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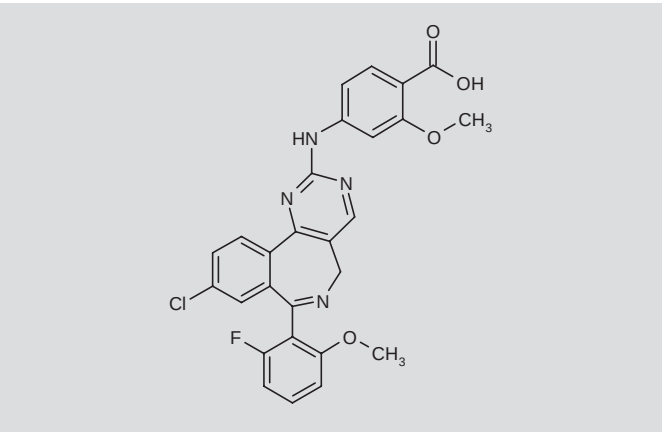
MONOGRAPH

MLN-8237

Aurora Kinase A Inhibitor
Oncolytic

4-[9-Chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-ylamino]-2-methoxybenzoic acid

InChI: 1S/C27H20ClFN4O4/c1-36-21-5-3-4-20(29)23(21)25-19-10-15(28)6-8-17(19)24-14(12-30-25)13-31-27(33-24)32-16-7-9-18(26(34)35)22(11-16)37-2/h3-11,13H,12H2,1-2H3,(H,34,35)(H,31,32,33)



$C_{27}H_{20}ClFN_4O4$
Mol wt: 518.924
EN: 437477

SUMMARY

Aurora serine/threonine-protein kinases localize in the centrosome and play a crucial role in cell division by regulating chromatid segregation in mitotic cells; moreover, defective chromatid segregation causes genetic instability, leading to tumorigenesis. Aurora kinases were first identified in Xenopus Eg2, yeast Ipl1 and Drosophila aurora. The human genome expresses three members of the mitotic Aurora kinase family: Aurora kinase A, B and C. Although Aurora kinase A and B are highly homologous, their localization and function differ during mitosis. Aurora kinase A and B have been extensively studied due to their overexpression in tumor cells. Since high AURKA gene expression has been correlated with centrosome amplification and Aurora kinase A is required for cytokinesis, defective Aurora kinase A may cause aneuploidy characteristic of tumors. Thus, inhibition of Aurora kinase A may prove to be therapeutically beneficial, and several inhibitors of Aurora kinase A are being tested in early-phase clinical trials. MLN-8237, a selective inhibitor of Aurora kinase A, is currently in phase I/II clinical trials in both adult and childhood solid tumors and hematological malignancies. Here we review the biology of Aurora kinase A and the role of MLN-8237 as a novel therapeutic agent for cancer.

