A Phase I and Pharmacokinetic Study of a New Camptothecin Derivative, 9-Aminocamptothecin

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ABSTRACT

Camptothecins are the only available antitumor agents which target the nuclear enzyme topoisomerase I. 9-Aminocamptothecin (9-AC) is a water-insoluble derivative of camptothecin which has demonstrated impressive antitumor activity in preclinical models. While two other water-soluble derivatives, CPT-11 and topotecan, have successfully completed Phase I and Phase II testing, biochemical and tissue culture studies suggest that camptothecin analogues differ in characteristics which may be important in determining antitumor activity. We performed a Phase I trial of 9-AC to determine the pharmacokinetics, dose-limiting toxicity, and maximum tolerated dose of this agent when administered as a 72-h continuous i.v. infusion. Thirty-one patients with resistant solid cancers received 5-60 μg/m²h 9-AC for 72 h, repeated at 3-week intervals. The drug was administered in a vehicle containing dimethylacetamide, polyethylene glycol, and phosphoric acid. Blood samples were collected and the lactone (closed ring) form of 9-AC was quantitated. The maximum tolerated dose of 9-AC was determined to be 45 μg/m²h. Dose-limiting toxicity consisted of neutropenia. Thrombocytopenia was also prominent. There were no significant nonhematological toxicities. Minimal responses were seen in patients with gastric, colon, and non-small cell lung cancer. Although significant interpatient variation in plasma 9-AC lactone levels was observed, pooled data were fit to a two-compartment model, with a terminal half-life of 36 h. Analyses of topoisomerase protein levels in peripheral blood cells indicated decreases in topoisomerase I accompanied by increases in topoisomerase II in two of three patients.

9-AC is an active antitumor agent and may be administered safely as a 72-h infusion in patients with cancer. Although Phase II trials with a 72-h infusion of 9-AC are warranted, alternate schedules should be evaluated given the dramatic preclinical activity seen with more prolonged administrations.

INTRODUCTION

Interest in CPT3 and related analogues has increased since the discovery that this class of agents inhibits DNA topo I (1). Topo I is a 100-kDa nuclear protein which relaxes DNA supercoils arising during DNA replication and transcription (2). This relaxation process is accomplished by the introduction of a single-stranded nick in one DNA strand with passage of the intact strand and subsequent religation (3). CPT binds to and stabilizes the topo I/DNA complex and thereby induces single-strand DNA breaks (1, 4). These strand breaks are believed to impair DNA replication and result in cell death (5). Although topo I is a ubiquitous enzyme, comparisons of malignant and adjacent normal tissue have demonstrated that malignant tissue may contain significantly higher levels of topo I (6, 7).

CPT is a water-insoluble alkaloid derived from the wood of the oriental tree *Camptotheca acuminata*. This agent was originally found to have antineoplastic activity during screening of a large number of natural products by the National Cancer Institute (8). In the 1970s, Phase I and II trials of the water-soluble sodium salt demonstrated minimal antitumor activity and several toxicities, including dose-limiting myelosuppression, hemorrhagic cystitis, nausea, vomiting, diarrhea, alopecia, and dermatitis (9-11). These findings led to discontinuation of clinical studies. However, later work indicated that the most active form of the drug contains an intact lactone ring which is hydrolyzed to the sodium salt (12). Subsequently, two groups have synthesized water-soluble derivatives in which the lactone ring remains intact. The first of these agents, CPT-11, is a prodrug which undergoes deesterification to yield the active metabolite SN-38 (13). The second agent, topotecan, contains modifications at carbons 9 and 10 of the A ring (14). Both CPT-11 and topotecan have exhibited significant antitumor activity in Phase I and II trials (15, 16).

The promise of agents that inhibit topo I has led to interest in other camptothecin analogues, such as 9-AC. In preclinical studies, complete responses have been obtained with 9-AC in mice with xenografts of human cancers resistant to common anticancer agents (6, 17, 18). Moreover, mice treated with 9-AC showed no signs of gastrointestinal or bladder toxicity which had been observed with other derivatives.

