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(54) Title: PROCESS FOR THE PREPARATION OF BREXPIPRAZOLE FROM 7-(4-CHLOROBUTOXY)QUINOLIN-2(1H)-ONE AND 1-(BENZO[B]THIOPHEN-4-YL)PIPERAZINE

(57) Abstract: The present invention relates to a process for the preparation of 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy} quinolin-2(1H)-one (brexpiprazole) from 7-(4-chlorobutoxy)quinolin-2(1H)-one and 1-(benzo[b]thiophen-4-yl)piperazine. The intermediate 7-(4-chlorobutoxy)quinolin-2(1H)-one is prepared from 7-hydroxy-quinolin-2(1H)-one and 1-bromo-4-chloro-butane at a temperature below 45°C. The crude intermediate 7-(4-chlorobutoxy)quinolin-2(1H)-one is then treated with a resin (e.g. AMBER LITE IR 120 h) in an alcohol solvent (e.g. methanol) whereby the dimer impurity D is removed. The brexpiprazole obtained by this process is substantially free from dimer impurity D. Brexpiprazole is a D2 dopamine partial agonist called serotonin-dopamine activity modulator (SDAM) used for the treatment of schizophrenia and as an adjunct for major depressive disorder.

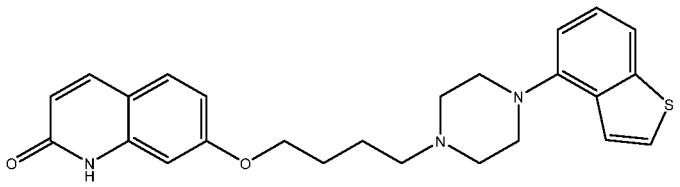
PROCESS FOR THE PREPARATION OF BREXPIPRAZOLE FROM 7-(4-CHLOROBUTOXY)QUINOLIN-2(1H)-ONE AND 1-(BENZO[B]THIOPHEN-4-YL)PIPERAZINE

FIELD OF THE INVENTION:

The present invention relates to process for the preparation of benzo[b]thiophene compound used for the treatment of schizophrenia and as an adjunct for major depressive disorder. More particularly, the present invention is directed to the process for the preparation of 7-{4-[4-(1-benzothiophen-4-yl) piperazin-1-yl] butoxy} quinolin-2 (1H)-one (Brexpiprazole) and its intermediates thereof.

BACKGROUND OF THE INVENTION:

Brexpiprazole is a D2 dopamine partial agonist called serotonin-dopamine activity modulator (SDAM). Brexpiprazole is chemically known as 7-{4-[4-(1-benzothiophen-4-yl) piperazin-1-yl] butoxy} quinolin-2 (1H)-one. It is known from US 7,888,362 and is represented by Formula I.

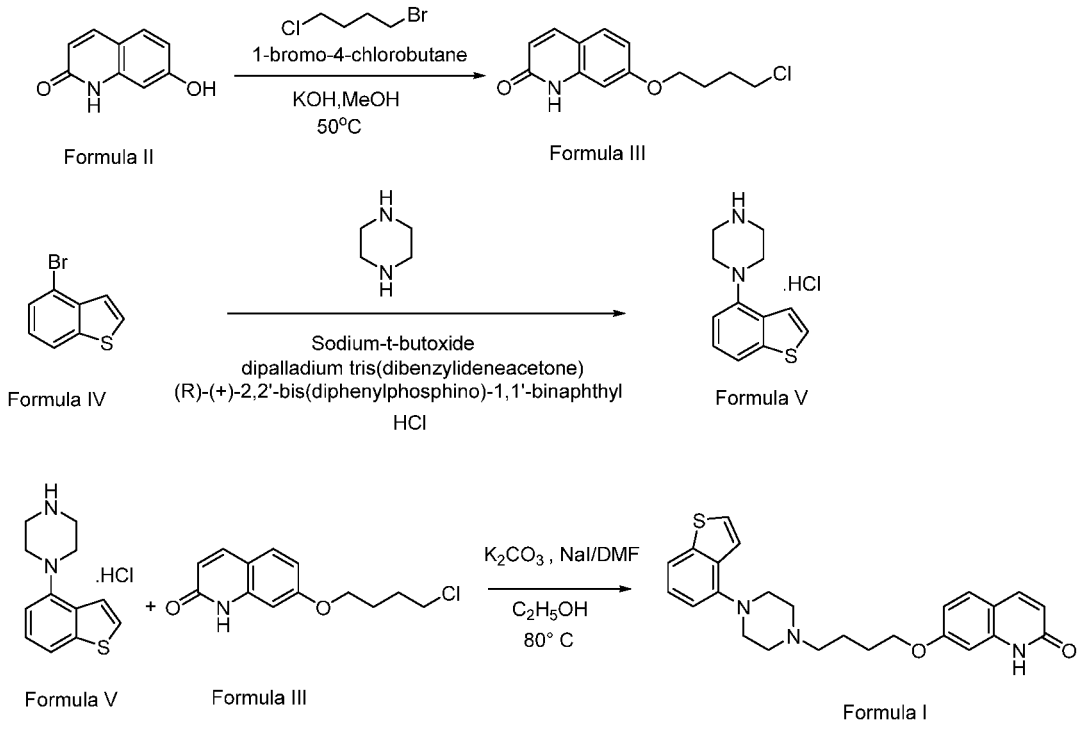


Formula I

Brexpiprazole is sold in USA under the proprietary name of "REXULTI" and is indicated for the treatment of schizophrenia and also as an adjunctive therapy to antidepressants in adults having major depressive disorder.

