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Facile One-Pot Process for Large-Scale Production of Highly Pure Bosentan Monohydrate, an Endothelin Receptor Antagonist[#]

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Supporting Information

ABSTRACT: Described is an efficient, economic, and one-pot process for the production of highly pure bosentan (**1**), an endothelin receptor antagonist. The synthesis comprises the reaction of 4,6-dichloro-5-(2-methoxyphenoxy)-2,2′-bipyrimidine (**2**) with 4-*tert*-butylbenzenesulfonamide (**3**) and ethylene glycol (**4**) in acetonitrile in the presence of potassium carbonate to yield bosentan (**1**) in the same pot. The present work also describes a novel purification method for the removal of critical dimer impurity (**7**) and 6-hydroxy impurity (**8**) in **1** by preparation of bosentan ammonium salt (**6**) using inexpensive ammonium hydroxide. Upon purification, bosentan monohydrate (**1**) with an overall yield of 68% and HPLC purity of 99.90% was achieved.

INTRODUCTION

Bosentan monohydrate (4-*tert*-butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]benzene-1-sulfonamide monohydrate), a dual endothelin receptor antagonist (ERA) is the first orally active drug developed by Actelion, approved by United States Food and Drug Administrative as Tracleer (65 mg and 125 mg) for the successful treatment of pulmonary arterial hypertension (PAH).[1] Tracleer improves the exercise ability and decreases the rate of clinical worsening in patients with WHO Class III or IV symptoms of PAH by blocking the binding of endothelin to its receptors, thereby negating endothelin's deleterious effects. Further, it has been demonstrated to be effective in remodeling the pulmonary vascular tree through several mechanisms including vasodilatation and antifibrotic and antithrombotic actions.[2] The first synthetic approach reported[3] for **1** involved the condensation of dichloro compound **2** with sulfonamide **3** in dimethylsulfoxide (DMSO) to provide *p*-*tert*-butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide (**5**). It was observed that this reaction was incomplete with several impurities; hence, isolation of **5** was difficult without column chromatography. Subsequent reaction of compound **5** with sodium ethylene glycolate [prepared by the reaction of ethylene glycol (**4**) with sodium metal] yielded the sodium salt of bosentan with an overall yield of 53% (Scheme 1, Path A). The sodium metal used for the preparation of sodium ethylene glycolate is explosive and thus not advisible for industrial preparations. Further, the product formed by this method requires purification by column chromatography in order to control unacceptable amounts of critical and potential impurities **7** and **8** and thus to provide ICH-grade bosentan suitable for formulation.

Another synthetic approach reported[4] for **1** with good yield 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, benzyltriethylammoniumchloride, to provide the potassium salt of **5**. Subsequent reaction of **5** with protected ethylene glycol [ethylene glycol mono-*tert*-butyl ether (**9**)] in toluene in the presence of granular sodium hydroxide offered protected bosentan (**10**). Deprotection of **10** using formic acid furnished intermittent intermediate bosentan formate monoethanolate with 84% yield, which was hydrolyzed with sodium hydroxide in absolute ethanol and further treated with hydrochloric acid to provide crude bosentan. Further purification of the crude using a mixture of ethanol and water yielded pure bosentan monohydrate (Scheme 1, Path B). The amount of ethylene glycol used in the above process is substantially less compared to costs in other processes: the costs of the protecting group and protection and deprotection, several extractions using different organic solvents, and isolations yielding too-low throughput. Subsequently, a few more reported processes[5−8] follow a reaction sequence similar to that represented in Path A, Scheme 1 wherein intermediates are isolated and dried before using the same in the next step. Isolation and drying operations in production are time consuming, expose the production personnel to different solvent vapors, and thereby impact productivity and economics. Herein, we are reporting an improved, efficient, and production friendly one-pot process for **1**, which provides multiple benefits such as safety and increased throughput with economic advantage over the reported processes. The present paper also describes a novel purification method for the removal of critical impurities (**7**, **8**) in **1** by the preparation of the ammonium salt of bosentan (**6**) (Figure 1).

