Molecular Cancer

REVIEW

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Aurora kinases signaling in cancer: from molecular perception to targeted therapies

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Abstract

Aurora kinases, AURKA, AURKB, and AURKC, are serine/threonine kinases that play a vital role in regulating cell division and mitosis, particularly in the separation of chromosomes. These kinases are often overexpressed in human tumor cell lines, indicating their potential involvement in tumorigenesis. Preliminary evidence supports the use of Aurora kinase inhibitors for certain types of tumors, several AURKs inhibitors are currently under phase I and II trials. As a result, there is a growing interest in identifying small-molecule Aurora kinase inhibitors to develop as anti-cancer agents. The regulation of the cell cycle, including mitosis, is increasingly recognized as a key target in the fight against various forms of cancer. Novel drugs are being designed to inhibit the function of regulatory proteins, such as Aurora kinases, with the goal of creating personalized treatments. This review summarizes the biology of Aurora kinases in the context of cancer, integrating both preclinical and clinical data. It discusses the challenges and opportunities associated with using Aurora kinases to enhance cancer treatment. Future directions for Aurora kinase-based therapies include developing more selective inhibitors that minimize off-target effects and improve therapeutic efficacy. Researchers are also exploring combination therapies that use Aurora kinase inhibitors alongside other targeted treatments to overcome resistance and improve patient outcomes. Additionally, advancements in biomarker discovery are expected to facilitate the identification of patients most likely to benefit from Aurora kinase-targeted therapies, paving the way for more personalized approaches to cancer treatment.

Keywords AURKA, AURKB, AURKC, AKIs, Cancer Diagnosis and Prognosis, Targeted Therapy

Introduction

Tumor heterogeneity can be categorized as intra-tumor or inter-tumor heterogeneity, referring to the presence of genetically and phenotypically distinct subpopulations of cancer cells within the same tumor or across tumors of the same histopathological subtype respectively [1]. This heterogeneity arises due to continuous genetic mutations, epigenetic modifications, and cellular microenvironmental influences, significantly contributing to various biological behaviors including therapy resistance, disease progression, metastatic potential, and treatment failure [2]. Cancer cells not only exhibit genetic heterogeneity but also exploit cell cycle plasticity to evade therapy.

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In normal cells, the progression through the G0/G_1, S, and G2/M phases is tightly regulated by checkpoint pathways that ensure genomic integrity [3]. Among these, the G2/M checkpoint is particularly crucial, acting as a barrier against mitotic errors by detecting DNA damage, replication stress, and spindle defects [4]. However, dysregulation of the G2/M checkpoint compromises DNA repair mechanisms, allowing damaged cells to undergo mitosis, leading to chromosomal instability (CIN), aneuploidy, and tumor evolution [5]. One of many challenges of translational oncology lies in effectively targeting these mechanisms while minimizing toxicity and resistance. Additionally, with the rise of personalized therapy, there is a growing emphasis on targeting oncogenic drivers that play a leading role in tumor evolution.

Aurora kinases (AURKs), members of the serine/threonine kinase family, are among the key regulators of mitotic fidelity by directing chromosome alignment, spindle organization, and cytokinesis [6]. Their activity dictates whether a cell progresses through mitosis with genomic accuracy or drives errors that fuel tumorigenesis. The family consists of three paralogs: Aurora Kinase A (AURKA), Aurora Kinase B (AURKB), and Aurora Kinase C (AURKC), each with distinct yet overlapping functions [7]. Under physiological conditions, Aurora kinases maintain genomic stability by regulating mitotic checkpoints and preventing chromosomal missegregation [8]. However, their dysregulation via gene amplification or overexpression, disrupts mitotic checkpoints and spindle assembly, leading to CIN, aneuploidy, and uncontrolled proliferation [9]. Elevated levels of Aurora kinases have been reported in various malignancies, including breast, lung, colorectal, ovarian, and prostate, where their oncogenic activity drives uncontrolled proliferation, resistance to apoptosis, and therapeutic resistance [6]. Given their pivotal role in oncogenesis, Aurora kinases have become a major focus of translational cancer research. Aurora kinase inhibitors (AKIs) have been designed to selectively block the ATP-binding pocket of these kinases, disrupting mitotic progression and inducing apoptosis in cancer cells [10]. However, despite these advancements, challenges such as off-target toxicity, compensatory survival pathways, and acquired resistance remain major obstacles to successful clinical translation [11]. To address these challenges, combining AKIs with chemotherapy, immunotherapy, and RNA-based therapeutics offers a multi-faceted approach to enhance treatment efficacy and combat resistance mechanisms [12]. Additionally, emerging strategies such as synthetic lethality, PROTAC degraders, and immunemodulatory approaches are being developed to exploit aurora kinase vulnerabilities in tumors with CIN-driven phenotypes [13, 14]. In this review, we have provided a comprehensive analysis of aurora kinases, detailing their structural and functional roles, dysregulation in cancer, and the latest advancements in therapeutic approaches. This review explores emerging strategies such as combination therapies, next-generation AKIs, and RNA-based inhibitors, highlighting the prospects of targeting aurora kinases for precision oncology. A deeper understanding of these pathways will be crucial for designing more effective and personalized cancer treatment strategies.

Evolution of Aurora kinases

From an evolutionary perspective, aurora genes have remained relatively conserved over time, sharing 78–84% similarity between humans and rodent [15]. Studies suggest that these genes have originated from Urochordates (Tunicates), the fungi, *Saccharomyces cerevisiae* have a single homologous ancestor of aurora, known as increase-in-ploidy 1 (Ipl1), which plays a pivotal role in chromosome biorientation and kinetochore-microtubule attachment, ensuring accurate chromosome segregation [16]. The necessity to ensure accurate chromosome segregation led to the functional diversification of Ipl1, leading to the emergence of distinct kinases in higher organisms with specialized roles. Speciation effects on Ipl1 and its orthologous evolution led to the emanation of AURKA (also known as AIK1, ARK1, and Eg2) and AURKB/C (AIK2, ARK2, and Eg1) genes in invertebrates and non-mammalian vertebrates (e.g., *Caenorhabditis Elegans*, *Xenopus Laevis,* and *Drosophila Melanogaster)* [17, 18] as illustrated in Fig. 1. In mammalian vertebrates (e.g. *Homo sapiens* and other mammals), the subsequent effects on speciation further gave rise to paralogous form of AURKA and on the other side AURKB/AURKC ancestors resulted in AURKB and AURKC paralogs [19]. During a genetic screening for protein factors required for chromosome segregation, aurora kinases were first identified in yeast [20]. Other species later identified within the family under different names, such as Aurora, Ipl1, AIR-2, pEg2, Ark1, and AIE1, AIE2. Carmena et al., (2003) confirmed the homology of AURKs and confirmed their essential roles in chromosomal attachment and maintenance of ploidy [21]. Eventually, researchers condensed the family nomenclature into the familiar Aurora A, B, and C kinases (AurA, AurB, and AurC). In mammals, AURKA, AURKB, and AURKC were mapped on chromosomes 20q13.2, 17p13.1, and 19q13.43, respectively [15]. Chromosomes and the spindle midzone express Aurora A and B, while testis and oocytes express Aurora C, which contributes to early embryonic divisions [22–24]. Interestingly, these variants have shown similar substrate preferences, compard to in vivo probably due to localization patterns, and functions because they interact with specific binding partners. The three

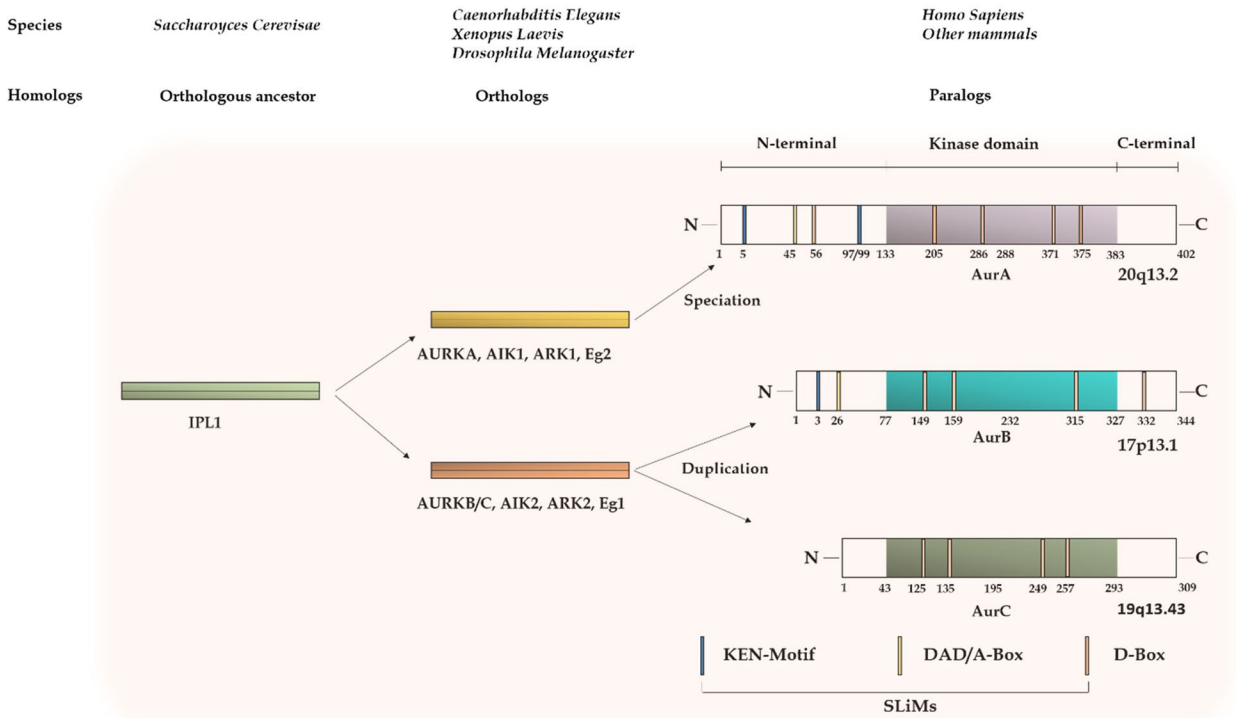


Fig. 1 The evolutionary relationship between Aurora kinases highlights their conserved roles in cell cycle regulation across species. The phylogenetic relationships among these kinases across various species shows structural similarities, including key functional regions like kinase domains, phosphorylation sites, and regulatory motifs. The evolutionary divergence of these kinases suggests functional adaptations, with some species retaining conserved sequences while others exhibit modifications. This evolutionary perspective provides insights into how Aurora kinases have developed specialized roles in cellular processes

mammalian aurora paralogues are highly conserved and have a homologous structure consisting of a N-terminal domain, a protein kinase domain, and a C-terminal domain [25].

Sequence and structural features of Aurora kinases

Aurora A

Aurora A enzyme, encoded by the AURKA gene, is a 403 amino acid protein with a predicted molecular mass of 45.8 kDa. The 251 amino acid long main kinase catalytic domain is flanked by 132 amino acid long non-catalytic N-terminal segment and a small 20 amino acid tail on C-terminal side [26]. Thr288/Thr287 phosphorylation within the activation loop of the kinase domain leads to recruitment of partner protein TPX2 which promotes Aurora A activation in mitosis by stimulating Aurora A autophosphorylation on Thr288 and thus regulation of catalytic activity of Aurora A. It has been observed that phosphorylation of Thr287 can also increase kinase activity suggesting critical role of Aurora A beyond mitosis [27]. Activation loop is flexible and adopts various conformations within the kinase domain depending upon its phosphorylation state, the presence of TPX2, and the type of ligand. Aurora kinase domains also contain three types of short linear motifs (SLiMs), known as degrons based on sequence signatures: the KEN motif, the DAD/A box, and the D box [28] (Fig. 1). The KEN motif, located at the 5th position in AURKA, serves as a recognition site for the anaphase-promoting complex/cyclosome (APC/C). Degrons help regulate protein degradation through the proteasome pathway. The Polo-like kinase 1 (PLK1) phosphorylates the KEN motif, which helps the APC/C break down AURKA, thereby reducing its levels as cells exit mitosis [29]. Similarly, the DAD/A box, located at the 45th position, governs the stability and activity of AURKA during the cell cycle. Phosphorylation of the DAD motif by kinases like GSK-3β (Glycogen Synthase Kinase-3β) helps the proteasome pathway break down AURKA at the end of mitosis, while dephosphorylation keeps AURKA stable during the G1 phase [7]. Structurally, the Aurora kinase domain consists of an N-terminal β-stranded lobe and a C-terminal α-helical lobe, connected by a flexible hinge that enables active conformation. The activation loop, also known as the catalytic T-loop, plays a crucial role in regulating the enzymatic activity of the kinase domain [30]. Understanding

the structure, function, and regulation of Aurora A can provide valuable insights about its role and significance as a drug target in cancer research which may potentially allow the development of novel therapeutic strategies. Dysregulation of these structural elements, particularly mutations or abnormalities in the C-terminal domain can impair AURKA's regulatory mechanism, leading to uncontrolled cell growth and potential tumorigenesis [31]. Additionally, aberrant AURKA activity has been associated with resistance to chemotherapeutic agents, as its dysregulation can interfere with normal cell cycle checkpoints and promote survival signaling pathways.

Aurora B

Aurora B is a complex protein composed of 345 amino acids with an estimated molecular mass of 39 kDa and is encoded by the AURKB gene, which is located on chromosome 17p13.1 [32]. Structurally, Aurora B consists of two regulatory domains at the N- and C-terminal ends and a central catalytic kinase domain [33]. AURKB also possesses three degrons, but in a different position compared to AURKA. The N-terminal domain consists of 75 amino acids (1–76 aa), while the kinase domain consists of 251 amino acids ranging from 76 to 327 aa (Fig. 1). AURKB's degrons include the KEN motif and the DAD/A box, both located in the N-terminal domain at positions 3 and 26, respectively, while the D-box is found in the C-terminal domain at position 332. Similar to AURKA, the KEN motif in AURKB is phosphorylated by Polo-like kinase 1 (PLK1), marking it for degradation by the anaphase-promoting complex/cyclosome (APC/C) during the G1 phase and mitotic exit [34]. This helps control the levels and activity of AURKB. The DAD/A box motif in AURKB is less well-characterized compared to AURKA, but it is believed to play a role in regulating AURKB's stability and activity during the cell cycle. AURKB also possesses a D-box motif (RxxL), which serves as a recognition site for the APC/C. KEN and D-box motifs both work in the same way to target AURKB for degradation by APC/C during the end of mitosis [35]. Structurally, the unique configuration of AURKB with its dual regulatory domains ensures its precise localization to centromeres and efficient coordination of chromosome segregation and cytokinesis [36]. Disruptions in AURKB expression or function can lead to chromosomal misalignment, aneuploidy, and genomic instability—key features in the development of various cancers [37]. Functionally, Aurora-B, encoded by a gene comprising nine exons, is essential for cell division and is tightly regulated by CPC [38]. INCENP, Survivin, and Borealin/Dasra B, the three regulatory subunits of the CPC (Chromosomal Passenger Complex), which form a stable 1:1:1 complex through a three-helix bundle, allowing for precise centromere targeting in living cells [39]. INCENP binding enhances Aurora B's basal activation, while Borealin/Dasra B promotes local clustering, leading to auto-activation at the centromere. Survivin appears to play a role in CPC localization at centromeres, though its direct influence on Aurora B activity remains a subject of debate [40].

Aurora C

AURKC is located on the long arm (q) of chromosome no. 19 (19q13.43). The AURKC gene encodes a protein of 309 amino acids with a predicted molecular mass of 35.6 kDa. Aurora kinase C (AURKC) has been less extensively explored compared to AURKA and AURKB. Aurora C also shares structural similarities, including an activation loop within its catalytic domain [23]. The N-terminal domain of Aurora kinase C comprises 38 amino acids (1–39 aa), the kinase domain spans from 39–290 aa, comprising 251 amino acids, and the C-terminal domain comprises 16 amino acids (290–306 aa) (Fig. 1). Unlike AURKA and AURKB, AURKC lacks the KEN motif and DAD/A box, but it is reported to have a D-box motif (RxxL) within its catalytic domain [41, 42]. Although specific details remain to be elucidated, phosphorylation of the D-box motif may regulate the degradation of AURKC by APC/C. Like other Aurora kinases, AURKC's activation loop sits within its catalytic domain, sandwiched between the N-terminal and C-terminal lobes. The phosphorylation takes place specifically at T195, and the T-loop undergoes conformational changes that facilitate ATP and substrate binding to the kinase domain [43, 44]. When AURKC is phosphorylated and activated, downstream targets involved in various cellular processes, such as cell division and meiosis, are phosphorylated.

Cofactors of Aurora kinases

Cofactors of Aurora A

Aurora A is a part of bipolar spindle assembly and works with regulatory cofactors such as TPX2, Ajuba, and Bora to manage its catalytic activity. These cofactors ensure tight control of the kinase's localization and activity throughout mitosis [45]. Some other well-known cofactors working at different mitotic steps include TACC3, NPM, CDC25C, CDK1, CCNB1, PLK1, and CEP192. These cofactors can either mediate auto-phosphorylation at the Thr288 residue to aid in AURKA activation, or they activate AURKA activation to aid in its functioning [46]. TPX2, the best-understood regulatory subunit, helps position it on spindle microtubules rather than directly at the centrosome, when depleted using siRNA, it results in abnormal spindle formation [47]. By dephosphorylating Thr288, protein phosphatase 6 (PP6) downregulates AURKA activity, causing abnormal spindle

assembly and chromosome alignment defects which can be prevented by the interactions of AURKA with TPX2 enabling it to autophosphorylation Thr288 in the T-loop. Elevated levels of AURKA and TPX2 can cause spindles that are misoriented or super-aligned [45]. Meanwhile, Ajuba, a protein with an LIM domain, is essential for mitotic commitment [48]. BORA, another cofactor of AURKA, activates PLK1 (Polo-like kinase 1), the master mitotic kinase, and participates in mitotic commitment [3]. Figure 2A depicts the interaction of AURKA and its co-factors, modulating several cell cycle processes. Understanding these cofactors' roles in cancer could pave the way for developing targeted therapies. By targeting certain cofactors like TPX2 or BORA, we might be able to stop AURKA from activating and working improperly. This would stop tumor growth and open new avenues of treatment for several types of cancer.

