

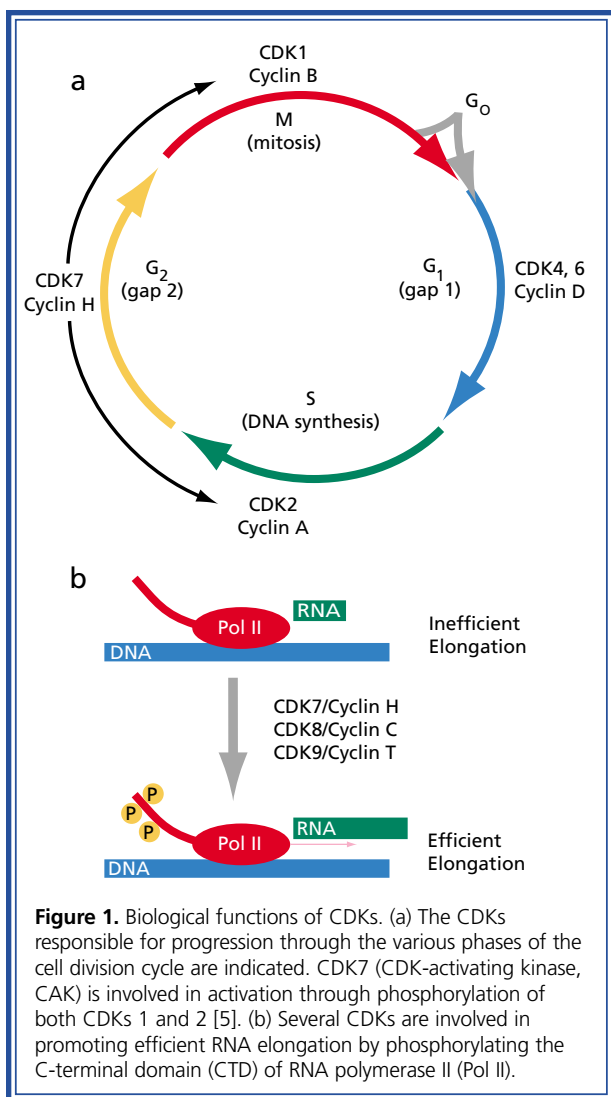
# Functions and Pharmacological Inhibitors of Cyclin-Dependent Kinases (CDKs)

Peter M. Fischer

Cyclin-dependent kinases (CDKs) are Ser/Thr protein kinases that become active when they associate with their respective cyclin subunits. Cyclins are so called because of their characteristic pattern of appearance and disappearance during the cell division cycle [1]. To date, 13 CDKs and 25 cyclins have been discovered and their biological functions remain incompletely understood [2]. CDKs were originally studied for their cell cycle functions (Figure 1a). Thus, orderly cell cycle progression is ensured by activation and deactivation through CDK phosphorylation of various tumor suppressor proteins (e.g. the retinoblastoma protein), transcription factors (e.g. E2F/DP1) and many other proteins that are important for DNA replication and cell division. CDKs themselves are tightly regulated through association with tumor suppressor proteins such as p16<sup>INK4a</sup>, p21<sup>WAF1</sup> and p27<sup>KIP1</sup>, by subcellular localization or by post-

translational modification. In normal cells, progression from one phase of the cycle to the next can be initiated only after passage through checkpoints, where correct completion of the preceding steps, e.g. faithful DNA replication at the end of S phase, is verified. If the steps have not been properly executed, the cell undergoes apoptosis (programmed cell death). Tumor cells possess faulty checkpoints and can proliferate despite a compromised genome. Very often the mechanisms by which transformed cells can override checkpoints are closely related to CDK function [3]. For this reason, restoration of cell cycle control through pharmacological inhibition of CDKs has been actively pursued over the last decade as a new strategy for the treatment of cancer [4]. More recently, however, it has become clear that CDKs are involved in many other cellular processes, including regulation of transcription, differentiation and cell death. Furthermore, many neuronal functions are regulated by CDKs, particularly CDK5.

Both CDK7/cyclin H and CDK9/cyclin T are components of transcription factors (TFIIH and P-TEFb, respectively), where they activate RNA elongation by phosphorylating the carboxyl-terminal domain of RNA polymerase II (Figure 1b). Although it has been known that CDKs are required for replication of viruses that replicate only in dividing cells, such as adeno- and papillomaviruses, it has been shown recently that CDKs are also required for the replication of viruses that can replicate in non-dividing cells, such as HIV-1 and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) [6]. Various CDK inhibitors, including **roscovitine** (Prod. No. [R 7772](#)) and flavopiridol, have already been shown to be potent anti-viral agents [7,8]. It remains to be determined, however, exactly which CDK(s) mediate such anti-viral effects.



