Sys Rev Pharm 2020;11(11):428-437
A multifaceted review journal in the field of pharmacy

Recent Development In Oxine Complexes And Their Medical Application: A Review

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ABSTRACT

This review is concluded of 8-Hydroxyquinline (8HQ) compound and derivatives which has a very significant interests with a strong fluorescence , furthermore the relationship between divalent metal ions and characteristic of chelating . In the same way coordinated features have increase of its organic action and inorganic behavior by giving many samples of compounds which are a good chelating agents ligands with more capable of forming very stable complexes.Therefore, the role of (8HQ) is not limited on complexes only but its applications in different fields so this review will focus on demonstration preparation methods and properties of (8HQ) derivatives with their complexes and applications, hopefully that we will cover a part of scientific information in order to present them to the researchers and obtain a major benefit in future .

Keywords: 8-Hydroxyquinoline(oxine), derivatives, metal binding compounds, Medical field applications

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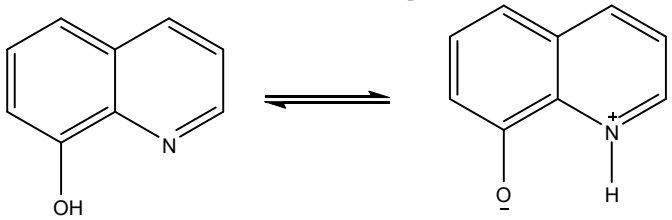
INTRODUCTION

8-Hydroxyquinoline (8HQ, 8-quinolinol, oxine), one of the quinolone isomers, has the formula (C_9H_7NO). (8HQ) and their derivative are important compounds which have the ability to coordinate with a various ions as bidentate through oxygen and nitrogen atoms of quinoline ring after deprotonation of hydroxyl group [1-2] to form five member ring with the central metal ion lead to increase the stability of the complexes, as well as its known biological activity[3], the capability of (8HQ) to form coordination complexes with more than 60 metals of d - transition metals or the earth and alkali metals. It is even used for the of rare earth metals using a binary mixture of sec-octylphenoxyacetic acid-8HQ[4]. Also, as ligand it is extensively used in coordination chemistry for determination of metal ions[5]. Due to their biological and chemical characteristic, these compounds which consist of quinoline group have a cosidrable attention in term of medical applications[6] .

In the medical field, all the (8HQ) derivatives, has an important application in antibacterial, anti-HIV agents insecticides, neuroprotective and fungicidal, [7-8]. Furthermore, privileged structures of (8HQ) and its derivatives representative qualities suitable for use as drugs and this led to the development of scientific research in this area. [9-10]. The chemical structures were studies and synthetic aspects of (8HQ) derivatives are invistegated with specific concentration to their recently applications and developed of (8HQ) derivatives in the various, area such as (OLEDs) , insecticidal agents, chemosensors organic, and medical drugs[11].

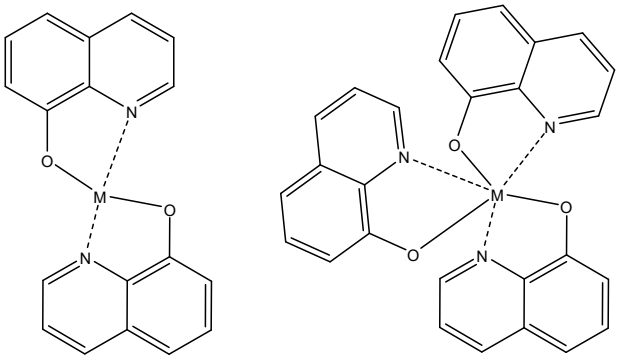
As other (8HQ) can be obtained an equal ratio of N - protonated zwitterion and hydroxyl as a mixture(Figure 1)



Hydroxyl N-protonated zwitterion

Figure (1): The forms of (8-HQ) Zwitterion

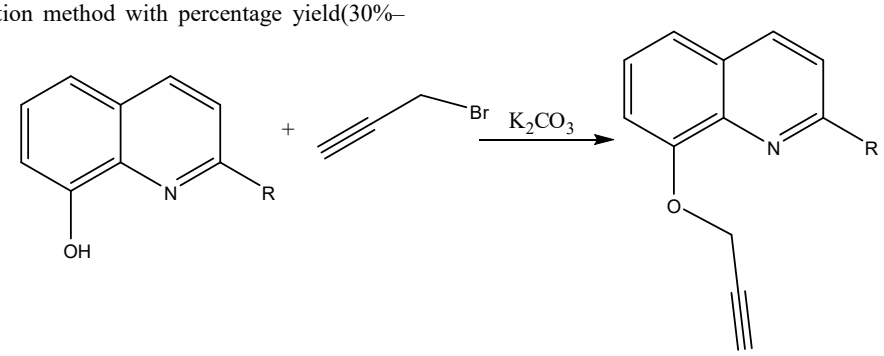
The result of the above mixture was a hydroxyl moiety [12] is near to the (N) atom of heterocyclic, also (8HQ) can form strong chelating solid complexes with different metals ions, involved, (M^{+2}) = (Mg , Mn , Ni , Cu , Zn and Bi) or (M^{+3}) = (Al and Fe) [13] . The hydrogen atom of OH moiety of (8HQ) is supplanted and both (O , N) bonded with a metal ion . 4 - coordinated of metal complexes can be obtained by 2- molecules of (8HQ) for every atom of (M=metal) and 6-coordinated with 3- molecules of (8HQ)(Figure 2).



Figures (2): 4 or 6 coordinated of (8HQ) complexes

Application of 8HQ in Medical Field:

***GÜMÜŞ1 et al.*, (2018)[14]** synthetized a new serious of derivatives of 2-substituted 8-propargyloxyquinoline by using o-propargylation method with percentage yield(30%–98%) these products was obtained from 2- substituted-8-hydroxyquinolines.**Scheme (1)**.



Scheme (1): Preparation of 8-(Prop-2-ynyloxy)Quinoline Derivatives.

The synthesized derivatives were examined for vitro antioxidant activities like DPPH lowering energy , radical scavenging activities also ferrous chelating.(46.5%) was the max radical scavenging with lowering energy efficiency, were obtained from 1 . (72.1%) was represented the maximum ferrous chelating effect was obtained from 6 at 500 µg/mL concentration. Calf thymus DNA was used to indicate DNA binding activity of the complexes, **Figure (3)** .

