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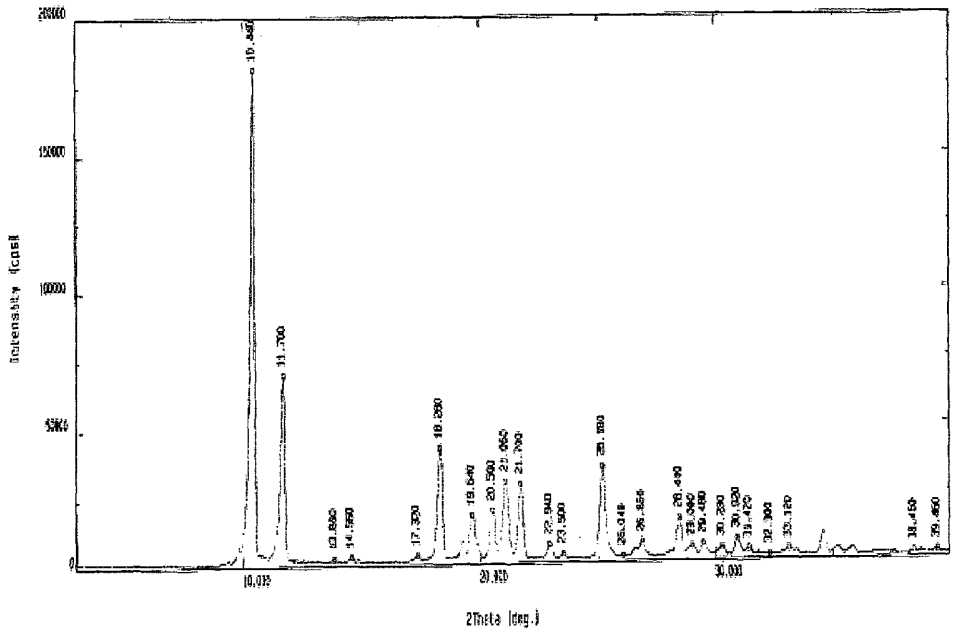
(54) **Title:** A POLYMORPHIC FORM OF NARWEDINE AND ITS USE IN THE SYNTHESIS OF GALANTAMINE



(57) **Abstract:** The present invention relates a polymorphic form of narwedine (Form B) and processes for the preparation thereof. Also provided is a process for the synthesis of galantamine using a polymorph of narwedine (Form B).

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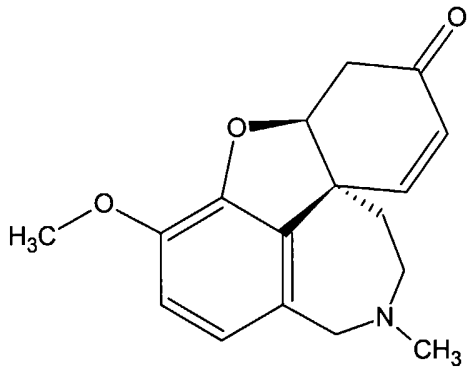
A POLYMORPHIC FORM OF NARWEDINE AND ITS USE IN THE SYNTHESIS OF GALANTAMINE

Field of the Invention

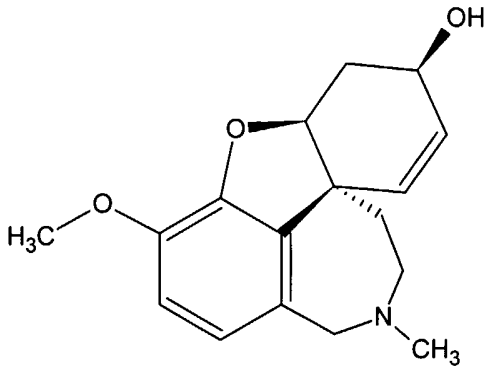
The present invention relates a polymorphic form of narwedine (Form B) and processes for the preparation thereof. Also provided is a process for the synthesis of galantamine using a polymorph of narwedine (Form B).

Background of the Invention

(4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2ef][2] benzazepin-6-one, commonly known as narwedine (Formula II), is a tertiary amaryllidaceae alkaloid which is useful as an intermediate in the synthesis of (-)-galantamine (Formula III). Galantamine is a 6-hydroxy derivative of narwedine and is indicated in the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.



FORMULA II



FORMULA III

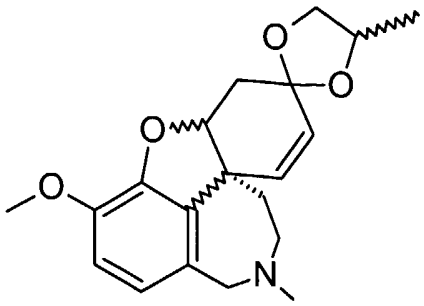
Narwedine is isolated from bulbs of nineteen species of trumpet narcissus, twelve species of cup narcissus, and eight species of filled narcissus (doubles) by an extraction process followed by chromatographic purification of the fractions to get crystalline narwedine (hereinafter referred to as Form A of narwedine) having a melting point of 188°C -190°C.

Galantamine can be isolated from daffodils (*Narcissus pseudonarciss us L.*) by an extraction process, but this method is quite expensive for pharmaceutical grade material, even when taking into account large-scale production efficiencies.

