(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 August 2014 (07.08.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/118240 A1

(51) **International Patent Classification**:
A01N 25/02 (2006.01) *A01P 1/00* (2006.01)
A01N 25/30 (2006.01) *A61K 8/00* (2006.01)
A01N 43/36 (2006.01)

(21) **International Application Number**:
PCT/EP2014/051731

(22) **International Filing Date**:
29 January 2014 (29.01.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
13153600.5 1 February 2013 (01.02.2013) EP

(71) **Applicant** *(for AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, VC, ZA, ZM, ZW only)*: **UNILEVER PLC** [GB/GB]; 41424 of Unilever House, 100 Victoria Embankment, London Greater London EC4Y 0DY (GB).

(71) **Applicant** *(for all designated States except AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, US, VC, ZA, ZM, ZW)*: **UNILEVER N.V.** [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).

(71) **Applicant** *(for US only)*: **CONOPCO, INC., D/B/A UNILEVER** [US/US]; 800 Sylvan Avenue, AG West, S. Wing, Englewood Cliffs, New Jersey 07632 (US).

(72) **Inventors**: **PARRY, Neil James**; Unilever R&D Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **O'KEEFFE, Joanne Clare**; Unilever R&D Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **SMITH, Christopher Francis**; 16 Paddock Close, Mansfield, Nottinghamshire NG18 5AS (GB).

(74) **Agents**: **HARDY, Susan, Margaret** et al.; Unilever PLC, Unilever Patent Group, Colworth House, Sharnbrook, Bedford Bedfordshire MK44 1LQ (GB).

(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, LT, 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, 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))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/118240 A1

(54) **Title**: ANTIMICROBIAL COMPOSITION COMPRISING A LACTAM AND A HYDROTROPE

(57) **Abstract**: Antimicrobial composition comprising a lactam and a hydrotrope.Antimicrobial additive composition containing a lactam and a hydrotrope.

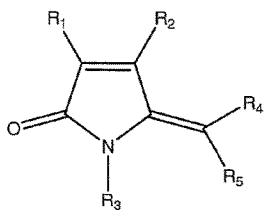
ANTIMICROBIAL COMPOSITION COMPRISING A LACTAM AND A HYDROTROPE

The present invention relates to an improved antimicrobial composition comprising a lactam.

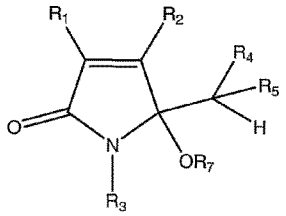
WO 2007/085042 and WO 2004/016588 disclose lactams for antimicrobial benefit.

Despite the prior art there remains a need for improved antimicrobial compositions.

Accordingly, and in a first aspect of the present invention there is provided an antimicrobial composition comprising a lactam and a hydrotrope preferably wherein the lactam is of formula (I) or (II):



(I)



or (II)

In a second aspect, there is provided an antimicrobial additive composition containing a lactam and a hydrotrope.

Preferably the anti-microbial composition and additive composition contains 0.000001 to 50% wt. lactam, more preferably 0.001 to 50% wt. even more preferably 0.01 to 5% wt, most preferably 0.01 – 2%.

In a third aspect of the invention there is provided an antimicrobial composition comprising an antimicrobial additive composition of the second aspect.

In a fourth aspect there is provided a method for making an antimicrobial composition comprising the steps:

(i) directly mixing a lactam with a hydrotrope to form an antimicrobial additive composition
(ii) mixing the antimicrobial additive composition of (i) with an aqueous carrier.

In a fifth aspect there is provided a method for making an antimicrobial additive composition comprising the step of directly mixing a hydrotrope with a lactam.

In a sixth aspect, the present invention provides the use of an antimicrobial composition according to the first and third aspect or an antimicrobial additive composition according to the second aspect for preventing or disrupting microbial growth.

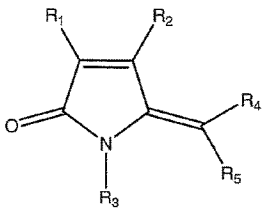
Preferably the antimicrobial additive composition and the method of making said additive composition is substantially free of further components.

The term "substantially free" as used herein shall be understood to mean relatively little to no amount of any content. Preferably the antimicrobial contains less than 1 wt. % more preferably less than 0.1 wt. % of further components.

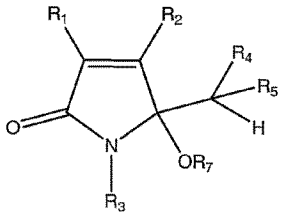
Preferably the aqueous carrier is suitable for use as a carrier for a home or personal care product. Preferred personal care products include shampoos, hair conditioners, deodorants, skin cleansing compositions and oral care products such as toothpastes and mouthwashes. Preferred home care products are for example a hard surface cleaner or laundry composition.

The antimicrobial additive composition according to the invention can be used as an antimicrobial raw material where it would be diluted in a further composition or the composition may be a consumer product the application of which is intended to provide antimicrobial effect to a substrate or even as a preservative when added to a consumer composition.

