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ORIGINAL PAPER

Improved and single-pot process for the synthesis of macitentan, an endothelin receptor antagonist, via lithium amide-mediated nucleophilic substitution

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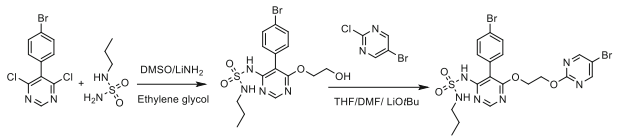
Abstract An improved, simple, efficient, and telescoped synthesis of macitentan, an endothelin receptor antagonist, starting from 5-(4-bromophenyl)-4,6-dichloropyrimidine in an overall yield of around 62% is described.

Graphical abstract



Keywords Macitentan · Endothelin receptor antagonist · Lithium amide · Formamide · Formamidine

Introduction

Macitentan (OPSUMIT®), an orally active endothelin receptor antagonist (ERA), has been approved by the United States Federal Drug Agency on October 13, 2013, for treatment of pulmonary arterial hypertension (PAH) and is chemically also known as *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N*′-propylsulfamide [1]. Macitentan is a dual ERA, i.e., acts as an antagonist of two endothelin (ET) receptor subtypes, ET_A and ET_B [2–6]. However, macitentan has 50-fold increased selectivity for the ET_A subtype compared to the ET_B subtype [7].

The first synthesis of macitentan (**1**), reported by Bolli et al. [8–11], is a multistep protocol involving the reaction of *N*-propylsulfamide (**3**) with potassium *tert* butoxide (KO*t*Bu) in the presence of methanol to provide a potassium salt of **3**, which is then condensed with 5-(4-bromophenyl)-4,6-dichloropyrimidine (**2**) in dimethyl sulfoxide (DMSO) to provide *N*-[5-(4-bromophenyl)-6-chloropyrimidin-4-yl]-*N*′-propylsulfamide, 6-chloro compound **4**. Compound **4** was then reacted with ethylene glycol (**5**) in the presence of KO*t*Bu in dimethoxyethane (DME) to provide 2-hydroxyethoxy compound **6**. Finally, nucleophilic substitution of **6** with 5-bromo-2-chloropyrimidine (**7**) in the presence of sodium hydride (NaH) in tetrahydrofuran (THF) and dimethyl formamide (DMF) solvent mixture provided **1** with an overall yield of 52% (Scheme 1).

The reported process has several disadvantages such as: (a) use of sodium hydride which is hazardous, expensive, flammable, and industrially not feasible, (b) purification of **6** by column chromatography is time consuming, requires tons of solvents, and is unfeasible at an industrial scale, (c) it involves multistep synthesis wherein intermediate steps are filtered and dried before use in the next step thereby reducing the production throughput. The time cycle to produce a batch is substantially high due to multiple reactions using different bases, filtrations, drying, packing, and analyses at each reaction step. Critical operations such as isolation and drying exposes the production personnel to different solvent vapors while handling, and hence is not

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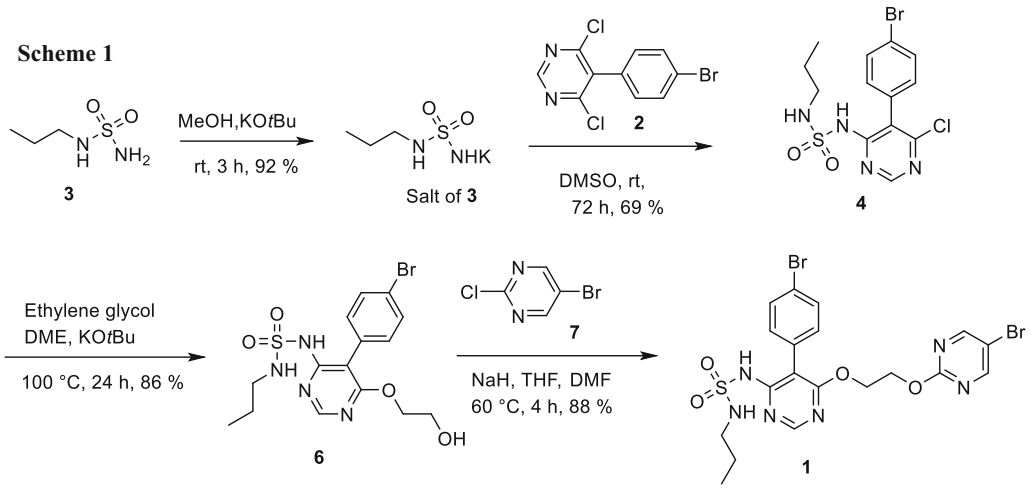
Scheme 1



labor friendly. Moreover, the product synthesized by this process requires repeated purification to control unacceptable amounts of critical and potential impurities formed in the reaction to achieve ICH grade of **1**, thereby making the process uneconomical. To overcome the above disadvantages, we explored various experiments during the development by selecting various reaction parameters such as alternative bases which are safe and convenient to use at the production facility, alternative solvents, mole ratios, reaction times, and temperatures. Further, we have eliminated the multiple isolation steps and use of multiple bases in different substitution reactions by telescoping the reactions after they are optimized independently using common base and solvent to provide efficient, industrially feasible, economically viable, and one-pot process for the manufacturing of **1** which is substantially free from process-related impurities.

