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(71) Applicant: **OLON S.P.A.** [IT/IT]; Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT).

(72) Inventors: **FRIGOLI, Samuele**; c/o OLON S.p.A., Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT). **LONGONI, Davide**; c/o OLON S.p.A., Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT). **ALPEGIANI, Marco**; c/o OLON S.p.A., Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT). **FUGANTI, Claudio**; c/o OLON S.p.A., Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT). **SERRA, Stefano**; c/o OLON S.p.A., Strada Rivoltana, Km. 6/7, 20090 Rodano (MI) (IT).

(74) Agent: **MINOJA, Fabrizio**; BIANCHETTI BRACCO MINOJA S.r.l., Via Plinio, 63, 20129 Milano (IT).

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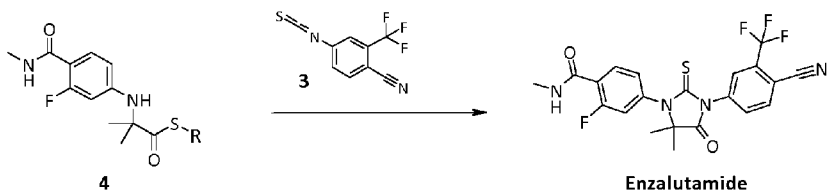
(54) Title: PROCESS FOR THE PREPARATION OF ENZALUTAMIDE



Scheme 2

(57) Abstract: Disclosed is a process for the preparation of Enzalutamide comprising the reaction (Scheme 2), wherein R can be alkyl, aryl, aryl-alkyl or heterocyclyl.

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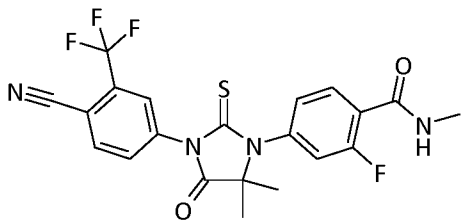
PROCESS FOR THE PREPARATION OF ENZALUTAMIDE

Object of the invention

The object of the invention is a process for the preparation of the active ingredient Enzalutamide.

Prior art

Enzalutamide, the chemical name of which is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-1-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide,

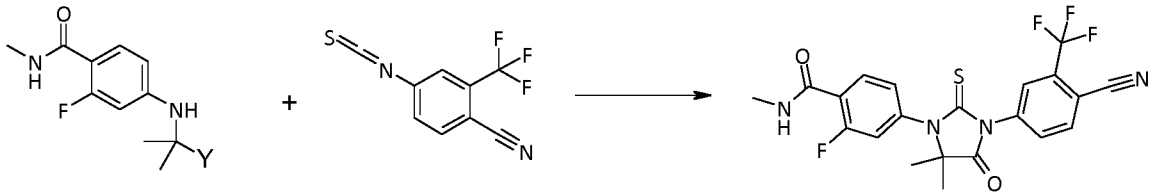


Enzalutamide

belongs to a class of compounds able to bind to the receptors of the androgen hormones used in the treatment of metastatic prostate cancer. It is known that the antiandrogen drugs used in the treatment of hormone-sensitive prostate tumours can trigger resistance due to a mechanism of over-expression of the androgen hormone receptors, thus making the drugs ineffective, and in some cases actually counterproductive. Molecules like Enzalutamide have demonstrated their ability to make forms of tumours which have become resistant treatable again.

WO2006124118 and WO2007127010 describe a method for the preparation of Enzalutamide (Scheme 1), the last step of which is microwave-assisted cycloaddition of isothiocyanate **3** with cyanoalkylamine derivative **1**. The reaction takes place with low yields, and chromatographic purification is required; moreover, the preparation of **1** requires the use of cyanides or cyanohydrin. A more efficient process for the preparation of Enzalutamide, disclosed in WO2011106570, involves cyclisation of isothiocyanate **3** with ester **2**, or a

superior homologue thereof (Scheme 1).



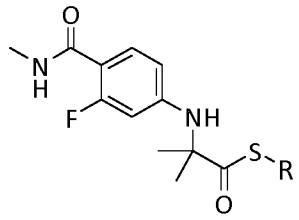
1 Y = CN
2 Y = CO_2Me

3

Enzalutamide

Scheme 1

We have now found that Enzalutamide can be advantageously obtained by reacting isothiocyanate **3** with a thioester of formula **4**.



