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Theoretical investigation of favipiravir antiviral drug based on fullerene and boron nitride nanocages

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ABSTRACT

Smart implementation of novel advanced nanocarriers such as functionalized C24 and B12N12 nanocages is used supplement for antiviral activity 5-Fluoro-2-hydroxypyrazine-3-carboxamide (Favipiravir; Avigan; T-705), as treatment of COVID-19. The interaction energies of Favipiravir with perfect (B12N12 and C24) and doped (BC23 and CB1N12) nanocages were studied at temperatures equal to 310.15 K and 298.15 K using DFT. Our results have shown that the interaction of the Favipiravir (C=O group) with BC23 and CB1N12 is more favorable than with the C24 and B12N12 nanocages in the gas and aqueous environments. Additionally, the natural bond orbital, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), energy gap, chemical reactivity, molecular electrostatic potential, and thermodynamic parameters of the optimized structure have been examined. Furthermore, the UV-Vis and infrared spectroscopy have been evaluated for the investigation of the molecular orbitals Participated in the absorption spectrum of the Favipiravir before and after the interaction with the C24, BC23, B12N12, and CB1N12 sites at maximum wavelength utilizing the time-dependent density functional theory (TD-B3LYP and TD-CAM-B3LYP). The intermolecular interactions have been analyzed by non-covalent interactions (NCI) and also, the electron localization function (ELF) is discussed.

1. Introduction

The 2019 infection pandemic (COVID-19) of the coronavirus is a serious bio-safety that has a serious impact on global society and the economy. COVID-19 has prompted the interest of scientists to treat this disease with an effective drug. Due to the ability of the COVID-19 virus to undergo antigenic changes and drug resistance, a significant objective of medical science and health care systems is the search for novel antivirals. Several developing drugs have been examined against COVID-19 [1]; favipiravir is one of the drugs cited for action against RNA-viral infections of COVID-19 [2] as broad-spectrum inhibitors [3]. Experimental treatment with Favipiravir for COVID-19 [4,5] has been provided that preliminary evidence for the prevention of viral infection with SARS-CoV-2. Favipiravir drug (5-Fluoro-2-hydroxypyrazine-3-carboxamide (T-705; Avigan; Favipiravir) was first prepared by Shi et al. [6], however, the performance of COVID-19 medications is still being questioned to date [7]. Consequently, the smart implementation of nanoscience has given great attention to exciting applications in the medical field and pharmaceutical studies [8]. The drug delivery systems are distinguished over free drugs in aspects such as selectivity, longer circulation time, and lower dosage with low side effects [9] and better therapeutic efficacy. Density functional studies were performed to the structure and energetics of the interaction of the drug pyrazinamide (PZA) with graphene-based nanomaterials using a noncovalent functionalization approach [10].

The synthesis and application of carbon and BN-nanocages has recently been of great interest as drug carriers or drug detectors due to their unique physical and chemical properties such as a great adsorbing capacity, high thermal stability, and low poisonous quality. First-principles calculations have been carried out on the effect of functionalization of B12N12 and C24 nanocage using heteroatoms such as C- and B-doping [11]. Compared to defect-free nanocage surface (B12N12 and C24), it is observed that their electronic properties can be modified by heteroatom doping. B- and C-atoms which can stimulate hole acceptor or donor states within the Fermi level [12,13] consequently enhance the electronic and conducting properties of B12N12 and C24 nanocage. Additionally, the drug molecule interacts with C-doped B12N12 and B-doped C24 nanocages with high sensitivity. Hosseinian et al. [14]
investigated the interaction between C$_{24}$ and a widely used molecule for treating cancer - 5-fluorouracil (5-FU). Nazari and Hadipour [15] investigated how modifications of fullerene C$_{60}$ doped with B, Si and Al atoms influence the adsorption of 5-FU. Comprehensive reviews have focused on boron-nitride (BN) fullerene-like materials since they have excellent properties [16-19]. A comprehensive experimental and theoretical study on BN nanomaterials for the adsorption of pharmaceutical drugs were performed to examine the synthesis and character of BN nanosheets and their applicability for the adsorption of pharmaceutical drugs [20].

The electronic and structural properties of 5-ALA functioned with B$_{12}$N$_{12}$ and B$_{10}$N$_{16}$ nanoclusters to further understand B$_{12}$N$_{12}$ and B$_{10}$N$_{16}$ capacity for use in drug delivery applications [21]. Interactions between fullerene C$_{24}$ as a potential carrier of ephedrine drug have been studied in detail by a combination of density functional theory (DFT), time dependent DFT (TD-DFT) calculations [22-24]. Parlak et al. [25] examined the interaction of favipiravir on undoped and Si-doped fullerene (C$_{60}$) and the results indicated that Si-doped fullerene are sensitive to the favipiravir molecule. Also, a recent study was conducted by Rad et al. [26] to analyze drug adsorption of favipiravir on first-row transition metals doped with fullerene (C$_{20}$) and the results showed that Fe, Cr, and Ni-doped fullerene would be potential drug delivery for COVID-19 treatment. Consequently, the objective of the present study is to investigate and compare theoretically the interaction of Favipiravir functionalized at perfect (B$_{12}$N$_{12}$ and C$_{24}$) and doped (BC$_{23}$) and CB$_{11}$N$_{12}$ nanocages to provide a useful guidance for the design and improvement of fullerene and boron nitride nanocages capacity for use in drug delivery applications.

2. Computational details

The quantum chemical calculations of structure optimizations, electronic structure, and adsorption properties of complexes that consist of Favipiravir drugs at the surface of un-doped C$_{24}$, B$_{12}$N$_{12}$, boron-doped C$_{24}$ (BC$_{23}$), and carbon-doped B$_{12}$N$_{12}$ (CB$_{11}$N$_{12}$) nanocages were performed in gaseous and aqueous phase using the density functional theory (DFT) method with Becke-3-Parameter-Lee-Yang-Parr (B3LYP) and 6-31 g(d,p) basis set to examine of Faviipiravir as antiviral for treatment of COVID-19. The aqueous phase was calculated using the self-consistency reaction field (SCRF) approach based on the conductor-like polarizable continuum model (CPCM) [27].

The adsorption energy ($E_{ads}$) for the full optimization of the Favipiravir (T-705) at the C$_{24}$, BC$_{23}$, B$_{12}$N$_{12}$ and CB$_{11}$N$_{12}$ nanocages was calculated by:

$$E_{ads} = E_{cage} - E_{T-705}$$}

where $E_{cage}$ is the energy of Favipiravir molecule@nanocage, Ecage is the total energy of nanocages, and $E_{T-705}$ is the total energy of the Favipiravir molecule.

