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A quantum chemical study of the inhibition of α-glucosidase by a group of oxadiazole benzohydrazone derivatives

Juan S. Gómez-Jeria* and Valeria Gazzano

Quantum Pharmacology Unit, Department of Chemistry, Faculty of Sciences, University of Chile. Las Palmeras 3425, Santiago 7800003, Chile

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ABSTRACT

A study of the relationships between electronic structure and α-glucosidase inhibition for a series of oxadiazole benzohydrazone derivatives. The electronic structure was obtained at the B3LYP/6-31G(d,p) level after full geometry optimization. The D-Cent-QSAR software and linear multiple regression analysis were used to obtain a statistically significant equation. Sites for the interaction with electron-rich and electron-deficient centers are proposed.

Keywords: Diabetes Mellitus, QSAR, KPG method, α-glucosidase, DFT, electronic structure.

INTRODUCTION

a-glucosidase is a glycosidic hydrolase enzyme present in the brush border surface of intestinal cells. It catalyzes the final step in the digestive process of carbohydrates and is essential in the release of monosaccharides from carbohydrates, as human intestine only absorbs monosacharides for blood circulation. Carbohydrate metabolism disorder results in an increase of glucose levels in blood. This complication gives birth to Diabetes Mellitus. α-glucosidase inhibitors can delay the liberation of d-glucose from complex carbohydrates and delay glucose absorption, causing reduced postprandial plasma glucose levels and the suppression of postprandial hyperglycemia. The interest for finding highly effective α-glucosidase inhibitors against diabetes led to an intensive search of natural sources as well as to the synthesis and testing to a great variety of molecular systems [1-35] (and references therein). In this paper we present the results of the application of the Klopman-Peradejordi-Gómez (KPG) method to the study of the relationships between the electronic structure of a series of oxadiazole benzohydrazone derivatives and their a-glucosidase inhibitory capacity.

MATERIALS AND METHODS

The Klopman-Peradejordi-Gómez (KPG) method employed here to obtain relationships between the electronic structure and biological activity is the only member of the formal methods class [36]. It is rooted on the statistical-mechanical definition of the equilibrium constant and Klopman's formula for the interaction energy between two molecular systems (ΔE) [37-39]. The first version of this model provided very good results for several kinds of molecules and receptors [40-44]. Between 1980 and 2013, the interaction energy expression was expanded to include the contribution of single molecular orbitals, the conceptual basis for calculating the orientational parameter of the substituents was presented and new local atomic reactivity indices were obtained from the ΔE expression [45-48]. During year 2013 an important advance was accomplished when it was shown that the method can be applied

productively to any biological activity [49]. From this moment the application of the KPG method to very different molecular systems and biological activities produced unexpectedly good results ([50-73] and references therein). Considering that the method has been presented and explained in detail in many publications, we shall discuss here only the resulting equations.

Selection of molecules and biological activities

The selected molecules are a group of oxadiazole benzohydrazone derivatives and were selected from a recent study [15]. Their general formula and biological activity are displayed, respectively, in Fig. 1 and Table 1.

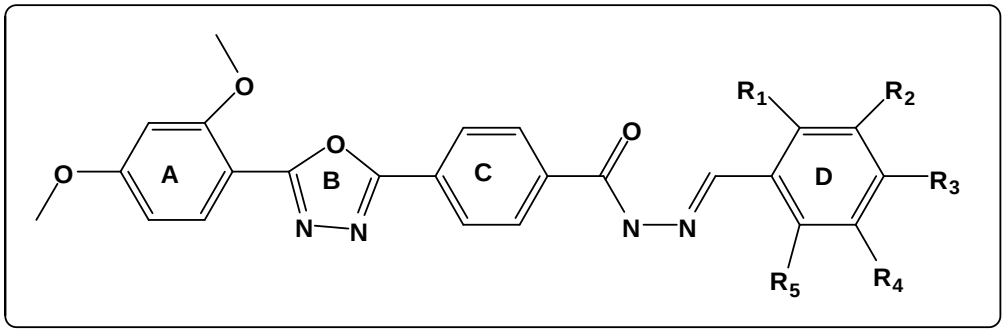

Figure 1. General formulas of oxadiazole benzohydrazone derivatives

Table 1. Oxadiazole benzohydrazone derivatives and α-glucosidase inhibition [15]

