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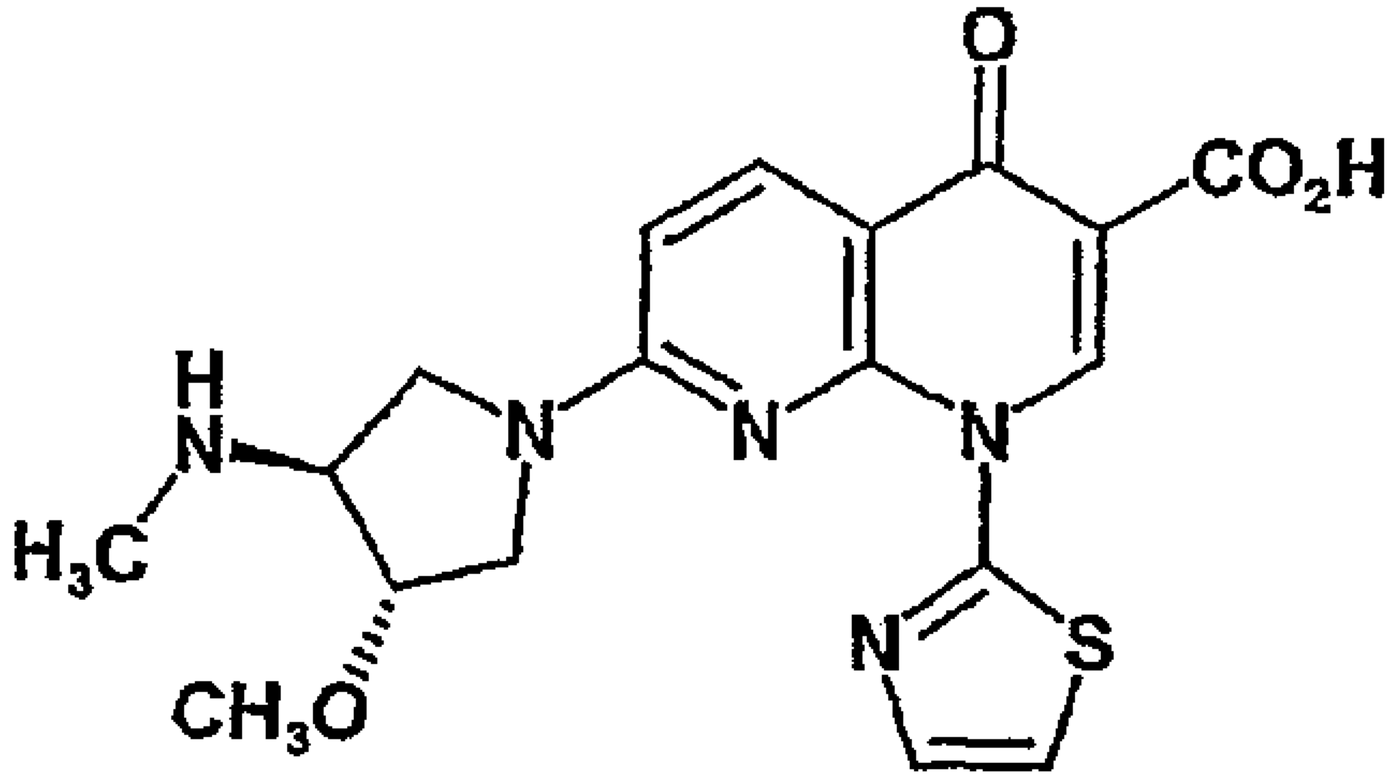
(54) Titre : MOYENS D'UTILISER SNS-595 DANS LE TRAITEMENT DU CANCER
(54) Title: METHODS OF USING SNS-595 IN TREATING CANCER



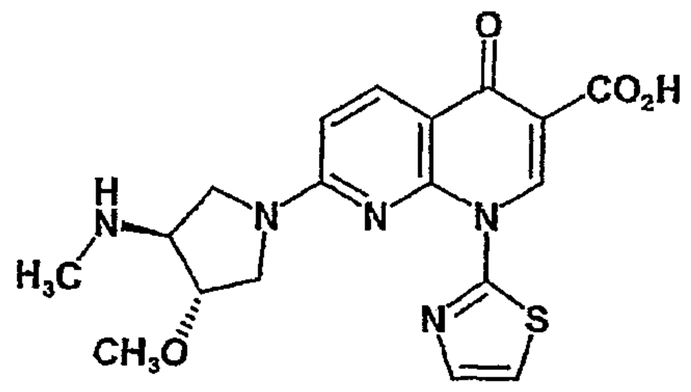
(57) Abrégé/Abstract:
The present invention relates to SNS-595 and methods of treating cancer using the same. Figure 1 depicts the plasma concentrations of SNS-595 over time among the various patient cohorts.

ABSTRACT

The present invention relates to SNS-595 and methods of treating cancer using the same. Figure 1 depicts the plasma concentrations of SNS-595 over time among the various patient cohorts.

