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A note on the relationships between electronic structure and inhibition of Chikungunya virus replication by a group of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives

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ABSTRACT

We present a study of the relationships between the electronic structure and the Chikungunya virus (CHIKV) inhibitory capacity of a group of [1,2,3]triazolo[4,5-d]pyrimidin-7(6H)-one derivatives. The electronic structure of all the molecules was obtained with the Density Functional Theory at the B3LYP/6-31g(d,p) level with full geometry optimization. We found a statistically significant relationship between the variation of the inhibitory capacity and the variation of the values of four local atomic reactivity indices belonging to a common molecular skeleton (n=14, adj R^2=0.91, F(4,9)= 32.81 (p<0.00002), SD=0.16). A partial inhibitory pharmacophore is proposed and discussed. It is shown that there is a full qualitative agreement between the molecular electrostatic potential structure and the pharmacophore features. Our results strongly suggest that we are dealing with a single site belonging to the CHIKV that it is related to the control of the viral replication machine.

Keywords: Chikungunya virus, CHIKV, DFT, RNA virus, QSAR, SAR, Quantum Pharmacology, local atomic reactivity indices.

INTRODUCTION

Chikungunya (CK) is a viral sickness first described in southern Tanzania in 1952 [1, 2]. The virus is transmitted from human to human through the bites of infected female mosquitoes. The name “chikungunya” originates from a word in the Kimakonde tongue meaning "to become contorted". The disease occurs in Asia, Africa and the Indian subcontinent and several outbreaks have occurred (2007 in Gabon, 1999-2000 in the Democratic Republic of the Congo, 2005 in islands of the Indian Ocean (2006 in La Réunion), 2006 and 2007 in India) [3-26]. Recently CK spread to Europe (CK transmission was reported for the first time in an outbreak in north-eastern Italy in 2007) and the Americas (2013 in Anguilla, British Virgin Islands, French Guiana, Guadeloupe, Martinique, St. Martin and St. Barthélémy) [27-37]. By July 2014 cases of CK have been reported in 23 countries and territories of the Americas (with about 350,000 suspected cases). CK causes myalgia, fever, headache, rash, nausea, vomiting, and arthralgia. The majority of patients recover completely, but in a number of cases joint pain may continue for some months or even years. There is no specific antiviral drug treatment or vaccine for CK. The treatment consists primarily in relieving the symptoms using fluids, anti-pyretics and analgesics. The causative agent of CK is the Chikungunya Virus (CHIKV) which is an RNA virus belonging to the alphavirus genus of the family Togaviridae [38-48]. In the search for antiviral agents, several molecules have been synthesized and tested [49-55]. Here we present the results of a quantum-chemical study relating the electronic structure and the CHIKV inhibitory activity for a group of recently reported [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives [55].

MATERIALS AND METHODS

Methods

The methodology employed in this work has been presented and discussed in detail in several papers [56-60] and it is now used as a standard quantum-pharmacological tool for extracting useful information from experimentally measured equilibrium constants (pA_2, IC_{50}, K, [61-78]) and biological activities [79-88]. The logarithm of the biological activity (BA) can be written as:

$$\log(BA)=a+\sum_j\left[e_jQ_j+f_jS_j^E+s_jS_j^N\right]+$$
$$+\sum_j\sum_m\left[h_j(m)F_j(m)+x_j(m)S_j^E(m)\right]+\sum_j\sum_{m'}\left[r_j(m')F_j(m')+t_j(m')S_j^N(m')\right]+$$
$$+\sum_j\left[g_j\mu_j+k_j\eta_j+o_j\omega_j+z_j\varsigma_j+w_jQ_j^{max}\right]+\sum_{B=1}^{W}O_B \qquad (1)$$

where Q_j is the net charge of atom *j*, S_j^E and S_j^N are the total atomic electrophilic and nucleophilic superdelocalizabilities of Fukui et al., $F_{j,m}$ is the Fukui index of the occupied [empty] molecular orbitals (MO) m [m'] located on atom j. $S_j^E(m)$ is the atomic electrophilic superdelocalizability of MO m on atom j, etc. The total atomic electrophilic superdelocalizability of atom j is the sum over occupied MOs of all the $S_j^E(m)$'s and the total atomic nucleophilic superdelocalizability of atom j is defined as the sum over the empty MOs of all $S_j^N(m')$'s [89]. The last bracket of Eq. 1 contains local atomic reactivity indices (local atomic electronic chemical potential, local atomic hardness, etc., see REF) recently obtained within the Hartree-Fock-Roothaan framework [60]. The last term of Eq. 1 includes the so-called orientational parameters of the substituents [58].

