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Research Article

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Synthesis and characterisation of process related impurity in bosentan monohydrate

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ABSTRACT

Bosentan Monohydrate(1), is the first of a new drug class, anEndothelinreceptor antagonist and belongs to of highly substituted pyrimidine derivatives with no chiral centres used for treatment of pulmonary arterial hypertension(PAH).One of the known impurity in Bosentan Monohydrate is,N,N'-(ethane-1,2diyl{oxy[5-(2-methoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-tert-butylbenzenesulphonamide(Dimer)(2), is formed during the laboratory optimization and later during its bulk synthesis. This impurity is synthesized by novel method and characterised it by [1]H-NMR, I.R., & Mass Spectroscopy.

Key words: Bosentan Monohydrate, Endothelinreceptor Antagonist, Dimer Impurity in Bosentan, International conference on Harmonization (ICH), Sodium tertiary butoxide, Dimethyl Formamide (DMF).

INTRODUCTION

In a recent time the FDA has become very strict on the issue of impurities in Active Ingredients. With the deluge of generics product in the market, the impurity profile of drug substances, drug product becomes a powerful tool to detect and regulate the quality of the product.

According to ICH guidelines, impurities in the drug substances produced by chemical synthesis can be broadly classified into following three categories;
i) Organic Impurities (Process & Drug related)
ii) Inorganic Impurities
iii) Residual Solvents

Organic impurities may arise during the manufacturing process and or storage of the drug substance may be identified or unidentified, volatile or non-volatile, and may include;

i) Starting materials or ingredients
ii)By-products
iii) Degradation products

Impurities are found in API's unless; a proper care is taken every step involved throughout the multi-step synthesis. In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of having by-products. In a consequence to this current scenario we are facing a research & development challenge in synthesizing these impurities arrived during the manufacturing of the Active Ingredient by overcoming the above

sources of impurities. The main problem which is faced is to isolate the impurities in pure form. It is need to develop a synthetic route for preparation of such impurities by utilizing the basic chemistry knowledge and good characterization technique.Control of pharmaceutical impurities is currently a problem to pharmaceutical industry but the most critical issue is to know the impurity (Chemical structure), thus International conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. The presence of unwanted chemicals even in small amount may influence the efficacy and safety of pharmaceutical product. Impurity profiling i.e. identification as well as the quantitation of impurity in the pharmaceutical industry is now gaining importance thus the current research paper explains the synthesis of *N,N'*-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-*tert*-butylbenzenesulfonamide)(DimerImpurity) (2),

EXPERIMENTAL SECTION

Preparation of *N,N'*-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-*tert*-butylbenzenesulfonamide) (Dimer Impurity in Bosentan):

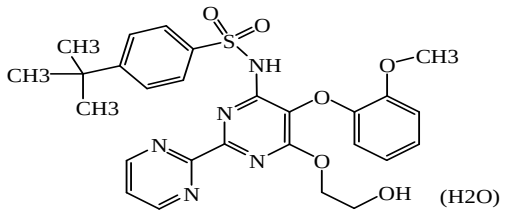
To a stirred solution of 3 (5.0 gm., 0.0095 mol) in Dimethyl Formamide (125 ml) under nitrogen atmosphere Sodium tertiary butoxide (3.0 gm., 0.0312 mol) was added slowly at 10-15°C. and stirred for 30 minutes at 15°C. A solution of (4) (5.4 gm., 0.0095 mol) in Dimethyl Formamide (15 ml) was added at 15°C. The reaction mass was then stirred at 25°C for 24 hrs. and quenched with saturated NaCl solution (250 ml) at 20-25°C. The resulting mixture was extracted with Dichloromethane (2 × 200 ml) at 25°C. The combined organic layer was washed with 10% aqueous HCl (100 ml) and evaporated under vacuum at 35-45°C to give oil (19.0 gm.). A mixture of Methanol (85 ml) and Ethyl Acetate (85 ml) was added to the oil and stirred for 1 hr. to precipitate out the product. The resulting slurry was filtered, and wet cake was dried under vacuum at 55-60°C to obtain 7.2 gms of crude *N,N'*-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-*tert*-butyl-benzenesulfonamide)having purity: 87.5% (by HPLC).

The crude material was purify by column chromatography on silica gel (60-120 mesh) using a mixture of Chloroform and Acetone as eluent to obtain 5.3 gm. of the pure product. The product was slurried with Methanol (50 ml), filtered and dried under vacuum at 55°C to give 4.85 gms of pure *N,N'*-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-*tert*-butyl-benzenesulfonamide) having purity: 97.03% (by HPLC).

