International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 6 Issue 3 ǁ March 2017 ǁ PP. 38-43

Antibacterial Activity of Schiff Bases Derived from Ortho-Diaminocyclohexane, Meta-Phenylenediamine and 1,6-Diaminohexane: Qsar Study with Quantum Descriptors

[1]Niameke Jean-Baptiste Kangah, [1]Mamadou Guy-Richard Koné, [1,2*]Charles Guillaume Kodjo, [3]Boka Robert N'guessan, [4]Ahmont Landry Claude Kablan, [1]Sénoung Arnaurd Yéo and [1]Nahossé Ziao

[1]*Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, UFR SFA, Université Nangui Abrogoua 02 BP 801 Abidjan 02, Côte-d'Ivoire,*

[2]*Laboratoire de Chimie BioOrganique et de Substances Naturelles, Université Nangui Abrogoua, UFR-SFA, 02 B.P. 801 Abidjan 02 Côte-d'Ivoire,*

[3]*Laboratoire de Chimie Organique Structurale, UFR SSMT, Université Félix-Houphouët Boigny, B.P 582 Abidjan 22, Côte-d'Ivoire,*

[4]*UFR des Sciences Biologiques, Université Péléforo Gon Coulibaly de Korhogo, BP 1328 Korhogo, Côte d'Ivoire*

Abstract: *Schiff bases (SBs) are known to possess many biological activities. In this paper we will be interested in nine SBs derived from ortho-diaminocyclohexane, meta-phenylenediamine, 1,6-diaminohexane and benzaldehydes variously substituted by nitro group. We had synthesized, characterized and tested these molecules for their antibacterial properties. Herein our study focuses in particular on the determination of quantum descriptors on which observed antibacterial activity depends, in order to be able to predict biological activities in analogue molecule series. Using quantum chemistry methods at B3LYP / 6-31G (d, p) level, we determined for each molecules, theoretical antibacterial potentials that we correlated to the experimental ones. Calculation results showed that, the energy of the Highest Occupied Molecular Orbital (**E_{HOMO}**), electronegativity (**χ**) and electronic energy (**E**), are the best quantum descriptors related to the antibacterial activity values of studied molecules. The correlation coefficient **R^2** indicates that 92.1% of the molecular descriptors defining this model are taken into account with a standard deviation of 0.152.The model significance is reflected by Fischer coefficient **F** = 7.721: Correlation coefficient of cross-validation **Q^2_{CV}**= 0.88. This model is acceptable with $R^2 - Q^2_{CV} = 0.921 - 0.88 = 0.041 < 0.3$. The values of the pCE_{50}theo/pCE_{50}exp values of the validation set tend to unity.*

Keywords: *Schiff base, Quantum chemistry, QSAR, Quantum Descriptors, Antibacterial activity*

I. Introduction

Organic Schiff base (SB) molecules, discovered by Hugo Schiff in 1864 are condensation products of primary amines with carbonyl compounds [**1**,**2**].The common structural feature of these compounds is the azomethine group with the general formula $R_1HC=N-R_2$, where R_1 and R_2 are alkyl, aryl, cycloalkyl, or heterocyclic groups. Imine or azomethine function present in various natural compounds and non-natural derivatives has been found to be critical for their biological activities [**3-5**].For this reason, SBs, which are very easy to synthesize, are inexhaustible source of promising multipurpose pharmacophores for design and development of new biologically important molecules. SBs are in reality known to have a wide range of biological properties such as antibacterial [**6-12**], anticancer [**13-15**], antiviral [**16**], antifungal [**8**,**12**,**17**,**18**], antiparasitic [**8**] in addition to other biological performances [**19**,**20**].As several authors [**21-23**], our systematic research on SBs has enabled us to synthesize many diimines. In this work we are interested in three types of diimine. We have recently synthesized, characterized and tested these compounds for their biological properties against bacterial strain *Staphylococcus aureus* [**24**]. The molecules used in this study are shown in Figure 1.

