Revista Virtual de Química

ISSN 1984-6835

Artigo

A Quantum Chemical and Chemometrical Study of *Styrylbenzylsulfones* and their Analogues with Citotoxic Activity against Prostate Cancer Cells

dos Santos, D. L.; Paula, C. B.; Carvalho-Silva, V. H.;* Camargo, A. J.; Camargo, L. T. F. M.

Rev. Virtual Quim., **2016**, *8* (2), 506-514. Data de publicação na Web: 9 de abril de 2016

http://rvq.sbq.org.br

Um Estudo Químico Quântico e Quimiométrico da *Styrylbenzylsulfones* e seus Análogos com Atividade Citotóxica contra Células do Câncer de Próstata

Resumo: O câncer é um termo genérico para um grande grupo de doenças baseado no desenvolvimento rápido de células anormais que crescem além dos seus limites usuais, e que podem se espalhar para outros órgãos. Este processo é referido como metástase. O câncer de próstata é o sexto tipo de câncer mais comum em todo o mundo, a quarta principal causa de morte por câncer no Brasil. As propriedades moleculares de 34 análogos de *Styrylbenzylsulfones* com atividade citotóxica contra células cancerosas humanas da próstata foi calculado através do método: Teoria do Funcional de Densidade com o nível B3LYP/6-31G .Quatro descritores (ângulo diedral entre os átomos: 17, 18, 23 e 24; as ordens de ligação entre átomos de 18-19 e 20-21; e polarizabilidade) foram responsáveis pela discriminação do dois grupos de moléculas (ativos e inativos) e para isto foi utilizado uma técnica de reconhecimento de padrão: Análise do Componente Principal (PCA). Este modelo foi capaz de discriminar 20 ativos de 14 inativos dos análogos usando apenas uma componente principal, sendo responsável por 51.20% da variância total e que permite melhor compreender a influência desses descritores eletrônicos na atividade citotóxica.

Palavras-chave: *Styrylbenzylsulfonas*; Câncer de Próstata; PCA; B3LYP.

Abstract

Cancer is a generic term for a large group of diseases related to rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then spread out to other organs. This process is referred to as metastasis. Prostate cancer is the sixth most common cancer worldwide, the fourth leading cause of death from cancer in Brazil. The Density Functional Theory method at B3LYP/6-31G* was employed to calculate a set of molecular properties (variables) of 34 *Styrylbenzylsulfones* analogues with cytotoxic activity against human prostate cancer cells. Four descriptors (dihedral angle between atoms 17, 18, 23 and 24; bond orders between atoms 18-19 and 20-21; and polarizability) were responsable to discriminate the two groups of molecules (active and inactive) and this result was used for pattern recognition method. This model was able to discriminate 20 active from 14 inactive of the analogues by using only one principal component, accounting for 51.20% of the total variance and allowing to better understand the influence of these electronic descriptors in the cytotoxic activity.

Keywords: *Styrylbenzylsulfonas*; Prostate Cancer; PCA; B3LYP.

* Universidade Estadual de Goiás, Unidade Universitária de Ciências Exatas e Tecnológicas, P.O. Box 459, CEP 75001-970, Anápolis-GO, Brasil..

fatioleg@gmail.com

DOI: 10.5935/1984-6835.20160037

Volume 8, Número 2 Março-Abril 2016

Revista Virtual de Química
ISSN 1984-6835

A Quantum Chemical and Chemometrical Study of *Styrylbenzylsulfones* and their Analogues with Citotoxic Activity against Prostate Cancer Cells

Daiane L. dos Santos,[a] Camila B. Paula,[a] Valter Henrique Carvalho-Silva,[a,*] Ademir J. Camargo,[a] Lilian T. F. M. Camargo[b]

[a] Universidade Estadual de Goiás, Unidade Universitária de Ciências Exatas e Tecnológicas, P.O. Box 459, CEP 75001-970, Anápolis-GO, Brasil.

[b] Instituto Federal Goiano, CEP 75131-457, Anápolis-GO, Brasil.

