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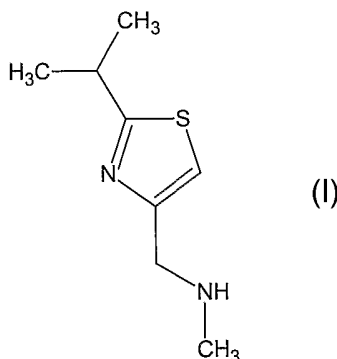
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(54) Title: ACID ADDITION SALT OF 2-ISOPROPYL-4-(((N-METHYL)AMINO)METHYL)THIAZOLE AND ITS USE IN THE PREPARATION OF RITONAVIR

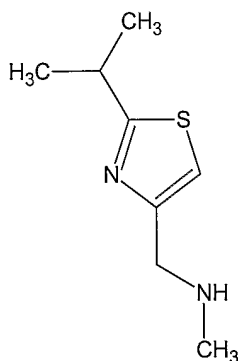


(57) Abstract: The present invention relates to a novel acid addition salt of 2-Iso-propyl-4-(((N-methyl)amino)methyl)thiazole of Formula (I) which is a useful intermediate for preparing HIV protease inhibitors. The present invention further provides a process for preparing ritonavir, a HIV protease inhibitor, using the compound of Formula (I).

ACID ADDITION SALT OF 2-ISOPROPYL-4-((N-METHYL)AMINO)METHYL)THIAZOLE AND ITS USE IN THE PREPARATION OF RITONAVIR

Field of Invention

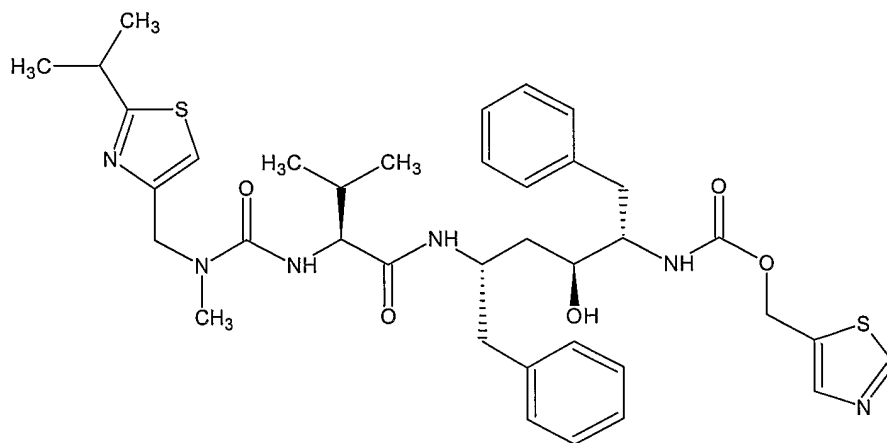
5 The present invention relates to a novel acid addition salt of 2-Isopropyl-4-((N-methyl)amino)methyl)thiazole of Formula I which is a useful intermediate for preparing HIV protease inhibitors. The present invention further provides a process for preparing ritonavir, a HIV protease inhibitor, using the compound of Formula I.



Formula I

Background of Invention

10 Ritonavir of Formula II is chemically, [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester and is
15 indicated in combination with other anti-retroviral agents for the treatment of HIV-infection.



Formula II

WO 94/14436 provides a process for the preparation of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole by reacting isobutyramide with phosphorus pentasulphide, followed by isolating the 2-methylpropane thioamide intermediate which is cyclised with 1,3-dichloroacetone. This is followed by isolating the 4-(chloromethyl)-2-isopropylthiazole hydrochloride intermediate which is then treated with aqueous methyl amine to get the required intermediate of Formula I in the form of a free base. The process provided yields the compound of Formula I after evaporation of water and purification of residue by silica-gel chromatography. It was noticed that the compound of Formula I so prepared has high levels of impurities.

10

Summary of Invention

The present inventors have found a simple process for preparing 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole or a salt thereof of Formula I of a high purity but that does not involve purification by silica-gel chromatography. The process involves purification by forming an acid addition salt of compound of Formula I, purifying the acid addition salt, if required, and then using the salt as such in the reaction sequence later to prepare the HIV protease inhibitor.

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Accordingly, in one general aspect there is provided an acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I.

