



- (51) **International Patent Classification:** Not classified
- (21) **International Application Number:** PCT/IN2014/000151
- (22) **International Filing Date:** 7 March 2014 (07.03.2014)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:** 685/DEL/2013 9 March 2013 (09.03.2013) IN
- (71) **Applicant:** **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; S.C.O. No. 850, Shivalik Enclave, NAC Manimajra, Chandigarh-160 101 (IN).
- (72) **Inventors:** **NAIK Rajesh Vinodrai**; Ind-swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali -160 055, Punjab (IN). **SARIN Gurdeep Singh**; Ind-swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali -160 055, Punjab (IN). **JOHAR Perminder Singh**; Ind-swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali -160 055, Punjab (IN). **BANGA Manjit Singh**; Ind-swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali -160 055, Punjab (IN). **CHONGTHAM Homendra Singh**; Ind-swift Laboratories Limited, E-5, Phase II, Industrial Area, S.A.S. Nagar, Mohali -160 055, Punjab (IN).
- (74) **Agent:** **IND-SWIFT LABORATORIES LIMITED**; AG-GARWAL Asha, E-5, Phase II, Industrial Area, Mohali -160 055, Punjab (IN).
- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

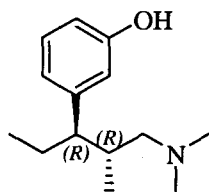
Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

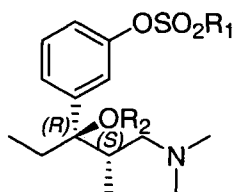
Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) **Title:** PROCESS FOR THE PREPARATION OF TAPENTADOL VIA NOVEL INTERMEDIATE



Formula I



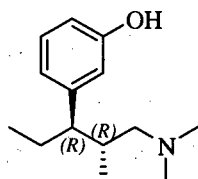
Formula III

(57) **Abstract:** The present invention relates to a commercially viable and improved process for preparation of tapentadol of formula I and its pharmaceutically acceptable salts, Formula I via novel intermediates tertiary hydroxy protected sulfonyl compound of formula III. Formula III wherein R_1 is selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl which can be substituted or unsubstituted; and R_2 represents CH_3-CO- , CF_3-CO- , CH_2ClCO- , $CHCl_2-CO-$, CCl_3-CO- , $CH_3O-CO-CO-$, CH_3O-CO- , CH_3CH_2O-CO- , $CH_3CH_2O-CO-CO-$, phenyl- $CO-$, or meta- CH_3COO -phenyl- $CO-$ or $-SO_2R'$; wherein R' can be selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and like which can be substituted or unsubstituted.

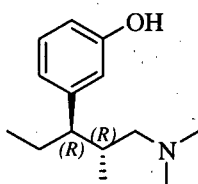


TITLE OF THE INVENTION**"Process for the preparation of Tapentadol via novel intermediate "****FIELD OF THE INVENTION**

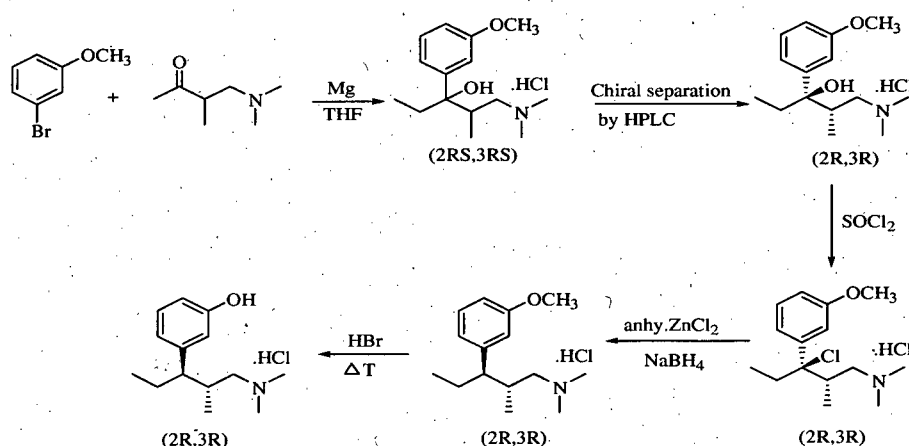
The present invention relates to a commercially viable and improved process for preparation of tapentadol of formula I and its pharmaceutically acceptable salts via novel intermediate.

**Formula I****BACKGROUND OF THE INVENTION**

Tapentadol of formula I, a centrally-acting analgesic compound, is chemically known as 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol and marketed in the form of hydrochloride salt under the trade name Nucynta.

**Formula I**

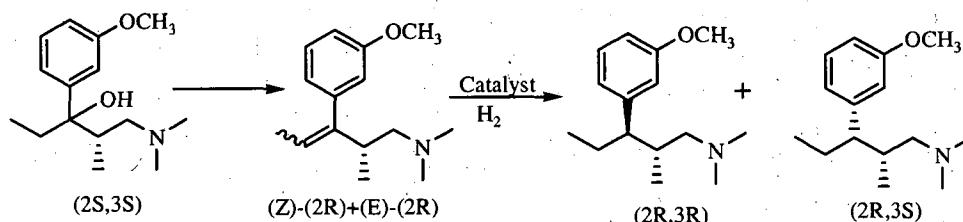
10 Tapentadol and its analogues were first disclosed in US patent USRE 39,593 herein referred as US '593 (reissue of US patent 6,248,737). According to the process disclosed in this patent, tapentadol is prepared as shown in below scheme:



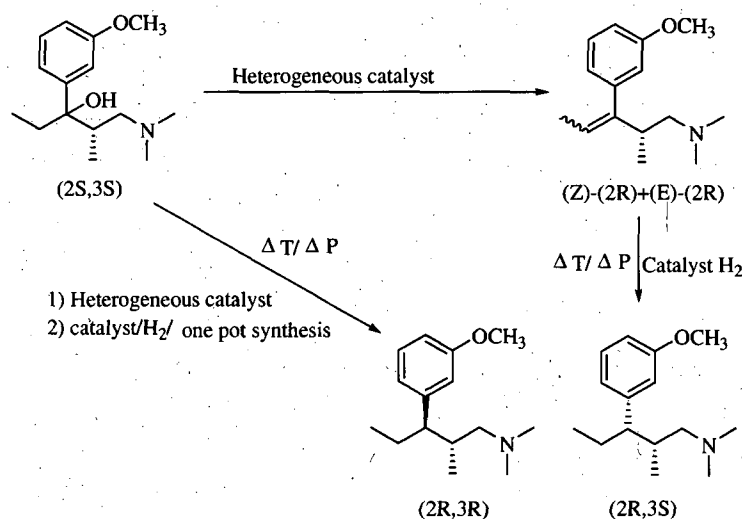
15 Process involves reacting 3-bromoanisole with 1-dimethylamino-2-methylpentan-3-one to form racemic tertiary alcohol intermediate, which is then resolved by chiral HPLC. The resolved intermediate is then converted into corresponding chloride compound using excess of thionyl chloride, followed by reduction with zinc borohydride, zinc cyanoborohydride or tin

cyanoborohydride and then finally transformed into tapentadol by demethylation using hydrobromic acid. The main disadvantage of this process is that resolution is performed by using chiral HPLC, chloro compound is prepared by using excess amount of thionyl chloride, which is considered to be a violent agent. Further reducing agents zinc borohydride, zinc cyanoborohydride or tin cyanoborohydride pose considerable fire and health hazards, so not amenable for industrial level synthesis.

