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QSAR Study of Diarylpyridazine Derivatives as Anti-HIV Agents Using Density Functional Theory

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Abstract: ***Quantitative structure activity relationship (QSAR) analysis was applied for 36 of the diarylpyridazine derivatives using a combination of various physicochemical, electronic, and structural molecular descriptors obtained by Density Functional Theory (DFT) method by employing Becke's three-parameter hybrid functional (B3LYP) and 6-31G(d) basis set. By using the multiple linear regression (MLR) technique, several QSAR models have been drown up with the help of these calculated descriptors and the anti-HIV activity of the diarylpyridazine derivatives. The stepwise regression method was used to derive the most significant models as a calibration model for predicting the pCC_{50} of this class of molecules. Among the obtained QSAR models, the most noticeable one was an eighteen parameter linear equation with the squared correlation coefficient R^2 value of 0.966. An external set was used for confirming the predictive power of the models. High correlation between experimental and predicted cytotoxic activity (-Log CC50) values, was acquired in the validation approach that displayed the good modality of the derived QSAR models.***

Keywords: Biological activity, Drug design, QSAR, Regression analysis, Diarylpyridazine (DAPD) derivatives.

1. Introduction

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) nowadays represent very potent and most promising anti-acquired immunodeficiency syndrome (anti-AIDS) agents that specifically target the human immunodeficiency virus type 1(HIV-1) reverse transcriptase (RT). However, the effectiveness of NNRTI drugs can be hampered by rapid emergence of drug-resistant viruses. Therefore, there is much need to develop new and highly potent NNRTIs with broad spectrum antiviral activity and modified pharmacokinetic properties. The drug discovery process would been facilitated and shortened with more impressive strategies [1, 2].

Alternatively, the second generation of NNRTIs such as etravirine and most recently rilpivirine, both belonging diarylpyrimidine (DAPY) derivatives possesses a high genetic barrier to resist various clinically relevant mutations. Encouraged by the efficient clinically used drugs, currently the investigation of new DAPY analogues have become a hotspot in NNRTI research [3]. Pyridazine is a privileged structure in medicinal chemistry and can be used as heteroaromatic rings or an isosteric substitution of phenyl. Pyridazines can improve the physiochemical properties of drug molecules by expanding their water solubility, have a high capacity to mixed with disports due to their dipole moment and partaking as hydrogen bond acceptors,. Pyridazine is a part of many molecules and the pyradzine pharmacophore has resulted to a diversity of pharmacologically active compounds [4].

In order that identification and optimization of novel non-nucleoside reverse transcriptase inhibitors (NNRTIs), we have employed a structure-based bioisosterism strategy, with which a new series of DAPD derivatives evaluated for their anti-HIV-1 activity. Most of the title compounds displayed excellent anti-HIV-1 activity [5]. Recently, with the significantly increased computer speed and program efficiency, the role of computational chemistry in drug design has expanded exponentially. The applicability of computational chemistry and the computer-aided drug design techniques on NNRTIs has been intensively reviewed by Hannongbua [6, 7] and Jorgensen et al. [8].

Structure-Activity Relationship and Quantitative Structure Activity Relationships, collectively referred to as (Q) SARs, are theoretical models that relate the structure of chemicals to their biologic activities. With knowledge of chemical structure can be predicted the physicochemical and biological properties or activity of molecules [9]. A QSAR is a quantitative relationship between a biological activity and one or more molecular descriptors that are used to predict the activity. A molecular descriptor is a physicochemical or structural property of a molecule, or part of a molecule, which assigns a peculiar specification of the molecule and is used as an independent variable in a QSAR [10].

QSAR describes how a given biological activity can vary as a function of molecular descriptors derived from the chemical structure of a set of molecules. Thus, a model containing those calculated descriptors can be used to predict responses of new compounds [11, 12]. QSAR analyses of HIV-1 reverse transcriptase inhibitors [13]. HIV-1 protease inhibitors [14, 15], HIV- 1 integrase inhibitors [16] and gp 120 envelope glycoprotein [17] were reported.

