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Large scale process to prepare highly pure Bosentan monohydrate

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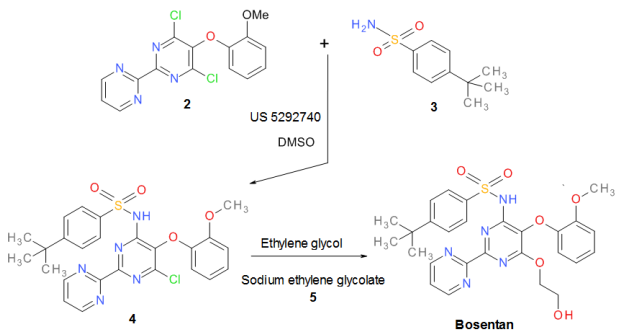
Abstract: Described is an improved process for the preparation of highly pure Bosentan monohydrate (>99.8% HPLC purity) 1 with pyrimidinone 8 and the dimer 9 impurities to less than 0.10% of HPLC analysis. The present work also provides processes for the preparation of pyrimidinone 8 and dimer 9 impurities.

Keywords: Bosentan Monohydrate, Highly Pure, Pulmonary Artery Hypertension

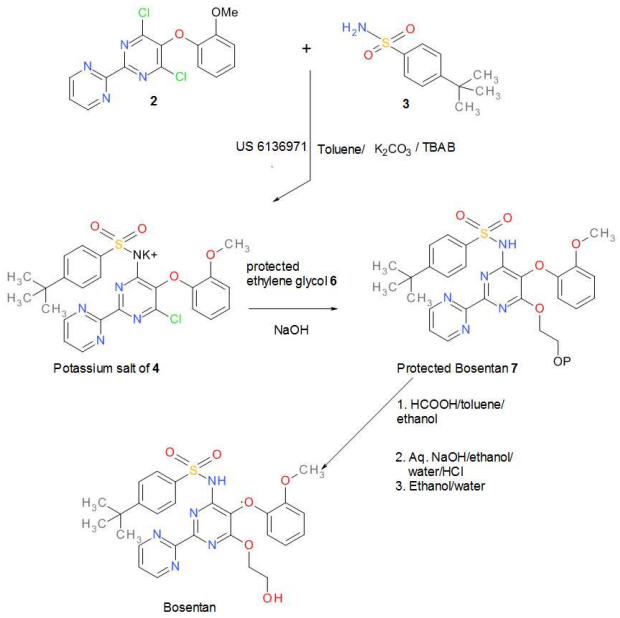
1. Introduction

Bosentan monohydrate (1, 4-*tert*-butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]benzene-1-sulfonamide monohydrate)is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH) [1]. It is licensed in the United States, the European Union and other countries by Actelion Pharmaceuticals for the management of PAH under the trade name Tracleer.The first synthetic pathway reported [2] for 1 involved the condensation of dichloro pyrimidine 2 with sulfonamide 3 in dimethylsulfoxide (DMSO) to provide p-tert-butyl-N-[6-chloro-5-(2-methoxyphenoxy)-4-pyrimidinyl] benzene sulfonamide4. Coupling of 4and sodium ethylene glycolate 5 in ethylene glycol as a solvent at a temperature of 100^{o}C gives crude sodium salt (Scheme1).