Several synthetic processes for the preparation of narwedine from galantamine and other related alkaloids are known. Barton et al., Journal of the Chemical Society, Abstracts, 806-817 (1962). Narwedine may be isolated from the reaction mass by several different column chromatography techniques. One such technique uses 95% ethanol, wherein racemic narwedine having a melting point range of 187-190°C is obtained. A similar melting point for narwedine was observed when it was isolated by column chromatography using ethyl acetate and benzene as an eluent. The product so obtained after sublimation gave racemic narwedine having a melting point in the range of 178°C - 186°C. However, when sublimation was carried out under a vacuum, the melting point of 186°C -190°C is observed again.

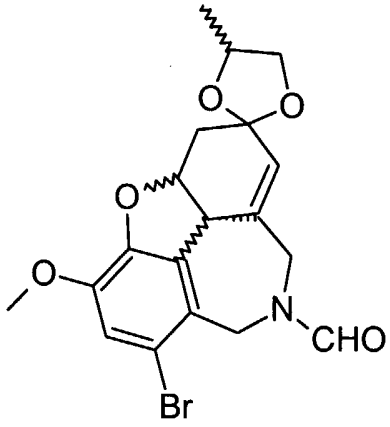
Notwithstanding these advances, the synthetic approach to commercial scale production of narwedine and (-)-galanthamine in a high purity, pharmaceutical grade is still problematic. Common problems include the formation of impurities, low cost effectiveness and low yields.

U.S. Patent No. 6,407,229 discloses a process for the preparation of narwedine and galantamine wherein narwedine isopropylene ketal (Formula I) (hereinafter referred to as IP ketal) is used as an intermediate.



FORMULA I

IP ketal is formed by reducing the N-formyl isopropylene glycol ketal (Formula IV), wherein the N-formyl group is reduced to a N-methyl group and debromo-hydrogenation is simultaneously achieved.



FORMULA IV

The IP ketal is isolated and then hydrolyzed using an acid to get narwedine (Formula II). The IP ketal formed via this process is unstable in acidic conditions and should not be stored for a long time before converting to narwedine.

The present inventors have now surprisingly found that IP ketal (Formula I) can be isolated as its acid addition salt by treating it with an acid. This provides a method for purification of the IP ketal in spite of having poor stability in acidic conditions. The salt of IP ketal that is formed is stable for about five to six days when stored under anhydrous conditions. The inventors have also found that it is possible to prepare a highly pure narwedine or salt thereof having a purity above 98% as measured by HPLC. This form of narwedine may then be used in the production of galantamine.

Summary of the Invention

In one general aspect there is provided a polymorphic form B of narwedine having a characteristic X-Ray Diffraction (XRD) pattern as depicted in Figure 1. Embodiments of the polymorphic form B of narwedine may include one or more of the following features. For example, the polymorphic form B of narwedine may be incorporated into a pharmaceutical composition. Further, the pharmaceutical composition may further include galantamine. The pharmaceutical composition may be administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

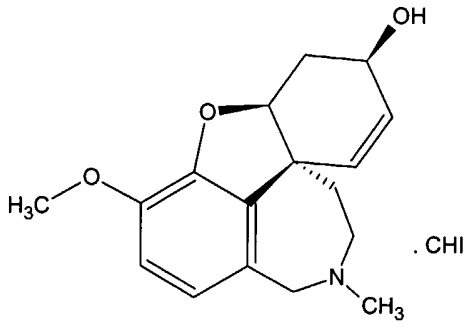
In another general aspect there is provided a polymorphic form B of narwedine, which includes XRD 2 theta values of 10.4, 11.7, 18.2 and 25.1. Embodiments of the polymorphic form B of narwedine may include one or more of the following features. For example, the polymorphic form B of narwedine may be present in a pharmaceutical composition. Further, the pharmaceutical composition further may include galantamine. The pharmaceutical composition may be administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

The polymorphic form B of narwedine may exhibit XRD which has 2 theta peaks at 10.44, 11.70, 13.85, 14.56, 17.32, 18.28, 19.64, 20.50, 21.05, 21.70, 22.94, 23.50, 25.18, 26.04, 26.86, 28.44, 29.00, 29.48, 30.28, 30.92, 31.42, 32.30, 33.12, 38.46 and 39.46.

In another general aspect there is provided a process for the preparation of polymorphic form B of narwedine. The process includes stirring narwedine with one or more C1-4 primary, secondary or tertiary alkanols; optionally heating the reaction mass to a reflux temperature; and isolating the polymorphic form B of narwedine from the reaction mass obtained thereof.

Embodiments of the polymorphic form B of narwedine may include one or more of the following features. For example, the one or more C1-4 primary, secondary or tertiary alkanols may be methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

The process may further include reducing the form B of narwedine with a reducing agent, in the presence of an organic solvent to get racemic galantamine or salt thereof; treating the racemic product of step a) with a chiral auxiliary to get (-)-isomer (Formula V),

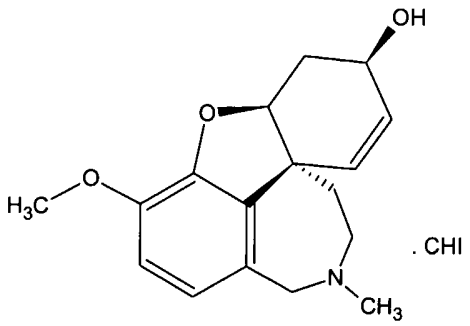


FORMULA V

wherein CHI represent the chiral auxiliary used; and converting the (-)- isomer (Formula V) to produce galantamine or a salt thereof.