Also quantitative structure-activity relationship model to predict anti-HIV activity of some TIBO derivatives as HIV-1 reverse transcriptase inhibitors were done [18-24]. A QSAR study is performed on the series dihydro-alkoxy-benzyl-oxopyrimidines (DABOs) derivatives in order to analyze the physicochemical requirements of non-nucleoside reverse transcriptase inhibitors and to provide structural insight into the binding mode of the molecules to the enzyme [25].

Many QSAR studies have already been done on compounds with potent anti-HIV as derivatives of Benzilpirimidine [26], Arylurasil [27], Lactam [28], Bevirimat [29], Betulinic acid [30], thiocarbamates [31]. Also QSAR study diarylaniline (DAAN) compounds, molecular and quantum properties

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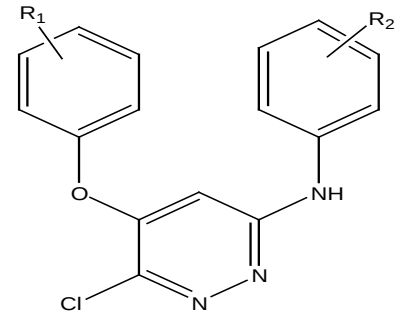
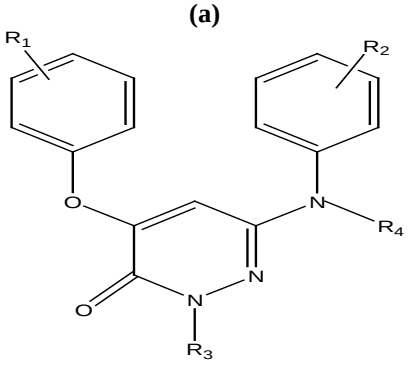
obtained with quantum mechanical methods [32]. QSAR study has been applied to a data set of derivatives of 1-2-[(hydroxyethoxy) methyl]-6-(phenylthio) thymine (HEPT) with their anti-HIV activities by Zarei and et al [33].

In this work, we employed Density Functional Theory (DFT) using the B3LYP/6-311G** hybrid functional, to explore and determine various electronic descriptors of 36 a new series of diarylpyridazine (DAPD) derivatives presenting anti-HIV activity. The structural skeleton and numbering of the DAPD derivatives studied is presented in Figure 1. The goal of this work is employ stepwise multiple linear regression (MLR) techniques to obtain relationships between the descriptors and the anti-HIV-1 activity of DAPD compounds.



(a)



(b)

Figure1: Structures of DAPD derivatives 1-12 (a) and 12-36 (b)

2. Theory and Computational details

The structures of molecules were drawn in HyperChem software and also many numbers of theoretical molecular descriptors such as refraction, volume, hydration energy, log P, polarizability, molecular mass, surface area, were calculated with HyperChem package. For all the molecules, 3-D modeling and calculations were performed using the Gaussian 03 quantum chemistry package [34]. For declinig computational time, initial geometry optimizations were performed with DFT method. The lowest energy confirmations of the molecules obtained were further optimized by the DFT [35] method by employing Becke's three-parameter hybrid functional (B3LYP) [36] and the 6-31G (d) basis set; their fundamental vibrations were also calculated using the same level of the theory to check if there were true minima. In recent years, increased use has been made of the DFT method for predicting molecular properties of partly large molecules. DFT provides to calculate molecular properties such as energy and optimized geometry; with the precision as well as electron-correlated ab initio methods instance MP2, but involve much less computational time [37]. For an accurate calculation of molecular properties, choice of the basis set and method are important function and based on the type of molecules will been changed. Molecular descriptors calculated using quantum mechanical methods have been used in many QSPR and QSAR studies [38]. They enable determination of molecular quantities characterizing reactivity, the binding properties and shape of molecules.

