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A Review of Heterocyclic Scaffolds for the Known Inhibitors of Cyclin-Dependent Kinases 1 and 2

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ABSTRACT
Cyclin-Dependent Kinases (CDKs) are established drug targets, particularly in the area of anti-cancer drug discovery. Several research groups in the academia as well as in the industry have used traditional as well as computational methods for the discovery of novel CDK inhibitors and a variety of novel small molecule inhibitors are reported in the literature over a long period of time. The journal literature has been reviewed, and a few important heterocyclic scaffolds found in CDK1 and CDK2 inhibitors are presented here. These include substituted benzofuranones, triazole amines, Hydroxychromones, purines, and pyrimidines etc.

KEYWORDS
Anti-cancer, Cyclin-Dependent Kinase, CDK1, Drug Discovery, Heterocycle, Inhibitor

INTRODUCTION
Cell division is a natural process that includes many stages through which a mother cell divides into two daughter cells.[1] The cells enter these stages, and then progress of many important processes within the cell division is controlled by many proteins.[2,3] These proteins are known to be activated by the process of phosphorylation. In mammalian cells, proliferation is controlled by the phenomenon of cell cycle, whereas protein phosphorylation is a post-translational modification. It regulates a large number of important cellular processes such as differentiation, division, proliferation, and apoptosis. However, the abnormal and sustained proliferation mediated by disruption of the regular cellular mechanisms that keep the cell cycle under control, is the key cause of almost all cancer cells.[4] The proteins known as Serine and Threonine kinases (STKs) play an important role in these signal transduction pathways. Within this kinase family, a specific class known as the Cyclin-Dependent Kinases (CDKs),[5,6] are responsible for the phosphorylation and the regulation of important checkpoints involved in the regulation of cell cycle, in particular the transitions of G1/S and G2/M phases.

Cyclin Dependent Kinases (CDKs) are known to be relatively small size proteins (molecular weights ranging from 34-40 kDa), and include a kinase domain. A Cyclin dependent kinase binds a cyclin protein and then becomes an active kinase. These kinases are known to be involved in regulating transcription as well as in the processing of mRNA. Cyclin Dependent Kinases (CDKs) are one of the most important classes of drug targets for the development of anti-cancer drugs. For this reason, there is a large interest in the use of CDK inhibitors as drugs. This evidence has led to an intense search for small molecule inhibitors (M.W. < 500) of the CDK family as an approach to cancer chemotherapy.[7] There are at least 20 different cyclin-dependent kinase (CDK) family members in the human kinome. Types of cyclin dependent kinases include CDK1, CDK2, to CDK11. However, one of the most attractive targets in the area of oncology remains CDK1, together with CDK2. A number of literature reports have pointed to the evidence that CDK1 inhibitors could block the cell cycle progression through mitosis, and also these are considered promising for treating cancer due to their abilities to check cell proliferation or to hinder tumor growth. Along this line, tremendous efforts have been devoted for discovering new CDK1 inhibitors in recent past.[8–10] The Figure 1 illustrates a few known molecules that inhibit several CDKs and these are either the approved drugs or are under the development for treating cancer.[6,8]

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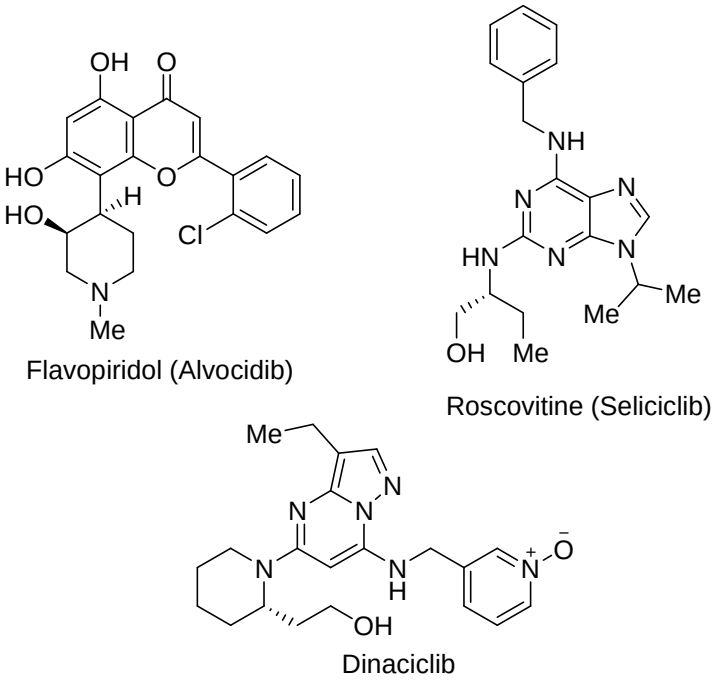

