CHEMICAL COMPOUNDS

Field of the Invention

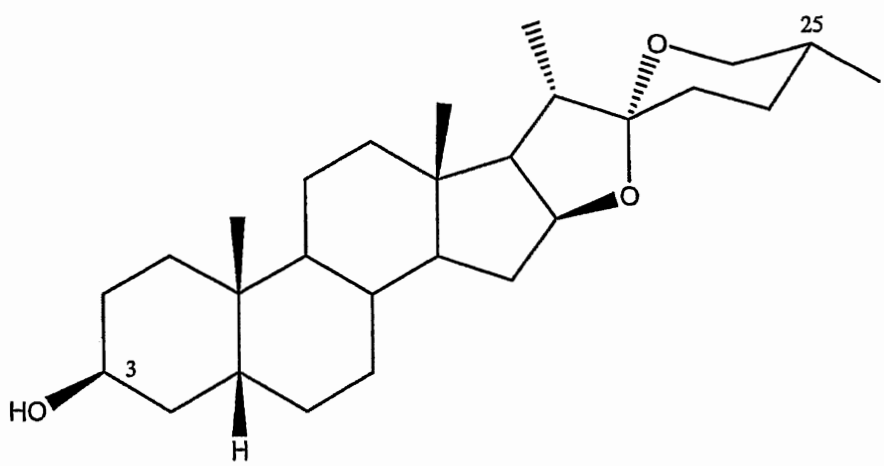
The present invention relates to novel amorphous and crystalline forms of smilagenin and its hydrates.

Background to the Invention

It is well established that some organic compounds can crystallise in a number of different polymorphic forms or crystal habits, which may comprise the compound as such, solvates of the compound, hydrates of the compound, or combinations thereof. Alternatively, the compound, solvate or hydrate may precipitate as an amorphous solid.

The stability and bioavailability of the drug product may vary according to the polymorphic form present. The choice of crystal form is thus a critical aspect of drug development (Brittain, *Pharm. Tech.* pp. 50-52, 1994; Yu *et al.*, *Pharm. Sci. Technol. Today,* **1**, pp. 118 to 127, 1998; Byrn *et al.*, *Chem. Mater.* **6**, pp. 1148 to 1158, 1994; Byrn *et al.*, *Pharm. Res.* , **12**, pp. 945 to 954, 1995; Henk *et al.*, *Pharm. Ind.* **59**, pp. 165 to 169, 1997).

Smilagenin is an A/B-*cis* steroidal sapogenin having the formula:



Smilagenin and its derivatives have been identified as valuable therapeutic agents in human and veterinary medicine and in non-therapeutic human and non-human animal treatments. See, for example, US Patent No. 3890438 (use of smilagenin and certain 4-substituted phenoxyisobutyric acid compounds against high blood cholesterol levels); US Patent No. 4680289 (use of smilagenin against obesity and diabetes obesity syndromes); US Patent No. 6258386 (use of smilagenin against cognitive dysfunction and allied conditions); WO-A-01/23406, WO-A-01/23407, WO-A-01/23408, and WO-A-01/49703 (use of smilagenin derivatives against cognitive dysfunction and allied conditions); and WO-A-02/079221 and WO-A-03/082893 (use of smilagenin and derivatives thereof against non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration and loss of receptor function in the absence of cognitive, neural or neuromuscular impairment).

In a key article (Marker *et al.*, *J. Am. Chem. Soc.* **65**, pp. 1199 to 1209, 1943, at p. 1207), it was reported that smilagenin acetate shows polymorphic forms melting at 110, 130 and 152 °C. The melting point of smilagenin from a number of sources was always in the range 183-185°C. However, the recrystallisation solvent was not stated and the article made no mention of polymorphic forms of smilagenin.

In *J. Am. Chem. Soc.* pp. 2525 to 2532, 1940, Marker *et al.* reported a melting point of 183-185°C for smilagenin crystallised from alcohol.

In *J. Am. Chem. Soc.* **64**, pp. 818 to 822, 1942, Marker *et al.* reported a melting point of 178-180°C for smilagenin crystallised from acetone.

Askew *et al.* reported that fractional crystallisation of smilagenin from acetone gave long silky needles with a melting point of 183-184°C. It was further reported that smilagenin appeared to form a hydrate when crystallised from methanol (Askew *et al.*, *J. Chem. Soc.* pp. 1399 to 1403, 1936). However, no evidence was provided to support this observation, and the reader was merely referred back to an earlier paper on a related compound (Power *et al.*, *J. Chem. Soc.*, **105**, pp. 201 to 219, 1914).

Scheer *et al.* crystallised smilagenin from aqueous ethanol and observed a melting point of 187-188°C, but made no mention of the formation of a hydrate (Scheer *et al.*, *J. Am. Chem. Soc.*, 77, pp. 641 to 646, 1955).

In *J. Am. Chem. Soc.*, 77, pp. 3086 to 3089, 1955, Wall *et al.* commented that the best samples of smilagenin from natural sources had a melting point of 188-189°C, whereas acetone or aqueous acetone failed to bring the melting point above 182-185°C on samples generated by isomerization of sarsasapogenin. Again, no mention was made of hydrate formation. The infra-red (IR) spectra of the synthetic and natural materials were identical. However, the X-ray powder diffraction (XRPD) patterns were not. These differences were not attributed to polymorphism, and the XRPD patterns were not presented. The authors concluded that there was a pronounced effect of traces of sarsasapogenin on certain properties of smilagenin that depend on crystal structure.

Wall *et al.*, (*J. Biol. Chem.*, **198**, pp. 533 to 543, 1952) reported the melting point of smilagenin to be 184°C. However, the recrystallisation solvent was not stated. The paper reported that the use of a Kofler microscopic melting point apparatus having polarizing disks allowed for the crystal form or habit to be observed. No mention was made of polymorphism but the impact of impurities upon the melting point was noted. In *J. Am. Chem. Soc.*, 77, pp. 1230 to 1237, 1954, Wall *et al.* reported the melting point of smilagenin to be 183°C.

Callow *et al.* (*J. Am. Chem. Soc.* 77, p. 1672, 1955) described the recrystallisation of smilagenin from acetone to yield crystals having melting point 157-160 °C.

Parsons *et al.* (*Henry Ford Hosp. Med. Bull.*, **12**, pp. 87 to 120, 1964) described a specific crystalline form of smilagenin by XRPD. From the data presented it cannot be concluded that this form corresponds to any of the forms described herein.

In US Patent No. 3169959 (1965), a melting point of 178-180°C was reported for smilagenin crystallised from heptane.

In *Phytochemistry*, **8**, pp. 1523 to 1531, 1969, Blunden *et al.* reported a melting point of 181-182°C for smilagenin crystallised from acetone.

In *J. Nat. Prod.*, **44**, pp. 441 to 447, 1981, Blunden *et al.* reported a melting point of 186°C for smilagenin crystallised from acetone.

The use of crystalline intermediate complexes to assist the extraction of relatively pure smilagenin and other sapogenins from their plant sources has been proposed. Thus, for example, US Patent No. 5017562 described a crystalline saponin-containing complex, derived from the saponin-containing plants *Agave*, *Yucca*, *Dioscorea*, *Quillaja*, *Medicago* and *Cyamopsis*, which is substantially free of fats and non-saponin carbohydrates and which, on hydrolysis, can yield smilagenin and other sapogenins.

The prior art publications acknowledged above are incorporated herein by reference.

Depending on the administration route desired in the therapy, it may be desirable to improve or at least control the stability and water solubility of the smilagenin, to obtain a desired bioavailability profile. Furthermore, it can assist the manufacturing or purification process if the stability and water solubility of the smilagenin can be controlled.

In principle, the water solubility of polymorphic forms of an organic compound is not necessarily the same for all forms. Therefore, the use of specific crystalline forms or habits can offer useful control of the water solubility. In the case of sparingly water-soluble compounds such as smilagenin, even a slight adjustment to the water-solubility by means of an adjustment to the polymorphic form can offer useful processing or biological advantages.

We have examined commercially available smilagenin and have found that it occurs in a specific crystalline form, which we have characterised as form II.

Figure 1 of the accompanying drawings shows an XRPD pattern obtained at $\lambda = 1.5406$ Angstroms from a sample of commercially available smilagenin obtained from Research Plus, Inc. This is an example of form II crystalline smilagenin. The intensities of the XRPD pattern for this crystalline form in the 2-theta range 5 to 50 degrees are shown in Table A below, in the column headed "Form II". These data are the intensities at regularly spaced 2-theta values, and are to be used in conjunction with the Figure of the drawings. From these data, the d-spacings may readily be calculated using the Bragg equation. For present purposes, the approximately 20 strongest peaks may generally be considered characteristic of the crystalline form, subject however to standard practice in crystallography.

The present invention is based on our surprising finding that at least three further crystalline forms of smilagenin exist, two of which appear typically to be anhydrous and have been characterised as form I and form III. We have further found that form III can exist in at least one variant form in which the crystal structure is modified ("form IIIA") and/or the hydration level is modified (smilagenin hemihydrate or smilagenin dihydrate). Furthermore, we have surprisingly found that smilagenin can form a crystalline monohydrate. We have characterised the typical crystalline form of this monohydrate as form V. Furthermore, we have surprisingly found that smilagenin can form a crystalline channel hydrate having variable smilagenin:water stoichiometry. We have characterised the typical crystalline form of this channel hydrate as form VI. It has also been found that smilagenin can be obtained in a non-crystalline form (the "amorphous form"). The prior art does not describe any amorphous form of smilagenin.

Furthermore, we have identified a crystalline solvate of smilagenin formed with *iso*-propyl alcohol. We have characterised the typical crystalline form of this *iso*-propyl alcohol solvate as form VII.

Surprisingly, we have found that form II of smilagenin can be converted to the monohydrate by a solvent mediated transformation in hexane or heptane. Further, we have found that the monohydrate may be obtained by other processes, including solvent mediated transformations in aqueous acetone, aqueous tetrahydrofuran and aqueous

ethanol. The water content was determined by Karl Fischer analysis was found to be in the range about 3 to 6% w/w. Analysis by thermogravimetric analysis (TGA) confirms a water weight in the region of 4%.

Furthermore, we have found methods of controlling the transitions between not only the novel amorphous and crystalline forms but between them and the known form II, by controlling the organic solvent used for recrystallisation.

Surprisingly, and advantageously, we have found that precipitation or crystallisation of smilagenin from certain organic solvents does not result in organic solvates of smilagenin. However, the *iso*-propyl alcohol solvate (believed to be a hemi-solvate) can be obtained under certain circumstances, and is a newly recognised material.

These novel forms of smilagenin and associated methods therefore offer enhanced control of the preparation of pharmaceutical or edible grade smilagenin, and the possibility of preparing pharmaceutical or edible grade smilagenin with improved delivery and bioavailability characteristics.

Brief Description of the Invention

According to a first aspect of the present invention, there is provided smilagenin in any one or more of crystalline forms I, III, IIIA, V, VI and VII as defined herein.

According to an example of this first aspect of the present invention, there is provided smilagenin in any one or more of crystalline forms I, III, IIIA and V as defined herein.

According to a second aspect of the present invention, there is provided smilagenin hemihydrate, optionally in crystalline form.

According to a third aspect of the present invention, there is provided smilagenin monohydrate, optionally in crystalline form.

According to a fourth aspect of the present invention, there is provided smilagenin dihydrate, optionally in crystalline form.

According to a fifth aspect of the present invention, there is provided smilagenin channel hydrate, optionally in crystalline form.

According to a sixth aspect of the present invention, there is provided amorphous smilagenin.

According to a seventh aspect of the present invention, there is provided smilagenin *iso*-propyl alcohol solvate, optionally in crystalline form. This material may be prepared by precipitation from a solution of relatively impure smilagenin in *iso*-propyl alcohol that has been reduced in volume by azeotropic distillation.

According to an eighth aspect of the present invention, there is provided crystalline pharmaceutical or edible grade anhydrous unsolvated smilagenin, when obtained by crystallisation from a solution of substantially pure smilagenin *iso*-propyl alcohol (IPA) solvate in an anhydrous IPA-compatible organic solvent which does not form a solvate with smilagenin, such as acetone. The smilagenin may be in crystalline form I or III as defined herein.

The crystalline or amorphous material of the present invention may be present substantially free of other forms of smilagenin and/or substantially free of other steroidal sapogenins and/or steroidal saponins.

The crystalline or amorphous material of the present invention may preferably be present in at least about 50% by weight pure form, for example at least about 70% by weight pure form, for example at least about 80% by weight pure form, for example at least about 85% by weight pure form, for example at least about 90% by weight pure form, for example at least about 95% by weight pure form, for example at least about 97% by weight pure form, for example at least about 98% by weight pure form.

Any of the materials according to the present invention may if desired be present in admixture with one or more other materials according to the present invention, another form of smilagenin, any other biologically active material, any biologically inactive material, or any combination thereof. The said other form of smilagenin, when present, may be crystalline form II.

The novel forms of smilagenin provided by the present invention possess a number of advantages over the known form, particularly in terms of their stability and handling characteristics. These advantages are applicable to one or more of the manufacturing, purification, formulation and storage phases of the marketed smilagenin compositions and/or to the delivery of the smilagenin from the composition to the human or non-human animal patient for achieving the desired pharmacological effect.

The present invention also provides methods for preparing the materials of the present invention, preferably by precipitation of smilagenin from a solution of smilagenin in an appropriate organic solvent or solvent mixture or by other crystallisation of smilagenin in an appropriate organic solvent or solvent mixture, optionally in the presence of water, as well as medicaments, foodstuffs and beverages containing the said materials, methods of preparing the medicaments, foodstuffs and beverages, uses of the said materials in the preparation of the medicaments, foodstuffs and beverages, and uses of the medicaments, foodstuffs and beverages in human and veterinary medicine and in non-therapeutic human and non-human animal treatments.

