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Spectroscopic and Structural Study of the Antiviral Idoxuridine Agent by Using DFT and SCRF Calculations

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ABSTRACT

In the present work, the theoretical molecular structures of five isomers of idoxuridine have been studied by using the hybrid B3LYP method with the Lanl2dz and 3-21G* levels of theory in gas and aqueous solution phases. The properties in solution were predicted by using the self-consistent reaction field (SCRF) method together with the integral equation formalism variant polarised continuum model (IEFPCM). Here, the structural properties and spectroscopic were performed only for the C4 and C5 isomers according to the experimental *anti*-structure reported for idoxuridine. On the other hand, the infrared, Raman, ^{1}H-NMR, ^{13}C-NMR and UV-visible spectra predicted for the two most stable isomers by using the 3-21G* basis set in the two studied media show a reasonable agreement with the corresponding available experimental spectra. The presence of the dimeric species of idoxuridine could explain some bands observed in the experimental FTIR spectrum. The atomic Mulliken, natural population (NPA) charges, solvation energies and the NBO and AIM studies evidence clearly the notable influence of the basis set on the properties analyzed. Hence, the antiviral activity observed for IDU could in part be justified using the 3-21G* basis set because these calculations show slightly polarizations of the C16←I1 bonds and electrons available in the *d* orbitals of the iodine atom. The frontier orbitals show that the presence of the iodine atom in idoxuridine increases their reactivity as compared with thymidine while idoxuridine is less reactive than brincidofovir, an antiviral drug used against the *Ebola* disease.

1. INTRODUCTION

From long time the pyrimidine nucleoside analogs and their derivatives are used as antiviral agents in the clinical treatment of numerous diseases, as reported in the literature [1-16] and, due to that they present a series of contraindications or side effects, new drugs were and are designed in order to improve their biological properties [1-6,9-16]. For instance, the structural changes implies the introduction of different atoms or groups in the pyrimidine or ribose rings to produce new drugs of therapeutic interest such as, halogen and/or sulphur atoms giving idoxuridine and trifluridine which are used respectively in the treatment of herpes simplex virus (HSV) and/or varicella-zoster virus (VZV) infections or emtricitabine used for the treatment of human immunodeficiency virus (HIV) infections [6]. The evaluations of some cytidine derivatives and of amino and halogenated pyrimidine analogs as potential antimicrobial agents were studied by Azhar et al. [4] and Sreenivas et al. [9], respectively while others authors have reported that the pyrimidine derivatives also exhibit the anti-inflammatory, anticancer, anticonvulsant, antibacterial, antioxidant and antifungal properties [1-5,9]. In particular, the nucleoside idoxuridine (IDU), is an analog of thymidine because the CH_3 group was replaced by an iodine atom, whose IUPAC name is 1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione. For the first time, Prusosif synthesized IDU and their biological activities reported in this opportunity [17]. The detailed crystal and molecular structure of IDU were determined by Camerman and Trotter [18] by using X-ray diffraction and a Mo *Kα* scintillation counter data. These authors have suggested that a probable explanation for the antiviral property of IDU could be the existence of charge transfer bonding involving the donation of oxygen lone-pairs electrons to vacant 5*d* orbitals of the iodine atom. They say that, the replacement of CH_3 by iodine atom increase the stability of IDU, in relation to thymidine [19], because in part modify the electronic density of the pyrimidine ring in order to strengthen the hydrogen bonding to the purine base in the complementary DNA chain [18]. This way, the structural properties of IDU are of interest to know and understand these experimental observations especially due to the presence of two chiral C atoms and to explain the changes observed when the pyrimidine environmental is modified, in relation to their very important antiviral activity. On the other hand, the structural studies are also necessary to identify the isomers of IDU in different media using their infrared, Raman, NMR and/or UV-visible spectra. In this context, the aims of this work are: (i) to study theoretically the stable isomeric structures of IDU in gas and aqueous solution phases by using the hybrid B3LYP method [20,21] and the

polarized continuum (PCM) [22,23] and solvation (SM) models [24], (ii) to predict the infrared, Raman, NMR and UV-visible spectra and, then, to compare these with the corresponding experimental available ones, (iii) to calculate the atomic charges, bond orders, molecular electrostatic potentials, stabilization energy, topological properties and solvation energy, (iv) to predict the reactivity and behaviour's of the different structures in the two media using the frontier orbitals and some descriptors reported in the literature [19,25-31] and, finally, (v) to perform the complete vibrational assignments combining the experimental available infrared spectra with the scaled harmonic quantum mechanical force field (SQMFF) methodology [32] and taking into account their natural internal coordinates. Here, the suggestions proposed by Camerman and Trotter [18] were confirmed by using natural bond orbital (NBO) [33, 34] and atoms in molecules (AIM) [35, 36] calculations and, moreover, new structural information is obtained with the aid of the theoretical calculations and the experimental available infrared, NMR and UV-visible spectra of IDU. The reactivity's and descriptors for all the isomers of IDU in both media were compared with the corresponding values obtained for thymidine [19] revealing that the presence of the iodine atom increase notably their reactivity's in both media, as proposed by Camerman and Trotter [18] while the NBO studies support the higher stability of IDU due to the higher number of charge transfers observed.

2. METHODOLOGY

In this work, we have considered five isomeric structures of IDU because this molecule has two chiral centres in the 2 and 5 positions of the ribose ring which are: the *cis* isomer (2R,5S) named C1; the *trans* isomer (2S,5S), named C2; the *cis* isomer (2S,5R) named C3; and the two *trans* isomers (2R,5R) named C4 and C5, respectively in similar form to those structures reported for emtricitabine by Bartra Sanmarti et al. [37]. The study of these structures are of interest for classify their properties taking into account that the *cis* (2R, 5S) isomer of emtricitabine has significant antiviral activity while low activities are observed in the other *cis* (2S,5R) isomer and in the two *trans* isomers (2S,5S) and (2R,5R), for which, these three latter forms have low therapeutic interest. The five structures of IDU can be seen in Figure 1 together with the labelling atoms. Here, in accordance to the packing of the IDU molecules observed by X-ray diffraction [18], two different dimeric species were also studied in order to explain the intensities of some infrared bands that cannot be justified with the monomeric species. Thus, Figure S1 shows the most stable dimeric species studied. Those five initial

structures were modelled with the *GaussView* program [38] and, later these species in both media were optimized using the Gaussian 09 program [39]. All the calculations were performed by using the hybrid B3LYP method [20,21] and the CEP-4G [40], Lanl2dz [41] and 3-21G* [42] basis sets because for the iodine atom there are few basis sets defined. Here, only the calculated properties using those two latter basis sets were considered because the energies obtained using the CEP-4G basis set were considerably lower than the other ones. Thus, the atomic natural population (NPA) and Mulliken's charges together with the bond order expressed as Wiberg indexes were analysed in both media. The stabilization energies and the topological properties were computed with the NBO [33, 34] and AIM2000 programs [35, 36] while the gap energies and some descriptors were calculated by using the frontier orbitals [19,25-31]. The harmonic force fields in both media at the Lanl2dz and 3-21G* levels of theory were obtained using the harmonic scaled quantum mechanical force field (SQMFF) procedure [32], the internal coordinates and the Molvib program [43]. The Moldraw program [44] was employed to calculate the volume variations that experiment the isomers in aqueous solution in relation to their values in the gas phase. The GIAO method [45] was used to predict the ^{1}H-NMR and ^{13}C-NMR spectra in aqueous solution while the ultraviolet-visible spectra for all the isomers in the same medium were predicted in solution by using the time-dependent density functional theory (TD-DFT) calculations at the same level of theory.

