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(71) Applicant: **MEGAFINE PHARMA (P) LTD.** [IN/IN]; 4th Floor, Sethna, 55, Maharshi Karve Road, Marine Lines, Mumbai - 400002, Maharashtra (IN).

(72) Inventors: **MATHAD Vijayavitthal Thippannachar**; Flat No.5, Nirman Classic, Behind HDFC Bank, Thatte Nagar, Nashik-422 005, Maharashtra (IN). **NIPHADE NAVNATH CHINTAMAN**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur Tal. Dindori, Dist. Nashik Maharashtra (IN). **KABRA SANJAY RAMESHWAR**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur Tal. Dindori, Dist. Nashik Maharashtra (IN). **JAGTAP KUNAL MADHAV**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur Tal. Dindori, Dist. Nashik Maharashtra (IN). **PAWAR ANIL RAMBHAU**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur Tal. Dindori, Dist. Nashik Maharashtra (IN).

(74) Agent: **LAXMI GURURAJA RAO**; Plot No. 31 to 35 & 48 to 51/201, Lakhmapur Tal. Dindori, Dist. Nashik-422202 (IN).

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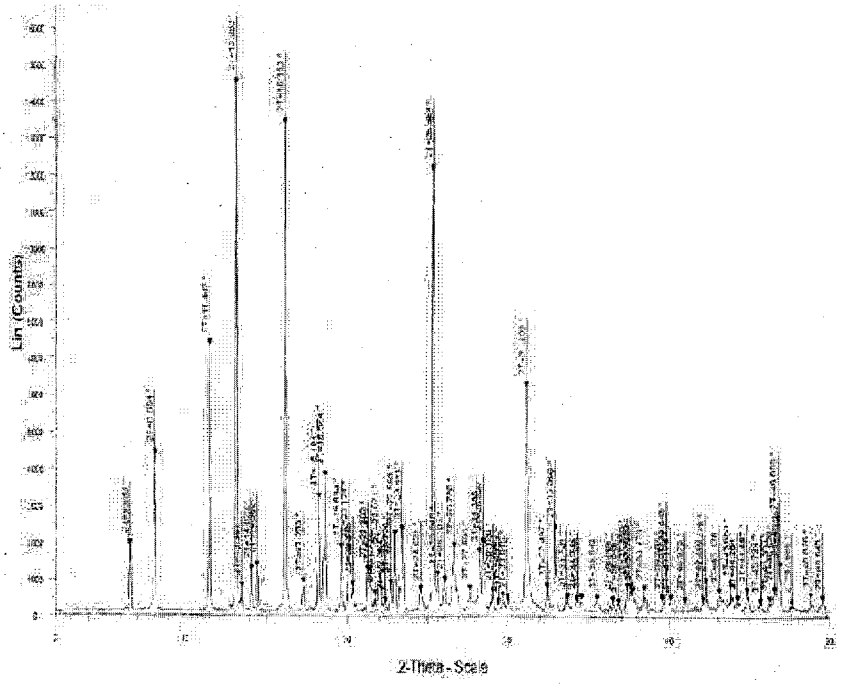
(54) Title: PROCESS FOR THE PREPARATION OF MACITENTAN AND INTERMEDIATES THEREOF



(57) Abstract: The present invention relates to an improved process for preparation of Macitentan and intermediates thereof. The present invention also relates to a novel ammonium salt of Macitentan. The present invention further relates to a process for the preparation of amorphous Macitentan.

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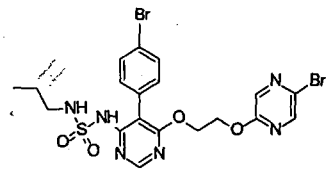
TITLE OF THE INVENTION

PROCESS FOR THE PREPARATION OF MACITENTAN AND INTERMEDIATES THEREOF

This application claims priority from provisional Indian patent application 2284/MUM/2015 which is incorporated herein by reference.

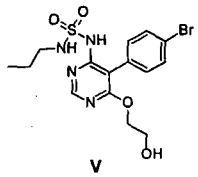
FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of *N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl] -*N'*-propylsulfamide, Macitentan (I), and its intermediates thereof.



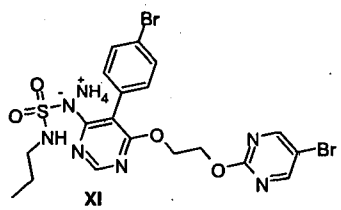
(I)

The present invention also relates to an improved process for the preparation of *N*-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-*N'*-propylsulfam -ide (V), an intermediate for the synthesis of highly pure Macitentan (I).



V

The present invention also relates to novel ammonium salt of Macitentan (XI).

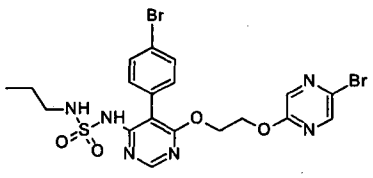


XI

The present invention also relates to process for preparation amorphous Macitentan (I).

BACKGROUND OF THE INVENTION:

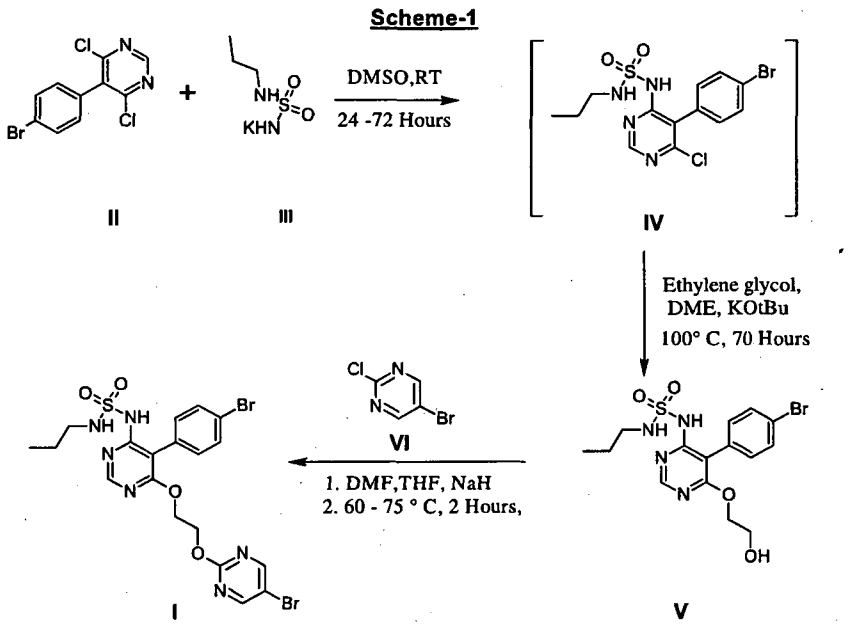
OPSUMIT® (Macitentan) is an orally active endothelin receptor antagonist (ERA) used for the treatment of pulmonary arterial hypertension (PAH). The chemical name of macitentan is *N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl) oxy]ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide. It has a molecular formula of $C_{19}H_{20}Br_2N_6O_4S$ with molecular weight of 588.27 and having CAS number of 441798-33-0. Macitentan (I) is achiral compound and has the following structural formula:



(I)

US 7,094,781 discloses Macitentan but does not exemplify the preparation of Macitentan. However, it discloses the process for preparation of various derivatives and intermediates of Macitentan.