Cofactors of Aurora B

The chromosomal passenger complex (CPC) is a complex of three main regulatory components: survivin, borealin, and INCENP which assemble in a 3:1:1 ratio to regulate the positioning and activity of AURKB as illustrated in Fig. 2B [49]. Any of the above-mentioned components' RNAi depletion can disrupt mitotic progression. INCENP, a highly conserved protein Aurora B via the C-terminal In-box, increasing its activity. Aurora B and INCENP may also exist independently as Aurora B-INCENP complex, crucial for activating PLK1 at the centromere in early mitosis [50]. Survivin, through its conserved BIR domain, guides the CPC to the inner centromere by recognizing histone H3 phosphorylated on Thr3 by Haspin. Meanwhile, Borealin helps position all four components of CPC at the inner centromere and may activate Aurora B via Mps1 [51]. Hence, any problem in the working of CPC members can disrupt cytokinesis, chromosomal condensation, and segregation, which could lead to genomic instability and tumor formation. Thus, CPC safeguards the integrity of the genome by ensuring accurate chromosome distribution and proper genetic material organization.

Cofactors of Aurora C

Like AURKB, AURKC also performs the localization and phosphorylation functions but is a more critical part in meiosis rather than mitosis. AURKC is expressed in reproductive tissues along with its presence in certain cancer cells. Its working is affected by

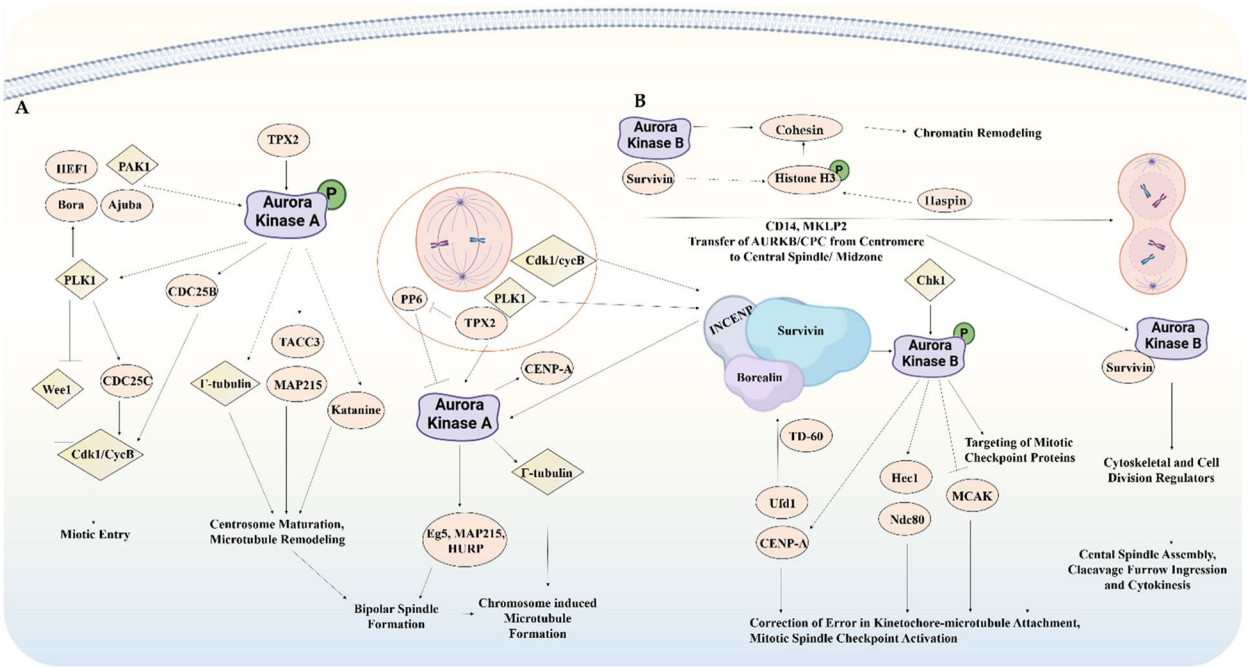


Fig. 2 This figure illustrates the roles of Aurora Kinases A and B in mitosis, highlighting their interactions with various regulatory proteins. In panel **A**, Aurora Kinase A is shown in early mitotic events, such as centrosome maturation, microtubule remodeling, and bipolar spindle formation. It interacts with key regulators like PLK1, CDC25B, TPX2, and MAP215, ensuring proper spindle assembly and chromosome alignment. In panel **B**, Aurora Kinase B is depicted as a crucial player in chromosome segregation and cytokinesis. It is part of the chromosomal passenger complex (CPC), which includes INCENP, Survivin, and Borealin, facilitating error correction in kinetochore-microtubule attachments and activating the spindle checkpoint. Aurora Kinase B also regulates chromatin remodeling via Histone H3 phosphorylation and participates in central spindle assembly and cleavage furrow ingression during cytokinesis

several cofactors like Survivin, INCENP, borealin, Protein Phosphatase 1 (PP1), Histone H3 and HASPIN kinase which are essential for cell division and targeted therapies for diseases like cancer [52]. Aurora C localization to centromeres and kinetochores is regulated by Survivin, whereas Inner Centromere Protein (INCENP) acting as a scaffold protein enhances its kinase activity. Borealin interacts with AURKC and stabilizes it, and also acts as a mediator for chromosome alignment and segregation, and on the other hand, PP1 negatively regulates AURKC activity by dephosphorylating its substrates, making it essential for proper progression of cell cycle [53]. HASPIN phosphorylates Histone H3 at threonine 3 thereby facilitating AURKC and CPC component recruitment on the chromosomal sites where AURKC will phosphorylate histone H3 on serine 10 and serine 28 leading to chromosome condensation [54]. These interactions between AURKC and its cofactors ensure chromosomal stability and their proper segregation, and more insights about them will reveal more effective and targeted treatments for diseases like cancer.

Roles of Aurora kinase's in cell cycle and molecular mechanism

Aurora kinase A

Aurora kinase A (AURKA), being a crucial cell cycle regulator, is primarily linked to centrosomes and microtubules near centrosomes. Its level decreases during the G1 phase and subsequently localize to centrosomes undergoing duplication during the S phase and early G2 phase [55]. AURKA participates in mitotic processes, centrosome maturation, and the assembly of the bipolar spindle, it also localizes at microtubule organizing centers (MTOCs) and astral microtubules at the onset of metaphase [56]. However, in both early and late anaphase, AURKA levels decline at the spindle microtubules and midbody region [57]. It plays a pivotal role in mitotic entry, with its activation during the M phase being mediated by the Cyclin B1-CDK1 complex. As the cell cycle advances to late G2, AURKA is initially activated with AJUBA and further gets fully activated by getting phosphorylated by activated cyclinB1/CDK1 [58]. Bora is a crucial regulator of AURKA, ensuring its proper function and progression through mitotic stages. When Bora is depleted via RNAi, an accumulation of AURKA and TPX2 occurs at centrosomes, leading to defects in mitotic spindle formation [59]. On the other hand, excessive Bora expression results in AURKA mislocalization away from centrosomes and promotes monopolar spindle formation [60].

Centrosome maturation

Centrosome maturation begins in the S phase but is most pronounced during the late G2 phase. During this stage, centrosomes enlarge as pericentriolar material (PCM) accumulates, facilitating their function as primary microtubule-organizing centers in mitosis [61]. Proteins such as Cep192 and spindle defective 2 (Spd-2) are responsible for targeting and activating AURKA. Once activated, AURKA recruits γ-tubulin, LATS2, NDEL1, centrosomin, and TACC to the PCM [62]. Centrosomin (CNN) binds directly with AURKA's C-terminal domain, while its N-terminal domain binds to the γ-tubulin ring complex. Apart from CNN, Large Tumor Suppressor Kinase2 (LATS2) is another AURKA substrate required for γ-tubulin recruitment [15]. Aurora A depletion through RNAi results in reduced microtubule nucleation and a defective spindle assembly along with prevented centrosomal accumulation [63, 64]. As the M phase begins, NDEL1 is phosphorylated by AURKA for the centrosomal targeting of TACC3 which is also further phosphorylated by AURKA playing a crucial role in stabilizing the spindle microtubule hence allowing proper microtubule growth [65].

Bipolar spindle assembly

The formation of a bipolar mitotic spindle necessitates the coordinated activity of microtubule-based motor proteins like dynein and Eg5, ensuring balanced forces within the spindle [66]. AURKA, a protein involved in mitotic spindle dynamics, is also involved in forming spindle-like asters through interactions with other proteins like TPX2, HURP, XMAP215, and Eg5 [67]. Aurora A plays a crucial role in maintaining the equilibrium between mitotic spindle assembly and disassembly, inhibiting a MT depolymerase, Kif2a, and recruiting TACC3, which facilitates microtubule growth via CKAP5-a [68–70]. In late prophase, AURKA phosphorylates Cyclin B1-CDK1 and releases spindle assembly factors TPX2, which in turn activates the Ran GTPase signaling pathway responsible for nuclear envelope breakdown (NEBD). Functioning downstream of the Ran GTPase pathway, AURKA displaces TPX2 from importin α/β, leading to the activation of its catalytic kinase domain [34]. This conformational change enables AURKA to associate with astral microtubules, undergo auto-phosphorylation at Thr288, and resist dephosphorylation by PP1 and PP6 phosphatases. Collectively, these processes facilitate proper spindle assembly during cell division [71, 72].

Aurora kinase B

Aurora kinase B (AURKB), a component of the chromosome passenger complex (CPC), is a crucial protein

in mitosis, regulating chromosome attachment to the mitotic spindle. It localizes various proteins at the centromere and kinetochore regions, ensuring accurate chromosome biorientation. Additionally, it contributes to the regulation of the spindle checkpoint and cytokinesis [73]. Aurora B is essential for chromosome alignment at the metaphase plate and functions during the spindle assembly checkpoint (SAC), also facilitating the proper positioning and formation of the cleavage furrow, which is crucial for cell division [74]. The activation of AURKB is a multistep process that begins with its binding to the In-box domain of INCENP, leading to a low initial level of kinase activity. This interaction allows AURKB to autophosphorylate specific residues, particularly Thr232 in the activation loop [75]. INCENP itself gets phosphorylated by AURKB at a C-terminal Thr-Ser-Ser (TSS) motif, stabilizing the interaction between AURKB and INCENP which is critical for full activation. Both autophosphorylation of AURKB and phosphorylation of INCENP typically occur in trans, ensuring robust activation and amplification of the kinase signal [76]. Fully activated AURKB, in complex with INCENP, Survivin, and Borealin forms the active chromosomal passenger complex (CPC), which localizes at centromeres during early mitosis and relocates to the spindle midzone and midbody during anaphase and cytokinesis, ensuring accurate chromosome segregation and completion of cell division.

Chromosome biorientation and segregation

Following nuclear envelope breakdown, prometaphase chromosomes establish connections with a nearby spindle pole, ensuring accurate microtubule-kinetochore interactions necessary for chromosome biorientation and alignment. This process can be monotelic, where one sister kinetochore gets attached, or bipolar or amphitelic, where both sister kinetochores secure attachments to microtubules originating from opposite poles [77]. However, incorrect kinetochore-microtubule attachments can still occur, preventing chromosomes from properly aligning at the metaphase plate, which, if not corrected before anaphase, can lead to lagging chromosomes and an unequal distribution of genetic material [78]. Aurora B plays a key role in correcting these errors by phosphorylating the Ser10 residue of histone H3. This modification triggers the release of heterochromatin protein 1 (HP1) and induces an epigenetic transition towards a more active chromatin state. This phosphorylation event may contribute to chromosome condensation and facilitate Aurora B's recruitment to the centromeres [79]. Additionally, Aurora B interacts with mitotic centromere-associated kinesin (MCAK), which plays a crucial role in regulating chromosome biorientation and alignment. MCAK, a kinesin-13 family member, possesses catalytic domains that enable microtubule depolymerization [80]. Recent findings indicate that Aurora B can recruit MCAK to the centromere and directly phosphorylate it at several conserved residues. This phosphorylation reduces MCAK's ability to depolymerize microtubules, thereby influencing proper chromosome segregation [5]. Disrupting MCAK function through siRNA-mediated knockdown, antibody-mediated inhibition, or the expression of phosphomimetic MCAK mutants leads to a higher proportion of incorrectly attached kinetochores [81].

The spindle assembly checkpoint

Aurora B plays a pivotal role in overseeing microtubule-kinetochore interactions and may contribute to regulating the spindle assembly checkpoint (SAC). This checkpoint ensures that cells do not proceed into anaphase if kinetochores remain unattached to microtubules or lack proper tension [82]. The SAC is triggered by checkpoint sensors such as Bub, MAD-1/2, MPS1, and CENP-E, with AURKB functioning upstream to facilitate their activation. Additionally, ATM kinase acts as a key regulator of the SAC by phosphorylating Bub1, thereby amplifying checkpoint signaling [83–86]. Inhibited AURKB activity leads to incorrect localization of checkpoint components, reduced phosphorylation of BubR1, and recruitment and phosphorylation of Kif2C to depolymerize incorrectly attached kinetochores [87]. Aurora B deficient cells fail to halt cell cycle progression without kinetochore tension, as a result, cells with impaired function often proceed through anaphase despite having misaligned chromosomes. The impairment of the spindle assembly checkpoint (SAC) in Aurora B-deficient cells may also be attributed to a reduced localization of key checkpoint proteins, such as Mad2 and BubR1, at kinetochores. This decrease compromises the ability of the cell to detect and correct improper microtubule-kinetochore attachments, allowing premature progression into anaphase and increasing the risk of chromosome mis-segregation. [88].

AURKB regulates cytokinesis

During late telophase, the CPC localizes to the midbody, a dense microtubule structure at the central spindle. This translocation is facilitated by the kinesin MKLP2 and relies on an AURKB activity gradient across the spindle midzone, which is believed to be essential for cleavage furrow positioning [89, 90]. During cytokinesis, Aurora B remains concentrated at the midbody, where it activates the RhoA GTPase following Rac-GAP1 phosphorylation. This activation promotes actin polymerization and myosin function, both of which are necessary for contractile ring formation [91]. Additionally, AURKB phosphorylates substrates such as Vimentin, Desmin, and

GFAP (Glial fibrillary acidic protein) to regulate cleavage furrow organization [92]. Collectively, Aurora B ensures proper chromosome segregation and cytoplasmic division, thereby maintaining genomic stability.

Aurora kinase C

Aurora Kinase C (AURKC), a member of the Aurora kinase family, is encoded on human chromosome 9 and is primarily known for its role in meiosis. Although it is less extensively studied than Aurora B, emerging evidence suggests that Aurora C plays a critical role in ensuring proper chromosome segregation during germ cell division, particularly in spermatogenesis. It is predominantly expressed in the testes, where it regulates meiotic progression, making it an essential kinase in germ cells [93, 94]. Both Aurora B and Aurora C exhibit high mRNA and protein expression during the G2/M phase. While Aurora C shares functional similarities with Aurora B, it performs distinct, non-redundant roles during mitosis and is primarily specialized for meiotic processes in oocytes and spermatocytes [42]. In somatic cells with reduced Aurora B levels, Aurora C can partially compensate by interacting with INCENP to support mitotic progression [95]. Interestingly, its localization closely resembles that of Aurora B within the chromosome passenger complex (CPC). In female mouse meiosis, Aurora C is present at the centromeres and chromosome arms during pro-metaphase I and metaphase I [96]. By metaphase II, it becomes concentrated at the centromeres, where it undergoes phosphorylation at Thr171. During the transition from anaphase to telophase, Aurora C dephosphorylates and relocates to the midzone and midbody, highlighting its role in ensuring accurate chromosome segregation [97].

Roles of Aurora kinase's expression in cancer

Aurora kinase A

Aurora A, encoded on chromosome 20q13.2, is frequently overexpressed in multiple human malignancies, including breast, lung, ovarian, colon, gastric, prostate, cervical, and pancreatic cancers [11, 52, 98]. This overexpression is not always linked with gene amplification, as it has been observed in 15% of ductal carcinoma in situ cases but is also associated with enhanced invasiveness, hormone receptor negativity, high ki67 proliferation, and genomic instability [99]. In hepatocellular carcinoma (HCC), AurA is overexpressed in 61% of cases, correlating with high tumor grade, β-catenin mutation, and poor survival outcomes [100]. There are various mechanisms contributing to the overexpression of Aurora kinase A and indicating its role as an oncogene, promoting tumorigenesis as shown in Fig. 3. Specifically, AURKA modulates cancer stem cells (CSCs) properties in gliomas, colorectal, and breast tumors. It can interact with the transcription factor FOXM1, promoting the self-renewal of breast CSCs and leading to drug resistance [101]. Experimental studies demonstrate that ectopic AURKA expression in Rat 1 and NIH3T3 fibroblasts induces tumor formation when introduced into nude mice [102]. Additionally, epithelial-mesenchymal transition is mediated by AurA by downregulating adhesion molecules which in turn facilitate tumor cell migration. Aurora kinase A regulates EMT either through indirect activation of the Wnt/Akt pathway or via direct transcriptional activation of Twist, Slug, Zeb [103]. Furthermore, AURKA influences tumor cell migration through MMP-2 secretion, stimulation of the DNA-binding protein Rap1, and FAK activation [104] as illustrated in Fig. 4. Clinically, high AURKA expression is associated with poor prognosis as it favors breast cancer stemness in cells [105]. Disrupted AURKA localization, particularly in cells with overexpressing AURKA, may contribute to the oncogenic activities, and often display defective mitotic spindle checkpoint functions, which may lead to taxane-based chemotherapy resistance [106]. Silencing of Aurora kinase A could significantly reduce the activity of SRC and downregulate ERK and Akt/mTOR pathways, leading to re-sensitization of resistant cells to Taxol [107]. In esophageal squamous cell carcinomas, upregulated Aurora A kinase is linked to dysregulated Cyclin B1 expression, a factor contributing to genomic instability and carcinogenesis [108].

