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Identification of CK2 inhibitors with new scaffolds by a hybrid virtual screening approach based on Bayesian model; pharmacophore hypothesis and molecular docking

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ABSTRACT

Protein kinase casein kinase 2 (CK2), a member of the serine/threonine kinase family, has been established as one of the most attractive targets for molecularly targeted cancer therapy. The discovery of CK2 inhibitors has thus attracted much attention in recent years. In this investigation, a hybrid virtual screening approach based on Bayesian classification model, pharmacophore hypothesis and molecular docking was proposed and employed to identify CK2 inhibitors. We first established a naïve Bayes classification model of CK2 inhibitors/non-inhibitors and pharmacophore hypotheses of CK2 inhibitors. The docking parameters and scoring functions were also optimized in advance. The three virtual screening methods were sequentially used to screen two large chemical libraries, Specs and Enamine, for retrieving new CK2 inhibitors. Finally 30 compounds were selected from the final hits for *in vitro* CK2 kinase inhibitory assays. Five compounds with completely novel scaffolds showed a good inhibitory potency against CK2, which have good potentials for a future hit-to-lead optimization.

1. Introduction

Protein kinase CK2 (an acronym of 'casein kinase 2') is a ubiquitous eukaryotic serine/threonine protein kinase distributed in the nucleus and cytoplasm [1–3]. CK2 exists as a tetramer composed of two catalytic isoforms (CK2α and CK2α′) and two regulatory β subunits (CK2β). It has been established that CK2 phosphorylates multiple substrates and plays important roles in cell proliferation, transformation, apoptosis and senescence [1,2,4]. Dysregulation of CK2 can lead to human diseases [5], particularly in cancers [6]. Indeed CK2 has been found to over-express in all the cancers that have been examined [7]. The presence of elevated CK2 in cancer appears to correlate with the cancer. Recent studies have indicated that CK2 is also a potent suppressor of apoptosis [8,9], further raising its key importance in cancer cell phenotype. All of these show that CK2 is an important target for cancer therapy. In addition, it has been found that some viruses use CK2 to phosphorylate their own proteins [5,10], hence CK2 is also considered as an attractive antivirus target.

Due to the potential therapeutic value of CK2 inhibitors in cancer as well as antivirus, many academic institutes and pharmaceutical companies have been involved in the development of CK2 inhibitors. Up to now, more than one hundred small molecule inhibitors against CK2 have been reported publicly [11–18]. However, except for very few compounds including CX-4945 (see Fig. 1) that has entered Phase I clinical trials for advanced solid tumors and multiple myeloma treatment [19], most of them have just moderate or weak inhibition potency. Additionally, the known CK2 inhibitors, especially those with higher potency, have very limited structural diversity; several known CK2 inhibitors with different chemical scaffolds are shown in Fig. 1. Thus, discovering more potent CK2 inhibitors especially with new scaffolds is still needed and important, which could offer more candidates for drug development targeting CK2.

Currently, virtual screening (VS) has emerged as a complementary method to high-throughput screening of large chemical databases, and has been widely used in the drug discovery. VS methods are designed for searching large compound databases *in silico* and selecting a limited number of candidate molecules for testing to identify novel chemical entities that have the desired biological activity. There are two classical VS approaches: molecular docking-based VS (DB-VS) and pharmacophore-based VS (PB-VS) [20,21]. These methods have been broadly applied and

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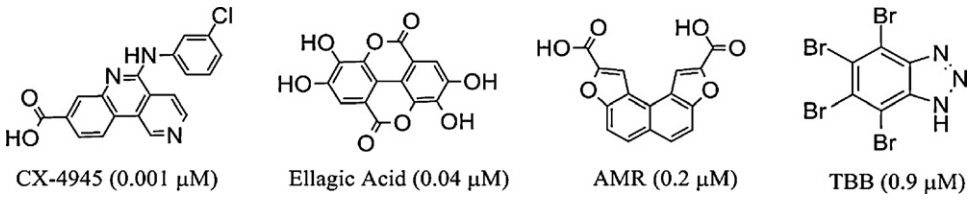

Fig. 1. Chemical structures of typical CK2 kinase inhibitors with novel scaffolds. IC_{50} values against CK2 are given in parentheses.

been becoming a major source of lead compounds in drug discovery. However, these methods are individually far from perfect in many aspects, including a low hit rate and a low enrichment factor, as well as a high false positive rate [22–24]. A combination of DB-VS and PB-VS in a hybrid protocol has been demonstrated to mutually compensate for these limitations and capitalize on their mutual strengths [25,26]. In addition, recent studies have shown that introduction of other newly emerging methods based on statistical learning theory could further increase the performance of the classical VS methods. For example, we recently employed a hybrid VS protocol of PB-VS and DB-VS, as well as support vector machine (SVM)-based VS (SB-VS) to discover novel potent Pim-1 inhibitors [23]. The results showed that the hybrid VS protocol had a much higher performance compared with individual PB-VS and DB-VS or their combination in terms of the screening speed and enrichment factor.

