Molecular Descriptors Family on Structure Activity Relationships 5. Antimalarial Activity of 2,4-Diamino-6-Quinazoline Sulfonamide Derivates

Lorentz JÄNTSCHI and Sorana BOLBOACĂ

Technical University of Cluj-Napoca and "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; http://lori.academicdirect.org

Abstract

Antimalarial activity of sixteen 2,4-diamino-6-quinazoline sulfonamide derivates was modeled using an original methodology which assess the relationship between structure of compound and theirs activity. The results shows us that the antimalarial activity of studied 2,4-diamino-6-quinazoline sulfonamide compounds is alike topological and geometrical and is strongly dependent on partial change of the molecule. The ability in prediction with SAR models is sustained by the results obtained through cross-validation analysis and by the stability of the models. The SAR methodology gives us a real solution in structure-activity relationships investigation of 2,4-diamino-6-quinazoline sulfonamide compounds, obtaining better results by the use of two and/or three descriptors compared with the best performing previous reported model.

Keywords

Structure - Activity Relationships (SAR), Molecular Descriptors Family (MDF), Multiple Linear Regression (MLR), Antimalarial Activity, 2,4-diamino-6-quinazoline sulfonamide derivates

Background

The sulfonamides are sulfa-related group of antibiotics used in bacterial and some fungal infections, killing the bacteria and fungi by interfering with cell metabolism. Sulfonamides and its derivates, including the 2,4-diamino-6-quinazoline sulfonamides [1], have been used in medicine for theirs antimalarial properties [2]. To date, for 2,4-diamino-6-quinazoline sulfonamide derivates, have been reported in specialty literature QSAR's models using electronic parameters, as energy of highest occupied molecular orbitals (EH), energy of lowest unoccupied molecular orbital (EL) and charge density (CD) [3] and topological properties (Wiener index - *W*, Szeged index - *Sz*, and indicator parameters, called dummy or de novo constants, which take two values – zero or one – and serve as indication of category or class membership - I_{p1}, I_{p2} and I_{p3}) [4]. Agrawal et all models the antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates by the use of topological properties and obtained mono-, bi-, tri-, and tetra-parametric models. The models obtained previously are in table 1, indicating the regression equations, the square of correlation coefficient (r^2), and cross-validation values (r^2_{cv}) where were available.

Table 1. QSAR models for antimalarial activity of sulfonamide derivates reported by Agrawal

No	QSAR model	r^2	r^2_{cv}
1	$6.9977-0.0032(\pm 9.9221\cdot 10^{-4})\cdot W$	0.4229	-
2	$6.8222-0.0019(\pm 6.3548\cdot 10^{-4})\cdot Sz$	0.3713	-
3	$9.6975-0.0045(\pm 0.0010)\cdot W-1.9814(\pm 0.08269)\cdot Ip_1$	0.5997	0.3325
4	$9.9246-0.0028(\pm 6.9413\cdot 10^{-4})\cdot Sz-2.1021(\pm 0.8938)\cdot Ip_1$	0.5590	-
5	$9.4033-0.0041(\pm 0.0010)\cdot W-2.1844(\pm 0.8013)\cdot Ip_1$ $-1.0922(\pm 0.7280)\cdot Ip_2$	0.6629	0.5009
6	$9.4696-0.0026(\pm 7.2234\cdot 10^{-4})\cdot Sz-2.2182(\pm 0.8888)\cdot Ip_1-0.9272(\pm 0.8072)\cdot Ip_2$	0.6027	0.3343
7	$9.0548-0.0019(\pm 7.5770\cdot 10^{-4})\cdot Sz-3.2559(\pm 0.9977)\cdot Ip_1$ $-2.6109(\pm 1.911)\cdot Ip_2-1.9345(\pm 1.0718)\cdot Ip_3$	0.6934	0.5579
8	$9.1679-0.0032(\pm 0.0010)\cdot W-3.1824(\pm 0.9143)\cdot Ip_1$ $-2.5978(\pm 1.0591)\cdot Ip_2-1.7911(\pm 0.9807)\cdot Ip_3$	0.7414	0.6493

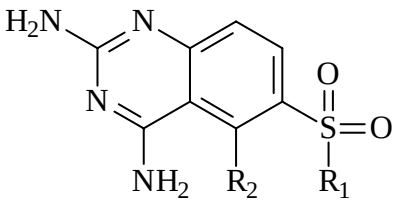
The aim of the research was to test the ability of SAR methodology in prediction of antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates and to compare the found models with previous reported QSARs.

