A High Throughput, Whole Cell Screen for Small Molecule Inhibitors of the Mitotic Spindle Checkpoint Identifies OM137, a Novel Aurora Kinase Inhibitor

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Abstract

In mitosis, the kinetochores of chromosomes that lack full microtubule attachments and/or mechanical tension activate a signaling pathway called the mitotic spindle checkpoint that blocks progression into anaphase and prevents premature segregation of the chromatids until chromosomes become aligned at the metaphase plate. The spindle checkpoint is responsible for arresting cells in mitosis in response to chemotherapeutic spindle poisons such as paclitaxel or vinblastine. Some cancer cells show a weakened checkpoint signaling system that may contribute to chromosome instability in tumors. Because complete absence of the spindle checkpoint leads to catastrophic cell division, we reasoned that drugs targeting the checkpoint might provide a therapeutic window in which the checkpoint would be eliminated in cancer cells but sufficiently preserved in normal cells. We developed an assay to identify lead compounds that inhibit the spindle checkpoint. Most cells respond to microtubule drugs by activating the spindle checkpoint and arresting in mitosis. In a rounded morphology, our assay depended on the ability of checkpoint inhibitor compounds to drive mitotic exit and cause cells to flatten onto the substrate in the continuous presence of microtubule drugs. In this study, we characterize one of the compounds, OM137, as an inhibitor of Aurora kinases. We find that this compound is growth inhibitory to cultured cells when applied at high concentration and potentiates the growth inhibitory effects of subnanomolar concentrations of paclitaxel. [Cancer Res 2009;69(4):1509–16]

Introduction

During mitosis in metazoans, the duplicated chromosomes, composed of two identical chromatids joined at the centromere, move as individuals to align at the metaphase plate. The mitotic spindle checkpoint is a cell signaling pathway that blocks the premature onset of chromatid separation until all the kinetochores of chromosomes are fully occupied by microtubules and/or under appropriate mechanical tension (reviewed in ref. 1). Spontaneous or chemically induced defects in the mitotic spindle can lead to long term activation of the spindle checkpoint, whereupon cells arrest at the preanaphase stage for many hours.

Many cancers show abnormal chromosome content, often being hyperdiploid. Certain lines derived from tumors have abnormal but relatively stable chromosome content, whereas others exhibit substantial chromosome instability (CIN), a condition in which chromosomes frequently missegregate. The role of CIN as a causative factor in oncogenesis is both complex and controversial (2, 3). However, it is likely that CIN contributes to the production of variant populations with the potential for increased malignancy or resistance to therapy. In some instances, tumor lines exhibiting CIN have been shown to have partially defective spindle checkpoint signaling, and these checkpoint defects have been shown to reflect checkpoint gene mutation or altered levels of checkpoint protein expression (4–6). Whether the partially inactive checkpoint that is characteristic of many tumor cells renders the cells more or less sensitive to treatments with microtubule drugs such as paclitaxel remains controversial (7–10). Whereas tumor cells often exhibit a partially defective spindle checkpoint, total inactivation of the checkpoint results in catastrophic cell division that is incompatible with cell survival (11, 12). We reasoned that differences in the potency of checkpoint systems in normal versus tumor cells might provide a therapeutic window for the development of useful drugs that target the mitotic spindle checkpoint. At appropriate doses, these drugs could fully eliminate the checkpoint response in tumor cells, whereas sparing sufficient checkpoint activity for survival of normal cells. Checkpoint inhibitor drugs might thus prove preferentially toxic to tumor cells, particularly when used in combination with microtubule drugs that cause checkpoint activation. We devised a cellular assay to test small molecules for compounds that would override the spindle checkpoint. Here, we describe the assay used to identify checkpoint inhibitors and characterize one of those lead compounds, OM137, which functions to override the spindle checkpoint primarily through inhibition of the class of mitotic kinases called the Aurora kinases.

