

THERAPEUTIC COMPOUNDS, A METHOD OF MANUFACTURING THEREOF AS WELL AS USES THEREOF**Technical field**

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The disclosure concerns compounds derived from phragmalin or part(s) thereof and new pharmaceutical compositions comprising said compounds as well as uses thereof in the treatment and/or prevention of sexual dysfunctions. The present disclosure also concerns a method for the preparation of the aforementioned compounds and compositions.

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Prior Art and Background

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or common general knowledge.

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Sexual dysfunctions are highly prevalent in both men and women, and have a significant impact on mood, self-esteem, interpersonal relationships and overall quality of life.

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Sexual dysfunction can arise from various causes and is often related to age. Sexual dysfunction can be caused by physical conditions such as diabetes, heart disease, hypertension, and/or obesity, whilst psychological factors such as depression, anxiety, low self-esteem, stress and relationship conflicts can also play a role. Neurological disorders, hormonal imbalances and certain medications can also contribute, and lifestyle factors such as smoking, excessive alcohol consumption, and lack of exercise can also increase the risk of sexual dysfunction.

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Most definitions of sexual dysfunction are based on a four-phase model of the sexual response cycle, which includes the sexual desire, sexual excitement, orgasm/climax and resolution phases. Based upon this model, four major categories of sexual dysfunction have been identified, including sexual desire disorders, sexual arousal disorders, orgasmic disorders, and sexual pain disorders, which can occur at one or more of the four respective phases.

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Hypoactive sexual desire disorder (HSDD) is characterized by the persistent lack of sexual fantasies or desire for any form of sexual activity. In many instances, HSDD is

secondary to another sexual dysfunction. However, HSDD can also result from medical and psychiatric disorders (particularly chronic illnesses and depression), as well as relationship conflicts and loss of attraction.

- 5 Sexual arousal disorders are characterized by the inability to achieve sufficient physiologic or subjective arousal during sexual stimulation. In women, the disorder is referred to as *female sexual arousal disorder* (FSAD) and is characterized by the inability to achieve an adequate lubrication-swelling response of the vagina and labia for the completion of sexual activity or a lack of subjective arousal during sexual
10 activity. FSAD prevalence increases with aging and has been linked to psychological factors such as anxiety and depression. In men, the disorder is referred to as *male erectile disorder* (ED or MED), or also commonly referred to as erectile dysfunction or impotence, and is characterized by the inability to achieve or maintain an erection sufficient for intercourse. ED prevalence also increases with age and has been linked
15 to physical conditions, such as diabetes, heart disease and hypertension, and psychological factors, such as depression.

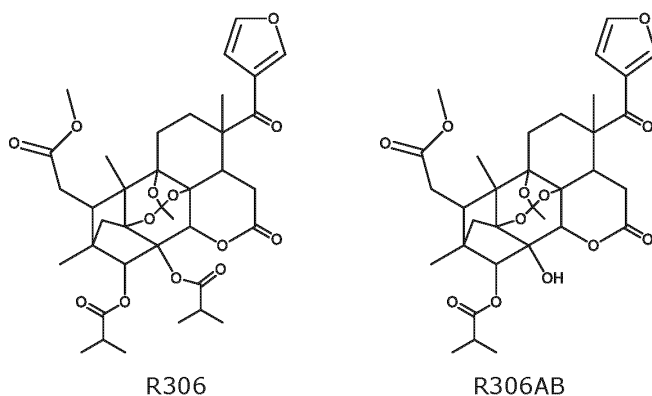
Female and male orgasmic disorders are characterized by persistent or recurrent difficulties in achieving orgasm despite adequate sexual stimulation. Situational or
20 secondary orgasmic dysfunction is characterized by the ability to achieve orgasm with masturbation or sexual foreplay with a partner whilst not being able to achieve orgasm during intercourse. Primary orgasmic dysfunction or anorgasmia is characterized by the inability to achieve orgasm through any means of stimulation and is more prevalent in women. The occurrence of rapid and uncontrolled ejaculation is referred to as
25 premature ejaculation (PE) and is the most frequent sexual complaint in men.

The introduction of the pharmaceutical drug sildenafil (Viagra®) in the 1990s was a major breakthrough in the treatment of Erectile Disorder. This drug is a so-called PDE5 inhibitor, i.e. an inhibitor of the enzyme Phosphodiesterase 5. Further drugs exerting
30 their activity through this mechanism of action have been developed, including tadalafil, vardenafil and avanafil.

The development of these drugs was a great step forward in the field of sexual medicine and a clear improvement in the sexual health of many patients, it has been reported
35 that about a third of all men suffering from ED fail to respond to the treatment. Further, the time for onset of action and duration of the treatment requires planning of the sexual activity and the treatment is not compatible with e.g. nitrate medication for treating e.g. angina pectoris.

Plant based extracts and pharmaceuticals have also been proposed for the treatment of sexual dysfunctions.

- 5 WO 2008/145996 discloses extracts and pharmaceuticals from *Neobeguea mahafalensis*, the procedures for their preparation, and their use for eliciting sexual enhancing effect and for treatment of sexual dysfunction, in particular erectile dysfunction and hypoactive desire disorders. The document describes that species of the genus *Entandophragma* are useful sources as raw materials in the synthesis of the compounds described in that document. It is stated that *Entandophragma caudatum* is a rich source of phragmalin which can be used as a precursor in the semisynthesis of the compound with the structure R306. The document describes that the compound R306 may be hydrolyzed to provide the compound R306AB.



- WO 2013/110744 discloses novel limonoids, methods for their synthesis, and the use of these compounds in the synthesis of other chemical compounds that, *inter alia*, may be used in the treatment of sexual dysfunction, and/or for eliciting enhancing effects on sexual behavior. It is stated that phragmalin is a preferred starting material for the synthesis and that the synthesis provides intramolecular lactonization. The document describes a process for preparing the compounds from phragmalin, and it is described that phragmalin can be obtained from *Entandrophragma caudatum* stem bark and leaves. Further, the document discloses the compound 20 (also denominated as SAE5) which is reported to be an oil. The chemical structure of compound 20 is the same as the one for R306AB above.
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- SE2251130-7, PCT/SE2023/050935 and US patent application serial number 18/469860 disclose improvements in preparing therapeutically active limonoids as well as new limonoid-type compounds.
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One of the foremost challenges in the synthesis of compounds based on the chemical structure of phragmalin lies in the sheer complexity of the phragmalin chemical structure, which contains multiple chiral centres, requiring precise stereochemical control during each synthetic step. A large number of process steps are therefore
5 required, and the synthesis often results in low overall yields, as each synthetic step introduces the potential for side reactions, a need for purification of the intermediate products and loss of material.

For this reason, phragmalin derived compounds from natural products is often used
10 as a starting material as it provides a large part of the desired chemical structure which may be subsequently transformed in only a few steps to the desired product.

However, the reliance on a natural product-derived starting material can present challenges of its own, particularly in terms of scalability. Natural products are typically
15 isolated from their native sources in minute quantities, making them impractical as starting materials for large-scale synthesis. Further, isolation and purification of the starting materials is often both difficult and time-consuming due to *inter alia* the large number of compounds present in the natural product and often requires advanced knowledge and skills in many different fields such as analytical chemistry, medicinal
20 chemistry, spectroscopy etc.

Thus, there is a need for natural product-derived compounds for treating sexual dysfunctions that can be provided in satisfactory amounts and in a satisfactory pure form as well as improved methods for preparing said compounds. Further, there is a
25 need to provide such compounds in a form in which they exhibit satisfactory pharmaceutical properties as well as satisfactory physical and chemical properties to enable easy handling and pharmaceutical formulation.

The present disclosure mitigates problems and/or disadvantages associated with the
30 compound SAE5 and analogues thereof, methods for its manufacture, and further describes improved processes of pharmaceutical formulation, including new forms of SAE5 and analogues thereof that give rise to improved physico-chemical and biological properties, providing advantages that are not provided or suggested by way of hitherto known techniques.

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Brief description of the drawings

Fig. 1A shows the numbering of the carbon atoms of the compound of Formula Ia.

Fig. 1B shows the numbering of the carbon atoms of the compound of Formula Ib.

Fig. 1C shows the numbering according to IUPAC of the compound of Formula IIc.

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Fig. 1D shows the numbering according to IUPAC of the compound of Formula V1.

Fig. 2 shows an overview of the preparation of a methanol extract from seeds of *Entandrophragma caudatum*.

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Fig. 3 shows an overview of the preparation of an extract composition of *Entandrophragma caudatum*.

Fig. 4 shows the synthesis of a mixture of the compound of Formula Ia1 and

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Formula Ib1.

Fig. 5 shows the synthesis of the compound of Formula Ib1.

Fig. 6 shows an IR spectrum of the monohydrate of Formula VII1.

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Fig. 7 shows a dissolution plot of a solvent spike experiment as described in Example 6.

Fig. 8 shows a SEM micrograph taken of a spray dried formulation comprising 25 %

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API + 75 % Soluplus as described in Example 7.

Fig. 9 shows a dissolution plot of six spray dried dispersions (SDD) in FaSSIF, pH 6.5, as described in Example 7.

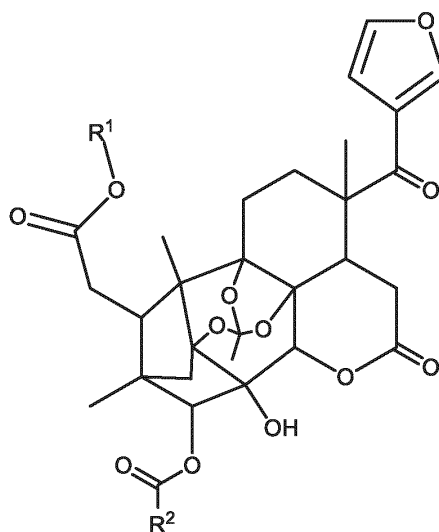
Fig. 10 shows an XRP diffractogram of a monohydrate of Formula VII1 or Formula VII11.

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Description

The present disclosure provides a compound of Formula IIb:

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Formula IIb

or a hydrate thereof,

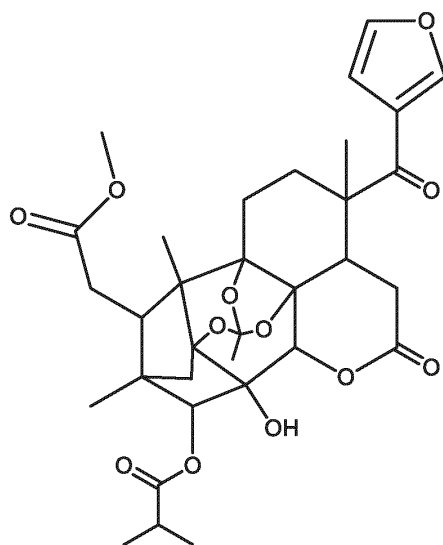
- 5 wherein R¹ and R² independently are C₁-C₆ alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I wherein said compound or hydrate thereof is in an essentially solid form.

As used herein, the term C₁-C₆ alkyl intends a straight, branched or cyclic alkyl group comprising one to six carbon atoms. Examples of C₁-C₆ alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, neopentyl, *n*-hexyl, *iso*-hexyl, 3-methylpentyl, 2,3-dimethylbutyl and neohexyl. Further examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

15 The term 'solid' will be understood by those skilled in the art to include any form of matter that retains its shape and density when not confined, and/or in which molecules are generally compressed as tightly as the repulsive forces among them will allow. Thus, 'in an essentially solid form' means that the above compound or hydrate thereof is at least about 80%, such as at least about 90%, including at least about 95% (or at least about 99%) in such a form.

- 20 In particular, there is provided a compound of Formula IIb wherein R¹ is methyl and R² is isopropyl.

Thus, there is provided a compound of Formula V:

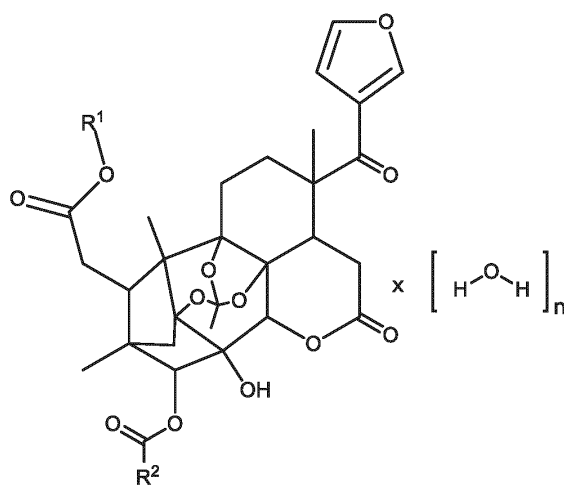


Formula V

or a hydrate thereof,

5 wherein said compound or hydrate thereof is in an essentially solid form.

There is further provided a hydrate of a compound of Formula IIb that is a combination of the compound of Formula IIb and water, as depicted by a compound of Formula VI:

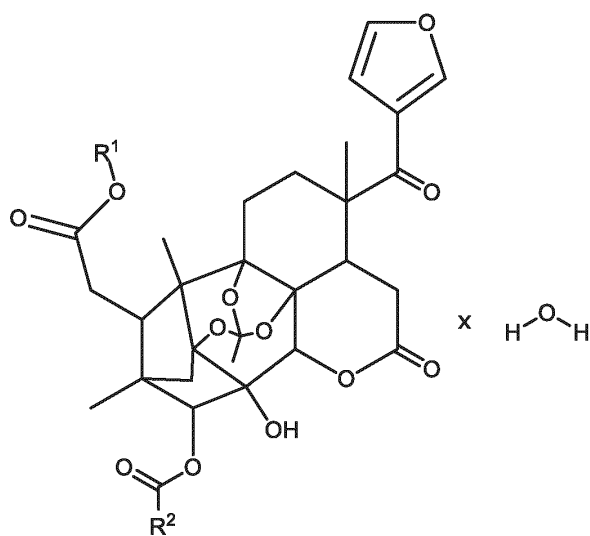


Formula VI

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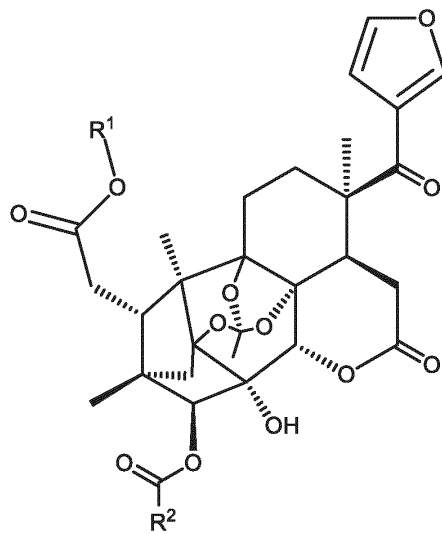
in a ratio of 1:n, wherein n has a value from 0.5 to 100 such as from 0.5 to 10 such as 1.

When n is 1, the hydrate of Formula VI is provided as a monohydrate of Formula VII:



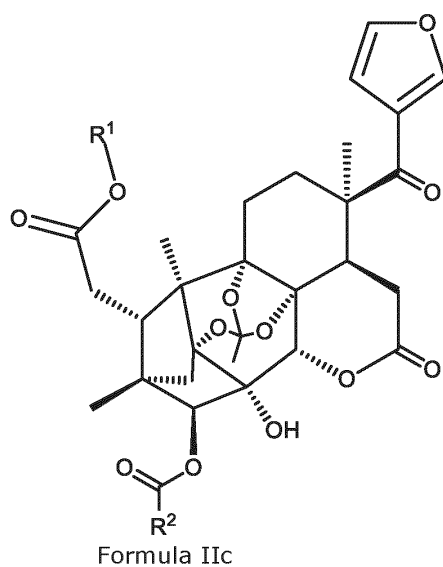
Formula VII

The compound of Formula IIb, as described herein, may be provided as a stereoisomer
5 of Formula IIc:

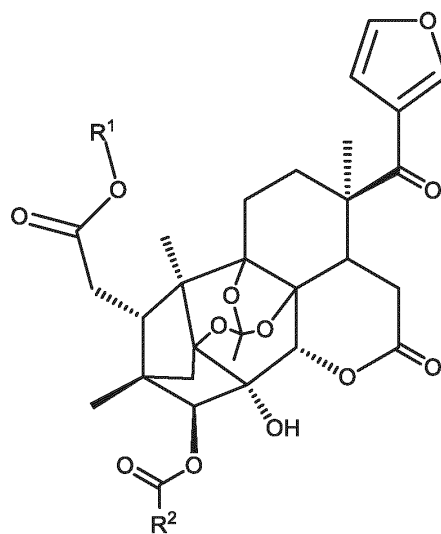


Formula IIc

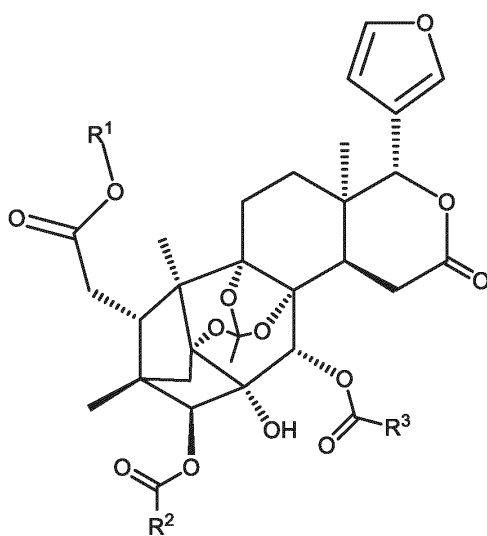
The stereochemistry of the compound of Formula IIc may also be depicted as shown
10 below.