In this investigation, we shall adopt a new hybrid VS protocol, which involves the classical PB-VS and DB-VS, as well as naïve Bayesian (NB) classification model-based VS (BB-VS), to identify novel CK2 inhibitors. A NB classification model or naïve Bayes classifier is a probabilistic classifier based on applying Bayes' theorem with strong independence assumptions. It is one of the most versatile machine learning algorithms, and has been widely applied to text classification [27,28], assignment of rRNA sequences [29], and recently to drug discovery [30–32]. We shall first establish and validate a NB classification model of CK2 inhibitors and non-inhibitors, followed by development of a pharmacophore hypothesis based on the known CK2 inhibitors. Then BB-VS, PB-VS and DB-VS will be sequentially applied to screen Specs and Enamine chemical libraries. We shall select some compounds from the final hits obtained in the screening to carry out further *in vitro* CK2 kinase assays.

2. Materials and methods

2.1. Bayesian classification modeling

The Bayesian classification model was developed using Discovery Studio (DS) version 2.5.5 (Accelrys Inc., San Diego, CA). A total of 209 ATP-competitive compounds were collected. The training set consists of 102 compounds, including 73 active and 29 inactive compounds (see Table S1 in Supporting information). The descriptors used include AlogP, molecular weight, number of aromatic rings, number of hydrogen bond acceptors, number of hydrogen bond donors, number of rings, number of rotatable bonds, molecular fractional polar surface area and functional class fingerprints (FCFP_6 descriptors) [33]; these descriptors were chosen since they represent the most important chemical features. Validation of the Bayesian model was carried out by leave-one-out cross validation method and external testing set, which contains 77 active and 30 inactive compounds (see Table S2 in Supporting information). Performances of the Bayesian model were evaluated by calculating true positives (TP), true negatives (TN), false negatives (FN), false positives (FP), sensitivity (SE), and specificity (SP).

2.2. Pharmacophore modeling

Pharmacophore modeling was carried out by using "common feature pharmacophore generation" protocol (HipHop algorithm) [34] in DS 2.5.5. The seven active CK2 inhibitors together with two CK2 non-inhibitors (see Fig. 2) were selected to form the training set. The most active compound, CX-4945, was taken as 'reference compound' specifying a 'principal' value of 2 and a 'MaxOmitFeat' value of 0. The 'principal' and 'MaxOmitFeat' values of the remaining 6 compounds were set to 1 and 0, respectively. The 'principal' and 'MaxOmitFeat' values of compounds 6 and 7 were set to 0 and 1, respectively. The 'excluded volume' value was set to 3. Three features, including hydrogen-bond acceptor, hydrogen-bond donor and hydrophobic, were selected as the initial input features. The "minimum interfeature distance" value was set to 2.5 Å. The other parameters were kept at their default values.

2.3. Docking study

All of the molecular docking studies were carried out by GOLD 4.0 [35]. GOLD adopts the genetic algorithm to dock flexible ligands into binding site of protein. The crystal structure of CK2 combined with emodin (PDB ID: 3BQC) [36] was chosen as the structure of reference protein. All water molecules in the crystal structure except one, which is a conserved water molecule, were removed. The Charmm force field [37] was assigned. The binding site was defined as a sphere containing the residues that stay within 7.5 Å from the ligand, which is large enough to cover the ATP binding region at the active site. Hydrogen atoms were added by DS 2.5.5.

2.4. Chemistry

Compounds that were selected to conduct *in vitro* kinase inhibitory assays were purchased from the market, which are shown in Table S4 (see Supporting information). According to the information provided by the suppliers, the purity of these compounds is >98%, which were confirmed by HPLC (high performance liquid chromatography) analysis.