Embodiments of the acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I may include one or more of the following features. For example, the acid salt may be an inorganic or organic acid addition salt. The organic acid addition salt may be one or more of acetate, maleate, succinate, valinate, glycinate, glutarate, aspartate, arginate, mesylate, and tosylate. The inorganic acid addition salt may be one or more of hydrochloride, hydrobromide, sulphate, nitrate, and phosphate. The acid addition salt may be the hydrochloride salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole. The acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I may be an impurity present in a dosage form of ritonavir.

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In another general aspect there is provided a process for preparing an acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I. The process includes the steps of:

- a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
- 5 b) cyclizing the product of step a) with 1,3-dichloroacetone;
- c) reacting the product of step b) with aqueous methyl amine to obtain 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base; and
- d) purifying the free base of Formula I by converting it to its acid addition salt.

- 10 Embodiments of the process may include one or more of the following features. For example, the solvent may be one or more of acetic acid, acetone, acetonitrile, benzene, 1-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chloroform, cyclohexane, diethylene, glycol, diglyme, dimethoxy-ethane (glyme), dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ether, ethyl acetate, ethylene glycol,
- 15 glycerin, heptane, hexane, methanol, methyl-t-butylether (MTBE), methylene chloride, pentane, 1-propanol, 2-propanol, tetrahydrofuran (THF), toluene, water, and p-xylene.

In another general aspect there is provided a process for purifying 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole. The process includes the steps of:

- a) treating 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base with
- 20 an acid;
- b) purifying the acid addition salt in an organic solvent; and
- c) converting the acid addition salt to a free base of Formula I.

- Embodiments of the process may include one or more of the following features. For example, the solvent may be one or more of acetic acid, acetone, acetonitrile, benzene,
- 25 1-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chloroform, cyclohexane, diethylene, glycol, diglyme, dimethoxy-ethane (glyme), dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ether, ethyl acetate, ethylene glycol, glycerin, heptane, hexane, methanol, methyl-t-butylether (MTBE), methylene chloride, pentane, 1-propanol, 2-propanol, tetrahydrofuran (THF), toluene, water, and p-xylene.

In another general aspect there is provided a process for preparing ritonavir or a pharmaceutically acceptable salt, ester or prodrug thereof. The process includes the steps of:

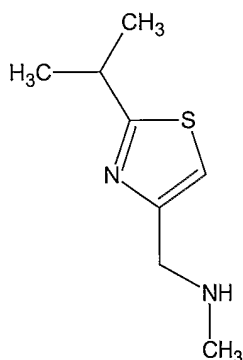
- a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
- 5 b) cyclizing the product of step a) with 1,3-dichloroacetone;
- c) reacting the product of step b) with aqueous methyl amine, to obtain 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base;
- d) purifying the free base of Formula I by converting it to its acid addition salt;
- 10 e) treating the acid addition salt obtained from the above step or free base generated thereof with N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester, to obtain N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester;
- f) hydrolyzing N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester to obtain N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine;
- 15 g) reacting N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with isobutylchloroformate and N-methyl succinamide to obtain a mixed anhydride of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine; and
- 20 h) reacting the mixed anhydride with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane to obtain ritonavir.

Embodiments of the process may include one or more of the following features. For example, the process may further include forming a dosage form by combining the ritonavir with one or more pharmaceutically acceptable excipients. The process may still
25 further include administering the dosage form to treat a condition for which the ritonavir is indicated. The dosage form may be administered in combination with one or more active pharmaceutical substances indicated for use in combination with ritonavir.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of Invention

- 5 A first aspect of the invention provides an acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I,



Formula I

- 10 The term acid addition salt with reference to the compound of Formula I refers to inorganic acid addition salts and organic acid addition salts. The inorganic acid addition salts may be, for example, hydrochloride, hydrobromide, sulphate, nitrate, phosphate and the like. The organic acid addition salts may be acetate, maleate, succinate, valinate, glycinate, glutarate, aspartate, arginate, mesylate, tosylate and the like.

- 15 A second aspect of the invention provides a hydrochloride salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I.

A third aspect of the invention provides a process for the preparation of an acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I. The process includes the steps of:

- 20 a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
b) cyclizing the product of step a) with 1,3-dichloroacetone;
c) reacting the product of step b) with aqueous methyl amine, to obtain 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base; and
d) purifying the free base of Formula I by converting it to its acid addition salt.

