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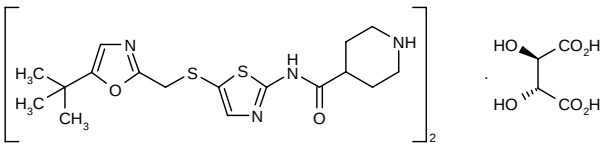
SNS-032

Cyclin-Dependent Kinase Inhibitor
Oncolytic

BMS-387032 (former code name)

N-[5-(5-*tert*-Butyloxazol-2-ylmethylsulfany)thiazol-2-yl]piperidine-4-carboxamide hemi(L-tartrate)

InChI=1/2C17H24N4O2S2.C4H6O6/c2*1-17(2,3)12-8-19-13(23-12)10-24-14-9-20-16(25-14)21-15(22)11-4-6-18-7-5-11;5-1(3(7)8)2(6)4(9)10/h2*8-9,11,18H,4-7,10H2,1-3H3,(H,20,21,22);1-2,5-6H,(H,7,8)(H,9,10)/t;;1-,2-/m..1/s1



$C_{38}H_{54}N_8O_{10}S_4$
Mol wt: 911.143

CAS: 345627-92-1

CAS: 345627-80-7 (free base)

CAS: 345627-90-9 (hydrochloride)

CAS: 345627-91-0 (hydrobromide)

CAS: 345627-96-5 (sulfate)

CAS: 345627-98-7 (methanesulfonate)

CAS: 960072-42-8 (trifluoroacetate salt)

CAS: 960072-43-9 (hydrate)

EN: 306651

Abstract

SNS-032 (formerly BMS-387032) is a small-molecule cyclin-dependent kinase (CDK) inhibitor currently in phase I clinical trials for the treatment of B-cell malignancies and advanced solid tumors. Preclinical studies have shown that SNS-032 is a specific and potent inhibitor of CDK2, 7 and 9 which induces cell cycle arrest and apoptosis in tumor cell lines. It was shown to inhibit in vitro angiogenesis and prostaglandin E_2 (PGE_2) production, both strongly associated with tumorigenesis. Phase I clinical trials support the safety and tolerability of SNS-032 as evaluated in dose-escalation studies. The compound is currently administered by i.v. infusion but has shown promising potential for oral delivery.

Synthesis*

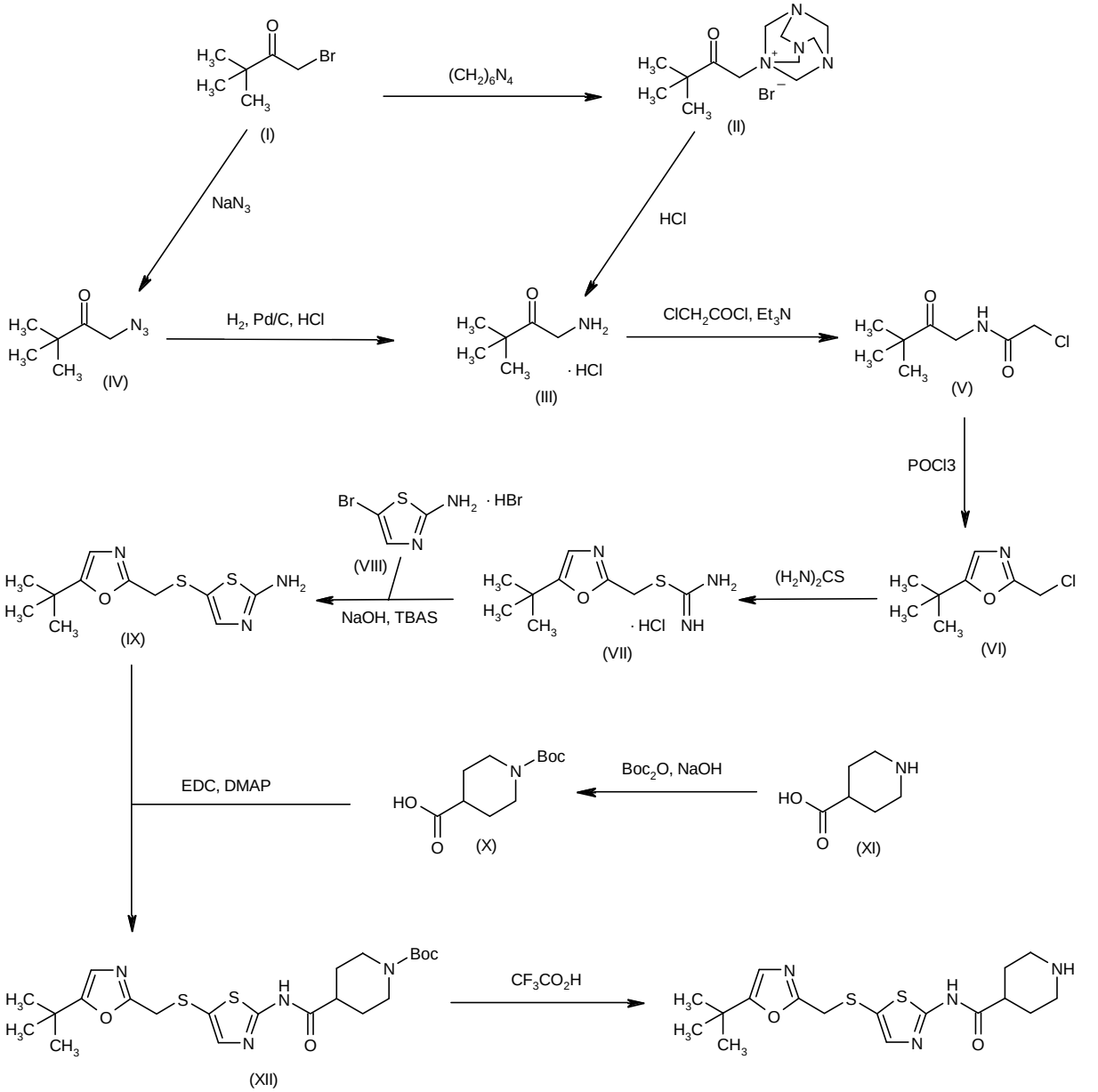
SNS-032 can be synthesized as follows:

Treatment of 1-bromo-3,3-dimethyl-2-butanone (I) with hexamethylenetetraamine affords the quaternary salt (II), which is then hydrolyzed to amino ketone (III) under acidic conditions (1-3). Alternatively, reaction of butanone (I) with sodium azide in acetone gives the azido derivative (IV), which is reduced with H_2 over Pd/C in methanol to yield 1-amino-3,3-dimethyl-2-butanone (III). Acylation of amine (III) with 2-chloroacetyl chloride by means of triethylamine in dichloromethane yields the chloroacetamide (V), which is cyclized in $POCl_3$ at 105 ºC to provide 5-*tert*-butyl-2-(chloromethyl)oxazole (VI) (1-4). Condensation of chloride (VI) with thiourea gives the *S*-alkylated thiouronium salt (VII), which is then submitted to alkaline hydrolysis followed by condensation with 2-amino-5-bromothiazole (VIII) under phase-transfer conditions in the presence of tetrabutylammonium sulfate, leading to thioether (IX) (1-3). Acylation of aminothiazole (IX) with 1-Boc-piperidine-4-carboxylic acid (X) —obtained by reaction of piperidine-4-carboxylic acid (XI) with Boc_2O and NaOH in dioxane/acetonitrile— by means of EDAC and DMAP in DMF/dichloromethane yields the carboxamide (XII), which is finally deprotected upon treatment with trifluoroacetic acid (1-3) or by means of HCl in hot dioxane/$CHCl_3$ (4). Scheme 1.

Alternatively, oxazole (VI) can be condensed with 2-amino-5-sulfanylthiazole (XIII) in refluxing ethanol to give thioether (IX). The intermediate 2-amino-5-sulfanylthiazole (XIII) can be obtained by reaction of 2-aminothiazole (XIV) with Br_2 and KSCN to give the thiocyanato derivative (XV), which is finally reduced with $NaBH_4$ in ethanol (4). Scheme 2.

S. Vasiliou. Neurotransmitter Biology Group, Department of Physiology, University of Liverpool, Crown St., L69 3BX Liverpool, U.K. *Synthesis prepared by R. Castañer, J. Bolós. Prous Science, Provenza 388, 08025 Barcelona, Spain.

