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- (71) **Applicant: FRESINIUS KABI ONCOLOGY LTD.**
[IN/IN]; B - 310, Som Datt Chambers - I, Bhikaji Cama Place, New Delhi 110066 (IN).
- (72) **Inventors: SINGH, Hemant Kumar;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **KUMAR, Sandeep;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **SONAVANE, Ghanashyam Madhukar;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **HANDA, Vishal;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **GUPTA, Chandan Kumar;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **SANGHANI, Sunil;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **SIVAIHAH, Potru;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **LAHIRI, Saswata;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN). **CABRI, Walter;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN).

GUPTA, Nitin; Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN).

(74) **Agent: TIWARI, Prachi;** Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No - 11, Sector-32, Haryana, Gurgaon 122001 (IN).

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(54) **Title:** A PROCESS FOR THE PREPARATION OF XYLENE LINKED CYCLAM COMPOUNDS

(57) **Abstract:** The present invention relates to an improved process for the preparation of xylene linked cyclam compounds. More particularly the invention provides a process for preparation of high purity plerixafor which does not involve the use of expensive chemicals, hazardous reagents or tedious purification techniques. Invention also provides novel intermediate useful for preparation of desired compound in high purity.



WO 2017/037639 A1

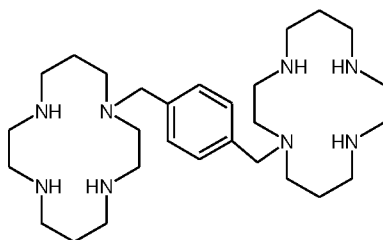
A PROCESS FOR THE PREPARATION OF XYLENE LINKED CYCLAM COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of xylene linked
5 cyclam compounds, more particularly, it relates to an improved process for
preparing 1,1'-[1,4-phenylenebis (methylene)]-bis [1,4,8,11-tetraazacyclotetra
decane] and its intermediates. In another aspect, the present invention relates to
intermediates used in the above processes.

BACKGROUND OF THE INVENTION

10 The compound 1,1'-[1,4-phenylenebis (methylene)]-bis [1,4,8,11-tetraazacyclo
tetradecane], also known as plerixafor is represented by the Formula (I):



Formula (I)

Plerixafor (marketed under the trade name Mozobil, Genzyme Corporation) is a
15 hematopoietic stem cell mobilizer and is inhibitor of the CXCR4 chemokine
receptors. It was approved by the U.S. Food and Drug Administration (FDA) on
15 December 2008 to mobilize hematopoietic stem cells (HSCs) to the peripheral
blood for collection and subsequent autologous transplantation in patients with
non-Hodgkin's lymphoma and multiple myeloma.

