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Theoretical studies of the contraction and extension effect in the β-ring of TIBO derivatives

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ABSTRACT

Some new non-nucleoside reverse transcriptase inhibitors are designed by contraction and extension of the seven-membered ring of TIBO to six- and eight-membered rings respectively using PM3, HF and DFT methods. Independently of calculations level, contracted seven-membered ring in C_{15} position, showed great similarity between the 3D geometry and the molecular properties of the TIBO and $6MRC_{15}$. Otherwise, the same ring when extend between N_4 and C_{15} atoms showed also a great similarity between TIBO and 8MR (N_4-C_{15}). The latter molecule can enter easily in the allosteric cavity of NNRTIs. These two TIBO derivating compounds conserve the butterfly-like conformation can constitute a new class of anti-HIV.

Key words: HIV, Reverse Transcriptase, 7 ring TIBO, contraction and extension ofTIBO, PM3, HF, DFT.

INTRODUCTION

The treatment in HIV infection domain considers Non-Nucleoside Reverse Transcriptase (NNRTIs) as more significant Inhibitors. These inhibitors include a very large diversity of chemical compounds, as TIBO derivatives which are the main aim of our work. Although many physicochemical properties of NNRTIs can differ, many theoretical studies seem to establish that these inhibitors possess a common three-dimensional feature which has a rigid butterfly-like configuration.

In the literature, some new TIBO-like derivatives have been designed by contraction and extension of the b-ring of TIBO derivatives from seven to six and eight-membered ring, respectively. In this work, we will examine the effect of modified structures on butterfly-like configuration, geometrical, electronic and physicochemical properties by using various quantum mechanics methods. Computational calculations shown in this work are in agreement with literature. Therefore, the resulting molecules can be considered as new candidates for synthesis of anti-HIV inhibitors.

Human Immunodeficiency virus (HIV) is a retrovirus which can be replicated in a human host cell. It appears to preferentially attack helper T cells. In fact, the viral particle becomes active only when it is in contact with a cell[1]. The treatment of the acquired immunodeficiency syndrome (AIDS) caused by HIV is one of the most challenging medical problem. This major issue is mainly due to the fact that the polymerase of virus HIV makes hundred more errors than a polymerase of a

bacterium. So, a vaccine or a drug which can eliminate or block the action of the virus is more difficult to be found[2].

To fight against this virus, many researches were directed towards the chemotherapy and the design of drugs decimating the HIV or blocking its replication. HIV Reverse Transcriptase enzyme (RT) appeared to be a key target of anti-HIV therapy, because it catalyzes an essential step in virus replication. This enzyme is the responsible in the conversion of viral genomic RNA into proviral DNA which later integrates the host genome[2,3]. There are two types of RT inhibitors: the Nucleoside (NRTIs) and the Non-Nucleoside (NNRTIs). NRTIs act on the catalytic site of the reverse transcriptase enzyme, preventing DNA synthesis, whereas NNRTIs bind non-competitively to a hydrophobic site close to the catalytic site, forcing the enzyme to adopt an inactive conformation[4,5]. The NNRTIs are much less toxic than the NRTIs[6,7].

Generally, the NNRTI compounds contain a carbonyl or thiocarbonyl group, an extra lipophilic site and a methyl group[8]. Though, many physicochemical properties of NNRTIs inhibitors can differ, many theoretical studies have shown clearly that these inhibitors possess a common three-dimensional feature which has a rigid butterfly-like configuration in the internal cavity of the allosteric area of the enzyme[9-13]. The degree of butterfly-like configuration depends on the overall shape parameters, the polarizability and the lipophilicity of the molecule[13]. According to its structural diversity, NNRTIs interact with different amino acid residues of the allosteric pocket. However the number of amino acid residues interacting with these inhibitors has an important relation with the angle formed by the two wings of the inhibitor butterfly-like configuration. Moreover, this angle can be closely correlated with the drug affinity for the enzyme and the probability of drug-resistance development[9-13]. Therefore, a great importance have to be given to this configuration in the conception of new inhibitors to HIV reverse transcriptase.

TIBO compounds and its derivatives that belong to NNRTIs, have been efficient to inhibit RT (Figure 1). Similarely to all the other NNRTIs structures, the TIBO inhibitors can be located in the Binding Pocket of RT and adopt a butterfly-like conformation[14].

