# Antibacterial and Molecular Study of Thiourea Derivative Ligand and its Dimethyltin(IV) Complex with the Superior of its Copper(II) Complex as a Hepatocellular Antitumor Drug

**Safaa S. Hassan[1]*, Rania N. Shallan[1] and Mabrouk M. Salama[2]**

**1 Department of chemistry, Faculty of science, Cairo University, Giza, Egypt.**

**Safaa_inorgchem@yahoo.com**

**2 Department of Chemistry, Faculty of Science, University of Benghazi, Benghazi, Libya**

**Mabrouk.salama@uob.edu.ly**

**Abstract:**

**1-benzoyl(1,2,4-triazol-3-yl)thiourea [BTThU] ligand and its [dimethyltin(IV), Pd(II) and Cu(II)] complexes are synthesized. The complexes are formed in molar ratio $Cu(BTThU)_2$, $DMT(BTThU)_2$ and $Pd(BTThU)_2$. The characterization has been done by using different physicochemical methods as elemental analyses, IR, $^1H$ NMR DMSO-$d^6$ and molar conductance measurements. The stability constants of the formed species that produced from the interaction of [BTThU] with dimethyltin(IV) [DMT], dibutyltin(IV) [DBT] and diphenyltin(IV) [DPT] were determined potentiometrically using the non-linear least-square program MINIQUAD-75 in 50% ethanol–water mixture and 0.1M ionic strength at 25°C. Concentration distribution diagrams for these system were evaluated. The theoretical conformational structure analyses were performed using density functional theory for thiol and thione tautomeric forms of [BTThU] ligand and its complex at B3LYP functional with 6-311G basis set for ligand and LANL2DZ basis set for complex. The theoretical vibrational frequency values of the optimized structures were calculated. The charge distribution within the ligand and its dimethyltin(IV) complex was calculated using Mulliken population analysis of [MPA] and natural population analysis [NPA]. The biological activity of BTThU ligand and its dimethyltin(IV) complex were tested in vitro against some selected species of fungi and bacteria. The hepatocellular antitumor effect of all compounds was investigated.**

**Keywords: dimethyltin(IV), dibutyltin(IV), diphenyltin(IV), HepG2, HOMO - LUMO, equilibrium studies, antitumor drug.**

## Introduction

**Cancer is one of the main causes of mortality and morbidity in world. Metal-based antitumor drugs play a relevant role in antiballistic chemotherapy. Cisplatin is regarded as one of the most effective drugs, even if severe toxicities and drug resistance phenomena limit its clinical use. Therefore, in recent years there has been a rapid expansion in research and development of novel metal-based anticancer drugs to improve clinical effectiveness, to reduce general toxicity and to broaden the spectrum of activity. Among non-Pt compounds, it was of considerable interest to develop novel antitumor Pd(II) complexes as the coordination chemistry of Pd(II) and Pt(II) is usually similar. Also, organotins are gaining more attention as anti-cancer agents due to their potent cytotoxicity properties[1] and copper complexes are potentially attractive as anticancer agents[2]. Copper complexes have attracted attention based on modes of action different from that of cisplatin (covalent binding to DNA). Therefore, copper complexes may provide, at least in principle, a broader spectrum of antitumor activity[2]. Heterocyclic compounds play one of the most important roles in modern medicinal compounds. One series of heterocyclic compounds of particular interest are Schiff bases of 1,2,4-triazoles that shows an important spectrum of biological uses [3-5] because of its an electron rich model so, it readily binds with a many enzymes and receptors in biological systems. Benzoyl derivatives of thiourea have gained a great deal of importance in the present day[6]. Thiourea linkages have contributed greatly to the observed enhancement in various activities including anticancer [7], antiviral [8], antibacterial [9-12], antifungal [13] and antimalarial [14, 15]. Therefore the combination between these two biologically active scaffolds is a chance to give a new compound of expected an acceptable biological activity, viz. [BTThU] 1-benzoyl(1,2,4-triazol-3-yl) thiourea. Extensive studies were done on organotin(IV) coordination geometries and their structural diversity (monomeric, dimeric, hexameric, and oligomeric) [16]. They showed success in the area of inorganic and metal organic chemistry through pharmacological [17,18] (antifungal, antibacterial and antitumor drugs) applications. So referring to the huge applications of the organotin(IV) complexes [19,20] specially the antibacterial and antifungal, It was of interest to investigate some of new tin**

