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A New Efficient Synthetic Process for an Endothelin Receptor Antagonist, Bosentan Monohydrate†

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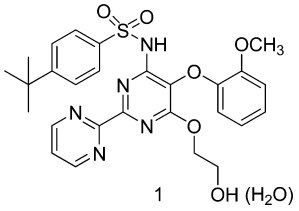
Supporting Information

ABSTRACT: A new and efficient synthetic process for the synthesis of an endothelin receptor antagonist, bosentan monohydrate, involves the coupling of *p*-*tert*-butyl-*N*-(6-chloro-5-(2-methoxy phenoxy)-2,2′-bipyrimidin-4-yl)-benzenesulfonamide (**7**) with (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**14**) as a key step. This new process provides desired bosentan monohydrate (**1**) with better quality and yields. Our new methodology consists of technical innovations/improvements which totally eliminate the probability for the formation of critical impurities such as pyrimidinone **8**, dimer impurity **9**, and N-alkylated impurity **13** in the final drug substance.

INTRODUCTION

Bosentan monohydrate, brand name Tracleer, is an anti-hypertensive drug approved by the FDA in 2001. It is mainly used in the treatment of pulmonary hypertension (PAH). PAH is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to shortness of breath, dizziness, fainting, and other symptoms such as cough, angina pectoris, syncope, swelling of ankles and feet. There are many pathways to control pulmonary hypertension, in those three are important because they have targeted with drugs like endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives.

Bosentan monohydrate having the structural formula **1** became the first approved endothelin receptor antagonist for dual type A (ET_A) and type B (ET_B) receptors. Bosentan is a widely used endothelin receptor antagonist when compared to all other currently available endothelin receptor antagonists because its cost is lower than theirs.



Also there are many costly drugs such as prostaglandins (prostacyclin, Epoprostenol, Iloprost) and some peptide drugs to control pulmonary hypertension. In this widely established market, 'cost' will play a major role for commercial success. In this competitive version a non-peptide drug, bosentan monohydrate, was developed as an endothelin receptor antagonist with more efficient action.

Many methods have been reported for the synthesis of bosentan. The earlier reported schemes are imbued with many drawbacks such as (a) the formation of many impurities and (b) the use of reagents and solvents that are toxic or hazardous in nature, presenting environmental liabilities. Therefore, there is a need for a process which can provide more qualified bosentan, especially without the formation of impurities in a commercially challenging, less costly, more eco-friendly and easily scalable industrial process.

As a part of our unceasing interest in the synthesis of active pharmaceutical ingredients (API), we report herein a novel synthetic route for the preparation of bosentan monohydrate (**1**). *p*-*tert*-Butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)[2,2′-bi-pyrimidin]-4-yl]benzenesulfonamide (**7**) and (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**14**) are devised as key starting materials, and high-quality bosentan monohydrate was efficiently obtained in 50−55% overall yield, which corresponds to an average step yield of 85% with simple steps and commercially available chemicals. The whole synthetic route is depicted in Scheme 3.

RESULTS AND DISCUSSION

The synthesis of bosentan monohydrate (**1**) has been reported by several authors using different methodologies. Each methodology has its own demerits. The first reported method by K. Burri et al.[1] is represented in Scheme 1 with overall yield of 40% from **4**. In this process toxic ethylene glycol and highly pyrophoric Na metal are used which cannot be handled in a large-scale commercial process. The need to use excess ethylene glycol leads to generation of aqueous ethylene glycol waste and formation of dimer impurity **9**. To get ICH-grade bosentan monohydrate from crude bosentan, more than three purifications are required to reduce the amount of dimer

