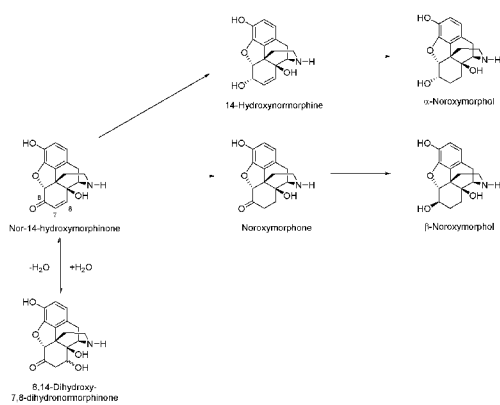




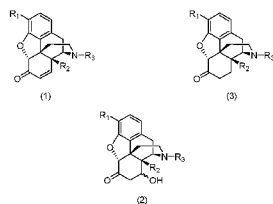
- (51) International Patent Classification:
C07D 489/08 (2006.01)
- (21) International Application Number:
PCT/GB2014/050324
- (22) International Filing Date:
5 February 2014 (05.02.2014)
- (25) Filing Language:
English
- (26) Publication Language:
English
- (30) Priority Data:
1313915.9 2 August 2013 (02.08.2013) GB
- (71) Applicant: JOHNSON MATTHEY PUBLIC LIMITED COMPANY [GB/GB]; 5th Floor, 25 Farringdon Street, London EC4A 4AB (GB).
- (72) Inventors: ARCHER, Nicolas; c/o Macfarlan Smith Limited, 10 Wheatfield Road, Edinburgh EH11 2QA (GB). DAVIES, Timothy; c/o Macfarlan Smith Limited, 10 Wheatfield Road, Edinburgh EH11 2QA (GB). PRICE, Amy; c/o University of Edinburgh, School of Chemistry, Joseph Black Building, West Mains Road, Edinburgh EH9 3JJ (GB). YOUNG, Maureen; c/o Macfarlan Smith Limited, 10 Wheatfield Road, Edinburgh EH11 2QA (GB).
- (74) Agent: WHITCOMBE, Nicole; Johnson Matthey PLC, Group Intellectual Property Department, Gate 20, Orchard Road, Royston, Hertfordshire SG8 5HE (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,

[Continued on next page]

(54) Title: PROCESS FOR THE PREPARATION OF MORPHINAN-6-ONE COMPOUNDS



(57) Abstract: The present provides a process for preparing a compound of formula (3), the process comprising the steps of: (a) providing an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2); and (b) treating the aqueous acidic solution of step (a) such that the compound of formula (2) dehydrates to form a compound of formula (1) and the compound of formula (1) is reduced to form an aqueous acidic solution of the compound of formula (3), wherein: the treating of step (b) is carried out at one or more temperatures greater than ambient in the presence of a hydrogenation catalyst and hydrogen gas; and wherein for the compounds of formulae (1), (2) and (3): i) R₁ is -OH, R₂ is -OH and R₃-H; or ii) R₁ is -OCH₃, R₂ is -H and R₃-CH₃; or iii) R₁ is -OH, R₂ is -H and R₃-CH₃; or iv) R₁ is -OCH₃, R₂ is -H and R₃-H; or v) R₁ is -OH, R₂ is -H and R₃-H; or vi) R₁ is -OCH₃, R₂ is -OH and R₃-H.



EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, **Published:**
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, — *with international search report (Art. 21(3))*
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

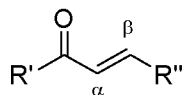
PROCESS FOR THE PREPARATION OF MORPHINAN-6-ONE COMPOUNDS

The present invention concerns processes for the synthesis of morphinan-6-one compounds, in particular noroxymorphone and salts thereof, having improved impurity profiles.

5

Findlay *et al* (Journal of the American Chemical Society, 1951, 73, 4001) describes the acid-catalyzed conversion of codeinone to 8-hydroxydihydrocodeinone.

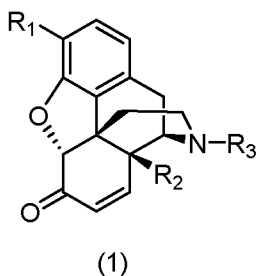
A recent concern in the pharmaceuticals industry has been to prepare Active Pharmaceutical Ingredients (APIs) which are free or substantially free of potentially genotoxic impurities (PGIs). Compounds which contain an α,β -unsaturated ketone moiety have been identified as potential genotoxins which need to be controlled. Routes to semi-synthetic opiate alkaloid APIs often involve intermediate compounds which contain an α,β -unsaturated ketone (ABUK). As intermediates, these compounds have no therapeutic benefit and, it has been argued, their presence in APIs as impurities increases the level of risk to a patient. As such, there has been much interest in reducing the level of ABUKs in APIs as far as possible.



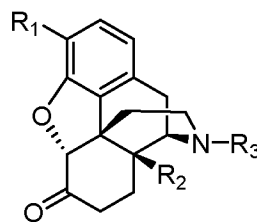
We have developed improved processes which overcome the disadvantages associated with prior art methods. The present processes are suitable for the large-scale or industrial manufacture of morphinan-6-one compounds, such as noroxymorphone and salts thereof.

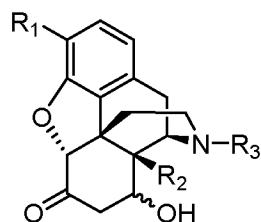
In a first aspect, therefore, the invention provides a process for preparing a compound of formula (3), the process comprising the steps of:

- (a) providing an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2); and
- (b) treating the aqueous acidic solution of step (a) such that the compound of formula (2) dehydrates to form a compound of formula (1) and the compound of formula (1) is reduced to form an aqueous acidic solution of the compound of formula (3),



(1)





(2)

wherein:

the treating of step (b) is carried out at one or more temperatures greater than ambient in the presence of a hydrogenation catalyst and hydrogen gas; and

5 wherein for the compounds of formulae (1), (2) and (3):

- i) R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$; or
- ii) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-CH_3$; or
- iii) R_1 is $-OH$, R_2 is $-H$ and R_3 $-CH_3$; or
- iv) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-H$; or
- 10 v) R_1 is $-OH$, R_2 is $-H$ and R_3 $-H$; or
- vi) R_1 is $-OCH_3$, R_2 is $-OH$ and R_3 $-H$.

In one preferred embodiment, R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$ for the compounds (1), (2) and (3).

15 The chemical names for the compounds (1), (2) and (3) are set out below:

	R_1	R_2	R_3	Compound (1)	Compound (2)	Compound (3)
i)	$-OH$	$-OH$	$-H$	Nor-14-hydroxymorphinone	8,14-Dihydroxy-7,8-dihydronormorphinone	Noroxymorphone
ii)	$-OCH_3$	$-H$	$-CH_3$	Codeinone	8-Hydroxy-7,8-dihydrocodeinone	Hydrocodone
iii)	$-OH$	$-H$	$-CH_3$	Morphinone	8-Hydroxy-7,8-dihydromorphinone	Hydromorphone
iv)	$-OCH_3$	$-H$	$-H$	Norcodeinone	8-Hydroxy-7,8-dihydronorcodeinone	Norhydrocodone
v)	$-OH$	$-H$	$-H$	Normorphinone	8-Hydroxy-7,8-dihydronormorphinone	Norhydromorphone
vi)	$-OCH_3$	$-OH$	$-H$	Nor-14-hydroxycodeinone	8,14-Dihydroxy-7,8-dihydronorcodeinone	Noroxycodone

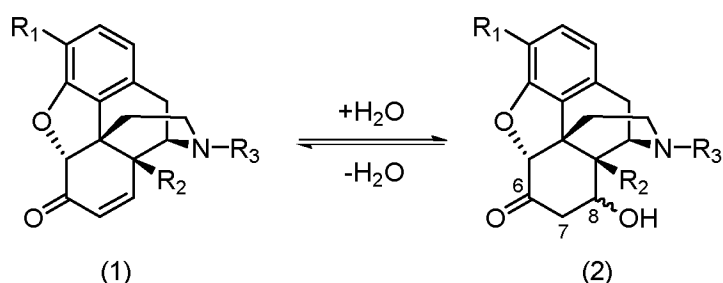
In step (a), the process comprises providing an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2).

20

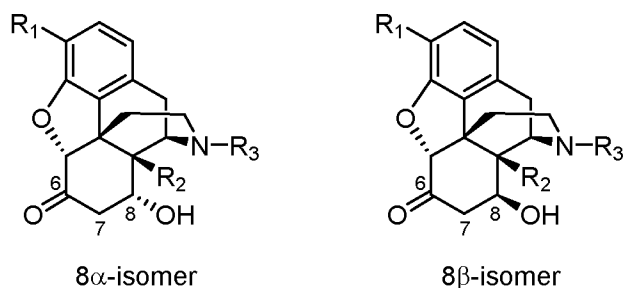
The compounds of formula (1) may be prepared by known methods. For example, nor-14-hydroxymorphinone and nor-14-hydroxycodeinone may be prepared by the methods described in

WO2005/028483 (to GlaxoSmithKline Australia Pty Ltd and Johnson Matthey PLC) starting from oripavine and thebaine respectively.

