The 25th International Electronic Conference on Synthetic Organic Chemistry

Session: Computational Chemistry

An *in silico* approach for potential natural compounds as inhibitors of protein CDK1/Cks2

Abu Saim Mohammad Saikat [1,*]

[1] Department of Biochemistry and Molecular Biology, Faculty of Life Sciences, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh

*Correspondence should be addressed to asmsaikat.bmb@gmail.com (Abu Saim Mohammad Saikat).

An *in silico* approach for potential natural compounds as inhibitors of protein CDK1/Cks2

Abstract

CDKs are pivotal mediators essential for the cellular cycle progression. CDKs have relatively constant levels, and their activity is regulated by cyclins, proteins whose concentrations fluctuate during each cell cycle. Consequently, more CDK family members were found that occupy crucial functions in a variety of processes. Moreover, CKS2 is a member of the CDK family, which has been implicated in several malignancies as an oncogene. Additionally, CKS2 is engaged in many biological processes, including the cell cycle transition. CKS2 may act synergistically to promote embryonic development and somatic cell division. Current CDK2 drugs, however, also suppress CDK1, posing a toxicity risk. Investigators demonstrated that the potential conformational maps of cyclin-free CDK1 and CDK2 exhibit slight but substantial differences. The CDK1 unique characteristics may be used to distinguish it from other CDKs in prospective cancer treatment design. Computational-based in silico docking investigations were performed to uncover promising CDK1/Cks2 (6GU7) inhibitors utilizing the Maestro tool. Curcumin, quercetin, withanolide, and genistein were selected against the protein CDK1/Cks2 for protein-ligand XP docking. The physicochemical, lipophilicity, water-solubility, pharmacokinetics, drug-likeness, medicinal chemistry, and toxicological properties were analyzed using SwissADME and pkCSM of the selected ligands. Curcumin exerted an excellent docking score complexed with 6GU7 compared to other ligands. The revealed hit may be a potent inhibitor of 6GU7. However, it will require to be assessed extensively in vivo and in vitro experimental models.

Keywords

The cell cycle; cyclin; cyclin-dependent kinase1; Cyclin-dependent kinases regulatory subunit 2; Structure-based docking; 6GU7

Introduction

CDKs are serine/threonine kinases that require a governing subunit component known as a cyclin to function. CDKs, MAPKs, Gsk3β, members of the DYRK family, and CDK-like kinases all contribute to the CMGC group of kinases (called after the initials of several members), together with MAPKs, Gsk3β, and CDK-like kinases. In closely similar kinases, including MAPKs, substrate sophistication is imparted via docking sites distinct from the catalytic region, but CDKs are defined by their reliance on distinct protein subunits that include different sequences essential for enzymatic activity. CDK family members undertake a plethora of activities in the cell, including cell cycle and transcription monitoring and differentiation in particular cell types. CDK function imbalance is closely attributed to atypical cell progression, and as a consequence, numerous members of the CDK family have been targeted as anticancer therapeutic targets. Moreover, CDKs are proteins that influence cell cycle progression and are consequently promising targets in cancer. The activity of CDKs is regulated by their interaction with cyclin-dependent kinases, phosphatases, and particular inhibitors. Multiple CDK complexes operate at distinct stages. CDK1 is a crucial regulator of the cell cycle commencement and progression through mitosis. Prior investigation has established that loss of CDK1 function or abnormal CDK1 expression is associated with G2 phase arrest and various tumor forms, confirming CDK1 as a therapeutic candidate. As a result, there has been a spike in attention in developing potent CDK1 inhibitors as promising chemotherapeutic agents. CKS2 belongs to the CDK family that has been pinpointed as an oncogene in a variety of cancers.

Results and Discussion

1. Analyzing Molecular Docking Results and Binding Interactions

Pharmaceutical research has effectively integrated various molecular modeling techniques into several drug development programs to explore complicated biological and chemical processes. Combining computational and experimental techniques has proven highly beneficial in identifying and developing innovative, promising chemicals. Frequently employed in contemporary drug design, molecular docking techniques investigate the conformations of ligands inside macromolecular target binding sites. Additionally, this technique calculates the free energy of ligand-receptor interaction by examining critical events engaged in the intermolecular interaction mechanism. The XP molecular docking (grid box size as of 10 Å × 10 Å × 10 Å) was performed using the GLIDE program. The XP docking measured the docking scores of the 6GU7–curcumin complex, 6GU7–quercetin complex, 6GU7–withanolide complex, and 6GU7–genistein complex as of -9.419 kcal/mol, -8.709 kcal/mol, -7.174 kcal/mol, and -6.301 kcal/mol, respectively.

