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Tables 1 to 7 are available in the Supplementary Files section.

**Investigation on Pure and Cr, Fe, Ni and Si-doped Fullerene
Nanostructures for Enhanced Warfarin Delivery: A DFT Study**

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Abstract

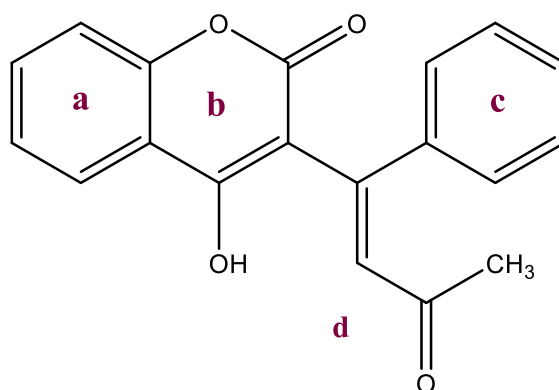
Anticoagulant drug delivery is a challenging approach for researchers because poses a significant challenge due to the concentration of this drug may lead to blood clots and stroke, and its high concentration can cause dangerous bleeding. In this work, the application of fullerene and metallofullerene nanostructures as anticoagulant drug delivery carriers has been investigated. Based on DFT calculations, first the fullerene nanostructure was optimized, then different metals (M=Cr, Fe, Ni, Si) were doped onto the fullerene to investigate changes in the fullerene properties. Then, the drug delivery properties of these nanostructures for anticoagulant warfarin were evaluated using the B3LYP/6-31G(d) level of theory. In this study, the adsorption energy, electronic parameters, and thermodynamic properties of the interaction of warfarin with C20/MC19 were studied. It has been observed that doping the studied metal's atoms on the fullerene has enhanced the drug delivery properties of the C20 nanostructure. Among the investigated nanostructures, CrC19 was identified as the most prominent nanostructure for warfarin drug delivery with high adsorption energy (-38.285 kcal/mol) and high recovery value. Favorable interaction between warfarin drug and nanostructures through frontier orbitals was confirmed. Fractional charge transfer, NCI, IGMH, ELF, LOL, and MEP analyses showed charge transfer from the drug molecule to MC19/C20 nanostructures. UV-Vis spectra were also plotted to investigate the excited state properties of the designed complexes, and showed the positive effect of nanostructures on the high adsorption of warfarin drug with nanostructures compared to single warfarin. Therefore, the present study reveals the mechanism of favorable interaction of warfarin with MC19.

Keywords: Anticoagulant, Warfarin, Nanostructures, Fullerene, Drug delivery

1. Introduction

It is impossible to overestimate the basic significance of creating innovative and effective drug delivery methods to enhance the pharmacological profile of medicinal medicines. Drug delivery and medicine have benefited greatly from nanotechnology in recent years. Carbon nanotubes and fullerenes have been studied and employed to deliver different medications to specific cells [1]. Because of their spherical structure, fullerenes may be even more effective than CNTs for medication delivery, according to advances in nanotechnology [2]. Innovations in the realm of fullerene-like materials and a greater interest in characterizing fullerene-based materials have resulted from this. One of the allotropes in the carbon family of nanomaterials are fullerenes, sometimes referred to as Buckminsterfullerenes or Buckyballs [4]. These structures feature a highly symmetrical cage with varying widths and are made of Sp^2 Hybridized carbon, which has special chemical and physical properties [5, 6]. C₂₀, which has been successfully synthesized and studied through experiments, is an excellent example of this kind of fullerene [7]. From a chemical standpoint, these cage systems' stability is essential, and how they interact with other materials affects their characteristics and chemical reactions for use in later applications [8]. The two primary objectives of drug delivery systems, which are always anticipated to serve as a means of transporting medications to the intended location, are precise drug delivery and maintaining appropriate efficacy while preventing adverse effects [9]. Impurity atom doping of C₂₀ fullerene can significantly enhance the complex's physical characteristics and increase its reactivity with nearby molecules [10]. Favipiravir [11], dacarbazine [12], desipramine [13], fluorouracil [3], and Aromasin [14], are only a few of the molecules for which theoretical chemistry techniques have been applied as effective drug carriers and adsorbents for pure and/or doped C₂₀. When treating venous and arterial thromboembolic disorders, anticoagulants are essential. Many of the drawbacks of traditional medications have been addressed by the development of novel oral anticoagulants that target a specific coagulation factor (factor Xa or thrombin) [15, 16]. Worldwide, thromboembolic illness is treated and prevented with warfarin (WAR), a coumarin anticoagulant [17]. Additionally, fullerenes have been employed in the delivery of highly bioactive compounds like warfarin [18]. Warfarin's narrow therapeutic index makes it a perfect choice for dose adjustments. Fullerene's biological profile can be altered and its blood concentration can be kept constant when warfarin and fullerene are combined. Additionally, this combination stabilizes the warfarin dosage and makes the medication controlled, which is a crucial idea that requires more research [19]. As a result, researching the use of nanomaterials as carriers for WAR is crucial for the scientific advancement of nanomaterial applications, and using complementary materials can improve the study of new protocols for the treatment of conditions related to

anticoagulants. For this reason, the current study was started to look into the problem of the anticoagulant medication WAR's C20 cage carrier and MC19 (M is anticipated to be the doped metal on the C20 nano cage). Until the ultimate solution is found, this problem should be solved theoretically and in accordance with the original precise specification in addition to the research approach. In this instance, chemical structures at the smallest feasible scale of molecules and atoms can be studied by computer-based tasks [20-22]. In this situation, such activities can always offer helpful information about the materials being studied and steer clear of the difficulties caused by the existence of interferers in order to arrive at a precise conclusion on a subject in the software environment [23]. Therefore, we tried to examine the drug delivery capability of C20 and metal-doped fullerenes for the anticoagulant WAR medicines, taking use of the remarkable features and favorable outcomes of fullerene nanostructures. In the current investigation, DFT simulations in the gas phase were used to examine the interaction of the WAR medication via the oxygen atom of the coumarin ring with C20/MC19 as the most active sites for interaction. To discover an appropriate adsorbent for the WAR medication, we also doped C20 fullerene with several metals [M = Co, Fe, Ni, and Si]. Notably, no theoretical research has been done on how WAR medications interact with metal-doped fullerenes. The study's findings could offer crucial information for the development of experimental medication delivery systems based on nanomaterials. Therefore, utilizing DFT/B3LYP methodologies, a thorough investigation was carried out on the thermodynamic characteristics, frontier orbitals, energy gap, DOS properties, adsorption, and nanocarrier properties of the drug warfarin on fullerenes and metallofullerenes.



Schame 1. The structure of warfarin.

2. Theoretical methodology

To find an efficient WAR drug carrier, several structural, chemical, electrical, and thermodynamic properties of the suggested structures were examined using the quantum mechanical technique known as Density Functional Theory (DFT). The well-known hybrid B3LYP functional and the 6-31G(d) basis set [24, 25] implemented in the GAMESS [26] program were used to thoroughly optimize all adsorbates and adsorbents prior to the adsorption procedure. The cohesive energy and vibrational frequency of the aforementioned adsorbents were computed in order to verify their structural stability and inherent biocompatibility. To create stable and energetically advantageous compounds, the optimized WAR drug's adsorption process was examined on optimized C20 and MC19. Thermodynamic parameters, such as enthalpy changes (ΔH), entropy changes (ΔS), and Gibbs free energy changes (ΔG), were examined across the contact duration to assess the thermal stability of both the pure and complexes. A thorough examination of the energy levels of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and the density of states (DOS) was carried out in order to obtain electronic insights into the interaction between nanocarriers and WAR drug as well as to evaluate the sensitivity of adsorbents to WAR. Advanced techniques like the quantum theory of atoms in molecules (QTAIM), reduced density gradient (RDG), and an independent gradient model based on Hirshfeld partitioning analysis (IGMH) were used for the complexes in order to obtain a more thorough knowledge of intermolecular interactions. Furthermore, pictures of the localized orbital locator (LOL) and electron localization function (ELF) were created to examine the variations in electron density brought about by complex formation [27-29]. In order to understand the chemical stability and reactivity of the complexes, a number of quantum mechanical descriptors were examined, such as chemical potential, global hardness, and global electrophilicity index. Additionally, it was predicted to evaluate the effectiveness of the developed carriers because recovery time is a crucial component in drug delivery applications.

