Theoretical studies of the rotational and tautomeric states, electronic and spectroscopic properties of favipiravir and its structural analogues: a potential drug for the treatment of COVID-19

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ABSTRACT
Favipiravir is a broad spectrum antiviral drug that has shown activity against many viruses. Sequel to the recent outbreak of COVID-19, favipiravir is investigated as one of the potential drugs for the treatment of SARS-CoV-2. To augment these efforts, this article reports the rotational isomers, tautomeric states, electronic and spectral properties of favipiravir and its five analogues (Cl, Br, H, CN and CH₃) using quantum chemical code. The enol forms are more stable and the calculated keto–enol relative energies are in the range of 7.86–10.72 kcal/mol in the gas phase and 1.07–3.46 kcal/mol in the solution phase. The relative stabilization of the more polar keto structure in water environment leads to a significant reduction in keto–enol relative energy by 68% for T705, 71% for T705–Cl and T705–Br, 86% for T1105 (H), 88% for T705–CN and 80% for T705–CH₃. The density functional theory and time-dependent density functional theory with the 6-311++G(d,p) basis set were used in the computation. The theoretical results were successfully compared with available experimental and theoretical data.

1. Introduction
Favipiravir (C₅H₄FN₃O₂, 6-fluoro-3-hydroxy-2-pyrazine carboxamide, T705) is a pyrazinecarboxamide based antiviral medicatin that has demonstrated activity against a number of viral infectious diseases such as influenza viruses (types A, B and C) [1], H5N1 virus [2], hepatotrophic pheleboviral disease [3], West Nile virus [4], Norwalk virus (norovirus) [5], encephalitis viruses [6], arenaviruses [7], bunyavirus [7] and Ebola virus [8,9].

Thus, favipiravir which is sold under the trade name Avigan is classified as a broad-spectrum antiviral agent that inhibits the replication of ribonucleic acid (RNA) viral infections [10]. Favipiravir was first reported in 2000 by Toyama Chemical Co., Ltd, Japan [11]. Due to its successful antiviral potency, various researchers have made considerable efforts to modify, optimize, and develop facile and cost effective routes to the synthesis of favipiravir [12–15]. Sequel to the recent outbreak of the novel Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the world, favipiravir is investigated as one of the potential drugs for the experimental treatment of the novel coronavirus disease [16–26].

Similarly, 3-hydroxy-2-pyrazinecarboxamide (T1105) which is a structural analogue of T705 has shown a good antiviral activity against influenza virus [27] and foot-and-mouth disease virus [9]. The T1105 and the brominated analogue of favipiravir (6-bromo-3-hydroxy-2-pyrazinecarboxamide, here after designated as T705–Br) are useful precursors for the synthesis of the stable and effective antiviral T1105–ribonucleotide and T705–Br–ribonucleotide prodrugs [28]. The chemical structures of favipiravir and its structural analogues are provided in Figure 1.

Favipiravir has a rotating carboxamide (CONH₂) moiety that makes it a potential pseudo base mimicking both guanine and adenine (as shown in Figure 2) similar to ribavirin, a broad spectrum antiviral RNA virus mutagen [29]. The virus mutagenic activity of ribavirin which was ascribed to the rotation of its carboxamide functional group could be applied to favipiravir and T1105. Similarly, the rotation of the hydroxyl (OH) group on pyrazine rings of T705 and T1105 can lead to another rotational conformer. In addition, these molecules have the potential to exhibit keto–enol tautomerism which could be of interest in drug design and development to determine which tautomeric form is bound to a target biomolecule. Despite the important applications of favipiravir, there are no systematic and comparative theoretical studies of the conformational analysis, electronic and spectroscopy properties of favipiravir and its structural analogues. Such studies will contribute to the understanding of the molecular structures, vibrational,
and electronic properties of favipiravir that could be used in the development of new pyrazinecarboxamide-based antiviral drugs. Thus, in this study, internal rotations of the carboxamide and hydroxyl groups of T705 and T1105 were examined to determine the different conformations of these molecules along the potential energy profile. The relative stability of the tautomeric states was determined in gas and aqueous solution. This work was extended to other structural analogues of T705 in which the fluorine atom was substituted with chlorine, bromine, cyano and methyl atoms/groups (Figure 1). In addition, detailed comparative studies of the structural, electronic and spectroscopic properties of the six molecules were carried out and the results were reported herein. The results and data from such studies could be useful at this moment of urgent need of the development of antiviral drugs for the treatment of novel COVID-19.