Materials and Methods

Cell culture. HeLa cells were grown in DMEM supplemented with 10% bovine calf serum or fetal bovine serum (FBS), 20 mmol/L Hepes, 1 × nonessential amino acids, 1 mmol/L sodium pyruvate, 60 μg/mL of penicillin, and 100 μg/mL streptomycin at 37°C under 5% CO2. Ptk1 (rat kangaroo kidney) cells were cultured in Minimal Essential Medium supplemented with 10% FBS, 20 mmol/L Hepes buffer, 1 × nonessential amino acids, 1 mmol/L sodium pyruvate, 60 μg/mL penicillin, and 100 μg/mL streptomycin. LLC-Pk (porcine kidney) cells were grown in

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).
High throughput assay for chemical inhibitors of the spindle checkpoint.

HeLa cells in 10-150 mm tissue culture dishes were blocked for 16 to 17 h with nocodazole at 100 ng/mL. The rounded mitotic cells were released from the substratum by gentle agitation and collected. Assays were conducted in duplicate in 384-well plates. A commercial library of 10,000 diverse small molecules (Chembridge Corp.) was stored at −20°C in 96-well plates at an approximate concentration of 2.5 mmol/L in DMSO. Ten microliters of medium were distributed to each well of the 384-well plate. A 0.5 μl pin transfer device (V.P. Scientific) was used to transfer an initial aliquot of the test compounds to the top left well (well A) of a 4-well quadrant in the 384-well plate. A 2.9 μl pin transfer device was used to make serial dilutions to the other 3 wells (wells B, C, D) of the quadrant. An additional 10 μL of medium containing −104 cells was added to each well. Assuming a uniform molecular weight of 500 for the compounds, each test compound is tested at concentrations of 55, 10, 1.7, and 0.3 μmol/L in the 4 wells of the quadrant. The nocodazole concentration was maintained at 20 ng/mL. Negative controls were included in each plate including wells with only medium or cells tested with carrier (DMSO). As a positive control, RO-31-8220 at 55 nmol/L was added. RO-31-8220 is an inhibitor of cyclin-dependent kinase 1 (13) and elicits mitotic exit and flattening onto the substrate for cells in nocodazole.

For the remainder of the protocol, one of the duplicate plates was rotated 180 degrees to counteract processing artifacts such as inhomogeneities in certain channels of the washer or fluorescent plate reader. Plates were incubated for 4 h at 37°C to allow mitotic exit and attachment of cells in wells where the spindle checkpoint was abrogated. Plates were then washed with 5 cycles in a Tacen PW-384 plate washer using MOPS/Triton/DNase [0.1% Triton X-100, 150 mmol/L NaCl, 1.8 mmol/L CaCl2, 0.8 mmol/L MgCl2, 10 mmol/L MOPS (pH 7.3), and 10 μg/ml DNase I (Sigma)]. The DNase serves to remove nonspecific background due to cells becoming trapped in DNA gel released by dead or dying cells. After the final wash, wells were treated with a fixation/permeabilization stabilization solution consisting of 2% paraformaldehyde, 0.5% Triton X-100, 60 mmol/L Pipes, 25 mmol/L HEPES, 10 mmol/L EGTA, 4 mmol/L MgSO4 (pH 6.9), and the fluorescent DNA label Syber Gold used at the manufacturer’s recommended concentration diluted 1:10,000 from the stock (Invitrogen). The plates were then read with a Tacen Genios fluorescent plate reader.

