Mechanism of Action of E7010, an Orally Active Sulfonamide Antitumor Agent: Inhibition of Mitosis by Binding to the Colchicine Site of Tubulin

Kentaro Yoshimatsu,1 Atsumi Yamaguchi, Hiroshi Yoshino, Nozomu Koyanagi, and Kyosuke Kitoh

Tsuchida Research Laboratories, Eisai Co. Ltd., I-1 Tokodai 3-chome, Tsuchi-shi, Ibaraki 300-26, Japan

ABSTRACT

E7010 (N-[2-[(4-hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide), an orally active sulfonamide antitumor agent that is currently in a Phase 1 clinical trial, showed rather consistent growth-inhibitory activities against a panel of 26 human tumor cell lines (IC50 = 0.06–0.8 μg/ml), in contrast to vincristine (VCR; IC50 = 0.0002–0.04 μg/ml), 5-fluorouracil (IC50 = 0.2–30 μg/ml), Adriamycin (IC50 = 0.002–0.7 μg/ml), mitomycin C (IC50 = 0.007–3 μg/ml), 1-b-D-arabinofuranosylcytosine (IC50 = 0.005 to >30 μg/ml), camptothecin (IC50 = 0.002–0.4 μg/ml), and cisplatin (IC50 = 0.5–20 μg/ml). It caused a dose-dependent increase in the percentage of mitotic cells in parallel with a decrease in cell proliferation, like VCR. It also showed a dose-dependent inhibition of tubulin polymerization, which correlated well with the cell growth-inhibitory activity. 14C-labeled E7010 bound to purified tubulin, and this binding was inhibited by colchicine but not by VCR. However, its binding properties were different from those of colchicine, as well as those of VCR. E7010 was active against two kinds of VCR-resistant P388 cell lines, one of which showed multidrug resistance due to the overexpression of P-glycoprotein (resistant to Taxol), and the other did not show multidrug resistance. Furthermore, four E7010-resistant P388 cell lines showed no cross-resistance to VCR, a different pattern of resistance to podophyllotoxin, and collateral sensitivity to Taxol. Therefore, E7010 is a novel tubulin-binding agent that has a wider antitumor spectrum than VCR and has different properties from those of VCR or Taxol.

INTRODUCTION

As part of the search for clinically effective antitumor drugs to treat refractory solid tumors, we have screened a number of sulfonamides, because this class of compounds is well known to have a variety of biological activities, such as antiinflammatory, insulin-releasing, carboxy anhydrase-inhibitory, and antithyroid activities (1). We found that E7010 showed a wide therapeutic range of antitumor activity in the colon 38 carcinoma model (2). It inhibited the growth of colon 38 cells inoculated s.c. by 60–99% when administered at doses of 25–100 mg/kg daily for 8 days (3). It was also active against mouse tumors (s.c. inoculated M5076 fibrosarcoma, s.c. inoculated Lewis lung carcinoma, and i.p. inoculated P388 leukemia), a rat tumor (s.c. inoculated SST-2 mammary carcinoma), and human xenografts (LC-376, LC-6, and LX-1 lung cancer; H-81, H-111, SC-2, and SC-6 gastric cancer; H-143, COLO320DM, and WiDr colon cancer; and H-31 and MX-1 breast cancer) upon oral administration (3). Moreover, E7010 was effective against VCR-resistant, CDDP-resistant, and 5-FU-resistant P388 cells in vivo (3).

The present study was designed to elucidate the mechanism of action of E7010, and we report here that E7010 is a novel antimitotic and tubulin-binding agent with different properties from those of Taxol, VCR, or CLC.

MATERIALS AND METHODS

Drugs. E7010 and 14C-labeled E7010 (specific activity, 56 mCi/mmol; phenyl-U-RING-14C; Fig. 3B) were synthesized at Tsuchida Research Laboratories, Eisai Co. Ltd. Reference compounds were obtained from the following sources: VCR, vinblastine, CDDP, CPT, VP16, and melphalan were obtained from Sigma (St. Louis, MO); 5-FU was obtained from Tokyo Kasei (Tokyo, Japan); ADM, MMC, CLC, POD, and MTX were obtained from Wako Junyaku (Tokyo, Japan); and Ara-C (Cycloide) was obtained from Nippon Sinyaku (Kyoto, Japan). Taxol was obtained from the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute. Trisnordolastatin was kindly provided by Dr. Shioiri (Nagoya City University, Nagoya, Japan). [3H]VCR was purchased from Amersham, and [3H]CLC was purchased from DuPont New England Nuclear.