The process may further include incorporating galantamine into a pharmaceutical composition. The pharmaceutical composition may further include polymorphic form B of narwedine and may be administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

In another general aspect there is provided a process for the preparation of (-)-galantamine or a salt thereof. The process includes reducing form B of narwedine with a reducing agent, in the presence of an organic solvent to get racemic galantamine or salt thereof; treating the racemic product of step a) with a chiral auxiliary to get (-)-isomer (Formula V),



FORMULA V

wherein CHI represent the chiral auxiliary used; and converting the (-)- isomer (Formula V) to produce galantamine or a salt thereof.

Embodiments of the process may include one or more of the following features. For example, the reducing agent may include metal hydrides and metal borohydrides. The reducing agent may be one or more of L-selectride, lithium aluminum hydride, lithium borohydride, and vitride.

The organic solvent may be one or more of tetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, N-methylpyrrolidine, and N,N-dimethylformamide. The chiral auxiliary may be di-4-toluoyl-D-tartaric acid.

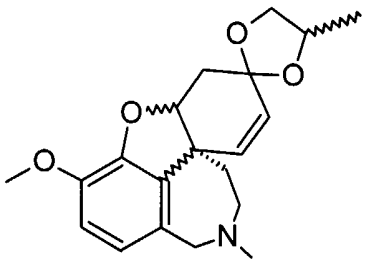
The process may further include purifying the galantamine or a salt thereof and the galantamine may be incorporated into a pharmaceutical composition. The pharmaceutical composition may be administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

Detailed Description of the Drawing

Figure 1 depicts the XRD pattern of Form B of narwedine.

Detailed Description of the Invention

The present invention provides for an acid addition salt of IP ketal (Formula I).

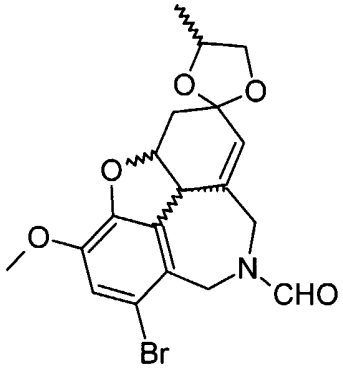


FORMULA I

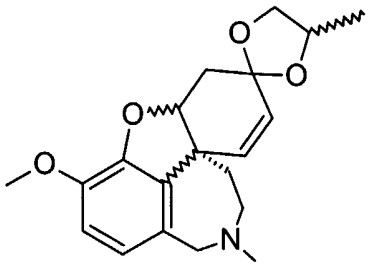
For example, a hydrobromide salt of IP ketal (Formula I) may be formulated. The hydrobromide salt of IP ketal is stable for about five to six days when stored in suitable anhydrous conditions.

Also provided is a process for preparation of an acid addition salt of IP ketal (Formula I). The process includes:

a) reducing N-formyl isopropylene glycol ketal (Formula IV) with a reducing agent to get IP ketal (Formula I);



FORMULA IV



FORMULA I

b) converting the IP ketal to its acid addition salt by treating it with suitable acid at a pH of about 3.2 to about 4.0; and

c) isolating the acid addition salt of IP ketal from the resulting reaction mass.

The N-Formyl propylene glycol ketal (Formula IV) used in the process may be prepared by the process described in Kueenburg et al., Organic Process Research & Development, 3(6), 425-431 (1999) and U.S. Patent No. 6,407,229.

The N-formyl isopropylene glycol ketal (Formula IV) is dissolved in a suitable organic solvent and reduced using a suitable reducing agent. Suitable reducing agents capable of reducing a formyl group to a methyl group are known to a person of ordinary skills in the art through several literature references. For example, metal hydrides and metal borohydrides, such as lithium aluminum hydride, lithium borohydride, Vitride®, and L-selectride® may be used as reducing agents. Suitable organic solvents include Tetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, N-methylpyrrolidine and

N,N-dimethylformamide. The reduction is carried out at temperature of between about -20°C to about 60°C.

After completion of reaction, the reaction mass is diluted with toluene and quenched by adding saturated sodium sulphate solution. The resultant mass is filtered and the organic layer is concentrated to get residue of IP ketal (Formula I).

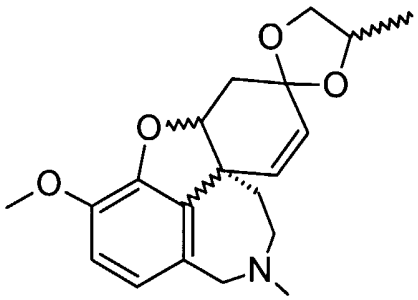
The residue is treated with a suitable acid at a pH of about 3.2 to about 4.0 to get a novel acid addition salt of IP ketal. Suitable acids include hydrobromic acid, hydroiodic acid, acetic acid, propionic acid, methensulphonic acid, and p-toluenesulphonic acid. For example, hydrobromic acid may be used to produce the hydrobromide salt of IP ketal.

The hydrobromide salt has been studied for its stability under different storage conditions. It was found that when the hydrobromide salt is stored at 35% relative humidity at about 15°C to 20°C, it is stable for a minimum of five to six days. The stability samples were analyzed by HPLC method.

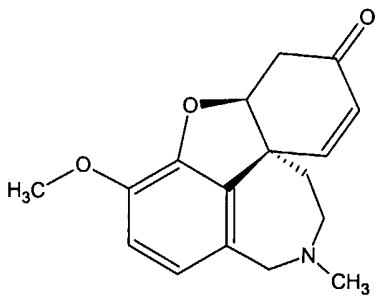
Also provided is a process for preparation of narwedine (Formula II) using the acid addition salt of IP ketal. The process includes:

a) hydrolyzing the acid addition salt of IP ketal (Formula I) using an acid; and

b) isolating the narwedine (Formula II) from the resulting reaction mixture.



