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Conformational analysis and excited – state properties of a highly potent antiviral drug, 2-[(acetyloxy)methyl]-4-(2-amino-7*h*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (famciclovir)

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Abstract

2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (famciclovir) is a highly potent and selective antiviral treatment of herpes zoster, herpes simplex virus 2, and herpes labialis. Conformational analysis studies of famciclovir were based on Arguslab software. The molecular mechanics potential energy function were evaluated in terms of energies associated with bonded interactions (bond length, bond angle and dihedral angle) as well as non-bonded interactions (Vander Waals and electrostatic). Surfaces were created to visualize excited state properties such as highest occupied molecular orbital's, lowest unoccupied molecular orbital's and electrostatic potential (ESP) mapped density. The steric energy for famciclovir was calculated to be 0.15851213 a.u. (99.46795152 kcal/mol). The most energetically favourable conformation of famciclovir was found to have a heat of formation of 1029.1798 kcal/mol. The self-consistent field (SCF) energy was calculated by geometry convergence function using RHF/AM1 method in ArgusLab software. The most feasible position for famciclovir to act as a highly potent and totally selective aromatase inhibitor was found to be -146.3592324336 au (-91841.8878 kcal/mol)

Keywords: Arguslab, famciclovir, herpes zoster, herpes simplex virus 2, herpes labialis, conformation analysis,

1. Introduction

2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (Famciclovir) is used for the treatment of herpes zoster (shingles), Tyring and Barbarash (1995). herpes simplex virus 2 (genital herpes), *Luber and Flaherty (1996)*. herpes labialis (cold sores) in immunocompetent patients and for the suppression of recurring episodes of herpes simplex virus 2 *Spruance* and *Bodsworth (2006)*. Several studies in humans and mice provide evidence that early treatment with famciclovir soon after the first infection with herpes can significantly lower the chance of future outbreaks MedlinePlus Drug (2007). Following oral administration, famciclovir is deacetylated and oxidized to form penciclovir. 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (Famciclovir) is a prodrug of penciclovir, which has demonstrated inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). In cells infected with HSV-1, HSV-2 or VZV, the viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted by cellular kinases to the active form penciclovir triphosphate. Biochemical studies demonstrate that penciclovir triphosphate inhibits HSV-2 DNA polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.The energies computed by molecular mechanics are usually conformational energies. This means that the energy computed is meant to be an energy that will reliably predict the diference in energy from one conformation to the next. The effect of strained bond lengths or angles is also included in this energy. This is not the same as the total energies obtained from ab initio programs or the heat of formation from semiempirical programs. Molecular mechanics methods are not generally applicable to structures very far from equilibrium, such as transition

structures. Arguslab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway Peng (1995). Conformational analysis of molecule is based on molecular mechanics, it is a method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. The energy (E) of the molecule is calculated as a sum of terms as in equation (1) Cramer and Truhlar (1992).

$E = E_{stretching} + E_{bending} + E_{torsion} + E_{Vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond}$ + cross term (Equation 1)

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called force field Thompson (2004) .

We hereby present, *in silico* conformational analysis and excited – state properties of a highly potent and totally selective aromatase inhibitor , 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (famciclovir).

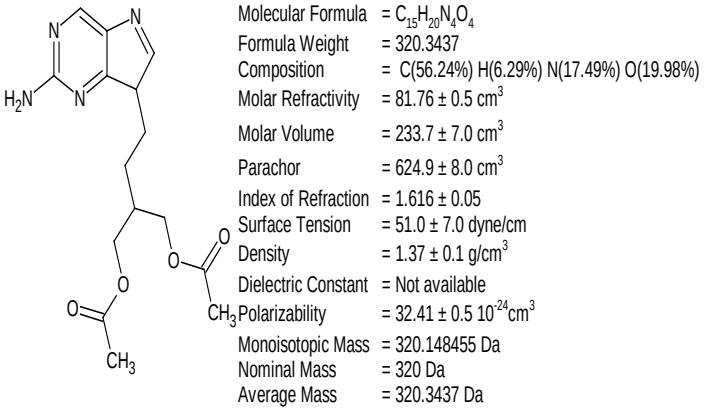
2. Materials and method

The structure of 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (famciclovir) was drawn and constructed using window based program of Arguslab [6] and ACDl ab ChemSketch [8] software. Conformational analysis (geometry optimization) of famciclovir was carried out using PM3 semi-empirical QM parameterization according to Hartree-Fock calculation method by ArgusLab 4.0.1 software. Geometry of the molecule was converged after the molecule was drawn and cleaned in Arguslab and the program computed the energy until the maximum cycles reached for the convergence (stopping point) of the molecule. Surfaces created to visualize the excited state properties such as orbital, electron densities, electrostatic potentials (ESP) mapped density. The final geometrical energy and SCF energy was calculated by RHF/AM1 method, as performed by Arguslab 4.0.1 suite.