## About the Author

**Peter M. Fischer** received his Ph.D. in bioorganic chemistry from Deakin University, Geelong, Victoria, Australia. He has worked in academia, as well as the biotechnology and pharmaceutical industries, on peptidomimetic and traditional medicinal chemistry projects related to drug discovery. For the last five years, he has been with the cancer research company Cyclacel, in Dundee, Scotland, for whom he established structure-based design and medicinal chemistry capabilities. He is currently Head of Discovery Research and focuses on cell cycle-related drug discovery targets, including cyclin-dependent kinases and other protein kinases.

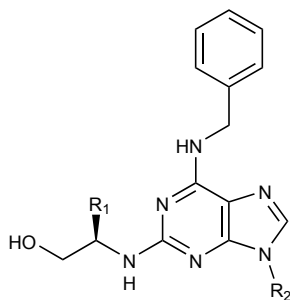
## Cyclin-Dependent Kinases (CDKs)...(continued)

### Pharmacological Inhibitors of CDKs

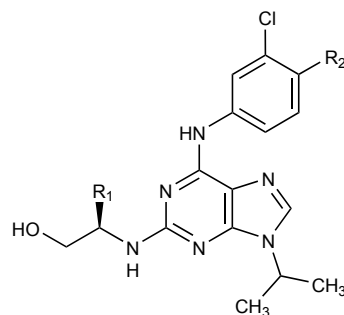
**Purines and Pyrimidines (Figure 2).** Substituted purines are the CDK inhibitors most structurally similar to **adenosine 5'-triphosphate** (ATP, Prod. No. **A 7699**), whose binding they antagonize. Surprisingly, however, all known purine-based inhibitors for which co-crystal structures with CDK2 have been solved do not bind to the kinase in a way that mimics ATP [9]. Substituted adenines yielded the first CDK-selective protein kinase inhibitors [10]. **Olomoucine** (Prod. No. **O 0886**) is a weak inhibitor of CDKs 1 and 2; examples of close analogs with improved potency are roscovitine and **N<sup>9</sup>-isopropylolomoucine**

**olomoucine** (Prod. No. **I 0763**) [11]. Roscovitine inhibits cyclin complexes of CDKs 1, 2, 5, 7 and 9 with low micromolar to high nanomolar IC<sub>50</sub> values [7,12], but exhibits a much weaker effect on CDKs 4 and 6. The purvalanols display a similar selectivity profile and contain 6-anilino rather than 6-benzyl-amino purine substituents. They are among the most potent CDK2 inhibitors reported to date [13,14]; thus purvalanol B inhibits CDKs 1 and 2 with IC<sub>50</sub> values of < 10 nM, but, unlike **purvalanol A** (Prod. No. **P 4484**), has no effect on cell proliferation, presumably due to the presence of a carboxyl group that is ionized at physiological pH, thus

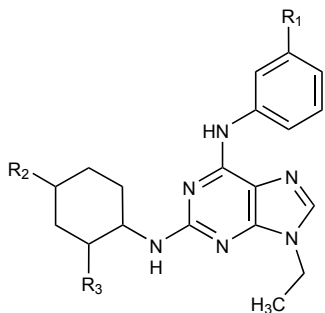
**Figure 2.** CDK inhibitors with purine- and pyrimidine-based skeletons.



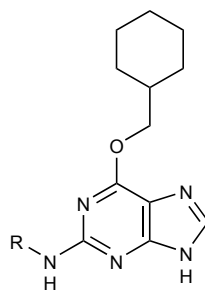
**Olomoucine** (R<sub>1</sub> = H, R<sub>2</sub> = Me) (Prod. No. **O 0886**)  
**Roscovitine** (R<sub>1</sub> = Et, R<sub>2</sub> = iPr) (Prod. No. **R 7772**)  
**N<sup>9</sup>-isopropylolomoucine** (R<sub>1</sub> = H, R<sub>2</sub> = iPr) (Prod. No. **I 0763**)



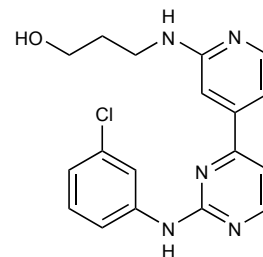
**Purvalanol A** (R<sub>1</sub> = iPr, R<sub>2</sub> = H) (Prod. No. **P 4484**)  
 Purvalanol B (R<sub>1</sub> = iPr, R<sub>2</sub> = COOH)  
 "Compound 52" (R<sub>1</sub> = H, R<sub>2</sub> = H)