FORMULA I



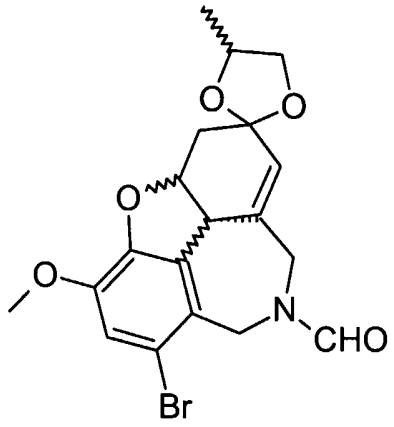
FORMULA II

The acid addition salt of IP ketal is hydrolyzed in aqueous conditions using a suitable mineral acid. The reaction is carried out at a temperature of about 25°C to 70°C. After completion of reaction, the pH of the reaction mass is adjusted to above 9, preferably 9.2, using an aqueous ammonia solution. The separated solid is filtered and washed with water to get narwedine.

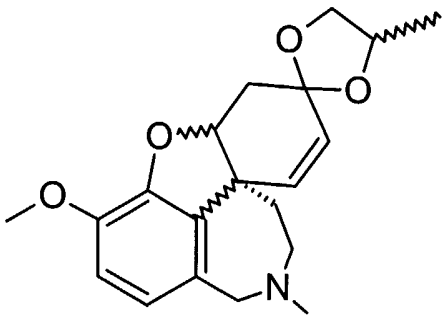
The narwedine is then crystallized from a suitable organic solvent to yield narwedine having a purity above 98% as measured by HPLC. Suitable organic solvents for crystallization include lower alkanols, ketones, esters, polar aprotic solvents, aromatic hydrocarbons, chlorinated hydrocarbons or mixtures thereof. The narwedine of Formula II thus obtained can then be converted to its salt by treating with suitable acid.

Also provided is a process for the preparation of substantially pure narwedine or salt thereof. The process includes:

a) reducing N-formyl propylene glycol ketal (Formula IV) with a reducing agent to get IP ketal (Formula I);



FORMULA IV



FORMULA I

b) optionally converting IP ketal (Formula I) to its salt at a pH of about 3.2 to about 4.0, and

c) hydrolyzing the IP ketal or salt thereof to get a substantially pure narwedine or salt thereof.

The present invention also provides a novel polymorphic form of narwedine (herein after designated as Form B of narwedine). Form B of narwedine has a characteristic X-Ray Diffraction (XRD) pattern as depicted in Figure 1. The XRD of Form B of narwedine shows characteristic 2 theta values of 10.44, 11.70, 13.85, 14.56, 17.32, 18.28, 19.64, 20.50, 21.05, 21.70, 22.94, 23.50, 25.18, 26.04, 26.86, 28.44, 29.00, 29.48, 30.28, 30.92, 31.42, 32.30, 33.12, 38.46 and 39.46.

The polymorphic Form B of narwedine may be prepared by:

a) stirring narwedine with a C_{1-4} primary, secondary or tertiary alkanol;

b) optionally heating the reaction mass to reflux temperature; and

c) isolating the narwedine polymorphic Form B from the reaction mass.

The narwedine used as the starting material may be prepared by any conventional process known in the art. Suitable C_{1-4} primary, secondary and tertiary alkanols include one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

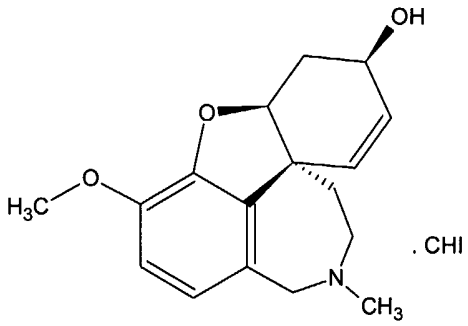
The reaction mass may be optionally heated to about reflux temperature of the alkanol used and then subsequently cooled to about -20°C to 35°C. The precipitated product is filtered and washed with a small quantity of alkanol and then dried to get Form B of narwedine having the XRD as depicted in Figure 1.

The XRD of the samples were determined by using X-Ray Diffractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1 0, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 A.

(-)-Galantamine or salt thereof may be produced from the substantially pure narwedine or salt thereof. The process includes;

a) reducing the substantially pure narwedine or salt thereof having a purity above 98% with a reducing agent in the presence of an organic solvent to get racemic galantamine or salt thereof;

b) treating the racemic product of step a) with a chiral auxiliary to get the (-)-isomer of Formula VI



FORMULA VI

wherein CHI represents the chiral auxiliary used; and

c) converting the (-)-isomer (Formula VI) to galantamine or salt thereof and then optionally purifying.

The preparation of the substantially pure narwedine or salt thereof having purity above 98% as measured by HPLC is described above. The substantially pure narwedine is added in lots to a pre-cooled solution of reducing agent in an organic solvent.

The suitable reducing agent may include metal hydrides and metal borohydrides, wherein the metal may be lithium, aluminum or sodium. For example, the reducing agent may be Vitride ®, L-selectride®, lithium aluminium hydride, or lithium borohydride.