3. RESULTS AND DISCUSSION

3.1. Optimized structures in both media

Table S1 shows the total and relative energies and dipole moment values for the five configurations of Idoxuridine by using the Lanl2dz and 3-21G* basis sets together with the population analysis in the two studied media. Analysing exhaustively the results we observed that the C5 isomer is the most stable in the gas phase with both basis sets but C4 is the most stable in solution by using Lanl2dz basis set while C5 is the most stable in this medium using the 3-21G* basis set, this way, these two isomers can probably be present in both media due to their higher populations, as can be seen in Table S1. The structure of the C4 isomer is in agreement with the *anti*-conformation experimentally reported for IDU by Camerman and Trotter [18] with an O2-C10-N7-C14 dihedral angle of -67º, as will see later. When these relative energies using both basis sets are represented in function of the five configurations we observed clearly different behaviours in both media, as can be seen in Figures S2a and 2b,

thus, C5 is the most stable isomer in both media using 3-21G* basis set while C4 is the most stable one in solution using the other basis set. Figures S2c and 2d show clearly that the higher changes in the dipole moment values are observed using the 3-21G* basis set while the graphic of the volume values with the five configurations show that C2 present the higher values in both media using both basis sets and that C3, C4 and C5 have different behaviours in the two media by using both basis sets. Thus, Figure S2 evidence the notable influence of the basis set on the three properties analysed.

It is very important to clarify that the C2, C4 or C5 structures correspond to *Trans* isomers while those corresponding to the C1 and C3 isomers have *Cis* conformations. In this analysis, we have considered only the *trans* C5 isomer in accordance with the better correlations with the experimental *anti*-structure [18], their high populations and low energies using the 3-21G* basis set. The calculated geometrical parameters for the C5 isomer in the two studied media by using both basis sets were compared in Table 1 with the corresponding experimental ones [18] by using the root-mean-square deviation (RMSD) values. Here, the bond lengths (0.038-0.037 Å) and angles (2.7-2.3 º) for that isomer show very good concordance with the experimental values. The two levels of approximation predict values for the glycosidic C10-N7 bonds closer to the experimental one (1.49 Å) [18]. Probably, the low dipole moment and the higher volume variation in solution explain their high stability in solution, as mentioned by Camerman and Trotter [18], because they have observed that when the CH_3 group in thymidine is replaced by iodine atom increase the stability of IDU. On the other hand, when the distances between the more electronegative atoms in gas and aqueous solution phases are investigated using both basis sets we observed that the high stability of C5 using 3-21G* basis set can in part be explained by the higher separation O2-O3 and O5-O3 distances and the low O6-I1 distances, as observed in Table S3. Apparently, a shorter O6-I1 distance is the structural requirement for the high stability of an isomer of IDU, as suggested by Camerman and Trotter [18]. Probably, this distance is a structural requirement due to the ability of the iodine atom to form charge transfer and, in other words, maybe the molecular basis for the antiviral activity of IDU, as reported by Camerman and Trotter [18].

3.2. Solvation energy

We have computed the solvation energy values for the five configurations of IDU using the two basis sets and the values are summarized in Table 2. Hence, Table 2 shows the uncorrected and corrected solvation energies using the two levels of theory together with the

values corresponding to the total nonelectrostatic terms due to the cavitation, dispersion and repulsion energies computed with the PCM [22,23] and SM [24] models at the same levels of theory. When these values are represented in function of the five configurations at different levels of theory, as can be seen in Figure S3, the Lanl2dz basis set predicted the most negative values but the 3-21G* basis set shows the higher difference among the isomers. Thus, the lower values observed for C1 and C5 using 3-21G* basis set could justify their low dipole moment values in solution (Table S1). **Figure S4** shows the different magnitude and directions of the dipole moments using the Lanl2dz basis set which evidence clearly that the different charge distributions in the five structures have to influence on their stabilities and reaction sites.

3.3. NPA charges, Wiberg indexes, and MEP studies

The study of the charge distributions in the different configurations of IDU are of particular interest taking into account the presence in their structures of the C-I, C=O, N-H and OH groups and of N and O atoms containing lone pairs because the attraction and repulsion effects in the molecules are controlled by a variety of weak interactions, as mentioned by Immel [46]. In fact, the charge distributions determine the different properties and behaviour's of the molecules in the different media. For this reason, in the section 3.1 we have analysed in Table S3 the separation O-N and O-O distances between the electronegative N and O atoms which have showed, for instance, that a shorter O6-I1 distance could be an important structural requirement for the high stability of an isomer of IDU due to the available *d* orbitals of the I atom. When we analyzed the NPA charges on all the O atoms in both media the most negative values are observed on the O3 and O4 atoms using the Lanl2dz basis set, as compared with the Mulliken charges while the Mulliken charges on the N7 and N8 atoms in both media at B3LYP/3-21G* level of theory show the most negative values, as observed in Table S4. The analysis of these charges on the iodine atoms shows that the NPA charges using both basis sets predicted higher values than those corresponding to the Mulliken ones. When we analysed the bond orders, expressed as Wiberg indexes, whose results are presented in Table S5, we observed that the Lanl2dz basis set predicted higher values for the I, N, C and H atoms in general and, lower values for the O atoms. Note that the higher bond order values are observed in the O5 and O6 atoms, as expected due to that their bonds have the double character.

A very important result was observed when the molecular electrostatic potential surface mapped was investigated for C5 in the gas phase at the B3LYP/3-21G* level of theory because the expected sites reacting with potential biological nucleophiles or electrophiles were clearly observed, as shown Figure S5. Thus, this map has shown strong red colors on the O4, O5 and O6 atoms indicating nucleophilic sites reacting with potential biological electrophiles while the blue colours are observed on the H25, H27 and I1 atoms indicating these sites as electrophilic sites reacting with potential biological nucleophiles. Obviously, the mapped surface observed in the C5 configuration compared with that corresponding to the most stable C3 conformer of thymidine (Figure S6) could explain the higher experimental antiviral property observed for IDU than thymidine.

