Quantitative Structure Antitumoral-Activity Relationships of Thiadiazinthione Derivatives Using the Novel Hybrid Molecular Index $^{p}MR\chi$

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Received October 26, 2005; Revised November 18, 2005, Accepted November 25, 2003, Published December 1, 2005

Abstract **Purpose**. The recently defined molar-refractivity-partition index was applied to a family of 1,3,5- thiadiazin-2-thione derivatives in order to establish quantitative structure-antitumoral models. The goal of this effort is to establish the relationships between the structure and biological response of these compounds. **Method**. After the splitting of the sample in two sets, their indices were correlated against the measured biological activity. The combined use of our index with others had been able to describe not only the topologic but also the London dispersive forces of any fragment in relation to the biological response of the sets. **Results.** The obtained models showed correlation coefficients of 0.87 and 0.81 respectively linking structural and biological features of the molecules. The mean relative error values were less than 7%. According to the models, the activity of the first sample is related mostly to molecular topology and dispersive forces. Sample two activity was associated to the size and branching of the substituents, and also to the London forces. **Conclusion**. The index was able to discriminate between pure topological features and those related to dispersive forces.

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INTRODUCTION

3,5-disubstituted-tetrahydro-2*H*-1,3,5-thiadiazin-2-thione derivatives (**I**) have a wide spectrum of antimicrobial activity.[1] Several studies related to the antifungic, antiviral, antihelmintic, and tuberculostatic activity of these compounds have been extensively reported.[1-3] Previously, two series of 3,5-disubstituted thiadiazinthiones have been synthesized and assayed *in vitro* and *in vivo* in order to obtain new antiparasitic chemical substances for assessment as potential antiprotozoal agents.[2] In a recent work the antitumoral activity of these compounds have been reported against several tumoral cell lines and also some features of the degradation pathways of this heterocycle[3] were outlined. Up to now, experimental evidence strongly suggests that the thiadiazinthione ring acts as a prodrug. [1] In a protic medium, the heterocycle undergoes a ring opening to form different active metabolites, which are indeed responsible of the biological activity [1]. The use of topologic and topographical indexes is widely accepted for molecular modeling. Recently, we reported the hybrid molar-refractivity-partition index ($^{p}MR\chi$)[4,5], based on Randic algorithm [6] and Ghose and Crippen partitioned molecular refractivity [7], that have the capability to portray London dispersive forces from a different perspective than the molecular refractivity. Then, the aim of this work is to test the index capability to relate structural features of this compound family with their antitumoral activity.

THEORETICAL DETAILS

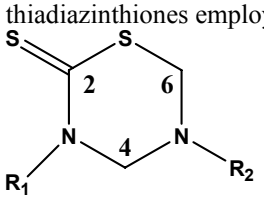
Molar Refractivity

The molar refractivity is a constitutive-additive property calculated by the Lorenz-Lorentz formula:

$$MR = \frac{n^2 - 1}{n^2 + 2} \bullet \frac{M}{\rho} \qquad (1)$$

where M is the molecular weight, *n* is the refraction index and ρ the density, and its value depends only of the wavelength of the light used to measure the refraction index. For a radiation of infinite wavelength, the molar refractivity represents the real volume of the molecules and its polarizability. Then, the molar refractivity is related, not only to the volume of the molecules but also to the London dispersive forces that act in the drug-receptor interaction.

Table 1. General formula and substituents of the thiadiazinthiones employed



I

R_1= -furfuryl
-cyclohexyl

Sample # 1		Sample # 2	
Compound	**R_2**	**Compound**	**R_2**
M1A	$(CH_2)_5COOH$	M2-A	$(CH_2)_5COOH$
M1BS	$CH(COOH)-CH_2-COOH$	M2BS	$CH(COOH)-CH_2-COOH$
M1C	CH_2-COOH	M2-C	CH_2-COOH
M1DS	$CH(CH_2Ph)-COOH$	M2-DS	$CH(CH_2Ph)-COOH$
M1DRS	$CH(CH_2Ph)-COOH$	M2DRS	$CH(CH_2Ph)-COOH$
M1ES	$CH[CH(CH_3)_2]-COOH$	M2FS	$CH[(CH_2)_2COOH]-COOH$
M1FS	$CH[(CH_2)_2COOH]-COOH$	M2-GS	$CH(CH_3)_2-COOH$
M1GS	$CH(CH_3)_2-COOH$	M2-H	$CH_2-CONH-CH_2-COOH$
M1H	$CH_2-CONH-CH_2-COOH$	M2-JS	$CH(CH_2CONH_2)-COOH$
M1IS	$CH[(CH_2)_2SCH_3]-COOH$	M2-M	CH_2-CH_2-COOH
M1JS	$CH(CH_2CONH_2)-COOH$	M2-NS	$C[CH_2-CH(CH_3)_2]-COOH$
M1JR	$CH(CH_2CONH_2)-COOH$		
M1K	$C[(CH_3)_2]-COOH$		
M1M	CH_2-CH_2-COOH		
M1NS	$C[CH_2-CH(CH_3)_2]-COOH$		
M1O	Furfuryl		