* fatioleg@gmail.com

Recebido em 8 de abril de 2016. Aceito para publicação em 8 de abril de 2016

1. Introduction

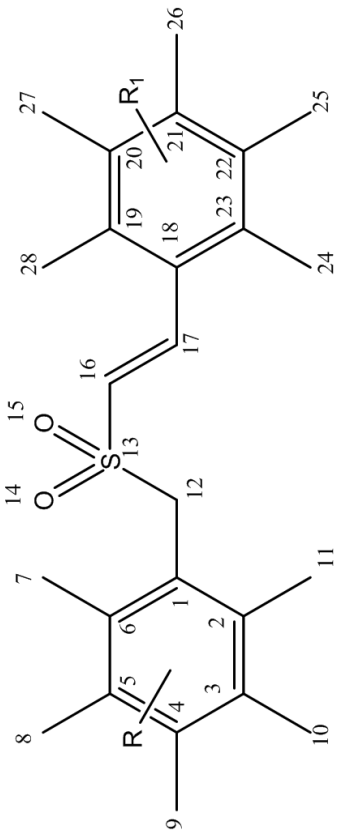
Cancer is a generic term used to more than hundred diseases whose character in common is the uncontrolled growth and spread of cells. It can affect almost any part of the body. According to the World Health Organization (WHO) more than 70% of all cancer deaths occurred in low- and middle – income countries. Deaths from cancer worldwide are projected to continue rising with an estimated of 12 million deaths in 2030.[1–3]

Currently, prostate cancer is the sixth most common cancer worldwide, the fourth leading cause of death from cancer in Brazil, representing about 10% of all cancer cases. In most cases, the tumor has a slow growth, long doubling time, taking about 15 years to reach 1 cm^3 and affects men over 50 years of age.[4,5]

The treatments used to combat prostate cancer are not effective and cause many side effects, then grows the interesting in discovering new drugs that are efficient to combat this disease.[6-11] The present work investigated the relationship between the geometric and electronic properties and the activity of a group of 34 compounds of *Styrylbenzylsulfones*[12] reported in the literature as presenting a certain degree of anti-prostate cancer[13-16] by using quantum

chemistry methods to calculate molecular descriptors. Multivariate statistical methods were used to analyze and classify a data set of the molecules into groups that can be correlated to their activity.

Table 1. Molecular structure and atomic label adopted in the calculation for *Styrylbenzylsulfones and their derivates analogues* and *activities*



Molecule	R	R_1	IC_{50}	Activity*
1	4-OMe	4-OMe	1.250	A
2	4-OMe	4-F	2.500	A
3	4-OMe	4-Cl	7.500	A
4	4-OMe	4-NO_2	3.500	A
5	4-OMe	4-NH_2	2.000	A
6	4-OMe	2-OMe	12.000	A
7	4-OMe	2-Cl,4-F	10.000	A
8	4-OMe	2,4-$(CH_3)2$	0.250	A
9	4-OMe	2-OMe,4-F	0.025	A
10	4-OMe	3,4-$(OMe)_2$	0.500	A
11	4-OMe	3,5-$(CH_3)_2$	4.000	A
12	4-OMe	2,6-$(CH_3)_2$	5.000	A
13	4-OMe	2,6-$(OMe)_2$	0.500	A
14	4-OMe	2,4-$(OMe)_2$	0.003	A
15	4-OMe	2,5-$(OMe)_2$	12.500	A
16	4-OMe	3,5-$(OMe)_2$	7.500	A
17	4-OMe	2,4,5-$(OMe)_3$	15.000	A
18	4-OMe	2,3,4-$(OMe)_3$	7.500	A
19	4-OMe	2,4,6-$(OMe)_3$	10.000	A
20	4-OMe	3,4,5-$(OMe)_3$	7.500	A
21	4-OMe	2,6-$(OMe)_2$,4-OH	>20	I
22	4-OMe	2,6-$(OMe)_2$,4-F	>20	I
23	4-OMe	2,4,6-$(CH_3)_3$	>20	I
24	4-OCF_3	2,4,6-$(OMe)_3$	>20	I
25	4-OMe,3-OH	2,4,6-$(OMe)_3$	>20	I
26	4-OMe,3-OH	2,6-$(OMe)_3$,4-OH	>20	I
27	4-OMe,3-OH	3,4,5-$(OMe)_3$	>20	I
28	3,4,5-$(OMe)_3$	2,4,6-$(OMe)_3$	>20	I
29	2,4,6-$(OMe)_3$	2,4,6-$(OMe)_3$	>20	I
30	4-Cl	2,4,6-$(OMe)_3$	>20	I
31	4-NO_2	2,4,6-$(OMe)_3$	>20	I
32	4-CN	2,4,6-$(OMe)_3$	>20	I
33	4-COOH	2,4,6-$(OMe)_3$	>20	I
34	4-OH	2,4,6-$(OMe)_3$	>20	I