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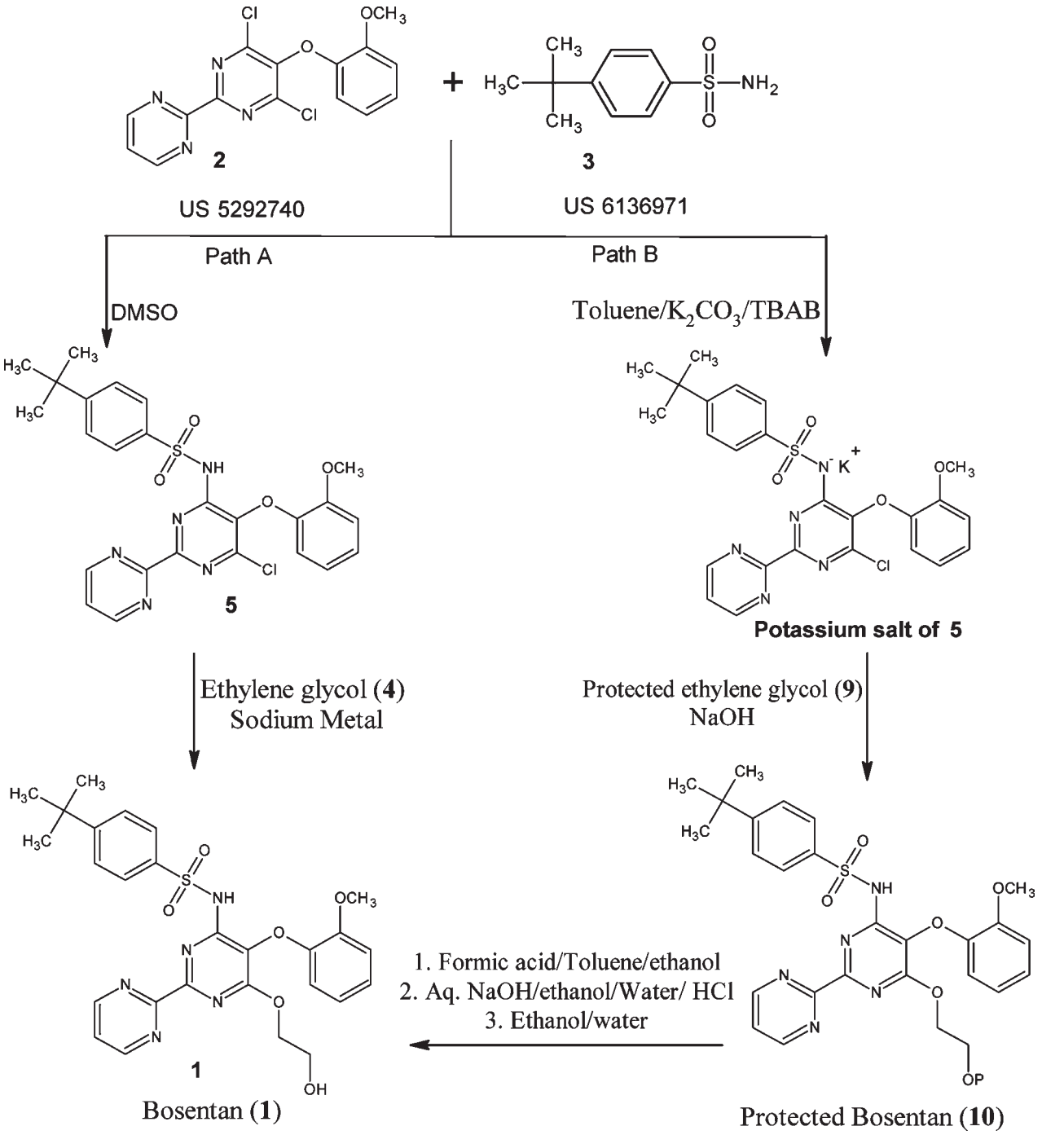
Scheme 1



