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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: LOSMAPIMOD FOR USE IN TREATING GLOMERULAR DISEASE

(57) Abstract: The use of a compound known in the art as a p38 kinase inhibitor in the treatment of a glomerular disease.

LOSMAPIMOD FOR USE IN TREATING GLOMERULAR DISEASE

Field of the Invention

This invention relates to a new pharmaceutical use of a compound which is known in the art as a p38 kinase inhibitor. More specifically this invention relates to the use of a nicotinamide derivative in the treatment of one or more glomerular disease(s) or conditions exhibiting glomerular pathology.

Background of the Invention

Many diseases affect kidney function by attacking the glomeruli, the clusters of looping blood vessels within the kidney where blood is cleaned/filtered. Glomerular diseases are those in which the glomeruli are no longer fulfilling this function. Damage to the glomeruli affects the kidney's ability to filter fluids and wastes properly. This leads to blood (hematuria) and/or protein (proteinuria) in the urine. Glomerular diseases are often associated with the signs and symptoms of nephrotic syndrome and predispose to acute renal failure, or progressive chronic kidney disease culminating in end-stage renal disease with dialysis or kidney transplantion.

Glomerular diseases include many conditions with a variety of differing causes but which can broadly categorised into two major categories namely, glomerulonephritis (inflammation of the tissue in the kidney that serve as a filter) and glomerulosclerosis (hardening or scarring of the blood vessels within the kidney).

Diabetic nephropathy, one of the leading causes of kidney failure in the USA, is a form of glomerular disease which is considered to be both a systemic disease, since diabetes itself is a systemic disease, and also a sclerotic diseases, because the specific damage done to the kidneys is associated with scarring.

Focal segmental glomerulosclerosis (FSGS) describes scarring in scattered regions of the kidney, typically limited to one part of the glomerulus and to a minority of glomeruli in the affected region. This condition may result from specific genetic mutations, systemic conditions, toxins or may develop as an idiopathic kidney disease.

Glomerular hypertension (or hypertensive renal disease) is a glomerular disease in which damage to the kidney is associated with chronic high blood pressure.

Current treatments for such diseases include medications that seek to control blood pressure and blood cholesterol e.g. angiotension converting enzyme inhibitors (ACE inhibitors), angiotension receptor blockers (ARBs) or statins. Despite current treatment, there still exists a need for novel therapies to halt progression of chronic kidney disease and/or treat the signs and symptoms of nephritic syndrome.

Patent application WO03/068747 (SmithKline Beecham Corporation) discloses a series of nicotinamide derivatives that are useful as p38 inhibitors. The compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide is specifically described therein. The statement of non-proprietary name adopted by the USAN Council for this compound is losmapimod.

Summary of the Invention

In a first aspect there is provided the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

In a second aspect there is provided a pharmaceutical formulation comprising the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

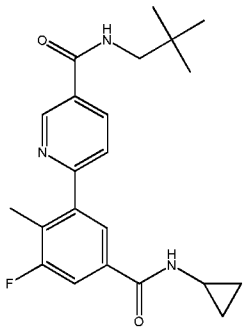
In a third aspect there is provided a combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof and one or more other therapeutic agents which are suitable for the treatment of a glomerular disease.

In a fourth aspect there is provided a method for treating a glomerular disease in a subject in need thereof which comprises administering to said subject the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof.

In a fifth aspect there is provided the use of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a glomerular disease.

Detailed Description of the Invention

According to the present invention there is provided the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide, that is to say, the compound having the formula (I)



(I)

or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

In one embodiment the glomerular disease is glomerulonephritis.

In one embodiment the glomerular disease is glomerulosclerosis.

In a particular embodiment the glomerular disease is focal segmental glomerulosclerosis (FSGS).

In a particular embodiment the glomerular disease is diabetic nephropathy.

In a particular embodiment the glomerular disease is glomerular hypertension.