^{1}H-NMR (δ, ppm): 1.26 (s, 18H, Aliphatic C(C<u>H</u>$_3$)$_3$), 3.85 (s, 6H, -OC<u>H</u>$_3$), 4.77 (s, 4H, -O-C<u>H</u>$_2$), 6.53 (t, 2H, *J* = 7.6 Hz, Aromatic C<u>H</u>), 6.78-6.80 (m, 2H, Aromatic C<u>H</u>), 6.83-6.86 (m, 4H, Aromatic C<u>H</u>), 7.37-7.39 (m, 2H, Aromatic C<u>H</u>), 7.43 (d, 4H, *J* = 8.4 Hz, Aromatic C<u>H</u>), 8.39 (d, 4H, *J* = 8.8 Hz, Aromatic C<u>H</u>), 8.75 (s, 2H, D_2O exchangeable, NH), 8.98 (d, 4H, *J* = 4.8 Hz, Aromatic C<u>H</u>); **IR (cm^{-1})** : 3284.6 (sulphonamide N-H), 3063.3, 3049.4, 3040.6 (Aromatic C-H), 2962.9, 2869.8 (Aliphatic C-H), 1579.3, 1558.2 (Aromatic C=C), 1499.1, 1478.5 (Aliphatic CH_2), 1449.1, 1437.4 (Aliphatic CH_2), 1385.6 (Sulphonamide S=O), 1335.6 (Sulphonamide N-H), 1177.4, 1163.2 (Sulphonamide S=O), 1098.1, 1082.0 (ether C-O).; **MS:** 1041.6 (M+)

RESULTS AND DISCUSSION

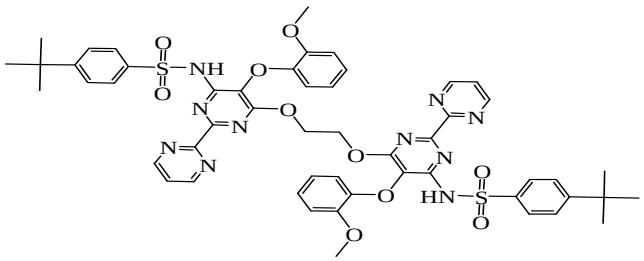
Bosentan Monohydrate is the first of a new drug class, an Endothelin receptor antagonist and belongs to of highly substituted pyrimidine derivatives with no chiral centres used for treatment of pulmonary arterial hypertension(PAH).It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy phenoxy)-[2,2]-bipyrimidine-4-yl]-benzene sulphonamide monohydrate and has the structural formula.



1

Bosentn Monohydrate

The synthesis of Bosentan Monohydrate (1) has been reported by several authors using different methodology has its own demerits. The first reported method by K.Burry etal[1] is represented in reaction scheme 1 with overall yield of 40%. In this process toxic ethylene glycol and highly pyrophoric Na metal are used which cannot be handled in a large commercial process. The need to use excess ethylene glycol leads to generation of aqueous ethylene glycol waste and formation of dimer impurity (2).



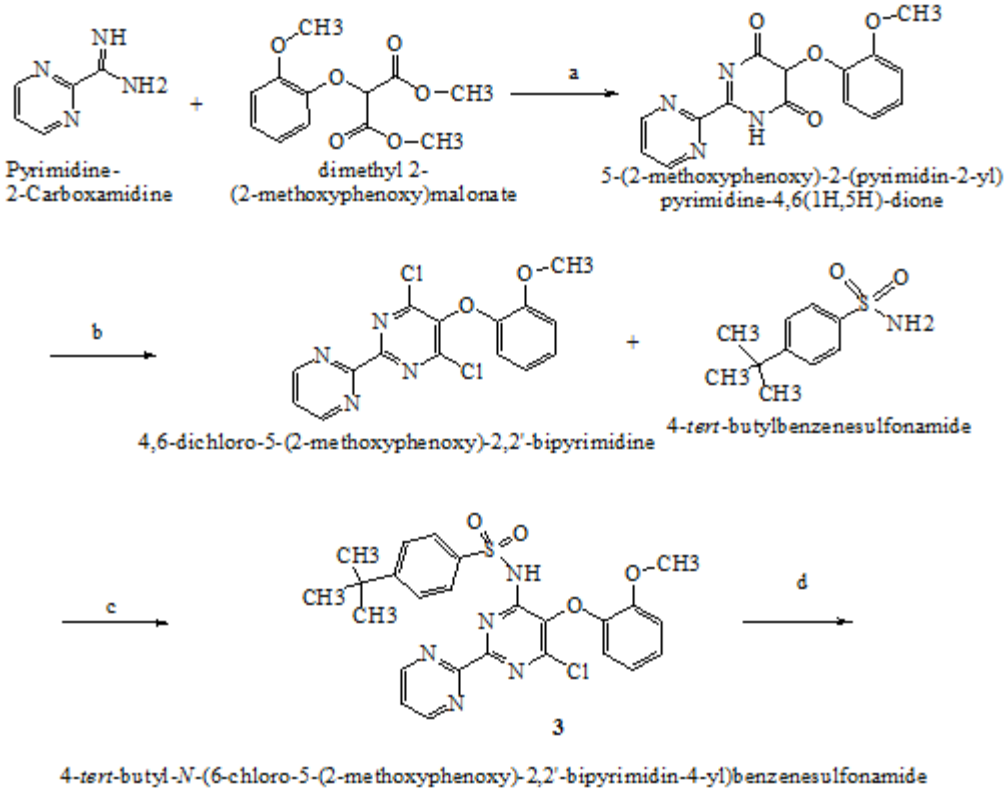
N,N'-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-tert-butylbenzenesulfonamide) (DimerImpurity)

