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(71) Applicant (for all designated States except US): **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; S.C.O. No. 850, Shivalik Enclave, Nac Manimajra, Chandigarh 160 101 (IN).

(71) Applicants and

(72) Inventors: **CHIDAMBARAM, Venkateswaran, Srinivasan** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phase-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **AGGARWAL, Ashvin, Kumar** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phase-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **WADHWA, Lalit** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phase-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN).

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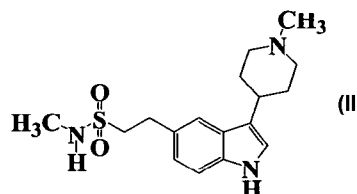
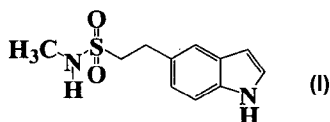
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(54) Title: PROCESS FOR PREPARING INDOLE DERIVATIVES



(57) Abstract: The present invention provides a process for the preparation of indole derivatives, specifically *N*-methyl-1H-indole-5-ethanesulfonamide of formula (I), involving novel intermediate, which is used as key intermediate for the synthesis of natriptan of formula (II), and its pharmaceutically acceptable salts thereof high yield and purity.

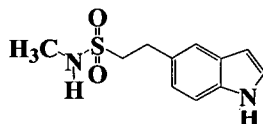


WO 2010/004580 A2

## PROCESS FOR PREPARING INDOLE DERIVATIVES

### FIELD OF THE INVENTION

The present invention provides a novel and efficient process for preparing indole derivatives. Particularly, the present invention provides a process for the preparation of *N*-methyl-1H-indole-5-ethanesulfonamide of formula I,



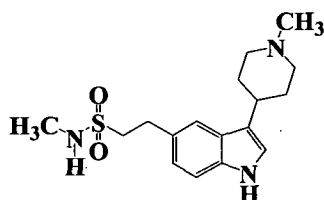
**Formula I**

a key intermediate for the preparation of naratriptan and its pharmaceutically acceptable salts thereof.

The present invention also provides an improved and industrially advantageous process for the preparation of naratriptan and its pharmaceutically acceptable salts thereof. Further, the present invention provides novel synthetic intermediates, which are useful in the processes of the present invention.

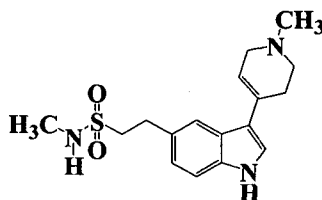
### BACKGROUND OF THE INVENTION

Naratriptan of formula II, is being sold as hydrochloride salt under the trade name AMERGE, for treating migraine and is chemically known as *N*-methyl-3-(1-methyl-4-piperidinyl)-1-*H*-indole-5-ethanesulfonamide.



**Formula II**

Naratriptan and its physiologically acceptable salts, solvates as well as its related compounds useful in the treatment of migraine were first disclosed in US patents 4,997,841 and 5,066,600. The patents also disclose the processes for preparation of these compounds. US patent 4,997,841 describes several processes for synthesizing the naratriptan, and according to one of the processes, naratriptan is prepared by the reaction of 5-bromoindole with *N*-methylvinylsulfonamide under Heck reaction conditions followed by hydrogenation to give *N*-methyl-1H-indole-5-ethane sulfonamide of formula I, a key intermediate. Condensation of above intermediate with *N*-methyl-4-piperidone in the presence of an acidic or basic medium gave following compound,

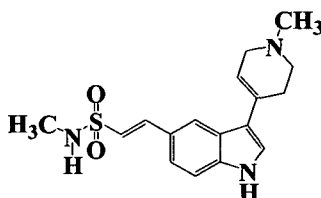


which on reduction in the presence of hydrogen and a noble metal catalyst such as palladium, Raney nickel, platinum, platinum dioxide or rhodium which may be supported on charcoal or homogenous catalyst such as tris(triphenylphosphine)rhodium chloride gives naratriptan of formula II.

- 5 In another process, naratriptan is prepared by the reduction of *N*-methyl-3-(1-methyl-piperidin-4-yl)-1*H*-indole-5-ethanesulphonamide in the presence of hydrogen and a noble metal catalyst as described above. The corresponding 5-ethanesulphonamide derivative is prepared by Heck reaction in the presence of tri-*o*-tolylphosphine, palladium catalyst and a base like triethyl amine.

In yet another process, naratriptan is prepared by the condensation of a phenyl hydrazine derivative  
10 with (1-methyl-piperidin-4-yl)-acetaldehyde under Fisher indolization conditions. Naratriptan, thus prepared on treatment with hydrochloric acid gives naratriptan hydrochloride.

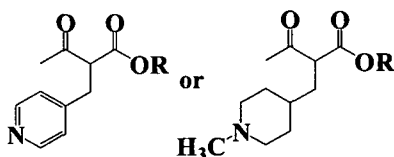
U.S. patent 5,659,040 discloses a process for preparing naratriptan hydrochloride by the reduction of  
15 *N*-methyl-2-[3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1-*H*-indol-5-yl]ethanesulphonamide, a diene intermediate in the presence of hydrogen and a noble metal catalyst like palladium, palladium oxide, Raney nickel, platinum, platinum oxide or rhodium or a homogenous catalyst like tris(triphenylphosphine)rhodium chloride. The synthesis of diene intermediate of following formula also involves Heck reaction.



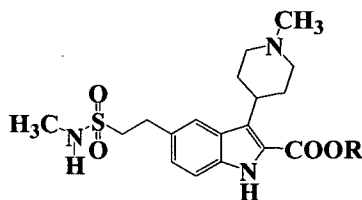
20 These processes require cumbersome operations like Heck reaction that are not useful at commercial scale as these involve the use of expensive Pd (II) salt or complex which is reduced *in situ* to an active palladium(0) species under homogeneous conditions. The Pd (II) species that is subsequently regenerated in the reaction is very difficult to separate and reuse, for the reaction directly without further processing, which makes these processes difficult to reproduce on a larger scale. Further, these processes involve purification of naratriptan and intermediates using chromatographic  
25 technique, which is again unpractical on commercial scale. Additionally, some intermediates like *N*-methylvinylsulfonamide are not commercially available and are very difficult to prepare due to their polymerization property. Main drawback in this process is the preparation of the aldehyde

intermediate. Process for preparation of this intermediate requires number of steps and thus the overall yield is very low.

PCT publication WO 2006/010079 discloses a process for preparing naratriptan by reacting a diazotized derivative of *N*-methyl-2-(4-aminophenyl)ethanesulfonamide with



to form a novel intermediate of the following formula through several steps,

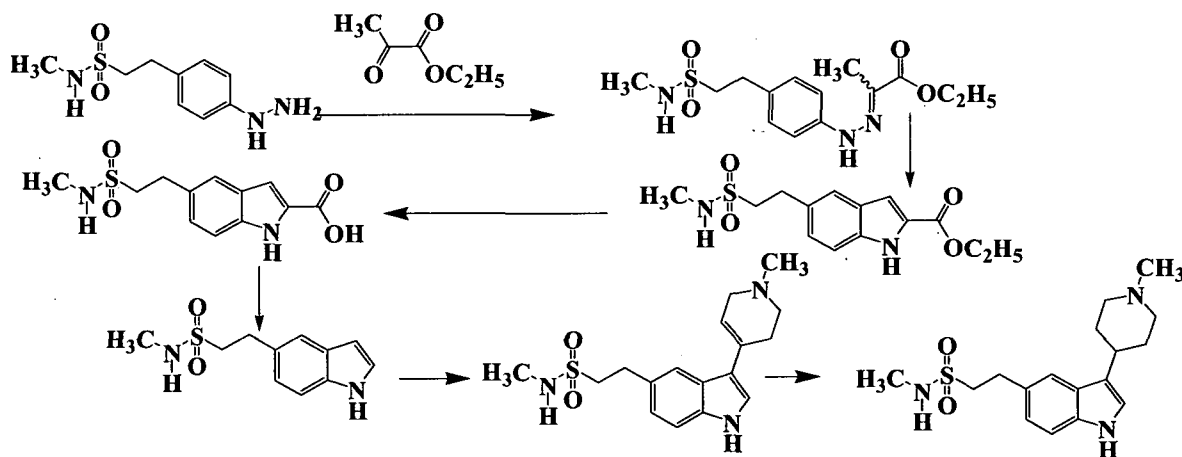


which upon saponification and decarboxylation gives naratriptan. Use of costly reagent like pyridine-4-carboxaldehyde in this process, makes the process unsuitable for use on industrial scale.