Scheme 1. *ROS of US 5292740*

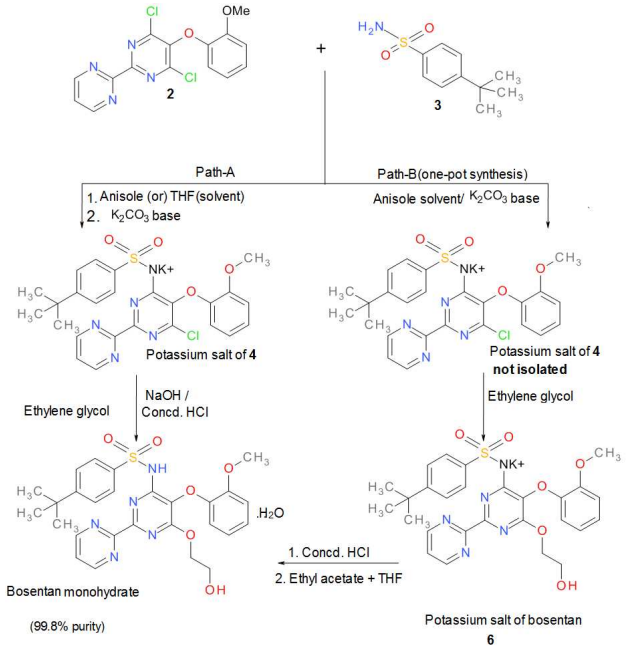
This process suffers from a number of drawbacks from the industrial point of view. In particular, the use of ethylene glycol sodium salt, which is a reagent difficult to prepare and use as it is toxic and irritant. Furthermore, this process involves the formation of the impurities: in particular the pyrimidinone 8 and the dimer 9. Complex purification processes of the final product are required in order to remove these by-products, thereby involving both operative and economic disadvantages. Another synthetic pathway reported [3] for 1 is a multistep process that involves the condensation of compound 2 with 3 in toluene in the presence of anhydrous potassium carbonate and a phase transfer catalyst, benzyltriethylammonium chloride to provide the potassium salt of 4. Subsequent reaction of compound 4 with protected ethylene glycol 6 offered protected bosentan 7. Deprotection of 7using formic acid yielded intermittent intermediate bosentan formate monoethanolate, which was hydrolyzed with ethanolic sodium hydroxide provided crude bosentan after acidification. Further purification of the crude bosentan using a mixture of ethanol and water afforded bosentan monohydrate (Scheme 2).



Scheme 2. *ROS of US 6136971*

It is apparent that although this process overcomes the drawbacks of the earlier process, i.e., it avoids the formation of the dimer 9, it involves at least two further reaction steps. From an industrial point of view, two additional steps obviously increase the cost of the process, thereby making it uneconomical. Another synthetic pathway reported [4] for 1comprises the reaction of 2 with 3, potassium carbonate and ethylene glycol in 1: 1.09: 8.6: 56.3 mole ratio in acetonitrile solvent in the same pot. It also describes a novel purification method for the removal of critical impurities 8 and 9 by preparation of Bosentan ammonium salt using ammonium hydroxide. This process when implemented on laboratory scale it was found that for reaction completion potassium carbonate fusion is necessary which is not viable on commercial scale. Without potassium carbonate fusion reaction is not going to completion even after prolonged hours (more than 40hours) thereby resulted in impure product after workup (HPLC purity: 99.25%; 0.55% impurity 8 and 0.13% impurity 9). Moreover all the mixed solvents are not recoverable.

Subsequently, a few other processes are reported [5] following the synthetic path way represented in Scheme 1 suffer from the disadvantage of less purity, multiple reactions, operations and purification steps, ultimately lowering the yield of Bosentan drastically. In this paper, we are reporting one pot synthesis using anisole as a solvent to provide Bosentan from less number of steps, extractions and reaction hours operating under milder conditions in comparison to known methods as follows [6]: (1) Condensing 4,6-dichloro-5-(2-methoxyphenoxy)-[2,2']bipyrimidine (2) with 4-tert-butyl benzene sulfonamide (3) in presence of potassium carbonate in anisole to form p-tert-butyl-N-[6-chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)pyrimidin-4-yl] benzenesulfonamide (potassium salt of (4), not isolated), which on reaction with ethylene glycol to obtain 4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2'] bipyrimidin-4-yl] benzenesulfonamide potassium salt (Bosentan K^+-salt); (4) Recrystallization of Bosentan K^+-salt with 5% aqueous acetonitrile followed by salt breaking with conc.HCl to give bosentan technical grade product (Bosentan-tech); (c) Carbon treatment of Bosentan technical grade product and recrystallization with a mixture of acetone and ethyl acetate gives purified bosentan. D). Carbon treatment in methanol and precipitation with water gives bosentan monohydrate final pharma grade product (bosenatan pharma) with improved color (Scheme 3). More particularly, this process provides Bosentan monohydrate of high purity (>99% by HPLC).



