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Der Pharma Chemica, 2015, 7(12):362-369
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

An exploratory quantum-chemical study of the anti-HIV-1 IIIB activity of a series of Etravirine-VRX-480773 hybrids

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ABSTRACT

A study relating electronic/molecular structure with anti HIV-1 IIIB activity of a group of Etravirine-VRX-480773 hybrids was carried out. A statistically significant relationship was found (n=20, adj-R^2= 0.88, F(5,14)= 29.943 (p<0.000001), SEE= of 0.19). The corresponding two-dimensional pharmacophore was built. From the analysis of the results we propose two new molecules for experimental testing.

Keywords: QSAR, DFT, HIV-1, local molecular orbitals, electronic structure, orientational effects, cytophatic effects.

INTRODUCTION

The human immunodeficiency virus (HIV) is a member of the genus *Lentivirus*, part of the family *Retroviridae*. It is the causal agent of HIV infection and acquired immunodeficiency syndrome (AIDS). Several pharmacological approaches have been employed to combat the HIV-1 infection. One of the favorite targets in this fight is the reverse transcriptase enzyme controlling the replication of the HIV genetic material. A group of drugs with antiretroviral activity are the non-nucleoside reverse-transcriptase inhibitors (see for example [1-23] and references therein). Two examples are Etravirine (approved for use in humans by the US FDA in 2008) and VRX-480773 (Fig. 1).

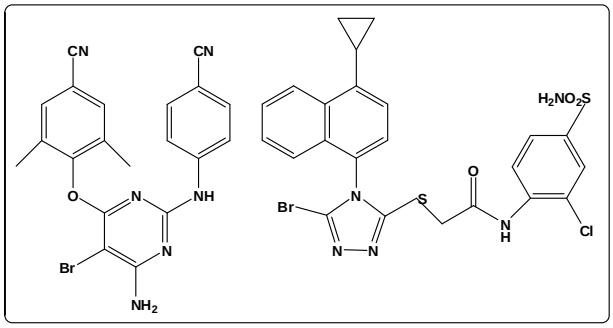

Figure 1. Etravirine (TMC-125, left) and VRX-480773 (right)

Recently, the anti-HIV-1 activity and cytotoxicity of a series of molecules constituted by a combination of parts the of Etravirine and VRX-480773 molecules was published (for some compounds the inhibitory activity against wild type HIV-1 reverse transcriptase was also reported) [3]. As in earlier works we carried out studies with different sets of molecules for HIV-1 reverse transcriptase inhibition, protection against cytopathic effects, cytostatic effects, HIV-1 replication and HIV-1 integrase enzyme inhibition and antiviral activity [24-27]. No formal relationships between the electronic structure and any biological activity of these molecules are known. With the aim of producing new knowledge about these molecular systems, we present here the results of a Density Functional Theory analysis relating several local atomic reactivity indices of the aforementioned molecules with anti HIV-1 activity.

METHODS, MODELS AND CALCULATIONS

Given that the model-based method employed here (the Klopman-Peradejordi-Gómez method, KPG, [28]) has been extensively explained and discussed in many publications, we refer the reader to the literature [24, 29-35]. The central feature of the model is that links any biological activity to a set of local atomic indices (LARIs) representing chemical reactivity. This set is augmented with the orientational parameters of the substituents. The application of the KPG model has given very good results when applied to very different groups of molecules and biological activities (see [27, 36-50] and references therein). In this paper we shall discuss only the LARIs appearing in the results.

The anti-HIV activity of the compounds was taken from the literature [3]. This activity was estimated against the wild-type HIV-1 III_B strain in MT-4 cell cultures using the MTT method and was expressed as the effective concentration necessary to protect the cell against viral cytopathicity by 50% (EC_{50}). MT-4 is a human T cell leukemia virus (HTLV-1) transformed human T cell sensitive to the cytophatic effects of HIV-1. Figure 2 and Table 1 show the selected molecules. As far as we know, the action mechanism and the site where these molecules exert their activity leading to cytophatic protection are not known.

