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Is Cdc25 a Druggable Target?

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Abstract

Proper control of cell cycle progression requires the functionality of a small family of activating phosphatases termed Cdc25, which have been implicated in cancer and Alzheimer's disease. These protein tyrosine phosphatases are therefore recognized as attractive molecular targets for small molecules. We review the rationale, approaches, progress and challenges for developing small molecule inhibitors of the Cdc25 family. A number of potential chemical probes are discussed and their characteristics are summarized.

Keywords

Protein tyrosine phosphatase; natural products; enzyme assays; reactive oxygen species

1. WHY TARGET Cdc25?

Reversible phosphorylation of proteins, lipids and other molecules is a fundamental mechanism for the control of life-sustaining processes in cellular organisms. It has been estimated that at least one third of all cellular proteins contain covalently bound phosphate [1]. Although in higher eukaryotes tyrosine phosphorylation is less common than serine or threonine phosphorylation, it is widely exploited for advanced cell signaling processes. Indeed, aberrant levels of tyrosine phosphorylation, derived from an imbalance of either activities or levels of either protein tyrosine kinases or protein tyrosine phosphatases, have been implicated in a host of human disorders including cancer, diabetes, Alzheimer's disease, Parkinson disease, infection, and obesity.

Large-scale RNA interference screens indicate that 73 (11%) of the 650 known or putative protein kinases in the human genome regulate tumor cell survival and apoptosis [2]. Thus, it is not surprising that US Food and Drug Administration has approved seven small molecule tyrosine kinase inhibitors for use against cancer with >25 different tyrosine kinase inhibitors currently being examined in >130 Phase I and II clinical cancer trials in the United States. In contrast, there are no clinically approved protein tyrosine phosphatase (PTP) inhibitors even though analogous RNA interference studies indicated that 45 (42%) of the 107 known or putative protein tyrosine phosphatases in the human genome regulate tumor cell survival and apoptosis [2]. This is an important observation because the substrate specificity of a PTP is not

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linked to that of any protein tyrosine kinase, thus affording a non-redundant cellular regulatory system.

There are several historical reasons for the dearth of PTP inhibitors. First, it is almost axiomatic that identification and characterization of the participants in catabolic pathways trail those of the anabolic pathway. PTP characterization is no exception, occurring almost a decade after the first tyrosine kinase was identified for the first publication of a human PTP [3]. Second, most investigators relegated PTP to uninteresting, constitutive, gene products with little regulatory functionality. Third, the energy demanding kinases were generally consider process activators, while phosphatases assumed a loss-of-function inhibitory role, making them less attractive as small molecule inhibitor targets. Fourth, PTP substrates are highly charged, conceptually making the design of small molecule substrate mimics that retain membrane permeability difficult. Finally, as with protein tyrosine kinases, it was generally thought that the active sites of PTPs were too similar to permit selective small molecular inhibitors to be identified. We now know that many PTPs are either directly or indirectly activators of processes, are highly regulated, and have distinct surface properties [4]. This information, coupled with gene knockout studies revealing PTP1B as a negative regulator of insulin signaling, greatly stimulated interest in discovering small molecule inhibitors of PTPs.[5,6] The disease associated human PTPs most aggressively studied are: PTP1B, PTPα, CD45, LMPTP, PRL-3, SHP-1, HePTP, MKP-1 and Cdc25[7-9].