3. Results and discussion

Atomic coordinates of famciclovir molecule is given in Table1. Bond length and bond angles are given in Tables 2 and 3 respectively, which are calculated after geometry optimization of famciclovir molecule from Arguslab by using molecular mechanics calculation. Tables 4, 5 and 6 shows the Mulliken atomic charges, ZDO atomic charges of famciclovir, Ground State Dipole (debye) of famciclovir and the calculated steric energy of famciclovir molecule respectively. Prospective view and calculated properties of Famciclovir molecule is shown in Figure1. The electron cloud density mapped, active conformation of famciclovir by Molegro molecular viewer software and active conformation of famciclovir by ACDlabs-3D viewer software is shown in Figures 2, 3 and 4 respectively. Figures 5 and 6 shows the highest occupied molecular orbital of molecule (HOMO) and the lowest unoccupied molecular orbital (LUMO) respectively, The positive and negative phases of the orbital are represented by two colors, the blue regions represent an decrease in electron density and the red regions shows a increase in electron density. Figure 7 shows electrostatic potential of molecular ground state mapped onto the electron density surface. The color map shows the ESP energy (in hartrees) for the various colors..

Heat of formation of 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (Famciclovir) was 1029.1798 kcal/mol. The standard heat of formation of a compound is the enthalpy change for the formation of 1 mole of the compound from its constituent elements in their standard states at 1 atmosphere. Its symbol is ΔH_f^{θ}. The steric energy calculated for famciclovir was 0.15851213 a.u. (99.46795152 kcal/mol) and SCF energy was found to be -146.3592324336 au (-91841.8878 kcal/mol) as calculated by RHF/AM1 using ArgusLab 4.0.1 suite**.** SCF was obtained as the minimum potential energy which is the needed energy for the interaction of drug with the receptor. The self-consistent field (SCF) energy is the average interaction between a given particle and other particles of a quantum-mechanical system consisting of many particles. Beacause the problem of many interacting particles is very complex and has no exact solution; calculations are done by approximate methods. One of the most often used approximated methods of quantum mechanics is based on the interaction of a self-consistent field, which permits the many-particle problem to be reduced to the problem of a single particle moving in the average self-consistent field produced by the other particles.