The present invention further provides a process for obtaining pharmaceutical or edible grade smilagenin or a derivative thereof, wherein at least one step of the process includes preparing smilagenin in one or more of the forms according to the present invention. The smilagenin may be prepared in any suitable level of hydration and in any suitable physical form, for example as an isolated dry solid or in a liquid medium such as a crystal slurry.

The resultant pharmaceutical or edible grade smilagenin or derivative thereof may be subsequently formulated into a suitable medicament, foodstuff or beverage form.

The present invention further provides methods of adjusting the crystalline form of smilagenin between the forms I, II, III, IIIA, V, VI and VII (for example between the forms I, II, III, IIIA and V), methods of adjusting the form of smilagenin between its amorphous and crystalline forms, methods of adjusting the hydration level of smilagenin, methods of forming the *iso*-propyl alcohol solvate of smilagenin and methods of adjusting the form of smilagenin between two or more of the hydrated, solvated and unhydrated and unsolvated forms.

The terms "crystallise", "recrystallise" and the like, used herein, refer to all methods suitable for forming a desired crystal form or habit or mixture or other combination thereof, and are not limiting. For example, crystal slurrying, crystal precipitation, and other solvent mediated crystal transformation, with or without seeding and/or nucleation, are all encompassed by the terms "crystallise", "recrystallise" and the like as used herein.

The materials according to the present invention may therefore conveniently be present in substantially pure isolated form. The materials may suitably be prepared on a kilogram scale.

Detailed Description of the Invention

Crystalline Form I

The term "crystalline form I" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figure 2 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 5 to 50 degrees may generally be considered

characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 5 to 50 degrees are shown in Table A below, in the column headed "Form I". These data are the intensities at regularly spaced 2-theta values, and are to be used in conjunction with the Figure of the drawings. From these data, the d-spacings may readily be calculated using the Bragg equation.

The form I material can be prepared by recrystallisation of commercially available smilagenin from acetone. Alternatively, the form I material can be prepared by a solvent mediated transformation of form II or form III material in acetone, or more preferably in acetonitrile.

Karl Fischer analysis, differential scanning calorimetry and thermogravimetric analysis confirmed that the crystal form I that we have obtained is neither hydrated nor solvated.

Crystalline Form II

The term "crystalline form II" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figure 1 of the accompanying drawings (λ = 1.5406 Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 5 to 50 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 5 to 50 degrees are shown in Table A below, in the column headed "Form II". These data are

the intensities at regularly spaced 2-theta values, and are to be used in conjunction with the Figure of the drawings. From these data, the d-spacings may readily be calculated using the Bragg equation.

The form II material was commercially available smilagenin obtained from Research Plus, Inc.

Differential scanning calorimetry (DSC), TGA, residual solvent and Karl Fischer analysis confirmed that the material was neither hydrated nor solvated.

Crystalline Form III

The term "crystalline form III" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figure 3 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 5 to 50 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 5 to 50 degrees are shown in Table A below, in the column headed "Form III". These data are the intensities at regularly spaced 2-theta values, and are to be used in conjunction with the Figure of the drawings. From these data, the d-spacings may readily be calculated using the Bragg equation.

The form III material may be prepared by solvent mediated transformation of commercially available smilagenin using methyl *t*-butyl ether, acetone, methyl *iso*-butyl ketone, ethyl acetate, *iso*-propyl acetate and toluene.

Solvent mediated transformations of commercially available smilagenin using butanone or from 50% aqueous ethanol yielded a mixture of crystal forms III and V.

These data show that crystal form II can be converted into form III by solvent mediated transformations using a range of solvents.

Karl Fischer analysis, differential scanning calorimetry and thermogravimetric analysis confirmed that the crystal form III that we have obtained is neither hydrated nor solvated.

Crystalline Form IIIA

The term "crystalline form IIIA" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figure 4 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 5 to 50 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The d-spacings may readily be calculated from the information in Figure 4, using the Bragg equation.

The form IIIA material may be prepared by a solvent mediated transformation of commercially available smilagenin using dimethylformamide.

Crystalline Form V

The term "crystalline form V" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figure 5 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 5 to 50 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 5 to 50 degrees are shown in Table A below, in the column headed "Form V". From this data, the d-spacings may readily be calculated using the Bragg equation.

The form V material may be prepared in relatively pure form by recrystallisation of commercially available smilagenin from ethanol, tetrahydrofuran, hexane or aqueous acetone. The acetone/water proportions in the aqueous acetone may vary widely, for example from about 0.5:1 (by volume) to about 25:1 (by volume), for example from about 1:1 (by volume) to about 20:1 (by volume), for example from about 2:1 (by volume) to about 19:1 (by volume),

A solvent mediated transformation of commercially available smilagenin in butanone or in 50% aqueous ethanol yielded a mixture of crystal forms III and V.

A solvent mediated transformation of commercially available smilagenin in dichloromethane yielded a mixture of crystal forms II and V.

Solvent mediated transformations in aqueous acetone, aqueous tetrahydrofuran or aqueous ethanol all yield crystal form V (monohydrate). In each case the proportions of

water to solvent in the medium can vary widely. The purity of the resultant crystalline material appears to be higher when aqueous acetone is used, in comparison with the alternative media.

Karl Fischer analysis, DSC (Figure 6) and TGA (Figure 7) confirmed that the crystal form V that we have obtained is a monohydrate of smilagenin.

Crystalline Form VI

The term "crystalline form VI" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figures 8 and 15 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 2 to 28 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 2 to 28 degrees can be obtained from Figures 8 and 15. The 2θ and d-spacings for the significant peaks, and the intensities of the significant peaks relative to the strongest peak, are given in Table B.

The form VI material may be prepared in relatively pure form by recrystallisation of commercially available smilagenin from methanol.

DSC (Figure 9), TGA (Figure 10) and vapour sorption (Figure 11) analysis suggest that the crystal form VI that we have obtained is a channel hydrate of smilagenin exhibiting variable smilagenin:water stoichiometry and the potential to form channel solvates with solvents having appropriately sized molecules. As is well known, a channel hydrate is

a hydrate in which the crystal lattice of the molecule forms a channel or cage enclosing a void which can wholly or partially accommodate water (or solvent) molecules. The stoichiometric (molar) ratio of smilagenin:water at any particular time will depend on such factors as the humidity of the surrounding atmosphere, as the water molecules are generally free to enter or leave the void.

Crystalline Form VII

The term "crystalline form VII" used herein means that crystalline form of smilagenin which has an XRPD pattern substantially as shown in Figures 12 and 16 of the accompanying drawings ($\lambda = 1.5406$ Angstroms).

The expression "an XRPD pattern substantially as shown" as used herein refers particularly to any XRPD pattern having 2-theta or d-spacing peaks corresponding to the diagnostic peaks of the Figure. For present purposes, the approximately 20 strongest peaks in the 2-theta range 2 to 28 degrees may generally be considered characteristic or diagnostic of the crystalline form, subject however to standard practice in crystallography.

The intensities of the XRPD peaks for this crystalline form in the 2-theta range 2 to 28 degrees can be obtained from Figures 12 and 16. The 2θ and d-spacings for the significant peaks, and the intensities of the significant peaks relative to the strongest peak, are given in Table C.

The form VII material may be prepared in relatively pure form by crystallisation of smilagenin from *iso*-propyl alcohol (IPA). The material may subsequently be aged if desired (e.g. at ambient temperature and e.g. for a period of at least about 24 hours, for example at least about 48 hours). If desired, the form VII material may be subsequently recrystallised from acetone to afford anhydrous unsolvated smilagenin in substantially pure form.

DSC (Figure 13) and TGA (Figure 14) indicate that the crystal form VII that we have obtained is a hemi-IPA solvate of smilagenin.

The form VII material is potentially important as an intermediate in the purification of smilagenin to produce pharmaceutical or edible grade smilagenin. Without wishing to be bound by theory, it is believed that a solution of relatively impure smilagenin in *iso*-propyl alcohol is especially convenient for being azeotropically distilled in order to efficiently remove water from the solution. The IPA solvate of smilagenin which is precipitated from the reduced solution after the said distillation can conveniently be recrystallised as pharmaceutical or edible grade anhydrous unsolvated smilagenin using an anhydrous IPA-compatible organic solvent such as acetone, which does not form a solvate with smilagenin.

Therefore, in one particular embodiment, the form VII material may be in substantially pure isolated, preferably dry, form and prepared by precipitation from a solution of relatively impure smilagenin in *iso*-propanol, which solution has preferably previously undergone distillation to reduce its volume and remove water or other impurities. Most preferably, the process by which the form VII material is made is conducted on an industrial scale (obtaining at least kilogram quantities of the form VII material). Preferably, anhydrous unsolvated smilagenin is subsequently recrystallised in pharmaceutical or edible grade from the said form VII material using an anhydrous IPA-compatible organic solvent such as acetone, which does not form a solvate with smilagenin. It is further preferred that at no stage in the preparation or purification of the smilagenin, including the stage of formation of any form VII material or other intermediate form of smilagenin, is it necessary (or done) to remove water from the smilagenin, or from any mixture containing it, using a solid hygroscopic material such as magnesium sulphate.

Examples 2, 6 and 7 of WO-A-2004/037845 describe certain laboratory scale batchwise procedures for purifying smilagenin via recrystallisation from *iso*-propyl alcohol (2-propanol). However, in none of these Examples is it stated that the precipitated material is an IPA solvate of smilagenin, let alone a hemi-IPA solvate. To the extent that it may

be necessary in any jurisdiction to exclude the disclosures of those examples and subject-matter that is obvious therefrom from the scope of protection for the form VII material, processes for its preparation, and uses thereof, such disclosures – and especially the disclosures of the purification of the initial impure smilagenin using *iso*-propyl alcohol - are hereby disclaimed from the present application. In particular, in such jurisdictions the form VII material according to the present invention may comprise the form VII material in substantially pure isolated form prepared on a kilogram scale. As mentioned above, this material is precipitated from the reduced IPA solution after azeotropic distillation and can conveniently be recrystallised as pharmaceutical or edible grade anhydrous unsolvated smilagenin (e.g. in form I or form III, e.g. in substantially pure isolated form prepared on a kilogram scale) using an anhydrous IPA-compatible organic solvent such as acetone, which does not form a solvate with smilagenin.

Amorphous Form

The amorphous form is non-crystalline. We have found that amorphous smilagenin appears to have potentially useful water-solubility and stability with respect to conversion to a crystal form. These characteristics offer improved manufacture, formulation, storage and bioavailability of smilagenin in comparison with the prior art crystalline form.

The amorphous smilagenin we have prepared has an XRPD pattern which shows no peaks that would be characteristic of any crystalline structure.

Derivatives

The term "derivatives" used herein refers particularly to the compounds defined and described in the prior art patent documents acknowledged above in relation to the known biological activities of smilagenin (US Patent No. 3890438; US Patent No. 4680289; US Patent No. 6258386; WO-A-01/23406; WO-A-01/23407; WO-A-01/23408; WO-A-01/49703; WO-A-02/079221; and WO-A-03/082893).

Such derivatives include pharmaceutically acceptable pro-drugs of smilagenin and pharmaceutically acceptable salts thereof.

Pro-drugs of smilagenin may especially include 3-position carboxylate esters such as the cathylate (ethoxycarbonyloxy), acetate, succinate, propionate, butyrate, valerate, isovalerate, caproate, isocaproate, diethylacetate, octanoate, decanoate, laurate, myristate, palmitate, stearate, benzoate, phenylacetate, phenylpropionate, cinnamate, p-nitrobenzoyloxy, 3,5-dinitrobenzoyloxy, p-chlorobenzoyloxy, 2,4-dichlorobenzoyloxy, p-bromobenzoyloxy, m-bromobenzoyloxy, p-methoxy-benzoyloxy, phthalyl, glycinate, alaninate, valinate, phenylalaninate, isoleucinate, methioninate, argininate, aspartate, cysteinate, glutaminate, histidinate, lysinate, prolinate, serinate, threoninate, tryptophanate, tyrosinate, fumarate and maleate esters.

"Pharmaceutically acceptable salts" means the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. See, for example S. M. Berge *et al.*, Pharmaceutical Salts, *J. Pharm. Sci.*, **66**: pp.1-19 (1977) which is incorporated herein by reference. Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Examples of suitable acid addition salts are those formed with acids selected from hydrochloric, sulphuric, phosphoric and nitric acids. Examples of suitable base addition salts are those formed with bases selected from sodium hydroxide, potassium hydroxide and ammonium hydroxide.

Medicaments, Foodstuffs, Food Supplements and Beverages

According to the invention, a composition may comprise a material as described above in admixture with one or more further component selected from: one or more other materials as described above, another form of smilagenin, any other biologically active material, and any biologically inactive material.

The composition may be prepared by a method comprising admixing a material as described above with one or more further component selected from: one or more other materials as described above, another form of smilagenin, any other biologically active material, and any biologically inactive material.

According to the invention, the material or the composition (e.g. the medicament, foodstuff, food supplement or beverage) may be used for the treatment of a condition selected from: high blood cholesterol levels, obesity and diabetes obesity syndromes, cognitive dysfunction and allied conditions, non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration and loss of receptor function in the absence of cognitive, neural or neuromuscular impairment.

Still further, the invention therefore provides a method of treatment of a human or non-human animal (e.g. a human) suffering from, or susceptible to, a condition selected from: high blood cholesterol levels, obesity and diabetes obesity syndromes, cognitive dysfunction and allied conditions, non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration and loss of receptor function in the absence of cognitive, neural or neuromuscular impairment, which comprises administering to the said human or non-human animal an effective amount of a material or composition as described above.

The active agent prepared according to the present invention may thus be formulated into any suitable composition form for administration to a human or non-human animal patient. The composition may consist of the active agent alone or may include the active agent and any suitable additional component, such as one or more

pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

The composition may, for example, be a pharmaceutical composition (medicament), a foodstuff, food supplement or beverage.

