Study of Pyrimidine-4-carboxamide Derivatives as HIV-1 Integrase Inhibitors Using QSAR and DFT Calculations

B. Elidrissi, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco
A. Ousaa, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco
M. Ghamali, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco
S. Chitita, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco
M. A. Ajana, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco
M. Bouachrine, High School of Technology, University Moulay Ismail, Meknes, Morocco
T. Lakhlifi, MCNS Laboratory, Faculty of Science, University Moulay Ismail, Meknes, Morocco

ABSTRACT

A Quantitative Structure–Activity Relationship (QSAR) study was performed to predict HIV-1 integrase inhibition activity (pIC\textsubscript{50}) of thirty-five 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamide compounds using the electronic and physico-chemical descriptors computed respectively, with Gaussian 03W and ACD/ChemSketch programs. The structures of all compounds were optimized using the hybrid Density Functional Theory (DFT) at the B3LYP/6-31G(d) level of theory. In both approaches, 28 compounds were assigned as the training set and the rest as the test set. These compounds were analyzed by the principal components analysis (PCA) method, the descendant Multiple Linear Regression (MLR) analyses and the Artificial Neural Network (ANN). The robustness of the obtained models was assessed by leave-many-out cross-validation, and external validation through a test set. This study shows that the MLR has served marginally better to predict pIC\textsubscript{50} activity, when compared with the results given by predictions made with a (4-3-1) ANN model.

KEYWORDS
Artificial Neural Network, Cross-Validation, DFT, HIV-1 Integrase Enzyme, QSAR

INTRODUCTION

Integrase is an enzymatic protein produced by RNA retroelements such as retroviruses or retrotransposons. It catalyses the integration step of the replicative cycle of these infectious agents. The foreign DNA is thus “integrated” into the genome of the host organism. This enzyme is particularly studied because it constitutes a therapeutic target of great interest for the treatment of infections by human retroviruses such as the AIDS virus (HIV) (Grinsztejn, 2007).

HIV infects the human immunity system when the viral genome penetrates the nuclear genome of vital cells. It then works through a recombination process catalyzed by the virus-encoded enzyme integrase. According to recent clinical findings, HIV integrase plays an important role during the HIV life cycle. However, the principal problem faced by antiretroviral drugs is emergence of drug resistant HIV strain and hence drug combination therapy, termed as highly active antiretroviral therapy.

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(HAART), was introduced (Moore & Chaisson, 1999). HIV integrase is a potential enzyme target for antiretroviral therapy (Moore & Chaisson, 1999; Li et al., 2015). It plays a specific role to mediate integration of viral DNA formed by reverse transcriptase from RNA template into host DNA. In the process of integration, the integrase enzyme along with several proteins binds on viral DNA to form pre-integration complex (PIC). The integrase enzyme in PIC cleaves off homologous dinucleotide from each 3’ end of viral DNA. This cleavage creates a reactive intermediate with 3’ hydroxyl group which is followed by strand transfer reaction. During this transfer generated by the last reaction, the 3’ hydroxyl group formed during 3’ processing attacks the opposite end of host DNA and forms a new bond. Hence, viral DNA is integrated into host DNA (Pommier et al., 2005). Now, there exist three integrase inhibitors approved by US-FDA: Dolutegravir approved in 2013, Elvitegravir was approved in August 2012 for use in adult patients starting HIV treatment for the first time and Raltegravir was approved by the FDA in October 2007 (Ribeiro et al., 2012). Resistance to Raltegravir and occasionally to Elvitegravir is identified (Gu, 2014). Dolutegravir is the only second-generation strand transfer integrase inhibitor approved by FDA for a large population of HIV-positive patients. Since August 2013, it has also been expected to treat HIV-2 infection (Charpentier et al., 2008).

In the current study, the authors have modeled the HIV-1 integrase inhibitor of 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamide derivatives with different substitutions (Table 1), using several statistical tools namely Principal Components Analysis (PCA), Multiple Linear Regression (MLR) and Artificial Neural Network (ANN) calculations (Shah et al., 2014). Using the Quantitative Structure–Activity Relationship (QSAR) method, the activities of chemical compounds can be determined from their molecular structures (Goodarzi et al., 2009). Thus, based on accurate experimental data of only some of the chemicals in one group, the biological activity of chemicals in the whole group can be predicted using the suitable models, including compounds that have not been experimentally synthesized yet (D J. et al., 1991; Burden et al., 2000).

The objective of this work is to develop predictive QSAR models of the HIV-1 integrase inhibitor activity of our studied molecules. Thus, a number of quantum chemical methods and calculations have been performed in order to study the molecular structure and their inhibitor activity (Sakar et al., 2004).

**MATERIAL AND METHODS**

**Material**

To find the quantitative relationship between molecular structure and HIV-1 integrase inhibitory activity for the data taken by Yu and Zhang (Yu et al., 2013; Zhang et al., 2014), the authors of this paper adopted the Multiple Linear Regression (MLR) and Artificial Neural Network (ANN). The training set was used to construct QSAR models and the test set to validate the external prediction ability of the resulting QSAR models. The authors calculated the electronic descriptors by Gaussian 03 software to generate QSAR sets. To select the structural features of the molecules relevant to the HIV-1 integrase inhibitor activity and to construct the linear models, the authors utilized the MLR. ANN was used to develop nonlinear models. Both models were validated by an internal validation methods including cross-validation to characterize robustness and external validation to estimate the predictive power of the models. Finally, the ultimate objective was to establish reliable QSAR models with an aim to design a novel HIV-1 integrase inhibitor prediction of 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamide derivatives. The developed models can be used for prediction purpose. Also, the methods can deliver / yield examinable data sets which contain structurally different compounds containing slightly different scaffolds than originally present among the training set compounds. However, the limitation of this technique is that the models are only predictive within the applicability domain, which has been covered by substructures of sufficient variation (Tommy et al., 2003).
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