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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2015 (11.06.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/082719 A1

(51) **International Patent Classification**:
C07C 231/02 (2006.01) ***C07C 237/46*** (2006.01)

(21) **International Application Number**:
PCT/EP2014/076885

(22) **International Filing Date**:
8 December 2014 (08.12.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/912,794 6 December 2013 (06.12.2013) US
61/969,932 25 March 2014 (25.03.2014) US

(71) **Applicant**: **GE HEALTHCARE AS** [NO/NO]; P.O. Box 4220 Nydalen, Nycoveien 1-2, N-0401 Oslo (NO).

(72) **Inventors**: **SAANUM, Inger, Dagny**; GE Healthcare AS, 4521 Lindesnes, Lab-Utvikl, N-4521 Lindesnes (NO). **HAALAND, Torfinn**; GE Healthcare AS, 4521 Lindesnes, Lab-Utvikl, N-4521 Lindesnes (NO). **KALLEBERG, Rita**; GE Healthcare AS, 4521 Lindesnes, Lab-Utvikl, N-4521 Lindesnes (NO).

(74) **Agents**: **BANNAN, Sally** et al.; GE Healthcare Limited, Pollards Wood, Nightingales Lane, Chalfont St Giles, Bucking HP8 4SP (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, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

WO 2015/082719 A1

(54) **Title**: ALTERNATIVE ACETYLATION PROCESS IN THE SYNTHESIS OF NON-IONIC XRAY CONTRAST AGENTS

(57) **Abstract**: An alternative acetylation process for the synthesis of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound A"), an intermediate in the industrial preparation of non-ionic X-ray contrast agents, is described. The process can be performed on an industrial scale to produce Compound A with improved purity and improved yields compared to the established processes.

Alternative Acetylation Process In The Synthesis of Non-Ionic X-ray Contrast Agents

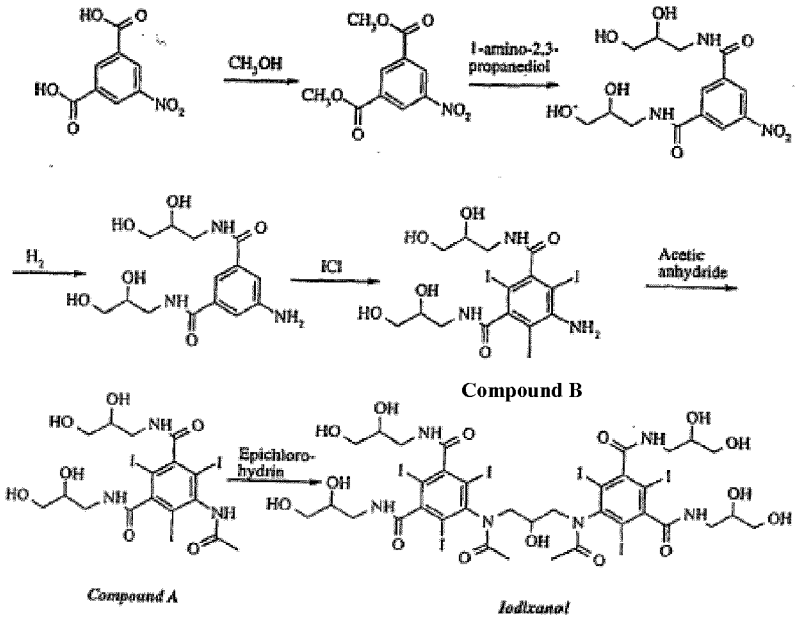
TECHNICAL FIELD

This invention relates generally to large-scale synthesis of non-ionic X-ray contrast agents. It further relates to an alternative acetylation process for the synthesis of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound A"), an intermediate in the industrial preparation of non-ionic X-ray contrast agents. The process can be performed on an industrial scale to produce Compound A with improved purity and improved yields compared to the established processes.

BACKGROUND OF THE INVENTION

Non-ionic X-ray contrast agents constitute a very important class of pharmaceutical compounds produced in large quantities. 5-[N-(2,3-dihydroxypropyl)-acetamido]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("iohexol"), 5-[N-(2-hydroxy-3-methoxypropyl)acetamido]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("iopentol") and 1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropyl-aminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane ("iodixanol") are important examples of such compounds. They generally contain one or two triiodinated benzene rings.

