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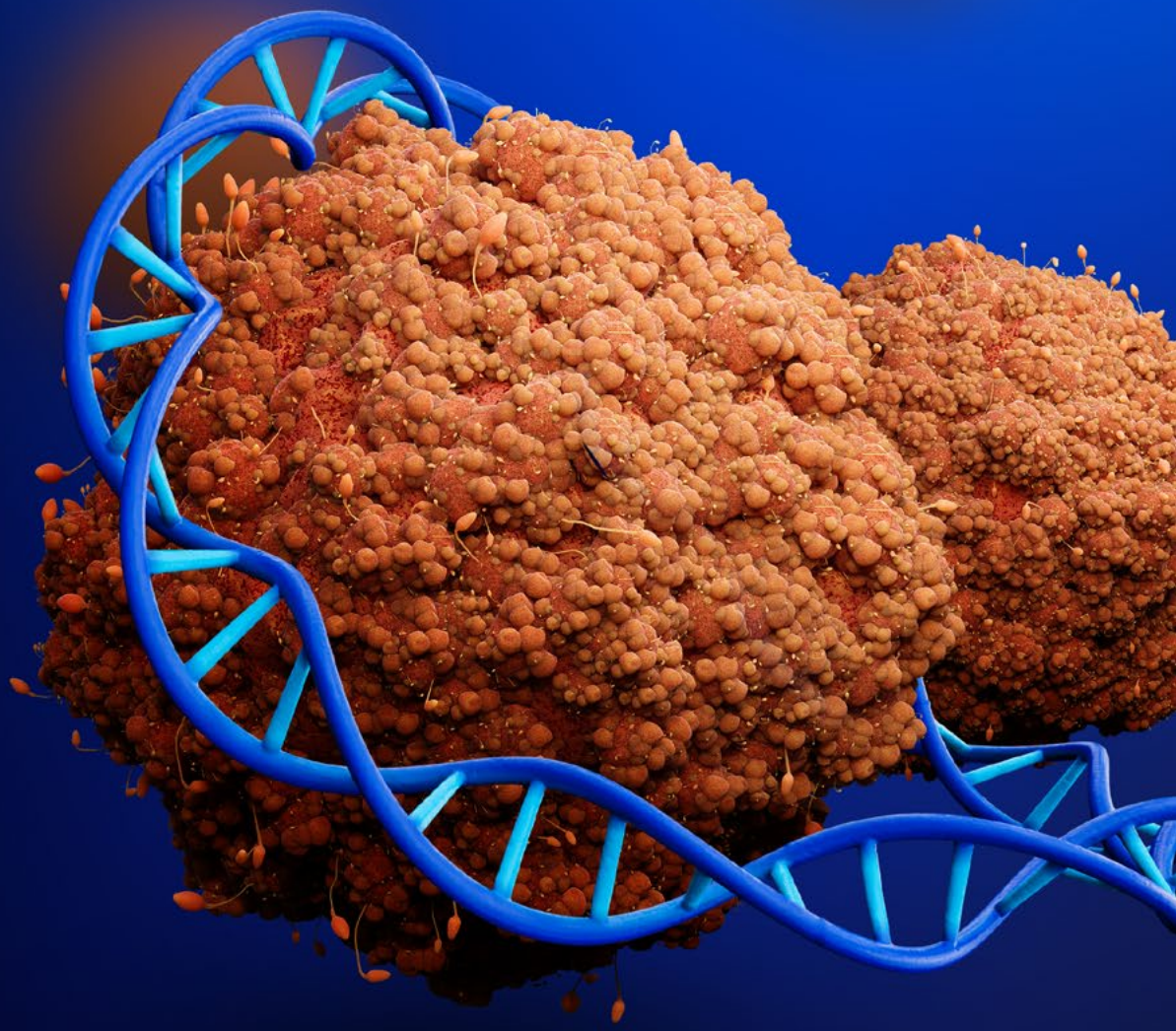
PRODUCT GUIDE
EDITION 01

Cell Cycle and DNA Damage



In normal cells, each stage of the cell cycle is tightly regulated. In cancer cells, many genes and proteins that influence the progression of the cell cycle are mutated or overexpressed – they become oncogenes. The proteins/molecules involved in the regulation of the cell cycle, in particular DNA replication and DNA damage, have been of great interest to cancer researchers.

Cell Cycle and Mitosis

There are three major regulatory cell cycle checkpoints – G_1/S, intra-S phase and G_2/M phase. A cell can only pass through these checkpoints in the presence of stimulatory signals and in the absence of DNA damage. The cell cycle checkpoints are controlled by tumor suppressors and cyclin-dependent kinases (CDK). CDKs act in concert with their regulatory subunits cyclins, to control cell cycle progression through its four phases: G_1, S, G_2 and mitosis (M). CDKs are constitutively expressed and are regulated by several kinases and phosphatases, including Wee1 kinase and Cdc25 phosphatase.

Misregulation of CDK activity can induce unscheduled proliferation, resulting in genomic and chromosomal instability (Figure 1). Useful compounds for investigating CDKs include Senexin A (Cat. No. 4875), Ro 3306 (Cat. No. 4181), CDK8/19i (Cat. No. 7372), FMF-04-159-2 (Cat. No. 7158) and NVP 2 (Cat. No. 6535). Senexin A is a CDK8 inhibitor that inhibits p21-induced transcription, and reverses doxorubicin-induced tumor-promoting paracrine activities *in vivo*. Ro 3306 is a potent CDK1 inhibitor that suppresses CDK1/cyclin B1 and CDK1/cyclin A, inducing G_2/M phase cell cycle arrest and apoptosis. CDK8/19i is a potent and selective inhibitor of both CDK8 and CDK19. CDK8 and CDK19 are promising targets in breast cancer and acute myeloid leukemia (AML), with CDK8/19 inhibitors entering clinical trials. The potent covalent CDK14 and CDK16 inhibitor, FMF-04-159-2, causes cell cycle arrest at G2/M in cancer cell lines, while NVP 2 is a potent and selective ATP-competitive CDK9 inhibitor, which suppresses proliferation of MOLT4 cancer cells and induces apoptosis.