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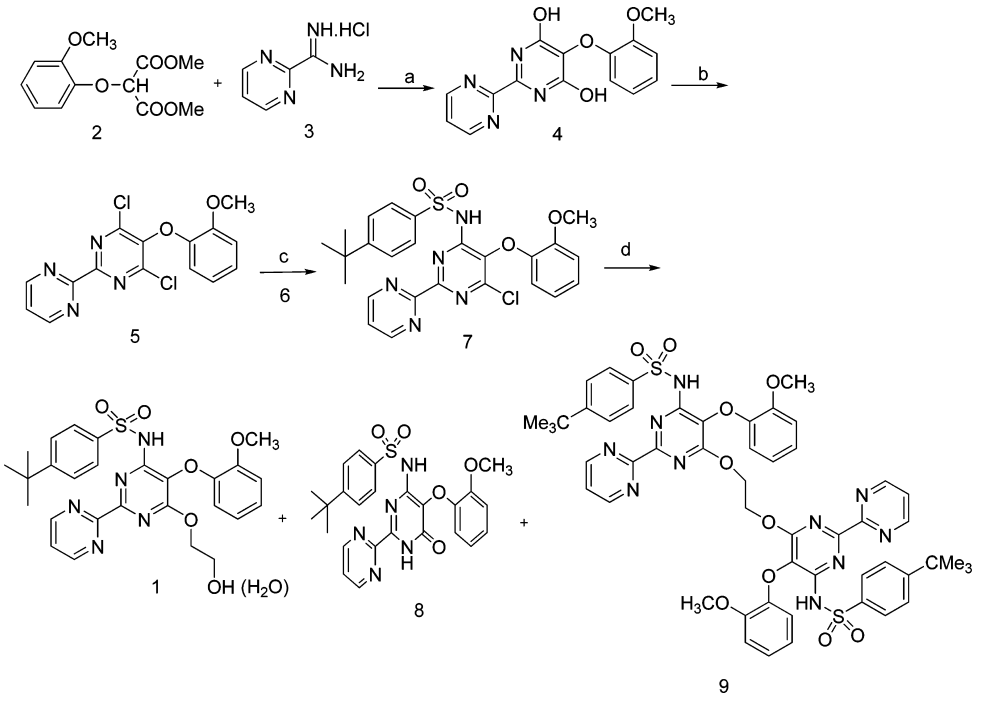
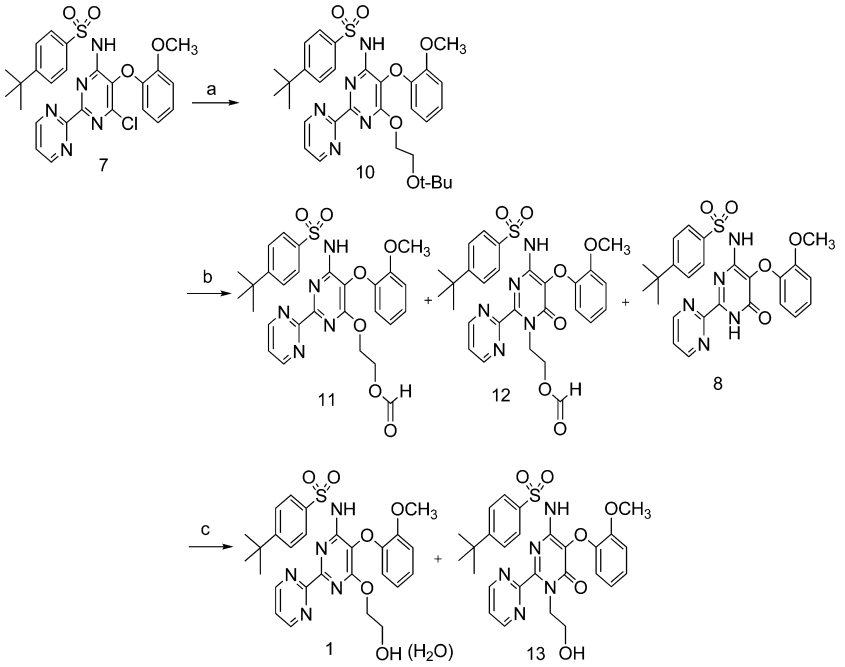
Scheme 1[a]



[a]Reagents and conditions: a) sodium methoxide, methanol; b) $POCl_3$; c) *p-tert*-butylbenzenesulfonamide (**6**), K_2CO_3, TBAB, toluene; d) sodium metal, ethylene glycol.