Bolli et al., J.Med.Chem. 2012, 55, 7849-7861 describes synthesis of Macitentan as shown in Scheme-1. The article also describes the process for the preparation of crystalline form of Macitentan free base having a melting point of 135°C-136°C.



IP:com Journal (2014), 14(3B), 1-2 (No. IPCOM000235526D) describes the method of preparation of crystalline form of Macitentan along with its X-ray powder diffraction ("XRPD") pattern.

IP.com Journal (2014), 14(6A), 1-6 (IPCOM000236886D) also describes a method of preparation of two crystalline forms (Form A and Form B) and amorphous form with their X-ray powder diffraction ("XRPD") pattern.

The processes reported in the prior art involves use of multi-step synthesis wherein intermediates are isolated by means of either filtration or centrifugation and subsequent drying of the obtained intermediates before using the same in the next step. The isolation and drying is a very critical step in the production which exposes the production executives to different solvent vapours and also to the isolated solids while handling. The time required to produce a batch is substantially increased as the number of isolations are increased during the production scale and thus multi-step

reactions involving multiple filtrations with less yield, drying are not suitable for the production. The reaction also requires longer time to complete and the yield obtained is not satisfactory. The reported process also uses hazardous bases such as sodium hydride and potassium tertiary butoxide which not only poses the problem of handling but also provide the Macitentan with less yield and more impurities.

Hence, there remains a need for providing efficient, industrially feasible and economically viable process for the manufacture of Macitentan to substantially eliminate the problems associated with the prior art, and that will be suitable for large-scale preparation such that the process will be safe to handle, simple and easy to carry out with high yield and purity of the product.

OBJECTS OF THE PRESENT INVENTION

The primary object of the present invention is to provide efficient, economic and industrially viable process for preparation of highly pure Macitentan (I).

Yet another object of the present invention is to provide an improved process for the preparation of N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V), which is a useful intermediate in the process for the preparation of highly pure Macitentan (I).

Yet another object of the present invention is to provide process for the preparation of compound (X), which is useful intermediate for the preparation of highly pure Macitentan (I).

Yet another object of the present invention is to provide novel and stable ammonium salt of Macitentan (XI).

Yet another object of the present invention is to provide process for the preparation of amorphous Macitentan (I).

BRIEF DESCRIPTION OF DRAWING

Figure-1: X-ray powder diffraction ('XRD') pattern of crystalline form of Macitentan (I).

Figure-2: X-ray powder diffraction ('XRD') pattern of crystalline form of ammonium salt of Macitentan (XI).

Figure-3: X-ray powder diffraction ('XRD') pattern of amorphous form of Macitentan (I).

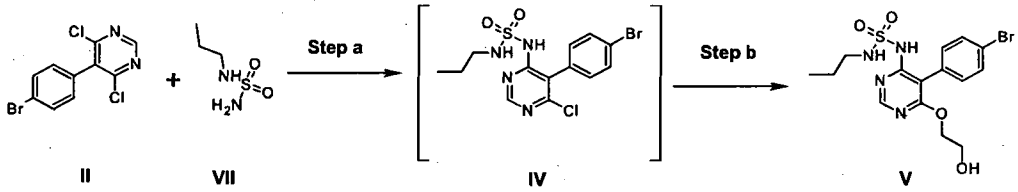
DETAILED DESCRIPTION OF THE INVENTION:

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims.

In one of the embodiments of the invention, there is provided an improved process for the preparation of N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V) comprising:

a) condensing 5-(4-bromophenyl)-4,6-dichloropyrimidine (II) with N-propylsulfamide (VII) in a solvent and in presence of base to give 5-(4-bromophenyl)-6-chloro-N-(propylsulfamoyl)pyrimidin-4-amine (IV), which may or may not be isolated; and



b) condensing the product of step (a) with ethylene glycol in a solvent and in the presence of a suitable base, to give N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V).

According to another embodiment of the present invention, the process of step (b) can be carried out without isolating the intermediate compound (IV) of step (a).

The solvent(s) used in step (a) and (b) may be either same or different and is organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; dialkylformamides such as but not limited to

dimethyl formamide; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water or mixtures thereof. Preferably, the solvent is selected from dialkylsulfoxides such as but not limited to dimethyl sulfoxide.

The bases used in step (a) and (b) of the present invention may be same or different and are selected from either organic or inorganic bases; organic bases include primary amines such as but not limited to methylamine, ethylamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarboriates such as

but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert. butoxide, potassium tert butoxide and the like; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide and the like; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride and the like. Preferably, the base is selected from metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert. butoxide, potassium tert butoxide and the like; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide and the like; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride and the like.

The step (a) is carried out at temperature in the range of 0°C to 150°C. Preferably, the reaction is carried out at temperature in the range of 15°C to 135°C.

The step (b) is carried out at temperature in the range of 0°C to 150°C. Preferably, the reaction is carried out at temperature in the range of 60°C to 135°C.

The product formed in step (a) can be used in the next stage with or without isolation of the product.

According to the present invention, isolation followed by purification of compound of the formula (V) from reaction mass of step (b) comprises the steps of:

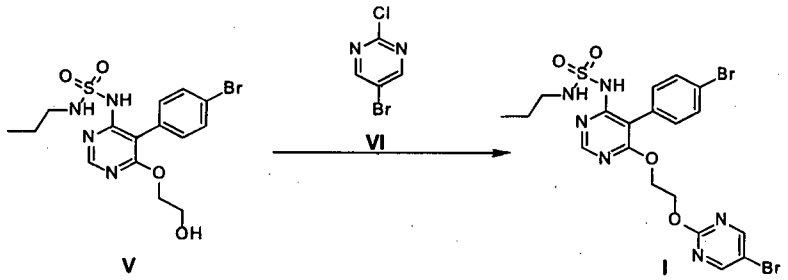
i. quenching reaction mass of step (b) with citric acid; extracting the product into a suitable solvent and washing the organic layer with brine;
ii. concentrating the said organic layer of step (i) to obtain compound (V);
iii. crystallizing obtained compound (V) using a solvent to obtain pure compound (V).

Further, in a preferred embodiment of the present invention, the solvent used in step (i) and (iii) may be either same or different and is selected from group consisting of alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters including alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids; water or mixtures thereof. Preferably the solvent used in step (i) is selected from esters including alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; and the solvent used in step (iii) is selected from alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like.

According to the present invention, the obtained N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V) can be further used for manufacturing of Macitentan (I).

According to another embodiment of the present invention, there is provided a process for the preparation of Macitentan (I) comprising:

a) condensing N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V) with 5-bromo-2-chloro-pyrimidine (VI) in a solvent and in presence of a suitable base, to give Macitentan (I), and
b) isolating and purifying Macitentan (I).



Purification of the Macitentan (I) obtained in step (b) of the embodiment is performed either by acid-base treatment or solvent crystallization.

