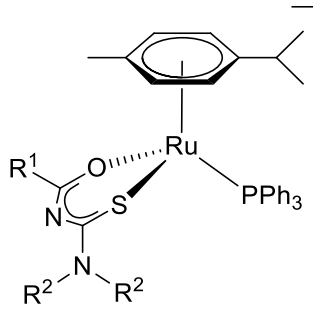
which occurred due to the increase in the length of the alkyl substituent.

With acylthiourea as a S^O donor ligand

(Arene)Ru(II) complexes (**39**) with the formula [Ru(cymene)(PPh_3)(S^O)]PF_6 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 R^1 was cytotoxic to all the above cell lines. The cytotoxicity was enhanced by the increase of the chain length of R^2, because the increase of chain length amplified the lipophilicity of the complexes, thereby increasing the cellular uptake of these agents.



(**39**)

	R^1	R^2
(39a)	thienyl	methyl
(39b)	thienyl	ethyl
(39c)	furyl	methyl
(39d)	furyl	ethyl
(39e)	phenyl	methyl
(39f)	phenyl	ethyl

Figure 16. (Arene)Ru(II) complexes with S^O 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 [(η^6-arene)Ru(L)(X)(Y)], [(η^6-arene)Ru(L^L)X]Y and [(η^6-arene)Ru(L^X)(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.* 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 ei 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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