*A - Active, I – Inactive.

2. Methodology

2.1. Studied data set

The IC_{50} values estimated by *Reddy*[13] were used in this work and are showed in Table 1. From 34 molecule studied, 14 compounds have been observed to be inactive against prostate cancer cell lines (IC_{50} > 20 μM), while the remaining compounds have been

considered inactive.

2.2. Molecular descriptors

The *Styrylbenzylsulfon* and their derivatives analogues presents several degrees of rotation been possible attain many geometrics conformations (Table 1). In the absence of crystallographic structure it is necessary to carry out conformation search to obtain the conformation of lowest energy. The conformation search was carried out by semi – empirical AM1[17] method using the software *Hyperchem 7.5.*[18]

The conformation of lowest energy of each compounds were optimized using the Density Functional Theory (DFT)[19] with the exchange-correlation functional B3LYP[20] and the basis set functions 6-31G*, implemented in the Gaussian G09[21] suite of programs. After optimization, it was calculate geometric and electronic properties to correlate with biological activity. Among many variables that can to be used in SAR studies the following were chosen: molecular volume (*V*), surface area (*A*), polarizability (α), refractivity, partition coefficient (*LogP* – ratio of the concentrations of a substance at two immiscible liquids in equilibrium), bond angles, dihedral angles, bond orders (obtained using NBO program,[22] included in the G09 package of programs), partial atomic charges (C_n) using the CHELPG (CHarge from ELectrostatic Potential using a Grid based method) scheme by Breneman and Wiberg,[23] molecular dipole moment (μ), frontier molecular orbital energies (E_{HOMO}, E_{LUMO}, hardness ($\eta = (E_{LUMO} - E_{HOMO})/2$) and *Gap.*[15,16,24]

2.3. Selection of descriptors by chemometrical methods

The aim of employ the PCA[25,26] method is to reduce the dimensionality of data set that presents a large number of interrelated variables explaining the variance-covariance structure. The method creates new variables as linear combinations of all the initial variables so that the first new variable contains the first largest variance and the new variable contain a second largest variance.

3. Results and Discussion

Before applying the PCA method, each one of the variables was autoscaled. This method is very important because each variable is equally weighted and this provides a measure of the ability of a descriptor to discriminate classes of compounds. Here, we used *autoscaling to unit variance*. Autoscaling to unit variance refers to mean-centering followed by dividing the standard deviation: $x'_{ik} = (x_{ik} - \bar{x}_k)/s_k$, where x'_{ik} is the variable autoscaled, s_k is the standard deviation of variable *k*, x_{ik} is the variable no autoscaled, and $\bar{x}_k$ is the mean of the variable *k*. It could be demonstrated that the variance of an autoscaled variable is equal to 1.0.

The best separation was obtained with four variables (Table 2): D1 (dihedral angle between : 17, 18, 23 and 24 atoms), (α) Polarizibility, O1 (bond orders between 19 e 20 atoms) and O2 (bond orders between 20 e 21 atoms).

