Chapter 1 : Taxanes for the Treatment of Metastatic Breast Cancer

Hongdoushans A-C are oxygenated taxane diterpenes, isolated from the wood of Taxus calendrierdelascience.comushan A (C 29 H 44 O 7), hongdoushan B (C 27 H 40 O 7), and hongdoushan C (C 27 H 42 O 6) are reported to have anticancer activity in vitro.

Open in a separate window Schedule: Furthermore, 5 patients in that study who previously had been treated with CrEL-paclitaxel achieved clinical responses. Breast Cancer Subtypes Histologic subtypes In the era of personalized medicine, it is prudent to consider how taxanes are used to treat different subtypes of breast cancer. CrEL-paclitaxel, docetaxel, and nab-paclitaxel are all among the preferred single-agent regimens for MBC. Unfortunately, the study only included 13 patients with BRCA2 mutation, making such comparisons somewhat less robust. Several studies have focused on identifying mechanisms that underlie resistance to taxane treatment. Overexpression of MDR1, a membrane-bound drug efflux pump, may lower the intracellular concentration of anticancer drugs, such as the taxanes. CrEL-Paclitaxel and Docetaxel in Early Breast Cancer The management of breast cancer continues to evolve with the introduction of new, more effective agents and the expanding role of taxanes in early breast cancer treatment. Analysis of data from 44, women treated in 33 trials of taxanes given either in combination or sequentially with anthracycline-based regimens vs. Until recently, capecitabine was the only approved agent for the treatment of patients with anthracycline- or taxane-resistant MBC. In these trials, the median TTPs were 3 to 6 months. In two small retrospective studies, patients had received CrEL-patients had received prior CrEL-paclitaxel or docetaxel, respectively. Among the 14 responders to taxane retreatment with CrEL-paclitaxel, half had documented primary resistance to docetaxel therapy, which was defined as disease progression during docetaxel treatment or within 12 months of completing docetaxel treatment. Prospective studies of taxane retreatment documented similar findings. The median duration from prior taxane therapy to retreatment with CrEL-paclitaxel was 83 days, and 28 patients had previously been exposed to a taxane within 3 months of retreatment. Among the 45 evaluable patients who had received prior taxane therapy, 7 patients An interesting finding from this study was that it appeared that the length of CrEL-paclitaxel infusion correlated with the response to retreatment with docetaxel. Many of the studies described above defined patients with prior exposure to a taxane in the metastatic setting and not exclusively the neoadjuvant or adjuvant setting. A recent study out of Germany called the Taxane Re-Challenge Cohort Study retrospectively identified patients with recurrent disease who were treated in the neoadjuvant or adjuvant setting with a taxane-based regimen. A total of patients A response rate of The ORR for later-line therapy was Response to taxane retreatment was dependent on the disease-free interval. If patients had disease recurrence within 1 year, response rates were Physicians must base the decision to treat patients with taxane-refractory disease by rechallenge with a taxane vs. If taxane rechallenge is desirable, the oncologist must consider the dosing schedule of previous taxane regimens. Another important consideration is the length of time that has passed from the completion of previous taxane therapy adjuvant or metastatic. Patients with disease recurrence several years after taxane therapy can receive taxane therapy again. For treatment very soon after the failure of a taxane, a different regimen, such as single-agent capecitabine, eribulin mesylate, or ixabepilone, may be considered. Sensory neuropathy is of particular concern because some cases are irreversible. Specifically, there is evidence that patients who have previously received solvent-based taxanes may benefit from treatment with nab-paclitaxel. Median OS values were 9. Grade 4 adverse events were rare in this trial, and the most common grade 3 adverse events observed were leukopenia, neutropenia, and sensory neuropathy. The results of this study suggested that nab-paclitaxel may provide a clinical benefit in patients with MBC who are refractory to treatment with other taxanes. The response rates in taxane-exposed patients in the Blum et al study described above agree with those of a study presented at the annual meeting of the American Society of Clinical Oncology in on the repeat use of taxanes for MBC. By contrast, among the 14 patients rechallenged with docetaxel, no patients achieved a clinical response. Although it must be noted that the number of patients analyzed in this study was small, these data are consistent with the idea that nab-paclitaxel is a reasonable option for patients with MBC whose disease has