**complexes with 1-benzoyl(1,2,4-triazol-3-yl) thiourea. This investigation provides a new opportunity for the development of novel antimicrobials to overcome the ever increasing of drug resistance problem.**

## Experimental

**Dimethyltin(IV) dichloride [DMT], diphenyltin(IV) dichloride [DPT] and dibutyltin(IV) dichloride [DBT] were obtained from Merck Chem. $CuCl_2 \cdot 2H_2O$ and $Na_2PdCl_4$ obtained from Sigma Chem. Co. Carbonate-free NaOH (titrant) was used for the standardized against potassium hydrogen phthalate solution.**

### *Preparation of 1-benzoyl(1,2,4-triazol-3-yl)thiourea ligand*

**The (1-benzoyl(1,2,4-triazol-3-yl)thiourea) abbreviated as [BTThU] was obtained by interaction of 3-amino-1,2,4-triazole with benzoylisothiocyanate in equimolar amounts as described previously [21]. Purification for reaction product was done by crystallization from ethanol. The ligand formed white crystals with yield 85%.**

**Calc. for $C_{10}H_9N_5SO$: C, 48.6; H, 3.64; N, 28.3; S, 12.97. Found: C, 49.0; H, 3.9; N, 27.8, S, 12.72.**

**I.R : 1702 ( νC=O carbonyl group), (3404, 3294 and 3205 (three νNH)), 1661 (νC=N), 920 ν(N-N) ring and 1519 ( νNCN).**

**The $^1$H NMR DMSO-d$^6$ and $^{13}$C NMR spectra of the BTThU in DMSO show the following:**

**$^1$H NMR shows multiplet signals at δ 7.49–8.4 (5H, Ar.), δ 7.474 (H, CH triazole) and δ 11.8, 12.6 & 14.0 (3H, 3NH).**

**$^{13}$C NMR DMSO-d$^6$ shows the chemical shifts of carbons pertaining to CONH and CSNH moieties resonance at 166.2 ppm and 177.1 ppm, respectively. Signals for aromatic carbons appeared in the region between 127−137 ppm. For triazole carbons (N-C-N) and (N-C-NH) appeared at 153 and 147 ppm respectively.**

### *Synthesis of metal complexes*

**All studied complexes DMT(IV), Cu(II) and Pd(II) complexes were prepared in 1:2 (metal:ligand) ratio. Cu(II) and Pd(II) complexes were separated as described in previous work[22]. Dimethyltin(IV) complex was prepared by using**

**dimethyltin dichloride (1 mmol, 0.2196 g) and the appropriate amount (2 mmoles, 0.2494g) of ligand, both dissolved in the smallest possible volume of EtOH. The mixture was refluxed in a water bath for 1 hour. The complex was precipitated, filtered and dried. A yellowish white precipitate was obtained with yield 67%.**

**Calc. for $SnC_{22}H_{22}N_{10}S_2O_2$: C, 41.4; H, 3.4; N, 21.8%. Found: C, 41.7; H, 3.0; N, 21.5.**

The I.R spectra for dimethyltin(IV) complex shows bands occurring at 1685 $cm^{-1}$ (ν C=O ), 1537 (ν NCN), 1022 ν(C-S) and 473 & 409 (ν M-O & M-S).

The $^{1}H$ NMR DMSO-$d^{6}$ spectrum of the DMT(IV) complex shows δ 1.3 (6H, Sn-Me), multiplet signals at δ 7.49–8.04 (5H, Ar.), δ 7.465 (H, CH triazole) and δ 8.1 & 11.4 (2H, 2NH).

