Jadomycin B, an Aurora-B kinase inhibitor discovered through virtual screening

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Abstract

Aurora kinases have emerged as promising targets for cancer therapy because of their critical role in mitosis. These kinases are well-conserved in all eukaryotes, and IPI1 gene encodes the single Aurora kinase in budding yeast. In a virtual screening attempt, 22 compounds were identified from nearly 15,000 microbial natural products as potential small-molecular inhibitors of human Aurora-B kinase. One compound, Jadomycin B, inhibits the growth of ipl1-321 temperature-sensitive mutant more dramatically than wild-type yeast cells, raising the possibility that this compound is an Aurora kinase inhibitor. Further in vitro biochemical assay using purified recombinant human Aurora-B kinase shows that Jadomycin B inhibits Aurora-B activity in a dose-dependent manner. Our results also indicate that Jadomycin B competes with ATP for the kinase domain, which is consistent with our docking prediction. Like other Aurora kinase inhibitors, Jadomycin B blocks the phosphorylation of histone H3 on Ser10 in vitro. We also present evidence suggesting that Jadomycin B induces apoptosis in tumor cells without obvious effects on cell cycle. All the results indicate that Jadomycin B is a new Aurora-B kinase inhibitor worthy of further investigation. [Mol Cancer Ther 2008;7(8):2386–93]

Introduction

In mammals, there are three Aurora kinases, Aurora-A, B, and C, which display >60% sequence identity (1). Although the catalytic domains of the three kinases are highly conserved, they show distinct subcellular localization and biological function (2, 3). Aurora-A, which is required for centrosome maturation and separation, localizes to centrosomes from early S phase to late M phase (4). Aurora-B is a component of chromosomal passenger complex, whose function in mitosis has been extensively studied. In addition to Aurora-B, the chromosomal passenger complex contains Survivin, Borealin, and inner centromere protein (5–7). The chromosomal passenger complex associates with centromeric regions of chromosomes in the early stages of mitosis, but it translocates to microtubules after the onset of anaphase. When cells undergo cytokinesis, the chromosomal passenger complex accumulates at the spindle midzone and finally concentrates at the midbody. As a serine/threonine kinase, Aurora-B phosphorylates histone H3 at Ser10, but the functional significance of this modification remains uncertain (8). Recent data from both yeast and mammal suggest that Aurora-B kinase activity is necessary for correct microtubule-kinetochore attachments, chromosome alignment and segregation, as well as cytokinesis (9). Aurora-C is highly expressed in testis along with other two human Aurora kinases and may play a role in tumorigenesis, especially in the absence of p53 (10, 11). Recent data indicate that Aurora-C acts such as Aurora-B in its localization during mitosis, and it is able to complement Aurora-B kinase function (12).

Accumulating evidence indicates that Aurora kinases are overexpressed in a wide range of tumor cells, including breast cancer (13, 14), colon cancer (15–17), pancreatic cancer (18), ovarian cancer (19), and gastric cancer (20). A recent systematic analysis of Aurora kinase mRNA levels in multiple primary tumors indicates that Aurora-A and B are significantly overexpressed (21). Because aberrant Aurora kinases can lead to errors in chromosome alignment and segregation, Aurora kinases are promising targets for antitumor drugs. Moreover, Aurora kinases are only expressed during mitosis, thus the inhibition of Aurora kinases will have no effect on quiescent cells, which makes Aurora kinases more attractive targets for anticancer therapy (22).

An effective approach to inhibit kinases is the blockage of their interaction with substrates. Therefore, molecules that show similar structure to the kinase substrates may function as competitive inhibitors. Three small-molecular inhibitors of Aurora kinases, ZM447439, Hesperadin, and VX-680, have recently been described (23–25). All three
molecules show antitumor activity \textit{in vitro} and some \textit{in vivo}, indicating the great potential of Aurora kinase inhibitors as antitumor drugs (26, 27). We are interested in identifying new Aurora kinase inhibitors from microbial natural products. The available crystal structure of Aurora-B kinase was used for virtual database screening (28). Jadomycin B was found to be able to occupy the ATP binding pocket of Aurora-B kinase by forming hydrogen bonds with amino acid residues around the pocket. The subsequent biochemical and genetic analysis confirms that Jadomycin B is an Aurora-B inhibitor. First, a yeast mutant allele that exhibits compromised Ipl1 (the yeast homologue of Aurora-B kinase) showed more dramatic sensitivity to Jadomycin B. We also showed that Jadomycin B inhibited the kinase activity of Aurora-B \textit{in vivo} and \textit{in vitro}. Finally, we observed that Jadomycin B induced apoptosis at lower concentration without disturbing cell cycle progression. Further investigations are necessary to explore the potential of Jadomycin B as an anticancer drug.