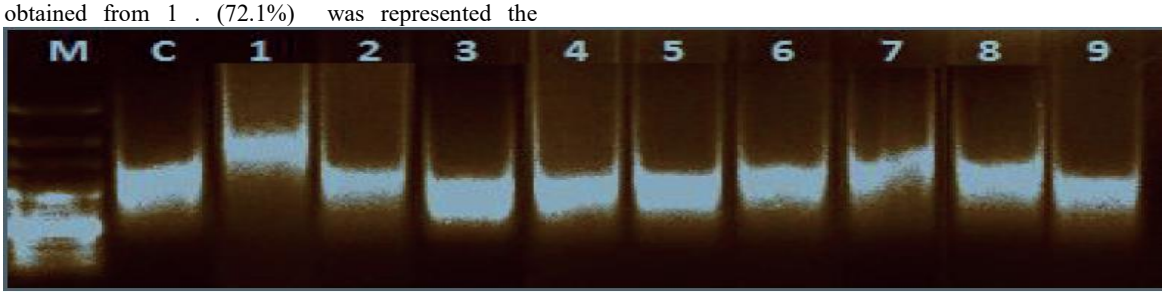


Figure (3):The Binding of DNA with New Synthesized Complexes Concentrations Information

***Pape et al.*, (2018)[15]** reported the effected of the binding properties for Cu , Fe upon antitumor effectiveness for (8HQ) to obtain Mannich bases through the complex formation with iron and copper ions as redox active. To compare the complex formation procedure and proton dissociation, they used Ultra-vis and EPR spectra of (8HQ), (Q-1) as a reference with three regarding Mannich bases . Each studied derivatives containing CH_2- N group on the site 7 connected with ,[Q2 = Morpholine , Q3 = Piperidine , Q4 = Chlorine , Fluorobenzylamino] it can be used as a substitute. **Figure (4)**.

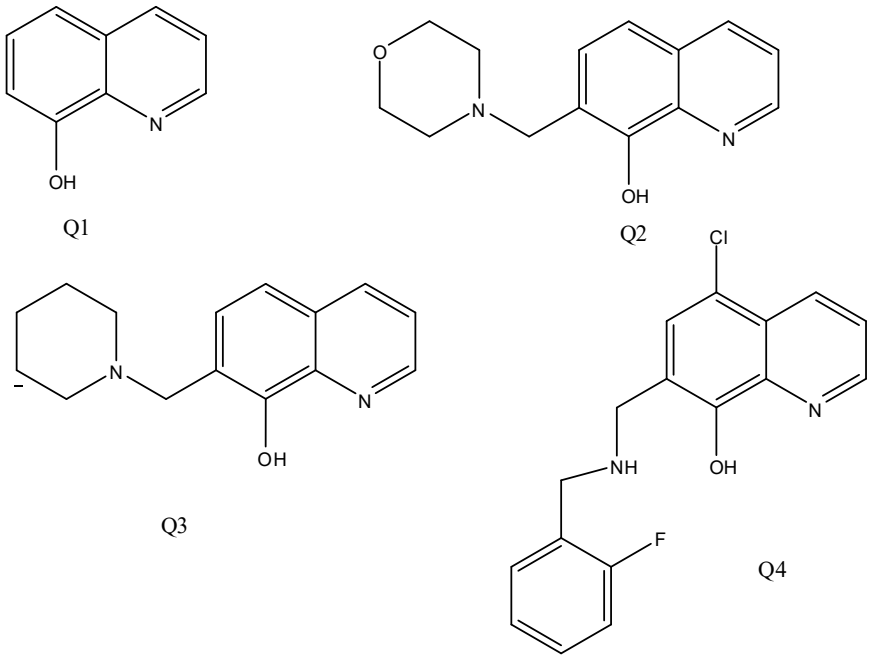
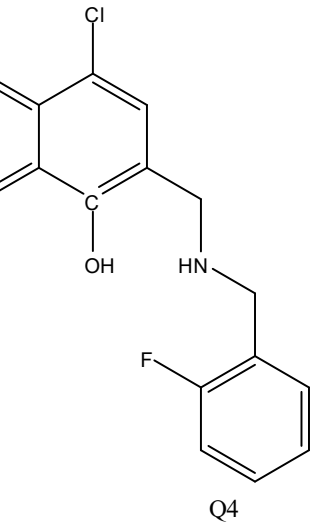


Figure (4): The chemical structure of [8HQ , Q1] as a standard compounds and [Q2,Q3 , Q4] derivatives .

Coupling method was used to synthesized (Q-4) from the reaction of 2 -fluorobenzylamine with 5-chloro-8-hydroxyquinoline(5-Cl-8HQ) ,with the existence of P - formaldehyde with some change in the reaction of Mannich and the use of microwave circumstances. [1,3]oxazino[5,6-h]quinolone compound was separated as derivative and solid material by using (ethyl acetate: n-hexane) mix and convert to the last produce, as [HCl - Q4] in ETOH solution with HCl in excellent, product 1H-NMR technique was an agreement with the prospective framework, enable to obtain of all [1H - NMR, C13 - NMR]. The pureness of [HCL - Q4] was more assured from the (C, H, N) elemental analysis, **Scheme (2)** .



Scheme (2): preparation of 5-chloro-7-((2-fluorobenzyl-amino) methyl)quinolin-8-ol [Q-4],