Mol.	Mol.	R_1	R_2	R_3	R_4	R_5	log(IC_{50})
1	6	H	H	OH	H	H	2.26
2	7	H	OH	H	H	H	2.32
3	8	H	OH	OH	H	H	1.45
4	9	OH	H	H	OH	H	1.94
5	12	H	OMe	OH	H	H	2.17
6	13	OH	H	OH	H	OH	1.47
7	16	Cl	H	H	H	H	0.79
8	18	OH	H	OH	OH	H	0.42
9	20	OH	H	H	OMe	H	2.41
10	22	H	H	*	H	H	2.66
11	23	OH	H	H	H	H	1.54
12	24	*	H	H	H	H	1.40
13	25	F	H	H	H	H	1.27
14	26	H	H	F	H	H	1.68
15	27	H	Cl	H	H	H	1.83
16	28	H	H	Cl	H	H	1.38

*In molecules marked *, the C atom (see Fig.2 below) was replaced by N.*

Calculations

The electronic structure of all molecules was calculated within the Density Functional Theory (DFT) at the B3LYP/6-31g(d,p) level with full geometry optimization [74]. The Gaussian suite of programs was used. All the information needed to calculate numerical values for the local atomic reactivity indices was obtained from the Gaussian results with the D-Cent-QSAR software [75]. All the electron populations smaller than or equal to 0.01 e were considered as zero [48]. Negative electron populations coming from Mulliken Population Analysis were corrected as usual [76]. Orientational parameters were taken from Tables [77]. Since the resolution of the system of linear equations is not possible because we have not enough molecules, we made use of Linear Multiple Regression Analysis (LMRA) techniques to find the best solution. For each case, a matrix containing the dependent variable (the biological activity of each case) and the local atomic reactivity indices of all atoms of the common skeleton as independent variables was. The Statistica software was used for LMRA [78]. We worked with the *common skeleton hypothesis* stating that there is a definite collection of atoms, common to all molecules analyzed, that accounts for nearly all the biological activity. The action of the substituents consists in modifying the electronic structure of the common skeleton and influencing the right alignment of the drug throughout the orientational parameters. It is hypothesized that different parts or this common skeleton accounts for almost all the interactions leading to the

expression of a given biological activity. The common skeleton for oxadiazole benzohydrazone derivatives is shown in Fig. 2.

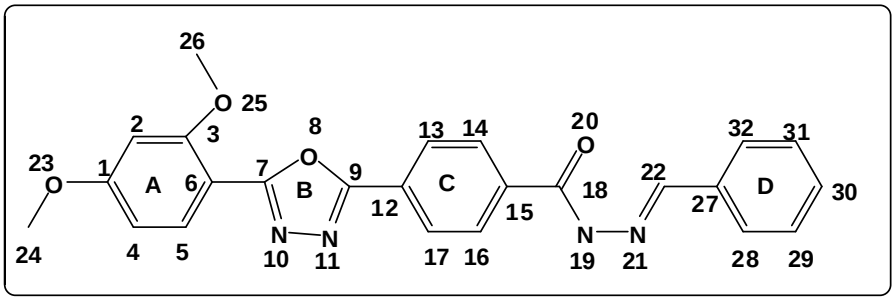

Figure 2. Common skeleton numbering of oxadiazole benzohydrazone derivatives

RESULTS

No statistically significant equation was obtained for the whole set of molecules (n=16). We used a technique consisting in the extraction from the set, one by one, the molecules having the highest values of log(IC_{50}). We obtained the following equation:

$$\log(IC_{50}) = -9.46 + 6.56S_7^{E}(\mathrm{HOMO}-2)^{*} + 0.78S_{30}^{N} - \\ -0.02S_{22}^{N} + 0.004\varphi_{R2} - 0.62S_{17}^{E}(\mathrm{HOMO}-1)^{*} \quad (1)$$

with n=13, R=0.99, R^2=0.98, adj-R^2=0.97, F(5,7)=77.69 (p<0.00001) and SD=0.09. No outliers were detected and no residuals fall outside the ±2σ limits. Here, S_7^{E}(HOMO-2)*is the electrophilic superdelocalizability of the third highest occupied MO localized on atom 7, S_{30}^{N} is the total atomic nucleophilic superdelocalizability of atom 30, S_{22}^{N} is the total atomic nucleophilic superdelocalizability of atom 22, φ_{R2} is the orientational parameter of the R_2 substituent and S_{17}^{E}(HOMO-1)* is the electrophilic superdelocalizability of the second highest occupied MO localized on atom 17. 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. 1. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed *vs.* calculated log(IC_{50}).

