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Original Article

Preliminary MLR studies of antimicrobial activity of some 3-hydroxypyridine-4-one and 3-hydroxypyran-4-one derivatives

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Abstract

Quantitative structure-activity relationship (QSAR) studies of a series of substituted 3-hydroxy-pyridine-4-ones and 3-hydroxy-pyran-4-ones as antibacterial and antifungal agents against a variety of microorganisms were performed. Multiple linear regression approach was used as variable selection method. The antimicrobial activities of these compounds against *Staphylococcus aureus*, *Aspergilus niger* and *Candida albicans* were subjected to QSAR analysis. The best QSAR models were achieved for the antimicrobial activity of the studied compounds against *Staphylococcus aureus* and *Candida albicans* Quantum, constitutional and geometrical parameters had important roles in the antimicrobial activity against *Staphylococcus aureus*. Geometrical, functional group and topological parameters of the compounds had important effect on the antimicrobial activity against *Candida albicans*. The equation describing this effect had a good statistical quality (R^2=0.81, SE=0.14, Q^2=0.73).

Keywords: QSAR; MLR analysis; 3-hydroxypyridin-4-ones; 3-hydroxypyran-4-ones; Antibacterial activity; Antifungal activity

INTRODUCTION

Iron is the forth abundant metal on earth and one of the trace elements needed for survival and proliferation of all living things, including microorganisms. In fact, iron is required for the growth and virulence of virtually all microbial pathogens (1,2). It is an essential element in a number of key enzyme systems in most bacterial species. Aerobic microorganisms need this element for a variety of cellular functions including synthesis of ATP, replication of DNA, energy production and protection of the cell against oxygen reactive species (3). Vertebrate hosts have developed strategies to withhold iron from microbial invaders while retaining their own access to the metal (2,4). It has been suggested therefore, that manipulation of iron availability be exploited as a therapeutic tool. This task is achieved by sequestration of iron with iron-binding proteins, the most abundant, haemoproteins which contain almost 80% of the total iron of the vertebrates (5). Many bacteria, including numerous human pathogens, synthesize small molecules known as siderophores to scavenge iron. These low-molecular weight- chelating agents possess high affinity to Fe and are excreted by microorganisms under Fe deficiency (3,6). There are many reports of the antimicrobial activity of chelating agents with different chemical structures including substituted 3-hydroxy-pyridine-4-ones and 3-hydroxy-pyran-4-ones (7-12). The bidentate chelating ligand 3-hydroxypyranone, which has a catechol-like function, forms stable complexes with

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several metal ions such as Fe^{3+}.

Quantitative structure activity relationship (QSAR) research field has been widely developed because of its powerful ability to predict drug activity. It gives information that is useful for drug design in medicinal chemistry (13-15). QSAR models are mathematical equations which construct a relationship between chemical structures and biological activities of a series of molecules as a linear regression model of the form y=Xb+e. This equation may be used to describe a set of predictor variables (X) with a predicted variable (y) by means of a regression vector (b). In the first step of a typical QSAR study one needs to find a set of molecular descriptors representing the higher impact on the biological activity of interest. Multiple linear regression (MLR), genetic algorithm, partial least square (PLS) and principle component analysis (PCA) are some of the variable selection methods to build up such a set (16,17).

In the present paper, we describe the QSAR studies for a series of 3-hydroxypyridine-4-one and 3-hydroxypyran-4-one derivatives which have been synthesized and evaluated for antimicrobial activity by Aytemir et al. (11,12). Some of the studied compounds were prepared and evaluated as antimicrobial agents by authors previously (unpublished data). In the present study the antimicrobial activities of these compounds against *Staphylococcus aureus*, Aspergilus niger and *Candida albicans* are subjected to QSAR analysis. The best QSAR models were achieved for describing the antimicrrobial activity of the studied compounds against *Staphylococcus aureus* and *Candida albicans* and are reported here.

MATERIALS AND METHODS

Data extraction

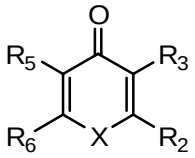
The biological data used in this study are antimicrobial activity, in terms of log MIC, of a set of thirty one 3-hydroxypyridine-4-one and 3-hydroxypyran-4-one derivatives (compounds 1-31). Compounds 1-10 were prepared in medicinal chemistry research lab of Isfahan faculty of pharmacy. Twenty one other derivatives (11-31) have been reported as antimicrobial agents previously (11,12). The structural features of these compounds are listed in Table 1. The calculated descriptors for each molecule are summarized in Table 2. The antimicrobial activities are summarized in Table 3 and then were used for subsequent QSAR analysis as dependent variables.