3. Results and discussion

3.1. Optimized geometries of the adsorbents and adsorbate

The WAR drug's interaction characteristics with the C20/MC19 drug and the surface of the C20/MC19 cage carrier for drug delivery were examined in the current study. It's interesting to note that metal nanoparticles (MNPs) have demonstrated intriguing roles in drug delivery since they can be precisely targeted by an externally controlled field [30]. The B3LYP functional with 6-31G(d) basis set was utilized in the DFT method to ascertain the ideal

geometry of pure fullerene. Following the optimization of the pure C20 structure, a number of elements (M = Cr, Fe, Ni, and Si) were substituted for one of the carbon atoms, and the doped structures were then optimized. Figures S1 and 1 depict the optimized structures of the WAR medication, C20/MC19 nanostructures, and complexes, respectively. The Ih symmetric structure of the C20 compound is deformed when one of its carbon atoms is substituted with the metals Cr, Fe, Ni, and Si, as shown in Fig. S1. The replaced metals' compression of the cage along one dimension, which pushes the carbon atoms (C) closer together, is most likely the cause of the deformation. Additionally, the MC19 fullerene nanocage's metal atom deformation appears fixed to protrude from the cage. According to Fig. 1, the equilibrium C_C bond distance ranges from 1.41 Å to 1.44 Å, which is similarly in line with the earlier theoretical investigation of MC19 nanocages [31]. The M_C bond distances lengthen following metal doping in comparison to the isolated fullerene. Additionally, Table 1 demonstrates that following doping with various metals, the C_M_C angles exhibit significant modifications. The angles change in the following order: C_Cr_C angle (86.01°) > C_Ni_C angle (85.07°) > C_Fe_C angle (82.66°) > C_Si_C angle (77.22°). This suggests that the symmetric Ih structure is distorted by metal doping, which is expected to change the material's electrical characteristics. Additionally, as shown in Fig. 1, WAR's geometric structure does not significantly change following its adsorption on the nanocage. Therefore, in medication delivery systems, these nanocages could serve as secure transporters of WAR without deteriorating it.

3.2. Adsorption and desorption processes

Structural characteristics, drug/carrier adsorption energies, and thermodynamic parameters were taken into account in order to identify the most advantageous desirable WAR drug combination with C20/MC19 drug carriers. The optimized drug, C20/MC19 nanostructures, and drug/carrier complex architectures are shown in Figures S1 and 1. The oxygen in the coumarin ring's carbonyl group allows the WAR drug molecule to bind with the investigated nanocarriers. The adsorption energies (E_{Ads}) of all conjugated structures were determined using equation 1 below in order to comprehend the adsorption process; the results are listed in Table 1 [32]. Table 1 presents the computed results of the aforementioned computations.

$$E_{\text{Ads}} = E_{\text{Complex}} - E_{\text{adsorbent}} - E_{\text{WAR}} \quad (1)$$

$E_{\text{adsorbent}}$ and E_{WAR} represent the energies of the bare adsorbent and the WAR molecule, respectively, whereas E_{Complex} represents the energy of the complexes. To gain an understanding of the thermal stability of the complexes under investigation, the thermodynamic characteristics were assessed at standard temperature (298.15 K) and pressure (1 atm). Whether a reaction is endothermic ($\Delta H > 0$) or exothermic ($\Delta H < 0$) depends on the fluctuation in

enthalpy (ΔH). Furthermore, whether the adsorbate-adsorbent interaction is spontaneous ($\Delta G < 0$) or not ($\Delta G > 0$) depends on the fluctuation in the Gibbs free energy (ΔG). ΔG and ΔH were estimated using the following formula [33].

$$\Delta U = U_{\text{complex}} - U_{\text{adsorbent}} - U_{\text{WAR}} \quad (2)$$

In this case, U stands for both the enthalpy (H) and the Gibbs free energy (G), and U_{Complex} , $U_{\text{adsorbent}}$, and U_{WAR} stand for the enthalpy of the WAR drug, the complexes, and the adsorbents, respectively. The following equation [33] was used to determine the change in entropy (ΔS):

$$\Delta S = \frac{\Delta H - \Delta G}{T} \quad (3)$$

ΔH , ΔG , and ΔS were computed and shown in Table 1 to compare the thermodynamic stability of the three examined complexes of WAR–C20/MC19. Table 1's study makes clear the adsorption pattern of the C20/MC19-WAR complex structures, where WAR interacts with C20/MC19 at a distance of a few angstroms. The WAR medication interacts with the metal atom of the adsorbent and the oxygen atom of the coumarin's carbonyl group in the MC19-WAR complex structures. All of the logically constructed drug delivery complexes have negative Eads, which provide stable adsorption of the WAR medication on the C20/MC19 nanostructures in a range of orientations. Structures 1 through 5 have Eads of -2.174, -38.285, -32.452, -30.894, and -2.208 kcal/mol, respectively. The drug delivery complexes 2 and 3 have comparatively large adsorption energies when compared to the other structures.

An Eads value of roughly -2 kcal/mol indicates weak physical adsorption, according to a prior work by Meryem Dardare et al. [10]. Therefore, it may be concluded that a weak physical mechanism of adsorption is how C20 and SiC19 interact with the WAR medication. Furthermore, the 2, 3, and 4 types of complexes exhibit larger negative adsorption energies than the 1 and 5 types. In a different investigation, Meryem Dardare et al. noted that a process of significant chemical adsorption is represented by an Eads of roughly -32 kcal/mol [10]. Therefore, it can be concluded that the WAR medication interacts with CrC19, FeC19, and NiC19 nanostructures by a mechanism of strong chemical adsorption with good adsorption efficacy and desorption with appropriate recovery durations. When the nanostructures are compared, it is evident that the CrC19 nanostructure interacts with the WAR medication more than the C20 nanostructure since its Eads value is more negative. For every complex of C20/MC19-WAR that was examined, the changes in Gibbs free energy (ΔG), enthalpy (ΔH), and entropy (ΔS) were computed to examine the thermodynamic stability. The results are

shown in Table 2. The thermodynamic parameters show relatively slight differences, according to the values in Table 2. As a result, several complexes lacked thermodynamic stability and energy. These findings imply that interactions between the SiC19-WAR and C20-WAR complexes are not spontaneous ($\Delta G > 0$).

Furthermore, the FeC19-WAR, CrC19-WAR, and NiC19-WAR complexes' negative values show that these three structures' interactions are exothermic, spontaneous, and thermodynamically advantageous. Even while the three structures 2, 3, and 4 showed considerable adsorption energies and suitable thermodynamic characteristics, these parameters are not enough to prove that the MC19 nanostructures are efficient drug carriers for WAR.

The recovery time (s), which is the amount of time needed for an adsorbate to desorb from the adsorbent, is another crucial factor in drug sensing applications. The recovery time must be calculated in order to evaluate the efficacy of C20/MC19 as a sensor for the WAR molecule, given that the WAR–C20/MC19 conjugated structures have achieved improved energetic and thermodynamic stability.

based on research by the second. According to Thomas and M. A. Zaeem, creating an effective sensing device benefit from an adsorbent's quick recovery time [34, 35]. In light of this, the following formula [36] was used to determine the recovery time assessment:

$$\tau = \nu^{-1} e^{-E_{Ads}/\kappa_B T} \quad (4)$$

In this case, T is the Kelvin temperature, κ_B is the Boltzmann's constant value (2.0×10^{-3} kcal/mol K), and Ψ is the attempt frequency. In practical terms, exposure to ultraviolet (UV) light releases an adsorbate molecule from the adsorbent [37].

The following Table 1 displays the estimated recovery times of the experiments carried out for the 1 and 5 complexes below the femtosecond scale, an interval that is far too short and thus unsuitable for sensing and carrier operations. The recovery times under UV conditions with $T=350$ K and $\nu = 1018 \text{ s}^{-1}$ were calculated. However, complexes 2, 3, and 4 have recovery durations of around 565947.3 s, 136.111 s, and 14.699 s, respectively. The nanostructures of the types CrC19, FeC19, and NiC19 may be regarded as attractive possibilities because their times are within the range of seconds.

3.3. Molecular electrostatic potential

By scanning the electronic density through molecules, molecular electrostatic potential (MEP) maps were used to display the locations of electrophilic and nucleophilic processes. The

electrostatic potential drift at various molecular locations is represented by a variety of colors. The MEP's negative (red) regions show electrophilic reactivity and are associated with regions with high electron density. The blue areas, on the other hand, are associated with nucleophilic reactivity and have low electron density [38]. To better describe the surface chemistry of the suggested nanocarriers, the WAR drug, and the complex, MEP analysis was carried out with an electron density contour of 0.002 a.u. [39, 40]. Figures S2 and 2 display the molecular electrostatic potential (MEP) maps of the drug and drug nanocarriers before and after contact. The drug's oxygen atoms feature red areas that show active locations for interaction with metal-doped nanocarriers (apart from Si), as seen in Fig. S2. An important metric that shows the net electrostatic potential at a particular location which is produced by the total charge distribution is the MEP map. Therefore, it can be anticipated that the doped metals are the most active sites for drug interaction with the MC19 nanocarrier and may therefore be the most likely region for adsorption based on the ESP study. The oxygen atom connected to the coumarin ring allowed the drug molecule to engage with MC19/C20 nanocarriers. The area surrounding the molecular structure that is repulsive for positive charge is called the positive electrostatic region, and the area that is attracting for positive charge is called the negative electrostatic region with increased charge density. Figure 2 displays the MEP maps of the MC19/C20 and WAR nanostructures. Furthermore, charge transfer from the WAR drug molecule to the nanostructures is indicated by the fact that a portion of the WAR molecule is blue and a portion of MC19 is red.