Table 2. The calculated descriptors that discriminate the compounds in active and inactive classes

Molecule	O1 (Å)	O2 (Å)	D1 (Degrees)	α (Å^3)
1	14.374	13.732	0.3987	2026.562
2	14.478	13.910	0.3542	1809.053
3	14.508	13.903	0.3920	1870.624
4	14.487	13.824	0.8515	2014.290
5	14.937	13.243	0.0585	1776.570
6	14.327	14.329	40.952	1909.083
7	14.509	13.827	-40.081	1878.953
8	14.460	13.981	25.551	1933.711
9	13.927	13.775	-0.0076	1893.639
10	14.184	14.215	-0.2990	2157.410
11	14.115	14.038	0.2466	1954.102
12	14.026	14.389	-0.8080	1915.109
13	13.565	14.419	24.555	2029.374
14	14.796	13.382	30.616	2117.830
15	13.855	13.496	35.495	2080.876
16	13.944	13.313	0.2874	2072.179
17	14.068	12.996	34.783	2277.892
18	14.436	13.624	40.657	2294.245
19	13.673	13.568	17.156	2286.645
20	13.684	13.250	0.8396	2241.279
21	13.592	13.771	24.144	2091.281
22	13.592	13.851	11.774	2126.372
23	14.046	14.117	38.518	2070.348
24	13.891	13.557	30.786	2184.954
25	13.649	13.262	0.6211	2223.211
26	13.575	13.777	27.633	2123.557
27	13.864	13.578	31.009	2232.668
28	13.867	13.573	29.373	2465.142
29	13.571	13.726	25.239	2557.978
30	13.589	13.706	26.938	2189.601
31	13.605	13.639	61.474	2234.276
32	13.988	1,3463	31.121	2283.633
33	13.977	13.476	29.213	2283.633
34	13.961	14.920	27.844	2169.569

The results of the PCA calculation show that the first three principal components (PC 1, PC 2 and PC 3) explain 93,03% of the total variance in the data set (Table 3), as follows: PC 1: 51,20%; PC2: 24,87% and PC3: 16,95%. Observed that the first component (PC 1) explain around 50% variance of the data set.

The Figure 1 shows that PC 1 is responsible for the discriminating between active (1 to 20) and inactive (21 to 34) compounds. The active compounds have positive scores on the first component and the inactive compounds have negative scores. The Table 4 contains the loadings of descriptors, being the polarizibility the variable of largest loading in first component (PC 1) and O2 the variable of largest loading in second component (PC 2).

Table 3. Variance explained by first three principal components

Components	Individual Percentage	Cumulative Percentage
PC 1	51.20	51.20
PC 2	24.87	76.08
PC 3	16.95	93.03