Preferably the lactam is of formula (I) or (II):



(I) or (II)



Preferably the lactam is of formula (I) or (II) wherein:

R1 and R2 are each independently selected from hydrogen, halogen, alkyl, cycloalkyl, alkoxy, oxoalkyl, alkenyl, heterocyclyl, heteroaryl, aryl and aralalkyl; and

R3 is selected from hydrogen, hydroxyl, alkyl, cycloalkyl, alkoxy, oxoalkyl, alkenyl, heterocyclyl, heteroaryl, cycloalkyl, aryl, aralalkyl and –C(O)CR6=CH2;

R4 and R5 are independently selected from hydrogen, aryl, heterocyclyl, heteroaryl, and arylalkyl; and

R6 is selected from hydrogen and methyl; and

R7 is selected from hydrogen and –C(O)CR6=CH2; and

Preferably, at least one of R4 and R5 is hydrogen; and

Preferably, at least one of R1 and R2 is selected from hetercyclyl, heteroaryl, aryl and arylalkyl; and

Preferably, R1 is hydrogen. Preferably, R3 is hydrogen. Preferably, R4 is hydrogen. Preferably, R5 is hydrogen. Preferably, R6 is hydrogen; and

Preferably, R2 is aryl or aralalkyl. More preferably, R2 comprises a halogen substituted phenyl group.

Preferably, the hydrotrope is selected from monopropylene glycol, dimethylsulphoxide, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene derivatives of castor oil and ethanol.

Preferably, the hydroptrope is present at from 0.001 to 25% wt. of the composition.

Preferred lactams are:

5-methylene-4-(4'-bromophenyl)-dihydroprrol-2-one (Ref. 295)

5-methylene-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 310)

5-methylene-4-phenyl-1H-pyrrol-2(5H)-one (Ref. unsubstituted)

methyl 2-(3-(4-fluorophenyl)-2-methylene-5-oxo-2,5-dihydro-1H-pyrrol-1-yl) (Ref. 309)

3-Bromo-4-hexyl-5-(bromomethylene)-2(5H)-furanone (Ref. 113)

4-(4-Trifluoromethyl)phenyl)-2(5H)-furanone (Ref. 265)

5-Hydroxy-5-methyl-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 313)

5-(Thiophenyl-3-methylene)furan-(2H)-one (Ref. 350)

The most preferred lactams are:

5-methylene-4-(4'-bromophenyl)-dihydroprrol-2-one (Ref. 295)

5-methylene-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 310)

5-methylene-4-phenyl-1H-pyrrol-2(5H)-one (Ref. unsubstituted)

methyl 2-(3-(4-fluorophenyl)-2-methylene-5-oxo-2,5-dihydro-1H-pyrrol-1-yl) (Ref. 309)

Preferably, the hydrotrope is selected from monopropylene glycol, dimethylsulphoxide, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene derivatives of castor oil and ethanol.

Preferably, the polyoxyethylene sorbitan fatty ester is a monoester selected from monolaurate, monopalmitate, monostearate and monooleate.

Preferably, the polyoxyethylene sorbitan fatty ester comprises from 5 to 80 oxyethylene units, more preferably from 10 to 45 and most preferably 20. Examples include Polysorbates 20, 40, 60 and 80.

The most preferred polyoxyethylene sorbitan fatty ester is Polysorbate 20.

Preferably, the polyoxyethylene derivative of castor oil comprises from 10 to 50 oxyethylene units, more preferably from 30 to 45 and most preferably 40. Examples include PEG-20, 40 and 60 hydrogenated castor oil.

The most preferred polyoxyethylene derivative of castor oil is PEG-40 hydrogenated castor oil.

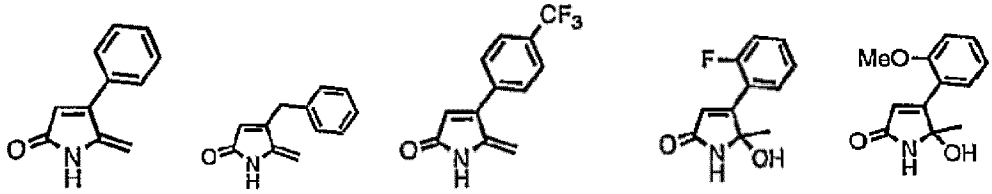
Preferably, the composition is a home care or personal care product.