3.4. NBO and AIM analysis

Evidently, the C-I, C=O, N-H and OH groups and N and O atoms lone pairs belonging to the C5 structure of IDU contribute to their energetic stability and, for this reason, the knowledge of the type and interaction degree among those groups is important in order to understand the chemical and biological properties of these species in the different media. Hence, NBO [34] and AIM [36] calculations were employed to compute the stabilization energies and some topological parameters of interest to evaluate the type and degree of interaction. Particularly, in this study, we observed the importance of the basis set on the observed properties. Thus, for C5, five main delocalization energy values are observed in Table S6 using the Lanl2dz basis set, which are the $\Delta E_{\sigma\rightarrow\sigma^*}$, $\Delta E_{\pi\rightarrow\pi^*}$, $\Delta E_{n\rightarrow\sigma^*}$, $\Delta E_{n\rightarrow\pi^*}$ and $\Delta E_{\pi^*\rightarrow\pi^*}$ charge transfers while when the 3-21G* basis set is used appear a new $\Delta E_{\sigma\rightarrow\pi^*}$ charge transfer while disappearing the $\Delta E_{\pi^*\rightarrow\pi^*}$ charge transfer. Besides, two new $LP(2)O2\rightarrow\sigma^*_{N7\text{-}C10}$ and $LP(2)O3\rightarrow\sigma^*_{O4\text{-}H28}$ charge transfers are observed in both media using the 3-21G* basis set. Note that using both bases sets the $\Delta E_{\sigma\rightarrow\sigma^*}$ charge transfers are very weak as compared with the other ones while the higher values are calculated for the $\Delta E_{n\rightarrow\sigma^*}$ charge transfers. This way, the total ΔE_{Total} contribution result higher using the Lanl2dz basis set than the other one due to the additional $\Delta E_{\pi^*\rightarrow\pi^*}$ charge transfer observed only for this basis set. The study in both media reveals the high stability of C5 due to the stabilization energies, which are mainly associated to the presence of double C=O and C=C bonds and the lone pairs of the I, O and N atoms, as indicated in Table S5. Here, the antiviral activity observed for IDU could in part be justified only using the 3-21G* basis set because the calculations show slightly polarizations of the C16←I1 bonds from the I1 atom (polarized a 42.31%) toward the C atoms (polarized a

57.69%) and, also, the presence of electrons available in the *d* orbitals (0.44%) of the iodine atom. On the contrary, the Lanl2dz basis set reveals only the I1 atom polarized a 41.98% and the C atoms polarized a 58.02%.

The topological properties for C5 in both media using both basis sets were also computed with the AIM2000 program [36] in the bond critical points (BCPs) and ring critical points (RCPs), as predicted the Bader's theory [35]. Hence, the intra-molecular interactions observed were characterized by using four parameters: (i) electron density distribution, $\rho(r)$, (ii) the Laplacian values, $\nabla^2\rho(r)$, (iii) the eigenvalues $(\lambda 1, \lambda 2, \lambda 3)$ of the Hessian matrix and, (vi) the $\lambda 1/\lambda 3$ ratio. In fact, the interaction is covalent if $\lambda 1/\lambda 3 > 1$, $\nabla^2\rho(r) < 0$ and $\rho(r)$ and $\nabla^2\rho(r)$ have high values while in the highly polar covalent or of hydrogen bonds ionic interaction those values are: $\lambda 1/\lambda 3 < 1$ and $\nabla^2\rho(r) > 0$ [47]. Here, the results for C5 in both media using both methods are presented in Table S7 and the same reveal different interactions, as observed in Figure S7 using the 3-21G* basis set. Thus, with this basis set three BCPs and five RCPs in the gas phase are observed for C5 in gas phase where, RCP1, RCP2, and RCP3 are the new RCPs formed by the three O---H BCPs and, where RCP_B and RCP_S are those RCPs corresponding to the base and sugar rings, respectively. In solution with this basis set, only two BCPs are predicted. Note that the lanl2dz basis set predicted in gas phase only two BCPs (O2---H26 and O3---H28) which are similar to those observed in solution by using 3-21G* basis set while in solution with the lanl2dz basis set, only the O5---H19 interaction and a new RCP with the same properties are observed. Obviously, the high stability of C5 is evidenced by these H bonds interactions, as can be seen in Table S7. Both NBO and AIM studies support the high stability of C5 in both media and, moreover, show the importance of the basis set on the determination of these properties. When the $\rho(r)$ and $\nabla^2\rho(r)$ values for both rings of IDU are compared with the values corresponding to the most stable C3 conformer of thymidine we observed that the effect of change the CH_3 group by an iodine atom is to increase those two values of the sugar ring ($\rho(r)$= 0.0386 a.u. and $\nabla^2\rho(r)$ = 0.2756 a.u.) while the values for the base ring decrease up to ($\rho(r)$= 0.0190 a.u. and $\nabla^2\rho(r)$ =0.1484 a.u.). The differences observed are justified because the calculations were performed on different basis sets.

3.5. Gap and descriptors values

Many works have reported the importance of the use of the frontier orbitals to predict reactivity and behaviors of species with different biological properties in diverse media [19,25-31]. Thus, for the C5 configuration of IDU in both media, the HOMO-LUMO orbitals and the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (E) descriptors were calculated at B3LYP/Lanl2dz and 3-21G* levels of theory. These properties are presented in Table S8 compared with the corresponding values for the antiviral thymidine [19] and brincidofovir agents, where the latter antiviral drug is used for the treatment of the *Ebola* disease [31]. The results show different behavior with the basis set and with the medium considered. Thus, the calculations using both basis sets show that C5 is less reactive in gas phase than in aqueous solution and, also, it is most reactive than thymidine and less than brincidofovir. Hence, the interchange of an iodine atom by a CH_3 group increases notably their reactivities in both media and with the two basis sets, as proposed by Camerman and Trotter [18]. Here, the low gap and global hardness (η) values and, the high global softness (S) values for brincidofovir could explain their high reactivity against to idoxuridine and thymidine. Besides, the pyrimidine ring of brincidofovir present high values of $\rho(r)$= 0.0212 a.u. and $\square^2\rho(r)$= 0.1644 a.u., as compared with the values of the base in IDU.

