

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number  
**WO 2006/010079 A2**

(51) International Patent Classification:  
A61K 31/4178 (2006.01)

Burdwan 713 101 (IN). **BHAR, Chandan** [IN/IN]; Flat No. A-12, Sai Vihar Residency, Pashan-SUS ROAD, PASHAN, PUNE 411 021 (IN).

(21) International Application Number:

PCT/US2005/024436

(74) Agent: **FRANKS, Robert, A.**; Dr. Reddy's Laboratories, Inc., Patent Prosecution Group, 200 Somerset Corporate Boulevard, 7th floor, Bridgewater, New Jersey 08807 (US).

(22) International Filing Date: 8 July 2005 (08.07.2005)

(25) Filing Language: English

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:  
656/CHE/2004 8 July 2004 (08.07.2004) IN

(71) Applicants (for all designated States except US): **DR. REDDY'S LABORATORIES LTD.** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016 (IN). **DR. REDDY'S LABORATORIES, INC.** [US/US]; 200 Somerset Corporate Boulevard, 7th floor, Bridgewater, New Jersey 08807 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ISLAM, Aminul** [IN/IN]; Ward No. 15, Jonaki Path, College Nagar, P. O. Bidyapara, Dist: Dhubri, Assam 783 324 (IN). **SAHADEV, Katam** [IN/IN]; Plot No. 182A, Road No. 6, R.K.H. Colony, Near Dr. A. S. Rao Nagar, ECIL-Post, Hyderabad 500 062 (IN). **REDDY, Madadi, Vijaypal** [IN/IN]; C/O: Raji reddy. K, H. No: 2-19-82/3, East Kalyanpuri, Uppal, Hyderabad 500 039 (IN). **KULKARNI, Ruturaj, Vijay** [IN/IN]; C/O V. G. Kulkarni, Near Nahata College, Mahesh nagar, Bhusawal, Dist: Jalgaon 425 201 Maharashtra (IN). **LAYEK, Mohammed, Mohosin** [IN/IN]; H. No.-168, Rasik Pur (Layek para),

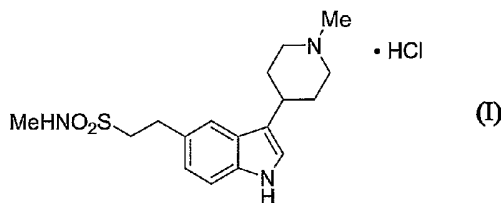
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING NARATRIPTAN HYDROCHLORIDE

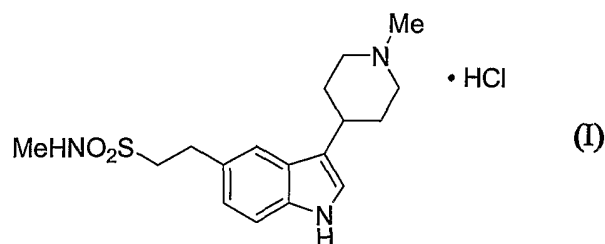


(57) Abstract: A process for preparing naratriptan hydrochloride, N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide hydrochloride having formula (I).

## PROCESS FOR PREPARING NARATRIPTAN HYDROCHLORIDE

### INTRODUCTION TO THE INVENTION

5        The present invention relates to a process for preparing N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride having formula (I).



10        The compound of formula (I) has the adopted name "naratriptan hydrochloride" and is being sold in pharmaceutical products using the trademark AMERGE, for treating migraine.

15        N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide and its physiologically acceptable salts and solvates are disclosed in GB 2208646. The compound exhibits selective vasoconstrictor activity and is indicated for use in the treatment of migraine.

      U.S. Patents 4,997,841 and 5,066,600 disclose N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride and its related compounds useful in the treatment of migraine and process for preparation of compounds.

20        In earlier disclosed processes, the key step is condensation of a 4-piperdone derivative with an appropriate substituted indole derivative in the presence of an acidic medium to obtain the compound of formula (I) and its related compounds.

25        The present invention relates to a process which has the following advantages over the earlier processes:

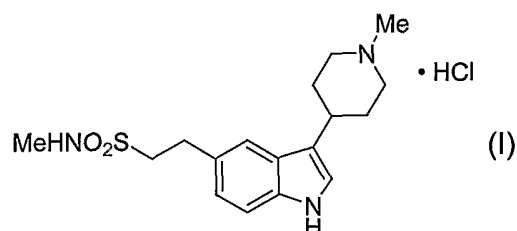
1)        Earlier processes comprise cumbersome operations like Heck reactions and tin (II) chloride reduction. These are difficult to reproduce in larger scale. The process claimed in this application is relatively more suitable for scaled-up operations.

2) The intermediates and reagents used in earlier processes are more expensive than those used in the process claimed in this application. The process described herein is economically more viable.

5

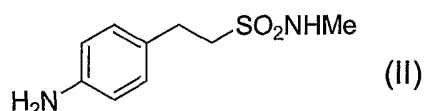
## SUMMARY OF THE INVENTION

A process for preparing a compound having formula (I)

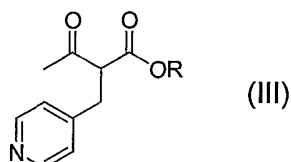


comprises:

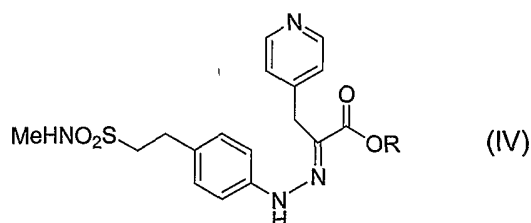
- 10 (i) reacting a diazotized derivative of a compound having formula (II),



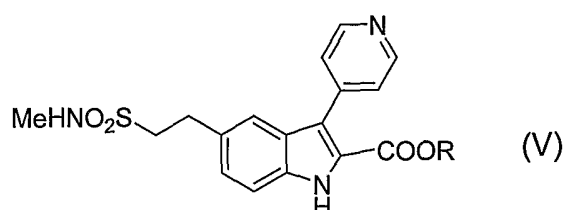
with a compound having formula (III), where R represents an alkyl group having 1 to 5 carbon atoms;



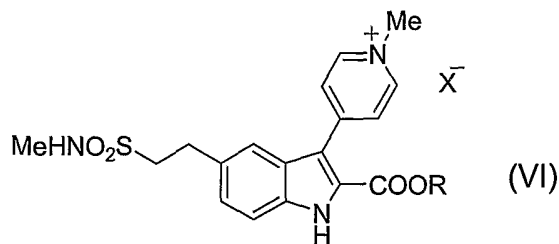
- 15 to produce a compound having formula (IV);



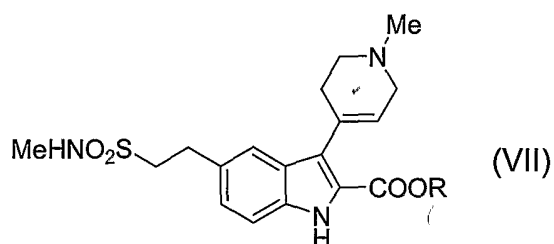
- (ii) cyclizing the compound having formula (IV) in the presence of an acid to produce a compound having formula (V);



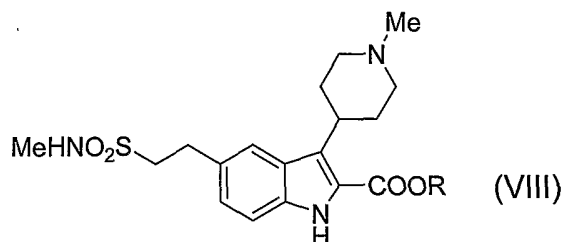
(iii) quaternizing the compound having formula (V) with an alkyl halide to produce a compound having formula (VI), where X is a halogen;



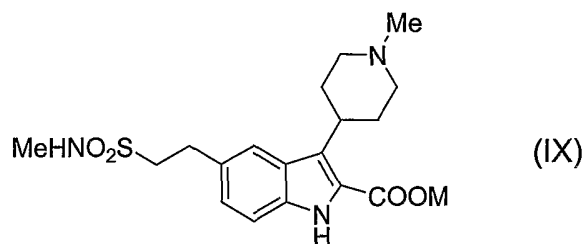
(iv) reacting the compound having formula (VI) with a reducing agent to produce a compound having formula (VII);



(v) hydrogenating the compound having formula (VII) to produce a compound having formula (VIII);

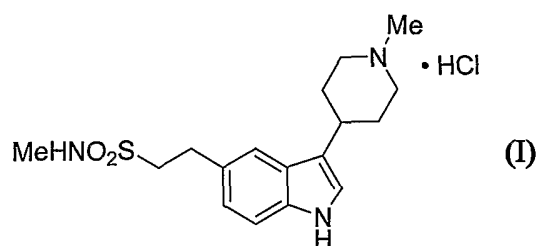


(vi) saponifying the compound having formula (VIII) with a base to produce a compound having formula (IX), where M is an alkali metal; and



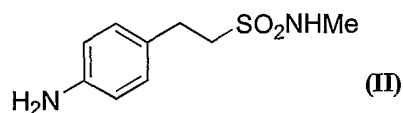
(vii) decarboxylating the compound having formula (IX) with an acid to produce the compound having formula (I).

An alternative process for preparing a compound having formula (I)

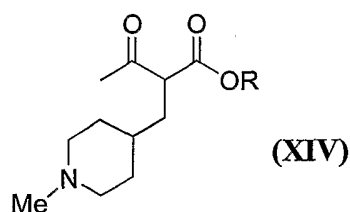


comprises:

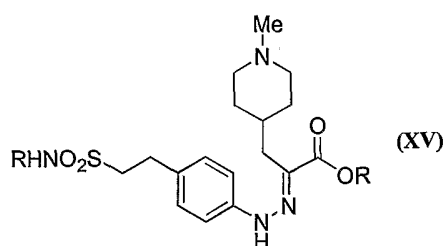
- (i) reacting a diazotized derivative of a compound having formula (II)



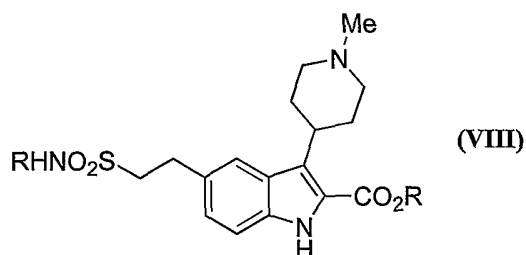
- 5 with a compound having formula (XIV), where R represents an alkyl group having 1 to 5 carbon atoms,



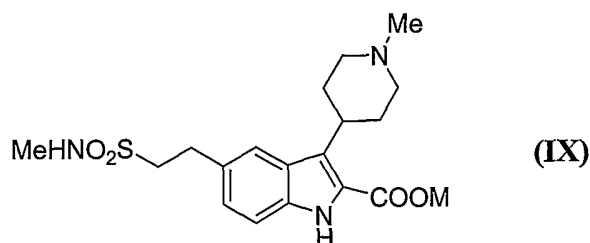
to produce a compound having formula (XV),



- 10 (ii) cyclizing the compound having formula (XV) to produce a compound having formula (VIII),



- (iii) saponifying the compound having formula (VIII) with a base to produce a compound having formula (IX), where M is an alkali metal; and

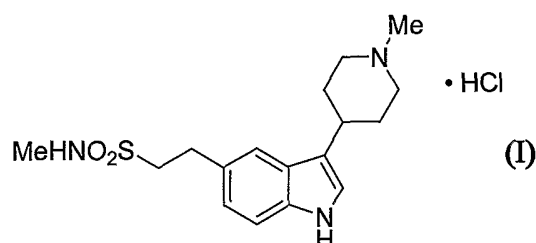


(iv) decarboxylating the compound having formula (IX) in an acidic medium to produce the compound having formula (I).

