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Amberlite IR-120 (H) mediated "on water" synthesis of fluorescent Ruthenium(II)-arene 8-hydroxyquinoline complexes for cancer therapy and live cell imaging

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ABSTRACT

A series of Ruthenium-Quinolinol complexes (**3a–d** & **4a–d**) has been synthesized by employing a simple, efficient and environmental friendly condition. Catalytic role of Amberlite IRA-120(H) has been demonstrated. The structures of the new compounds were elucidated by the analysis of spectroscopic data. The stability of these complexes was measured by UV spectroscopy & time dependent NMR spectroscopy. These newly developed complexes were represented as potential anticancer agent against human breast carcinoma cell line (MCF-7), human Epitheloid Cervix Carcinoma (HeLa), human lung adenocarcinoma epithelial cell line (A549) and human colon cancer cell line (Caco-2). Most of the ruthenium complexes showed higher anticancer activity in MCF-7, HeLa and Caco-2 cell lines than cisplatin. A high selectivity (9–28 folds) was observed with these newly developed organoruthenium compounds in human cancer cell lines (MCF-7, HeLa and Caco-2) with respect to normal fibroblast cell line (MRC-5). Complex [(η6-hexamethylbenzene)RuCl(κ2-O,N-5-chloro-HyQ)]·Cl (**4b**), [(η6-hexamethylbenzene)RuCl(κ2-O,N-5,7-dibromo-HyQ)]·Cl (**4c**) and [(η6-hexamethylbenzene)RuCl(κ2-O,N-5-chloro-7-iodo-HyQ)]·Cl (**4d**) exhibited best cytotoxicity profiles in three reported human cancer cell lines (MCF-7, HeLa, Caco-2). Cellular imaging study was also performed with these newly developed organoruthenium compounds. Compound **4c** might be utilized for cancer theranostic agents because of its significant quantum yield in water, high potency, selectivity and high cellular uptake in cancer cell lines.

1. Introduction

Nowadays, metal-based complexes came into picture as an anticancer drug with the discovery of cisplatin. Cisplatin was first successful transition metal discovered and approved by Food Drug and Administration (FDA) for the treatment of ovarian and testicular cancer [1]. Three other structurally related platinum drugs (carboplatin, nedaplatin, and oxaliplatin) have also entered widespread clinical use. However, due to their serious side effects, such as high toxicity, inherent and acquired resistance [2–6], have drawn our attention towards nonplatinum metal complexes for anticancer drug discovery [7–11].

There are several metal complexes such as, antimalarial ferrocene–quinoline conjugates [12], and the antineoplastic ruthenium complexes NAMI-A and KP-1019 [13], currently in Phase I clinical trial. Presently, Ruthenium complexes have shown promising results to come up as next possible anticancer therapeutic because of their rate of ligand exchange, the range of accessible oxidation states, aqueous solubility and stability in biological environment [14]. The ability of ruthenium to mimic iron in binding to certain biological molecules with minimal side effects and immunity to the acquisition of drug resistance made these complexes for better candidates in drug discovery [15]. Currently, the coordination of bioactive ligands with various metal ions is a promising strategy in drug discovery [16]. 8-hydroxyquinoline has been explored as antiseptic, disinfectant, bactericidal agent [17,18] and a potent anticancer drug as well [19]. It can impulsively bind with tumor cellular copper forming proteasome inhibitors and hence, it has provided a new dimension in anti-proteasome and anti-angiogenesis chemotherapy [20]. Currently, Clioquinol (CqH), has been utilized for successful treatment of microbial infections, Alzheimer's and Parkinson's disease [21,22]. Clioquinol has the ability to cross the blood–brain barrier by chelating metal ions, such as Cu(II) and Zn(II) [23]. It also prevents the proteasomal activity and arrests the proliferation of cultured human cancer cells [24,25]. Interestingly, Clioquinol acts as an inducer of cell death in leukemia and myeloma cell lines [26]. 8-

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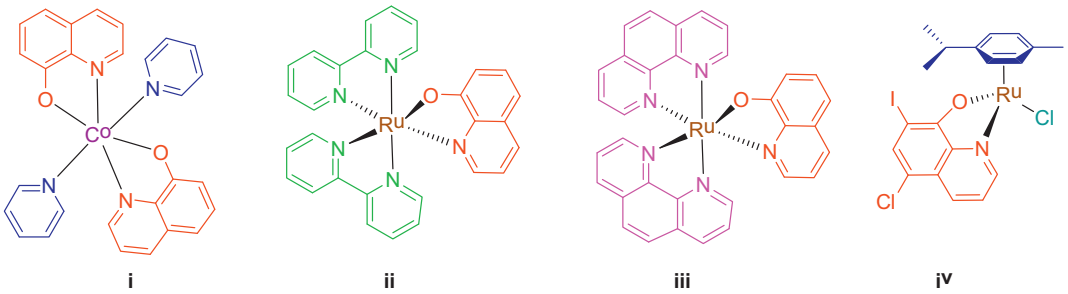

Fig. 1. Newly developed metal quinolinol complexes.

hydroxyquinoline complexes with several metal ion including cobalt (II), lanthanide, tin(IV), nickel, Ruthenium(II) exhibits high cytotoxicity in human cancer cell lines (Fig. 1) [27–31].

