Novel Microtubule Polymerization Inhibitor with Potent Antiproliferative and Antitumor Activity

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Abstract

Microtubule-stabilizing and microtubule-destabilizing agents are commonly used as anticancer agents. Although highly effective, success with these agents has been limited due to their relative insolubility, cumbersome synthesis/purification, toxic side effects, and development of multidrug resistance. Hence, the identification of improved agents that circumvent one or more of these problems is warranted. We recently described the rational design of a series of triazole-based compounds as antimitotic agents. Members of this N-substituted 1,2,4-triazole family of compounds exhibit potent tubulin polymerization inhibition and broad spectrum cellular cytotoxicity. Here, we extensively characterize the in vitro and in vivo effects of our lead compound from the series 1-methyl-5-(3-(3,4,5-trimethoxyphenyl)-4H-1,2,4-triazole-4-yl)-1H-indole, designated T115. We show that T115 competes with colchicine for its binding pocket in tubulin, produces robust inhibition of tubulin polymerization, and disrupts the microtubule network system inside the cells. In addition, T115 arrests human cancer cells in the G2-M phase of cell cycling, a hallmark of microtubule destabilizing drugs. T115 also inhibits cell viability of several cancer cell lines, including multidrug-resistant cell lines, in the low nanomolar range. No cytotoxicity was observed by T115 against normal human skin fibroblasts cell lines, and acute toxicity studies in normal non-tumor-bearing mice indicated that T115 is well-tolerated in vivo (maximum total tolerated dose, 400 mg/kg). In a mouse xenograft model using human colorectal (HT-29) and prostate (PC3) cancer cells, T115 significantly inhibited tumor growth when administered i.p. Taken together, our results suggest that T115 is a potential drug candidate for cancer chemotherapy. [Cancer Res 2009;69(5):1910–5]

Introduction

Microtubules, as major components of the cytoskeleton, are indispensable for the formation and disappearance of the mitotic spindle that, in turn, is responsible for separation of duplicated chromosomes during cell division (1). The basic structural unit of microtubules is the heterodimer composed of alternating α tubulin and β tubulin subunits (2). The formation of microtubules is a dynamic process that involves the polymerization and depolymerization of α and β tubulin heterodimers (2, 3). Disruption of microtubule formation, either by inhibiting polymerization or by preventing depolymerization of tubulin, results in cell-cycle arrest and cell death (4–7). Therefore, the microtubule system of eukaryotic cells is widely regarded as an attractive target for the development of anticancer therapeutic agents.

Tubulin-binding compounds that suppress the microtubule dynamics and disrupt the formation of mitotic spindles have been in the treatment of many cancers (8, 9). Prominent examples include the taxanes such as Taxol and Taxotere, and the Vinca alkaloids such as vincristine, vinorelbine, and vinblastine. Despite their broad utility as anticancer agents, these antimitotic drugs used in the clinic encounter issues related to their neural and systemic toxicity, marginal water solubility, poor bioavailability, complex synthetic pathways, and difficult isolation procedures (10–14). Moreover, development of intrinsic and extrinsic resistance to these agents further limits their clinical utility (13–15). The typical mode of administration of these compounds is i.v., thereby adding discomfort and inconvenience for the patient and caregiver. Therefore, an urgent need exists for potent antimitotic agents that combine fewer side effects, reduced drug resistance, oral activity, and ease of synthesis.

Using computational approaches based on structure based drug design, we previously identified a defined series of triazole-based compounds designated as T111-T115 that showed robust tubulin antipolymerization activity and exceptional cytotoxicity (16). Chemical synthesis of these compounds was accomplished via an efficient four-step procedure (16). The encouraging results from these initial studies have motivated us to further characterize the mechanism of action and antitumor activity of our lead compound T115.

Herein, we show that T115 exhibits potent cytotoxicity in the low nanomolar range against a wide array of cancer cell lines, including multidrug-resistant cell lines, yet lacks cytotoxicity against normal skin fibroblasts. Furthermore, results from in vivo studies in mice reveal that T115 is well-tolerated even at very high doses (maximum total tolerated dose, 400 mg/kg) in healthy non-tumor bearing mice and inhibits tumor growth in colorectal xenografts.

Materials and Methods

Drugs and reagents. 1-Methyl-5-(3-(3,4,5-trimethoxyphenyl)-4H-1,2,4-triazole-4-yl)-1H-indole (T115) was rationally designed and synthesized in our laboratory following procedures described elsewhere (16). Samples were purchased from the following vendors: Combretastatin A-4 from Tocris Bioscience, [3H] colchicine from Perkin-Elmer, [3H]Paclitaxel and [3H]Vinblastine from Morevex Biochemicals, and unlabeled Paclitaxel and colchicine from Sigma.

