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Research Article

A DFT BASED QSAR STUDY OF NOVEL 4-SUBSTITUTED 1,5-DIARYLANILINES AS POTENT HIV-1 AGENTS USING QUANTUM CHEMICAL DESCRIPTORS

Nosrat Madadi Mahani*, Fatemeh Sabermahani and Seyed Ali Mahdavi

Chemistry Department, Payame Noor University, 19395-4697 Tehran, Islamic Republic of Iran

ABSTRACT

In this study, a set of novel synthesized Diarylanilines derivatives was investigated by quantitative structure–activity relationship (QSAR) analysis using density functional theory (DFT) based descriptors. The best molecular descriptors identified were Polarisability, Charge O_{17} and Entropy that contributed to the anti-HIV activity of the Diarylanilines as independent factors. The correlation of these descriptors with their anti-HIV activity increases indicating their importance in studying biological activity. Quantitative structure activity relationship (QSAR) analysis was applied to 23 of the above mentioned derivatives using physicochemical and structural molecular descriptors obtained by the DFT method by employing Becke's three-parameter hybrid functional (B3LYP) and 6-31G basis set. By using the multiple linear regression (MLR) technique several QSAR models have been drown up with the help these calculated descriptors and the anti-HIV activity of Diarylanilines derivatives. The stepwise regression method was used to derive the most significant models as a calibration model for predicting the $LogEC_{50}$ of this class of compounds. Among the obtained QSAR models presented in the study from the MLR method, statistically the most significant one is the last model with the squared correlation coefficient 0.946 and F= 3.856 that could be useful to predict the biological activity of Diarylanilines derivatives as Potent HIV-1 Drugs.

Keywords: QSAR, Diarylanilines, MLR, DFT, HIV.

1. INTRODUCTION

Human immunodeficiency virus (HIV) is the primary cause of AIDS (acquired immunodeficiency syndrome). In the last decades, many anti-HIV drugs have been developed, but the most these drugs have problems like the serious adverse side effects of the available drugs and the emergence of drug-resistance, because research to discover and develop additional novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) drugs with diverse molecular scaffolds for more efficacious therapy and potential AIDS prevention[1]. A series of diarylaniline compounds with low nanomolar anti- HIV potency against wild-type and HIV-1 RT-resistant viral strains, as well as a new chemo-type scaffold and simplified synthesis [2].

QSAR is fast emerging as a useful tool in medicinal chemistry, biology, and drug discovery[3]. A QSAR model is a mathematical equation that correlates the biological, chemical, or physical activity of a molecular system to its geometry and chemical characteristics. The molecular descriptors are used to define the electronic properties of a molecule owing to the presence of limitations of fundamental physical and chemical laws in direct quantification of biological activity. QSAR studies containing those

calculated descriptors can be used to predict responses of new synthesized drugs [4]. Many physiological activities of molecules can be related to their composition and structures. Also QSAR studies have predictive ability and simultaneously provide deeper insight into mechanism of drug receptor interactions [5]. The quantum chemical descriptors computed by density functional theory (DFT) method has found increasing use in modern QSAR analysis[6]. In this study, there are a large number of molecular descriptors that can be used in QSAR studies. Once validated, the findings can be used to predict the activities of new synthesis compounds that not yet tested. QSAR studies have been successfully employed to develop new drugs for the treatment of SARS, cancer, AIDS and other diseases[7]. Many QSAR studies have already been done on compounds with potent anti-HIV as derivatives of Benzilpirimidine[8], Arylurasil [9], Lactam[10], Bevirimat [11], Betulinic acid [12], thiocarbamates[13].

For QSAR study diarylaniline compounds, molecular and quantum properties obtained by quantum mechanical methods[14]. Multiple linear regression (MLR) models[15] have been developed as a mathematical equation which can relate chemical structure to the anti-HIV activity of these compounds. All the anti-HIV activities used in the present study were expressed as pEC50 = $-\log_{10}EC_{50}$, where EC_{50} is the micro molar concentration of the compounds producing 50% reduction in the cytopathic effect caused by the virus is stated as the means of at least two experiments. Quantum chemical descriptors, which are numerical representations of the molecular structures, are used for performing QSAR analysis[14]. The aim of the present study is to build QSAR models using multiple regression method, to explore the correlations between the experimental the EC50 and calculated molecular descriptors of 23 Diarylaniline derivatives as a distinct class of HIV-1 non-nucleoside reverse transcriptase inhibitors. Herein, we report physicochemical properties of the new 4-substituted 1, 5-diarylaniline analogues (DAANs). Its structure–activity relationship (SAR) is discussed. The findings can be helpful for designing new active derivatives and better understanding the anti-HIV inhibition of Diarylaniline derivatives. The basic structure of these compounds is shown in Figure 1. The biological activity values and structural features of the Diarylaniline derivatives used in this study are presented in Table 1.