The quantum molecular descriptors [28,29] of the optimized compounds for instance $E_{HOMO}$, $E_{LUMO}$, energy gap between HOMO and LUMO, dipole moment and natural charges [30,31], ionization potential ($I = -E_{HOMO}$), electron affinity ($A = -E_{LUMO}$), electronegativity ($\chi = \frac{E_{HOMO} + E_{LUMO}}{2}$), global hardness ($\eta = \frac{E_{HOMO} - E_{LUMO}}{2}$), electronic chemical potential ($\mu = -\frac{1}{2}(\frac{E_{HOMO} + E_{LUMO}}{2})$), electrophilicity ($\omega = \chi(\chi + \eta)$) [32], chemical softness ($\sigma = \frac{1}{\chi(\chi + \eta)}$) were determined. The present proposals are to investigate the therapeutic potential of C$_{24}$, BC$_{23}$, B$_{12}$N$_{12}$, and CB$_{11}$N$_{12}$ nanocage as a drug-delivery system for Favipiravir for treatment of COVID-19 and to explore the efficiency of nanostructure as a drug-delivery system. The principle aspects such as interaction mechanism between Favipiravir drug and C$_{24}$, B$_{12}$N$_{12}$, BC$_{23}$, and CB$_{11}$N$_{12}$ nanocages using DFT and TD-DFT calculations have been exhausted to further understand nanocages capacity that has attracted tremendous attention as a most promising drug delivery nanomaterial.

To comparatively analyze the interaction properties of Favipiravir drug based on BN and C$_{24}$ nanocages, the bonding characteristics, adsorption ability, charge transfer, dipole moment, frontier orbitals, energy gaps, molecular electrostatic potential (MEP), partial density of states (PDOS), natural bond orbital (NBO), changes in Gibbs free energy of these complexes have been examined. The time-dependent density functional calculations (TD-B3LYP and TD-CAM-B3LYP) were used to simulate UV and infrared spectroscopy and to exhibit whether the interaction between B$_{12}$N$_{12}$ and C$_{24}$ nanocages and Favipiravir produces some significant changes in the UV spectrum and vibrational frequencies during the detection of Favipiravir. The effect of long-range corrections has been carried out using the TD-CAM-B3LYP methods [33]. TD-CAMB3LYP methods [34] are used to provide a relatively accurate description of the energies of spectral bands, when there is a significant
charge transfer character in the excited states [35]. K. Petrushenko et al. [36] suggested that the Coulomb-attenuated CAM-B3LYP functional containing 19% short-range exact orbital exchange and 65% long-range exact orbital exchange improves sufficiently the description of CT transitions in comparison with the B3LYP hybrid functional, involving a fixed amount (20%) of exact exchange. Therefore, the TD-CAM-B3LYP method can be used for the interpretation of experimental data of the close-lying LE and CT transitions. The thermodynamic parameters such as enthalpy change ($\Delta H$), entropy change ($\Delta S$), and Gibbs free energy ($\Delta G$) were examined in the gas and aqueous phases for T-705@nanocages at 310.15 K (human body temperature) and 298.15 K (storage room temperature). These properties are elucidated using the Gaussian 09 [37]. The GaussSum program was used for PDOS of these systems [38].

### Table 1: Total energies of T-705/nanocages.

| System              | HF(Hartree)  |
|---------------------|--------------|
| C$_{24}$ + Drug(N)  | $-1521.28179258$ |
| C$_{24}$ + Drug(NH2) | $-1521.29976973$ |
| C$_{24}$ + Drug(O)  | $-1521.30380089$ |
| B$_{12}$N$_{12}$ + Drug(N) | $-1563.66432686$ |
| B$_{12}$N$_{12}$ + Drug(NH2) | $-1563.64235103$ |
| B$_{12}$N$_{12}$ + Drug(OH) | $-1563.65185512$ |
| B$_{12}$N$_{12}$ + Drug(O)  | $-1563.6383936$ |
| C$_{23}$B + Drug(N) | $-1508.11200329$ |
| C$_{23}$B + Drug(OH) | $-1508.12609456$ |
| C$_{23}$B + Drug(O)  | $-1508.12609456$ |
| C$_{23}$B + Drug(NH2) | $-1508.12609456$ |
| C$_{23}$B + Drug(OH) | $-1508.12609456$ |
| C$_{23}$B + Drug(NH2) | $-1508.12609456$ |
| C$_{23}$B + Drug(OH) | $-1508.12609456$ |

Fig. 2. Optimized geometries of the possible interactions between the T-705 drug with (a) C$_{24}$, and (b) B$_{12}$N$_{12}$ nanocarrier calculated at B3LYP/6-31G(d,p) level of theory.

Fig. 3. Optimized geometries of the possible interactions between the T-705 drug with functionalized (a) BC$_{23}$, and (b) CB$_{11}$N$_{12}$ carrier calculated at the B3LYP/6-31G(d,p) level of theory.
3.1. The interaction of Favipiravir with functionalized C

Structural parameters of T-705 in the gas phase.

Table 3

| Structure         | Bond angle (°) | Experimental  | B3LYP  | Experimental  | B3LYP  | Dihedral angle (°) | Experimental  | B3LYP  |
|-------------------|---------------|---------------|--------|---------------|--------|-------------------|---------------|--------|
| C1-C4             | 1.390         | C2-O14-H15    | 109.5  | 106.0         | N8-C6-C3-N11 | -0.4              | -0.02821 |
| C1-N12            | 1.306         | O14-C2-N12    | 115.6  | 117.0         | N8-C5-C3-C2 | 178.9             | 179.97212 |
| C1-H5             | 0.930         | O14-C2-C3     | 123.5  | 121.7         | N11-C3-C2-N12 | 0.2               | 0.01715  |
| C2-N12            | 1.306         | C2-C3-C6      | 120.7  | 122.6         | N11-C4-C1-N12 | 0.6               | 0.02034  |
| C2-O14            | 1.328         | O7-C6-C3      | 119.7  | 122.6         | C3-C2-N12-C1  | 0.3               | -0.00888 |
| C2-C3             | 1.397         | C7-C6-N8      | 123.1  | 124.0         | C3-N11-C4-C1 | -0.9              | -0.01187 |
| C3-C6             | 1.481         | C6-N8-H9      | 120.7  | 118.0         | O7-C6-C3-C2  | -1.0              | -0.00135 |
| C3-N11            | 1.335         | C6-N8-H10     | 120.7  | 120.7         | O7-C6-C3-N2  | 179.1             | 179.99833 |
| C4-F13            | 1.339         | C6-C3-N11     | 121.4  | 117.2         | O14-C2-N12-C1 | 179.7            | 179.98897 |
| C4-N11            | 1.295         | C3-N11-C4     | 116.3  | 118.6         | F13-C4-C1-N12 | 179.2             | 179.98897 |
| C6-O7             | 1.244         | N11-C4-F13    | 116.8  | 117.6         | F13-C4-N11-C3 | 0.4               | 0.01907  |
| C6-N8             | 1.318         | N11-C4-C1     | 123.3  | 122.7         | O14-C2-C3-C6 | -1.0              | -0.00902 |
| N8-H9             | 0.860         | F13-C4-O14    | 119.9  | 119.7         | C2-N12-C1-N12 | -0.9              | -0.01187 |
| N8-H10            | 0.860         | N12-C1-H5     | 119.4  | 118.6         | C1-C4-N11-C3 | -0.7              | -0.00632 |
| O14-H15           | 0.820         | O14-C2-N12    | 117.0  | 118.5         | C1-N12-C2-C2 | -1.0              | -0.00902 |

3. Results and discussion

3.1. The interaction of Favipiravir with functionalized C

Structural analysis

Initially, to identify the most favorable adsorption configurations, geometrically optimization of an individual T-705 at C