In a further particular embodiment the glomerular disease is selected from the group consisting of systemic lupus erythematosus (SLE), IgA nephropathy, Goodpasture Syndrome, membrous nephropathy, hereditary renal disease, infection related glomerular disease, chronic pyelonephritis, Alport's Syndrome, periarteritis nodosa nephritis associated with amyloidosis, glomerular disease caused by HIV and toxins.

The compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof may be prepared according to procedures described in patent application WO03/068747 (as example 36).

Pharmaceutically acceptable salts of the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide are non toxic salts and include examples described in patent application WO03/068747, the contents of which is incorporated by reference. For a review of suitable pharmaceutically acceptable salts see also Berge *et al.*, J. Pharm. Sci., 66:1-19, (1977).

In one embodiment the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide is in the form of a free base.

Whilst it is possible for the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof to be administered as the raw chemical it would typically be administered in the form of a pharmaceutical composition. 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt may therefore be formulated for administration in any suitable manner that is known to those skilled in the art. It may, for example, be formulated for topical administration, transdermal administration, administration by inhalation, oral administration or parenteral administration (e.g. intravenously, intravascularly or subcutaneously). Suitable methods for formulating 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt include those described in patent application WO03/068747 and / or the methods that are familiar to

those skilled in the art, which are described in Remington: The Science and Practice of Pharmacy, 21st Edition 2006.

In a further aspect there is provided a pharmaceutical formulation comprising the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

In one embodiment there is provided a pharmaceutical formulation comprising the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of focal segmental glomerulosclerosis (FSGS).

In one embodiment the pharmaceutical formulation is adapted for oral administration.

In a particular embodiment 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof is administered orally with a dosage in the range 1 mg twice per day (bid) to 30 mg twice per day (bid), particularly 2.5 mg twice per day (bid) to 15mg twice per day (bid), even more particularly 7.5mg twice per day (bid) or 15mg twice per day (bid).

The present invention also provides for a method for treating a glomerular disease in a subject in need thereof which comprises administering the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt.

Suitably the subject in need thereof is a mammal, particularly a human.

In one embodiment there is provided a method for treating a glomerular disease in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof.

In a particular embodiment there is provided a method for treating focal segmental glomerulosclerosis (FSGS) in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof.

As used herein, the term "therapeutically effective amount" means that amount of a 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore,

the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Also provided is the use of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a glomerular disease.

In a particular embodiment there is provided the use of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of focal segmental glomerulosclerosis (FSGS). It will be appreciated that 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof may be employed alone or in combination with other therapeutic agents which are suitable for the treatment of a glomerular disease.

Therefore, the present invention further provides a combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof and one or more other therapeutic agents which are suitable for the treatment of a glomerular disease.

In a particular embodiment there is provided a combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof and one or more other therapeutic agents which are suitable for the treatment of focal segmental glomerulosclerosis (FSGS).

6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide and the other therapeutically active agent(s) may be administered together or separately and, when administered separately, this may occur simultaneously or sequentially in any order. The amounts of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical

characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

In one embodiment there is provided a combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide, or a pharmaceutically acceptable salt thereof, together with an ACE inhibitor, ARB or a statin.

In a further embodiment there is provided a combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide, or a pharmaceutically acceptable salt thereof, together with a corticosteroid or a calcinerun inhibitor (e.g. tacrolimus).

The following example illustrates the invention.

Example 1

A pharmaceutical formulation of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide (losmapimod) suitable for oral administration

A representative formulation for use in this invention is shown in the table below.