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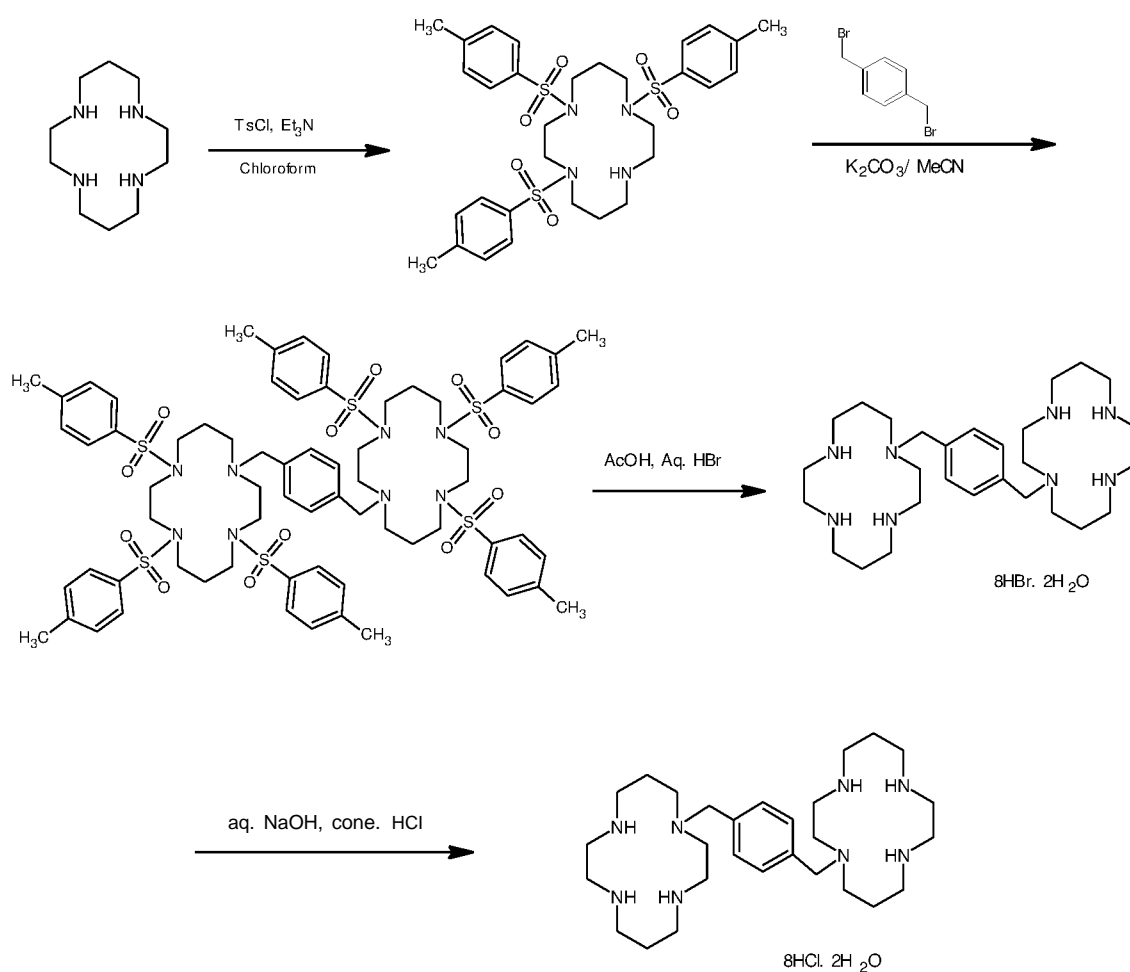
Plerixafor, as represented by Formula (I) was first reported by Ciampolini et al. in
Inorg. Chem, 1987, 26 (21), pp 3527-3533.

Various processes for the preparation of plerixafor have been described in
literature. Conventionally, the compound of formula (I) is prepared by selective

functionalization of the cyclam ring, followed by reaction with a, a'-dihalo-p-xylene and dimerization. The product is deprotected to obtain the compound of formula (I) which is further purified by recrystallization in various solvents.

WO 93/12096 describes the synthesis of different xylene linked polyamine macrocyclic compounds as explained above, wherein the cyclam ring is tosyl protected and reacted with an activated xylene diol intermediate to obtain an intermediate which is purified by column chromatography and deprotected to obtain the final product.

A similar process for the synthesis of compound of formula (I) is described in the WO 00/28987. The synthetic scheme is depicted below as scheme- 1:

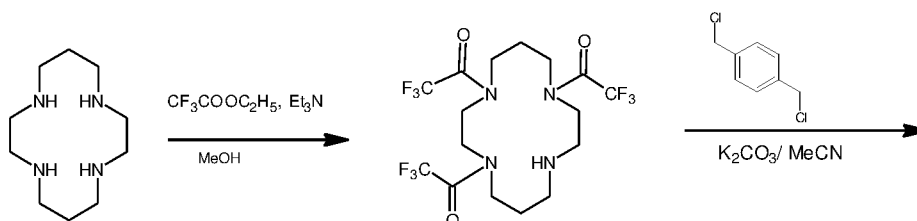


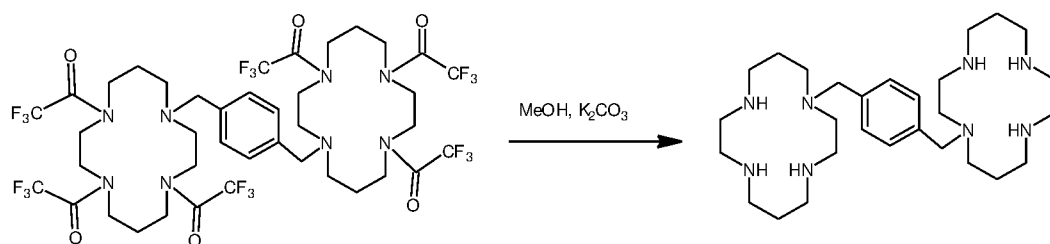
Cyclam is reacted with p-toluene sulfonyl chloride in the presence of triethylamine to obtain tris-(p-toluenesulfonyl) - 1, 4, 8, 11-tetraazacyclotetradecane in 33% yield. This tosyl protected cyclam ring is reacted with α,α' -dibromo-p-xylene in the presence of base in solvent at reflux temperature to give 1,1'-[1,4- phenylenebis(methylene)]-bis[4,8,11-tris-(p-toluene sulfonyl)- 1,4,8,11 - tetraazacyclotetradecane which is purified by chromatography. Finally this intermediate is subjected to hydrolysis in a mixture of acetic acid and hydrobromic acid to afford the final compound as octahydrobromide salt, the purity of which is not mentioned.

Further, WO 2014/125499 also describes a similar process for the preparation of plerixafor. Cyclam is protected with tosyl groups in the presence of triethylamine in dichloromethane. The yield is 36.4%. The resulting compound was reacted with α,α' -dibromo-p-xylene in the presence of potassium carbonate in dimethylformamide. The yield is 40%. Deprotection of this intermediate in the presence of acetic acid and hydrobromic acid gives plerixafor octahydrobromide dihydrate in 90.3% yield.

The above mentioned synthetic processes do not afford the intermediate compounds in good yield or purity. Column chromatography is required to purify the intermediates and therefore a significant amount of yield is lost.

In WO 02/26721A1, the authors disclose a process for the preparation of plerixafor base using ethyl trifluoroacetate as protecting reagent instead of p-toluene sulfonyl chloride. The reaction scheme is summarized below in scheme-2.