\textbf{Materials and Methods}

\textbf{Structure-Based Virtual Screening}

To identify potential inhibitors of Aurora-B kinase, the crystal structure of Aurora-B solved at 1.8-Å resolution was retrieved from the Protein Data Bank (PDB ID code 2BFY). The compound database used in our virtual screening is Microbial Natural Product Database developed by Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences, which contains the structural information of ~15,000 microbial natural products. In this study, the ATP-binding pocket of Aurora-B was the target of interest and the active sites were defined as all atoms within a radius of 6.5 Å from Hesperadin cocrystallized in the ATP-binding pocket. A docking program FlexX encoded in SYBYL7.1 (Tripos Inc) that uses an incremental construction algorithm was applied to optimize the interaction between flexible ligands and the rigid binding sites. To obtain an optimal starting conformation, all ligands were minimized using Tripos standard force field and Gasteiger-Hückel atomic partial charges with termination gradient assigned 0.42 J/(mol nm) before docking. As for Aurora-B protein, all crystal water molecules were removed from the original structure, hydrogen was added using Biopolymer module in SYBYL, and standard AMBER atomic charges were assigned. During soft docking simulations, the free energy of binding was calculated mainly by the sum of hydrogen bonds and hydrophobic interactions. The sum of the lowest estimated free energy from various binding conformations of each ligand was calculated and ranked by CScore function in SYBYL with default variables. One hundred fifty compounds with top docking score were selected as candidates. Among them, 22 compounds were obtained.

\textbf{Determination of the Activity of Selected Compounds Using Budding Yeast}

Wild-type and \textit{ipl1-321} mutant yeast strains were used for this purpose. Saturated yeast cells were 1/100 diluted into YPD (1% yeast extract, 2% peptone, and 2% glucose) medium containing tested compound at final concentration 10 μg/mL. After incubation at 25°C for 24 h, the growth of the yeast cultures in the presence of tested compounds was determined by measuring OD\textsubscript{600}.

\textbf{In vitro Aurora-B Kinase Activity Assays}

To determine the inhibition of Aurora-B kinase activity by Jadomycin B, the Aurora-B kinase activity assay kit (Cell Signaling Technology) was used according to the manufacturer’s instruction. Briefly, 100 ng purified recombinant human Aurora-B kinase was added to a 100 μL reaction mixture containing 1× kinase buffer and 25 μmol/L cold ATP in the presence of different concentrations of Jadomycin B (ranging from 10^{-4} to 10^{-10} mol/L). After incubation at room temperature for 15 min, biotinylated peptide substrate (Cell Signaling Technology) was added to each reaction mixture at a final concentration of 1.5 μmol/L, and the mixtures were further incubated for 30 min. A parallel control experiment was done under the same conditions without Jadomycin B. The reaction was stopped by addition of 50 μmol/L EDTA (pH 8). Then, 25 μL reaction mixture was transferred to a streptavidin-coated 96-well plate (PerkinElmer, Inc.) and incubated at room temperature for 60 min. After washing thrice with PBS/T, the phospho-PLK (Ser10) antibody (Cell Signaling Technology) was added to the plate for further incubation at 37°C for 120 min. After washing, FITC-labeled secondary antibody (Santa Cruz) was added. After incubation at room temperature for 30 min, the plate was finally washed five times and the fluorescence signal was determined with BMG Polarstar Galaxy (Germany) at 535 nm. The inhibition ratio by Jadomycin B at each concentration was calculated according to the following equation: \( \% \text{Inhibition} = 100 \times (1 - \text{counts}_{\text{treated}}/\text{counts}_{\text{control}}) \). The inhibition curve was then fitted by OriginPro7.5 program, and the IC\textsubscript{50} value of Jadomycin B was determined.