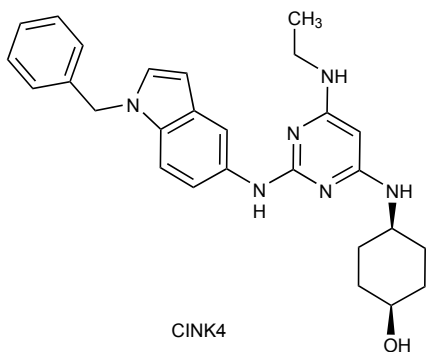
**CGP79807** (R<sub>1</sub> = CN, R<sub>2</sub> = OH, R<sub>3</sub> = H)  
**CGP74514** (R<sub>1</sub> = Cl, R<sub>2</sub> = H, R<sub>3</sub> = NH<sub>2</sub>) (Prod. No. **C 3353**)



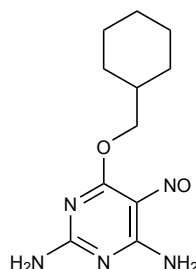
**NU2058** (R = H)  
**NU6102** (R = 4-(SO<sub>2</sub>NH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>)



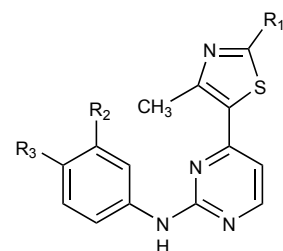
**CGP60474**



**CINK4**



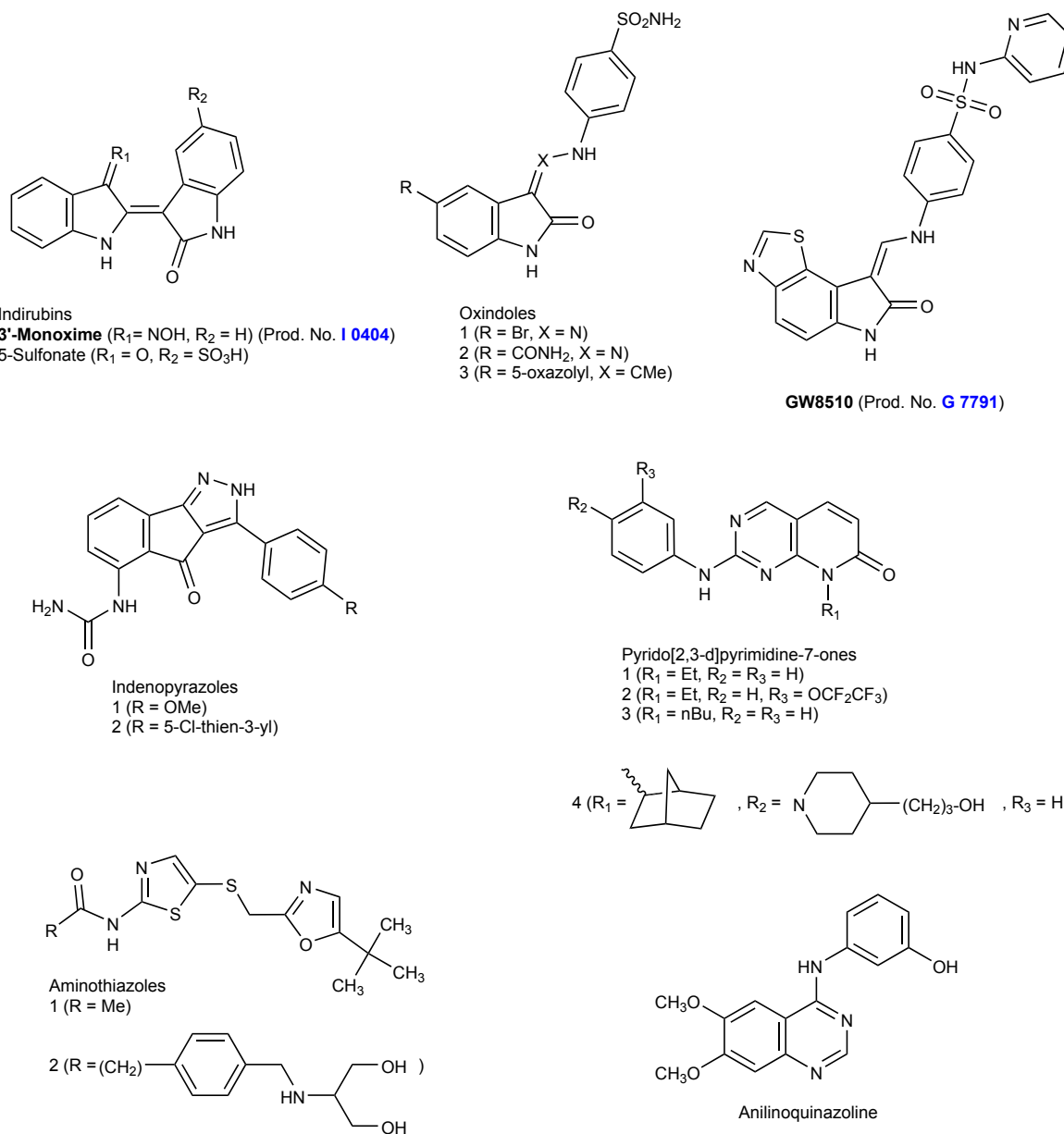
**NU6027**



**Thiazolopyrimidines**  
 1 (R<sub>1</sub> = Me, R<sub>2</sub> = H, R<sub>3</sub> = CF<sub>3</sub>)  
 2 (R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = NO<sub>2</sub>, R<sub>3</sub> = H)  
 3 (R<sub>1</sub> = Me, R<sub>2</sub> = H, R<sub>3</sub> = NMe<sub>2</sub>)