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SYNTHESIS*

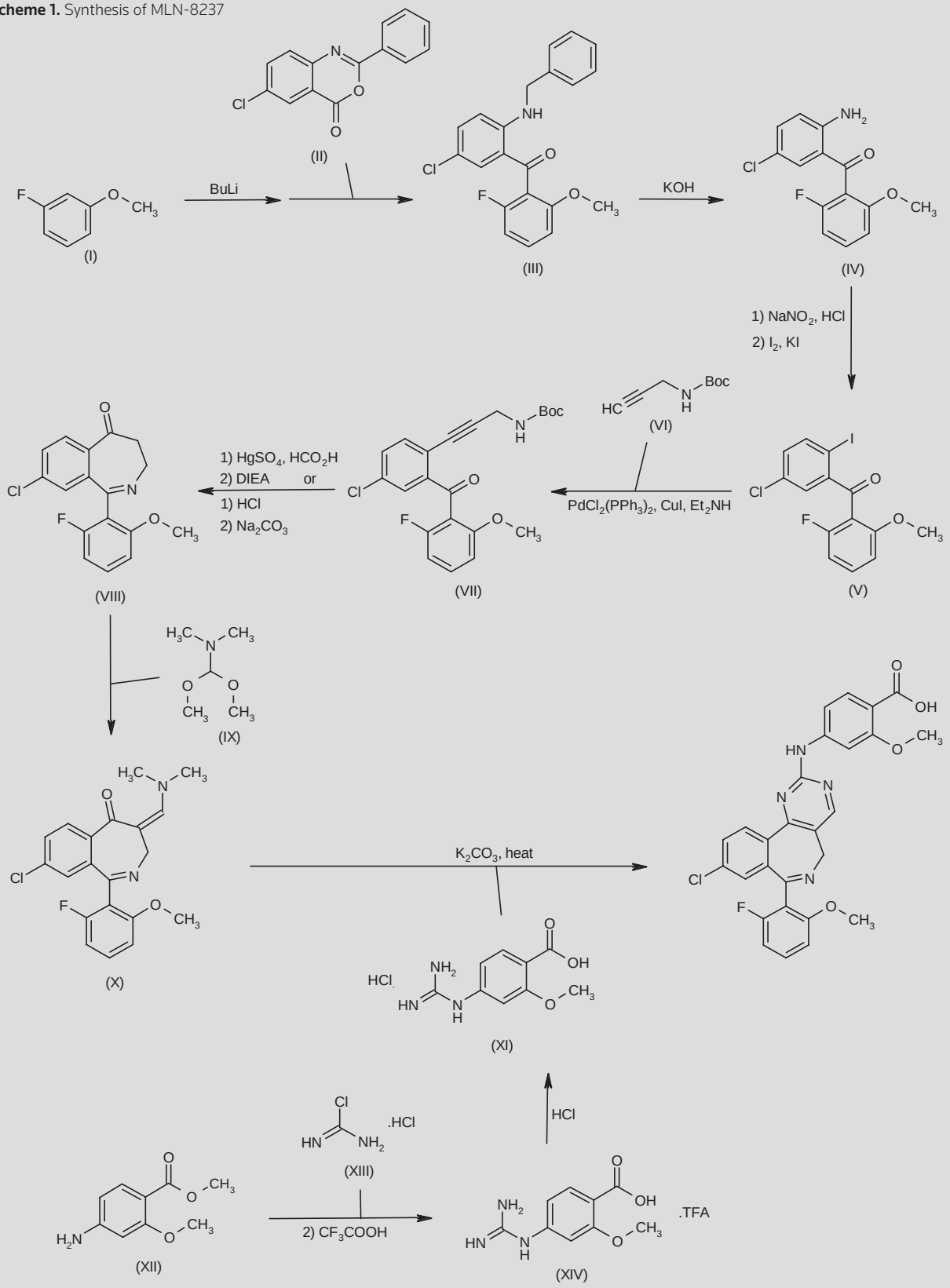
Condensation of the *ortho*-metalated derivative of 3-fluoroanisole (I) –generated in situ by treatment of anisole (I) with BuLi in THF at –78 °C– with 6-chloro-2-phenyl-3,1-benzoxazin-4-one (II) gives the diaryl ketone (III), which is *N*-deprotected by means of KOH in refluxing MeOH/H_2O, yielding the aniline derivative (IV). Diazotization of amine (IV) with $NaNO_2$ and HCl in AcOH/H_2O, followed by treatment with I_2 in the presence of KI in cold EtOAc/H_2O affords the aryl iodide (V). Iodobenzophenone (V) is then subjected to Heck coupling with *N*-Boc-propargylamine (VI) in the presence of $PdCl_2(PPh_3)_2$, CuI and Et_2NH in CH_2Cl_2 to provide adduct (VII), which is submitted sequentially to triple bond hydration, *N*-Boc deprotection and cyclization by sequential treatment with $HgSO_4$ and formic acid in CH_2Cl_2 at 0 °C, and then DIEA in CH_2Cl_2 or by treatment with HCl in dioxane/H_2O and then Na_2CO_3 in CH_2Cl_2 to give the 3,4-dihydro[2]benzoazepinone (VIII). Condensation of benzazepinone (VIII) with *N,N*-dimethylformamide dimethylacetal (IX) in toluene at 80 °C yields the 4-(dimethylaminomethylene)[2]benzoazepinone derivative (X) (1), which is finally condensed with methyl 4-guanidino-2-methoxybenzoate hydrochloride (XI) in the presence of K_2CO_3 in refluxing MeOH (2). Scheme 1.

Intermediate (XI) is prepared by condensation of methyl 4-amino-2-methoxybenzoate (XII) with chloroformamidine hydrochloride (XIII) in Me_2SO_2 at 120 °C, followed by acidification with TFA to yield methyl 4-guanidino-2-methoxybenzoate trifluoroacetate salt (XIV). Subsequent treatment of the trifluoroacetate salt with HCl at 80 °C provides the corresponding hydrochloride (XIV) (3). Scheme 1.