A fourth aspect of the invention provides a process for the purification of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole I. The process includes the steps of:

- a) treating 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base with an acid;
- 5 b) purifying the acid addition salt in an organic solvent; and
- c) converting the acid addition salt to free base of Formula I.

With reference to the above aspects, phosphorus pentasulphide is added in portions to Isobutyramide in an organic solvent. The reaction mixture is stirred at ambient temperature and filtered. The filtrate is concentrated under reduced pressure to provide 2-10 methylpropane thioamide.

The 2-methylpropane thioamide thus obtained is taken in an organic solvent and reacted with 1,3-dichloroacetone. The resultant mixture is refluxed for 2-6 hours, cooled and filtered. The filtrate is concentrated under reduced pressure to provide 4-(chloromethyl)-2-isopropylthiazole hydrochloride.

15 The 4-(chloromethyl)-2-isopropylthiazole hydrochloride taken in a polar solvent is slowly added to aqueous methylamine at about 20-25°C. The reaction mixture is stirred and then extracted with methylene chloride. The organic extract is washed and concentrated under reduced pressure to provide crude 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

20 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole is taken in an organic solvent, and an acid is added. The resulting mixture is stirred from ambient temperature to about 60°C for 0.5-3 hours. The mixture is completely concentrated under reduced pressure to provide a residue. The residue is dissolved in an organic solvent from ambient temperature to about 75°C and the mixture is cooled to about 20°C. The resultant slurry is 25 stirred at about 20°C for 2-6 hours and then at about 0°C for 0.5-4 hours and filtered. The acid addition salt obtained as a solid is washed and dried.

The organic solvent referenced above may be one or more of acetic acid, acetone, acetonitrile, benzene, 1-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chloroform, cyclohexane, diethylene, glycol, diglyme, dimethoxy-ethane (glyme), 30 dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ether, ethyl acetate, ethylene glycol, glycerin, heptane, hexane, methanol, methyl-t-butylether

(MTBE), methylene chloride, pentane, 1-propanol, 2-propanol, tetrahydrofuran (THF), toluene, water, p-xylene and the like.

The polar solvent referenced above may be any polar solvent, such as those known to one of ordinary skill in the art, for example, through literature references and the like.

5 The acid addition salt was defined above and for the preparation, any corresponding inorganic acid or organic acid may be used.

A fifth aspect of the present invention provides a process for preparing ritonavir of Formula II or a pharmaceutically acceptable salt, ester or prodrug thereof. The process includes:

- 10 a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
- b) cyclizing the product of step a) with 1,3-dichloroacetone;
- c) reacting the product of step b) with aqueous methyl amine to obtain 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base;
- d) purifying the free base of Formula I by converting it to its acid addition salt;
- 15 e) treating the acid addition salt obtained from the above step, or the free base obtained from the acid addition salt, with N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester to obtain N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester;
- f) hydrolyzing N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester to obtain N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine;
- 20 g) reacting N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with isobutylchloroformate and N-methyl succinamide to obtain a mixed anhydride of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine; and
- 25 h) reacting the mixed anhydride with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane to obtain ritonavir.

The salt obtained from the third aspect of the invention is reacted with N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester to obtain N-((N-Methyl-N-((2-isopropyl-

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4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester, which on hydrolysis results in the free acid, N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine. The free acid is converted into a mixed anhydride by reacting with isobutylchloroformate and N-methyl succinamide. The mixed anhydride of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine is reacted with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane to obtain ritonavir.

EXAMPLE 1

2-METHYLPROPANETHIOAMIDE

To a mixture of isobutyramide (5.0 g) in methyl-*t*-butylether (150 ml), phosphorus penta sulphide (3.0 g) was added in portions. The reaction mixture was stirred at 20°C for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound.

Yield: 4.77 g

EXAMPLE 2

4-(CHLOROMETHYL)-2-ISOPROPYLTHIAZOLE HYDROCHLORIDE

2-Methylpropanethioamide (50.0 g) was dissolved in acetone (750 ml). 1,3-dichloroacetone (61.6 g) and anhydrous magnesium sulphate (58.2 g) was charged to the mixture and the resultant mixture was refluxed for about 4 hours. The reaction mixture was cooled and then filtered. The filtrate was concentrated under reduced pressure to provide 4-(chloromethyl)-2-isopropylthiazole hydrochloride as a yellow liquid.