Cell Lines. P388 murine leukemia and MX-1 were supplied by Cancer Chemotherapy Center, Japan Foundation for Cancer Research (Tokyo, Japan). VCR-resistant P388 cell line (P388/VCR) with overexpression of P-glycoprotein (4) was kindly supplied by Dr. M. Inaba (Cancer Chemotherapy Center, Japan Foundation for Cancer Research). H-460, H520, H596, HCT-116, SW480, SW620, COLO205, DLD-1, HCT-15, HT-29, MIApaCa-2, and HL-60 were obtained from the American Type Culture Collection (Rockville, MD). PC1, PC9, and MKN28 were obtained from the Immuno Biology Laboratory (Gunma, Japan). A549, WIDR, LS174T, COLO320DM, ZR-75-1, CCRF-CEM, and K562 were obtained from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). PC10, MKN45, and KATO-3 were obtained from the Japanese Cancer Research Resources Bank (Tokyo, Japan). All cell lines were maintained in RPMI 1640 containing 10% heat-inactivated fetal bovine serum, penicillin (100 units/ml), streptomycin (100 μg/ml), 2-mercaptoethanol (50 μM), and sodium pyruvate (1 mM).

MTT Assay. Exponentially growing cells were plated into 96-well tissue culture plates and preincubated for 1 day. Various concentrations of test compounds were added, and the cells were incubated for an additional 3 days. The antiproliferative activity was measured by MTT assay, and the IC50 values were determined.

Mitotic Index. P388 cells were treated with the indicated concentrations of E7010 or VCR for 12 h. Viable cell numbers were determined by the trypan blue dye exclusion method, and cells were treated with 0.075 M KCl fixed (3:1, methanol/acetic acid), and stained with 0.1% crystal violet. The mitotic index was determined by counting at least 500 cells.

Microtubule Polymorization Assay. Microtubule protein from bovine brain was prepared by two cycles of assembly and disassembly in assembly buffer [0.1 M morpholinooctanesulfonate, 1 mM EGTA, and 0.5 mM MgCl2 (pH 6.8); Ref. 5]. Protein concentration was determined using the Bio-Rad protein assay kit. The reaction mixture contained 2 mg/ml microtubule protein and the half-log step concentrations (0.89, 2.7, 8.9, and 27 μM) of E7010 in assembly buffer containing 1 mM GTP. Microtubule polymerization was initiated by warming the sample from 0°C to 37°C in a 1-ml cuvette, and turbidity (ΔA350) was recorded during the indicated time intervals with a spectrophotometer (Fig. 3A). In the study of the relationship between antiproliferative activity and microtubule polymerization-inhibitory activity (Fig. 3B), the wells of 96-well plates contained 1 mg/ml microtubule protein and log step concentrations of E7010 derivatives. The plates were incubated at 37°C, and the turbidity was recorded with a microplate reader (ThermoMax; Molecular Devices) for 20 min kinetically. The turbidity at 20 min (the polymerization in the control reached a plateau level) was plotted on a linear scale versus the concentration of the test compound on a log scale, and the concentration causing a 50% inhibition of polymerization was determined.
The relative resistance was determined in the absence of verapamil by 4.0 ng/ml and 10 μM verapamil to avoid the development of the mdr phenotype (8, 9). When the relative resistance of VCR-resistant cells to VCR reached about 10 times, the VCR-resistant clone P388-D-4 was cloned in a buffer. The reaction was stopped by rapid cooling to 4°C, and then the mixture was diluted with 5 ml of 0.1X assembly buffer, filtered through a stack of three Whatman DE81 ion exchange paper discs using a BRANDEL cell harvester. The reaction mixture (0.2 ml) contained tubulin and [3H]-labeled E7010 (2 μM, 0.0224 μCi/reaction), [3H]VCR (0.25 μM; 0.05 μCi/reaction), or [3H]CLC (1 μM; 0.1 μCi/reaction) in assembly buffer. The reaction was stopped by rapid cooling to 4°C, and then the mixture was diluted with 5 ml of 0.1X assembly buffer, filtered through a stack of three Whatman DE81 ion exchange paper discs using a BRANDEL cell harvester (Biomedical Research and Development Laboratories, MD), and washed with 10 ml of 0.1X assembly buffer.

