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An Improved Synthesis of Bazedoxifene Acetate

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Abstract: An improved process for Bazedoxifene acetate **1** is described. This process features chlorination of an alcohol **8**, a key intermediate, amenable to large scale operations by using HCl gas instead of thionyl chloride. In addition to this, an alternate synthetic route for **1** is also disclosed.

Keywords:

Introduction

Osteoporosis, one of the bone disorders, is attributed to unavailability of new bones in adequate quantity to replace the feeble or broken ones. In this condition, the bones gradually become thin and fragile and more likely to get fractured. Osteoporosis is more common in women after the menopause when the level of the female hormone estrogen decreases. Bazedoxifene, is a selective estrogen receptor modulator (SERM)¹⁻³ that acts as an agonist of the estrogen receptor in some tissues in the body

and helps in the management of osteoporosis.

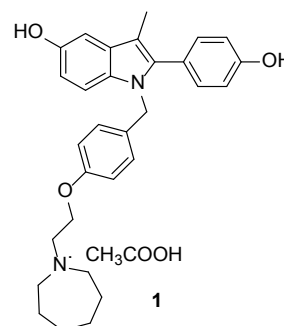


Figure 1. Structure of Bazedoxifene acetate **1**

Bazedoxifene 1 acetate was first synthesized by Miller & Collini et al.^{4,5} Herein, we report an improved, relatively high yielding, scalable synthesis of Bazedoxifene acetate 1 (Figure 1). We have also developed an alternate synthetic route for 1 as shown in Scheme 2.

Results & discussion

Synthesis of Bazedoxifene Acetate 1

Indole derivative 2 and azepane derivative 3 (Figure 2) are the two key intermediates of bazedoxifene.

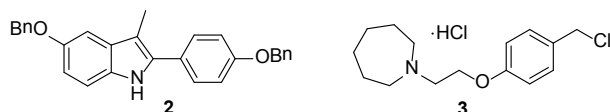


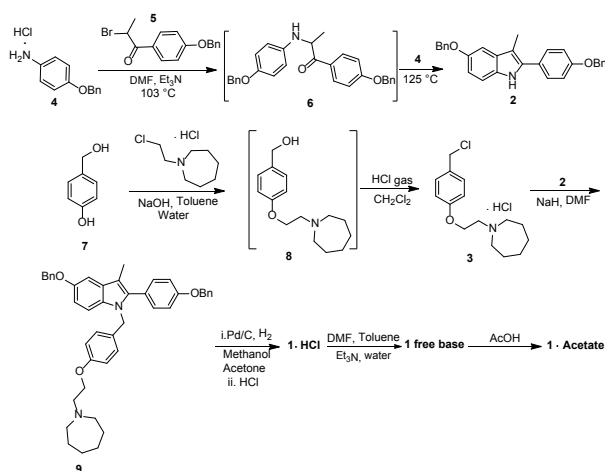
Figure 2. Structure of key intermediates 2 and 3

In the synthesis of 2 , various reaction parameters were studied in order to improve the yield and quality. There were several solvents screened e.g. dimethylformamide, toluene, xylene, isopropyl alcohol, butanol, ethyl acetate, tetrahydrofuran, dimethoxyethane and chlorobenzene and it was found out that the reaction gets completed in only dimethylformamide. Similarly, several bases like triethylamine, sodium hydroxide, potassium carbonate, sodium bicarbonate and *N*-methylmorpholine were screened. Among all the bases screened, triethylamine was found to be suitable base for reaction completion. Moreover, reaction temperature was found to be one of the key parameters. In the reported process, reaction was performed at 150°C that afforded product in poor yields (54%). The root cause of this was the formation of several impurities and degradation of the product. Compound 10 (Figure 3) derived from dimethylformamide was found to be a major impurity.

Essentially, synthesis of 2 is a two stage *in situ*

process; intermediate 6 was formed at 105°C and consumed in the next step without isolation. This step was conducted at 125°C to obtain 2 in 70% yields. During work up, a cluttered emulsion was encountered and the layer separation was found to be difficult, moreover after the isolation of 2 , the color was found to be a dark brown. This color was carried forward up to final stage impacting the description of the title compound bazedoxifene Acetate 1 . This difficulty was overcome by quenching the reaction mass into 5% acetic acid solution that afforded the product in cream color without imposing any emulsion related challenges during work up.

Scheme 1. Improved synthesis of 1



The reported process to prepare 3 involves the coupling of *p*-hydroxybenzaldehyde with 1-(2-chloroethyl) azepane.HCl using NaH and DMF followed by the reduction of aldehyde with NaBH_4 to give 8 and subsequent chlorination with SOCl_2 provides the product 3 . We simplified the process by coupling *p*-hydroxybenzyl alcohol with 1-(2-chloroethyl) azepane.HCl in toluene and water biphasic system using NaOH and TBAB catalyst to afford 8 in >90% yields. Several bases like K_2CO_3 , Na_2CO_3 , NaOH, LiOH, $\text{Ba}(\text{OH})_2$ in different solvents like acetone, DMF, IPA, THF, MTBE, toluene and solvent mixtures along with water were

screened. The best yield and quality were obtained in toluene and water biphasic system using NaOH and TBAB catalyst (>90% yield and >97% purity) whereas in other bases either the yield is low or the formation of impurities were high. Moreover, output has been improved from 80% to > 90% by increasing the solvent dilution from 10 to 25 vol. Optimization efforts in the synthesis of **8**, led us to replace expensive bases like NaBH_4 and NaH with inexpensive NaOH. Similarly, DMF, ether, methanol and ethyl acetate solvents were replaced with easily recoverable solvent toluene.

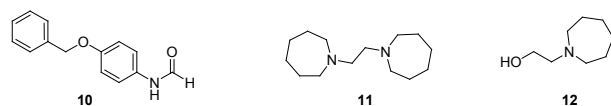


Figure 3. Structures of the impurities **10**, **11** and **12**

NaOH equivalent effects on the preparation of compound **8** by using 1-(2-chloroethyl) azepane hydrochloride (CEA.HCl) salt in terms of percentage yield are captured in the Table 1. Impurity **11** (Figure 3) was effectively controlled to less than 2% by optimizing the quantity of

NaOH. Optimization efforts revealed that 2.4 eq of NaOH was found to be optimal to control the impurity **11**.

