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The CDK inhibitors in cancer research and therapy

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Abstract Chemical compounds that interfere with an enzymatic function of kinases are useful for gaining insight into the complicated biochemical processes in mammalian cells. Cyclin-dependent kinases (CDK) play an essential role in the control of the cell cycle and/or proliferation. These kinases as well as their regulators are frequently deregulated in different human tumors. Aberrations in CDK activity have also been observed in viral infections, Alzheimer's, Parkinson's diseases, ischemia and some proliferative disorders. This led to an intensive search for small-molecule CDK inhibitors not only for research purposes, but also for therapeutic applications. Here, we discuss seventeen CDK inhibitors and their use in cancer research or therapy. This review should help researchers to decide which inhibitor is best suited for the specific purpose of their research. For this purpose, the targets, commercial availability and IC_{50} values are provided for each inhibitor. The review will also provide an overview of the clinical studies performed with some of these inhibitors.

Keywords CDK · Kinases · Small-molecule inhibitors · Cancer · Cell cycle

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Introduction

Protein kinases are a large family of enzymes catalyzing protein phosphorylation. The phosphorylation results in a change in function of proteins such as their location, interaction with other proteins or enzymatic activity. The human genome contains more than 500 protein kinase genes. Protein phosphorylation plays a central role in the regulation of cell proliferation, differentiation and apoptosis. Therefore, deregulation of kinase activity can result in striking changes in these processes. Particularly, deregulated kinases are often found to be oncogenic and can be central for the survival of cancer cells (Hunter and Cooper 1985). Moreover, the phosphorylation of some proteins, such as ErbB2 (Cicenas et al. 2006; Cicenas 2007; DiGiovanna et al. 2005), EGFR (Cicenas 2007; Kanematsu et al. 2003), Erk (Milde-Langosch et al. 2005; Bergqvist et al. 2006; Svensson et al. 2005), SchA (Cicenas et al. 2010), p21Cip1 (Xia et al. 2004), p27Kip1 (Clarke 2003), Akt (Cicenas et al. 2004, 2005; Cicenas 2008) and retinoblastoma protein (Rb) (Derenzini et al. 2007), is associated with prognosis in cancers.

Cyclin-dependent kinases (CDKs) are protein kinases involved in important cellular processes, such as cell cycle or transcription regulation. Human genome contains 21 genes encoding CDKs and five genes encoding more distant protein kinases entitled CDK-like (CDKL) kinases. Recently, the new nomenclature for the CDKs had been proposed (Malumbres et al. 2009). The roles of "classical" 11 CDK proteins have been investigated to a different extent. Different CDKs are responsible for the activation of the cell cycle of quiescent cells as well as for the progression of the cell cycle from G1 to mitosis. Each of the CDKs controls a specific checkpoint of the cell cycle. CDKs are activated by the binding to the cyclins and thus forming

specific complexes. Cdk4–CyclinD, Cdk6–CyclinD and Cdk2–CyclinE complexes regulate the G0–G1 transition and the early phases of G1 through phosphorylation of the Rb. Cdk2–CyclinE complexes are also involved in the G1–S transition. Cdk2 can also associate with CyclinA throughout the progression of S phase. Cdk1–CyclinA complex participates in the S–G2 and Cdk1–CyclinB G2–M (Malumbres and Barbacid 2005). Cdk3 seems to also participate in Rb phosphorylation. It is highly related to Cdk2 and Cdk1 and interacts with CyclinE and CyclinA. Cdk5 is activated by p35 and p39 proteins that are not cyclins and are typically expressed in brain. Cdk5 mostly acts in neural cells and is involved in the regulation of cell survival, transcription, migration and membrane transport (Dhariwala and Rajadhyaksha 2008). Cdk7 is a component of the Cdk-activating kinase (CAK), which acts upstream of cell-cycle CDKs. It is also a component of the general transcription factor TFIIH and is involved in transcription (Fisher 2005). Cdk8 binds to CyclinC and Cdk9 binds to CyclinT, and they are also involved in the regulation of transcription (Malumbres and Barbacid 2005). No cyclin partner for Cdk10 has been identified so far; however, this kinase seems to be involved in regulating the G2–M phase by inhibition of Ets2 transactivation (Kasten and Giordano 2001). Cdk11 binds to CyclinL and is involved in mRNA splicing (Loyer et al. 2008). It can also interact with CyclinD and repress proliferation (Duan et al. 2010).