$^{13}C$ NMR DMSO-$d^{6}$ shows the chemical shifts of carbons pertaining to CONH and CSNH moieties resonate at 157.2 ppm and 172.1 ppm, respectively. Signals for aromatic carbons appeared in the region between 127−133 ppm. For triazole carbons (N-C-N) and (N-C-NH) appeared at 155 and 147 ppm respectively.

***Computational methods***

**Density Functional Theory [DFT] calculations have been carried out to investigate the equilibrium geometry of 1-benzoyl(1,2,4-triazol-3-yl)thiourea and its dimethyltin(IV) complex using Gaussian 09 program[23] at b3lyp/6-311G level of theory for BTThU and B3LYP/LANL2DZ for the complex [24].**

***Biological measurements***

**A modified Kirby-Bauer disc diffusion method [25] was used to evaluate the antimicrobial activity of the tested samples as described with the Cu(II) and Pd(II) complexes in previous work[22].**

*Apparatus and measuring techniques*

**Metrohm 751 Titrino instrument was used to carry out the potentiometric measurements. Potassium hydrogen phthalate, (pH 4.008) and a mixture of $KH_2PO_4$ and $Na_2HPO_4$ (pH 6.865) buffer solutions were used to calibrate the electrode.**

**The acid dissociation constants of the ligand 1-benzoyl(1,2,4-triazol-3-yl)thiourea were determined potentiometrically. The ligand was prepared in the protonated form with standard $HNO_3$ solution. The ligand solution ,40 mL at a concentration of $2.5\times10^{-3}$ M was titrated with NaOH. Diorganotin(IV), as DMT, DPT and DBT, hydrolysis constants were determined by titrating a solution of each, 40 mL of concentration $2.5 \times 10^{-3}$ M with (0.05 M) NaOH. The formation constants of diorganotin(IV) complexes were determined by titrating solution mixture , 40 mL, containing diorgantin(IV) ($1.25\times10^{-3}$ M) and ligand ($2.5\times10^{-3}$ M) of the ligand. In all titrations,the ionic strength was maintained 0.1M by $NaNO_3$. Also, all titrations were performed in 50% (ethanol-water system) and in a purified $N_2$ atmosphere, using aqueous 0.05 M NaOH.**

**The computer program [26] MINIQUAD-75 was used to perform the calculations.**

**Various possible composition models were tried to determine the stoichiometries and stability constants of the complexes formed. The model which gave the best statistical fit was selected and was chemically consistent with the titration data without giving any systematic drifts in the magnitudes of various residuals, as described elsewhere [26]. The fitted model was tested by comparing the experimental titration data points and the theoretical curve calculated from the values of the acid dissociation constant of the ligand and formation constants of the corresponding complexes.**

**The equilibrium constants were evaluated from titration data, defined by Eqn. (1) and Eqn. (2).**

$$l(M) + p(L) + q(H) \rightleftharpoons (M)_l (L)_p (H)_q \quad (1)$$

$$\beta_{pqr} = \frac{[(M)_p (L)_q (H)_r]}{[M]^p [L]^q [H]^r} \quad (2)$$

**Where M, L and H represent Diorganotin(IV), 1-benzoyl(1,2,4-triazol-3-yl)thiourea and proton respectively.**

**(Table 6 ) lists the formation constants obtained from the program MINIQUAD-75.**

**The speciation diagrams were obtained using the program SPECIES [27].**

**Elemental analysis was done by CHNS Automatic Analyzer, Vario EL III-Elementar, Germany. IR spectra were measured on a Shimadzu 8001-PC FT-IR spectrophotometer using KBr pellets. $^1$H NMR spectra were recorded on a Varian GEMINI 200 spectrometer at 200 MHz using $d_6$-DMSO as solvent.**

## Results and discussion

### Solid complexes characterization

**The chemical composition of the dimethyltin(IV) complex was characterized by elemental analysis. The data is supporting the formation of 1:2 complex (dimethyltin(IV): ligand). The molar conductance of the complex solution is very low value indicating that the complex is having nonelectrolyte nature. This indicated that the complex is self-neutralized by the attached ligands with the absence of any ionic chloride ions in the outer sphere of the complex, therefore the ligand coordinated as mono-negatively charged anion.**