The solvent(s) used in step (a) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl

ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water or mixtures thereof. Preferably the solvent used is selected from ethers, cyclic ethers, substituted cyclic ethers and dialkylformamides like tetrahydrofuran, 2-methyl tetrahydrofuran, dimetylformamide, and dimethylacetamide.

The base used in step (a) of the present invention may be organic or inorganic base; organic bases such as but not limited primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarboriates such as but not limited to sodium bicarbonate, potassium

bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert. butoxide, potassium tert butoxide and the like; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide and the like; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride and the like; liquor ammonia and the like. Preferably the base is selected from metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert. butoxide, potassium tert butoxide and the like; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide and the like; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride and the like.

The step (a) is carried out at temperature in the range of 0°C to 150°C. Preferably, the reaction is carried out at temperature in the range of 25°C to 135°C.

According to the present invention, isolation followed by purification of compound of the formula (I) from reaction mass of step (b) comprises the steps of:

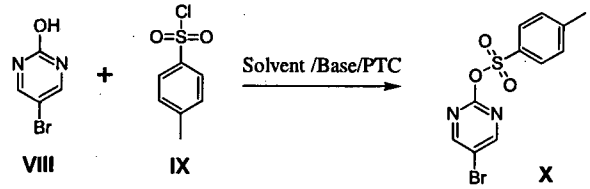
i. quenching reaction mass of step (b) with citric acid; extracting the product using suitable solvent and washing the organic layer with brine;
ii. concentrating the organic layer of step (i) to obtain compound (I);
iii. isolating obtained compound (I) from step (ii) using a solvent; and
iv. crystallizing the obtained compound (I) in step (iii) in a solvent; to obtain pure compound (I).

Further, in a preferred embodiment of the present invention, the solvent used in step (i), (iii) and (iv) may be either same or different and is selected from group consisting of alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters including alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids; water or mixtures thereof. Preferably the solvent used used in step (i) is selected from esters including alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate and the like; and the solvent used in step (iii) and (iv) is selected from alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and like.

According to another embodiment, the present invention provides a process for the preparation of 5-bromopyrimidin-2-yl-4-methylbenzenesulfonate (X) comprising:

a) condensing 5-bromo-2-hydroxy pyrimidine (VIII) with para-toluene sulfonyl chloride (IX) in a solvent, in the presence of a base and a phase transfer catalyst to give a compound (X); and

b) isolating and purifying the compound (X).



The solvent used in step (a) is selected from C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; C_3 to C_6 ketones; N-methylpyrrolidine; propylene glycol; dimethylsulfoxide; C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol and the like; nitriles; esters; C_2 to C_8 straight or substituted cyclic ethers; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; chlorinated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and the like; halogenated hydrocarbons; ionic liquids; hexamethylphosphorous triamide; hexamethylphosphoramide; water or mixture thereof.

The base used in step (a) of the present invention may be organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and

the like; pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; metal alkoxides and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

Phase transfer catalyst used in step (a) is selected from alikuat 175, alikuat 134, alikuat 100, alikuat HTA-1, Arquad® 2HT-75,Tetrabutylammonium acetate, Tetrabutylammonium bisulfate, Tetrabutylammonium cyanate, Tetrabutylammonium hydrogensulfate, Tetrabutylammonium nitrate, Tetrabutylammonium hexafluorophosphate, Tetrabutylammonium methoxide solution, tertiary alkyl ammonium halide like Tetrabutylammonium bromide, Tetrabutylammonium chloride, Tetrabutylammonium iodide.

According to the present invention, isolation and purification of compound of the formula (X) from reaction mass of step (b) comprises the steps of:

i. quenching the reaction mass of step (b) with water;
ii. extracting the product into a solvent and washing the organic layer with brine solution;
iii. concentrating the organic layer of step (iv) to provide compound (X); and
iv. crystallizing obtained compound (X) in a solvent to obtain pure crystalline solid of compound (X).

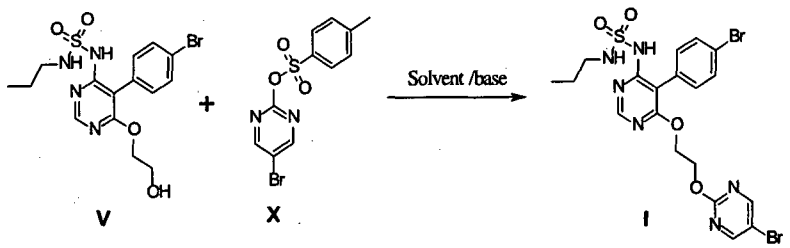
Further, in a preferred embodiment of the present invention, the solvent used in step (i) and (iv) is selected from group consisting of alcohol, esters, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated aliphatic hydrocarbons, ethers, cyclic ethers, substituted cyclic ethers, ketones, nitriles, ionic liquids, water or mixtures thereof.

According to the present invention, the obtained 5-bromopyrimidin-2-yl-4-methylbenzenesulfonate (X) can be further used for manufacturing of Macitentan (I).

According to another embodiment, the present invention provides a process for the preparation of Macitentan (I) comprising:

a) condensing *N*-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-*N'*-propylsulfamide (V) with 5-bromopyrimidin-2-yl-4-methylbenzenesulfonate (X) in a solvent and in presence of suitable base to give Macitentan (I); and

b) isolating & purifying Macitentan of formula (I).



Purification of the Macitentan (I) obtained in step (b) of the embodiment is performed either by acid-base treatment or solvent crystallization.

The solvent(s) used in the above step (a) is an organic solvent selected from the group consisting of alkyl acetate such as but not limited to ethyl acetate,

isopropyl acetate and the like; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane and the like; aromatic hydrocarbons such as but not limited to toluene, xylene, naphthalene and the like; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, ethylene dichloride and the like; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, 1,4-dioxane and the like; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran and the like; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, diethylene glycol and the like; esters; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide , hexamethylphosphoramide and water or mixtures thereof.

The base used in the above step (a) of the present invention may be organic or inorganic base; organic bases include primary amines such as but not limited to methylamine, ethanolamine aniline, propyl amine, 2-propyl amine, butyl amine, 2-amino ethanol and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, pyrrole methylethanolamine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and

amides; metal silanoates and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarboriates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert butoxide, potassium tert butoxide and the like; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide and the like; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride and the like; liquor ammonia and the like.

According to the present invention, isolation followed by purification of compound of the formula (I) from reaction mass of step (b) comprises the steps of:

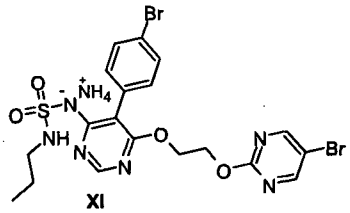
i. quenching reaction mass of step (b) with citric acid; extracting the product using suitable solvent and washing the organic layer with brine;
ii. concentrating the organic layer of step (i) to obtain compound (I);
iii. isolating obtained compound (I) from step (ii) using solvent; and
iv. crystallizing the obtained compound (I) in step (iii) in a solvent to provide pure crystalline compound (I).