Yield: 93.0 g

EXAMPLE 3

2-ISOPROPYL-4-((N-METHYL)AMINO)METHYL)THIAZOLE

A mixture of 4-(chloromethyl)-2-isopropylthiazole (33.0 g) in water (85 ml) was added to the solution of aqueous methylamine (330 ml) at 20-25°C. The reaction mixture was stirred for 1 hour at 20-25°C and then extracted with methylene chloride (2 X 330 ml). The combined organic extract was washed with water (165 ml). The organic layer was

concentrated under reduced pressure to give dark brown crude 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

Yield: 21.6 g

EXAMPLE 4

5 **2-ISOPROPYL-4-(((N-METHYL)AMINO)METHYL)THIAZOLE HYDROCHLORIDE**

Hydrochloric acid (20 ml) was added to a solution of 2-Isopropyl-4-(((N-methyl)amino)methyl thiazole (9.0 g) in isopropyl alcohol (90 ml) and the resultant mixture stirred at 60°C for 1 hour. The mixture was concentrated completely under
10 reduced pressure and the residue dissolved again in isopropyl alcohol (90 ml) at about 75°C. The solution was cooled to 20°C and the resulting slurry stirred at 20°C for 4 hours and then at 0°C for 2 hours and filtered. The solid was washed with ethyl acetate twice (2 X 10 ml) and dried at 50°C under reduced pressure for 3 hours.

Yield: 8.0 g

15 HPLC purity: 99.50%

EXAMPLE 5

N-(((4-NITROPHENYL)OXY)CARBONYL)-L-VALINE METHYL ESTER

L- valine methyl ester hydrochloride (10 g) was added to a cooled solution of 4-nitrophenylchloroformate (12.0 g) in dichloromethane (200 ml) at about 0°C. The
20 resultant mixture was treated with N-methyl morpholine (12 g). The mixture was brought to room temperature and stirred for overnight. The reaction mixture was washed twice with 10% sodium bicarbonate (50 ml), twice with water (100 ml) and then with hydrochloric acid (100 ml). The organic layer was concentrated under reduced pressure to provide the title compound as a pale yellow oil.

25 Yield: 17.95 g

EXAMPLE 6**N-((N-METHYL-N-((2-ISOPROPYL-4-THIAZOLYL)METHYL)AMINO)CARBONYL)-L-VALINE METHYL ESTER**

2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole hydrochloride prepared from
5 Example 4 (6.0 g) was suspended in THF (100 ml). N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester from Example 5 (12.4 g), dimethylaminopyridine (0.6 g), and triethylamine (5.85 g) were mixed with the suspension and the mixture heated to about 70°C for 8 hours. The solid impurities were filtered and the filtrate concentrated under reduced pressure. The oil obtained was dissolved in dichloromethane (50 ml) and washed
10 thrice with 10% potassium carbonate solution (30 ml) and thrice with water (30 ml). The organic layer was concentrated completely under reduced pressure to provide the title compound as a light brown color oil.

Yield: 12 g

EXAMPLE 7**N-((N-METHYL-N-((2-ISOPROPYL-4-THIAZOLYL)METHYL)AMINO)CARBONYL)-L-VALINE**

Aqueous lithium hydroxide (2.85 g in 50 ml) was added to a solution of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl ester (11 g) from Example 6 in dioxane (110 ml). The resultant mixture was stirred for 1 hour at 25°C
20 and then acidified with dilute hydrochloric acid to pH 2.5-3.0. The reaction mixture was concentrated under reduced pressure and the oil that separated was extracted twice with dichloromethane (55 ml). The combined organic portion was washed with water (55 ml) and then concentrated under reduced pressure. The residue was redissolved in 10% sodium bicarbonate solution (100 ml) and washed twice with ethyl acetate (55 ml). The
25 organic portion was discarded and the aqueous portion acidified with dilute hydrochloric acid (2N) to pH 3.0. The reaction mixture was extracted twice with dichloromethane (55 ml) and concentrated under reduced pressure to give the title compound.