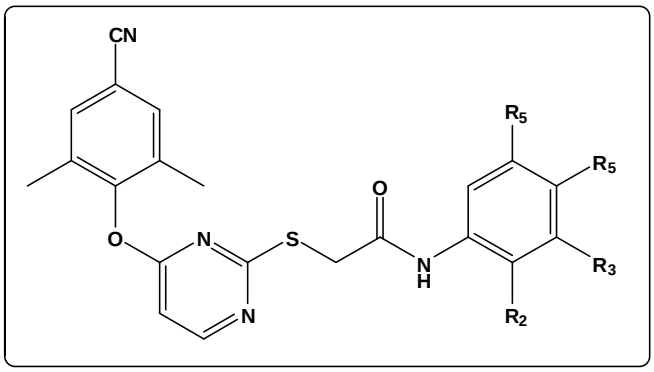

Figure 2. Etravirine-VRX-480773 hybrids

Table 1. Etravirine-VRX-480773 hybrids and biological activity

Mol.	R	log(EC_{50}) III_B
1	3-F	0.91
2	4-F	0.90
3	2-Cl	-0.62
4	3-Cl	0.90
5	4-Cl	0.59
6	2,4-Di-Cl	0.08
7	3,4-Di-Cl	0.72
8	3,5-Di-Cl	1.03
9	4-Br	0.15
10	2-NO_2	-0.47
11	3-NO_2	1.61
12	4-NO_2	0.15
13	4-CN	0.63
14	2-F,4-CN	0.78
15	4-SO_2NH_2	0.90
16	2-Me	0.77
17	4-Me	0.71
18	2-Me, 4-SO_2NH_2	-0.09
19	4-OMe	0.86
20	4-OH	0.92

We worked within the usual common skeleton proposal, accepting that the variation of the numerical values of a group of reactivity indices belonging to a group of atoms common to all the molecules analyzed accounts for almost all the variation of the biological activity. The effect of the substituents comprises the modification of the electronic structure of this common skeleton and/or the influence on the correct placement of the drug (through the orientational parameters). The common skeleton is presented in Fig. 3 together with the atom numbering employed in the resulting equations.

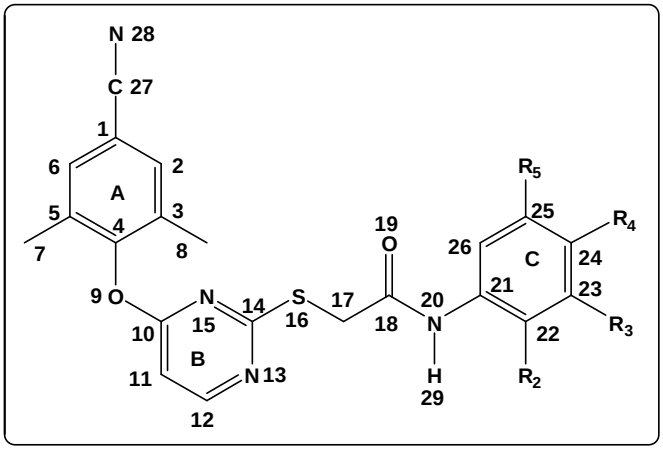

Figure 3. Numbering used for the common skeleton etravirine-VRX-480773 hybrids

All molecular geometries were fully optimized at the B3LYP/6-31G(d,p) level of theory with the Gaussian package [51]. From the corrected Mulliken Population Analysis results the numerical values for all electronic local atomic reactivity indices (LARIS) were calculated [52]. The D-CENT-QSAR software was used [53]. Orientational parameters were calculated with the STERIC software [54]. Since the system of linear equations cannot be solved because the number of molecules is smaller than the number of unknown coefficients, linear multiple regression analysis (LMRA) was carried out. The Statistica software was used [55].