3.6. NMR study

Tables S9 and S10 show for the C5 isomer of IDU in aqueous solution the ^{1}H- and ^{13}C-NMR chemical shifts, respectively by using the GIAO method [43] at the B3LYP/Lanl2dz and 3-21G* levels of theory. These values were compared with the corresponding experimental available for thymidine in DMSO-d6 and D_2O from Refs. [48,49] by means of the RMSD values. Note that the better correlation is observed for the H nuclei (2.34-2.33 ppm) whose little differences could be attributed: (i) to that thymidine differs of idoxuridine by a CH_3 group, (ii) to the medium, because the theoretical values were calculated in aqueous solution while the experimental ones were registered in DMSO-d6 solution and, (iii) to the presence of intra-molecular O---H bonds where the H25 and H28 atoms are involved, as observed by the MEP map and AIM studies. Note that both methods predicted very low values for those two H atoms in relation to the experimental ones observed of 5.25-5.04 ppm. In relation to the calculated chemical shifts for the ^{13}C nucleus, we observed that the Lanl2dz basis set predicted slightly higher values than the experimental ones, as can be seen in Table S10.

Obviously, the correlation for these atoms isn't very good due to presence of the CH_3 group in thymidine that modify principally the properties of the pyrimidine ring including the dipole moment value that increases in solution up to 11.02 D, in relation to idoxuridine whose dipole moment values are 9.14 and 4.00 D using the Lanl2dz and 3-21G* basis sets, respectively. Possibly, another isomer of idoxuridine can be present in the solution that modifies the chemical shifts, as reported for the antiviral emtricitabine by Shi-Yun et al. [50].

3.7. Vibrational analysis

To perform this analysis we have considered the C4 and C5 isomers because these species are energetically stables using the Lanl2dz basis set while using the other one basis set C5 is the only stable. In Figure 2 it is compared the available infrared spectrum of idoxuridine taken from Ref [51] in Mujol mull with the corresponding predicted for C4 and C5 by using both levels of calculations while their predicted Raman spectra for these species are compared in Figure 3 with the available experimental in the solid phase taken from Ref. [52]. The influence of the basis set on the infrared spectrum of the C5 isomer of idoxuridine in gas phase using the hybrid B3LYP method and 3-21G* and Lanl2dz levels of theory can be clearly seen in Figure S8. Note that the presence of the dimeric species justifies the two strongest bands observed in the infrared spectrum in the higher wavenumbers region. The optimized structures of both species using the two basis sets present C_1 symmetries and 78 normal vibration modes where all these modes have activity in IR and Raman. The observed and calculated wavenumbers and assignments for the C4 and C5 isomers of idoxuridine are summarized in Table 3. In fact, in this table we have also added the IR bands of IDU in the solid phase taken from Ref [53]. The vibrational assignments were performed following the SQMFF procedure [32] with the Molvib program using both levels of approximations. In this case, to calculate the corresponding harmonic force fields we used scale factors defined for the 6-31G* basis set [32]. The assignments for some groups are discussed below.

3.7.1. Band Assignments

Region 4000-2500 cm^{-1}. In this region, the N-H, OH and C-H stretching modes and, the CH_2 antisymmetric and symmetric modes are expected for C4 and C5 in both media. In general, we observed that the SQM calculations for C5 using the Lanl2dz basis set predicted the frequencies to higher wavenumbers than the 3-21G* basis set, as observed in Table 3. Hence, the broad and intense IR band at 3319 cm^{-1} can be easily assigned to the N-H, OH and C-H

stretching modes while the weak Raman band at 3088 cm^{-1} and the very intense band at 2866 cm^{-1} are assigned to the antisymmetric and symmetric CH_2 stretching modes, respectively and, to the C9-H18 and C12-H22 stretching modes, as predicted by SQM calculations. Note that the two intense bands predicted at 3370 and 3212 cm^{-1} in the IR spectrum of the dimer also support the two strong bands observed in the experimental IR spectrum, as shown Figure 2. Besides, these wide bands suggest the intra-molecular H bonds formation, as reported for the antiviral thymidine [19].

Region 2000-1000 cm^{-1}. The Lanl2dz and 3-21G* SQM calculations predicted modes strongly coupled in this region, thus between 1692 and 1542 cm^{-1} are predicted the C14=O5, C17=O6, C15=C16 stretching modes while between 1564 and 1400 cm^{-1} are predicted some in-plane N-H, C-H, and OH deformation modes together with the CH_2 deformation modes, hence, all these modes are associated with the bands observed in those regions, as indicated in Table 3. Probably, that coupling increase the intensities of the IR bands located at 1446 and 1258 cm^{-1} in the experimental spectrum. On the other hand, the CH_2 wagging, rocking and twisting modes and the N7-C15, N8-C14, N8-C17, C12-C13, C9-O3, C16-C17 stretching modes are also expected in this region, for this reason, the IR and Raman bands observed between 1401 and 1010 cm^{-1} are assigned to those vibration modes. Notice that for C5 in both media, the 3-21G* basis set predicted a deformation ring mode between 1039-1020 cm^{-1} while the remaining modes are predicted at lower wavenumbers. Additionally, we observed from Figure 2 that the IR spectrum for C5 using the 3-21G* basis set present a better concordance in this region with the corresponding experimental one.

Region 1000-20 cm^{-1}. Some expected C-O and N-C stretching and out-of-plane NH, CH and OH deformation modes in this region are strongly coupled among them and, besides, these modes are observed in different regions using the different basis sets, as can be seen in Table 3. For these reasons, all these modes were assigned in accordance with the calculations. In both conformers, the torsion rings modes are predicted using the two basis sets between 410 and 20 cm^{-1}, as shown in Table 3 while the SQM calculations with both bases sets predicted the C-I stretching modes between 215 and 193 cm^{-1}, for this reason, this mode in both isomers can be associated to the Raman band at 210 cm^{-1}.

3.8. Force fields

The harmonic force fields for C4 and C5 using the Lanl2dz and 3-21G* basis sets were computed with the SQM method [32] and the Molvib program [43] in order to obtain the harmonic force constants expressed in internal coordinates. Afterwards, these constants were compared with those calculated for the antiviral zalcitabine [54] using the B3LYP/6-31G* method in Table 5. The results for C4 and C5 show slight variations with the basis sets and with the different media employed, thus, the *f(νO-H)*, *f(νN-H)* and *f(νC=O)* force constants evidence the higher changes presenting the *f(νC=O)* constants the higher values using the 3-21G* basis set. Notice that for both conformers the $f(\nu C\text{-}O)_{OH}$, *f(νO-H)* and *f(νC=O)* force constants are slightly modified in solution as a consequence of the hydration of these sites with water molecules. The variation in the $f(\nu C\text{-}O)_{A5}$ constants corresponding to the sugar rings show the influence of the hydration of these OH sites on the C-O distances of the ribose ring. The higher force constant values for zalcitabine, in relation to idoxuridine can probably in part be justified because their values were calculated using the 6-31G* basis set and, in part by the absences of a C=O group and the presence of an NH_2 group in the pyrimidine ring and of an OH group in the sugar ring. In general, it is possible to observe a very good concordance in the force constant values in relation to those reported for compounds with similar groups [19,27-29].

