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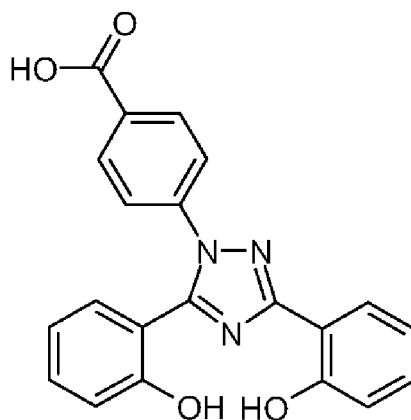
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(54) Title: PROCESS FOR THE PRODUCTION OF DEFERASIROX



(I)

(57) Abstract: A new process is described for the preparation of deferasirox, 4-[(3Z,5E)-3,5-bis(6-oxo-1-cyclohexa-2,4-dienylidene)-1,2,4-triazolidin-1-yl]benzoic acid, having the following structural formula (I).

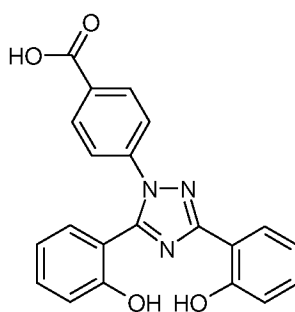
“PROCESS FOR THE PRODUCTION OF DEFERASIROX”

Field of the invention

The present invention relates to a process for the industrial production of deferasirox.

State of the art

Deferasirox is the compound having the IUPAC name 4-[(3*Z*,5*E*)-3,5-bis(6-oxo-1-cyclohexa-2,4-dienylidene)-1,2,4-triazolidin-1-yl]benzoic acid, and the following structural formula:



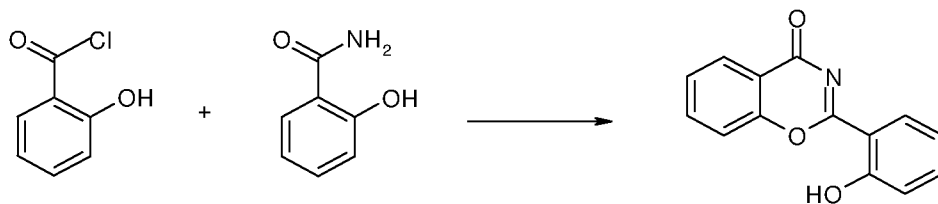
(I)

Deferasirox is used for the treatment of chronic iron overload, a pathological condition which can have metabolic causes, but is more often due to continual transfusions that are necessary in the treatment of various forms of anaemia, such as thalassaemia. Chronic iron overload can impact negatively on the functioning of organs such as the heart and liver, in the most severe cases leading to the death of the patient.

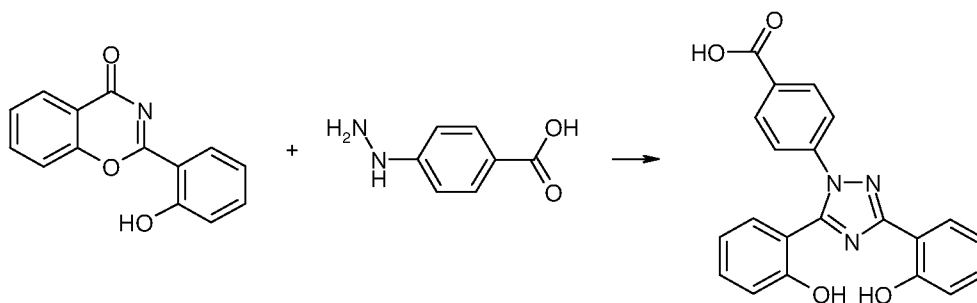
For the treatment of chronic iron overload, substances which sequester the element are used, chelating molecules that are capable of binding it irreversibly, giving way to species that can be eliminated in the faeces.

The group of compounds to which deferasirox belongs, and methods for their preparation, were described the first time in international patent WO 97/49395 A1 in the name of NOVARTIS AG, which markets a formulation containing the principle with the name Exjade[®].