Selection of molecules and experimental data

The selected molecules were taken from a recent study and are shown in Figure 1 and Table 1 [55]. The biological activity to be analyzed is the antiviral activity of these molecules against CHIKV (defined as the compound concentration that is required to inhibit the virus-induced cytopathic effect by 50% and reported as EC_{50}) in Vero cells (African green monkey kidney cells). The mechanism of action of these molecules is not known. However, it is interesting to note that molecules 1 and 14 do not have the same antiviral ratio when compared against various CHIKV strains. Also, 14 has antiviral activity against the Vietnam strain of the Semliki forest virus and the HRsp strain of the Sindbis virus while 1 has no activity at all (see Table 2 of [55]).

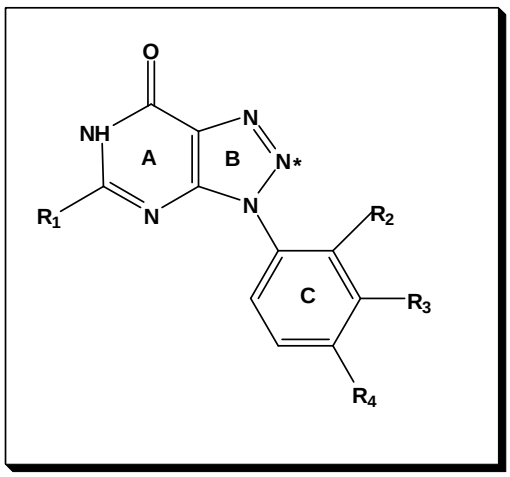

Figure 1. General formula of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives

Table 1. [1,2,3]Triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives and CHIKV inhibitory activity in Vero cells

Mol.	Mol.	R_1	R_2	R_3	R_4	$\log(EC_{50})$
1	2	Me	H	COMe	H	1.28
2*	6A*	Me	H	COMe	H	2.10
3	11A	Me	OMe	H	H	2.54
4	11B	Me	H	OMe	H	1.45
5	11C	Me	H	Cl	H	1.51
6	11D	Me	H	COPh	H	1.36
7	11E	Me	H	$OCH(CH_3)_2$	H	1.08
8	11F	Me	H	NHCOMe	H	2.50
9	11H	Me	H	CN	H	2.12
10	11J	Me	H	H	COMe	2.51
11	11K	Me	H	H	$OCH_2CH_2CH_3$	2.23
12	11M	Me	H	COOEt	H	2.31
13	15A	CF_3	H	$OCH(CH_3)_2$	H	1.83
14	15B	CH_2Me	H	$OCH(CH_3)_2$	H	0.48
15	15C	CH_2CN	H	$OCH(CH_3)_2$	H	2.06
16	15E	$CH(CH_3)_2$	H	$OCH(CH_3)_2$	H	2.45
17	15F	Ph	H	$OCH(CH_3)_2$	H	2.31
18	15G	4-Py	H	$OCH(CH_3)_2$	H	1.88