Software & descriptor generation

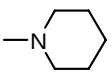
The two-dimensional structures of molecules were drawn using Hyperchem 7.0 software. The final geometries were obtained with the semi-empirical AM_1 method in Hyperchem program. The molecular structures were optimized using the Polak-Ribiere algorithm until the root mean square gradient was 0.01 kcal mol^{-1}. The structures should be optimized to give the closest form of the molecule to the stable conformation of the drug in the biological medium. Semi empirical methods serve as efficient computational tools which can yield fast quantitative estimates for a number of properties. This may be usful for correlating large sets of experimental and theoretical data (18).

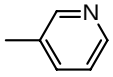
AM_1 is generally the most accurate computational method included in Hyperchem and is often the best method for collecting quantitative information. Polak-Ribiere algorithm is a good general-purpose optimizer. Hyperchem provides two versions of the conjugate gradient method, Fletcher-Reeves and Polak-Ribiere. Polak-Ribiere is more refined and is the default choice in Hyperchem (19).

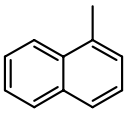
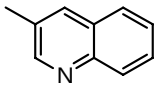
Table 1. Chemical structure of the compounds used in QSAR analysis.



Compd.	X	R_2	R_3	R_5	R_6
1	NH	CH_3	OH	CH_2-R^a	H
2	NH	C_2H_5	OH	CH_2-R^a	H
3	NH	CH_3	OH	CH_2-N $(CH_3)_2$	H
4	NH	C_2H_5	OH	CH_2-N $(CH_3)_2$	H
5	NH	CH_3	OH	CH_2-N $(C_2H_5)_2$	H
6	NH	C_2H_5	OH	CH_2-N $(C_2H_5)_2$	H
7	N-Ph	CH_3	OH	H	H
8	N-*m*-OH-Ph	CH_3	OH	H	H
9	N-C_3H_7	CH_3	OH	H	H
10	N-C_4H_9	CH_3	OH	H	H
11	O	CH_2Cl	H	OH	H
12	O	CH_3	H	OH	H
13	O	CH_2OH	OH	H	CH_3
14	O	CH_2OH	OCH_2Ph	H	CH_3
15	O	CHO	OCH_2Ph	H	CH_3
16	O	COOH	OCH_2Ph	H	CH_3
17	O	$CONHR^b$	OCH_2Ph	H	CH_3
18	O	$CONHR^c$	OCH_2Ph	H	CH_3
19	O	$CONHR^d$	OCH_2Ph	H	CH_3
20	O	$CONHR^b$	OH	H	CH_3
21	O	$CONHR^c$	OH	H	CH_3
22	O	$CONHR^d$	OH	H	CH_3
23	O	CH_2OH	H	OCH_2Ph	H
24	O	COOH	H	OCH_2Ph	H
25	O	CONHPh	H	OCH_2Ph	H
26	N-CH_3	CONHPh	H	OCH_2Ph	H
27	N-CH_3	CONHPh	H	OH	H
28	O	CONH-R^e	H	OCH_2Ph	H
29	N-CH_3	CONH-R^e	H	OCH_2Ph	H
30	N-CH_3	CONH-R^e	H	OH	H
31	O	CH_2OH	H	OH	H

R^a is 

, R^b is 

, R^c is 
, R^d is 

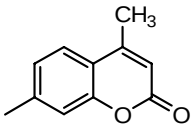
, R^e is 

Table 2. Brief description of some descriptors used in this study.