3.4. Frontier molecular orbitals (FMOs)

A molecule's electrical characteristics and reactivity parameters can be determined by FMO (Frontier Molecular Orbital) analysis [41]. LUMO (lowest unoccupied orbital) values are electrophilic or electron-accepting, whereas HOMO (highest occupied orbital) values act as nucleophiles or electron donors. The charge distribution inside the molecule is described by HOMO and LUMO. Chemical reactivity, polarizability, and reaction stability can be calculated thanks to the relationship between the charge transfer from HOMO to LUMO and the change in energy gap (E_{gap}) [42, 43]. A molecule's kinetic stability is reduced and its chemical reactivity is increased when its energy band gap is limited [44]. Figures S2 and 3 display the HOMO and LUMO orbital diagrams for the WAR, C20/MC19 structures, and complexes, respectively. In order to investigate the sensitivity of the electronic properties of the C20 and MC19 compounds towards the WAR molecule, the carrier properties of the C20 and MC19 structures have been analyzed using the following two parameters: E_{gap} and the work function (Φ). The HOMO and LUMO of nanostructures, specifically the frontier molecular orbitals,

play a central role in describing the interactions between adsorbents and adsorbates. The ionization potential is related to the level of HOMO because it is an electron donor, while the level of LUMO is associated with electron affinity because it lacks an electron. It has already been confirmed in earlier publications that E_{gap} is an appropriate measure for measuring the sensitivity of nanostructures [45, 46]. The work function (Φ) is the amount of energy needed to extract an electron from the Fermi level.

$$\Phi = V_{el}(+\infty) - E_F \quad (5)$$

Here, the Fermi level energy is represented by E_F , and the electrostatic potential energy of the electron at a large distance from the material surface is expressed as $V_{el}(+\infty)$, which is taken as zero. Assuming that the value of $V_{el}(+\infty)$ is 0, Φ is expressed as $-E_F$. The value of the Fermi level is then calculated as follows:

$$E_F = E_{HOMO} + \frac{E_{gap}}{2} = \frac{E_{HOMO} + E_{LUMO}}{2} \quad (6)$$

Table 3 shows the E_{HOMO} , E_{LUMO} , Fermi level, and the work function (Φ) values. C20/MC19's HOMO and LUMO diagrams are dispersed equally throughout their structures. WAR's LUMO is primarily found in the a and b regions, whereas its HOMO is dispersed across the molecule (Scheme 1). Following the drug's interaction with the nanostructures, these diagrams show notable changes. As can be seen, the HOMO of the complex is concentrated only on MC19 (M= Cr, Fe, Ni), and its LUMO is concentrated on WAR with an absolute density separation, indicating the charge transfer between WAR and the MC19 nanostructures. According to the data in Table 4, the HOMO and LUMO values of fullerene (C20) changed after doping with metals (M=Cr, Fe, Ni, Si) on C20. However, the HOMO and LUMO values of the complexes increased after the WAR drug interacted with the nanostructures; these changes in E_{HOMO} and E_{LUMO} after drug adsorption led to a change in the E_{gap} value; compounds with low E_{gap} are more reactive and less stable, which confirms their semiconducting behavior; the electrical conductivity of the studied complexes is directly related to E_{gap} because compounds with reduced E_{gap} value have a higher ability to transport electrons through the conduction band, and vice versa. Table 3 shows that a significant change in conductivity occurred. Paria Fallahi et al. claim that the rise in the nanostructure's conductivity may be connected to the decline in E_{gap} [47]. Additionally, the WAR drug's work function was computed on C20/MC19 nanostructures, and Table 3's findings demonstrate that the work function values dropped following the drug's interaction with the nanostructures. Akbar Hassanpour et al. claim that naturally, metal atoms cause the drug's electrons to flow similarly

to those of a metal, creating a surface dipole moment between the positively charged metal atoms and the negatively charged drug that lowers the work function [48].

3.5. The density of states (DOS) analysis

The density of states (DOS) analysis presented in Figures 4 and S3 has been used to confirm the interactions between the WAR medication and the MC19 nanostructures. The analysis's main goal is to assess drug delivery behavior by examining how the WAR medication interacts with C20/MC19. Important details regarding the number of states accessible for electrons at various energy levels are defined by DOS analysis. To put it another way, a larger DOS value denotes a substantial amount of electronic states that can be occupied, whilst a lower value denotes a small number of states that can be occupied. Significant variations in E_{gap} are seen following the adsorption of the WAR medication on MC19/C20 nanostructures, as seen in Fig. 5. It is evident from comparing the peak heights that there are more states available for occupation since the total density of states (TDOS) is at a higher energy level than the partial density of states (PDOS). Additionally, there was no hybridization between TDOS and PDOS, suggesting that these nanostructures had good drug adsorption. The analysis's findings demonstrated that a considerable drop in E_{gap} followed the WAR drug's contact with C20/MC19 nanostructures, altering the nanocarrier's behavior to become semiconducting. From the PDOS analysis given in Fig. 5, it can be seen that the predominant contribution to the LUMO was due to the drug molecules, and the HOMO value was larger for the fullerene-doped metals (MC19) because they engaged in the adsorption process through the HOMO orbital.

3.6. Quantum molecular descriptors

Understanding the chemical stability and reactivity of an adsorbate and its corresponding adsorbent is largely dependent on quantum molecular descriptor analyses. According to Koopman's theorem, the electrophilicity index (ω) is the most important parameter used in measuring the energy stabilization process of a system when it acquires an extra charge from the ambient [49]. Additionally, the electronic chemical potential (μ), chemical hardness (η), global softness (S), and electrophilicity (ω) calculated using the following equation [50].

$$\mu = \frac{(E_{\text{HOMO}} + E_{\text{LUMO}})}{2} \quad (7)$$

$$\eta = \frac{(E_{\text{LUMO}} - E_{\text{HOMO}})}{2} \quad (8)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (9)$$

$$S = \frac{1}{2\eta} \quad (10)$$

The barrier to charge transfer can be understood as the chemical hardness (η), so the greater the value, the lower the chemical reactivity and the higher the chemical stability. As demonstrated in Table 4, this aids in elucidating the type of chemical reaction between the medicine and the suggested nanostructures. The global softness of the suggested nanostructures (C20/MC19) dropped following interaction with the medication WAR, according to the data obtained in Table 4. In comparison to the uncharged nanostructures, this suggests a higher reactivity. On the other hand, the global softness (S) and electrophilicity index (ω) of the complexes decreased compared to the initial nanostructures, as shown in Table 4.

In conclusion, MC19 has a stronger interaction with the WAR drug than other nanostructures. The kinetics and thermodynamics of the drug (donor) and C20/MC19 nanostructures (acceptor) interaction were examined. The interactions of C20/MC19-WAR were assessed in terms of the ΔN parameter, which represents the number of electrons transferred from the donor towards the acceptor. The value of the ΔN factor is calculated as:

$$\Delta N = \frac{\mu_B - \mu_A}{\eta_A + \eta_B} \quad (17)$$

In this case, the parameters μ and η represent the chemical potential and hardness of the donor (A) and acceptor (B), respectively. Charge transfer from the donor to the acceptor is indicated by negative values of ΔN , whereas charge transfer from the acceptor to the donor is shown by positive values of ΔN . The most stable noncovalent interactions can be identified using charge transfer and its many components in conjunction with the stabilization energy (SE), as demonstrated by a detailed investigation of the SE [51, 52]. The following formulas have been used to compute the structure stability, the energy change of species A ($\Delta E_{A(B)}$), the energy change of species B ($\Delta E_{B(A)}$), and the total stability energy $\Delta E_{SE(AB)}$.

$$\Delta E_{A(B)} = \Delta N(\mu_A + \frac{1}{2}\eta_A\Delta N) \quad (18)$$

$$\Delta E_{B(A)} = \Delta N(-\mu_B + \frac{1}{2}\eta_B\Delta N) \quad (19)$$

$$\Delta E_{SE} = \Delta E_{B(A)} + \Delta E_{A(B)} \quad (20)$$

The individual molecular values of the WAR and C20/MC19 molecules and the variations in the electron donor energy ($\Delta E_{A(B)}$) and electron acceptor energy ($\Delta E_{B(A)}$) Were computed and are reported in Table 5. The individual values of the drug WAR attached to the C20/MC19 nanostructures have been probed by applying $\Delta E_{A(B)}$, $\Delta E_{B(A)}$, and $\Delta E_{SE(AB)}$ for the estimation of the resultant complex thermodynamic stability. In this work, the drug WAR molecule has been considered an electron giver, with the nanostructure acting as an electron acceptor.

