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- *as to the identity of the inventor (Rule 4.17(i))*
- *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))*
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(54) **Title:** BROMINE FREE PREPARATION OF 5H-DIBENZO [A,D] CYCLOHEPTEN-5-ONE

(57) **Abstract:** The invention relates to a convenient procedure for the preparation of 5H- Dibenzo[a,d] cyclohepten-5-one in high yield an purity from 10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-one. The procedure is not only convenient to be adopted on an industrial scale but also safe and environment friendly.

BROMINE FREE PREPARATION OF 5H-DIBENZO [A,D] CYCLOHEPTEN-5-ONE

FIELD OF THE INVENTION

The invention relates to synthetic organic chemistry. In particular, the invention relates to a process for preparation of 5H-Dibenzo[a,d]cyclohepten-5-one. The process involves environmentally benign reagents and conditions to provide 5H-Dibenzo[a,d]cyclohepten-5-one in high yield and purity.

BACKGROUND OF INVENTION

For a wide range of synthetic and medicinal applications 5H-Dibenzo [a,d] cyclohepten-5-one is an important scaffold. 5H-Dibenzo [a,d] cyclohepten-5-one is the key ingredient for the synthesis of several pharmacologically active products(e.g. Cyclobenzaprine Hydrochloride (Muscle relaxant), Protriptyline Hydrochloride (Antidepressant), Cyproheptadine Hydrochloride (Non-ulcerative dyspepsia), Amitriptyline and Nortriptyline (Antidepressants) and the like. Many procedures have been developed to satisfy the gravity of its demand; Marcello Bonchio et al in “Co^{II} induced radical oxidations by peroxomolybdenum complexes”; J. Chem Perkin Transactions 3, 1993 discuss about the method of preparation of 5H-Dibenzo[a,d] cyclohepten-5-one by radical oxidation method, the method is however not scalable to an industrial scale. H. Garcia et al in “Involvement of Oxirane Intermediates in the Electron Transfer Photo oxygenation of 1, 1- and 1,2-Diarylethylenes Sensitized by 2,4,6-Triphenylpyrylium Tetrafluoroborate” Tetrahedron 1994, 50, 8773-8780 provides a method of preparation by photosynthesis, the yield is very low. Patent documents GB 2132618 discuss bromination of 5,6-dihydrodibenzo [2,1-b:2’,1’-f][7]annulen-11-one with N-bromosuccinimide and elimination of the brominated intermediate to obtain 5H-Dibenzo[a,d] cyclohepten-5-one; US 6617473 discuss about catalytic dehydrogenation mediated by palladium on carbon at a temperature range of 220-250 °C. Palladium used as catalyst is pyrophoric and hence strict nitrogen atmosphere is to be maintained which renders it to be uneconomical. The reaction is 80-85% complete and therefore the separation of starting material from the product is tedious and time consuming.

Considering the importance of 5H-Dibenzo [a,d] cyclohepten-5-one, it is necessary to develop a method that can overcome the lacuna with respect to the method of preparation. The present invention aims to provide facile, economical, high yielding environmentally benign method that can cater to the demand.

SUMMARY OF THE INVENTION

This invention provides a process of preparation of 5H-Dibenzo [a, d] cyclohepten-5-one, said process comprising acts of, adding 10,11-Dihydro-5*H*-dibenzo[a, d]cyclohepten-5-one to a solution of a base to obtain a reaction mixture, adding a phase transfer catalyst and heating the reaction mixture under air flow, cooling and washing the reaction mixture with an organic solvent to obtain 5H-Dibenzo [a ,d] cyclohepten-5-one, and optionally purifying the 5H-Dibenzo [a, d] cyclohepten-5-one.

BRIEF DESCRIPTION OF FIGURES

The features of the present invention can be understood in detail with the aid of appended figures. It is to be noted however, that the appended figures illustrate only typical embodiments of this invention and are therefore not to be considered limiting of its scope for the invention.