For example, iodixanol, marketed under the trade name Visipaque®, is one of the most used agents in diagnostic X-ray procedures. It is produced in large quantities by GE Healthcare in Lindesnes, Norway. The industrial production of iodixanol involves a multistep chemical synthesis as shown in Scheme 1 below. *See also* U.S. Patent No. 6,974,882. To reduce the cost of the final product, it is critical to optimize each synthetic step. Even a small improvement in reaction design can lead to significant savings in a large scale production.



Scheme I

5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound A") is a key intermediate in both the industrial scale synthesis of such non-ionic X-ray contrast agents. Compound A is prepared by the acetylation of 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (Compound B). The acetylation is achieved by using a mixture of acetic anhydride and acetic acid as the acetylating reagent. However, upon acetylation, not only is Compound A produced but several by-products are formed as well.

Thus there exists a need in the art for an acetylation process that can produce Compound A with a lower level of by-products; thus increasing both purity and yield of Compound A. Such an acetylation process must not only be able to be performed on a laboratory scale but also on an industrial scale. The instant invention, as described below, answers such a need.

SUMMARY OF THE INVENTION

According to the present invention, it has now been found that by significantly reducing the reaction temperature during the Compound B acetylation reaction, a reduction in the level of by-products produced can be achieved; hence higher yields and higher purity of Compound A can be produced. It has also now been found how to achieve such lower

reaction temperature during the Compound B acetylation step on an industrial scale. Specifically, it has now been found that by adding a catalytic amount of an acid catalyst as described herein (e.g. para-toluene sulfonic acid (PTSA)) carefully into the Compound B acetylation reaction mixture over a period of several hours, lower acetylation temperatures can be achieved. In turn, the level of by-products formed in the acetylation is reduced which in turn results in improved purity of Compound A and consequently increased yield of Compound A in the subsequent purification steps. The present invention provides an alternative acetylation process for producing Compound A that can be performed on both a laboratory and/or industrial scale. In a preferred embodiment of the invention, the process is performed as a batch process. The present invention provides an alternative acetylation process for producing Compound A that can be performed as either a batch process or a continuous process. In a preferred embodiment of the invention, the process is performed as a batch process.

The present invention provides process comprising the steps of:

(i) reacting 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound B") with a mixture of acetic anhydride/acetic acid to form a slurry;

(ii) heating said slurry to about 60 °C; and

(iii) adding an acid catalyst (preferably, para-toluene sulfonic acid (PTSA)) to said slurry at a rate such that the reaction temperature is maintained at a temperature range of about 65-85 °C.

The present invention also provides an industrial scale process comprising the steps of:

(i) reacting 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound B") with a mixture of acetic anhydride/acetic acid to form a slurry;

(ii) heating said slurry to about 60 °C;

(iii) adding an acid catalyst (preferably, para-toluene sulfonic acid (PTSA)) to said slurry at a rate such that the reaction temperature is maintained at a temperature range of about 65-85 °C to form overacetylated Compound A; and

(iv) deacetylating said overacetylated Compound A to form Compound A.

The present invention also provides an industrial scale process comprising the steps of:

(i) reacting 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound B") with a mixture of acetic anhydride/acetic acid to form a slurry;

(ii) heating said slurry to about 60 °C; and

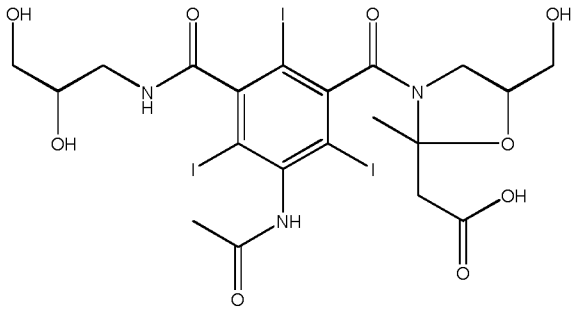
(iii) adding an acid catalyst (preferably, para-toluene sulfonic acid (PTSA)) to said slurry at a rate such that the reaction temperature is maintained at a temperature range of about 65-85 °C to form overacetylated Compound A;