US 7,888,362 describes a process for the preparation of Brexpiprazole compound of Formula I wherein compound of Formula II reacts with 1-bromo-4-chlorobutane using potassium hydroxide as base in methanol at 50°C to obtain compound of Formula III which was purified by silica gel column chromatography (dichloromethane: methanol=100:3) to obtain pure compound of Formula III. Another intermediate 1-benzo[b]thiophene-4-yl-piperazine hydrochloride compound of Formula V is prepared by

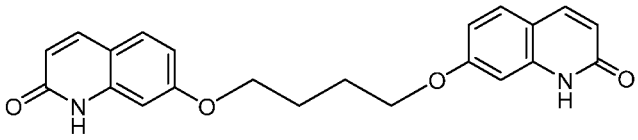
reacting compound of Formula IV with anhydrous piperazine using (R) (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(BINAP), dipalladiumtris (dibenzylidene acetone) in presence of sodium *t*-butoxide by heating under reflux. The resulting 1-benzo[b]thiophene-4-yl-piperazine hydrochloride compound of Formula V then reacts with compound of Formula III to obtain brexpiprazole compound of Formula I as residue which was purified by silica gel column chromatography (dichloromethane: methanol=100:3) followed by recrystallization with ethanol to obtain pure compound of Formula I as shown in Scheme-I.



Scheme-I

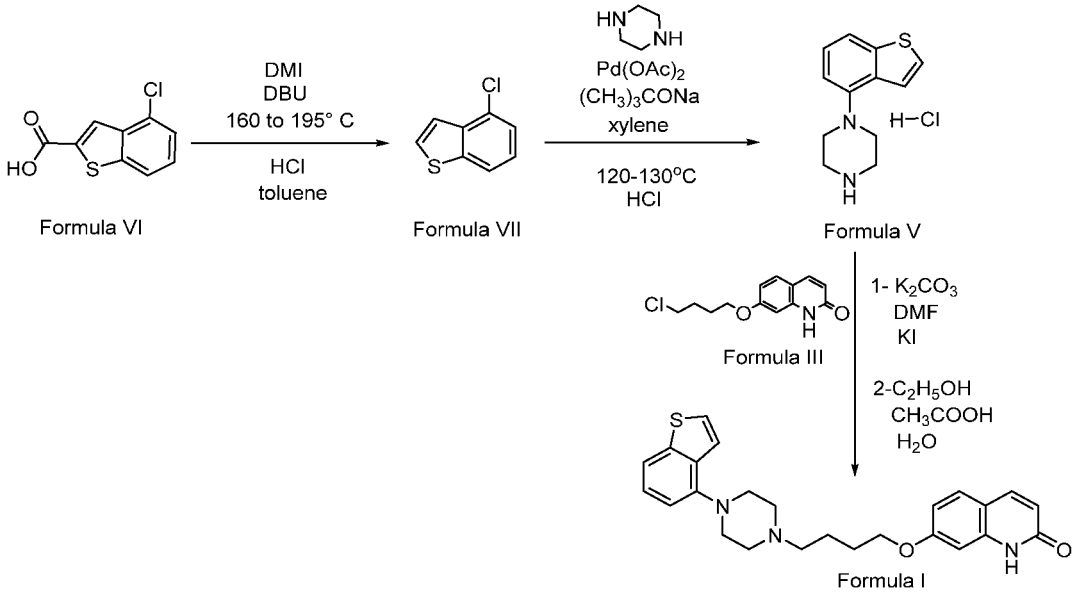
The main drawback of this process is the use of expensive and laborious column chromatographic purification at various stages, which not only require handling of large volume of solvent at commercial scale but also makes the process expensive and time consuming. Another drawback of the process is the formation of by-product mainly Impurity D (dimer impurity) during the reaction of compound of Formula II with 1-

bromo-4-chlorobutane, which is difficult to separate, thus require multiple purification which in turn decreases the yield and increases the cost of the final product.



Impurity D (Dimer impurity)

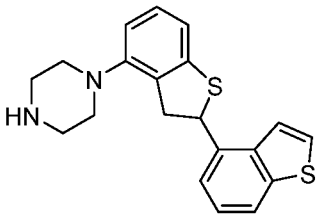
US 9,206,169 describes an improved process for the preparation of 4-(1-piperazinyl)benzo[b]thiophene compound of Formula V which involves reaction of compound of Formula VII with piperazine in presence of (a) a palladium compound and a tertiary phosphine or (b) a palladium carbene complex, in an inert solvent or without a solvent to obtain compound of Formula V which further reacts with compound of Formula III to obtain Brexpiprazole of Formula I as shown in (Scheme II)



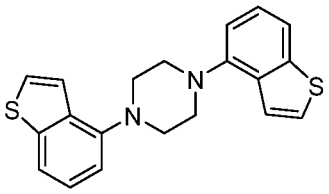
Scheme-II

The main drawback of the said process is the use of expensive palladium carbene complex on commercial scale, which makes the process costly and needs special handling equipment for industrial scale production. Another disadvantage of this process is the formation of impurity A and impurity B during the reaction of compound of Formula V with compound of Formula III which is difficult to separate from the final

product and requires multiple purifications, thus in order to attain the purity of final compound, it leads to undue operational steps for removal of impurities, thus makes the process expensive and tedious on commercial scale.