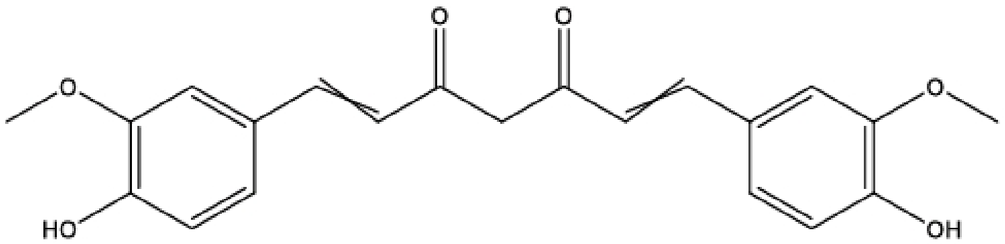
Continued...

Results and Discussion

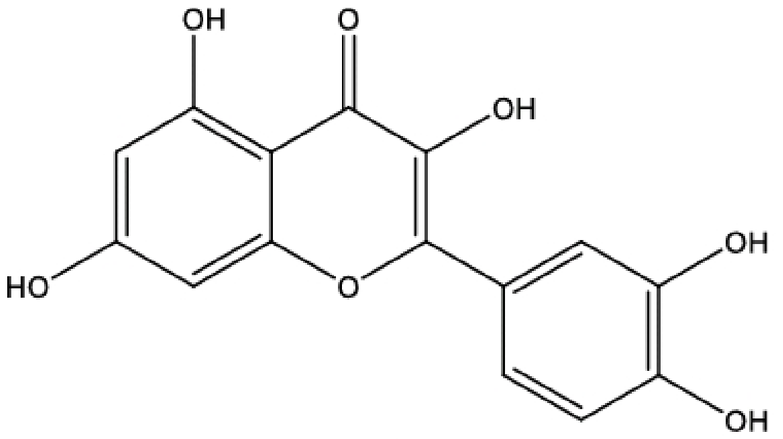
The 6GU7–curcumin complex interacts at ASP146, LYS33, GLU81, LEU83 through H-bonds (Figure 2). Also, 6GU7–curcumin complex interacts via different non-bonding interactions, including polar (THR14, SER84, GLN132, GLN49), hydrophobic (LEU149, ILE10, ALA145, VAL18, ALA31, VAL64, PHE80, PHE82, LEU83, LEU135), negative charged (GLU12, ASP146, GLU81, ASP86), and positively charged (LYS33, LYS88, LYS89). However, the 6GU7–quercetin complex illustrates H-bond interactions at ASP146, LEU83, SER84, ASP86, and non-bonding interactions as of polar (SER84), hydrophobic (Val18, ALA145, VAL64, ALA31, PHE80, LEU135, ILE10, PHE82, LEU83, MET85), negative charged (ASP146, GLU81, ASP86), and positively charged (LYS33, LYS89). The 6GU7–withanolide complex interrelates through H-bonding at LEU83, and non-bonding interactions as of polar (GLN132, ASN133, THR14, GLN49), hydrophobic (VAL165, LEU135, ALA145, VAL64, PHE80, ALA31, PHE82, LEU83, VAL18, ILE10), negative charged (ASP146, GLU81, ASP86, GLU12), and positively charged (LYS130, LYS33). Moreover, the 6GU7–genistein complex interconnects via H-bond at ASP146, SER 84, and non-bonding interactions as of polar (GLN132, SER84), hydrophobic (LEU135, VAL18, ALA145, LEU149, VAL64, VAL31, PHE80, ILE10, PHE82, LEU83, MET85), negatively charged (ASP146, ASP86), and positively charged (LYS33, LYS89). Consequently, the 6GU7–curcumin complex (-9.419 kcal/mol) constituted higher binding affinities compared to the 6GU7–quercetin complex (8.709 kcal/mol), 6GU7–withanolide complex (-7.174 kcal/mol), and 6GU7–genistein complex (-6.301 kcal/mol).

Continued...