progressed during treatment with taxanes. Although the studies above describe clinical outcomes in patients who had received taxanes as a previous course of therapy for MBC, it is also important to establish the role of nab-paclitaxel among patients whose metastatic disease had progressed during treatment with other chemotherapeutic regimens. These results demonstrated greater clinical activity for nab-paclitaxel vs. CrEL-paclitaxel among patients who had previously received chemotherapy, particularly anthracycline-based regimens, for the treatment of MBC. Conclusions As discussed throughout this review, the taxanes remain a key component of MBC treatment. Data presented here demonstrate the gains in efficacy that have been seen with the evolution of taxane treatment from the development of CrEL-paclitaxel beginning in the s through the ongoing investigation of nab-paclitaxel, which has demonstrated median OS values as high as Indeed, taxanes are among the agents recommended for both the adjuvant and neoadjuvant treatment of early-stage breast cancer. Resistance to taxane treatment has spurred investigation of numerous combination therapies. Although many taxane-containing combination therapies are recognized as possessing benefits in terms of response rates and PFS, NCCN guidelines point to the lack of OS benefit and increased toxicities that combination therapies have demonstrated as disadvantages to combination therapy. In addition to enhanced efficacy in some patients, the use of albumin in place of chemical solvents to deliver paclitaxel to the tumor allows patients to avoid pretreatment with corticosteroids and antihistamines and to benefit from a shorter infusion time of 30 minutes. Furthermore, despite a higher dose of paclitaxel, the safety profile of nab-paclitaxel compares favorably with that of CrEL-paclitaxel.

Chapter 2 : List of chemotherapeutic agents - Wikipedia

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The article may be redistributed, reproduced, and reused for non-commercial purposes, provided the original source is properly cited. This article has been cited by other articles in PMC. Abstract Nanoparticle albumin-bound paclitaxel nab-paclitaxel is currently approved in Japan for treatment of breast cancer. However, apart from phase I clinical trials, data regarding Japanese patients are scant. In the present study, the efficacy and safety of nab-paclitaxel therapy were retrospectively analyzed in 22 patients with advanced or metastatic breast cancer who were treated at the National Hospital Organization Shikoku Cancer Center between November and June The nab-paclitaxel was administered once every three weeks. The median age of the patients was 59 years. None of the patients had HER2-positive breast cancer. The median number of treatment cycles was six range, two to Six patients exhibited a partial response; the response rate was The response rate and clinical benefit rate were higher in patients who received nab-paclitaxel as first- or second-line treatment. The median time to treatment failure was days range, 27â€” The results suggest that nab-paclitaxel is a well-tolerated and clinically useful anticancer preparation. The Taxanes include paclitaxel and docetaxel. In Japan, weekly paclitaxel has been widely used due to good efficacy and high tolerability 1. Consequently, patients must receive premedication with corticosteroids, antihistamines and histamine-2 receptor antagonists prior to administration of paclitaxel. Premedication with polyoxyethylated castor oil may also result in peripheral neuropathy and alter the pharmacokinetics of paclitaxel 3. Paclitaxel also has other solvent-related problems: Only limited types of intravenous infusion sets may be used and treating patients who exhibit alcohol intolerance is difficult 4. Compared with conventional preparations of paclitaxel, nab-paclitaxel has a number of advantages: Nab-paclitaxel has thus overcome the predominant disadvantages of paclitaxel, and exerts enhanced antitumor activity. The present study reports the clinical experience of female breast cancer patients treated with nab-paclitaxel, and describes the adverse event management. Written informed consent was obtained from all patients. Patients and methods Patients Data regarding 22 women with advanced or recurrent breast cancer who received nab-paclitaxel in the National Hospital Organization Shikoku Cancer Center Matsuyama, Japan between November and June were retrospectively analyzed. The general condition of the patients who received nab-paclitaxel had to satisfy the following conditions: Treatment Nab-paclitaxel was administered as a continuous intravenous infusion over the course of 30 min every three weeks. The patients did not receive any particular premedication. Response and toxicity assessment Computed tomography and magnetic resonance imaging scans were performed at baseline and after three months to assess the radiological response of each patient according to the Response Evaluation Criteria in Solid Tumors, version 1. The clinical benefit ratio CBR was defined as the percentage of patients who had a complete response CR , partial response PR or stable disease. Time to treatment failure TTF was defined as the time period between the initiation of treatment and the cessation of treatment for any reason, including progressive disease, treatment-related toxicity and fatality, and was estimated by the Kaplan-Meier method. Countermeasures against adverse events In the National Hospital Organization Shikoku Cancer Center, pharmacists provide patients with a detailed explanation with regard to the time periods when greatest bone marrow suppression occurs nadir white-cell count , the countermeasures against infection, and the management of fever prior to chemotherapy and prior to discharge, using a patient compliance manual. Subcutaneous injection of granulocyte colony-stimulating factor G-CSF and treatment with antibacterial agents requires consideration in patients with grade 3 or higher febrile neutropenia, or grade 4 neutropenia. The patients were informed in advance with regard to when these symptoms were most likely to occur and were instructed to take the prescribed drugs, so as to avoid enduring pain. In our center, patients who receive nab-paclitaxel monotherapy are not usually administered antiemetics. The initial dose of nab-paclitaxel is administered during hospitalization, and the second and subsequent doses are prescribed on an outpatient basis. Pharmacists provide patients with drug management counseling prior to treatment, including