To determine the mode of inhibition of Aurora-B by Jadomycin B, the kinase activity was also examined in the presence of different concentrations of ATP (25, 50, 75, 100, and 200 μmol/L). The inhibition ratio of Aurora-B kinase activity by Jadomycin B at various concentrations was calculated as described above, and the inhibition curve was fitted. The IC\textsubscript{50} value of Jadomycin B at each ATP concentration was then determined and a linear fit was made with all five IC\textsubscript{50} values. The \( K_i \) was determined from the intercept of the plot of [ATP] versus IC\textsubscript{50} values (IC\textsubscript{50} = \( K_i/K_m \text{[ATP]} + K_i \)).

\textbf{Cell Growth Assay}

AS49, HeLa, and MCF-7 cell lines were cultured in 96-well tissue culture plates at a cell density of 5,000 cells per well in RPMI 1640 or MEM containing 10% fetal bovine serum and 2 mMol/L l-glutamine. After attachment overnight, the medium was replaced and cells were incubated with increasing concentrations of Jadomycin B or its two derivatives, Jadomycin S and T (ranging from \( 10^{-4} \) to \( 10^{-8} \) mol/L). After treatment for 48 h, 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
assays were carried out in triplication. The concentration-viability curves were fitted and IC_{50} values were determined. Cells were also plated at a cell density of 10,000 cells per well in 6-well tissue culture plates. After attachment overnight, cells were treated with 0, 5, or 10 μg/mL Jadomycin B for 96 h. Cells were detached every 24 h by trypsinization to count the cell number. All experiments were repeated thrice.

**Fluorescence-Activated Cell Sorting**

A549 cells in exponential growth phase were treated with 0 or 5 μg/mL Jadomycin B for up to 48 h. Cells collected at the indicated times were fixed and stained with Propidium Iodide. Fluorescence-activated cell sorting (FACS) analysis was done to determine the percentage of apoptotic cells and cell cycle distribution by using the EPICS XL flow cytometer and System II software.

**Detection of Chromatin Condensation and Apoptotic Body**

Hoechst 33342 is a fluorescence dye that can be embedded in DNA double helix and emit blue fluorescence when excited with UV light. Treated and untreated A549 cell samples with 5 μg/mL Jadomycin B for 48 h were...
stained with 100 ng/mL Hoechst 33342 for 10 min in dark. Stained cells were visualized with a Nikon ECLIPSS TE2000-U fluorescence microscope (Japan) at 100 and 400 magnification. Apoptotic cells show brightly stained nuclei because of the chromosome condensation and the appeared apoptotic bodies.

**Results**

**Identification of Jadomycin B through Structure-Based Virtual Screening**

The crystal structure of Aurora-B shows that Aurora-B is composed of two homotypal subunits. Each subunit has two protein kinase domains, the NH2-terminal lobe (residues 86–174) rich in β-strands and COOH-terminal lobe (residues 175–347) that mainly consists of a α-helix. The NH2-terminal lobe offers the binding sites of nucleotides and kinase regulators, whereas the COOH-terminal lobe contains the active center where substrates are docked and catalytic reactions occur. The ATP-binding pocket that is composed of several spatially close residues (Lys122, Lys103, Glu171, Ala173, Leu99, Val1107, and Glu177) lies at the interface between the two lobes. Figure 1A shows the crystal structure of Aurora-B with Hesperadin, a known Aurora-B–competitive inhibitor docked in the ATP-binding pocket. The indolinone moiety of Hesperadin occupies the catalytic cleft with the oxygen and nitrogen atoms of this moiety hydrogen bonded to Glu171 and Ala173 (28). Also, the sulfur and oxygen atoms of the sulfonamide moiety are hydrogen bonded to Lys122 and Lys103, occupying the position where the α-phosphate of ATP should be. The central phenyl ring of Hesperadin occupies the entry site to the catalytic cleft by van der Waals contact with other residues.