### 2. Computational method

Calculations were done using Density Functional Theory (DFT) method implemented on Gaussian 09 program package [30]. DFT methods are well known to give accurate and reliable description of the molecular geometry, rotational barrier, vibrational frequency and electronic properties of organic compounds [31–36]. The hybrid B3LYP functional [37, 38] method and the 6-311++G(d,p) basis set were used for the calculations. The internal rotations along the dihedral angles $\phi_1$(NC–CO) and $\phi_2$(NC–OH) (Figure 1) were carried out from 0 to 180° to determine the more stable conformer along the energy profiles of favipiravir and its structural analogues (Figure 1). The geometry of the minimum energy conformers was optimized with no restrictions, and the optimized structural parameters were used to calculate electronic parameter, NBO atomic charges, IR and UV-visible spectra. The molecules have the potential to exist in keto–enol tautomeric forms. Thus, the geometry optimizations of the tautomeric forms of the studied molecules were carried out to determine the keto–enol relative energies in gas and solution phases.

Water was used as a solvent, and the solution calculations were carried out using the Polarizable Continuum Model (PCM), as well as the integral equation formalism variant (IEF-PCM) [39], as implemented in Gaussian 09. Time dependent density functional theory (TD-DFT) was used for the electronic absorption spectra calculations. The normal vibrational modes were characterized on the basis of Potential Energy Distribution (PED) using the VEDA4 program [40]. The PED analysis requires the construction of 3N-6 linearly independent local mode coordinates that represent stretching, bending, and torsional motions in the molecule. The VEDA4 program automatically extracts input data from the Gaussian output files (.log and .fchk, renamed as .fch) and proposes an introductory set of local modes coordinates. More adequate coordinates are then proposed, and optimized by the program to obtain maximal elements of each coordinate of the PED matrix [41].

### 3. Result and discussion

#### 3.1. Structural parameters and potential energy profile analysis

The structures of favipiravir (T705) and its structural analogues (T705–Cl, T705–Br, T1105, T705–CN and T705–CH3) contain carboxamide (CONH2) and hydroxyl (OH) functional groups attached to the pyrazine at positions 2 and 3 respectively. Gas phase geometry optimization of these molecules was carried out at B3LYP/6-311++G(d,p) without any symmetry constraint and convergence criteria. Figure 3 shows the minimum energy geometry and atom numbering for T705 and its five other structural analogues. The bond lengths and some of the bond angles of the optimized structures are provided in Table 1 along with the experimental values for T705 [13]. The calculated structural parameters for T705 are excellent agreement with the experimental values obtained from the X-ray structure of T705. The root mean square deviation (RMSD) values and the correlation ($R^2$) between the experimental and theoretical values are determined to be 0.084/0.9865 for the

| Compound | X   | Name                                      | Designation    |
|----------|-----|-------------------------------------------|----------------|
| a        | F   | 6-fluoro-3-hydroxy-2-pyrazinecarboxamide  | T705 (Favipiravir) |
| b        | Cl  | 6-chloro-3-hydroxy-2-pyrazinecarboxamide  | T705-Cl        |
| c        | Br  | 6-bromo-3-hydroxy-2-pyrazinecarboxamide   | T705-Br        |
| d        | H   | 3-hydroxy-2-pyrazinecarboxamide           | T1105          |
| e        | CN  | 6-cyano-3-hydroxy-2-pyrazinecarboxamide   | T705-CN        |
| f        | CH3 | 6-methyl-3-hydroxy-2-pyrazinecarboxamide  | T705-CH3       |

Figure 1. Chemical structures of favipiravir and its structural analogues.
bond lengths, and 0.653/0.9852 for the endocyclic bond angles of the pyrazine ring.

