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Synthesis, Structural Characterization, Thermal Behavior and Anticancer Properties of a Bis[3-Nitro Benzylidene Amino-5-Methyl-2, 4-Dihydro-3h-1, 2, 4-Triazole-3-Thione] Uranyl(Vi)Nitrate $[Uo_2(Nbamdt)_2]^{2+}$

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Abstract: *Bis[3-nitro benzyliden amino-5-methyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione]* abbreviated as NBAMDT was synthesized and characterized. *Bis[3-nitro benzyliden amino-5-methyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione] Uranyl(VI)nitrate* prepared by reaction of nitrate salt of $UO_2(NO_3)_2.6H_2O$ with NBAMDT. In this research, some of the inorganic complexes of uranyl with N-donor ligands were synthesized. Complexes were characterized by FT-IR and UV, ^{1}HNMR, ^{13}CNMR spectra, TG/DTG measurements and some physical properties. The results of simultaneous TG-DTG-DTA analyses of the complexes show the final degradation product for these complexes are UO_3. The antitumor activity of used ligands and their complexes against a panel of human tumor cell lines (HT29) Haman colon adenocarcinoma cell line (T47D) human breast adenocarcinoma cell line were studied and determined by MTT *3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide* assay. These data suggest that some of these compounds provide good models for the further design of potent antitumor materials. Also the results show chelation causes drastic change in the biological properties of the ligands and also the metal moiety.

Key words: FT-IR · UV-Visible Spectroscopy · Schiff Bases · Anticancer Activity · ^{1}HNMR · ^{13}CNMR Spectra

INTRODUCTION

Schiff bases can be synthesized from an aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. Many efforts have been done on preparation of new uranyl compounds. The coordination chemistry of transition metals with ligands from the uranyl family has been of interest due to different bonding modes shown by these ligands with both electron rich and electron poor metal. In principle, the central transition metal atoms of different soft and hard Lewis acidity usually need to be satisfied in the most suitable fashion. Schiff base metal complexes have been widely studied because they have industrial, antifungal, antibacterial, anticancer and herbicidal applications.

Nitrogen-containing ligands such as Schiff bases and their metal complexes played an important role in the development of coordination chemistry resulting in an enormous number of publications, ranging from pure synthetic work to physicochemical [1] and biochemically relevant studies of metal complexes [2-6] and found wide range of applications. Other kinds of nitrogen-containing ligands are well-known pyrimidine systems such as purine analogues that exhibit a wide range of biological activities. Fused pyrimidine compounds are valued not only for their rich and varied chemistry, but also for many important biological properties. Among them, the furopyrimidine ring system, because of a formal isoelectronic relationship with purine, is of special biological interest. It has numerous pharmacological and agrochemical applications, namely, antimalarials, antifolates and antivirus, as well as potential radiation protection agents.

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Recently, some furopyrimidines were shown to be potent a vascular endothelial growth factor receptor 2 (VEGFR2) and epidermal growth factor receptor (EGFR) inhibitors. Because of the importance of furo (2,3-d) pyrimidine derivatives, several methodologies for synthesizing them have already been developed. However, many of the synthetic protocols reported so far prolonged reaction times, harsh reaction suffer from disadvantages, such as relying on multistep reactions, needing anhydrous conditions, low yields, use of metal-containing reagents and special instruments or starting materials. Therefore, the development of new and efficient methods for the preparation of furo (2, 3-d) pyrimidine derivatives is still strongly desirable [7]. Pyrimidines represent a very interesting class of compounds because of their wide applications in pharmaceutical, phytosanitary, analytical and industrial aspects, for example, as antibacterial, fungicide [8], antihelmintics, antitubercular, anti-HIV, antidegenerative and hypothermic activities and herbicides and have biological activities [9-13].

It has long been known that metal ions involve in biological processes of life and have been subject of interest. The modes of action of these metal ions are often complex but are believed to involve bonding to the heteroatom of the heterocyclic residues of biological molecules, that is, proteins, enzymes, nucleic acids and so forth [14]. From these points of view, it is interesting to study different types of transition metal complexes of these biologically active ligands.

