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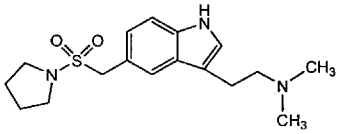
(54) **Title**: PROCESS FOR THE PREPARATION OF 1-[[[3-[2-(DIMETHYLAMINO)ETHYL]-1H-INDOL-5-YL]METHYL]SULFONYL] PYRROLIDINE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS



Formula-1

(57) **Abstract**: The present invention relates to an improved process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl] methyl] sulfonyl]pyrrolidine compound of formula- 1 and its pharmaceutically acceptable salts.

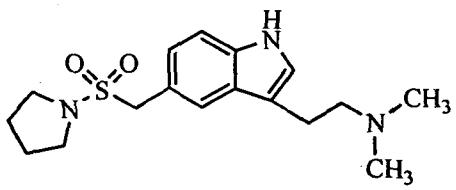
Process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl] methyl]sulfonyl] pyrrolidine and its pharmaceutically acceptable salts

Related Application:

This application claims the benefit of priority of our Indian patent application numbers 774/CHE/2009 filed on 3/4/2009 and 546/CHE/2010 filed on 3/3/2010, which are incorporated herein by reference.

Field of the Invention:

The present invention relates to an improved process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine and its pharmaceutically acceptable salts, which is commonly known as Almotriptan and is represented by the following structural formula-1



Formula-1

The present invention also relates to novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 and their use.

Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. The malate salt of almotriptan is indicated for the acute treatment of migraine with or without aura in adults. Almotriptan malate is commercially available under the brand name of AXERT® and ALMOGRAN®.

Background of the Invention:

Almotriptan and its pharmaceutically acceptable salts as well as the process for their preparation are disclosed in US 5565447. The disclosed process involves the decarboxylation of 1-[2-carboxy-3-dimethylaminoethyl)-5-indolyl]methanesulfonyl] pyrrolidine using copper oxide and quinoline. The decarboxylation reaction requires very high temperature and hence is difficult to carry out in a commercial scale.

ES 2084560 describes a process for the preparation of almotriptan based on Fisher indole synthesis using a phenyl hydrazine and 4-chloro-butyraldehyde diethyl acetal to provide 1-[[3-(2-aminoethyl)-5-indolyl]methanesulfonyl]pyrrolidine, which is further treated with aqueous formaldehyde and then with sodium borohydride to provide almotriptan. Thus obtained almotriptan is converted into its DL-malate salt. This process provides almotriptan in poor yields. Moreover it was observed that the purity of the intermediates like 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine (herein after referred as "amino indole" intermediate) and final products are not of adequate quality and are having approximately 75-80% of purity by HPLC. Specifically the amino indole intermediate obtained as a residue and is not stable at ambient temperature.

WO 2006/129190 describes a process for the preparation almotriptan malate. The disclosed process comprises of treating 5-(1-pyrrolidinyl-sulfonylmethyl)-1H-indole-3-ethanol with methane sulfonyl chloride and then dimethylamine followed by column purification of almotriptan. The said application schematically represents the conversion of almotriptan into almotriptan succinate and subsequent conversion in to almotriptan malate. Other than the schematic representation, the applicant has not disclosed/exemplified the process for the preparation of almotriptan succinate and neither has disclosed any physical properties. Moreover the preparation of 5-(1-pyrrolidinyl-sulfonylmethyl)-1H-indole-3-ethanol involves the usage of n-butyl lithium. As this process involves the usage of reagents like n-butyl lithium and purification techniques like column chromatography, they are commercially not recommendable.

WO 2008/151584 describes a process for the preparation of almotriptan malate, which involves the conversion of 4-(pyrrolidinylsulfonylmethyl) phenyl hydrazine 4-chloro-1-hydroxybutane-1-sulfonate or 4-(pyrrodinylsulfonylmethyl) phenyl hydrazine toluene sulfonate into crude almotriptan and then converting the crude almotriptan into its fumarate salt. Thus formed almotriptan fumarate is converted into crystalline almotriptan free base. The crystalline free base was treated with malic acid to provide almotriptan malate. Even though this process avoids some of problems of above reported process, it involves the additional steps like isolation of intermediate complex and almotriptan free

base, which are time consuming and decrease the yields of the products. Moreover the fumarate salt of almotriptan is obtained in very poor purity of about 92%.

US 2007/112055 describes the process for the preparation of crystalline almotriptan free base, which involves treating the organic layer containing almotriptan with aqueous succinic acid then basifying the aqueous layer containing almotriptan succinate, followed by extraction of almotriptan into isopropyl acetate and then its conversion into crystalline almotriptan. Even though this process involves the formation of almotriptan succinate, which has been carried out in solution phase only and does not involve its isolation, further it does not disclose its physical properties.

In general, the reported processes for the preparation of almotriptan or its salts proceed through the amino indole intermediate in the form of crude with very less purity of about 75-80%. The said intermediate was not stable at ambient temperature and usage of same in further steps leads the final compound contaminated with high level of impurities. When the present inventors working to resolve these problems, the present inventors surprisingly found that the salts of amino indole intermediate make it highly stable at ambient condition and having the purity of greater than 97% by HPLC and does not require any specific equipment and temperature for storage.

It has been observed that the almotriptan malate prepared as per the reported processes containing amino indole and monomethyl compounds as a major impurities in the range of 0.5 to 1% by HPLC along with other known and unknown impurities in the limit of more than 0.1% by HPLC. Hence it is necessary to have a process for the purification of almotriptan malate to eliminate the above said impurities. Also there is a need in the art for an improved process for the preparation of almotriptan malate through a high pure intermediate salt compounds, which avoids the addition crystallization steps to make it economically affordable.

The required purity of almotriptan malate free of impurities is attained by the present inventor in three different ways one is by preparing the acid addition salts of amino indole compound and second way by proceeding through the almotriptan succinate and in third way, by specific purification of almotriptan malate from a suitable solvent.

Brief Description of the Invention:

The first aspect of the present invention is to provide novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2, process for its preparation and its use in the preparation of highly pure almotriptan and its pharmaceutically acceptable salts.

The second aspect of the present invention is to provide a process for the preparation of highly pure almotriptan compound of formula-1 through the novel salt compound of formula-2, which comprises of the following steps;

a) treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine or its salt compound of formula-3 with source of 4-chlorobutyraldehyde in presence of disodium hydrogen phosphate and acid in a suitable solvent, followed by treating the obtained compound with a suitable acid to provide the corresponding acid addition salt of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2,

b) reacting the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide free base compound of formula-5, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a,

c) optionally purifying the obtained almotriptan malate compound of formula-1a.

The third aspect of the present invention is to provide novel crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate compound of formula-2a and process for its preparation. The novel crystalline form of the present invention is characterized by its powder X-ray diffractogram.

The fourth aspect of the present invention is to provide an improved process for the purification of almotriptan malate compound of formula-1a, which comprises of treating almotriptan malate with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The fifth aspect of the present invention is to provide an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine or its salt compound of formula-3 with protected derivative of 4-chlorobutyraldehyde compound of formula-4 in presence of disodium hydrogen phosphate in a suitable solvent, to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with a suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The sixth aspect of the present invention is to provide an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps;

a) treating the alkali metal salt of 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6 with a suitable aqueous base, and then extracting the obtained 4-chlorobutyraldehyde into a suitable solvent, which on in-situ reaction with 1-(4-hydrazinylbenzyl sulfonyl)pyrrolidine compound of formula-3 or its salts thereof in presence of disodium phosphate in a suitable solvent provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ

treatment with suitable acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The seventh aspect of the present invention is to provide novel crystalline forms of almotriptan succinate. The crystalline forms of the present invention are characterized by its PXRD, IR spectrum and DSC thermogram.

The eighth aspect of the present invention is to provide a novel crystalline form of almotriptan oxalate. The crystalline form of the present invention is characterized by its PXRD, IR spectrum and DSC thermogram.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD of crystalline compound of formula-2a

Figure-2: Illustrates the PXRD of crystalline form-1 of almotriptan succinate

Figure-3: Illustrates the PXRD of crystalline form-2 of almotriptan succinate

Figure-4: Illustrates the PXRD of crystalline form-M of almotriptan oxalate

Figure-5: Illustrates the PXRD of crystalline almotriptan malate prepared as per the present invention.

Detailed Description of the Invention:

Unless otherwise specified, as used herein the term "suitable solvent" refers to the solvents selected from "alcoholic solvent" such as methanol, ethanol, n-propanol, isopropnol, n-butanol and isobutanol; "chloro solvent" such as to methylene chloride, chloroform and ethylene dichloride; "ketone solvent" such as acetone, methyl ethyl ketone, methyl isobutyl ketone; "hydrocarbon solvent" such as to toluene, hexane, heptane and cyclohexane; "nitrile solvent" such as acetonitrile; "ester solvent" such as ethyl acetate, methyl acetate and isopropyl acetate; "ether solvent" such as tetrahydrofuran, diethyl ether and methyl tert-butyl ether; "polar solvent" such as water.

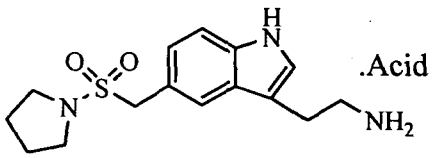
As used herein the term "suitable base" refers to the bases selected from alkali metal hydroxide like sodium hydroxide, potassium hydroxide; alkali metal carbonate like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution.

The term "protected 4-chlrobutyraldehyde" refers to a derivative of 4-chlorobutyraldehyde in which the aldehyde group is protected by converting it into an acetal or an adduct.

As used herein the term "source of 4-chlorobutyraldehyde" refers to alkali metal adduct of 4-chlorobutyraldehyde, acetal protected 4-chlorobutyraldehyde or its free form.

