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Sagopilone

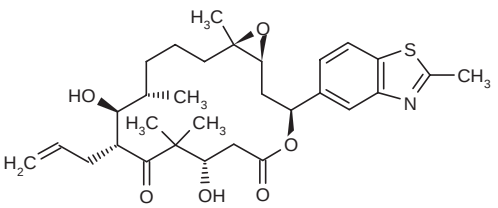
Rec INN

Microtubule-Stabilizing Agent
Epothilone
Oncolytic

SH-Y03757A
ZK epothilone
ZK-219477
ZK-EPO

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-10-Allyl-7,11-dihydroxy-8,8,12,16-tetramethyl-3-(2-methylbenzothiazol-5-yl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

InChI=1/C30H41NO6S/c1-7-9-20-27(34)17(2)10-8-13-30(6)25(37-30)15-22(19-11-12-23-21(14-19)31-18(3)38-23)36-26(33)16-24(32)29(4,5)28(20)35/h7,11-12,14,17,20,22,24-25,27,32,34H,1,8-10,13,15-16H2,2-6H3/t17-,20+,22-,24-,25-,27-,30+/m0/s1



$C_{30}H_{41}NO_6S$
Mol wt: 543.7157

CAS: 305841-29-6

EN: 429500

Abstract

Sagopilone is a fully synthetic epothilone. Epothilones are cytotoxic antimicrotubule drugs, six of which have been studied in clinical trials. Sagopilone has potential advantages over other antimicrotubule agents such as taxanes as it is water-soluble, evades multidrug resistance efflux pumps *in vitro* and may be able to cross the blood-brain barrier in humans. Sagopilone has been shown to be active in taxane-resistant models *in vitro* and *in vivo*. There are little published data on the clinical efficacy of sagopilone and the currently available preclinical and clinical data are reviewed here. Proof of concept was achieved in a phase II trial in platinum-resistant ovarian cancer; results from several ongoing phase II and future phase III studies are required to confirm whether the advantages of sagopilone seen in preclinical and early clinical studies will translate into a clear clinical benefit for patients.

Synthesis

Sagopilone is synthesized by the assembly of three modular building blocks, designated as segments A (V), B (II) and C (I). Wittig reaction of phosphonium salt (I) (segment C) with ketone (II) (segment B) in the presence of NaHMDS provides, after acidic hydrolysis of the tetrahydropyranyl protecting group, adduct (III) as a nearly equimolecular mixture of *E/Z* olefins. After chromatographic isolation of the target *Z*-isomer, Swern oxidation of the primary alcohol affords aldehyde (IV). This compound is then condensed with ketone (V) (segment A) in the presence of LDA and $ZnCl_2$ to produce diastereoselectively the aldol adduct (VI). Subsequent acidic hydrolysis of the acetonide (VI) followed by protection of the free hydroxyls with TBDMSOTf and 2,6-lutidine generates the tetrasilyl ether (VII). The primary silyl ether of (VII) is then selectively removed by means of camphorsulfonic acid in $MeOH/CH_2Cl_2$, and the resulting alcohol is stepwise oxidized to carboxylic acid (VIII) by treatment with DMSO and oxalyl chloride followed by sodium chlorite in the presence of NaH_2PO_4 and 2-methyl-2-butene. Selective deprotection of the benzylic alcohol of (VIII) is accomplished by desilylation with TBAF, and the linear hydroxy acid is then cyclized to the key 16-membered macrolactone by means of 2,4,6-trichlorobenzoyl chloride (TCBCl) and DMAP under Yamaguchi conditions. After removal of the remaining silyl ether groups using hydrogen fluoride-pyridine complex in the presence of