10 PCT publications WO 2008/56378 and WO 2008/072257 disclose a process for the preparation of naratriptan through novel intermediates. The process involves the reaction of the hydrazine derivative with pyruvate esters in a solvent medium to give the hydrazone derivative, which undergoes cyclisation in the presence of an acid catalyst in a solvent medium to give the indole ester derivative. Hydrolysis of indole ester derivative in presence of base followed by decarboxylation

15 results in the formation of *N*-methyl-1H-indole-5-ethanesulfonamide, a key intermediate. The above intermediate is condensed with *N*-methyl-4-piperidone in the presence of a base catalyst in a solvent to give naratriptan, which can be further converted to its pharmaceutically acceptable salts thereof.

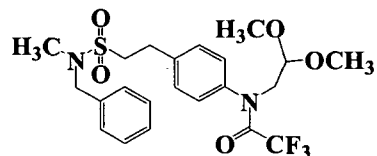
The complete process can be described as:



The decarboxylation reaction performed in the above process requires high temperature condition, nearly 150 to 250 °C that makes the process unattractive to operate on commercial scale.

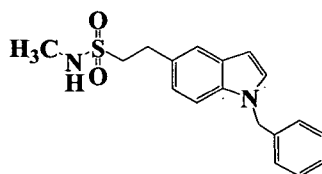
Heterocycles, 2003, 60, 2441 by Bela Pete discloses a process for the preparation of naratriptan, starting from p-nitrobenzaldehyde and isopropyl methanesulfonate to

5 give an intermediate of following formula through several steps.



The above intermediate is then cyclized in presence of titanium tetrachloride to give indole derivative, which on hydrolysis followed by condensation with *N*-methyl-4-piperidone gave another novel intermediate. Hydrogenation and *N*-debenzylation of the intermediate using sodium/liquid ammonia gave naratriptan base in overall yield of 3.6% from p-nitrobenzaldehyde. The process reported in this article is not suitable for commercialization due to low yield. Further process involves the use of costly reagents like trifluoroacetic anhydride and potassium t-butoxide, which makes the process unattractive from industrial point of view.

15 Heterocycles 2006, 68, 713 by Laszlo discloses a process for the preparation of naratriptan by the oxidation of 1-benzylindoline-5-carboxaldehyde followed by condensation with methanesulfonamide to give an intermediate which is then hydrogenated to give benzyl protected compound of following formula,



Above benzyl protected compound is condensed with *N*-methyl-4-piperidone followed by hydrogenation and *N*-debenzylation to give naratriptan. The main draw back of the process disclosed by Laszlo is the use of costly raw material like indoline-5-carboxaldehyde and poor yields. This process also uses titanium salts which are not suitable for commercialization due to pollution. Keeping in view of the difficulties in commercialization of the above-described processes for the preparation of naratriptan and its pharmaceutically acceptable salts thereof, we aimed of developing a simple and economical process for commercial production of naratriptan and its pharmaceutically acceptable salts thereof in high yield and purity.

25 Thus, the present invention fulfills the need in the art by providing an industrial advantageous process for the preparation of naratriptan and its pharmaceutically acceptable salts thereof that is

cost effective, eco-friendly, commercially viable as well as reproducible on industrial scale and meets the needs of regulatory agencies.

### OBJECT OF THE INVENTION

The principal object of the present invention is to provide a novel and efficient process for the preparation *N*-methyl-1H-indole-5-ethanesulfonamide, a key intermediate for the preparation of naratriptan and its pharmaceutically acceptable salts thereof.

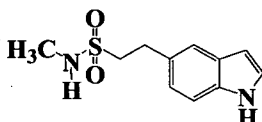
Another object of the present invention is to provide an improved and industrially advantageous process for the preparation of naratriptan and its pharmaceutically acceptable salts thereof, which is unique with respect to its simplicity, cost effectiveness, and scalability.

Yet another object of the present invention is to provide novel intermediates, which serve as industrially useful starting compound for the efficient synthesis of naratriptan and its pharmaceutically acceptable salts thereof.

### SUMMARY OF THE INVENTION

The present invention provides a novel and efficient process for the preparation of indole derivative by employing novel intermediates and unique reaction conditions.

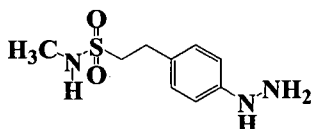
According to one aspect, the present invention provides a process for the preparation *N*-methyl-1H-indole-5-ethanesulfonamide of formula I,



**Formula I**

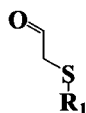
which comprises the step of:

(a) reacting hydrazine derivative of formula III or a salt or protected derivative thereof,



**Formula III**

with a compound of formula IV or a salt thereof,

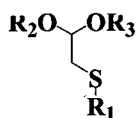


**Formula IV**

wherein  $R_1$  can be selected from straight or branched chain  $C_{1-8}$  alkyl, straight or branched chain  $C_{1-8}$  alkenyl, straight or branched chain  $C_{1-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl,  $C_{1-4}$  alkyl substituted phenyl, monocyclic or bicyclic heterocyclic ring containing one or more heteroatom selected from nitrogen, oxygen, sulfur and the like, the above mentioned

groups can be optionally substituted with halo, nitro, hydroxy, amino, lower  $C_{1-4}$  alkyl,  $N$ -lower( $C_{1-4}$ )alkylamino;  $N,N$ -di-lower( $C_{1-4}$ )alkylamino, lower( $C_{1-4}$ )alkoxy, preferably  $R_1$  can be selected from methyl, phenyl, benzyl, phenethyl, benziimidazole and the like

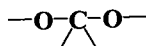
or with a compound of formula V,



5

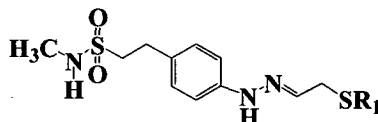
Formula V

wherein  $R_1$  is as described above and  $R_2$  and  $R_3$  can be same or different and individually can be selected from  $C_{1-6}$  alkyl, aryl or  $R_2$  and  $R_3$  can be combined together with the



moiety to complete a cyclic acetal or acetal having three to four carbon atoms in the ring

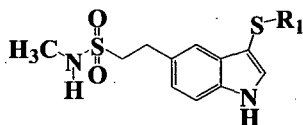
10 in the presence of an acid catalyst in a suitable solvent to form a compound of formula VI;



Formula VI

wherein  $R_1$  is as defined above

(b) cyclising the compound of formula VI in presence of an acid catalyst to form a compound of formula VII; and



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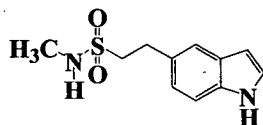
Formula VII

wherein  $R_1$  is as described above

(c) desulfurizing the compound of formula VII using a suitable desulfurizing reagent to form compound of formula I.