(iv) deacetylating overacetylated Compound A to form Compound A; and

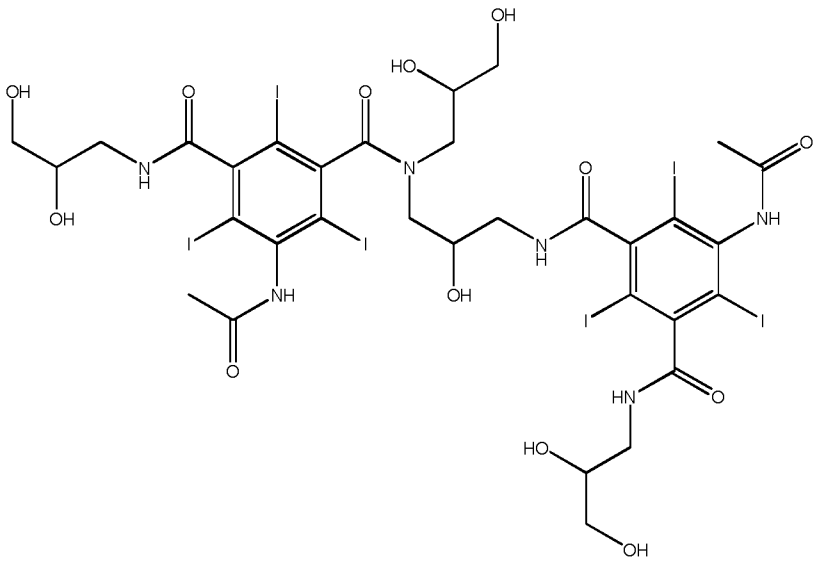
(v) isolating Compound A.

DETAILED DESCRIPTION OF THE INVENTION

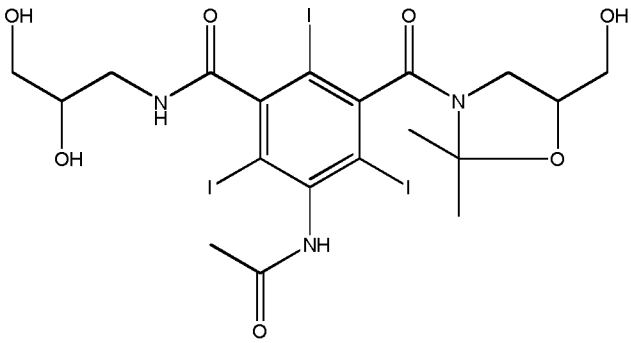
In the established industrial scale process, Compound B is added to a mixture of acetic anhydride and acetic acid. The resulting slurry is then heated to approximately 60 °C. When the temperature is achieved, an acid catalyst (*e.g.*, para-toluene sulfonic acid (PTSA)(s)) is added in one portion and in catalytic amounts. Despite maximum cooling in the reactor jacket, the temperature of the reaction mixture increases rapidly to about 120-125 °C due to the exothermic acetylation reaction. The main part of the acetylation reaction will accordingly occur at 120-125 °C. Because of the high reaction temperature, considerable levels of the following by-products I, II, and III in addition to Compound A are formed:



I



II



III

According to the present invention, an alternative acetylation process is provided. According to the present invention, Compound B is added to a mixture of acetic anhydride and acetic acid. The resulting slurry is then heated to approximately 60 °C. At this temperature, a catalytic amount of an acid catalyst is added. Examples of a suitable acid catalyst include, for example, a sulfonic acid such as methanesulfonic acid, para-toluenesulfonic acid (PTSA) and sulphuric acid. Of these, para-toluenesulfonic acid (PTSA)

is preferred. According to the invention, the acid catalyst can be added as a solid or as a solution. Examples of suitable solvents to form such a solution include acetic acid, acetic anhydride or a mixture of acetic acid and acetic anhydride. The addition is performed carefully while the temperature is controlled. In one embodiment, the PTSA is added as a solid in several portions. In one embodiment, the PTSA is added as a solution where PTSA is dissolved in a small volume of acetic acid. In one embodiment, the PTSA is added as a solution where PTSA is dissolved in a small volume of acetic anhydride. In one embodiment, the PTSA is added as a solution where PTSA is dissolved in a small volume of a mixture of acetic acid and acetic anhydride. The rate/speed of the addition of the acid catalyst, preferably PTSA, is such that the maximum reaction temperature is maintained at about 65-85 °C. In general, the addition time will be over several hours in order to control the exothermic reaction.