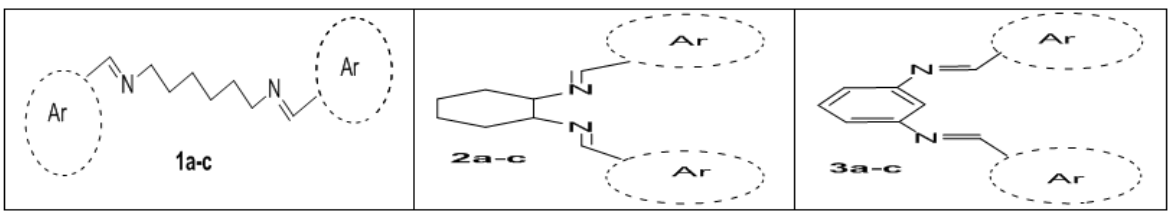
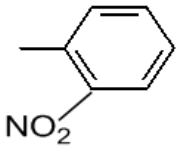
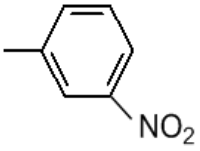
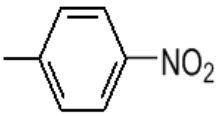


Figure 1: Molecular structures of the types of Schiff bases studied

These derivatives differ from each other by the aryl groups (**Ar**). These aryl groups are shown in the table below.

Table 1: The different aryl groups and molecule codes corresponding

Molecule code	**Ar** Group
1a-3a	
1b-3b	
1c-3c	

These synthesized molecules have shown, among other things, promising antibacterial activity for several of them. On the other hand, their structures offer a high probability of structural change, implying high degree of molecular diversity, which remains very useful for the development of new, less toxic and potent therapeutic agents. Our research work up to now has been limited to the synthesis and the research of activities of these molecules. By implementing the methods of quantum chemistry, this work focus on determining the quantum descriptors whose antibacterial activities observed depend on, in order to be able to predict biological activities in analogue molecule series taking into account these important theoretical results.

II. Experimental Section

2. Materials and methods of calculation

2.1. The calculation level

The six molecules of the training set and the three other validation set molecules used in this study, have various antibacterial concentrations ranging from 48.87 to 375µg/mL. This range of concentrations makes it possible to define a quantitative relationship between the antibacterial activity and the theoretical descriptors. Biological data are generally expressed as the opposite of the log 10 base of activity ($-\boldsymbol{log_{10}(C)}$) in order to obtain higher mathematical values when the structures are biologically very efficient [**25**,**26**]. The antibacterial activity is expressed by the antibacterial potential pCE_{50}. The antibacterial potential is defined from equation (1):

$$pCE_{50} = -log_{10}\left(\frac{CE_{50}}{M} * 10^{-3}\right) (1)$$

Where M is the molecular weight (g/mol) and CE_{50} is the potential concentration 50 in bacteria, it gives the concentration of substance required to destroy 50% bacteria in a population of bacteria under the conditions of the experiment (µg/mL).

The performance of a mathematical model, for Eriksson *et al.* [**27**], is characterized by a value of $Q_{cv}^2 > 0.5$for a satisfactory model when for the excellent model $Q_{cv}^2 > 0.9$. According to them, from a given test set, a model will be performant if the acceptance criterion $R^2 - Q_{cv}^2 < 0.3$ is respected.

In order to find a link between the values of antibacterial activity of the molecules studied and their molecular structures, calculations of quantum chemistry were carried out using the software Gaussian 03 [**28**]. DFT methods are generally known to generate a variety of molecular properties [**29-36**] in Quantitative Structure Activity Relationship (QSAR) studies that increase predictability, reduce calculation time and cost implications in the design of new drugs [**37**, **38**]. The theory level B3LYP/6-31G (d, p) was used to determine the molecular descriptors. As for the choice of the split-valence and double-dzeta bases, they are sufficiently wide and the diffuse and polarization functions are to be taken into account in the quantification of the

molecular descriptors obtained. The modeling was done using the multilinear regression method implemented in Excel and XLSTAT spreadsheets.