Targeted Protein Degradation (TPD) is a new approach for the knockdown of target proteins within cells using Degraders, and has been used to investigate CDK function. Key Degrader tools are the selective CDK6 Degrader BSJ-03-123 (Cat. No. 6921), the selective CDK4 Degrader BSJ-04-132 (Cat. No. 6937) and the potent and selective CDK9 Degrader THAL SNS 032 (Cat. No. 6532). See PROTAC® feature box on page 7 for more details about this technology and application.

DNA replication occurs in five stages during the S-phase; initiation, unwinding, primer synthesis, elongation and termination. Helicase enzymes 'unwind' the DNA double helix, and telomerases reduce the resulting torsional strain, the single strands are now exposed and the replication fork is initiated. The leading strand of DNA is synthesized by Pol ε and the lagging strand is synthesized by Pol δ. Proliferating cell nuclear antigen (PCNA) is a cofactor for both DNA polymerase δ and ε, where it acts as a DNA clamp, which is important in both DNA synthesis and repair. At the end of the termination phase, DNA ligases form a phosphodiester bond, which joins the DNA strands together, forming new doubled-stranded DNA. There are many different compounds for targeting the enzymes involved in the replication of DNA including mithramycin A (Cat. No. 1489), NSC 617145 (Cat. No. 5340) and L189 (Cat. No. 3561). Mithramycin A binds to G-C-rich DNA and inhibits RNA and DNA polymerase action. NSC 617145 is a Werner syndrome helicase (WRN) inhibitor, which acts synergistically with Mitomycin C (Cat. No. 3258) to induce double-strand breaks and chromosomal abnormalities *in vitro*. L189 is a DNA ligase I, III and IV inhibitor that blocks DNA binding and inhibits base excision repair (BER) and non-homologous end joining (NHEJ). In addition L189 specifically sensitizes cancer cells to DNA damage and increases the cytotoxicity of DNA-damaging agents.

During mitosis, a small number of kinases coordinate a complex series of events. In particular, Aurora kinases, CDKs and polo-like kinases (PLKs) work in concert to ensure chromosomes are segregated to daughter cells with high fidelity. Improper chromosome segregation has significant effects on cellular function. It can contribute not only to decreased viability, but also to malignant transformation through the generation of genomic instability and aberrant cell division. A process known as mitotic catastrophe – a form of cell death, which is initiated by disturbances in mitotic machinery – helps limit the risk of malignancy by eliminating potentially tumorigenic cells. Due to their role in chromosome segregation, Aurora kinases and PLKs are closely linked to mitotic progression. PLK1 promotes mitotic entry by inducing degradation of Wee1 and activation of cyclin B/CDK1, and has additional roles in chromosome segregation and cytokinesis. PLK2 and PLK3 are involved in checkpoint-mediated cell cycle arrest and help ensure genetic stability.

Aurora A has been linked to centrosome maturation and spindle assembly, and is overexpressed in many human cancers. Aurora B is involved in the spindle assembly checkpoint and cytokinesis, amongst other mitotic processes. Inhibitors of these enzymes therefore inhibit critical mitotic processes, halting cell division. One key compound for modulating mitosis is GW 843682X (Cat. No. 2977), a selective inhibitor of PLK1 and PLK3 that inhibits proliferation of many tumor cell types *in vitro*.

Other mitotic spindle associated proteins being studied as potential therapeutic targets are the mitotic kinesin Eg5 and monopolar spindle 1 (Mps1). Eg5 is a motor protein essential for bipolar spindle formation, with inhibition of Eg5 by compounds such as Monastrol (Cat. No. 1305) resulting in mitotic arrest. Mps1 is a mitotic checkpoint kinase involved in the spindle assembly checkpoint, where it ensures correct chromosome segregation. The selective Mps1 kinase inhibitor Mps1-IN-1 (Cat. No. 5142), increases the frequency of multipolar mitosis and decreases cell viability in bone cancer cells *in vitro*.