## Cyclin-Dependent Kinases (CDKs)...(continued)

**Figure 3.** Oxindole, indenopyrazole, pyridopyrimidine, anilinoquinazoline and aminothiazole CDK inhibitors.

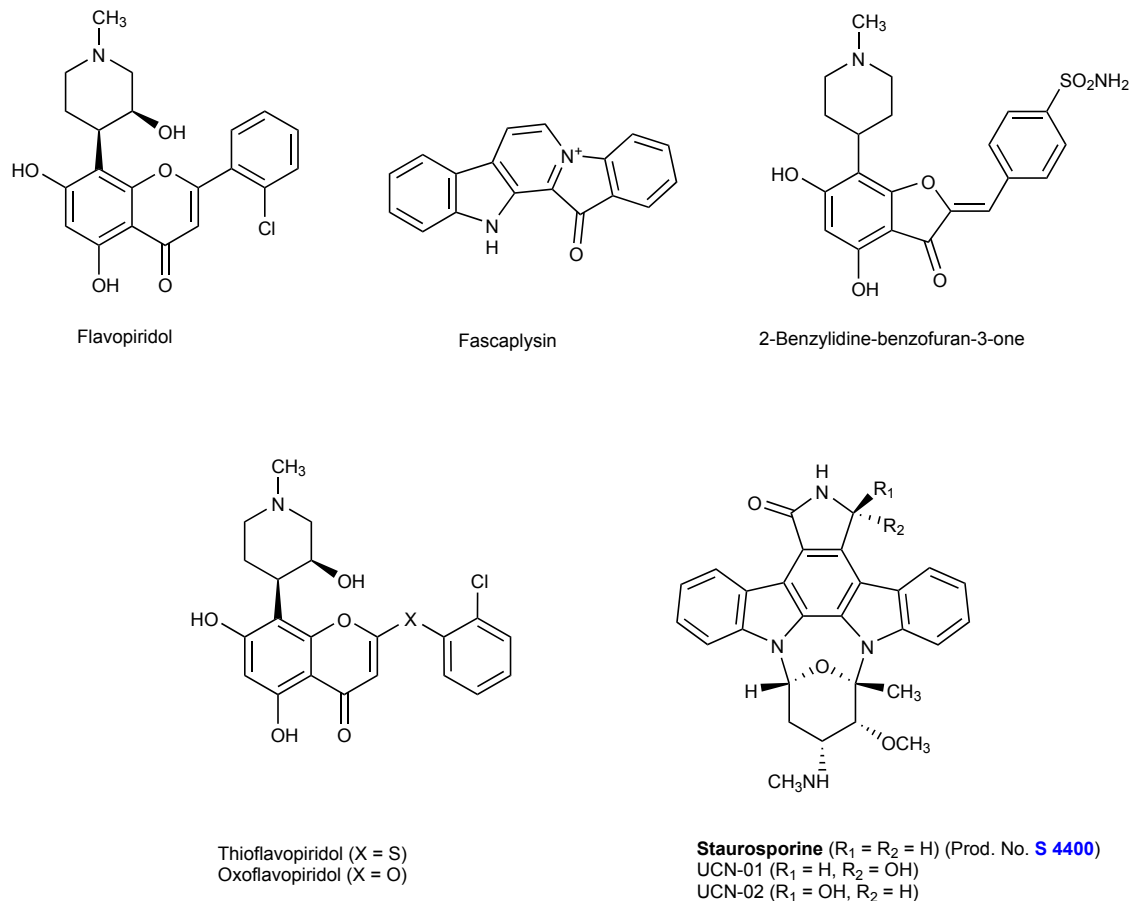


preventing cellular uptake. Potent purine-based CDK inhibitors, such as CGP79807 and **CGP74514** (Prod. No. **C 3353**), with cyclic hydroxy- or amino-alkyl-amino groups present at C2, have also been described [15,16]. Guanine derivatives, e.g. compounds NU2058 and NU6102, represent yet another subgroup of purine-derived inhibitors [17]. Compound NU2058 is modestly potent against CDKs 1 and 2; structure-based design starting from this compound led to the identification of NU6102 [18], which possesses both increased potency and aqueous solubility [19].

Phenylaminopyrimidines have provided a rich source of protein kinase inhibitors [20], including certain CDK-selective compounds. Thus CGP60474 [21] and CINK4 [22] were reported as CDK1/2- and CDK4-selective inhibitors, respectively. The nitrosopyrimidine NU6027 was designed as an alternative to the corresponding purine-based compound NU2058 and the designed mimicry was confirmed crystallographically [19]. We have also introduced thiazolopyrimidines such as structures 1-3 in Figure 2 [23], that were shown to be potent *in vitro* and *in vivo* CDK2 inhibitors. Thiazolopyrimidine 2 is an