The results of a Phase I and pharmacokinetic analysis of 9-AC administered as a 72-h continuous infusion are summarized in the present report. This schedule was chosen as a result of preclinical studies that suggested greater antitumor activity with prolonged administration schedules (6). Factors related to drug formulation and the desire to treat patients in the outpatient setting limited the infusion duration to 72 h. In this trial, we

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1 The abbreviations used are: CPT, camptothecin; topo I, topoisomerase I; 9-AC, 9-aminocamptothecin; AUC, area under the curve.

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have also studied alterations in topoisomerase levels in peripheral blood cells obtained from patients during therapy.

PATIENTS AND METHODS

Patient Selection

Patients were selected on the basis of the following eligibility criteria: (a) histologically confirmed solid cancer with no curative or standard treatment regimen; (b) measurable or evaluable disease; (c) life expectancy of >2 months; (d) Eastern Cooperative Oncology Group performance status 0–2; (e) preserved organ function evidenced by WBC > 3000/µl, platelets > 100,000/µl, bilirubin and AST < 1.5 x upper normal, creatinine < 1.5 mg/dl; (f) 0–2 prior chemotherapy regimens for metastatic disease; (g) >3 weeks since radiotherapy or chemotherapy and >1 week since surgery; (h) no uncontrolled or chronic diarrhea; (i) no uncontrolled serious medical or psychiatric disorder; (j) for women of childbearing potential, use of contraception, and no pregnancy; and (k) indwelling central venous catheter. All patients gave written informed consent according to federal and institutional guidelines.

Dosage and Drug Administration

9-AC Dosing. 9-AC (NSC 603071) was administered as a continuous i.v. infusion for 72 h via an ambulatory infusion pump with 5 µg/m²/h chosen as the initial dose level. This starting dose corresponded to one-tenth the maximum tolerated dose in dogs. Patients were treated in cohorts of 3–5; dose escalation was based on the Fibonacci method and included the following dose levels: 5, 10, 16.5, 25, 35, 45, and 60 µg/m²/h for 72 h. In the absence of dose-limiting toxicity or disease progression, patients received additional cycles of treatment at 21-day intervals. In addition, in the absence of dose-limiting toxicity after three cycles of therapy, patients were allowed to receive treatment at the next highest dose level.

9-AC Formulation and Administration. 9-AC was supplied by the National Cancer Institute in a two-part formulation: (a) a 1-ml ampul containing sterile drug concentrate of 5 mg/ml 9-AC in dimethylacetamide and (b) a sterile diluent containing 49 ml of 50% polyethylene glycol 400 and 50% 0.01 M phosphoric acid. On the first day of treatment, each ampul of the drug concentrate was drawn up in a plastic syringe and immediately added to 49 ml of the diluent. The diluted solution (100 µg/ml 9-AC) was filtered through a 5-µm filter and further diluted with polyethylene glycol/phosphoric acid diluent to a final volume of 25 ml. The 25 ml of diluted drug solution were added to a 50-ml medication cassette reservoir (Pharmacia Deltec, Inc., St. Paul, MN). A CADD-1 pump (Pharmacia Deltec, Inc.) was programmed to deliver 25 ml over 24 h and connected to the patient’s central venous catheter. As a result of stability considerations the infusion was replaced with a fresh drug solution at 24 and 48 h. Starting Phase I doses required additional dilution of the 100 µg/ml stock solution, which was performed using 0.9% sodium chloride. The drug concentration was maintained at ≤1 µg/ml in this salt solution since precipitation will occur at higher concentrations.

Treatment Plan. Pretreatment evaluation included physical examination, complete blood count, serum chemistries, electrocardiogram, urinalysis, and chest X-ray. All measurable or evaluable disease was quantified by examination and appropriate imaging studies. Relevant biochemical markers of disease (e.g., carcinoembryonic antigen) were also assayed prior to treatment. 9-AC was administered in the outpatient setting. After treatment, a history, physical examination, urinalysis, and serum biochemistries were repeated weekly (complete blood counts were performed twice weekly). Disease measurable by examination or plain radiographs was reevaluated after each cycle of therapy. Other imaging procedures required for disease measurement were repeated after two cycles. Tumor markers were obtained after each cycle of treatment.