The carbonyl (C9 = O10), hydroxyl (O14−H15) and C6−F8 bond lengths of T705 are calculated to be 1.237, 0.990 and 1.344 Å. These values are in agreement with the experimental values of 1.224, 0.8200 and 1.339 Å. The data in Table 1 show that these molecules adopt a planar geometry in which the pyrazine ring, carboxamide and hydroxyl groups lie in the same plane. The dihedral angles \( \phi_1(N1–C2–C9–O10) \) and \( \phi_2(N4–C3–O14–H15) \) that connect the carboxamide and hydroxyl groups to the pyrazine ring are calculated to be 180.0° for all the molecules. In general, the geometric parameters of the six molecules are very similar suggesting that the substitution of the fluorine atom of T705 with Cl, Br, H, CN and CH₃ has little or no effect on the structural parameter. The pyrazine rings C−N and C−C bond lengths for the six molecules are shorter than the normal C−N single bond value of 1.49 Å [42] and the normal C−C single bond of 1.54 Å [43]. The pyrazine bond lengths and angles are similar to the calculated values reported for 5-chloro-N-(3-nitrophenyl)pyrazine-2-carboxamide [44]. The carbonyl (C9 = O10) bond lengths are calculated to be 1.237 for T705, T705–Cl, T705–Br and T705–CN; and 1.238 Å for T1105 and T705–CH₃. The hydroxyl (O14−H15) bond lengths are calculated in the range of 0.989−0.994 Å while the N−H bond lengths of the amine group are determined to be 1.007 Å (N11−H12) and 1.009 Å (N11−H12) for the all the molecules. All these structural data are in agreement with the theoretical results reported by Lydia et al. [45].

### 3.2. Potential energy profile analysis

The minimum energy structure of these molecules has the nitrogen (N1) atom of pyrazine ring trans to the oxygen atom (O10) of the carboxamide group.
Table 1. Some of the optimized structural parameters for favipiravir and its analogues.

| Parameters | Expt. | T705 | T705–Cl | T705–Br | T1105 | T705–CN | T705–CH₃ |
|------------|-------|------|---------|---------|--------|---------|----------|
| R(N1–C2)  | 1.335 | 1.340 | 1.337   | 1.337   | 1.333  | 1.325   | 1.334    |
| R(N1–C6)  | 1.295 | 1.302 | 1.312   | 1.311   | 1.330  | 1.337   | 1.334    |
| R(C2–C3)  | 1.388 | 1.388 | 1.337   | 1.337   | 1.325  | 1.325   | 1.329    |
| R(C2–C9)  | 1.481 | 1.491 | 1.492   | 1.492   | 1.493  | 1.497   | 1.493    |
| R(C3–N4)  | 1.330 | 1.328 | 1.325   | 1.327   | 1.335  | 1.335   | 1.335    |
| R(C5–C6)  | 1.325 | 1.324 | 1.323   | 1.323   | 1.324  | 1.324   | 1.324    |
| R(C9–O10) | 1.224 | 1.237 | 1.237   | 1.237   | 1.237  | 1.237   | 1.237    |

Bond length (Å)

Bond angle (°)

Dihedral angle (°)

3.3. Keto–enol tautomerism

In addition to the rotational isomers discussed above, these molecules have the potential to exhibit keto–enol tautomerism as shown in Scheme 1. The tautomeric isomers of these molecules could be of interest in drug design and development to determine which tautomeric form is bound to a target biomolecule. Some of the molecules in drug discovery data base are potentially tautomeric, and the knowledge of the exact tautomer in different stages of drug design is very essential. Examples of drugs that have keto–enol potential include milrinone (Primacor), curcumin, warfarin (Coumadin), piroxicam and hydroxyquinoline [47–49]. Thus, the tautomeric isomers of these molecules were optimized at the same level of theory and the keto–enol relative energies (ΔE = Eₖeto − Eₐenol) for the six molecules were determined. The keto rotomer (B) was found to be more stable than keto (A) and as such keto (B) forms were used for all tautomeric calculations. The potential energy scan for rotation of the carboxamide group on the keto tautomers of the six molecules are presented in Figure 5.