The preparation of the compound deferasirox is described in the aforementioned document with a biphasic synthetic pathway. In the first phase (example 1.a of WO 97/49395 A1), salicyloyl chloride and salicylamide are reacted, producing the compound 2-(2-hydroxyphenyl)-benzo-4H-[e][1,3]oxazin-4-one:



In the second phase (example 5 of WO 97/49395 A1), the compound (II) is reacted with 4-hydrazinobenzoic acid, to obtain the desired product:



This synthetic pathway results in a raw substance containing residual quantities of 4-hydrazinobenzoic acid within the range from 50 to 100 ppm. Because this impurity is potentially genotoxic and carcinogenic, a purification phase is necessary following the production of the compound.

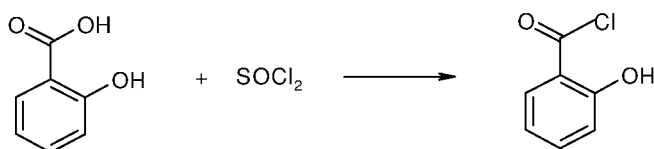
International patent applications WO 2008/065123 A2, WO 2008/094617 A2 and WO 2010/023685 A2 describe the preparation of particular crystalline (polymorphic) forms of deferasirox.

International patent application WO 2009/147529 A1 describes two processes for purifying deferasirox.

The aim of the present invention is to provide an improved process for synthesising deferasirox, that produces the desired compound with the minimum possible amounts of impurities, with particular regard to 4-hydrazinobenzoic acid.

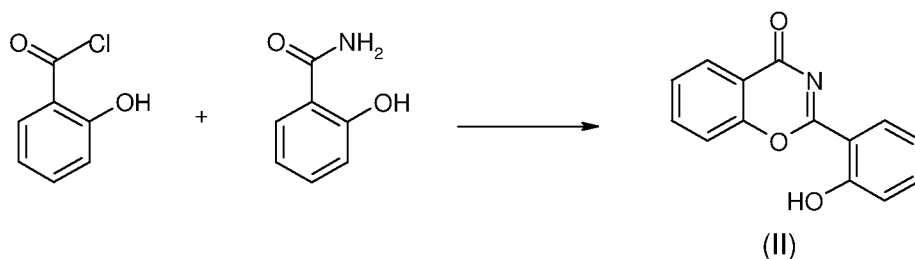
This and other aims are achieved with the present invention, which relates to a process for producing deferasirox, which comprises the following steps:

a) reaction of salicylic acid with thionyl chloride to form salicyloyl chloride:

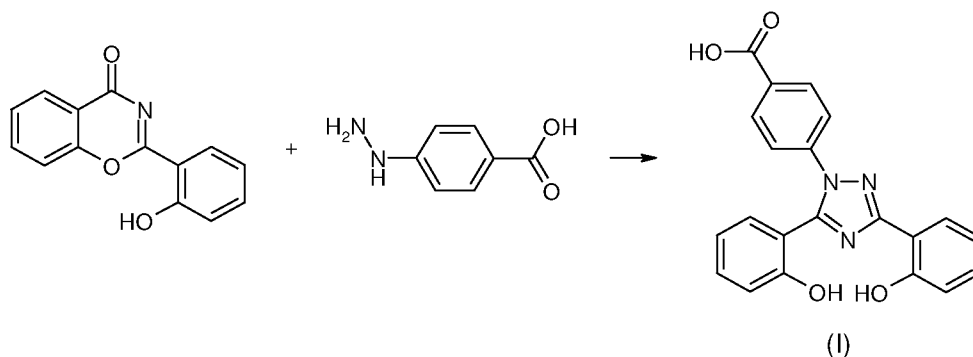


b) reaction of salicyloyl chloride with salicylamide to form compound (II),

2-(2-hydroxyphenyl)-benzo-4H-[e][1,3]oxazin-4-one:



c) reaction of compound (II) thus formed with 4-hydrazinobenzoic acid to form deferasirox, (I):



characterised in that:

- the reaction of step a) is carried out by using methylene chloride as the starting solvent and distilling the mixture up to the end of the reaction until an oily residue is obtained, to which toluene is added;
- the reaction of step b) is carried out initially in toluene, working in such a way as to completely eliminate the water that forms, then by adding methanol and distilling to a dense residue, and finally by adding ethanol, heating under reflux, and centrifuging the reaction mixture to separate compound (II);
- the reaction of step c) is carried out in ethanol under reflux, then adding N,N-dimethyl formamide and solubilising under reflux, filtering the solution and adding thereto phosphoric acid and distilled water, and reacting under reflux.

The product obtained in the process described above is already of suitable purity for use in the pharmaceutical field, but it may be further purified by crystallization treatment from a mixture of water and ethanol, as detailed below.

Typically, the first step of the process of the invention, a) comprises the reaction between salicylic acid and thionyl chloride, with formation of salicyloyl chloride. For this reaction, an equimolar ratio between salicylic acid and thionyl chloride may be

used, or preferably, a slight excess of the latter. In certain embodiments, the reaction is conducted in the presence of pyridine, having the function of accelerating the reaction, and present in molar amounts varying between approximately 1/50 and 1/70 relative to salicylic acid; and in methylene chloride as the solvent, forming a starting solution of concentration within the range from approximately 1 to 5 moles/litre for salicylic acid. In certain embodiments, the temperature of reaction is within the range from ambient temperature to approximately 50 °C, preferably approximately 40 °C. In certain embodiments, the mixture is allowed to react for times within the range from approximately 30 minutes to 3 hours, after which it is distilled until an oily residue is obtained. The residue is taken up by addition of toluene in amounts within the range conveniently from approximately 40 to 100 cc (preferably between 50 and 70) per starting mole of salicylic acid.

According to certain embodiments, in the second step of the process of the invention, b), the solution of salicyloyl chloride obtained is poured slowly into a second receptacle, containing a solution of salicylamide in toluene having a concentration within the range from approximately 2 to 6 moles/litre; the receptacle is maintained at temperature within the range from approximately 100 to 120 °C. Typically, the ratio between the moles of salicylamide present in the second receptacle and the starting moles of salicylic acid is within the range from approximately 1:1 to 0.5:1, and preferably between approximately 0.6:1, and 0.9:1. Typically, at the end of addition of the solution of salicyloyl chloride to that of salicylamide, the mixture is allowed to react under reflux (at approximately 115 °C) for at least 15 hours and preferably for 20 hours, continually separating off and eliminating the water of condensation. In certain embodiments, the mixture obtained is then cooled to approximately 65-70 °C, a volume of methanol within the range from approximately 1/5 to one half of the total volume of toluene is added, and distillation is carried out until a dense residue results. In certain embodiments, to this residue, ethanol, preferably denatured (for example with cyclohexane-methanol), is added in a volume within the range from approximately 2 to 10 times the volume of methanol previously used; the mixture thus obtained is heated under reflux for a time within the range from 10 minutes to one hour, after which it is centrifuged (preferably first allowing it to cool to ambient temperature) and washed with ethanol (preferably denatured with cyclohexane-methanol).

The compound (II) thus obtained proves to have an HPLC purity greater than 99.0% and does not need further purification (as described for example in WO 2010/023685 A2), or drying (as described for example in WO 97/49395 A1), and used moist directly in the next step of the process of the invention.

The third step of the process of the invention, c), comprises reacting the compound (II) with 4-hydrazinobenzoic acid to form deferasirox.

