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A Priori Prediction of Tissue: Plasma Partition Coefficients (Log BP) of Drugs to Facilitate the Usc of MLR and MLR-GA Methods

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ABSTRACT

It is important tn determine whether a candidate mnlecule is capahle nf penetrating the plasma-hrain barrier in drug discovery and development. The aim of this paper is to establish a predictive model for plasma-brain barrier penetration using simple descriptors The usefulness nf the quantum chemical descriptors, calculated at the level uf the DFT and HF thenries using 6-31G* basis set for QSAR study of anti-viral Nuclenside Analogues drugs was examined. Delivery of anti-viral agents into the central nervnus system (CNS) is clinically important. Nucleoside analngues are a majnr source of cliaically used antiviral agents. The QSAR model developed cantributed to a mechanistie understanding of the investigated biological effects. The first step in this study was tn use a datasct contaiaing 23 drugs with known activity. In the next steps some of them with the large secoadary chain branches were remnved tn make nur approach. Multiple Linear Regressions (MLR) was emplnyed to model the relationships between molecular descriptors and biological activnies nf molecules using stepwise method and genetie algorithm as variable selection tools. Binlogical activities contain the logarithm of the ratio of the steady-state concentration of a compound in the brain to in the plasma, log *Bp*. A multi-parametric equatinn containing maximum six descriptors at HF/6-31G* and eight descriptors at B3LYP/6-31G* method with good statistical qualities

(R_{MAX}= 0.976 , R^2_{MAX}= 0.959 at HF/6-31G* and R_{MAX}= 0.979 , R^2_{MAX}= 0.952 at B3LYP/6-31G*) was nbtained hy Multiple Linear Regression using stepwise method. The model derived in this paper appears to he very simple but rnbust and effective fnr predictive ose. This method relates log Bp values to fundamental molecular properties, soch as Electrostatic Pntential, Local charge, Electric Field Gradieat, Isotropic parameters, Natural Population Analysis. Also, GA-MLR regression was used to model the structure – activity relationships.

Keywords: Plasma-Brain; Nucleoside analogues: QSAR; DFT; GA-MLR

INTRODUCTION

There is a general agreement that drug delivery to the brain is a major therapeutic challenge. Adequate delivery is essential for drugs that act directly nn targets in the hrain, such as anticonvulsants, antidepressants. anesthetics, antihiotics, anticancer, and antiviral agents. Since the central nervous system(CNS) can acts as a reservnir nf viral lnading. the delivery of anti-viral agents to the brain represents a valid and useful npproach in such therapy.

The hlnnd–hrain harrier (BBB) protects the brain by limiting the penetratinn of exogenous compounds. The ability tn understand the penetration of drug candidates thrnugh the BBB is pivotal during drug development. It allows

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scientists to choose drug candidates that possess more selective pharmacologic properties with fewer side effects and toxicities. However, using in vivo methods to measure the logarithmic values of brain-to-plasma drug concentration ratios (log BP) in humans is not possible, and to do so in animal models is expensive and time consuming. In order to improve the efficiency of drug discovery and development and to facilitate high-throughput drug screening, many prediction methods for estimating log BB have been developed based on a drug's physicochemical properties. A common measure of the degree of Plasma-Brain penetration is the ratio of the steady-state concentration of the drug molecule in the brain to in the plasma, usually expressed as log (C_{brain}/C_{plasma}) or log *BP*. Both *in vivo* [1,2] and *in vitro* [3-6] experiments have been conducted for measuring log BP of organic compounds.