In a preferred embodiment, the rate/speed of the addition of the acid catalyst, preferably PTSA, is such that the maximum reaction temperature is maintained at about 70-80 °C.

According to the present invention, addition of the acid catalyst, preferably PTSA, produces a reaction mixture comprising overacetylated Compound A with lower levels of by-products compared to the established acetylation process. The reaction mixture comprising overacetylated Compound A can then be deacetylated using a deacetylating agent. There is no particular restriction upon the nature of the deacetylating agent used, and any deacetylating agent commonly used in conventional reactions may equally be used here. Examples of suitable deacylating agents include aqueous inorganic bases including alkali metal carbonates, such as sodium carbonate, potassium carbonate or lithium carbonate; and alkali metal hydroxides, such as sodium hydroxide, potassium hydroxide or lithium hydroxide. Of these, the alkali metal hydroxides, particularly sodium hydroxide or potassium hydroxide, and most preferably sodium hydroxide are preferred. For example, the reaction mixture comprising overacetylated Compound A can be deacetylated by the addition of base, such as sodium hydroxide, to form Compound A which in turn can then be purified (e.g., crystallization) and isolated by techniques known in the art.

The invention is illustrated further by the following examples that are not to be construed as limiting the invention in scope to the specific procedures described in them.

EXAMPLES

Examples 1 and 2 (established acetylation):

Acetylation: For both **Examples 1 and 2**, Compound B (200 g) was added to a mixture of acetic anhydride (191.8 mL) and acetic acid (103.3 mL). The slurry was heated to approximately 60 °C, before PTSA powder (1.0 g) was added in one portion. Because of the exothermic reaction, the temperature rapidly increased to approximately 120-125 °C.

In **Example 1**, the temperature were held at about 120 °C for approximately 2 hours to form over-acetylated Compound A, before moving on to the next deacetylation process step to form Compound A.

In **Example 2**, the solution was cooled in a reactor jacket to 70 °C immediately after reaching the maximum temperature of approximately 120-125 °C. The cooling rate was about 1 °C/minute, and the solution was held at 70 °C overnight to form over-acetylated Compound A before moving on to the next deacetylation process step to form Compound A.

Deacetylation: After acetylation, the reaction solution containing over-acetylated Compound A was concentrated under reduced pressure, before methanol and water was added prior to the deacetylation step. Sodium hydroxide was then added to methanol-water reaction mixture to carry out the deacetylation. The resulting reaction mixture was then further diluted with water before crystallization.

Crystallization: To achieve crystallization, hydrochloric acid was first added until the reaction mixture until it was slightly turbid, and then the reaction mixture was seeded with Compound A. The resulting slurry was stirred for 45 minutes before additional hydrochloric acid was added until about pH 7. The slurry was then cooled to 15 °C over night. Next day the slurry was filtered, and the filter cake was washed with methanol and then dried in a vacuum oven.

The reaction mixture was analysed by HPLC prior to the crystallization step, and the total level of by-products formed during the acetylation synthesis was 1.38 % in **Example 1**, and 1.34 % in **Example 2**. The majority of the by-products being formed during the acetylation step.

Both experiments resulted in a total concentration of Compound A and by-products in the mother liquor separated in the filtration step after the crystallization of 1.1 g/100 mL.

Comparative Examples 3 and 4 (Alternative acetylation):

Acetylation: For each of **Examples 3 and 4**, Compound B (200 g) was added to a mixture of acetic anhydride (150.4 mL) and acetic acid (141.6 mL) to form a slurry. PTSA (1.6 g) was separately dissolved in a small amount of acetic anhydride (3.0 mL). The slurry was heated to approximately 60 °C, before the PTSA solution was added over a period of approximately 2 hours to form over-acetylated Compound A, before moving on to the next deacetylation process step to form Compound A.