Most of the CDKs have been implicated in human cancers. CDK1 had been shown to have a diagnostic value in esophageal (Hansel et al. 2005) and breast cancers (Kim et al. 2008; Nakayama et al. 2009). CDK2 expression or activity has been used for the prognosis of breast (Kim et al. 2008), ovarian (Marone et al. 1998) and oral (Mihara et al. 2001) cancers. Aberrant expression of CDK4 has been implicated in ovarian (Kusume et al. 1999), urinary bladder (Simon et al. 2002), endometrial (Semczuk et al. 2004) and oral (Poomsawat et al. 2010) cancers. CDK5 has been shown to be involved in lung cancer (Choi et al. 2009; Liu et al. 2010). The expression of CDK 6 is also altered in oral cancer (Poomsawat et al. 2010). CDK7 polymorphisms have been shown to have an effect on breast cancer (Jeon et al. 2010).

Aberrations in CDK expression, activity and regulation have also been found in viral infections, neurodegenerative disorders, proliferative diseases, etc. That led to an intensive hunt for small-molecule CDK inhibitors for the therapeutic purposes. All CDK inhibitors developed to date can be subdivided into two main groups: broad-range inhibitors (such as flavopiridol, olomoucine, roscovitine, kenpaullone, SNS-032, AT7519, AG-024322, (S)-Roscovitine and R547) and specific inhibitors (such as fascaplysin, ryuvidine, purvalanol A, NU2058, BML-259, SU 9516, PD 0332991 and P-276–00). The aim of this review is to discuss the properties as well as the use of these inhibitors in cancer research and therapy in more detail.

Broad-range inhibitors

Flavopiridol (Fig. 1) (also L-868275, HMR-1275, Alvocidib or NSC-649890) is a broad-range CDK inhibitor. It inhibits CDK1, CDK2, CDK4 and CDK7 at IC_{50} value range of 0.04–0.4 μM (Losiewicz et al. 1994; Carlson et al. 1996). It was first discovered as epidermal growth factor receptor (EGFR) inhibitor, which inhibits at IC_{50} value of 21 μM. Later, it was shown that flavopiridol could inhibit the growth of breast and lung cancer cell lines (Kaur et al. 1992) and prostate, head and neck cancer and leukemia xenografts (Drees et al. 1997; Patel et al. 1998; Arguello et al. 1998). Since it did so at much lower concentrations than those needed for the inhibition of the EGFR, new targets were investigated and its effect on CDKs was found.

Flavopiridol is a commercially available inhibitor broadly used in the research. It is also the first CDK inhibitor used in human clinical trials. Several phase I clinical trials showed that flavopiridol as single agent has an antitumor effect in patients with renal, prostate and colon cancer, metastatic gastric cancer and non-Hodgkin's lymphoma (Senderowicz et al. 1998; Tan et al. 2002; Thomas et al. 2002; Whitlock et al. 2005). Secretory diarrhea, neutropenia, nausea, vomiting and proinflammatory syndrome were reported as main drug adverse effects (DAE). Another phase I clinical study of sequential paclitaxel and flavopiridol showed clinical activity in patients with esophagus, lung and prostate cancer including patients who had not