Criteria for Dose-limiting Toxicity and Maximum Tolerated Dose

Dose-limiting toxicity was defined as either: (a) <500/µl neutrophils or <25,000/µl platelets for >7 days, or (b) irreversible grade 2 or any grade 3–5 nonhematological toxicity. Maximum tolerated dose was defined as the dose level that preceded a dose level where two of three patients experienced dose-limiting toxicity.

Response Criteria

Complete response was defined as disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor, for longer than 4 weeks, during which no new lesions appeared. Partial response was defined as reduction of >50% in the sum of the products of the perpendicular diameters of all measurable lesions lasting longer than 4 weeks, during which no new lesions appeared and no existing lesions enlarged. Minimal response was defined as reduction of <50%
in at least one measurable lesion lasting longer than 4 weeks. Progressive disease was defined as an increase of >25% in measurable lesions. Stable disease was defined as insufficient change in lesions to meet criteria for either response or progression. For nonmeasurable cancers with an elevated tumor marker, complete response required normalization of the marker for at least 6 consecutive weeks. Partial response required a decline in the marker by 80% from the baseline value for at least 6 consecutive weeks.

**Pharmacokinetics**

Heparinized blood samples (10 ml) were obtained immediately prior to treatment, and at 1, 4, 8, 24, 48, 72, 73, 74, 75, 80, 96, 104, and 120 h after infusion initiation. The 9-AC lactone was quantitated using an assay developed by Supko and Malspeis (19-21). Briefly, 50-μl aliquots of the plasma samples were deproteinized immediately with 2 volumes of methanol and stored at −80°C. After addition of the internal standard (camptothecin lactone), 15–90 pA of each sample were manually injected onto an 8NVPH 4μ radial compression cartridge (Waters) contained in an RCM100 radial compression module (Waters). The samples were eluted with acetonitrile:methanol:0.1 M ammonium acetate, pH 5.5 (25:10:65, v/v/v), at a flow rate of 1.0 ml/min driven by a Waters model 510 pump. Retention times were 7.0 min for 9-AC and 12.0 min for the internal standard. Postcolumn acidification was achieved with 0.3 M trifluoroacetic acid mixed in line with the column effluent at a rate of 0.3 ml/min. The drug was detected using a Waters model 470 fluorescence detector at λex=365, λem=440. The 9-AC lactone was quantitated by comparison to a standard curve of the peak height ratios using linear least-squares regression. The limit of detection of this assay was 5 ng/ml, and variation among replicate samples was found to be <5%.

Pharmacokinetic analysis included data from 12 patients treated at 45 μg/m²/h and 3 patients treated at 60 μg/m²/h. For each dose level, a least-squares nonlinear regression program (model 10, PC NONLIN; Statistical Consultants, Lexington, KY) was used to fit both individual patient values and mean pooled concentrations to a two-compartment open model. Possible relationships between pharmacokinetic parameters and leukocyte counts were assessed by calculating correlation coefficients.

**Analysis of Topo I and II Levels in Peripheral Blood Cells**

Mononuclear cells were obtained from selected patients using approximately 10 ml peripheral blood and Ficoll gradient centrifugation. These cells were lysed in a buffer containing 10 mM HEPES (pH 7.4), 1 mM EGTA, and 1 mM phenylmethylsulfonyl fluoride, subjected to SDS-PAGE, and transferred to nitrocellulose membranes. Analysis of bound topo I protein was performed using a polyclonal human antibody derived from patients with scleroderma (Topogen, Inc., Columbus, OH) as described (22). Topo II protein was quantitated on the same blots by stripping (incubation at 50°C for 30 min in a buffer containing 100 mM 2-mercaptoethanol, 2% SDS, and 62.5 mM Tris-HCl, pH 6.7) and reprobing with a polyclonal antibody prepared against a synthetic peptide derived from the carboxyl terminus of human topo II (Topogen, Inc.).

**RESULTS**

**Patient Characteristics.** Table 1 summarizes selected characteristics of the 31 patients who received a total of 122 courses of 9-AC. Gender was almost equally represented. Most patients had previously received both chemotherapy and radiotherapy,
although only three had impaired performance status. The majority of patients had metastatic colon or lung carcinoma; a variety of tumor types were present in the remainder of patients. Patients typically received multiple courses of 9-AC, with a median of 3 (range, 1–11). The dose levels which were evaluated in this study were 5, 10, 16.5, 25, 35, 45, and 60 μg/m²/h for 72 h.