METHODS OF USING SNS-595 IN TREATING CANCER

SNS-595 is novel naphthyridine cytotoxic agent that was previously known as AG-7352 (see e.g., Tsuzuki *et al., Tetrahedron-Asymmetry* **12**: 1793-1799 (2001) and U.S. Patent No. 5,817,669). The chemical name of SNS-595 is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazoyl)-1,8-naphthyridine-3-carboxylic acid and has the structure shown below



The present invention relates to pharmaceutical compositions and methods of using SNS-595 to treat cancer.

DESCRIPTION OF THE FIGURES

Figure 1 depicts the plasma concentrations of SNS-595 over time among the various patient cohorts.

DETAILED DESCRIPTION

In one aspect of the present invention, pharmaceutical composition is provided comprising:

a) SNS-595 and

b) an acid

in an aqueous solution wherein the pH of the solution is 2-3.5. As used herein, a numerical range is intended to be inclusive. For example, the range of pH 2-3.5 includes both pH 2 and pH 3.5. In one embodiment, the pH of the composition is 2-3. In another embodiment, the pH of the composition is 2.3-2.7. As used herein, an aqueous solution is a liquid comprising water.

Suitable examples of acids include both organic and inorganic acids such as acetic acid, ascorbic acid, benzene-sulfonic acid, ethanesulfonic acid, glycolic acid, hydrogen chloride,

hydrogen bromide, hydroxyethanesulfonic acid, lactic acid, maleic acid, methanesulfonic acid, proprionic acid, succinic acid, sulfuric acid, trifluoroacetic acid, and toluenesulfonic acid. In one embodiment, the acid is hydrochloric acid, methanesulfonic acid or lactic acid. In another embodiment, the acid is methanesulfonic acid.

In another embodiment, the pharmaceutical composition further comprises a tonicity agent. Suitable examples of a tonicity agent include amino acids (e.g., alanine and glycine), electrolytes (e.g., sodium chloride and potassium chloride), monosaccharides (e.g. glucose or galactose), disaccharides (e.g. sucrose) and hexahydric alcohols (e.g., mannitol and sorbitol). In another embodiment, the tonicity agent is sodium chloride, glucose, mannitol, or sorbitol. In another embodiment, the tonicity agent is a hexahydric alcohol. In another embodiment, the tonicity agent is sorbitol.

SNS-595 is a cytotoxic agent for the treatment of cancer. The types of cancers that can be treated using the inventive methods include but are not limited to: bladder cancer, breast cancer, cervical cancer, colon cancer (including colorectal cancer), esophageal cancer, head and neck cancer, leukemia, liver cancer, lung cancer (both small cell and non-small cell), lymphoma, melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma (including osteosarcoma), skin cancer (including squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, and uterine cancer.

In another aspect of the invention, a method of using SNS-595 to treat a human cancer is provided. The method comprises administering to a patient on the basis of body surface area, a dose of 10 mg/m^2-150 mg/m^2 of SNS-595. Body surface area calculations can be calculated for example, with the Mosteller formula wherein:

BSA (m^2) = square root of [(height (cm) x weight (kg)/3600].

In another embodiment, the dose is 10 mg/m^2-100 mg/m^2. In another embodiment, the dose is 30 mg/m^2-75 mg/m^2. In another embodiment, the dose is 40 mg/m^2-80 mg/m^2. In another embodiment, the dose is 50 mg/m^2-90 mg/m^2.

In another embodiment the dose is 20 mg/m^2-30 mg/m^2. In another embodiment the dose is 25 mg/m^2-35 mg/m^2. In another embodiment the dose is 40 mg/m^2-50 mg/m^2. In another embodiment the dose is 45 mg/m^2-55 mg/m^2. In another embodiment the dose is 50 mg/m^2-60

mg/m^2. In another embodiment the dose is 55 mg/m^2-65 mg/m^2. In another embodiment the dose is 60 mg/m^2-70 mg/m^2. In another embodiment the dose is 65 mg/m^2-75 mg/m^2. In another embodiment the dose is 70 mg/m^2-80 mg/m^2. In another embodiment the dose is 75 mg/m^2-85mg/m^2. In another embodiment the dose is 80 mg/m^2-90 mg/m^2. In another embodiment the dose is 85 mg/m^2-95 mg/m^2. In another embodiment the dose is 90 mg/m^2-100 mg/m^2.

In another embodiment the dose is 95 mg/m^2-105 mg/m^2. In another embodiment the dose is 100 mg/m^2-110 mg/m^2. In another embodiment the dose is 105 mg/m^2- 115 mg/m^2. In another embodiment the dose is 110 mg/m^2-120 mg/m^2. In another embodiment the dose is 115 mg/m^2-125 mg/m^2. In another embodiment the dose is 120 mg/m^2-130 mg/m^2. In another embodiment the dose is 125 mg/m^2- 135 mg/m^2. In another embodiment the dose is 130 mg/m^2-140 mg/m^2. In another embodiment the dose is 135 mg/m^2-145 mg/m^2. In another embodiment the dose is 140 mg/m^2-150 mg/m^2.

