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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF IBRUTINIB

(57) Abstract: The present invention relates to an improved process for the preparation of Ibrutinib with high purity and high yields. The present process is cost effective and feasible in large scale production also. The present process avoids the mitsunobu reagent conditions also. The present Invention also relates to a process for the preparation of Crystalline form A and Crystalline form C of Ibrutinib.



## 5 AN IMPROVED PROCESS FOR THE PREPARATION OF IBRUTINIB

### Field of the Invention:

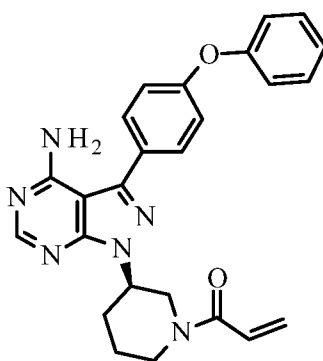
The present invention relates to an improved process for the preparation of Ibrutinib with high purity and high yields. The present Invention also relates to a process for  
10 the preparation of Crystalline form A and form C of Ibrutinib.

### Background of the Invention:

Ibrutinib is a kinase inhibitor indicated for the treatment of mantle cell lymphoma, chronic lymphocytic leukaemia and waldenstrom's macroglobulinemia.

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Ibrutinib is chemically is known as 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidiny]-2-propen-1-one and structurally represented as below.



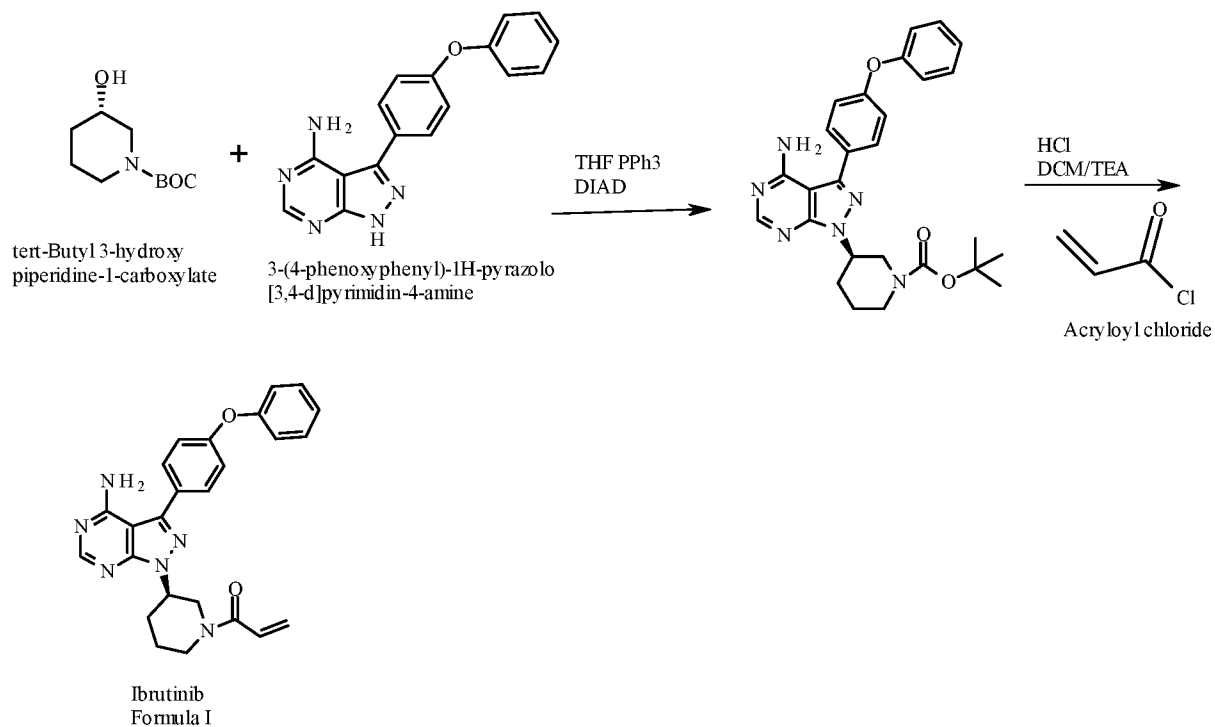
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IBRUTINIB