Materials and Methods

Material and Pharmacology

Sixteen 2,4-diamino-6-quinazoline sulfonamide derivates was included into analysis. The planar structure of 2,4-diamino-6-quinazoline sulfonamide derivates, the substituents X and Y, and the measured antimalarial activity (Y_{aa}) are in table 2. Antimalarial activity used in the study was taken from the paper reported by Elslager et all [1], and is defined as difference between the average survival times (in days) of treated mice and the average survival times (in days) of control mice.

Table 2. Planar structure of 2,4-diamino-6-quinazoline sulfonamide derivates and measured antimalarial activity



No	R_1	R_2	Y_{aa}
mol_01	$N(C_2H_5)_2$	H	3.3
mol_02	$N(CH_2)_5$	Cl	2.3
mol_03	$N(CH_2\ CH_2\ CH3)_2$	H	0.3
mol_04	$N(CH_2\ CH_2\ OH)_2$	H	0.3
mol_05	$N(CH_3)CH\ (CH_3)_2$	H	0.7
mol_06	$N(CH_3)CH_2CH_2N(C_2H_5)_2$	H	0.1
mol_07	$N(CH_2)_5$	H	4.4
mol_08	$N(CH_2)_4$	H	5.0
mol_09	$N[(CH_2)_2]_2O$	H	4.7
mol_10	$N[(CH_2)_2]_2S$	H	2.5
mol_11	$N[(CH_2)_2]_2NCH_3$	H	1.0
mol_12	$N[(CH_2)]_2NC(=O)OC_2H_5$	H	0.2
mol_13	$NH\text{-}C_6H_4\text{-}4Cl$	H	0.7
mol_14	$NH\text{-}C_6H_4\text{-}3Br$	H	0.3
mol_15	$NCH_3\text{-}C_6H_4\text{-}4Cl$	H	0.3
mol_16	$NCH_3\text{-}C_6H_5$	H	0.3

SAR modeling

The steps of molecular descriptors family on structure activity relationships modeling of antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates were [5]:

- Step 1: Sketch of 2,4-diamino-6-quinazoline sulfonamide compounds by the use of HyperChem software [6];
- Step 2: Create the file with measured antimalarial activity (Y_{aa}) of 2,4-diamino-6-quinazoline sulfonamide derivates;
- Step 3: Generate the MDF members for the sixteen 2,4-diamino-6-quinazoline sulfonamide derivates. Based on topological and geometrical representations of the sixteen 2,4-diamino-6-quinazoline sulfonamide, were calculated a total number of 289206 molecular descriptor. By applying significance selector to biases the values, and a significant difference value of 10^{-9} for mono-varied scores a number of 93362 molecular descriptors were found to be significant different and were included into analysis.
- Step 4: Find the SAR models for 2,4-diamino-6-quinazoline sulfonamide compounds. The criterion imposed in finding the SAR models was represented by the correlation coefficient and squared correlation coefficient most closed to the value equal with one.
- Step 5: Validation of the obtained SAR models were performed through computing the cross-validation leave-one-out correlation score [7], and the difference between this parameter and the squared correlation coefficient. The cross-validation leave-one-out correlation score was obtain after each compound from the whole set sixteen 2,4-diamino-6-quinazoline sulfonamide was deleted and the coefficients for the corresponding model (mono-, bi-, or tri-varied) were computed. The antimalaria activity of deleted compound was predicted by the use of new calculated equation (mono-, bi-, or tri-varied).
- Step 6: Analyze the selected SAR models and comparing them with previous reported model. The comparison between the SAR models and best performing previous reported QSAR was performed by applying the Steiger's Z-test.

Results

The best performing mono-, bi-, and tri-varied SAR models, together with associated statistics of regression analysis are in table 3.

Table 3. SARs for antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates with MDF members