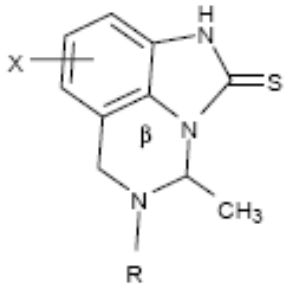

Fig. 1: Basic structure of TIBO

Some calculations[15-16] was carried out AM1 study of some new compounds resulting from the contraction and extension of the β- diazepine ring of TIBO derivatives, from seven- to six- and eight-membered rings, respectively (Fig. 2 and 3). This work revealed that some six- and eight-membered rings derivatives bond to the receptor better than the seven-membered ring derivatives.

Because this work presents several important results based only on semi-emperical approach, we aim to confront them to more precise technique calculations. Therefore new structures presenting butterfly-like configuration has been studied.. Geometrical, electronic and some pertinent physicochemical properties were calculated using various theoretical approaches and codes.

Table 1: PM3, HF and DFT Calculated angle limited between wings I and II of TIBO, 6MRC15 and 6MRC18 butterfly-like conformations

Method	α(°)		
	C15 atom	TIBO	C18 atom
PM[3]	113.3	111.43	160.8
HF/6-31G*	114.5	110.22	169.22
B3LYP/6-31*	113.0	110.45	157.04

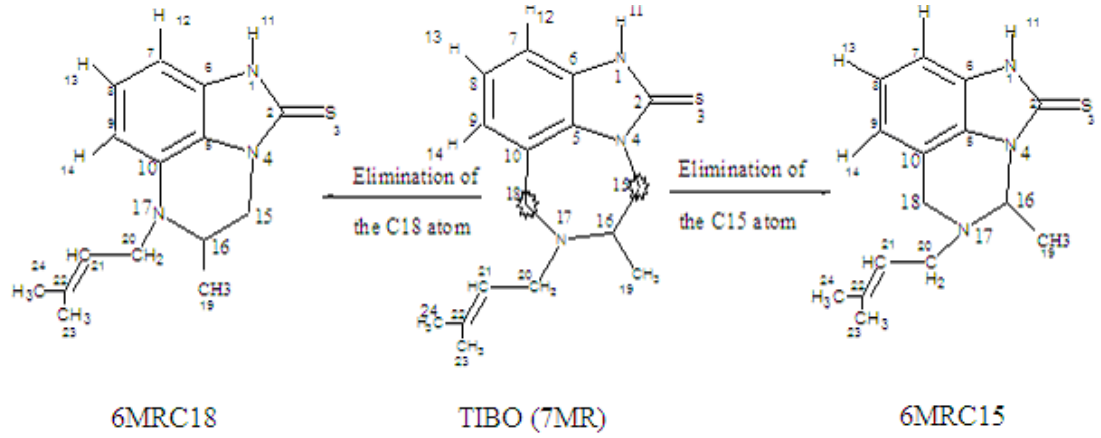

Fig. 2: Structure and labeling of TIBO(7MR) and two 6MR derivatives obtaind by contaction in C15 and C18

