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Ruthenium (II) complexes containing dehydroacetic acid and its imine derivative ligands. Synthesis, characterization and cancer cell growth anti-proliferation activity (GI_{50}) study

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ABSTRACT

Two dehydroacetic acid (DHA, **L_1H**) related imine ligands, **L_2H** and **L_3H** were obtained in moderate yields by reacting DHA with 2,4,6-trimethylaniline and phenylhydrazine, respectively. Refluxing [Ru (η^6-*p*-cymene)$Cl_2]_2$ with two equivalents of **L_1Na**, **L_2H** and **L_3H** in methanol generated ruthenium compounds [Ru (η^6-*p*-cymene)Cl (L_1)] (**1**), [Ru (η^6-*p*-cymene)Cl (L_2)] (**2**), [Ru (η^6-*p*-cymene)Cl (L_3)] (**3**), respectively. The chloride atom of **2** and **3** was substituted by ambidentate ligands N_3, NCO and NCS to generate a series of ruthenium compounds **4a**-**4c** and **5a**-**5b**. All of these ligands and ruthenium compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. Compounds **1**–**3**, **4a**-**4c**, and **5a** were also structural determined by single crystal X-ray crystallography showing a three-legged piano stool geometry with the *p*-cymene acting as the seat plane. Anti-proliferative activity study using these ruthenium complexes against PC-3 and DU-145 cell-lines shows that compounds **2** and **4a**-**4c** have the best activity than other ruthenium compounds. The results indicate that the ruthenium *p*-cymene compounds with large steric hindrance of dehydroacetic acid imine derivative ligands exhibit higher anti-proliferative activity against PC-3 and DU-145 cell-lines.

1. Introduction

Dehydroacetic acid (DHA), a pyrone derivative, has been used as a preservative in the food industry because of its anti-fungal and antibacterial activity [1]. The dehydroacetic acid contains variable organic functional groups and there is a keto-enol tautomerism as shown in Scheme 1. The existing carbonyl groups of the dehydroacetic acid can be converted into different functional groups to fine tune their electronic and steric properties. The combination of DHA derivatives with metals forms a number of new organometallic complexes that were used as catalysts [2] or biology-related chemicals [3]. A review paper published by Gupta summarized the chemistry of DHA-amine condensed Schiff bases and their metal complexes [4].

The incidence of prostate cancer in Taiwan [5] ranked as the fifth common cancer for male in 2015 and cis-platin related drugs are still the main drugs for chemotherapy. However, the price of the platinum increases yearly and the side effects of using cisplatin related chemicals for chemotherapy such as diarrhea, nausea and losing hair are inevitable [6]. Therefore, developing new metal related anti-cancer drugs with lower price and less side effects are currently a strong field in the organometallic chemistry. Nowadays, several ruthenium compounds [7] have been used in clinical trial and ruthenium arene chemistry [8] has raised attentions because of (i) the availability of starting material (ii) the variable substituents on the arene and the ruthenium atom (iii) the affordable price of these ruthenium compounds.

Developing new ruthenium *p*-cymene compounds as anti-cancer cells drugs is one of the research topics in our group [9]. The questions here we want to answer are (i) can the anti-fungi and anti-bacteria DHA and related imine condensation ligands combine with [Ru (*p*-cymene)$Cl_2]_2$ (ii) can the ruthenium-DHA or Ru-DHA-imine compounds exhibit anti-proliferative activity toward PC-3 and DU-145 cell-lines (iii) can the chloride atom of these

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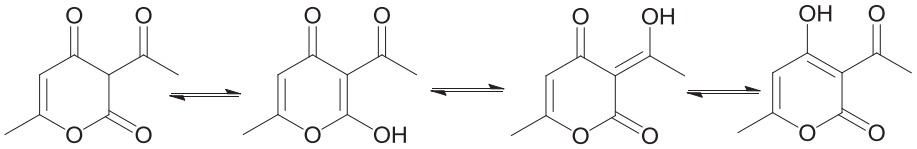


Scheme 1. The keto-enol tautomerism of dehydroacetic acid.