Table 2. Atomic refractivity values reported by Ghose et. al.

Atom type	Atomic Refractivity	Atom type	Atomic Refractivity
Csp_3	2.8158	N (Ar)	2.7662
Csp_2	3.8278	NO_2	3.5054
Csp	3.8974	Ar-N=X	3.8095
C (Ar)	3.5090	F	1.0632
C=X	3.0887	Cl	5.6105
H	0.9155	Br	8.6782
-O-	1.6351	I	13.8741
=O	1.7956	Ssp_3	7.3190
O=N	2.1407	Ssp_2	9.1680
Nsp_3	3.0100	R-SO-R	6.0762
Nsp_2, Nsp	3.2009	$R-SO_2-R$	5.3321

The atomic contribution to molecular refractivity calculated by Ghose and Crippen method

Ghose and Crippen defined 110 atom types, [7] representing most commonly occurring atomic states of carbon, hydrogen, oxygen, nitrogen, halogens, and sulphur in organic molecules to split the molar refractivity. They stated that this classification partially differentiates the polarizing effects of heteroatoms and the effect of overlapping with non-hydrogen atoms, although they accepted that this classification might be weak in differentiating the conjugation effects. The authors stated that the classification may not completely cover all organic molecules, and that addition of atom types is always feasible. Further on, the 110 atom types were reduced to 22 (table 2). They assumed that the sum of the atomic values (a_i) is the molecular value of the molar refractivity (eq. 2):

$$MR_{calc.} = \sum n_i a_i \qquad (2)$$

Graph theory. The Randic-type graph theoretical invariant

Graph theory is a branch of mathematics related to topology and combinatorial problems.[18] Different authors have reported a large number of topological and topographical indices as well as its broad and successful applicability in QSAR and QSPR studies. However, the principal problems of the use of this approach are related to the physical meaning and the information redundancy among indices of similar definition, commonly expressed by high correlation values. [19] In this sense, Randic postulated [20] that any novel molecular descriptor 1) need to be simple, 2) add more insights to the problem, 3) or to solve a unexplained problem by alternative schemes, among others features. Randic molecular connectivity index for path of order p ($^p\chi$) is defined as [6]:

$$^p\chi = \sum (\upsilon_i \upsilon_j)^{-1/2} \qquad (3)$$

It was modified by Kier and Hall[21,22] by defining subgraphs G_j tree type in the G graph containing edges. To each vertex i of graph *G* is associated a term δi (for example δi = vi). After this, to each subgraph Gi with vertices j1,..., jh+1 is calculated the F magnitude (Eq. 4)

$$F(\delta_{j_1},...,\delta_{j_{h+1}}) = \prod_{k=1}^{h+1} \delta_{i_k}^{-1/2} \qquad (4)$$

The numbers $F(\delta_{i1}, \delta_{j(h+1)})$ are then added in all the subgraph Gi.. To include the multiple bonds and heteroatoms, Kier and Hall suggested the employ of δi as,

$$\delta_i = Z_i^v - h_i \qquad or \quad \delta_i = \frac{Z_i^v - h_i}{Z_i - Z_i^v - 1} \qquad (5)$$

where Z_i is the total number of electrons, Z^v_i is the number of valence electrons and h_i is the hydrogen atoms number bonded to atom i. The connectivity indices obtained by this formula are known as valence indices [22] and represented by $^p\chi^v$. A more detailed explanation of the graph theory and calculation procedures can be found elsewhere.[23]

Molar refractivity partition index pMRχ

Molar refractivity partition index[6,7] ($^pMR\chi$) use the Randic-type graph-theoretical invariant, and is defined as follow (Eq. 6),

$$^pMR\chi = \sum [\delta^{MR}(v_i)\delta^{MR}(v_j)^{-1/2} \qquad i \neq j \qquad (6)$$

where the sum is all over adjacent vertices in the graph. $\delta MR(v_i)$ is the atomic refractivity value of the v_i atom.