Aurora kinase B

Aurora B, a highly expressed gene in proliferating cells is frequently upregulated in various cancers, including, mesothelioma, oral cancer, colon, non-small cell lung carcinoma, malignant endometrium, testicular germ cell tumors, hepatocellular carcinoma, glioblastoma, ovarian, thyroid, and prostate [11, 109–112]. Elevated Aurora B expression positively correlated with poor prognosis and is often observed in high grades of malignancy in different neoplastic lesions [113]. In prostate cancer, AURKB elevated levels correlates with Gleason grade [114], while in colorectal cancer, its expression aligns with Duke's classification [115]. Similarly, in ovarian and thyroid cancer, elevated Aurora B levels are linked to dedifferentiation [116]. In epithelial ovarian cancer (EOC) patients, Aurora B kinase expression was evaluated, showing that expression of Aurora B in poorly and moderately differentiated carcinomas was significantly higher than in well-differentiated carcinomas [117]. Studies on colorectal cancer patients, revealed lower overall survival rate correlated with overexpression of Aurora B [118]. Additionally, a single-nucleotide polymorphisms analysis identified that patients carrying the G-allele in the 885A > G variant

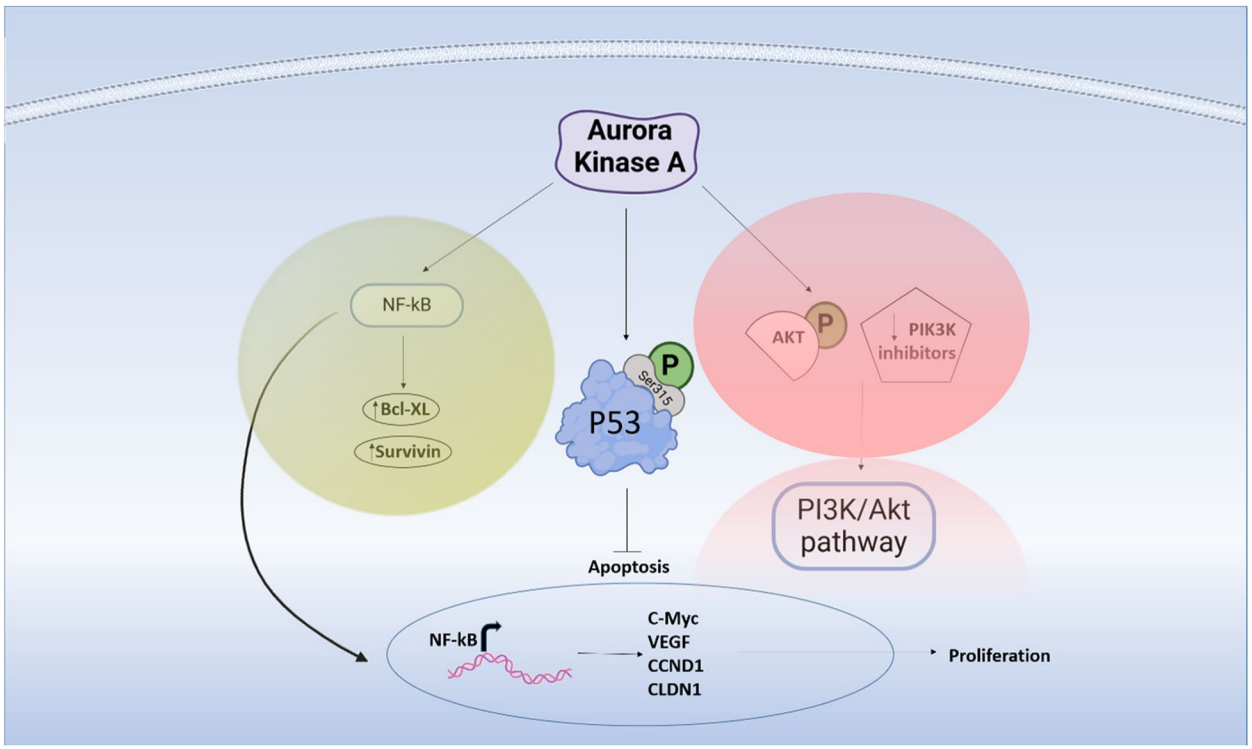


Fig. 3 Role of Aurora Kinase A (AURKA) in promoting cell survival and proliferation by modulating key signaling pathways. AURKA interacts with and phosphorylates p53 at Ser315, leading to its degradation and inhibition of apoptosis. Additionally, AURKA activates the NF-κB pathway, increasing the expression of anti-apoptotic proteins such as Bcl-XL and Survivin, further promoting cell survival. Another critical pathway influenced by AURKA is the PI3K/Akt signaling cascade, which is activated through Akt phosphorylation. This activation leads to the transcription of oncogenic genes like C-Myc, VEGF, CCND1, and CLDN1, driving uncontrolled cell proliferation. The presence of PI3K inhibitors can potentially block this pathway, reducing proliferation. Overall, AURKA functions as an oncogenic kinase by suppressing apoptosis and enhancing cell survival, making it a key target in cancer research and therapy

had significantly reduced overall survival outcomes. This suggests that Aurora B plays a crucial role in cancer progression, influencing both tumor growth and treatment response. Functionally, Aurora B phosphorylates key substrates involved in mitotic regulation, such as histone H3 and components of the spindle checkpoint machinery, allowing cancer cells to override normal cell cycle control mechanisms [119]. As illustrated in Fig. 5, Aurora B facilitates apoptosis evasion by phosphorylating p53 at Ser315, leading to its degradation and suppression of apoptotic genes such as BAX and BAD [120]. Additionally, Aurora B enhances STAT3 phosphorylation at Ser727, promoting transcription of anti-apoptotic genes that sustain tumor cell survival [121]. AURKB increases the expression of MMPs, which are enzymes responsible for degrading the extracellular matrix (ECM degradation). This degradation enables cancer cell invasion, allowing cells to migrate and spread [122]. Furthermore, FAK, which plays a key role in cell adhesion and migration, also gets activated by AURKB along with Rho GTPase signaling, which leads to increased motility and eventual invasion as depicted in Fig. 4. The role of Aurora A in the neoplastic lesion development was established first, whereas the role of Aurora B in cancer development is still under investigation. However, in vitro studies performed employing several Aurora B inhibitors, dominant-negative mutants, or RNAi approaches indicate that Aurora B deficiency disrupts cell cycle progression, causing treated cells to undergo mitotic defects and polyploidy. The effects of longer depletion of Aurora B seem to be cell line dependent, with some cells entering additional cell cycles but becoming massively polyploid, while others undergo apoptosis or arrest in a pseudo G1 state. A direct evidence linking AURKB to carcinogenesis was demonstrated in Chinese hamster embryo (CHE) cells carrying wild type p53 (CHEp53wt) or an inactivating mutation (CHEp53-/-), which abrogates the p53-dependent G1 checkpoint, where AURKB overexpressing stable clones were isolated and injected in nude mice, revealing that untransfected CHE cells induce tumors when injected in nude mice, but they do not metastasize [123]. Additionally, recent findings highlight RASSF7, a

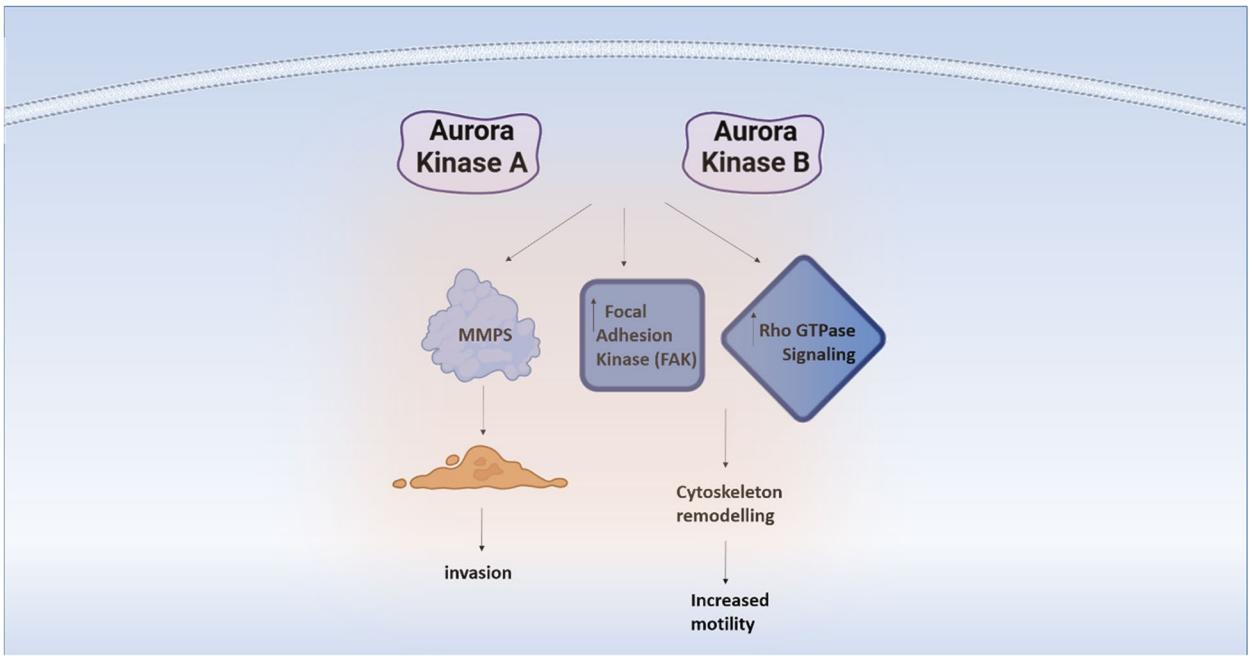


Fig. 4 The role of Aurora Kinase A and Aurora Kinase B in cancer cell invasion and motility. Both kinases contribute to tumor progression through different pathways. Aurora Kinase A enhances the activity of matrix metalloproteinases (MMPs), which leads to extracellular matrix (ECM) degradation, a critical step in cancer cell invasion. Meanwhile, both Aurora Kinase A and B upregulate focal adhesion kinase (FAK), which promotes cell adhesion dynamics, and Rho GTPase signaling, which is involved in cytoskeletal remodeling. The activation of Rho GTPase signaling results in increased cell motility, further facilitating invasion. Together, these pathways contribute to cancer metastasis by enabling tumor cells to degrade surrounding tissue and migrate to new locations

member of the N-terminal Ras association domain family, as a regulator of Aurora B activity, exerting its oncogenic role [124] Aurora kinases have been shown to bind to RasGAP SH3, which is essential for Ras effector function in cancer cells and disrupting this interaction has shown to induce apoptosis in treated cells [125].

Aurora kinase C

Aurora C, exhibits oncogenic activity by promoting aberrant cell division, resulting in multinucleation and amplification of centrosomes. While primarily expressed in germ cells, it is also overexpressed in various somatic cancers, influencing tumorigenicity. Its overexpression has been identified in colorectal, thyroid and breast cancers, with gene amplification observed in breast cancer cell lines. Compared to non-invasive and prostate cancer cell lines, Aurora C expression is seen significantly elevated in invasive cancer cell lines [126]. Studies suggest that Aurora C promotes tumorigenicity by influencing the PI3K/AKT pathway, which is a critical regulator of cell survival and proliferation. As shown in Fig. 5, Aurora C activates PI3K signaling, leading to AKT phosphorylation and subsequent activation of MDM2, which inhibits p53-mediated apoptosis. This allows cancer cells to bypass cell death mechanisms and continue proliferating uncontrollably. Additionally, Aurora C overexpression correlates with lymph node metastasis in colorectal cancer. Notably, survivin, an inhibitor of apoptosis (IAP) protein, is frequently co-expressed with Aurora C in aggressive tumors, contributing to chemoresistance. This highlights a potential therapeutic target for cancer treatment. The interplay between Aurora C, p53, and apoptotic regulators such as BAX, PUMA, and NOXA, as depicted in Fig. 5, further underscores the kinase's role in tumor survival and progression.

Role of Aurora Kinase's inhibitors in cancer

Aurora kinase inhibitors are a class of targeted cancer therapies designed to block the activity of Aurora kinases (AURKA, AURKB, and AURKC), which play essential roles in mitotic progression, chromosomal segregation, and cytokinesis. The mechanism of Aurora kinase inhibitors (AKIs) involves ATP-competitive binding to the kinase domain, thereby preventing phosphorylation of downstream substrates required for mitotic spindle assembly and chromosome alignment. Several inhibitors associated with AURK are listed in Table 1.

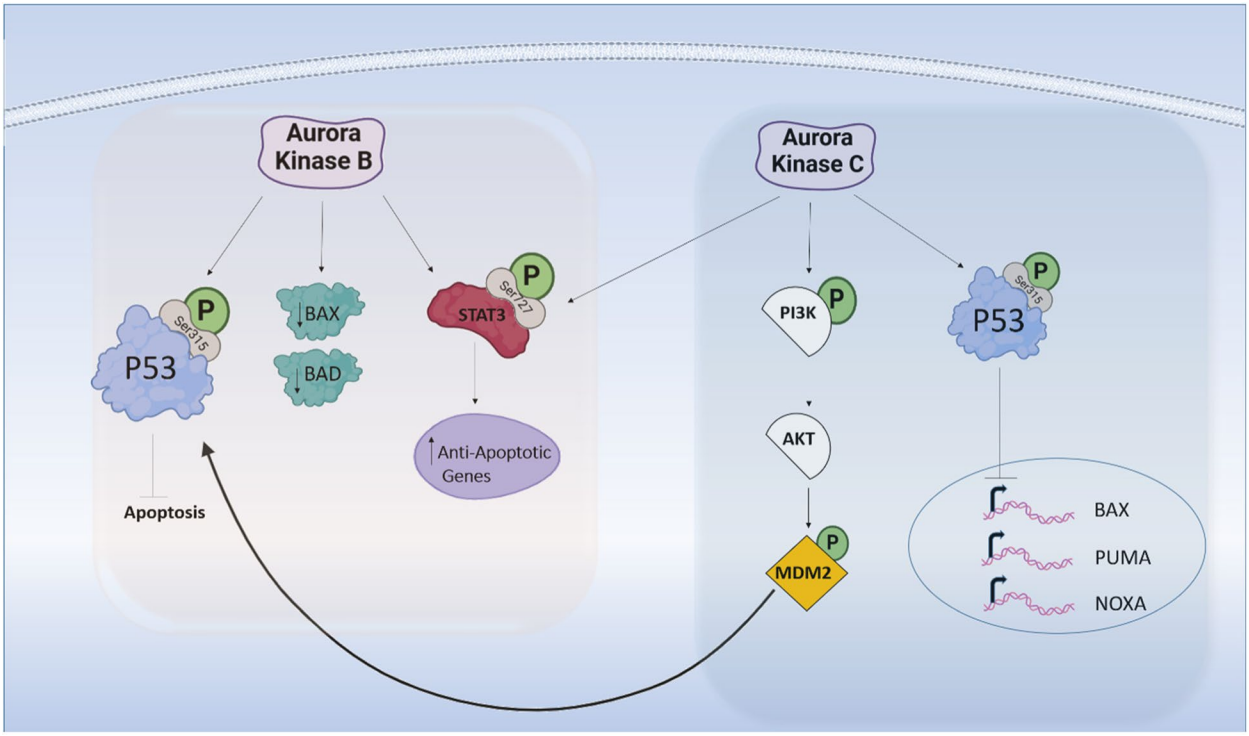


Fig. 5 The roles of Aurora Kinase B and Aurora Kinase C in regulating apoptosis and cell survival through different molecular pathways. Aurora B can induce apoptosis by phosphorylating p53 at Ser315, activating pro-apoptotic proteins like BAX and BAD. However, it also promotes survival by activating STAT3 (Ser727), which drives the expression of anti-apoptotic genes. Aurora Kinase C, on the other hand, promotes cell survival through the PI3K/Akt pathway. It phosphorylates PI3K, leading to the activation of Akt, which in turn phosphorylates MDM2, a negative regulator of p53. Phosphorylated MDM2 promotes p53 degradation, thereby reducing apoptosis. Active p53, transcribes pro-apoptotic genes such as BAX, PUMA, and NOXA, further influencing the balance between cell survival and death. Overall, Aurora Kinases B and C exhibit dual roles in cancer progression by modulating apoptotic and survival pathways, making them significant targets for therapeutic interventions

Inhibitors of Aurora kinase A

MLN8237 (Alisertib)

Alisertib acts as a selective inhibitor of AURKA, demonstrating moderate activity against AURKB. It has been reported to induce aberrant G2/M cell cycle arrest, apoptosis, and mitotic spindle abnormalities in esophageal and gastric cancer cells in preclinical studies [127, 128]. Moreover, it is a second-generation derivative of MLN8054, which serves as an ATP-competitive AURKA inhibitor in chronic myeloid leukemia (CML), where the compound binds to and suppresses AURKA phosphorylation at T288 [129]. Despite its enhanced potential and selectiveness in solid tumors as well as hematological malignancies, Alisertib is known to carry a high risk of toxicity in gastrointestinal malignancies [130]. Notably, Alisertib advanced to a Phase III clinical trial in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) (NCT01482962). Although some clinical benefit was observed, the trial failed to meet its primary endpoint of progression-free survival and was associated with hematologic toxicities such as neutropenia and anemia. Consequently, the further development of Alisertib in this indication was discontinued [131].