Descriptor type	Molecular Description
Constitutional	Molecular weight, no. of atoms, no. of non-H atoms, no. of bonds, no. of heteroatoms, no. of multiple bonds (nBM), no. of aromatic bonds, no. of rings, no. of circuits, no of H-bond donors, no of H-bond acceptors, no. of Nitrogen atomes (nN), chemical composition, some of Kier-Hall electrotopological states (Ss), mean atomic polarizability (Mp), number of rotable bonds (RBN), mean atomic sanderson electronegativity (Me), etc.
Topological indices	Molecular size index, molecular connectivity indices (X1A, X2v, X2Av, X3Av, X4Av), information content index (IC), path/walk-Randic shape indices, Schultz indices, Balaban J index (such as MSD) Wiener indices, topological charge indices, Sum of topological distances between F..F (T(F..F), Ratio of multiple path count to path count (PCR), Mean information content vertex degree magnitude (IVDM), Eigenvalue sum of Z weighted distance matrix (SEigZ), reciprocal hyper-detour index (Rww), etc.
Geometrical	3D petijean shape index (PJI3), Gravitational index, Balaban index, Wiener index,
Quantum	Highest occupied Molecular Orbital Energy (HOMO) , Lowest Unoccupied Molecular Orbital Energy (LUMO), Most positive charge (MPC), Sum of positive charges (SUMPC),\Sum of negative charges (SUMNC), Total dipole moment (DM_t), Molecular dipole moment at X-direction (DM_X), Molecular dipole moment at Y-direction (DM_Y), Molecular dipole moment at Z-direction (DM_Z), Electronegativity (χ=- 0.5 (HOMO-LUMO), Electrophilicity ($\omega = \chi^2/2\,\eta$), Hardness (η=0.5 (HOMO+LUMO)), Softness ($S=1/\eta$), etc.
Functional group	Number of total tertiary carbons (nCt), Number of H-bond acceptor atoms (nHAcc), number of total hydroxyl groups (nOH), number of unsubstituted aromatic C(nCaH), number of ethers (aromatic) (nRORPh), etc.
Chemical descriptors	LogP, Hydration Energy (HE), Polarizability (Pol), Molar refractivity (MR), Molecular volume (V), Molecular surface area (SA), etc.

The resulted geometry was transferred into Dragon program package (20). The z-matrix of the structures were provided by Hyperchem program and transferred to the Gaussian 98 program (21). Complete geometry optimization was performed taking the most extended conformation as starting geometries. Semi-empirical molecular orbital calculation (AM_1) of the structures was performed using Gaussian 98 program. A large number of molecular descriptors were calculated using these packages (21). Some chemical parameters including molecular volume (V), molecular surface area (SA), hydrophob-icity (Log P), hydration energy (HE) and molecular polarizability (MP) were calculated using Hyperchem Software. Dragon software calculated different functional groups, topological, geometrical and constitutional descriptors for each molecule (20). Gaussian 98 was employed for calculation of different quantum chemical descriptors including, dipole moment (DM), local charges, HOMO and LUMO energies, hardness (η), softness (S), electronegativity (χ) and electrophilicity (ω) according to the method proposed by Thanikaivelan et al. (22).

Data processing and modeling

The selection of significant descriptors, which describe the antimicrobial data according to the molecular structures, is an important step in QSAR modeling. Selection of significant descriptors was performed through the following steps:

i) The calculated descriptors were collected in a data matrix, D. First the descriptors were checked for constant or near constant values and those detected

Table 3. Experimental and predicted activity of compounds against *Staphylococcus aureus* and Candida albicans.

Compdound	*Staphylococcus aureus*			*Candida albicans*		
	Experimental pMIC	**Predicted pMIC [a]**	**REP [b] (%)**	**Experimental pMIC**	**Predicted pMIC**	**REP (%)**
1	3.29	3.2740	-0.4896	ND [c]	ND	ND
2	3.29	3.3778	2.5988	3.29	3.4139	3.6304
3	3.29	3.4068	3.4282	ND	ND	ND
4	3.29	3.3380	1.4371	3.29	3.4693	5.1687
5	4.19	3.3956	-23.395	3.89	3.8920	0.0514
6	3.29	3.3888	2.9149	3.29	3.3591	2.0577
7	3.89	3.6841	2.5545	3.29	3.3835	2.7631
8	3.29	3.7262	3.6552	3.59	3.5477	-1.1929
9	3.29	3.9372	1.1998	3.29	3.3208	0.9272
10	3.89	3.9027	15.700	3.59	3.3296	-7.8211
11	3.59	3.8341	-1.4593	3.89	4.1726	6.7734
12	3.59	3.7706	12.745	3.89	3.7481	-3.7870
13	3.59	3.3679	-6.5962	3.89	3.9092	0.4922
14	3.59	3.5431	-1.3228	3.89	3.7076	-4.9191
15	4.19	3.6348	-15.273	3.89	3.6892	-5.4426
16	3.59	3.9065	8.1017	3.89	3.8422	-1.2433
17	3.59	3.6552	1.7832	4.49	4.4661	-0.5351
18	3.59	3.6858	2.5978	4.49	4.5076	0.3913
19	3.89	4.1990	7.3598	3.89	3.7076	-4.9191
20	4.19	4.0003	-4.7429	3.89	3.8014	-2.3296
21	3.59	3.9141	8.2810	3.89	3.9525	1.5813
22	5.10	4.9038	-4.0008	ND	ND	ND
23	3.59	3.3188	-8.1726	3.89	3.7450	-3.8727
24	3.59	3.3813	-6.1734	3.89	3.9956	2.6429
25	3.89	3.7959	-2.4801	3.89	3.9969	2.6755
26	3.89	4.0353	3.6002	3.89	3.8489	-1.0691
27	4.80	4.3001	-11.624	3.89	3.7574	-3.5304
28	3.89	3.6856	-5.5473	3.89	3.9503	1.5262
29	3.59	4.1235	12.938	3.89	3.9964	2.6619
30	4.49	4.4502	-0.8936	3.89	3.8978	0.2006
31	3.59	3.3324	-7.7289	3.89	4.0322	3.5259

