



- (51) **International Patent Classification:**
C07D 413/14 (2006.01) *A61P 25/20* (2006.01)
A61K 31/5513 (2006.01)
- (21) **International Application Number:**
PCT/CZ2016/000016
- (22) **International Filing Date:**
10 February 2016 (10.02.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
PV 2015-87 10 February 2015 (10.02.2015) CZ
- (71) **Applicant:** ZENTIVA, K.S. [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).
- (72) **Inventors:** DAMMER, Ondrej; Novotneho 975, 253 01 Hostivice (CZ). ZVATORA, Pavel; Rude Armady 300, 798 03 Plumlov (CZ). KREJCIK, Lukas; Moravanska 474, 190 17 Praha-Vinor (CZ). HERT, Jakub; Slejnicka 1, 160 00 Praha 6 (CZ). BERANEK, Josef; Rooseveltova 49, 160 00 Praha 6 (CZ). VRTILOVA, Sarka; Krunsnohorske namesti 1, 362 33 Hroznetin (CZ).
- (74) **Agents:** JIROTKOVA, Ivana et al.; Rott, Ruzicka & Guttman, Vinohradská 37, 120 00 Praha 2 (CZ).

- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

Published:

- with international search report (Art. 21(3))

(54) **Title:** AN AMORPHOUS SOLID FORM OF SUVOREXANT WITH SULPHURIC ACID

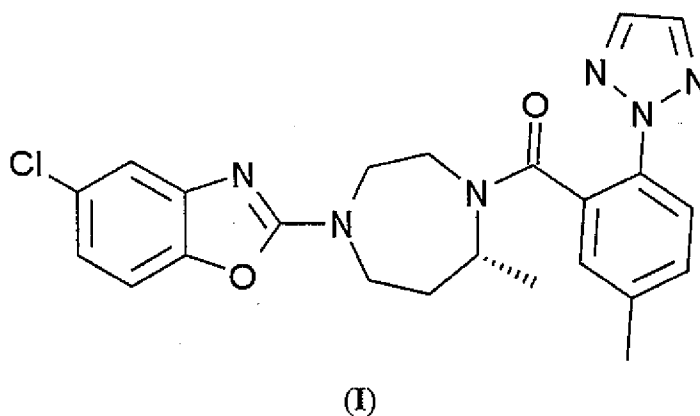
(57) **Abstract:** The invention relates to a novel, physically stable, solid form of suvorexant, chemically [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl] [5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone with sulphuric acid, methods of its preparation and a physically stable pharmaceutical composition containing this solid form.



An amorphous solid form of suvorexant with sulphuric acid

Technical Field

The invention relates to a novel, physically stable, solid form of suvorexant (I), chemically [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone, with sulphuric acid, methods of its preparation and a physically stable pharmaceutical composition containing this solid form.



Suvorexant is a highly selective antagonist of the OX1R and OX2R orexin receptors, which is used for the treatment of insomnia. The medicinal product containing suvorexant has currently been approved by FDA (U. S. Food and Drug Administration) under the name Belsomra from Merck and is available in four different strengths, namely 5, 10, 15 and 20 mg. Compared to placebo, it proved acceleration of the start of the effect, i.e. falling asleep, as well as extension of the sleeping time.

Background Art

Suvorexant and its synthesis are described in WO2008069997. A reproduction of the process described in this patent application provided a white solid substance exhibiting a diffraction pattern and melting point corresponding to Form I, later described in WO2012148553. The patent application WO2012148553 further described Form II of suvorexant. According to this patent application, both the said forms are anhydrous and enantiotropically related. Form I is thermodynamically stable at a temperature lower than 35°C while Form II is stable at a temperature higher than 40°C. The conversion temperature between the individual forms is in

the range of 35 to 40°C. The described Form II exhibits advantageous physical-chemical characteristics as compared to form I, e.g. better crystallinity, filtration properties, chemical purity. The description of preparation of Form II involves crystallization of suvorexant from an isopropyl acetate/heptane mixture with the use of sonication and inocula of Form II at a higher temperature than 40°C. However, a reproduction of this process did not provide Form II and all the crystallization experiments provided Form I. Other polymorphic forms of suvorexant, Forms A, B, C, D, E, G and H, are described in the patent application WO2014072961. This patent application further mentions examples of preparation of an amorphous form of suvorexant and its solid dispersions with pharmaceutically acceptable carriers or excipients (e.g. Povidone K-30).

Pharmaceutical compositions consisting of suvorexant or its salt and a polymer, or surfactant are described in WO2013181174. The polymer used in the composition increases solubility of suvorexant and thus its biological availability, it is soluble in water, or can be easily dispersed in water. Preparation examples of these compositions represent two processes: (i) spray drying of a solution of suvorexant and a polymer or surfactant; and (ii) hot-melt extrusion of a mixture of suvorexant, a polymer, or surfactant.

Other solid forms of salts of suvorexant have not been described yet.

Disclosure of Invention

The invention provides a stable solid form of a salt of suvorexant of formula (I), its physical-chemical characterization and methods of its preparation. The novel solid form of suvorexant with sulphuric acid exhibits a higher glass transition temperature than that of the pure amorphous suvorexant and even comparable to the melting point of the crystalline thermodynamically most stable form of suvorexant (Form I). In addition, the amorphous character of this novel salt increases the solubility (the release rate is 6 time higher compared to Form I) and thus the biological availability of the API, which makes it suitable for use in a pharmaceutical composition.