information regarding drug names, treatment goals, treatment schedules, and potential adverse events with possible times of onset and countermeasures. Pharmacists are stationed in outpatient clinics and interview patients with regard to adverse events. Nurses at the center provide patients with guidance concerning daily activities, accounting for the background characteristics of each patient. The nurses also describe the typical patient experience development and management of adverse events , thereby attempting to relieve anxiety. In addition, the nurses provide patients with information regarding the severity of adverse events that would require treatment withdrawal or dose reduction, or the possibility of switching to other regimens, and the patients may seek consultation at any time. Results Patients The clinical characteristics of the patients are shown in Table I. The median age at the initiation of treatment was 59 years range, 35 to A total of 18 patients exhibited postoperative recurrence and four had stage IV disease. The hormone receptor HR and human epidermal growth factor receptor-2 HER2 protein expression status of patients was as follows: No patient had HER2-positive tumors. The metastatic sites were the lymph nodes in 15 patients, liver in 12, lung in 11, bone in seven, pleura in five and skin in one. A total of 15 patients had metastases to multiple organs. Table I Demographic characteristics of females with advanced breast cancer who received nab-paclitaxel between November and June

Chapter 3 : USB2 - Taxane anticancer agents - Google Patents

This is a list of chemotherapeutic agents (also known as cytotoxic agents) that are known to be of use in chemotherapy for cancer. This list is organized by type of agent, although the subsections are not necessarily definitive and are subject to revision.

Notify your healthcare provider immediately premedication regimen has significantly decreased the incidence of this reaction. Swelling of the feet or ankles edema. Increases in blood tests measuring liver function. These return to normal once treatment is discontinued. Low blood pressure occurring during the first 3 hours of infusion. Darkening of the skin where previous radiation treatment has been given radiation recall - see skin reactions. Nail changes discoloration of nail beds - rare see skin reactions. However, you should always inform your health care provider if you experience any unusual symptoms. When to contact your doctor or health care provider: Contact your health care provider immediately, day or night, if you should experience any of the following symptoms: The following symptoms require medical attention, but are not an emergency. Contact your health care provider within 24 hours of noticing any of the following: If you notice any redness or pain at the site of injection Nausea interferes with ability to eat and unrelieved with prescribed medication Vomiting vomiting more than times in a 24 hour period Diarrhea episodes in a hour period Unusual bleeding or bruising Black or tarry stools, or blood in your stools or urine Extreme fatigue unable to carry on self-care activities Mouth sores painful redness, swelling or ulcers Yellowing of the skin or eyes Swelling of the feet or ankles. Sudden weight gain Signs of infection such as redness or swelling, pain on swallowing, coughing up mucous, or painful urination. Always inform your health care provider if you experience any unusual symptoms. Before starting Taxol treatment, make sure you tell your doctor about any other medications you are taking including prescription, over-the-counter, vitamins, herbal remedies, etc. Do not take aspirin, or products containing aspirin unless your doctor specifically permits this. Inform your health care professional if you are pregnant or may be pregnant prior to starting this treatment. Pregnancy category D Taxol may be hazardous to the fetus. Women who are pregnant or become pregnant must be advised of the potential hazard to the fetus. For both men and women: Do not conceive a child get pregnant while taking Taxol. Barrier methods of contraception, such as condoms, are recommended. Discuss with your doctor when you may safely become pregnant or conceive a child after therapy. Do not breast feed while taking Taxol. Taxol, or the medications that you take with Taxol may cause you to feel dizzy or drowsy. Do not operate any heavy machinery until you know how you respond to Taxol. If you notice any redness or pain at the injection site, place a warm compress, and notify your healthcare provider. Drink at least two to three quarts of fluid every 24 hours, unless you are instructed otherwise. You may be at risk of infection so try to avoid crowds or people with colds and those not feeling well, and report fever or any other signs of infection immediately to your health care provider. Wash your hands often. Use an electric razor and a soft toothbrush to minimize bleeding. Avoid contact sports or activities that could cause injury. Taxol causes little nausea. But if you should experience nausea, take anti-nausea medications as prescribed by your doctor, and eat small frequent meals. Sucking on lozenges and chewing gum may also help. However, be sure to talk with your doctor before taking it. You may experience drowsiness or dizziness; avoid driving or engaging in tasks that require alertness until your response to the drug is known. Taxol will make you sensitive to sunlight. You must wear sunglasses when outside, and avoid sun exposure. Wear protective clothing, and also wear SPF 15 or higher sun block. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely. You should discuss this with your doctor. Get plenty of rest. If you experience symptoms or side effects, be sure to discuss them with your health care team. You will be checked regularly by your health care professional while you are taking Taxol, to monitor side effects and check your response to therapy. Periodic blood work to monitor your complete blood count CBC as well as the function of other organs such as your kidneys and liver will also be ordered by your doctor. Cancerous tumors are characterized by cell division, which is no longer controlled as it is in normal tissue. Cancerous cells lose this ability. Cancer cells no longer have the normal checks and balances in place that control and limit cell division. The process of cell division, whether normal or cancerous