The administered dose of SNS-595 can be delivered simultaneously (e.g. a single bolus injection) or over a 24-hour period (e.g., continuous infusion over time or divided bolus doses over time) and is repeated until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter of measurable lesions has not increased by 25% or more from the last measurement. See e.g., Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, *Journal of the National Cancer Institute* **92(3)**: 205-216 (2000). Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

The administered dose of SNS-595 can be expressed in units other than as mg/m^2. For example, doses can be expressed as mg/kg. One of ordinary skill in the art would readily know how to convert doses from mg/m^2 to mg/kg to given either the height or weight of a subject or both . For example, a dose of 10 mg/m^2 -150 mg/m^2 for a 65 kg human is approximately equal to 0.26 mg/kg-3.95 mg/kg.

In another aspect of the present invention, SNS-595 is administered according to a dosing schedule. In one embodiment, the method comprises:

i) administering a dose of 10 mg/m^2-150 mg/m^2 of SNS-595 to a patient;

ii) waiting a period of at least one day where the subject is not administered any SNS-595;

iii) administering another dose of 10 mg/m^2-150 mg/m^2 of SNS-595 to the patient; and,

repeating steps ii)-iii) a plurality of times.

For example, if the waiting period were 6 days, then the initial dose of SNS-595 is administered on Day 1 (step i); the waiting period is six days (step ii); and the following dose of SNS-595 is administered on Day 8 (step iii). Other exemplary time periods include 2 days, 3 days, 13 days, 20 days, and 27 days. In another embodiment, the waiting period is at least 2 days and steps ii) through iii) are repeated at least three times. In another embodiment, the waiting period is at least 3 days and steps ii) through iii) are repeated at least five times. In another embodiment, the waiting period is at least 3 days and steps ii) through iii) are repeated at least three times. In another embodiment, the waiting period is at least 3 days and steps ii) through iii) are repeated at least five times. In another embodiment, the waiting period is at least 6 days and steps ii) through iii) are repeated at least three times. In another embodiment, the waiting period is at least 6 days and steps ii) through iii) are repeated at least five times. In another embodiment, the waiting period is at least 20 days and steps ii) through iii) are repeated at least three times. In another embodiment, the waiting period is at least 20 days and steps ii) through iii) are repeated at least five times. In another embodiment, the waiting period is at least 27 days and steps ii) through iii) are repeated at least three times. In another embodiment, the waiting period is at least 27 days and steps ii) through iii) are repeated at least five times.

In another embodiment, the dosing method comprises administering a weekly dose of SNS-595 to a subject. In another embodiment, the dosing method comprises administering a dose of SNS-595 to a subject every two weeks. In another embodiment, the dosing method comprises administering a dose of SNS-595 to a subject every three weeks. In another embodiment, the dosing method comprises administering a dose of SNS-595 to a subject every four weeks.

In another embodiment, the dosing method comprises a cycle wherein the cycle comprises administering a dose of SNS-595 to a subject every week for three weeks followed by a period of at least two weeks where no SNS-595 is administered to said subject and wherein the cycle is repeated a plurality of times. In another embodiment, the period where no SNS-595 is administered is two weeks. In another embodiment, the period where no SNS-595 is administered is three weeks.

In another aspect of the invention, a method of treating a solid tumor is provided. The method comprises:

i) administering a dose of 10 mg/m^2-100 mg/m^2 of SNS-595 to a patient;

ii) waiting a period of at least six days where the subject is not administered any SNS-595;

iii) administering another dose of 10 mg/m^2-100 mg/m^2 of SNS-595 to the patient; and,

iv) repeating steps ii)-iii) a plurality of times.

In another aspect of the invention, a method of treating a hematologic cancer such as leukemias and lymphomas is provided. The method comprises:

i) administering a dose of 60 mg/m^2-150 mg/m^2 of SNS-595 to a patient;

ii) waiting a period of at least two days where the subject is not administered any SNS-595;

iii) administering another dose of 60 mg/m^2-150 mg/m^2 of SNS-595 to the patient; and,

iv) repeating steps ii)-iii) a plurality of times.

In another aspect of the present invention, a method is provided supportive care to patients being treated with SNS-595. The method comprises:

a) administering to a patient a dose of 10 mg/m^2-150 mg/m^2 of SNS-595 and

b) administering a therapeutically effective amount of a supportive care agent.

The supportive care agent is any substance that prevents or manages an adverse effect from SNS-595 treatment and is administered according to the appropriate dosing regimen for that substance. For example, different supportive care agents for treating nausea have different

dosing regimen. While some are administered prophylactically, others are co-administered with SNS-595 while still others are administered after the administration of SNS-595. Illustrative examples of supportive care agents their doses and dosing regimens are found in The Physician's Desk Reference 57 th edition, 2003 (Montvale, NJ: Thomson PDR.

