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Research Article

ATOMIC DESCRIPTORS BASED QSAR STUDY OF CYCLIC UREA DERIVATIVES AS ANTI-HIV DRUG OF PROTEASE INHIBITOR GROUP

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ABSTRACT

The use of QSAR has become increasingly helpful in understanding many aspects of chemical -biological interactions in peptidic and non peptidic drug research. With a properly designed and carefully tested programs it has become easy to derive a QSAR model for almost any set of biologically active compounds. In the present study, atomic property-based descriptors are calculated at each active site of the proposed model. The atomic descriptors that have been used are ionisation potential (IP), atom electron density, softness of atom, density distribution function, Fukui function. Semi-empirical model PM3 has been used for the calculation and the results obtained by using various MLR equations have been analyzed to interpret the biological activity of proposed models.

Keywords: QSAR, Atomic Descriptors, Atom Electron Density, Fukui Function.

1. INTRODUCTION

The HIV life cycle begins with the high affinity binding GP-120 envelope protein to its receptor CD4 on the host cell surface [1]. The CD4 receptor is a protein molecule and predominantly on a subset of T-lymphocytes responsible for helper or inducer functions in the immature response. Following binding the fusion of virus with host cell membrane occurs via the GP-41 molecule and the HIV genome RNA is uncoated and internalised. The enzyme reverse transcription of genomic RNA into double stranded DNA. The DNA migrates to the nucleus to be integrated into the host cell chromosome through the action of virally encoded enzyme, integrase. The incorporation of this provirus may remain transcription ally latent or manifest in high level of gene expression with active production of virus [2]. The activation of provirus from the latent state by selective and constructive host transcription factors leads to the sequential production of various viral m -RNAs. Thus, the replicative cycle of HIV- 1 presents several targets that could be exploited for the development of anti-HIV chemotherapy and an HIV agent should arrest the virulence and further infection of healthy cells without displaying significant toxicity towards normal cellular physiology.

The cleavage of large polypeptide precursor into smaller functional protein fragments required for packaging and infectivity of budding virion needs HIV- protease. Protease inhibitors (PIs) block the protease enzyme [3, 4]. Since HIV-1 PR is an aspartic protease and because of that its substrate is peptidic in nature, a number of peptide derived compounds have been identified as HIV-1 PR inhibitors [5]. The development of anti-HIV chemotherapy based on protease inhibition will always be an ongoing need because the virus has the ability to rapidly generate resultant mutants [6-8]. The present study discusses the derivable QSAR on nonpeptidic inhibitors based on atomic descriptors with the help of PM-3 and Cache software.

The replicative cycle of HIV-1 protease presents several targets that could be exploited for the development of anti-HIV chemotherapy. Therefore, this atomic descriptor-based study gave a valuable inference into structural and binding features of the predicted models. Thus, this atomic descriptor based QSAR study and the results obtained therefore may serve as a basis to design biologically active HIV protease inhibitor compound of this class.

2. MATERIAL AND METHODS

The concept of qualitative drugs design is based on the fact that the biological properties of a compound are a function of its physicochemical parameters, which are physical properties as solubility, lipophilicity, electronic

effect, ionization and stereochemistry. The most studied descriptors are hydrophobic, electronic and steric. 26 cyclic urea derivatives of non peptidic PR-inhibitors have been used as study materials along with their observed biological activity in terms of log/Ki [9, 10].The structure of parent compound of cyclic urea derivatives is shown in Fig.1.

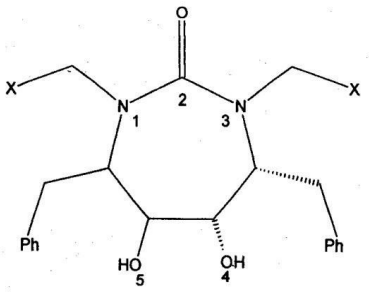

Fig. 1: Structure of Cyclic Urea Compound

In present work PM-3 has been used to calculate the quantum chemical descriptor for the 26 derivatives of non peptidic cyclic urea derivatives of protease inhibitor group.

Klopmann [11] provided a very useful parameter to describe the chemical reactivity of a compound with the help of atomic softness values in terms of $E_m^{\neq}$ and $E_n^{\neq}$. This concept was based on the charge and frontier orbital controlled chemical reaction of perturbation theory. Later the softness of an atom in a molecule further modified by Singh et al. [12-13] to make it applicable for a neutral chemical system. The Klopmann equation is given by:

$$E_m^{\neq} = IP_m - a^2(IP_m - EA_m) - \left[x_r(C_r^m)^2 / R_r\right](1 - 1/\in)[q_r + 2b^2 x_r(C_r^m)^2] \quad (1)$$

$$E_n^{\neq} = IP_n - b^2(IP_n - EA_n) - \left[x_s(C_s^n)^2 / R_s\right](1 - 1/\in)[q_s - 2b^2 x_s(C_s^n)^2] \quad (2)$$

The electron affinity values can be calculated by the following equation

$$EA = -(\in HOMO + \in LUMO) - (IP)$$

By using MLR equations and the predicted activity obtained by MLR analysis is compared with the observed biological activity and this resulted in achieving the best prediction power for the respective combination of descriptors [10].