Scheme 3. *Novel route of synthesis*

2. Results and Discussion

2.1. Optimization of the Process for the Preparationof4-Tert-Butyl-N-[6-(2-Hydroxyethoxy)-5-(2-Methoxyphenoxy)-2-(Pyrimidin-2-yl) Pyrimidin-4-yl] Benzene-1-Sulfonamide Monohydrate (1)

The key starting material dichloro pyrimidine 2 utilized in the present work was synthesized according to the reported process [2]. During development condensation of dichloro pyrimidine 2and sulfonamide 3 has been attempted in solvents such as anisole and THF using different inorganic bases such as sodium hydroxide and potassium carbonate at various temperatures. Among these combinations anisole solvent is selected based on its high boiling, recovery and water immiscibility for the ease of work up. Anisole with potassium carbonate base yielded potassium salt of 4with optimum HPLC purity 99.3% at 140°C.Then condensation of potassium salt of 4with ethylene glycol to yield bosentan was studied with solvents such as acetonitrile, ethylene glycol and anisole using different inorganic bases such as sodium

hydroxide and potassium carbonate at various temperatures. Among these combinations it was found that with potassium carbonate base yielded potassium salt of bosentan with optimum HPLC purity 99.0% at 90-95^{o}C.As high boiling solvent anisole with potassium carbonate base was found to be suitable for both the stages one pot synthesis for bosentan potassium salt was designed starting from dichloro pyrimidine 2 and sulfonamide 3 condensation. Solvent anisole recovery up to 90% was established on commercial scale.

2.1.1. Temperature Study for Bosentan-K-Salt Formation with Anisole Solvent and Potassium Carbonate Base

Temperatures varying from 90^{o}C to 150^{o}C were studied. Reaction completion at 4-potassium salt stage and at bosentan-K-salt stage was monitored using TLC technique. At low temperatures (90-120^{o}C) reaction was slow thus resulting in objectionable quantities of impurities thereby rendering in low yield after workup. At high temperatures (126-135^{o}C) although the reaction was fast impurities are formed in objectionable quantities thereby rendering in low yield after workup. At very high temperatures (150-155^{o}C) product got converted into impurity 8 completely. At 120-125^{o}C optimum yield and quality were obtained (Table 1). So, based on these results temperature 120-125^{o}C is selected for further optimization.

Table 1. *Temperature study in anisole solvent and potassium carbonate base for Bosentan-K-salt*

entry	Temp (^{o}C)	Reaction Time by TLC (h) for 4-K-salt for Bosentan-K-salt (Check-1)(Check-2)		Bosentan-K-salt Purity (%)	Yield (%)
1.0	90-100	18	31	98.7 with 0.16% impurity 8 and 0.35% impurity 9	65.4
2.0	110-115	10	6	98.7 with 0.21% impurity 8 and 0.17% impurity 9	80.3
3.0	120-125	6.5	3.5	98.9 with 0.50% impurity 8 and 0.16% impurity 9	88.9
4.0	126-130	6.5	3.5	98.9 with 0.56% impurity 8 and 0.16% impurity 9	78.5%
5.0	131-135	4.0	1.5	99.0 with 0.68% impurity 8 and 0.10% impurity 9	64.3
6.0	150-155[a]	1.0	1.0	-	-

[a]Product is not formed and impurity 8 is formed exclusively

2.1.2. Potassium Carbonate Moles Study for Bosentan-K-Salt Formation with Anisole Solvent

Molar equivalents of 2, 4, 5 and 6 potassium carbonate were studied with respect to 4,6 dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine 2. The experimental results indicated that optimum yield and quality were obtained with 6 molar equivalents of potassium carbonate (Table 2).

Table 2. *Potassium carbonate moles study in anisole solvent at 120^{o}C for Bosentan-K-salt*

entry	moles	Reaction Time by TLC (h) for 4-K-salt for Bosentan-K-salt (Check-1) (Check-2)		Bosentan-K-salt Purity (%)	Yield (%)
1.0	2[a]	40	-		
2.0	4	14	15	99.2 with 0.32% impurity 8 and 0.11% impurity 9	68.4
3.0	5	12	15	99.1 with 0.33% impurity 8 and 0.16% impurity 9	59.5
4.0	6	06	05	99.1 with 0.40% impurity 8 and 0.16% impurity 9	88.9%

[a]Reaction is incomplete and product is not isolated

2.1.3. Ethylene Glycol moles Study for Bosentan-K-Salt Formation with Potassium Carbonate Base

Molar equivalents of 60, 100 and 125 ethylene glycol were studied with respect to 4,6- dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine 2. The experimental results indicated that optimum and quality with were obtained with 125 moles of ethylene glycol (Table 3).

