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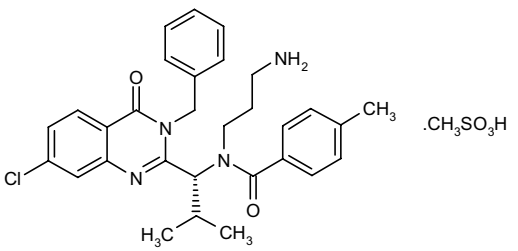
Ispinesib Mesilate

Antimitotic Drug
KSP Inhibitor

Prop INNM; USAN

715992
SB-715992
CK-0238273

N-(3-Aminopropyl)-*N*-[1(*R*)-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl]-4-methylbenzamide methanesulfonate



$C_{31}H_{37}ClN_4O_5S$
Mol wt: 613.1681

CAS: 514820-03-2

EN: 308633

Abstract

In the search for novel mitotic targets for the development of antineoplastic agents, *Homo sapiens* Eg5 kinesin spindle protein (KSP, *Hs*Eg5/KSP) was identified. KSP is a member of a subfamily of kinesins that are involved in centrosome separation and bipolar spindle formation during mitosis. It has been shown to function exclusively in mitosis and is preferentially overexpressed in malignant cells. Inhibition of KSP interferes with the formation of the bipolar spindle required for proper separation and lining of chromosomes during mitosis, which ultimately leads to cell death. KSP inhibitors may therefore effectively interfere with mitosis while showing an improved therapeutic index. Ispinesib mesilate (715992, SB-715992, formerly CK-0238273) is one such KSP inhibitor that was found to be more selective for KSP over other members of the kinesin family. It effectively induced tumor regression in several preclinical models. Ispinesib was chosen for further development as an antimitotic agent and has shown efficacy in phase I and II trials in patients with solid tumors.

Synthesis

Ispinesib mesilate can be synthesized by several methods.

1) 4-Chloroanthranilic acid (I) is acylated with isovaleryl chloride (II), giving amide (III), which is cyclized to the benzoxazinone (IV) by heating with acetic anhydride. Subsequent condensation of (IV) with benzylamine, followed by cyclization in hot ethylene glycol in the presence of KOH, provides the quinazolinone (V). After bromination of the isobutyl side-chain of (V), the resulting bromide (VI) is displaced with NaN_3 to produce the azide (VII). Reduction of (VII) utilizing PPh_3 in THF yields the racemic amine (VIII), which is resolved by means of dibenzoyl-D-tartaric acid to afford the (*R*)-enantiomer (IX). Reductive alkylation of amine (IX) with *N*-Boc-3-aminopropanal (X) and $NaBH(OAc)_3$ provides the monoprotected diamine (XI), which is acylated by means of *p*-toluoyl chloride (XII), yielding the amide (XIII). Ispinesib mesilate is then obtained by trifluoroacetic acid-promoted deprotection of (XIII), followed by treatment with methanesulfonic acid (1). Scheme 1.

The intermediate amine (IX) can be obtained by two related alternative procedures. Acylation of 4-chloroanthranilic acid (I) with *N*-Boc-D-valine (XIV) via activation with isobutyl chloroformate affords the valinamide (XV), which upon further treatment with isobutyl chloroformate undergoes cyclization to the benzoxazinone (XVI). Reaction of (XVI) with benzylamine produces amide (XVII), which is cyclized to the quinazolinone (XVIII) under alkaline conditions. Alternatively, the quinazolinone (XVIII) is prepared by reaction of the oxazinone (XVI) with ammonia in THF, producing the benzamide (XIX), which is cyclized to (XX) by means of LiOH in boiling THF. The resulting quinazolinone (XX) is then alkylated with benzyl bromide to give (XVIII). Removal of the *N*-Boc group of (XVIII) by treatment with *p*-TsOH in refluxing toluene affords the deprotected amine (IX) (1). Scheme 2.

2) An alternative method leading to racemic ispinesib has been disclosed. Ethyl 2-bromo-3-methylbutyrate (XXI) is condensed with *N*-Boc-1,3-propanediamine (XXII) to afford the diamino ester (XXIII), which is acylat-