Pre-DoE experiments also suggested that the maximum conversion towards **8** can be obtained at the temperature ranging from 85 to 90 °C as shown in Table 2.

Table 2. Effect of temperature on compound **8**

Temperature	Yield (%)	HPLC (%)
75-80 °C	83.0	83.65
85-90 °C	99.60	88.01

Based on effect of various process parameters on the compound **8**, the variables and ranges for DoE were selected. The objective of the DoE was to obtain the design space where compound **8** could be consistently obtained by controlling the impurity of **11**. In this context, we defined the CQAs (Critical Quality Attributes: Responses) as maximum purity and yield (Table 3).

Table 3. Attributes and specification limits for DoE studies

Table 1. Effect of NaOH equivalents on compound **8**

NaOH (Eq)	CEA·HCl (Eq)	Yield (%)	Impurity 11 by G.C. (%)
2.6	1.5	88.0	0.52
2.4	1.5	69.0	0.21
2.2	1.5	71.0	0.51
2.4	1.4	86.0	2.24
2.3	1.3	75.0	0.58
2.4	1.3	90.0	0.85
2.1	1.3	75.0	0.49
1.9	1.3	89.0	0.78
2.3	1.2	75.0	1.00

CQA (Responses)	Unit	Target
Purity	%	Maximize
Yield	%	Maximize

We also understood the rationale behind deciding on the fixed parameters e.g. toluene volume, water volume and temperature. More than 10 vol of toluene and less than 15 vol of water tend to afford product in lower yields. In addition to this, reaction at less than 85°C temperature gives rise the product also in lower yields as mentioned the Table 4.

Table 4. Fixed process parameters for the DoE studies

Factors	Fixed level	Rationale
Toluene Volume	10	Higher volumes would decrease yield
Water Volume	15	Lower volumes would decrease yield
Temperature	85-90°C	Reaction conversion is less with lower temperature

Initial experiments show that 2.4 equivalents and 1.3 equivalents of NaOH and CEA·HCl can afford intermediate **8** in significantly high yields (Table 1) therefore we considered these two components as variables for DoE studies as shown in Table 5.

Table 5. Ranges of variables

Variables	Unit	Minimum	Maximum
NaOH	Eq	2.2	2.6
CEA.HCl	Eq	1.2	1.4

Two CQAs have been modeled (Figure 4):

1. Yield has significant model with no pure error. R^2 and Predicted R^2 values of this have

good predictability and hence its contour plots may be used.

2. Only % purity has an insignificant model

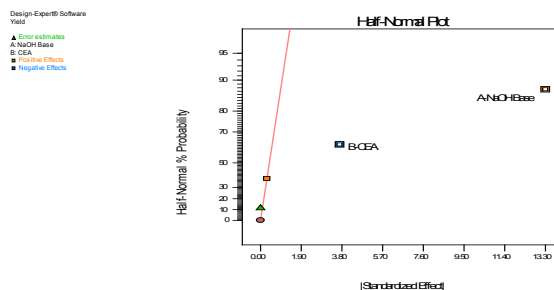


Figure 4. Half-Normal plot for yield (%)

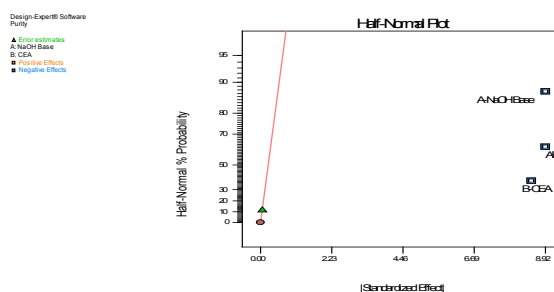


Figure 5. Half-Normal plot for Purity (%)

Experimental runs were conducted and the following were observed in this order of % effect contribution (Figure 5):

1. Purity depended negatively on concentration of NaOH base and CEA.HCl mol equivalents.
2. There is interaction effect NaOH base and CEA.HCl on purity
3. Yield (%) depends positively on NaOH and negatively on concentration CEA.HCl mol equivalents.

In conclusion, DoE studies helped us to develop an efficient process and we successfully scaled it up with 10 kg batch size without any failure. Thereafter, compound **8** was subjected to chlorination using dry HCl gas in

dichloromethane that afforded **3** in 81% yields. Our process is found to be superior to the reported one as it generates water as a byproduct whereas the preceded one involves thionyl chlorides in combination with dry HCl that yields the sulphur dioxide as a byproduct. Typical process involves the dissolution of **8** in dichloromethane and continuous purging of the dry HCl gas for 2 h at 25-35°C followed by distillation and isolation of the product **3** in acetone solvent under nitrogen atmosphere. The product was hygroscopic in nature therefore we had to screen several solvents for this reaction, interestingly only dichloromethane afforded the product **3** with dry HCl gas whereas with other solvents, thionyl chloride only affords the product (Table 6).

Table 6. Effect of solvent on the chlorination of **8**

Solvent	Yield (%)	HPLC (%)
Ethyl acetate	40	96.45
Toluene	50	97.66
THF	45	97.83
Dichloromethane	82	99.20

We also studied the effect of temperature as shown in Table 7. We found that the maximum conversion was obtained almost at ambient temperature (25-35 °C).

Table 7. Effect of Temperature on the chlorination of **8**

Temperature (°C)	Yield (%)	HPLC (%)
0-5	66	95
25-35	82	97

In conclusion, an efficient, chlorination process yielding **3** was developed and scaled it up with 20 kg batch size.