No	SAR model	
	Characteristic	Notation and Value
1	Mono-varied model: $\hat{Y}_{mono\text{-}v} = 3.26\cdot10^{-2} + 8.72\cdot10^{5}\cdot IsPmSQt$	
	Correlation coefficient	$r = 0.934$
	Squared correlation coefficient	$r^2 = 0.873$
	Adjusted squared correlation coefficient	$r^2_{adj} = 0.864$
	Standard error of estimated	$s_{est} = 0.659$
	Fisher parameter	$F_{est} = 96$
	Probability of wrong model	$p_{est}(\%) = 1.2\cdot10^{-5}$
	t parameter for intercept; p-values 95% probability CI_{int} [lower 95%; upper 95%]	$t_{int} = 0.140$; $p_{tint} = 0.89$ $_{95\%}CI = [-0.467; 0.533]$
	t parameter for IsPmSQt descriptor; p for $t_{IsPmSQt}$ 95% probability $CI_{IsPmSQt}$ [lower 95%; upper 95%]	$t_{IsPmSQt} = 9.802$; $p_{IsPmSQt} = 1.2\cdot10^{-7}$ $_{95\%}CI_{IsPmSQt} = [6.81\cdot10^{5}; 10.63\cdot10^{5}]$
	Cross-validation leave-one-out (loo) score	$r^2_{cv\text{-}loo} = 0.840$
	Fisher parameter for loo analysis	$F_{pred} = 73$
	Probability of wrong model for loo analysis	$p_{pred}(\%) = 6.2\cdot10^{-7}$
	Standard error for leave-one-out analysis	$s_{loo} = 0.741$
	The difference between r^2 and $r^2_{cv(loo)}$	$r^2 - r^2_{cv(loo)} = 0.033$

2	Bi-varied model: $\hat{Y}_{bi\text{-}v} = 4.81\cdot10^{-3}+1.95\cdot10^{5}\cdot IsMMEQt+2.27\cdot10^{7}\cdot IIMMTQt$	
	Correlation coefficient	$r = 0.985$
	Squared correlation coefficient	$r^2 = 0.971$
	Adjusted squared correlation coefficient	$r^2_{adj} = 0.967$
	Standard error of estimated	$s_{est} = 0.324$
	Fisher parameter	$F_{est} = 220$
	Probability of wrong model	$p_{est}(\%) = 9.4\cdot10^{-9}$
	t parameter for intercept; p_{tint} 95% probability CI_{int} [lower 95%; upper 95%]	$t_{int} = 0.039$; $p_{tint} = 0.969$ $_{95\%}CI_{int} = [-0.261; 0.271]$
	t parameter for IsMMEQt descriptor; $p_{IsMMEQt}$ 95% probability $CI_{IsMMEQt}$ [lower 95%; upper 95%]	$t_{IsMMEQt} = 7.702$; $p_{IsMMEQt} = 3.4\cdot10^{-6}$ $_{95\%}CI_{IsMMEQt} = [1.4\cdot10^{5}; 2.5\cdot10^{5}]$
	t parameter for IIMMTQt descriptor; $p_{IIMMTQt}$ 95% probability $CI_{IIMMTQt}$ [lower 95%; upper 95%]	$t_{IIMMTQt} = 17.74$; $p_{IIMMTQt} = 1.7\cdot10^{-10}$ $_{95\%}CI_{IIMMTQt} = [2\cdot10^{7;}\ 2.5\cdot10^{7}]$
	Cross-validation leave-one-out (loo) score	$r^2_{cv\text{-}loo} = 0.961$
	Fisher parameter for loo analysis	$F_{pred} = 163$
	Probability of wrong model for loo analysis	$p_{pred}(\%) = 6.19\cdot10^{-8}$
	Standard error for leave-one-out analysis	$s_{loo} = 0.375$
	The difference between r^2 and $r^2_{cv(loo)}$	$r^2 - r^2_{cv(loo)} = 0.00958$
	The squared correlation coefficient between descriptor and measured antimalarial activity, and between descriptors	$r^2(IsMMEQt, Y_{aa}) = 0.277$ $r^2(IIMMTQt, Y_{aa}) = 0.840$ $r^2(IsMMEQt, IIMMTQt) = 0.035$