US patent 7,417,170 herein referred as US '170 discloses a process for the preparation of racemic 3-(3-methoxyphenyl)-N,N-2-trimethylpentenamine, an intermediate of tapentadol by the reaction of (2S,3S)-1-(dimethylamino)-3-(3-methoxyphenyl)-2-methyl-3-pentanol with an acid to form a mixture of cis and trans isomer of alkene intermediate, the resulting mixture is then hydrogenated to form a mixture of (2R,3R) (2R,3S)-3-(3-methoxyphenyl)-N,N-2-trimethylpentanamine as

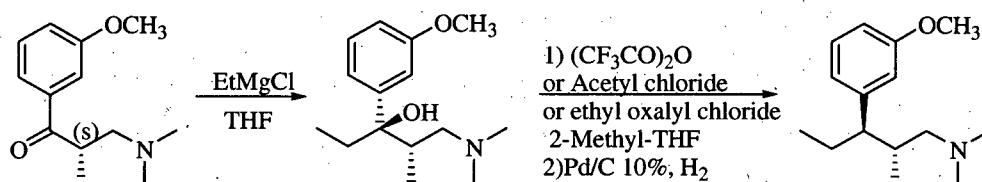


US patent publication 2006/0167318 herein referred as US '318 discloses a process for preparation of racemic 3-(3-methoxyphenyl)-N,N-2-trimethylpent- enamine, an intermediate of tapentadol, by dehydrating corresponding (2S,3S) tertiary alcohol intermediate, followed by reduction of resulting alkene intermediate using heterogeneous catalyst to form a mixture of (2R,3R) and (2R,3S)-3-(3-methoxyphenyl)-N,N-2-trimethylpentanamine as outlined below:



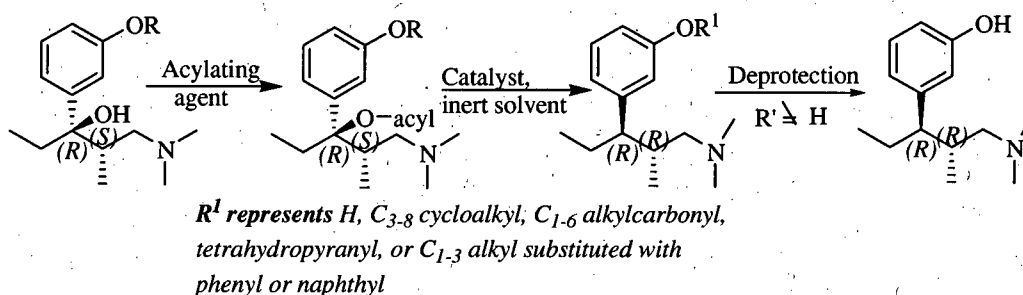
In both the above disclosures [US'170 and US'318], the undesired (2R,3S) stereoisomer forms in substantial amount and has to be separated from mixture of two isomers to obtain pure desired (2R,3R) stereoisomer. Further undesired isomer has to be disposed of as chemical waste, resulting in low yields, which is economically undesirable for any industrial scale production.

US patent 8,138,376 discloses a process for the preparation of (2R,3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentanamine, an intermediate of tapentadol, by treating corresponding tertiary alcohol intermediate with ethyl oxalyl chloride or trifluoro acetic acid anhydride, then converted to (2R,3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentanamine or its acid addition salts as outlined below:



This patent is silent about further conversion to tapentadol, may be converted by known processes.

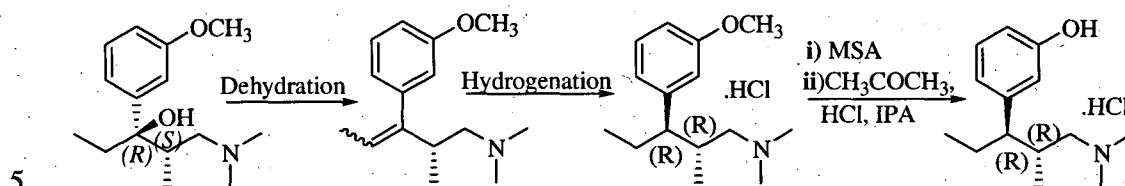
US patent 8,263,809 discloses a process for preparation of (2R,3R)-[3-acyl-3-(3-hydroxy protected-phenyl)-2-methyl-pentyl]-dimethyl-amine, an intermediate of tapentadol, by treating tertiary alcohol intermediate with acylating agent, then converted the resulting compound into tapentadol free base or its acid addition salts as outlined below:



US patent publication 2009/0043132 discloses a process for preparation of (E/Z)-[3-(3-substituted-phenyl)-2-methyl-pent-3-enyl]-dimethyl-amine, an intermediate of tapentadol, by dehydrating tertiary alcohol intermediate, followed by reduction of (E/Z) alkene intermediate, using homogeneous catalyst and chiral ligand. This process yield product in which undesired compound is present in higher ratio.

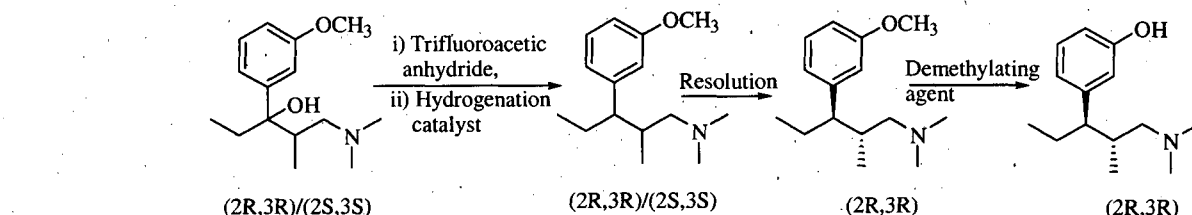
US patent publication 2010/0099916 discloses a process for the preparation of tapentadol hydrochloride comprising racemic 3-(3-methoxyphenyl)-N,N,2-trimethylpentanamine, an

intermediate of tapentadol, prepared by dehydrating corresponding (2S,3R) tertiary alcohol intermediate, followed by hydrogenation of alkene intermediate and finally it converts into tapentadol hydrochloride by demethylation using methanesulfonic acid and methionine as outlined below:



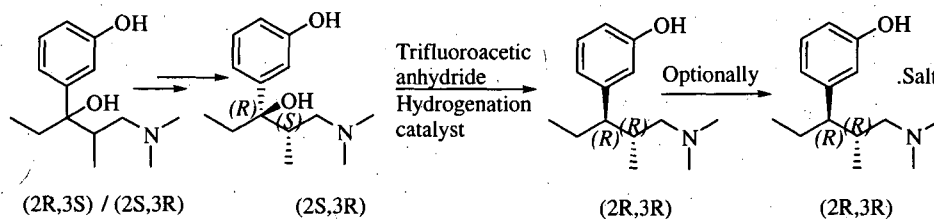
This process may generate methylmethanesulfonate using methanesulfonic acid during demethylation, reaction, which is carcinogenic and its formation should be avoided. Therefore, above process is not an attractive option for industrial scale synthesis.

PCT publication WO 2011/107876 discloses preparation of tapentadol through racemic [3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amine, an intermediate of tapentadol, prepared by acylating corresponding racemic tertiary alcohol intermediate, followed by hydrogenation and then resolution of resulting compound to achieve desired isomer and finally demethylation to give tapentadol as outlined below:



15 In this process, chances of complete conversion of undesired isomer into desired isomer are less because of non-availability of acidic protons on carbon and hence undesired isomer remains in higher amounts.