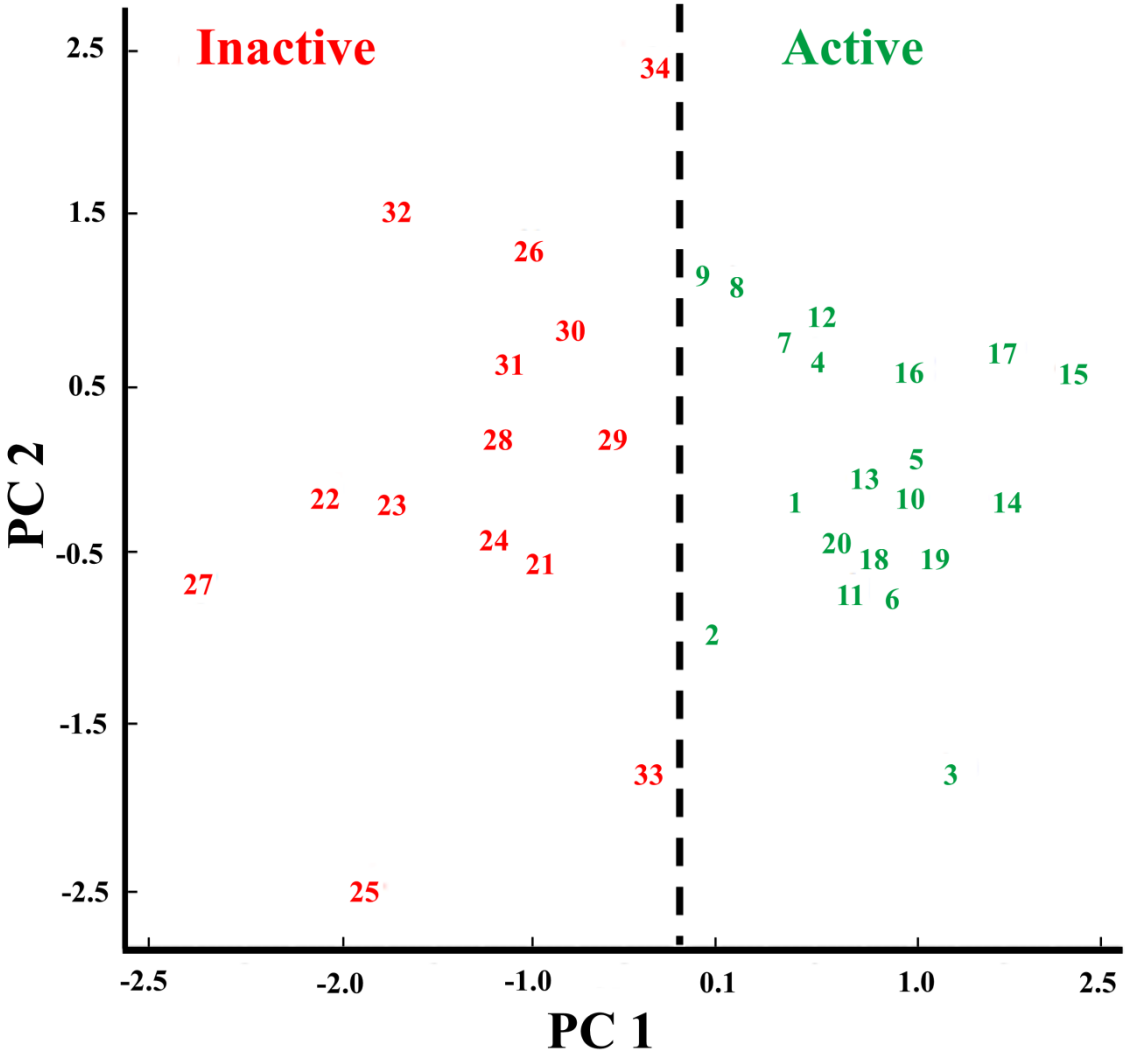


Figure 1. Graphic bmm b representation of *scores*

The Equation 1 presents the loading values of each variable (Table 4) in the PC 1, which is responsible for the discrimination between active and inactive compounds.

$$PC\ 1 = 0.634\ (\alpha) + 0.499\ (D1) - 0.490\ (O1) - 0.329\ (O2) \quad (1)$$

Table 4. *Loadings* (weights) of the variables in the first, second and third components

Variables	PC 1	PC 2	PC 3
A	0.634	-0.048	-0.152
D1	0.499	0.113	0.823
O1	-0.490	-0.516	0.512
O2	-0.329	0.848	0.193

It is worth noting that the variables responsible for the separation of the compounds are electronic descriptors and geometrical descritors, suggesting that both properties are important to understand the *Styrylbenzylsulfones* activity against prostate cancer.

From Equation 1 we can see that more active molecules can be obtained when we have higher values for D1 and α, with small values for the bond order between O1 e O2 atoms. This can also be done by analyzing the Table 4, where: D_1 and α variables are the positive side of loading (as well as the active molecules), and the variables: O_1 and O_2 are the negative side of the graph loading (as well as the inactive molecules).

Dihedral angles are very important parameters for the study of structure activity relationship of a molecule. They vary with the exchange of substituent directly influencing the geometry of this molecule and, consequently, interfering with the drug-receptor activity. Higher values for D1 is important to molecules to be active (Figure 1), this indicates the compound has a great probability of fit with the biological receptor.[27]

Regarding the bond order descriptor we can define it as half of the difference among electrons in bonding and anti-bonding molecular orbital. As increasing the bond order, increasing the dissociation energy and decreasing the bond length. For the active compounds we can suggest that in positions between atoms 19 – 20(O1) and 20 – 21(O2) should presents low values electronic density and consequently, a low bond order.

