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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

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(54) Title: A PROCESS FOR THE PREPARATION OF A THIAMINE DERIVATIVE AND SALT THEREOF

(57) Abstract: A process for the preparation of a thiamine derivative and salt thereof, the process comprising the steps of: reacting thiamine chloride hydrochloride with phosphoric acid in the presence of a catalyst to produce a reaction mass of thiamine polyphosphates; isolating said thiamine derivative from said reaction mass of thiamine polyphosphates; and preparing salt of said thiamine derivative.

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Title: A PROCESS FOR THE PREPARATION OF A THIAMINE DERIVATIVE AND SALT THEREOF

FIELD OF THE INVENTION

The present invention relates to a process for preparing thiamine derivatives. More particularly, the present invention relates to novel processes for preparing thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof.

BACKGROUND OF THE INVENTION

Thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof are useful as therapeutics and nutrients. Further, some of the thiamine derivatives are known to be biochemically important compounds.

There are processes known where thiamine derivatives have been prepared by reacting thiamine with polyphosphoric acid derived from phosphoric acid; heating of the two gives a mixture of thiamine phosphate comprising thiamine O-monophosphate, thiamine O-diphosphate, thiamine O-triphosphate and thiamine O-polyphosphate. Each polyphosphate may be isolated from the reaction mixture. However, the above prior process is commercially unpractical, because yields of the desired phosphates isolated are extremely poor.

In another process, orthophosphoric acid is used as phosphorylating agent to convert thiamine hydrochloride into thiamine monophosphate. The process demands heating acids like orthophosphoric acid which is considered to be highly unsafe up to 270º C. Moreover, this prior art process does not produce the desired product immediately after work up. The process requires 7 days to get all higher phosphates derivatives eq. Thiamine diphosphate (cocarboxylase) and thiamine triphosphate to convert into thiamine monophosphate. The prepared thiamine monophosphate dihydrate is converted into S-benzoyl thiamine monophosphate by reaction with benzoyl chloride or dibenzyl sulfide or Sodium

benzoyl thiosulfate. Due to such drastic conditions the intermediate purity and in turn the product purity is extremely poor requiring series of purification steps.

In yet another process, compounds like P_2O_5 which are unsafe from operation point of view since it requires changing into orthophosphoric acid at considerably high temperature. This process gives the mixture of mono, di, tri and tetra phosphate derivatives of thiamine. The process provides that even after hydrolysis, the reaction mass contains only 61-62% desired thiamine monophosphate dihydrate along with 31-32 % cocarboxylase and 2-3 % thiamine triphosphate. Further, it requires their separation by means of techniques like Ion Exchange which is again troublesome and not advantageous from process point of view.

Thus, the processes known hitherto for the production of such thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof have cost and/or lower yield with poor quality disadvantages. The prior art processes also suffer in that the workup of reaction mass is tedious which eventually increases the manufacturing cost.

Accordingly, there exists a need for a process which possesses none of the above-discussed disadvantages and gives the desired products not only in higher yields but also in high purity. It is therefore an object of the present invention to provide a process for the production of thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof of high purities and in higher yield. Other objects will become apparent to those skilled in this art as the description proceeds.

SUMMARY OF THE INVENTION

The present invention relates to a novel process for the preparation of thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof.

As a result of numerous studies in order to find a new and commercially viable

process for preparing thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof, it has now been found that the desired thiamine derivatives and salts thereof may be prepared in excellent yields with high purity by use of highly concentrated phosphoric acid containing 90% to 120% of phosphoric acid and metal pyrophosphate catalyst in very simple way without any intermittent treatment/process/steps. The process provides for the reaction to operate at about 85 to 125º C and the subsequent hydrolysis at 55 to 95 º C to yield immediately desired product thiamine monophosphate dihydrate in high yield and higher purity.

Thus, one aspect of the present invention relates to a novel and commercially viable process for the preparation of thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof.

Accordingly, the present invention relates to a process for the preparation of a thiamine derivative and salt thereof, the process comprising the steps of: reacting thiamine chloride hydrochloride with phosphoric acid in the presence of a catalyst to produce a reaction mass of thiamine polyphosphates; isolating said thiamine derivative from said reaction mass of thiamine polyphosphates; and preparing salts of said thiamine derivative. The said reaction is carried out at temperature ranging between 50^0C - 130^0C, preferably between 85^0C -125^0C. The catalyst is metal pyrophosphate catalyst, which is selected from a group, not being limited to, sodium pyrophosphate, potassium pyrophosphate, calcium pyrophosphate. The content of said catalyst is preferably 1 to 10% with respect to the content of thiamine chloride hydrochloride. The phosphoric acid is highly concentrated containing preferably 90% to 120% of phosphoric acid.

