(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016582 A1

(51) International Patent Classification[7]: C07C 303/40, 311/37

(21) International Application Number: PCT/IN2002/000200

(22) International Filing Date: 7 October 2002 (07.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
599/MAS/2002 14 August 2002 (14.08.2002) IN

(71) Applicant *(for all designated States except US)*: **NATCO PHARMA LIMITED** [IN/IN]; Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, Andra Pradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KONAKANCHI, Durga, Prasad** [IN/IN]; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad-500 033, Andhra Pradesh (IN). **SAMBASIVA, Ramachandran** [IN/IN]; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad-500 033, Andhra Pradesh (IN). **VENKAIAH CHOWDARY, Nannapaneni** [IN/IN]; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad-500 033, Andhra Pradesh (IN).

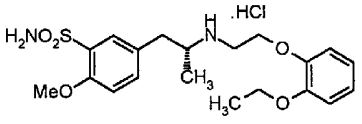
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

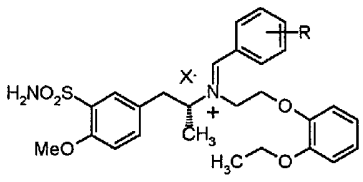
Published:
— *with international search report*

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.

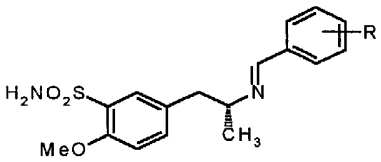
(54) **Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF TAMSULOSIN HYDROCHLORIDE



(I)



(II)



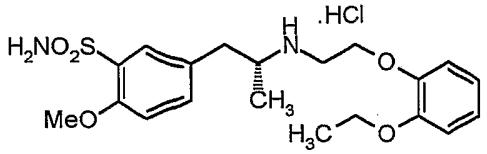
(III)

(57) **Abstract:** The present invention relates to an improved process for the preparation of Tamsulosin hydrochloride. Tamsulosin hydrochloride is a widely used drug for the treatment of benign prostate hyperplasia. Tamsulosin hydrochloride has the formula-I given below. (I) The process employs the novel intermediates quarternised benzylidene ammonium salts, N-(phenyl substituted)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoylphenyl)-1(R)-methyl-ethyl]ammonium halides of the formula-II, (II) where R represents H, 4-OCH_3, 4-OH or 4-fluoro and X represents C1, Br or I. And Schiff's bases, novel phenyl substituted 2-methoxy-5-[(2R)-[(1-E/Z-phenyl methylene)amino]propyl]benzenesulfonamide of the formula-III. (III) where R represents H, 4-OCH_3, 4-OH or 4-fluoro.

WO 2004/016582 A1

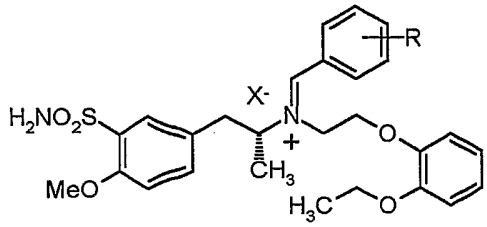
AN IMPROVED PROCESS FOR THE PREPARATION OF TAMSULOSIN HYDROCHLORIDE

The present invention relates to an improved process for the preparation of Tamsulosin hydrochloride. Tamsulosin hydrochloride is a widely used drug for the treatment of benign prostate hyperplasia. Tamsulosin hydrochloride has the formula-I given below.



Formula-I

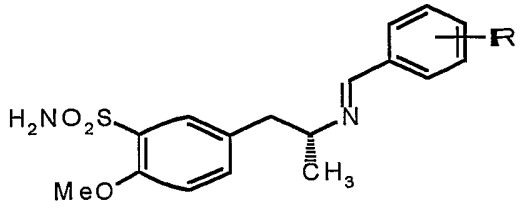
The process employs the novel intermediates quarternised benzylidene ammonium salts, N-(phenyl substituted)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoylphenyl)-1(R)-methyl-ethyl]ammonium halides of the formula-II,



Formula-II

where R represents H, 4-OCH_3, 4-OH or 4-fluoro and X represents Cl, Br or I.

and Schiff's bases, novel phenyl substituted 2-methoxy-5-[(2R)-[(1-E/Z-phenyl methylene)amino]propyl]benzenesulfonamide of the formula-III.



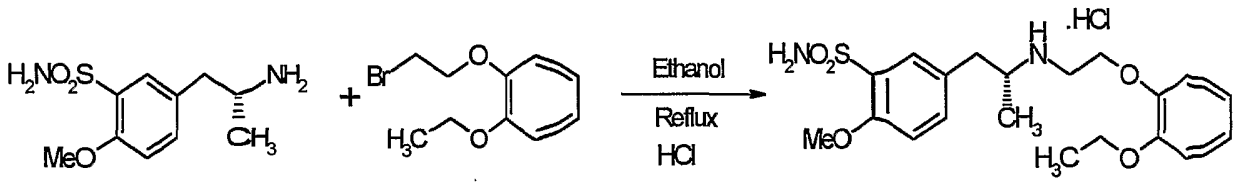
Formula-III

where R represents H, 4-OCH_3, 4-OH or 4-fluoro.

The novel intermediates of the above mentioned formulae-II & III which are useful for the preparation of Tamsulosin hydrochloride and the processes for their preparation have been made the subject matters of our co pending applications nos. **598/MAS/2002 & 597/MAS/2002** respectively.

Prior Art:

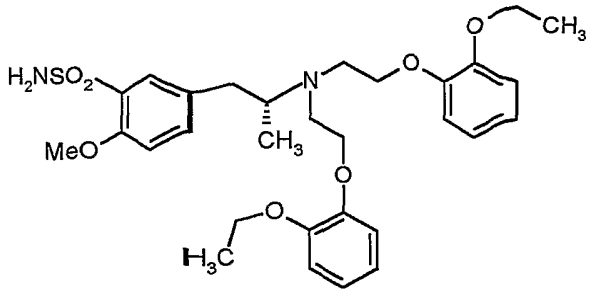
Tamsulosin hydrochloride is first disclosed in JP 55-14382 dt. 8-2-1980 and its equivalent US 4731,478 dt. 1 5/3/1988, wherein the intermediate R(-)-5-[(2-amino-2-methyl)ethyl]-2 - methoxybenzenesulfonamide of formula-IV is refluxed for 16hrs with another intermediate 2-(2–ethoxyphenoxy) ethylbromide of Formula-V in ethanol medium to obtain crude Tamsulosin base, which is purified by column chromatography to get pure base. The pure Tamsulosin base is treated with HCl in ethanol to obtain Tamsulosin hydrochloride of formula-I in 36.8% of yield based on the expensive intermediate of formula-IV. The synthetic route is given below in scheme-A.