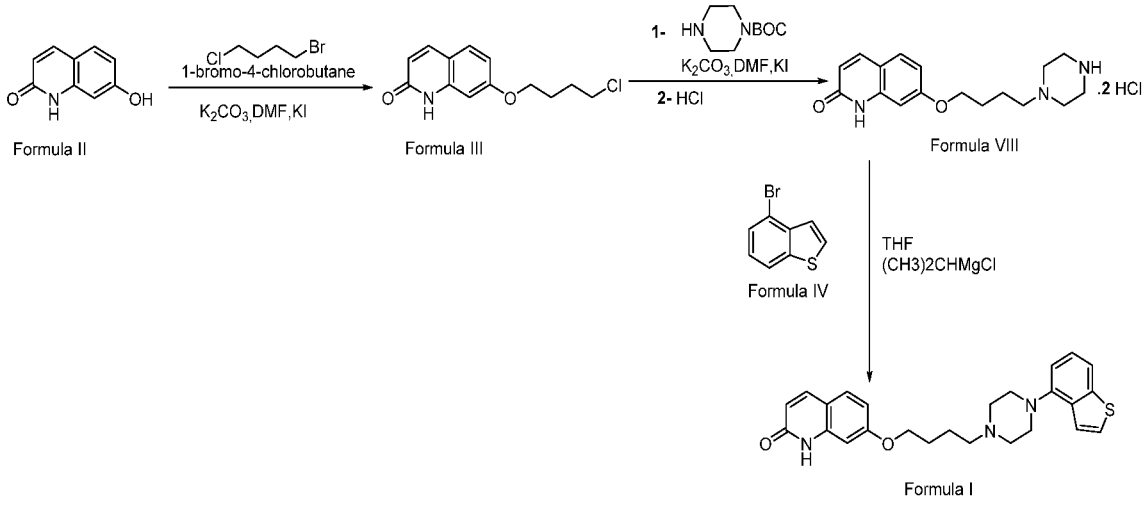


Impurity -A



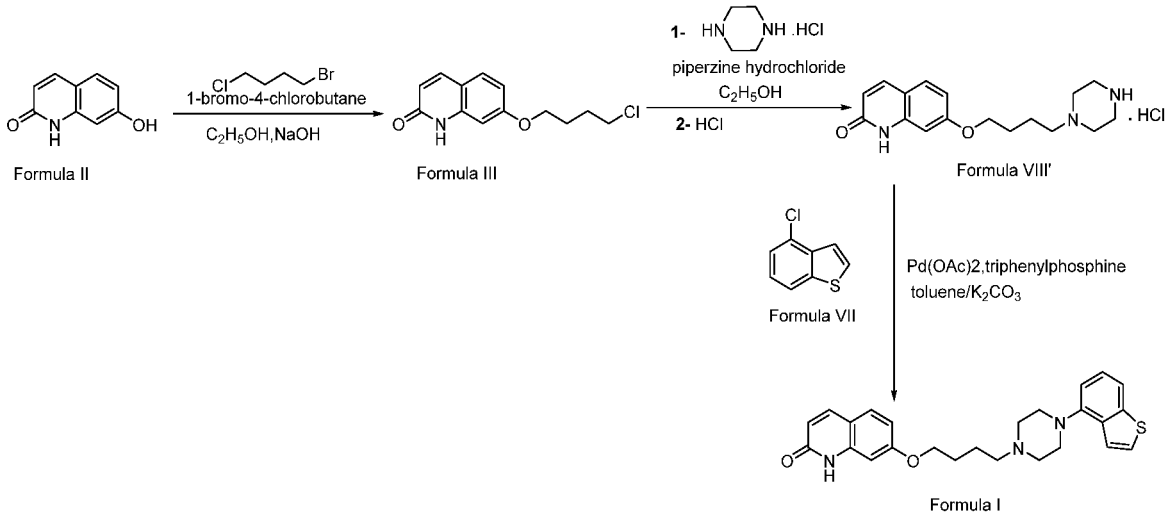
Impurity - B

CN 105175401A discloses the synthesis of Brexpiprazole wherein 7-hydroxyl-1H-quinolin-2-one of Formula II reacts with 1-chlorine-4-bromobutane to obtain 7-(4-chlorobutoxy)-1H-quinolin-2-one of Formula III, which then reacts with N-Boc piperazine to obtain 7-(1-piperazine) butoxy-1H-quinolin-2-one dihydrochloride of Formula VIII followed by reaction with compound of Formula IV and isopropyl magnesium chloride in THF to obtain brexpiprazole compound of Formula I according to Scheme-III.



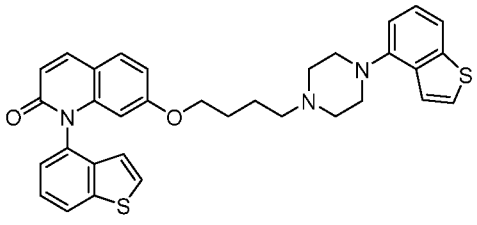
Scheme-III

CN 105440026A discloses the synthesis of Brexpiprazole wherein 7-hydroxyl-1H-quinolin-2-one of Formula II reacts with 1-chloro-4-bromobutane to obtain 7-(4-chlorobutoxy)-1H-quinolin-2-one of Formula III which reacts with piperazine monohydrochloride to obtain 7-(4-(piperazin-1-yl)butoxy)quinolin-2(1H)-one hydrochloride compound of formula VIII'. The resulting compound of Formula VIII' then reacts with 4-chlorobenzo [b] thiophene in presence of a base and palladium triphenyl complex to give Brexpiprazole compound of Formula I according to Scheme-IV.



Scheme-IV

The main drawback of the processes disclosed in Scheme-III & IV is the formation of di-benzo[b]thiophene impurity (Impurity C) during the reaction of compound of Formula VIII or VIII' with compound of Formula IV or VII using isopropyl magnesium chloride or palladium triphenylphosphine complex used as a catalyst which once formed, is difficult to remove and gets carried forward to the final step and affects the yield and purity of the final product.