The said thiamine derivative includes, not being limited to, thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate. The isolated thiamine derivative is thiamine monophosphate dihydrate and salt of said thiamine derivative is salt of said S-benzoyl thiamine monophosphate.

The said thiamine polyphosphates includes, not being limited to, thiamine monophosphate, thiamine diphosphate (cocarboxylase), thiamine tetraphosphate.

The step of isolating said thiamine derivative from said reaction mass of thiamine polyphosphates, further comprising the steps of: hydrolysing said reaction mass of thiamine polyphosphates; adding Tri-n-butyl amine and chloroform to said reaction mass of thiamine polyphosphates resulting in formation of an aqueous layer; and recovering said thiamine monophosphate dihydrate by separation of the aqueous layer by adding methanol by filtration. The hydrolysis reaction is carried out at temperature ranging between 50^0C - 100^0C, preferably between 55^0C -95^0C.

The step of preparing salts of said thiamine derivative, further comprising the steps of: converting said isolated thiamine monophosphate dihydrate into said S-benzoyl thiamine monophosphate; and preparing salts of said S-benzoyl thiamine monophosphate.

The step of converting said isolated thiamine monophosphate dihydrate into said S-benzoyl thiamine monophosphate, further comprising the steps of: treating said thiamine monophosphate dihydrate in water with a solution of benzoyl chloride forming a reaction mixture; maintaining said reaction mixture alkaline by addition of aqueous sodium hydroxide; drying said reaction mixture; andisolating said S-benzoyl thiamine monophosphate from the dried reaction mixture by adding acetone.

The step of preparing salts of said S-benzoyl thiamine monophosphate, further comprising the steps of:treating S-benzoyl thiamine monophosphate in water with a solution of metal salts of hydroxide to form a resulting solution;filtering and adding acetone to the resulting solution to precipitate crystals of metal salt of S-benzoyl thiamine monophosphate; filtering and dissolving crystals of metal salt of S-benzoyl thiamine monophosphate in a small amount of water; and adding acetone to the resulting solution to produce a recrystallization of purified product of metal salt of S-benzoyl thiamine monophosphate.

Another aspect of the present invention relates to the compositions/formulations produced by the processes claimed herein.

Accordingly, the primary object and advantage of the present invention is to provide a novel and commercially viable process for the preparation of thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof with higher purity and higher yield.

Another object and advantage of the present invention is to provide a process involving use of highly concentrated phosphoric acid containing 90% to 120% of phosphoric acid and metal pyrophosphate catalyst in very simple way without any intermittent treatment/process/steps.

Another object and advantage of the present invention is to provide a process involving use of safe chemicals capable of operating at low temperature which is safe from operational point of view.

Another object and advantage of the present invention is to provide a process wherein the intermediates generated have higher yield and higher purities.

Another object and advantage of the present invention is to provide a process involving use of catalysts which facilitate the O-phosphorylation of thiamine to thiamine monophosphate dihydrate with very high selectivity.

Yet another object and advantage of the present invention is to provide a process providing controlled hydrolysis of thiamine poly phosphate (mono, cocarboxylase, tri and tetra phosphate) into thiamine monophosphate dihydrate of high purity with higher yield.