Formula-IV Formula-V Formula-I

Scheme-A

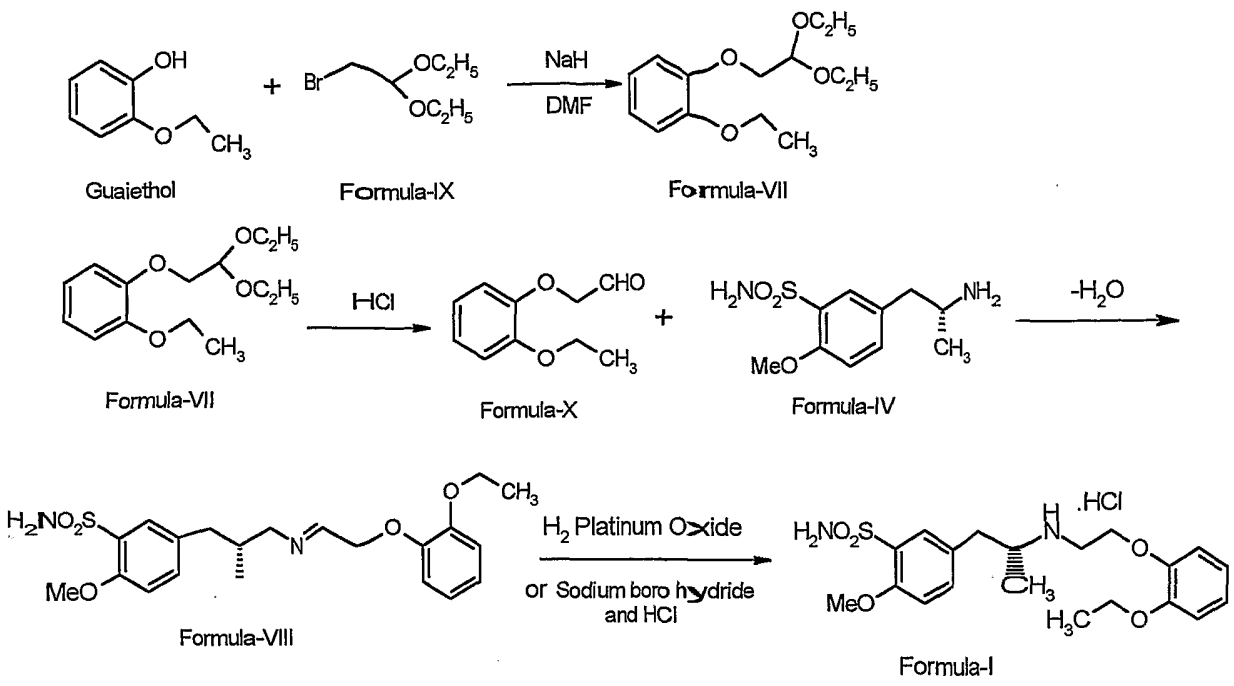
The drawbacks in this process are low yields of compound of formula-I due to formation of side products mainly the dialkylated compound of formula-VI,



Formula-VI

further the reaction time required is very long (i.e) more than 16hrs resulting in poor yields. The expensive intermediate R(-)-5-[(2-amino-2-methyl)ethyl-2-methoxybenzenesulfonamide of formula-IV is required in 2 mole equivalents to the other intermediate 2-(2-ethoxyphenoxy) ethylbromide of formula-V as the compound of formula-IV is reacted to form salt with the liberated HBr formed during the coupling reaction.

It is also disclosed in JP 254326 and its Austrian equivalent patent AT 397960 B that R(-) 5-[(2-amino-2-methyl)ethyl]-2-methoxybenzenesulfonamide of formula-IV is reacted with 2-(2-ethoxyphenoxy)acetaldehyde of formula-X, which is generated insitu by acid treatment of 2-(2-ethoxyphenoxy)acetaldehyde dimethyl acetal of formula-VII to get an imine compound of formula-VIII. Then the imine compound of formula-VIII is reduced with either platinum oxide or sodium borohydride / sodium cyano borohydride and on further treatment with HCl to obtain Tamsulosin hydrochloride of formula-I. The process for making compound of formula-VII is also disclosed. Guaiethol is reacted with bromo acetaldehyde diethylacetal of formula-IX using sodium hydride as base and dimethyl formamide as solvent. The reaction sequence is shown in scheme-B.



Scheme-B

The main drawbacks in this process are:

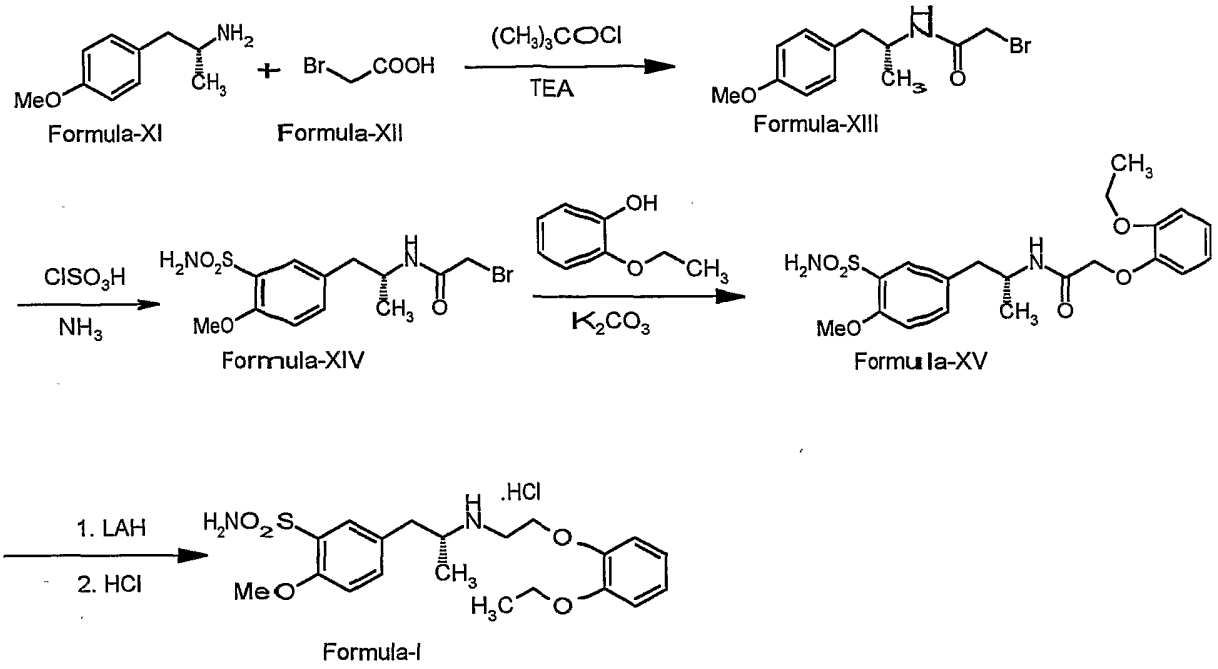
1. For the preparation of intermediates 2-(2-ethoxyphenoxy) acetaldehyde of formula-X, more steps are involved and pyrophoric reagents like sodium hydride has to be used for synthesis of the compound of formula-X.

2. For the reduction of imine of formula-VIII expensive and pyrophoric hydrogenation catalyst platinum oxide has to be used and special hydrogenation equipment is necessary to carry out the catalytic hydrogenation.

3. For the reduction of imine of formula-VIII expensive reagent sodium borohydride / sodium cyano borohydride is necessary.

JP 02306958 (1988-Hokuriku) discloses an alternate process for making Tamsulosin hydrochloride of formula-I. (2R)-4-Methoxyphenylisopropylamine of formula-XI is reacted with 2-bromoacetic acid of formula-XII using pivaloyl chloride and triethylamine

to obtain N-2-(bromoacetoxy)-2(R)-4-methoxyphenylisopropylamine of formula-XIII. The compound of formula-XIII is reacted with chlorosulphonic acid and then with ammonia solution to obtain its sulfonamide derivative of formula-XIV, which is reacted with guaiethol using potassium carbonate as base to obtain an amide derivative of formula-XV. The amide derivative of formula-XV is reduced with lithium aluminium hydride to secondary amine compound, which on treatment with HCl gives Tamsulosin hydrochloride of formula-I. The synthetic route is outlined in the following scheme-C.



Scheme-C

The main drawbacks in this process are:

1. More steps are involved there-by making the route very cumbersome.

2. Highly pyrophoric and expensive reagent lithium aluminium hydride is necessary to carry out the reduction of amide to secondary amine.