4. UV-visible spectrum

In Figure 4 are presented the predicted electronic spectra for the C5 isomer of IDU in aqueous solution using both basis sets compared with the available experimental spectra for thymidine in aqueous solution [55] and for idoxuridine in methanol, water and 0.1 M HCl solutions [56,57] while in Table S11 are presented the positions and intensities of the observed bands and of the TD-DFT calculated absorption wavelengths. Note in all the cases the influence of the solvent on the positions of the two experimental bands. The assignments of these bands were performed taking into account the different charge transfers predicted by using NBO calculations. In fact, the position of the maxima in the different spectra can be attributed to the $n \rightarrow \pi^*$ transitions from the lone pairs of the *I1*, *N7*, *N8* atoms to the C=O and C=C antibonding orbitals, as was detailed in Table S6. When we compared the electronic spectra of thymidine and idoxuridine we observed clearly that the presence of a CH_3 group and the absence of a C=O in thymidine produce the shifting of both bands toward lower

wavelengths whiles the presence of the iodine atom and of two C=O groups in idoxuridine shift the bands towards higher wavelengths.

5. CONCLUSIONS

In the present work, the theoretical molecular structures of five isomers of idoxuridine, two *Cis*, and three *Trans* configurations, were determined by using the hybrid B3LYP method with the Lanl2dz and 3-21G* levels of theory in gas and aqueous solution phases. Here, the structural properties and the spectroscopic studies were performed only for the C4 and C5 isomers according to the experimental *anti*-structure reported for idoxuridine. Hence, the infrared, Raman, ^{1}H-NMR, ^{13}C-NMR and UV-visible spectra predicted for the two most stable isomers by using the 3-21G* basis set in the two studied media show a reasonable agreement with the corresponding available experimental spectra. The presence of bands associated with a dimeric species of idoxuridine was also evidenced in the experimental FTIR spectrum. The Mulliken, NPA charges, solvation energies and the NBO and AIM studies evidence clearly the notable influence of the basis set on the properties analyzed. Hence, the antiviral activity observed for IDU can in part be justified using the 3-21G* basis set because these calculations show slightly polarizations of the C16←I1 bonds and electrons available in the *d* orbitals of the iodine atom. The frontier orbitals show that the presence of the iodine atom in idoxuridine increases their reactivity as compared with thymidine while idoxuridine is less reactive than brincidofovir, an antiviral drug used against the *Ebola* disease.

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Table 1. **Comparison of calculated geometrical parameters for the most stable C5 isomer of Idoxuridine in gas and aqueous solution phases**

Parameters	B3LYP/LANL2DZ[a]		B3LYP/3-21G*[a]		Exp[b]
	Gas phase	PCM	Gas phase	PCM	
Bond lengths (Å)					
C16-I1	2.111	2.112	2.116	2.118	2.050
C16-C17	1.469	1.457	1.459	1.450	1.490
C15-C16	1.366	1.366	1.350	1.354	1.340
C17-O6	1.248	1.267	1.233	1.245	1.210
C17-N8	1.423	1.405	1.420	1.406	1.360
C14-N8	1.390	1.388	1.386	1.383	1.380
C14-N7	1.403	1.396	1.402	1.396	1.370
C15-N7	1.403	1.388	1.379	1.370	1.370
C10-N7	1.490	1.490	1.509	1.511	1.490
C10-O2	1.451	1.465	1.446	1.451	1.420
C12-O2	1.490	1.494	1.497	1.496	1.420
C10-C11	1.544	1.544	1.533	1.532	1.550
C9-C11	1.539	1.540	1.540	1.536	1.560
C9-C12	1.548	1.537	1.552	1.551	1.530
RMSD	**0.037**	**0.038**	**0.037**	**0.037**	
Bond angles (°)					
N8-C17-O6	119.8	119.6	120.7	120.5	121.0
N8-C14-O5	123.3	121.6	124.0	123.7	119.0
C17-C16-I1	118.3	119.1	116.4	116.5	119.0
C15-C16-I1	121.4	121.3	122.6	122.7	123.0
C14-N7-C15	122.0	121.3	122.0	122.2	123.0
N7-C10-O2	108.1	108.6	108.0	107.7	109.0
N7-C10-C11	114.0	113.9	111.4	111.3	114.0

C10-O2-C12	109.7	109.4	109.7	109.6	111.0
C11-C10-O2	105.4	106.2	106.1	106.8	109.0
C9-C11-C10	102.6	103.7	102.4	102.8	104.0
C9-C12-O2	105.7	104.3	104.9	104.4	110.0
C12-C13-O4	110.5	110.5	109.7	109.6	113.0
RMSD	**2.3**	**2.3**	**2.7**	**2.7**	
Dihedral angle (º)					
O2-C10-N7-C14	-168.7	-128.7	-179.9	-172.2	-67.0#
O2-C10-N7-C15	9.6	50.4	-6.8	5.3	81.0
C11-C10-N7-C14	74.3	112.9	63.7	70.8	
C11-C10-N7-C15	-107.2	-67.8	-123.1	-111.5	
N7-C15-C16-I1	179.9	179.9	-179.4	-179.7	
O2-C12-C13-O4	168.1	-174.4	-171.6	-178.3	
O2-C12-C9-O3	-95.7	-83.0	-147.8	-149.1	
N7-C10-O2-C12	-142.9	-123.8	-103.5	-109.8	
N7-C10-C11-C9	152.6	142.5	84.2	88.2	
RMSD#	**101.7**	**61.7**	**79.8**	**74.4**	
RMSD	**71.9**	**43.6**	**87.8**	**75.7**	

[a]This work, [b]From Ref [18]

Table 2. Calculated solvation energies (ΔG) for the stable C5 conformers of idoxuridine

PCM/B3LYP[a]			
ΔG (kJ/mol)			
LanL2DZ			
Conformers	$\Delta G_u^{\#}$	ΔG_{ne}	ΔG_c
C1	-147.94	24.95	-172.89
C2	-162.10	25.46	-187.56
C3	-157.38	26.12	-183.50
C4	-159.48	25.58	-185.06
C5	-137.18	25.58	-162.76
3-21G*			
C1	-74.49	25.00	-99.49
C2	-131.15	24.12	-155.27
C3	-110.28	25.37	-135.65
C4	-108.59	26.50	-135.09
C5	-99.67	24.83	-124.50