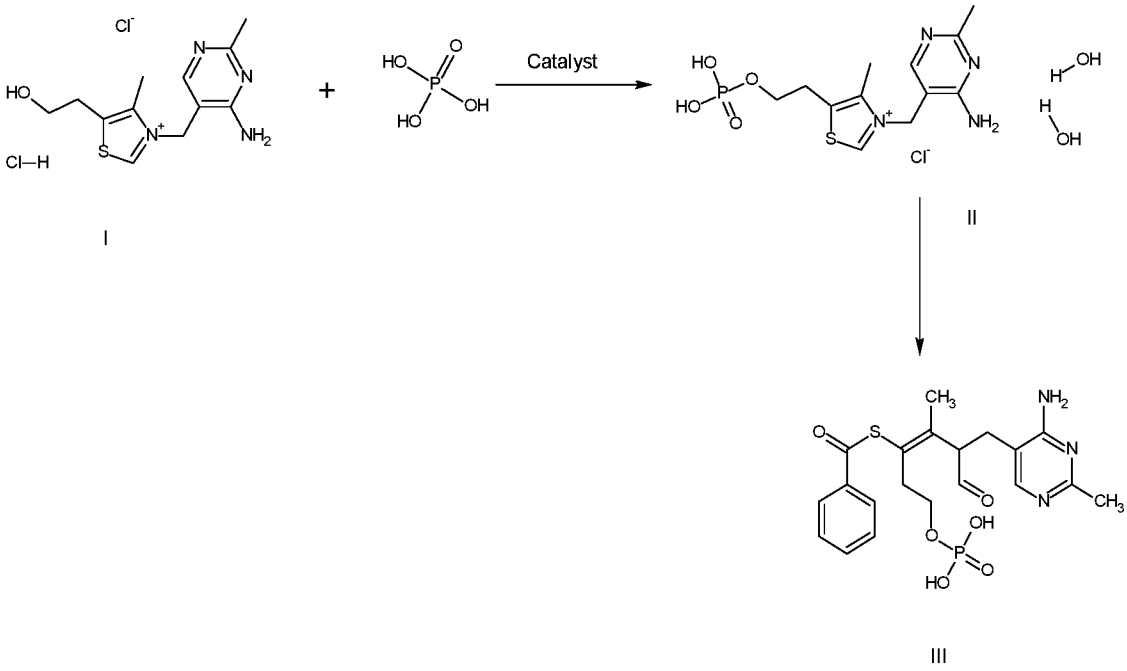
DESCRIPTION OF THE INVENTION:

The invention provides a novel and commercially viable process for the preparation of thiamine derivatives such as thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate compounds and salts thereof using

highly concentrated phosphoric acid which contains 90 % to 120 % of phosphoric acid along with catalyst such as metal pyrophosphate such as, not being limited to, Sodium pyrophosphate, potassium pyrophosphate, calcium pyrophosphate etc. The process providing concentration of catalyst at 1 to 10% with respect to thiamine chloride hydrochloride. The reaction operates at 85 to 125º C yielding thiamine monophosphate dihydrate along with small amount of cocarboxylase and the subsequent hydrolysis at 55 to 95º C to yield immediately desired product with high yield and higher purity. Thus, the production of high yield with higher purity of thiamine monophosphate dihydrate is possible without any intermittent treatment/process/step due to the properly designed process of O-phosphorylation in the presence of catalyst and controlled hydrolysis of thiamine poly phosphates (mono, coacarboxylase and tetra phosphate).

The resultant thiamine monophosphate dihydrate obtained is converted into S-benzoyl thiamine monophosphate (a fat soluble form of Vitamin B2) and its metal salts which includes sodium, potassium, lithium, calcium, iron, magnesium, barium etc.

The reaction diagram of the process is depicted below:



The first step in the process of present invention comprises reacting a compound having the above Formula (I) with phosphoric acid to form a thiamine derivative having the above Formula (II). Thereafter, controlled hydrolysis of the resultant compound of Formula (II) yields immediately the desired compound having the above Formula (III).

Example

In order to more clearly describe the nature of the present invention, specific examples will hereinafter be described. It should be understood, however, that this is done solely by way of example, and is intended neither to delineate the scope of the invention nor limit the ambit of the appended claims.

EXAMPLE 1

Preparation of Thiamine monophosphate

To the solution of 2500 g of Polyphosphoric acid and 25 g sodium pyrophosphate was added 700 g thiamine hydrochloride chloride and the mixture was heated slowly at 120 Deg C. After the ceasing of HCl gas evolution, which generally takes 3-4 hours. It was maintained for 2 hours and was further cooled to 50 Deg C. HPLC analysis shown the following analysis

7% of cocarboxylase (thiamine diphosphate)
88.0% of thiamine monophosphate
1.0% of thiamine triphosphate
1.5% of thiamine chloride

After cooling hot demineralized water was added and the reaction mass heated to 90 Deg C. The reaction mass was maintained at this temperature for 5-6 hours.

HPLC analysis of reaction mass shown the following analysis.

1% of cocarboxylase
95% of thiamine monophosphate
1.0% of thiamine chloride

The reaction mass is allowed to cool up to 25 Deg C. To this was added 4000 ml Tri-n-butyl amine and 5000 ml chloroform. The two layer formed was separated and product was recovered from aqueous layer by adding 5000 ml methanol by filtration. Dry weight of thiamine monophosphate dihydrate was 862 g (almost 100 % yield) of purity 99 % by HPLC. Melting point 198-200 Deg C.