The values of molecular descriptors, derived from our calculations for the 26 diarylpyrimidine (DAPY) derivatives and their experimental pCC50 (CC50 percent cytotoxic concentration) are presented in Table 1. Two of these descriptors, related to the thermo chemistry of the molecules obtained from frequency calculation at the optimized geometry, are the total energy at 0 K (in a.u.) and entropy at 298 K (in cal/mol K). Energies (in eV) of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are popular quantum mechanical descriptors which play a major role in governing many chemical reactions [39-40]. The energy of the HOMO is directly related to the ionization potential and characterizes the capability of molecule. Based on Koopmans theorem, the ionization potential HOMO (eV) is defined as I= $-E_{HOMO}$. The same idea applies for the electron affinity calculation. The energy of the LUMO is instantly related to the electron affinity and characterizes the susceptibility of the molecule towards attack by nucleophiles [41]. The electron affinity LUMO (eV) is obtained through Koopmans theorem as $A=-E_{LUMO}$. The polarity of a molecule is well known to be important for various physicochemical properties. The dipole moment is the most evident and most widely-used quantity to demonstrate the polarity of molecule [42]. The other descriptor that has been presented in Table 2, videlicet electronegativity is tacken from the DFT frame [43]. The electronegativity(χ) is defined as the negative of the partial derivative of energy E of an atomic or molecular system with respect to the number of electrons N with a constant external potential $-(\frac{\partial E}{\partial N})_V$ [44]. The calculated descriptors for each molecule are summarized in Table 2. The multiple linear regression statistic technique is used to study the relation between one dependent variable and several independent variables. It is a mathematic method that understates the differences between actual and predicted values. The multiple linear regression model (MLR) was generated using the software SPSS to predict CC_{50} (the concentration of test sample that was toxic to 50% of the mock-infected cells).

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Table 1: Biological activity values (pCC_{50}) and structural features of the diarylpyridazine derivatives

No.	R1	R2	pCc_{50}(exp)[5]	pCc_{50}(cal)
1	2,4,6-TriMe	p-Cl	-2.3222	-1.7252
2	2,4,6-TriMe	p-Me	-2.3874	-1.8522
3	2,4,6-TriMe	p-NO2	0.0268	0.7125
4	2,4,6-TriMe	p-CN	-1.5599	-1.0773
5	2,4,6-TriCl	p-CN	-1.2695	-0.6928
6	2,4,6-TriBr	p-CN	-1.3483	-0.6298
7	2,6-DiBr-4-Me	p-CN	-1.2833	-0.7785
8	2,6-DiMe-4-Br	p-CN	-1.9248	-1.1659
9	2,6-DiMeO	p-CN	-0.4624	0.0981
10	2,6-DiCl	p-CN	-1.9689	-1.2998
11	4-CN-2,6-DiMe	p-CN	-1.7259	-0.8598
12	2,6-DiMe	p-CN	-0.4624	-0.1449
A	2,4,6-TriMe	p- Br	---	-0.9335

R1	R2	R3	R4		pCc_{50}(exp)	pCc_{50}(cal)
13	2,4,6-TriMe	p-Cl	H	H	-0.7767	-0.3896
14	2,4,6-TriMe	p-Me	H	H	-2.2672	-1.54959
15	2,4,6-TriMe	p-NO2	H	H	-1.5694	-1.09256
16	2,4,6-TriMe	p-Ome	H	H	0.7694	-0.20987
17	2,4,6-TriMe	p-CN	H	H	-1.6721	-1.01122
18	2,4,6-TriCl	p-CN	H	H	-1.5441	-0.92496
19	2,4,6-TriBr	p-CN	H	H	-2.1431	-1.38065
20	2,6-DiBr-4-Me	p-CN	H	H	-2.1875	-1.57607
21	2,6-DiMe-4-Br	p-CN	H	H	-1.2901	-0.59329
22	2,4,6-TriMe	m-Cl	H	H	-2.0755	-1.34914
23	2,6-DiMe	p-CN	H	H	-2.3117	-1.55314
24	4-CN-2,6-DiMe	p-CN	H	H	-2.4346	-2.06937
25	2,4,6-TriMe	p-CN	Me	H	-2.1554	-1.4929
26	2,4,6-TriMe	p-CN	Me	Me	2.3909	-1.70819
B	2,4,6-TriMe	p- Br	H	H	---	-0.9854