In one embodiment, the supportive care agent is an antiemetic. Illustrative examples of antiemetics include but are not limited to phenothiazines, butyrophenones, benzodiazapines, corticosteroids, serotonin antagonists, cannabinoids, and NK_1 receptor antagonists. Examples of phenothiazine antiemetics include prochlorperazine and trimethobenzamide. An example of a butyrophenone antiemetic is haloperidol. An example of a benzodiazapine antiemetic is lorazepam. An example of a corticosteroid antiemetic is dexamethasone. Examples of a serotonin antagonist antiemetic include ondansetron, granisetron, and dolasetron. An example of a cannabinoid antiemetic is dronabinol. An example of an NK1 receptor antagonist is aprepitant.

In another embodiment, the antiemetic is prochlorperazine. In another embodiment, the antiemetic is prochlorperazine and the therapeutically effective amount is 10 mg. In another embodiment, the antiemetic is prochlorperazine and the therapeutically effective amount is an oral dose of 10 mg before the administration of SNS-595. In another embodiment, the antiemetic is prochlorperazine and the therapeutically effective amount is an oral dose of 10 mg every four to six hours as needed after the administration of SNS-595.

In another embodiment, the antiemetic is dexamethasone. In another embodiment, the antiemetic is dexamethasone and the therapeutically effective amount is at least 4 mg. In another embodiment, the antiemetic is dexamethasone and the therapeutically effective amount is an oral dose of 4 mg before the administration of SNS-595. In another embodiment, the antiemetic is dexamethasone and the therapeutically effective amount is an oral dose of 8 mg before the administration of SNS-595. In another embodiment, the antiemetic is dexamethasone and the therapeutically effective amount is an intravenous dose of between about 10 mg and about 20 mg before the administration of SNS-595. In another embodiment, the antiemetic is dexamethasone and the therapeutically effective amount is an oral dose of 4 mg every six to twelve hours as needed after the administration of SNS-595.

In another embodiment, the antiemetic is lorazepam. In another embodiment, the antiemetic is lorazepam and the therapeutically effective amount is 1 mg. In another embodiment, the antiemetic is lorazepam and the therapeutically effective amount is an oral dose of 1 mg before the administration of SNS-595. In another embodiment, the antiemetic is lorazepam and the therapeutically effective amount is an intravenous dose of 1 mg before the administration of SNS-595. In another embodiment, the antiemetic is lorazepam and the therapeutically effective amount is an oral dose of 1 mg every four to six hours as needed after the administration of SNS-595.

In another embodiment, the antiemetic is dolasetron. In another embodiment, the antiemetic is dolasetron and the therapeutically effective amount is 100 mg. In another embodiment, the antiemetic is dolasetron and the therapeutically effective amount is an oral dose of 100 mg before the administration of SNS-595. In another embodiment, the antiemetic is dolasetron and the therapeutically effective amount is an intravenous dose of 100 mg before the administration of SNS-595.

In another embodiment, the antiemetic is ondansetron. In another embodiment, the antiemetic is ondansetron and the therapeutically effective amount is at least 10 mg. In another embodiment, the antiemetic is ondansetron and the therapeutically effective amount is an intravenous dose of 10 mg before the administration of SNS-595. In another embodiment, the antiemetic is ondansetron and the therapeutically effective amount is an intravenous dose of 32 mg before the administration of SNS-595.

In another embodiment, the antiemetic is granisetron. In another embodiment, the antiemetic is granisetron and the therapeutically effective amount is 10 μg/kg. In another embodiment, the antiemetic is granisetron and the therapeutically effective amount is an intravenous dose of 10 μg/kg before the administration of SNS-595. In another embodiment, the antiemetic is granisetron and the therapeutically effective amount is at least 1 mg. In another embodiment, the antiemetic is granisetron and the therapeutically effective amount is an oral dose of 1 mg before the administration of SNS-595. In another embodiment, the antiemetic is granisetron and the therapeutically effective amount is an oral dose of 2 mg before the administration of SNS-595.

In another embodiment, the antiemetic is aprepitant. In another embodiment, the antiemetic is aprepitant and the therapeutically effective amount is at least 80 mg. In another embodiment, the antiemetic is aprepitant and the therapeutically effective amount is an oral dose of 125 mg before the administration of SNS-595. In another embodiment, the antiemetic is aprepitant and the therapeutically effective amount is a daily oral dose of 80 mg for at least two days after the administration of SNS-595.

In another embodiment, the supportive care agent is a hematopoietic agent. A hematopoietic agent is a molecule that stimulates hematopoiesis. Illustrative examples of hematopoietic agents include but are not limited to granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin and erythropoiesis stimulating protein, and derivatives thereof. Examples of G-CSF include but are not limited to filgrastim and its derivatives including pegfilgrastim. An example of GM-CSF includes sargramostim. An example of erythropoietin is epoetin alfa. An example of erythropoiesis stimulating protein is darbepoetin alfa.