RESULTS

The best equation obtained was:

$$\log(EC_{50}) = 3.59 - 0.01\phi_2 - 0.53\eta_{26} - 0.0012\phi_4 + 0.019S_{27}^{N}(LUMO+2)* - \\ -0.69F_{26}(HOMO-2)* \quad (1)$$

with n=20, R= 0.96, R^2= 0.91, adj-R^2= 0.88, F(5,14)= 29.943 (p<0.000001) and a standard error of estimate of 0.19. No outliers were detected and no residuals fall outside the ±2σ limits. Here, ϕ_2 is the orientational effect of the R_2 substituent, η_{26} is the local atomic hardness of atom 26, ϕ_4 is the orientational effect of the R_4 substituent, $S_{27}^{N}(LUMO+2)*$ is the nucleophilic superdelocalizability of the third lowest vacant MO localized on atom 27 and $F_{26}(HOMO-2)*$ is the Fukui index of the third highest occupied MO localized on atom 26. Table 2 displays the beta coefficients and the results of the t-test for significance of coefficients of Eq. 1. Table 3 shows the squared correlation coefficients for the variables appearing in Eq. 1. We can observe that there are no significant internal correlations. Fig. 4 displays the plot of observed *vs.* calculated $\log(EC_{50})$ values. The associated statistical parameters of Eq. 1 indicate that this equation is statistically significant and that the variation of the numerical value of a group of five local atomic reactivity indices explains about 88% of the variation of the anti-HIV activity.

Table 2. Beta coefficients and t-test for significance of coefficients in Eq. 1

	Beta	t(14)	p-level
ϕ_2	-1.13	-11.06	<0.000001
η_{26}	-0.61	-5.46	<0.00008
ϕ_4	-0.32	-3.93	<0.001
$S_{27}^{N}(LUMO+2)*$	0.38	34.00	<0.001
$F_{26}(HOMO-2)*$	-0.24	-2.66	<0.02

Table 3. Matrix of squared correlation coefficients for the variables in Eq. 1

	ϕ_2	η_{26}	ϕ_4	$S_{27}^{N}(LUMO+2)*$
η_{26}	0.32	1		
ϕ_4	0.03	0.03	1	
$S_{27}^{N}(LUMO+2)*$	0.01	0.17	0.05	1
$F_{26}(HOMO-2)*$	0.0004	0.10	0.04	0.16

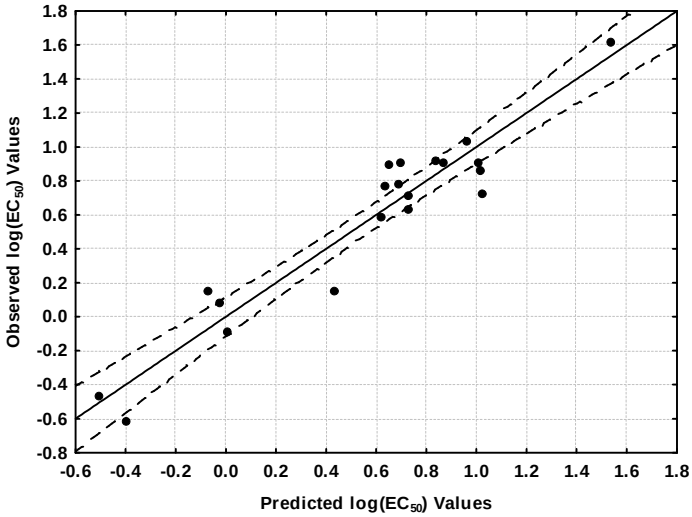

Figure 4. Observed *vs.* calculated $\log(\mathrm{EC}_{50})$ values (Eq. 1). Dashed lines denote the 95% confidence interval

LOCAL MOLECULAR ORBITALS

Table 4 shows the local molecular orbital structure of some atoms appearing in the Eq. 1 (Reading: Molecule's number (HOMO)/ (HOMO-2)*, (HOMO-1)*, (HOMO)*- (LUMO)*, (LUMO+1)*, (LUMO+2)*) [31].

