In search for new and promising coumarin compounds as HIV-1 integrase inhibitors, chemoinformatic methods like quantitative structure-activity relationships (QSAR) modeling and molecular docking have an important role since they can predict desired activity and propose molecule binding to enzyme.

The aim of this study was building of QSAR models for coumarin derivatives as HIV-1 integrase inhibitors with the application of Monte Carlo method. SMILES notation was used to represent the molecular structure and for defining optimal SMILES-based descriptors. Molecular docking into rigid enzyme active site with flexible molecule was performed.

Computational results indicated that this approach can satisfactorily predict the desired activity with very good statistical significance. For best built model statistical parameters were: a) 3' Processing activity: $R^2=0.9980$ and $Q^2=0.9977$ for training set and $R^2=0.9788$ for test set and b) Integration activity: $R^2=0.9999$ and $Q^2=0.9998$ for training set and $R^2=0.9213$ for test set. Built QSAR models were applied to selected 4-phenyl hydroxycoumarins for calculating desired activity and for HIV-1 integrase inhibition estimation. Additionally, molecular docking study was performed to a newly identified pocket in the HIV-1 integrase enzyme structure for determination of selected 4-phenyl hydroxycoumarins binding mode.

Monte Carlo method proved to be an efficient approach to build up a robust model for estimating HIV-1 integrase inhibition of coumarin compounds. Based on QSAR and molecular docking studies, 4-phenyl hydroxycoumarins can be considered as promising model compounds for developing new HIV-1 integrase inhibitors.

**Key words:** coumarins, HIV-1 integrase inhibition, QSAR, molecular docking
INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), reported in 1981 (1), is a fatal disorder resulting from a chronic persistent infection by the human retrovirus, human immunodeficiency virus (HIV) (2). Today, AIDS is considered as one of the most devastating diseases faced by mankind, with an estimation of 34 million people living with HIV worldwide at the end of 2010 according to Joint United Nations Programme on HIV/AIDS (3). Up to now, successful chemotherapy has not been developed. Currently, Reverse Transcriptase (RT) and Protease (PT) inhibitors are the main targets for the majority of available drugs for HIV treatment. However, toxicity and rapid development of resistance to these inhibitors are the main issues related to the current therapy (4). Therefore, the development of new anti-HIV agents with varied structure and mechanisms of action is of great importance. HIV-1 integrase (HIV-1IN) is a very attractive and unexplored target for developing of new anti-HIV drugs as it plays a vital role in replication cycle and it has no cellular counterpart (5-7).

Various compounds exhibit HIV-1IN inhibitory activity, including lignanolides (8), curcumin (9), aurintricarboxylic acids (10), dicaffeoyl quinic acids and analogues (11, 12), diaryl sulfones (13). Unfortunately, all of stated inhibitors have the 1,2-dihydroxy (catechol) moiety, separated by an appropriate linker, so all of them have significant cytotoxicity because of catechol moiety autoxidation to reactive quinone species (14, 15). To overcome this problem, a series of coumarin derivatives which do not contain catechol functionality but possess good HIV-1IN inhibition activity was synthesized (16).

The importance of quantitative structure-reactivity relationship (QSAR) studies in modern drug design is well established since QSAR can make the early prediction of activity-related characteristics of drug candidates and can eliminate molecules with undesired properties (17). The main goal of QSAR approach is to correlate the biological activity of a series of compounds with the calculated molecular properties in terms of descriptors (18). Thousands of molecular descriptors are used in QSAR studies for the purpose of encoding molecules chemical and structural features (19, 20) with great importance of topological descriptors calculated on the basis of molecular graphs (21). The simplified molecular input line entry system (SMILES) is an alternative to molecular graphs and it can be used for representation of molecular structures (22). Recent papers have reported the applicability of SMILES based descriptors in QSAR analysis with models built on the basis of Monte Carlo method (23-27). Several QSAR studies dealing with coumarin compounds as HIV-1IN inhibitors are reported (28-31).