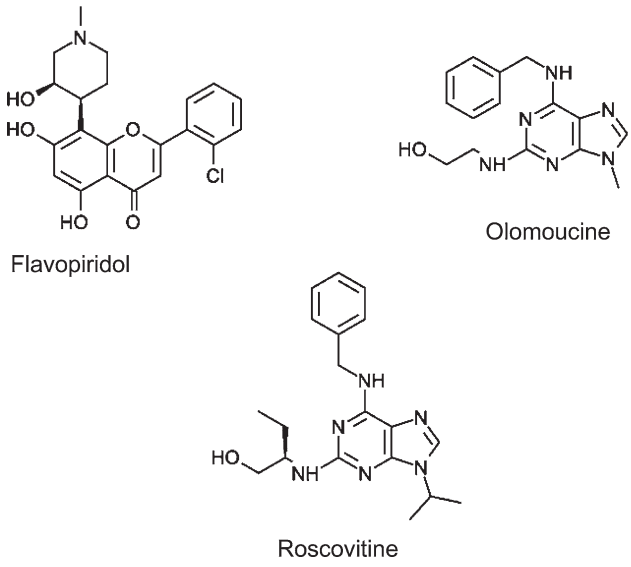

Fig. 1 Flavopiridol, Olomoucine and Roscovitine

responded to paclitaxel alone (Schwartz et al. 2002). The combination of flavopiridol and docetaxel has been shown to be quite promising in several phase I clinical studies (Fornier et al. 2007; El-Rayes et al. 2006; Tan et al. 2004). The combinations of flavopiridol with gemcitabine and irinotecan (Fekrazad et al. 2010), vorinostat (Dickson et al. 2010), oxaliplatin and fluorouracil/leucovorin (Rathkopf et al. 2009), paclitaxel and carboplatin (George et al. 2008), cisplatin and carboplatin (Bible et al. 2005) and irinotecan (Shah et al. 2005) were also assessed in various solid tumors in phase I clinical trials. In leukemias, flavopiridol both as single agent (Phelps et al. 2009; Blum et al. 2010) and in combinations with 1-beta-D-arabinofuranosylcytosine and mitoxantrone (Karp et al. 2005) and cytosine arabinoside and mitoxantrone (Karp et al. 2011) showed a promise in phase I clinical trials.

Phase II clinical trials involving flavopiridol have also been carried out. Flavopiridol, however, did not have a desired effect in advanced gastric carcinoma (Schwartz et al. 2001), non-small-cell lung cancer (Shapiro et al. 2001), advanced colorectal cancer (Aklilu et al. 2003), androgen-independent prostate cancer (Liu et al. 2004), melanoma (Burdette-Radoux et al. 2004), endometrial carcinoma (Grendys et al. 2005) and advanced soft tissue sarcoma (Morris et al. 2006). It did have a modest effect in mantle cell lymphoma (Kouroukis et al. 2003) and advanced renal cell carcinoma (Van Veldhuizen et al. 2005). Yet in another phase II clinical trial, flavopiridol achieved significant clinical activity in patients with relapsed chronic lymphocytic leukemia (Lin et al. 2009). A phase II study of flavopiridol in combination with docetaxel in pancreatic cancer was also disappointing (Carvajal et al. 2009).

Olomoucine (Fig. 1) is another broad-range CDK inhibitor. It inhibits CDK1 (IC_{50} = 7 μM), CDK2 (IC_{50} = 7 μM) and CDK5 (IC_{50} = 3 μM). It can also inhibit ERK1 kinase at higher concentrations (IC_{50} = 25 μM). Olomoucine is also a commercially available inhibitor and was first purine CDK inhibitor discovered. Olomoucine has never been used in any clinical trials, since the preference was given to its derivative—roscovitine.