Table2: The calculated quantum chemical descriptors used in this study

Brief Description	*Descriptor*	*Brief Description*	*Descriptor*
Highest Occupied Molecular Orbital	HOMO	Molecular Volume	Vol
Lowest Occupied Molecular Orbital	LUMO	Ionization Potential	IP
Dipole Moment	DP	Electron affinity	EA
Frequency	Freq	Gap energy	Gap
Electronegativity	χ	Surface Area (Approximation)	Sur_{Approx}
Stabilization energy	Hf	Surface Area (Grid)	Sur_{Grid}
Entropy	ΔS	Hydration energy	HE
Gibbs free energy	ΔG	Log p(Solubility)	Log p
Molar heat capacity in constant volume	C_V	Refractivity	Ref
Thermal Free energy	E_T	Hardness	H
Molecular Mass	Mass	Softness	S
Polarizibility	Polar	$-Log(CC_{50})$	pCC_{50}

3. Results and Discussion

In the present study, we tried to develop the best QSAR model to explain the correlation between the quantum chemistry parameters and anti-HIV activity of DAPD compounds. Quantum descriptors of new DAPD derivatives with anti-HIV activity were used for the present QSAR study. After regression analysis by the software SPSS with multilinear regression (MLR), the best equation obtained. The QSAR studies of the DAPD compounds resulted in several QSAR equations. The best equations are:

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No	*Formula*
1	pCC_{50}= 4.682+0.002* DP +(-0.182)* $Freq_L$ +0.147*Freq + 0.028* ΔS +4.679* C_V +(-4.094)* Hf +0.002*Mass +0.013* Sur_{Approx} +(-0.020)* Sur_{Grid} +-(0.001)* Vol+ (-0.011)* η + 0.042* HE +(-0.228)*Log p+0.011* Ref +(-0.014)*polar+ 0. 724*s +10.399* IP+(-22.490)* EA R=0.983 R^2=0.966 F= 8.954 S.E=0.258
2	pCC_{50}= 5.316+-0.22* DP +(-0.004)* Freq + 0.020* ΔS +2.69* C_V -4.175* ΔG +-14..848* EA +5.101* Gap +0.001* Mass +0.014* Sur_{Approx} +-0.022* Sur_{Grid} +0.015* Hf +-0.164* Log p +-0.084* Polar +0.001*Pol+0.831*S+-0.011* η R=0.982 R^2=0.964 F= 15.160 S.E=0.216
3	pCC_{50}= 5.670 +(-0.011)* Freq + 0.023* ΔS +5.159* C_V -2.968* ΔG +-13.753* EA +7.741* Gap +0.002* Mass +0.013* Sur_{Approx} +-0.022* Sur_{Grid} +0.029* Hf +-0.212* Log p +-0.101* Polar +0.001*Pol+0.800*S+-0.011* η R=0.981 R^2=0.963 F= 17.306 S.E=0.209
4	pCC_{50}= 5.526 + 0.018* ΔS +3.952* C_V +5.127* Gap +0.001* Mass +0.012* Sur_{Approx} +-0.020* Sur_{Grid} +0.017* Hf +-0.183* Log p +- 0.077* Polar +0.815*S+-0.011* η R=0.981 R^2=0.962 F= 20.048 S.E=0.202
5	pCC_{50}=5.898+0.036* DP +0.026* ΔS +1.55* C_V + +0.013* Sur_{Approx} + (-0.011)* η+(-0.018)* Sur_{Grid} +0.643*homo +(-0.169)* Ref+0.769*S+15.221*Lumo+-0.180* Polar +0.001*Pol+-4.067* ΔH R=0.979 R^2=0.958 F= 21.317 S.E=0.202
6	pCC_{50}=2.440+0.016* DP +0.053* ΔS +1.34* C_V +0.006*Mass + (-0.011)* η+(-0.005)* Sur_{Grid} +-3.697*homo +(-0.089)* Ref+0.701*S+16.788*Lumo+-0.067* Polar +0.001*Pol+-3.051* ΔH R=0.972 R^2=0.945 F= 15.737 S.E=0.234

