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Synthesis, Characterization and Antitumor Activity Studies of $[UO_2(HMBUD)]^{+2}$,$[UO_2(HMND)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ Complexes on HT29 andT47D Cell Line

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Abstract. The synthesis and structures of four new uranyl complexes with [*ONNO'*] type ligands are described. The reaction between uranyl nitrate hexahydrate and HMBUD, HMND, HMPBD ligands generate uranyl complexes with the formula[ML]. They were synthesized and characterized through NMR.UV-Vis, FT-IR andTG techniques.The synthesized compounds have been screened for antimicrobial activity. The results of antitumor activity show that the metal complexes exhibit antitumor properties and it is important to note that they show enhanced inhibitory activity compared to the parent ligand. It has also been proposed that concentration plays a vital role in increasing the degree of inhabitation. structures three complexes $[UO_2(HMBU)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ and$[UO_2(HMND)]^{+2}$ suggest by ^{1}HNMR, ^{13}CNMR, FT-IR and UV-Vis.

Keywords: Complexes, Antitumor, Uranyl nitrate hexahydrate.

1. Introduction

Schiff bases have often been used as chelating ligands in the field of coordination chemistry and their metal complexes are of great interest for many years. It is well known that N and S atoms play a key role in the coordination of metals at the active sites of numerous metallobiomolecules [1]. Schiff bases of o-phenylenediamine and its complexes have a variety of applications including biological, antitumor, clinical and analytical . Earlier work has shown that some drugs showed increased activity when administered as metal chelates rather than as organic compounds[1,2] and that the coordinating possibility of o-phenylenediamine has been improved by condensing with a variety of carbonyl compounds. A search through literature [2–12]reveals that no work has been done on the transition metal complexes of the Schiff base derived from o-phenylenediamine and acetoacetanilide. Schiff base metal complexes have been widely studied because they have industrial, Antifungal, antibacterial, anticancer and herbicidal applications [13-14]. As a part of our continuing work on dissymmetric tetradentate Schiff base complexes containing N, S and O donor atoms [16-17] and our research group in the recent years, we now report the synthesis and characterization of three uranyl complex of the tetradentate unsymmetric Schiff base ligand such as $[UO_2(HMBUD)]^{+2}$,$[UO_2(HMND)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ and a brief study of its antitumor behavior with the MTT(3-[4,5dimethyllthiazol-2-yl] -2,5diphenyl-tetrazolium bromide)assay.

2. Materials and Methods

2.1. Chemicals and Reagents

Uranyl(VI) nitrate $UO_2(NO_3)_2.6H_2O$, aceto nitrile, HMBUD,HMND,HMPBD ligands were Merck chemicals(Darmstadt, Merck, Germany) and were used without further purification . Organic solvents were reagent Grade. Electronic spectra were recorded by Camsp UV- Visible spectrophotometer model shimadzu 2100(Wpa bio Wave S2 100). The IR spectra were recorded using FT-IR Bruker Tensor 27 spectrometer(model420). ^{1}H-NMR and^{13}C-NMR were recorded on a Bruker AVANCE DRX 500

spectrometer (in DMSO, acetone, CDCL3 solvent). All the chemical shifts are quoted in ppm using the high-frequency positive convention; ^{1}H and ^{13}C-NMR spectra were referenced to external $SiMe_4$. (TG-DTA analysis were recorded using PerkinElmer by thermal program 20°C/min in 400-700 °C thermal rang.

2.2. Cell Culture

The human tumor cell line (H29:human colon adenocarcinoma cell line, T47D:humanbreast adenocarcinoma cell line, used for treatment with the drug were provided.H29 and T47D Cell were grown at 37°C in an atmosphere containing 5٪ CO_2, wet 95٪ with RPMI-1640 Medium HEPES Modification with 2mM L-glutamine and 25 mM HEPES (Sigma-Aldrich Chemie GmbH, Germany) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco, Carlsbad,Calif, USA), 20gr/lit sodium bicarbonate, and 500 mg/L (100uint/ml) ampicillin,ester petomysin 100micro gram/ml.