5

## DETAILED DESCRIPTION

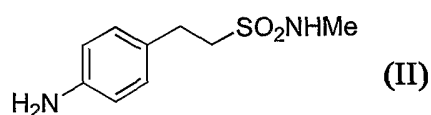
The present invention provides an improved process for the preparation of compound of formula (I)



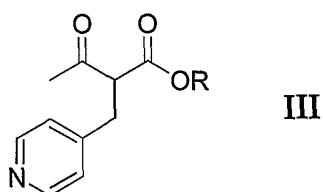
10

comprising:

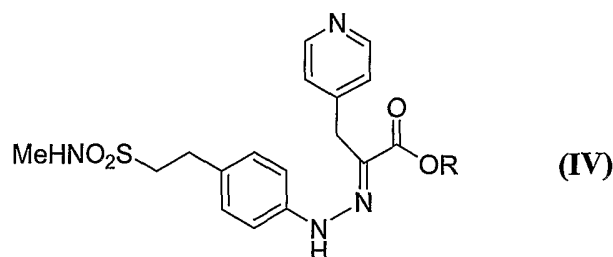
- (i) diazotizing the aniline derivative of formula (II),



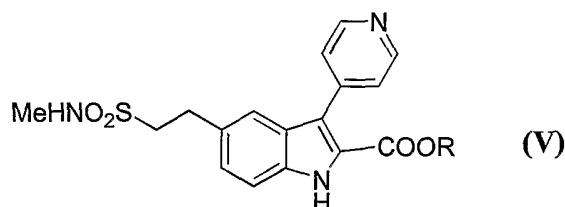
- 15 with the pyridine  $\beta$ -keto ester of formula (III), where R represents a straight or branched alkyl group having 1 to 5 carbon atoms,



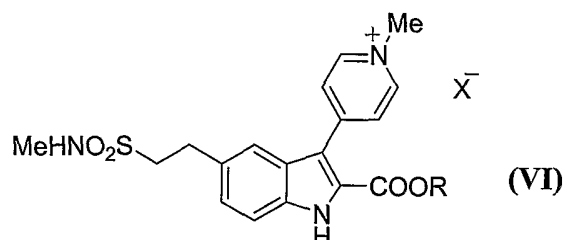
under Japp-Klingemann coupling conditions to afford the hydrozone of formula (IV)



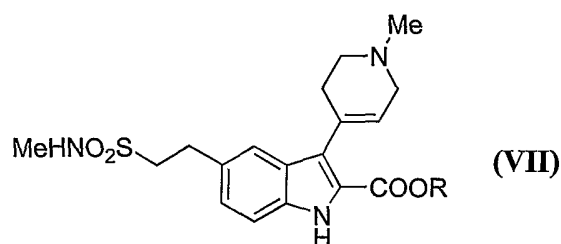
- (ii) cyclizing the hydrazone derivative of the formula (IV) in the presence of an acid in a solvent to give the indole derivative of formula (V). Examples of acids that can be used are hydrochloric acid, sulfuric acid, phosphoric acid, and organic acids like para-toluene sulfonic acid or Lewis acids like boron trifluoride in solvents like dichloromethane, chloroform, and alcohols such as methanol, ethanol, propanol, iso propanol and the like.



- (iii) quaternizing the compound of formula (V) with an alkyl halide such as methyl iodide or ethyl iodide in the presence of a solvent like dimethyl sulfoxide to give the compound of formula (VI), where X is a halogen,

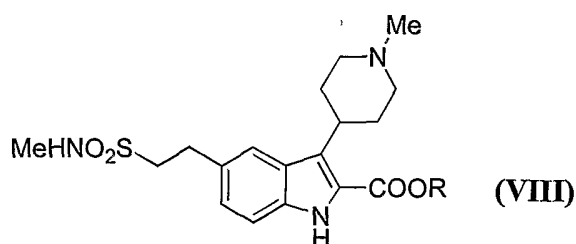


- (iv) reducing the compound (VI) with a reducing agent like sodium tetrahydridoborate in the presence of a solvent like alcohol such as methanol, ethanol and propanol and the like to give a compound of the formula (VII)

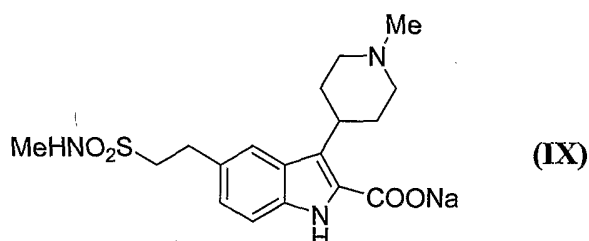


- (v) reducing the compound of formula (VII) to the N-methyl piperidinyll derivative of the formula (VIII) by catalytic hydrogenation using a noble metal

catalyst such as Raney nickel, palladium oxide/charcoal, palladium/charcoal, or rhodium/charcoal, in the presence of hydrogen gas and a solvent like ethanol, methanol, ethers like dioxane, esters such as ethyl acetate, or an amide

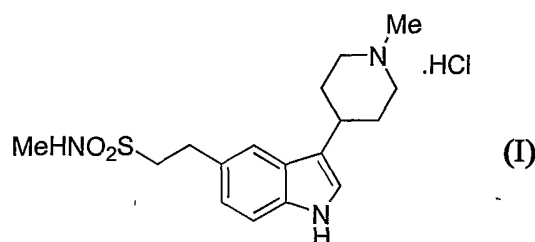


- 5 (vi) saponifying the ester group in formula (VIII) in presence of a base such as metal hydroxides like sodium hydroxide, potassium hydroxide, or metal carbonates like sodium or potassium carbonate, in the presence of a solvent like water to give the acid of formula (IX)



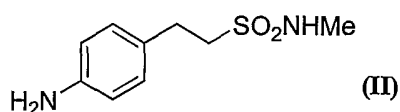
- 10 (vii) decarboxylating the compound of formula (IX) in an acidic medium such as in the presence of an acid like hydrochloric acid to give N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride of the formula (I).

- 15 According to another aspect the present invention provides a process for preparing the compound of the formula (I)

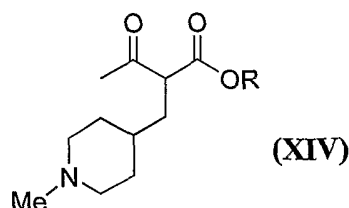


comprising:

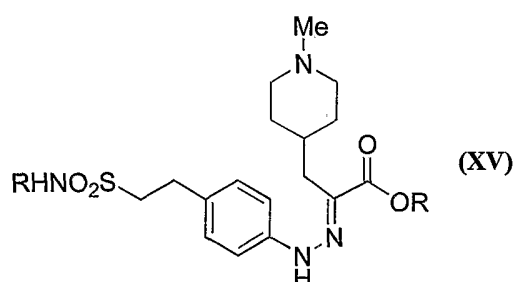
- (i) diazotization of the aniline derivative of the formula (II) to the corresponding diazonium salt



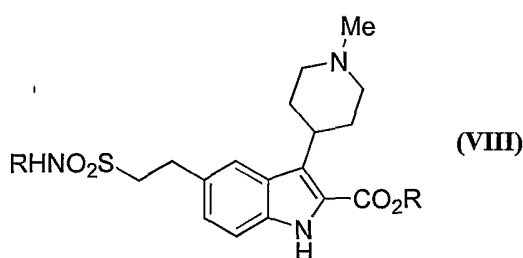
with pyridine  $\beta$ -keto ester of formula (XIV), wherein R represents an alkyl group having 1 to about 5 carbon atoms, which is straight chained or branched, such as methyl, ethyl, propyl, isopropyl and the like,



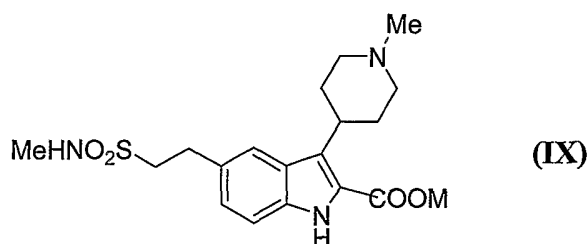
- 5 under the Japp-Klingemann reaction conditions to afford the hydrazone of the formula (XV),



- (ii) cyclization of the hydrazone of the formula (XV) in presence of acid and solvent to form the indole derivative of the formula (VIII), useful acids including, without limitation, inorganic acids like hydrochloric acid, sulfuric acid, phosphoric acid or organic acids like para-toluenesulphonic acid or Lewis acids like boron trifluoride and the like, in presence of solvents like alcohols such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol and the like or mixtures thereof,

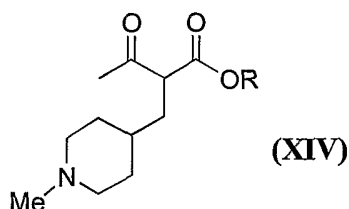


- 15 (iii) saponifying the ester group in formula (VIII) in the presence of a base such as metal hydroxides like sodium hydroxide or potassium hydroxide, or metal carbonates like sodium or potassium carbonate, in the presence of a solvent like water, to give the compound of formula (IX), where M is a metal,



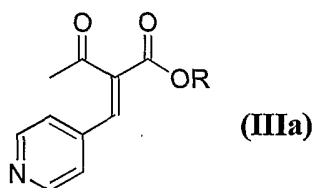
(iv) decarboxylating the compound of formula (IX) in an acidic medium such as an acid like hydrochloric acid to give N-methyl-3-(1-methyl-4-piperidyl)-1H-indole-5-ethanesulphonamide hydrochloride of the formula (I).