**The IR and $^1$H NMR bands of the BTThU and $Me_2Sn(IV)(BTThU)_2$ were pointed out in the synthesis part. The Important IR absorption bands for BTThU and $Me_2Sn(IV)(BTThU)_2$ are given in (Table 1).**

**The $^1$H NMR spectrum of the $Me_2Sn(IV)(BTThU)_2$ complex shows shift in the multiplet signals of the aromatic protons with the appearance of new signals at 1.3ppm, related to the (6H, Sn-Me). The two signals that appeared at 8.1 and 11.4 ppm in complex are attributed mainly to the two NH groups with the disappearance of the peak corresponding to NH group occurring between C=S and triazole ring. The IR spectrum of the ligand shows the disappearance of the**

**C=S group with the formation of C-S band at 1022cm$^{-1}$ [28]. NCN vibration band [29] is shifted also to 1537 cm$^{-1}$. This is due to the increased double bond character of the C=N bond and the shift in Carbonyl group (C=O) to the region 1685cm$^{-1}$. The IR spectrum of the complex shows appearance of new bands at 473 cm$^{-1}$ and 409 cm$^{-1}$ , due to M-O and M-S [30] bonds respectively. This indicates that the co-ordination of carbonyl oxygen atom of the ligand with Sn ion and the sulfur atom is participated in the formation of the complex [31] as S$^{-}$, i.e. the ligand reacted as monoanionic ligand by using the sulfur atom. The structure of $Me_2Sn(IV)(BTThU)_2$ complex is given in (Figure 1).**

**Therefore, it is assumed that the coordinated species of the ligand is the thiol form. The thiol form may exist in two tautomers, thiol 1 and thiol 2, as given in (Figure 2). Their stability will be investigated from DFT calculations.**

**Cu(II) and Pd(II) complexes were characterized and confirmed in previous work [22].**

## DFT Calculations

**The values of dipole moment, energy gap, hardness [η], ionization potential [IP], electron affinity [EA] and total energies of the optimized structures of the different tautomeric forms of the ligand (Figure 3) and $(CH_3)_2Sn(BTThU)_2$ complex are evaluated. The highest occupied molecular orbital [HOMO] and lowest unoccupied molecular orbital [LUMO] energies are investigated for their importance in the study of the chemical reactivity [32-34]. All of the previous values are collected in (Table 2).**

### *Geometry Optimization and Electronic Properties:*

**The absolute energy values of the ligand tautomers, given in (Table 2), are compared. The values are very close to each other, but one may consider that thiol 2 tautomer as the most stable form. Further studies may be required to give a strong evidence to assign the most stable tautomer of the ligand.**

**The chemical reactivity of the ligand is dependent on the energy of HOMO, LUMO, ionization energy [IE], electron affinity [EA] and hardness. The corresponding values are given in (Table 2). The chemical reactivity relies on the energy gap between HOMO and LUMO energy levels, the lower the energy gap, the higher reactive system so [35]. This means that a molecule with a small**

**HOMO-LUMO gap is more reactive and is a softer molecule. The reactivity order of the different forms are Thione > Thiol 2 > Thiol 1. For the two thiol forms, Thiol 2 is more reactive than thiol 1. Thiol 1 tautomer is having the highest value for the hardness as calculated by the equation η [Hardness=1/2 ($E_{LUMO}$ - $E_{HOMO}$)]. The high value implies resistance to charge transfer and reactivity [35, 24]. The soft molecules undergo changes in electron density more easily and are more reactive than hard molecules. Therefore Thiol 2 tautomer is the most predicted form for complexation with dimethyltin(IV). The polar nature is estimated by the calculated values of dipole moment.**

**The optimized structures of Thiol 2 and its dimethyltin(IV) complex, numbering system, the vector of the dipole moment and the generated molecular orbital energy diagrams - HOMO, LUMO are presented in (Figure 3).**