Brief Description of Drawings

Fig. 1. An X-ray powder pattern of the solid form of suvorexant with sulphuric acid (according to Example 1).

Fig. 2. An ssNMR spectrum of the solid form of suvorexant with sulphuric acid (according to Example 1).

Fig. 3. A DSC record of the solid form of suvorexant with sulphuric acid (according to Example 1).

Fig. 4. An IR spectrum of the solid form of suvorexant with sulphuric acid (according to Example 1).

Fig. 5. Comparison of the dissolution rate of suvorexant with sulphuric acid (according to Example 1), crystalline form I and amorphous suvorexant.

Detailed description of the invention

Salts of pharmaceutically active ingredients are a widely used group of solid forms due to a higher solubility and the related higher biological availability than in the case of the corresponding polymorphic (neutral) forms. Biological availability depends on the physical type of active ingredients. Generally, an active ingredient can exist as a crystalline, amorphous or semicrystalline substance. Crystalline active ingredients exhibit a long-distance order (over 100 Å), a sharp melting point and they can be described by the respective parameters of the internal structure (grid parameters, interplanar distances, positions of atoms, spatial symmetry group etc.). Amorphous and semicrystalline active ingredients exhibit a short-distance order (under 100 Å), a glass transition temperature and their structure cannot be described by any structural parameters. Thus, the X-ray powder pattern of amorphous substances exhibits a characteristic amorphous halo. Although crystalline active ingredients are more frequently used in pharmaceutical formulations as compared to amorphous substances, a higher solubility, dissolution rate and better dissolution profile of amorphous substances cause an increasingly more frequent use of these types of substances in the resulting formulations, especially in the case of substances with a low solubility.

The invention describes a solid form of suvorexant with sulphuric acid in an amorphous form, its preparation and characterization. The amorphous character of this solid form and interaction of the API with sulphuric acid significantly increases the biological availability of the API as compared to a crystalline form and thus it appears to be advantageous for use in pharmaceutical compositions.

The preparation of the novel solid form of suvorexant is based on a reaction of suvorexant with sulphuric acid. The reaction is conducted in a suitable solvent, which can be

ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water or their mixtures. Aliphatic C₁-C₄ alcohols, esters or their mixtures are preferred. The most commonly used solvents are acetone, ethanol, ethyl acetate, isopropanol, acetonitrile, tetrahydrofuran or their mixtures.

The final product is typically precipitated or crystallized at temperatures in the range of – 30°C to the boiling point of the solvent and is obtained in high yields and high chemical purity.

An X-ray powder pattern of the amorphous solid form of suvorexant with sulphuric acid (prepared according to Example 1) is shown in Figure 1.

Figure 2 shows a solid-phase NMR spectrum of the described solid form. The molar ratio of suvorexant:sulphuric acid can be in the range of 10:1 to 1:3, preferably 1:1.

A DSC record of suvorexant with sulphuric acid (prepared according to Example 1) is shown in Figure 3. According to this example it exhibits the onset temperature of glass transition at 116°C.

An infrared spectrum of sulphuric acid (prepared according to Example 1) is shown in Figure 4.

Figure 5 shows a comparison of the release rate for crystalline Form I, amorphous form and the novel solid form of suvorexant with sulphuric acid. The measured release rate of 24 µgmin⁻¹·cm⁻² for the novel solid form of suvorexant is 6 times higher than for the crystalline form I. This result indicates that suvorexant with sulphuric acid will exhibit a higher biological availability as compared to the crystalline form and a similar biological availability to the amorphous form of suvorexant.

The amorphous form of suvorexant is characterized by high chemical and polymorphic stability. The glass transition temperature of the novel solid form of suvorexant (116°C) is higher than the glass transition temperature of the amorphous form of suvorexant (67°C) and it even approximates the melting point of the crystalline Form I (119°C).

A sample of the novel solid form of suvorexant with sulphuric acid together with the amorphous form and crystalline Form I of suvorexant was loaded for three and seven days at the temperature of 60°C and the relative humidity values of 0 and 75%. The novel solid form of suvorexant exhibited polymorphic stability that was comparable to the crystalline form I – no polymorphic change was observed. However, the amorphous form exhibited a high rate of polymorphic instability – it was already after three days at the relative humidity of 0% that partial conversion to Form I was registered; at 75% humidity the conversion to Form I was

complete after three days already. After seven days, complete conversion was registered even at the zero relative humidity value. At the zero relative humidity and temperature of 60°C the chemical purity of the novel solid form of suvorexant is comparable to the chemical purity of the crystalline form I as well as the amorphous form – they exhibit similar values of the sum of chemical impurities. At a higher relative humidity value (75%) an increase of the contents of chemical impurities is registered in the solid form of suvorexant with sulphuric acid as compared to the crystalline or amorphous form of suvorexant, although no polymorphic change of the API occurs.