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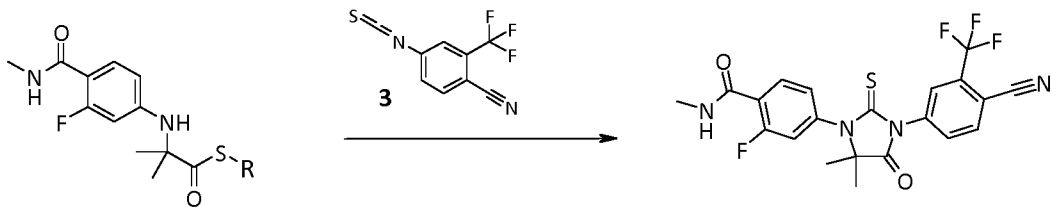
Description of the invention

The object of the present invention is a process for the preparation of Enzalutamide which comprises reacting isothiocyanate **3** with a thioester of formula **5** (Scheme 2),



4

3

Enzalutamide

Scheme 2

wherein R can be alkyl, aryl, aryl-alkyl or heterocyclyl.

The alkyl is preferably straight or branched (C1-C10)-alkyl.

The aryl is preferably phenyl or naphthyl.

The aryl-alkyl is preferably a (C1-C4)-alkyl residue substituted by an aryl group.

The heterocyclyl is preferably a group consisting of a five or six atom ring, saturated or unsaturated, containing one or more heteroatoms selected from oxygen, sulphur and nitrogen, optionally fused to a benzene ring.

Said alkyl, aryl and heterocyclic groups can be non-substituted or substituted by one or more groups comprising: halogen, cyano, nitro, halogen, (C1-C3)-alkyl, (C3-C6)-cycloalkyl, trifluoromethyl, methoxy, methylthio, methanesulphonyl, vinyl, allyl, carbomethoxy and carbethoxy.

The condensation between isothiocyanate **3** and a compound of formula **4** to give Enzalutamide is typically effected in an organic solvent or a mixture of solvents, selected from an ester such as propyl acetate, isopropyl acetate or butyl acetate, an amide such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methyl pyrrolidone, a carboxylic acid such as acetic acid or propionic acid, an aromatic hydrocarbon such as toluene or xylene, a urea such as 1,3-dimethyl-2-imidazolidinone or *N,N'*-dimethyl-propylene urea, or a sulphur-containing solvent such as dimethylsulphoxide or sulfolane.

The reaction temperature typically ranges from +50°C to +150°C, preferably from +70 to +120°C; the reaction time ranges from 5 hours to 50 hours, preferably from 10 hours to 30 hours.

The molar ratio of compound **4** to isothiocyanate **3** usually ranges from 1:1 to 1:4, preferably from 1:1.5 to 1:2.5.

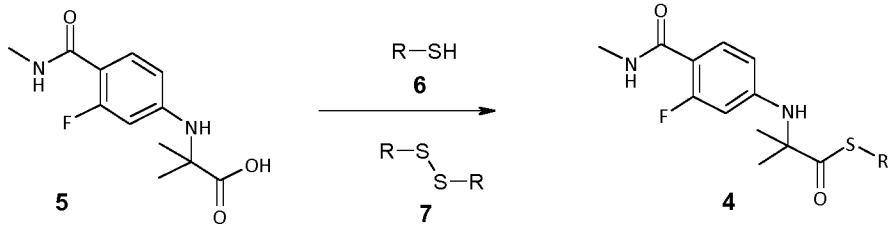
The reaction is usually effected under conditions of high concentration, with a reagent weight to solvent volume ratio preferably ranging from 1:1 to 1:4.

Enzulatamide can then be isolated by one of the classic methods, such as precipitation of the crude product by adding an anti-solvent to the reaction mixture; or dilution with a suitable solvent, optional washing of the organic solution with aqueous solutions, and obtaining the crude product by concentrating the organic phase.

The quality of the crude product can then be improved by treatment with

solvent (slurry) or by crystallisation.

The compounds of formula **4** can be prepared by known methods from known products, for example by subjecting 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-propionic acid **5** to the thioesterification reaction with an R-SH thiol of formula **6**, or with an R-S-S-R disulphide of formula **7** (Scheme 4), wherein R is defined as for the compounds of formula **4**.



Scheme 3

Isothiocyanate **3** and acid 5 are known products.

The invention will now be illustrated by the following examples.

Example 1

Synthesis of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid S-benzothiazol-2-yl ester

A solution of triethylamine (0.5 ml) in dichloromethane (12 ml) is added at room temperature to a mixture of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-propionic acid (10 g), 2-mercaptobenzothiazolyl disulphide (15.7 g) and triethylphosphite (8.20 g) in dichloromethane (50 ml), and stirred for 4 hours. The suspension is filtered, and the organic phase is washed several times with water and a 4% sodium bicarbonate aqueous solution. The mixture is then filtered through silica, washing with DCM/AcOEt. The filtrate is evaporated to obtain 15 g of mercaptobenzothiazolyl thioester.