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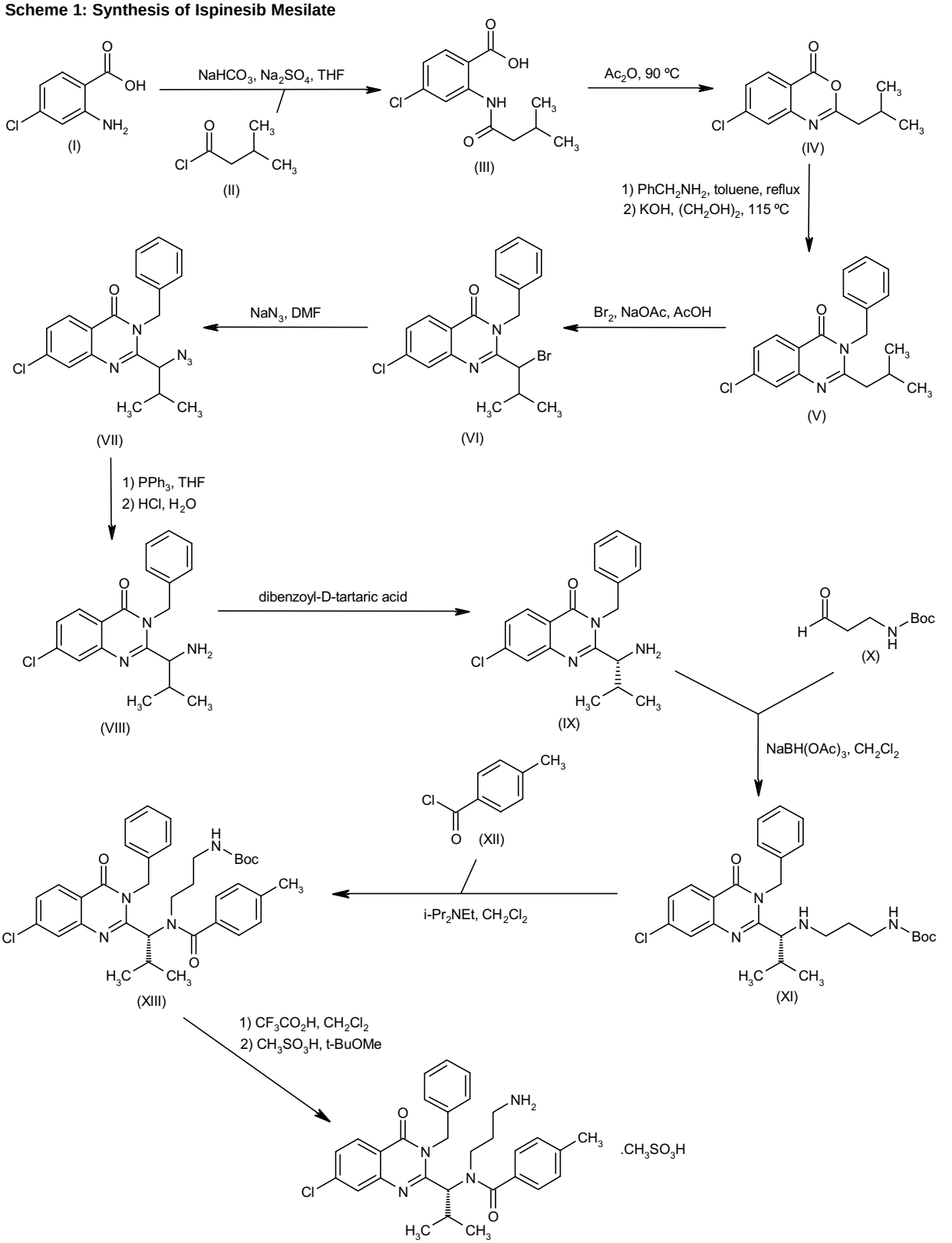
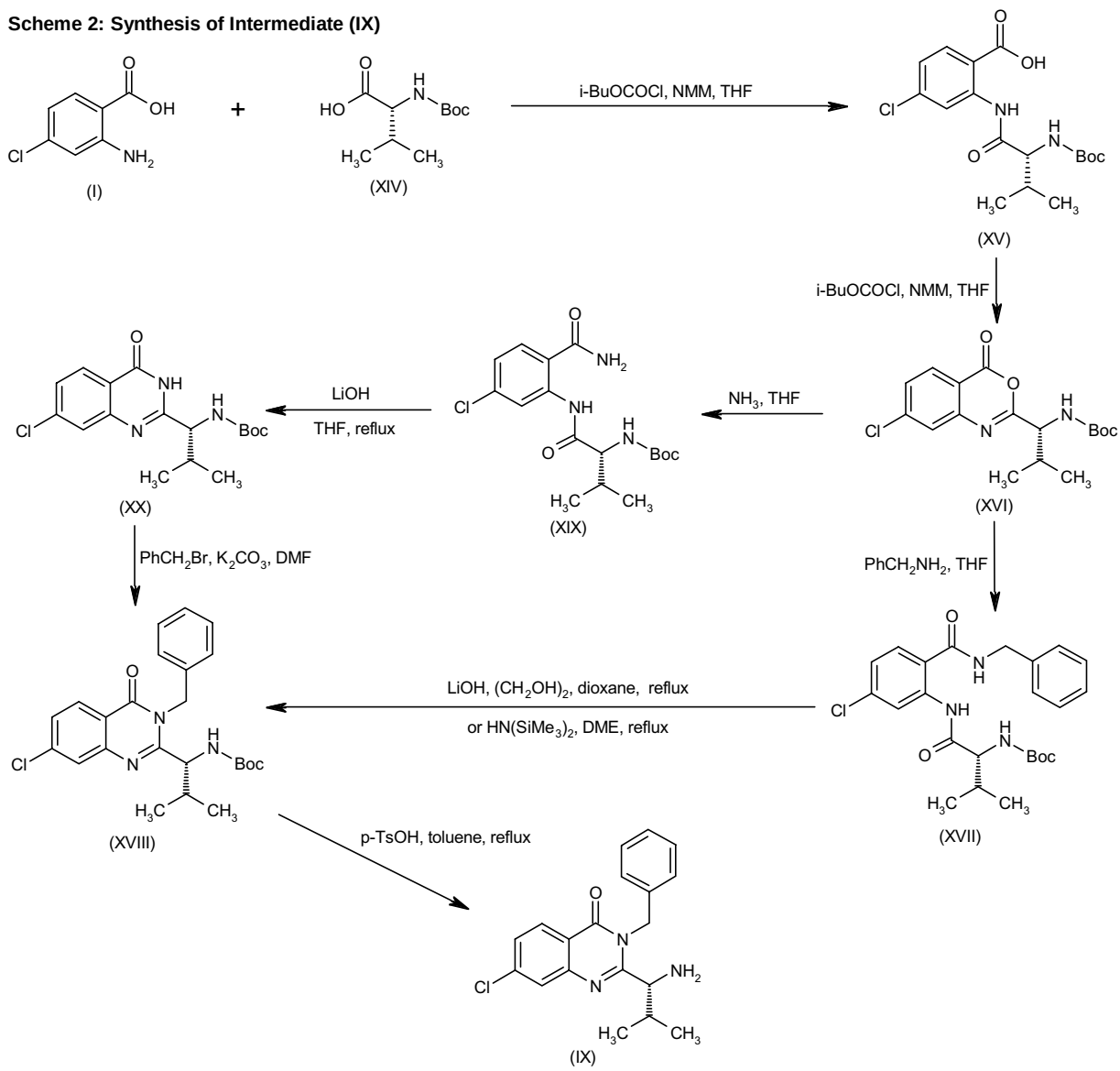
Scheme 1: Synthesis of Ispinesib Mesilate



