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ABSTRACT

Ten synthetic dihydropyridine analogues were investigated for their ability to reverse drug resistance in a multidrug-resistant human carcinoma cell line, KB-CI. Four dihydropyridine analogues completely reversed the resistance, three lowered the resistance, and three had little effect.

The radioactive photoactive dihydropyridine calcium channel blocker, $[^3]$H]azidopine, photolabels P-glycoprotein in membrane vesicles from KB-CI cells. This photolabeling was almost completely inhibited by excess dihydropyridine analogues that reversed or lowered drug resistance. In contrast, the labeling was not significantly inhibited by analogues that do not reverse resistance. Among other reversing agents, cepharanthine and reserpine inhibited the $[^3]$H]azidopine photolabeling, but thioridazine did not. N-Solanesyl-N',N''-bis(3,4-dimethoxybenzyl)ethylenediamine slightly inhibited the labeling at 100 µM. An anticancer agent, vinblastine, also inhibited the labeling.

The correlation between the reversing of the drug resistance and the inhibition of the $[^3]$H]azidopine photolabeling of P-glycoprotein by dihydropyridine analogues suggests a role for P-glycoprotein in multidrug resistance and also the reversing of the resistance by dihydropyridine analogues.

INTRODUCTION

The development of multiple resistance to anticancer agents in human tumor cells has been recognized as one of the major obstacles to successful cancer chemotherapy. Multidrug resistance is frequently characterized by enhanced drug efflux due to a M, 170,000 membrane glycoprotein (P-glycoprotein) encoded by the MDR1 gene in human cancer cells (1–4).

Cornwell et al. (5) have demonstrated that a photoaffinity analogue of vinblastine specifically labels P-glycoprotein. Most drugs that reverse multidrug resistance block drug efflux from cells and also inhibit photoaffinity labeling of P-glycoprotein with a photoanalog of vinblastine (6). Agents that reverse multidrug resistance appear to compete with an anticancer agent, vinblastine, for a binding site on the drug efflux pump, P-glycoprotein.

Recently, the photoactive dihydropyridine calcium channel blocker, azidopine, has been shown to photolabel P-glycoprotein (7). Vinblastine and nimodipine inhibited this labeling. P-glycoprotein seems to be an acceptor for some calcium channel blockers, such as verapamil, diltiazem, and dihydropyridine analogues, that are reported to reverse multidrug resistance (6, 7). In this study, we have used newly synthesized dihydropyridine analogues and investigated their ability to reverse multidrug resistance and also to inhibit photolabeling of P-glycoprotein by $[^3]$H]azidopine.

MATERIALS AND METHODS

Cell Culture and Cell Lines. Human epidermal KB carcinoma cells were obtained from Dr. Gottesman (National Cancer Institute, Bethesda, MD). The multidrug-resistant mutant KB-CI (KB-Ch1-8-5-11-24 cell line maintained in 1 µg/ml colchicine) was selected from human epidermal KB carcinoma cells with increasing concentrations of colchicine and maintained as described previously (8).

Cell Survival by Colony Formation. Cell survival was determined by plating 300 cells in 60-mm dishes in the absence of any drug. The various drugs were added 16 h later. After incubation for 10 days at 37°C, the colonies were stained with 0.5% methylene blue in 50% ethanol and counted. Solutions of all the drugs in dimethyl sulfoxide were freshly prepared before use. Relative resistance to vincristine was determined by dividing the Dso of KB for vincristine in the presence of dihydropyridine analogues by Dso of KB for vincristine or by dividing Dso of KB-CI for vincristine in the presence or absence of dihydropyridine analogues by Dso of KB for vincristine.