Yield: 7.5 g

EXAMPLE 8**(2S,3S,5S)-5-AMINO-2-(N-((5-THIAZOLYL)METHOXYCARBONYL)AMINO)-1,6
DIPHENYL-3-HYDROXY HEXANE**

5 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole hydrochloride (3.0 g) and sodium bicarbonate (4.0 g) were mixed into a stirring suspension of (2S,3S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane succinate (3.8 g) in ethyl acetate solution (45 ml). Water (40 ml) was charged to the resultant mixture and the stirring continued for two hours at about 25°C. The organic layer was separated and
10 heated at 60°C for 7 hours. The solution was cooled to about 30°C and 28% aqueous ammonia (0.41 g) added. After stirring for two hours the reaction mixture was washed thrice with 10% potassium carbonate solution (40 ml). Concentrated hydrochloric acid (2.7 ml) was added to the organic layer and the resultant slurry stirred at 50°C for three hours. The solid was filtered and washed twice with ethyl acetate (10 ml). The wet solid
15 was suspended in ethyl acetate (35 ml) and the suspension treated with dilute ammonia water (9 ml). The layers were separated and the organic layer was concentrated to obtain the title compound as an oil residue.

Yield: 3.3 g

EXAMPLE 9

20 **(2S,3S,5S)-5-(N-(N-((N-METHYL-N-((2-ISOPROPYL-4-THIAZOLYL)METHYL)AMINO) CARBONYL)-L-VALINYL)AMINO)-2-(N-((5-THIAZOLYL)METHOXY CARBONYL)AMINO)-1,6 DIPHENYL-3-HYDROXY
HEXANE**

N-methyl morpholine (1.35 g) was added to a solution of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (2.5 g) in ethyl acetate (35 ml). The
25 resultant mixture was cooled to about -18°C and isobutylchloroformate (1.15 g) in ethyl acetate (5.3 ml) added drop wise while maintaining the temperature between -18 to -15°C. The reaction mixture was stirred for 45 minutes at about -15°C and then N-hydroxysuccinimide (1.0 g) was added and the stirring continued. The reaction mixture
30 was allowed to attain 0°C at which the mixture was stirred for another 90 minutes. To this

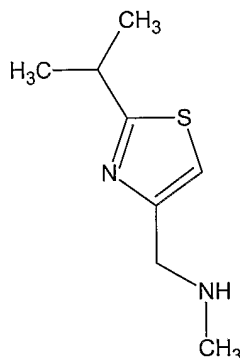
mixture a precooled (0°C) solution of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl) amino)-1,6-diphenyl-3-hydroxy hexane (3.2 g) in ethyl acetate (12 ml) was mixed. The resultant combined mixture was warmed to ambient temperature and stirred for 18 hours. The reaction mixture was washed successively twice
5 with 10% potassium carbonate solution (30 ml), thrice with citric acid solution (45 ml) and thrice with water (25 ml). The solvent was stripped off under reduced pressure and the oil obtained was taken in ethyl acetate solution (28 ml). The mixture was heated at 60°C and hexane (21 ml) was added to the hot mixture. The resultant mixture was cooled to 25°C and stirred for 24 hours. The solid material was filtered, washed twice with ethyl acetate
10 and hexane mixture (1:1, 10 ml) and dried under reduced pressure at 55°C for overnight.

Yield: 2.6 g

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example,
15 The ritonavir made according to the processes described herein may be used in forming a dosage form by combining the ritonavir with one or more pharmaceutically acceptable excipients. The dosage form may further be administered to treat a condition for which the ritonavir is indicated, such as to provide anti-viral activity in treating HIV AIDS and related conditions. Moreover, the dosage form may be administered in combination, as a
20 separate of combined dosage form, with one or more active pharmaceutical substances indicated for use in combination with ritonavir. Finally, the acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of Formula I may be present as an impurity in a dosage form of ritonavir. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

We Claim:

- 1 1. An acid addition salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole of
 2 Formula I,