Figure 1: HPLC diagram relating to sample of example 1

Figure 2: HPLC diagram relating to sample of example 2

Figure 3: HPLC diagram relating to sample of example 3

DETAILED DESCRIPTION OF THE INVENTION

The foregoing description of the embodiments of the invention has been presented for the purpose of illustration. It is not intended to be exhaustive or to limit the invention to the precise form disclosed as many modifications and variations are possible in light of this disclosure for a person skilled in the art in view of the figures, description and claims. It may further be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by person skilled in the art.

The present invention is in relation to a process of preparation of 5H-Dibenzo [a,d] cyclohepten-5-one, said process comprising acts of,

a) adding 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one to a solution of a base to obtain a reaction mixture;

b) adding a phase transfer catalyst and heating the reaction mixture under air flow;

c) cooling and washing the reaction mixture with an organic solvent to obtain 5H-Dibenzo [a,d] cyclohepten-5-one; and

d) optionally purifying the 5H-Dibenzo [a,d] cyclohepten-5-one.

In an embodiment of the present invention, the base is selected from a group comprising Sodium Hydroxide and Potassium Hydroxide.

In still another embodiment of present invention, the phase transfer catalyst is selected from a group comprising N-Hydroxy pthalimide, Tetra butyl ammonium hydroxide, Tetra butyl ammonium hydrogen sulphate and Tetra butyl ammonium bromide.

In an embodiment of the present invention, heating is carried out at a temperature ranging from 75°C to 85°C.

In an embodiment of the present invention, the air flow is at a rate ranging from 4Lt/min to 8Lt/min.

In an embodiment of the present invention, the organic solvent is selected from a group comprising cyclohexane, toluene, ethanol, methanol, and alkylesters including ethyl acetate.

In an embodiment of the present invention, the purity of 5H-Dibenzo [a,d] cyclohepten-5-one is ranging from 95% to 99.8%.

In an embodiment of the present invention, the 5H-Dibenzo [a,d] cyclohepten-5-one is obtained in an yield ranging from 95% to 98%.

The invention provides a process for preparation from of 5H-Dibenzo[a,d] cyclohepten-5-one in a suitable organic solvent from 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one as depicted in scheme I in one pot synthesis. The process involves dehydrogenation of 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one by treating with a base in the presence of air and phase transfer catalyst in a suitable solvent at a temperature ranging from about 80°C-90°C.

Scheme I

The Dibenzo[a,d] cyclohepten-5-one is obtained in high yield ranging from 95% to 99% in high purity 95% to 99.8% as determined using high performance liquid chromatography (FIGURE-1,2 and 3).

The solvent is selected from a group comprising water, alkyl esters, preferably preferably ethyl acetate, acetonitrile, cyclohexane, toluene and mixture thereof.

The phase transfer catalyst is selected from a group comprising N-Hydroxy pthalimide, Tetrabutyl ammonium hydroxide, Tetrabutylammonium hydrogen sulphate, Tetra butyl ammonium bromide and mixture thereof.

The base is selected from a group comprising Sodium hydroxide and Potassium Hydroxide.

The reaction is supported by continous purging of air as oxidant at a constant flow rate ranging from 5-7 lt/min. The crystalline form of Dibenzo[a,d] cyclohepten-5-one is separated from the reaction mixture by a method selected from a group of filtration, filtration under vacuum, centrifugation, decantation and the like; and dried to achieve moisture values.