Example 2

Synthesis of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid S-phenyl ester

A solution of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-propionic acid (5 g) and *N*-methyl morpholine (2 g) in anhydrous THF (60 ml) at about 0°C is treated in sequence with isobutyl chloroformate (2.7 g), *N*-methyl morpholine (2 g) and thiophenol (2.2 g); the mixture is then left under stirring for 15 hours at 20°C. The mixture is diluted with ethyl acetate (100 ml), and the organic phase is washed with water, dilute hydrochloric acid, and finally with a sodium chloride saturated solution. The organic phase is concentrated, and the residue is crystallised from toluene to obtain 6 g of phenyl thioester.

Example 3

Synthesis of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid S-benzyl ester

N,N'-Dicyclohexyl carbodiimide (5 g) and a catalytic amount of 4-dimethylaminopyridine (40 mg) are added to a solution of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-propionic acid (5 g) and benzyl mercaptan (5 g) in dichloromethane (40 ml). The mixture is left under stirring for 15 hours at room temperature and then filtered, washed with water, sodium bicarbonate aqueous solution, dilute hydrochloric acid, and finally with a sodium chloride saturated solution. The solvent is removed, and 6.3 g of benzyl thioester is obtained.

Example 4

By operating as described in Example 3, the following thioesters were prepared:

- 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid S-ethyl ester
- 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid S-isopropyl ester
- 1-(3-fluoro-4-methylcarbamoyl-phenylamino)-1-methyl-ethylsulphanyl]-acetic acid methyl ester

- 2-fluoro-4-[1-(4-methoxy-benzylsulphanyl)-1-methyl-ethylamino]-*N*-methyl-benzamide

Example 5

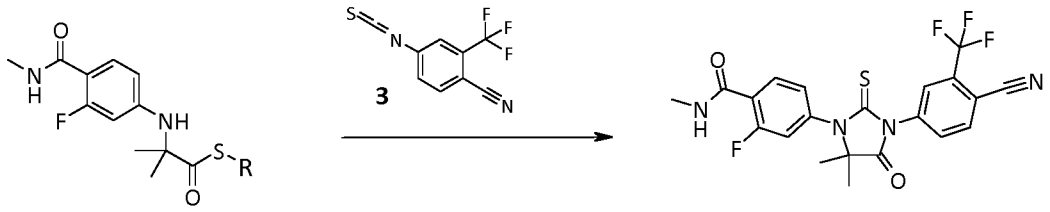
Synthesis of Enzalutamide: general procedure

A mixture of 2-(3-fluoro-4-methylcarbamoyl-phenylamino)-2-methyl-thiopropionic acid thioester (10 mmol) and 4-isothiocyanato -2-trifluoromethyl-benzonitrile (15 mmol) in DMSO/isopropyl acetate 2:1 (5 ml) is heated at about 90°C for 24 hours. The reaction is then cooled, diluted with isopropyl acetate and washed with water, dilute hydrochloric acid, aqueous sodium bicarbonate and brine. Crude Enzalutamide is obtained by concentrating the organic phase, and then recrystallised from isopropyl acetate/*n*-heptane or purified by chromatography.

The yields obtained using the thioesters described in Examples 1-4 range from 45 to 90%.

CLAIMS

1. A process for the preparation of 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-1-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide (Enzalutamide) comprising the reaction of isothiocyanate **3** with a thioester of formula **4**,



4 **Enzalutamide**

wherein R can be alkyl, aryl, aryl-alkyl or heterocyclyl.

2. The process of claim 1 wherein the reaction isothiocyanate 3 and thioester 4 is carried out in a solvent selected from an ester, an amide, a carboxylic acid, an aromatic hydrocarbon, a urea or a sulphur-containing solvent or a mixture thereof.

3. The process of claim 2 wherein the solvent is selected from propyl acetate, isopropyl acetate, butyl acetate, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl pyrrolidone, acetic acid, propionic acid, toluene, xylene, 1,3-dimethyl-2-imidazolidinone, *N,N'*-dimethyl-propylene urea, dimethylsulphoxide, sulfolane or a mixture thereof.

4. The process according to claim 1, 2 or 3 wherein the reaction temperature ranges from +50°C to +150°C, preferably from +70 to +120°C, and the reaction time from 5 hours to 50 hours, preferably from 10 hours to 30 hours.

5. The process according to any one of the above claims, wherein the molar ratio of compound 4 to compound 3 ranges from 1:1 to 1:4, preferably from 1:1.5 to 1:2.5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/061690

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/86
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.
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A	WO 2006/124118 A1 (UNIV CALIFORNIA [US]; SAWYERS CHARLES L [US]; JUNG MICHAEL E [US]; CHE) 23 November 2006 (2006-11-23) cited in the application example 56 -----	1-5

☐ 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	Date of mailing of the international search report
8 September 2016	16/09/2016

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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