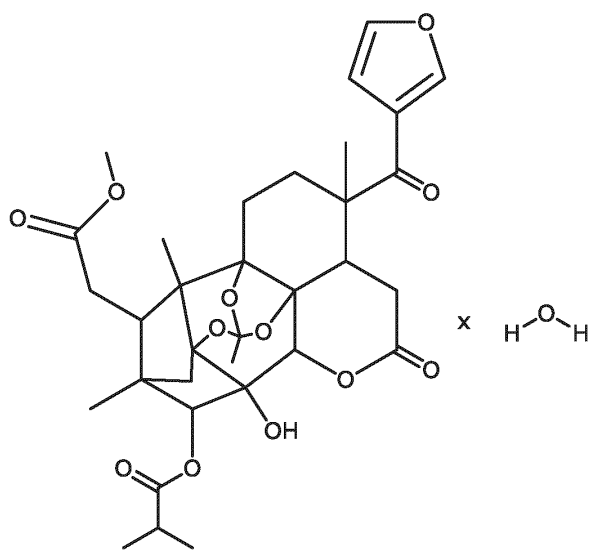
5 In still a further example, the compound of Formula IIb may be a stereoisomer as depicted below:



10 It will be appreciated that the starting materials for preparing the compound of Formula IIb as described herein, such as the compound of Formula IIa, as well as the compounds resulting from processing of the starting materials may have the same or essentially the same stereochemistry as the stereochemistry depicted for the compound of Formula IIb. For instance, the compound of Formula IIa may be provided
15 as a stereoisomer as shown below:



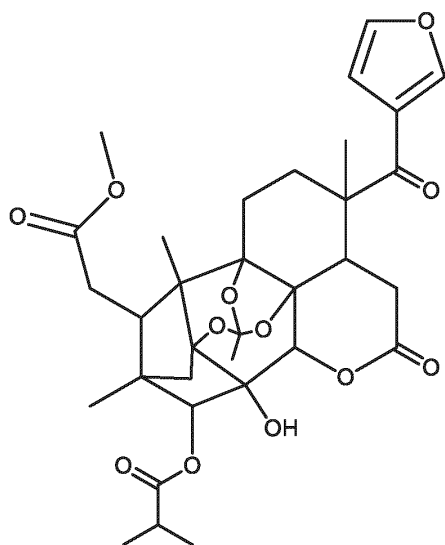
In particular, the present disclosure provides a monohydrate of Formula VII1:



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Formula VII1

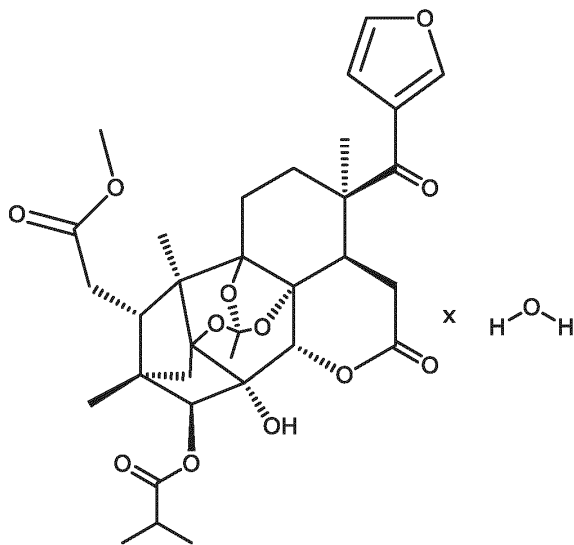
said monohydrate being a combination of a compound of Formula V:



Formula V

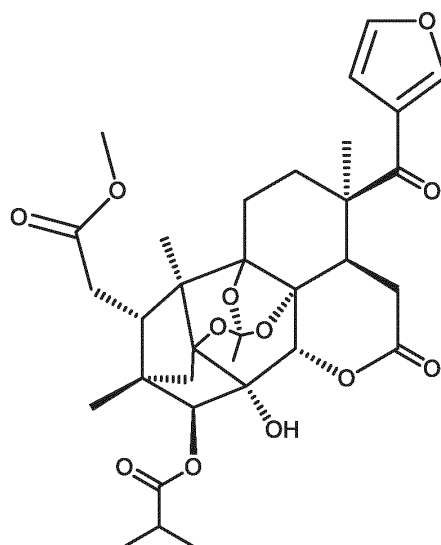
and water taken in a ratio of 1:1.

- 5 There is also provided a stereoisomer of the monohydrate of Formula VII1, which may be denominated a monohydrate of Formula VII11:



Formula VII11

- 10 said monohydrate being a combination of a compound of Formula V1:



Formula V1

and water taken in a ratio of 1:1.

- 5 The IUPAC name of the compound of Formula V1 has been found to be methyl
(3a*R*,4*R*,6a*S*,8*S*,9a*R*,11*R*,12*S*,12a*S*,12b*R*,12c*R*,14*S*,15*R*)-4-(3-
furanylcarbonyl)decahydro-12a-hydroxy-4,8,11,15-tetramethyl-12-(2-methyl-1-
oxopropoxy)-2-oxo-10*H*-8,12c-epoxy-11,6a,9a-
ethanylylidenecyclopenta[*d*]pyrano[2,3,4-*fg*] [1,3]benzodioxocin-14-acetate.

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The IUPAC name of the monohydrate of Formula VI11 has been found to be methyl
(3a*R*,4*R*,6a*S*,8*S*,9a*R*,11*R*,12*S*,12a*S*,12b*R*,12c*R*,14*S*,15*R*)-4-(3-
furanylcarbonyl)decahydro-12a-hydroxy-4,8,11,15-tetramethyl-12-(2-methyl-1-
oxopropoxy)-2-oxo-10*H*-8,12c-epoxy-11,6a,9a-

- 15 ethanylylidenecyclopenta[*d*]pyrano[2,3,4-*fg*] [1,3]benzodioxocin-14-acetate
monohydrate.

It has been unexpectedly found that the compound of Formula IIb, or a hydrate thereof, such as the monohydrate of Formula VII1 as described herein may be provided
20 in an essentially solid form such as an essentially crystalline solid form. Thus, there is provided a compound of Formula IIb, or a hydrate thereof, as described herein that is characterized by being substantially crystalline.

Of course, the fact that the compound of Formula IIb, or a hydrate thereof, may be
25 provided in essentially solid form, such as essentially crystalline form, is a significant benefit as it facilitates e.g. handling, storage, characterization, reduction of batch

variation and product development such as development of a pharmaceutical formulation. For example, the crystallinity makes it well-defined with respect to, for instance, melting point which is a benefit for e.g. making tablets. Such substantially crystalline forms also provide for enhanced physical and chemical properties and therefore storage stability.

In particular, the present disclosure provides a monohydrate of Formula VII1 or Formula VII11 characterized by having an XRP diffractogram as shown in Figure 10. Further, the salt of Formula VII11 may be characterized by an XRP diffractogram comprising one or more of the following peaks: about 19.41, about 10.92, and about 9.66 degrees 2θ and optionally one or more of the following peaks: about 20.71, about 19.88, about 12.88, about 11.16 degrees 2θ . The aforementioned values are based on the measurement as described herein.

The methods described herein may produce the compound of Formula IIb, or a hydrate thereof, in forms that are about 80% or more, such as about 85% or more, about 90% or more, about 95% or more, about 99% or more, or about 100% crystalline. By 'substantially crystalline', we include greater than about 60%, preferably greater than about 75%, and more preferably greater than about 80% (such as about 90%) crystalline. The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used. In particular, the crystallinity of the compound of Formula IIb, or a hydrate thereof, may be about 95% or more such as about 99% or more.

Surprisingly, it has been found that the compound of Formula IIb, or a hydrate thereof, such as the hydrate of Formula VII1 may be prepared in very high chemical purity despite the necessity to prepare the compound from a plant material including complex phragmalin derivatives and the purification challenges associated therewith. Further, it has also unexpectedly been found that the compound of Formula V, or a hydrate thereof, has a high chemical stability.

Thus, there is provided a compound of Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1 in a high chemical purity such as a chemical purity equal to or above about 95% such as equal to or above about 97%, about 98% or about 99%, as measured by e.g. a standardized chemical purity assay. The high chemical purity allows for the use of the compound of Formula IIb, or a hydrate thereof, in highly regulated

products such as pharmaceuticals, where requirements and safety standards are very demanding.

5 The compound of Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1, also has a high chemical stability such as a chemical stability wherein the amount of the compound or hydrate thereof after storage is equal to or above about 90%, such as about 95%, such as about 99%, of the amount at the time when the storage was initiated. The storage may take place in isolated solid form, when formulated into a pharmaceutical formulation, spray-dried pharmaceutical composition or dosage form.

10 The measurement of the chemical stability may be performed using methods known in the art such as HPLC. The chemical stability may be measured at a temperature from about 20°C to about 30°C such as about 25°C and/or at a relative humidity measured from about 40% to about 80% such as about 60%. The chemical stability may be measured over a time period of from about 3 months to about 12 months such as

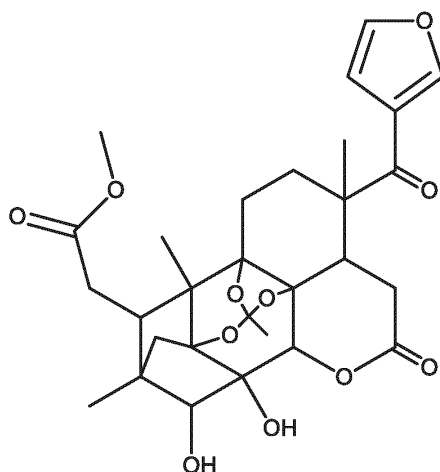
15 about six months. The high chemical stability is a great benefit as it allows for storage of the compound of Formula IIb, or a hydrate thereof, with an insignificant degree of degradation or decomposition so that it may be used at a desired and suitable point in time. For instance, the compound of Formula IIb, or a hydrate thereof, may be stored prior to being used for preparing a pharmaceutical composition such as a spray-dried

20 pharmaceutical composition or a pharmaceutical formulation as described herein.

Further, the compound of Formula Ib may have the advantageous properties stated for the compound of Formula IIb such as being a solid such as a crystalline solid and/or having a high chemical purity. For instance, the crystallinity of the compound of

25 Formula Ib may be may be about 95% or more such as about 99% or more and/or the chemical purity may be above about 95% such as equal to or above about 97%, about 98% or about 99%. Further, the storage stability may be essentially equal to or higher than that for the compound of Formula IIb. It will be appreciated that the compound of Formula Ib may be a compound of Formula Ib1, i.e. the R¹ substituent may be

30 methyl, as shown below. Further, the compound of Formula Ib may be provided as stereoisomer such as a stereoisomer described herein and/or as a hydrate such as a monohydrate.



Formula Ib1

We have also found surprisingly that the physico-chemical (e.g. dissolution) properties of compounds and hydrates described hereinbefore can be vastly improved by spray-drying along with a polymer or co-polymer that is capable of forming physico-chemical interactions with such compounds or hydrates. The vast improvement in dissolution properties is unexpected in view of the very low solubility of the compounds and hydrates described herein.

- 10 The present disclosure also provides a spray-dried pharmaceutical composition comprising:
- (a) a compound of Formula IIb, such as a compound of Formula V, or a compound of Formula Ib, and
 - (b) an excipient suitable for spray-drying. The excipient suitable for spray-drying may
- 15 comprise a polymer or co-polymer capable of forming physico-chemical interactions with the compound of Formula IIb.

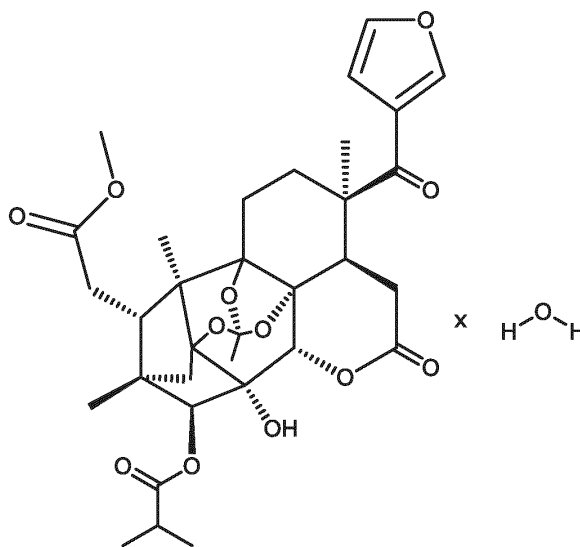
For example, the excipient suitable for spray-drying may comprise one or more of a cellulose ester, N-vinylpyrrolidone-vinyl acetate co-polymer, polyvinyl caprolactam-
 20 polyvinyl acetate-polyethylene glycol graft co-polymer and methacrylic acid-methyl methacrylate co-polymer.

Further, the excipient suitable for spray-drying may comprise a cellulose ester such as a non-ionic cellulose ester. The cellulose ester may comprise or consist of
 25 hydroxypropylmethyl cellulose (HPMC) or a derivative thereof. For instance, the derivative of HPMC may comprise or consist of HPMC is HPMC-AS and/or HPMC-P.

Additionally or alternatively, one or more of the following polymers may be used: Hypromellose phthalate, polyvinylpyrrolidone-vinyl acetate (i.e. PVP-vinyl acetate), polymethacrylates, olyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft Co-Polymer. In still a further example, one or more of the following polymers may be used: PVP, PVP-vinylacetate, crospovidone, PEG, methylcellulose, hydroxypropyl methyl cellulose.

The ratio of the compound of Formula Ib or Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1, may be from 1:5 to about 5:1, such as about 1:4 to about 4:1, about 1:3 to about 3:1, about 1:2 to about 2:1 or about 1:1. For instance, the ratio of the compound of Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1, may be about 1.3.

Further, it will be appreciated that the compound of Formula Ib or Formula IIb, or a hydrate thereof, in the spray-dried pharmaceutical composition may be provided as a stereoisomer such as a stereoisomer of Formula IIc, or a hydrate thereof. In an example, the spray-dried composition described herein comprises a stereoisomer of the hydrate of Formula VII1 such as the monohydrate of Formula VII11 depicted below.



Formula VII11

The spray-dried composition may comprise particles having a particle size distribution with a Dv90 of 120 mm or less, such as 100 mm or less, such as from 10 mm to 120 mm. The skilled person will understand that the parameter. As used herein, the term 'Dv90' means the size (or diameter) in a particle size distribution in which 90% of the

total volume of the material is contained. The particle size distribution may be measured using methods used in the art. For example, the measurement may be performed using laser diffraction, dynamic light scattering, Scanning Electron Microscopy (SEM), sieve analysis and any combination thereof.

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Further, the spray-dried composition may comprise or consist of a powder, granules, pellets and/or beads.

It will be appreciated that it is believed that spray-drying will convert any hydrate of the compound of Formula I(I)b, i.e. Formula Ib or Formula IIb, into the compound of Formula I(I)b as the spray-drying process conditions result in evaporation of the volatile spray-drying solvent (which may comprise one or more organic solvents, such as lower alkyl alcohols (e.g. methanol, isopropanol or, more especially, ethanol), hydrocarbons (e.g. C₅₋₁₀ alkanes), haloalkanes (e.g. dichloromethane), dimethylformamide, dimethylsulfoxide, ethyl acetate, acetone, etc., or mixtures thereof or, more preferably aqueous solvents, such as water. Further, the spray drying conditions will provide the spray-dried pharmaceutical composition comprising the compound of Formula I(I)b in a form that is wholly or predominantly amorphous. For example, more than about 50% by weight, such as more than about 75% by weight, such as more than about 90% by weight, such as more than about 95% by weight, including more than about 99% by weight of the spray-dried composition may be amorphous.

The pharmaceutical composition of may also be prepared in such a way that it allows for including a compound of Formula Ib or Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1 in a pharmaceutical formulation that is suitable for administration to patients. Thus, there is provided a pharmaceutical formulation comprising a compound of Formula Ib or Formula IIb, or a hydrate thereof, such as a hydrate of Formula VII1.

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It follows that the spray-dried pharmaceutical composition may comprise a therapeutically effective amount of the compound of Formula Ib or Formula IIb while the pharmaceutical formulation may comprise a therapeutically effective amount of the compound of Formula Ib or Formula IIb or a hydrate thereof.

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The term "therapeutically effective amount", as used herein, refers to an amount of a compound that confers a therapeutic effect on the treated patient. The effect may be

objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of and/or feels an effect).

5 The amount of the compound of Formula Ib or Formula IIb, or a hydrate thereof, to be administered may vary depending on factors such as age, weight and the severity of the condition to be treated. In an example, the compound of Formula Ib or Formula IIb, or a hydrate thereof, may be administered in a dosage from about 1 microgram to about 500 milligrams per day. In a further example, a patient may be treated with a dosage of from about 1 mg to about 100 mg per day.

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Thus, there is provided a pharmaceutical formulation comprising:
a therapeutically effective amount of a compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described herein, or
a spray-dried composition as described herein, said spray-dried composition
15 comprising a therapeutically effective amount of a compound of Formula Ib and/or Formula IIb as described herein
in admixture with a pharmaceutically acceptable excipient, carrier and/or diluent.

20 The pharmaceutical formulation, such as the pharmaceutical composition comprising the spray-dried composition, may be formulated for oral administration. For instance, the pharmaceutical formulation may be provided as a tablet, capsule or lozenge. In a further example, the pharmaceutical formulation may be provided as a liquid such as a syrup.

25 Compound and/or spray-dried compositions as described herein may thus be presented following their preparation (e.g. by spray-drying) in the form of simple powder mixtures, powder microspheres, coated powder microspheres, a lyophilised liposomal dispersion, or a combination thereof.

30 Such pharmaceutical formulations and/or dosage forms may be provided in the form of a single unit dosage form, such as a pill, a capsule, a cake, a film (e.g. an intraoral film) or a tablet.

35 Capsules may be prepared by loading a compound or a spray-dried composition as described herein directly into a pharmaceutically-acceptable capsule made from an appropriate material designed for e.g. peroral delivery, or by mixing said compound or a spray-dried composition along with excipients prior to loading into such a capsule,

which may involve a granulation step (as described below), prior to loading into a capsule for such delivery.

Compound and/or spray-dried compositions as described herein may in this respect be granulated into a pellet or a pill, but they may also be formulated (that is, provided for administration) in the form of a dry, free-flowing powder. By 'dry' we include essentially free of water and other liquid solvents, which includes that there is less than about 10%, such as less than about 6%, including less than about 5%, or less than about 4%, more preferably less than about 3%, such as less than about 2%, e.g. less than about 1% of the formulation is a liquid, such as water.