Dual specificity phosphatases (DSPs) are catalytically noteworthy enzymes because they dephosphorylate contiguous or semi-contiguous phosphorylated tyrosine, serine, and threonine residues on a protein substrate. The human genome encodes at least 33 DSPs. Among them are three structurally distinct DSPs, namely Cdc25A, Cdc25B and Cdc25C, which are homologs of a protein encoded by the cell division cycle 25 gene (Cdc25) found in *Schizosaccharomyces pombe* ("fission yeast") and which have critical roles in regulating the mammalian cell cycle through their ability to dephosphorylate and activate cyclin-dependent kinase complexes, as comprehensively reviewed elsewhere [7,10-13]. Overexpression of Cdc25A and Cdc25B has been observed in many human tumors, and complete loss of Cdc25A phosphatase is incompatible with cell proliferation or survival. The co-expression of Cdc25A or Cdc25B cooperates with either oncogenic HRAS or the loss of RB1 to transform mouse embryonic fibroblasts enabling them to form tumors in mice [14]. It is widely believed that overexpression of Cdc25A and Cdc25B enables the bypass of normal cell cycle checkpoints, which leads to a loss of genome integrity [10,15]. Indeed, deregulation of Cdc25A expression promotes mammary tumorigenesis and causes genomic instability [16]. Additionally, Cdc25A may contribute to cellular transformation and decrease responsiveness to stress by ablating the actions of the redox-sensitive apoptotic signaling kinase ASK1. Cdc25A has been shown to inhibit ASK1 activation by a non-catalytic protein-protein interaction that blocks ASK1 dimerization, which is critical for enzyme activation [17]. There is also evidence that Cdc25B acts as a co-activator for the estrogen, progesterone, glucocorticoid, and androgen receptors in mammary and prostate tissue. Interestingly, co-activation may not require functional phosphatase activity [18,19].

2. HOW COULD ONE TARGET Cdc25?

As might be expected for a vital protein, Cdc25 family members are regulated by a complex constellation of at least seven distinct intracellular mechanisms, each of which represents potential small molecule target sites (Fig. **1**). Because of the relatively short half-life of the Cdc25 family members, namely <20 min [20], one potential target for suppressing the total protein would be inhibition of transcription or translation. Both positive and negative regulators of human Cdc25A transcription have been reported, including c-Myc, HIF-1α, p53, p21 and E2F [21,22]. Of interest most of these transcriptional targets have been targeted for small

molecule inhibition [23-26]. In fission yeast, the eukaryotic translational initiation factor 4A (eIF4A) controls Cdc25 expression. All of the Cdc25 family members are extensively phosphorylated, which alters protein-protein interactions, degradation rates, and possibly subcellular localization [10,27]. There is considerable interest in designing inhibitors of protein-protein interactions and proteasomal activity. Nonetheless, the most obvious small molecule target remains the catalytic site. There are now several high quality crystal structures of the catalytic domain and, encouragingly, the overall core fold of the Cdc25s is unique among PTPs, consistent with its lack of significant sequence homology. Moreover, some investigators have suggested that in contrast to other PTPs, Cdc25 family members might not have an overhanging loop containing an aspartic acid, which acts as the cognate catalytic acid [13].

Strategies to identify small molecule inhibitors of Cdc25s generally followed the approaches used for other PTPs, especially PTP1B [1]. Either low or high throughput screens have been developed using recombinant protein with a variety of small molecule substrates including *p*-nitrophenyl phosphate, 6,8-difluoro-4-methylumbelliferyl phosphate, fluorescein diphosphate or *O*-methyl-fluorescein phosphate. The choice of these artificial substrates rather than the native substrate reflects the difficulties of making two proteins, namely the cyclin dependent kinase (CDK) and the cognate cyclin, and then phosphorylating the substrate complex with a kinase, namely Myt1 or Wee1. The general conditions and challenges for configuring *in vitro* phosphatase assays will not be discussed because they have been adequately addressed elsewhere [1]. Of particular note, however, are the limits of the detection methodologies and sensitivity to redox active agents. Thus, oxidizing compounds or Michael-acceptors that irreversibly bind to the thiolate in the catalytic cysteine or adjacent moieties, including reactive "hotspot" cysteine residues, are often identified as inhibitors. Compounds that generate reactive oxygen species (ROS, which includes superoxide radical anion ($O_2^{-\bullet}$), H_2O_2 and $HO^{\bullet}$), especially in the presence of strong reductants such as dithiothreitol found in many high throughput screens, also populate commercially available small molecule libraries and have to be viewed as promiscuous inhibitors in the absence of more detailed investigations [28].