Recognizing the importance of Tamsulosin hydrochloride of the formula-I as a widely used drug for the treatment of benign prostate hyperplasia, and taking into account the

difficulties of the hitherto known processes for its preparation, we under-took research to develop a simple, cheap and commercially viable process for producing Tamsulosin hydrochloride, starting with (R)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide of formula-IV.

The main objective of the present invention, therefore, is to provide an improved process for the preparation of Tamsulosin hydrochloride, which is commercially viable.

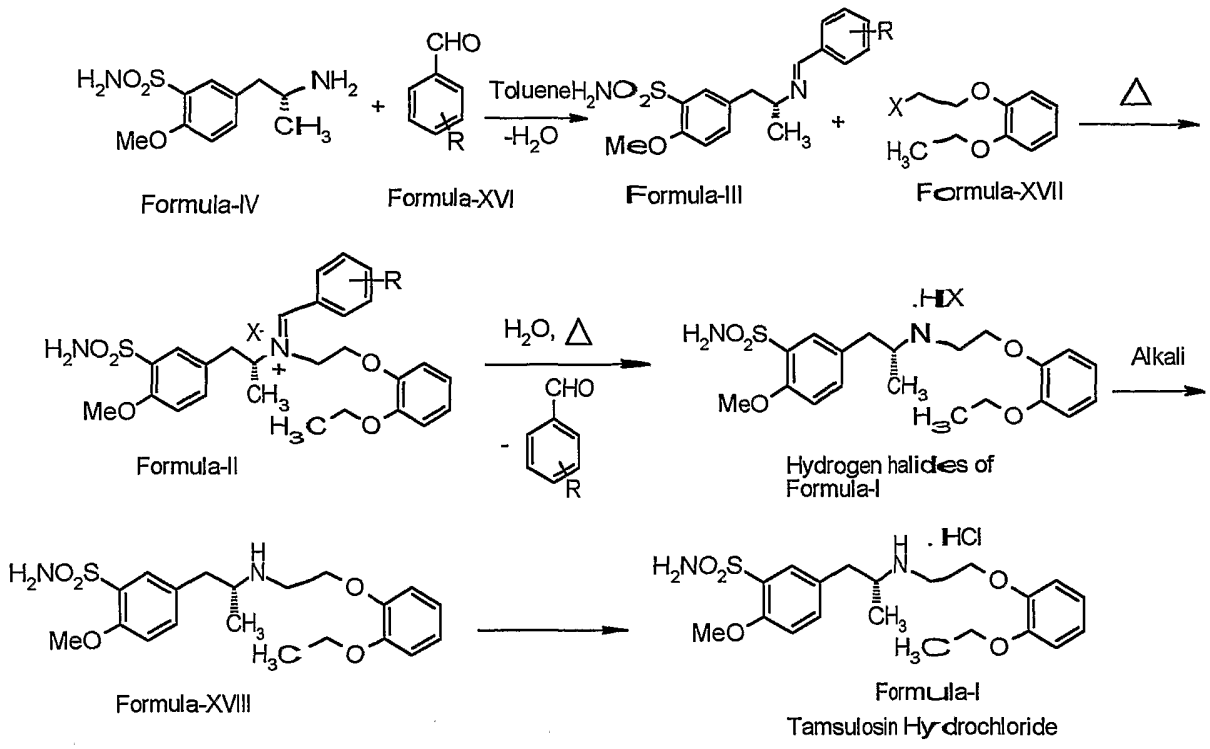
Another objective of the present invention is to provide an improved process for the preparation of Tamsulosin hydrochloride having single largest impurity less than 0.1% and total impurities less than 0.5%.

Yet another objective of the present invention is to provide an improved process for the preparation of Tamsulosin hydrochloride having a chiral purity (enantiomeric excess) of more than 99.9%.

Yet another objective of the present invention is to provide an improved process for the preparation of Tamsulosin hydrochloride, wherein the usage of specialized equipment like hydrogenator is not necessary thereby making the process simple.

Yet another objective of the present invention is to provide an improved process for the preparation of Tamsulosin hydrochloride, wherein the usage of pyrophoric and expensive reagents like Lithium aluminium hydride, platinum oxide and also expensive reagent like sodium borohydride are not used thereby making the process safer and economical.

The scheme of the process of the present invention is shown in scheme-D.



Scheme-D

where R = H, 4-OH, 4-OCH_3 or 4-fluoro and X = Cl, Br and I.

The monoalkylation of the primary amine of formula-IV is carried out by the method of Decker & Becker [Decker & Becker, Ann, **395**, 328 (1913)]. So far this method has not been used earlier for making Tamsulosin hydrochloride of formula-I.

Accordingly the present invention provides an improved process for the preparation of Tamsulosin hydrochloride of formula-I.

Which comprises following steps:

(i) reacting the compound of the formula-IV with a substituted aromatic benzaldehyde of the formula-XVI, where R represents group such as H, 4-OH, 4-OCH_3 or 4-fluoro to obtain novel compounds namely phenyl substituted 2-methoxy-5-[(2R)-[(1-E/Z-pheylmethylene)amino] propyl] benzenesulfonamide of formula-III, where R represents H, 4-OH, 4-OCH_3 or 4-fluoro

(ii) reacting the resulting compound of the formula-III with 2-(2-ethoxyphenoxy) ethylhalide of the formula-XVII, where the halo group is Cl, Br or I at a temp in the range of 80° to 130° to obtain the novel quarternary ammonium salts, namely N-(phenyl substituted)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3 - sulphamoyl-phenyl)-1(R)-methylethyl]ammonium halides of the formula-II, where R represents H, 4-OH, 4-OCH_3 or 4-fluoro groups and X represents Cl, Br or I

(iii) hydrolysing the quarternary ammonium salts of the resulting compound of the formula-II by heating in water to obtain the corresponding hydrogen halide salts of formula-I

(iv) neutralising the hydrogen halide salts of the formula-I thus obtained by conventional methods to produce the Tamsulosin base of the formula-XVIII, and

(v) converting the Tamsulosin base of the formula XVIII into Tamsulosin hydrochloride of formula-I by conventional methods.

In a preferred embodiment of the present invention the step (i) may be effected by azeotropically removing the water using a solvent such as toluene, xylene etc. or by simultaneous distillation of the water formed using an alcoholic solvent such as methanol, ethanol, isopropyl alcohol, n-butanol etc. The reaction of step (ii) may be performed either neatly or by using solvent such as toluene, xylene, n-butanol, dimethyl formamide, dimethyl acetamide etc. The compound of formula-II is isolated by filtration or by removal of the solvent and by simple leaching with a suitable solvent such as methylene chloride etc., to remove the unreacted alkylhalide. In step (iii) the hydrolysis may be carried out using hot water. The liberated aldehyde, may be removed by steam distillation or by extraction with a solvent such as methylene chloride.

The neutralization in step (iv) may be done using solutions of alkali bicarbonates, carbonates such as sodium bicarbonate, potassium bicarbonate etc. and sodium carbonate,

potassium carbonate, etc and alkali hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide etc, to obtain the crude base compound of Tamsulosin of formula-XVIII. The crude Tamsulosin base may be purified by column chromatography or by recrystallization using suitable solvents such mixtures of dimethyl formamide and acetonitrile, dimethyl formamide and isopropyl ether etc.

The Tamsulosin hydrochloride is prepared using solvents such as methanol, ethanol, isopropyl alcohol etc and hydrogen chloride solution in isopropyl alcohol.