Roscovitine (Fig. 1) (also CY-202, (R)-Roscovitine, Seliciclib) is also a broad-range purine inhibitor, which inhibits CDK1, CDK2, CDK5 and CDK7 (IC_{50} ~ 0.5–0.2 μM) but is a poor inhibitor for CDK 4 and CDK 6 (IC_{50} > 100 μM). It is also commercially available CDK inhibitor broadly used in the research. Oddly, in a scientific literature, it is frequently referred to as a selective CDK5 inhibitor, despite the fact that it inhibits at least other 3 CDKs. A phase I clinical trial with roscovitine showed no objective tumor responses, but disease stabilization was observed in eight patients (Benson et al. 2007). Main DAEs included fatigue, skin rash, hyponatremia and hypokalemia. Emesis and reversible abnormal liver function were also observed. In another phase I clinical trial, one patient with hepatocellular carcinoma showed partial response and six patients achieved tumor (two patients with NSCLC, one with parotid cylindroma, one with corticosurrenaloma, one with thymic carcinoma and one with adenocarcinoma of unknown primary) (Le Tourneau et al. 2010). DAEs included nausea, vomiting, asthenia and hypokalemia. Roscovitine is presently under investigation in several phase II clinical trials in leukemias as monotheraphy and in combination trials against NCLC (with gemcitabine/cisplatin or docetaxel) and metastatic breast cancer (with capecitabine) (Fischer and Gianella-Borradori 2005).

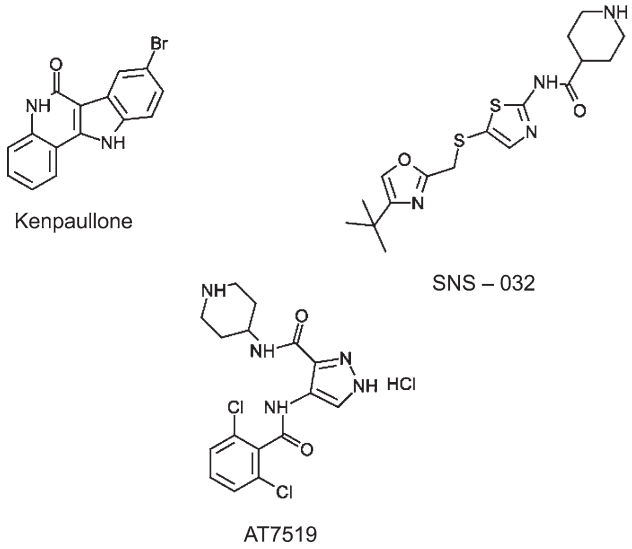

Fig. 2 Kenpaulollone, SNS-032 and ATZ519

Kenpaullone (Fig. 2) (also NSC 664704, 9-Bromopaullone), another commercially available broad-range CDK inhibitor, inhibits CDK1 (IC_{50} = 0.4 μM), CDK2 (IC_{50} = 0.7 μM) and CDK5 (IC_{50} = 0.9 μM). It is much less potent toward CDK4 (IC_{50} > 100 μM). It also inhibits GSK3β (IC_{50} = 0.23 μM). Kenpaullone was found as an in vitro antiproliferative agent in the NCI's anticancer drug screen panel, and molecular modeling studies have shown that it binds to the ATP-binding pocket of CDK2 similar to other CDK2 inhibitors. Although it is a commercially available inhibitor vastly used in research, it had not entered clinical trials so far.

SNS-032 (also BMS-387032) (Fig. 2) is a broad-range inhibitor, which inhibits CDK9 (IC_{50} = 0.004 μM), CDK2 (IC_{50} = 0.038 μM) and CDK7 (IC_{50} = 0.062 μM). It can inhibit other CDKs at higher concentration (IC_{50} > 0.3 μM), but at that concentration, it also inhibits GSK3 kinase. SNS-032 was initially synthesized by Bristol-Myers Squibb Pharmaceutical Research Institute in an attempt to produce a selective inhibitor of CDK2. It was named BMS-387032 at the time. Two phase I clinical trials were carried out for

metastatic refractory solid tumors and one in lymphoma. All those trials showed that this drug was well tolerated by the patients. Later, already under SNS-032 name, the phase I clinical trial was performed with 21 patients. Patients with metastatic solid tumors or refractory lymphoma were treated with an intravenously administered SNS-032 in a dose-escalation manner. Drug was well tolerated, DAEs being fatigue and nausea. The best clinical response was stable disease in 3 (15%) patients (Heath et al. 2008). Another phase I trial was performed in 19 patients with advanced chronic lymphocytic leukemia and multiple myeloma (Tong et al. 2010). Major toxicity in that case was myelosuppression. One patient with a chronic lymphocytic leukemia had more than 50% reduction in measurable disease, and two patients with multiple myeloma had stable disease and one had normalization of spleen size.