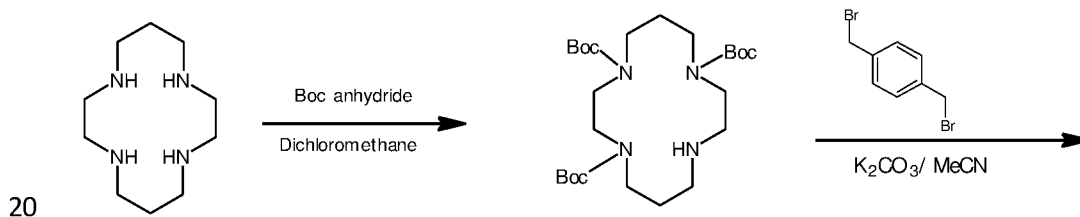


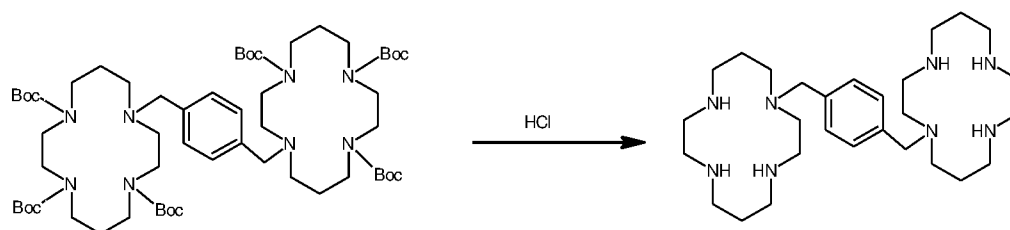
Scheme-2

Cyclam is reacted with ethyl trifluoroacetate in the presence of triethylamine in methanol to give tris trifluoroacetyl cyclam. The resulting compound is isolated by column chromatography technique. The yield is 92.5%. The purity of the compound is not mentioned. The compound is coupled with α,α' -dichloro-p-xylene in the presence of potassium carbonate and potassium iodide in acetonitrile at reflux temperature to get the product in 85% yield. Here also compound purity is not mentioned. Deprotection of trifluoro acetyl group of the product is carried out by treatment with potassium carbonate in methanol to afford plerixafor base in 86% yield. The compound is isolated from toluene but the purity is not mentioned.

This process gives better yield but the purity of the intermediates or of plerixafor base is not mentioned. Also, column chromatography is required for the isolation of the tris trifluoroacetyl cyclam intermediate. Column chromatography, needless to say, is a tedious process which makes this route unfit for commercial purposes.

Indian patent application IN2011CH2459 describes a process for the preparation of plerixafor using tert-butoxycarbonyl as the protecting group. The reaction scheme is summarized below in scheme 3:

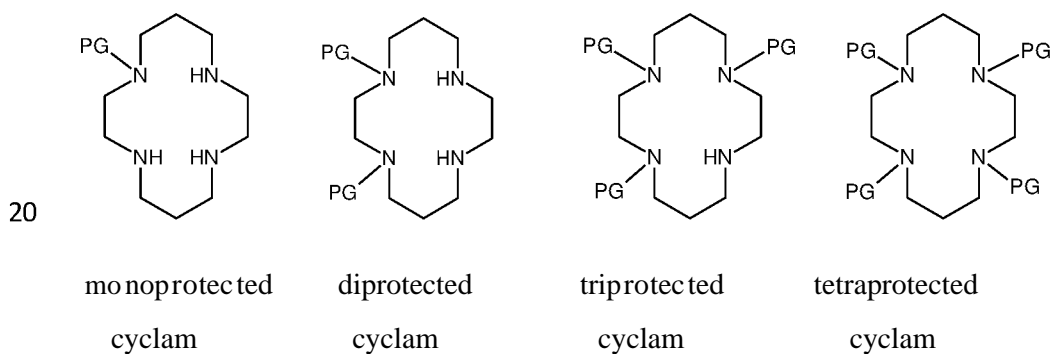




Scheme- 3

wherein, "Boc" means tert-butoxycarbonyl. Cyclam is reacted with di-tert-butyl dicarbonate in methylene chloride to give tris-Boc protected cyclam. The compound is reacted with α,α' -dibromoxylene in the presence of potassium carbonate in acetonitrile to yield 1,1'-xylyl-bis [4,8,11-tris(tert-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane]. The resulting compound is subjected to treatment with 1N hydrochloric acid and later with sodium hydroxide to obtain plerixafor, which is crystallized from acetone. The purity of final compound or intermediates is not mentioned and the overall yield is extremely low.