Subsequently, **2&3** were coupled by using NaH in DMF solvent to afford **9** in 75% yields. Several bases were screened to replace NaH, e.g. Na₂CO₃, TEA, NaOMe, K₂CO₃, KOH and NaOH, but the best yield and quality were obtained with NaH only. (Table 8)

Table 8. Effect of base on the synthesis of **9**

Base	Yield (%)
Na ₂ CO ₃	--
TEA	--
NaOMe	--
K ₂ CO ₃	20
KOH	46
NaOH flakes	25
NaOH powder	49
KOH powder	43
NaH	75

Around 20% potential impurity **13** (Figure 6) was formed in this reaction. This impurity (**13**) is obtained in significant quantity as a result of contiguous C-alkylation along with *N*-alkylation affording **9**.

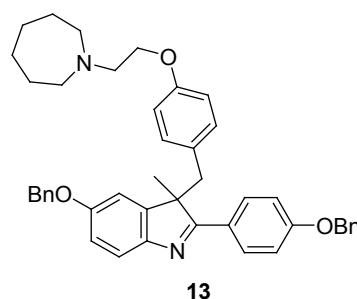


Figure 6. Structure of impurity **13**

Various conditions were screened to control this impurity but it was not possible to impede or avoid its formation (Table 9). Eventually, we decided to develop the process with the NaH/DMF reducing system that afforded **9** at the

minimum 15% of impurity **13** in reaction mass.

Table 9. Different conditions screened to control impurity 13

Base (2 Eq)	Solvent	Temp (°C)	Impurity 13(%) (In reaction mass)
K ₂ CO ₃	DMF	30	17
NaOH powder	DMF	25	19
KOH powder	DMF	25	18
NaH	Toluene	2	23
NaH	THF	2	17
NaH	DMAc	2	18
NaH	DMF	- 10	16
NaH	DMF	- 20	15
NaH	DMF	70	18
NaH	DMF	90	19
NaH	DMF	2	15

Preliminary experiments was conducted with different equivalent of NaH with 10 vol of DMF, but with 2.4 eq of NaH only providing 0.08 % of impurity 13 in final solid as shown in Table 10.

Table 10. Different equivalence of base screened by using 10 vol of DMF to understand the control the impurity **13**.

NaH (eq)	Yield(%)	Impurity 13 (%) (Final solid)
2.1	66.47	0.36
2.3	60.60	0.20
2.4	64.77	0.08
2.5	71.56	0.57
3.0	68.29	0.40

The effect of various process parameters of

compound **9** were studied. The variables and ranges for DoE were selected with the objective that the compound **9** could be consistently crystallized while gaining insights into the interaction of parameters responsible for CQAs like maximum purity (minimum percentage of impurity **13**) and yield as shown in Table 11.

Table 11. Attributes and specification limits for DoE study

CQA (Responses)	Unit	Target
Purity	%	Maximize
Impurity13	%	Minimize
Yield	%	Maximize

Preliminary experiments have indicated that more than 8 vol of DMF and 0.5 equiv of acetic acid do not favor the reaction to obtain **9** in good yields. Considering these observations we considered 8 vol of DMF and 0.5 equiv of acetic acid as fixed variables as shown in Table 12.

Table 12. Process parameters that are fixed at a particular level for the DoE study

Factors	Fixed level	Rationale
DMF volume	8	Higher volumes decrease yield
Acetic acid quantity (eq)	0.5	Higher volumes decrease yield

Considering the pre-DOE experiments, we have defined the ranges of variables i.e. NaH eq, compound 3 eq and reaction temperature as shown in Table 13.

Table 13. Process parameters that are part of the DoE study and their ranges

Variables	Minimum	Maximum
NaH (eq)	2.2	2.6
Compound 3 or BAZ-3 (eq)	1.0	1.2
Reaction temperature (°C)	-5	5

Experimental runs were conducted and the following were observed in this order of % effect contribution (Figures 7, 8 and 9):

1. Purity depended negatively on concentration of NaH base and Reaction temperature and positively on compound 3 (BAZ-3) mol equivalents.
2. Impurity **13** (Benzyl alkylated impurity) depended positively on concentration of NaH base and inversely on compound 3 (BAZ-3) mol equivalents.
3. Yield (%) depends positively on reaction temperature and negatively on concentration of NaH base.

Half Normal Plots of effects of Factors:

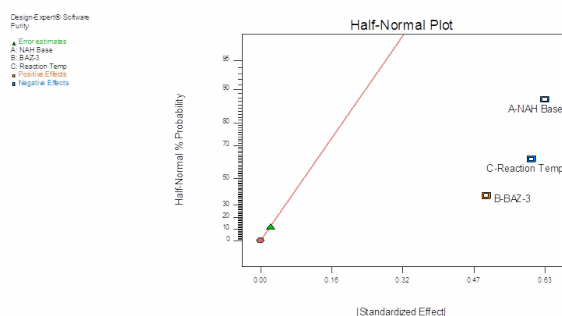


Figure 7. Half-Normal plot for Purity (%)

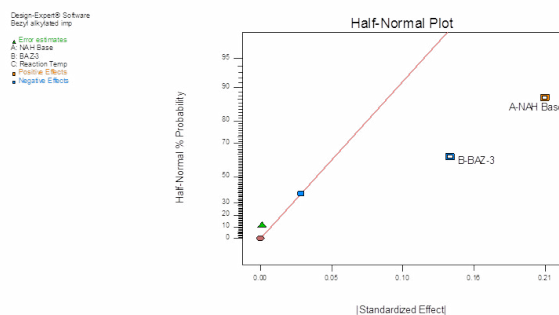


Figure 8. Half-Normal plot for Impurity **13** (Benzyl alkylated impurity)

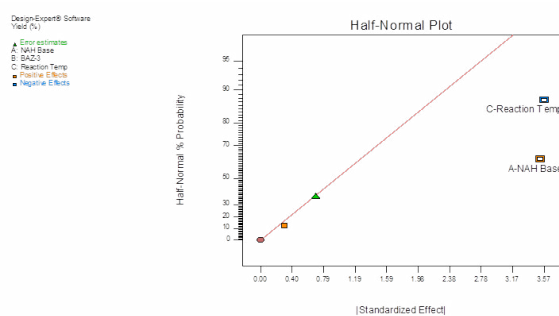


Figure 9. Half-Normal plot for yield (%)

This DoE study was used to define a control strategy which was verified by conducting three experiments with 2.4 eq of NaH, 1.1 eq of compound 3 and reaction temperature at 0-5 °C and all three validation experiments were found to be consistent with respect to expected yield and quality.