A dynamic vapour sorption (DVS) measurement has shown that a sample of the novel solid form of suvorexant with sulphuric acid absorbs approx. 5% of water up to 50% relative humidity. At higher relative humidity values there is more significant sorption of water vapours – approx. 12% at 80% relative humidity. When the sample was loaded by two cycles – sorption, desorption from 0 to 90% relative humidity, the polymorphic (amorphous) form did not change. Thus, the load tests and DVS measurement have shown that during handling of this form its contact with higher relative humidity values should preferably be avoided.

The prepared amorphous solid form of suvorexant with sulphuric acid in accordance with this invention can be used for the preparation of pharmaceutical compositions, especially solid dosage forms, e.g. tablets. Such pharmaceutical compositions can contain at least one excipient from the group of fillers (e.g. lactose), binders (e.g. microcrystalline cellulose), disintegrants (e.g. sodium salt of croscarmellose), lubricants (e.g. magnesium stearate), surfactants etc. These tablets can be coated with common coating compounds, e.g. polyvinyl alcohol or polyethylene glycol.

The invention is clarified in a more detailed way using the working examples below. These examples in accordance with the invention only have an illustrative character and do not restrict the scope of the invention in any respect.

Experimental part

X-ray powder diffraction

The diffraction pattern was obtained using an X'PERT PRO MPD PANalytical powder diffractometer, used radiation $\text{CuK}\alpha$ ($\lambda = 1.542 \text{ \AA}$), excitation voltage: 45 kV, anode current: 40 mA, measured range: $2 - 40^\circ 2\theta$, increment: $0.02^\circ 2\theta$ at the dwell time at a reflection of 300

s. The measurement was carried out with a flat sample that was applied onto a Si plate. 0.02 rad Soller slits, a 10mm mask and a $1/4^\circ$ fixed anti-dispersion slit were used for the correction of the primary array. The irradiated area of the sample is 10 mm, programmable divergence slits were used. 0.02 rad Soller slits and a 5.0 anti-dispersion slit were used for the correction of the secondary array.

Infrared spectroscopy

ATR (Ge – single reflection) infrared spectra of the powder samples were measured with an infrared spectrometer (Nicolet Nexus, Thermo, USA) equipped with a DTGS KBr detector, in the measurement range of $600\text{--}4000\text{ cm}^{-1}$ and the spectral resolution of 4.0 cm^{-1} . The data were obtained at 64 spectrum accumulations. The OMNIC 6.2 software was used to process the spectra.

Differential Scanning Calorimetry (DSC)

The DSC records were measured using a Discovery DSC device made by TA Instruments. The sample charge in a standard Al pot (40 μL) was between 4-5 and 5 mg and the heating rate was $5^\circ\text{C}/\text{min}$. The temperature program that was used consists of 1 min of stabilization at the temperature of 0°C and then of heating up to 220°C at the heating rate of $5^\circ\text{C}/\text{min}$ (Amplitude = 0.8°C and Period = 60 s). As the carrier gas 5.0 N_2 was used at the flow of 50 ml/min.

ssNMR

Carbon spectra of solid-state nuclear magnetic resonance were measured with the use of an Avance 400 WB Bruker device, using the CP/MAS method in a 4mm rotor at the speed of 13 kHz, normally at 25°C .

Determining the dissolution rate using the true dissolution method

The dissolution rate was measured using an Agilent 708-DS dissolution device. Disks for true dissolution with the surface area available for dissolution of 0.125 cm^2 were prepared using a Specac press. The pressing time was 30 seconds under the pressure of 1 ton. The dissolution was carried out in 500 ml of a solution with pH 1.2 (67 mM HCl, 33 mM NaCl) at the constant speed of 100 rpm. Samples were extracted in 5-minute intervals and the concentration of dissolved suvorexant was measured with an Agilent Cary 60 UV/Vis spectrophotometer at the wavelength of 280 nm.

Examples

Example 1

Preparation of suvorexant with sulphuric acid in ethyl acetate.

A 1035 mg (2.295 mmol) charge of suvorexant was dissolved in 153 ml of ethyl acetate at the room temperature. 0.126 ml (2.269 mmol) of sulphuric acid (96%) was added to this solution, which was stirred on a magnetic stirrer. After addition of sulphuric acid the occurrence of a white suspension was observed. This suspension was left to be stirred for an hour and then it was left in a fridge to cool down overnight. The next day, the cool solution was filtered with the use of vacuum filtration and the product was dried at 70°C in a vacuum drier overnight. Yield 83%.

Example 2

Preparation of suvorexant with sulphuric acid in acetonitrile.

An 805 mg (1.785 mmol) charge of suvorexant was dissolved in 160 ml of acetonitrile at the room temperature. 0.100 ml (1.801 mmol) of sulphuric acid (96 %) was added to this solution, which was stirred on a magnetic stirrer. This solution was left to be stirred for an hour and then it was left to cool down in a fridge overnight. The next day the solution was evaporated in a vacuum evaporator at the pressure of 200 mbar and the temperature of 60°C. The product was dried at 50°C in a vacuum drier overnight. Yield 97%.