The terms "foodstuff", "food supplement" and "beverage" used herein have the normal meanings for those terms, and are not restricted to pharmaceutical preparations. The appropriate pharmaceutical or edible grade of ingredients will be used, according to the desired composition form.

For further details of suitable composition forms and dosages, please refer to US Patent No. 3890438, US Patent No. 4680289; US Patent No. 6258386; WO-A-01/23406; WO-A-01/23407; WO-A-01/23408; WO-A-01/49703; WO-A-02/07922; and WO-A-03/082893.

Brief Description of the Drawings

In the accompanying drawings:

Figure 1 shows an XRPD pattern (λ = 1.5406 Angstroms) obtained from a sample of commercially available smilagenin in crystalline form II (prior art);

Figure 2 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form I;

Figure 3 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form III;

Figure 4 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form IIIA;

Figure 5 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form V;

Figure 6 shows a DSC trace of a sample of smilagenin in crystalline form V, shown to be a monohydrate;

Figure 7 shows a TGA of a sample of smilagenin in crystalline form V, shown to be a monohydrate;

Figure 8 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form VI (believed to be smilagenin channel hydrate);

Figure 9 shows a DSC trace of a sample of smilagenin in crystalline form VI;

Figure 10 shows a TGA of a sample of smilagenin in crystalline form VI;

Figure 11 shows a vapour sorption graph of a sample of smilagenin in crystalline form VI;

Figure 12 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin *iso*-propyl alcohol (IPA)-solvate in crystalline form VII;

Figure 13 shows a DSC trace of a sample of smilagenin IPA-solvate in crystalline form VII;

Figure 14 shows a TGA of a sample of smilagenin IPA-solvate in crystalline form VII, shown to be a hemi-IPA-solvate;

Figure 15 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin in crystalline form VI, with significant peaks marked by arrows; and

Figure 16 shows an XRPD pattern (λ = 1.5406 Angstroms) of a sample of smilagenin IPA-solvate in crystalline form VII, with significant peaks are marked by arrows.

Examples and Detailed Description of the Drawings

The following non-limiting Examples are provided as further illustration of the present invention, but without limitation, and are discussed with reference to the drawings.

Starting Materials

Samples of commercially available smilagenin were purchased from Research Plus Inc and Steraloids Inc.

The samples were analysed by XRPD and defined as form II by our nomenclature. A sample from Research Plus was examined by DSC and TGA and found to be anhydrous.

Example 1

Crystalline Form I

A. Crystallisation from Acetone

Smilagenin (10.0 g) was suspended in acetone (250 ml) and the mixture heated to reflux. The resultant solution was decanted from some undissolved solids and reheated to reflux to afford a clear solution. The solution was allowed to cool over about 3.5 hours to 29°C and further cooled with an ice/water batch to 2°C. The resultant solid was harvested by filtration, washed with cold (5°C) acetone (50 ml) and dried in a vacuum oven for 3 days to afford 7.4 g of pure smilagenin, which was characterised by XRPD as form I under our nomenclature.

B. Crystallisation from Acetonitrile

A suspension of smilagenin (1.05 g) in acetonitrile (10 ml) was stirred at ambient temperature overnight. The solid was harvested by filtration and dried in a vacuum oven at 80°C to afford smilagenin form I (0.92 g, 88% yield).

Example 2

Crystalline Form II

Smilagenin was manufactured by stereospecific reduction of diosgenin according to the process described in PCT Patent Application No. PCT/GB2003/001780 (WO-A-2004/037845).

The smilagenin was subjected to XRPD and the pattern was found to be substantially similar to that shown in Figure 1 of the drawings. On this basis, the material was characterised as form II under our nomenclature.

Examples 3 and 4

Crystalline Form III

Example 3

Smilagenin (10.0g) was suspended in acetone (250 ml) and the mixture heated to reflux. The resultant solution was cooled to 2°C over about 15 minutes and the solid harvested by filtration, washed with cold (5°C) acetone (250 ml) and dried in a vacuum oven for about 24 hours to afford 8.1 g of pure smilagenin, which was characterised by XRPD as form III under our nomenclature.

Example 4

Smilagenin (200 mg; form II) was suspended in tert-butyl methyl ether (4 ml) and stirred for about 48 hours. The solid was harvested by filtration and dried to afford 40 mg, which was characterised as form III under our nomenclature by XRPD, DSC and TGA.

Examples 5 to 9

Crystalline Form V

Example 5

Water (200 ml) was added to a suspension of smilagenin (20 g) in acetone (200 ml) and the mixture stirred for about 2 hours. The solid was harvested by filtration, dried in a vacuum oven at 40°C for about 24 hours to afford 20.5 g which was characterised by XRPD as form V under our nomenclature. The water content was determined as 4.4% by Karl Fischer analysis.

Example 6

Smilagenin (200 mg; form II) was suspended in hexane (10 ml) and stirred for about 48 hours. The solid was harvested by filtration and dried to afford 80 mg which was characterised as form V under our nomenclature by XRPD, DSC and TGA.

Example 7

Smilagenin (500 mg; form II) was suspended in tetrahydrofuran (2 ml) and stirred for about 48 hours. The solid was harvested by filtration and dried to afford 80 mg which was characterised as form V under our nomenclature by XRPD, DSC and TGA.

Examples 8 and 9

Smilagenin (Research Plus Inc.) was recrystallised using slurry crystallisation with butanone (Example 8) or 50% aqueous ethanol (Example 9) as the recrystallisation solvent. In each case the recrystallised material was subjected to XRPD and was characterised as a mixture of forms III and V under our nomenclature.

Example 10

Crystalline Form IIIA

Smilagenin (Research Plus Inc) was recrystallised using slurry crystallisation with dimethylformamide as the recrystallisation solvent.

The recrystallised material was subjected to XRPD and on this basis the material was characterised as crystalline form IIIA under our nomenclature.

Example 11

Crystalline Form VI (smilagenin channel hydrate)

Smilagenin (260 mg) was weighed into a round bottomed flask and methanol (10 ml) was added. The contents were heated to 70°C to affect complete dissolution, allowed to cool to room temperature and stirred at room temperature for 60 minutes. The solid was collected by filtration and air dried for about 2.5hours.

The X-ray powder diffraction pattern is shown in Figure 8, the differential scanning calorimetry trace is shown in Figure 9 and the thermogravimetric analysis is shown in Figure 10.

The DSC trace shows a weak broad endothermic transition up to 50°C, an exothermic transition at 120°C followed by a final high energy melting transition at 188°C. TGA

analysis confirms that the initial endotherm is associated with loss of water and that the transition at 121°C is not associated with any solvent loss. Analysis of the sample by Karl Fischer titration confirmed that the solvent was water.

Vapour sorption studies (see Figure 11) show that the sample is hygroscopic and adsorbs up to 9% water (about 2 mol. eq. water; i.e. a dihydrate) at high humidity and reversibly loses the water at low humidity. This suggests that this form is a channel hydrate of variable smilagenin:water stoichiometry, depending on the surrounding temperature and humidity.

Example 12

Crystalline Form VII (smilagenin IPA-solvate)

Smilagenin (150 mg) was added to *iso*-propyl alcohol (IPA) (5 ml) and the mixture heated to 70°C to ensure dissolution. The clear solution was then allowed to cool to 40°C over 2 hours, whereupon sudden precipitation occurred. The mixture was re-heated to 65°C to dissolve the material and the solution re-cooled to 45°C, held at 45°C for 15 minutes, cooled to 40°C, and held at 40°C for 2 hours. The slurry was then cooled to room temperature and aged over a weekend at room temperature. After this time the solid was collected by filtration and air dried for about 3 hours.

The X-ray powder diffraction pattern is shown in Figure 12, the differential scanning calorimetry trace is shown in Figure 13 and the thermogravimetric analysis is shown in Figure 14.

The DSC shows a broad endotherm between 40°C and 140°C that is consistent with loss of IPA from the sample. This is confirmed by TGA analysis which indicates 6.3% IPA present in the sample which is consistent with a hemi-IPA solvate of smilagenin. The IPA appears to be loosely bound in the crystal as it is lost from about 40°C upwards in the DSC.

Example 13

Amorphous smilagenin

Smilagenin (10 g) was heated to its melt using a temperature controlled heating mantle and held until a complete molten liquid was formed. The molten mass was poured into a Dewar containing approximately 150ml of liquid nitrogen. The sample was decanted into a glass beaker and the liquid nitrogen allowed to evaporate. The sample was then transferred to a glass vial, flushed with dry nitrogen and then sealed. The sample was characterised as amorphous smilagenin on the basis of the XRPD pattern, which showed a lack of significant diffraction lines.

TABLE A

XRPD Intensities for Smilagenin Crystal Forms I, II, III and V (λ = 1.5406 Angstroms) at regularly spaced intervals in the 2-theta Range 5 to 50 degrees

λ = 1.5406 Å	Degrees (2θ)	Form I	Form II	Form III	Form V
	5	225	174	384	231
	5.02	231	154	404	204
	5.04	231	159	384	193
	5.06	228	185	380	240
	5.08	225	177	365	199
	5.1	199	172	392	225
	5.12	210	202	365	188
	5.14	199	172	428	222
	5.16	213	188	392	207
	5.18	169	207	396	210
	5.2	185	164	357	213
	5.22	216	196	404	216
	5.24	174	185	350	193
	5.26	196	188	420	213
	5.28	156	177	396	213
	5.3	216	202	361	231
	5.32	185	180	396	202
	5.34	207	188	396	216
	5.36	207	202	372	234
	5.38	216	190	369	234
	5.4	228	185	400	216

5.42	188	193	369	231
5.44	185	193	365	207
5.46	190	228	342	246
5.48	196	222	376	228
5.5	246	207	372	256
5.52	193	199	458	262
5.54	202	216	346	279
5.56	202	185	357	262
5.58	222	228	361	339
5.6	196	262	350	306
5.62	210	219	369	335
5.64	202	279	357	353
5.66	207	250	365	372
5.68	199	256	324	404
5.7	204	256	346	392
5.72	199	256	372	484
5.74	204	282	350	520
5.76	210	335	392	511
5.78	222	317	380	620
5.8	231	412	353	756
5.82	210	441	357	864
5.84	190	458	353	1116
5.86	253	471	342	1347
5.88	222	471	388	1529
5.9	193	372	342	1731
5.92	193	174	365	1576
5.94	196	177	384	918
5.96	210	172	396	424
5.98	199	146	380	231
6	202	161	365	243
6.02	193	146	369	185
6.04	213	185	400	177
6.06	196	149	392	174
6.08	216	139	424	159
6.1	216	149	428	159
6.12	272	169	449	154
6.14	240	128	462	174
6.16	219	237	467	180
6.18	210	151	506	182
6.2	250	164	502	154
6.22	289	156	529	154
6.24	262	149	552	154
6.26	246	137	543	154
6.28	272	154	424	156
6.3	269	128	380	177
6.32	272	174	342	185
6.34	259	164	313	164
6.36	310	117	369	146
6.38	313	137	324	128

6.4	331	159	320	161
6.42	384	137	339	146
6.44	365	137	350	156
6.46	384	144	299	135
6.48	437	151	339	151
6.5	467	151	335	146
6.52	543	137	317	139
6.54	590	137	328	166
6.56	600	144	361	146
6.58	751	142	372	159
6.6	864	142	335	142
6.62	986	156	328	154
6.64	1116	156	346	169
6.66	1274	151	335	177
6.68	1274	135	396	137
6.7	1190	146	388	159
6.72	1183	159	328	151
6.74	1325	182	376	159
6.76	1747	123	412	132
6.78	2070	132	380	151
6.8	2470	137	365	159
6.82	3226	137	380	149
6.84	3192	149	441	135
6.86	4122	144	424	130
6.88	6906	149	416	180
6.9	6939	161	449	144
6.92	4638	166	506	164
6.94	2162	151	520	159
6.96	718	139	515	161
6.98	342	161	576	169
7	310	135	566	151
7.02	272	132	640	151
7.04	259	146	671	123
7.06	250	154	745	139
7.08	276	146	801	132
7.1	256	128	858	139
7.12	237	114	847	144
7.14	269	128	1076	154
7.16	266	144	1082	159
7.18	259	137	1190	132
7.2	246	139	1267	146
7.22	234	149	1225	146
7.24	225	130	1043	156
7.26	213	137	740	144
7.28	185	128	534	154
7.3	174	142	400	139
7.32	164	146	369	164
7.34	180	114	380	172
7.36	166	151	313	169

7.38	164	128	342	146
7.4	172	142	286	123
7.42	169	135	313	139
7.44	146	154	299	154
7.46	169	142	289	139
7.48	164	144	296	149
7.5	164	117	306	159
7.52	151	128	286	156
7.54	166	142	299	169
7.56	154	154	303	144
7.58	144	130	299	119
7.6	128	156	292	144
7.62	154	156	289	154
7.64	164	117	286	139
7.66	146	144	269	144
7.68	137	121	256	144
7.7	159	169	286	161
7.72	149	144	269	142
7.74	161	164	266	166
7.76	132	125	266	139
7.78	151	112	282	130
7.8	161	130	289	149
7.82	156	128	269	151
7.84	142	161	299	139
7.86	166	128	272	149
7.88	135	139	276	146
7.9	139	142	269	142
7.92	128	144	266	159
7.94	132	130	256	172
7.96	210	144	276	161
7.98	128	146	279	151
8	146	128	292	146
8.02	146	130	253	137
8.04	151	137	299	159
8.06	259	119	256	161
8.08	125	121	276	154
8.1	142	123	276	156
8.12	128	135	292	142
8.14	149	139	289	137
8.16	177	123	253	137
8.18	135	139	299	137
8.2	130	121	272	144
8.22	121	137	262	172
8.24	100	106	262	139
8.26	213	119	266	132
8.28	144	110	276	139
8.3	130	117	279	128
8.32	135	112	269	137
8.34	139	130	266	135