COMPUTATIONAL DETAILS

The two-dimensional structures of molecules were drawn in HyperChem software and also many numbers of theoretical molecular descriptors such as refraction, polarizability, molecular mass, surface area, volume, hydration energy, log P, were calculated with HyperChem package[16]. HOMO energy, LUMO-energy, ΔE (gap energy), Gibbs free energy, formation enthalpy and other quantum descriptors have been computed with the Gaussian 09 quantum chemistry package[17]. These descriptors used to modeling Quantitative structure–activity relationship of DAAN derivatives. The equilibrium geometries of all Diarylaniline derivatives were fully optimized using the DFT/B3LYP method[18] with the 6-31G basis set. No molecular symmetry constraint was applied, rather full optimization of all bond lengths and angles was carried out. 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 technique that minimizes the differences between actual and predicted values. The multiple linear regression model (MLR) was generated using the software SPSS to predict EC_{50}.

3. RESULTS AND DISCUSSION

In the present study, tried to develop the best QSAR model to explain the correlation between the quantum chemistry parameters and anti-HIV activity of DAAN compounds. After regression analysis on the software SPSS with multilinear regression (MLR), the best equation received. The QSAR studies of the DAAN compounds resulted in several QSAR equations. The three best equations are:

Model 1:

R=0. 930 R^2=0. 865 F=1. 426

pEC_{50}=-178.563+0.164*Mass-4.031*Polar+0.709*Ref+0.267*Logp +0.388*HE+0.001*Vol+0.186*Sur_{grid}-0.103*Sur_{app}-0.371*Freq+0.0000793*E_T-208.285*LUMO+0.101*DM-444.665*Q_{N9}-

19.606*Q_{N8}+5.552*Q_{N16}+1.527*Cv-0.519* ΔS -112.484*Gap

Model 2:

R=0. 919 R^2=0. 845 F=1. 601

pEC_{50}=-109.479+.13*Mass-0.558*Polar+.27*Logp+.191*HE+0.14*Sur_{grid}-0.082*Sur_{app}-0.359*Freq+0.0000256*ET-115.383*LUMO+0.155*DM-319.436*Q_{N9}-2.092*Q_{N16}+13.715*Q_{O17}+.556*Cv-0.431* ΔS -56.729*Gap.

Model 3:

R=0.972 R^2=0.946 F=3.856

pEC_{50}=61.091-0.201*Mass+2.871*Pol+1.277*Logp-0.048*HE-0.062*Sur_{grid}+0.003*Sur_{app}+0.198*Freq+0.060*DM-358.988*Q_{N9}-0.308*Q_{N16}+ 25.540*Q_{O17} -1.699*Cv+0.456* ΔS -7.923*10^{-5}*ΔG-41.263*Gap-475.394*η-7.861*S.

The best QSAR model is said to have good predictive power in the value of the regression coefficient (R^2), also called correlation coefficient, is greater than 0.5 as the value of regression coefficient increases, the predictive power of QSAR model increases. Percent 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 3 can explain 94.6% of the variance in the activity of DAAN derivatives. Values of predicted pEC_{50} of derivatives of diarylaniline have been calculated by substituting the values of the described 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 was trained and how well it predicts the activity of the compounds. The Compound of DAAN derivatives (Figure 1, A) with R^1=NH_2 and R^2= CH_2OH was investigated and their quantum mechanic descriptors were extracted. Using model 3, EC50 of this compound as anti-HIV activity was predicted 31.62 that in comparison to table 1, is suitable and has anti-HIV activity appropriate.

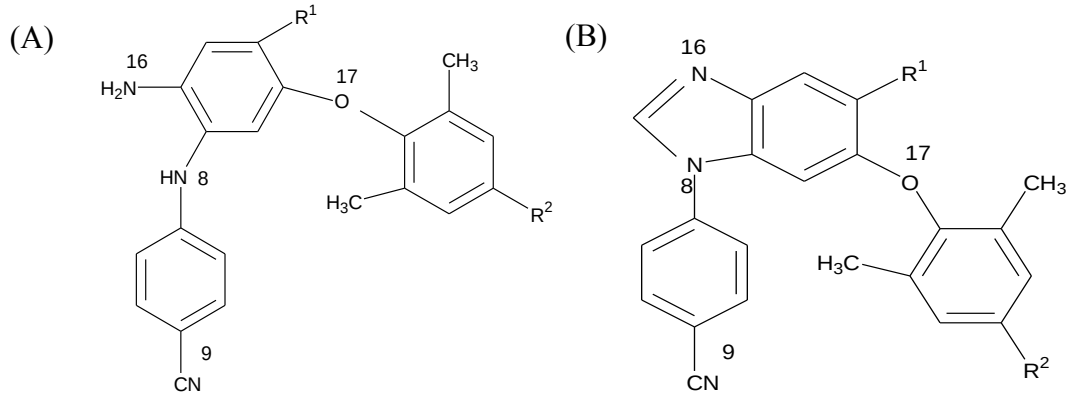

Fig. 1: Structures of 4-Substituted 1,5-Diarylanilines derivatives 1-21 (A) and 22- 23 (B)