5 According to another aspect, the present invention provides a process for preparing the compound of formula (XIV)



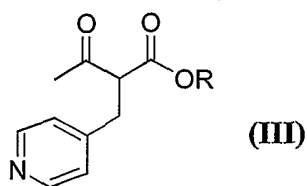
wherein R represents an alkyl group, which is straight chained or branched, such as methyl, ethyl, propyl, isopropyl and the like, the process comprising:

10 (i) dissolving a mixture of pyridine 4-carboxyldehyde and alkyl acetoacetate like methylacetoacetate, ethylacetoacetate, propylacetoacetate, isopropylacetoacetate and the like, in a solvent like n-hexane followed by addition of pyridinium para toluene sulfonate and refluxing the mixture to obtain the  
15 compound of formula (IIIa).

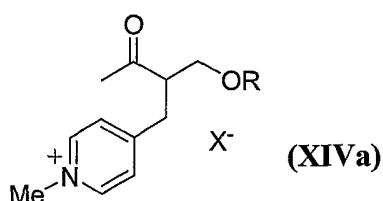


where R represents an alkyl group which is straight or branched chained, such as methyl, ethyl, propyl, isopropyl and the like.

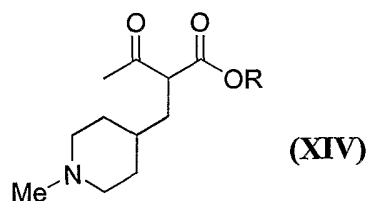
20 (ii) reducing the compound of formula (IIIa) to the compound of formula (III) by catalytic hydrogenation using a noble metal catalyst like Raney nickel, palladium oxide/charcoal, palladium /charcoal, or rhodium/charcoal, such as at a hydrogen pressure of about 0.7 to 2.5 Kg/cm<sup>2</sup>



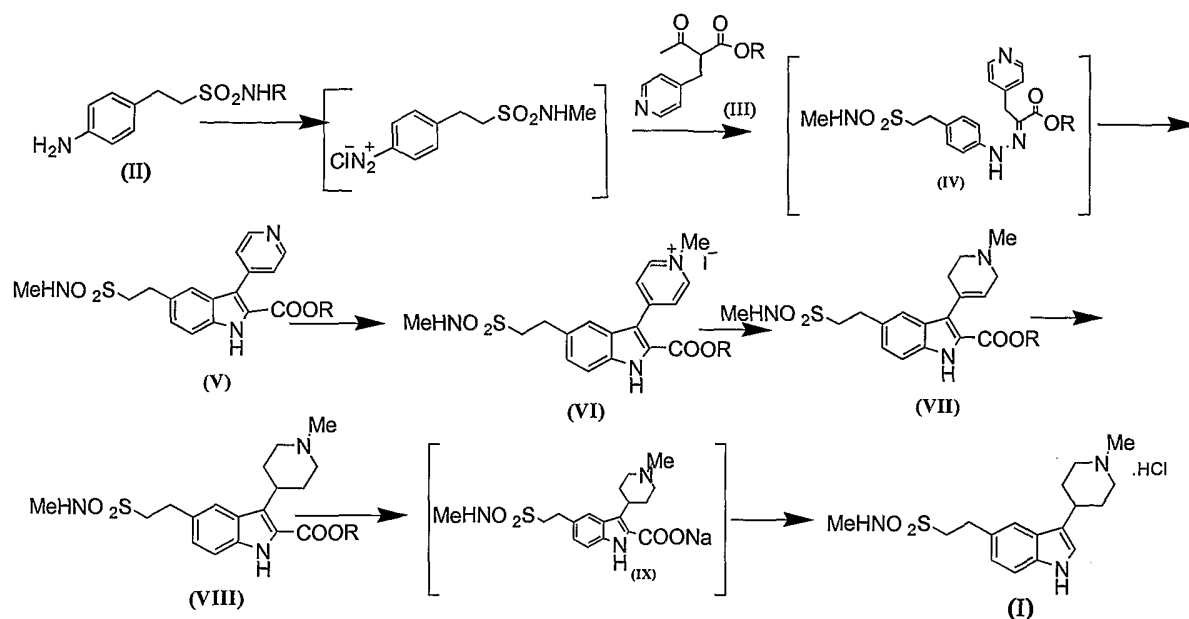
- (iii) quaternizing the compound of formula (III) with an alkyl halide like methyl iodide, ethyl iodide, propyl iodide and the like in the presence of a solvent like alcohols such as methanol, ethanol, propanol, butanol, or isobutanol to give the compound of formula (XIVa), where X is a halogen,



- (iv) reducing the compound of formula (XIVa) to give the compound of formula (XIV) by catalytic hydrogenation, using a noble metal catalyst like Raney nickel, palladium oxide/charcoal, palladium/charcoal, rhodium/charcoal and the like in the presence of a solvent like methanol, ethanol, propanol, butanol, isopropanol, isobutanol, an ether like dioxane, or an ester such as ethyl acetate, and the like.



Scheme 1 illustrates a process for preparing N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulphonamide hydrochloride of formula (I):



SCHEME 1

5 Diazotization of compound (II) can be conveniently carried out by conventional methods using reagents like sodium nitrite, amyl nitrite and the like. The reaction may be carried at a temperature of about -20 to 30°C, preferably about -15 to 25°C until the reaction is complete, such as for a period of about 15 to 45 minutes, or about 20 to 40 minutes.

10 The compound of formula (IV) can be prepared by reacting the diazonium salt obtained, with a compound of formula (III) in the presence of metal hydroxides like sodium hydroxide, potassium hydroxide, barium hydroxide and the like, in the presence of a solvent like alcohols such as methanol, ethanol, propanol, isopropanol and the like, or mixtures thereof. The temperature of the reaction is usually maintained at about 0 to 5°C, or 0°C, to reaction completion, such as for a period of about 1 to 4 hours, or about 2 to 4 hours.

15 Cyclization of the hydrozone compound of formula (IV) to form the indole derivative of formula (V) can be effected in the presence of an acid in a solvent. Useful acids include inorganic acids like hydrochloric acid, sulfuric acid, and phosphoric acid, or organic acids like para-toluenesulphonic acid, or Lewis acids like boron trifluoride, in the presence of a solvent like dichloromethane, chloroform, and alcohols such as methanol, ethanol, propanol, isopropanol and the like, or mixtures thereof.. Alternatively, the cyclization may also be achieved

by refluxing the compound of formula (IV) in a protic solvent like n-butanol and the like. The reaction temperature is typically about 45 to 70 °C, or about 55 to 65 °C. Completion of the reaction is typically achieved in about 8 to 15 hours, or about 12 to 14 hours.

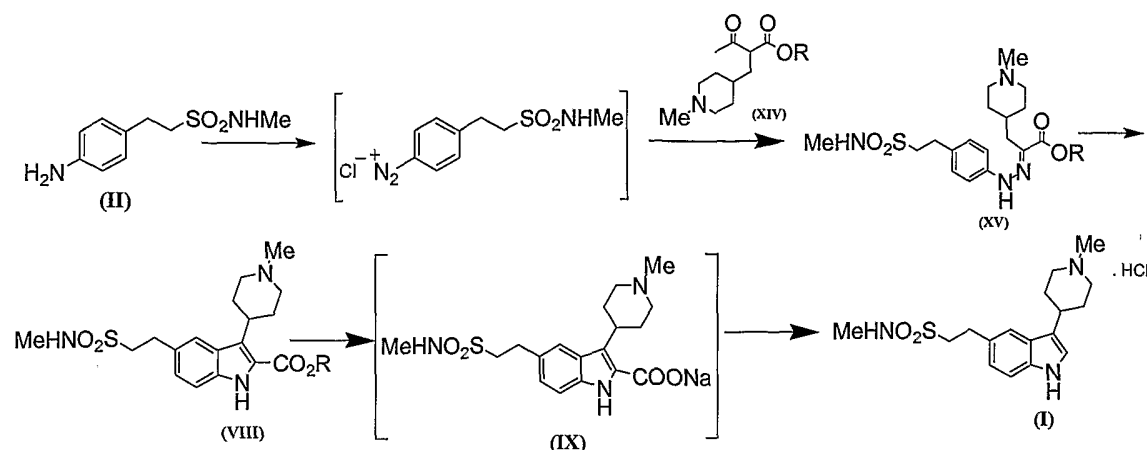
5           Quaternization of a compound of formula (V) can be carried out by reacting with an alkyl halide such as methyl iodide, ethyl iodide and the like, in the presence of a solvent like dimethyl sulfoxide, dimethylformamide and the like. The reaction can be carried out at a temperature of about 10 to 40°C, or about 20 to 35°C and is usually complete in a period of about 2 to 10 hours, or about 4 to 5  
10   hours.

          Reduction of compound of formula (VI) to a compound of formula (VII) is carried out in the presence of reducing agents like sodium tetrahydridoborate in the presence of a solvent such as alcohols such as methanol, ethanol, propanol, isopropanol and the like, or mixtures thereof. The temperature of the reaction can  
15   be in the range of about 20 to 40°C, or about 25 to 35°C. Completion of the reaction can require about 2 to 5 hours, or about 3 to 5 hours.

          Further reduction of the compound of formula (VII) to a compound of formula (VIII) can be carried out in the presence of a reducing agent such as hydrogen gas using a catalyst such as Raney nickel, palladium oxide/charcoal,  
20   palladium/charcoal, rhodium/charcoal, and the like. The reduction can be carried out in a solvent such as an alcohol such as methanol, ethanol, propanol, isopropanol, or their mixtures; ethers like dioxane; esters such as ethyl acetate; or an amide; at temperatures about 50 to 80°C, or about 60 to 75°C. Completion of the reaction can require about 5 to 12 hours, or about 8 to 12 hours.

25           Basic hydrolysis of compound (VIII) can be carried out in the presence of a base like metal hydroxides like sodium hydroxide and potassium hydroxide and the like, or metal carbonates like sodium carbonate, potassium carbonate and the like, in water at a temperature of about 10 to 120°C, typically requiring a period of about 5 to 8 hours, or about 7 to 8 hours, followed by decarboxylation in an acidic  
30   medium like hydrochloric acid at about 40 to 140°C to obtain a compound of formula (I), the reaction frequently requiring about 12 to 14 hours for completion.

          Scheme 2 illustrates an alternative process for preparing the compound of formula (I)



SCHEME 2

5 Diazotization of the compound of formula (II) can be conveniently carried out by conventional methods using reagents like sodium nitrite, amyl nitrite and the like. The reaction is usually carried at temperatures about -20 to 30°C, or about -15 to 25°C and frequently requires about 15 to 45 minutes, or about 20 to 40 minutes.