Determination of Calcium Channel-blocking Activities. Calcium channel blocking activities of compounds were determined by the ability of the compounds to inhibit the contraction of the taenia caecum from a guinea pig in the presence of calcium. A taenia caecum was excised from a male Hartley strain guinea pig (300–400 g) and suspended in an organ bath containing physiological salt solution (135 mM NaCl-5 mM KCl-2 mM CaCl2-1 mM MgCl2-15 mM NaHCO3-5.5 mM glucose) aerated with 95% O2 and 5% CO2 at 37°C. The taenia caecum was then stretched to an initial tension of 1 g and isometric contraction was measured with a force displacement transducer. After 30 min equilibration, the bathing solution was replaced by a Ca2+-free, high K+ (100 mM KCl-40 mM NaCl) solution. The taenia caecum relaxed completely within 30 min. Then CaCl2 (10 mM) was added. After further equilibration (30 min), the test compound solution (10−10−10−3 M) was cumulatively added. The result was expressed as a minus logarithm of the dose required for 50% of the maximum relaxation produced by 10−5 M papaverine.

Membrane Vesicle Preparation. Membrane vesicles from KB-CI cells were prepared as described (6) from cells grown in 24- x 24-cm dishes (GIBCO) under standard growth conditions (8). Protein concentrations were determined by the method of Bradford (9).

Photoaffinity Labeling. Membrane vesicles were incubated with 0.75 µM $[^3]$H]azidopine (53 Ci/mmol) for 15 min at room temperature in the presence or absence of various drugs. After continuous irradiation at 366 nm for 20 min at 25°C, samples were solubilized in a sodium dodecyl sulfate sample buffer as described by Debenham et al. (10).

Sodium Dodecyl Sulfate Gel Electrophoresis. Samples labeled with $[^3]$H]azidopine were analyzed by electrophoresis on a sodium dodecyl sulfate-polyacrylamide-urea gel using a modification of the system described by Debenham et al. (10) on a 5% polyacrylamide/4.5 M urea gel, pH 7.6, without a stacking gel, and by fluorography (11). Proteins were stained with Coomassie blue (0.25% in 50% (w/v) trichloroacetic acid).

Immunoprecipitation. Membrane vesicles containing 100 µg protein were photolabeled as described above except that the concentration of $[^3]$H]azidopine was 1.5 µM.

Labeled membrane vesicles were suspended in 2 ml of buffer A [50

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2 To whom requests for reprints should be addressed.

The abbreviations used are: Dso, concentration reducing cell survival by 50%; SDB-ethylenediamine, N-solanesyl-N',N''-bis(3,4-dimethoxybenzyl)ethylenediamine; NMR, nuclear magnetic resonance.

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mm Tris-HCl (pH 8.0)–150 mM NaH2PO4·2 mM MgCl2 containing 1% 3-[3-cholamidopropyl]dimethylammonio]-1-propanesulfonate and incubated for 30 min at 4°C (12). The membrane vesicles were incubated with 4 μg of monoclonal antibody, C-219 (Centocor, PA), that specifically recognize P-glycoprotein, at 4°C for 2 h. Then 200 μl of 20% protein A-Sepharose CL-4B (Pharmacia LKB Biotechnology, Inc.) suspension in buffer A were added. The mixture was incubated for 30 min at 4°C with continuous mixing, and the precipitates were washed four times with buffer A containing 1% 3-[3-cholamidopropyl]dimethylammonio]-1-propanesulfonate. The precipitates were used for sodium dodecyl sulfate-urea-polyacrylamide analysis.

Chemicals. Dihydropyridine analogues were newly synthesized by Nissan Chemical Ind., Ltd. (Chiba, Japan) with the following methods. For PAK-1, a solution of 1.0 g of ethyl N,N-dimethyl-P-acetonylphosphonamidate and 1.0 g of 2-(N-benzyl-N-methylamino)ethyl 3-amino- crotonate in 20 ml of toluene was refluxed for 15 h. The solvent was removed under reduced pressure for 15 h. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel with ethyl acetate: methanol (9:1) as an elutant to obtain 1.39 g (yield, 20%) of pure PAK-7, followed by the recrystallization from diethyl ether to yield pale yellow crystals (m.p. 104–106°C).