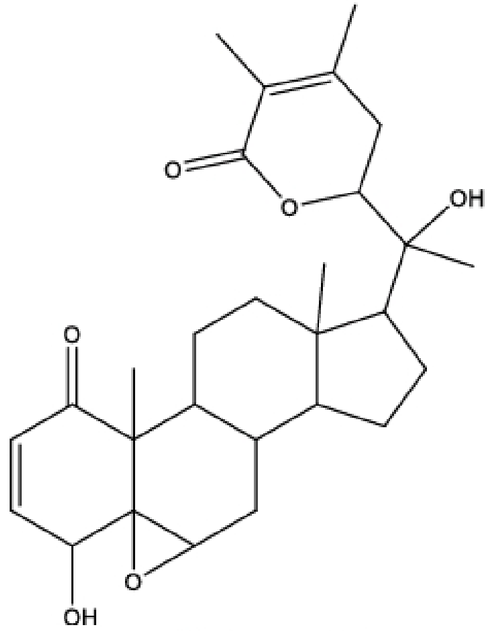
Results and Discussion



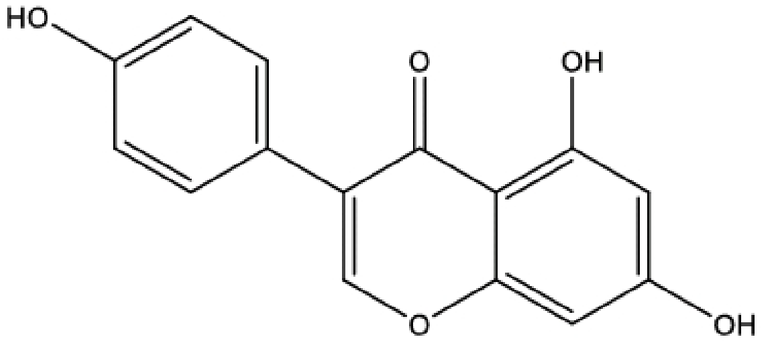
Curcumin



Quercetin



Withanolide

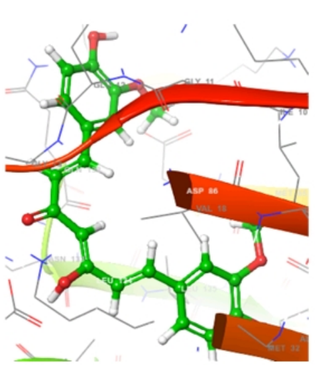


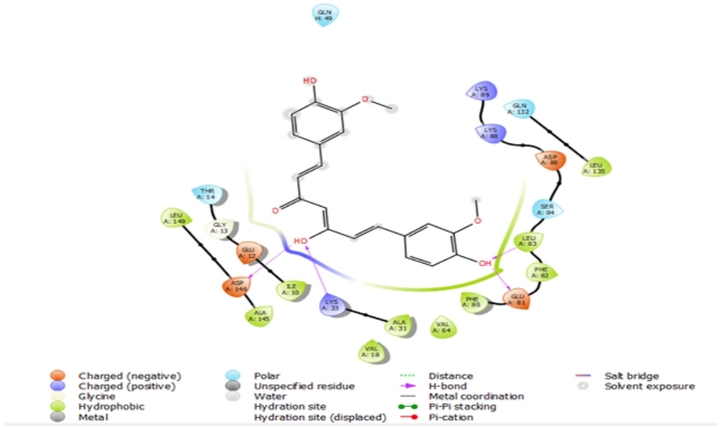
Genistein

Figure 1: The chemical structures of curcumin, quercetin, withanolide, and genistein.

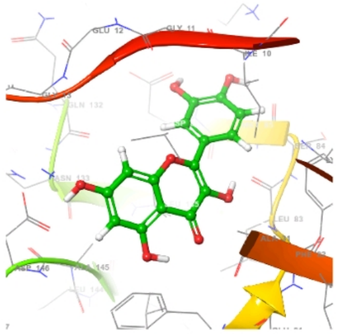
Continued...