In conclusion, an efficient, process was developed and successfully scaled it up to 10 kg.

Thereafter, compound **9** was debenzylated by using Pd/C/H₂ in a mixture of methanol and acetone solvents followed by reaction with Aq. HCl that afforded the bazedoxifene HCl (**1**·HCl) in 72% yield. We have screened several solvents/solvent mixtures to obtain the high yield and purity. The best results were obtained in the mixture of methanol and acetone medium. After screening of different ratios of methanol and acetone, 4:12 combination was found to be

the best to get the maximum yield and purity as shown in Table 14.

Table 14. Effect of solvent on the debenzylation to get 1·HCl

Solvent	Yield (%)	Total imp. (%)
Methanol	91	1.30
Acetone	77	0.65
Ethyl acetate	80	1.1
Methanol and ethyl acetate	87	0.66
Methanol and THF	51	0.47
Methanol and Dimethoxyethane	75	1.12
Methanol and Dioxane	68	0.61
Methanol and Acetone (5:10)	80	0.86
Methanol and Acetone (5:15)	75	0.45
Methanol and Acetone (5:20)	73	0.94
Methanol and Acetone (4:12)	72	0.20

BazedoxifeneHCl was then treated with triethylamine/DMF/toluene/water medium to isolate the bazedoxifene free base as a stable crystalline polymorph in 90% yields. Bazedoxifene free base was then treated with acetic acid to afford bazedoxifene acetate **1** as a stable crystalline polymorph. Alternatively, bazedoxifene free base was prepared by treating **9** with Pd/C and ammonium formate (3 eq) in ethylacetate at 50°C for 3 h to afford as amorphous solid in a quantitative yield.

There were few degradation impurities identified (**14**, **15** and **16**) during the synthesis as mentioned in Figure 10.

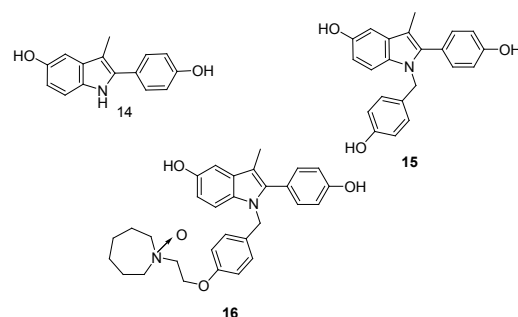
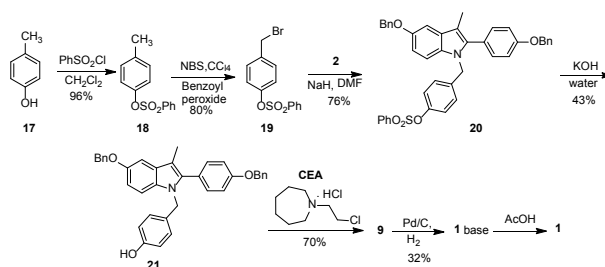


Figure 10. Structure of impurities 14, 15, and 16

Alternate synthesis of Bazedoxifene Acetate

We have alternatively developed a synthetic route for Bazedoxifene acetate as showed in Scheme 2. Synthesis commences with the protection of *p*-cresol **17** with benzene sulphonyl chloride followed by bromination using NBS and benzoyl peroxide to afford **19** which was then coupled with **2** followed by deprotection of benzene sulphonyl group that afforded **21**.

Scheme 2. Alternate synthetic route for bazedoxifene acetate



Thereafter, compound **21** was coupled with 2-chloroethylazepane.HCl (CEA) to provide intermediate **9**. Subsequently, debenzylation and addition of acetic acid afforded acetate salt of **1**.

Conclusion

In conclusion, we have addressed several process related challenges by understanding the implications of various reaction parameters through DoE. Eventually we were able to

develop an efficient and robust process for the preparation of Bazedoxifene acetate and related salts. Moreover, we could identify few process and degradation related impurities which helped us to produce material with consistent quality. Inquisitively, we also developed an alternate synthetic route for Bazedoxifene acetate.

Experimental section

Solvents and reagents were used for all the reactions as received. ^1H NMR spectra were recorded on a Varian Mercury spectrometer at 200 or 400 MHz. The proton signal of residual, non-deuterated solvents (δ 7.26 for CDCl_3 , 2.2 ppm for $\text{DMSO}-d_6$) was used as an internal reference for ^1H NMR. Infrared (IR) spectra were recorded as thin films on a Mattson Galaxy Series FTIR 3000 spectrometer referenced to polystyrene standard.

Preparation of 5-benzyloxy-2-(4-benzyloxyphenyl)-3-methyl-1H-indole (2). To a mixture of **5** (10 Kg, 0.031 mol) and **4** (8.1 Kg, 0.034 mol) in dimethylformamide (60 L) was added triethyl amine (10 L, 0.072 mol). The reaction mass was heated to 100-105°C and stirred for 3-4 h. Thereafter, it was cooled to 50-55°C. Subsequently another lot of **4** (8.1 Kg, 0.034 mol) was added. The reaction mass was heated to 125°C and stirred for 5-6 h. Thereafter, it was cooled to 25-35°C and added to 5% acetic acid solution (10 L) and stirred for 30 min. Then the reaction mass was extracted with ethyl acetate (200 L). Organic layer was washed with 5% NaHCO_3 solution (200 L) and 10% NaCl solution (200 L). Solvent was evaporated at below 70°C and to the obtained residue was added methanol (80 L) and stirred for 2 h. The product was filtered and washed with methanol (90 L). Dried the solid under vacuum at below 70°C to provide 8.8 Kg of title compound **2** (67% yield, 99.6% purity by HPLC); ^1H NMR (CDCl_3 , 400 MHz) : δ (ppm) 7.50-7.31 (m, 12H), 7.24-7.22 (m, 1H), 7.11-7.03 (m, 3H), 6.93- 6.87 (m, 1H), 5.13-5.11

(d, 4H, $J = 7.2$ Hz), 2.38 (s, 3H), mass 420.2 $[\text{M}+\text{H}]^+$.