cells, is through the cell cycle. The cell cycle goes from the resting phase, through active growing phases, and then to mitosis division. The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division. If the cells are unable to divide, they die. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells, causing the tumor to shrink. They also induce cell suicide self-death or apoptosis. Chemotherapy drugs that affect cells only when they are dividing are called cell-cycle specific. Chemotherapy drugs that affect cells when they are at rest are called cell-cycle non-specific. The scheduling of chemotherapy is set based on the type of cells, rate at which they divide, and the time at which a given drug is likely to be effective. This is why chemotherapy is typically given in cycles. Chemotherapy is most effective at killing cells that are rapidly dividing. Unfortunately, chemotherapy does not know the difference between the cancerous cells and the normal cells. The "normal" cells will grow back and be healthy but in the meantime, side effects occur. Different drugs may affect different parts of the body. Taxol belongs to a class of chemotherapy drugs called plant alkaloids. Plant alkaloids are made from plants. The vinca alkaloids are made from the periwinkle plant catharanthus rosea. The taxanes are made from the bark of the Pacific Yew tree taxus. The vinca alkaloids and taxanes are also known as antimicrotubule agents. The podophyllotoxins are derived from the May Apple plant. Camptothecan analogs are derived from the Asian "Happy Tree" Camptotheca acuminata. Podophyllotoxins and camptothecan analogs are also known as topoisomerase inhibitors. The plant alkaloids are cell-cycle specific. This means they attack the cells during various phases of division. Vincristine, Vinblastine and Vinorelbine. Antimicrotubule agents such as Taxol , inhibit the microtubule structures within the cell. Inhibition of these structures ultimately results in cell death. We strongly encourage you to talk with your health care professional about your specific medical condition and treatments. The information contained in this website is meant to be helpful and educational, but is not a substitute for medical advice. For information about the 4th Angel Mentoring Program visit www.

Chapter 4 : Taxane anticancer agents: a patent perspective | Read by QxMD

Since combination therapy of taxane anticancer agents has been successful in clinic and drug combination is one of the most translational approach for drug development, preclinical development of new drug combinations is quite active with a large number of patent applications.