$\Delta G_c = \Delta G_{uncorrected}^{\#} - \Delta G_{Total\ non\text{-}electrostatic}$

Table 3. Observed and calculated wavenumbers (cm^{-1}) and assignments for the C4 and C5 isomers of idoxuridine in gas phase and aqueous solution

Experimental			B3LYP/LANL2DZ[a]								B3LYP/3-21G*[a]			
			C5				C4				C5			
			Gas phase		Aqueous solution		Gas phase		Aqueous solution		Gas phase		Aqueous solution	
IR[b]	IR[c]	Raman[d]	SQM[e]	Asignment	SQM[e]	Asignment	SQM[e]	Asignment	SQM[e]	Asignment	SQM[e]	Asignment	SQM[e]	Asignment
			3549	νO3-H25	3546	νO4-H28	3544	νO3-H25	3535	νO4-H28	3389	νN8-H27	3377	νO3-H25
3359 sh	3388 m		3498	νO4-H28	3535	νO3-H25	3526	νO4-H28	3535	νO3-H25	3376	νO3-H25	3354	νN8-H27
3319 s	3343 sh		3457	νN8-H27	3433	νN8-H27	3457	νN8-H27	3422	νN8-H27	3242	νO4-H28	3141	νC15-H26
3240 sh		3203sh	3143	νC15-H26	3138	νC15-H26	3138	νC15-H26	3136	νC15-H26	3132	νC15-H26	3065	νO4-H28
	3176 w	3088w	3040	$\nu_s CH_3$(C13)	3062	νC10-H19	3073	$\nu_s CH_3$(C13)	3064	νC10-H19	3064	$\nu_s CH_3$(C11)	3063	$\nu_s CH_3$(C11)
	3028 sh	3028w	3038	$\nu_s CH_3$(C11)	3047	$\nu_s CH_3$(C13)	3044	$\nu_s CH_3$(C11)	3056	$\nu_s CH_3$(C13)	3005	νC12-H22	3024	νC10-H19
2991 vw			2991	νC10-H19	3042	$\nu_s CH_3$(C11)	2994	νC10-H19	3042	$\nu_s CH_3$(C11)	3002	νC10-H19	3016	νC12-H22
	2952 vs	2977m	2985	νC9-H18	3003	νC9-H18	2965	$\nu_s CH_2$(C11)	3000	νC9-H18	2988	$\nu_s CH_3$(C13)	2993	νC9-H18
	2921 vs	2973sh	2966	νC12-H22	2981	$\nu_s CH_2$(C13)	2946	νC9-H18	2975	$\nu_s CH_2$(C11)	2977	$\nu_s CH_2$(C11)	2981	$\nu_s CH_2$(C11)
2866 vs	2863 sh	2949w	2961	$\nu_s CH_2$(C13)	2976	$\nu_s CH_2$(C11)	2928	$\nu_s CH_2$(C13)	2958	νC12-H22	2933	νC9-H18	2978	$\nu_s CH_3$(C13)
2826 vs	2851 vs	2921w	2958	$\nu_s CH_3$(C11)	2969	νC12-H22	2918	νC12-H22	2955	$\nu_s CH_3$(C13)	2883	$\nu_s CH_3$(C13)	2896	$\nu_s CH_3$(C13)
1689 vs	1702 vs	1695sh	1646	νC14=O5	1604	νC15=C16	1645	νC14=O5	1599	νC15=C16	1692	νC17=O6	1635	νC14=O5
1665 vs	1675 vs	1675vs	1617	νC17=O6	1564	βN8-H27	1616	νC17=O6	1558	νC14=O5	1679	νC14=O5	1616	νC17=O6
1600 m	1609 s	1608s	1583	νC15=C16	1542	νC17=O6	1582	νC15=C16	1542	νC17=O6	1587	νC15=C16	1575	νC15=C16
1445 s	1461 s	1464m	1448	δCH_3(C13)	1449	ρ'C10-H19	1445	δCH_3(C11)	1455	ρ'C10-H19	1503	δCH_3(C13)	1503	δC13O4H28
1434 sh	1427 w	1448sh	1443	δCH_3(C11)	1437	δCH_3(C13)	1425	δCH_3(C13)	1429	δCH_3(C13)	1489	δC13O4H28	1490	δCH_3(C13)
1416 w	1413 w	1416vw	1425	ρ'C10-H19	1424	δCH_3(C11)	1417	ρ'C10-H19	1426	δCH_3(C11)	1483	δCH_3(C11)	1459	δCH_3(C11)
1401 w		1397w	1399	ρ'C9-H18	1413	βC15-H26	1403	$wagCH_3$(C13)	1407	ρ'C9-H18	1417	βN8-H27	1422	ρ'C9-H18
1394 sh	1397 w		1394	βN8-H27	1407	ρ'C9-H18	1396	ρ'C9-H18	1400	βC15-H26	1415	ρ'C9-H18	1416	ρ'C10-H19
1385 w	1381 m		1389	$wagCH_3$(C13)	1396	ρC12-H22	1392	βN8-H27	1398	$wagCH_3$(C13)	1402	ρC12-H22	1402	βN8-H27
1373 sh		|	1373	ρC12-H22	1382	$wagCH_3$(C13)	1372	ρC10-H19	1372	βN8-H27	1395	ρ'C10-H19	1398	ρC12-H22
1369 m		1365sh	1371	ρC10-H19 βC15-H26	1379	νC14=O5	1361	ρCH_2(C13) δC13O4H28	1369	δC13O4H28	1376	ρC9-H18	1369	$wagCH_3$(C13)
1360 sh	1354 w	1353s	1358	δC13O4H28	1358	ρC10-H19	1356	ρC12-H22	1367	ρC10-H19	1353	ρC10-H19	1357	ρC10-H19
1341 w			1345	βC15-H26	1345	δC13O4H28	1343	βC15-H26	1352	ρC12-H22	1350	$wagCH_3$(C13)	1337	ρ'C10-H19 ρC10-H19
1337 sh			1334	βC15-H26 ρC9-H18	1341	δC13O4H28 νN7-C14	1334	ρC9-H18 $wagCH_3$(C11)	1340	ρC10-H19 ρ'C10-H19	1328	βC15-H26	1334	ρC9-H18
1328 sh			1327	ρC10-H19	1329	ρC9-H18	1325	ρC10-H19	1336	$wagCH_3$(C11)	1318	νN7-C14	1312	νN7-C14
1294 sh	1298 m	1313w	1313	ρ'C12-H22	1316	ρ'C12-H22	1301	ρ'C12-H22	1312	ρ'C12-H22	1287	ρ'C12-H22	1300	δC9O3H25
1289 m	1270 m	1269w	1283	$wagCH_3$(C11)	1291	$wagCH_3$(C11)	1281	$wagCH_3$(C11)	1293	ρC9-H18	1265	$wagCH_3$(C11)	1274	ρ'C12-H22
1258 s	1257 m		1265	νN7-C15	1257	νN8-C14	1262	νN7-C15	1258	νN8-C14	1256	δC9O3H25	1256	$wagCH_3$(C11)
1245 m		1241w	1209	ρCH_2(C13)	1215	ρCH_2(C11)	1212	ρC9-H18	1214	ρCH_2(C13)	1236	νN7-C15	1242	νN7-C15
1193 m	1206 w	1202m	1206	ρC9-H18	1202	δC9O3H25	1197	ρCH_2(C11)	1203	ρCH_2(C11)	1220	ρCH_2(C13)	1212	ρCH_2(C13)
1180 sh			1173	δC9O3H25 νN8-C14	1182	νN8-C17	1168	νN8-C14	1188	δC9O3H25	1187	ρCH_2(C11)	1181	ρCH_2(C11)
1169 sh	1150 w	1150w	1167	ρCH_2(C11)	1163	ρCH_2(C13)	1164	δC9O3H25	1166	νN7-C15	1114	νN8-C14	1126	νN8-C14
1132 sh			1114	νN8-C17	1136	νC12-C13	1112	νN8-C17	1131	νN7-C10	1083	νN8-C17	1105	νC12-C13
1095 s	1104 s	1098w	1100	νN7-C14 νC12-C13.	1114	νN7-C10	1083	νN7-C10 νC9-C12	1092	νC12-C13	1070	νC12-C13	1087	νN8-C17 βR_1(A6)
1065 m	1078 m	1074w	1051	νC9-O3	1050	νC10-C11	1070	νC12-C13	1064	νC12-C13	1045	νC9-O3	1038	δC9C12C13
1049 m	1061 w	1054w	1043	τCH_2(C11) νC10-C11	1028	νC9-C11	1037	νC10-C11	1029	νC9-O3 νC9-C11	1039	βR_1(A5)	1020	νC12-C13 βR_1(A5)
1022 w	1031 w	1027w	1010	νC9-C11	1008	νC16-C17	1013	νC9-C11	1006	νC16-C17	1021	γC15-H26	1004	γC15-H26
995 w	999 w	999w	988	νC13-O4	996	βR_1(A5)	985	βR_1(A6)	997	βR_1(A5)	1011	νC10-O2	991	νC9-O3
983 m	989 m		985	νC16-C17	965	νC13-O4	984	γC15-H26	968	γC15-H26	985	νC13-O4	981	νC16-C17