The present invention relates to novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 and their use in the preparation of highly pure almotriptan compound of formula-1.

Accordingly the first aspect of the present invention provides novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2



Formula-2

wherein "Acid" is an acid group which is capable of forming acid addition salt with 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 and is selected from group comprising of oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid or hydrobromic acid and hydrochloric acid.

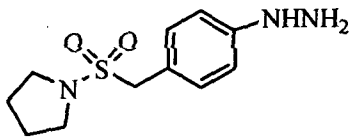
The novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 of the present invention is highly stable and having high purity when compared to the free base obtained as per the prior art. It also used to prepare pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-

yl)ethanamine free base, almotriptan and its pharmaceutically acceptable salts thereof. The 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound prepared from above novel salts having purity greater than 97 % by HPLC, preferably >98.5% and more preferably >99% by HPLC.

The present invention also provides a process for the preparation of novel salts compound of general formula-2, which comprises of treating the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with a suitable acid as defined above. in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, to provide the corresponding salt compound of general formula-2.

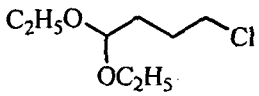
The second aspect of the present invention provides a process for the preparation of highly pure almotriptan malate compound of formula-1a through novel salts compound of general formula-2, which comprises of the following steps;

a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride



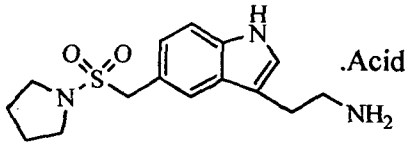
Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or a source of 4-chlorobutyraldehyde,



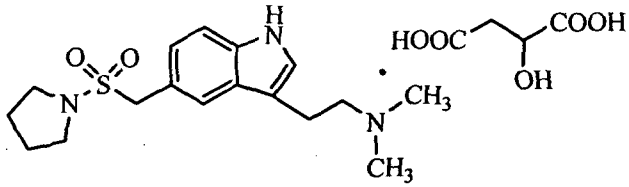
Formula-4

in presence of disodium hydrogenphosphate and a suitable acid in a suitable solvent followed by treating the obtained product with suitable acid in a suitable polar solvent to provide the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

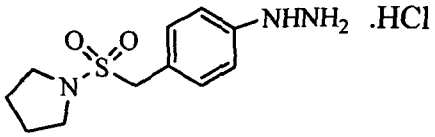
b) treating the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which is followed by in-situ treatment with malic acid in a suitable solvent to provide almotriptan malate compound of formula-1a,



Formula-1a

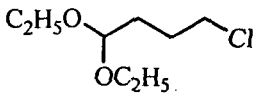
In a preferred embodiment, improved process for the preparation of highly pure almotriptan malate compound of formula-1a comprises of the following steps;

a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride compound of formula-3a



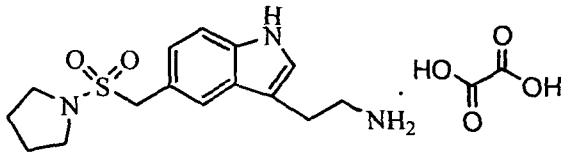
Formula-3a

with 4-chloro butyraldehyde diethyl acetal compound of formula-4



Formula-4

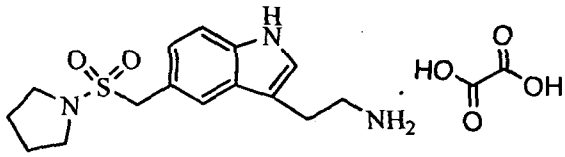
in presence of disodium hydrogen phosphate, aqueous hydrochloric acid in methanol provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine, which on-insitu treatment with oxalic acid in water provides the 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate compound of formula-2a



Formula-2a

b) treating the oxalate salt compound of formula-2a with aqueous ammonia and extracting the obtained 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine into methylene chloride, which on in-situ reaction with formalin in presence of sodium borohydride in aqueous sodium hydroxide, in methanol provides almotriptan, followed by treating it in-situ with malic acid in methanol provides almotriptan malate compound of formula-1a.

The third aspect of the present invention provides a novel crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate salt represented by the following structural formula



The novel crystalline oxalate salt of the present invention is characterized by its powder X-ray diffractogram having peaks at about 7.97, 14.06, 16.52, 16.85, 17.28, 18.26, 19.45, 19.94, 21.16, 22.74, 24.52, 25.13, 26.29, 30.08, 33.41, 36.28 and 39.91 ± 0.2 degrees 2θ. The novel crystalline form of the present invention is used to prepare highly pure almotriptan or its pharmaceutically acceptable salts.

The fourth aspect of the present invention provides a process for the purification of almotriptan malate compound of formula-1a, which comprises of treating the almotritpan malate with a suitable base selected from alkali metal hydroxides like sodium hydroxide, potassium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from ester solvents, hydrocarbon solvent, chloro solvents or mixtures thereof, to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent selected from alcohols, ketones,

nitrile or polar solvents or mixtures thereof, to provide highly pure almotriptan malate compound of formula-1a.

A process for the purification of almotriptan malate compound of formula-1a is provided to reduce the amount of impurities particularly amino indole impurity and monomethyl impurity present in it to the level of 0.5-1% by HPLC along with other impurities to the concentration of around 0.05% to levels of non detection. The said purification process comprises of the following steps;

a) Treating the almotritpan malate with a suitable base in a suitable solvent selected from ester solvents, hydrocarbon solvents and chloro solvents,
b) separating the organic and aqueous layers,
c) distilling off the solvent from organic layer under reduced pressure,
d) dissolving the obtained residue in suitable solvent or mixtures thereof at reflux temperature,
e) subjecting the reaction mixture to carbon treatment,
f) filtering the reaction mixture through hyflow,
g) adding malic acid or its solution in a suitable solvent to the filtrate at 35-80°C and stirring,
h) cooling the reaction mixture to 25-30°C and stirring
i) filtering the solid and washing with a suitable solvent,
j) drying the solid to get the highly pure almotriptan malate.

In a preferred embodiment, process for the purification of almotriptan malate compound of formula-1a comprises of the following steps,

a) treating the almotritpan malate in ethylacetate with aqueous ammonia,
b) separating the organic and aqueous layers,
c) distilling off the ethylacetate from organic layer under reduced pressure,
d) dissolving the obtained residue in a mixture of isopropylalochol and methanol at reflux temperature,
e) subjecting the reaction mixture to carbon treatement,
f) filtering the reaction mixture through hyflo,

g) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,

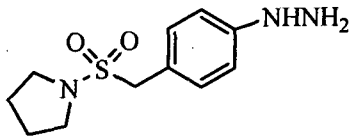
h) cooling the reaction mixture and stirring

i) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,

j) drying the solid to get the highly pure almotriptan malate.

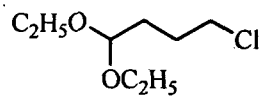
The almotriptan malate prepared as per the prior art processes containing residual solvents like methanol and ethanol in high levels than the required levels set by ICH. The same problem has been rectified by the present inventors by adding malic acid to the almotriptan free base in a mixture of isopropyl alcohol and methanol in the ratio of 1:6 to 9:4 at reflux temperature, which controls the residual solvent well below the limits of solvents set by ICH.

The fifth aspect of the present invention provides an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof



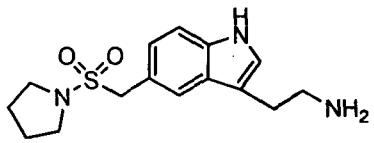
Formula-3

preferably hydrochloride salt of the compound of formula-3, with protected 4-chlrobutyralehyde derivative, 4-chloro-1,1-diethoxybutane compound of formula-4



Formula-4

in presence of a disodium hydrogen phosphate in a suitable solvent selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof, preferably aqueous alcohols, to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,



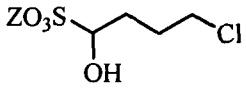
Formula-5

Reacting the 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable alcoholic solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, provides corresponding almotriptan acid addition salt compound of formula-1,

Optionally purifying the obtained almotriptan acid addition salt compound of formula-1 using a suitable solvent selected from alcoholic solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents, water or mixtures thereof to provide high pure almotriptan acid addition salt compound of formula-1.

The pure almotriptan acid addition salt compound of formula-1 is treated with a suitable base selected from alkali metal hydroxides like sodium hydroxide, potassium hydroxide; alkali metal carbonate like sodium carbonates, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents or mixtures thereof, to provide almotriptan which on in-situ treatment with malic acid in a suitable solvent described above to provide almotriptan malate compound of formula-1a.

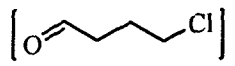
The sixth aspect of the present invention provides an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of treating the alkali metal salt compound of 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6, preferably sodium or potassium salt of 4-chloro-1-hydroxybutane sulfonate,



Formula-6

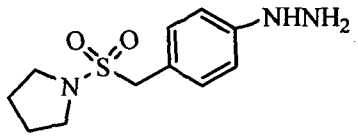
Wherein Z is Na or K ion,

with a suitable aqueous base selected from sodium carbonate or potassium carbonate, followed by extraction of the obtained 4-chlorobutaraladhyde compound of formula-7 into a suitable chloro solvent,



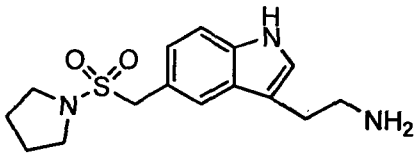
Formula-7

which on in-situ treatment with 1-(4-hydrazinyl benyzlsulfonyl)pyrrolidine compound of *formula-3 or its salts thereof,*



Formula-3

preferably hydrochloride salt of compound of formula-3, in presence of disodium hydrogen phosphate in a suitable solvent selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof, preferably aqueous alcohol provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5



Formula-5

Reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide in a suitable alcoholic solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, provides corresponding almotriptan acid addition salt compound of formula-1,

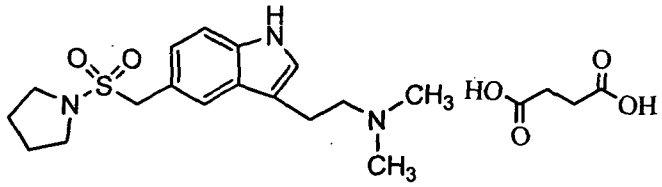
Optionally purifying the obtained almotriptan acid addition salt compound of formula-1 using a suitable solvent selected from alcoholic solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents, water or mixtures thereof to provide high pure almotriptan acid addition salt compound of formula-1.