Further, in a preferred embodiment of the present invention, the solvent used in step (i), (iii), and (iv) may be either same or different and is selected from group consisting of alcohol, esters, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated aliphatic hydrocarbons, ethers, cyclic ethers,

substituted cyclic ethers, ketones, nitriles, ionic liquids, water or mixtures thereof

The Macitentan (I) prepared by the processes of present invention provides crystalline form I of Macitentan having purity not less than 99.8% by HPLC.

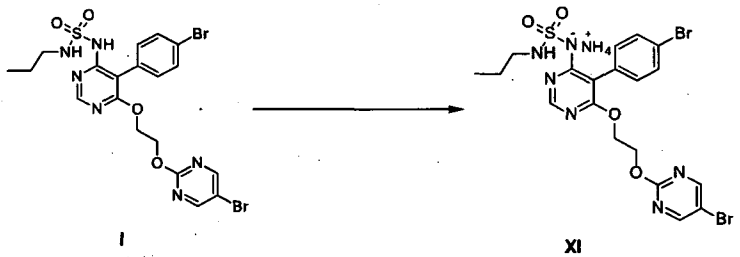
According to another embodiment of the invention, there is provided a novel crystalline form of ammonium salt of Macitentan (XI); characterized by XRD. The PXRD data reported herein obtained using Cu K alpha^{-1} Radiation, having the wavelength 1.541 A°, and were obtained using Bruker Axe D8 Advance Powder X-ray Diffractometer. XRD spectrum of ammonium salt of Macitentan of formula (XI) is shown in figure (2). The novel crystalline form of ammonium salt of Macitentan is characterized by its XPRD pattern having characteristic peaks at 3.57, 6.06, 6.811, 7.16, 7.72, 7.91, 10.77, 11.61, 12.16, 15.04, 15.57, 18.07, 18.55, 19.31, 21.66, 23.39, 26.24, 27.60, 32.48 and 37.67 ± 0.2 degrees 2θ.



XI

A process for preparing a novel crystalline form of ammonium salt of Macitentan of the compound (XI) comprises:

a) providing solution of Macitentan in a solvent or mixture of solvents; and
b) adding ammonia or ammonium hydroxide or ammonia gas to the solution of step (a) and heating the obtained mixture till clear solution is obtained, followed by cooling the reaction mass, filtering and drying the obtained solid to get the ammonium salt of Macitentan (XI).



I XI

In a preferred embodiment, the solvent used in step (a) includes but does not limited to alcohols like methanol, ethanol, isopropanol, and the like; halogenated hydrocarbons like dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones like acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters like ethyl acetate, n-propyl acetate, n-butyl acetate, iso-propyl acetate, t-butyl acetate and the like; ethers like diethyl ether, dimethyl ether, diisopropyl ether and the like; substituted cyclic ethers like 2-methyl tetrahydrofuran and the like hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof. Preferably, the said solvent is ethyl acetate, iso-propyl acetate, dichloromethane, methanol and aqueous ammonia. More preferably the solvent used is a mixture of isopropyl acetate, ethanol and aqueous ammonia.

According to another embodiment, the present invention provides a process for preparation of the amorphous form of Macitentan, the said process comprising:

a) providing solution of Macitentan in a solvent;
b) removing the said solvent for isolating the amorphous form of Macitentan.

In a preferred embodiment of the present invention, Macitentan used in step (a) can be either a crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

The solution of Macitentan may be obtained by dissolving Macitentan in a suitable solvent, or such a solution may be obtained directly from a reaction in which Macitentan is formed.

In a preferred embodiment, the solvent used in step (a) includes but does not limit to alcohols like methanol, ethanol, isopropanol, and the like; halogenated hydrocarbons like dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones like acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters like ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers like diethyl ether, dimethyl ether, diisopropyl ether and the like; substituted cyclic ethers like 2-methyl tetrahydrofuran and the like hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof. Preferably, the said solvent is dichloromethane and methanol.

The removal of the solvent in step (b) may be affected at an increased temperature, preferably at reflux temperature, and/or reduced pressure. The removal of solvent is carried out by filtration, distillation, evaporation, atmospheric distillation, distillation under vacuum, lyophilization, Freeze drying, spray drying, agitated thin film drying (ATFD), etc.

The solid residue obtained after solvent removal may be isolated and dried using conventional methods. The advantages of the process include simplicity, eco-friendliness and suitability for commercial use.

The purity of the amorphous form of Macitentan obtained by the process disclosed herein is greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.85% as measured by HPLC. For example, the purity of the amorphous form of Macitentan can be about 99% to about 99.85%.

BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

EXAMPLE-1: *N*-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-*N'*-propylsulfamide (V)

To a solution of *N*-propylsulfamide (25.0 gm, 0.180 mol) in dimethylsulfoxide (250.0 ml) was added Lithium amide (7.6 gm, 0.33 mol) under nitrogen atmosphere at 15-25° C, followed by addition of 5-(4-bromophenyl)-4,6-dichloropyrimidine (50.0 gm, 0.164 mol). The reaction mass was stirred for 2 hr. at room temperature and the progress of reaction was monitored by HPLC. After reaction completion this reaction mass was drop wise added to the solution containing Lithium amide (7.6 gm, 0.33 mol) and ethylene glycol (250.0 ml) at 15-25° C under nitrogen atmosphere. After the addition reaction mixture was heated to 105 - 110°C, maintained for 18-24 hours and the reaction progress was monitored by HPLC. After completion of reaction, resulting mass was cooled to 25-30° C and 5% w/v citric acid solution

(1000.0 ml) was added to the reaction mass. The product was extracted twice with ethyl acetate (1000.0 ml x 2), further organic layer was washed twice with 10% w/v brine solution (500.0 ml x 2). Organic layer was concentrated at 55-60°C under reduced pressure to produce *N*-5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl-*N'*-propylsulfamide as a residue. The obtained residue was dissolved in methanol 65-70° C and maintained for 30 min. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained reaction mass at 0-5°C for 60-90 min. Obtained solid was filtered, washed with methanol (50.0 ml), suck dried and dried at 55-60°C to afford white solid of *N*-5-(4-bromophenyl)-6-(-2hydroxyethoxy)-4-pyrimidinyl-*N'*-propylsulfamide.

[Yield = 50.0 gm (70.48 %); Purity (HPLC) = 98.50 %]

$(M + H)^+/z$= 433.0. ^1H NMR ($CDCl_3$): δ 8.46-8.45 (s, 1H), 7.65-7.62 (m, 2H), 7.25-7.17 (m, 2H), 6.91 (s, br, 1H), 5.62-5.69 (t, 1H), 4.48-4.46 (m, 2H), 3.84-3.81 (m, 2H), 2.97-2.92 (q, 2H), 2.97-2.92 (t, 1H), 1.16-1.52 (h, 2H), 0.94-0.91 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 11.31, 22.07, 44.74, 59.20, 68.32, 104.94, 121.42, 129.84, 131.55, 132.79, 155.91, 156.38, 166.26.