Results and discussion

The development of a practical synthetic process for macitentan mainly focused on the following three aspects: (a) to develop robust and industrially feasible process for regulatory starting material **2**, (b) to develop a one-pot process for the manufacture of **6** starting from **2**, (c) to establish efficient and impurity-free synthesis for the preparation of **1** without chromatographic purifications and to demonstrate the consistency and robustness of the process with respect to the desired impurity profile, yield, and quality of **1**. All three sections have been discussed herewith in details.

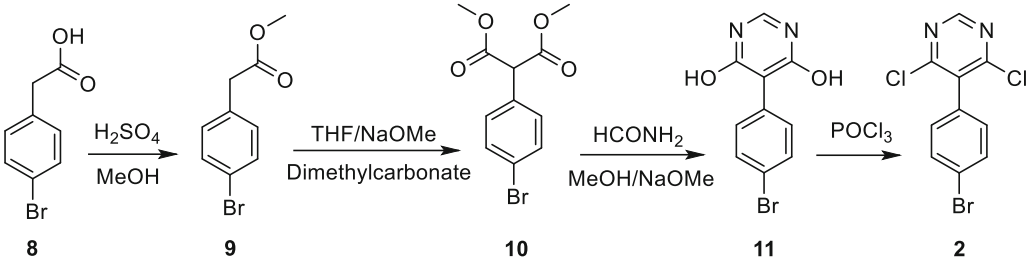
Development of robust and industrially feasible process for regulatory starting material 2

The most critical and cost-contributing key starting material **2** was prepared with substantial process improvements over the reported methods [8]. The synthesis of **2** was achieved by replacing the hazardous NaH with NaOMe for condensation of dimethyl carbonate with ester **9** and for cyclization of the obtained ester to get the diester **10**. Further, remarkable improvement in the preparation of **2** lies in the usage of formamide in place of expensive and unstable formamidine during the formation of pyrimidine compound **11**, which is then chlorinated using $POCl_3$ to obtain the desired dichloropyrimidine **2** with 99.90% purity by HPLC (Scheme 2). This optimized process is cost-effective, simple, and industrially feasible in providing a consistent quality of regulatory starting material **2** over the reported process.

Development of the one-pot process for the preparation of compound 6

Synthesis of **6** involves two key chemical steps, namely base-catalyzed substitution of 4,6-dichloro compound **2** with sulfamide intermediate **3** to obtain 6-chloro intermediate **4**, followed by a base-catalyzed condensation of the obtained compound **4** with ethylene glycol (**5**) to provide the disubstituted compound **6**. A protocol was made to establish the robust synthetic process for 6-chloro compound **4** and hydroxyethoxy compound **6** independently to achieve a simple, efficient, and single-pot process from **2** to **6** without isolation of **4**. As both the stages comprise base-catalyzed substitution reactions, a common base and solvent suitable for reactions were investigated. The impurity

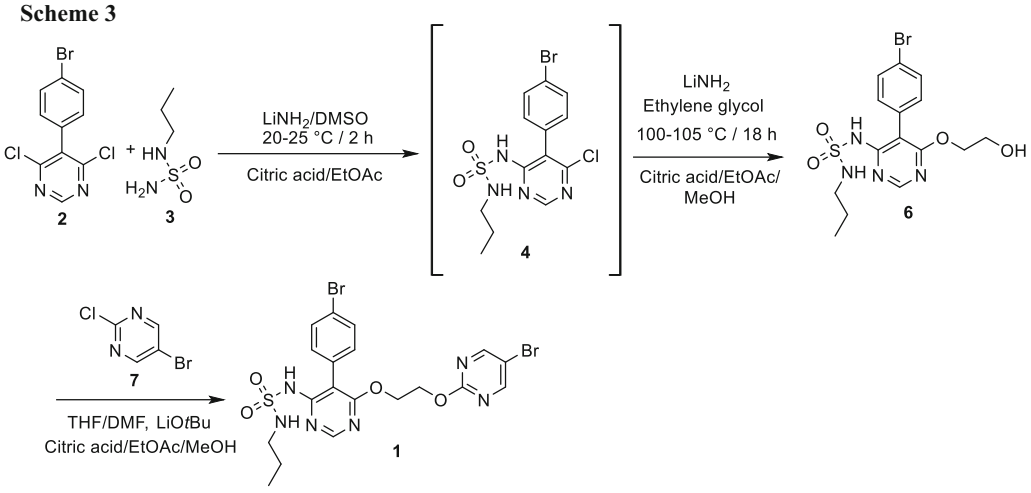
Scheme 2



profiles and yields were evaluated by conducting independent optimizations to establish the critical process parameters for both the reaction steps and then telescoped conveniently to perform both the reactions in one pot (Scheme 3). Systematic screening of bases and solvents was conducted as part of the optimization. Bases such as potassium hydroxide, potassium carbonate, cesium carbonate, potassium *tert* butoxide, lithium *tert* butoxide, sodium methoxide, and sodium ethoxide were explored in combinations with DMSO, DMF, acetonitrile, THF, and 2-methyltetrahydrofuran as solvents. Among the above, KO*t*Bu as a base in DMSO provided around 75% reaction conversion after 80 h of reaction at 25–30 °C. Performing the reaction at higher temperature (80 °C) though expedited the reaction and resulted in 15–20% impurities. The major impurity ($\sim$ 10%) observed in this stage was characterized as amino-chloro compound **12**. To minimize the formation of this impurity, the reaction was performed below 25–30 °C without compromising on the longer reaction times.