Component	**mg /tablet**	**% w/w**
Intragranular		
6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide (micronized)	7.5	5.0
Lactose Monohydrate	67.9	45.3
Microcrystalline Cellulose	30.0	20.0
Sodium Starch Glycolate	4.5	3.0
Povidone	4.5	3.0
Extragranular		
Microcrystalline Cellulose	30.0	20.0
Sodium Starch Glycolate	4.5	3.0
Magnesium Stearate	1.125	0.75
Core Compression Weight	150 mg	
Film Coat		
Opadry White OY-S-28876	4.5	3.0

Example 2

An efficacy, safety and tolerability study relating to losmapimod in the treatment of primary (idiopathic) focal segmental glomerulosclerosis (FSGS)

This evaluation may be carried out by treatment of FSGS patients having nephrotic range proteinuria (urinary protein/creatinine [Up/c] ratio > 3) and a history of steroid resistance, including relapse of proteinuria after steroid treatment (n = approximately 20). Losmapimod is orally administered twice daily over a 24-week treatment phase (7.5 mg BID for 2 weeks followed by 15 mg BID for 22 weeks). The primary efficacy endpoint of proteinuria is evaluated by the measurement of the Up/c ratio, assessed from a first morning urine sample, with a responder being a patient with a 50% proteinuria reduction from baseline at the end of treatment. Safety and tolerability is monitored by clinical laboratory evaluations (including liver function tests and serum creatinine), vital signs, ECGs, and adverse events.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Claims:

1. The compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

2. The compound according to claim 1 in which the glomerular disease is focal segmental glomerulosclerosis (FSGS).

3. The compound according to claim 1 in which the glomerular disease is diabetic nephropathy.

4. The compound according to claim 1 in which the glomerular disease is glomerular hypertension.

5. The compound according to claim 1 in which the glomerular disease is selected from the group consisting of systemic lupus erythematosus (SLE), IgA nephropathy, Goodpasture Syndrome, membrous nephropathy, hereditary renal disease, infection related glomerular disease, chronic pyelonephritis, Alport's Syndrome, periarteritis nodosa nephritis associated with amyloidosis, glomerular disease caused by HIV and toxins.

6. The compound according to any one of claims 1 – 5 which is in the form of a free base.

7. A pharmaceutical formulation comprising the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof for use in the treatment of a glomerular disease.

8. A pharmaceutical formulation according to claim 7 which is adapted for oral administration.

9. A combination product comprising 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof and one or more other therapeutic agents which are suitable for the treatment of a glomerular disease.

10. A method for treating a glomerular disease in a subject in need thereof which comprises administering to said subject the compound 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof.

11. The use of 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a glomerular disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/064508

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/455 A61K45/06 A61P13/12
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)
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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/014706 A1 (GLAXOSMITHKLINE LLC [US]) 23 January 2014 (2014-01-23) page 9, lines 19-26	9

X	WO 03/068747 A1 (SMITHKLINE BEECHAM CORP [US]; ASTON NICOLA MARY [GB]; BAMBOROUGH PAUL) 21 August 2003 (2003-08-21) cited in the application	1,6-11
Y	page 18, lines 1-12 page 22, line 6 - page 23, line 3 page 23, lines 17-18 example 36 page 66, line 16 - page 67, line 22 claims 10, 12	2-5

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2014	25/09/2014

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	Herdemann, Matthias

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/144390 A1 (SMITHKLINE BEECHAM CORP [US]; CORSI MAURO [IT]; FAIFERMAN ISIDORE [US]) 21 December 2007 (2007-12-21)	9
Y	page 9, line 32 - page 10, line 4	1-8,10, 11

Y	C. STAMBE: "p38 Mitogen-Activated Protein Kinase Activation and Cell Localization in Human Glomerulonephritis: Correlation with Renal Injury", JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 15, no. 2, 1 February 2004 (2004-02-01), pages 326-336, XP055140252, ISSN: 1046-6673, DOI: 10.1097/01.ASN.0000108520.63445.E0 abstract page 327, left-hand column, paragraph 2 tables 1-2	1-8,10, 11