3	Tri-varied model: $\hat{Y}_{tri\text{-}v} = -17.6 + 6.83\cdot10^{8}\cdot IsMMTQt + 3.58\cdot10^{-1}\cdot LsMrKQg - 8.47\cdot10^{-1}\cdot lsDMTQt$	
	Correlation coefficient	$r = 0.998$
	Squared correlation coefficient	$r^2 = 0.997$
	Adjusted squared correlation coefficient	$r^2_{adj} = 0.996$
	Standard error of estimated	$s_{est} = 0.1059$
	Fisher parameter	$F_{est} = 1415$
	Probability of wrong model	$p_{est}(\%) = 1.4\cdot10^{-13}$
	t parameter for intercept; p_{tint} 95% probability CI_{int} [lower 95%; upper 95%]	$t_{int} = -14.86$; $p_{tint} = 4.32\cdot10^{-9}$ $_{95\%}CI_{int} = [-20.23; -15.05]$
	t parameter for IsMMTQt descriptor; $p_{IsMMTQt}$ 95% probability $CI_{IsMMTQt}$ [lower 95%; upper 95%]	$t_{IsMMTQt} = 47.03$; $p_{IsMMTQt} = 5.58\cdot10^{-15}$ $_{95\%}CI_{IsMMTQt} = [6.5\cdot10^{8}; 7.1\cdot10^{8}]$
	t parameter for LsMrKQg descriptor; $p_{LsMrKQg}$ 95% probability $CI_{LsMrKQg}$ [lower 95%; upper 95%]	$t_{LsMrKQg} = 10.50$; $p_{LsMrKQg} = 2.09\cdot10^{-7}$ $_{95\%}CI_{LsMrKQg} = [0.28; 0.43]$
	t parameter for lsDMTQt descriptor; $p_{lsDMTQt}$ 95% probability $CI_{lsDMTQt}$ [lower 95%; upper 95%]	$t_{lsDMTQt} = -17.07$; $p_{lsDMTQt} = 8.8\cdot10^{-10}$ $_{95\%}CI_{lsDMTQt} = [-0.95; -0.74]$
	Cross-validation leave-one-out (loo) score	$r^2_{cv\text{-}loo} = 0.9959$
	Fisher parameter for loo analysis	$F_{pred} = 970$
	Probability of wrong model for loo analysis	$p_{pred}(\%) = 1.4\cdot10^{-12}$
	Standard error for leave-one-out analysis	$s_{loo} = 0.1279$
	The difference between r^2 and $r^2_{cv(loo)}$	$r^2 - r^2_{cv(loo)} = 0.0013$
	The squared correlation coefficient between descriptor and measured antimalarial activity, and between descriptors	$r^2(IsMMTQt, Y_{maa}) = 0.8448$ $r^2(LsMrKQg, Y_{maa}) = 0.1556$ $r^2(lsDMTQt, Y_{maa}) = 0.2493$ $r^2(IsMMTQt, LsMrKQg) = 0.0135$ $r^2(IsMMTQt, lsDMTQt) = 0.6140$ $r^2(LsMrKQg, lsDMTQt) = 0.0242$

The list of descriptors and associated values used in mono-, bi-, and tri-varied models and estimated antimalarial activity ($\hat{Y}$) are in table 4.

Graphical representations of the antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates, obtained from structure for mono-, bi-, and tri-varied models vs. measured ones are in figures 1 to 3.

Assessment of the MDF SAR model was performed by applying a correlated correlation analysis, which took into consideration mono-, bi-, and tri-varied SAR models and compared them with the best performing (model with four variables, $r^2 = 0.7414$, $r^2_{cv} = 0.6493$) previous reported model [4] by the use of Steiger's Z test. The results of comparison are in table 5.

Table 4. Descriptors used in MDF SAR models, theirs values and estimated antimalarial activities