Cytotoxicity is the superiority of being toxic to cells. Cells exposed to a cytotoxic compound can respond in a sum of behaviors. Cytotoxicity assays are used for drug screening and cytotoxicity exams of chemicals. The cytotoxicity studies were limited by the point that in most cases the requirement of time of revelation and surface functionalization remained unexplored [15]. The cells may suffer necrosis, in which they lose sheath integrity and die quickly as a product of cell lysis; they can halt developing and separating; or they can activate a hereditary program of controlled cell death, called apoptosis.

In this paper, the synthesis characterization and antitumor properties of a number of the ligands and uranyl complexes have been studied. In this work, we report the synthesis and structural studies of the ligand and complex isolated from the reactions of: *Bis[3-nitro benzyliden amino-5-methyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione] Uranyl(VI)nitrate.*

MATERIALS AND METHODS

Solvents were purified by standard methods. All reagents were supplied by Merck and were used without further purification. Melting point was determined in an Electro thermal 9200. The FT-IR spectra were recorded in the range 400-4000 cm^{-1} by KBr disk using a Bruker Tensor 27 M 420 FT-IR spectrophotometer. The UV-Vis spectra in CH_3CN were recorded with a WPA bio Wave S2 100 spectrophotometer. Thermo gravimetric analyses were done on a Perkin Elmer TGA/DTA lab system l (Technology by SII) in nitrogen atmosphere with a heating rate of 20ºC/min from 35-700 ºC. ^1H and $^{13}CNMR$ spectra were measured on a BRUKER DRX-500 AVANCE spectrometer at 500 MHz.

Synthesis of the $[UO_2(NBAMDT)_2]^{2+}$: For synthesis of the $[UO_2(NBAMDT)_2]^{2+}$ to a magnetically stirred of ligand (1.6g, 6mmol) in acetonitrile(10ml) was added to uranyl (VI) nitrate (1.5g, 3 mmol) at room temperature. The reaction mixture was further stirred for 3 hours to ensure the completion and precipitation of the formed complex. The precipitated solid complex was filtered and washed several times with diethyl ether to remove any traces of the unreacted starting materials. Yield, 80%. Anal. Calcd of $[UO_2(NBAMDT)_2]^{2+}$; C; 22.53, H; 0.88, N; 6.91; found: C; 22.64, H. 0.92, N; 6.99. Mp: 223-225 °C. ^1HNMR (DMSO): 7.9-8.7 (CH nitrophenyl), 2.3 (CH_3), 9.3 (CH azomethyne), FT-IR (KBr, cm^{-1}): 751 m (ν C-S), 1503 s (ν C=N), 626 m (ν U-S), 490 w (ν U-N),944 s (ν O=U=O), UV-vis (DMSO): λ_{max}260nm(ε 28000), 300nm(ε 8000), 380nm(ε 3000) Fig. 1-8. $[UO_2(NBAMDT)_2]^{2+}$ is soluble in dichloro methane and DMSO and insoluble in water, hexane, acetonitrile, chloroform and methanol and little soluble in DMF, acetone, diethyl ether and ethanol. Fig. 8 shows TGA and DTA curves for $[UO_2(NBAMDT)_2]^{2+}$ and Figs. 9 and 10 shows chemical structures of NBAMDT and $[UO_2(NBAMDT)_2]^{2+}$.

Analysis of NBAMDT Ligand: Anal: %65. Calcd of $C_{10}H_9N_5O_2S$; C; 61.46, H; 2.42, N; 18.85; found: C; 61.51, H. 2.51, N; 18.94. Mp 232-234 °C, ^1HNMR (DMSO): 7-88 (CH nitrophenyl), 2.3 (CH_3), 9.2 (CH azomethyne), 10.5 (NH), FT-IR (KBr, cm^{-1}): 1094 m (ν C=S), 1530 s (ν C=N), UV-vis (DMSO): λ_{max}265nm (ε 32000), 310nm (ε 8000). NBAMDT is soluble in DMSO, acetone, DMF, acetonitrile and insoluble in diethyl ether,also methanol, ethanol, water, dichloromethane and hexane and little soluble in chloroform.