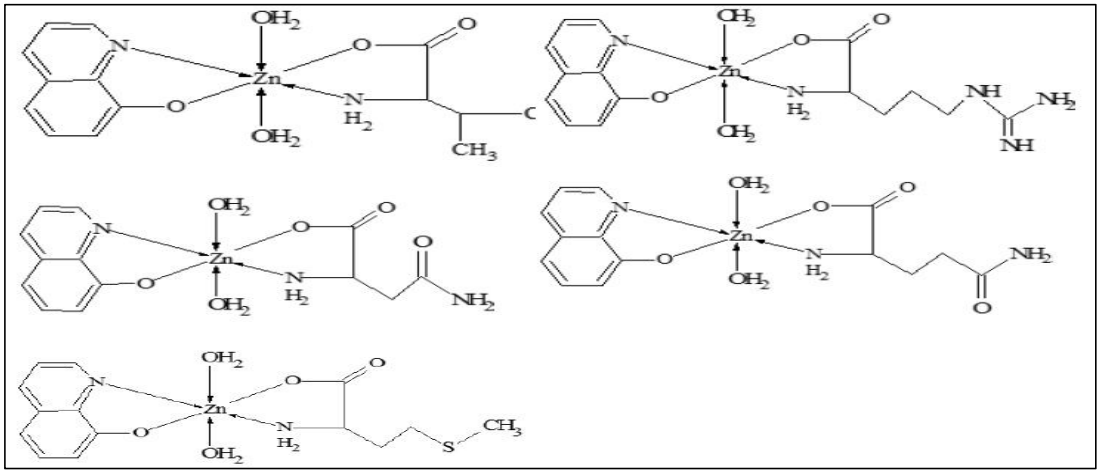
Single crystal (XDR) analysis were employed to identify of following structures (1) - Q3, (2) - Q4·HCl·H_2O, (3)- $[(Cu(HQ2)_2)_2]\cdot (CH_3OH)_2\cdot Cl_4\cdot(H_2O)_2$,(4) - $[Cu(Q3)_2]\cdot Cl_2$ (5) - $[Cu(HQ4)_2(CH_3OH)]\cdot ZnCl_4\cdot CH_3OH$. Cyclic voltammetry can used to studied the redox properties of iron and copper complexes .Physiologically and direct reaction of the relevant reductants such as [ascorbic acid and glutathione] was observed. The metal binding properties and correlation analysis of the anticancer activity to a number of molecules mention to the physiological pH Fe (+3) of the coordinated finding with high toxicity ,and weaker copper(II) (e.g. Q4: pCu = 13.0, p^{iron} = 6.8, IC50 = 0.2 micro gram and Q1: p^{copper} = 15.1, p^{iron} = 13.0 IC50 = 2.5 micro gram)

According to their results (Q-1) prefer to bind to the metal ion of Cu $^{2+}$ rather than the metal ion of Fe^{3+}. It has been observed that highly toxic ligands are preferred to stable at the low oxidative numbers of metallic ions, and this has been proven through the use of cyclic voltammetry.

The outline, of this work includes the diagnosis of the compound [Q4] due to its importance in terms of the specificity of its work and also the importance of its role and effectiveness towards malignant tumors in addition to the presence of high toxicity and drug-resistant, in addition to that most of the molecules show a clear indication of the toxic activity of cells as the values of (IC50) between (0.20 -3.27) micromole inside the affected cells, allowing the opportunity to be investigated depending on the following sequence where Q4 is the largest of them and then

comes after Q3, Q2 and finally Q1. According to the values of (IC50) recorded and defined for primary hepatobiliary cells, it appeared that they gave a very good selectivity against cancer cells more than the chemotherapy used and called (agent doxorubicin). However, the picture was not clearly shown in terms of the link or affinity towards a number of derivatives and their toxicity. The scientific explanation for this is that the permeability of the membrane is not directly dependent on the toxicity of cells .

Bhagat and Vaidya (2018)[16] were synthesized of mixed ligand Zn^{+2} complexes type $[M(Q)(L)].2H_2O$ by using (8HQ) as the first compound – (N , O) is granter = (HL) (amino acid) : L-asparagine ,valine , asparagine , glutamine , arginine , methionine respectively represented the minor compounds ligands. The complexes of metals **Figures (5)**. Identified by, molar conductivity at 25 C^o, elemental analysis , measurements of magnetic susceptibility & studies of thermal analysis .



Figures (5): Ligand – Zn complexes

Chobot, et al., **(2018)[17]** were explored the character of (8HQ) such as (antioxidant, pro) specially, the case of complexes of metal ions of (M^{+n})= (Fe^{+2} , Fe^{+3}) : techniques differential pulse voltammetry, (nano-ESI) and disintegration of deoxyribose, Fe^{+2} spontaneous oxidation, also examine the death – rate of brine shrimp. Outcome: The (8HQ) gave a mixture complexes coordinated with (M^{+n}) = (Fe^{+2} , Fe^{+3}). Moreover, (8HQ) exhibited no pro-oxidant and only antioxidant effects. (8HQ) of brine shrimp mortality observed that the poisoning decreased with existence, of Fe^{+3}. Showed that effective of (8HQ) as antioxidant not be based on the structure of complexes coordinated with iron ions, however certainly, on the activity scavenging cause of the oxidation - reduction characterization of the 8-OH moiety. The examination of the collection of the used exhibited no pro-oxidant effect. The: examine of the disintegration of deoxyribose scout the ability of different materials to stop the disintegration of 2-deoxyribose by OH radicals, who are produced by the Fe- catalyzed. The reaction of Fenton. From Chobot study, the PH of (8HQ) solution reaction is an important factor that effects on the antioxidant activity of (8HQ). This factor is clearly was further effective antioxidant at (pH = 7.4 than at pH = 6.0) . Non the less, the compound (8HQ) Clearly showed the capability to stop the oxidative disintegration of 2-deoxyribose by OH radical .

The $iron^{+2}$ autoxidation examination: Shows the potential of research the influences of different materials on (ROS) work product that is exactly gives rise to the auto-oxidation of Fe(+2). The (8HQ) essentially influenced the reactions led to the decomposition of (2-DeoxyRibose). Anywise, in this examination, the dependence of PH was less effective compare with the (DeoxyRibose) hydrolysis examination . The results of the (8HQ) compound exhibited an effective antioxidant and capable of the preserve (2-DeoxyRibose) versus reactive oxygen kinds offensive caused by Fe(+2) auto - oxidation. The examination of the death –rate of shrimp in the seawater showed that (8HQ) was sensitive towards the larvae of the invertebrate crustacean kind : Artemia Salina . L , . About 125µM of concentration rise to the death - rate roughly (%100) . Obverse , forming iron complexes with (8HQ) makes the death – rate to lower . The results values of the toxicity agree with the monitored solution values of Fe (+2) chloride .

Oktavia al et.,**(2018)[18]** were used iron to enhance the manufacture operation that needs Fe as a crude component to make roundabout test for Fe(+2) metal ions complexes with (8HQ).The analysis was performed using (HpLC) at 470nm with an ODS C18 column.

They used three methods to preform Fe-oxinate complexes.The chromatogram results display that three routes supply the best chromatogram for Fe test .