In certain embodiments, the moist compound (II) obtained in step b) is reacted with 4-hydrazinobenzoic acid in a molar ratio within the range from 0.8:1 and 1:0.8, and preferably essentially an equimolar ratio, in a solvent comprising ethyl alcohol containing approximately 3 vol.% of toluene (in a quantity indicatively within the range from 1 to 3 litres of solvent per mole of compound (II)). Typically, the mass is heated under reflux for at least 2 hours, after which N,N-dimethylformamide (DMF) is added in a molar amount equal to approximately 5 times the moles in the compound (II), and the mixture is left for a further period of time under reflux with stirring, until complete solubilisation of the mass is achieved. In certain embodiments, to the solution thus obtained, decolourising carbon (of pharmaceutical quality) is then added, and the solution is maintained with heating under reflux for a time within the range from 30 minutes to 2 hours, after which it is filtered.

Typically, to the clear solution obtained distilled water and phosphoric acid are added, respectively in quantities within the range from approximately 0.5 to 1 litre (water) and from approximately 0.15 to 0.30 moles (phosphoric acid) per mole of starting compound (II). The mixture is allowed to react under reflux (at around 80 °C) for a time preferably within the range from 30 minutes to 2 hours, then it is cooled to a temperature of approximately 30-35 °C, the system remains at this temperature for at least 30 minutes, and is centrifuged. The solid substance obtained by centrifugation is then washed, for example with a mixture of water/ethanol in a ratio of 3:1 in volume (wherein "ethanol" means the above-mentioned 3 vol.% toluene/ethanol mixture).

The product obtained, when dried, is deferasirox, having the same crystalline form as the product obtained by the procedure described in WO 97/49395 A1; furthermore, this product has an HPLC purity greater than 99.8%. The total yield of the process of the invention, calculated on the basis of the starting salicylic acid, is at least 35%.

One extremely important result achieved with the process of the invention is that the substance directly obtained by the process of synthesis ("raw" deferasirox) is of a quality that is already ideal for pharmaceutical applications, having a content of the impurity 4-hydrazinobenzoic acid that is below 0.5 ppm, in contrast with the substance obtained according to WO 97/49395 A1, which contains this impurity in quantities not less than 50 ppm. The process of the invention therefore enables a direct reduction (that is, without a need for further purification) of the relevant impurity that is 100 times greater than in the first document to have described synthesis of the compound.

The "raw" deferasirox obtained as described above, can be further purified using a procedure suited to the particular composition of this raw substance.

IN certain embodiments, this procedure comprises a suspension of said product with an ammonia solution in a water/ ethanol/toluene mixture (produced by adding to water a 3 vol.% toluene/ethanol mixture) of concentration within the range from approximately 0.2 to 1 M, preferably of approximately 0.4 M; heating the mass thus obtained under reflux (at approximately 78 °C); adding decolourising carbon, maintaining the system with heating under reflux for at least a further 30 minutes; cooling to 60-65 °C and filtering; heating the filtered solution under reflux and addition of acetic acid (for example, in the form of 80 wt.% solution), in a molar ratio of acetic acid/deferassirox within the range from 1:1 to 4:1, and preferably approximately 2:1; leaving to be heated under reflux for at least 30 minutes, then cooling to ambient temperature, centrifuging and washing the solid with a mixture comprising approximately 3 steps by volume of water to one step of an ethanol/toluene mixture as defined above; and finally drying (an operation that can be performed in stages at a temperature of approximately 85-95 °C). As a result of the procedure, deferassirox of HPLC purity greater than 99.98%, with a yield of approximately 83%; the final product is in the same crystalline form as the raw substance.

In certain embodiments in step c) of the process of the invention for synthesizing deferassirox, just as in the further optional process of purification, it is also possible to use pure ethanol instead of the ≤ 3 vol.% toluene/ethanol mixture; the use of this mixture is however preferred according to the present invention, because the inventors have verified that excellent results are obtained with its use, and its commercialisation is not subject to all the restrictions and controls imposed by fiscal

regulations (UTIF) that apply to pure ethanol.

The invention will be illustrated by the following examples.

EXAMPLE 1

Preparation of salicyloyl chloride.