**Formula I**

- 1 2. The compound of claim 1, wherein the acid salt is an inorganic or organic acid
 2 addition salt.
- 1 3. The compound of claim 2, wherein the inorganic acid addition salt comprises one
 2 or more of hydrochloride, hydrobromide, sulphate, nitrate, and phosphate.
- 1 4. The compound of claim 2, wherein the organic acid addition salt comprises one or
 2 more of acetate, maleate, succinate, valinate, glycinate, glutarate, aspartate, arginate,
 3 mesylate, and tosylate.
- 1 5. The compound of claim 1, wherein the acid addition salt comprises the
 2 hydrochloride salt of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.
- 1 6. A process for the preparation of an acid addition salt of 2-Isopropyl-4-(((N-
 2 methyl)amino)methyl)thiazole of Formula I, the process comprising the steps of:
 3 a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
 4 b) cyclizing the product of step a) with 1,3-dichloroacetone;
 5 c) reacting the product of step b) with aqueous methyl amine to obtain 2-Isopropyl-4-
 6 (((N-methyl)amino)methyl)thiazole free base; and
 7 d) purifying the free base of Formula I by converting it to its acid addition salt.
- 1 7. The process of claim 6, wherein the solvent comprises one or more of acetic acid,
 2 acetone, acetonitrile, benzene, 1-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride,
 3 chloroform, cyclohexane, diethylene, glycol, diglyme, dimethoxy-ethane (glyme),

4 dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ether, ethyl
5 acetate, ethylene glycol, glycerin, heptane, hexane, methanol, methyl-t-butylether
6 (MTBE), methylene chloride, pentane, 1-propanol, 2-propanol, tetrahydrofuran (THF),
7 toluene, water, and p-xylene.

1 8. A process for the purification of 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.
2 the process comprising the steps of:
3 a) treating 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole free base with an acid;
4 b) purifying the acid addition salt in an organic solvent; and
5 c) converting the acid addition salt to a free base of Formula I.

1 9. The process of claim 8, wherein the solvent comprises one or more of acetic acid,
2 acetone, acetonitrile, benzene, 1-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride,
3 chloroform, cyclohexane, diethylene, glycol, diglyme, dimethoxy-ethane (glyme),
4 dimethyl-formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ether, ethyl
5 acetate, ethylene glycol, glycerin, heptane, hexane, methanol, methyl-t-butylether
6 (MTBE), methylene chloride, pentane, 1-propanol, 2-propanol, tetrahydrofuran (THF),
7 toluene, water, and p-xylene.

1 10. A process for preparing ritonavir or a pharmaceutically acceptable salt, ester or
2 prodrug thereof, the process comprising the steps of:
3 a) reacting isobutyramide in a solvent with phosphorus pentasulphide;
4 b) cyclizing the product of step a) with 1,3-dichloroacetone;
5 c) reacting the product of step b) with aqueous methyl amine, to obtain 2-Isopropyl-4-
6 (((N-methyl)amino)methyl)thiazole free base;
7 d) purifying the free base of Formula I by converting it to its acid addition salt;
8 e) treating the acid addition salt obtained from the above step or free base generated
9 thereof with N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester, to obtain N-
10 ((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine methyl
11 ester;
12 f) hydrolyzing N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-
13 L-valine methyl ester to obtain N-((N-Methyl-N-((2-isopropyl-4-
14 thiazolyl)methyl)amino)carbonyl)-L-valine;

- 15 g) reacting N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-
16 valine with isobutylchloroformate and N-methyl succinamide to obtain a mixed
17 anhydride of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-
18 L-valine; and
- 19 h) reacting the mixed anhydride with (2S,3S,5S)-5-amino-2-(N-((5-
20 thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane to obtain
21 ritonavir.
- 1 11. The process of claim 10, further comprising forming a dosage form by combining
2 the ritonavir with one or more pharmaceutically acceptable excipients.
- 1 12. The process of claim 11, further comprising administering the dosage form to treat
2 a condition for which the ritonavir is indicated.
- 1 13. The process of claim 12, wherein the dosage form is administered in combination
2 with one or more active pharmaceutical substances indicated for use in combination with
3 ritonavir.
- 1 14. The compound of claim 1, wherein the compound is an impurity present in a
2 dosage form of ritonavir.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/28 A61K31/41

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 A61K

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, WPI Data, 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	EP 0 657 442 A (ASAHI CHEMICAL CO., LTD) 14 June 1995 (1995-06-14) example 1	1-14
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A	WO 01/21603 A (ARCHIMICA SPA; BELLANI, PIETRO; FRIGERIO, MARCO; CASTOLDI, PATRIZIA) 29 March 2001 (2001-03-29) the whole document	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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