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

Var.	Beta	t(7)	p-level
S_7^{E}(HOMO-2)*	1.01	15.84	<0.000001
S_{30}^{N}	0.69	10.63	<0.00001
S_{22}^{N}	-0.52	-7.87	<0.0001
φ_{R2}	0.23	3.98	<0.005
S_{17}^{E}(HOMO-1)*	-0.25	-3.19	<0.02

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

	S_7^{E}(HOMO-2)*	S_{30}^{N}	S_{22}^{N}	φ_{R2}
S_{30}^{N}	0.27	1.00		
S_{22}^{N}	0.17	0.22	1.00	
φ_{R2}	0.09	0.07	0.01	1.00
S_{17}^{E}(HOMO-1)*	0.31	0.31	0.34	0.21

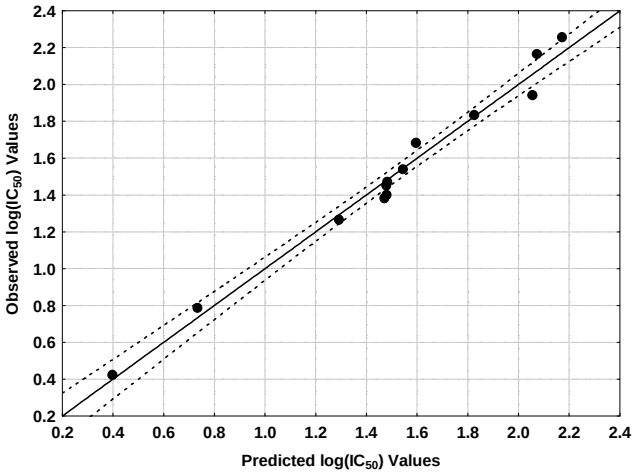

Table 4. Local MO structure of atoms 7 and 17

Mol.	Atom 7 (C)	Atom 17 (C)
1 (116)	114π115π116π-117π118π119π	114π115π116π-117π119π120π
2 (116)	112π113π116π-117π118π119π	112π113π116π-117π118π119π
3 (120)	116π117π119π-121π122π123π	116π117π119π-121π123π124π
4 (120)	116π117π119π-121π122π123π	116π117π119π-121π122π123π
5 (124)	120π121π123π-125π126π127π	120π121π123π-125π127π128π
6 (124)	121π123π124π-125π126π127π	119π121π123π-125π127π128π
7 (120)	117π118π120π-121π122π123π	115π117π120π-121π122π123π
8 (124)	119π121π123π-125π126π127π	120π121π12 π-125π127π128π
9 (124)	120π121π123π-125π126π127π	120π121π123π-125π126π127π
10 (112)	108π110π112π-113π114π115π	107π108π112π-113π114π115π
11 (116)	112π113π116π-117π118π119π	113π115π116π-117π118π119π
12 (112)	109π110π112π-113π114π115π	109π110π112π-113π114π116π
13 (116)	113π114π116π-117π118π119π	113π114π116π-117π118π119π
14 (116)	113π114π116π-117π118π119π	113π114π116π-117π118π119π
15 (120)	117π118π120π-121π122π123π	115π117π120π-121π122π123π
16 (120)	117π118π120π-121π122π123π	116π117π120π-121π122π123π

Figure 3. Plot of predicted *vs*. observed log(IC_{50}) values (Eq. 1). Dashed lines denote the 95% confidence interval.