***Atomic Charges, NBO Analysis and Structural Analysis:***

**The geometric change of the ligand upon complex formation with dimethyltin(IV) is investigated. The bond lengths and angles are compared, (Tables 3,4). Many bonds undergo increasing and decreasing in their lengths upon complexation with Sn(IV) ion. The vibrational frequencies of the optimized BTThU (Thiol 2) ligand and its dimethyltin(IV) complex were calculated and no imaginary frequencies are observed. The most important calculated frequency bands of BTThU and its dimethyltin(IV) complex, in $cm^{-1}$ are :**

**BTThU: 1698 ν(C=O carbonyl group), (3204 ν(- NH)), 1662 ν(C=N), 916 ν(N-N) ring and 1509 ν(NCN).**

**Dimethyltin(IV) complex: 1652 ν (C=O carbonyl group), 1521 ν(NCN), 1016 ν(C-S) and 462 & 417 ν(M-O & M-S respectively).**

**The atomic charge distribution of the Thiol 2 form of the ligand and its dimethyltin(IV) complex is determined by Mulliken population analysis [MPA] and natural population analysis [NPA] at b3lyp/6-311G and LANL2DZ(Sn) level of theory. The results for some selected atoms are presented in (Table 5).**

**The attribution of the net atomic charges in the molecular system is determined by the Population analysis [36]. Further, the distribution of positive and negative**

**charges is important from the perspective of increase or decrease in the bond length between atoms.**

**The results pointed out that the most negative atomic charges are related to oxygen and nitrogen atoms in the BTThU, and to oxygen, nitrogen and organotin(IV) carbon atoms in its $Me_2Sn(IV)(BTThU)_2$. In the NBO analysis of the $Me_2Sn(IV)$ derivative, the most negative charges are at the organic carbon atoms. Further, in the BTThU the nitrogen atoms have high positive charge than the oxygen atoms and also upon chelation the charge become more negative on the oxygen atom and more positive on the nitrogen atom relative to the BTThU. This is most probably due to the involvement of oxygen atom in coordination to the tin(IV) atom [37]. The cloud density on S increases after deprotonation of the thiol group with the decrease of the electron densities on the neighboring atoms. The electron density on the tin atom increases after complexation due to the charge transfer from the ligand (BTThU) to the central tin ion i.e. L→M. Sn (IV) ion attached to the ligand via O and S donor atoms.**

## Potentiometric study

**The acid dissociation constants (pKa) of 1-benzoyl(1,2,4-triazol-3-yl)thiourea [BTThU] ($H_2L^+$) in the protonated form were determined by direct potentiometric measurements. The $pK_a$ values were found to be 4.10 and 10.25 corresponding to the protonated triazole ring and proton release may be from –SH group as seen in (Figure 4).**

**The potentiometric data fitting for the hydrolysis of the dimethyltin(IV) [DMT], dibutyltin(IV) [DBT] and diphenyltin(IV) [DPT] ions in 50% ethanol-water were considering the formation of the three hydroxo species 10-1, 10-2 and 20-1 (Table 6). The aqua-hydroxo complexes tendency for dimerization is described by the general equilibrium:**

$$\underset{(100)}{[R_2Sn(H_2O)_2]^{2+}} + \underset{(10\text{-}1)}{[R_2Sn(H_2O)(OH)]^{+}} \overset{\log K_{dimer}}{\rightleftharpoons} [(H_2O)R_2Sn(OH)SnR_2(H_2O)]^{3+} + H_2O$$

$$(20\text{-}1)$$

**Where R = methyl- , butyl- or phenyl- group.**

**The dimerization constants can be determined by (Eqn. 3), the values are 4.38, 7.58 and 3.89 for dimethyltin(IV), dibutyltin(IV) and diphenyltin(IV); respectively.**

$$\log K_{dimer} = \log \beta_{20-1} - \log \beta_{10-1} \quad (3)$$

**By the comparison of the potentiometric titration curves of 1-benzoyl(1,2,4-triazol-3-yl)thiourea (Figure 5) in the presence and absence of diorganotin(IV), diphenyltin(IV) and dibutyltin(IV). The complex titration curve is significantly lower than BTThU curve; indicate the complex formation through the releasing of a hydrogen ion.**