Negative ΔN readings confirmed the transport of the drug electrons to the nanostructure acceptor. The transfer of electrons from the WAR molecule to the C20/MC19 acceptor nanostructures is an energy-positive process, as indicated by positive $\Delta E_{A(B)}$ values. The complex's stability following its interaction with the medication was verified by the negative $\Delta E_{B(A)}$ values. Finally, the thermodynamic viability of all the complexes under investigation was confirmed by the negative $\Delta E_{SE(AB)}$ values computed from the equation; complex 3 with Fe-doped nanostructures was the most stable. Following drug adsorption on metal-doped nanostructures, this one-way electron transport dramatically changed the polarizability.

3.7. RDG analysis and IGMH

To investigate the noncovalent index (NCI) and identify the noncovalent interactions between the adsorbates and adsorbents, the electron density (ρ), derivative ($\rho\rho$), and Laplacian ($\Delta^2\rho$) are suggested. Plotting the decreased density gradient versus the electron density yields the NCI [53]. While high electron densities are found to have RDG values approaching zero, suggesting the presence of both covalent and noncovalent interactions, large positive RDG values are discovered at distant locations from the molecule, demonstrating the exponential decay of the electron densities to zero. However, when both the electron density and RDG values are low, weak interactions, such as van der Waals (vdW) forces, are demonstrated. It's interesting to note that different kinds of repulsive and attractive interactions can happen at the same RDG values and electron densities. The Laplacian of the electron density ($\nabla^2\rho$) is suggested to categorize the various kinds of interactions in order to remove the uncertainty. In other words, $\nabla^2\rho = \lambda_1(r) + \lambda_2(r) + \lambda_3(r)$, where the conditions $\lambda_1(r) < \lambda_2(r) < \lambda_3(r)$, is made up of the sum of three eigenvalues obtained from the electron densities Hessian matrix along the maximum variation directions. The second eigenvalue $\lambda_2(r)$ is critical to differentiate the interactions: $\lambda_2(r) < 0$ is for the bonding interactions, $\lambda_2(r) > 0$ is for the nonbonding interactions, while $\lambda_2(r) \approx 0$ is for the vdW interactions [54, 55]. These interactions are further studied based on the electron density to predict their strengths.

Rather than RDG vs. electron density, the relations are displayed against the signature for λ_2 . Furthermore, rather of depicting individual paired atom-atom interactions, the RDG isosurface-colored surfaces offer a comprehensive picture for the various interactions, indicating huge spatially broad regions. For both the RDG scatterplot and the colored-filled RDG isosurface map, our blue, green, and red hues represent strong hydrogen bonding, weak contacts, and strong repulsion (strong steric interactions). The Multiwfn 3.7 software program was used to carry out the RDG study. Gnuplot was used to create three-dimensional (3D) isosurface

maps of the complexes [56, 57]. By using different colors to display the sign function $(\lambda_2)\rho$ on the IGMH δg^{inter} isosurface, the independent gradient model based on the Hirschfeld molecular density (IGMH) partitioning can visualize the interaction regions between different molecules and identify the type and strength of these interactions. According to the IGMH analysis, the surface colors of the isosurface regions are generally blue, green, and red, respectively, indicating the presence of repulsive, van der Waals, and attractive interactions between molecules [58]. Consequently, the interactions between MC19/C20 and the WAR medication were visualized using the IGMH approach; their IGMH δg^{inter} isosurface color maps are displayed in Figures 5 and S4, respectively. Figure 5 displays color maps of the IGMH δg^{inter} isosurface between the WAR medication and the nanocarriers under consideration. The blue isosurface between the metal atoms ($M=\text{Cr, Fe, and Ni}$) on the $=\text{O}$ group of the coumarin ring of the WAR medication was seen, as illustrated in Fig. 5, suggesting a strong interaction and the formation of a strong connection between them.

3.8. QTAIM investigations

In order to comprehend the nature of atom-atom interactions at bond critical points (BCPs), QTAIM analysis is a crucial method for examining bond characteristics [59]. To determine the values of topological parameters like electron density ($\rho_{(r)}$), Laplacian of electron density ($\nabla^2\rho_{(r)}$), total energy density ($H_{(r)}$), kinetic energy density ($G_{(r)}$), and potential energy density (V_r), QTAIM analysis is crucial. Closed-shell interactions, including hydrogen bonds, ionic bonds, and van der Waals interactions, are indicated by positive values of $(\nabla^2\rho_r)$ [60, 61]. Also, negative values of both parameters $H_{(r)}$ and ∇^2_r indicate strong covalent interactions, and positive values of $H_{(r)}$ and $\nabla^2\rho_{(r)}$ indicate the presence of electrostatic interactions. In contrast, a positive value of $\nabla^2\rho_{(r)}$ together with a negative value of H_r indicates partial covalent interactions [62].

To further understand the nature of the interactions, the computed values $-G_r/V_r$ are also utilized. Covalent interactions are indicated by values $-G_r/V_r < 1$, whereas weak electrostatic interactions are indicated by values $-G_r/V_r > 1$ [63]. QTAIM analysis was carried out using AIMALL software to gather crucial information regarding the type and strength of interactions, such as electrostatic, covalent, etc., between the WAR drug and the C20/MC19 adsorbent nanostructures. Table 6 displays the significant topological parameters found at the binding critical points (BCPs) for these complexes. The molecular diagrams of the studied complexes are shown in Figure 6.

As can be seen from the diagrams in Fig. 6, in complexes 2 and 3, in addition to the M-O bond, these complexes show an unconventional C-H/C hydrogen bond. Also, for complex 4, two

unconventional bonds (one C-H/C bond and one C-O bond) are observed between WAR and the nanostructure. This has also been reported in previous scientific papers [64]. Some relevant topological parameters describing these interactions are summarized in Table 6. The M–O bonds are all positive $\nabla^2\rho_r$ values, while the total energy density values H_r are negative for complexes 3 and 4 but positive for complex 2. Furthermore, the values of the ratio $(-G_r/v_r)$ for complexes 3 and 4 range from 0.5–1, but the value of this parameter for complex 2 is greater than 1. These observations indicate that the interactions of complexes 3 and 4 Suggesting partial covalent interactions similar to dative bond in all molecular complexes, and that of complex 2 is indicating a weak electrostatic interaction.

3.9. ELF and LOL analysis

Plots of the localized orbital locator (LOL) and electron localization function (ELF) show the electron localization of electrons, with their corresponding color shade plots in Fig. 7. This analysis of the surface topology is used to highlight the area of covalent bonding with high electron pair density. Since both metrics rely on kinetic-energy density, the chemical meaning of LOL and ELF is comparable. The gradients of the localized orbitals that become significant with overlap are represented by ELF, which is based on electron pair density [28]. The value of the ELF is a number between 0.0 and 1.0, with a value of 0.5–1.0 corresponding to regions with both localized bonding as well as nonbonding electrons. Low values (lower than 0.5) indicate regions that tend towards electrons being delocalized [65]. The value of LOL is $\eta(r)$, which is maxed (higher than 0.5) in regions with electron density that is mainly defined by localization [66]. The high localization of electrons is due to the occurrence of covalent bonds in regions with high ELF value [67].

ELF values that are large (complete substitution, red areas) and tiny (low charge density, blue areas) indicate strong and weak interactions, respectively. Fig. 7 shows a graphical representation of the ELF analysis of the studied complexes. According to Fig. 7, the ELF value of the Cr-O bond in complex 2 is higher than that of complexes 3 and 4, indicating a higher strength of the interaction between WAR and the CrC19 nanocarrier.