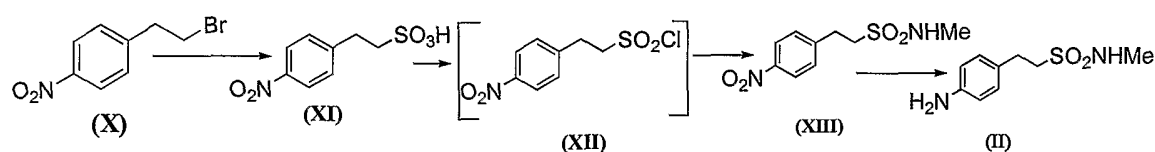
10 The compound of formula (XV) can be prepared by reacting the diazonium salt with a compound of formula (XIV) in the presence of a metal hydroxide like sodium hydroxide, potassium hydroxide, barium hydroxide and the like, in the presence of a solvent like alcohols such as methanol, ethanol, propanol, isopropanol and the like. The temperature of the reaction usually is maintained at  
15 about 0 to 5°C, or about 0°C and the reaction requires about 1 to 4 hours, or about 2 to 4 hours.

The hydrazone intermediate of formula (XV) may or may not be isolated. The intermediate of formula (XV) can be converted *in situ* to the indole derivative of formula (VIII), through an acid catalyzed 3,3-sigmatropic shift in a moisture  
20 controlled medium. This cyclization step can be carried out in the presence of an alcohol such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol and the like or mixtures thereof, which is straight or branched chained, having free hydrogen ion dissolved in it (for example, hydrochloric acid) and may be affected by the presence of excess moisture (such as >20%) and also by lower  
25 concentrations of dissolved hydrogen ion (such as <5%). The temperature of reaction is normally in the range of about 45 to 125°C, or about 55 to 100°C.

Completion of the reaction typically occurs within about 5 to 18 hours, or about 8 to 12 hours.

The final step can be a one-pot reaction wherein basic hydrolysis of compound (VIII) is carried out in the presence of a base like metal hydroxides like sodium hydroxide, potassium hydroxide and the like or metal carbonates like sodium or potassium carbonate and the like, in presence of solvent like water at a temperature of about 10 to 120°C, such as for period of about 5 to 8 hours, or about 7 to 8 hours, followed by decarboxylation in an acidic medium like hydrochloric acid at about 40 to 140°C to obtain a compound of formula (I); the decarboxylation can require about 8 to 20 hours, or about 12 to 14 hours. If the one-pot option is used, compound (IX) will not be isolated.

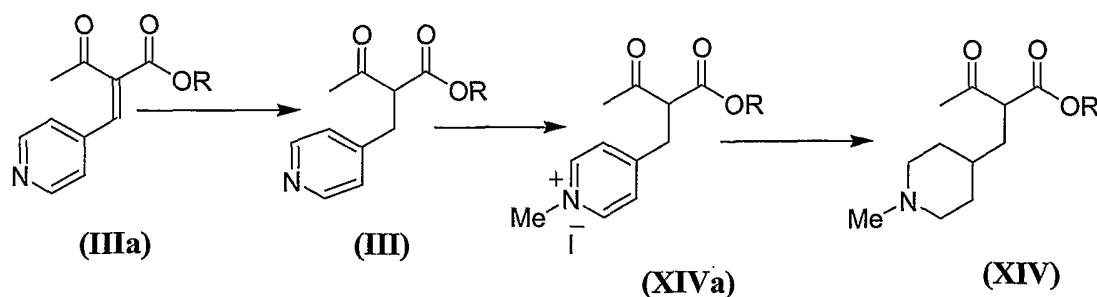
Scheme 3 is an illustration of a process for preparing the compound of formula (II)



SCHEME 3

An appropriate starting material for producing the compound having formula (I) in the present invention includes compounds of formula (II), which is disclosed in US Patent 4,994,483, incorporated by reference herein. Accordingly, a process for preparing the compound of formula II is described in Scheme 3.

Scheme 4 is an illustration of a representative process for preparing the intermediate compound of formula (XIV):



SCHEME 4

The compound of formula (IIa), where R represents an alkyl group, which is straight or branched chain, such as methyl, ethyl, propyl, isopropyl and the like, can be prepared by dissolving a mixture of pyridine-4-carboxyaldehyde and an alkylacetoacetate like methylacetoacetate, ethylacetoacetate, propylacetoacetate, isopropylacetoacetate and the like, in a solvent like n-hexane and the like, and adding pyridinium p-toluene sulfonate. The mixture is refluxed to reaction completion, such as for a period of about 2 to 6 hours, or about 3 to 5 hours. Solvent is then removed from the reaction mixture and a solvent like ethyl acetate or water is added and the mixture stirred, such as for a period of about 10 to 15 minutes.

Reducing a compound of formula (IIa) to a compound of formula (III) is accomplished by catalytic hydrogenation using a noble metal catalyst like Raney nickel, palladium oxide/charcoal, palladium /charcoal, rhodium/charcoal and the like, such as using a hydrogen pressure of about 0.5 to 2.5 Kg/cm<sup>2</sup>, typically over a period of about 1 to 3 hours, or about 1.5 to 2.5 hours.

Quaternizing the compound of formula (III), to obtain the compound of formula (XIVa) is accomplished by reacting with an alkyl halide such as methyl iodide, ethyl iodide and the like, in the presence of a solvent like an alcohol such as methanol, ethanol, propanol, butanol, isopropanol, isobutanol and the like, or mixtures thereof. The reaction can require about 8 to 14 hours, or about 8 to 12 hours.

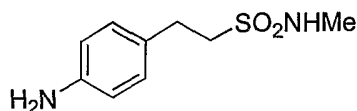
Reducing the compound of formula (XIVa) to the compound of formula (XIV) occurs using a reducing agent like hydrogen gas with a noble metal catalyst such as Raney nickel, palladium oxide/charcoal, palladium/charcoal, rhodium/charcoal and the like. The reduction can be carried out in the presence of a suitable solvent like an alcohol such as methanol, ethanol, propanol, butanol, isopropanol, isobutanol and the like, or mixtures thereof; ethers like dioxane; esters like ethyl acetate and the like. The duration of the reaction is frequently about 5 to 7 hours, or about 5 to 6 hours.

The manner in which the specific compounds can be prepared is illustrated in the following examples, which are illustrative only and should not be construed so as limiting the scope of the claimed invention in any manner. In these examples, the identities of final compounds and intermediates were confirmed by

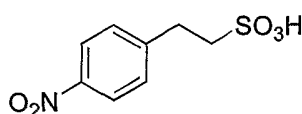
infrared (IR), nuclear magnetic resonance (NMR) spectral analysis, and/or mass spectral (MS) analysis as necessary.

Preparation of some starting materials is described below:

5      Preparation 1: N-Methyl-2-(4-amino phenyl) ethane sulfonamide



Step 1: Preparation of 2-(4-Nitro phenyl)-1-ethane sulfonic acid



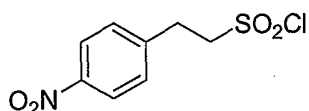
10      A mixture of 4-nitrophenyl ethyl bromide, sodium sulfite and tetrabutyl ammonium bromide (25 grams, 20.54 grams, 1.168 grams, respectively) was suspended in water and refluxed for 3 hours. The reaction was monitored by thin layer chromatography (20% methanol in ethyl acetate). The reaction mass was cooled to 30 to 40°C and washed with 50 ml of ethyl acetate. The aqueous layer

15      was acidified and concentrated as such to give a gummy residue. This residue was then stirred for 30 minutes with methanol (100 ml) and filtered. The residue was extracted with methanol (75 ml x 2). Combined filtrate was concentrated under reduced pressure to give the crude product, which was taken to the next step as such. Weight of crude compound: 37.0 grams, melting point: 250 °C.

20      <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz): δ 2.8 (m, 2H), 3.15 (m, 2H), 7.21 (d, 2H), 8.10 (d, 2H)

MS (m/z): 150 (M<sup>+</sup>+1)

Step 2: Preparation of 2-(4-Nitro phenyl)-ethane sulfonyl chloride (XII)

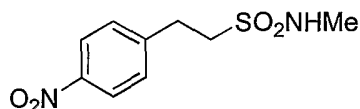


25

The compound obtained in step 1 above was taken in toluene and refluxed, then residual methanol and water was removed through a Dean-Stark apparatus. When clear toluene was coming from condenser, the suspension was cooled to 10°C and phosphorous pentachloride (83.08 grams, 0.4 moles) was added in

small portions. The mixture was slowly heated to reflux temperature with stirring and maintained for 30 minutes. The reaction mixture was then brought to 30 to 40°C, dichloromethane was added (80 ml) to the reaction mixture. The formed salt was separated by filtration and washed with dichloromethane, and the combined filtrate was used for the next step.

Step 3: Preparation of N-Methyl-2-(4-nitro phenyl) ethane sulphonamide



Methylamine gas was passed into chilled dichloromethane at 0°C over a period of 2 to 3 hours. After sufficiently saturating the dichloromethane with methylamine, the solution was cooled to 0 to -5°C. The dichloromethane/toluene solution of acid chloride obtained in step 2 above was added slowly to above methylamine solution, while maintaining a temperature below 0 °C. The mixture was stirred at the same temperature for 30 minutes and then at 30 to 40°C for 3 hours. Reaction progress was checked by thin layer chromatography (40% ethyl acetate in petroleum ether). The separated solid was filtered and washed with dichloromethane. The combined filtrate was concentrated under reduced pressure to give a gummy solid, which was stirred with cold water (100 to 150 ml) for 30 minutes, filtered, washed with water, and then washed with 20% ethyl acetate in petroleum ether to remove impurities. Weight of compound: 15.50 grams Yield: 58.00 %, melting range: 132-136°C

<sup>1</sup>H NMR: (CDCl<sub>3</sub>, 200 MHz): δ 2.82 (d, 3H) 3.21 (m, 4H), 4.10 (br, 1H, NH), 7.21 (d, 2H), 8.21 (d, 2H)

MS (m/z): 245 (M<sup>+</sup>+1)

Step 4: Preparation of N-Methyl-2-(4-amino phenyl)ethanesulfonamide

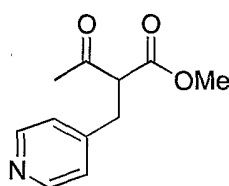
The compound (15.5 grams, 0.07 moles), obtained in step 3 above, was dissolved in methanol-ethyl acetate mixture (120:100 ml) and charged with 20% of Raney nickel catalyst into a hydrogenation flask. Hydrogen pressure was maintained at 4.7 to 5 Kg/cm<sup>2</sup> (temperature raised to 45 to 50°C) for 4 to 5 hours. Progress of the reaction was monitored by thin layer chromatography (50% ethyl

acetate in petroleum ether). Catalyst was removed by filtration through a celite bed and the bed was washed with methanol, then the combined filtrate was concentrated under vacuum to give a solid, which was triturated with 60% ethyl acetate in petroleum ether and filtered to recover the title compound. Weight of compound: 10.00 grams. Yield: 75.00%, melting range: 125 –128 °C.