The compound (2) is an impurity. By "impurity" we mean a compound which is undesirably present and typically occurs in small quantities. The impurity may be present in the starting material, produced during the course of the reaction and/or is present in the product. Without wishing to be bound by theory, the inventors believe the compound (2) may originate from two sources – first, it may be formed during the synthesis of compound (1). Secondly, it is believed that under aqueous acidic conditions an equilibrium occurs between the compounds (1) and (2). This means that the compound (2) can be formed from the compound (1) when the compound (1) is treated with an aqueous acid:



Compound (2) contains a hydroxy substituent at C-8 and, as such, may comprise an 8 α -isomer, an 8 β -isomer or a combination thereof.



The aqueous acid solution may be prepared from water and an acid selected from the group consisting of acetic acid, phosphoric acid, citric acid, tartaric acid, oxalic acid, hydrochloric acid and hydrobromic acid. In one embodiment, the acid is acetic acid. In another embodiment, the acid is phosphoric acid. In yet another embodiment, the acid is hydrochloric acid.

Any suitable v/v ratio of water : acid may be used. For example, the v/v ratio of water : acid may be from about 100 : 0.01 to about 0.01 : 100, such as about 100 : 1 to about 1 : 100. In one embodiment, the v/v ratio of water : acid is from about 40 : 1 to about 60 : 1.

The quantities of water and/or acid are not particularly limiting provided there is enough water and/or acid to substantially dissolve the compound (1) (and compound (2)) and the water and/or acid do not significantly adversely affect the reaction. The quantity of water present in the catalyst and/or compound (1) (which may also be used wet) may be taken into account when calculating the total quantity of water to be used. The quantity of water present in the acid may also be taken into account when calculating the total quantity of water to be used.

The wt/wt ratio of compound (1) : acid may be in the range of about 0.01 : 200 g/g to about 200 : 0.1 g/g, such as about 100 : 1. The ratio of compound (1) : water may be in the range of about 20 : 0.005 to about 0.005 : 20, such as about 0.75 : 15 to about 15 : 0.75 g/g, for example about 1 : 10 to about 1 : 15 g/g.

The compound (1) (and compound (2)) is substantially dissolved in the water and acid. The dissolution of the compound (1) may be encouraged through the use of an aid such as stirring and/or sonication.

The pH of the initial reaction mixture may be any suitable pH which does not adversely affect the impurity profile of the reaction. In one embodiment, the pH of the initial reaction mixture may be in the range of about ≥ 1.0 to about < 7.0 . In some embodiments, the pH may be \geq about 1.5. In some embodiments, the pH may be \geq about 2.0. In some embodiments, the pH may be \leq about 6.5. In some embodiments, the pH may be \leq about 6.0. In some embodiments, the pH may be \leq about 5.5. In one embodiment, the pH of the initial reaction mixture may be in the range of about ≥ 2.0 to about \leq about 5.0. The pH of the reaction mixture may increase during the course of the reaction and, if desired, the pH may be lowered through the addition of further acid or a solution of acid/water.

The major part of compound (1) is present as a result of charging it as the starting material. A small proportion of compound (1), however, may be generated by dehydrating compound (2) which is present in the starting material as an impurity. Alternatively or in addition, compound (1) may be generated by the hydration of a small proportion of compound (1) to form compound (2) and the subsequent dehydration of compound (2) to reform compound (1). In step (b), the aqueous acidic solution of step (a) is treated such that the compound of formula (2) dehydrates to form a compound of formula (1) and the compound of formula (1) is reduced to form the aqueous acidic solution of the compound of formula (3). It is desirable to minimise the level of the compound (2) in the preparation of the compound (3) because, if it is allowed to remain, a phenomenon known as "ABUK regrowth" may occur. That is, the level of the compound (1) may increase in the compound (3) when the compound (3) is subjected to certain conditions which are commonly used in industry during the preparation of the compounds (3). These conditions include increasing the pH of an acidic solution of a compound (3) in order to precipitate it out of solution and/or drying the so formed free alkaloid. In the present instance, however, the process is carried out under forcing conditions such that the compound (2) dehydrates to the compound (1). The compound (1) is then chemically reduced by

hydrogenating the compound (1) in the presence of a hydrogenation catalyst and hydrogen gas to form the compound (3). In the present invention, therefore, the product (i.e. the compound of formula (3)) displays a greater resistance to ABUG regrowth. ABUG regrowth may be assessed by heating samples of the compound (3) at 80 °C overnight in order to force the growth of ABUG. This is known as "stress testing". Stress testing, therefore, is a method for assessing the propensity of a sample of compound (3) to undergo ABUG regrowth.

By "ambient temperature", we mean a temperature of 30°C or less, such as 0°C to 30°C, for example 10°C to 30°C. In the present process, however, the hydrogenation is carried out at one or more temperatures greater than ambient temperature i.e. greater than 30 °C and below the boiling point of the reaction mixture. The boiling point of the reaction mixture may vary depending on the pressure under which the hydrogenation reaction is conducted. In one embodiment, the hydrogenation may be carried out at one or more temperatures in the range of \geq about 75 °C to about \leq about 100 °C. In some embodiments, the hydrogenation is carried out at one or more temperatures \geq about 76 °C. In some embodiments, the hydrogenation is carried out at one or more temperatures \geq about 77 °C. In some embodiments, the hydrogenation is carried out at one or more temperatures \leq about 95 °C. In some embodiments, the hydrogenation is carried out at one or more temperatures \leq about 90 °C. In some embodiments, the hydrogenation is carried out at one or more temperatures \leq about 85 °C. In one preferred embodiment, the hydrogenation is carried out at one or more temperatures in the range of \geq about 77 °C to about \leq 85 °C, such as about 80 ± 2 °C.

The reaction mixture is generally heated to temperature before the hydrogenation reaction starts. Heating the reaction mixture to temperature may be carried out by purging the reaction vessel with one or more nitrogen/vacuum cycles (e.g. one, two, three or four cycles), optionally followed by one or more hydrogen/vacuum cycles (e.g. one, two or three cycles). The use of hydrogen in the purge cycles may be used on a small scale. However, on a larger, or indeed industrial scale, the hydrogen/vacuum cycles are generally not performed. During purging the reaction mixture may be agitated to encourage removal of dissolved oxygen. After the final purge cycle the vessel may be left under vacuum and agitated (by either stirring or shaking) whilst the vessel is heated. Once the reaction mixture reaches the desired temperature, the hydrogenation reaction may begin by exposing the reaction mixture to hydrogen gas.

The hydrogenation catalyst may be a heterogeneous or homogeneous catalyst, preferably a heterogeneous catalyst. The catalyst (whether heterogeneous or homogeneous) should be selected such that the catalyst preferentially reduces the double bond at C-7 and C-8 rather than reducing the C=O bond at C-6 (see Figure 1). In one embodiment, the heterogeneous catalyst is a heterogeneous platinum group metal (PGM) catalyst, for example, a heterogeneous palladium or platinum catalyst. In one embodiment, the heterogeneous catalyst is a heterogeneous palladium catalyst. Examples of palladium catalysts include but are not limited to colloidal palladium, palladium sponge, palladium

plate or palladium wire. Examples of platinum catalysts include but are not limited to colloidal platinum, platinum sponge, platinum plate or platinum wire.

5 The heterogeneous PGM catalyst may be a PGM on a solid support. The support may be selected from the group consisting of carbon, alumina, calcium carbonate, barium carbonate, barium sulfate, titania, silica, zirconia, ceria and a combination thereof. When the support is alumina, the alumina may be in the form of alpha-Al₂O₃, beta-Al₂O₃, gamma-Al₂O₃, delta-Al₂O₃, theta-Al₂O₃ or a combination thereof. When the support is carbon, the carbon may be in the form of activated carbon (e.g. neutral, basic or acidic activated carbon), carbon black or graphite (e.g. natural or synthetic
10 graphite). An example of a heterogeneous PGM catalyst is palladium on carbon. An example of another heterogeneous PGM catalyst is platinum on carbon.

The catalyst loading may be up to about 20 mole%. In one embodiment, the catalyst loading may be up to 10 mole% and, in another embodiment, may be in the range of about 0.001-10 mole %, for
15 example, 0.01-10 mole %. In another embodiment, the catalyst loading may be in the range of about 0.1-10.0 mole %.

While it is typically sufficient for a single charge of hydrogenation catalyst to be added to the reaction mixture, a second or further charge may be added and the hydrogenation continued if it has been
20 determined (e.g. via in-process analysis) that the reaction has not gone to completion and starting material remains.