The atomic refractivity values of bonded hydrogen to heavy atoms are also added to this term, to take into account their contribution in the graph.

EXPERIMENTAL PART

Table 1 shows the compound sets. Reported antitumoral activity [3] is shown in tables 3 and 5. Biological activity is given as *log* IC_{50} against HeLa cells (*logA*). All structures were optimized to 0.01 convergence by the semiempirical method PM3 [9,10] implemented in MOPAC 6.0 program.[11-13] In all the indexes employed the superscript p and c indicates path and cluster order, respectively. Randić ($^p\chi$) and valence ($^p\chi^c_V$), based on the vertices connectivity matrix and $^p\varepsilon$ Estrada indices, in the edge connectivity matrix [14] were used as topological descriptors. As topographic descriptors, the $^p\Omega$, $^p\Omega_q$, $p\Omega_q^C$ and $^p\varepsilon_\rho$ Estrada indices [14] were employed. The Ω indices are based in the matrix of the vertices, weighted by the bond orders, the charge density and the charge density with spatial correction respectively. In the case of $^p\varepsilon_\rho$, the connectivity matrix of the edges is weighted with the bond orders. The χ, χ^V, Ω, Ω_q, Ω_q^C, ε and ε_ρ were calculated with the MODEST program [15]. Both the bond orders and the charge density were taken from the output of the semiempirical calculations.

$^pMR\chi$ index was included to portray the importance of the London dispersive forces. Paths of order 1 to 6, clusters of order 3 and 4, and combinations of cluster 3 with path order 1 to 3 were calculated, using a program developed in the authors laboratory [16] The log *P* and MR values were calculated by the Ghose and Crippen methodology.

The 27 compounds in the sample were divided in two, according the nature of R_1 substituent. Forward stepwise multiple regression analysis was employed to establish the quantitative regression models, using the STATISTICA package. [17] A statistical outlier was defined as any compound that failed in three of the several criteria included in the program. In such case it was excluded from the sample and the analysis was restarted. Both models were cross-validated, reporting the Q^2 value.

RESULTS AND DISCUSSION

The mechanism of the antitumoral action of these compounds is not well established. It has been previously described that, in biological environment, the thiadiazinthione ring breaks to generate active metabolites.

Since only two different substituents in position 1 are represented in the series, it is possible to use an indicator (dummy) variable (taking values 1 or 0 for the presence or not of a given substituent) to described the whole set. However, we had preferred to treat the sample separately. Therefore the sample was divided in two: Sample #1 with R_1=furfuryl and Sample #2 with R_1=cyclohexyl.

Analysis of the sample set #1

This sample set includes sixteen N^1-furfuryl derivatives. After the exclusion of the compound M1JS as a statistical outlier (predicted value error > 55 %) the regression analysis affords the equation 7:

$$\log A = 1.80(\pm 0.28) + 7.73(\pm 1.22)^{6}MR\chi - 0.49(\pm 0.09)^{3}\chi - 1.60(\pm 0.50)^{2}MR^{3}\chi \quad (7)$$
$$R = 0.898 \quad R^2 = 0.807 \quad F_{(3,11)} = 15.294 \quad p < 0.00031$$
$$s = 0.096 \quad n = 15 \quad Q^2 = 0.648$$

The prediction results are shown in table 3. According to Kubinyi,[18] the analysis for the exclusion of statistical outliers must be an arbitrary process. As the exclusion of compound M1DRS (error = 16.67%) as a statistical outlier does not improve the quality of the model it was maintained in the sample. Although the Q^2 value of the cross validation is higher than 0.5 (suggesting that the equation has predictive capability), it is decreased by more than 10% with respect to the R^2 value of the regression model. For this reason, we consider the predictive capability of the equation as low, although Golbraigkh and Tropsha [19] accept Q^2 values higher than 0.5. The mean contribution to the activity of each variable is 3.149, -3.314 and –0.666 for $^{6}MR\chi$, $^{3}\chi$ and $^{2}MR^{3}\chi$ respectively. The analysis of these values suggests that the inclusion of long fragments in the structure decreases the antitumoral activity. This could be due to an increase in the possibility to form instantaneous dipoles, taking into account the presence of heteroatoms as S and O. Then, an increased macromolecular union described by this variable could explain the role of the London forces described by $^{6}MR\chi$.