Although there is no available structural information concerning any full length Cdc25 family member, more than a dozen crystal structures of the catalytic domains of Cdc25A and Cdc25B have been reported, the best having a 1.52 resolution. Access to these coordinates is enabling virtual screening for inhibitors of the catalytic activity of Cdc25. Some investigators [29], for example, have docked published Cdc25B inhibitors to the catalytic domain of Cdc25B with AutoDock and GOLD and have suggested a possible explanation for the inhibition mechanism of the examined Cdc25B ligands. They postulate that a tight interaction between the inhibitor and arginine residues 482 and 544 is important for reversible enzyme inhibition, while the proximity of a quinone ring in some inhibitors to the Cys473 catalytic thiolate could lead to irreversible inhibition (Fig. **2**). An innovative receptor-based virtual ligand screen of Cdc25B with 310,000 drug-like compounds yielded 1,500 molecules, which were further validated *in vitro* providing 99 compounds that inhibited Cdc25B activity at 100 μM [30]. Studies like these provide encouragement that computational methods could accelerate future searches for inhibitors of Cdc25 family members.

3. WHAT SMALL MOLECULES INHIBIT Cdc25 ACTIVITY?

While the discovery of the first Cdc25 inhibitors dates back to 1994 – a class of relatively unselective alkaloid natural products, the dnacins [31] – the dysidolides represent the first highly publicized inhibitors [32]. They were reported in 1996 (only eight years after the first PTP was identified) and set the stage for the discovery of a large number of natural and unnatural compounds that modulated the activity of Cdc25 family members. The level of inhibition, as well as the selectivity, found for dysidiolides remained controversial [33]. In fact,

to this date it still is difficult to reproduce published 50% inhibitory concentration (IC_{50}) data, due to different assay conditions and the lipophilic nature of many low-micromolar inhibitors.

In Fig. (**3**) we highlighted 6 distinct classes of Cdc25 inhibitors: (A) Natural products such as dnacins, dysiodolides and sulfircins; (B) lipophilic acids such as SC-ααδ9; (C) vitamin K analogs and other quinones, such as menadione and DA3003−1; (D) electrophiles such as fascaplysin; (E) phosphate mimics such as the xenicane diterpenoids; and (F) peptides and peptide analogs that have been found bound to the active site.

Class A comprises a heterogeneous group of compounds that have structural features typical for other inhibitor classes, including redox active, electrophilic, lipophilic and acidic elements. In addition to the dnacins and dysidiolides, sulfircin is another typical example of a natural product inhibitor of DSPs [34]. The activity of these natural products rarely exceeds the single-digit micromolar range, and the selectivity for Cdc25 is limited. Their binding sites and the kinetics of inhibition are poorly characterized.

Class B compounds form the largest group of Cdc25 inhibitors. Almost any lipophilic acid is capable to provide a low-affinity inhibitor in an *in vitro* Cdc25 enzyme assay. SC-ααδ9 was the first reported member in this class [35], which also comprises steroid derivatives [36], heterocycles [37], and α,β-unsaturated acids [38], representative of many others.

Quinones are controversial pharmacophores in medicinal chemistry (see, for example, [39-41] and references cited therein), and the delicate balance between potency and selectivity typical for quinones is also a major challenge for modulating their Cdc25 inhibitory properties. DA3003−1 (also known as NSC663284), for example, has an *in vitro* IC_{50} of ~500 nM for Cdc25 inhibition [42], but it is also an irreversible inhibitor, displays mixed kinetics, and its activity is strongly dependent on DTT concentrations [28], suggesting redox cycling and thiol-capture properties. DA3003−1 does, however, have modest activity using *in vivo* tumor models [43] (Table **1**). Other quinones, such as vitamin K derivatives and indole-substituted analogs, have also been extensively investigated and also have modest *in vivo* activity but like DA3003 −1 have toxicity at higher doses probably due to off-target effects [44-46].