In another embodiment, the hematopoietic agent is G-CSF. In another embodiment, the hematopoietic agent is filgrastim. In another embodiment, the hematopoietic agent is filgrastim and the therapeutically effective amount is at least 4 μg/kg. In another embodiment, the hematopoietic agent is filgrastim and the therapeutically effective amount is a daily dose of at least 4 μg/kg for at least 7 days after the administration of SNS-595. In another embodiment, the hematopoietic agent is filgrastim and the therapeutically effective amount is a daily subcutaneous dose of between about 4 μg/kg and about 8 μg/kg for at least 7 days starting from the third day after the administration of SNS-595. In another embodiment, the hematopoietic agent is filgrastim and the therapeutically effective amount is a daily subcutaneous dose of between about 4 μg/kg and about 10 μg/kg for at least 14 days starting from the third day after the administration of SNS-595.

In another embodiment, the hematopoietic agent is pegfilgrastim. In another embodiment, the hematopoietic agent is pegfilgrastim and the therapeutically effective amount is 6 mg. In another embodiment, the hematopoietic agent is pegfilgrastim and the therapeutically effective amount is a daily subcutaneous dose of 6 mg after the administration of SNS-595. In another embodiment, the hematopoietic agent is pegfilgrastim and the therapeutically effective

amount is 100 μg/kg. In another embodiment, the hematopoietic agent is pegfilgrastim and the therapeutically effective amount is a daily dose of 100 μg/kg after the administration of SNS-595.

In another embodiment, the hematopoietic agent is GM-CSF. In another embodiment, the hematopoietic agent is sargramostim. In another embodiment, the hematopoietic agent is sargramostim and the therapeutically effective amount is 250 $\mu g/m^2$. In another embodiment, the hematopoietic agent is sargramostim and the therapeutically effective amount is a daily intravenous or subcutaneous dose of 250 $\mu g/m^2$. In another embodiment, the hematopoietic agent is sargramostim and the therapeutically effective amount is a daily intravenous or subcutaneous dose of 250 $\mu g/m^2$ as needed starting from the third day after the administration of SNS-595. In another embodiment, the hematopoietic agent is sargramostim and the therapeutically effective amount is a daily intravenous or subcutaneous dose of 250 $\mu g/m^2$ as needed starting from the tenth day after the administration of SNS-595.

In another embodiment, the hematopoietic agent is erythropoietin. In another embodiment, the hematopoietic agent is epoetin alfa. In another embodiment, the hematopoietic agent is epoetin alfa and the therapeutically effective amount is at least 150 units/kg. In another embodiment, the hematopoietic agent is epoetin alfa and the therapeutically effective amount is an intravenous or subcutaneous dose of 150 units/kg three times a week after the administration of SNS-595. In another embodiment, the hematopoietic agent is epoetin alfa and the therapeutically effective amount is an intravenous or subcutaneous dose of 300 units/kg three times a week after the administration of SNS-595. In another embodiment, the hematopoietic agent is epoetin alfa and the therapeutically effective amount is 40,000 units. In another embodiment, the hematopoietic agent is epoetin alfa and the therapeutically effective amount is a weekly dose of 40,000 units after the administration of SNS-595.

In another embodiment, the hematopoietic agent is erythropoiesis stimulating protein. In another embodiment, the hematopoietic agent is darbepoetin alfa. In another embodiment, the hematopoietic agent is darbepoetin alfa and the therapeutically effective amount is between about 1.5 μg/kg and about 4.5 μg/kg. In another embodiment, the hematopoietic agent is darbepoetin alfa and the therapeutically effective amount is a weekly dose of between about 1.5 μg/kg and about 4.5 μg/kg.

EXAMPLE 1

Pharmaceutical composition suitable for injection or intravenous infusion

Acidic compositions (< pH 4) provided the appropriate balance of increased solubility of SNS-595 and desirable pharmaceutical properties (e.g. increased patient comfort by causing less irritation at the delivery site). An illustrative example of a suitable composition comprises: 10 mg SNS-595 per mL of aqueous solution of 4.5% sorbitol that is adjusted to pH 2.5 with methanesulfonic acid. One protocol for making such a solution includes the following for making a 100mg/10mL presentation: 100 mg of SNS-595 and 450 mg D-sorbitol are added to distilled water; the volume is brought up to a volume of 10 mL; and the pH of the resulting solution is adjusted to 2.5 with methanesulfonic acid. The resulting composition is also suitable for lyophilization. The lyophilized form is then reconstituted with sterile water to the appropriate concentration prior to use.

EXAMPLE 2

Pharmacokinetics of SNS-595 in cancer patients

SNS-595 was administered to enrolled patients for up to six cycles. A cycle is defined as a three-week period, with SNS-595 administered on the first day of each cycle (day 0), followed by at least 21 days of observation. SNS-595 was administered to cohorts of at least 3 patients and dose escalation occurred by sequential cohort. Doses of SNS-595 were linear with AUC∞ and its pharmacokinetic properties were remarkably consistent among patients in the same cohort. Figure 1 depicts the plasma concentrations of SNS-595 over time among the various patient cohorts and Table 1 shows the pharmacokinetic parameters derived there from.