Flowability of powder compositions may be measured by standard techniques known to those skilled in the art including bulk density measurements, or measurements taken on a powder flow analyser (for example those sold by Stable Micro Systems or Meritics, both UK), including powder flow speed dependence tests, caking tests, cohesion tests, etc. A preferred measurement of flowability is the standard angle of repose, which may be carried out using a revolving cylinder, a fixed funnel or a tilting box.

In the context of the present invention, the term 'free-flowing' may include that the powder exhibits an angle of repose of no more than about 50°, such as no more than about 45°, including no more than about 40°, for example no more than about 35°, and more particularly no more than about 30°; a bulk density of no less than about 0.3 g/mL, for example no less than about 0.4 g/mL, such as no less than about 0.5 g/mL, and more particularly no less than about 0.6 g/mL; and/or a tap density of no less than about 0.5 g/mL, such as no less than about 0.6 g/mL, for example no less than about 0.7 g/mL, and in particular no less than about 0.8 g/mL.

Appropriate techniques for making dosage forms comprising dry powders or granulates include simple dry mixing, granulation (including dry granulation, wet granulation, melt granulation, thermoplastic pelletising, spray granulation), extrusion/spheronisation or, more preferably, freeze-drying or spray-drying (*vide infra*).

Compositions of the invention may in the alternative be provided in the form of a tablet for e.g. peroral use. Such tablets may be formed for example by direct compression/compaction of a composition of the invention, optionally following mixing it together with one or more appropriate excipients, such as a diluent, a disintegrant, a glidant and/or a lubricant, and may be achieved using techniques such as those

described in, for example, *Pharmaceutical Dosage Forms: Tablets. Volume 1*, 3rd Edition, Augsburger et al (eds.), CRC Press (2008) and the documents cited therein. Suitable compacting equipment includes standard tableting machines, such as the Kilian SP300 or the Korsch EK0, XP1, XL 100, and XL 200.

5

Suitable disintegrants (as defined in, for example, Rowe *et al*, *Handbook of Pharmaceutical Excipients*, 6th ed. (2009)) that may be employed in tablets include cellulose derivatives such as hydroxypropyl cellulose (HPC), low substituted HPC, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, microcrystalline cellulose, modified cellulose gum; starch derivatives such as moderately cross-linked starch, modified starch, hydroxylpropyl starch and pregelatinized starch; and other disintegrants such as calcium alginate, sodium alginate, alginic acid, chitosan, colloidal silicon dioxide, docusate sodium, guar gum, magnesium aluminum silicate, polacrilin potassium and polyvinylpyrrolidone. Combinations of two or more disintegrants may be used.

10
15

Preferred disintegrants include so-called 'superdisintegrants' (as defined in, for example, Mohanachandran *et al*, *International Journal of Pharmaceutical Sciences Review and Research*, **6**, 105 (2011)), such as cross-linked polyvinylpyrrolidone, sodium starch glycolate and croscarmellose sodium. Combinations of two or more superdisintegrants may be used.

20

When disintegrants and/or superdisintegrants are employed in tablets, they may be employed in an (e.g. total) amount of between 0.5 and 15% by weight based upon the total weight of a composition. A preferred range is from 1 to 8%, such as from about 2 to about 7% (e.g. about 5%, such as about 4%) by weight.

25

If present, binder is preferably employed in an amount of between 0.5 and 20% by weight based upon the total weight of the tablet formulation. A preferred range is from 1.0 to 15%, such as from about 2.0 to about 12% (e.g. about 10%) by weight. Suitable binders include cellulose gum and microcrystalline cellulose.

30

The spray-dried pharmaceutical composition may further comprise an enteric substance, such as a coating, that serves to prevent release of the compound, hydrate or spray-dried composition in the stomach.

35

Alternatively, compounds or, especially, spray-dried pharmaceutical composition as described herein may be reconstituted with a liquid that is a vehicle for oral administration, such as an oil-based or water-based vehicle. The vehicle may comprise

a cellulose-based agent, such as a non-ionic cellulose based agent, such as carboxymethylcellulose (CMC), (microcrystalline cellulose) MC, hydroxyethyl cellulose (HEC), hydroxypropyl methylcellulose (HPMC), and/or hydroxyethyl methylcellulose (HEMC), or a derivative of any of the foregoing cellulose-based agents. In particular
5 the cellulose-based agent may comprise or consist of HPMC, which may also be denominated hypromellose, or a derivative thereof. The HPMC may be HPMC-AS such as HPMC-AS of grade M or grade USP/NF. Additionally or alternatively, one or more of the following polymers may be used: Hypromellose phthalate, PVP-vinyl acetate, polymethacrylates, Polyvinyl Caprolactam-Polyvinyl Acetate-Polyethylene Glycol Graft
10 Co-Polymer. In still a further example, one or more of the following polymers may be used: PVP (i.e., polyvinylpyrrolidone), PVP-vinylacetate, crospvoldone, PEG, methylcellulose, hydroxypropyl methyl cellulose.

The compound of Formula IIb, or a hydrate thereof, or a pharmaceutical formulation
15 or composition described herein may also be provided for parenteral administration such as intramuscular, intravenous, and intradermal administration. For example, the administration may be buccal, sublingual, rectal, intranasal, transdermal, vaginal or take place through inhalation. In such a situation, compounds or, especially, spray-dried pharmaceutical composition as described herein may also be reconstituted with
20 a liquid that is a vehicle suitable for injection, such as an oil-based or water-based vehicle.

The present disclosure also provides:
a compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described
25 herein, or
a spray-dried composition as described herein, or
a pharmaceutical formulation as described herein
for use as a medicament in therapy.

30 There is also provided
a compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described herein, or
a spray-dried composition as described herein, or
a pharmaceutical formulation as described herein
35 for use in the treatment and/or prevention of or more of the following dysfunctions or disorders: a sexual dysfunction, erectile dysfunction, ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder, neurological disorder.

There is also provided the use of
a compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described
herein, or

a spray-dried composition as described herein, or

5 a pharmaceutical formulation as described herein

for the manufacture of a medicament for the treatment and/or prevention of or more
of the following dysfunctions or disorders: a sexual dysfunction, erectile dysfunction,
ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder,
neurological disorder.

10

There is also provided a a method of treatment and/or prevention of or more of the
following dysfunctions or disorders: a sexual dysfunction, erectile dysfunction,
ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder,
neurological disorder, which comprises administration of a therapeutically effective

15 amount of:

a compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described
herein, or

a spray-dried composition as described herein, or

a pharmaceutical formulation as described herein

20 to a patient in need thereof.

As used herein, the term prevention includes references to the prophylaxis and/or
preventing of the disease, disorder and/or condition. In particular, the term may refer
to achieving a reduction in the likelihood of the patient (or healthy subject) developing
25 the condition (for example, at least a 10% reduction, such as at least a 20%, 30% or
40% reduction, e.g. at least a 50% reduction).

Sexual dysfunction disorders may include disorders associated with sexual desire,
sexual excitement, orgasm/climax and/or resolution phases, as described hereinbefore
30 and well sexual dysfunction disorders that include sexual desire disorders, sexual
arousal disorders, orgasmic disorders, and sexual pain disorders, which can occur at
one or more of the four respective phases identified above, and are described in detail
above.

35 In particular, the dysfunctions or disorders described herein may be erectile
dysfunction and/or premature ejaculation. For example, the dysfunction or disorder
may comprise or consist of erectile dysfunction. In a further example, the dysfunction
or disorder may comprise or consist premature ejaculation.

The compound of Formula Ib and/or Formula IIb, or a hydrate thereof, as described herein, or
the spray-dried composition as described herein, or
5 the pharmaceutical formulation as described herein
may be administered to a patient suffering from the dysfunctions or disorders described herein.

The patient may be a man or a woman. Further, the patient may be a poor responder
10 to treatment with PDE5 inhibitors, may be suffering from a condition for which there is
a contraindication for PDE5 inhibitors or may be subjected to a pharmaceutical drug
that should not be administered in conjunction with a PDE5 inhibitor. Such conditions
include e.g. vascular health problems such as hypertension, blood glucose related
conditions such as diabetes such as diabetes mellitus, hyperlipidemia and smoking.
15 Examples of pharmaceutical drugs that should not be administered in conjunction with
a PDE5 inhibitor include alpha-blockers, soluble guanylate cyclase stimulators or nitrate
medications such as isosorbide mononitrate or isosorbide dinitrate.

Combinations

20 The compound of Formula Ib and/or Formula IIb, or a hydrate thereof, or a
pharmaceutical formulation comprising the compound of Formula Ib and/or Formula
IIb, or a hydrate thereof, may be combined with a further pharmaceutical drug in
order to achieve a greater beneficial effect in respect of the dysfunctions or disorders
described herein. For example, the compound of Formula Ib and/or Formula IIb, or a
25 hydrate thereof, or a pharmaceutical formulation comprising the compound of Formula
Ib and/or Formula IIb, or a hydrate thereof, may be combined with a PDE5 inhibitor
such as sildenafil, tadalafil, vardenafil or avanafil.

Salts

30 Some compounds of the present disclosure may be provided as a salt such as
pharmaceutically acceptable salt. For example, the compound of Formula III or the
compound of Formula IV, or a stereoisomer thereof, may be provided as a salt such as
a metal salt or a base addition salt.

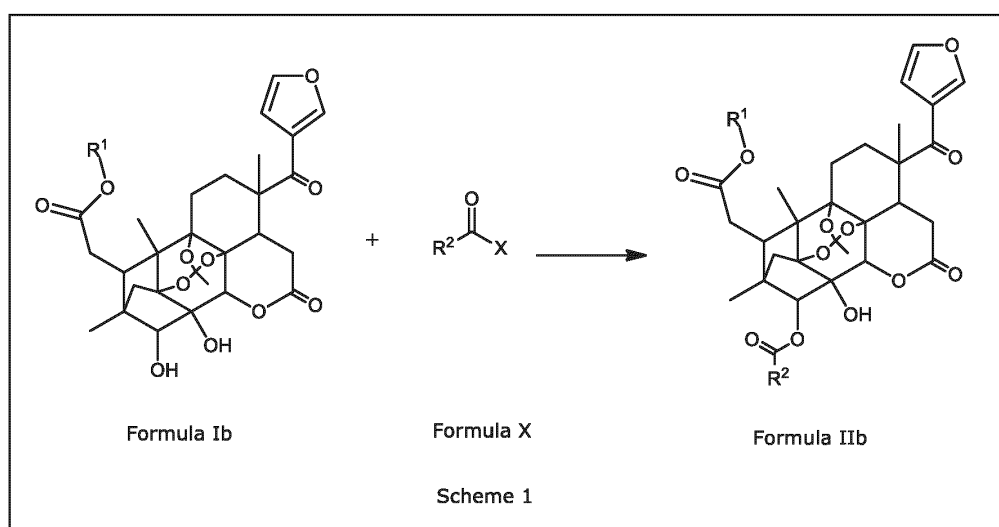
Isotopes

35 The compounds of the present disclosure such as a compound of Formula Ib or of
Formula IIb may contain an atomic isotope at one or more of the atoms that constitute
said compounds, i.e. said compound may be labelled with an isotope. For example,

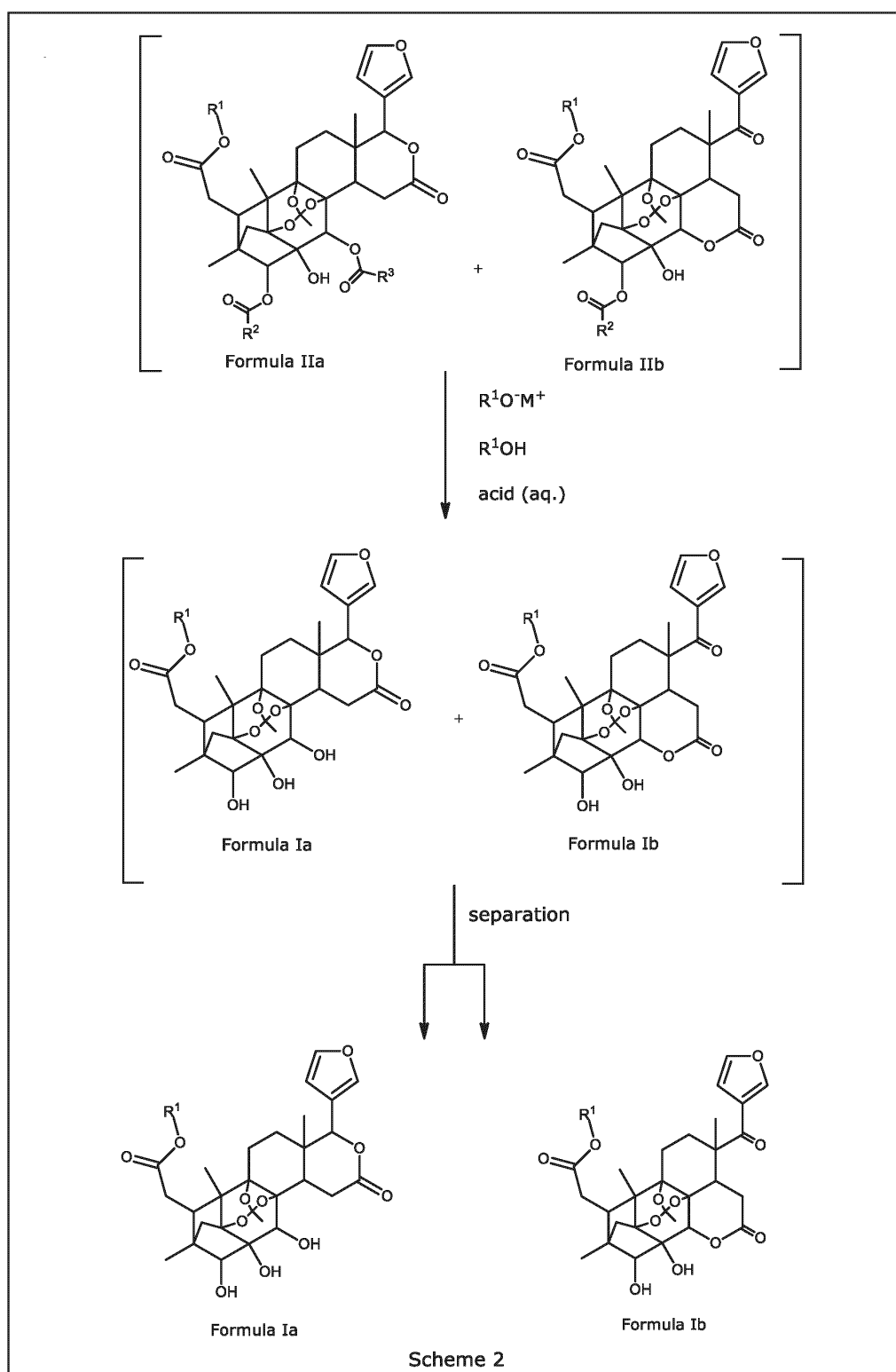
the compound of Formula V may be labelled with one or more isotopes, such as for example tritium (^3H), deuterium (^2H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In an example, the compound is labelled with one or more deuterium atoms. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

Methods of preparation

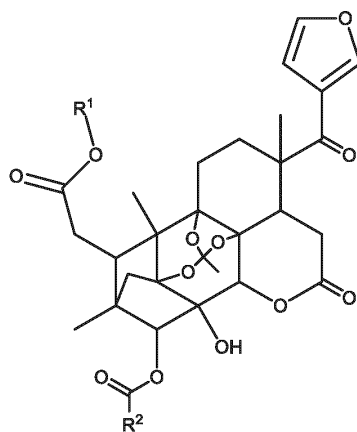
The compounds of the present disclosure, or hydrate(s) thereof, may be prepared as described herein. For example, the compounds of the present disclosure may be prepared as depicted in Scheme 1.



Further, the starting material of Formula Ib may be prepared from a compound of Formula IIa or from a mixture of the compound of Formula IIa and the compound of Formula Iib. For instance, the compound of Formula IIa, the compound of Formula Iib or a mixture thereof may be converted to a mixture of compounds of Formula Ia and Formula Ib followed by separation as depicted in Scheme 2, wherein $\text{R}^1\text{O}^-\text{M}^+$ denotes a metal alkoxide such as sodium methoxide, R^1OH denotes an alcohol such as methanol and acid (aq.) denotes an aqueous acid such as aqueous acetic acid.