953 m	959 w	963w	976	γC15-H26	956	γC15-H26	968	νC13-O4	952	νC13-O4 τCH$_3$(C13)	975	νC16-C17 νN7-C14	972	νC13-O4	
948 sh			937	νC12-O2	930	τCH$_3$(C13)	952	νC10-O2	937	νC13-O4 νC10-O2	960	νC10-C11	961	νC10-C11	
912 m	919 w	915w	933	τCH$_3$(C13)	921	τCH$_3$(C11)	926	νC10-C11 νC10-O2	921	νC10-O2	936	τCH$_3$(C13) τCH$_3$(C11)	929	τCH$_3$(C13)	
907 m			900	νC10-O2	879	νC10-O2	901	τCH$_3$(C13) τCH$_3$(C11)	902	τCH$_3$(C11) νC9-C12	901	νC12-O2	906	νC12-O2 τCH$_3$(C11)	
880 w	886 w	883w	847	νC9-O3	854	νC9-O3	835	νC9-O3	832	νC9-O3	893	νC9-C11	892	νC10-O2	
873 w	877 w	859w	827	τCH$_3$(C11) βR$_i$(A5)	816	νC12-O2	819	βR$_i$(A5)	806	βR$_i$(A5)	863	τR$_i$(A6)	836	νC9-C11 τR$_i$(A6) γC17=O6	
795 vw			807	γN8-H27	789	τR$_i$(A6)	806	γN8-H27	782	τR$_i$(A6)	785	γC14=O5	785	γC14=O5	
775 w	782 w	780vs	783	νC9-C12	781	νC9-C12	788	νC12-O2	774	νC12-O2	773	νC9-C12	778	νC9-C12	
754 w	761 w	756w	747	βR$_i$(A6)	755	βR$_i$(A6)	767	βR$_i$(A5)	758	δO3C9C12	769	νN7-C10	769	δO2C10N7	
747 m	752 w	737sh	736	γC14=O5 γC17=O6	738	νN7-C14 γC14=O5 γC17=O6	745	νC16-C17 νN7-C14	752	νN7-C14	751	νC16-C17 βR$_i$(A6)	755	νN7-C10	
717 vw	726 w		719	βR$_i$(A5)	718	νC9-C12 νC9-O3	736	γC14=O5 γC17=O6	740	γC14=O5 γC17=O6	732	γN8-H27	724	βR$_i$(A5)	
709 vw	695 w	691sh	709	τR$_i$(A6)	708	γN8-H27	709	τR$_i$(A6)	684	βR$_i$(A5)	719	βR$_i$(A5)	700	τO4-H28	
670 vw	675 w	672w	660	βN7-C10	680	βR$_i$(A5)	666	βN7-C10	673	γN8-H27	658	βC14=O5	673	γN8-H27	
	639 m	637w	624	βC17=O6	636	βC14=O5	618	βC14=O5	631	βC14=O5	636	βR$_i$(A5) δO3C9C12	652	βC14=O5	
	609 w	605w	592	βR$_i$(A6) βR$_i$(A6)	605	βR$_i$(A6)	595	βR$_i$(A6) βR$_i$(A6)	604	βR$_i$(A6) βR$_i$(A6)	616	τO4-H28	635	δC9C12C13 δO3C9C12	
	560 m	560w	565	δC9C12C13	550	δO2C10N7	557	δO2C10N7 δN7C10C11	553	δO2C10N7	603	βR$_i$(A6)	605	βR$_i$(A6)	
537 vw	550w	548	δO2C10N7 δN7C10C11	548	δC9C12C13	491	δO3C9C12	494	δO2C12-C13	561	δO3C9C12	564	δO3C9C12		
517 vw		516	τO4-H28	483	δN7C10C11	463	δO2C12-C13	487	δN7C10C11	520	δO2C10N7	521	βR$_i$(A6)		
491 vw	482 w	445	δO2C12-C13	442	δO3C9C11	419	τR$_i$(A6)	440	γN7-C10	477	δN7C10C11	479	δN7C10C11		
482 vw	445w	431	δO3C9C11 τR$_i$(A6)	412	τR$_i$(A6)	408	βC17=O6	405	βC17=O6	438	τR$_i$(A6)	429	τR$_i$(A6)		
	395w	409	δO3C9C11 τR$_i$(A6)	399	βC17=O6	380	δO3C9C11	384	γC16-I1	403	βC17=O6	408	βC17=O6		
	369w	390	τR$_i$(A6) βC14=O5	349	γC16-I1	369	γC16-I1	375	δO3C9C11	392	δO2C12C13	390	δO2C12C13		
	332w	350	γC16-I1	304	τO4-H28	323	δC12C13O4	313	δC12C13O4	343	δO3C9C11	351	δO3C9C11		
		315	δO3-C9C12	281	δO3-C9C12	274	τO3-H25	276	τO4-H28	332	δC9C12C13	337	δC9C12C13		
	291w	292	τO3-H25	260	βN7-C10	272	τO3-H25	263	βN7-C10	290	δC12C13O4	297	δC12C13O4		
		270	γN7-C10	252	γC16-I1 δC9C12C13	250	τO4-H28	244	τO3-H25 γC16-I1	279	γC16-I1 γN7-C10	276	γN7-C10 γC16-I1		
	256w	241	δC12C13O4	233	βR$_i$(A6)	224	δC9C12C13	233	δO3C9C12 τR$_i$(A6)	237	τR$_i$(A6)	271	τO3-H25		
	234w	223	τR$_i$(A6) γC16-I1	217	τO3-H25	217	τR$_i$(A6) τR$_i$(A6)	229	τO3-H25	208	νC16-I1	231	τR$_i$(A6) τR$_i$(A6)		
	210w	201	νC16-I1	206	τR$_i$(A6)	191	νC16-I1	196	νC16-I1	200	τO3-H25	215	νC16-I1		
		187	τR$_i$(A6)	193	τR$_i$(A6) νC16-I1	179	τR$_i$(A6)	189	τR$_i$(A6)	198	τR$_i$(A6) τR$_i$(A6)	204	τR$_i$(A6) τR$_i$(A6)		
	162w	163	τR$_i$(A6) τR$_i$(A6) τR$_i$(A6)	179	τR$_i$(A6) τR$_i$(A6)	157	τR$_i$(A6) τR$_i$(A6)	171	δC9C12C13	192	τR$_i$(A6)	204	τR$_i$(A6)		
		125	τwC12-C13	123	δO2C12-C13	125	τR$_i$(A5)	121	τR$_i$(A5) τR$_i$(A5)	174	τwC12-C13	172	τwC12-C13		