More particularly, the invention provides novel paclitaxel derivatives, pharmaceutical formulations thereof, and their use as antitumor agents. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is used clinically against a number of human cancers. It is an important cancer agent both therapeutically and commercially. Numerous clinical trials are in progress to expand the increase the utility of this agent for the treatment of human proliferative diseases. A very recent compilation of articles by a number of different authors is contained in the entire issue of Seminars in Oncology , 26 1 , Suppl 2. Other examples are such as by Rowinsky et al. Chen, Iwao Ojima, and Dolotrai M. The structures of paclitaxel and docetaxel are shown below along with the conventional numbering system for molecules belonging to the class; such numbering system is also employed in this application. Some of the background art pertaining to this invention are shown below. Several Publications have described the synthesis or attempted synthesis of the 7-deoxy analog of paclitaxel. Preparation of 7-deoxytaxol, a highly bioactive taxol derivative, and interconversion of taxol and 7-epi-taxol". Matovic, Radomir; Saicic, Radomir N. Cambridge , 16 , , Other than actual supporting examples already claimed in the above mentioned U. This application also does not provide details of the preparation of any C-7 deoxy taxanes which are not covered by the above mentioned U. Patent 5, , to Holton et al was granted. Metabolism and pharmacology of taxoids. Isolation, purification, and biological activity of mono- and dihydroxylated paclitaxel metabolites from human feces. Isolation and identification of three major metabolites of taxol in rat bile. Preparation of Phenolic Paclitaxel Metabolites. WO published May 1 , However, this patent does not describe the synthesis or administration of para-hydroxyphenyl taxanes nor any actual efficacy results. Thus, the art clearly shows that the phydroxy phenyl sidechain analog of paclitaxel will be less potent than the parent drug. Methods for administering taxanes in the presence of modulators have been been reported to increase the amount of taxanes in the plasma after oral administration: Co-administration of cyclosporin enables oral therapy with paclitaxel. Lancet , , A method of making taxanes orally bioavailable by coadministration with cinchonine. WO published August 7, Broder, Samuel; Duchin, Kenneth L. Method and compositions for administering taxanes orally to human patients using a cyclosporin to enhance bioavailability. WO published December 3, These reports contain no antitumor efficacy data but the presence of taxanes in the plasma is extrapolated to show their potential for anaticancer utility. At least one report of oral activity of taxane analogs or prodrugs in preclinical animal models has appeared in the prior art: Preparation of paclitaxel prodrug derivatives. EP published December 11 , The oral bioavailability of the prodrug which had oral efficacy was not disclosed and no further reports of these compounds progressing to man have appeared. Thus it is clear that taxanes with both good oral bioavailability and good oral efficacy are at minimum, exceedingly rare. There are no such compounds which have been reported to demonstrate both oral bioavailbility and anticancer activity in man. Several Publications have described the synthesis or attempted synthesis of some 7-deoxy taxane analogs and these are included only because they are additional references in the area of 7-deoxy taxanes. Tetrahedron, 53 37 , , Tetrahedron, 53 14 , , Synthesis of the 7-deoxy ABC taxane skeleton, and reactions of the A-ring". Tetrahedron, 52 45 , , Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula I. The method of administration may be oral or intravenous or any other suitable route. Yet, another aspect of the present invention provides a pharmaceutical formulation which comprises an antitumor effective amount of a compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. Yet, another aspect of the present invention provides a process for preparing 7-deoxy taxanes or baccatins by hydrogneation of the corresponding 6,7-olefin taxane intermediates. In this