2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate

Figure 1: Prospective view of Famciclovir by ACD/ChemSketch

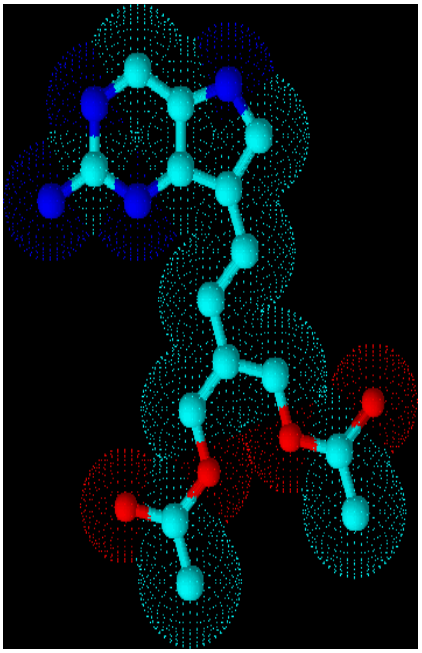


Figure 2: Electron density clouds of Famciclovir by ACD Labs3D Viewer

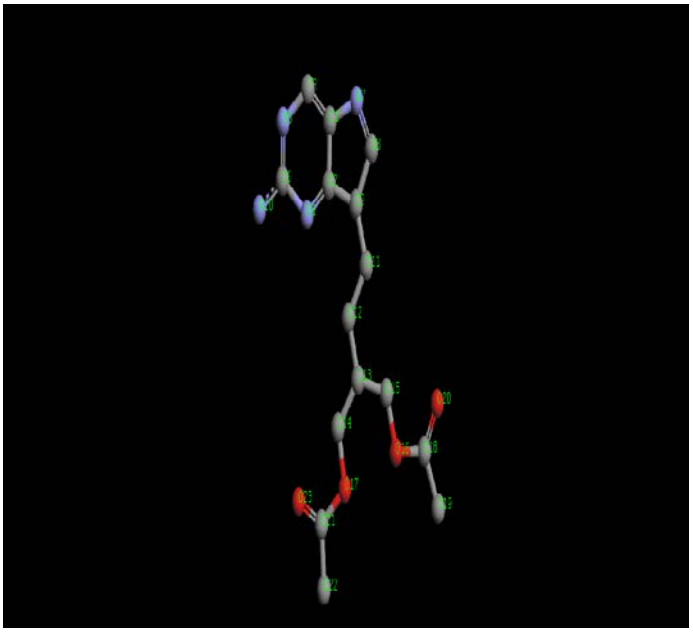


Figure 4: Prospective view of active comformation of Famciclovir by Arguslab

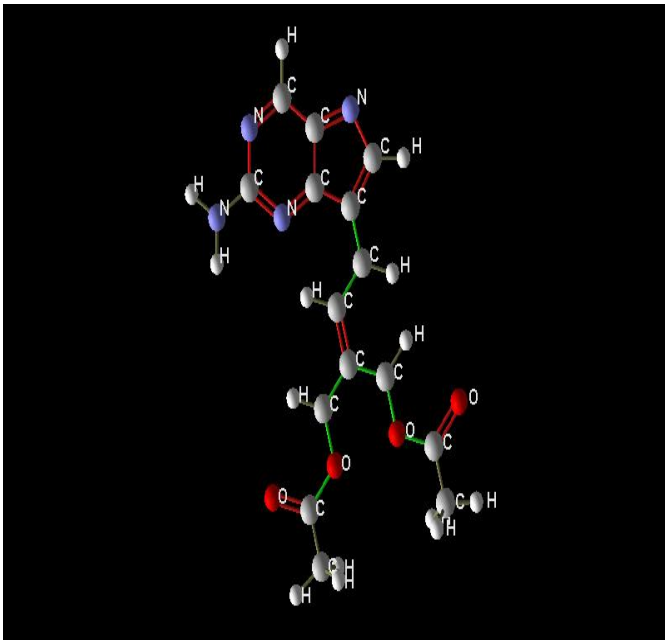


Figure 3: Prospective view of active comformation of Famciclovir by Molegro molecular viewer