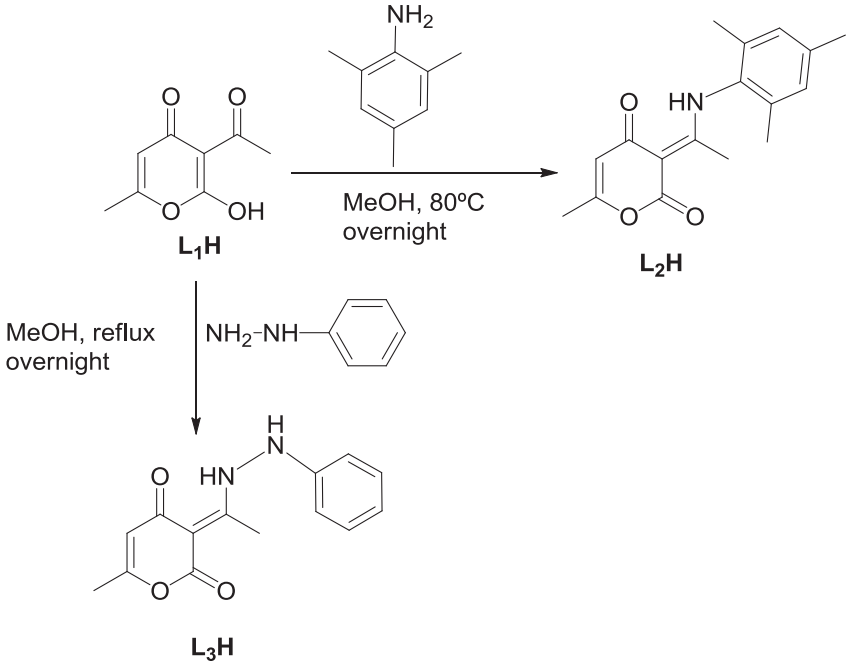
ruthenium compounds be replaced by ambidentate ligands (iv) do the ambidentate ligands affect the anti-proliferative activity of these ruthenium compounds. Here we report the synthesis and characterization of a series of ruthenium compounds containing ruthenium-*p*-cymene and DHA and DHA-imine ligands. In addition, ambidentate azido, cyanato, and thiocyanato ligands were introduced into the ruthenium compounds. The anti-proliferative activity (GI_{50}) of these ruthenium compounds toward prostate cancer cell lines DU-145 and PC-3 are measured.

2. Results and discussion

2.1. Synthesis and characterization of ligands and ruthenium compounds

Two DHA (**L_1H**) related imine ligands, **L_2H** and **L_3H** were obtained in moderate yields by refluxing DHA with one equivalent of 2,4,6-trimethylaniline or phenylhydrazine in methanol for overnight (Scheme 2). The white **L_2H** and yellowish **L_3H** are both soluble in methanol and methylene chloride, but not in hexane. The ^{1}H and ^{13}C NMR spectra of **L_2H** and **L_3H** were recorded with a 300 MHz NMR spectrometer using $CDCl_3$ as solvent. The distinct proton resonance of pyrone ring was used for monitoring the reactions. The methine proton of pyrone ring for **L_2H** and **L_3H** are located at δ 5.74 and 5.77 as a singlet, respectively which are similar to the results in the literature [10]. A series of ruthenium compounds were synthesized as shown in Scheme 3. Refluxing [Ru (*p*-cymene)$Cl_2]_2$ with sodium dehydroacetic acid in methanol generated ruthenium dehydroacetic compounds [Ru (η^6-*p*-cymene)Cl (L_1)] (**1**) in moderate yield [11]. Similarly, reacting [Ru (*p*-cymene)$Cl_2]_2$ with two equivalents of **L_2H** and **L_3H** in the presence of NaOMe afforded [Ru (η^6-*p*-cymene)Cl (L_2)] (**2**) and [Ru (η^6-*p*-cymene)Cl (L_3)] (**3**), respectively, in moderate yield. The sodium methoxide was used for removing the hydrogen chloride which was generated from the metathesis reactions. The methine protons of pyrone for **1**–**3** showed a resonance between δ 5.38–5.98. Interestingly to note that the four *p*-cymene aromatic protons for compounds [Ru (*p*-cymene)$Cl_2]_2$, **1** and **3** are located in the range of δ 5.60–4.93 but one of the *p*-cymene aromatic protons of **2** was found much upfield shift at δ 3.81 presumably due to intramolecular ring current effect which was resulted from the 2,4,6-trimethylphenyl ring current [12]. The ^{13}C NMR chemical shifts of the pyrone and *p*-cymene ring of **1**–**3** are quite similar. However, we noticed that the NMR signals of **2** are more complicate than those of **1** and **3**. The reason for this phenomenon is that the compound **2** has a high amine N-C bond rotation energy barrier due to the large steric hindrance between the trimethylphenyl and *p*-cymene fragments [13].

Further reacting compound **2** with sodium salt NaX, where X = N_3, NCO, and NCS, in ethanol generated **4a**-**4c**, [Ru (η^6-*p*-cymene)X (L_2)] via metathesis in ca 60% yield. Several other sodium salts such as $NaPF_6$ and Na [$N(CN)_2$] have also been tried, however, small amount of impurities presented in the products even after repeating recrystallization. Compounds **4a**-**4c** are soluble in methanol, methylene chloride and toluene but not in diethyl ether and heptane. Similarly, reacting **3** with NaN_3 and NaNCO in ethanol generated [Ru (η^6-*p*-cymene)(N_3)(L_3)] (**5a**) and [(Ruη^6-*p*-cymene)(NCO)(L_3)] (**5b**), respectively. Several other sodium salts were also used to react with **3**; similar products can also be isolated.



Scheme 2. Synthesis of **L_2H** and **L_3H**.