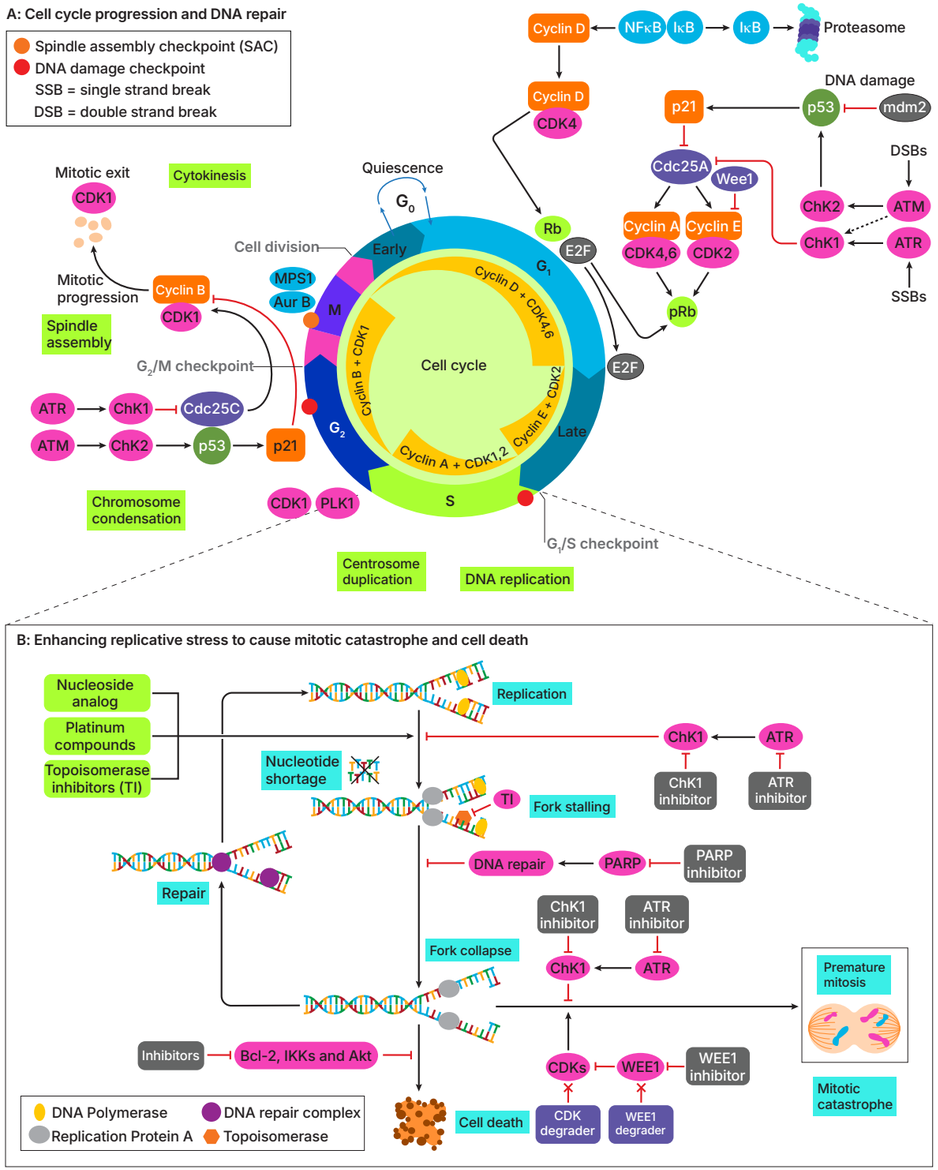
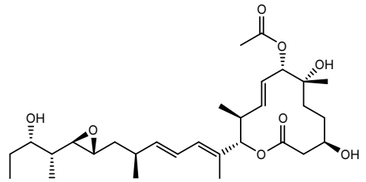
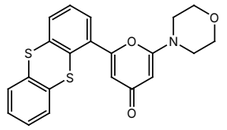


Figure 1. Cell Cycle Progression and DNA Repair. A) At specific points in the cell cycle, DNA damage is detected and repaired. The process is initiated by the DNA damage sensors, ATM and ATR kinase. Checkpoint kinases Chk1 and Chk2 initiate signaling cascades that activate DNA damage checkpoints in G1 and G2. The spindle assembly checkpoint (SAC) delays anaphase of mitosis until all chromosomes are properly aligned on the spindle, preventing aneuploidy. Kinases including aurora kinase B (Aur B), PLK1 and Mps1 are implicated at various control points in the cell cycle. B) Enhancing replicative stress by targeting critical DNA replication checkpoints and replication machinery, as well as depleting nucleotides, encourages fork stalling and fork collapse, which leads to mitotic catastrophe and cell death.

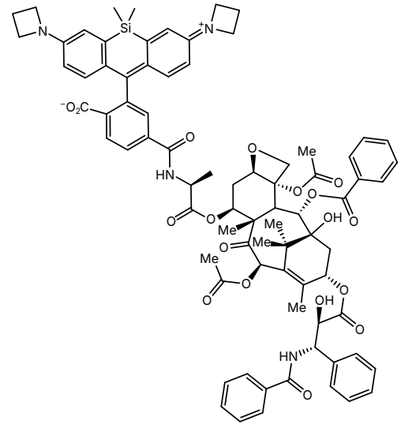
Box 1: Cell Cycle and DNA Damage Repair Products



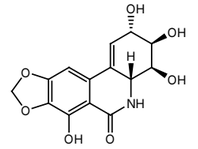
Pladienolide B (Cat. No. 6070)
Arrests cell cycle in G_1 and G_2/M



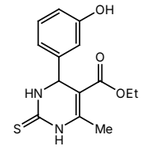
KU 55933 (Cat. No. 3544)
Potent and selective ATM kinase inhibitor



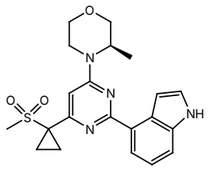
Taxol Janelia Fluor® 646 (Cat. No. 6266)
Fluorogenic red fluorescent taxol derivative for microtubule staining



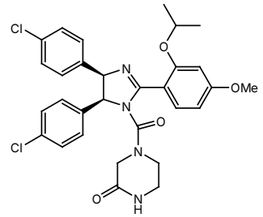
Narciclasine (Cat. No. 3715)
Antiproliferative agent; slows cell cycle progression



Monastrol (Cat. No. 1305)
Selective inhibitor of mitotic kinesin Eg5



AZ 20 (Cat. No. 5198)
Potent and selective ATR kinase inhibitor; antitumor



Nutlin-3 (Cat. No. 3984)
MDM2 antagonist; inhibits MDM2-p53 interaction

DNA Damage and p53

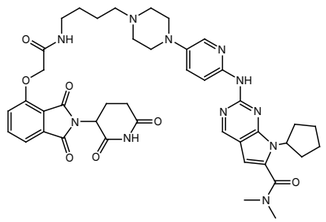
DNA damage is a common occurrence in all cells, and must be repaired in order for proliferation to occur successfully and accurately. Several cellular DNA repair mechanisms exist to fix DNA damage and prevent its transmission to daughter cells. Genomic instability is a key characteristic of cancer cells, which results from DNA damage, inefficient DNA repair, and failure to stop the cell cycle, often through aberrant activity or expression of key checkpoint enzymes and proteins, such as cell cycle checkpoint kinases (Chks), Ataxia telangiectasia mutated (ATM), Ataxia telangiectasia and Rad3 related (ATR) and p53.