Table 3. *Ethylene glycol moles study in anisole solvent at 120^{o}C for Bosentan-K-salt*

entry	moles	Reaction Time by TLC (h) for 4-K-salt for Bosentan-K-salt (Check-1) (Check-2)		Bosentan-K-salt Purity (%)	Yield (%)
1.0	60	7.0	6.0	97.8 with 1.22% impurity 8 and 0.40% impurity 9	77.0
2.0	100	7.0	6.0	98.0 with 1.16% impurity 8 and 0.38% impurity 9	74.1
3.0	125	7.0	4.0	99.0 with 0.50% impurity 8 and 0.16% impurity 9	88.9

Table 4. *Solvent selection for Bosentan-K-salt purification*

entry	Bosentan-K-salt purity before purification (%)	Bosentan-K-salt purity after purification (%)	Yield % (wt/wt)*	Remarks
1.0	98.8 with 0.17% impurity 8 and 0.37% impurity 9	99.3 with 0.10% impurity 8 and 0.34% impurity 9	66	Crystallization with 5 volumes DM water
2.0	98.8 with 0.77% impurity 8 and 0.17% impurity 9	99.0 with 0.03% impurity 8and 0.16% impurity 9	75	Crystallization with 9.3:0.7DM water + acetonitrile
3.0	98.6 with 0.77% impurity 8 and 0.42% impurity 9	99.68 with 0.19% impurity 8 and 0.10% impurity 9	41	Two crystallizations 9.5:0.5 acetonitrile+water 0.5 acetonitrile + 9.5 DM water
4.0	98.3 with 1.1% impurity 8 and 0.36% impurity 9	99.30 with 0.38% impurity 8 and 0.11% impurity 9	65	Crystallization with 9.5:0.5 acetonitrile + DM water (10 volumes)
5.0	99.0 with 0.68% impurity 8 and 0.16% impurity 9	99.30 with 0.08% impurity 8 and 0.06% impurity 9	62	Crystallization with 9.5:0.5 acetonitrile + DM water (8 volumes)

3.1.4. Solvent Selection for Bosentan-K-Salt Purification

Bosenatan-K-salt purification was tried in DM water, acetonitrile and mixture of these two based on solubility of potassium salt impurities. This purification was aimed for the minimization (<0.1) of dimer impurity 9 which was difficult to remove after liberating bosentan from potassium salt. It was found that crystallization with 9.5:0.5 acetonitrile + DM water (8 volumes) gave product with dimer impurity within limits (<0.1%) (Table 4).

3.1.5. Solvent Selection for Bosentan Technical Grade Product (Bosentan-Tech) Purification

Bosentan-tech purification was attempted in mixture of solvents such as ethyl acetate, THF and acetone. Although with THF and ethyl acetate mixture yielded product with minimum pyrimidinone impurity 8 residual solvent test failed in THF content. So, finally acetone and ethyl acetate mixture yielded passing quality bosentan. Experiments were conducted on maintenance time and temperature after crystallization with ethyl acetate and acetone (Table 5). Based on the experimental data maintenance temperature is fixed as RT (28°C) and maintenance time is fixed as 5hours. For color improvement of the product and to facilitate monohydrate formation methanol and water precipitation step was introduced.

Table 5. *Experimental data for maintenance temperature/time study of Bosentan - tech*

entry	Bosentan-K-salt purity before purification (%)	Bosentan-K-salt purity after purification (%)	Reaction Temp(°C)	Time(h)	Yield %
1.0	99.7 with 0.25% impurity 8 and 0.02% impurity 9	99.88 with 0.09% impurity 8 and 0.02% impurity 9	10-15	2.0	84.0
2.0	99.7 with 0.25% impurity 8 and 0.02% impurity 9	99.69 with 0.08% impurity 8 and 0.02% impurity 9	15-20	2.0	80.0
3.0	99.77 with 0.19% impurity 8 and 0.04% impurity 9	99.77 with 0.0.06% impurity 8 and 0.03% impurity 9	RT	3.0	78.8
4.0	99.77 with 0.19% impurity 8 and 0.04% impurity 9	99.77 with 0.0.06% impurity 8 and 0.03% impurity 9	RT	5.0	77.7