Table 2

| Gas phase | Experimental [6] | B3LYP  | Experimental [6] | B3LYP  | Dihedral angle (°) | Experimental [6] | B3LYP  |
|-----------|------------------|--------|------------------|--------|-------------------|------------------|--------|
| T-705/C24 | -0.085           | 3.355  | 121.319          | 121.055 | 120.511           | 121.253          | 120.303 |
| T-705/   | -1.434           | 1.539  | 123.179          | -0.947 | 1.519             | 121.579          |        |
| C24      | -1.120           | 1.557  | 124.989          | -1.218 | 1.527             | 122.994          |        |
| B12N12   | -1.128           | 1.555  | 125.397          | -1.208 | 1.525             | 123.193          |        |

a Isolated T-705.
Table 4

| Structure | Gas phase | Aqueous phase | $\Delta$E (eV) | $\Delta\mu$ (eV) | $\omega^-$ (eV) | $\omega^+$ (eV) |
|-----------|-----------|---------------|----------------|-----------------|----------------|----------------|
| T-705     | 4.52      | 2.30          | 11.82          | 1.257           | 2.469          | 0.217          |
| C$_{23}$N$_{12}$ | 5.870 | 3.055 | 3.13 | 1.256 | 6.317 | 0.398 |
| B$_{12}$N$_{12}$ | 7.70 | 4.533 | 3.11 | 1.256 | 7.881 | 0.399 |
| T-705/C$_{24}$ | 4.532 | 1.256 | 8.174 | 0.398 |
| T-705/B$_{12}$N$_{12}$ | 6.57 | 2.683 | 4.22 | 1.124 |

3.2. Frontier molecular orbital analysis

The eigenvalue of the Frontier molecular orbitals (HOMO and LUMO) and $\Delta E_{\text{HOMO-LUMO}}$ energy gap for these complexes play a significant role in controlling many chemical activity, electrical, and optical properties [42, 43]. They are responsible for properties of charge transfer, the energies of HOMO and LUMO values indicate the ability of a system to donate and accept an electron. The aforementioned results show that the doping atoms reduce the energy gap of the nanocarriers. As seen in Table 4 the energy gap of the complex is much lower than those of isolated nanocages and T-705. Concerning the Favipiravir molecule, the energy gap of 4.6 eV that is consistent with [5].

3.3. Molecular electrostatic potential (MEP) analysis

Molecular electrostatic potential (MEP) analysis explored the reactivity and the interaction mechanism between T-705 and B$_{12}$N$_{12}$, C$_{23}$N$_{12}$, C$_{24}$, and BC$_{23}$ nanocages. MEP plots are used for predicting nucleophilic and electrophilic attacks and hydrogen bonding interaction [44]. Electrophilic reactivity was associated with the negative (red color) of MEP with the high electron density and the positive regions (blue color) with the low electron density. As demonstrated in these configurations, the positive charges over the T-705 were illustrated by the blue colors in the adsorption process that acts as an electron donor (Fig. 4). Whereas the negative charges over the B$_{12}$N$_{12}$, C$_{23}$N$_{12}$, C$_{24}$, and BC$_{23}$ nanocages are represented by the red colors that acts as an electron acceptor. Hydrogen atoms of OH group of drug molecules have the lowest electron density with blue color (electropositive atom), consequently it can be considered as the acidic hydrogen atom, the electrons around the B-O bond are depleted and accumulated on O atom with a small charge of about 0.08 eV transfer from the gas molecule to the surface.

3.4. Thermodynamic parameters and nature of the binding forces

The thermodynamic parameters such as enthalpy change ($\Delta H$), entropy change ($\Delta S$), and Gibbs free energy ($\Delta G$) were evaluated in the gas and aqueous phases for T-705@nanocages at 310.15 K (human body temperature) and 298.15 K (storage room temperature). The values of $\Delta G$, $\Delta H$, and $\Delta S$ are collected in Table 6. The adsorption of drug molecules is an exothermic process. As seen in Table 5 that the positive $\Delta G$ value of T-705@C$_{24}$ indicated that the reactions are non-spontaneous that not favorable adsorption at ambient conditions in agreement with [45]. In contrast, the thermodynamic parameters imply that the adsorption of T-705 @ B$_{12}$N$_{12}$, T-705 C$_{23}$N$_{12}$, and T-705 BC$_{23}$ complexes is strongly favorable due to the spontaneously adsorption of drug on the host nanocage surface. Comparison results of thermodynamic parameters demonstrate that the adsorption of T-705 on functionalized (C$_{23}$N$_{12}$, and BC$_{23}$) nanocages are more favorable than the pristine model (B$_{12}$N$_{12}$ and C$_{24}$) surfaces.

To examine the effect of solvent on the interaction of T-705 drug at the pristine surface, C-doped B$_{12}$N$_{12}$ and B-doped C$_{24}$ nanocages, the
changes of $\Delta G$ in the water as an important solvent in the biological system are calculated. According to the provided results in Table 5, all the thermodynamic functions of C$_{24}$ and BC$_{23}$ in the gas phase are higher than those in the aqueous phase, whereas for B$_{12}$N$_{12}$ and CB$_{11}$N$_{12}$ they are higher in the aqueous phase than gas phase. This can be explained due to the molecular polarities of B$_{12}$N$_{12}$ and CB$_{11}$N$_{12}$ in the gas phase are lower than in the aqueous phase, which in turn increased the thermodynamic parameters to some extent. Furthermore, compared to the $\Delta H$ values, the calculated $\Delta G$ values are less negative, implies an entropy reduction associated with the examined complexes. The negative value of $\Delta S$ indicates that the interaction that takes place between T-705 drug and B$_{12}$N$_{12}$, CB$_{11}$N$_{12}$, and BC$_{23}$ nanocage $\Delta H < 0$, $\Delta S < 0$ is corresponding to the van der Waals interaction and hydrogen bond formation, this is agreement with [46]. The thermodynamic parameters and adsorption calculations indicate that B$_{12}$N$_{12}$ and the functionalized CB$_{11}$N$_{12}$, BC$_{23}$ nanocage can be a good promising candidate for delivery of T-705 drug.

3.5. Non-covalent interactions

The non-covalent interactions (NCI) are visualization tools that play an essential role in maintaining the 3D structure. The NCI used to recognize non-covalent interactions involve intermolecular forces within molecules such as van der Waals, hydrogen bonds, and steric clashes based on electron density and gradient electron density (RDG). RDG is defined as

$$\text{RDG}(r) = \frac{1}{2(3\pi)^{1/3}} \left| \nabla \rho(r) \right| \rho(r)^{1/3}$$

(4)

To examine the non-covalent interactions between the favipiravir drug and the nanocage, as plotted in Figs. 5 and 6 the scatter graphs between the reduced density gradient (RDG) and the electron density ($\rho$). From the graph, sign ($\lambda_2$) $\rho$ decreases for strong interactions such as H-bond are represented by blue color, sign ($\lambda_2$) $\rho$ increases for red colors that represented strong repulsion such as steric effect in cage, while near zero for the van der Waals (vdW) interactions are represented by green color. The vdW interactions are short-range and weak interaction. As seen from Figs. 5 and 6, The non-covalent interactions of T-705 drugs with nanocages are weak interactions which is an advantage for drug release from the nanocage.