3.10. Excited-state properties

The creation of a drug delivery system that can effectively transfer drug molecules with few harmful side effects depends heavily on the detection and monitoring of drug concentrations in the human body. High-performance liquid chromatography can be used to quantify the WRF

medication concentration, but it requires intricate preparation and sophisticated equipment before detection. One effective method for examining the biological system's parameters is Time-Dependent Density Functional Theory (TD-DFT). Furthermore, UV-Vis spectral spectroscopy of the complexes may enable real-time monitoring and immediate drug concentration detection. UV-Vis spectrum research has already been used to study the drug's excited-state characteristics and metal-doped complexes [68]. Table 7 provides the wavelengths at which the maximum absorption occurs, λ_{max} , and the minimum excitation energy (E_g) for each of the complexes under study. Fig. 8 also displays the UV-Vis spectra. The data in Table 7 indicates that the WAR drug's absorption peak is at 313.65 nm with an oscillation power of $f=0.1079$. The experimental UV-Vis spectrum indicates that the WAR drug exhibits maximum absorption between 200 and 350 nm [69]. It was discovered that the predicted UV-Vis spectra of the WAR medication in the gas phase, $\lambda_{\text{max}} = 319$ nm, closely match the observed absorption spectrum, $\lambda_{\text{max}} = 290$ nm. Additionally, the graph in Figure 8 demonstrates that, in comparison to the medication prior to contact, the absorption peak of the complexes in issue has considerably risen. Thus, complex 2 has the lowest excitation energy and the largest absorption value. This suggests that the crC19 nanostructure is a viable option for medication delivery.

4. Conclusion

Using DFT calculations, the effectiveness of metallofullerenes (MC19) and solitary fullerenes (C20) as nanocarriers for anticoagulant drug delivery was examined in this work. The stability of this interaction is indicated by the fact that the geometric properties of the WAR medication did not alter appreciably before or after adsorption. Additionally, metal-doped fullerenes ($M = \text{Cr, Fe, Ni}$) were more reactive with WAR than C20 and SiC19. Additionally, the positive interaction between nanocarriers and WAR is indicated by the negative adsorption energy values for all complexes, particularly for the complexes listed. These complexes are spontaneous and exothermic, according to thermodynamic analysis. For pure and Si-doped fullerene, however, this is not the case. The findings also shown that MC19 nanocarriers, particularly those doped with Cr, enhanced WAR absorption and had a significant stabilizing effect. Additionally, QMD, ELF, LOL, MEP, and fractional charge transfer number (ΔN) calculations verified that charge transfer from WAR to CrC19 took place during this adsorption process. Additionally, QTAIM and NCI studies revealed that the drug's interaction with CrC19 was electrostatic, while for complexes Fe or Ni-doped, partial covalent connections took place between the WAR molecule and the FeC19/NiC19 adsorbent. Consequently, we may suggest that MC19 ($M=\text{Cr, Fe, Ni}$) will be a viable nanocarrier for WAR drug delivery. In order to address the electrical behavior of a drug structure when interacting with a nanocarrier, this

computational study used a variety of theoretical and computational techniques. The distribution of numerous medications that are either in clinical trials or now in use has benefited greatly from this study methodology. In order to help avoid the negative effects of the WAR medication, future research will try to replicate the findings of this study experimentally.

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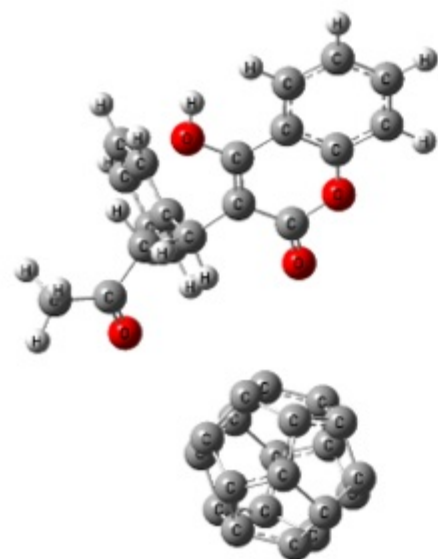
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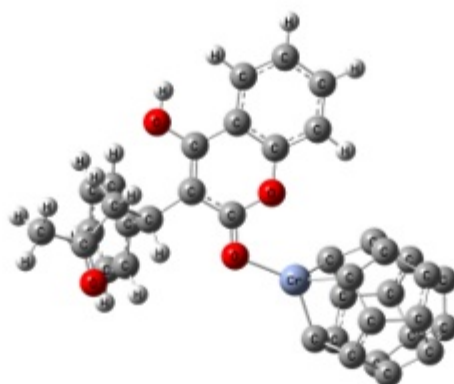
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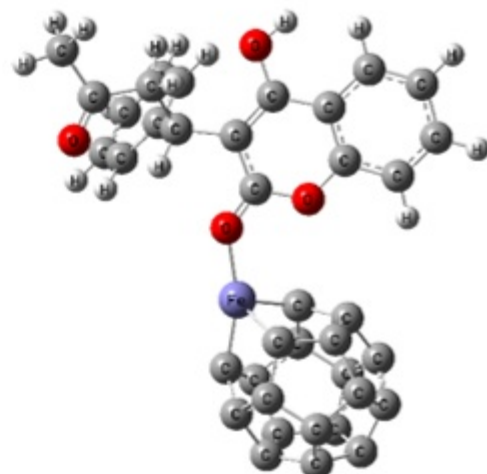
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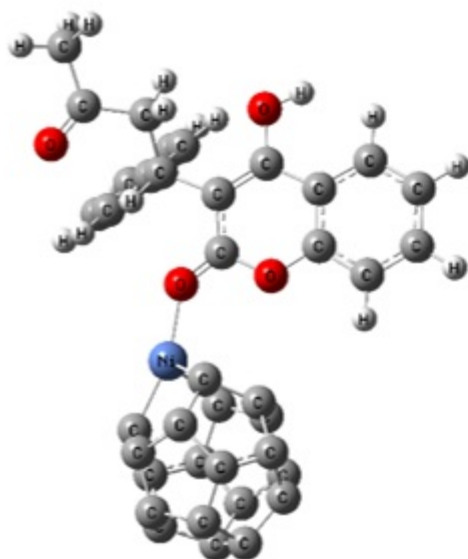
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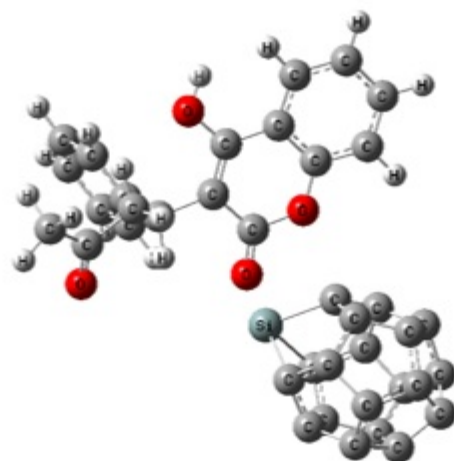
Complex 2



Complex 3

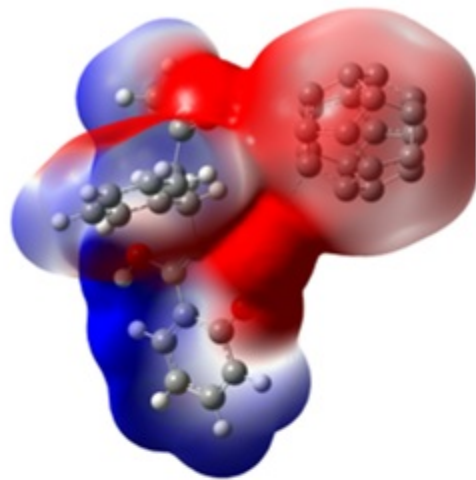


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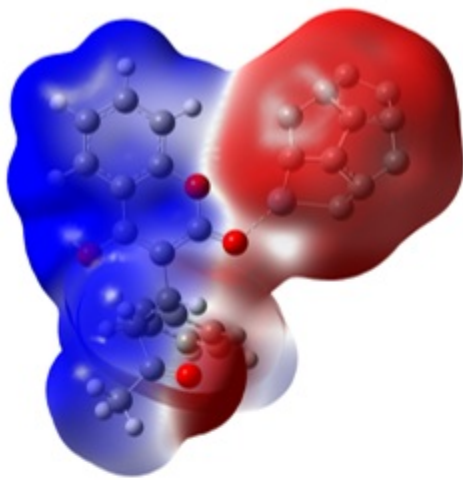


Complex 5

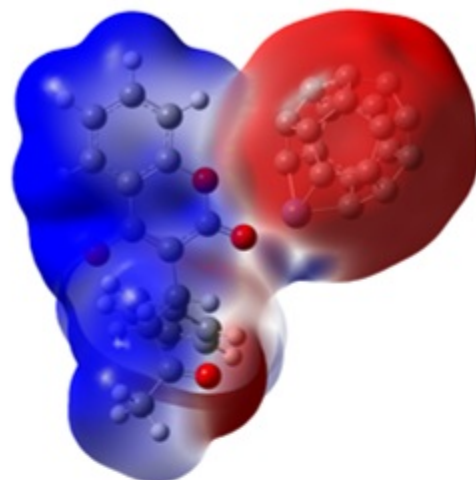
Fig. 1. Optimized geometry of drug adsorbed on C20 (complex 1), CrC19 (complex 2), FeC19 (complex 3), NiC19 (complex 4), SiC19 (complex 5).



