In-silico Comparative Study and Quantitative Structure-activity Relationship Analysis of Some Structural and Physiochemical Descriptors of Elvitegravir Analogs

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ABSTRACT

Elvitegravir is a new-generation drug which acts as an integrase inhibitor of the HIV virus. The potential inhibition has been tested from the clinical trial data. Here the work basically deals with the quantitative structure-activity relationship (QSAR) analysis by considering some of the physiochemical descriptors like molecular weight, logP, molar volume, and structural descriptors like Winers index, and molecular topological index of the drug analogs. The descriptors were calculated from the E-Dragon server and the multiple linear regression equation models were built by using Minitab tools. The different combinations of structural and physiochemical descriptors were considered for model derivation. The best three models were chosen by observing high R-Sq value, high F-value and low residual errors. The *P* values (regression) for the three models indicates the significance of the considered descriptors.The overall results obtained with these model suggest that for this perticular drug the activity is dependent on physiochemical descriptors.

Key words: Integrase inhibitor, multiple regression analysis, physiochemical descriptor, quantitative structure-activity relationship, structural descriptor

INTRODUCTION

According to the IAVI (International AIDS Vaccine Initiative) report almost 7000 people are newly infected with HIV, and the death rate per day is around 6000. Still it is in a pandemic state hence currently a great international concern.[1] Many potential drug molecules have been discovered to inhibit a specific part of the viral lifecycle as a current approach to control the disease.[2] An area of much recent progress has been that of HIV integrase inhibitor design. Integrase is an essential enzyme for viral replication, and it has no human homolog.[3] Integrase catalyzes the insertion of reverse-transcribed viral cDNA into the host cell genome via a multi-step process. The first step in integration occurs in the host cell cytosol and is referred to as 3' end processing. During this step, integrase cleaves a dinucleotide from each viral DNA terminus at a conserved sequence, yielding two reactive 3'

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hydroxyl groups. After this processing step a number of viral and cellular proteins form a complex which is known as pre-integration complex (PIC), and then migrates to the nucleus. Within the nucleus the reactive hydroxyl groups are utilized in nucleophilic attack upon the host cell genome, a process known as strand transfer.[4] Elvitegravir is a potential drug for HIV integrase enzyme inhibitor which is in its Phase III clinical trials.[5,6]

To analyze different potential drug molecules the quantitative structure-activity relationship (QSAR) method is a useful approach. QSAR is basically used to study the biological activities with various properties associated with the structures, which is helpful to explain how structural features in a drug molecule influence the biological activities. Also a successful in silico-based QSAR analysis provides the advantages of higher speed and lower costs for bioactivity evaluation as compared to experimental testing.[7] Therefore, correlating the physiochemical properties or structural features of the integrase inhibitor compounds with their biological activity will surely provide useful information for the design of new HIV drugs. To address this issue, an in silico approach has been adopted to calculate some selected physiochemical and structural descriptors of Elvitegravir analogs. Quantitative structural activity relationship study has been done by taking combinations of different physiological and structural descriptors by multiple linear regressions analysis to figure out the major molecular factor as associated with the activity of the drug molecule.

MATERIALS AND METHODS

All 26 analogs of the drug molecule Elvitegravir along with the IC50 value were obtained from the literature[8] and corresponding log IC50 values were calculated. The derivatives of the Elvitegravir molecules were drawn in Marvin sketch 5.0 tools.[9] Then the molecules were subjected to energy minimization by Prodrg server.[10] Prodrg is an online server where the energy minimization of the molecule was performed by using Gromos 96 force field. The various descriptors considered for the present work were molecular weight (MW), molar volume (MV), LogP (Octanol/Water partition co efficient) as physiochemical descriptors, and molecular topological index (MTI), Wiener index (WI), and total E-state topological parameter (TIE) as structural descriptors for the molecules. All these descriptors were calculated by the E-Dragon server.[11] The different combinations of the above two types of descriptors were subjected to multiple regression analysis by MINITAB 14 software.[12] For the best model selection various parameters like high F value, R-Sq and *P* value were chosen from regression analysis and equations were derived. From the equations the predicted and experimental log IC50 values were compared.

RESULTS

In the present study an attempt has been made to develop the best QSAR model to explain the correlation between the combined effect of physiochemical and structural

Table 1: The Elvitegravir drug analogs along with their Log IC50 value

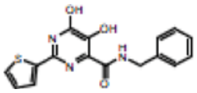
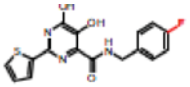
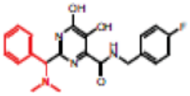
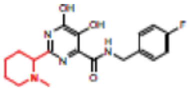
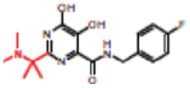
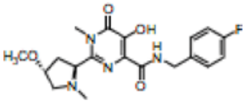
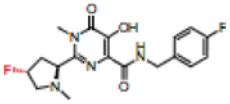
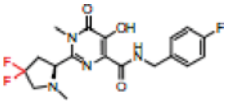
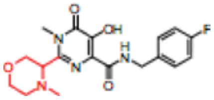
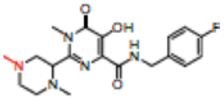
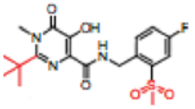
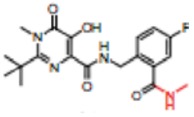
Structure	Log IC50 value
	0.90
	1.90
	1.0
	2.3
	2.3
	1.69
	2.25
	1.30
	1.47
	1.77
	2.0
	1.30

Table 1 contd.