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(54) **Title**: PROCESS FOR THE PREPARATION OF BENZAZEPINE-2-ONE DERIVATIVE

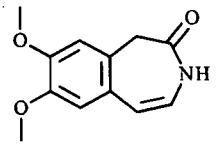
(57) **Abstract**: The present, invention relates to a cost effective, environment friendly industrially viable process for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, an intermediate used in the preparation of ivabradine, without using acid chloride intermediate and condensing agent.

TITLE OF THE INVENTION

PROCESS FOR THE PREPARATION OF BENZAZEPINE-2-ONE DERIVATIVE

FIELD OF THE INVENTION

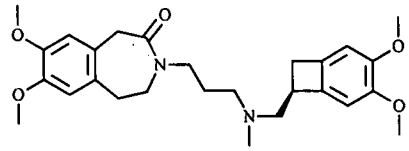
The present invention relates to an efficient and industrially advantageous process for preparation of benzazepine-2-one derivative of formula I. Benzazepine-2-one derivative namely 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, of formula I, is a key intermediate in the preparation of ivabradine.



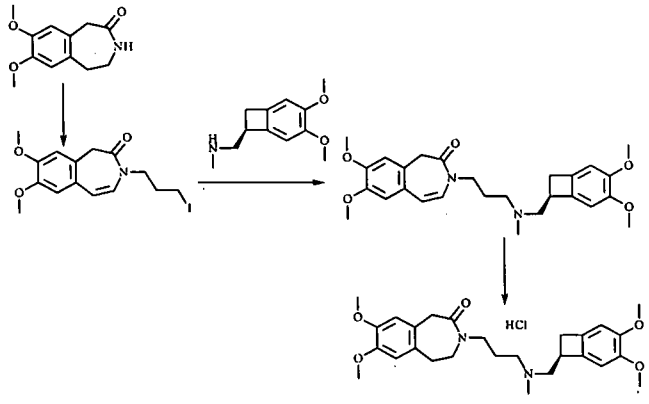
Formula I

BACKGROUND OF THE INVENTION

Ivabradine, chemically known as (S)-7,8-dimethoxy-3-{3-{N-[(4,5-dimethoxy benzocyclobut-1-yl) methyl-N-(methyl)amino)propyl)-1,3,4,5-tetrahydro-2H-3-benzazepine-2-one is useful in many cardiovascular diseases such as angina pectoris, myocardial infarction and associated rhythm disturbances and it is represented by following structure.

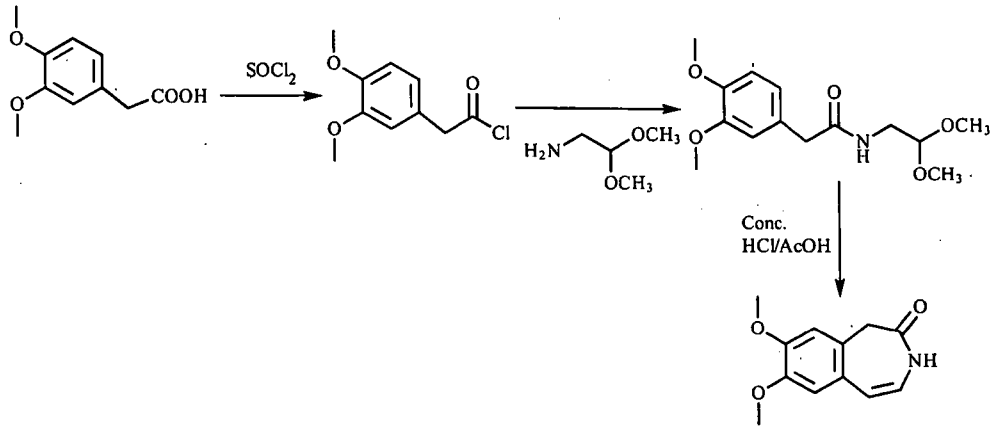


Ivabradine and its pharmaceutically acceptable salts were first disclosed in US patent 5,296,482. The patent also discloses a process for the preparation of ivabradine and its pharmaceutically acceptable salts by the process as shown in below scheme 1



Scheme 1

As shown above, compound 7,8-dimethoxy-3-[3-chloropropyl]-1,3-dihydro-2H-3-benzazepin-2-one of formula I, is an important intermediate in the preparation of ivabradine. It is disclosed that 7,8-dimethoxy-3-[3-chloropropyl]-1,3-dihydro-2H-3-benzazepin-2-one of formula I is obtained using the method describes in the literature *Journal of Medicinal Chemistry 1990, Volume 33(5), 1496-1504,* and the process is as depicted in below scheme 2:



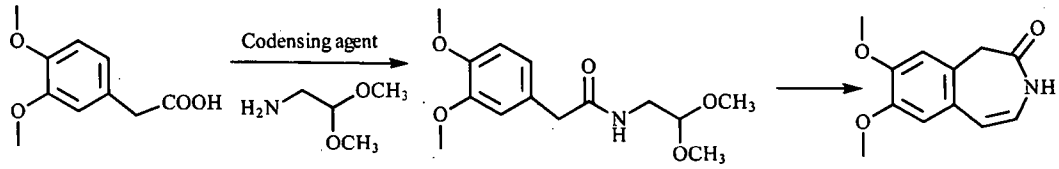
Scheme 2

As shown above,(3,4-dimethoxyphenyl)acetic acid is reacted with thionyl chloride to give (3,4-dimethoxyphenyl)acetic acid chloride. The resulting acid chloride is reacted with N-(2,2-dimethoxyethyl)amine to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxy-phenyl)acetamide, followed by cyclisation of the resulting phenylacetamide in the presence of concentrated hydrochloric acid and glacial acetic acid to give 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one.

Several other patents such as US 4,584,293; US 4,604,389; and US 4,737,495 also disclose similar process for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, wherein (3,4-dimethoxyphenyl)acetic acid chloride intermediate has been prepared as intermediate using thionyl chloride/oxalyl chloride, during preparation of 7,8-dimethoxy-3-[3-chloropropyl]-1,3-dihydro-2H-3-benzazepin-2-one. All these processes give overall low yields, [40-57%] with respect to (3,4-dimethoxyphenyl)acetic acid.

US patent 7,928,223 and CA patent 1215045 disclose two approaches to prepare7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one . One is similar as above, i.e. through the acid chloride intermediate. The second approach reported for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, involves condensation of (3,4-dimethoxyphenyl)acetic acid with N-(2,2-dimethoxyethyl)amine in the presence of

condensing agent to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide and followed by cyclisation of the resulting phenylacetamide in the presence of acidic cyclizing agents in acetic acid, as shown in below scheme 3



Scheme 3

The condensing agent can be selected from 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI)/1-hydroxybenzotriazole (HOBT), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI)/1-hydroxy-7-azabenzotriazole (HOAT), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI)/N-hydroxy succinimide (NHS), dicyclohexylcarbodiimide (DCC), dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole (HOBT), dicyclohexylcarbodiimide (DCC)/1-hydroxy-7-azabenzotriazole (HOAT), dicyclohexylcarbodiimide (DCC)/N-hydroxysuccinimide (NHS), O-(7-azabenzo triazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), O-(benzotriazol-1-yl)-oxytripyrrolidinophosphonium hexafluoro phosphate (PyBOP), carbonyldiimidazole (CDI), n-propane phosphonic anhydride (T3P).

US patent 7,928,223 shows advantage of not isolating N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide, intermediate.

It has been observed that the above processes suffer from several drawbacks, such as a need for a separate activating step in acid chloride intermediate process. Further, the use of thionyl chloride, which is a hazardous chemical and is difficult to handle, is not an attractive option for industrial use. During the synthesis of acid chloride using thionyl chloride, an equivalent amount of hydrogen chloride gas formed, which is very dangerous for the environment and to absorb and neutralize this hazardous gas, cost of production of product increases, economic point of view. Further its removal till trace amount, from the reaction mass is very difficult and if it remains in the reaction, it hampers the

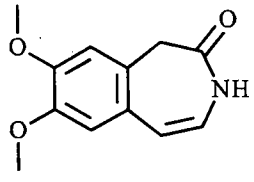
condensation reaction in next stage to prepare phenylacetamide, intermediate. The acid chloride, formed in the reaction is found to be unstable and decomposes in the presence of water and results in yield loss. Alternatively, each of condensing agents has their own disadvantages being unstable, toxic, expensive or commercially unavailable, and requires the removal of bye product.

Further it is also very cumbersome to carry out amidation reaction using condensing agents like carbodiimide and carbonyldiimidazole on bigger scale, since carbodiimides and carbonyldiimidazolesare unstable compounds and hydrolyze very easily. Another drawback of using carbodiimide and carbonyldiimidazole is that byproduct generated after their use is difficult to remove completely and these compounds are allergic in nature. We have not found any reference, for the synthesis of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, wherein (3,4-dimethoxyphenyl)acetic acid is reacted with N-(2,2-dimethoxyethyl)amine to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxy-phenyl) acetamide, without preparing acid halide [chloride] or without using condensing agent.

In view of the above, there is an urgent need to develop an efficient, cost effective, industrially viable process for the synthesis of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, wherein use of acid chloride or condensing agents can be avoided. Therefore, the present invention fulfills the need in the art and provides a cost effective, environment friendly and industrially viable process for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one without using acid chloride intermediate and condensing agent.

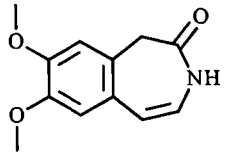
OBJECT OF THE INVENTION

The main object of the present invention is to provide an efficient, environment friendly and industrially advantageous process for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I.



Formula I

An another object of the present invention is to provide an efficient and industrially advantageous process for the preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I,

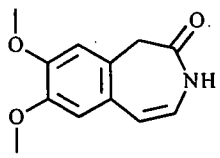


Formula I

and its application in the preparation of ivabradine or its pharmaceutically acceptable salt thereof.