The associated statistical parameters of Eq. 1 indicate that this equation is statistically significant and that the variation of the numerical values of a group of five local atomic reactivity indices of atoms of the common skeleton explains about 97% of the variation of log(IC_{50}). Figure 3, spanning about 2 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values and that almost all points are inside the 95% confidence interval. This can be considered as an indirect evidence that the common skeleton hypothesis works relatively well for this set of molecules. A very important point to stress is the following. When a local atomic reactivity index of an inner occupied MO (i.e., HOMO-1 and/or HOMO-2) or of a higher vacant MO (LUMO+1 and/or LUMO+2) appears in any equation, this means that the remaining of the upper occupied MOs (for example, if HOMO-2 appears, upper means HOMO-1 and HOMO) or the remaining of the empty MOs (for example, if LUMO+1 appears, lower means the LUMO) contribute to the interaction. Their absence in the equation only means that the variation of their numerical values does not account for the variation of the numerical value of the biological property.

Local Molecular Orbitals

Table 4 shows the local MO structure of atoms 7 and 17 (see Fig. 2). Nomenclature: Molecule (HOMO) / (HOMO-2)* (HOMO-1)* (HOMO)* - (LUMO)* (LUMO+1)* (LUMO+2)*.

DISCUSSION

Table 2 shows that the importance of variables in Eq. 1 is S_7^E(HOMO-2)*> S_{30}^N> S_{22}^N> S_{17}^E(HOMO-1)*> φ_{R2}. A high inhibitory activity is associated with low numerical values for the orientational parameter of the R_2 substituent (φ_{R2}) and S_{17}^E(HOMO-1)* and with high (negative) numerical values for S_7^E(HOMO-2)*. If S_{30}^N is positive, low

numerical values for this index are associated with high activity. If S_{22}^{N} is positive, high numerical values for this index are associated with high activity. Atom 7 is a carbon in ring B (Fig. 2). The three highest occupied local MOs have a π nature (Table 4). The high value of S_7^{E}(HOMO-2)* suggests that this MO seems to be engaged in an interaction with empty MOs of the site. Regarding S_7^{E}(HOMO-1)* and S_7^{E}(HOMO)*, that do not appear in Eq. 1, a plot of log(IC_{50}) *versus* their values (not shown here) also suggests that they are engaged in interactions with one or more empty MOs of the site. These data allow us to suggest that atom 7 is interacting with an electron-deficient center. Atom 17 is a carbon in ring C (Fig. 2). A high inhibitory activity is associated with low (negative) numerical values for S_{17}^{E}(HOMO-1)*. Table 4 shows that the three highest occupied local MOs have π nature. A plot of S_{17}^{E}(HOMO-1)* *versus* inhibitory activity (not shown here) indicates that also a high inhibitory activity is associated with low (negative) numerical values. Therefore, it seems that these two MOs are engaged in repulsive interactions with one or more occupied MOs of the site. Then atom 17 seems to interact with an electron-rich center. Atom 22 is a carbon in the chain linking rings C and D (Fig. 2). High numerical (positive) values for S_{22}^{N} are obtained by shifting downwards the associated eigenvalue. Let us remember that the LUMO and close vacant MOs are the main numerical components of S^{N}. This procedure makes the LUMO more reactive. Therefore, we suggest that atom 22 is interacting with an electron-rich center. Atom 30 is a carbon in ring D (Fig. 2). If positive, low numerical values for S_{30}^{N} are associated with high inhibitory activity. These low values are obtained by shifting upwards the value of the associated eigenvalue and making the vacant MOs less reactive. Therefore we suggest that atom 30 is interacting with an electron-deficient center. A high inhibitory activity is also associated with low values for the orientational parameter of the R_2 substituent. In our case, R_2 is H, Cl, OH or OMe (Table 1). To suggest the nature of the optimal substituent is rather complicated for two reasons. The first one is the direct influence of the substituent upon the electronic structure of ring D, and especially on atom 30. The second reason is that a substituent may affect the *whole* electronic structure of the molecule producing changes in the MO localization. It seems that the most reliable approach is to carry out electronic structure calculations with substituents of different sizes but having in common a similar effect on the ring. All the suggestions are displayed in the partial 2D pharmacophore of Fig. 4.