If DNA damage is severe enough, apoptosis is induced in order to eliminate the cell and its tumorigenic potential. In cancer, the ability to evade apoptosis helps to promote the survival of malignant cells. Pro- and antiapoptotic proteins are involved in the complex network governing cell death. Mutations that activate prosurvival genes and/or disable proapoptotic

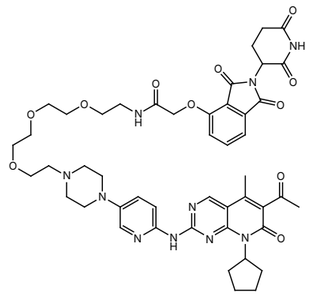
genes are evident in many human cancers, providing evidence for the link between defective apoptosis and cancer development. There are many types of compounds that can induce apoptosis, such as NQDI 1 (Cat. No. 4429), a selective inhibitor of apoptosis signal-regulating kinase 1 (ASK1). Another useful tool is Apoptosis Activator 2 (Cat. No. 2098), which selectively induces tumor cell apoptosis, with no observable effects on non-cancerous cell lines.

ATM and ATR kinases are DNA damage sensor proteins that are activated in response to DNA damage and induce cell cycle arrest by coordinating the initiation, amplification and activation of the DNA damage checkpoint. In cancer cells with DNA damage, inhibiting these enzymes could be therapeutically beneficial, because if the cell cycle continues in spite of significantly toxic DNA lesions, it will result in the death of the cell. KU 55933 (Cat. No. 3544) is a potent and selective ATM kinase inhibitor, which decreases the viability of breast, lung and colon cancer cells, as well as decreasing p21 levels *in vitro*. KU 55933 has also been shown to act as a radio- and chemotherapy-sensitizer. The ATR-Chk1 kinase pathway plays a major cytoprotective role by reducing replicative stress. ATR phosphorylates Chk1, which upregulates its activity and thus is a viable target for modulating replicative stress.

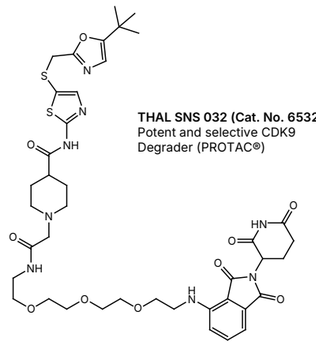
Box 2: Featured CDK Inhibitors and Degraders



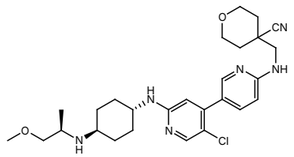
BSJ-04-132 (Cat. No. 6937)
Selective CDK4 Degrader (PROTAC®)



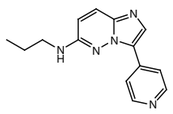
BSJ-03-123 (Cat. No. 6921)
Selective CDK6 Degrader (PROTAC®)



THAL SNS 032 (Cat. No. 6532)
Potent and selective CDK9 Degrader (PROTAC®)



NVP (Cat. No. 6535)
Potent and selective ATP-competitive CDK9 inhibitor



CDK8/19i (Cat. No. 7372)
Potent and selective CDK8 and CDK19 inhibitor

PROTAC® Degraders & Targeted Protein Degradation

Protein Degraders are an emerging class of bifunctional small molecule that encompasses PROTAC® Degraders, SNIPERs, PHOTACs, Degronimids and uSMITE™ compounds. They offer a mechanistically differentiated way to modulate target proteins using small molecules. While a small molecule inhibitor will block or modulate a specific protein domain or function (for example an enzymatic role), a Degrader will knockdown the entire protein, removing all possible functions. They work by hijacking the cell's ubiquitin-proteasome system to selectively induce target protein degradation via the 26S proteasome.

Degraders are attractive tools for use in basic research to induce selective protein knockdown in a reversible and tunable manner, without the requirement for genetic modification to cells. Degraders also have therapeutic potential as an approach to target the 'undruggable' proteome and overcome common resistance mechanisms to current therapies.

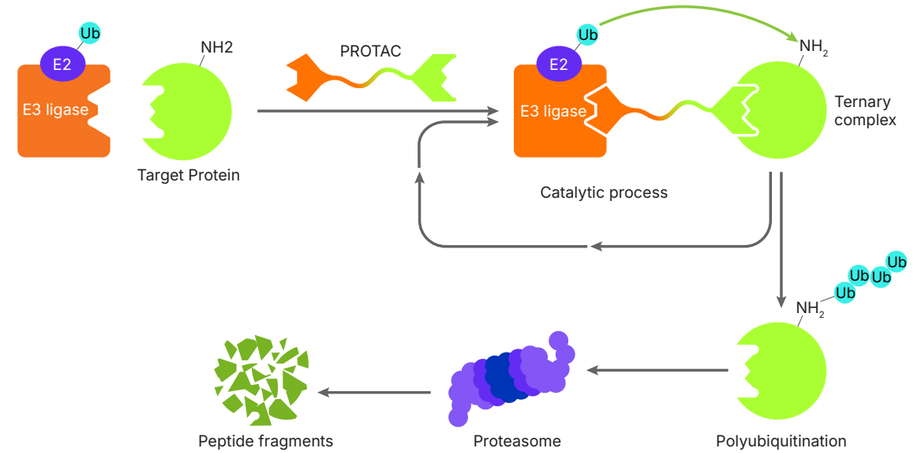


Figure 2: Schematic showing the catalytic mode of action of heterobifunctional degrader molecules. Degraders initiate the formation of a ternary complex between an E3 ubiquitin ligase and a target protein which results in polyubiquitination of the target protein, its recognition by the proteasome and subsequent degradation. Degraders act catalytically by repeatedly engaging and directing the ubiquitination of target molecules. Adapted from *Tinworth et al. (2016) MedChemComm 7 2206.*

Inhibition of Chk1 and ATR have shown some promising preclinical results, especially in p53 mutant breast cancer. ATR inhibition also limits fork regression and suppresses replication fork collapse. The potent and selective ATR kinase inhibitor AZ 20 (Cat. No. 5198) inhibits growth in cell lines with high baseline levels of replication stress and displays antitumor effects *in vivo*.