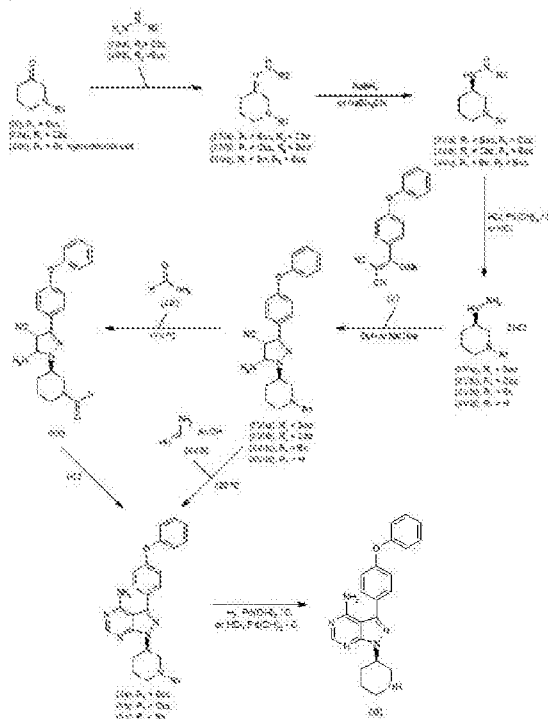
Formula-I

Ibrutinib is first disclosed in US 7514444 and marketed as IMBRUVICA<sup>®</sup>. US  
'444 patent is disclosed the Ibrutinib process, wherein 4-amino-3-(4-  
phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine is reacted with tert-Butyl 3-  
25 hydroxypiperidine-1-carboxylate and diisopropyl diazodicarboxylate to obtain  
intermediate under mitsunobu reaction conditions by converting the hydroxy  
moiety of the tert-Butyl 3-hydroxypiperidine-1-carboxylate to a better leaving  
group, thereby allowing a substitution reaction. Further it is converted to ibrutinib

- 5 by deprotection of Boc and acylation with acryl chloride. The reaction steps as illustrated by the following scheme I:



- US 9156847 patent has disclosed another process for the preparation of ibrutinib
- 10 intermediate, wherein the pyrazolo [3,4-D] pyridine-4-amine ring of ibrutinib is prepared through cyclization with use of formamide acetate and the reaction steps are illustrated in the below scheme II:



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According to this patent the process which is disclosed in US 7514444 patent has a number of disadvantages, such as those associated with cost, efficiency and environmental disadvantages. For instance the Mitsunobu step may be wasteful, costly and cumbersome.

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US9296753 patent has disclosed the crystalline forms A, B, C, D, E and F and their process for the preparation.

The present inventors of the present invention has developed an improved process for the preparation of Ibrutinib with high yield and high purity. The present process is cost effective and feasible in large scale production also. The present process avoids the mitsunobu reagent conditions also.

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### Summary of the present Invention:

One aspect of the present invention is to provide a process for the preparation of ibrutinib comprising the steps of:

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- 5 a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
- b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-  
10 phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,
- c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,
- 15 d) optionally purifying the ibrutinib.

Another aspect of the present Invention is to provide a process for the preparation of Ibrutinib Crystalline form A comprising the steps of:

- 20 a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
- b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine  
25 hydrochloride,
- c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,
- d) optionally purifying the ibrutinib.
- 30 e) dissolving ibrutinib in polar aprotic solvent and
- f) isolating Crystalline form A of ibrutinib.

Yet another aspect of the present Invention is to provide a process for the preparation of Ibrutinib Crystalline form C comprising the steps of:

- 5 a) reacting (S)-1-boc-3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
- b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,
- 10 c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,
- 15 d) optionally purifying the ibrutinib.
- e) dissolving ibrutinib in polar protic solvent and
- f) isolating Crystalline form A of ibrutinib.