Scheme 2[a]



[a]Reagents and conditions: a) ethylene glycol mono-*tert*-butyl ether, NaOH; b) formic acid; c) NaOH, ethanol, water.

impurity **9** and pyrimidinone impurity **8** which are formed during the reaction.

The second-generation process for the preparation of bosentan, reported by Peter J. Harrington et al.,[2] is represented in Scheme 2. In this process formation of the dimer impurity is eliminated by taking mono-*tert*-butyl protected ethylene glycol instead of ethylene glycol. But during the cleavage of bosentan *tert*-butyl ether using formic acid produces bosentan formate **11** along with a typical N-substituted compound **12** and pyrimidinone impurities **8** by thermal degradation. Further hydrolysis using sodium hydroxide solution produces the bosentan monohydrate (**1**) along with N-alkylated impurity **13** and pyrimidinone **8** impurities which are difficult to wash out and requires three to four recrystallizations to reduce them.

In all the above previously reported commercial processes for the preparation of bosentan monohydrate (**1**), formation of

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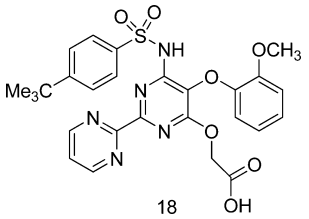
impurities such as pyrimidinone **8**, dimer **9**, and N-alkylated impurity **13** affects the quality and yield of the bosentan. To overcome these problems, many other methods[3−8] have been reported, which have their own disadvantages. Shreerang et al.[8] reported a novel synthesis of bosentan monohydrate using glycolaldehyde diethyl acetal instead of ethylene glycol. In this approach bosentan monohydrate is obtained by coupling of **7** with glycolaldehyde diethyl acetal using a pyrophoric base sodium hydride followed by treatment with hydrochloric acid (HCl) providing aldehyde intermediate **17** and finally providing the bosentan by reduction of **17** with only 25% overall yield. The main drawback is that the use of sodium hydride is not suitable for commercial synthesis of bosentan. All the remaining processes[3−7] also provide bosentan with many of the reported impurities and lead to decreased yield of the bosentan monohydrate, **1**.

To overcome the above-mentioned disadvantages, we have devised a novel synthetic route which utilizes (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol[9−11] (**14**) instead of ethylene glycol or mono-protected glycol. By using this new synthetic route we have been able to eliminate the complete formation of the chronic pyrimidinone **8**, dimer **9**, and N-alkylated **13** impurities. In the novel process only the acid impurity **18** was observed, due to over-oxidation of diol intermediate **16**. This impurity was completely washed out during the workup and isolation process of bosentan monohydrate and was controlled in the final product with specification of not more than (NMT) 0.15% to comply with ICH guidelines.



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Novel Synthesis of Bosentan Monohydrate (1). We designed a novel synthesis of bosentan monohydrate by using the key starting materials *p-tert*-butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]benzenesulfonamide (**7**) and (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol[12] (**14**), as depicted in Scheme 3.