Preparation of 1-[2-(4-Chloromethyl-phenoxy)-ethyl]-azepane hydrochloride (3)

To a solution of **8** (20 Kg, 0.2 mol) in dichloromethane (200 L) was passed dry hydrochloric acid gas (approximately 10.9 Kg) for 1 h at 25-35°C under nitrogen atmosphere. Thereafter, the reaction mass was stirred for 1-2 h at 25-35°C. Reaction mass was distilled completely under vacuum. Added acetone (2 x 50 L) and distilled under vacuum below 50°C. After that acetone (40 L) was added to this residue and stirred for 5 h at 0-5°C. The product was filtered and washed with acetone (20 L). Dried the solid under vacuum at 50-55°C for 4-5 h to afford 15.4 Kg of **3** (63.1% yield, and 98.90 % purity by HPLC); ^1H NMR ($\text{DMSO}-d_6$) δ (ppm) 10.5 (s, 1H), 7.4 (d, 2H, $J = 8.6$ Hz), 7.01 (d, 2H, $J = 8.68$ Hz), 4.74 (s, 2H), 4.40 (d, 2H, $J = 4.32$ Hz), 3.52 (s, 2H), 3.45-3.42 (m, 2H), 3.33-3.21 (m, 2H), 1.85-1.64 (m, 4H), 1.63-1.58 (m, 4H). Mass 268.1 $[\text{M}+\text{H}]^+$, IR 3447, 2942, 2478, 1514, 1247.

Preparation of 2-(4-benzyloxy)phenyl amino)-1-(4-(benzyloxy)phenyl)propan-1-one (6)

To a mixture of **5** (50 g, 0.156) and **4** (44.50 g, 0.187 mol) in ethanol (400 mL) was added triethylamine (36.3 g, 0.359 mol). The reaction mass was heated to 75-80 °C for 5-6 h. Thereafter it was cooled to 25-30 °C and stirred for 2 h. The solid was filtered and washed with ethanol (50 mL). Dried the solid at 40 °C under vacuum for 2 h to afford the 61.5 g of title compound **24** (89.9% yield, 99.4% purity by HPLC) (isolated only for characterization purpose); ^1H NMR ($\text{DMSO}-d_6$) δ (ppm) 7.98 (d, 2H, $J = 8.8$ Hz), 7.29-7.44 (m, 10H), 7.03 (d, 2H, $J = 8.8$ Hz), 6.82 (d, 2H, $J = 4.8$ Hz), 6.61 (d, 2H, $J = 4.8$ Hz), 5.1 (s, 2H), 4.99 (s, 2H), 4.4 (s, 1H), 1.56 (s, 3H), Mass 438 $[\text{M}+\text{H}]^+$.

Preparation of [4-(2-Azepan-1-yl-ethoxy)-

phenyl]-methanol (8)

To a solution of sodium hydroxide (7.74 Kg, 0.193 mol) in water (150 L) was added *p*-hydroxy benzyl alcohol (10 kg, 0.08 mol) and stirred for 20 min. To this sequentially added toluene (100 L), 1-(2-chloroethyl) azepanhydrochloride (20.74 Kg, 0.105 mol) and tetra butyl ammonium bromide (0.52 Kg, 0.0016 mol). Thereafter, the reaction mass was heated to reflux (85-90°C) and stirred vigorously for 1-2 h. Subsequently it was cooled to 25-35°C and separated the organic layer. Organic layer was washed with 10% NaCl solution (100 L) at 55-60 °C and distilled the solvent completely under vacuum below 65 °C to provide 20 Kg of the title compound **8** (99.6% yield, 95% purity by HPLC). ¹H NMR (CDCl₃, 400 MHz) : δ (ppm) 7.28-7.26 (m, 2H), 6.90- 6.87 (m, 2H), 4.59 (s, 2H), 4.05-4.02 (m, 2H), 2.94-2.80 (m, 2H), 2.77-2.74 (m, 4H), 1.66-1.58 (m, 8H), Mass 249.9 [M+H]⁺.

Preparation of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H iodole (9) To a mixture of sodium hydride (60%) (2.5 Kg, 0.104 mol) in dimethylformamide (11 L) at -10 to 0°C was slowly added a solution of **2** (10.87 kg, 0.026 mol) in dimethyl formamide (22 L) in the presence of nitrogen atmosphere atm. After stirring for 1 h at -10 to 0°C, was slowly added a solution of **3** (8.59 Kg, 0.028 mol) in dimethylformamide (54 L) at -10 to 0 °C. The reaction mass was stirred for 2-3 h at 25-35°C. Thereafter chilled water (109 L) was slowly added at below 10°C followed by the addition of acetic acid (0.8 L). Subsequently ethyl acetate (109 L) was added followed by water (109 L). Filtered the reaction mass to remove unwanted solid and washed the cake with ethyl acetate (11 L). Layers were separated from filtrate and the aqueous layer was extracted with ethyl acetate (2x82 L). The combined organic layer was washed with 10% NaCl solution (2x110 L). Evaporated the organic layer completely and added methanol (130 L) to the obtained residue and stirred for

1 h. The precipitated solid was filtered and washed with methanol (2x27 L). Methanol (109 L) was added to the wet cake and stirred for 1 h. Filtered the solid and washed with methanol (54 L). The obtained compound was dried at 50°C under vacuum to a constant weight. (10.3 Kg, 62%, 99.5 % purity by HPLC); ¹H NMR (CDCl₃) δ (ppm) 7.49 – 6.73 (m, 21H), 5.13-5.09 (m, 6H), 4.01 (t, 2H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 6.0 Hz), 2.79-2.76 (m, 4H), 2.24 (s, 3H), 1.66–1.58 (m, 8H); IR 3444, 2922, 1478, 1242 cm⁻¹; Mass 651.4 [M+H]⁺.