There is no particular limitation on the pressure at which the hydrogenation is carried out. In this regard, the hydrogenation may conveniently be carried out with an initial hydrogen pressure in the
25 range of up to about 100 psi e.g. about 40 ± 5 psi.

While the use of protecting groups are generally not required in the present process, if it is found that the compound (1) has one or more substituents which may be adversely affected during the reduction, such as 3-hydroxy or 17-NH groups, these may be protected in a conventional manner.
30 Alternatively, if these substituents have been protected prior to the present process (for example, in steps leading to the synthesis of the compound (1)), the protecting group(s) may be selected such that simultaneous hydrogenation of the compound (1) and deprotection occurs to form the compound (3). Suitable protecting groups which are capable of withstanding hydrogenation or are removed during hydrogenation are known in the art (see, for example, "Protective Groups in Organic
35 Chemistry", Peter G. M. Wuts and Theodora W. Greene, Wiley Blackwell) and include unsubstituted or substituted benzyl groups.

The hydrogenation reaction is carried out for a period of time until it is determined that the reaction is complete. Completion of the reaction may be determined by in-process analysis or by identifying that
40 there is no longer an uptake of hydrogen gas. Typically the hydrogenation is complete within about 4

hours or less. The period of time over which the hydrogenation is carried out should be taken in account when carrying out the present process as it may adversely affect the impurity profile of the resulting compound (3). For example, when the compound (1) is nor-14-hydroxymorphinone and the compound (3) is noroxymorphone, it is generally not desirable to extend the duration of the hydrogenation as it has been found that this may lead to increased levels of 6 β -noroxymorphol. 6 β -Noroxymorphol is a known impurity in the synthesis of noroxymorphone and which may be identified using the HPLC method provided below. Without wishing to be bound by theory, it is believed that β -noroxymorphol may be produced from noroxymorphone via the ketone reduction at C-6 (see Figure 1). Extended hydrogenation therefore may lower the yield of the desired product through its further reaction, as well as generating an increased level of an unwanted impurity.

On completion of the reaction, the reaction vessel may be cooled and purged to remove excess hydrogen gas (or vice versa). The hydrogenation catalyst may be removed by any appropriate method, such as filtration, and the filtrate (containing the compound (3)) may be further treated as desired.

In one embodiment, the present process provides an aqueous acidic solution of compound (3) comprising \leq about 0.05 area % of the compound of formula (1) as determined by HPLC, such \leq about 0.04 area %, for example, \leq about 0.03 area %. In some embodiments, the process provides an aqueous acidic solution of compound (3) comprising \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide an aqueous acidic solution of compound (3) comprising \leq about 0.005 area % of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide an aqueous acidic solution of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

In another embodiment, the process further comprises treating the aqueous acidic solution of compound (3) to form solid salts of compound (3) (i.e. acid adducts of the compound (3) which are in a solid form, such as a precipitate). Examples of solid salts include but are not limited to noroxymorphone acetate or noroxymorphone hydrochloride. It is also envisaged that the aqueous acidic solution compound (3) may undergo a salt exchange to form an aqueous acidic solution of compound (3) comprising a different acid. For example, a solution of noroxymorphone acetate may undergo a salt exchange to form a solution of noroxymorphone hydrochloride.

In one embodiment, the solid salt of compound (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC, such \leq about 0.04 area %, for example, \leq about 0.03 area %. In some embodiments, the solid salt of compound (3) comprises \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide a solid salt of compound (3) comprising \leq about 0.005 area

% of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide an aqueous acidic solution of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

5

In yet another embodiment, the process further comprises treating the aqueous acidic solution of compound (3) at about 45-50 °C with a base to form the alkaloid of compound (3). An example of a suitable base is ammonium hydroxide. Sufficient base is typically added so that the compound (3) precipitates out of solution. Generally, precipitates of compound (3) start to become visible at about pH 7 and typically sufficient base is added to increase the pH to about 8.5-9.0 or above. This ensures that the compound (3) is in free base form, as well as allowing maximum recovery of the compound (3). The alkaloid of compound (3) may be collected (e.g. by filtration), optionally washed one or more times (e.g. with Alcohol M, which is 96% ethanol denatured with 4% methanol) and dried.

10

In another embodiment, the process further comprises treating the solid salt of compound (3) to form the free alkaloid. This may be carried out by redissolving the solid salt to form a solution of the salt of compound (3) and treating the solution with a base as described above. The alkaloid of the compound (3) may be collected (e.g. by filtration), optionally washed one or more times and dried.

15

Howsoever the alkaloid of compound (3) is prepared, the alkaloid may comprise \leq about 0.05 area % of the compound of formula (1) as determined by HPLC, such as \leq about 0.04 area %, for example, \leq about 0.03 area %. In some embodiments, the alkaloid of compound (3) comprises \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide the alkaloid of compound (3) comprising \leq about 0.005 area % of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide the alkaloid of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

20

In a second aspect, the invention provides a process for preparing a compound of formula (3), the process comprising the steps of:

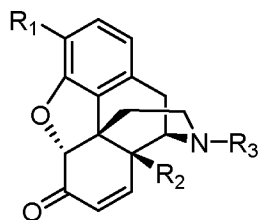
30

(I) hydrogenating an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2), wherein the hydrogenation is carried out at ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas; and

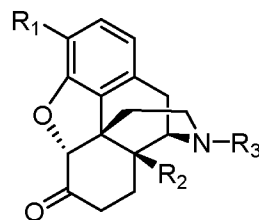
35

(II) hydrogenating the product of step (I) at one or more temperatures greater than ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas to form an aqueous acidic solution of the compound of formula (3) comprising \leq 0.05 area % of the compound of formula (1) as determined by HPLC and \leq 2.00 area % of a compound of formula (4) as determined by HPLC,

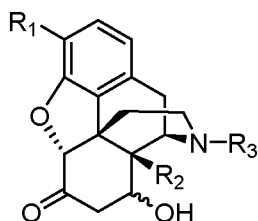
40



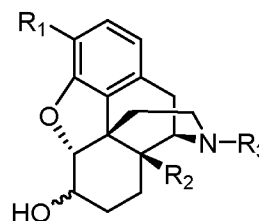
(1)



(3)



(2)



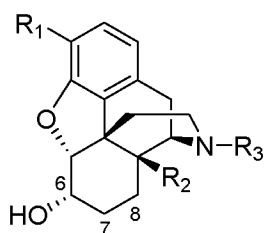
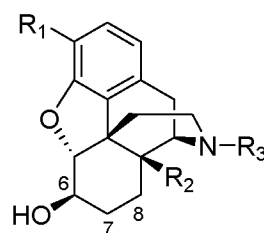
(4)

wherein for the compounds of formulae (1), (2), (3) and 4:

- 5 i) R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$; or
 ii) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-CH_3$; or
 iii) R_1 is $-OH$, R_2 is $-H$ and R_3 $-CH_3$; or
 iv) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-H$; or
 v) R_1 is $-OH$, R_2 is $-H$ and R_3 $-H$; or
 10 vi) R_1 is $-OCH_3$, R_2 is $-OH$ and R_3 $-H$.

Compounds (1), (2), (3) and the acidic solution are as generally described above. In one preferred embodiment, R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$ for the compounds (1), (2), (3) and (4).

- 15 The compound of formula (4) is produced as an impurity in the transformation of compound (1) to compound (3). The compound (4) contains a hydroxy substituent at C-6 and, as such, may comprise a 6α -isomer, a 6β -isomer or a combination thereof.

 6α -isomer 6β -isomer

20

Carrying out a hydrogenation reaction at temperatures greater than ambient on some compounds of formula (1) may result in increased levels of the compound of formula (4) being produced. For example, during the synthesis of noroxymorphone, increased levels of 6α -noroxymorphol may occur during the hydrogenation of nor-14-hydroxymorphinone at one or more temperatures above ambient.

As can be seen from Figure 1, without wishing to be bound by theory, it is believed that 6 α -noroxymorphol is generated from 14-hydroxynormorphinone and that 6 β -noroxymorphol from noroxymorphone. Accordingly, it is desirable to develop a process which is capable of minimising or eliminating the production of the compound (4). Without wishing to be bound by theory, therefore, it is believed that the two-step process is suitable for (a) minimising or eliminating the production of compound (4) from compound (1), (b) dehydrating compound (2) to compound (1) under forcing conditions, and (c) chemically reducing compound (1) to form compound (3). As described above, the product of the reaction (i.e. the compound of formula (3)) displays a greater resistance to ABUG regrowth.

In step (I), therefore, the aqueous acidic solution comprising the compound of formula (1) and, as an impurity, the compound of formula (2) is hydrogenated at ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas.