Yet another aspect of the present invention is to provide a purification of ibrutinib comprising the steps of:

20

- a) dissolving ibrutinib in non-polar solvent or polar aprotic solvent or mixture thereof and
- b) isolating pure ibrutinib.

25 Yet another aspect of the present invention is to provide a process for the preparation of Crystalline form A of Ibrutinib comprising the steps of:

- a) dissolving ibrutinib in polar aprotic solvent and
- b) isolating Crystalline form A of ibrutinib.

30 Yet another aspect of the present invention is to provide a process for the preparation of Crystalline form C of Ibrutinib comprising the steps of:

- a) dissolving ibrutinib in polar protic solvent and
- b) isolating Crystalline form C of ibrutinib.

Yet another aspect of the present invention is to provide a process for the purification of ibrutinib comprising the steps of:

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- 5           a) dissolving ibrutinib in methylene chloride and toluene, and  
          b) isolating pure ibrutinib.

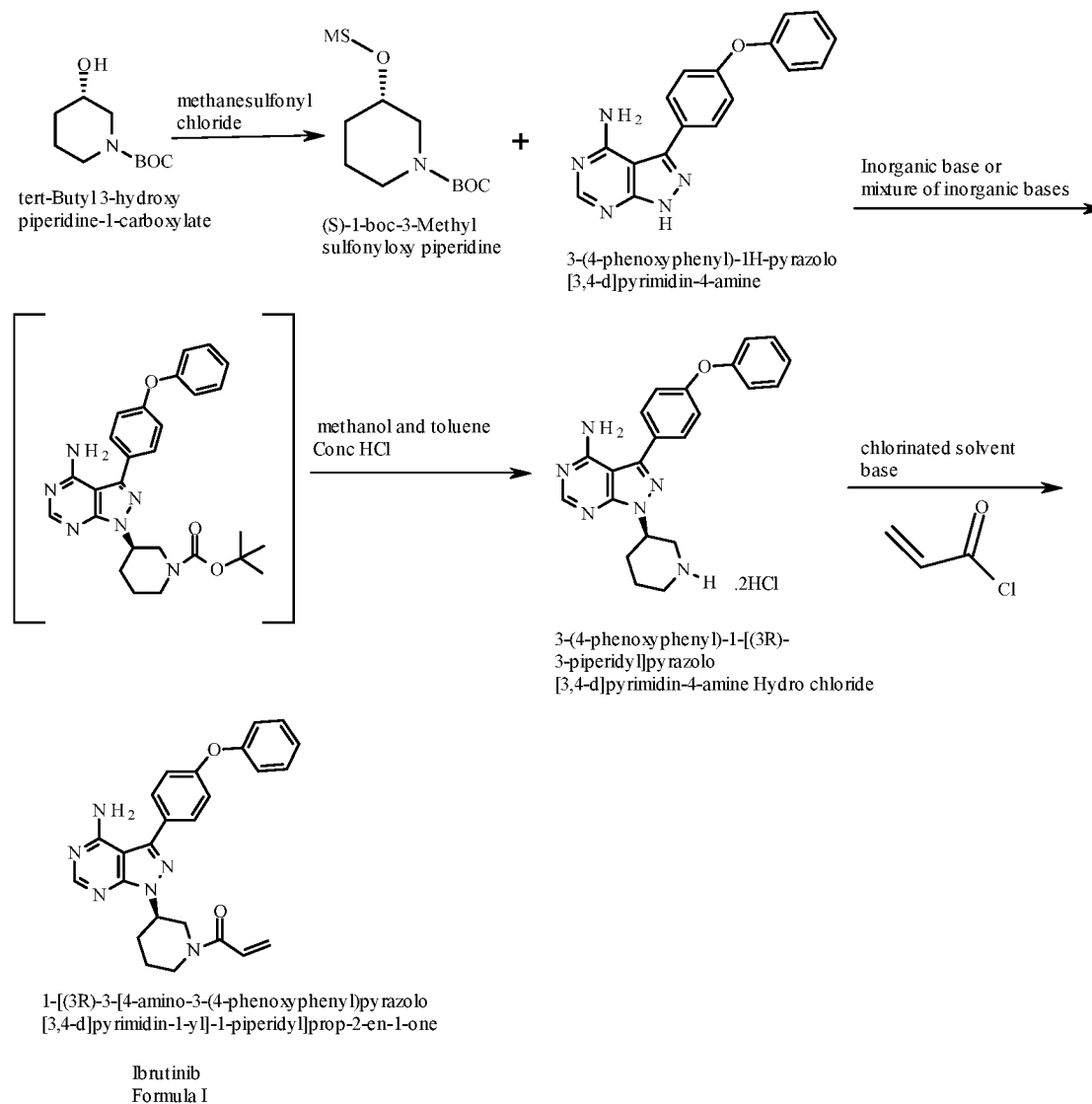
**Detailed description of the Invention:**

