Biological Activity of A-289099: An Orally Active Tubulin-binding Indolyloxazoline Derivative

Stephen K. Tahir,1 Michael A. Nukkala, Nicolette A. Ziellinski Mozy, R. Bruce Credo, Robert B. Warner, Qin Li, Keith W. Woods, Akiyo Claiborne, Stephen L. Gwaltney II, David J. Frost, Hing L. Sham, Saul H. Rosenberg, and Shi-Chung Ng

Cancer Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, Illinois 60064

Abstract
In this report, we describe the antitumor activity of A-289099, an indolyloxazoline derivative with antimitotic activity. A-289099 decreased the proliferation of a variety of cells with EC50 values ranging from 5.1 to 12.8 nM in a P-glycoprotein-independent manner. In cultured cells, microtubules depolymerized in a time- and dose-dependent manner when treated with A-289099. In competition-binding assays, A-289099 competed with [3H]colchicine for binding to tubulin (Ki = 0.65 μM); however, it did not compete with [3H]paclitaxel or [3H]vincristine. There was an accumulation of cells in G2-M after treatment with A-289099 for 8 h and a subsequent increase in a subhypodiploid population and an increase in caspase-3 activity, indicative of apoptosis after treatment for 24 and 48 h. The antitumor activities of A-289099 were evaluated using the syngeneic M5076 murine reticulum sarcoma flank tumor model. Animals size-matched for established tumors (∼350 mm3) were dosed p.o. (50 mg/kg every day) for 11 days starting on day 10 postinoculation. Tumors from A-289099-treated animals regressed throughout the 11-day dosing period with a percentage of the average vehicle-control-tumor-volume divided by the average vehicle-control-tumor-volume (% T/C) value of 11% after treatment for 7 days. Examination of tumor sections revealed an increase in internucleosomal DNA fragmentation or cell death within the central core after drug-treatment. A decrease in the perfusion of tumors was observed after drug-treatment that was localized primarily to the central core and closely associated with the regions of cell death. In summary, our findings indicate A-289099 is a promising, orally active tubulin-binding compound with antitumor activity in vivo.

Introduction
Tubulin is a major protein component of microtubules, and it is the target of numerous antimitotic drugs (1–4). Antimitotic agents such as the Vinca alkaloids and the taxanes have been applied in the clinical treatment of various neoplastic diseases; however, the usefulness of these agents is limited generally by the development of drug resistance (5–8). Colchicine and colchicine-like molecules are related by their binding to a common site on tubulin known as the colchicine site and their prevention of the normal polymerization of microtubules (9). No representatives of this class have yet been approved for use in cancer chemotherapy; however, several colchicine-like compounds with promising activity have been identified (10, 11).

We have recently reported on a series of oxadiazoline compounds, represented by A-105972 and A-204197, that bind to tubulin at the colchicine site and, in our study, inhibited microtubule polymerization with IC50 values of 3.4 and 4.5 μM, respectively (12, 13). The lack of stability and low oral bioavailability of A-105972 and A-204197, respectively, limit their in vivo activity. As part of our efforts to identify more potent and clinically effective antitumor compounds, we discovered a series of indolyloxazolines with antiproliferative activity (14). A potent derivative of A-204197, A-259745 inhibited tumor cell proliferation in vitro and showed dose-dependent growth delay of M5076 solid tumors in vivo (15). It was determined that A-259745 was a racemic mixture of inactive and active stereoisomers. The active stereoisomer A-289099 (Fig. 1) was tested as the most potent compound in this indolyloxazoline series, inhibiting tubulin polymerization with an IC50 of 2.3 μM, comparable with a similar clinical candidate, combretastatin A4 (1.6 μM; 14). Combretastatin A4, originally isolated from the African shrub, Combretum caffrum, is a tubulin-binding drug that has been shown to have both antitumor as well as antivascular effects (11). The tubulin polymerization IC50 of the inactive stereoisomer (A-289101) was >700 μM (14).