	Mono-varied		Bi-varied			Tri-varied			
Mol	IsPmSQt	$\hat{Y}_{mono}$	IsMMEQt	IIMMTQt	$\hat{Y}_{bi}$	IsMMTQt	LsMrKQg	lsDMTQt	$\hat{Y}_{tri}$
mol_01	$2.23 \cdot 10^{-6}$	1.98	$-2.01 \cdot 10^{-6}$	$1.53 \cdot 10^{-7}$	3.07	$7.63 \cdot 10^{-9}$	$-4.03 \cdot 10^{0}$	$-2.02 \cdot 10^{1}$	3.24
mol_02	$2.92 \cdot 10^{-6}$	2.58	$-1.46 \cdot 10^{-7}$	$6.98 \cdot 10^{-8}$	1.56	$3.17 \cdot 10^{-9}$	$-4.49 \cdot 10^{0}$	$-2.28 \cdot 10^{1}$	2.23
mol_03	$2.11 \cdot 10^{-7}$	0.22	$-1.12 \cdot 10^{-6}$	$1.57 \cdot 10^{-8}$	0.14	$7.13 \cdot 10^{-10}$	$-3.56 \cdot 10^{0}$	$-2.21 \cdot 10^{1}$	0.29
mol_04	$2.11 \cdot 10^{-7}$	0.22	$-1.12 \cdot 10^{-6}$	$1.57 \cdot 10^{-8}$	0.14	$7.13 \cdot 10^{-10}$	$-3.60 \cdot 10^{0}$	$-2.21 \cdot 10^{1}$	0.28
mol_05	$6.62 \cdot 10^{-7}$	0.61	$-1.28 \cdot 10^{-6}$	$6.60 \cdot 10^{-8}$	1.25	$3.30 \cdot 10^{-9}$	$-4.28 \cdot 10^{0}$	$-2.08 \cdot 10^{1}$	0.73
mol_06	$6.94 \cdot 10^{-7}$	0.64	$-6.59 \cdot 10^{-7}$	$1.94 \cdot 10^{-8}$	0.32	$8.08 \cdot 10^{-10}$	$-4.47 \cdot 10^{0}$	$-2.22 \cdot 10^{1}$	0.14
mol_07	$3.54 \cdot 10^{-6}$	3.12	$9.86 \cdot 10^{-6}$	$1.05 \cdot 10^{-7}$	4.31	$5.00 \cdot 10^{-9}$	$-1.45 \cdot 10^{0}$	$-2.26 \cdot 10^{1}$	4.40
mol_08	$5.91 \cdot 10^{-6}$	5.19	$4.82 \cdot 10^{-6}$	$1.73 \cdot 10^{-7}$	4.87	$8.65 \cdot 10^{-9}$	$-3.96 \cdot 10^{0}$	$-2.14 \cdot 10^{1}$	4.95
mol_09	$5.18 \cdot 10^{-6}$	4.55	$-1.76 \cdot 10^{-6}$	$2.31 \cdot 10^{-7}$	4.89	$1.10 \cdot 10^{-8}$	$-4.69 \cdot 10^{0}$	$-1.96 \cdot 10^{1}$	4.76
mol_10	$4.20 \cdot 10^{-6}$	3.69	$1.39 \cdot 10^{-6}$	$1.15 \cdot 10^{-7}$	2.89	$5.49 \cdot 10^{-9}$	$-4.37 \cdot 10^{0}$	$-2.13 \cdot 10^{1}$	2.60
mol_11	$7.38 \cdot 10^{-7}$	0.68	$-5.86 \cdot 10^{-6}$	$8.47 \cdot 10^{-8}$	0.78	$3.85 \cdot 10^{-9}$	$-5.24 \cdot 10^{0}$	$-2.10 \cdot 10^{1}$	0.93
mol_12	$1.17 \cdot 10^{-7}$	0.13	$-4.82 \cdot 10^{-7}$	$1.28 \cdot 10^{-8}$	0.20	$4.92 \cdot 10^{-10}$	$-4.41 \cdot 10^{0}$	$-2.24 \cdot 10^{1}$	0.07
mol_13	$1.02 \cdot 10^{-6}$	0.93	$-5.55 \cdot 10^{-7}$	$4.25 \cdot 10^{-8}$	0.86	$1.85 \cdot 10^{-9}$	$-4.68 \cdot 10^{0}$	$-2.20 \cdot 10^{1}$	0.55
mol_14	$1.86 \cdot 10^{-7}$	0.20	$-5.58 \cdot 10^{-7}$	$1.22 \cdot 10^{-8}$	0.17	$5.31 \cdot 10^{-10}$	$-5.03 \cdot 10^{0}$	$-2.28 \cdot 10^{1}$	0.26
mol_15	$7.33 \cdot 10^{-7}$	0.67	$-1.24 \cdot 10^{-7}$	$2.33 \cdot 10^{-8}$	0.51	$9.70 \cdot 10^{-10}$	$-4.13 \cdot 10^{0}$	$-2.24 \cdot 10^{1}$	0.51
mol_16	$1.12 \cdot 10^{-6}$	1.01	$-3.72 \cdot 10^{-7}$	$2.27 \cdot 10^{-8}$	0.45	$9.88 \cdot 10^{-10}$	$-5.09 \cdot 10^{0}$	$-2.27 \cdot 10^{1}$	0.43