SUMMARY OF THE INVENTION

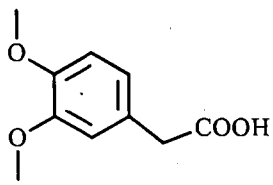
Accordingly, the present invention provides an efficient, environment friendly and industrially advantageous process for preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I,



Formula I

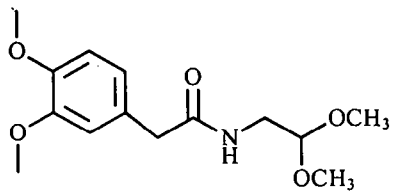
comprises:

i) reacting (3,4-dimethoxyphenyl)acetic acid of compound of formula II,



Formula II

with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide of compound of formula III,

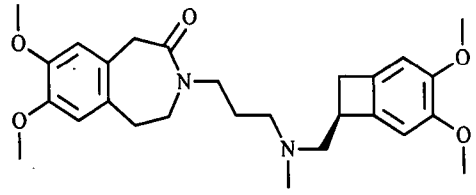


Formula III

ii) cyclizing the resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxy phenyl)acetamide of compound of formula III in the presence of a suitable acid,

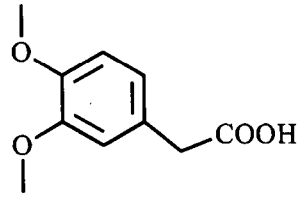
iii) isolating 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of formula I.

In another embodiment, the present invention provides an industrially advantageous and efficient process for preparation of ivabradine having structure,



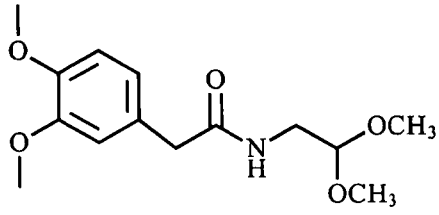
or its pharmaceutically acceptable salt thereof comprises:

i) reacting (3,4-dimethoxyphenyl)acetic acid of compound of formula II,



Formula II

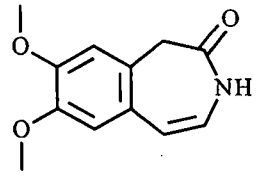
with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III,



Formula III

ii) cyclizing the resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxy phenyl)acetamide of formula III in the presence of a suitable acid,

iii) isolating 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I,



Formula I

iv) converting 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I into ivabradine or its pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an industrially advantageous, environment friendly and efficient process for preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I by reacting (3,4-dimethoxyphenyl)acetic acid of formula II with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent to give a reaction mixture.

The suitable solvent used in the reaction mixture can be any suitable organic solvent, which can form azeotrope with water. The suitable organic solvent can be selected from toluene, cyclohexane; methyl ethyl ketone, methyl isobutyl ketone, di-isobutyl ketone and a like or mixture thereof.

The suitable temperature used in the reaction can be in the range of 10°C to the reflux temperature of the solvent and it takes about 5 hours to 30 hours for completion of reaction.

The water generated in-situ during condensation reaction can be removed by using any suitable means to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxy phenyl) acetamide of compound of formula III. The resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III can be isolated or can be used as such for next reaction without its isolation.

It has been observed that it is advantageous to remove the water, generated in-situ during condensation reaction to avoid the backward reaction. The removal of water can be accomplished by azeotropical distillation or using activated molecular sieves.

Generally, after completion of reaction, solvent may be distilled out from reaction mass to isolate N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide. Alternatively, reaction mass may be cooled to a temperature of below 35°C, and proceeded for further cyclization step. The resulting reaction mass can be treated with a suitable acid to carried out cyclization reaction of N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III. The compound of formula III, prepared by direct condensation of (3,4-dimethoxyphenyl)acetic acid of compound of formula II with N-(2,2-dimethoxyethyl)amine is of high synthetic applicability, since it avoids use of toxic reagents.

It is not crucial for next cyclization reaction, whether to isolate compound of formula III or used as such from reaction mass.

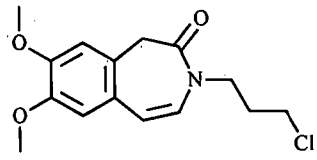
The suitable acid used for cyclization reaction can be selected from concentrated hydrochloric acid in aqueous solution, concentrated hydrochloric acid in solution in acetic acid, hydrobromic acid, hydrobromic acid solution in acetic acid, sulphuric acid, methanesulphonic acid or a mixture thereof.