**The complex formation equilibria of dimethyltin(IV) with BTThU is characterized by the fitting of the potentiometric data to various models. It was found that 110 and 120 stoichiometric coefficients were the best model for the formed complexes.**

## Speciation study

**The concentration distribution diagram for the dialkyltin(IV) complexes are given in (Figures 6-8). The speciation of dimethyltin(IV) complex given in (Figure 6), displays that the 110 species is formed at low pH with formation degree of 44% at pH ≈ 6.5, the concentration of the 120 species increases by increasing the pH. At the physiological pH range (6-8), both 110 and 120 species are predominating. From the biological point of view, It is interesting to note that the 110 species predominates at the physiological pH range and consequently, the interaction with DNA is feasible.**

## The cytoxic activity studying

**The cytoxic activity results of the synthesized complexes against the human hepatocellular carcinoma cell line (HepG-2) are plotted in (Figure 9). According to Shier[38,39], The compounds have $IC_{50}$ value within 10.00–25.00 µg/mL range are weak anticancer agents, compounds display $IC_{50}$ value between 5.00–10.00 µg/mL are moderate while those exhibiting $IC_{50}$ value below 5.00 µg/mL are considered strong anticancer agents. Cu(II) complex has the superior cytotoxic activity between the three synthesized complexes against HepG-2 cell line, while both Pd(II) and DMT(IV) complexes are considered weak anticancer agents. The highest cytotoxic activity may due to the high affinity of Copper to bind DNA than any other divalent cation, thus promoting DNA oxidation [40, 41]. On the**

**opposite of classical anticancer drugs that display a high selectivity for their molecular target, copper complexes affect DNA and a myriad of proteins to induce a general toxicity that is lethal to cancer cells. Due to its ability to participate in redox reactions, copper is able to produce large amounts of ROS through a Fenton-like reaction to damage DNA and proteins [42].**

## The microbial activity and molecular docking investigation:

**The antibacterial and antifungal activity of BTThU and DMT(BTThU)$_2$ are listed in (Table 7) and (Figure 10). The dimethyltin(IV) complex is inactive against (*Candida albicans and Aspergillus flavus*) fungi but the free ligand is active against them. The results of the antibacterial activity showed that the free ligand and its DMT(BTThU)$_2$ complex is active against Gram positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*). On the chelation theory [43], we can explain the inhibition zones results. The tin ion polarity will be decreased after chelation mostly due to of the partial positive charge sharing with the donor groups within the chelate ring system which formed during the coordination and also possibly due to the chelate ring π-electron delocalization as supported by the dipole values (Table 2). This process of chelation, in turn, increases the lipophilic nature of the central metal atom which represented by the calculated dipole moment of the complex (1.366 D), which subsequently favors its permeation more efficiently through the lipid layer of the microorganism as *Escherichia coli* as resulting in the interference with normal cell process, and hence destroying them more aggressively [44]. The different numerous compounds effectiveness variations depend on the impermeability of the cells of microbes or difference in ribosome of the microbial cells [45]. The coordination processes of BTThU with metal ions decreased antifungal activity. An interpretation to this fact can be present in the high reactive capacity of ligands with the necessary microelements for fungal nutrition [46].**

**Mol format file was used for docking process by using the optimized structures which obtained from gaussian 09 as shown in the (Figure 3(a)). Molecular docking investigation proved that, BTThU and its DMT complex have shown interesting interaction with active site amino acids of ribosyltransferase [code: 3GEY]. All forms of BTThU have multiple interactions including both polar and arene type**

**bond. The –NH- group of triazole ring helped to form acidic binding interaction with Asp540 and phenyl ring formed arene-arene interaction with Tyr582 or Tyr569. In case of DMT complex the three nitrogen groups as observed in (Figure 11), gave polar interaction with Asp 540.**