In this report, we characterize the biological effects of the active stereoisomer A-289099 on cancer cells by assessing its binding to tubulin, its effect on proliferation in a variety of tumor cells, cell cycle kinetics, and induction of apoptosis in vitro. We tested the oral activity of A-289099 by measuring its ability to regress the size of murine ovarian reticular sarcoma (M5076) tumors in mice. In addition to assessing changes in tumor volume, we also evaluated changes in the pattern of cell death and blood flow in tumors from drug-treated mice, to better understand the potential mechanism(s) of A-289099 on tumor growth delay and regression.

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1 To whom requests for reprints should be addressed, at Abbott Laboratories, Cancer Research, Global Pharmaceutical Research and Development, Department R4N6, AP8, 100 Abbott Park Road, Abbott Park, IL 60064. Phone: (847) 938-3709; Fax: (847) 938-1674; E-mail: stephen.k.tahir@abbott.com.
Materials and Methods

Chemicals. A-289099 [S-2-(1-methyl-5-indolyl)-5-(3,4,5-trime thoxyphenyl)-4,5-dihydro-oxazole] and its enantiomer were prepared by total synthesis at Abbott Laboratories (14). The ee\(^2\) was determined by high-performance liquid chromatography on a Chirapack AS column eluting with 15% ethanol in hexane. A-289099 had a \([\alpha]_D^{25}\) of +195.7° (c = 1.04, CH\(_2\)Cl\(_2\); 99% ee), and its enantiomer had a \([\alpha]_D^{25}\) of -184.5° (c = 1.04, CH\(_2\)Cl\(_2\); 98% ee). Colchicine, vincristine, and paclitaxel were purchased from Sigma Chemical Co. (St. Louis, MO), \([3H]\)colchicine (specific activity, 61.4 Ci/mmol), \([3H]\)paclitaxel (specific activity, 2.4 Ci/mmol), and \([3H]\)vincristine (specific activity, 4.6 Ci/mmol) were purchased from New England Nuclear (Boston, MA), Moravek Biochemicals (Brea, CA), and Amersham Pharmacia Biotech (Piscataway, NJ), respectively.

Cell Culture. The human cell lines A-549, NCI-H460, DLD-1, HCT-15, HCT-116, MDA-MB-231, and U-87-MG were purchased from American Type Culture Collection (Manassas, VA). NCI-H460/T200, a paclitaxel-resistant subline that overexpresses P-gp, was derived from NCI-H460 cells (12). Human cancer cells were cultured in RPMI 1640 (MEM was used for U-87-MG cells), supplemented with 10% fetal bovine serum and 1% antibiotic-antimycotic in a humidified chamber at 37°C containing 5% CO\(_2\).

MTS Assay. Cell proliferation was assessed using the colorimetric MTS assay (Promega, Madison, WI). Cells were plated in 96-well plates at 10,000 cells/well and treated with the compound for 48 h. After treatment, the plates were processed using the MTS assay according to manufacturer’s instructions.

Immunohistochemistry and Confocal Microscopy. Cells were grown and treated with 90 \(\mu\)M A-289099 in 8-chamber slides as described previously using a FITC-conjugated \(\alpha\)-antitubulin IgG (Sigma; diluted 1:75 in PBS) to label microtubules, and 15 \(\mu\)g/ml Hoechst 33342 to stain the DNA (12). Cells were imaged with a Bio-Rad MRC-1000 Confocal Imaging System.

Tubulin Competition-binding Scintillation Proximity Assay. The colchicine and paclitaxel competition-binding SPAs were conducted as described previously (12, 16) using biotin-labeled tubulin and streptavidin-coated SPA beads. The SPAs were conducted as described previously (12, 16) using biotin-labeled tubulin (Cytoskeleton, Denver, CO), and 0.2 mg polyvinyl tolune (PVT) SPA beads (Amersham Pharmacia Biotech) were used per reaction.

Flow Cytometric Analysis. Control and drug-treated cells were stained with PI, and the DNA content was analyzed using a Becton Dickinson FACSCalibur Flow Cytometer (San Jose, CA) as described previously (12).

Caspase-3 Activation Assay. The activation of caspase-3 in HCT-15 cells was measured by the cleavage of the fluorometric substrate Ac-DEVD-AMC (Biomol Research Laboratories, Plymouth Meeting, PA) as described previously (18) after A-289099 treatment for 24 and 48 h at 37°C in 96-well microtiter plates.