BACKGROUND

Cell cycle regulatory kinases including cyclin-dependent kinases (CDKs), Polo-like kinases (PLKs) and Aurora kinases regulate mitosis and consequent division of genetic material to two daughter cells (4, 5). Deregulation of the cell cycle or altered expression and function of these cell cycle regulatory kinases may cause aneuploidy, leading to tumorigenesis (5). New therapeutic approaches in cancer have been developed targeting these cell cycle regulatory kinases, partic-

Scheme 1. Synthesis of MLN-8237



ularly Aurora kinase-specific or Aurora kinase-selective inhibitors (6). In this review, the role of Aurora kinase A in tumorigenesis and the potential of Aurora kinase A inhibition by the Aurora kinase A-selective small-molecule inhibitor MLN-8237 as a novel therapeutic approach are discussed.

Over the last decade, the Aurora kinase family has been identified as critical regulators of mitosis in mammalian cells (7-9). The human genome expresses three homologous Aurora kinases: Aurora kinase A, B and C. Although Aurora kinase A and B are highly homologous, their localization and functions differ during mitosis: Aurora kinase A localizes to centrosomes in early S phase and to spindle microtubules proximal to the spindle poles (10), and shows dynamic localization during mitosis (10-14). Aurora kinase A functions in mitotic entry, centrosome maturation, spindle bipolarity and formation, regulating G_2/M transition, as well as meiotic maturation (12, 15). Aurora kinase A is necessary for centrosome separation after mitotic spindle formation. Conversely, in the absence of Aurora kinase A, γ-tubulin will accumulate in centrosomes, causing immature centrosomes; the mitotic spindle will not be separated, resulting in unseparated centrosomes; and cytokinesis, the separation of parental cytoplasm into two daughter cells, will not be completed. Since Aurora kinase A is required for cytokinesis, defective protein may cause aneuploidy characteristic of tumors.

Aurora kinases are activated by autophosphorylation at threonine residue 288 (Thr288) in the T loop (16). Additionally, the Aurora kinase A interaction with the microtubule-associated protein TPX2 stabilizes Aurora kinase A autophosphorylation at Thr288 (17-21).

Aurora kinase A shows distinct localization patterns in normal tissues, including nuclear expression in skin and colon, and both nuclear and cytoplasmic expression in oral mucosa, stomach, pancreatic gland, small intestine, testis and lymph node. Additionally, Aurora kinase A also shows cytoplasmic expression in highly proliferating cells such as endometrium and spermatocytes. Aurora kinase A and B have been extensively studied due to their overexpression in tumor cells. Defective chromatid segregation causes genetic instability, leading to tumorigenesis (11). During a normal cell cycle, the expression and activity of all Aurora kinases increase in mitosis and decrease rapidly during mitotic exit. During the G_2/M transition Aurora kinase A localizes with centrosomes and mitotic spindles in normal cells. However, in the majority of tumor cells, Aurora kinase A is constitutively expressed in the cytoplasm, thereby causing malignant transformation by inducing constitutive activation of normal cytoplasmic target proteins (22-24).

The human *AURKA* gene is located in the frequently amplified chromosome 20q13.2 region (12), and increased *AURKA* gene transcripts and protein expression have been reported in many malignant diseases, including ovarian, breast, bladder, colon and pancreatic cancers (25-34). Ectopic introduction of the *AURKA* gene in several cell lines confirmed an association between overexpression of Aurora kinase A and malignant transformation (35, 36), suggesting *AURKA* as an oncogene. Moreover, studies performed in ovarian cancer and carcinogen-induced rat mammary tumors have demonstrated that Aurora kinase A is overexpressed in early stages of tumor development, further indicating a tumor-promoting role for Aurora kinase A (24, 37, 38). Additionally, high expression of Aurora kinase A has been determined in primary colorectal tumor cells, in the colorectal cancer stem cell fraction and in stem cell-derived differentiated cells compared to normal colon tissue (39), suggesting Aurora kinase A as a novel target for colorectal cancer treatment.

Overexpression of Aurora kinase A disrupts cell cycle checkpoints such as spindle checkpoints activated by taxanes or nocodazole and DNA damage-induced G_2 checkpoints (40-42), thereby allowing genetically aberrant cells to undergo cell division. Additionally, Aurora kinase A overexpression can also lead to polyploidy by centrosome amplification as a consequence of failure in cytokinesis and uncontrolled multinucleation (43, 44).