The pure almotriptan acid addition salt compound of formula-1 is treating with a suitable base selected from alkali metal hydroxide like sodium hydroxide, potassium hydroxide, alkali metal carbonate like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon

solvents, ketone solvents, nitrile solvents or mixtures thereof to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent described above provides almotriptan malate compound of formula-1a.

The almotriptan malate can be further purified by recrystallisation from a suitable solvent selected from alcoholic solvents, ketone solvents, ester solvents or mixtures thereof to get high pure almotriptan malate.

The seventh aspect of the present invention provides a novel crystalline form of almotriptan succinate compound of formula-1b having the following structure.



Formula-1b

The crystalline almotriptan succinate compound of formula-1b of the present invention is characterized by its powder X-ray diffractogram having 2θ peaks at about 9.2, 14.7, 16.1, 16.9, 18.0, 18.7, 20.3, 21.8, 22.9, 23.4, 24.7, 26.0, 29.8, 35.0 and 41.3 ± degrees 2θ. This novel crystalline form of the presence invention is herein designated as "form-1". The crystalline form-1 is also characterized by its IR spectrum having peaks at 3373.62, 2981.26, 2887.95, 2397.10, 1708.66, 1563.89, 1463.94, 1411.65, 1373.46, 1358.76, 1322.83, 1322.83, 1202.40, 1122.84, 1015.63, 829.03, 804.79 and 656.64 cm^{-1} and also characterized by its DSC thermogram showing endothermic peak at 178.14°C.

The present invention further provides a process for the preparation of crystalline form-1 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

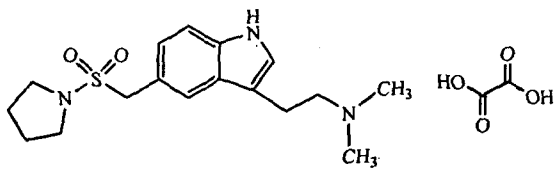
a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from alcoholic solvents, nitrile solvents, water or mixtures thereof to reflux,
b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-1 of almotriptan succinate.

Further the present invention provides another novel crystalline almotriptan succinate compound of formula-1b characterized by its Powder X-ray diffractogram having 2θ peaks at about 6.7, 10.2, 12.2, 13.7, 14.5, 15.2, 15.8, 16.9, 17.4, 19.0, 19.9, 20.3, 21.2, 23.4, 24.4, 25.0, 26.5, 27.0, 28.5 and 32.9 ± degrees 2θ. This novel crystalline form of the present invention is herein designated as "form-2". The crystalline form-2 of the present invention is also characterized by its IR spectrum having peaks at 3424.20, 3218.62, 3198.16, 2976.28, 2918.84, 2478.49, 1711.46, 1559.15, 1486.01, 1398.27, 1342.21, 1320.92, 1236.06, 1218.29, 1175.83, 1133.61, 986.79, 959.54, 818.70, 754.90, 667.41 and 610.17 cm^{-1} and also characterized by its DSC thermo gram showing endothermic peak at 169.96°C.

The present invention further provides a process for the preparation of crystalline form-2 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from ester solvents; ketone solvents, hydrocarbon solvents, alcoholic solvents, water or mixtures thereof to reflux,
b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction mixture further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-2 of almotriptan succinate.

The eighth aspect of the present invention is to provide crystalline form of almotriptan oxalate compound of formula-1c having the following structure.



Formula-1c

The novel crystalline form almotriptan oxalate of the present invention is characterized by its powder X-ray diffractogram having 2θ peaks at about 6.5, 11.7, 12.9, 14.6, 15.9, 17.8, 18.4, 19.9, 20.3, 20.7, 21.9, 25.5, 26.6, 36.0 and 39.7 ± degrees 2θ. This

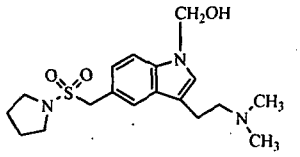
crystalline form of the presence invention is herein designated as crystalline "form-M". The crystalline form-M of the present invention is also characterized by its IR spectrum 3418.28, 3298.26, 2927.01, 2683.12, 2512.94, 1731.28, 1631.54, 1483.10, 1434.19, 1310.03, 1196.21, 1011.26, 963.96, 805.23, 710.27 and 643.84 cm^{-1} and by its DSC thermo gram showing endothermic peaks at 208.30°C and 227.33°C.

The novel crystalline form-M of almotriptan oxalate is prepared by heating a mixture of almotriptan and oxalic acid in a suitable alcoholic solvent to reflux temperature and then cooling the reaction mixture to 25-30°C followed by stirring the reaction mixture for 2 hours, then the obtained solid was filtered, washed with alcoholic solvent and dried to get the crystalline form-M of almotriptan oxalate.

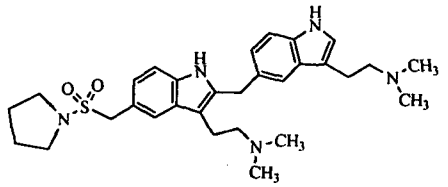
The novel crystalline form-1, form-2 of almotriptan succinate compound of formula-1b and novel crystalline form-M of almotriptan oxalate compound of formula-1c were used to prepare high pure almotriptan and its pharmaceutically acceptable salts especially malate salt.

As used herein the term "highly pure" refers to the compound with purity greater than 98 % by HPLC, preferably greater than 99 % by HPLC and more preferably greater than 99.50% by HPLC.

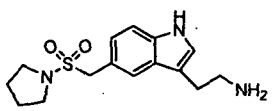
The following impurities are the possible impurities which are formed during the process for the preparation of almotriptan and its pharmaceutically acceptable salts.



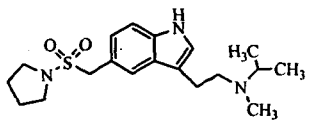
N-Hydroxymethyl impurity



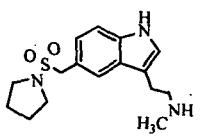
Dimer impurity



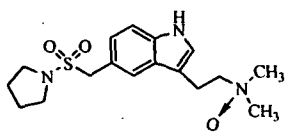
Aminoindole impurity



N-Isopropyl impurity



Monomethyl impurity



N-Oxide impurity

One of the major focus of the invention was to control the impurities formed in the process to as minimum levels as possible in the final pharma. This is ensure by purification process involving the conversion of almotriptan malate into free base by treating it with base followed by extracting it with a suitable solvent and then subsequently subjecting it to carbon treatment and treating it with malic acid to convert it into almotriptan malate with high purity. The major impurities formed in substantial quantities were the amino indole impurity and mono methyl impurity which were purified from the levels of 0.5 to 1% each to the level of non-detection and 0.02% respectively. All the above impurities are well controlled in the process to the levels of 2.0% which were reduced to the levels of 0.2% after purification. The each individual impurities are reduced to the levels of 0.1%, preferably to the level of 0.05% by the purification method.

Almotriptan or its pharmaceutically acceptable salts can be further micronized or milled to get the desired particle size. Almotriptan malate particles prepared as per the present invention having D_{90} particles in the range of 40 to 200 microns and mean particle size is in the range of 15 to 70 microns.