## Cyclin-Dependent Kinases (CDKs)...(continued)

**Figure 4.** CDK inhibitors related to Flavopiridol, Staurosporine and other structurally related CDK inhibitors.



extremely potent CDK2 inhibitor ( $IC_{50} < 1$  nM). Despite the large number of purine- and pyrimidine-based CDK inhibitors already known, new analogs continue to be reported [24-27].

### Other Heterocyclic Pharmacophores (Figure 3).

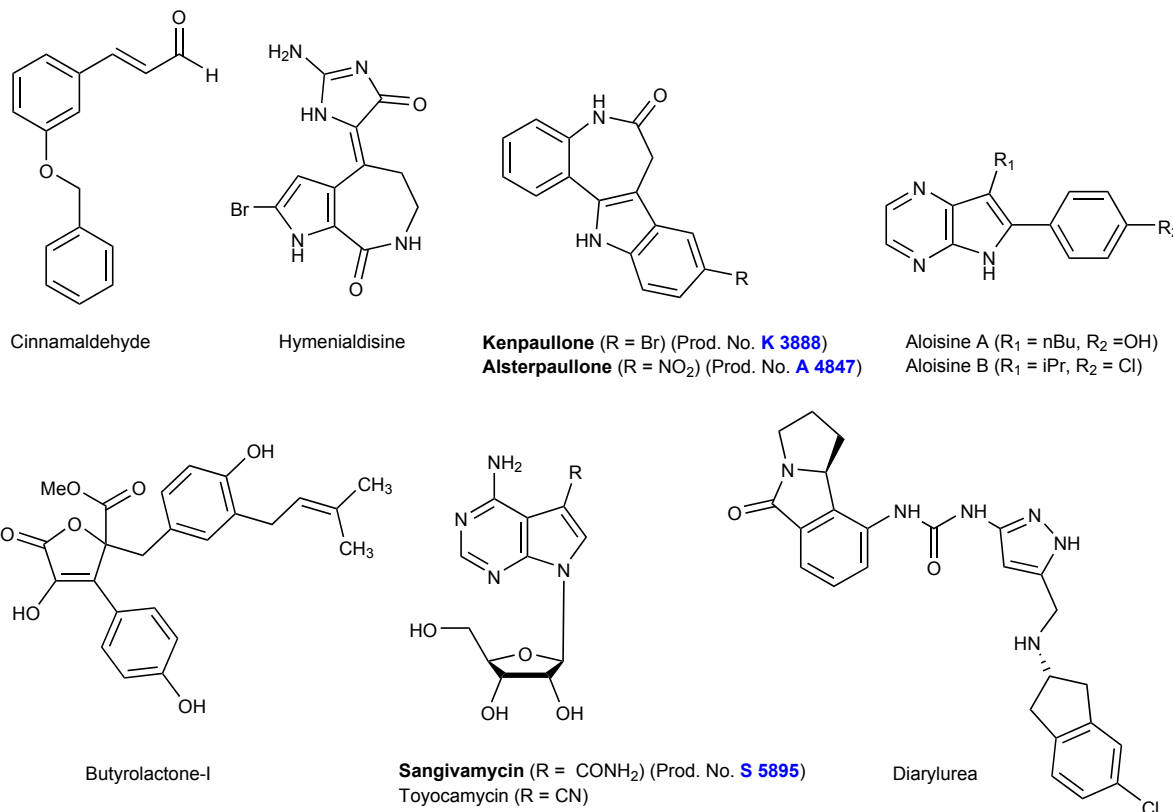
Isoindigo is a dye that contains two fused oxindole groups; its red-colored isomer indirubin is the active constituent of a traditional Chinese anti-leukemia medicine and was found to be a CDK inhibitor [28]. Both **indirubin-3'-monoxime** (Prod. No. **I 0404**) and indirubin 5-sulfonate [29] are potent and apparently selective inhibitors of CDK1 and CDK2 [30]. Numerous oxindole-based CDK inhibitors have been described [31] and an extensive study was published [32] showing both phenylhydrazone (1 & 2) and anilinomethylene (3) oxindoles. A potent fused thiazole derivative (**GW8510**, Prod. No. **G 7791**) inhibits CDKs 1, 2 and 4 at low nanomolar concentrations and blocks G<sub>1</sub>/S cell cycle transition. This compound has been proposed as an agent that may prevent chemotherapy-induced alopecia through

