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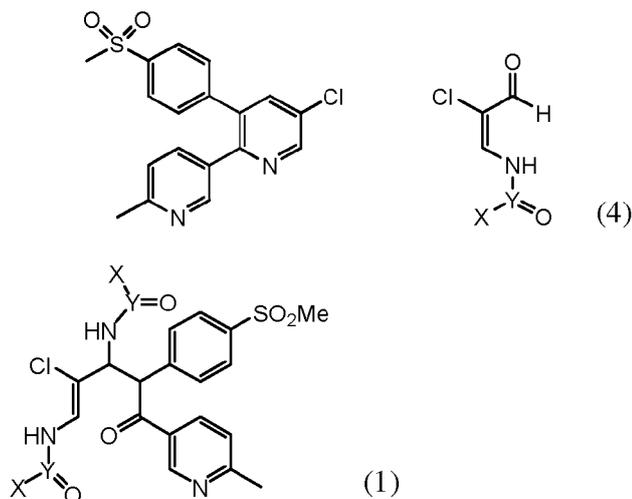
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

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(54) Title: PROCESS FOR MAKING ETORICOXIB



(57) Abstract: The invention relates to an improved process and novel intermediates (4) and (6) for the preparation of pharmaceutically active compound etoricoxib of formula (1).

## PROCESS FOR MAKING ETORICOXIB

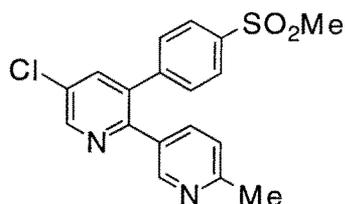
The invention relates to an improved process and novel intermediates for the preparation of the pharmaceutically active compound etoricoxib.

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## BACKGROUND OF THE INVENTION

Etoricoxib, i.e. 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine of formula

(1)



10 (1)

is a COX-2-inhibitor which is currently approved, in the free base form, for the treatment of various inflammatory diseases, e.g. rheumatoid arthritis. It is marketed in the form of a film-coated tablet, e.g., under the brand name Arcoxia.

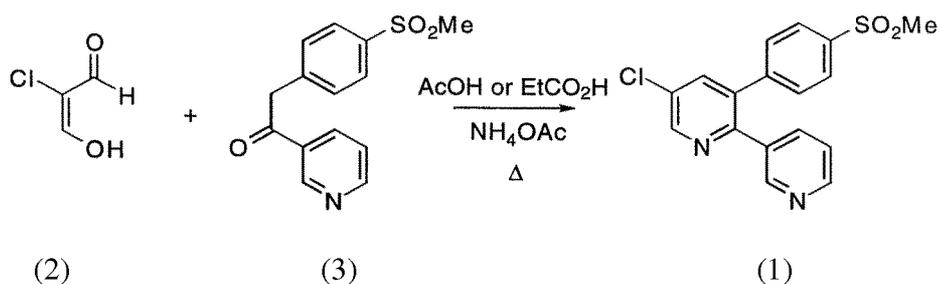
Etoricoxib was first disclosed in WO9803484. In the solid state, etoricoxib may exist in various polymorphic forms, which are disclosed, e.g. in WO0137833 and WO0192230.

WO9803484 discloses a process for making etoricoxib which comprises bromination of 2-amino pyridine derivatives, the coupling of the resulting bromide derivative with 4-(methylthio)phenyl-boronic acid in the presence of a suitable base, and the oxidation of the product to give the corresponding sulfone. The amino group of the sulfone is further converted to the corresponding halide. A palladium-catalyzed coupling of the sulfone halide derivative with an appropriately substituted metal-containing aromatic group gives etoricoxib of formula (1).

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This method has several disadvantages such as the costly catalyst palladium used for the coupling and the difficulties to purify the resulting product.

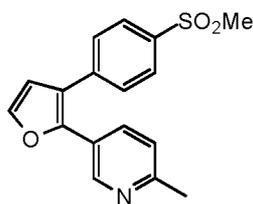
W09847871 discloses a method for the preparation of etoricoxib (see Scheme 1 below) which comprises reacting an aldehyde compound of formula (2) with a ketosulfone of formula (3), which after heating in the presence of an ammonium salt yields etoricoxib of formula (1).