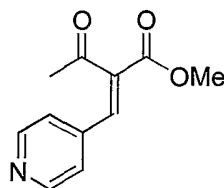
$^1\text{H}$  NMR (DMSO- $d_6$ , 200 MHz):  $\delta$  2.60 (d, 3H), 2.78 (m, 2H), 3.17 (m, 2H), 3.38 (s, 1H), 4.91 (br, 2H), 6.52 (d, 2H), 6.95 (d, 2H),

MS (m/z): 215 ( $M^+$ +1)

10 Preparation 2: Methyl-2-acetyl-3-pyridyl propanoate



Step 1: Preparation of (Cis-trans)-methyl-2-acetyl-3-pyridyl-2-propionoate



15 Pyridine 4-carboxyldehyde (200 grams, 1.87 moles) and methyl acetoacetate (217 grams, 1.87 moles) were taken in n-hexane (1000 ml), then 5 grams of pyridinium p-toluene sulfonate were added and the mixture was refluxed in a Dean-Stark apparatus for 3 to 4 hours. After reaction completion, n-hexane was removed from the reaction mixture under reduced pressure and ethyl acetate  
20 (1000 ml) and water (500 ml) were added, and stirred for 10 to 15 minutes, then the organic layer was separated, dried, and concentrated to get a crude mass of the title compound as a viscous liquid. Yield: 290 grams.

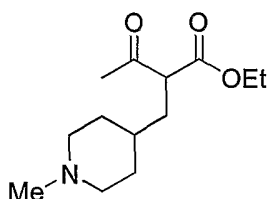
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz):  $\delta$  2.3 (2s, 3H), 2.4 (2s, 3H), 3.78 (2s, 3H), 3.82 (2s, 3H), 7.2 (t, 2H), 7.42 (2s, 1H), 7.56 (2s, 1H), 8.6 (t, 2H)

25 MS (m/z): 206( $M^+$ +1)

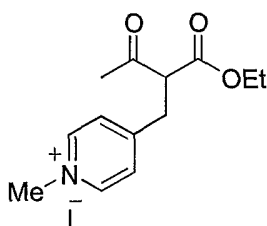
Step 2: Preparation of Methyl-2-acetyl-3-pyridylpropanoate

(Cis-trans)-methyl-2-acetyl-3-pyridyl-2-propanoate (100 grams, 0.49 mole) obtained in step 1 above was taken in ethyl acetate (500 ml) and was hydrogenated in the presence of a catalytic amount of 10% palladium/charcoal (5 grams) at 0.8 to 1.5 Kg/cm<sup>2</sup> of hydrogen pressure for 1.5 to 2.5 hours. After completion of the reaction, catalyst was removed by filtration through a celite bed and the filtrate was concentrated under reduced pressure to give a thick mass, which was then crystallized from a heptane/ethyl acetate mixture (200 ml, 3:1) to give a pure solid product. Yield: 65 grams (65 %), melting range: 58-62 °C  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  2.2 (s, 3H), 3.18 (dd, 2H) 3.7 (s, 3H), 3.8 (t, 1H), 7.15 (d, 2H), 8.46 (d, 2H),  
MS (m/z): 208 (M+1).

Preparation 3: Ethyl-2-acetyl-3(4-N-methylperidiny) propionate



Step 1: Preparation of 4-(2-acetyl-2-ethoxycarbonyl-ethyl)-1-methylpyridinium iodide



Ethyl-2-acetyl-3-pyridyl propionate (7.2 grams, 0.0324 moles), obtained according to preparation 2, except using ethylacetoacetate, was dissolved in 100 ml of tetrahydrofuran. To this, methyl iodide (11.45 grams, 0.0182 moles) was added and the mixture was stirred overnight. The reaction was monitored by thin layer chromatography (50% ethyl acetate: petroleum ether). Finally, ethanol was evaporated from the reaction mixture to get title product as a low melting point solid. Yield: 8 grams  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  1.24(t, 3H, J= 8.0 Hz), 2.36 (s, 3H), 3.41(m, 4H), 4.22 (m, 4H), 8.07(d, 2H, J= 6.0 Hz), 9.09 (d, 2H, J=6.0 Hz).

MS (m/z): 236 ( $M^+ + 1$ ).

5      Step 2: Preparation of Ethyl-2-acetyl-3(4-N-methylpiperidiny) propionate

4-(2-Acetyl-2-ethoxycarbonyl-ethyl)-1-methyl-pyridinium iodide (4.80 grams, 0.0203 moles) obtained in step 1 above, was dissolved in methanol, charged along with a platinum oxide catalyst (0.48 grams) into a hydrogenation flask and a 2.8 Kg/cm<sup>2</sup> hydrogen pressure was applied. Hydrogenation was continued for 6 hours. The mixture was filtered through a perlite bed, and the filtrate was concentrated to give a yellow colored liquid. Yield: 4.6 grams.

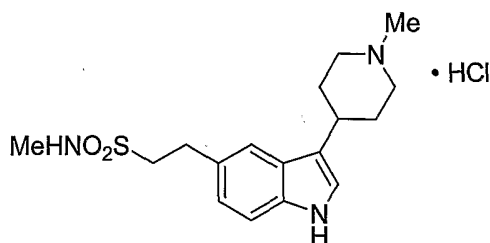
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz):  $\delta$  1.26 (t, 3H, J= 6.2 Hz), 16.4 (m, 2H), 2.23(s, 3H), 2.79 (s, 3H), 2.79(s, 3H), 2.95 (br, 2H), 3.44 (m, 4H), 4.20(q, 2H, J=6.0 Hz)

MS (m/z): 242 ( $M^+ + 1$ )

15

EXAMPLE 1

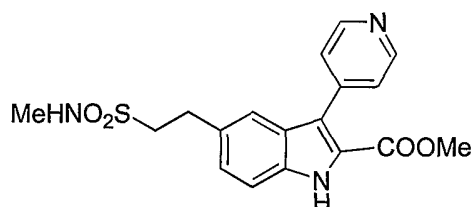
N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride of the following formula:



20

was prepared, as follows:

Step 1: Preparation of Methyl-5-methyl sulfamoyl ethyl-3-(4-pyridyl)-1H-2-indole carboxylate



25

N-Methyl-2-(4-amino phenyl)ethanesulfonamide (5.23 grams, 0.025 moles), obtained in preparation 1, was stirred in methanol (50 ml) and sodium acetate

(16.5 grams, 0.2 moles) at 30 to 40°C for 2 hours. In another flask, the compound obtained in preparation 2 (5.0 grams, 0.023 moles) in water (100 ml) was treated with hydrochloric acid (3.4 grams, 9.7 ml, 0.093 moles) at -5 to 0°C. To this was added sodium nitrite solution in water (4.7 grams, 0.23 moles, 10 ml) slowly at -5 to 0°C. After addition, the reaction mixture was stirred at the same temperature for another hour. This solution of diazonium salt was added to methyl-2-acetyl-3-pyridyl propanoate, obtained in preparation 2, and sodium sulfate in methanol at 0°C for 30 minutes. The reaction mixture was stirred at 30 to 40°C for 3 hours. The reaction was monitored by thin layer chromatography (50% ethyl acetate in petroleum ether). Dichloromethane was added to the reaction mixture and the layers were separated; the aqueous layer was extracted with dichloromethane (two times). The combined organic layer was dried (sodium sulfate) and concentrated under reduced pressure to give a thick liquid (10 grams, crude compound (IV), where R represents the methyl group). The resultant compound was taken in 50 ml of methanolic hydrochloric acid (17.0%) and refluxed for 12 to 14 hours. The reaction was monitored by thin layer chromatography (50% ethyl acetate in petroleum ether). The reaction mass was cooled to 30 to 40°C, and the formed solid was filtered and washed with methanol to give 5.0 grams of the hydrochloride salt of methyl-5-methylsulfamoylethyl-3-(4-pyridyl)-1H-2-indole carboxylate. The hydrochloride salt was taken into water and neutralized with sodium bicarbonate (pH 7-7.5); then the solid was filtered and dried under vacuum. Weight of the compound: 4.2 grams, yield: 48.2%, melting range: 222-225 °C

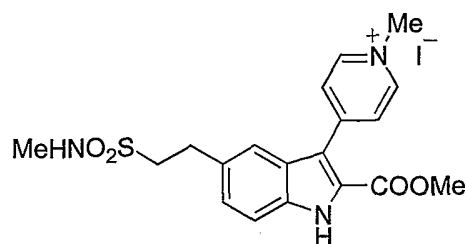
IR (KBr, cm<sup>-1</sup>): 3278, 2925, 2853, 1705, 1603, 1500, 1581, 1440, 1322, 1231, 1281, 1130, 779, 625

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 2.59 (d, 3H, J= 5.2 Hz), 3.01 (m, 2H), 3.28 (m, 2H), 3.80 (s, 3H), 6.90 (q, 1H J=5.2 Hz), 7.28 (dd, 1H J= 8.8, 1.6 Hz), 7.45 (s, 1H), 7.48 (d, 1H, J=8.4 Hz), 7.54 (d, 2H, J=5.6 Hz), 8.64 (d, 2H, J=6.4 Hz), 12.20 (bs).

MS (m/z): 374(M<sup>+</sup>+1)

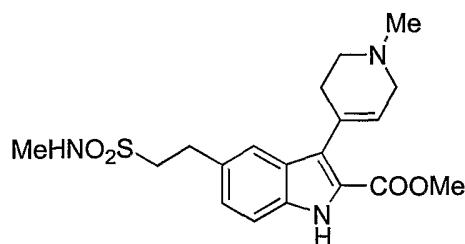
30

Step 2: Preparation of 1-Methyl-4-(2-methoxy carbonyl-5-methylsulphamoylethyl-1H-3-indolyl) pyridinium iodide



Methyl-5-methyl sulfamoyl-3-(4-pyridyl)-1H-2-indole carboxylate, obtained in step 1 above, was dissolved in dimethylsulfoxide (200 ml). To the resultant mixture methyl iodide (38 grams, 0.26 moles) was added at one time at 30 to 40°C and the mixture was stirred for 12 hours. 800 ml of ethyl acetate was added to the reaction mass and the solid was recovered by filtration and dried. Weight of the compound: 29.0 grams, yield: 85 %, melting range: 239-249 °C IR (KBr, cm<sup>-1</sup>): 3349, 3171, 2946, 1698, 1638, 1549, 1511, 1382, 1490, 1311, 1342, 1283, 1248, 1149, <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 2.60 (d, 3H, J= 4.8 Hz), 3.05 (m, 2H), 3.30 (m, 2H), 3.85 (s, 3H), 4.37 (s, 3H), 6.95 (q, 1H J=4.8 Hz), 7.36 (dd, 1H J= 8.8, 1.6 Hz), 7.55 (d, 1H, J=8.8), 7.59 (br), 8.32 (d, 2H, J=6.8 Hz), 8.95 (d, 2H, J=6.4 Hz) 12.70 (bs). MS (m/z):388(M<sup>+</sup>+1)

Step 3: Preparation of Methyl-5-methylsulfamoyl-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-2-indole carboxylate