Scheme 2: Synthesis of Intermediate (IX)

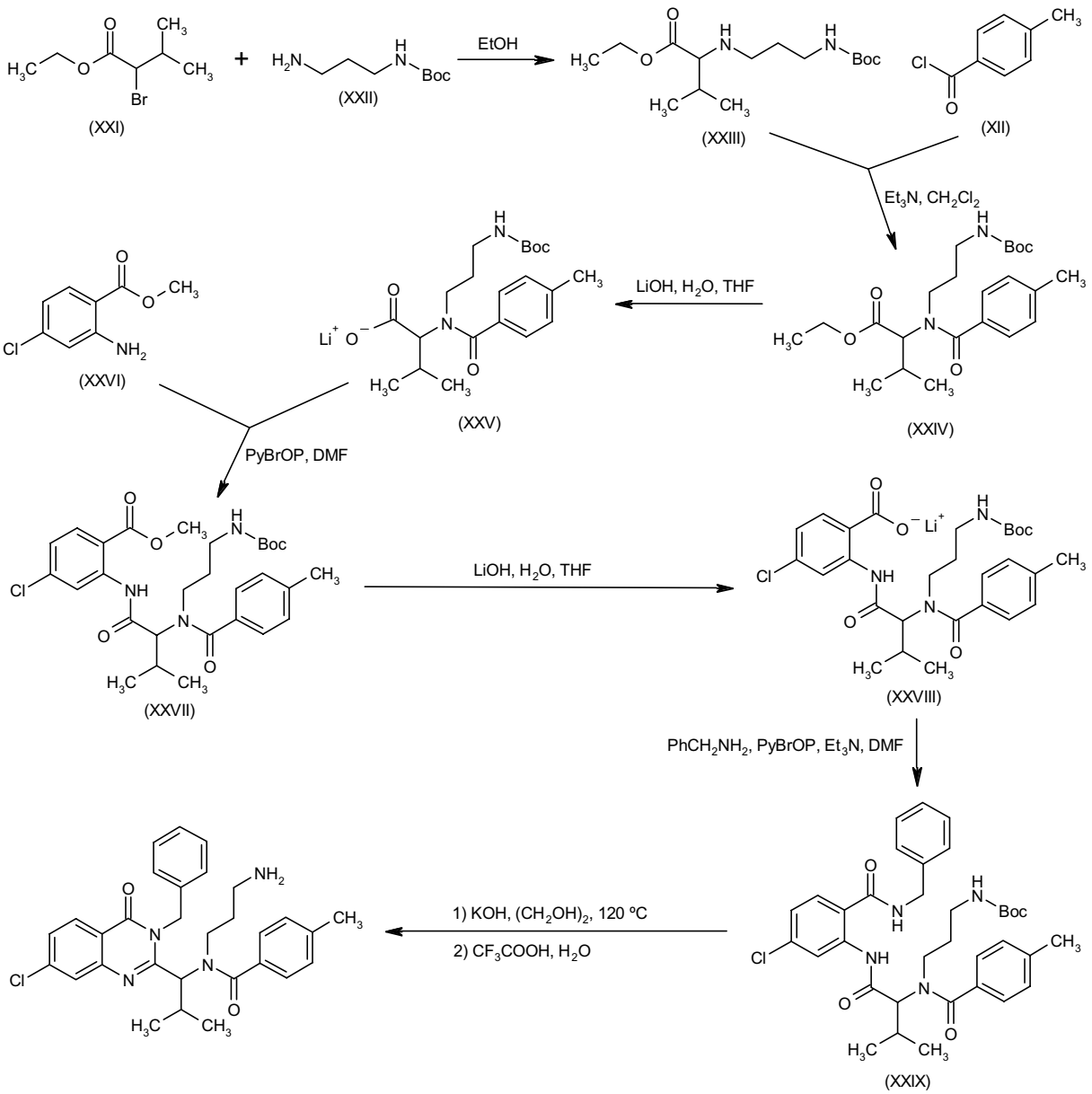


ed with *p*-toluoyl chloride (XII) to give the amide (XXIV). After hydrolysis of the ethyl ester (XXIV) with LiOH in aqueous THF, the resulting lithium carboxylate (XXV) is coupled with methyl 4-chloroanthranilate (XXVI) to produce the diamide (XXVII). Subsequent methyl ester (XXVII) hydrolysis, followed by coupling of the carboxylic acid salt (XXVIII) with benzylamine, yields adduct (XXIX). Finally, cyclization of (XXIX) with KOH in hot ethylene glycol and subsequent acidic Boc group cleavage furnishes the target quinazolinone compound (1). Scheme 3.