A reactor is charged with 10 kg of salicylic acid, 100 g of pyridine and 30 kg of methylene chloride, and the mixture is heated to 40 °C. 9 kg of thionyl chloride is then added, and the reaction mass is maintained at 40 °C for one hour. The resultant mass is then distilled to obtain an oily residue, to which 4 kg of toluene is added. A solution of salicyloyl chloride is obtained by monitoring the end of the reaction by TLC (conversion to salicyloyl chloride greater than 98%).

EXAMPLE 2

Preparation of 2-(2-hydroxyphenyl)-benzo-4H-[e][1,3]oxazin-4-one, compound (II).

The solution obtained in example 1 is poured into a second reactor, maintained at a temperature of 110 °C and containing 7 kg of salicylamide and 11 kg of toluene. The resultant mass is allowed to react under reflux at approximately 115 °C, for 20 hours, continually removing the water liberated by the reaction. The solution is then cooled to 65 °C, and 5 kg of methanol is added. Distillation is performed until a dense residue is obtained, to which 25 kg of denatured ethanol (denatured using cyclohexane-methanol) is then added; the whole is heated under reflux for 30 minutes, then cooled to ambient temperature and centrifuged, finally, it is washed with 7 kg of denatured ethanol.

Approximately 8 kg of compound (II), dry equivalent, is obtained, determined by a weight loss test on step of the product, for a yield equal to approximately 66% in this step. The product is analysed by HPLC, determining a purity of more than 99.0%.

EXAMPLE 3

Preparation of raw deferasirox.

The moist product obtained at the end of example 2 is placed in a reactor, together with 4.88 kg of 4-hydrazinobenzoic acid and 48 kg of a 3 wt.% toluene/ethanol mixture. The mass is heated under reflux (approximately 77 °C) for 2 hours. To the mass maintained with heating under reflux, 12 kg of DMF is then added, and heating under reflux is continued (at a temperature of approximately 80

°C) until complete dissolution of the components present in the mixture is observed. 400 g of pharmaceutical quality decolourising carbon is then added. The suspension is heated under reflux (approximately 80 °C) with stirring for 30 minutes, then it is cooled to 60 °C and filtered. The filtered solution is placed in a reactor, heated under reflux, and 800 g of 85 wt.% of phosphoric acid, and 24 kg of distilled water are added. A precipitate is formed, which is heated under reflux (approximately 80 °C) with continuous stirring for 30 minutes, after which the mixture is cooled to 30 °C, centrifuged, and the solid is washed with a mixture consisting of 24 kg of distilled water and 8 kg of 3% toluene/ethanol.

9.6 kg of raw deferasirox, dry equivalent, is obtained, determined by a weight loss test on step of the product, for a yield equal to approximately 77% in this step. The product is analysed by HPLC, determining a purity of more than 99.8%. By HPLC analysis it is determined that the 4-hydrazinobenzoic acid content of the product is below 0.5 ppm (which represents the limit of detection, LOD, of the analytical method.).

EXAMPLE 4

Purification of raw deferasirox.

The raw product obtained in example 3 is further purified by placing in a reactor, together with 38.4 kg of 3 wt.% toluene/ethanol mixture, 13 kg of distilled water, and 1.44 kg of a 30 wt.% solution of ammonia in water. The mixture is heated under reflux (approximately 78 °C), so as to achieve complete dissolution of the solid. 380 g of decolourising carbon Picapure SP Pharma suspended in water is added, and the suspension is maintained with stirring under reflux for 30 minutes; the suspension is then cooled to 60 °C and filtered. The filtered solution is then put into a reactor, heated under reflux, and 3.94 kg of 80 wt. % acetic acid is added. Precipitation of a solid occurs. The precipitated mass is stirred under reflux (at approximately 80 °C) for 30 minutes, then it is cooled to ambient temperature, centrifuged separating the solid, and finally washed with the mixture formed from 19.2 kg of distilled water and 4.8 kg of ethanol/toluene as described previously. The solid obtained is dried overnight at 90 °C, resulting in 8 kg of a crystalline product, which analyses confirm as being crystalline deferasirox of HPLC purity greater than 99,98%. The yield from purification is equal to approximately 83% relative to raw deferasirox.