Suitable organic solvents include tetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, N-methylpyrrolidine and N,N-dimethylformamide. The reduction is carried out at a temperature of between about -70°C to 10°C. After completion of the reduction, the temperature of the reaction mass may be raised to about 20°C and the excess reducing agent, as well as side products formed, can be quenched by addition of ethanol.

The resultant mass after filtration yields racemic galantamine which may be isolated by converting it to a salt. For example, the racemic galantamine may be treated

with hydrobromic acid thus producing the hydrobromide salt of galantamine. The solid salt may be filtered from the reaction mass and dried suitably.

Racemic galantamine or its salt obtained is then dissolved in a suitable organic solvent, water or mixtures thereof. If salt is used then it is first converted to free base by treating with dilute alkali solution.

Suitable organic solvent may be water-miscible or immiscible and may include ethyl acetate, methyl formate, methyl acetate, n-butyl acetate, tetrahydrofuran, methanol, ethanol, isopropanol, n-butanol, dichloromethane, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, ethyl methyl ketone, diisobutyl ketone and acetonirile.

The separated base is then extracted in a water immiscible organic solvent. Suitable water immiscible organic solvents include ethyl acetate, methyl formate, methyl acetate, n-butyl acetate, dichloromethane, chloroform and carbon tetrachloride.

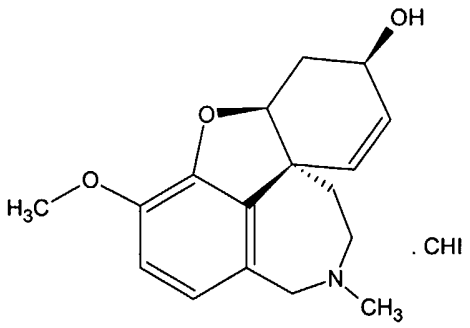
The organic extract is concentrated and the residue obtained is re-dissolved in an alcoholic solvent, such as methanol, ethanol, isopropanol, n-butanol and n-propanol. To this solution a chiral auxiliary is added and the resultant mass is stirred for sufficient time at lower temperature to induce crystallization of the desired (-)-isomer of galantamine as its salt of chiral auxiliary (Formula V). For example, the chiral auxiliary may be di-4-toluoyl-D-tartaric acid. The precipitated product is filtered, washed with cold alcoholic organic solvent and recrystallized if required to get desired purity.

The chiral auxiliary salt (Formula V) is then converted to (-)-galantamine by treating it with a dilute alkali solution. For example, the alkali solution may be ammonia. (-)-Galantamine is then isolated from the reaction mass by an extractive work-up. The solution of (-)-galantamine may then optionally be treated with an acid thus producing the salt of galantamine. The salt or the free base may also be optionally recrystallized to get galantamine or salt thereof.

(-)-Galantamine or a salt thereof may also be prepared from the polymorphic Form B of narwedine. The process includes:

a) reducing Form B of narwedine with a reducing agent in the presence of an organic solvent to get racemic galantamine or salt thereof;

b) treating the racemic product of step a) with a chiral auxiliary to get (-)-isomer (Formula V)



FORMULA V

wherein CHI represent the chiral auxiliary used; and

c) converting the (-)-isomer (Formula V) to produce galantamine or salt thereof, which may be optionally purified.

Figure 1 depicts XRD pattern of Form B of narwedine.

Powder XRD of the samples were determined by using X-Ray Difractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1 0, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 A.

The following examples are intended to illustrate the invention and not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

PREPARATION OF HYDROBROMIDE SALT OF IP KETAL

To a mixture of lithium aluminum hydride (32 gm) in tetrahydrofuran (560 ml), a slurry of N-formyl isopropylene glycol ketal (Formula IV) (80 gm) in tetrahydrofuran (160ml) was added at 0°C-10°C. The reaction mixture was stirred at 5°C-15°C for 1 hour followed by at 40°C-50°C for about 20 hours. It was cooled to 0°C-5°C and a mixture of toluene (400 ml) and hyflosupercel (20 gm) was added. Then a saturated sodium sulphate solution was added to quench the reaction mixture. It was filtered, washed with a mixture of toluene and tetrahydrofuran (1:1, 1600 ml) and the organic layer was recovered at 45°C-50°C under reduced pressure. The residue was dissolved in acetone (480 ml) and

aqueous hydrobromic acid (~48% w/w) was added to adjust the pH to about 3.5-3.8. The precipitated solids were filtered and washed with acetone to get the title compound.

Yield: 65 g

EXAMPLE 2

PREPARATION OF NARWEDINE

The solid narwedine propylene glycol ketal hydrobromide salt was stirred with a mixture of concentrated hydrochloric acid (32 ml) and water (48 ml) at 55°C-60°C for 30 minutes. After completion of the hydrolysis, the pH of the reaction mixture was adjusted with aqueous ammonia to about 9.0-9.2. The separated solids were filtered, washed with water (240 ml) and dried.

Yield: 30-31 grams

The product obtained above (20 gm) was stirred in a denatured spirit (60 ml) at a temperature of about 60°C-65°C for 30 minutes. The resultant mass was cooled to about 0°C-10°C and filtered after stirring for 30 minutes. The product was washed with a denatured spirit (20 ml) and dried under a vacuum to get the title compound.