The calculated gas phase keto–enol relative energies are 10.72, 10.34, 10.21, 20.1 kcal/mol for T705 and its halogenated analogues (T705–Cl and T705–Br); 19.4 kcal/mol for T1105, 20.1 kcal/mol for T705–CN, and 18.8 kcal/mol for T705–CH₃. Therefore, it could be concluded that the formation of pseudo base guanine-like conformer by this set of molecules is unlikely due to the relatively high energy difference. Similarly, internal rotations of the hydroxyl group from Φ₂ = 0° (where the N₄ atom of the pyrazine ring is cis to hydroxyl O₁₄) to Φ₂ = 180° (where N₄ is trans to hydroxyl O₁₄) were carried out. The molecules show similar PES pattern (Figure 4) with the trans NCOH conformer having the lowest energy and the transition state structure at dihedral angle (Φ₂) = 75°.
enol form is energetically favoured due to the aromatic character of the pyrazine ring which is absent in the ketone form. In addition, the enol form is stabilized by the intramolecular hydrogen bond between the hydrogen atom (H_{15}) of the hydroxyl group and the oxygen atom (O_{10}) of the carbonyl group. The keto form, however, has two non-conjugated carbonyl groups. The gas phase O_{14}−H_{15}⋯O_{10} intramolecular hydrogen bond distances are 1.723 Å (T705), 1.719 Å (T705–Cl), 1.720 Å (T705–Br), 1.715 Å (T1105), 1.697 Å (T705–CN), 1.724 Å (T705–CH_{3}), and the experimental value of 1.880 Å was reported for crystal structure of
T705. The dipole moments, keto–enol relative energies and Gibb’s free energies, and the percentage of the enol tautomer in both gas and aqueous media for all the molecules are presented in Table 2. The results suggest that the keto forms are unlikely to exist in the gas phase.

The geometry optimization of the tautomeric forms of the studied molecules was carried out in aqueous medium using the IEF-PCM solvation model [39] which was previously used for organic compounds [47,48]. The results of the calculations of the energies of the keto and enol forms in water environment as a solvent show strong stabilization of keto form. Although the aromaticity is not preserved, the keto form predominates in the in aqueous media. This is because the keto forms have higher dipole moment than the enol forms. The solution phase calculated relative energies are 3.46, 3.01, 1.12, 1.07, and 1.53 kcal/mol for T705, T705–Cl, T705–Br, T1105, and T705–CH3 respectively. The relative stabilization of the more polar keto structures in water environment leads to significant reduction in keto–enol energy differences. The reduction in energy gap is about 7 kcal/mol (for T705, T705–Cl, T705–Br, and T1105), 8 kcal/mol (for T705–CN) and 6 kcal/mol (for T705–CH3). The tautomeric N–H proton in keto form is available for interaction with proton acceptor solvent. In enol form, however, the interaction of tautomeric O–H proton with water molecules disrupts the intramolecular hydrogen bond. The effect of water in keto–enol equilibrium shift by the stabilization of one of the tautomers has been observed in piroxicam [47], curcumin [48] and pyrazine carboxamide based drugs [49]. The substitution of fluorine atom in T705 with Cl, Br, H, CN and CH3 leads to further stabilization of the keto tautomers in aqueous medium. The percentage of enol (provided in the last column of Table 2) decreases upon the replacement of fluorine atom in T705, with T-1105 having the highest reduction. However, the M06-2X/def2TZVP and TautLYP/6-31++G(d,p) showed that the T-1105 is unlikely to exist in the aqueous phase [50] but the gas phase results agree with what is reported herein. Though prediction of tautomeric equilibrium depends on the method of theoretical calculation, the availability of experimental data will help in clarifying the theoretical results.