- the reaction of step c) is carried out in refluxing ethanol, then adding N,N-dimethylformamide and causing dissolution by heating to reflux, filtering the solution and adding phosphoric acid and distilled water and causing to react to reflux.
2. Process according to claim 1, further comprising a final step of purification of Deferasirox, comprising:
 - suspending raw Deferasirox in a solution of ammonia in a water/ethanol mixture;
 - heating to reflux (about 78 °C) the thus obtained mass;
 - adding decolorizing carbon and heating to reflux for at least 30 minutes;
 - cooling down to a temperature comprised between about 60 and 65 °C and filtering;
 - heating to reflux the filtered solution and adding acetic acid;
 - allowing to react for at least 30 minutes, then cooling down to room temperature, centrifuging and washing the solid with a water/ethanol mixture; and
 - drying.
 3. Process according to claim 1, wherein the reaction of step c) is carried out in an ethanol/toluene mixture containing 3% by volume of the latter component.
 4. Process according to any one of claims 2 or 3, wherein in said final step of purification of Deferasirox in place of said water/ethanol mixture a water/ethanol/toluene mixture is employed, formed adding to water an ethanol/toluene mixture containing 3% by volume of toluene.
 5. Process according to any one of the preceding claims, wherein the reaction of said step a) is carried out with an equimolar ratio between salicylic acid and thionyl chloride or with a slight excess of thionyl chloride; in the presence of pyridine in molar amounts varying between about 1/50 and 1/70 with respect to salicylic acid; with a starting concentration of salicylic acid comprised between about 1 and 5 mol/liter; and at a temperature comprised between room temperature and about 50 °C.
 6. Process according to any one of the preceding claims, wherein the reaction of said step b) is carried out by slowly adding the salicyloyl chloride solution

obtained in step a) in a vessel containing a solution of salicylamide in toluene having a concentration comprised between about 2 and 6 mol/litre, maintaining the vessel at a temperature comprised between about 100 and 120 °C, and with a ratio between the moles of salicylamide and the starting moles of salicylic acid comprised between about 1:1 e 0.5:1; then cooling down the obtained mixture to about 65-70 °C, adding methanol in a volume comprised between about 1/5 and 1/2 of the total amount of toluene and distilling until a dense residue is obtained; adding then ethanol or denatured ethanol in a volume comprised between about 2 and 10 times said volume of methanol; heating to reflux the thus obtained mixture for a time comprised between 10 minutes and 1 hour; centrifuging the mixture in order to separate the obtained crystalline product; and washing with ethanol or denatured ethanol said crystalline product.

7. Process according to claim 6, wherein the ratio between the moles of salicylamide and the starting moles of salicylic acid is comprised between about 0.6:1 e 0.9:1.
8. Process according to any one of the preceding claims, wherein the reaction of said step c) is carried out reacting the wet product obtained in step b) with 4-hydrazinobenzoic acid in a molar ratio comprised between 0.8:1 e 1:0.8; adding, after heating to reflux for at least 2 hours, N,N-dimethylformamide (DMF) in a molar amount of at least about 5 times the moles of compound (II), leaving the system in reflux conditions under stirring until complete solubilization of the mass; decolorizing and filtering the thus obtained solution; adding to the clear solution thus obtained between about 0.5 and 1 liters of distilled water and between about 0.15 and 0.30 moles of phosphoric acid per starting mole of compound (II); allowing the mixture to react in reflux conditions; cooling down at a temperature of about 30-35 °C; centrifuging the suspension in order to separate the obtained crystalline product; and washing with ethanol or denatured ethanol said crystalline product with a water/ethanol mixture in a 3:1 volume ratio.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/055753

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/08
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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/023685 A2 (MATRIX LAB LTD [IN]; KARUSALA NAGESWARA RAO [IN]; CHAVHAN BHAUSAHEB SH) 4 March 2010 (2010-03-04) the whole document -----	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/055753

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WO 2010023685	A2	04-03-2010	NONE