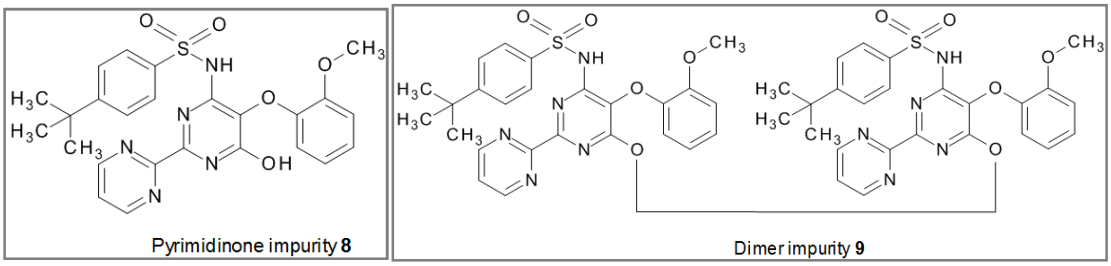


Figure 1. *Pyrimidone impurity 8 and Dimer impurity 9*

3.1.6. Discussion on other Impurities

Table 6. *Experimental data for fixing limit of diethylene glycol in ethylene glycol*

entry	Input	Bosentan-K-salt (RC) purity with bosentan-diethylene glycol impurity (BOS-DEG) content	Bosentan-tech purity with bosentan-diethylene glycol impurity (BOS-DEG) content	Bosentan purity with bosentan-diethylene glycol impurity (BOS-DEG) content
1.0	Ethylene glycol spiked with 1% diethylene glycol	99.57% with 0.28% BOS-DEG	99.57% with 0.28% BOS-DEG	99.72% with 0.18% BOS-DEG
2.0	Ethylene glycol spiked with 0.5% diethylene glycol	99.71% with 0.13% BOS-DEG	99.71% with 0.13% BOS-DEG	99.87% with 0.07% BOS-DEG

As diethylene glycol (DEG) is an expected impurity in ethylene glycol the following impurity is prepared by condensing potassium salt of 4 with DEG (Figure-2). Although this impurity is not present in our product, to fix the limit of DEG in commercial grade ethylene glycol, 1% and 0.5% concentrations of DEG is spiked in ethylene glycol and the corresponding Bosentan-DEG impurity level is monitored at various stages of bosentan (Table 6). Based on the data limit of DEG in ethylene glycol is fixed as 0.5%.

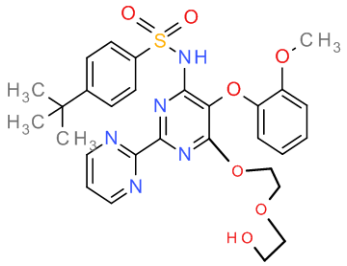


Figure 2. *(Bosentan - DEG impurity)*

2.1.7. Discussion of Drying Conditions

As bosentan is monohydrate at temperatures (60^{o}C) it loses its bound water and turns into anhydrous from. So, for Bosentan pharma drying operation 30-35^{o}C/ vacuum, 35-40^{o}C/vacuum, and 35-40^{o}C/without vacuum were studied. At 30-35^{o}C/ vacuum product failed in residual methanol content. At 35-40^{o}C/vacuum residual methanol content was within limit but its water content was below theory (2.22% w/w against 3.0% by theory). At 35-40^{o}C/without vacuum bosentan pharma passed residual methanol content and its hydrate content is intact. So, bosentan monohydrate drying condition is fixed as 35-40^{o}C/without vacuum.

Thus all the reaction parameters were studied thoroughly and bosentan monohydrate was implemented on commercial scale without any problems.

3. Summary

A cost effective effective, high yielding, production friendly process for the production of highly pure bosentan monohydrate is described.

3.1. Experimental Section

Melting points were determined on mettler melting point apparatus, in open capillary tubes and are uncorrected. The ^{1}H NMR (400MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker avance-III 400MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as an internal standard and are given in δ units. The solvent used for NMR spectra is deuterodimethylsulfoxide unless otherwise stated. Infrared spectra were taken on Bruker in potassium bromide pellets unless otherwise stated. High-resolution mass spectra were obtained with a waters mass spectrometer. All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60F254 (Merck) plates using UV light (254 and 366 nm). The gas chromatography on Agilent Technologies 6890B with head space was used for analyzing the residual solvents. Common reagent grade commercially available chemicals were used without further purification.