By "ambient temperature", we mean a temperature of 30°C or less such as 0°C to 30°C, for example 10°C to 30°C. The hydrogenation conditions described above for the first aspect (other than the temperature) generally apply to this aspect of the invention.

In step (II), the product of step (I) is hydrogenated at one or more temperatures greater than ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas to form an aqueous acidic solution of the compound of formula (3) comprising ≤ 0.05 area % of the compound of formula (1) as determined by HPLC and ≤ 2.00 area % of a compound of formula (4) as determined by HPLC. The hydrogenation conditions described above for the first aspect (including the temperature) generally apply to this aspect of the invention.

In one embodiment, the hydrogen gas present in step (I) may be substantially removed from the reaction vessel before the reaction mixture is heated to one or more temperatures above ambient. The hydrogen gas may be removed from the reaction vessel by purging. Once the reaction mixture is at the desired temperature, the reaction mixture may be exposed once again to hydrogen.

On completion of the reaction, the reaction vessel may be cooled and purged to remove excess hydrogen gas (or vice versa). The hydrogenation catalyst may be removed by any appropriate method, such as filtration, and the filtrate (containing the compound (3)) may be further treated as desired.

The process forms an aqueous acidic solution of the compound of formula (3) comprising ≤ 0.05 area % of the compound of formula (1) as determined by HPLC and ≤ 2.00 area % of a compound of formula (4) as determined by HPLC.

In one embodiment, the process provides an aqueous acidic solution of compound (3) comprising \leq about 0.04 area % of compound (1) as determined by HPLC, for example, \leq about 0.03 area %. In some embodiments, the process provides an aqueous acidic solution of compound (3) comprising \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide an aqueous acidic solution of compound (3) comprising \leq about 0.005 area % of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide an aqueous acidic solution of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

In one embodiment, the process provides an aqueous acidic solution of comprising \leq 1.75 area % of a compound of formula (4) as determined by HPLC, such as \leq 1.50 area %, for example, \leq 1.25 area % or \leq 1.00 area %.

In another embodiment, the process further comprises treating the aqueous acidic solution of compound (3) to form solid salts of compound (3) (i.e. acid adducts of the compound (3) which are in a solid form, such as a precipitate). Examples of solid salts include but are not limited to noroxymorphone acetate or noroxymorphone hydrochloride. It is also envisaged that the aqueous acidic solution compound (3) may undergo a salt exchange to form an aqueous acidic solution of compound (3) comprising a different acid. For example, a solution of noroxymorphone acetate may undergo a salt exchange to form a solution of noroxymorphone hydrochloride.

In one embodiment, the solid salt of compound (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC, such \leq about 0.04 area %, for example, \leq about 0.03 area %.

In some embodiments, the solid salt of compound (3) comprises \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide a solid salt of compound (3) comprising \leq about 0.005 area % of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide a solid salt of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

In another embodiment, the solid salt of compound (3) comprises \leq 1.75 area % of a compound of formula (4) as determined by HPLC, such as \leq 1.50 area %, for example, \leq 1.25 area % or \leq 1.00 area %. In some embodiments, the solid salt of compound (3) comprises \leq 1.00 area % of the 6 α -isomer of a compound of formula (4), such as \leq 0.75 area %, for example, \leq 0.50 area % or \leq 0.40 area %. In some embodiments, the solid salt of compound (3) comprises \leq 1.00 area % of the 6 β -isomer of a compound of formula (4), such as \leq 0.75 area %, for example, \leq 0.50 area % or \leq 0.40 area %.

In yet another embodiment, the process further comprises treating the aqueous acidic solution of compound (3) at about 45-50 °C with a base to form the alkaloid of compound (3). An example of a suitable base is ammonium hydroxide. Sufficient base is typically added so that the compound (3) precipitates out of solution. Generally, precipitates of compound (3) start to become visible at about pH 7 and typically sufficient base is added to increase the pH to about 9. This ensures that the compound (3) is in free base form, as well as allowing maximum recovery of the compound (3). The alkaloid of compound (3) may be collected (e.g. by filtration), optionally washed one or more times (e.g. with Alcohol M) and dried.

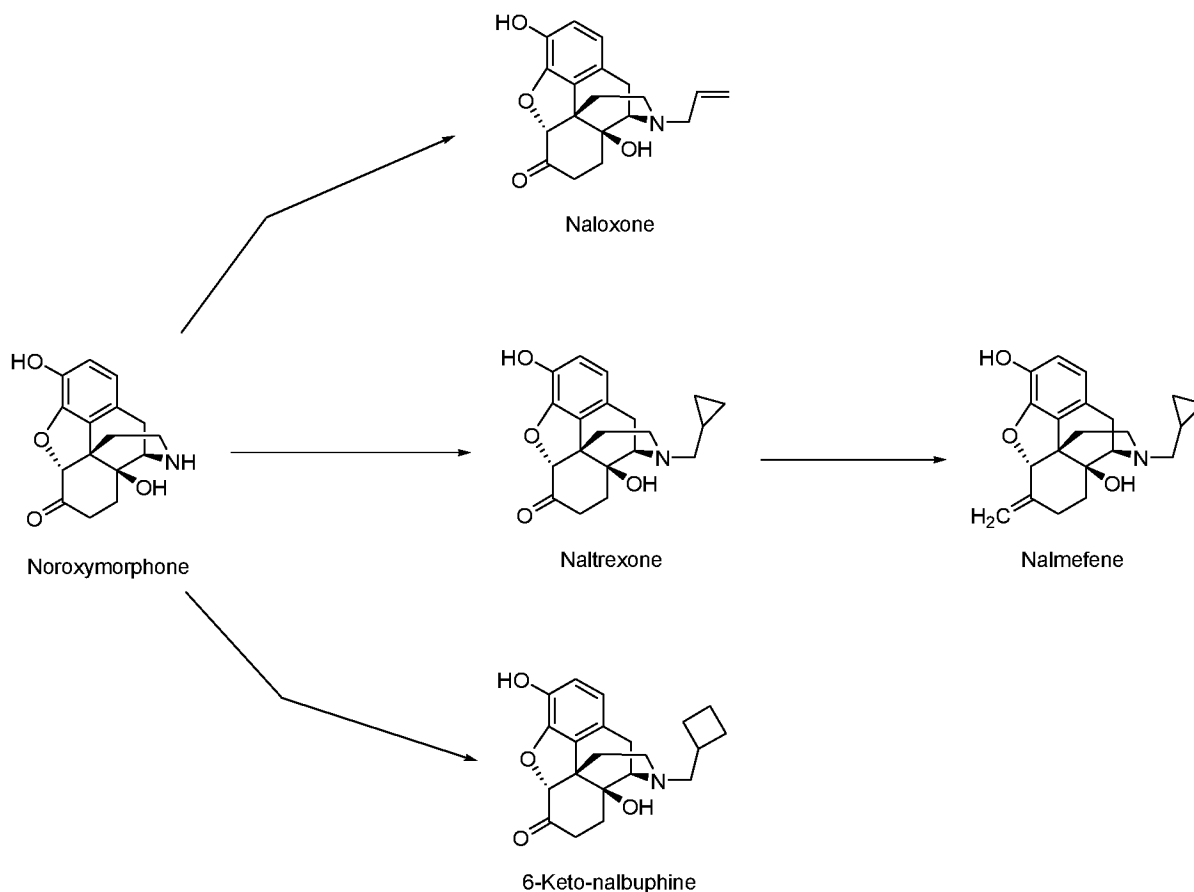
10 In another embodiment, the process further comprises treating the solid salt of compound (3) to form the free alkaloid. This may be carried out by redissolving the solid salt to form a solution of the salt of compound (3) and treating the solution with a base as described above. The compound (3) alkaloid may be collected (e.g. by filtration), optionally washed one or more times and dried.

15 However the alkaloid of compound (3) is prepared, the alkaloid may comprise \leq about 0.05 area % of the compound of formula (1) as determined by HPLC, such as \leq about 0.04 area %, for example, \leq about 0.03 area %. In some embodiments, the alkaloid of compound (3) comprises \leq about 0.02 area % of the compound of formula (1), for example, \leq about 0.01 area %. It is envisaged that, in some embodiments, the process could provide the alkaloid of compound (3) comprising \leq about 0.005 area % of the compound of formula (1), such as \leq about 0.004 area %, for example \leq about 0.003 area % e.g. \leq about 0.002 area % or \leq about 0.001 area %. In some embodiments, the process may provide the alkaloid of compound (3) comprising compound of formula (1) in a non-detectable amount (as determined by HPLC).

25 In another embodiment, the alkaloid of compound (3) comprises \leq 1.75 area % of a compound of formula (4) as determined by HPLC, such as \leq 1.50 area %, for example, \leq 1.25 area % or \leq 1.00 area %. In some embodiments, the solid salt of compound (3) comprises \leq 1.00 area % of the 6 α -isomer of a compound of formula (4), such as \leq 0.75 area %, for example, \leq 0.50 area % or \leq 0.40 area %. In some embodiments, the solid salt of compound (3) comprises \leq 1.00 area % of the 6 β -isomer of a compound of formula (4), such as \leq 0.75 area %, for example, \leq 0.50 area % or \leq 0.40 area %.