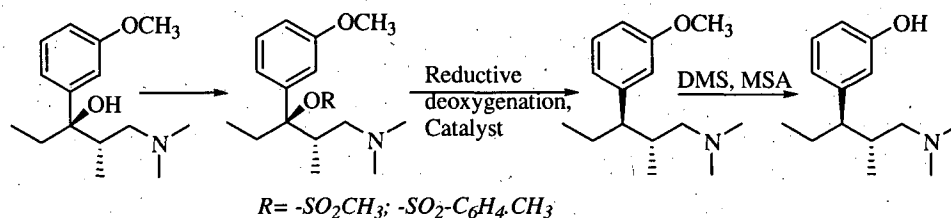
PCT publication WO2011/128784 discloses a preparation of tapentadol comprising resolution of tertiary alcohol tapentadol derivative followed by separation of desired isomer and converting desired (2R,3R) tertiary alcohol tapentadol derivative into tapentadol or its salt thereof as shown below:



Major drawback of above process is that it involves resolution step after Grignard reaction. If resolution is carried out at dihydroxy compound as in above scheme, then desired isomer is

obtained in very low yield because undesired isomer cannot be converted into desired isomer completely because of non-availability of acidic protons and hence yields are less. Further two free hydroxy groups are available at acylation stage and it is very difficult to acylate selectively only one hydroxy group, so this may require double amount or excess of acylating agent, which is additional burden and hence amounts to more cost.

PCT publication WO2012/023147 discloses a process of preparation of tapentadol comprising of activating hydroxyl group of 1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol by using methanesulfonic acid or methylbenzene sulfonic acid in the presence of mineral acid, followed by reductive deoxygenation of resulting compound to afford [3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethyl-amine and converting it into tapentadol by demethylating using methanesulfonic acid and dimethyl sulfide as outlined below:



This disclosure is silent about purity/chiral purity, no where it is mentioned, how much undesired isomer is present is not clear, therefore to achieve desired purity, additional purification steps are required. Further chances of formation of carcinogenic impurities makes the process unappealing as per regulatory requirements.

PCT publication WO2012/038974 discloses a process of preparation of tapentadol comprising racemic 3-(3-methoxyphenyl)-*N,N*-2-trimethylpentenamine, an intermediate of tapentadol, prepared by dehydrating corresponding (2*S*,3*R*)-tertiary alcohol intermediate, followed by hydrogenation of resulting alkene intermediate and converting into tapentadol hydrochloride.

In view of the above, most of the disclosures use hydrobromic acid or methanesulfonic acid for demethylation. Hydrobromic acid is a corrosive liquid and can cause irritation to body tissues, respiratory tract and eyes; and methane sulfonic acid may generate carcinogenic impurities. So, there is an urgent need to develop a cost effective, commercially viable and improved process for synthesis of tapentadol, wherein use of corrosive reagents has been avoided. Thus, present invention provides an industrially advantageous process for preparing tapentadol of formula I and its pharmaceutically acceptable salts using novel intermediates.

OBJECT OF THE INVENTION

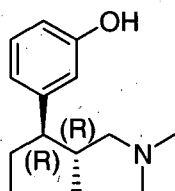
The main object of the present invention is to provide a commercially viable and improved process for the preparation of tapentadol and pharmaceutically acceptable salts thereof using novel intermediate.

Another object of the present invention is to provide novel intermediate including its isomers, stereoisomers, enantiomers, diastereomers, racemates, solvates, hydrates or pharmaceutically acceptable salts thereof

Yet another object of the present invention is to provide a process for preparation of novel intermediate which is useful in the preparation of tapentadol and pharmaceutically acceptable salts thereof.

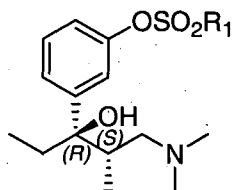
10. SUMMARY OF THE INVENTION

Accordingly, the present invention provides a commercially viable and improved process for preparation of tapentadol of formula I and pharmaceutically acceptable salts thereof



Formula I

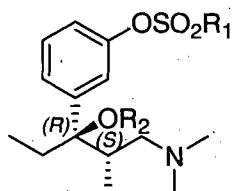
from tertiary hydroxy sulfonyl compound of formula II or its salts,



Formula II

wherein R_1 represents hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and the like which can be substituted or unsubstituted

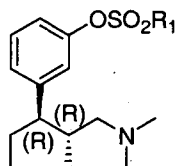
via tertiary hydroxy protected sulfonyl compound of formula III.



Formula III

wherein R_1 is same as above and R_2 represents CH_3-CO- , CF_3-CO- , CH_2ClCO- , $CHCl_2-CO-$, CCl_3-CO- , $CH_3O-CO-CO-$, CH_3O-CO- , CH_3CH_2O-CO- , $CH_3CH_2O-CO-CO-$, phenyl-CO-, or meta- CH_3COO -phenyl- CO- or $-SO_2R'$; wherein R' can be selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and like which can be substituted or unsubstituted.

According to one other embodiment, the present invention provides a process for converting tertiary hydroxy protected sulfonyl compound of formula III or its salts into sulfonyl protected compound of formula IV or its salts,



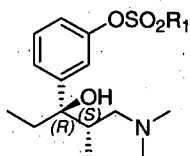
Formula IV

wherein R_1 is same as above

- 5 According to one other embodiment, the present invention provides a process for converting tertiary hydroxy protected sulfonyl compound of formula III into tapentadol compound of formula I or pharmaceutically acceptable salt thereof.

According to one another embodiment, the present invention provides a process for the preparation of tapentadol compound of formula I or pharmaceutically acceptable salt thereof
10 comprises:

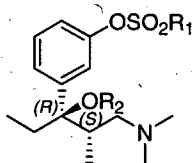
- a) activating tertiary hydroxy sulfonyl compound of formula II,



Formula II

wherein R_1 is same as above

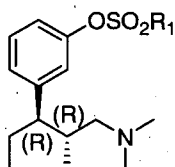
using a suitable activating agent in an organic solvent to give a tertiary hydroxy protected sulfonyl compound of formula III,



Formula III

wherein R_1 and R_2 are same as above

- 15 b.) hydrogenating the tertiary hydroxy protected sulfonyl compound of formula III in the presence of a suitable hydrogenating catalyst and suitable solvents or mixture of solvents to give a sulfonyl protected compound of formula IV,



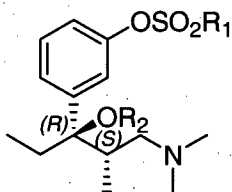
Formula IV

c.) deprotecting the resulting sulfonyl protected compound of formula IV using a suitable deprotecting reagent to give tapentadol of formula I,

d.) optionally converting tapentadol into its pharmaceutically acceptable salts.