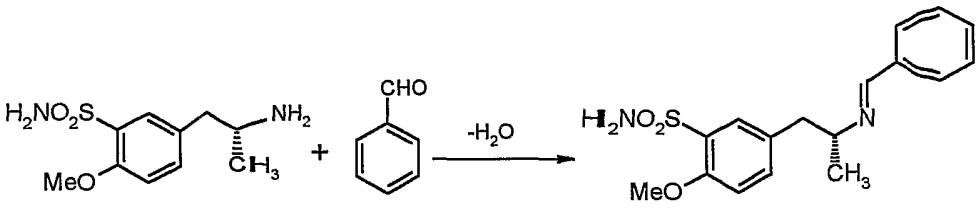
In an embodiment of the present invention the reaction of the compound of the formula-I with a substituted aromatic benzaldehyde of the formula-XVI, where R represents group such as H, 4-OH, 4-OCH_3 or 4-fluoro to obtain novel compounds namely phenyl substituted 2-methoxy-5-[(2R)-[(1-E/Zpheylmethylene)amino]propyl]benzenesulfonamide of formula–III, where R represents H, 4-OH, 4-OCH_3 or 4-fluoro.

In another embodiment of the invention the reaction of the resulting compound of the formula-III with 2-(2-ethoxyphenoxy) ethylhalide of the formula-XVII, where the halo group is Cl, Br or I at a temp in the range of 80° to 130° to obtain the novel quarternary ammonium salts, namely N-(phenyl substituted)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoylphenyl)-1(R)-methyl-ethyl]ammonium halides of the formula-II, where R represents H, 4-OH, 4-OCH_3 or 4-fluoro groups.

The details of the invention are given in the examples given below which are given to illustrate the invention only and therefore should not be construed to limit the scope of the invention.

Example-1

(i) Preparation of 2-methoxy-5-(2R)-2-{[(1-E/Z-phenylmethylene)amino]propyl} benzenesulfonamide of formula-IIIa.



Formula-IV Formula-IIIa

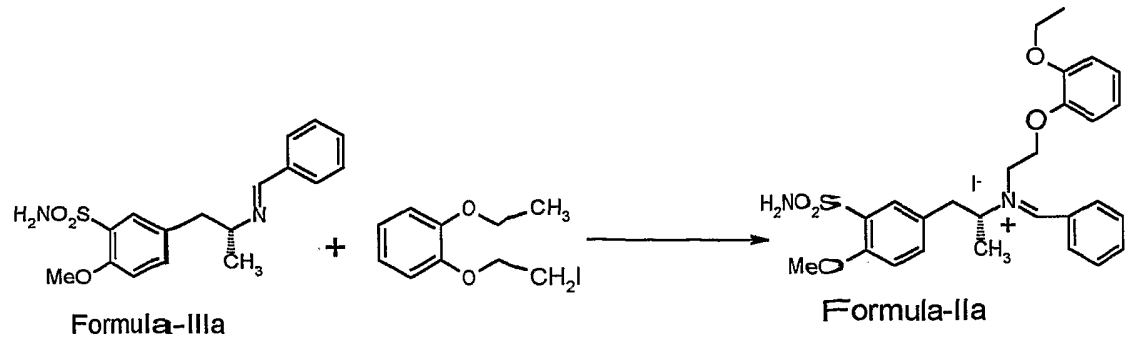
Into a 4-necked 500ml round bottom flask equipped with Dean-Stark apparatus, 150.0ml of toluene, 24.4gms (0.1mole) of (R)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide of the formula-IV and 10.6gms (0.1mole) of benzaldehyde are charged. Azeotropic distillation was carried out and 1.8ml (0.1mole) of water separated. Then the toluene is distilled off completely under vacuum at temp max. 80°C. The reaction mixture is cooled to 25 – 35°C and the vacuum is released under nitrogen atmosphere. A thick oily compound 2-methoxy-5-(2R)-2{[(1-E/Z-phenylmethylene)amino]propyl}benzenesulfonamide of formula-IIIa (33.0gm) formed, crystallized soon. Purified sample (recrystallized from IPA) has the following characteristics.

MR : 121 – 126°C

1H NMR : (200MHz, $CDCl_3$+DMSO-d6) δ 1.26 – 1.29 (d, 3H), 2.86 – 2.90 (t, 2H), 3.49 - 3.59 (m, 1H), 3.92 (s, 3H), 6.0 (broad, 2H), 6.9 – 7.7 (aromatic, 8H), 8.07 (s, imine, 1H)

IR : (KBr), 3385, 3294, 2847, 1640, 1492, 1344, 1158 cm^{-1}

(ii) Preparation of N-benzylidene-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoyl phenyl)-1(R)-methyl-ethyl]ammonium iodide of formula-IIa.



Formula-IIIa Formula-IIa

The oily mass of formula-IIIa obtained in step (i) (a) is taken and dissolved in 125.0ml of n-butanol. The solution is heated to 100°C under nitrogen atmosphere. A solution of 29.1gms (0.1mole) of 2-(2-ethoxyphenoxy) ethyl iodide in 30ml of n-butanol is slowly added at 100 – 105°C over a period of 3 – 4 hrs and maintained at 100 – 110°C for further 4hrs. Then n-butanol is distilled off under vacuum at temp not exceeding 80°C.The resulting mass is cooled to 20°C and vacuum released under nitrogen atmosphere. Added 50.0ml of n-hexane. The resulting uniform slurry is allowed to solidify at 0 – 5°C. The reaction mixture is filtered, washed with 50ml of n-hexane and the product is dried at 40 — 50°C under vacuum to obtain a solid of novel quarternary ammonium salt of formula-IIa 35.0gms. Recrystallized (from acetonitrile) sample has the following characteristics.

MR : 208 – 210°C

1H NMR : (200MHz, DMSO-d6) δ 1.14 – 1.17 (d, 3H), 1.24 – 1.36 (t, 3H), 2.79 – 2.83 (m, 2H), 3.40 (broad, 2H), 3.46 – 3.54 (m, 3H), 3.84 (s, 3H), 3.87 – 4.01(dd, 4H), 4.20- 4.22 (t, 2H), 6.92 –7.67 (aromatic, 12H), 8.10 (s, imine, 1H)

IR : (KBr), 3306, 3270, 3000, 2926, 2840, 1638, 1609, 1494, 1331, 1282, 1251, 1167, 1011 cm^{-1}

(iii) Hydrolysis of quarternary ammonium iodide salts of formula-IIa.

To the solid mass novel quarternary ammonium salt of formula IIa obtained in step ii (b) 500.0ml of water is added and the resultant solution is heated at reflux temp for 2hrs. Then

liberated benzaldehyde is steam distilled and is separated (10.0gms) from distillate. Proceeded with the residue for neutralization step.

(iv) Neutralization of Tamsulosin hydrochloride salt to obtain Tamsulosin crude base.

To the residue obtained from step-IIIa is added 300ml of water. The pH was adjusted to 9.0 – 10.0 using K_2CO_3 powder. A white precipitate is obtained. The crude product is extracted into ethyl acetate (500.0ml) and the solvent is removed by distillation. The crude mass is purified by column chromatography (Ethyl acetate : methanol : ammonia 9 : 1 : 0.2) to obtain Tamsulosin base (18.0gm). Dried the material under vacuum at 40°C. HPLC purity 99.8% with single largest impurity <0.1%. Chiral purity > 99.9%.

(v) Preparation of Tamsulosin hydrochloride of formula-I.