Truc et al.,(**2019)[19]** employed 8HQ as a corrosion inhibitor (8HQ). The group of phyllosilicate with clay was used in the percentage of weight (3% wt.) as an epoxy coating in the presence of a free solvent. The carbon steel is prepared for precipitation. Moreover, electrochemical techniques have been used to identify the nature of the action of the (8HQ) inhibitor. The measurements were performed adequately to assess the effect (MMT- 8HQ) on the corrosion of the epoxy coating and how to maintain it. A comparison of the results was made with a standard sample that is considered a reference in addition to containing the same type of coating as it is made of modified quaternary ammonium. The study showed two results, the first is that there are features of a suitable barrier, and the second is an improvement in dry and wet adhesion in the case of fusion (MMT- 8HQ) compared to the reference sample. It was concluded from the study that (8HQ) affects the surface of the metal when painting and is with a very low concentration and this gives him protection against corrosion of hard carbon.

Rbaa et al., **(2019)[20]** were synthesized a new series of derivatives of pyranoquinoline by bearing an (8HQ) moiety on their structure, Figure(6).

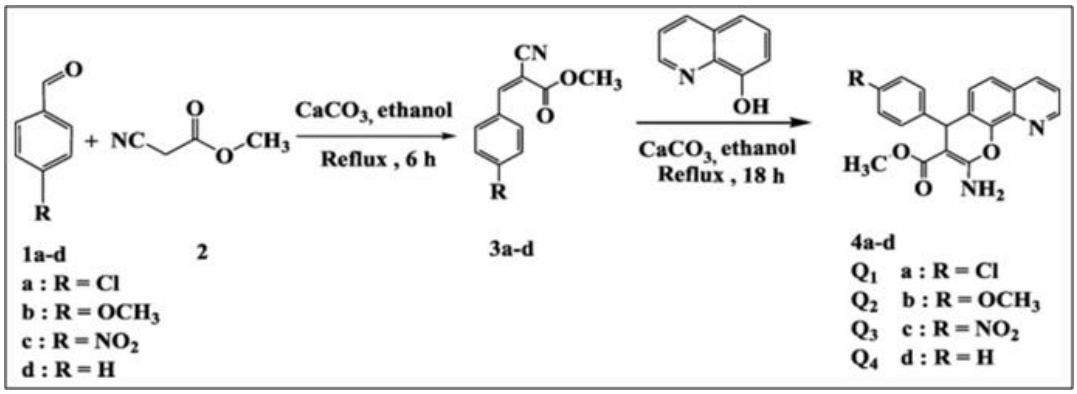
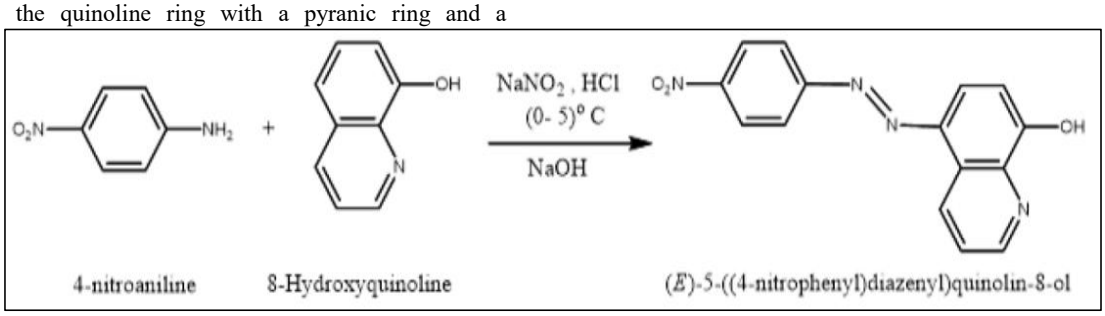


Figure (6): Synthesis of New Series of Derivatives of Pyranoquinoline

pyranoquinoline derivatives were tested against both positive and negative pathogenic bacteria strains (Escherichia coli (ATCC35218), Staphylococcus aureus (ATCC29213), Vibrio parahaemolyticus (ATCC17802), and Pseudomonas aeruginosa (ATCC27853) . The screening test was determined through the standard protocol from disk diffusion method (DDM). The results of the analyzes were that all the compounds Q1, Q2, Q3 and Q4 that showed a clear effect against Gram positive and Gram negative bacteria compared with the standard antibiotic (penicillin G). which had higher activity against Gram positive bacteria than Gram negative bacteria.

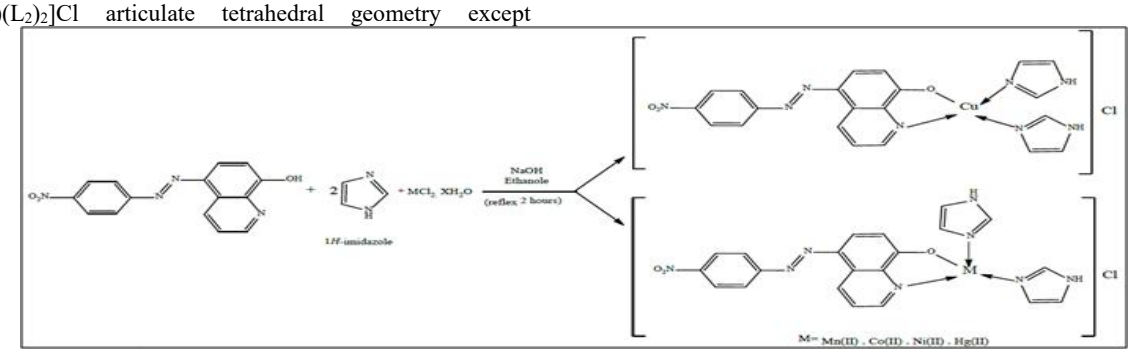
These results were interpreted according to the literature, since the weak results against Gram negative bacteria due to the presence of another membrane reduce the transport of compounds Q1, Q2, Q3 and Q4 through the cytoplasmic membrane and these results are in agreement with Himmi et al. [21].

The anti-bacterial activities were explained through the presence of a quinoline nucleus. In order to improve the anti-bacterial, the quinoline ring with a pyranic ring and a benzene ring bearing electrondonor substituents such as –Cl, –OCH3, and –OC2H5. It has been shown that the heterocyclic compounds carring electron-with drawing substituents (nitro, acid function, etc.) showed little anti-microbial activity against Gram positive and Gram negative bacteria such as Staphylococcus aureus, Vibrio parahaemolyticus, and Escherichia coli, compared carrying electron-donor substituents such as O-alkyl, O-aryl, and chlorophenyl [22]. It has shown through obtaining the results through the diffusion method that the benzene nucleus carries chlorine to the compound, which makes it more active compared to other compounds to the blank of penicillin G.Thus, the against Gram postive bacteria is more important than that of the Gram negative bacteria such as the St. Witwit *et al*., (2019)[23] reported complexes of the new series mixed ligand (M^{+2}) = (Mn, Co, Ni, Cu, Hg) metal ions were prepared in two general formula {$[M(L_1)_2(L_2)_2]Cl$-$[M(L_1)(L_2)_2]$}for each ion with (L_1) : [E-5-(4-nitro phenyldiazanyl)quinoline-8-ol] as first (L_1) and molecular compound of imidazole was (L_2) ligand, Scheme (3).