2

There are several impurities /related substance associated with the manufacture of Bosentan Monohydrate. Different process related impurities have been observed with various routes and/or manufacturing processes. One of the most abundant impurity in Bosentan Monohydrate is *N,N'*-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-*tert*-butylbenzenesulfonamide)(DimerImpurity) (2).

It was observed that the formation of (2) takes place in the final step during the formation of Bosentan with respect to any base we can choose for the reaction.Niphade etal [6] has reportedthe first synthetic approach for **(2)** represented in reaction scheme 2involved the condensation of Bosentan with ethylene glycol in the presence of sodium metal at 115-120°C for 60-90 h. It was observed that this reaction is very slow even at elevated temperature and the direct use of sodium metal make this process unsafe.

Reaction Scheme 1:



Pyrimidine-2-Carboxamidine

dimethyl 2-(2-methoxyphenoxy)malonate

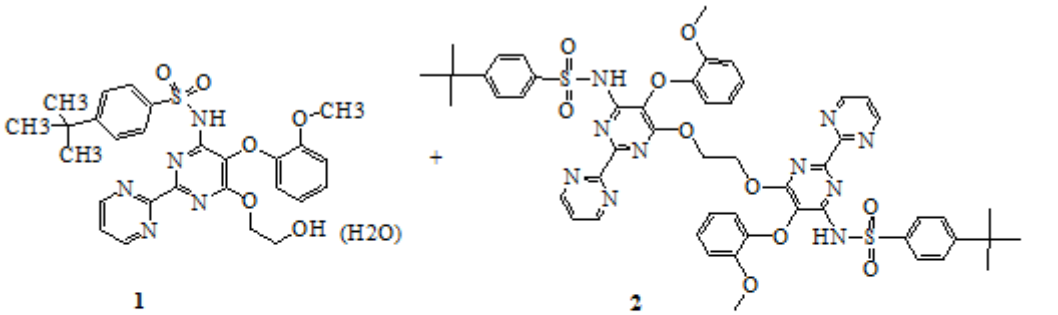
5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidine-4,6(1H,5H)-dione

4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine

4-*tert*-butylbenzenesulfonamide

3

4-*tert*-butyl-*N*-(6-chloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide

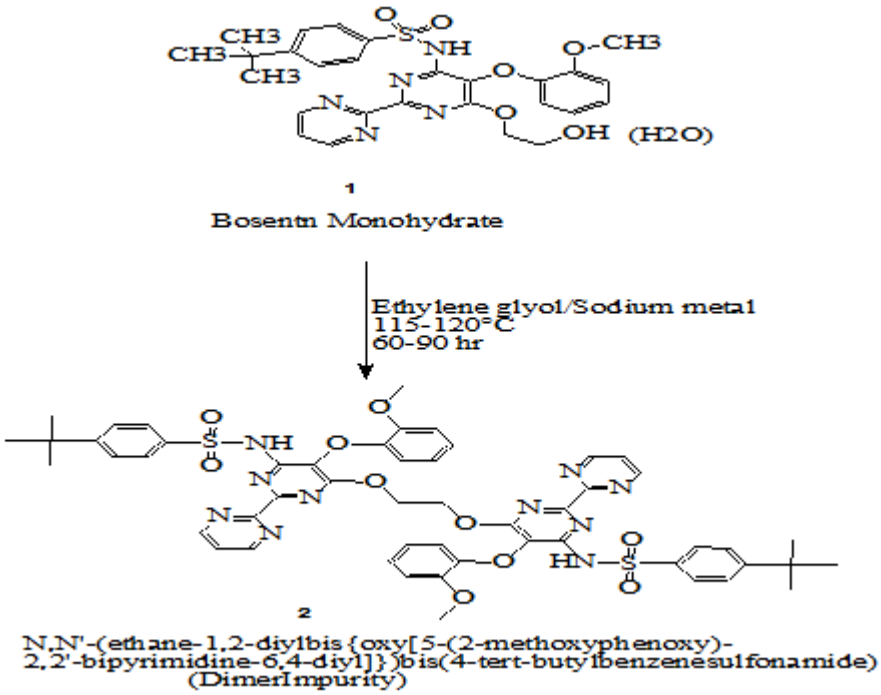


1 2

Bosentn Monohydrate N,N'-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-tert-butylbenzenesulfonamide) (DimerImpurity)