Impurity C

Thus the processes disclosed in the prior arts suffer from one or more disadvantages like use of expensive chemicals, purification via column chromatography, formation of by-products/impurities at various stages, which makes the process unsuitable for commercial scale production.

Thus, there is a need in the art for an efficient and economical process for the preparation of Brexpiprazole of Formula I which not only overcomes one or more problems of the prior art processes as mentioned above, but also is simple, cost effective, environment friendly, industrially feasible, capable of restricting undesired by-products and avoids the use of column chromatographic purification at various stages.

OBJECT AND SUMMARY OF THE INVENTION

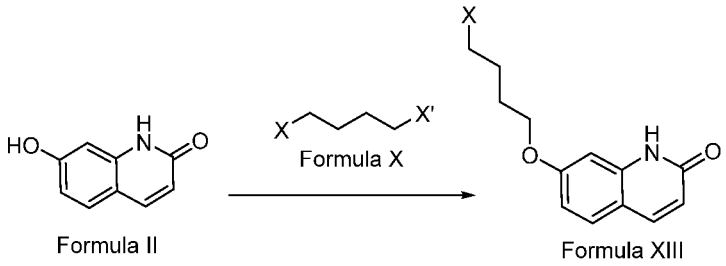
The principal object of the present invention is to provide a process for the preparation of Brexpiprazole of Formula I, which alleviates one or more drawbacks of prior art processes.

According to one aspect of the present invention, there is provided a commercially viable, safe and cost effective process for the preparation of Brexpiprazole of Formula I.

According to another aspect of the present invention there is provided a process that avoids the use of column chromatography for purification of Brexpiprazole and its intermediates and provides a pure product substantially free of impurities preferably dimer impurity of Formula D.

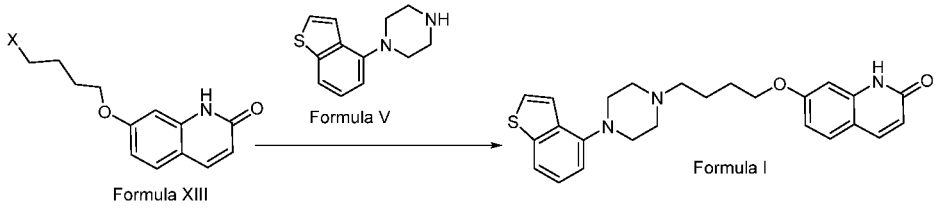
According to another aspect of the present invention, there is provided a process for the preparation of Brexpiprazole of Formula I, comprising the steps of:

AA) reacting compound of Formula II with compound of Formula X in presence of a base and solvent at temperature below 45°C to obtain compound of Formula XIII;



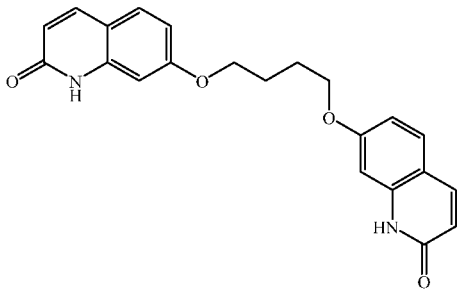
wherein X and X' are independently selected from halogen;

BB) reacting compound of Formula XIII with compound of Formula V or its salt in presence of base and solvent to obtain Brexpiprazole compound of Formula I.



wherein X is as defined above.

According to another aspect of the present invention, there is provided a process for the removal of dimer Impurity of formula D from compound of Formula XIII, comprising treating compound of Formula XIII with resin in suitable solvent.



Impurity D (Dimer impurity)

DETAIL DESCRIPTION OF THE INVENTION:

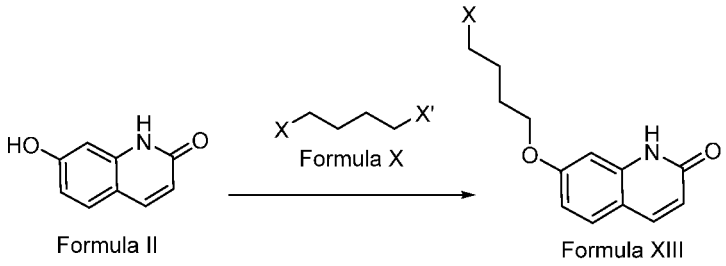
While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

During the laboratory optimization of brexpiprazole, many process related impurities were identified. The formation of impurities and in-turn the control of formation of impurities is dependent upon the reagents, solvents and conditions used for carrying out various reactions, therefore it is a challenge to reach at such reaction conditions, selection of solvents and reagents in such a way that they provide brexpiprazole with desired purity standards, wherein the process should not involve working difficulties, high costs, expensive techniques/reagents etc, rather the process should be simple, convenient, easy to operate, environment friendly and economical on industrial scale. Further as per the guidelines recommended by ICH state that the acceptable levels for a known and unknown compound (impurity) in the drug should be less than 0.15 and 0.10%, respectively.

In view of above requirements, the present invention is directed to a process of preparing brexpiprazole that is simple, convenient, environment friendly and economical for industrial application. The method utilizes a careful reaction condition and reagent for reducing the formation of known and unknown impurities while at the reaction stage itself, avoids the additional requirements of purifying intermediates at various stages and accordingly reduces the use of solvents and reagents. This in turn results in decrease in costs attributed to a more efficient use of reagents and solvents and at the same time becomes more environment friendly and cost effective.

