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(54) **Title**: A PROCESS FOR THE PREPARATION OF LENALIDOMIDE

(57) **Abstract**: Improvements in the preparation process of 3-(4-amino-1-oxo-1,3-dihydro-2H- isoindol-2-yl)piperidine-2,6-dione (Ienalidomide), wherein the intermediate 2-methyl- 3-nitrobenzoic acid methyl ester is brominatcd with N-bromosuccinimide in methyl acetate and the end product is obtained from 3-(4-nitro-l-oxo-l,3-dihydro- 2H-isoindol-2-yl)piperidine-2,6-dione by reducing with iron and ammonium chloride reducing system.

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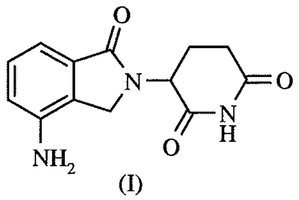
A PROCESS FOR THE PREPARATION OF LENALIDOMIDE

TECHNICAL FIELD

[0001] The invention relates to a process for the preparation of pharmacologically active substance. In particular, the invention relates to the preparation process of anticancer agent lenalidomide (I).

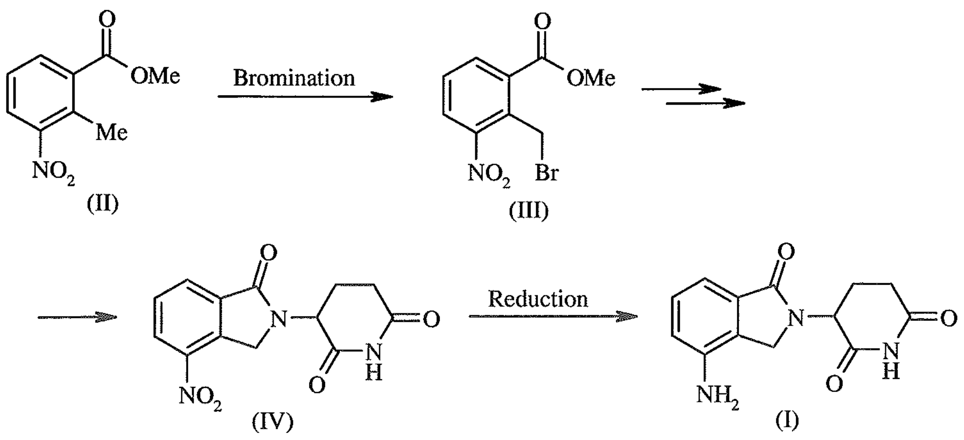
BACKGROUND ART

[0002] Lenalidomide or (RS)-3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-piperidine-2,6-dione (I) is an immunomodulator designed for the various types of melanomas and certain myelodysplastic syndrome subtypes causing anemia [1].



(I)

[0003] The main steps in the preparation process of lenalidomide (I) are bromination of 2-methyl-3-nitrobenzoic acid methyl ester (II) to yield 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) and reduction of nitro group of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (IV).

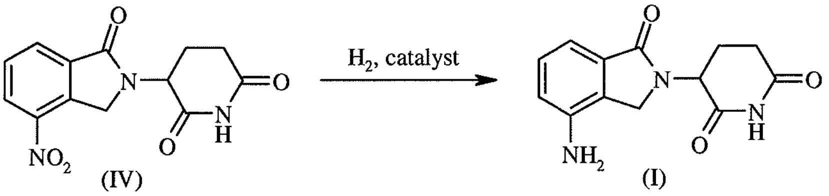


[0004] Known methods of obtaining the intermediate (III) of lenalidomide involve bromination by the free-radical mechanism, which usually occurs at temperatures between 90 to 140°C, using bromine source (bromine or N-bromosuccinimide) and a radical initiator (benzoyl peroxide [1, 2], 2,2'-azobisizobutyronitrile [3, 21]), light [4] or a combination of radical initiator and light [5].

For successful reaction it is necessary to use inert chlorine-containing solvents such as carbon tetrachloride, chlorobenzene, dichlorobenzene, dichlormethane, dichloroethane, chloroform.

It is known that these solvents are hazardous to health and environment, also their price is higher than that of the chlorine-free solvents, as well as their use requires additional expenses on disposal and environmental pollution control.