According to one another embodiment, the present invention provides a novel intermediate,

5 tertiary hydroxy protected sulfonyl compound of formula III



Formula III

wherein R_1 and R_2 are same as above.

including its isomers, stereoisomers, enantiomers, diastereomers, racemates, solvates, hydrates or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention provides a commercially viable and improved process for the preparation of tapentadol and pharmaceutically acceptable salts thereof. According to one embodiment, the present invention provides a process for the preparation of tapentadol or pharmaceutically acceptable salts thereof via a novel intermediate, tertiary hydroxy protected sulfonyl compound of formula III. The tertiary hydroxy protected sulfonyl compound of formula III is prepared

15 starting from the corresponding tertiary hydroxy sulfonyl compound of formula II, wherein R_1 can be selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and the like which can be substituted or unsubstituted. The tertiary hydroxy sulfonyl compound of formula II, as used herein includes its pure stereoisomers, enantiomers, diastereomers, or racemates, or mixture of stereoisomers, mixture of enantiomers,

20 and mixture of diastereomers in any ratio, as salts, as solvates and as hydrates thereof. The tertiary hydroxy sulfonyl compound of formula II can be prepared by methods known in the art or by following the process as disclosed in PCT publication WO2012/038974. Typically, the process involves reaction of starting material, 1-(3-hydroxy-phenyl)-propan-1-one with a suitable sulfonyl compound in the presence of base to protect hydroxy group with suitable substituted sulfonyl group. Thereafter, the resulting substituted sulfonyl compound undergoes

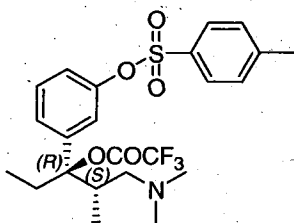
25 amino methylation using a suitable amino methylating reagent which includes, but is not limited to formaldehyde and dimethyl amine or N-methyl-N-methylenemethane ammonium halide and acetyl halide. The resulting compound can be used as such for further reaction or

can be first resolved to form a specific desired enantiomer by using a suitable resolving reagent, preferably L-dibenzoyl tartaric acid. The chiral salt is optionally purified and hydrolyzed using a base to give the corresponding pure desired diastereomer of corresponding sulfonyl amino compound, followed by reaction with an ethyl anion under strictly anhydrous reaction conditions to provide desired corresponding tertiary hydroxy sulfonyl compound of formula II. The ethyl anion can be added via an ethyllithium or ethylmagnesium halide, diethylzinc or any other organometallic reagent equivalent to EtMX, wherein M is a suitable metal and X is a suitable ligand. The addition of the ethyl anion in this reaction introduces a second asymmetric carbon atom, so tertiary hydroxy sulfonyl compound of formula II prepared by the process may be contaminated with specific diastereomers such as (R)(R), (R)(S), (S)(S), (S)(R) or mixture of two or more in any proportion.

According to one another embodiment of the present invention, tertiary hydroxy sulfonyl compound of formula II can be activated by converting tertiary hydroxy group to better leaving group and thus forming tertiary hydroxy protected sulfonyl compound of formula III. The activation can be executed via acylation or sulfonylation reaction. Generally, tertiary hydroxy sulfonyl compound of formula II is treated with a suitable activating agent in a suitable solvent at suitable temperature ranging from 0°C to reflux temperature of solvent, preferably at 0-65°C, more preferably at 0-50°C for sufficient time, selected from for few minutes to few hours, preferably till the completion of the reaction. A suitable activating agent can be an acylating agent or a sulfonylating agent. The acylating reagent used for the reaction can be selected from acetic anhydride, acetyl chloride, trifluoroacetic anhydride, pentafluoropropionic anhydride, heptafluorobutyric anhydride, chloroacetic anhydride, chloroacetylchloride, dichloroacetic anhydride, trichloroacetic anhydride, methyloxalyl chloride, ethyl oxalyl chloride, methylchloroformate, ethyl chloroformate, benzoic anhydride, benzoyl anhydride, benzoyl chloride, or acetylsalicyloyl chloride or any other suitable acylating agent which subsequently introduces the acyl group at position of tertiary hydroxy group of compound of formula II thereby activating the tertiary hydroxy group of compound of formula II. Particularly, acylating reagent used for reaction can be selected from acetic anhydride, acetyl chloride, trifluoroacetic anhydride and alike. The sulfonylating reagent used for the reaction can be selected from alkyl or arylsulfonyl halides or anhydrides and includes but not limited to methane sulfonyl chloride, p-toluene sulfonyl chloride, methane sulfonic anhydride, toluene sulfonic anhydride etc.

The solvent used in the reaction can be selected from solvents such as C₄₋₁₂ ethers, C₅₋₁₀ aliphatic hydrocarbons, C₆₋₁₀ aromatic hydrocarbons, halogenated hydrocarbons, C₃₋₇ ketones, C₃₋₁₀ ester aliphatic nitrile, polar aprotic solvent and mixture thereof. Particularly, solvent can be selected from tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, isopropyl ether, methyl tert-butyl ether, 1,4-dioxane, methyl cyclopentyl ether, acetonitrile, dichloromethane, dimethylacetamide, dimethylformamide, dimethylsulfoxide or mixtures thereof. Optionally the reaction can be carried out with or without base. If desired base is selected from organic base having general formula NR¹R²R³, wherein R¹, R² and R³ can be independently selected from hydrogen, alkyl, alkaryl or arylalkyl. Particularly organic base can be trialkyl amine such as triethylamine and etc.

In other embodiment, the tertiary hydroxy protected sulfonyl compound of formula III can optionally be isolated or can be proceeded further without isolation for next reaction. Preferably, the tertiary hydroxy protected sulfonyl compound of formula III may be isolated by aqueous or non-aqueous workup. The tertiary hydroxy protected sulfonyl compound of formula III forms a inventive part of present invention wherein R₁ can be selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and the like which can be substituted or unsubstituted preferably sulfonyl group substituents. R₂ represents CH₃-CO-, CF₃-CO-, CH₂ClCO-, CHCl₂-CO-, CCl₃-CO-, CH₃O-CO-CO-, CH₃O-CO-, CH₃CH₂O-CO-, CH₃CH₂O-CO-CO-, phenyl-CO-, or meta-CH₃COO-phenyl-CO- or -SO₂R'; wherein R' can be selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and like which can be substituted or unsubstituted. When R₁ is para-methyl phenyl group and R₂ is trifluoromethyl then it forms the preferred embodiment of invention and represents the tertiary hydroxy protected sulfonyl compound of formula IIIa.



Formula IIIa

The tertiary hydroxy protected sulfonyl compound of formula III or IIIa as prepared herein, includes its pure stereoisomer, enantiomer, diastereomer, or racemates, or mixture of stereoisomer, mixture of enantiomer, and mixture of diastereomer in any ratio, as salts, as solvates, and as hydrates thereof.

- 5 In one another embodiment the tertiary hydroxy protected sulfonyl compound of formula III as obtained above, is converted into compound of formula I or its pharmaceutically acceptable salt thereof.

In one other embodiment the tertiary hydroxy protected sulfonyl compound of formula III is converted to sulfonyl protected compound of formula IV by hydrogenolysis or its salts
10 followed by deprotection of sulfonyl group substituents resulting in preparation of tapentadol of formula I or its pharmaceutically acceptable salt thereof. Generally hydrogenolysis can be carried out using a suitable catalyst in the presence of an inert solvent under hydrogen pressure or in the presence of hydrogen transfer reagent.

The suitable catalyst used for hydrogenolysis includes but is not limited to palladium, Raney
15 nickel, platinum, ruthenium or rhodium catalysts. The preferred catalyst can be palladium catalyst which may be selected from homogenous catalyst such as Pd(OAc)₂, PdCl₂, Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd₂(dba)₃ (tris(dibenzylidene acetone) dipalladium), palladium thiomethylphenyl- glutaramide metallacycle and the like, or a heterogeneous catalyst like
20 palladium, palladium on charcoal, palladium hydroxides on charcoal, palladium on metal oxides, palladium on zeolites, palladium on alumina,; or platinum catalyst like platinum on carbon and platinum on alumina or lithium aluminium hydride, sodium borohydride or like and with or without additives. Percentage of palladium metal in the catalyst can vary from 0.1%-50%, preferably it can be between 2-30%. Further the catalyst can be wet or dry and water content can vary between 0.05% to 75%w/w, preferably it is desired between 0.05% to
25 60%w/w.