Cell lines and culture conditions. Human cervical cancer cell line (HeLa), normal human fibroblasts (GM05659, FBC1), human cervical
carcinoma cell line (KB-3-1), its multidrug-resistant variant (KB-V1), and cell line overexpressing ABCG2/BCRP (KB-H5.0) were kindly provided by Prof. L. F. Liu (Pharmacology Department, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, NJ). The other cell lines were obtained courtesy of Dr. W. N. Hait (Cancer Institute of New Jersey, New Brunswick, NJ). All of the cells were maintained at 37°C, 5% CO2 humidity atmosphere in media.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Cells were plated with densities from 3,000 to 6,000 cells per well based on growth characteristics in 96-well tissue culture plates, allowed to attach overnight, and then exposed to various concentrations of tested drugs for 72 h. Thiazolyl Blue Tetrazolium Bromide [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)] dissolved in PBS was added to each well with a final concentration of 0.5 mg/mL, and cells were incubated at 37°C for 2 to 4 h. After removal of MTT containing medium, 150 μL DMSO were added to dissolve formazan crystals in each well. Absorbance at 595 nm was determined using a TECAN GENios multifunction microplate reader (TECAN U.S., Inc.). IC50 values were calculated by nonlinear regression analysis using Prism 3.03 (Graphpad Software Inc.). All experiments were performed in triplicate and repeated three independent times. Average values were reported here.

Flow cytometry. The effect of T115 on the cell cycle of proliferating cells was studied by monitoring the DNA content in HeLa cells in the presence or absence of T115 at specified concentrations. The cells were treated at the indicated concentrations of T115 for 24 h, trypsinized, washed with PBS twice, and fixed by adding cold 70% ethanol dropwise on ice for 30 min. Approximately 1 × 106 cells were treated with 0.1 mg/mL RNaseA and 5 μg/mL propidium iodide in PBS for 30 min at room temperature. Fluorescence intensity data were collected and analyzed by quantitative flow cytometry system Cytometers FC 500 (Beckman Coulter, Inc.).

Immunofluorescence staining. Cells were grown on glass coverslips in a 12-well tissue culture plate until ~60% confluent, and then were treated at different concentrations for 24 h. After fixing with ice-cold methanol at ~20°C, coverslips were blocked with 3% bovine serum albumin and stained with α-tubulin antibody (clone DM1A; Sigma) or FITC-conjugated secondary antibody (Sigma). Coverslips were then mounted using the ProLong Antifade kit (Molecular Probes) and stored at ~20°C.

Tubulin competitive binding assay. Tubulin (>99% pure; Cytoskeleton, Inc.; 0.2 mg/mL) was incubated with tritiated tubulin binders (0.1 μmol/L [3H]colchicine, 0.2 μmol/L [3H]vinblastine, or 0.05 μmol/L [3H]paclitaxel) and test compounds at various concentrations in 100 μL G-PEM buffer [80 mmol/L PIPES (pH 6.8), 0.5 mmol/L EGTA, 2.0 mmol/L MgCl2, 1.0 mmol/L GTP plus 5% glycerol] at 37°C for 1 h. The binding mixture was filtered with GF/C glass microfiber filter (Whatman) and washed twice before scintillation counting was performed on a Packard TRI-CARB 2300TR liquid scintillation analyzer (Perkin-Elmer).

Tubulin polymerization assay. Tubulin polymerization assays were conducted using the CytoDYNAMIX Screen 03 (Cytoskeleton, Inc.) assay system following the manufacturer's instructions. Tubulin (>99% pure) was reconstituted to 3 mg/mL using G-PEM buffer. One hundred microliters of the reconstituted tubulin were added to each well of a prewarmed 96-well plate and exposed to test compounds at varying concentrations (0.1–10 μmol/L). The absorbance at 340 nm was recorded every 60 s for 1 h using a TECAN GENios multifunction microplate reader (TECAN U.S., Inc.) at 37°C. The dose-response curves were plotted using Prism 3.03 (Graphpad Software, Inc.).