The most important features that determine the antitumoral activity are the presence of fragments of three atoms and path-clusters combinations as described by variables $^{3}\chi$ and $^{2}MR^{3}\chi$ respectively. Although it is risky to say that equation 7 is predictive, it was useful to evaluate which structural features are involved in the biological response of this compounds set in the HeLa assay.

The figures 1 and 2 show the plot of Predicted vs. Observed values and Residuals vs. Deleted Residuals from equation 7.

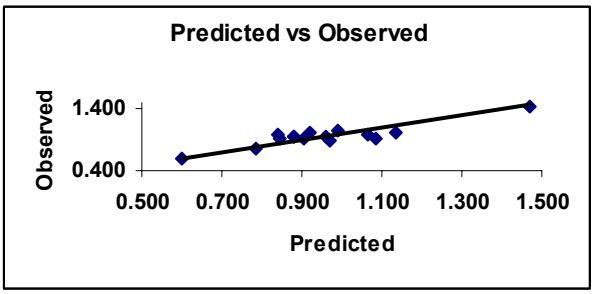


Figure 1. Predicted vs. observed values for sample 1 with equation 7

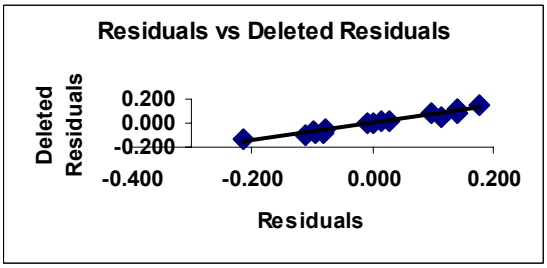


Figure 2. Deleted vs. deleted residuals from equation 7

Summarizing, these results suggests that topological features and the dispersive forces described by the hybrid index $^{p}MR\chi$ affect the antitumoral activity of the compounds of sample 1, which can be associated to the presence of long fragments (up to six carbon atoms). These fragment types are also topologically described by the Randic index. The branching ($^{2}MR^{3}\chi$) and the size ($^{6}MR\chi$, $^{3}\chi$) of the molecules in this sample may be the principal structural features that modulate the activity of these compounds.

The correlation matrix (table 4) demonstrates that correlation between variables in eq. 7 is less than 0.88, which is a good performance taking into account the nature of the variables employed in the analysis. [7]

If this equation is used only for classification as active or inactive, and the threshold of the error is accepted as 10 %, it can be concluded that 80% of the sample was correctly predicted.

Table 3. Results, sample 1 with R1= furfuryl

Compound	R_2	Exp.	Pred.	Res.	% Error
M1A	$(CH_2)_5COOH$	0.60	0.59	0.01	1.67
M1BS	$CH(COOH)-CH_2-COOH$	0.96	0.97	-0.01	1.04
M1C	CH_2-COOH	0.99	1.05	-0.06	6.06
M1DS	$CH(CH_2Ph)-COOH$	1.06	0.98	0.09	8.49
M1DRS	$CH(CH_2Ph)-COOH$	0.84	0.98	-0.14	16.67
M1ES	$CH[CH(CH_3)_2]-COOH$	0.90	0.90	0.00	0.00
M1FS	$CH[(CH_2)_2COOH]-COOH$	1.47	1.43	0.04	2.72
M1GS	$CH(CH_3)_2-COOH$	0.97	0.88	0.09	9.28
M1H	$CH_2-CONH-CH_2-COOH$	0.79	0.77	0.01	1.27
M1IS	$CH[(CH_2)_2SCH_3]-COOH$	0.88	0.96	-0.08	9.09
M1JS	$CH(CH_2CONH_2)-COOH$	0.53	**OUTLIER**		
M1JR	$CH(CH_2CONH_2)-COOH$	0.88	0.96	-0.08	9.09
M1K	$C[(CH_3)_2]-COOH$	0.92	1.02	-0.10	10.87
M1M	CH_2-CH_2-COOH	0.85	0.90	-0.06	7.06
M1NS	$C[CH_2-CH(CH_3)_2]-COOH$	1.09	0.93	0.15	13.76
M1O	Furfuryl	1.13	1.02	0.11	9.73
Mean					7.12

Table 4. Correlation matrix of variables in eq. 7.