In in vivo experiments, peripheral application of radio-labeled compounds to rats is followed by brain concentration level measurements. In in vitro experiments, the partition of the compound between an aqueous and an organic phase, or its penetration in specific cell types is measured and the results are used for relative log BP ranking of compounds. Therefore the experimental determination of log BP *is* a time-consuming, expensive, and difficult technique, requiring animal experiments and the synthesis of the test compounds, usually in radio-labeled form [7]. In spite of the existence of large databases on molecular structure and the continuous growth of numerical experimental data on physicochemical properties and biological activities, the problem of the estimating the properties of substances that have not yet been tested could be approached in a more accurate way, at least in the next few decades. During the last half century it has become common practice to employ topological, physical, chemical, and biological numerical characteristics, depending on the molecular structure, to predict the properties of substances that remain unknown for different reasons, such as because they are unstable, toxic, or simply that their measurement requires too much time. The field of natural science, which aims to construct mathematical models to search for regularities in data and permit their systematization, has been addressed by the quantitative structure-property/activity relationship theory (QSPR/QSAR) [8]. QSAR models, mathematical equations relating chemical structure to their biological activity, give information that is useful for drug design and medicinal chemistry [9– 11]. There have been numerous attempts to employ theoretical and computational methodologies to predict the Plasma-Brain partition or Plasma-Brain coefficient. Yiannis and co-workers proposed a model that correlated log BB (Blood-Brain coefficient) with physically significant descriptors. They employed Monte Carlo simulations of compounds in water to calculate such properties as the solvent-accessible surface area (SASA), the number of hydrogen bond donors and acceptors, the solute dipole, and the hydrophilic and amphiphilic components of SASA [12].

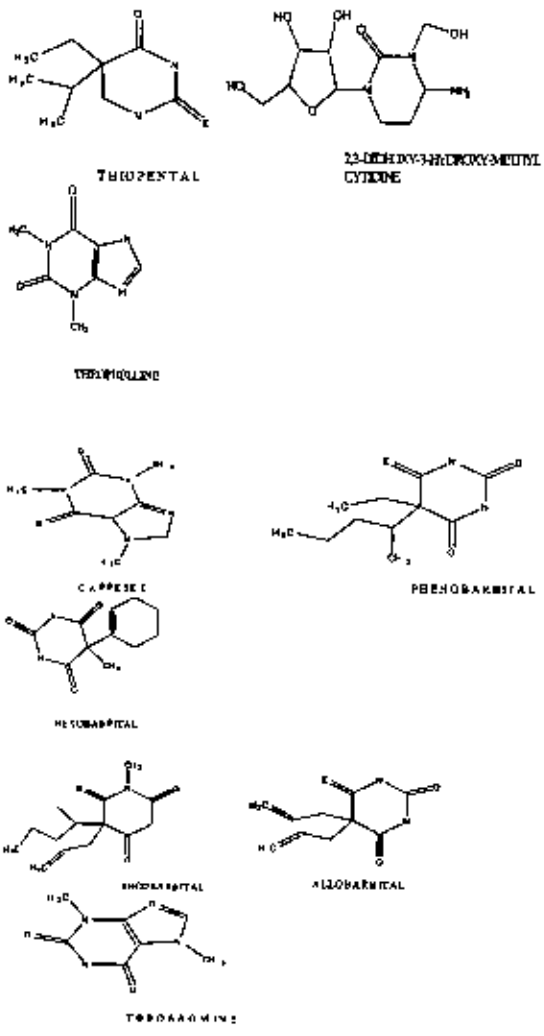
Hutter used semi-empirical AM1 calculations to compute Molecular electrostatic potential and fundamental electronic properties such ass the ionization potential and use those to compute properties such as the polar surface area of compounds [13]. In addition to simple multiple linear regression methods, a number of comprehensive computational approaches based on neural network and genetic algorithms results in the development of log BB QSARs [14, 15].

In a QSPR study, a mathematical model is developed which relates the structure of a set of compounds to a physical property such as Electric Potential, Solvation free energy, Electric Field Gradient, unsymmetrical parameters, Natural Population Atomic charge.

Recently, Karelson et al. reported a comprehensive review on these types of descriptors [16]. Also, Thanikaivelan et al. defined some new quantum chemical descriptors, including hardness, softness, electro negativity, and electrophilicity, and used them for a QSAR study of alkanes [17]. we have successfully applied the ab initio theory to derive quantum chemical descriptors for the QSAR studies of some drugs [18 – 21]. Semi-empirical Molecular Orbital (MO) calculations have been used to obtain electronic descriptors for many years. However, the latest development of the computer technology and software of electronic structure theory allows calculating quantum chemical descriptors at first-principles levels, such as Density Functional Theory (DFT) [22] and Hartree Fock (HF) Theory with higher accuracy.