In vivo antitumor activity. The effect of T115 on growth of colorectal and prostate xenografts was studied at Washington Biotechnology, Inc. HT-29, human colorectal carcinoma cells, and PC3, human prostate cancer cells, were injected s.c. in the left and right flank (1 × 106) of NCR nu–/nu–

![Figure 1](image-url)
mice. After 10 d (day 0) when tumors reached a mean volume of 300 to 400 mm³, mice were randomized into 2 groups (6 mice each group) and treatment was started. T115 was administered by i.p. injection at 90 or 60 mg/kg on days 0, 2, 4, 6, and 8. Maximum tolerable dose in a single injection is represented by 90 mg/kg, which was established before the efficacy experiments. No weight loss or other signs of distress such as hunched posture were observed at either dose. As a vehicle control, DMSO was injected at 2 mL/kg concentration. Measurements of mice weight and tumor volumes were recorded every other day with digital caliper.

**Results**

T115 (Fig. 1A) is the lead compound from a family of novel tubulin polymerization inhibitors that were rationally designed and synthesized in our laboratory. These compounds, which possess a triazole core structure, were easily prepared using a four-step procedure as described previously (16). The results presented here support our conclusion that T115 is a highly potent and worthy of further development as a viable drug candidate for anticancer therapy.

**T115 binds to colchicine binding site.** Clinically used compounds targeting microtubule system have been classified into three major categories based on notable ligands that target specific binding sites: taxane, Vinca alkaloid, and colchicine (9). T115 (in concentrations ranging from 0.01–100 μmol/L) inhibited [3H]colchicine binding, but not [3H]vinblastine or [3H]paclitaxel, to >99% pure tubulin protein (Fig. 1B–D). The ability of T115 to compete effectively and specifically with [3H]colchicine suggests that T115 binds to the colchicine binding site located in the tubulin β-subunit (17) but not to the Vinca alkaloid or paclitaxel sites.

**T115 inhibits microtubule polymerization.** To investigate the effect of T115 on microtubule polymerization, bovine brain tubulin (>99% pure) was treated with T115 or CA-4 at the indicated concentrations (0.1–10 μmol/L) for 60 minutes at 37°C (Fig. 2). The content of polymerized microtubules was monitored by measuring absorbance at 340 nm every minute for an hour. At all concentrations tested, T115 exhibited inhibition of microtubule formation comparable with the known microtubule polymerization inhibitors CA-4 and colchicine, suggesting that T115 possesses strong antitubulin polymerization activity.

**T115 arrests HeLa cells in G2-M phase and disrupts microtubule apparatus inside these cells.** To examine the effect of T115 on the cell cycle, HeLa cells were exposed to 10, 20, and 40 nmol/L T115 for 24 h. The distributions of treated cells at different phases of cell cycle (G1, S, G2-M) were analyzed using flow cytometry by propidium iodide staining of DNA. As shown in Fig. 3, cells treated with T115 arrest in G2-M phase: 78% cells accumulated in G2-M phase at 40 nmol/L concentration compared with only 13% in vehicle treated control. These results suggest that T115 arrests cell cycling at the G2-M phase in a dose-dependent manner.
We further investigated the effect of T115 on microtubule reorganization inside the cells by immunostaining. HeLa and MCF-7 cells were exposed to medium containing either 25, 50, or 100 nmol/L of T115 for 24 h after which microtubules were visualized with FITC-conjugated antibody (green) and visualized by fluorescent microscopy with a 40x oil immersion lens. Cell nuclei were stained with DAPI (blue). Images are representative of two independent experiments.

**Figure 4.** Effect of T115 on microtubule network organization. HeLa (A) or MCF-7 (B) cells were grown in DMEM containing either 0.1% DMSO, CA-4, or T115 at indicated concentrations for 24 h, stained for α-tubulin using FITC-conjugated secondary antibody (green), and visualized by fluorescent microscopy with a ×40 oil immersion lens. Cell nuclei were stained with DAPI (blue). Images are representative of two independent experiments.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CA4-25 nmol/L</th>
<th>CA4-100 nmol/L</th>
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<tr>
<td><strong>A</strong></td>
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<td>T115-25</td>
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<td>T115-50</td>
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<td>T115-100</td>
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**T115 inhibits viability of cancer cells from various tissues of origin.** Next, we examined the effect of T115 on the viability of cancer cells using MTT assays as described in Materials and Methods. As shown in Table 1, additional evaluation indicated that T115 exhibits uniformly potent cytotoxicity against a broad spectrum of carcinoma cells (Table 1) including ovarian, prostate, and leukemia-derived cell lines. In contrast, T115 was noncytotoxic to normal human cell line GM05659 and FBLC at concentrations of 10 μmol/L, providing a selectivity index of 500- to 1,000-fold when compared with GI50 values for cancer cell lines. These data suggest that T115 exhibits both potent and selective cytotoxicity against cancer cells.