Table 1

Dose (mg/m2)	HL (hr)	C0 (ng/mL)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	Cl_obs (mL/min/kg)	Vz_obs (L/kg)	Vss_obs (L/kg)	MRTINF_obs (hr)
3	16.27	152.25	138.80	750.98	1139.55	1.14	1.55	1.44	21.96
SD	4.871	82.282	80.566	87.622	263	0.318	0.297	0.277	6.836
6	20.69	376.59	347.00	2400.00	2990.29	0.71	1.28	1.24	29.05
SD	0.327	243.598	214.96	170.556	245.64	0.153	0.295	0.218	1.15
12	17.81	2888.66	2246.67	5395.53	6329.15	0.78	1.17	1.07	23.67
SD	3.898	1302.71	1065.145	292.281	181.804	0.126	0.258	0.184	5.021
24	16.14	2924.46	2703.33	11133.03	12655.32	0.83	1.15	1.08	21.65
SD	2.601	2884.702	2573.02	468.453	851.458	0.108	0.124	0.165	5.261
48	21.32	1984.52	2868.00	21098.53	27347.36	0.99	1.57	1.46	28.90
SD	6.32	189.677	2379.899	9405.346	14382.787	0.616	0.567	0.47	8.91
60	17.63	4797.47	4537.50	28112.17	33616.18	0.83	1.20	1.08	23.71
SD	4.15	2215.20	1947.89	9127.12	13081.44	0.352	0.37	0.218	6.93

The embodiments of the present invention for which an exclusive property or privilege is claimed are defined as follows:

1. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 60 mg/m^2.

2. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 70 mg/m^2.

3. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 80 mg/m^2.

4. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 90 mg/m^2.

5. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 100 mg/m^2.

6. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 110 mg/m^2.

7. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 120 mg/m^2.

8. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 130 mg/m^2.

9. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 140 mg/m^2.

10. A compound which is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid for use in treating leukemia in a patient, wherein the compound is for administration to the patient in a weekly dose of 150 mg/m^2.

11. The compound for use according to any one of claims 1 to 10, wherein the administration of the compound to the patient is in combination with a supportive care agent selected from the group consisting of phenothiazine, butyrophenone, benzodiazepine, corticosteroid, serotonin antagonist, cannabinoid, NK receptor antagonist, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, erythropoietin, erythropoiesis stimulating protein, darbepoietin alfa, and derivatives thereof.

12. The compound for use according to any one of claims 1 to 11, wherein the administration comprises:

i) weekly;

ii) followed by a period of at least six days where the compound is not for administration;

iii) administration of a second weekly dose; and

iv) repeating ii) and iii) a plurality of times.

13. The compound for use of claim 12, wherein the period is at least 13 days, at least 20 days, or at least 27 days.

14. The compound for use of claim 12, wherein the period is at least 6 days and steps ii) through iii) are repeated at least three, or at least five times.

15. The compound for use of claim 12, wherein the period is at least 20 days and steps ii) through iii) are repeated at least three, or at least five times.

16. The compound for use of claim 12, wherein the period is at least 27 days and steps ii) through iii) are repeated at least three, or at least five times.

17. The compound for use according to any one of claims 1 to 10, wherein the administration is every two, three, or four weeks.

18. The compound for use according to any one of claims 1 to 10, wherein the administration is every week for three weeks followed by a period of at least two weeks where the compound is not for administration, and wherein administration is repeated a plurality of times.

19. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 30 mg/m^2.

20. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 35 mg/m^2.

21. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 40 mg/m^2.

22. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 45 mg/m^2.

23. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 50 mg/m^2.

24. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 55 mg/m^2.

25. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 60 mg/m^2.

26. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 65 mg/m^2.

27. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-

thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 70 mg/m^2.

28. A compound for use in treating leukemia in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 75 mg/m^2.

29. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 10 mg/m^2.

30. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 20 mg/m^2.

31. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 25 mg/m^2.

32. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 30 mg/m^2.

33. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 35 mg/m^2.

34. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 40 mg/m^2.

35. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 45 mg/m^2.

36. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 50 mg/m^2.

37. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 55 mg/m^2.

38. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 60 mg/m^2.

39. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 65 mg/m^2.

40. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-

1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 70 mg/m^2.

41. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 75 mg/m^2.

42. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 80 mg/m^2.

43. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 85 mg/m^2.

44. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 90 mg/m^2.

45. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 95 mg/m^2.

46. A compound for use in treating ovarian cancer in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid and the compound is for administration to the patient in a dose of 100 mg/m^2.