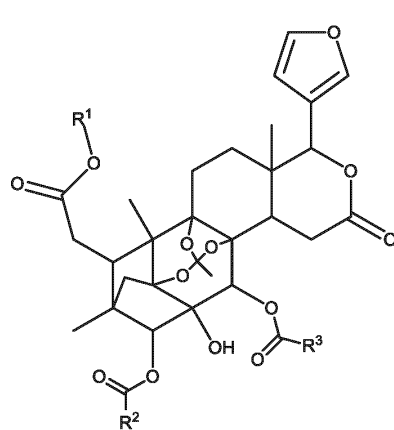
Thus, there is provided a method for preparing a compound of Formula Ib



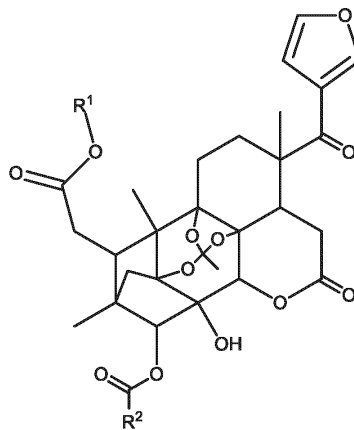
Formula IIb

or a hydrate thereof,
comprising the steps of:

- 5 a) providing a compound of Formula IIa , a compound of Formula IIb or a mixture thereof:



Formula IIa



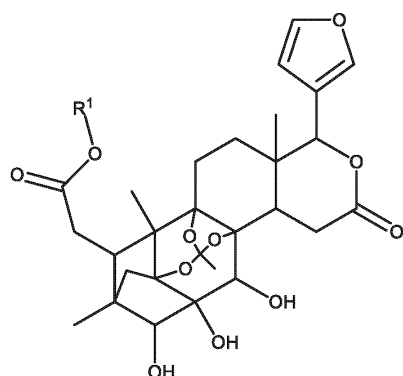
Formula IIb

wherein R^1 , R^2 and R^3 independently are C_1 - C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I;

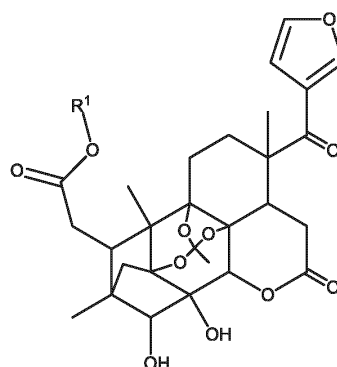
10

- b) subjecting the mixture of step a) to an alkoxide of Formula $R^1O^-M^+$, an alcohol of Formula R^1OH , wherein R^1 is as defined for the compound of Formula IIa and/or the compound of Formula IIb and M^+ is a metal cation such as Li^+ , Na^+ or K^+ , and an aqueous acid thereby providing a mixture comprising a compound of Formula Ia and a compound of Formula Ib:

15

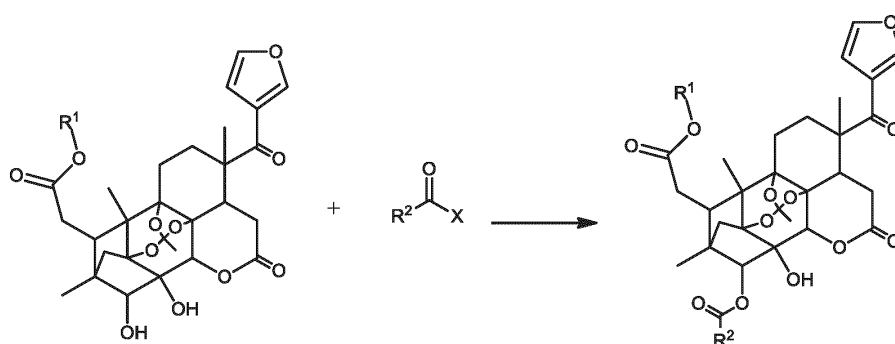


Formula Ia



Formula Ib,

- c) separating the compound of Formula Ia from the compound of Formula Ib,
 d) optionally converting the compound of Formula Ia into a compound of
 5 Formula Ib,
 e) reacting the compound of Formula Ib with a compound of Formula X, optionally
 in the presence of an ester forming promoting agent such as a coupling reagent,
 to provide the compound of Formula IIb :



Formula Ib

Formula X

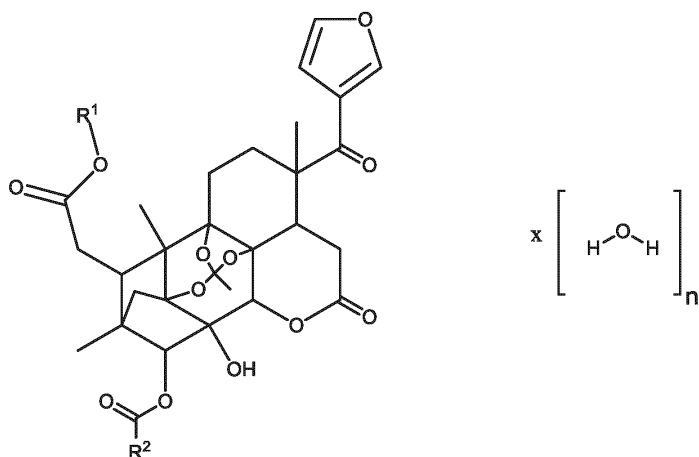
Formula IIb,

wherein

R² for the compound of Formula X is as defined for the compound of Formula
 IIa and/or the compound of Formula IIb, and

15 X is selected from the group consisting of OH, halide such as Cl and
 OC(O)CH(CH₃)₂,

- f) optionally combining the compound of Formula IIb with water to provide a
 hydrate of Formula VI:



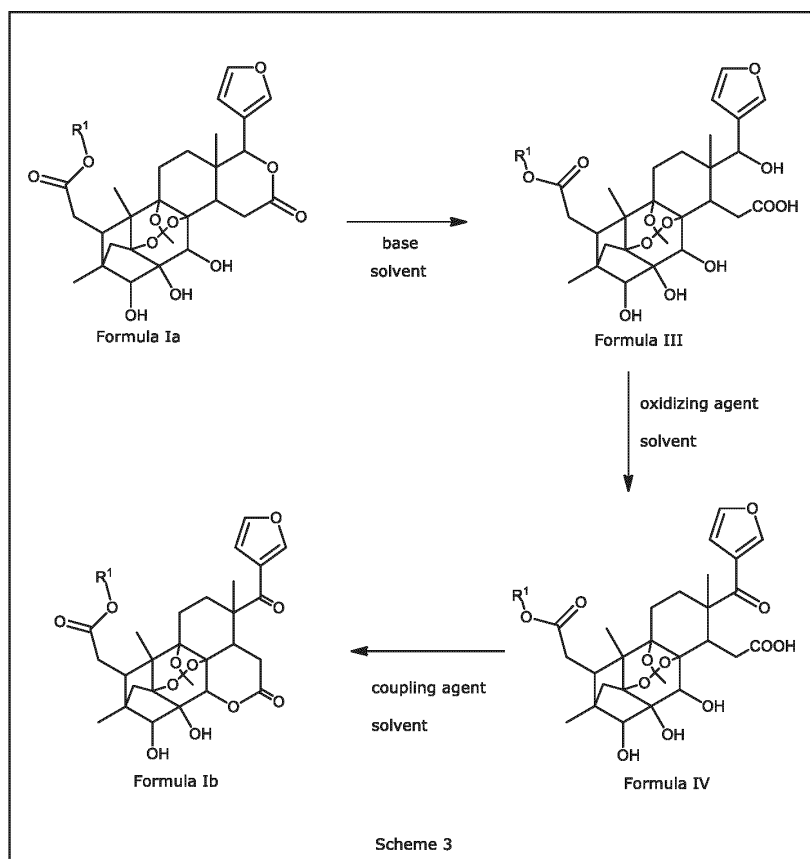
Formula VI

said hydrate being a combination of the compound of Formula IIb and water taken in a ratio of 1:n, wherein n has a value from 0.5 to 100, such as from 0.5 to 10, such as 1.

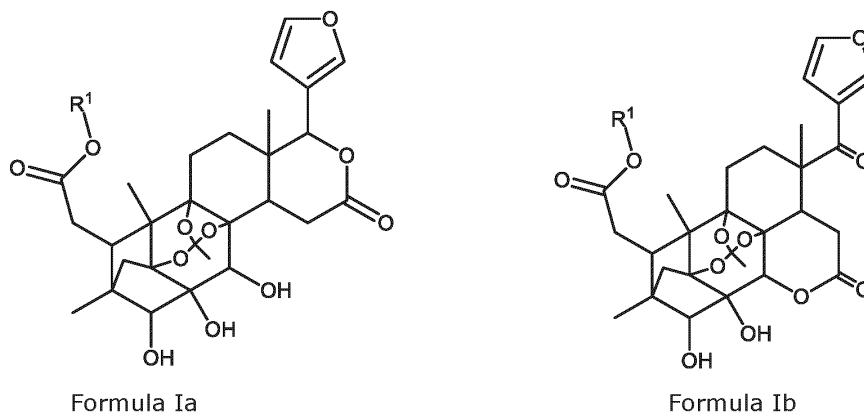
The ester forming promoting agent such as DMAP HCl salt and/or the compound of Formula X such as isobutyryl chloride in step e) may be added in one or more portions and/or aliquots in order to form the compound of Formula IIb without or substantially without impurities such as a diester impurity where both hydroxyl groups of the compound of Formula Ib are converted into ester groups.

The combination of the compound of Formula IIb with water into a hydrate of Formula VI in step f) may take place using a mixture of acetone and water. Further, the hydrate of Formula VI may be subjected to a mixture of acetone and water to increase its purity.

The compound of Formula Ia may be converted into a compound of Formula Ib using a synthesis as depicted in Scheme 3.



Thus, there is provided a method for converting a compound of Formula Ia into a compound of Formula Ib:

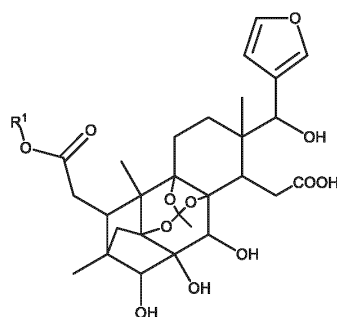


5

wherein R^1 is C_1 - C_6 alkyl optionally substituted with one or more substituents selected from OH, Cl, Br, F and I, said method comprising the steps of:

- a) subjecting the compound of Formula Ia to lactone ring opening conditions thereby providing a compound of Formula III:

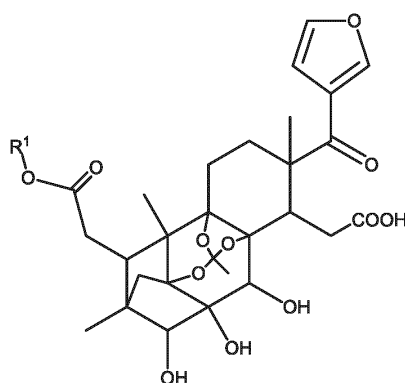
10



Formula III

wherein R¹ is as defined for the compound of Formula Ia,

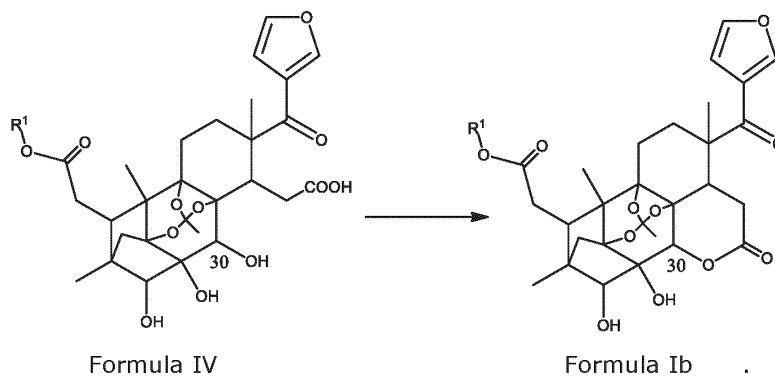
- b) oxidizing the compound of Formula III into a compound of Formula IV:



Formula IV

wherein R¹ is as defined for the compound of Formula Ia,

- c) reacting the carboxylic acid of the compound of Formula III with the hydroxy group at carbon 30 thereby providing the compound of Formula Ib:



Formula IV

Formula Ib

It will be appreciated that the compound of Formula Ia and/or the compound of Formula Ib may be prepared as described for steps a) to c) in the method for preparing a compound of Formula IIb as described herein.

The steps a), b) and/or c) in the method for converting a compound of Formula Ia into a compound of Formula Ib may be as follows:

5 step a) may comprise a base such as barium hydroxide, such as barium hydroxide octahydrate, in the presence of a solvent such as methanol, and/or

step b) may comprise an oxidizing agent such as Dess Martin periodinane, and/or

10 step c) may comprise a coupling agent such as coupling agent comprising a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide or a HCl salt thereof in the presence of a sterically hindered base such as N,N-diisopropylethyleamine.

15 Preferably, step b) follows directly onto step a) without letting the compound of Formula III formed in step a) be kept in solution for a long time period or being isolated. In this way, the risk that the compound of Formula III undergoes ring closure back to the compound of Formula Ia is minimized.

20 The substituents of the compounds described herein, such as the substituents of the compounds of the methods described herein, may have the following values: R^1 may be methyl, and/or R^2 and R^3 may independently be methyl, ethyl or isobutyl. In an example, R^1 may be methyl, R^2 may be isopropyl and R^3 , if present, may be ethyl or isopropyl.

25 Further, it will be appreciated that the compound of Formula IIa described herein may be a phragmalin derivative such as phragmalin 3,30-diisobutyrate, pharamgmalin 3-isobutyrate-30-proprionate and/or phragmalin 3-nicotinate-30-isobutyrate. Additionally or alternatively, the compound of Formula IIa may be provided in admixture with phragmalin-3-nicotinate-30-isobutyrate.

30 Moreover, the compound of Formula IIa, the compound of Formula IIb or a mixture thereof may be provided by a plant or a plant material selected from the Meliaceae family such as a plant or plant material selected from the group consisting of *Xylocarpus granatum*, *Khaya senegalensis*, *Xylocarpus moluccensis*, *Pseudocedrela kotschy*, *Swietenia macrophylla*, *Neobeuga mahafalensis*, *Chukrasia tabularis*, *Entandrophragma caudatum* and any combination thereof. For instance, the plant or plant material may be selected from leaves, branches, roots and/or seeds of the plant

or plant material. In particular, the plant or plant material may be provided by *Entandophragma caudatum* seeds such as disintegrated seeds such as ground seeds.

5 There is also provided a method for preparing a spray-dried pharmaceutical composition as described herein, said method comprising spray-drying a compound of Formula IIb, or a hydrate thereof, such as a monohydrate of Formula VII1, or a compound of Formula Ib as defined in claim 10, or a hydrate thereof, along with excipients that are suitable for spray-drying.

- 10 The method for preparing the spray-dried pharmaceutical composition may comprise the steps of:
- a) providing a spray drier with a solution comprising the compound of Formula I or Formula IIb, or a hydrate thereof, and the excipients suitable for spray-drying, as well as a solvent system comprising at least two polar solvents, of which at least one of
 - 15 said polar solvents is miscible with water and at least one solvent is aprotic and non-miscible with water; and
 - b) spray drying the solution of step a).

20 Further, the method for preparing the spray-dried pharmaceutical composition may comprise an additional step of dissolving said compound or hydrate in said solvent non-miscible with water and dissolving said excipient in said solvent miscible with water and mixing to provide the solution for the spray-drier.

25 The solvents of the solvent system of the method for preparing the spray-dried pharmaceutical composition may be as follows:

The non-water miscible polar aprotic solvent may optionally be halogenated. For instance, the non-water miscible polar aprotic solvent may comprise or consist of dichloromethane. Additionally or alternatively, the water miscible polar solvent may

30 be selected from polar aprotic and protic solvents, preferably methanol and/or acetone. It will be appreciated that the water miscible polar solvent and the non-water miscible polar aprotic solvent may be mixed in various ratios such as various volume ratios. For instance, the water miscible polar solvent and the non-water miscible polar aprotic solvent may be mixed in a ratio from about 1:5 to about 5:1, such as about 1:4 to

35 about 4:1, about 1:3 to about 3:1, about 1:2 to about 2:1 or about 1:1.

Wherever the word 'about' is employed herein in the context of amounts, for example absolute amounts, such as doses, weights, volumes, sizes, diameters, aspect ratios,

angles, pH values, etc., or relative amounts (e.g. percentages) of individual constituents in a composition or a component of a composition (including concentrations and ratios), timeframes, and parameters such as temperatures, pressure, relative humidities, etc., it will be appreciated that such variables are approximate and as such may vary by $\pm 10\%$, for example $\pm 5\%$ and preferably $\pm 2\%$ (e.g. $\pm 1\%$) from the actual numbers specified herein. This is the case even if such numbers are presented as percentages in the first place (for example 'about 10%' may mean $\pm 10\%$ about the number 10, which is anything between 9% and 11%).

Compounds of the disclosure have the advantage that they are capable of being stored over a wide range of temperatures and/or relative humidities (in appropriate pharmaceutical packaging, which packaging may or may not provide a barrier to moisture). Compounds of the disclosure may also have the advantage that they are more physically and chemically stable at a wide range of storage temperatures.

The compounds, uses and methods described herein may also have the advantage that, in the treatment of the conditions for which the active ingredients are known for, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, have a lower inter-patient variability, and/or may have other useful pharmacological properties over, compounds or methods (treatments) known in the prior art, whether for use in the treatment of the aforementioned conditions or otherwise.

The present disclosure is illustrated by the following non-limitative examples.

EXAMPLES

30

Materials

Seeds of *Entandrophragma caudatum* were purchased from Parceval Ltd, Wellington, South Africa.

35 Abbreviations

Fig.	Figure
DCM	dichloromethane
DIPEA	diisopropylethylamine

	DMAP	4- <i>N,N</i> -dimethylaminopyridine hydrochloride
	DMSO	dimethylsulfoxide
	DCS	Differential Scanning Calorimetry
	DVS	Dynamic Vapour Sorption
5	EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
	EtOAc	ethyl acetate
	eq.	equivalent(s)
	g	gram(s)
	h	hour(s)
10	HDPE	High Density Polyethylene
	HPLC	High Pressure Liquid Chromatography
	HPMC	hydroxypropyl methylcellulose, Hypromellose
	HPMC-AS	Hypromellose Acetate Succinate
	HPMC-P	Hypromellose Phthalate
15	kg	kilogram(s)
	LDPE	Low Density Polyethylene
	min.	minute(s)
	mm	millimeter(s)
	mL	milliliter(s)
20	µg	microgram(s)
	MDSC	Modulated Differential Scanning Calorimetry
	NLT	not less than
	NMR	Nuclear Magnetic Resonance
	L	liter(s)
25	LOD	loss of drying
	Ph. Eur.	European Pharmacopeia
	PLM	Polarized Light Microscopy
	PTFE	polytetrafluoroethylene
	RH	Relative Humidity
30	rpm	revolutions per minute
	RRT	relative retention time
	SDI	Spray Dried Intermediate
	SDD	Spray Dried Dispersion
	SEM	Scanning Electron Microscopy
35	T _c	crystallization temperature
	T _g	glass transition temperature
	TLC	Thin Layer Chromatography
	USP	United States Pharmacopeia

V	Equivalent volumes in relation to batch input (e.g. 5 V and 2.5kg input gives 12.5 L)
vol.	same meaning as V
XRD	X-Ray Diffraction
5 w/w	weight by weight
Å	Ångström

Example 1: Preparation of extract composition from seeds of *Entandrophragma caudatum*

10

Step 1: Preparation of a methanol extract from seeds of Entandrophragma caudatum

The procedure in this step is outlined in Fig. 2.

15 In Fig. 2 DCT001 stands for the oil that is formed in the extraction process and IBC stands for Intermediate Bulk Container.