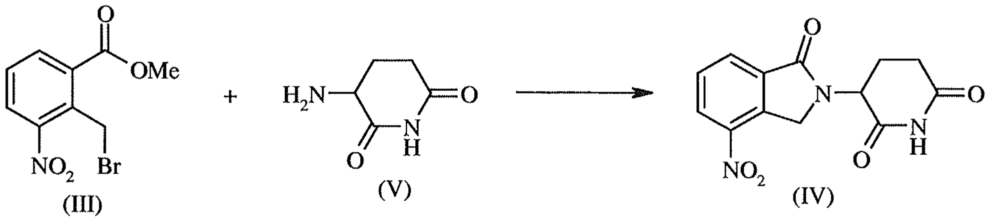
[0005] The most convient precursor for the preparation of lenalidomide is 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (IV). The most common conditions for the conversion of the starting material is reduction of a nitro group by catalytic hydrogenation [6–15, 23].



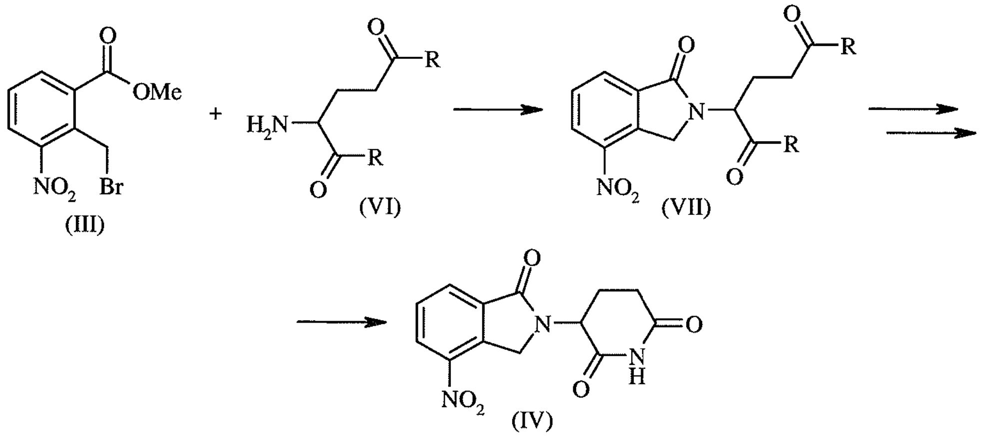
[0006] The catalytic hydrogenation requires the use of transition metal catalysts (Pd/C, PtO_2) and hydrogen as a reductant. This raises the product's overall cost due to necessarity to install specialized hydrogenation equipment and safety devices for the work with the explosive gases. Also it is requred to control the impurity level of transition metals in the final product. During the reaction, products of partial reduction of nitro group, as well as diproportionation products of intermediate nitrozo compounds, are formed. Product purification from the structurally related byproducts is a very complex process, which adversely affects product yield and raises the expenses of the process.

[0007] Other known non-catalytic process for the preparation of lenalidomide is reduction of nitro compound (IV) with an iron in hydrochloric acid, thus obtaining a lenalidomide hydrochloride (V), which is further treated with the aqueous ammonia yielding the desired product lenalidomide base (I) [20].

[0008] 3-(4-Nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (IV) might be obtained by different methods and routes. In publications [22, 23], as well as in patents [16–19] the intermediate (IV) is obtained by cyclization of 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) and 3-aminopiperidine-2,6-dione (V).