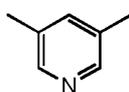
Scheme 1

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Although the use of the costly palladium catalyst is avoided, this method has other disadvantages such as the formation of two impurities:



Impurity I



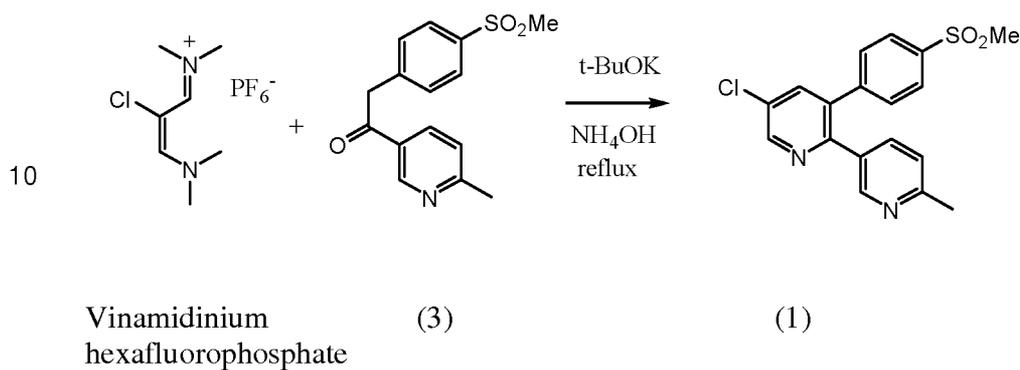
Impurity II

15

JOC, VOL. 65, No 25, 2000 reports on page 8418, second column, that impurity I is obtained in 15% assay yield and impurity II in 5% assay yield.

The reaction uses a carboxylic acid such as acetic acid or propanoic acid as a solvent and refluxes at a temperature  $>120^{\circ}\text{C}$  for more than 16 hours. Such reaction conditions lead to a product which is difficult to purify.

In order to obtain a more efficient process, WO9955830 prepares etoricoxib by reacting a  
5 ketosulfone derivative with a special vinamidinium hexafluorophosphate salt (see Scheme 2 below). The synthesis includes three steps, which have been optimized to a one-pot process.



Scheme 2

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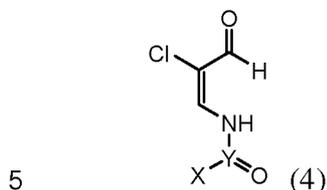
This reaction has the disadvantage that vinamidinium hexafluorophosphate has to be prepared and is expensive.

Further, in the prior art, the reaction between compound (2) or the vinamidinium salt and ketosulphone (3) has been performed in the presence of ammonium reagents. However, some of  
20 these reagents are known for not being easy to handle. For instance, ammonia solutions are corrosive and have a strong odour.

Hence, there is a need for an alternative process for preparing the pharmaceutically active compound etoricoxib of formula (1) that is efficient, cost effective and does not need ammonium reagents.

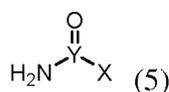
## BRIEF DESCRIPTION OF THE PRESENT INVENTION

The subject of the present invention is an improved synthetic route to etoricoxib of formula (1). The approach is based on the use of a novel reagent of formula (4) in a synthetic route leading to etoricoxib,

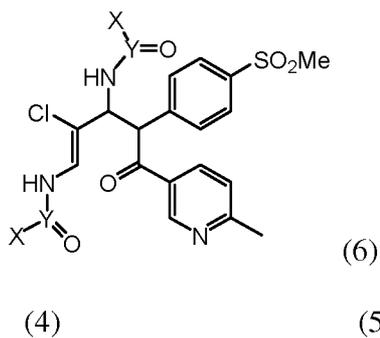


wherein X is Alkyl, Aryl, O-alkyl, O-aryl or H and Y is C or S=O.

Compound (4) can be obtained *in situ* when compound (2) reacts with an  $\text{NH}_2\text{YOX}$  compound (5), where (X) and (Y) are as defined above.