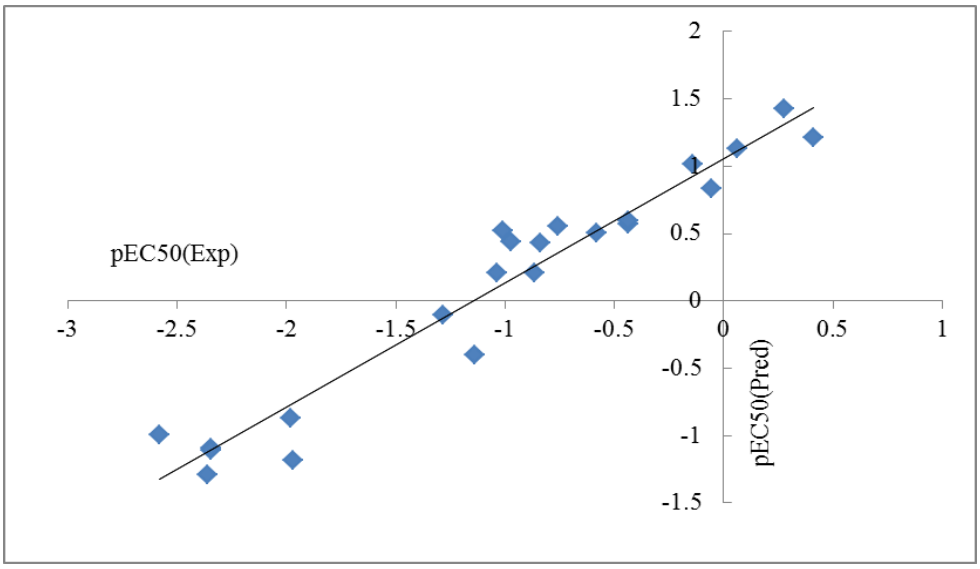

Fig. 2: The relationship between predicted and experimental pEC50 for DAAN compounds. The symbols represent experimental pEC50 values.

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

No.	R^1	R^2	EC_{50}	pEC_{50}
1	$COOCH_3$	CH=CHCN	2.74	-0.4377
2	COOH	CH=CHCN	230	-2.3617
3	$CONH_2$	CH=CHCN	0.87	0.0604
4	$CONHCH_3$	CH=CHCN	5.72	-0.7573
5	CH_2OH	CH=CHCN	0.53	0.2757
6	SO_2NH_2	CH=CHCN	93.70	-1.9717
7	$COOCH_3$	CH_2CH_2CN	4.32	-0.6354
8	COOH	CH_2CH_2CN	96.00	-1.9822
9	$CONH_2$	CH_2CH_2CN	1.39	-0.1430
10	$CONHCH_3$	CH_2CH_2CN	2.73	-0.4361
11	$CONHNH_2$	CH_2CH_2CN	19.10	-1.2810
12	CH_2OH	CH_2CH_2CN	0.39	0.4089
13	NH_2	CH_2CH_2CN	7.30	-0.8633
14	SO_2NH_2	CH_2CH_2CN	380	-2.5797
15	CF_3	CH=CHCN	9.38	-0.9722
16	CF_3	CH_2CH_2CN	1.13	-0.0530
17	CH_2OH	CH_2OH	10.20	-1.0086
18	CF_3	$CH=CHCOCH_3$	10.90	-1.0374
19	CF_3	$CH_2CH_2COCH_3$	6.85	-0.8356
20	CF_3	CN	3.79	-0.5786
21	CF_3	NH_2	13.80	-1.1398
22	$CONHCH_3$	CH=CHCN	220.00	-2.3424

23	$CONHCH_3$	CH_2CH_2CN	220.00	-2.3424

Table 2: The calculated quantum chemical descriptors in this study

Descriptor	Brief Description	Descriptor	Brief Description
Mass	Mass	HOMO	Energy of the highest occupied molecular orbital
Polar	Polarizability	LUMO	Energy of the lowest unoccupied molecular orbital
LogP	LogP	DM	Dipole Moment
HE	Hydration Energy	CV	Thermal Capicity (Volume constant)
Vol	Volume	ΔS	Entropy
Sur_{grid}	Surface grid	ΔG	Gibbs Free Energy
Sur_{app}	Surface approx	Gap	Gap Energy
Freq	Frequency	TE	Thermal Energy
E_T	Stabilization energy	TEF	Thermal Free Energy
ZPE	Zero point Energy	η	Hardness
Q_{N8}	Charge N_8	S	Softness
Q_{N9}	Charge N_9	Q_{N16}	Charge N_{16}
Q_{O17}	Charge O_{17}	Ref	Refractivity

CONCLUSIONS

In the study, a QSAR model for the activity DAAN derivatives was successfully developed based on various DFT descriptors. Significant regression equations were obtained by MLR for 23 DAAN compounds according to their anti-HIV activity. The QSAR model indicates that the quantum chemical descriptors such as polarizibility, Log P, dipole moments, Charge O_{17} (Q_{O17}) and Entropy play an important role for the anti-HIV activity and pEC50 of DAAN derivatives. The results of the present study may be useful on the designing of more potent DAAN analogues as anti-HIV agents.

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