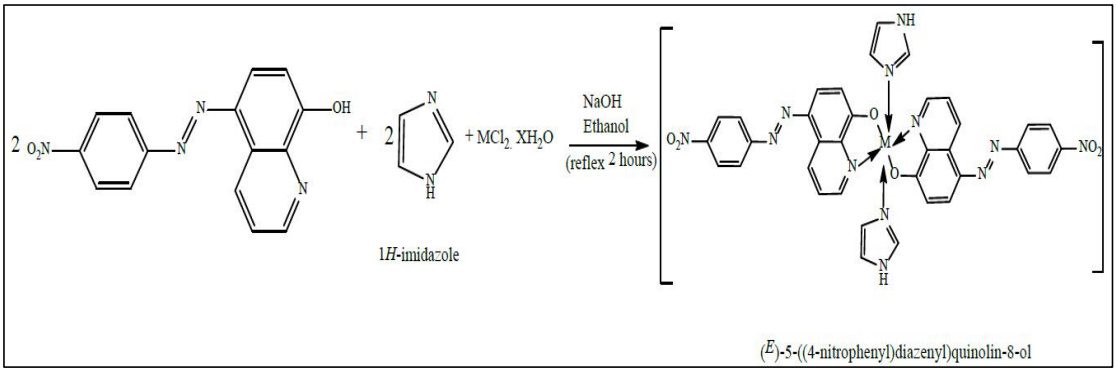


Scheme (3): preparation of L_1 Ligand

Free ligands and their complexes characterized via UV-vis.,MS , FTIR , ^{1}HNMR, molar conductivity and magnetic susceptibility , Molar Conductivity . The results indicating the octahedral geometry for all compounds with $[M(L_1)_2(L_2)_2]$ formula while the complexes which have general formula $[M(L_1)(L_2)_2]Cl$ articulate tetrahedral geometry except $[Cu(L_1)(L_2)_2]Cl$ which has square planer geometry .(L_1) ligand behaved as bi dentate through and (O - atom) of OH moiety and (N- atom) in presence of basic medium whereas imidazole coordinated through nitrogen (3) as a neutral mono dentate ligand, **Scheme (4-5).**

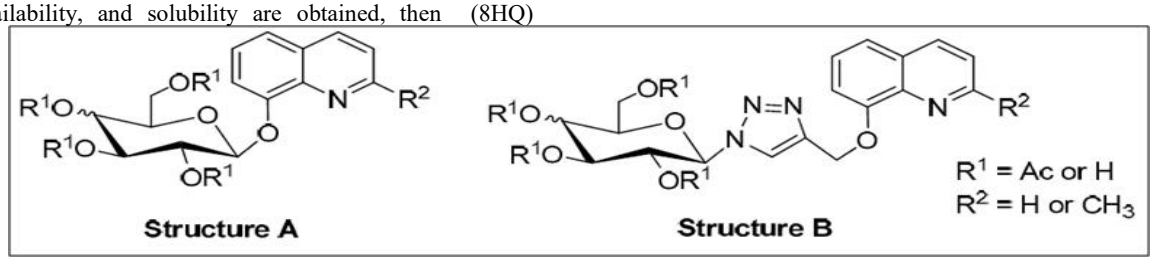


Scheme (4): Synthesis of $[M(L_1)(L_2)_2]Cl$ Complexes

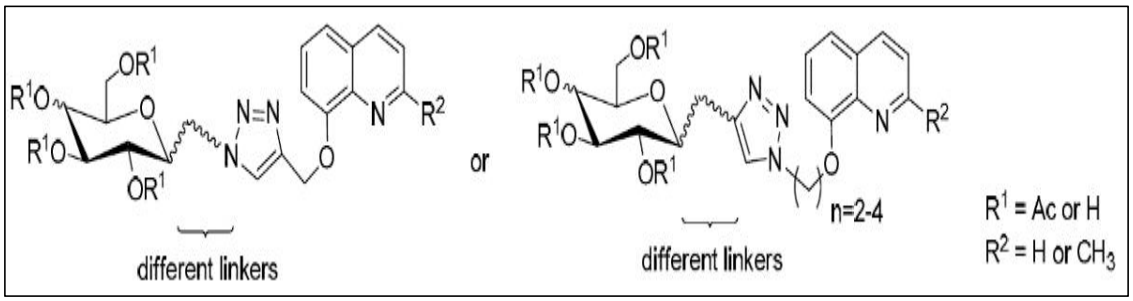


Scheme (5): Synthesis of $[M(L_1)_2(L_2)_2]Cl$ Complexes

Krawczyk *et al.*,(2019)[24] were successful to design a very important structures by using of (8HQ) derivatives for potential pharmaceuticals. Conjugating (8HQ) derivatives with sugar derivatives moleculars are used to design promising anti-cancer agents with better selectivity, bioavailability, and solubility are obtained, then (8HQ) compounds are functionalized at the (8OH) site and combined together with sugar compounds. The result was new derivatives compounds of (D-galactose) and (D-glucose)with the new various species has an abnormal site, **Figures (7-8).**



Figure(7): Glycoconjugates Structures [25].



Figure(8) : General Structure with Different Linkers of the Glycoconjugates

They used of (CuAAC) Cu(I)-stimulated by cycloaddition and glycoconjugates of 1,3-dipolar azide-alkyne then examined the inhibition of the increase of tumor cell lines (MCF-7, HCT 116) and inhibited of β-1,4-galactosyltransferase , efficacy, which combined associated with tumor improvement. The study appeared that Glycoconjugates have been examined and evaluated to determine the effect of its efficacy in the direction of cancerous cells in vitro. Also, an examination (MIT) was performed on cancer cell lines, an examination (HCT116) on the colon and rectal cancer cell line, and an examination (MCF- 7) on glandular and breast cancer cells. Diabetic association sites and the materials used for their synthesis have been exposed to cellular toxicity assay. As the study showed an increase in lactose and glucose transporters [25-27].