[a]pMIC=-log (MIC)
[b]REP=Relative Error of Prediction
[c]ND=Not Determined

were removed from the original data martrix. The correlation of descriptors withi each others and with the activity data was determined.

ii) The input variable in MLR must not be highly correlated. Among the collinear descriptors detected (r>0.9) one with the highest correlation with the activity was retained and the rest were omitted.

iii) The selected descriptors from each class and the experimentally antimicrobial data were analyzed by the stepwise regression SPSS (version 12.0) software.

In the present study, MLR with stepwise selection and elimination of variables was applied for developing QSAR models using SPSS software. The resulted models were validated by leaveone out cross-validation procedure (using MATLAB software) to check their predictability and robustness.

RESULTS

In Tables 4 and 5 equations obtained by the MLR analysis with different types of descriptors of tested compounds against

Table 4. The results of MLR analysis with different types of descriptors of all compounds *(Staphylococcus aureus).*

No.	*Descriptor source*	*MLR Equations*	*N* [a]	R^2 [b]	*S.E* [c]	RMS_{CV} [d]	Q^2 [e]	*F* [f]
E_1	Quantum	pIC_{50}=2.505 (±0.647) + 3.507 (± 1.691) MPC + 0.121 (± 0.048) DMy	31	0.45	0.34	0.37	0.31	11.52
E_2	Constitutional	pIC_{50}=3.775 (±0.254) + 0.148 (± 0.036) nDB - 0.115 (±0.049) RBN	31	0.41	0.36	0.42	0.18	8.74
E_3	Topological	pIC_{50}=20.128 (± 4.595) - 35.306 (± 9.853) X1A -0.001 (± 0.001) piPCO7	31	0.34	0.37	0.39	0.23	7.20
E_4	Geometrical	pIC_{50}= 4.531 (± 0.570) + 0.031 (± 0.009) DELS - 1.859 (± 0.688) PJI3	31	0.37	0.36	0.40	0.21	8.51
E_5	Functional group	pIC_{50}=3.605 (±0.081) + 0.521 (± 0.151) nCONHR	31	0.30	0.38	0.40	0.17	11.95
E_6	Molecular descriptor	pIC_{50}=4.544 (± 0.495) + 0.130 (± 0.040) DMy + 0.082 (± 0.031)nDB - 1.275 (± 0.584) PJI3	31	0.55	0.50	0.36	0.35	11.24

[a]N=Number of Molecules
[b]R^2=Correlation Coefficient
[c]S.E=Standard error of regression
[d]RMS_{CV}=Root mean square of cross validation
[e]Q^2=Leave-one-out cross-validation correlation coefficient
[f]F=Fisher ratio

Staphylococcus aureus and *Candida albicans* are listed.

Table 4 provides the equations for the studied compounds against *Staphylococcus aureus.* In this series the chemical parameter did not have a significant impact on the antimicrobial activity. The equation E_1 shows that among quantum descriptors, MPC and DMy have a positive effect on the antimicrobial activity; this contribution suggests that electronic interaction plays an important role in inhibitory activity of these compounds. The positive coefficient of MPC reveals the presence of columbic interactions between the ligands and receptors. According to equation E_1 a negative region in receptor produces columbic interaction; ligands with most MPC could interact with receptor more efficiently. This could propose other mechanism than chelation of Fe^{3+}; a receptor mediated one, if R^2 and Q^2 had significant values for the antimicrobial activity of these compounds.