**Immunofluorescence.** Xenopus S3 cells were grown on glass coverslips and incubated in 25 μmol/L MG132 for 90 min to accumulate cells arrested at metaphase. Cells were then incubated in media containing 25 μmol/L MG132 and OM137 ranging from 0.8 to 100 μmol/L for 60 min. Cells were treated with fixation-extraction solution [0.5% Triton X-100, 1.5% paraformaldehyde, 60 mmol/L Pipes, 25 mmol/L HEPES, 10 mmol/L EGTA, 4 mmol/L MgSO4, 400 μmol/L Microcystin-LR (pH 6.9)] for 15 min at room temperature. Mouse anti-phospho-histone H3 (Cell Signaling Technology, 1:1,000) antibody bodies were used to detect phosphorylated histone H3. DNA was stained with 4’,6-diamidino-2-phenylindole (DAPI). Labeled cells were mounted in Vectashield (Vector Laboratories) containing 10 mmol/L MgSO4. Three-dimensional images were collected using a Zeiss Axiosplan Ilc microscope, ×100 objective (Plan-APochromat, 1.4 NA) and a Hamamatsu C4742-98 CCD camera. Fluorescence images were analyzed using Metamorph software (Molecular Devices).

**Chromosome isolation and immunofluorescence.** HeLa cells were treated with 330 μmol/L nocodazole for 4 h to accumulate mitotic cells. Mitotic cells were collected by shake-off and their media was exchanged to 330 μmol/L nocodazole and 25 μmol/L MG132. OM137 was added to experimental cultures for a final concentration of 100 μmol/L, whereas control cultures received an equivalent volume of DMSO. Mitotic cells were washed in 10 mmol/L HEPES (pH 7.4), 40 mmol/L KCl, 5 mmol/L EGTA, 4 mmol/L MgSO4, and 400 mmol/L Microcystin-LR by centrifugation at 200 × g for 4 min. Mitotics were lysed in 60 mmol/L Pipes, 25 mmol/L HEPES (pH 6.9), 10 mmol/L EGTA, 4 mmol/L MgSO4 (PHEN), 0.5% Triton X-100, 1 mmol/L DTT, 400 mmol/L Microcystin-LR, and 5 μg/ml protease inhibitor cocktail. The extracts were centrifuged through a cushion of lysing buffer containing 10% glycerol over poly-l-lysine–treated glass coverslips at 1,500 × g for 10 min at 4°C to collect chromosomes for immunofluorescence labeling. The chromosome-coated coverslips were then fixed in PHEM and 1.5% formaldehyde for 15 min and processed for immunofluorescence analysis as described previously (14). Mouse anti-Aurora B (BD Biosciences), Rabbit anti-MAD2 (generously provided by Dr. Rey Chen, Academia Sinica, Taiwan) and Rabbit anti-BUBR1 (generously provided by Dr. Todd Stukenberg, University of Virginia, Charlottesville, VA) were used at 1:25, 0.5 μg/ml, and 1:100, respectively. chromosome fluorescence image capture and analysis was performed with a Zeiss Axioplan II microscope equipped with a 100 × (NA 1.4) objective, a Hamamatsu Orca 2 camera (Hamamatsu Photonics), and Metamorph imaging software (Molecular Devices).

**Kinase assays.** All kinase assays were carried out in 30 μL. Reaction mixes contained 50 μmol/L ATP, 1 mmol/L DTT, 1 mmol/L Na3VO4, 5 μCi [γ-32P]-ATP, 1 μg of the appropriate substrate (see below), 1 μL DMSO or drugs dissolved in DMSO, and 50 to 100 ng kinase. Reaction mixes were incubated for 1 h at 30°C, quenched with SDS loading buffer and resolved on 14% SDS-PAGE. Incorporation of 32P was visualized by autoradiography. Densitometry analysis was performed using ImageJ software (W. Rasband, NIH). IC50 values were calculated from log-dose response curves using Prism 4 software (Graph Pad). Aurora A,tcP2X, Aurora B/NCN, and CDK5/p52 purification protocols and kinase assay conditions have been described previously (15–17). Plk1 and CDK1/Cyclin B were kind gifts of Dr. Dan Goodenough (University of Colorado, Denver, CO). Anti-β-tubulin (1:10,000 from the stock; Invitrogen). The plates were then read with a Tacen Genios fluorescent plate reader.