According to one another aspect, the present invention provides a process for the preparation  $N$ -methyl-1H-indole-5-ethanesulfonamide of formula I,

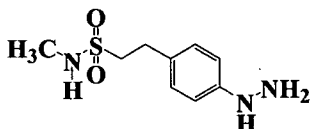
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Formula I

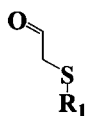
which comprises the step of:

(a) reacting hydrazine derivative of formula III or a salt or protected derivative thereof,



Formula III

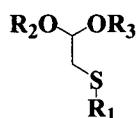
with a compound of formula IV,



**Formula IV**

wherein  $R_1$  is as described above

or with a compound of formula V,

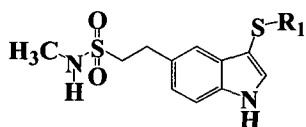


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**Formula V**

wherein  $R_1$ ,  $R_2$  and  $R_3$  are as described above

in the presence of an acid catalyst in a suitable solvent to form a compound of formula VII; and

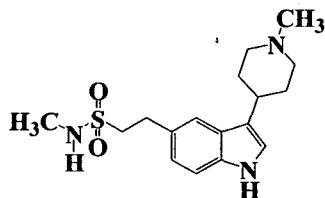


**Formula VII**

wherein  $R_1$  is as described above

- 10 (b) desulfurizing the compound of formula VII using a suitable desulfurizing agent to form *N*-methyl-1H-indole-5-ethanesulfonamide of formula I.

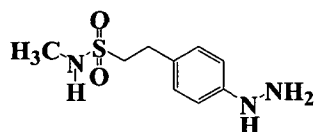
According to another aspect, the present invention provides an improved and industrially advantageous process for the preparation of naratriptan of formula II and its pharmaceutically acceptable salts thereof,



**Formula II**

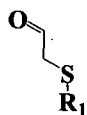
which comprises the step of:

- (a) reacting hydrazine derivative of formula III or a salt or protected derivative thereof,



**Formula III**

- 25 with a compound of formula IV,

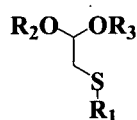


**Formula IV**

wherein  $R_1$  is as described above

or with a compound of formula V,

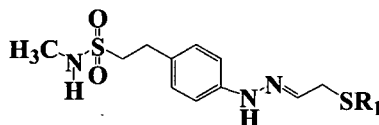




Formula V

wherein  $R_1$ ,  $R_2$  and  $R_3$  are as described above

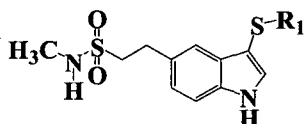
in the presence of an acid catalyst in a suitable solvent to form a compound of formula VI;



Formula VI

wherein  $R_1$  is as described above

(b) cyclising the compound of formula VI in the presence of an acid catalyst to form a compound of formula VII;

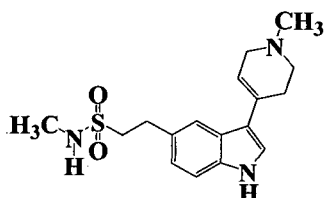


Formula VII

wherein  $R_1$  is as described above

(c) desulfurizing the compound of formula VII using suitable desulfurizing agent to form *N*-methyl-1H-indole-5-ethanesulfonamide of formula I;

(d) condensing intermediate of formula I with *N*-methyl-4-piperidone to form *N*-methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide of formula VIII; and



Formula VIII

(e) reducing the compound of formula VIII to form naratriptan of formula II and its pharmaceutically acceptable salts thereof.

According to yet another aspect, the present invention provides novel intermediates of formula VI and VII including their salts, hydrates, solvates, polymorphs and derivatives thereof.

## 20 DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention is a high throughput, novel and efficient for the preparation of indole derivatives, particularly *N*-methyl-1H-indole-5-ethanesulfonamide of formula I, which is then converted to desired product, naratriptan of formula II, and its pharmaceutically acceptable salts thereof in high yield and purity.

25 According to one aspect, the present invention provides a process for the preparation of *N*-methyl-1H-indole-5-ethanesulfonamide of formula I by the reaction of hydrazine derivative of formula III

or its salt or its protected derivative thereof with a compound of formula IV or with a compound of formula V in the presence of a suitable acid catalyst in a suitable solvent to form a compound of formula VI or compound of formula VII. Compound of formula VI, thus formed, *in situ*, is cyclised to form a compound of formula VII, which is then desulfurized to prepare a compound of formula I, an important intermediate for the preparation of naratriptan that further forms the inventive part of the invention.

Generally, the synthesis of compound of formula I by the reaction of hydrazine derivative of formula III with compound of formula IV or V is carried out in the presence of an acid catalyst and a suitable solvent at a temperature of about 0 to 150 °C for few minutes to few hours. Preferably, the reaction is carried out at a temperature 20 to 100 °C, more preferably at 35 to 75°C till the completion of the reaction. The reaction can conveniently be effected in aqueous or non- aqueous reaction media. The solvent includes, but not limited to protic or aprotic solvents selected from water, alcohols such as ethanol, methanol; ethers such as iso-propyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane; aliphatic or aromatic hydrocarbons such as heptane, cyclohexane; amide solvent such as *N,N*-dimethylformamide; nitriles solvent such as acetonitrile; and the like or mixtures thereof. There is no restriction on the acid catalyst employed for the reaction, provided they can effectively take part in the reaction. Preferably, acid catalyst used can be an organic, inorganic acid or Lewis acid or combination thereof. Organic acid includes, but not limited to aliphatic or aromatic carboxylic acid or sulfonic acid such as acetic acid, formic acid, methansulfonic acid, trifluoromethanesulfonic acid and the like. The acid catalyst used can be a Lewis acid. Lewis acid includes, but not limited to boron trifluoride, boron tribromide, zinc chloride, magnesium chloride, titanium tetrachloride, stannous chloride, aluminium chloride, ferric chloride, and the like. Inorganic acid includes hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, polyphosphoric acid, phosphorus acid, and the like. After the completion of the reaction, compound of formula VI can optionally be isolated from the reaction mixture by suitable technique such as extraction with solvent.

Specifically, the compound of formula VI, if desired, can be isolated as an intermediate by the carrying out the reaction in water or suitable solvent as described above. Optionally, an acid catalyst is added to the reaction mixture. If the reaction is carried out with a compound formula V, it is necessary to add acid. The cyclisation of compound of formula VI can be carried out using appropriate conditions or suitable conditions used for the Fisher-Indole Synthesis (B. Robinson p488-Wiley 1982).

However, it will be appreciated in this aspect of cyclisation process, a compound of formula VI is formed as an intermediate and reacted *in situ* to form a desired compound of formula VII. It is advantageous to proceed to the next step without isolation of compound of formula VI as such intermediates are not stable and prone to readily cyclisation in the presence of acid catalyst, which is present in reaction mixture. The reaction mixture is usually found to be a mixture of compound of formula VI and cyclised compound of formula VII, which can be reacted with a suitable acid catalyst to provide complete formation of the cyclised compound of formula VII in the reaction mixture and to minimize the amount of uncyclised compound of formula VI in the reaction mixture. Acid catalyst can be selected from the list as described above. Generally, the compound of formula VI is found to be 5- 10%, preferably 3-6%, more preferably up to 2% in the reaction mixture. The ratios of compound of formula VI in the reaction mixture can vary depend upon the nature and amount of the acid catalyst employed for the reaction.