Sulfamide intermediate **3** is a weak nucleophile and thus requires a strong base and a polar aprotic solvent to raise the kinetics of the reaction in a desired fashion. Thus, selection of a strong base was made in the second-level optimization plan based on the pK_a values of different bases known in the literature. The pK_a values of hydrides and amides is around 35.0, for *tert* butoxides around 17, for methoxide and ethoxide around 15–16, for carbonates around 10, and for hydroxides about 15.7. Hence, based on the pK_a values, amides and hydrides seem to be bases of choice for this reaction. Since handling of hydrides such as sodium hydride, potassium hydride, and lithium hydride is difficult and unsafe compared to amides, we decided to explore amides such as sodium amide and lithium amide. As a starting point, we explored lithium amide as a base in polar aprotic solvents such as DMSO, DMF, THF, 2-methyltetrahydrofuran, and dimethoxyethane. As expected, the reaction conducted with lithium amide in DMSO was completed within 2–3 h at 20–25 °C with a clean impurity profile and excellent yields and thus was selected. After completion of the reaction, the reaction mass was quenched with saturated solution of citric acid, extracted compound **4** in ethyl acetate, and usual work up provided residue containing **4** (Scheme 3). The residue was dissolved in methanol and the pH adjusted to 1–2 using concentrated hydrochloric acid. The precipitated solid was isolated by filtration and dried to furnish hydrochloride salt

Scheme 3



of 6-chloro compound **4** with purity of 99.50% by HPLC containing amine impurity **12** less than 0.15%.

With the above learning, the next step, the substitution of ethylene glycol (**5**) with 6-chloro compound **4**, was straight away performed with lithium amide in DMSO at various reaction temperatures. The reaction performed at 100–105 °C for 18–20 h provided excellent reaction yields with a clean impurity profile. Similarly, the downstream process was established as follows: the reaction mass was quenched with a saturated solution of citric acid, the hydroxyethoxy compound **6** was extracted in ethyl acetate, the ethyl acetate layer was washed with brine solution, and the solvent concentrated under reduced pressure to provide a residue of hydroxyethoxy compound **6**. The obtained residue was suspended in methanol, stirred, and the solid was isolated by filtration to yield compound **6** with 99.4% purity by HPLC with content of amine impurity **14** at the level of NMT 0.15%. Upon establishing the critical process parameters, both these steps were telescoped and conducted in one pot. The process involved the condensation reaction of compound **2** (1.0 mol) with **3** (1.1 mol) in DMSO in the presence of lithium amide (2.0 mol) at 20–25 °C for 2–6 h (Scheme 3). After completion of the reaction (by HPLC), ethylene glycol (**5**, 44.0 mol) and an additional quantity of lithium amide (2.0 mol) were added to the same pot and the reaction mass heated at 100–105 °C for 18–20 h (the completion of the reaction was monitored by HPLC). The downstream operations for workup and isolations were followed as described above to furnish hydroxyethoxy compound **6** with an overall yield of 70.92% (starting from **2**) with 99.0% purity by HPLC.

Preparation of macitentan (1)

The next reaction step further involves base-catalyzed nucleophilic substitution of compound **6** with compound **7** to provide macitentan (**1**). Thus, it is critical with respect to controlling the formation of impurities and achieve the maximum yield and the desired polymorphic form [12, 13]. Preliminarily, the reaction was performed using $LiNH_2$ as base and DMSO as a solvent, but unfortunately the reaction end up with lot of impurities along with 80% reaction yield. A systematic screening of solvents (acetonitrile, ethyl acetate, NMP, DME, DMSO, THF, 2-methyltetrahydrofuran, DMF, and their mixtures) and bases (such as potassium hydroxide, potassium carbonate, cesium carbonate, lithium amide, potassium *tert* butoxide, sodium *tert* butoxide, lithium *tert* butoxide, and sodium hydride) was conducted. Among these combinations, lithium *tert* butoxide in the presence of a mixture of THF/DMF found to be the best choice as this combination ended up with around 95% reaction yield with comparatively better impurity profile at 40–45 °C within 2.0 h. The use of catalyst such as potassium iodide and sodium acetate did not have any significant advantage in the process. After completion of the reaction, the reaction mass was cooled to room temperature (20–25 °C), quenched with 5% citric acid solution, and the product **1** was extracted in ethyl acetate. The ethyl acetate layer was washed with 10% brine solution and concentrated under reduced pressure to provide a syrup containing around 90–94% of **1** by HPLC (Scheme 3). The syrup was dissolved in methanol under heating and cooled to get the crystals of **1** having 99.9% purity (ICH grade) by HPLC and with an isolated yield of around 88% (calculated from **6**). The process capability in controlling and/or eliminating the impurities in the downstream process of **1** is described in Table 1.