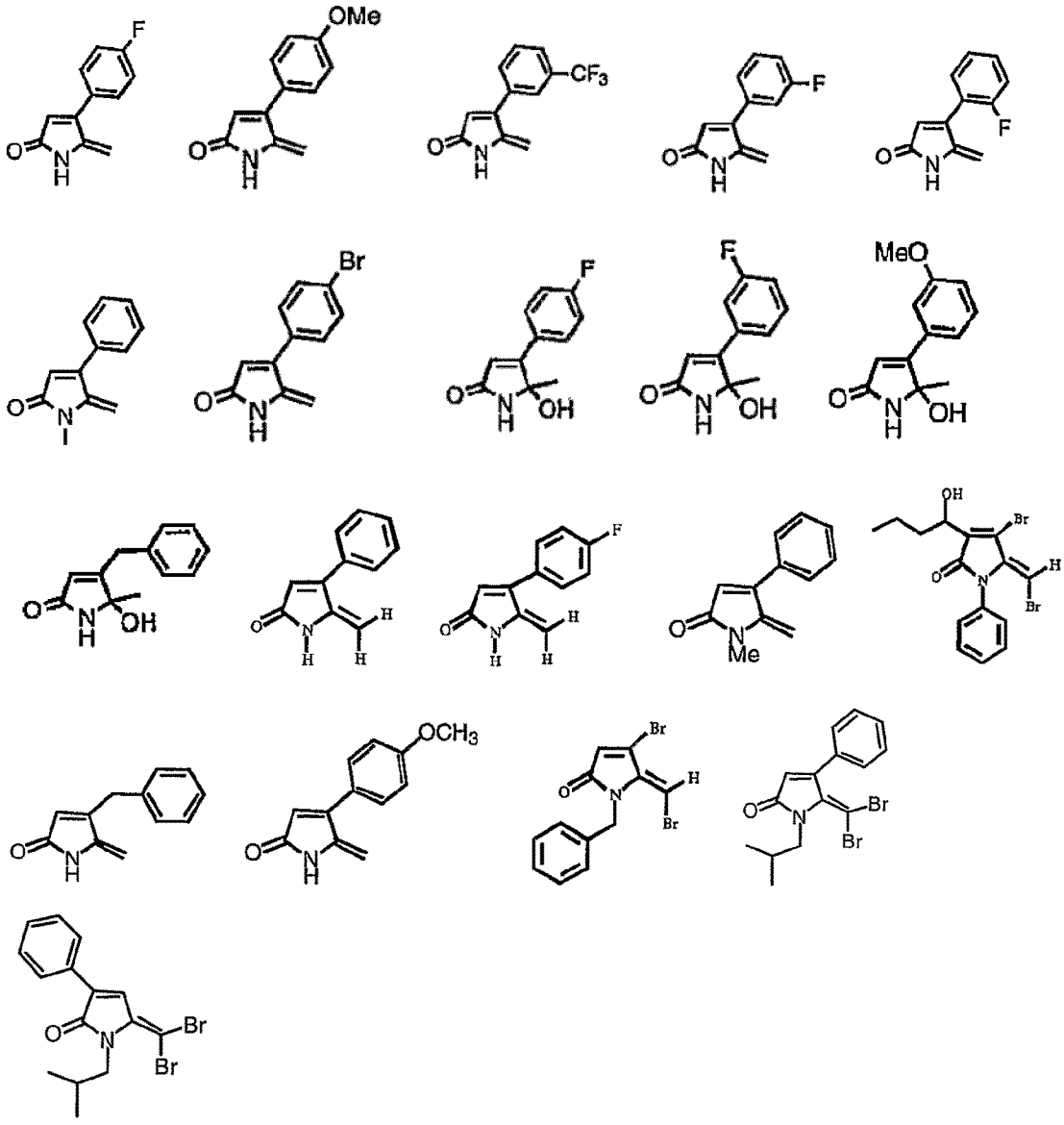
Preferred personal care products include shampoos, hair conditioners, deodorants, skin cleansing compositions and oral care products such as toothpastes and mouthwashes. Preferred home care products include a hard surface cleaner or laundry composition.

lactams

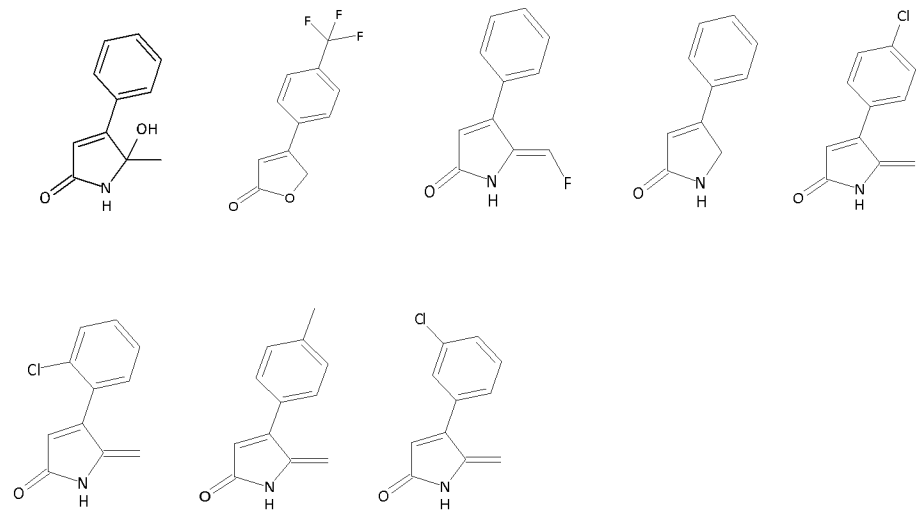
Suitable lactams are disclosed in WO 2007/085042 and WO 2004/016588 the contents of which with particular regard to the manufacture of lactams and from WO 2007/085042 the manufacture of acrylate polymers with certain lactams associated thereto, is incorporated by reference.

For example:





5



EXAMPLE 1

The following data illustrates the antimicrobial efficacy of a laundry composition (hereinafter 'base composition') comprising a lactam (Ref. 295 and Ref. Unsubstituted) and a hydroptrope (monopropylene glycol) but only where hydroptrope is mixed with lactam before adding to the remainder of the composition. The test samples were as follows:

A lactam and hydroptrope only

B lactam added directly to base formulation (which contains MPG) – no pre-mixing prior to addition

C lactam pre-mixed with hydrotrope and then added to base formulation

D hydrotrope only added to base formulation

Base Formulation

% activity	% required	Component	Amount in 100g
100	45.87	Demin Water	39.05
100	4.13	Glycerol	4.13
100	7.43	Mono Propylene Glycol (with or without lactam according to BDC above)	7.43
47	2.12	NaOH	4.51
100	2.10	Triethanolamine (TEA)	2.10
100	16.59	Primary Alcohol Ethoxylate (7EO)	16.59
68	0.10	Optical Brightener	0.15
50	0.81	Citric Acid	1.62
97.1	11.06	LAS Acid	11.39
100	3.10	Fatty Acid	3.10
70	5.53	SLES 3EO	7.90
32	0.41	Diethylenetriamine penta(methylene phosphonic acid)	1.28
100	0.75	Liquid Protease	0.75
	100.00		

Test samples were diluted in sterile water to achieve a 11.5ppm level of lactam. Dilute solution (80µl) was added to a *S. epidermidis* suspension (20µl) of bacteria at a concentration of 8 logs in a microplate. Growth media (100µl tryptone soya broth) was added to each well of the microplate and incubated for 20 hours. Bacterial respiration was measured every 30 minutes and the results werea:

A – lactam + hydrotrope only (respiration of surviving bacteria detected ~4-5h)
B – lactam added directly to base formulation (which contains MPG) – no pre-mixing prior to addition (respiration of surviving bacteria detected 4-5hrs)
C – lactam pre-mixed with hydrotrope and then added to base formulation (respiration of surviving bacteria not detected – 20hrs is max detection time)
D –hydrotrope added to base formulation (respiration of surviving bacteria detected 3-4hrs).