### 3.4. Infra-red and UV-visible absorption spectra

The IR vibrational wavenumbers were obtained from the frequency calculations using the structural parameters of the more stable conformer of the studied molecules. T705, T705–Cl, T705–Br, and T1105 are composed of 15 atoms with 39 active vibrational modes. On the other hand, T705–CN and T705–CH3 contain 16 and 18 atoms which give 42 and 48 vibrational modes respectively. The vibrational wavenumbers (scaled and unscaled) and their corresponding intensities for the six molecules are provided in Tables S1–S6 of the supplementary information along with the proposed assignments of the vibrational modes. These molecules contain amide and hydroxyl functional groups at positions 2 and 3 of the pyrazine ring. For all the molecules, the calculated vibrational wavenumbers at around 3590 and 3560 cm\(^{-1}\) are attributed to N–H asymmetric and symmetric stretching. These modes are pure NH vibrations with 99% contributions to PED. The carbonyl C=O vibrations of these molecules are calculated to

### Table 2. Dipole moment (Debye), keto–enol relative energy (kcal/mol), keto–enol relative free energy (kcal/mol), and percentage enol for favipiravir and its analogues in gas and aqueous medium.

| Molecule | Gas Phase | Water medium |
|----------|-----------|--------------|
|          | Dipole moment | Dipole moment |
|          | Enol | Keto | \(\Delta E^a\) | \(\Delta G^b\) | % Enol | Enol | Keto | \(\Delta E^a\) | \(\Delta G^b\) | % Enol |
| T705     | 3.24 | 6.17 | 10.72 | 10.00 | 100 | 4.54 | 8.70 | 3.46 | 3.35 | 99.7 |
| T705–Cl  | 3.35 | 6.06 | 10.34 | 9.64 | 100 | 4.64 | 8.64 | 3.01 | 2.85 | 99.2 |
| T705–Br  | 3.40 | 5.97 | 10.21 | 9.43 | 100 | 4.71 | 8.58 | 2.92 | 2.64 | 98.9 |
| T1105    | 4.61 | 6.23 | 8.02  | 7.19 | 100 | 6.35 | 8.75 | 1.12 | 0.65 | 75.2 |
| T705–CN  | 2.75 | 7.38 | 9.23  | 8.45 | 100 | 3.51 | 10.40 | 1.07 | 0.99 | 84.2 |
| T705–CH3 | 5.19 | 6.07 | 7.86  | 7.79 | 100 | 7.11 | 8.68 | 1.53 | 1.84 | 95.8 |

\(^a\)Keto–enol relative energy, \(\Delta E = E_{\text{keto}} - E_{\text{enol}}\).

\(^b\)Keto–enol relative free energy, \(\Delta G = G_{\text{keto}} - G_{\text{enol}}\).

\(^c\)The percentage of enol at 298.15 K is calculated using \(K_{eq}\) derived from the equation \(\Delta G = RT \ln K_{eq}\).
be around 1600 cm\(^{-1}\), a wavenumber shorter than normal carbonyl absorption but typical of \(\text{C} = \text{O}\) stretching absorption band (amide I band) due to the resonance effect \([51]\). The resonance effect in the amide group increases the \(\text{C} = \text{O}\) bond length and reduces the frequency of absorption. The OH stretching modes are calculated to be around 3200 cm\(^{-1}\) (for T705, T705–Cl, T705–Br, T1105 and T705–CH\(_3\)) and 3145 cm\(^{-1}\) (for...
T705–CN). These are all pure OH vibrations with 99% contributions to PED.

The pyrazine ring CH stretching modes, which are all 100% pure modes with weak intensities, are estimated to be at 3045 cm$^{-1}$ for T705–CH$_3$, 3064 cm$^{-1}$ for T705–CN, and at around 3070 cm$^{-1}$ for T705, T705–Cl, T705–Br and T1105. The C≡N stretching of T705–CN is calculated to be at 2263 cm$^{-1}$, while the CH stretching of T705–CH$_3$ is determined to be at 3010, 2987 and 2934 cm$^{-1}$. The computed vibrational wavenumbers computed in this work agree quite well with those of previous theoretical study [45] as well as those reported for 5-chloro-N-(3-nitrophenyl)pyrazine-2-carboxamide [44]. Figure 6 shows the simulated infrared spectra of all the six studied molecules. This figure reveals the spectra characteristics of the molecules. The peaks associated with the carbonyl, amino, hydroxyl, cyano and methyl groups are assigned in the individual spectrum of the molecules.