3.2. Preparation of 4-Tert-Butyl-N-[6-(2-Hydroxyethoxy)-5-(2-Methoxyphenoxy)-2-(Pyrimidin-2-yl) Pyrimidin-4-yl] Benzene-1-Sulfonamide Monohydrate (I)

3.2.1. Step-A: Preparation of 4-Tert-Butyl-N-[6-(2-Hydroxyethoxy)-5-(2-Methoxyphenoxy)-2-(Pyrimidin-2-yl)Pyrimidin-4-yl]Benzene-1-Sulfonamide Potassium Salt (Bosentan Potassium Salt)

4, 6- Dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine 2 (20kg, 0.057 moles) and anisole(300L)were placed in a reaction flask. Potassium carbonate (47.4kg, 0.343 moles) was added and reaction mass was stirred for 15 minutes. 4-tert-butylbenzenesulphonamide 3 (30.5g, 0.057 moles) was added to reaction mass and heated to 120^{o}C for 7 hours. Ethylene glycol (444kg, 7.16 moles) was charged to reaction mass and maintained at 120^{o}C for 5 hours and brought to room temperature. Reaction mass was poured into purified water (1500 L) and stirred for 30 minutes. The precipitated solid was isolated by filtration, washed with acetonitrile and dried at 60-65^{o}Cin laboratory oven to afford bosentan potassium salt. (30.3kg, yield 90%, purity by HPLC: 98.9% with 0.703% impurity 8, 0.165% impurity 9)

3.2.2. Step-B: Preparation of Bosentan Technical Grade Product

The bosentan potassium salt (100kg) obtained above was dissolved in aqueous acetonitrile (5% water, 1000L) at 60-65^{o}C and brought to room 20-25^{o}C. Reaction mass was maintained at room temperature for 2 hours, filtered and washed acetonitrile (100L) to yield bosentan potassium salt (wet weight: 125kg). The wet compound was dissolved in DM water (2000L) and adjusted pH with concentrated hydrochloric acid (90L). Reaction mass was maintained at room temperature for 2 hours, filtered and washed with DM water (200L). The wet bosentan technical grade product was dried at 30-35^{o}C for 4 hours in laboratory oven (58kg, purity by HPLC: 99.64% with 0.28% impurity 8, 0.047% impurity 9).

3.2.3. Step-C: Preparation of Bosentan Monohydrate

Bosentan technical grade (55kg) product was dissolved in a mixture of ethyl acetate (165L) and acetone (60L) at 60-65^{o}C. Reaction mass was brought to 40-45^{o}C and activated carbon (2.75kg) was added. Reaction mass filtered on hyflow and washed with ethyl acetate (55L). Filtrate was cooled to 15-20^{o}C and maintained at the same temperature for 2 hours. Separated bosentan was filtered and washed with chilled ethyl acetate (28L). The wet product was dissolved in methanol (616L) at reflux temperature. Reaction mass was brought to 50-55^{o}C and activated carbon

(2.5kg) was added. Charcoalized solution was filtered on hyflow and washed with methanol (44L). Filtrate was heated to reflux temperature and slowly added DM water (990L) at the same temperature for 30minutes. Reaction mass was brought to room temperature, maintained for 2 hours, filtered and washed with DM water (150L). Wet product was dried in vacuum oven at 35-40^{o}C for 8 hours. (42kg, purity by HPLC: 99.90% (with 0.05% impurity 8 and 0.02% impurity 9)); Melting range: 114-118°C.IR (KBr, cm^{-1}):3627.82, 3438.77, 2962.19, 1558.60, 1252.77, 1171.69, 1083.34; ^{1}H NMR (AV 400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 9.01-6.85 (m, 11H), 4.86 (t, 1H), 4.58 (t, 2H), 3.94 (s, 3H), 3.85 (t, 2H), 1.28 (s, 9H); ^{13}C NMR (AV100 MHz, $CDCl_3$):δ 161.28, 161.61, 157.59, 157.10, 155.50, 151.55, 149.48, 145.45, 136.00, 129.23, 125.27, 124.47, 121.22, 121.08,.118.81, 112.37, 71.37, 62.13, 55.90, 35.00, 30.90.(21 signals); MS m/z (%): 550.2 $[M - 1]^{+}$ (100).