According to the above results, we can postulate that increasing the values of the D_1 and α and decreasing the values of the O_1 and O_2 variables, increase the probability for the *Styrylbenzylsulfones* and its analogues to become active. These features can be useful in the design of new *Styrylbenzylsulfones* analogues with activity against prostate cancer.

4. Conclusions

Principal component analysis (PCA) showed that the 34 *Styrylbenzylsulfones* compounds studied can be classified into two groups: active and inactive according to prostate cancer activity. The D1, α, O1 and O2 are responsible for the separation between active and inactive molecules and it is interesting to notice that these variables represent two distinct classes of interactions between the compounds and the biological receptor: electronic (α, O1 and O2) and conformational (D1) interactions. The behavior of these variables can be useful when one is trying to obtain compounds with activity against prostate cancer.

Acknowledgement

The authors would like to acknowledge the Pró-Reitora de Pesquisa e Pós – Graduação (PrP) of the Universidade Estadual de Goiás (UEG) for financial support for this research.

References

[1] WHO | New guide on palliative care services for people living with advanced cancer. Disponível em: <http://www.who.int/mediacentre/news/notes/2007/np31/en/>. Acesso em: 6 novembro 2014.

[2] Are, C.; Rajaram, S.; Are, M.; Raj, H.; Anderson, B. O.; Chaluvarya Swamy, R.; Vijayakumar, M.; Song, T.; Pandey, M.; Edney, J. A.; et al. A Review of Global Cancer Burden: Trends, Challenges, Strategies, and a Role for Surgeons. *Journal of Surgical Oncology* **2013**, *107*, 221. [CrossRef] [PubMed]

[3] Adams, J. The Development of Proteasome Inhibitors as Anticancer Drugs. *Cancer Cell* **2004**, *5*, 417. [CrossRef]

[4] Portal - Instituto Nacional de Câncer - INCA Disponível em: <http://www2.inca.gov.br/wps/wcm/connect/inca/portal/home>. Acesso em: 6 novembro 2014.

[5] Heidenreich, A.; Bellmunt, J.; Bolla, M.; Joniau, S.; Mason, M.; Matveev, V.; Mottet, N.; Schmid, H.-P.; van der Kwast, T.; Wiegel, T.; Zattoni, F. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localised Disease. *European Urology* **2011**, *59*, 61. [CrossRef] [PubMed]

[6] Médicos, Brasil. Ministério Da Saúde; Câncer Fundamentos; Secretaria de Assistência Médica-Divisão Nacional de Câncer: Brasília, 2006; pp. 345–357.

[7] Temmink, O. H.; Prins, H.-J.; van Gelderop, E.; Peters, G. J. The Hollow Fibre Assay as a Model for *in Vivo* Pharmacodynamics of Fluoropyrimidines in Colon Cancer Cells. *British Journal of Cancer* **2007**, *96*, 61. [CrossRef] [PubMed]

[8] Wang, A. Z.; Langer, R.; Farokhzad, O. C. Nanoparticle Delivery of Cancer Drugs. *Annual Review of Medicine* **2012**, *63*, 185. [CrossRef] [PubMed]

[9] Mans, D. R. A. Anti-Cancer Drug Discovery and Development in Brazil: Targeted Plant Collection as a Rational Strategy to Acquire Candidate Anti-Cancer Compounds. *Oncologist* **2000**, *5*, 185. [CrossRef] [PubMed]

[10] Lu, M.; Merali, S.; Gordon, R.; Jiang, J.; Li, Y.; Mandeli, J.; Duan, X.; Fallon, J.; Holland, J. F. Prevention of Doxorubicin Cardiopathic Changes by a Benzyl Styryl Sulfone in Mice. *Genes Cancer* **2011**, *2*, 985. [CrossRef] [PubMed]

[11] Reddy, M. V. R.; Venkatapuram, P.; Mallireddigari, M. R.; Pallela, V. R.; Cosenza, S. C.; Robell, K. A.; Akula, B.; Hoffman, B. S.; Reddy, E. P. Discovery of a Clinical Stage Multi-Kinase Inhibitor Sodium (E)-2-2-Methoxy-5-[(2',4',6'-Trimethoxystyrylsulfonyl)methyl]phenylamino Acetate (ON 01910.Na): Synthesis, Structure-Activity Relationship, and Biological Activity. *Journal of Medicinal Chemistry* **2011**, *54*, 6254. [CrossRef] [PubMed]