In light of the important cysteine residues present in Cdc25, it is not surprising that electrophiles, which scavenge thiol functions, can abolish catalytic activity. Typical representatives of Class D agents are fascaplysin (which could also be listed in Class A [47]) and PM-20 [44]. These compounds are very reminiscent of typical promiscuous enzyme inhibitors [48]. The phenol BN82002, which is not a typical electrophile, is a novel Cdc25 inhibitor that is active both in cells and animal models [49]. Nonetheless, due the very electron-rich phenol nucleus, the benzylic amine could be eliminated upon protonation, thus generating a reactive *ortho*-quinomethane type Michael acceptor.

The development of suitable phosphate bioisostere is of great potential for the development of both new kinase as well as phosphatase inhibitors. Unfortunately, this is a challenging task, further compounded by the requirement for analogs to pass through the hydrophobic cell membrane in order to reach the intracellular target. Relatively little specific research has been done for Cdc25 phosphatases using this approach, but some natural products, such as the xenicane diterpenoids [47] and Ugi library products [50], have been identified that are possibly mimicking the charged phosphate function in phosphorylated tyrosine and serine/threonine residues. Additional studies for the development of specific and potent phosphate bioisosteres interacting with the Cdc25 active site would clearly be desirable.

While the development of Class F peptide derived inhibitors of Cdc25, based on sequence homology with the protein substrates, is relatively straightforward, the challenge to use these compounds as drugs remains formidable, due to their lack of suitable absorption, distribution,

metabolism and excretion properties and the concomitant absence of *in vivo* antitumor effects. However, peptide substrates can provide excellent binding data through x-ray studies and thus provide the basis for molecular modeling studies and virtual library screens [29,51].

4. WHAT ARE POTENTIAL FUTURE DIRECTIONS?

It is apparent from a review of the published work that, at this time, the development of small-molecule, specific and *in vivo* active inhibitors of Cdc25 is still an unmet challenge. The rather shallow active site on Cdc25 can only partially explain this lack of success in identifying solid quality chemical lead structures. Quite likely, past and current high-throughput based screening of commercial libraries poorly differentiated between promiscuous, lipophilic or electrophilic agents that interact strongly with surface residues on this target enzyme and site-selective lower affinity agents. The latter active compounds, while probably more readily chemically optimized, have therefore be less enthusiastically been pursued, and future success will depend on new assay paradigms with structurally more thoroughly filtered, chemically robust library collections.

It seems quite likely that further refinements of the existing small molecule inhibitors will continue because of the enormous potential of Cdc25 as a therapeutic target. As the functional significance of post-translation modification becomes better understood, the enzymes responsible for Cdc25 modification could become proximal targets. Thus, activation of one or more of the kinases that target Cdc25 for degradation could result in a marked reduction in enzyme levels. Alternatively, the transient interactions between Cdc25 and its Cdk2 substrate afford a very attractive new site for intervention [12]. Although the interface between Cdc25B and Cdk2/cyclinA has been estimated to be $3,800 \text{ Å}^{-2}$, deep pockets of $\sim 200 \text{ Å}^{-2}$ exist on the surface of Cdc25B, which house amino acids that are essential for substrate-phosphatase interactions. Thus, compounds that selectively bind in this site are predicted to have the potential of disrupting the enzymatic activity of Cdc25B. Moreover, the inhibition should be isoform specific, as Cdc25A and Cdc25C have different amino acids residing in the pocket.

The challenges for finding drug-like inhibitors for the Cdc25s remain substantial. Nonetheless, insights gleaned from even the limited number of small molecule inhibitors that are currently available suggest that Cdc25 phosphatases are biologically important targets well worthy of more potent and selective inhibitor development. Moreover, lessons learned on this enzyme family will likely benefit searches for inhibitors of other phosphatases and drug discovery in general.