The suitable temperature to carry out cyclization reaction is preferably 10 to 40°C. Generally, after completion of cyclization reaction, the reaction mixture is diluted with a suitable medium. Preferably water is added to the reaction mixture and reaction mass is further stirred for 2 to 10 hours for complete crystallization of desired product. The resulting solid can optionally be purified by using a suitable solvent. The suitable solvent includes but not limited to alcohols selected from ethanol, methanol; ester and ether solvent such as ethylactetate, diethyl ether and a like or mixture thereof. The compound of formula I, can be isolated from reaction mass by using a suitable means known in the art like filtration, centrifugation or the like. The resulting solid product can be washed with suitable solvent including demineralized water and then can be dried at a temperature range of 40°C to 80°C to give 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I. The completion of reaction can be monitored by any one of chromatographic techniques such as thin layer chromatography (TLC), high pressure liquid chromatography (HPLC), Ultra-pressure liquid chromatography (UPLC) and the like

The 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I, prepared according to present invention is highly useful in the synthesis of ivabradine or its pharmaceutically acceptable salt thereof, as it is an important intermediate.

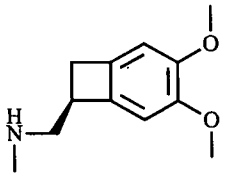
Accordingly, the present invention provides a convenient, industrially advantageous and efficient process for preparation of ivabradine or its pharmaceutically acceptable salt thereof by using 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I prepared by reacting (3,4-dimethoxy phenyl)acetic acid of compound of formula II with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent, to prepare N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III, followed by cyclization of N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III in acidic medium to prepare 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I, and converting 7,8-dimethoxy-1,3-

dihydro-2H-3-benzazepine-2-one of compound of formula I to ivabradine or its pharmaceutically acceptable salt thereof by the methods known in the art or as described. Generally 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I can be alkylated with 1-bromo-3-chloro-propane in presence of a suitable base in an organic solvent to obtain 7,8-dimethoxy-3-[3-chloropropyl]-1,3-dihydro-2H-3-benzazepin-2-one of compound of formula IV.



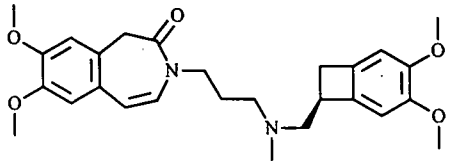
Formula IV

The compound of formula IV can be then condensed with methylamine derivative of formula V or salt thereof,



Formula V

to prepare benzazepine intermediate of formula VI;



Formula VI

which is then reduced to prepare ivabradine and converting into ivabradine pharmaceutically acceptable salt thereof.

Particularly 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I can be alkylated with 1-bromo-3-chloro-propane in presence of a suitable base in an organic solvent to benzazepin-2-one compound of formula IV. The suitable base includes potassium tertiary butoxide, alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or the like. The organic solvent can be selected from acetone, dimethylsulfoxide, dimethylformamide, etc. or mixtures thereof. Benzazepin-2-one compound of formula IV can optionally be purified to achieve purity of greater than 99%w/w. Any suitable purification method can be employed for purification; preferably benzazepin-2-one compound of formula IV can be crystallized by using suitable solvent or a mixture of solvents or slurry washed in a suitable solvent. The suitable solvent can

be selected from water, acetates, ketones and mixture thereof. Preferably water, acetone and a mixture of acetone and ethyl acetate have been used.

Thereafter benzazepin-2-one compound of formula IV can be then condensed with methylamine derivative of formula V or salt thereof, to prepare benzazepine intermediate of formula VI.

The methylamine derivative of formula V or salt thereof can be prepared by methods known in literature. Specifically camphorsulphonic acid salt of methylamine derivative of formula V is used and treated with base to prepare methylamine derivative of formula V. The methylamine derivative of formula V can be isolated or used *in situ* for further reaction. The condensation reaction can be carried out in demineralized water and in the presence of a base at 45-60°C preferably at 50-55°C and it takes 10-20 hours for completion of reaction. The progress of reaction can be monitored by high performance liquid chromatography (HPLC). The suitable base used in the condensation step can be selected from alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides and preferably potassium carbonate is used. Benzazepine intermediate of formula VI, prepared by process as given, can be hydrogenated and converted into highly pure ivabradine or its pharmaceutically acceptable salt thereof.

Typically, the condensed product Benzazepine intermediate of formula VI is converted to ivabradine or its pharmaceutically acceptable salt selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and hydrates thereof. Preferably hydrochloride or oxalate salt is prepared. The compound of formula VI is catalytically hydrogenated using palladium on carbon catalyst in suitable solvent such as alcohols like under hydrogen pressure of 3-10 kg/cm^2. The hydrogenation reaction is conducted at ambient temperature and it takes 4-12 hours for completion of reaction, which is monitored by high performance liquid chromatography (HPLC). The catalyst is filtered out and the product is isolated from reaction mass by removal of solvent by distillation from the filtrate. Thereafter crude ivabradine is treated with suitable acid i.e. hydrochloric acid or oxalic acid to prepare the desired salts. The acid salt is then purified using a suitable solvent such as acetates, alcohols, nitriles, and the like and preferably

ethyl acetate, acetonitrile are used. Purification steps can be repeated, if required, to achieve the desired purity level. Ivabrdaine salts can also be converted to one another like ivabradine hydrochloride can be converted to ivabradine oxalate and ivabradine oxalate can be converted to ivabradine hydrochloride. Preferably hydrochloride or oxalate salt is prepared. In an alternate embodiment, compound of formula IV can be reduced before condensation with compound of formula V and results directly to prepare ivabradine.