Methanol (ca 800 L) was added to a nitrogen filled glass reactor and stirred. Ground seeds of *Entandrophragma caudatum* (ca 100 kg) were then added and the reactor was evacuated and refilled with nitrogen. The temperature of the reactor was set to 40
20 °C and the contents stirred for at least 15-20 h. The mixture was then filtered through a polyamide filter cloth (having a mesh size of 25 µm) by applying pressurized nitrogen atmosphere and the filtrate was collected in a vessel. Methanol was added to the feeding vessel (100 L). From the feeding vessel methanol was passed through the filter bypassing the glass reactor (twice, 50 L each time) and the filtrate was collected into
25 a vessel. The mixture was then filtered again through the polyamide filter cloth by repeating the procedure. The resulting filter cake was then dried under vacuum for at least 1 h. The filtrate was then added to the glass reactor (ca 800 L in total) and the contents stirred. The methanol solvent was distilled off under vacuum at a jacket temperature of 40-70 °C (internal temperature during distillation was approx. 21-29
30 °C). The distillation was continued until approximately 200 L was left in the glass vessel. Care was taken to not distill off too much methanol, as the remaining content would be too sticky to be removed from the glass vessel. The jacket temperature was then adjusted to approximately 20-25 °C and the concentrated methanol extract was collected.

35

Step 2: Preparation of the extract composition of Entandrophragma caudatum in ethyl acetate

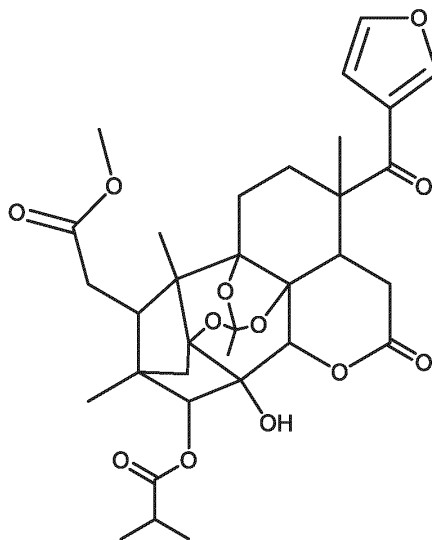
This step is outlined in Figure 3.

In Fig. 3 DCT001 stands for the oil that is formed in the extraction process and IBC stands for Intermediate Bulk Container.

Concentrated methanol extract as prepared in Step 1 above (ca 400 L, i.e. two batches of step 1) was added to a nitrogen filled glass reactor. The temperature of the reactor was adjusted to 75 °C and stirring was started. The methanol was distilled off under vacuum to obtain a dry mixture and, thereafter, the temperature was adjusted to 20 °C. Ethyl acetate (EtOAc) (ca 400 L) was then added to the dry mixture in the reactor followed by water (ca 170 L). The temperature of the reactor was set to 40 °C and the contents of the reactor were stirred for ca 30 min. while maintaining the temperature at 40 °C. The stirring was then stopped and the two phases were allowed to separate for 30 to 60 min. The aqueous layer was then discarded. The temperature of the reactor was adjusted to 55-75 °C and the mixture remaining after water removal was concentrated under vacuum until the volume had been reduced to ca 50 L (i.e., when ca 350 L of distillate had been distilled off and collected). The resulting extract composition of *Entandrophragma caudatum* in EtOAc was then collected as a dark yellow solution and stored at 5 °C ± 3 °C before further use.

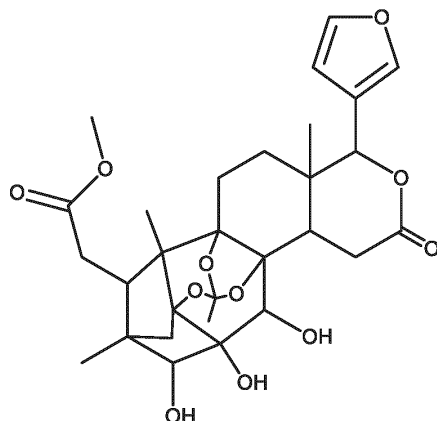
The thus obtained extract composition of *Entandrophragma caudatum* contained a mixture of phragmalin-3,30-di-isobutyrate, phragmalin-3-isobutyrate-30-propionate, phragmalin-3-nicotinate-30-isobutyrate, and a precursor to the compound of Formula Ib1. The chemical structure of the precursor was not established.

Example 2: Synthesis of the compound of Formula V

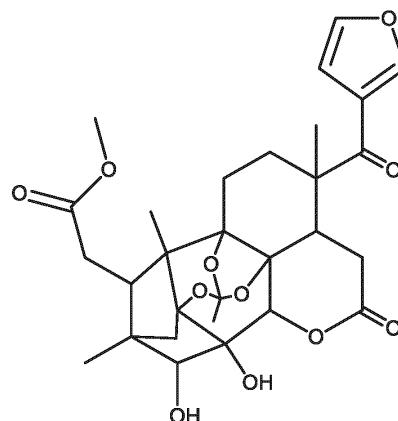


Formula V

Step 1: Synthesis of the compound of Formula Ia1 and the compound of Formula Ib1



Formula Ia1



Formula Ib1

The procedure in this step is outlined in Fig. 4.

5

The extract composition of *Entandrophragma caudatum* in EtOAc from Example 1 (138 kg) was dissolved in methanol (690 L, 5 vol) and distilled until no distillate was observed. Methanol (690 L, 5 vol) was added to reaction which was then further distilled at 45 °C until no distillate was observed to distill off thereby affording a solvent free extract residual as a brown syrup (105 kg).

10

The extract residual (105 kg, 1.0 eq) was dissolved in methanol (1050 L, 10.0 V) and cooled to 15 °C ± 5°C. Sodium methoxide (15.75 kg, 0.15 % w/w) was added in four equal amounts in time intervals of 10 min at temperature below 30 °C (an exotherm of 5-10 °C was observed during addition of sodium methoxide). The reaction mixture was then stirred for 40 h at 45 °C ± 5 °C.

15

Work up:

The pH of the reaction mixture was adjusted to 6.0 to 7.0 using aqueous acetic acid (ca 15.75 kg, ca 0.15 % w/w) at 15 °C ± 5 °C and purified water (315 L, 3.0 V) was added at a temperature below 30 °C. The reaction mixture was concentrated under reduced pressure at a temperature of less than 45 °C to remove the methanol. The residue was diluted with EtOAc (1050 L, 10.0 V). Purified water (420 L, 4.0 V) was then added followed by sodium chloride (21 kg, 0.2 % w/w) and stirred for 15 min. The biphasic medium was then separated and the aqueous phase was reextracted with EtOAc (735 L, 7.0 V). The combined organic layer was washed with 10% sodium chloride solution (735 L, 7.0 V), separated, and dried over anhydrous sodium sulfate (ca 21 kg, 0.2 % w/w). The organic layer was concentrated under reduced pressure at

25

a temperature of less than 45 °C to afford a crude mixture of compounds of Formula Ia1 and Ib1.

Hexane slurry followed by column purification:

- 5 Hexane (1050 L, 10.0 V) was added to the crude mixture which was then heated to 40 °C $\pm$ 5°C and stirred for 2 h. The mixture was then cooled to 25°C $\pm$ 5 °C and stirred for 8 h. The precipitate was collected by filtration and washed with hexane (210 L, 2.0 V) to afford a crude mixture of compounds of Formula Ia1 and Ib1 as a pale yellow solid (*ca* 13.36 kg) (all non-polar impurities were washed out with hexane purification).
- 10 The compounds of Formula Ia1 and Ib1 were separated from the crude mixture by column chromatography on silica gel to afford the compound of Formula Ia1 (*ca* 4.17 kg) and the compound of Formula Ib1 (*ca* 2.94 kg).

Purification of the compound of Formula Ia1:

- 15 The crude compound of Formula Ia1 (4.17 kg) was stirred with isopropyl alcohol (IPA) (8.3 L, 2.0 V) at 50 °C $\pm$ 5 °C for 1 h. The temperature was then slowly reduced (for NLT 1 hour) to 25 °C $\pm$ 5 ° and the crude compound was left to stir for 6 h. The solid was collected by filtration and washed with IPA (2.1 L, 0.5 V). The wet solid (2.32 kg) was dried under vacuum at 40 °C $\pm$ 5 °C to afford the compound of Formula Ia1 (*ca* 2.13 kg) as a solid.
- 20

Analytical data: Purity (HPLC): 98.4 %.

Purification of a compound of Formula Ib1:

- 25 The crude compound of Formula Ib1 (2.94 kg) was stirred with IPA (8.8 L, 3.0 V) at 50°C $\pm$ 5 °C for 1 h. The temperature was then slowly reduced (for NLT 1 hour) to 25 °C $\pm$ 5 ° and the crude compound was left to stir for 6 h. The solid was collected by filtration and washed with IPA (2.9 L, 1.0 V).
- 30 The wet solid (1.53 kg (after loss of drying (LOD) correction)) was stirred with EtOAc (4.6 L, 3.0 V) at 50 °C $\pm$ 5 °C for 1 h. The temperature was then slowly reduced to 25 °C $\pm$ 5 ° and left to stir for 6 h. The solid was collected by filtration and washed with EtOAc (1.5 L, 1.0 V).
- 35 The wet solid (1.07 kg) was stirred with EtOAc (4.6 L, 3.0 V) at 50 °C $\pm$ 5 °C for 1 h. The temperature was then slowly reduced to 25 °C $\pm$ 5 °C and left to stir for 6 h. The solid was collected by filtration and washed with EtOAc (1.5 L, 1.0 V).

The wet solid (0.85 kg) was stirred with EtOAc (1.7 L, 2.0 V) at 50 °C $\pm$ 5 °C for 1 h. The temperature was then slowly reduced to 25 °C $\pm$ 5 ° and left to stir for 6 h. The solid was collected by filtration and washed with EtOAc (0.4 L, 0.5 V).

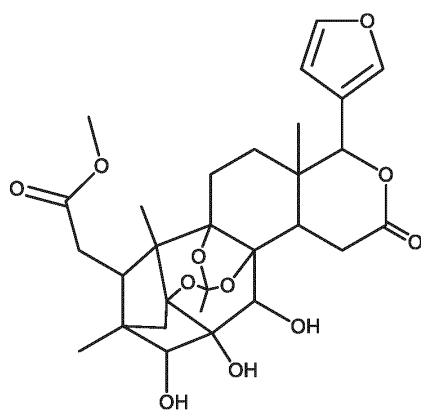
- 5 The wet solid (0.58 kg) was dried under vacuum at 40 °C $\pm$ 5 °C to afford the compound of Formula Ib1 (*ca* 0.335 kg) as a solid.

Analytical data: Purity (HPLC): 99.5 %.

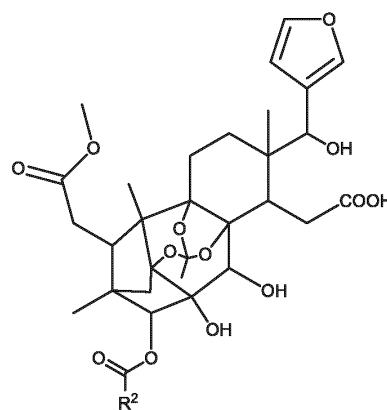
- 10 *Step 2: Three step synthesis for the conversion of the compound of Formula Ia1 to the compound of Formula Ib1*

This step is illustrated in Fig. 5.

- 15 *Step 2(a): Ring opening of lactone ring: Conversion of the compound of Formula Ia1 to the compound of Formula III1*



Formula Ia1



Formula III1

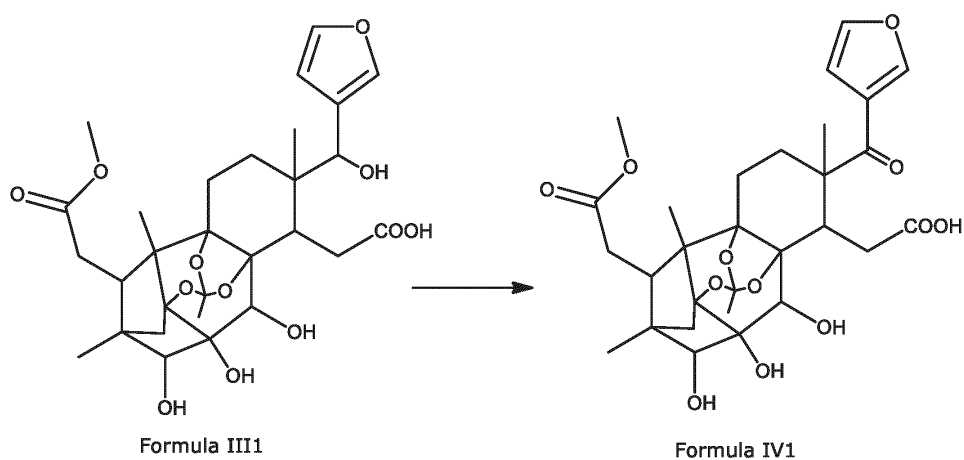
- 20 A suspension of barium hydroxide octahydrate (1.16 kg, 1.0 eq) in methanol (10.3 L, 5.0 V) was cooled to 0-5 °C and the compound of Formula Ia1 (2.06 kg, 1.0 eq) was added in four equal amounts over 15 min at 0-5°C. The resulting reaction mixture was stirred at 0-10 °C for 2 h (the reaction mixture became homogenous as the reaction progressed). The progress of the reaction was monitored by thin-layer chromatography
- 25 (TLC) (60 % EtOAc/hexane, for starting material consumption and 10 % methanol/methylene chloride (MeOH/DCM) for product elution; visualization: potassium permanganate (KMnO₄) stain).

Work up:

After complete consumption of the starting material, the reaction mixture was acidified to pH 5-6 using 10 % aqueous acetic acid (~8.24 L, 4.0 V) and concentrated at a temperature below 40 °C to remove the methanol. The residue was extracted twice with (10.3 L*2, 5 V*2). The combined organic layer was washed with brine solution (8.2 L, 4.0 V), dried over anhydrous sodium sulfate and filtered.

Analytical data: Purity (HPLC): 99.5 %.

- 10 *Step 2(b): Oxidation: Conversion of the compound of Formula III1 to the compound of Formula IV1*



- 15 A suspension of Dess-Martin periodinane (1.72 kg, 1.1 eq) in DCM (16.5 L, 8 V) was added to the organic layer of Step 2(a) (i.e. the compound of Formula III1) at 0-5 °C whilst stirring. The resulting reaction mixture (white suspension) was stirred at 10-15 °C for 3 h. The progress of the reaction was monitored by TLC (5 % MeOH/DCM + a drop of acetic acid; visualization: KMnO₄ stain).

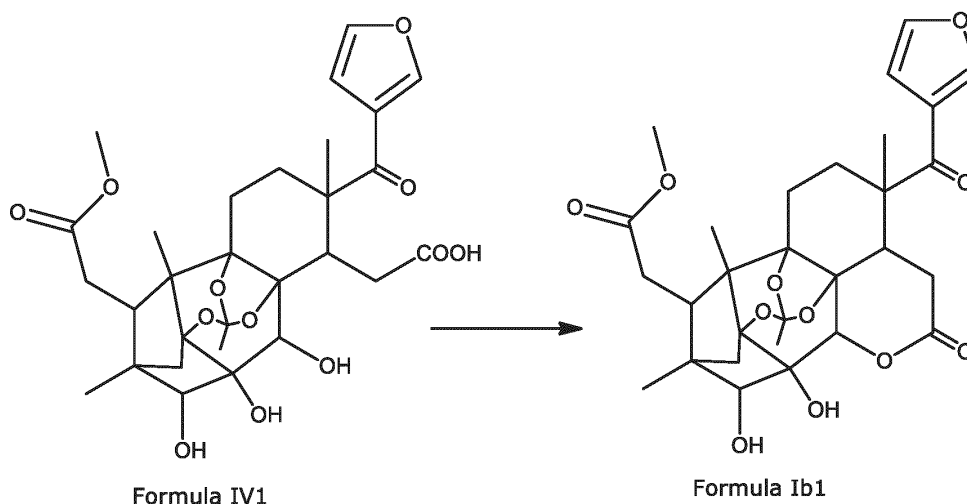
20

Work up:

- After complete consumption of the compound of Formula III1, the reaction mixture was quenched with 20 % sodium thiosulfate solution (20.6 L, 10 V) in purified water and stirred for 30 min (the reaction mixture became clear and a clear separation of the organic and aqueous layers was observed). The layers were separated, and the aqueous layer was extracted with DCM (10.3 L, 5.0 V). The combined organic layer
- 25

was washed with brine solution (10.3 L, 5.0 V), dried over anhydrous sodium sulfate and filtered. The organic layer was concentrated to 10.0 volume level with regards to the compound of Formula Ia1 at below 40 °C.

- 5 *Step 2(c): Ring formation: Conversion of the compound of Formula IV1 to the compound of Formula Ib1*



- To the organic layer of Step 2(b) (i.e. the compound of Formula IV1) was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC x HCl) (0.702 kg, 1.0 eq.) followed by diisopropylethylamine (DIPEA) (0.957 L, 1.5 eq) at 10 °C ± 5 °C over a period of 30 min whilst stirring. The resulting reaction mixture was stirred at 10 °C ± 5 °C for 2 h. The progress of the reaction was monitored by TLC (10 % MeOH/DCM for starting material consumption and 80 % EtOAc/hexane for product elution; visualization: KMnO₄ stain).

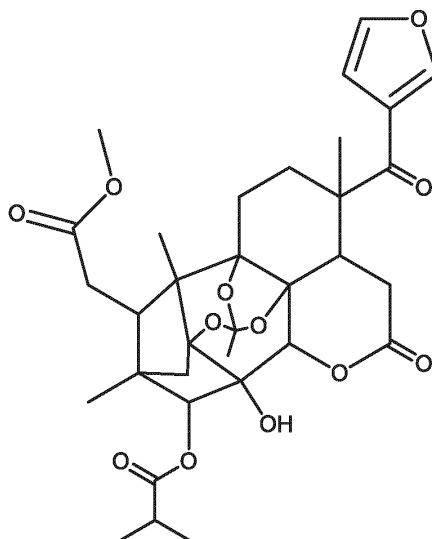
Work up:

- After complete consumption of the compound of Formula IV1, the reaction mixture was quenched with water (20.6 L, 10.0 V). The layers were separated, and the aqueous layer was extracted with DCM (10.3 L, 5.0 V). The organic layer was washed with brine solution (10.3 L, 5.0 V). The layers were separated, and the organic layer was dried over anhydrous sodium sulfate and filtered. The combined organic layer was concentrated under reduced pressure at 40 °C until no distillate was observed.