It have been concluded that all glycoconjugates are conserved and that their effect, which falls within the range of laboratory focus, is toxic to cancer cells. It has been found that the structure associated with the amide group helps to improve the effectiveness of glycoconjugates, possibly due to the possibility of cancer cells to chelate with metallic ions. The study also showed the effect of the presence of additional amide bonds on the examination of cancer cells. It turns out that it becomes more effective as it was observed that the compounds prepared from (8HQ) are better toxic in comparison with its compounds with (2Me8HQ) Moreover, the quality of the sugar unit is not affecting the effectiveness of glycoconjugates that has been created and, and the amazing and important thing is that glycoconjugates Containing an amide group that does not affect the inhibition of the effectiveness of β-1,4-Gal, In addition, the length of the alkyl chain that lies between quinolone and triazole increases the ability of glycoconjugates, which inhibits the activity of the enzyme. In spite of this, the value of IC50 which has been determined does not necessitate its use for pharmacological purposes, as it is possible to change the position of the composition so that it becomes regular and this improves the activity of its molecules. It was found through this research report that the presence of protective groups in the unit of sugar and the length and type of bond during the sugar parts and the glycoconjugates affects its existence and is considered a reliable basis for the effectiveness of the glycoconjugates that we get. While the heteroaromatic works to increase the effectiveness of the glycoconjugates and it is possible that the reason for this is the ability of metal ions to chelate with many cancer cells, so a study of the properties of complexes demonstrated that the glycoconjugates have the ability to chelate with ions of Cu And the formation of complexes, as this ability increases in compounds containing 1,2,3-triazole fragment. The end result of these results and by determining the mathematical equivalents of the complex of glycoconjugate. It has been found that the tested compounds are chelated with Cu ions at

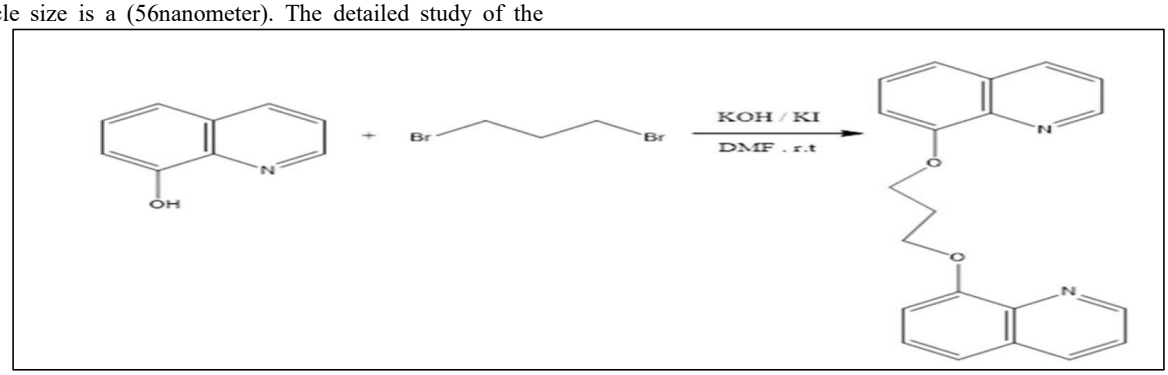
a molar ratio of 1: 1, while the ratio of (8HQ) forms chelates was 2:1.

Liu et al., (2019)[28] were proposed, were proposed novel produce of preparation the (8HQ)and the complex of M(II). BaQ2. This metal complex was excited by using high – energy UV – lighting with a maximal [(λ) = 408 nm]. Turns out the proposed of this study was synthesized luminescent material of vis-lighting -irritable BaQ2 by using the (mechanochemical activation method) and explained the adequacy of the (MCAM) by studying the rules of dynamic and thermodynamic principles..

Notional conclusion explained about the occurrence of red displacement of the compound (BaQ2) is when it is excited at the greatest wavelength by reducing the size of the above class. According to the equation (Scherrer), the average particle size is a (56nanometer). The detailed study of the theory of (photoluminescence) has shown that the data of this theory can be used and applied to the (BaQ2) which can be excited through the use of visible light, which in turn works to improve the theory of.) photoluminescenc

Through its application to the study of the bivalent metal complex with (8HQ). The results of this research have shown that it can give us a way in which some of the luminescent substances can be used in order to conserve energy. As for other methods of investigation and diagnosis, they can be useful for developing these theories better.

***Alamshany and Ganash* (2019)[29]** synthesized a new derivative of (BQYP): represented one of quinolines derivatives . The novel derivative of (BQYP) has been identified by using different techniques such as FTIR,^{1}HNMR, and^{13}C NMR **Scheme (6)** .



Scheme (6): Synthesis of novel (BQYP)derivative .

According to the different measuring range of concentrations (1-0.05mM) of 2M H_2SO_4 and different temperatures, the electrochemical technique has been used to investigated and tested of the anti-abrasion characteristics for (Bis quinoline derivative) versus the abrasion of moderate steel. The preliminary findings suggest that absorption proceed Consequently to Langmuir's relevance . The Reducing of the orbital effect of (LOMO) and increasing the orbital effect of (HUMO) increases the adsorption process of the inhibitor. The (LOMO) , (HUMO) orbitals have an important role in giving the integrated geometrical shape of the compound.

***Matos et al*., (2019)[30]** were used metallodrugs of iron – based for therapeutic through the 2- novel mixed-ligand Fe^{+3} complexes having the participate – ligands and tripodal hydroxyquinoline, may be 5-chloro-8-hydroxyquinoline (8HQ - Cl) and compound kind of : aminobisphenolate or N,N-bis(3,5-dimethyl-2-hydroxybenzyl)-N-(2-pyridylmethyl)amine (H_2L) . These mixed compounds were synthesized with fully identified to gave two formulated compounds : [Fe(L)(8HQ -Cl)] (2) and [Fe(L)(8HQ)] (1),as shown in **Figures (9)** .