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ABBREVIATIONS

ASK1, Apoptosis signaling-regulating kinase 1; Cdc25, Cell division cycle 25; Cdk, Cyclin dependent kinase; DSP, Dual specificity phosphatase; IC_{50}, 50% Inhibitory concentration; PTP, Protein tyrosine phosphatase; ROS, Reactive oxygen species.

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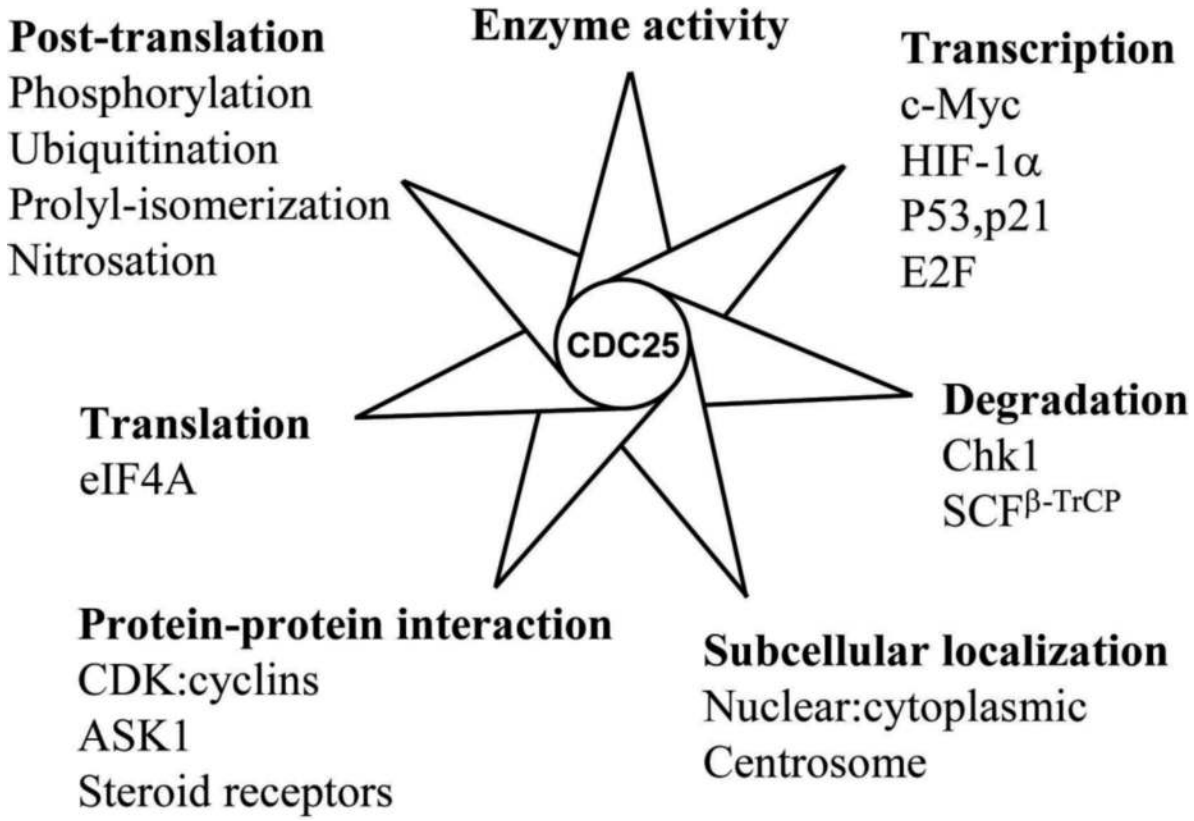


Fig. (1).
Potential druggable targets for Cdc25. The expression levels and activity of this phosphatase family are regulated by at least seven distinct mechanisms.