Table 4. Local molecular orbital structure of atoms 26 and 27

Mol.	Atom 26 (C)	Atom 27 (C)
1 (106)	104π105π106π-110π111π112π	96π97π103π-107π108π115π
2 (106)	98π102π106π-110π111π112π	96π 97π104π-108π115π117π
3 (110)	108π109π110π-114π116π117σ	100π101π107π-111π112π120π
4 (110)	108π109π110π-114π115π116π	100π108π109π-112π114π120π
5 (110)	102π106π110π-114π115π 117π	99π100π108π-112π120π122π
6 (118)	115π117π118π-121π122π123π	107π108π116π-119π120π129π
7 (118)	109π114π118π-120π121π122π	108π116π117π-120π122π129π
8 (118)	116π117σ118π-121π122π123π	106π107π115π-119π120π129π
9 (119)	111π115π119π-123π124π125π	108π109π117π-121π129π131π
10 (113)	111π112π113π-114π116π117π	103π106π111π-115π116π117π
11 (113)	110π112π113π-114π118π119π	102π112π113π-116π117π118π
12 (113)	109π112σ113π-119π120π121π	100π101π111π-116π123π125π
13 (108)	100π104π108π-111π114π116π	97π 98π106π-109π110π111π
14 (112)	110π111π112π-113π117π120σ	103π105π111π-115π116π123π
15 (122)	118π121σ122π-125π126π128π	108π109π120π-123π124π132π
16 (106)	104σ105π106π-111π112π113π	96π97π103π-107π108π115π
17 (106)	104π105σ106π-110π112π113π	96π97π104π-108π115π117π
18 (126)	123π125σ126π-129π130π132π	111π112π124π-127π128π136π
19 (110)	106π107π110π-114π115π116π	100π101π108π-112π113π119π
20 (106)	102π103π106π-110π112π113π	96π97π104π-108π109π115π

DISCUSSION

The beta values (Table 2) specify that the importance of the variables is ϕ_2 >> η_{26} >> $S_{27}^{N}(LUMO+2)^*$ > ϕ_4 > $F_{26}(HOMO-2)^*$. A variable-by-variable (VbV) analysis of Eq. 1 indicates that a high protection against the cytopathic effects is associated with high values of ϕ_2, η_{26}, ϕ_4 and $F_{26}(HOMO-2)^*$. Atom 26 is a carbon in ring C (Fig. 2). Table 4 shows that almost all the three highest occupied and the three lowest vacant local MOs have a π nature. A high anti cytopathic effect is associated with a low numerical value of $F_{26}(HOMO-2)^*$. This indicates that $(HOMO-2)_{26}^{*}$ is engaged in a repulsive interaction with one or more occupied MOs of the site. If this is true, then this atom seems to be interacting with an electron deficient center through its first two highest occupied

MOs. The interaction could be stronger if these two MOs have a π nature. Note that in several molecules the local LUMO* does not coincide with the molecular LUMO. η_{26} is the local atomic hardness of atom 26 (the $(HOMO)_{26}^{*}$-$(LUMO)_{26}^{*}$ distance), and it is always a positive number. Considering that η_{26} has a high statistical significance, and that high numerical values of this index are required for a high protection against the cytopathic effects, the optimal situation occurs when the local (LUMO)* is energetically far from the molecular LUMO. Atom 27 is a carbon of the CN substituent in ring A. Table 4 shows that all the three highest occupied and the three lowest vacant local MOs have a π nature. A high anti cytopathic effect is associated with a low numerical value of $S_{27}^{N}(LUMO+2)*$ is the numerical value of this index is negative. To obtain higher negative values, we must shift upwards the associated eigenvalue. This, in turn, makes this MO less reactive. The same reasoning holds for the case of positive values of $S_{27}^{N}(LUMO+2)*$. We suggest that this atom is interacting with an electron rich center through its first two lowest vacant MOs.

Regarding the orientational effects, Table 2 shows that ϕ_2 has a very high statistically significance. Both, ϕ_2 and ϕ_4, are positive numbers and should have high values for optimal anti cytophatic effects. Is this statement is true, then compounds having R_2= R_4= Br or NO_2 substituents are good candidates for experimental testing. All the above suggestions are contained in the partial two-dimensional (2D) pharmacophore of Fig. 5.