EXAMPLE 2

Preparation of S-benzoyl thiamine monophosphate

100 g thiamine monophosphate dihydrate was added to 300 ml water and cooled up to 0 to 5 Deg C. 10 % caustic solution is run in to this solution to make pH 8 - 10. 75 g of benzoyl chloride was added drop wise to the mixture with stirring within 4 hours and maintained the reaction mixture alkaline by occasional addition of 25% aqueous sodium hydroxide. After the completion of reaction, the mass is concentrated to dryness and the product was isolated by adding acetone. The precipitated solid was filtered and dried. Dry weight of product was 75 g.

EXAMPLE 3

Preparation of Lithium salt of S-benzoyl thiamine monophosphate

To a mixture of 12 g of S-benzoyl thiamine O-monophosphate dihydrate with 35 ml of water is added with stirring and ice cooling a 10% solution of lithium hydroxide to adjust pH to about 8.0. The resulting solution is filtered, added with acetone and allowed to stand at cold place to precipitate crystals of Lithium salt of S-benzoyl thiamine O-monophosphate. The crystals are filtered and dissolved in a small amount of water. Acetone is then added to the solution to give a recrystallization of purified product, which is dried in vacuum oven. Yield -9 g and MP - decomposes at about 190°C.

EXAMPLE 4

Preparation of Barium salt of S-benzoyl thiamine monophosphate

To a mixture of 15 g of S-benzoyl thiamine O-monophosphate dihydrate with 35 ml of water is added with stirring and ice cooling a 10% solution of Barium hydroxide to adjust pH to about 8.0. The resulting solution is filtered, added with acetone and allowed to stand at cold place to precipitate crystals of Barium salt of S-benzoyl thiamine O-monophosphate. The crystals are filtered and dissolved in a small amount of water. Acetone is then added to the solution to give a recrystallization of purified product, which is dried in vacuum oven. Yield 9 g and melt with decomposition at 180 Deg C.

EXAMPLE 5

Preparation of Magnesium salt of S-benzoyl thiamine monophosphate

To a mixture of 15 g of S-benzoyl thiamine O-monophosphate dihydrate with 35 ml of water is added with stirring and ice cooling a 10% solution of Magnesium hydroxide to adjust pH to about 8.0. The resulting solution is filtered, added with acetone and allowed to stand at cold place to precipitate crystals of Magnesium salt of S-benzoyl thiamine O-monophosphate. The crystals are filtered and dissolved in a small amount of water. Acetone is then added to the solution to give a recrystallization of purified product, which is dried in vacuum oven. Yield 9 g and melt with decomposition at 205 Deg C.

Although this invention has been disclosed in the context of certain preferred embodiments and examples, it will be understood by those skilled in the art that the present invention extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses of the invention and obvious modifications and equivalents thereof. Thus, from the foregoing description, it will be apparent to one of ordinary skill in the art that many changes and modifications

can be made thereto without departing from the spirit or scope of the invention as set forth herein.

Accordingly, it is not intended that the scope of the foregoing description be limited to the description set forth above, but rather that such description be construed as encompassing all of the features of patentable novelty that reside in the present invention, including all the features and embodiments that would be treated as equivalents thereof by those skilled in the relevant art. Thus, it is intended that the scope of the present invention herein disclosed should not be limited by the particular disclosed embodiments described above but should be determined only by a fair reading of the appended claims.

CLAIMS:

1. A process for the preparation of a thiamine derivative and salt thereof, the process comprising the steps of:

reacting thiamine chloride hydrochloride with phosphoric acid in the presence of a catalyst to produce a reaction mass of thiamine polyphosphates;
isolating said thiamine derivative from said reaction mass of thiamine polyphosphates; and
preparing salt of said thiamine derivative.

2. The process according to claim 1, wherein said thiamine derivative includes, not being limited to, thiamine monophosphate dihydrate and S-benzoyl thiamine monophosphate.

3. The process according to claim 1, wherein said isolated thiamine derivative is thiamine monophosphate dihydrate.

4. The process according to claim 1, wherein salt of said thiamine derivative is salt of said S-benzoyl thiamine monophosphate.

5. The process according to claim 1, wherein the thiamine polyphosphates includes, not being limited to, thiamine monophosphate, thiamine diphosphate (cocarboxylase), thiamine tetraphosphate.

6. The process according to claim 1 and claim 3, wherein the step of isolating said thiamine derivative from said reaction mass of thiamine polyphosphates, further comprising the steps of:

hydrolysing said reaction mass of thiamine polyphosphates;
adding Tri-n-butyl amine and chloroform to said reaction mass of thiamine polyphosphates resulting in formation of an aqueous layer; and

recovering said thiamine monophosphate dihydrate by separation of the aqueous layer by adding methanol by filtration.