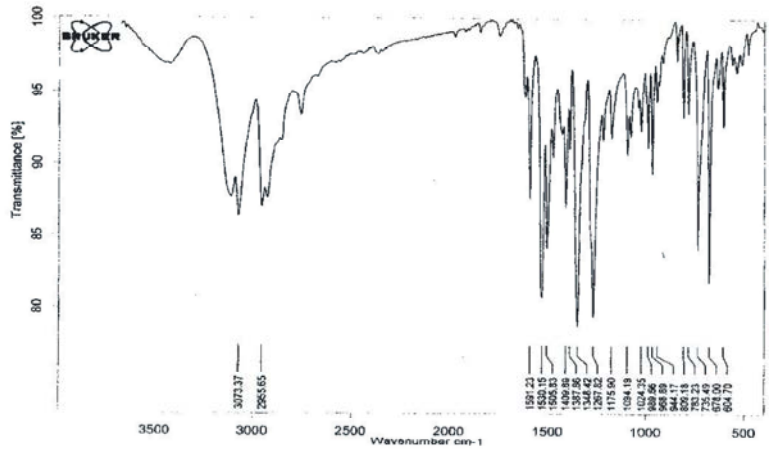

Fig. 1: FTIR spectrum of NBAMDT (KBr Disk).

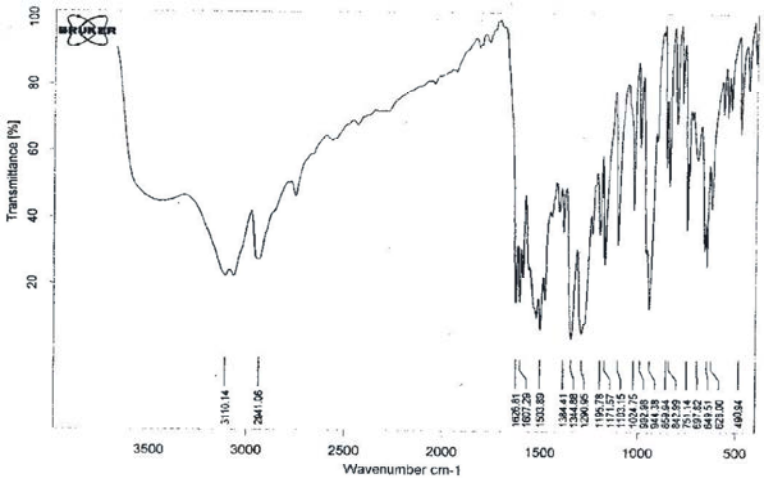

Fig. 2: FTIR spectrum of $[UO_2(NBAMDT)_2]^{2+}$ (KBr Disk).

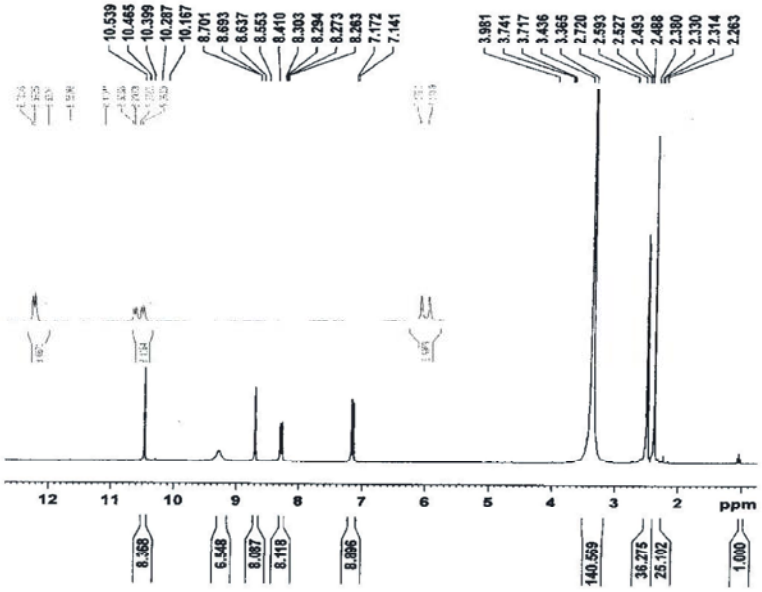

Fig. 3: [1]HNMR spectrum of NBAMDT.