Ivabradine prepared by using the compound of formula I, prepared by using process of present invention, can be converted in to pharmaceutically acceptable salt selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and hydrates thereof. Ivabrdaine and its salts have been prepared in comparable purity and better yield by using 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, prepared by using the process of present invention.

Major advantages realized in the present invention are that yield of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one has been increased many folds, as thionyl chloride has not been used. Further time cycle for preparation method has also been reduced. Since time cycle is reduced, so in same time period more of the 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, with improved yield will be generated, so production cost will down and hence process is cost effective.

EXAMPLES:

Example 1: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (50g) in toluene (175 ml) N-(2,2-dimethoxyethyl)amine (32.5g) was added at 15-35°C. The resulting reaction mixture was heated to reflux, and maintained at same temperature for 26 hours, with removal of water azeotropically. After completion of reaction, the reaction mixture was cooled to a temperature of 20°C to 30°C. Concentrated hydrochloric acid (150ml) was added to the reaction mixture and stirred. The layers were separated and toluene layer was further extracted with concentrated hydrochloric acid (100ml). The acidic layers were combined and concentrated sulphuric acid (25ml) was added to it. The resulting reaction mixture

was stirred at a temperature of 25°C to 30°C for 17 hours. After completion of reaction, demineralized water (250ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter methanol (25ml) was added, and reaction mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at a 50-60°C to obtain 44g of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, having purity 97.18% measured by HPLC.

Example 2: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (25g) in toluene (87.5ml) N-(2,2-dimethoxyethyl)amine (16.2g) was added at 15-35 °C. The resulting reaction mixture was heated to reflux, maintained at reflux temperature for further 30 hours, and water was removed azeotropically. After completion of the reaction, reaction mixture was cooled to a temperature of 25°C to 30°C. Concentrated hydrochloric acid (100ml) was added to the reaction mixture and stirred. The layers were separated and toluene layer was further extracted with concentrated hydrochloric acid (25ml). The acidic layers were combined and concentrated sulphuric acid (12.5ml) was added to it. The resulting reaction mixture was stirred at a temperature of 25°C to 30°C for 15 hours. After completion of reaction, demineralized water (125ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter, methanol (12.5ml) was added and reaction mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at 50-60°C to afford 22.2g of title compound, having purity 97.9% measured by HPLC.

Example 3: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (100g) in toluene (350ml) N-(2,2-dimethoxyethyl)amine (65g) was added at 15-35°C. The resulting reaction mixture was heated to reflux, maintained reaction mixture at reflux temperature for 30 hours, and water was removed azeotropically. After completion of the reaction, the reaction mixture was cooled to a temperature of 20°C to 30°C. Concentrated hydrochloric acid (400ml) was added to the reaction mixture and stirred. The layers were separated and toluene layer was further extracted with concentrated hydrochloric acid (100ml). The acidic layers were combined and concentrated sulphuric acid (50ml) was added to it. The resulting reaction mixture was stirred at a temperature of 25°C to 30°C for 15 hours.

After completion of reaction demineralized water (500ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter, methanol (50ml) was added and reaction mixture was further stirred for 45 minutes, The resulting solid was filtered and washed with demineralized water and dried at 50-60°C to afford 91g of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, having purity 98.4% measured by HPLC.

Example 4: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (10g) in methyl isobutyl ketone (40ml) N-(2,2-dimethoxyethyl)amine (6.5g) was added at 15-35°C. The resulting reaction mixture was heated to reflux, maintained at reflux temperature for 27 hours, and water was removed azeotropically. After completion of reaction, the reaction mixture was cooled to a temperature of 20°C to 30°C. Concentrated hydrochloric acid (50ml) was added to the reaction mixture and stirred. The layers were separated and the acidic layers were combined and concentrated sulphuric acid (5 ml) was added to it. The resulting reaction mixture was stirred at a temperature of 25°C to 30°C for 16 hours. After completion of reaction, demineralized water (50ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter methanol (5ml) was added, and reaction mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at 50-60°C to obtain the title compound.

Example 5: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (50g) in toluene (175ml) N-(2,2-dimethoxyethyl)amine (22.5g) was added at 15-35°C. The resulting reaction mixture was reflux, maintained reaction mixture at reflux temperature for 29 hours, and water was removed azeotropically. After completion of reaction, the reaction mixture was cooled to a temperature of 20°C to 30°C. Concentrated hydrochloric acid (200ml) was added to the reaction mixture and stirred. The layers were separated and toluene layer was further extracted with concentrated hydrochloric acid (50ml). The acidic layers were combined and divided into two equal parts.

One part of acidic layer was stirred at a temperature of 25-30°C for 15-17 hours and demineralized water (125ml) was added and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter methanol (12.5ml) was added and reaction

mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at a 50-60°C to obtain 22g of title compound.