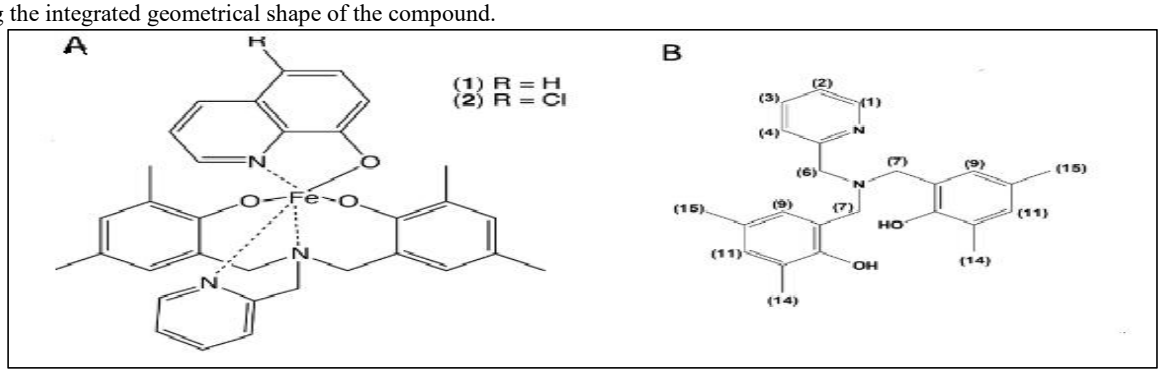


Figure (9): The Structure of (1) and (2) Ligands

The study found that the high-spin Fe^{+3} complexes using the equivalent ratio of (BSA): Bovine serum Albumin in liquid media which are stable and that indicated of obtaining of protein connection reaction. The measurement of the binding constant is (log values) PH = 7 when HSA complexes (1,2) is (5.08, 6.35). These complexes are toxic versus cancer cells of humans (triple-negative breast adenocarcinoma) and (cervical carcinoma) (HeLa).

The insertion of the participate -ligands (8HQ- CL), (8HQ) to the primary iron ligand complex has led to improve the activity, and also 2, 1 are further efficient than (8HQ - Cl), (8HQ). The lower Incubation time at the range (24 -48) hour and also examined and treated of cell complexes which show representative properties of the dead cells and understand cellular morphology, DNA condensation, then by using several methods, for example, the condensation for DNA and TUNEL test. COMET rapid assay exhibited that both drug filters bring genomic harm in both cell lines. The activity fission for DNA and harm DNA damage are exhibited in the complexes which linked to their capacity to produce ROS .

Both compounds are efficient, antitumor medicinal nominated with the decrease of the micromolar range, and having an important role in the event of the breast MDA-MB-231 line, this is a sample for triplex -negatory breast tumor that is an attacker form of breast tumor extremely invasive and with limited treatment options and very poor prognosis. metal complexes both showed a better anti-Mycobacterium tuberculosis efficiency. It was proposed from 2 with 1 possibly have a broad series of biological evaluation.

***Bhagat* (2020)[31]** has been synthesized a (pure) ,(Mn^{+2}) of transition metal complexes of (8HQ) (Alq_3) by using a

simple method of precipitation with preservestochiometric ratio / at room temperature,**Figure (10)**.

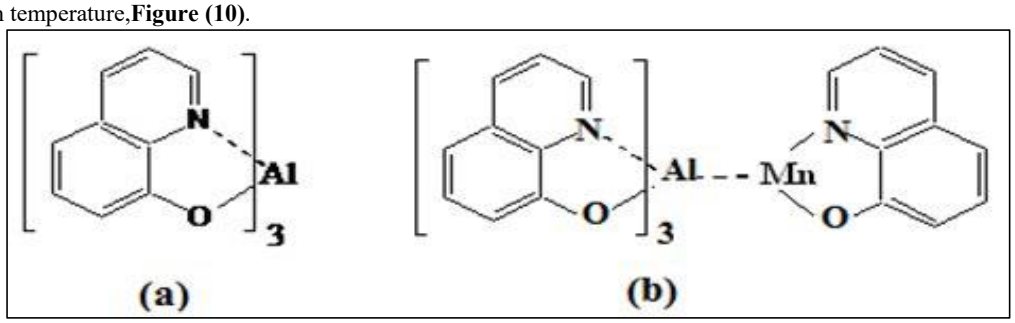


Figure (10): Alq_3 (b) Mn^{2+} doped Alq_3

The Alq_3 complexes were identified by photoluminescence – PL and X-rayDiffractogram(XRD) spectra methods . The poly crystalline nature has been observed for these complexes through X- ray diffraction lines which confirmed the polycrystalline structure **Figure (11)** .

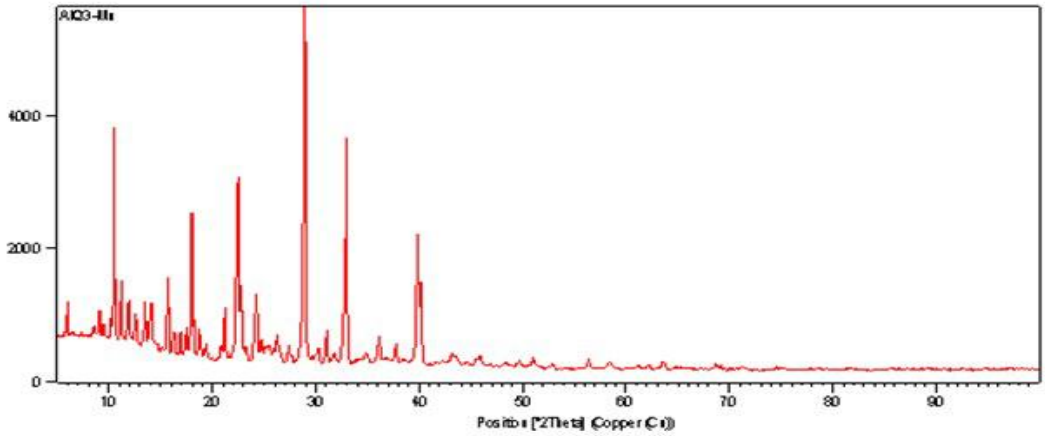


Figure (11): X-ray Diffractogram on Mn^{2+} Doped Alq_3.

The comparison of the photoluminescence (PL) between Mn^{+2} doped complexes and Alq_3 complexes with a various combinations was reported . The preparation of the phosphors has been carried out in laboratory at room temperature were α-phase out of four phases. The intensity of AlQ_3: Mn (0.5%) was highest in comparison other Mn^{2+} dofoped Alq3 phosphors. Mn^{2+} changes PL emission intensity of Alq_3 phosphor Excitation and emission spectra are within the limits of the wavelengths of [416 – 438nm] ,[492 -498 nm] for Mn^{+2}doped phosphor assign to bluish green emission respectively.

Phopin *et al.*, (2020)[32] Cloxyquin (5-chloro-8-hydroxyquinoline);compound has been reported. The best site has been identified for the association of cloxyquin on $BS_{\odot}A$. The studies were conducted competitively, including studying the displacement of signs and a known site with the use of digitoxin, warfarin, and ibuprofen as shown in Figure **(12)**.