Yield: 17.82 grams

Purity: 99.28% as measured by HPLC

EXAMPLE 3

PREPARATION OF SUBSTANTIALLY PURE NARWEDINE

To a mixture of lithium aluminum hydride (32 gm) in tetrahydrofuran (560 ml), a slurry of N-formyl propylene glycol ketal (Formula V) (80 gm) in tetrahydrofuran (160ml) was added at 0°C-10°C. The reaction mixture was stirred at 5°C-15°C for 1 hour followed by at 40°C-50°C for 20 hours. It was cooled to 0°C-5°C and a mixture of toluene (400 ml) and hyflosupercel (20 gm) was added. A saturated sodium sulphate solution was added to quench the reaction mixture. It was filtered, washed with a mixture of toluene and tetrahydrofuran (1:1, 1600 ml) and the organic layer was recovered at 45°C-50°C under reduced pressure. The residue was dissolved in acetone (480 ml) and aqueous hydrobromic acid (~48% w/w) was added to adjust the pH to about 3.5-3.8. The precipitated solids were filtered and washed with acetone. The solid narwedine propylene

glycol ketal hydrobromide salt was stirred with a mixture of concentrated hydrochloric acid (32 ml) and water (48 ml) at 55°C-60°C for 30 minutes. After completion of the hydrolysis, the reaction mixture was adjusted by adding aqueous ammonia to raise the pH to about 9.0-9.2. The separated solids were filtered, washed with water (240 ml) and dried.

Yield: 30-31 grams

The product obtained above (20 gm) was stirred in denatured spirit (60 ml) at a temperature of about 60°C-65°C for 30 minutes. The resultant mass was cooled to about 0°C-10°C and filtered after stirring for 30 minutes. The product was washed with a denatured spirit (20 ml) and dried under a vacuum to get the title compound.

Yield: 17.82 grams

Purity: 99.28% as measured by HPLC

EXAMPLE 4

PREPARATION OF POLYMORPHIC FORM B OF NARWEDINE

Narwedine (20 gm) was stirred in denatured spirit (60 ml) at a temperature of about 60°C-65°C for 30 minutes. The resultant mass was cooled to about 0°C-10°C and filtered after stirring for 30 minutes. The product was washed with denatured spirit (20 ml) and dried under a vacuum to get the title compound.

Yield: 17.82 g

XRD: As per Figure I

EXAMPLE 5

PREPARATION OF RACEMIC GALANTAMINE HYDROBROMIDE

L-Selectride (lithium tri-sec-butylborohydride, 1.0 M solution in tetrahydrofuran) (396.5 g) was charged under a nitrogen atmosphere, followed by THF (100 ml) at 0°C-5°C. This mixture was cooled to –20°C to -22°C and narwedine (100 g) was charged in lots over a period of about 3 hours at –18°C to –20°C. Tetrahydrofuran (25 ml) was used to wash the addition vessel and the reaction mixture was stirred for 30 minutes at –15°C to –20°C. It was heated to 20°C and ethanol (400 ml) was added. The reaction mixture was stirred for 30 minutes at 20°C – 30°C, filtered and washed with a mixture of

tetrahydrofuran and ethanol (200 ml, 1:1). The filtrate was cooled to 0°C to 5°C and aqueous hydrobromic acid (~48%, 82 ml) was added to adjust the pH at 3.0 to 3.5 at 0°C to 5°C. It was stirred for 2 hours at 0°C – 5°C. The separated solids were filtered, washed with cold ethanol (300 ml) and air dried at 50°C – 55°C till loss on drying was NMT 2.5%.

Yield: 116 grams

EXAMPLE 6

PREPARATION OF (-) GALANTAMINE TARTARATE

Racemic galantamine hydrobromide (100 gm) was dissolved in water (3200 ml) and the solution was filtered through a celite bed. The celite bed was washed with water (300 ml) and washings were combined with the filtrate. The combined aqueous layer was washed with dichloromethane (300 ml) and the organic layer was discarded. To the aqueous layer was charged dichloromethane (1000 ml) and adjusted the pH of the aqueous layer to 8.9 to 9.1 using aqueous ammonia at 0°C – 5°C. The aqueous layer was separated and extracted with dichloromethane (1000 ml). The combined organic layers were washed with water (2 x 300 ml) and the organic layer was concentrated under a vacuum at 30°C – 35°C. The residue was dissolved in methanol (200 ml) and cooled to 5°C – 10°C. Di-p-toluoyl-D-tartaric acid (105 gm) was separately dissolved in methanol (300 ml) and cooled to 5°C – 10°C. A solution of tartaric acid was added to the solution of the compound and methanol (250 ml) was used to transfer the total material. This mixture was stirred for 30 min at 5°C – 10°C and for 24 hours at 0°C – 2°C. The solids were filtered and washed with cold methanol (300 ml). The wet product was crystallized in ethanol (400 ml) by refluxing for 30 minutes followed by stirring at 0°C – 2°C for 3 hours, the solid was filtered and washed with cold ethanol (100 ml). Crystallization in ethanol was repeated again. Finally the product was refluxed with methanol (400 ml) for 30 minutes, cooled to 15°C – 20°C, stirred for 3 hours and filtered. It was washed with methanol (100 ml) and air dried at 50°C – 55°C till loss on drying was NMT 1.0%.