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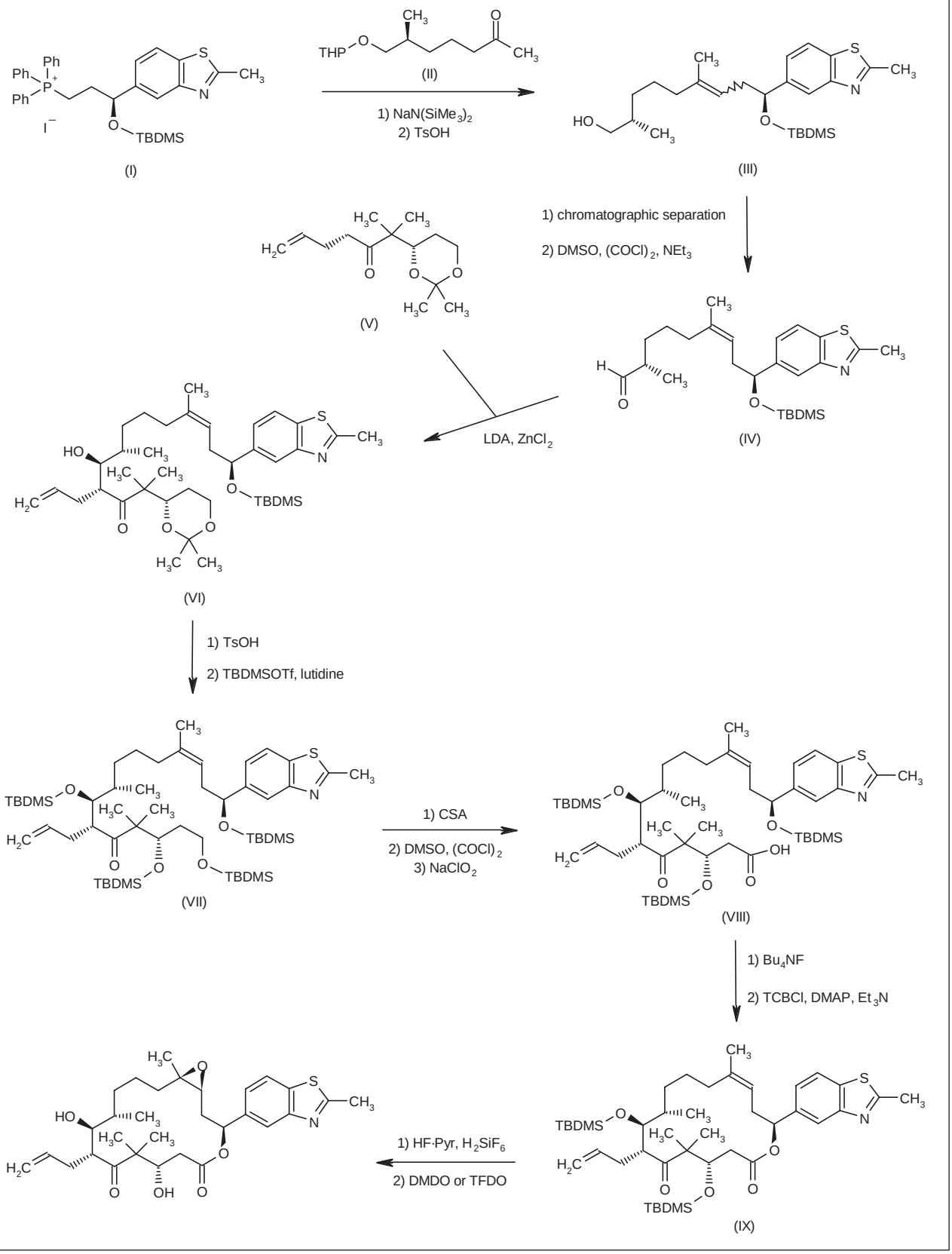
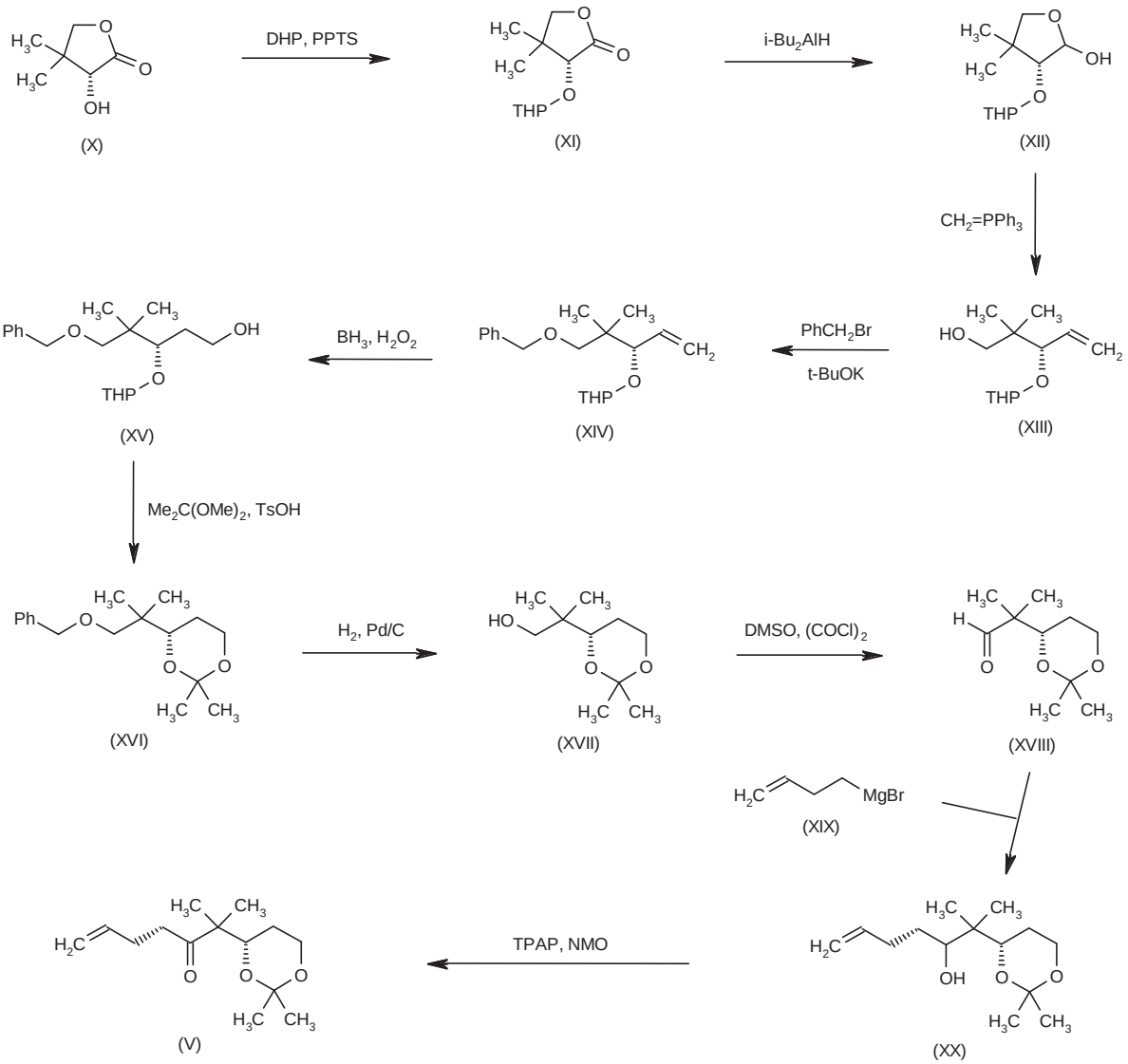
Scheme 1: Synthesis of Sagopilone



