targets. This selective recognition is critical for the activity of the drugs that mainly targets DNA. (Arene)Ru(II) complexes with indoloquinolines as N^N ligands have been used, because they can act as kinase inhibitors.

(ii) The nature of the exchangeable ligand (X/Y) is another factor that can be varied in order to tune the cytotoxicity of arene ruthenium complexes, because it affects the extent of hydrolysis of the Ru-X bond. For an example, though the hydrolysis difference between chloride and bromide is negligible, the hydrolysis of iodide as a halide is up to seven-fold slower than the chloride and bromide ligands. Ruthenium-pyridine bond is even more inert than iodide, and it completely blocks the hydrolysis. These inert halides are not cytotoxic and these inert species can be triggered to undergo hydrolysis using various strategies. $[(cym)Ru(bpm)(py)](PF_6)_2$ (bpm = 2,20-bipyrimidine) in which pyridine is inert, is activated using visible light to dissociate the pyridine ligand (Barragán et al., 2011). By using controlled irradiation, reactive aqua species can be cleanly generated, and it gains ability to bind with DNA, through photo-triggered binding of anticancer pro-drugs.

(iii) Activation by ligand oxidation is another mechanism for fine tuning of ruthenium arene complexes. Redox mechanisms are involved in ruthenium arene thiolato-complex activation (Jaouen & Dyson, 2007). For an example, the tripeptide glutathione (GSH) is involved in the activation by oxidation of RM175 (**10**) in buffered solutions (Wang, Xu et al., 2005).

(iv) Another main factor is the nature of the arene ligand. The arene complexes are not static, where benzene or hexamethylbenzene in (arene)Ru(II) complexes, can rotate around the perpendicular axis compared to biphenyl, which allows the optimization of arene interactions with DNA (Palermo et al., 2016). Thermodynamic properties and DNA recognition can be modified site-specifically in ruthenium arene complexes by varying the type of arene as, *para*-, *meta*- and *ortho*-isomers (Palermo et al., 2016). It is shown that the *para* complex displays higher cytotoxicity towards cancer cells, compared to the *meta*- and *ortho*- isomers (Bugarcic et al., 2008). *para*-Arene complexes can bind to DNA bases through both intercalation and coordination, whereas the other less toxic isomers are able to bind only through monofunctional coordination.

Conclusions

(Arene)ruthenium complexes are an emerging class of anticancer drugs, owing to their fewer side effects compared to platinum anticancer agents. The relationship between the structure and cytotoxicity of (arene)Ru(II) complexes of the types [(arene)Ru(L)(X)(Y)], [(arene)Ru(N[^]N)X]Y, [(arene)Ru(N[^]O)X]Y, [(arene)Ru(N[^]S)X]Y, and [(arene)Ru(O[^]O)X] is elaborated in this review. The properties of these complexes depend on the arene, and the choice of the co-ligands. The researchers hope that this review would provide an insight on the development of ruthenium complexes as emerging anticancer agents.

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