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Research Article

3D QSAR Pharmacophore Based Virtual Screening for Identification of Potential Inhibitors for CDC25B

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ABSTRACT

Owing to its fundamental roles in cell cycle phases, the cell division cycle 25B (CDC25B) was broadly considered as potent clinical drug target for cancers. In this study, 3D QSAR pharmacophore models for CDC25B inhibitors were developed by the module of Hypogen. Three methods (cost analysis, test set prediction, and Fisher's test) were applied to validate that the models could be used to predict the biological activities of compounds. Subsequently, 26 compounds satisfied Lipinski's rule of five were obtained by the virtual screening of the Hypo-1-CDC25B against ZINC databases. It was then discovered that 9 identified molecules had better binding affinity than a known CDC25B inhibitors-compound 1 using docking studies. The molecular dynamics simulations showed that the compound had favorable conformations for binding to the CDC25B. Thus, our findings here would be helpful to discover potent lead compounds for the treatment of cancers.

1. INTRODUCTION

Cancer is a set of disease characterized by indisciplinable cell division leading to the growth of unusual tissue. There were about 12.7 million cancer patients in 2008. The morbidity of cancer patients will increase 50% before 2020 (Han et al., 2007; The World Cancer Report, 2003). Therefore, the development of specific anticancer drugs is pressing.

CDC25B becomes key target in cancers therapy due to their overexpression in several cancers (Sibille et al., 2012). The function of CDC25B is to remove phosphates from cyclin-dependent kinases and to further activate cylin-cdk complexes, which controls cell cycle progression. It seems to play a significant role in the regulation of G2/M transition by regulating CDK2/cyclin A and CDK1/cyclinA(Karlsson et al., 1999). The expression levels of CDC25B in tumor tissue are 3 times than normal levels, which in turn may promote tumor growth (Rudolph, 2007; Boutros et al., 2006). CDC25B isoform also operates specifically in the nucleus to reinitiate G2/M transition after DNA damage (Boutros et al., 2007; Niida and Nakanishi, 2006). Furthermore, it is showed that the abnormal level of CDC25B takes place in inchoate stage of cancer cell cycle including breast and lung, head and neck cancer, and so on (Sasaki et al., 2001). Indeed, aberrant levels of cell proliferation deriving from an imbalance of either the levels or activities of CDC25B have been implicated in a host of human cancers (Kristjansdottir and Rudolph, 2004). Thus, CDC25 B became a promising target for treating cancer.

The CDC25B shared the highly conserved active site loop structure, HC(X)5R (Lazo et al., 2001). Owing to its surprisingly flat and extremely shallow, the active site is lack of auxiliary loops and has no obvious features for mediating substrate recognition, indicting a broad protein interface. Thus, it is difficult to design CDC25B inhibitors. With the joint effort of chemists, powerful CDC25B inhibitors with antitumor activity have been found. There are a great number of compounds, including quinonoids, phosphate surrogates or electrophilic inhibitors, which were observed in order to inhibit CDC25B through screening of natural products or synthetic libraries. However, these compounds were not suited for clinical use due to their poor selectivity and irreversibility (Lavecchia et al., 2012a). The mechanism of action of

Abbreviation: CDC25B, cell division cycle 25B; CADD, computer aided drug design; HBA, hydrogen bond acceptors; HBD, hydrogen bond doners; HYP, hydrophobe area; RMSD, root mean squared deviation; RMSF, root mean square fluctuations.

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many compounds is the oxidation and inactivation of the CDC25 active site cysteine by ROS (Brisson et al., 2005; Brisson et al., 2007; Keinan et al., 2008). The potent and specific CDC25B inhibitors could fundamentally facilitate analysis of the CDC25B in complicated cellar signal pathways and might provide better therapeutics in the therapy of a group of cancers (He et al., 2013). Therefore, the discovery of novel lead compounds against CDC25B has become an urgent need.

In current study, the method of computer aided drug design (CADD) was utilized to design CDC25B inhibitors, because of the advantages of this method, including higher the success rate of experiment, cost reduction of development, and short cycle of research (Faver et al., 2013). A large number of drugs have been designed through this method, such as tofisopam, captopril l (Ondetti et al., 1977; Talele et al., 2010), and the inhibitor of AChE (Liu et al., 2007). CADD provides a novel thinking model which can be used in each stage of drug design. In this work, we built 3D-QSARpharmacophore of CDC25B to screen ZINC database to find the potent hits targeting CDC25B. Subsequently, the hits were sorted out by Lipinski's rule of five. The technique of the flexible docking was further utilized to analyze the binding interactions between the drug-like compounds and CDC25B. Finally, molecular dynamic study was done to observe the binding interactions of receptor and the potential inhibitors. Hopefully, the study here may find a new way to discover CDC25B inhibitors to treat cancer.