Scheme 2: Synthesis of Segment A (V)

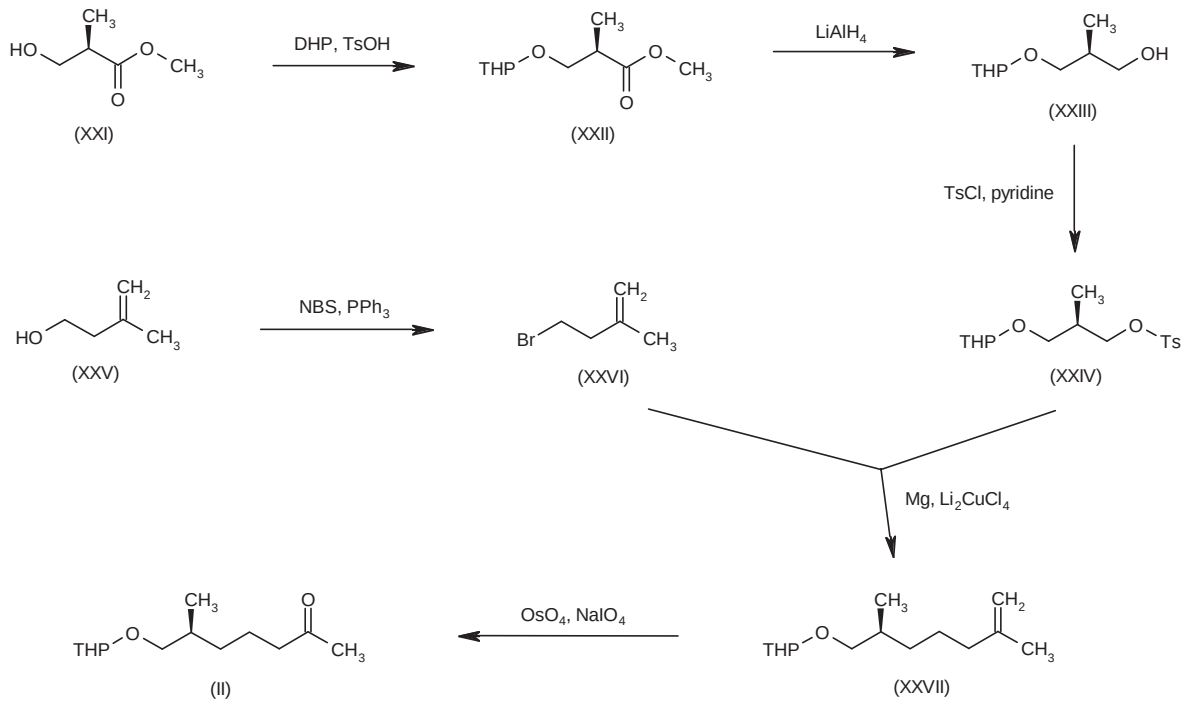


hexafluorosilicic acid, epoxidation of the endocyclic double bond with either dimethyldioxirane (DMDO) or methyl(trifluoromethyl)dioxirane (TFDO) furnishes the target epothilone (1, 2). Scheme 1.

The C1-C6 building block (V) (segment A) can be obtained as follows. Protection of (–)-pantolactone (X) as the tetrahydropyranyl ether (XI) using dihydropyran and pyridinium tosylate, followed by reduction of the lactone ring with DIBAL in cold toluene, gives the lactol (XII). Subsequent Wittig reaction of the cyclic hemiacetal (XII) with methylene triphenylphosphorane affords the hydroxy olefin (XIII), which is protected as the benzyl ether (XIV) by treatment with benzyl bromide and potassium *tert*-butoxide. Hydroboration of olefin (XIV) followed by quenching with alkaline H_2O_2 provides the primary alcohol (XV) as the major isomer, which is converted to the acetonide (XVI) by treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid. After catalytic hydrogenolysis of the benzyl ether (XVI), the deprotected alcohol (XVII) is oxidized to aldehyde (XVIII) under Swern conditions. Then, addition of 3-butenylmagnesium bromide (XIX) to the aldehyde (XVIII) provides alcohol (XX), which is oxidized to the target ketone (V) by treatment with *N*-methylmorpholine *N*-oxide and a catalytic amount of tetrapropylammonium perruthenate (3). Scheme 2.

The preparation of the C7-C12 building block (II) (segment B) is performed as follows. Protection of methyl 3-hydroxy-2(*R*)-methylpropionate by means of dihydropy-

Scheme 3: Synthesis of Segment B (II)



ran and *p*-toluenesulfonic acid in CH_2Cl_2 gives the tetrahydropyranyl ether (XXII), which is then reduced with $LiAlH_4$ in Et_2O to yield alcohol (XXIII) and derivatized to tosylate (XXIV) under the usual conditions. Reaction of 3-methyl-3-buten-1-ol (XXV) with *N*-bromosuccinimide and triphenylphosphine in CH_2Cl_2 affords the butenyl bromide (XXVI) which, after conversion to the corresponding Grignard reagent, is coupled with tosylate (XXIV) in the presence of catalytic Li_2CuCl_4 leading to adduct (XXVII). Then, dihydroxylation of olefin (XXVII) and subsequent oxidative cleavage employing OsO_4 and $NaIO_4$ gives the desired ketone (II) (2). Scheme 3.