3.3. Preparation of Pyrimidinone Impurity (8)

4, 6- dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine 2 (10 g, 0.0285 moles) and anisole(750ml)were placed in a reaction flask. Potassium carbonate (34 g, 0.246 moles) was added and reaction mass was stirred for 15 minutes. 4-tert-butylbenzenesulphonamide 3 (6.7 g, 0.0315 moles) was added to reaction mass and heated to 150^{o}C for 1 hour. Ethylene glycol (177.6 g, 2.86 moles) was charged to reaction mass and maintained at 150^{o}C for 6hours and brought to room temperature. Reaction mass was poured into purified water (300 ml) stirred for 30 minutes and acidified with hydrochloric acid. The precipitated solid was isolated by filtration, drying to afford pyrimidone impurity 8(4 g, yield, purity by HPLC: 98.2%); Melting range: 223-226°C;IR (KBr, cm^{-1}): 32.14.49, 3039.53, 2962.09, 1564.20, 1247.89, 1170.25, 1080.61; ^{1}H NMR (AV 400 MHz, DMSO-d_6): δ 10.94 (s, 1H), 9.04(s, 1H), 8.99-6.87(m, 11H), 4.08 (s, 3H). 1.29 (s, 9H); MS m/z (%): 506.3 $[M - 1]^{+}$(100).

3.4. Preparation of Dimer Impurity (9)

Bosentan (10 g, 0.01755 moles) and dimethyl acetamide (200 ml) were placed in a reaction flask under nitrogen atmosphere. Sodium hydride (2.1g, 0.0877 moles) was added slowly and reaction mass was stirred for one hour. 4-tert-butyl-N-[6-chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyridinyl]benzene sulfonamide 4 (9.2 g, 0.01755 moles) was dissolved in dimethyl acetamide (100 ml) and added slowly to the reaction mass. Reaction mass was maintained at room temperature for 50 hours. Reaction mass was quenched with purified water (2.6 L), acidified with hydrochloric acid and filtered. Thus obtained dimer impurity 9 (16 g) was purified further by recrystallization with THF (6g, purity by HPLC: 98%);Melting point: 201°C (decom); IR (KBr, cm^{-1}):3280.49, 2962.17, 1557.23, 1256.46, 1162.81, 1097.67; ^{1}H NMR (AV 400 MHz, DMSO-d_6): δ 11.33 (s, 2x1H), 9.03-6.02 (m, 2x11H), 4.50 (s, 2x2H), 3.62 (s, 2x3H), 1.26 (s. 2x9H); MS m/z (%): 1039.2 $[M - 1]^{+}$ (100).

3.5. Preparation of Digol Impurity

4,6- Dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine 2 (50g, 0.143 moles) and anisole (750 ml) were placed in a reaction flask. Potassium carbonate (118.4g, 0.858 moles) was added and reaction mass was stirred for 15 minutes. 4-tert-butylbenzenesulphonamide 3 (30.5g, 0.143 moles) was added to reaction mass and heated to 120^{o}C for 7 hours. Diethylene glycol (1900g, 17.9 moles) was charged to reaction mass and maintained at 120^{o}C for 5 hours and brought to room temperature. Reaction mass was poured into purified water (4.5 L) and stirred for 30 minutes. The precipitated solid was isolated by filtration, washed with acetonitrile. The wet product was acidified with concentrated hydrochloric acid, recrystallized with mixture of methanol and water and dried at 60-65^{o}C in laboratory oven to afford digol impurity.(60g, purity by HPLC: 99.1%); Melting range: 108-111°C ; IR (KBr, cm^{-1}):3300.63, 3068.05, 2955.23, 1558.39, 1253.99, 1171.76, 1081.35; ^{1}H NMR (AV 400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 9.01-6.83 (m, 11H), 4.69 (t, 2H), 3.96 (s, 3H). 3.73 (t, 2H), 3.61 (t, 2H), 3.47 (t, 2H), 2.15 (t, 1H), 1.29 (t, 9H); MS m/z (%): 596.3 $[M + 1]^{+}$ (100)

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