The solvent used for hydrogenolysis reaction can be selected from C₄₋₁₂ ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, 1,2-dimethyl ether, 1,2-diethyl ether or C₃₋₁₂ ester such as ethyl acetate; C₃₋₁₀ aliphatic ketone such as acetone, methyl ethyl ketone; C₆₋₁₂ hydrocarbon such as toluene, xylene, hexane, heptane, cyclohexane and the like; halogenated
30 solvent such as dichloromethane, 1,2-dichloroethane; aliphatic nitriles such as acetonitrile, propionitrile and the like or mixture thereof. Particularly, solvent can be selected from tetrahydrofuran, 2-methyl tetrahydrofuran 1,2-dimethyl ether, 1,2-diethyl ether or mixtures

thereof. The hydrogenolysis can be accomplished at a temperature of 0 °C to reflux temperature of solvent for few minutes to few hours, preferably till the complete hydrogenolysis takes place. Preferably hydrogenolysis reaction can be carried out at a temperature of 30-70 °C for 8-16 hours. The sulfonyl protected compound of formula IV, can be isolated by aqueous or non-aqueous workup and if desired, can be purified by using suitable solvents or mixture of solvents or by forming acid addition salt of sulfonyl protected compound of formula IV or by using extraction method comprising suitable solvent and aqueous carbonate or any other purification method can be employed to enhance the purity or to reduce the amount of impurity in the product. The suitable solvents used in extraction can be selected from C₄₋₁₂ ether, C₆₋₁₂ aromatic or aliphatic hydrocarbon or halogenated hydrocarbon and alike or mixture thereof. Particularly solvent can be selected from tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, isopropyl ether, methyl tert-butyl ether, 1,4-dioxane, methyl cyclopentyl ether or mixtures thereof and the aqueous carbonate can be selected from sodium bicarbonate, sodium carbonate, potassium carbonate, potassium bicarbonate or alike.

The sulfonyl protected compound of formula IV can be reacted with a suitable acid to form a salt, which upon filtration followed by neutralization to obtain a purified sulfonyl protected compound of formula IV or its salt can be directly used for further reaction. The acids used for the salt formation can be selected from achiral acids which includes inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid; organic acids such as formic acid, acetic acid, oxalic acid and the like or chiral acids such as camphor sulfonic acid, mandelic acid, substituted or unsubstituted tartaric acid, L-dibenzoyl tartaric and the like. Solvent for salt formation can be selected from water, aliphatic alcohols, aliphatic ethers, aliphatic esters, nitriles, aliphatic or aromatic hydrocarbon, ketones, halogenated solvent and or mixture thereof. The sulfonyl protected compound of formula IV as prepared herein includes its pure stereoisomer, enantiomer, diastereomer, or racemates, or mixture of stereoisomers, mixture of enantiomers, and mixture of diastereomers in any ratio, as salts, as solvates, and as hydrates thereof. Alternatively, the sulfonyl protected compound of formula IV or salts thereof can be purified by crystallization or stirring in a suitable solvent.

In one another embodiment the sulfonyl protected compound of formula IV is converted into tapentadol of compound of formula I via deprotection of sulfonyl group substituents such as hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and the like which can be substituted or unsubstituted and thus obtained the tapentadol of formula I.

The deprotection of sulfonyl group can be proceeded using methods known in the art or by following the process as disclosed in PCT publication WO2012/038974.

Generally, the process involves reaction of sulfonyl protected compound of formula IV with a suitable deprotecting reagent at a temperature of -10 to 180 °C for 48 hours. Deprotection

5 reaction involves the removal of $-SO_2R_1$ group by any suitable reagent known for the deprotection of hydroxyl protecting group depending upon the nature of protecting group that effectively serves the purpose and are well known in the field of organic synthesis. Preferably deprotection reaction can be carried in the presence of a suitable base. Suitable bases employed for the reaction can be organic or inorganic base. Organic base used for the reaction can be
10 selected from amine such as triethylamine, diisopropylethylamine, and the like. Inorganic base that can be selected from alkali or alkaline metal hydroxide, carbonates, bicarbonates, hydrides or alkoxides thereof such as sodium carbonate, lithium carbonate, potassium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like or combination thereof. The reaction can be
15 carried out using a suitable solvent which includes water, C_{1-8} alcohols such as methanol, ethanol, propanol, isopropanol; aliphatic or aromatic hydrocarbon solvent, C_{4-10} ethers, nitriles, C_{3-12} ketones, C_{3-12} esters, halogenated solvents, polar aprotic solvents and the like or mixture thereof. The reaction can take place over a wide range of temperature depending upon the nature of $-SO_2R_1$ group as well as on deprotecting reagent employed for the reaction. Usually
20 reaction can be carried out at 0 °C to 180°C for 1 to 48 hours, till the completion of the reaction.

In a preferred embodiment, sulfonyl protected compound of formula IV is treated with a suitable base such as sodium hydroxide in presence of a suitable solvent such as alcohol or ether to deprotect phenol functionality and forms tapentadol free base. The reaction completion at any stage can be monitored by suitable techniques such as HPLC, TLC, GC or UPLC and the
25 like. After completion of the reaction, the desired product can be isolated from the reaction mixture using suitable conventional methods or can be converted *in situ* to the next step. The resulting compound can be isolated by aqueous or non-aqueous workup.

Specifically, tapentadol of formula I can be converted to tapentadol hydrochloride using a suitable source of hydrochloric acid. The process involves the reaction of tapentadol in a
30 suitable solvent with a source of hydrochloric acid at a temperature of -20 to 80 °C for 15 minutes to several hours, preferably till the salt formation. The source of hydrochloric acid employed for the reaction can be aqueous, concentrated hydrochloric acid, gaseous hydrogen

chloride, solvent purged with hydrogen chloride gas or hydrochloric acid in a solution with a solvent or hydrochloride salts of amines. Solvent used for the generation of source of hydrochloric acid can be selected from water or C₁₋₁₀ alcohol such as methanol; C₄₋₁₀ ethers such as diethylether, isopropyl ether; C₃₋₁₀ esters such as ethyl acetate; aliphatic nitriles such as acetonitrile and the like or mixture thereof. Solvents employed for the salt formation reaction can be selected from halogenated solvent such as dichloromethane; aliphatic nitriles such as acetonitrile; ethers such as tetrahydrofuran; alcohols such as methanol; aliphatic ketones such as acetone and the like or mixture thereof. After completion of the salt formation, tapentadol hydrochloride can be isolated from reaction mixture by the suitable techniques such as solvent removal by evaporation, distillation, filtration and the like.

Compound of formula I or tapentadol or pharmaceutically acceptable salt thereof thus isolated can be purified using a suitable purification method such as crystallization, sublimation, extraction, chromatography, slurry wash, refluxing, washing, acid base treatment, carbon treatment, silica or alumina treatment. Suitable solvents employed for the purification includes but are not limited to water, alcohols such as methanol, ethanol and isopropanol, aliphatic ester such as ethyl acetate; aliphatic nitriles such as acetonitrile, aliphatic ethers such as isopropyl ether, aliphatic ketones such as acetone, aliphatic or aromatic hydrocarbon solvents, halogenated solvents and the like or mixture thereof.