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The cells in wells containing inactive compounds remained rounded and were easily washed from the dishes (Fig. 1B). After fixation in a solution containing a fluorescent DNA label, we used a fluorescence plate reader to rapidly assess which test compounds could induce mitotic exit and cell reattachment. Because the assay requires cells to actively flatten onto the substrate it selects against compounds that are merely cytotoxic.

The screen was also designed to eliminate a number of false positives. Because a fluorescent DNA label was used it was simple matter to examine microscopically, all the wells scored as positive from the plate reader analysis and confirm that they contained live cells that had been induced to exit mitosis (Fig. 1C). In wells where cells exited mitosis, the chromatin was decondensed and assembled into one or more rounded nuclei within the attached cells. In a few instances however, we noted that positive wells contained a high proportion of attached cells in which chromatin remained condensed in mitotic chromosomes. These false positives were excluded from further analysis.

The spindle checkpoint functions by inhibiting the ubiquitylation pathway that targets cyclin B and other proteins for degradation by the proteasome. Thus, proteasome activity is downstream of the checkpoint and is absolutely required for mitotic exit induced by chemical inhibitors of the spindle checkpoint. As a secondary screen potential spindle checkpoint inhibitors were tested for the ability to override a mitotic block imposed by a combination of nocodazole and the proteasome.
inhibitor MG132 (Fig. 1D). Thus, those compounds that induced mitotic exit of nocodazole-treated cells in the absence of MG132 but failed to induce mitotic exit in its presence were scored as positive inhibitors of the mitotic spindle checkpoint. As controls for this assay, we used chemical inhibitors of cyclin-dependent kinase 1, which are able to induce mitotic exit in the presence of proteasome inhibitors (13).

We screened a commercial library of 10,000 small molecules (Chembridge Corp.) From these, we identified 11 compounds of distinct structure that inhibited the spindle checkpoint at micromolar concentrations. Most often hits scored at the highest concentration tested. Here, we report in detail the characterization of the cell biological effects and the molecular targets of one compound, OM137, which scored as a hit at the highest concentration tested in the initial screen. Characterization of other lead compounds and identification of cellular targets for other compounds identified in the screen is under way and will be reported subsequently.

**Compound OM137 is an inhibitor of Aurora kinases.** To obtain clues to the potential molecular targets of lead compounds, we assayed their effects on phosphorylation of serine 10 in histone H3 using an antibody that specifically binds this site when phosphorylated. Serine 10 phosphorylation of histone H3 is catalyzed by Aurora B kinase, which becomes activated in mitosis. We and others have shown that Aurora B activity is required for inhibitor MG132 (Fig. 1D). Thus, those compounds that induced mitotic exit of nocodazole-treated cells in the absence of MG132 but failed to induce mitotic exit in its presence were scored as positive inhibitors of the mitotic spindle checkpoint. As controls for this assay, we used chemical inhibitors of cyclin-dependent kinase 1, which are able to induce mitotic exit in the presence of proteasome inhibitors (13).

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maintenance of the spindle checkpoint (19–21). To ensure that loss of phosphorylation of histone H3 was a direct consequence of inhibition of Aurora B and not an indirect effect of mitotic exit, we carried out the assay using cells cultured in the presence of the proteasome inhibitor, MG132. Certain lead compounds, particularly F and K, showed partial inhibition of Aurora kinase activity, reflected by reduced expression of the serine 10 phosphoepitope on histone H3. However, as shown in Fig. 2A and B, OM137 showed the most potent inhibition among the lead compounds. Accordingly, we found that OM137 treatment of cells led to significant reduction in the concentrations of spindle checkpoint-signaling proteins, Mad2 and BubR1, at the kinetochores of chromosomes (Fig. 2C and D). When tested at a range of concentrations for inhibition of histone H3 phosphorylation in mitotic cells, OM137 showed an IC50 of ~15 μmol/L (Fig. 3A and B).