**Carbon instead of nitrogen at position marked * in Fig. 1.*

Calculations

The electronic structure of the molecules was obtained with the Density Functional Theory at the B3LYP/6-31g(d,p) level using the Gaussian suite of programs [90]. After full geometry optimization and single point calculations, the values of the LARIs were calculated with D-CENT-QSAR [91]. Negative electron populations or MO populations greater than 2 arising from Mulliken Population Analysis were corrected as usual [92]. Orientational parameters were calculated as usual [58]. We employed Linear Multiple Regression Analysis (LMRA) to find out which atoms are involved in the variation of the biological activity. We worked with the hypothesis that there is a set of atoms common to all the molecules (the common skeleton), encoding the variation of the biological activity throughout the group of molecules. It is the variation of the values of one or more local atomic reactivity indices of the atoms of the common skeleton that accounts for the variation of the inhibition of CHIKV-induced cytopathic effect in the series. The substituents modify the electronic structure of the common skeleton and direct the precise orientation of the common skeleton with its partner through the orientational parameters. For the LMRA, we built a matrix containing the logarithm of the dependent variable (EC_{50}), the local atomic reactivity indices of the atoms constituting the common skeleton and the orientational parameters of substituents R_1 to R_4. The Statistica software was used for LMRA [93]. In this kind of model statistics is employed as a slave and not as a master. The common skeleton numbering is depicted in Fig. 2.

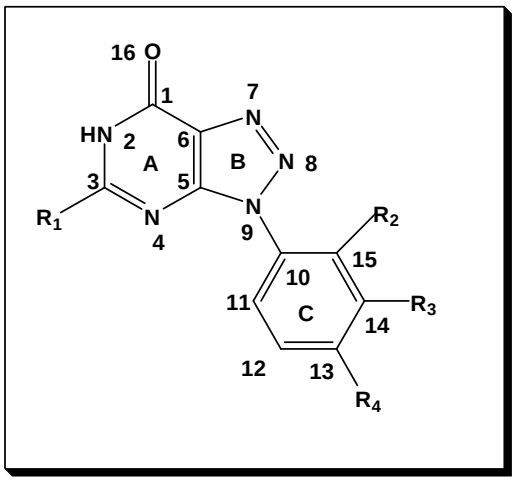

Figure 2. Numbering used here for the common skeleton of the [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives

RESULTS

A first LMRA was carried out with all the molecules (n=18). No statistically significant equation was obtained. Considering that the experimental inhibitory capacities are reported in μM, we have tested the hypothesis that the highest EC_{50} values might represent another inhibitory mechanism, a mixture of mechanisms or a saturation effect.

We have consequently eliminated from the original set those molecules having an EC_{50}> 2.45 μM, aware that 2.45 is an arbitrary value determined only from the set of experimental data. Earlier work on other systems has shown that this technique produces good results when all other possibilities of forming a molecular set have been explored without success. We obtained the following equation (n=14):

$$\log(EC_{50}) = 2.02 - 3.05F_9(LUMO+2)^* - 0.28S_7^E(HOMO-2)^* - \\ -6.42F_2(LUMO+1)^* + 2.02F_{15}(LUMO+1)^* \quad (2)$$

with n=14, R=0.97, R^2=0.94, adj R^2=0.91, F(4,9)=32.81 (*p<0.00002*) and SD=0.16. No outliers were detected and no residuals fall outside the ±2σ limits. Here, $F_9(LUMO+2)^*$ is the Fukui index (the electron population) of the third lowest vacant MO localized on atom 9, $S_7^E(HOMO-2)^*$ is the orbital atomic electrophilic superdelocalizability of the third highest occupied MO localized on atom 7, $F_2(LUMO+1)^*$ is the Fukui index of the second lowest vacant MO localized on atom 2 and $F_{15}(LUMO+1)^*$ is the Fukui index of the second lowest vacant MO localized on atom 15. Tables 2 and 3 show the beta coefficients, the results of the t-test for significance of coefficients and the matrix of squared correlation coefficients for the variables of Eq. 2. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed *vs.* calculated log(EC_{50}) values. The associated statistical parameters of Eq. 2 indicate that this equation is statistically significant and that the variation of the value of a group of four local atomic reactivity indices of atoms of the common skeleton explains about 91% of the variation of the inhibitory capacity in this group of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives.