Figure 1. Commercial/Experimental drugs known to inhibit Cyclin-dependent Kinases (CDKs).[6,8]

Moreover, due to our continuous interest in the synthesis of important heterocyclic compounds,[11,12] and also drug discovery,[13,14] we became interested in the biological profile of these important drug targets (CDKs). In this brief review, various classes of recently discovered potent compounds/scaffolds for the inhibition of CDK1/2 are discussed. Nevertheless, the discussion has been limited to the small molecules and heterocyclic compounds with Mole. Wt. <500, and the large molecules such as the carbohydrates, peptides, nucleotides, *etc*. have been skipped in this review.

DISCUSSION

Various classes of heterocyclic compounds have been explored against the CDK1 and CDK2. The structures of the individual inhibitors or their generic structures/scaffolds of the inhibitors have been presented in the Table 1.

2-Benzylidene-benzofuran-3-one derivatives **1** were tested in CDK inhibition assays and were found to be very potent against CDK1 with IC_{50} value of 0.009-0.060 μM.[15] Additionally these compounds were found to be more selective for CDK1 as compared to other cancer related kinase targets, such as CDK4, PKC, EGFR, *etc*. Furthermore these 4-hydroxybenzofuranone derivatives exhibited anti-proliferative activity when tested in the In vitro cellular assay. 3-hydroxychromone derivatives **2** exhibited highly potency against CDK1 with IC_{50} values of 0.019-0.063 μM.[16] These compounds also showed potent growth inhibition in various cancer cell lines. Griffin et al. synthesized a series of substituted aminopyrimidine derivatives **3** containing 2-arylamino substituents evaluated the compounds for CDK1/CDK2 inhibitory activity.[17] As found with the O^6-cyclohexylmethylpurines, 2-arylaminopyrimidines containing a sulfonamide or carboxamide group at the 4'-position were found to have potent activity against CDKs. The co-crystal structure also confirmed the predicted binding mode of the inhibitor. Huang et al. discovered a novel series of 2-amino-4-(7-azaindol-3-yl) pyrimidines **4** and upon evaluation of their biological activities against the CDKs, these compounds showed good potency for CDK1 as well as the anti-proliferative activity in cell lines.[18] In the cell proliferation assay, all of the tested compounds showed excellent activity in the HeLa cell line. The authors also described the structure–activity relationship (SAR) in the series of compounds that were tested.