In **Example 3**, the temperature was held at 80-85 °C while PTSA solution was added, and kept at 80 °C overnight.

In **Example 4**, the temperature was held at 65-70 °C while PTSA was added, and kept at 65 °C overnight.

Deacetylation: After acetylation, the reaction mixture containing overacetylated Compound A was concentrated under reduced pressure, before methanol and water was added prior to the deacetylation step. Sodium hydroxide was then added to methanol-water reaction mixture to carry out the deacetylation. The resulting reaction mixture was then further diluted with water before crystallization.

Crystallization: To achieve crystallization, hydrochloric acid was first added until the reaction mixture until it was slightly turbid, and then the reaction mixture was seeded with Compound A. The resulting slurry was stirred for 45 minutes before additional hydrochloric acid was added until about pH 7. The slurry was then cooled to 15 °C over night. Next day the slurry was filtered, and the filter cake was washed with methanol and then dried in a vacuum oven.

The reaction mixture was analysed by HPLC prior to the crystallization step, and the total level of by-products formed during the acetylation synthesis was 0.11 % in **Example 3**, and 0.10 % in **Example 4**.

Both experiments resulted in a total concentration of Compound A and by-products in the mother liquor separated in the filtration step of 0.6 g/100 mL. The alternative acetylation

gave an increased total purity of A by approximately 0.2 % points after crystallization, compared to the established process, analysed by HPLC.

All patents, journal articles, publications and other documents discussed and/or cited above are hereby incorporated by reference.

5

We claim:

1. A process comprising the steps of:

(i) reacting 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide ("Compound B") with a mixture of acetic anhydride/acetic acid to form a slurry;

(ii) heating said slurry to about 60 °C; and

(iii) adding an acid catalyst to said slurry at a rate such that the reaction temperature is maintained at a temperature range of about 65-85 °C.

2. The process according to claim 1, further comprising the step of:

(iv) adding a deacetylating agent to the reaction mixture of step (iii).

3. The process according to claim 2, further comprising the step of:

(v) purifying the reaction mixture of step (iv).

4. The process according to claim 3, wherein said purifying step is a crystallization step.

5. The process according to claim 4, wherein said crystallization step achieved by seeding with Compound A.

6. The process according to any one of claim 1-5 wherein said acid catalyst is a sulfonic acid.

7. The process according to claim 6, wherein said acid catalyst is para-toluene sulfonic acid (PTSA).

8. The process according to claim 7, wherein said PTSA is added in a catalytic amount as a solid.

9. The process according to claim 7, wherein said PTSA is added in a catalytic amount as a solution of PTSA dissolved in a small volume of acetic anhydride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/076885

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/02 C07C237/46
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)
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)

EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 277 851 A1 (GE HEALTHCARE AS [NO]) 26 January 2011 (2011-01-26) examples 1,2	1-9
A	US 7 754 920 B1 (HOLMAAS LARS TERJE [NO] ET AL) 13 July 2010 (2010-07-13) example 1	1-9
A	US 4 250 113 A (HOLTERMANN HUGO [NO] ET AL) 10 February 1981 (1981-02-10) column 12, line 15 - line 25	1-9

☐ 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	Date of mailing of the international search report
20 January 2015	29/01/2015

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	Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/076885

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2277851 A1	26-01-2011	NONE	
US 7754920 B1	13-07-2010	CA 2707150 A1	29-11-2010
		CN 101863798 A	20-10-2010
		EP 2281791 A1	09-02-2011
		KR 100996769 B1	25-11-2010
		US 7754920 B1	13-07-2010
US 4250113 A	10-02-1981	BE 855580 A1	12-12-1977
		CH 630064 A5	28-05-1982
		DE 2726196 A1	22-12-1977
		DK 258477 A	12-12-1977
		FR 2354316 A1	06-01-1978
		GB 1548594 A	18-07-1979
		HK 56683 A	25-11-1983
		JP S5321137 A	27-02-1978
		JP S5654310 B2	24-12-1981
		NL 7706385 A	13-12-1977
		SE 441181 B	16-09-1985
		US 4250113 A	10-02-1981