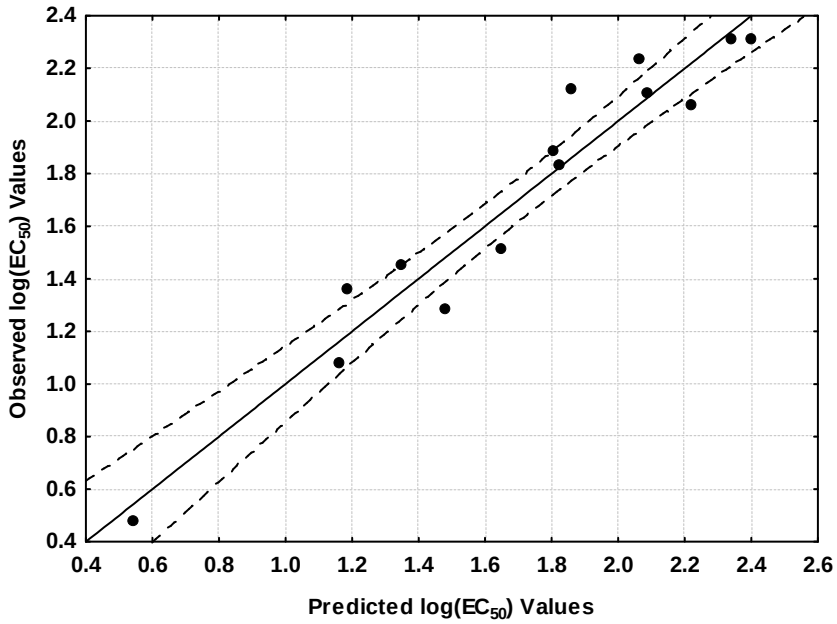

Figure 3. Plot of predicted *vs*. observed log(EC_{50}) values (Eq. CC). Dashed lines denote the 95% confidence interval

Table 2. Beta coefficients and t-test for significance of coefficients in Eq. 2

	Beta	t(9)	*p-level*
$F_9(LUMO+2)^*$	-0.48	-4.54	0.001
$S_7^E(HOMO-2)^*$	-0.67	-7.00	0.00006
$F_2(LUMO+1)^*$	-0.48	-5.03	0.0007
$F_{15}(LUMO+1)^*$	0.34	3.17	0.01

Table 3. Matrix of squared correlation coefficients for the variables in Eq. 2

	$F_9(LUMO+2)^*$	$S_7^E(HOMO-2)^*$	$F_2(LUMO+1)^*$
$S_7^E(HOMO-2)^*$	0.03	1.00	
$F_2(LUMO+1)^*$	0.14	0.06	1.00
$F_{15}(LUMO+1)^*$	0.23	0.17	0.01

DISCUSSION

Despite the fact that the mechanism(s) of action of these molecules is(are) not known, the ensuing discussion is based on the hypothesis that they act directly on the CHIKV. Table 3 shows that the relative importance of the calculated indices is $S_7^E(HOMO-2)^*$ > $F_9(LUMO+2)^*$ = $F_2(LUMO+1)^*$ > $F_{15}(LUMO+1)^*$. A high inhibitory capacity of CHIKV-induced cytopathic effect is associated with high values for $F_9(LUMO+2)^*$ and $F_2(LUMO+1)^*$ and with small values for $S_7^E(HOMO-2)^*$ and $F_{15}(LUMO+1)^*$. Table 4 shows the local MO structure of atoms 2 (nitrogen), 7 (nitrogen), 9 (nitrogen) and 15 (carbon) (see Fig. 2). Nomenclature: Molecule (HOMO) / (HOMO-2)* (HOMO-1)* (HOMO)* - (LUMO)* (LUMO+1)* (LUMO+2)*. The molecules not employed in the generation of Eq. 2 are highlighted in boldface.