We tested OM137 for direct inhibition of Aurora A and Aurora B kinase as well as with a variety of other mitotic kinases. We found that OM137 inhibited Aurora A kinase (IC50, 21.7 μmol/L) and Aurora B kinase (IC50, 2.4 μmol/L; Fig. 4A). When tested with other mitotic kinases Mps1, Bub1, Plk1, Nek2A, and Tao1 that have been implicated in spindle checkpoint signaling, OM137 showed no significant inhibition (Fig. 4B). We did observe that OM137 showed in vitro activity in inhibiting cyclin-dependent kinases, Cdk1/cyclinB and Cdk5/p25 with an approximate IC50 of 20 μmol/L.

Analogues of OM137. A number of compounds with alternative substitutions on the aryl ring were available commercially. We tested several in our checkpoint assay. As shown in Fig. 5, we found several analogues with activities in the spindle checkpoint assay similar to (compounds 3 and 4) or even stronger than (compound 2) OM137 and we noted certain substitutions (compounds 5–8) led to loss of activity. These structure-activity relationship data highlight the importance of the amino group on the thiazole moiety and the presence and position of the hydroxyl group on the aryl moiety as important determinants for checkpoint inhibition.

Compound OM137 induces mitotic exit in cells arrested by the spindle checkpoint. With video microscopy, we studied cellular responses to abrogation of the spindle checkpoint by OM137 using cells that remain relatively flat in mitosis. In cultured Xenopus S3 cells treated with OM137 before nuclear envelope breakdown, many chromosomes failed to align at the metaphase plate. Cells then entered anaphase with massive chromosome missegregation; cytokinesis failed, and mitotic exit resulted in the formation of a misshapen and multilobed nucleus (Supplementary Video S1; Fig. 6A). Similarly, when cells were treated with OM137 in the early stages of prometaphase after nuclear envelope breakdown, premature mitotic exit mitotic exit occurred accompa-
also caused restructuring of the microtubule network from the mitotic spindle array to the interphase pattern (Supplementary Video S2; Fig. 6B). As expected, OM137 also overrode chronic checkpoint activation induced by treatment of cells with microtubule poisons. Ptk1 cells treated with nocodazole remained arrested with condensed mitotic chromosomes for several hours (Supplementary Video S3; Fig. 6C, left column). In contrast when nocodazole-arrested cells were cotreated with OM137, the chromosomes rapidly decondensed and an interphase nucleus reformed around the undivided chromosomes (Supplementary Video S4; Fig. 6C, right column).

**Compound OM137 inhibits cell growth and enhances growth inhibitory effects of paclitaxel.** Paclitaxel is a commonly used antitumor drug. We tested whether OM137 would inhibit HeLa cell growth when used alone or in combination with paclitaxel. At higher concentrations, OM137 showed growth inhibition, and inhibition was significantly increased when OM137 was applied with subnanomolar concentrations of paclitaxel (Fig. 6D, right). Subnanomolar concentrations of paclitaxel showed only minimal growth inhibition when used alone (Fig. 6D, left).

**Discussion**

Human tumors have also been reported to show altered spindle checkpoint signaling characteristics that, in some instances, are due to mutations or altered levels of checkpoint signaling proteins. Aurora kinases are often misregulated in human tumors (reviewed in refs. 22, 23). These changes may lead to alterations in events of mitosis, e.g., malfunctions in spindle assembly and chromosome segregation. Aurora B is required for normal function of the mitotic spindle checkpoint (19–21). Mitotic defects may contribute to chromosome missegregation and aneuploidy in human cancers and these chromosomal abnormalities may contribute to tumor malignancy (reviewed in refs. 2, 10). However, altered checkpoint activity due to improper expression of Aurora kinases in tumor cells may also present a target for tumor-specific anticancer therapeutics. A number of other Aurora kinase inhibitors have been reported and several of these are currently in clinical trial (reviewed in ref. 23).