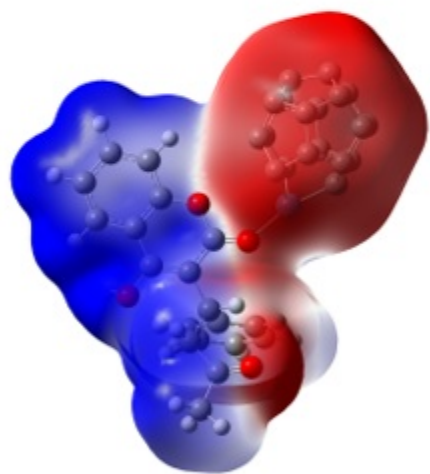
Complex 1



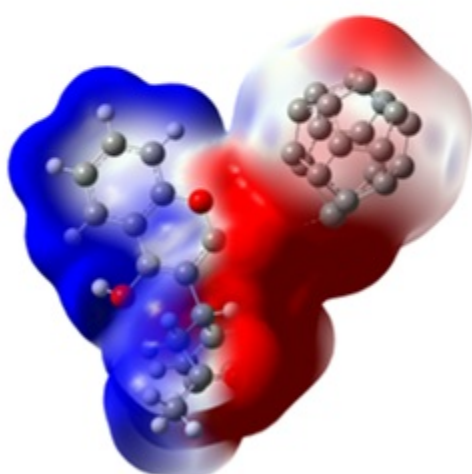
Complex 2



Complex 3



Complex 4



Complex 5

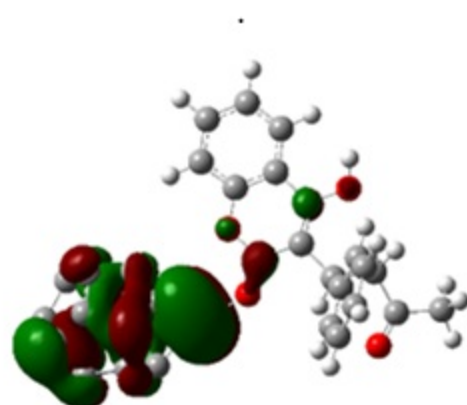
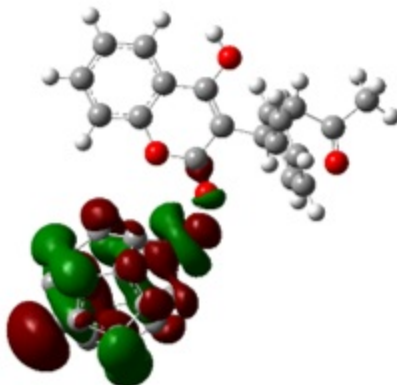
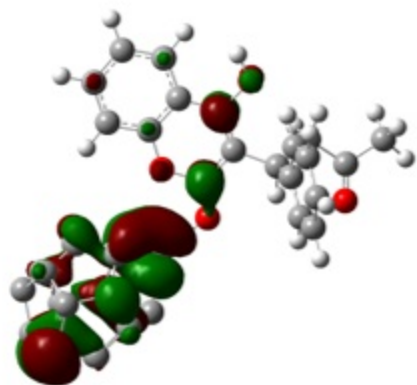
Fig. 2. Molecular electrostatic potential maps of the investigated complexes.

Complex 2

Complex 3

Complex 4

HOMO



LUMO

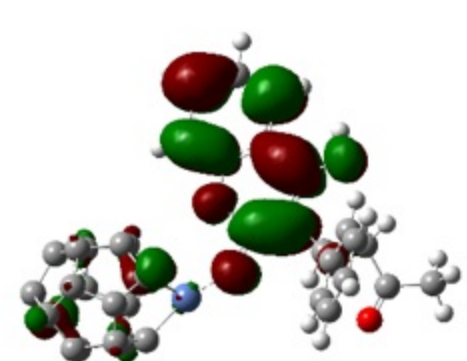
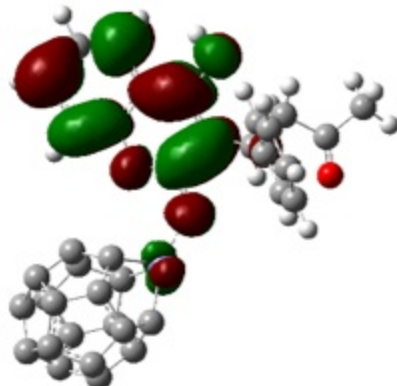
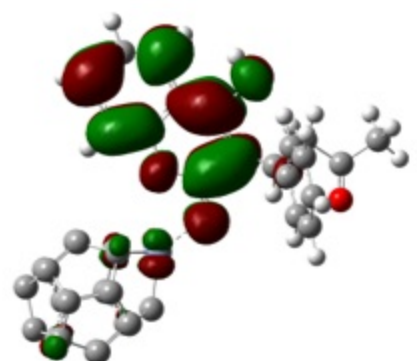
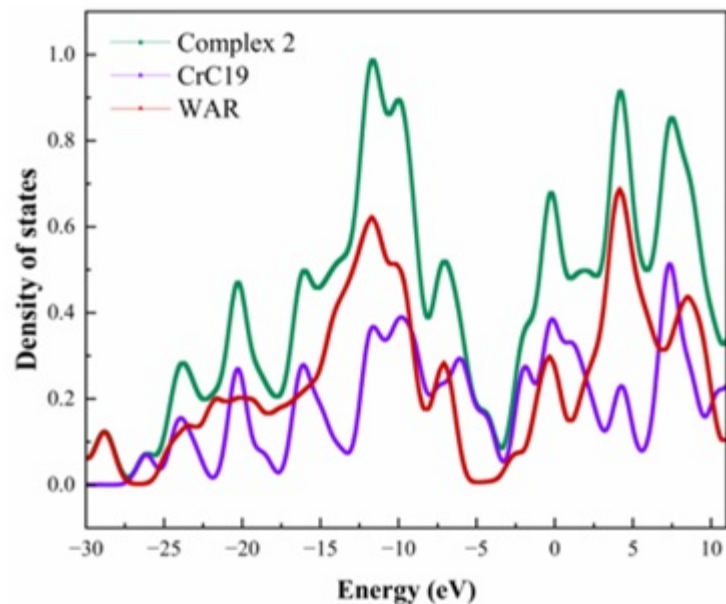
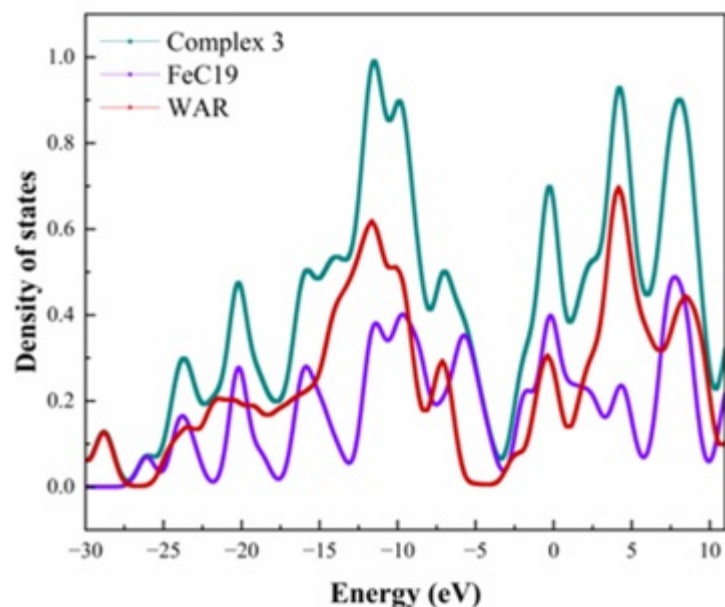


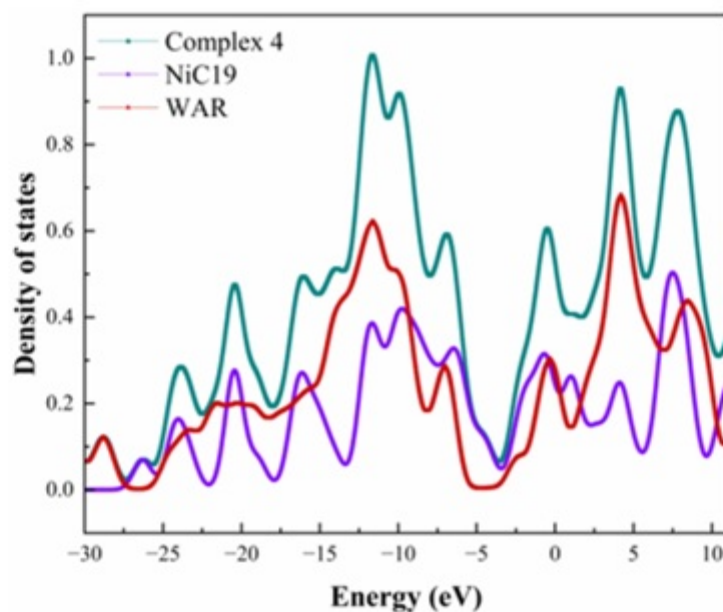
Fig. 3. Diagram of HOMO and LUMO orbitals for the studied complexes.