Evaluation of impurities

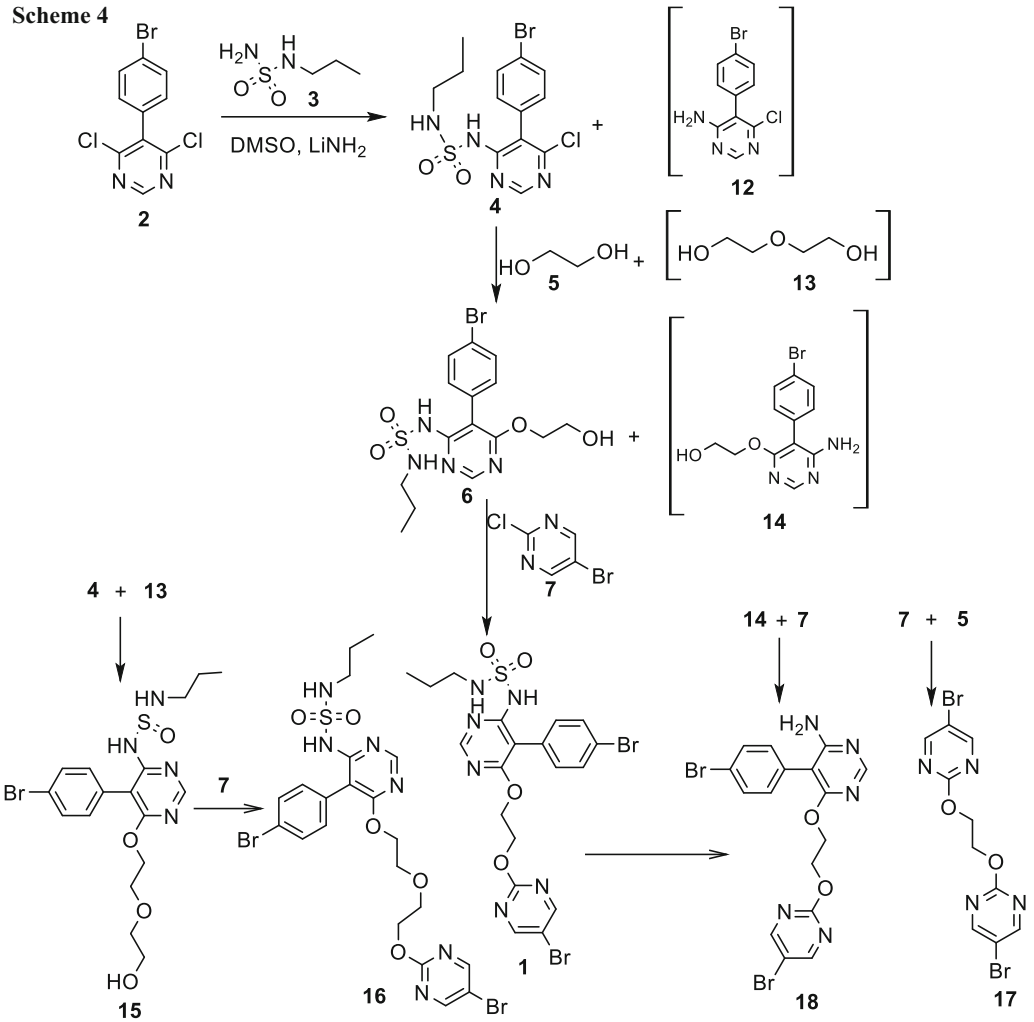
Evaluation (identification, characterization, and synthesis) of impurities (by-products, starting materials, intermediates, carryover impurities from starting materials, etc.) formed in the reaction mass and their control in the product consistently during the manufacturing phase and shelf life period is an important challenge and a critical objective to meet the regulatory norms (ICH quality) [14]. In parallel to the process development of **1**, a detailed study on impurities conducted is presented in this report. HPLC analysis of the reaction mass of **1** showed several impurity peaks (Table 1), which were subjected to LC–MS analysis to propose the probable structures. The proposed impurities were synthesized, characterized, and confirmed by spiking/purging studies using the HPLC technique. Based on the elucidation of impurity structures and possible side reactions and by-products formed, a detailed evaluation has been conducted to understand the genesis of these impurities (Scheme 4).

Six potential impurities, viz. **12**, **14**, **15**, **16**, **17**, and **18** were identified, synthesized, and characterized by spectroscopic studies such as LC–MS, ^{1}H NMR, and ^{13}C NMR. Hydrolysis of the sulfonamide group in **4** under basic conditions can lead to an amine compound **12** and similarly hydrolysis **6** can result in the formation of another amine compound **14**. These amines **12** and **14** were washed out selectively during the methanol purification of **6**. The starting material **2** and intermediate **4** present in the crude sample of **6** were also washed out selectively in the methanol purifications. Diethylene glycol (**13**), a common and obvious impurity present in **5**, can react with monochloro intermediate **4** to form impurity **15** in sample **6**. Thus, a control of **13** in **5** was established with a limit of NMT 0.5% which controlled the impurity **15** in API below the ICH limits. Further, the traces of compound **15** in **6** can react with compound **7** to form impurity **16** in **1**. Thus, an intermittent control of **15** in **6** was established based on the

Table 1 Monitoring and elimination of impurities in downstream process for **1** in laboratory batches

Sr. no.	Sample station	Impurities and their content in **1** by HPLC/%										
		1	**2**	**4**	**6**	**7**	**14**	**15**	**16**	**17**	**18**	SMUI
1	Reaction mass	94.08	ND	0.11	0.26	0.32	1.11	0.01	0.14	0.01	1.72	1.5
	Syrup	95.24	ND	0.09	0.16	0.11	0.64	ND	0.09	ND	1.11	0.65
	Crude	99.38	ND	ND	ND	ND	ND	ND	0.01	ND	0.11	0.08
	Methanol purification	99.89	ND	ND	ND	ND	ND	ND	ND	ND	0.03	0.02
2	Reaction mass	93.37	ND	0.04	0.52	0.68	0.86	0.01	0.08	0.01	0.91	1.37
	Syrup	94.62	ND	ND	0.20	0.02	0.79	ND	0.08	ND	0.79	0.92
	Crude	99.59	ND	ND	ND	ND	0.01	ND	0.01	ND	0.08	0.13
	Methanol purification	99.88	ND	ND	ND	ND	ND	ND	ND	ND	0.03	0.03
3	Reaction mass	93.93	ND	0.09	0.19	0.80	1.05	0.01	0.11	0.03	0.78	0.98
	Syrup	95.09	ND	0.07	0.08	0.18	0.87	ND	0.09	ND	0.57	0.87
	Crude	99.49	ND	ND	ND	0.01	ND	ND	0.02	ND	0.08	0.20
	Methanol purification	99.89	ND	ND	ND	ND	ND	ND	ND	ND	0.03	0.04

