Benzo[e]pyridoindoles, novel inhibitors of the aurora kinases

Hoang T.M.-N., Favier B., Valette A., Barette C., Chi H.N., Lafanechere L., Grierson D.S., Dimitrov S., Molla A.

INSERM: U823 Institut Albert Bonniot, Université Joseph Fourier, La Tronche, France; GREPI/TIMC-IMAG CNRS: UMR 5525 - Université Joseph Fourier, Grenoble, France; CNRS: 5088 Université Paul Sabatier, Toulouse, France; CEA, DSV, Centre de Criblage Pour Molécules Bio-Actives, Grenoble, France; UMR 176 CNRS-Institut Curie, Institut Curie, Orsay, France; Faculty of Biology, Hanoi University of Sciences, VNU, Viet Nam; UJF Site Santé- La Tronche, Institut Albert Bonniot, INSERM U823 Eq 4, BP170, 38 042 Grenoble, Cedex 9, France

Abstract: Aurora kinases are serine/threonine protein kinases that are involved in cancer development and are important targets for cancer therapy. By high throughput screening of a chemical library we found that benzo[e]pyridoindole derivatives inhibited Aurora kinases. The most potent compound (compound 1) was found to be an ATP competitive inhibitor, which inhibited in vitro Aurora kinases at the nanomolar range. It prevented, ex vivo, the phosphorylation of Histone H3, induced mitosis exit without chromosome segregation, known phenomena observed upon Aurora B inactivation. This compound was also shown to affect the localization of Aurora B, since in the presence of the inhibitor the enzyme was delocalized on the whole chromosomes and remained associated with the chromatin of newly formed nuclei. In addition, compound 1 inhibited the growth of different cell lines derived from different carcinoma. Its IC_{50} for H358 NSCLC (Non-Small Cancer Lung Cells), the most sensitive cell line, was 145 nM. Furthermore compound 1 was found to be efficient towards multicellular tumor spheroid growth. It exhibited minimal toxicity in mice while it had some potency towards aggressive NSCLC tumors. Benzo[e]pyridoindoles represent thus a potential new lead for the development of Aurora kinase inhibitors. ©2009 Landes Bioscience.

Author Keywords: Aurora kinase; Chromosomal passenger complex; Mitosis; Mitotic slippage; Pyridoindoles; Small-molecule inhibitors

Index Keywords: aurora B kinase; aurora kinase inhibitor; benzo[e]pyridoindole derivative; histone H3; paclitaxel; unclassified drug; animal experiment; animal model; antineoplastic activity; article; cancer cell; cell viability; chromosomal localization; chromosome segregation; concentration response; controlled study; human; human cell; lung non small cell cancer; mitosis; mouse; nonhuman; protein expression; protein localization; protein phosphorylation; tumor growth; Animals; Cell Line, Tumor; Chromatin; Chromosome Segregation; Hela Cells; Histones; Humans; Indoles; Inhibitory Concentration 50; Mice; Phosphorylation; Protein Kinase Inhibitors; Protein-Serine-Threonine Kinases; Pyridones; Small Molecule Libraries; Mus

Year: 2009
Source title: Cell Cycle
Volume: 8
Issue: 5
Page : 765-772
Cited by: 1

Link: Scorpus Link
Chemicals/CAS: paclitaxel, 33069-62-4; Chromatin; Histones; Indoles; Protein Kinase Inhibitors; Protein-Serine-Threonine Kinases, 2.7.11.1; Pyridones; Small Molecule Libraries; aurora kinase, 2.7.1.-
Correspondence Address: Molla, A.; UJF Site Santé- La Tronche, Institut Albert Bonniot, INSERM U823 Eq 4, BP170, 38 042 Grenoble, Cedex 9, France; email: annie.molla@ujf-grenoble
ISSN: 15384101
PubMed ID: 19221479
Language of Original Document: English
Abbreviated Source Title: Cell Cycle
Document Type: Article
Source: Scopus
Authors with affiliations:

- Hoang, T.M.-N., INSERM: U823 Institut Albert Bonniot, Université Joseph Fourier, La Tronche, France, Faculty of Biology, Hanoi University of Sciences, VNU, Viet Nam
- Favier, B., GREPI/TIMC-IMAG CNRS: UMR 5525 - Université Joseph Fourier, Grenoble, France
- Valette, A., CNRS: 5088 Université Paul Sabatier, Toulouse, France
- Barette, C., CEA, DSV, Centre de Criblage Pour Molécules Bio-Actives, Grenoble, France
- Chi, H.N., UMR 176 CNRS-Institut Curie, Institut Curie, Orsay, France
- Lafanechère, L., CEA, DSV, Centre de Criblage Pour Molécules Bio-Actives, Grenoble, France
- Grierson, D.S., UMR 176 CNRS-Institut Curie, Institut Curie, Orsay, France
- Dimitrov, S., INSERM: U823 Institut Albert Bonniot, Université Joseph Fourier, La Tronche, France
- Molla, A., INSERM: U823 Institut Albert Bonniot, Université Joseph Fourier, La Tronche, France, UJF Site Santé- La Tronche, Institut Albert Bonniot, INSERM U823 Eq 4, BP170, 38 042 Grenoble, Cedex 9, France

References:

- Vader, G., Lens, S.M., The aurora kinase family in cell division and cancer (2008) Biochim biophys Acta, 1786, pp. 60-72
- Ruchaud, S., Carmena, M., Earnshaw, W.C., Chromosomal passengers conducting cell division (2007) Nat Rev Mol Cell Biol, 8, pp. 798-812
- Sardon, T., Peset, I., Petrova, B., Vernos, I., Dissecting the role of Aurora A during spindle assembly (2008) EMBO J, 27, pp. 2567-2579
- Hannak, E., Kirkham, M., Hyman, A.A., Oegema, K., Aurora-A kinase is required for centrosome maturation in Caenorhabditis elegans (2001) J Cell Biol, 155, pp. 1109-1116
- Seki, A., Coppinger, J.A., Jang, C.Y., Yates, J.R., Fang, G., Bora and the kinase Aurora A cooperatively activate the kinase Plk1 and control mitotic entry (2008) Science, 320, pp. 1655-1658
- Lens, S.M., Medema, R.H., The survivin/Aurora B complex: Its role in coordinating tension and attachment (2003) Cell Cycle, 2, pp. 507-510
- Ditchfield, C., Johnson, V.L., Tighe, A., Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2 and Cenp-E to kinetochores (2003) J Cell Biol, 161, pp. 267-280
- Ditchfield, C., Keen, N., Taylor, S.S., The Ipl1/Aurora kinase family: Methods of inhibition and functional analysis in mammalian cells (2005) Methods Mol Biol, 296, pp. 371-381
- Sen, S., Zhou, H., White, R.A., A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is amplified and overexpressed in human breast cancer cell lines (1997) Oncogene, 14, pp. 2195-2200