In Vivo Regression Trial. For the solid tumor model, a 1:10 (w/v) M5076 tumor homogenate was made from s.c. tumors using HBSS, and 0.5 ml was injected s.c. into the flank of female C57BL/6 mice (15). Tumor volume was estimated by measuring the length and width of the tumor mass with digital calipers and applying the formula \((L \times W^2)/2\). Animals (10 per treatment group) were size matched for established tumors (<350 mm\(^3\)), and therapy was administered 10 days post-tumor-inoculation. Mice were dosed p.o. with A-289099 at 50 mg/kg every day on days 10–21 and housed in isolation barrier facilities with food and water ad libitum. The vehicle used was 4% ethanol (Ethanol), 15% polyethylene glycol 400 (PG), and 81% D5W (dextrose 5% in water). Drug efficacy was based on percentage of the average treated-tumor-volume divided by the average vehicle-control-tumor-volume (% T/C).

Pharmacokinetic Analysis. A-289099 was extracted from plasma or tumor homogenates using liquid-liquid extraction with 1:1 (v/v) ethyl acetate:hexane at neutral pH. Samples were vortexed for 30 s and centrifuged for 15 min at 2500 rpm at 4°C. The upper organic layer was removed, evaporated to dryness at 35°C, reconstituted with 0.2 ml of mobile phase (see below this section), and analyzed on a 10-cm by 4.6-mm, 5-\(\mu\)m Kromasil C18 column (Higgins Analytical, Inc.) with acetonitrile:1%-acetic-acid mobile phase (50:50 by volume) at a flow rate of 1 ml/min with a 50-\(\mu\)l injection. A-289099 was quantified with MS/MS detection of 367.2 →156.8 m/z. Spiked plasma and tumor homogenates standards were assayed simultaneously with the samples, and hemoglobin concentrations were determined for all of the tumor homogenates to correct for blood contamination.

TUNEL Staining in Situ. Tumors were excised, frozen in liquid nitrogen and stored at \(-80°C\). Several 10-\(\mu\)m-thick frozen sections were collected from each tumor. Internucleosomal DNA fragmentation was detected with the Trevigen Apopotic Cell System (TACS) TUNEL assay kit (Trevigen, Inc., Gaithersburg, MD) according to the manufacturer’s instructions for fresh, unfixed tissues. Whole tumor sections were imaged with a Sony 3CCD color video camera using Image-Pro Plus (Media Cybernetics, Silver Spring, MD) imaging software.

Staining of Perfused Tumor Vessels. The DNA-binding dye Hoechst 33342 was used to visualize perfused blood vessels in tumors. Hoechst was dissolved in sterile saline at 9 mg/ml. Hoechst solution (0.1 ml) was injected i.v. into the mice via one of the lateral tail veins, and mice were sacrificed.

\(^2\) The abbreviations used are: ee, enantiomeric excess; P-gp, P-glycoprotein; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; SPA, scintillation proximity assay; PI, propidium iodide; DEVD-AMC, N-acetyl-Asp-Glu-Val-Asp-(7-amino-4-methylcoumarin); TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling.
12.8 nM) in contrast to the wide range of – (5.1 lines with various expression levels of P-gp were very similar with \([3H]\text{colchicine binding to tubulin (560 nM).} \]

Microtubules were stained with a FITC-conjugated A-289099 on microtubule organization. Microtubules were disrupted after treatment with 90 nM A-289099. After an 8-h treatment, cells appeared round, lacked intact microtubules and contained punctate staining (Fig. 2, B). At 24 and 48 h, there was a diffuse staining pattern in cells (Fig. 2, C and D, respectively). By 48 h, there was a noticeable increase in drug-treated cells with fragmented nuclei as compared with the untreated controls (Fig. 2, E and F, respectively).