8.36	177	130	216	137
8.38	128	130	296	144
8.4	139	132	279	123
8.42	125	92	282	125
8.44	125	112	272	154
8.46	114	121	256	135
8.48	303	130	262	137
8.5	114	117	289	142
8.52	119	128	256	139
8.54	149	110	282	125
8.56	132	121	289	188
8.58	119	132	279	142
8.6	110	128	243	121
8.62	106	98	272	137
8.64	110	130	289	159
8.66	125	117	313	128
8.68	125	117	299	114
8.7	114	104	303	313
8.72	135	128	317	132
8.74	121	125	303	135
8.76	112	128	306	121
8.78	112	130	313	112
8.8	130	106	320	135
8.82	119	142	350	151
8.84	119	125	320	137
8.86	114	144	259	142
8.88	117	142	286	146
8.9	130	156	303	130
8.92	139	137	269	164
8.94	137	149	262	144
8.96	110	182	262	164
8.98	142	144	292	154
9	119	151	282	137
9.02	135	154	269	166
9.04	130	159	262	207
9.06	130	161	286	169
9.08	149	188	279	199
9.1	137	188	303	202
9.12	144	199	313	210
9.14	130	210	306	225
9.16	130	210	292	222
9.18	144	216	286	219
9.2	149	253	303	250
9.22	142	222	313	225
9.24	149	276	313	276
9.26	164	310	328	269
9.28	193	335	310	303
9.3	182	369	357	342
9.32	182	392	392	361

9.34	188	441	380	433
9.36	228	511	400	388
9.38	213	543	408	449
9.4	246	529	462	502
9.42	250	625	428	557
9.44	213	635	506	625
9.46	210	600	480	600
9.48	199	562	562	605
9.5	219	372	557	586
9.52	210	250	635	471
9.54	202	172	595	384
9.56	207	125	620	222
9.58	180	108	493	169
9.6	182	125	454	128
9.62	130	100	376	146
9.64	149	94	282	135
9.66	137	121	299	130
9.68	121	112	259	128
9.7	135	104	282	98
9.72	119	100	286	119
9.74	125	108	228	117
9.76	123	92	272	119
9.78	123	96	292	137
9.8	108	108	250	98
9.82	110	102	276	106
9.84	119	83	286	108
9.86	125	79	276	98
9.88	123	137	292	106
9.9	112	98	256	108
9.92	114	102	262	106
9.94	121	88	272	106
9.96	123	86	262	112
9.98	119	98	279	123
10	119	106	282	94
10.02	96	98	250	98
10.04	130	108	286	117
10.06	144	112	266	102
10.08	125	108	269	108
10.1	146	108	289	83
10.12	125	102	256	125
10.14	146	114	292	106
10.16	132	121	289	104
10.18	142	108	286	114
10.2	156	94	282	125
10.22	164	130	269	123
10.24	169	104	256	98
10.26	154	102	286	114
10.28	182	100	286	110
10.3	172	102	292	125

10.32	161	90	286	94
10.34	172	79	269	102
10.36	204	313	276	102
10.38	219	164	266	94
10.4	240	96	289	96
10.42	225	92	306	100
10.44	188	90	292	110
10.46	219	81	306	119
10.48	234	86	262	106
10.5	266	79	292	98
10.52	279	100	272	106
10.54	320	88	317	108
10.56	346	108	262	96
10.58	353	100	303	106
10.6	428	76	303	112
10.62	590	108	324	112
10.64	812	102	372	119
10.66	888	100	303	100
10.68	745	96	286	100
10.7	681	92	289	110
10.72	671	100	292	98
10.74	818	108	299	117
10.76	1050	102	339	108
10.78	1116	112	353	125
10.8	1005	96	357	137
10.82	853	92	384	144
10.84	812	110	437	132
10.86	484	94	376	139
10.88	328	96	420	104
10.9	250	121	437	161
10.92	256	102	433	154
10.94	289	121	408	144
10.96	269	135	458	172
10.98	335	132	506	172
11	339	142	552	144
11.02	372	137	515	185
11.04	303	161	586	207
11.06	213	135	640	190
11.08	144	185	666	240
11.1	128	177	708	234
11.12	202	188	708	306
11.14	112	199	713	292
11.16	119	228	724	328
11.18	110	199	676	317
11.2	119	237	620	396
11.22	125	253	557	408
11.24	112	225	467	400
11.26	132	204	420	433
11.28	130	204	365	445

11.3	130	231	365	441
11.32	132	237	324	350
11.34	123	207	328	433
11.36	125	276	324	441
11.38	139	246	289	493
11.4	139	310	320	506
11.42	149	276	296	610
11.44	146	346	342	645
11.46	154	350	310	708
11.48	139	372	331	824
11.5	169	445	335	955
11.52	161	488	306	1089
11.54	207	524	335	1225
11.56	204	610	335	1414
11.58	207	702	313	1544
11.6	237	756	324	1840
11.62	225	847	310	2200
11.64	296	992	313	2694
11.66	328	1239	328	3434
11.68	335	1521	335	3844
11.7	250	1962	342	4173
11.72	256	2275	365	4651
11.74	188	1656	369	6147
11.76	161	870	420	7006
11.78	121	369	392	5227
11.8	149	193	384	2714
11.82	154	137	388	992
11.84	151	104	404	441
11.86	154	123	437	299
11.88	139	114	445	234
11.9	144	112	471	169
11.92	142	86	511	182
11.94	149	121	511	154
11.96	177	102	471	164
11.98	159	108	538	146
12	169	102	566	123
12.02	132	88	511	142
12.04	169	102	615	114
12.06	180	96	676	104
12.08	190	106	676	98
12.1	182	110	702	108
12.12	166	77	801	100
12.14	182	94	824	106
12.16	210	83	900	104
12.18	250	83	1018	104
12.2	231	79	1082	117
12.22	279	83	1204	100
12.24	269	92	1246	98
12.26	259	74	1362	92

12.28	324	77	1429	100
12.3	353	102	1560	98
12.32	376	98	1632	110
12.34	445	85	1714	108
12.36	428	92	1689	94
12.38	462	79	1722	108
12.4	420	98	1624	100
12.42	437	100	1592	108
12.44	497	92	1513	100
12.46	562	83	1296	104
12.48	676	90	1190	110
12.5	615	94	1096	90
12.52	635	110	1037	94
12.54	557	102	1024	102
12.56	497	102	986	123
12.58	488	117	980	128
12.6	493	98	924	119
12.62	497	108	936	106
12.64	400	108	1037	130
12.66	339	102	992	108
12.68	289	108	1050	144
12.7	262	92	1204	117
12.72	272	108	1260	256
12.74	303	102	1376	132
12.76	313	119	1513	121
12.78	328	132	1656	110
12.8	380	114	1747	98
12.82	353	135	1849	125
12.84	396	142	2153	121
12.86	388	117	2352	128
12.88	408	144	2570	121
12.9	562	128	2809	123
12.92	467	114	3025	128
12.94	529	146	3387	121
12.96	581	130	3516	114
12.98	534	154	3906	137
13	630	149	4238	135
13.02	581	142	4225	137
13.04	640	142	3881	151
13.06	610	166	3469	135
13.08	671	190	2894	132
13.1	660	146	2228	151
13.12	681	190	1927	172
13.14	718	199	1875	156
13.16	773	219	1823	164
13.18	894	213	1875	182
13.2	999	262	1998	222
13.22	1163	306	2237	262
13.24	1239	276	2343	228

13.26	1318	328	2530	228
13.28	1362	331	2725	228
13.3	1529	369	2841	240
13.32	1673	396	3069	262
13.34	1789	424	3329	279
13.36	1840	502	3457	282
13.38	2034	524	3672	292
13.4	2285	524	3697	350
13.42	2381	605	3528	376
13.44	2460	605	3493	396
13.46	2560	713	3505	380
13.48	2704	650	3341	424
13.5	2560	708	3341	462
13.52	2490	697	3457	467
13.54	2034	724	3446	529
13.56	1989	835	3318	548
13.58	2088	778	3181	581
13.6	2304	801	2884	590
13.62	2746	807	2520	655
13.64	3457	686	2247	610
13.66	3672	581	2162	576
13.68	3469	445	2125	497
13.7	3612	433	2247	416
13.72	3807	428	2294	392
13.74	4436	433	2372	320
13.76	5580	437	2470	324
13.78	7362	441	2621	317
13.8	10547	557	2756	331
13.82	10424	534	2798	361
13.84	7762	620	2841	380
13.86	4900	751	2809	357
13.88	2172	807	2714	458
13.9	1176	930	2601	511
13.92	778	1018	2314	562
13.94	650	1176	1945	610
13.96	718	1376	1665	729
13.98	702	1537	1296	734
14	745	1884	1176	900
14.02	724	2181	1037	949
14.04	740	2372	1011	1018
14.06	773	2673	1011	1163
14.08	894	3036	1043	1354
14.1	876	3411	1043	1490
14.12	936	3721	1211	1632
14.14	1024	4032	1218	1781
14.16	1082	4624	1318	2007
14.18	1076	4679	1421	2209
14.2	1170	5170	1490	2304
14.22	1163	5213	1764	2591

14.24	1142	5098	1772	2611
14.26	1050	4665	1892	2735
14.28	912	4199	2079	2735
14.3	724	3192	2266	2440
14.32	625	2098	2352	2061
14.34	497	1318	2500	1640
14.36	449	818	2746	1354
14.38	433	595	2884	1109
14.4	441	590	3025	818
14.42	484	600	3170	745
14.44	408	605	3283	778
14.46	480	702	3204	858
14.48	408	650	3047	930
14.5	404	740	2530	1109
14.52	445	734	2088	1102
14.54	376	784	1697	1183
14.56	339	876	1384	1310
14.58	396	924	1318	1399
14.6	372	906	1310	1490
14.62	328	858	1289	1482
14.64	328	681	1296	1296
14.66	250	471	1354	1089
14.68	286	331	1325	795
14.7	299	256	1436	571
14.72	310	279	1482	350
14.74	306	228	1600	256
14.76	292	243	1697	199
14.78	296	262	1731	188
14.8	331	272	1927	204
14.82	339	306	1989	222
14.84	369	317	2125	204
14.86	388	380	2352	240
14.88	449	412	2460	262
14.9	484	408	2601	262
14.92	571	420	2756	279
14.94	605	449	2970	262
14.96	713	449	3181	289
14.98	740	502	3283	328
15	900	511	3226	339
15.02	992	497	3260	342
15.04	1043	488	3329	320
15.06	1089	484	3552	353
15.08	1156	484	3493	365
15.1	1267	471	3624	372
15.12	1444	484	3931	380
15.14	1632	538	4147	408
15.16	1537	511	4083	392
15.18	1592	524	4382	433
15.2	1697	484	4436	369

15.22	1608	493	4382	404
15.24	1498	475	4122	342
15.26	1340	493	3931	350
15.28	1102	515	3457	420
15.3	918	600	2767	400
15.32	697	615	2362	437
15.34	660	724	1971	449
15.36	566	795	1731	506
15.38	600	882	1706	571
15.4	586	1063	1537	635
15.42	635	1183	1544	708
15.44	702	1362	1584	930
15.46	790	1467	1444	1018
15.48	807	1616	1399	1089
15.5	876	1884	1362	1211
15.52	882	2162	1369	1310
15.54	942	2266	1406	1391
15.56	1063	2460	1362	1616
15.58	1142	2735	1310	1858
15.6	1267	3025	1406	1936
15.62	1332	3125	1421	2190
15.64	1310	3238	1444	2352
15.66	1282	3295	1498	2470
15.68	1197	3249	1467	2570
15.7	1050	3114	1560	2540
15.72	1024	3058	1560	2550
15.74	1109	3014	1656	2652
15.76	1030	3114	1673	2809
15.78	1089	3047	1632	3102
15.8	1030	2894	1608	3283
15.82	1037	2520	1537	3014
15.84	961	1884	1436	2611
15.86	949	1225	1475	2116
15.88	973	734	1498	1537
15.9	942	400	1568	1063
15.92	894	259	1616	681
15.94	1030	219	1722	392
15.96	1050	199	1789	246
15.98	1096	161	1849	193
16	1037	185	1910	199
16.02	894	159	1962	169
16.04	692	164	2025	164
16.06	502	144	2007	196
16.08	416	130	1901	154
16.1	350	144	1849	174
16.12	310	137	1600	132
16.14	256	137	1544	151
16.16	269	121	1325	216
16.18	237	146	1197	130

16.2	269	151	1122	135
16.22	259	151	1136	149
16.24	256	161	1142	137
16.26	243	161	1260	144
16.28	303	151	1232	159
16.3	282	199	1414	161
16.32	313	188	1505	151
16.34	328	174	1592	177
16.36	320	234	1714	213
16.38	331	262	1875	202
16.4	361	299	1989	219
16.42	384	303	2200	210
16.44	361	292	2372	240
16.46	376	339	2725	266
16.48	420	342	2767	306
16.5	400	365	2992	313
16.52	449	396	3238	331
16.54	424	428	3422	342
16.56	471	428	3636	342
16.58	420	475	3697	365
16.6	424	428	3576	384
16.62	353	488	3295	412
16.64	339	529	2873	412
16.66	353	548	2673	408
16.68	339	543	2611	428
16.7	328	543	2652	437
16.72	313	557	2500	467
16.74	292	502	2500	441
16.76	317	449	2632	416
16.78	313	538	2683	380
16.8	296	529	2510	369
16.82	350	566	2530	396
16.84	350	605	2343	384
16.86	331	660	2070	404
16.88	369	671	1798	462
16.9	420	734	1459	538
16.92	420	762	1253	600
16.94	416	795	1129	590
16.96	454	882	1056	702
16.98	493	980	1030	729
17	538	1050	906	888
17.02	557	1274	949	955
17.04	548	1310	942	1056
17.06	571	1537	955	1197
17.08	620	1608	980	1303
17.1	630	1892	930	1459
17.12	671	2016	986	1568
17.14	801	2190	1050	1764
17.16	847	2480	1030	1971