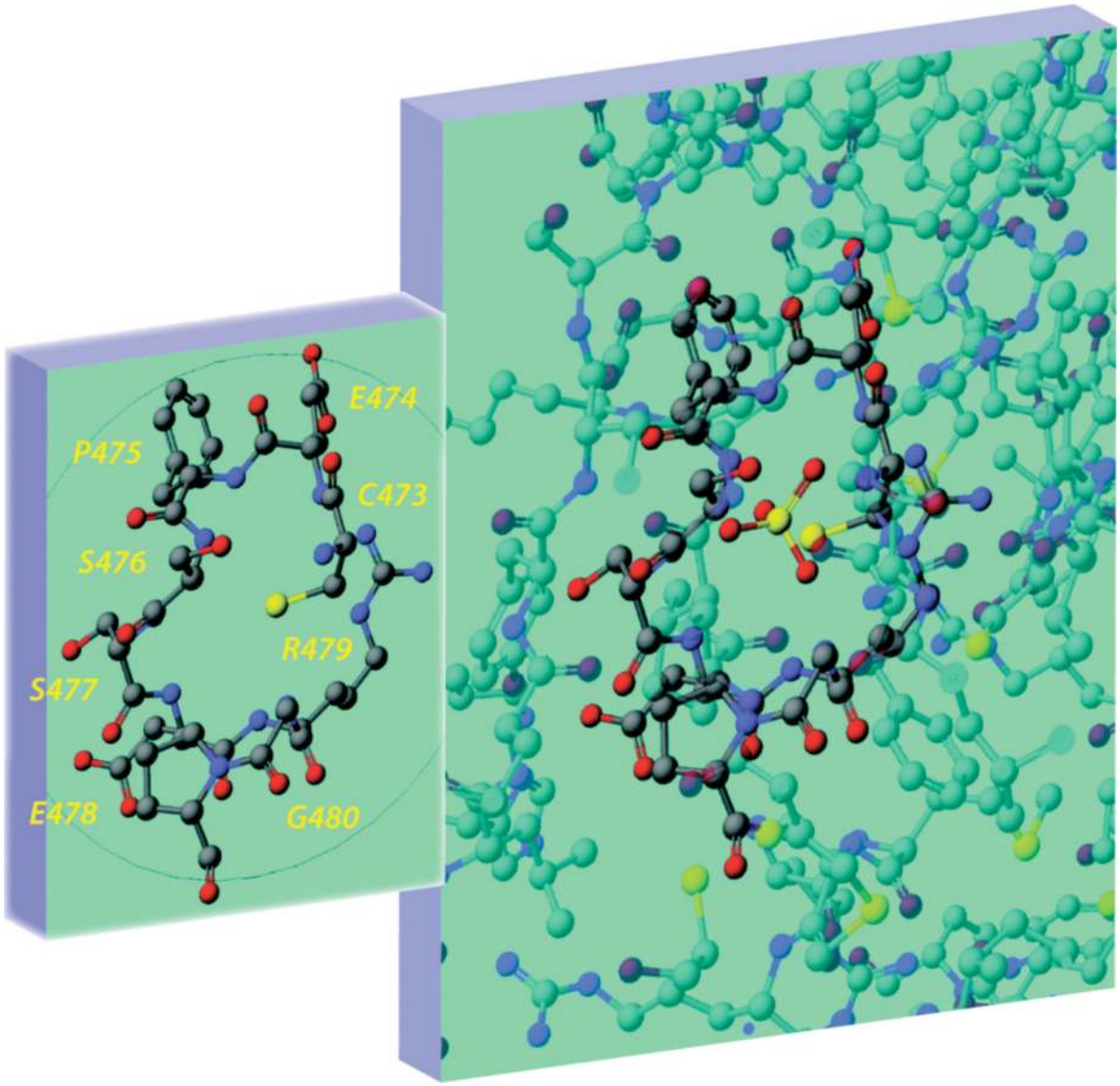
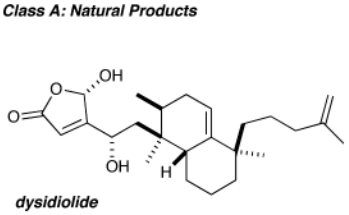
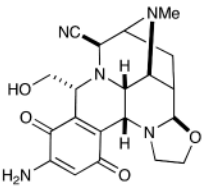


Fig. (2).
A detailed view of the catalytic core of Cdc25B. In the right panel a sulfate moiety is seen bound in the catalytic site.