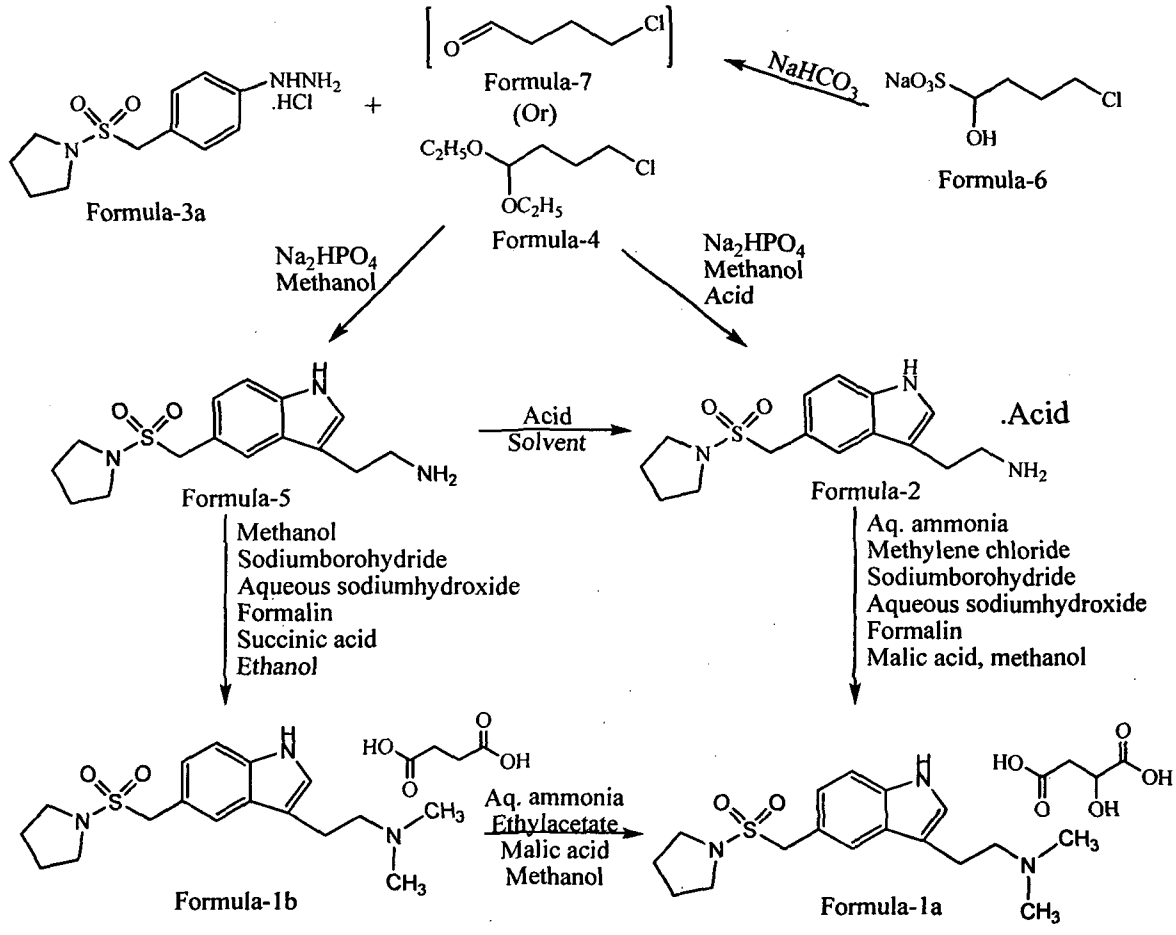
XRD analysis of pharmaceutically acceptable salts of almotriptan were carried out using SIEMENS/D-5000 X-Ray diffractometer using Cu, Ka radiation of wavelength 1.54 A° and continuous scan speed of 0.045°/min. FT-IR spectrum of pharmaceutically acceptable salts of almotriptan was recorded on Thermo model Nicolet-380 as KBr pellet. The thermal analysis of pharmaceutically acceptable salts of almotriptan was carried out on Waters DSC Q-10 model differential scanning calorimeter.

The related substance of pharmaceutically acceptable salts of almotriptan was analyzed by HPLC using the following conditions: Column: X-terra, 259 x 4.6 mm, 5.0 µm ; Flow rate: 1.0 ml/min; wavelength: 227 nm ; Temperature: 40°C; Load: 10 µl; Run time: 50 min; and using monobasic sodium phosphate in water and methanol as diluents.

The related substance of almotriptan malate and salts of 2(5-(pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine were were analyzed by HPLC using the following conditions: Column: Symmetry C18 250 x 4.6 mm, 5.0 µm ; Flow rate: 1.6

ml/min; wavelength: 228 nm ; Temperature: 35°C; Load: 20 µl; Run time:50 min; Elution: gradient; and using mixture of buffer and acetonitirle as a diluent and mobile phase. The buffer is prepared by a mixture of triethylamine and water.

The present invention is represented by the following schematic representation



The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a:

A mixture of 4-chlorobutaraldehyde diethyl acetal (120 grams), hydrochloric acid (48 ml) and water (1050 ml) was stirred at 20-25°C. This mixture was added to a mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (150 grams), water (450 ml) and methanol (1.2 l) at 10-15°C and stirred. The solid obtained was filtered and washed with water. Methanol followed by disodium hydrogen phosphate solution ((73 grams in 600 ml of water) was added to the solid and the acidified the reaction mixture with aqueous hydrochloric acid. The reaction mixture was heated to reflux and stirred at reflux. After completion of the reaction, methanol was distilled off completely under reduced pressure. The residue was cooled, water (1.5 L) and methylene chloride (450 ml) was added to it and basified with sodium carbonate solution. The aqueous layer was separated and expelled with nitrogen. Oxalic acid (51.8 grams) was added to it and stirred at 25-30°C. The reaction mixture was cooled to 5-10°C and stirred. The obtained solid was filtered, washed with water and dried to get the title compound. The PXRD of crystalline form of the obtained oxalate salt is represented in figure-1.

Yield: 95 grams

M.R: 128-133°C; Purity by HPLC: 98.95%

Example-2: Preparation of almotriptan malate of formula-1a:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a (50 grams), water (500 ml) and methylene chloride (250 ml) was stirred and basified with aqueous ammonia then stirred. The organic layer was separated and solvent from it distilled off completely under reduced pressure. The residue was dissolved in methanol (770 ml) and cooled to 5-15°C. Sodiumborohydride (24 grams) in aqueous sodium hydroxide (0.77 grams in 335 ml of water) and formalin solution (161.4 ml) in methanol (161.4 ml) was added to the reaction mixture lotwise at 5-15°C and stirred. After completion of the reaction, quenched it with aqueous

hydrochloric acid and stirred. The reaction mixture was basified with sodium bicarbonate solution and methanol was distilled off completely under reduced pressure. The reaction mixture washed with ethylacetate and then basified with potassium carbonate. The reaction mixture extracted into ethylacetate and then washed with sodium chloride solution and then ethylacetate was distilled off completely under pressure. Methanol was added to the obtained residue followed by malic acid (17.9 grams) and stirred for 45 minutes. The reaction mixture was heated to reflux and stirred. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered and washed with methanol. The obtained wet solid was recrystallized from methanol to get the title compound.

Yield: 32 grams

Purity by HPLC: 99.02%; 0.06% (amino indole impurity); 0.13 % (monomethylimpurity)

Example-3: Purification of almotriptan malate of formula-1a:

Almotriptan malate (having purity of 98.57% and containing 0.59% of aminoindole impuriy & 0.40% of monomethylimpurity) (100 grams) was dissolved in water (1L), and then added ethyl acetate (600 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off completely under reduced pressure at a temperature below 60°C. The residue was dissolved in methanol (200 ml) and subjected to carbon treatment, then filtered through hyflow. Malic acid (37.2 grams) was added to the filtrate and heated to reflux temperature then stirred for 30 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with methanol and dried to get the pure title compound.

Yield: 77 grams

Purity by HPLC: 99.84%; 0.02% (amino indole impurity); 0.06% (monomethylimpurity)

Particle Size Distribution: D(0.1): 5.41 μm ; D(0.5): 4.59 μm ; D(0.9):128.61 μm ; D(1.00): 275.38 μm;

Example-4: Purification of almotriptan malate of formula-1a:

Almotriptan malate (having purity of 98.39% and containing 0.20% of aminoindole impurity & 0.60% of monomethyl impurity) (55 grams) was dissolved in water (550 ml), added ethyl acetate (330 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off under reduced pressure at below 60°C. The residue was dissolved in a mixture of isopropylalcohol and methanol in the ratio of 6:4 (55 ml) and subjected to carbon treatment, then filtered through hyflow. Malic acid (9 grams) in a mixture of IPA:MeOH (220 ml) was added and heated to reflux temperature then stirred for 30 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with a mixture of isopropylalcohol and methanol and dried to get the pure title compound.

Yield: 49 grams: RS/OVI: Methanol: 2865 ppm

Purity by HPLC: 99.87%; 0.01% (amino indole impurity); 0.04% (monomethylimpurity)

Particle Size Distribution: D(0.1):4.25 μm ; D(0.5): 34.85 μm ; D(0.9): 115.61 μm ; D(1.00): 235.14 μm.

Example-5: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude:

A mixture of 4-chlorobutaraldehyde diethyl acetal (120 grams), hydrochloric acid (48 ml) and water (1050 ml) was stirred at 20-25°C. This mixture was added to a mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (150 grams), water (450 ml) and methanol (1.2 l) at 10-15°C and stirred. The solid obtained was filtered and washed with water. Methanol followed by disodium hydrogen phosphate solution (73 grams in 600 ml of water) was added to the solid and the acidified the reaction mixture with aqueous hydrochloric acid. The reaction mixture was heated to reflux and stirred. After completion of the reaction, methanol was distilled off completely under reduced pressure. The residue was cooled, water (1.5 L) and methylene chloride (450 ml) was added to it and basified with sodium carbonate solution. The aqueous layer was separated, basified it with sodium carbonate and then product extracted into methylene chloride. The

methylene chloride layer was dried over sodium sulphate and distilled off completely under reduced pressure to get the title compound.

Yield: 90 grams

Example-6: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine succinate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Succinic acid (0.77 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.

Yield: 2.2 grams

M.R: 163-167°C; Purity by HPLC: 99.10%

Example-7: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine malate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Malic acid (0.9 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.

Yield: 1.9 grams

M.R: 167-171°C; Purity by HPLC: 98.87%

Example-8: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine tartarate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Tartaric acid (0.97 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.