109	βC16-I1	107	βC16-I1	114	γN7-C10	109	βC16-I1	139	τR$_i$(A6)	139	τR$_i$(A6) τR$_i$(A5)
90	τR$_i$(A5)	84	τR$_i$(A6) γN7-C10	89	βC16-I1	97	τwC12-C13	111	τR$_i$(A6) βC16-I1 βN7-C10	110	βC16-I1 βN7-C10
81	τR$_i$(A6)	68	τR$_i$(A6)	74	τwC12-C13	77	τR$_i$(A6)	87	τR$_i$(A5) τR$_i$(A6)	90	τR$_i$(A6) τR$_i$(A5)
56	τR$_i$(A6)	59	τwC12-C13 τR$_i$(A5)	56	τR$_i$(A6)	58	τR$_i$(A5)	55	τR$_i$(A5)	58	τR$_i$(A5)
30	τR$_i$(A5)	41	τwC10-N7	34	γN7-C10 τR$_i$(A5)	37	τR$_i$(A5)	33	τR$_i$(A5)	32	τR$_i$(A5)
20	τwC10-N7	35	τR$_i$(A5)	20	τwC10-N7	30	τwC10-N7	29	τwC10-N7	28	τwC10-N7

□ , stretching; □ , scissoring; wag, wagging or out of plane deformation; □ , rocking; □ , torsion; twist, twisting; a, antisymmetric; s, symmetric ; ip, in-phase; op, out-of-phase; R, ring; pyrimidine ring, (A6); sugar ring, (A5)

[a]This work, [b]From Ref [51], [c]From Ref [52], [d]From Ref [53], [e,f]From scaled quantum mechanics force field B3LYP/Lanl2dz, [g]From scaled quantum mechanics force field B3LYP/3-21G*

Table 4. Scaled harmonic force constants for the stable conformers of in gas and aqueous solution phases by using

Idoxuridine[a]							Zalzitabine[b]			
Force constant	B3LYP/LanL2dz				B3LYP/3-21G*		B3LYP/6-31G*			
	Gas		PCM		Gas	PCM	Gas		PCM	
	C4	C5	C4	C5	C5	C5	C1	C2	C1	C2
f(νO-H)	6.98	6.94	6.99	7.01	6.12	5.79	7.15	7.17	7.14	7.19
f(νN-H)	6.63	6.63	6.49	6.53	6.38	6.24	6.79	6.82	6.78	6.74
$f(\nu C\text{-}H)_{A6}$	5.39	5.41	5.37	5.38	5.38	5.41	5.30	3.48	5.38	5.31
$f(\nu C\text{-}H)_{A5}$	4.85	4.89	5.04	5.04	4.84	4.97	4.80	4.65	4.84	4.74
f(νC=C)	7.77	7.80	7.77	7.79	7.99	7.80	7.83	7.97	7.92	8.07
f(νC=O)	9.79	9.81	8.75	8.73	10.74	10.00	11.30	11.45	9.72	9.99
$f(\nu C\text{-}O)_{A5}$	3.94	3.92	3.68	3.71	4.01	3.96	4.36	4.47	4.68	4.27
$f(\nu C\text{-}O)_{OH}$	4.39	4.18	4.23	4.23	4.45	4.27	5.18	5.09	4.83	4.79
f(νC-N)	5.26	5.28	5.39	5.39	5.04	5.13	5.99	6.01	6.06	6.09
$f(\nu C\text{-}C)_{A6}$	4.87	4.85	5.16	5.17	4.62	4.85	5.57	5.55	5.73	5.73
$f(\nu C\text{-}C)_{A5}$	3.97	4.02	4.04	4.04	3.90	3.94	3.96	3.96	3.98	3.97
f(δH-C-H)	0.74	0.76	0.70	0.74	0.81	0.80	0.76	0.54	0.74	0.74
f(δC-O-H)	0.75	0.80	0.79	0.79	0.96	1.03	0.83	0.82	0.79	0.75

ν, stretching; *δ*, angle deformation.
Units in mdyn $Å^{-1}$ for stretching and mdyn Å rad^{-2} for angle deformations
[a]This work
[b]From Ref [54]