## Conclusions

**The present work investigates the synthesis of a thiourea derivative having a triazole and benzoyl groups [BTThU] and its dimethyltin(IV) complex. The calculation of the charge distribution within the ligand and its dimethyltin(IV) complex Mullikan population analysis [MPA] and natural population analysis [NPA] suggests that upon coordination of 1-benzoyl(1,2,4-triazol-3-yl)thiourea [BTThU] molecule to dimethyltin(IV) moiety, the electron density is concentrated around coordinating oxygen and sulfur atoms and the ligand is coordinated to DMT(IV) by S and O donor sites as mono-negatively charged anion through the mononegatively charged sulfur ($S^-$) atom with the formation of 1:2 (M : L) complex. The speciation diagrams confirm that 110 and 120 species formed at the physiological pH are the active type of species with large stability constant values due to the interaction of BTThU with dimethyltin(IV) [DMT], dibutyltin(IV) [DBT] and diphenyltin(IV) [DPT]. From the biological point of view, it is interesting to note that the 110 species is predominating and the interaction with receptors in biological systems is feasible. The results showed that the free ligand and its DMT$(BTThU)_2$ complex is active against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative bacteria (*Escherichia coli and Pseudomonas aeruginosa*). The DMT complex inactive against fungi (*Candida albicans and Aspergillus flavus*) but the free ligand showed activity against them. The binding model of BTThU and DMT$(BTThU)_2$ from docking stimulation demonstrated that the substitution accommodated the hydrogen bond formation in the active sites of receptors. The arene motif plays an important role by the interaction with amino acid residues in active binding sites. Thus, the present findings provide new opportunity for the development of novel antimicrobials to overcome the ever increasing problem of drug resistance. Cu(II) complex show suprior liver antitumor effect more than the Pd(II) and DMT(IV) complexes.**

## References


1- N. Awang, N.F. Kamaludin and A.R. Ghazali,. *PJBS* 2011, 14, 768.

2- C. Marzano, M. Pellei, F. Tisato and C. Santini, *Anticancer Agents Med. Chem.* 2009, 9, 185.

3- J. J. Criado, E. Rodríguez - Fernández, E. García, M. R. Hermosa and E. Monte, *J. Inorg. Biochem.*, 1998, 69, 113.

4- D. C. Schroeder, *Chem. Rev.* 1955, 55, 181.

5- R. P. Rao, *Indian J. Appl. Chem.* 1960, 23, 110.

6- I. Fakhar, B. M. Yamin, and S. A. Hasbullah, *Chem. Cent. J.* 2017, 11, 76

7- M. G. Mostafa, M. S. Alsaid, M. S. Al-Dosary, Y. M. Nissan, S. M. Attia, *Chem. Cent. J.* 2016, 10, 19.

8- C. W. Sun and X. D. Zhang, Chin. *J. Struc. Chem.* 2007, 26, 153

9- A. Saeed, R. A. Khera, N. Abbas, M. Latif, I. Sajid and U. Flörke, *Turk J. Chem.*, 2010, 34, 335

10- L. K. Ahmadi and L. Shirmohammadzadeh, *J Nanostruct Chem.* 2017, 7, 179

11- S. Kumar, W. Purcell, J. Conradie, R. R. Bragg and E. H. G. Langner, *New J. Chem.* 2017, 41, 10919.

12- H. Pasdar, B. H. Saghavaz, N. Foroughifar and M. Davallo, Molecules, 2017, 22, 2125.

13- M. Eweis, S. S. Elkholy and M. Z. Elsabee, *Inter. J. Biol. Macromolec.* 2006, 38, 1.

14- T. J. Egan, K. R. Koch, P. L. Swan, C. Clarkson, D. A. Van Schalkwyk and P. J. Smith, *J. Med. Chem.* 2004, 47, 2926

15- K. R. Koch, C. Sacht, and C. Lawrence, *J. Chem. Soc. Dalton Trans.* 1998 689

16- Y. F. Win, S. G. Teoh, E. K. Lim, S. L. Ng, and H. K. Fun, *J. Chem. Crystallogr.* 2008, 38, 345

17- R. Joshi, P. Kumar,V. Kumar, and A. A. Hashmi, *J. Coord. Chem.* 2008, 61 1283.