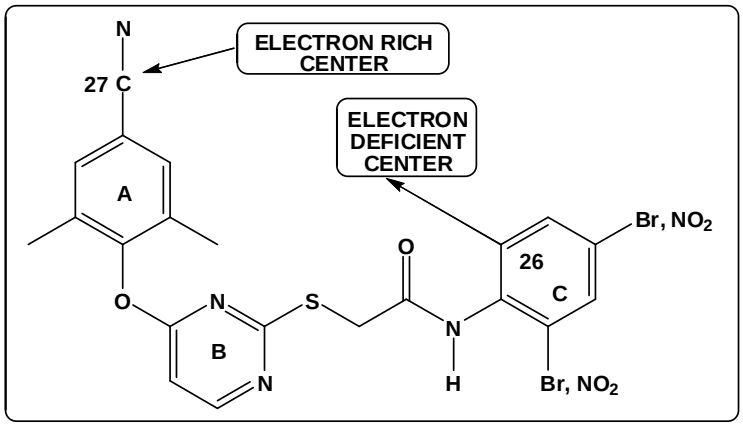

Figure 5. Partial 2D pharmacophore for anti cytopathic effects

We expected that the variation of the nature of the R_2-R_5 substituents produces some changes in the electronic structure of rings A and B and the chain linking ring B with ring C (because of the appearance of new MOs). Only one statistically significant atomic reactivity index belonging to these regions appears in Eq. 1. We must stress that the partial 2D pharmacophore contains only those variables explaining the variation of the biological activity. Therefore, all variables participating in the molecule-site interaction that are not statistically significant do not appear in Eq. 1. This is the weak side of this procedure.

Some words about the philosophical basis of the work presented here seem important. The DFT calculations provide us with *data* that can be considered *as given* despite the fact that it was produced within a model structured on the basis of a group of ideas about the structure of the molecular systems (for example, the MO representation). The data is transformed in *information* encoded in each one of the local atomic reactivity indices (and the orientational effect). This *information* is inserted in a *physically-based model* relating structure with activity to obtain a partial model of a certain level of the physical reality. In this case, *reality* is represented by the partial pharmacophore. If the pharmacophore is more or less correct, then we have a *tool* to be employed for the generation of *new knowledge* (new molecules with enhanced or diminished activity). On the other hand, there is a problem with the Molecular Orbitals themselves. It is well known that the Hartree-Fock (HF) wave function is invariant under any unitary transformation carried out on the canonical MOs. Among all possible unitary transformations, the chemists' taste likes the ones leading, for example, to natural bond orbitals (NBO, corresponding to the Lewis structure

representation of the molecule describing localized electrons in bonds and lone pairs). But this *directed* choice leaves the main problem unsolved and many people embrace fiercely the idea that molecular orbitals have no physical meaning because they do not exist and therefore they cannot be observed [56-62]. If we accept that quantum chemistry is a genuine child of quantum mechanics we must add that molecular orbitals are not quantum-mechanical observables. But the molecular orbitals, canonical or localized, occupied or empty, have shown beyond all reasonable doubt that they serve to explain a great variety of chemical phenomena. The alert reader surely noted that in this and earlier papers we employed canonical MOs and that the results relating several kinds of structures with activity are very good (we employed DFT results instead of HF ones, but it must be remembered that the Kohn and Sham density functional approach is also an orbital-based method). He or she probably also noted that we used the term "*vacant*" (empty) to refer to the resulting MOs having no electrons, instead of "*virtual*". Sometimes we have proposed interactions between vacant MOs [63, 64], *as if they were there*. Another point of view has been proposed by Labarca and Lombardi by asking the question: *what privilege does quantum mechanics carries for becoming the clue witness about what exists and does not exist in the world?* [65]. They conclude that *orbitals exist in the ontology of molecular chemistry, in spite of the fact that they do not exist in the quantum world*. As Lombardi suggested, the conceptual breakdown or discontinuity between quantum mechanics and quantum chemistry seems to occur with the Born-Oppenheimer approximation and with the concept of molecular orbitals [66]. If this is the case, then there are no formal reasons preventing the direct or indirect visualization of molecular orbitals.