2.2. Quantum descriptors used

For the development of QSAR models, some theoretical descriptors related to conceptual DFT have been determined. In particular, the energy of the Highest Occupied Molecular Orbital ($\mathbf{E_{HOMO}}$), electronegativity ( ) and electronic energy (**E**), which are determined from the optimized molecules. It should be noted that the descriptors related to the boundary molecular orbitals ($\mathbf{E_{HOMO}}$,) were calculated very simply in the framework of the Koopmans approximation [**39**] and the electronic energy (**E**).The lowest molecular orbital energy ($\mathbf{E_{HOMO}}$) is obtained after optimization of the molecules. As for electronegativity, it is obtained from equation (2):

$$\chi = -1/2\ (\varepsilon_{LUMO} + \varepsilon_{HOMO}) \qquad (2)$$

For all the descriptors studied, bivariate data analysis, that is to say the calculation of the linear correlation coefficient R between each of the pairs of the set of descriptors is less than 0.95 (**R<0.95**), Which means that these different descriptors are independent of each other [**40-45**].

III. Results And Discussion

3.1. Results

The test set of the six (6) SBs molecules and the three (3) molecules of the validation set (**Table 2**) are shown in Table 2. Subsequently, the values of the bivariate linear correlation coefficients R of the descriptors are also presented in **Table 3**.

Table 2: Quantum descriptors and experimental antibacterial activities of the test and validation set

Code	$E_{HOMO(eV)}$	$_{(eV)}$	*E(U.a)*	$CE_{50\ exp}$(µg/mL)	$pCE_{50\ exp}$
Training Set					
1a	-0.092	0.172	-1295.085	375	3.008
1c	-0.100	0.181	-1295.104	375	3.008
2b	-0.095	0.177	-1293.901	375	3.006
2c	-0.105	0.185	-1293.905	187.5	3.307
3b	-0.097	0.164	-1290.278	187.5	3.299
3c	-0.108	0.173	-1290.278	48.87	3.884
Validation Set					
1b	-0.093	0.176	-1295.105	187.5	3.309
2a	-0.095	0.176	-1293.890	93.75	3.608
3a	-0.097	0.160	-1290.263	375	2.999

Table 3: Values of the bivariate linear correlation coefficients of the descriptors

	$E_{HOMO(eV)}$	$_{(eV)}$	*E(U.a)*
$E_{HOMO(eV)}$	**1**		
$_{(eV)}$	0.272	**1**	
E(U.a)	0.42	0.718	**1**

For all the descriptors used, the analysis of the data two by two, that is to say the calculation of the linear correlation coefficient R between each of the pairs of the set of descriptors is less than 0.95 (R < 0.95).

3.2. Quantitative Structure Activity Relationship (QSAR) model and contribution of descriptors

It should be noted that the negative or positive sign of the coefficient of a descriptor of the model reflects the effect of proportionality between the evolution of the biological activity of interest and this parameter of the regression equation. Thus, the negative sign indicates that when the value of the descriptor is high, the biological activity decreases while the positive sign translates the opposite effect. The model equation (3) obtained using the theoretical descriptors related to the optimized molecules and the statistical indicators are presented below:

$$pCE_{50} = -7.949 - 58.869E_{HOMO} - 28.168\,\chi - 0.008\mathbf{E} \quad (3)$$

N = 6 $\quad R^2 = 0.921 \quad Q^2_{CV} = 0.88$ S = 0.152 F = 7.721

The negative signs of the different coefficients of the model parameters indicate that the antibacterial activity (pCE_{50}) evolves inversely with ($\mathbf{E_{HOMO}}$, and **E**).The correlation coefficient R^2indicates that 92.1% of the molecular descriptors that define this model are taken into account at a standard deviation of 0.152.The significance of the model is reflected by the Fischer coefficient F = 7.721: The correlation coefficient of cross-validation Q^2_{CV}= 0.88. This model is acceptable with $R^2 - Q^2_{CV} = 0.921 - 0.88 = 0.041 < 0.3$.