arresting rapidly dividing hair follicle cells [33\*]. Structurally related to the oxindoles are the indenopyrazoles [34], which have also been shown to be CDK inhibitors with potency and selectivity against CDKs 1, 2 and 4. Compounds 1 and 2 are examples for which an anti-proliferative effect, consistent with CDK inhibition, has been demonstrated [35,36]. Using the simple pyrido[2,3-d]pyrimidine-7-one compound 1 as a starting point and applying a structure-based design approach [37], compounds with differing CDK selectivity were developed [38]. Thus compounds 2, 3 and 4 had up to 20-fold selectivity for CDK1 ( $IC_{50} = 91$  nM), CDK2 ( $IC_{50} = 37$  nM), and CDK4 ( $IC_{50} = 8$  nM) [39], respectively. Anilinoquinazolines, another CDK2 inhibitor class, emerged from an extensive medicinal chemistry program [40]. Thiazole-based compounds have also been reported. Thus aminothiazole compound 1 appears to be a CDK-selective protein kinase inhibitor, whereas compound 2 represents a second generation example from this compound class with improved cellular and *in vivo* potency [41].

\* Note added in proof: It should be noted that the report on prevention of chemotherapy-induced alopecia by CDK inhibitors [33] has recently been retracted: Davis, S.T. et al., *Science*, **298**, 1095 (2002).

## Cyclin-Dependent Kinases (CDKs)...(continued)

**Figure 5.** Various small-molecule CDK inhibitors.



### Flavonoids and Staurosporines (Figure 4).

Flavopiridol is the most advanced CDK inhibitor in terms of clinical development [42]. It was originally discovered as an EGF-receptor tyrosine kinase inhibitor but it was found later to be 100-fold more potent as a CDK inhibitor [43]. However, the mechanism of action of flavopiridol remains an area of active research [44]. Extensive structure-activity relationships around flavonoid compounds in general, and rohitukine derivatives in particular, have been established [9]. Thio- and oxo-flavopiridol analogs with somewhat altered selectivity profiles were also published [45]. Furthermore, synthetically simpler flavopiridol analogs, 2-benzylidene-benzofuran-3-ones, have been described [46]. These rationally designed flavopiridol mimics appear to have good CDK selectivity and potency, particularly for CDK1, but possess only modest cellular activity. Staurosporines are obtained from bacterial fermentations and are promiscuous protein kinase inhibitors. Nevertheless, the fact that at least part of the biological effects of both **staurosporine** (Prod. No. **S 4400**) and UCN-01 may be due to CDK inhibition has been demonstrated [9]. A marine sponge pigment known as fascaplysin, whose structure is somewhat related to staurosporines, was reported as a CDK4-selective inhibitor [47].