The aim of this research is to build QSAR modes for coumarin derivatives as HIV-1IN inhibitors with SMILES based optimal descriptors and application of Monte Carlo method by using CORAL software. Built QSAR models were applied to selected 4-phenyl hydroxycoumarins with good antioxidant properties (32) but with no literature data about their HIV-1IN inhibition activity. Further, docking study is performed to a newly identified pocket right behind catalytic core domain (CCD) helix 4 (33) in the HIV-1IN enzyme for determining the possible binding mode of selected 4-phenyl hydroxycoumarins.

METHOD

Data. A dataset of 26 coumarin derivatives with determined HIV-1 integrase inhibition activity was selected for QSAR study (16). Figure 1 presents general structures of used coumarin compounds for QSAR modeling. As an endpoint for QSAR model building pIC₅₀ for enzyme 3’ processing and integration was used.

Figure 1. General molecular structures of used molecules

Canonical SMILES for all compounds were generated with the ACD/ChemSketch program (ACD/Chem Sketch v.11.0) in order to preserve consistency because different software may generate different SMILES notations. One random split into the training and test set was examined (20% of molecules are taken as test compounds). The role of the training set is in developing of the model. The role of test set is selection of preferable values for the number of epoch of the Monte Carlo optimization and the threshold value.

Optimal descriptors. SMILES is a representation of the molecular structure by sequence of symbols. Some symbols represent molecular fragments, such as atoms or bonds (e.g. ‘C’, ‘N’, ‘=’, ‘#’, etc.). Some of these fragments are represented by two symbols (e.g. ‘Br’, ‘Cl’, ‘@@’, etc.) which cannot be separated. Optimal SMILES-based descriptors, determined by descriptor correlation weight (DCW(T,Nepochs)), were calculated with CORAL software (http://www.insilico.eu/coral) as:

\[
\text{DCW}(T,N_{epochs}) = \alpha \Sigma \text{CW}(Sk) + \beta \Sigma \text{CW}(SSk) + \gamma \Sigma \text{CW}(SSSk)
\]  

where Sk, SSk, and SSSk are one-, two-, and three-component SMILES attributes, respectively; the component of SMILES attribute is SMILES symbol previously defined (27).

Two parameters in Eq. 1 should be defined for the Monte Carlo optimization: threshold (T) and the number of epochs (Nepochs). The classification of components of the representation of the molecular structure into two classes is done with the following criteria: rare and active which is defined with the T. The correlation weight of a rare component is fixed as zero, because this component brings noise to the model, so rare component is discarded from building up of the model and T is zero. The Nepochs is the number of epochs of the Monte Carlo
optimization (one epoch is the cycle of modifications of all correlation weights involved in the model). The predictive potentials of the model are mathematical functions $T$ and $N_{\text{epoch}}$ in the Monte Carlo optimization. The searches for the most predictive combination of $T$ and $N_{\text{epoch}}$ were concluded from values 0-7 for $T$ and 0-70 for $N_{\text{epoch}}$, for all models, according to previously published methodology (23-27).

Having numerical data on these correlation weights (CW) one can calculate DCW ($T$, $N_{\text{epoch}}$) for compounds of training and test set. Least squares method was used to calculate endpoint from these data.

$$\text{Endpoint} = C_0 + C_1 \times \text{DCW}(T, N_{\text{epoch}})$$

Molecular docking. 3D structures of the compounds for docking simulation were constructed using MarvinSketch 6.1.0, 2013, ChemAxon (http://www.chemaxon.com). Geometry optimization was carried out by employing MMFF94 molecular force field (34). To date, no full strength structure of HIV-1IN is available to elucidate the spatial arrangement of its three domains: N-terminal (NTD), catalytic core (CCD) and C-terminal (CTD). In the field of the development of allosterically targeted HIV-1IN inhibitors a new advantageous approach for the discovery of compounds effective against HIV-1IN strand-transfer drug-resistant viral strains has been proposed recently (35). A new site in integrase, a valid region for the structure-based design of allosteric integrase inhibitors, has been identified using a structure-based design process (protein data bank code: 3NF7) (33). The compounds were docked into enzyme binding sites using the MolegroVirtual Docker (MVD) (36). The Molegro Virtual Docker (MVD v. 2013.6.0.1.) software was employed for docking ligands to the rigid enzyme model for identification of hydrogen bonds and hydrophobic interactions between residues at the active site. The binding site was computed with a grid resolution of 0.3 Å. The MolDock SE as a search algorithm was used and the number of runs was set to 100. The parameters of docking procedure were: population size 50, maximum number of iterations 1500, energy threshold 100.00 and maximum number of steps 300. The number of generated poses was 10. The estimation of ligand–receptor interactions was described by the MVD-related scoring functions: MolDock Score, Rerank Score, Hbond Score, Similarity Score, and Docking Score. The ligand was docked into computed cavity instead ligand from 3NF7 using the MolDock Optimizer algorithm and its interactions were monitored using detailed energy estimates. A maximum population of 100 and maximum iterations of 10,000 were used for each run and the 5 best poses were retained.

RESULTS

The chemical structures represented with SMILES notation, the experimental activity for 3’ Processing and Integration (expr) data, the calculated data (calc) with CORAL and difference (diff) between expr and calc are presented in Table 1. Statistical criteria of the predictability of the models are represented in Table 2 (37).

Using Eq. 2 for predicting $pIC_{50}$, following equations were calculated from best Monte Carlo runs:

3’ Processing:

$$pIC_{50} = 1.8584 \pm 0.0036 + 0.0187 \pm 0.000215 \times \text{DCW}(0,3)$$

Integration:

$$pIC_{50} = 2.5636 \pm 0.0004 + 0.0180 \pm 0.0000034 \times \text{DCW}(0,3)$$

Built QSAR models were applied for predicting $pIC_{50}$ values of selected 4-phenyl hydroxycoumarins (7-hydroxy-4-phenyl coumarin (7C), 5,7-dihydroxy-4-phenyl coumarin (5,7C) and 7,8-dihydroxy-4-phenyl coumarin (7,8C)) with good antioxidant properties (32) but with no literature data about their HIV-1IN inhibition activity. Eq. 3 and Eq. 4 were applied for calculation of $pIC_{50}$ for enzyme 3’ Processing and Integration for selected 4-phenyl hydroxycoumarins. Calculated values and molecular structures of used coumarin derivate are presented in Table 3.

Monte Carlo method can be used for classification of molecular features (SAk) calculated with SMILES notation based descriptors. The list of the SAk together with correlation weights for the three probes of the Monte Carlo optimization for all enzyme activities is given in the Table 4.

In order to gain insight into the plausible mechanism for 3’ Processing and Integration actions docking simulations were performed for 7C, 5,7C and 7,8C. Figure 2 presents the best docking poses for all investigated coumarins inside enzyme binding pocket.