Scheme 1: Synthesis of SNS-032

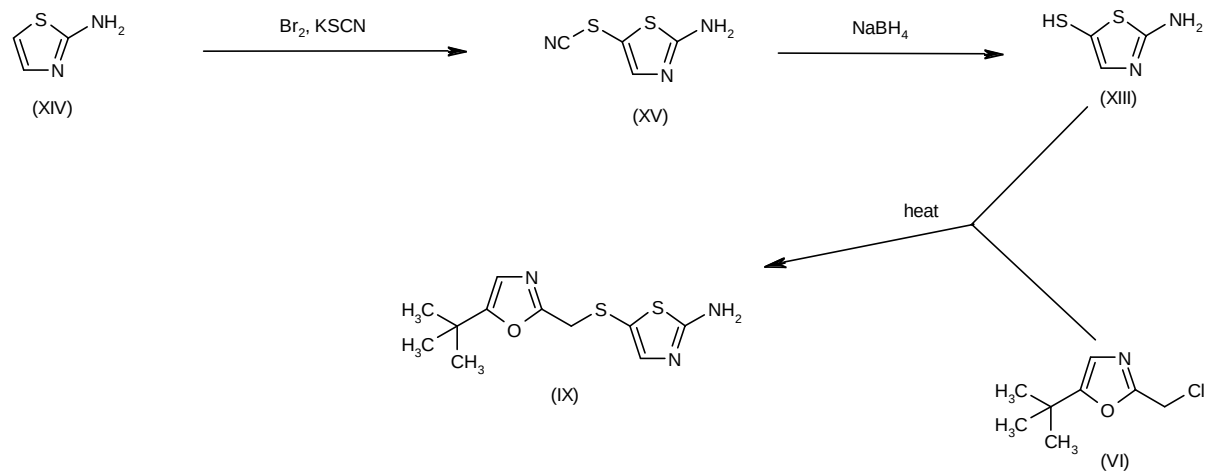


Background

The development of drugs that inhibit cyclin-dependent kinases (CDKs) for cancer therapy has been an ongoing effort in preclinical research for over 15 years. CDKs are serine/threonine protein kinases that form heterodimeric complexes with cyclins, proteins involved in the regulation of cell cycle progression. These complexes are able to phosphorylate a number of substrates involved in cell cycle control and transcriptional regulation of gene expression (5). The 13 putative CDKs encoded by the human genome are divided into two groups based on their involvement in either of those processes (6). CDK1, 2, 3, 4 and 6 are implicated in cell cycle progression and cell division when bound to their corresponding cyclins, whereas CDK8 and 9 are referred to as transcriptional kinases, as they can control RNA polymerase II activity and thus regulate the transcription cycle (7). CDK7 plays a dual role as a cyclin activator and a transcriptional regulator (8).

CDKs display increased activity in proliferative diseases such as cancer and exhibit abnormal activities and

Scheme 2: Synthesis of Intermediate (IX)



dysregulation following viral infections and in certain neurodegenerative disorders, namely Alzheimer's disease, Parkinson's disease and traumatic brain injury (9, 10). This dysregulation of CDKs may be a result of upregulation of their partner cyclins, aberrant activation of CDKs themselves, or inactivation of cellular CDK inhibitors. Inactivation of CDK inhibitors has been shown to play a key role in CDK malfunction in cancer (11), and therefore the identification of small-molecule CDK inhibitors for therapeutic purposes has been an active pursuit of pharmacological research.

SNS-032 (formerly known as BMS-387032) is a new-generation CDK inhibitor belonging to the class of *N*-acyl-2-aminothiazoles with nonaromatic side-chains, which has shown high potency and selectivity for CDK2, 7 and 9 and potent cytotoxicity in preclinical studies (4, 12, 13). It is currently undergoing phase I clinical trials for the treatment of B-cell malignancies and advanced solid tumors. B-cell malignancies account for over 90% of all lymphoid neoplasias and include B-cell lymphoma, B-cell chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) (14). SNS-032 is currently administered i.v., although its potential for oral delivery and the possibility for use both as monotherapy and also in combination with other medicines render this compound a potential therapeutic candidate for cancer treatment.

Preclinical Pharmacology

The in vitro efficacy of SNS-032 was originally investigated by Bristol-Myers Squibb. In a cell-free enzyme assay, the compound showed an IC_{50} of 48 nM against CDK2/cyclin E and was found to have 10- and 20-fold selectivity, respectively, for this complex over CDK1/cyclin B and CDK4/cyclin D. The antiproliferative activity of the compound was established (IC_{50} = 95 nM) in a cellular toxicity assay carried out in the human ovarian carcinoma cell line A2780, and it was shown to inhibit the phosphorylation of CDK2 and some of its known downstream targets (4).