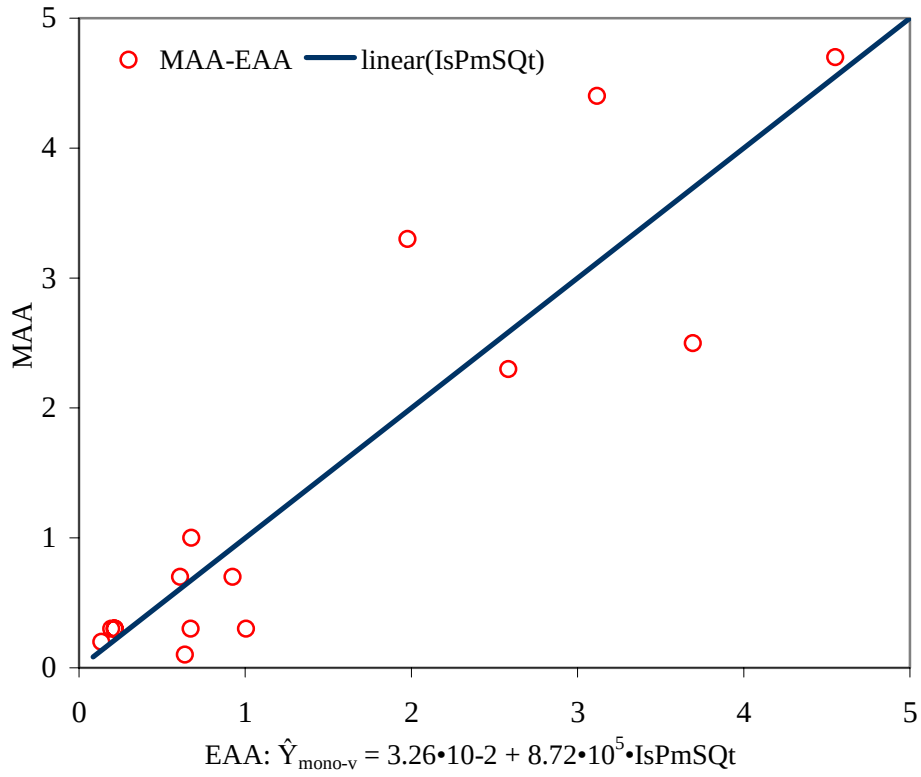


Figure 1. Measured antimalarial activity (MAA) vs. estimated (EAA) with mono-varied model