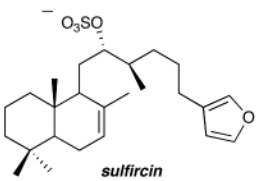
Class A: Natural Products



dysidiolide

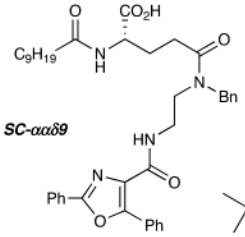


dnacin A$_1$

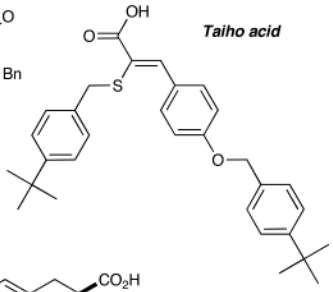


sulfircin

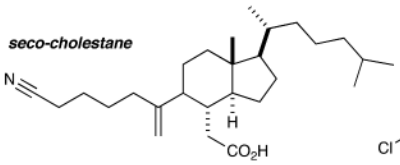
Class B: Lipophilic Acids



SC-ααδ9



Taiho acid



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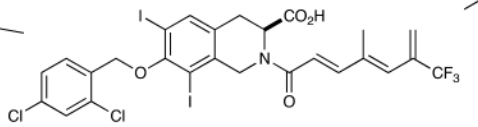
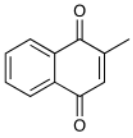
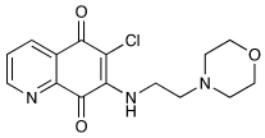


Pharmacia-Upjohn tetrahydroisoquinoline

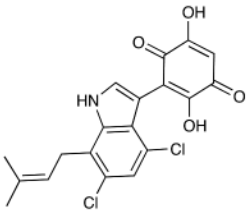
Class C: Quinones



menadione

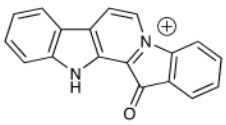


DA3003-1 (NSC663284)