The results are shown in Figure 1.

EXAMPLE 2

The following illustrates the broad application of the invention within the realm of lactams.

The example below is from data obtained when pre-blending lactams with hydrotrope before adding to the remainder of the composition, and diluting to 11.5ppm and 0.575ppm in sterile water in order to assess efficacy against *S. epidermidis* suspension Dilute solution (80µl) was added to a *S. epidermidis* suspension (20µl) of bacteria at a concentration of 8 logs in a microplate. Growth media (100µl tryptone soya broth) was added to each well of the microplate and incubated for 20 hours. Bacterial respiration was measured every 30 minutes. Data of the test samples were then compared to un-treated cell suspensions (sterile water added instead of test samples) and percent inhibition calculated.

Test	Result (inhibition of bacterial respiration versus water control)
5-methylene-4-(2'-fluorophenyl)-dihydropyrrol-2-one	79.4%
5-methylene-4-(4'-bromophenyl)-dihydroprrol-2-one	82.5%
5-methylene-4-phenyl-1H-pyrrol-2(5H)-one	82.5%

EXAMPLE 3

The aim of this example was to investigate methods of achieving solubility of 5-methylene-4-phenyl-1H-pyrrol-2(5H)-one (Ref. unsubstituted) into the following above described base formulation.

An Ultrasonic mixer was used to obtain determine solubility.

We used a Hielscher UP200S (200W) Sonic Tip on batches of 5-20ml. We sonicated for up to 60 minutes.

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to base @ 5%
3% in Polysorbate 20	Magnetic stirring 1 hour	~25% of lactam solubilised. Particles visible.	Clear solution with a large quantity of particles visible
3% in PEG-40 Hydrogenated Castor Oil	Magnetic stirring 1 hour	~25% of lactam solubilised. Particles visible.	Clear solution with a large quantity of particles visible
3% in Isopentyldiol	Magnetic stirring 1 hour	No solubility observed.	-
3% in MMB	Magnetic stirring 1 hour	No solubility observed.	-
3% in Diglycerin	Magnetic stirring 1 hour	No solubility observed.	-
3% in Diglycerin	Magnetic stirring 1 hour	No solubility observed.	-
3% in Pentylene	Magnetic stirring 1 hour	No solubility observed.	-

Glycol			
3% in Hexylene Glycol	Magnetic stirring 1 hour	No solubility observed.	-
3% in Hexylene Glycol	Magnetic stirring 1 hour	No solubility observed.	-
3% in PEG-60 Hydrogenated Castor Oil	Magnetic stirring 1 hour	~10% of lactam solubilised. Particles visible.	Cloudy in solution
3% in Polysorbate 60	Magnetic stirring 1 hour, 50C	~10% of lactam solubilised. Particles visible.	Cloudy and gel-like lumps in solution
3% in Polysorbate 80	Magnetic stirring 1 hour	~10% of lactam solubilised. Particles visible.	Cloudy and gel-like lumps in solution
3% in Dipropylene Glycol	Magnetic stirring 1 hour	~5% of lactam solubilised (slight colour change observed showing this. Particles visible.	-
3% in Sorbitan Oleate	Magnetic stirring 1 hour, 50C	~5% of lactam solubilised (slight colour change	Cloudy when cooled or added to M30

		observed showing this. Particles visible.	
3% in Sisterna SP30-C	Magnetic stirring 1 hour	~5% of lactam solubilised (slight colour change observed showing this. Particles visible.	Cloudy solution with large number of particles visible.
3% in Sisterna SP50-C	Magnetic stirring 1 hour	~5% of lactam solubilised (slight colour change observed showing this. Particles visible.	Hazy solution with large number of particles visible.
3% in Sisterna SP70-C	Magnetic stirring 1 hour	~5% of lactam solubilised (slight colour change observed showing this. Particles visible.	Cloudy solution with large number of particles visible.

The polysorbates and Pegylated castor oil were considered suitable enough to pursue further experimentation.

Further evaluations with each candidate solubiliser

We then tested the candidate solubilisers with 1% lactam, both with 72 hours high speed magnetic stirring (with held temperature of ~50C in the cases of solubilisers that solidify alone at room temperature) and also 20 minutes Sonication.

Preparation of the lactam solutions

In each case we incorporated the lactam powder into the solubilisers (at the levels indicated in the below table) using high speed stirring to avoid lumps from forming. Once the powder was added, the described mixing method (either continued high speed stirring or Ultrasonic mixing) commenced. In the cases of Sorbitan Oleate and Polysorbate-60, we applied initial heating to approx. 50C to ensure the solubilisers were fully liquid prior to commencing addition of the lactam. Both of these materials are non-flowing at room temperature. PEG-40 Hydrogenated Castor required initial heating to ~35C to ensure complete fluidity prior to commencing.

Incorporation of the lactam solutions into base

The base sample provided had a 5% 'gap' purposely left out as space for the lactam solution to be added. We ensured the lactam solutions were fully uniform through constant mechanical agitation (to avoid the settling of any unsolubilised lactam material) and added them to base using slow speed stirring to incorporate them without generating aeration.