Aurora kinase A also plays an important role in tumorigenesis by interacting with the tumor suppressor proteins p53, breast cancer type 1 susceptibility protein and CHFR (24-28, 44). The tumor suppressor protein p53 is a direct substrate for Aurora kinase A; conversely, p53 suppresses Aurora kinase A overexpression-induced centrosome amplification through GADD45 alpha activation. Aurora kinase A regulates Mdm2-mediated p53 degradation by phosphorylating p53 at serine 215. However, phosphorylation of p53 at serine 215 by Aurora kinase A suppresses p53 expression, as well as the p53 target genes *CDKN1A* and *PTEN*. Thus, Aurora kinase A overexpression with p53 inactivation induces tumor development. It has recently been reported that Aurora kinase A also regulates p73 transcription activity in p53-deficient cancer cell lines (28, 29). Additionally, Aurora kinase A phosphorylates the breast cancer type 1 susceptibility protein tumor suppressor protein at serine 308, whereas inhibition of Aurora kinase A-mediated breast cancer type 1 susceptibility protein phosphorylation induces decreased mitotic activity in mouse embryo fibroblasts (25). It has also been demonstrated that the mitotic checkpoint protein CHFR can regulate Aurora kinase A function by ubiquitination; conversely, downregulation of CHFR contributes to tumor development by inducing uncontrolled Aurora kinase A expression (26, 30).

Besides inactivation of tumor suppressor proteins, recent studies have shown that Aurora kinase A is involved in the regulation of glycogen synthase kinase GSK-3β and β-catenin/TCF complex transcriptional activity (31) in gastric cancer cells, as well as the induction of human telomerase reverse transcriptase in breast and ovarian cancers (32). Furthermore, constitutive activation of mitogen-activated protein kinase MAPK 1 leads to Aurora kinase A overexpression in pancreatic cancers (33). Therefore, Aurora kinase A directly interacts with several tumor suppressor genes and cell signaling pathways to regulate the cell cycle; in contrast, disruption of Aurora kinase A activity induces malignant transformation.

Since Aurora kinase A is a key mediator of mitosis and functions in malignant transformation, disruption of Aurora kinase expression or activity provides an attractive approach for anticancer therapy. Earlier studies with the inhibition of Aurora kinase A using small interfering RNA (siRNA) and antisense oligonucleotides showed antiproliferative effects in cancer cells (34, 45). Over the last decade, intensive studies focusing on inhibition of Aurora kinase A and/or B or pan-Aurora kinase activity in cancer cells led to the development of small-molecule inhibitors. Recent studies have shown that inhibition of Aurora kinase A induces cell cycle arrest at G_2/M, with abnormal microtubule assembly, whereas Aurora kinase B inhibition causes polyploidy in cancer cells. Inhibition of both Aurora kinase A and B in cells demonstrates a phenotype consistent with Aurora kinase B

inhibition (46). Two different types of Aurora kinase A inhibitors have been developed: type I inhibitors block the interaction between Aurora kinase A and substrate or cofactor, and type II inhibitors block serine/threonine-protein kinase activity. A large number of these novel small-molecule inhibitors of Aurora kinase A have recently entered phase I/II clinical studies.

PRECLINICAL PHARMACOLOGY

MLN-8237 is an orally bioavailable, second-generation, highly selective and reversible small-molecule inhibitor of Aurora kinase A. MLN-8237 is similar in structure to MLN-8054, the parent selective small-molecule inhibitor of Aurora kinase A (47-49). MLN-8237 is designed to avoid the benzodiazepine-like central nervous system effects (somnolence) observed with MLN-8054. It exhibits potent activity against Aurora kinase A (IC_{50} = 1 nM) in both enzyme and cell-based assays. MLN-8237 shows 200-fold greater selectivity for Aurora kinase A compared to the related Aurora kinase B. Moreover, MLN-8237 does not have any significant activity against a Novascreen panel of receptors and ion channels (49, 50).