MLN8054

MLN8054, discovered in early 2000s by Millennium Pharmaceuticals, is a selective inhibitor of recombinant AURKA, exhibiting high specificity with an IC50 of 4 nM and demonstrating efficacy in cancer models [132, 133]. It forms a benzazepine core scaffold with a fused amino pyrimidine ring and an aryl carboxylic acid which disrupts spindle assembly and mitotic progression by specifically targeting the ATP-binding pocket of AURKA [134]. Despite its specificity, dose-limiting toxicity, including somnolence, was observed with MLN8054 administration, limiting it to preclinical trials only.

AT9283

A broad spectrum kinase inhibitors known for its inhibitory activity against multiple kinases and functions as a dual inhibitor targeting both AURKA and AURKB along with inhibiting JAK2 [135]. Though it is associated with a multi target profile, its lack of specificity can lead to

Table 1 Comprehensive list of Aurora Kinases Inhibitors

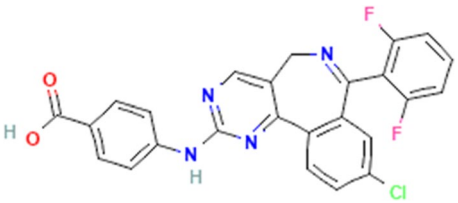
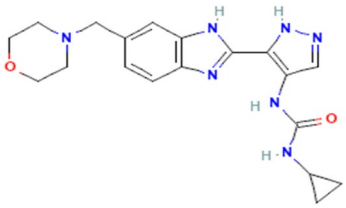
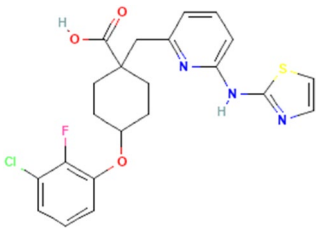
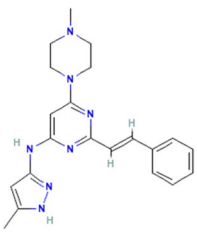
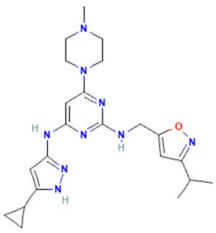
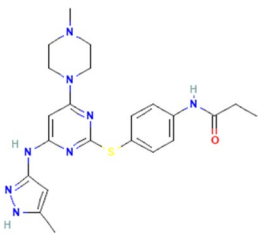
S. No	Inhibitor Name	Structure	Mode of Action	Reference
Inhibitors of Aurora Kinase A				
1	MLN8054		Disrupts spindle assembly, causes mitotic arrest and apoptosis	PubChem CID: 11712649
2	AT9283		Leads to defective mitosis and apoptosis	PubChem CID: 135398495
3	MK-5108		Induces spindle defects and mitotic arrest	PubChem CID: 24748204
4	ENMD-2076		Has anti-angiogenic and anti-proliferative effects and disrupts mitosis	PubChem CID: 16041424
5	XL228		Disrupts mitosis and other signalling pathways for cancer survival	PubChem CID: 59757974
6	VE-465		Induces mitotic catastrophe and apoptosis	PubChem CID: 10343860

Table 1 (continued)

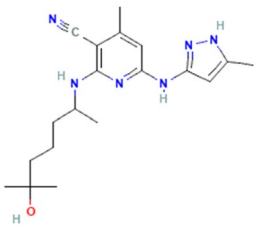
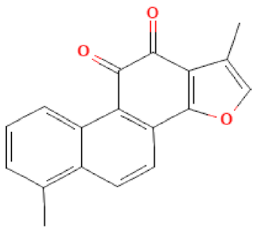
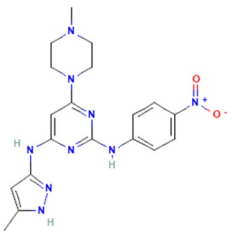
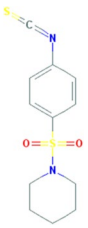
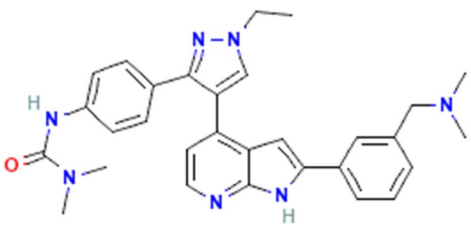
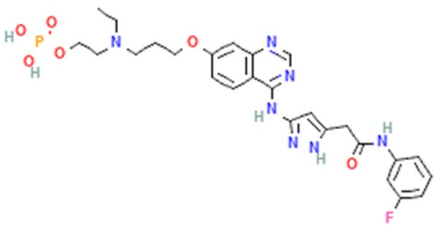
S. No	Inhibitor Name	Structure	Mode of Action	Reference
7	TC-A2317		Causes defective cytokinesis and leads to apoptosis	PubChem CID: 46911725
8	Tanshinone		Induces mitotic catastrophe and apoptosis	PubChem CID: 114917
9	AKI603		Disrupts spindle formation and induces mitotic arrest	PubChem CID: 72194397
10	R1498		Leads to defective mitosis and apoptosis	PubChem CID: 225231697
Inhibitors of Aurora Kinase B				
1	GSK1070916		Leads to failed cytokinesis, polyploidy, and causes cancer cell death	PubChem CID: 46885626
2	Berasertib/ AZD2811/ AZD1152 AZD1152-HQPA		Interferes with chromosome segregation and cytokinesis and induces cell death	PubChem CID: 11497983

Table 1 (continued)

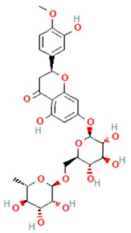
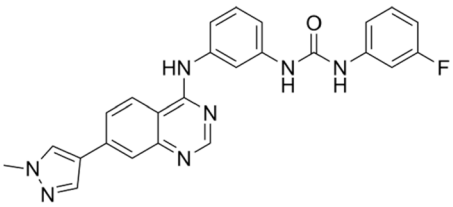
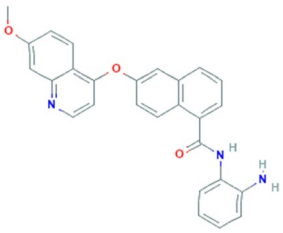
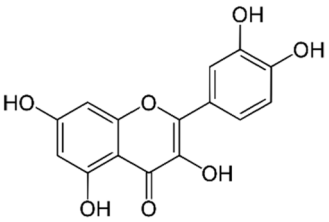
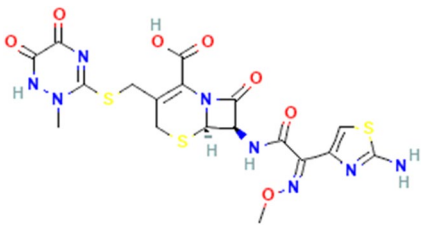
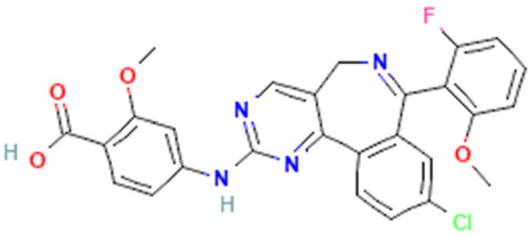
S. No	Inhibitor Name	Structure	Mode of Action	Reference
3	Hesperidin		Induces G2/M cell cycle arrest	PubChem CID: 10621
4	SP-96		Impairing mitotic progression and promotes apoptosis	PubChem
5	CS2164/Chiauranib		Inhibits AURKB and angiogenic pathways causing anti-tumor effects	PubChem CID: 49779393
6	Quercertin		Inhibits AURKB and disrupts mitosis and causes cell death	PubChem CID: 5280343
7	Ceftriaxone		Induces mitotic defects and apoptosis in cancer cells	PubChem CID: 5479530
Inhibitors of Aurora Kinase A and B				
1	MLN8237 / Alisertib		Disrupts spindle formation and induces mitotic arrest	PubChem CID: 24771867

Table 1 (continued)

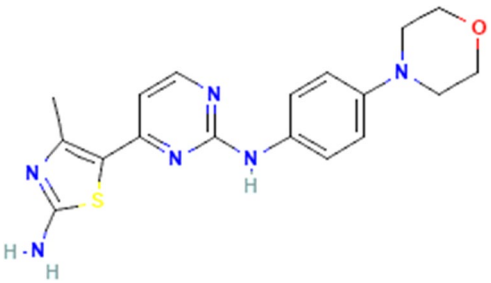
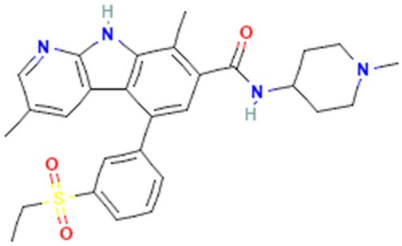
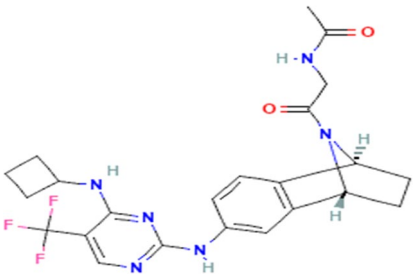
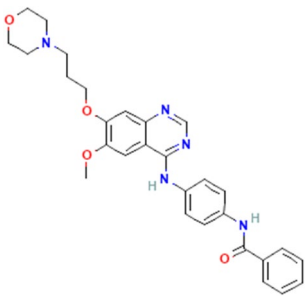
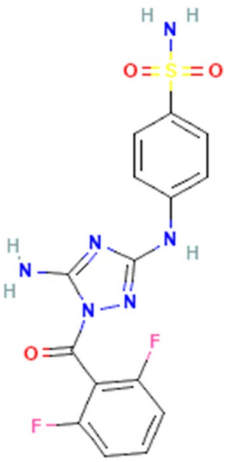
S. No	Inhibitor Name	Structure	Mode of Action	Reference
2	CYC116		Impairs mitotic progression and leads to apoptosis	PubChem CID: 6420138
3	TAK-901		Prevents proper chromosome segregation and mitosis	PubChem CID: 16124208
4	PF-03814735		Causes mitotic defects and apoptosis	PubChem CID: 51346455
5	ZM447439		Disrupts cytokinesis and induces mitotic catastrophe	PubChem CID: 9914412
6	JNJ-7706621		Interferes with mitotic processes and cell cycle progression	PubChem CID: 5330790

Table 1 (continued)

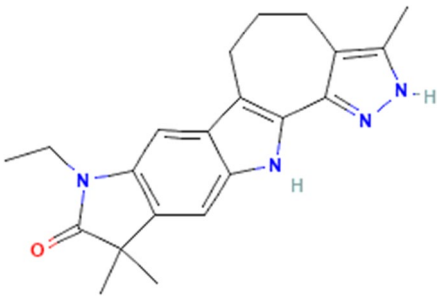
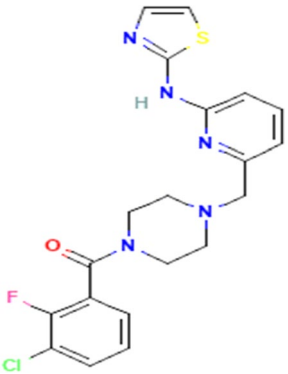
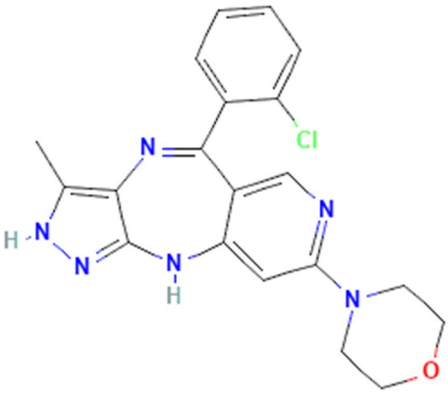
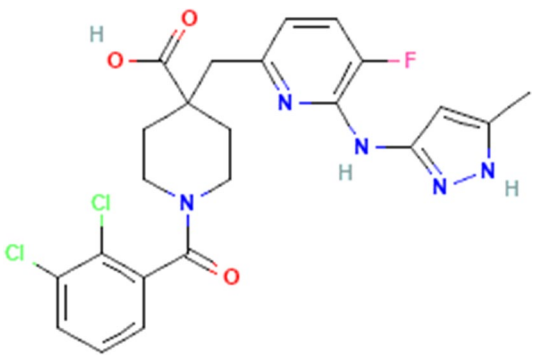
S. No	Inhibitor Name	Structure	Mode of Action	Reference
7	AKI-001		Potent AURK inhibitor disrupts spindle assembly and mitotic progression	PubChem CID: 135564980
8	MK-8745		Disrupts spindle formation and causes cell death	PubChem CID: 11676373
9	TT00420		Targets additional oncogenic pathways in addition to mitosis	PubChem CID: 137279257
10	TAS-119		Dual aurora kinase inhibitor induces mitotic defects and causes cancer cell death	PubChem CID: 71696703

Table 1 (continued)

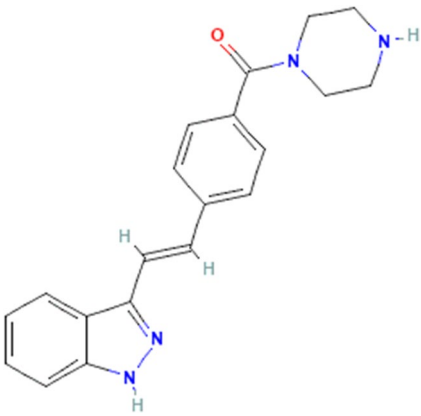
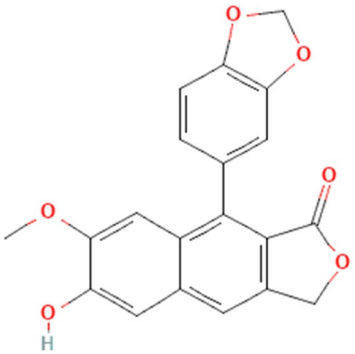
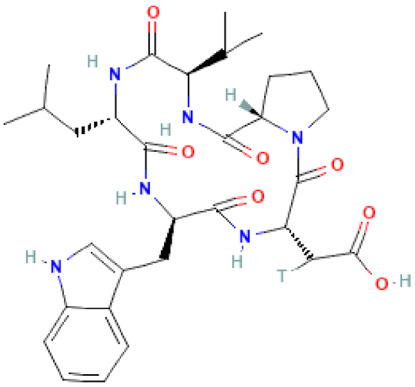
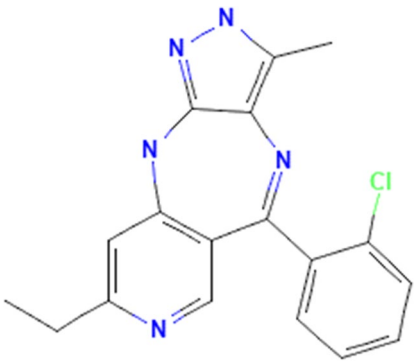
S. No	Inhibitor Name	Structure	Mode of Action	Reference
11	KW-2449		Multi-target inhibitor, disrupts mitosis and targets additional oncogenic pathways	PubChem CID: 11427553
12	Daurinol		Selective AURKB inhibitor, disrupts cytokinesis and leads to apoptosis	PubChem CID: 14704582
13	CYC-3		Interferes with spindle assembly and cytokinesis	PubChem CID: 70686617
14	TY-011		Impairs chromosome segregation and cytokinesis	PubChem CID: 505055848

Table 1 (continued)

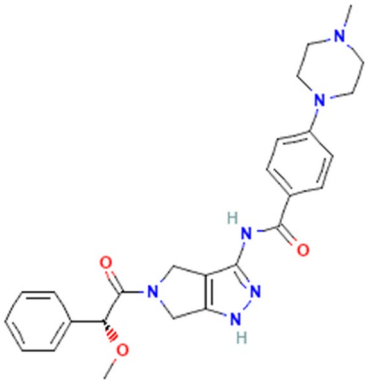
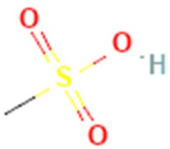
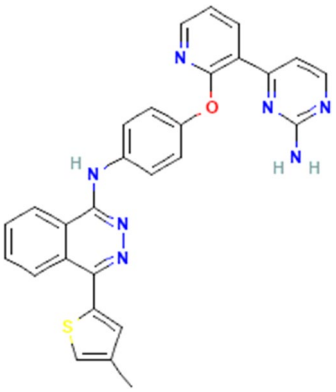
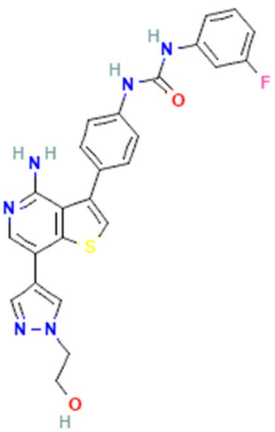
S. No	Inhibitor Name	Structure	Mode of Action	Reference
Inhibitors of Aurora Kinase A, B and C				
1	Danusertib/ PHA739358		Broad-spectrum AURK inhibitor particularly effective against cells with aberrant BCR-ABL	PubChem CID: 11442891
2	SNS-314/ Mesylate		Causes mitotic checkpoint failure, leading to apoptosis. Shows broad anticancer efficacy	PubChem CID: 6395
3	AMG-900		Disrupts spindle dynamics and chromosome segregation	PubChem CID: 24856041
4	ABT-348/Ilora-sertib		Multi-kinase inhibitor; targets mitosis through Aurora kinases and disrupts angiogenesis via VEGFR/FGFR inhibition	PubChem CID: 46207586

Table 1 (continued)