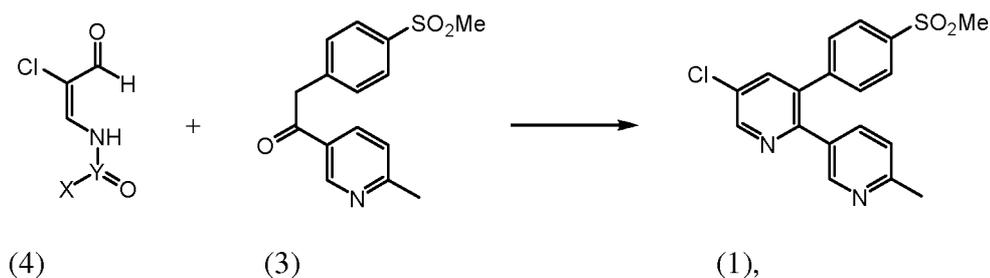


In an aspect, the invention provides the compound of formula (6), or a salt thereof,



In another aspect, the invention provides a process to make Etoricoxib of formula (1) comprising the step of reacting in a suitable solvent a compound of formula(3) with compound of formula (4) wherein (X) and (Y) are as defined above.

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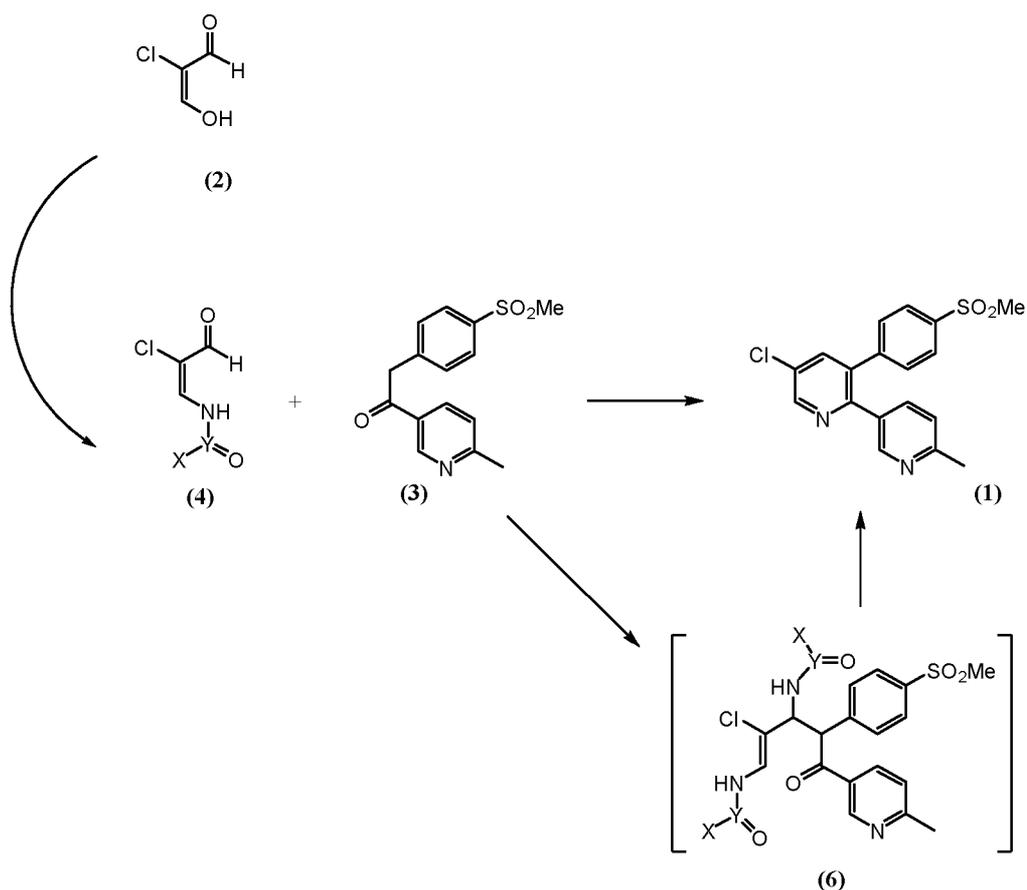


Scheme 3

5 The compounds of formulas (4) and (6), the processes of making them, and the use thereof as a starting material for making etoricoxib of formula (1) form next particular aspects of the present invention.