Synthesis and Deprotection of Protected Diol 15. The coupling of **7** and **14** in the presence of a base at elevated temperatures affords the key precursor **15**. After optimization studies of this stage it was observed that the most suitable method to carry out the reaction was by performing the coupling of **7** and **14** in acetonitrile solvent in the presence of NaOH at 80 °C. The coupling reaction involves the formation of dialkoxide ion of **14** on reaction with a strong base, sodium hydroxide, which is further reacting with compound **7** to provide **15**. Since a strong base is being used, protic solvents are not favorable when compared to aprotic solvents. During development studies we have attempted this condensation reaction using acetonitrile, tetrahydrofuron (THF), and toluene. When toluene or THF was used, a highly viscous reaction mass was obtained, leading to a difficulty in stirring the reaction mass and hampering the reaction. Hence, the starting material is not completely converted into the product. The stirring state of the reactants was improved when acetonitrile was used as a solvent, and the yield also increased. Thus, acetonitrile is preferred for this reaction. During optimization studies for which base to use, sodium hydroxide (NaOH), sodium carbonate (Na_2CO_3), sodium methoxide (NaOMe), and potassium carbonate (K_2CO_3) were investigated. By using NaOMe, Na_2CO_3, and K_2CO_3 complete conversion of **7** was not observed, and isolated yields were less. NaOH was found to be the most efficient in terms of yield and handling, and hence was recommended. The results of these studies are provided in Table 1. Deprotection of key precursor **15** using 2 N HCl was attempted in methanol, ethanol, and acetonitrile. We found the deprotection using alcoholic solvents gave only 70−75%. Thus, we examined acetonitrile as the solvent and observed that complete deprotection could be achieved in 4−5 h at room temperature. Facile extracting workup using dichloromethane[13] provided compound **16** in quantitative yield of 91%.

Cleavage of Diol to Aldehyde 17. Generally cleavage of diol is well reported using sodium periodate and lead tetraacetate (LTA). The convenient strategy was to use sodium periodate for oxidative cleavage of diol as it is very cheap and easy to handle when compare to LTA and, hence, is useful for a scale-up process. Thus, we have chosen sodium periodate[14] for the cleavage of **16** to afford **17**. The progress of the reaction is dependent on the solvent used in the reaction and the temperature of the reaction. When toluene or acetonitrile was used, it was found that, even after 7−9 h, complete conversion of starting material to the product was not observed, whereas by using acetone the reaction was completed in 2−3 h, and the aldehyde **17** was obtained in good quality and yield (Table 2).

Reduction of Aldehyde 17 and Isolation of Bosentan Monohydrate (1). Conversion of aldehyde **17** to bosentan monohydrate can be easily done using sodium borohydride ($NaBH_4$). This reaction was conducted in toluene, THF, and alcoholic solvents such as ethanol and methanol. Rate of reaction in toluene and THF was found to be slow, whereas in alcoholic solvents the reaction was complete in 2−3 h, and the crude bosentan was obtained by quenching in chilled water, and adjusting the pH to 2−3 using 6 N HCl, followed by extraction and isolation using methanol and water.

Purification of this crude bosentan to obtain pure bosentan monohydrate is the challenging task. Our primary aim was to decrease the production cost by minimizing the loss of the product during the purification process. Therefore, we have attempted several purifications using various solvents such as methanol, isopropyl alcohol, ethanol, ethylacetate, isopropyl acetate, *tert*-butylacetate, and combinations of these solvents. Finally, a combination of ethylacetate and methanol in 1:1 ratio with 1% water provided good (∼75%) yields of pure bosentan monohydrate (**1**) having ICH-grade quality. The residual solvents present in the finished bosentan were analyzed using a GC method, and it was found that all the solvents were well within the specified ICH limits (Table 3).

Polymorphic Stability of Bosentan Monohydrate, 1. The polymorphism was investigated as a step in the development of a new synthetic design for APIs. The polymorphic stability of bosentan monohydrate was examined under different temperatures and humidities by powder X-ray diffraction studies and thermogravimetric analysis. The PXRD pattern of bosentan monohydrate shows a prior art form. We have also studied the polymorphic stability at 25 °C/60% RH and 40 °C/75% RH for 6 months and obtained a polymorph found to be stable under both conditions.

