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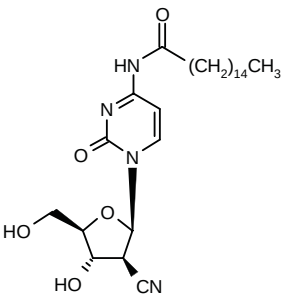
CS-682

Antineoplastic
Antimetabolite

2'-Cyano-2'-deoxy1-(β-D-arabinofuranosyl)-N^4-palmitoylcytosine

N-[1-(2-Cyano-2-deoxy-β-D-arabinofuranosyl)-1,2-dihydro-2-oxo-4-pyrimidinyl]hexadecanamide



$C_{26}H_{42}N_4O_5$ Mol wt: 490.6408

CAS: 151823-14-2

EN: 195704

Synthesis*

CS-682 has been synthesized by several related ways (1):

1) By acylation of 2'-cyano-2'-deoxy-1-(β-D-arabinofuranosyl)cytosine (I) with hexadecanoyl chloride (II) and trimethylsilyl chloride in pyridine. Scheme 1.

2) By acylation of 2'-cyano-2'-deoxy-1-(β-D-arabinofuranosyl)cytosine (I) with hexadecanoyl anhydride (III) in hot DMF. Scheme 1.

3) The protection of the OH groups of 2'-cyano-2'-deoxy-1-(β-D-arabinofuranosyl)cytosine (I) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine gives the 3',5'-cyclic disiloxane (IV), which is acylated by means of hexadecanoic acid (V) and DCC in THF, yielding the silylated compound (VI). Finally, this compound is deprotected with tetrabutylammonium fluoride (TBAF) in acetic acid. Scheme 1.

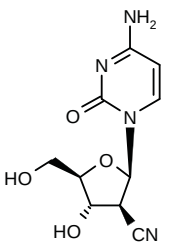
4) The acylation of cytidine (VII) with hexadecanoyl anhydride (III) in hot DMF gives N^4-hexadecanoylcytidine (VIII), which is protected with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine, yielding the 3',5'-cyclic disiloxane (IX). The oxidation of (IX) with pyridinium dichromate in dichloromethane affords the ketonic derivative (X), which is treated with NaCN in ethyl acetate/phosphate buffer to give 2'-*C*-cyano-N^4-hexadecanoyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (XI). The reaction of (XI) with phenoxythiocarbonyl chloride and DMAP in triethylamine provides the thiocarbonate (XII), which is reduced with AIBN and tributyltin in refluxing toluene to give the 2'-deoxy compound (VI). Finally, this compound is desilylated with TBAF in acetic acid. Scheme 2.

Introduction

A novel deoxycytidine antimetabolite of cytosine, 1-(2-cyano-2-deoxy-β-D-*arabino*-pentofuranosyl)cytosine (CNDAC) [I] was found to have antitumor activity but was easily metabolized to an inactive metabolite by cytidine deaminase. The stability of various CNDAC derivatives was examined and the N^4-palmitoyl derivative, CS-682, was selected as the most promising compound (2).

Pharmacological Actions

CS-682 was active against subcutaneously implanted murine tumors when administered orally every 3 days for 6 times and when administered intraperitoneally on days 1, 5 and 9 at 50 mg/kg/day (2). CS-682 was also active against human tumors implanted in nude mice by oral



[I]