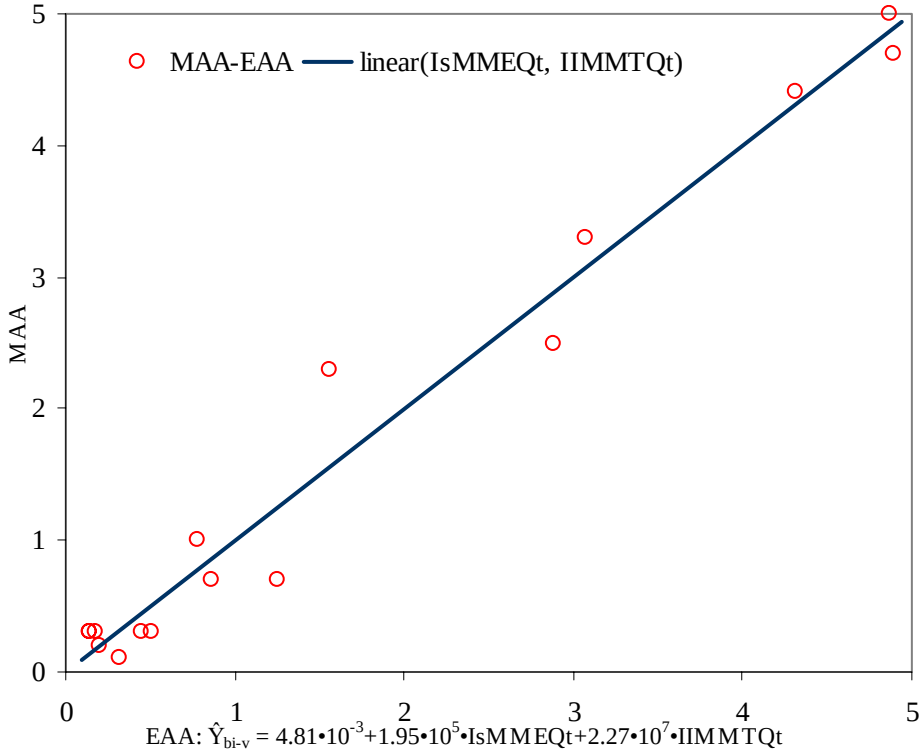


Figure 2. Measured antimalarial activity vs. estimated with bi-varied model

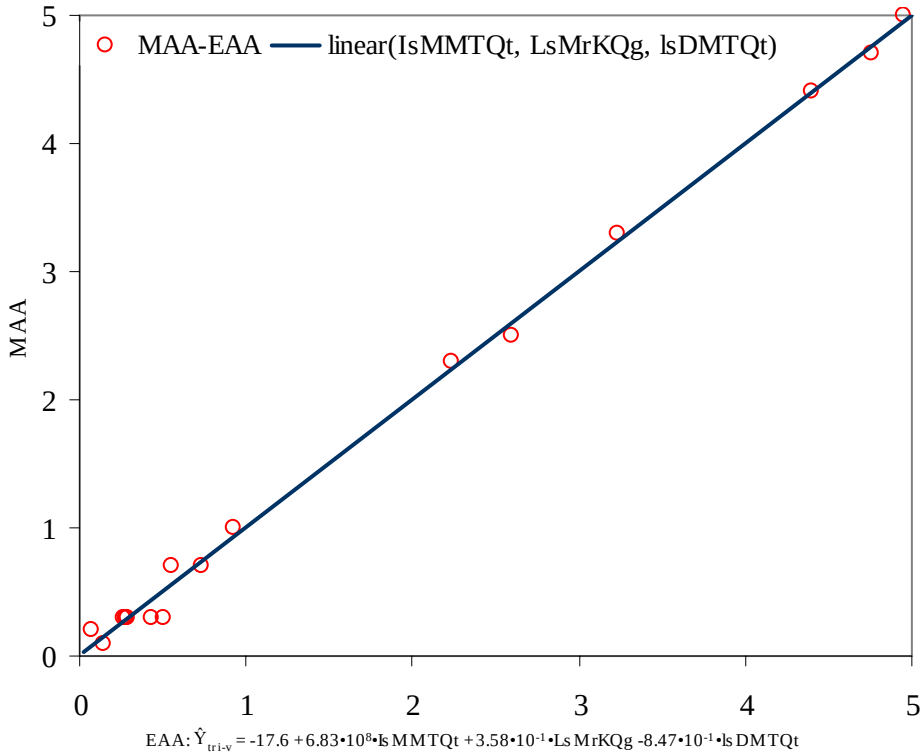


Figure 3. Measured antimalarial activity vs. estimated with tri-varied model

Table 5. The results of comparison obtained and best performing previous reported models

Characteristic	Values		
Number of descriptors used in MDF SAR model	3	2	1
$r(Y_{aa}, \hat{Y}_{MDF\ SAR})$	0.9986	0.9856	0.9342
$r(Y_{aa}, \hat{Y}_{Previous})$	0.8598	0.8598	0.8598
$r(\hat{Y}_{MDF\ SAR}, \hat{Y}_{Previous})$	0.8641	0.8624	0.8139
Steiger's Z test parameter	7.8891	3.9686	1.3229
$p_{Steiger's\ Z}$ (%)	$1.5 \cdot 10^{-13}$	$3.6 \cdot 10^{-3}$	9.2926

Discussions

Antimalarial activity of sixteen 2,4-diamino-6-quinazoline sulfonamide derivates was modeled by the use of an original methodology which take into consideration the structure of the compound and try to explain the interest activity. Applying the MDF SAR methodology, three models, one mono-varied, one bi-varied and one-tri-varied prove to obtained performances in antimalarial activity prediction. All presented SAR models are statistically significant at a significance level less than 0.001. The mono-varied SAR model use a descriptor that take into consideration the topology of molecule (*IsPmSQ**t***) and the partial change as atomic property (*IsPmSQt*). Almost 87 percent of variation in antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates can be explainable by its linear relation with IsPmSQt descriptor. The mono-varied model is significant different by the best performing four-varied model previous reported at a significance level equal with 0.09. As the mono-varied SAR model, the bi-varied one took into consideration the topology of molecule (IsMMEQ**t**, IIMMTQ**t**) as well as partial change as atomic property (IsMME**Q**t, IIMMT**Q**t). All coefficients of the bi-varied equation are significantly differed by zero, except the intercept of the slop. The performance of the bi-varied SAR model is sustained by the correlation coefficient and the squared of the correlation coefficient. Ninety-seven percent of variation in antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates can be explainable by its linear relation with IsMMEQt, IIMMTQt descriptors. The stability of the bi-varied model is proved by the very lower value of the differences between squared correlation coefficient and cross-validation leave-on-out squared correlation coefficient. The cross-validation leave-one-out score ($r^2_{cv\text{-}loo} = 0.961$) sustain the stability of the bi-varied SAR model. Looking at the values of the squared correlation coefficient between descriptors and