1-Methyl-4-(2-methoxycarbonyl-5-methylsulfamoyl-1H-3-indolyl)pyridinium iodide, (10.0 grams, 0.019 moles), obtained in step 2 above, was taken in methanol (300 ml) then sodium borohydride (2.95 grams, 0.077 moles) was added in small portions. After the addition, the mixture was stirred at 30 to 40°C for 1 hour. The reaction was monitored by thin layer chromatography (ethyl acetate). Water (100 mL) was added to the reaction mass and the methanol was evaporated under reduced pressure. The compound was precipitated from water,

then filtered and dried. Weight of the compound: 5.4 grams, yield: 71.0 %, melting range: 190-195 °C

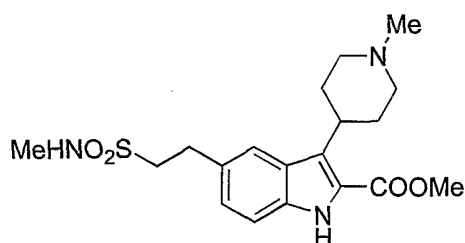
IR (KBr,  $\text{cm}^{-1}$ ): 3340, 2947, 2796, 1710, 1540, 1462, 1332, 1305, 1242, 1145, 1112, 808, 752, 647

5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  2.32 (s, 3H), 2.44 (br, 2H), 2.60 (d, 3H,  $J = 4.8$  Hz), 2.60 (t, 2H,  $J = 4.8$  Hz), 3.01 (m, 2H), 3.07 (d, 2H,  $J = 2.8$  Hz), 3.28 (m, 2H), 3.84 (s, 3H), 5.67 (bs, 1H), 6.92 (q, 1H,  $J = 4.8$  Hz), 7.19 (dd, 1H  $J = 8.8, 1.6$  Hz), 7.36 (d, 1H,  $J = 8.4$ ), 7.42 (s, 1H), 11.65 (bs, 1H).

MS ( $m/z$ ): 391 ( $M^+ + 1$ )

10

Step 4: Preparation of Methyl-3-(1-methyl-4-piperidyl)-5-methyl sulfamoyl ethyl-1H-2-indole carboxylate



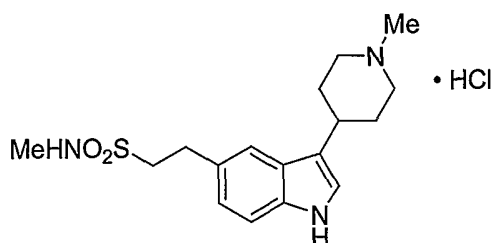
Methyl-3-(1-methyl-4-piperidyl)-5-methyl sulfamoyl ethyl-1H-2-indole  
15 carboxylate (18.0 grams, 0.046 moles), obtained in step 3 above, was taken in methanol (1000 ml). Raney nickel catalyst was added and the compound was hydrogenated in an autoclave under 10.7  $\text{Kg}/\text{cm}^2$  hydrogen pressure at 50°C for 12 hours. Reaction was monitored by mass spectrum and high performance liquid chromatography (HPLC) methods. Catalyst was removed by filtration  
20 through a celite bed, then the bed was washed with methanol and combined filtrate was concentrated under reduced pressure to give the solid title compound. Weight of the compound: 13.0 grams, yield: 72.0 %, melting range: 175-180 °C  
IR (KBr,  $\text{cm}^{-1}$ ): 3324, 2947, 1710, 1537, 1462, 1449, 1305, 1242, 1190, 1138, 782  
 $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz):  $\delta$  1.65 (bd, 2H), 2.05 (m, br, 4H), 2.10 (s, 3H),  
25 2.60 (d, 3H,  $J = 4.8$  Hz), 2.80- 3.05 (m, 4H), 3.30 (m, 2H), 3.60 (m, 1H) 3.85 (s, 3H), 6.95 (br, 1H), 7.18 (d, 1H,  $J = 8.8$  Hz), 7.29 (d, 1H,  $J = 8.8$  Hz), 7.65 (s, 1H), 8.32 (s, 1H), 11.50 (s, 1H)  
MS ( $m/z$ ): 394 ( $M^+ + 1$ )

Step 5: Preparation of N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride

Methyl-3-(1-methyl-4-piperidyl)-5-methylsulfamoyl-1H-2-indole  
carboxylate (22.0 grams, 0.055 moles), obtained in step 4 above, was added to a  
5 stirred solution of sodium carbonate (29.6 grams, 0.27 moles) in water (300 ml)  
and was refluxed for 7 hours (clear solution observed; thin layer chromatography  
was used to check for an absence of starting material, with a methanol mobile  
phase). The reaction mass was cooled to 30 to 40°C, and concentrated  
hydrochloric acid was added slowly to obtain a pH about 2. After acidifying, the  
10 reaction mixture was refluxed for 12 hours. Formation of the compound of formula  
(IX) was checked by TLC using a 10% ammonia solution in methanol as the  
mobile phase. The reaction mass was cooled to 10 to 15°C and stirred for 30 to  
40 minutes. The formed solid was separated by filtration, washed with methanol  
(2×25 ml), and dried under vacuum to get the title compound. Weight of the  
15 compound: 15.5 grams, yield: 75 %, melting range: 247-249 °C.  
IR (KBr,  $\text{cm}^{-1}$ ): 3328, 2965, 2993, 1474, 1315, 1153, 885, 779, 639  
 $^1\text{H}$  NMR: ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  2.10 (m, br, 4H), 2.62 (d, 3H,  $J = 4.4$ ), 2.78 (d,  
3H,  $J = 5.2$  Hz), 3.02 (m, 1H), 3.02 (m, br, 2H), 3.10 (m, br, 2H), 3.30 (m, br, 2H),  
3.48 (m, bs, 2H), 6.95 (m, 1H, NH), 6.98 (d, 1H,  $J = 8.4$  Hz), 7.10 (d, 1H  $J = 2.4$   
20 Hz), 7.28 (d, 1H,  $J = 8.4$ ), 7.58 (brs, 1H), 10.50 (br, NH), 10.80 (s, 1H).  
MS ( $m/z$ ): 336 ( $M^+ + 1$ )

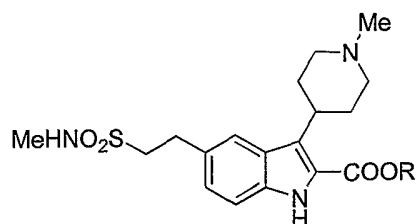
EXAMPLE 2

25 N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride



was prepared by the following procedure:

Step 1: Preparation of Ethyl/methyl 3-(1-methyl-4-piperidyl)-5-(2-  
30 methylsulfamoyl-ethyl)-1H-2-indolecarboxylate



Where R = Ethyl/Methyl

N-methyl-2-(4-aminophenyl)-1-ethanesulfonamide (3.5 grams, 0.016 moles), obtained in preparation 1, was dissolved in methanol (35 ml) and cooled to 5 to 10°C, then concentrated hydrochloric acid (6.8 ml, 0.065 moles) was added dropwise to avoid heat generation and the mixture was stirred for 10 minutes. To this mixture a sodium nitrite (1.35 grams, 0.019 moles) solution in water (5ml) was added slowly at -5 to 0°C. After addition, the solution was maintained under stirring at the same temperature for 30 minutes. This solution is called "Part A" below.

Meanwhile, in a separate vessel, methyl-2-(1-methyl-4-piperidinylmethyl)-3-oxobutanoate (4.0 grams, 0.017 moles), obtained in preparation 3, was taken in methanol (20ml), sodium acetate (10.7 grams, 0.13 moles) was added, and the mixture was stirred at 30 to 40°C for 1 hour. The mixture was cooled to 0 to -5°C and Part A was added slowly. After addition, the mixture was stirred for 2 to 3 hours at 30 to 40°C. After reaction completion, the reaction mass was extracted with dichloromethane several times. The combined dichloromethane layer was washed with water twice, dried over anhydrous sodium sulfate and concentrated. The crude residue (containing 2-(4-nitro phenyl)-1-ethane sulfonic acid, characterized by spectral evidence) can be used directly for cyclization to form the indole moiety. To this crude residue (5.1 grams), 100ml of methanolic hydrochloric acid (about 15%) was added and the material was heated to reflux for 12 hours. The reaction mass was then cooled to 30 to 40°C and concentrated to give the title compound. Melting Range: 175-180°C

IR (KBr,  $\text{cm}^{-1}$ ): 3324, 2947, 1710, 1537, 1462, 1449, 1305, 1242, 1190, 1138, 782  
 $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 200 MHz):  $\delta$  1.65 (bd, 2H), 2.05 (m, br, 4H), 2.10 (s, 3H), 2.60 (d, 3H,  $J = 4.8$  Hz), 2.80- 3.05 (m, 4H), 3.30 (m, 2H), 3.60 (m, 1H) 3.85 (s, 3H), 6.95 (br, 1H), 7.18 (d, 1H,  $J = 8.8$  Hz), 7.29 (d, 1H,  $J = 8.8$  Hz), 7.65 (s, 1H), 8.32 (s, 1H), 11.50 (s, 1H)

MS (m/z): 394 ( $M^+ + 1$ )

Step 2: Preparation of N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride of formula (I)

5 Ethyl/methyl-3-(1-methyl-4-piperidyl)-5-methyl sulfamoyl ethyl-1H-2-indole carboxylate (22.0 grams, 0.055 moles), obtained in step 1 above, was added to a stirred solution of sodium carbonate (29.6 grams, 0.27 moles) in water (300 ml) and was refluxed for 7 hours (clear solution observed, thin layer chromatography was used to check for an absence of starting material, using a methanol mobile  
10 phase). The reaction mass was cooled to 30 to 40°C, and concentrated hydrochloric acid was added slowly to obtain a pH about 2. After acidifying, the reaction mixture was refluxed for 12 hours. Formation of compound of formula (IX) was checked by TLC using a 10% ammonia solution in methanol mobile phase. The reaction mass was cooled to 10 to 15°C and to stirred for 30 to 40  
15 minutes. The produced solid was filtered, washed with methanol (2×25 ml), and dried under vacuum to give the title compound. Weight of the compound: 15.5 grams, yield: 75 %, melting range: 247-249 °C.

IR (KBr,  $\text{cm}^{-1}$ ): 3328, 2965, 2993, 1474, 1315, 1153, 885, 779, 639

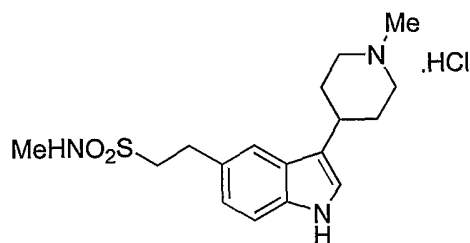
$^1\text{H}$  NMR: ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  2.10 (m, br, 4H), 2.62 (d, 3H,  $J = 4.4$ ), 2.78 (d, 3H,  $J = 5.2$  Hz), 3.02 (m, 1H), 3.02 (m, br, 2H), 3.10 (m, br, 2H), 3.30 (m, br, 2H),  
20 3.48 (m, bs, 2H), 6.95 (m, 1H, NH), 6.98 (d, 1H,  $J = 8.4$  Hz), 7.10 (d, 1H  $J = 2.4$  Hz), 7.28 (d, 1H,  $J = 8.4$ ), 7.58 (brs, 1H), 10.50 (br, NH), 10.80 (s, 1H).