To the second part of acidic layer, concentrated sulphuric acid (12.5ml) was added slowly at a temperature of 20-30°C and the resulting reaction mixture was stirred for 15-17 hours. After completion of reaction, demineralized water (125ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter methanol (12.5ml) was added, and reaction mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at a 50-60°C to obtain 24.8g of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one having purity 99.03% measured by HPLC.

Example 6: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To a suspension of (3,4-dimethoxyphenyl)acetic acid (50g) in toluene (150ml) N-(2,2-dimethoxyethyl)amine (32.5g) was added at 15-35°C. The resulting reaction mixture was heated to reflux, maintained at reflux temperature for 30 hours, and water was removed azeotropically. After completion of reaction, the reaction mixture was cooled to a temperature of 25°C to 30°C. Concentrated hydrochloric acid (250ml) was added to the reaction mixture. The resulting reaction mixture was stirred at a temperature of 25°C to 30°C for 22 hours. After completion of reaction, demineralized water (150ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 3 hours for complete crystallization. The resulting solid was filtered and washed with demineralized water and dried at a 50-60°C to obtain 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, having purity 98.07% measured by HPLC.

Example 7: Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

a) Preparation of N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide

To a suspension of (3,4-dimethoxyphenyl)acetic acid (50g) in toluene (175 ml) N-(2,2-dimethoxyethyl)amine (32.5 g) was added at 15-35 °C. The resulting reaction mixture was heated to reflux, maintained reaction mixture at reflux temperature for 30 hours, and water was removed azeotropically. Thereafter, toluene was distilled to obtain N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide.

b) Preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one

To the resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide, concentrated hydrochloric acid (250 ml) and concentrated sulphuric acid (25 ml) were

added. The resulting reaction mixture was heated at a temperature of 25°C to 30°C for 4 hours. After completion of reaction, demineralized water (250 ml) was added at a temperature of 20°C to 30°C and reaction mixture was further stirred for 4 hours for complete crystallization. Thereafter methanol (25 ml) was added, and reaction mixture was further stirred for 45 minutes. The resulting solid was filtered and washed with demineralized water and dried at a 50-60°C to obtain 43.6g of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one, having purity 98.4% measured by HPLC.

Example 8: Preparation of 7,8-dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2H-3-benzazepin-2-one

7,8-Dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one (90 g) prepared as above, was taken in dimethylformamide (270 ml) and potassium hydroxide (45 g) was added. The resulting reaction mixture was stirred at a temperature of 0°C to 5°C for 15 minutes. Thereafter, 1-bromo-3-chloro-propane (67.5 ml) was added, and maintained the reaction mixture at same temperature for 3 hours. After completion of reaction (monitored by HPLC), demineralized water (270 ml) was slowly added at a temperature of 0°C to 5°C, and reaction mixture was further stirred at a temperature of 25°C to 30°C for 1 hour. The resultant product was filtered, washed with demineralized water and dried at 50-60°C to obtain 102 g of title compound, having purity 98.5% measured by HPLC.

Example 9: Purification of 7,8-Dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2H-3-benzazepin-2-one

7,8-Dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2H-3-benzazepin-2-one, prepared as above was taken in acetone (306 ml) and stirred at a temperature of 45°C to 55°C for 30 minutes till complete dissolution. The resultant reaction mass was filtered through hyflo and washed with acetone (102 ml). Combined acetone solution was distilled out till acetone (120-125) remained. Thereafter demineralized water (612 ml) was added to the resulting acetone solution at temperature 40-45°C and maintained the reaction mixture at ambient temperature for 1 hour. The resulting solid was filtered, washed with demineralized water and dried at 50-60°C to obtain 98 g of pure title compound, having purity 99.81% measured by HPLC.

Example 10: Preparation of (S)-7,8-dimethoxy-3-{3-{N-[(4,5-dimethoxy benzo cyclobut-1-yl)methyl]-N-(methylaminopropyl)-1,3-dihydro-2H-3-benzazepine-2-one

To a mixture of (S)-[(4,5-dimethoxy benzocyclobut-1-yl)-methyl]-N-(methyl amine

camphorsulphonic acid (35 g) and water [47 ml], potassium carbonate (44.3 g) was added at temperature below 30°C and stirred for 15-20 minutes. To this, 7,8-dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2H-3-benzazepin-2-one (23.8 g) was added and stirred for further 30 minutes. Thereafter the reaction mixture was to 55-60°C and maintained the temperature for 24-30 hours. After completion of reaction (monitored by HPLC), ethyl acetate (175 ml) was added at same temperature, and stirred for 15 minutes. Thereafter water (70 ml) was added and cooled the reaction mixture to 30-35°C. The layers were separated and the resulting aqueous layer was further extracted with ethyl acetate. The combined ethyl acetate layer was washed twice with sodium hydroxide solution (4 g sodium hydroxide + 105 ml water). The ethyl acetate was distilled completely under vacuum at 55-66°C to obtain 36 g of the title compound as oil.