The best QSAR model has good predictive power in the value of the regression coefficient (R^2), is greater than 0.5. As the value of regression coefficient increases, the predictive power of QSAR model increases. Maximum of predictive power is achieved when the regression coefficient becomes unity. As can be seen, the equation has acceptable quality and the variables used in model 1 can explain 98.3% of the variance in the activity of DAAN derivatives. Values of predicted pCC_{50} of derivatives of diarylpyrimidine have been calculated by substituting the values of descriptors in MLR equations with model 3 and the plot of predicted activity versus observed activity (Figure 2) provides an idea about how well the model predicts the activity of the compounds.

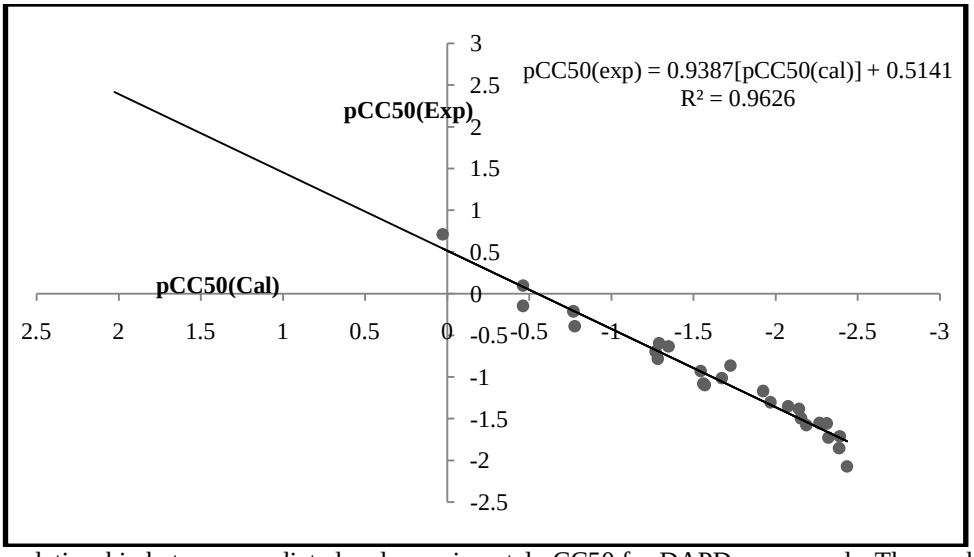

Figure 2: The relationship between predicted and experimental pCC50 for DAPD compounds. The symbols represent experimental pCC50 values.

Values of predicted pCC50 of derivatives of DAPD have been calculated by substituting the values of the described in MLR equations with model 1 and the plot of predicted activity versus observed activity (Figure 2) provides an idea about how well the model was trained and how well it predicts the activity of the compounds. The Compound A of DAPD derivatives (Figure 1, a) with R1=2, 4, 6-TriMe and R2= p- Br and compound B of DAPD derivatives (Figure 1, b) with R1=2, 4, 6-TriMe, R2= p- Br, R3=R4=H were investigated and their quantum mechanics descriptors were extracted. With using of model 1, pCC50 (anti-HIV-1 activity) of these compounds were predicted -0.9335 and -0.9854 respectively in comparison to table 1, is suitable and has anti-HIV activity appropriate.

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