Toxicity. Intravenous infusions of 9-AC were well tolerated. No toxicities occurred during the infusions other than mild to moderate nausea, suggesting that polyethylene glycol/phosphoric acid is an acceptable diluent. Few, if any, toxicities related to 9-AC therapy were evident at doses below 45 μg/m²/h. The most common toxicities were hematological; 50% of first courses administered at the highest two dose levels were associated with grade 4 neutropenia (Table 2). A nadir in neutrophil counts typically occurred 2 weeks after initiation of the infusion (median, day 12; range, 7–17), with recovery in counts usually evident 1 week later (median, day 19; range, 11–29). A similar pattern was seen in platelet count nadirs at the higher dose levels (data not shown). Anemia was also common in patients treated at these doses (Table 2). Neutropenia was defined as the dose-limiting toxicity, and 45 μg/m²/h as the maximum tolerated dose. Eight of 70 courses (11%) administered at or above the maximum tolerated dose were associated with dose-limiting neutropenia. Notably, three of seven of these courses were also associated with grade 4 thrombocytopenia. An apparent lack of cumulative myelosuppression was evidenced by similar or less prominent neutrophil nadirs in later courses compared to initial courses (Table 3). A significant interpatient variation in myelosuppression was also apparent (Table 3).

While hematological toxicities were common at the higher dose levels, nonhematological toxicity was minimal (Table 4). Antiemetics were not routinely used as premedications and mild to moderate nausea or vomiting occurred in 15% of courses administered at 45 μg/m²/h and in 27% of courses given at 60 μg/m²/h (Table 4). Alopecia was also common at these dose levels. Transient and mild diarrhea and mucositis were seen less commonly, and typically occurred within the first or second week of therapy. These gastrointestinal toxicities were easily managed with oral medications alone. There was no evidence of bladder or pulmonary toxicity.

Responses. Although there were no complete or partial responses, 9-AC treatment resulted in minimal responses in three patients. One of these patients had metastatic gastric carcinoma previously treated with cisplatin, with 5-fluorouracil and leucovorin, and with 5-fluorouracil, doxorubicin, and mitomycin C. After two courses of 9-AC a greater than 50% decrease was evident in several pulmonary lesions. Another response occurred in a patient with metastatic colon cancer previously treated with 5-fluorouracil-based therapies, in whom decreases in multiple pulmonary lesions occurred after one course of 9-AC. The third response, detectable after one course of 9-AC therapy, was manifested by a >50% decrease in a malignant pleural effusion in a patient with non-small lung cancer. Decreases in carcinoembryonic antigen of approximately 50% without change in measurable disease were seen in two other patients with colon and non-small cell lung cancer. Other patients experienced a relatively long period of stable disease while receiving 9-AC, including eight patients treated for at least 6 months.

Pharmacokinetics. Blood samples were analyzed for the 9-AC lactone using an assay developed by Supko and Malspeis (19–21). Although the lactone was detectable in some patients treated at lower doses, data sufficient for analyses were available only at the 45-μg/m²/h and 60-μg/m²/h dose levels. Pooled patient data from the two dose levels were fit to a two-compartment open model as described in "Patients and Methods" (Fig. 1). Significant variation in plasma concentrations of the 9-AC lactone was apparent, particularly at the 72-h measurement in patients receiving 45 μg/m²/h (Fig. 1A). The pharmacokinetic parameters determined by this model are listed in Table 5. Models of non-pooled data yielded results similar to those obtained from the pooled data (Table 5).

Topo I and II Levels in Peripheral Blood Cells. In order to investigate possible alterations in topoisomerase expression during 9-AC infusion, we prepared extracts from pe-
DISCUSSION