The protein structure was extracted from the 2bfy.pdb file, and structure-based virtual screening was done. One hundred fifty compounds with top docking score were selected as candidates. Among them, 22 were obtained, including Jadomycin B, a natural product (MW 563) isolated from *Streptomyces venezuelae* (Fig. 1D). The docking data showed that Jadomycin B could fit into the catalytic cleft of Aurora-B kinase and bind strongly to the residues surrounding the cleft (Fig. 1B). Elaborate docking indicates that Jadomycin B occupies the ATP-binding pocket of the active center of Aurora-B with multiple interactions with the residues around the pocket: the two hydroxyls of L-digitoxose are hydrogen bonded to Glu171 and Ala173, whereas the two oxygen atoms of the oxazolone ring are hydrogen bonded to Lys122 and Lys103, respectively. At the same time, the hydroxyl of the solvent-exposed angular phenyl ring in Jadomycin B binds to Glu177 with hydrogen bond, occupying the entry site to the catalytic cleft in Aurora-B (Fig. 1C).
Because Ipl1 kinase is essential for chromosome segregation, its inhibition will stop cell growth. *ipl1-321* is a temperature-sensitive mutant that grows well at 25°C but fails to grow at the restrictive temperature (37°C; ref. 30). Published data indicate that the Ipl1 kinase activity is compromised even when incubated at the permissive temperature 25°C (31). We reason that *ipl1-321* mutant cells should exhibit more dramatic sensitivity to Aurora-B inhibitors. Therefore, we examined the growth of wild-type and *ipl1-321* cells in the presence of 10 μg/mL of the 22 compounds, including Jadomycin B. After 24 h of incubation, the presence of 10 μg/mL Jadomycin B inhibited the growth of *ipl1-321* cells almost completely compared with the untreated control, whereas the growth of wild-type cells was uninhibited. Other compounds did not show any toxicity to yeast cells or exhibited similar toxicity to wild-type and *ipl1-321* mutant cells (Fig. 2B). We also tested the effect of two Jadomycin derivatives, Jadomycin S and Jadomycin T, on the growth of *ipl1-321* mutant cells, but neither showed inhibitory effect at 10 μg/mL (data not shown).

To further determine whether the toxicity of Jadomycin B is due to its inhibition of Ipl1 kinase, we compared the growth inhibition on wild-type and *ipl1-321* mutant cells by Jadomycin B at different concentrations. At 5 μg/mL, Jadomycin B inhibited 50% of the growth of *ipl1-321* mutant cells, but there is little growth inhibition for wild-type cells. In the presence of 100 μg/mL of Jadomycin B, the growth of wild-type cells was inhibited by 60% (Fig. 2C). The different sensitivity of wild-type and *ipl1-321* cells indicates that Jadomycin B could be an unidentified Aurora-B inhibitor.

**Jadomycin B Inhibits the Kinase Activity of Purified Recombinant Aurora-B**

As the budding yeast Ipl1 kinase is the homologue of mammalian Aurora-B kinase, the result from yeast cells suggests that Jadomycin B might inhibit the kinase activity of mammalian Aurora-B. To test this possibility, we examined the inhibition of purified human Aurora-B kinase by Jadomycin B using ELISA (Enzyme-linked ImmunoSorbent Assay). The kinase activity of Aurora-B, as indicated by fluorescence counts, was inhibited by micromolar concentration of Jadomycin B in a dose-dependent fashion, with an IC_{50} value of 10.5 μmol/L (Fig. 3A). As controls, we also tested the inhibitory effect of Jadomycin S and Jadomycin T on Aurora-B under the same condition, no inhibitory activity was detected (data not shown).

We next sought to determine the mode of Jadomycin B-dependent inhibition of Aurora-B kinase. We speculate that Jadomycin B inhibits Aurora-B by preventing the access of ATP to the kinase domain based on the structure analysis. Therefore, the inhibition of the kinase activity by Jadomycin B was analyzed in the presence of ATP at different concentrations (25, 50, 75, 100, or 200 μmol/L). The IC_{50} values with a given concentration of ATP was determined by fitting the inhibition curve and they were 12.46 μmol/L (25 μmol/L ATP), 16.60 μmol/L (50 μmol/L ATP), 24.50 μmol/L (75 μmol/L ATP), 32.16 μmol/L (100 μmol/L ATP), and 53.09 μmol/L (200 μmol/L ATP; Fig. 3B). The titration experiments using 5 different concentrations of ATP revealed a competitive inhibition of Aurora-B kinase by Jadomycin B with respect to ATP, and the K_{i} of Aurora-B by Jadomycin B is 6.8 μmol/L.