Scheme 4



optimization data. Further, genesis for the formation of impurities **17** and **18** was established. Traces of ethylene glycol (**5**) present in **6** can react with two molecules of compound **7** to form dimer impurity **17**. Similarly, traces of impurity **14** present in **6** can react with compound **7** to form impurity **18**. The crystallization process established for **1** using methanol was found to be capable of controlling **15**, **16**, **17**, and **18** below the ICH limits.

In conclusion, traces of carryover impurities, i.e., **4**, **5**, **13**, and **14** present in **6**, react with 7 to form process-related impurities **15**, **17**, **16**, and **18**, respectively. Thus, an appropriate control for **4**, **5**, **13**, and **14** was established with suitable limits in **6**. All these impurities were effectively controlled below the ICH limits during purification of **1** using methanol.

Conclusion

An efficient, scalable, economic, and one-pot process for the synthesis of advanced intermediate **6** of macitentan was achieved via lithium amide-mediated nucleophilic substitution, avoiding column purifications, multiple isolations, drying, and downstream processes with control of all process-related and carryover impurities to a desired level. Synthesis of highly pure macitentan (**1**) was then achieved by treating **6** with **7**, followed by purification by crystallization using methanol with an overall yield of around 62% and purity of 99.90% by HPLC.

Experimental

Melting points were determined on Analab melting point apparatus in open capillary tubes. The ^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Gemini 300 MHz FT NMR spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as internal standard and are given in δ units. The solvents used for the NMR spectra were deuterated chloroform and deuterated dimethylsulfoxide unless otherwise stated. Infrared spectra were taken on Perkin Elmer Spectrum 100 in potassium bromide pellets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer and the results were within $\pm$ 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 the 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 for detection. Gas chromatography on Agilent Technologies 7683B with head space was used for analyzing the residual solvents. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

N-[5-(4-bromophenyl)-6-(2-hydroxyethoxy)pyrimidin-4-yl]-N′-propylsulfamide (**6**)

To a stirred solution of 2.0 kg 5-(4-Bromophenyl)-4,6-dichloropyrimidine (**2**, 6.57 mol) in 20 dm^3 DMSO, 0.303 kg lithium amide (13.15 mol) and 1.0 kg *N*-propylsulfamide (**3**, 7.23 mol) were added at 20–25 °C. The reaction mass was stirred at 20–25 °C for 2–6 h (completion of the reaction was monitored by HPLC). To this reaction mass, 17.93 kg ethylene glycol (**5**, 289.30 mol) and 0.303 kg lithium amide (13.15 mol) were added; the reaction mass was heated to 100–105 °C and maintained until completion of the reaction (around 18–20 h, monitored by HPLC). After ensuring the completion of the reaction, the reaction mass was cooled to 25–30 °C and quenched with 20 dm^3 5% citric acid solution. The resulting reaction mass was extracted with ethyl acetate (20 dm^3 × 2). The ethyl acetate layer was washed with 5% brine solution (20 dm^3 × 2) and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 4 dm^3 methanol; the resulting solution was heated at 60–65 °C for 30 min, cooled to 0–5 °C, and the reaction mass maintained for 1 h. The obtained solid was filtered, washed with 300 cm^3 methanol, suck dried, and dried at 40–45 °C for 2 h to offer the title compound **6**. Yield: 2.0 kg (70.92%, calculated starting from **2**); purity by HPLC: 99.00%. The spectral data of compound **6** were found to agree with the reported data [8].

Macitentan (**1**)

To a stirred solution of 1.0 kg *N*-[5-(4-bromophenyl)-6-(2-hydroxyethoxy)pyrimidin-4-yl]-*N′*-propylsulfamide (**6**, 2.31 mol) in 4 dm^3 THF and 4 dm^3 DMF, 0.557 kg lithium *tert* butoxide (6.95 mol) was added at 25–30 °C. The reaction mass was heated to 40–45 °C and a solution of 0.538 kg 5-bromo-2-chloropyrimidine (**7**, 2.78 mol) in a mixture of 1 dm^3 THF and 1 dm^3 DMF was added at 40–45 °C. The reaction mass was maintained at the same temperature until completion of the reaction (around 1–2 h, monitored by HPLC). After ensuring the completion of the reaction, the reaction mass was cooled to 25–30 °C and the reaction mass quenched with 10 dm^3 5% citric acid solution. The resulting reaction mass was extracted with ethyl acetate (10 dm^3 × 2). The ethyl acetate layer was washed with 5% brine solution (10 dm^3 × 2) and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 25 dm^3 methanol and the resulting solution was heated at 60–65 °C for 30 min. The reaction mass was cooled to 0–5 °C and maintained for 60 min. The

obtained solid was filtered and washed with 1 dm^3 methanol to provide crude **1**. Then, the wet solid was dissolved in 25 dm^3 methanol at 60–65 °C, maintained for 30 min, and the reaction mass cooled slowly to 0–5 °C and maintained for 60 min. The obtained solid was filtered, washed with 1 dm^3 methanol, suck dried, and dried at 50–55 °C for 2–4 h to offer pure **1**. Yield: 1.20 kg (88.0%, calculated starting from **6**); purity by HPLC 99.90%. The spectral data of compound **1** were found to agree with the reported data [8].