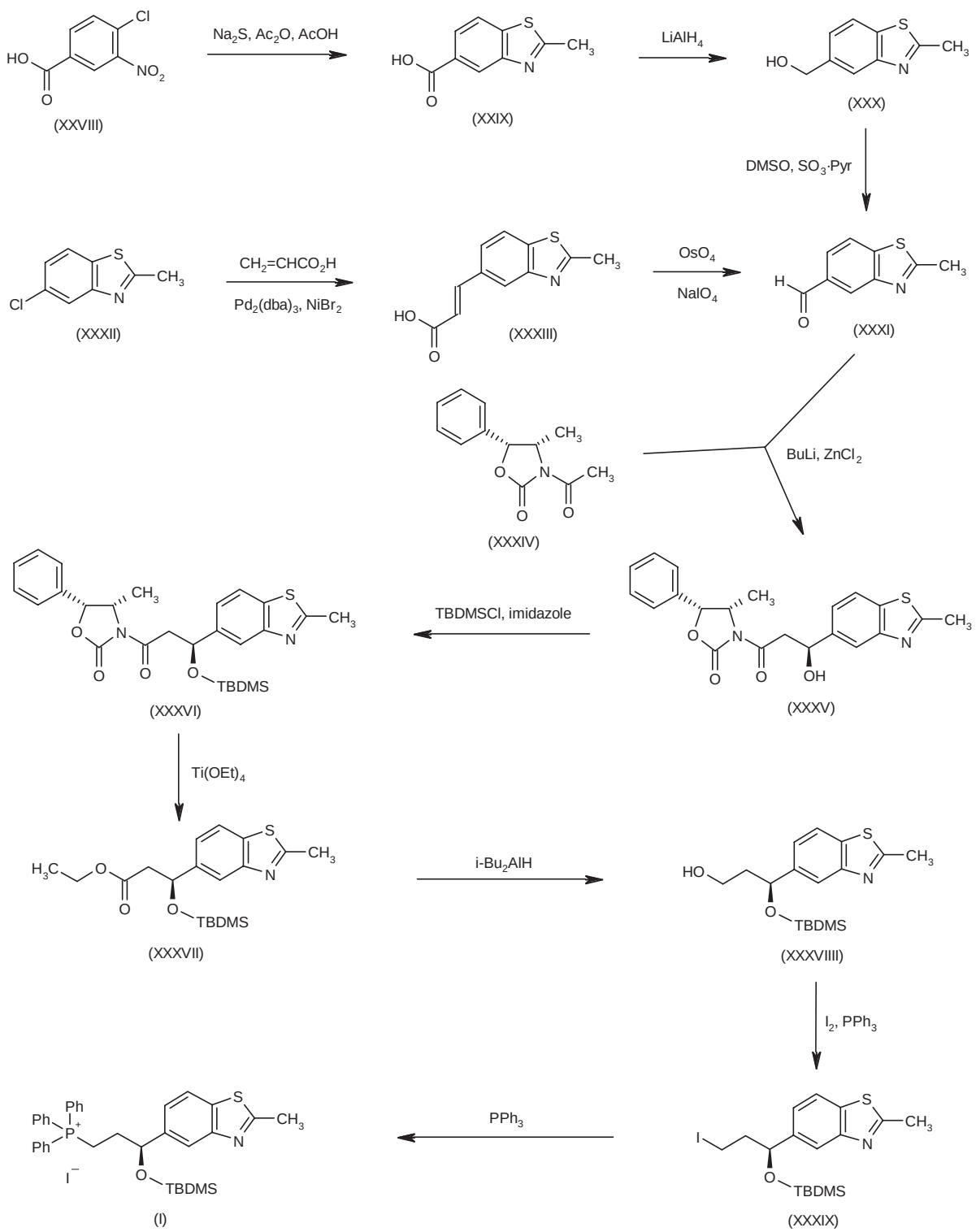
The preparation of segment C (I) can be accomplished as follows. One-pot treatment of 4-chloro-3-nitrobenzoic acid (XXVIII) with Na_2S and Ac_2O/AcOH gives 2-methylbenzothiazole-5-carboxylic acid (XXIX), which is subsequently reduced with $LiAlH_4$ in boiling THF followed by reoxidation of the obtained alcohol (XXX) with DMSO and SO_3-pyridine complex to give the aldehyde (XXXI) (2). In an alternative procedure, aldehyde (XXXI) is produced by coupling of 5-chloro-2-methylbenzothiazole (XXXII) with acrylic acid in the presence of $Pd_2(dba)_3$ and $NiBr_2$ followed by oxidative cleavage of the resulting arylacrylic acid (XXXIII) with OsO_4 and $NaIO_4$ (1). Aldol condensation of aldehyde (XXXI) with the chiral *N*-acetyloxazolidinone (XXXIV) by means of BuLi and $ZnCl_2$ produces adduct (XXXV) as the major diastereoisomer. After protection of the free hydroxyl group of (XXXV) as the corresponding *tert*-butyldimethylsilyl ether (XXXVI), the chiral auxiliary group is removed by treatment with titanium ethoxide in boiling EtOH. The resulting ethyl ester (XXXVII) is then reduced to alcohol (XXXVIII) employing DIBAL in cold toluene/CH_2Cl_2. Subsequent reaction of alcohol (XXXVIII) with I_2 and PPh_3 provides the alkyl iodide (XXXIX), which is then displaced with triphenylphosphine in hot toluene, producing the target phosphonium salt (I) (1, 2). Scheme 4.