Background

Targeting mitosis has long been recognized as an important strategy for the treatment of cancer. Paclitaxel (Taxol) and the *Vinca* alkaloids were the first antimitotic agents identified. They were shown to bind to the microtubules that form the mitotic spindle and arrest cell division, eventually leading to cell death. For years, the microtubule was the only target for antimitotic anticancer therapy. However, microtubules are also present in normal cell types throughout the body and targeting them may result in serious adverse events. For example, paclitaxel is associated with severe neuropathies due to interference with microtubule-mediated axonal molecular transport. Fortunately, the mitotic process involves many components and thus comprises numerous potential targets. Thus, researchers have focused attention on identifying these novel targets to create potent and safer antineoplastic compounds (2-4).

Scheme 3: Synthesis of Racemic Ispinesib



Microtubules are arranged in a heterodimer and are associated with other proteins, such as mitogen-activated proteins (MAPs), dynein, tau and kinesins. Kinesins are ATP-dependent motor proteins that are tightly bound to and move unidirectionally along microtubules and play important roles in spindle and chromosome motility (2, 3, 5, 6). One such kinesin, *Homo sapiens* Eg5 kinesin spindle protein (KSP, *Hs*Eg5/KSP), has been identified as a particularly promising antimitotic target. KSP is a member of the BimC (blocked in mitosis) subfamily of kinesins that are involved in centrosome separation and bipolar spindle formation. During the early stages of mitosis, KSP pushes the centrosome toward the plus end of microtubules. It has been shown to function exclusively in mitosis and therefore is predominantly expressed in proliferating tissues. KSP is not expressed on normal, nondividing cells, such as terminally differentiated neurons, and it is preferentially overexpressed in malignant cells. Inhibition of KSP interferes with the formation of the bipolar spindle required for proper separation and lining of chromosomes during mitosis. This abnormality in chromosome formation and alignment in mitotic cells leads to programmed cell death or death from mitotic catastrophe (7-11).

Table I: Antimitotic kinesin-like spindle (KSP, Eg5) inhibitors under active development for the treatment of cancer (from Prous Science Integrity®).

Drug	Source	Phase
Ispinesib mesilate	GlaxoSmithKline/Cytokinetics	II
CRx-026 (chlorpromazine/ pentamidine isethionate)	CombinatoRx/HenKan	I/II
743921	GlaxoSmithKline/Cytokinetics	I/II

Researchers have therefore focused on targeting KSP as an antimitotic strategy for the treatment of cancer. Not only would KSP inhibitors effectively interfere with mitotic spindle formation, but they may also have an improved therapeutic index. Of the approximately 119 antimitotic agents currently under active development for the treatment of cancer, 3 target KSP, as shown in Table I. Ispinesib mesilate (715992, SB-715992, formerly CK-0238273) is one such KSP inhibitor. The agent was found to be 70,000-fold more selective for KSP over other members of the kinesin family. In addition, it effectively interfered with the assembly of functional mitotic spindle, resulting in cell cycle arrest and consequent cell death. Ispinesib was therefore chosen for further development as an antimitotic agent for the treatment of cancer (2, 4).

Preclinical Pharmacology

Ispinesib inhibited KSP *in vitro* with a K_i of 0.6 nM and exerted potent cytotoxic activity against a broad spectrum of tumor cells. Moreover, the agent had no effect in a mouse model of peripheral neuropathy, in contrast to paclitaxel. The IC_{50} value for ispinesib for *Hs*Eg5 ATPase activity obtained in a high-throughput robotic fluorescence-based assay developed to screen KSP inhibitors was 30.6 nM (12, 13).

Ispinesib (15 and 30 nM for 72 h) inhibited proliferation (48.7% and 52.2%, respectively) and induced apoptosis (1094.9% and 1516.7%, respectively) in the human prostate cancer PC-3 cell line. Moreover, combination treatment including ispinesib and genistein (30 μM) resulted in significantly enhanced induction of apoptosis and inhibition of cell growth as compared to either agent alone. Further analysis of the effects of ispinesib in this cell line showed that it caused upregulation of genes related to apoptosis induction and inhibition of cell cycle progression and cell signaling, and downregulation of genes involved in cell survival, such as those that encode protein kinases, growth factors and mediators of transcription and translation. For example, after 48 h of treatment with 10 nM ispinesib, a decrease in the expression of epidermal growth factor receptor (EGFR) was observed, suggesting downregulation of EGFR gene expression. Increased expression of p27 (CDKN2B) and p15 (CDKN1B) was also observed (14).

Ispinesib exhibited potent antimitotic activity in several *in vivo* tumor xenograft models. Analysis of advanced human colon adenocarcinoma COLO 205 tumor xenografts taken from mice 24 h after treatment with ispinesib revealed a significantly greater number of cells with a 4N DNA content as compared to placebo, suggesting mitotic arrest. In addition, staining of tumor sections for the mitotic epitope phosphorylated histone H3 and for chromatin with DAPI (*i.e.*, an indicator of monopolar spindles) indicated dose-related accumulation of mitotic cells in tumors from ispinesib-treated animals (15).

According to histone H3 staining results, a single dose of ispinesib (30 mg/kg i.p.) was shown to increase mitotic cell number 1 and 2 days postdosing in human colon adenocarcinoma COLO 205 and HT-29 tumors and human mammary carcinoma MX-1 tumors implanted in mice. However, efficacy varied with tumor type, suggesting that mitotic arrest is not a good predictor of the antitumor activity of ispinesib. Ispinesib caused complete regression of advanced human colon cancer COLO 205 and COLO 201 xenografts and tumor growth delay of HT-29 tumors in mice. However, MX-1 xenografts were refractory to the agent. Results from *in vitro* washout, cell cycle and clonogenic survival assays suggest that mitotic arrest must be sustained before cell death occurs. The agent (10 nM) induced mitotic arrest at 6 h, although significant decreases in cell viability were not observed. However, mitotic arrest and reductions in cell viability were both seen at 24 h following treatment with 25 nM ispinesib (12, 16).