Figure 7 shows the UV-visible absorption spectra of the studied molecules in methanol as a solvent. Time Dependent-DFT (TDDFT) with 6-311++G(d,p) basis set was used for the UV-visible absorption spectral calculations using the equilibrium structural parameters of molecules. The UV-visible spectrum absorption maximum values for T705, T705–Cl, T705–Br, T1105, T705–CN and T705–CH$_3$ were calculated to be 311, 315, 317, 323, 320 and 326 nm. These maximum absorption values are attributed to HOMO$\rightarrow$ LUMO transition with percentage molecular orbital contribution of about 99%. For the halogenated analogues, the absorption maximum ($\lambda_{\text{max}}$) slightly shifts to longer wavelength as the size of the halogen atom increases. The absorption wavelength ($\lambda$), excitation energies ($E$), and oscillator strengths ($f$) obtained from the TDDFT calculations for the first six transition of the studied molecules are provided in Table S7 of the supporting information. For all the molecules, the HOMO$\rightarrow$ LUMO transitions have the highest oscillator strength, and thus, the most probable transition. This transition is the second transition for all the molecules (Table S7).

### 3.5. Electronic properties

Figure 8 shows the 3D plots of Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) for T705 and its structural analogues. These plots are generated from optimized and frequency calculations. As clearly observed in the figure, the HOMO orbitals are spread over the entire molecules, while the LUMO orbitals are localized on the pyrazine ring and carboxamide group. The similarities in HOMO and LUMO energy values have reflected in the HOMO$\rightarrow$ LUMO energy gaps which are determined to be 4.52 (T705), 4.52 (T705–Cl), 4.52 (T705–Br), 4.52 (T1105), 4.52 (T705–CN) and 4.52 eV (T705–CH$_3$). For the halogenated molecules, the substitution of fluorine atom of T705 with chlorine (T705–Cl) and bromine (T705–Br) atoms leads to a slight decrease in HOMO–LUMO energy gap (T705(F) < T705–Cl < T705–Br) as the size of the halogen atom increases. Among the six molecules, T1105 has the highest HOMO–LUMO energy gap, while T705–Br has the lowest. The calculated HOMO, LUMO and HOMO–LUMO energy values are presented in Table 3 along with the global reactivity descriptors including ionization potentials (IP), electron affinity (EA), electronegativity ($\chi$), chemical hardness ($\eta$), chemical potential ($\mu$), chemical softness (S) and electrophilicity index ($\omega$). For halogenated molecules, there is no trend in the relationship between the electronegativity of the halogen atoms (F, Cl, and Br) and the electron affinity of the compounds (T705, T705–Cl and T705–Br). However, the substitution of fluorine atom with less electronegative Cl and Br atoms slightly decreases the IP, EN, $\eta$ and $\omega$ of the molecules. As evident in Table 3, T705–CN has the highest IP (7.81 eV), EA (3.13 eV), EN (5.47 eV) and $\mu$ ($-$5.47 eV); T705 has the highest $\chi$ (5.77 eV); T705–Br has the highest S (0.23 eV$^{-1}$); and T1105 has the highest $\eta$ (5.47 eV).

### 3.6. Atomic charges and molecular electrostatic potentials

The atomic charges were calculated from the B3LYP/6-311++G(d,p) equilibrium geometrical structures of the molecules using NBO method of the Gaussian 09. The atomic charges of T705 along with five other structural analogues are illustrated in Figure 9, and the corresponding values are given in Table S8. The charge distribution for all the molecules is similar but the magnitude of the charges is slightly different. For all the molecules, the N$_1$, N$_4$, O$_{10}$, N$_{11}$ and O$_{14}$ are negatively charged due to a relatively higher electronegativity of these atoms than carbon and hydrogen atoms. The hydrogen atoms (H$_7$ and H$_{15}$) are positively charged but hydroxyl H$_{15}$ is more positive due to the electron withdrawing effect of...
Figure 8. Frontier molecular orbitals for favipiravir and its analogues.