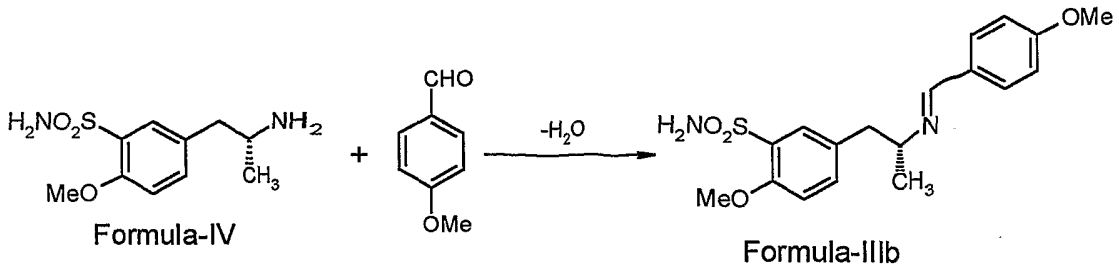
The pure base of Tamsulosin (18.0gms) obtained from example-iv (a) is dissolved in 360ml of methanol at 55°C. IPA HCl (12% w/w – 13.4ml) is added at 25 – 35°C over a period of 1hr. stirred at same temp for further 1hr. Cooled to 0 – 5°C. Maintained at 0 – 5°C for further 3hrs. Filtered. Dried the material at 50°C under vacuum. Yield 18.0gms.

MR : 229 – 230°C

HPLC : Purity > 99.8% (with single impurity < 0.1%)
Chiral Purity > 99.9%.

Example 2.

(i) Preparation of 2-Methoxy-5-(2R)-2-{[(1-E/Z-4-methoxyphenylmethylene) amino] propyl} benzene sulfonamide of formula-IIIb.



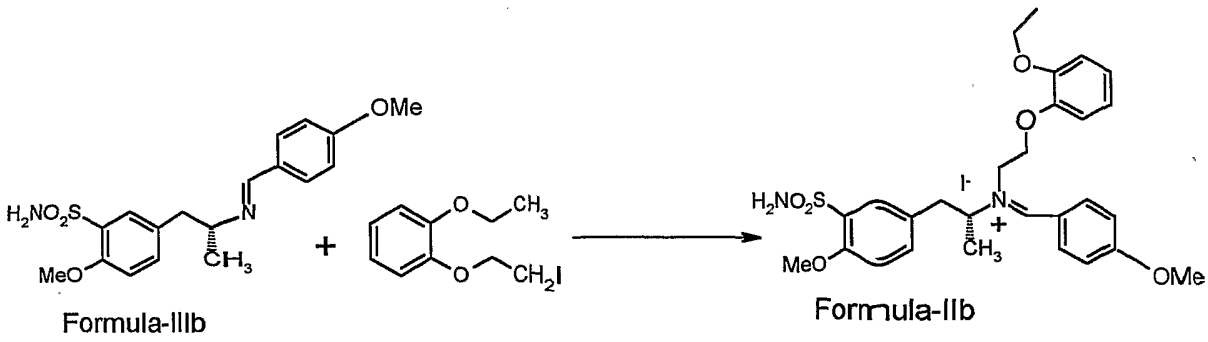
Into a 4-necked 500ml round bottom flask, equipped with Dean-Stark apparatus, 150.0ml of toluene, 24.4gm (0.1mole) of R-5-(2-aminoproply)-2-methoxy benzene sulfonamide of formula-IV and 13.6gm (0.1mole) of 4-methoxybenzaldehyde are charged . Carried out azotropy and separated the water (1.8ml collected. The solvent is removed under vacuum at temp max. 80°C. The reaction mixture is cooled to 25 – 35°C and the vacuum is released under N2 atmosphere. A thick oily mass of compound of 2-methoxy-5-(2R)-2-{[(1-E/Z-phenylmethylene)amino]propyl} benzene sulfonamide of formula-IIIb is obtained (37.0gms). Recrystallized sample (from IPA) has the following characteristics.

MR : 122 – 128°C

1H NMR : (200MHz, $CDCl_3$+DMSO-d6) δ 1.24 – 1.27 (d, 3H), 2.82 — 2.86 (t, 2H), 3.41 - 3.51 (m, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 4.5 (broad, 2H), 6.9 – 7.7 (aromatic, 8H), 8.07 (s, imine, 1H)

IR : (KBr), 3352, 2841, 1636, 1606, 1495, 1335, 1253, 1183, 1157, 1024 cm^{-1}

(ii) Preparation of N-(4-methoxybenzylidene)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoylphenyl)-1(R)-methyl ethyl]ammonium iodide of formula-IIb.



Formula-IIIb Formula-IIb

The oily mass of formula-IIIb obtained in step (i) (b) is taken and dissolved in 125.0ml of n-butanol. The solution is heated to 100°C under nitrogen atmosphere. A solution of 29.1gms (0.1mole) of 2-(2-ethoxyphenoxy) ethyl iodide in 30ml of n-butanol is slowly added at 100 – 105°C over a period of 3 – 4 hrs and maintained at 100 – 110°C for further 4hrs. Then n-butanol is distilled off under vacuum at temp not exceeding 80°C. The resultant mass is cooled to 20°C and vacuum released under nitrogen atmosphere. Added 50.0ml of n-hexane and stirred to make uniform slurry and is cooled 0 – 5°C. The compound is filtered and washed with 50ml of n-hexane. The resultant product is dried at 40 – 50°C under vacuum to obtain a solid quarternary ammonium salt of formula-IIb (40.0gms). Recrystallized sample (from acetonitrile) has the following characteristics.

MR : 115 – 120°C

1H NMR : (200MHz, DMSO-d6) δ 1.14 – 1.17 (d, 3H), 1.24 – 1.36 (t, 3H), 2.79 – 2.83 (m, 2H), 3.40 (broad, 2H), 3.46 – 3.54 (m, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.87 – 4.01(dd, 4H), 4.20- 4.22 (t, 2H), 6.92 –7.67 (aromatic, 11H),
8.13 (s, imine, 1H)

IR : (KBr), 3352, 2841, 1636, 1605, 1495, 1354, 1269, 1157, 1074, 1023cm^{-1}

(iii) Hydrolysis of quarternary ammonium iodide salt of formula-IIb.

To the solid mass obtained in step-IIb 500.0ml of water is added and the resultant solution is heated at reflux temp for 2hrs. Then it is steam distilled and 4-methoxybenzaldehyde (11.0gms) is separated from distillate. The residue is proceeded with neutralization step.

(iv) b) Neutralization of Tamsulosin hydrochloride salt to obtain Tamsulosin crude base.

To the residue obtained from step-IIIb is added 300ml of water. Adjusted pH to 9.0 – 10.0 with K_2CO_3 powder. A white precipitate is obtained. The crude product is extracted into ethyl acetate (500.0ml) and the solvent is removed by distillation. Purified the crude mass by column chromatography (Ethyl acetate : methanol : ammonia 9 : 1 : 0.2) and obtained 19.0gms of Tamsulosin base. Dried the material under vacuum at 40°C. HPLC purity 99.8% with single largest impurity <0.1%. Chiral purity > 99.9%.

(v) Preparation of Tamsulosin hydrochloride of formula–I.

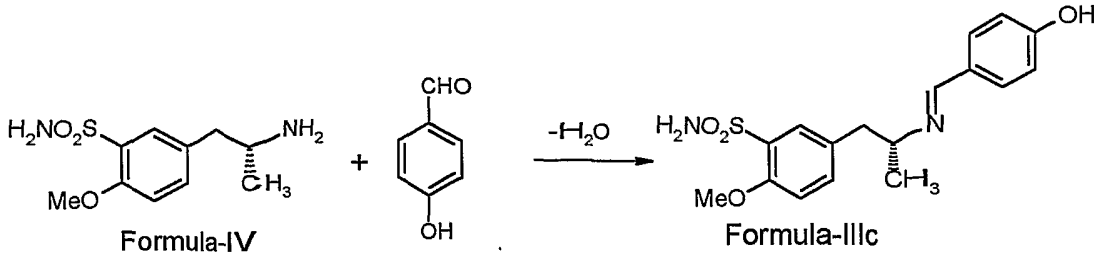
The pure base of Tamsulosin (19.0gms) obtained from step-iv (a) is dissolved in 380ml of methanol at 55°C. IPA HCl (12% w/w – 14.8ml) is added at 25 – 35°C over a period of 1hr. stir at same temp for further 1hr. Cooled to 0 – 5°C. Maintained at 0 – 5°C for further 3hrs. Filtered. Dried the material at 50°C under vacuum. Yield 19.0gms.