Isolation of Non-MDR VCR-resistant P388. VCR-resistant cell lines that did not show the MDR phenotype were isolated from MNNG (Aldrich)-treated P388 cells by selection with both increasing doses of VCR (0.5, 1.0, 2.0, and 4.0 ng/ml) and 10 μM verapamil to avoid the development of the mdr phenotype (8, 9). When the relative resistance of VCR-resistant cells to VCR reached about 10 times, the VCR-resistant clone P388-V4-4 was cloned in VCR and verapamil-containing medium using the limiting dilution method. The relative resistance was determined in the absence of verapamil by MTT assay.

Isolation of E7010-resistant P388. E7010-resistant cell lines 0.5r-D, 1.0r-H, and 4.0r-M were isolated by MNNG-treated P388 cells by selection with increasing doses of E7010 (0.1, 0.2, 0.3, 0.4, 0.5, 0.7, 0.8, 0.9, 1.0, 1.2, 2.0, 3.0, and 4.0 μg/ml). When the relative resistance of E7010-resistant cells to E7010 reached about 5 (13 weeks), 10 (18 weeks), and 40 times (21 weeks), E7010-resistant clones 0.5r-D, 1.0r-H, and 4.0r-M were cloned, respectively. E7010-resistant cell line 0.6r-8 was isolated by a four-step selection. MNNG treatment was used at each step, and the dose of E7010 at each step was 0.1, 0.2, 0.3, and 0.6 μg/ml. After the four-step selection, 0.6r-8 was cloned.

RESULTS

The Effects of E7010 and Antitumor Drugs on the Proliferation of Human Tumor Cell Lines. The antiproliferative activities of E7010 and various clinically used antitumor drugs were tested against a panel of 26 human tumor cell lines (7 lung cancers, 10 colon cancers, 3 stomach cancers, 1 pancreatic cancer, 2 breast cancers, and 3 leukemias) by MTT assay. E7010 showed a dose-dependent and broad-spectrum antiproliferative activity (Fig. 1). The IC_{50} values of E7010 on various human tumors were rather similar (0.06—0.8 μg/ml), in contrast to those of VCR (0.0002—0.04 μg/ml), 5-FU (0.2—30 μg/ml), ADM (0.002—0.7 μg/ml), MMC (0.007—3 μg/ml), Ara-C (0.005—30 μg/ml), CPT (0.002—0.4 μg/ml), and CDDP (0.5—20 μg/ml).

The Effect of E7010 on Cell Cycle Progression. Antitumor agents are known to arrest cell cycle progression in S phase, G2, or M phase (10, 11). Therefore, the effect of E7010 on the cell cycle progression of P388 cells was examined by flow cytometry, and E7010 was found to arrest P388 cells in the G2-M phase. Next, we examined whether E7010 increases the percentage of mitotic cells, because agents that arrest cells in M phase, such as VCR, increase the mitotic index, but agents that cause G2 arrest, such as VP16, decrease it. E7010 caused a dose-dependent increase in the mitotic index, like VCR (Fig. 2), and the rise in mitotic index was well correlated with the decrease in cell proliferation. We also observed an increase in the mitotic index of s.c. implanted M5076 tumor at 18—24 h after the oral administration of E7010 (data not shown).

The Effects of E7010 and Its Derivatives on Microtubule Polymerization. The results described above and the immunofluorescence observation that E7010 caused the disappearance of cytoplasmic microtubules in colon 38 cells (data not shown) led us to examine E7010 for effects on microtubule polymerization. E7010 caused dose-dependent inhibition of microtubule polymerization (Fig. 3A). Furthermore, a linear relationship between the antiproliferative activity and the mitotic index was observed (Fig. 3B). The numbers of viable cells (□, □) and the mitotic index (□, □□) were determined as described in "Materials and Methods." Values represent the mean ± SE (bars) of three independent experiments.
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Inhibition of \(^{14}\text{C}\)-labeled E7010, \(^{3}\text{H}\)VCR, or \(^{3}\text{H}\)CLC Binding to Tubulin. To determine the binding site of E7010, inhibition of the binding of \(^{14}\text{C}\)-labeled E7010, \(^{3}\text{H}\)VCR, or \(^{3}\text{H}\)CLC to tubulin by each unlabeled compound was examined. The binding of E7010 to tubulin was inhibited by CLC and enhanced by VCR (Fig. 5A). The binding of CLC was inhibited by E7010 and was also enhanced by VCR (Fig. 5B). The enhancement of the binding by VCR was caused by stabilization of the CLC-binding activity of tubulin (12, 16). The binding of VCR was not inhibited by E7010 or CLC (Fig. 5C).