The clinical development of CPT analogues has led to the synthesis and evaluation of the water-soluble agents CPT-11 and topotecan. Both agents have demonstrated antitumor activity in a variety of cancers (16, 24–27). The toxicities associated with CPT-11 appear to depend on the schedule of administration, with diarrhea being prominent during intermittent or continuous dosing (28, 29) and leukopenia predominating during single-dose schedules (30). In contrast, dose-limiting toxicity for topotecan appears to be hematological, with leukopenia predominant during trials of short infusion schedules (15, 31, 32) and thrombocytopenia more evident in a trial using a 21-day infusion (26). The fact that these CPT derivatives differ substantially in their pharmacokinetics, toxicity, and effectiveness against tumor cell lines in vitro and in vivo indicates that clinical evaluation of other CPT derivatives is warranted (33–36). Moreover, recent work has identified other inhibitors of topo I which are different than CPT in both structure and possibly mechanism of topo I inhibition. These new agents include the fungal metabolite bulgarein (37), DNA minor groove ligands such as the Hoechst dye 33342 (38), and the plant product β-lapachone (39). Preliminary data using cell culture models suggest that some of these agents may be non-cross-resistant with CPT (38).

The results of our Phase I trial of 9-AC indicate that a 72-h infusion is safe and associated with minimal but detectable antitumor activity. Our trial indicated 45 μg/m²/h to be the maximum tolerated dose, and we recommend this dose for Phase II studies utilizing this infusion schedule. Dose-limiting toxicity consisted of neutropenia, which was similar to that seen with common cytotoxic agents. Significant thrombocytopenia was also common, and suggests that attempts at further dose escalation using myeloid cytokines will be difficult. Notably absent were significant nonhematological toxicities such as diarrhea or hemorrhagic cystitis, which have complicated trials of other CPT derivatives (11, 40).

Pharmacokinetic analyses of data obtained during the 45-μg/m²/h and 60-μg/m²/h infusions indicated a terminal half-life of approximately 36 h for the 9-AC lactone. This relatively prolonged elimination phase has been evident in trials of other CPT analogues: a terminal half-life of approximately 20 h was reported for total plasma CPT in a trial of CPT-Na⁺ (9), and a terminal half-life of 30 h for total CPT was seen in a recent trial of oral CPT.⁴ These findings contrast with the more rapid elimination of the water-soluble agents topotecan and CPT-11, where terminal half-lives in the range of 2–14 h have been found for both lactone and total drug (15, 27, 29, 31, 32). Notably, the terminal half-life of the SN-38 lactone appears to be longer than that of the CPT-11 lactone (27, 29).

Our data also indicate significant interpatient variation in peak plasma lactone levels. Moreover, the volumes of distribu-

⁴ J. S. Stehlin, personal communication.
Table 5  Two-compartment model parameters for the 9-AC lactone at dose levels of 45 \( \mu \text{g/m}^2/\text{h} \) and 60 \( \mu \text{g/m}^2/\text{h} \)

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>45 ( \mu \text{g/m}^2/\text{h} )</th>
<th>60 ( \mu \text{g/m}^2/\text{h} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled(^a)</td>
<td>Non-pooled(^a)</td>
</tr>
<tr>
<td>( t_{1/2a} (\text{h}) )</td>
<td>7.07</td>
<td>8.45 (8.2)</td>
</tr>
<tr>
<td>( t_{1/2b} (\text{h}) )</td>
<td>36.0</td>
<td>42.2 (34.4)</td>
</tr>
<tr>
<td>Clearance (liter/min/m(^2))</td>
<td>1.1</td>
<td>0.92 (0.30)</td>
</tr>
<tr>
<td>AUC (ng/ml ( \times \text{h} ))</td>
<td>2988</td>
<td>3899 (1243)</td>
</tr>
<tr>
<td>( C_{\text{max}} (\text{ng/ml}) )</td>
<td>38.8</td>
<td>52.0 (15.0)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>20.8</td>
<td>15.9 (8.44)</td>
</tr>
<tr>
<td>( V_{\text{central}} ) (liter/m(^2))</td>
<td>13.9</td>
<td>8.66 (5.43)</td>
</tr>
<tr>
<td>( V_{\text{steady state}} ) (liter/m(^2))</td>
<td>22.5</td>
<td>12.6 (3.60)</td>
</tr>
<tr>
<td>( k_{10} (\text{h}^{-1}) )</td>
<td>0.078</td>
<td>0.40 (0.53)</td>
</tr>
<tr>
<td>( k_{12} (\text{h}^{-1}) )</td>
<td>0.015</td>
<td>0.80 (1.40)</td>
</tr>
<tr>
<td>( k_{21} (\text{h}^{-1}) )</td>
<td>0.024</td>
<td>0.05 (0.05)</td>
</tr>
<tr>
<td>Regression coefficient</td>
<td>0.86</td>
<td>0.88 (0.075)</td>
</tr>
</tbody>
</table>

\(^a\) Modeling was performed after all available data were pooled (including 12 patients treated with 45 \( \mu \text{g/m}^2/\text{h} \) and 3 patients treated with 60 \( \mu \text{g/m}^2/\text{h} \)).