MS (m/z): 336 ( $M^+ + 1$ )

25

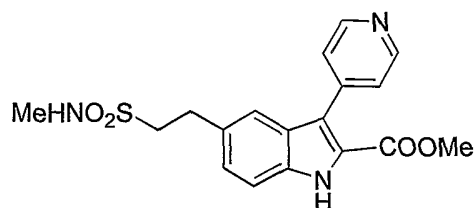
EXAMPLE 3

N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride



30 was prepared using the following procedure:

Step 1: Preparation of Methyl-5-methylsulfamoyl-ethyl-3-(4-pyridyl)-1H-2-indole carboxylate



5 N-Methyl-2-(4-aminophenyl) ethane sulfonamide (17 Kg), obtained in preparation 1, was stirred in water (255 liters). Hydrochloric acid (20 liters) was added slowly and the mixture was maintained at a temperature at -5 to 8 °C. To this, sodium nitrite solution in water (11 Kg in 35 liters) was added slowly at -5 to 0°C. After this addition, methylene chloride (80 liters) was added slowly at -5 to 10 0°C to give a diazonium salt solution.

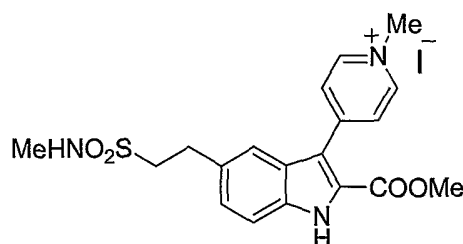
In another reactor Methyl-2-acetyl-3-pyridyl propanoate obtained in preparation 2 (16.5 Kg) was dissolved in methanol (35 liters). To this, caustic potash solution in water (11 Kg in 35 liters) was added slowly at -5 to 0°C. The diazonium salt solution from above was added to the methyl-2-acetyl-3- 15 pyridyl propanoate and caustic potash solution in methanol at -5 to 0°C. The reaction mass was stirred at -5 to 0°C for 30 to 50 minutes and then at 25 to 30°C for 1 hour. The reaction progress was monitored by thin layer chromatography. Dichloromethane (40 liters) was added to the reaction mixture and the layers were separated; the aqueous layer was extracted with dichloromethane (2 x 40 liters).

20 The combined organic layer was dried using sodium sulfate and concentrated under reduced pressure to give a thick liquid. This liquid was taken into 170 liters of methanolic hydrochloric acid (13-18%), maintained at 15 to 20°C for 30 minutes, and heated to 61 to 62°C to distill off solvents. The reaction mass was maintained for 3 hours at 15 to 20°C. The formed solid was filtered and 25 washed with ethyl acetate to give a wet cake of the hydrochloride salt of methyl-5-methylsulfamoyl-ethyl-3-(4-pyridyl)-1H-2-indole carboxylate. This hydrochloride salt was taken into water and neutralized with sodium bicarbonate (pH 7.5-8.5); filtered, and dried under vacuum. Weight of the compound: 12 Kg, yield: 40%, melting range: 222-225 °C

IR (KBr,  $\text{cm}^{-1}$ ): 3278, 2925, 2853, 1705, 1603, 1500, 1581, 1440, 1322, 1231, 1281, 1130, 779, 625

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  2.59 (d, 3H,  $J=5.2$  Hz), 3.01 (m, 2H), 3.28 (m, 2H), 3.80 (s, 3H), 6.90 (q, 1H  $J=5.2$  Hz), 7.28 (dd, 1H  $J=8.8, 1.6$  Hz), 7.45 (s, 1H), 7.48 (d, 1H,  $J=8.4$  Hz), 7.54 (d, 2H,  $J=5.6$  Hz), 8.64 (d, 2H,  $J=6.4$  Hz), 12.20 (bs).  
MS ( $m/z$ ): 374( $\text{M}^++1$ )

Step 2: Preparation of 1-Methyl-4-(2-methoxy carbonyl-5-methyl sulfamoyl-ethyl-1H-3-indolyl) pyridinium iodide



10

Methyl-5-methyl sulfamoyl-ethyl-3-(4-pyridyl)-1H-2-indole carboxylate (8 Kg), obtained in step 1 above, was dissolved in dimethyl sulfoxide (40 liters). To the resultant solution methyl iodide (12.2 Kg) was added slowly at 25 to 30°C and the mixture was stirred for 4 to 5 hours. The mixture was added to a vessel containing ethyl acetate (240 liters) and the resulting solid was filtered and dried. Weight of the compound: 8.0 to 11.0 Kg, Yield: 85 to 100 %, Melting Range: 239-249 °C

15

IR (KBr,  $\text{cm}^{-1}$ ): 3349, 3171, 2946, 1698, 1638, 1549, 1511, 1382, 1490, 1311, 1342, 1283, 1248, 1149

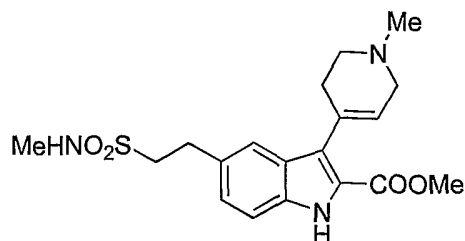
$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  2.60 (d, 3H,  $J=4.8$  Hz), 3.05 (m, 2H), 3.30 (m, 2H), 3.85 (s, 3H), 4.37 (s, 3H), 6.95 (q, 1H  $J=4.8$  Hz), 7.36 (dd, 1H  $J=8.8, 1.6$  Hz), 7.55 (d, 1H,  $J=8.8$ ), 7.59 (br), 8.32 (d, 2H,  $J=6.8$  Hz), 8.95 (d, 2H,  $J=6.4$  Hz) 12.70 (bs).

20

MS ( $m/z$ ): 388( $\text{M}^++1$ )

25

Step 3: Preparation of Methyl-5-methylsulfamoyl-ethyl-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-2-indole carboxylate



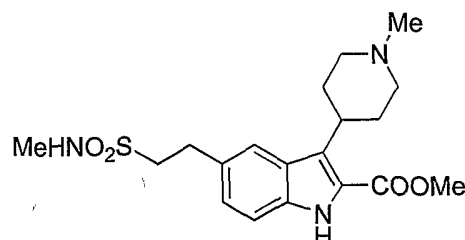
1-Methyl-4-(2-methoxycarbonyl-5-methylsulfamoyl ethyl-1H-3-indolyl) pyridinium iodide, (11 Kg), obtained in step 2 above, was taken in methanol (330 liters). Sodium borohydride (5.7 Kg) was added slowly to the reaction mass at 30 to 40°C. The mixture was stirred at 25 to 35°C for 4 to 6 hours. The reaction was monitored for completion by thin layer chromatography. A portion of the methanol (80 liters) was evaporated under reduced pressure at 35°C and water (110 liters) was added to the reaction mass. A solid precipitated and was filtered and dried. Weight of the compound: 5.7 to 8.3 Kg, Yield: 68 to 99 %, melting range: 190-195°C.

IR (KBr,  $\text{cm}^{-1}$ ): 3340, 2947, 2796, 1710, 1540, 1462, 1332, 1305, 1242, 1145, 1112, 808, 752, 647

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  2.32 (s, 3H), 2.44 (br, 2H), 2.60 (d, 3H,  $J = 4.8$  Hz), 2.60 (t, 2H,  $J = 4.8$  Hz), 3.01 (m, 2H), 3.07 (d, 2H,  $J = 2.8$  Hz), 3.28 (m, 2H), 3.84 (s, 3H), 5.67 (bs, 1H), 6.92 (q, 1H,  $J = 4.8$  Hz), 7.19 (dd, 1H  $J = 8.8, 1.6$  Hz), 7.36 (d, 1H,  $J = 8.4$ ), 7.42 (s, 1H), 11.65 (bs, 1H).

MS ( $m/z$ ): 391 ( $M^+ + 1$ )

Step 4: Preparation of Methyl-3-(1-methyl-4-piperidyl)-5-methyl sulfamoyl ethyl-1H-2-indole carboxylate



Methyl-3-(1-methyl-4-piperidyl)-5-methyl sulfamoyl ethyl-1H-2-indole carboxylate (6.5 Kg), obtained in step 3 above, was taken in methanol (65 Kg). Raney nickel (6.5 Kg) in methanol (65 Kg) was added to the above reaction mixture and hydrogenation was conducted in an autoclave under 11 to 14  $\text{Kg/cm}^2$  pressure at 70 to 80°C for 1 to 3 hours. The reaction progress was monitored by

high performance liquid chromatography. Catalyst was removed by filtration through a celite bed, and the bed was washed with methanol or toluene and the combined filtrate was concentrated under reduced pressure to give the solid title compound. Weight of the compound: 3.9 to 6.5 Kg, Yield: 60 to 100.0 %, melting range: 175-180 °C.

IR (KBr,  $\text{cm}^{-1}$ ): 3324, 2947, 1710, 1537, 1462, 1449, 1305, 1242, 1190, 1138, 782

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 200 MHz):  $\delta$  1.65 (bd, 2H), 2.05 (m, br, 4H), 2.10 (s, 3H), 2.60 (d, 3H,  $J = 4.8$  Hz), 2.80- 3.05 (m, 4H), 3.30 (m, 2H), 3.60 (m, 1H) 3.85 (s, 3H), 6.95 (br, 1H), 7.18 (d, 1H,  $J = 8.8$  Hz), 7.29 (d, 1H,  $J = 8.8$  Hz), 7.65 (s, 1H),

8.32 (s, 1H), 11.50 (s, 1H)

MS ( $m/z$ ): 394 ( $M^+ + 1$ )

Step 5: Preparation of N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride

Methyl-3-(1-methyl-4-piperidyl)-5-methylsulfanylethyl-1H-2-indole carboxylate (6.0 Kg), obtained in step 4 above, was added to a stirred solution of sodium carbonate (8.0 Kg) in water (12 liters) and was refluxed for 7 to 8 hours. The reaction mass was cooled to 50 to 55°C, and hydrochloric acid (17.5 liters) was added slowly. After acidifying, the reaction mixture was refluxed for 12 to 14

hour. The reaction mass was cooled to 10 to 15°C and stirred for 90 to 140 minutes. The produced solid was filtered, washed with methanol (2×12 liters) and dried under vacuum to give the title compound. Weight of the compound: 2 to 4 Kg, Yield: 40-75 %. The compound was further dissolved in methanol, the solution was treated with activated carbon, and the compound crystallized.