The present invention is related to an improved process for the preparation of  
10   Ibrutinib, wherein reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl  
          chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine and treating (S)-1-boc-3-  
          methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-  
          d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases  
          to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-  
15   4-amine hydrochloride and converted to ibrutinib reacting with acryloyl chloride.  
          Further ibrutinib is converted to crystalline form A and crystalline form C.

One embodiment of the present invention is to provide a process for the preparation  
of ibrutinib comprising the steps of:

- 20           a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to  
          get (S)-1-boc-3-methylsulfonyloxy piperidine,  
          b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-  
          phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of  
          inorganic base or mixture of inorganic bases to get (R)-3-(4-  
25   phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine  
          hydrochloride,  
          c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-  
          d]pyrimidine-4-amine hydrochloride with base followed by acryloyl  
          chloride to obtain ibrutinib,  
30           d) optionally purifying the ibrutinib.

The present invention is shown in the below scheme:



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According to the present invention, triethylamine is added to the reaction mixture of (S)-1-Boc-3-hydroxypiperidin and methanesulfonyl chloride in methylenechloride at -10 to 10°C. The reaction mass is allowed to ambient
 10 temperature and stirred for 30 min and washed with water. The organic layer is concentrated, stirred with hexane, filtered the solid and dried to yield (S)-1-boc-3-methylsulfonyloxy piperidine.

The solution of (S)-1-boc-3-methylsulfonyloxy piperidine in dimethylacetamide is
 15 added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-d]



- 5 pyrimidine-4-amine, inorganic base and another inorganic base in N-methyl pyrrolidine at 45-60°C. The reaction mass is heated to 75-90°C, stirred for 14h, filtered and concentrated. The concentrated mass is dissolved in 1:1 mixture of methanol-toluene and added hydrochloric acid. The reaction mixture is stirred for 4-6 h at 35-50°C, separated the aqueous layer and concentrated under vacuum. The
- 10 concentrated mass is stirred with methanol and ethyl acetate, filtered the solid and dried. The resulting dried product is dissolved in DM water and added to sodium carbonate solution and Ethyl acetate mixture. The product is filtered, washed with DM water and then the wet product is dissolved in Con.HCl and methanol mixture. The resulting reaction mass is concentrated, stirred with methanol and ethyl acetate
- 15 The product is filtered, washed and dried to to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride.

- The solution of (S)-1-boc-3-methylsulfonyloxy piperidine in dimethylacetamide is added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-
- 20 d]pyrimidine-4-amine, inorganic base and another inorganic base in dimethylacetamide at 45-60°C. The reaction mass is heated to 75-90°C, stirred for 14h, filtered and concentrated. The concentrated mass is dissolved in 1:1 mixture of methanol-toluene and added hydrochloric acid. The reaction mixture is stirred for 4-6 h at 35-50°C, separated the aqueous layer and concentrated under vacuum.
- 25 The concentrated mass is stirred with methanol and ethyl acetate, filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride.