For PAK-2, a solution of 1.0 g of 1,3-dimethyl-2-[1-(3-chlorobenzylidene)acetonyl]-1,3-diazaphospholidine and 0.9 g of 2-(N-benzyl-N- methylamino)ethyl 3-amino-crotonate in 20 ml of toluene was refluxed for 150 h. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel with ethyl acetate:methanol (9:1) as an eluant to give 1.14 g (yield, 66%) of pure PAK-2 which was recrystallized from ethyl acetate to yield yellow crystals (m.p. 147–148°C).

For PAK-3 and -4, a solution of 1.7 g of (1R,3R,1R)-1,3-dimethylpropylene 1-(3-nitrobenzylidene)acetonylphosphonate derived from (2R,4R)-2,4-pentanediol as starting material and 1.9 g of 4-diphenylmethyl-1-piperadinoethyl 3-amino-crotonate in 10 ml of toluene was refluxed for 10 h. After cooling, the reaction mixture was subjected to chromatography on a silica gel with ethyl acetate:methanol (9:1) as an eluant to give 2.3 g (yield, 67%) of a mixture of diastereomers of PAK-3 and PAK-4 as yellow viscous oil.

To a solution of 28.8 g of ethanol, 5.76 g of a mixture of diastereomers of PAK-3 and PAK-4 and 1.89 g of 35% hydrochloric acid were added and the solvent was evaporated off under reduced pressure. Viscous hydrochloride obtained was recrystallized twice from 43 g of the same amount of acetone used in the previous step to give 2.0 g (yield, 31%) of pure PAK-4 as dihydrochloride.

For PAK-5, a solution of 0.45 g of 2-(N-benzyl-N-methylamino)ethyl 3-amino-crotonate and 0.53 g of 2,2-dimethylpropylene 1-(3-nitrobenzylidene)acetonylphosphonate in 20 ml of toluene was refluxed for 10 h. The solvent was removed under reduced pressure, and the residue was subjected to chromatography on a silica gel with ethyl acetate:ethyl alcohol (9:1) as an eluant to give 0.53 g (yield, 60%) of pure PAK-5.

For PAK-7, a solution of 4.0 g of O-3-(N-benzyl-N-methylamino)propyl-O'-methyl acetonylphosphonate, 2.1 g of m-nitrobenzaldehyde, and a few drops of pipericvine in 30 ml of benzene was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in 30 ml of toluene. To this solution, 2.0 g of methyl 3-amino-crotonate was added and this mixture was refluxed for 6 h. After solvent was distilled off under reduced pressure, the residue was subjected to chromatography on aluminum oxide with ethyl acetate:ethyl alcohol (9:1) as an eluant to obtain 1.39 g (yield, 20%) of pure PAK-7, followed by the recrystallization from CHCl3:CH2Cl2:CH3OH to give yellow needles (m.p. 108–109°C). This compound is a 1:1 mixture of diastereomers based on NMR analysis.

For PAK-8, a solution of 7.68 g of 2,2-dimethylpropylene 2-[3-(3-nitrobenzylidene)acetonylphosphonate and 4.28 g of N-octyl 3-amino-crotonate in 50 ml of toluene was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel with ethyl acetate as elutant to give 5.21 g (yield, 46%) of pure PAK-8, followed by recrystallization from diethyl ether to give pale yellow crystals (m.p. 104–106°C).

PAK-6, -9, and -10 were synthesized according to the method of Morita et al. (13, 14).

The structures and purities of these analogues were determined using the following procedures. Melting points were determined on Yanaco micromelting point apparatus. 1H-NMR spectra in CDCl3 solution were recorded on a Jeol FX90Q (36.2 MHz) spectrometer and chemical shifts were given in ppm with tetramethylsilane as an internal standard. 3P-NMR spectra in CDCl3 solution were recorded on a Jeol JMS D-300 instrument. Chromatography was carried out on a Merck Kieselgel 60 plate (70–230 mesh ASTM) or Merck aluminium oxide 60 plate.