**Table 1.** Effect of compounds on cell proliferation of various cell lines after 48-h treatment

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Cell type</th>
<th>P-gp statusa</th>
<th>A-289099</th>
<th>Paclitaxel</th>
<th>Colchicine</th>
<th>Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>H460/T200</td>
<td>Lung</td>
<td>Very high</td>
<td>9.2 ± 0.5</td>
<td>530 ± 23.9</td>
<td>397 ± 9.5</td>
<td>560 ± 34.5</td>
</tr>
<tr>
<td>HCT-15</td>
<td>Colon</td>
<td>High</td>
<td>5.1 ± 0.1</td>
<td>150 ± 50.6</td>
<td>61.5 ± 11.4</td>
<td>275 ± 35.8</td>
</tr>
<tr>
<td>NCI-H460</td>
<td>Lung</td>
<td>Low</td>
<td>10.4 ± 0.7</td>
<td>8.9 ± 1.3</td>
<td>23.6 ± 0.8</td>
<td>11.7 ± 1.3</td>
</tr>
<tr>
<td>A-549</td>
<td>Lung</td>
<td>Low</td>
<td>12.8 ± 3.4</td>
<td>31.4 ± 13.0</td>
<td>33.5 ± 7.0</td>
<td>53.7 ± 2.9</td>
</tr>
<tr>
<td>HCT-116</td>
<td>Colon</td>
<td>Low</td>
<td>6.1 ± 0.4</td>
<td>2.5 ± 1.2</td>
<td>5.9 ± 0.1</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>DLD-1</td>
<td>Colon</td>
<td>ndc</td>
<td>12.1 ± 3.0</td>
<td>8.9 ± 4.2</td>
<td>15.3 ± 2.9</td>
<td>18.4 ± 1.8</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>Breast</td>
<td>nd</td>
<td>6.3 ± 4.5</td>
<td>1.3 ± 0.3</td>
<td>6.2 ± 2.0</td>
<td>3.0 ± 3.3</td>
</tr>
<tr>
<td>U-87-MG</td>
<td>Glioblastoma</td>
<td>nd</td>
<td>9.3 ± 2.0</td>
<td>3.6 ± 0.9</td>
<td>5.5 ± 1.2</td>
<td>1.1 ± 1.0</td>
</tr>
</tbody>
</table>

a Relative P-gp levels were determined from National Cancer Institute quantitative polymerase chain reaction database (http://dtp.nci.nih.gov/mktargets/mt_index.html) and from data reported previously (12).

b Mean ± SD (n = 3). c nd, not determined.

Results

**A-289099 Inhibits Cell Proliferation and Disrupts Microtubules in Cancer Cells.** The effect of A-289099 on the proliferation of a variety of human cell lines is summarized in Table 1. The EC_{50} values for A-289099 for a variety of cell lines with various expression levels of P-gp were very similar (5.1–12.8 nM) in contrast to the wide range of EC_{50} values for paclitaxel (1.3–530 nM), colchicine (5.5–397 nM), and vincristine (1.1–560 nM).

HCT-15 human colorectal carcinoma cells, which overexpress P-gp, were used to demonstrate the effect of A-289099 on microtubule organization. Microtubules were stained with a FITC-conjugated α-antitubulin IgG, and the DNA was stained with Hoechst 33342. The normal microtubule distribution in untreated HCT-15 cells is shown in Fig. 2A. The cellular distribution of microtubules was rapidly disrupted after treatment with 90 nM A-289099. After an 8-h treatment, cells appeared round, lacked intact microtubules and contained punctate staining (Fig. 2B). At 24 and 48 h, there was a diffuse staining pattern in cells (Fig. 2, C and D, respectively). By 48 h, there was a noticeable increase in drug-treated cells with fragmented nuclei as compared with the untreated controls (Fig. 2, E and F, respectively).

**A-289099 Binds to the Colchicine-binding Site on Tubulin.** We assessed the interaction of A-289099 with tubulin by measuring its ability to bind to either the colchicine, paclitaxel, or Vinc-β-binding domains on tubulin using \([3H]\text{colchicine, [3H]paclitaxel, or [3H]vincristine in a competition-binding scintillation proximity assay (12, 16). We found that, over a concentration range of 0.1–100 μM, A-289099 competed with [3H]colchicine binding to tubulin (K_i = 0.65 μM); however, it did not compete with either [3H]paclitaxel or [3H]vincristine binding to tubulin (Fig. 3).}