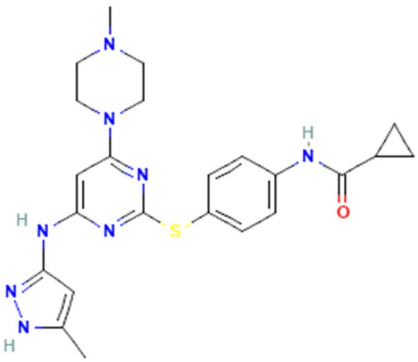
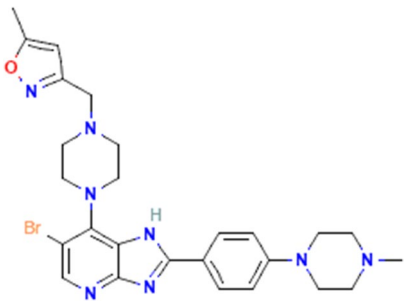
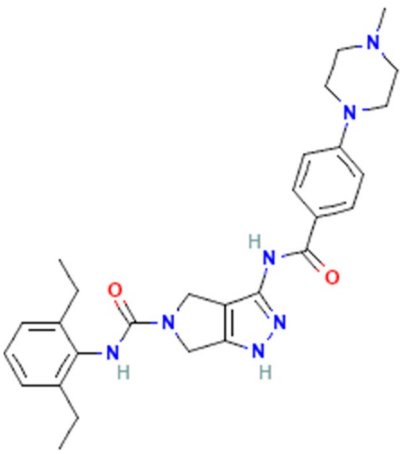
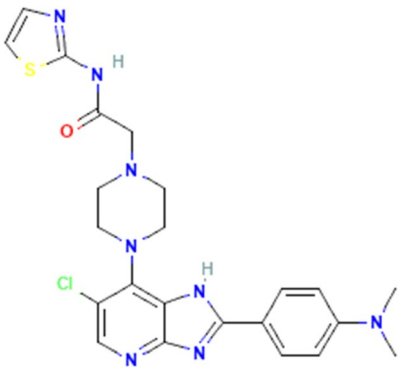
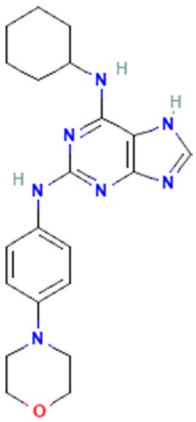
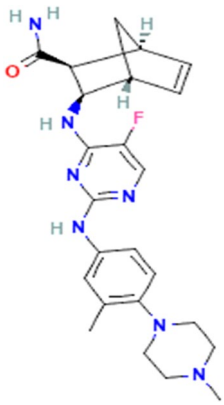
S. No	Inhibitor Name	Structure	Mode of Action	Reference
5	VX-680/ MK-0457/ Tozasertib		Causes polyploidy, mitotic catastrophe, and apoptosis. Effective against BCR-ABL-positive leukemias, including T315I mutation	PubChem CID: 5494449
6	CCT137690		Disrupts centrosome maturation and spindle checkpoint. Promotes mitotic catastrophe and apoptosis in tumor cells	PubChem CID: 25154041
7	PHA-680632		Induces mitotic spindle defects and G2/M phase arrest, leads to mitotic slippage, polyploidy, and apoptosis in cancer cells	PubChem CID: 11249084
8	CCT129202		Blocks chromosome alignment, spindle formation, and cytokinesis	PubChem CID: 16202152

Table 1 (continued)

S. No	Inhibitor Name	Structure	Mode of Action	Reference
9	Reversine		Leads to aneuploidy and apoptotic cell death, shows potential in inducing differentiation in certain cancer models	PubChem CID: 210332
10	Cenisertib		Causes mitotic arrest, polyploidy, and apoptosis, shows activity in various solid tumors and hematological malignancies	PubChem CID: 11569967

increased off-target effects and can cause toxicity due to JAK2 inhibition [136].

MK-5108

Also referred to as VX-689, is a highly selective ATP-competitive inhibitor targeting AURKA with an IC50 value of 0.046 nM, which works by disrupting spindle assembly and chromosomal segregation [137, 138]. Upon inhibiting AURKA using MK-5108, regulated polyploidy and cell cycle arrest was observed. Additionally, in the case of ovarian cancer stem cells, suppression in NF-kB activity and decreased cytokine production was observed [139]. However, failure in efficiency in monotherapy due to compensatory pathways in cancer cells is seen as a disadvantage.

ENMD-2076

It has been identified as a selective Aurora A kinase inhibitor with half maximal inhibitory concentration (IC_{50}) of 14 nM, exerting its inhibitory effect by inducing G2/M phase cell cycle arrest and apoptosis [140]. Interestingly, a six-hour exposure to ENMD-2076 is sufficient to trigger apoptosis and reduce AURKA autophosphorylation at Thr288. The compound has demonstrated selective cytotoxicity in multiple myeloma (MM) cells while exhibiting minimal toxicity toward hematopoietic progenitor cells. In-vitro studies further indicate that ENMD-2076 treatment results in the inhibition of AKT phosphorylation in multiple myeloma cells. However, its multi-target nature raises concerns regarding off-target toxicity and potential drug resistance [141].

XL228

XL228 is a selective AKI with activity against wild-type Aurora-A kinase with an IC50 value of 3.1 nM and works as a multi-kinase inhibitor by blocking mitotic progression and survival signaling pathways [142]. It holds a potential to overcome resistance to single target therapies and serves a broad spectrum of activity in diverse tumor types. Despite the advantages XL228 has, it has drawbacks associated with it, such as dose-limiting toxicity due to inhibition of multiple kinases [143].

VE-465

VE-465 is a pan AURK inhibitor, targeting AURKA, AURKB, AURKC. Preclinical studies have demonstrated its anticancer effects on hepatocellular carcinoma cell lines such as Huh-7 and HepG2 by suppressing AURKB activity in a dose-dependent manner [52]. It specifically inhibits AURKA-dependent functions, such as centrosome maturation, prometaphase cell formation, and spindle bipolarization in hepatocellular carcinoma cells [144]. However, there is a narrow therapeutic window associated with the administration of VE-465 due to the high likelihood of dose-limiting toxicity [145].

Other Aurora Kinase inhibitors include TC-A2317, SLAN, Tanshinone, BPRIK060951, AKI603 and R1498, which either work in ATP competitive manner or by inhibiting AURKA-mediated spindle assembly, but possess off-target or resistance risks and require further validation due to limited clinical data [52].

Inhibitors of Aurora kinase B

GSK1070916

Discovered in mid-2000s, a reversible Aurora B inhibitor which inhibits histone H3 phosphorylation at serine 10, disrupting chromosomal alignment and cytokinesis [146]. This inhibitor has demonstrated efficacy in treating multiple cancers, including lung, breast, and colon cancers, by selectively targeting AURKB and AURKC with minimal off-target effects [147]. Despite its selectivity, GSK1070916 is often combined with other therapeutic agents to enhance its efficacy against high-proliferation cancers [148].

Barasertib

Also known as AZD2811, AZD1152, and AZD1152-HQPA, this is an ATP-competitive Aurora B inhibitor demonstrating significant potential for cancer therapy. It suppresses Aurora B and C kinases with IC50 values of 3.5 nM and 6.5 nM, respectively [149]. Barasertib exhibits a 100-fold higher selectivity for AURKB compared to AURKA, particularly in hematopoietic malignant cells [150]. Barasertib is a prodrug that is converted to the active form, AZD2811, causing mitotic arrest and apoptosis, which inhibit tumor growth in breast cancer, small cell lung cancer, and colon cancer at doses of 10 to 150 mg/kg/day in preclinical models [151–153]. Despite its promising preclinical results, Barasertib's development did not advance further following a Phase III clinical trial in acute myeloid leukemia (AML) (ClinicalTrials.gov ID: NCT03217838). The trial did not meet its primary endpoint of improved overall survival and was associated with hematologic toxicities, such as neutropenia and febrile neutropenia, which ultimately led to the discontinuation of its clinical development [154].

Hesperidin

Identified as a natural compound in the 2000s, hesperidin is a small molecule that inhibits chromosomal alignment and segregation through AURKA and AURKB inhibition, and is used to treat cancer cell lines with AURKB phenotype [155]. It is an effective flavonoid that works by interacting with the ATP-binding site and reducing phosphorylation of histone H3, thereby altering chromosome condensation and cell cycle progression in cancer cells [156]. Although it has low toxicity profiles, there is low potency and poor bioavailability associated with hesperidin as compared to synthetic AURKB inhibitors [157].

SP-96

Discovered in late 2000s, SP-96 is a synthetic inhibitor of AURKB which phosphorylates AURKB substrates and disrupts SAC signaling [158]. SP-96 is a highly specific inhibitor perfect for targeting mitotic cancers, however, more data and investigation are still required for testing its efficacy and combating its safety concerns [159].

CS2164

CS2164, also known as Chiauranib, discovered in the 2010s, is a promising ATP-competitive Aurora B inhibitor with an IC50 value of 9 nM [160]. A multi-target kinase inhibitor that offers broad-spectrum simultaneous blocking of tumor angiogenesis as well as mitosis, also suitable for AURKB, VEGFR, FGFR and CSF1R inhibition. Nevertheless, the multi-target ability of Chiauranib leads to high chances of off-target toxicity resulting in treatment challenges [161, 162].

Quercertin

Quercertin is a natural flavonoid which binds to AURKB's kinase domain by competing with ATPs thereby inhibiting it [163]. The disruption in chromosome condensation and the mitotic progression is due to the reduction of histone H3 phosphorylation at serine 10 by Quercetin [164]. Being a natural compound, Quercetin has antioxidant and anti-cancer properties and is associated with low toxicity which is beneficial for its use in combination therapies. However, it is less efficient compared to synthetic inhibitors and requires high doses for introducing any effect [165].

Ceftriaxone

A third-generation cephalosporin antibiotic that was developed in the 1980s, has been identified as a potential AURKB inhibitor in recent years, which works by interfering with AURKB kinase activity [166]. The mechanism of AURKB inhibition is still being investigated, but it may entail structural interactions that obstruct substrate phosphorylation. Further clinical studies are required to

minimize safety concerns and maximize specificity and efficacy of Ceftriaxone [167].

HOI-07

A small-molecule synthetic inhibitor of AURKB, working by inducing apoptosis in cancer cells by inhibiting the ATP-binding site of AURKB [168]. The performance of it is precise and potential making it effective even in small tumors, thereby lowering the chances of off-target effects, but it is limited to preclinical settings only, as it develops resistance over time [169].

Inhibitors of Aurora kinase A and B

CYC116

It is a potent inhibitor of AKI, demonstrating suppression of AURKA and AURKB with inhibition constants of 8.0 nM and 9.2 nM, respectively [170]. CYC116 underwent initial screening utilizing solid tumor cell lines and a cohort of leukemia, employing the MTT assay for cytotoxicity evaluation. Administration of CYC116 results in the inhibition of Aurora protein autophosphorylation, a reduction in polyploidy and phosphohistone H3 (pHH3), which subsequently leads to cytokinesis failure and ultimately results in apoptosis [171]. However, clinical trials of CYC116 discontinued in phase 1 trial due to limited availability of clinical data [172, 173].

TAK-901

An Aurora kinase inhibitor that suppresses AURKA and AURKB with IC50: 21 nM and 15 nM, respectively [174]. In-vitro studies have demonstrated that TAK-901 inhibits AURKA/TPX2 and AURKB-INCENP interaction in a time-dependent manner [52]. It has been shown to suppress cancer cells growth across multiple human cancer tissues (IC50: 40-500 nM) as studied by Murai et al., 2017 [175]. Even though TAK-901 has successfully completed phase 1 level of clinical trials more relevant clinical data for safety and efficacy is still required.

PF-03814735

It is a selective and reversible AKI that targets the action of both AURKA and AURKB with IC50 values of 0.8 nM and 5 nM, respectively [176]. It hinders cytokinesis, leading to polyploidy, forming cells with one or more nuclei and impaired cell proliferation [177]. In-vitro studies demonstrated that this compound reduces the phosphorylation of Thr288 and Thr232 on AURKA and AURKB, respectively, serving as a biomarker for AURK inhibition. Despite showing effectiveness in SCLC and colon cancer cell lines, its further clinical development is halted due to low efficacy and high toxicity risks [178].

ZM447439

It is a pan-AURK inhibitor that disrupts cytokinesis, causing cells to enter mitosis and witness compromised spindle checkpoint leading to polyploidy [179]. By inhibiting Aurora kinases, ZM447439 activate caspase 3 and 7, induces DNA fragmentation, and ultimately triggers apoptotic cell death [180]. Nevertheless, this compund has high risks of off-target effects and is associated with poor specificity.

JNJ-7706621

This compound serves as a powerful inhibitor of the cell cycle, demonstrating the ability to inhibit multiple cyclin-dependent kinases (CDKs) and aurora kinases. The application of JNJ-7706621 on human cancer cells resulted in the activation of apoptosis and a decrease in colony formation, independent of p53, retinoblastoma, or P-glycoprotein status [181]. The compound demonstrates a targeted inhibition of tumor cell proliferation, specifically in cell lines such as HCT116, HeLa, PC3, DU145, and MDA-MB-231 [182]. In contrast, JNJ-7706621 exhibits a significantly reduced efficacy, being ten times less effective in suppressing the growth of aortic smooth muscle cells (HASMC) and umbilical vein endothelial cells (HUVEC) in vitro [181]. Additionally, its mechanism of action is linked to toxicity arising from the concurrent inhibition of both kinases.

AKI-001

Is derived from a pentacyclin scaffold and is hence, termed as a prototype pentacyclic inhibitor [183]. A novel dual inhibitor targeting ATP-binding domains of both AURKA and AURKB, inducing mitotic arrest and apoptosis in cancer cells thereby offering promising preclinical efficacy with high potency [58]. Nevertheless, AKI-001 is still in the early development phase and requires extensive validation in clinical trials.

MK-8745

It is a more efficient and selective inhibitor of AURKA with moderate effects on AURKB and was discovered in the early 2010s by Merck [52]. MK-8745 performs its inhibitory effects by inducing p53-dependent apoptosis in AURKA overexpressing cancer cells, which also serves as its limitation, as it is dependent on p53 activity only and becomes less efficient in p53-mutated cancers [184].

Except for the ones mentioned above, there are other inhibitors of both AURKA and AURKB as well, such as TT00420, TAS-119, KW-2449, Daurinol, CYC-3, and TY-011, which possess the same mode of action for inhibiting both AURKA and AURKB. These dual inhibitors compete with ATP for ATP-binding sites of AURKA

and AURKB or block phosphorylation of histone H3 (AURKB) and spindle-associated proteins (AURKA), hence disrupting mitotic progression either by inhibiting spindle assembly and cytokinesis or by inducing apoptosis [185–190]. Nevertheless, their usage requires more clinically relevant data to minimize their associated toxicity concerns and off-target effects.

Inhibitors of Aurora kinase A, B and C

PHA739358

Also known as Danusertib, discovered in mid-2000s, is a broad-spectrum AKI, highlighting inhibitory effects against AURKA, -B, and -C with IC50 values of 13 nM, 79 nM, and 61 nM, respectively. It induces mitotic arrest at the 4N polyploidy stage, maintaining it up to 48 h [191]. Additionally, the compound enhances p53 expression and increases p21 protein levels under transcriptional regulation by p53, thereby inducing apoptosis [192]. Studies have shown that increasing the concentration of danusertib results in dose-dependent reduction of cell proliferation after 48 h in BCR-ABL-negative (K562, BV173) and BCR-ABL-positive [193]. Although Danusertib is synergistically potential when incorporated with other therapies, but has moderate efficacy when used as a monotherapy and also employs toxic effects, especially in hematological malignancies [194].

SNS-314

Commonly referred to as Mesylate, this compound acts as a nonselective AKI, inhibiting AurA kinase, AurB kinase and AurC Kinase with IC50 values of 9 nM, 31 nM, and 3 nM, respectively [195]. In vitro investigations involving HCT-116 cell lines demonstrated that the drug promotes spindle checkpoint assembly and increases their effectiveness when administered alongside other chemotherapeutic agents. In conjunction with docetaxel, it primarily diminishes tumor growth by as much as 72.5% within 24 h, exhibiting a dose-dependent effect in the HCT-116 xenograft model [193, 196]. However, its efficacy as a monotherapy is limited, and is associated with off-target effects and toxicity concerns.

AMG-900

It is a highly potent, orally bioavailable inhibitor selectively targeting AURKA, AURKB, and AURKC, with IC50 values of 5 nM, 4 nM, and 1 nM, respectively. The compound primarily inhibits AURKB by competing with ATP at its binding site, leading to polyploidy in cancer cells while upregulating p53 and p21^kip1^. This has demonstrated effectiveness in preclinical studies and multidrug-resistant cancers [197, 198]. It maintains consistent efficacy across multiple cell lines, including BCRP-expressing and multidrug-resistant (MDR) P-gp cell lines, as well as an AZD1152-resistant HCT116 variant with a missense mutation in one Aurora gene allele (W221L) [199]. However, toxicity was observed in gastrointestinal and hematological malignancies along with its limited efficiency in solid tumors [200].

ABT-348

Currently, four clinical trials have been conducted to evaluate its pharmacodynamic and pharmacokinetic properties in advanced solid tumors, though its multikinase inhibition is associated with high off-target effects [201]. ABT-348, also known as Ilorasertib, is a pan-AKI that competes with ATP and potently inhibits Aurora A, B, and C, with IC50 values of 120 nM, 7 nM, and 1 nM, respectively [202]. Preclinical research has revealed that Ilorasertib suppresses histone H3 phosphorylation and has been tested in various in vitro models, including solid tumors, leukemia, and lymphoma. Additionally, in vivo studies have confirmed its efficacy in murine xenografts of MV-4–11 acute myeloid leukemia, showing considerable tumor volume reduction [203].