application, the symbols once defined retain the same meaning throughout the application, until they are redefined. The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. Depending on the context, "C alkenyl" can also refer to C alkenediyl which bridges two groups; examples include ethylene-1 ,2-diyl vinylene , 2-methyl butene-1 ,4-diyl, 2-hexene-1 ,6-diyl, etc. As used herein t-butyloxy and t- butoxy are used interchangeably. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings. Additional examples of hydroxy protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed. The products in accordance with the invention can be utilized to prevent or delay the appearance or reappearance, or to treat these pathological conditions. While some of the products of general formula I are of interest due to advantages over commercial taxanes following iv administration others are of interest due to their unique properties after oral administration. The compounds of this invention can be made by techniques from the conventional organic chemistry repertoire. Schemes I - V, which depict processes that compounds within the scope of formula I can be made, are only shown for the purpose of illustration and are not to be construed as limiting the processes to make the compounds by any other methods. The methods can be readily adapted to variations in order to produce compounds within the scope of formula but not specifically disclosed. Further variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art. One of the ways the compounds of this invention can be made is by the general method which shown is Scheme I. All disclosures are herein incorporated by reference in their entirety. The methods that can be adapted to variations in order to produce other azetidinones within the scope of formula IV, but not specifically disclosed herein or in the above references or reported elsewhere, will be obvious to anyone skilled in the art. The baccatin III derivatives II can be attached to a sidechain using any of the methodology which is now already well known in the art. The many references cited in this invention disclosure and Tetrahedron, 48, No. In Step a of Scheme I, it is advantageous to convert the hydroxy group on the C carbon into a metal alkoxide before the coupling. The formation of a desired metal alkoxide may be done by reacting a compound of formula II with a strong metal base, such as lithium diisopropylamide, C alkyllithium, lithium bis trimethylsilyl amide, phenyllithium, sodium hydride, potassium hydride, lithium hydride, or the like base. For example when lithium alkoxide is desired, a compound of formula II may be rea cted with n-butyllithium in an inert solvent such as tetrahydrofuran. For examples of attachment of substituted baccatins with a suitably substituted lactam via the method of Holton see U. This patent also describes an alternative method for attaching substituted isoserine sidechains to substituted baccatins which would be applicable for the compounds of this invention. This same alternate method is described in another publication by Kingston et. Further information on alternative methods to attach sidechains to baccatins are contained in Thottathil, et. As used herein, R3 is a conventional hydroxy protecting group. Conventional hydroxy protecting groups are moieties which can be employed to block or protect a hydroxy function, and they are well known to those skilled in the art. Preferably, said groups are those which can be removed by methods which result in no appreciable destruction to the remaining portion of the molecule. Examples of such readily removable hydroxy protecting groups include chloroacetyl, methoxymethyl, 1-methylmethoxyethyl , tetrahydropyranyl, tetrahydrothiopyranyl, dialkylsilylethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t- butyldimethylsilyl ether, dialkyl alkoxy silyl ethers such as diisopropyl methoxy silyl ethers;2,2,2-trichloroethyoxymethyl, 2,2,2- trichloroethyloxycarbonyl or simply trichloroethyloxycarbonyl , benyloxycarbonyl and the like. Other suitable protecting groups which may be used are found in Chapter 2 of "Protecting Groups in Organic Synthesis", 3rd Ed. Greene and Peter G. A protecting group for formula IV compounds which has been used frequently in the literature is trialkylsilyl. In Step b , the protecting group R3 is removed. If R3 equals triCalkylsilyl, such as triethylsilyl, it can be removed with fluoride ion or with mineral acid in alcohol or acetonitrile. The removal with fluoride ion is conducted in an inert solvent such as tetrahydrofuran, methylene chloride, 1 ,4-dioxane, DMF, chloroform, or in the like solvent; and the reaction medium may be buffered with a weak acid such as acetic acid. An example of

mineral acid is hydrochloric acid. In compounds of this invention R2 may also be hydroxy. In compounds where R2 is hydroxy, a suitable protecting group must be utilized prior to sidechain cleavage or installed selectively on the C hydroxy group prior to the coupling reaction. Trialkylsilyl, dialkylalkoxysilyl, CBz, or Troc protecting groups are suitable for this protecting group step and can be attached using methodology which is well known in the art. The protecting groups can ideally be removed simultaneously in step b or or in a separate deprotection step immediately preceding or following step b. The simple 7-deoxy baccatin core II can be prepared as described in the previously mentioned U. Alternatively, the desired 7-deoxy baccatin core can be obtained using the chemistry shown in Scheme II. As shown in Scheme II, the starting material is a known taxane analog. This protecting group is by now well known in the taxane art and has been described by several authors including Kingston and George. Although this group is preferred, other protecting groups can be utilized. The preparation of intermediates arising from step c and step d are now well known in the art. The synthesis of the 7-trifluoromethanesulfonate triflate intermediate is shown in step d and is by now well known in the art. The preparation of triflates and their conversion into cyclopropane and olefin has been divulged by Johnson, R. The preferred synthesis utilizes DMAP as the base and triflic anhydride as the activating agent. Experimental details for the preparation of the olefin arising from step d are contained in U. Hydrogenation of the olefin is carried out in step f to provide the 7- deoxy taxane interemediate. Many hydrogenation catalysts could be used for this hydrogenation reaction.

Chapter 5 : Taxane anticancer agents: a patent perspective. - Abstract - Europe PMC

taxane anticancer agents has been focusing on addressing these limitations of the first-generation taxanes. Although the primary mechanism of taxanes is to induce.