**T115 is active against multidrug-resistant cancer cell lines.** The cytotoxicity of T115 was also evaluated against six drug-resistant carcinoma cell lines (Table 1). T115 consistently yielded low-nanomolar IC50 values in all tested drug-resistant cells independent of phenotypes (P-gp/MDR or MRP or ABC G1). In addition, T115 inhibited the growth of both endogenous MDR1 overexpressing cells (MCF-7-Adr) and MDR1-transfected cells (BC-19). Both paclitaxel and colchicine are ineffective against many of these drug-resistant cell lines. Thus, the present results indicate that T115 is not a substrate for the P-gp/MDR, MRP1, or ABCG2 pumps.

**T115 inhibits tumor growth in colorectal and prostate xenografts in vivo.** We next examined the effect of T115 on colorectal and prostate tumor growth in mice. HT-29 (1 × 10⁶), colorectal cancer cells and PC3, prostate cancer cells were inoculated in each flank of NCR nude mice. The treatment started when tumor reached a mean volume of 300 to 400 mm³. T115 was administered by i.p. injection at 90 or 60 mg/kg on days 0, 2, 4, 6, and 8. As a vehicle control, DMSO was injected at 2 mL/kg concentration.

As shown in Fig. 5A and B, therapeutic treatment with T115 at doses of 60 or 90 mg/kg significantly inhibited tumor growth (P = 0.02) after the first dose. After 5 doses of T115, the tumor growth continued to remain significantly (P < 0.001) inhibited for at least 10 d, after which the study was terminated due to excessive tumor load in vehicle treated group. No clinical signs of distress, such as weight loss or hunched posture, were associated with T115 treatment at this dose. These results thus show that T115 inhibits the growth of tumors in vivo.

**Discussion**

The microtubule system is a well-validated target for the development of anticancer drugs. Controlled regulation of microtubule assembly and disassembly is critical for normal cell division, and thus cancer growth.

The general mode of action of these microtubule binding molecules is to arrest cell cycle progression by interrupting mitotic spindle formation and chromosome segregation (18). However, most if not all clinically available microtubule binding compounds encounter problems associated with chemical instability, poor bioavailability, and peripheral neurotoxicity (10–14, 19). In addition, many clinically used microtubule drugs induce several drug resistance phenotypes (15, 20, 21). We have developed a novel family of 1,2,4-triazole–based compounds that may overcome many of these difficulties.

In this report, we describe the characterization of one of our lead compounds, T115, from this triazole-based series. T115 is a structural analogue of CA-4 (Fig. 1); however, the double bond in the cis-stilbene core structure of several CA-4 analogues is known to racemize to a trans conformation, which abolishes tubulin antipolymerization activity and cytotoxicity against tumor cell lines (10, 11, 19). In contrast, the 1,2,4-triazole core structure in T115 and its analogues were specifically designed to stabilize the biologically active cis conformation that might account for their excellent cytotoxicity (Table 1).
T115 was shown to inhibit tubulin polymerization by targeting the colchicine binding pocket in β tubulin. T115 exhibited a dose-dependent inhibitory effect on the polymerization of tubulin heterodimers, suggesting that T115 is a potent microtubule polymerization inhibitor. Using cell-based immunofluorescence staining assays against α-tubulin, we observed that T115 causes disorder and fragmentation of the microtubule network and disrupts mitotic spindle formation. At low concentrations (25–50 nmol/L), T115 inhibited chromosome separation during mitosis that results in the formation of multinucleated cells. When HeLa and MCF-7 cells were treated with T115 at increased concentration (100 nmol/L), significant loss of FITC fluorescence was observed reflecting severe destruction of the microtubule system.

Table 1. Growth inhibitory effect of T115 in major cancer cell lines and their drug resistance subclones