Purification of the compound of Formula Ib1:

The crude product of the compound of Formula Ib1 was charged with EtOAc (12.3 L, 6.0 V) at a temperature below 40 °C, concentrated to 3.0 vol level with regards to compound of Formula IIb1 and stirred at 50 °C $\pm$ 5 °C for 1 h. The reaction mixture was gradually cooled to 25 °C $\pm$ 5 °C over 1 h and left to stir at 25 °C $\pm$ 5 °C for 6 h. The solid was collected by filtration and washed with EtOAc (2.1 L, 1.0 V) to obtain the wet solid of the compound of Formula Ib1 (1.1 kg). The wet solid was dried under vacuum at 40°C $\pm$ 5 °C to afford the compound of Formula Ib1 (0.85 kg) as a solid.

10 Analytical data: Purity (HPLC): 95.4 %.

Step 3: Synthesis of the compound of Formula V

Formula V

15 To a solution of the compound of Formula Ib1 (obtained from both Steps 1 and 2 above) (322 g, 1.0 eq.) in dry dimethyl formamide (DMF) (1.6 L, 5.0 V) was added 4-*N,N*-dimethylaminopyridine hydrochloride (DMAP x HCl) (91 g) followed by isobutyryl chloride (92 g, 1.5 eq.) at 25 °C $\pm$ 5 °C. The reaction was heated to 60 °C $\pm$ 5 °C and stirred for 6 h. DMAP x HCl (45.6 g) was then added to the reaction followed by isobutyryl chloride (61.2 g, 1.0 eq.), and the reaction was continued for a further 4 h and monitored by HPLC.

Work up:

25 Once the reaction was complete, the reaction mixture was cooled to 25 °C $\pm$ 5 °C, filtered through a celite bed and washed with DMF (320 mL, 1.0 V). The filtrate was passed through a 0.2 μ m cartridge and washed with DMF (320 mL, 1.0 V).

Purified water (8.0 L, 25.0 V) was added to another reaction vessel and cooled to 15 °C ± 5 °C. The filtrate was then added slowly over a period of 1 h at 15 °C ± 5 °C (reverse quench). The reaction contents were allowed to attain a temperature of 25 °C ± 5 °C and left stirred for 4 h at the same temperature. The solid was collected by filtration and washed with purified water (0.65 L, 2.0 V).

The wet solid was stirred with purified water (1.6 L, 5 V) at 40 °C ± 5 °C for 2 h then collected by filtration and washed with purified water (0.65 L, 2 V).

The wet solid was dried under reduced pressure at 40 °C ± 5 °C for 12 h to afford the crude product of the compound of Formula V (456 g).

Analytical data: Purity (HPLC): 79.97 %.

Ethyl acetate purification:

Ethyl acetate slurry-1: The crude product (456 g) was stirred with EtOAc (1.36 L, 3.0 V) at 50 °C ± 5 °C for 1 h. The reaction was gradually cooled to 25 °C ± 5 °C over 1 h and left to stir at 25 °C ± 5 °C for 4 h. The solid was collected by filtration and washed with EtOAc (0.45 L, 1.0 V).

Wet solid weight: 295 g, after LOD correction: 249 g (LOD: 15.6 % w/w). Purity by HPLC: 97.7% and impurities: RRT 0.68: 1.38%.

Ethyl acetate slurry-2: The crude product (249 g) was stirred with EtOAc (373 mL, 1.5 V) at 50 °C ± 5 °C for 1 h. The reaction was gradually cooled to 25 °C ± 5 °C over 1 h and left to stir at 25 °C ± 5 °C for 4 h. The solid was collected by filtration and washed with EtOAc (0.45 L, 1.0 V).

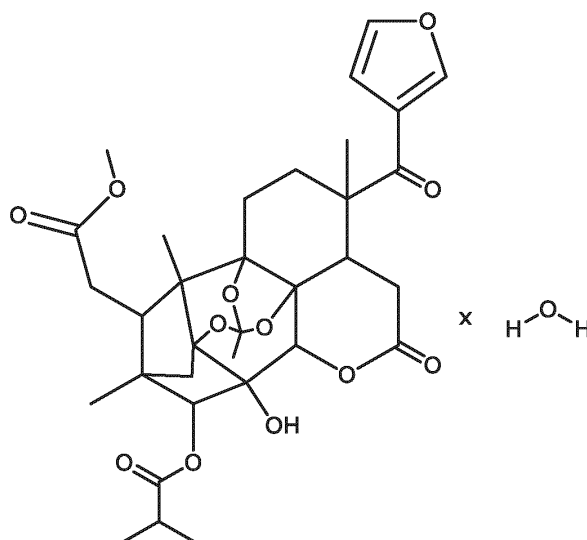
Wet solid weight: 236.6 g, after LOD correction: 230 g (LOD: 2.6 % w/w). Purity by HPLC: 98.68% and impurities: RRT 0.68: 1.38%.

Ethyl acetate slurry-3: The crude product (230 g) was stirred with EtOAc (460 mL, 2.0 V) at 50 °C ± 5 °C for 1 h. The reaction was gradually cooled to 25 °C ± 5 °C over 1 h and left to stir at 25 °C ± 5 °C for 4 h. The solid was collected by filtration and washed with EtOAc (115 mL, 1.0 V).

Wet solid weight: 191.6 g. Purity by HPLC: 99.8% and impurities: RRT 0.68: 0.12%.

The wet solids were dried under reduced pressure at $40\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ for not less than (NLT) 10 h to afford the crude product of the compound of Formula V (185.4 g).

5 **Example 3: Synthesis of the monohydrate of Formula VII1**



Formula VII1

10 *In this example, acetone/purified water purification took place in order to obtain the desired monohydrate form:*

The crude product of the compound of Formula V (181.4 g) was stirred with acetone (1.3 L, 7.0 V) at $45\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ for 30 min. to obtain a clear solution. Purified water (2.8 L, 15.0 V) was added to the reaction over 1 h and stirred for additional 1 h at $45\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$. The reaction was gradually cooled (for NLT 1 h) to $25\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ and stirred for 6 h. The solid was collected by filtration and washed with acetone/purified water (278 mL, 1.0 V) to afford the wet product of the monohydrate of the compound of Formula V1, i.e., the monohydrate of Formula VII1 (188 g). The wet solid was dried under reduced pressure at $40\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$ for NLT 16 h and sieved to afford of the monohydrate of Formula VII1 (179 g).

Analytical data: Purity (HPLC): 99.9 %.

Specific optical rotation: -49.8° .

25

The IR spectrum of the monohydrate of Formula VII1 produced is shown in Fig. 6.

NMR data for the monohydrate of Formula VII1:

¹H-NMR (DMSO, 400 MHz): δ 8.64 (s, 1 H), 7.78 (s, 1 H), 6.75 (dd, 1 H), 5.09 (s, 1 H), 4.69 (s, 1 H), 3.92 (s, 1 H), 3.41 (s, 3H), 2.68 (m, 3 H), 2.35 (m, 2H), 2.24 (m, 3 H), 1.95 (m, 2 H), 1.67 (m, 1 H), 1.55 (d, 4 H), 1.42 (s, 3 H), 1.26 (d, 6 H), 1.18 (m, 1H), 1.04 (s, 1H), 0.76 (s, 3H) LCMS : 629.4 [M+H], HPLC purity: 98.50 %.

Example 4

The hydrate of Formula VII1 was prepared as described herein and tested for solubility by checking the uptake in a saturated solution of a number of biorelevant media at different pH values as shown in Table 1 below.

Table 1:

Biorelevant medium	Formula VII1 uptake (mg/mL)
Fasted State Simulated Gastric Fluid(FaSSGF) at pH 1.6	9
Fed Gastric Fluid (FeDGAS) at pH 4.5	8
Fed State Simulated Intestinal Fluid (FeSSIF) at pH 5.0	8
Fasted State Simulated Intestinal Fluid (FaSSIF) at pH 6.5	36

Thus, the best solubility was found when FaSSIF at pH 6.5 was used.

Example 5

Based on studies performed at Thermo Fisher, Oregon, USA, using Thermo Fisher’s in silico platform for solubilization technology selection it was decided to try spray-drying of the hydrate of Formula VII1. In the following examples, the abbreviation “API” is used for the hydrate of Formula VII1.

Example 6

A solvent spike assessment was set up, where approximately 100 mg of polymers/excipients (see list below) were added to a scintillation vial and dissolved in 20 ml of FaSSIF at pH 6.5 media with the aid of a magnetic stirrer bar.

- Vinylpyrrolidone- vinylacetate copolymer, (Kollidon VA 64, PVP-VA 64, BASF Corporation, 100 Park Avenue, Florham Park, New Jersey, USA)
- Hypromellose (HPMC, Pharamacoat, Shin-Etsu Chemicals, Tokyo, Japan)

- PEG 6000/vinyl caprolate /vinylacetate, BASF Corporation, 100 Park Avenue, Florham Park, New Jersey, USA Hypromellose Acetate Succinate (HPMCAS-M, Harke Pharma, Muelheim a. d. Ruhr, Germany)
- Methacrylic acid-ethyl acrylate coploymer (1:1) , Evonik Operations GmbH Kirschenallee, 64293 Darmstadt, Germany
- Hypromellose phtalate (HPMCP-HP55, Harke Pharma, Muelheim a. d. Ruhr Germany)

A control prepared with 20 mL of FaSSIF media (pH 6.5) was added to a scintillation vial with no excipient added. A 5 mg/mL API stock solution was prepared by weighing 50 mg API into a 10 mL volumetric flask and dissolving in DMSO before making up to a 10 mL volume with DMSO. This is the concentrated dissolved stock drug solution. 1,0 mL of the thus prepared stock solution was added to each scintillation vial containing polymer/excipient and FaSSIF or just FaSSIF (i.e., the control).

The solutions were then left to stir using a magnetic stirrer plate for 15 minutes, 30 minutes or 60 minutes, an aliquot of each solution was then transferred into a centrifuge tube and centrifuged for at least 5 minutes at 10,000 rpm or until a clear supernatant solution was produced. The resulting supernatant was then analyzed by HPLC. Figure 7 presenting the dissolution plot of the solvent spike experiment shows a significant increase in solubility of the hydrate of the API observed for all excipients in comparison to the control sample (pure API).

Based on this data, 6 formulations of API and excipients (Soluplus®, HPMC-HP55 and HPMC-AS M) load were selected at 25 % and 50% API load (Table 2) for spray drying feasibility batch manufactures.

Table 2: Selected formulations for feasibility batch experiments

Formulation 1	25 % API + 75 % Soluplus®
Formulation 2	50 % API + 50 % Soluplus®
Formulation 3	25 % API + 75 % HPMC-HP55
Formulation 4	50 % API + 50 % HPMC-HP55
Formulation 5	25 % API + 75 % HPMC-AS M
Formulation 6	50 % API + 50 % HPMC-AS M

Example 7

The 6 formulations of Table 2 for spray drying feasibility studies were prepared accordingly.

Since the hydrate of Formula VII1 (the API) is highly soluble in dichloromethane (DCM) and the excipients are highly soluble in acetone, it was decided to use 1:1 acetone and DCM mixture to allow both the hydrate of Formula VII1 and the excipients to dissolve in the solvent mixture at high solid loading for the manufacture of spray drying solution formulations (see Table 3). The excipients described here are equally soluble in methanol (MeOH). Spray drying with MeOH and DCM using the method of the invention has also been tested and confirmed to give a spray-dried formulation product with the same chemical and physical characteristics as for formulations spray-dried using acetone and DCM (data not shown). Thus, the spray-drying method of the invention can be performed using e.g. either acetone/DCM or methanol/DCM. Therefore, examples given in this document of ratios, amounts, volumes etc of acetone can be interchangeably used also for MeOH.

To prepare each feed solution, the selected excipient was added to a duran with the required mass of 1:1 w/w acetone:DCM and allowed to dissolve under mixing. Once the excipient was fully dissolved, the required mass of the API was added, and the solution further stirred until the API had dissolved. The solutions were then spray dried immediately after preparation.

The feed solutions were spray dried using a Buchi B-290 laboratory-scale spray dryer, fitted with an inert loop. Nitrogen was used as drying gas, a Buchi two fluid spray nozzle (0.7 mm tip diameter) and a standard Buchi cyclone were used. Spray drying parameters were as follows:

- Drying outlet temperature of 65°C
- Atomisation pressure of 1.0 bar
- Solution feed rate of 6 g/min.
- Tubing: PTFE with a Masterflex L/S pump, i.e., a peristaltic pump, fitted with a PTFE head.

After spray drying the bulk material was transferred to stainless steel trays and vacuum dried for 24 hours at 25°C, using either a Gallenkamp vacuum oven or an Edwards freeze dryer equipped with a vacuum pump, under a continuous vacuum.

Table 3 shows the prepared formulations and the yield obtained in the spray drying process. All formulations were successfully spray-dried.

Table 3:

Formulation	Mass of API (g)	Mass of Excipient (g)	Mass of 1:1 Acetone:DCM added (g)	Yield (g)	Yield (%)
25 % API + 75 % Soluplus	5.04	14.47	175.5	16.2	82.9
50 % API + 50 % Soluplus	10.07	9.43	175.5	16.0	82.1
25 % API + 75 % HPMC-HP55	3.87	11.13	135.0	11.4	75.9
50 % API + 50 % HPMC-HP55	7.75	7.25	135.0	11.2	74.7
25 % API + 75 % HPMC-AS M	3.87	11.13	135.0	11.1	73.7
50 % API + 50 % HPMC-AS M	7.75	7.25	135.0	11.3	75.4

Observations: Formulations with either Soluplus or HPMC-AS M produced a fine, white powder with soft agglomerates. Formulations comprising HPMC-HP55 produced a slightly adhesive, white powder with soft agglomerates.

All six powders resulting from the spray-drying were placed in a stainless-steel tray covered in foil pierced with small holes and the tray was placed in a vacuum oven at 25 ° C and maximum vacuum was pulled for 24 hours (>1000 mbar). The weight was recorded before and after vacuum drying for all six powders as presented in Table 4.

Table 4:

Formulation	Pre drying weight (g)	Post drying weight (g)
25 % API + 75 % Soluplus	16.2	15.9
50 % API + 50 % Soluplus	16.0	15.7
25 % API + 75 % HPMC-HP55	11.4	11.1
50 % API + 50 % HPMC-HP55	11.2	11.0
25 % API + 75 % HPMC-AS M	11.1	10.9
50 % API + 50 % HPMC-AS M	11.3	11.1

DSC, XRD and SEM analysis:

DSC, XRD and SEM tests were performed on the spray dried powder from the six feasibility formulations in Table 4 (data not shown). No evidence of API crystallization

was observed in any of the batches of the spray dried dispersion as analyzed by these techniques, indicating all manufactured formulations were amorphous. Figure 8 shows a SEM micrograph taken of the spray dried formulation comprising 25 % API + 75 % Soluplus.

5

Dissolution analysis:

The six spray dried formulations were also tested for two-stage dissolution in FaSSGF (pH 1.6, 30 mins), followed by switching the dissolution to FaSSIF (pH 6.5, 90 mins). Figure 9 shows a dissolution plot of the six spray dried dispersions (SDD) in FaSSIF, pH 6.5. The data shows that the solubility of the API has improved significantly with HPMC-HP55 formulation giving the highest dissolution. The dissolution test was performed by USP basket type I apparatus.

10

Tg vs. % RH (MDSC)

To test for long term stability these six spray dried intermediate (SDI) formulations were exposed to 75% RH for 4 hours using a dynamic vapour sorption machine (DVS). The term "intermediate" is used as the formulations may be processed further into formulations such as tablets and capsules. All formulations absorbed moisture in these conditions. The humidity-equilibrated samples were sealed in hermetic pans and analyzed by modulated differential scanning calorimetry (MDSC). No significant changes in the glass transition temperature (Tg) of the samples pre and post exposure to humidity was found, indicating all formulations were stable.

20

Based on the results of the DSC, XRD and SEM, dissolution, and DVS tests four lead formulations were selected for large scale manufacture (see Example 8).

25

Long term stability

A long-term stability test was also conducted on the spray-dried formulation comprising 25 % API + 75 % HPMC-AS M by packaging the spray dried intermediate powder in a double LDPE bag, each one goose necked and sealed with a cable tie. One 0.5 g desiccant was added between the LDPE bags and the bags were then placed in a 75cc HDPE bottle which was capped but not heat sealed. The bags were kept at 25°C/60%RH for up to 6 months before analysis on the stored formulation was performed. As can be seen in Table 5 here below the spray-dried formulation of the invention shows good stability up to 6 months in the tested conditions.

30

35

Table 5:

Test	Procedure, USP, Ph. Eur	t=0 (Release)		1 month		3 month		6 month	
Appearance (Visual)	AM-0002	White powder		White powder		White powder		White powder	
Assay (HPLC)	DM-0470	24,60%		25,10%		24,90%		23,90%	
Individual impurities and Related substances (HPLC)									

	Ph.Eur. 2.9.33				
Thermal analysis (mDSC)	DM-0046 USP <891> Ph. Eur. 2.2.34 n=3 replicates	Tg = 107.23 °C Tc = 165.20 °C No other thermal events observed	Tg = 106.77 °C Tc = 164.25 °C No other thermal events observed	Tg = 106.93 °C Tc = 163.38 °C No other thermal events observed	Tg = 109.37 °C Tc = 163.41 °C No other thermal events observed
Water content (KF)	AM-0414 USP <921> Ph. Eur. 2.5.32	0.96%	1.48 %	0.93 %	0.81%

Suspension stability

Four formulations (25 % API + 75 % Soluplus, 50 % API + 50 % Soluplus, 50% API / 50% HPMC-HP55 and 50% API / 50% HPMC-ASM) were formulated as small-batch size suspensions in three oral suspension vehicles (a. 0.5% methylcellulose in water, b. corn oil and c. Ora-Blend SF). The Ora-Blend SF was obtained from Perrigo/Padagis, Grand Rapids, Michigan, USA and reported to contain water, sorbitol, glycerin, berry citrus flavour, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, calcium sulfate. These suspensions were visually assessed for homogeneity and syringeability for oral gavage and examined for recrystallisation by polarized light microscopy (PLM) up to 6 hours after preparation. Ora-blend SF suspension formulation gave issues with high performance liquid chromatography (HPLC) analysis of the materials, where gelling of the materials was observed upon extraction of suspensions with solvent methanol. Consequently, Ora-blend SF was not selected as a dosing vehicle. Subsequently four suspension formulation, dose strength of 21 mg/ml, were put on stability and tested for appearance and syringeability (visual), amorphous character (light microscopy) and potency. All four formulations passed in a syringeability test and showed no evidence of API crystallization under the microscope.