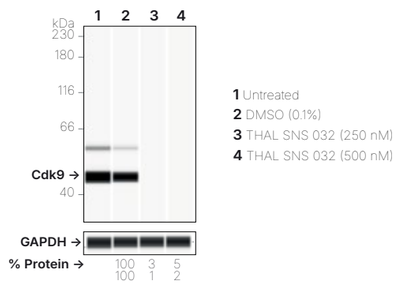
Chks are essential components in regulating cell cycle progression in normal and damaged cells, acting at all three cell cycle checkpoints. Chks and CDKs act as control switches at various transition points in the cycle, ensuring that damaged DNA is not replicated. ATR kinase phosphorylates Chk1 in response to single strand DNA breaks, while ATM kinase phosphorylates Chk2 in response to double strand breaks. Chks phosphorylate Cdc25 phosphatase, leading to Cdc25 sequestration in the cytoplasm, as well as phosphorylating p53 and Wee1, which in turn leads to the phosphorylation of CDK1 and progression of the cell cycle. Inhibition of Chk1 can be carried out through direct inhibition using selective Chk1 inhibitors or by inhibiting the kinase Wee1. If CDK activity is increased before the correct time, DNA can undergo inappropriate replication leading to fork stalling or collapse, meaning cells can enter mitosis prematurely. In addition, bursts of CDK activity promote increased rates of replication, which can lead to nucleotide shortages (Figure 2). Several small molecule Chk1 inhibitors have shown promising results and some are currently in clinical trials. Useful research tools for studying Chks include PF 477736 (Cat. No. 4277), a Chk1 inhibitor, which abrogates cell cycle arrest at S and G2/M checkpoints, and sensitizes cells to DNA damage; as well as enhancing Docetaxel (Cat. No. 4056) efficacy in tumor cells and xenografts. Another useful compound is PD 407824 (Cat. No. 2694), a selective inhibitor of Chk1 and Wee1, which may also benefit from being used in combination with Hsp90 inhibitors such as 17-AAG (Cat. No. 1515), because inhibition of Hsp90 has been shown to destabilize Wee1.

In response to DNA damage, tumor suppressor proteins, such as retinoblastoma-associated protein (Rb) and p53, prevent cell cycle progression. p53 has been a thoroughly studied cancer target since its discovery over 30 years ago. It regulates a large number of genes involved in tumor suppression, including those with roles in cell cycle arrest, DNA repair and apoptosis. p53 is activated by several mechanisms, including phosphorylation by Chk1, and Chk2. These modifications inhibit its association with MDM2, an E3 ubiquitin ligase that targets p53 for degradation by the ubiquitin proteasome pathway (UPP). Phosphorylation prevents the turnover of p53, not only increasing its levels within the cell, but also increasing its affinity for the p53 DNA binding site. Inactivating mutations of p53 occur in a significant number of human cancers, making it a key target for gene and drug therapies. Nutlin-3 (Cat. No. 3984) is an MDM2 antagonist sold by Tocris under license. It potently inhibits the interaction between MDM2 and p53, therefore inducing apoptosis in cancer cells. Other compounds, such as PRIMA-1^{MET} (Cat. No. 3710) and SCH 529074 (Cat. No. 4240) bind p53 directly to reactivate its wild-type functions and suppress tumor growth.

Featured Degrader

THAL SNS 032 Cat. No. 6532

Wes data showing knockdown of both CDK9 isoforms after THAL SNS 032 (Cat. No. 6532) treatment of MOLT-4 cells (4 h incubation). Protein quantification (relative to DMSO-only control) is shown beneath the corresponding lane. Data obtained with Protein Simple® automated, fully quantitative western blotting platform, Simple Western™



Poly(ADP-ribose) polymerases (PARPs) play an important role in regulating DNA repair and transcription, as well as the maintenance of chromatin structures. PARP inhibitors are important cancer therapeutic targets because they suppress homologous recombination, the major pathway for repairing DNA damage. Several PARP inhibitors have already demonstrated success in a clinical setting, with notable examples including increased survival for castration-resistant prostate cancer patients and ovarian cancer patients.

PARP inhibitors block the repair of single-strand breaks (SSB) by base excision repair (BER), leading the SSB to form double-strand breaks (DSB), which can lead to replicative stress and ultimately cell death. PARP inhibitors enhance the efficacy of radiation therapy and chemotherapy by blocking the repair of toxic DNA lesions, so preventing homologous recombination. PJ 34 (Cat. No. 3255), a potent inhibitor of PARP, has been shown to potentiate the cytotoxic effects of the proapoptotic agent Cisplatin (Cat. No. 2251).

Among our extensive collection of PARP probes is the cell-permeable, fluorescent PARP inhibitor PARPi-FL (Cat. No. 6461). This potent probe colocalizes with PARP immunostaining in multiple cancer cell lines, accumulating in tumor cells and tumor-associated macrophages. PARPi-FL enables high temporal and subcellular spatial resolution of drug distribution. Another valuable tool is the orally bioavailable, brain penetrant, high affinity PARP-2 and PARP-1 inhibitor Veliparib (Cat. No. 7026). This compound inhibits the repair of radiation-induced DNA damage and sensitizes lung cancer cells to radiation; it has also been shown to increase autophagy and apoptosis in lung cancer cells.

Tumor cells can replicate in spite of incomplete DNA repair, in addition, most types of tumor cells seem to acquire the ability to proliferate endlessly, negating a barrier that normally limits the number of times a cell can divide. This replicative potential is linked to the loss of protective nucleotide sequences at the ends of chromosomes, known as telomeres. Telomeres are progressively shortened during each round of cell division, to the point where they lose their ability to protect the ends of DNA – this gradual reduction in length is known as ‘telomere attrition’. Consequently, the chromosome ends fuse and cell death occurs. The inhibition of telomerase, which adds telomeres, could therefore provide a mechanism through which unlimited cell proliferation is curbed. BIBR 1532 (Cat. No. 2981) is one such telomerase inhibitor; it causes telomere shortening in rapidly proliferating cancer cells and induces growth arrest.

