(54) Title: PROCESS FOR THE PREPARATION OF CEFIDINIR

(57) Abstract: Provided are intermediates for use in synthesis of Cefdinir and processes for preparing cefdinir with such intermediates.
PROCESS FOR THE PREPARATION OF CEFDINIR

Field of the Invention

The present invention relates to a process for preparing cefdinir and precursors thereof.

Background

Cefdinir, currently marketed as OMNICEF, is as an antibiotic prescribed in a 300mg oral capsule or a suspension of 125mg/5ml. OMNICEF is particularly prescribed for respiratory and ear infections.

Cefdinir is 7-(Z)[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetimido]-3-vinyl-3-cephem-4-carboxylic acid and has the following structure:

![Chemical Structure](image)

Cefdinir is disclosed in examples 14 and 16 of USP 4,559,334. In these examples cefdinir is obtained by starting with benzhydroxy 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate in dichloromethane and acetic acid, adding isoamyl nitrate at a temperature below 0°C, stirring for 45 minutes, adding acetylacetone and stirring for 30 minutes at 5°C, adding thiourea, cleaving the benzhydroxy group with trifluoroacetic acid and precipitation of the salt from diethyl ether.

According to USP 4,935,507, cefdinir may be made by starting with a carboxyl-protected 7-amino-3-vinyl-3-cephem-4-carboxylic acid, reacting with a butanedioicacid chloride, reaction with a nitrosating agent, formation of the thiazole ring via condensation with thiourea and removal of the carboxy protective group.
USP 6,093,814 discloses the synthesis of a dimethylacetamide solvate of a tosyl salt of cefdinir using a (Z)-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid 2-benzothiazolyl thioester and 7-amino-3-vinyl-3-cephem-4-carboxylic acid.

WO02/098884 provides for preparing cefdinir by treating a cefdinir intermediate with a formic acid-sulfuric acid mixture or a formic acid-methanesulfonic acid mixture to obtain a crystalline salt of cefdinir and reacting the crystalline salt with a base in a solvent.

WO03/091261 discloses a process for preparation of a cefdinir intermediate having a trityl protecting group.

The synthesis of a complex organic molecule such as cefdinir is challenging in that many steps are involved, with each step affecting the quantity and quality of the final product obtained. Accordingly, there is a need for a viable commercial synthesis of cefdinir with as few synthetic steps as possible.

**Objects and Summary of the Invention**

The present invention provides a process for preparing cefdinir comprising reacting an active thioester having the following formula:

![Chemical Structure](image)

with an intermediate to obtain protected cefdinir, wherein Z is a protecting group that can be hydrolyzed under mild basic conditions, removing the protecting group under such mild basic conditions and recovering cefdinir. Preferred protecting groups are tetrahydropyranyl and acetyl protecting groups.

In one embodiment that is exemplified, the process comprises:

a) reacting the active thioester with 7-amino-3-vinyl-3-cephem-4-carboxylic acid in an aqueous reaction mixture in presence of an organic amine base to obtain protected cefdinir;
b) extracting impurities from the aqueous mixture with a water immiscible organic solvent;

c) adjusting pH of the aqueous mixture to above 7 to remove the protecting group;

d) acidifying the aqueous mixture to precipitate cefdinir; and

e) recovering the precipitate.

The present invention also provides a compound having the following formula:

wherein Z is an acetyl or tetrahydropyranyl protecting group.

**description of the invention**

We have now discovered that cefdinir may be prepared by reacting 7-amino-3-vinyl-3-cephem-4-carboxylic acid with a reactive thioester having the following structure (I):

Wherein Z is any protecting group which may be removed under mild basic conditions, such as acetyl protective groups or tetrahydropyranyl ether protective
groups. The remarkable facility with which these protecting groups are introduced and removed upon completion of synthesis, under mild reaction conditions, makes these groups particularly useful for carrying out the process of the present invention.

The acetyl groups may be removed from the same solvent mixture used to prepare and precipitate cefdinir. Also, the acetyl groups may be removed with a mild base, at a pH of about 7 to about 9, that is commercially available at relatively cheap prices. The mild base limits formation of impurities that may be catalyzed at higher pH values. Further, since cefdinir is often precipitated under acidic conditions, the use of an acetyl group allows for a continuous process where a mild base is used to remove the group, followed by acidification to precipitate cefdinir. The basification also allows for removal of impurities that are insoluble under basic conditions. This continuous process under mild basic conditions results in a product with a relatively high purity. The cefdinir obtained has a purity of about 90 to about 100% purity as area percentage HPLC, preferably about 95%, more preferably about 97%, even more preferably about 99%, most preferably about 99.5%. In another embodiment, a tetrahydropyranyl ether protecting groups is used.

The acetyl and tetrahydropyranyl protecting groups may be added to the thioester by routine nature in the art. For example, the protecting group may be added by reacting the thioester with acetyl chloride in presence of triethyl amine in a suitable solvent such as tetrahydrofuran. The protected thioester is then reacted with an intermediate, preferably 7-amino-3-vinyl-3-cephem-4-carboxylic acid.