REFERENCES

[1] H-Q Wu, J Yao, Q-Q He, W-X Chen, F-E Chen, et al., *Bioorg. Med. Chem.*, **2015**, 23, 624-631.
[2] Z-Y Wan, J Yao, Y Tao, T-Q Mao, X-L Wang, et al., *Eur. J. Med. Chem.*, **2015**, 97, 1-9.
[3] Z-Y Wan, Y Tao, Y-F Wang, T-Q Mao, H Yin, et al., *Bioorg. Med. Chem.*, **2015**, 23, 4248-4255.
[4] W Li, X Li, E De Clercq, P Zhan, X Liu, *Eur. J. Med. Chem.*, **2015**, 102, 167-179.
[5] X Han, H Wu, C Dong, P Tien, W Xie, et al., *RSC Adv.*, **2015**, 5, 10005-10013.
[6] KM Frey, DE Puleo, KA Spasov, M Bollini, WL Jorgensen, et al., *J. Med. Chem.*, **2015**, 58, 2737-2745.
[7] Z-H Yan, H-Q Wu, W-X Chen, Y Wu, H-R Piao, et al., *Bioorg. Med. Chem.*, **2014**, 22, 3220-3226.
[8] Z-H Yan, X-Y Huang, H-Q Wu, W-X Chen, Q-Q He, et al., *Bioorg. Med. Chem.*, **2014**, 22, 2535-2541.
[9] Z Xu, M Ba, H Zhou, Y Cao, C Tang, et al., *Eur. J. Med. Chem.*, **2014**, 85, 27-42.
[10] J Wang, P Zhan, Z Li, H Liu, E De Clercq, et al., *Eur. J. Med. Chem.*, **2014**, 76, 531-538.
[11] V Murugesan, N Makwana, R Suryawanshi, R Saxena, R Tripathi, et al., *Bioorg. Med. Chem.*, **2014**, 22, 3159-3170.
[12] A-M Monforte, S Ferro, L De Luca, G Lo Surdo, F Morreale, et al., *Bioorg. Med. Chem.*, **2014**, 22, 1459-1467.
[13] G Meng, Y Liu, A Zheng, F Chen, W Chen, et al., *Eur. J. Med. Chem.*, **2014**, 82, 600-611.
[14] Y Liu, G Meng, A Zheng, F Chen, W Chen, et al., *Eur. J. Pharmac. Sci.*, **2014**, 62, 334-341.
[15] X Han, H Wu, W Wang, C Dong, P Tien, et al., *Org. Biomol. Chem.*, **2014**, 12, 8308-8317.
[16] V Famiglini, G La Regina, A Coluccia, S Pelliccia, A Brancale, et al., *J. Med. Chem.*, **2014**, 57, 9945-9957.
[17] V Famiglini, G La Regina, A Coluccia, S Pelliccia, A Brancale, et al., *Eur. J. Med. Chem.*, **2014**, 80, 101-111.
[18] B Côté, JD Burch, E Asante-Appiah, C Bayly, L Bédard, et al., *Bioorg. Med. Chem. Lett.*, **2014**, 24, 917-922.
[19] S Yang, C Pannecouque, D Daelemans, X-D Ma, Y Liu, et al., *Eur. J. Med. Chem.*, **2013**, 65, 134-143.
[20] UP Singh, HR Bhat, A Verma, MK Kumawat, R Kaur, et al., *RSC Adv.*, **2013**, 3, 17335-17348.
[21] A Li, Y Ouyang, Z Wang, Y Cao, X Liu, et al., *J. Med. Chem.*, **2013**, 56, 3593-3608.
[22] X Chen, X Liu, Q Meng, D Wang, H Liu, et al., *Bioorg. Med. Chem. Lett.*, **2013**, 23, 6593-6597.
[23] M Bollini, R Gallardo-Macias, KA Spasov, J Tirado-Rives, KS Anderson, et al., *Bioorg. Med. Chem. Lett.*, **2013**, 23, 1110-1113.
[24] JS Gómez-Jeria, M Flores-Catalán, *Canad. Chem. Trans.*, **2013**, 1, 215-237.
[25] DA Alarcón, F Gatica-Díaz, JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2013**, 58, 1651-1659.
[26] F Soto-Morales, JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2007**, 52, 1214-1219.
[27] J Valdebenito-Gamboa, JS Gómez-Jeria, *Der Pharma Chem.*, **2015**, 7, 543-555.
[28] YC Martin, *Quantitative drug design: a critical introduction*, M. Dekker, New York, 1978.
[29] JS Gómez-Jeria, *SOP Trans. Phys. Chem.*, **2014**, 1, 10-28.
[30] JS Gómez-Jeria, *Canad. Chem. Trans.*, **2013**, 1, 25-55.
[31] JS Gómez-Jeria, *Elements of Molecular Electronic Pharmacology (in Spanish)*, Ediciones Sokar, Santiago de Chile, **2013**.
[32] T Bruna-Larenas, JS Gómez-Jeria, *Int. J. Med. Chem.*, **2012**, 2012 Article ID 682495, 1-16.
[33] JS Gómez-Jeria, M Ojeda-Vergara, *J. Chil. Chem. Soc.*, **2003**, 48, 119-124.