Here, we show that a screen to detect compounds that inhibit the spindle checkpoint identified an inhibitor of Aurora kinases termed OM137. OM137 is an aminothiazole derivative. Thiazole derivatives have previously been identified as Aurora kinase inhibitors (24). Recently a large scale screen was carried out assaying compounds for inhibition of Aurora A kinase *in vitro* that identified and characterized a large number of small molecule aminothiazole compounds related to but distinct from OM137 (25). Although many of the compounds analyzed in that study were more potent inhibitors of Aurora A kinase *in vitro*, the authors reported that obtaining responses consistent with Aurora kinase inhibition in living cells required concentrations 10 to 100 fold higher than that required *in vitro*, attributing the difference in potency to problems with cell permeability of the compounds.

![Figure 5. Active and inactive analogues of OM137. Analogue 2 to 4, similar activity to OM137 in inducing mitotic exit. EC50s for the checkpoint assay are depicted. Analogues 5 to 8, no activity in the checkpoint assay.](image-url)
Our screen for checkpoint inhibitor activity was conducted with whole cells and therefore required that effective compounds be cell permeable. In addition, we found that OM137 was a more potent inhibitor of Aurora B compared with Aurora A \textit{in vitro}, consistent with the effects of OM137 on checkpoint function in living cells. We also found that OM137 showed inhibitory activity against cyclin-dependent kinases. Cdk1 inhibitors can drive mitotic exit when applied to cells in culture (13, 26). However, unlike other Cdk1 inhibitors, OM137 was unable to drive mitotic exit when the proteasome was inhibited. Thus, it is likely that the major mode by which OM137 drives mitotic exit of cells arrested in M phase via the spindle checkpoint is through its inhibitory activity against Aurora B kinase. Inhibition of Aurora B kinase is known to induce override of the spindle checkpoint (19–21). We hypothesize that OM137 induces catastrophic mitotic exit in cultured cells through its activity on Aurora kinases. Compounds that inhibit the spindle checkpoint may provide a novel approach toward directly targeting tumors that show partially defective checkpoints. Such compounds may also enhance the antitumor potency of M phase checkpoint activators such as paclitaxel and other microtubule poisons.

Figure 6. OM137 inhibits chromosome alignment at metaphase, induces premature anaphase, overrides the mitotic spindle checkpoint, and promotes the growth inhibitory activity of paclitaxel. A, a Xenopus S3 cell was treated before nuclear envelope breakdown with OM137 at 100 \( \mu \text{mol/L} \) and then imaged by time lapse phase contrast microscopy. A minority of the chromosomes aligned at the metaphase plate (single arrow) and these underwent chromatid separation when the cell entered premature anaphase (double arrow). B, a Xenopus S3 cell stably expressing GFP-tubulin was treated with OM137 at 50 \( \mu \text{mol/L} \) and imaged by phase contrast and fluorescence microscopy. Shortly after treatment at time 0, chromosomes (arrows) begin to decondense eventually forming an abnormally shaped interphase nucleus by 30 min. In the GFP-tubulin image, the cell at time 0 has bright mitotic spindle poles (arrowheads) and a nascent mitotic spindle. Treatment with OM137 leads to loss of the spindle structure and reversion to the interphase microtubule array. C, cultures of flat epithelial PtK1 cells were treated with 100 ng nocodazole for 20 min before DIC imaging. Control cultures that did not receive OM137 (left column) remain arrested in mitosis. At time 0, one cell is already arrested at prometaphase (bottom arrow), whereas another cell is in prophase (top arrow). A few minutes later, both cells are arrested at prometaphase and remain arrested for the duration of imaging (165 min). D, subnanomolar concentrations of paclitaxel caused only minor inhibition of HeLa cell growth over 8 d (left). OM137 at higher concentrations inhibited cell growth. When used in combination with subnanomolar concentrations of paclitaxel, growth inhibition was enhanced (right).
Disclosure of Potential Conflicts of Interest

G.J. Gorbsky: Consultant, Eisai Research Institute. The other authors disclosed no potential conflicts of interest.

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References

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