3.6. The electron localization function

The electron localization function (ELF) is a method used to measure electron localization in atomic and molecular systems [47]. ELF images

| Structure | 298.15 | 310.15 |
|-----------|--------|--------|
|           | Gas phase | Aqueous phase | Gas phase | Aqueous phase |
|           | $\Delta$G | $\Delta$S | $\Delta$H | $\Delta$G | $\Delta$S | $\Delta$H | $\Delta$G | $\Delta$S | $\Delta$H |
| T-705/C$_{24}$ | 7.472 | -27.948 | -1.048 | 8.256 | -27.487 | 0.066 | 7.612 | -26.348 | -0.562 | 8.586 | -27.343 | 0.109 |
| T-705/C$_{23}$B | -19.805 | -41.235 | -30.666 | -19.427 | -49.797 | -34.266 | -8.303 | -44.096 | -21.972 | -18.829 | -49.79 | -34.264 |
| T-705/B$_{12}$N$_{12}$ | -10.897 | -45.233 | -24.467 | -13.384 | -44.155 | -26.542 | -10.445 | -45.173 | -24.448 | -12.854 | -44.079 | -26.519 |
| T-705/CB$_{11}$N$_{12}$ | -11.237 | -45.065 | -24.858 | -13.552 | -43.362 | -26.475 | -10.890 | -43.533 | -24.391 | -13.033 | -43.28 | -26.449 |

Fig. 4. ESP of the most stable T-705 @ nanocages.
of nanocages and drug-nanocages are shown in Fig. 6. The values of ELF are in range from 0.0 to 1.0 that value of 0.0 corresponding to zero localization (blue areas) where the value 0.5 and 1.0 corresponding to the electron gas (green areas) and perfect localization (red areas), respectively [48,49]. The electron density of nanocages were changed after the nanocage-drug formation as ELF seen in Figs. 7 and 8.

Images of ELF provide information about transition occurring from nanocages to drug and from drug to nanocages as seen in Table 6 of NBO analysis of the complexes.

3.7. Natural bond orbital (NBO) analysis

NBO analysis is effective for identifying inter- and intra-molecular bonding [50,51]. On the basis of the NBO analysis, this bonding–antibonding interaction can be described quantitatively using second-order perturbation interaction energy \( E^{(2)} \). From the second-order perturbation approach, the stabilization energy \( E^{(2)} \) associated with \( i \) (donor) - \( j \) (acceptor) delocalization is investigated:

\[
E^{(2)} = q_i F^{ij} (\epsilon_j - \epsilon_i)
\]

where \( q_i \) is the occupancy of donor orbital, \( \epsilon_i \) and \( \epsilon_j \) are orbital energies (diagonal elements) and \( F^{ij} \) is the off-diagonal Fock matrix element. The analysis of NBO for these complexes represented that the binding of T-705 drug to the functionalized \( \text{BC}_{23} \), \( \text{B}_{12}\text{N}_{12} \), and \( \text{CB}_{11}\text{N}_{12} \) nanocage arises essentially from the induced polarization of the T-705 molecule under the electric field created by the doped nanocages. In the most stable configurations, the charges of about 0.323, 0.299, and 0.303 electrons are transferred from the T-705 molecule as an electron donor to the \( \text{BC}_{23}, \text{B}_{12}\text{N}_{12}, \) and \( \text{CB}_{11}\text{N}_{12} \) (electron acceptor). Therefore, the strongest stabilization of the interaction occurs between effective acceptors and effective doners.

As given in Table 6, for T-705/\( \text{BC}_{23} \) the value of \( E^2 \) for the intramolecular interactions within T-705 was mainly between \( \Pi^* (\text{C}_{37}-\text{C}_{30}) \) and \( \Pi^* (\text{C}_{26}-\text{O}_{25}) \) is equal 83.07 kcal mol\(^{-1} \). It is remarkable to mention that the intermolecular interactions between \( \text{C}_{24} \) and T-705 was lower with \( E^2 \) value of 0.99 kcal mol\(^{-1} \). The T-705/\( \text{BC}_{23}, \text{T-705/B}_{12}\text{N}_{12}, \) and T-705/\( \text{CB}_{11}\text{N}_{12} \) complexes show strong intermolecular between nanocage and drug molecule with \( E^2 \) values of 153.22, 131.59, and 98.19 kcal mol\(^{-1} \). The intermolecular interactions of The T-705/\( \text{BC}_{23} \) was mainly between LP (\( \text{O}_{25} \)) and \( \sigma^* (\text{B}_{3}) \), for T-705/\( \text{B}_{12}\text{N}_{12} \) was mainly between LP (\( \text{N}_{20} \)) and \( \sigma^* (\text{B}_{6}-\text{O}_{25}) \), and for T-705/\( \text{CB}_{11}\text{N}_{12} \) was mainly between \( \sigma (\text{C}_{30}-\text{N}_{31}) \) and \( \sigma^* (\text{C}_{26}-\text{O}_{25}) \).

The stabilization energy of T-705/\( \text{BC}_{23} \) is greater than those for T-705/\( \text{B}_{12}\text{N}_{12} \) and T-705/\( \text{CB}_{11}\text{N}_{12} \) complexes due to the stronger hyper-conjugative intermolecular interactions. Intramolecular interactions for T-705/\( \text{BC}_{23} \) within \( \text{BC}_{23} \) was between \( \Pi (\text{C}_{5}-\text{C}_{6}) \) and LP* (\( \text{B}_{3} \)) with \( E^2 \) value 9.53 kcal mol\(^{-1} \), for T-705/\( \text{B}_{12}\text{N}_{12} \) within \( \text{B}_{12}\text{N}_{12} \) was between LP (\( \text{N}_{20} \)) and \( \sigma^* (\text{B}_{6}-\text{O}_{25}) \) with \( E^2 \) value 12.07, and for T-705/\( \text{CB}_{11}\text{N}_{12} \) within T-705 was between \( \sigma (\text{C}_{30}-\text{N}_{31}) \) and \( \sigma^* (\text{C}_{26}-\text{O}_{25}) \) with \( E^2 \) value 0.92 kcal mol\(^{-1} \). In terms of the NBO approach, it can be shown that strong intermolecular interactions have mainly contributed to the increased stability in the T-705/\( \text{BC}_{23}, \text{T-705/B}_{12}\text{N}_{12}, \) and T-705/\( \text{CB}_{11}\text{N}_{12} \) systems.

3.8. The projected density of states (PDOS) analysis

The projected density of states (PDOS) of T-705 adsorbed at \( \text{C}_{24}, \text{BC}_{23}, \text{B}_{12}\text{N}_{12}, \) and \( \text{CB}_{11}\text{N}_{12} \) in gas and aqueous media as a real living...
environment has been explained to analyze the interactions between the T-705 drug and the C_{24}, BC23, B_{12}N_{12}, and CB_{11}N_{12} sites. The PDOS of the T-705 at BC23, B_{12}N_{12}, and CB_{11}N_{12} complexes in different forms was significantly affected owing to the interaction with various nanocages. The PDOS of the studied complex show lowering in the energy gap as compared to isolated nanocages due to the formation of a new peak in the region of the band gap. The band gap of nanocage BC_{23}, B_{12}N_{12}, and CB_{11}N_{12} are 2.683, 6.841, 4.533 eV, while the band gap of the T-705 adsorbed at BC23, B_{12}N_{12}, and CB_{11}N_{12} complexes are 2.247, 3.194, 1.137 eV. As observed in Figs. 9 and 10, the calculated PDOS of C-2p, B-2p, O-2p orbitals on B_{12}N_{12}, CB_{11}N_{12}, and BC_{23} appear stronger hybridization than C_{24} due to 2p states distribution from −7.3 to −16.8 eV below the Fermi level.