Experimental

Example 1:

To a clean flask, 70 g of commercially available 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one is mixed with 30g of NaOH and 30ml of water to form a reaction mixture. 21g of Tetrabutyl hydrogen sulphate as phase transfer catalyst is added to the reaction mixture. Air is purged continuously at flow rate of 5-7 Lt/min to the reaction mixture while heating the reaction mixture to about 80°C for 12 hours. The conversion ratio of 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one to Dibenzo[a,d] cyclohepten-5-one is checked on TLC which should be ideally 90%. If the conversion is less (shown by Thin layer chromatography, TLC), more air is purged to the reaction mixture for a period of 2-3 hours. The reaction mixture is cooled to about 25°C and the mixture is diluted with 500mL of Toluene. The worked out diluted reaction mixture is washed with 500mL dilute HCl and then with water. The product is distilled using about 95% of Toluene.100mL of Cyclohexane is added to the product and the flask is chilled. The precipitate formed is obtained and is dried at 60°C for 3 hours to get

58g of Dibenzo[a,d] cyclohepten-5-one having purity greater than 98.5 %. One more crystallization gives more than 99.80 % pure compound (figure 1).

Example 2:

To a clean flask, 70 g of commercially available 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one is added to 40g of NaOH and 40ml of water to form a reaction mixture. 35 g of tetra butyl hydrogen sulphate is added as catalyst to the reaction mixture. Air is purged continuously at flow rate of 5-7 Lt/min and the reaction mixture is heated to about 80°C for 12 hours. The reaction mixture is brought to 25°C and the mixture is diluted with 500mL of Toluene. The worked-out reaction mixture is washed with 200mL dilute HCl and then with water. The product is distilled using about 90% of Toluene. The flask is chilled and precipitate formed is filtered out. The solid obtained is dried at 60°C for 3 hours to get 56g of Dibenzo[a,d] cyclohepten-5-one having purity greater than 99.5 % (figure 2).

Example 3:

To a clean flask, 70 g of commercially available 10, 11-Dihydro-5*H*-dibenzo [a,d] cyclohepten-5-one is taken with 30g of KOH and 30ml of water to form a reaction mixture. 1.4 g of N-Hydroxy pthalimide as catalyst is added to the reaction mixture. Air is purged continuously at flow rate of 5-7 Lt/min and the reaction mixture is heated to about 80°C for 12 hours. The reaction mixture is brought to 25°C and is diluted with 500mL of Toluene. The diluted reaction mixture is washed with 200mL dilute HCl and then with water. The product is distilled using about 90 % of Toluene. The flask is chilled and the precipitate formed is filtered out. The solid obtained is dried at 60°C for 3 hours to get 62g of Dibenzo[a,d] cyclohepten-5-one having purity greater than 99.5 %. After obtaining the first crop, mother liquor is concentrated and the reaction is repeated to achieve greater than 95% conversion to Dibenzo[a,d] cyclohepten-5-one 9 (figure 3).

Example 4:

To a clean flask, 70 g of commercially available 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one is taken with 50g of KOH and 30ml of water to form a reaction mixture.30g of tetra butyl hydrogen sulphate is added to the reaction mixture as catalyst. Air is purged continuously at flow rate of 5-7 Lt/min and the reaction mixture is heated to about 80°C for 12 hours. The reaction mixture is brought to 25 °C and the mixture is diluted with 500mL of Toluene. The reaction mixture is washed with 200mL dilute HCl and then with water. The product is distilled using about 95% of Toluene. 100mL of Cyclohexane is added to the product and the flask is chilled. The precipitate formed is filtered and dried at 60°C for 3 hours to get 55g of 5H-Dibenzo[a,d] cyclohepten-5-one having purity greater than 98.5 %. One more crystallization gives more than 99.80 % pure compound.

The present invention thus provides a facile preparation of 5H- Dibenzo [a,d] cyclohepten-5-one reducing the thrust on the environment, also the process can be easily adopted on an industrial scale facilitating great reduction in cost to help the consumers.

WE CLAIM:

1. A process of preparation of 5H-Dibenzo [a,d] cyclohepten-5-one, said process comprising acts of,

a) adding 10,11-Dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one to a solution of a base to obtain a reaction mixture;

b) adding a phase transfer catalyst and heating the reaction mixture under air flow;

c) cooling and washing the reaction mixture with an organic solvent to obtain 5H-Dibenzo [a,d] cyclohepten-5-one; and

d) optionally purifying the 5H-Dibenzo [a,d] cyclohepten-5-one.