Melting range: 247-249 °C.

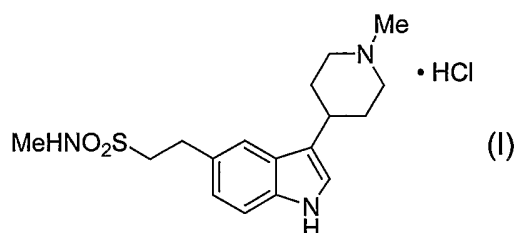
IR (KBr,  $\text{cm}^{-1}$ ): 3328, 2965, 2993, 1474, 1315, 1153, 885, 779, 639

$^1\text{H}$  NMR: ( $\text{DMSO-d}_6$ , 400 MHz):  $\delta$  2.10 (m, br, 4H), 2.62 (d, 3H,  $J = 4.4$ ), 2.78 (d, 3H,  $J = 5.2$  Hz), 3.02 (m, 1H), 3.02 (m, br, 2H), 3.10 (m, br, 2H), 3.30 (m, br, 2H), 3.48 (m, bs, 2H), 6.95 (m, 1H, NH), 6.98 (d, 1H,  $J = 8.4$  Hz), 7.10 (d, 1H  $J = 2.4$  Hz), 7.28 (d, 1H,  $J = 8.4$ ), 7.58 (brs, 1H), 10.50 (br, NH), 10.80 (s, 1H).

MS ( $m/z$ ): 336 ( $M^+ + 1$ )

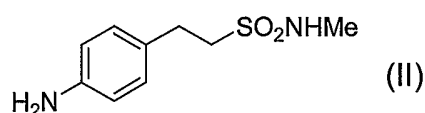
## CLAIMS:

1. A process for preparing a compound having formula (I)

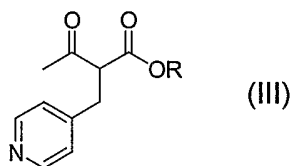


comprising:

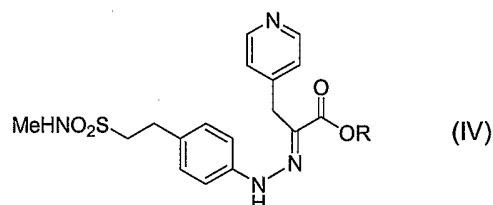
- (i) reacting a diazotized derivative of a compound having formula (II),



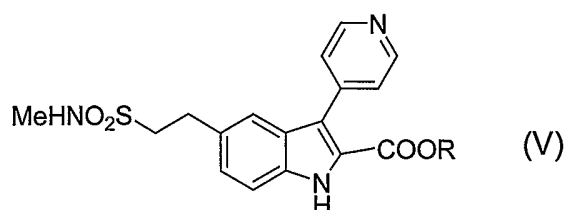
with a compound having formula (III), where R represents an alkyl group having 1 to 5 carbon atoms;



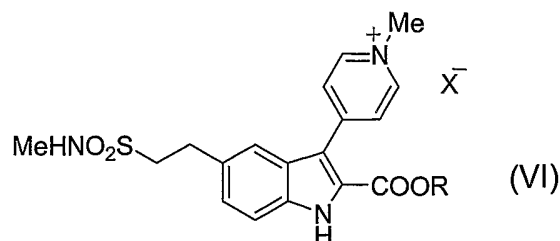
to produce a compound having formula (IV);



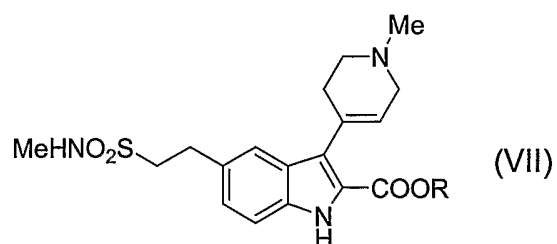
- (ii) cyclizing the compound having formula (IV) in the presence of an acid to produce a compound having formula (V);



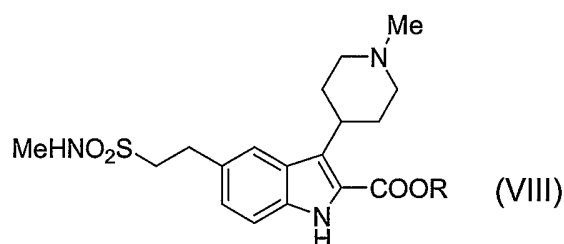
- (iii) quaternizing the compound having formula (V) with an alkyl halide to produce a compound having formula (VI), where X is a halogen;



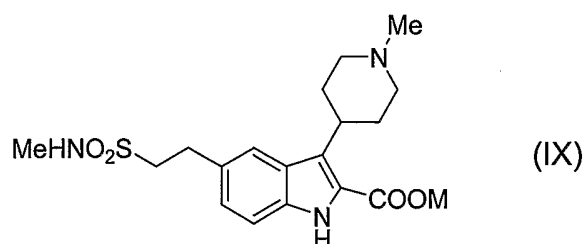
(iv) reacting the compound having formula (VI) with a reducing agent to produce a compound having formula (VII);



(v) hydrogenating the compound having formula (VII) to produce a compound having formula (VIII);



(vi) saponifying the compound having formula (VIII) with a base to produce a compound having formula (IX), where M is an alkali metal; and

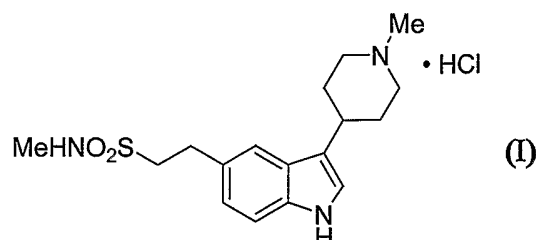


(vii) decarboxylating the compound having formula (IX) with an acid to produce the compound having formula (I).

2. The process according to claim 1, wherein the compound having formula (VI) is not isolated prior to step (iv).

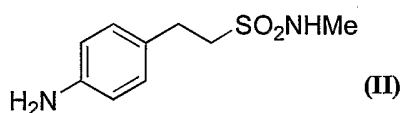
3. The process according to claim 1, wherein steps (vi) and (vii) are conducted sequentially in a vessel, without isolating the compound having formula (IX).

4. A process for preparing a compound having formula (I)

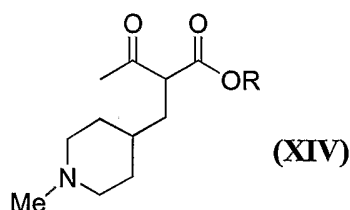


comprising:

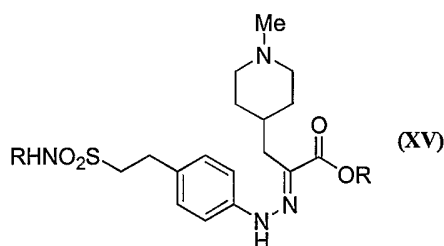
(i) reacting a diazotized derivative of a compound having formula (II)



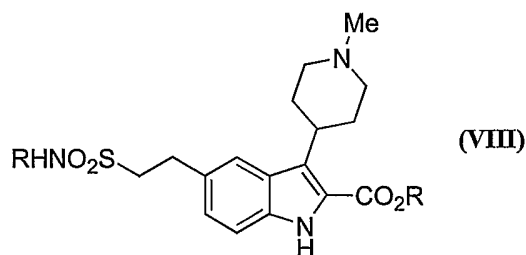
with a compound having formula (XIV), where R represents an alkyl group having 1 to 5 carbon atoms,



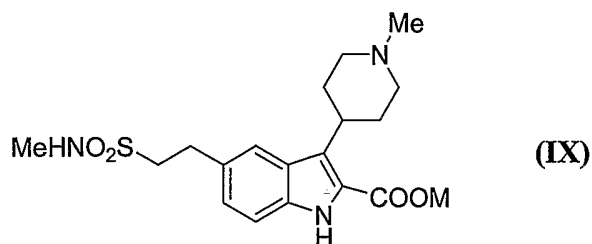
to produce a compound having formula (XV),



(ii) cyclizing the compound having formula (XV) to produce a compound having formula (VIII),



(iii) saponifying the compound having formula (VIII) with a base to produce a compound having formula (IX), where M is an alkali metal, and

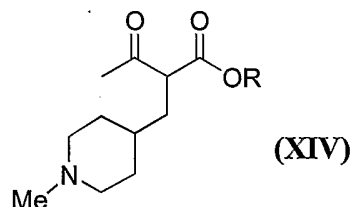


(iv) decarboxylating the compound having formula (IX) in an acidic medium to produce the compound having formula (I).

5. The process according to claim 4, wherein the compound having formula (XV) is not isolated, prior to conducting step (ii).

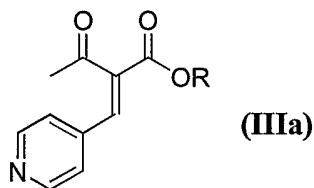
6. The process according to claim 4, wherein steps (iii) and (iv) are conducted sequentially in a vessel, without isolating the compound having formula (IX).

7. A compound having formula (XIV), where R is an alkyl group having 1 to 5 carbon atoms:



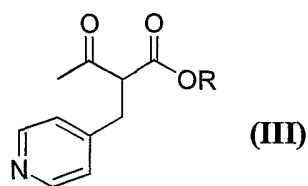
8. The compound according to claim 7, prepared by a process comprising:

(i) reacting a mixture of pyridine 4-carboxyldehyde and an alkyl acetoacetate to prepare a compound having formula (IIIa).

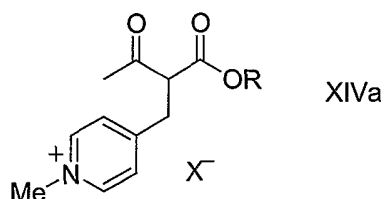


where R represents an alkyl group having 1 to 5 carbon atoms;

(ii) hydrogenating the compound having formula (IIIa) to prepare a compound having formula (III);

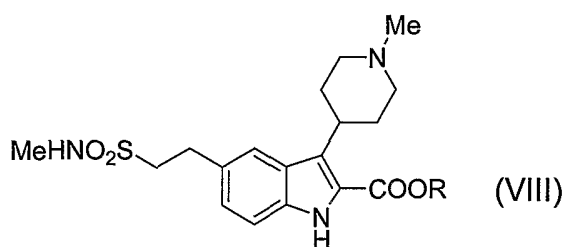


(iii) quaternizing the compound having formula (III) with an alkyl halide to prepare a compound having formula (XIVa), where X is a halogen; and



(iv) hydrogenating the compound having formula (XIVa) to produce the compound having formula (XIV).

9. A compound having formula (VIII):



10. A compound having formula (IX), wherein M is an alkali metal:

