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Anticancer Drug Design: Development of Cyclin-Dependent Kinase Inhibitors Using In Silico Techniques

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ABSTRACT

In mammalian cells, proliferation is controlled by the cell cycle, where cyclin-dependent kinases regulate critical checkpoints. CDK4 is considered highly validated anticancer drug target due to its essential role regulating cell cycle progression at the G1 restriction point. Our objective is designing novel CDK4 inhibitors using Structure-Based Drug Design and Quantitative Structure-Activity Relationship techniques. We used bioinformatics tools and biological databases. QSAR study of CDK4 inhibitors has given us an idea on the physicochemical features of studied compounds and their correlation with the IC_{50} activity. The docking study has helped to highlight the molecule key elements to refine in order to get a more potent compound of CDK4.The Molecule under the code 21366124 which has the low IC_{50}= 3 nmole shows the most binding affinity with score value of ΔG=-9,8 kcal/mol. As prospects, it would be very interesting to synthesize this drug candidate and to test its inhibitory activity on cell culture of breast cancer.

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Introduction

The strategy of Structure-Based Drug Design (SBDD) has accelerated many drug discovery projects and already yielded several promising anticancer leads acting towards different targets, including Cyclin-Dependent-Kinases (CDKs) [1]. The Quantitative Structure-Activity Relationship (QSAR) techniques have been widely used for predicting a broad spectrum of biological activities [2]. Protein kinases are key enzymes in regulatory signals of major physiological functions. Dysfunction of these proteins is often associated with diseases such as cancer, inflammatory or neuro-degenerative diseases. That's why protein kinases have become essential therapeutic targets [3]. Sustained proliferative capacity is a hallmark of cancer. In mammalian cells, proliferation is controlled by the cell cycle, where CDKs regulate critical checkpoints. CDK4 is considered highly validated anticancer drug target due to its essential role regulating cell cycle progression at the G1 restriction point [4].

In this study, our main objective is to identify new anticancer drug candidates, using the SBDD and QSAR techniques for designing novel CDK4 inhibitors.

Materials and Methods

The present study combines ligand-based drug design and structure-based drug design approaches. In one hand, 2D quantitative structure activity relationship (2D-QSAR) was used to generate models from 83 compounds belonging to CDK4 inhibitors and separated to training and test sets. Validation of the QSAR models was judged by root-mean-square error (RMSE) and the correlation factor (R^2) [5-7].

In the other hand, docking studies of six inhibitors were carried to determine their binding mode into the active site of CDK4 and to interpret the efficacy of molecules that's capable to inhibit CDK4 [8,9].

We used software's of SBDD and QSAR there are based on molecular modeling techniques and in silico virtual screening [9,10].

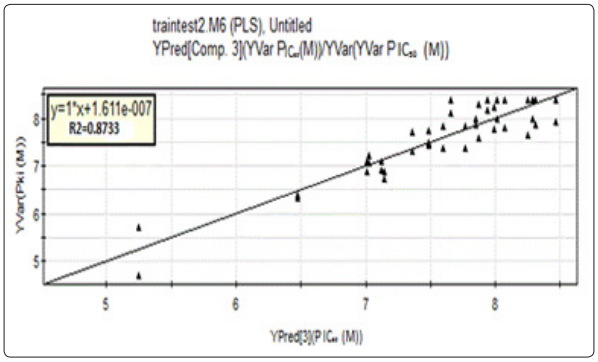

Figure 1: Linear correlation plots of 2D-QSAR

Results and Discussion

2D-QSAR Study

2D-QSAR study was performed in order to find a mathematical correlation between the structure and physicochemical properties of CDK4 inhibitors and their inhibitory activity that was expressed as PIC_{50} (-log IC_{50}).

The model I showed in Figure 1 exhibited a correlation between the experimentally observed and predicted values of CDK4 inhibitors. The resultant correlation regression analysis plot showed a linear relationship in model I with RMSE=0.2458, R=0.9345 and R^2=0.8733. No molecule was an outlier in the database using MOE's plotting applications in the model. we have also verified that the model is valid with R2 = 0.15 and Q2 = - 0.37 (Figure 2).

The correlation coefficient between the experimental observed and predicted value of test set compounds of inhibitors was 0,70.