Also, the intensity of carbon and boron states of T-705@BC_{23} and T-705@CB_{11}N_{12} above the Fermi level reduces when compared with boron and carbon states without T-705 as shown in Figs. 9 and 10, meaning that 2p orbitals of T-705 not interact only with C-π orbitals but also with C-π* orbitals that doped at BN nanocage. The oxygen atom of C=O (T-705) form essentially a planar structure with c-doped and B-doped atoms (functionalized nanocages) which means sp^3 orbital hybridization. It is worth noting that the PDOS of C atoms show stronger intensity near the Fermi level, indicating the BC_{23} is more active than the CB_{11}N_{12}, corresponds to the binding energies listed in Tables 2 and 6. The interaction of T-705 with the BC23, B_{12}N_{12} and CB_{11}N_{12}, the overlap between the B atom states (BC_{23}) and the states of oxygen atom (C=O T-705) spread over from −6.4 eV to −16.8 eV as seen in Figs. 9 and 10. Moreover, a significant overlap of C atom (CB_{11}N_{12}) with oxygen atom of C=O (T-705) between −7.6 eV and −17.3 eV has been observed. Additionally, the PDOS of T-705 at the C_{24} and CB_{11}N_{12} in water solvent, no band appear in the region of the band gap and this is due to the inclusion of water molecules in the system. The positions of HOMO and LUMO changed due to inclusion of water molecules and this led to decreasing the band gap value of T-705@C_{24}, T-705@BC23 but increasing of T-705@B_{12}N_{12} and T-705@CB_{11}N_{12}.

3.9. UV–visible analysis

The time-dependent density functional theory (TD-DFT) calculations were investigated with the CAM-B3LYP functional [50] since it gives rise to more reliable results compared to pure B3LYP on the nature of electronic transitions spectra to get further insights into the electronic absorption of T-705–nanocage complexes in the gas and aqueous phases. The theoretical UV–vis parameters of T-705, nanocages, and the T-705–nanocage complexes are summarized in Tables 7 and 8. According to theoretical calculations represented in Table 7, the T-705 shows four strong peaks at 287.37, 208.63, 181.49, and 163.23 nm with energies of 4.314, 5.943, 6.831 and 7.596 eV for the main electronic transitions, respectively. The UV spectrum of T-705 has a sharply intense peak in 165.72–289.33 nm in the water phase. The largest contribution to charge transition at 287.4 nm for T-705 was 98% from HOMO to LUMO [51,52]. The pure CB_{11}N_{12} UV spectrum shows two separated peaks of absorption, located at wavelengths of 216.00 and 261.56 nm. It displayed that the maximum absorption at 518.47, 191.45, 272.61 nm for the BC_{23}, B_{12}N_{12}, CB_{11}N_{12} corresponds to 2.391, 6.476, and 4.548 eV that represent the HOMO to LUMO excitation, and in turn is a charge transfer from the T-705 to nanocage. After the interaction of T-705 and nanocage with the B atom of B_{12}N_{12}, B-doped of the BC_{23} and C-doped of, CB_{11}N_{12}, the main absorption peaks are shifted to higher
wavelengths ($\lambda_{\text{max}}$) at 299.75, 571.96 and 329.38 nm and the adsorption intensity decreased to 4.136, 2.168 and 3.764 eV than isolated T-705 and nanocage.

For the aqueous phase the first absorption peak of the complexes (T-705 at C$_{24}$, BC$_{23}$, and B$_{12}$N$_{12}$), is located at the wavelength of 381.17, 563.71, and 305.22 nm, which is a shift of 4.96–8.25 nm in comparison with the gas phase, however, the shift of the T-705-CB$_{11}$N$_{12}$ absorption peak is even more pronounced (22.74) nm. For T-705/BC$_{23}$ complex, the maximum absorption at 571.96 nm is assigned to the transition from the HOMO-2 to the LUMO (55%) molecular orbital in the visible region. This predicted transition is $n$-$\pi^*$ nature. The HOMO-3 - LUMO (88%) transition (n - $\pi^*$ nature) is assigned to the absorption band of T-705-CB$_{11}$N$_{12}$ located at 329.2 nm in the calculated spectrum ($f$ = 0.0032). The most significant contribution form T-705@B$_{12}$N$_{12}$ complex noticed from HOMO-3 - LUMO+1 with 56% of the 0.0592 oscillator strength.

Furthermore, it is significant that, when T-705 is adsorbed over the C$_{24}$ nanocage, the wavelength of adsorption is significantly increased to 386.1 nm, which arises from HOMO-3 to LUMO+1 with 56% of the 0.0592 oscillator strength and $\pi$-$\pi^*$ transition. In contrast, the CAM-B3LYP method exhibited slight overestimates on the excitation energies of T-705/BC$_{23}$, T-705/B$_{12}$N$_{12}$ and T-705/CB$_{11}$N$_{12}$ complexes and underestimates at T-705/C$_{24}$ as compared to the UB3LYP method in gas and aqueous phases, Tables 9 and 10.

### 3.10. IR spectrum

Vibrational frequencies for the perfect (B$_{12}$N$_{12}$ and C$_{24}$) and doped (BC$_{23}$ and CB$_{11}$N$_{12}$) nanocages and their complexes with Favipiravir drug were investigated to evaluate the changes in the bonds stretching vibrational frequency of the Favipiravir before and after the interaction with nanocages. According to Fig. 11, the location of each vibration for doped (BC$_{23}$ and CB$_{11}$N$_{12}$) differ compared to the pure (B$_{12}$N$_{12}$ and C$_{24}$) nanocages due to the presence of doped B and C atoms. Literature review revealed that the stretching vibration of B–C is about 1020 cm$^{-1}$ [53], that is in agreement with the calculated values. As expected, the number of vibration peaks for doped (BC$_{23}$ and CB$_{11}$N$_{12}$) is greater than those for perfect (B$_{12}$N$_{12}$ and C$_{24}$) [53]. The most important associated vibration frequencies were strongly examined: $\nu$(C=O) and $\nu$(N–H) bonds of amid functional group and $\nu$(O–H) bond of the Favipiravir molecule were completely in accordance with the Favipiravir molecule in the literature [5]. When Favipiravir get adsorbed on the surface of perfect (B$_{12}$N$_{12}$ and C$_{24}$) and doped (BC$_{23}$ and CB$_{11}$N$_{12}$) nanocages, the value of vibrational frequencies as well as IR intensity were altered. Fig. 11 shows that not only the new vibrations bond appeared upon adsorption of this molecule on doped (BC$_{23}$ and CB$_{11}$N$_{12}$) nanocages, but also some peaks were shifted. For instance, the $\nu$(C=O) of the drug before adsorption (1802 cm$^{-1}$) shifted to the low values (1785, 1716, 1724 and 1723 cm$^{-1}$) depending on the kind of nanocage C$_{24}$.
BC_{23}, B_{12}N_{12}, and CB_{11}N_{12} sites. It is observed that a low-intensity vibrational frequency associated with the interaction of Favipiravir with C_{24}, BC_{23}, B_{12}N_{12}, and CB_{11}N_{12} sites complex.