Table 4. Local Molecular Orbital structure of atoms 2, 7, 9 and 15

Mol.	Mol.	Atom 2	Atom 7	Atom 9	Atom 15
2 (70)	1	66σ68π70π-71π72π73π	65σ66σ70π-71π73π74π	65σ66σ70π-71π72π75π	68π69σ70π-71π72π73π
6A (70)	2	67σ69π70π-72π73π74π	67σ69π70π-71π72π74π	63σ65σ69π-72π73π74π	63σ68σ69π-71π72π73π
11A (67)	**3**	**65π66π67π-68π69π70π**	**65π66π67π-68π69π70π**	**64σ65π67π-68π70π72π**	**65π66π67π-68π69π70π**
11B (67)	4	64σ65π66π-68π69π70π	64σ66π67π-68π69π70π	65π66π67π-68π71π72π	65π66π67π-68π69π70π
11C (67)	5	64σ66π67π-68π69π71π	65π66π67π-68π69π71π	64σ65π67π-68π71π72σ	62π65π67π-68π70π71π
11D (86)	6	80σ85π86π-88π89π91π	84σ85π86π-87π88π89π	79σ80σ86π-88π93π95π	81π84σ86π-87π88π89π
11E (75)	7	72σ73π74π-76π77π78π	73π74π75π-76π77π78π	73π74π75π-76π80π83σ	73π74π75π-76π77π78π
11F (74)	**8**	**70σ72π73π-75π76π78π**	**72π73π74π-75π76π78π**	**72π73π74π-75π79π80π**	**72π73π74π-75π77π78π**
11H (65)	9	61σ62σ65π-66π67π68π	63π64π65π-66π68π69π	63π64π65π-66π67π68π	63π64π65π-66π67π68π
11J (70)	**10**	**66σ68π70π-71π72π73π**	**65σ66σ70π-71π72π73π**	**65σ66σ70π-71π72π75π**	**68π69σ70π-71π72π74π**
11K (75)	11	72σ74π75π-76π77π79π	72σ74π75π-76π77π79π	71σ72σ75π-76π80π83σ	67σ69σ75π-76π78π79π
11M (78)	12	74σ75σ78π-79π80π81π	75σ77π78π-79π80π81π	75σ77π78π-79π80π81π	75σ77π78π-79π81π82π
15A (87)	13	84σ85π86π-88π89π90π	85π86π87π-88π89π90π	84π86π87π-88π90π91π	82σ86π87π-88π90π91π
15B (79)	14	76σ77π78π-80π81π82π	77π78π79π-80π81π82π	77π78π79π-80π83π84π	77π78π79π-80π81π82π
15C (81)	15	78σ79π80π-82π83π84π	78σ80π81π-82π83π84π	79π80π81π-82π86π87π	79π80π81π-82π83π84π
15E (83)	**16**	**79σ80π82π-84π85π86π**	**81π82π83π-84π85π86π**	**81π82π83π-84π88π91σ**	**81π82π83π-84π85π86π**
15F (91)	17	87σ88σ90π-92π93π94π	89π90π91π-92π93π94π	89π90π91π-92π94π96π	89π90π91π-92π94π95π
15G (91)	18	87σ88σ90π-92π95π96π	89π90π91π-93π94π95π	89π90π91π-92π94π95π	89π90π91π-92π94π95π

Atom 9 is a nitrogen atom belonging to ring B (see Fig. 2). A higher value for $F_9(LUMO+2)^*$ is achieved by raising this MO's population. $(LUMO+2)_9$* is of π nature in 11 molecules and of σ n nature in 3. We suggest that atom 9 is interacting with a rich-electron moiety of CHIKV through at least $(LUMO)_9$* and $(LUMO+1)_9$*. An optimal molecular system should have its three lowest local vacant MOs of atom 9 of π nature. Figure 4 shows four examples of $(LUMO+2)_9$* [94].