Lineweaver-Burk analysis demonstrated that E7010 is a competitive inhibitor of the binding of CLC and binds at the CLC site on tubulin (Fig. 5D). The \(K_i\) value for E7010 of \(^{3}\text{H}\)CLC was 3.3 \(\mu\text{M}\) (Fig. 5D), and the \(K_i\) values for CLC, POD, and NOC, reported to bind at the CLC site, were 2.7, 0.94, and 2.3 \(\mu\text{M}\), respectively (data not shown).

Cross-Resistance in VCR-resistant P388 Cells. Antimitotic drugs that are widely used in cancer chemotherapy, such as VCR, vinblastine, and Taxol, are good substrates for transport by P-glycoprotein (classical MDR phenotype; Refs. 17—19). Moreover, other types of resistance to Vinca alkaloids have been reported (20—22), and we isolated VCR-resistant cells (P388/V4—4) that did not show the classical MDR phenotype. Therefore, the effects of VCR, Taxol, ADM, CLC, and E7010 on two MDR P388 cells (P388/VCR and P388/V0.256) and P388/V4—4 cells were examined. The results are summarized in Table 1. P388/VCR and P388/V0.256 cells, which overexpress P-glycoprotein, were significantly resistant to VCR, Taxol, CLC, and ADM but were sensitive to E7010. P388/V4—4 cells, which...
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Fig. 5. A comparison of the effects of E7010, CLC, and VCR on the binding of $^{14}$C-labeled E7010, $[^3]$H]CLC, and $[^3]$H]VCR to tubulin. Microtubule protein (0.4 mg/ml) was incubated with $^{14}$C-labeled E7010 (A), $[^3]$H]CLC (B and D) or $[^3]$H]VCR (C) and the indicated concentrations of unlabeled compounds for 2 h at 37°C. A, B, and C: ●, E7010; □, CLC; O, VCR. In the Lineweaver-Burk analysis (D), the following concentrations of $[^3]$H]CLC were used: 0.56, 0.83, 1.25, 2, 4, and 8 μM. The binding was determined by the DEAE-cellulose filter method as described in “Materials and Methods.” Points, the mean for duplicate samples in a single experiment, which was repeated with similar results.

which were isolated by exposure to VCR in the presence of verapamil, showed cross-resistance to vinblastine, vindesine, and trisnordolastatin (a dolastatin analogue; Ref. 23) with resistance factors of 4.7, 9.4, and 8.7, respectively, but they had a collateral sensitivity to Taxol. P388/V4—4 cells were sensitive to E7010 and slightly resistant to CLC.

Cross-Resistance in E7010-resistant P388 Cell Lines. For the clinical application of a new drug, understanding the mechanisms by which resistance is developed is important. Therefore, we isolated four E7010-resistant cell lines and examined the sensitivity of E7010-resistant cell lines to clinically used antitumor drugs (VP16, 5-FU, CDDP, ADM, MTX, MMC, Ara-C, and melphalan; Fig. 6A) and antimitotic agents (VCR, Taxol, CLC, NOC, and POD; Fig. 6B). None of E7010-resistant cell lines (0.6r-8, 0.5r-D, 1.0r-H, and 4.0r-M) showed cross-resistance to any of the antitumor drugs of which the target is not tubulin. On clinically used antimitotic drugs, E7010-resistant cell lines exhibited no significant resistance to VCR but had increased sensitivity to Taxol. Among antimitotic agents that bind to the CLC site, NOC showed a similar pattern of resistance across the spectrum of E7010-resistant cell lines (resistance factor, 4.0r-M ≥ 1.0r-H > 0.5r-D ≥ 0.6r-8). On the other hand, POD exhibited a different pattern of resistance (resistance factor, 0.5r-D and 1.0r-H > 0.6r-8 and 4.0r-M). The pattern of resistance to CLC was similar to that of POD, although the resistance to CLC was minimal.