2.5. CK2 kinase inhibitory assays

CK2 kinase inhibitory assays were performed using labeled γ-33P-ATP method, and the incorporation of labeled phosphate onto the peptide RRRDDDSDDD substrate was monitored. The kinase buffer used contains: 20 mM HEPES, pH 7.6, 0.15 M NaCl, 0.1 mM EDTA, 5 mM DTT, 0.1% Triton X-100, 165 μM RRRDDDSDDD, 10 mM MgAcetate and [γ-33P-ATP] (specific activity approx. 500 cpm/pmol, Km Assay concentration (15 μM) was used). The reaction was initiated by the addition of the Mg ATP mix. After incubation for 40 min at room temperature, the reaction was stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction was then spotted onto a P30 filtermat and washed three times for 5 min in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

The inhibition profiles of the test compounds were expressed as the percentage of the residual kinase activity for an inhibitor

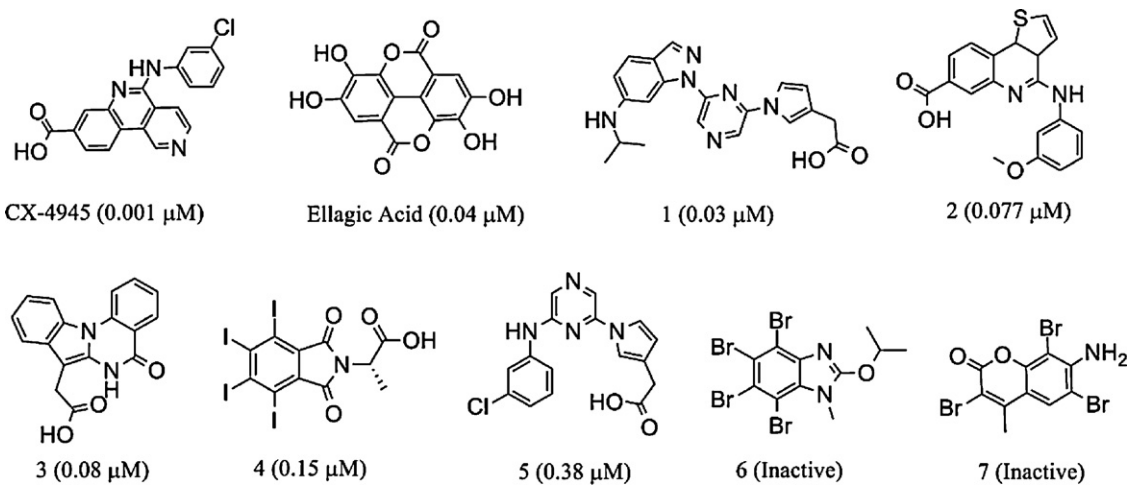

Fig. 2. Chemical structures and biological activities (IC_{50}) of the training set compounds for pharmacophore modeling.

concentration of 10 μM. The IC_{50} values of inhibitors were determined from dose–response curves after carrying out assays at 10 different concentrations of each compound. All the assays were replicated twice and the means of the replicates were calculated.

3. Results and discussion

3.1. Development and validation of the naïve Bayesian classification model

The training set adopted to generate the NB classification model consists of 102 compounds, including 73 CK2 inhibitors and 29 non-inhibitors. The features used include FCFP_6 and eight interpretable descriptors. The established NB classification model was initially evaluated by a leave-one-out cross validation approach. The cross-validated receiver operator curve (ROC) is given in Fig. S1 (see Supporting information). Table 1 lists the results of leave-one-out cross validation for the training set. The area under the curve (XV ROC AUC) for the model is 0.85 and the best split is −0.592. The prediction accuracy for CK2 inhibitors (sensitivity, SE) is 0.72 and that for CK2 non-inhibitors (specificity, SP) is 0.90. The overall prediction accuracy (*Q*) is 0.77. These data show that the established NB classification model has a good performance in differentiating the CK2 inhibitors and non-inhibitors from the training set.

An external test set, containing 77 inhibitors and 30 non-inhibitors, was further used to validate the NB classification model. Of the 77 inhibitors, 61 were correctly predicted, indicating a prediction accuracy of 0.79 for inhibitors. For the 30 non-inhibitors, 22 were properly predicted. The prediction accuracy for non-inhibitors is 0.73. Collectively, of all the 107 compounds, 83 were correctly predicted and 24 were wrongly predicted. The overall prediction accuracy (*Q*) is 0.78. These data further demonstrate that the established NB model has considerably good ability for distinguishing between CK2 inhibitors and non-inhibitors, hence being able to be used in the virtual screening.