Preparation of N-(4-benzyloxy) phenyl formamide (10).

To a solution of **4** (30 g, 0.127 mol) in dimethylformamide (180 mL) at 25-35 °C, was added triethylamine (12.85 g, 0.127 mol). The reaction mass was heated to reflux (150-154 °C) and stirred for 6-7 h. Thereafter, it was cooled to 25-30 °C and added 5% acetic acid solution (600 mL) followed by ethyl acetate (1200 mL). After stirring for 30 min, separated the organic layer and it was washed with 5% NaHCO₃ solution (600 mL) followed by 10% NaCl (600 mL) solution. The organic layer was separated and distilled off completely below 65 °C under vacuum. The obtained residue was cooled to 25-30 °C and added methanol (240 mL) and stirred for 2 h. The solid was filtered and washed with methanol (180 mL). The compound was dried at 60 °C under vacuum to provide the 10 g of title compound **10** (34.6% yield, 98.4% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm) 8.50 (d, 1H, *J* = 11.6), 8.34 (s, 1H), 7.03-9.92 (m, 9H), 5.06 (s, 2H).

Preparation of 1-(2-azepan-1-yl) ethyl

azepane (11). To a solution of NaOH (12.09 g, 0.302 mol) in water (150 mL) was sequentially added azepane (10 g, 0.1 mol), toluene (100 mL), 1- (2-chloroethyl) azepane hydrochloride (29.95 g, 0.151 mol) and tetra butyl ammonium bromide (0.65 g, 0.002 mol). Thereafter, the reaction mixture was heated to reflux (85-90°C) and stirred vigorously for 2-3 h. It was cooled to 25-30 °C and separated the organic layer

and washed with water. The organic layer was distilled off completely under vacuum at below 60 °C to provide 20.5 g of title compound **11** (90.8% yield, 96.5% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm) 2.6 (d, 12H, *J* = 5.6 Hz), 1.58-1.62 (m, 16H), Mass 225 [M+H]⁺.

Preparation of 2-(azepan-1-yl) ethanol (12). A solution of azepane (20 g, 0.202 mol), toluene (200 mL) and 2-chloro ethanol (20.33 mL, 0.303 mol) was heated to reflux (110 °C) for 4-5 h. Thereafter reaction mass was distilled completely under vacuum below 60 °C. Thereafter, it was purified by column chromatography (5% methanol: chloroform) to provide 10 g of title compound **12** (51.4% yield, 92% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm) 5.11 (bs, 1H), 4.01 (d, 2H, *J* = 4.8 Hz), 3.22-3.35 (m, 6H), 1.73-2.00 (m, 4H), 1.72 (s, 4H), Mass 144 [M+H]⁺.

Preparation of 3-(4-(2-azepan-1-yl)ethoxy) benzyl)-2-(4-hydroxyphenyl)-3-methyl-3H-indol-5-ol (13). To a mixture of sodium hydride (60%) (9.6 g, 0.238 mol) in dimethylformamide (80 mL) was added a solution of **2** (40 g, 0.095 mol) in dimethylformamide (80 mL) at 0 °C in the presence of nitrogen atmosphere. After stirring for 1 h at 0 °C again slowly added a solution of **3** in dimethylformamide (200 mL) at 0 °C. The reaction mass was stirred for 2-3 h at reflux and chilled water (800 mL) was slowly added at below 10 °C. Subsequently, the reaction mass extracted with ethyl acetate (3x600 mL). The organic layer was washed with water (500 mL), dried over sodium sulphate, and evaporated. To the obtained residue methanol (400 mL) was added and stirred for 1 h. The solid was filtered and washed with methanol (100 mL). Thereafter filtrate was distilled completely under vacuum and product was crystallized in ethyl acetate (50 mL) to provide 23 g of title compound **13** (35.68% yield, 96.85% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm), 8.12 (d, 2H, *J* = 8.8 Hz), 7.48 (d, 4H, *J* = 7.6 Hz), 7.43 (t, 4H, *J* = 7.2 Hz), 7.37-7.

.32 (m, 3H), 7.1 (d, 2H, *J* = 9.2 Hz), 6.9 (dd, 2H, *J* = 2.0 Hz, *J* = 2.4), 6.41 (s, 4H), 5.15 (s, 2H), 5.12 (d, *J* = 5.2), 3.03 (t, 4H, *J* = 5.2), 1.76 (s, 8H), 1.67 (s, 3H).

Preparation of 2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (14).

To a solution of **2** (10 g, 0.0153 mol) in ethylacetate (100 mL) at 40-45 °C was added 10% wet Pd/C (4 g) and ammonium formate (3.87 g, 0.061 mol). The reaction mass was stirred for 2 h at 55-60 °C and cooled to 25-35 °C. Thereafter it was filtered on a celite bed and the bed was washed with ethyl acetate (20 mL). Filtrate was distilled completely under vacuum to provide the title compound **14** (5.15 g, 90% yield, and 92% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm) 8.92 (s, 1H), 8.88 (s, 1H), 7.86 (s, 1H), 7.41 (d, 2H, *J* = 4.0 Hz), 7.16 (d, 1H, *J* = 7.2 Hz), 6.92-6.95 (m, 3H), 6.73 (d, 1H, *J* = 1.60 Hz), 2.34 (s, 3H); Mass 240 [M+H]⁺.

Preparation of 1-(4-hydroxybenzyl)-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol (15).