Subsequent investigations at Sunesis revealed that the compound also inhibited CDK7/cyclin H and CDK9/cyclin T at low nanomolar concentrations and was highly selective over other kinases. Moreover, SNS-032 induced rapid cell cycle arrest and cell death in tumor cells (13).

In another in vitro study, the compound was identified as a regulator of the cyclooxygenase COX-2, a precursor of prostaglandins, the overexpression of which strongly correlates with tumorigenesis (15). The non-small cell lung cancer (NSCLC) cell line NCI-H358 exhibited significant inhibition of IL-1β-mediated induction of COX-2 expression following 1-h treatment with SNS-032 (82% inhibition at 150 nmol/l), with complete inhibition at 300 nmol/l. The compound (15 pg/ml) was also able to inhibit IL-1β-induced prostaglandin E_2 (PGE_2) synthesis in NCI-H358 cells by > 90%. However, SNS-032 did not affect the expression of endogenous COX-2 (not induced by IL-1β treatment) in the NSCLC cell line HCC3255.

In a more recent study, the ability of SNS-032 to regulate cell proliferation and viability was assessed using a model of in vitro angiogenesis in human umbilical vein endothelial cells (HUVEC) and human glioblastoma cells (U-87 MG) (16). SNS-032 displayed a concentration-dependent inhibition of cellular proliferation in both cell lines tested. HUVEC exhibited a 2-fold reduction in cell growth when treated with 0.1 μM SNS-032 for 48 and 72 h and complete growth inhibition was observed following 48-h treatment with 0.3 and 0.5 μM SNS-032. HUVEC viability was reduced by more than 60% following treatment with 0.5 μM SNS-032 for 72 h. U-87 MG cells showed a similar reduction in proliferation upon exposure

to SNS-032 (2-fold inhibition by 0.1 μM SNS-032 and 3-fold inhibition by 0.3 and 0.5 μM SNS-032), but cell viability was not affected by the treatment. No cytotoxic effect was observed in either cell line following 24 h of exposure to SNS-032. The formation of a three-dimensional capillary network in HUVEC was inhibited in a concentration-dependent manner by treatment with SNS-032 for 8 h (27% inhibition at 0.1 μM, 65% inhibition at 0.3 μM and 90% inhibition at 0.5 μM). HUVEC migration was also inhibited by 36%, 50% and 60%, respectively, at 0.1, 0.3 and 0.5 μM SNS-032. In a co-culture system of HUVEC and U-87 MG cells, SNS-032 completely prevented the U-87 MG-mediated formation of capillaries in HUVEC and prevented HUVEC migration. Following treatment with SNS-032 for 24 h, both cell lines exhibited a significant reduction in the secretion of vascular endothelial growth factor (VEGF), a tumor angiogenic factor that affects the proliferation, migration and survival of endothelial cells (72% and 50% reduction of VEGF secretion, respectively, in U-87 MG and HUVEC cells at 0.3 μM). This reduction in VEGF secretion was concomitant with a decrease in VEGF mRNA levels in U-87 MG cells, suggesting that SNS-032 affected VEGF gene expression.

Other in vitro studies have demonstrated the potential of SNS-032 to enhance the antitumor activity of cytotoxic agents and ionizing radiation. Using human colon carcinoma cells, SNS-032 was shown to result in synergistic cytotoxicity when used in combination with cisplatin that was concentration- and sequence-dependent, as well as dependent on length of interdrug interval (17). Using the colony formation assay in human non-small cell lung carcinoma NCI-H460 and A549 cell lines, SNS-032 (500 nM) prior to irradiation significantly increased radiosensitivity in hypoxic and quiescent tumor cells, which may involve cell cycle-independent mechanisms (18).

The in vivo antitumor activity of SNS-032 was examined using several tumor models and compared to flavopiridol. In the P388 murine leukemia model, the optimal dose of SNS-032 of 11 mg/kg/day i.p. for 7 days prolonged survival of mice by 40% compared to 10% for flavopiridol. I.p. or i.v. administration of SNS-032 was also associated with more marked log cell kill compared to flavopiridol in the human ovarian carcinoma A2780 and human colon carcinoma COLO 205 tumor xenograft models, and, unlike the latter, it produced complete regressions and cures. It was also at least as effective as flavopiridol in the human squamous cell carcinoma A-431 xenograft model and in a cyclin E-overexpressing transgenic mouse breast carcinoma model (19).

Pharmacokinetics and Metabolism

In in vivo studies, the oral bioavailability of SNS-032 in mice, rats and dogs was estimated to be 100%, 31% and 28%, respectively, with a half-life of 5-7 h (4).