Stability testing

We conducted stability testing on all test variants that looked positive (i.e. a reasonable proportion of lactam was solubilised). We prepared samples of the test

variants in clear plastic jars and placed them at various temperature conditions:

* Ambient temperature.
* 40C.
* 50C.
* Refrigerator.
* High light ('shop' window).

The aim was to observe any difference in colour, viscosity, solubility or general physical stability. The samples were evaluated every day and compared to the ambient temperature sample to note any changes. All samples were allowed to equilibrate to ambient temperature before being evaluated.

Isopentyldiol

% lactam in solvent	**Mixing method**	**Observations of solvent solution**	**Observations when added to M30 @ 5%**
1% in Isopentyldiol	Magnetic stirring 72 hours	No solubility observed at any stage.	-
1% in Isopentyldiol	20 minutes sonication. Temp reached 60-70C	~5% of lactam solubilised (forced). Large number of particles visible.	-

3-Methoxy-3-methyl-1-butanol

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours	No solubility observed at any stage.	-
1%	20 minutes sonication. Temp reached 60-70C	~5% of lactam solubilised (forced). Large number of particles visible.	-

Diglycerin

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours	No solubility observed at any stage.	-
1%	20 minutes sonication. Temp reached 60-70C	No solubility observed.	-

Pentylene Glycol

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours	~5% of lactam solubilised. Large number of particles visible.	-
1%	20 minutes sonication. Temp reached 60-70C	~5% of lactam solubilised. Large number of particles visible.	-

5

PEG-60 Hydrogenated Castor Oil

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Polysorbate 60

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Polysorbate 80

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Sisterna SP30-C

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Sisterna SP50-C

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Sisterna SP70-C

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
1%	Magnetic stirring 72 hours at 50C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.
1%	20 minutes sonication. Temp reached 60-70C	~25% of lactam solubilised. Particles visible.	Cloudy in solution. Particles visible.

Polysorbate 20

% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
3%	Magnetic stirring 1 hour	~25% of lactam solubilised. Particles visible.	Clear solution with a large quantity of particles visible
4.2%	Magnetic stirring. 24 hours	~25% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
4.2%	Magnetic stirring. 24 hours.	~25% of lactam solubilised, Particles visible. Initially stirred for 2, 4 and 6 hours. No real changed observed during this time (all max.	Clear solution with a large quantity of particles visible

		25% solubilised).	
4.2%	20 minutes sonication. Temp reached 60-70C	~50% of lactam solubilised. Particles visible	Clear solution with a large quantity of particles visible
4.2%	60 minutes sonication. Temp reached 90C	~60-70% of lactam solubilised. Particles visible	Clear solution with a large quantity of particles visible
2.1%	20 minutes sonication. Temp reached 60-70C	~90% of lactam solubilised. Dark colour formed	Clear solution. A very small number of remaining unsolubilised lactam particles visible
2.1%	60 minutes sonication. Temp reached 90-100C	90% of lactam solubilised. Some small particles visible.	Clear solution with a minute number of particles visible.
4.2%	Magnetic stirring. 48 hours	~25% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
2.1%	Magnetic stirring. 24 hours	~50% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
2.1%	Magnetic stirring. 48 hours	~75% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
2.1%	Magnetic stirring, heated to 50C. 8 hours.	~50% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
3%	20 minutes sonication. Temp	~50% of lactam solubilised.	Clear solution with a large quantity of

	reached 60-70C	Particles visible	particles visible
% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to base @ 5%
3%	60 minutes sonication. Temp reached 90C	~60-70% of lactam solubilised. Particles visible	Clear solution with a large quantity of particles visible
1%	Magnetic stirring. 24 hours	~75% of lactam solubilised, Particles visible.	Clear solution with a few particles visible
1%	Magnetic stirring. 72 hours	~95% of lactam solubilised A few particles visible. After 48 hours it was approx. 80-85%.	Clear solution with a few particles visible
2.1%	Magnetic stirring, heated to 50C. 72 hours.	~75% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
1.5%	Magnetic stirring. 48 hours	~50% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
1.5	Magnetic stirring, heated to 50C. 72 hours.	~75% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
1.5%	20 minutes sonication. Temp reached 60-70C	~75% of lactam solubilised. Some Particles visible	Clear solution with a number of particles visible
1.5%	60 minutes sonication. Temp reached 80-90C	~95% of lactam solubilised. Particles visible.	Clear solution with a minute number of particles visible

		Dark brown colour.	
2.1%	60 minutes sonication. Temp reached 80C	90% of lactam solubilised. Some small particles visible.	Clear solution with a minute number of particles visible.

PEG-40 Hydrogenated Castor Oil

% lactam in solvent	**Mixing method**	**Observations of solvent solution**	**Observations when added to M30 @ 5%**
3%	Magnetic stirring 1 hour	~25% of lactam solubilised. Particles visible.	Clear solution with a large quantity of particles visible
4.2%	Magnetic stirring. 24 hours	~25% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
4.2%	Magnetic stirring. 24 hours.	~25% of lactam solubilised, Particles visible. Initially stirred for 2, 4 and 6 hours. No real changed observed during this time (all max. 25% solubilised).	Clear solution with a large quantity of particles visible
4.2%	Magnetic stirring. 48 hours	~25% of lactam solubilised,	Clear solution with a large quantity of