17.18	900	2560	1043	2134
17.2	912	2673	1102	2381
17.22	967	2938	1102	2735
17.24	1030	2873	1129	2809
17.26	999	2894	1082	2916
17.28	1005	2591	1122	2809
17.3	1050	2088	1082	2470
17.32	942	1421	986	2285
17.34	955	858	1011	1927
17.36	949	534	1018	1429
17.38	1037	353	961	853
17.4	1218	269	924	590
17.42	1482	210	918	380
17.44	1781	185	999	250
17.46	1980	154	955	250
17.48	1962	169	1056	253
17.5	2043	169	1030	240
17.52	1989	169	1037	286
17.54	1866	174	1018	276
17.56	2162	219	1122	313
17.58	2218	219	1142	286
17.6	2088	240	1190	320
17.62	2275	190	1190	388
17.64	2694	174	1183	433
17.66	2611	144	1082	376
17.68	2430	154	1037	272
17.7	2323	123	999	253
17.72	2266	128	930	180
17.74	2266	128	942	119
17.76	2007	161	973	121
17.78	1927	117	918	149
17.8	1163	135	936	135
17.82	829	132	1018	149
17.84	506	139	1063	137
17.86	396	139	1136	154
17.88	376	180	1218	151
17.9	380	190	1332	137
17.92	493	185	1406	159
17.94	400	180	1444	190
17.96	376	182	1568	159
17.98	412	174	1640	204
18	412	164	1756	196
18.02	428	210	1866	180
18.04	433	286	2043	190
18.06	396	216	2034	216
18.08	353	196	2079	222
18.1	372	222	2052	213
18.12	320	182	1823	213
18.14	328	172	1640	202

18.16	246	154	1414	196
18.18	234	137	1156	149
18.2	246	132	936	177
18.22	222	151	801	146
18.24	237	130	740	159
18.26	216	121	630	164
18.28	253	144	625	164
18.3	262	154	640	182
18.32	213	180	655	161
18.34	225	166	671	199
18.36	228	188	692	207
18.38	225	185	692	225
18.4	272	185	745	246
18.42	256	253	745	276
18.44	269	250	778	269
18.46	250	282	745	320
18.48	269	331	829	324
18.5	317	372	876	388
18.52	282	392	900	408
18.54	339	480	924	420
18.56	369	502	961	515
18.58	369	562	924	581
18.6	404	615	1024	660
18.62	428	702	1037	713
18.64	441	724	1011	784
18.66	506	778	942	864
18.68	520	790	924	980
18.7	581	936	870	1156
18.72	620	980	795	1142
18.74	734	1005	724	1260
18.76	724	967	666	1176
18.78	692	992	605	1176
18.8	790	955	635	1136
18.82	864	864	576	1122
18.84	900	835	534	1063
18.86	900	818	529	961
18.88	900	692	538	870
18.9	847	543	543	762
18.92	858	376	511	620
18.94	853	289	529	497
18.96	864	369	534	369
18.98	900	166	557	231
19	864	130	586	196
19.02	912	112	586	144
19.04	1122	117	586	130
19.06	1282	90	595	132
19.08	1429	98	640	102
19.1	1436	104	640	112
19.12	1310	128	650	100

19.14	1218	98	671	130
19.16	1190	112	676	114
19.18	1296	85	686	106
19.2	1616	104	666	119
19.22	1475	112	655	114
19.24	1149	108	581	135
19.26	1043	128	543	117
19.28	773	130	576	114
19.3	562	142	543	110
19.32	488	128	557	117
19.34	458	121	590	106
19.36	380	142	600	132
19.38	380	166	615	128
19.4	384	174	566	144
19.42	408	151	686	130
19.44	424	169	713	146
19.46	441	199	778	154
19.48	441	188	773	164
19.5	506	180	745	154
19.52	484	180	801	174
19.54	534	185	773	144
19.56	671	202	762	149
19.58	625	196	740	161
19.6	552	213	692	169
19.62	686	234	713	210
19.64	751	196	660	185
19.66	762	210	630	199
19.68	864	219	620	199
19.7	1089	188	650	207
19.72	1163	202	666	213
19.74	1170	228	692	207
19.76	1414	253	620	262
19.78	1739	246	645	279
19.8	1632	246	625	253
19.82	1576	262	595	292
19.84	1475	272	625	306
19.86	1467	246	576	259
19.88	1498	225	534	276
19.9	1376	266	600	246
19.92	1096	256	543	207
19.94	692	292	645	190
19.96	524	259	650	219
19.98	441	372	660	240
20	292	400	610	246
20.02	266	404	718	262
20.04	256	471	708	253
20.06	313	515	734	331
20.08	339	562	767	380
20.1	306	571	790	392

20.12	320	671	847	420
20.14	328	702	858	441
20.16	350	829	829	515
20.18	353	853	888	467
20.2	331	930	829	576
20.22	372	900	751	543
20.24	369	1030	745	615
20.26	392	1018	676	681
20.28	424	1056	620	671
20.3	416	986	640	713
20.32	420	1005	586	702
20.34	408	818	610	692
20.36	416	686	640	615
20.38	384	488	655	511
20.4	372	353	600	471
20.42	380	296	713	339
20.44	388	222	645	279
20.46	357	190	630	231
20.48	376	154	620	180
20.5	372	161	600	164
20.52	365	156	600	154
20.54	384	172	552	144
20.56	484	182	586	166
20.58	433	210	493	151
20.6	441	185	538	156
20.62	471	199	529	193
20.64	458	231	488	185
20.66	548	246	488	190
20.68	650	289	543	202
20.7	697	276	475	210
20.72	812	306	475	246
20.74	980	353	506	279
20.76	1204	350	520	276
20.78	955	424	529	303
20.8	986	437	586	317
20.82	812	475	595	335
20.84	538	520	562	412
20.86	529	600	605	437
20.88	449	676	650	524
20.9	404	686	686	511
20.92	400	713	676	576
20.94	433	767	740	650
20.96	433	829	762	713
20.98	462	773	824	713
21	467	807	767	713
21.02	449	745	870	729
21.04	420	713	847	686
21.06	404	640	882	660
21.08	376	620	888	676

21.1	342	595	870	620
21.12	350	543	847	615
21.14	324	576	778	605
21.16	350	615	745	702
21.18	369	630	655	756
21.2	380	645	615	818
21.22	361	660	524	955
21.24	339	666	543	1011
21.26	296	581	515	1076
21.28	262	562	511	967
21.3	246	412	520	824
21.32	240	365	511	692
21.34	202	262	484	548
21.36	219	222	524	392
21.38	188	185	562	324
21.4	207	159	590	234
21.42	199	139	590	169
21.44	199	128	620	159
21.46	199	144	562	144
21.48	231	144	620	139
21.5	182	119	625	130
21.52	202	151	666	159
21.54	174	125	660	130
21.56	207	142	660	123
21.58	196	112	740	123
21.6	237	154	724	139
21.62	213	139	650	149
21.64	193	125	708	137
21.66	213	110	751	135
21.68	213	119	795	132
21.7	213	114	756	128
21.72	272	137	734	159
21.74	276	174	734	132
21.76	286	151	702	142
21.78	286	169	686	166
21.8	306	174	640	144
21.82	289	182	620	174
21.84	306	213	605	219
21.86	289	225	557	216
21.88	324	306	576	234
21.9	342	276	590	276
21.92	412	299	640	286
21.94	433	331	615	282
21.96	462	350	686	353
21.98	515	376	660	433
22	515	433	702	454
22.02	586	480	640	445
22.04	708	625	697	529
22.06	686	562	762	534

22.08	992	625	734	586
22.1	1170	630	713	671
22.12	1459	697	724	778
22.14	1303	767	708	870
22.16	999	795	692	864
22.18	812	858	708	912
22.2	645	900	671	1024
22.22	458	955	666	1050
22.24	313	900	734	1037
22.26	306	835	773	942
22.28	269	660	778	894
22.3	246	595	773	801
22.32	243	484	807	635
22.34	240	454	835	524
22.36	250	437	795	428
22.38	246	420	841	400
22.4	243	404	894	384
22.42	276	441	824	365
22.44	222	346	894	380
22.46	246	335	942	342
22.48	234	361	942	331
22.5	202	237	1076	350
22.52	222	210	1050	259
22.54	216	180	1018	250
22.56	210	161	1096	210
22.58	199	151	1018	185
22.6	182	121	986	196
22.62	151	112	980	159
22.64	164	125	882	161
22.66	177	110	807	166
22.68	193	144	734	159
22.7	196	146	630	159
22.72	188	123	557	174
22.74	188	125	605	146
22.76	246	121	515	172
22.78	193	159	497	154
22.8	256	174	493	149
22.82	243	146	529	190
22.84	246	164	484	174
22.86	250	174	488	182
22.88	262	188	467	193
22.9	279	164	454	190
22.92	282	185	454	253
22.94	299	210	445	237
22.96	303	204	437	256
22.98	317	199	412	276
23	306	216	424	310
23.02	384	269	467	303
23.04	365	246	416	331

23.06	342	289	471	388
23.08	361	282	445	428
23.1	292	313	458	502
23.12	313	384	484	543
23.14	243	365	538	520
23.16	210	376	562	562
23.18	180	384	524	615
23.2	196	342	557	595
23.22	240	306	586	600
23.24	199	346	630	620
23.26	199	317	605	630
23.28	202	296	635	605
23.3	216	289	681	600
23.32	240	286	635	640
23.34	210	339	645	676
23.36	207	350	666	734
23.38	225	396	708	824
23.4	222	388	697	847
23.42	237	416	650	961
23.44	243	543	635	1082
23.46	240	571	635	1267
23.48	286	745	620	1391
23.5	292	1109	615	1490
23.52	310	1354	552	1640
23.54	286	1069	529	1849
23.56	292	762	467	2209
23.58	313	681	445	2052
23.6	282	475	437	1225
23.62	286	299	428	1122
23.64	328	243	420	900
23.66	346	234	424	475
23.68	361	216	480	328
23.7	350	213	441	253
23.72	342	219	458	243
23.74	372	210	475	256
23.76	400	222	506	250
23.78	408	210	506	350
23.8	384	196	484	222
23.82	357	164	506	188
23.84	306	164	484	204
23.86	253	166	480	196
23.88	246	139	462	161
23.9	240	117	433	151
23.92	174	96	376	123
23.94	154	106	372	132
23.96	132	110	388	132
23.98	174	92	357	119
24	142	96	392	125
24.02	139	104	350	154

24.04	144	90	353	100
24.06	166	112	380	128
24.08	123	85	357	135
24.1	137	98	328	114
24.12	149	123	369	128
24.14	139	125	357	119
24.16	159	112	384	149
24.18	130	135	400	144
24.2	164	135	372	159
24.22	164	144	404	164
24.24	177	177	372	164
24.26	172	185	369	193
24.28	207	161	388	188
24.3	164	222	408	234
24.32	182	216	365	207
24.34	188	234	392	253
24.36	196	225	467	276
24.38	216	256	388	361
24.4	213	262	475	335
24.42	207	286	428	342
24.44	222	286	445	369
24.46	253	313	515	396
24.48	216	342	506	396
24.5	231	400	475	471
24.52	253	380	493	467
24.54	286	424	520	538
24.56	237	428	511	515
24.58	256	467	524	497
24.6	286	462	506	529
24.62	339	357	552	576
24.64	299	388	538	552
24.66	259	286	511	462
24.68	234	289	538	433
24.7	193	246	581	335
24.72	172	213	562	269
24.74	172	196	557	199
24.76	169	196	625	225
24.78	172	193	655	202
24.8	161	216	645	193
24.82	159	199	605	188
24.84	166	199	666	190
24.86	174	225	650	210
24.88	169	222	615	228
24.9	161	272	581	250
24.92	159	259	552	231
24.94	159	213	506	222
24.96	159	256	462	188
24.98	156	213	462	213
25	174	180	454	199

25.02	169	172	420	202
25.04	193	161	416	172
25.06	207	164	404	159
25.08	193	135	467	149
25.1	213	144	458	151
25.12	234	130	441	146
25.14	202	121	480	121
25.16	199	125	445	110
25.18	202	149	480	117
25.2	193	112	458	121
25.22	228	106	467	130
25.24	185	112	493	339
25.26	202	112	471	108
25.28	225	128	484	121
25.3	250	161	502	137
25.32	269	123	524	128
25.34	259	128	524	121
25.36	237	154	493	137
25.38	262	142	529	161
25.4	276	146	581	172
25.42	219	142	571	149
25.44	207	164	571	169
25.46	188	169	557	180
25.48	207	166	590	159
25.5	188	266	529	159
25.52	190	169	471	144
25.54	193	164	475	128
25.56	182	166	449	154
25.58	207	204	445	128
25.6	161	210	420	180
25.62	169	269	400	149
25.64	185	228	412	172
25.66	185	266	372	177
25.68	174	266	404	182
25.7	193	292	328	182
25.72	185	269	346	219
25.74	161	286	342	182
25.76	154	289	346	210
25.78	166	365	331	219
25.8	196	296	331	222
25.82	190	266	331	246
25.84	169	279	342	246
25.86	188	276	306	243
25.88	166	320	313	219
25.9	185	296	328	222
25.92	484	324	279	237
25.94	169	310	279	237
25.96	177	299	299	213
25.98	188	292	310	199