DISCUSSION

E7010 was found by screening a number of sulfonamides with widely different chemical structures (2) and shows a broad spectrum of activity against mouse and human tumors (3). In a Phase I study of E7010 using a single-dose schedule, some responses were observed (24), and a 5-day continuous administration study is in progress. We have demonstrated here that E7010 is an antimitotic agent, and the target of its antiproliferative action is tubulin. CQS was reported to have antiproliferative activity in vitro (25, 26), but the mechanism of its action has not yet been elucidated. Therefore, we examined the effect of CQS on cell cycle progression and tubulin polymerization. CQS did not arrest P388 cells in the G2-M phase and did not affect tubulin polymerization. Therefore, E7010 seems to be a unique sulfonamide antitumor agent.

Most of the tumor cell lines tested were almost equally sensitive to E7010 ($IC_{50} = 0.06–0.8 \mu g/ml$). This is consistent with the idea that the target of E7010 is tubulin, because microtubules in the mitotic spindle are important for cell proliferation of all cells. In contrast, a wider range of $IC_{50}$ values (0.002–0.04 μg/ml) was observed with VCR. This might be due to the differential drug accumulation of VCR among these tumor cells, which express P-glycoprotein to various extents. Indeed, HCT-15 and DLD-1, which were sensitive to E7010 ($IC_{50}$ values of 0.08 and 0.14 μg/ml, respectively) but very insensitive...
to VCR, were reported to express P-glycoprotein and to show differential sensitivity to non-MDR versus MDR drugs (27). These observations are consistent with the finding that P388/VCR and P388/V0.256 were resistant to VCR but sensitive to E7010. The patterns of antiproliferative activity against tumor cell lines except HCT-15 and DLD-1 were similar for VCR and E7010, although the ranges of IC\textsubscript{50} values were different.

To examine the mechanism of action of E7010, we first examined the effect on cell cycle progression, because this is related to the mechanism of action (10, 11). Antimetabolites, such as MTX and Ara-C, cause cells to accumulate in the S phase. Topoisomerase inhibitors, VP16 and CPT, ADM, and MMC inhibit cell cycle progression in the G\textsubscript{2}-M phase. Vinca alkaloids and Taxol arrest cells in the M phase. By flow cytometric analysis, we found that E7010 accumulated P388 cells in G\textsubscript{2}-M phase. E7010 caused dose-dependent increases in the mitotic index in parallel with an inhibition of cell proliferation, like VCR.

Because the antimitotic effects of antimitotic agents may be mediated by disruption (VCR) or stabilization (Taxol) of microtubules in mitotic spindles, the effects of E7010 on microtubule structure in colon 38 cells were examined, and E7010 was shown to cause the disappearance of cytoplasmic microtubules and mitotic spindles (data not shown). Therefore, the effects of E7010 and E7010 derivatives on microtubule assembly in a cell-free system were examined and compared with the growth-inhibitory activities. These experiments clearly demonstrated that the growth-inhibitory activity of E7010 is caused by the inhibition of microtubule assembly. Next, we examined whether E7010 can bind to tubulin and compared the binding properties of E7010 with those of VCR and CLC, although the structure of E7010 is quite different from that of the known tubulin binders, which bind to the CLC site or Vinca site on tubulin, such as CLC, NOC, Vinca alkaloids, rhizoxin, halichondrin, and so on. We found that E7010 binds to purified tubulin and that the binding site is the CLC site, not the Vinca site, although the binding properties of E7010 to tubulin were quite different from those of CLC. Therefore, E7010 is quite distinct in its action from clinically used Vinca alkaloids or Taxol. The preliminary structure-activity study (Fig. 3B) reveals that the addition of methoxyl groups to the lower phenyl ring decreases the activity (compounds 2, 14, and 19), which is intriguing in relation to the structural factors of other CLC site ligands such as CLC, and suggests that the ligand recognition on tubulin may be different between E7010 and CLC.

The antimitotic drugs, Vinca alkaloids and Taxol, are key drugs in cancer chemotherapy, but drug resistance mediated by P-glycoprotein limits their usefulness against MDR tumors that have acquired resistance in the course of chemotherapy or naturally (17–19). In this study and in the previous one (3), we found that MDR cells selected by exposure to VCR did not show cross-resistance to E7010. In the \textit{in vitro} tumor panel study, E7010 seemed to be effective against naturally resistant MDR cell lines such as HCT15, DLD-1, and OVCAR-4. There was also no cross-resistance with other MDR cell lines (KB 8–5, KB C-1, and KB C-2; data not shown). Because other types of drug resistance to \textit{Vinca} alkaloids have been reported (20–22), we selected VCR-resistant P388/V4-4 cells, which did not show the classical MDR phenotype, by exposure to VCR and verapamil. Interestingly, P388/V4-4 cells showed resistance to \textit{Vinca} alkaloids (VCR, vinblastine, and vindesine) and trisnordolastatin, an analogue of dolastatin 10 that binds to the \textit{Vinca} site on tubulin (13) but had collateral sensitivity to Taxol. Surprisingly, P388/V4-4 cells were not cross-resistant to E7010. Furthermore, to clarify the resistance to

### Table 1 The effects of VCR, Taxol, ADM, CLC, and E7010 on three VCR-resistant P388 cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>VCR IC\textsubscript{50} (\textmu M)</th>
<th>Taxol IC\textsubscript{50} (\textmu M)</th>
<th>E7010 IC\textsubscript{50} (\textmu M)</th>
<th>CLC IC\textsubscript{50} (\textmu M)</th>
<th>ADM IC\textsubscript{50} (\textmu M)</th>
</tr>
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<tbody>
<tr>
<td>P388/VCR</td>
<td>11.0 ± 2.4</td>
<td>6.3 ± 0.9</td>
<td>1.2 ± 0.2</td>
<td>6.4 ± 0.2</td>
<td>29.9 ± 2.9</td>
</tr>
<tr>
<td>P388/V0.256</td>
<td>82.8 ± 7.7</td>
<td>16.9 ± 0.3</td>
<td>1.5 ± 0.3</td>
<td>64.5</td>
<td>29.9 ± 2.9</td>
</tr>
<tr>
<td>P388/V4-4</td>
<td>8.4 ± 0.7</td>
<td>0.18 ± 0.05</td>
<td>1.3 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>0.58 ± 0.08</td>
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Values represent the mean ± SE.
E7010, four E7010-resistant P388 cell lines were selected by exposure to E7010. E7010-resistant P388 cell lines were not cross-resistant to VCR, but collateral sensitivity to Taxol was observed. The pattern of the cross-resistance to tubulin binders that bind at the CLC binding site was very interesting. The pattern of the cross-resistance to NOC across the spectrum of four E7010-resistant P388 cell lines was similar to that of E7010, but the pattern of the cross-resistance to POD was quite different. The pattern of cross-resistance to CLC was similar to that of POD, although the resistance to CLC was minimum. These differences in the resistance pattern seem to be consistent with the differences of the binding properties (binding site, temperature dependency, rate of binding, and reversibility of binding) among tubulin binders. These suggest the involvement of alterations of the target, tubulin itself or the polymerization state of tubulin, that specifically affect the binding of the E7010-type agent to tubulin in E7010-resistant cell lines, because the accumulation of 14C-labeled E7010 was similar in sensitive P388 cells and in E7010-resistant cell lines (data not shown). CDDP-, 5-FU-, VP16-, and CPT-resistant cell lines also lacked cross-resistance to E7010 (data not shown).

Few CLC site binding agents are active in in vivo solid tumor models, although many compounds have been reported to bind to the CLC site on tubulin, such as CLC analogues (28), steganacin (29), POD analogues (30), combretastatin analogues (31), benzimidazole derivatives (32), 1,2-hydropyrido[3,4-b]pyrazine derivatives (33), 2-styrylquinazolin-4(3H)-one derivatives (34), 2,3-dihydro-2-(aryl)-4(1H)-quinazolinone derivatives (35), and curacin A (36). We have shown here that E7010 is a unique antimitotic agent with a broad spectrum of antitumor activity. This drug is considered to be a candidate for clinical use, either alone or in combination chemotherapy.

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