[3H]Azidopine (53 Ci/mmol) was obtained from Amersham Corp. Vincristine, Adriamycin, reserpine, and actinomycin D were purchased from Sigma. SDB-ethylenediamine and cepharanthine were obtained from Nisshin Flour Milling Co. (Saitama, Japan) and Kaken Pharmaceutical Co., Ltd. (Osaka, Japan).

RESULTS

Reversing of Resistance in KB-CI Cells by Dihydropyridine Analogues. We have used newly synthesized dihydropyridine analogues to determine their ability to reverse resistance in multidrug-resistant KB-CI cells. The chemical structures of these newly synthesized dihydropyridine analogues are shown in Fig. 1. We used two concentrations of the dihydropyridine analogues. The lower concentration of the analogue did not inhibit colony formation of KB and KB-CI cells, whereas the higher one reduced the colony formation of both cell lines to about 95% of the initial value.

Fig. 2 shows an example of the colony formation assays used to test reversing effects of dihydropyridine analogue, PAK-1. KB-CI showed about 1200 times higher resistance to vincristine than KB. A combination of vincristine with 10 μg/ml PAK-1 almost completely reversed the drug resistance of KB-CI (Fig. 2). PAK-1 also completely reversed the resistance of KB-CI cells to Adriamycin and actinomycin D as well as vincristine (data not shown). Table 1 summarizes data from dose-response curves of combinations of various dihydropyridine analogues and vincristine. The reversing activities of nifedipine and nicardipine were also studied.

Four newly synthesized dihydropyridine analogues almost completely reversed the resistance of KB-CI cells to vincristine (Group 1), 3 lowered the resistance (Group 2), and 3 had little effect (Group 3). Nicardipine completely reversed and nifedipine lowered the drug resistance in KB-CI cells.

Calcium Channel Blocking Activities of Dihydropyridine Analogues. Table 2 shows the calcium channel blocking activity of 10 newly synthesized compounds. Nifedipine and nicardipine were also tested. Nicardipine was the most active compound among them and PAK-10 was the weakest blocker. PAK-5 was the most active calcium channel blocker among the newly synthesized compounds.

Effect of Dihydropyridine Analogues on Photoaffinity Labeling of P-Glycoprotein by [3H]Azidopine. A photoactive radioactive dihydropyridine analogue, [3H]azidopine, photolabels P-glycoprotein in plasma membranes of multidrug-resistant Chinese hamster lung cells (7). The ability of P-glycoprotein to recognize calcium channel blockers suggests that P-glycoprotein plays a role in the reversal of drug resistance by calcium channel blockers.

Because some dihydropyridine analogues in Group I and II
reverse multidrug resistance in human KB-C1 cells, and 10 μg/ml PAK-1 completely inhibited the efflux of vincristine from KB-C1 cells (data not shown), we investigated whether [3H]azidopine photolabels P-glycoprotein in membrane vesicles from KB-C1 cells and studied the effect of dihydropyridine analogues on the labeling. As shown in Fig. 3, [3H]azidopine specifically labels a Mr, 150,000–170,000 protein (Lane A) and the labeled protein is immunoprecipitated by the monoclonal antibody to P-glycoprotein, C-219 (Lane B), but not by normal mouse IgG (Lane C). The labeling of the Mr, 150,000–170,000 protein was not seen in drug-sensitive KB cells (data not shown).

We also examined whether dihydropyridine analogues inhibited the photolabeling of P-glycoprotein. Fig. 4 shows examples of the inhibitory effects of 3 representative dihydropyridine analogues of each group, PAK-2 (Group 1), PAK-7 (Group 2), and PAK-10 (Group 3) on the photolabeling.

Three analogues inhibited the photolabeling with relative potencies as follows: PAK-2 > PAK-7 > PAK-10. To quantify the data, gel slices corresponding to the bands on the autoradiogram were cut out and their radioactivities were determined.