RESULTS AND DISCUSSION

1. Preparation of Bosentan 1. Critical and cost-contributing intermediate **2** was prepared as per the literature procedure.[3] During development, reaction of **2** with **3** has been attempted using various solvents such as DMSO, toluene, DMF, and acetonitrile using different inorganic bases such as alkali metal hydroxides, alkali metal carbonates, or alkali metal bicarbonates with or without phase transfer catalysts. Among those combinations, it was found that acetonitrile using potassium carbonate as a base at reflux temperature (78−83 °C) for 2−4 h provided the intermediate **5** with quantitative yield and 99.6% purity by HPLC. The intermediate **5** was isolated by quenching the reaction mass over water, filtering and drying the product under vacuum at 60−65 °C for 10−12 h with excellent purity by HPLC (99.56%) and without additional purifications. Further, condensation of intermediate **5** with ethylene glycol (**4**) was then explored in various solvents (toluene, ethylene glycol, DMF, and acetonitrile) using different bases (Na metal, KOH, NaOH, K_2CO_3, Cs_2CO_3, or Na_2CO_3). During the exploration, it was observed that, in addition to the handling difficulty and safety issues of sodium metal with different solvents at higher temperature (≥100 °C),

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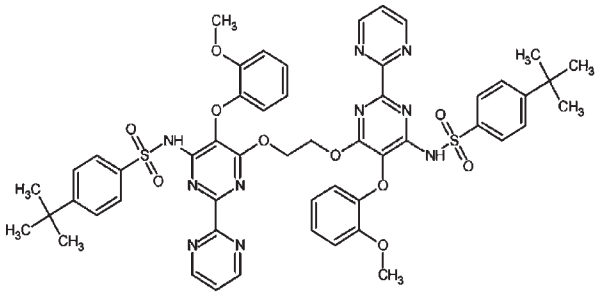
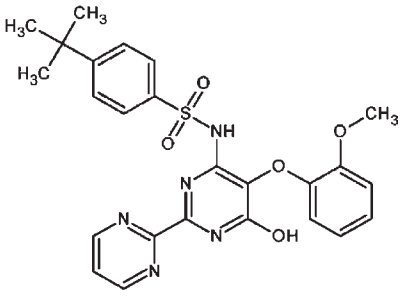


Dimer Impurity (7)



6-hydroxy impurity (8)

Figure 1. Potential impurities of bosentan.

there is also the formation of large quantities of dimer (7) and hydroxy (8) impurities. It was observed that reaction at 150 °C exclusively provided the hydroxy impurity (8) either in neat ethylene glycol, DMF, or DMSO along with base such as KOH or NaOH, whereas the reaction in acetonitrile in the presence of K_2CO_3 proceeded smoothly with a reduced amount of impurities (~1.0% by HPLC) at 75−85 °C. Hence, acetonitrile has been selected as a reaction medium and K_2CO_3 as a base. Further, the attempts to eliminate these two critical impurities (7 and 8) from the product **1** were explored. Reactions with lesser concentrations of ethylene glycol ended up with higher amounts of impurities 7 and 8 with prolonged reaction time (45−50 h), whereas higher concentrations of ethylene glycol controlled the level of impurities 7 and 8 in the reaction mass along with reducing the time of reaction to 18−20 h.

The workup involved diluting the reaction mass with water, adjusting the pH to 3−4 using conc. HCl, extracting the bosentan hydrochloride in dichloromethane, and distilling the solvent to provide the residue. The residue was then treated with a 25% solution of aqueous ammonia in isopropyl acetate and ethanol to furnish bosentan ammonium salt (6) as a white, crystalline solid having the dimer impurity (7) below 0.10% by HPLC;[9] however, hydroxy impurity (8) did not respond completely to the above purification process. Thus, a crystallization process was established for bosentan free base using a mixture of acetonitrile and methanol as a solvent system to control hydroxy impurity 8 below 0.10%, meeting the ICH requirements (Scheme 2, Table 1).