- The solution of (S)-1-boc-3-methylsulfonyloxy piperidine in dimethylacetamide is added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-d]
- 30 pyrimidine-4-amine, inorganic base in dimethylacetamide at 45-55°C. The reaction mass is heated to 80-90°C, stirred for 14h, filtered and concentrated. The concentrated mass is dissolved in 1:1 mixture of methanol-toluene and added hydrochloric acid. The reaction mixture is stirred for 5-6 h at 40-50°C, separated
- 35 the aqueous layer and concentrated under vacuum. The concentrated mass is stirred

- 5 with methanol and ethyl acetate, filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride.

Acryloyl chloride is dissolved in methylene chloride and added to the cold reaction  
10 mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride and base in methylene chloride at -75 to -85°C. The reaction mass is stirred for 10 min at -80 to -90°C and washed with aqueous citric acid solution followed by aqueous sodium bicarbonate solution and water. The organic layer is concentrated, stirred with ethyl acetate and hexane, filtered the  
15 solid and dried to yield Ibrutinib.

Acryloyl chloride is dissolved in methylene chloride and added to the cold reaction mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride and base in methylene chloride at -75 to -85°C.  
20 The reaction mass is stirred for 10 min at -80 to -90°C and washed with aqueous citric acid solution followed by aqueous sodium bicarbonate solution and water. The organic layer is concentrated, to yield syrupy mass and dissolved in MDC and then added Toluene to crystallize product. The solid product is filtered and dried to yield Ibrutinib.

25

According to the present invention, Inorganic bases is selected from cesium carbonate, potassium carbonate, sodium carbonate, sodium bicarbonate, sodium phosphate, potassium phosphate, potassium phosphate, sodium acetate, potassium acetate, preferably potassium carbonate and cesium carbonate.

30

According to the present invention, base employed in step c) is selected from diisopropylethylamine and trimethylamine, preferably diisopropylethylamine.

Another embodiment of the present invention is to provide a purification of  
35 ibrutinib comprising the steps of:

- 5       a) dissolving ibrutinib in non-polar solvent or polar aprotic solvent or mixture thereof and  
b) isolating pure ibrutinib.

According to the present invention, non-polar solvent is selected from pentane,  
10   hexane, toluene and cyclophexane, preferably hexane.

According to the present invention, polar aprotic solvent is selected from tetrahydrofuran, ethyl acetate and dimethyl formamide, preferably ethylacetate.

15   Yet another embodiment of the present Invention is to provide a process for the preparation of Ibrutinib Crystalline form A comprising the steps of:

- a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,  
b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-  
20   phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,  
c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-  
25   d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,  
d) optionally purifying the ibrutinib.  
e) dissolving ibrutinib in polar aprotic solvent and  
f) isolating Crystalline form A of ibrutinib.

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Yet another embodiment of the present invention is to provide a process for the preparation of Crystalline form A of Ibrutinib comprising the steps of:

- a) dissolving ibrutinib in polar aprotic solvent and  
b) isolating Crystalline form A of ibrutinib.

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- 5 According to the present invention, polar aprotic solvent is selected from methylene chloride, ethyl acetate, acetone preferably ethyl acetate.

Yet another embodiment of the present Invention is to provide a process for the preparation of Ibrutinib Crystalline form C comprising the steps of:

- 10 a) reacting (S)-1-boc-3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,  
b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,  
15 c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,  
20 d) optionally purifying the ibrutinib.  
e) dissolving ibrutinib in polar protic solvent and  
f) isolating Crystalline form A of ibrutinib.

- Yet another embodiment of the present invention is to provide a process for the preparation of Crystalline form C of Ibrutinib comprising the steps of:

- 25 a) dissolving ibrutinib in polar protic solvent and  
b) isolating Crystalline form C of ibrutinib.

- According to the present invention, polar protic solvent is selected from methanol, ethanol, n-propanol preferably methanol.

Yet another embodiment of the present invention is to provide a process for the purification of ibrutinib comprising the steps of:

- a) dissolving ibrutinib in methylene chloride and toluene, and  
35 b) isolating pure ibrutinib.