Yield: 57 grams

EXAMPLE 7

PREPARATION OF CRUDE GALANTAMINE HYDROBROMIDE

(-) Galantamine tartarate (100 grams) was taken in a mixture of dichloromethane (600 ml) and water (400 ml), and the pH of the mixture was adjusted to 8.9 to 9.1 using aqueous ammonia at 5°C – 10°C. The organic layer was separated and the aqueous layer was extracted with dichloromethane (600 ml). The combined organic layer was washed with water (2 x 300 ml). A mixture of ethanol and ~48% aqueous hydrobromic acid (1:1, 1 ml) was added to the organic layer and the mass was concentrated at 30°C – 35°C under reduced pressure. The free base obtained was dissolved in a mixture of ethanol (1260 ml) and water (110 ml). It was then cooled to 0°C – 5°C. A mixture of ethanol and ~48% aqueous hydrobromic acid (1:1, 32 ml) was added at 0°C – 5°C to bring pH 2.5 – 3.0, and stirred for 3 hours at 0°C – 5°C. The separated solids were filtered and washed with ethanol (200 ml) to afford crude wet galantamine hydrobromide. This material was carried as such for the next step.

Yield: 62 grams

EXAMPLE 8

PREPARATION OF HIGHLY PURE GALANTAMINE HYDROBROMIDE

Crude wet Galantamine hydrobromide (62 g) was taken in water (220 ml) and the pH of the mixture was adjusted to 8.9 to 9.1 using aqueous ammonia at 10°C – 15°C. The free base thus obtained was extracted in ethyl acetate (2 x 750 ml + 375 ml). The combined organic layers were washed with water (2 x 200 ml) and were concentrated at 45°C – 50°C at reduced pressure. The free base was dissolved in a mixture of ethanol (1150 ml) and water (100 ml) at 40°C – 50°C. The solution was filtered through micron filter and cooled to 0°C – 5°C. An ethanolic aqueous hydrobromic acid solution (1:1, 30 ml) was added to adjust pH at 2.5 to 3.0 at 0°C – 5°C. The resultant mass was stirred for 3 hours at 0°C – 5°C, filtered and washed with ethanol (300 ml). The solid product was dried under a vacuum at 50°C – 55°C till loss on drying is NMT 0.2% to get highly pure galantamine hydrobromide.

Yield: 38 grams

Impurity profile: a) Any single impurity: Less than 0.2% w/w

b) Total impurities: 0.42% w/w

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We claim:

1. A polymorphic form B of narwedine having a characteristic X-Ray Diffraction (XRD) pattern as depicted in Figure 1.

2. The polymorphic form B of narwedine of claim 1, wherein the polymorphic form B of narwedine is present in a pharmaceutical composition.

3. The polymorphic form B of narwedine of claim 2, wherein the pharmaceutical composition further comprises galantamine.

4. The polymorphic form B of narwedine of claim 2, wherein the pharmaceutical composition is administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

5. A polymorphic form B of narwedine comprising XRD 2 theta values of 10.4, 11.7, 18.2 and 25.1.

6. The polymorphic form B of narwedine of claim 5, wherein the polymorphic form B of narwedine is present in a pharmaceutical composition.

7. The polymorphic form B of narwedine of claim 6, wherein the pharmaceutical composition further comprises galantamine.

8. The polymorphic form according to claim 7, wherein the pharmaceutical composition is administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

9. The polymorphic form B of narwedine of claim 5, wherein the XRD has 2 theta peaks at 10.44, 11.70, 13.85, 14.56, 17.32, 18.28, 19.64, 20.50, 21.05, 21.70, 22.94, 23.50, 25.18, 26.04, 26.86, 28.44, 29.00, 29.48, 30.28, 30.92, 31.42, 32.30, 33.12, 38.46 and 39.46.

10. A process for the preparation of polymorphic form B of narwedine, the process comprising:

    a) stirring narwedine with one or more C_{1-4} primary, secondary or tertiary alkanols;

b) optionally heating the reaction mass to a reflux temperature; and

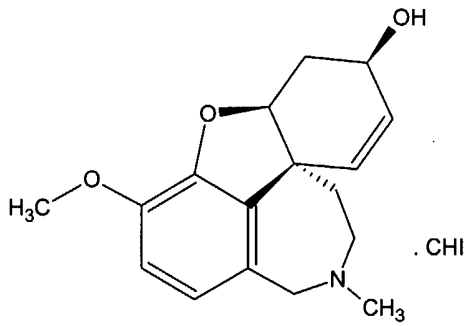
c) isolating the polymorphic form B of narwedine from the reaction mass obtained thereof.

11. The process according to claim 10, wherein the one or more C_{1-4} primary, secondary or tertiary alkanols comprise methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

12. The process of claim 10, further comprising:

a) reducing the Form B of narwedine with a reducing agent, in the presence of an organic solvent to get racemic galantamine or salt thereof;

b) treating the racemic product of step a) with a chiral auxiliary to get (-)-isomer (Formula V),



FORMULA V

wherein CHI represent the chiral auxiliary used; and

c) converting the (-)- isomer (Formula V) to produce galantamine or a salt thereof.

13. The process of claim 12, further comprising incorporating the galantamine into a pharmaceutical composition.

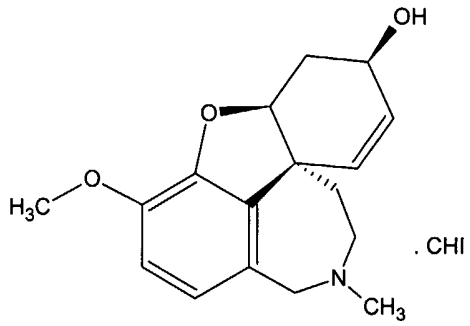
14. The process of claim 13, wherein the pharmaceutical composition further comprises polymorphic form B of narwedine.

15. The process of claim 13, wherein the pharmaceutical composition is administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.