Example 11: Preparation of Ivabradine hydrochloride

Benzazepine compound (35 g) obtained as above, was taken in methanol [210ml] and was hydrogenated in the presence of Pd/C [10% 7.0 g] under a hydrogen pressure of 7-8 kg/cm^2 at temperature of 25-30°C for about 8-10 hours. After completion of hydrogenation, catalyst was filtered off and washed with methanol. Methanol was distilled out completely under vacuum at 25-30°C. The resulting reaction mass was taken in dilute hydrochloric acid solution [175 ml) and methylene chloride [230ml]. The layers were separated and the resulting aqueous layer was extracted twice with methylene chloride [2x140ml]. The combined methylene chloride was filtered, and distilled completely under vacuum. To the residue, acetonitrile (70ml) was added and distilled to remove traces of methylene chloride. To the resulting reaction mass, acetonitrile (700ml) was added and heated to reflux till clear solution. Thereafter 50% of acetonitrile was distilled out and the reaction mixture was cooled to 25-30°C and stirred at same temperature for further 2 hours. The resultant product was filtered, washed with acetonitrile and suck dried. The same purification was repeated again in acetonitrile. Further the resulting wet material was taken in ethyl acetate (420ml) and heated to reflux till clear solution. Distilled out one sixth of ethyl acetate, cooled the reaction mixture was to 30-35°C and stirred at same temperature for further 1 hour. The product thus obtained was filtered, washed with ethyl acetate and dried at 70-80°C to obtain the title compound (28.48 g), having purity 99.90% w/w by HPLC.

Example 12: Preparation of Ivabradine oxalate

Ivabradine (23 g) was taken in acetonitrile (230 ml) and the temperature was raised to 65-70°C. To this, oxalic acid solution (7 g in 75 ml acetonitrile) was added and filtered the reaction mixture and stirred for 15 minutes. The temperature of reaction mixture was raised to 80-85°C and stirred for 2 hours. Cooled the resulting solution to ambient temperature slowly and stirred for further 4 hours. The resulting solid was filtered and washed with acetonitrile (10 ml). The wet cake was recrystallized in acetonitrile (230 ml) and resulting product was dried under vacuum at 60-65°C to obtain 24.0 g of title compound.

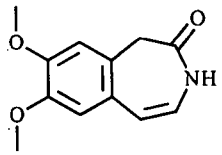
Example 13: Preparation of Ivabradine oxalate

Ivabradine hydrochloride (25 g) was taken in demineralized water (75 ml) and sodium hydroxide solution (6.25 g in 13 ml water) was added at temperature 25-30°C, to adjust the pH above 11.5. Thereafter, ethyl acetate (125 ml) was added, and stirred for further 30 minutes. The layers were separated and the resulting aqueous layer was further extracted with ethyl acetate. The combined ethyl acetate layer was washed with sodium hydroxide solution (1.5 g in 75 ml water), then with ethyl acetate and then treated with sodium sulphate (2.5 g). The ethyl acetate was distilled completely under vacuum at 55-60°C. To the residue, acetonitrile was added (25 ml) to remove the traces of ethyl acetate from the solution. Acetonitrile (225 ml) was added and raised the temperature to 65-70°C, to this, oxalic acid solution (7 g in 75 ml acetonitrile) was added and filtered the reaction mixture and stirred for 15 minutes. The temperature of reaction mixture was raised to 80-85°C and stirred for 2 hours. Cooled the resulting solution to ambient temperature slowly and stirred for further 4 hours. The resulting solid was filtered and washed with acetonitrile (13 ml). The wet cake was recrystallized in acetonitrile (250 ml) and resulting product was dried under vacuum at 60-65°C to obtain 24.1 g of title compound.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention and specific examples are provided herein without departing from the spirit and scope of the invention. Thus, it is intended that the present invention covers the modifications and variations of this invention that come within the scope of any claims and their equivalents

We claim

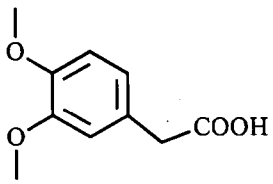
1. A process for preparation of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I,



Formula I

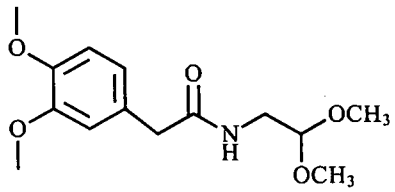
comprises:

i) reacting (3,4-dimethoxyphenyl)acetic acid of compound of formula II,



Formula II

with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide of compound of formula III,



Formula III

ii) cyclizing the resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide of compound of formula III in the presence of a suitable acid,

iii) isolating 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of formula I.

2. The process as claimed in claim 1, wherein in step i) the suitable temperature is from 10°C to the reflux temperature of the solvent used.

3. The process as claimed in claim 1, wherein in step i) the suitable solvent is an organic solvent that forms azeotrope with water.