To a solution of **21** (4 g, 0.0076 mol) in ethyl acetate (40 mL) at 40-45 °C was added 10% Pd/C wet (1.6 g) and ammonium formate (1.92 g, 0.030 mol). The reaction mass was stirred for 2 h at 55-60 °C and cooled to 25-35 °C. Thereafter, it was filtered on a celite bed and the bed was washed with ethyl acetate (20 mL). Filtrate was distilled completely under vacuum to provide the title compound **15** (2.15 g, 81.8% yield); ¹H NMR (CDCl₃) δ (ppm) 9.64 (s, 1H), 9.23 (s, 1H), 8.67 (s, 1H), 7.16 (d, 2H, *J* = 6.8 Hz), 7.07 (d, 1H, *J* = 7.2 Hz), 6.86 (d, 2H, *J* = 6.4 Hz), 6.79 (d, 1H, *J* = 1.6 Hz), 6.66 (d, 2H, *J* = 6.8 Hz), 6.58-6.55 (m, 3H), 5.04 (s, 2H), 2.09 (s, 3H); Mass 346 [M+H]⁺.

Preparation of 1-(2-(4-((5-hydroxy-2-(4-hydroxyphenyl)-3-methyl-1H-indol-1-yl) methyl)phenoxy)ethyl)azepane 1-oxide (16).

To a solution of **1** base (10 g, 0.021 mol) in chloroform (100 mL) and methanol (10 mL) was added slowly 50% hydrogen peroxide solution

in 15 min and stirred for 18-20 h. The reaction mass was quenched with 10% sodium sulfite solution (200 mL). Thereafter, ethyl acetate (200 mL) was added to the reaction mass and stirred for 2-3 h. The solid was filtered and washed with ethyl acetate (20 mL). The solid was purified by column chromatography (15% MeOH:CHCl₃) to provide the 2.8 g of title compound **19** (27.07% Yield, 95.76% purity by HPLC); ¹H NMR (CDCl₃) δ (ppm), 7.96(s, 1H), 7.89(s, 1H), 7.10 (d, 2H, *J* = 8.8Hz), 6.99(d, 1H, *J* = 8.8 Hz), 6.88(s, 1H), 6.79-6.82(m, 6H), 6.61(d, 1H, *J* = 2.4Hz), 5.11(s, 2H), 4.43(t, 2H, *J* = 4.4Hz), 3.62-3.68(m, 2H), 3.39-3.44(q, 2H, *J* = 8.0), 2.98(s, 1H), 2.85(s, 1H), 2.15(s, 3H), 2.03-2.14(m, 2H), 1.67-1.74(m, 6H); Mass 487 [M+H]⁺.

Preparation of *p*-toluoyl benzene sulphonate(18). To a solution of **17** (50 g, 0.462 mol) in dichloromethane(300 mL) was added triethylamine (70.8 mL, 0.508 mol). The reaction mass was cooled to 0-5 °C. Thereafter benzene sulphonyl chloride(65.11g, 0.508 mol) was added slowly at 0-5 °C and stirred for 3-4 h. Subsequently water (300 mL) was added and stirred for 10 min. The organic layer was separated and washed with 1N HCl (500 mL) followed by 2% NaOH (100 mL). Organic layer was dried over sodium sulphate (50 g) and distilled the solvent completely under vacuum at below 50 °C. To the resulting crude hexane (100 mL) was added and stirred for 1 h at 25-35 °C. Thereafter the product was filtered and washed with hexane (50 mL) and dried the solid under vacuum at 40 °C for 2 h to provide the title compound**18**(110.2 g, 96% yield). ¹H NMR (CDCl₃) δ (ppm), 7.81-7.83(m, 2H), 7.63-7.67(m, 1H), 7.49-7.53(m, 2H), 7.048(d, 2H, *J* = 8.4Hz), 6.83-6.85(d, 2H, *J* = 8.4Hz), 2.29(s, 3H).

Preparation of 4-(bromomethyl)phenyl benzene sulphonate(19). To a solution of **18**(25 g, 0.1 mol) in carbon tetra chloride (300 mL) was added *N*-bromosuccinamide (21.53 g, 0.12

mol) and benzoyl peroxide(1.21 g, 0.005 mol). The resulting mixture was heated to reflux (76 °C) and stirred for 2-3 h. After completing the reaction, the reaction mixture was cooled to 0-5 °C. Filtered the reaction mixture and washed with carbon tetra chloride (75 mL). Filtrate was distilled completely under vacuum at below 45 °C. The resulting residue was cooled to 25-35 °C and added hexane(150 mL) and stirred for 1 h. The product was filtered and washed with hexane(50 mL) and the solid was dried at 30 °C under vacuum for 2h to provide the title compound**19**(28.7 g, 87.3% yield). ¹H NMR (CDCl₃) δ (ppm), 7.81-7.85(m, 2H), 7.65-7.69(m, 1H), 7.51-7.64(m, 2H), 7.30-7.33(m, 2H), 6.94-6.97(m, 2H), 4.42(s, 2H).

Preparation of 4-(5-Benzyloxy)-2-(4-benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenyl benzene sulphonate (20). To a mixture of sodium hydride (60%) (2.38g, 0.0595 mol) in dimethylformamide (20 mL) was slowly added a solution of **2** (10 g, 0.0238 mol) in dimethylformamide (20 mL) under the nitrogen atmosphere at -5 to 0 °C. After stirring for 1 h at -5 to 0 °C again slowly added the solution of **19** in dimethylformamide (50 mL) at -5 to 0 °C. The reaction mass was stirred for 3-4 h at 25-35 °C and chilled water (200 mL) was slowly added at below 0-5 °C. Subsequently the reaction mass extracted with ethyl acetate (2x100 mL). The organic layer was washed with water (2x50 mL) and distilled completely to provide the title compound**20** (12.1 g, 76.2% yield). ¹H NMR (CDCl₃) δ (ppm), 7.49-7.33 (m, 13H), 7.23-7.20 (m, 3H), 7.14-7.13 (m, 2H), 7.09-6.99 (m, 2H), 6.89-6.79 (m, 4H), 6.67-6.65 (m, 2H), 5.13-5.09 (m, 6H), 2.17 (s, 3H).