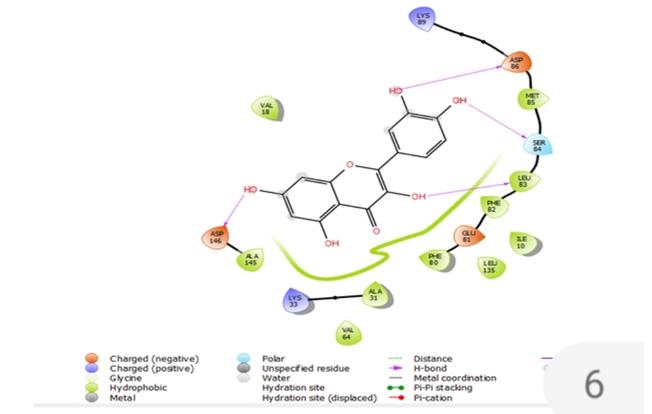
Results and Discussion



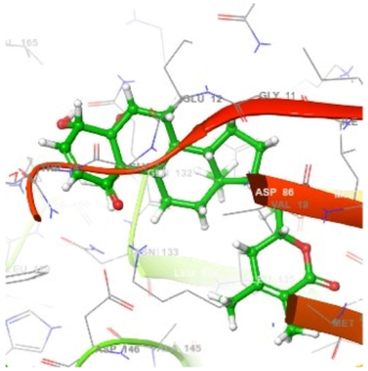


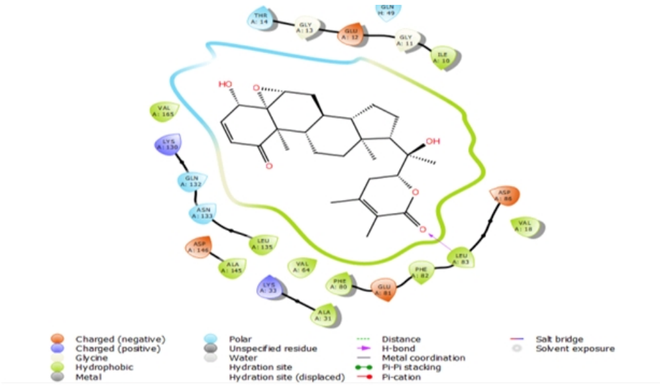
6GU7– curcumin complex



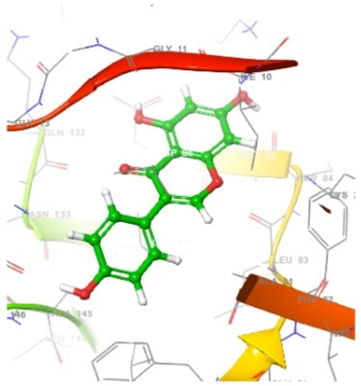


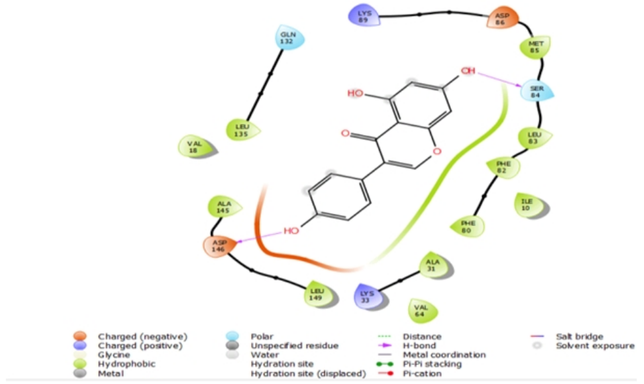
6GU7– quercetin complex





6GU7– withanolide complex





6GU7 – genistein complex

Figure 2: Interactions of 6GU7 with curcumin, quercetin, withanolide, and genistein.

Continued...