N-[5-(4-Bromophenyl)-6-[2-(2-hydroxy-ethoxy)ethoxy]pyrimidin-4-yl]-N′-propylsulfamide (**15**, $C_{17}H_{23}BrN_4O_5S$)

To a stirred solution of 50.0 g 5-(4-bromophenyl)-4,6-dichloropyrimidine (**2**, 0.164 mol) in 500 cm^3 DMSO, 7.6 g lithium amide (0.32 mol) and 25.0 g *N*-propylsulfamide (**3**, 0.18 mol) were added at 20–25 °C. The reaction mass was stirred at 20–25 °C for 2–6 h (completion of the reaction was monitored by HPLC). To this reaction mass, 446.5 g diethylene glycol (**13**, 4.20 mol) and 7.6 g lithium amide (0.32 mol) were added and the reaction mass heated to 100–105 °C. The reaction mass was maintained at the same temperature until completion of the reaction (around 18–20 h, monitored by HPLC). After ensuring the completion of the reaction, the reaction mass was cooled to 25–30 °C and quenched with 500 cm^3 5% citric acid solution. The resulting reaction mass was extracted with ethyl acetate (500 cm^3 × 2). The ethyl acetate layer was washed with 5% brine solution (500 cm^3 × 2) and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 250 cm^3 diisopropyl ether and the resulting solution was heated at 55–60 °C for 30 min. The reaction mass was slowly cooled to 0–5 °C and maintained for 60 min. The solid obtained was filtered, washed with 12 cm^3 diisopropyl ether, and dried at 40–45 °C for 2 h to offer compound **15**. Yield: 48.5 g (62.0%); purity by HPLC: 90.0%; m.p.: 83–85 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.83 (s, 1H), 8.49 (s, 1H), 7.64–7.61 (d, J = 8.1 Hz, 2H), 7.27–7.24 (d, J = 8.1 Hz, 2H), 4.58 (bs, 1H), 4.42–4.39 (t, J = 9.6 Hz, 2H), 3.36–3.60 (t, J = 8.1 Hz, 2H), 3.42–3.35 (m, 4H), 2.78 (t, 2H), 1.48–1.36 (m, 2H), 0.82–0.77 (t, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ = 165.96 (C), 156.28, 155.87 (C), 132.73, 131.43, 129.72, 121.32, 104.88, 72.41, 68.30, 66.03, 60.26, 44.63, 21.99 (CH_2), 11.26 (CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3310, 1570, 1430, 1340, 1170, 1080, 836 cm^{-1}; MS (70 eV): m/z = 477.0 [M^+].

N-[5-(4-Bromophenyl)-6-[2-[2-(5-bromo-2-pyrimidinyloxy)ethoxy]ethoxy]pyrimidin-4-yl]-N′-propylsulfamide (**16**, $C_{21}H_{24}Br_2N_6O_5S$)

To a stirred solution of 25.0 g **15** (0.052 mol) in 100 cm^3 THF and 100 cm^3 DMF, 12.63 g lithium *tert* butoxide (0.157 mol) was added at 25–30 °C. The reaction mass was heated to 40–45 °C and a solution of 12.20 g 5-bromo-2-chloropyrimidine (**7**, 0.063 mol) in a mixture of 25 cm^3 THF and 25 cm^3 DMF was added. The reaction mass was maintained at 40–45 °C until completion of the reaction (around 1–2 h, monitored by HPLC). After ensuring the completion of the reaction, the reaction mass was cooled to 25–30 °C and quenched with 250 cm^3 5% citric acid solution. The resulting reaction mass was extracted with ethyl acetate (250 cm^3 × 2) and the ethyl acetate layer was washed with 5% brine solution (250 cm^3 × 2) and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 250 cm^3 diisopropyl ether and the resulting solution was heated at 55–60 °C for 30 min. The reaction mass was cooled to 10–15 °C and maintained for 60 min. The solid obtained was filtered and washed with 25 cm^3 diisopropyl ether. The wet solid crystallized in a mixture of ethyl acetate and diisopropyl ether to give the title compound **16**. Yield: 25.0 g (86%); purity by HPLC 98.91%; m.p.: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 2H), 8.46 (s, 1H), 7.63–7.60 (d, J = 8.4 Hz, 2H), 7.24–7.21 (d, J = 8.1 Hz, 2H), 6.96 (s, NH), 5.67–5.63 (t, J = 12.3 Hz, NH), 4.52–4.39 (m, 4H), 3.78–3.74 (m, 4H), 2.99–2.92 (q, J = 6.6 Hz, 2H), 1.64–1.52 (h, J = 7.2 Hz, 2H), 0.96–0.91 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ = 166.46 (C), 163.69 (C), 159.69, 156.51, 155.63, 132.81, 131.76, 128.26, 123.40, 112.12, 104.63, 96.19, 96.16, 67.48, 66.47, 45.79, 22.41, 11.32 ppm; IR (KBr): $\bar{\nu}$ = 3292, 3060, 2972, 2873, 1569, 1556, 1431, 1312, 1172, 1087, 934 cm^{-1}; MS (70 eV): m/z = 634.0 [M^+].