EXAMPLE-2: Preparation of *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide, Macitentan

To a solution of THF (2000.0 ml) and sodium hydride (17.0 gm, 0.708 mol), was added *N*-5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl-*N'*-propylsulfamide (100.0 gm, 0.23 mol) at 25-30°C. Stirred the content for 30 min at 25-30° C. DMF (400.0 ml) and 5-bromo-2-chloro-pyrimidine (65.0 gm; 0.033 mol) was added to the reaction mass at 25-30° C. Stirred and heated reaction mass to 60-65°C and maintain the reaction mass at 60-65° C for 2-4 hr. After completion of reaction monitored by HPLC, cooled the reaction mass to 25-30° C and 5% w/v citric acid solution (2500.0 ml) was added.

The compound was extracted twice with ethyl acetate (1500.0 ml x 2), followed by organic layer was washed with 10% w/v brine solution (1500.0 ml). Ethyl acetate layer was concentrated at 55-60°C under reduced pressure to produce *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide as a crude residue. Obtained residue was dissolved at 65-70°C in methanol (2400.0 ml), stirred and maintained for 30 min. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained reaction mass at 0-5°C for 45-60 min. Obtained solid was filtered, washed with methanol (100.0 ml), suck dried to afford crude *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide [Macitentan].

[Yield = 121.5 gm; Purity (HPLC) = 99.68%]

Purification of Macitentan (I)

Macitentan crude (121.5 gm, 0.202 mol) wet solid was dissolved at 65-70°C in methanol (2400.0 ml) and decolorized with activated charcoal. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained for 45-60 min. Obtained solid was filtered, washed with methanol (100.0 ml), suck dried and dried under vacuum at 55-60°C to afford highly pure Macitentan.**[Yield = 111.5 gm; Purity (HPLC) = 99.94%]**

$(M + H)^+/z$= 589.0. ^1H NMR ($CDCl_3$): δ 8.49 (s, 2 H), 8.45 (s, 1H), 7.57-7.54 (m, 2H), 7.16-7.12 (m, 2H), 6.87 (s, 1H), 5.60-5.57 (t, *J* = 6.24 Hz, 1H), 4.71-4.69 (m, 2H), 4.61-4.59 (m, 2H), 2.97-2.92 (q, 2H), 1.61-1.52 (h, *J* = 7.36 Hz, 2H), 0.94-0.91 (t, *J* = 7.36 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 11.24, 21.97, 44.62, 64.68, 65.48, 104.80, 111.85, 121.31, 129.48, 131.35, 132.51, 155.82, 156.41, 159.68, 163.10, 165.75.

EXAMPLE-3: Preparation of 5-bromopyrimidin-2-yl-4-methyl benzene sulfonate

To a solution of 5-bromo-2-hydroxy pyrimidine (50.0 gm 0.285 mol) in dichloromethane (500 ml) in presence of pyridine (200.0 ml) and tetrabutyl ammonium bromide (22.0 gm, 0.142 mol), was added *para*-toluene sulfonyl chloride (147.0 gm, 0.771 mol) at 0-5 °C. The reaction mass was heated to 25-30°C; maintain for 24-30 hrs. and the progress of reaction was monitored by HPLC. After completion of reaction, water (500 ml) was added to the reaction mass; stirred and organic layer was separated. The product was extracted with dichloromethane (500 ml), further washed the organic layer with water (250 ml) and 10% w/v sodium chloride solution (250 ml). Dichloromethane was evaporated at 40-50°C under reduced pressure to produce residue. The residue was dissolved in methanol (500.0 ml) at 65-70° C; Maintained for 60 min. The obtained solid was filtered, washed with methanol (50.0 ml), suck dried and dried at 40-45 °C under vacuum to offered 5-bromopyrimidin-2-yl-4-methylbenzenesulfonate.

[Yield = 30.0 gm (31.89%); Purity (HPLC) = 96.13%].

EXAMPLE-4: Preparation of *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide, Macitentan

To a solution of THF (200.0 ml) and lithium amide (3.20 gm, 0.139), *N*-5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl-*N'*-propylsulfamide (10.0 gm, 0.023 mol) was added at 0-5° C under nitrogen atmosphere and stirred the content at 0-5° C for 30 min, further DMF (40.0 ml) and 5-bromopyrimidin-2-yl 4-methylbenzenesulfonate (15.0 gm; 0.045 mol) was added to the reaction mass at 0-5° C. Stirred and heated reaction mass to 25-30°C and Maintain the reaction mass at 25-30° C for 24-30 hr. After completion of reaction monitored by HPLC, 5% w/v citric acid solution (250.0 ml) was added and the compound was extracted twice with ethyl acetate (150.0 ml x 2), followed by ethyl acetate layer was washed with 10% brine

solution w/v (150.0 ml). Ethyl acetate layer was concentrated at 55-60°C under reduced pressure to produce *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N'*-propyl sulfamide as a crude residue. The obtained residue was dissolved in methanol (240.0 ml) at 65-70 °C and decolorized by activated charcoal. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained reaction mass at 0-5°C for 45-60 min. Obtained solid was filtered, washed with methanol (10.0 ml), suck dried to afford crude *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide [Macitentan]. **[Yield = 7.0 gm; Purity (HPLC) = 99.50%]**

EXAMPLE-5: Preparation of Macitentan Ammonium salt (XI)

Macitentan (5.0 gm) was dissolved in isopropyl acetate (30 ml), ethanol (5.0 ml); ammonium hydroxide solution (1.5 ml) was added and heated to 40-45 °C; stirred for 25-30 min. The resulting solution was gradually cooled to 25-30 °C and maintain for 30-45 min. Obtained solid was filtered; washed with isopropyl acetate (5 ml), suck dried and dried at 55-60 ° C under vacuum to offered ammonium salt of Macitentan.

[Yield = 4.09 gm (79.57%); Purity (HPLC) = 99.89%]

Example- 6: Preparation of Amorphous Macitentan.

Macitentan (5.0 gm, 0.0084) was dissolved in dichloromethane (300.0 ml) and filtered through hyflo bed to get clear solution and washed bed with dichloromethane (10 ml). Dichloromethane was evaporated under vacuum at 50° C using rotary evaporator to give solid. The obtained solid was characterized by PXRD to provide Macitentan amorphous form.

[Yield = 4.0 gm (80.0%), Purity (HPLC) = 99.85%].