5

The following examples are provided for illustrative purpose only and are not intended to limit the scope of invention in anyway.

**Example-1: PREPARATION OF (S)-1-boc-3-METHYLSULFONYLOXY  
10 PIPERIDINE**

Triethylamine (120.7 g) was added to the reaction mixture of (S)-1-Boc-3-hydroxypiperidin (200 g) and methanesulfonyl chloride (125.3g) in methylenechloride (2000 ml) at 0°C. The reaction mass was allowed to ambient temperature and stirred for 30 min and washed with water (2 x 2 l). The organic  
15 layer was concentrated, stirred with hexane (1.4 l), filtered the solid and dried to yield (S)-1-boc-3-methylsulfonyloxy piperidine (265 g; 96.0%).

**Example-2: PREPARATION OF (S)-1-boc-3-METHYLSULFONYLOXY  
PIPERIDINE**

20 Triethylamine (120.7 g) was added to the reaction mixture of (S)-1-Boc-3-hydroxypiperidin (200 g) and methanesulfonyl chloride (125.3g) in methylenechloride (2000 ml) at 0°C. The reaction mass was allowed to ambient temperature and stirred for 30 min and washed with water (2 x 2 l). The organic layer was concentrated, stirred with mixture of methylene chloride (120.0 ml) and  
25 hexane (1.4 l), filtered the solid and dried to yield (S)-1-boc-3-methylsulfonyloxy piperidine (254.0 g; 91.2%).

HPLC Purity: 99.5%; chiral purity: 100%

**Example-3: PREPARATION OF (R)-3-(4-PHENOXYPHENYL)-1-  
30 (PIPERIDIN-3-YL-1H-PYRAZOLO[3,4-d]PYRIMIDINE-4-AMINE  
HYDROCHLORIDE**

The solution of (S)-1-boc-3-methylsulfonyloxy piperidine (173.3 g) in N-methyl-2-pyrrolidone (525 ml) was added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine (75 g), cesium carbonate (217.7 g) in N-

5 methyl-2-pyrrolidone (600 ml) at 55°C. The reaction mass was heated to 80-85°C, stirred for 6-8h, water workup and partially concentrated. The partial concentrated mass was dissolved in methanol (935 ml) and added hydrochloric acid (186 ml; 18% w/v). The reaction mixture was stirred for 4-6 h at 45°C, separated the aqueous layer and concentrated under vacuum. The concentrated mass was stirred with  
10 methanol (225 ml) and ethyl acetate (975 ml), filtered the solid and dried. The resulting dried product was dissolved in DM water (800 ml) and added to sodium carbonate (55.4 g) solution and Ethyl acetate (160 ml) mixture. The product was filtered, washed with DM water and then the wet product was dissolved in Con.HCl (69 ml) and methanol (375 ml) mixture. The resulting reaction mass was  
15 concentrated, stirred with methanol (255 ml) and ethyl acetate (425 ml). The product was filtered, washed and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride (69 g; 60.7%).

HPLC Purity: 99.9%; chiral purity: 99.9%

20

**Example-4: PREPARATION OF (R)-3-(4-PHENOXYPHENYL)-1-(PIPERIDIN-3-YL-1H-PYRAZOLO[3,4-d]PYRIMIDINE-4-AMINE HYDROCHLORIDE**

The solution of (S)-1-*boc*-3-methylsulfonyloxy piperidine (115.5 g) in  
25 dimethylacetamide (300 ml) was added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine (50 g), cesium carbonate (13.4 g) and potassium carbonate (108.3 g) in dimethylacetamide (450 ml) at 55°C. The reaction mass was heated to 85°C, stirred for 14h, filtered and concentrated. The concentrated mass was dissolved in 1:1 mixture of methanol-toluene (1250 ml)  
30 and added hydrochloric acid (117 ml; 18% w/v). The reaction mixture was stirred for 6 h at 45°C, separated the aqueous layer and concentrated under vacuum. The concentrated mass was stirred with methanol (100 ml) and ethyl acetate (625 ml), filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride (59 g; 78.4%).