4. Conclusions

The computational calculations were conducted to characterize the mechanism of the interaction between the drug 5-Fluoro-2-hydroxypyrazine-3-carboxamide (T-705) and C_{24}, BC_{23}, B_{12}N_{12}, and CB_{11}N_{12} based nanocarriers using the density functional theory (DFT) and the time-dependent density functional theory (TD-B3LYP and TD-CAM-B3LYP). Adsorption properties of these complexes: geometry optimization, molecular structure, MEP, spectroscopic (UV/Vis, excited State and IR), and the thermodynamic parameters have been examined. Interestingly, the presence of nanocage does not induce any major structural deformation in the T-705, and the incorporation of heteroatoms in perfect C_{24} and B_{12}N_{12} (BC_{23} and CB_{11}N_{12}) nanocages exhibits comparatively higher interacting energies compared to perfect nanocage. Moreover, the energy gap of CB_{11}N_{12} drastically lowers by 2.31 eV, indicating increase in reactivity and a decrease in stability. For the T-705/CB_{11}N_{12} complexes, the excitation from the HOMO to LUMO. The reduction of the energy gap of excited-state showed that the \( \lambda_{\text{max}} \) was red-shifted by 79 nm.

MEP predict the electrophilic and nucleophilic sites and NBO analysis explored the charge transfer within different orbitals in the studied complexes. The projected density of states (PDOS) of these complexes without and with solvent has been explained to examine the role of water in the interaction of T-705 with C_{24}, B_{12}N_{12}, BC_{23} and CB_{11}N_{12} nanoparticles. The essence of interaction between T-705 drug and nanocage is explored by NCI which illustrated that weak interaction between drug molecule and the nanocage. The change in electron density after drug adsorption on nanocage is investigated by ELF maps.

The two different temperatures (298.15 to 310.15 K) were examined for the interaction of the T-705 molecule with B_{12}N_{12}, CB_{11}N_{12}, C_{24}, BC_{23} in the gas and aqueous. The derived thermodynamic parameters of T-705@BC_{23}, T-705@B_{12}N_{12} and T-705@CB_{11}N_{12} with negative \( \Delta G \) implying the spontaneity of the interaction. Consequently, the BC_{23}, B_{12}N_{12}, and CB_{11}N_{12} nanocages can be utilized as promising drug delivery vehicles for a potential antiviral T-705. T-705 can be considered a highly promising antiviral drug for COVID-19.

CRediT authorship contribution statement

K. A. Soliman conceived of the idea, writing-original draft of the manuscript and reviewed it. S. Abdel Aal writing-original draft of the manuscript and reviewed it.
| Donor (i) | Acceptor (j) | $E^{(2)}$ | $E(j) - E(i)$ | $F(i,j)$ |
|-----------|-------------|----------|----------------|---------|
| T-705/C24 | $\pi$ (C26-O25) | $\pi^*$ (C3-C5) | 0.06 | 2.05 | 0.047 |
|           | $\pi$ (C26-O25) | $\pi^*$ (C3-C5) | 0.06 | 0.39 | 0.023 |
|           | LP (O25) | $\pi^*$ (C2-C19) | 0.99 | 0.27 | 0.040 |
|           | $\sigma$ (C30-C26) | $\sigma^*$ (C26-O25) | 0.54 | 1.26 | 0.019 |
|           | $\sigma$ (C30-N31) | $\sigma^*$ (C26-O25) | 1.35 | 1.46 | 0.047 |
|           | $\pi$ (C26-O25) | $\pi^*$ (C26-N27) | 2.33 | 1.15 | 0.010 |
|           | LP (O25) | $\sigma^*$ (C10-C26) | 1.91 | 1.06 | 0.005 |
|           | $\pi^*$ (C37-C30) | $\pi^*$ (C26-O25) | 83.07 | 0.03 | 0.005 |
|           | LP (O25) | $\sigma^*$ (C26-N27) | 2.33 | 1.15 | 0.015 |
| T-705/C23B | $\sigma$(C26-O25) | $\sigma^*$ (B3) | 20.06 | 1.17 | 0.201 |
|           | LP (O25) | $\sigma^*$ (B3) | 8.25 | 0.58 | 0.101 |
|           | LP (O25) | $\sigma^*$ (C2-B3) | 1.40 | 0.97 | 0.047 |
|           | $\sigma$(C26-O25) | $\sigma^*$ (N27-H28) | 1.22 | 0.89 | 0.042 |
|           | LP (C5-C6) | LP* (B3) | 9.53 | 0.35 | 0.074 |
|           | LP (C5-C6) | LP* (C17-C8) | 1.42 | 1.00 | 0.048 |
|           | $\pi$(C7-C14) | $\pi^*$ (C4-B3) | 2.11 | 1.00 | 0.055 |
|           | $\sigma$(C6-C10) | $\sigma^*$ (C26-O25) | 1.40 | 0.97 | 0.047 |
|           | $\sigma$(C2-C19) | $\sigma^*$ (C2-B3) | 1.02 | 1.07 | 0.042 |
|           | LP (C19-C2) | LP* (B3) | 5.33 | 0.35 | 0.057 |
|           | $\sigma$(C19-C2) | $\sigma^*$ (C26-O25) | 1.14 | 0.63 | 0.036 |
|           | $\sigma$(C4-B3) | $\sigma^*$ (C7-C4) | 1.74 | 1.05 | 0.055 |
|           | $\sigma$(C4-B3) | $\sigma^*$ (C18-C1) | 3.42 | 1.00 | 0.075 |
| T-705/B12N12 | $\sigma$(B6-O25) | RY*1 (C26) | 3.26 | 1.67 | 0.066 |
|           | $\sigma$(B6-O25) | RY*4 (C26) | 0.51 | 3.13 | 0.036 |
|           | $\sigma$(B6-O25) | $\sigma^*$ (B6-N19) | 0.63 | 1.23 | 0.025 |
|           | $\sigma$(B6-O25) | $\sigma^*$ (B6-N20) | 1.03 | 1.16 | 0.031 |
|           | $\sigma$(B6-O25) | $\sigma^*$ (C30-C26) | 5.22 | 1.19 | 0.071 |
|           | $\sigma$(B6-O25) | $\sigma^*$ (C26-O25) | 17.38 | 1.28 | 0.037 |
|           | $\pi$(B7-N19) | $\sigma^*$ (B6-O25) | 13.26 | 0.58 | 0.080 |
|           | $\sigma$(C30-C26) | $\sigma^*$ (B6-O25) | 4.19 | 1.01 | 0.059 |
|           | $\pi$(C26-O25) | $\sigma^*$ (B6-O25) | 1.63 | 1.32 | 0.042 |
|           | LP (N17) | $\sigma^*$ (B6-O25) | 8.25 | 0.56 | 0.064 |
|           | LP (N20) | $\sigma^*$ (B6-O25) | 12.07 | 0.54 | 0.078 |
|           | LP (O25) | $\sigma^*$ (B6) | 131.59 | 1.70 | 0.047 |
| T-705/CB11N12 | $\sigma^*$ (N19-B6) | $\sigma^*$ (C26-O25) | 0.57 | 1.11 | 0.032 |
|           | $\sigma^*$ (N20-B6) | $\sigma^*$ (C26-O25) | 0.29 | 1.04 | 0.022 |
|           | $\sigma^*$ (N20-B6) | $\pi^*$ (C26-O25) | 0.31 | 0.50 | 0.018 |
|           | $\sigma^*$ (C30-N31) | $\sigma^*$ (C26-O25) | 0.92 | 1.36 | 0.045 |
|           | $\sigma^*$ (C26-O25) | $\sigma^*$ (N25-B6) | 0.80 | 1.32 | 0.042 |
|           | $\sigma^*$ (N19-B6) | $\sigma^*$ (N19-B6) | 0.84 | 0.84 | 0.039 |
|           | $\sigma^*$ (C26-O25) | $\sigma^*$ (N20-B6) | 15.34 | 0.78 | 0.051 |
|           | LP (O25) | LP* (B6) | 18.68 | 1.74 | 0.044 |
|           | LP (O25) | $\sigma^*$ (N17-B6) | 98.19 | 0.78 | 0.052 |
|           | LP (O25) | $\sigma^*$ (N19-B6) | 0.93 | 0.90 | 0.037 |
|           | LP (O25) | $\sigma^*$ (O25-B6) | 0.25 | 0.76 | 0.018 |
|           | $\sigma^*$ (O25-B6) | $\sigma^*$ (C26-O25) | 1.66 | 0.18 | 0.087 |
Fig. 9. The projected density of states (PDOS) of (a) C_{24}, (b) T-705/C_{24} in gas phase, (c) T-705/C_{24} in aqueous phase (d) C_{23}B, (e) T-705/C_{23}B in gas phase and (f) T-705/C_{23}B in aqueous phase. The Fermi level is set to be 0.