Two dimensional representation of the best docking poses for all investigated coumarins inside enzyme binding pocket are shown in Figure 3 (38).
| SMILES NOTATION | DCW | Expr | Calc | Diff (DCW) | Expr | Calc | Diff |
|-----------------|-----|------|------|------------|------|------|------|
| 1 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 133.901 | 4.367 | 4.362 | 0.005 | 130.045 | 4.411 | 4.423 | -0.012 |
| 2 Oc1ccc(cc1)(C2=C(O)c3ccc3cO2=C(O)c4=C(O)c5ccccc5cO4=C=0)C(=O)Oc5c6ccc5 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 3 Oc1ccc(cc1O)c2=C(O)c3ccc3cO2=C=Oc4=C(O)c5ccccc5cO4=C=0)C(=O)Oc5c6ccc5 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 4 CN(c1ccc(cc1)c2=C(O)c3ccc3cO2=C(O)c4=C(O)c5ccccc5cO4=C=0)C(=O)Oc5c6ccc5 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
| 5 [O-][N+](=O)c1ccc(cc1)c2=C(O)c3ccc3cO2=C=Oc4=C(O)c5ccccc5cO4=C=0)C(=O)Oc5c6ccc5 | 130.123 | 4.301 | 4.289 | 0.012 | 156.225 | 4.921 | 4.925 | -0.004 |
| 6 O=C1ccc(cc1)c2=C(O)c3ccc3cO2=C=Oc4=C(O)c5ccccc5cO4=C=0)C(=O)Oc5c6ccc5 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 7 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 133.901 | 4.367 | 4.362 | 0.005 | 130.045 | 4.411 | 4.423 | -0.012 |
| 8 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 9 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 10 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
| 11 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 130.123 | 4.301 | 4.289 | 0.012 | 156.225 | 4.921 | 4.925 | -0.004 |
| 12 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 13 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 14 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
| 15 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 130.123 | 4.301 | 4.289 | 0.012 | 156.225 | 4.921 | 4.925 | -0.004 |
| 16 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 17 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 18 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
| 19 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 130.123 | 4.301 | 4.289 | 0.012 | 156.225 | 4.921 | 4.925 | -0.004 |
| 20 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 21 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 22 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
| 23 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 130.123 | 4.301 | 4.289 | 0.012 | 156.225 | 4.921 | 4.925 | -0.004 |
| 24 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 112.152 | 3.893 | 3.956 | -0.063 | 117.992 | 4.131 | 4.191 | -0.06 |
| 25 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 101.154 | 3.752 | 3.75 | 0.002 | 114.24 | 4.119 | 4.119 | 0 |
| 26 OC=1c5ccc5cO5(=O)C=1C(C2=C(O)c3ccc3cO2=C=O)c4c6ccc4 | 116.902 | 4.055 | 4.044 | 0.011 | 123.728 | 4.301 | 4.301 | 0 |
### Table 2. Statistical quality of built QSAR models

|          | 3' PROCESSING |          | INTEGRATION |          |          |          |          |          |          |          |          |          |          |          |
|----------|---------------|----------|-------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|          | Training      | Test     | Training    | Test     | Training | Test     | Training | Test     | Training | Test     | Training | Test     | Training | Test     |
|          | R²            | Q²       | s           | R²       | r_m (av)² | ∆r_m²   | s         | R²       | Q²       | s         | R²       | r_m (av)² | ∆r_m²   | s         |
| 1        | 0.9993        | 0.9992   | 0.020       | 0.9671   | 0.8083   | 0.0577   | 0.305     | 0.9999   | 0.9998   | 0.010     | 0.9185   | 0.5230   | 0.1825   | 0.248     |
| 2        | 0.9977        | 0.9974   | 0.033       | 0.9368   | 0.6138   | 0.1677   | 0.265     | 0.9999   | 0.9998   | 0.005     | 0.9213   | 0.5678   | 0.2041   | 0.268     |
| 3        | 0.9980        | 0.9977   | 0.032       | 0.9788   | 0.6213   | 0.1467   | 0.341     | 0.9999   | 0.9998   | 0.008     | 0.9186   | 0.5798   | 0.1965   | 0.239     |
| Av       | 0.9983        | 0.9981   | 0.028       | 0.9609   | 0.6811   | 0.1240   | 0.304     | 0.9999   | 0.9998   | 0.008     | 0.9195   | 0.5569   | 0.1945   | 0.252     |

Av is average value from three independant Monte Carlo runs (1, 2 and 3)

R² is correlation coefficient

Q² is cross-validated correlation coefficient

s is standard error of estimation

r_m (av)² should be > 0.5 (37)

Δr_m² should be < 0.2 (37)

### Table 3. Molecular structures of used coumarin derivates with calculated pIC₅₀ values for enzyme 3' Processing and Integration activities using Eq. 3 and 4.