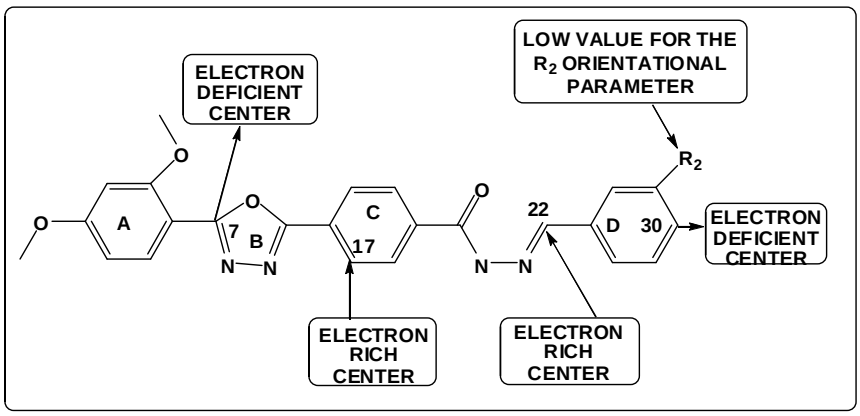

Figure 4. Partial 2D pharmacophore for the inhibition of α-glucosidase by a group of oxadiazole benzohydrazone derivatives

In summary, we obtained a statistically significant relationship between electronic structure and α-glucosidase inhibition for a group of oxadiazole benzohydrazone derivatives. This information should serve as a basis for proposing new molecular systems endowed with a higher inhibitory activity.

REFERENCES

[1]M-H Yu, Z-F Shi, B-W Yu, E-H Pi, H-Y Wang, et al., *Fitoter.*, **2014**, 98, 143-148.
[2]Y-M Ying, L-Y Zhang, X Zhang, H-B Bai, D-E Liang, et al., *Phytochem.*, **2014**, 108, 171-176.
[3]M Yar, M Bajda, L Shahzadi, SA Shahzad, M Ahmed, et al., *Bioorg. Chem.*, **2014**, 54, 96-104.
[4]S-M Wang, J-J Han, K Ma, T Jin, L Bao, et al., *Fitoter.*, **2014**, 98, 149-155.
[5]AB Shori, AS Baba, *J. Saudi Chem. Soc.*, **2014**, 18, 456-463.
[6]R Ramu, PS Shirahatti, F Zameer, LV Ranganatha, MN Nagendra Prasad, *South Af. J. Bot.*, **2014**, 95, 54-63.
[7]T Pozzo, M Plaza, J Romero-García, M Faijes, EN Karlsson, et al., *J. Mol. Catal. B.*, **2014**, 107, 132-139.
[8]R Mendes, VCM Duarte, A Gil Fortes, MJ Alves, *Carbohyd. Res.*, **2014**, 395, 52-57.
[9]BTT Luyen, BH Tai, NP Thao, SY Yang, NM Cuong, et al., *Bioorg. Med. Chem. Lett.*, **2014**, 24, 4120-4124.