26	159	259	310	204
26.02	161	292	292	207
26.04	177	222	313	202
26.06	154	207	296	177
26.08	149	156	331	164
26.1	169	156	289	135
26.12	144	125	320	130
26.14	139	142	292	132
26.16	114	106	303	146
26.18	144	104	292	114
26.2	135	112	317	110
26.22	144	104	320	123
26.24	142	106	324	117
26.26	164	128	292	144
26.28	164	130	313	132
26.3	177	130	299	125
26.32	180	137	328	142
26.34	196	142	328	135
26.36	225	185	320	202
26.38	279	177	342	161
26.4	310	207	350	188
26.42	306	207	331	159
26.44	342	228	369	164
26.46	335	199	365	169
26.48	353	225	353	174
26.5	331	237	388	166
26.52	369	240	416	185
26.54	372	272	424	222
26.56	454	262	437	196
26.58	433	313	384	202
26.6	529	317	449	243
26.62	655	335	458	250
26.64	858	350	458	246
26.66	1109	320	454	256
26.68	1490	380	497	253
26.7	1347	331	454	234
26.72	1102	317	449	282
26.74	1063	335	458	269
26.76	1030	324	408	286
26.78	894	328	412	272
26.8	610	320	376	269
26.82	497	365	376	292
26.84	408	342	420	339
26.86	396	376	388	342
26.88	350	365	376	286
26.9	292	372	416	320
26.92	328	339	388	313
26.94	331	342	445	353
26.96	346	303	412	328

26.98	384	289	441	299
27	412	279	380	331
27.02	384	246	416	266
27.04	412	213	433	289
27.06	441	231	353	262
27.08	471	196	404	272
27.1	458	213	396	279
27.12	416	190	372	228
27.14	475	190	388	240
27.16	511	169	380	246
27.18	493	159	353	250
27.2	480	139	412	222
27.22	534	169	342	185
27.24	543	154	400	169
27.26	458	174	454	169
27.28	437	169	441	172
27.3	462	159	467	193
27.32	420	154	433	188
27.34	313	174	445	161
27.36	243	182	428	166
27.38	246	182	441	174
27.4	222	174	400	188
27.42	199	177	471	190
27.44	166	177	458	174
27.46	156	154	441	207
27.48	144	172	475	164
27.5	166	174	458	169
27.52	166	144	428	137
27.54	159	174	433	123
27.56	159	139	400	149
27.58	164	172	420	137
27.6	161	156	384	151
27.62	164	149	361	123
27.64	161	123	361	135
27.66	188	159	384	128
27.68	204	142	396	154
27.7	193	144	392	169
27.72	219	135	404	156
27.74	204	128	420	164
27.76	199	156	441	185
27.78	216	154	412	180
27.8	231	159	441	231
27.82	234	156	428	190
27.84	313	193	506	204
27.86	306	172	502	210
27.88	306	172	515	231
27.9	335	185	511	210
27.92	313	204	511	231
27.94	317	237	562	253

27.96	317	237	548	250
27.98	324	243	600	276
28	303	256	557	320
28.02	306	256	557	303
28.04	269	286	566	282
28.06	243	279	543	342
28.08	231	286	576	372
28.1	219	299	548	369
28.12	210	306	576	342
28.14	219	250	576	388
28.16	202	234	557	361
28.18	199	204	586	306
28.2	225	196	520	243
28.22	161	182	529	202
28.24	177	159	497	188
28.26	169	151	480	188
28.28	210	144	420	177
28.3	222	132	467	161
28.32	202	146	449	137
28.34	237	142	484	142
28.36	256	125	428	142
28.38	234	156	424	114
28.4	234	146	437	130
28.42	286	159	437	142
28.44	306	161	420	174
28.46	339	177	445	135
28.48	310	172	458	166
28.5	303	169	416	169
28.52	276	174	437	159
28.54	259	182	458	156
28.56	256	169	437	149
28.58	240	169	449	174
28.6	216	172	433	161
28.62	231	174	441	149
28.64	237	174	445	185
28.66	234	177	433	161
28.68	259	207	424	144
28.7	213	185	416	169
28.72	180	185	408	144
28.74	169	174	441	139
28.76	159	164	420	144
28.78	159	166	408	144
28.8	144	156	458	151
28.82	174	137	388	117
28.84	149	128	408	125
28.86	144	130	416	117
28.88	149	100	420	119
28.9	151	106	380	117
28.92	156	110	428	108

28.94	132	88	404	144
28.96	159	98	376	123
28.98	199	88	396	123
29	169	119	365	110
29.02	199	104	342	123
29.04	193	144	342	151
29.06	228	117	335	159
29.08	210	130	357	169
29.1	216	132	296	164
29.12	246	137	317	151
29.14	246	151	361	174
29.16	276	159	303	185
29.18	253	182	289	225
29.2	269	182	310	199
29.22	246	172	339	219
29.24	266	196	317	231
29.26	228	207	339	234
29.28	240	202	328	234
29.3	234	225	324	266
29.32	210	228	313	282
29.34	202	243	306	320
29.36	177	266	335	339
29.38	204	286	299	342
29.4	169	320	335	388
29.42	177	292	282	388
29.44	159	335	320	384
29.46	182	313	328	416
29.48	169	339	324	437
29.5	169	353	306	416
29.52	159	306	342	335
29.54	149	306	376	365
29.56	149	279	350	328
29.58	156	324	388	303
29.6	159	303	376	279
29.62	156	269	369	282
29.64	161	276	372	259
29.66	174	303	372	266
29.68	207	250	420	234
29.7	199	320	388	262
29.72	210	276	396	259
29.74	210	299	400	240
29.76	190	328	384	269
29.78	180	269	420	282
29.8	199	339	449	262
29.82	210	269	416	276
29.84	219	276	400	262
29.86	207	276	404	253
29.88	225	228	400	259
29.9	185	234	412	250

29.92	210	213	408	202
29.94	213	216	384	204
29.96	231	196	396	210
29.98	222	177	384	193
30	234	166	365	166
30.02	213	139	372	182
30.04	231	137	376	159
30.06	259	112	384	128
30.08	222	102	376	146
30.1	182	108	357	128
30.12	166	90	384	114
30.14	185	98	357	104
30.16	169	100	365	121
30.18	123	123	353	110
30.2	164	114	346	117
30.22	159	106	320	112
30.24	149	88	357	128
30.26	146	114	339	123
30.28	225	123	365	128
30.3	144	130	339	112
30.32	164	117	357	125
30.34	132	137	365	125
30.36	144	144	376	108
30.38	149	123	350	144
30.4	207	137	328	123
30.42	159	151	365	128
30.44	234	142	361	144
30.46	174	151	376	159
30.48	185	169	380	146
30.5	207	166	380	166
30.52	193	177	342	151
30.54	219	156	376	169
30.56	243	193	365	164
30.58	219	169	353	139
30.6	253	169	404	177
30.62	246	166	335	146
30.64	303	169	408	144
30.66	357	146	365	159
30.68	408	177	365	149
30.7	416	166	376	180
30.72	365	137	353	164
30.74	400	193	372	190
30.76	380	174	404	174
30.78	365	177	437	180
30.8	365	185	412	177
30.82	306	174	412	199
30.84	272	177	380	177
30.86	262	161	416	204
30.88	250	151	471	161

30.9	228	149	445	164
30.92	202	172	462	146
30.94	185	161	458	149
30.96	164	169	437	177
30.98	269	185	441	174
31	182	180	428	144
31.02	193	172	445	169
31.04	207	193	449	185
31.06	216	190	441	166
31.08	234	182	420	164
31.1	228	161	437	154
31.12	190	190	416	154
31.14	202	182	449	169
31.16	282	121	424	159
31.18	279	128	445	144
31.2	276	119	400	137
31.22	237	100	408	142
31.24	234	121	380	121
31.26	231	108	313	123
31.28	250	110	365	132
31.3	193	104	339	104
31.32	240	106	342	119
31.34	222	108	313	110
31.36	196	106	350	114
31.38	190	121	350	125
31.4	204	144	320	119
31.42	161	128	335	164
31.44	202	144	335	135
31.46	188	144	266	159
31.48	177	177	306	216
31.5	159	193	286	207
31.52	185	207	324	210
31.54	166	219	313	225
31.56	166	228	313	259
31.58	174	259	317	269
31.6	177	279	313	292
31.62	182	292	324	303
31.64	213	320	339	310
31.66	207	324	335	310
31.68	213	365	331	331
31.7	207	369	335	404
31.72	240	365	357	416
31.74	228	396	339	502
31.76	243	420	357	497
31.78	237	433	328	502
31.8	231	475	350	534
31.82	231	511	369	502
31.84	210	493	384	520
31.86	199	484	372	605

31.88	225	484	350	586
31.9	210	433	339	590
31.92	210	400	346	506
31.94	228	369	342	497
31.96	199	313	331	441
31.98	210	310	350	384
32	199	253	306	328
32.02	190	196	317	296
32.04	177	216	317	246
32.06	193	182	313	259
32.08	174	180	331	199
32.1	166	185	317	225
32.12	156	190	328	188
32.14	182	190	331	216
32.16	144	207	328	213
32.18	151	207	353	240
32.2	132	188	342	228
32.22	142	216	372	256
32.24	161	225	339	219
32.26	144	259	350	256
32.28	149	266	331	246
32.3	159	240	346	262
32.32	149	256	342	299
32.34	156	253	353	286
32.36	135	246	324	320
32.38	128	243	369	306
32.4	135	250	357	306
32.42	151	204	339	320
32.44	154	188	331	289
32.46	123	188	350	276
32.48	149	234	331	250
32.5	149	204	346	266
32.52	151	231	335	256
32.54	112	204	376	269
32.56	154	199	320	231
32.58	146	174	342	222
32.6	139	169	342	210
32.62	130	154	317	185
32.64	125	144	339	177
32.66	137	174	286	177
32.68	139	169	324	174
32.7	166	196	310	169
32.72	164	204	320	164
32.74	139	154	306	166
32.76	182	174	324	159
32.78	166	182	286	166
32.8	185	216	324	164
32.82	188	210	335	193
32.84	210	222	317	202

32.86	213	228	306	210
32.88	202	256	289	234
32.9	196	282	303	234
32.92	216	289	324	266
32.94	213	289	306	246
32.96	210	306	339	269
32.98	228	313	313	276
33	202	328	306	286
33.02	180	369	324	306
33.04	188	353	296	328
33.06	190	369	292	335
33.08	210	433	310	369
33.1	222	437	299	433
33.12	207	445	286	424
33.14	216	392	289	428
33.16	207	441	310	404
33.18	216	449	313	449
33.2	225	416	299	420
33.22	228	437	296	428
33.24	219	441	272	392
33.26	225	388	292	392
33.28	190	357	303	380
33.3	231	324	317	376
33.32	246	276	335	361
33.34	222	269	331	299
33.36	210	272	335	256
33.38	259	262	339	289
33.4	259	243	335	289
33.42	310	231	339	320
33.44	350	213	376	299
33.46	324	256	376	313
33.48	240	240	372	266
33.5	289	225	400	286
33.52	299	207	365	240
33.54	289	213	400	256
33.56	292	213	392	213
33.58	272	210	404	234
33.6	234	253	412	225
33.62	286	253	424	253
33.64	292	228	449	216
33.66	292	237	400	269
33.68	266	240	441	231
33.7	292	253	420	243
33.72	259	250	449	222
33.74	262	256	480	234
33.76	225	282	462	266
33.78	228	253	506	246
33.8	219	269	471	269
33.82	210	279	471	253

33.84	204	269	493	246
33.86	204	269	488	262
33.88	174	282	484	228
33.9	210	328	449	269
33.92	210	303	471	296
33.94	193	365	441	240
33.96	213	353	396	262
33.98	225	369	400	282
34	240	353	392	292
34.02	222	396	412	365
34.04	246	433	384	339
34.06	259	441	392	350
34.08	303	458	353	412
34.1	272	445	331	408
34.12	286	449	342	372
34.14	276	467	350	408
34.16	272	493	320	428
34.18	279	488	339	428
34.2	282	488	317	433
34.22	266	462	306	449
34.24	272	420	342	454
34.26	272	433	350	428
34.28	272	412	306	388
34.3	240	376	320	388
34.32	262	317	306	369
34.34	246	292	342	331
34.36	246	262	296	296
34.38	266	237	353	262
34.4	240	216	292	237
34.42	296	196	317	234
34.44	199	199	331	216
34.46	190	185	353	196
34.48	202	202	339	185
34.5	204	182	339	188
34.52	210	177	350	185
34.54	222	185	353	196
34.56	219	190	384	219
34.58	240	188	384	199
34.6	253	199	365	237
34.62	246	196	380	180
34.64	237	193	416	216
34.66	292	202	388	228
34.68	313	174	433	222
34.7	331	231	380	246
34.72	335	213	420	256
34.74	303	216	416	246
34.76	331	246	420	196
34.78	310	225	404	250
34.8	365	219	428	276

34.82	310	246	471	262
34.84	357	199	428	259
34.86	331	259	458	272
34.88	346	225	506	296
34.9	313	225	441	250
34.92	259	266	480	240
34.94	243	231	480	272
34.96	234	259	506	279
34.98	240	262	484	299
35	202	216	471	269
35.02	185	266	462	282
35.04	177	231	502	266
35.06	180	231	497	246
35.08	193	243	437	289
35.1	182	234	484	306
35.12	204	246	441	286
35.14	204	250	428	346
35.16	193	299	400	376
35.18	219	292	404	372
35.2	213	282	408	392
35.22	246	320	420	420
35.24	256	310	396	475
35.26	276	365	339	493
35.28	250	361	384	471
35.3	259	384	380	529
35.32	282	400	335	511
35.34	292	408	353	576
35.36	272	428	357	562
35.38	269	454	350	660
35.4	292	467	376	666
35.42	320	462	328	734
35.44	320	416	380	745
35.46	320	416	369	784
35.48	328	412	396	853
35.5	320	408	369	824
35.52	317	424	365	847
35.54	324	502	376	900
35.56	282	576	369	949
35.58	292	586	353	1030
35.6	286	529	365	1069
35.62	262	396	376	992
35.64	266	353	357	924
35.66	279	306	404	767
35.68	250	292	416	581
35.7	225	266	388	502
35.72	213	199	412	441
35.74	256	210	324	365
35.76	250	154	380	317
35.78	282	149	388	266