MR : 229 – 230°C

HPLC : Purity > 99.8% (with single impurity < 0.1%)
Chiral Purity > 99.9%.

Example 3.

(i) Preparation of 2-methoxy-5-(2R)-2-{[(1-E/Z-4-hydroxyphenylmethylene)amino] propyl} benzenesulfonamide of formula-IIIc.



Formula-IV Formula-IIIc

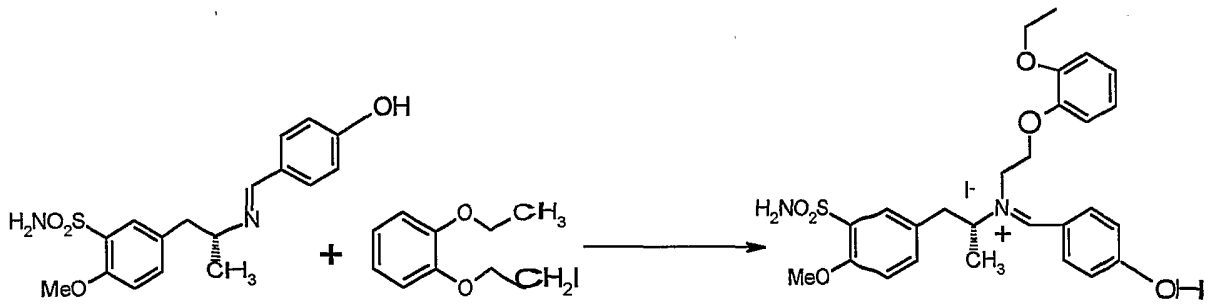
Into a 4-necked 500ml round bottom flask, equipped with Dean-stark apparatus, 150ml of toluene, 24,4gms (0.1mole) of (R)-5-(2-aminopropyl)-2-methoxy benzene sulfonamide of formula-IV and 12.2gms (0.1mole) of 4-hydroxybenzaldehyde are charged .The reaction was carried out azeotrophically and the water (1.8ml) collected and separated. Then the solvent is removed under vacuum at temp max 80°C. Cooled to 25 – 30°C .The vacuum is released under N_2 atmosphere. A thick oily mass which solidified on storage which is the compound of 2-methoxy-5-(2R)-2-{[(1-E/Z-4-hydroxyphenylmethylene)amino]propyl} benzenesulfonamide of formula-IIIc (35.0gms). Recrystallized sample (from IPA) has the following characteristics.

MR : 96 – 100°C

1H NMR : (200MHz, $CDCl_3$+DMSO-d6) δ 1.23 – 1.26 (d, 3H), 2.84 – 2.87 (t, 2H), 3.43 - 3.52 (m, 1H), 3.92 (s, 3H), 6.0, (broad, 2H), 6.8 – 7.7 (aromatic, 7H), 7.95 (s, imine, 1H)

IR : (KBr), 3352, 3257, 2969, 1640, 1606, 1585, 1484, 1394, 1158, 1070, 1018 cm^{-1}

(ii) Preparation of N-(4-hydroxybenzylidene–[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoyl phenyl)- 1(R)-methyl ethyl]ammonium iodide of formula-IIb.



Formula-IIIc Formula-IIc

The oily mass of formula-IIIc obtained in step (i) (c) is taken and dissolved in 125.0ml of n-butanol. The solution is heated to 100°C under nitrogen atmosphere. A solution of 29.1gms (0.1mole) of 2-(2-ethoxyphenoxy) ethyl iodide in 30ml of n-butanol is slowly added at 100 – 105°C over a period of 3 – 4 hrs and maintained at 100 – 110°C for further 4hrs. Then n-butanol is distilled off under vacuum at temp not exceeding 80°C. The resulting mass is cooled to 20°C and vacuum released under nitrogen atmosphere. Added 50.0ml of n-hexane. Uniform slurry is made and the product is allowed to solidify at 0 – 5°C. The reaction mixture is filtered. And washed with 50ml of n-hexane. The product is dried at 40 – 50°C under vacuum to obtain the solid quarternary ammonium salt of formula-IIc (30.0gms). Recrystallized sample (from IPA) has the characteristics.

1H NMR : (200MHz, DMSO-d6) δ 1.10 – 1.12 (d, 3H), 1.28 – 1.31 (t, 3H), 2.79 – 2.83 (m, 2H), 3.40 (broad, 2H), 3.46 – 3.54 (m, 3H), 3.84 (s, 3H), 3.87 – 4.01(dd, 4H), 4.20- 4.22 (t, 2H), 6.92 –7.67 (aromatic, 12H), 8.20 (s, imine, 1H)

IR : (KBr), 3352, 3243, 2973, 1639, 1606, 1586, 1495, 1322, 1281, 125 5, 1157,

1072, 1017 cm^{-1}

(iii) Hydrolysis of quarternary ammonium iodide salts of formula-IIc.

To the solid mass obtained in step-IIb 500.0ml of water is added and the solution is heated at reflux temp for 2hrs. Then steam distilled and 4-hydroxybenzaldehyde (9.0gms) is separated from distillate. Proceeded with the residue for neutralization step.

(iv) Neutralization of Tamsulosin hydrochloride salt to obtain Tamsulosin crude base.

To the residue obtained from step-IIIc 300ml of water is added .The pH is adjusted to 9.0 – 10.0 with K_2CO_3 powder. A white precipitate is obtained. The crude product is extracted with ethyl acetate (500.0ml) and the solvent is removed by distillation. The crude mass is purified by column chromatography (Ethyl acetate : methanol : ammonia 9 : 1 : 0.2) and 15.0gms of Tamsulosin base is obtained . The material is distilled under vacuum at 40°C. HPLC purity 99.8% with single largest impurity <0.1%. Chiral purity > 99.9%.

(v) Preparation of Tamsulosin hydrochloride of formula-I.

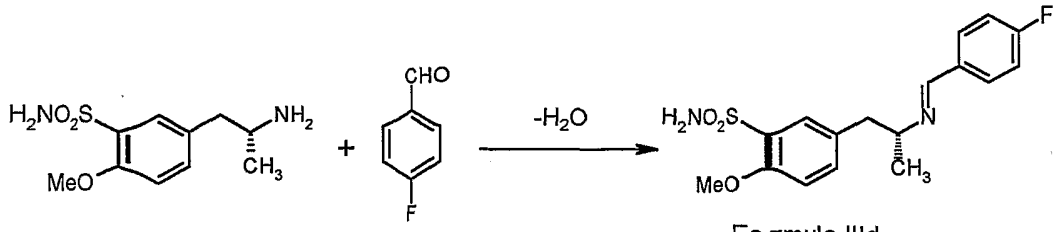
The pure base of Tamsulosin (15.0gms) obtained from step-iv (c) is dissolved in 300ml of methanol at 55°C. IPA HCl (12% w/w – 10.0 ml) is added at 25 – 35°C over a period of 1hr. stir at same temp for further 1hr. Cooled to 0 – 5°C. Maintained at 0 – 5°C for further 3hrs. Filtered. Dried the material at 50°C under vacuum. Yield 15.0gms.