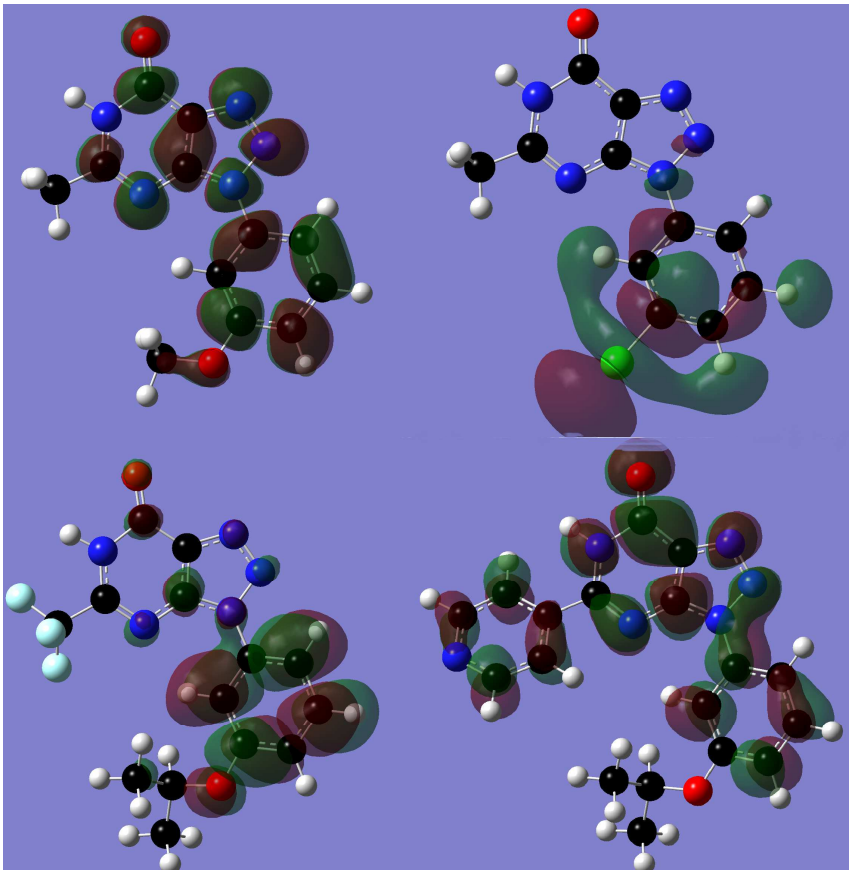

Figure 4. $(LUMO+2)_9$* in molecules 4 (upper left), 5 (upper right), 13 (lower left) and 18

We can see that in molecules 4, 5 and 18 that atom 9 belongs to π systems possessing different localizations and population densities. Atom 2 is a nitrogen atom belonging to ring A (see Fig. 2). A higher value for $F_2(LUMO+1)^*$ is obtained by raising the corresponding MO population. $(LUMO+1)_2$* is of π nature in all molecules. This suggests that atom 2 is interacting with an electron-rich moiety of CHIKV through at least $(LUMO)_2$* and $(LUMO+1)_2$*. Atom 7 is a nitrogen atom belonging to ring B (see Fig. 2). A lower value of $S_7^E(HOMO-2)^*$ is obtained by shiftingthe MO energy downwards, by decreasing the MO population or by both methods. $(HOMO-2)_7$* is of π nature in 7 molecules and of σ nature in 7. We know that occupied π MOs can act as electron donors and σ occupied ones cannot. In general terms, $(HOMO-2)_7$* (σ or π) seems to participate in a repulsive interaction with occupied MOs of some part of CHIKV. Then, a way to minimize this repulsive interaction is by shifting the $(HOMO-2)_7$* energy downwards and keeping its σ nature. This is because σ MOs lie in the plane of ring B (see Fig. 2) while π MOs are perpendicular to that plane and therefore interact more strongly with the occupied MOs of a CHIKV moiety. In summary: atom 7 seems to interact with empty MOs located on a CHIKV moiety through at least $(HOMO)_7$* and perhaps $(HOMO-1)_7$*. This moiety has one or more occupied MOs, probably of π nature, that repel $(HOMO-2)_7$*. The participation of $(HOMO-1)_7$* is not mandatory because there is at least one molecule in which $(HOMO-1)_7$* is of σ nature. Atom 15 is a carbon atom belonging to ring C (see Fig. 2). $(LUMO+1)_{15}$* is of π nature in all molecules. A low value of $F_{15}(LUMO+1)^*$ suggests that atom 15 interacts through $(LUMO)_{15}$* with an electron-rich CHIKV moiety. This moiety probably also contains one or more vacant MOs repelling $(LUMO+1)_{15}$*. All these suggestions are encompassed in the partial two-dimensional (2D) inhibition pharmacophore shown in Fig. 5.