Ubiquitin Proteasome Pathway (UPP)

The UPP is essential for normal cell division and plays a critical role in cancer progression. The upregulation of cyclins necessary for the progression of the cell cycle is mirrored by the downregulation of cyclin dependent kinase inhibitors (CDKIs), which are responsible for the degradation of the cyclin/CDK complex. CDKIs are rapidly degraded by the proteasome contributing to the uncontrolled growth of cancer cells. Proteasomes are also involved in the degradation of tumor suppressor proteins such as p53, p27 and p21. Inhibition of the proteasome attenuates this degradation, which causes an accumulation of proteins in the cell. This induces the unfolded protein response (UPR), causing cell cycle arrest and if protein levels reach a cytotoxic level, apoptosis.

Compounds for studying the UPR or related integrated stress response (ISR) include GSK 2606414 (Cat. No. 5107), Eeyarestatin I (Cat. No. 3922) and APY 29 (Cat. No. 4865). The UPR and ISR are initiated by ER stress, hypoxia and aberrant protein synthesis, which are all important factors in cancer. GSK 2606414 has been shown to inhibit thapsigargin-induced PERK phosphorylation in a lung carcinoma cell line and attenuate pancreatic human tumor xenograft growth in mice. The potent inhibitor of endoplasmic reticulum associated protein degradation (ERAD) eeyarestatin I, selectively targets the p97-associated deubiquitinating process (PAD) and inhibits ataxin-3 (atx3)-dependent deubiquitination. It has been found that Eeyarestatin I

exhibits cytotoxic activity preferentially against cancer cells and induces cell death via the proapoptotic protein NOXA. APY 29 is an allosteric modulator of IRE1α, which activates IRE1α ribonuclease activity, a key enzyme involved in monitoring the quality of synthesized proteins.

Another principal effect of proteasome inhibitors such as MG 132 (Cat. No. 1748), is the suppression of NFκB. NFκB activates cyclin D, which binds CDK 4/6 in the G_1/S transition phase. This results in the phosphorylation of Rb and prevents p21 and p27 from inhibiting cyclin E/CDK2. A potent CDK4/6 inhibitor PD 0332991 (Cat. No. 4786), may prove a useful tool for studying this pathway. It has been shown to induce G_1 cell cycle arrest and block growth of glioblastoma xenografts in mice. Another useful compound for investigating proteasomes in cancer is lactacystin (Cat. No. 2267), which is a proteasome inhibitor that also prevents activation of NF-κB (Figure 1).

Chemotherapy

Many chemotherapy treatments damage DNA directly or use nucleotide analogs to disrupt replication leading to cell death. Another strategy is to increase cell replication and replicative stress to such a degree that the cell cannot endure. When DNA replication is carried out in such an uncontrolled manner, the normal process of error checking is not carried out and essential stages are missed, so DNA damage accumulates – leading to apoptosis and cell death. Thus, it may be therapeutically beneficial to promote tumor cell proliferation, forcing immature cells through cell cycle checkpoints causing premature termination of the replication fork and premature progression into mitosis promoting cell death.

Chemotherapeutic agents commonly used include alkylating agents and platinum compounds, which form DNA intrastrand and interstrand crosslinking, and topoisomerase inhibitors, which cause DNA strand breaks. Platinum compounds include Carboplatin (Cat. No. 2626), Cisplatin (Cat. No. 2251) and Oxaliplatin (Cat. No. 2623). These antitumor agents form platinum-DNA adducts and enhance radiation-induced single-strand DNA breakage. Another commonly used chemotherapeutic compound is the alkylating and methylating agent Temozolomide (Cat. No. 2706), which binds to DNA and modifies the O6 of guanine residues, leading to DNA cross-linking. This alkylation is readily reversed by the activity of O6-methylguanine-DNA methyltransferase (MGMT). Inhibition of MGMT by compounds such as Lomeguatrib (Cat. No. 4359) can therefore enhance the antitumor activity of these alkylating agents. Topoisomerase inhibitors, such as Etoposide (Cat. No. 1226), SN 38 (Cat. No. 2684) and Topotecan (Cat. No. 4562), trap topoisomerases in complex with DNA, causing single and double strand breaks. Another DNA repair protein is DNA-dependent protein kinase (DNA-PK), which is involved in DNA double-strand break (DSB) repair. Cells that exhibit defective DNA-PK activity are more sensitive to ionizing radiation (IR) than normal cells. NU 7026 (Cat. No. 2828) is a DNA-PK inhibitor, which radiosensitizes both proliferating and quiescent fibroblast cells to IR and inhibits DSB repair.

Current therapeutic strategies rely on combinations of chemotherapy, but are going more towards targeted approaches which attack crucial points in replication pathways. By exploiting a cancer's phenotype and rapid cell proliferation, preclinical research shows therapeutic potential for multiple combinations of drugs that modulate cell cycle regulation and DNA damage, especially those involved in creating replicative stress.

View the product list below to see a snapshot of our products for this research area. For the most up to date product list for each target, visit tocris.com and either search for your target name, the product name or product catalog number. Product pages contain descriptions of product actions, product uses, references, customer reviews, protocols, images and more.