**Figure 4.** Jadomycin B inhibits the growth of several human cancer cell lines in a dose-dependent manner. **A**, A549, HeLa, and MCF-7 cells were exposed to increasing concentrations of Jadomycin B, Jadomycin S, and Jadomycin T for 48 h. The IC_{50} values were determined as described in Materials and Methods; columns, mean from three independent experiments; bars, SD. **B**, A549, HeLa, and MCF-7 cells were treated with different concentrations of Jadomycin B for 96 h. Cells were detached by trypsinization and counted every 24 h as described in Materials and Methods. **JB**, Jadomycin B.
Jadomycin B Inhibits the Proliferation of Cancer Cells

It has been reported that Jadomycin B inhibits the proliferation of IM-9, IM-9/Bcl-2, HepG2, and H460 cells (32). We examined the effects of Jadomycin B on the growth of other three cancer cell lines, A549, HeLa, and MCF-7. The growth curves indicated that all these cell lines were sensitive to Jadomycin B and the growth inhibition is in a dose-dependent manner (Fig. 4B). The IC₅₀ values of Jadomycin B and its two derivatives determined by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assays against these cancer cell lines are shown in Fig. 4A. Although A549 cells are most sensitive to Jadomycin B, the inhibitory potency did not differ significantly among these cell lines.

Jadomycin B Induces Apoptosis without Blocking Cell Cycle

FACS analysis was used to examine the mechanism of cell growth inhibition by Jadomycin B. Jadomycin B was added to A549 cell cultures in the exponential growth phase to a final concentration of 5 μg/mL. Treated and untreated cell samples were taken at 3, 12, 24, and 48 hours and fixed for FACS analysis. Although treatment with 5 μg/mL Jadomycin B induced an increase of cells in S phase by 2%, the difference between treated and untreated cells was so negligible that no obvious accumulation of cells in a specific cell cycle stage was observed, indicating that Jadomycin B does not block cell cycle at this concentration (Fig. 5B). Instead, we found increased cell population with sub-G₁ content of DNA (Fig. 5A), suggesting that apoptosis occurs. After 3 hours of incubation, there was almost no difference in the percentage of apoptotic cells between the treated and untreated cells. After longer exposure to Jadomycin B, however, the portion of apoptotic cells in treated samples increased to 17.8%, 44%, and 71.7% at 12, 24, and 48 hours, respectively, whereas those of untreated sample remained at <5% (Fig. 5A). Hochest 33342 staining confirmed that more and more cells underwent apoptosis after long-time exposure to Jadomycin B, as indicated by the appearance of brightly stained compressed chromosomes (Fig. 5C). Meanwhile, the apoptotic body could be detected at a ×400 magnification under a fluorescence microscope (Fig. 5C).

Jadomycin B Inhibits Histone H₃ Phosphorylation

It has been shown that Aurora-B kinase phosphorylates histone H3 on serine 10. We reason that this phosphorylation should be impaired in the presence of Jadomycin B if it inhibits the activity of Aurora-B kinase. To test this idea, we examined the phosphorylation of histone H3 in A549 cells after 24 hours of treatment with Jadomycin B at different concentrations. In untreated cells, a clear

![Figure 5.](Image)
Jadomycin B inhibits Aurora-B kinase

Figure 6. Jadomycin B inhibits Aurora-B–dependent H3 phosphorylation in a dose-dependent manner. **A**, Jadomycin B inhibits H3 phosphorylation in A549 cells. Jadomycin B was added into the cell cultures to different concentrations. After incubation for 24 h, cells were harvested and 30 μg protein from each sample was subjected to SDS-PAGE and Western blot analysis with the anti–phospho-H3 (Ser10) antibody. **B**, H3 phosphorylation in HeLa and HepG2 cells treated with Jadomycin B. Cells were cultured in the absence and presence of 10 μg/mL Jadomycin B for 24 h. The cells were then harvested for protein preparation. Thirty micrograms of protein were subjected to SDS-PAGE and Western blot analysis with anti–phospho-H3 antibody. **C**, quantitative analysis of the inhibition of H3 phosphorylation in A549 cells by Jadomycin B. H3 phosphorylation in the presence of different concentrations of Jadomycin B was measured by grayscale scanning after Western blotting. The percentage of phospho-H3 (P-H3) phosphorylation was determined by using untreated cells as control; columns, mean (n = 3); bars, SD.