Background

Sagopilone (ZK-EPO, ZK-219477) is a fully synthetic third-generation analogue of epothilone B. It was developed and selected from over 350 synthetic analogues due to its performance in preclinical studies with respect to potency and toxicity profiles (2).

Six epothilones have reached clinical development: patupilone (epothilone B or EPO-906), ixabepilone (azaepothilone B or BMS-247550; Ixempra™), KOS-862 (epothilone D or desoxyepothilone B), BMS-310705 (a more water-soluble epothilone B derivative), KOS-1584 (9,10-didehydroepothilone D) and sagopilone (Fig. 1). Ixabepilone and BMS-310705 are prepared from the natural product epothilone B, whereas sagopilone requires a total synthesis due to its different structural elements. The natural macrolides epothilones A to D were discovered as metabolites from the supernatant of the culture of the

Scheme 4: Synthesis of Segment C (I)



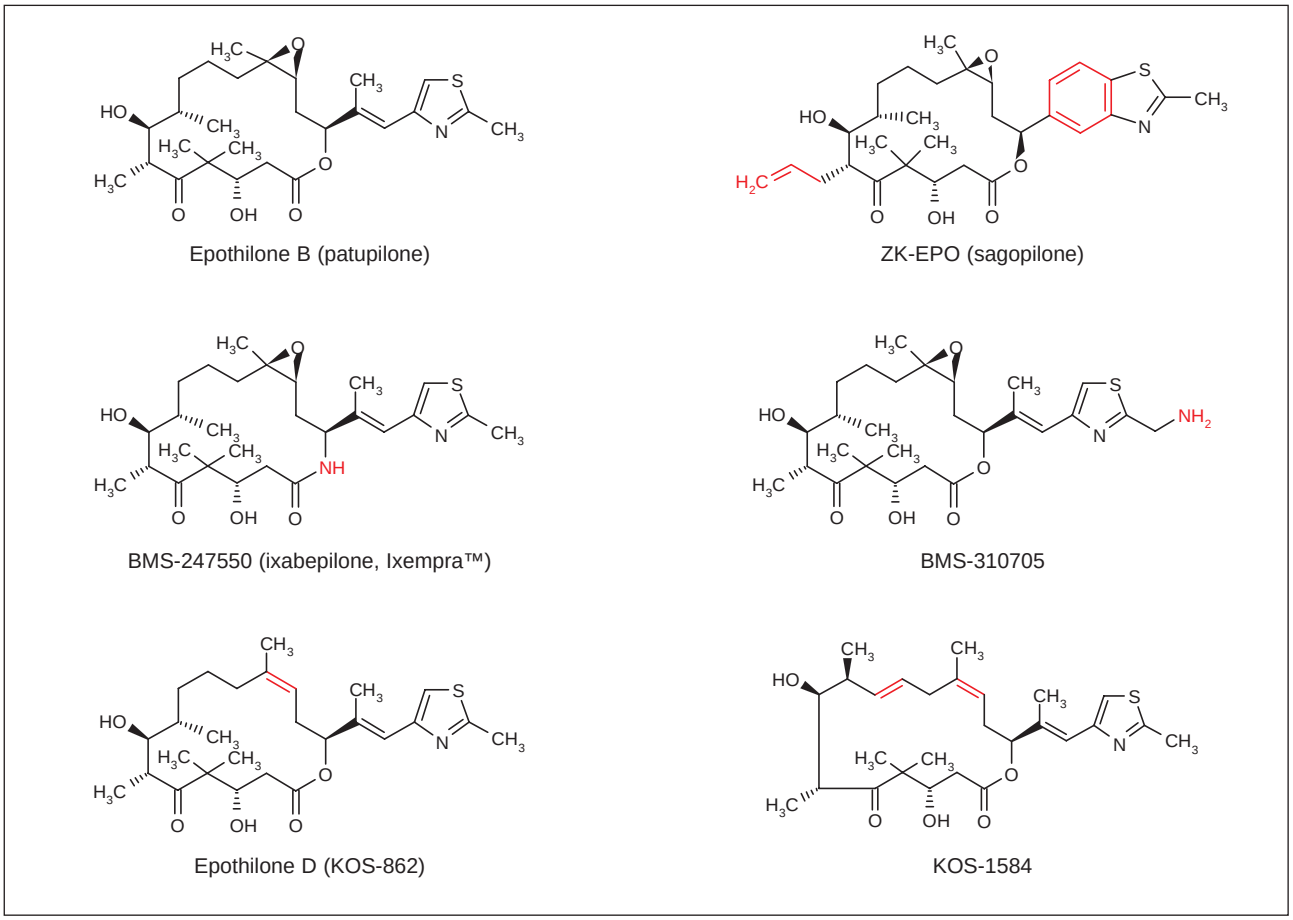


Fig. 1. Structures of the 6 epothilones that have entered clinical trials. The red labels indicate the individual structural changes compared to the natural product epothilone B.

myxobacterium *Sorangium cellulosum* (4). Epothilone B, the most active metabolite, was subsequently shown to have cytotoxic and antifungal properties and its cytotoxic mechanism of action was demonstrated to be microtubule stabilization (4, 5).