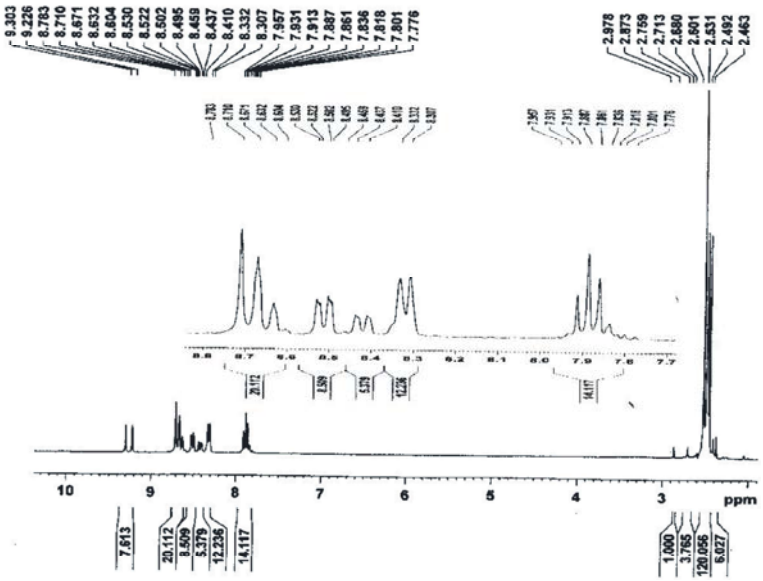

Fig. 4: ^{1}HNMR spectrum of $[UO_2(NBAMDT)_2]^{2+}$.

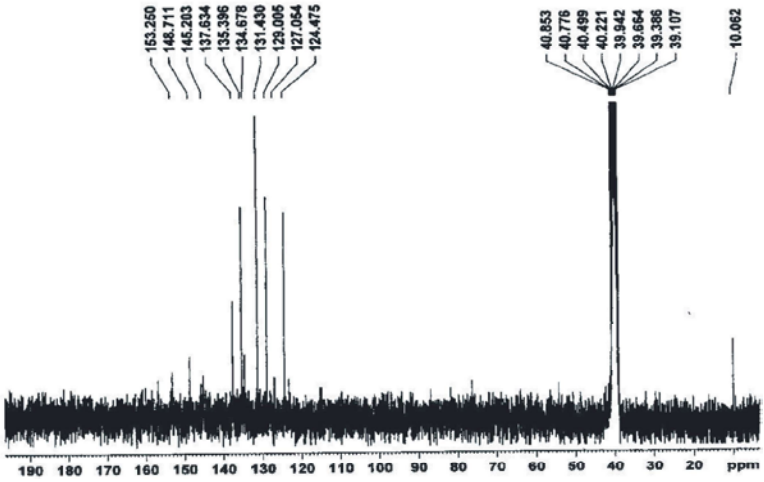

Fig. 5: ^{13}CNMR spectrum of $[UO_2(NBAMDT)_2]^{2+}$.

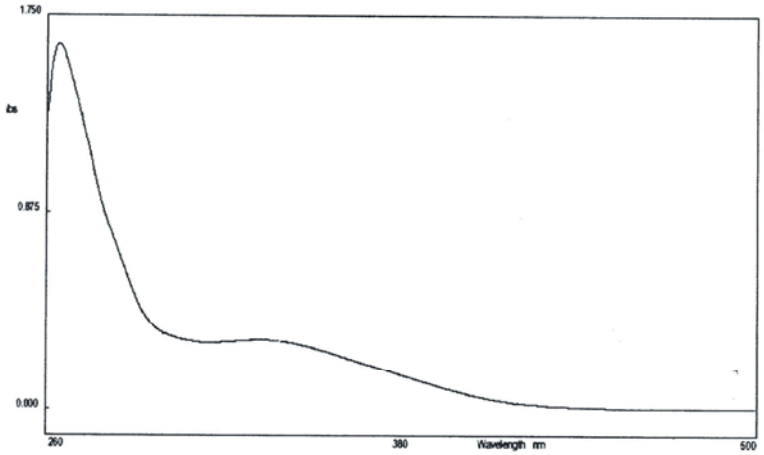

Fig. 6: UV/ Vis spectrum of NBAMDT (DMSO, 5×10^{-4} M).