Further analysis of the cytotoxic effects of ispinesib against COLO 205, HT-29 and MX-1 tumor xenografts revealed that efficacy was dose-related, with complete regression seen in sensitive models at doses one-third lower than the maximum tolerated dose (MTD; 13 mg/kg every 4 days x 3). Ispinesib was equally effective regardless of administration route (i.v., s.c. and i.p.). It was also effective against murine solid tumors, where treatment resulted in regression of Madison 109 lung carcinoma and M5076 sarcoma. Moreover, treatment of mice bearing Lewis lung carcinoma xenografts resulted in significant reductions in lung tumor burden and enhanced survival, and treatment of mice bearing advanced systemic L1210 and P388 leukemia caused multi-log cell kill. The agent was found to be most effective against P388 leukemia when administered as a single dose or on an intermittent schedule; daily treatment or continuous infusion had little efficacy due to the decreased tolerability of the total dose (12).

Experiments using B6D2F1 mice inoculated with murine P388 lymphocytic leukemia cells showed that cisplatin enhanced the activity of ispinesib. Single-agent treatment with the MTD of ispinesib (5-10 mg/kg i.p.) or cisplatin (4 mg/kg i.p.) resulted in an increase in lifespan of 160-184% and 140%, respectively, and a net cell kill of

about 4 and 2 log, respectively. Combination treatment with the MTD for each agent every 4 days x 3 (1 h apart) was well tolerated and led to significant improvement in survival. Moreover, combination treatment with doses half the MTD (5 mg/kg i.p. ispinesib and 1 mg/kg cisplatin every 4 days x 3) enhanced the increase observed in lifespan (230%) and net cell kill (7.7 log) as compared to either agent alone given at its MTD. Efficacy was dependent on the sequence of administration, such that co-administration was the least effective and administration of cisplatin 24 h before ispinesib provided the best efficacy. The results suggest that previous induction of DNA damage makes tumor cells more sensitive to the actions of ispinesib (17).

Another study showed that, in addition to efficacy observed in HT-29 colon carcinoma xenograft models, ispinesib administered every 3 days x 4 and weekly x 3 exerted antitumor activity in a nude mouse model of PANC-1 pancreatic carcinoma xenografts. A tumor growth inhibition rate of over 75% and partial tumor regressions were observed with both ispinesib dosing schedules in this model; for comparison, gemcitabine administration was associated with a tumor growth inhibition rate of 73% and no regressions. In the HT-29 model, ispinesib produced tumor growth inhibition of 69%, which was comparable to the rate of 73% obtained with CPT-11. Ispinesib was significantly less effective against non-small cell lung carcinoma (NSCLC) MV522 xenografts. However, the agent displayed efficacy in two syngeneic tumor models. A T/C ratio (mean survival of treated mice/mean survival of control mice) of 188 was obtained in B6D2F1 mice inoculated i.p. with murine melanoma B16 and treated with ispinesib on a weekly x 3 schedule. Ispinesib also caused significant tumor growth inhibition and a reduction in lung metastases in C57BL/6 mice bearing s.c. implants of LL/2 Lewis lung carcinoma. Ispinesib was best tolerated in these models when given on intermittent schedules (18).

A study has identified the binding site of ispinesib on KSP and the mutations at this site conferring resistance to ispinesib. Loop 5 within the KSP motor domain was shown to form the critical portion of the binding pocket for ispinesib. Further studies using HCT 116 colorectal tumor cells revealed that point mutations in loop 5 of KSP are responsible for acquired resistance to ispinesib. However, examination of the genomes of 94 human subjects did not show any polymorphisms in loop 5 of KSP, suggesting that germline polymorphisms may not be a frequent resistance mechanism in humans. Further studies are required before definitive conclusions can be made (19).

Pharmacokinetics and Metabolism

The pharmacokinetics and safety of ispinesib (1, 2 and 4 mg/m^2 every 21 days) were investigated in the first phase I trial in patients with advanced solid tumors. Results from 8 patients (5 colorectal, 2 sarcoma, 1 renal) who had received 21 courses indicated dose-proportional pharmacokinetics. $AUC_{0\text{-}48h}$ values for the 1 and 2 mg/m^2 doses were 136-378 and 221-413 ng.h/ml, respectively, and C_{max} and $t_{1/2}$ values for both doses were 23-64 ng/ml and 29-54 h, respectively. Grade 1 diarrhea was reported in 2 patients at 1 mg/m^2 and 1 patient at 2 mg/m^2 (20).

The pharmacokinetics and safety of ispinesib (starting at 1 mg/m^2 every 21 days) were investigated in another phase I trial in patients with advanced solid tumors. Results were available from 5 patients (2 breast, 1 gastric, 1 mesothelioma, 1 renal) who had received 6 courses at 1 and 2 mg/m^2; no significant toxicities were seen. At the 1 mg/m^2 dose, $AUC_{0\text{-}\infty}$, C_{max} and $t_{1/2}$ values were 302.7 ng.h/ml, 28-39 ng/ml and 43 h, respectively (21).