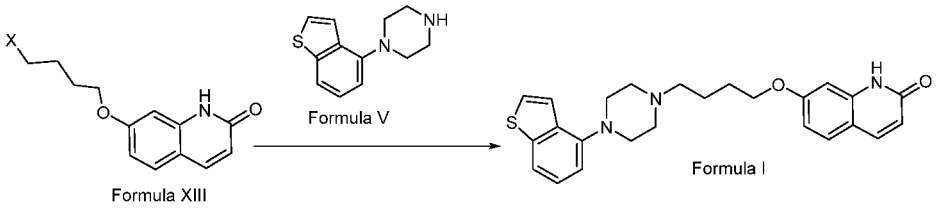
According to one embodiment of the present invention, there is provided a process for the preparation of Brexpiprazole of Formula I, comprising the steps of:

AA) reacting compound of formula II with compound of formula X in the presence of a base and solvent at temperature below 45°C to obtain compound of formula XIII;



wherein X and X' are independently selected from halogen;

BB) reacting compound of formula XIII with compound of formula V or its salt in presence of base and solvent to obtain Brexpiprazole compound of Formula I.



wherein X is defined as above.

According to the present invention, reaction of compound of formula II with compound of formula X in step AA) is carried out in presence of a base and solvent wherein the base is selected from the group comprising of inorganic or organic base. The organic base is selected from the group comprising of triethylamine, diisopropylethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like; aromatic amines such as pyridine, lutidine, N,N-dimethylaniline and the like. The inorganic base is selected from the group comprising of alkali and alkaline earth metal hydroxide, carbonate, bicarbonate, hydride and the like, wherein the alkali and alkaline earth metal is selected from the group comprising of sodium, potassium, cesium, calcium, magnesium and the like. The solvent

is selected from the group comprising of ethers such as dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, methyl *tert*-butyl ether, and the like; esters such as ethyl acetate, propyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; ketones such as acetone, methyl ethyl ketone and the like; nitriles such as acetonitrile, propionitrile and the like; aromatic hydrocarbons such as toluene, xylene chloroxylene, and the like; polar solvents such as DMF, DMSO, DMA, sulfolane, hexamethylphosphoric triamide, or mixture thereof.

The reaction of compound of formula II with compound of formula X in step AA) is carried out at a temperature of about 20 to 45°C, preferably 35 to 45°C for about 2 to 8 hours, more preferably 6-8 hours.

The applicant observed that crude compound of formula XIII obtained in step AA) contains high amount of dimer impurity. The inventors of present invention observed the presence of dimer impurity of formula D in an amount higher than regulatory recommendations, in brexpiprazole obtained by prior art process. Also, the inventors of present invention observed that removal of dimer impurity of formula D is not possible by general purification techniques and is difficult to remove once formed. Accordingly, the present invention provides a simple and efficient process for removal of dimer impurity of formula D at the intermediate stage by treating the 7-(4-halobutoxy) quinolin-2(1H)-one compound of formula XIII using resin in suitable solvent. The resin is selected from the group comprising of polystyrene-divinylbenzene, acrylic resins, crosslinked organic monomer preferably AMBER LITE IR 120 H brand of resins, silica and the like. The solvent is selected from alcohols such as methanol, ethanol, propanol, butanol and the like.

According to the present invention, the reaction of compound of formula XIII with compound of formula V or its salt in step BB) is carried out in presence of a base and solvent, wherein the base is selected from the organic or inorganic base. The organic base is selected from triethylamine, diisopropylethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like; aromatic amines such as pyridine, lutidine, N,N-

dimethylaniline and the like. The inorganic base is selected from the group comprising of alkali and alkaline earth metal hydroxide, carbonate, bicarbonate, hydride and the like, wherein the alkali and alkaline earth metal is selected from the group comprising of sodium, potassium, cesium, calcium, magnesium and the like.

The solvent used for the reaction of compound of formula XIII with compound of formula V or its salt in step BB) is selected from the group comprising of ethers such as dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, methyl *tert*-butyl ether, diethylene glycol, ethylene glycol and the like; esters such as ethyl acetate, propyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; ketones such as acetone, methyl ethyl ketone and the like; nitriles such as acetonitrile, propionitrile and the like; aromatic hydrocarbons such as toluene, xylene chloroxylene, and the like; polar solvents such as DMF, DMSO, DMA, sulfolane, hexamethylphosphoric triamide, water or mixture thereof.

The reaction of compound of formula XIII with compound of formula V or its salt is optionally carried out in presence of reaction accelerator selected from sodium iodide, potassium iodide and the like at a suitable temperature selected from 80 to 120^0C, preferably 90-100^0C to obtain Brexpiprazole compound of Formula I.

Brexpiprazole obtained from above process is optionally further purified by techniques already known in prior art technique such as crystallization, solvent anti-solvent method etc. The solvent used for purification is selected from the group comprising of alcohol such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol and the like; chlorinated solvent such as dichloromethane and the like; esters such as ethyl acetate, propyl acetate and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; water or mixture thereof.

Brexpiprazole obtained by the process of the present invention is in fact substantially pure, and in particular substantially free from the dimer impurity of Formula D, wherein the dimer impurity is less than 0.1%. The expression "substantially pure" means having a purity degree equal to or higher than 99%.

Table no. 1: Comparative data for dimer impurity of Formula D of prior art *vis-a-vis* present invention:

Impurity D in 7-(4-chlorobutoxy) quinolin-2(1H)-one (%)	Impurity D in Brexpiprazole (pure) (%)
Prior art process (US 7,888,362)	
2.56	0.05 (after column purification)
As per the present invention	
0.014 - 0.027	Not detected (Batch process)

The process of present invention has following advantages:

(a) The reaction conditions are very simple and do not involve stringent critical operating parameters.