The progress of the reaction can be monitored by suitable chromatographic method such as high-performance liquid chromatography or thin layer chromatography. After the completion of reaction, the desired compound of formula VII can be isolated by suitable conventional methods or preceded as such for the next step. The suitable conventional methods can be selected amongst but not limited to precipitation induced by cooling or by the addition of water, distillation of the solvent, distillation followed by extraction with a suitable solvent, addition of a solvent to the reaction mixture, which precipitate the product and the like, whichever is applicable. Specifically, the compound of formulas VII can be isolated by either removal of solvent followed by extraction; or by addition of water/ a solvent to precipitate the product. Solvent for extraction can be selected from water immiscible organic solvent that includes, but not limited to esters such as ethyl acetate; halogenated solvents such as dichloromethane; and the like or mixture thereof, preferably solvent can be selected from ethyl acetate, butyl acetate and the like or mixture thereof.

Thus, compound of formula VII can be prepared directly by the reaction of hydrazine derivative of formula III or its salt or protected derivative thereof with a compound of formula IV or V with the *in situ* formation of hydrazone of compound of formula VI.

The compound of formula VII, thus prepared, by the process of present invention can be used as such in next step or its purification can be effected by various techniques such as crystallization, slurry wash or re-crystallization, solvent-antisolvent system or combination of one or more procedure. The solvent used for the purification includes aliphatic or aromatic hydrocarbon, alcohols, esters, ketones, nitriles, ethers, water, and the like or mixture thereof. Preferably, the

solvents can be selected from hexane, cyclohexane, heptane, acetone, ethyl acetate, isopropyl ether, or mixture thereof.

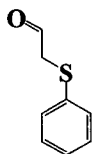
The novel compound of formula VII is then converted to *N*-methyl-1*H*-indole-5-ethanesulfonamide of formula I, which is a key intermediate for the preparation of naratriptan and pharmaceutically acceptable salts thereof by treatment with a desulfurizing agent.

Generally, reaction is carried out in presence of a desulfurizing/reducing agent and a suitable solvent at ambient temperature to reflux temperature of the solvent under inert reaction conditions. Preferably, the reaction is carried out at a temperature of 40 to 150 °C, more preferably at a temperature of 60 to 70 °C. Suitable desulfurizing reducing agent can be selected from any reagent

which is able to remove sulfur from the compound, but not limited to Raney nickel, noble metal catalysts such as palladium, platinum, ruthenium, alkali metal hydride, alkali metal aluminium hydride or alkali metal borohydride and the like, preferably Raney nickel is used. Suitable solvent for the reaction includes, but not limited to protic or aprotic solvents preferably such as alcohols, ethers, halogenated solvent, water and the like or mixtures thereof. Preferably, the solvent can be

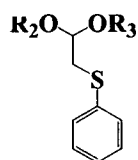
selected from methanol, ethanol, isopropanol; water and the like or mixture thereof. The reaction can be carried out for few minutes to few hours, preferably 2 to 14 hours or more preferably till the completion of the reaction. Completion of the reaction can be monitored by suitable chromatographic method such as high performance liquid chromatography or thin layer chromatography. After the completion of reaction, desulfurizing/reducing agent can be removed by suitable techniques such as filtration. Compound of formula I can be isolated from the reaction mixture by any suitable techniques such as evaporation, distillation, extraction with solvent and the like, preferably distillation, optionally followed by crystallization with ethers such as isopropyl ether; aliphatic or aromatic hydrocarbon such as hexane, heptane, cyclohexane and the like or mixture thereof.

Preferably, compound of formula I, may be prepared by the reaction of hydrazine derivative of formula III or its salt thereof with a compound of formula IVa,



**Formula IVa**

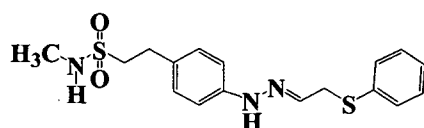
or with a compound of formula Va,



Formula Va

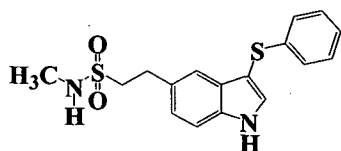
wherein  $R_2$  and  $R_3$  are as described above

in the presence of an acid catalyst in a solvent to form compound of formula VIa,



Formula VIa

5 or directly compound of formula VIIa, a variant of compound of formula VII.

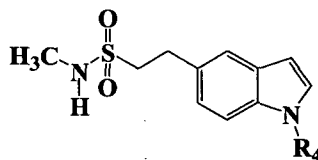


Formula VIIa

Compound of formula VIa is then, preferably *in situ*, cyclised to form compound of formula VIIa, which is then desulfurized to give intermediate compound of formula I.

Specifically compound of formula I is prepared by starting from 4-hydrazino-*N*-methyl-benzene ethanesulfonamide hydrochloride. The process involves the reaction of 4-hydrazino-*N*-methyl-benzene ethanesulfonamide hydrochloride with 2-(phenylthio)-acetaldehyde dimethylacetal in the presence of acid such as acetic acid in alcoholic solvent to prepare *N*-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide. The reaction is advantageously carried out 60-70°C and it takes about 3-4 hours for completion of reaction. Thereafter, solvent is removed and resulting product is isolated in a suitable solvent. The suitable solvent includes but not limited to esters such as ethyl acetate; halogenated solvents such as dichloromethane; and the like or mixture thereof, preferably solvent can be selected from ethyl acetate, butyl acetate and the like or mixture thereof. Thereafter, solvent is distilled off to isolate the pure compound, which is further desulfurized using Raney nickel. Desulfurization reaction may be carried out in alcoholic solvents at reflux temperature. After completion of reaction, the catalyst is recovered by filtration and compound of formula I is isolated from filtrate by distillation or evaporation.

The intermediate of formula I may contain the *N*-alkylated impurity of following formula,



wherein  $R_4$  is selected from alkyl

The impurity may be generated in the compound of formula I, during desulfurization reaction, when reaction is carried out in alcoholic solvent of general formula  $R_4\text{-OH}$  wherein  $R_4$  is as defined above. The compound of formula I may undergo alkylation in the presence of desulfurizing agent such as Raney Nickel in alcoholic solvent to give N-alkylated impurity. During this step, Raney Nickel can play various roles, for instance, Raney nickel acts as a desulfurizing agent, oxidizing agent in the transformation of alcohols to corresponding carbonyl compound and also act as a base in the condensation of indole and carbonyl compound.

It is also observed that impurity generation is less in case, when higher alcohols are used for the reaction and it follows the following trend regarding the amount of impurity:  $R_4$  : methyl > ethyl > propyl and so on.

As is well known in the art, the management of process impurities is greatly enhanced by understanding their chemical structures and by identifying the parameters that influence the amount of impurities in the final product. Moreover, it is important that the presence or absence of an impurity in a product can be identified in any quality control process in order to ensure that the process complies with the required standards set down in the regulatory approval of that product prior to it being released for commercial sale. Therefore, N-alkylated impurity can be characterized by various spectroscopic techniques like  $^1\text{H}$  and  $^{13}\text{C}$  Nuclear magnetic resonance (NMR), Ultraviolet spectroscopy (UV), Mass spectrometry (MS), Infrared spectroscopy (IR). The percentage of impurity present in compound of formula I can be identified by chromatographic techniques like thin layer chromatography (TLC) or high pressure liquid chromatography (HPLC) preferably, by high pressure liquid chromatography.