Many cytotoxic agents disrupt DNA synthesis. In contrast, taxanes, vinca alkaloids and epothilones act by preventing mitotic cell division. The targets of these agents are the microtubules, and specifically the tubulin subunits (6). Microtubules are long, slender protein polymers composed of α- and β-tubulin heterodimers (7) and form the cytoskeleton in eukaryotic cells. The cytoskeleton of the cell stabilizes cell shape, aids in intracellular transport and is crucial at the time of cell division. An integral part of normal microtubule function at mitosis is the formation of the mitotic spindle, which allows for cell division and replication (8). Drugs that act at the microtubule level have been shown to cause spindle dysfunction and G2/M-phase arrest of the cell cycle (9, 10). This causes the production of an apoptotic signal and hence cell death (11). Sagopilone, like the other epothilones and taxanes, causes enhanced polymerization of tubulin, leading to an increased stability of microtubules and thus an inability to function effectively (12).

There is currently much interest in epothilones, as they have several potential advantages over taxanes. Firstly, some epothilones, such as sagopilone, are not recognized by efflux pumps such as the multidrug resistance (MDR) protein, and so theoretically may be useful in some chemotherapy-resistant tumors. Epothilones have shown efficacy in taxane-resistant models *in vitro* (13, 14). Secondly, some, *e.g.*, sagopilone and BMS-310705, are water-soluble and therefore do not need to be mixed with solvents such as polyethylene glycol (PEG). This negates the need for steroid premedication and should potentially prevent the allergic reactions and administration problems that have been seen with taxanes. Thirdly, epothilones may have a different toxicity profile from taxanes. Although the dose-limiting toxicity (DLT) for many epothilones is also neuropathy, there appears to be less alopecia, which is an important consideration for patients.

Patupilone is currently under evaluation in phase II and III trials. Its promise as a cytotoxic agent has led to the design of further analogues. Sagopilone is the first fully synthetic epothilone and is currently being tested in phase II studies in various solid tumors, including metastatic breast, prostate and lung cancer, as well as in rarer tumors such as glioblastomas.

Preclinical Pharmacology

Sagopilone has been tested in a range of tumor cell lines known to be a target for microtubule-stabilizing drugs, *e.g.*, breast, ovarian and lung tumor cell lines, and was shown to have efficacy (15). Studies have compared sagopilone with a number of other cytotoxic agents, *e.g.*, paclitaxel, cisplatin and doxorubicin, in both normal cell lines and human tumor cell lines. Sagopilone was shown to be a potent antiproliferative agent with significantly greater activity than other cytotoxics in all human tumor cell lines (2, 15, 16). The potency of a drug is often expressed as the concentration required to inhibit cell proliferation by 50% (IC_{50}). For example, antiproliferative activity in breast cancer MCF7 cells was greater for sagopilone (IC_{50} < 1 nM) compared with paclitaxel and ixabepilone (IC_{50} > 3 nM) (16). Sagopilone has also been tested in normal proliferating and nonproliferating cells, such as human immortal keratinocyte cell lines (HaCat). Growth was potently inhibited by sagopilone and paclitaxel in the proliferating HaCat cells, whereas only minor effects were noted on nondividing cells, suggesting a favorable toxicity profile (2).

Sagopilone has shown promise in other tumor types which are thought to be intrinsically chemotherapy-resistant. It was superior to gemcitabine in four pancreatic cancer cell lines and it demonstrated strong antiproliferative activity in paclitaxel- and dacarbazine-resistant human melanoma models *in vivo* (SK-MEL-28 and A-375) (17).

Several studies have shown that sagopilone also has activity in cell lines that have acquired resistance to cytotoxic agents, in particular taxanes (2, 15, 16, 18). For example, sagopilone has subnanomolar mean IC_{50} values in a series of MDR human tumor cell lines, in contrast to values of > 100 nM for paclitaxel or ixabepilone and > 5 nM for patupilone (18). Further work has shown that sagopilone has subnanomolar IC_{50} values in drug-resistant breast and lung tumor cell lines (*e.g.*, MDR NCI/ADR), in contrast to patupilone (IC_{50} > 1 nM) and paclitaxel or ixabepilone (IC_{50} > 1 μM) (16). This study also demonstrated that the taxane-resistant cell lines MaTu/ADR and NCI/ADR had much greater cellular uptake of sagopilone compared with paclitaxel (7.5 and 290 times greater than paclitaxel, respectively).

Klar *et al*. showed that sagopilone, unlike paclitaxel and patupilone, is unaffected by efflux mechanisms such as P-glycoprotein (P-gp), the product of the *MDR1* gene. Verapamil is frequently used to block P-gp, thus allowing drug accumulation within drug-resistant cells and proving efflux was mediated via these pumps. Using NCI/ADR cell lines, verapamil 10 μM was added along with paclitaxel, patupilone and sagopilone. Verapamil enhanced the antitumor activity of both patupilone and paclitaxel, but had no effect on sagopilone activity, indicating that patupilone and paclitaxel are recognized by these pumps, whereas sagopilone is not (2).

Sagopilone has also been evaluated in fresh ovarian tumor cell cultures (19). Tumor cell cultures newly isolated from 27 ovarian cancer patients were plated with sagopilone, docetaxel, paclitaxel, ixabepilone, KOS-862 and patupilone. Sagopilone demonstrated a high level of antitumor activity against all isolates and was significantly more active than the other epothilones and taxanes in these cultures. Activity was evident after only 1 h of exposure, and after 3 days sagopilone showed IC_{50} values of < 1 nM for all 27 isolates tested compared with higher nanomolar concentrations for the other compounds. These results were independent of whether the parent tumor was platinum-sensitive or -resistant.