Example 3

Pharmaceutical composition of the product - core

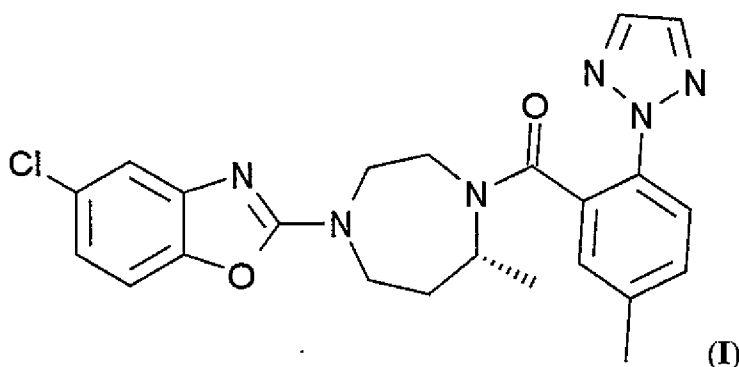
<u>Substance</u>	<u>Amount – core /mg/</u>
Suvorexant sulphate	12.2
Lactose monohydrate	34.0
Microcrystalline cellulose	67.9
Sodium crosscarmellose	12.5
Magnesium stearate	0.6

Procedure

The following ingredients were loaded into a homogenizer: suvorexant sulphate, lactose monohydrate, microcrystalline cellulose and sodium crosscarmellose. The mixture was homogenized at 20 rpm for 15 min. Finally, magnesium stearate was added and the mixture was homogenized at 20 rpm for another 3 min. The tableting matter produced in the above mentioned way was compressed in a rotary tableting machine and used for the production of cores with the approximate weight of 127.2 mg. The obtained cores may possibly be coated (a lactose monohydrate, hypromellose, titanium dioxide, triacetin, iron oxide mixture).

CLAIMS

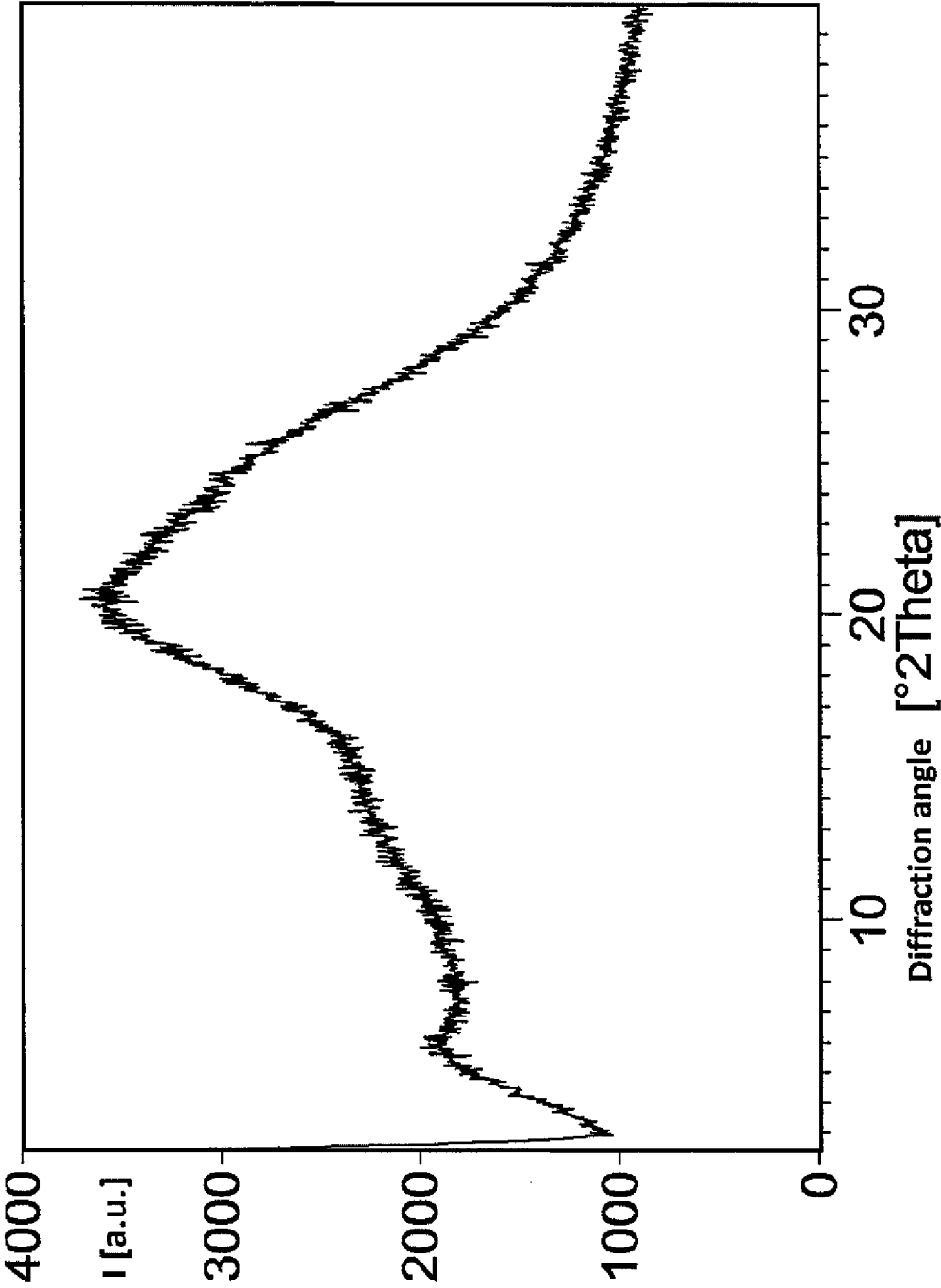
1. A solid form of the salt of suvorexant of formula I with sulphuric acid.