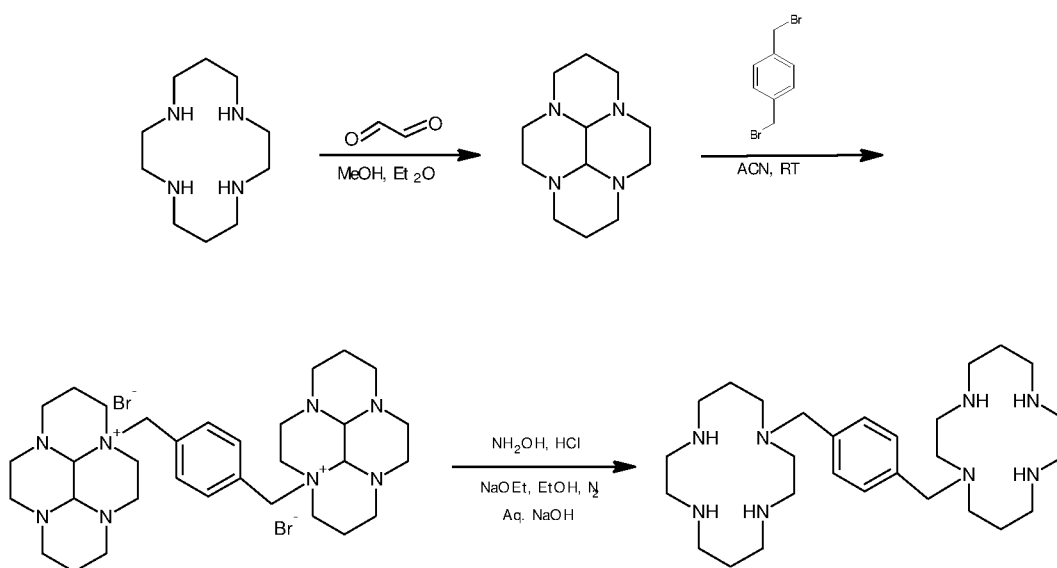
The inventors of the present invention have found that in all the above mentioned processes the purity of intermediate compounds is very low leading to significant yield losses during purification. A possible reason for such high amount of impurity formation appears to be the presence of four secondary nitrogen atoms in cyclam, out of which only three need to be protected. But during the reaction of cyclam with p-toluene sulfonyl chloride, Boc anhydride or ethyltrifluoroacetate, mono, di, tri and tetraprotected cyclam is formed. The structures of these are as shown below:



wherein PG represents a protecting group like Tosyl or Boc etc.

Such mono- or di-protected cyclam rings will give side reactions leading to further impurities while the tetra protected cyclam will remain unreacted as an impurity in the subsequent steps. These impurities are difficult to remove and
5 result in low yield and purity of further steps as well.

New J. Chem. 2001, 25, 1168-1174, describes an alternative process for the preparation of plerixafor. The cyclam ring is protected with the help of glyoxal, the protected cyclam ring is then reacted with dibromo-p-xylene to yield an intermediate which is deprotected with the help of hydroxykmine hydrochloride
10 and sodium ethoxide to yield the final compound. The overall synthesis is shown in scheme-4:



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Scheme-4

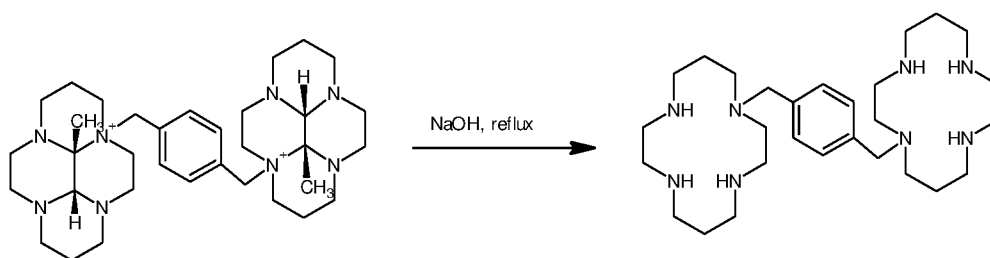
The glyoxal protection of the cyclam ring prevents the formation of mono, di or tetra-protected impurities and therefore it is expected that the yield and purity of the final compound be better than those of the other processes.

However, it was found that the purity of plerixafor obtained via this process is
20 very low. It was further found by the inventors that the glyoxal protected cyclam is a low melting and hygroscopic solid which is impossible to isolate or purify.

Any process generated impurities are carried forward to the next stages leading to an impure final compound.

Also, the final deprotection reaction involves the use of the hazardous, difficult to handle and hygroscopic reagent, sodium ethoxide. The use of strong reagents like sodium ethoxide leads to large amounts of impurity formation. Thus the final compound obtained by this process has very low purity.