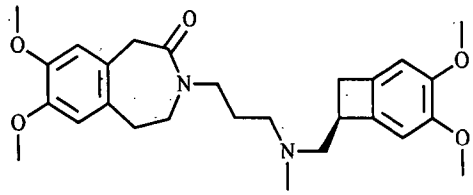
4. The process as claimed in claim 1, wherein in step i) the suitable solvent is toluene, cyclohexane; methyl ethyl ketone, methyl isobutyl ketone, di-isobutyl ketone and a like or mixture thereof.

5. The process as claimed in claim 1, wherein in step ii) the suitable acid is selected from concentrated hydrochloric acid in aqueous solution, concentrated hydrochloric

acid in solution in acetic acid, hydrobromic acid, hydrobromic acid solution in acetic acid, sulphuric acid, methanesulphonic acid or a mixture thereof.

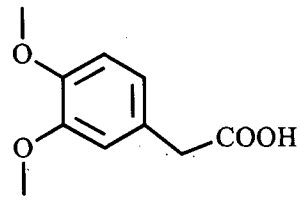
6. The process as claimed in claim 1, wherein in step ii) the reaction is performed at 10°C to 40°C.

7. A process for preparation of ivabradine of following formula,



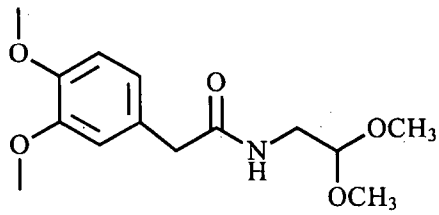
or its pharmaceutically acceptable salt thereof comprises:

i) reacting (3,4-dimethoxyphenyl)acetic acid of compound of formula II,



Formula II

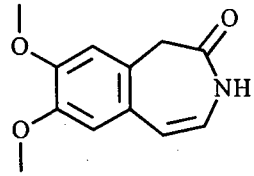
with N-(2,2-dimethoxyethyl)amine at a suitable temperature in a suitable solvent, in the absence of coupling/condensing agent to give N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl)acetamide of compound of formula III,



Formula III

ii) cyclizing resulting N-(2,2-dimethoxyethyl)-2-(3,4-dimethoxyphenyl) acetamide of formula III in the presence of a suitable acid,

iii) isolating 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I,

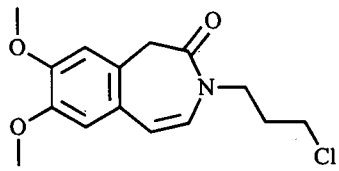


Formula I

iv) converting 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I into ivabradine or its pharmaceutically acceptable salt thereof.

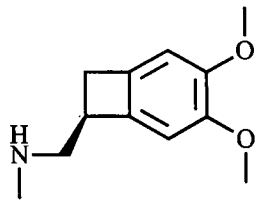
8. The process as claimed in claim 7, wherein in step iv) the converting of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I into ivabradine or its pharmaceutically acceptable salt thereof comprises the step of

i) alkylating 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepine-2-one of compound of formula I with 1-bromo-3-chloro-propane in presence of a suitable base in an organic solvent to obtain 7,8-dimethoxy-3-[3-chloropropyl]-1,3-dihydro-2H-3-benzazepin-2-one of compound of formula IV.



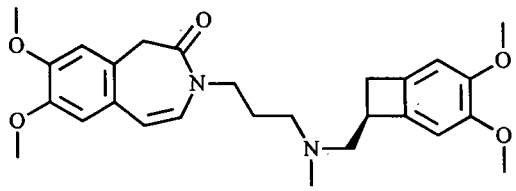
Formula IV

ii) condensing of the resulting compound of formula IV with methylamine derivative of formula V or salt thereof,



Formula V

to prepare benzazepine intermediate of formula VI;



Formula VI

iii) reducing the benzazepine intermediate of formula VI by catalytic hydrogenation to prepare ivabradine and

iv) converting ivabradine into ivabradine pharmaceutically acceptable salt thereof by reacting with a suitable acid.

9. The process as claimed in claim 8, wherein in step i) the suitable base is selected from potassium tertiary butoxide, alkali metal hydroxide such as sodium hydroxide, potassium hydroxide; the organic solvent is selected from acetone, dimethylsulfoxide, dimethylformamide or mixtures thereof.

10. The process as claimed in claim 8, wherein in step ii) condensation is carried out in demineralized water and in the presence of a base at 45-60°C; in step iii) reduction is carried out using palladium on carbon catalyst in suitable solvent under hydrogen pressure of 3-10 kg/cm^2; in step iv) ivabradine is converted to suitable acid by reacting with a suitable acid in a suitable solvent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000031

A. CLASSIFICATION OF SUBJECT MATTER
C07C217/74 Version=2017.01

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)

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2010072409 A1 ;01 July 2010; KRKA, D. D., NOVO MESTO see e.g. 6-12; Claims	1-10
A	EP 0534859 B1, 17 Nov 1994; ADIR ET COMPAGNIE See claims, examples	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family 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 application or patent 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

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