An open-label, nonrandomized, dose-escalation phase I trial in 42 patients with solid tumors examined the safety and pharmacokinetics of ispinesib (1-21 mg/m^2 i.v. every 21 days). Dose-related increases in $AUC_{0\text{-}\infty}$ and C_{max} were seen. At the 18 mg/m^2 dose level, the median C_{max}, $AUC_{0\text{-}\infty}$, $t_{1/2}$, clearance (CL) and volume of distribution at steady state (V_{ss}) in cycle 1 were 473 ng/ml, 5074 ng.h/ml, 33 h, 6656 ml/h and 236 l, respectively (22).

The pharmacokinetics of ispinesib (2, 4, 6 and 8 mg/m^2/day i.v. over 1 h on days 1-3 of a 21-day cycle or 18 mg/m^2 x 1 every 21 days) obtained in a dose-escalating phase I study conducted in 27 patients with advanced solid tumors were linear and dose-proportional, with comparable exposures observed in cycles 1 and 2. The median $AUC_{0\text{-}\infty}$ value at 6 mg/m^2/day x 3 was 4349.86 ng.h/ml, which was 13% lower but not clinically significantly different from the $AUC_{0\text{-}\infty}$ observed at 18 mg/m^2/day x 1 (5187.67 ng.h/ml). $AUC_{0\text{-}\infty}$ values obtained in this study varied 15-93%, possibly due to the small sample size and variability in CYP3A-modulated clearance of the agent (23).

The pharmacokinetic profile of ispinesib (1-8 mg/m^2 i.v. over 1 h on days 1, 8 and 15 in 28-day cycles) was determined in another phase I trial in 27 patients with solid tumors. $AUC_{0\text{-}\infty}$ and C_{max} values increased with dose, with no accumulation observed after multiple dosing. The respective median pharmacokinetic values on days 1 and 15 for the MTD (7 mg/m^2) in cycle 1 were: C_{max} = 349 and 218 ng/ml; $AUC_{0\text{-}\infty}$ = 2965 and 1994 ng.h/ml; $t_{1/2}$ = 37 and 22 h; CL = 5196 and 7546 ml/h; and V_{ss} = 235 and 240 l (24).

Safety

Neutropenia has been reported to be the dose-limiting toxicity (DLT) of ispinesib in phase I trials (see below). A preclinical study in mice, however, has shown that at effective antitumor doses the agent does not induce severe neutropenia. Administration of single and multiple (every 4 days x 3) i.p. doses induced dose-dependent panleukopenia. The neutrophil population was the most affected, with nadir reached 5 days after a single dose and recovery seen by day 10; red blood cell or platelet counts were not altered. Multiple dosing even in the presence of neutropenia did not have a cumulative effective on neutrophil counts; nadir was delayed until day 9, but

recovery occurred by day 14. The median duration of neutropenia using this multiple-dose schedule was 3, 7 and 8 days, respectively, at doses of 5, 10 and 20 mg/kg i.p. Severe neutropenia of a median duration of 2 and 5 days was seen only at doses of 10 and 20 mg/kg, respectively. In efficacy experiments using nude mice bearing advanced human COLO 205 tumors, the MTD of ispinesib was concluded to be 20 mg/kg (every 4 days x 3); tumor regression and tumor inhibition were observed at doses as low as 10 and 5 mg/kg, respectively. The 10 mg/kg dose caused severe but brief neutropenia. Similar results were obtained in a P388 murine lymphocytic leukemia model, where significant increases in survival were observed at ispinesib doses that did not cause severe neutropenia (25).

Clinical Studies

The open-label, nonrandomized, dose-escalation phase I trial in 42 patients with solid tumors (colorectal cancer, renal cell carcinoma, sarcoma, hepatocellular carcinoma, squamous cell carcinoma of the head and neck [SCCHN] and lung cancer) also determined the MTD, safety and efficacy of ispinesib (1-21 mg/m^2 i.v. every 21 days). DLT of grade 4 neutropenia for 5 days or more and grade 4 neutropenic fever developed in 1 patient each at the highest dose and 18 mg/m^2 was concluded to be the MTD and the recommended dose for phase II trials. Of the 12 patients treated at the MTD, grade 4 neutropenia lasting for 5 days or more was observed in 7 patients and non-dose-limiting grade 3 or 4 neutropenia plus grade 4 leukopenia was reported in 1 patient. Neutropenia nadir occurred on day 8 and lasted for 2-4 days. At a dose of 6 mg/m^2 or more, grade 2 or greater toxicities included fatigue, leukopenia and anemia. Four patients with colorectal cancer, hepatocellular carcinoma, SCCHN or renal cell carcinoma had stable disease for 5-11 cycles. A tumor biopsy taken from a patient with SCCHN treated at 16 mg/m^2 exhibited monopolar mitotic spindles. Modeling of absolute neutrophil counts (ANC) using E_{max} and ordinal models identified dose (mg/m^2), total dose (mg) and AUC or C_{max} (log transformed) as independent predictors of the decrease in ANC seen with ispinesib administered once every 21 days. Dose was the most accurate predictor of the ANC response and probability of grade 4 neutropenia (22, 26). The results of this and some of the following studies are summanzed in Table II.

In addition to pharmacokinetics, the efficacy, safety and tolerability of ispinesib (1, 2, 4, 6 and 8 mg/m^2/day i.v.