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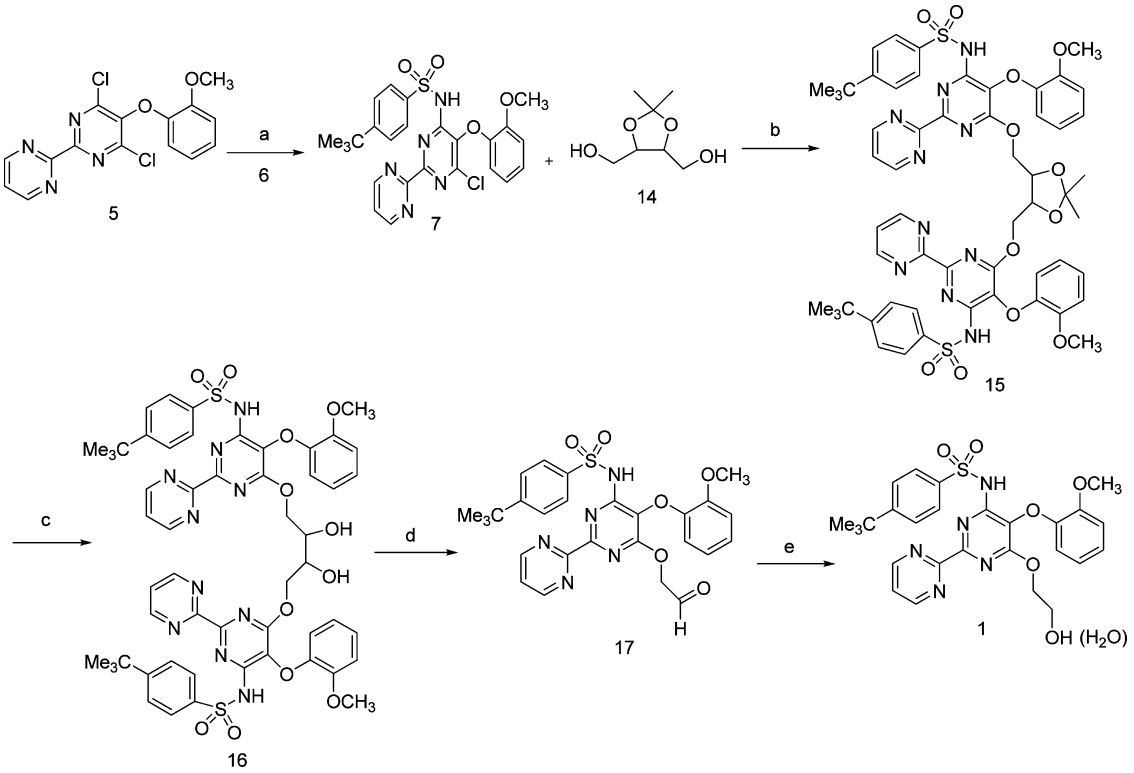
Scheme 3[a]



[a]Reagents and conditions: a) *p-tert*-butylbenzenesulfonamide **6**, K_2CO_3, TBAB, toluene; b) NaOH, acetonitrile; c) 2 N HCl, acetonitrile; d) $NaIO_4$, acetone; e) $NaBH_4$, methanol.

Table 1. Condensation of 7 with 14 using various conditions

s. no.	base	solvent	T[a] [°C]	yield[b] [%]
1	NaOH	THF[c]	65	75
2	NaOH	acetonitrile	80	90
3	NaOH	toluene	110	65
4	Na_2CO_3	acetonitrile	80	45
5	K_2CO_3	acetonitrile	80	55
6	NaOMe	acetonitrile	80	58

[a]Reaction temperature. [b]Isolated yield of **15**. [c]THF = tetrahydrofuran.

Table 2. Reaction conditions and yield from 16 to 17

s. no.	solvent	T[a] [°C]	maintenance time (h)	yield[b] (%)
1	toluene	25−30	9	50
2	acetonitrile	25−30	7.5	58
3	acetone	25−30	2.5	87
4	acetone	0−5	8	70

[a]Reaction temperature. [b]Isolated yield of **17**.

