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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF 7-((3-CHLORO-6-METHYL-5,5-DIOXO-6,11-DIHYDRODIBENZO(C,FX 1,2) THIAZEPIN- 11-YL)AMINO)HEPTANOATE

(57) Abstract: The present invention relates to a novel process for the preparation of sodium 7-((3-Chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo(c,f)(1,2)thiazepin-11-yl)amino)heptanoate and intermediates. The invention also encompasses isolation of an essentially non-hygroscopic compound which is substantially pure.

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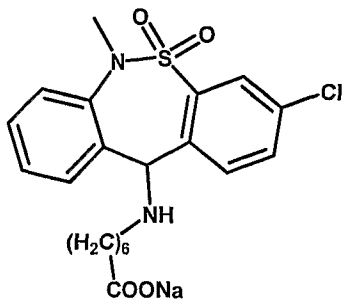
Novel Process for the Preparation of 7-((3-Chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo(c,f)(1,2)thiazepin-11-yl)amino)heptanoate

FIELD OF INVENTION

The present invention relates to a novel process for the preparation of sodium 7-((3-Chloro-6-methyl-5,5-dioxo-6,11-dihydrodibenzo(c,f)(1,2)thiazepin-11-yl)amino)heptanoate and intermediates. The invention also encompasses isolation of an essentially non-hygroscopic compound which is substantially pure.

BACKGROUND

Tianeptine is currently marketed in Europe as an antidepressant. Unlike the currently used antidepressants which inhibit the serotonin reuptake, Tianeptine enhances serotonin uptake without significant activity at any receptors or other monoamine transporters. The present invention relates to a novel process for the synthesis of Tianeptine.



Formula-I

STATE OF THE ART

Patents describing synthetic procedures for Tianeptine are listed below.

FR 2104728 describes a synthetic process for the preparation of Tianeptine and its therapeutic use. The patent describes the synthesis by the reaction of compound of Formula II and ethyl-7-aminoheptanoate.

EP 0671173 describes the synthesis of Tianeptine by the reaction of compound of Formula III and ethyl-7-bromoheptanoate.

US 6441165 describes a process for the synthesis of the intermediate of 11-amino-3-chloro-6,11-dihydro-5,5-dioxo-6-methyldibenzo[c,f][1,2]thiazepine.

European Pharmacopeia describes Tianeptine as a hygroscopic product. The content limit for water is about 5%. This poses problems for the handling and formulation of Tianeptine sodium. Hence there is a need for developing a stable and non-hygroscopic form of Tianeptine Sodium. The compound of Formula II, impurity D Ph Eur is 0.1%.