Another challenging problem in QSAR studies is the selection of the suitable modeling method. The classical QSAR methods rely principally on the mathematical technique of Multiple Linear Regressions (MLR) [23]. Variable selection methods range from simple methods such as stepwise selection to more elaborate methods such as simulated annealing [24], evolutionary programming [25], and Genetic Algorithms (GAs) [26].

A GA is a stochastic method to solve optimization problems defined by a fitness criteria applying evolution hypothesis of Darwin and different genetic functions, i.e., crossover and mutation [27].



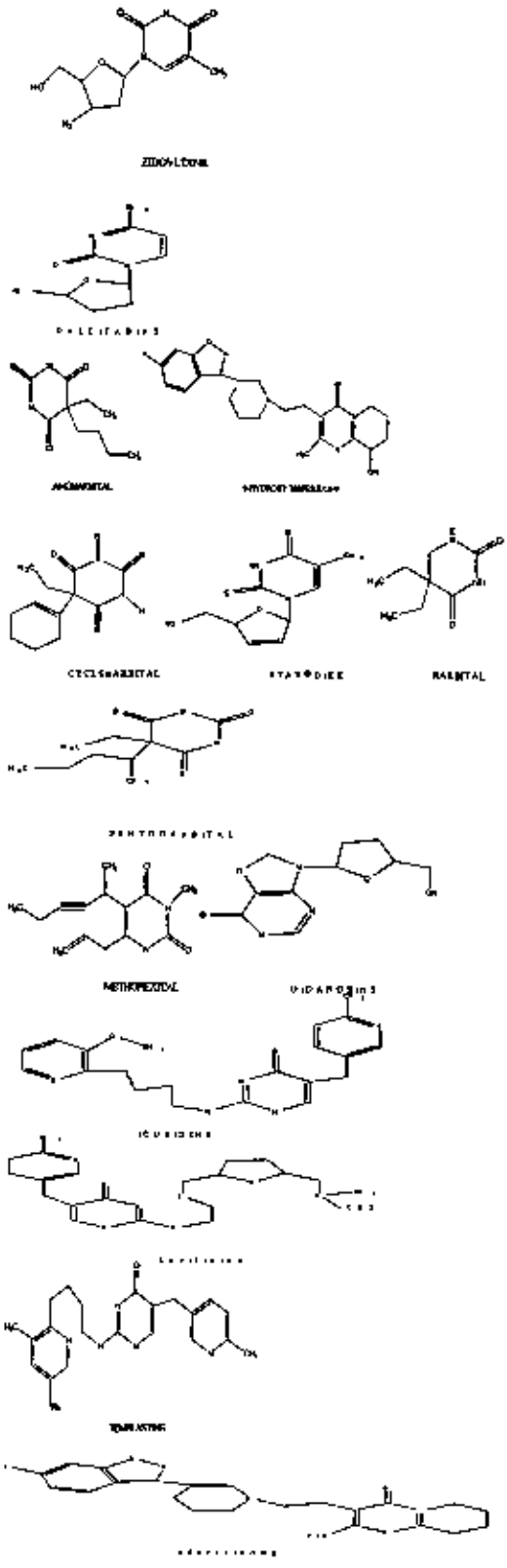


Fig.1.

METHOD

The biological data used in this study are the plasma-Brain Barrier partitioning coefficient activity ta(log Bp) of the set of 23 Nucleoside derivatives. Chemical structure of drugs that illustrated in this study is shown in Figure 1.

Ta derive QSAR models, an appropriate representation of the chemical structure is necessary. For this purpose, descriptors of the structure are commonly used. These descriptors are generally understood as being any term, index or parameter conveying structure information. Commonly used descriptors in the QSAR analysis are presented in Table 1.

Some of the descriptors are obtained directly from the chemical structure, e. g. constitutional, geometrical, and topological descriptors. Other chemical aad physicochemical properties were determined by the chemical structure (lipophilicity, hydrophilicity descriptors, electronic descriptors, energies of interaction). In this work, we used Gaussian 98 for ab initia calculatinas. HF and DFT methods at 6-31G* were applied for optimization of Nucleaside analogues and calculation of many of the descriptors. At first Nucleoside analogues were built by Hyperchem software and same of the descriptors such as partition coefficient, surface area, hydration eaergy, and refractivity were calculated through it. The rest of the descriptors were obtained af Gaussian calculatians.