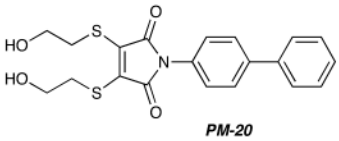


indolyldihydroxyquinone

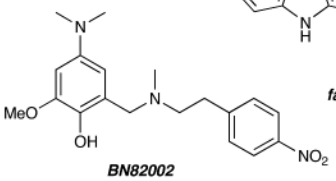
Class D: Electrophiles



fascaplysin



PM-20



BN82002

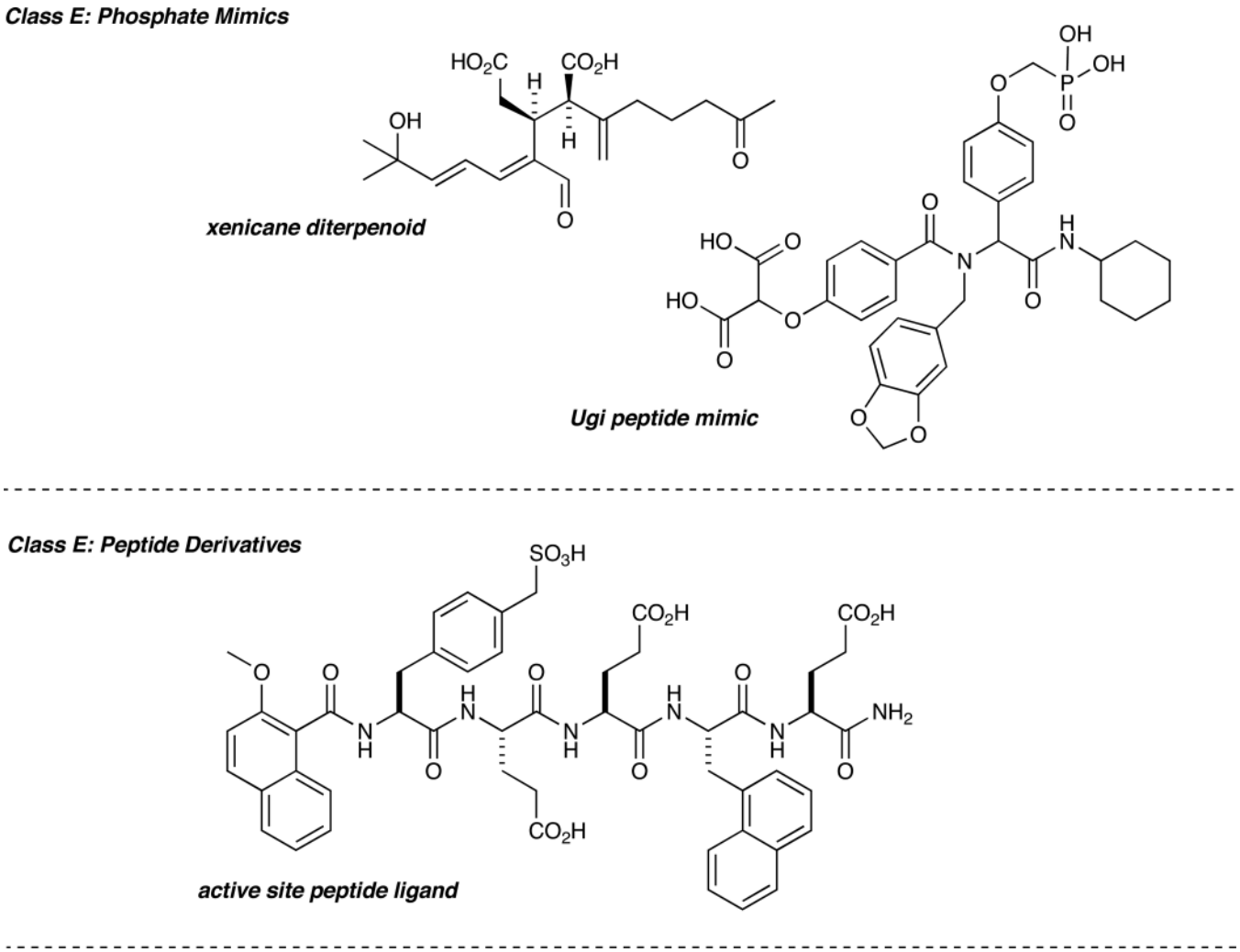


Fig. (3).
Structural classification of known inhibitors of Cdc25 phosphatases.

Table 1

Cdc25 Inhibitors with Reported Antitumor Activity

Inhibitor	IC50 (μM)			Cell Growth Inhibition	Tumor Growth Inhibition	Reference
	Cdc25A	Cdc25B	Cdc25C			
DA3003−1 (NSC663284)	0.50	0.91	0.47	MCF-7, tsFT210, HCT-116, MDA-MD-231, HT29	HT29 adenocarcinoma	[28,43,52]
BN82002	2.4	3.9 [a] –6.3 [b]	5.4	MIA PaCa-2,DU-145, U87MG, LNCaP, HT-29, U2OS, HeLa	MIA PaCa-2 pancreatic	[49]
BN82685	0.11	0.16[a]–0.25 [b]	0.20	MIA PaCa-2,DU-145, U87MG, LNCaP, HT-29, U2OS, NCI-H69, A-427, Caco-2, SW480, SW620, A2058, HL60, CCRF-CEM	MIA PaCa-2 pancreatic	[53]
PM-20	1.0	10	40	MCF-7, SKBR3, FemX, HR, PC-1, LS180, Hep3B	JM-1 hepatoma	[44]

[a]Tested against Cdc25B2.

[b]Tested against Cdc25B3.