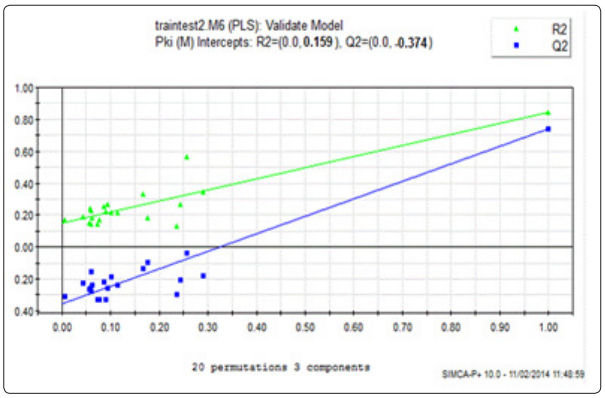

Figure 2: Model validation

Molecular Docking Study

Figure 3 shows the 3D crystal structure of CDK4 extracted from PDB (Code: 4DHU)

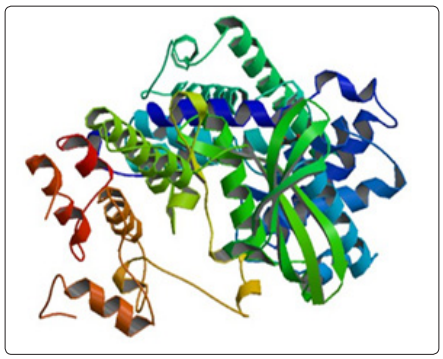

Figure 3: 3D crystal structure of CDK4

The Coumpond under the code 21366124 is successfully docked in the active site of CDK4. Its IC_{50}= 3 nmole and its binding energy= -9.8 Kcal /mol, therefore, it proved the most affine. It formed three hydrogen bonds with the residues: Arg136, Thr165 and Asp73 whose lengths: 3.04 A°, 2.94 A° and 2.92 A°. Three hydrophobic pockets formed and interaction pi-Stacking between imidazole nucleus of ligand and pyrrolidine nucleus of L-proline amino acid (Figure 5).

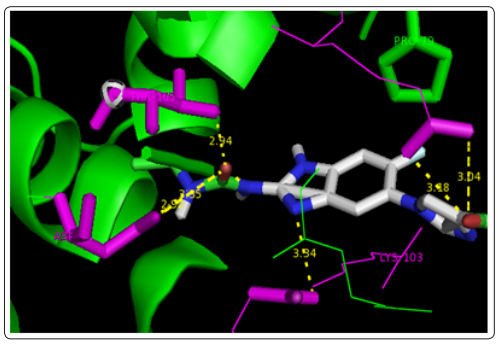

Figure 4: Interaction between CID 21366124 and CDK4

and Figure 4 shows the selected target site of CDK4, the magenta spheres represent where the molecular docking was focused.

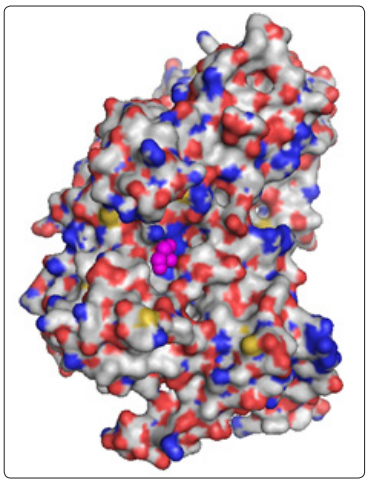

Figure 5: selected target site of CDK4

Conclusion

We have performed a structure-activity relationships study of CDK4 as potential therapeutic target. QSAR study of CDK4 inhibitors has given us an idea on the physicochemical features of studied compounds and their correlation with the IC_{50} activity. Furthermore, the docking study has helped to highlight the molecule key elements to refine in order to get a more potent compound of CDK4.

The Molecule under the code 21366124 which has the low IC_{50}= 3 nmole shows the most binding affinity with score value of ΔG=-9,8 kcal/mol and it presents the best interactions and energy score testifying the complex stability. As prospects, it would be very interesting to synthesize this drug candidate and to test its inhibitory activity on cell culture of breast cancer.

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