7. The process according to any one of the preceding claims, wherein the step of preparing salt of said thiamine derivative, further comprising the steps of:

converting said isolated thiamine monophosphate dihydrate into said S-benzoyl thiamine monophosphate; and

preparing salts of said S-benzoyl thiamine monophosphate.

8. The process according to claim 7, wherein the step of converting said isolated thiamine monophosphate dihydrate into said S-benzoyl thiamine monophosphate, further comprising the steps of:

treating said thiamine monophosphate dihydrate in water with a solution of benzoyl chloride forming a reaction mixture;

maintaining said reaction mixture alkaline by addition of aqueous sodium hydroxide;

drying said reaction mixture; and

isolating said S-benzoyl thiamine monophosphate from the dried reaction mixture by adding acetone.

9. The process according to claim 7, wherein the step of preparing salt of said S-benzoyl thiamine monophosphate, further comprising the steps of:

treating S-benzoyl thiamine monophosphate in water with a solution of metal salts of hydroxide to form a resulting solution;

filtering and adding acetone to the resulting solution to precipitate crystals of metal salt of S-benzoyl thiamine monophosphate;

filtering and dissolving crystals of metal salt of S-benzoyl thiamine monophosphate in a small amount of water; and

adding acetone to the resulting solution to produce a recrystallization of purified product of metal salt of S-benzoyl thiamine monophosphate.

10. The process according to claim 1, wherein said reaction is carried out at temperature ranging between 50^0C - 130^0C, preferably between 85^0C -125^0C.

11. The process according to claim 6, wherein said hydrolysis reaction is carried out at temperature ranging between 50^0C - 100^0C, preferably between 55^0C -95^0C.

12. The process according to claim 1, wherein said catalyst is metal pyrophosphate catalyst, which is selected from a group, not being limited to, sodium pyrophosphate, potassium pyrophosphate, calcium pyrophosphate.

13. The process according to claim 12, wherein the content of said catalyst is preferably 1 to 10% with respect to the content of thiamine chloride hydrochloride.

14. The process according to claim 1, wherein said phosphoric acid is highly concentrated containing preferably 90% to 120% of phosphoric acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/066347

A. CLASSIFICATION OF SUBJECT MATTER

C07F 9/6558 (2006.01)

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)

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)

STN: REGISTRY, CAPLUS: Keywords: 67-03-8, 7664-38-2, thiamine hydrochloride, phosphoric acid and like terms

EPOQUE: EPODOC, WPIAP: thiamine hydrochloride, betaxin, vitamin B1, phosphoric acid, H3PO4 and like terms

GOOGLE: applicant search: Ashmi Life Sciences Private Limited; inventor search: Muralidhar Ingale, Kamlesh Patel, Jaysukh Mangrolia; keywords; thiamine hydrochloride, phosphoric acid

PATENTSCOPE: applicant search: Ashmi Life Sciences Private Limited; keywords: thiamine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

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

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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
26 March 2015	26 March 2015
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Jean Todd AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0399359608

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/IB2014/066347**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SU 1594179 A1 (INSTITUTE OF BIOCHEMISTRY, ACADEMY OF SCIENCES, BELORUSSIAN S.S.R.) 23 September 1990 & CAPLUS Accession Number 1991:229149 abstract	1, 2, 5, 10 & 14
X	CN 103724374 A (ZHUHAI KINHOO PHARMACEUTICAL CO., LTD.) 16 April 2014 & CAPLUS Accession Number 2014:627878 abstract	1-5, 7-10 & 14
X	US 5047223 A (SCHUL ET AL.) 10 September 1991 columns 1 and 2; and examples	1-3, 5, 6, 10, 11 & 14
X	CA 2012928 A1 (BASF AKTIENGESELLSCHAFT) 23 September 1991 abstract; page 2, lines 1-9 and 25-37; and example 1	1-3, 5, 6, 10, 11 & 14
X	ES 8305778 A1 (LABORATORIOS MENARINI S. A.) 16 July 1983 English abstract retrieved from EPODOC database	1-3, 5, 10 & 14

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2014/066347**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
SU 1594179 A1	23 September 1990		
CN 103724374 A	16 April 2014		
US 5047223 A	10 September 1991	DE 3906633 A1	06 Sep 1990
		EP 0385378 A2	05 Sep 1990
		EP 0385378 B1	11 Jan 1995
		JP H02273687 A	08 Nov 1990
CA 2012928 A1	23 September 1991		
ES 8305778 A1	16 July 1983		

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.