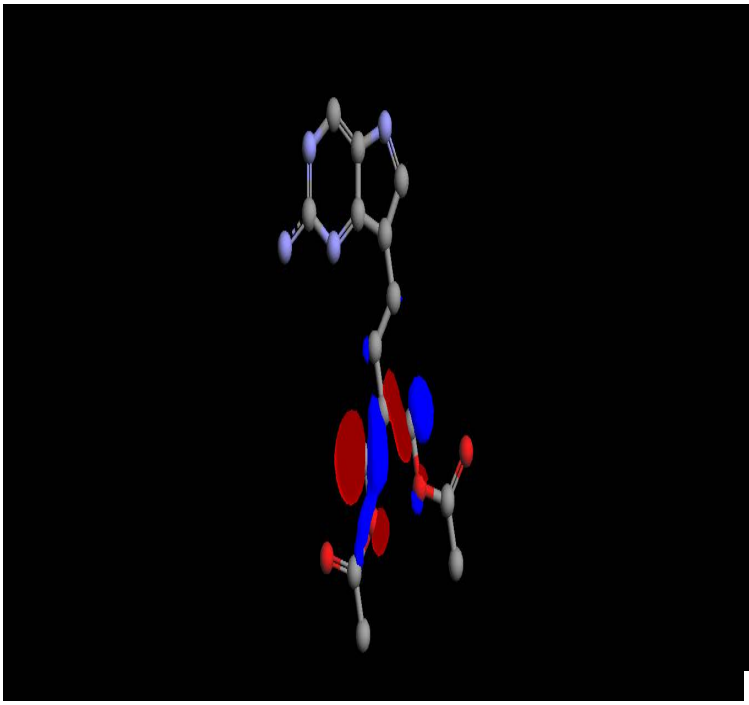


Figure 5 : Highest occupied molecular orbital's (HOMO) of Famciclovir

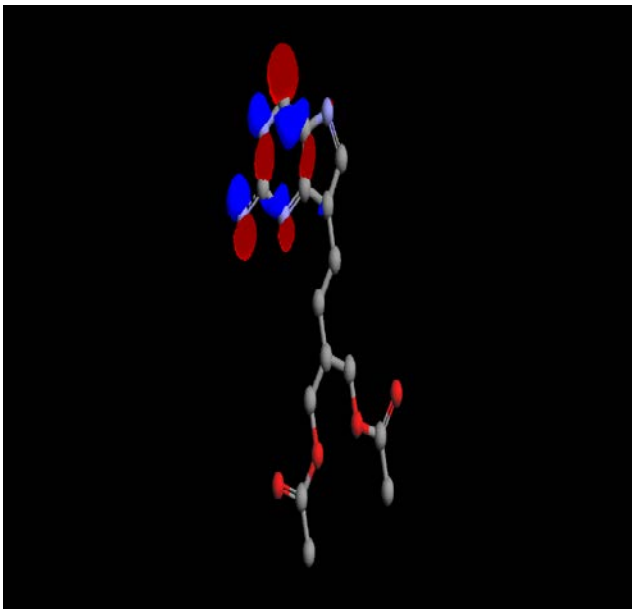


Figure 6 : Lowest unoccupied molecular orbital's (LUMO) of Famciclovir

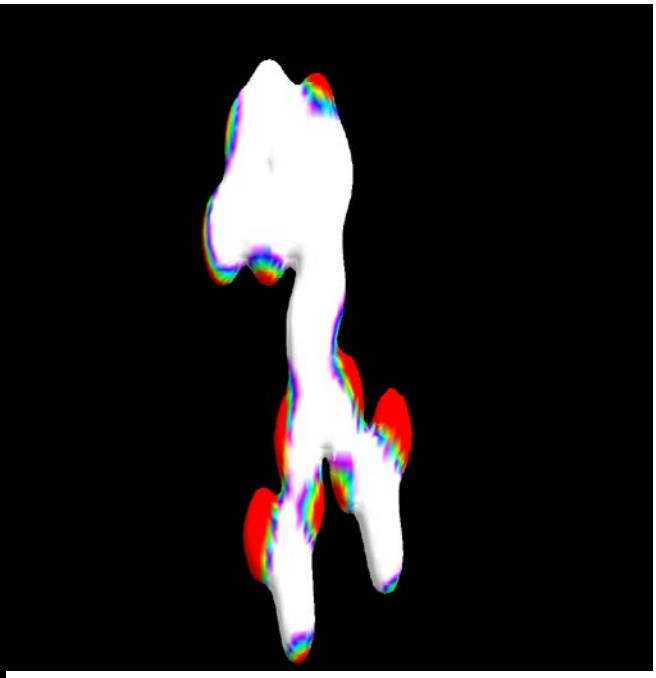


Figure 7: Electrostatic potential mapped density of Famciclovir

Table 1: Atomic Coordinate of Famciclovir

S.NO	Atoms	X	Y	Z
1	C	17.929100	8.260400	0.000000
2	C	17.929100	9.590400	0.000000
3	C	16.777200	7.595400	0.000000
4	N	16.777200	10.255400	0.000000
5	N	15.625400	8.260400	0.000000
6	C	15.625400	9.590400	0.000000
7	N	19.193900	7.849500	0.000000
8	C	19.975700	8.925400	0.000000
9	C	19.194100	10.001400	0.000000
10	N	14.473600	10.255400	0.000000
11	C	19.605200	11.266300	0.000000
12	C	18.715300	12.254800	0.000000
13	C	19.126400	13.519600	0.000000
14	C	18.236500	14.508100	0.000000
15	C	20.427300	13.796100	0.000000
16	O	20.838400	15.061000	0.000000
17	O	18.647500	15.772900	0.000000
18	C	22.139300	15.337400	0.000000
19	C	22.550400	16.602300	0.000000
20	O	23.029200	14.349000	0.000000
21	C	17.757600	16.761400	0.000000
22	C	18.168700	18.026300	0.000000
23	O	16.456700	16.484900	0.000000

Table 2: Bond length of famciclovir

Atoms	Bond length
1 3 (C)-(C)	1.323387
1 7 (C)-(N)	1.433804
1 2 (C)-(C)	1.458000
2 4 (C)-(N)	1.301961
2 9 (C)-(C)	1.458000
3 5 (C)-(N)	1.433804
4 6 (N)-(C)	1.433804
5 6 (N)-(C)	1.301961
6 10 (C)-(N)	1.343384
7 8 (N)-(C)	1.301961
8 9 (C)-(C)	1.458000
9 11 (C)-(C)	1.461000
11 12 (C)-(C)	1.464000
12 13 (C)-(C)	1.464000
13 14 (C)-(C)	1.464000
13 15 (C)-(C)	1.464000
14 17 (C)-(O)	1.410739
15 16 (C)-(O)	1.410739
16 18 (O)-(C)	1.410739
17 21 (O)-(C)	1.410739
18 19 (C)-(C)	1.464000
18 20 (C)-(O)	1.260307
21 22 (C)-(C)	1.464000
21 23 (C)-(O)	1.260307