Upon establishing critical process parameters for each step, both the steps were telescoped and conducted in a single pot wherein the process involved the reaction of compound **2** with **3** in acetonitrile (10 volumes with respect to compound **2**)[10] in the presence of potassium carbonate at 78−83 °C for 2−3 h (monitored by TLC). Ethylene glycol (4) was then added in the same pot and maintained until completion of the reaction (18−20 h, monitored by HPLC). After ensuring the completion, the reaction mass was cooled and quenched over water, and the pH was adjusted to 3−4 using concentrated hydrochloric acid. The resulting mixture was extracted with dichloromethane and concentrated under reduced pressure to obtain the residue. The residue was treated with mixture of isopropyl acetate, ethanol, and ammonium hydroxide to furnish bosentan ammonium salt (6) with 86% yield (on dry basis) and 99.25% purity by HPLC.

2. Preparation of Bosentan Monohydrate. The 6 obtained above was hydrolyzed in water using hydrochloric acid and extracted bosentan free base in dichloromethane. Distillation of the organic layer followed by treating the residue with the mixture of acetonitrile and methanol provided bosentan free base which is filtered and directly converted into monohydrate. The wet bosentan free base obtained above was decolorized using activated charcoal in ethanol at 50−55 °C followed by addition of water to the filtrate at the same temperature under stirring. The solution was cooled to 25−30 °C during 1−2 h and maintained for 60 min at 25−30 °C. The crystalline bosentan monohydrate obtained was filtered, washed with chilled ethanol, and dried under vacuum at 35−40 °C for 2−4 h. The residual solvents in the final product were checked using GC−HS and found that all solvents are well within the specified ICH limit (Table 2).

CONCLUSION

A convenient, economic, production friendly, one-pot process for the production of highly pure bosentan monohydrate is described. The present work also describes a novel purification method for the removal of critical dimer impurity (7) and 6-hydroxy impurity (8) in **1** by preparation of bosentan ammonium salt (6) using inexpensive ammonium hydroxide followed by crystallization in a mixture of methanol and acetonitrile.

EXPERIMENTAL SECTION

General. Melting points were determined on Analab melting point apparatus, in open capillary tubes and are uncorrected. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as an internal standard and are given in δ units. The solvents for NMR spectra were deuterochloroform and deuterodimethylsulfoxide unless otherwise stated. Infrared spectra were taken on Perkin-Elmer Spectrum 100 in potassium bromide pallets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer, and the results were within ±0.3% of the calculated values. High-resolution mass spectra were obtained with a Shimadzu GC−MS QP mass spectrometer with an ionization potential of 70 eV. 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) or high performance liquid chromatography (HPLC) on Agilent Technologies 1200 series. The gas chromatography on Agilent Technologies 7683B with head space was used for analyzing the residual solvents. Common reagent grade chemicals used were