20

Formulation 1. 25%w/w API:Soluplus SDD in 0.1%w/w Hypromellose solution

Formulation 2. 50 %w/w API:Soluplus in in 0.1%w/w Hypromellose solution

Formulation 3. 50 %w/w API:HPMC-HP55 in oleic acid

Formulation 4. 50%w/w API:HPMC-AS in 0.1%w/w Hypromellose solution

25

All four formulations gave >95% assay value at a time T = 6 hours indicating that suspensions were stable in respective dosing vehicle. The pH of all the suspensions was around pH 4, indicating suspensions were slightly acidic to dose.

- 5 Thus, all suspensions tested are physically and chemically stable for a period of at least 6 hours.

Example 8 : Spray drying- Scale up experiment

- 10 Out of the six spray dried formulations from the feasibility studies (see Table 4) four were selected for the scale-up test with the goal to produce more than 100 g of spray dried powder.

The four formulations selected for scale-up were:

- 25 % API + 75 % Soluplus®
- 15 • 50 % API + 50 % Soluplus®
- 50 % API + 50 % HPMC-HP55
- 50 % API + 50 % HPMC-AS M

- 20 Table 6 shows the amount of API, excipient and acetone:DCM that was mixed and subsequently spray dried with settings as presented here above. Note that the nozzle cleaner was set to "1" for all scale up batches.

Table 6:

Formulation	Mass of API (g)	Mass of Excipient (g)	Mass of 1:1 Acetone:DCM added (g)	Yield (g)	Yield (%)
25 % API + 75 % Soluplus	34.9	100.1	1215.0	108.2	80.2
50 % API + 50 % Soluplus	69.7	65.3	1215.0	105.1	77.9
50 % API + 50 % HPMC-HP55	72.3	67.7	1260.0	118.8	84.8
50 % API + 50 % HPMC-AS M	72.3	67.7	1260.0	105.9	75.6

- 25 Observations: Formulations with either Soluplus or HPMC-AS M produced a fine, white powder with soft agglomerates. The formulation comprising HPMC-HP55 produced a slightly adhesive, white powder with soft agglomerates.

- 30 A comparison with the results in Table 3 shows that the upscaling gave slightly lower yields for the tests with Soluplus. Further, a comparison with Table 3 shows that the

upscaling provided higher yields for HPMC as evidenced by the results in Table 6 for the formulation with HPMC-HP55 and HPMC- AS M, respectively.

Particle size distribution:

5 To determine the particle size distribution of the spray-dried particles of the invention a Malven Mastersizer 3000 with an Aero S dispersion unit was used. The spray-dried powder was dispergated in nitrogen, hopper height set to 1.0 mm, gas pressure 1.0 bar, 50% feed rate, 0.1-6% obscuration limits and a refractive index of 1.681.

The two batches were manufactured with a 25 % API loading using HPMC-AS M as excipient. A comparison between the two batches with respect to particle size distribution presented in Table 7 shows similar distributions regardless of batch size. It will be appreciated that Dv90 is as described herein. In the same way, ‘Dv50’ means the size (or diameter) in a particle size distribution in which 50% of the total volume of the material is contained, and ‘Dv10’ means the size (or diameter) in a particle size distribution in which 10% of the total volume of the material is contained. D[4,3] is mean diameter based on volume-weighted mean results.

Table 7:

Test	Batch D-22-095				Batch G-23-020			
	Batch size (total solids): 2.9 kg				Batch size (total solids): 0.382 kg			
	Dv10	Dv50	Dv90	D[4,3]	Dv10	Dv50	Dv90	D[4,3]
Particle size distribution by Laser Light Diffraction (µm)	6	23	60	29	7	23	61	29

Example 9

20 The long term stability of the compound of Formula V and the hydrate of Formula VII1 were studied. The storage was performed at a temperature of 25 °C and a relative humidity of 60%. The results are shown in Table 8. The area % was measured using HPLC. The sum of related substances reported if > 0.1%.

25

30

Table 8:

Test	Initial		6 months	
	Compound of Formula V	Hydrate of Formula VII1	Compound of Formula V	Hydrate of Formula VII1
Appearance	White solid	White solid	White solid	White solid
Assay/(area%)	95.7	100.0	98.9	99.5
Related substances*/(area %)	0.76	0.0	0.91	0.0
Water content/(%w/w)	0.43	2.6	0.44	2.8

It was concluded that long term storage, such as storage equal to six months, of the hydrate of Formula VII1 resulted in an amount of so-called related substances (i.e. compounds other than the compound of Formula V or the hydrate of Formula VII1 that are structurally related to the compound of Formula V) that was lower than that formed for the compound pf Formula V. In fact, no related substances appeared to be formed during storage of the hydrate of Formula VII1 while an increase was observed for the compound of Formula V.

10

Example 10

An X-ray powder diffractogram was recorded for the hydrate of Formula VII1. The XRPD data were collected on a powder X-ray diffractometer instrument with the following settings:

15 Radiation Copper K α , λ =1.54060 Å, Anode voltage: 45 kV, Anode current 40 mA, Scan Axis: Theta-2Theta, Divergence Slit: 1.00°, Scattering Slit: 1.00°, Receiving Slit: 0.15 mm, Sampling Pitch: 0.0140°, Scan Speed: 6°/min, Preset Time: 0.14 s. Scan Range (2 θ): 3 - 35° in 2 θ scale.

20

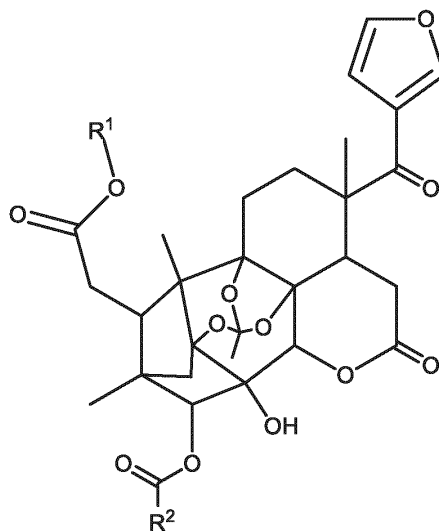
The resulting XRP diffractogram is shown in Fig. 10. The positions and intensities of the major peaks in the X-ray powder diffractogram are shown in Table 9.

Table 9:

Angle $2\theta/^\circ$	d-value/ $\text{\AA}$	% Relative intensity
9.66	9.14	100
10.92	8.09	8
11.16	7.92	5
12.88	6.87	4
19.41	4.57	42
19.88	4.46	6
20.71	4.29	4

Claims

1. A compound of Formula IIb



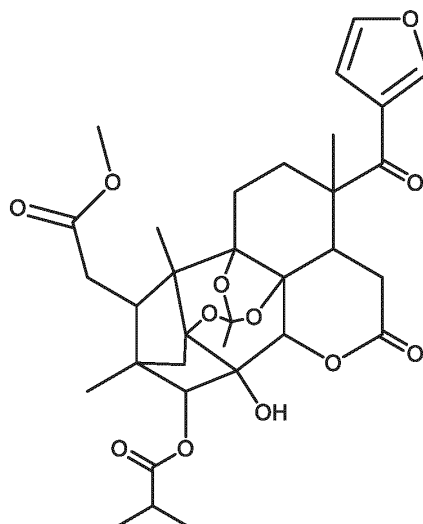
Formula IIb

or a hydrate thereof,

wherein R^1 and R^2 independently are C_1 - C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I

wherein said compound or hydrate thereof is in an essentially solid form.

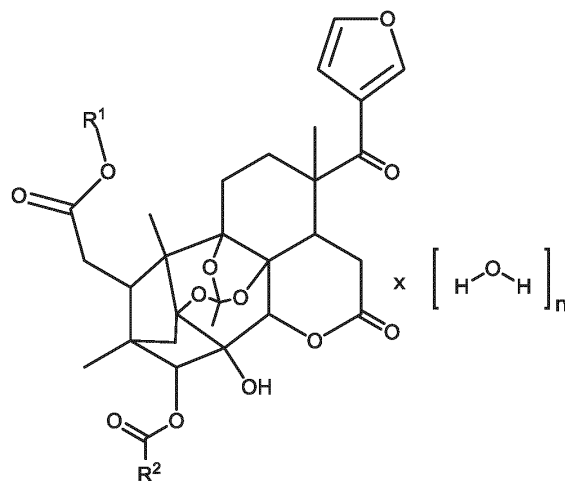
2. The compound according to claim 1, wherein R^1 is methyl and R^2 is isopropyl thereby providing a compound of Formula V



Formula V

or a hydrate thereof.

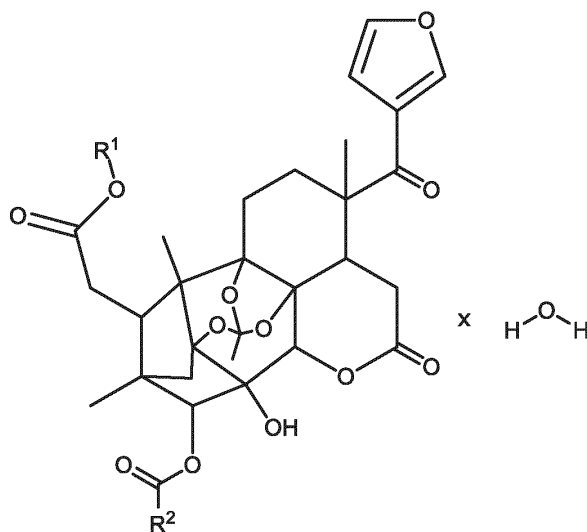
3. The hydrate according to claim 1 or 2, wherein said hydrate is a combination of the compound of Formula IIb and water in a ratio of 1:n thereby providing a hydrate of Formula VI:



Formula VI

wherein n has a value from 0.5 to 100.

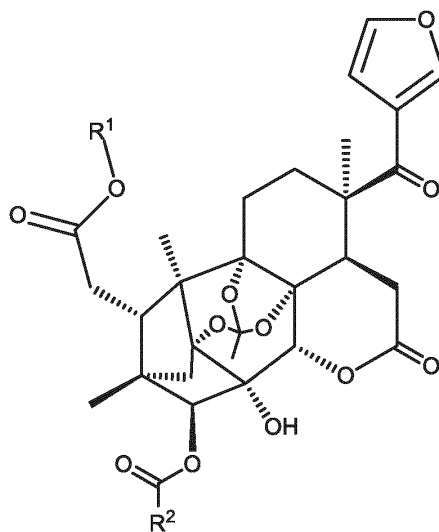
4. The hydrate according to claim 3, wherein n is 1 thereby providing a monohydrate of Formula VII:



Formula VII

5. The compound according to claim 1 or 2, or a hydrate thereof, or the hydrate according to claim 3 or 4

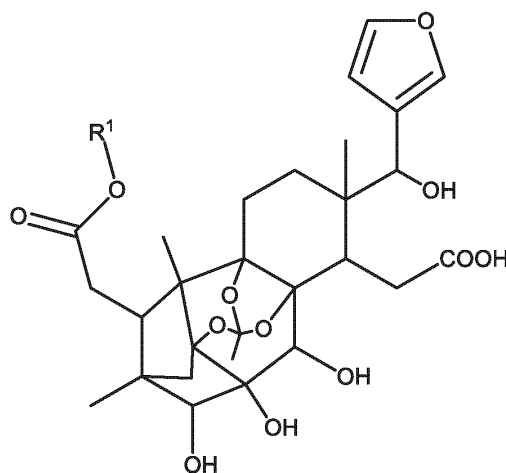
wherein the compound of Formula IIb is provided as a stereoisomer of Formula IIc:



Formula IIc

5

6. A compound of Formula III:



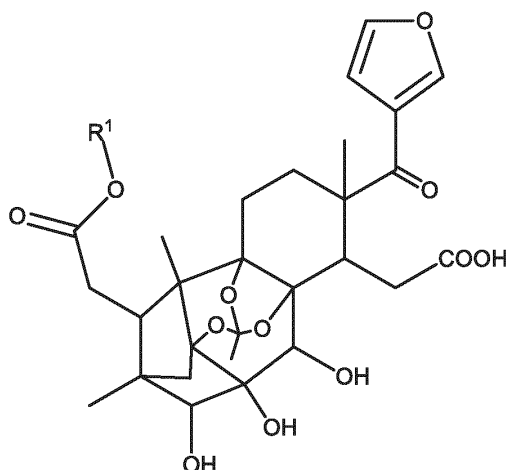
Formula III

or a salt, such as a pharmaceutically acceptable salt, and/or a stereoisomer thereof

wherein R^1 is C_1 - C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I.

7. A compound of Formula IV:

15



Formula IV

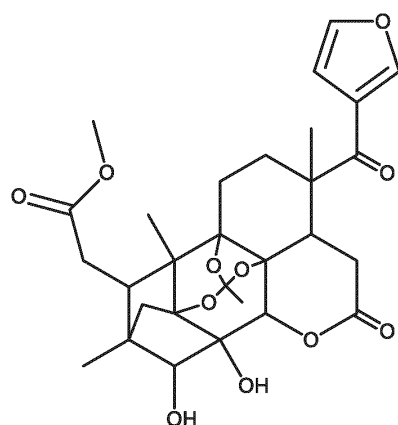
or a salt, such as a pharmaceutically acceptable salt, and/or a stereoisomer thereof

5 wherein R¹ is C₁-C₆alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I.

8. The compound according to any one of claims 1, 2 or 5 to 7, or a hydrate thereof,
or the hydrate according to claim 3 or 4
10 characterized by being essentially crystalline.

9. The compound according to any one of claims 1, 2 or 5 to 8, or a hydrate thereof,
or the hydrate according to claim 3, 4 or 8,
characterized by
15 having a chemical purity equal to or above about 90%, such as about 95%,
such as about 99%, and/or
a chemical stability equal to or above about 90% such as about 95%, such as
about 99%.

20 10. A spray-dried pharmaceutical composition comprising:
(a) a compound as defined in any one of claims 1, 2, 5 to 7 or 9, or a hydrate
thereof, or a hydrate as defined in any one of claims 3, 4 or 9, or a
compound of Formula Ib:



Formula Ib

or a hydrate thereof; and
(b) an excipient suitable for spray-drying.

5

11. The spray-dried composition according to claim 10, wherein the excipient suitable for spray-drying comprises a polymer or co-polymer capable of forming physico-chemical interactions with the compound as defined in claim 1, 2, 5 to 7 or 9, or hydrate thereof, or the hydrate as defined in claim 3, 4 or 9, enabling re-solubilization of said compound.

10

12. The spray-dried composition according to claim 11, wherein the excipient suitable for spray-drying comprises one or more of a cellulose ester, N-vinylpyrrolidone-vinyl acetate co-polymer, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer and methacrylic acid-methyl methacrylate co-polymer.

15

13. The spray-dried composition according to any one of claims 10 to 12, wherein the excipient suitable for spray-drying comprises a cellulose ester such as a non-ionic cellulose ester.

20

14. The spray-dried composition according to claim 13, wherein the cellulose ester is a hydroxypropylmethyl cellulose (HPMC) or a derivative thereof.

25

15. The spray-dried composition according to claim 14, wherein the derivative of HPMC is HPMC-AS or HPMC-P.

16. The spray-dried composition according to any one of claims 13-15, wherein the HPMC or derivative thereof is HPMC-AS such as HPMC-AS of grade M.

17. The spray-dried composition according to any one of claims 10 to 16, wherein the ratio between the compound or hydrate and the excipient is from about 1:5 to about 5:1, such as about 1:4 to about 4:1, about 1:3 to about 3:1, about 1:2 to about 2:1 or about 1:1.
18. The spray-dried composition according to claim 17, wherein the ratio of the compound or the hydrate and the excipient is about 1:3.
19. The spray-dried composition according to any one of claims 10 to 18, wherein the compound is as defined in claim 5, or hydrate thereof, or the hydrate as defined in claim 4.
20. The spray-dried pharmaceutical composition according to any one of claims 10 to 19, wherein particles in the composition have a particle size distribution with a Dv90 of 120 μ m or less, such as 100 μ m or less, such as from 10 μ m to 120 μ m.
21. A pharmaceutical formulation comprising a therapeutically effective amount of a compound as defined in any one of claims 1, 2 or 5 to 9, or a hydrate thereof, or a hydrate as defined in any one of claims 3, 4, 8 or 9, or a spray-dried composition as defined in any one of claims 10 to 20, or a compound of Formula Ib as defined in claim 10, or a solvate thereof, comprising a therapeutically effective amount of the relevant compound, in admixture with a pharmaceutically acceptable, excipient, carrier and/or diluent.
22. The pharmaceutical formulation according to claim 21, wherein the composition is formulated for oral administration.
23. The pharmaceutical formulation according to claim 22, which is formulated as a tablet or a capsule.
24. The pharmaceutical formulation according to claim 22 or claim 23, which composition further comprises an enteric substance, such as a coating, that serves to prevent release of the compound, hydrate or spray-dried composition in the stomach.