2. The solid form of the salt of suvorexant with sulphuric acid according to claim 1, in an amorphous form.
3. The solid form of the salt of suvorexant with sulphuric acid according to claims 1 and 2, exhibiting the glass transition temperature of 116°C.
4. A method of preparing the solid form of the salt of suvorexant with sulphuric acid according to claims 1 to 3, characterized in that [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone is mixed with sulphuric acid and a suitable solvent.
5. The method according to claim 4, characterized in that the selected suitable solvent comprises: ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water or their mixtures.
6. The method according to claims 4 and 5, characterized in that the selected suitable solvent is selected from the group: acetone, ethanol, ethyl acetate, isopropanol, acetonitrile, tetrahydrofuran, or their mixtures.
7. The method according to any of claims 4 to 6, characterized in that the resulting product is isolated by precipitation or crystallization.

8. A pharmaceutical composition, characterized in that it contains the salt of suvorexant with sulphuric acid according to any of the preceding claims.
9. The pharmaceutical composition according to claim 8 in the tablet form.
10. A method of preparing a pharmaceutical composition containing the solid form of the salt of suvorexant with sulphuric acid according to claims 1 to 7, characterized in that suvorexant with sulphuric acid is mixed with other excipients.
11. The pharmaceutical composition according to claim 10, wherein the other excipients comprise lactose monohydrate, microcrystalline cellulose, sodium crosscarmellose and magnesium stearate.
12. Use of the solid form of suvorexant with sulphuric acid according to claim 1 for the treatment of insomnia and other sleep disorders.

