ARTICLE

Electrophilic Group Chemical Potential as Sole DFT based Descriptor in a QSAR Model for Non-Nucleoside HIV-1 Reverse Transcriptase Inhibition Activity of a Series DABO Derivatives

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ABSTRACT

The molecular modelling studies of a series of dihydroalkoxybenzyloxopyrimidine (DABO) derivatives have been undertaken by establishing a quantitative structure activity relationship (QSAR) model towards their reverse transcriptase activity. An efficient QSAR model based on a sole descriptor, namely 'group chemical potential' has been established. The QSAR model with this DFT based descriptor has a q^2 value 0.646 and r^2 value 0.650.

KEYWORDS

Dihydroalkoxybenzyloxopyrimidine, HIV-1 Reverse transcriptase inhibition, QSAR, Group chemical potential.

INTRODUCTION

HIV-1 is a retrovirus which affects the cells of human immune system causing acquired immunodeficiency syndrome (AIDS) [1]. HIV-1 replicates through the action of resverse transcriptase (RT) enzyme. Currently available drugs to treat AIDS are based on their action towards inhibition of this reverse transcriptase enzyme. These drugs are broadly classified into two categories *viz*., nucleosidic inhibitors and non-nucleosidic inhibitors [2]. Some of the nucleosidic inhibitors currently in use are 3′-azidomythidine (AZT) [3] and non-nucleosidic inhibitors are HEPT [4], TIBO [5], *etc*. Drugs belonging to both these categories are beset with problems of cytotoxicity and drug-resistance [6]. Thus search is on for better drug molecules to contain the activity of HIV-1 retrovirus.

Molecules based on dihydroalkoxybenzyloxopyrimidines (DABO) have been reported to exhibit efficient anti-HIV-1 activity [7]. Design of better drug molecules is fundamentally dependent on the clear understanding of the electronic nature of a series of closely related molecules. Quantitative structure activity realtionship (QSAR) is a standard methodology in this direction in which one establishes a mathematical relationship describing the activity of a particular class of motlecules in terms of suitable descriptors that encode the common chemical characteristics [8,9]. Choice of descriptors is the most crucial part of establishing a successful QSAR model. A good QSAR

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model is one in which the activity can be described in terms of minimum number of descriptors.

Recently a number of descriptors based on conceptual DFT have been introduced in the literature, like chemical hardness [9], NICS [10], Fukui function [11], group frontier electron density [12], *etc*. Chemical potential is a classical concept widely employed in chemistry to express the reactivity of chemicals but it is not limited by its use only in chemistry, instead it is widely used in describing diverse physical phenomena and processes like phase transitions of materials, electric currents in semiconductor junctions and nuclear reactions, *etc*. [13]. It is a generalized intuitive concept equally applicable in the world of atoms, molecules and bulk materials as well.

Generally, the concept of chemical potential [14] is used in a global sense - a single parameter that describes the nature of the whole system. In case of atomic systems, this parameter is sufficient to describe the system as a whole due to coincidence of local and global nature. But for a molecular system one feels the necessity of defining local chemical potential specific to localized regions within a particular molecule which is conceptually different from global chemical potential and it is more appropriate in case of macro molecules. In the present work, we introduce the concept of group chemical potential which is defined as the chemical potential for a group of atoms with in a large parent molecule. We used this as the sole descriptor in establishing a QSAR model for reverse transcriptase (RT) inhibition activity of a series of dihydroalkoxybenzyloxopyrimidine (DABO) molecules. This new descriptor appears to work successfully as the QSAR model based on this has acceptable square correlation coefficient $r^2 = 0.64$.

EXPERIMENTAL

Chemical potential: Chemical potential (μ) is a global reactivity index for atoms, molecules and clusters [15-18]. It is defined as the change of energy of a system due to the addition or withdrawal of electrons from the system.

From density functional theory (DFT), it is also defined as:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \quad (1)$$

where ∂E is the change of energy of a system of N electrons due to the change of ∂N electrons of the system under a constant external potential v(r).

The finite difference approximation of eqn. 1 gives:

$$\mu = -\frac{1}{2}(IP + EA) \quad (2)$$

Where, EA and IP are the electron affinity and ionization potential of the system, respectively.

According to Koopman's theorem [19], eqn. 2 reduces to

$$\mu = -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad (3)$$

where E_{HOMO} is the energy of highest occupied molecular orbital and E_{LUMO} is the energy of lowest unoccupied molecular orbital.

A detailed theoretical explanation was given by Sanderson and Parr *et al.* [19-22].