![Molecular Structure](image)

| Molecule | R₁  | R₂  | R₃  | pIC₅₀ (3' Processing) | pIC₅₀ (Integration) |
|----------|-----|-----|-----|-----------------------|--------------------|
| 7C       | H   | OH  | H   | 3.329                 | 3.640              |
| 5,7C     | OH  | OH  | H   | 3.138                 | 3.451              |
| 7,8C     | H   | OH  | OH  | 3.259                 | 3.402              |
Table 4. The list of the SAk with correlation weights for three independent Monte Carlo optimization runs for best QSAR model

| SAk | Run 1 | Run 2 | Run 3 | SAk | Run 1 | Run 2 | Run 3 |
|-----|-------|-------|-------|-----|-------|-------|-------|
| n......... | -3.997 | -3.248 | -5.004 | n...c...c... | -3.999 | -3.002 | -2.497 |
| s...c...c... | -1.002 | -1.502 | -4.005 | n........ | -2.998 | -2.248 | -2.247 |
| N...+.... | -0.745 | -1.252 | -0.004 | O...C...=... | -1.253 | -0.996 | -1.245 |
| C...(...C... | -0.502 | -1.249 | -0.999 | O...=...(... | -1 | -0.998 | -0.998 |
| N...(...C... | -0.496 | -1.246 | -2.251 | O...=......... | -0.496 | -0.997 | -1.005 |
| O...(...C... | 0.252 | 1.003 | 1.25 | c...O....... | 0.245 | 0.753 | 1.001 |
| c........ | 0.504 | 0.746 | 0.998 | O...C... | 0.502 | 0.996 | 0.999 |
| o........ | 0.997 | 0.996 | 0.997 | C.../...... | 0.997 | 0.504 | 0.004 |
| C...=....... | 4.254 | 4.5 | 2.748 | c...C...... | 1.001 | 1.501 | 1 |
| C...C....... | 4.5 | 3.496 | 3.497 | C...{...... | 1.505 | 0.747 | 0.998 |

Figure 2. Surface diagram showing docked selected 4-phenyl hydroxycoumarins

Figure 3. Two dimensional representations of the best docking pose for a) 7-hydroxy-4-phenyl coumarin, b) 5,7-dihydroxy-4-phenyl coumarin and c) 7,8-dihydroxy-4-phenyl coumarin inside binding pocket
DISCUSSION

QSAR study

Results from Table 2 show that the predictability for all models is good. Also, the results are satisfactory from the point of view of new criteria (37).

The correlation weights for molecular features calculated with SMILES can be used for classification of the aforementioned features according to their values from three probes for defined Monte Carlo model. They could be divided into three categories: features with stable positive values of correlation weights (promoters of increase of an endpoint); features with stable negative values of correlation weights (promoters of decrease of an endpoint); and unstable features which have positive values of correlation weights together with negative correlation weights values for several models (26, 27). For example, if the correlation weight of Sk CW(Sk) is >0 in all three runs of the optimization, then the Sk is promoter of Ac increase. However, if CW(Sk) is <0 in all three runs of the optimization, then the Sk is promoter of Ac decrease. In the end, if there are both CW(Sk) >0 and CW(Sk) <0, or Sk is blocked in three runs of optimization then Sk has an undefined role. Same rule is applied for all SAk. It must be noted that SAk have mechanistic interpretation and according to presented results from Table 4 SAk can be classified as following. For example, for 3’ Processing ‘n………………’ , ‘N...+………’ and ‘C...(...C...’ are promoters of decrease while ‘C...C………’ , ‘C...=………’ and ‘o………………’ are promoters of increase. ‘n………………’ can be interpreted as aromatic nitrogen atom, ‘N...+………’ as sp2 nitrogen atom with positive charge and ‘C...(...C...’ as sp3 carbon atoms with branching. ‘C... C………’ can be interpreted as two sp3 carbon atoms without branching, ‘C...=………’ as sp3 carbon atom since ‘=’ is a symbol for double bond, ‘o………………’ as aromatic oxygen atom.

Molecular docking

The results of molecular docking studies are presented in Figure 2 and 3. On the surface diagram (Figure 2) it can be seen that hydrophobic parts of the molecules are oriented toward the hydrophobic parts of the enzyme binding pocket (red colored surface). Two dimensional representations of the best docking pose for selected coumarins (Figure 3) give a more detailed insight into the interactions with particular amino acids in enzyme binding pocket. Based on the presented results, it can be concluded that hydrophobic interactions between investigated coumarins and binding pocket play an important role.