The efficacy of sagopilone compared with paclitaxel, cisplatin and doxorubicin has also been tested in human tumor xenografts, including breast, pancreatic, melanoma, ovarian, cervical and non-small cell lung cancer (NSCLC) xenografts (15). This study showed a high level of activity for sagopilone in chemotherapy-sensitive and -resistant models and greater efficacy for sagopilone in comparison with paclitaxel in all cell lines. Further *in vivo* data from human cervical tumors (HeLa/MaTu) showed inhibition of tumor growth after 5 days' exposure to paclitaxel (12 mg/kg/day) and following exposure to a single dose of sagopilone, compared to rapid growth in untreated controls. There was a dose-dependent response to sagopilone as a single dose, and 8 mg/kg was sufficient to completely inhibit tumor growth. The authors report that this dose was well tolerated in nude mice, as demonstrated by only modest weight loss and a recovery time of < 7 days. In the MDR cervical cancer model (HeLa/MaTu/ADR) it was demonstrated that there was almost complete inhibition of tumor growth with sagopilone compared to no antitumor effect for paclitaxel. There was complete regression of tumors in 50% of the animals treated with a single dose of 6 mg/kg of sagopilone. No severe side effects were noted (2).

Data from a study specifically investigating the activity of sagopilone in ovarian cancer xenografts in SCID mice were presented recently (19). Sagopilone showed significant, dose-dependent inhibition of OVCAR-3 and OVCAR-8 tumor growth compared with paclitaxel and cisplatin. Primary ovarian cancer cell lines were established in SCID mice and their sensitivities to treatment with sagopilone were reported to correlate with the *in vitro* data discussed above. The authors conclude as a result that sagopilone has a high level of activity in ovarian cancer models *in vitro* and *in vivo*.

Several preclinical studies have documented the predominantly nuclear uptake of sagopilone in comparison with other cytotoxics such as paclitaxel (15, 16, 18). Paclitaxel appears to preferentially accumulate in the cytosolic fraction and sagopilone almost fully localized to the nuclear/cytoskeletal fraction in all cell types examined in one study (16). This was confirmed by another study, where it was shown that > 80% of sagopilone was taken up in the nuclear/cytoskeletal fraction, whereas paclitaxel was taken up more slowly and approximately half was in the cytosolic fraction (18). The clinical relevance of these observations is unknown.

Winsel *et al*. also provided evidence of the cellular changes caused by sagopilone, thus supporting its antimi-

crotubular mechanism of action (18). Tubulin polymerization, multiple mitotic spindle formations, abnormal chromosomal alignment and cell cycle blockade were demonstrated to occur after sagopilone exposure. FACS analysis showed that at concentrations of 10 nM and above sagopilone blocked cell cycle progression at G2/M. There was evidence of apoptotic pathway induction in the form of caspase activity and TUNEL staining. At lower concentrations of sagopilone there was evidence of a sub-G1 peak formation suggestive of apoptotic fragments.

Data from a mouse model suggest that sagopilone may cross the blood-brain barrier (20). Sagopilone was given intravenously to SCID mice and the concentration in the brain compared with plasma levels 10 min after injection. This revealed concentrations of 0.9 μg/g in brain and 1.2 μg/g in plasma. The ratio of the areas under the curve between 0 and 40 min (AUC brain/AUC plasma) was approximately 0.8. This was compared to the distribution of paclitaxel. For paclitaxel, the concentration in the brain was below the limit of quantitation. This suggests relatively free access of sagopilone to the brain in an immunocompromised mouse model; however, these data may not necessarily equate with the situation in an immunocompetent human. Given these results and the antiproliferative activity found *in vivo* in the orthotopic U-373 MG glioma nude mouse model, phase II studies of sagopilone in glioblastomas are currently under way.

Clinical Studies

The initial results of a phase I trial evaluating sagopilone were published in abstract form at the ASCO Annual Meeting in 2005 (21) (Table I). The study enrolled 47 patients with histologically confirmed solid tumors who were refractory to standard treatment (n=44) or for whom no standard treatment was available (n=3). Sagopilone was given as a 30-min infusion every 3 weeks at a starting dose of 0.6 mg/m^2. At the time of presentation, 151 courses of sagopilone had been administered to the 47 patients, with a median of 3 (range: 1-23 courses). Doses up to 29 mg/m^2 had been given and the maximum tolerated dose (MTD) had not been reached at the time the abstract was filed. DLT was reached in 2 patients: common terminology criteria (CTC) grade 3 peripheral neuropathy at 16 mg/m^2 in 1 and grade 3 ataxia at 29 mg/m^2 in the other. No other DLT was reported. Common adverse effects were grade 1-2 peripheral sensory neuropathy (16 patients) and nausea (8 patients). Grade 2 leukopenia was observed in 2 patients. Interestingly, 2 patients who had received prior taxane treatment for breast cancer had a partial response at doses of 12-16 mg/m^2. Stable disease was demonstrated in 13 patients, 1 of whom remained on treatment after more than 16 months. The patients with stable disease had a variety of tumors, including NSCLC, cholangiocarcinoma, head and neck cancer and uveal melanoma. An overall clinical benefit (stable disease plus response to treatment) was seen in 15 patients (32%), although objective responses were only obtained in 2 patients (4%).