	Log *A*	$^3\chi$	$^6MR\chi$	$^2MR^3\chi$
Log *A*	1.000			
$^3\chi$	-0.237	1.000		
$^6MR\chi$	-0.361	**0.865**	1.000	
$^2MR^3\chi$	-0.321	0.668	**0.875**	1.000

Analysis of the sample set #2

This sample set includes the 11 derivatives where R_1 = cyclohexyl. The regression analysis allows us to obtain the equation 8, which includes $^1\chi_v^3$ and $^3MR^3\chi$ indices. Both of them describe the role of molecular branching, but with different sign and fragments. The mean contribution values of each variable to the activity are -2.779 and 0.682 respectively.

This result suggests that in this compound set topological features given by variable $^1\chi_v^3$ are more important than dispersive forces.

$$\log A = 3.60(\pm 0.32) - 1.34(\pm 0.20)^1\chi_V^3 + 3.15(\pm 0.65)^3 MR^3\chi \quad (8)$$
$$R = 0.934 \quad R^2 = 0.871 \quad F_{(2,7)} = 23.731 \quad p < 0.00076$$
$$s = 0.080 \quad n = 10 \quad Q^2 = 0.804$$

Activity prediction for sample 2 is shown in table 5.

Table 5. Results, sample 2 with R1= cyclohexyl

Compound	R_2	Exp.	Pred.	Res.	% Error
M2-A	$(CH_2)_5COOH$	1.48	1.42	0.06	4.05
M2BS	$CH(COOH)-CH_2-COOH$	1.66	1.64	0.01	0.60
M2-C	CH_2-COOH	1.46	1.55	-0.08	5.48
M2-DS	$CH(CH_2Ph)-COOH$	1.14	1.29	-0.16	14.04
M2DRS	$CH(CH_2Ph)-COOH$	1.37	1.29	0.08	5.84
M2FS	$CH[(CH_2)_2COOH]-COOH$	1.46	1.42	0.04	2.74
M2-GS	$CH(CH_3)_2-COOH$	1.14	1.14	0.00	0.00
M2-H	$CH_2-CONH-CH_2-COOH$	1.66	1.64	0.02	1.20
M2-JS	$CH(CH_2CONH_2)-COOH$	1.18	*Outlier*		
M2-M	CH_2-CH_2-COOH	1.54	1.54	0.00	0.00
M2-NS	$C[CH_2-CH(CH_3)_2]-COOH$	1.18	1.16	0.02	1.69
Mean					3.24

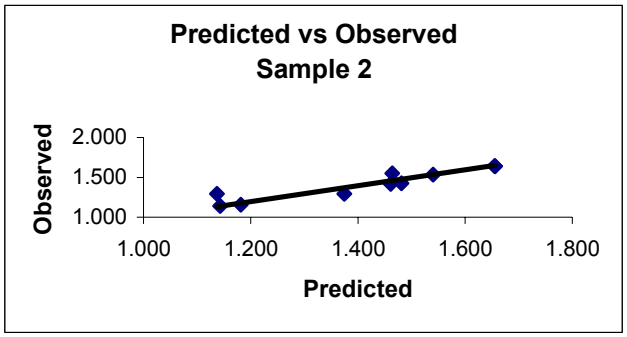


Figure 3. Predicted vs. observed values calculated with equation 8 for sample 2.

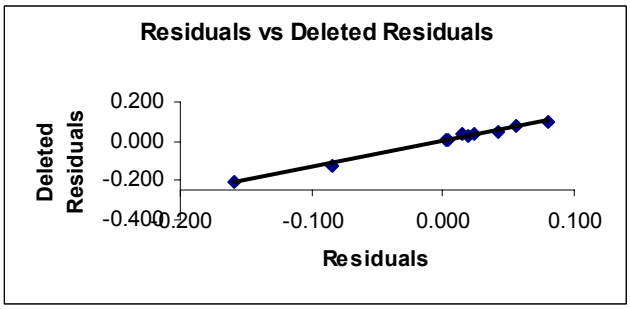


Figure 4. Residuals vs. deleted residuals obtained from equation 8.