The reaction of the protected intermediate to obtain cefdinir may be carried out in a mixture of water and a water-miscible organic solvent. Suitable water-miscible organic solvents include tetrahydrofuran, ethanol, methanol, propanol, isopropanol, N,N-dimethyl formamide, dimethyl acetamide, acetonitrile and mixtures thereof. Preferably, the water-miscible organic solvent is tetrahydrofuran. The ratio of the water-miscible solvent to water is preferably about 1:1 to about 10:1 (v:v), more preferably about 2.5:1 (v:v).

The synthesis of the present invention may also include the addition of an organic amine base to the reaction mixture of 7-amino-3-vinyl-3-cephem-4-carboxylic acid and the thioester. Suitable organic amine bases include C3-C12 amines such as diethyl amine, triethyl amine, diisopropylethylamine, tri-n-butylamine, triethylene diamine, pyridine, and the like. Preferably, the organic amine is a C3-C9 amine. More preferably, triethylamine could be used as the organic amine base.
The reaction mixture of the present invention may then be stirred. The reaction mixture is preferably stirred for about 2 to about 8 hours, more preferably about 4 to about 6 hours. A suitable temperature for the reaction is about 0°C to about 50°C, more preferably about 20°C to about 30°C, and most preferably about room temperature.

After completion of the reaction, the reaction mixture may be extracted with a water immiscible organic solvent to remove impurities, such as reactants not consumed during the reaction. Suitable water immiscible organic solvents include dichloromethane, C_4 to C_8 ethers and C_4 to C_7 esters or ketones. Preferably, the water immiscible organic solvent is dichloromethane. Extraction may be carried out by creating a biphasic mixture and physically stirring the two phases to facilitate moving of the impurities into the organic phase.

The organic phase of the biphasic mixture is then discarded and protected cefdinir recovered from the aqueous phase. The aqueous layer may be further purified before precipitation of cefdinir, for example, by treatment with a decolorizing agent. Suitable decolorizing agents include celite, silica gel, alumina, activated carbon and the like. The decolorizing agents may then be removed by filtration.

Where the biphasic mixture has been separated, the pH of the aqueous phase is adjusted to basic pH, preferably about 7 to about 9, more preferably about 8 to about 8.5 to hydrolyze and remove the protecting group. Suitable bases include inorganic bases such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, and the like. Preferably, the base is potassium carbonate.

To induce precipitation, the pH of the basic aqueous phase may then be lowered to an acidic pH, preferably about 1 to about 5. Preferably, the pH of the acidified aqueous phase could be about 2 to about 2.5. Suitable inorganic acids for the acidification of the aqueous phase are hydrochloric, hydrobromic, acetic, trifluoroacetic, sulfuric and the like. Preferably, the inorganic acid is sulfuric acid. The precipitate may be recovered by conventional techniques such as filtration, and preferably washed with water. The precipitation conditions may be modified to obtain various polymorphic forms of cefdinir.

After recovery, the precipitate may be dried. Drying may be carried out under ambient or reduced pressure. Further, the precipitate may be heated to accelerate the
drying process. A suitable elevated temperature for drying is about 30°C to about 50°C.

Pharmaceutical compositions of the present invention contain crystalline cefdinir, or cefdinir amorphous. The cefdinir prepared by the processes of the present invention are ideal for pharmaceutical formulation. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carborner (e.g. carbolpol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegartant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose,
polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, cefdinir and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin. Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the
lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste. Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and losenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.
A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

The present invention will be more specifically explained by the following example. However, it should be understood that the following examples are intended to illustrate the present invention and not to limit the scope of the present invention in any manner.
EXAMPLE 1

10.0 grams (44.2 mmol) of 7-amino-3-vinyl-3-cephem-4-carboxylic acid and 18.0 grams (44.7 mmol) of (Z)-(2-amionthiazol-4-yl)-2-acetoxyiminoacetic acid 2-benzothiazolyl thioester were suspended in 100ml tetrahydrofuran and 40 ml DM water at room temperature and 4.7 grams (46.5 mmol) of triethylamine was added. Then, the reaction mixture was stirred for 4-6 hrs at ambient temperature and 70 ml dichloromethane was added to reaction mixture and stirred for 10-30 minutes. Layers were separated and the aqueous layer treated with carbon, filtered, adjusted to pH 8.0-8.2 with potassium carbonate solution, and the mixture stirred for 30-45 minutes at room temperature. The pH of the solution adjusted to 2-2.5 with sulfuric acid. The product obtained was filtered off, washed with water and dried to obtain 7-(Z)-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid in a purity of 95%.
What is claimed is:

1. A process for preparing cefdinir comprising reacting an active thioester having the following formula:

\[ \text{H}_2\text{N} - \text{N} - \text{N} - \text{C} - \text{O} - \text{N} - \text{S} - \text{S} \]

with an intermediate to obtain protected cefdinir, wherein Z is a protecting group that can be hydrolyzed under mild basic conditions, removing the protecting group under such mild basic conditions and recovering cefdinir.

2. The process of claim 1, wherein the protecting group is an acetyl protecting groups or a tetrahydropyranyl protecting groups.