2. MATERIALS AND METHODS

2.1. Selection of compounds and dataset preparation

Based on the principal of structural diversity and activity coverage to produce quantitative 3D QSAR model, 38 CDC25B inhibitors reported elsewhere were selected (Sohn et al., 2003; Chen et al., 2010; Sodeoka et al., 2001). The bioactivity data for the

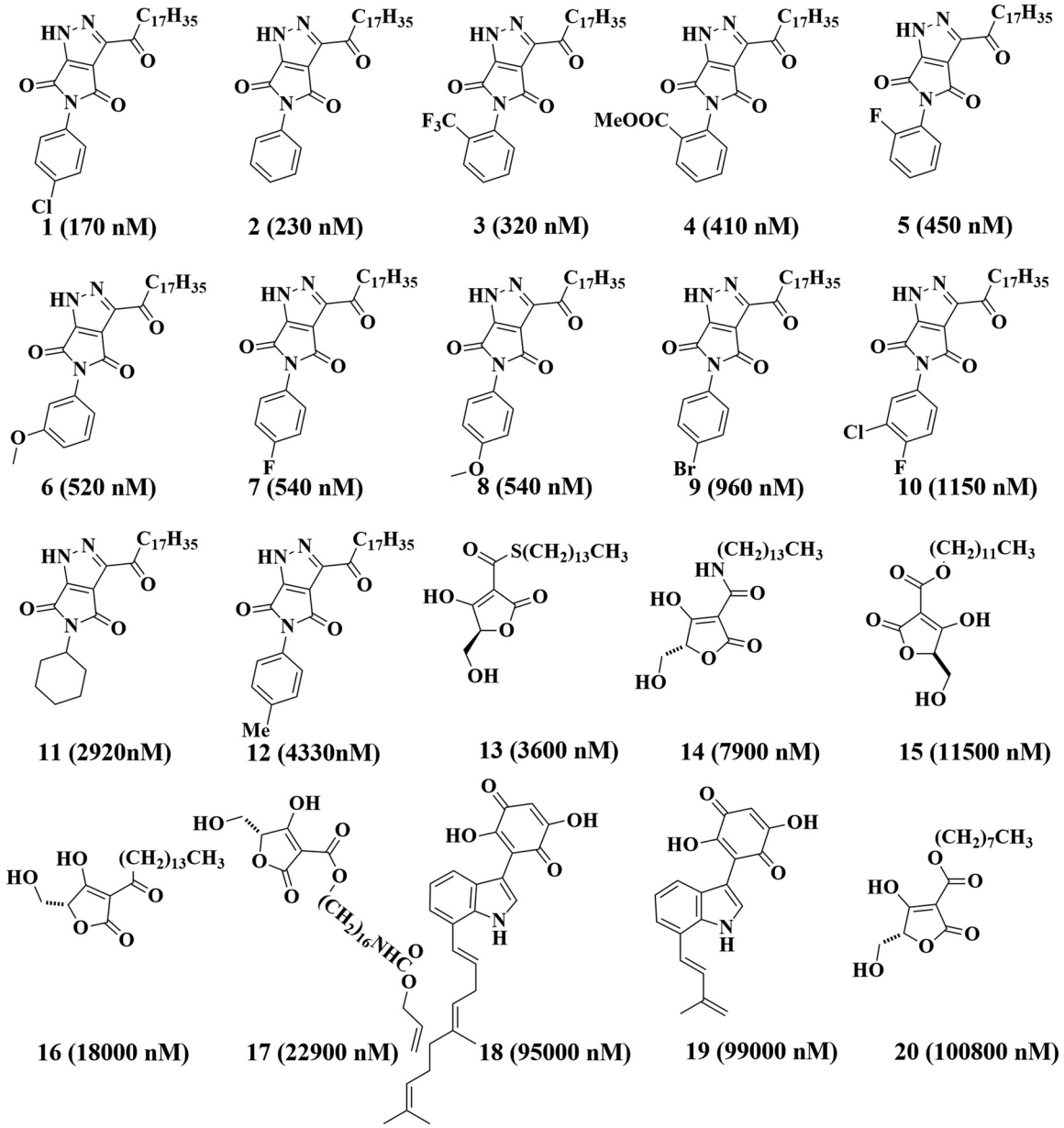

Fig 1. Chemical structures of 20 training set compounds for CDC25B.