Inhibition of Aurora kinase A targets proliferating cancer cells. Preclinical studies with MLN-8237 revealed that the compound induces disruption of mitotic spindle assembly, disruption of chromosome segregation and inhibition of cell proliferation in tumor cell lines and tumor xenograft models. Maris et al. have recently reported that MLN-8237 showed significant antitumor activity against most Pediatric Preclinical Testing Program (PPTP) tumor cell lines in vitro (median IC_{50} = 61 nM) (51). However, MLN-8237 has demonstrated differential antitumor effects in vivo using PPTP xenograft models. Oral MLN-8237 treatment (20 mg/kg twice daily for 5 days a week over a period of 6 weeks) significantly prolonged survival in 32 of 40 models tested, including rhabdoid, Wilms and Ewing tumors, rhabdomyosarcoma, neuroblastoma, medulloblastoma, ependymoma, glioblastoma and osteosarcoma, as well as B-cell precursor and T-cell acute lymphoblastic leukemia. Moreover, complete remissions have been observed in leukemia and neuroblastoma.

Preclinical studies have also suggested that MLN-8237 can synergize with other therapeutic agents such as rituximab in diffuse large B-cell lymphoma and the microtubule-targeted drugs docetaxel, paclitaxel and vincristine in several adult solid tumors (50, 51).

In addition to other Aurora kinase inhibitors, we have recently assessed the in vitro and in vivo activity of MLN-8237 against multiple myeloma (52). Treatment of cultured multiple myeloma cells with MLN-8237 resulted in mitotic spindle abnormalities and mitotic accumulation, as well as inhibition of cell proliferation through apoptosis and senescence. Moreover, MLN-8237 upregulated the expression of p53 and the tumor suppressor genes *CDKN1A* and *CDKN1B* in these cultured multiple myeloma cell lines. In vivo activity of MLN-8237 was confirmed using a murine xenograft model of human multiple myeloma. Tumor burden was significantly reduced and overall survival was significantly increased in animals treated with 30 mg/kg MLN-8237 for 21 days. Evaluation of combination therapies demonstrated that combining MLN-8237 with dexamethasone, doxorubicin or bortezomib may induce synergistic/additive activity against multiple myeloma.

SAFETY

Initial clinical evaluation of MLN-8237 in pediatric and adult cancers demonstrated that it is well tolerated. In adult cancers dose-limiting toxicities (DLTs) of MLN-8237 treatment included neutropenia, pancytopenia, stomatitis, somnolence, nausea, diarrhea, fatigue and alopecia, which were reversible with dose reduction (53). Longer follow-up is required to evaluate the effects of MLN-8237 on disease progression and quality of life.

CLINICAL STUDIES

The antitumor activity of MLN-8237 against various adult advanced solid tumors, lymphomas and multiple myeloma, as well as childhood cancers, is currently being evaluated in phase I/II clinical studies. MLN-8237 is being tested in a Children's Oncology Group (COG)-sponsored dose-escalating phase I/II clinical study (NCT00739427) in children with relapsed or refractory solid tumors or acute lymphoblastic leukemia. In this study, the dosing schedule has been designed parallel to the phase I clinical study in adult patients with advanced tumors: once- or twice-daily administration over a period of 7 days, followed by 2 weeks of recovery from the expected myelosuppression for up to 24 months (54).

In adults, the antitumor activity of MLN-8237 has been evaluated in early phase I clinical studies in patients with colorectal, non-small cell lung, head and neck, and ovarian cancers. The first phase I study examined the safety, pharmacokinetics and pharmacodynamics of MLN-8237 administered orally in 27 patients with advanced solid tumors. Patients received increasing doses of MLN-8237 orally once daily (q.d.) or twice daily (b.i.d.) for 7 days, followed by a 14-day recovery period, until DLT. DLTs were observed at 60-100 mg orally b.i.d., including neutropenia, pancytopenia, stomatitis and somnolence (54). The second phase I clinical study was conducted to assess dose-escalation treatment with MLN-8237. MLN-8237 was given orally for 7, 14 or 21 days, with a 2-week rest between cycles, to 65 patients (median age 62 years) with solid tumors, including colorectal, lung, ovary, head and neck, prostate and other cancers. Patients received 5-150 mg q.d. for 7 days or 25-70 mg q.d. for 14 or 21 days. DLTs included neutropenia, thrombopenia, somnolence and mucositis. The most common adverse events included nausea, diarrhea, fatigue and alopecia, which were reversible with dose reduction (53).

MLN-8237 combined with bortezomib is currently being evaluated in an ongoing clinical trial in multiple myeloma (NCT01034553). MLN-8237 has recently entered phase II clinical trials in patients with advanced solid and hematological malignancies to investigate its clinical antitumor activity. It has generally been well tolerated, with somnolence, nausea and neutropenia being the most common adverse events.