A Selection of Related Products

Category	Cat. No.	Product Name	Description
Apoptosis signal-regulated kinase 1 (ASK1)			
Inhibitors	5641	MSC 2032964A	Potent and selective ASK1 inhibitor; orally bioavailable
ATM & ATR Kinase			
Inhibitors	5198	AZ 20	Potent and selective ATR kinase inhibitor; antitumor
	6330	AZ 5704	Potent and selective ATM kinase inhibitor; orally bioavailable
	3544	KU 55933	Potent and selective ATM kinase inhibitor
	3190	Mirin	MRN-ATM pathway inhibitor
Aurora Kinases			
Activators	3084	Anacardic acid	Aurora kinase A activator; also inhibits histone acetyltransferase
Inhibitors	3988	Hesperadin	Potent Aurora kinase B inhibitor
	4066	TC-A 2317	Potent, selective Aurora kinase A inhibitor
	5286	TC-S 7010	Potent and selective Aurora kinase A inhibitor
	2458	ZM 447439	Aurora kinase B inhibitor
Calpains			
Inhibitors	2950	Acetyl-Calpastatin (184-210) (human)	Selective calpain inhibitor
	5208	E 64	Potent and irreversible cysteine protease inhibitor
	1748	MG 132	Proteasome and calpain inhibitor; inhibits NF-κB activation
	1269	PD 150606	Cell permeable calpain inhibitor
Casein Kinase 1			
Inhibitors	2902	D 4476	Selective CK1 inhibitor; also inhibits TGF-βRI
	4281	PF 4800567	Selective CK1ε inhibitor
	6346	PF 5006739	Potent CK1δ/ε inhibitor
	3316	PF 670462	Potent and selective CK1ε and CK1δ inhibitor
Casein Kinase 2			
Inhibitors	2275	TBB	Selective cell-permeable CK2 inhibitor
	4432	TTP 22	High affinity, selective CK2 inhibitor
Caspases			
	2098	Apoptosis Activator 2	Promotes apoptosome formation and activates caspase-9/caspase-3 pathway. Selectively induces tumor cell apoptosis
Cdc25 Phosphatase			
Inhibitors	1867	NSC 663284	Potent, selective Cdc25 phosphatase inhibitor
	1547	NSC 95397	Selective Cdc25 dual specificity phosphatase inhibitor

Category	Cat. No.	Product Name	Description
Cell Cycle Inhibitors			
	4406	10058-F4	Inhibits c-Myc-Max dimerization
	6782	Indisulam	Arrests cell cycle at G1 phase; molecular glue
	1230	Methotrexate	Cytotoxic agent
	3715	Narciclasine	Antiproliferative agent; slows cell cycle progression
	6070	Pladienolide B	Arrests cell cycle in G1 and G2/M; mRNA splicing inhibitor
	4763	Pyridostatin	Stabilizes G-quadruplexes; induces DNA damage and cell cycle arrest
Checkpoint Kinases			
Inhibitors	6454	LY 2603618	Potent and selective Chk1 inhibitor
	3034	NSC 109555	Selective Chk2 inhibitor
	2694	PD 407824	Selective inhibitor of Chk1 and Wee1
	4277	PF 477736	Selective Chk1 inhibitor
	2560	SB 218078	Inhibitor of Chk1
	3038	TCS 2312	Potent Chk1 inhibitor
Chemotherapeutics			
Inhibitors	3389	Bicalutamide	Non-steroidal androgen receptor antagonist
	1100	Camptothecin	DNA topoisomerase inhibitor
	4799	Capecitabine	Prodrug of 5-Fluorouracil (Cat. No. 3257); inhibits DNA synthesis
	2626	Carboplatin	DNA cross-linking antitumor agent
	2251	Cisplatin	Potent pro-apoptotic anticancer agent; activates caspase-3
	2600	Clofarabine	Deoxycytidine kinase (dCK) substrate
	2688	CPT 11	DNA topoisomerase I inhibitor; antitumor
	4091	Cyclophosphamide	Alkylating agent; chemotherapeutic
	4520	Cytarabine	Nucleoside analog; inhibits DNA replication
	1467	Daunorubicin	RNA synthesis inhibitor
	1467	Daunorubicin	RNA synthesis inhibitor
	2624	Decitabine	DNA methyltransferase inhibitor
	3857	Dexrazoxane	Topoisomerase II inhibitor
	4056	Docetaxel	Microtubule stabilizer
	2252	Doxorubicin	Antitumor antibiotic agent; inhibits DNA topoisomerase II
	1226	Etoposide	Topoisomerase II inhibitor
	3495	Fludarabine	Purine analog; inhibits DNA synthesis
	3257	5-Fluorouracil	Inhibits RNA and DNA synthesis
	4094	Flutamide	Non-steroidal androgen receptor antagonist

Category	Cat. No.	Product Name	Description
Chemotherapeutics			
Inhibitors	3259	Gemcitabine	DNA synthesis inhibitor
	4619	Melphalan	DNA alkylating agent; cytotoxic and antineoplastic
	1230	Methotrexate	Cytotoxic agent
	3258	Mitomycin C	DNA cross-linking antitumor agent
	2623	Oxaliplatin	DNA cross-linking antitumor agent
	2033	Pentostatin	Adenosine deaminase inhibitor
	2684	SN 38	DNA topoisomerase I inhibitor; antitumor
	1621	Streptozocin	DNA alkylator; antitumor and induces diabetes
	1097	Taxol	Promotes assembly and inhibits disassembly of microtubules
	2706	Temozolomide	DNA-methylating antitumor agent
	4061	6-Thioguanine	Anticancer and immunosuppressive agent
Inhibitors	1256	Vinblastine	Disrupts microtubules
	1257	Vincristine	Disrupts microtubules
	4562	Topotecan	DNA topoisomerase I inhibitor; camptothecin (Cat. No. 1100) analog
Cyclin-dependent Kinases			
Inhibitors	6921	BSJ-03-123	Selective CDK6 Degrader (PROTAC®)
	6937	BSJ-04-132	Selective CDK4 Degrader (PROTAC®)
	7372	CDK8/19i	Potent and selective CDK8 and CDK19 inhibitor; maintains pluripotency of mouse PSCs in culture
	3094	Flavopiridol	CDK inhibitor
	7158	FMF-04-159-2	Potent covalent CDK14 and CDK16 inhibitor; also inhibits other TAIRE kinase family members
	1398	Kenpaullone	Potent CDK inhibitor; also inhibits GSK-3
	3135	NU 2058	CDK1 and CDK2 inhibitor
	3301	NU 6140	CDK2 inhibitor
	6535	NVP 2	Potent and selective ATP-competitive CDK9 inhibitor
	4786	PD 0332991	Potent, selective CDK4/6 inhibitor; brain penetrant
	3140	PHA 767491	Dual CDK9/cdc7 inhibitor; also inhibits MK2
	1580	Purvalanol A	CDK inhibitor
	1581	Purvalanol B	CDK inhibitor
	7050	Ribociclib	Dual CDK4/CDK6 inhibitor; orally bioavailable
	4181	Ro 3306	CDK1 inhibitor
	2609	Ryuvidine	CDK4 inhibitor; also SETD8 inhibitor
	4875	Senexin A	CDK8 inhibitor
	7192	SMIP 004	CDK2 inhibitor; also S-phase kinase-associated protein 2 (SKP2) inhibitor
	4075	SNS 032	Potent CDK2, CDK7 and CDK9 inhibitor
	6532	THAL SNS 032	Potent and selective CDK9 Degrader (PROTAC®)