35 HPLC Purity: 99.6%

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**Example-5: PREPARATION OF (R)-3-(4-PHENOXYPHENYL)-1-(PIPERIDIN-3-YL-1H-PYRAZOLO[3,4-d]PYRIMIDINE-4-AMINE HYDROCHLORIDE**

The solution of (S)-1-*boc*-3-methylsulfonyloxy piperidine (11.55 g) in dimethylacetamide (20 ml) was added to the reaction mixture of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine (5 g) and potassium carbonate (6.15 g) in dimethylacetamide (55 ml) at 55°C. The reaction mass was heated to 100°C, stirred for 28h, filtered and concentrated. The concentrated mass was dissolved in 1:1 mixture of methanol-toluene (86 ml) and added hydrochloric acid (86 ml; 18% w/v). The reaction mixture was stirred for 30 h at 25°C, separated the aqueous layer and concentrated under vacuum. The concentrated mass was stirred with ethyl acetate (65 ml), filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride (3.5 g; 46.1%).

HPLC Purity: 98.5%

**Example-6: PREPARATION OF (R)-3-(4-PHENOXYPHENYL)-1-(PIPERIDIN-3-YL-1H-PYRAZOLO [3, 4-d] PYRIMIDINE-4-AMINE (IBRUTINIB)**

Acryloyl chloride (9.85 g) was dissolved in methylene chloride (150 ml) and added to the cold reaction mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride (50 g) and diisopropylethylamine (63.2 g) in methylene chloride (1000 ml) at -85°C. The reaction mass was stirred for 10 min at -85°C and washed with aqueous citric acid solution (500 ml; 5% w/w) followed by aqueous sodium bicarbonate solution (500 ml; 5% w/w) and water (500 ml). The organic layer was concentrated, stirred with ethyl acetate (300 ml) and hexane (300 ml), filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine crude (40.6 g; 84.8%).

HPLC Purity: 99.7%

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**Example-7: PREPARATION OF (R)-3-(4-PHENOXYPHENYL)-1-(PIPERIDIN-3-YL-1H-PYRAZOLO [3, 4-d] PYRIMIDINE-4-AMINE (IBRUTINIB)**

Acryloyl chloride (1 g) was dissolved in methylene chloride (10 ml) and added to  
10 the cold reaction mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo [3, 4-d] pyrimidine-4-amine hydrochloride (5 g) and diisopropylethylamine (5.6 g) in methylene chloride (75 ml) at -45°C. The reaction mass was stirred for 30 min at -45°C and washed with aqueous citric acid solution (50 ml; 5% w/w) followed by aqueous sodium bicarbonate solution (50 ml; 5%  
15 w/w) and water (50 ml). The organic layer was concentrated, stirred with ethyl acetate (30 ml), filtered the solid and dried to yield (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine crude (2.9 g; 60.6%).

**Example-8:PREPARATION OF 1-[(3R)-3-[4-AMINO-3-(4-PHENOXYPHENYL)-PYRAZOLO-[3,4-d]PYRIMIDIN-1-YL]-1-PIPERIDYL]PROP-2-EN-1-ONE) (IBRUTINIB)**

Acryloyl chloride (10.34 g) was dissolved in methylene chloride (50 ml) and added to the cold reaction mixture of (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride (50 g) and  
25 diisopropylethylamine (63.3 g) in methylene chloride (1000 ml) at -85°C. The reaction mass was stirred for 10 min at -85°C and washed with aqueous citric acid solution (2X500 ml; 5% w/w) followed by aqueous sodium bicarbonate solution (500 ml; 2% w/w) and water (500 ml). The organic layer was concentrated to yield syrupy mass and dissolved in MDC (50 ml) and then added Toluene (400 ml) to  
30 crystallize product. The solid product was filtered and dried to yield 1-[(3R)-3-[4-Amino-3-(4-Phenoxyphenyl)-Pyrazolo-[3,4-d]Pyrimidin-1-Yl]-1-Piperidyl]Prop-2-en-1-one (51 g)

HPLC Purity: 99.8%; chiral purity: 99.9%.