Table 3: Bond Angles of Famciclovir

Atoms	Bond angles	Alternate angles
3 1 7 (C)-(C)-(N)	120.000000	295.980973
3 1 2 (C)-(C)-(C)	120.000000	216.488007
1 3 5 (C)-(C)-(N)	120.000000	295.980973
7 1 2 (N)-(C)-(C)	120.000000	257.053574
1 7 8 (C)-(N)-(C)	120.000000	227.506158
1 2 4 (C)-(C)-(N)	120.000000	294.480480
1 2 9 (C)-(C)-(C)	120.000000	188.442082
4 2 9 (N)-(C)-(C)	120.000000	294.480480
2 4 6 (C)-(N)-(C)	120.000000	227.506158
2 9 8 (C)-(C)-(C)	120.000000	188.442082
2 9 11 (C)-(C)-(C)	120.000000	187.861407
3 5 6 (C)-(N)-(C)	120.000000	227.506158
4 6 5 (N)-(C)-(N)	120.000000	402.764879
4 6 10 (N)-(C)-(N)	120.000000	385.642256
5 6 10 (N)-(C)-(N)	120.000000	446.697620
7 8 9 (N)-(C)-(C)	120.000000	294.480480
8 9 11 (C)-(C)-(C)	120.000000	187.861407
9 11 12 (C)-(C)-(C)	120.000000	186.707708
11 12 13 (C)-(C)-(C)	120.000000	186.134654
12 13 14 (C)-(C)-(C)	120.000000	186.134654
12 13 15 (C)-(C)-(C)	120.000000	186.134654
14 13 15 (C)-(C)-(C)	120.000000	186.134654
13 14 17 (C)-(C)-(O)	120.000000	236.478255
13 15 16 (C)-(C)-(O)	120.000000	236.478255
14 17 21 (C)-(O)-(C)	104.510000	300.539799
15 16 18 (C)-(O)-(C)	104.510000	300.539799
16 18 19 (O)-(C)-(C)	120.000000	236.478255
16 18 20 (O)-(C)-(O)	120.000000	353.333872
17 21 22 (O)-(C)-(C)	120.000000	236.478255
17 21 23 (O)-(C)-(O)	120.000000	353.333872
19 18 20 (C)-(C)-(O)	120.000000	275.966448
22 21 23 (C)-(C)-(O)	120.000000	275.966448

Tables 4: ZDO atomic charges and Mulliken atomic charges of Famciclovir

S.NO	Atoms	ZDO	Mulliken
1	C	0.0459	0.0519
2	C	-0.0817	-0.0841
3	C	0.1200	0.1496
4	N	0.0260	-0.0257
5	N	-0.0172	-0.0924
6	C	-0.0865	-0.0153
7	N	-0.1268	-0.1712
8	C	-0.0527	0.0578
9	C	-0.1131	-0.1595
10	N	0.0719	0.0763
11	C	0.2129	0.2143

12	C	0.0781	0.0962
13	C	-0.0985	-0.1520
14	C	0.2897	0.3370
15	C	0.2483	0.3016
16	O	-0.0829	-0.1571
17	O	-0.0790	-0.1533
18	C	-0.0460	-0.0731
19	C	0.2868	0.3648
20	O	-0.4081	-0.4191
21	C	-0.0499	-0.0771
22	C	0.2803	0.3586
23	O	-0.4175	-0.4283

Table 5: Ground State Dipole (debye) of famciclovir

X	Y	Z	Length
-2.38893272	-0.40809964	-0.00000000	2.42353974

Table 6: Final energyevaluation of famciclovir.

S.No.	Force field	Energy components (au)
1	Molecularmechanics bond (Estr)	0.00398749
2	Molecular mechanics angle (Ebend)+ (Estr-bend)	0.06595007
3	Molecularmechanicsdihedral (Etor)	0.06374400
4	MolecularmechanicsImpTor (Eoop)	0.00000000
5	MolecularmechanicsvdW (EVdW)	0.02483057
6	Molecularmechanics coulomb (Eqq)	0.00000000
Total		0.15851213 a.u. (99.46795152 kcal/mol)

Conclusion

Arguslab software was used to study 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (Famciclovir) an antiviral drug. The excited state properties such as highest occupied molecular orbital's (HOMO), lowest unoccupied molecular orbital's (LUMO), and electrostatic potential mapped density of 2-[(acetyloxy)methyl]-4-(2-amino-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)butyl acetate (Famciclovir) were created. The molecular mechanics potential energy (steric energy), heat of formation and self-consistent field (SCF) energy were calculated.

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