#### DETAILED DESCRIPTION OF THE PRESENT INVENTION

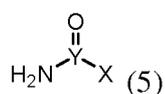
10 The present invention provides a route for making etoricoxib of formula (1) based on using milder reaction conditions than the prior art: avoiding the use of ammonia, avoiding the use of a large amount of carboxylic acid and carrying out the reaction at a lower temperature. The process according to the various aspects of the present invention is shown in Scheme 4 below.



Scheme 4

The starting material of the present invention is 1-(6-methylpyridin-3-yl)-2-(4-(methylsulfonyl)phenyl)ethanone or ketosulphone (3). This compound is known. It may be produced by a suitable process, e.g. the one described in WO9955830. The second starting material, 2-chloro-3-hydroxyacrylaldehyde is the reagent of general formula (2) described in WO9847871. This starting material is also commercially available.

Compound (4) can be obtained *in situ* when compound (2) reacts with an  $\text{NH}_2\text{YOX}$  compound (5)



wherein X is Alkyl, Aryl, O-alkyl, O-aryl or H and Y is C or S=O in a suitable solvent.

Suitable solvents are, without limitations, organic polar solvents, such as toluene, tetrahydrofuran, DMF, dichloromethane and 1,2-dichloroethane. This reaction is performed at temperatures higher than 40°C, preferably from 40 to 130°C, most preferably from 50 to 120°C, even more preferably from 50 to 100°C.

Compound (5) may suitably be an amide, a carbamate or a sulphonamide. Preferably, compound (5) is a C1-C6 alkyl amide, an O-alkyl carbamate or a formamide. Even more preferably, compound (5) is ethyl carbamate, formamide or acetamide.

Compound (4) may be isolated from the reaction mixture and optionally purified.

Surprisingly, it has been found that when the OH-group from compound (2) is derivatized with an NH<sub>2</sub>YOX compound (5) to form compound (4), the conditions for the condensation reaction with compound (3) are much improved. The process of the invention allows milder reaction conditions and/or provides higher yields than the reactions disclosed in the prior art. The prior art reactions proceed at 130 or 140°C, while the process of the present invention can be carried out at temperatures higher than 50°C, preferably from 50 to 130°C, most preferably from 50 to 120°C, even more preferably from 50 to 100°C.

Contrary to the reaction conditions disclosed in the prior art where a high excess of acid is needed, in the process of the invention not as much extra acid is needed, or the reaction can be performed with only a catalytical amount of acid or even without acid. Suitable acids are, without limitations, a sulphonate acid such as methanesulfonic acid or tosylsulphonic acid.

Furthermore, the use of ammonia is not needed. Whereas the yield reported in the prior art (WO9847871, page 11) is only 55%, the yield obtained in the process of the invention may be 70% or higher.

A specific aspect of the present invention provides a novel compound of formula (4), useful as an intermediate for preparing etoricoxib of formula (1). The group (X) and (Y) from compound (4) are as defined above.

Compound (6) can be obtained by reaction of ketosulphone (3) with a compound of formula (4), with or without the addition of an acid catalyst. Suitable acids are, without limitations, a sulphonate acid such as methanesulfonic acid or tosylsulphonic acid. The condensation is performed in the presence of a non-reactive solvent. Suitable solvents are, without limitations, organic polar solvents, such as toluene, tetrahydrofuran, DMF, dichloromethane and 1,2-dichloroethane. In particular, intermediate (6) may be obtained by reaction of the compound of formula (3) with N-(2-chloro-3-oxopropyl)formamide (4) in the presence of methanesulfonic acid and 1,2-dichloroethane. Compound (6) can be further heated to form the desired etoricoxib of formula (1). If desired or advantageous, the etoricoxib obtained can be recrystallized.