3. Experimental

3.1. Synthesis of the $[UO_2(HMBUD)]^{+2}$ Complex

HMBUD ligand (0/45gr) was solved in acetonitryl (10 ml),obtained yellow color Solution,then uranylenitrate $UO_2(NO_3)2.6H_2O$ (0/69gr)was solved in acetonitril(10ml)and obtained solution was added on the ligand solution and stirring with magnetic stirrer bar. All mixture stirring ,After 3 hours stirring precipitated solid complexes washed with diethyl ether.

$$C_{20}H_{24}N_2O_2 + UO_2(NO_3)_2.6H_2 \longrightarrow [UO_2(HMBUD)]^{+2}$$

3.1.1. Analysis of $[UO_2(HMBUD)]^{+2}$ Complex

Yield, 85%. ^{1}HNMR (DMSO):3/1 (CH2), 6/8-8 (CH,phenol), 2/7(CH3); FT-IR(KBr,cm^{-1}): 2929br, 1622s,1287s,921s,464m,572m;UV-vis (DMSO): λ_{max} 260nm(ε22000) , 320nm(ε10000). 410nm(ε3600) $[UO_2(HMBUD)]^{+2}$ is soluble in acetone, DMF and DMSO and not soluble in water, hexane, acetonitryl and methanol .

3.1.2 Analysis of HMBUD Ligand

Mp 192-194 °C, ^{1}HNMR(DMSO): 12/8(OH) ,3/6(CH_2), 6/7-7/6 (CH,phenol), 1/5(CH_3);FT-IR(KBr,cm^{-1}): 2931br,1612s,1309s; UV-vis (DMSO): λ_{max} 268nm (ε28000),355nm(ε10000) HMBUD is soluble in diethylether , acetonitrile, DMSO dicholoromethane and choloroform And not soluble in water ,hexane,ethanol and methanol.

3.2. Synthesis of $[UO_2(HMPBD)]^{+2}$ Complex

HMPBD ligand (0/47gr) was solved in acetonitryl (10 ml), then uranylenitrate $UO_2(NO_3)_2.6H_2O$ (0/68gr)was solved in acetonitril (10ml)and yellow color solution salt was added on the ligand solution and stirring with magnetic stirrer bar. After 3 hours stirring precipitated solid complexes washed with acetonitriyl.

$$C_{22}H_{20}N_2O_2 + UO_2(NO_3)_2.6H_2O \longrightarrow [UO_2(HMPBD)]^{+2}$$

3.2.1. Analysis of $[UO_2(HMPBD)]^{+2}$Complex:

Yield, 80%.^{1}HNMR (DMSO):6/9 (CH benzyl) 7/2-7/6(CH phenol), 2/5(CH_3); FT-IR(KBr,cm^{-1}): 2935br,1588s,1305s,920s,422w580m ; UV-vis (DMSO): λ_{max} 265nm(ε30000) , 310nm(ε9000). 400nm(ε 2000) $[UO_2(HMPBD)]^{+2}$ is soluble in acetone, DMF and DMSO and not soluble in water, acetonitryl, hexane and methanol .

3.2.2. Analysis of HMPBD Ligand

Mp 233-235 °C, ^{1}HNMR(DMSO): 11/7(OH) 6/9 (CH bezyl), 7/2-7/6 (CH,phenol), 2/4(CH_3);FT-IR(KBr,cm^{-1}): 2417br,1609s.1204s UV-vis (DMSO): λ_{max}260nm (ε30000) , 340nm(ε15000) HMPBD is soluble in acetonitrile, ,dicholoromethane DMF and DMSO And not soluble in water ,hexane,ethanol and methanol.

3.3. Synthesis of the $[UO_2(HMND)]^{+2}$Complex:

HMND ligand (0/63r) was solved in acetonitryl (10 ml), obtained yellow color Solution then uranylenitrate $UO_2(NO_3)_2.6H_2O$ (0/5gr)was solved in acetonitril (10ml) and solution salt was added on the ligand solution and stirring with magnetic stirrer bar, After 3 hours stirring precipitated solid complexes washed with acetonitriyl.

$$C_{25}H_{34}N_2O_2 + UO_2(NO_3)_2.\ 6H_2 \longrightarrow [UO_2(HMND)]^{+2}$$

3.3.1. Analysis of $[UO_2(HMND)]^{+2}$ Complex

Yield, 88%. ^{1}HNMR (DMSO):2/7(CH_2),6/7-7/6(CH,phenol),3/5(N-CH2) 1/7(CH_3); FT-IR(KBr,cm^{-1}): 2928br,1630s, 1284s, , 919s,472w,574m;UV-vis (DMSO): λ_{max} 265nm(ε27000), 320nm(7000), 400nm(ε 3400). $[UO_2(HMND)^{+2}]$is soluble in acetone , DMF and DMSO and not soluble in water ,hexane and acetonitryl.