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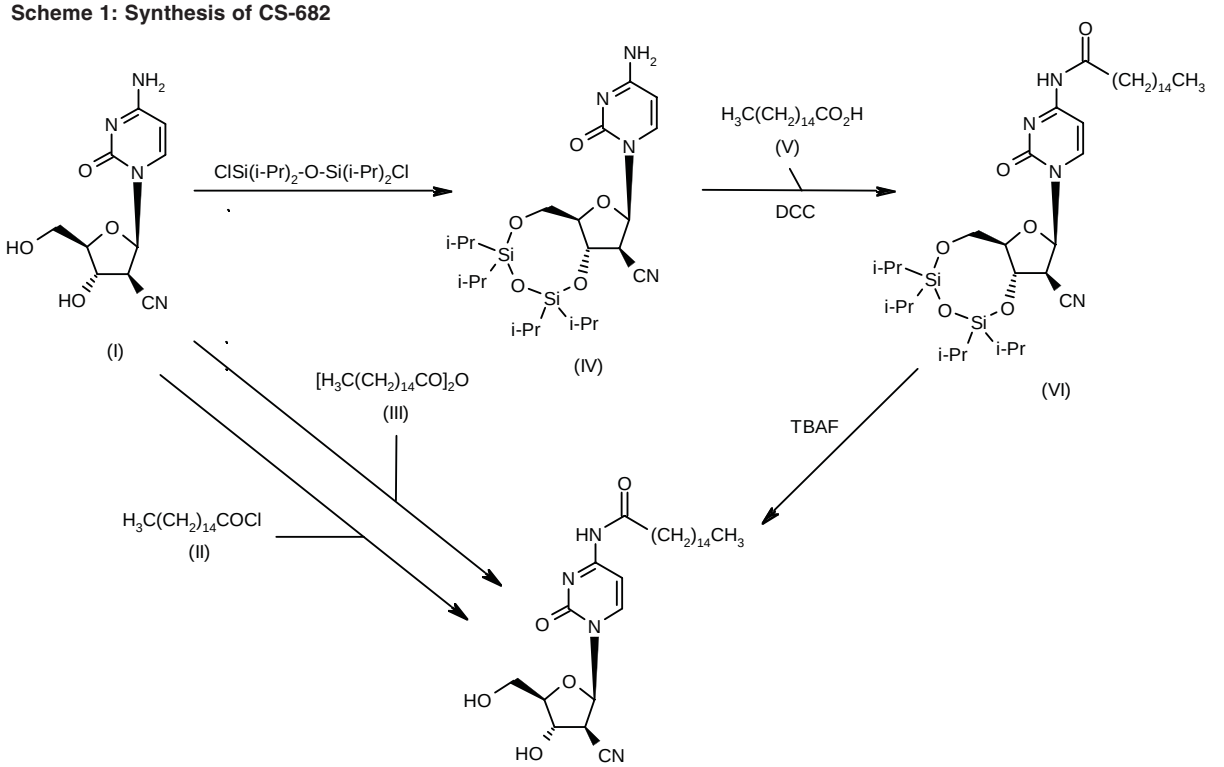
Scheme 1: Synthesis of CS-682



administration on a schedule of 5 times weekly for 6 weeks or every 3 days for 6 weeks. Treatment with CS-682 resulted in complete regressions in 4 gastric, 3 breast, 1 lung and 1 hepatic tumors (3, 4). Inhibition rates after CS-682 treatment were 97-100%, 80-90%, 74-100% and 86-98% for stomach, colon, lung and spleen carcinomas, respectively, and 83-100% in other tumors such as liver, ovary, kidney and esophagus (4).

In nude mice implanted with human tumor xenografts, the therapeutic ratios (maximum tolerated dose/minimum effective dose) after oral treatment with CS-682 (every 3 days for 6 times) were 25.3, 10.6 and 5.94 in MC-2 breast, St-40 stomach and WiDr colon carcinomas, respectively (5).

CS-682 was also active against P388 leukemia cells resistant to mitomycin, vincristine, 5-fluorouracil and cisplatin. Survival time of mice implanted with these tumors was in the range of 105-437% (5).