Two phase II studies have been published in abstract form (Table I). The preliminary results of the ZK-EPO Study Group in Platinum Resistant Ovarian Cancer were reported at the 2007 ASCO meeting (22). Patients were eligible at first or second relapse with a platinum-free interval of < 6 months. Disease could be assessed by measurable disease or CA125 measurements. Sagopilone was given every 3 weeks in both groups but patients were randomized to either a 30-min infusion of sagopilone at a dose of 16 mg/m^2 or the same dose as a 3-h infusion. Simon's two-step design was used and the 30-min infusion arm was discontinued after the initial stage recruitment due to a low response rate (1 of 13). Data were reported for 30 of the patients in step 1, following 101 infusions. Most of the patients had previous taxane exposure (n=25); 4 patients were excluded from efficacy analysis (as per protocol) due to tumor histology, *i.e.*, clear cell or mucinous tumors. In the toxicity analysis, grade 2-3 peripheral neuropathy was more common with the 3-h infusion than the 30-min infusion (9 of 15 patients and 5 of 15 patients, respectively). Two patients in the 3-h infusion group withdrew due to neurotoxicity. Other reported adverse effects greater than grade 1 in severity were arthralgia (n=3), nausea (n=3), fatigue (n=3) and lethargy (n=2). Four patients (30.8%) responded in step 1 with the 3-h infusion. The authors concluded that sagopilone has promising activity in ovarian carcinoma, with neuropathy as the only noteworthy toxicity.

The results of another phase II trial in NSCLC patients were presented at ECCO in September 2007. This trial investigated 44 patients with stage IIIB or IV NSCLC who had relapsed after initial platinum-based chemotherapy. Patients were treated with 3-h infusions of sagopilone at a dose of 16 mg/m^2 every 21 days for up to 6 cycles. The abstract reports efficacy data on the first 38 patients. Four patients responded, for an objective response rate of 10.5%. This response rate compares favorably with other second-line therapies in NSCLC (23, 24). Grade 1-2 peripheral sensory neuropathy was seen in 45% of participants and grade 3 in 14%. Seven patients discontinued the study drug due to neuropathy. Other adverse effects (grade unspecified) included myalgia (23%), alopecia (18%), fatigue (16%), nausea (16%) and vomiting (14%). The authors concluded that sagopilone has second-line activity in NSCLC and have escalated the dose in future patients recruited to include the option of 22 mg/m^2 (25).

Currently there are several phase I/II trials recruiting throughout North America and Europe using sagopilone as a single agent and in combination (Table II). These include single-agent studies in NSCLC, metastatic breast cancer and melanoma. Trials using sagopilone in combination include: with cisplatin in small cell lung cancer, with carboplatin in recurrent ovarian carcinoma and with prednisone in metastatic hormone-refractory prostate cancer. The potential ability of sagopilone to cross the blood-brain barrier has led to phase II studies in recurrent glioblastoma and in patients with advanced breast cancer and brain metastases.

Table I: Published clinical trials of sagopilone.

Type of study	Title	Ref.
Phase I	A phase I study of the novel, third-generation epothilone ZK-EPO in patients with advanced solid tumors	21
Phase II	Phase II trial of the novel epothilone ZK-EPO in patients with platinum resistant ovarian cancer	22
Phase II	Phase II trial of the novel epothilone ZK-EPO as second-line therapy in patients with stage IIIB or IV non-small cell lung cancer	25

Table II: Current phase II trials of sagopilone.

Title	Tumor site	Line of treatment	Country open	Phase
ZK-EPO given with carboplatin in patients with recurrent ovarian cancer (NCT00325351)	Ovary	2nd line	USA, Canada	I/II
A study of a new chemotherapy agent in combination with cisplatin to treat small cell lung cancer (NCT00359359)	Lung (small cell)	1st line	Germany	I/II
Safety and efficacy study of a new chemotherapy agent to treat non-small cell lung cancer (NCT00160069)	Lung (NSCLC)	2nd line	Germany	II
Safety and efficacy study of a new chemotherapy agent to treat metastatic breast cancer (NCT00288249)	Breast	1st-3rd line; no previous taxanes or vinca alkaloids	Europe	II
Evaluation of a new agent for treatment of advanced-stage breast cancer (NCT00313248)	Breast	2nd-4th line	USA, Canada	II
ZK-EPO given with prednisone in patients with metastatic androgen-independent prostate cancer (NCT00350051)	Prostate	1st line cytotoxic	USA, Argentina	II
Epothilone in recurrent glioblastoma patients (NCT00397072)	Glioblastoma	2nd line and later	Italy	II
Epothilone ZK 219477 in treating patients with recurrent glioblastoma (NCT00424060)	Glioblastoma	2nd line	EORTC/Switzerland	II
ZK-219477 in patients with breast cancer and brain metastases (NCT00496379)	Breast	2nd line following radiation	USA	II
Phase II trial of ZK-EPO (ZK 219477) in metastatic melanoma (NCT00598507)	Melanoma	2nd line after standard therapy	USA	II

Summary

Preclinical data suggest that sagopilone is a more potent antitumor agent than the taxanes and other epothilones. Sagopilone shows some promise as a realistic alternative or additional line of treatment to taxane therapy. The fact that the compound is water-soluble offers administration advantages over the taxanes. Preclinical data suggest that sagopilone evades cellular efflux pumps responsible for MDR and is active in taxane-resistant models. Whether this will be clinically relevant in treating drug-resistant cancers remains to be proven. Preclinical data also suggest a potentially wider range of activity than the vinca alkaloids and taxanes. Further clinical studies need to be conducted to confirm whether the advantages of sagopilone seen in preclinical and early clinical studies will translate into a clear clinical benefit for patients.

Source

Bayer Schering Pharma (DE).

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