Yield: 2.3 grams;

M.R: 156-158°C; Purity by HPLC: 98.10%

Example-9: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine fumarate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Fumaric acid (0.76 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.
Yield: 1.5 grams
M.R: 189-191°C; Purity by HPLC: 98.17%

Example-10: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

A mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (35.0 grams), hydrochloric acid (6.6 ml) and water (330 ml) was stirred for an hour at 25-30°C. In another vessel a mixture of 4-chloro-1,1-diethoxybutane (27.2 grams), hydrochloric acid (12.5 ml), water (82 ml) and methanol (375 ml) was stirred for an hour at 25-30°C and then added this mixture to the mixture containing 1-(4-hydrazinylbenzylsulfonyl) pyrrolidine. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered and washed with aqueous methanol. Water (90 ml), disodium hydrogen phosphate (15 grams), methanol (560 ml) and hydrochloric acid (30 grams) was added to the obtained wet solid, heated the reaction mixture to reflux and stirred at reflux for 12 hours. The methanol was distilled off from the reaction mixture and water (375ml) was added to it. The reaction mixture was neutralized with sodium carbonate, washed with methylene chloride, saturated with sodium carbonate and then extracted into methylene chloride. The methylene chloride from the reaction mixture was distilled off under reduced pressure. Thus obtained residue isolated using diisopropyl ether.
Yield: 30 grams

Example-11: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

A mixture of 4-chloro-1,1-diethoxybutane (4.6 grams), hydrochloric acid (0.95 ml) and water (47.5 ml) was stirred for an hour at 20-25°C. Methanol (52.5 ml) was

added to 1-(4-hydrazinylbenzylsulfonyl) pyrrolidine hydrochloride (5 grams) in water (15 ml) and the reaction mixture was acidified with hydrochloric acid at 10-15°C and to this 4-chlorobutyraldehyde layer was added and stirred for 3 hours at 10-15°C. The reaction mixture was cooled to 10-15°C and stirred for 2 hours. The obtained solid was filtered and washed with water. The solid was dissolved in methanol and aqueous disodium hydrogen phosphate (2.67 grams in 18 ml of water) at 10-15°C and reaction mixture was acidified with hydrochloric acid. The reaction mixture was heated to reflux and stirred at reflux for 10 hours. The methanol was distilled off completely under reduced pressure then water (15 ml) was added to it. The reaction mixture was washed with methylene chloride. The reaction mixture was basified with sodium carbonate and the reaction mixture was extracted into methylene chloride. The methylene chloride was distilled off under reduced pressure to give the title compound.

Yield: 2.5 grams

Example-12: Preparation of almotriptan succinate compound of formula-1b:

A solution of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4 (15 grams) in methanol (300 ml) was cooled to 0-10°C. Sodium borohydride (9.28 grams) in aqueous sodium hydroxide (0.3 gram in 130 ml water) and formalin solution (63 ml in 64 ml of methanol) was added to the above reaction mixture slowly at 5-15°C and then stirred for an hour. The reaction mixture was quenched with aqueous hydrochloric acid and stirred for 20 minutes at 25-30°C. The pH of the reaction mixture was adjusted to 6.5 with aqueous acetic acid. The methanol from the reaction mixture was distilled off under reduced pressure and then reaction mixture washed with ethyl acetate. Potassium carbonate (75 grams) was added to the reaction mixture, stirred for 35 minutes at 25-35°C and then the reaction mixture extracted into ethyl acetate. Succinic acid (5.7 grams) was added to the ethyl acetate layer and stirred for 15 hours 25-35°C. The solid was filtered, washed with ethanol. Isopropyl alcohol (12 ml) was added to the wet solid and heated to reflux then stirred for an hour at reflux. The reaction mixture was cooled slowly to 25-30°C in 90 minutes. The solid obtained was filtered, washed with isopropyl alcohol and then dried to get the title compound.

Yield: 18 grams

Purity by HPLC: 97.81 %

Example-13: Preparation of almotriptan malate compound of formula-1a:

Ethyl acetate (15 ml) was added to a solution of almotriptan succinate (2.3 grams in 23 ml of water) and stirred for 15 minutes. The reaction mixture was basified with ammonia and stirred for 30 minutes at 25-30°C. The layers were separated, aqueous layer extracted with ethyl acetate and organic layer washed with water. The solvent from the organic layer was distilled off under reduced pressure. Methanol was added to the residue and then distilled off the methanol. The residue was dissolved in methanol and subjected to carbon treatment and then filtered through hyflow and the bed was washed with methanol. Malic acid solution (0.8 gram in 2 ml methanol) was added to the filtrate and then the reaction mixture was heated to reflux, stirred for an hour. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. The solid obtained was filtered, washed with methanol and the dried to get the title compound.

Yield: 1.8 grams; Yield: 99.51 %

Example-14: Purification of almotriptan malate compound of formula-1a:

A mixture of almotriptan (1.7 grams) and methanol (10 ml) was heated to reflux and stirred for 1.5 hours. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. The solid obtained was filtered, washed with methanol and dried to get the pure title compound.

Yield: 1.5 grams; Purity by HPLC: 99.95 %

Particle Size Distribution: D(0.1):3.51 μm ; D(0.5):17.01 μm ; D(0.9):91.60 μm ; D(1.00): 173.53 μm.

Example-15: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

Sodium carbonate (18 grams) was added to a solution of 4-chlorobutyraldehyde sodium bisulphate (54 grams in 750 ml of water), stirred for 30 minutes at 25-35°C and extracted the 4-chlorobutyraldehyde into methylene chloride (350 ml). 1-(4-hydrazinyl benzylsulfonyl) pyrrolidine hydrochloride (75 grams) was added to aqueous sodium bicarbonate (52 grams in 750 ml) and then the above extracted 4-chlorobutyraldehyde in methylene chloride was added to it. The reaction mixture was stirred for 1.5 hours at 25-30°C and then methylene chloride distilled off at 40-45°C. Hyflow was added to the

residue and stirred for 45 minutes at 25-30°C. The reaction mixture was filtered and extracted the filtrate with methylene chloride. The hyflow solid is slurried with methylene chloride. The extracted methylene chloride layer was dried with sodium sulphate and then distilled off methylene chloride under reduced pressure at below 40°C. The residue was dissolved in methanol then water (450 ml), disodium hydrogen phosphate (43 grams) and hydrochloric acid (20.3 ml) was added to it and heated to reflux temperature. The reaction mixture was stirred at reflux (65-70°C) for 12 hours and then distilled off the solvent under reduced pressure at below 60°C. Water (1200 ml) was added to the reaction mixture, washed with methylene chloride and sodium carbonate (450 grams) was added to it. The reaction mixture extracted into methylene chloride and distilled off the solvent from reaction mixture to get the title compound.
Yield: 23 grams.

Example-16: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

Hydrochloric acid (300 ml) was added to 4-((pyrrolidin-1-ylsulfonyl)methyl aniline (35 grams) was added and cooled to -10°C. Sodium nitrite solution (13.6 grams in 80 ml) was added to it and stirred for 1.5 hours at -10 to 0°C. The reaction mixture was added slowly to the cooled mixture of stannous chloride dihydrate (164.6 grams) and hydrochloric acid (120 ml) at -10 to 0°C and stirred for 1.5 hours. The obtained 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride was filtered off and washed with hydrochloric acid. 4-chloro-1,1-diethoxybutane (27.2 grams), hydrochloric acid (12.5 ml) and water (82 ml) was stirred for an hour at 25-30°C. In another vessel a previously obtained 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (35 grams), hydrochloric acid (12.5 ml) and water (82 ml) was stirred for an hour at 25-30°C and to this mixture to the above 4-chlorobutyraldehyde layer was added and stirred for 2 hours. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with aqueous methanol. Water (90 ml), disodium hydrogen phosphate (15 grams), methanol (560 ml) and hydrochloric acid (30 grams) was added to the obtained wet solid, heated the reaction mixture reflux and stirred at reflux for 12 hours. The methanol was distilled off from the reaction mixture and water was added to it. The reaction mixture was basified with sodium carbonate. The reaction mixture was washed

with methylene chloride, saturated with sodium carbonate and then extracted into methylene chloride. The methylene chloride from the reaction mixture was distilled off under reduced pressure to get the title compound.

Yield: 29 grams.

Example-17: Purification of almotriptan succinate compound of formula-1b:

Almotriptan succinate (3.2 grams) was dissolved in water (32 ml), added ethyl acetate (25 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off under reduced pressure at below 60°C. The residue was dissolved in ethanol (10 ml) and succinic acid (1.09 ml) was added and heated to reflux temperature then stirred for 60 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with ethanol and dried to get the pure title compound.

Yield: 2.1 grams; Purity by HPLC: 99.72 %

Example-18: Preparation of crystalline form-1 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) in ethanol (15 ml) and succinic acid (1.17 grams) was heated reflux and stirred for 45 minutes. The reaction mixture was cooled to 25-30°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with ethanol and then dried to get the crystalline form-1 of almotriptan succinate:

Yield: 2.4 grams

Example-19: Preparation of crystalline form-1 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) and succinic acid (1.17 grams) in acetonitrile (15 ml) was heated to reflux and stirred for 45 minutes at reflux. The reaction mixture was cooled to 25-35°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with acetonitrile and then dried to get the crystalline form-1 of almotriptan succinate:

Yield: 2.2 grams

Example-20: Preparation of crystalline form-2 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) and succinic acid (1.17 grams) in acetone (15 ml) was heated to reflux and stirred for 45 minutes at reflux. The reaction mixture was cooled to 25-35°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with acetonitrile and then dried to get the crystalline form-2 of almotriptan succinate:
Yield: 2.6 grams

Example-21 & 22: Preparation of crystalline form-2 almotriptan succinate compound of formula-1b:

The crystalline form-2 of almotriptan succinate has been prepared analogues manner to example-11 using the appropriate solvent as shown in the following table in place of acetone.