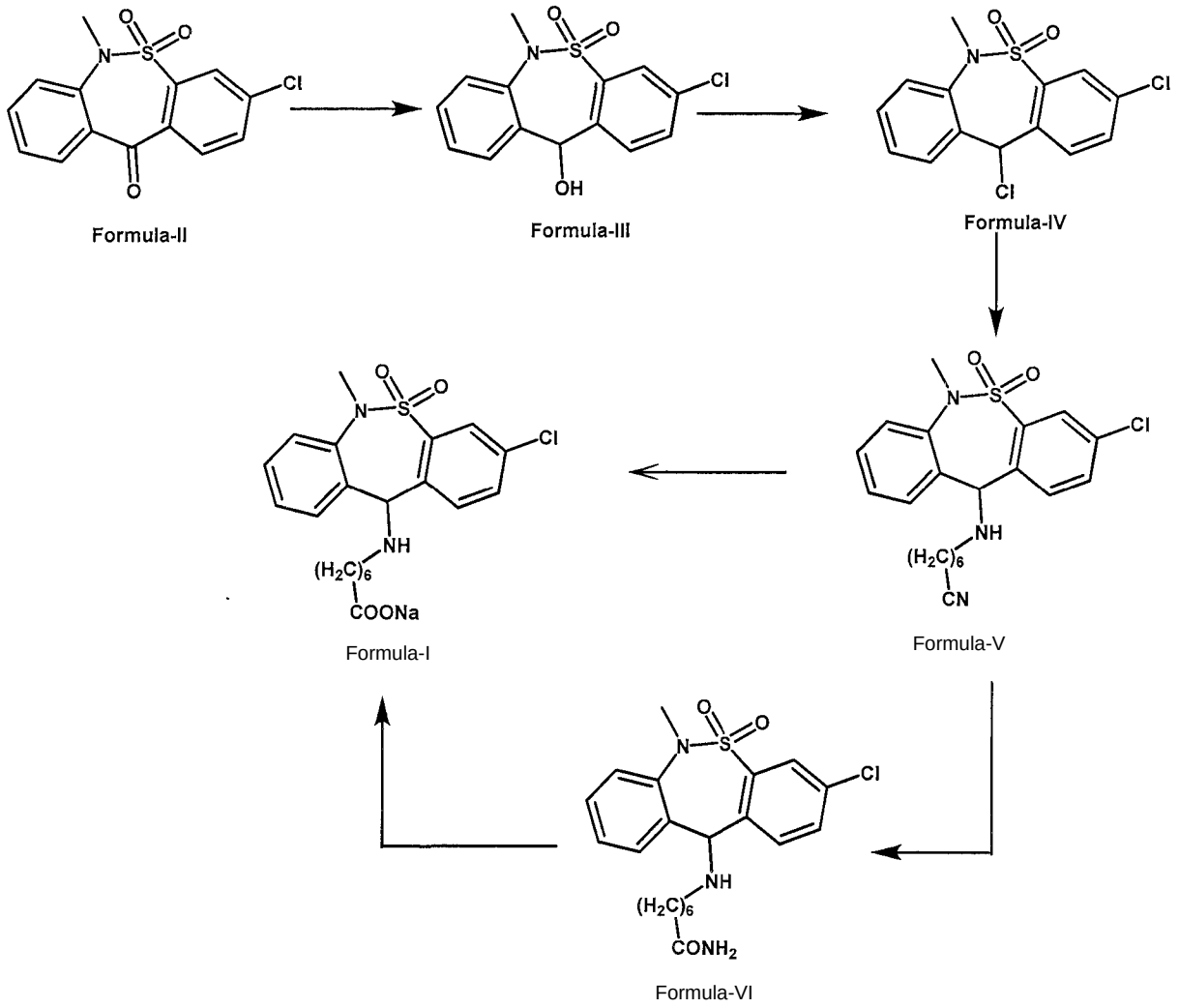
SUMMARY OF THE INVENTION

One of the objects of the invention was to provide a process for preparing of Tianeptine with improved yields.

Another object of the invention was to develop a process devoid of any dinner impurity and provide an improved method for the synthesis of Tianeptine.

Yet another object of the invention was to develop a process for Tianeptine which is commercially viable.

This invention provides an alternative method for preparing Tianeptine. 3-Chloro-6-methyl-dibenzo[c,f][1, 2]thiazepin-1 1(6H)-one-5,5-dioxide is reduced to give an alcohol which is further chlorinated to give compound of formula IV. The compound of formula IV is condensed with 7-aminoheptanitrile in the presence of a solvent with or without a base to give an intermediate for Tianeptine which is further hydrolyzed to give Tianeptine.

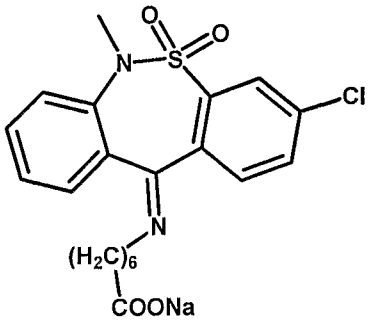


Scheme - 1

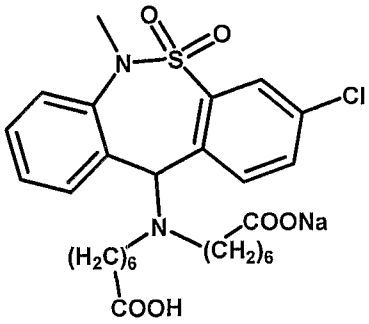
One of the objects of the invention was to provide a process for preparing of Tianeptine with improved yields and process.

One object of the invention was to develop Tianeptine sodium salt which is essentially non-hygroscopic.

Another object of the invention was to develop a process and thereby substantially pure Tianeptine which is devoid of any unsaturated impurity of Formula VII and dimer impurity of Formula VIII and provide an improved method for the synthesis of Tianeptine.