[10]BT Zhao, DD Le, PH Nguyen, MY Ali, J-S Choi, et al., *Chem. Biol. Int.*, **2016**, 253, 27-37.
[11]G Wang, J Wang, D He, X Li, J Li, et al., *Bioorg. Med. Chem. Lett.*, **2016**, 26, 2806-2809.
[12]M Taha, NH Ismail, S Imran, MH Mohamad, A Wadood, et al., *Bioorg. Chem.*, **2016**, 65, 100-109.
[13]L Dinparast, H Valizadeh, MB Bahadori, S Soltani, B Asghari, et al., *J. Mol. Struct.*, **2016**, 1114, 84-94.
[14]J Chen, Y Wu, J Zou, K Gao, *Bioorg. Med. Chem.*, **2016**, 24, 1488-1494.
[15]M Taha, NH Ismail, S Imran, MQB Rokei, SM Saad, et al., *Bioorg. Med. Chem.*, **2015**, 23, 4155-4162.
[16]YH Song, DW Kim, MJ Curtis-Long, C Park, M Son, et al., *Eur. J. Med. Chem.*, **2016**, 114, 201-208.
[17]W Worawalai, S Wacharasindhu, P Phuwapraisirisan, *Bioorg. Med. Chem. Lett.*, **2015**, 25, 2570-2573.
[18]H Sun, Y Li, X Zhang, Y Lei, W Ding, et al., *Bioorg. Med. Chem. Lett.*, **2015**, 25, 4567-4571.
[19]H Niaz, H Kashtoh, JAJ Khan, A Khan, A-t Wahab, et al., *Eur. J. Med. Chem.*, **2015**, 95, 199-209.
[20]Y-Y Ma, D-G Zhao, A-Y Zhou, Y Zhang, Z Du, et al., *J. Ag. Food Chem.*, **2015**, 63, 8162-8169.
[21]Z-X Liu, C-T Liu, Q-B Liu, J Ren, L-Z Li, et al., *J. Funct. Foods*, **2015**, 18, Part A, 512-519.
[22]K Javaid, SM Saad, S Rasheed, ST Moin, N Syed, et al., *Bioorg. Med. Chem.*, **2015**, 23, 7417-7421.
[23]G-L Li, C-Y Cai, J-Y He, L Rao, L Ma, et al., *Bioorg. Med. Chem.*, **2016**, 24, 1431-1438.
[24]OO Johnson, M Zhao, J Gunn, BD Santarsiero, Z-Q Yin, et al., *J. Nat. Prod.*, **2016**, 79, 224-229.
[25]K Wang, L Bao, K Ma, N Liu, Y Huang, et al., *Tetrahedron*, **2015**, 71, 9557-9563.
[26]M Taha, NH Ismail, K Javaid, S Imran, EH Anouar, et al., *Bioorg. Chem.*, **2015**, 63, 24-35.
[27]E Rattanangkool, P Kittikhunnatham, T Damsud, S Wacharasindhu, P Phuwapraisirisan, *Eur. J. Med. Chem.*, **2013**, 66, 296-304.
[28]F Panahi, R Yousefi, MH Mehraban, A Khalafi-Nezhad, *Carbohyd. Res.*, **2013**, 380, 81-91.
[29]S Long, FR Stefani, S Biondi, G Ghiselli, M Panunzio, *Bioorg. Med. Chem.*, **2013**, 21, 5811-5822.
[30]X Bian, Q Wang, C Ke, G Zhao, Y Li, *Bioorg. Med. Chem. Lett.*, **2013**, 23, 2022-2026.
[31]SF Sulaiman, KL Ooi, Supriatno, *J. Ag. Food Chem.*, **2012**, 61, 10080-10090.
[32]Y-C Lai, C-K Chen, S-F Tsai, S-S Lee, *Phytochem.*, **2012**, 74, 206-211.
[33]Y Natori, T Imahori, K Murakami, Y Yoshimura, S Nakagawa, et al., *Bioorg. Med. Chem. Lett.*, **2011**, 21, 738-741.
[34]H-H Chan, H-D Sun, MVB Reddy, T-S Wu, *Phytochem.*, **2010**, 71, 1360-1364.
[35]G Tanabe, W Xie, A Ogawa, C Cao, T Minematsu, et al., *Bioorg. Med. Chem. Lett.*, **2009**, 19, 2195-2198.
[36]YC Martin, *Quantitative drug design: a critical introduction*, M. Dekker, New York, 1978.
[37]RF Hudson, G Klopman, *Tet. Lett.*, **1967**, 8, 1103-1108.
[38]G Klopman, RF Hudson, *Theoret. Chim. Acta*, **1967**, 8, 165-174.
[39]G Klopman, *J. Am. Chem. Soc.*, **1968**, 90, 223-234.
[40]F Peradejordi, AN Martin, A Cammarata, *J. Pharm. Sci.*, **1971**, 60, 576-582.
[41]F Tomas, JM Aulló, *J. Pharm. Sci.*, **1979**, 68, 772-776.
[42]JS Gómez-Jeria, L Espinoza, *Bol. Soc. Chil. Quím.*, **1982**, 27, 142-144.
[43]JS Gómez-Jeria, D Morales-Lagos, The mode of binding of phenylalkylamines to the Serotonergic Receptor, in *QSAR in design of Bioactive Drugs*, M. Kuchar Ed., pp. 145-173, Prous, J.R., Barcelona, Spain, 1984.
[44]JS Gómez-Jeria, DR Morales-Lagos, *J. Pharm. Sci.*, **1984**, 73, 1725-1728.
[45]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**.
[46]JS Gómez-Jeria, M Ojeda-Vergara, *J. Chil. Chem. Soc.*, **2003**, 48, 119-124.
[47]JS Gómez-Jeria, *Elements of Molecular Electronic Pharmacology (in Spanish)*, Ediciones Sokar, Santiago de Chile, **2013**.
[48]JS Gómez-Jeria, *Canad. Chem. Trans.*, **2013**, 1, 25-55.
[49]JS Gómez-Jeria, M Flores-Catalán, *Canad. Chem. Trans.*, **2013**, 1, 215-237.
[50]C Barahona-Urbina, S Nuñez-Gonzalez, JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2012**, 57, 1497-1503.
[51]DA Alarcón, F Gatica-Díaz, JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2013**, 58, 1651-1659.
[52]A Paz de la Vega, DA Alarcón, JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2013**, 58, 1842-1851.
[53]I Reyes-Díaz, JS Gómez-Jeria, *J. Comput. Methods Drug Des.*, **2013**, 3, 11-21.
[54]F Gatica-Díaz, JS Gómez-Jeria, *J. Comput. Methods Drug Des.*, **2014**, 4, 79-120.
[55]JS Gómez-Jeria, *Int. Res. J. Pure App. Chem.*, **2014**, 4, 270-291.
[56]JS Gómez-Jeria, *Der Pharm. Lett.*, **2014**, 6., 95-104.
[57]JS Gómez-Jeria, *Brit. Microbiol. Res. J.*, **2014**, 4, 968-987.
[58]JS Gómez-Jeria, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 688-697.
[59]JS Gómez-Jeria, MB Becerra-Ruiz, *Der Pharma Chem.*, **2015**, 7, 362-369.
[60]JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 755-783.