[34] JS Gómez-Jeria, "Modeling the Drug-Receptor Interaction in Quantum Pharmacology," in *Molecules in Physics, Chemistry, and Biology*, J. Maruani Ed., vol. 4, pp. 215-231, Springer Netherlands, **1989**.
[35] JS Gómez-Jeria, *Int. J. Quant. Chem.*, **1983**, 23, 1969-1972.
[36] A Robles-Navarro, JS Gómez-Jeria, **2015**
[37] MS Leal, A Robles-Navarro, JS Gómez-Jeria, *Der Pharm. Lett.*, **2015**, 7, 54-66.
[38] JS Gómez-Jeria, J Valdebenito-Gamboa, *Der Pharma Chem.*, **2015**
[39] JS Gómez-Jeria, J Valdebenito-Gamboa, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 203-218.
[40] JS Gómez-Jeria, J Valdebenito-Gamboa, *Der Pharma Chem.*, **2015**, 7, 323-347.
[41] JS Gómez-Jeria, J Valdebenito-Gamboa, *Der Pharm. Lett.*, **2015**, 7, 211-219.
[42] JS Gómez-Jeria, A Robles-Navarro, *Amer. J. Chem. App.*, **2015**, 2, 66-80.
[43] JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 1358-1373.
[44] JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 1811-1841.
[45] JS Gómez-Jeria, A Robles-Navarro, *J. Comput. Methods Drug Des.*, **2015**, 5, 15-26.
[46] JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 755-783.
[47] JS Gómez-Jeria, A Robles-Navarro, *Der Pharma Chem.*, **2015**, 7, 243-269.
[48] JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 1337-1351.
[49] JS Gómez-Jeria, I Reyes-Díaz, J Valdebenito-Gamboa, *J. Comput. Methods Drug Des.*, **2015**, 5, 25-56.
[50] JS Gómez-Jeria, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 688-697.
[51] MJ Frisch, GW Trucks, HB Schlegel, GE Scuseria, MA Robb, et al., "G03 Rev. E.01," Gaussian, Pittsburgh, PA, USA, **2007**.
[52] JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2009**, 54, 482-485.
[53] JS Gómez-Jeria, "D-Cent-QSAR: A program to generate Local Atomic Reactivity Indices from Gaussian 03 log files. 1.0," Santiago, Chile, **2014**.
[54] JS Gómez-Jeria, "STERIC: A program for calculating the Orientational Parameters of the substituents " Santiago, Chile, **2015**.
[55] Statsoft, "Statistica 8.0," 2300 East 14 th St. Tulsa, OK 74104, USA, 1984-**2007**.
[56] A Julg, *Bull. Soc. Chim. Belges*, **1976**, 85, 985-994.
[57] RG Woolley, BT Sutcliffe, *Chem. Phys. Lett.*, **1977**, 45, 393-398.
[58] A Julg, *Int. J. Quant. Chem.*, **1984**, 26, 709-715.
[59] JF Ogilvie, *J. Chem. Ed.*, **1990**, 67, 280.
[60] WHE Schwarz, *Ang. Chem. Int. Ed.*, **2006**, 45, 1508-1517.
[61] P Mulder, *Hyle - Int. J. Phil. Chem.*, **2011**, 17, 24-35.
[62] JF Ogilvie, *Found. Chem.*, **2011**, 13, 87-91.
[63] E Joselevich, *ChemPhysChem*, **2004**, 5, 619-624.
[64] E Joselevich, *Ang. Chem. Int. Ed.*, **2004**, 43, 2992-2994.
[65] M Labarca, O Lombardi, *Found. Chem.*, **2010**, 12, 149-157.
[66] O Lombardi, "The Ontological Autonomy of the Chemical World: Facing the Criticisms," in *Philosophy of Chemistry*, E. Scerri, L. McIntyre Eds., vol. 306, pp. 23-38, Springer Netherlands, **2015**.