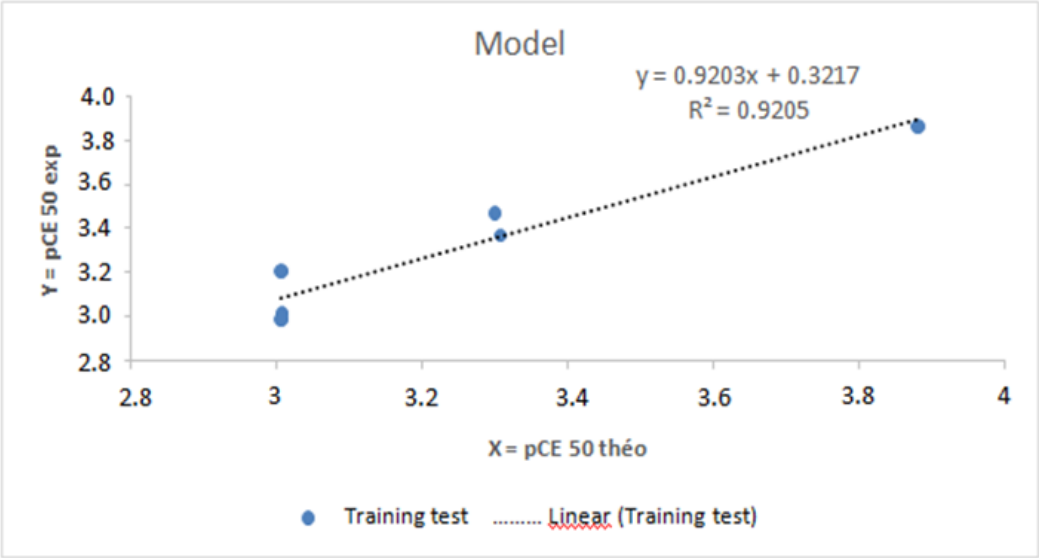


Figure 2: The regression line of the model

The values of the ratio pCE_{50}theo/pCE_{50}exp of the validation set which tend to unity (**Table 4**) reflect the good correlation between the theoretical and experimental potentials of the molecules studied.

Table.4: Values of the relationship between theoretical and experimental antibacterial potentials of the validation set.

Validation Set		
pCE_{50}theo	pCE_{50}exp	pCE_{50}theo/pCE_{50}exp
3.037	3.608	0.842
2.929	3.309	0.885
3.577	2.999	1.193

The study of the contribution of each of the three parameters in the prediction of antibacterial activity was made. The various contributions are illustrated by **Figure 3**.

The energy of the Highest Occupied Molecular Orbital ($\mathbf{E_{HOMO}}$) shows a large proportion followed by electro negativity (□) and finally the lowest proportion is attributed to the electron energy (E). Thus it is clear that the Highest Occupied Molecular Orbital energy ($\mathbf{E_{HOMO}}$) is the priority descriptor in the prediction of antibacterial activity in the molecule series studied.