N-Alkylated impurity can be enriched in the compound of formula I by the prolonged refluxing the compound of I with the desulfurizing agent in alcoholic solvents. After few hours, the reaction mixture is found to be a mixture of N-alkylated impurity and compound of formula I. Thereafter, the N-alkylated impurity can be isolated from the reaction mixture by any suitable method for example using chromatographic techniques such as column chromatography, preparative chromatography, crystallization or the like. Specifically, N-methyl and N-ethyl impurities are isolated by column chromatography.

The purity of the key intermediate is a very important criterion in the field of pharmaceutical chemistry, as the purity and yield of the final API depend upon the purity of the key intermediate. Therefore, compound of formula I may be optionally purified to enhance the purity as well to remove impurities, if present in the intermediate. The compound of formula I, may be purified by various methods such as crystallization, slurry wash or re-crystallization, solvent-antisolvent system

or combination of one or more procedure. The solvent used for the purification of compound of formula I includes, but not limited to aliphatic, aromatic hydrocarbons, alcohols, esters, ketones and water or mixture thereof, Preferably the solvents can be selected from water, hexane, cyclohexane, heptane, acetone, ethyl acetate, isopropyl alcohol, or mixture thereof. Specifically, compound of formula I can be purified in a suitable solvent or solvent mixture at a temperature of 40 to 70°C. Thereafter, compound of formula I can be recovered from the mixture by cooling followed by filtrating the resulting solid. The purified compound of formula I may contain the N-alkylated impurity in less than 1.0 %, preferably less than 0.5%, more preferably free from the impurity.

Further, *N*-methyl-1H-indole-5-ethanesulfonamide of formula I may be converted to naratriptan and pharmaceutically acceptable salts thereof by any method already known in the prior art. Specifically, naratriptan and pharmaceutically acceptable salts thereof can be prepared by the condensation of *N*-methyl-1H-indole-5-ethanesulfonamide with *N*-methyl-4-piperidone in the presence a suitable base in a suitable solvent, at a temperature of 25 °C to reflux temperature of the solvent to form *N*-methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide of formula VIII.

Suitable bases include alkali metal hydroxides, alkali metal alkoxides, alkali metal hydrides, alkali metal amides and the like. Suitable solvent for the reaction includes alcohol such as methanol, ethanol and the like. Generally, the reaction is carried out at a temperature of 40 to 75°C for 20 hours, preferably till the completion of the reaction. After the completion of the reaction, the desired compound of formula VIII can optionally be isolated from the reaction mixture or preceded as such for the next step i.e for the preparation of naratriptan and pharmaceutically acceptable salts thereof. Specifically, the compound of formula VIII can be isolated by adding water to the reaction mixture to precipitate the product or cooling the reaction mixture to initiate precipitation.

The condensed product can, optionally be purified to enhance its purity. The compound of formula VIII can be washed with a suitable solvent selected from water, alcoholic solvent such as methanol, ethanol; ketones such as acetone; ester such as ethyl acetate; ethers such as isopropyl ether; and the like or mixture thereof.

The compound of formula VIII is further catalytically reduced to give naratriptan. The process involves the reaction of compound of formula VIII in a suitable solvent with a suitable reducing agent. The time and temperature can be varied depend upon the nature of the reducing agent employed for the reaction. Generally, the reaction is carried out at ambient temperature to 35°C for few minutes to several hours, preferably till the completion of reaction. The reduction process can preferably be carried out in the presence of hydrogen and a noble metal catalyst (may or may not be with support), such as palladium, Raney nickel, platinum, platinum oxide or rhodium, palladium on

carbon and the like. There is no restriction on the nature of the solvent employed provided they can be chosen based on the nature of reducing agent, preferably reduction can be performed in the presence of a suitable solvent selected from alcoholic solvents such as methanol or ethanol; ethers such as dioxane, tetrahydrofuran; amide solvents such as dimethylacetamide, dimethylformamide; 5 esters such as ethyl acetate, butyl acetate and the like or mixture thereof. After completion of the reaction, naratriptan may be isolated from the reaction mixture using methods known in the art. Specifically, naratriptan is isolated from the reaction mixture by removal of solvent. The resulting residue is dissolved in a suitable solvent followed by washing with water, removal of solvent to give naratriptan free base. Suitable solvent include water immiscible solvent selected from esters such as 10 ethyl acetate and the like.

Naratriptan can optionally be purified using a suitable techniques such as crystallization, slurry wash or re-crystallization, acid base treatment, solvent-antisolvent system or combination of one or more procedure. The solvent used for the purification of naratriptan includes, but not limited to ethers, esters, aliphatic or aromatic hydrocarbon, ketones, water, alcohol or mixture thereof, preferably 15 solvent is selected from isopropyl ether, acetone, cyclohexane, water and the like or mixture thereof. Specifically, naratriptan is purified by crystallization with a suitable solvent or by acid base treatment and the like.

Naratriptan, thus prepared, by the process of present invention can be converted to its pharmaceutical acceptable salts by the process known in the art. Specifically, naratriptan free base in 20 a suitable solvent is made acidic with suitable acid in the presence of suitable solvent till complete salt formation. Suitable solvent include alcoholic solvent such as methanol, ethanol and the like or mixture thereof. Acid employed for the reaction can be hydrochloric acid. Acid used here can be gaseous, aqueous or in combination with a suitable solvent selected from alcoholic hydrochloride, ester hydrochloride, ether hydrochloride and the like. Naratriptan hydrochloride can optionally be 25 purified with a suitable solvent to enhance the purity of the product. Specifically, naratriptan hydrochloride is crystallized with a solvent such as water and mixture of water with alcoholic and ketone solvents and the like.

Starting compound of formula III or its salt or its protected derivative thereof can be procured from the commercial source or can be prepared by any method well known in the prior art.

30 Generally, hydrazine derivative of formula III or its salt or its protected derivative thereof is prepared by methods disclosed in US 4,994,483, PCT publication WO 2006/010079. Preferably, compound of formula III is isolated as hydrochloride salt.

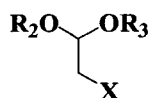


Specifically, hydrazine derivative of formula III may be prepared by the reaction of 4-nitro phenyl ethyl bromide with sodium sulfite to give 2-(4-nitrophenyl)-1-ethane sulfonic acid, which is then reacted with methyl amine in the presence of thionyl chloride to give *N*-methyl-2-(4-nitrophenyl)ethanesulphonamide. The above intermediate is then reduced with a suitable reducing agent such as palladium carbon to give corresponding amine intermediate. The resulting amine intermediate, on diazotization using sodium nitrite and hydrochloric acid followed by reduction in the presence of stannous chloride with hydrochloric acid give hydrazine derivative of formula III. Preferably, hydrazine derivative of formula III is isolated as hydrochloride salts which is optionally purified using a suitable solvent selected from alcohols, alcoholic hydrochloride, water and mixtures thereof.

In addition, starting compound of formula IV and V, can be procured from the commercial source or can be prepared by any methods well known in the art.

Generally, the compound of formula IV can be prepared by the reaction of thiol of general formula  $R_1SH$  wherein  $R_1$  is as defined above with haloacetaldehyde under suitable reaction conditions.

Similarly, the compound of formula V, can be prepared by the reaction of thiol of general formula  $R_1SH$  wherein  $R_1$  is as defined above with acetal derivative of following formula



wherein  $R_2$  and  $R_3$  are as defined above and  $X$  is halo can be selected from chloro, bromo or fluoro and the like

under suitable reaction conditions.