[61]JS Gómez-Jeria, A Robles-Navarro, *Res. J. Pharmac. Biol. Chem. Sci.*, **2015**, 6, 1358-1373.
[62]JS Gómez-Jeria, J Valdebenito-Gamboa, *Der Pharm. Lett.*, **2015**, 7, 211-219.
[63]JS Gómez-Jeria, J Valdebenito-Gamboa, *Res. J. Pharmac. Biol. Chem. Sci*., **2015**, 6, 203-218.
[64]JS Gómez-Jeria, J Valdebenito-Gamboa, *Der Pharma Chem.*, **2015**, 7, 103-121.
[65]MS Leal, A Robles-Navarro, JS Gómez-Jeria, *Der Pharm. Lett.*, **2015**, 7, 54-66.
[66]J Valdebenito-Gamboa, JS Gómez-Jeria, *Der Pharma Chem.*, **2015**, 7, 543-555.
[67]HR Bravo, BE Weiss-López, J Valdebenito-Gamboa, JS Gómez-Jeria, *Res. J. Pharmac. Biol. Chem. Sci*., **2016**, 7, 792-798.
[68]JS Gómez-Jeria, S Abarca-Martínez, *Der Pharma Chem.*, **2016**, 8, 507-526.
[69]JS Gómez-Jeria, HR Bravo, *Der Pharma Chem.*, **2016**, 8, 25-34.
[70]JS Gómez-Jeria, R Cornejo-Martínez, *Der Pharma Chem.*, **2016**, 8, 329-337.
[71]JS Gómez-Jeria, C Moreno-Rojas, *Der Pharma Chem.*, **2016**, 8, 475-482.
[72]JS Gómez-Jeria, Í Orellana, *Der Pharma Chem.*, **2016**, 8, 476-487.
[73]A Robles-Navarro, JS Gómez-Jeria, *Der Pharma Chem.*, **2016**, 8, 417-440.
[74]MJ Frisch, GW Trucks, HB Schlegel, GE Scuseria, MA Robb, et al., G03 Rev. E.01, Gaussian, Pittsburgh, PA, USA, **2007**.
[75]JS Gómez-Jeria, D-Cent-QSAR: A program to generate Local Atomic Reactivity Indices from Gaussian 03 log files. v. 1.0, Santiago, Chile, **2014**.
[76]JS Gómez-Jeria, *J. Chil. Chem. Soc.*, **2009**, 54, 482-485.
[77]JS Gómez-Jeria, *Res. J. Pharmac. Biol. Chem. Sci*., **2016**, 7, 288-294.
[78]Statsoft, Statistica v. 8.0, 2300 East 14 th St. Tulsa, OK 74104, USA, **1984-2007**.