3. The process of claim 1, wherein Z is a tetrahydropyranyl protecting group.

4. The process of claim 1, wherein Z is an acetyl protecting group.

5. The process of claim 1, wherein the intermediate is 7-amino-3-vinyl-3-cephem-4-carboxylic acid.

6. The process of claim 5, wherein the process comprises:

   b) reacting the active thioester with 7-amino-3-vinyl-3-cephem-4-carboxylic acid in an aqueous reaction mixture in presence of an organic amine base to obtain protected cefdinir;
   b) extracting impurities from the aqueous mixture with a water immiscible organic solvent;
   c) adjusting pH of the aqueous mixture to above 7 to remove the protecting group;
   d) acidifying the aqueous mixture to precipitate cefdinir; and
   e) recovering the precipitate.

7. The process of claim 6, wherein the reaction mixture in step a) further comprises water-miscible organic solvent.
8. The process of claim 7, wherein the water-miscible organic solvent is selected
from the group consisting of tetrahydrofuran, ethanol, methanol, propanol,
isopropanol, N, N dimethyl formamide, dimethyl acetamide, acetonitrile and
mixtures thereof.

9. The process of claim 8, wherein the water-miscible organic solvent is
tetrahydrofuran.

10. The process of claim 6, wherein the organic amine base is a C₃ C₁₂ amine base.

11. The process of claim 10, wherein the amine base is selected from the group
consisting of diethyl amine, triethyl amine, diisopropylethyleneamine, tri-n-
butylamine, triethylene diamine and pyridine.

12. The process of claim 10, wherein the organic amine base is a C₃ to C₉ amine base.

13. The process of claim 12, wherein the organic amine base is triethylamine.

14. The process of claim 6, wherein the reaction mixture obtained in step a) is stirred
for about 2 to about 8 hours.

15. The process of claim 14, wherein the reaction mixture obtained in step a) is stirred
at a temperature of about 0°C to about 50°C.

16. The process of claim 6, wherein the water immiscible organic solvent for
extraction is selected from the group consisting of: C₄ to C₈ ethers, C₄ to C₇ esters
and C₄ to C₇ ketones.

17. The process of claim 6, wherein the water immiscible organic solvent for
extraction is dichloromethane.

18. The process of claim 6, wherein prior to step c) a biphasic mixture is obtained.

19. The process of claim 18, wherein the obtained biphasic mixture is separated to an
aqueous phase and an organic phase.

20. The process of claim 19, wherein the aqueous phase is treated with decolorizing
agent.

21. The process of claim 20, wherein the decolorizing agent is selected from the group
consisting of: celite, silica gel, alumina and activated carbon.

22. The process of claim 22, wherein the inorganic base is selected from the group
consisting of: sodium carbonate, sodium bicarbonate, potassium carbonate,
potassium bicarbonate, sodium hydroxide, potassium hydroxide, and the like.

23. The process of claim 23, wherein the inorganic base is potassium carbonate.
25. The process of claim 6, wherein acidifying is carried out with an inorganic acid.
26. The process of claim 25, wherein the inorganic acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, acetic acid, trifluoroacetic acid and sulfuric acid.
27. The process of claim 6, wherein acidifying is carried out to a pH of about 1 to about 5.
28. The process of claim 27, wherein acidifying is carried out to a pH of about 2 to about 2.5.
29. The process of claim 6, wherein said cefdinir is obtained in about 90% to about 100% purity as area percentage HPLC, by precipitation from said acidic aqueous phase.
30. The process of claim 29, wherein the cefdinir is obtained in about 95% purity as area percentage HPLC.
31. A compound having the following formula:

![Formula Image]

wherein Z is an acetyl or tetrahydropyranyl protecting group.
32. The compound of claim 31, wherein Z is a tetrahydropyranyl protecting group.
33. The compound of claim 31, wherein Z is an acetyl protecting group.
34. The compound of claim 31, wherein the compound is isolated.
**INTERNATIONAL SEARCH REPORT**

PCT/US2005/020141

### A. CLASSIFICATION OF SUBJECT MATTER

| IPC | 7 C07D501/22 | C07D277/74 |

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)

| IPC | 7 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 practical, search terms used)

- EPO-Internal
- CHEM ABS Data
- WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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| X        | LIN G-C ET AL: "THE SYNTHESIS OF CEFIDINIR"
          | HECHENG HUAXUE, ZHONG-KE-YUAN CHENGDU YOUCHI HUAXUESUO TASHU QINGBAOSHI, CN,
          | vol. 9, no. 5, 2001, pages 385-388, XP009019882
          | ISSN: 1005-1511
          | Scheme 2
          |                                                                   | 1-34 |
          |                                                                   | 1,2, 4-31, 33, 34 |
| Y        | examples 3,5-9                                                        | 3 |

| X        | Further documents are listed in the continuation of box C. |

| X        | Patent family members are listed in annex. |

**Note:**
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document 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 invention 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

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- "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
- "A" document member of the same patent family

Date of the actual completion of the international search: 24 August 2005

Date of mailing of the International Search Report: 02/09/2005

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Authorized officer: Usuelli, A
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