Y	OLZINSKI A R ET AL: "Hypertensive target organ damage is attenuated by a p38 MAPK inhibitor: role of systemic blood pressure and endothelial protection", CARDIOVASCULAR RESEARCH, OXFORD UNIVERSITY PRESS, GB, vol. 66, no. 1, 1 April 2005 (2005-04-01), pages 170-178, XP027645592, ISSN: 0008-6363 [retrieved on 2005-04-01] abstract page 170, left-hand column, paragraph 1 - page 171, left-hand column, paragraph 1 page 172, right-hand column, paragraph 2	1,4,6-8, 10,11

Y	R. N. WILLETTE ET AL: "Differential Effects of p38 Mitogen-Activated Protein Kinase and Cyclooxygenase 2 Inhibitors in a Model of Cardiovascular Disease", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 330, no. 3, 1 September 2009 (2009-09-01), pages 964-970, XP055075774, ISSN: 0022-3565, DOI: 10.1124/jpet.109.154443 abstract figures 1, 4	1-8,10, 11

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1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	COULTHARD L R ET AL: "p38<MAPK>: stress responses from molecular mechanisms to therapeutics", TRENDS IN MOLECULAR MEDICINE, ELSEVIER CURRENT TRENDS, GB, vol. 15, no. 8, 1 August 2009 (2009-08-01) , pages 369-379, XP026471469, ISSN: 1471-4914, DOI: 10.1016/J.MOLMED.2009.06.005 [retrieved on 2009-08-06] table 3 -----	1-8,10, 11
A	THOMAS N J ET AL: "Chronic type IV phosphodiesterase inhibition protects glomerular filtration rate and renal and mesenteric blood flow in a zymosan-induced model of multiple organ dysfunction syndrome treated with norepinephrine", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, vol. 296, no. 1, 1 January 2001 (2001-01-01), pages 168-174, XP002278930, ISSN: 0022-3565 abstract -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/064508

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014014706 A1	23-01-2014	NONE	
WO 03068747 A1	21-08-2003	AT 375980 T	15-11-2007
		AT 485275 T	15-11-2010
		AU 2003207298 A1	04-09-2003
		BR 0307351 A	14-12-2004
		CA 2474192 A1	21-08-2003
		CN 1633416 A	29-06-2005
		CO 5611147 A2	28-02-2006
		DE 60316913 T2	20-11-2008
		DK 1474395 T3	11-02-2008
		DK 1864975 T3	24-01-2011
		EP 1474395 A1	10-11-2004
		EP 1864975 A2	12-12-2007
		EP 2258687 A1	08-12-2010
		ES 2295553 T3	16-04-2008
		ES 2400486 T3	10-04-2013
		HK 1070896 A1	01-08-2008
		HK 1113056 A1	07-10-2011
		IL 163090 A	16-06-2010
		IS 7337 A	28-06-2004
		JP 4472349 B2	02-06-2010
		JP 2005519932 A	07-07-2005
		JP 2010111699 A	20-05-2010
		KR 20040082425 A	24-09-2004
		MX PA04007838 A	15-10-2004
		NO 327418 B1	22-06-2009
		NZ 533865 A	24-02-2006
		PL 212910 B1	31-12-2012
		PT 1474395 E	02-01-2008
		PT 1864975 E	27-12-2010
		RU 2309951 C2	10-11-2007
		SI 1474395 T1	29-02-2008
		SI 1864975 T1	31-01-2011
		US 2005176964 A1	11-08-2005
		US 2006264479 A1	23-11-2006
		US 2006276516 A1	07-12-2006
		US 2010215652 A1	26-08-2010
		US 2010215661 A1	26-08-2010
		WO 03068747 A1	21-08-2003
WO 2007144390 A1	21-12-2007	AT 494008 T	15-01-2011
		AU 2007259224 A1	21-12-2007
		CA 2657390 A1	21-12-2007
		CN 101500567 A	05-08-2009
		EA 200900034 A1	30-06-2009
		EP 2029139 A1	04-03-2009
		ES 2358931 T3	16-05-2011
		JP 2010528980 A	26-08-2010
		KR 20090020703 A	26-02-2009
		US 2010016377 A1	21-01-2010
		WO 2007144390 A1	21-12-2007