Complex 2

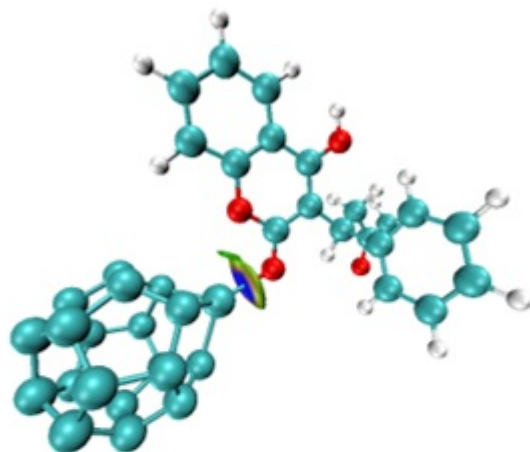
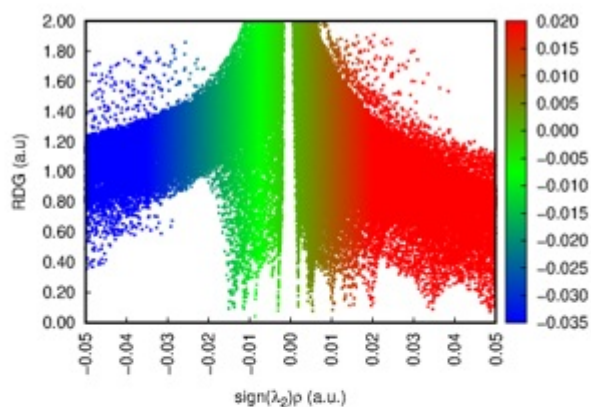


Complex 3

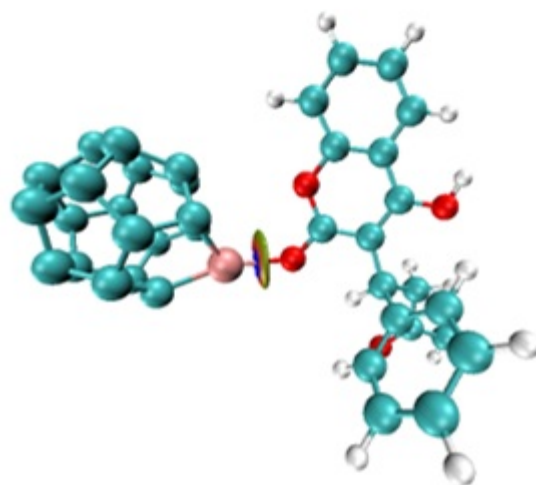
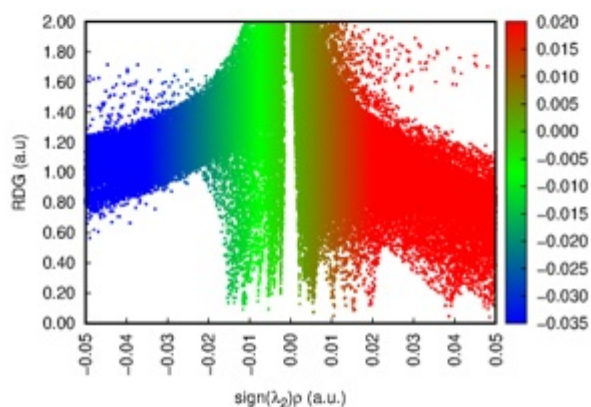


Complex 4

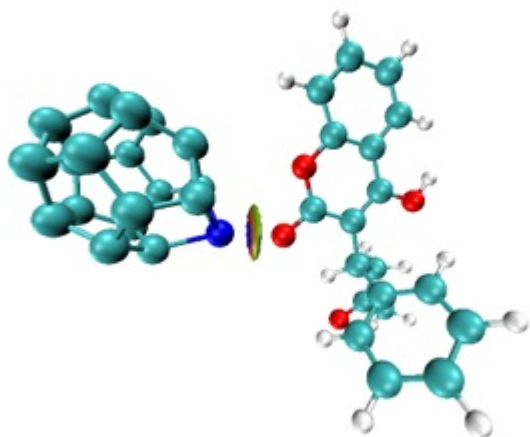
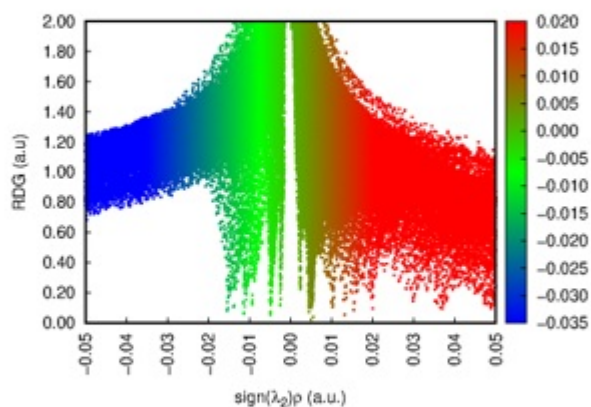
Fig. 4. Calculated electron density states TDOS and PDOS for Complex 2, Complex 3, and Complex 4.



Complex 2

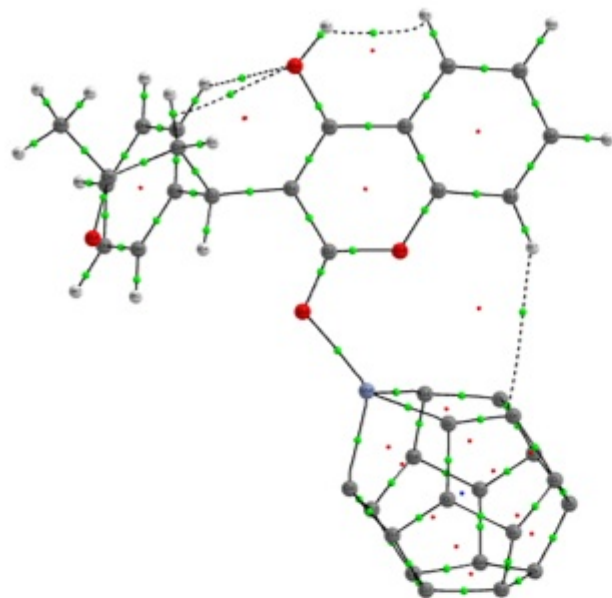


Complex 3

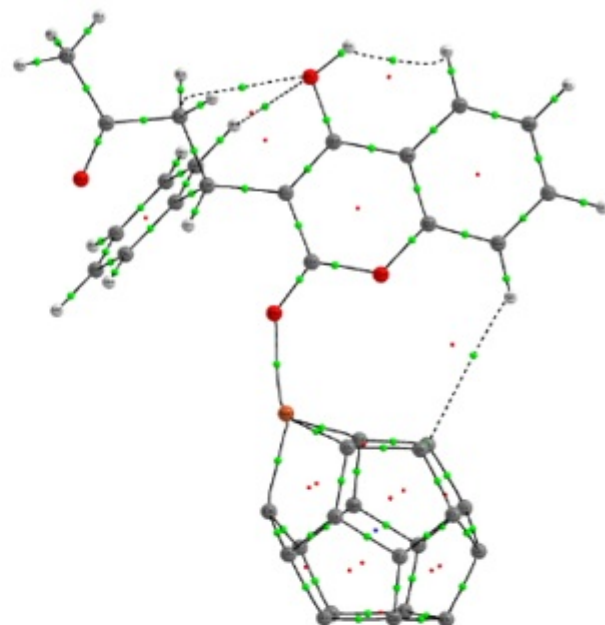


Complex 4

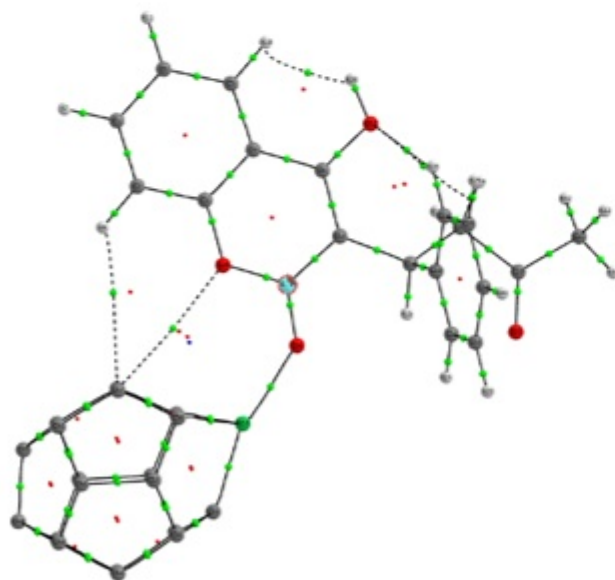
Fig. 5. The molecular graphs, RDG scatter maps, and color-filled IGMH δg^{inter} isosurface map of Complex 2, Complex 3, and Complex 4.