EXAMPLE-7: Preparation of *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide, Macitentan

To a solution of THF (400.0 ml) and DMF (400.0ml) and lithium tert. butoxide (56.0 gm, 0.695 mol), under inert atmosphere was added *N*-5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl-*N'*-propylsulfamide (100.0 gm, 0.23 mol) at 25-30°C. Stirred the content for 30-45 min at 45-50° C. 5-bromo-2-chloro-pyrimidine (54 gm; 0.278 mol) solution in DMF (100.0 ml) and THF (100.0 ml) was added to the reaction mass at 45-50° C. Stirred and heated reaction mass to 40-45°C and maintain the reaction mass for 1-2 hr. After completion of reaction monitored by HPLC, cooled the reaction mass to 25-30° C and 5% w/v citric acid solution (1000.0 ml) was added to the reaction mass. The compound was extracted twice with ethyl acetate (1000.0 ml x 2), followed by organic layer was washed with 10% w/v brine solution (1000.0 ml) and decolorized with activated charcoal. Ethyl acetate layer was concentrated at temperature below 60°C under reduced pressure to produce *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide as a solid. Obtained solid was dissolved at 65-70°C in methanol (2400.0 ml), stirred and maintained for 30 min. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained reaction mass at 0-5°C for 60-90 min. Obtained solid was filtered, washed with methanol (100.0 ml), suck dried to afford *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy] ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide [Macitentan]. **[Yield = 121.5 gm; Purity (HPLC) = 99.68%]**

Purification of Macitentan (I)

Macitentan (121.5 gm, 0.202 mol) wet solid was dissolved at 65-70°C in methanol (2400.0 ml) and decolorized with activated charcoal. The resulting solution was gradually cooled to room temperature then cooled to 0-5°C and maintained for 45-60 min. Obtained solid was filtered, washed with methanol

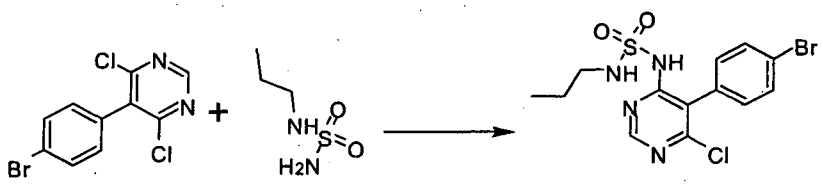
(100.0 ml), suck dried and dried under vacuum at 55-60°C to afford highly pure Macitentan.**[Yield = 111.5 gm; Purity (HPLC) = 99.94%]**

$(M + H)^+/z$= 589.0. ^1H NMR ($CDCl_3$): δ 8.49 (s, 2 H), 8.45 (s, 1H), 7.57-7.54 (m, 2H), 7.16-7.12 (m, 2H), 6.87 (s, 1H), 5.60-5.57 (t, *J* = 6.24 Hz, 1H), 4.71-4.69 (m, 2H), 4.61-4.59 (m, 2H), 2.97-2.92 (q, 2H), 1.61-1.52 (h, *J* = 7.36 Hz, 2H), 0.94-0.91 (t, *J* = 7.36 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 11.24, 21.97, 44.62, 64.68, 65.48, 104.80, 111.85, 121.31, 129.48, 131.35, 132.51, 155.82, 156.41, 159.68, 163.10, 165.75.

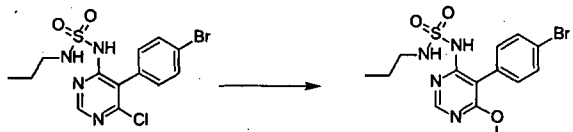
We claim:

1. A process for preparation of Macitentan, the said process comprising:
   a) condensing 5-(4-bromophenyl)-4,6-dichloropyrimidine (II) with N-propylsulfamide (VII) in a solvent and in presence of a base to give 5-(4-bromophenyl)-6-chloro-N-(propylsulfamoyl)pyrimidin-4-amine (IV), and optionally isolating compound of formula (IV);



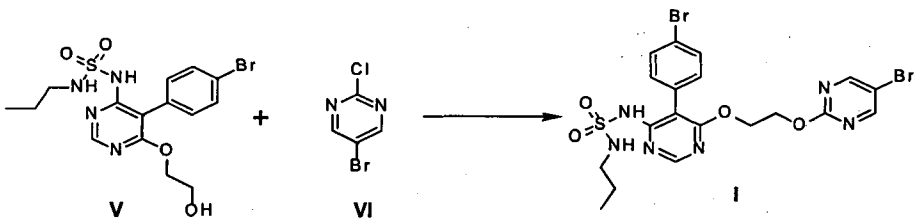
II VII IV

   b) condensing the compound of formula (IV) with ethylene glycol in a solvent and in presence of a base, to give N-[5-(4-bromophenyl)-6-(-2-hydroxyethoxy)-4-pyrimidinyl]-N'-propylsulfamide (V), isolating and purifying compound of formula (V); and



IV V

   c) condensing compound of formula (V) with 5-bromo-2-chloro-pyrimidine (VI) in a solvent and in presence of a base to give Macitentan (I), and isolating and purifying Macitentan of formula (I).



V VI I

2. The process of claim 1, wherein the solvent used in step (a), (b) and (c) may be either same or different and is organic solvent selected from the group consisting of esters selected from alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; dialkylformamides such as but not limited to dimethyl formamide; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; dialkylsulfoxides such as but limited to dimethyl sulfoxide; dialkylacetamides such as but not limited to N,N,-dimethyl acetamide; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids, hexamethylphosphorous triamide, hexamethylphosphoramide; water or mixtures thereof.

3. The process of claim 1, wherein the base used in step (a), (b) and (c) may be same or different and are selected from either organic or inorganic bases; organic bases include primary amines such as but not limited to methylamine, ethylamine aniline, propyl amine, 2-propyl amine, butyl amine, and 2-amino ethanol; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl

propyl amine, and pyrrole methylethanolamine; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine, pyrimidine, and N,N-dimethylethyl amine; tetraalkylammonium and phosphonium hydroxides; metal alkoxides and amides; metal silanoates; and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarboriates such as but not limited to sodium bicarbonate, and potassium bicarbonate; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, and lithium hydroxide; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, lithium tert. butoxide, and potassium tert butoxide; alkali metal amide such as but not limited to lithium amide, sodium amide, potassium amide, cesium amide and rubidium amide; alkali metal hydrides such as but not limited to sodium hydride, potassium hydride, lithium and calcium hydride.

4. The process of claim 1, wherein, the compound of the formula (V) is isolated and purified from reaction mass of step (b) comprises the steps of:
   i. quenching reaction mass of step (b) with citric acid; extracting the product into a suitable solvent and washing the organic layer with brine;
   ii. concentrating the said organic layer of step (i) to obtain compound (V);
   iii. crystallizing obtained compound (V) using a solvent to obtain pure compound (V).

5. The process of claim 4, wherein the solvent used in step (i) and (iii) may be either same or different and is selected from group consisting of

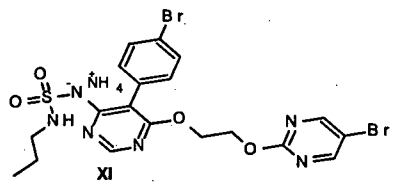
alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters including alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, and ethylene dichloride; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids; water or mixtures thereof.

6. The process of claim 1, wherein, the compound of the formula (I) is isolated and purified from reaction mass of step (c) comprises the steps of:
   i. quenching reaction mass of step (b) with citric acid; extracting the product using suitable solvent and washing the organic layer with brine;
   ii. concentrating the organic layer of step (i) to obtain compound (I);
   iii. isolating obtained compound (I) from step (ii) using solvent; and
   iv. crystallizing the obtained compound (I) in step (iii) in a solvent; to obtain pure compound (I).

7. The process of claim 6, wherein the solvent used in step (i), (iii) and (iv) may be either same or different and is selected from group consisting of alcohols such as but not limited to methanol, ethanol, n-propanol, iso-

propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; esters including alkyl acetate such as but not limited to ethyl acetate, and isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, and pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to are dichloromethane, chloroform, and ethylene dichloride; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; ketones such as but not limited to acetone, methyl ethyl ketone, and methyl isobutyl ketone; nitriles such as but not limited to acetonitrile, and propionitrile; ionic liquids; water or mixtures thereof.