Fig. 10. The projected density of states (PDOS) of (a) B_{12}N_{12}, (b) T-705/B_{12}N_{12} in gas phase, (c) T-705/B_{12}N_{12} in aqueous phase (d) CB_{11}N_{12}, (e) T-705/CB_{11}N_{12} in gas phase and (f) T-705/ CB_{11}N_{12} in aqueous phase. The Fermi level is set to be 0.
Table 7
Selected excitation energies (E, eV), wavelength (λ, nm) oscillator strength (f), and relative orbital contributions calculated for the most stable configuration of T-705, C_{24}, B_{12}N_{12}, and CB_{11}N_{12} nanocages in the gas and aqueous phase using B3LYP approximations.

| Structure | E    | λ  | f   | MO contributions            | Structure | E    | λ  | f   | MO contributions            |
|-----------|------|----|-----|-----------------------------|-----------|------|----|-----|-----------------------------|
| Gas phase |      |    |     |                             | Aqueous phase |      |    |     |                             |
| T-705     | 4.3144 | 287.37 | 0.1088 | HOMO→LUMO (98%)            | T-705     | 4.2852 | 289.33 | 0.1819 | HOMO→LUMO (94%)            |
|           | 5.9429 | 208.63 | 0.1460 | H-5→LUMO (11%), H-1→L+1 (79%), H-2→L+1 (7%) |           | 5.8746 | 211.05 | 0.1591 | HOMO→L-1 + 1 (88%), H-5→LUMO (9%) |
|           | 6.8316 | 181.49 | 0.1803 | H-5→LUMO (78%), H-9→LUMO (4%), H-6→LUMO (4%), H-1→L+1 (8%) |           | 6.7875 | 182.67 | 0.2341 | H-5→LUMO (82%), H-6→LUMO (3%), HOMO→L-1 (9%) |
|           | 7.5955 | 163.23 | 0.1420 | H-5→L+1 (19%), H-1→L+2 (73%) |           | 7.4814 | 165.72 | 0.1557 | H-5→L-1 + 1 (16%), HOMO→L+2 (78%) |
| C_{24}    | 3.7436 | 331.19 | 0.0182 | H-4→L+2 (17%), H-3→LUMO (26%), H-2→L+6 (11%) | C_{24}    | 3.7362 | 331.84 | 0.0228 | H-5→LUMO (12%), H-4→L+1 (15%), H-4→L+2 (14%), H-3→LUMO (19%) |
| C_{23}B   | 2.3913 | 518.47 | 0.0104 | H-2(B)→LUMO(B) (78%), H-3(A)→L+2 (A) (4%), HOMO(A)→L+2(A) (3%) | C_{23}B   | 2.3772 | 521.54 | 0.0141 | H-2(B)→LUMO(B) (78%), H-3(A)→LUMO(A) (2%), H-3(A)→L+2(A) (3%) |
| B_{12}N_{12} | 6.4762 | 191.45 | 0.0336 | H-1→L+3 (36%), HOMO→L+4 (16%), H-4→L+2 (9%), L-3→LUMO (3%), L-3→L+2 (16%) | B_{12}N_{12} | 6.5100 | 190.45 | 0.0470 | H-1→L+3 (36%), HOMO→L+4 (22%), H-4→LUMO (5%), L-3→L+2 (9%) |
| CB_{11}N_{12} | 5.7400 | 216.00 | 0.0131 | H-4(B)→LUMO(B) (74%), H-2(A)→L+2 (A) (2%), HOMO(A)→L+11(A) (9%), H-1(A)→LUMO(B) (3%) | CB_{11}N_{12} | 5.7120 | 217.06 | 0.0230 | H-4(B)→LUMO(B) (85%), H-1(B)→LUMO(B) (3%), H-1(B)→L+13(B) (3%) |
|           | 4.5481 | 272.61 | 0.0116 | HOMO(A)→L+5(A) (84%), HOMO(A)→L+2(A) (8%), HOMO(A)→L+9(A) (3%) |           | 4.6087 | 269.02 | 0.0162 | HOMO(A)→L+5(A) (82%), HOMO(A)→L+2(A) (8%), HOMO(A)→L+9(A) (3%) |

Table 8
Selected excitation energies (E, eV), wavelength (λ, nm) oscillator strength (f), and relative orbital contributions calculated for the most stable configuration of T-705/C_{24}, T-705/C_{23}B, T-705/B_{12}N_{12} and T-705/CB_{11}N_{12} complexes in the gas and aqueous phase using B3LYP approximations.