### Other CDK Inhibitors (Figure 5).

Diarylureas are highly represented in screening libraries and it is thus not surprising that CDK inhibitors from this class have been described; the analog shown in Figure 5 inhibited CDK4 with an IC<sub>50</sub> value of 2.3 nM and was 190- and 780-fold selective with respect to CDK2 and CDK1, respectively [48,49]. In a particularly interesting study designed to identify CDK4-selective compounds, the functional status of the CDK4/6-specific tumor suppressor protein 16<sup>INK4a</sup> of the 60 cancer cell lines of the National Cancer Institute's drug screen panel was matched to the growth inhibitory activity of more than 50,000 compounds previously screened in that panel [50]. Compounds were then ranked according to Pearson correlation coefficients using the COMPARE algorithm [51]. A number of high-ranking compounds from this analysis, including 9-thio(10H)-acridones and benzothiadiazines, were subsequently shown to be CDK inhibitors with selectivity for CDK4. Other recently reported ATP antagonists with selectivity for CDK4 are certain cinnamaldehydes, derived from *Cinnamomum cassia* extracts [52]. Yet another marine natural product with CDK inhibitory properties is hymenialdisine [53]. Compounds containing the 7,12-dihydro-indolo[3,2-d][1]benzazepin-6(5H)-one structure are now termed paullones in honor of

## Cyclin-Dependent Kinases (CDKs)...(continued)

Ken Paull, the late inventor of the COMPARE algorithm that led to their discovery. Paullones were found to be potent CDK inhibitors [54]; thus **kenpaullone** (Prod. No. [K 3888](#)) is a selective inhibitor of CDKs 1, 2 and 5 with nanomolar activity. The most potent derivative in this series was named **alsterpaullone** (Prod. No. [A 4847](#)) [55]. Another fermentation product with potent CDK1 and CDK2 inhibition properties is butyrolactone-I [56]. The nucleoside antibiotic **sangivamycin** (Prod. No. [S 5895](#)) has been known for some time to inhibit **protein kinase A** (Prod. No. [P 5511](#)) and **protein kinase C** (Prod. No. [P 0329](#)) and to possess potent anti-proliferative properties [57]. In the course of a screen of culture media from soil microorganisms against CDK1, a potent inhibitor was identified [58]: toyocamycin is structurally related to sangivamycin, differing only in a nitrile instead of carboxamide substituent on the pyrrolopyrimidine ring. The most recently reported pharmacophore with high CDK potency and selectivity encompasses compounds containing the 6-phenyl[5H]pyrrolo[2,3-b]pyrazine core structure, e.g. aloisines A and B [59].

### Selectivity

Many small-molecule CDK inhibitors have also been found to inhibit certain other kinases. Considering the fact that the human genome probably encodes in excess of 800 protein kinases, such observations are hardly surprising. Many ATP antagonist kinase inhibitors previously thought to be selective were, in fact, later found to be less than selective when assayed against a large panel of functionally diverse kinases [60]. CDKs are phylogenetically closely related to extracellular signal-regulated kinases (ERK-1 and **ERK-2**, Prod. No. [M 3172](#)), as well as to **glycogen synthase kinase-3** (GSK-3, Prod. No. [G 1663](#)). These latter enzymes are frequently also affected by CDK inhibitors. In particular, many CDK2 inhibitors, including hymenialdisine, flavopiridol, certain oxindoles, indirubins, paullones and aloisines, but apparently not purine-based inhibitors such as roscovitine, are practically equipotent against GSK-3 [2]. The structural basis for rationalizing and designing inhibitor selectivity for individual CDKs is still comparatively weak, since only CDK2-inhibitor complex X-ray co-crystal structures have so far been obtained [61], whereas other CDKs have not so far proven amenable to crystallization. In terms of selectivity within the CDK class, inhibitors can be classified as belonging to four groups. The most prominent exponent of the non-specific protein kinase inhibitor group with activity against CDKs is staurosporine. Next there exists a group of apparently pan-CDK inhibitors (CDKs 1, 2, 4, 6, 9), examples are flavopiridol, oxindole 1 and GW8510.

## Additional Cyclin-Dependent Kinase Products Available from Sigma-RBI

### Cyclin-Dependent Kinases and Phosphatases

- [C 7484](#) CDC25A, Active
- [C 7609](#) CDC25B, Active
- [W 4387](#) Wee 1, Active