VX-680 (MK-0457)

Also known as Tozasertib, MK-0457 functions as a broad-spectrum Aurora inhibitor classified as an ATP-competitive 4,6-diaminopyrimidine derivative. The compound exhibits a selectivity ratio exceeding 200 in favor of Aurora A compared to Aurora B, with IC50 values recorded at 0.6 nM for Aur A, 18 nM for Aur B, and 4.6 nM for Aur C [204]. Research conducted in vitro has shown its sensitivity in leukemia, lymphoma, and colorectal cancer cells, with cellular mortality linked to apoptosis induction [160]. With AURKA inhibition it disrupts centrosome maturation and spindle pole formation, with AURKB inhibition CPC function gets impaired and with AURKC inhibition cytokinesis failure is seen. Nevertheless, its development has been discontinued, highlighting the potential toxic effects, short half-life and poor pharmacokinetics [205].

CCT137690

This inhibitor, derived from the imidazopyridine scaffold and optimized through structure–activity relationship (SAR) studies, has shown promising results by inhibiting AURK-mediated phosphorylation events, leading to mitotic arrest. However, clinical trials have revealed significant toxicity concerns [206]. To date, five key clinical trials have been conducted, targeting malignancies such as advanced solid tumors, leukemia, non-small cell lung carcinoma, chronic myelogenous leukemia, and Philadelphia chromosome-positive acute lymphoblastic leukemia [207]. While the trials demonstrated favorable efficacy,

the high toxicity levels led to the discontinuation of further clinical testing [208].

PHA-680632

This compound was developed through SAR-based modifications of various pyrrolopyrazole core subclasses of ATP-mimetic pharmacophores. It selectively induces polyploidy in HCT116 cancer cells while leaving normal human dermal fibroblasts unaffected [209]. Furthermore, Aurora A kinase silencing through siRNA in tumor cells results in the accumulation of active 9 and 3 caspases, facilitating apoptosis [210]. PHA-680632 has been found to inhibit phosphorylation of histone H3 without any signs of toxicity in the A2780 mouse xenograft model. Even though it is known to possess broad anti-cancer potential and good preclinical activity, there is still limited clinical data available, and it requires combination with other therapies for more efficient results [211].

CCT129202

An imidazopyridine derivative and a Pan-Aurora kinases ATP-competitive inhibitor more efficient for Aurora B, exhibits IC50 values of 42 nM, 198 nM, and 227 nM for Aurora kinase A, Aurora kinase B, and Aurora kinase C, respectively [212]. The compound has been observed to activate p21, a cyclin-dependent kinase inhibitor, which plays a key role in tumor suppression by disrupting centrosome function, kinetochore dynamics, also triggering premature mitotic exit leading to apoptosis [213]. It aids the tumor suppressing effects of chemotherapeutic agents, but is in the early development phase and requires further validation in clinical trials [176].

Reversine

A purine derivative that acts as an ATP-competitive Aurora B inhibitor, Reversine features a morpholine group that facilitates its interaction with the solvent-exposed region of the Aurora B ATP-binding site [214]. By blocking Aurora B, Reversine disrupts kinetochore-microtubule interactions leading to mis-segregated chromosomes. Preclinical studies have highlighted its anti-tumor effects in breast cancer models, including BRCA-positive and triple-negative breast cancer (TNBC) cell lines [215]. Additionally, it has the unique ability to induce differentiation in cancer stem cells while promoting apoptosis in undifferentiated cells [216]. However, no clinical trials have been initiated, and there are currently no identified malignant targets of clinical interest. Although Reversine presents an interesting potential as an Aur B kinase inhibitor, it appears to be appropriate for Aurora A target [217]. Other lesser-known inhibitors of AURKA, AURKB, and AURKC are Cenisertib and SARI56497, and have the same mechanism of action, which involves targeting the ATP-binding sites of AURKA/B/C and competing with ATPs to bind to them thereby selectively inhibiting their overexpression. Despite their offered advantages in terms of effectiveness and selectiveness, there are several challenges associated, namely increased chances of toxicity and limited clinical data or trial success [170].

Aurora kinases: therapy targets

Combination therapy is a treatment method that uses multiple therapeutic agents to enhance effectiveness and reduce drug resistance. It targets key biological pathways, reducing tumor growth, metastatic potential, and inhibiting rapidly dividing cells [218]. However, 5-year survival rates for metastatic cancers remain low, and developing new anti-cancer drugs is costly and time-consuming. Researchers are exploring strategies focusing on survival pathways, including repurposing therapeutic agents designed for other diseases [219]. FDA-approved agents targeting similar pathways to those involved in cancer can lower overall costs associated with combination therapy research [220]. Early results suggest this approach may also effectively reduce tumor burden. This systematic review examines key pathways commonly targeted in cancer therapy and emphasizes repurposed or primary anti-cancer agents.

Synergy between AKIs and chemotherapy or radiotherapy

In preclinical and clinical research, AURKA inhibitors have shown tremendous potential in improving the effectiveness of several already approved medicinal medicines. The combination of AURKA inhibitors with docetaxel results in improved therapeutic outcomes compared to docetaxel monotherapy in mantle cell lymphoma and upper gastrointestinal adenocarcinomas [221]. Under a 21-day cycle, a phase I clinical trial found that a dosage of 20 mg of alisertib given twice daily from day 1 to 7, together with intravenous docetaxel at 75 mg/m2 on day 1, was effectively tolerated. Moreover, this combination treatment showed antitumor effect over several cancer types [222]. In an orthotopic xenograft model of EOC, combination therapy with alisertib and paclitaxel demonstrated stronger inhibition of tumour growth and dissemination compared to single targeted treatment [223]. In tumour cell lines and xenografts resistant to paclitaxel, AMG900 shows strong inhibitory efficiency [224]. Furthermore under consideration for combination therapy with AKIs is gemcitabine [225]. Alisertib enhances the efficiency of cytarabine in a FOXO-dependent fashion in AML [226]. In patients with AML, further two clinical trials have shown that alisertib combined induction chemotherapy with cytarabine and idarubicin is safe and effective [227]. In aggressive B cell NHL, MLN8237 acts

in concert with vincristine and rituximab [228]. A combination of 50 mg of alisertib b.i.d. plus 40 mg of rituximab or alisertib b.i.d. plus rituximab and vincristine is well tolerated and exhibits activity against non-germinal centre B-cell DLBC [229]. AURKA inhibitors also show synergistic effects when used in combination with radiotherapy [230]. Particularly in p53-deficient in vitro or in vivo cells, PHA680632 therapy before radiation treatment produces an additional effect in cancer cells [210]. Other AURKA inhibitors, MLN8237 and ENMD-2076, enhance radiation sensitivity in cancer cells [221]. The safety and well-tolerance of 40 mg of alisertib twice daily in combination with irradiation were demonstrated in a phase I trial of alisertib with fractionated stereotactic reirradiation therapy for patients with recurrent high-grade glioma.

Aurora kinase B (AURKB) inhibitors are emerging as promising drugs in oncological treatment due to their ability to interrupt mitosis and increase tumor cell susceptibility. AURKB inhibitors can demonstrate synergistic effects when used in conjunction with chemotherapy or radiotherapy by targeting mitotic pathways, hindering DNA repair, and inducing death in cancer cells [110]. For example, AURKB inhibitors, like barasertib, interfere with chromosomal alignment and segregation in mitosis [231]. This intensifies DNA damage induced by agents such as taxanes (e.g., paclitaxel) or DNA-damaging pharmaceuticals (e.g., cisplatin), resulting in mitotic catastrophe [232–234]. Inhibition of AURKB hinders cytokinesis and induces polyploidy, hence rendering cells more susceptible to death in conjunction with chemotherapy. AURKB suppression impairs DNA damage repair mechanisms, including homologous recombination and non-homologous end joining (NHEJ), exacerbating radiation-induced DNA damage [235]. Barasertib together with cytarabine is under investigation for hematological malignancies [236]. Initiatives are in progress to evaluate AURKB inhibitors in conjunction with paclitaxel or radiation for malignancies such as breast, ovarian, and non-small cell lung cancer (NSCLC).

Chemotherapy targets rapidly proliferating cells, causing stress through mechanisms such as DNA damage or microtubule destabilization [237]. Inhibition of AURKC can enhance these effects by interfering with mitotic and survival pathways. AURKC inhibitors interfere with chromosomal alignment and segregation in mitosis, exacerbating the effects of microtubule-targeting chemotherapeutics such as paclitaxel or vincristine [238]. Conversely, the suppression of AURKC promotes polyploidy, potentially amplifying the cytotoxic effects of DNA-damaging drugs like cisplatin or doxorubicin [238]. Tumor cells that acquire resistance to chemotherapeutic drugs frequently depend on alternate survival mechanisms. Inhibition of AURKC can hinder these pathways, thereby re-sensitizing cells to chemotherapy. Radiation may induce mitotic stress, and the inhibition of AURKC intensifies this by impairing centrosome clustering and correct spindle assembly [239]. The combination of AURKC inhibition and radiation results in amplified mitotic catastrophe, particularly in tumor cells with defective checkpoints.

Combination of AKIs with targeted therapies

The efficacy of AKIs may be improved by targeting multiple oncogenes simultaneously, as cancer is a multistep disease that involves multiple genes. HDAC (Histone deacetylases) inhibitors have been demonstrated to suppress the expression of AURKA in a variety of cancer cells, and AKIs can reduce the activity of HDAC proteins [240, 241]. Research has demonstrated that the lethality of MK-0457 in leukaemia and breast cancer cells is synergistically enhanced by the HDAC inhibitor vorinostat [242, 243]. The combination treatment of vorinostat and MK-0457 or MK-5108 promotes the destruction of lymphoma cells by reducing the levels of c-Myc, hTERT, and microRNA. The combination of alisertib and the HDAC inhibitor romidepsin is highly synergistic due to the modulation of cytokinesis [244]. EGFR inhibitors have been a significant advancement in the treatment of NSCLC; however, resistance to them has been detected through a variety of mechanisms. AKIs are susceptible to EGFR-mutant LUAD cells that exhibit acquired resistance to third-generation EGFR inhibitors [245]. In an EGFR-mutant LUAD PDX model, the combination of AKIs and EGFR inhibitors has been demonstrated to significantly reduce tumour growth. At the translational and posttranslational levels, both BRD4 and AURKA are regulators of the MYC gene, targeting both at once may result in combined therapeutic effects [246]. Two studies have examined the efficacy of combined treatment involving a p53-activating MDM2 antagonist and senescence-inducing AKIs in the context of melanoma therapy [247, 248]. Additional molecules, including SRC, CHEK1, mTOR, WEE1, PDK1, and MEK, have been selected as targets alongside AURKA in preclinical investigations [249–255].

Combination of AKIs with immunotherapy and non-coding RNAs

Combining Aurora kinase inhibitors (AKIs) with immunotherapy and non-coding RNAs (ncRNAs) has emerged as a promising approach for enhancing cancer treatment [256]. MK-5108 enhances the efficacy of an antiganglioside (GD2) 14G2a antibody in human neuroblastoma cells, resulting in a decrease in N-Myc expression and an increase in PHLDA1 and p53 protein levels [257]. This

combination results in an increased rate of autophagy in IMR-32 neuroblastoma cells. An agonist antibody targeting death receptor 5 triggers significant apoptosis in tumour cells that are experiencing therapy-induced senescence as a result of MLN8237 treatment [110]. Alisertib induces an anticancer immune surroundings with higher numbers of active CD8 + and CD4 + T lymphocytes and fewer myeloid-derived suppressor cells [258, 259]. This suggests that combining Aurora kinase inhibitors (AKIs) like alisertib with immune checkpoint inhibitors, such as anti-PD-1/PD-L1 therapies, could be an effective strategy for cancer treatment [260]. More recently, researchers have been exploring how AKIs can work alongside non-coding RNAs (ncRNAs) to improve cancer therapy [261]. Non-coding RNAs, which include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play key roles in controlling gene activity and can influence cancer cell growth, survival, and spread. For example, in neuroblastoma cells, pairing alisertib with miR-542-3p significantly reduces cancer cell survival and promotes cell death by lowering levels of N-Myc and Bcl-2—two proteins involved in cancer progression. Similarly, in triple-negative breast cancer, the lncRNA MALAT1 enhances the effectiveness of alisertib by influencing the PI3K/AKT signaling pathway, leading to slower cancer growth and increased cell death. These findings highlight the potential of combining AKIs with ncRNAs to make cancer treatments more powerful [262].

Combining Aurora kinase and Tyrosine kinase inhibitors

Recent advancements in cancer therapeutics have highlighted the potential of combining Aurora kinase inhibitors (AKIs) with tyrosine kinase inhibitors (TKIs) to overcome drug resistance, mitigate compensatory oncogenic signaling, and enhance antitumor efficacy [263, 264]. Aurora kinases contribute to mitotic fidelity, chromatin remodeling, DNA repair, and oncogene-driven survival signaling, making them suitable partners in dual-targeted strategies [265]. Combining AKIs with EGFR-TKIs has emerged as a promising approach in managing both intrinsic and acquired resistance in non-small cell lung cancer (NSCLC). This approach disrupts multiple pathways involved in cancer cell growth and survival, enhancing treatment effectiveness and potentially leading to better outcomes and longer remission periods [266]. Research and clinical trials are ongoing to investigate the efficacy and safety of these inhibitors across different types of cancer and stages.

Alisertib, a selective AURKA inhibitor, has shown synergy with osimertinib in EGFR-mutant NSCLC models, where it suppresses c-Myc stabilization and downstream PI3 K/AKT signaling, restoring sensitivity to EGFR inhibition [267]. Notably, a Phase I trial evaluating the combination of VIC- 1911 (an AURKA inhibitor) with osimertinib demonstrated a disease control rate of 80% in osimertinib- naive patients and 53. 8% in those with osimertinib-resistant disease, illustrating the translational potential of this combination in clinical applications [268]. Beyond EGFR, AKIs also exhibit synergy with TKIs targeting other critical oncogenic drivers such as KRAS, BRAF, and FLT3 [7, 269]. In addition, KRAS- mutant NSCLC, dual inhibition of AURKA and EGFR with alisertib and erlotinib induces significant tumor regression and apoptosis, even in EGFR- wild- type backgrounds. The rationale lies in AURKA' s role in promoting mitotic survival and bypassing KRAS- induced checkpoint failures [270]. Similarly, preclinical studies in AML have shown that CCT 137690 and CCT 245718—dual inhibitors of Aurora kinases and FLT3—are effective in FLT3-ITD + and FLT3 D 835 Y- resistant models, suppressing leukemic proliferation and inducing apoptosis. These dual- action inhibitors impair both mitotic progression and tyrosine kinase- driven survival signals, enhancing therapeutic efficacy in otherwise refractory leukemias [207, 271]. Moreover, BRAF- mutant tumors, although direct clinical trials combining BRAF inhibitors with AKIs are limited, mechanistic studies suggest AURKA inhibition may enhance responses to BRAF inhibitors like vemurafenib by destabilizing MYC and suppressing downstream MAPK reactivation—a common resistance mechanism [272, 273]. Moreover, in head and neck squamous cell carcinoma (HNSCC), combining the EGFR- TKI erlotinib with AS 703569 (an Aurora kinase inhibitor) led to enhanced anti- proliferative activity in vitro, emphasizing the broad utility of these combinations in EGFR- overexpressing malignancies [274]. Collectively, these findings reinforce the therapeutic rationale for co- targeting mitotic regulators and tyrosine kinase pathways across various cancers. Combining AKIs with TKIs may not only target tumor cell division and survival simultaneously but may also delay the onset of resistance and broaden the range of tumor subtypes responsiveness to treatment. These AKI–TKI combinations may demonstrate synergistic antitumor effects, which can be quantified using models such as the Combination Index (CI), where $CI < 1$ indicates synergy [275]. Moving forward, biomarker-guided selection, such as MYC amplification, EGFR or FLT3 mutation status, and AURKA overexpression, along with optimized dosing regimens, will be critical to translating these combinations into durable clinical responses [274]. These strategies reflect a broader shift toward multi- pathway inhibition and offer renewed

momentum for the clinical advancement of Aurora kinase inhibitors.

Biomarkers enable precision targeting of Aurora kinases

Biomarkers are measurable indicators that can signal the presence of cancer or other diseases, aiding in early detection by identifying abnormal levels of proteins, genes, or other molecules [276]. Several types of biomarkers exist, including diagnostic, prognostic, and predictive. Diagnostic biomarkers help identify the presence of cancer, while prognostic biomarkers provide information on the disease's course or outcome [277]. Predictive biomarkers indicate a patient's response to a particular treatment, allowing for more personalized therapeutic approaches [278]. Recent research has shown that aurora kinase biomarkers play a significant role in cancer progression and treatment response, with elevated levels often associated with aggressive tumor behavior and poor prognosis [279].

Recent advances in transcriptomics, proteomics, and functional genomics have facilitated the identification of candidate biomarkers associated with AKI sensitivity. Among key predictive biomarkers, TPX2, a critical activator of AURKA, is frequently overexpressed in proliferative cancers, correlating with poor prognosis and potentially enhancing sensitivity to AKIs [280, 281]. Similarly, FOXM1, a transcriptional effector of AURKA, governs a wide range of cell cycle and stemness-related genes, with its overexpression linked to AKI efficacy in breast and hepatocellular carcinoma [58, 282]. Furthermore, Survivin (BIRC5), a core component of the chromosomal passenger complex regulated by AURKB, serves both as a proliferation marker and a determinant of resistance, particularly in colorectal and hematological malignancies [283, 284]. Elevated AURKA/B mRNA levels themselves often indicate chromosomal instability and mitotic addiction, making them actionable vulnerabilities in multiple cancers [285]. Non-coding RNAs (ncRNAs) further refine the biomarker landscape. For instance, miR-21-5p, microRNA-490-3p and miR-331-5p downregulate AURKA [286–288], enhancing AKI sensitivity, whereas lncRNA MALAT1 stabilizes AURKA via PI3K/AKT signaling, contributing to drug resistance [289]. These ncRNAs have promising roles in liquid biopsy–based diagnostics due to their dynamic regulation of kinase signaling [290, 291].