A large number of descriptors were calculated by Gaussian package and Hyperchem software. One way to avoid data redundancy is to exclude descriptors that are highly intercorrelated with each other before perfarming statistical analysis. Reduced multi collinearity and redundancy in the data will facilitate selection of relevant variables and models for the investigated endpoint. Variable-selecuinn for the QSAR modeling was carried out by stepwise linear regressinn method . A stepwise technique was employed that only one parameter at a time was added ta a model and always in the order of most significant to least significant in terms of F-test values. Statistical parameters were calculated subsequently for each step in the process, so the significance of the added parameter could be verified. The goodaess of the carrelatinn is tested by the regressian coefficient (R^2), the F-test and the standard error of the estimate (SEE). The t-test and the level of significance, as well as the canfidence limits of the regression coefficient, are . alsn reported. : The squared correlatian coefficient, R^2, is a measure of the fit of the regression model. Correspondingly, it represents the part of the variation in the observed (experimental) data that is explained by the model. The correlation coefficient values closer to 1.0 represent the better fit of the madel. The F-test reflects the ratio af the variance explained by the model and variance due to the error in the model. High values af the F-test indicate that the model is statistically significant. The better regression models were selected on the basis of the higher R^2, F value (a statistic of assessing the overall significance) and the lower SEE. The experimental and calculated values of biological activity (lag BP) listed in Table 2.

Table 1. The calculated descriptors used in this study

Descriptors	Symbol	Example
Quantum chemical descriptors	Molecular Dipole Moment	MDP
	Molecular Polarizability	MP
	Electric Field Gradient[a]	EFG
	Natural Population Analysis[b]	NPA
	Electrostatic Potential[c]	EP
	Highest Occupied Molecular Orbital	HOMO
	Lowest Unoccupied Molecular Orbital	LUMO
	difference between LUMO and HOMO	E_{GAP}
	Hardness [η=1/2 (HOMO-LUMO)]	η
	Softness (S=1/ η)	S
	Electro negativity [χ= -1/2 (HOMO-LUMO)]	χ
	El Electro philicity ($\omega=\chi^2/2\eta$)	ω
	Thermal Energy	E_{th}
	Zero point energy	E_{zero}
	solvation Free Energy (in 1-Octanol)	ΔG_{OCT}
	solvation Free Energy (in water)	ΔG_w
	Isotropic Parameter[d]	σ
	Coupling Constant[e]	Π
	Unsymmetrical Parameters[f]	ξ
	Local Charge[g]	LC
Chemical properties	Partition Coefficient	Log P
	Mass	M
	Molecule volume	V
	Molecule surface area	SA
	Hydration Energy	HE
	Refractivity	REF

a: Electric Field Gradient for each of nitrogen atom in principal ring of molecules was showed according the aumber of atom ia that riag whit EFG_1 and EFG_2

b: Natural Population Aualysis for each of atoms in principal ring of molecules was shuwed according the aumber of atom in that ring whit NPA1, NPA2, and e.t. [28]

Table 2. The experimental lag BP values nf the Nucleoside used in this study and their predicted values by MLR

COMPIIUND	Log Bp (exp)(a)	Fq. (8)	Eq. (9)
2,3.. (b)	-1 5	-1.583	-1.5941
Amobarbital	•,•••	-0.1511	-0.1995
Cyclobarbital	-0.3010	-0 219	-8.2873
Phenobarbital	-0 12	-0.829	-0.29
Zidovudine	-0 72	8.82	-8.8875
Didanosine	-1 28	-1.29	-1.2898
Methohexital	-0.060	-0.0577	-0.2230
Theobromine	-0 29	-0.2768	-0.5568
Zalcytabine	1.50	1.4598	1.3740
Barbital	-0 25	-0.1141	-0.1852
Hexobromine	-0 31	-0.1568	-0 2437
Secobarbital	0 20	-0.09339	-0 2436
Theophelline	-0 38	-0 2485	-0.5765
Allobarbital	-0 22	-0.12980	-0.1956
Caffeine	0.01	-0 050	-0 1132
Phenobarbital	0.10	-0 175	-0 2731
Stavudine	0.2040	0.2776	-0.035
Thiopental	-0.45	0.49018	-0 6916