Table 3. Calculated HOMO and LUMO energies, HOMO–LUMO energy gap, and global reactivity descriptors for favipiravir and its analogues.

| Molecules   | HOMO   | LUMO   | Energy gap |
|-------------|--------|--------|------------|
| T705        | ![Image](image1) | ![Image](image2) | 4.52 eV    |
| T705–Cl     | ![Image](image3) | ![Image](image4) | 4.48 eV    |
| T705–Br     | ![Image](image5) | ![Image](image6) | 4.41 eV    |
| T1105       | ![Image](image7) | ![Image](image8) | 4.79 eV    |
| T705–CN     | ![Image](image9) | ![Image](image10) | 4.67 eV    |
| T705–CH₃    | ![Image](image11) | ![Image](image12) | 4.60 eV    |

adjacent O₁₄. The hydrogen atoms (H₁₂ and H₁₃) and carbonyl carbon atom C₉ of the carboxamide group are all positively charged with almost equal magnitude for all the molecules. The C₂, C₃ and C₅ of the pyrazine ring are positive but C₃ is more positive due to the influence of the hydroxyl O₁₄ attached to it. The significant
Figure 9. NBO atomic charges for favipiravir and its analogues.

difference in the charge distributions of the studied molecules is the atomic charge of C₆ which is calculated to be 0.552e for T705, 0.136e for T705–Cl, 0.067e for T705–Br, −0.012e for T1105, and 0.050e for T705–CN and 0.165e for T705–CH₃.

The possible interaction sites of the studied molecules are illustrated by molecular electrostatic potentials (MEP) surfaces (Figure 10). The MEP surface is colour coded to depict the variation of charge density. The regions that are prone to nucleophilic and electrophilic attacks are coded blue (positively charged) and red (negatively charged) respectively. The charge density on MEP surfaces are in consistent with the charge distribution provided in Table S8 and Figure 10. For all the molecules, the electrophilic region lies around amine moiety of carboxamide group. In contrast, the nucleophilic region spreads over the carbonyl oxygen, hydroxyl oxygen and the pyrazine ring nitrogen (N₁) ortho to the hydroxyl group. In addition, T705–CN has a strong nucleophilic centre around the cyano group. The nucleophilic nitrogen atom N₁ represents the potential protonation site for these molecules especially in biologically active environment. The pyrazine represents the potential site for
intramolecular interaction. T1105 and T705–CH$_3$ have a potential electrophilic region around methyl and hydrogen moieties attached to C$_5$ and C$_6$.

4. Conclusion

Theoretical analyses of a broad-spectrum antiviral drugs favipiravir (T705) and 3-hydroxy-2-pyrazine carboxamide (T1105) and their chlorine, bromine, cyano and methyl analogs were systematically carried to determine the more stable rotational isomer and tautomeric form in gas and aqueous phase. The results show that the formation of pseudo base guanine-like rotational conformer by this set of molecules is unlikely due to the relatively high energy differences. The more stable conformers have both dihedral angles $\phi_1$ (N1–C2–C9–O10) and $\phi_2$ (N4–C3–O14–H15), which are equal to $180.0^\circ$. This is an orientation that favours intramolecular hydrogen bonding. For the tautomeric studies, the aromatic enol tautomer is energetically more stable in the gas phase and aqueous medium. However, the tautomeric equilibrium is shifted towards the keto form in aqueous because the water environment stabilizes the more polar keto tautomer. The results suggest that the keto forms of the studied molecules are unlikely to exist in the gas phase, while the solution phases are predominantly enol tautomers with traces of keto tautomer except for T1105 with about 25% of keto form. The six molecules exhibit similar electronic properties, molecular electrostatic potential and charge distributions, and are therefore expected to have similar characteristics. This research gives precise and invaluable information that will help in understanding the structures and properties of favipiravir that could be used in the development of new pyrazinecarboxamide-based antiviral drugs.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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