3.3.2. Analysis of HMND ligand

Mp 83-85 °C, ^{1}HNMR(DMSO): 10/5(OH), 2/5 (CH_2), 6/8-8(CH,phenol) 3/7 (N-CH_2), 1/7(CH_3); FT-IR (KBr, cm^{-1}):2921br,1612s,1307s; UV-vis (DMSO): λ_{max} 260nm(ε15000),313nm(7000) HMND is soluble in acetonitrile choloroform, , DMF and DMSO and not soluble in water and Hexane, diethylether methanol and ethanol.

4. Results and Discussion

4.1. Preparation for $[UO_2(HMBUD)]$,$[UO_2(HMPBD)]$,$[UO_2(HMND)]$ Complexes

The reaction of uranyl nitrate salts with the ligand in acetonitryl solvent results in M=U , L = HMBUD, HMPBD and HMND in the molar ratio 1:1(metal:ligand).All complexes are quite stable and could be stored without any appreciable change. All complexes were characterized by several techniques using FT-IR, electronic spectra NMR, UV-ViS and TG.The complexes$[UO_2(HMBUD)]^{+2}$,$[UO_2(HMPBD)]^{+2}$and,$[UO_2(HMND)]^{+2}$was decomposed in 225°C,250°C210°C respectively and insoluble in common organic solvents, such as hexane however, they are soluble in DMSO and DMF. Their structures were characterized by^{1}HNMR,^{13}CNMR,FT-IR and UV-ViS. The spectral data of the complexes have good relationship with the literature data**.**

4.2. Cytotoxicity Assays In Vitro

HMBUD, HMPBD and HMND ligands and $[UO_2(HMBUD)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ and $[UO_2(HMND)]^{+2}$ complexes have been tested against two human cancer cell lines: HT29 and T47D. The IC_{50} cytotoxicity values of the complexes were compared to those found for the starting organic bases as well as for some of the anticancer agents used nowadays, that are cisplatin and oxaplatin compounds [17]. The general method used for testing on antitumor properties of these compounds is the standard testing method that has been previously described in greater detail. After preincubation lasting for 24 hours at 37ºC in 5٪ CO2 atmosphere and 95% humidity the tested compounds in the concentration ranges of 0.1,0.01, 0.001 M for HMBUD, HMPBD and HMND ligands and two complexes. The incubation lasted for 72 hours and at the end of this period IC_{90} and IC_{50} of the dead cells and live cells were measured by trypan blue. The mechanism by which these complexes act as antitumor agents is apoptosis. $IC_{90}$and IC_{50}values that are the compounds concentrations lethal for90% and 50% of the tumor cells were determined both in control and in compounds concentrations lethal for both in compounds-treated cultures. The compounds were first dissolved in DMSO and then filtrated.

5. Conclusion

It is clear from the above discussion that $[UO_2(HMBUD)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ and$[UO_2(HMND)]^{+2}$ complexes and HMBUD , HMPBD and HMND ligand offer a new outlook for chemotherapy. The results of antitumor activity show that the metal complexes exhibit antitumor properties and it is important to note that they show enhanced inhibitory activity compared to the parent ligand. The mechanism by which these complexes act as antitumor agents is apoptosis. It has also been proposed that concentration plays a vital

role in increasing the degree of inhabitation. structures three complexes $[UO_2(HMBU)]^{+2}$, $[UO_2(HMPBD)]^{+2}$ and$[UO_2(HMND)]^{+2}$ suggest by ^{1}HNMR, ^{13}CNMR,FT-IR and UV-ViS.

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