CONCLUSIONS

Aurora kinase A is a key regulator of the cell cycle and disruption of Aurora kinase A function leads to cell cycle arrest, inducing cell death. Aurora kinase A represents an attractive therapeutic target due to its overexpression in many tumor cells. Intensive studies have led to the development of small-molecule inhibitors of Aurora kinase A, and several early-phase clinical trials are ongoing. The Aurora

kinase A inhibitor MLN-8237 has shown promising tolerability in these early clinical trials, providing the basis for phase II clinical trials in a variety of cancers.

SOURCE

Millennium Pharmaceuticals, Inc. (US).

DISCLOSURES

Dr. Anderson is a member of the Board of Directors or Advisory Committees of Celgene, Millennium and Novartis. The other authors state no conflicts of interest.

REFERENCES

1. Claiborne, C.F., Payne, L.J., Boyce, R.J. et al. (Millennium Pharmaceuticals, Inc.). *Compounds and methods for inhibiting mitotic progression by inhibition of Aurora kinase.* EP 1771450, EP 1905773, JP 200753768, JP 2008285484, US 200525602, US 7572784, WO 2005111039.
2. Claiborne, C.F., Sells, T.B., Stroud, S.G. (Millennium Pharmaceuticals, Inc.). *Compounds for inhibiting mitotic progression*. EP 2086981, JP 2010510215, US 2008167292, WO 2008963525.
3. Sugiki, M., Sagi, K., Fujita, K., Kayahara, T., Takehana, S., Sakurai, K., Tashiro, K., (Ajinomoto Co., Inc.). *Amidinophenylpyruvic acid derivative*. US 2003109547, US 6710056, WO 2001042199.
4. Carmena, M., Ruchaud, S., Earnshaw, W.C. *Making the Auroras glow: Regulation of Aurora A and B kinase function by interacting proteins.* Curr Opin Cell Biol 2009, 21(6): 796-805.
5. Malumbres, M., Barbacid, M. *Cell cycle kinases in cancer*. Curr Opin Genet Dev 2007, 17(1): 60-5.
6. de Carcer, G., Perez de Castro, I., Malumbres, M. *Targeting cell cycle kinases for cancer therapy.* Curr Med Chem 2007, 14(9): 969-85.
7. Glover, D.M., Leibowitz, M.H., McLean, D.A., Parry, H. *Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles.* Cell 1995, 81(1): 95-105.
8. Kimura, M., Matsuda, Y., Eki, T. et al. *Assignment of STK6 to human chromosome 20q13.2—>q13.3 and a pseudogene STK6P to 1q41—>q42.* Cytogenet Cell Genet 1997, 79(3-4): 201-3.
9. Kimura, M., Kotani, S., Hattori, T. et al. *Cell cycle-dependent expression and spindle pole localization of a novel human protein kinase, Aik, related to Aurora of Drosophila and yeast Ipl1.* J Biol Chem 1997, 272(21): 13766-71.
10. Hannak, E., Kirkham, M., Hyman, A.A., Oegema, K. *Aurora-A kinase is required for centrosome maturation in Caenorhabditis elegans.* J Cell Biol 2001, 155(7): 1109-16.
11. Bolanos-Garcia, V.M. *Aurora kinases.* Int J Biochem Cell Biol 2005, 37(8): 1572-7.
12. Carmena, M., Earnshaw, W.C. *The cellular geography of aurora kinases*. Nat Rev Mol Cell Biol 2003, 4(11): 842-54.
13. Nigg, E.A. *Mitotic kinases as regulators of cell division and its checkpoints.* Nat Rev Mol Cell Biol 2001, 2(1): 21-32.
14. Marumoto, T., Zhang, D., Saya, H. *Aurora-A - A guardian of poles.* Nat Rev Cancer 2005, 5(1): 42-50.
15. Moore, A.S., Blagg, J., Linardopoulos, S., Pearson, A.D. *Aurora kinase inhibitors: Novel small molecules with promising activity in acute myeloid and Philadelphia-positive leukemias.* Leukemia 2010, 24(4): 671-8.
16. Walter, A.O., Seghezzi, W., Korver, W. et al. *The mitotic serine/threonine kinase Aurora2/AIK is regulated by phosphorylation and degradation.* Oncogene 2000, 19(42): 4906-16.