2,2′-[Ethane-1,2-diylbis(oxy)]bis(5-bromopyrimidine) (**17**, $C_{10}H_8Br_2N_4O_2$)

To a stirred solution of 50.0 g 5-bromo-2-chloropyrimidine (**7**, 0.258 mol) in 359.7 g ethylene glycol (**5**, 5.79 mol), 18.0 g lithium amide (0.781 mol) was added at 5–10 °C. The temperature of the reaction mass was raised to 25–30 °C and maintained for 3–6 h (completion of the reaction was monitored by HPLC). The reaction mass was quenched with 500 cm^3 10% citric acid solution and the resulting reaction mass was extracted with ethyl acetate (500 cm^3 × 2); the ethyl acetate layer was washed with 250 cm^3 10% brine solution and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 200 cm^3 THF and 200 cm^3 DMF, and 55.0 g lithium *tert* butoxide (0.69 mol) and 53.0 g 5-bromo-2-chloropyrimidine (**7**, 0.274 mol) were added. The reaction mass was heated to 45–50 °C and maintained as such for 1 h (completion of the reaction was monitored by HPLC). After completion of the reaction, the reaction mass was cooled to 25–30 °C and quenched with 500 cm^3 10% citric acid solution. The resulting reaction mass was extracted

with ethyl acetate (500 cm^3 × 2) and the ethyl acetate layer was washed with 500 cm^3 10% brine solution and concentrated under reduced pressure to obtain the residue. The residue was dissolved in 350 cm^3 methanol and the resulting solution was heated at 60–65 °C for 30 min, cooled to 25–30 °C and maintained for 60 min, and the solid obtained was filtered, washed with 50 cm^3 methanol, and dried at 40–45 °C for 2 h to offer **17**. Yield: 50.0 g (58.60%); purity by HPLC: 99.99%; m.p.: 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.52$ (s, 4H), 4.73 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 163.57$, 159.68, 112.23, 65.87 (CH_2) ppm; IR (KBr): $\bar{\nu} = 3049$, 2969, 1568, 1433, 1320, 943 cm^{-1}; MS (70 eV): $m/z = 377.0$ [M^+].

5-(4-Bromophenyl)-6-[2-[(5-bromopyrimidin-2-yl)oxy]ethoxy]pyrimidin-4-amine (**18**, $C_{16}H_{13}Br_2N_5O_2$)
A solution of 50.0 g **1** (0.085 mol) in 250 cm^3 conc. HCl was stirred at 25–30 °C for 6–10 h (completion of the reaction was monitored by HPLC). The reaction mass was diluted with 100 cm^3 water at 25–30 °C and maintained for 60 min. The obtained solid was filtered and washed with water. The wet solid was suspended in a mixture of 100 cm^3 water and 100 cm^3 methanol and the pH of the reaction mass adjusted to 7–8 with aqueous ammonia. The reaction mass was stirred at 25–30 °C for 30 min, and the obtained solid was filtered, washed with methanol, suck dried, and dried at 45–50 °C for 2 h to offer **18**. Yield: 35.0 g (88.16%); purity by HPLC: 98.01%; m.p.: 173–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.48$ (s, 2H), 8.22 (s, 1H), 7.53–7.50 (d, $J = 8.4$ Hz, 2H), 7.22–7.19 (d, $J = 8.4$ Hz, 2H), 4.81 (br s, 2H), 4.68–4.59 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.54$, 163.63, 161.75, 159.64, 156.54, 132.28, 131.84, 130.62, 122.11, 100.78, 66.03, 64.39 ppm; IR (KBr): $\bar{\nu} = 3391$, 3306, 3167, 2958, 1643, 1575, 1453, 1307, 1148, 933 cm^{-1}; MS (70 eV): $m/z = 468.0$ [M^+].

2-[[6-Amino-5-(4-bromophenyl)pyrimidin-4-yl]oxy]-ethanol (**14**, $C_{12}H_{12}BrN_3O_2$)
A solution of 50.0 g *N*-[5-(4-bromophenyl)-6-(2-hydroxyethoxy)pyrimidin-4-yl]-*N*′-propylsulfamide (**6**, 0.115) in 250 cm^3 of conc. HCl was stirred at 25–30 °C for 24 h (completion of the reaction was monitored by HPLC). After ensuring the completion of the reaction, the reaction mass was quenched with 250 cm^3 water and maintained for 60 min. The obtained solid was filtered and washed with 50 cm^3 water and dried at 40–45 °C for 2 h to offer **14**. Yield: 34.0 g (94.54%); purity by HPLC: 90.0%; m.p.: 130–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.15$ (s, 1H), 7.62–7.59 (d, $J = 7.8$ Hz, 2H), 7.29–7.27 (d, $J = 7.8$ Hz, 2H), 6.40 (br s, NH_2), 4.44 (br s, OH) 4.24–4.23 (t, 2H), 3.57–3.56 (t, 2H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 165.23$, 161.71, 155.73, 132.53–131.30, 120.70, 99.09, 67.60, 59.31 ppm; IR (KBr): $\bar{\nu} = 3463$, 3443, 3341, 3294, 3136, 2914, 1640, 1578, 1432, 1313, 1140, 900 cm^{-1}; MS (70 eV): $m/z = 312.0$ [M^+].