AT7519 (Fig. 2) is a broad-range CDK inhibitor, which inhibits CDK1 ($IC_{50} = 0.21$ μM), CDK2 ($IC_{50} = 0.047$ μM), CDK4 ($IC_{50} = 0.1$ μM), CDK5 ($IC_{50} = 0.13$ μM), CDK6 ($IC_{50} = 0.17$ μM) and CDK9 ($IC_{50} \leq 0.01$ μM). This compound had lower potency against other CDKs tested (CDK3 and CDK7) and was inactive against all of the non-CDK kinases tested with the exception of GSK3β ($IC_{50} = 0.089$ μM). Phase I clinical trial was carried out in 28 patients with refractory solid tumors (Mahadevan et al. 2011). Electrocardiogram showed a dose-dependent increase in QTc. Other adverse effects included fatigue and mucositis. Four patients showed stable disease for more than 6 months and one had an extended partial response. In 2010, Astex Therapeutics and the Multiple Myeloma Research Consortium announced the initiation of a phase II clinical trial of the AT7519 to treat patients with relapsed or refractory multiple myeloma.

AG-024322 (Fig. 3) is a broad-range inhibitor, which inhibits CDK1, CDK2 and CDK4 ($IC_{50} = 0.1$–0.3 μM). AG-024322 was synthesized by Pfizer Global Research and Development. This inhibitor had been entered into phase I clinical trials, which, however, had been terminated due to the inability of the compound to effectively discriminate from other treatment modalities.

(*S*)-*Roscovitine* (Fig. 3) is an inhibitor, which potently inhibits CDK1 ($IC_{50} = 0.55$ μM), CDK5 ($IC_{50} = 0.35$ μM) and CDK9 ($IC_{50} = 0.9$ μM). It has been neglected as a therapeutical agent in favor of its isomer (R)-Roscovitine, mentioned above.

R547 (also Ro-4584820) (Fig. 3) is an inhibitor selective for CDK1 ($IC_{50} = 0.001$ μM), CDK2 ($IC_{50} = 0.003$ μM) and CDK4 ($IC_{50} = 0.001$ μM). In 2006, Hoffmann-La Roche initiated a phase I study of R547 against locally advanced or metastatic solid tumors; however, results had not been published to date. On the other hand, the expression in patient blood samples of eight genes (FLJ44342, CD86, EGR1, MKI67, CCNB1, JUN, HEXIM1 and