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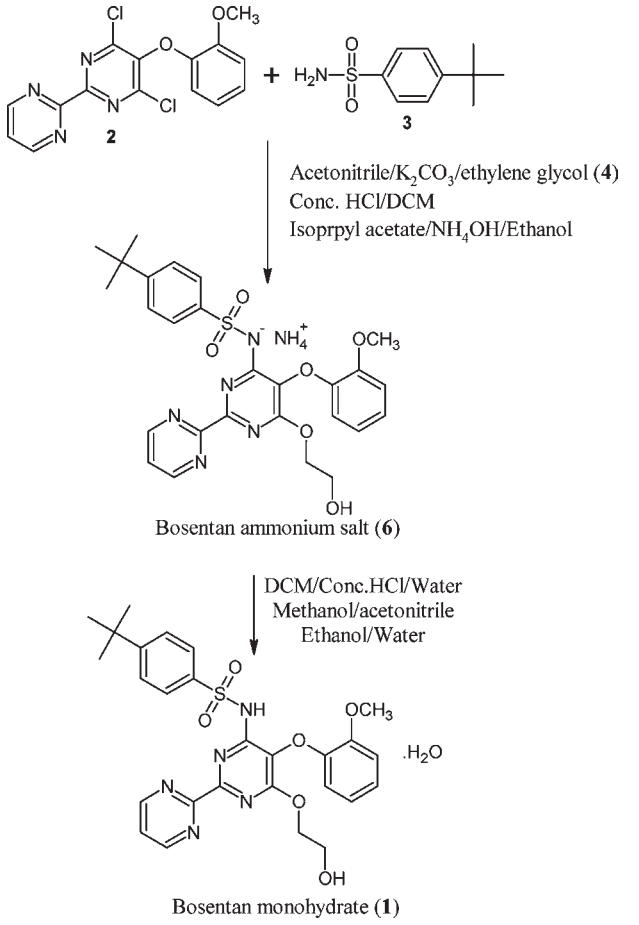
either commercially available and were used without further purification or prepared by standard literature procedures.

One-Pot Process for the Preparation of Bosentan (1). To a stirred solution of 4,6 dichloro-5-(2-methoxybenzyl)-2,2-bipyrimidine (**2**, 2.0 kg, 5.72 mol) in acetonitrile (20.0 L), were added 4-*tert*-butylbenzenesulphonamide (**3**, 1.34 kg, 6.28 mol) and potassium carbonate (6.8 kg, 49.27 mol) at 25−30 °C. The reaction mass was stirred at 78−83 °C for 2−3 h (completion of the reaction was monitored by TLC). To this reaction mass, ethylene glycol (**4**, 20.0 L, 322.58 mol) was added and maintained until completion of the reaction (around 18−20 h, monitored by HPLC). After ensuring the completion of reaction, the reaction mass was cooled to 25−30 °C and quenched with water (20.0 L). The pH of reaction mass was adjusted to 3−4 using concentrated hydrochloric acid, and the resulting reaction mass was extracted with dichloromethane (20.0 L). The dichloromethane layer was washed with 5% brine solution (2 × 20.0 L) and concentrated under reduced pressure to obtain the residue. The residue was dissolved in the mixture of isopropyl acetate (16.0 L), ethanol (5.3 L), and 25% solution of aqueous ammonia (3.2 L). The resulting solution was heated at 50−55 °C for 30 min, cooled to 5−10 °C and maintained for 6−8 h, and the solid (bosentan ammonium salt) obtained was filtered and washed with mixture of isopropyl acetate (0.7 L) and ethanol (0.3 L). The obtained wet solid was suspended in mixture of dichloromethane (10.0 L) and water (10.0 L), the pH of the solution was adjusted to 1−4 using concentrated hydrochloric acid, and the layers were separated. The organic layer was washed with water (10.0 L) and concentrated under reduced pressure to obtain the residue.[11] The residue was further dissolved in acetonitrile (3.0 L) and methanol (16.0 L), heated at 50−55 °C for 30 min, cooled to 5−10 °C, and maintained for 1−2 h; the solid was filtered and washed with methanol (1.0 L) to furnish the pure bosentan (**1**) which was then used directly for the preparation of bosentan monohydrate.

Scheme 2



Bosentan Ammonium Salt (6). The ammonium salt of bosentan (**6**) obtained in the above examples was dried and characterized by melting point, IR, NMR, and elemental analysis. Melting point: 172−174 °C; IR having characteristic peaks at 580, 1136, 1251, 1558, 2965, 3277 cm^{-1}; ^1H NMR (DMSO) δ 8.97−8.98 (d, 2H), 7.97−7.99(d, 2H), 7.55−7.58 (t, 1H), 7.25−7.27 (d, 2H), 7.00−7.02 (d, 1H) 6.86−6.90) (t, 1H) 6.70−6.74 (t, 1H) 6.35−6.37 (d, 1H) 4.86−4.89 (t, 1H), 4.22−4.25 (t, 2H) 3.83 (s, 3H) 3.51−3.52 (q, 2H) 1.23 (s, 9H); Anal. Calcd for $C_{27}H_{32}N_6O_6S$ (568.63): C, 56.98; H, 5.62; N, 14.77; S, 5.62. Found: C, 56.67; H, 5.46; N, 14.81; S, 5.65 (%).