CONCLUSION

In conclusion, we have designed and developed a novel, cost-effective, industrially scalable synthetic route to the endothelin receptor antagonist, bosentan monohydrate (**1**). The synthetic route developed uses cheaper raw material (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**14**) and provided bosentan monohydrate with an overall yield of 53%, which corresponds to an average step yield of more than 85%. The synthetic process involves the formation of novel intermediates **15** and **16**. The new process does not use any hazardous reagents and thus minimizes the generation of hazardous waste, which makes the process more environmentally friendly.

Table 3. Trend data for residual solvents in bosentan monohydrate

			trend data for residual solvents (ppm)		
s. no.	solvent	ICH limit (ppm)	batch 1[a]	batch 2[a]	batch 3[a]
1	acetonitrile	410	ND	ND	ND
2	dichloromethane	600	ND	ND	40
3	methanol	3000	560	510	416
4	acetone	5000	ND	15	ND
5	cyclohexane	3880	115	142	43
6	ethylacetate	5000	1185	970	825

[a]Not detected.

EXPERIMENTAL SECTION

The preparation of (2,2-dimethyl-1,3-dioxolane-4,5-diyl)-dimethanol (**14**) is described in refs 9−11. 4-*tert*-Butylbenzenesulfonamide (**6**) was purchased from Spectrochem and used as received. Common reagent-grade chemicals used were commercially available and were used without further purification. FT-IR spectra were determined on a Perkin-Elmer 100 FT-IR spectrophotometert. Melting points were determined on polmon instrument. The mass spectrum was recorded on Agilent 6150 quadrapole LC/MS spectrometer, ^{1}H NMR spectra were acquired in $CDCl_3$ as solvent on a Bruker 300 MHz or 400 MHz spectrometer using TMS as internal standard, and ^{13}C NMR spectra were recorded on a Bruker 100 MHz spectrometer using TMS as internal standard. Elemental

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analyses were determined using Heraeus CHN-O-Rapid analyzer. High performance liquid chromatography (HPLC) analysis was carried out on Agilent Technologies 1200 series. The gas chromatography analysis was carried out on Agilent Technologies 7683B for analyzing the residual solvents.

***p-tert*-Butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]benzenesulfonamide (7).** A mixture of 4-*tert*-butylbenzenesulfonamide (**6**) (0.85 kg, 4.0 mol), toluene (2.8 L), and potassium carbonate (1.1 kg, 8.0 mol) was heated to 50 °C for 30 min. To the reaction mixture was added **5** (1.4 kg, 4.0 mol) followed by heating to 110 °C for 10 h. The reaction mixture was cooled to 25 °C, water (28 L) was added, and the pH was adjusted to below 3 by using 5 N hydrochloric acid and stirred for 30 min. The precipitated solid was filtered, washed with water (4.8 L), and dried in the oven at 60 °C for 6 h to afford 7 (2.05 kg, 97%). **Mp:** 214−216 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.21 (9H, s), 3.72 (3H, s), 6.54−6.55 (1H, d), 6.72−6.76 (1H, t), 6.86−6.98 (2H, m), 7.23−7.25 (2H, d), 7.43−7.49 (3H, m), 8.97−8.98 (2H, d); **MS:** *m*/*z* 526.3 (M + H); **IR (KBr) (υ_{max}, cm^{-1}):** 3466.7 (−NH stretching), 1592.9 (C═O stretching).