If desired or advantageous, the compound of formula (6) may be isolated from the reaction mixture as such or in the form of a salt, and optionally purified.

In a specific aspect of the invention, a novel compound of formula (6), useful for preparing etoricoxib of formula (1) is provided. The group (X) and (Y) are as defined above.

The two steps of the reaction (from (2) to (4) and to etoricoxib) are performed at temperatures higher than 50°C, preferably from 50 to 130°C, most preferably from 50 to 120°C, even more preferably from 50 to 100°C.

In a preferred embodiment the reaction can be performed in one pot.

Etoricoxib, produced according to the process of the present invention or otherwise obtainable by a process which includes the use of any of the compounds of formulas (4) or (6) as

a starting material or intermediate, may be advantageously provided in an isolated, typically solid and crystalline form, details of which procedures are known in the art. Accordingly, the obtained etoricoxib may be used in pharmaceutical compositions, e.g. for the treatment of inflammatory diseases.

5           The invention will be further described with reference to the following non-limiting examples.

## EXAMPLES

### Example 1

#### 10           **Synthesis ethyl (2-chloro-3-oxoprop-1-en-1-yl)carbamate (compound 4)**

A mixture of 2-chloromalonaldehyde (5.0 g, 46.9 mmol), ethyl carbamate (4.5 g, 50.5 mmol) in the presence of sulfuric acid (0.2 ml, 3.75 mmol) in tetrahydrofuran (50 ml) was stirred at 50°C over night.

15           After cooling down to ambient temperature, isopropylether (25 ml) was added, followed by water (10 ml). The mixture was stirred for 10 min. The separated organic layer was washed again with brine (10 ml), dried and concentrated to give a solid product (8.45 g).

### Example 2

#### 20           **Synthesis diethyl ((1Z,3E)-2-chloro-4-(4-(methylsulfonyl)phenyl)-5-oxo-5-(pyridin-3-yl)penta-1,3-diene-1,3-diyl)dicarbamate (compound 6)**

A mixture of ethyl 2-chloro-3-oxoprop-1-enylcarbamate (200 mg), 1-(6-methylpyridin-3-yl)-2-(4-(methylsulfonyl)phenyl)ethanone (200 mg), ethyl carbamate (2 g) and propionic acid (0.1 ml) in CHCl<sub>3</sub> (1 ml) was stirred at 140°C for 2 hrs and 20 min.

CHCl<sub>3</sub> (0.5 ml) was added, and the mixture was further stirred at 110°C over night. The reaction mixture was diluted in DCM, washed twice with water, base (5%NaOH), water, dried and concentrated to give a dark mixture. The crude product was partly purified by chromatography. It was further isolated by prep. HPLC and the structure was proved by MS.

### 5      **Example 3**

#### **Synthesis of etoricoxib in a one-pot reaction**

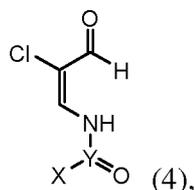
A mixture of 2-chloro-3-hydroxyacrylaldehyde (2 g), 1-(6-methylpyridin-3-yl)-2-(4-(methylsulfonyl)-phenyl)ethanone (2 g), formamide (4 ml), methanesulfonic acid (0.5 ml) and 1,2-dichloroethane (2 ml) was stirred (80°C heating block) for 20 hrs and further stirred at  
10 (100°C heating block) for 4 hrs.

After cooling down to ambient temperature, water (10 ml) was added, followed by addition of ethyl acetate (25 ml) and ether (25 ml). The mixture was stirred for 15 min, and layers were separated. The water layer was extracted with ethyl acetate (50 ml). Combined organic layers were washed with water (10 ml), dried and concentrated to give a crude product (3 g).

15 The above material was re-dissolved in ethyl acetate (30 ml) and treated with HCl 1M (10 ml) for 10 min. Separated ethyl acetate layer was extracted again with 1M HCl (5 ml). Combined water layers were basified to pH 7 by addition of NaOH solution (2M), and extracted with ethyl acetate (50 ml). The combined ethyl acetate layers were washed with water, brine, dried and concentrated to give desired product (1.81 g, solid), yield 73%.