Specifically, compound of formula Va (where  $R_1$  is phenyl) may be prepared by the treatment of thiophenol with a suitable base in a suitable solvent at a temperature of about 25 to 80 °C for few minutes to few hours, preferably the reaction is carried out at a temperature of 30 to 60 °C for one hour to several hours. More preferably, the reaction is carried out till the completion of the reaction.

Acetal derivatives of haloacetaldehyde, preferably bromoacetaldehyde dimethylacetal in a suitable solvent is added to the reaction mixture at a temperature of about 10 to 45 °C for few minutes to few hours, preferably the reaction is carried out at room temperature. Suitable solvent for the reaction can be selected from, but not limited to alcoholic solvents, preferably methanol, ethanol and the like is used. After the completion of reaction, compound of formula V can be isolated by suitable technique such as extraction with solvent or preceded as such for the next step. Solvent for extraction of the product can be selected from, but not limited to esters; preferably, solvent used is ethyl acetate. Specifically, the compound of formula V (where  $R_1$  is phenyl and  $R_2$  and  $R_3$  are

*methyl*) is isolated from the reaction by removal of solvent followed by extraction with a water immiscible solvent. Water immiscible solvent may be selected from esters such as ethyl acetate; ethers such as tetrahydrofuran, methyl tert-butyl ether; halogenated solvents such as dichloromethane; hydrocarbon solvents such as hexane, toluene; alcoholic solvent such as isoamyl alcohol; and the like or mixture thereof. Thereafter, desired product can be isolated from the reaction mixture by the removal of the solvent.

The intermediates of the present invention can be isolated or used as such in the next step. The purification of final compound and intermediates described here in the present invention can be effected, if desired, by any suitable purification procedure such as, for example, filtration, extraction, crystallization, derivatization, slurry wash, salt preparation or combination of these procedures. However, other equivalent procedures such as acid-base treatment could, of course, also be used.

The intermediate described here in the present invention include salts, hydrates, solvates, polymorphs and complex thereof. Novel intermediates of formulae VI and VII of the present invention also forms the inventive part of the present invention and may be characterized by at least one of the spectroscopic techniques such as mass spectroscopy, infra-red spectroscopy,  $^1\text{H}$  or  $^{13}\text{C}$  nuclear magnetic resonance spectroscopy or differential scanning calorimetry and identified by the chromatographic technique such as high performance liquid chromatography or thin layer chromatography during the reaction.

Major advantages realized in the present invention are high yields and high purity. The process of present invention involves reduced number of steps using novel intermediates, prepared by using inexpensive reagents and hence process is cost-effective.

Although, the following examples illustrate the present invention in more detail, but should not be construed as limiting the scope of the invention.

## EXAMPLES

### Example 1: Preparation of 2-(phenylthio)-acetaldehyde dimethylacetal

To a solution of thiophenol (10 g) in methanol (70 ml) was added sodium hydroxide (7.6 g). After completion of the addition, the reaction mixture was stirred at 30-60 °C for 60 minutes. A solution of bromoacetaldehyde dimethylacetal (15.2 g) in methanol (30 ml) was added to above mixture at 25-30 °C, the reaction mixture was allowed to stir at the same temperature. After completion of reaction, the solvent was distilled off and the resulting residue was extracted with ethyl acetate (100 ml). The solvent was distilled off under vacuum to obtain 15 g of the title compound.

**Example 2: Preparation of 2-(phenylthio)-acetaldehyde dimethylacetal**

To a solution of thiophenol (100 g, 0.90mol) in methanol (1.0L), sodium hydroxide (54.5 g) was added and mixture was stirred. The reaction mixture was allowed to cool. Thereafter 184.3 g (1.09 mol) of bromoacetaldehyde dimethylacetal (184.3 g, 1.09 mol) was added to the reaction mixture and stirred for 18 hours at room temperature under nitrogen atmosphere. After completion of reaction, the solvent was distilled off and the resulting residue was extracted with ethyl acetate (600 ml). The organic layer was washed with demineralized water (600 ml) and then distilled to give 174g of title compound having purity 97.54% by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.10-3.11 (d, 2H); 3.35 (s, 6H); 4.50-4.53 (t, 1H); 7.15-7.36 (m, 5H)

**10 Example 3: Preparation of N-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide**

**Method A:** Acetic acid (2 ml) was added to a suspension of 4-hydrazino-N-methyl-benzene ethanesulfonamide hydrochloride (6.0 g) and 2-(phenylthio)-acetaldehyde dimethylacetal (4.5 g) in ethanol at 25-30°C. Reaction mixture was allowed to stir for 3 hours at 60-70 °C. After completion of the reaction, solvent was distilled out and the reaction mass was extracted with ethyl acetate. The solvent was distilled out under vacuum and the resulting compound was crystallized from cyclohexane to give 6.5 g of title compound.

**Method B:** A mixture of 4-hydrazino-N-methyl-benzene ethanesulfonamide hydrochloride (150g, 0.56mol) and 2-(phenylthio)-acetaldehyde dimethylacetal (134.3g, 0.678mol) was refluxed in ethanol (1500 ml) at 55-60°C for 3-4 hours in the presence of acetic acid (30 ml). After completion of the reaction, the reaction mixture was cooled to ambient temperature. Thereafter, water was added (4.5 L) to the reaction mixture and the product, thus precipitated, was filtered to give crude compound.

The resulting product was purified with isopropyl ether (450 ml) at 75-80°C. The mixture was cooled to 15-20°C and filtered to give 157 g of pure title compound having 98.8% by HPLC.

<sup>1</sup>H NMR (DMSO): δ 2.62-2.63(d, 3H); 3.06-3.10(m, 2H); 3.19-3.24(m, 2H); 6.60-6.64(q, 1H); 6.97-7.66(m, 9H, aromatic); 11.22(s, 1H).

**Example 4: Preparation of N-methyl-1H-indol-5-ethanesulfonamide**

**Method A:** To a solution of the N-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide (5.0 g) in ethanol (50ml) was added Raney Nickel (25.0 g in water) in ethanol and reaction mixture was stirred at reflux temperature for 4 hours under inert atmosphere. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered through hyflo bed to remove the catalyst

and the catalyst was washed with ethanol. The collective filtrate was distilled under vacuum to obtain compound, which was crystallized with cyclohexane to obtain 2.5 g of the title compound.

**Method B:** *N*-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide (10g, 0.042mol) in ethanol (100ml), Raney Nickel (50g) was added and heated at 70-75°C for 12 hours. After completion of reaction, the reaction mixture was cooled to ambient temperature and Raney Nickel was filtered through hyflo bed. The filtrate was concentrated to obtain 3.2g (47%) of the tile compound.

**Method C:** *N*-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide (30g, 0.126mol) in tetrahydrofuran (180ml), Raney Nickel (150g) was added and heated at 70-75°C for 6 hours. After completion of the reaction, the reaction mixture was cooled to ambient temperature and Raney Nickel was filtered through hyflo bed. The filtrate was concentrated to give crude title which was further purified using isopropyl ether (90ml) to give 18 g title compound.

**Method D:** To a solution of *N*-methyl-3-(phenylthio)-1H-indol-5-ethanesulfonamide (145 g, 0.419 mol) in isopropanol (1.45 L), Raney Nickel (725g) was added and heated to 70-75 °C for 3 hours. After completion of the reaction, the reaction mixture was cooled to ambient temperature and Raney Nickel was filtered through hyflo bed. The filtrate was concentrated to give crude title compound having purity 96.88% and N-alkylated impurity 1.86% by HPLC. The resulting product was purified using mixture of isopropanol: water: cyclohexane (435 ml, 1:1:1) to give 75g (75%) of the pure title having purity 99.41% and N-alkylated impurity 0.07% by HPLC.