Specifically, tapentadol free base can be purified to enhance the enantiomeric purity or to minimize the other impurities in final product. It can be purified by crystallization, sublimation, chromatography, extraction using suitable solvents, refluxing, slurry wash, acid base treatment, carbon treatment, silica or alumina treatment. Suitable solvents for purification includes but are not limited to water; hydrocarbons such as n-hexane, n-heptane, cyclohexane; alcohols such as methanol, ethanol and isopropanol; aliphatic ester such as ethyl acetate; aliphatic ketone such as acetone, methyl ethyl ketone; ether such as diisopropylether, methyl tert-butyl ether, tetrahydrofuran, isopropyl ether, 2-methyltetrahydrofuran, 1,4-dioxane; halogenated solvent such as dichloromethane; nitriles acetonitrile, propionitrile and the like or mixture thereof. Specifically, tapentadol hydrochloride can be purified to enhance the enantiomeric purity or to minimize the other impurities in final product. It can be purified by crystallization, extraction, slurry wash in a suitable solvent. Preferably, tapentadol hydrochloride can be stirred in a suitable solvent at a temperature of -10 to 80°C for 15 minutes to several hours. Suitable solvent for purification includes but not limited to alcohols such as methanol, ethanol and

isopropanol; aliphatic ester such as ethyl acetate; aliphatic ketone such as acetone, methyl ethyl ketone; ether such as diisopropylether, methyl tert-butyl ether, tetrahydrofuran, isopropyl ether, 2-methyl tetrahydrofuran, 1,4-dioxane; hydrocarbons such as n-hexane, n-heptane, cyclohexane and the like; halogenated solvent such as dichloromethane; nitriles such as acetonitrile, propionitrile and the like or mixture thereof. Particularly, solvents used for purification of tapentadol hydrochloride to enhance the enantiomeric purity or to minimize the other impurities in final product are selected from alcohols such as methanol, ethanol and nitriles such as acetonitrile, propionitrile or mixture thereof. Thereafter, the mixture can be cooled to a temperature of -30 °C to ambient temperature.

10 Tapentadol hydrochloride obtained by the process of present invention having high enantiomeric excess, preferably more than 99 %, more preferably 100 % e.e.

Major advantages of present invention is to provide an industrially advantageous and efficient process for preparation of highly enantiomerically pure tapentadol hydrochloride and avoiding the use of corrosive acids in the final deprotecting step to prepare tapentadol from protected tapentadol. The process of present invention is efficient, reproducible as well as industrially advantageous.

15 Having described the invention with reference to certain preferred aspects, other aspects will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail by the preparation of compounds of the invention.

20 **EXAMPLE 1: Preparation of (1R,2R)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenyl ester**

Method A: To a cooled solution of (1R,2S)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenyl ester (200g) in tetrahydrofuran (100 ml), trifluoroacetic anhydride (200g) was slowly added at 0-5 °C and the reaction mixture was stirred at 20-25 °C for 15 hours. After completion of the reaction, reaction mass was transferred to an autoclave under nitrogen gas atmosphere. A suspension of 20% of palladium/carbon (20g) and tetrahydrofuran (3.0 L) were added to the reaction mass. Hydrogen gas pressure of 5-6kg was applied to the reaction mass and the temperature was slowly raised to 50-55 °C and stirred the reaction mass at same temperature. After completion of the reaction, the mass was cooled to 20-25 °C and filtered. The filtrate was concentrated under reduced pressure at 45-50 °C to give an residue. The resulting residue was dissolved in methyl tert-butyl ether (1.0 L) and the

reaction mixture was washed with aqueous sodium bicarbonate (12%, 700 ml). The layers were separated and the aqueous layer was extracted with methyl tert-butyl ether (2 x 250 ml). The combined organic layer was dried, filtered and then distilled under reduced pressure at 35-40°C to obtain 170g of title compound.

5 **Method B:** To a cooled solution of (1R,2S)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenyl ester (200g) in tetrahydrofuran (100 ml), trifluoroacetic anhydride (200g) was slowly added at 0-5°C and the reaction mixture was stirred at 20-25°C for 15 hours. After completion of the reaction, the mass was transferred to an autoclave under nitrogen gas atmosphere. A suspension of 20% of palladium hydroxide/carbon
10 (40g, 50% water) and tetrahydrofuran (3.0L) was added to the reaction mass and hydrogen gas pressure of 5-6 kg was applied to the reaction mass. Temperature of the reaction was slowly raised to 50-55°C and further stirred till completion of the reaction. Thereafter, the reaction mass was cooled to 20-25°C and filtered. The filtrate was concentrated under reduced pressure at 45- 50°C to give an oily residue. The resulting residue was dissolved in methyl
15 tert-butyl ether (1.0 L) and washed with aqueous sodium bicarbonate solution (12%, 700ml). The layers were separated and aqueous layer was extracted with methyl tert-butyl ether (2x250 ml). The combined organic layer was dried over sodium sulfate (50 g), filtered and the organic solvent was distilled off under reduced pressure at 35-40°C to give (1R,2R)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenyl ester (175g).

20 **Example 2: Preparation of Tapentadol hydrochloride**

Method A: Step 1- Preparation of Tapentadol:

To a solution of (1R,2R)-toluene-4-sulfonic acid 3- (3-dimethylamino-1-ethyl-2-methyl-propyl)-phenyl ester (35g) in methanol (280ml), a solution of sodium hydroxide (19g, in 70ml water) was added at 5-10°C. The temperature of reaction mixture was raised to 30-35°C and
25 stirred for further 20 hours. After completion of reaction [checked by TLC], solvent was distilled off at 45-50°C, the resulting residue was washed with cyclohexane (70ml) and then extracted with ethyl acetate (350 ml). The reaction mass was cooled to 0-5°C, filtered over hyflo to remove any suspended material. The hyflo bed was washed with ethyl acetate (50 ml) and the combined filtrate was concentrated under vacuum to give an oily residue. The resulting
30 oily residue was dissolved in ethyl acetate (350 ml) and washed with water (3 x 50 ml). The organic layer was dried over sodium sulfate, filtered and solvent was distilled off to afford tapentadol as a viscous oil (20.5g).

Step 2- Preparation of Tapentadol hydrochloride:

Tapentadol (20g) was dissolved in ethyl acetate (20ml), cooled and mixed with a solution of ethyl acetate-hydrochloride (35 ml, 12%) at 0-5 °C. The resulting mixture was stirred for 1 hour, filtered and dried to give a crude tapentadol hydrochloride (15g). The resulting solid was stirred in acetonitrile (75 ml) at reflux temperature for 1 hour. The suspension was cooled to 20-25°C, stirred for 30 minutes, filtered and suck dried to give tapentadol hydrochloride (13.5g, 98.5%). The resulting tapentadol hydrochloride was further refluxed in a mixture of acetonitrile (64ml) and methanol (3.4ml) for 60 minutes. The suspension was cooled to 20-25°C, further stirred for 30 minutes, filtered and suck dried under vacuum at 75-90 °C for 24 hours to afford pure tapentadol hydrochloride as a white crystalline solid (12.7g, 99.91%, diastereomeric impurity 0.03%).

Method B Step 1- Preparation of Tapentadol:

To a solution of (1R,2R)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenyl ester (9g) in methanol (72ml), a solution of sodium hydroxide (4g) in water (18ml) was added at 20-25°C. The temperature of the reaction mixture was raised to 35-45°C, stirred further for 20 hours. After completion of the reaction, the solvent was distilled off to give a residue. Water (45 ml) was added to the resulting residue followed by extraction with dichloromethane (2 x 27ml). Layers were separated and dichloromethane layer was dried over molecular sieves, filtered through hyflo and concentrated to afford 4.24g (yield- 80%) of title compound as a viscous oil.