\(^a\) Modeling was performed with only complete individual patient data sets (four patients treated with 45 \( \mu \text{g/m}^2/\text{h} \) and three patients treated with 60 \( \mu \text{g/m}^2/\text{h} \)). Data are presented as means with SD in parentheses.

Fig. 2  Topo I and II protein levels in blood mononuclear cells during 9-AC administration. Blood mononuclear cells were collected at the indicated times for three patients treated with 45 \( \mu \text{g/m}^2/\text{h} \). Whole cell lysates were prepared by Western blotting using antibodies to topo I and II as described in ‘‘Patients and Methods.’’ Molecular weight markers are indicated.

Interpatient variation in myelosuppression was also evident in our trial, and attempts to correlate \( C_{\text{max}} \) or AUC to neutrophil decreases were unsuccessful. This result may be related to prior exposure of certain patients to myelopoietic toxins, or to other variables, such as cellular levels of topo I, which affect the cellular toxicity of 9-AC. Our findings are consistent with those from several trials of other CPT derivatives. For example, in a Phase I trial of CPT-11 significant interpatient variation was found in the maximum plasma concentrations and AUCs of the CPT-11 and SN-38 lactones at a given dose level, and little correlation was seen between pharmacokinetic parameters and...
toxicity (27). Similar observations were made in a trial of CPT-11 utilizing a 5-day continuous infusion (28). Moreover, in trials of topotecan utilizing 1-day or 21-day infusions, no relationship could be discerned between steady-state concentration and hematological toxicity (26, 31). Although some investigators have reported statistically significant associations between toxicities and AUCs for CPT-11 and SN-38 (44, 45), these contradictory findings suggest that for this class of agents, pharmacokinetic parameters such as AUC and steady-state concentration may not be predictive of biological effects.

As part of this Phase I trial, we were interested in studying the effects of 9-AC administration on cellular topoisomerase activity. Tumor tissue was not accessible in this population of patients, and consequently we chose to evaluate peripheral blood mononuclear cells in a small number of patients. Infusion of 9-AC resulted in an apparent decrease in cellular topo I in two patients, possibly as a result of cleavable complex formation. Experiments using cell culture models have indicated that the formation of these complexes results in an apparent decrease in cellular topo I levels as detected by Western blotting (46). In contrast, increases in cellular topo II levels were evident in the two patients coincident with the decline in topo I levels. Similar findings have been reported by Eckardt et al. (47), who found elevated topo II levels in a patient’s tumor tissue obtained shortly after treatment with topotecan. Although the basis for this up-regulation of topo II is unclear, increases in topo II levels have been observed in CPT-resistant cell lines with diminished topo I levels (48–50). Indeed, many CPT-resistant cell lines have been shown to be colaterally sensitive to topo II inhibitors (22, 50–52). In future trials of 9-AC or other CPT derivatives, examination of cellular topoisomerase levels may be useful in optimizing infusion schedules and in designing combination trials with topo II inhibitors.

We believe that additional evaluation of 9-AC is warranted. Given the modest antitumor activity seen with this 72-h infusion, continued evaluation should include studies of prolonged exposure to the drug. Notably, the dramatic results seen with 9-AC in preclinical models of human colon cancer involved biweekly s.c. injections for 5–6 weeks (6). Moreover, a recent Phase I trial of a 21-day continuous infusion of topotecan has demonstrated that this schedule is well tolerated and associated with significant antitumor activity (26). Since the current formulation of 9-AC may be difficult to use in prolonged or frequent intermittent infusion schedules, development of other formulations or even an oral compound may be advantageous for future studies.

REFERENCES


A phase I and pharmacokinetic study of a new camptothecin derivative, 9-aminocamptothecin.


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