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A Review on Role of Cyclin-Dependent Kinase (CDK) Enzyme and their Inhibitor

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Abstract:

CDKs are small but significant molecules that acts like authorizing molecules absence, or presence of which could show their effect over any process of cell cycle. Various kinds of CDKs are involve in different process like cell cycle, cell adhesion, migration, and division. The involvement of CDKs which are basically signaling molecules has increased the chances of treatment of oncological conditions. Moreover, in breast cancer the inhibition of CDKs can give better results and that so by using even small molecules to inhibit the CDKs. The phosphorylation process is important and long process. So, it has various stages to target and inhibit the process and ultimately CDKs can be stopped. This review consists of the various kinds of available CDKs inhibitors and their mechanism of action and their relationship with cell cycle.

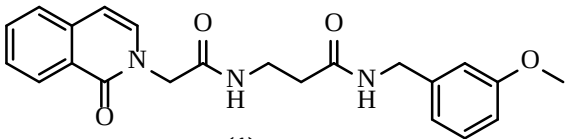
Keywords: Cyclin, CDKs, Cancer, Phosphorylation, Cell cycle, Cell division, cytotoxicity.

INTRODUCTION

Cyclin-dependent kinase enzymes (CDKs) sometime referred as cell division protein kinase are kind of enzymes that works on the principle of signal cascade, but their signaling depends on the kinase domains [1]. The gene (CDK7) that regulates the all the CDKs is present over 5th chromosome. The CDKs are comprises of two parts namely kinase domain and cyclin domain, both are dependent to each other for their activation. Kinase domain will remain dormant and inactive until cyclin domain binds with the kinase. The kinase domain specifically consists of serine/threonine because these are the only amino acids which excites and amplifies any signal for activation of base protein. Except this all the other activation phenomenon and functioning of CDKs are like other kinase enzymes such as tyrosine kinase etc. [2]. Because of having crucial roles in cell cycle especially in G_2 and M phase, it is known as cell division protein kinase [3]. In signaling phenomenon it prepares a specific/targeted protein to take charge of running action at cellular level by phosphorylating. Moreover, it works in close interaction with ATP as it requires phosphate group (PO_3^-) for activating the targeted protein to become in charge for cellular functioning [4]. Various kind of CDKs are playing their role in different sort of cell functioning such as CDK1 uses cyclin-A & B, controls the cell cycle from G_2 to M phase where as CDK2 uses cyclin-A & E, drives the cell cycle from G_1 to S phase. Another is the CDK4 and CDK6, both are using cyclin-B and regulates the restriction point in G_1 phase [5]. Moreover, these two CDKs have significant involvement in the cell division, adhesion, and migration. During the activation process by CDKs there are some loops that must be open to hydrolyze the ATP, to remove phosphate from ATP [6]. Because of having crucial roles in cell cycle, they are being used as primary targets for treatment of oncological conditions. Such significant roles make it an easy and reasonable target for treatment of breast cancer by inhibition using small molecules [7].

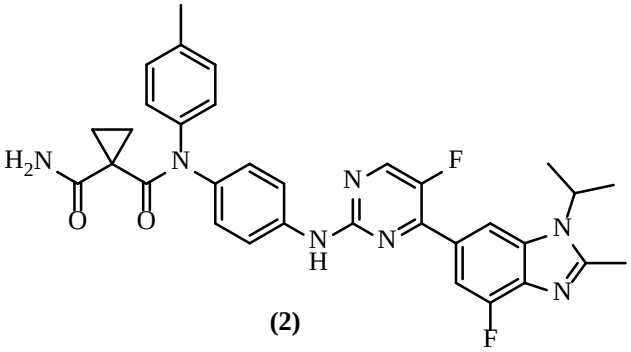
REORTED CYCLIN-DEPENDENT KINASE (CDK) INHIBITORS

Wu and their group members used a hybrid virtual screening strategy for developing CDK 9 inhibitors which were further processed for molecular dynamics (MD) simulations and analyzed by CDK9 kinase biochemical assay. Their results showed that almost three compounds have exhibited signification inhibition of CDK-9 enzyme. The most active compound was **(1)** which has shown its activity at IC50 value of 6.21 µM via showing docking score 53.85. Reports suggests that this compound can be further used as lead compounds for designing new analogues [8].