measured antimalarial activity it can be observed that there is no correlation between IsMMEQt descriptor and measured antimalarial activity but there is a strong correlation between IIMMTQt descriptor and antimalarial activity. Even if the correlation is strong, the IIMMTQt is not the one that obtained best performances in terms of squared correlation coefficient and cross-validation leave-one-out score in mono-varied SAR model. It could not be observed a significant correlation between descriptors of the bi-varied model (r^2(IsMMEQt, IIMMTQt) = 0.035). The bi-varied SAR model obtained a correlation coefficient significantly greater compared with the previous reported four-varied model at a significance level equal with $3.6 \cdot 10^{-3}$ %. Note that, it is possible to obtained useful information about antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates with a bi-varied model instead of a model with four variable. Looking at the bi-varied model, we can say that the antimalarial activity is of molecular topology and depend on partial change of molecule. Looking at the cross-validation leave-one-out score, we can say that the tri-varied model is the best performing SAR model. Ninety-nine percent of variation in antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates can be explainable by its linear relation with IsMMTQt, LsMrKQg, and lsDMTQt descriptors. Two descriptors (IsMMTQ**t**, and lsDMTQ**t**) take into consideration the topology of the molecule while another one (LsMrK**Q**g) the molecular geometry. All three descriptors (IsMMT**Q**t, LsMrK**Q**g, lsDMT**Q**t) take into consideration the partial change of the molecule. The values of squared correlation coefficient (r^2 = 0.997) demonstrate the goodness of fit of the tri-varied MDF SAR model. The power of the tri-varied model in prediction of the antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide compounds is demonstrate by the cross-validation leave-one-out correlation score ($r^2_{cv(loo)}$ = 0.9959), procedure which did not take into consideration one molecule from the whole set. The stability of the best performing tri-varied MDF SAR model is give by the difference between the squared correlation coefficient and the cross-validation leave-one-out correlation score (r^2 - $r^2_{cv(loo)}$ = 0.0013). Looking at the tri-varied SAR model we can say that the antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates is alike topological and geometrical and depend by the partial change of molecule. Looking at the correlated correlations analysis results, it can be observed that the tri-varied SAR model obtained a significantly greater correlation coefficient compared with the previous reported four-varied model, at a significance level equal with $1.5 \cdot 10^{-13}$ %. Starting with the knowledge learned from the studied set of 2,4-diamino-6-quinazoline

sulfonamide compounds, antimalarial activity of new compound from the same class can be predict by the use of an original software, which is available at the following address:

http://vl.academicdirect.org/molecular_topology/mdf_findings/sar/

Thus, the software id able to predict the antimalarial activity of new 2,4-diamino-6-quinazoline sulfonamide compounds with low costs.

Acknowledgement

Research was in part supported through project ET36/2005 by UEFISCSU Romania.

Conclusions

Antimalarial activity of the studied 2,4-diamino-6-quinazoline sulfonamide compounds is alike to be by topological and geometrical nature and is strongly dependent by partial change. The MDF SAR methodology is a real solution in predicting antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide compounds and could be use in developing of new 2,4-diamino-6-quinazoline sulfonamide compounds with antimalarial properties.

Even if using of MDF in QSAR modeling is time consuming, it has doubtless advantages, such as better QSAR of antimalarial activity of 2,4-diamino-6-quinazoline sulfonamide derivates and a much closer structure activity explanation.

References

[1] Elslager E. F., Colbry N. L., Davoll J., Hutt M. P., Johnson J. L., Werbel L. M., *Folate antagonists. 22. Antimalarial and antibacterial effects of 2,4-diamino-6-quinazolinesulfonamides*, J. Med. Chem., 27(12), p. 1740-1743, 1984.

[2] Shao B. R., *A review of antimalarial drug pyronaridine*, Chin. Med. J. (Engl), 103, p. 428-434, 1990.

[3] Agrawal V. K., Sinha S., Bano S., Khadikar P. V., *QSAR studies on antimalarial 2,4-diamino-6-quinazoline sulfonamides*, Acta Microbiol Immunol Hung, 48(1), p. 17-26, 2001.

[4] Agrawal K. V., Srivastavaa R., Khadikarb V. P., *QSAR Studies on Some Antimalarial Sulfonamides*, Bioorgan. Med. Chem., 9, p. 3287-3293, 2001.

[5] Jäntschi L., *Molecular Descriptors Family on Structure Activity Relationships 1. The review of Methodology*, Leonardo Electronic Journal of Practices and Technologies, AcademicDirect, 6, p. 76-98, 2005.

[6] ***, HyperChem, Molecular Modelling System [Internet page]; © 2003, Hypercube, Inc., available at: http://hyper.com/products/

[7] ***, Leave-one-out Analysis. ©2005, Virtual Library of Free Software, available at: http://vl.academicdirect.org/molecular_topology/mdf_findings/loo/