Table 1. Monitoring the elimination of impurities in downstream process for bosentan 1 at laboratory and scale-up batches

		impurities and their content by HPLC (%)[9]			
		dimer (**7**)	6-hydroxy (**8**)	unknown	cmpd **1**
sr. no.	sample station (for HPLC analysis)	(RRT 2.07)	(RRT 0.95)	(RRT 1.23)	(RRT 1.23)
1	reaction mass	1.11	1.00	0.04	93.07
	ammonium salt	0.05	0.34	0.06	99.23
	bosentan freebase	0.03	0.11	0.04	99.83
	bosentan monohydrate	0.03	0.07	0.03	99.84
2	reaction mass	1.46	0.45	0.02	90.11
	ammonium salt	0.03	0.52	0.06	99.19
	bosentan freebase	0.02	0.12	0.04	99.81
	bosentan monohydrate	0.02	0.06	0.03	99.89
3	reaction mass	1.44	0.48	ND[a]	90.11
	ammonium salt	0.03	0.46	0.07	99.25
	bosentan freebase	0.02	0.14	0.05	99.78
	bosentan monohydrate	0.03	0.03	0.06	99.88

[a] ND = not detected.

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Table 2. Trend data of residual solvent

sr. no.	solvent name	ICH limit (ppm)	trend data for residual solvents (ppm) batch 1[a]	batch 2[a]	batch 3[a]
1	methanol	3000	123	85	71
2	ethanol	5000	1383	257	304
3	acetonitrile	410	ND	ND	ND
4	dichloromethane	600	ND	ND	ND
5	isopropyl acetate	5000	ND	ND	ND
6	ethylene glycol	620	3	ND	ND

[a] Not detected.

Preparation of Bosentan Monohydrate. The wet bosentan (**1**, 2.30 kg, 4.17 mol), ethanol (5.06 L), and activated charcoal (5% wt/wt, 115 g) were heated at 50−55 °C and filtered hot. Water (5.06 L) was then added to the obtained filtrate under stirring at the same temperature, and reaction mass was maintained for 20 min. The solution was cooled to 25−30 °C and maintained for 60 min. The crystalline solid obtained was filtered, washed with chilled ethanol, and dried under vacuum (650−700 mm/Hg) at 35−40 °C for 2−4 h to afford bosentan monohydrate as a white, crystalline solid. Yield 2.20 kg, (68.7%); HPLC purity:[9] 99.90%; IR (KBr): 3629, 3064, 2962, 2837, 1579, 1559, 1342, 1252, 1171, 1083, 1052, 685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.98−8.99 (d, 2H), 8.75 (s, 1H), 8.39 −8.41 (d, 2H), 7.41 (t, 1H), 7.39−7.40 (d, 2H), 6.84−7.13 (m, 4H), 4.89 (s, 1H), 4.58−4.56 (t, 2H), 3.93 (s, 3H), 3.84 (t, 2H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.99, 55.97 (CH_3), 62.48, 71.7 (CH_2), 35.10, 62.48, 112.41, 121.32, 125.35, 129.33, 135.99, 145.47, 149.5, 151.7, 155.15, 157.2, 157.69, 161.30 (CH). MS *m*/*z* (%): 552.10 $[M + 1]^+$ (100). Anal. Calcd for $C_{27}H_{31}N_5O_6S$ (Mol wt: 569.64): C, 56.87; H, 5.44; N, 12.28; S, 5.62; Found: C, 57.23; H, 5.44; N, 12.32 ; S, 5.68 % ; water content: 3.2 % wt/wt (theory: 3.16 %); melting point: 114−118 °C.