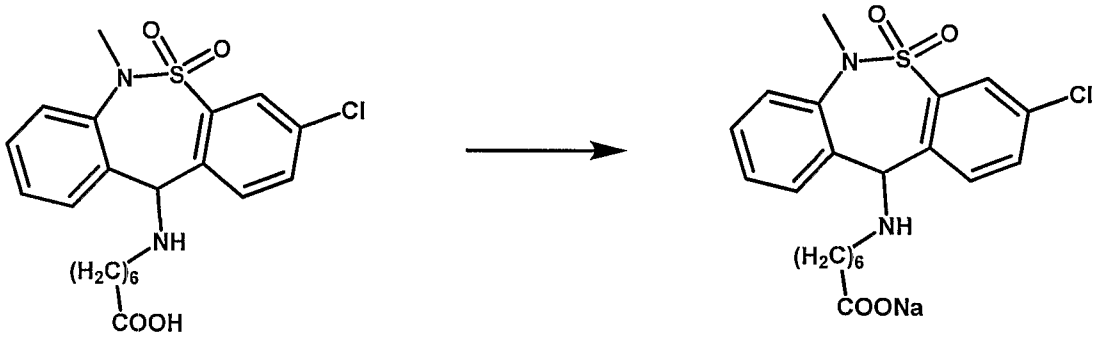


Formula-VII



Formula-VIII

This invention also provides an alternative method for preparing Tianeptine sodium salt I from Tianeptine free acid IX.



Formula IX

Formula-I

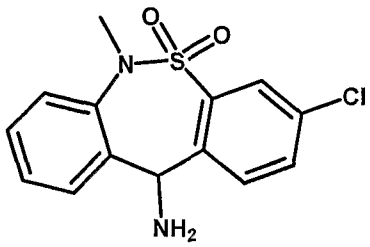
DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The compound of formula I is prepared by hydrolysis of cyano intermediate compound of Formula-V. The hydrolysis is carried out either in acidic conditions or basic conditions. The reaction is carried out preferably in presence of hydrochloric acid solution. The reaction is preferably carried out at room temperature to reflux conditions. Partial hydrolysis of compound of Formula-V can result in the amido compound of Formula-VI which can be further hydrolyzed either in acidic conditions or basic conditions to provide Tianeptine.

According to one aspect of the invention synthesis of the compound of Formula-V can be carried out by the reaction of 7-aminoheptanenitrile with compound of Formula IV. The reaction can be performed with or without a solvent and in presence or absence of a base. The reaction can be carried out at temperatures of 10-130 °C.

According to another aspect of the invention compound of Formula-V can be synthesized by the reaction of compound of Formula-X and 7-bromoheptanenitrile. The reaction can be performed with or without a

solvent and in presence or absence of a base. The reaction can be carried out at temperatures of 10-130 C.



Formula X

The compound of Formula I can be obtained from compound of Formula V either in presence of Acid or basic. The reaction is preferably carried out in presence of hydrochloric acid or sulfuric acid solutions at temperature ranging from 0 °C to reflux conditions. The compound of Formula VI can also be converted to Formula I in presence of Acid solutions or basic solutions preferably in presence of hydrochloric acid or sulfuric acid solutions at temperature ranging from 0 ^{0}C to reflux conditions.

The compound of Formula I is prepared from compound of Formula-IV in presence of sodium hydroxide and an alcohol or dichloromethane. The reaction is carried out preferably in presence of sodium hydroxide solution added in 0.85 to 1.1 equivalents ratio and preferably 0.9 to 0.95 equivalents with respect to compound of Formula IV. The reaction is carried out at -20 to 65 °C and is preferably carried out at 25-65 ^{0}C. The alcohols employed are methanol, ethanol, propanol, isopropanol, butanol preferably methanol and ethanol. The alkoxide employed is sodium methoxide, sodium ethoxide, sodium propoxide, sodium butoxide and the like and preferably sodium methoxide and sodium ethoxide.

According to one aspect of the invention the compound of Formula I i.e. Tianeptine sodium is prepared from compound of Formula-X i.e. Tianeptine free acid in presence of sodium alkoxide and an alcohol or dichloromethane. The reaction is carried out preferably in presence of sodium alkoxide added in 0.85 to 1.1 equivalents ratio with respect to compound of Formula IX. The reaction is carried out at -20 to 65 ^{0}C and is preferably carried out at 25-65 °C. The alcohols employed are methanol, ethanol, propanol, isopropanol, butanol preferably methanol and ethanol. The alkoxide employed is sodium methoxide, sodium ethoxide, sodium propoxide, sodium butoxide and the like and preferably sodium methoxide and sodium ethoxide.