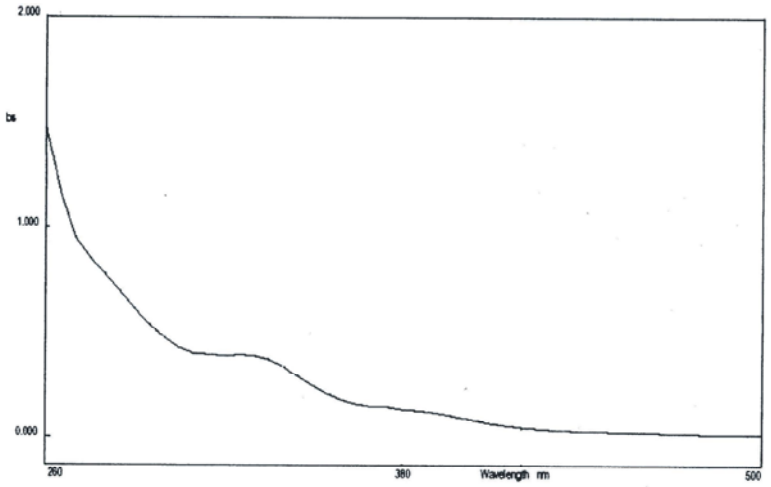

Fig. 7: UV/ Vis spectrum of $[UO_2(NBAMDT)_2]^{2+}$ (DMSO, 5×10^{-4} M).

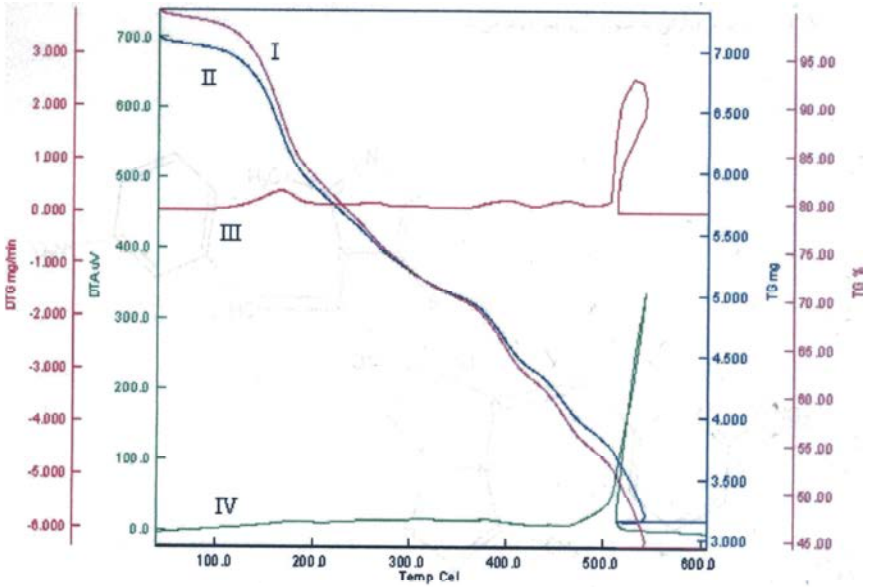

Fig. 8: Thermal analysis data of $[UO_2(NBAMDT)_2]^{2+}$.

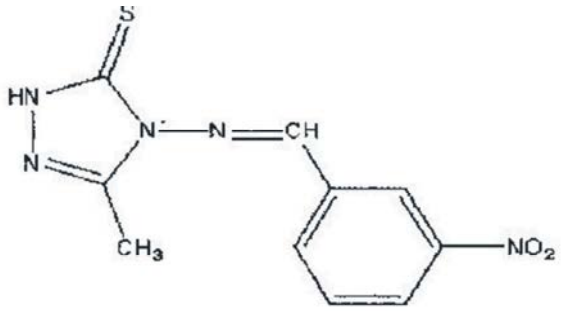

Fig. 9: Chemical structure of NBAMDT.

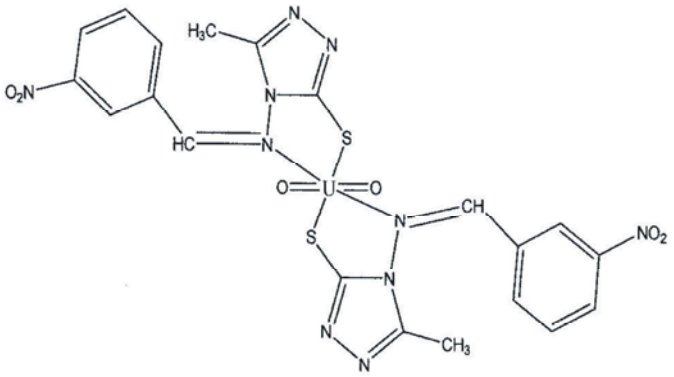

Fig. 10: Chemical structure of $[UO_2(NBAMDT)_2]^{2+}$.