***N,N′*-(6,6′-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(oxy)bis(5-(2-methoxy phenoxy)-2,2′-bipyrimidine-6,4-diyl))bis(4-*tert*-butylbenzenesulfonamide) (15).** To a solution of (2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (**14**) (60.8 g, 0.37 mol) in acetonitrile (2.5 L) was added sodium hydroxide (95.05 g, 2.38 mol) and heated to 80−85 °C for 4 h. To this *p-tert*-butyl-*N*-[6-chloro-5-(2-methoxyphenoxy)[2,2′bipyrimidin]-4-yl]benzene sulphonamide (**7**) (250 g, 0.48 mol) was added followed by heating to 80−85 °C for 14 h. Then water (2.0 L) was added, and the pH was adjusted to 5.0−6.0 by using 5 N hydrochloric acid and stirred for 30 min. The resulting precipitate was collected, washed with water (1.25 L), and dried in the oven at 60 °C for 6 h to afford **15** (490 g, 90%). **Mp:** 72−74 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25 (6H, s), 1.29 (18H, s), 3.84−3.90 (4H, m), 4.27−4.31 (2H, m), 6.84−6.87 (3H, t), 6.97−7.00 (2H, dd), 7.09−7.13 (3H, t), 7.43−7.45 (10H, m), 9.0−9.01 (4H, d), 8.43 (2H, br s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 25.88, 30.02, 34.10, 55.01, 61.53, 77.36, 108.43, 111.4, 118.73, 120.4, 124.09, 124.34, 126.67, 127.38, 128.35, 135.30, 138.25, 144.74, 148.62, 150.99, 156.07, 156.71, 160.56; **MS:** *m*/*z* 1142.2 (M + H); **Elem. Anal:** Found: C 59.87, H 5.20, N 12.38; Calcd for $C_{57}H_{60}N_{10}O_{12}S_2$: C 59.99, H 5.30, N 12.27.

***N,N′*-(6,6′-(2,3-Dihydroxybutane-1,4-diyl)bis(oxy)bis(5-(2-methoxyphenoxy)-2,2′-bipyrimidine-6,4-diyl))bis(4-*tert*-butylbenzenesulfonamide) 16.** The solution of *N,N′*-(6,6′-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(oxy)bis(5-(2-methoxyphenoxy)-2,2′-bipyrimidine-6,4-diyl))bis(4-*tert*-butylbenzenesulfonamide) **15** (150 g, 0.14 mol) in acetonitrile (750 mL), 2 N HCl (750 mL) was added slowly for 20−30 min, and stirring continued for 5 h. Then the reaction mass was extracted twice with dichloromethane (2 × 750 mL). The organic solvent was evaporated, and the residue dissolved in methanol (150 mL) was added slowly to water (750 mL) for 45 min. The resulting precipitate was filtered, washed with water (150 mL), and dried in the oven at 60 °C for 6 h to provide **16** (132 g, 91%). **Mp:** 108−111 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.31 (18H, s), 3.58 (2H, broad s), 3.84−3.87 (2H, m), 3.95 (6H, s), 4.11−4.16 (2H, m), 4.32−4.36 (2H, dd), 6.88−6.92 (2H, m), 6.98−7.04 (6H, t), 7.11−7.15 (2H, t), 7.44−7.47 (8H, d), 8.45 (2H, s), 8.96−9.02 (4H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 30.02, 34.11, 54.93, 62.96, 69.74, 111.5, 117.95, 120.21, 123.56, 123.57, 124.4, 128.35, 135.23, 144.5, 148.52, 150.8, 151.05, 153.81, 156.16, 156.75, 160.19; **MS:** *m*/*z* 1102.3 (M + H); **Elem. Anal:** Found: C 58.77, H 5.20, N 12.87; Calcd for $C_{54}H_{56}N_{10}O_{12}S_2$: C 58.90, H 5.13, N 12.72.