According to another aspect of the invention the sodium salt I , once obtained as crude can be slurried in ethyl acetate, toluene or acetonitrile and allowed to stir at -20 to 35 °C and filtered and dried under vacuum to below 1.0% and preferably below 0.5% moisture content, the product becomes essentially non-hygroscopic.

According to another aspect of the invention a non-hydroscopic product can be prepared by slurry of hygroscopic Tianeptine sodium in a suitable organic solvent preferably ethyl acetate, acetonitrile, and toluene and filtration of the compound. The compound when dried under vacuum to below 1.0% and preferably below 0.5% moisture content, the product becomes essentially non-hygroscopic.

The product prepared by the above process is substantially pure and contains impurities of compound VII and compound VIII in less than 0.1% and is essentially non-hygroscopic.

EXAMPLES

Example 1

3-Chloro-6-methyldibenzo[c,/][1,2]thiazepin-11 (6W)-ol S,S-dioxide

To a solution of compound of Formula II (62.5 g) in methanol (500 ml) was charged sodium borohydride (15.04 g) at 0-5 °C. The reaction mass was stirred for 30 minutes at 0-5 ^{0}C, and for 30-60 minutes at RT. After the completion of the starting material, the solid was filtered and washed with methanol. The solid compound was dried until constant weight to provide the title compound in 90-95% yield.

Example 2

S^I-Dichloro- **6,**H -dihydro-e-methyl-**5,**δ-dioxodibenzo**[C,f][I ,2J**thiazepine

A suspension of compound of Formula III (58.0 g) in dichloromethane (600 ml) is cooled to 0-10 ^{0}C, HCI gas is bubbled through the above suspension for 2-4 hour at 0-10 ^{0}C. Upon completion of starting material, filter the precipitate and dry the solids obtained until constant weight to provide the title compound in 90-95% yield.

Example 3

Z-jniiRSJ-S-Chloro-e-methyl-e.ii-dihydrodibenzoIC **,**fHI.ZJthiazepin-H-yllaminolheptanenitrile S,S-dioxide

To compound of Formula III (50.0 g) in dichloromethane (400 ml) charge triethylamine (18.41 g) and stir the contents for 10 minutes, To the reaction charge 1-amino,6-cyanohexane (23.0 g) over a period of 5-10 minutes and stir for 2-6 hours at RT. Upon completion of starting material wash the organic layer with 5% citric acid solution (3x200 ml). Wash the organic layer with 200 ml brine solution, Distill off the solvent under vacuum, Take the crude to next step without further purification

Example 4

Tianeptine Free Acid

To the crude obtained in example 3, charge cone. HCI (635 ml) to the reaction, Reflux for 18-20 hours and upon the completion of the reaction, cool the reaction mass to 0-5 ^{0}C adjust the pH of the reaction mass to ~5.8 to 6.2 using 50% NaOH solution. Once the pH is adjusted cool the reaction mass to 0-5 °C, Stir the reaction at 0-5 ^{0}C for 2-3 h, Filter the solids obtained, Extract the aqueous mother liquors with ethyl acetate (3*200 ml). Dry the organic layer with sodium sulfate and distill off the solvent. Combine the solid filtered and the residue obtained, Charge toluene (150 ml) to the combined solids, Heat the reaction mass to 50-60 ^{0}C, Stir the mass at 50-60 ^{0}C for 2-3 h, Cool the reaction to 0-5 °C for 2-4 h and filter the solids obtained to get a pure solid.

Example 5

Tianeptine Sodium Preparation and Purification

To a solution of methanol (300 ml) and Tianeptine free acid (50 g) is charged 40% NaOH solution (5.042 g of NaOH, 0.126 mol) over a period of 10-20 minutes. Heat the contents of the flask to 60-65 ^{0}C for 30

minutes, charge activated carbon (5 g) to the flask and continue heating at reflux for 30-45 minutes, Filter the suspension over a celite pad in hot condition. Distill of methanol and charge dichloromethane (300 ml) to the flask and charge sodium sulfate (30 g) and distill off dichloromethane. Charge 100 ml acetonitrile to the residue cool the reaction mass to -5 to 5 °C and stir the contents for 2-4 hours, Filter the solid dry the compound under vacuum **until** constant weight.