RESULTS

Preparation of Ligand and Complex: In this paper, we report a new method of the synthesis of *Bis[3-nitro benzyliden amino-5-methyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione] Uranyl(VI)nitrate*. The compound was obtained by reaction of $UO_2(NO_3)_2.6H_2O$ with NBAMDT and was synthesized through a one-step reaction.

Our procedure for producing compound has some advantages. For example, there is no side product in preparing $[UO_2(NBAMDT)_2]^{2+}$ in our method, the reaction is quite fast and does not require any severe conditions such as high pressure or high temperature. Compounds are quite stable and could be stored without any appreciable changes for long time. Compounds were characterized by several techniques using FT-IR, UV-Visible and NMR spectra Thermal analysis were studied for these compounds. The $[UO_2(NBAMDT)_2]^{2+}$ has 223-225°C melting points respectively. It is soluble in dichloro methane and DMSO and insoluble in water, hexane, acetonitrile, chloroform and methanol and little soluble in DMF, acetone, diethyl ether and ethanol. The spectral data of the complexes have good relationship with the literature data.

Thermo Gravimetric Analyses: The thermal properties of these compounds were investigated by thermo grams (TG, DTG and DTA). In the temperature range 200-550°C, 38.7% weight losing were observed which were related to the loss of most parts of compound.

Cytotoxicity Studies: NBAMDT ligand and $[UO_2(NBAMDT)_2]^{2+}$complex are two compounds which were assayed for cytotoxicity *in vitro* against (HT29) Haman colon adenocarcinoma cells and (T47D) human breast adenocarcinoma cell line cells. The two cell lines were provided by the Pasteur Institute in Iran. The procedure for cytotoxicity studies was similar to that

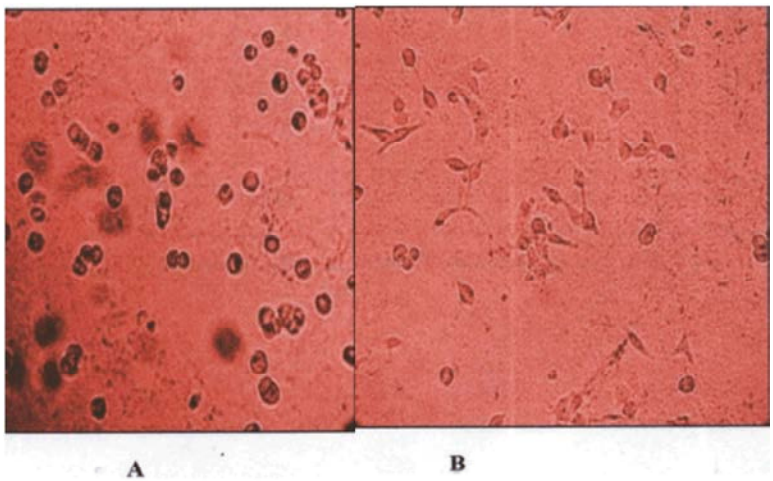

Fig. 11: Morphology cells A, B (A: HT-29, B: T47-D) containing NBAMDT (0/001M).

reported earlier [16]. Briefly, in order to calculate the concentration of each drug that produces a 50% inhibition of cell growth (IC_{50}), 190 mL of cell suspension (4×10^5 cell/cm^3) was exposed to various concentrations of ligand and complexes dissolved in sterile DMSO. The final concentration of DMSO in the growth medium was 2% (v/v) or lower, concentrations without effect on cell replication. After the incubation period's 72 hours for all cell lines, the cell concentrations were determined both in control and in drug-treated cultures. All experiments were done for six times.Figure 11 showes the effect of NBMPT ligand on two kind of cancer cells (HT-29 and T47D). As seen the cancer cells destroid and apoptoized.

DISCUSSION

In this research, some of the inorganic complexes of uranyl with N-donor ligands were synthesized. Complexes were characterized by FT-IR and UV, ^{1}HNMR, ^{13}CNMR spectra, TG/DTG measurements and some physical properties. The results of simultaneous TG-DTG-DTA analyses of the complexes show the final degradation product for these complexes are UO_3. The antitumor activity of used ligands and their complexes against a panel of human tumor cell lines (HT29: Haman colon adenocarcinoma cell line T47-D: human breast adenocarcinoma cell line) were studied and determined by MTT *3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide* assay.

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