Genomic and proteomic analyses have revealed both inherited (germline) and acquired (somatic) mutations in AURKA, AURKB, and AURKC, reinforcing their potential utility as predictive or prognostic indicators [17, 292]. Biomarker-guided therapy enables stratification of patients based on mutation burden, signaling context, and resistance potential, supporting more effective Aurora kinase–targeted strategies [293]. Additionally, the genomic profiling in glioblastoma multiforme revealed that single nucleotide polymorphisms (SNPs) in AURKB (rs2289590) and AURKC (rs11084490) were associated with reduced disease risk and may influence transcription factor binding and kinase regulation [294]. In lung adenocarcinoma, transcriptomic profiling revealed that AURKA–FOXM1 overexpression drives immune evasion by reducing CD4 + T cell infiltration, marking this axis as both prognostic and immunologically relevant [295]. Furthermore, studies have also emphasized the enrichment of signaling pathways such as cell cycle regulation, DNA replication, homologous recombination, mismatch repair, p53 signaling, and apoptosis among Aurora co-regulated genes [296–298]. AURKA's oncogenic specific signaling involves feedback interactions with tumor suppressors (p53, BRCA1, VHL, FAF1) and oncogenes (LIMK2, TWIST1, NSD2, ALDH1A1, YBX1), engaging pathways like β-catenin, PI3K/AKT, GSK3β, ERα, and MYC regulation [45]. Proteomic data from triple-negative breast cancer (TNBC) showed that chemotherapy resistance correlates with elevated phosphorylation and expression of AURKA/B, highlighting AURKB as a potential marker of mitotic burden and drug resistance [299]. Additionally, analysis of ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) [300], a National Institutes of Health (NIH) database, revealed the presence of 40, 52, and 96 germline mutations in AURKA, AURKB, and AURKC, respectively. While somatic mutations in all three Aurora kinase genes were identified through the Catalogue of Somatic Mutation in Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cosmic/) [301], AURKA: 3461, AURKB: 1074, AURKC: 1364, underscoring their clinical significance across inherited and acquired oncogenic contexts. However, despite the growing evidence, several factors have limited the translation of AURKA and AURKB into standard-of-care biomarkers.

Earlier attempts to validate these biomarker candidates were hampered by the limitations of RNA interference (RNAi) techniques, which suffered from incomplete knockdown and off-target effects [302]. These issues often masked the true biological impact of RNAi-based inhibition or depletion, leading to inconsistent or inconclusive phenotypes in preclinical studies [303]. Early 2000s and 2010s findings frequently noted discrepancies between RNAi-based gene silencing and the phenotypes observed with pharmacological inhibition, raising concerns about the reliability of RNAi as a functional alternative. A key challenge is the off-target effect, where siRNAs and shRNAs may suppress unintended transcripts through partial sequence complementarity, often mimicking microRNA-like behavior and disrupting non-target genes involved in essential cellular pathways [304,

305]. Additionally, RNAi-mediated silencing often results in incomplete knockdown of target genes, especially for transcripts with high basal expression or long half-lives [306, 307]. Moreover, long-term shRNA/siRNA expressions can trigger innate immune responses and saturation of the endogenous RNAi machinery, which may affect microRNA processing and lead to cytotoxicity or altered gene expression profiles [308–310]. These technical and biological limitations have constrained RNAi's effectiveness in characterizing gene function and identifying reliable therapeutic targets. Such limitations may have contributed to the delay in the precise mapping of gene-phenotype relationships and created challenges in proposing Aurora kinases as reliable biomarkers.

The emergence of CRISPR-Cas9 gene editing has dramatically improved functional genomics, enabling precise and stable knockout of AURK family genes [93, 311, 312]. Genome-wide CRISPR screens have revealed synthetic lethal interactions, such as AURKA with TP53 or RB1, highlighting genetic contexts where AKIs may exhibit maximal efficacy [313–316]. These findings help identify susceptible cancer genotypes and inform the rational design of combination therapies. More recent iterations of CRISPR technology, including CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa), allow for fine-tuned, non-lethal modulation of Aurora kinases and their co-regulators, supporting exploration of dose sensitivity, resistance adaptation, and context-specific vulnerabilities [317–320]. Furthermore, CRISPR-based lineage tracing and barcoding approaches may enable real-time tracking of clonal evolution under AKI treatment pressure, providing insights into resistance emergence and tumor relapse. Additionally, the expanding CRISPR toolbox, including CRISPR-Cas13 systems which target RNA directly, offers a non-invasive, real-time strategy for disease monitoring [321–323] and could be leveraged for ultra-sensitive detection of AURKA/B mRNAs.

In summary, the lack of robust biomarkers and functional validation tools initially impeded the clinical progress of Aurora kinase-targeted therapy. Integration of multi-omics profiling with CRISPR-enabled functional genomics and diagnostics is revolutionizing how we identify, target, and monitor Aurora kinase-driven malignancies. These advances position Aurora kinases not only as therapeutic targets but also as actionable biomarkers in the emerging framework of precision oncology.

Emerging role of Aurora kinases and recent advances

Aurora kinases play important role in cell division, ensuring proper chromosome segregation and mitotic progression and its regulations. However, recent research has uncovered a much broader influence, showing that these kinases are involved in DNA repair, metabolism, immune evasion, and cancer stem cell regulation, all of which contribute to tumor progression and therapy resistance [324]. One of the most surprising discoveries is Aurora kinases' role in DNA damage repair. While AURKA helps cells fix damaged DNA, its overexpression in cancer increases genetic instability, driving tumor growth [110]. This suggests that targeting AURKA with inhibitors, especially in combination with DNA-damaging treatments like PARP inhibitors, could be an effective anti-cancer strategy. Aurora kinases are not just involved in cell division, they also influence how cancer cells generate and use energy, playing a key role in their metabolism. AURKA has been linked to mitochondrial function, while AURKB influences glycolysis through key cancer-related pathways like MYC and HIF-1α signaling [325, 326]. Since cancer cells often rely on altered metabolism for survival, Aurora kinase inhibitors (AKIs) could potentially be combined with metabolic drugs to cut off the energy supply to tumors.

Another exciting area of study is how Aurora kinases enable cancer cells to escape detection by the immune system. AURKA has been found to regulate PD-L1 expression, a key molecule that tumors use to hide from the immune system [327]. Research suggests that blocking AURKA could strengthen the body's immune response against cancer, making it a promising option to combine with immune checkpoint inhibitors like anti-PD-1/PD-L1 therapies [328]. Cancer stem cells (CSCs), which drive tumor relapse and resistance to treatment, also appear to rely on Aurora kinases. AURKA and AURKB activate pathways like Wnt/β-catenin and Notch, which help CSCs survive and self-renew. Targeting Aurora kinases in CSCs could help eliminate these therapy-resistant cells and prevent cancer recurrence. Finally, Aurora kinases interact with other major cancer pathways, including PI3K/AKT, Hippo, and JAK/STAT, which help tumors develop resistance to treatment [329]. Understanding these interactions is essential for designing better combination therapies that can attack cancer from multiple angles at once. In short, Aurora kinases are much more than just mitotic regulators, they are deeply embedded in the complex web of cancer biology. Future research should explore how to target these non-traditional roles, potentially leading to more effective, long-lasting cancer treatments that go beyond simply stopping cell division.

Challenges and future prospects

Inhibitors targeting Aurora kinases have become priority targets for cancer treatment, but their development presents challenges due to the high similarity between these kinases and other kinases, which can lead to off-target

effects [330]. Moreover, the complex regulatory mechanisms and feedback loops within cancer cells can also diminish the effectiveness of these inhibitors. Drug resistance is another significant hurdle, necessitating continuous research to overcome these obstacles [331, 332]. To address this, researchers have tried to combine Aurora kinase inhibitors with other therapeutic agents. Furthermore, identifying and targeting specific biomarkers can predict a patient's response to treatment, allowing for more personalized therapy. The development of next-generation inhibitors with improved selectivity and reduced off-target effects could help minimize resistance and enhance patient outcomes [333, 334]. A primary challenge lies in the lack of isoform selectivity, especially between AURKA and AURKB, which share significant sequence and structural similarity in their catalytic domains. In response, researchers have created inhibitors that specifically target certain Aurora kinase isoforms, reducing the chances of affecting other kinases [335, 336]. Additionally, new formulations and delivery methods are being explored to increase the concentration of the drug at the tumor site, enhancing its efficacy while minimizing systemic side effects [337]. Personalized medicine plays a crucial role in cancer treatment, allowing therapies to be customized based on the specific genetic and molecular characteristics of a patient's tumor [338]. This approach not only improves patient outcomes but also promotes efficient use of healthcare resources.

Aurora kinase inhibitors (AKIs), despite showing strong preclinical efficacy, have faced multiple challenges that have limited their translation into successful clinical applications. As previously mentioned, AURKs' structural similarities complicate the design of specific inhibitors and often result in pan-Aurora inhibition, leading to unintended suppression of non-targeted isoforms and increased toxicity [171]. The associated dose-limiting hematologic side effects, particularly neutropenia and mucositis, have been major contributors to the early termination of several clinical trials [339, 340]. Aurora kinase inhibitors have entered various phases of clinical trials—ranging from Phase I, which assesses safety, tolerability, and pharmacokinetics, to Phase II and III trials that focus on efficacy and comparative effectiveness in larger patient populations [341]. These phases are essential for establishing both the clinical utility and regulatory viability of new therapies [342]. Table 2 summarizes key Aurora kinase inhibitors, detailing their target isoforms, associated cancer types, reported adverse effects, clinical trial phases, and IC_{50} values. However, many AKIs have struggled to advance beyond early-phase trials due to insufficient therapeutic windows, toxicity profiles, and limited patient responses. For instance, several Phase I/II studies have reported suboptimal responses or high-grade adverse events, prompting trial discontinuation or reformulation efforts [343–345]. These clinical setbacks highlight the need for improved pre-clinical-to-clinical translation models and better biomarker-based patient stratification.

Another major hurdle, as mentioned earlier, has been the emergence of both intrinsic and acquired resistance to AKIs. Resistance mechanisms include mutations in the ATP-binding pocket of Aurora kinases, altered expression of downstream mitotic regulators, and activation of parallel cell survival pathways that bypass Aurora kinase blockade [11, 346]. These compensatory responses diminish the therapeutic efficacy of AKIs and pose a significant barrier to sustained clinical benefit. To overcome these challenges, the development of isoform-selective inhibitors remains a high priority to mitigate off-target effects while preserving therapeutic potency. Structural insights into unique regulatory domains and allosteric pockets of each Aurora kinase isoform could facilitate the rational design of highly selective molecules. In parallel, dual-target inhibitors that simultaneously suppress Aurora kinases and synergistic mitotic kinases such as PLK1 or Haspin are gaining attention for their potential to overcome redundancy and therapeutic escape mechanisms within the mitotic machinery [54]. Another promising direction lies in the application of degradation-based strategies, such as PROTACs (proteolysis targeting chimeras), which offer the ability to selectively degrade Aurora kinases rather than merely inhibit their catalytic activity [347]. This approach may enhance target specificity, reduce the required dosing, and minimize resistance associated with kinase reactivation. Moreover, integrating systems biology and multi-omic approaches will be vital to better characterize context-specific AURK dependencies and to inform rational design of future therapeutic strategies. Overall, the path to successful Aurora kinase-based therapies lies in addressing these mechanistic and pharmacological limitations through advanced drug design, rational combination strategies, and context-aware translational frameworks. These efforts will be crucial for repositioning Aurora kinases as viable and durable targets in precision cancer therapy.

Discussion

Aurora kinases are a well-conserved family of serine/threonine kinases that are essential for cell division, helping to ensure proper chromosome separation, spindle formation, and the final splitting of cells [119]. Their dysregulation has been strongly implicated in oncogenesis, where aberrant expression disrupts genomic integrity, leading to chromosomal instability and uncontrolled proliferation [7]. Among them, Aurora kinase A (AURKA) is primarily involved in centrosome maturation and mitotic

Table 2 Clinical Trails, Adverse Effect, and IC_{50} values of AKIs

S. No	Inhibitor Name	Type of Cancer	Clinical Trial	Govt. ID	Adverse Effect	IC_{50} value	Reference
Inhibitors of Aurora Kinase A							
1	**MLN8054**	Advanced malignancies	Terminated	NCT00249301	Somnolence, sedation, fatigue, hepatotoxicity	4 nM	[364]
2	**AT9283**	Leukemia	Phase 1	NCT01431664	Neutropenia, anemia, fatigue	3 nM	[365]
		Multiple Myeloma	Phase 2	NCT01145989			
		Unspecified Childhood Solid Tumor	Phase 1	NCT00985868			
		Non-Hodgkins Lymphoma	Phase 1	NCT00443976			
		Acute Lymphoblastic Leukemia/ Acute Myeloid Leukemia/ Chronic Myeloid Leukemia/ Myelodysplastic Syndromes/ Myelofibrosis	Terminated	NCT00522990			
3	**MK-5108**	Refractory Solid Tumors	Phase 1	NCT00543387	Febrile neutropenia, infections, fatigue, nausea	0.064 nM	[366]
4	**ENMD-2076**	Advanced Fibrolamellar Carcinoma	Phase 2	NCT02234986	Hypertension, fatigue, diarrhea, neutropenia	14 nM	[367]
		Ovarian Clear Cell Carcinoma	Phase 2	NCT01914510			
		Soft Tissue Sarcoma	Phase 2	NCT01719744			
		Triple Negative Breast Cancer	Phase 2	NCT01639248			
		Ovarian Cancer	Phase 2	NCT01104675			
5	**XL228**	Lymphoma	Terminated	NCT00526838	Fatigue, thrombocytopenia, nausea, diarrhea	3.1 nM	[368]
		Chronic Myeloid Leukemia Leukemia, Lymphoblastic, Acute, Philadelphia-Positive	Terminated	NCT00464113			
6	**VE-465**	human hepatocellular carcinoma	Preclinical trials	Lin et al. [369]	Neutropenia, GI toxicity, fatigue	2.00 ± 6.5 uM	[369]
7	**TC-A2317**	Not Specified	Not Specified	Not Specified	GI disturbances, neutropenia, mucositis	50 uM	[370]
8	**Tanshinone/ Tanshinone IIA sulfonate**	Acute Myocardial Infarction	Phase 4	NCT02524964	Mild hepatotoxicity, GI upset, allergic reactions	3–15 uM	[371]
		Promyeloid Leukemia	Phase 4	NCT02200978			
		Pulmonary Hypertension	Phase 2 Phase 3	NCT01637675			
		Polycystic Ovary Syndrome	Not Specified	NCT01452477			
9	**AKI603**	Not Specified	Not Specified	Not Specified	Myelosuppression, fatigue, GI upset	0.032–0.039 uM	[372]
10	**R1498**	Not Specified	Not Specified	Not Specified	Fatigue, GI toxicity, hematologic adverse effects	67 ± 4 nM range	[373]
Inhibitors of Aurora Kinase A and B							
1	**GSK1070916**	Advanced Solid Tumors	Phase 1	NCT01118611	Neutropenia, anemia, diarrhea, ventricular repolarization prolongation	0.38 nM	[374]

Table 2 (continued)

S. No	Inhibitor Name	Type of Cancer	Clinical Trial	Govt. ID	Adverse Effect	IC_{50} value	Reference
2	**Barasertib/ AZD2811/ AZD1152/ AZD1152-HQPA**	Relapsed Acute Myeloid Leukemia	Phase 1	NCT00497991	Neutropenia, febrile neutropenia, mucositis, diarrhea	0.37 nM	[375]
		B-cell Lymphoma	Phase 1 Phase 2	NCT01354392			
3	**Hesperidin**	Breast Cancer	Phase 3	NCT06811220	Headache, GI discomfort, allergic reactions, dizziness	250 nM	[376]
4	**SP-96**	Not Specified	Not Specified	Not Specified	Hematologic, GI toxicity	0.316 nM	[377]
5	**CS2164/Chiauranib**	Pancreatic Ductal Adenocarcinoma	Phase 2	NCT06492915	Hypertension, fatigue, neutropenia, liver enzyme elevation	9 nM	[378]
		Small Cell Lung Cancer	Phase 1 Phase 2	NCT05505825			
		Soft Tissue Sarcoma	Phase 2	NCT05497843			
		Triple-negative Breast Cancer	Terminated	NCT05336721			
		Ovarian Cancer	Phase 3	NCT04921527			
6	**Quercetin**	Childhood Cancer	Phase 2	NCT04733534	Tingling limbs, headache, kidney toxicity (high dose), nausea	2.4–5.4 µM	[379]
7	**Ceftriaxone**	Pleural Effusion Diagnosis	Not Specified	NCT06946498	Diarrhea, nausea, pseudomembranous colitis, rashes	Not Specified	Not Specified
Inhibitors of Aurora Kinase A and B							
1	**MLN8237 /Alisertib**	HER2-negative Recurrent or Metastatic Breast Cancer	Phase 2	NCT06369285	Neutropenia, stomatitis, diarrhea, fatigue	1.2 nM (AURKA) 396.5 nM (AURKB)	[365]
		Small Cell Lung Cancer	Phase 2	NCT06095505			
		Head and Neck Squamous Cell Carcinoma	Terminated	NCT04555837			
		Stage IIIB or IV Non-Small Cell Lung Cancer	Phase 1	NCT04479306			
		EGFR-mutant Lung Cancer	Phase 1	NCT04085315			
2	**CYC116**	Solid Tumors	Terminated	NCT00560716	GI disturbances, myelosuppression, fatigue, alopecia	44 nM (AURKA) 16 Nm (AURKB)	[7]
3	**TAK-901**	Advanced Solid Tumors, Lymphoma	Phase 1	NCT00935844	Neutropenia, anemia, diarrhea, nausea	21 nM (AURKA) 15 nM (AURKB	[7]
		Advanced Hematologic Malignancies	Phase 1	NCT00807677			
4	**PF-03814735**	Solid Tumors	Phase 1	NCT00424632	Diarrhea, fatigue, nausea, anemia	5 nM (AURKA) 0.8 nM (AURKB)	[365]
5	**ZM447439**	Not Specified	Preclinical	CHEMBL202721	Unknown	110 nM (AURKA) 130 nM (AURKB)	[380]
6	**JNJ-7706621**	Not Specified	Preclinical	CHEMBL191003	Unknown	11 nM (AURKA) 15 nM (AURKB)	[181]
7	**AKI-001**	Not Specified	Preclinical	CHEMBL223147	hematologic and GI adverse effects	AURK-A and B (< 100 nM)	[7]
8	**MK-8745**	Not Specified	Preclinical	CHEMBL4303177	Neutropenia, leukopenia, fatigue, nausea	0.6 nM (AURKA) 280 nM (AURKB)	[184]