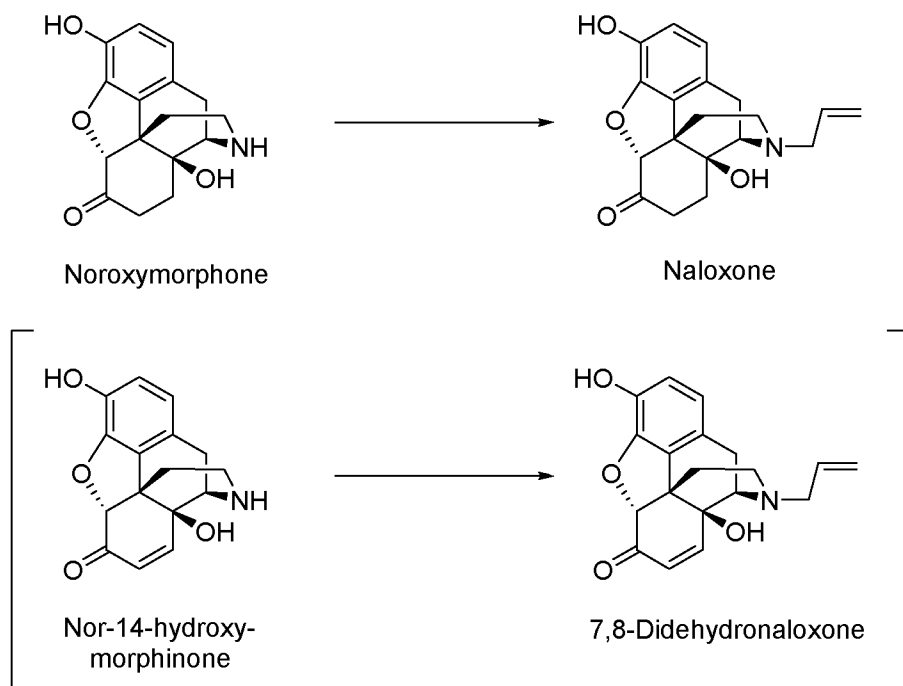
In another aspect, the present invention provides a compound of formula (3) comprising a compound of formula (1) in an amount \leq 0.01 area % as determined by HPLC,

35



Naloxone, naltrexone, nalmefene, and 6-keto-nalbuphine may be prepared by known methods. In this regard, naloxone may be prepared by reacting noroxymorphone with sodium hydrogencarbonate and allyl bromide (see for example US3254088 to Lewenstein et al). Naltrexone and 6-keto-nalbuphine may be prepared according to the reductive alkylation method described in US8318937 and US8119803 (to Johnson Matthey PLC). Nalmefene may be prepared from naltrexone using methylenetriphenylphosphorane (Hahn et al, J. Med. Chem., 18, 259 (1975)).

10 Noroxymorphone prepared according to the processes of the present invention comprises a low level of ABUG and, furthermore, displays a greater resistance to ABUG regrowth. As such, products prepared from noroxymorphone may also exhibit lower levels of ABUG and a greater resistance to ABUG regrowth. For example, noroxymorphone prepared according to the processes of the present invention has been allylated to prepare naloxone comprising ≤ 35 ppm of the ABUG 7,8-
 15 didehydronaloxone.



Embodiments and/or optional features of the invention have been described above. Any aspect of the invention may be combined with any other aspect of the invention, unless the context demands otherwise. Any of the embodiments or optional features of any aspect may be combined, singly or in combination, with any aspect of the invention, unless the context demands otherwise.

The invention will now be described by way of the following non-limiting Examples and with reference to the accompanying figures in which:

Figure 1 illustrates the conversion of nor-14-hydroxymorphinone (a compound of formula (1)) to noroxymorphone (a compound of formula (3)). The figure also illustrates 8,14-dihydroxy-7,8-dihydromorphinone (a compound of formula (2)) and the equilibrium between it and nor-14-hydroxymorphinone. The formation of α -noroxymorphol and β -noroxymorphol is also shown.

Figure 2 is a graph comparing related substances levels (6α -noroxymorphol, and 6β -noroxymorphol/oxymorphone) in hydrogenation liquors where the duration of the 80 °C hydrogenation was varied.

20 **Examples**

HPLC Method

Naloxone Hydrochloride European Pharmacopeia Method

25 Column : Zorbax Eclipse XDB-C8 5 microns 12.5cm x 4.0 mm

Mobile Phase : Prepare a solution as follows: dissolve 1.17 g sodium octanesulphonate in 1000 ml water, adjust to pH 2.0 with a 50% v/v solution of phosphoric acid
 : A 20 ml acetonitrile, 40 ml THF and 940 ml of above solution
 : B 170 ml acetonitrile, 40 ml THF and 790 ml of above solution

5 Flow rate : 1.5 ml / minute
 Temperature : 40 °C
 Detector : UV @ 230 nm
 Injection Volume : 20 microlitres
 Run Time : 45 minutes

10

Linear gradient:

Time (min)	A % v/v	B % v/v
0	100	0
40	0	100
50	0	100
55	100	0
65	100	0

Sample Preparation

Noroxymorphone liquors

15 The hydrogenation liquors were sampled (100 mL) and diluted in a 5 mL volumetric flask with 0.1M HCl to the mark.

Noroxymorphone solids

Sample 25 mg of solid and dilute to the mark in 25 mL volumetric flask with 0.1M HCl.

20

Naloxone In Process Check (IPC) liquors

Sample 300 µL of reaction liquors and dilute to the mark in a 5 mL volumetric flask with 0.1M HCl.

Naloxone Solids

25 Sample ~40 mg of solids and dilute to the mark in a 25 mL volumetric flask with 0.1M HCl.

Retention times of known impurities in Noroxymorphone

Approximate Retention Time (min)	Relative Retention Time	Substance
10.5	0.70	6α-Noroxymorphol
12	0.81	6β-Noroxymorphol/ Oxymorphone
16	1.10	Nor-14-hydroxymorphinone

Retention times of known impurities in Naloxone

Approximate Retention Time (min)	Relative Retention Time	Substance
11.5	0.83	Noroxymorphone
43	3.1	3-O-Allylnaloxone
46.5	3.4	2,2-Bisnaloxone

Experimental Methods

The following are the general experimental procedures. Experimental variables e.g. pressure were altered depending on the parameter investigated. The masses and volumes used for each material input for each experiment given in the text are supplied in the tables below along with any deviations from the general experimental method.

Apparatus Used

The hydrogenations were carried out on either a Parr Shaker or Stirrer hydrogenator. All basifications were carried out in appropriately sized flange flasks fitted with a thermocouple, condenser and a temperature controlled isomantle.

Analysis

The analysis was carried out using High Performance Liquid Chromatography (HPLC) using the Naloxone European Pharmacopeia method. The method was used as good separation of the majority of impurities with Noroxymorphone is achieved.

A) General Experimental Outline for Single Hydrogenation Followed by Basification

20

General Ambient Only Hydrogenation

- 1) Charge Nor-14-hydroxymorphinone (A g) to a hydrogenation flask. Add water (B mL), 85% w/w phosphoric acid (C mL) and 5% Pd/C catalyst (D g).
- 2) Fit the vessel to the hydrogenator and purge the vessel with nitrogen (3 x) and hydrogen (3 x).
- 3) Pressurise the hydrogenation vessel with hydrogen to 40 ± 3 PSI.
- 4) Commence the agitation (the shaker hydrogenator is fixed rate, for the stirrer hydrogenator fitted with a gas entrainment stirrer the agitator was set to 1200 rpm).
- 5) Allow the hydrogenation reaction to continue for 2 hours.
- 6) Turn off the agitation, vent the hydrogen and remove the hydrogenation vessel from the hydrogenator.
- 7) Deposit harbolite (~2 g) on a 42 mm filter.
- 8) Filter the hydrogenation liquors through the harbolite and wash the filter with water (A mL).

35

Isolation of Noroxymorphone Alkaloid

- 9) Charge the hydrogenation liquors to an appropriately sized flange flask, fitted with a thermocouple, temperature controlled isomantle, stirrer and condenser.
- 5 10) Heat the batch to 45-50 °C.
- 11) Mix Ammonia S.G. 0.88 (E mL) with water (E mL) to make 50:50 aqueous ammonia.
- 12) pH adjust the batch with the aqueous ammonia to pH 8.5-9.0, checking the pH with a calibrated pH meter.
- 13) Stir the batch at 45-50 °C for 15 minutes and recheck the pH is within range.
- 10 14) Allow the batch to cool to ambient temperature and stir for 2 hours.
- 15) Filter the batch under suction filtration and wash the filter cake with water (A mL) and Alcohol M (A mL). Alcohol M is 96% ethanol denaturated with 4% methanol.
- 16) Dry the Noroxymorphone Alkaloid in a 55 °C oven overnight.