Figures 3 and 4 show the plots of the predicted vs. observed values with equation 8, and the graph of residuals vs. deleted residuals.

This last graph (fig. 4) suggests that this regression model is more stable than that given with equation 7 for the first compounds set. This can be explained from the definition of deleted residuals. They are the residuals that one would obtain if the respective case would be excluded from the estimation of the multiple regression (i.e., the computation of the regression coefficients).

Thus, if there are large discrepancies between the deleted residuals and the regular standardized residuals, then it can be concluded that the regression coefficients are not very stable, that is, they are greatly affected by the exclusion of single cases. If these results are analyzed in the same manner as for sample 1, it may be concluded that, qualitatively speaking, 90% of the sample was correctly predicted.

CONCLUSION

As a general remark, when the substituent in R1 is furfuryl, an increased activity is obtained except when R is CH[$(CH_2)_2$COOH]-COOH. Equations 7 and 8 suggest that the presence of path-cluster fragments type ($^2MR^3_\chi$ and $^3MR^3_\chi$ respectively) in both series also increases the activity. These two features suggest that this pattern of substitution affords leads compounds in both series. On the other hand, it was determined that the $^pMR\chi$ index is useful to describe the antitumoral activity of the thiadiazinthiones set studied in this work. The index was able to discriminate between pure topological features and those related to dispersive forces.

ACKNOWLEDGEMENTS

This work has been partially supported by Ministry of Public Health of Cuba grants. The authors wish to thanks the referees and the editorial board for their useful comments and kindly patient.

REFERENCES

[1] Ertan, M.; Bilgil, A.A.; Palaska, E. and Yulug, N.; Synthesis and Antifungal Activities of some 3-(2-Phenylethyl)-5-substituted-tetrahydro-2-1,3,5-thiadiazine-2-thione, *Arzneimitttel Forschung-Drug Research*, 42:160-171, 1992.

[2] a) Ochoa, C.; Pérez, E.; Pérez, R.; Suárez, M.; Ochoa, E.; Rodríguez, H.; Barrio, A.G.; Muelas, S.; Nogal, J.J. and Martínez, R.A.; Synthesis and Antiprotozoan Properties of New 3,5-Disubstituted-Tetrahydro-2H-1,3,5-Thiadiazin-2-Thione Derivatives. *Arzneimitttel Forschung-Drug Research*, 49:(II), 464-469, 1999. b) Muelas, S.; Suárez, M.; Pérez, R.; Rodríguez, H.; Ochoa, C.; Escario, J.A. and Gómez-Barrio, A.; In Vitro and In Vivo Assays of 3,5-Disubstituted Tetrahydro-2*H*-1,3,5-thiadiazin-2-thione Derivatives Against Trypanosoma cruzi. *Mem. Inst. Oswaldo Cruz*, Río de Janeiro, 97:(2), 269-272, 2002.

[3] Pérez, R.; Rodríguez, H.; Pérez, E.; Suárez, M.; Reyes, O.; González, L.J.; López de Cerain, A.; Ezpeleta, O.; Pérez, C. and Ochoa. C.; Study on the Decomposition Products of Thiadiazinthione and their Anti-Cancer Properties. *Arzneim. Forsch. - Drug Res.*; 50(II): 854-857, 2000.

[4] Padrón, J.A.; Carrasco, R. and Pellón, R.; Definition of New Descriptor Based on Molar Refractivity Partition Using Randic Type Graph-Theoretical Invariant.; Revista Cubana de Farmacia, 34 Special Supp. Especial June 2000 pp. 328-2.

[5] Padrón, J. A.; Carrasco, R. and Pellón, R.F.; Molecular Descriptor Based on a Molar Refractivity Partition using Randic-type Graph-theoretical Invariant, *J.Pharm.Pharmaceut. Sci.*(www.ualberta.ca/~csps) 5(3):234-231, 2002.

[6] Randic, M.; On Characterization of Molecular Branching, *J. Am. Chem. Soc*., 97:6609-6615, 1975.