2. The process of preparation as claimed Claim 1, wherein the base is selected from a group comprising Sodium Hydroxide and Potassium Hydroxide.

3. The process of preparation as claimed Claim 1, wherein the phase transfer catalyst is selected from a group comprising N-Hydroxy pthalimide, Tetra butyl ammonium hydroxide, Tetra butyl ammonium hydrogen sulphate and Tetra butyl ammonium bromide.

4. The process of preparation as claimed Claim 1, wherein heating is carried out at a temperature ranging from 75°C to 85°C.

5. The process of preparation as claimed Claim 1, wherein the air flow is at a rate ranging from 4Lt/min to 8Lt/min.

6. The process of preparation as claimed Claim 1, wherein the organic solvent is selected from a group comprising cyclohexane, toluene, ethanol, methanol, and alkylesters including ethyl acetate.

7. The process of preparation as claimed Claim 1, wherein the purity of 5H-Dibenzo [a,d] cyclohepten-5-one is ranging from 95% to 99.8%.

8. The process as claimed in claim 1, wherein the 5H-Dibenzo [a,d] cyclohepten-5-one is obtained in an yield ranging from 95% to 98%.

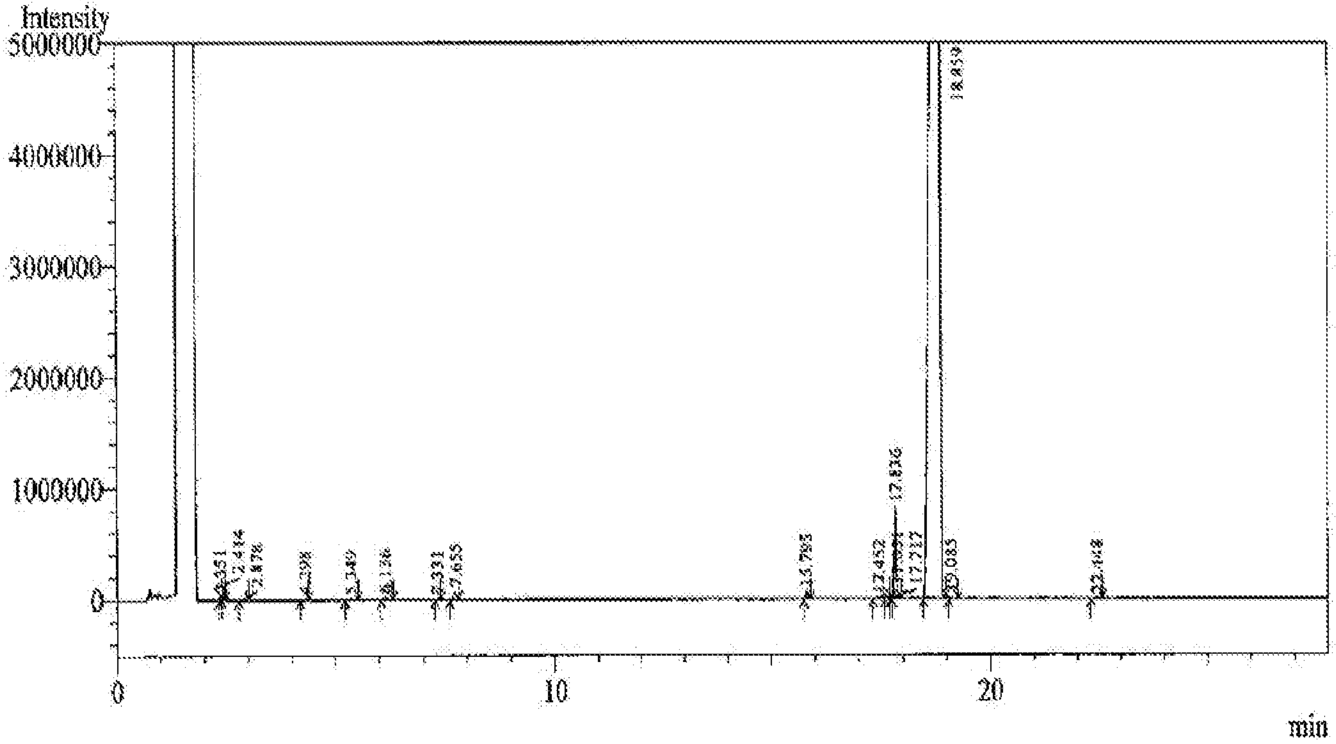
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FIGURE 1