However, number, bond length and bond energy of hydrogen bonds formed between ligand and enzyme has an important role in ligand effect on investigated activity. It was observed from in silico studies of compounds binding to 3NF7 that 7C oxygen from carbonyl group forms hydrogen bond with Asn-144 (bond length 4.67 Å). 5,7C does not form any hydrogen bonds with enzyme. Compound 7,8C hydroxyl group in position 8 forms three hydrogen bonds, two with Ser-147 (2.19 Å and 4.59 Å) and one with Asn-144 (4.23 Å). Oxygen from carbonyl group forms one with Asn-144 (4.69 Å) and sp3 oxygen one with Tyr-143 (3.55 Å).

CONCLUSION

QSAR models for coumarin compounds as potent HIV-1 integrase inhibitors were built. Monte Carlo method proved to be an efficient tool to build up a robust model for estimating HIV-1 integrase inhibition. For suggested modeling process optimal descriptors were based on SMILES notation. The predictive potential of the applied approach was tested with one split into the training and test set. The robustness of model was confirmed with different methods. The SMILES attributes which are promoters of increase/decrease of HIV-1 integrase inhibition were identified. Built QSAR models were applied to selected 4-phenyl coumarins for inhibition prediction. Further, the correlation between calculated inhibitory activity and the in silico molecular docking scores of these compounds was obtained through hydrogen bonding interactions. Our results suggest that 4-phenyl hydroxycoumarins may be considered as good molecular templates for potential HIV-1 integrase inhibitors.

Acknowledgment

This work has been financially supported by Ministry of Education and Science, Republic of Serbia, under Project Numbers OI 172044 and TR 31060.

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QSAR MODELOVANJE DERIVATA KUMARINA KAO POTENTNIH INHIBITORA HIV-1 INTEGRAZE BAZIRANO NA MONTE KARLO METODI I STUDIJE MOLEKULARNOG DOKINGA ODABRANIH 4-FENIL HIDROXIKUMARINA

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Sažetak

U potrazi za novim i obećavajućim kumarinskim jedinjenjima koja su inhibitori HIV-1 integraze veoma značajnu ulogu imaju hemoinformatičke metode, kao što je modelovanje kvantitativnog odnosa strukture i aktivnosti (QSAR) i molekularni doking, jer mogu da predvide željenu aktivnost i objasne način vezivanja molekula za enzim. Cilj ovog rada bio je uspostavljanje QSAR modela za derivate kumarina kao inhibitore HIV-1 integraze korišćenjem Monte Karlo metode. SMILES notacija je korišćenja kao reprezentacija molekulske strukture i za definisanje optimalnih deskriptora baziranih na SMILES notaciji. Primjenjen je i molekularni doking u kruto aktivno mesto enzima sa fleksibilnim molekulom. Rezultati kompjuterske studije ukazuju da ovaj pristup može na zadovoljavajući način da predvidi željenu aktivnost sa veoma dobrom statističkom značajnošću. Za najbolji model statistički parametri su bili: a) “3’ Processing” aktivnost: R²=0.9980 i Q²=0.9977 za skup molekula koji su korišćeni za konstruisanje modela (trening set) i R²=0.9788 za skup molekula koji su korišćeni za proveru modela (test set) i b) “Integration” aktivnost: R²=0.9999 i Q²=0.9998 za trening set i R²=0.9213 za test set. Uspostavljeni QSAR modeli su primjenjeni na odabrane 4-fenil hidroxikumarine radi izračunavanja željene aktivnosti u cilju procene inhibicije HIV-1 integraze. Dodatno je urađena doking studija u novom identifikovanom džepu unutar strukture enzima HIV-1 integraze radi određivanja načina vezivanja ispitivanih 4-fenil hidroxikumarina.

Monte Karlo metoda se pokazala kao efikasan pristup u uspostavljajući robusnog modela za procenu inhibicije HIV-1 integraze od strane kumarinskih jedinjenja. Na osnovu rezultata QSAR i doking studija, 4-fenil kumarini se mogu oarakterisati kao dobra model jedinjenja za razvijanje novih inhibitora HIV-1 integraze.

Ključne reči: kumarini, Inhibitori HIV-1 integraze, QSAR, molekularni doking