**Example 5: Preparation of *N*-methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide**

**Method A:** *N*-methyl-1H-indol-5-ethanesulfonamide (2 g, 0.008 mol) was added to stirred solution of methanolic solution of potassium hydroxide (11.2 g) in methanol (100 ml) at 25-35 °C. After stirring for 10 minutes, a solution of *N*-methyl-4-piperidone was slowly added at 25-35 °C and the mixture was refluxed for 24 hours. After completion of reaction, the reaction mixture was cooled to 30 °C. The precipitated solid was filtered, and successively washed with cold water, methanol and isopropyl ether to obtain 1.6 g of the title compound.

**Method B:** A mixture of *N*-methyl-1H-indol-5-ethanesulfonamide (100g, 0.42mol), *N*-methyl-4-piperidone (113.9g, 1 mol), potassium hydroxide (141.2g) and methanol (600ml) was refluxed for 18 hours at 70-75°C. After completion of the reaction, the reaction mixture was cooled to room temperature. Thereafter, water (1800ml) was added to the reaction mixture to precipitate an off-white solid. The precipitated solid was filtered, and washed with a mixture of methanol and water (400g, 3:1) to give 130g of title compound having purity 99.79% by HPLC.

**Example 6: Preparation of naratriptan**

**Method A:** *N*-Methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide (1.6 g, 0.005 mol) was dissolved in ethanol (150 ml) and dimethylformamide (3 ml). The reaction mixture was subjected to hydrogen gas pressure of 5.5-7.0 kg/cm<sup>2</sup> for 2 hours at 25-35 °C in presence of 10% palladium on carbon. After completion of the reaction, the mass was filtered and the filtrate was concentrated under vacuum to 1.5 g of give title compound.

**Method B:** *N*-Methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide (100g, 0.30mol) in ethanol (1.5 L) was hydrogenated using hydrogen pressure 2.5-4.0 kg/cm<sup>2</sup> with 10% palladium on carbon (50g) for 24 hours at ambient temperature. After completion of reaction, the reaction mixture was filtered through hyflo bed to remove the catalyst and the filtrate was concentrated to obtain a residue. The resulting residue was dissolved in ethyl acetate (1 L) and washed with water. The organic layer was distilled under vacuum to obtain crude title compound which was crystallized with isopropyl ether (300ml) and filtered under vacuum to give 90g of title compound.

**Example 7: Preparation of naratriptan hydrochloride**

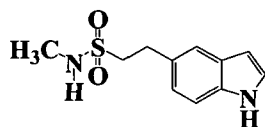
Naratriptan (50g) was dissolved in a mixture of methanol and ethanol (1:9) at 60°C till clear solution was obtained. Thereafter, pH of the reaction mixture was adjusted to 1.0 with ethanolic hydrogen chloride at 25°C. The reaction mixture was cooled to 5 °C and stirred for 1 hour at same temperature. The solid thus precipitated was filtered and recrystallized from water (300ml). The resulting product was filtered, washed with ethanol to 80.8g (71.7%) of the tile compound having purity 99.95% by HPLC.

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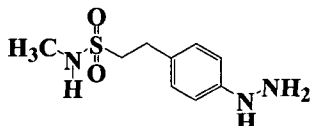
**WE CLAIM:**

1). A process for the preparation *N*-methyl-1H-indole-5-ethanesulfonamide of formula I,

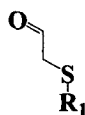
**Formula I**

which comprises the steps of:

(a) reacting hydrazine derivative of formula III or a salt or protected derivative thereof,

**Formula III**

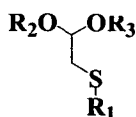
5 with a compound of formula IV,

**Formula IV**

wherein  $R_1$  can be selected from straight or branched chain  $C_{1-8}$  alkyl, straight or branched chain  $C_{1-8}$  alkenyl, straight or branched chain  $C_{1-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl,  $C_{1-4}$  alkyl substituted phenyl, monocyclic or bicyclic heterocyclic ring containing one or more heteroatom selected from nitrogen, oxygen, sulfur and the like, the above mentioned groups can be optionally substituted with halo, nitro, hydroxy, amino, lower  $C_{1-4}$  alkyl, *N*-lower( $C_{1-4}$ )alkylamino; *N,N*-di-lower( $C_{1-4}$ )alkylamino, lower( $C_{1-4}$ )alkoxy

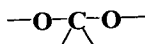
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or with a compound of formula V,

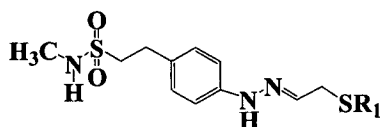
**Formula V**

wherein  $R_1$  is as described above and  $R_2$  and  $R_3$  can be same or different and individually can be selected from  $C_{1-6}$  alkyl, aryl or  $R_2$  and  $R_3$  can be combined together with the

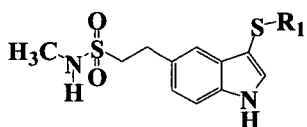
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moiety to complete a cyclic acetal or acetal having three to four carbon atoms in the ring in the presence an acid catalyst in a suitable solvent to form a compound of formula VI;

**Formula VI**

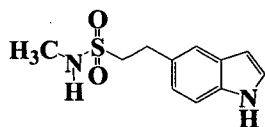
20 (b) cyclising the compound of formula VI in presence of an acid catalyst to form a compound of formula VII; and



Formula VII

wherein  $R_1$  is as described above

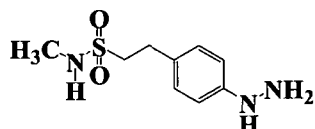
- (c) desulfurizing the compound of formula VII in the presence of suitable desulfurizing agent to form a compound of formula I.
- 2). The process according to claim 1, wherein acid catalyst is selected from organic acid, inorganic acid or Lewis acid or combination thereof.
- 5
- 3). The process according to claim 2, wherein organic acid includes aliphatic or aromatic carboxylic acid or sulfonic acid such as acetic acid, formic acid, methanesulfonic acid, trifluoromethanesulfonic acid and the like; Lewis acid includes boron trifluoride, boron tribromide, zinc chloride, magnesium chloride, titanium tetrachloride, stannous chloride, aluminium chloride, ferric chloride, and the like; and inorganic acid includes hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, polyphosphoric acid, phosphorus acid, and the like; or combination thereof.
- 10
- 4). The process according to claim 1, wherein suitable solvent includes protic or aprotic solvents selected from water, alcohols such as ethanol, methanol; ethers such as iso-propyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane; aliphatic or aromatic hydrocarbons such as heptane, cyclohexane; amide solvent such as *N,N*-dimethylformamide; nitriles solvent such as acetonitrile; and the like or mixtures thereof.
- 15
- 5). The process according to claim 1, wherein in step c) desulfurizing agent is selected from Raney nickel, noble metal catalysts such as palladium, platinum, ruthenium, alkali metal hydride, alkali metal aluminium hydride or alkali metal borohydride and the like.
- 20
- 6). A process for the preparation *N*-methyl-1H-indole-5-ethanesulfonamide of formula I,



Formula I

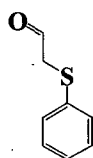
which comprises the step of:

- (a) reacting hydrazine derivative of formula III or a salt or protected derivative thereof,



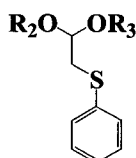
Formula III

with a compound of formula IVa,



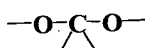
Formula IVa

or with a compound of formula Va,

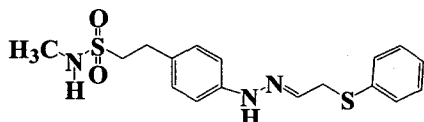


Formula Va

wherein  $R_2$  and  $R_3$  can be same or different and individually can be selected from  $C_{1-6}$  alkyl, aryl or  $R_2$  and  $R_3$  can be combined together with the

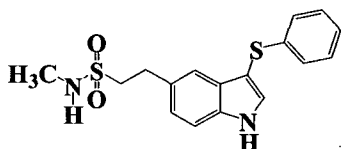


- 5 moiety to complete a cyclic acetal or acetal having three to four carbon atoms in the ring in the presence an acid catalyst in a suitable solvent to form a compound of formula VIa;



Formula VIa

- (b) cyclising the compound of formula VIa in presence of an acid catalyst to form a compound of formula VIIa; and



Formula VIIa

- (c) desulfurizing the compound of formula VIIa in the presence of suitable desulfurizing agent to form a compound of formula I.