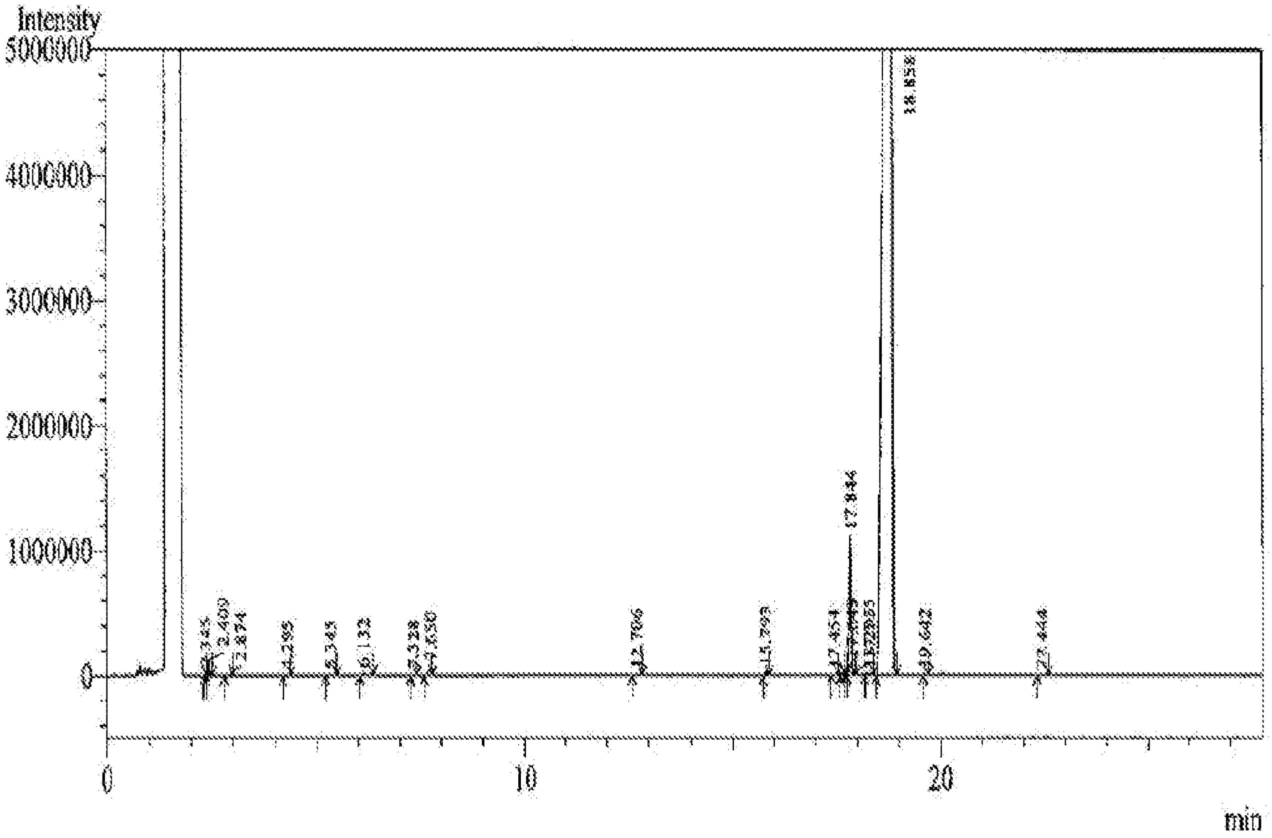
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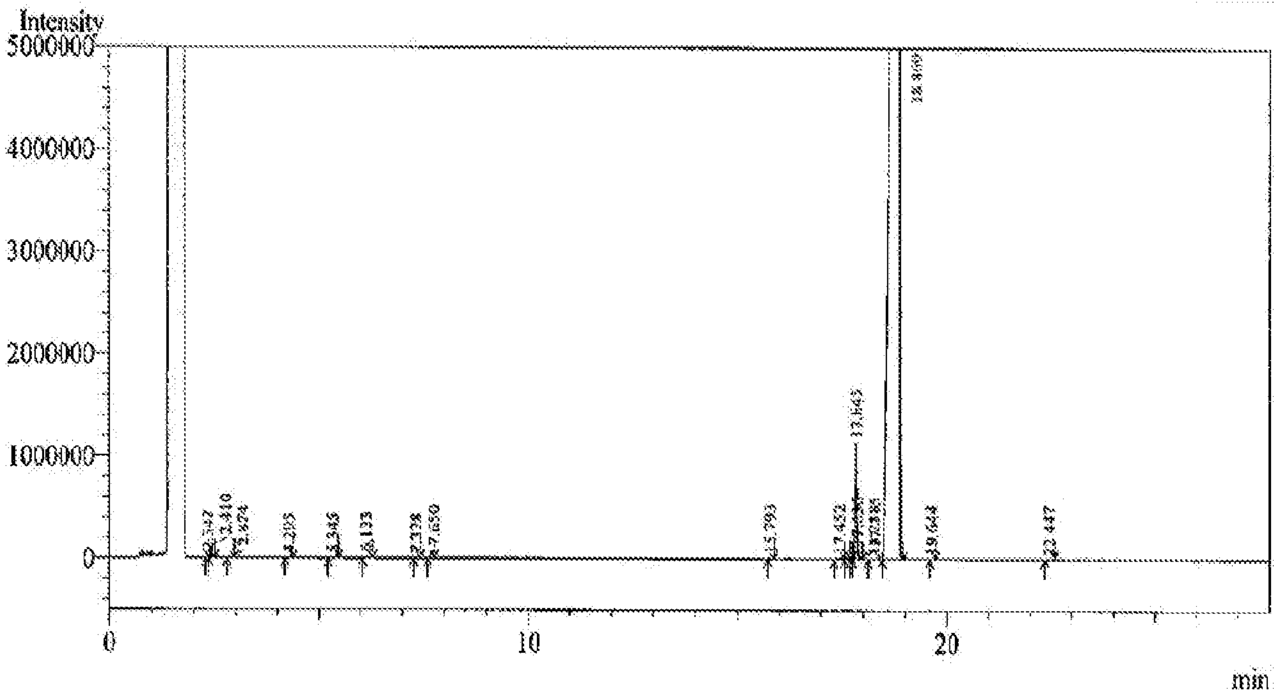
FIGURE 2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20
min

FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2018/058319

A. CLASSIFICATION OF SUBJECT MATTER

C07C49/675 Version=2018.01

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)

C07C

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Houben-Weyl Methods of Organic Chemistry Vol. E 9d, 4th Edition, Additional and Supplementary Volumes to the 4th Edition (K.H.Buchel et al.) 29 December 1997 (29-12-1997)) page-235	1-8
A	EP 2665700 B1 (HARMAN FINOCHEM LTD[IN]) 13 January 2016 (13-01-2016) page-3, para-0008	1-8
A	Synthesis, Properties and Reactions of Novel Quinone Methides (Jana Helose Taljaard) url: https://core.ac.uk/download/pdf/145048538.pdf January 2007 page-79, para-3.2.1	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"E"	earlier application or patent but published on or after the international filing date	"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
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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Citation	Pub.Date	Family	Pub.Date
EP 2665700 B1	13-01-2016	WO 2012098563 A2	26-07-2012