Preparation of 4-(5-Benzyloxy)-2-(4-benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenol(21). To a solution of **20**(8 g, 0.012 mol) in ethanol (40 mL) was added a solution of KOH (3.36 g, 0.06 mol) and water (40 mL). The reaction mixture was refluxed (85 °C) for 7 h. Thereafter it was cooled to 25-35 °C

and stirred for 30 min. The product was filtered and washed with water (10 mL). Dried the solid at 50 °C under vacuum to get title compound **21** (5.7 g, 90.3% yield). ¹H NMR (CDCl₃) δ (ppm), 9.85(s,1H), 7.48-7.30 (m, 11H), 7.23-7.21 (m, 2H), 7.14-7.13 (m, 1H), 7.08-7.06 (m, 1H), 7.01-6.99 (m, 2H), 6.90-6.79 (m, 3H), 6.68-6.66 (m, 1H), 5.13-5.09 (m, 6H), 2.23 (s, 3H).

Preparation of (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-olHCl (1·HCl. To a heterogeneous solution of **9** (8.5 Kg, 0.013 mol) in acetone (102 L) was added methanol (34 L) and warmed to 50 °C to get clear solution. Then the reaction mass was cooled to 25-35 °C and immediately was added 10% wet Pd/C (1.7 Kg) in water (4 L) at 25-35 °C. Thereafter the reaction mass was transferred to autoclave vessel and applied 10kg/cm² pressure. The reaction was slowly heated to 45-50°C and stirred for 2-3 h. Thereafter Pd catalyst was filtered on celitebed and washed the bed with methanol (26 L). The pH of the filtrate was adjusted to below 1.5 with conc.HCl at below 30 °C. The resulting mixture was stirred for 22-26 h at 25-35 °C. Subsequently the reaction mixture was filtered and washed with methanol (8.5 L). Acetone (51 L) and water (10.2 L) was added to the wet cake and the pH was adjusted to 9 with triethylamine (2.6 L, 0.04 mol) at below 30 °C. After stirring for 1 h, pH was adjusted to below 1.5 with conc.HCl at below 30 °C. The resulting mixture was stirred for 12-14 h at 25-35 °C. Thereafter, the product was filtered and washed with acetone (10.2 L). The compound was dried at 70 °C under vacuum for 5 h to provide the title compound **1** (4.7 Kg, 71% yield, 99.9% purity by HPLC). ¹H NMR (CDCl₃, 400 MHz) : δ (ppm) 10.36(s,1H), 9.72(s,1H), 8.72(s,1H), 7.17 (d,2H,*J*=6.8), 7.07(d,1H, *J*=6.8), 6.87-6.79(m, 7H), 6.59 (q, 1H,*J*=1.6), 5.12 (s, 2H), 4.29(t,2H,*J*=4), 3.45-3.33(m,4H), 3.18-3.14(m, 2H), 2.1(s,3H), 1.8(d,4H,*J*=4), 1.63-1.55(m,4H); Mass 471 [M+H]⁺.

Preparation of (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (1 free base). To a heterogeneous solution of hydrochloride salt of **1** (3 Kg, 0.006 mol) in dimethylformamide (30 L) at 25-35 °C was added triethyl amine (1.2 L g, 0.579 mol) followed by water (6 L). Thereafter sequentially added toluene (60 L) and water (129 L) and stirred for 6-8 h. Thereafter it was cooled to 10 °C and stirred for 3-4 h. The product was filtered and washed with mixture of toluene (6 L) and water (6 L). The solid was dried at 50-60 °C under vacuum to provide a 2.45 Kg of stable novel crystalline polymorph of title compound **1** (bazedoxifene freebase) (88.1 % yield, 99.9 % purity). ¹H NMR (CDCl₃, 400 MHz) : δ (ppm) 9.65(s,1H), 8.68(s,1H), 7.16 (d, 2H,*J*=8.4), 7.07(d, 1H,*J*=8.8), 6.86 (d, 2H,*J*=8.8), 6.80(s, 1H), 6.7 (s, 4H), 6.58-6.55 (dd,1H,*J*=2.4), 5.09 (s, 2H), 3.9(m, 2H), 2.78 (t, 2H,*J*=5.6), 2.67-2.61 (m, 4H), 2.09(s,3H), 1.51 (s, 8H); Mass 471 [M+H]⁺.

Alternate preparation of (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol (1 free base). To a solution of **9** (20 g, 0.0307 mol) in ethyl acetate (160 mL) at 40-45 °C was added 10% wet Pd/C (5 g) and ammonium formate (5.81g, 0.092 mol). The reaction mass was stirred for 4 h at 55-60°C. Thereafter it was cooled to 25-35°C and filtered on a Celite bed and the bed was washed with ethyl acetate (20 mL). Filtrate was distilled completely under vacuum at below 50°C to provide a 14.2 g of Amorphous form of Bazedoxifene (**1** freebase) (98% yield and 95.4 %purity by HPLC).

Preparation of (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol. acetate (1). ⁶ Bazedoxifene freebase (18 g) and acetone (162 mL) are mixed and stirred at 45-50°C to make a clear solution. The said solution is cooled to room temperature and filtered to make particle free. To the filtrate, seed crystals of bazedoxifene acetate (360 g)

are added at room temperature and mixture is cooled to 15-20 °C followed by addition of solution of acetic acid (2.34 g) in acetone (18 mL) at the same temperature. To the mixture, heptane (486 mL) is added over a period of 5-10 minutes and mixture is stirred at 15-20°C for solid formation. The solid so obtained is collected by filtration and washed with heptanes (50 mL) and dried under vacuum at below 80°C to afford 17.8 g of crystalline Bazedoxifene acetate **1** (87.7% yield and 99.68% purity by HPLC). ¹H NMR (CDCl₃, 400 MHz) : δ (ppm) 9.75(s, 1H), 8.69(s, 1H), 7.16 (d, 2H, $J=8.8$), 7.07(d, 1H, $J=8.4$), 6.86 (m, 7H), 6.58-6.55 (q, 1H, $J=2$), 5.09 (s, 2H), 3.9(t, 2H, $J=5.6$), 2.79 (t, 2H, $J=6$), 2.63-2.5 (m, 4H), 2.09(s, 3H), 1.90(s, 3H), 1.5(s, 8H); Mass 471 [M+H]⁺.

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