15 **B) General Experimental Outline for Noroxymorphone Pure Process (Low ABUK hydrogenation and Basification)**

Low ABUK Hydrogenation of Nor-14-hydroxymorphinone to Noroxymorphone

- 20 1) Charge Nor-14-hydroxymorphinone (A g) to a hydrogenation flask. Add water (B mL), 85% w/w phosphoric acid (C mL) and 5% Pd/C catalyst (D g).
- 2) Fit the vessel with the heating jacket on to the hydrogenator and purge the vessel with nitrogen (3 x) and hydrogen (3 x).
- 3) Pressurise the hydrogenation vessel with hydrogen to 40 ± 3 PSI.
- 25 4) Commence the agitation (the shaker hydrogenator is fixed rate, for the stirrer hydrogenator fitted with a gas entrainment stirrer the agitator was set to 1200 rpm).
- 5) Allow the ambient hydrogenation reaction to continue for 2 hours.
- 6) Evacuate the flask and turn the heater on to the set point 80 °C.
- 7) Allow the flask to heat to 80 ± 2 °C with agitation.
- 30 8) Once a temperature of 80 ± 2 °C is attained, pressurise the hydrogenation vessel with hydrogen to 40 ± 3 PSI.
- 9) Allow the hydrogenation reaction to continue for 2 hours.
- 10) Evacuate the hydrogenation vessel and allow the reaction liquors to cool to ~30°C.
- 11) Turn off the agitation and remove the hydrogenation vessel from the hydrogenator.
- 35 12) Deposit harbolite (~2 g) on a 42 mm filter.
- 13) Filter the hydrogenation liquors through the harbolite and wash the filter with water (A mL).

Isolation of Noroxymorphone Alkaloid

- 14) Charge the hydrogenation liquors to an appropriately sized flange flask, fitted with a thermocouple, temperature controlled isomantle, stirrer and condenser.
- 15) Heat the batch to 45-50 °C.
- 16) Mix Ammonia S.G. 0.88 (E mL) with water (E mL) to make 50:50 aqueous ammonia.
- 5 17) pH adjust the batch with the aqueous ammonia to pH 8.5-9.0, checking the pH with a calibrated pH meter.
- 18) Stir the batch at 45-50 °C for 15 minutes and recheck the pH is within range.
- 19) Allow the batch to cool to ambient temperature and stir for 2 hours.
- 20) Filter the batch under suction filtration and wash the filter cake with water (A mL) and Alcohol M (A mL). Alcohol M is 96% ethanol denaturated with 4% methanol.
- 10 21) Dry the Noroxymorphone Alkaloid in a 55 °C oven overnight.

Example 1

- 15 The following experiments were carried out using a Parr Shaker hydrogenator.

Expt.	A	B	C	D	E	Comments
1.1*	3.75	51	1	0.037	--	Method A, steps 1-8 carried out.
1.2 [‡]	3.75	51	1	0.037	--	Method A was carried out where steps 3-6 (of Method A) were replaced by steps 7-10 of Method B.
1.3 [‡]	3.75	49	3	0.037	--	Method A was carried out where steps 3-6 (of Method A) were replaced by steps 7-10 of Method B. C = acetic acid.

* Comparative

[‡] According to the invention

- 20 HPLC analysis:

Expt.	Reaction temp. (°C)	6 α -Noroxymorphol (area %)	6 β -Noroxymorphol/ Oxymorphone (area %)
1.1*	Ambient	0.41	0.43
1.2 [‡]	80	1.39	0.10
1.3 [‡]	80	1.22	0.14

* Comparative

[‡] According to the invention

Example 2

- 25 Example 2 was carried out where the duration of the ambient phase of the hydrogenation was kept at 2 hours and the length of the 80 °C hydrogenation of Method B was varied at 2, 4 and 10 hours. The hydrogenation liquors were analysed for related substances using the European Pharmacopeia HPLC Method provided above.

The experiment was carried out using a Parr Shaker hydrogenator.

A	B	C	D	E	Comments
20	275	5	0.2	5	Method B, steps 1-21 carried out. Liquors split into three lots after the ambient hydrogenation; Examples 2.2, 2.3 and 2.4 were hydrogenated hot (steps 7-10) for 2, 4 and 10 hours respectively.

5 HPLC analysis:

Sample	Example 2.1	Example 2.2	Example 2.3	Example 2.4
Related Substances (Area %)	2 hr ambient hydrogenation	2 hr 80 °C hydrogenation	4 hr 80 °C hydrogenation	10 hour 80 °C hydrogenation
6α-Noroxymorphol	0.42	0.54	0.54	0.63
6β-Noroxymorphol/ Oxymorphone	0.19	0.49	0.59	0.99
Nor-14- hydroxymorphinone	0.02	--	--	--
Sample		Example 2.5	Example 2.6	Example 2.7
Related Substances (Area %)	(Liquors put through to 80 °C hydrogenation)	Noroxymorphone from Example 2.2	Noroxymorphone from Example 2.3	Noroxymorphone from Example 2.4
6α-Noroxymorphol	n/a	0.39	0.48	0.42
6β-Noroxymorphol/ Oxymorphone	n/a	0.50	0.58	0.68
Nor-14- hydroxymorphinone	n/a	0.01	0.01	--

The data above demonstrates that the levels of nor-14-hydroxymorphinone are 0.01 area % or less for the high temperature hydrogenations (see Examples 2.2-2.7). In Examples 2.2-2.4 and 2.7, the ABUK (nor-14-hydroxymorphinone) was non-detectable by HPLC.

Figure 2 illustrates the results provided in the table above where it can be seen that the level of α -noroxymorphol does not substantially increase greatly after the 2 hours 80 °C.

15 **Example 3** (comparative)

The following experiment was carried out using a Parr stirrer hydrogenator.

A	B	C	D	E	Comments
---	---	---	---	---	----------

20	275	5	0.2	16	Method A used (steps 1-16)
----	-----	---	-----	----	----------------------------

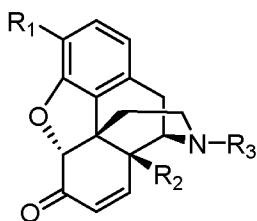
HPLC analysis:

Sample	Example 3.1	Example 3.2	Example 3.3
	Hydrogenation liquors after hydrogenation for 2 hrs at ambient temperature	Isolated noroxymorphone (i.e. product obtained after Method A, step 16)	Noroxymorphone dried at 80 °C
Nor-14-hydroxymorphinone (ppm, corrected for LOD)	41.8	280.04	301.52

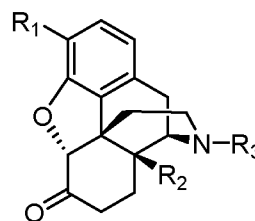
- 5 The ABUK level in the hydrogenation liquors appeared low at 41.8 ppm. However, regrowth of the ABUK occurred upon basification of the liquors at 45 °C with the ABUK level increasing to 280 ppm. Furthermore, on stress-testing the isolated noroxymorphone at 80 °C, the ABUK level increased even more to 301.52 ppm.
- 10 This Example can be compared with Example 2 where the ABUK level consistently remained at 0.01 area % (i.e. 100 ppm) or less throughout the experiment. In Examples 2.2-2.4 and 2.7, the ABUK was non-detectable by HPLC.

Claims

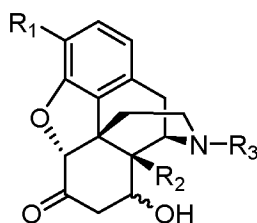
1. A process for preparing a compound of formula (3), the process comprising the steps of:
- (a) providing an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2); and
- (b) treating the aqueous acidic solution of step (a) such that the compound of formula (2) dehydrates to form a compound of formula (1) and the compound of formula (1) is reduced to form an aqueous acidic solution of the compound of formula (3),



(1)



(3)



(2)

wherein:

the treating of step (b) is carried out at one or more temperatures greater than ambient in the presence of a hydrogenation catalyst and hydrogen gas; and

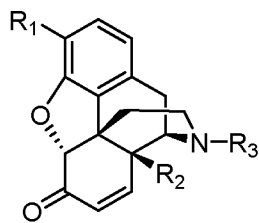
wherein for the compounds of formulae (1), (2) and (3):

- i) R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$; or
- ii) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-CH_3$; or
- iii) R_1 is $-OH$, R_2 is $-H$ and R_3 $-CH_3$; or
- iv) R_1 is $-OCH_3$, R_2 is $-H$ and R_3 $-H$; or
- v) R_1 is $-OH$, R_2 is $-H$ and R_3 $-H$; or
- vi) R_1 is $-OCH_3$, R_2 is $-OH$ and R_3 $-H$.