Table II: Clinical studies of ispinesib mesilate (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Cancer	Open	Ispinesib, 1-21 mg/m^2 i.v. 1x/21 d	42	Ispinesib 18 mg/m^2 was the recommended dose, with grade 3-4 neutropenia and grade 4 leukocytopenia as the dose-limiting toxicites. Relevant biological effects were seen in patients with solid tumors	22
Cancer	Open	Ispinesib, 1 mg/m^2 i.v. infusion over 1 h o.d. x 3 d 1x/3 wks Ispinesib, 2 mg/m^2 i.v. infusion over 1 h o.d. x 3 d 1x/3 wks Ispinesib, 4 mg/m^2 i.v. infusion over 1 h o.d. x 3 d 1x/3 wks Ispinesib, 6 mg/m^2 i.v. infusion over 1 h o.d. x 3 d 1x/3 wks Ispinesib, 8 mg/m^2 i.v. infusion over 1 h o.d. x 3 d 1x/3 wks	27	Ispinesib was well tolerated and the maximum tolerated dose in patients with advanced solid tumors was 6 mg/m^2/day administered for 3 consecutive days on a 3-week cycle	23
Cancer	Open	Ispinesib, 1-8 mg/m^2 i.v. over 1 h on d 1, 8, 15 1x/28 d	27	Ispinesib 7 mg/m^2 was the maximum tolerated dose in patients with solid tumors	24
Cancer	Open	Carboplatin, AUC 4-6 i.v. infusion over 30 min + Ispinesib, 9-21 mg/m^2 i.v. infusion over 1 h 1x/21 d	28	Preliminary results suggested that ispinesib at a dose of 18 mg/m^2 in combination with carboplatin AUC 6 exhibited antitumor activity and an acceptable tolerability profile in patients with advanced solid tumors	28
Cancer, breast	Open	Ispinesib, 18 mg/m^2 i.v. 1x/21 d x 2 [median] cycles	34	Ispinesib was associated with acceptable tolerability in patients with advanced or metastatic breast cancer, and signs of activity included stable disease in 7 patients and a partial response in 1 patient	30
Cancer, metastatic colorectal	Randomized	Ispinesib, 7 mg/m^2 1x/wk x 3 wks 1x/4 wks [until progression/toxicity] (n=33) Ispinesib, 18 mg/m^2 1x/3 wks [until progression/toxicity] (n=31)	64	Ispinesib did not demonstrate significant antitumor activity in patients with metastatic colorectal cancer	31

over 1 h on days 1-3 of a 21-day cycle or 18 mg/m^2 x 1 every 21 days) were investigated in 27 patients with advanced solid tumors (7 colorectal, 5 renal, 2 bladder, 2 lung, 2 pharynx, 2 pancreas, 7 other). The MTD was concluded to be 6 mg/m^2/day x 3 every 21 days. Grade 3/4 neutropenia developed in 2, 1 and 3 patients at 4, 6 and 8 mg/m^2, respectively, and grade 3/4 leukopenia was seen in 1 patient each in the 4 and 6 mg/m^2 dose groups. Other toxicities observed in the MTD cohort (n= 6) were 1 case each of grade 1 fatigue, grade 1 infusion-related flushing, grade 3 febrile neutropenia, grade 4 neutropenia and grade 4 leukopenia. Stable disease was seen in 2 patients with renal cell carcinoma in cycles 4 and 5 and a minor response was reported in a patient with bladder cancer (23).

The safety and efficacy of ispinesib (1-8 mg/m^2 i.v. over 1 h given on days 1, 8 and 15 of 28-day cycles) were also determined in the phase I trial in 27 patients with solid tumors (most common types: 5 colorectal, 4 renal, 4 breast, 3 lung). DLT of grade 3 neutropenia was observed in 2 patients in the 8 mg/m^2 group. No grade 3 or 4 toxicities were seen at a dose of 7 mg/m^2, which was concluded to be the MTD and was recommended for phase II studies. Other toxicities observed included grade 2 constipation (n=1) and grade 2 anemia (n=1) at doses less than 4 mg/m^2, and grade 2/3 neutropenia (n=2/1), grade 2/3 anemia (n=1/1) and grade 3 transaminitis (n=1) at doses of 4 mg/m^2 or greater. Stable disease was seen in 3 patients (renal cell carcinoma, SCCHN and colorectal cancer) in cycles 3 and 4 (24).

Another phase I trial in 24 patients with advanced solid tumors, including 14 with prostate cancer, examined the safety and efficacy of docetaxel (60-75 mg/m^2 i.v. over 1 h) followed by ispinesib (8-12 mg/m^2 i.v. over 1 h) every 21 days. A median of 3 cycles were administered and safety data were reported for 17 patients. A total of 6 patients developed DLT of prolonged (> 5 days) grade 4 neutropenia and/or febrile neutropenia, of whom 1, 2 and 3 received ispinesib/docetaxel doses of 8/60, 8/75 and 12/60 mg/m^2, respectively. The optimally tolerated regimen was concluded to be 10 mg/m^2 ispinesib plus 60 mg/m^2 docetaxel every 21 days, since the incidence of grade 4 neutropenia at this dose level was 33% compared to a rate of 75% reported for docetaxel (60 mg/m^2) monotherapy. The most common toxicities were grade 1-4 neutropenia (n=9), grade 1-2 fatigue (n=7), grade 1-2 alopecia (n=6), grade 1-4 anemia (n=5), grade 1-2 constipation (n=5), grade 2-3 diarrhea (n=5), grade 1-3 nausea (n=5), grade 1-2 vomiting (n=4), grade 1-2 cough (n=3) and grade 1 and 3 decreases in white blood cell counts (n=3). Stable disease of up to 6 months' duration was obtained in 12 patients (10 prostate, 1 renal and 1 bladder); 2 patients with prostate cancer had a confirmed decrease in prostate-specific antigen (PSA) levels of > 50% (27).