(1)

Huang and their group members reported inhibitors for targeting CDK4 as well as VEGFR2. They have found that compound Roxy-ZV-5J **(2)** was most active potent compound at nano molar range via arresting G2/M phase. It was also assumed as anti-proliferative and anti-angiogenesis agent [9].



(2)

Jing et al uses Scaffold hopping strategy on compound CAN508 and further evaluated pyrazolo[3,4-*b*]pyridine analogues for CDK inhibition. Their results have showed that compound **2e** was most potent at IC_{50} values of 0.36 μM and 1.8 μM against CDK2 and CDK9, respectively. Their study results also revealed that compound **(3)** and **(5)** exhibited significant selectivity toward CDK2 with respect to CAN508 **(4)** [10].

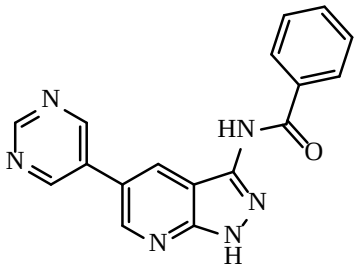
Park and their group members have been reported that analogues bearing *N*9-*cis*-cyclobutyl moiety is capable for inhibiting actions of CDK family. Their study results showed that compound 81 have exhibited its biological activity at IC_{50} = 2.1 and 4.8 nM, respectively against CDK2 and CDK5, respectively with moderate cytotoxicity towards HCT116 and MCF7 cell lines [11].

Chiou and their group members have reported that anti-cancer activity of 3-ylideneoxindole acetamides analogues **(7)**. These compounds have been shown remarkable like CDK inhibitor roscovitine. Among all, compound **10** showed significant activity via arresting cells in the G1 phase. Molecular docking studies confirms the binding of compound 10 with active site of enzyme [12].

Criscitiello and his group members worked on CDK enzymes due to its major role in gene transcription and cell cycle progression. Their results indicated that compound Dinaciclib (MK-7965, formerly SCH727965) participates in cell cycle dysregulation via showing inhibition of CDK 1/2/5/9 enzymes and can be employed for the treatment of breast cancer [13].

Zatloukal and their group members have synthesized and evaluated 2,6,9-trisubstituted purine analogues via changing the moieties at positions 2 and 6 of roscovitine against CDK enzymes.

They have shown that many of the compounds have shown significant activity with respect to reference compound roscovitine and olomoucine II, respectively. The most promising compound **(9)** and **(10)** acted via blocking cell cycle progression and inducing apoptosis in cells [14]. Wilson and his colleagues prepared and evaluated a series of 6-pyridylmethylaminopurines class as CDK inhibitors. They have observed that these analogues have improved solubility characteristics and potency with reduced metabolic clearance. The most active compound alpha SbR-21 have shown its CDK2/cyclin E, CDK7-cyclin H, CDK9-cyclinT inhibition at IC50 values of 30 nm, 1.3 μM and 0.11 μM, respectively [15].



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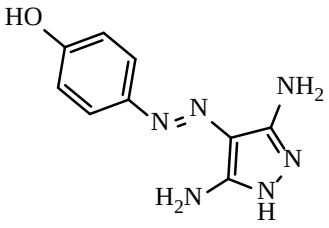

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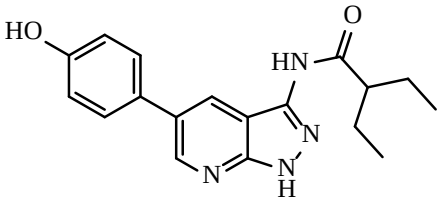