Mechanism of Action

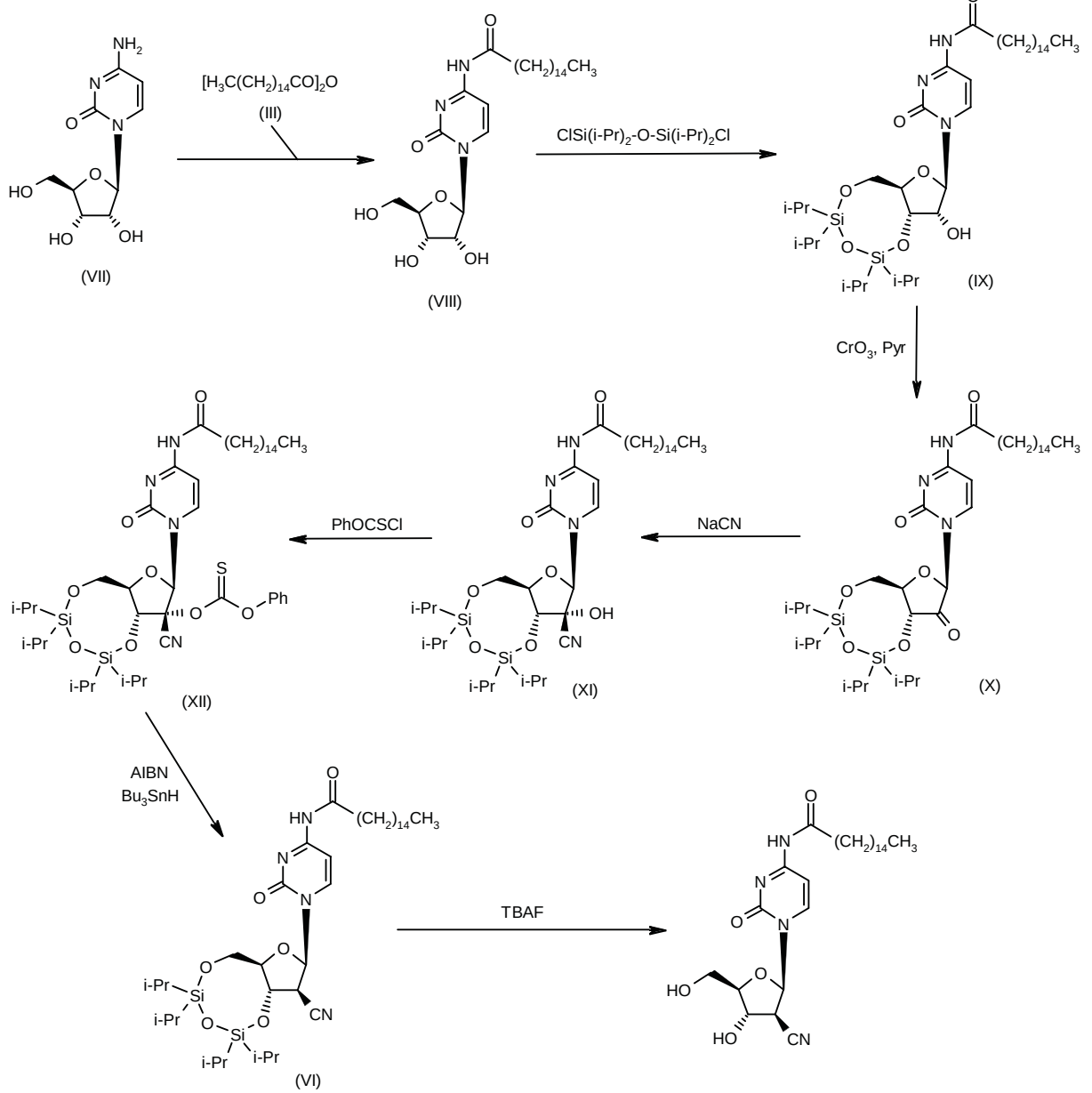
CS-682 is a masked form of CNDAC which is activated in tumor cells. After incubation with CS-682, CNDAC monophosphate (CNDACMP), CNDAC diphosphate (CNDACDP) and CNDAC triphosphate (CNDACTP) were found in KB cells. CNDACTP inhibited purified DNA polymerase α (K_i = 0.16 μM). These metabolites were easily incorporated into DNA, and 2'-*C*-cyano-2',3'-didehydro-2',3'-dideoxycytidine (ddCNC) was detected after hydrolyzing the extracted DNA. ddCNC was generated only when the DNA strand breakage at the site of intranucleotide-CNDACMP occurred. This novel DNA-self-strand-breaking mechanism may contribute to the potent antitumor activity of CS-682 (6-8).

Clinical Studies

Interim results from an ongoing phase I trial at Johns Hopkins Oncology Center of oral CS-682 have been reported. Twenty-one patients with refractory solid tumors, all of whom had had prior chemotherapy, have received a total of 36 cycles of therapy with escalating doses of CS-682 (1, 2.5, 5, 7.5, 10, 13 and 17.5 mg/m^2/day). The most frequent side effects, all of which were mild to moderate, have been low-grade fever, fatigue, nausea, anorexia, vomiting, dry skin or pruritus, diarrhea, diaphoresis and musculoskeletal discomfort. Although no responses have been obtained, 2 patients have had stable disease for at least 24 weeks. Dose escalation continues (9).

According to a spokesperson from Sankyo, CS-682 is in phase I clinical trials in the U.S.

Scheme 2: Synthesis of CS-682



Manufacturer

Sankyo Co., Ltd. (JP).

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