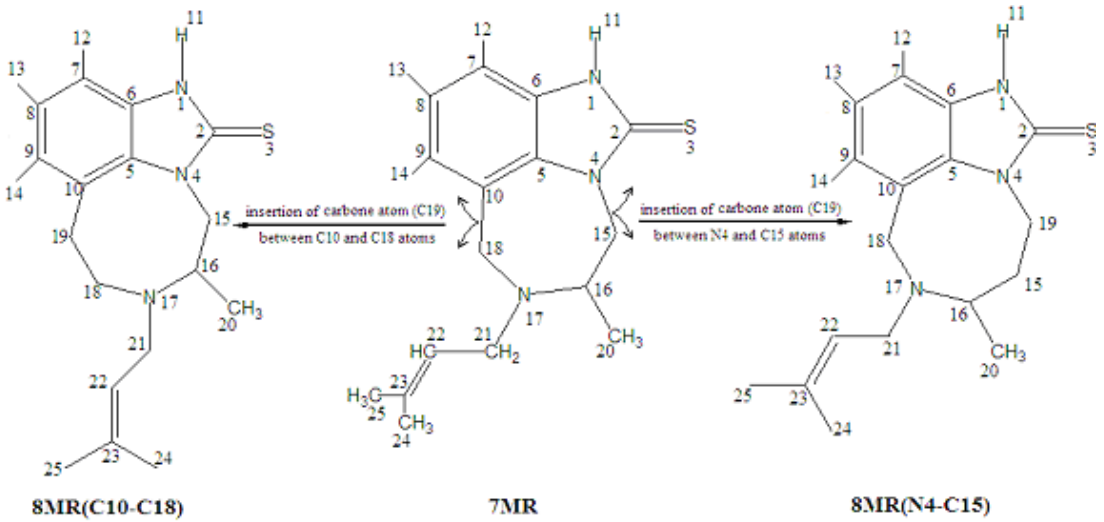

Fig. 3: Structure and labeling of TIBO(7MR) and two 6MR derivatives obtaind by insertion of carbon atom C19

Computational methods

The calculations discussed in this work have been done at the Austin Model one (AM1), Hartree-Fock (HF), and DFT levels using a standard Gaussian 98 program package[17] with 6-31G* basis sets for the ab initio and DFT levels. The computations carried at DFT level[18-22] using the hybrid method B3LYP. A vibrational analysis has been performed on the HF and DFT/B3LYP and indicates that all optimized structures correpond to minima on the potential energy surface confiremed by the absence of any imaginary frequency.

In addition, physicochemical properties such as molar refractivity, ovality, volume and LogP were calculated using Chem-3D program. However, other properties as chemical hardness (η) [23], chemical potential (μ) [23] and global electophilicity (ω) [24] were obtained using DFT results.

RESULTS AND DISCUSSION

The background molecular structure of TIBO derivatives is formed from a seven-membered diazepine ring (β-ring) fused to a bicycle-aromatic moiety (Fig. 1). In order to propose new inhibitors, two modifications were made on the seven-membered ring, by eliminating or adding a carbon atom[15,16]. The contraction of β-ring[15], produced by eliminating of a carbon atom in position 15 or 18, was lead to two new compounds containing a six-membered ring (Fig. 2). We will adopt the following notation: 7MR designs a seven-membered ring compound., 6MRC15 and 6MRC18 design six-membered ring compounds produced by eliminating of C_{15} and C_{18}, respectively.

However, the extension of the seven-membered ring to eight-membered rings[16], produced by insertion of a carbon atom (C_{19}) between N_4 and C_{15}, or C_{10} and C_{18} atoms, was lead to two other compounds 8MR(N_4-C_{15}) and 8MR(C_{10}-C_{18}), respectively (Fig. 3).

Table 2: CIculated of selected electronic and physicochemical properties of TIBO, 6MRC_{15} and 6MRC_{18} using 6-31G* on DFT method

DFT/6-31G*	X=H		
	C_{15} atom	TIBO	C_{18} atom
E(HOMO)	-0.0919	-0.093	-0.082
E(LUMO)	0.0797	0.079	0.093
E(HOMO-LUMO)	-0.1716	-0.172	-0.175
Molar Refractivity	86.69	92.28	88.16
Ovality	1.491	1.465	1.471
V	588.67	598.92	552.1
LogP	3.62	3.53	4
η	0.0858	0.086	0.087
μ	0.0061	0.007	0.005
$\omega.10^4$	2.168	2.841	1.728

Table3: Selected calculated electronic and physicochemical properties of TIBO and 8MR compounds

B3LYP/6-31G*	8MR(C_{10}-C_{18})	TIBO	8MR(N_4-C_{15})
E(HOMO)	-0.193	-0.093	-0.189
E(LUMO)	-0.022	0.079	-0.021
E(HOMO-LUMO)	-0.171	-0.172	-0.168
Molar Refractivity	97.04	92.28	97.15
Ovality	1.411	1.465	1.425
V	692	598.92	711
LogP	3.95	3.53	3.77
η	0.085	0.086	0.084
μ	0.107	0.007	0.105
$\omega.10^2$	6.75	$2.841.10^{-2}$	6.56

Note that the insertion of C_{19} between C_{15} and C_{16} atoms or C_{18} and N_{17} atoms gives the same compounds.