4-*tert*-Butyl-*N*-(5-(2-methoxyphenoxy)-6-(2-oxoethoxy)-2,2′-bipyrimidin-4-yl)benzenesulfonamide (17). To a solution of *N,N′*-(6,6′-(2,3-dihydroxybutane-1,4-diyl)bis(oxy)bis(5-(2-methoxy phenoxy)-2,2′-bipyrimidine-6,4-diyl))bis(4-*tert*-butylbenzenesulfonamide) was slowly added **16** (100 g, 0.09 mol) in acetone (500 mL) and sodium periodate (44 g, 0.2 mol) in water (200 mL) for 30 min. The reaction mixture was stirred for 2−3 h at 25−35 °C. The remaining solid was removed by filtration, and the solvent was evaporated under reduced pressure. The residue was extracted with methylene chloride (600 mL) and washed with water (250 mL), and the solvent was evaporated under reduced pressure. Cyclohexane (250 mL) was added to the obtained residue and stirred for 30−45 min at 25−30 °C. The precipitated solid was filtered and washed with cyclohexane (50 mL) and dried in the oven at 60 °C for 6 h to afford **17** (85 g, 87%). **Mp:** 208−210 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 1.26 (9H, s), 3.98 (3H, s), 5.15 (2H, s), 6.85−7.6 (7H, m), 8.42−8.45 (2H, d), 9.0 (2H, d), 9.72 (1H, s); **MS:** *m*/*z* 550.5 (M + H); **IR (KBr) (υ_{max}, cm^{-1}):** 1720 (C═O stretching).

4-*tert*-Butyl-*N*-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2,2′-bipyrimidin-4-yl)benzenesulfonamide, Bosentan Monohydrate (1). A solution of **17** (100 g, 0.18 mol) in methanol (500 mL) was cooled to 0−5 °C, and sodium borohydride (6.91 g, 0.18 mol) was slowly added in portions. The reaction mass was stirred for 2−3 h; methanol was distilled off and quenched with ice-cold water; pH adjusted to 2−3 using 6 N HCl, and the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 5% brine solution (2 × 500 mL) and concentrated under reduced pressure to obtain the residue. The obtained residue was dissolved in methanol (120 mL) and reprecipitated with water (240 mL); precipitated solid was filtered and washed with water (100 mL). The resultant solid was dissolved in ethylacetate (100 mL), methanol (100 mL), and water (1 mL), was heated to 65−70 °C for 1 h, cooled to 30 °C, and maintained for 4−5 h. The solid was filtered and washed with cyclohexane (25 mL), dried under vacuum at 30−35 °C for 3−4 h to get highly pure bosentan monohydrate **1** (77.6 g, 75%) as a white to pale-yellow solid. **Mp:** 138−140 °C. **^{1}H NMR (300 MHz, $CHCl_3$):** δ 1.29 (9H, s), 3.86 (2H, s), 4.0 (3H, s), 4.57 (2H, m), 4.88 (1H, s), 6.85 (1H, m), 7.10 (2H, m), 7.15 (1H, m), 7.41 (3H, m), 8.42 (2H, d), 8.8 (1H, br), 9.0 (2H, d); **MS:** *m*/*z* 552 (M + H); **IR (KBr) (υ_{max}, cm^{-1}):** 3437.4 (−NH); 1342 ($-SO_2$); **HPLC purity**: 99.70%; **water content:** 3.2% (w/w).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Structure elucidation for compounds **15** and **16** (^{1}H NMR, ^{13}C NMR); HPLC methods for related substances of bosentan and GC method for residual solvents; 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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[*]The authors declare no competing financial interest.

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(12) The advantage of synthon **14** is that the two moles of the starting material **7** condenses with a single mole of synthon **14** to provide a dimeric product **15** which is deprotected and cleaved to provide two moles of **17**. This is finally converted to bosentan monohydrate **1** free of impurities.
(13) The motivation to use dichloromethane for extraction of intermediates **16** and **17** is it provided better yields and could be distilled off and reused, thereby conserving and decreasing the use of solvent, avoiding pollution.
(14) As sodium periodate is used as an oxidizing agent, there is a possibility of the formation of *N*-oxide impurities, but on the contrary it was observed that they were not formed. The experiments to specifically prepare *N*-oxides using hydrogen peroxide also reiterated the fact.