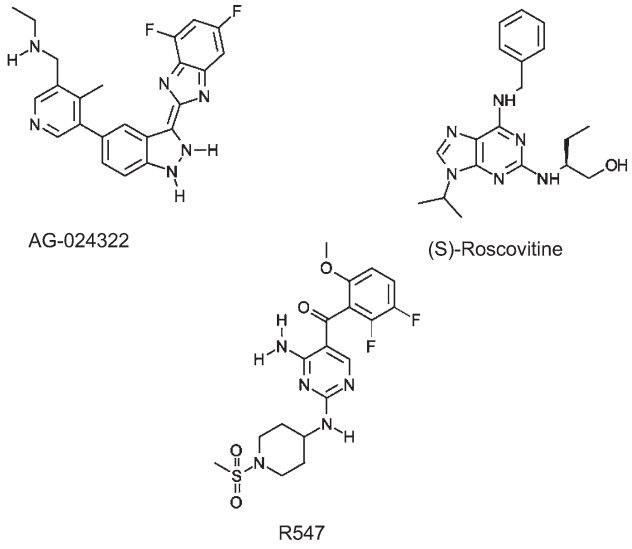

Fig. 3 AG-024322, (S)-Roscovitine, R547

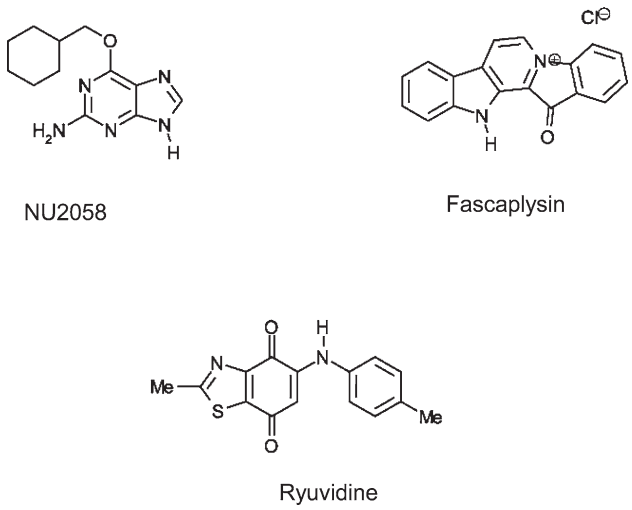

Fig. 4 NU2058, Fascaplysin and Ryuvidine

PFAAP5) was selected as dose-responsive pharmacodynamic parameter for phase II clinical trials (Berkofsky-Fessler et al. 2009).

Selective inhibitors

Fascaplysin (Fig. 4) is an inhibitor selective for CDK4 ($IC_{50} = 0.35$ μM) and CDK6 ($IC_{50} = 3.4$ μM) and not selective for the other CDKs or other kinases. It was originally isolated as a compound showing antimicrobial activity from the sponge *Fascaplysinopsis* sp. (Roll et al. 1988). It is a commercially available compound, broadly used for the research purposes; however, it has never been entered into clinical trials.

Ryuvidine (Fig. 4) is an inhibitor selective for CDK4 ($IC_{50} = 6.0$ μM) and displays >33-fold selectivity over