The second equation of Table 4 was found by using constitutional descriptors (E_2). This equation explained the positive effect of number of double bonds (nDB) and number of rotatable bonds (RBN) on the antimicrobial activity of studied compounds.

The equation E_3 of Table 4 obtained from the pool of topological descriptors, explained the negative effect of average connectivity index chi-1 (X1A) and molecular multiple path count of order 7 (piPC07) on antimicrobial activity of the compounds.

The equation E_4 of Table 4 was found by using geometrical descriptors. This

equation explained the positive effect of molecular electrotopological variation (DELS) and the negative effect of 3D petijean shape index (PJI3) on the antimicrobial activity of compounds.

The effect of functional groups on the antimicrobial activity of the studied compounds has been described by equation E_5 of Table 4. This equation explained the positive effect of the number of secondary amides (aliphatic) (nCONHR) on the antimicrobial activity of the studied.compuonds.

The positive sign of the coefficient of nCONHR proposed that an increase in the number of secondary amides (aliphatic) resulted in enhanced activity.

The last equation (E_6) of Table 4 was obtained from the all calculated descriptors. Stepwise selection and elimination of variables produced a three-parametric QSAR equation. In this model DMy and nDB have a positive effect and PJI3 has a negative effect on inhibitory activity.

In Table 5 the resulted equations for all compounds against *Candida albicans* are listed. The first equation of Table 5 was found by using quantum descriptors (E_7). It explained the positive effect of SUMPC, in the same manner as the previous strain, and softness on antimicrobial activity of the compounds. The positive coefficient of SUMPC reveals the presence of columbic interactions between the ligands and receptors and demonstrates that ligands with most SUMPC could interact with receptor more efficiently. This could propose again the receptor mediated mechanism for the antimicrobial activity of these compounds if R^2 and Q^2 had significant values. The second equation of table 5 was found by using chemical descriptors (E_8). It shows the positive effect of Mass and the negative effect of surface area (SA) on the antimicrobial activity of the compounds. The negative coefficient of surface area indicates that increasing this parameter hinders the ligand to pass through the cell membrane and thus decreases the activity.

The effect of constitutional descriptors on the antimicrobial activity of the studied compounds has been described by equation E_9 of Table 5. It explained the positive effect of mean atomic Sanderson electronegativity (scaled on Carbon atom) (Me) and number of multiple bonds (nBM) on the antimicrobial activity. The MLR equation of Table 5 was obtained from the pool of topological descriptors (E_{10}). It includes the positive effect of Eigenvalue sum from Z weighted distance matrix (Barysz matrix) (SEigZ) and distance/ detour ring index of order 10 (D/Dr10) and the negative effect of Balaban centric index (BAC) on the antimicrobial activity.

The equation obtained from the effect of geometricalparameters on the antimicrobial activity of the studied compounds (E_{11}), shows a negative effect of 3D Balaban centric index (J3D) and asphericity (ASP) on the antimicrobial activity.

The MLR equation of Table 5 obtained from the pool of functional group descriptors (E_{12}) explained the positive effect of the number of secondary amides (aliphatic) (nCONHR), which is also in agreement with those obtained for the other strain in this series, and the number of substituted aromatic C (SP^2) (nCaR) and the negative effect of the number of tertiary amines (aliphatic) (nNR2) on the antimicrobial activity. It shows that a decrease in the number of nNR2 and an increase in the number of nCONHR and nCaR results in enhanced activity. The last equation E_{13} was derived from the pool of all calculated descriptors. It shows the negative effect of J3D, ASP and superpendentic index (SPI) and the positive effect of the number of total secondary C (SP^3) (nCs) on the antimicrobial activity. This equation, which

Table 5. The results of MLR analysis with different types of descriptors of all compounds (*Candida albicans*).