Drawings
Fig. 1



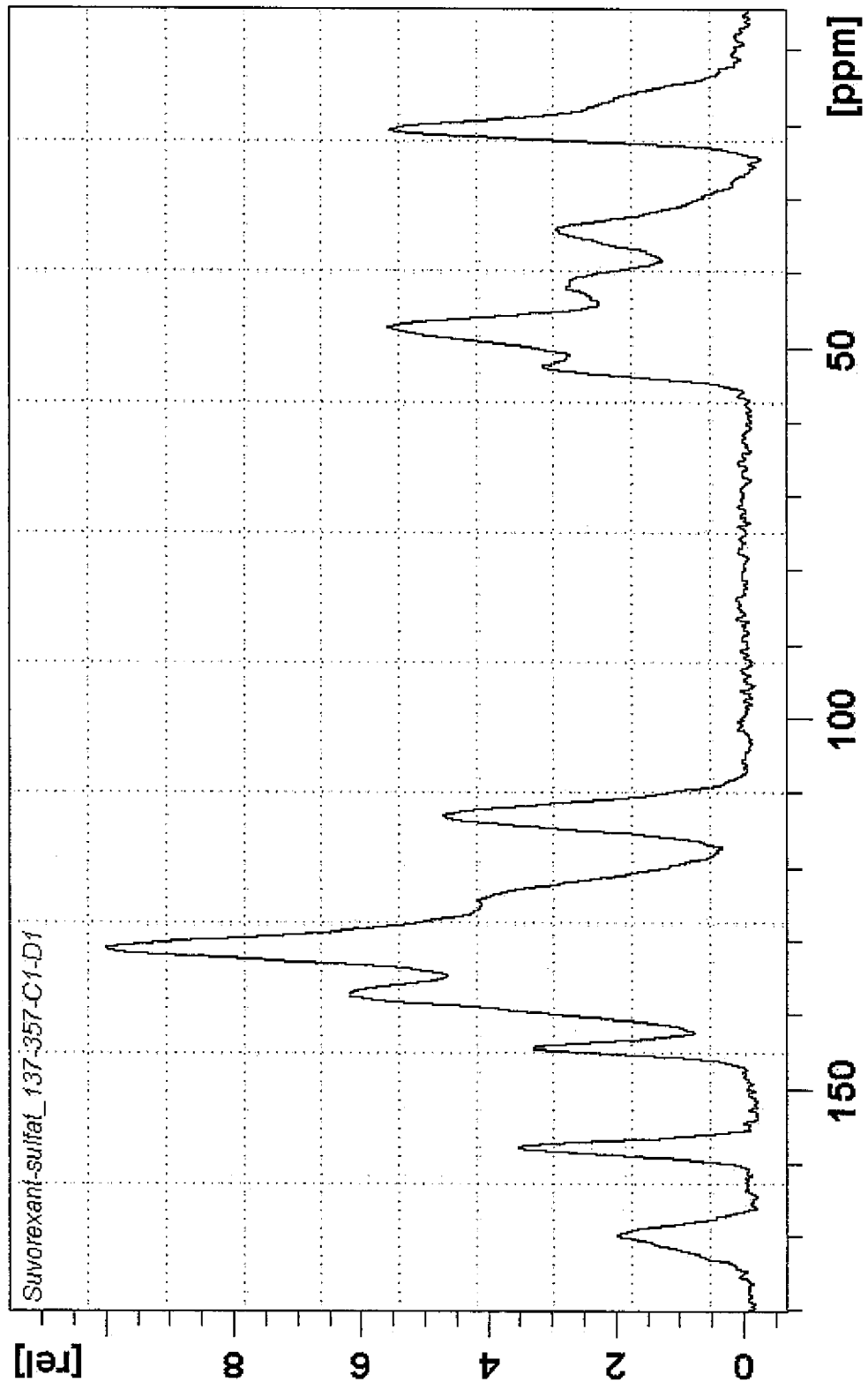


Fig. 2

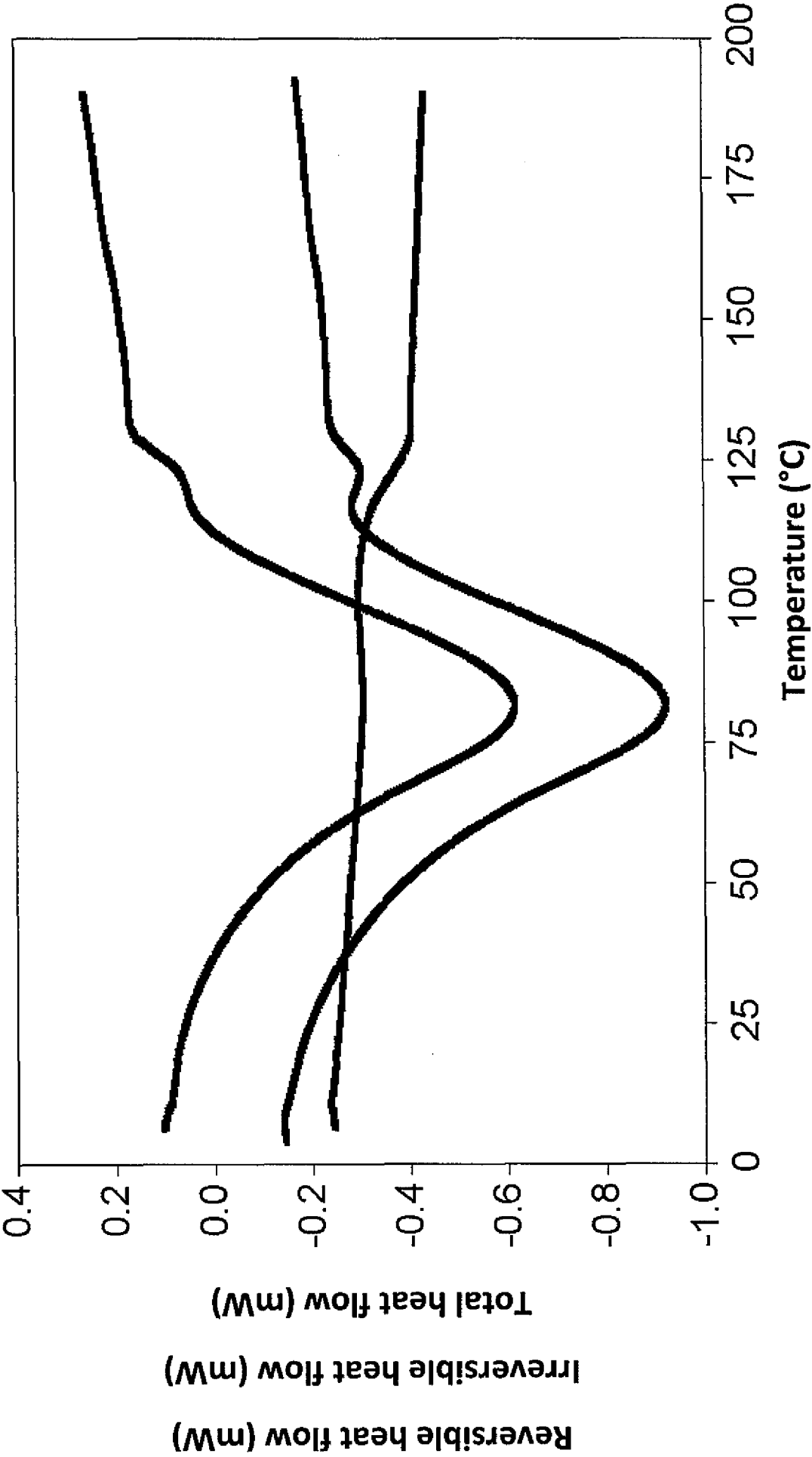


Fig. 3

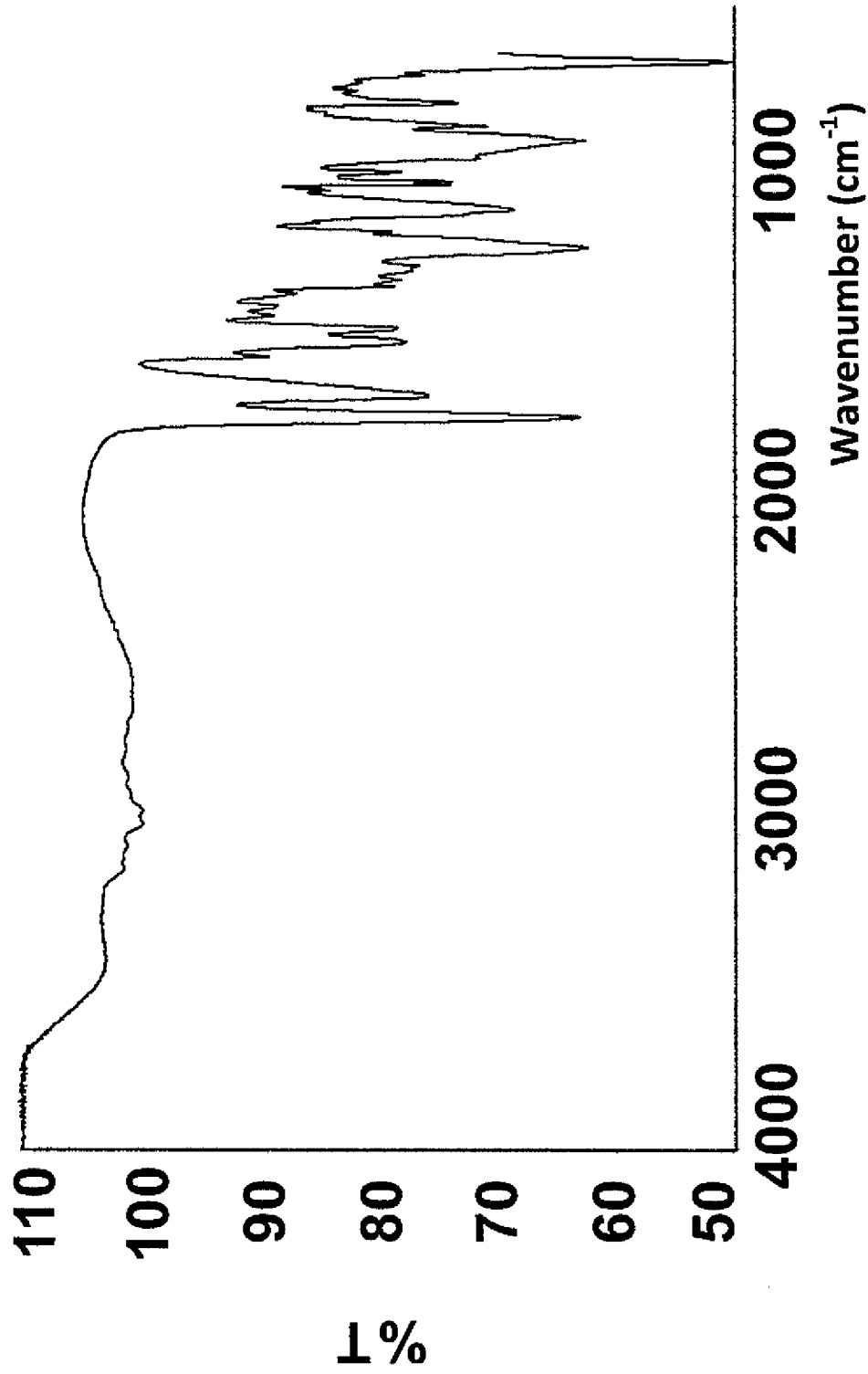


Fig. 4

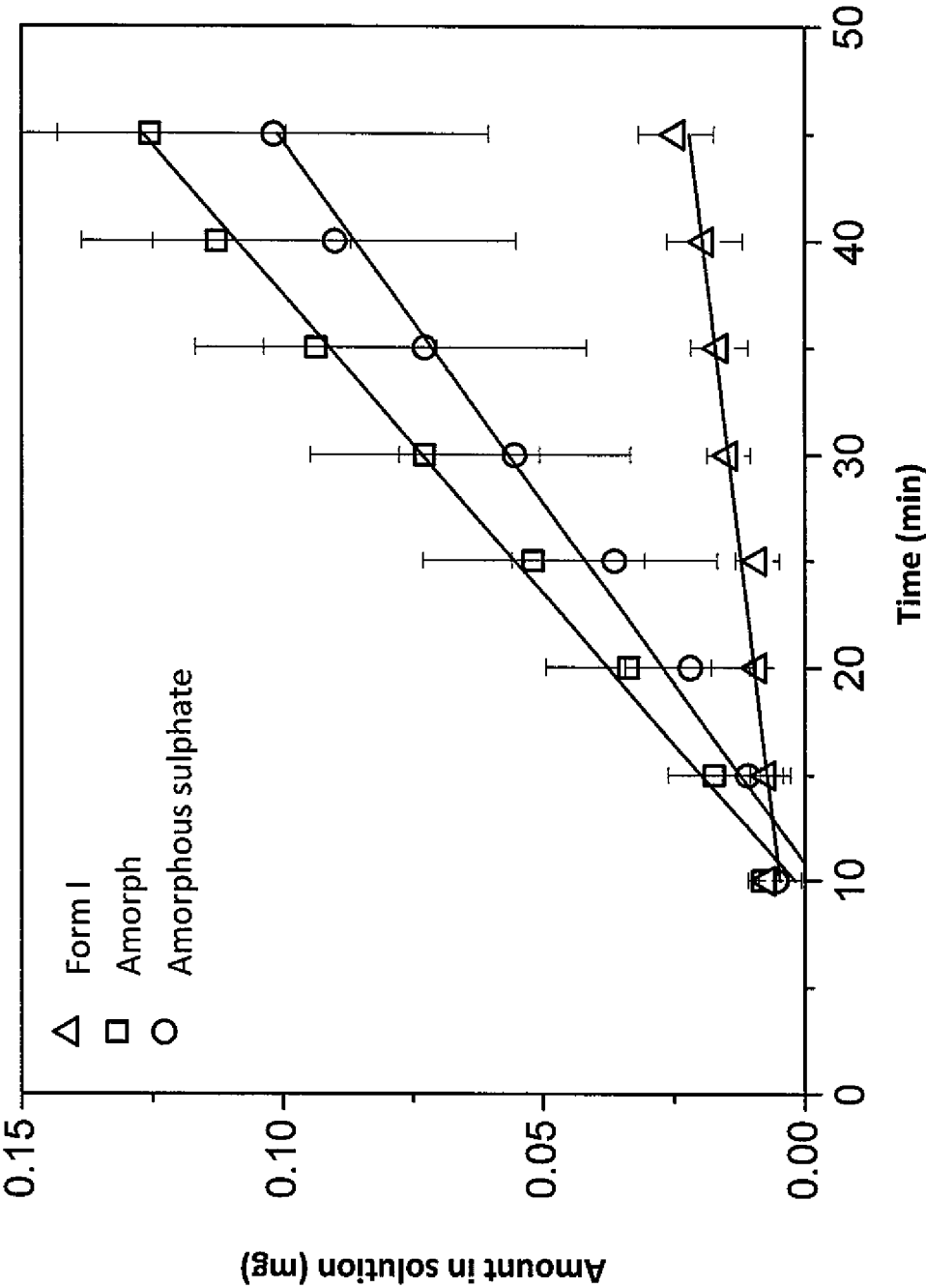


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000016

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/14 A61K31/5513 A61P25/20
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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/072961 A2 (DR. REDDY'S LABORATORIES LTD.) 15 May 2014 (2014-05-15) cited in the application claims 33-43; examples 68-77 -----	1,3-12
X	WO 2008/069997 A1 (MERCK & CO. INC.) 12 June 2008 (2008-06-12) cited in the application	1,8,9,12
Y	page 12 line 31,; page 55, line 2 - line 3; claims -----	1,3-12
X	WO 2013/181174 A2 (MERCK SHARP & DOHME CORP.) 5 December 2013 (2013-12-05)	1,8,9,12
Y	page 1, line 35; claims; examples -----	1,3-12
	-/-	



Further documents are listed in the continuation of Box C.



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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 2016