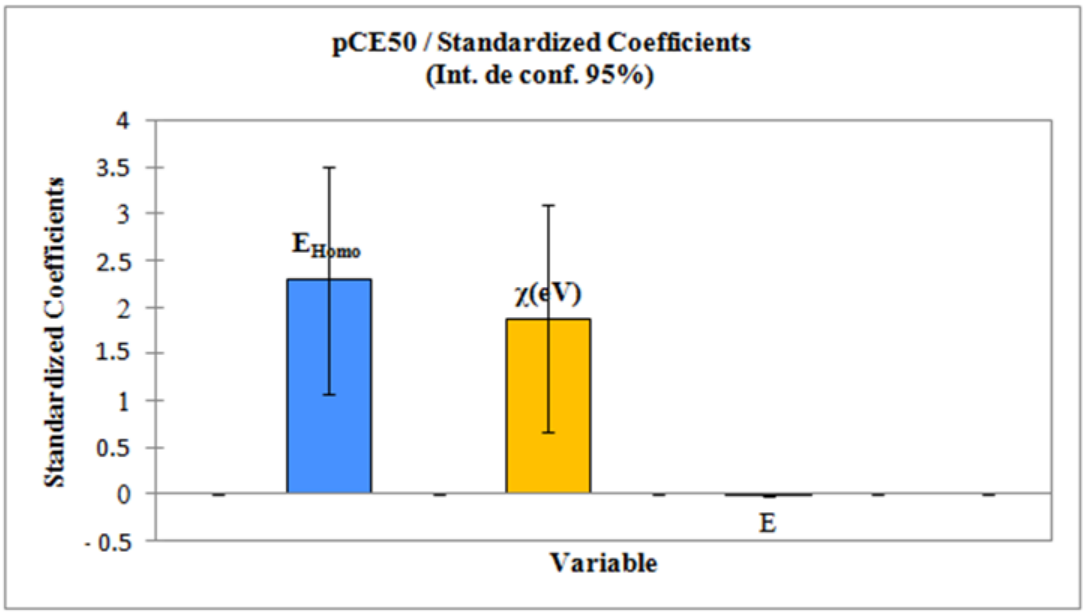


Figure 3: Contribution of descriptors in the model

IV. Conclusion

This study made it possible to demonstrate a relationship between the antibacterial activity pCE_{50} (μg/mL) and the quantum descriptors. Thus, we have established a multilinear regression equation between the antibacterial activity and the descriptors of the optimized molecules. The descriptors of the optimized molecules ($\mathbf{E_{HOMO}}$, □ and **E**) make it possible to explain and predict the behavior of the molecules studied because there is a strong correlation between the calculated and experimental values of the antibacterial activity. This model presents good statistical indicators ($\mathbf{R^2}$ = 0.921, **S** = 0.152, **F**= 7.721). The model QSAR obtained allows us to predict the activity of new molecules on the one hand and on the other hand, to identify descriptors that improve the antibacterial activity thus giving guidance to design new molecules more active against bacteria. The Highest Occupied Molecular Orbital ($\mathbf{E_{HOMO}}$) energy is the priority descriptor in the prediction of antibacterial activity in the studied molecule series. The model obtained was validated using a test set comprising three molecules.