No.	*Descriptor source*	*MLR Equations*	*N*	R^2	*S.E*	RMS_{CV}	Q^2	*F*
E_7	Quantum	pIC_{50}=5.727 (± 0.572) +0.391 (± 0.093) Softness + 0.117 (± 0.049) SUMPC	28	0.50	0.22	0.24	0.35	12.05
E_8	Chemical	pIC_{50}=4.241 (± 0.252) + 0.006 (± 0.001) Mass - 0.005 (± 0.001) SA	28	0.62	0.19	0.21	0.52	20.65
E_9	Constitutional	pIC_{50}=-3.598 (± 2.072) + 0.0.039 (± 0.007) nBM + 6.897 (± 2.019) ME	28	0.62	0.19	0.21	0.51	20.96
E_{10}	Topological	pIC_{50}=3.724 (±0.190) + 0.003 (±0.001) D/Dr10 -0.023 (± 0.005) BAC + 0.360 (± 0.160) SEigz	28	0.73	0.16	0.19	0.60	22.16
E_{11}	Geometrical	pIC_{50}=5.173 (± 0.202) - 0.370 (± 0.056) J3D -0.983 (±0.301) ASP	28	0.51	0.18	0.19	0.60	25.88
E_{12}	Functional group	pIC_{50}=3.781 (± 0.065) - 0.312 (± 0.077) nNR2 + 0.247 (± 0.078) nCONHR + 0.095 (± 0.032) nCaR	28	0.67	0.18	0.20	0.53	16.16
E_{13}	Molecular descriptor	pIC_{50}=6.192 (±0.292) - 0.714 (± 0.097) J3D -1.519 (± 0.269) ASP + 0.249 (± 0.065) nCs - 0.001 (± 0.00) SPI	28	0.82	0.14	0.15	0.73	25.30

has a high statistical quality could explain and predict 0.82% and 0.73% of variance in pMIC data, respectively. Plots of the cross-validated predicted activity against the experimental activity for the MLR model obtained against two micro-organisms are given in Fig. 1.

DISCUSSION

A series of substituted 3-hydroxy-pyridine-4-ones and 3-hydroxy-pyran-4-ones as antibacterial and antifungal agents against a variety of microorganisms were subjected to QSAR studies. Quantitative relationships between molecular structure and antimicrobial activity of them were discovered by MLR method. As it is shown in the last row of Table 4, the resulted QSAR model (E_6) represents moderate ability (more than 50%) to explain and predict the activity of the studied compounds. Quantum parameter (DMy), constitutional descriptor (nDB) and geometrical parameter (PJI3) have important roles in the antimicrobial activity against *Staphylococcus aureus*. According to Table 5, geometrical parameters (J3D, ASP), functional group descriptor (nCs) and topological parameter (SPI) have important effects on the antimicrobial activity against *Candida albicans.* This equation has a good statistical quality (R^2=0.81, SE=0.14, Q^2=0.73).

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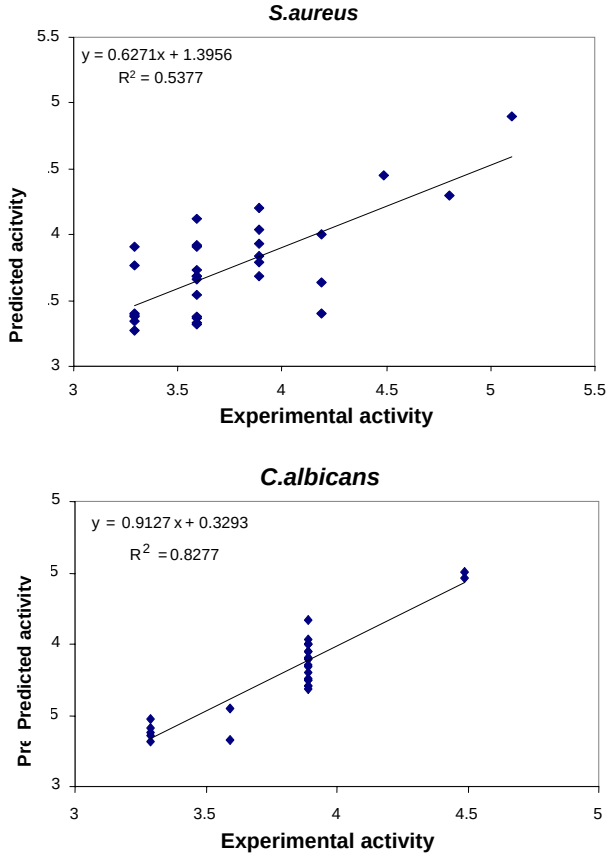

Fig. 1. Plots of the cross-validated predicted activity against the experimental activity for the MLR model obtained against two microorganisms.