[12] Prasad, A.; Park, I.-W.; Allen, H.; Zhang, X.; Reddy, M. V. R.; Boominathan, R.; Reddy, E. P.; Groopman, J. E. Styryl Sulfonyl Compounds Inhibit Translation of Cyclin D1 in Mantle Cell Lymphoma Cells. *Oncogene* **2009**, *28*, 1518. [CrossRef] [PubMed]

[13] Reddy, M. V. R.; Mallireddigari, M. R.; Cosenza, S. C.; Pallela, V. R.; Iqbal, N. M.; Robell, K. A.; Kang, A. D.; Reddy, E. P. Design, Synthesis, and Biological Evaluation of (E)-Styrylbenzylsulfones as Novel Anticancer Agents. *Journal of Medicinal Chemistry* **2008**, *51*, 86. [CrossRef] [PubMed]

[14] Karelson, M.; Lobanov, V. S.; Katritzky, A. R. Quantum-Chemical Descriptors in QSAR/QSPR Studies. *Chemical Reviews* **1996**, *96*, 1027. [CrossRef] [PubMed]

[15] Martins, G. R.; Napolitano, H. B.; Camargo, L. T. F. M.; Camargo, A. J. Structure-Activity Relationship Study of Rutaecarpine Analogous Active against Central Nervous System Cancer. *Journal of the Brazilian Chemical Society* **2012**, *23*, 2183. [CrossRef]

[16] Camargo, L. T. F. M.; Sena, M. M.; Camargo, A. J. A Quantum Chemical and

Chemometrical Study of indolo[2,1-B]quinazoline and Their Analogues with Cytotoxic Activity against Breast Cancer Cells. *SAR and QSAR in Environmental Research* **2009**, *20*, 537. [CrossRef] [PubMed]

[17] Dewar, M. J. S.; Jie, C.; Zoebisch, E. G. AM1 Calculations for Compounds Containing Boron. *Organometallics* **1988**, *7*, 513. [CrossRef]

[18] HyperChem, Release 7.0, Hypercube Inc.; Gainesvile, FL 32601, USA.

[19] Parr, R. G.; Yang, W.; *Density Functional Theory of Atoms and Molecules*, Oxford: New York, 1989.

[20] Becke, A. D. Density-Functional Exchange-Energy Approximation with Correct Asymptotic Behavior. *Physical Review A* **1988**, *38*, 3098. [CrossRef] [PubMed]

[21] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09 Revision D.01, 2009.

[22] Weinhold, F.; Landis, C. R. Natural Bond Orbital and Extensions of Localized Bonding Concepts. *Chemistry Education Research and Practice* **2001**, *2*, 91. [CrossRef]

[23] Breneman, C. M.; Wiberg, K. B. Determining Atom-Centered Monopoles from Molecular Electrostatic Potentials. The Need for High Sampling Density in Formamide Conformational Analysis. *Journal of Computational Chemistry* **1990**, *11*, 361. [CrossRef]

[24] Lameira, J.; Medeiros, I. G.; Reis, M.; Santos, A. S.; Alves, C. N. Structure-Activity Relationship Study of Flavone Compounds with Anti-HIV-1 Integrase Activity: A Density Functional Theory Study. *Bioorganic & Medicinal Chemistry* **2006**, *14*, 7105. [CrossRef] [PubMed]

[25] Sharaf, M. A.; Illman, D. L.; Kowalski, B. R.; *Chemometrics*, A Wiley-Interscience publication, 1986. [PubMed]

[26] Brereton, R. G. Introduction to Multivariate Calibration in Analytical Chemistry. *Analyst* **2000**, *125*, 2125. [CrossRef]

[27] Kubinyi, H.; Mannhold, R.; Krogsgaard-Larsen, P.; Timmerman, H.; *QSAR: Hansch Analysis and Related Approaches; Methods and Principles in Medicinal Chemistry*, Wiley, 2008.