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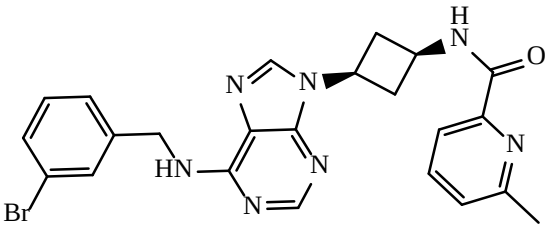

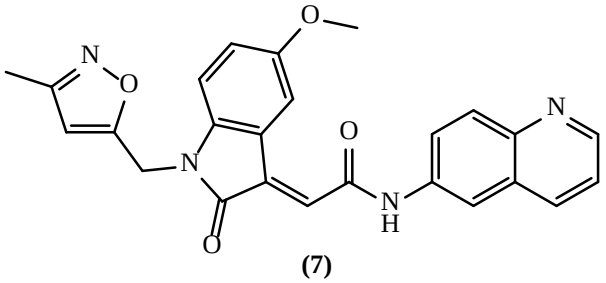

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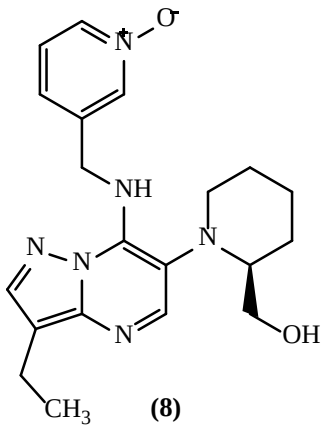

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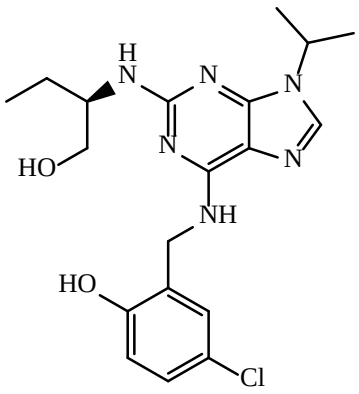

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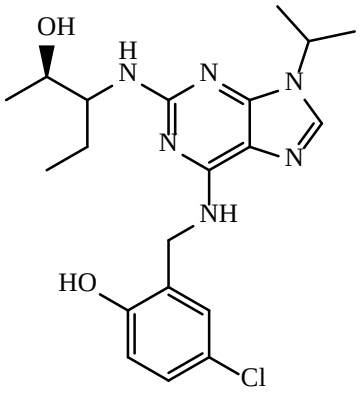

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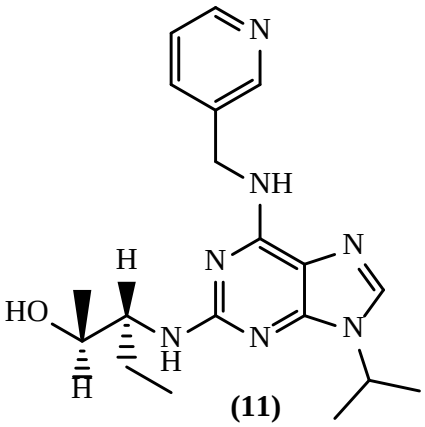

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CONCLUSION

In earlier few years CDK has emerged as significant molecule targeting which various cellular level diseases can be inhibited. The specialty of having various target points for inhibition, it has attracted the interest of world researchers and scholars. Various oncological conditions like breast cancer, prostate cancer etc. can be controlled if CDKs are accessed. This approach is most effective in case of the metastasis as CDKs has roles in cell division and targeting it will inhibit the cellular division and ultimately no metastasis will be there. Its interaction with ATP which activates CDKs for further actions can also be effective target as ATPs have four sites of interactions and ATP interactions can be also inhibited using small molecular weight inhibitors. Targeting CDKs produces variety of options for inhibition so, it can be more promising while treating cancers.

Authors Contribution

All authors have contributed equally to collection of data and preparation, updating and submission of manuscript.

Conflict of Interest

Authors declared no conflict of interest.

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