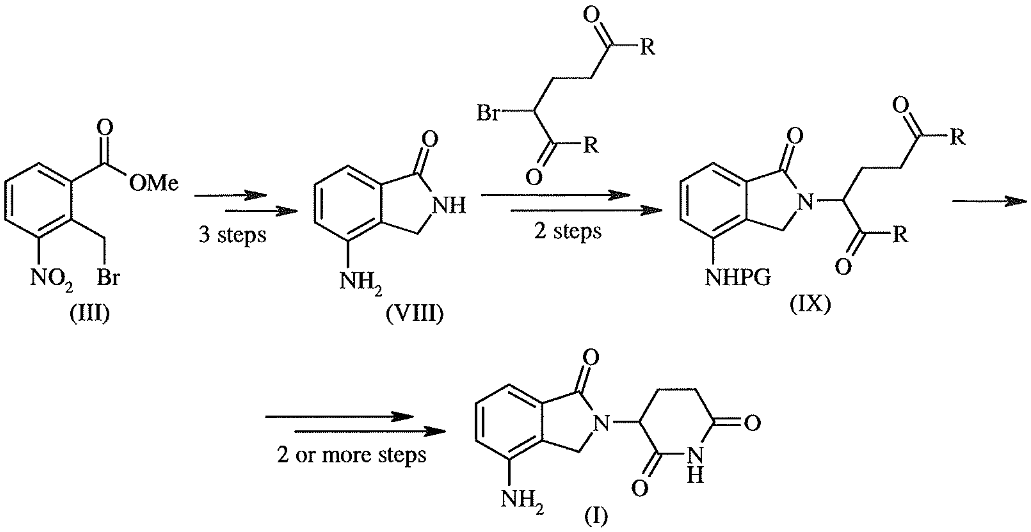


[0009] Another synthetic path is described in the patent [11] for the synthesis of precursor (IV) by using different glutamine and glutamic acid derivatives (VI): their reaction with 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) yielded compounds (VII), which were cyclized to provide lenalidomide intermediate (IV). Hence, lenalidomide can be obtained as fast as in four steps starting from the 2-methyl-3-nitrobenzoic acid methyl ester (II).



R = OH, OMe, NH_2

[0010] Another route, that is much longer and less beneficial, is described in patent [8]. This synthetic route involves cyclization of the 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) and the reduction of nitro group, thereby obtaining 4-aminoisoindoline-1-one (VIII). After the protection of amino group and alkylation of the amide with 2-bromoglutaric acid derivatives compound (IX) is obtained, which is cyclized and upon cleavage of the protecting group, yielded lenalidomide (I). One of the most suitable protecting groups used in such reactions, as well as it is described in the patent [8], is benzyloxycarbonyl group (Cbz), which usually is removed by catalytic hydrogenation.



R = OH, OMe, NH_2; PG – protecting group (Cbz or other)

[0011] As follows from the previous schemes, 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) is a key intermediate in the overall synthetic scheme of lenalidomide (I) regardless of the synthetic route.

Considering that this compound is synthesized at the early stages of the process, it has to be synthesized in bulk quantities, which requires using of a large amount of halogen-containing solvent. It makes the overall lenalidomide production process pricier by increasing the costs of solvents and disposal. The aforementioned requires the search of other synthetic methods that could make the process cheaper and environmentally cleaner, thus making the end product – lenalidomide – more accessible to cancer patients.

[0012] If lenalidomide is obtained by hydrogenation of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (IV) in the presence of transition metals, it usually contains a significant amount of partial hydrogenation and nitroso intermediate disproportionation products as well as residual amounts of transition metals. In order to obtain a pharmaceutical grade product it should be recrystallized several times, or converted in the form of a salt, purified, and then converted into a base. The most challenging task is to remove metal impurities, because their acceptable levels in the final product are counted in parts per million.

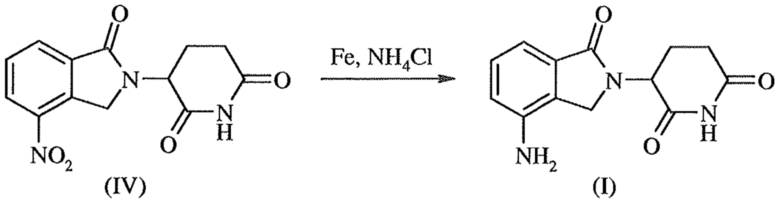
[0013] In the case of reduction of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-piperidine-2,6-dione (IV) with iron in hydrochloric acid, lenalidomide hydrochloride is obtained, which is soluble in water and it is problematic to separate it from iron salts. In this case, in order to obtain lenalidomide in a base form it is necessary to neutralize the hydrochloride with a stronger base, but this process is problematic due to a large amount of iron hydroxide, which formed during neutralization process. All previously mentioned additional purification procedures reduce the product yield and increase the cost of the technological process.

SOLUTION OF PROBLEM

[0014] We unexpectedly found, that the known lenalidomide preparation process can be improved with new routes of obtaining 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) and the final product.

[0015] 2-(Bromomethyl)-3-nitrobenzoic acid methyl ester (III) can be obtained from the 2-methyl-3-nitrobenzoic acid methyl ester (II) using halogen-free solvent – methyl acetate. This newly developed method has several advantages: the process takes place at a relatively low temperature (57°C) and the product obtained in almost quantitative yield, high purity, and without additional purification (98% by HPLC). Considering that 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III) is indispensable raw material for the synthesis of lenalidomide, this method allows to achieve a significant reduction in use of environmentally harmful solvents in the process, as well as it avoids safety measures associated with their use and disposal, thus reducing the total cost of the lenalidomide synthesis. Methyl acetate has limited citations as a solvent for radical bromination reaction.