Table 2 (continued)

S. No	Inhibitor Name	Type of Cancer	Clinical Trial	Govt. ID	Adverse Effect	IC_{50} value	Reference
9	**TT00420**	Prostate Cancer	Phase 1 Phase 2	NCT06457919	Neutropenia, elevated liver enzymes, fatigue	1.2 nM (AURKA) 3.3 nM (AURKB)	[381]
		Advanced Solid Tumors, Cholangiocarcinoma		NCT06370013			
		Advanced Urological Tumors	Phase 1 Phase 2	NCT06221774			
		Cholangiocarcinoma	Phase 2	NCT06057571			
		Advanced Solid Tumors	Phase 1 Phase 2	NCT05253053			
10	**TAS-119**	Advanced Solid Tumors	Terminated	NCT02448589	Fatigue, stomatitis, thrombocytopenia, GI upset	1.04 nM (AURKA) 95 ± 11 nM (AURKB)	[7]
Inhibitors of Aurora Kinase A, B and C							
1	**Danusertib/ PHA739358**	Multiple Myeloma	Terminated	NCT00872300	Neutropenia, febrile neutropenia, anemia, fatigue	13 nM (AURKA) 79 nM (AURKB) 61 nM (AURKC)	[365]
		Hormone Refractory Prostate Cancer	Phase 2	NCT00766324			
		Leukemia	Phase 2	NCT00335868			
2	**SNS-314/Mesylate**	Non-Small Cell Lung Cancer	Phase 2	NCT06962865	Fatigue, nausea, diarrhea, neutropenia	9 nM (AURKA) 31 nM (AURKB) 6 nM (AURKC)	[7]
		Solid Tumor Cancer	Phase 1	NCT06962254			
		Acute Myeloid Leukemia	Phase 2	NCT06954987			
3	**AMG-900**	Myeloid Leukemia	Phase 1	NCT01380756	Neutropenia, anemia, fatigue, thrombocytopenia	5 nM (AURKA) 4 nM (AURKB) 1 nM (AURKC)	[365]
		Advanced Solid Tumors	Phase 1	NCT00858377			
4	**ABT-348/Ilorasertib**	Metastatic Solid Cancers	Phase 1	NCT02540876	Hypertension, fatigue, diarrhea, nausea	116 nM (AURKA) 5 nM (AURKB) 1 nM (AURKC)	[7]
		Solid Tumors	Terminated	NCT02478320			
		Advanced Hematologic Malignancies	Phase 1	NCT01110473			
5	**VX-680/MK-0457/ Tozasertib**	Advanced Solid Tumors, Colorectal Cancer	Terminated	NCT00099346	Neutropenia, nausea, fatigue	0.6 nM (AURKA) 18 nM (AURKB) 4.6 nM (AURKC)	[7]
6	**CCT137690/ AS703569/ R763**	Solid Tumors	Phase 1	NCT00391521	Neutropenia, fatigue, nausea, diarrhea	0.7 nM- 1000 nM (AURKA) (AURKB) (AURKC)	[382]
7	**PHA-680632**	Solid Tumors	Phase 1	NCT00391521	Neutropenia, anemia, fatigue, nausea	27 nM (AURKA) 135 nM (AURKB) 120 nM (AURKC)	[209]
8	**CCT129202**	Not Specified	Preclinical	CHEMBL392525	Neutropenia, fatigue, nausea, diarrhea	42 nM (AURKA) 198 nM (AURKB) 227 nM (AURKC)	[383]
9	**Reversine**	Not Specified	Preclinical	CHEMBL188343	Unknown	400 nM (AURKA) 500 nM (AURKB) 400 nM (AURKC)	[7]
10	**Cenisertib**	Haematological Malignancies	Terminated	NCT01080664	Neutropenia, thrombocytopenia, anemia, fatigue	Not Specified	Not Specified
		Solid Tumors	Phase 1	NCT00391521			

spindle assembly, while Aurora kinase B (AURKB) plays a key role in chromosome alignment, the spindle assembly checkpoint, and cytokinesis [7]. Aurora kinase C (AURKC), though less extensively studied, has been implicated in meiosis and has emerging links to tumorigenesis [7]. Elevated levels of Aurora kinases have

been observed across several cancers, contributing to increased metastatic potential, therapy resistance, and poor prognosis. AURKA amplification has been frequently reported in breast, colorectal, and pancreatic cancers, where it drives centrosome amplification and aneuploidy, leading to aggressive tumor behavior [324, 348]. Similarly, AURKB overexpression in hematologic malignancies such as leukemia and lymphoma, as well as in solid tumors, has been associated with defective cytokinesis and polyploidy, accelerating tumor progression [170]. While AURKC remains less well characterized in cancer biology, recent evidence suggests its involvement in testicular cancer and leukemia, with a potential compensatory role alongside AURKB [349, 350]. Given their fundamental role in mitotic regulation, Aurora kinases are considered promising therapeutic targets, with increasing interest in their inhibition for treating cancer.

Several AKIs have been developed, with much progressing through preclinical and clinical trials. AURKA inhibitors, such as alisertib (MLN8237), have shown efficacy in inducing mitotic arrest and apoptosis in tumor cells, both as monotherapy and in combination with chemotherapeutic agents [11]. Similarly, AURKB inhibitors, such as barasertib (AZD1152), disrupt cytokinesis and induce polyploidy, triggering cell death. [351]. While selective AURKC inhibitors remain underdeveloped, the structural similarities between AURKB and AURKC suggest that certain inhibitors could be optimized for dual targeting. Despite these advancements, the clinical success of Aurora kinase inhibitors has been hindered by several challenges, including drug resistance, off-target effects, and systemic toxicity.

One of the major bottlenecks in Aurora kinase-targeted therapy is the development of resistance mechanisms which compromise drug efficacy. Cancer cells can develop resistance by mutating the ATP-binding pocket of Aurora kinases, lowering drug effectiveness and reducing treatment success [7]. Additionally, compensatory activation of alternative mitotic kinases, such as Polo-like kinases (PLKs) and cyclin-dependent kinases (CDKs), can allow cancer cells to bypass Aurora kinase inhibition [3, 352]. Additionally, increased activity in survival pathways like PI3K/AKT and Wnt/β-catenin signaling helps tumors continue growing even when Aurora kinases are blocked [353]. These resistance mechanisms highlight the need for novel strategies to enhance drug efficacy and overcome adaptive resistance in cancer cells. In addition to resistance, off-target toxicity is another significant challenge in the clinical application of Aurora kinase inhibitors. Given their essential role in normal cell division, systemic inhibition of Aurora kinases often leads to hematologic toxicity, bone marrow suppression, and gastrointestinal side effects, limiting their therapeutic window [349, 354]. To mitigate these adverse effects, efforts are being directed toward the development of next-generation inhibitors with enhanced selectivity and improved drug delivery strategies. Novel approaches such as allosteric inhibitors, which target non-ATP sites, offer the potential for greater specificity and reduced resistance. Additionally, PROTAC-based degradation of Aurora kinases presents an emerging strategy to selectively degrade aberrant Aurora kinase activity while sparing normal cells [355]. Nanoparticle-mediated drug delivery is also being explored to enhance tumor specificity and minimize systemic toxicity.

To further improve the clinical efficacy of Aurora kinase inhibitors, combination therapy approaches are being actively investigated [356]. Combining AKIs with traditional chemotherapy, such as taxanes and vincristine, has shown promise in enhancing mitotic stress and preventing resistance [357]. Combining Aurora kinase inhibitors (AKIs) with immune checkpoint inhibitors like anti-PD-1/PD-L1 therapy could enhance the body's ability to fight and clear tumors through the immune system [358]. Targeting Aurora kinases alongside epigenetic modulators, such as HDAC or BET inhibitors, may also counteract adaptive resistance mechanisms and enhance antitumor effects [359]. These combination strategies represent a promising avenue for overcoming the limitations of AKIs and improving their clinical success. Although we've made great progress, there are still many important questions about how Aurora kinases influence cancer and its treatment. Emerging evidence suggests that Aurora kinases may have non-canonical functions beyond mitosis, including roles in DNA repair, immune evasion, metabolic reprogramming, and cancer stem cell maintenance [265, 360–362]. Understanding these additional functions could open new therapeutic opportunities and further refine targeted treatment strategies. Additionally, the role of Aurora kinases in tumor metastasis and drug resistance remains underexplored and warrants further investigation. Identifying predictive prognostic biomarkers for Aurora kinase inhibition is another crucial area of research, as biomarker-driven patient selection could enable more personalized treatment approaches and improve clinical outcomes. The integration of AI-driven drug discovery and computational modeling may also aid in optimizing AKI selection based on tumor-specific genetic landscapes using diagnostics biomarkers [363]. In conclusion, Aurora kinases play a pivotal role in cancer progression, and their inhibition represents a promising therapeutic strategy. While Aurora kinase inhibitors have demonstrated significant potential in preclinical and clinical settings, challenges related to drug resistance, off-target toxicity, and patient heterogeneity remain

key obstacles to their widespread clinical use. Future research should focus on developing next-generation inhibitors with improved selectivity, optimizing combination therapy strategies, and leveraging biomarker-driven approaches for personalized cancer treatment. By addressing these challenges, Aurora kinase-targeted therapies could play a crucial role in advancing precision oncology and improving patient outcomes.

Abbreviations

AURK	Aurora Kinase
AIE 1/2	Anaerobically Inducible Early 1/2
AIK	ABA-insensitive protein kinase
AIR-2	Aurora-Ipl1-related protein kinase 2
AKI	Aurora Kinase Inhibitor
ARK	Actin Regulating Kinase 1
CPC	Chromosomal Passenger Complex
CIN	Chromosomal Instability
EMT	Epithelial-Mesenchymal Transition
G2/M	Gap 2/Mitosis Phase
PDX	Patient-Derived Xenograft
ORR	Objective Response Rate
IC50	Half Maximal Inhibitory Concentration
Ipl1	Increase-in-ploidy 1
pEg2	Polo-like kinase Enhancer of G2
Ark1	Aurora-related kinase 1
TACC3	Transforming Acidic Coiled-Coil Containing Protein 3
KEN	*KEN box motif*
NPM	*Nucleophosmin*
DAD/A	Docking and Dimerization/Activation Domain of Aurora A
CDC25C	Cell Division Cycle 25C
PLK1	Polo-Like Kinase 1
PROTAC	Proteolysis Targeting Chimera
DSB	DNA Double-Strand Break
HR	Homologous Recombination
NHEJ	Non-Homologous End Joining
TME	Tumor Microenvironment
NSCLC	Non-Small Cell Lung Cancer
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
ROS	Reactive Oxygen Species
PD-L1	Programmed Death-Ligand 1
SLiMs	Short Linear Motifs
shRNA	Short Hairpin RNA
siRNA	Small Interfering RNA
RNAi	RNA Interference
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRISPRi	CRISPR Interference
CRISPRa	CRISPR Activation
Cas9	CRISPR-associated Protein 9
Cas13	CRISPR-associated Protein 13
Eg	Endoglucanase
TKI	Tyrosine Kinase Inhibitor
TPX2	Targeting Protein for Xklp2
FOXM1	Forkhead Box M1
BIRC5	Baculoviral IAP Repeat Containing 5 (Survivin)
ATM/ATR	Ataxia Telangiectasia Mutated / Rad3-related Kinases
RB1	Retinoblastoma Protein 1
TP53	Tumor Protein p53
APC/C	Anaphase-Promoting Complex/Cyclosome
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
FLT3	Fms-like Tyrosine Kinase 3
MDR	Multidrug Resistance
BRD4	Bromodomain-containing Protein 4
m6A	N6-Methyladenosine
SELEX	Systematic Evolution of Ligands by Exponential Enrichment
FACS	Fluorescence-Activated Cell Sorting
GSK-3β	Glycogen Synthase Kinase-3β
PCM	Pericentriolar Material
NEBD	Nuclear Envelope Breakdown
MTOCs	Microtubule Organizing Centers
MCAK	Mitotic Centromere-Associated Kinesin
SAC	Spindle Assembly Checkpoint
GFAP	Glial fibrillary acidic protein
CHE	Chinese Hamster Embryo
RASSF7	Ras Association Domain Family Member 7
MDM2	Murine Double Minute 2
BAX	Bcl-2-Associated X protein
PUMA	*p53 Upregulated Modulator of Apoptosis*
JAK2	Janus Kinase 2
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
VEGFR	Vascular Endothelial Growth Factor Receptor
FGFR	*Fibroblast Growth Factor Receptor*
CSF1R	Colony Stimulating Factor 1 Receptor
pHH3	Phosphohistone H3
CDK	Cyclin-Dependent Kinases
HASMC	Human Aortic Smooth Muscle Cells
HUVEC	Human Umbilical Vein Endothelial Cells
MDR	Multidrug-Resistant
SAR	Structure-Activity Relationship
HDAC	Histone Deacetylase
CEP192	Centrosomal Protein 192
Mps1	*Monopolar Spindle 1 kinase* (Also known as TTK)
INCENP	Inner Centromere Protein
MTOC	Microtubule-Organizing Center
PCM	Pericentriolar Material
CNN	Centrosomin
Spd-2	Spindle Defective 2
LATS2	Large Tumor Suppressor Kinase 2
NDEL1	Nuclear Distribution Protein NudE-Like 1
HURP	Hepatoma Up-Regulated Protein
Wnt	*Wingless/Integrated* Signaling pathway
NEBD	Nuclear Envelope Breakdown
BUB	Budding Uninhibited by Benzimidazole
MAD	Mitotic Arrest Deficient
Kif	Kinesin Family
MKLP2	Mitotic Kinesin-Like Protein 2
HCC	Hepatocellular Carcinoma
CSC	Cancer Stem Cells
MMP	Matrix Metalloproteinase
FAK	Focal Adhesion Kinase
mTOR	Mechanistic Target of Rapamycin
EOC	Epithelial Ovarian Cancer
STAT	Signal Transducer and Activator of Transcription
CML	Chronic Myeloid Leukemia
BAD	Bcl-2-Associated Death Promoter
PTCL	Peripheral T-cell Lymphoma
MM	Multiple Myeloma
AML	Acute Myeloid Leukemia
BCR-ABL	Breakpoint Cluster Region–Abelson Murine Leukemia Viral Oncogene
CHEK1	Checkpoint Kinase 1
PDK1	3-Phosphoinositide-Dependent Protein Kinase 1
MEK	MAPK/ERK Kinase
ncRNA	Non-Coding RNA
lncRNA	Long Non-Coding RNA
SNP	Single Nucleotide Polymorphism
PARP	Poly (ADP-Ribose) Polymerase
MYC	Myelocytomatosis Oncogene
HIF-1α	Hypoxia-Inducible Factor 1-alpha
PD-L1	Programmed Death-Ligand 1
BET	Bromodomain and Extra-Terminal domain Family of proteins
ATP	AdenosineTriphosphate
RNA	RibonucleicAcid
CCNB1	Cyclin B1
LIM	LIN-11, Isl-1, and MEC-3 Domain
MAP215	Microtubule-Associated Protein 215
PP6	Protein Phosphatase 6

HP1	Heterochromatin Protein 1
ECM	Extracellular Matrix
RasGAPSH3	Ras GTPase-Activating Protein Src Homology 3 Domain
Noxa/PMAIP1	PMA-Induced Protein 1 (also known as Phorbol-12-myristate 13-acetate-induced protein 1)
IAP	Inhibitor of Apoptosis Protein
NHL	Non-Hodgkin Lymphoma
DLBC	Diffuse Large B-Cell Lymphoma
MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
HNSCC	Head and Neck Squamous Cell Carcinoma
NIH	National Institutes of Health
BRCA1	Breast Cancer 1
VHL	Von Hippel–Lindau Tumor Suppressor
FAF1	Fas-Associated Factor 1
LIMK2	LIM Domain Kinase 2
TWIST1	Twist Family BHLH Transcription Factor 1
NSD2	Nuclear Receptor Binding SET Domain Protein 2
ALDH1A1	Aldehyde Dehydrogenase 1 Family Member A1
YBX1	Y-Box Binding Protein 1
PI3K/AKT	Phosphoinositide 3-Kinase / AKT Signaling Pathway
GSK3β	Glycogen Synthase Kinase 3 Beta
ERα	Estrogen Receptor Alpha
TNBC	Triple-Negative Breast Cancer

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Authors' contributions
RN: Conception, study design, critical reading, and intellectual assessment of the manuscript, Study design, and preparation of the manuscript. PV: Study design, and preparation of the manuscript. BB: Study design, and preparation of the manuscript. CS: Study design, and preparation of the manuscript. AK: Conception, study design, critical reading, and intellectual assessment of the manuscript, Study design, and preparation of the manuscript. SKS: critical reading, and preparation of the manuscript. ASK: Study design, and preparation of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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