		Particles visible.	particles visible
2.1%	Magnetic stirring. 24 hours	~50% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
2.1%	Magnetic stirring. 48 hours	~75% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
4.2%	20 minutes sonication. Temp reached 60-70C	50% of lactam solubilised. Large number of particles visible. Very dark colour.	Clear solution with a large number of particles visible
4.2%	60 minutes sonication. Temp reached 110C	75% of lactam solubilised. Very dark colour.	Some fragments visible in M30, suggesting partial breakdown of solvent.
4.2%	60 minutes sonication. Temp reached 80C	75% of lactam solubilised. Very dark colour.	Fragments avoided due to temperature control. Clear solution with some small particles visible.
2.1%	20 minutes sonication. Temp reached 80C	90% of lactam appeared to solubilise however small amount of 'burnt' spots visible.	Clear solution with a small number of black particles visible
2.1%	60 minutes	lactam solubilised.	Some fragments

	sonication. Temp reached 110C	Very dark colour.	visible in M30, suggesting partial breakdown of solvent.
2.1%	Magnetic stirring, heated to 50C. 8 hours.	~50% of lactam solubilised, Particles visible.	Clear solution with a large quantity of particles visible
% lactam in solvent	Mixing method	Observations of solvent solution	Observations when added to M30 @ 5%
3%	20 minutes sonication. Temp reached 60-70C	~75% of lactam solubilised. Particles visible	Clear solution with a large quantity of particles visible
3%	60 minutes sonication. Temp reached 80C	~75% of lactam solubilised. Particles visible	Clear solution with a large quantity of particles visible
1%	Magnetic stirring. 24 hours	~75% of lactam solubilised, Particles visible.	Clear solution with a few particles visible
1%	Magnetic stirring. 72 hours	~90% of lactam solubilised, A few particles	Clear solution with a few particles visible
1%	Magnetic stirring. 72 hours with temp. at 50C	~99% of lactam solubilised, A tiny number of particles remained	Clear solution with a very small number of particles visible
2.1%	30 minutes sonication. Temp reached 90C	lactam appeared to solubilise however 'burnt' spots visible.	Clear solution with a small number of black particles visible

Observation and Formulation rules

Temperature and colour change

One of our first observations was the colour change which was visible in all successful (or partially successful) samples. We saw development of a slight amber tinge to the solution when some lactam was starting to become solubilised. This colour change progressed rapidly when samples exceeded 50C, resulting in a dark brown colour. When the temperature reached 65C, the dark brown colour was virtually opaque*.

** This level of temperature was only tested for the Polysorbate-20 and PEG-40 Hydrogenated Castor Oil variants.*

From observations throughout the project, we concluded that ~50C was the optimum temperature for solubilising the lactam.

Mixing conditions

Very long periods of mechanical stirring (48-72 hours) resulted in improvements in solubilisation compared to shorter periods; however we did not find this length of mixing to be sufficient for full solubilisation. Ultrasonic mixing did prove to be far more successful and we concluded would be required for effective solubilisation, certainly with the shortlisted Polysorbate-20 and PEG-40 Hydrogenated Castor Oil candidates.

From all of the trials conducted, we believe with the right Ultrasonic mixing conditions (of energy versus batch size versus controlled max. 50C temperature), efficient solubilisation could be achieved.

CLAIMS

1. Antimicrobial additive composition containing a lactam and a hydrotrope.

2. Antimicrobial additive composition according to claim 1 wherein the additive composition is substantially free of further components.

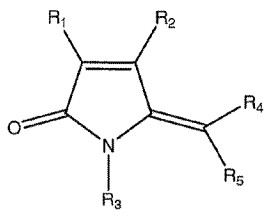
3. Antimicrobial composition comprising a lactam and a hydrotrope.

4. Antimicrobial composition comprising an antimicrobial additive composition of claim 1 or 2.

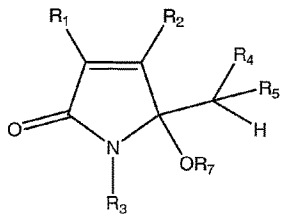
5. Antimicrobial composition or additive composition according to any preceding claim wherein the hydrotrope is selected from monopropylene glycol, dimethylsulphoxide, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene derivatives of castor oil and ethanol.

6. Antimicrobial composition according to any of claims 1, 4-5 wherein the hydroptrope is present at from 0.001 to 5% wt. of the composition.

7. Antimicrobial composition or additive composition according to any preceding claim wherein the lactam is of formula (I) or (II):



(I) or (II)



preferably wherein:

R1 and R2 are each independently selected from hydrogen, halogen, alkyl, cycloalkyl, alkoxy, oxoalkyl, alkenyl, heterocyclyl, heteroaryl, aryl and aralalkyl;

R3 is selected from hydrogen, hydroxyl, alkyl, cycloalkyl, alkoxy, oxoalkyl, alkenyl, heterocyclyl, heteroaryl, cycloalkyl, aryl, aralalkyl and –C(O)CR6=CH2;

R4 and R5 are independently selected from hydrogen, aryl, heterocyclyl, heteroaryl, and arylalkyl; and

R6 is selected from hydrogen and methyl; and

R7 is selected from hydrogen and –C(O)CR6=CH2; and

8. Antimicrobial composition or additive composition according to any preceding claim wherein the lactam is selected from:

5-methylene-4-(4'-bromophenyl)-dihydroprrol-2-one (Ref. 295), 5-methylene-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 310), 5-methylene-4-phenyl-1H-pyrrol-2(5H)-one (Ref. unsubstituted), methyl 2-(3-(4-fluorophenyl)-2-methylene-5-oxo-2,5-dihydro-1H-pyrrol-1-yl) (Ref. 309), 5-methylene-4-phenyl-dihydro-pyrrol-2-one (Ref. 219), 3-Bromo-4-hexyl-5-(bromomethylene)-2(5H)-furanone (Ref. 113), 4-(4-Trifluoromethyl)phenyl)-2(5H)-furanone (Ref. 265), 5-Hydroxy-5-methyl-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 313), 5-(Thiophenyl-3-methylene)furan-(2H)-one (Ref. 350) and mixtures thereof.