REFERENCES

1. Weinberg ED. Cellular iron metabolism in health and diseased. Drug Metab Rev. 1990;22:531-579.
2. Weinberg ED. Iron and infection. Microbiol Rev. 1978;42:45-66.
3. Neilands JB. Siderophores: Structure and function of microbial iron transport compounds. J Biol Chem. 1995;270:26723-26726.
4. Weinberg ED. Iron withholding: A defense against infection and neoplasia. Physiol Rev. 1984;64:65-102.
5. Skaar EP, Gaspar AH, Schneewind O. Bacillus anthracis IsdG, a heme-degrading monooxygenase. J Bacteriol. 2006;188:1071-80.
6. Sebat JL, Paszczynski AJ, Cortese MS, Crawford RL. Antimicrobial properties of pyridine-2,6-dithiocarboxylic acid, a metal chelator produced by *Pseudomonas* spp. Appl Envir Microbiol. 2001;67:3934-3942.
7. Weinberg GA. Iron chelators as therapeutic agents against *Pneumocystis carinii*. Antimicrob. Agents Chemother. 1994;38:997-1003.
8. Van Asbeck BS, Marcelis JH, Marx JM, Struyvenberg A, Van Kats JH, Verhoef J. Inhibition of bacterial multiplication by the iron chelator deferoxamine: Potentiating effect of ascorbic acid. Eur J Clin Microbiol Infect Dis. 1983;2:426-431.
9. Erol DD, Yulug N. Synthesis and antimicrobial investigation of thiazolinoalkyl-4 (1H) pyridones. Eur J Med Chem. 1994;29:893.897.
10. Min-Hua F, van der Does L, Bantjes A. Iron (III)-chelating resins. 3. Synthesis, iron (III)-chelating properties, and in vitro antibacterial activity of compounds containing 3-hydroxy-2-methyl-4(1H)- pyridinone ligands. J Med Chem. 1993;36:2822-2827.
11. Aytemir MD, Erol DD, Hider RC, Ozalp M. Synthesis and evaluation of antimicrobial activity of new 3-hydroxy-6-methyl-4-oxo-4H-pyran-2-carboxamide derivatives. Turk J Chem. 2003;27:757-764.
12. Aytemir MD, Hider RC, Erol DD, Ozalp M, Ekizoglu M. Synthesis of new antimicrobial agents; amide derivatives of pyranones and pyridinones. Turk J Chem. 2003;27:445-452.
13. Schmidi H. Multivariate prediction for QSAR. Chemom Intell Lab Sys. 1997;37:125-134.
14. Hansch C, Kurup A, Garg R, Gao H. Chem-bioinformatics and QSAR. A review of QSAR lacking positive hydrophobic terms. Chem Rev. 2001;101:619-672.
15. Hemmateenejad B, Miri R, Akhond M, Shamsipur M. QSAR study of the calcium channel antagonist activity of some recently synthesized dihydropyridine derivatives. An application of genetic algorithm for variable selection in MLR and PLS methods. Chemom Intell Lab Sys. 2002;64:91-99.
16. Horvath D, Mao B. Neighborhood behavior. Fuzzy molecular descriptors and their influence on the relationship between structural similarity and property similarity. QSAR. Comb Sci. 2003;22:498-509.
17. Putta S, Eksterowicz J, Lemmen C, Stanton R. A novel subshape molecular descriptor. J Chem Inf Comput Sci. 2003;43:1623-1635.
18. Thiel W. Semi empirical methods In: Grotendorst J, editor. Modern methods and algorithms of quantum chemistry. 2nd ed, Jülich: NIC Series; Vol. 3. 2000. p. 261-283.
19. HyperChem® release 7 for windows, Molecular modeling system: HyperCube, 2002, Manual, 61-132.
20. Todeschini R. Milano chemometrics and QSPR Group. Available from: URL: http://michem.disat.unimib.it

21. Frisch MJ, Trucks MJ, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 98, Revision A.7. Pittsburgh PA: Gaussian; 1998.
22. Thanikaivelan P, Subramanian V, Rao JR, Nair BU. Application of quantum chemical descriptor in quantitative structure activity and structure property relationship, Chem Phys Lett. 2000;323:59–70.