3.2. Generation of common pharmacophore models of CK2 inhibitors

Seven most active CK2 inhibitors together with two CK2 non-inhibitors (see Fig. 2) were used to develop qualitative pharmacophore models; here the use of non-inhibitors was for building optional pharmacophore models. A total of ten pharmacophore models were generated by using HipHop algorithm. Fig. 3a presents the best hypothesis, Hypo1, which involves two hydrogen bond acceptors and one hydrophobic feature. Three excluded volumes

Table 1
Results of the Bayesian model validation by leave-one-out cross validation method (TP, true positive; TN, true negative; FP, false positive; FN, false negative; SE: sensitivity, SE = TP/(TP + FN); SP(%): specificity, SP = TN/(TN + FP); Q(%): overall accuracy, Q = (TP + TN)/(TP + TN + FP + FN)).

XV ROC AUC	Best split	TP/FN	FP/TN	SE	SP	*Q*	In category
0.85	−0.592	52/21	3/26	0.71	0.90	0.77	73

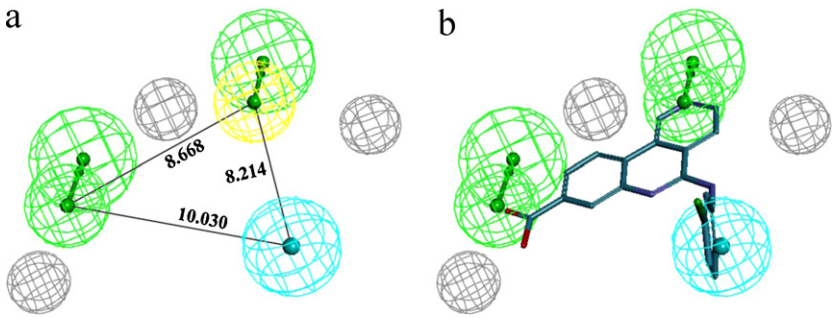

Fig. 3. (a) The best pharmacophore model (Hypo1) of CK2 inhibitors generated by HipHop and (b) Hypo1 aligned with CX-4945.

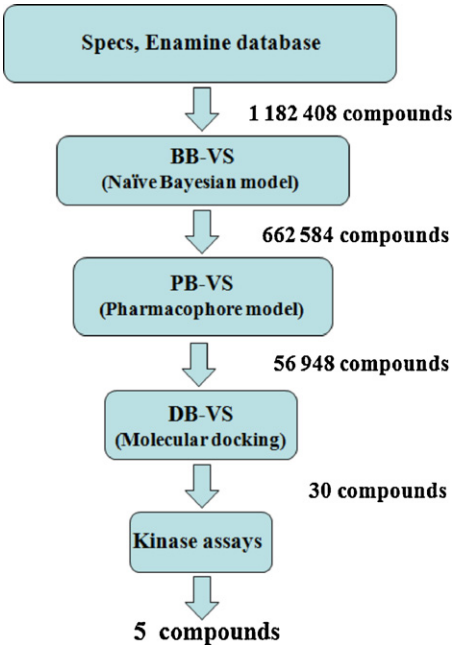

Fig. 4. The flowchart for the hybrid virtual screening protocol in this study.

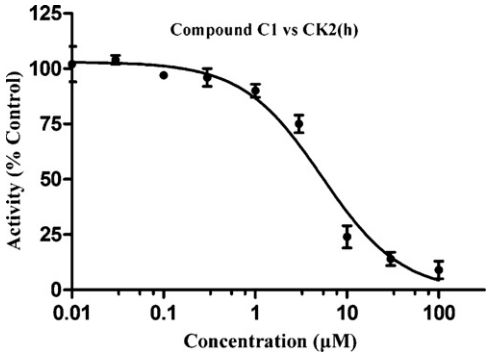

Fig. 6. The inhibitory profile of compound **C1** against human CK2.

are also included, which indicate the unfavorable regions occupied by the ligand atoms. Fig. 3b shows the Hypo1 mapped with the most active compound CX-4945. Obviously, the pyridine nitrogen and carbonyl oxygen of CX-4945 perfectly map onto the two hydrogen-bond acceptor features, and chlorobenzene ring rightly maps onto the hydrophobic feature. No collision between atoms of CX-4945 and excluded volumes is found. All of these show that Hypo1 is a good pharmacophore model for CK2 inhibitors.

3.3. Parameter setting and scoring function selection for the docking study

Since docking parameters and scoring functions have important influence on the performance of molecular docking based virtual screening, we shall carry out optimization for the docking parameters and scoring functions in advance.