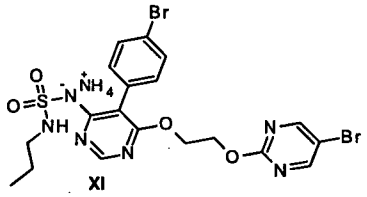
8. An ammonium salt of Macitentan (XI)



XI

9. A crystalline form of ammonium salt of Macitentan (XI) characterized by XRD as depicted in figure (2).

10. A process for preparing a novel crystalline form of ammonium salt of Macitentan of the compound (XI) comprises:



XI

a) providing solution of Macitentan in a solvent or mixture of solvents; and
b) adding ammonia or ammonium hydroxide or ammonia gas to the solution of step (a) and heating the obtained mixture till clear solution is obtained, followed by cooling the reaction mass, filtering and drying the obtained solid to get the ammonium salt of Macitentan (XI).

11. The process of claim 10, wherein the solvent used is organic solvent selected from the group consisting of esters selected from alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; nitriles such as but not limited to acetonitrile, and propionitrile; or mixtures thereof.

12. A process for preparation of the amorphous form of Macitentan, the said process comprising:
a) providing solution of Macitentan in a solvent;
b) removing the said solvent for isolating amorphous form of Macitentan.

13. The process of claim 12, wherein the macitentan used in step (a) can be either a crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

14. The process of claim 12, wherein the solvent used is organic solvent selected from the group consisting of esters selected from alkyl acetate such as but not limited to ethyl acetate, isopropyl acetate; aliphatic hydrocarbons such as but not limited to cyclohexane, n-hexane, n-heptane, pentane; aromatic hydrocarbons such as but not limited to toluene, xylene, and naphthalene; halogenated aliphatic hydrocarbons such as but not limited to dichloromethane, chloroform, and ethylene dichloride; ethers such as but not limited to methyl tertiary butyl ether, di-isopropyl ether, di-ethyl ether and di-methyl ether, methyl butyl ether; cyclic ethers such as but not limited to tetrahydrofuran, and 1,4-dioxane; substituted cyclic ethers such as but not limited to 2-methyl tetrahydrofuran; alcohols such as but not limited to methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, n-pentanol, ethylene glycol, and diethylene glycol; ketones such as but not limited to acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; nitriles such as but not limited to acetonitrile, and propionitrile; or mixtures thereof.

15. The process of claim 12, wherein the removal of solvent can be carried out by filtration, distillation, evaporation, atmospheric distillation, distillation under vacuum, lyophilization, Freeze drying, spray drying, or agitated thin film drying (ATFD).