25. The pharmaceutical formulation according to claim 22, wherein a spray-dried composition as defined in claim 21 is reconstituted with a liquid that is a vehicle for oral administration, such as an oil-based or water-based vehicle.
- 5 26. The pharmaceutical formulation according to claim 22, wherein said vehicle further comprises a cellulose-based agent, such as a non-ionic cellulose based agent, such as CMC, MC, HEC, HPMC, and/or HEMC.
- 10 27. A compound as defined in any one of claims 1, 2 or 5 to 9, or a hydrate thereof, a hydrate as defined in any one of claims 3, 4, 8 or 9, a spray-dried composition as defined in any one of claims 10 to 20, or a pharmaceutical formulation as defined in to any one of claims 21 to 26, or a compound of Formula Ib as defined in claim 10, or a hydrate thereof for use as a medicament in therapy.
- 15 28. A compound as defined in any one of claims 1, 2 or 5 to 9, or a hydrate thereof, a hydrate as defined in any one of claims 3, 4, 8 or 9, a spray-dried composition as defined in any one of claims 10 to 20, or a pharmaceutical formulation as defined in any one of claim 21 to 26, or
- 20 a compound of Formula Ib as defined in claim 10, or a hydrate thereof for use in the treatment and/or prevention of or more of the following dysfunctions or disorders: a sexual dysfunction, erectile dysfunction, ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder, neurological disorder.
- 25 29. The compound, hydrate, composition, or formulation, for use according to claim 28, wherein the dysfunction and/or disorder comprises erectile dysfunction and/or premature ejaculation.
- 30 30. Use of a compound as defined in any one of claims 1, 2 or 5 to 9, or a hydrate thereof, a hydrate as defined in any one of claims 3, 4, 8 or 9, a spray-dried composition as defined in any one of claims 10 to 20, or a pharmaceutical formulation as defined in any one of claim 21 to 26, or
- 35 a compound of Formula Ib as defined in claim 10, or a hydrate thereof for the manufacture of a medicament for the treatment and/or prevention of or more of the following dysfunctions or disorders: a sexual dysfunction, erectile

dysfunction, ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder, neurological disorder.

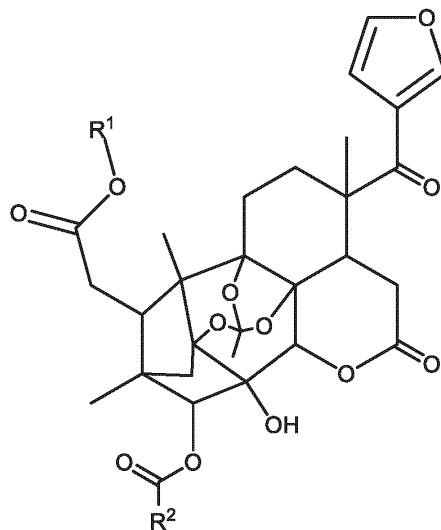
5 31. The use according to claim 30, wherein the dysfunction and/or disorder comprises erectile dysfunction and/or premature ejaculation.

32. A method of treatment and/or prevention of or more of the following dysfunctions or disorders: a sexual dysfunction, erectile dysfunction, ejaculatory dysfunction, hypoactive sexual desire disorder, psychiatric disorder, neurological disorder, which comprises administration of:
10 a compound as defined in any one of claims 1, 2 or 5 to 9, or a hydrate thereof, a hydrate as defined in any one of claims 3, 4, 8 or 9, a spray-dried composition as defined in any one of claims 10 to 20, or a pharmaceutical formulation as defined in any one of claims 21 to 26, or
15 a compound of Formula Ib as defined in claim 10, or a hydrate thereof to a patient in need thereof.

33. The method according to claim 32, wherein the dysfunction and/or disorder comprises erectile dysfunction and/or premature ejaculation.

20

34. A method for preparing a compound of Formula IIb:



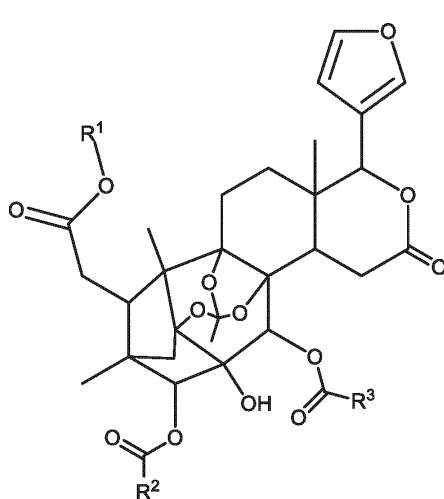
Formula IIb

or a hydrate thereof,

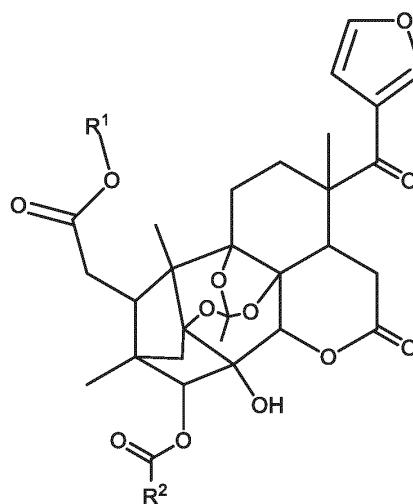
wherein R^1 and R^2 independently are C_1 - C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I,

said method comprising the steps of:

- 5 a) providing a mixture comprising a compound of Formula IIa and optionally a compound of Formula IIb:



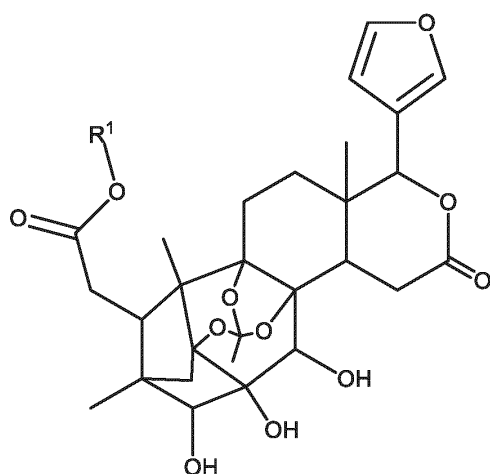
Formula IIa



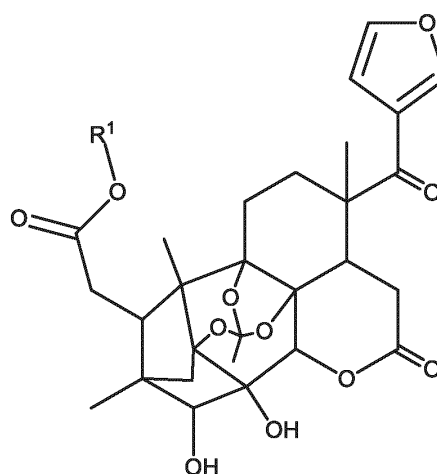
Formula IIb

wherein R^1 , R^2 and R^3 independently are C_1 - C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of OH, Cl, Br, F and I;

- 10 b) subjecting the compound of Formula IIa and optionally the compound of Formula IIb of step a) to an alkoxide of Formula $R^1O^-M^+$, an alcohol of Formula R^1OH , wherein R^1 is as defined for the compound of Formula IIa and/or the compound of Formula IIb and M^+ is a metal cation such as Li^+ , Na^+ or K^+ , and
- 15 an aqueous acid thereby providing a compound of Formula Ia and/or a compound of Formula Ib:

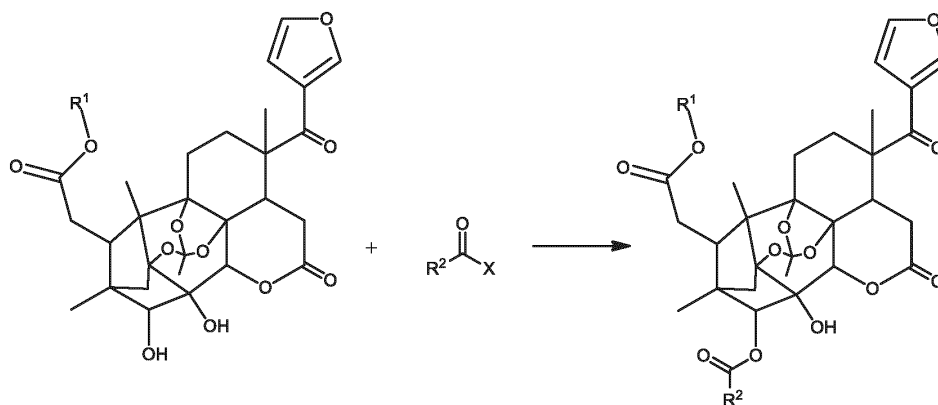


Formula Ia



Formula Ib,

- c) separating the compound of Formula Ia from the compound of Formula Ib,
 d) optionally converting the compound of Formula Ia into a compound of Formula Ib,
 e) reacting the compound of Formula Ib with a compound of Formula X, optionally in the presence of an ester forming promoting agent such as a coupling reagent, to provide the compound of Formula IIb:



Formula Ib

Formula X

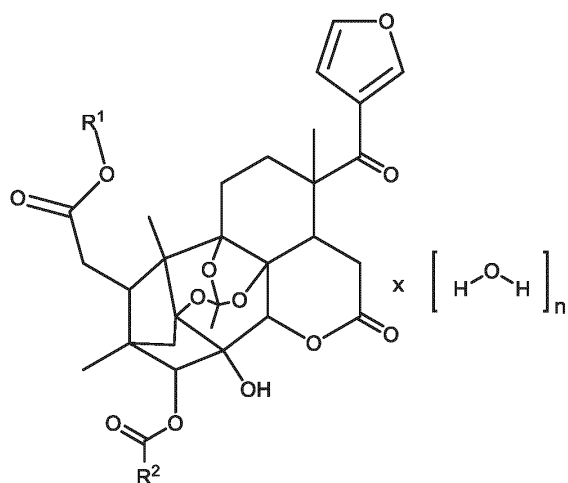
Formula IIb

wherein

R^2 in the compound of Formula X is as defined for the compound of Formula IIa and/or the compound of Formula IIb, and

X is selected from the group consisting of OH, halide such as Cl and $OC(O)CH(CH_3)_2$, and

- f) optionally combining the compound of Formula IIb with water to provide a hydrate of Formula VI:

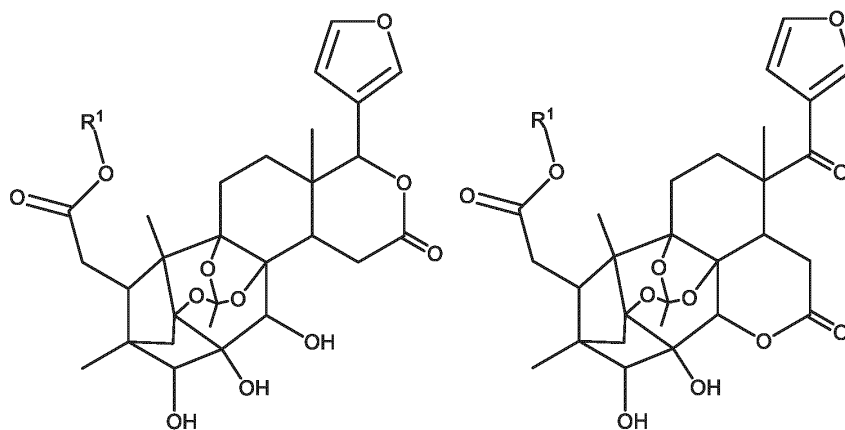


Formula VI

said hydrate being a combination of the compound of Formula IIb and water taken in a ratio of 1:n, wherein n has a value from 0.5 to 100 such as 1.

5

35. A method for converting a compound of Formula Ia into a compound of Formula Ib:



Formula Ia

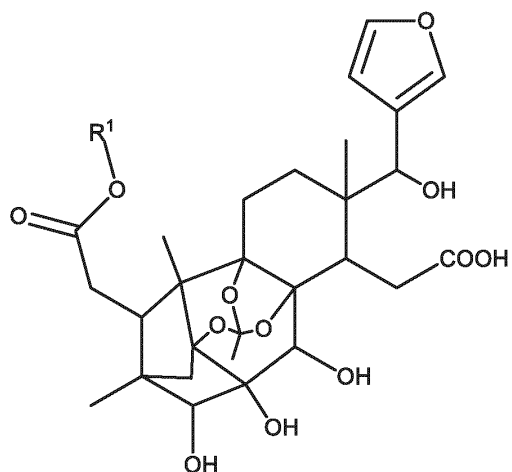
Formula Ib

10

wherein R¹ is C₁-C₆alkyl optionally substituted with one or more substituents selected from OH, Cl, Br, F and I,

said method comprising the steps of:

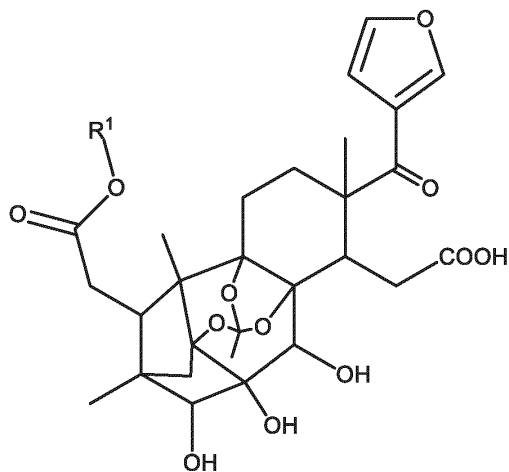
- a) subjecting the compound of Formula Ia to lactone ring opening conditions thereby providing a compound of Formula III:



Formula III

wherein R¹ is as defined for the compound of Formula Ia,

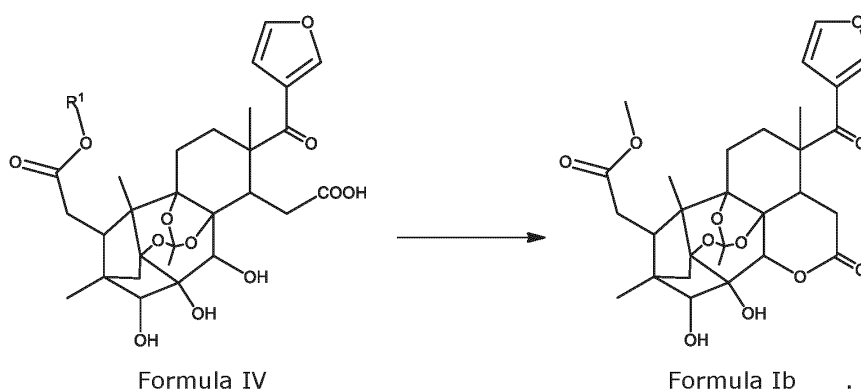
b) oxidizing the compound of Formula III into a compound of Formula IV:



Formula IV

wherein R¹ is as defined for the compound of Formula Ia,

c) reacting the carboxylic acid of the compound of Formula IV with the hydroxy group at carbon 30 thereby providing the compound of Formula Ib:



36. The method according to claim 35, wherein the compound of Formula Ia is provided by steps a), b) and c) of claim 34.

37. The method according to claim 35, wherein step a) comprises a base such as barium hydroxide, such as barium hydroxide octahydrate, in the presence of a solvent such as methanol, and/or step b) comprises an oxidizing agent such as Dess Martin periodinane, and/or step c) comprises a coupling agent such as coupling agent comprising a carbodiimide, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide or a HCl salt thereof in the presence of a sterically hindered base such as N,N-diisopropylethyleamine.

38. The method according to claim 34, wherein step d) is present and performed in accordance with claim 35 and/or 37.

39. The method according to any one of claims 34-38, wherein
 R^1 is methyl, and/or
 R^2 and R^3 independently are methyl, ethyl or isobutyl.

40. The method according to any one of claims 34-39, wherein
 R^1 is methyl,
 R^2 is isopropyl, and
 R^3 , if present, is ethyl or isopropyl.

41. The method according to any one of claims 34-40, wherein the compound of Formula IIa comprises phragmalin 3,30-diisobutyrate and/or phragmalin 3-isobutyrate-30-propionate.

42. The method according to any one of claims 34-41, wherein the compound of Formula IIa, the compound of Formula IIb or a mixture thereof is provided by a plant or a plant material selected from the Meliaceae family such as a plant or plant material selected from the group consisting of *Xylocarpus granatum*, *Khaya senegalensis*, *Xylocarpus moluccensis*, *Pseudocedrela kotschyi*, *Swietenia macrophylla*, *Neobeugea mahafalensis*, *Chukrasia tabularis*, *Entandrophragma caudatum* and any combination thereof.
43. The method according to claim 42, wherein the plant or plant material comprises *Entandrophragma caudatum* or seeds thereof.
44. The method according to claim 42 or 43, wherein the compound of Formula IIa, the compound of Formula IIb or a mixture thereof is provided by an extract from *Entandrophragma caudatum* seeds.
45. A method for preparing a spray-dried pharmaceutical composition as defined in any one of claims 10-20, said method comprising spray-drying a solution comprising a compound as defined in any one of claims 1, 2, 5 to 7 or 9, or a hydrate thereof, or a hydrate as defined in any one of claims 3, 4 or 9, or a compound of Formula Ib as defined in claim 10, or a hydrate thereof, along with said excipients that are suitable for spray-drying.
46. The method according to claim 45, comprising the steps of:
- a) providing a spray drier with a solution comprising said compound or hydrate and said excipients, as well as a solvent system comprising at least two polar solvents, of which at least one of said polar solvents is miscible with water and at least one solvent is aprotic and non-miscible with water; and
 - b) spray drying the solution of step a).
47. The method according to claim 46, comprising the additional step of dissolving said compound or hydrate in said solvent non-miscible with water and dissolving said excipient in said solvent miscible with water and mixing to provide the solution for the spray-drier.
48. The method according to any one of claims 46 or 47, wherein the non-water miscible polar aprotic solvent of the solvent system optionally is halogenated.

49. The method according to any one of claims 46-48, wherein the non-water miscible polar aprotic solvent of the solvent system is dichloromethane.
50. The method according to any one of claims 46-49, wherein the water miscible polar solvent is selected from polar aprotic and protic solvents, preferably methanol and/or acetone.
51. The method according to any one of claims 46-50, wherein the water miscible polar solvent and the non-water miscible polar aprotic solvent are mixed in a ratio from about 1:5 to about 5:1, such as about 1:4 to about 4:1, about 1:3 to about 3:1, about 1:2 to about 2:1 or about 1:1.