One half of the newly synthesized dihydropyridine analogues in Group I inhibited photolabeling by 50% at 1 to 10 μM (Fig. 5A). The other half of the analogues in Group 1 and all analogues in Group 2 inhibited labeling by 50% at 10 to 100 μM (Fig. 5B), whereas half-maximal inhibition of labeling did not occur even at 100 μM in the case of analogues in Group 3.

Inhibition of Photolabeling by Vinblastine and Other Reversing Agents. Vinblastine inhibited [3H]azidopine photolabeling...
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Table 1 Effect of dihydropyridine analogues on the resistance of KB-Cl cells to vincristine

<table>
<thead>
<tr>
<th>Dihydropyridine analogues (μg/ml)</th>
<th>Relative resistance* to vincristine of KB-Cl</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>KB</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>PAK-1 5</td>
<td>0.1</td>
</tr>
<tr>
<td>PAK-2 10</td>
<td>0.1</td>
</tr>
<tr>
<td>PAK-3 5</td>
<td>0.3</td>
</tr>
<tr>
<td>PAK-4 5</td>
<td>0.3</td>
</tr>
<tr>
<td>Nicardipine 3</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
</tr>
<tr>
<td>PAK-5 5</td>
<td>0.3</td>
</tr>
<tr>
<td>PAK-6 10</td>
<td>0.2</td>
</tr>
<tr>
<td>PAK-7 10</td>
<td>0.1</td>
</tr>
<tr>
<td>Nifedipine 5</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td>PAK-8 5</td>
<td>0.7</td>
</tr>
<tr>
<td>PAK-9 10</td>
<td>0.7</td>
</tr>
<tr>
<td>PAK-10 30</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Determined as described in "Materials and Methods."
* Mean of two experiments.
—, not determined.

Table 2 Calcium channel-blocking activities of dihydropyridine analogues

<table>
<thead>
<tr>
<th>Agents</th>
<th>pIDso*</th>
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<td>Group 1</td>
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</tr>
<tr>
<td>PAK-1</td>
<td>7.54</td>
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<tr>
<td>PAK-2</td>
<td>7.37</td>
</tr>
<tr>
<td>PAK-3</td>
<td>8.02</td>
</tr>
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<td>PAK-4</td>
<td>7.12</td>
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<tr>
<td>Nicardipine</td>
<td>9.38</td>
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<tr>
<td>Group 2</td>
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</tr>
<tr>
<td>PAK-5</td>
<td>8.45</td>
</tr>
<tr>
<td>PAK-6</td>
<td>7.11</td>
</tr>
<tr>
<td>PAK-7</td>
<td>7.18</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>8.55</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td>PAK-8</td>
<td>6.16</td>
</tr>
<tr>
<td>PAK-9</td>
<td>7.51</td>
</tr>
<tr>
<td>PAK-10</td>
<td>6.53</td>
</tr>
</tbody>
</table>

* pIDso, minus logarithm of the dose required for 50% of the maximum relaxation produced by 10^-4 M papaverine.

of P-glycoprotein by 50% at between 1 and 10 μM. We also investigated other agents that reverse multidrug resistance, including SDB-ethylenediamine, thoridazine, reserpine, and cepharanthine.

Cepharanthine and reserpine inhibited the photolabeling of P-glycoprotein by [3H]azidopine by 50% at concentrations between 10 and 100 μM, whereas SDB-ethylenediamine and thoridazine inhibited labeling to only about 95 and 80%, respectively, at 100 μM (Fig. 6).

DISCUSSION

In this study, we screened a series of newly synthesized dihydropyridine analogues for their ability to reverse multidrug resistance in human KB cells. PAK-1 has weaker calcium channel-blocking activity compared with PAK-5 and nifedipine.
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but completely reverses drug resistance. PAK-5 and nifedipine are better at blocking calcium channels than PAK-1, but they only partially reverse the resistance. PAK-9, a more potent calcium channel blocker than PAK-6 and PAK-7, has a weaker reversing effect than either of them. There does not appear to be a direct relationship between the calcium channel-blocking activity of dihydropyridine analogues and their ability to reverse drug resistance.