Contraction effect in β-ring

In the binding pocket of reverse transcriptase, TIBO structures, as all NNRTI inhibitors, adopt a *butterfly–like conformation* (fig. 4), in which dimethylallyl group (*Wing I)* interacts with Pro95, Tyr181, Tyr188, Gly190 and Trp229 amino acid residues of P66. However, the benzodiazepinone group (*Wing II*) interacts with Lys101, Lys103, Val106, Phe227, His235, Pro236, and Tyr318 of P66. Residues Leu100 and Leu234 of P66 interact with both Wings I and II from the top, Val179 from the front, and Tyr188 from the back of the butterfly[14].

All calculations have shown that TIBO molecular structure yields as a butterfly-like conformation which is in agreement with literature[15,25-28]. The seven-membered ring contraction in position C_{15} leads to a butterfly-like geometry, but it is comparable to that calculated in NNRTIs like the nevirapine which shown an angle of 108 to 115°[10].

Otherwise, the ring contraction in position C_{18} was lead to a slight planarity of the two wings (Fig. 5). Then, the butterfly-like geometry hasn't been kept for this structure. Indeed, the geometrical

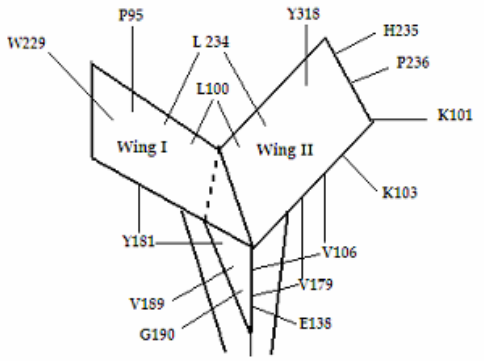

Fig. 4 : Representation of NNRTI's butterfly-like configuration in interaction with aminoacid residues of P66 [2]

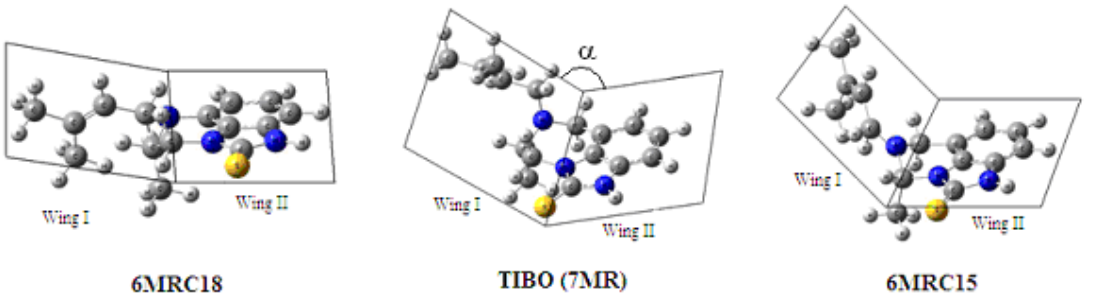

Fig. 5: Butterfly-like structures adopted by TIBO (7MR) and contracted homologues MRC18 and 6CRC15 calculated at B3LYP/6-31G* level

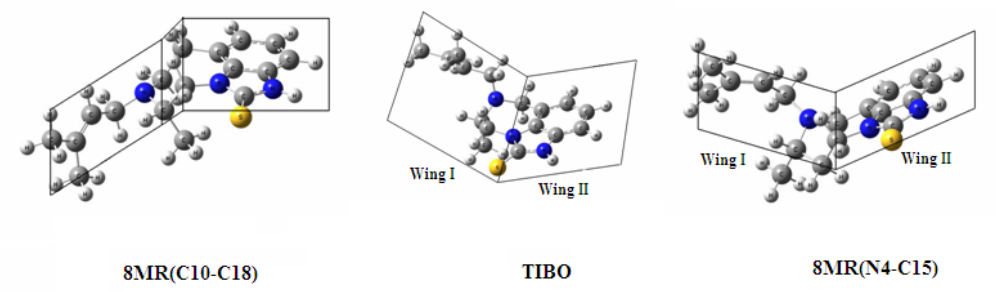

Fig. 6: Butterfly-like structures of TIBO and its 8MR derivatives through B3LYP/6-31G* optimization

optimization of this compound shows planar torsion angles $N_4C_5C_{10}N_{17}$ and $C_{20}N_{17}C_{10}C_5$. For this structure, the nitrogen N_{17} and carbon C_{20} (dimethylallyl group) are in the same plane carrying the fragment $C_{10}C_5N_4C_{15}$. In contrary, the same nitrogen N_{17} in the TIBO and $6MRC_{15}$ is outside of plane. We can conclude that the position of the nitrogen N_{17} in 6MRC18 structure differs from those of TIBO and $6MRC_{15}$. Consequently, the position of the C_{20} atom linked to N_{17}, will be different. These results are confirmed by the values of the α angle (Fig. 5), formed by the two wings in the TIBO derivatives. These calculated values of α, at different levels of theories, are summarized in the following table.