Preparation of 1,2-Bis[[5-(2-methoxy phenoxy)-2-(2-pyrimidin-2-yl-pyrimidin-4-yl]-4-*tert*-butylbenzenesulfonamide]-ethanediol (Dimer Impurity 7). To a stirred solution of bosentan (**1**, 150.0 g 0.27 mol) in ethylene glycol (240.0 mL), were added **5** (143.19 g, 0.27 mol) and sodium metal (7.5 g, 0.32 mol) at 25−30 °C. The reaction mass was stirred at 115−120 °C for 60−90 h (monitored by TLC). The reaction mass was cooled to 25−30 °C and quenched in water (750.0 mL). The resulting reaction mass was extracted with dichloromethane (750.0 mL × 2), and the DCM layer was washed with water (750.0 mL) and distilled off completely to obtain the residue. The crude residue was then purified by column chromatography (silica gel: 60−120 mesh) using ethyl acetate−chloroform (9:1) as eluent to yield compound **7** as a light-yellow solid. Yield: 15.00 g; HPLC purity: 99.15%; IR (KBr): 3063, 2963, 2869, 2837, 1574, 1558, 1335, 1257, 1163, 749 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09−1.17 (s, 18H), 3.72 (s, 6H), 3.81 (t, 2H), 4.0 (t, 2H), 6.13−6.99 (m, 8H), 7.25−7.32 (d, 4H), 7.44 (d, 4H), 8.29 (s, 2H), 8.89 (t, 2H), 8.98 (d, 4H). MS *m*/*z* (%): 1041.20 $[M + 1]^+$ (100).

Preparation of *p*-*tert*-Butyl-*N*-[6-hydroxy-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4- pyrimidinyl]benzenesulfonamide. (Hydroxy Impurity 8). To a stirred solution of **5** (40.0 g 0.076 mol) in ethylene glycol (240.0 mL) was added sodium hydroxide (9.0 g, 0.22 mol) at 25−30 °C. The reaction mass was stirred at 150−160 °C until the completion of reaction (monitored by TLC). After ensuring the completion of reaction, the reaction mass was cooled at 25−30 °C and quenched with water (200.0 mL). The resulting reaction mass was extracted with dichloromethane (200 mL × 2). The combined dichloromethane layer was washed with water (200 mL) and concentrated under reduced pressure to obtain crude residue. The obtained residue was dissolved in ethanol (120 mL) and reprecipitated with di-isopropyl ether (240 mL), and cooled to 10−15 °C; the solid was filtered, washed with di-isopropyl ether (20.0 mL), and dried under vacuum (650−700 mm/Hg) to afford compound **8** as a light-yellow solid. Yield: 25.00 g, (64.71%); HPLC purity: 99.34%; IR (KBr): 3447, 3214, 3039, 2962, 1663, 1565, 1345, 1248, 1170, 1081, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 (s, 9H), 4.1 (s, 3H), 6.84−6.94 (t, 1H), 6.95−7.03 (d, 1H), 7.07−7.14 (t, 1H), 7.40−7.44 (d, 3H), 7.45−7.55 (t, 1H), 8.35−8.45 (d, 2H), 8.99−9.02 (d, 2H), 9.1 (s, 1H), 11.1 (s, 1H). MS *m*/*z* (%): 508.49 $[M + 1]^+$ (100).

■ ASSOCIATED CONTENT

Supporting Information. Additional information related to physical characteristics of bosentan monohydrate, such as DSC, TGA and XRD data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(10) Volume of acetonitrile required for the reaction has been critically evaluated during optimization [3, 5, 8, and 10 times with respect to compound **2**] and found that any amount less than 10 times leads to the formation of thick mass and creates problems in stirring and mixing.

(11) Distillation of the dichloromethane layer is ceased once the collection of the solvent is stopped at the solvent receiver unit. Further, the DCM is monitored in the residue with the limit of NMT 5.0% to have control over the subsequent process operations.