35.8	282	164	346	250
35.82	256	159	339	237
35.84	286	144	335	458
35.86	292	177	357	256
35.88	303	130	342	222
35.9	286	149	342	240
35.92	262	132	324	246
35.94	234	137	339	210
35.96	225	128	328	216
35.98	190	130	342	190
36	166	112	299	164
36.02	174	130	313	146
36.04	146	106	342	166
36.06	137	110	320	137
36.08	130	85	324	142
36.1	132	94	328	151
36.12	135	110	342	112
36.14	112	114	324	130
36.16	149	144	289	125
36.18	130	102	328	112
36.2	121	108	310	125
36.22	142	110	320	128
36.24	151	117	289	139
36.26	146	88	335	128
36.28	135	121	324	142
36.3	137	104	361	137
36.32	146	253	324	125
36.34	149	146	346	125
36.36	135	119	317	142
36.38	161	128	331	146
36.4	146	149	353	151
36.42	169	144	365	159
36.44	161	132	365	169
36.46	154	159	380	159
36.48	144	161	357	182
36.5	159	146	353	188
36.52	169	182	424	177
36.54	177	177	396	164
36.56	182	177	376	188
36.58	159	196	380	193
36.6	159	199	420	303
36.62	154	219	412	199
36.64	151	202	420	216
36.66	182	193	404	216
36.68	169	193	437	210
36.7	169	210	424	207
36.72	161	185	449	213
36.74	166	213	416	243
36.76	166	177	433	219

36.78	177	185	412	225
36.8	185	190	404	219
36.82	182	154	408	202
36.84	216	132	449	207
36.86	174	164	400	213
36.88	222	144	428	190
36.9	207	130	437	161
36.92	250	164	388	177
36.94	225	137	420	149
36.96	204	149	412	199
36.98	207	139	428	180
37	225	164	408	182
37.02	228	151	416	169
37.04	231	142	404	177
37.06	219	156	388	207
37.08	219	139	433	196
37.1	234	123	412	199
37.12	207	130	353	182
37.14	234	128	388	177
37.16	216	121	396	144
37.18	216	125	400	161
37.2	193	121	416	154
37.22	207	125	404	159
37.24	234	149	392	164
37.26	225	149	376	174
37.28	222	142	424	182
37.3	216	117	384	177
37.32	234	156	369	166
37.34	228	159	365	216
37.36	237	174	372	196
37.38	243	164	350	182
37.4	276	177	392	199
37.42	262	156	369	196
37.44	279	210	420	234
37.46	266	202	384	243
37.48	225	202	357	250
37.5	243	207	361	259
37.52	222	228	361	292
37.54	202	225	392	289
37.56	177	269	408	331
37.58	207	243	346	317
37.6	169	262	376	331
37.62	177	234	357	339
37.64	137	225	372	299
37.66	139	234	357	350
37.68	161	216	408	335
37.7	142	234	365	240
37.72	146	237	372	250
37.74	156	225	384	216

37.76	146	204	357	240
37.78	190	188	412	246
37.8	159	182	396	231
37.82	202	196	408	219
37.84	193	207	412	234
37.86	172	199	392	250
37.88	172	199	408	250
37.9	177	196	384	231
37.92	193	177	392	222
37.94	169	169	380	246
37.96	177	196	400	222
37.98	185	202	408	243
38	193	180	376	207
38.02	177	174	388	199
38.04	177	172	384	210
38.06	156	161	380	177
38.08	219	161	404	159
38.1	169	159	380	172
38.12	166	169	392	166
38.14	199	177	396	199
38.16	202	154	392	185
38.18	225	172	404	169
38.2	282	196	412	182
38.22	213	169	388	196
38.24	180	169	365	185
38.26	269	174	350	196
38.28	199	199	384	174
38.3	193	182	412	185
38.32	202	185	384	199
38.34	199	185	380	202
38.36	202	156	369	219
38.38	237	151	324	174
38.4	292	166	369	169
38.42	266	199	388	196
38.44	253	199	380	182
38.46	262	166	380	196
38.48	246	182	424	188
38.5	259	199	392	180
38.52	222	202	404	213
38.54	231	182	392	219
38.56	225	188	372	185
38.58	234	210	369	199
38.6	246	219	412	196
38.62	259	193	396	199
38.64	262	207	400	228
38.66	231	231	404	250
38.68	286	210	400	259
38.7	219	199	372	222
38.72	216	193	384	225

38.74	193	142	396	219
38.76	196	196	328	207
38.78	213	166	384	188
38.8	199	164	384	202
38.82	193	159	361	196
38.84	193	139	369	190
38.86	174	132	369	177
38.88	169	132	380	174
38.9	169	156	372	188
38.92	151	130	346	149
38.94	154	144	388	190
38.96	142	139	380	210
38.98	159	159	361	188
39	159	146	365	216
39.02	159	159	357	207
39.04	182	149	320	216
39.06	164	135	346	219
39.08	146	151	320	210
39.1	142	151	339	234
39.12	169	149	331	188
39.14	156	137	331	190
39.16	174	151	353	177
39.18	144	135	335	177
39.2	161	110	335	154
39.22	174	144	303	154
39.24	149	139	335	185
39.26	154	119	317	139
39.28	164	108	328	125
39.3	146	144	299	139
39.32	177	100	339	130
39.34	169	128	342	161
39.36	182	121	320	121
39.38	188	128	299	128
39.4	199	121	317	130
39.42	172	125	296	112
39.44	174	132	331	154
39.46	204	144	313	132
39.48	188	119	380	149
39.5	182	149	365	128
39.52	169	108	350	156
39.54	182	125	369	139
39.56	207	137	365	142
39.58	174	137	369	144
39.6	185	154	342	142
39.62	199	144	388	164
39.64	204	130	384	144
39.66	207	149	372	149
39.68	219	149	428	128
39.7	188	144	396	149

39.72	182	128	384	130
39.74	196	125	408	180
39.76	174	142	396	135
39.78	180	125	388	154
39.8	164	156	433	177
39.82	182	128	384	137
39.84	161	125	369	142
39.86	174	132	416	132
39.88	151	125	388	142
39.9	146	114	408	130
39.92	142	151	408	112
39.94	164	137	400	151
39.96	182	114	416	144
39.98	199	125	388	144
40	196	125	416	130
40.02	193	135	396	135
40.04	213	135	380	144
40.06	234	151	404	144
40.08	231	159	424	142
40.1	240	149	412	137
40.12	256	144	400	151
40.14	231	130	384	156
40.16	279	146	424	142
40.18	317	139	372	161
40.2	335	156	404	135
40.22	342	164	396	149
40.24	335	172	388	149
40.26	342	159	396	169
40.28	357	180	376	164
40.3	433	149	392	159
40.32	424	156	388	156
40.34	437	177	384	151
40.36	412	149	396	159
40.38	396	172	400	156
40.4	424	164	428	144
40.42	454	151	404	128
40.44	428	149	408	144
40.46	388	154	392	161
40.48	282	185	420	262
40.5	303	139	380	151
40.52	292	154	392	149
40.54	286	180	392	174
40.56	269	149	380	156
40.58	237	161	380	185
40.6	225	174	384	164
40.62	234	154	416	177
40.64	219	164	400	185
40.66	237	199	388	164
40.68	213	193	396	159

40.7	199	196	416	190
40.72	222	219	412	169
40.74	234	196	369	177
40.76	222	207	404	182
40.78	361	228	384	169
40.8	193	240	396	188
40.82	196	213	384	180
40.84	240	231	384	199
40.86	231	243	412	207
40.88	266	237	388	213
40.9	234	292	396	222
40.92	253	259	392	231
40.94	282	289	396	225
40.96	303	292	404	250
40.98	303	296	412	250
41	317	299	400	237
41.02	286	328	449	246
41.04	262	306	404	240
41.06	289	262	408	213
41.08	328	266	396	231
41.1	339	253	384	231
41.12	310	246	408	231
41.14	286	243	400	225
41.16	292	240	392	222
41.18	250	182	400	199
41.2	246	296	416	174
41.22	228	188	400	182
41.24	210	185	388	174
41.26	207	193	400	193
41.28	193	180	416	164
41.3	193	188	380	193
41.32	169	193	404	180
41.34	174	185	428	210
41.36	180	182	433	182
41.38	199	177	458	225
41.4	177	185	454	193
41.42	174	185	467	164
41.44	185	172	441	169
41.46	193	199	471	213
41.48	199	193	445	193
41.5	213	204	467	182
41.52	207	190	484	210
41.54	196	202	462	185
41.56	202	182	488	228
41.58	216	166	475	182
41.6	193	207	449	210
41.62	190	188	467	182
41.64	172	151	454	196
41.66	225	177	454	199

41.68	213	188	467	207
41.7	204	169	420	228
41.72	202	193	475	237
41.74	225	207	428	259
41.76	216	210	416	324
41.78	204	199	437	250
41.8	210	207	420	213
41.82	228	237	392	269
41.84	228	237	376	253
41.86	243	243	380	286
41.88	237	219	357	272
41.9	234	216	372	259
41.92	225	196	392	259
41.94	231	246	353	250
41.96	250	250	353	259
41.98	272	256	346	259
42	262	231	335	286
42.02	250	276	365	282
42.04	225	259	353	272
42.06	219	276	384	313
42.08	240	228	320	262
42.1	228	259	416	246
42.12	216	216	380	243
42.14	219	207	353	256
42.16	188	188	384	231
42.18	193	174	408	213
42.2	193	180	384	202
42.22	172	166	380	193
42.24	169	144	437	172
42.26	182	154	416	180
42.28	188	156	416	199
42.3	159	132	420	172
42.32	144	159	428	139
42.34	146	135	396	166
42.36	139	112	424	139
42.38	146	117	441	154
42.4	135	137	437	139
42.42	159	144	420	182
42.44	125	128	437	159
42.46	139	130	416	164
42.48	128	130	467	154
42.5	139	154	475	154
42.52	154	135	433	166
42.54	132	146	408	151
42.56	146	159	441	144
42.58	159	142	454	193
42.6	139	149	424	177
42.62	137	166	396	146
42.64	137	174	424	182

42.66	151	174	441	177
42.68	159	169	428	188
42.7	159	185	454	219
42.72	166	177	449	207
42.74	174	164	404	207
42.76	172	185	408	207
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42.8	177	196	424	266
42.82	169	199	454	276
42.84	177	262	467	259
42.86	161	234	396	299
42.88	164	210	420	272
42.9	156	222	408	272
42.92	159	234	392	331
42.94	144	246	449	299
42.96	174	231	416	342
42.98	164	250	404	306
43	182	237	404	320
43.02	196	269	433	328
43.04	159	272	372	376
43.06	180	276	437	353
43.08	174	299	396	400
43.1	193	303	388	445
43.12	185	331	380	467
43.14	177	324	502	454
43.16	199	310	388	484
43.18	188	353	396	538
43.2	210	346	392	534
43.22	182	388	365	552
43.24	222	346	339	534
43.26	207	388	331	534
43.28	216	384	376	534
43.3	207	400	380	538
43.32	222	404	353	524
43.34	216	372	342	543
43.36	216	396	335	571
43.38	234	384	372	538
43.4	190	416	320	566
43.42	216	467	350	566
43.44	219	400	310	605
43.46	225	480	342	605
43.48	240	437	339	610
43.5	240	441	335	635
43.52	243	480	320	660
43.54	250	441	310	655
43.56	250	449	317	645
43.58	262	506	331	660
43.6	259	416	324	581
43.62	253	342	303	581

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43.68	204	306	328	416
43.7	240	269	286	376
43.72	185	234	331	369
43.74	202	225	335	328
43.76	193	199	320	310
43.78	154	225	313	262
43.8	159	204	320	253
43.82	193	225	286	237
43.84	180	228	282	202
43.86	156	210	313	193
43.88	185	193	346	202
43.9	202	216	299	228
43.92	185	196	313	196
43.94	159	207	299	210
43.96	188	204	353	207
43.98	196	199	324	202
44	161	199	299	202
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44.04	164	182	335	185
44.06	188	180	306	174
44.08	213	177	339	169
44.1	196	159	328	151
44.12	210	154	328	177
44.14	180	169	357	154
44.16	204	159	342	146
44.18	196	161	342	169
44.2	196	154	357	169
44.22	196	146	571	174
44.24	149	128	372	164
44.26	177	169	357	159
44.28	180	137	357	174
44.3	149	159	350	188
44.32	169	177	346	149
44.34	156	185	376	151
44.36	190	166	342	174
44.38	154	185	384	174
44.4	154	188	361	169
44.42	159	199	380	240
44.44	137	202	342	185
44.46	137	213	313	199
44.48	159	199	365	222
44.5	156	237	335	213
44.52	139	231	365	243
44.54	135	225	353	216
44.56	154	253	361	282
44.58	146	262	324	246
44.6	159	234	361	266

44.62	151	246	369	292
44.64	159	286	376	299
44.66	177	253	350	310
44.68	156	276	369	296
44.7	174	259	342	303
44.72	156	272	331	303
44.74	142	272	353	289
44.76	180	240	324	328
44.78	177	266	339	286
44.8	166	272	342	286
44.82	149	262	328	282
44.84	151	237	339	286
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44.9	149	228	384	299
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44.94	149	234	350	279
44.96	144	266	353	303
44.98	144	193	350	262
45	156	196	317	286
45.02	146	199	350	231
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45.06	159	161	306	210
45.08	149	174	299	202
45.1	151	156	310	182
45.12	144	144	296	180
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45.16	169	166	320	146
45.18	166	180	289	169
45.2	177	180	286	172
45.22	169	146	328	174
45.24	185	159	269	169
45.26	188	139	306	149
45.28	169	159	310	177
45.3	190	169	320	185
45.32	190	151	292	161
45.34	188	166	289	182
45.36	182	146	286	202
45.38	193	172	306	193
45.4	196	193	289	172
45.42	182	161	276	193
45.44	172	177	317	188
45.46	169	188	272	196
45.48	185	149	262	219
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45.52	159	169	279	174
45.54	169	154	317	182
45.56	177	154	272	166
45.58	164	154	289	164