Reagents and conditions:a) sodium methoxide, methanol;b) POCl3; c)K2CO3,TBAB,toluene; d)Sodium metal,ethylene glycol

Reaction Scheme 2:



1

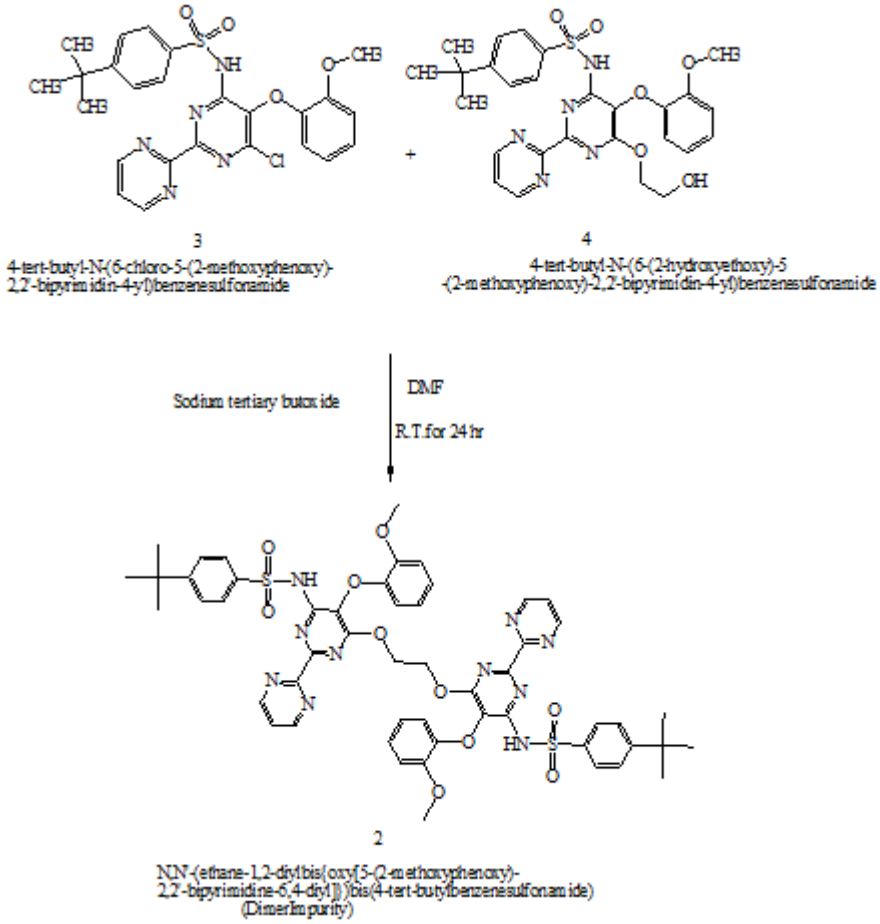
Bosentn Monohydrate

2

N,N'-(ethane-1,2-diylbis{oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-tert-butylbenzenesulfonamide) (DimerImpurity)

Herein, we are reporting an improved ,efficient and safe process for 2 by the reaction of Bosentan(4)&(3) at ambient temperature and using sodium tertiary butoxide as a base in a polar aprotic solvent such as DMF represented in reaction scheme 3.

Reaction Scheme 3.



3
4-tert-butyl-N-(6-chloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide

4
4-tert-butyl-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2,2-bipyrimidin-4-yl)benzenesulfonamide

2
N,N'-(ethane-1,2-diylbis(oxy[5-(2-methoxyphenoxy)-2,2'-bipyrimidine-6,4-diyl]))bis(4-tert-butylbenzenesulfonamide)
(Dimer Impurity)

CONCLUSION

The Dimer Impurity of Bosentan Monohydrate N N'-(ethane-1,2diyl{oxy[5-(2-methoxy)-2,2'-bipyrimidine-6,4-diyl]})bis(4-tert-butylbenzenesulphonamide is effectively synthesize by using Bosentan Monohydrate and 4-(1,1-Dimethylethyl)-*N*-[6-chloro-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]-benzenesulfonamide at 25°c in presence of Sodium tertiary butoxide and DMF as a solvent.

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