MR : 229 - 230°C

HPLC : Purity > 99.8% (with single impurity < 0. 1%)
Chiral Purity > 99.9%.

Example 4.

(i) Preparation of 2-methoxy-5-(2R)-2-{[(1-E/Z-4-fluorophenylmethylene)amino] propyl} benzene methane sulfonamide of formula-IIId.



Formula-IV Formula-IIId

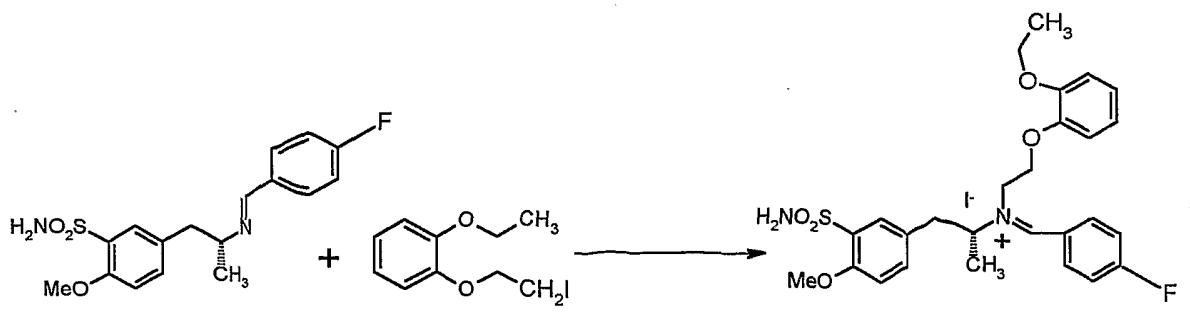
Into a 4-necked 500ml round bottom flask, equipped with Dean-stark apparatus 150.0ml of toluene, 24.4gms of (R)-5-(2-aminopropyl)-2-methoxy benzene sulfonamide of the formula-IV and 12.4gms (0.1mole) of 4-fluorobenzaldehyde are charged. The reaction is effected azeotropically and the water 1.8ml (0.1mole) is separated. Then the toluene is distilled off completely under vacuum at temp max 80°C. Cooled 25 – 35°C and released the vacuum under nitrogen atmosphere. 25.0gm of thick oily compound of 2-methoxy-5-(2R)-2-{[(1-E/Z-4-fluorophenylmethylene)amino] propyl} benzenesulfonamide of formula-IIId is obtained. Recrystallized sample (from IPA) has the following characteristics.

MR : 140 – 148°C

1H NMR : (200MHz, $CDCl_3$+DMSO-d6) δ 1.01 – 1.04 (d, 3H), 2.80 – 2.88 (t, 2H), 3.14 - 3.18 (m, 1H), 3.88 (s, 3H), 6.0, (broad, 2H), 7.12 – 7.57 (aromatic, 7H),
8.20 (s, imine, 1H)

IR : (KBr), 3385, 3315, 2948, 1643, 1606, 1576, 1495, 1404, 1334, 1249, 1154,
1074, 1114, 518, 471 cm^{-1}

(ii) Preparation of N-(4-fluorobenzylidene-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoyl phenyl)-1(R)-methyl ethyl] ammonium iodide of formula-IId.



Formula-IIId Formula-IId

The oily mass of formula-IIId obtained in step (i) (c) is taken and dissolved in 125.0ml of n-butanol. The solution is heated to 100°C under nitrogen atmosphere. A solution of 29.1gms (0.1mole) of 2-(2-ethoxyphenoxy) ethyl iodide in 30ml of n-butanol is slowly added at 100 – 105°C over a period of 3 – 4 hrs and maintained at 100 – 110°C for further 4hrs. Then n-butanol is distilled off under vacuum at temp not exceeding 80°C. The resulting mass is cooled to 20°C and vacuum released under nitrogen atmosphere. 50.0ml of n-hexane is added to the mixture. An uniform slurry is made and the product is allowed to solidify at 0 – 5°C. It is filtered and washed with 50ml of n-hexane. The product is dried at 40 – 50°C under vacuum to obtain 22.0gms solid of quarternary ammonium salt of formula-IId. Recrystallized (from acetonitrile) has the following characteristics.

MR : 200 - 208°C

1H NMR : (200MHz, DMSO-d6) δ 1.15 – 1.19 (d, 3H), 1.28 – 1.31 (t, 3H), 2.60 – 2.70 (m, 2H), 3.40 (broad, 2H), 3.46 – 3.54 (m, 3H), 3.9 (s, 3H), 3.87 – 4.01(dd, 4H), 4.20- 4.22 (t, 2H), 6.92 –7.67 (aromatic, 11H), 8.15 (s, imine, 1H)

IR : (KBr), 3305, 3210, 2930, 1632, 1609, 1494, 1439, 1330, 1282, 1252, 1456, 1075, 1011, 533, 522, 454 cm^{-1}

(iii) Hydrolysis of quarternary ammonium iodide salts of formula-IId.

To the solid mass obtained in step IId 500.0ml of water is added and heated at reflux temp for 2hrs. Then steam distilled with 4-fluorobenzaldehyde (8.0gms) and is separated from distillate. Proceeded with the residue for neutralization step.

(iv) Neutralization of Tamsulosin hydrochloride salt to obtain Tamsulosin crude base.

To the residue obtained from step-IIId 300ml of water is added. The pH is adjusted to 9.0 – 10.0 with K_2CO_3 powder. A white precipitate is obtained. The crude product is extracted with ethyl acetate (500.0ml) and the solvent is removed by distillation. The crude mass is separated by column chromatography (Ethyl acetate: methanol: ammonia 9 : 1 : 0.2) and 10.0gms of Tamsulosin base is obtained . The material is dried under vacuum at 40°C. HPLC purity 99.8% with single largest impurity <0.1%. Chiral purity > 99.9%.

(v) Preparation of Tamsulosin hydrochloride of formula-I.

The pure base of Tamsulosin (10.0gms) obtained from step-iv (d) is dissolved in 360ml of methanol at 55°C. IPA HCl (12% w/w – 8.0 ml) at 25 – 35°C over a period of 1hr. stir at same temp for further 1hr. Cooled to 0 – 5°C. Maintained at 0 – 5°C for further 3hrs. The reaction mixture is filtered & dried and at 50°C under vacuum. Yield 10.0gms.

MR : 229 – 230°C

HPLC : Purity > 99.8% (with single impurity < 0.1%)
Chiral Purity > 99.9%.

Advantages of the invention:

1) The N-alkylation step of the process has several advantages over the previous methods mentioned in the prior art.

   a) The dialkylation of the primary amine is totally avoided as the reaction is carried out on the imine nitrogen.

   b) Expensive reagents like platinum oxide and sodium borohydride and sodium cyano borohydride are avoided there by making the process economical.

   c) Usage of intermediate, such as 2-(2-ethoxyphenoxy) acetaldehyde diethyl acetal, which is prepared by multi step synthesis is not necessary as the alkylation is carried out with 2-(2-ethoxyphenoxy) ethyl halide of formula-V, which can be prepared easily. Thus the process is simplified.

2) The starting materials which are unused can be recovered and reused making the process economical.

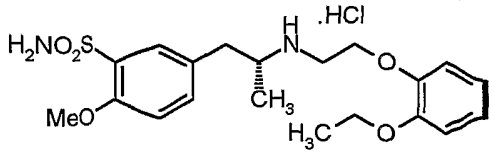
3) The yield of the compound of the formula-I is about 58% calculated on compound of formula-IV.