**A-289099 Induces Cell Cycle Arrest in G_2-M and Induces Apoptosis in Cultured Cells.** The cell cycle distribution based on DNA content was determined by flow cytometry. HCT-15 cells were treated with 90 nM A-289099 for 48 h, and the DNA was stained using PI. There was an accumulation of HCT-15 cells in G_2-M and a concomitant...
decrease in cells in G<sub>0</sub>-G<sub>1</sub> after treatment from 4–12 h as compared with untreated controls (Fig. 4). The maximal increase in cells in G<sub>2</sub>-M was observed around 12 h. At 24 and 48 h, the cells in G<sub>2</sub>-M decreased, and a concurrent increase in subdiploid cells, indicative of apoptosis, was observed. We used the substrate for activated caspase-3, DEVD-AMC, to measure the induction of apoptosis after treatment with A-289099. Consistent with the increase in subdiploid cells by flow cytometry, we observed an increase in the ability of lysates from drug-treated HCT-15 cells to cleave DEVD-AMC in a time- and dose-dependent manner (Fig. 5).

Regression of M5076 Tumors after A-289099 Treatment. Animals were size matched for established tumors (~350 mm<sup>3</sup>), and therapy was administered 10 days post-tumor-inoculation. Animals were dosed p.o. with A-289099 at 50 mg/kg every day on days 10–21. There was clear regression in tumor volume after treatment for 4 days (Fig. 6). After 7 days of therapy, the average tumor volume was 1817, 1831, and 198 mm<sup>3</sup> in the untreated and vehicle controls and drug-treated animals, respectively, with a % T/C of 11%. After 11 days of treatment, the average tumor size had decreased to 111 mm<sup>3</sup>; however, once drug-therapy was stopped, the tumor volume began to increase.

In a separate arm, we compared the plasma and tumor concentrations of A-289099 for up to 12 h after multiple oral dosing for 5 days (50 mg/kg/day every day) in mice bearing established M5076 tumors. The tumor/plasma ratios were ~1:1 for both C<sub>max</sub> and area under the curve (AUC). The peak mean (±SE) concentrations in the plasma and tumors were 7.65 ± 0.4 µg/ml and 6.87 ± 0.6 µg/g, respectively, and the
AUC values in plasma and tumors were 12.7 and 14.3 μg·h/ml, respectively. By 12 h, the mean plasma and tumor concentrations were 0.174 ± 0.03 μg/ml and 0.355 ± 0.1 μg/g, respectively.

**Increase in TUNEL Staining after A-289099 Treatment.** A subset of tumors from the regression trial was used to evaluate cell death and blood perfusion in M5076 tumors. TUNEL staining was used to observe the extent and location of internucleosomal DNA fragmentation or cell death in control and drug-treated animals. After 17 days of growth, there was only a small degree of TUNEL staining observed in the central mass of untreated control tumors (Fig. 7A). Examination of tumor sections from drug-treated animals revealed an increase in internucleosomal DNA fragmentation or cell death primarily within the central core. In tumors after 7 days of treatment, there was a noticeable increase in the area of TUNEL-positive stained cells, within the central core of the tumors (Fig. 7C). After 11 days of treatment, most of the central tumors mass was TUNEL-positive in the drug-treated tumors (Fig. 7, E and G) surrounded by an outer rim of viable cells.

**Decrease in Vascular Flow in Tumors after A-289099 Treatment.** By injecting Hoechst dye into the tail vein of mice just before sacrifice, we were able to assess the degree of vascular perfusion in control and drug-treated tumors. Numerous perfused blood vessels (blue) were observed throughout the untreated control tumors (Fig. 7, B and H). A decrease in perfused regions of M5076 tumors was observed after 7 and 11 days of treatment (Fig. 7, D and F, respectively). The perfused regions of drug-treated tumors were localized mainly to the outer rim after 11 days of treatment. In addition, the apparent nonperfused regions in drug-treated tumors after 7- and 11-day treatments appeared to closely correspond to the TUNEL-positive regions of the tumors.