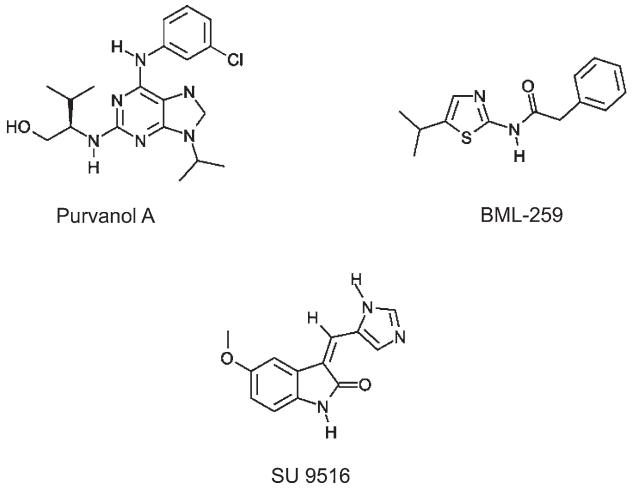

Fig. 5 Purvalanol A, BML-259 and SU 9516

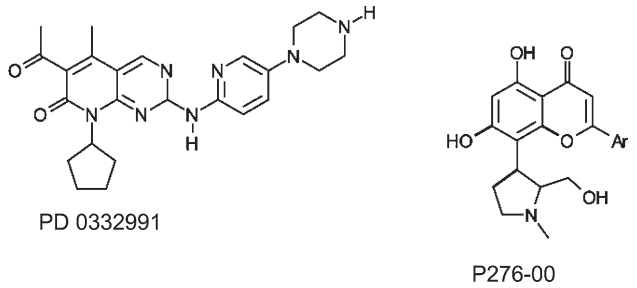

Fig. 6 PD 0332991 and P276-00

CDK2 (IC50 > 200 μM). Despite the fact that this inhibitor is commercially available, it has not been used widely in the research, nor had it ever entered the clinical trials. However, given its selectivity toward CDK4, as well as cytotoxicity against various cancer cells (IC_{50} = 0.61, 1.08, 0.30 and 1.21 mg/ml against A 549, Col 1, HL-60 and HepG2 tumor cells, respectively) (Ryu et al. 2000), it seems to be quite potent tool for cancer research.

Purvalanol A (Fig. 5) is an inhibitor selective for CDK2 (IC_{50} = 4–70 nM) and CDK5 (IC_{50} = 75 nM), but less selective toward CDK4 (IC_{50} = 850 nM). This inhibitor was identified by combinatorial chemistry approach structure–activity relationship (SAR). It is also a commercially available inhibitor, quite widely used in cancer research (Villerbu et al. 2002). However, purvalanol A has never been entered into clinical trials.

NU2058 (Fig. 4) is an inhibitor selective for CDK2 (IC_{50} = 17 μM) and CDK1 (IC_{50} = 26 μM). NU2058 is a competitive inhibitor that binds in the ATP-binding pocket in a different orientation from other purine-based inhibitors, such as olomoucine and roscovitine (Arris et al. 2000). So far, only preclinical studies had been performed, showing the potential of the compound against several cancer cell lines. This inhibitor had not been entered into clinical trials yet. It is also commercially available.

BML-259 (Fig. 5) is an inhibitor selective for CDK5 (IC_{50} = 64 nM) and CDK2 (IC_{50} = 98 nM). It is an ATP competitive CDK inhibitor discovered by molecular modeling studies (Helal et al. 2004). Although it definitely needs further validations and preclinical studies, this compound is already available commercially. So far, no clinical study has been reported for this agent.

SU 9516 (Fig. 5) is an inhibitor selective for CDK2 (IC_{50} = 0.022 μM) and CDK1 (IC_{50} = 0.04 μM), but less selective toward CDK4 ($IC_{50} \geq$ 10 μM). At higher concentrations, it can also inhibit PKC ($IC_{50} \geq$ 10 μM), p38 ($IC_{50} \geq$ 10 μM), PDGFR ($IC_{50} \geq$ 18 μM) and EGFR ($IC_{50} \geq$ 100 μM). It was identified by the means of high-throughput screening with CDK2 and tested on colon cancer cell line in which it decreased cell cycle progression and induced apoptosis (Lane et al. 2001). So far, it has been only tested in preclinical studies.

PD-0332991 (Fig. 6) is a highly specific inhibitor of CDK4 (IC_{50} = 0.011 μM) and CDK6 (IC_{50} = 0.016 μM), having no activity against a panel of 36 additional protein kinases (Fry et al. 2004). It was an effective antiproliferative agent against retinoblastoma-positive tumor cells, inducing G1 arrest and reducing the phosphorylation of the Rb protein. Administration of PD-0332991 reduces tumors in mice bearing the Colo-205 human colon carcinoma. Several phase I/II clinical studies with PD 0332991 have been initiated, such as: a study in patients with advanced solid tumors (excluding SCLC and retinoblastoma) or follicular and diffuse large-cell non-Hodgkin's lymphoma, phase I Trial of PD-0332991 plus bortezomib in patients with relapsed mantle cell lymphoma, phase 1 trial of PD0332991 and paclitaxel in patients with Rb-expressing advanced breast cancer, phase II study of PD 0332991 in patients with recurrent Rb positive glioblastoma; however, the results are not ready yet. Another phase I study of sequential combination of PD-0032991 with bortezomib and dexamethasone had been performed in 21 relapsed and refractory multiple myeloma patients (Niesvizky et al. 2010). The most common treatment-related DAEs were thrombocytopenia and neutropenia. One patient achieved a very good partial response, 1 achieved a partial response, and 3 had stable disease for more than 3 months. Very good partial response was in a patient who had relapsed on lenalidomide, bortezomib and carfilzomib therapies as well as on stem cell transplant. The phase II portion of the trial to evaluate the antitumor activity of PD 0332991 is ongoing. Yet another phase I study of the combination of PD 0332991 and letrozole for first-line treatment of patients with ER-positive, HER2-negative breast cancer had been performed in 12 patients (Slamon et al. 2010). Most common DAEs included neutropenia, leucopenia and fatigue. Three patients had partial response and 9 patients had stable disease. A randomized phase II study has been initiated.