Example No.	Solvent	Yield
21	IPA + Toluene	3.6 grams
22	Ethyl acetate	3.8 grams

Example-23: Preparation of crystalline form-M of almotriptan oxalate compound of formula-1c:

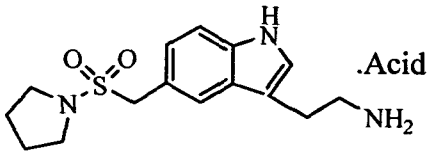
A mixture of almotriptan (5 grams) and oxalic acid (2 grams) in ethanol (25 ml) was heated to reflux and stirred for 45 minutes. The reaction mixture was cooled to 25-30°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with ethanol and then dried to get the crystalline form-M of almotriptan oxalate.
Yield: 2.8 grams

Example-24: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine of formula-5:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a (25 grams), water (250 ml) and methylene chloride (125 ml) was stirred and basified with aqueous ammonia then stirred. The organic layer was separated and solvent from it distilled off completely under reduced pressure to get the title compound.
Yield: 17 grams; Purity by HPLC: 98.80%

We Claim:

1. Novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine represented by the following general formula-2

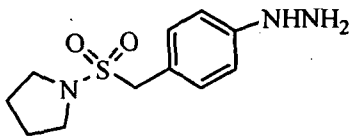


Formula-2

wherein "Acid" is an acid group which is capable of forming acid addition salt with 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine and is selected from oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid, hydrobromic acid or hydrochloric acid.

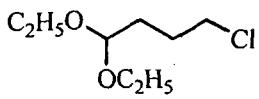
2. A process for the preparation of novel salts compound of general formula-2, which comprises of treating the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with a suitable acid as defined in claim 1 in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof.

3. A process for the preparation of novel salts compound of general formula-2, which comprises of reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride salt,



Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or a source of 4-chloro butyraldehyde

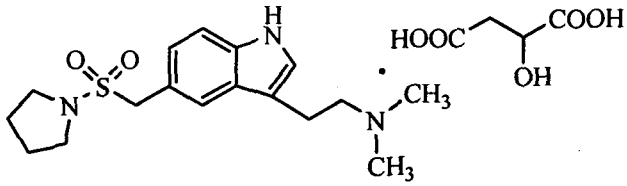


Formula-4

in presence of disodium hydrogen phosphate and acid in a suitable solvent followed by treating the obtained product with a suitable acid in a suitable solvent like alcohols or polar solvent or mixtures thereof, provides the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2

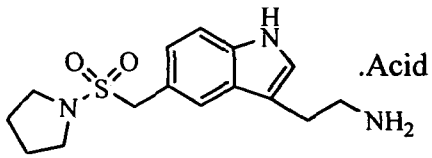
4. Use of novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2 as claimed in claim 1, in the preparation of highly pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine, almotriptan or its pharmaceutically acceptable salts.

5. A process for the preparation of highly pure almotriptan malate compound of formula-1a,



Formula-1a

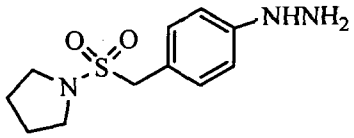
Which comprises of treating the acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

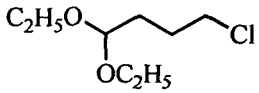
with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

6. An improved process for the preparation of highly pure almotriptan malate compound of formula-1a, which comprises of the following steps;
   a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride salt,



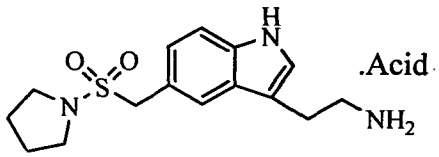
Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or 4-chloro butyraldehyde



Formula-4

in presence of disodium hydrogen phosphate and acid in a suitable solvent followed by treating the obtained product with a suitable acid in a suitable solvent like alcohols or polar solvent or mixtures thereof, provides the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

b) treating the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

7. A process according to claim 5& 6, wherein the acid addition salt compound of formula-2 selected from oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid, hydrobromic acid or hydrochloric acid.

8. Crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate salt characterized by its powder X-ray diffractogram having peaks at about

7.97, 14.06, 16.52, 16.85, 17.28, 18.26, 19.45, 19.94, 21.16, 22.74, 24.52, 25.13, 26.29, 30.08, 33.41, 36.28 and 39.91 ± 0.2 degrees 2θ.

9. Succinic acid, malic acid, fumaric acid and tartaric acid salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine as a crystalline solids.

10. Use of crystalline salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine as claimed in claim 8 & 9 in the preparation of highly pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine free base, almotriptan or its pharmaceutically acceptable salts.

11. A process for the purification of almotriptan malate compound of formula-1a, which comprises of
    a) treating the almotritpan malate with a suitable base in a suitable solvent selected from ester solvents, hydrocarbon solvents and chloro solvents,
    b) separating the organic and aqueous layer,
    c) distilling off the solvent from organic layer under reduced pressure,
    d) dissolving the obtained residue in suitable solvent or mixtures thereof at reflux temperature,
    e) subjecting the reaction mixture to carbon treatment,
    f) filtering the reaction mixture through hyflo,
    g) adding malic acid or its solution in a suitable solvent to the filtrate,
    h) cooling the reaction mixture,
    i) filtering the solid and washing with a suitable solvent,
    j) drying the solid to get the highly pure almotriptan malate.

12. A process for the purification of almotriptan malate compound of formula-1a, which comprises of
    a) treating the almotritpan malate in ethylacetate with aqueous ammonia,
    b) separating the organic and aqueous layer,
    c) distilling off the ethylacetate from organic layer under reduced pressure,
    d) dissolving the obtained residue in a mixture of isopropylalochol and methanol at reflux temperature,

e) subjecting the reaction mixture to carbon treatment,

f) filtering the reaction mixture through hyflo,

g) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,

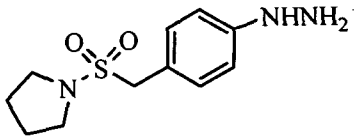
h) cooling the reaction mixture,

i) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,

j) drying the solid to get the highly pure almotriptan malate.

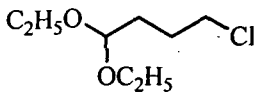
13. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the 1-(4-hydrazinylbenyzlsulfonyl)pyrrolidine compound of formula-3 or its salt thereof,



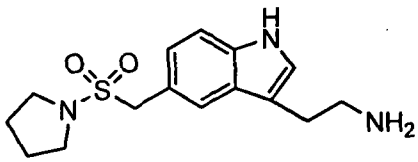
Formula-3

with 4-chloro-1,1-diethoxybutane compound of formula-4,



Formula-4

in presence of disodium hydrogen phosphate in a suitable solvent, to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,



Formula-5

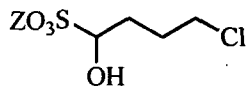
b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with a suitable base in suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

14. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

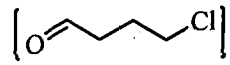
a) treating the alkali metal salt compound of 4-chloro-1-hydroxybutane-1-sulfonic acid compound of formula-6



Formula-6

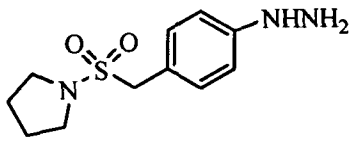
Wherein in Z is Na or K ion,

with a suitable aqueous base, and then extracting the obtained 4-chloro butyraldehyde compound of formula-7 into a suitable solvent,



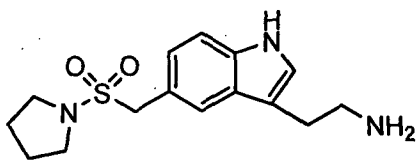
Formula-7

which on in-situ treatment with 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof



Formula-3

in presence of disodium hydrogen phosphate in a suitable solvent to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,



Formula-5

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid like oxalic acid or succinic acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

15. The process of claim 13 or 14, comprising at least one of the following;

i) in step a) wherein the suitable solvent is selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof; and base is selected from aqueous sodium carbonate and potassium carbonate;

ii) in step b) & c), wherein the suitable solvent is selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents and water or mixtures thereof;

iii) in step d) suitable solvent is selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents and water or mixtures thereof; and base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and ammonia or mixtures thereof.

16. A process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the hydrochloride salt of 1-(4-hydrazinylbenyzlsulfonyl)pyrrolidine hydrochloride compound of formula-3a with 4-chloro-1,1-diethoxybutane compound of formula-4 in presence of disodium hydrogen phosphate in aqueous methanol to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in methanol to provide almotriptan, which on in-situ treatment with succinic acid in ethanol or acetonitrile provides almotriptan succinate compound of formula-1b,

c) purifying the almotriptan succinate compound of formula-1b using ethanol, ethyl acetate, water or mixtures thereof,

d) treating the almotriptan succinate compound of formula-1b with aqueous ammonia and then extracting the almotriptan with ethyl acetate, and then treating it with malic acid in methanol to provide almotriptan malate compound of formula-1a.

17. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the sodium 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6a with aqueous sodium carbonate, and then extracting the obtained 4-chloro butyraldehyde compound of formula-7 into methylene chloride, which on in-situ reaction with 1-(4-hydrazinylbenzyl sulfonyl)pyrrolidine hydrochloride compound of formula-3a in the presence of disodium hydrogen phosphate in aqueous methanol, provides 2-(5-((pyrrolidin-1-ylsulfonyl) methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide in methanol to provide almotriptan, which on in-situ treatment with succinic acid in ethanol provides almotriptan succinate compound of formula-1b,

c) treating almotriptan succinate compound of formula-1b with aqueous ammonia and then extracting the almotriptan with ethyl acetate, and then treating it with malic acid in methanol to provide almotriptan malate compound of formula-1a.

18. A novel crystalline form-1 of almotriptan succinate characterized by any one of the following;

a) its power X-ray diffractogram having 2θ peaks at about 9.2, 14.7, 16.1, 16.9, 18.0, 18.7, 20.3, 21.8, 22.9, 23.4, 24.7, 26.0, 29.8, 35.0 and 41.3 ± degrees 2θ. This crystalline form is herein designated as "form-1";

b) its IR spectrum having peaks at 3373.62, 2981.26, 2887.95, 2397.10, 1708.66, 1563.89, 1463.94, 1411.65, 1373.46, 1358.76, 1322.83, 1322.83, 1202.40, 1122.84, 1015.63, 829.03, 804.79 and 656.64 cm^{-1};

c) its DSC thermo gram showing endothermic peak at 178.14°C.