16. A process for the preparation of (-)-galantamine or a salt thereof, the process comprising:

a) reducing Form B of narwedine with a reducing agent, in the presence of an organic solvent to get racemic galantamine or salt thereof;

b) treating the racemic product of step a) with a chiral auxiliary to get (-)-isomer (Formula V),



FORMULA V

wherein CHI represent the chiral auxiliary used; and

c) converting the (-)- isomer (Formula V) to produce galantamine or a salt thereof.

17. The process according to claim 16, wherein the reducing agent comprises metal hydrides and metal borohydrides.

18. The process according to claim 16, wherein the reducing comprises one or more of L-selectride, lithium aluminum hydride, lithium borohydride, and vitride.

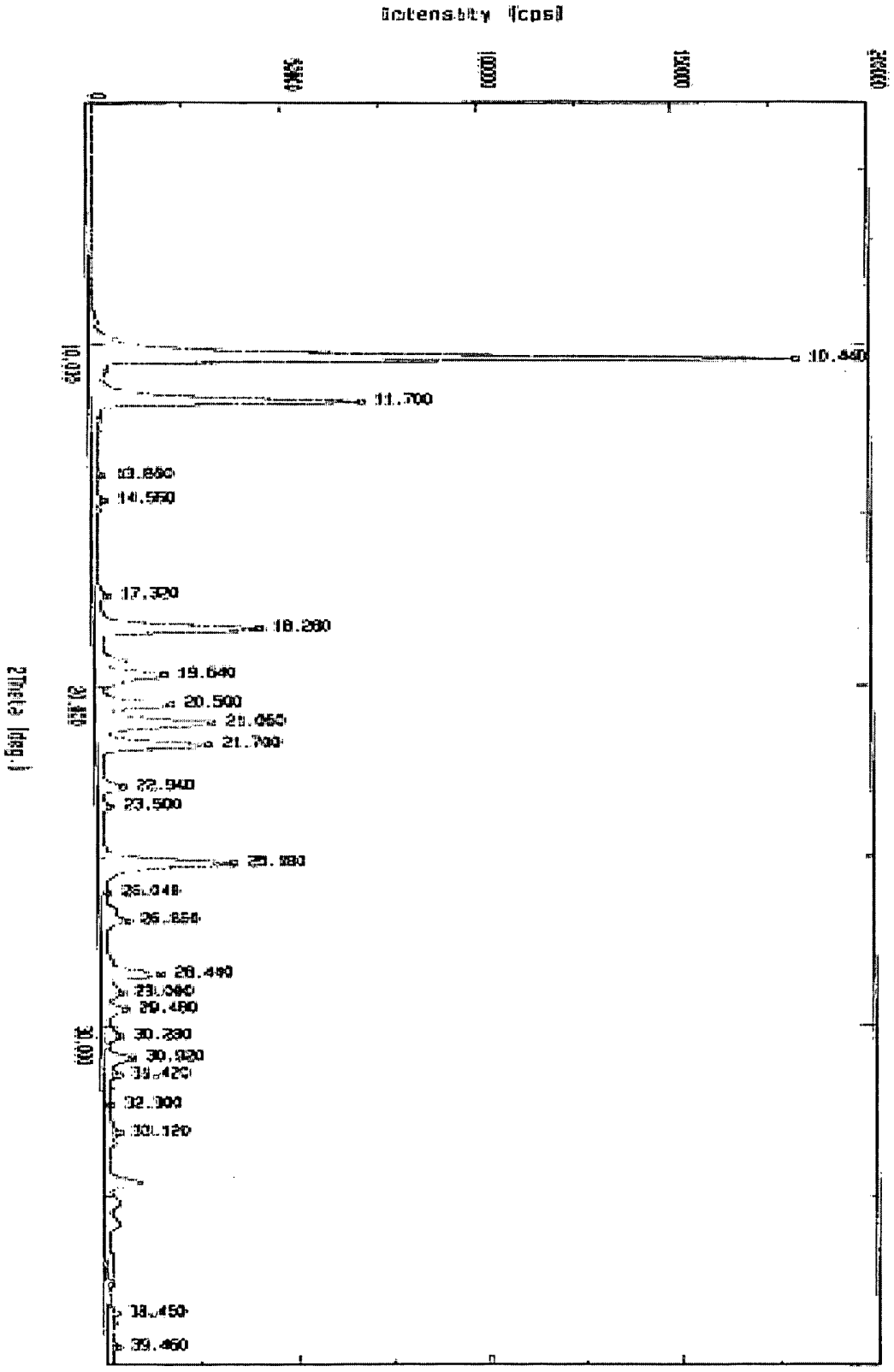
19. The process according to claim 16, wherein the organic solvent comprises one or more of tetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, N-methylpyrrolidine, and N,N-dimethylformamide.

20. The process according to claim 16, wherein the chiral auxiliary comprises di-4-toluoyl-D-tartaric acid.

21. The process according to claim 16, further comprising purifying the galantamine or a salt thereof.

22. The process according to claim 16, further comprising incorporating the galantamine into a pharmaceutical composition.

23. The process according to claim 22, wherein the pharmaceutical composition is administered for one or more of the treatment of Alzheimer's disease, dementia, mania, fatigue syndrome, schizophrenia and for inhibiting acetyl cholinesterase activity.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13.880
14.560
17.320
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19.640
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25.880
26.040
26.860
28.440
29.060
29.480
30.280
30.920
31.420
32.300
33.120
38.450
39.460

Figure 1