17. Eyers, P.A., Erikson, E., Chen, L.G., Maller, J.L. *A novel mechanism for activation of the protein kinase Aurora A.* Curr Biol 2003, 13(8): 691-7.
18. Bayliss, R., Sardon, T., Vernos, I., Conti, E. *Structural basis of Aurora-A activation by TPX2 at the mitotic spindle.* Mol Cell 2003, 12(4): 851-62.
19. Kapitein, L.C., Peterman, E.J., Kwok, B.H. et al. *The bipolar mitotic kinesin Eg5 moves on both microtubules that it crosslinks.* Nature 2005, 435(7038): 114-8.
20. Crane, R., Gadea, B., Littlepage, L. et al. *Aurora A, meiosis and mitosis.* Biol Cell 2004, 96(3): 215-29.
21. Giet, R., McLean, D., Descamps, S. et al. *Drosophila Aurora A kinase is required to localize D-TACC to centrosomes and to regulate astral microtubules*. J Cell Biol 2002, 156(3): 437-51.
22. Tanaka, T., Kimura, M., Matsunaga, K. et al. *Centrosomal kinase AIK1 is overexpressed in invasive ductal carcinoma of the breast.* Cancer Res 1999, 59(9): 2041-4.
23. Takahashi, T., Futamura, M., Yoshimi, N. et al. *Centrosomal kinases, HsAIRK1 and HsAIRK3, are overexpressed in primary colorectal cancers.* Jpn J Cancer Res 2000, 91(10): 1007-14.
24. Gritsko, T.M., Coppola, D., Paciga, J.E. et al. *Activation and overexpression of centrosome kinase BTAK/Aurora-A in human ovarian cancer.* Clin Cancer Res 2003, 9(4): 1420-6.
25. Ouchi, M., Fujiuchi, N., Sasai, K. et al. *BRCA1 phosphorylation by Aurora-A in the regulation of G2 to M transition.* J Biol Chem 2004, 279(19): 19643-8.
26. Yu, X., Minter-Dykhouse, K., Malureanu, L. et al. *Chfr is required for tumor suppression and Aurora A regulation.* Nat Genet 2005, 37(4): 401-6.
27. Katayama, H., Sasai, K., Kawai, H. et al. *Phosphorylation by aurora kinase A induces Mdm2-mediated destabilization and inhibition of p53.* Nat Genet 2004, 36(1): 55-62.
28. Liu, Q., Kaneko, S., Yang, L. et al. *Aurora-A abrogation of p53 DNA binding and transactivation activity by phosphorylation of serine 215.* J Biol Chem 2004, 279(50): 52175-82.
29. Dar, A.A., Belkhiri, A., Ecsedy, J. et al. *Aurora kinase A inhibition leads to p73-dependent apoptosis in p53-deficient cancer cells.* Cancer Res 2008, 68(21): 8998-9004.
30. Chaturvedi, P., Sudakin, V., Bobiak, M.L. et al. *Chfr regulates a mitotic stress pathway through its RING-finger domain with ubiquitin ligase activity. Cancer Res* 2002, 62(6): 1797-801.
31. Dar, A.A., Belkhiri, A., El-Rifai, W. *The aurora kinase A regulates GSK-3beta in gastric cancer cells.* Oncogene 2009, 28(6): 866-75.
32. Yang, H., Ou, C.C., Feldman, R.I. et al. *Aurora-A kinase regulates telomerase activity through c-Myc in human ovarian and breast epithelial cells.* Cancer Res 2004, 64(2): 463-7.
33. Furukawa, T., Kanai, N., Shiwaku, H.O. et al. *AURKA is one of the downstream targets of MAPK1/ERK2 in pancreatic cancer.* Oncogene 2006, 25(35): 4831-9.
34. Tatsuka, M., Sato, S., Kitajima, S. et al. *Overexpression of Aurora-A potentiates HRAS-mediated oncogenic transformation and is implicated in oral carcinogenesis.* Oncogene 2005, 24(6): 1122-7.
35. Zhou, H., Kuang, J., Zhong, L. et al. *Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation.* Nat Genet 1998, 20(2): 189-93.
36. Bischoff, J.R., Anderson, L., Zhu, Y. et al. *A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers*. EMBO J 1998, 17(11): 3052-65.
37. Jeng, Y.M., Peng, S.Y., Lin, C.Y., Hsu, H.C. *Overexpression and amplification of Aurora-A in hepatocellular carcinoma.* Clin Cancer Res 2004, 10(6): 2065-71.