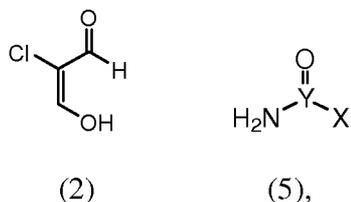
## CLAIMS

1. A compound of formula (4)



wherein X an alkyl, aryl, O-alkyl, O-aryl or H-group and Y is C or S=O.

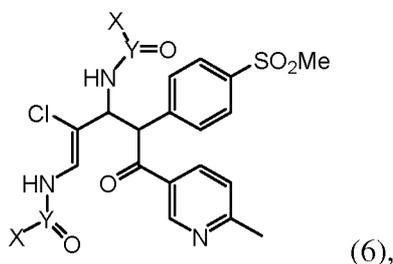
- 5 2. A process for making a compound of formula (4) comprising reacting in a suitable solvent a compound of formula (2) with a compound of formula (5)



wherein X is an alkyl, aryl, O-alkyl, O-aryl or H-group and Y is C or S=O.

- 10 3. The process according to claim 2, wherein the compound of formula (5) is ethylcarbamate or formamide.

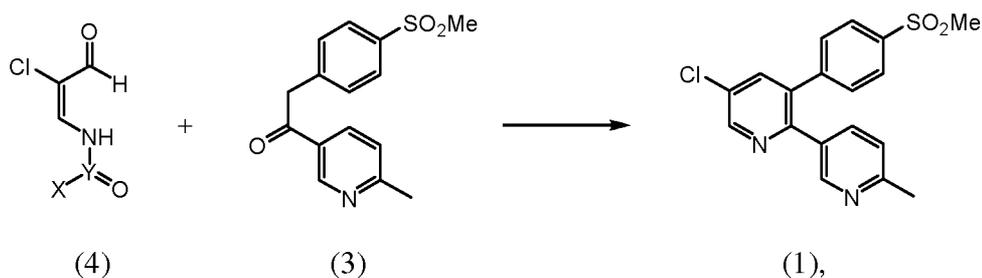
4. A compound of formula (6) or a salt thereof



wherein X is an alkyl, aryl, O-alkyl, O-aryl or H-group and Y is C or S=O, preferably

- 15 where X is an O-alkyl or O-aryl and Y is C.

5. A process for making etoricoxib of formula (1) comprising the step of reacting in a suitable solvent a compound of formula (3) with a compound of formula (4).



wherein X in the compound of formula (4) is an alkyl, aryl, O-alkyl, O-aryl or H-group and Y is C or S=O.

- 5 6. The process according to claim 5, wherein the suitable solvent is 1,2-dichloroethane.
7. The process according to claim 5 or 6, wherein the compound of formula (4) is prepared according to the process of claim 2 or 3.
8. The process according to any one of claims 5 to 7, wherein an acid is added in a catalytic amount, preferably methanesulfonic acid.
- 10 9. The process according to any one of claims 5 to 8 performed as a one-pot reaction.
10. The process according to any one of claims 5 to 8, wherein an intermediate compound of formula (6) is isolated.
11. Use of a compound of formula (4) for the preparation of etoricoxib.
12. Use of a compound of formula (6) for the preparation of etoricoxib.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2014/069515

A. CLASSIFICATION OF SUBJECT MATTER INV. C07C271/18 C07D213/50 C07D213/61 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) C07C 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, WPI Data, BEILSTEIN 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	WO 99/15503 A2 (MERCK & CO INC [US]; DAVIES IAN W [US]; GERENA LINDA [US]; JOURNET MIC) 1 April 1999 (1999-04-01) claims; example 1	1-12
A	----- DAVIES I W ET AL: "A PRACTICAL SYNTHESIS OF A COX-2-SPECIFIC INHIBITOR", THE JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 65, 1 January 2000 (2000-01-01), pages 8415-8420, XP002326845, ISSN: 0022-3263, DOI: 10.1021/J0000870Z the whole document -----	1-12
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search  17 November 2014	Date of mailing of the international search report  25/11/2014	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Zervas, Brigitte	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/069515

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