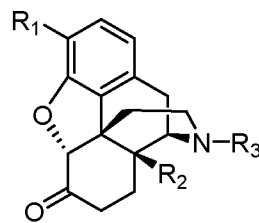
2. A process according to claim 1, wherein R_1 is $-OH$, R_2 is $-OH$ and R_3 $-H$ for the compounds (1), (2) and (3).

3. A process according to claim 1 or claim 2, wherein the acid in the aqueous acidic solution is selected from the group consisting of acetic acid, phosphoric acid, citric acid, tartaric acid, oxalic acid, hydrochloric acid, hydrobromic acid and a mixture thereof.

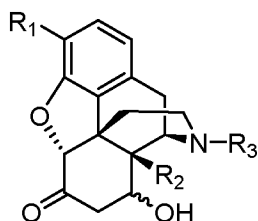
4. A process according to any one of the preceding claims, wherein the treating of step (b) is carried out at one or more temperatures in the range of \geq about 75°C to about \leq 100°C.
5. A process according to any one of the preceding claims, wherein the hydrogenation catalyst is a heterogeneous or homogenous catalyst, preferably a heterogeneous catalyst.
6. A process according to claim 5, wherein the heterogeneous catalyst is a heterogeneous platinum group metal (PGM) catalyst, preferably a heterogeneous palladium catalyst.
7. A process according to any one of the preceding claims, wherein the aqueous acidic solution of the compound of formula (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC.
8. A process according to any one of the preceding claims, wherein the process further comprises treating the aqueous acidic solution of the compound of formula (3) to form solid salts of compound (3).
9. A process according to claim 8, wherein the solid salt of the compound of formula (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC.
10. A process according to claim 8 or claim 9, wherein the process further comprises treating the solid salt of the compound of formula (3) to form the free alkaloid.
11. A process according to any one of claims 1 to 7, wherein the process further comprises treating the aqueous acidic solution of the compound of formula (3) at about 45-50 °C with a base to form the alkaloid of the compound of formula (3).
12. A process according to 10 or claim 11, wherein the alkaloid of the compound of formula (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC.
13. A process for preparing a compound of formula (3), the process comprising the steps of:
- (I) hydrogenating an aqueous acidic solution comprising a compound of formula (1) and, as an impurity, a compound of formula (2), wherein the hydrogenation is carried out at ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas; and
 - (II) hydrogenating the product of step (I) at one or more temperatures greater than ambient temperature in the presence of a hydrogenation catalyst and hydrogen gas to form an aqueous acidic solution of the compound of formula (3) comprising \leq 0.05 area % of the compound of formula (1) as determined by HPLC and \leq 2.00 area % of a compound of formula (4) as determined by HPLC,



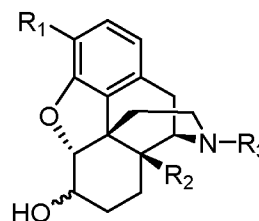
(1)



(3)



(2)



(4)

wherein for the compounds of formulae (1), (2), (3) and 4:

5

- i) R_1 is $-OH$, R_2 is $-OH$ and $R_3 -H$; or
- ii) R_1 is $-OCH_3$, R_2 is $-H$ and $R_3 -CH_3$; or
- iii) R_1 is $-OH$, R_2 is $-H$ and $R_3 -CH_3$; or
- iv) R_1 is $-OCH_3$, R_2 is $-H$ and $R_3 -H$; or
- v) R_1 is $-OH$, R_2 is $-H$ and $R_3 -H$; or
- vi) R_1 is $-OCH_3$, R_2 is $-OH$ and $R_3 -H$.

10

14. A process according to claim 13, wherein R_1 is $-OH$, R_2 is $-OH$ and $R_3 -H$ for the compounds (1), (2), (3) and (4).

15

15. A process according to claim 13 or claim 14, wherein the acid in the aqueous acidic solution is selected from the group consisting of acetic acid, phosphoric acid, citric acid, tartaric acid, oxalic acid, hydrochloric acid, hydrobromic acid and a mixture thereof.

16.

A process according to any one of the preceding claims, wherein the hydrogenation catalysts of step (I) and step (II) are independently selected from a heterogeneous or homogenous catalyst, preferably a heterogeneous catalyst.

20

17. A process according to claim 16, wherein the heterogeneous catalyst is a heterogeneous platinum group metal (PGM) catalyst, preferably a heterogeneous palladium catalyst.

25

18. A process according to any one of claims 13 to 17, wherein the hydrogenation of step (II) is carried out at one or more temperatures in the range of \geq about $75^\circ C$ to about $\leq 100^\circ C$.

19. A process according to any one of claims 13 to 18, wherein the process further comprises treating the aqueous acidic solution of the compound of formula (3) to form solid salts of compound (3).

5 20. A process according to claim 19, wherein the solid salt of the compound of formula (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC.

21. A process according to claim 19 or claim 20, wherein the process further comprises treating the solid salt of the compound of formula (3) to form the free alkaloid.

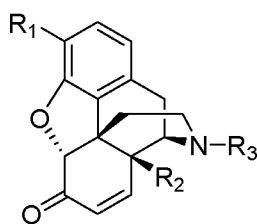
10

22. A process according to any one of claims 13 to 18, wherein the process further comprises treating the aqueous acidic solution of the compound of formula (3) at 45-50 °C with a base to form the alkaloid of the compound of formula (3).

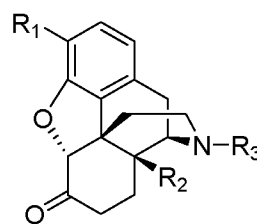
15 23. A process according to 21 or claim 22, wherein the alkaloid of the compound of formula (3) comprises \leq about 0.05 area % of the compound of formula (1) as determined by HPLC.

24. A compound of formula (3) comprising a compound of formula (1) in an amount \leq 0.01 area % as determined by HPLC,

20



(1)



(3)

wherein for the compounds of formulae (1) and (3):

- 25
- i) R₁ is -OH, R₂ is -OH and R₃ -H; or
 - ii) R₁ is -OCH₃, R₂ is -H and R₃ -CH₃; or
 - iii) R₁ is -OH, R₂ is -H and R₃ -CH₃; or
 - iv) R₁ is -OCH₃, R₂ is -H and R₃ -H; or
 - v) R₁ is -OH, R₂ is -H and R₃ -H; or
 - vi) R₁ is -OCH₃, R₂ is -OH and R₃ -H.

30

25. A compound according to claim 24, wherein the compound of formula (3) and compound of formula (1) (if present) are solid salts.

26. A compound according to claim 25, wherein the solid salts are selected from the group consisting of the acetate, phosphate, tartrate, citrate, hydrochloride or hydrobromide.

35

27. A compound according to claim 24, wherein the compound of formula (3) and compound of formula (1) (if present) are solid alkaloids.