[0016] Also, we found that the final product – lenalidomide – can be obtained by the reduction of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (IV) with ammonium chloride and iron. It is remarkable that lenalidomide (I) can be obtained by this method with very low impurity content (~2% by HPLC). Moreover, it is obtained in the base form, that is impossible when using metal–acid system. Advantage of the invention is a low cost (iron and ammonium chloride are cheap and easy to store), short reaction time (4 hours) and high efficiency (high yields of a product, purity of the raw product ~98%). Cycle opening side reactions are not typical for this method. By using a simple recrystalization it is possible to obtain pharmaceutical grade product with a total yield of around 80%.



[0017] Example 1

Preparation of 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (III).

2-Methyl-3-nitrobenzoic acid methyl ester (100.0 g, 0.51 mol) is loaded in a reactor equipped with reflux condenser and mechanical stirrer, then N-bromosuccinimide (134.0 g, 0.75 mol) and methyl acetate (1.0 L) are added. 2,2'-Azobisisobutyronitrile (8.4 g, 0.05 mol) is added to the resulting suspension which then is refluxed and stirred for 18 hours (the reaction temperature is 57°C). Next, the reaction mixture is cooled, washed with 10% Na_2SO_3 aq. solution, then with 10% NaCl aq. solution. The organic layer is filtered and evaporated and to obtain orange-yellow oil. A mixture of isopropyl alcohol and water (2:1, 90 mL) is added to the product immediately after evaporation, and the mixture is stirred at room temperature, that results in the crystallization of the product. The precipitate is filtered and dried for 6 hours at 50–55°C in vacuum (10–20 mbar). Yield 138.0 g (98%), pale yellow crystals, purity 98% (by HPLC).

[0018] Example 2

Preparation of lenalidomide (I).

Ammonium chloride (95.6 g, 1.76 mol) is dissolved in water (580 mL). After that, 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (65.0 g, 0.22 mol) and ethanol (2,9 L) are added. The reaction mixture is heated to 60°C and iron powder (49.0 g, 0.88 mol) is added with stirring. The reaction mixture is stirred at 80°C for 4 hours, then filtered hot; the precipitate washed twice with hot ethanol–water mixture

(50 mL water + 150 mL ethanol). The filtrate is evaporated, water (200 mL) is added to dry residue, and the mixture is stirred for 30 min. The precipitated product is filtered off and washed twice with water (50 mL). The raw product is boiled for 2.5 hours in a mixture of ethanol (900 mL) and water (600 mL), then activated charcoal (6 g) is added, and the mixture is boiled for 1 hour more. The hot mixture is filtered, the filtrate is allowed to crystallize at temperature 0–5°C, and the precipitated product is filtered off. Obtained product is dried for 6 hours at 60°C under 15–20 mbar pressure. Yield 47.6 g (84%), pale yellow substance, purity 99.8% (by HPLC).

[0019] If necessary, the product can be recrystallized from water, methanol, acetone or other solvents to obtain the required polymorph.

[0020] All methods can be realized in industrial production, yielding important pharmaceutically active substance for treating various types of cancer by cost-effective and environmentally-friendly production methods.

CITATION LIST

PATENT LITERATURE

1. US2003/139451 A1, 2003
2. WO2010/56344 A1, 2010
3. US2010/10060 A1, 2010
4. US6335/349 B1, 2002
5. US5534481 A1, 1996
6. US6335/349 B1, 2002
7. WO2009/114601 A2, 2009
8. WO2010/139266 A1, 2010
9. WO2010/56384 A1, 2010
10. WO2011/50962 A1, 2011
11. WO2011/27326 A1, 2011
12. WO2011/69608 A1, 2011
13. US2011/237802 A1, 2011
14. US2011/223157 A1, 2011
15. US2012/71509 A1, 2012
16. WO2010/100476A2, 2010
17. WO2011/27326A1, 2011
18. WO2011/111053A1, 2011
19. US2012/71509A1, 2012
20. WO2010/61209 A1, 2010

NON-PATENT LITERATURE

21. *Bioorg. Med. Chem. Lett.*, **14**, 81 (2004).
22. *Bioorg. Med. Chem. Lett.*, **9**, 1625 (1999).
23. *Bioorg. Med. Chem. Lett.*, **3**, 1019 (2011).