Example 6

Tianeptine Sodium Preparation

To a solution of methanol (300 ml) and Tianeptine free acid (50 g) is charged 40% NaOH solution (5.042 g of NaOH) over a period of 10-20 minutes at 20-30 ^{0}C. Stir the contents of the flask for 30 minutes, charge activated carbon (5 g) to the flask and filter the suspension over a celite pad. Distill of methanol and charge ethyl acetate (500 ml) to the flask cool the reaction mass to -5 to 5 ^{0}C and stir the contents for 2-4 hours. Filter the solid dry the compound under vacuum until constant weight. The limit of water is NMT1.0% The product thus obtained is essentially non-hygroscopic. HPLC purity 99.8%. Compound II: 0.05%, Compound 111: Not detected.

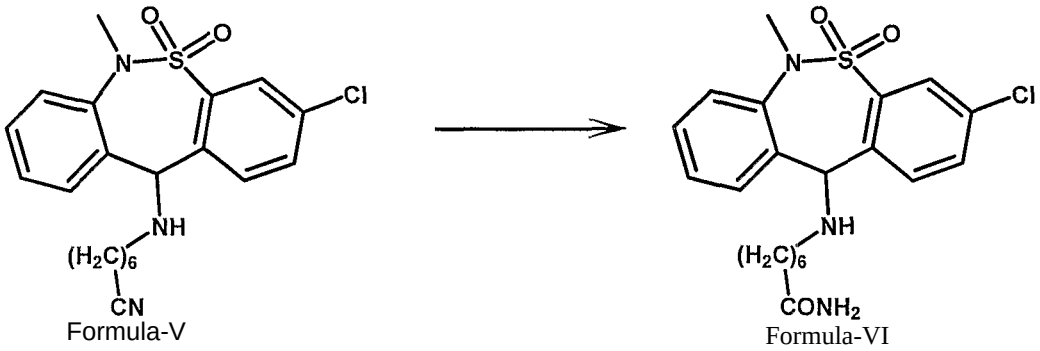
Example 7

Tianeptine Sodium Preparation

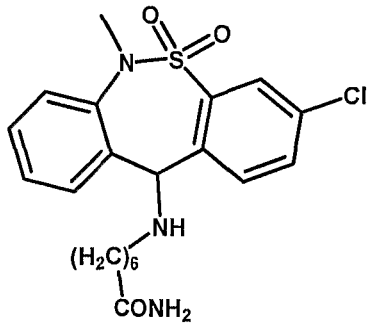
To a solution of methanol (300 ml) and Tianeptine free acid (50 g) is charged Sodium methoxide (1.1 eq) dissolved in methanol over a period of 10-20 minutes at 20-30 ^{0}C. Stir the contents of the flask for 30 minutes, charge activated carbon (5 g) to the flask and filter the suspension over a celite pad. Distill of methanol and charge dichloromethane (300 ml) to the flask and charge sodium sulfate (30 g) and distill off dichloromethane. Charge 100 ml acetonitrile to the residue cool the reaction mass to -5 to 5 °C and stir the contents for 2-4 hours, Filter the solid and dry the compound under vacuum until constant weight. Slurry the dried compound in ethyl acetate and stir at 20 to 35 °C and filter the solid and dry the compound under vacuum. The product thus obtained is essentially non-hygroscopic. HPLC purity 99.7%. Compound II: 0.07%, Compound III: Not detected.