Discussion

Recent studies have showed that Aurora kinases are implicated in tumorigenesis, therefore they are thought to be promising targets for anticancer drug development (33, 34). Although Aurora-A and B are always coexpressed, Aurora-B is believed to be the primary target on the basis of the observation that inhibition of this kinase results in a catastrophic mitosis (35, 36). Because the Aurora kinases are highly conserved, and the function of Aurora-B in mammals is similar with that of Ipl1 in budding yeast (36), it is reasonable to use yeast cells to evaluate the bioactivity of the compounds obtained. In this study, the compound that showed inhibitory effect on ipl1-321 mutant was subsequently proved to be able to inhibit the purified Aurora-B kinase. This testified the functional parallelism and credibility of yeast cells in screening Aurora-B inhibitors. Recently, budding yeast has been used as a model system in our laboratory to investigate the antitumor mechanism of DH334, a β-carboline derivative. The data from yeast indicate that DH334 inhibits the activity of cyclin-dependent kinase (37). Because of the availability of the powerful genetic and biochemical tools and the short doubling time, yeast cells can be used for extensive screen and mechanistic studies for anticancer drugs.

In this study, we used computational screening to identify small molecules that inhibit Aurora-B kinase from 15,000 microbial natural products. Among the 22 candidate compounds tested, Jadomycin B exhibited specific inhibition of Aurora-B kinase on the basis of the following observations. First, Jadomycin B is more toxic to ipl1-321 mutant cells, in which the kinase activity of Ipl1 (Aurora-B homologue in budding yeast) is compromised. Second, the kinase activity of recombinant human Aurora-B kinase is inhibited by Jadomycin B in vitro. Finally, we showed that Aurora-B–dependent phosphorylation of histone H3 at serine 10 decreased in the presence of Jadomycin B. Therefore, we conclude that Jadomycin B is a new Aurora-B inhibitor.

Several Aurora kinase inhibitors have been identified, including Hesperadin, ZM447439, and VX-680 (23–25). All these compounds inhibit Aurora-B kinase phosphorylation and prevent cell division. Moreover, VX-680 induces apoptosis in several tumor cell lines. Here, we showed that Jadomycin B also induced apoptosis at 5 μg/mL, but no obvious cell cycle disturbance was observed. For instance, FACS analysis did not show polyploid cells after treatment with 5 μg/mL Jadomycin B. One possibility is that Jadomycin B inhibits other kinases more efficiently and results in apoptosis. Another possible explanation is that Jadomycin B does not compromise the spindle checkpoint function as other inhibitors do. Therefore, more work needs to be done to determine the specificity of Jadomycin B against other kinases, including Aurora-A, Aurora-C, PLK et al. In addition to Jadomycin B, Jadomycin S and T also showed inhibitory effects on proliferation of IM-9, IM-9/Bcl-2, HepG2, and H460 cells (32). In this study, we found that Jadomycin S and
T inhibited the growth of A549, HeLa, and MCF-7 cells, although the inhibition was not as dramatic as Jadomycin B. Unlike Jadomycin B, neither the kinase activity of Aurora-B, nor the growth of ipt1-321 cells, was inhibited by Jadomycin S and T. The antitumor effect of Jadomycin S and T is probably caused by the inhibition of other targets other than Aurora-B. In summary, we identified a new Aurora-B inhibitor, Jadomycin B, through the combination of yeast genetics and biochemical approaches, and we will further investigate the anticancer activity of Jadomycin B.

Disclosure of Potential Conflicts of Interest
There is no potential conflicts of interest.

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