| Structure | E    | λ  | f   | MO contributions            | Structure | E    | λ  | f   | MO contributions            |
|-----------|------|----|-----|-----------------------------|-----------|------|----|-----|-----------------------------|
| Gas phase |      |    |     |                             | Aqueous phase |      |    |     |                             |
| T-705/C_{24} | 3.2109 | 386.13 | 0.0592 | H-3→LUMO (15%), H-3→L+1 (56%), H-3→L+2 (27%) | T-705/C_{24} | 3.2527 | 381.17 | 0.0072 | H-4→LUMO (48%), H-4→L+1 (13%), H-4→L+2 (29%), H-8→L+1 (3%) |
| T-705/C_{23}B | 2.1677 | 571.96 | 0.0014 | HOMO(A)→L+4(A) (33%), H-2(B)→LUMO(B) (55%), H-2(A)→L+1(A) (3%), HOMO(B)→L+5(B) (5%) | T-705/C_{23}B | 2.1994 | 563.71 | 0.0015 | H-2(A)→LUMO(A) (47%), H-2(A)→L+1(A) (18%), H-1(B)→L+4(B) (12%) |
| T-705/B_{12}N_{12} | 4.1363 | 299.75 | 0.1837 | H-3(A)→LUMO(A) (88%), H-12(A)→LUMO(A) (2%), H-12(B)→LUMO(B) (2%) | T-705/B_{12}N_{12} | 4.0621 | 305.22 | 0.2867 | H-2→LUMO (97%) |
| T-705/CB_{11}N_{12} | 3.7641 | 329.38 | 0.0032 | H-3(A)→LUMO(A) (88%), H-12(A)→LUMO(A) (2%), H-12(B)→LUMO(B) (2%) | T-705/CB_{11}N_{12} | 4.0432 | 306.65 | 0.2600 | H-2(A)→LUMO(A) (50%), H-3(B)→LUMO(B) (44%), H-4(A)→LUMO(A) (2%) |
Table 9
Selected excitation energies (E, eV), wavelength (λ, nm) oscillator strength (f), and relative orbital contributions calculated for the most stable configuration of T-705, C_{24}, B_{12}N_{12} and CB_{11}N_{12} nanocages in the gas and aqueous phase using CAM-B3LYP approximations.

| Structure | E     | λ     | f   | MO contributions  | Structure | E     | λ     | f   | MO contributions  |
|-----------|-------|-------|-----|------------------|-----------|-------|-------|-----|------------------|
| T-705     | 4.1240| 300.64| 0.0017| H-1(A) → LUMO(A) (44%), H-1(B) → LUMO(B) (44%) | T-705/C_{24} | 4.3214| 286.91| 0.0028| H-1(A) → LUMO(A) (43%), H-1(B) → LUMO(B) (43%) |
|           | 4.5547| 272.21| 0.1749| H-2(A) → LUMO(A) (37%), H-2(B) → LUMO(B) (37%) |           | 4.4953| 275.81| 0.2202| HOMO(A) → LUMO(A) (48%), LUMO(B) (48%) |
|           | 5.4011| 229.56| 0.0212| H-2(A) → LUMO(A) (49%), H-2(B) → LUMO(B) (49%) |           | 5.5953| 221.59| 0.0340| H-2(A) → LUMO(A) (49%), H-2(B) → LUMO(B) (49%) |
|           | 6.1749| 200.79| 0.1395| HOMO(A) → LUMO(A) (37%), HOMO(B) → LUMO(B) (37%) |           | 6.1103| 202.91| 0.1690| HOMO(A) → LUMO(A) (37%), HOMO(B) → LUMO(B) (37%) |
| C_{24}    | 4.2472| 291.92| 0.0462| H-2 → LUMO(A) (10%), HOMO → LUMO(B) (10%)|        | 4.2037| 292.56| 0.0589| H-2 → LUMO(A) (10%), HOMO → LUMO(B) (10%) |
|           | 2.9533| 419.82| 0.0070| HOMO(A) → LUMO(A) (79%) |           | 2.9468| 420.74| 0.0104| HOMO(A) → LUMO(A) (79%) |
| B_{12}N_{12}| 6.3118| 193.50| 0.0231| H-4 → LUMO(A) (10%), H-4 → LUMO(B) (10%) |           | 6.7057| 192.43| 0.0358| H-4 → LUMO(A) (10%), H-4 → LUMO(B) (10%) |
|           | 5.3745| 230.69| 0.0146| HOMO(A) → LUMO(A) (84%), HOMO(B) → LUMO(B) (78%) |           | 5.3533| 231.60| 0.0184| HOMO(A) → LUMO(A) (84%), HOMO(B) → LUMO(B) (78%) |
| CB_{11}N_{12}| 4.4042| 281.52| 0.0007| HOMO(A) → LUMO(A) (84%), HOMO(B) → LUMO(B) (78%) |           | 4.4665| 277.59| 0.0009| HOMO(A) → LUMO(A) (84%), HOMO(B) → LUMO(B) (78%) |

Table 10
Selected excitation energies (E, eV), wavelength (λ, nm) oscillator strength (f), and relative orbital contributions calculated for the most stable configuration of T-705/C_{24}, T-705/C_{23}B, T-705/B_{12}N_{12} and T-705/CB_{11}N_{12} complexes in the gas and aqueous phase using CAM-B3LYP approximations.

| Structure | E     | λ     | f   | MO contributions  | Structure | E     | λ     | f   | MO contributions  |
|-----------|-------|-------|-----|------------------|-----------|-------|-------|-----|------------------|
| T-705/C_{24} | 4.2502| 291.71| 0.0356| H-2 → LUMO(A) (26%), HOMO → LUMO(A) (26%) | T-705/C_{24} | 3.0527| 287.20| 0.0011| H-3 → LUMO(A) (36%), H-2 → LUMO(A) (36%) |
|           | 2.4801| 499.91| 0.0013| HOMO(A) → LUMO(A) (79%) |           | 2.5204| 491.92| 0.0037| HOMO(A) → LUMO(A) (79%) |
| T-705/C_{23}B | 4.3493| 285.06| 0.2057| H-6(A) → LUMO(A) (21%), HOMO(A) → LUMO(B) (18%), H-6(B) → LUMO(B) (18%) | T-705/C_{23}B | 4.3215| 289.06| 0.3890| H-5(A) → LUMO(A) (22%), HOMO(A) → LUMO(A) (19%), HOMO(B) → LUMO(B) (23%) |
|           | 4.3718| 283.60| 0.2738| H-6(A) → LUMO(A) (21%), HOMO(A) → LUMO(B) (18%), H-6(B) → LUMO(B) (18%) |           | 4.2919| 288.88| 0.3420| H-2(A) → LUMO(A) (27%), H-1(A) → LUMO(A) (21%), H-2(B) → LUMO(B) (21%), H-1(B) → LUMO(B) (21%) |
Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diamond.2021.108458.

Fig. 11. IR spectra of T-705, nanocages and their complexes.

References

[1] A.E. Allam, H.K. Assaf, H.A. Hassan, K. Shimizu, A.M.M. Elshaier, An in silico perception for newly isolated flavonoids from peach fruit as privileged avenue for a countermeasure outbreak of COVID-19, RSC Adv. 10 (2020) 29983–29998.

[2] Y. Furuta, K. Takahashi, K. Shiraki, K. Sakamoto, D.F. Smee, D.L. Barnard, B. Gowen, J.G. Julander, J.D. Morrey, T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections, Antiviral Res. 82 (2009) 95–102.

[3] Y. Furuta, B. Gowen, K. Takahashi, K. Shiraki, D.F. Smee, D.L. Barnard, Favipiravir (T-705), a novel viral RNA polymerase inhibitor, Antiviral Res. 100 (2013) 446–454.