19. A novel crystalline form-2 of almotriptan succinate characterized by any of the following;

a) its Powder X-ray diffractogram having 2θ peaks at about 6.7, 10.2, 12.2, 13.7, 14.5, 15.2, 15.8, 16.9, 17.4, 19.0, 19.9, 20.3, 21.2, 23.4, 24.4, 25.0, 26.5, 27.0, 28.5 and 32.9 ± degrees 2θ;

b) its IR spectrum having peaks at 3424.20, 3218.62, 3198.16, 2976.28, 2918.84, 2478.49, 1711.46, 1559.15, 1486.01, 1398.27, 1342.21, 1320.92, 1236.06, 1218.29, 1175.83, 1133.61, 986.79, 959.54, 818.70, 754.90, 667.41 and 610.17 cm^{-1};

c) its DSC thermo gram showing endothermic peak at 169.96°C.

20. A novel crystalline form-M of almotriptan oxalate is characterized by any one of the following;

i. its powder X-ray diffractogram having 2θ peaks at about 6.5, 11.7, 12.9, 14.6, 15.9, 17.8, 18.4, 19.9, 20.3, 20.7, 21.9, 25.5, 26.6, 36.0 and 39.7 ± degrees 2θ;

ii. its IR spectrum 3418.28, 3298.26, 2927.01, 2683.12, 2512.94, 1731.28, 1631.54, 1483.10, 1434.19, 1310.03, 1196.21, 1011.26, 963.96, 805.23, 710.27 and 643.84 cm^{-1};

iii. its DSC thermo gram showing peaks at 208.30°C and 227.33°C.

21. A process for the preparation of crystalline form-1 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from alcoholic solvents; nitrile solvents and water or mixtures thereof to reflux,

b) stirring the reaction mixture for 45 minutes at reflux,

c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,

d) filtering the solid, washing with suitable solvent,

e) drying the solid to get the crystalline form-1 of almotriptan succinate.

22. A process for the preparation of crystalline form-2 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from ester solvents; ketone solvents, hydrocarbon solvents, alcoholic solvents and water or mixtures thereof to reflux,

b) stirring the reaction mixture for 45 minutes at reflux,

c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,

d) filtering the solid, washing with suitable solvent,

e) drying the solid to get the crystalline form-2 of almotriptan succinate.

23. Almotriptan or its pharmaceutically acceptable salts having purity more than 99.80% by HPLC, preferably more than 99.90%.

24. Almotriptan malate having purity more than 99.90% by HPLC.

25. Almotriptan or its pharmaceutically acceptable salts containing less than 0.1% any individual impurity namely N-hydroxymethyl impurity, dimer impurity, amino indole impurity, N-isopropyl impurity, monomethyl impurity or n-oxide impurity, preferably 0.05% by HPLC and total impurities taken together less than 1.0 % by HPLC.

26. Crystalline oxalic acid, succinic acid, malic acid, fumaric acid and tartaric acid salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine having purity greater than 97% by HPLC, preferably greater than 98% by HPLC.

27. 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 having purity greater than 97% by HPLC, preferably > 98% by HPLC.

28. A process for the preparation of almotriptan malate free from methanol, which comprises of the following steps,
    a) dissolving the almotriptan in a mixture of isopropylalochol and methanol at reflux temperature,
    b) subjecting the reaction mixture to carbon treatment,
    c) filtering the reaction mixture through hyflow,
    d) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,
    e) cooling the reaction mixture,
    f) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,
    g) drying the solid to get the highly pure almotriptan malate.

29. A process according to claim 28, wherein isopropyl alcohol and methanol taken in the ratio of 6:4.

30. Usage of mixture of Isopropyl alcohol/MeOH in the ratio of 6:4 at reflux temperature in the preparation of almotriptan malate for the reduction of RS/OVI levels of solvents.