We have recently reported that the synthetic isopenoid, SDB-ethylenediamine, does not block calcium channels but completely reverses drug resistance in multidrug-resistant KB cells (15, 16). Calcium channel-blocking activity seems not to be needed for the reversing agents to overcome multidrug resistance.

The reversing compounds all have a cationic nitrogen atom in their molecules; nonreversing analogues do not. This observation coincides with our previous reports that most of the reversing agents are cationic (2, 17, 18). However, not enough dihydropyridine analogues were examined in these studies to draw conclusions about the correlation between structure and reversing activity. More precise studies with more analogues are needed to formulate a hypothesis about structure-activity relationships.

Recently Safa et al. (7) and Yang et al. (19) reported that [3H]azidopine photolabels P-glycoprotein and the labeling is inhibited by vinblastine and some calcium channel blockers. We also studied for the ability of dihydropyridine analogues to inhibit [3H]azidopine labeling of P-glycoprotein in membrane vesicles from multidrug-resistant cells. All the dihydropyridine analogues (Groups 1 and 2) that reverse resistance inhibited photolabeling by [3H]azidopine, whereas the analogues in Group 3 unable to reverse the resistance only slightly inhibited the labeling. These data suggest that dihydropyridine analogues that reverse drug resistance may do so by a mechanism that involves interaction with P-glycoprotein. Some of the analogues, however, increased the sensitivity to vincristine of the parent KB cells which express only low levels of P-glycoprotein. Such analogues may also interact with molecules other than P-glycoprotein and may change the sensitivity of the cells to vincristine.

The binding of [3H]azidopine to P-glycoprotein was also inhibited by other reversing agents, cepharanthine (18) and reserpine (20), but not by thiordiazine (2). SDB-ethylenediamine only slightly inhibited the labeling. The binding sites of [3H]azidopine on P-glycoprotein may be identical with or partially overlap those of cepharanthine, reserpine, and dihydropyridine analogues that reverse drug resistance. We have recently synthesized a 125I-labeled photoaffinity analogue of SDB-ethylenediamine and demonstrated that SDB-ethylenediamine binds directly to P-glycoprotein. The binding of 125I-labeled photoanalogue of SDB-ethylenediamine is reduced by vinblastine. SDB-ethylenediamine inhibits 125I-NASV photolabeling of P-glycoprotein (6). The binding site of SDB-ethylenediamine on P-glycoprotein seems to overlap or be identical with that of vinblastine but not that of azidopine. However, since vinblastine inhibits the [3H]azidopine labeling of P-glycoprotein, the binding sites of SDB-ethylenediamine and azidopine appear to be very close or slightly overlapping.

Other possibilities are that the binding site of these agents to P-glycoprotein is identical but the affinity of these agents to P-glycoprotein is different, or the binding of one of these agents to P-glycoprotein induces conformational change of the protein and modulates its binding ability to other agents. We recently demonstrated that the $K_d$ of SDB-ethylenediamine photoanalogue is greater than that of azidopine. Further study is needed to elucidate the specific binding sites of anticancer agents and reversing agents on P-glycoprotein and their topological relationships.

The above results also suggest that it may be possible to screen quickly for dihydropyridine analogues that reverse multidrug resistance by measuring the inhibition of [3H]azidopine labeling of P-glycoprotein. Some analogues, however, may need to be metabolized by a cell before functioning as blockers of P-glycoprotein. Such analogues will be missed by this screen.

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* S. Akiyama et al., unpublished data.

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Correlation between Reversing of Multidrug Resistance and Inhibiting of [3H]Azidopine Photolabeling of P-Glycoprotein by Newly Synthesized Dihydropyridine Analogue in a Human Cell Line

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