The rate of SNS-032 absorption and first-pass metabolism were investigated following single intraarterial (9.1 mg/kg), oral (9.1 mg/kg) or intraportal (10 mg/kg) doses of SNS-032 to male rats (20). While all three routes displayed slow rates of metabolism in rat liver microsomes, intraportal and intraarterial doses resulted in higher exposure of SNS-032 compared to oral delivery, suggesting that poor absorption of the compound may play a more significant role than extensive first-pass metabolism in the low oral bioavailability observed in rats. The limited absorption of the compound may be a consequence of its binding to the efflux transporter P-glycoprotein, since SNS-032 brain penetration in P-glycoprotein knockout mice is 3.5-fold higher compared to in wild-type mice.

In patients with metastatic refractory solid tumors, following i.v. administration of 4-16 mg/m^2 for 1 h weekly every 21 days, the mean terminal half-life of SNS-032 was estimated to be between 5 and 10 h, with plasma concentrations of the drug declining in a biphasic manner. The mean C_{max} (0.067-0.287 μg/ml) and $AUC_{0\text{-}inf}$ (0.103-0.553 μg.h/ml) increased almost linearly. Increasing doses of SNS-032 had no effect on the clearance and steady-state volume of distribution (average of 38 l/h/m^2 and 212 l/m^2, respectively). In cohorts of patients receiving oral drug (13 or 16 mg/m^2) on day 1 of cycle 2, peak plasma levels were reached in 1.5-3.3 h, with C_{max} of 0.017-0.033 μg/ml and an oral bioavailability of 11-25% (21).

In another open-label, dose-escalation study in patients with metastatic refractory solid tumors, SNS-032 was administered at doses ranging from 9.6 to 59 mg/m^2 by 1-h infusion every 3 weeks. Again, C_{max} and exposure increased with dose, although slightly less than proportionally. The half-life ranged from 5.6 to 18 h, clearance from 207 to 741 ml/m^2 and steady-state volume of distribution from 58 to 315 l/m^2 (22).

Safety

In phase I studies, SNS-032 has been well tolerated, the most common treatment-related adverse events being fatigue, nausea, anorexia, vomiting, diarrhea, constipation and abdominal pain or cramping, which were generally mild to moderate. No grade 3 or 4 hematological toxicities were observed and the only serious adverse events were one episode each of grade 4 acute renal failure, bleeding gastric ulcer and premature ventricular complexes (21-23).

Clinical Studies

The results of a phase I clinical study (see above) carried out by Sunesis aiming to establish the maximum tolerated dose (MTD), the maximum administered dose (MAD) and the dose-limiting toxicity (DLT) following 1-h infusions of SNS-032 for the treatment of advanced solid tumors were published recently (21). The study also aimed to define a recommended dose of SNS-032 for phase II clinical trials and to assess the safety and tolerability of the compound, as well as its potential bioavailability as an oral solution. SNS-032 was administered i.v. at a starting dose of 4 mg/m^2 over 1 h weekly every 21 days to patients with metastatic solid tumors. To evaluate the oral availability of SNS-032 in humans, the first dose

of cycle 2 in the 13 and 16 mg/m^2 dose cohorts was administered orally. A total of 39 cycles of treatment were performed on 20 patients. The best clinical response was stable disease in 3 patients. Study enrollment was terminated during dose escalation due to a change in the development strategy for the drug, and consequently the MTD for i.v. administration was not obtained.

Two earlier studies performed by Bristol-Myers Squibb in patients with metastatic refractory solid tumors evaluating SNS-032 as a 1-h infusion every 3 weeks at doses of 9.6-59 mg/m^2 (22) and by 24-h infusion every 2 weeks at doses of 4.8-17 mg/m^2 (23) also found stable disease in several patients.

An ongoing phase I clinical trial by Sunesis, due to be completed in March 2009, is aiming to study the safety and tolerability of escalating doses of SNS-032 administered i.v. (loading dose followed by 6-h infusion for 3 weeks every 28 days) to patients with advanced B-lymphoid malignancies. The conditions targeted by the study include chronic lymphocytic leukemia (CLL), mantle cell lymphoma and multiple myeloma (24, 25). Another phase I trial is also ongoing in patients with advanced solid tumors receiving 1-h infusions once daily for 5 days on a 21-day treatment cycle (26).

Sources

Sunesis Pharmaceuticals, Inc.; licensed from Bristol-Myers Squibb for worldwide development and commercialization.

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