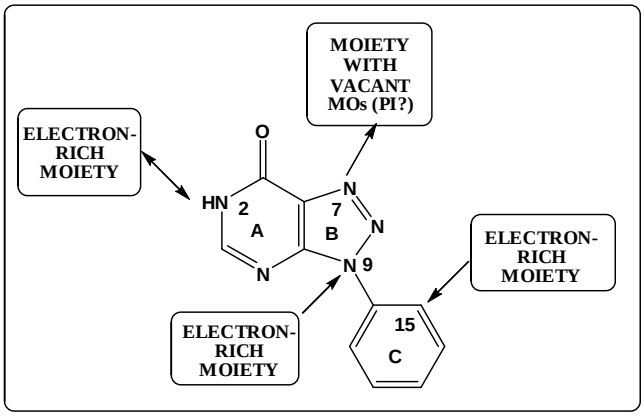

Fig. 5. Partial 2D inhibition pharmacophore

A corollary of these results is that the common skeleton hypothesis seems to be validated for this case.

Molecular Electrostatic Potential (MEP)

Molecules that need to be recognized and guided to an interaction site should have a qualitatively similar three-dimensional MEP map. Figure 6 shows the MEP map of molecules 2 and 11F at 4.5 Å from the nuclei [95].

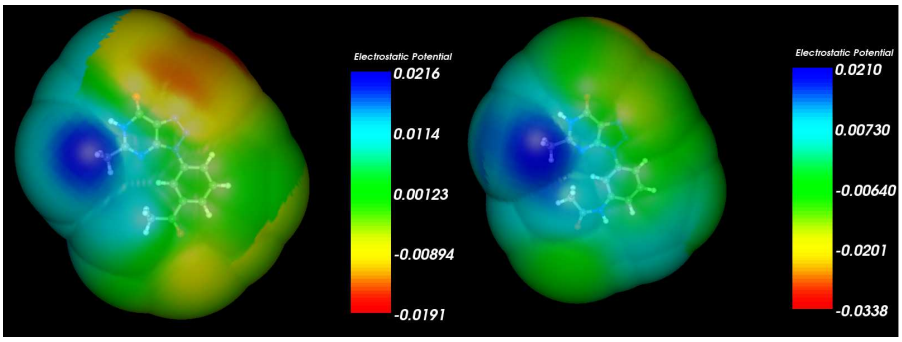

Figure 6. MEP map of molecules 1 (left) and 8 (right) at 4.5 Å from the nuclei

We can see that there are at least three perceptible common areas in the figure. The first one is the dark blue region of positive MEP at the left-center part of the molecules. The second and third ones are the weakly negative regions located at the bottom and upper right parts of the molecules. Figure 7 shows the MEP map of the same molecules for surfaces with isovalues of ±0.01 [94].

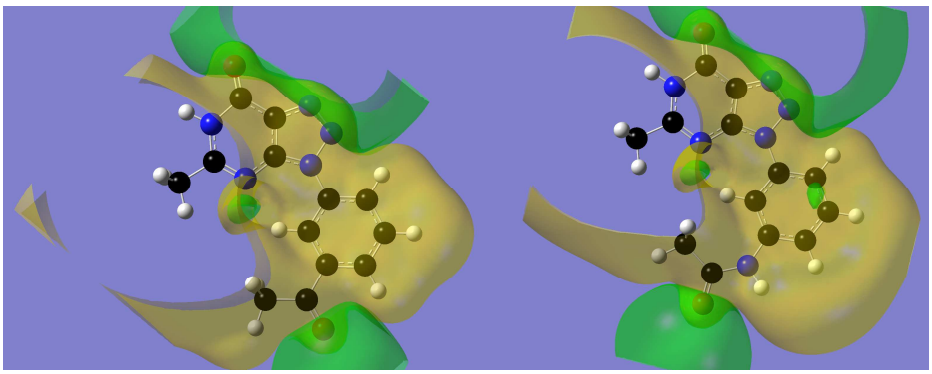

Figure 7. MEP map of molecules 1 (left) and 8 (right). The green isovalue surface corresponds to negative MEP values (-0.01) and the yellow isovalue surface to positive MEP values (0.01)

We can see that the two MEP maps are very similar. The most important fact to notice is the direct relationship between the sign of the MEP map at certain volumes in the molecules and the proposed pharmacophore depicted in Fig. 5. It was suggested that atoms 2, 9 and 15 could interact with electron-rich moieties. These moieties can effectively interact with these atoms if the MEP map around them is positive, a condition that is fully satisfied. The other suggestion is that atom 7 seems to interact with a region with vacant MOs. From Fig. 7 we can see that a

negative MEP area surrounds atom 7, facilitating the interaction of this atom with its partner. Therefore, the QSAR results are in full qualitative agreement with the MEP map structure.