4) The process is safe as it does not use pyrophoric palladium catalyst and also any specialized equipment like hydrogenator.

5) The purity of the compound of the formula prepared by this process is over 99.8% with single largest impurity less than 0.1%.

We claim

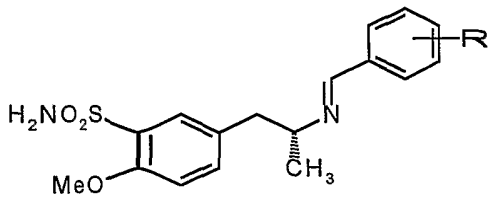
1. An improved process for the preparation of Tamsulosin hydrochloride of formula-I, which comprises



Formula-I

which comprises,

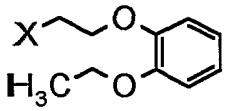
(i) reacting the compound of the formula-IV with a substituted aromatic benzaldehyde of the formula-XVI, where R represents group such as H, 4–OH, 4-OCH_3 or 4-fluoro to obtain novel compounds namely phenyl substituted 2-methoxy-5-(2R)-2-{[(1-E-/Z-pheylmethylene)amino]propyl}benzenesulfonamide of the formula-III,



Formula-III

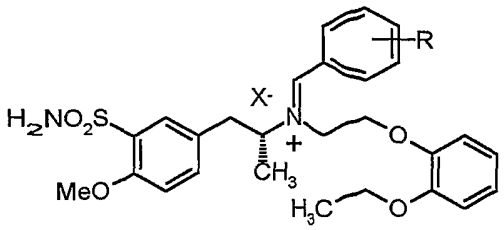
where R represents H, 4-OH, 4-OCH_3 or 4-fluoro

(ii) reacting the resulting compound of the formula-III with 2-(2-ethoxyphenoxy) ethylhalide of the formula-XVII,



Formula-XVII

where the halo group is Cl, Br or I at a temp in the range of 80° to 130° to obtain the novel quarternary ammonium salts, namely N-(phenyl substituted)-[2-(2-ethoxyphenoxy)ethyl]-[2-(4-methoxy-3-sulphamoyl-phenyl)-1(R)-methyl-ethyl]ammonium halides of the formula-II,

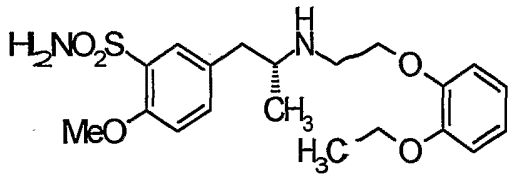


Formula-II

where R represents H, 4-OH, 4-OCH_3 or 4-fluoro groups

(iii) hydrolysing the quarternary ammonium salts of the resulting compound of the formula-II by heating in water to obtain the corresponding hydrogen halide salts of formula-I

(iv) neutralising the hydrogen halide salts of the formula-I thus obtained by conventional methods to produce the Tamsulosin base of the formula-XVIII, and



Formula-XVIII

(vi) converting the Tamsulosin base of the formula XVIII into Tamsulosin hydrochloride of formula-I by conventional methods.

2. An improved process as claimed in claim 1 wherein the step (i) is effected by azeotropically removing the water using a solvent

3. An improved process as claimed in claim 2 wherein the solvent such as toluene, xylene etc. is used.
4. An improved process as claimed in claim 1 wherein the step (i) is effected by simultaneous distillation of the water formed using an alcoholic solvent such as methanol, ethanol, isopropyl alcohol, n-butanol etc.

5. An improved process as claimed in claims 1 to 4 wherein the reaction of step-ii is carried out neatly without using a solvent.

6. An improved process as claimed in claims 1 to 5 wherein the reaction of step-ii is also carried out by using solvent such as toluene, xylene, n-butanol, dimethyl formamide, dimethyl acetamide etc.

7. An improved process as claimed in claims 1 to 6 wherein the compound of formula-III is isolated by filtration.

8. An improved process as claimed in claims 1 to 6 wherein the compound of the formula-II is also isolated by removal of the solvent and by simple leaching with a suitable solvent such as methylene chloride etc.

9. An improved process as claimed in claims 1 to 8 wherein the hydrolysis in step (iii) is carried out using hot water and the liberated aldehyde, is removed by steam distillation or by extraction with a solvent such as methylene chloride.

10. An improved process as claimed in claims 1 to 9 wherein the neutralization in step (iv) is effected by using solutions of alkali bicarbonates, carbonates such as sodium bicarbonate, potassium bicarbonate etc. and sodium carbonate, potassium carbonate, etc and alkali hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide etc.

11. An improved process as claimed in claims 1 to 10 wherein the crude Tamsulosin base is purified by column chromatography or by recrystallization using suitable solvents such as mixture of dimethyl formamide and acetonitrile, dimethyl formamide and isopropyl ether etc.

12. An improved process as claimed in claims 1 to 11 wherein the Tamsulosin base is converted into Tamsulosin hydrochloride by using solvents such as methanol, ethanol, isopropyl alcohol etc and hydrogen chloride solution in isopropyl alcohol.

13. An improved process for the preparation of Tamsulosin hydrochloride of formula-I, as defined in claim 1 substantially as herein described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/IN 02/00200

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/40 C07C311/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AT 397 960 B (YAMANOUCHI PHARMACEUTICAL) 25 August 1994 (1994-08-25) cited in the application example 4 ---	1
A	US 4 731 478 A (K. NIIGATA, ET AL.) 15 March 1988 (1988-03-15) cited in the application example 20 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2003	02/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	T. SHIOZAWA, ET AL.: "Isolation and identification of a new 2-phenylbenzotriazole-type mutagen (PBTA-3) in the Nikko river in Aichi, Japan" CHEMICAL RESEARCH IN TOXICOLOGY, vol. 13, no. 7, 3 June 2000 (2000-06-03), pages 535-540, XP002249815 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US page 537, left-hand column, line 22 - line 48 -----	1

INTERNATIONAL SEARCH REPORT

Inter nal application No.
PCT/IN 02/00200

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/IN 02/00200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
AT 397960 B	25-08-1994	JP 1037391 B	07-08-1989
		JP 1553822 C	04-04-1990
		JP 62114952 A	26-05-1987
		AT 203286 A	15-12-1993
		CA 1282077 C	26-03-1991
		ES 2000382 A6	16-02-1988
		KR 9407746 B1	24-08-1994
US 4731478 A	15-03-1988	JP 1443699 C	08-06-1988
		JP 56110665 A	01-09-1981
		JP 62052742 B	06-11-1987
		AR 227533 A1	15-11-1982
		AR 230433 A1	30-04-1984
		AT 7223 T	15-05-1984
		AU 541720 B2	17-01-1985
		AU 6689681 A	13-08-1981
		CA 1177849 A1	13-11-1984
		DE 3163257 D1	30-05-1984
		EP 0034432 A2	26-08-1981
		ES 8201966 A1	01-04-1982
		GR 73827 A1	04-05-1984
		IE 50862 B1	06-08-1986
		LU 90000 A9	04-03-1997
		MX 6859 E	08-09-1986
		MX 9203592 A1	31-07-1992
		PT 72460 A ,B	01-03-1981
		SU 1082320 A3	23-03-1984
		SU 1181540 A3	23-09-1985
		SU 1248533 A3	30-07-1986
		US 5391825 A	21-02-1995
		US 4373106 A	08-02-1983
		US 4868216 A	19-09-1989
		US 5447958 A	05-09-1995
		US 4987152 A	22-01-1991
		US 4558156 A	10-12-1985
		US 4703063 A	27-10-1987
		US 4761500 A	02-08-1988