The GOLD 4.0 was employed for DB-VS in this study. The crystal structure of CK2 complexed with emodin (PDB ID: 3BQC) was chosen as the reference receptor structure since it has the highest resolution (1.5 Å) among all the known CK2 crystal structures. Another reason is that it contains one conservative water molecule nearing TRP176; this water molecule exists in all of the reported 15 human CK2 crystal structures. We adjusted the docking parameters until the docked pose is as close as possible to the original crystallized structure in the ATP binding site of CK2. The finally optimized docking parameters mainly include: (1) the "number of dockings" was set to 10; (2) the genetic algorithm (GA) parameter was set to "7–8 times speed up"; (3) "pose saving rotated hydrogens" was turn off and the other parameters were kept at the default settings. The RMSD value is 0.46 Å, which indicates that the docked pose is in accordance with the pose of the bound ligand in the crystal structure.

For the selection of scoring functions, we chose a set of known CK2 inhibitors whose IC_{50} values span a range of three orders. These inhibitors were docked into the ATP binding site of CK2, in which the docking parameters just optimized were used. Different scoring functions, including GoldScore, ChemScore, and a modified ChemScore that is an optimized scoring function for the kinase-related docking (hereafter called KCS), were calculated. Then the correlation coefficient between the experimentally measured IC_{50} values and the scoring function values was calculated for each scoring function. It was found that KCS gave the best correlation coefficient. Therefore, KCS will be used in the subsequent DB-VS study.

3.4. Database screening

We have just finished the setup of these three VS methods. Next these methods will be applied to screen two large chemical

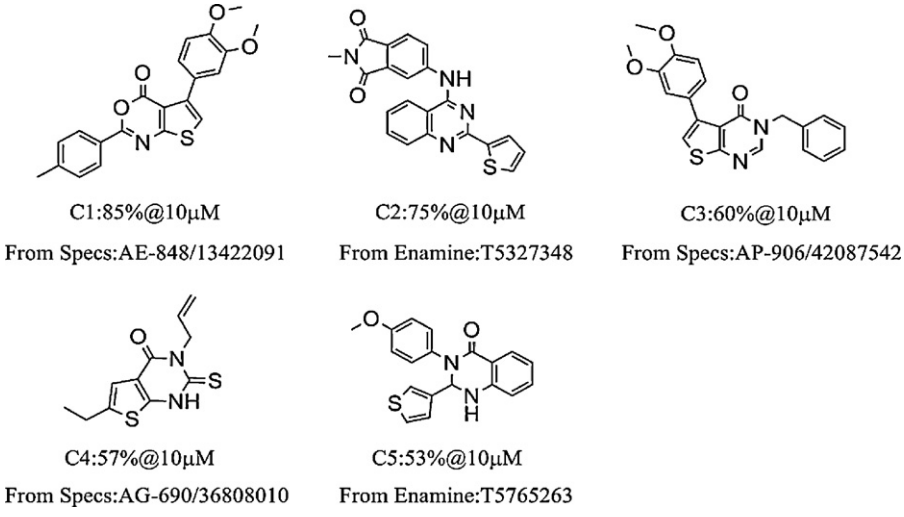

Fig. 5. Chemical structures of the five CK2 inhibitors obtained in this study.

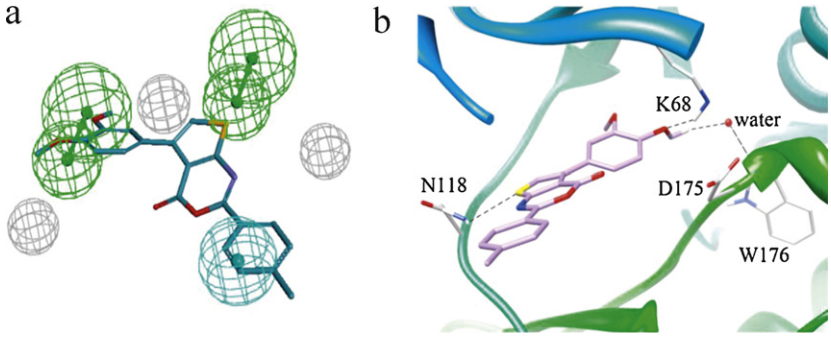

Fig. 7. (a) Hypo1 mapping with compound **C1** and (b) interactions of compound **C1** with residues in the active site of CK2. Hydrogen bonds are shown by dotted lines.