(b) The process provides brexpiprazole with purity of pharmacopoeial standard without involving any crystallization or cumbersome chromatographic purifications of intermediates or final brexpiprazole.

(c) The process is carried out in precisely selected solvents, which is integrated with in-process control of impurity formation or removal of impurities to provide intermediates and final brexpiprazole with high purity.

The process for the preparation of Brexpiprazole described in the present invention is demonstrated in the examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLE:

Example 1: Synthesis of 7-(4-chlorobutoxy) quinolin-2(1H)-one

Add 7-Hydroxy quinolin-2(1H)-one (20g) in DMF (100ml) in round bottom flask at 25-30°C. To this, added aqueous solution of potassium carbonate (17.2 g) at 25-30°C and heated the mixture to 35-40°C. To this added 1-Bromo-4-chloro butane (28.6 ml) at 35-40°C and stirred the reaction mass for 6-8 hours. Water (200ml) was added over a period of 30-40 minutes. The resulting mass was stirred for 30-40 minutes at 35-40°C and cooled to 10°C and filter. The resulting wet material was taken in methanol (200 ml) at 25-30°C and heated to reflux till complete dissolution. Cooled the solution to 5-10 ^{0}C and stirred for 30 minutes. Filtered the resulting solid, washed with methanol (20 ml) and dried at 60-65°C for 6-8 hours to obtain title compound.

Yield 24.5 g.

Example 2: Synthesis of 7-(4-chlorobutoxy) quinolin-2(1H)-one

Add potassium carbonate (9.42 g) in water (10ml) in round bottom flask and stirred for 10-15 min at 30-35°C. To this add DMF (50ml) and 7-Hydroxy quinolin-2(1H)-one (10g), heated the resulting mixture to 35-40°C and stirred for 10-15 min. To this added 1-Bromo-4-chloro butane (21.29 g) and stirred the reaction mass for 6-8 hours at 35-40°C, added water (20ml) drop wise over a period of 30-40 minutes and stirred the reaction mass for 30-40 min at 35-40°C. Cooled the reaction mass to 10°C, filtered and washed with methanol (20 ml) and DM water (20 ml) at 25-30°C to obtain wet material.

Yield: 11.0 g, HPLC purity- 95.8%; Dimer Impurity: 1.49%

To the resulting wet material (11.0 g), methanol (200ml) was added at 25-30°C and heated to reflux till complete dissolution. To this added AMBER LITE IR 120 H (10g) at 65-70°C and stirred for 1-1.5 hours at reflux temperature. Filtered the resulting mixture through hyflo at 60-65°C and cooled the filtrate to 5-10°C and stirred for 30 minutes. Filtered the material, washed with methanol (10 ml) and dried at 60-65°C for 5-8 hours.

Yield: 8.0 g, HPLC purity: 97.3%; Dimer impurity: 0.027%.

Example 3: Synthesis of 7-(4-chlorobutoxy) quinolin-2(1H)-one

Add 7-Hydroxy quinolin-2(1H)-one (10g) in DMF (50ml) in round bottom flask at 25-30°C. To this, added aqueous solution of potassium carbonate (9.87 g) and heated the mixture to 35-40°C under stirring. To this added 1-Bromo-4-chloro butane (21.3 ml) at 35-40°C and stirred the reaction mass for 5-6 hours. Water (15 ml) was added over a period of 30-40 minutes in 45-60 minutes. The resulting mass was stirred for 30-40 minutes at 35-40°C and cooled to 10-15°C and filter. The resulting wet material was washed with water, and suck dried.

Yield: 10.9 g, HPLC purity: 95.4%; Dimer Impurity: 1.48%;

To the resulting wet material (11.0 g), methanol (200ml) was added at 25-30°C and heated to reflux till complete dissolution. To this added AMBER LITE IR 120 H (10g) at 65-70°C and stirred for 1-1.5 hours at reflux temperature. Filtered the resulting mixture through hyflo at 60-65°C and cooled the filtrate to 5-10°C and stirred for 30 minutes. Filtered the material, washed with methanol (10 ml) and dried at 60-65°C for 5-8 hours.

Yield: 7.9 g, HPLC purity: 97.3% Dimer impurity: 0.014%.

Example 4: Synthesis of 7-(4-chlorobutoxy) quinolin-2(1H)-one

Add 7-Hydroxy quinolin-2(1H)-one (100g) in DMF (500ml) in round bottom flask at 25-30°C. To this, added aqueous solution of potassium carbonate (98.62 g)) at 25-30°C and heated the mixture to 35-40°C. To this added 1-Bromo-4-chloro butane (212 g) at 35-40°C and stirred the reaction mass for 6-8 hours. Water (150ml) was added over a period of 30-40 minutes. The resulting mass was stirred for 30-40 minutes at 35-40°C and cooled to 10°C and filter. The resulting wet material was taken in methanol (1000 ml) at 25-30°C and heated to reflux till complete dissolution. Cooled the solution to 10-15°C. Filtered the resulting solid, wash with methanol (100 ml) and dried at 60-65°C for 12-15 hours under vacuum to obtain title compound.