(a)Ref: (29-31)

(b) 2,3-dideoxy -3 – hydroxyl - methyl cytidine

The internal coasistency of the selected models was assessed by cross-validation method [leave-one-out (Q^2 LOO)] following a leave-one-out scheme using the Matlab 7.1 program. five splits of test and calibratuon sets were prepared in order ta check predictivity of modelx which were shown in Table 3

Table 3. The results of randam splitting of the data to five sets for equatioas of different descriptors using B3LYP/6-31G* and HF/6-31G* methods

HF/6-31G*		B3LYP/6-31G*	
$R^2_{calibration}$	$R^2_{prediction}$	$R^2_{calibration}$	$R^2_{prediction}$
8.866	0.866	0.970	0.9
0.919	0.953	0 937	0 958
0.919	0.995	0.993	0.970
0.961	0.904	0.925	0.919
0.892	0.924	0 927	0 892

The MLR analysis was employed to derive the QSAR models fnr different Nucleoside analogues. MLR and correlation analyses were carried out hy the statistics software SPSS 16.0 (Table 4, 5).

Table 4. The correlation coefficient existing between the variables used in different MLR along with equations of HF/6-31G* method

	Lag Bp	EFG_3	EP_3	EP_4	NPA_4	NPA_5	LC_3
Log Bp	1						
EFG3	-0 340	1					
EP3	0 563	0.203	1				
EP4	-0 093	0.005	0 487	1			
NPA4	-0 487	0 318	-0 464	0 503	1		
NPA5	0 205	0.493	0 093	-0.303	0 199	1	
LCS	-0 318	0 486	-0 538	0 011	0.046	6.577	1

Table 5. The correlation coefficient existing betweea the variables used in different MLR along with equations nf B3LYP/6-31G* method

	Log BP	EP_1	NPA_2	σ
Log BP	1			
EP1	-0.442	1		
NPA2	0.350	0.053	1	
σ	0.528	8.284	0 07	1

In order to assess the risk of chance correlation [32, 33], input scrambling was performed [4]. According to the results there was nD risk for chance correlation (R^2_{max}= 0.527, Q^2_{max}= 0.306).

GA-MLR

In order to select the most relevant descriptors, the evolution of the population was simulated. Each individual of the populatinn defined by a chromosome of hinary values represented a subset of descriptors. The number nf genes at each chromosome was equal to the number nf descriptors. A gene would take a value of 1, if its corresponding descriptor was included in the subset; ntherwise it would take value of zero. The population nf the first generation was selected randomly. The number of genes with a value of one was kept relatively low to have a small subset of descriptors in the MLR method, i.e., the probability of generating n zero value for a gene was set greater than that for o generating o value of one.

RESULTS AND DISCUSSION

The molecules for this study were selected as follows. Our starting point was 23 Nucleoside analogues. For each of the selected molecules, geometry optimizotion was employed and then the descriptors were calculated through HF and B3LYP methods at 6-31G* hasis set. MLR models were constructed in the present work uoing SPSS software. Those descriptors that were too strongly correlated with the others were rejected. The first twn QSAR models were derived from using all descriptors and molecules followed by these equations:

Lng Bp = -0.016 S(± 0.004) – 6.585X (± 2.885) + 0.213 (± 0.893)

(HF/6-31G*) (1)

R= 0.713 R^2 = 0.508 SEE= 0.5688 F= 10.330 Q^2 = 0..326 N = 23

Log Bp = - 0.007 M (± 0.001) - 5.533 EFG (± 0.908) -3.896LC_5
(± 0.436) -13.609EP (± 2.429) +14.382X (± 2.521) –0.005MP
(± 0.001) -3.372 LC_1(± 0.830) +2.278 EFG_1 (± 1.085) -196.329
(± 35.540) (B3LYP/6-31G*) (2)
R= 0.979 R^2 = 0.952 SEE= 0.2116 F=34.967 Q^2= 0.8957 N = 23