5     **Example-9: PREPARATION IBRUTINIB FORM - A**

1-[(3R)-3-[4-Amino-3-(4-Phenoxyphenyl)-Pyrazolo-[3,4-d]Pyrimidin-1-Yl]-1-Piperidyl]Prop-2-en-1-one (5.0 g), was dissolved in ethyl acetate (35 ml) at 25-35°C, filtered and crystallized from ethyl acetate. The product was filtered, washed and dried to yield pure Ibrutinib crystalline Form-A (3.3 g)

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**Example-10: PREPARATION IBRUTINIB PHARMA FORM - C**

1-[(3R)-3-[4-Amino-3-(4-Phenoxyphenyl)-Pyrazolo-[3,4-d]Pyrimidin-1-Yl]-1-Piperidyl]Prop-2-en-1-one (70.0 g) was dissolved in methanol (875 ml) at 50-55°C, filtered and crystallized from methanol. The product was filtered, washed and dried to yield pure Ibrutinib crystalline Form-C (51 g; 72.8%).

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HPLC Purity: 99.68%; chiral purity: 99.9%.

**5 We Claim:**

1. A process for the preparation of Ibrutinib comprising the steps of:
  - a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
  - b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of  
10 inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,
  - c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl  
15 chloride to obtain ibrutinib,
  - d) optionally purifying the ibrutinib.
2. A process for the preparation of Ibrutinib Crystalline form A comprising the  
20 steps of:
  - a) reacting (S)-1-boc -3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
  - b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of  
25 inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,
  - c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride with base followed by acryloyl  
30 chloride to obtain ibrutinib,
  - d) optionally purifying the ibrutinib,
  - e) dissolving ibrutinib in polar aprotic solvent and
  - f) isolating Crystalline form A of ibrutinib.

- 5     3. A process for the preparation of Ibrutinib Crystalline form C comprising the steps of:
- a) reacting (S)-1-boc-3-hydroxy piperidine with methane sulfonyl chloride to get (S)-1-boc-3-methylsulfonyloxy piperidine,
  - b) treating (S)-1-boc-3-methylsulfonyloxy piperidine with 3-(4-  
10     phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine in presence of inorganic base or mixture of inorganic bases to get (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4-amine hydrochloride,
  - c) reacting (R)-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-  
15     d]pyrimidine-4-amine hydrochloride with base followed by acryloyl chloride to obtain ibrutinib,
  - d) optionally purifying the ibrutinib,
  - e) dissolving ibrutinib in polar protic solvent and
  - f) isolating Crystalline form C of ibrutinib.
- 20
4. A process for the preparation of Crystalline form A of Ibrutinib comprising the steps of:
- a) dissolving ibrutinib in polar aprotic solvent and
  - b) isolating Crystalline form A of ibrutinib.
- 25
5. A process for the preparation of Crystalline form C of Ibrutinib comprising the steps of:
- a) dissolving ibrutinib in polar protic solvent and
  - b) isolating Crystalline form C of ibrutinib.
- 30
6. A process according to claims 1,2 and 3, wherein, Inorganic base is selected from cesium carbonate, potassium carbonate, sodium carbonate, sodium bicarbonate, sodium phosphate, potassium phosphate, potassium phosphate, sodium acetate, potassium acetate.
- 35

5     7. A process according to claims 1, 2 and 3, wherein, base employed in step c) is selected from diisopropylethylamine and trimethylamine.

8. A process according to claims 2 and 4, wherein, polar aprotic solvent is selected from methylene chloride, ethyl acetate.

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9. A process according claims 3 and 5, wherein, polar protic solvent is selected from methanol, ethanol, n-propanol.

10. A process for the purification of ibrutinib comprising the steps of:

- 15         a) dissolving ibrutinib in methylene chloride and toluene, and  
             b) isolating pure ibrutinib.

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