Conformational aspects

Molecule 14 is the most active in the series and molecule 16 one of the least active ones. Figure 8 shows the ten lowest energy conformers of these two molecules obtained with MarvinView and superimposed with Hyperchem [96, 97].

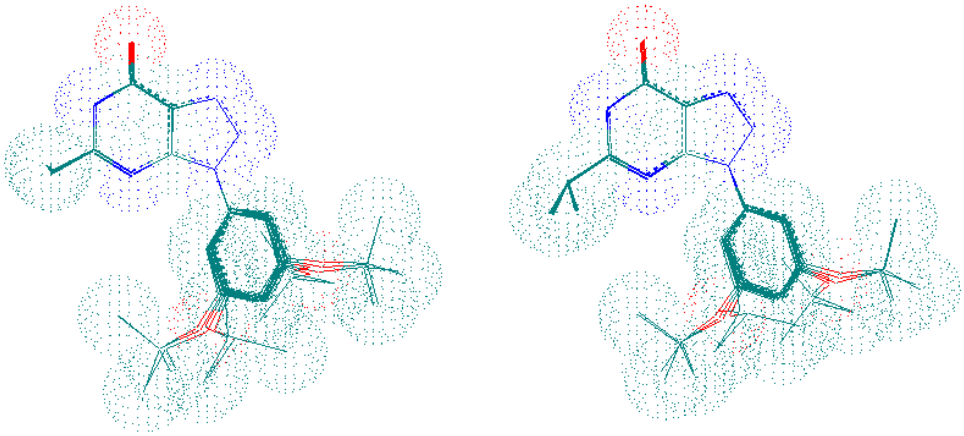

Figure 8. Superimposition of the ten lowest energy conformers of 14 (left) and 16 (right)

We can see that the -$OCH(CH_3)_2$ substituent can adopt four spatial orientations in both molecules. Before the molecule approaches the site, it is highly possible that a mixture of conformers exists, a mixture that will depend on the exact microscopic composition of the *in vitro* milieu. Results from the X-ray structure of frozen drug-site complexes or drug-site docking studies can be useful only if it is first demonstrated that they reflect the reality of the dynamic situation existing in the experimental setting. In the case of these molecules, two facts are noteworthy. The first is that the relative positions of rings A, B and C is almost the same in both molecules. The second is that their only structural difference lies in an ethyl substituent (in 14) *versus* a $CH(Me)_2$ (in 16). Then, the only explanation for such different inhibitory activities must involve the effect that these substituents have on the whole molecular orbital structure and not only on the specific carbon atom to which they are attached. Simple quantum chemical considerations within a LCAO-MO framework indicate that the $CH(Me)_2$ substituent will add three more σ MOs than the ethyl substituent. These "extra" MOs will produce changes in the energies and localization of the remaining MOs with the consequent changes in the values of the local atomic reactivity indices and in the composition of the set of local atomic MOs (compare the local MOs of atom 9 in both molecules, Table 4). This is the same case when we compare molecules 1 and 2: N8 has been exchanged for CH (see Fig. 2), the aromaticiy has been preserved but the inhibitory activity is considerably reduced in the latter case. Finally, equation 2 indicates a very high degree of orbital control [98, 99], suggesting that the site (or sites) involved in the inhibition process are very selective. The results strongly suggest that we are dealing with a single site on the CHIKV that it is related to the control of the viral replication machine.

CONCLUSION

We have obtained a formal relationship between the inhibition of CHIKV-induced cytopathic effect and electronic structure for a group of [1,2,3]triazolo[4,5-*d*]pyrimidin-7(*6H*)-one derivatives. We have established some conditions that could lead to more active molecules. Although the action mechanism is unknown, the results obtained here suggest that these molecules act on a single site involved in the viral replication system.

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