47. A compound for use in treating a solid tumor in a patient, wherein the compound is (+)-1,4-dihydro-7-[(3S,4S)-3-methoxy-4-(methylamino)-1-pyrrolidinyl]-4-oxo-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acid, for administration to the patient at a dose selected from the group consisting of 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2 and 100 mg/m^2:

i) followed by a period of at least six days in which the compound is not for administration;

ii) administration of a second dose selected from the group consisting of 10 mg/m^2, 20 mg/m^2, 30 mg/m^2, 40 mg/m^2, 50 mg/m^2, 60 mg/m^2, 70 mg/m^2, 80 mg/m^2, 90 mg/m^2 and 100 mg/m^2 of the compound; and,

iii) repeating steps i) and ii) a plurality of times.

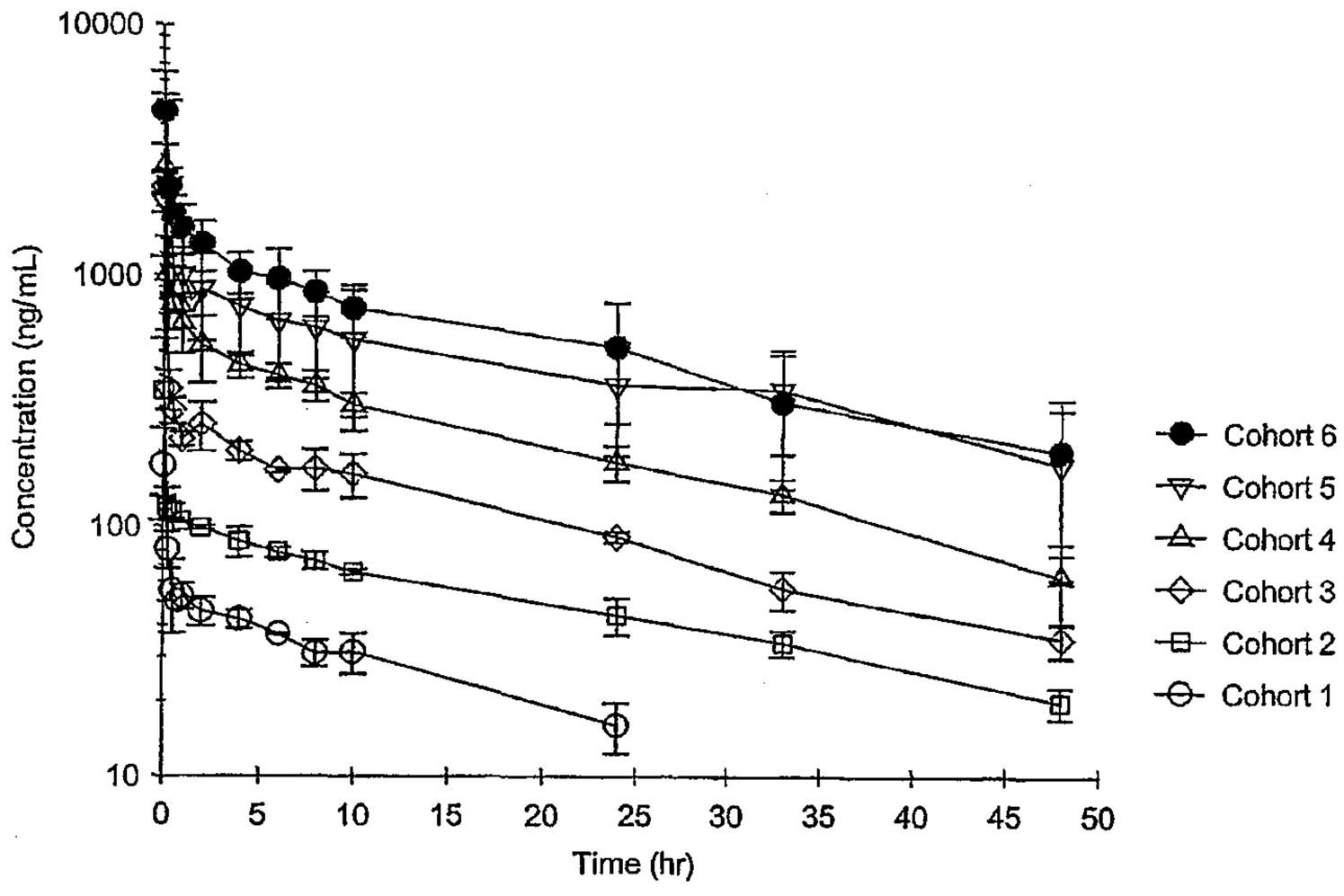
48. The compound for use according to any one of claims 19 to 47, wherein the administration of the compound to the patient is in combination with a supportive care agent selected from the group consisting of phenothiazine, butyrophenone, benzodiazepine, corticosteroid, serotonin antagonist, cannabinoid, NK receptor antagonist, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, erythropoietin, erythropoiesis stimulating protein, darbepoietin alfa, and derivatives thereof.