Yield 120 g (76%); HPLC purity: <96%

Example 5: Synthesis of crude Brexpiprazole

Add 1-(benzo[b]thiophen-4-yl) piperazine (21.20 g) and potassium carbonate (11.60g) in DMF (5ml) in round bottom flask at 25-30°C, heated the reaction mixture to 40-45°C

under stirring for 30 minutes. To this added 7-(4-chlorobutoxy) quinolin-2(1H)-one (20.0 g) and potassium iodide (13.8 g) at 40-45°C and heated the reaction mixture to 85-90°C followed by stirring for 2-3 hours. Cooled the reaction mixture to 45-50^{0}C, water (300 ml) was added at a temperature of 45-50 ^{0}C over a period of 30-40 minutes. Stirred the resulting mass for 30-40 minutes. Filtered the mixture at 30-35°C to obtain wet material (40g). The resulting wet material was taken in a mixture of ethanol (400 ml) and acetic acid (50 ml) at 30-35^{0}C and heated to reflux at 80^{0}C. Cooled the resulting solution to 30-35^{0}C and filter, washed the wet material with ethanol. Charged the wet material to a mixture of ethanol (400 ml) and water (100 ml) at 30-35^{0}C, heated to 75-80^{0}C for complete dissolution. Added activated charcoal (1 g), stirred the resulting mixture for 30-40 minutes filter at 75-80 ^{0}C. The resulting filtrate was heated to 75-80^0, and to this add aqueous solution of sodium bicarbonate (100 ml) at 75-80^{0}C under stirring for 1 hours. Cooled the resulting mass to 35-40^{0}C, filtered, wash with water and dried at 60-70^{0}C for 8-10 hours to obtain title compound. Yield 23 g.

Example 6: Synthesis of pure Brexpiprazole

Crude Brexpiprazole (20 g) was taken in ethanol (300 ml) in round bottom flask at 30-35^{0}C and heated to reflux at 75-80^{0}C followed by stirring for 30-40 minutes. Cooled the reaction mass to 30-35^{0}C and filter. Washed the wet cake with ethanol and dried under vacuum at 60-65^{0}C for 8-10 hours to obtain title compound. Yield 17.7 g.

Example 7: Synthesis of pure 7-{4-[4-(1-benzothiophen-4-yl) piperazin-1-yl] butoxy} quinolin-2 (1H)-one:

Add 1-(benzo[b]thiophen-4-yl) piperazine (106 g) and potassium carbonate (60g) in DMF (500ml) in round bottom flask at 25-30°C, heated the reaction mixture to 45-50^{0}C under stirring for 30 minutes. To this added 7-(4-chlorobutoxy) quinolin-2(1H)-one (100 g) and potassium iodide (69.25 g) and heated the reaction mixture to 90-95^{0}C for 2-3 hours. Cooled the reaction mixture, water (1500 ml) was added. Stirred the resulting mass for 30-40 minutes. Cooled to 10-15^{0}C, filtered and the resulting wet material was washed with water and ethanol. The resulting wet material was taken in a mixture of ethanol (3200 ml) and acetic acid (240 ml) and heated to reflux at 75-80^{0}C. Conc HCl (36 ml)

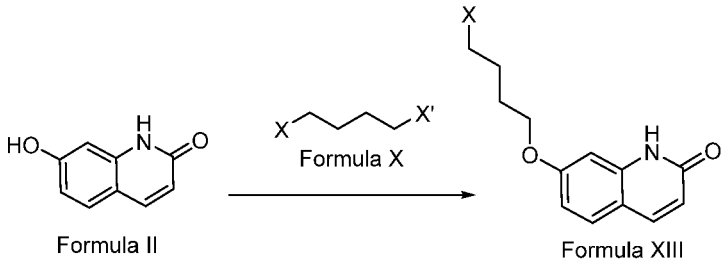
was added and stirred for 30-40 minutes. Cooled the resulting solution and then heated to 75-80^{0}C under stirring for 1-2 hours. Cooled, filtered and the resulting wet material was washed with ethanol. The resulting wet material was taken in ethanol (3200 ml) and water (100 ml) and heated to 75-80^{0}C for complete dissolution. Added activated charcoal (16 g), stirred the resulting mixture for 1-2 hours, filtered through hyflow. The resulting filtrate was heated to 75-80^0, and to this added aqueous solution of sodium bicarbonate (40 g in 800 ml water) under stirring. Added water (480 ml) at 75-80^{o}C. Cooled the resulting mass to 35-40^{0}C, filtered, washed with water. The resulting wet material was taken in ethanol (348 ml) and stirred for 1-2 hours. Filtered the material, washed the wet cake with ethanol and dried at 60-70^{0}C for 12-16 hours to obtain title compound.

Yield 110g (63.98%); HPLC purity: <99%; Dimer impurity: Not detected.

Claims:

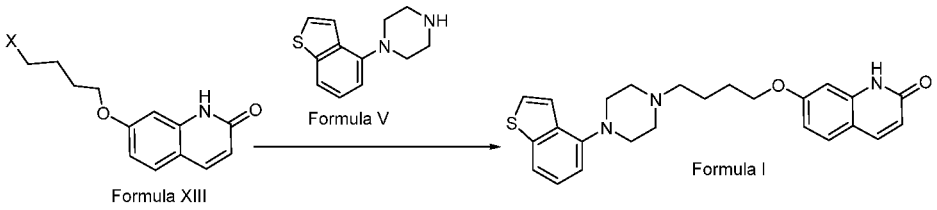
1. A process for the preparation of Brexpiprazole of Formula I, substantially free of dimer impurity of Formula D, comprising the steps of:

AA) reacting compound of Formula II with compound of Formula X in the presence of a base and solvent at temperature below 45°C to obtain compound of Formula XIII;



wherein X and X' are independently selected from halogen;

BB) reacting compound of Formula XIII with compound of Formula V or its salt in presence of base and solvent to obtain Brexpiprazole compound of Formula I



wherein X is defined as above.