38. Miyoshi, Y., Iwao, K., Egawa, C., Noguchi, S. *Association of centrosomal kinase STK15/BTAK mRNA expression with chromosomal instability in human breast cancers.* Int J Cancer 2001, 92(3): 370-3.

39. Cammareri, P., Scopelliti, A., Todaro, M. et al. *Aurora-a is essential for the tumorigenic capacity and chemoresistance of colorectal cancer stem cells.* Cancer Res 2010, 70(11): 4655-65.

40. Anand, S., Penrhyn-Lowe, S., Venkitaraman, A.R. *AURORA-A amplification overrides the mitotic spindle assembly checkpoint, inducing resistance to Taxol.* Cancer Cell 2003, 3(1): 51-62.

41. Jiang, Y., Zhang, Y., Lees, E., Seghezzi, W. *AuroraA overexpression overrides the mitotic spindle checkpoint triggered by nocodazole, a microtubule destabilizer.* Oncogene 2003, 22(51): 8293-301.

42. Marumoto, T., Hirota, T., Morisaki, T. et al. *Roles of aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells.* Genes Cells 2002, 7(11): 1173-82.

43. Meraldi, P., Honda, R., Nigg, E.A. *Aurora-A overexpression reveals tetraploidization as a major route to centrosome amplification in p53-/- cells.* EMBO J 2002, 21(4): 483-92.

44. Fujiwara, T., Bandi, M., Nitta, M. et al. *Cytokinesis failure generating tetraploids promotes tumorigenesis in p53-null cells.* Nature 2005, 437(7061): 1043-7.

45. Evans, R., Naber, C., Steffler, T. et al. *Aurora A kinase RNAi and small molecule inhibition of Aurora kinases with VE-465 induce apoptotic death in multiple myeloma cells.* Leuk Lymphoma 2008, 49(3): 559-69.

46. Yang, H., Burke, T., Dempsey, J. et al. *Mitotic requirement for aurora A kinase is bypassed in the absence of aurora B kinase.* FEBS Lett 2005, 579(16): 3385-91.

47. Manfredi, M.G., Ecsedy, J.A., Meetze, K.A. et al. *Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase.* Proc Natl Acad Sci U S A 2007, 104(10): 4106-11.

48. Pollard, J.R., Mortimore, M. *Discovery and development of aurora kinase inhibitors as anticancer agents.* J Med Chem 2009, 52(9): 2629-51.

49. Sells, T.S.S., Janowick, D., Hoar, K. et al. *MLN8237: An orally active small molecule inhibitor of Aurora A kinase in phase I clinical trials.* Proc Am Assoc Cancer Res (AACR) 2008, 49: Abst 237.

50. Zhang, M.H.J., Sells, T., Claiborne, C., Manfredi, M.G. *In vivo characterization of the Aurora A kinase inhibitor MLN8237 in subcutaneous and disseminated models of human cancer.* Proc Am Assoc Cancer Res (AACR) 2008, 49: Abst 5646.

51. Maris, J.M., Morton, C.L., Gorlick, R. et al. *Initial testing of the aurora kinase A inhibitor MLN8237 by the Pediatric Preclinical Testing Program (PPTP).* Pediatr Blood Cancer 2010, 55(1): 26-34.

52. Gorgun, G., Calabrese, E., Hideshima, T. et al. *A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma.* Blood 2010, 115(25): 5202-13.

53. Dees, E.C., Burris, H.A., Astsaturov, I.A. et al. *Phase I study of the investigational drug MLN8237, an Aurora A kinase (AAK) inhibitor, in patients (pts) with solid tumors.* J Clin Oncol [46th Annu Meet Am Soc Clin Oncol (ASCO) (June 4-8, Chicago) 2010] 2010, 28(15, Suppl.): Abst 3010.

54. Cervantes-Ruiperez, A., Elez, M.E., Rosello, S. et al. *Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of MLN8237, a novel selective Aurora A kinase (AAK) inhibitor, in patients (pts) with advanced solid tumors.* J Clin Oncol [45th Annu Meet Am Soc Clin Oncol (ASCO) (May 29-June 2, Orlando) 2009] 2009, 27(15, Suppl.): Abst 2565.