References

[1]. Schiff H, *Ann Chem.* Paris. **1864**, 131,118–119.
[2]. Arulmurugan S, Kavitha P H, Venkatraman Biological activities of Schiff base and its complexes: a review. *Rasayan J Chem*. **2010**, 3(3),385–410.
[3]. Bringmann G, Dreyer M, Faber J H, Dalsgaard PW, Staerk D, Jaroszewski J W Ancistrotanzanine C and related 5,1'- and 7,3'-coupled naphthylisoquinoline alkaloids from Ancistrocladustanzaniensis. *J Nat Prod*. **2004**, 67(5):743–748.
[4]. Salimon J, Salih N, Ibraheem H, Yousif E, *Asian J Chem*., **2010**, 22(7), 5289–5296.
[5]. Guo Z, Xing R, Liu S, Zhong Z, Ji X, Wang L, *Carbohydr Res*., **2007**, 342(10), 1329–1332.
[6]. Amin R, Krammer B, Abdel-Kader N, Verwanger T, El-Ansary A, Antibacterial effect of some benzopyrone derivatives. *Eur. J. Med. Chem*. **2010**, 45 (1), 372–378.
[7]. Abdel Aziz A A, Salem A N M, Sayed M A, Aboaly M M, Synthesis, structural characterization, thermal studies, catalytic efficiency and antimicrobial activity of some M(II) complexes with ONO tridentate Schiff base N-salicylidene-O-aminophenol (saphH2), *J. Mol. Struct*. **2012**, 1010, 130–138.
[8]. Al-Kahraman Y M S A, Madkour H M F, Ali D, Yasinzai M, Antileishmanial, antimicrobial and antifungal activities of some new aryl azomethines, *Molecules*, **2010**, 15 (2), 660–671.
[9]. Karthikeyan M S, Prasad D J, Poojary B, Bhat K S, Holla B S, Kumari N S, Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. *Bioorg.Med. Chem.* **2006**, 14 (22), 7482–7489.
[10]. Przybylski P, Huczynski A, Pyta K, Brzezinski B, Bartl F, Biological properties of Schiff bases and azo derivatives of phenols. *Curr.Org. Chem.* **2009**, 13 (2), 124–148.
[11]. Ronad P M, Noolvi M N, Sapkal S, Dharbhamulla S, Maddi V S, Synthesis and antimicrobial activity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives. *Eur. J. Med. Chem.* **2010**, 45 (1), 85–89.
[12]. Vukovic N, Sukdolak S, Solujic S, Niciforovic N, Substituted imino and amino derivatives of 4-hydroxycoumarins as novel antioxidant, antibacterial and antifungal agents: synthesis and in vitro assessments, *Food Chem*. **2010**, 120 (4), 1011–1018.
[13]. Desai S B, Desai P B, Desai K R, Synthesis of some Schiff bases, thiazolidinones and azetidinones derived from 2,6-diaminobenzo 1,2-d: 4,5-d 0 bisthiazole and their anticancer activities, *Heterocycl.Commun*. **2001**, 7(1), 83–90.
[14]. Przybylski P, Pyta K, Wicher B, Gdaniec M, Brzezinski B, Structure of a new Schiff base of gossypol with 1-(3-aminopropyl)-2-pyrrolidinone studied by the X-ray, FT-IR, NMR, ESI-MS and PM5 methods. *J. Mol. Struct*. **2008**, 889 (1–3), 332–343.
[15]. Sinha D, Tiwari A K, Singh S, Shukla G, Mishra P, Chandra H, Mishra A K, Synthesis, characterization and biological activity of Schiff base analogues of indole-3-carboxaldehyde. *Eur. J. Med. Chem*. **2008**, 43(1), 160–165.
[16]. Jarrahpour A, Khalili D, De Clercq E, Salmi C, Brunel J M, Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. *Molecules*, **2007**, 12 (8), 1720–1730.
[17]. Panneerselvam P, Nair R R, Vijayalakshmi G, Subramanian E H, Sridhar S K, Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents. *Eur. J. Med. Chem*. **2005**, 40(2), 225–229.
[18]. Saravanan G, Pannerselvam P, Prakash C R, Synthesis andanti-microbial screening of novel Schiff bases of 3-amino-2-methylquinazolin 4-(3H)-one. *J. Adv. Pharm. Technol. Res.* **2010**, 1(3), 320–325.
[19]. Odabasoglu M, Arslan F, Olmez H, Buyukgungor O, Synthesis, crystal structures and spectral characterization of transbisaquabis (o-vanillinato) copper(II), cis-aquabis (o-vanillinato) copper (II) and aqua bis (o-vanillinato)-1,2-ethylenediimin copper(II). *Dyes Pigm.* , **2007**, 75 (3), 507–515.
[20]. Vicini P, Geronikaki A, Incerti M, Busonera B, Poni G, Cabras C A, La Colla P, Synthesis and biological evaluation of benzo d isothiazole, benzothiazole and thiazole Schiff bases. *Bioorg.Med. Chem.* **2003**, 11(22), 4785–4789.
[21]. Avadanei M, Tigoianu R, Serpa C, Pina J, Cozan V, *Journal of Photochemistry and Photobiology A: Chemistry*,**2017**,332, 475–486.
[22]. Mohammad H H, Mohammad K S, Kazem B, Ross W H, William C *Z, Naturforsch*, **2007** 62b, 621 – 624.
[23]. Özlem Ö, *Journal of Molecular Structure*, **2016**, 1125, 260-271.
[24]. Kangah N J B, Kodjo C G, Kablan A L C, Koné M W, Ahoua A R C and Ziao N, Synthesis, characterization and antimicrobial evaluation of symmetric A-Diimine Schiff bases derived from *cis* and *trans* racemic mixture of cyclohexanediamine, *IRA-International Journal of Applied Sciences*, **2017**, 6(1), 2455-4499.
[25]. Chaltterjee S, Hadi A, Price B, *Regression Analysis by Examples*; Wiley VCH: New York, USA, **2000**.
[26]. Phuong HTN, « *Synthèse et étude des relations structure/activité quantitatives (QSAR/2D) d'analogues Benzo [c] phénanthridiniques* » Doctorat Thesis, Angers University, (France), **2007**.
[27]. Eriksson L, Jaworska J, Worth A, Cronin MTD, Dowell Mc, Gramatica RM, Methods for Reliability and Uncertainty Assessment and for Applicability Evaluations of Classification- and Regression-Based QSARs, *Environmental Health Perspectives*, **2003**, 111(10):1361-1375.
[28]. Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., J. R.,Cheeseman J. A., Montgomery Jr., Vreven T.,Kudin K. N.,Burant J. C., MillamJ. M., Iyengar S. S., Tomasi J.,Barone V., Mennucci B.,Cossi M.,Scalmani G.,Rega N.,PeterssonG. A., NakatsujiH.,Hada M.,Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y.,Kitao O., Nakai H.,Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Bakken V.,Adamo C., Jaramillo J.,Gomperts R.,Stratmann R. E.,YazyevO.,

Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y.,Morokuma K., Voth G. A., Salvador P., Dannenberg J.J.,Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas O.,Malick D. K.,Rabuck A. D.,Raghavachari K.,Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S.,Cioslowski J., Stefanov B. B., Liu G., Liashenko A.,Piskorz P.,Komaromi I., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A.,Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Gonzalez C., J. A. and Pople, Gaussian 03, revision E.01; Gaussian, Inc.: Wallingford C. T, **2004**.

[29]. Chattaraj P K, Cedillo A, Parr RG, *J. Phys. Chem*., **1991**, 103: 7645.
[30]. Ayers P W and Parr RG, **2000**, *J. Am Chem., Soc*, **2010**, 122.
[31]. De Proft F, Martin JML and Geerlings P, *Chem. Phys Let.*, **1996**, 250: 393.
[32]. Geerlings P, De Proft F and Martin JML, In Theoretical and Computational Chemistry; Seminario J., *Ed. Elsevier*; Amsterdam.Vol-4 (Recent Developments in Density Functional Theory), **1996**, p773.
[33]. De Proft F, Martin JML and Geerlings P, *Chem. Phys Let.*, **1996**, 256: 400.
[34]. De Proft F and Geerlings P, *J Chem Phys*, **1997**, 106: 3270.
[35]. Geerlings P, De Proft F and Langenaeker W, **1996**, *Adv. Quantum Chem*.33: 303.
[36]. R G, Donnelly R A, Levy M and Palke W E, *J. Chem. Phys*., **1978**, 68: 3801.
[37]. Hansch C, Sammes P G and Taylor J B, Computers and the medicinal chemist; in: Comprehensive Medicinal Chemistry, vol. 4, Eds. Pergamon Press, Oxford, **1990,** pp. 33-58.
[38]. Franke R, Theoretical Drug Design Methods, *Elsevier*, Amsterdam, **1984**.
[39]. Koopmans T, Úber die Zuordnung von Wellenfunktiomen und Eigenwertenzu den einzelnen Elektroneneines Atoms, *Physica*, **1934**, 1: 104-113.
[40]. Katritzky A R, Lobanov V S, Karelson M, *CODESSA Comprehensive Descriptors for Structural and Statistical Analysis*, Reference Manual, version 2.0, University of Florida, FL Gainesville, **1994**.
[41]. Nalimov V Y, The *Application of Mathematical Statistics to Chemical Analysis*, Addison-Wesley, Reading, M A, **1962**.
[42]. Calcutt R, Body R, *Statistics for Analytical Chemists*, Champman & Hall, New York, **1983**.
[43]. Miller J C, Miller JN, *Statistics for Analytical Chemistry*, 2nd ed. Ellis Horwood, New York, **1988**, p. 137.
[44]. Meier P C, Zund RE, *Statistical Methods in Analytical Chemistry*, John Wiley & Sons, New York, **1993**, pp 84-120.
[45]. Dagnélie P, *Statistique Théorique et Appliquée: Statistique descriptive et bases de l'inférence statistique*, Tomes 1, De Boeck et S. Larcier, Bruxelle, **1998** p.508(french)