Category	Cat. No.	Product Name	Description
DNA-dependent Protein Kinase (DNA-PK)			
Inhibitors	2828	NU 7026	Selective DNA-PK inhibitor
	3712	NU 7441	Potent and selective DNA-PK inhibitor
	6792	Omipalisib	Potent DNA-PK inhibitor
DNA Methyltransferases			
Inhibitors	4359	Lomeguatrib	MGMT inhibitor
DNA, RNA and Protein Synthesis			
Inhibitors	3561	L189	DNA ligase I, III and IV inhibitor
	1489	Mithramycin A	Inhibitor of DNA and RNA polymerase
	5340	NSC 617145	Werner syndrome helicase (WRN) helicase inhibitor
Hsp70			
Inhibitors	3803	VER 155008	Hsp70 inhibitor
Hsp90			
Inhibitors	1515	17-AAG	Selective Hsp90 inhibitor
IRE1			
Modulators	4865	APY 29	Inhibits IRE1α autophosphorylation; activates IRE1α endoribonuclease activity
Kinesin			
Inhibitors	5261	Dimethylenastron	Inhibitor of mitotic motor kinesin Eg5
	6837	GSK 923295A	Potent and selective centromere associated protein E (CENP-E) allosteric inhibitor
	6664	Kinesore	Kinesin-1 modulator; cell permeable
	1305	Monastrol	Selective inhibitor of mitotic kinesin Eg5
	2191	S-Trityl-L-cysteine	Potent, selective inhibitor of mitotic kinesin Eg5
Microtubules			
	1364	Colchicine	Inhibitor of tubulin
	3728	Indibulin	Microtubule destabilizer
	5231	MPC 6827	Inhibitor of microtubule polymerization; antimitotic and antitumor
	1228	Nocodazole	Microtubule inhibitor
	1097	Taxol	Promotes assembly and inhibits disassembly of microtubules
Stains	2226	Flutax 1	Fluorescent taxol derivative; microtubule stain
	6266	Taxol Janelia Fluor® 646	Fluorogenic red fluorescent taxol derivative; probe for microtubule staining; protocol available
Monopolar Spindle 1 Kinase			
Inhibitors	3994	AZ 3146	Potent and selective monopolar spindle 1 (Mps1) kinase inhibitor
	5142	Mps1-IN-1	Selective monopolar spindl e1 (Mps1) kinase inhibitor
	4750	TC Mps1 12	Potent and selective monopolar spindle 1 (Mps1) kinase inhibitor; orally active
Activators	6904	Idasanutlin	Potent MDM2 inhibitor; inhibits MDM2-p53 interaction
	3984	Nutlin-3	MDM2 antagonist; inhibits MDM2-p53 interaction
	6075	Nutlin 3a	MDM2 antagonist; active enantiomer of Nutlin-3 (Cat. No. 3984)
	2443	RITA	MDM2-p53 interaction inhibitor
	3356	WR 1065	p53 activator; also ROS scavenger

Category	Cat. No.	Product Name	Description
Inhibitors	3843	Cyclic Pifithrin-α	p53 inhibitor
	3503	HLI 373	Hdm2 inhibitor; activates p53-dependent transcription
	1267	Pifithrin-α	p53 inhibitor; also aryl hydrocarbon receptor agonist
	2653	Pifithrin-μ	Inhibitor of p53-mitochondrial binding
	3362	MIRA-1	Restores mutant p53 activity; proapoptotic
	1862	PRIMA-1	Restores mutant p53 activity; induces apoptosis
	3710	PRIMA-1^{MET}	Restores mutant p53 activity
PERK			
Inhibitors	5107	GSK 2606414	Potent and selective PERK inhibitor; orally bioavailable
Polo-like Kinase (PLK)			
Inhibitors	2977	GW 843682X	Selective inhibitor of PLK1 and PLK3
	4459	TC-S 7005	Potent and selective PLK2 inhibitor
Poly(ADP-ribose) Polymerase (PARP)			
Inhibitors	4140	EB 47	Potent PARP-1 inhibitor
	4106	Nicotinamide	PARP-1 inhibitor
	6344	OUL 35	Selective PARP-10 inhibitor
	6461	PARPi-FL	Potent fluorescent PARP inhibitor; cell permeable
	3255	PJ 34	Potent PARP inhibitor
	6230	Rucaparib camsylate	PARP inhibitor
	7026	Veliparib dihydrochloride	Tankyrase inhibitor
	4855	WIKI4	Tankyrase inhibitor; inhibits Wnt signaling
	3748	XAV 939	Tankyrase inhibitor; inhibits Wnt signaling
PROTAC® Degraders			
Degraders	6921	BSJ-03-123	Selective CDK6 Degrader
	6938	BSJ-03-204	Selective CDK4/6 Degrader
	6937	BSJ-04-132	Selective CDK4 Degrader
	6532	THAL SNS 032	Potent and selective CDK9 Degrader
	7240	ZNL 02-096	Potent and selective Wee1 Degrader
Control	6922	BSJ-Bump	Negative control for BSJ-03-123 (Cat. No. 6921)
Telomerase			
Inhibitors	2981	BIBR 1532	Selective telomerase inhibitor
	5312	BRACO 19 trihydrochloride	Telomerase inhibitor
	5311	RHPS 4 methosulfate	Telomerase inhibitor
	4253	TMPyP4 tosylate	Inhibitor of human telomerase
Translocation			
Inhibitors	3922	Eeyarestatin I	Potent inhibitor of ER-associated protein degradation and translocation

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