Fukui function: The term 'Fukui Function' was introduced by Parr and Yang [19]. Actually, it measures the sensitivity of chemical potential of a system in response to an external perturbation at a particular site or the sensitivity of electron density of a system at a particular site if an infinitesimally small number of electrons is excluded or added to the system. Mathematically, it is defined as:

$$f(r) = \left(\frac{\partial \mu}{\partial v(r)}\right)_N = \left(\frac{\partial \rho(r)}{\partial N}\right) \quad (4)$$

where ρ(r) is the electron density.

The reactivity of an atom of in a molecule can be described by a single valued atomic Fukui functions (f_k) which is obtained by condensing values of f(r) around each atomic site k of the molecule.

Using finite difference approximation, Yang and Mortier [23] proposed approximated atomic Fukui indices as:

$$f_k^+ = \rho_k(N+1) - \rho_k(N) \quad \text{For nucleophilic attacks} \quad (5)$$

$$f_k^- = \rho_k(N) - \rho_k(N-1) \quad \text{For electrophilic attacks} \quad (6)$$

$$f_k^0 = \frac{1}{2}(f_k^+ + f_k^-) \quad \text{For radical attacks} \quad (7)$$

Local and group chemical potential: Local chemical potential is the product of global chemical potential (μ) and the Fukui function indices at a particular atomic site.

For an atomic site 'k', the electrophilic, nucleophilic and radical reactions are respectively described by the following three local chemical potentials which are defined as:

$$\mu_k^+ = f_k^+ \mu \quad \text{(suited for studies of nucleophilic attack)} \quad (8)$$

$$\mu_k^- = f_k^- \mu \quad \text{(suited for studies of electrophilic attack)} \quad (9)$$

$$\mu_k^0 = f_k^0 \mu \quad \text{(suited for studies of radical attack)} \quad (10)$$

In the present paper, we introduce two new descriptors, namely (i) electrophilic group chemical potential (μ_g^E) and (ii) nucleophilic group chemical potential (μ_g^N) which are defined respectively as:

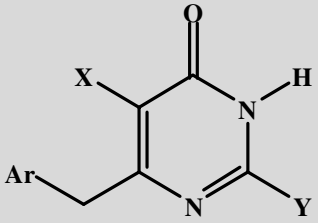
$$\mu_g^E = \sum_{i=1}^{n} \mu_i^E \quad (11)$$

$$\mu_g^N = \sum_{i=1}^{n} \mu_i^N \quad (12)$$

Here the summation extends over a group of n relevant atoms within a parent molecule.

Selection of dataset: Anti-HIV activity data of a series of DABO derivatives have been taken from the literature [24-27] for the present QSAR study and has been listed in Table-1. The biological profile of the compounds were evaluated in HIV-1 RT affinity binding assays, using 3[H]-dGTP as the radio-ligand. IC_{50} values of the compounds were transformed into log ($1/IC_{50}$), abbreviated as pIC_{50}, ranges from 4.23 to 6.70 M. A training set of 34 molecules has been used to generate the QSAR model whereas a test set of eight molecules has been used to determine the external predictivity of the resulting QSAR model. This test set evenly spanned the activity range as well as the chemical and structural diversity of the whole dataset.

TABLE-1
CHEMICAL STRUCTURE AND HIV-1 REVERSE TRANSCRIPTASE
NON-NUCLEOSIDE INHIBITION ACTIVITY DATA OF DABO DERIVATIVES



No.	X	Ar	Y	pIC_{50}	No.	X	Ar	Y	pIC_{50}
1#	Me	2-Naphthyl	S-*sec*-Bu	4.23	22	H	Ph	S-Cyclopentyl	5.55
2#	H	1-Naphthyl	S-Cyclopentyl	4.31	23	H	3-Me-Ph	S-Cyclopentyl	5.59
3	Me	1-Naphthyl	S-Cyclopentyl	4.35	24#	Me	3-Me-Ph	S-Me	5.60
4	Me	4-F-Ph	S-*sec*-Bu	4.59	25	Me	3-Me-Ph	S-*iso*-Pr	5.60
5	Me	4-Cl-Ph	S-*sec*-Bu	4.77	26	Me	3-Me-Ph	S-Cyclohexyl	5.66
6	H	1-Naphthyl	S-*sec*-Bu	4.79	27	Me	Ph	S-*tert*-Bu	5.72
7	H	2-Naphthyl	S-*sec*-Bu	4.83	28	Me	2,6-di-Cl-Ph	S-Cyclopentyl	5.80
8#	H	4-Cl-Ph	S-*sec*-Bu	5.02	29	H	2,6-di-Cl-Ph	S-*iso*-Pr	5.89
9	H	3-Me-Ph	4-*tert*-Ph	5.09	30	Me	2,6-di-Cl-Ph	S-*iso*-Pr	5.94
10#	Me	2,6-di-Cl-Ph	S-Cyclohexyl	5.31	31	Me	2,6-di-Cl-Ph	S-*n*-Pr	5.94
11	Me	Ph	S-Me	5.31	32	Me	2,6-di-Cl-Ph	S-*tert*-Pr	5.96
12	Me	Ph	S-*sec*-Bu	5.32	33#	H	2,6-di-F-Ph	S-Me	6.10
13	Me	3-Me-Ph	S-*tert*-Bu	5.34	34	Me	2-Cl-Ph	S-*sec*-Bu	6.10
14	Me	Ph	S-Cyclohexyl	5.37	35	Me	2-F-Ph	S-*sec*-Bu	6.10
15	H	3-Cl-Ph	S-*sec*-Bu	5.42	36#	Me	3-NO2-Ph	S-*sec*-Bu	6.10
16	Me	3-Me-Ph	S-Cyclohexyl	5.47	37	H	2-F-Ph	S-*sec*-Bu	6.22
17	H	2-Cl-Ph	S-*sec*-Bu	5.49	38	H	3-NO2-Ph	S-*sec*-Bu	6.22
18	Me	3-F-Ph	S-*sec*-Bu	5.52	39	H	2,6-di-Cl-Ph	S-*tert*-Bu	6.22
19#	H	2, 6-di-Cl-Ph	S-Me	5.52	40	H	2,6-di-Cl-Ph	S-*n*-Bu	6.30
20	H	Ph	S-Cyclohexyl	5.52	41	H	2,6-di-Cl-Ph	S-Cyclopentyl	6.40
21	H	3-Me-Ph	S-*iso*-Pr	5.54	42	H	2,6-F-Cl-Ph	S-*n*-Bu	6.70