5-(4-Bromophenyl)-6-chloropyrimidin-4-amine (**12**, $C_{10}H_7BrClN_3$)
To a stirred solution of 5-(4-bromophenyl)-4,6-dichloropyrimidine (**2**, 50.0 g, 0.164 mol) in 250 cm^3 THF, 500 cm^3 ammonium hydroxide was added at 25–30 °C and the resulting mass was maintained for 24–30 h (completion of the reaction was monitored by HPLC). After ensuring the completion of the reaction, the resulting reaction mass was extracted with dichloromethane (250 cm^3 × 2). The dichloromethane layer was washed with 250 cm^3 10% brine solution and concentrated under reduced pressure to obtain the residue. The residue was suspended in 100 cm^3 *n*-heptane and the resulting suspension was heated at 45–50 °C for 30 min. The reaction mass was cooled to 25–30 °C and maintained for 60 min. The obtained solid was filtered, washed with 25 cm^3 *n*-heptane, suck dried, and dried at 40–45 °C for 2 h to offer **12**. Yield: 35.0 g (74.78%); purity by HPLC: 99.75%; m.p.: 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.22$ (s, 1H), 7.70–7.67 (d, $J = 8.1$ Hz, 2H), 7.28–7.25 (d, $J = 8.1$ Hz, 2H), 6.67 (br s, NH_2) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 162.73$, 157.05, 156.48, 132.18, 132.03, 122.00, 114.20 ppm; IR (KBr): $\bar{\nu} = 3467$, 3293, 3166, 1651, 1569, 994 cm^{-1}; MS (70 eV): $m/z = 286$ [M^+].

Methyl (4-bromophenyl)acetate (**9**)
To a stirred solution of 100 g 4-bromophenylacetic acid (**8**, 0.46 mol) in 300 cm^3 methanol, 30 cm^3 sulfuric acid was added in 1 h. The reaction mass was heated to 70 °C and the temperature maintained until the completion of the reaction (monitored by HPLC). After completion of the reaction, methanol was distilled under reduced pressure at 70 °C, the resulting solution was cooled to 25–30 °C, diluted with 200 cm^3 water and the product was extracted into 300 cm^3 dichloromethane. The dichloromethane layer was washed with 5% solution of sodium bicarbonate and concentrated under reduced pressure to offer **9** as light brown oil. Yield: 101 g (94.83%); purity by HPLC: 99%; b.p.: 265–270 °C. The spectral data of compound **9** were found to agree with the reported data [8].

Dimethyl (4-bromophenyl)malonate (**10**)
To a stirred solution of 100 g methyl-(4-bromophenyl)acetate (**9**, 0.436 mol) in 300 cm^3 tetrahydrofuran, 95 g sodium methoxide (1.75 mol) was added at 0–5 °C and maintained for 1 h. 80 g dimethyl carbonate (0.88 mol) was added at 0–5 °C over a period of 2 h. The reaction mass was maintained at 25–30 °C until the completion of the reaction (monitored by HPLC). After completion of the reaction, tetrahydrofuran was concentrated under reduced pressure at 45 °C to obtain the syrup. The syrup was

diluted in 500 cm^3 water and the product was extracted in 250 cm^3 dichloromethane. The organic layer was concentrated under reduced pressure at 45 °C to obtain the thick solution which was dissolved in 200 cm^3 isopropyl alcohol at 70 °C and maintained for 1 h. The solution was cooled to 0 °C and maintained for 60 min. The obtained solid was filtered, washed with isopropyl alcohol, and dried at 50–55 °C for 4–6 h to provide **10**. Yield: 80 g; purity by HPLC: 99%; m.p.: 72–76 °C. The spectral data of compound **10** were found to agree with the reported data [8].

5-(4-Bromophenyl)pyrimidine-4,6-diol (**11**)

To a stirred solution of 100 g dimethyl(4-bromophenyl)-malonate (**10**, 0.348 mol) in 400 cm^3 methanol, 30 g formamide (0.66 mol) and 30 g sodium methoxide (0.555 mol) were added at 20–25 °C. The reaction mass was heated to 70 °C and maintained until completion of reaction (monitored by HPLC). After completion of the reaction, methanol was distilled off from the reaction mass under reduced pressure at 70 °C to obtain the syrup. The syrup was cooled to 25–30 °C and diluted with 2 dm^3 water. The pH of the solution was adjusted to 2–2.5 using conc. hydrochloric acid and maintained for 45 min. The obtained solid was filtered and washed with water until the pH of the filtrate became 7–7.5. The product was suck dried and dried under reduced pressure at 100 °C to obtain crude **11**. The crude solid was dissolved in 500 cm^3 methanol at 60–65 °C and maintained for 1 h. The reaction mass was cooled to 25–30 °C and maintained for 30 min. The obtained solid was filtered, washed with methanol, and dried at 50–55 °C under reduced pressure to offer **11**. Yield: 70 g (75.25%); purity by HPLC: 99.5%; m.p.: 176–180 °C. The spectral data of compound **11** were found to agree with the reported data [8].

5-(4-Bromophenyl)-4,6-dichloropyrimidine (**2**)

A stirred solution of 100 g 5-(4-bromophenyl)pyrimidine-4,6–diol (**11**, 0.374 mol) was added to 300 cm^3 phosphorous oxychloride. The reaction mass was heated to 90 °C and maintained until completion (monitored by HPLC). After completion of the reaction, the reaction mass was cooled to 10–15 °C and quenched over water below 15 °C. The obtained solid was filtered and washed with water until the pH of the filtrate became 6.5–7.0. The material was dried under reduced pressure at 65 °C to obtain the crude solid. The crude solid was further recrystallized in methanol and the obtained solid was filtered and dried to provide **2**. Yield: 90 g (79%); purity by HPLC: 99.7%; m.p.: 100–103 °C. The spectral data of compound **2** were found to agree with the reported data [8].

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