49. The compound for use according to any one of claims 1 to 48, wherein the administration of the compound is in the form of a pharmaceutical composition comprising the compound and an acid in an aqueous solution, wherein the pH of the solution is 2-3.5.

50. The compound for use of claim 49, wherein the acid is acetic acid, ascorbic acid, benzene-sulfonic acid, ethanesulfonic acid, glycolic acid, hydroxyethyethanesulfonic acid, lactic acid, maleic acid, methanesulfonic acid, propionic acid, succinic acid, sulfuric acid, trifluoroacetic acid, or toluenesulfonic acid.

51. The compound for use according to claim 49 or claim 50, wherein the acid is methanesulfonic acid.

52. The compound for use according to any one of claims 49 to 51, wherein the pH of the solution is 2.5.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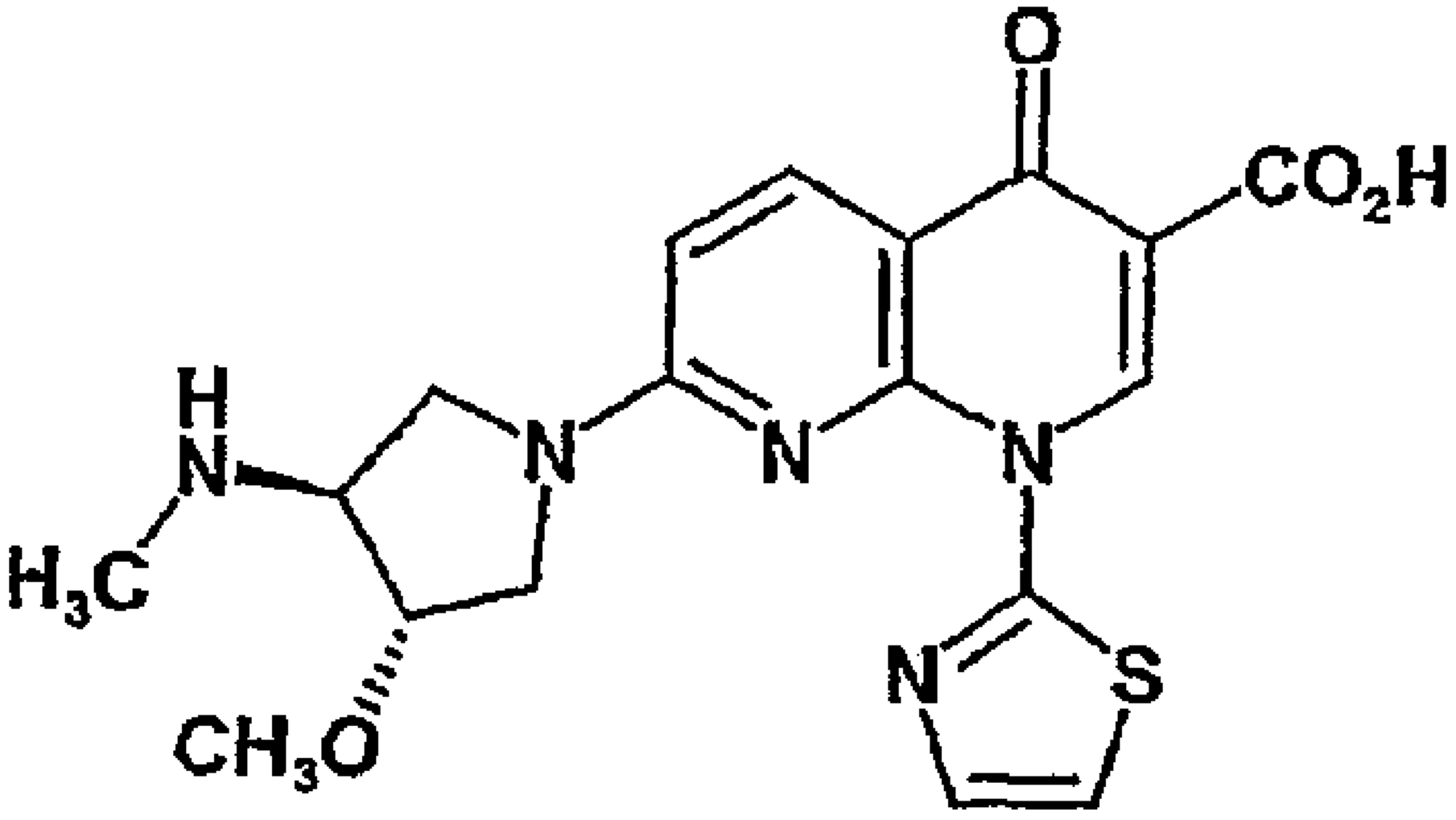
1000
100
10
Concentration (ng/mL)
0
5
10
15
20
25
30
35
40
45
50
Time (hr)
Cohort 6
Cohort 5
Cohort 4
Cohort 3
Cohort 2
Cohort 1

FIGURE 1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N
H3C
N
N
N
N
S
CH3O