9. Antimicrobial composition or additive composition according to any preceding claim wherein the lactam is selected from:

5-methylene-4-(4'-bromophenyl)-dihydroprrol-2-one (Ref. 295), 5-methylene-4-(2'-fluorophenyl)-dihydropyrrol-2-one (Ref. 310), 5-methylene-4-phenyl-1H-pyrrol-2(5H)-one (Ref. unsubstituted), methyl 2-(3-(4-fluorophenyl)-2-methylene-5-oxo-2,5-dihydro-1H-pyrrol-1-yl) (Ref. 309) and mixtures thereof.

10. Antimicrobial composition or additive composition according to any preceding claim wherein the lactam is present at from 0.001 to 50% wt. of the composition, preferably 0.01 to 5% wt. of the composition, more preferably 0.01 – 2%.

11. Antimicrobial composition or additive composition according to claim 5 wherein the polyoxyethylene derivative of castor comprises from 10 to 50, preferably from 30 to 45 and most preferably 40 oxyethylene units.

12. Antimicrobial composition or additive composition according to claim 5 wherein the polyoxyethylene sorbitan fatty ester comprises from 5 to 80 oxyethylene units, more preferably from 10 to 45 and most preferably 20.

13. Antimicrobial composition or additive composition according to any preceding claim which is a home or personal care composition.

14. Antimicrobial composition or additive composition according to claim 13 which is selected from a shampoo, conditioner, deodorant, skin cleansing composition, antiperspirant.

15. Antimicrobial composition or additive composition according to claim 13 which is selected from a laundry composition, hard surface cleaner and toilet cleaner.

16. Method of making an antimicrobial additive composition comprising the step of directly mixing a hydrotrope with a lactam.

17. Method for making an antimicrobial composition comprising the steps:
(i) directly mixing a lactam with a hydrotrope to form an antimicrobial additive composition; and
(ii) mixing the antimicrobial additive composition of step (i) with an aqueous carrier.

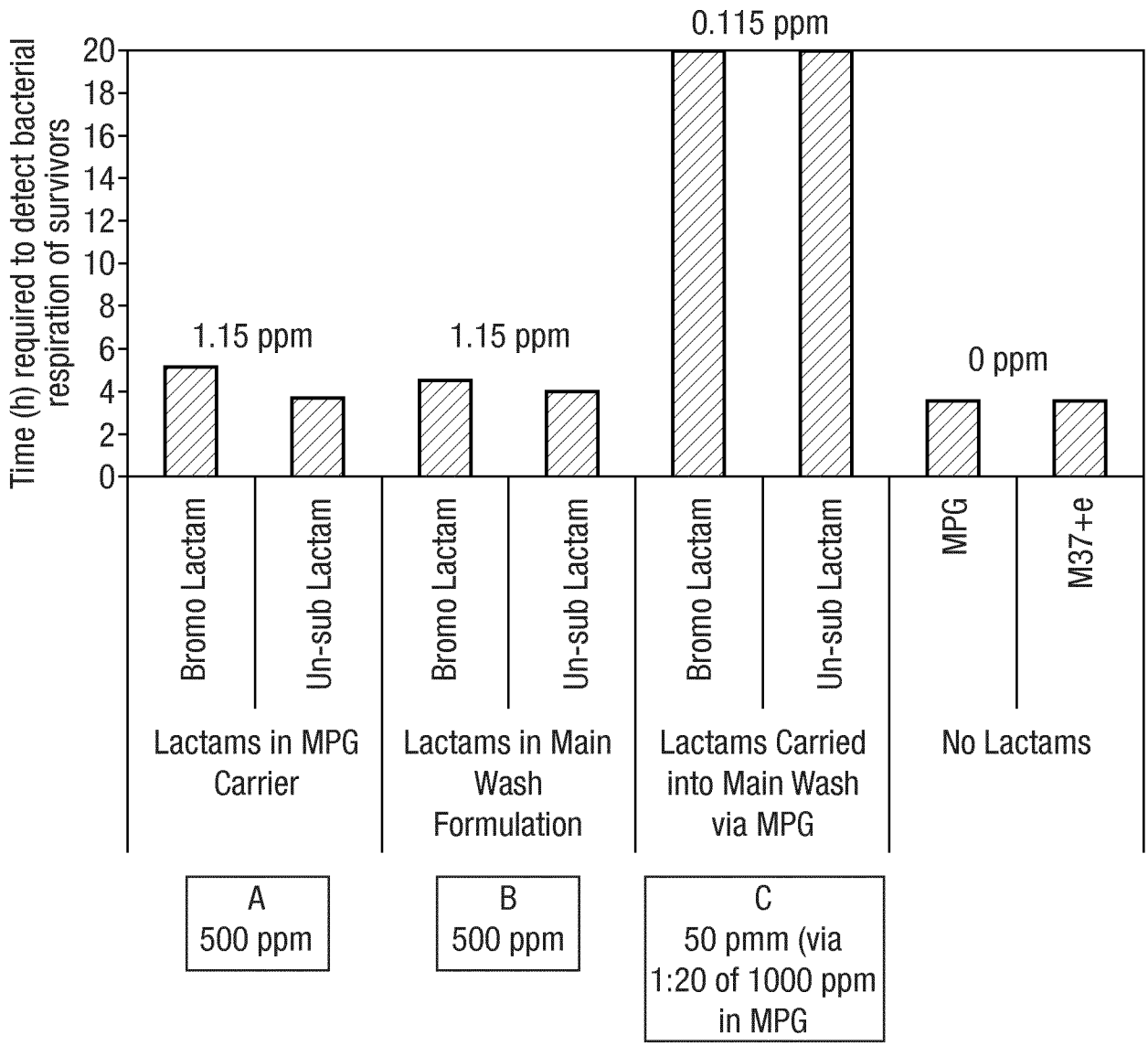
18. Method according to claim 16 wherein the antimicrobial additive composition is according to any of claims 1, 2, 5-15.