For these reasons, 6MRC18 cannot have a butterfly-like geometry and no have anti-HIV activity.

The interaction of NNRTIs with the allosteric site of the RT adopts key-lock mode. The molecules are selected according to their shape to get into the receptor site cavity [29]., in this case, the calculation of molecular volume (V) has shown that $6MRC_{15}$ owns an average volume when compared to TIBO and $6MRC_{18}$:

$$V\ (TIBO) > V\ (6MRC_{15}) > V\ (6MRC_{18})$$

The different results show that $6MRC_{15}$ possesses a more oval structure than TIBO and $6MRC_{18}$. We notice that contraction effect in position C_{15} leads to a decrease of 1.67% in volume and more over the $6MRC_{15}$ structure becomes more oval. It is known that the compounds which have weak sizes and which can set the best interactions have chances to be more active than the big sized compounds [29]. Indeed, the big molecules can have access a difficult to the receptor site, unlike the small molecules which enter more easily in the allosteric site cavity of the NNRTIs which has a Ω form [30].

The table 2 summarizes all calculated electronic and physicochemical properties for various studied structures.

A different computational level shows a great similarity between 3D geometrical and molecular properties of TIBO and $6MRC_{15}$ which confirms those found by ref. [15].

Extension effect in β-ring

The extension of the seven-membered ring between the N_4 and C_{15} atoms leads to a butterfly-like conformation. The calculated angle, separating the two wings shows 108.55 degrees at DFT/B3LYP/6-31G* method (Fig. 6). This is close to 110.45 degrees, angle obtained for TIBO structure at the same level. Otherwise, this angle remains comparable to that found in NNRTIs, such as the nevirapine (108 to 115 degrees) [10].

On the other hand, the extension of b-ring between C_{10} and C_{18} atoms doe not lead to a butterfly–like geometry. In fact, we notice that this compound is composed of three planes having a chair form, as shown in Fig. 6.

In this issue, the volume V of the two eight-membered ring structures was calculated and compared to that of TIBO as follows:

$$V_{8MR\ (N4\text{-}C15)} > V_{8MR\ (C10\text{-}C18)} > V_{TIBO}$$

This shows that 8MR (N_4-C_{15}) compound has a similar structure to TIBO, but exhibits a bigger volume with a less oval structure. We should remember that the rayon a_0 is equal to 5.49 Å that remains inferior to the one obtained in the TIBO when we substitute the hydrogen (H_{14}) carried by the C_9 carbon, by the group ($-OC_2H_5$). This latter has a ray of a_0=5.60 Å and its experimental anti-HIV activity is 7.02 [8, 31-33]. We conclude that 8MR (N_4-C_{15}) can enter in the allosteric cavity of NNRTIs. In addition to the volume and Ovality other electronic and physicochemical properties are presented in the following table.

We can conclude that the 8MR (N_4-C_{15}) has a great similarity of 3D geometry than TIBO. Thus, the molecules resulting from the extension of the 7-membered ring between N_4 and C_{15} atoms can constitute a new class of anti-HIV compounds.

CONCLUSION

Our calculation focus on some new non-nucleoside reverse transcriptase inhibitors are designed by contraction and extension of the seven-

membered ring of TIBO to six- and eight-membered rings respectively using PM3, HF and DFT methods. When we contract the seven-membered ring in C_{15} position, these results found at all level of calculations, have shown that there is a great similarity between the 3D geometry and the molecular properties of the TIBO and $6MRC_{15}$. Otherwise, when we extend the same ring between N_4 and C_{15} atoms, results have shown that there is, also, a great similarity between TIBO and 8MR (N_4-C_{15})., this molecule can enter easily in the allosteric cavity of NNRTIs. So, our results confirm those found in the literature. These two resulting compounds which conserve the butterfly-like conformation can constitute a new class of anti-HIV compounds.

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