18- T. S. Basu Baul, A. Paul and L. Pellerito et al., *J. Inorg. Biochem.* 2012, 107, 119.

19- A. Kumar, P. Chaudhary. R. Singh and N.K. Kaushik, *Main Group Chem.*, 2016, 15, 163
20- A. D. Becke, *J. Chem. Phys.* 1993, 98, 5648.
21- M. H. Elnagdi, M. R. H. Elmoghayar, D. H. Fleita, E. A. Hafez and S. M. Fahmy, *J. Organometal Chem.* 1976, 41, 3781.
22- Safaa S. Hassan, Mohamed M. Shoukry, Rania N. Shallan and Rudi Van Eldik, J. *Coord. Chem.* 2017, 70, 1761.
23- A. D. Becke, *j. Chem. Phys.* 1993, 98, 5648.
24- P. Sandeep, Res. *J. Chem. Sci.* 2014, 4, 56.
25- National Committee for Clinical Laboratory Standards. (2002). Reference Methods for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi:proposed standard M38-A. NCCLS, wayne, PA, USA.
26- P. Gans, A. Sabatini, A. Vacca. *Inorg. Chim. Acta*, 1976, 18, 237.
27- L. Pettit, University of Leeds, Personal communication
28- C. Li, W. Yang, H. Liu, M. Li, W. Zhou and J. Xie, *Molecules*, 2013, 18 15737.
29- G. B. Aitken, J. L. Duncan and G. P. M. Millan, *J. Chem. Soc.* 1971, 2695
30- K. Singh, P. Puri, Y. Kumar and Ch. Sharma, *Inorg. Chem.* 2013, 2013, 1.
31- P. L. Pathak and B. C. Haldar, *J. md. Chem. Soc.* 1972, 49, 743.
32- B. Sireesha, S. P. Mydhili, G. Sravan and CH. Venkataramana Reddy, *j. Appl. Chem.* 2016, 9, 2278.
33- S. Rajeev, D. Kumar, S. Bhoop, V. K. Singh and R. Sharma, *J. Chem. Sci.* 2013, 3, 79.
34- R. Singh, D. Kumar, Y.C. GOswami and R. Sharma, *Arab. J. Chem.*, 2014.
35- B. Sireesha, S. P. Mydhili, G. Sravan and CH. Venkataramana Reddy, *IOSR-JAC.* 2016, 9, 49.
36- G. Berger, *Comput. Theor. Chem.* 2013, 1010, 11.
37- M. Naseh, T. Sedaghat, A. Tarassoli and E. Shakerzadeh, *Comput. Theor. Chem.* 2013, 1005, 53.
38- W. T. Shier, Mammalian Cell Culture on $5 a Day: A Lab Manual of Low Cost Methods, University of the Philippines, Los Banos 1991.

39- **M. Gaber, A. M. Khedr,| M. Elsharkawy, *Appl. Organometal. Chem.* 2017, 31, 1.**

40- **C. Marzano1, M. Pellei, F. Tisato and C. Santini, *Anticancer Agents Med. Chem.* 2009, 9, 185.**

41- **M. J. Burkitt, *Methods Enzymol.* 1994, 234, 66.**

42- **C. Santini, M. Pellei, V. Gandin, M. Porchia and F. Tisato et al. *Chem Rev.* 2014, 114, 815.**

43- **R. J. Angelici and J. W. Allison, *Inorg. Chem.* 1971, 10, 2238.**

44- **R.W. Hay and P. J. Morris, ", Ed., H. Sigel Marcel Dekker, New York, 5 1976, 173**

45- **F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reaction Mechanisms", 2nd Ed, Wiley, New York, N.Y. 1967.**

46- **W. Q. Zhou, K. Sh. Leng, Y. Zhang and L. D. Lu, *J. Mol. Struct.* 2003, 215 657.**