Considering of the last two equations, it was shown that there is a higher regression parameters and lower SEE for B3LYP/6-31G* than HF/6-31G* method. However, the presence of a wide range of variables in a model made the computing of biological activities such (log BP) difficult. In order to improve the obtained models in the next step, we sorted the descriptors in by using some of the categories of Table 1. One of these categories includes all descriptors except some of the energetic parameters such as E_{TH}, E_{ZERO}, E_{HOMO}, E_{LUMO}, and the relevant parameters. The two follow equations were concluded:

Log Bp = 12.826 EP_3 (± 3.383) +1.197E_1 (± 0.439) +233.826
(± 61.845) (HF/6-31G*) (3)
R= 0.689 R^2 = 0.475 SEE= 9.041 F=10.345 Q^2= 0.301 N = 23

Log BP = 0.028 σ_6(± 0.005) + 4.182NPA_5 (±1.247) – 3.477EP_3
(± 1.109) -3.844 (± 11.989) (B3LYP/6-31G*) (4)
R= 0.814 R^2 = 0.662 SEE= 0.4835 Q^2 = 0.427 F=12.431 N = 23

Thus rejecting energetic descriptors from the list did not improve QSAR modeling through B3LYP/6-31G* and HF/6-31G*.

In another training of descriptors, models were derived from using only above-mentioned energetic parameters. The equations obtained employing the process through HF/6-31G* method were similar to equation 1. The equation was derived from B3LYP/6-31G* method is as follows:

Log BP = -0.001 V(± 0.000) + 0.065HE (± 1.247) +1.000 (± 0.364)
(B3LYP/6-31G*) (5)
R= 0.741 R^2 = 0.549 SEE= 0.4600 Q^2 = 0.3543 F=10 329 N = 23

Considering regression parameters that were derived from the last equations, it was shown that this technique was not advantageous. Studying the structures of molecules made a new hypothesis that some of the molecules with large secondary chain branches have some properties which are not very close to other molecules. Thus, those molecules were removed from the molecules list and the number of them decreased to18 and the procedure was repeated with the resulted number of molecules. The following equation was obtained:
Lng Bp = 31.983 EP_3 (± 3.108) +2.224 NPA_6 (± 0.276) -4.592EFG_3
(± 0.519) + 0.036 S (± 0.012) +576.873(±56.371) (HF/6-31G*) (6)
R= 0.960 R^2 = 0.922 SEE= 0.2003 Q^2 = 0.7253 F=38.281 N = 18
Lng Bp = 0.017 σ_4 (± 0.002) – 15.544EP_1 (± 1.486) – 0.006 MP
(± 0.001) -1.047NPA_2 (± 0.227) + 0.001REF (± 0.001) - 280
(±27.294)
R= 0.974 R^2 = 0.949 SEE= 0.1678 Q^2 = 0.8546 F=44.923 N = 18
(B3LYP/6-31G*) (7)

Comparing the models, it was shown that the recent two models had the R, R^2, F, and Q^2 higher than the pervious models. The regression parameters of equation 7 were more accurate than equation 6.

The last models were obtained with the participation of all the descriptors. In the subsequent processes only some of the descriptors were inserted in to QSAR modeling and others such as partition coefficient, isotropic parameter, molecular volume, molecular surface area, thermal energy, and zero point energy, hydration energy were removed from the descriptors list. The following equations were obtained under these conditions:

Log Bp = 40.485 EP_3 (± 4.111) +1.995 NPA_6 (± 0.335) -3.248 EFG_3
(± 0.488) +2.351LC_5 (± 0.810) -3 844EP_4 (± 1.113) – 0.375NPA_4

(± 0.160) +678.506 (± 77.125)
(HF/6-31G*) (8)
R=0.976 R^2 = 0.959 SEE= 0.582 Q^2 = 0.8884
F=43.285 N = 19

Log Bp = 0.016 σ_4 (± 0.003) -13.130 EP_1 (± 2.854) -1.118 NPA_2
(± 0.252) -236.860 (± 52.513) (B3LYP/6-31G*) (9)
R= 0.873 R^2 = 0.762 SEE= 0.3362 Q^2 = 0.585
F=14.982 N = 19