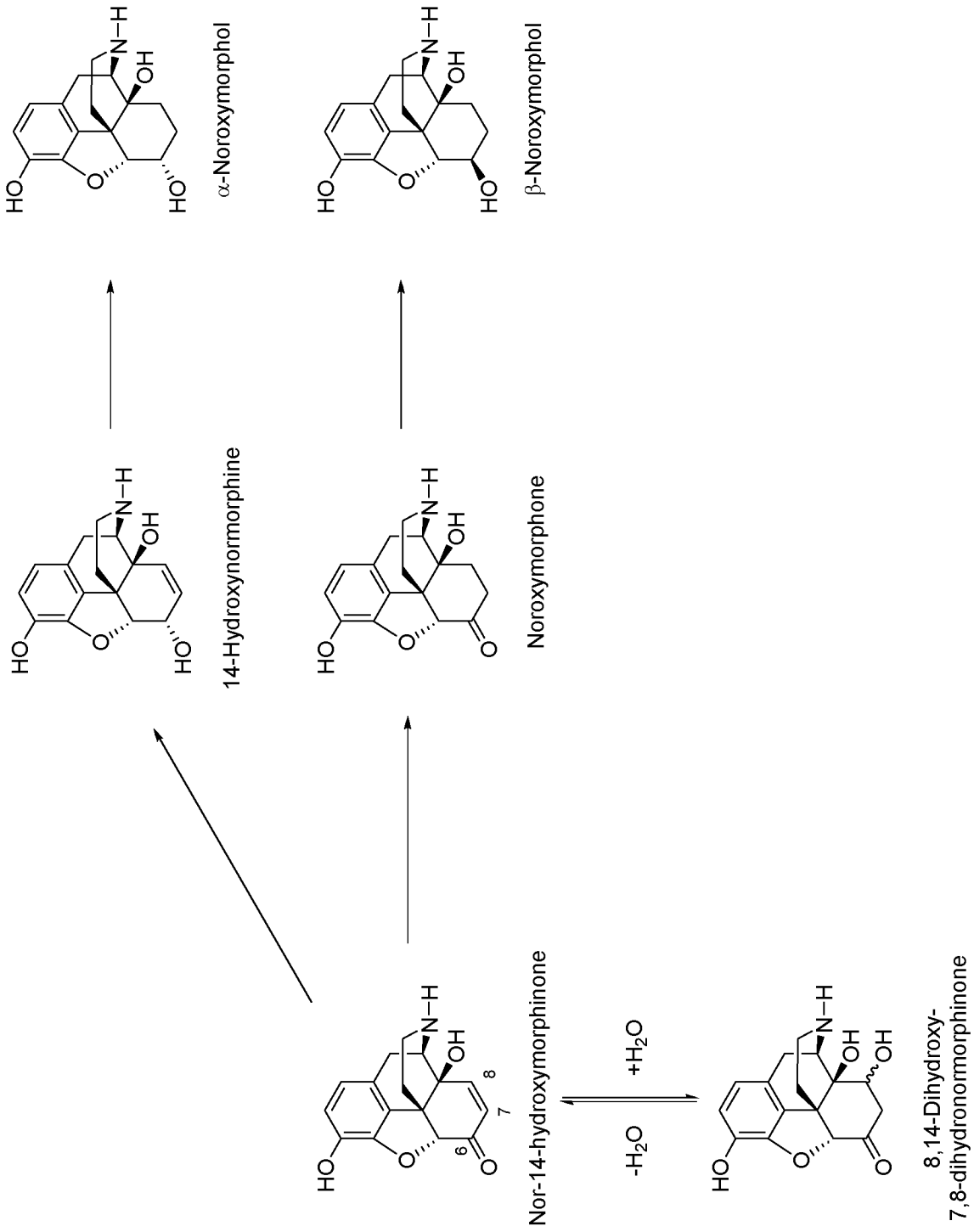


FIGURE 1

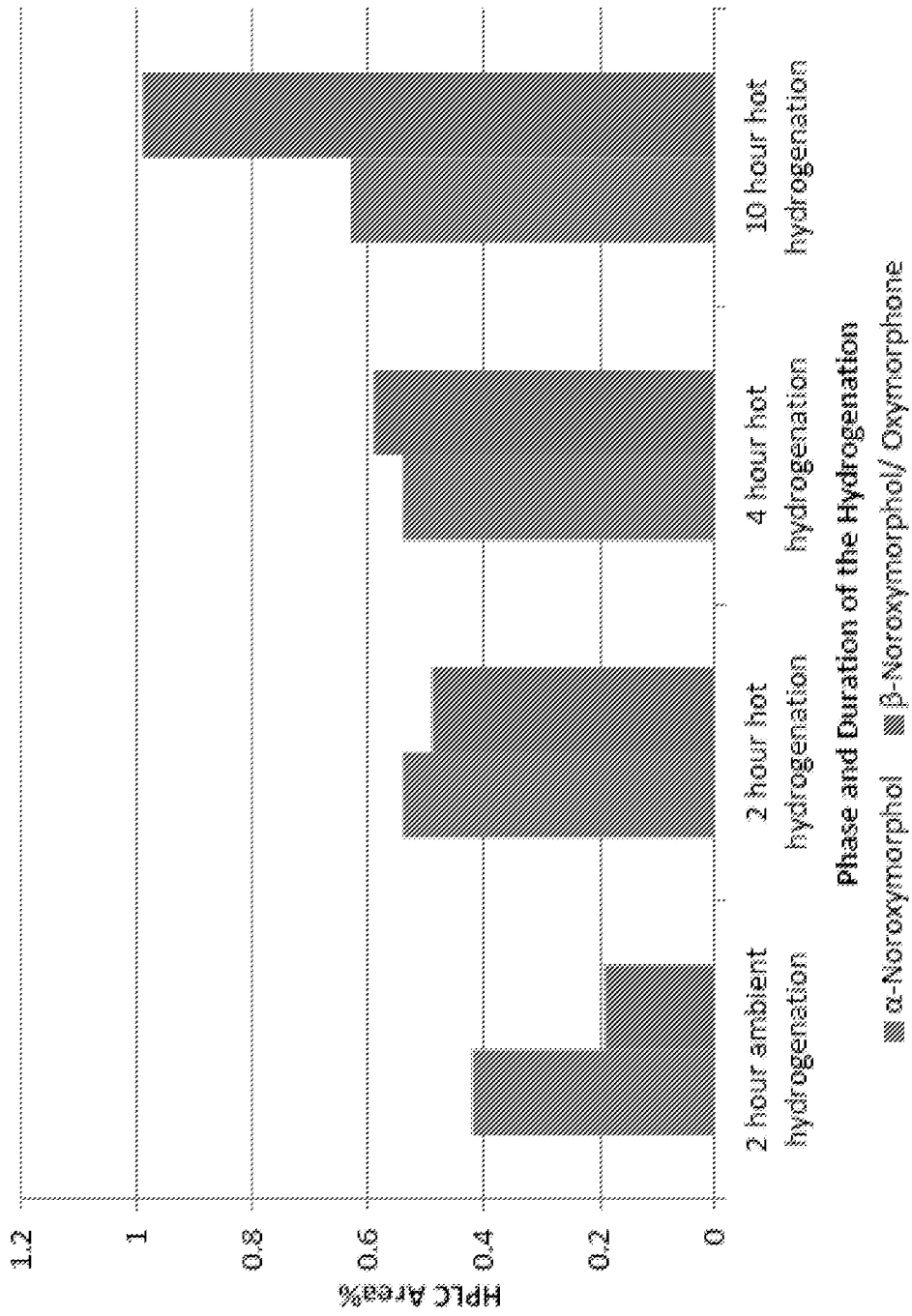


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/050324

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D489/08
 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 272 541 A (KOTICK MICHAEL P ET AL) 9 June 1981 (1981-06-09)	24-27
Y	example 8A	1-3, 5-17, 19-23
A	----- DE 22 05 225 A1 (HOECHST AG) 9 August 1973 (1973-08-09) the whole document	1-27
Y	----- WO 2008/072018 A1 (JOHNSON MATTHEY PLC [GB]; DUNG JEN-SEN [US]; KESKENY ERNO M [US]; MENC) 19 June 2008 (2008-06-19) page 2; claims 1,3,6	1-3, 5-17, 19-23
Y	----- US 2013/102784 A1 (REISCH HELGE ALFRED [US] ET AL) 25 April 2013 (2013-04-25) example 2	1-10, 13-23
	----- -/--	

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 27 March 2014	Date of mailing of the international search report 04/04/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Grassi, Damian

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2014/050324

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/118654 A1 (MALLINCKRODT INC [US]; WANG PETER X [US]; JIANG TAO [US]; CANTRELL GAR) 2 October 2008 (2008-10-02) examples 2-7	1-10, 13-23
X	----- US 2008/206883 A1 (BLACK JOSHUA P L [US]) 28 August 2008 (2008-08-28) paragraph [0160]; claim 1 -----	24-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/GB2014/050324

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4272541	A	09-06-1981	CA 1135691 A1 16-11-1982
			DE 3060589 D1 12-08-1982
			EP 0023576 A1 11-02-1981
			JP S582956 B2 19-01-1983
			JP S5615290 A 14-02-1981
			US 4272541 A 09-06-1981
DE 2205225	A1	09-08-1973	NONE
WO 2008072018	A1	19-06-2008	AU 2007331223 A1 19-06-2008
			BR PI0720232 A2 24-12-2013
			CA 2672644 A1 19-06-2008
			CN 101652371 A 17-02-2010
			CN 102391271 A 28-03-2012
			EP 2102213 A1 23-09-2009
			JP 4786748 B2 05-10-2011
			JP 2010513260 A 30-04-2010
			JP 2011201906 A 13-10-2011
			RU 2009126774 A 20-01-2011
			US 2008146601 A1 19-06-2008
			WO 2008072018 A1 19-06-2008
			ZA 200904317 A 25-08-2010
US 2013102784	A1	25-04-2013	AU 2011263416 A1 29-11-2012
			CA 2802294 A1 15-12-2011
			EP 2580218 A1 17-04-2013
			JP 2013529595 A 22-07-2013
			TW 201213278 A 01-04-2012
			US 2013102784 A1 25-04-2013
			WO 2011154826 A1 15-12-2011
WO 2008118654	A1	02-10-2008	AU 2008231127 A1 02-10-2008
			CA 2681740 A1 02-10-2008
			EP 2125824 A1 02-12-2009
			ES 2438997 T3 21-01-2014
			JP 2010522189 A 01-07-2010
			US 2010113787 A1 06-05-2010
			WO 2008118654 A1 02-10-2008
US 2008206883	A1	28-08-2008	NONE