19. Method according to claim 17 wherein the antimicrobial composition is according to any of claims 1- 15.

20. Use of an antimicrobial additive composition or composition according to any of claims 1-15 for preventing or disrupting microbial growth.

21. Composition, method and/or use as substantially described herein with reference to the accompanying drawings.

Fig. 1


Inhibiting S. epidermidis (high bars = greater efficacy; 20h max)
Time (h) required to detect bacterial respiration of survivors
20
18
16
14
12
10
8
6
4
2
0
1.15 ppm
1.15 ppm
0.115 ppm
0 ppm
Bromo Lactam
Un-sub Lactam
Bromo Lactam
Un-sub Lactam
Bromo Lactam
Un-sub Lactam
MPG
M37+e
Lactams in MPG Carrier
Lactams in Main Wash Formulation
Lactams Carried into Main Wash via MPG
No Lactams
A
500 ppm
B
500 ppm
C
50 pmm (via 1:20 of 1000 ppm in MPG

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/051731

A. CLASSIFICATION OF SUBJECT MATTER
INV. A01N25/02 A01N25/30 A01N43/36 A01P1/00 A61K8/00
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)
A01N 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/052031 A2 (ALCON MANUFACTURING LTD) 2 May 2008 (2008-05-02) the whole document	1-12, 16-18, 20,21
X	EP 2 404 502 A2 (LABORATORI BALDACCI S.P.A.) 11 January 2012 (2012-01-11) examples 1, 4	1-5,7-9, 13-21
X	WO 2004/016588 A1 (BIOSIGNAL PTY LTD [AU]; KUMAR NARESH [AU]) 26 February 2004 (2004-02-26) cited in the application the whole document	7-9
X	WO 98/27811 A1 (BASF CORPORATION) 2 July 1998 (1998-07-02) the whole document	1-9,20

-/--

[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

"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	Date of mailing of the international search report
25 February 2014	04/03/2014

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	Breimaier, Waltraud

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/051731

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 92/13454 A1 (ISP INVESTMENTS INC.) 20 August 1992 (1992-08-20) the whole document	1-4,7-9, 20
X	WO 99/19256 A2 (ISP INVESTMENTS INC.) 22 April 1999 (1999-04-22) page 12 - page 13; claims 1, 5 page 8, line 6 - line 10	1-9,20
X	DE 39 10 921 C1 (BAYER AG) 17 May 1990 (1990-05-17) the whole document	7-9
X	US 5 266 590 A (ISP INVESTMENTS INC.) 30 November 1993 (1993-11-30) the whole document	1-5,7-9, 20
X	KR 2010 0068265 A (AGENCY SCIENCE TECH&RES) 22 June 2010 (2010-06-22) the whole document	1-4,7-9, 20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/051731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008052031 A2	02-05-2008	US 2008095863 A1	24-04-2008
		WO 2008052031 A2	02-05-2008
EP 2404502 A2	11-01-2012	NONE	
WO 2004016588 A1	26-02-2004	CA 2495784 A1	26-02-2004
		CN 1688543 A	26-10-2005
		EP 1539692 A1	15-06-2005
		JP 2006514610 A	11-05-2006
		US 2005215772 A1	29-09-2005
		WO 2004016588 A1	26-02-2004
WO 9827811 A1	02-07-1998	AU 5727498 A	17-07-1998
		CA 2270983 A1	02-07-1998
		EP 0946089 A1	06-10-1999
		ID 19230 A	28-06-1998
		US 6255250 B1	03-07-2001
		WO 9827811 A1	02-07-1998
WO 9213454 A1	20-08-1992	AU 656568 B2	09-02-1995
		AU 1419392 A	07-09-1992
		CA 2097707 A1	13-08-1992
		DE 69229169 D1	17-06-1999
		DE 69229169 T2	18-11-1999
		EP 0574492 A1	22-12-1993
		JP 3307930 B2	29-07-2002
		JP H06505270 A	16-06-1994
		WO 9213454 A1	20-08-1992
WO 9919256 A2	22-04-1999	AT 248773 T	15-09-2003
		AU 9799398 A	03-05-1999
		DE 69817857 D1	09-10-2003
		DE 69817857 T2	08-07-2004
		EP 1027288 A2	16-08-2000
		US 6255350 B1	03-07-2001
		WO 9919256 A2	22-04-1999
DE 3910921 C1	17-05-1990	AT 76254 T	15-06-1992
		AU 618889 B2	09-01-1992
		AU 5259090 A	11-10-1990
		BR 9001528 A	23-04-1991
		CA 2013729 A1	05-10-1990
		DE 3910921 C1	17-05-1990
		DE 59000129 D1	25-06-1992
		DK 0391168 T3	13-07-1992
		EP 0391168 A1	10-10-1990
		ES 2043157 T3	16-12-1993
		HU 204406 B	28-01-1992
		JP 2894622 B2	24-05-1999
		JP H02290802 A	30-11-1990
		MX 171046 B	27-09-1993
		US 5369118 A	29-11-1994
		ZA 9002586 A	30-01-1991
US 5266590 A	30-11-1993	NONE	
KR 20100068265 A	22-06-2010	EP 2192887 A1	09-06-2010
		JP 2010537977 A	09-12-2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/051731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		KR 20100068265 A	22-06-2010
		US 2013237613 A1	12-09-2013
		WO 2009029046 A1	05-03-2009