Step 2- Preparation of Tapentadol hydrochloride:

The resulting tapentadol was dissolved in ethylacetate (10ml) and cooled to 0-5°C and mixed with a solution of ethyl acetate-hydrochloride (1.7ml, 12%) at 0-5°C and stirred for further 1 hour. Thereafter reaction mixture was filtered to obtain tapentadol hydrochloride (3.0g). A slurry of tapentadol hydrochloride (3.0g) in acetonitrile (15ml) was refluxed at 75-80 °C for 1 hour, cooled to 20-25°C and stirred for 30 minutes, filtered and dried to afford tapentadol hydrochloride (2.7g, 98.7% by HPLC). Again a slurry of crude tapentadol hydrochloride (2.7g) in acetonitrile (12.8ml) was refluxed for 1 hour. The suspension was cooled to 20-25°C, stirred for 30 minutes, filtered and dried under vacuum at 75-90 °C for 24 hours to afford pure tapentadol hydrochloride as a solid (2.5g, 99.84%, diastereomeric impurity 0.10%).

EXAMPLE 03: Preparation of highly pure Tapentadol hydrochloride

Method A: Step 1: Preparation of (1R,2R)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenyl ester :

Trifluoroacetic anhydride (200g) was slowly added to a cooled solution of (1R,2S)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenyl ester (200g) in tetrahydrofuran (100 ml) and the reaction mass was stirred for 15 hours at 20-25°C. After completion of reaction, reaction mass was transferred to an autoclave under nitrogen gas atmosphere. A suspension of 20% palladium hydroxide/carbon (40g, 50% water) and tetrahydrofuran (3.0 L) was added to the reaction mass and hydrogen gas pressure of 5-6 kg was applied. The temperature of reaction mixture was raised to 50-55 °C, after completion of the reaction, the mass was cooled to 20-25 °C and filtered. The filtrate was concentrated and resulting residue was dissolved in methyl tert-butyl ether (1.0L) and treated with aqueous sodium carbonate (10%, 300 ml). The layers were separated, the aqueous layer was extracted with methyl tert-butyl ether (2 x 250 ml) and the combined organic layer was dried over molecular sieve (20 g), filtered and distilled at 35-40 °C to give 188g of title compound.

Step 2- Preparation of Tapentadol hydrochloride :

To the above compound (188g) in methanol (1.5L), a solution of sodium hydroxide (100g) and water (376 ml) was added at 5-10 °C and temperature of reaction mass was slowly raised to 30-35°C. After completion of reaction, solvent was distilled off at 45-50°C and the resulting residue was dissolved in ethyl acetate (1.9L) and then slowly cooled the reaction mass to 0-5°C and stirred it for 30 minutes. The reaction mass was filtered over hyflo and the filtrate was washed with water (3 x 270 ml), stirred with activated charcoal (10g), dried over molecular sieves (3A, 30g) and filtered. Then approx 50% of ethyl acetate was distilled off and the reaction mixture was cooled to 5-10 °C and mixed with a solution of ethyl acetate-hydrochloride (198 ml, 12%) at 0-5 °C, stirred for 1 hour and filtered to give tapentadol hydrochloride (86g, 93.3% by HPLC). The resulting tapentadol hydrochloride (81g) was suspended in acetonitrile (405 ml) and the suspension was refluxed for 90 minutes. The suspension was then cooled to 25-30 °C, stirred for 60 minutes, filtered, washed with acetonitrile (40 ml) and dried to obtain title compound (30g , 99.88%, diastereomeric impurity 0.08%).

Step 3- Preparation of highly pure Tapentadol hydrochloride:

Tapentadol hydrochloride (30g, 99.88%, diastereomeric impurity 0.08%) obtained above, was suspended in acetonitrile (150 ml) and methanol (7 ml) and suspension was refluxed for 1

hour. The suspension was then cooled to 25-30°C, stirred for 60 minutes, filtered and dried. The solid was then refluxed in ethyl acetate (120 ml) for 30 minutes and cooled to 0-5°C, stirred for further 30 minutes, filtered and dried at 75-90°C for 48 hours to afford pure tapentadol hydrochloride as solid (26.4g, 99.96%, diastereomeric impurity 0.02%).

5 **Method B: Step 1-Preparation of (1R,2R)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenyl ester :**

To a cooled solution of (1R,2S)-toluene-4-sulfonic acid 3-(3-dimethylamino-1-ethyl-1-hydroxy-2-methyl-propyl)-phenyl ester (100g) in trifluoroacetic anhydride (150g) was slowly added at 0-5°C and the reaction mass was stirred for 18 hours at 20-25 °C. After completion
10 of the reaction the reaction mass was then subjected to heating under vacuum for 4 hours till most of the volatiles was evaporated [removal of in-situ generated trifluoroacetic acid and excess of unreacted trifluoroacetic anhydride]. The reaction mass was then diluted with tetrahydrofuran (500ml) and after complete dissolution, the reaction mass was transferred to an autoclave, under inert atmosphere and 20% palladium hydroxide/carbon (20g, 50% water) and
15 tetrahydrofuran (1L) were successively added to the reaction mass. Nitrogen was replaced by hydrogen gas and pressure of 5-6 Kg was applied to the reaction mass. The temperature was slowly raised to 50-55°C and stirred the reaction mass at same temperature. After completion of reaction, the reaction mass was cooled to 20-25°C, filtered and the filtered catalyst was washed with tetrahydrofuran (100ml). Solvent was then distilled off at 45-50°C to produce an
20 oily residue and dissolved in methyl tertiary-butyl ether (500ml) and washed with aqueous sodium carbonate (20%, 250ml). The layers were separated, the aqueous layer was extracted with methyl tertiary-butyl ether (300ml) and the combined organic layer was dried over molecular sieve, filtered and then distilled at 35-40°C to give 82g of title compound.

Step 2- Preparation of Tapentadol hydrochloride :

25 To the above compound (82g) in methanol (820 ml), a solution of sodium hydroxide (43.7g) and water (164ml) was added at 5-10°C and the temperature of the reaction mass was slowly raised to 30-35°C. The reaction mass was stirred at that temperature for 20 hours and then at 45-50°C for 6 hours. After completion of the reaction, the solvent was distilled off under vacuum at 45-50°C and the resulting residue was then dissolved in ethyl acetate (300 ml) and
30 then distilled and degas at 50-60°C . Ethyl acetate (820ml) was then added and the reaction mass was washed with demineralized water (164ml), the layers were separated and the aqueous layer was washed with ethyl acetate (2 x 246 ml) and the combined organic layer was

again washed with demineralized water (3 x 164ml) and filtered. The solvent was then distilled under vacuum at 50-60°C to give 45g of tapentadol free base as an oil. Tapentadol was dissolved in acetonitrile (54ml) and cooled to 0-5°C and stirred. acetonitrile-hydrochloride (68.6ml, 12%) was then added to the reaction mass at 0-5°C. The temperature of the reaction was slowly raised to 25-30°C and then reaction mass was stirred for 2 hrs at 25-30 °C. The reaction mass was then cooled to 0-5 °C, stirred for 1 hour. The resulting solid was filtered, washed with acetonitrile (10ml) and resulting compound was suspended in acetonitrile (225 ml) and heated at reflux temperature for 60 minutes. The suspension was then cooled to 25-30°C, stirred for 60 minutes, filtered, washed with acetonitrile (45ml) and suck dried for 60 minutes to give title compound (40g).