molecules belonging to the test set

Computation of molecular descriptors: The structures of selected molecules have been optimized fully using the DFT method [28-32] using B3LYP/6-31G(d,p), Becke's three parameter hybrid density functional. It include Hartree-Fock exchange and DFT exchange correlation functional both using Gaussian 03W program [33]. The optimized structures were characterized by harmonic-vibrational frequencies which established that the obtained structures are at minimum on the potential energy surface. Various global and local reactivity descriptors have been calculated from the Gaussian 03 optimized geometries by a customized software.

RESULTS AND DISCUSSION

Derivation and validation of 2D QSAR model: In order to find out the relationship between anti-HIV activity of selected DABO derivatives and their chemical structures, we have created various QSAR models using different combinations of DFT based global and local reactivity descriptors such as local chemical potential, group chemical potential, hardness, softness and so on. The best QSAR model was searched based on the logic that the number of descriptors should be as small as possible and the model should have maximum correlation coefficient for the HIV-1 RT inhibition activities. Surprisingly, the best QSAR model was found to be dependent only on a single descriptor *i.e.*, electrophilic group chemical potential (μ_g^E), calculated using eqn. 11 over the central ring. The model has satisfactory statistical quality. The QSAR equation so obtained is:

$$pIC_{50} = 4.121 + 0.103\ \mu_g^E \qquad (13)$$

with $r^2 = 0.650$, $r^2_{adj} = 0.635$, $q^2 = 0.646$, P = 0.000, F = 58.36 and SEE = 0.327.

The high r^2 value and low SEE value both indicate a reliable goodness of fit and a large F value indicates that the choice of the descriptors in the model is not a chance occurrence. The high T-test value (7.64) of the descriptor implies that the descriptor is statistically signigicant.

The model was validated by calculating the cross-validated squared correlation coefficient (q^2) which also has a quite high value ($q^2 = 0.646$). The experimental and predicted pIC_{50} values of the molecules given by eqn. 13 is given in Table-2, and the graph of actual activity *versus* predicted activity of the training set and test set has been illustrated in Fig. 1. The value of the r^2_{pred} is also quite high (0.715) which indicates that the model has a high predictive ability.

From eqn. 13, one can see that anti-HIV activity of DABO molecules solely depend on a new quantum chemical descriptor, namely the electrophilic group chemical potential. The electrophilic group chemical potential is a measure of how easily a group of atoms within a molecule gets perturbed when an elecrophile attacks a molecule. It characterizes the cohesiveness of a group of atoms that act as a local entity within the parent molecular framework. The calculated values of the electro-

TABLE-2
DFT BASED DESCRIPTOR ELECTROPHILIC GROUP CHEMICAL POTENTIAL (μ_g^E)
AND PREDICTED pIC_{50} VALUES ACCORDING TO QSAR eqn. 13