45.6	174	149	276	149
45.62	161	156	289	193
45.64	172	164	266	180
45.66	188	154	266	213
45.68	151	172	299	188
45.7	149	213	276	164
45.72	207	169	299	193
45.74	237	180	279	213
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45.78	196	190	272	196
45.8	185	219	282	193
45.82	204	204	296	202
45.84	172	219	279	207
45.86	185	210	272	204
45.88	216	193	276	219
45.9	196	188	286	237
45.92	196	188	276	219
45.94	225	225	292	213
45.96	240	204	286	222
45.98	174	193	296	234
46	169	199	292	213
46.02	166	166	266	216
46.04	193	164	269	243
46.06	185	331	269	240
46.08	161	146	292	219
46.1	164	159	259	190
46.12	159	154	243	231
46.14	139	135	262	216
46.16	289	128	250	161
46.18	185	128	262	164
46.2	159	135	286	185
46.22	151	137	292	161
46.24	169	130	299	156
46.26	154	114	286	139
46.28	137	117	299	125
46.3	137	117	286	137
46.32	135	137	296	125
46.34	132	144	282	130
46.36	121	182	303	137
46.38	156	125	262	142
46.4	139	139	286	154
46.42	144	119	292	130
46.44	142	154	299	137
46.46	125	137	276	156
46.48	130	149	289	161
46.5	132	154	272	161
46.52	130	159	266	154
46.54	154	154	259	156
46.56	121	166	292	142

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46.6	154	154	269	142
46.62	161	159	276	159
46.64	161	146	276	161
46.66	149	142	272	166
46.68	149	169	299	164
46.7	174	154	286	154
46.72	151	172	276	146
46.74	159	139	259	135
46.76	159	144	246	169
46.78	159	146	292	159
46.8	128	149	282	180
46.82	142	159	262	154
46.84	154	142	246	156
46.86	137	161	243	174
46.88	125	139	262	142
46.9	146	159	237	164
46.92	130	142	243	156
46.94	137	144	266	125
46.96	132	159	228	164
46.98	151	149	253	156
47	117	180	269	164
47.02	123	177	259	154
47.04	146	199	250	159
47.06	128	180	234	172
47.08	125	154	228	177
47.1	144	177	250	185
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47.16	144	204	228	193
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47.22	154	174	240	185
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47.32	166	174	259	172
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47.38	164	151	243	156
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47.48	193	156	262	159
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47.52	188	121	262	166
47.54	185	132	237	161

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47.64	164	144	237	172
47.66	159	130	259	190
47.68	161	139	246	180
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47.72	151	156	225	213
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47.78	130	130	234	174
47.8	123	164	246	210
47.82	156	121	210	188
47.84	137	130	253	149
47.86	146	123	250	164
47.88	137	121	243	174
47.9	164	128	231	135
47.92	151	139	246	121
47.94	144	135	228	146
47.96	149	110	259	144
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48.02	132	121	240	149
48.04	139	110	243	144
48.06	132	96	272	137
48.08	125	135	256	135
48.1	130	121	253	144
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48.14	142	100	253	123
48.16	137	123	259	146
48.18	125	125	272	123
48.2	130	119	262	128
48.22	146	100	246	149
48.24	139	132	259	121
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48.28	139	114	292	130
48.3	151	137	266	128
48.32	161	149	289	130
48.34	177	130	269	154
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48.44	121	151	266	159
48.46	166	139	266	135
48.48	144	193	231	169
48.5	154	154	253	164
48.52	132	154	269	166

48.54	135	151	276	159
48.56	139	161	246	161
48.58	117	164	282	166
48.6	128	159	272	180
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48.64	137	142	289	174
48.66	128	169	266	172
48.68	123	161	246	188
48.7	102	137	222	180
48.72	125	142	253	164
48.74	135	159	256	159
48.76	121	130	243	135
48.78	159	110	256	151
48.8	135	137	240	151
48.82	121	119	262	149
48.84	135	130	231	142
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48.88	132	121	253	132
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48.94	144	135	237	108
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49.04	146	117	225	117
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49.08	142	94	246	114
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49.18	156	104	213	117
49.2	130	112	216	130
49.22	128	92	234	130
49.24	135	123	240	135
49.26	121	130	207	135
49.28	132	128	216	132
49.3	117	108	207	135
49.32	135	108	225	149
49.34	128	98	216	154
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49.4	110	125	243	146
49.42	121	130	234	219
49.44	121	114	219	151
49.46	119	92	213	156
49.48	137	130	202	149
49.5	144	123	240	121

49.52	102	123	216	117
49.54	117	117	225	151
49.56	114	130	228	139
49.58	108	149	222	128
49.6	112	121	207	139
49.62	110	110	210	139
49.64	123	128	210	137
49.66	100	119	222	137
49.68	92	121	213	149
49.7	135	128	237	110
49.72	121	110	193	130
49.74	119	119	207	139
49.76	128	112	207	128
49.78	108	132	225	121
49.8	104	130	222	125
49.82	106	108	199	121
49.84	119	137	222	130
49.86	100	135	207	144
49.88	112	104	222	137
49.9	114	132	225	130
49.92	102	112	210	137
49.94	92	94	204	161
49.96	121	102	202	123
49.98	98	100	196	125
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TABLE B

2θ and d-spacing values of the significant XRPD peaks shown by arrows in Figure 15 for smilagenin in form VI (smilagenin channel hydrate). The relative intensity of each peak as a percentage of the intensity of the strongest peak is also shown. λ is 1.5406Å and the 2θ range is 2.4° to 27.5°. The measurements were conducted at 25°C (room temperature).

Angle (2θ)/°	*d* / Å	Relative intensity (%)
3.463	25.49368	3.0
3.930	22.46393	7.1
6.467	13.65546	15.6
7.000	12.61750	3.6
7.851	11.25135	11.3
8.667	10.19453	3.2
10.130	8.72471	8.3
11.213	7.88477	3.5

11.844	7.46603	4.2
12.421	7.11998	8.7
13.007	6.80100	12.1
13.642	6.48582	20.4
13.959	6.33900	42.5
14.236	6.21630	29.5
14.625	6.05196	28.8
15.059	5.87850	23.5
15.566	5.68787	15.5
16.550	5.35198	24.2
16.900	5.24192	48.0
17.221	5.14492	100.0
17.818	4.97399	26.7
18.377	4.82384	34.3
19.354	4.58246	18.7
19.752	4.49103	19.8
20.312	4.36847	26.0
21.837	4.06663	16.2
23.125	3.84295	19.7
23.630	3.76205	15.8
24.904	3.57235	11.7
25.868	3.44136	17.0
26.540	3.35581	13.2
27.100	3.28765	12.4

TABLE C

2θ and d-spacing values of the significant XRPD peaks shown by arrows in Figure 16 for smilagenin in form VII (smilagenin IPA solvate). The relative intensity of each peak as a percentage of the intensity of the strongest peak is also shown. λ is 1.5406Å and the 2θ range is 2.4° to 27.5°. The measurements were conducted at 25°C (room temperature).

Angle (2θ)/°	*d* / Å	Relative intensity (%)
6.459	13.67403	43.0
7.184	12.29531	18.4
10.215	8.65248	11.5
11.581	7.63461	25.4
12.639	6.99803	73.1
13.030	6.78879	100.0
13.658	6.47790	61.2
14.176	6.24260	93.2
15.150	5.84325	53.7

15.534	5.69963	82.5
16.378	5.40768	67.2
16.700	5.30424	56.8
17.276	5.12881	53.3
18.129	4.88935	51.4
18.820	4.71129	65.6
19.316	4.59146	60.0
20.334	4.36377	66.7
22.965	3.86941	44.9
23.523	3.77887	42.3
24.752	3.59400	37.5
25.448	3.49721	39.3

The foregoing broadly describes the present invention without limitation. Variations and modifications as will be readily apparent to those of ordinary skill in this art are intended to be covered by the present application and resultant patent(s).

CLAIMS

1. Smilagenin in any one or more of crystalline forms I, III, IIIA, V, VI and VII as defined herein.

2. Smilagenin according to claim 1, in crystalline form I.

3. Smilagenin according to claim 1, in crystalline form III.

4. Smilagenin according to claim 1, in crystalline form IIIA.

5. Smilagenin according to claim 1, in crystalline form V.

6. Smilagenin according to claim 1, in crystalline form VI.

7. Smilagenin according to claim 1, in crystalline form VII.

8. Smilagenin channel hydrate.

9. Smilagenin monohydrate.

10. Smilagenin hydrate at a hydration stoichiometry other than 1:1.

11. Smilagenin *iso*-propyl alcohol solvate.

12. Amorphous smilagenin.

13. A material according to any one of the preceding claims, substantially free of another form of smilagenin and/or substantially free of other steroidal sapogenins and/or steroidal saponins.

14. A material according to any one of the preceding claims in at least about 50% by weight pure form.

15. A material according to any one of the preceding claims in at least about 90% by weight pure form.

16. A material according to any one of the preceding claims in at least about 95% by weight pure form.

17. A material according to any one of the preceding claims in substantially pure isolated form prepared on a kilogram scale.

18. Smilagenin *iso*-propyl alcohol solvate according to claim 11, when present in substantially pure isolated form prepared on a kilogram scale by precipitation from a solution of relatively impure smilagenin in *iso*-propyl alcohol that has been reduced in volume by azeotropic distillation.

19. Crystalline pharmaceutical or edible grade anhydrous unsolvated smilagenin, when obtained by crystallisation from a solution of substantially pure smilagenin *iso*-propyl alcohol (IPA) solvate in an anhydrous IPA-compatible organic solvent which does not form a solvate with smilagenin.

20. Smilagenin according to claim 19, in crystalline form I or III as defined herein.

21. Smilagenin according to claim 19 or claim 20, when prepared on a kilogram scale.

22. Smilagenin according to any one of claims 19 to 21, when prepared by a non-batchwise process.

23. Smilagenin according to any one of claims 19 to 21, wherein the anhydrous IPA-compatible organic solvent which does not form a solvate with smilagenin comprises acetone.

24. A composition comprising a material according to any one of the preceding claims in admixture with one or more further component selected from: one or more other materials according to any one of the preceding claims, another form of smilagenin, any other biologically active material, and any biologically inactive material.

25. A composition according to claim 24, wherein the other form of smilagenin, when present, is crystalline form II as defined herein.

26. A composition according to claim 24 or claim 25, for use as a medicament, foodstuff, food supplement or beverage.

27. A material according to any one of claims 1 to 23, for use as a medicament, foodstuff, food supplement or beverage.

28. A method of preparing a composition according to any one of claims 24 to 26, comprising admixing a material according to any one of claims 1 to 23 with one or more further component selected from: one or more other materials according to any one of claims 1 to 23, another form of smilagenin, any other biologically active material, and any biologically inactive material.

29. Use of a material or composition according to any one of claims 1 to 25 in the manufacture of a medicament, foodstuff, food supplement or beverage.

30. Use according to claim 29, wherein the medicament, foodstuff, food supplement or beverage is for the treatment of a condition selected from: high blood cholesterol levels, obesity and diabetes obesity syndromes, cognitive dysfunction and allied conditions, non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration and loss of receptor function in the absence of cognitive, neural or neuromuscular impairment.

31. A method of treatment of a human or non-human animal suffering from, or susceptible to, a condition selected from: high blood cholesterol levels, obesity and diabetes obesity syndromes, cognitive dysfunction and allied conditions, non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration and loss of receptor function in the absence of cognitive, neural or neuromuscular impairment, which comprises administering to the said human or non-human animal an effective amount of a material or composition according to any one of claims 1 to 23.

32. A method according to claim 31, wherein the animal is a human.

33. A method for obtaining pharmaceutical or edible grade smilagenin or a derivative thereof, wherein at least one step of the process includes preparing a material according to any one of claims 1 to 25.

34. A method according to claim 33, wherein the material is prepared in the physical form of an isolated dry solid or in a liquid medium such as a crystal slurry.

35. A method according to claim 33 or claim 34, wherein the smilagenin is prepared in the form of anhydrous unsolvated smilagenin.

36. A method according to any one of claims 33 to 35, further comprising formulating the resultant pharmaceutical or edible grade smilagenin or derivative thereof into a medicament, foodstuff, food supplement or beverage.

37. A method of adjusting smilagenin between the amorphous form and the crystalline forms I, II, III, IIIA, V, VI and VII as herein defined, comprising precipitation of an adjusted form of smilagenin from a solution of a first such form of smilagenin in an appropriate organic solvent or solvent mixture, optionally in the presence of water, to obtain the adjusted form of smilagenin.

38. A method according to claim 37, wherein the smilagenin is adjusted between the amorphous form and the crystalline forms I, II, III, IIIA and V as herein defined.

39. A method according to claim 37 or claim 38, wherein the adjusted form of smilagenin comprises a material according to any one of claims 1 to 23.

40. A method of adjusting the hydration level of smilagenin between the anhydrous, dihydrate and intermediate levels, comprising precipitation or other crystallisation of a first form of smilagenin from a solution thereof in an appropriate organic solvent or solvent mixture, optionally in the presence of water, to obtain smilagenin at a said adjusted hydration level.

41. A method according to claim 40, wherein the adjusted form of smilagenin comprises a material according to any one of claims 1 to 10, 12 to 17 and 19 to 23.

42. A method according to any one of claims 33 to 41, further comprising preparing a derivative of smilagenin from the material initially obtained.

43. A method according to claim 42, wherein the derivative is a prodrug of smilagenin.

44. Smilagenin, when prepared by a method according to any one of claims 33 to 41.

45. A method of preparing a prodrug of smilagenin, which comprises esterifying a material according to any one of claims 1 to 23 and 44.