Complex 2



Complex 3



Complex 4

Fig. 6. Critical points of interaction of the WAR drug with the studied carriers.

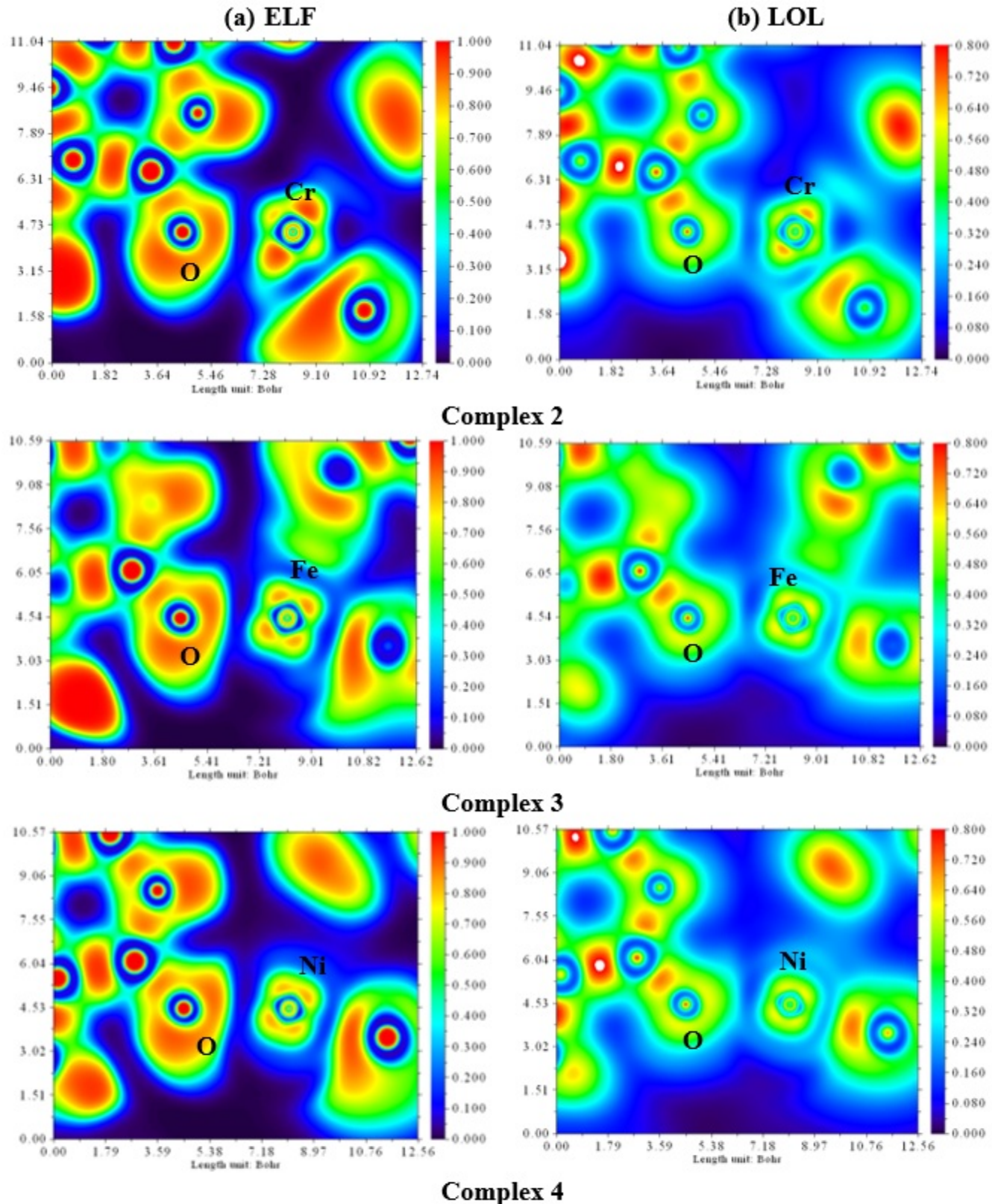


Fig. 7. ELF (a) (Electron localization function), and LOL (b) (Localized orbital locator) of complexes.

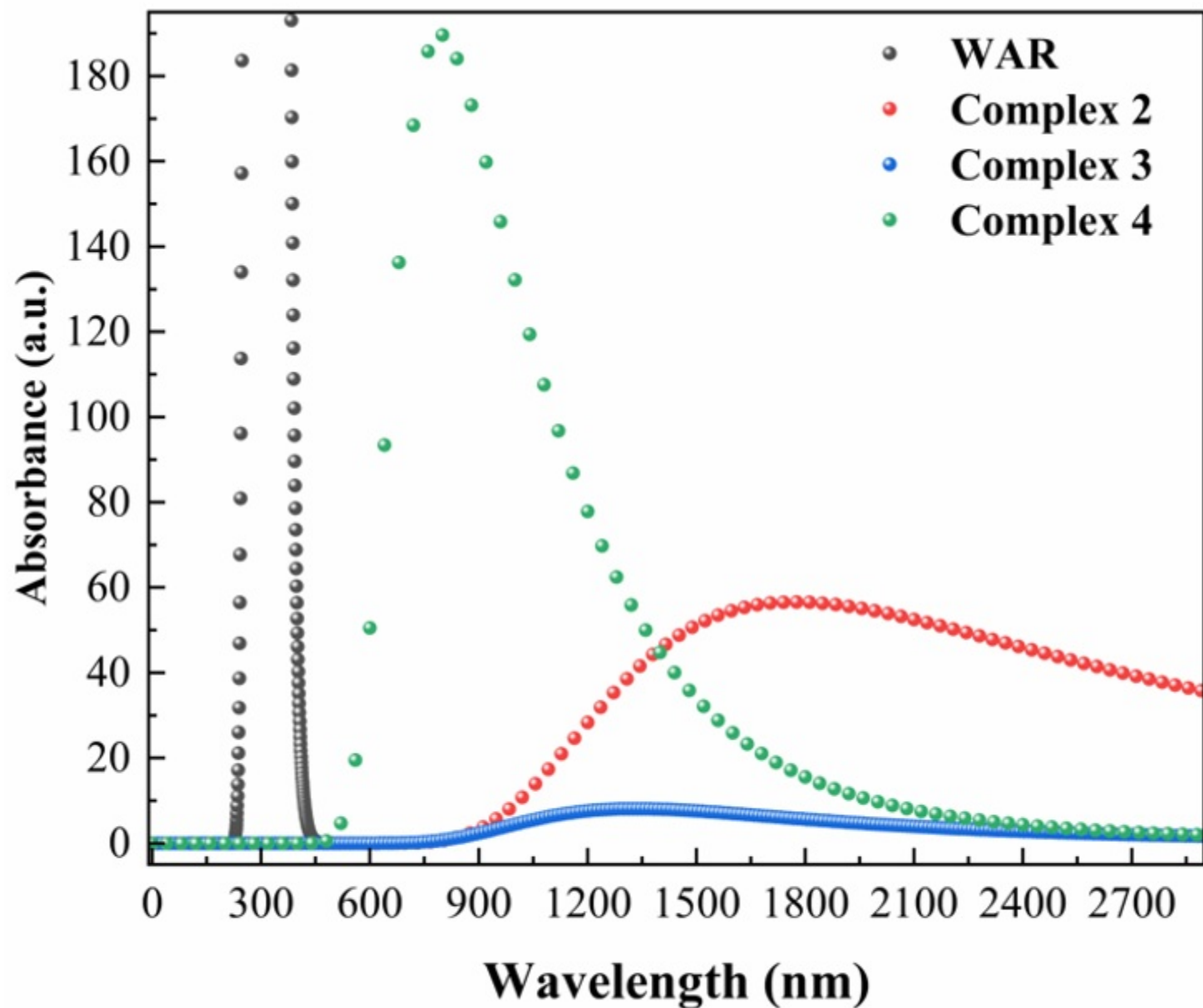


Fig. 8. Simulated UV-Vis spectra for WAR drug and complexes.

Supplementary Files

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- [supplfile.pdf](#)