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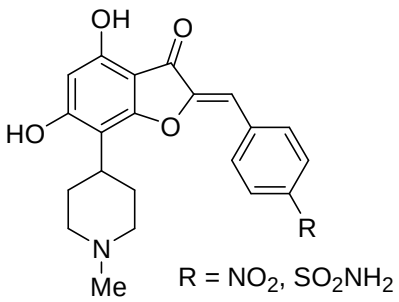
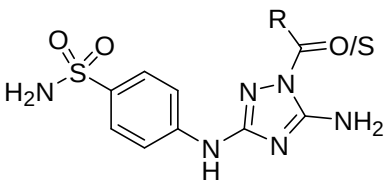
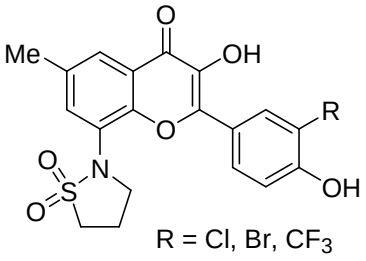
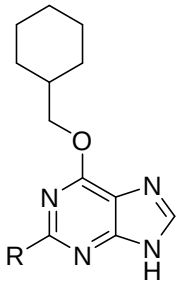
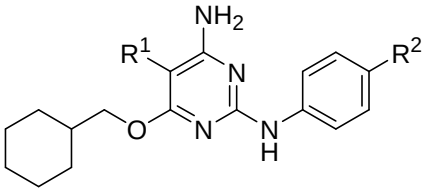
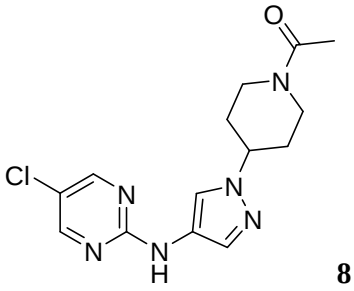
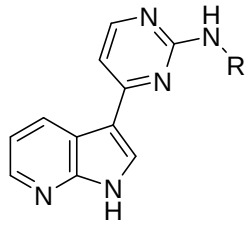
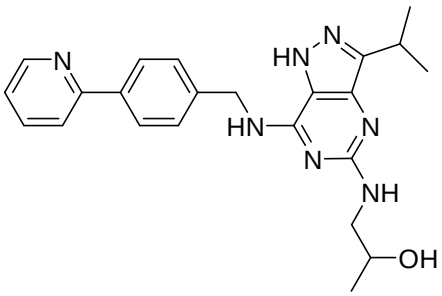
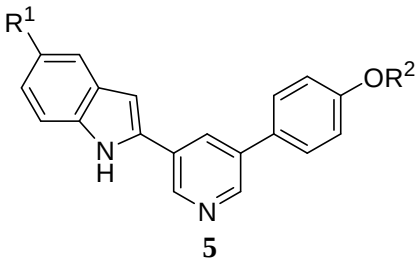
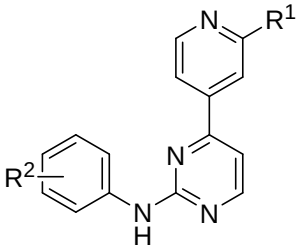
Routier *et al.* reported the synthesis and assay results of a new series of interesting V-shaped 3-[(2-indolyl)-5-phenyl]pyridine (**5**) CDK inhibitors.[19] The synthesis included Stille/Suzuki type cross-coupling reactions on the 3,5-dibromopyridine. Several derivatives inhibited CDK1 in the 0.3– 0.7 micromolar range in Kinase assays, with good selectivity over other kinases like GSK-3. Cytotoxicity was also evaluated using the human leukemia cells with IC_{50} falling in the range of 5–15 μM. The SAR was also evaluated using the molecular modeling tools that suggested that these compounds presumably fit in the ATP binding pocket of the human CDK1. Lin *et al.* reported the synthesis and biological activities of several of 1-acyl-1H-[1, 2, 4] triazole-3, 5-diamine derivatives **6**.[20] These compounds were found to be active for *in vitro* proliferation activity against various human cell lines such as HeLa cell lines. A representative compound also exhibited activity in an *in vivo* mice model. Using structure-based drug discovery program, Davies *et al.* designed and synthesized O^6-cyclohexylmethyl-2-(4′-sulfamoylanilino)purine derivatives 7.[21] Also, Hardcastle *et al.* modified and made similar compounds.[22] These purine/guanine derivatives were found to be very potent against CDK1 and CDK2. Several co-crystal X-ray structures were obtained and SAR was studied.

Table 1. Privileged Heterocyclic Scaffolds for the Inhibition of CDK1/CDK2.

 **1** 2-Benzylidene-benzofuran-3-ones	 **6** Acyl-Substituted [1,2,4]triazole-3,5-Diamines
 **2** 3-Hydroxychromones	 **7** O^6-cyclohexylmethyl-substituted purines
 **3** 2-Aryl Aminopyrimidines	 **8** 2-(Pyrazol-4-ylamino)-pyrimidine

 **4** 2-amino-4-(7-azaindol-3-yl)pyrimidines	 **9** Pyrazolo[4,3-d]pyrimidine
 **5** 3-[(2-indolyl)-5-phenyl]pyridines	 **10** Substituted pyrimidines
*R = substituent(s)	

Degorce *et al.* recently reported the synthesis and activities of a series of inhibitors for the Insulin-like Growth Factor-1 Receptor (IGF-1R).[23] One of the compounds containing 2-(Pyrazol-4-ylamino)-pyrimidine Inhibitor scaffold **8** exhibited CDK1 inhibitory activity, however, it was found that it was not a selective inhibitor. Krystof *et al.* recently reported a series of novel substituted pyrazolo[4,3-d]pyrimidine derivatives that showed good potency against several CDKs.[24] One such compound **9** showed activity against CDK1 (0.777 μM) and CDK2 (0.021 μM) and was found to be quite selective for these CDKs. Gopalsamy *et al.* at Pfizer reported a series of hSMG-1 kinase inhibitors that exhibited anti-cancer activities.[25] Several such compounds containing substituted pyrimidine scaffold **10** also showed interesting CDK1/CDK2 activities.

CONCLUSIONS

Thus a variety of heterocyclic scaffolds have been reviewed as inhibitors for CDK1 and CDK2. Although there are several marketed drugs that are known to inhibit the Cyclin dependent kinases, there is still a vast scope for the discovery of novel potent and selective inhibitors. Several heterocyclic scaffolds especially the substituted pyrimidines seem promising. Given the importance this area of biochemical research holds, further advancement is expected in the future.

CONFLICT OF INTEREST

There is no conflict of interest.

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