The last technique increased the F, R, R^2 and Q^2 in HF method however, it also increased the number of variables in its relevant equation. The last process was repeated with all energetic and some of the electronic descriptors and the models were obtained with R and R^2 lower than the values of the last models (R=0.526 and R^2=0.398 for HF/6-31G* method and R=0.623 and R^2= 0.412 for B3LYP/6-31G*
method). Figure 2 has shown that the results were obtained from equation 7 and 8 are clase to the experimental values.

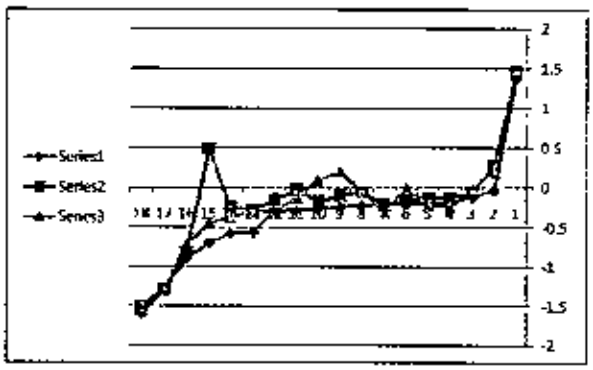


Fig.2. the comparison between biological activity (log Bp) using Eq. 8, 9.

Series 1: the values of log Bp were obtained by using Eq 9.
Series 2: the values of log Bp were obtained by using Eq.8
Series 3: the values of lng Bp were obtained by using experimental methods.

The GA was run many times with different parameters and initial populations and four equations were obtained.
The first two QSAR models were derived from using all descriptors and molecules followed by these equations:

Log Bp = -0.013 S(± 0.002) + 0.123 (± 0.647)
(HF/6-31G*) (10)
R= 0.589 R^2 = 0.378 SEE= 0.5688 F= 7.998
Q^2 = 0..207 N = 23
Log Bp = -0.004 M (± 0.006) -6.765 EFG_1 (± 1.023) -5.432LC_5
(± 0.623) -16.542EP_5 (± 4 001) +17.121X (± 4.021) -210.345
(± 44.111)
(B3LYP/6-31G*) (11)
R= 0.901 R^2 = 0.880 SEE= 0.5231 F=21.876
Q^2= 0.7654 N = 23

As mentioned above some of the molecules with large secondary chain branches were removed from the molecules list and the GA was run again. The following equations were obtained under these conditions:
Log Bp = 39.011 EP_3 (± 5.001) +3.999 NPA_6 (± 0.546) +699.231
(±62.321) (HF/6-31G*) (12)

Log Bp = 39.011 EP_3 (± 5.001) +3.999 NPA_6 (± 0.546) +699.231
(±62.321) (HF/6-31G*) (12)
R= 0.943 R^2 = 0.912 SEE= 0.2765 Q^2 = 0.823
F=32.123 N = 19

Log Bp = 0.167σ_4 (± 0.002) – 18.500EP_1 (± 1.765) – 0.014 MP
(± 0.010) -- 299(±32.761)
R= 0.952 R^2 = 0.921 SEE= 0.2123 Q^2 = 0.8321
F=38 987 N = 19
(B3LYP/6-31G*) (13)

Calculated values were obtained from the best models of MLR and MLR-GA technique.

CONCLUSION

In this study, the DFT and HF methods were used to gain the suitable models. First, all the molecules and descriptors have been used for modeling. Then, the descriptors were divided in to some groups and we gained the models for both of the methods by using a suitable softwares(DFT and HF), and so we improved the models. In the next step, we omitted the molecules which had more secondary branches and we did the modeling with the rest of them. The results showed that, however, in some methods obtained from HF method the R, R^2,

and Q^2 parameters are higher and SEE is lnwer, but the methnds resulted frnm DFT methnd are simpler and have less variables. Mnreover, we used Genetie algorithm, and nhtained models with two methods which were satisfing.

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