Date of mailing of the international search report

12/04/2016

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

Helps, Ian

INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2016/000016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P Y,P	WO 2015/158910 A2 (SANDOZ AG) 22 October 2015 (2015-10-22) page 15, line 4 - line 5; claims; examples -----	1,2,8,9, 12 3-7,10, 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/CZ2016/000016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014072961 A2	15-05-2014	AU 2013343027 A1 CA 2890949 A1 CN 104918920 A EP 2917187 A2 JP 2015536975 A KR 20150097486 A WO 2014072961 A2	18-06-2015 15-05-2014 16-09-2015 16-09-2015 24-12-2015 26-08-2015 15-05-2014
WO 2008069997 A1	12-06-2008	AR 063979 A1 AR 088881 A2 AU 2007328267 A1 AU 2010249269 A1 BR PI0719361 A2 CA 2670892 A1 CL 2007003441 A1 CN 101880276 A CO 6190524 A2 CR 10859 A DK 2089382 T3 EC SP099374 A EP 2089382 A1 EP 2392572 A1 ES 2397188 T3 HK 1128691 A1 HR P20130002 T1 JP 4675427 B2 JP 5335758 B2 JP 5767803 B2 JP 2010511621 A JP 2011068665 A JP 2011079848 A KR 20090087110 A KR 20100031767 A MA 31016 B1 NZ 577334 A PE 12292008 A1 PT 2089382 E RS 52617 B RU 2009125024 A RU 2010150818 A SI 2089382 T1 SV 2009003276 A TW 200831494 A TW 201109318 A US 2008132490 A1 US 2011195957 A1 WO 2008069997 A1	04-03-2009 16-07-2014 12-06-2008 06-01-2011 04-02-2014 12-06-2008 30-05-2008 10-11-2010 19-08-2010 25-06-2009 04-02-2013 31-07-2009 19-08-2009 07-12-2011 05-03-2013 12-04-2013 31-01-2013 20-04-2011 06-11-2013 19-08-2015 15-04-2010 07-04-2011 21-04-2011 14-08-2009 24-03-2010 01-12-2009 30-09-2011 28-08-2008 24-01-2013 28-06-2013 10-01-2011 20-06-2012 28-02-2013 09-11-2009 01-08-2008 16-03-2011 05-06-2008 11-08-2011 12-06-2008
WO 2013181174 A2	05-12-2013	AU 2013267613 A1 CN 104321059 A EP 2854816 A2 JP 2015518867 A KR 20150014940 A US 2015190402 A1 WO 2013181174 A2	02-10-2014 28-01-2015 08-04-2015 06-07-2015 09-02-2015 09-07-2015 05-12-2013
WO 2015158910 A2	22-10-2015	NONE	