31. Almotriptan malate having purity greater than 99.90% and containing methanol at level of less than 3000 ppm.

32. Almotriptan malate particles having D_{90} particles in the range of 40 to 200 microns.

33. Almotriptan malate particle having mean particle size is in the range of 15 to 70 microns.

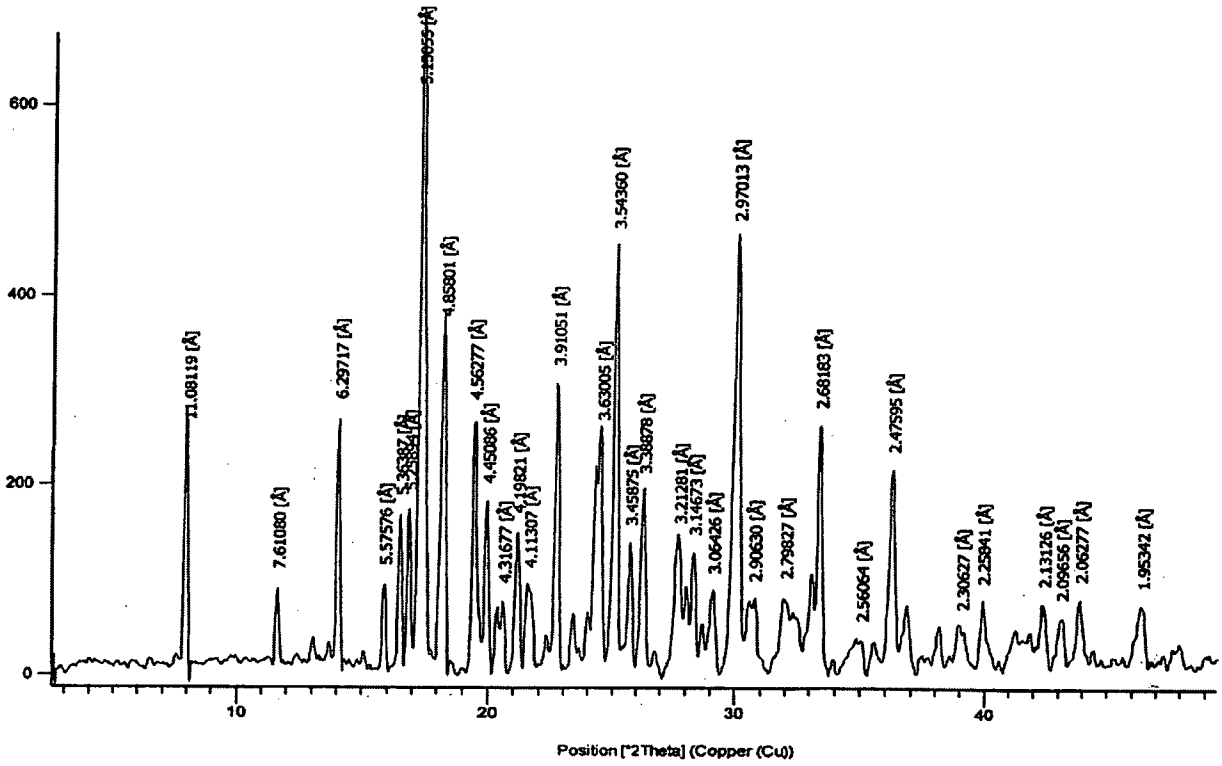


Figure-1

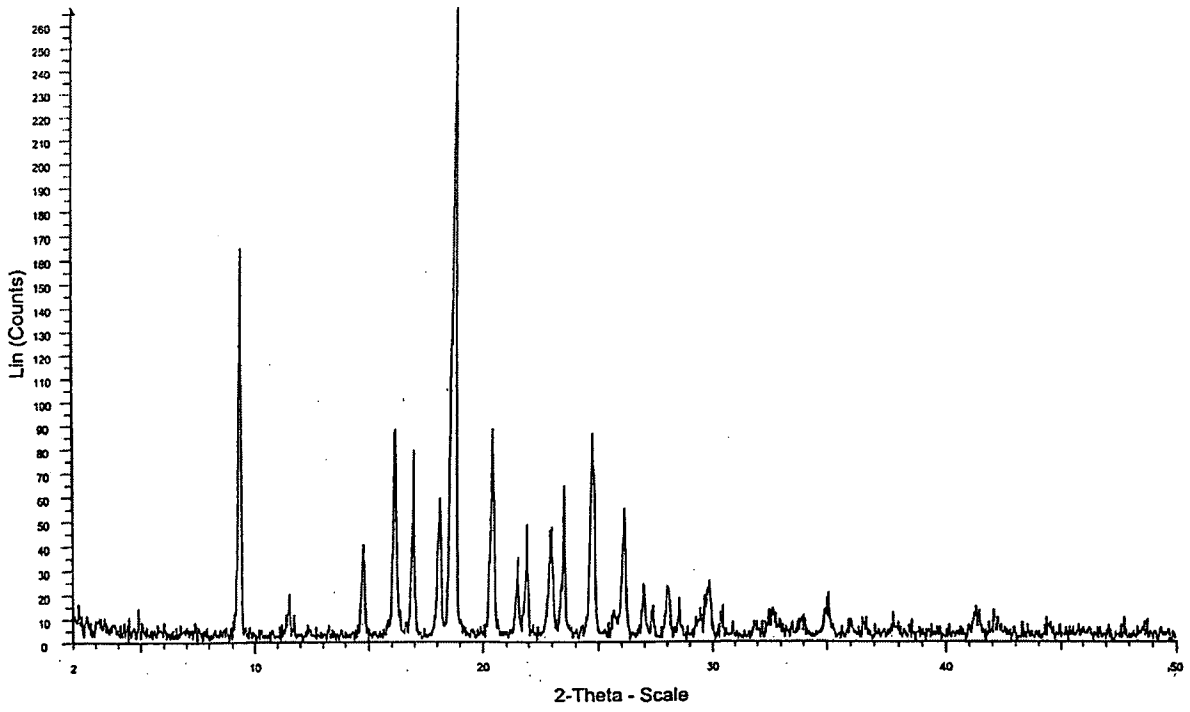


Figure-2

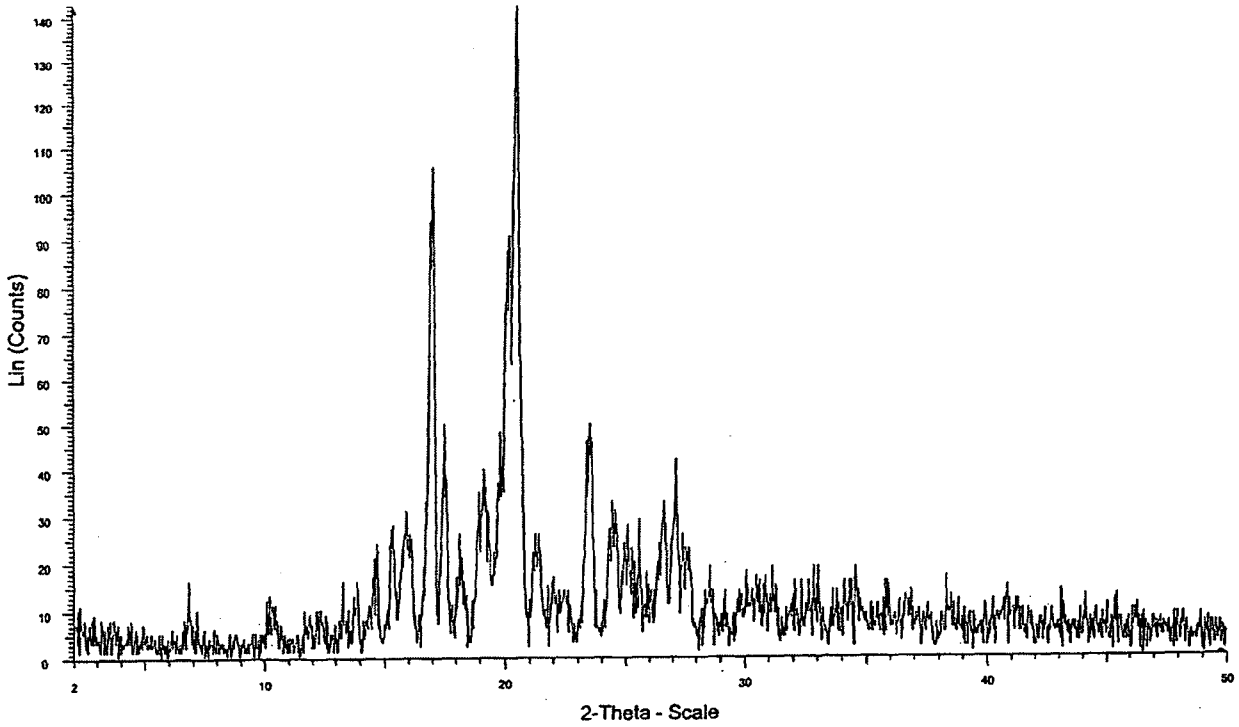


Figure-3

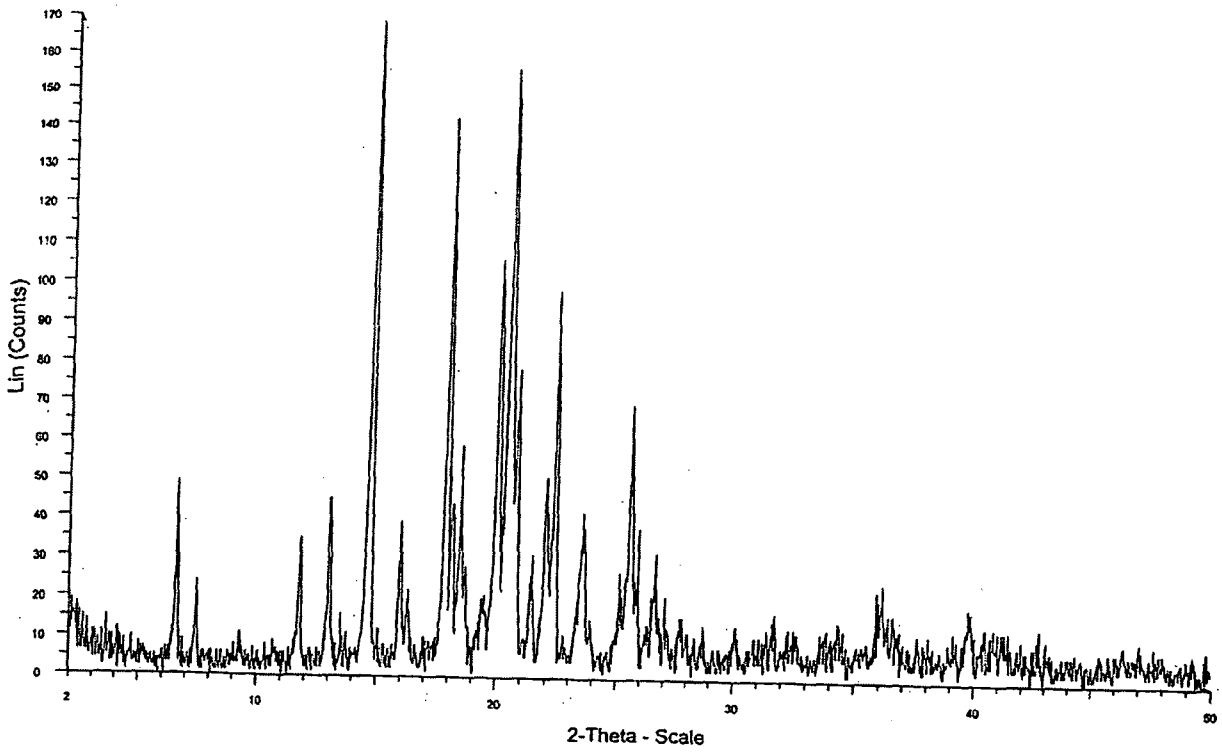


Figure-4

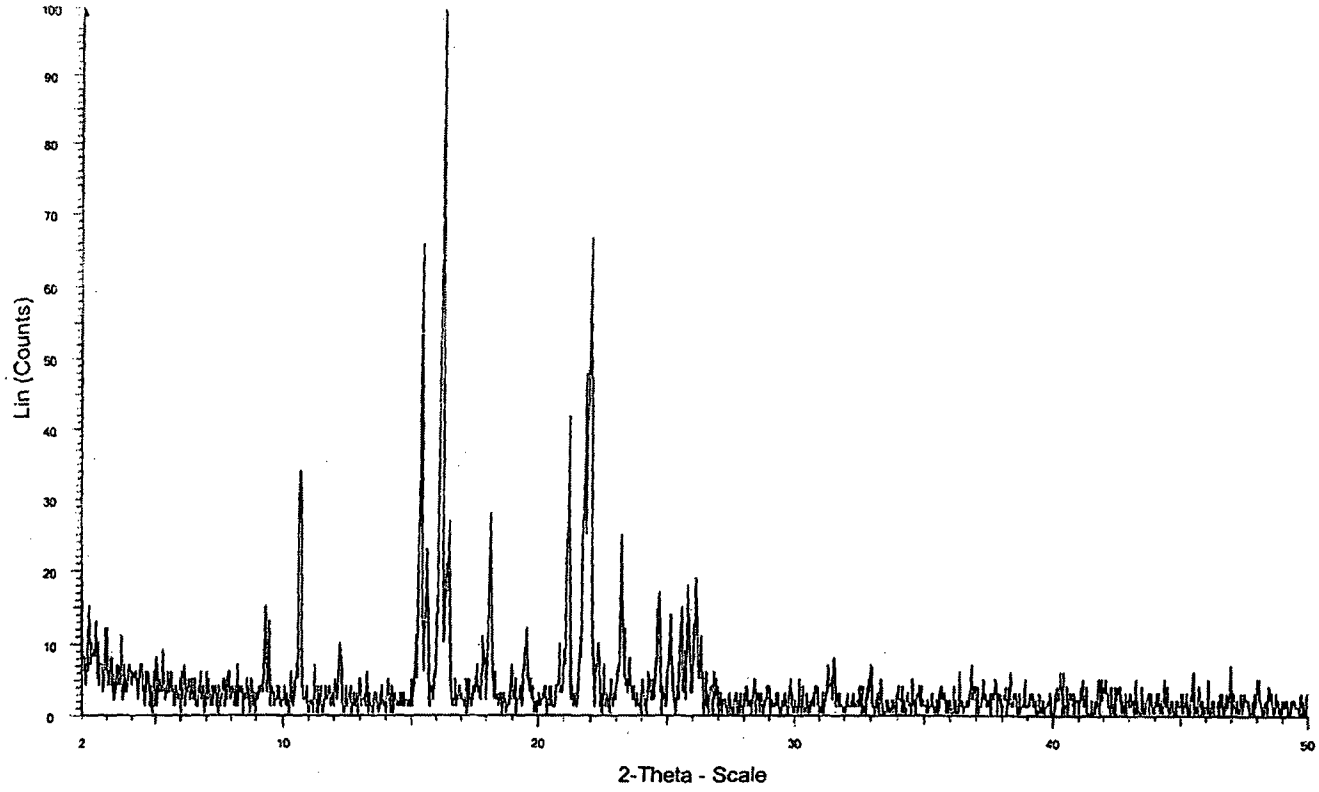

Lin (Counts)
0
10
20
30
40
50
60
70
80
90
100
2
10
20
30
40
50
2-Theta - Scale

Figure-5