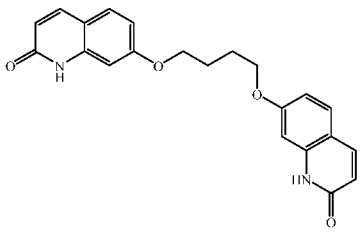
2. The process according to claim 1, wherein the base used in step (AA) and step (BB) are selected from inorganic and organic.

3. The process according to claim 2, wherein organic base is selected from the group comprising of triethylamine, diisopropylethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, N-methylpiperidine, N-methyl pyrrolidine, N-methylmorpholine; aromatic amines such as pyridine, lutidine and N,N-dimethylaniline.

4. The process according to claim 2, wherein the inorganic base is selected from the group comprising of alkali and alkaline earth metal hydroxide, carbonate, bicarbonate, hydride wherein the alkali and alkaline earth metal is selected from the group comprising of sodium, potassium, cesium, calcium and magnesium.

5. The process according to claim 1, wherein the solvent used in step (AA) and step (BB) is independently selected from the group comprising of ethers such as dioxane, tetrahydrofuran, 2-methyltetrahydrofuran, methyl *tert*-butyl ether; esters such as ethyl acetate, propyl acetate; halogenated hydrocarbons such as dichloromethane, chloroform; ketones such as acetone, methyl ethyl ketone; nitriles such as acetonitrile, propionitrile; aromatic hydrocarbons such as toluene, xylene chloroxylene,; polar solvents such as DMF, DMSO, DMA, sulfolane, hexamethylphosphoric triamide, or mixture thereof.

6. A process for the removal of dimer impurity of Formula D from compound of 7-(4-halobutoxy) quinolin-2(1H)-one compound of Formula XIII, comprising treating 7-(4-halobutoxy) quinolin-2(1H)-one compound of Formula XIII with resin in suitable solvent selected from the group of alcohols such as methanol, ethanol, propanol and butanol.



Impurity D (Dimer impurity)

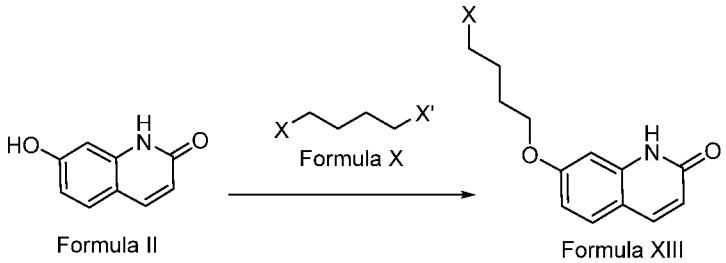
7. The process according to claim 6, where in the resin is selected from the group comprising of polystyrene-divinylbenzene, acrylic resins, crosslinked organic monomer and silica.

8. Brexpiprazole, substantially free from dimer impurity of Formula D obtained according to the claim 1, wherein the dimer impurity of Formula D is less than 0.15%.

9. A pharmaceutical composition comprising brexpiprazole substantially free from dimer impurity of Formula D obtained according to the claim 1.

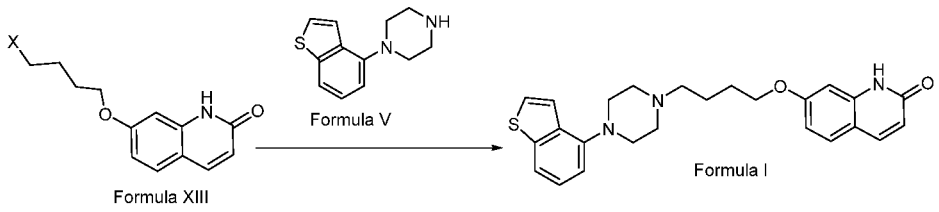
10. A process for the preparation of Brexpiprazole of Formula I, substantially free of dimer impurity of Formula D, comprising the steps of:

AA) reacting compound of Formula II with compound of Formula X in the presence of a base and solvent at temperature below 45°C to obtain compound of Formula XIII;



wherein X and X' are independently selected from halogen;

BB) reacting the resulting compound of Formula XIII with resin in alcohol solvent to obtain compound of Formula XIII, substantially free from dimer impurity of Formula D, followed by reaction with compound of Formula V or its salt in presence of base and solvent to obtain Brexpiprazole compound of Formula I.



wherein X is defined as above.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/22 C07D333/54 C07D409/12 A61K31/4709 A61P25/18 A61P25/24
ADD.
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)
C07D

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)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 9 206 169 B2 (OTSUKA PHARM CO LTD [JP]) 8 December 2015 (2015-12-08)	1-5,8,9
A	column 27; reference example 9; example 4	10

X	US 7 888 362 B2 (OTSUKA PHARMA CO LTD [JP]) 15 February 2011 (2011-02-15)	1-5,8,9
A	column 19; reference example 1 column 30; example 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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2017	24/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cortés Suárez, José

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/053018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 9206169 B2	08-12-2015	BR 112014001520 A2	14-02-2017
		CA 2843241 A1	31-01-2013
		CN 103717587 A	09-04-2014
		EP 2736894 A1	04-06-2014
		ES 2601457 T3	15-02-2017
		JP 5832558 B2	16-12-2015
		JP 2014523852 A	18-09-2014
		KR 20140054116 A	08-05-2014
		RU 2014107545 A	10-09-2015
		TW 201309679 A	01-03-2013
		US 2014187782 A1	03-07-2014
		WO 2013015456 A1	31-01-2013
US 7888362 B2	15-02-2011	AT 496911 T	15-02-2011
		US 2010179322 A1	15-07-2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/053018

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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

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

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

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

see annexes

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5, 8-10

The process of claim 1

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2. claims: 6, 7

The process of claim 6