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Origin</th>
<th>GI50 (nmol/L)*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T115 Colchicine Paclitaxel</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Breast</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>MCF-7-Adr</td>
<td>Breast (MDR+)</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>BC-19</td>
<td>Breast (MDR+)</td>
<td>3.2 ± 2.3</td>
</tr>
<tr>
<td>A2780</td>
<td>Ovarian</td>
<td>21 ± 8</td>
</tr>
<tr>
<td>A2780-DX</td>
<td>Ovarian (MDR+)</td>
<td>24 ± 6</td>
</tr>
<tr>
<td>KB-3-1</td>
<td>Cervix</td>
<td>9.9 ± 1.5</td>
</tr>
<tr>
<td>KB-4-D-10</td>
<td>Cervix (MDR+)</td>
<td>5.7 ± 2.1</td>
</tr>
<tr>
<td>KB-V1</td>
<td>Cervix (MDR+)</td>
<td>21 ± 0.7</td>
</tr>
<tr>
<td>KB-H5.0</td>
<td>Cervix</td>
<td>13.8 ± 3.5</td>
</tr>
<tr>
<td>PC-3</td>
<td>Prostate</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>PC-3-Adr</td>
<td>Prostate (MDR+)</td>
<td>24 ± 12</td>
</tr>
<tr>
<td>P388S</td>
<td>Leukemia</td>
<td>21 ± 1.0</td>
</tr>
<tr>
<td>P388-VMDRC</td>
<td>Leukemia (MDR+)</td>
<td>2.3 ± 1.1</td>
</tr>
<tr>
<td>GM 06659</td>
<td>Normal</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>FBCL</td>
<td>Normal</td>
<td>&gt;10000</td>
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Abbreviation: ND, not determined.
*Mean ± SD (n = 3).

Tubulin-binding agents are capable of interfering with the progression of cell cycle at the early mitotic (M2) phase (22, 23). After exposure to 20 nmol/L T115 for 24 hours, ~70% of the HeLa cells were observed to have doubled in DNA content. This finding suggests that the chromosomes failed to segregate after replication, stalling the cell cycle at the metaphase checkpoint and allowing mitotic arrest.

An intriguing feature of our study is that T115 exhibits potent antiproliferative activities against multidrug-resistant cell lines. Exposure to T115 decreased the viability of both endogenous and transfected P-gP overexpressing cells, specifically MCF-7-Adr (breast), BC-19 (breast), A2780-DX (ovary), KB-V1 (cervix), and P388-VMDRC (murine leukemia) in vitro. Moreover, T115 showed

Figure 5. In vivo activity of T115 in mice bearing HT-29 colorectal (A) or PC3 prostate (B) xenografts. NCR nu/nu mice were inoculated with 1 × 10⁶ HT-29 or PC3 cells and after tumor formation treated with either T115 (60 and 90 mg/kg) or vehicle i.p. Treatments were given on days 0, 2, 4, 6, and 8 as described in Materials and Methods. The tumor volumes were recorded every other day using digital caliper. Each point represents mean tumor volume for the six animals in each group.
consistently high cytotoxicity across the National Cancer Institute-Developmental Therapeutics Program (NCI-DTP) panel of 60 cell lines. T115 maintained high cytotoxicity among MDR phenotypes in the NCI-DTP panel, including the in vitro drug selected NCI/ADR cell line (breast), and the naturally MDR cancer cell lines HCT-15 (colon), UO-31 (renal), and TK10 (renal; refs. 16, 24). Taken together, these data suggest that T115 possesses broad-spectrum cytotoxicity activity and is not a substrate for either P-gp/MDR, MRP, or ABCG2 (BCRP) in contrast to many clinically used chemotherapeutic drugs.

The robust antimitotic and antiproliferative effects of T115 confirm its potential as a candidate for cancer therapy. Due to the uniformly strong lethality by T115 against colorectal cells in the NCI-DTP panel (16), a colorectal cancer xenograft model was chosen to evaluate the antitumor activity of T115 in vivo. The in vivo study on human colorectal xenograft tumors in mice revealed that T115 inhibited tumor growth in a statistically significant manner at a dose of 90 mg/kg compared with vehicle-treated mice. Furthermore, at these treatment doses T115 exhibited negligible visible side effects such as weight loss, hunch posture, etc., that are commonly seen with other chemotherapeutic agents.

To further expand our characterization of T115, we investigated its effect on prostate cancer xenografts. Encouragingly, we found that T115 inhibited the growth of prostate cancer tumors even at a lower dose of 60 mg/kg. T115 represents a novel molecular structure with potent and selective inhibitory effect against several cancer cells and, importantly, their drug resistance variants. From a structural standpoint, T115 eliminates the instability of stilbene-like CA-4 analogues by incorporating the 1,2,4-triazole core as a bridge to retain the biologically active cis configuration. This compound is synthetically accessible via a simple four-step mechanism (16). The hydrochloride salt of T115 was found to be soluble in water up to 2 mg/mL in our studies. Furthermore, the T115 base is soluble in 0.1% DMSO and 99.9% water at concentrations as high as 100 μmol/L. Furthermore, T115 exhibited significant reduction of tumor load and inhibition of tumor growth in vivo. In conclusion, the results presented here encourage further preclinical development of T115 as a potential drug candidate for chemotherapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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