Claims

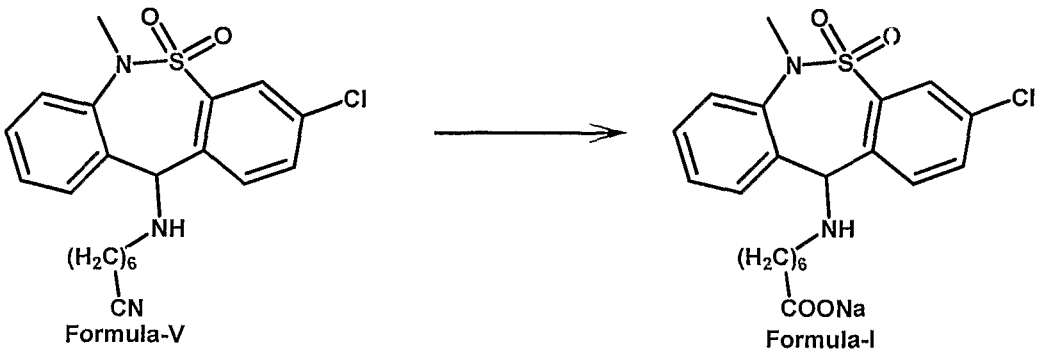
1. A process for the preparation of Tianeptine intermediate of formula VI by the hydrolysis of compound of Formula V.



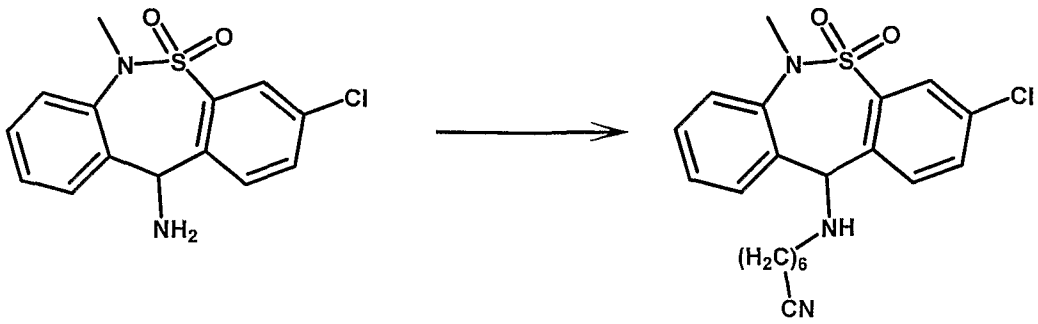
2. A compound of formula VI



3. A process for the preparation of Tianeptine by the hydrolysis of the compound of formula V in the presence of an acid or base and optional conversion into its sodium salt.

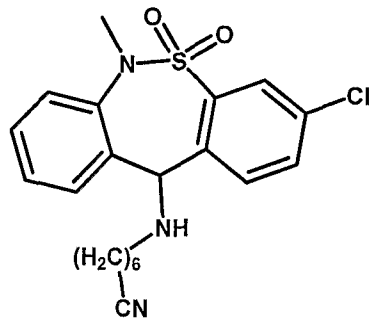


4. A process for the preparation of compound of formula V by the reaction of compound of formula X with 7-bromoheptanenitrile optionally in the presence of a solvent and base.



Formula-X Formula-V

5. A compound of formula V



6. A process for the preparation of compound of formula V by the reaction of compound of formula IV with 7-aminohepatanenitrile optionally in the presence of a solvent and base.

7. A process for the preparation of Tianeptine sodium salt from Tianeptine free acid in the presence of sodium hydroxide and an alcohol or dichloromethane.

8. The process of claim 7 wherein the alcohol is methanol, ethanol propanol, isopropanol, butanol preferably methanol.

9. A process for the preparation of Tianeptine sodium salt from Tianeptine free acid in the presence of sodium alkoxide and an alcohol or dichloromethane.

10. The process of claim 9 wherein the alcohol is methanol, ethanol propanol, isopropanol, butanol preferably methanol and the sodium alkoxide is methoxide, ethoxide, propoxide, isopropoxide, butoxide preferably sodium methoxide and sodium ethoxide.

11. A process for the preparation of non-hygroscopic Tianeptine sodium salt which involves slurrying the crude Tianeptine sodium salt in a solvent followed by removal of solvent and vacuum drying.

12. The process of claim 11 wherein the solvent employed is ethyl acetate or acetonitrile.

13. The process of claims 9 & 11 wherein the Tianeptine sodium salt is essentially free of the unsaturated impurity of Formula VII.

14. The process of claims 9 & 11 wherein the Tianeptine sodium salt obtained is essentially free of the dimer impurity of Formula VIII.

15. Substantially pure Tianeptine sodium salt.

16. Non-hygroscopic Tianeptine sodium salt.

17. Tianeptine sodium salt which has purity greater than about 99% and the impurities of compound of formula VII and Formula VIII less than 0.1%.