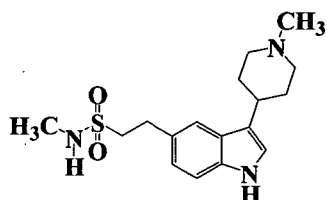
- 10
- 7). The process according to claim 6, wherein acid catalyst is selected from organic acid, inorganic acid or Lewis acid or combination thereof.
- 8). The process according to claim 7, wherein organic acid includes aliphatic or aromatic carboxylic acid or sulfonic acid such as acetic acid, formic acid, methansulfonic acid, trifluoromethanesulfonic acid and the like; Lewis acid includes boron trifluoride, boron tribromide, zinc chloride, magnesium chloride, titanium tetrachloride, stannous chloride, aluminium chloride, ferric chloride, and the like; and inorganic acid includes hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, polyphosphoric acid, phosphorus acid, and the like; or combination thereof.
- 15
- 9). The process according to claim 6, wherein suitable solvent includes protic or aprotic solvents selected from water, alcohols such as ethanol, methanol; ethers such as iso-propyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane; aliphatic or aromatic hydrocarbons
- 20



such as heptane, cyclohexane; amide solvent such as *N,N*-dimethylformamide; nitriles solvent such as acetonitrile; and the like or mixtures thereof.

10) The process according to claim 6, wherein in step c) desulfurizing agent is selected from Raney nickel, noble metal catalysts such as palladium, platinum, ruthenium, alkali metal hydride, alkali metal aluminium hydride or alkali metal borohydride and the like.

11) The process according to claims 1 and 6, further comprising converting the compound of formula I into naratriptan of formula II,

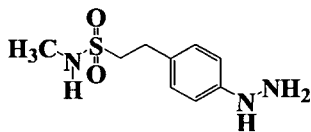


**Formula II**

and its pharmaceutically acceptable salts thereof.

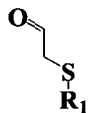
12) A process for the preparation of naratriptan of formula II, and its pharmaceutically acceptable salts thereof, which comprises the step of:

a). reacting hydrazine derivative of formula III or a salt or protected derivative thereof,



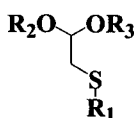
**Formula III**

with a compound of formula IV,



**Formula IV**

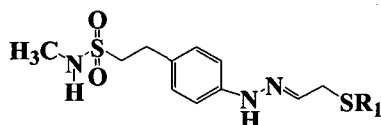
or with a compound of formula V,



**Formula V**

wherein  $R_1$ ,  $R_2$  and  $R_3$  are as defined above

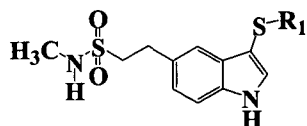
in the presence an acid catalyst in a suitable solvent to form a compound of formula VI;



**Formula VI**

wherein  $R_1$  is as described above

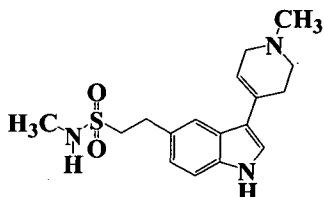
b). cyclising the compound of formula VI in presence of an acid catalyst to form a compound of formula VII; and



**Formula VII**

wherein  $R_1$  is as described above

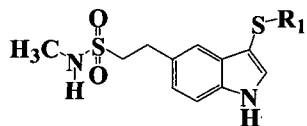
- c). desulfurizing the compound of formula VII in the presence of suitable desulfurizing agent to form compound of formula I;
- d). condensing compound of formula I with *N*-methyl-4-piperidone to form *N*-methyl-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-ethanesulfonamide of formula VIII; and



Formula VIII

- e). reducing the compound of formula VIII to form naratriptan of formula II.
- 13). The process according to claim 12, wherein acid catalyst is selected from organic acid, inorganic acid or Lewis acid or combination thereof.
- 14). The process according to claim 13, wherein organic acid includes aliphatic or aromatic carboxylic acid or sulfonic acid such as acetic acid, formic acid, methanesulfonic acid, trifluoromethanesulfonic acid and the like; Lewis acid includes boron trifluoride, boron tribromide, zinc chloride, magnesium chloride, titanium tetrachloride, stannous chloride, aluminium chloride, ferric chloride, and the like; and inorganic acid includes hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, polyphosphoric acid, phosphorus acid, and the like; or combination thereof.
- 15). The process according to claim 12, wherein in step a) solvent includes protic or aprotic solvents selected from water, alcohols such as ethanol, methanol; ethers such as iso-propyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane; aliphatic or aromatic hydrocarbons such as heptane, cyclohexane; amide solvent such as *N,N*-dimethylformamide; nitriles solvent such as acetonitrile; and the like or mixtures thereof.
- 16). The process according to claim 12, wherein in step c) desulfurizing agent is selected from Raney nickel, noble metal catalysts such as palladium, platinum, ruthenium, alkali metal hydride, alkali metal aluminium hydride or alkali metal borohydride and the like.
- 17). The process according to claim 12, wherein in step d) condensation is carried out in the presence of a suitable base that includes alkali metal hydroxides, alkali metal alkoxides, alkali metal hydrides, alkali metal amides and the like.
- 18). The process according to claim 12, wherein in step e) reduction is carried out in the presence of hydrogen and a noble metal catalyst such as palladium, palladium on carbon, Raney nickel, platinum, platinum oxide or rhodium, and the like.

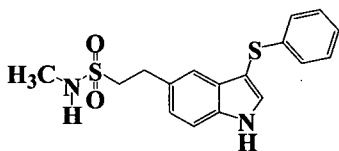
19). A compound of formula VII, including their salts, hydrates, solvates, polymorphs and derivatives thereof



Formula VII

wherein  $R_1$  can be selected from straight or branched chain  $C_{1-8}$  alkyl, straight or branched chain  $C_{1-8}$  alkenyl, straight or branched chain  $C_{1-8}$  alkynyl,  $C_{3-8}$  cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl,  $C_{1-4}$  alkyl substituted phenyl, monocyclic or bicyclic heterocyclic ring containing one or more heteroatom selected from nitrogen, oxygen, sulfur and the like, above mentioned groups can be optionally substituted with halo, nitro, hydroxy, amino, lower  $C_{1-4}$  alkyl,  $N$ -lower( $C_{1-4}$ )alkylamino;  $N,N$ -di-lower( $C_{1-4}$ ) alkylamino, lower( $C_{1-4}$ )alkoxy and the like.

20). A compound of formula VII according to claim 19, wherein  $R_1$  is phenyl has structure  
10 formula VIIa,



Formula VIIa