**Discussion**

Antimitotic compounds have been useful clinical agents to treat patients with neoplastic disease. Currently, there are several new drugs that both stabilize or destabilize microtubules that are in various stages of development (19). A major drawback for the use of antimitotic compounds, however, has been the development of drug resistance, often caused by the overexpression of efflux pumps such as P-gp and other multidrug resistance (MDR) proteins (5, 6). Because different clinically used classes of antimitotic compounds such as the Vinca alkaloids and the taxanes are substrates for P-gp, we tested A-289099 against a panel of cell lines with different expression levels of P-gp. Consistent with A-105972 and A-204197 (12, 13), A-289099 effectively inhibited tumor cell proliferation in a P-gp-independent manner.

Many antimitotic drugs that interfere with the normal formation of the mitotic spindle, either by increasing microtubule stability or depolymerization, can cause cells to arrest at the prometaphase/metaphase to anaphase transition known as the mitotic checkpoint (20). Our results show that, in addition to binding with tubulin and directly disrupting microtubules, treatment with A-289099 resulted in cell cycle arrest at G2-M. A-289099 cells were most likely arrested in mitosis because we have previously shown that a close analogue of A-289099, A-204197, initiated a phosphorylation cascade resulting in the engagement of active Cdc2 kinase, phosphorylation of Cdc25C, Bcl-2, and MPM-2 epitopes (12). These changes in protein phosphorylation are consistent with cell cycle arrest in mitosis as shown previously (21). Depending on the cell type, the mitotic block induced by other antimitotic compounds may persist for various lengths of time; however, most cells will exit the cell cycle and undergo apoptosis (20, 22). Consistent with other antimitotic compounds, we observed a decrease in mitotic cells, an increase in a subdiploid population and activation of...
caspase-3, suggesting that cells treated with A-289099 eventually became apoptotic.

We chose the murine reticular cell sarcoma M5076 to test the oral activity of A-289099 in vivo because it provides a consistent and rapid screening model, and they have been found to be refractory to conventional chemotherapy such as paclitaxel and vincristine (15). In this study, we observed a decrease in tumor volume of established M5076 tumors in mice dosed p.o. with A-289099, 50 mg/kg/day, for 11 days with a % T/C value of 11% after 7 days of treatment. In general, compounds with T/C values ≥42% are considered to be moderately active, whereas compounds with T/C values ≤10% are considered to have good activity (23, 24). The effect of A-289099 was reversible after 11 days of treatment because the tumor volume increased once therapy was stopped. Presumably, tumor growth after drug-treatment withdrawal came primarily from the rim of viable tumor cells.

Associated with the decrease in tumor volume was an increase in tumor cell death (TUNEL-positive cells) and a reduction in tumor perfusion, primarily in the central core of the tumors surrounded by a rim of viable, well-perfused cells. A-289099 should have been sufficient to inhibit cell proliferation in the tumors based on the MTS cell proliferation 

in vitro data (Table 1) given that the tumor concentration of A-289099 was 0.355 μg/g or ~890 nM after 12 h.

The decrease in tumor perfusion raises the possibility that A-289099 may not only act directly on tumor cell proliferation but may also have antivascular activity in vivo. Indeed, tubulin-binding agents such as colchicine and combretastatin A4 have been shown to be effective in disrupting the vasculature in a variety of tumor models (11, 25). Combretastatin A4 was shown previously to affect blood flow in tumors and to induce hemorrhagic necrosis, consistent with an antivascular mode of action (11). Considering its close homology in structure to Combretastatin A4, it seems plausible that A-289099 may exert its effect on tumor growth, in part, by affecting the tumor vasculature, possibly on the endothelial cells of newly formed tumor blood vessels (14). Thus, another advantage of A-289099 treatment may be to circumvent the problem of acquired drug resistance by having an effect on endothelial cells because they are genetically more stable than tumor cells (26).

In summary, we have demonstrated that A-289099 is a potent, p.o. active antimitotic compound. It disrupted microtubules, decreased cell proliferation in a P-gp-independent manner, and induced cell cycle arrest and apoptosis in cultured cells. M5076 murine ovarian sarcoma tumors regressed after oral administration of A-289099. Changes in tumors from drug-treated animals had an increase in apoptotic cells and a decrease in perfused tumor regions. Additional studies in vitro and in vivo with A-289099, used either alone or in combination with other agents, will help further elucidate the effectiveness of A-289099 as an antitumor as well as an antivascular drug with tubulin-binding properties.

References


Molecular Cancer Therapeutics

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