An open-label, nonrandomized, dose-escalating phase I trial in 28 patients with advanced solid tumors (7 prostate, 5 breast, 3 hepatocellular, 2 NSCLC, 2 renal, 2 pancreas, 7 other) examined the safety and efficacy of a combination of escalating carboplatin (AUC4-6 i.v. over 30 min) followed by escalating ispinesib (9-21 mg/m^2 i.v. over 1 h) every 21 days. A median of 3 cycles were administered and combination treatment was well tolerated. DLTs included prolonged (5 days or more) grade 4 neutropenia, grade 4 thrombocytopenia and grade 3 febrile neutropenia. The optimally tolerated regimen was concluded to be 18 mg/m^2 ispinesib and AUC6 carboplatin. At this dose level, gastrointestinal toxicities were limited to grade 1 and 2 and only a few cases of grade 1 neuropathy were reported. One patient with breast cancer had a partial response in cycle 2 and stable disease lasting 3-9 months was seen in 13 patients (28).

The efficacy and tolerability of ispinesib (12-15 mg/m^2 i.v. over 1 h on day 1 of a 21-day cycle) combined with capecitabine (750-1000 mg/m^2 b.i.d. for 14 days) were examined in a further phase I trial conducted in 13 patients with advanced solid tumors. One patient receiving 15 mg/m^2 ispinesib and 2000 mg/m^2 capecitabine developed DLT of prolonged (> 5 days) grade 4 neutropenia. Four patients (1 tongue, 1 colon, 1 breast, 1 bladder) had stable disease lasting for up to 8 months. The most frequent adverse event seen in the 7 evaluable patients was grade 2 fatigue (n=2) (29).

The efficacy of ispinesib (18 mg/m^2 i.v. over 1 h once every 21 days) in 34 patients with advanced or metastatic breast cancer (refractory or relapsed after treatment with anthracycline- and taxane-based chemotherapies) was examined in an open-label phase II study. A median of 2 cycles were administered. The tolerability of ispinesib was concluded to be manageable. Neutropenia requiring a dose reduction to 15 mg/m^2 occurred in 4 patients in cycle 2. The most common toxicities reported were grade 4 neutropenia (n=15), grade 1 infusion-site pain (n=13), grade 1 fatigue (n=7) and grade 1 anorexia (n=5). At the time of reporting, 1 patient had a confirmed partial response in cycles 2-6, 7 patients had stable disease in cycles 3-6 and 22 patients had progressive disease at the end of cycle 2 (30).

A randomized, noncomparative phase II trial conducted in 64 patients with metastatic colorectal cancer (California Cancer Consortium Study [CCC-P]) failed to demonstrate the efficacy of two different ispinesib dosing schedules (A: 7 mg/m^2 i.v. once weekly x 3 weeks every 28 days; B: 18 mg/m^2 i.v. every 21 days). A median of 2 cycles were completed for each dosing schedule. Stable disease was obtained in 3 and 5 patients in groups A and B, respectively, and progressive disease was seen in 25 and 24 patients, respectively; progression-free survival was 49 and 37 days, respectively. The most common grade 3/4 toxicities (groups A and B, respectively) were neutropenia (n=3 and 20), nausea and vomiting (n=3 and 1) and neurological toxicity (n=1 and 2). Febrile neutropenia and peripheral sensory neuropathy were only observed in 1 patient each (31).

Results from a planned interim analysis of a phase II trial of ispinesib evaluating its safety and efficacy as a second-line treatment for patients with either platinum-sensitive or platinum-refractory NSCLC indicated that

ispinesib did not satisfy the criteria for advancement to the next stage in the platinum-sensitive treatment arm. The trial was designed to require a minimum of 1 confirmed partial or complete response out of 20 evaluable patients in a treatment arm to proceed to stage 2 in that treatment arm. The primary endpoint of the trial was response rate as determined using RECIST criteria. The best overall responses to date in the platinum-sensitive treatment arm of this clinical trial have been stable disease in 10 of 20 evaluable patients. Overall, median time to disease progression was 6 weeks. In the 10 patients whose best response was stable disease, median time to progression was 17 weeks. The platinum-refractory treatment arm was completed in 2005 and also failed to satisfy the criteria for advancement to the next stage of evaluation. In that treatment arm, stable disease was observed in 5 of 20 evaluable patients. Overall, median time to disease progression was 6 weeks. In the 5 patients whose best response was stable disease, median time to progression was 12 weeks (32).

Ispinesib continues to undergo phase II development for the treatment of breast, ovarian, colorectal, head and neck, prostate, malignant melanoma, liver and renal cell cancers. Phase I development continues for the treatment of solid tumors, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndromes, Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). In addition, phase I testing of ispinesib in combination with capecitabine, docetaxel or carboplatin for the treatment of multiple tumor types is ongoing (33-44).

Drug Interactions

Analysis of preliminary pharmacokinetic data from 13 of 24 patients with advanced solid tumors participating in a phase I trial and receiving a combination of docetaxel (60-75 mg/m^2 i.v. over 1 h) followed by ispinesib (8-12 mg/m^2 i.v. over 1 h) every 21 days indicated no pharmacokinetic interaction between the two compounds. Similarly, no significant pharmacokinetic interaction between ispinesib and capecitabine was observed in a phase I trial in which 13 patients with advanced solid tumors were given ispinesib (12-15 mg/m^2 by 1-h i.v. infusion on day 1 of a 21-day cycle) combined with capecitabine (750-1000 mg/m^2 b.i.d. for 14 days) (27, 29).

Sources

GlaxoSmithKline, Inc. (US); Cytokinetics, Inc. (US).

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