Mol. No.	Obs. Act.	Descriptor (μ_g^E)	Pred. act.	Res.	Mol. No.	Obs. Act.	Descriptor (μ_g^E)	Pred. act.	Res.
01#	4.23	7.9861	4.94	0.71	22	5.55	15.4494	5.71	0.16
02#	4.31	5.5849	4.70	0.39	23	5.59	11.2297	5.28	-0.31
03	4.35	7.7499	4.92	0.57	24#	5.60	10.9154	5.25	-0.35
04	4.59	8.5303	5.00	0.41	25	5.60	18.2347	6.00	0.40
05	4.77	10.8148	5.23	0.46	26	5.66	13.0537	5.47	-0.19
06	4.79	5.3801	4.68	-0.11	27	5.72	15.4036	5.71	-0.01
07	4.83	6.5093	4.79	-0.04	28	5.80	21.2749	6.31	0.51
08#	5.02	12.4041	5.40	0.38	29	5.89	15.7924	5.75	-0.14
09	5.09	12.2078	5.38	0.29	30	5.94	21.3651	6.32	0.38
10#	5.31	15.1992	5.69	0.38	31	5.94	20.4101	6.22	0.28
11	5.31	11.6983	5.33	0.02	32	5.96	19.3942	6.12	0.16
12	5.32	13.9393	5.56	0.24	33#	6.10	15.5155	5.72	-0.38
13	5.34	14.7198	5.64	0.30	34	6.10	13.1877	5.48	-0.62
14	5.37	11.0836	5.26	-0.11	35	6.10	16.6272	5.83	-0.27
15	5.42	12.9527	5.46	0.04	36#	6.10	21.1883	6.30	0.20
16	5.47	13.0463	5.46	-0.01	37	6.22	14.3149	5.60	-0.62
17	5.49	11.2283	5.28	-0.21	38	6.22	21.6839	6.35	0.13
18	5.52	14.5424	5.62	0.10	39	6.22	16.4138	5.81	-0.41
19#	5.52	15.3214	5.70	0.18	40	6.30	18.3920	6.02	-0.28
20	5.52	13.7250	5.53	0.01	41	6.40	18.9440	6.07	-0.33
21	5.54	12.8597	5.45	-0.09	42	6.70	19.6152	6.14	-0.56

molecules belonging to the test set

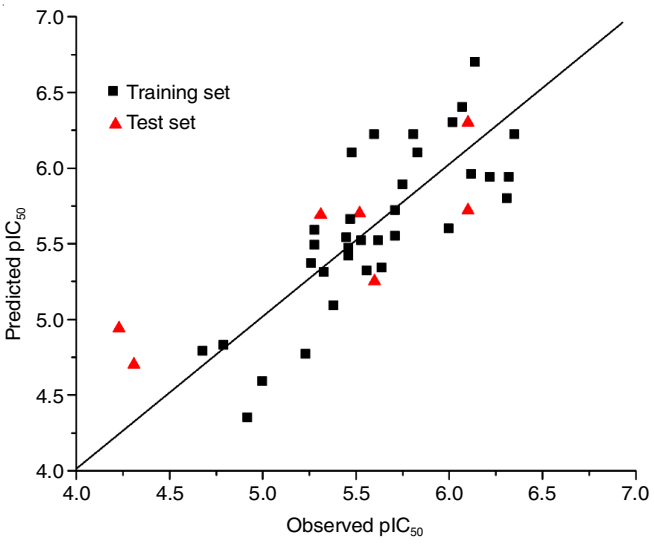


Fig. 1. Plot of observed pIC_{50} *versus* predicted pIC_{50} values

philic group chemical potential computed over the group of atoms constituting the core aromatic ring of the DABO molecules is always positive which increases the pIC_{50} values described in eqn. 13. Molecule 42 has the highest electrophilic group chemical potential and also exhibits highest activity. It has an electron withdrawing normal butyl group at Y, which draws the electrons from the central aromatic ring and thus makes it difficult for an electrophilic group to perturb the electron distribution in the ring. This translates into increased elctrophilic group chemical potential. As can be seen from Table-1, the series of DABO molecules 33 to 42 all of which has electron withdrawing groups at Y either in the form of normal, *sec*- or *tert*-butyl show higher anti-HIV activity compared to molecules with other less effective electron withdrawing groups. Thus QSAR model given by eqn. 13 indicates that stronger electron withdrawing groups directly attached to the core aromatic ring of DABO molecules are likely to increase the anti-HIV potency of DABO molecules.

Conclusion

The salient feature of the present QSAR study is the introduction of "group chemical potential" as a new DFT based descriptor. A QSAR model with "group chemical potential" as the sole descriptor successfully explains the anti-HIV activity of a series of dihydroalkoxybenzyloxopyrimidine (DABO) derivatives. The group chemical potential in the present study has been computed collectively for the atoms constituting the central ring of DABO derivatives. The present study shows that if instead of the whole molecule, the chemical potential is assigned to a relevant subset of atoms then it can capture the chemical activity of molecule in a more specific manner. Present study establishes that stronger electron withdrawing groups substituted to the core aromatic ring of DABO molecules are more appropriate to increase the anti-HIV activity.

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