- Bischoff, J.R., Anderson, L., Zhu, Y., A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers (1998) EMBO J, 17, pp. 3052-3065
- Giet, R., Petretti, C., Prigent, C., Aurora kinases, aneuploidy and cancer, a coincidence or a real link? (2005) Trends Cell Biol, 15, pp. 241-250
- Keen, N., Taylor, S., Aurora-kinase inhibitors as anticancer agents (2004) Nat Rev Cancer, 4, pp. 927-936
- Girdler, F., Gascoigne, K.E., Eyers, P.A., Validating Aurora B as an anti-cancer drug target (2006) J Cell Sci, 119, pp. 3664-3675
- Jackson, J.R., Patrick, D.R., Dar, M.M., Huang, P.S., Targeted anti-mitotic therapies: Can we improve on tubulin agents? (2007) Nat Rev Cancer, 7, pp. 107-117
- Hauf, S., Cole, R.W., LaTerra, S., The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint (2003) J Cell Biol, 161, pp. 281-294
- Gadea, B.B., Ruderman, J.V., Aurora kinase inhibitor ZM447439 blocks chromosome-induced spindle assembly, the completion of chromosome condensation, and the establishment of the spindle integrity checkpoint in Xenopus egg extracts (2005) Mol Biol Cell, 16, pp. 1305-1318
- Harrington, E.A., Bebbington, D., Moore, J., VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo (2004) Nat Med, 10, pp. 262-267
- Fancelli D, Moll J, Varasi M, et al. 1,4,5,6-tetrahydropyrrolo[3,4-c] pyrazoles: identification of a potent aurora kinase inhibitor with a favorable antitumor kinase inhibition profile. J Med Chem 2006
- 49:7247-51Soncini, C., Carpinelli, P., Gianellini, L., PHA-680632, a novel Aurora kinase inhibitor with potent antitumoral activity (2006) Clin Cancer Res, 12, pp. 4080-4089
- Hoar, K., Chakravarty, A., Rabino, C., MLN8054, a small-molecule inhibitor of Aurora A, causes spindle pole and chromosome congression defects leading to aneuploidy (2007) Mol Cell Biol, 27, pp. 4513-4525
- Gautschi, O., Heighway, J., Mack, P.C., Purnell, P.R., Lara Jr, P.N., Gandara, D.R., Aurora kinases as anticancer drug targets (2008) Clin Cancer Res, 14, pp. 1639-1648
- Bain, J., Plater, L., Elliott, M., The selectivity of protein kinase inhibitors: A further update (2007) Biochem J, 408, pp. 297-315
- Noronha, G., Cao, J., Chow, C.P., Inhibitors of ABL and the ABL-T315I mutation (2008) Curr Top Med Chem, 8, pp. 905-921
- Badouel, C., Körner, R., Frank-Vaillant, M., Couturier, A., Nigg, E.A., Tassan, J.P., M-phase MELK activity is regulated by MPF and MAPK (2006) Cell Cycle, 5, pp. 883-889
- Cheetham, G.M., Charlton, P.A., Golec, J.M., Pollard, J.R., Structural basis for potent inhibition of the Aurora kinases and a T315I multi-drug resistant mutant form of Abl kinase by VX-680 (2007) Cancer Lett, 251, pp. 323-329
- Cheetham, G.M., Knegtel, R.M., Coll, J.T., Crystal structure of aurora-2, an oncogenic serine/threonine kinase (2002) J Biol Chem, 277, pp. 42419-42422
- Bayliss, R., Sardon, T., Vernos, I., Conti, E., Structural basis of Aurora-A activation by TPX2 at the mitotic spindle (2003) Mol Cell, 12, pp. 851-862
- Sessa, F., Mapelli, M., Ciferri, C., Mechanism of Aurora B activation by INCENP and inhibition by hesperadin (2005) Mol Cell, 18, pp. 379-391
- Alvarez, M., Roman, E., Santos, E.S., Raez, L.E., New targets for non-small-cell lung cancer therapy (2007) Expert Rev Anticancer Ther, 7, pp. 1423-1437
- Zhang, J.H., Chung, T.D., Oldenburg, K.R., A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays (1999) J Biomol Screen, 4, pp. 67-73
- Nguyen, C.H., Bisagni, E., Lavelle, F., Bissery, M.C., Huel, C., Synthesis and antitumor properties of new 4-methyl-substituted-

pyrido[4,3-b]indoles (gamma-carbolines) (1992) Anticancer Drug Des, 7, pp. 219-233

- Delacour-Larose, M.M.A., Skoufias, D.A., Margolis, R.L., Dimitrov, S., Distinct dynamics of Aurora B and Survivin during mitosis (2004) Cell Cycle, 3, pp. 1418-1426
- Del Duca, D., Werbowetski, T., Del Maestro, R.F., Spheroid preparation from hanging drops: Characterization of a model of brain tumor invasion (2004) J Neurooncol, 67, pp. 295-303
- Delacour-Larose, M., Thi, M.N., Dimitrov, S., Molla, A., Role of survivin phosphorylation by aurora B in mitosis (2007) Cell Cycle, 6, pp. 1878-1885