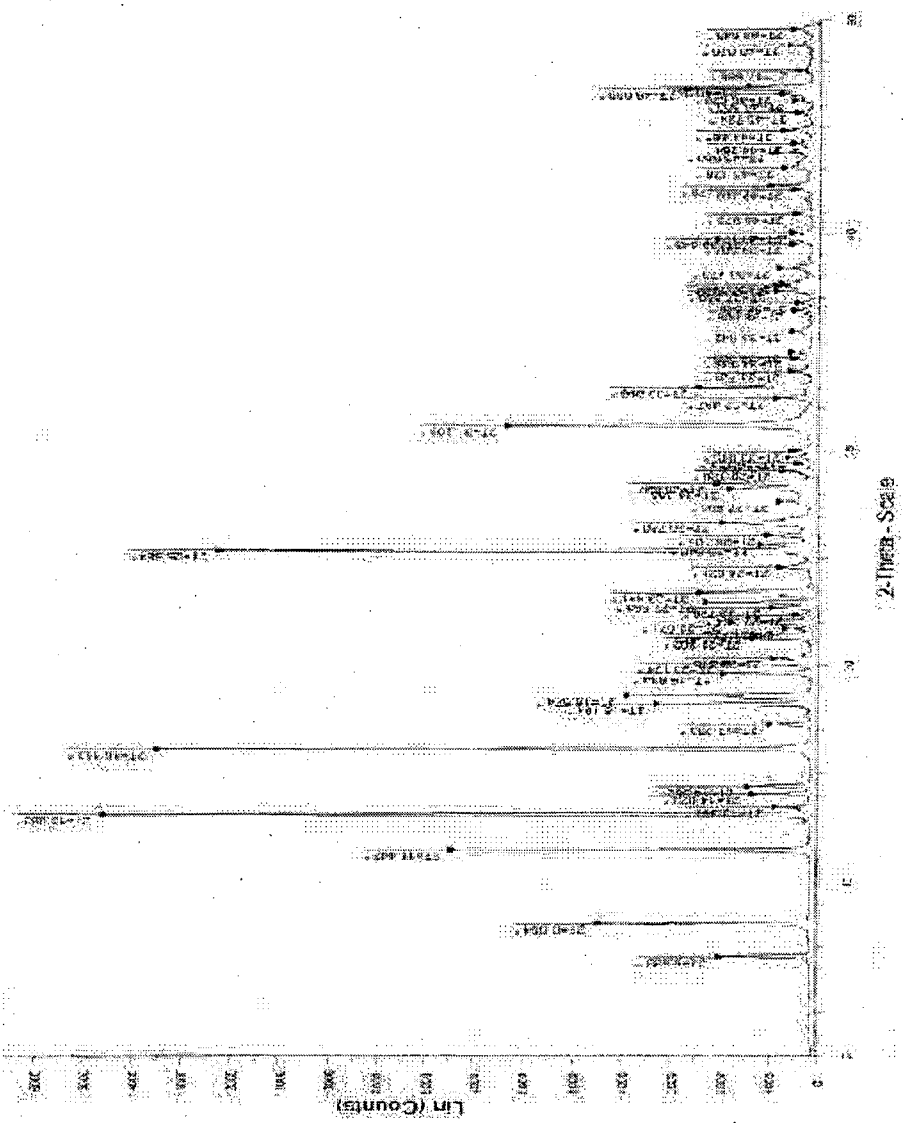


Figure-1

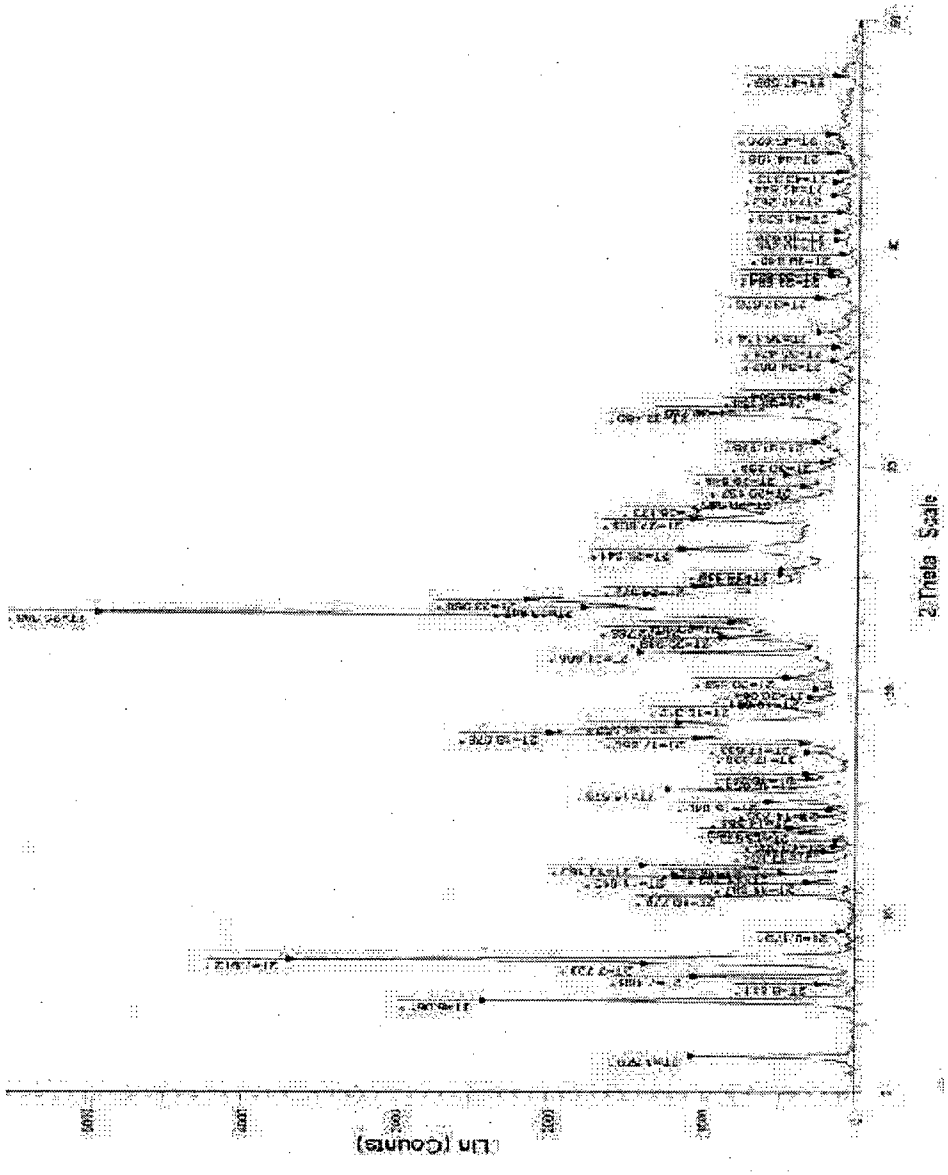


Figure-2

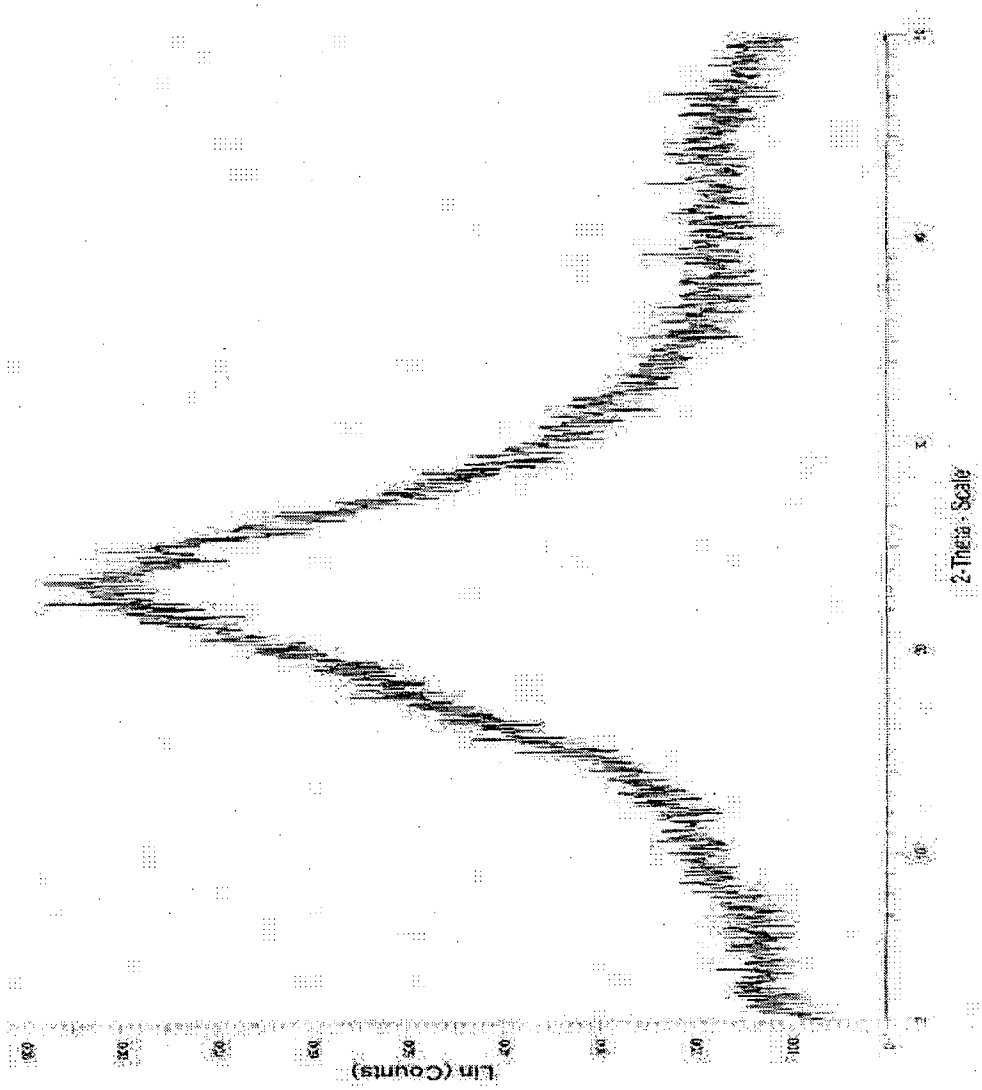


Figure-3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/000137

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/505 A61P9/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. H. BOLLI ET AL.: "The Discovery of N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide(Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist", JOURNAL OF MEDICINAL CHEMISTRY., vol. 55, 3 August 2012 (2012-08-03), pages 7849-7861, XP055078934, AMERICAN CHEMICAL SOCIETY, WASHINGTON D.C.; US ISSN: 0022-2623, DOI: 10.1021/jm3009103 cited in the application Scheme 3; page 7851 page 7858, paragraph 4 - page 7859, paragraph 1 ----- -/--	1-7, 12-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2016	16/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/000137

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/144477 A2 (AUSPEX PHARMACEUTICALS INC [US]; RAO TADIMETI [US]; ZHANG CHENGZHI [US) 16 December 2010 (2010-12-16) page 2, paragraph 3 page 13, paragraph 46 page 14, paragraph 48 -----	8-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2016/000137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010144477 A2	16-12-2010	US 2011082151 A1	07-04-2011
		WO 2010144477 A2	16-12-2010