The Klopmann atomic softness values $E_n^{\#}$ and $E_m^{\#}$, atom electron density, IP, EA, density distribution function and average atomic softness are the various descriptors used for preparing 50 combinations to be used for multiple linear regression analysis. We have compared the predicted activity obtained by the MLR analysis with the available literature values, which has resulted in achieving the best prediction power for the respective combination of descriptors [14].

3. RESULTS AND DISCUSSION

In the MLR analysis the regression equations are developed by the combination of two or three atomic descriptors viz atom electron density, fukui function, ionisation potential, electron affinity, softness values and density distribution function. These values are calculated for the five active sites of the urea derivatives. Excluding outlier compounds which do not show better regression results we have considered 50 3D QSAR models using MLR analysis with the help of various descriptors. The highest values of descriptors based on atomic properties of the compounds are given in the Table 1.

The QSAR models having significant results for cross validation coefficients and correlation coefficients with the combination of different descriptors are given in Table 2.

Table 1: Values of atomic descriptors based on atomic properties of compounds in MLR analysis

Compound	Highest $E_m^{\neq}$	Highest $E_n^{\neq}$	Atom Electron Density (AED)	Ionization Potential (IP)	Electron Affinity (EA)	Density Distribution Function (DDF)	Fukui Function	Activity
T1C1	16.259	-4.529	1.874	23.248	-14.186	12.900	0.234	5.240
T1C2	16.335	-4.855	1.872	23.518	-14.691	9.842	0.234	7.000
T1C3	16.315	-4.905	1.874	23.475	-14.666	12.900	0.234	8.100
T1C4	16.369	-5.003	1.873	23.609	-14.851	12.893	0.235	8.850
T1C5	16.318	-4.892	1.874	23.477	-14.657	12.899	0.234	8.800
T1C6	15.750	-7.286	1.872	23.565	-17.168	12.885	0.234	8.340
T1C7	16.315	-4.903	1.874	23.478	-14.672	12.898	0.234	6.590
T1C8	16.403	-4.890	1.874	23.602	-14.706	12.899	0.234	6.100
T1C9	16.133	-4.309	1.871	23.030	-13.960	12.880	0.234	5.960
T1C10	15.748	-3.653	1.869	22.236	-12.991	12.864	0.234	7.310
T1C11	16.152	-4.932	1.873	23.250	-14.612	12.897	0.234	7.920

T1C12	14.165	-3.814	1.874	23.598	-23.653	12.902	0.234	8.160
T1C13	16.379	-4.924	1.872	23.618	-14.816	12.885	0.234	7.520
T1C14	16.226	-4.757	1.871	23.342	-14.557	12.879	0.234	7.440
T1C15	16.378	-4.714	1.869	23.592	-14.691	12.865	0.234	8.280
T1C16	14.588	-1.308	1.811	20.534	-11.352	12.465	0.226	8.140
T1C17	16.226	-4.556	1.873	23.227	-14.236	12.893	0.232	7.660
T1C18	15.947	-3.792	1.869	22.576	-13.267	12.870	0.234	8.680
T1C19	16.482	-4.960	1.873	23.761	-14.872	12.893	0.234	8.890
T1C20	16.340	-4.842	1.874	23.491	-14.612	12.899	0.234	8.370
T1C21	16.368	-4.842	1.872	23.572	-14.716	12.884	0.234	7.430
T1C22	14.761	-2.008	1.807	21.203	-12.683	12.440	0.226	8.520
T1C23	15.496	-3.671	1.866	21.905	-12.929	12.848	0.233	6.840
T1C24	16.032	-3.284	1.868	22.530	-12.457	12.859	0.233	7.050
T1C25	15.935	-3.798	1.870	22.564	-13.262	12.871	0.234	7.070
T1C26	14.775	-2.886	1.862	20.572	-11.578	12.816	0.233	9.510

Table 2: Combination of descriptors and regression values

Model	Atomic Descriptors	Cross Validation coefficient r ^	Correlation coefficient ^{2}
TC12	-52.0334* AED+1.12734*IP+78.8736	0.374719	0.527176
TC17	1.12741* IP-7.55861*DDF+78.874	0.374642	0.527153
TC31	-47.2293* AED+9.63148*IP-0.549203*EA+72.9548	0.555787	0.724159
TC32	-8069.04* AED+1.11395*IP+1164.62*DDF+78.5434	0.275543	0.528917
TC33	-75.0046*AED+1.10762*IP+190.688*FF+77.715	0.346464	0.538043
TC34	0.963254*IP-0.0549296*EA-6.86123*DDF+72.9602	0.556158	0.724211
TC35	0.859446*IP-0.0562594*EA-328.852*FF+63.8845	0.493108	0.641017
TC38	-0.0480376* +1.03098*IP-7.4343*DDF+79.2676	0.135629	0.541102
TC46	-0.187519* - 49.0579*AED+1.15624*IP+75.6479	0.159365	0.540532

4. CONCLUSION

The correlation coefficient and cross validation values obtained using regression equation by the combination of atomic descriptors for the 50 TCs shows that the compound TC12,17,31,32,33,34,35,38&46 have good regression results as the values of $\hat{r}^2$ is more than 0.5. Among these compounds the decreasing order of protease inhibitor activity is found to be 34>31>35> 38>46>33>32>17>12.The replicative cycles of HIV 1 protease present several targets that could be explained for the development of anti-HIV chemotherapy. Therefore, this atomic descriptor based QSAR study and the result obtained thereafter may serve as a fine basis to design biologically active HIV protease inhibitor compounds of this class.

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