CLAIMS

1. A process for the preparation of 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione (lenalidomide), involving bromination of 2-methyl-3-nitrobenzoic acid methyl ester, reaction of the obtained 2-(bromomethyl)-3-nitrobenzoic acid methyl ester with 3-aminopiperidine-2,6-dione, and reduction of obtained 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione to 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-piperidine-2,6-dione, characterized by that the bromination of 2-methyl-3-nitrobenzoic acid methyl ester is performed with N-bromosuccinimide in methyl acetate and the reduction of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione is performed with an iron and ammonium chloride reducing system.

2. A process according to claim 1, wherein bromination of 2-methyl-3-nitrobenzoic acid methyl ester is performed at the boiling point of methyl acetate in the presence of radical formation initiator – 2,2'-azobisisobutyronitrile.

3. A process according to claim 1, wherein the solvent in the reduction phase of 3-(4-nitro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione is methanol, ethanol, 2-propanol, 1-butanol or water; more preferable – mixture of ethanol and water.

INTERNATIONAL SEARCH REPORT

International application No
PCT/LV2014/000010

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04
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	MULLER G W ET AL: "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 9, no. 11, 7 June 1999 (1999-06-07), pages 1625-1630, XP004169632, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(99)00250-4 cited in the application scheme 2 -----	1-3
A	WO 2011/111053 A1 (NATCO PHARMA LTD [IN]; KONAKANCHI DURGA PRASAD [IN]; GONGALLA BUCHAPPA) 15 September 2011 (2011-09-15) cited in the application examples 1-3 ----- -/--	1-3

☒ 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 13 November 2014	Date of mailing of the international search report 27/11/2014
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 Brandstetter, T

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. N. BALAEV ET AL: "Alternative synthesis of lenalidomide", PHARMACEUTICAL CHEMISTRY JOURNAL, vol. 46, no. 11, 1 February 2013 (2013-02-01), pages 676-678, XP055152353, ISSN: 0091-150X, DOI: 10.1007/s11094-013-0868-7 scheme 2 -----	1-3
A	WO 2010/061209 A1 (GENERICS UK LTD [GB]; MYLAN DEV CT PRIVATE LTD [IN]; BHOSALE PRIYANKA) 3 June 2010 (2010-06-03) cited in the application example 1 -----	1-3
A	LUKE W. JUDD ET AL: "From cholapod to cholaphane transmembrane anion carriers: accelerated transport through binding site enclosure", CHEMICAL COMMUNICATIONS, vol. 46, no. 13, 1 January 2010 (2010-01-01), page 2227, XP055152266, ISSN: 1359-7345, DOI: 10.1039/b927005a scheme 1, step i -----	1-3
A	MARIA BARBOSA ET AL: "Synthesis and Pharmacological Evaluation of Novel Phenyl Sulfonamide Derivatives Designed as Modulators of Pulmonary Inflammatory Response", MOLECULES, vol. 17, no. 12, 1 January 2012 (2012-01-01), pages 14651-14672, XP055152660, DOI: 10.3390/molecules171214651 scheme 5, step g -----	1-3
A	EP 1 847 532 A1 (KYOWA HAKKO KOGYO KK [JP] KYOWA HAKKO KIRIN CO LTD [JP]) 24 October 2007 (2007-10-24) example 216, step 2; page 115; example 216 step 2 -----	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/LV2014/000010

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011111053 A1	15-09-2011	CA 2793312 A1	15-09-2011
		EP 2545043 A1	16-01-2013
		KR 20130038232 A	17-04-2013
		US 2013059889 A1	07-03-2013
		US 2014121245 A1	01-05-2014
		WO 2011111053 A1	15-09-2011
WO 2010061209 A1	03-06-2010	AU 2009321374 A1	03-06-2010
		CA 2741927 A1	03-06-2010
		CN 102272118 A	07-12-2011
		EP 2364305 A1	14-09-2011
		JP 2012507496 A	29-03-2012
		US 2011263649 A1	27-10-2011
		WO 2010061209 A1	03-06-2010
EP 1847532 A1	24-10-2007	AU 2006209712 A1	03-08-2006
		CA 2596527 A1	03-08-2006
		CN 101111483 A	23-01-2008
		EP 1847532 A1	24-10-2007
		ES 2426482 T3	23-10-2013
		JP 4257389 B1	22-04-2009
		JP 2009108069 A	21-05-2009
		KR 20070108881 A	13-11-2007
		US 2009054508 A1	26-02-2009
		WO 2006080450 A1	03-08-2006