### Cyclin-Dependent Kinase Inhibitors

- [A 3145](#) Apigenin

### Cyclin-Dependent Kinase Antibodies

- [C 0228](#) Anti-phospho-Cdc2 (Cdk1) (pTyr<sup>15</sup>)
- [C 3085](#) Monoclonal Anti-p34cdc2
- [C 9479](#) Monoclonal Anti-Cdc25A
- [C 0349](#) Monoclonal Anti-Cdc25C
- [C 4973](#) Anti-Cdk1 (p34cdc2)
- [C 0231](#) Anti-Phospho-Cdk1 (pThr<sup>14</sup>/pTyr<sup>15</sup>)
- [C 5223](#) Anti-Cdk2
- [C 9987](#) Anti-Cdk3, C-Terminal
- [C 8218](#) Monoclonal Anti-Cdk4
- [C 8343](#) Monoclonal Anti-Cdk6
- [C 7089](#) Monoclonal Anti-Cdk7/CAK
- [C 0238](#) Anti-Cdk8
- [C 4710](#) Monoclonal Anti-Cyclin A
- [C 7464](#) Monoclonal Anti-Cyclin D1
- [C 7339](#) Monoclonal Anti-Cyclin D2
- [C 7214](#) Monoclonal Anti-Cyclin D3
- [C 4976](#) Monoclonal Anti-Cyclin E
- [C 4210](#) Anti-Cyclin A
- [C 8831](#) Anti-Cyclin B1
- [C 5588](#) Anti-Cyclin D1
- [C 5226](#) Anti-Cyclin G
- [C 5351](#) Anti-Cyclin H

### Oligonucleotide Primer Sets for PCR

- [P 8092](#) Cyclin A Primer Set
- [P 8467](#) Cyclin B Primer Set
- [P 8842](#) Cyclin D Primer Set
- [P 9217](#) Cyclin E Primer Set

The group of semi-selective CDK inhibitors remains poorly defined, especially as far as the "new" CDKs of interest are concerned (CDKs 7, 8 and 9). Nevertheless, semi-selective compounds usually preferentially inhibit CDKs 1, 2 and 5 (and 9?), or CDKs 4 and 6. The former subgroup contains e.g. olomoucine, roscovitine, purvalanols, paullones, aloisines and butyrolactone-I, whereas the latter comprises compounds such as CINK4, fascaplysin and pyrido[2,3-d]pyrimidine-7-one compound 4. Finally, there is a hypothetical group representing individual CDK selectivity. To date, no such compounds have been identified and perhaps this is unlikely to happen due to the high homology between individual CDKs, particularly within the ATP binding pocket. Nevertheless, such highly selective

## Cyclin-Dependent Kinases (CDKs)...(continued)

inhibitors would be extremely useful tools for cellular pharmacology studies and perhaps also as therapeutic agents. It should be noted that a complete selectivity picture for an inhibitor is not usually available because only a limited number of CDK/cyclin complexes can or are being assayed; thus, in our laboratories we routinely screen against the following complexes: 1-B, 2-E, 2-A, 4-D, 7-H and 9-T. The fact that potencies are difficult to compare when  $IC_{50}$  rather than  $K_i$  values are reported, particularly if the ATP concentrations in the assays are not identical, should also be kept in mind [9].

### Cellular Mode of Action

In general, pharmacological inhibitors of CDKs display selective anti-proliferative effects on cycling cells, especially tumor cells. Depending on the selectivity profile, growth arrest in  $G_0/G_1$  (CDK4/6-selective) or in  $G_1/S$  and  $G_2/M$  (pan-CDK- and CDK1/2-selective) is observed. More importantly, many compounds, especially potent CDK2 inhibitors, have been observed to induce apoptosis selectively in transformed cells [62]. As discussed above, many compounds with very high potency against CDKs *in vitro* are available. However, in many cases this biochemical potency does not translate into cellular potency, presumably due to unknown mechanistic reasons and perhaps because of high physiological ATP concentrations. Connected with this problem is the question of what are the actual cellular targets of a biochemical CDK inhibitor. One technique that has been applied to CDK inhibitors is affinity chromatography of cell lysates on immobilized inhibitor preparations. Indeed it was found that, apart from CDKs, other proteins were also bound [63,64].

### Conclusion

Because of the clear connection between pharmacological CDK inhibition and cell cycle regulation, the potential use of CDK inhibitors in oncology was appreciated some time ago and the first molecules are now undergoing clinical evaluation [4]. However, recent novel understanding of CDK biology suggests additional potential applications. Apart from virology, which was discussed above, several other indications where cell proliferation plays a part may be amenable to therapy with CDK inhibitors. Some of these include nervous system disorders such as Alzheimer's disease (CDK5), infection by unicellular parasites that possess CDKs (malaria, leishmaniasis), glomerulonephritis (mesangial cell proliferation), and cardiovascular diseases (atherosclerosis, restenosis, cardiac hypertrophy) [65,66].

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