libraries: Specs (202,408 compounds) and Enamine (980,000 compounds). We used the three filters in the following order: BB-VS, PB-VS and DB-VS, since a preliminary virtual screening test showed that BB-VS is the fastest one and DB-VS is the lowest one in terms of the screening speed. This arrangement ensures that the first filter (BB-VS) is fast while successive ones (PB-VS and DB-VS) are more time-consuming, but are applied only to a small subset of the entire database, which benefits to improve the screening efficiency. The flowchart of screening is shown in Fig. 4. 662,584 compounds passed through the first filter BB-VS. These compounds were then filtered by PB-VS and 56,948 compounds remained. The 56,948 compounds were subsequently sorted according to their scoring function values calculated in DB-VS. Finally 30 compounds were visually chosen from the top hits to carry out *in vitro* kinase assays; these compounds must satisfy the following criteria: (1) they have good interactions with the key residues in the active site of CK2, such as ASP175, TRP176, and LYS68, as well as residues in the hinge region (GLU114 to ASN118); (2) the KCS value should be greater than 20; (3) these compounds should have scaffolds different from that of the known CK2 inhibitors; (4) these compounds can be easily purchased from the market.

3.5. *In vitro CK2 kinase inhibition assays*

I*n vitro* CK2 kinase inhibition assays were carried out for the selected 30 compounds. The inhibitory potency was tested with the compound at a fixed concentration of 10 μM. Five compounds (**C1**-**C5**, see Fig. 5) showed an inhibition rate greater than 50%. The scaffolds of these compounds are 2,5-diphenyl-4H-thieno[2,3-d][1,3]oxazin-4-one for **C1**, 2-thiophen-4-(5-aminoisoindoline-1,3-dione)-quinazolin for **C2**, 3-benzyl-5-phenylthieno[2,3-d]pyrimidin-4(3H)-one for **C3**, 2-thioxo-2,3-dihydrothieno[2,3-d] pyrimidin-4(1H)-one for **C4** and 3-phenyl-2-(thiophen-3-yl)-2,3-dihydroquinazolin-4(1H)-one for **C5**. In order to further check the novelty of **C1**-**C5**, the Tanimoto coefficients (Tc) between **C1**-**C5** and all the known CK2 inhibitors were calculated through a similarity analysis based on the FCFP_6. The known CK2 inhibitors (**Max1**-**Max5**) that have the largest Tc values are given in Table S3 (see Supporting information); the Tc values are all less than 0.5 (see Table S3), implying completely novel structures of **C1**-**C5** as being CK2 inhibitors (though **C1** and **C3**, as well as **C2** and **C5** show some degree of similarity). Finally we measured the dose-response relation of **C1** at enzymatic level, which gave an IC_{50} value of 5.85 μM (see Fig. 6).

Fig. 7a shows the Hypo1 aligned with **C1**. Fig. 7b depicts the interaction mode of one of the hit compounds, **C1** (5-(3,4-dimethoxyphenyl)-2-p-tolyl-1H-thieno[2,3-d][1,3]-oxazin-4-one), with the active site of CK2. The most apparent interactions are the three hydrogen bonds formed between them. The first one is between the sulfur atom of **C1** and ASN118, and the second one between the oxygen of 4-methoxy group and LYS68. The third one is formed between the hydrogen of 4-methoxy group and the conserved water molecule, which acts as a bridge by forming a hydrogen bonding interaction with TRP176. The tolyl group is directed toward the solvent accessible region.

4. Conclusions

In the present study, a hybrid virtual screening approach, which is based on Bayesian categorization model, pharmacophore hypothesis and molecular docking, was employed to identify new CK2 inhibitors. In the first step, we established a naïve Bayesian classification model of CK2 inhibitors/non-inhibitors. This model was then validated, which results showed that the overall prediction accuracy (Q) was 0.77 and 0.78 for the training set and the test set, respectively. In the second step, we developed qualitative pharmacophore hypotheses of CK2 inhibitors. After that, the Bayesian model and the pharmacophore model together with the molecular docking were used to screen several large chemical libraries including Specs and Enamine for retrieving CK2 inhibitors. Thirty compounds were chosen from the final hits to conduct *in vitro* CK2 kinase inhibitory assays. And five compounds with completely novel scaffolds were found to have an inhibitory rate of more than 50% at a concentration of 10 μM. These compounds have been advanced to further chemical modification, which results will be reported in the near future.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jmgm.2012.03.004.

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