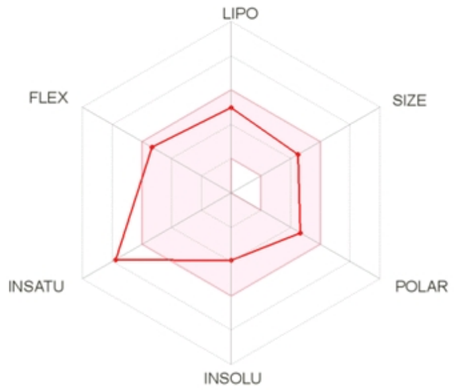
Results and Discussion

2. ADMET Analysis

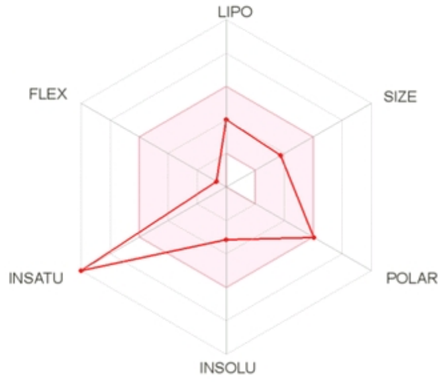
In the field of efficient medication, a potent molecule must approach its target in the body in a bioactive state and remain there long enough for the predicted physiological activities to transpire. Drug development progressively incorporates ADMET screening early in the discovery phase, when the number of candidate compounds is large, but availability to physical samples is restricted. In this situation, computer models are viable substitutes for experimentation. Investigators implement the existing SwissADME web platform that provides free access to a reservoir of rapid yet reliable prognostic models for pharmacokinetics, physicochemical characteristics, drug-likeness, and medicinal chemistry pleasantness, including proprietary methods the iLOGP, BOILED-Egg, and Bioavailability Radar to assist in their drug development accomplishments. Moreover, the pkCSM employs the utilization of graph-based identifications to anticipate pharmacokinetic characteristics. These reflect the tiny molecule and are exploited to train prediction algorithms .

Continued...

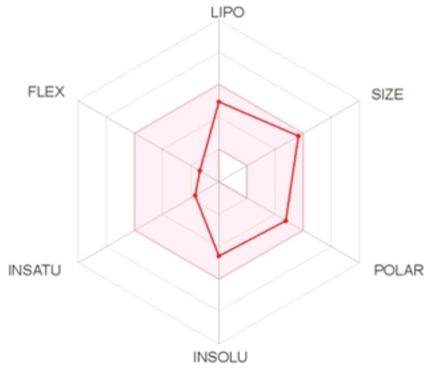
Results and Discussion



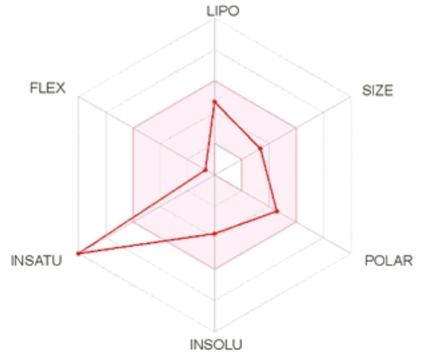
Curcumin (PubChem CID: 969616)



Quercetin (PubChem CID: 5280343)



Withanolide (PubChem CID: 53477765)



Genistein (PubChem CID: 5280961)

Figure 3 The physicochemical space for oral bioavailability. The bioavailability radar provides an initial assessment of drug-likeness of a molecule. The colored zone is the suitable physicochemical space for oral bioavailability. The comprehending outcomes for physicochemical space of Curcumin (PubChem CID: 969616), Quercetin (PubChem CID: 5280343), Withanolide (PubChem CID: 53477765), and Genistein (PubChem CID: 5280961) were illustrated following the parameters as of LIPO (Lipophility): – 0.7 < XLOGP3 < +5; SIZE: 150g/mol< MW < 500g/mol; POLAR (Polarity): 20Å2< TPSA < 130 Å2; INSOLU (Insolubility): 0 < Log S (ESOL) < 6; INSATU (Insaturation): 0.25 < Fraction Csp3 < 1; and FLEX (Flexibity): 0 < Num. rotatable bonds < 9.

Conclusions

CDK1 is an essential mediator of the initiation and advancement of the cell cycle during mitosis. CKS2 is a member of the CDK family, which has been implicated in several malignancies as an oncogene. Because CDK1 alone or in tandem with other treatment options has been connected to powerful anticancer effects, it has been postulated that CDK1 may be the preferred CDK benchmark for cancer treatment. The present investigation used an in-silico strategy targeting potential inhibitors against the CDK1/Cks2 protein (6GU7) for advancements in cancer treatment. Curcumin, quercetin, withanolide, and genistein were selected as promising candidates for XP molecular docking against 6GU7 with the Maestro program. The SwissADME and the pkCSM anticipated the ADMET properties of the selected ligands. Analyzing the different binding interactions, curcumin showed a high binding affinity with 6GU7 compared to quercetin, withanolide, and genistein. However, in vivo and in vitro investigations are required to evaluate the current study.


THANK
YOU