Step 3- Preparation of highly pure Tapentadol hydrochloride:

Tapentadol hydrochloride (45g) obtained above, was suspended in mixture of acetonitrile (190ml) and methanol (10ml), the suspension was refluxed for 1hour and cooled to 25-30°C, stirred for 60 min, filtered washed with acetonitrile (40ml) to give 37g of solid tapentadol hydrochloride. The resulting tapentadol hydrochloride (37g) again purified in acetonitrile (175.75 ml) and methanol (9.25 ml), the suspension was refluxed for 1hour, cooled to 25-30°C, stirred for 60 minutes, filtered and washed with acetonitrile (37ml) and dried under vacuum at 65-70 °C for 24 hours to afford pure tapentadol hydrochloride as a crystalline solid (32g , 99.9%, diastereomeric impurity 0.04%).

20

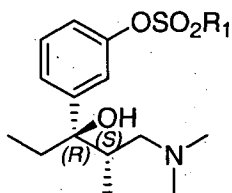
25

30

WE CLAIM:

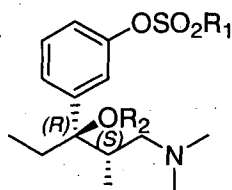
1. A process for the preparation of tapentadol of formula I and pharmaceutically acceptable salts thereof comprising the steps of :

a.) activating tertiary hydroxy sulfonyl compound of formula II,

**Formula II**

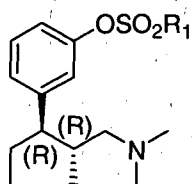
5 wherein R_1 represents hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, which is substituted or unsubstituted;

using a suitable activating agent in an organic solvent, optionally in the presence of a base to give a tertiary hydroxy protected sulfonyl compound of formula III,

**Formula III**

10 wherein R_1 is same as defined above and R_2 represents CH_3-CO- , CF_3-CO- , CH_2ClCO- , $CHCl_2-CO-$, CCl_3-CO- , $CH_3O-CO-CO-$, CH_3O-CO- , CH_3CH_2O-CO- , $CH_3CH_2O-CO-CO-$, phenyl- $CO-$, or meta- CH_3COO -phenyl- $CO-$ or $-SO_2R'$; wherein R' is selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl and like; which is substituted or unsubstituted

15 b.) hydrogenating tertiary hydroxy protected sulfonyl compound of formula III in the presence of a suitable hydrogenating catalyst in a suitable solvent to prepare sulfonyl protected compound of formula IV,

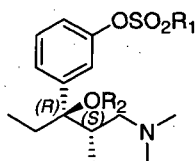
**Formula IV**

wherein R_1 is same as defined above

c.) deprotecting the resulting sulfonyl protected compound of formula IV using a suitable deprotecting reagent to give tapentadol of formula I,

20 d.) optionally converting tapentadol into its pharmaceutically acceptable salt.

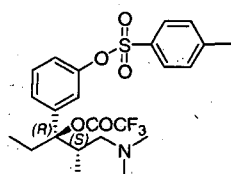
2. The process as claimed in claim 1, wherein in step a) activating agent is an acylating agent or sulfonylating agent selected from acetic anhydride, acetyl chloride, trifluoroacetic anhydride, pentafluoropropionic anhydride, chloroacetic anhydride, chloroacetylchloride, dichloroacetic anhydride, trichloroacetic anhydride, methyloxalyl chloride, ethyloxalyl chloride, methylchloroformate, ethylchloroformate, benzoicanhydride, benzoylanhydride, benzoyl chloride, or acetylsalicyloyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride, methanesulfonic anhydride, toluenesulfonic anhydride.
3. The process as claimed in claim 1, wherein in step a) solvent is selected from C₄₋₁₂ ethers, C₅₋₁₀ aliphatic hydrocarbons, C₆₋₁₀ aromatic hydrocarbons, halogenated hydrocarbons, C₃₋₇ ketones, C₃₋₁₀ ester aliphatic nitrile, polar aprotic solvent and mixture thereof.
4. The process as claimed in claim 1, wherein in step a) base is organic base.
5. The process as claimed in claim 1, wherein in step b) suitable hydrogenating catalyst is selected from palladium, Raney nickel, platinum, ruthenium or rhodium catalysts; lithium aluminium hydride, sodium borohydride and with or without additives; solvent used for hydrogenolysis reaction is selected from C₄₋₁₂ ethers, C₃₋₁₂ ester, C₃₋₁₀ aliphatic ketone, C₆₋₁₂ hydrocarbon, halogenated solvent, aliphatic nitriles and the like or mixture thereof.
6. The process as claimed in claim 1, wherein in step c.) suitable deprotecting reagent is selected from an organic base or an inorganic base.
7. A tertiary hydroxy protected sulfonyl compound of formula III,



Formula III

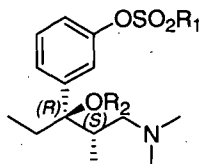
wherein R_1 represents hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, which is substituted or unsubstituted; and R_2 represents CH_3-CO- , CF_3-CO- , CH_2ClCO- , $CHCl_2-CO-$, CCl_3-CO- , $CH_3O-CO-CO-$, CH_3O-CO- , CH_3CH_2O-CO- , $CH_3CH_2O-CO-CO-$, phenyl- $CO-$, or meta- CH_3COO -phenyl- $CO-$ or $-SO_2R'$; wherein R' is selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl.

8. The hydroxy protected sulfonyl compound of formula III as claimed in claim 7, is IIIa,



Formula IIIa

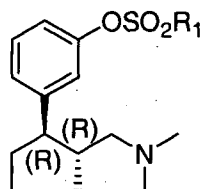
9. A process for the preparation of tapentadol of formula I or pharmaceutically acceptable salts thereof, comprising the step of
- a.) hydrogenating the tertiary hydroxy protected sulfonyl compound of formula III



Formula III

wherein R_1 represents hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, which is substituted or unsubstituted; and R_2 represents $\text{CH}_3\text{-CO-}$, $\text{CF}_3\text{-CO-}$, $\text{CH}_2\text{ClCO-}$, $\text{CHCl}_2\text{-CO-}$, $\text{CCl}_3\text{-CO-}$, $\text{CH}_3\text{O-CO-CO-}$, $\text{CH}_3\text{O-CO-}$, $\text{CH}_3\text{CH}_2\text{O-CO-}$, $\text{CH}_3\text{CH}_2\text{O-CO-CO-}$, phenyl-CO-, or meta- $\text{CH}_3\text{COO-phenyl-CO-}$ or $-\text{SO}_2\text{R}'$; wherein R' is selected from hydrogen, straight chain or branched alkyl, aryl, aralkyl, alkaryl, heteroalkyl, heteroaryl and like; which is substituted or unsubstituted

in the presence of a suitable hydrogenating catalyst in a suitable solvent to prepare sulfonyl protected compound of formula IV,



Formula IV

wherein R_1 is same as above

b.) deprotecting the resulting sulfonyl protected compound of formula IV using a suitable deprotecting reagent to give tapentadol of formula I,

c.) optionally converting tapentadol into its pharmaceutically acceptable salt.

10. The process as claimed in claim 9, wherein in step a.) a suitable hydrogenating catalyst is selected from palladium, Raney nickel, platinum, ruthenium or rhodium catalyst; lithium aluminium hydride, sodium borohydride or like and with or without additives; solvent used for hydrogenolysis reaction is selected from C_{4-12} ethers, C_{3-12} ester, C_{3-10} aliphatic ketone, C_{6-12} hydrocarbon, halogenated solvent, aliphatic nitriles and the like or mixture thereof; a suitable deprotecting reagent in step b.) is selected from an organic base or an inorganic base.