Description This application claims benefit of U. Field of the Invention The present invention concerns antitumor compounds. More particularly, the invention provides novel paclitaxel derivatives, pharmaceutical formulations thereof, and their use as antitumor agents. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is used clinically against a number of human cancers. It is an important cancer agent both therapeutically and commercially. Numerous clinical trials are in progress to expand the increase the utility of this agent for the treatment of human proliferative diseases. A very recent compilation of articles by a number of different authors is contained in the entire issue of Seminars in Oncology , 26 1, Suppl 2. Other examples are such as by Rowinsky et al. Chen, lwao Ojima, and Dolotrai M. The structures of paclitaxel and docetaxel are shown below along with the conventional numbering system for molecules belonging to the class; such numbering system is also employed in this application. Some of the background art pertaining to this invention are shown below. Several Publications have described the synthesis or attempted synthesis of the 7-deoxy analog of paclitaxel. Matovic, Radomir; Saicic, Radomir N. Other than actual supporting examples already claimed in the above mentioned U. This application also does not provide details of the preparation of any C-7 deoxy taxanes which are not covered by the above mentioned U. Metabolism and pharmacology of taxoids. Isolation, purification, and biological activity of mono- and dihydroxylated paclitaxel metabolites from human feces. Isolation and identification of three major metabolites of taxol in rat bile. Preparation of Phenolic Paclitaxel Metabolites. WO published May 1, However, this patent does not describe the synthesis or administration of para-hydroxyphenyl taxanes nor any actual efficacy results. Thus, the art clearly shows that the phydroxy phenyl sidechain analog of paclitaxel will be less potent than the parent drug. Methods for administering taxanes in the presence of modulators have been been reported to increase the amount of taxanes in the plasma after oral administration: Meerum; Beijnen, Jos H. Co-administration of cyclosporin enables oral therapy with paclitaxel. Lancet , , A method of making taxanes orally bioavailable by coadministration with cinchonine. WO published Aug. Broder, Samuel; Duchin, Kenneth L. Method and compositions for administering taxanes orally to human patients using a cyclosporin to enhance bioavailability. WO published Dec. These reports contain no antitumor efficacy data but the presence of taxanes in the plasma is extrapolated to show their potential for anaticancer utility. At least one report of oral activity of taxane analogs or prodrugs in preclinical animal models has appeared in the prior art: Preparation of paclitaxel prodrug derivatives. EP published Dec. The oral bioavailability of the prodrug which had oral efficacy was not disclosed and no further reports of these compounds progressing to man have appeared. Thus it is clear that taxanes with both good oral bioavailability and good oral efficacy are at minimum, exceedingly rare. There are no such compounds which have been reported to demonstrate both oral bioavailbility and anticancer activity in man. Several Publications have described the synthesis or attempted synthesis of some 7-deoxy taxane analogs and these are included only because they are additional references in the area of 7-deoxy taxanes. Cambridge , 16 , , Tetrahedron, 53 37 , , Tetrahedron, 53 14 , , Tetrahedron, 52 45 , , Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula I. The method of administration may be oral or intravenous or any other suitable route. Yet, another aspect of the present invention provides a pharmaceutical formulation which comprises an antitumor effective amount of a compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. Yet, another aspect of the present invention provides a process for preparing 7-deoxy taxanes or baccatins by hydrogneation of the corresponding 6,7-olefin taxane intermediates. In this application, the symbols once defined retain the same meaning throughout the application, until they are redefined. As used herein t-butyloxy and t-butoxy are used interchangeably. Additional examples of hydroxy

protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed. An even more preferred embodiment are compounds I, or pharmaceutically acceptable salts thereof in which R2 is hydrogen, hydroxy, or acetyloxy; Rg is parahydroxyphenyl; and R1 is Calkyloxycarbonyl. These pathological conditions can also include psoriasis: The products in accordance with the invention can be utilized to prevent or delay the appearance or reappearance, or to treat these pathological conditions. While some of the products of general formula I are of interest due to advantages over commercial taxanes following iv administration others are of interest due to their unique properties after oral administration. The compounds of this invention can be made by techniques from the conventional organic chemistry repertoire. Schemes I-V, which depict processes that compounds within the scope of formula I can be made, are only shown for the purpose of illustration and are not to be construed as limiting the processes to make the compounds by any other methods. The methods can be readily adapted to variations in order to produce compounds within the scope of formula but not specifically disclosed. Further variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled in the art. One of the ways the compounds of this invention can be made is by the general method which shown is Scheme I. All disclosures are herein incorporated by reference in their entirety. The methods that can be adapted to variations in order to produce other azetidinones within the scope of formula IV, but not specifically disclosed herein or in the above references or reported elsewhere, will be obvious to anyone skilled in the art. The baccatin III derivatives II can be attached to a sidechain using any of the methodology which is now already well known in the art. The many references cited in this invention disclosure and Tetrahedron, 48, No. In Step a of Scheme I, it is advantageous to convert the hydroxy group on the C carbon into a metal alkoxide before the coupling. The formation of a desired metal alkoxide may be done by reacting a compound of formula II with a strong metal base, such as lithium diisopropylamide, C alkyllithium, lithium bis trimethylsilyl amide, phenyllithium, sodium hydride, potassium hydrides lithium hydride, or the like base. For example when lithium alkoxide is desired, a compound of formula II may be reacted with n-butyllithium in an inert solvent such as tetrahydrofuran. For examples of attachment of substituted baccatins with a suitably substituted lactam via the method of Holton see U. This patent also describes an alternative method for attaching substituted isoserine sidechains to substituted baccatins which would be applicable for the compounds of this invention. This same alternate method is described in another publication by Kingston et. Further information on alternative methods to attach sidechains to baccatins are contained in Thottathil, et. EP published Oct. As used herein, R3 is a conventional hydroxy protecting group. Conventional hydroxy protecting groups are moieties which can be employed to block or protect a hydroxy function, and they are well known to those skilled in the art. Preferably, said groups are those which can be removed by methods which result in no appreciable destruction to the remaining portion of the molecule. Examples of such readily removable hydroxy protecting groups include chloroacetyl, methoxymethyl, 1-methylmethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, dialkylsilylethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyidimethylsily ether, dialkyl alkoxy silyl ethers such as diisopropyl methoxy silyl ethers; 2,2,2-trichloroethyoxymethyl, 2,2,2-trichloroethyloxycarbonyl or simply trichloroethyloxycarbonyl , benyloxycarbonyl and the like. Greene and Peter G. A protecting group for formula IV compounds which has been used frequently in the literature is trialkylsilyl. In Step b , the protecting group R3 is removed. If R3 equals triCalkylsilyl, such as triethylsilyl, it can be removed with fluoride ion or with mineral acid in alcohol or acetonitrile. The removal with fluoride ion is conducted in an inert solvent such as tetrahydrofuran, methylene chloride, 1,4-dioxane, DMF, chloroform, or in the like solvent; and the reaction medium may be buffered with a weak acid such as acetic acid. An example of mineral acid is hydrochloric acid. In compounds of this invention R2 may also be hydroxy. Trialkylsilyl, dialkylalkoxysilyl, CBz, or Troc protecting groups are suitable for this protecting group step and can be attached using methodology which is well known in the art. The protecting groups can ideally be removed simultaneously in step b or or in a separate deprotection step immediately preceding or following step b. The simple 7-deoxy baccatin core 11 can be prepared as described in the previously mentioned U. Alternatively, the desired 7-deoxy baccatin core can be obtained using the chemistry shown in Scheme II. As shown in

Scheme II, the starting material is a known taxane analog. This protecting group is by now well known in the taxane art and has been described by several authors including Kingston and George. Although this group is preferred, other protecting groups can be utilized. The preparation of intermediates arising from step c and step d are now well known in the art. The synthesis of the 7-trifluoromethanesulfonate triflate intermediate is shown in step d and is by now well known in the art. The preparation of 7-O triflates and their conversion into cyclopropane and olefin has been divulged by Johnson, R. The preferred synthesis utilizes DMAP as the base and triflic anhydride as the activating agent. Experimental details for the preparation of the olefin arising from step d are contained in U. Hydrogenation of the olefin is carried out in step f to provide the 7-deoxy taxane intermediate. Many hydrogenation catalysts could be used for this hydrogenation reaction. Palladium based catalysts such as palladium on carbon or palladium hydroxide are suitable as well as Rhodium, Iridium, or platinum based catalysts. Solvents such as lower molecular weight alcohols are suitable for the reaction.

Chapter 6 : WOA1 - Taxane anticancer agents - Google Patents

In metastatic breast cancer, cytotoxic chemotherapy is the treatment of choice for patients with hormone receptor negative tumors, refractory to hormone therapy, or with rapidly progressive disease, regardless of hormone status.

Chapter 7 : Taxol - Chemotherapy Drugs - Chemocare

TAXANE ANTICANCER AGENTS. BACKGROUND OF THE INVENTION. Field of the Invention. The present invention concerns antitumor compounds. More particularly, the invention provides novel paclitaxel derivatives, pharmaceutical formulations thereof, and their use as antitumor agents.

Chapter 8 : Taxane - Wikipedia

The intention of this invention is to provide new 7-deoxy taxane analogs with useful anticancer properties. Some of the background art pertaining to this invention are shown below. Several Publications have described the synthesis or attempted synthesis of the 7-deoxy analog of paclitaxel.