P276–00 (Fig. 6) is a highly specific inhibitor of CDK2 (IC_{50} = 10 nM), which is much less selective toward CDK1 (IC_{50} = 110 nM) and CDK4 (IC_{50} = 130 nM), with no significant activity toward 12 other kinases tested (IC_{50} = 2 μM). It showed potent antiproliferative effects against various human cancer cell lines, such as MCF-7 and H-460 (Joshi et al. 2007). Several phase I/II clinical studies with P279-00 have been initiated, such as an open-label, multicenter phase I/II study of selective cyclin-dependent kinase inhibitor P276-00 in combination with radiation in subjects with recurrent and/or locally advanced squamous cell carcinoma of head and neck and a phase I/II study to evaluate safety and efficacy of P276-00 in combination with gemcitabine in patients with pancreatic cancer. The results of these studies are still in progress. Another phase I study in patients with refractory neoplasms was performed. Major DAEs were fatigue, hypotension, nausea, sweating and dry mouth. No responses were observed (Hirte et al. 2007).

Conclusions

The field of CDK inhibitor development had seen a significant enthusiasm and optimism in the past couple of decades. Recent developments in the small-molecule CDK inhibitor field led to several marketed products with a different spectrum of the inhibited targets. Actually, there are many more CDK inhibitors developed than are described in this review. Many more are still in development. These developments provided the investigators, interested in the role of CDKs in cancer or other cellular processes, with a whole panel of tools. The variety of these inhibitors allows us to choose the most effective and relevant approaches suited for the particular experiments. How to choose the appropriate inhibitor? First of all, most of the researchers would be limited by the availability of the compounds. However, there are quite a number of commercially inhibitors to choose from. Secondly, the investigator has to choose the specificity of the inhibitor, according to the CDK (or several CDKs) he would like to inhibit. Wishful thinking, like “roscovitine is selective CDK5 inhibitor”, will certainly not help in this decision. Lastly, if working on a disease model, it would certainly help to consider using the inhibitors, which are already under the investigation in clinical trials. In some cases, if not most cases, the results obtained using CDK inhibitors should be validated using other techniques, such as siRNA,/micro-RNA knockdowns, dominant-negative CDKs or knockout mice.

The basic as well as preclinical cancer research is not the only fields, which can profit from the use of CDK inhibitors. They continue to hold much potential as new agents in the treatment of cancer. The crucial question that remains unanswered is which CDK or range of CDKs should be targeted. Studies with the inhibitors should determine whether highly selective or rather broad-range CDK inhibitors are more effective for anticancer therapy. The therapeutic significance of inhibiting particular CDKs is greatly dependent on the genetic background and the specific signaling pathways that direct proliferation of the tumor cells. Preclinical studies in suitable animal models ought to provide important information for the design of more clinical studies assessing improved efficacy of these agents. The results from clinical studies to date imply that monotherapy might not be the best application of CDK inhibitors. However, the results of these agents in combination with chemotherapy seem to be more optimistic. On the other hand, there is also the lack of clinically useful prognostic and predictive biomarkers that associate directly with CDK inhibition. In addition, new insights into CDK biology will provide innovative biomedical rationales for the therapeutic applications.

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