Hartinger et al. have already reported some Ru(II) 8-hydroxyquinoline complexes and evaluated their anticancer property in Human Cancer Cell Lines HCT116, NCI-H460, and SiHa [31]. Coordination of hydroxyquinolines to a Ruthenium Bis-dimethyl-phenanthroline scaffold radically improves potency and these are used as potential antineoplastic agents [32]. However, except this report [32] none of them have tested the compounds for selectivity in cancer cell lines with respect to normal cells. Likewise, theranostic application of these compounds was also virtually unexplored. As a result, we have kept some important aspects in mind to design our ruthenium drug for bio-evaluation (Fig. 2). The key factors of this strategy are (i) a variety of η^6–arene moiety should be attached with ruthenium as it stabilizes the oxidation state of metal ion and may assist its transportation through cell membrane [33,34] (ii) the three remaining coordination sites must be occupied with a bidentate ligand (i.e. 8-hydroxyquinoline derivatives) and a labile halogen ligand (i.e. chlorine), forming a typical "piano stool" geometry [35,36]. Interestingly, halide ligands can dissociate in aqueous solution such that it confers the multifunctional potential to the target complex [26].

Nowadays, we are interested to develop a new green technology in synthetic processes since the environmental impacts of chemicals are very harmful. The tight legislation for maintaining the greenness necessitates us to prevent the waste generation, avoid the use of auxiliary substances (e.g., organic solvents, additional reagents) and also minimize the energy requirement [37]. In our previous report, we have successfully synthesized the Ru(II)-*p*-cymene 8-hydroxyquinoline derivatives and evaluated their antibacterial properties [38]. However, an efficient green methodology for the preparation of these types of ruthenium scaffolds is highly warranted.

Herein, we employed water in the reaction medium as a solvent which recommends several advantages like noninflammable, nontoxic, cheap and safe solvent for organic reaction; it eliminates the consumption of drying agents, energy and time to dry the reagent & substrate; and the product may be simply isolated by filtration [39,40]. Nowadays, Amberlite resin has been widely employed as an ion exchange resin as well as an effective catalyst in organic reactions [41]. Recently, our group has also been reported Amberlite IR-120(H) resin mediated Ru(II)-arene benzothiazole, benzoxazole and benzimidazole complexes in water [42]. We have also discovered Amberlite IRA 402(OH), a basic resin mediated green synthesis of novel benzothiazole–quinoline Conjugates as cancer theranostics [43]. In the course of our research on the development of green technique for the synthesis of bioactive heterocycles, herein we have introduced the similar protocol for the synthesis of Ruthenium(II)-arene 8-hydroxyquinoline complexes and evaluated their anticancer activity and live cell imaging.

2. Experimental Section

2.1. Materials and Methods

The melting points were determined using capillary melting point apparatus. Also, dichloro *p*-cymene Ruthenium(II)chloride, dichloro hexamethylbenzene Ruthenium(II)chloride, 8-hydroxyquinoline derivatives, Ct-DNA, ethidium bromide, bovine serum albumin (BSA) were purchased from Sigma Aldrich Chemical Limited. All the required organic solvents were used for chemical synthesis and also for chromatographic technique obtained from E. Merck (India) of analytical grade. HeLa, MCF-7, Caco-2 & MRC-5 cell lines were purchased from NCCS, Pune. ^{1}HNMR and ^{13}CNMR spectra has been recorded on a Bruker DPX spectrometer in 400 MHz and 100 MHz respectively with tetramethylsilane as internal standard and the chemical shifts are reported in ppm units. Abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. The melting points of the ruthenium complexes were measured on Elchem Microprocessor based DT apparatus using open capillary tubes and are uncorrected. The synthesized compounds were also characterized by Schimadzu LCMS-4000 LC-MS instrument, having 4000 triple quadraupole MS, using Methanol as the solvent. Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminum sheets (E. Merck, Germany) using the solvent system in Methanol/Ethyl Acetate mixture and spots were identified by UV light. The UV–Visible spectrum was obtained on UV-2550, Shimadzu Corporation, and Kyoto, Japan. The fluorescence spectra were recorded on Hitachi F-7000 FL spectrophotometer. Elisa

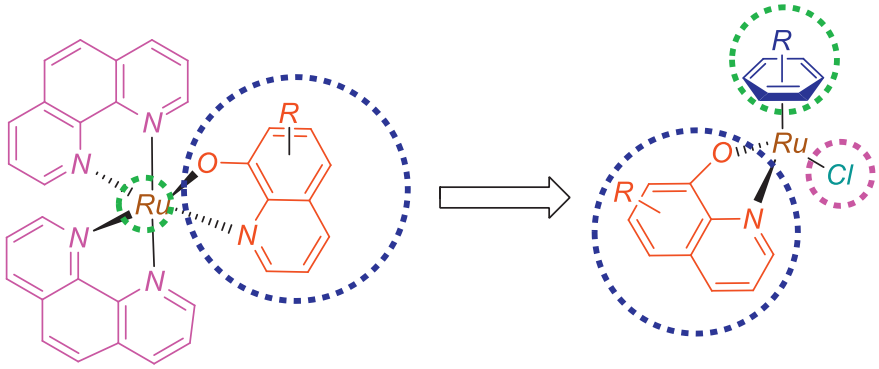

Fig. 2. design of Ru(II)-arene quinolinol complex.