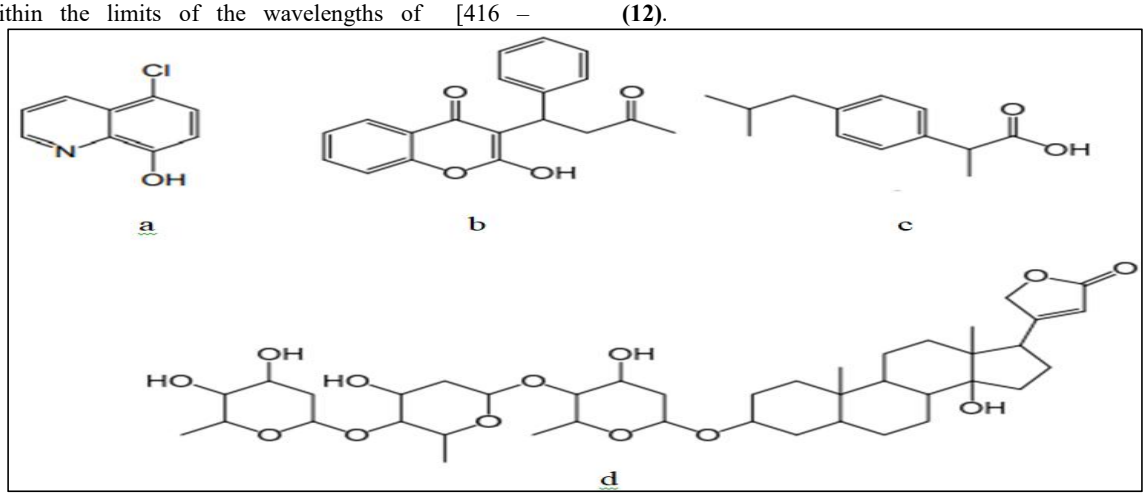


Figure (12): Chemical structure of a-Cloxyquin , b-Warfarin , c-Ibuprofen , d-Digitoxin .

The chlorinated derivative of (8HQ) possessing various therapeutic potentials and bioactivities like antifungal, pain relief , antibacterial and cardio protective . The mechanism of interaction between (BSA) (bovine serum albumin) and (cloxyquin) has been elucidated . Some pharmacodynamics and pharmacokinetic concepts have been used in order to a further update of the Medication therapy, through a proposed biophysical test procedure where different techniques have been used where the inference has been inferred through the spectral study of the sample (Cloxyquin) where the study demonstrated that it interacts with the (BSA) through a process that includes the formation of the stable state of the complex. Thermodynamic examination showed that the hydrophobic group is the primary driving force behind the formation of the(BSA complex). It has been found that both (Cloxyquin) and H-bonds are considered as a loading stand

for (hydrophobic) interference with the remnants of (Leu574, Leu 531) and (Phe 506) with the formation of (Pi-Pi) interactions in addition to the H- bonds with each of (Phe506, Tyr 400).) Respectively. By observing the two-dimensional study of surface topology and documented with the tape of the (Cloxyquin) molecule interferences, which may be shown through the hypothetical sites of connection with (BSA) structure. The color ball is represented by Trp 134 and Trp 213 . The second and third docking locations are illustrated by the two-dimensional plot diagram of the interference networks between the PSA and the Claccaine, **Figure (13)**.

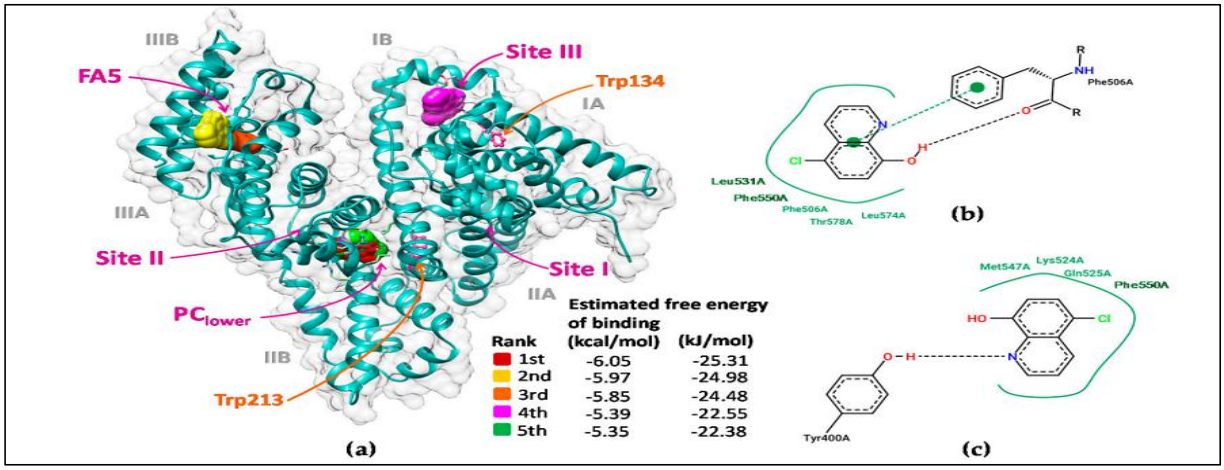


Figure (13): Demonstrate the surface topology , ribbon view and explain of the site interaction of BSA , (Cloxyquin) . The stick structures for visual guidance and the pink ball is represented Trp134 and Trp213 . (b,c) is 2D diagram explaining the [(Cloxyuin) , BSA] networks interaction at the second and third with the posed docking .

Overcoming biophysical analysis and mathematical simulation indicates the importance of albumin serum, as it works to transport the (cloxyquin) through the bloodstream. Moreover, since there is a slight increase in the size of mono-molecular (BSA), as the (Cloxyquin) is not affecting the locations of the (BSA) agglomeration, due to the fact that the molar ratio of (cloxyquin) is very small compared to the (BSA) in the circulatory system. Through the schematic diagram (c, b) above, it is clear from the positions of adhesion (2, 3) in addition to the interference networks belonging to both (PSI and (Cloxquine) (Figure 13) above (a.) represents the surface topology in the form of a strip as well as the reactions of the compound of the (cloxyquin) with the clarification of the sites of the various links that come on the installation of (BSA) where it is (Trp213, Trp134) in the form of a pink ball.

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