[7] a) Ghose, A.K. and Crippen, G.M.; Atomic Physicochemical Parameters for Three-dimensional Structure-Directed Quantitative Structure-Activity Relationships. I. Partition Coefficients as a Measure of Hydrophobicity. *J.Comput. Chem.*, 7:(4), 565-577, 1986; b) Ghose, A.K. and Crippen, G.M.; Atomic Physicochemical Parameters for Three-Dimensional Structure-Directed Quantitative Structure-Activity Relationships. 2. Modeling Dispersive and Hydrophobic Interactions; *J. Comput. Chem.*; 27(1):21-35, 1987.

[8] HyperChem, (1993) Hypercube, Inc. and Autodesk, Inc. Release 3 for Windows.

[9] Stewart, J.J.P.; Optimization of Parameters for Semi-empirical Methods I-Method; *J.Comp.Chem.,* 10:209-220, 1989.

[10] Stewart, J.J.P.; Optimization of Parameters for Semi-empirical Methods II-Applications; *J.Am.Chem.Soc.* 10:221-264, 1989.

[11] Stewart, J. J. P.; *MOPAC* 6.0. Indiana University, Bloomington, IN, *Manual QCPE* # 581.

[12] Stewart, J. J. P.; Mopac: A Semiempirical Molecular Orbital Program, *J. Comp. Aid. Mol. Design*, **4(**1)**:** 1-103, 1990.

[13] MOPAC v.6 for 3/486/Pentium PC's. Release 1.02; March 1997; Windows 95 and NT environments. Universidad de La Habana, Cuba, 1994-97.

[14] a) Estrada, E. and Montero, L.A.; Bond Order Weighted Graphs in Molecules as Structure-property Indices. *Mol. En*g., 2:363-373, 1993. b) Estrada, E. and Ramírez, A.; Edge Adjacency Relationships and Molecular Topographic Descriptors. Definition and QSAR Applications. *J. Chem. Inf. Comput. Sc*i., *3*7:837-843, 1997; c) Estrada, E. Three-dimensional Molecular Descriptors Based on Electron Charge Density Weighted Graphs. *J. Chem. Inf. Comput. Sc*i. *3*5:708-713, 1995; d) Estrada, E.; Edge Adjacency Relationships and a Novel Topological Index Related to Molecular Volume. *J. Chem. Inf. Comput. Sci.*, 35:31-33, 1995; e) Estrada, E. and Molina, E.; 3D Connectivity Indices in QSPR/QSAR Studies. *J. Chem. Inf. Comput. Sc*i. 41:791-797, 2001.

[15] Rodríguez, L.; Estrada, E.; Muñoz, I. and Gutiérrez Y.; *MODEST (Molecular DESign Tools) 2.0.* Universidad Central de Las Villas: Santa Clara, 1994.

[16] Padrón, J.A. and Carrasco, R.; La Habana, Program for the calculation of ^{p}MRχ Index. Pharmaceutical Chemistry Center, 2002.

[17] STATISTICA for WINDOWS, version 4.0, Statsoft, Inc. 1993.

[18] Harary, F.; Graph Theory, Addison-Wesley, Reading MA, 1969.

[19] Basak, S.C.; Magnuson, V.R.; Niemi, G.J.; Regal, R.R. and Veith, G.D.; Topological Indices: Their Nature, Mutual Relatedness, and Applications, *Math. Model*, 8:300-305, 1987.

[20] Kubinyi, H., QSAR: Hansch Analysis and Related Approaches, pp. 59-60. In: Methods and Principles in Medicinal Chemistry, R. Mannhold, P. Krogsgaard-Larsen y H. Timmerman, Eds. **1993**,

[19] Golbraikh, A. and Tropsha, A. *J. Mol. Graph. Model*., 20, 269-276(2002).

[20] Randic, M.; Hansen, P.J. and Jurs, P.C.; Search for Useful Graph Theoretical Invariants of Molecular Structure, *J. Chem. Inf. Comput.Sci*., 28:60-68, 1988.

[21] Kier, L.B. and Hall, L.H.; *Molecular Connectivity in Chemistry and Drugs Researc*h, Academic Press, New York, 1976.

[22] Kier, L.B. and Hall, L.H.; *Molecular Connectivity in Structure-Activity Analysis*; Research Studies Press Ltd., Hertfordshire, England and John Wiley and Sons, New York 1986.

[23] Molconn-Z 3.50 Manual; http://www.eslc.vabiotech.com/molconn/manuals/350/