Various inorganic bases have been described in literature for the removal of bis-aminal bridge from the cyclam moiety. J. Org. Chem., 2005, 70, 7042-7053 describes the use of sodium hydroxide for the deprotection of cyclam rings from plerixafor. But no information about the quality or purity of the product is mentioned.



From the foregoing, it is apparent that the reported methods for the preparation of plerixafor suffer from one or more of the following drawbacks:

- (a) extensive column chromatography needed to purify the intermediates used in the process,
- (b) low yields obtained due to the formation of impurities, and
- (c) use of hazardous and moisture sensitive reagents.

Thus, there still remains the need to formulate an efficient, simple and industrially viable synthetic process which can overcome the drawbacks of the prior art and which provides plerixafor and its intermediates free of impurities.

OBJECT OF THE INVENTION

It is an objective of the present invention to overcome the above-mentioned drawbacks of the prior art.

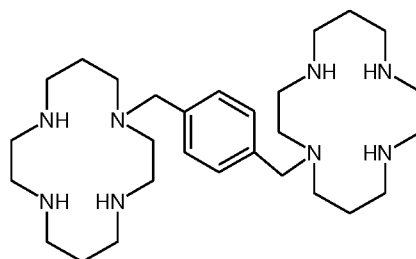
It is another objective of the present invention to provide an improved and commercially viable process for the synthesis of plerixafor without the use of
5 expensive and hazardous reagents.

It is a further objective of the present invention to provide useful intermediates for the synthesis of plerixafor.

SUMMARY OF THE INVENTION

10 The present invention provides an improved, commercially viable process for the preparation of plerixafor. The process of the present invention is easy and cost effective when implemented on industrial scale.

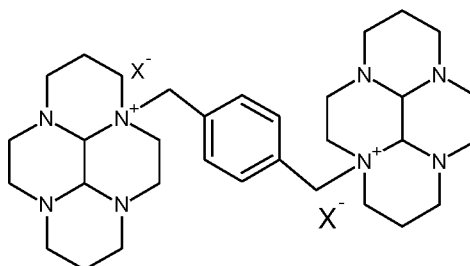
In first aspect, the present invention relates to a process for the preparation of a compound of formula (I),



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Formula (I)

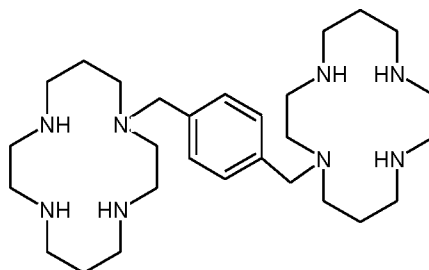
comprising, the reaction of the compound of formula (VII),



Formula (VII)

20 wherein X⁻ is ion of a leaving group with hydroxylamine or hydroxylamine hydrochloride in the presence of tertiary amine or tertiary alkoxide.

In another aspect, the present invention provides a process for the preparation of a compound of formula (I),

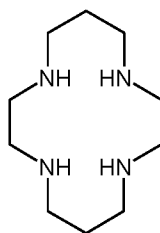


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Formula (I)

comprising the steps of:

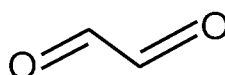
a) reacting a compound of formula (II),



Formula (II)

10

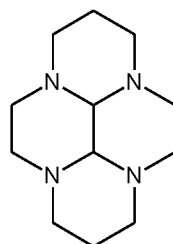
with a compound of formula (III),



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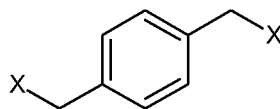
Formula (III)

to obtain a compound of formula (IV) or its salts,



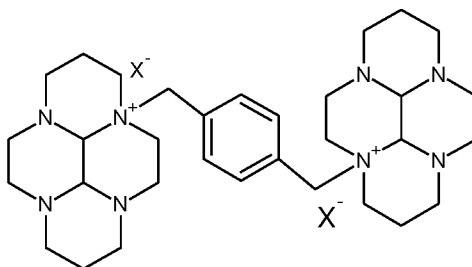
Formula (IV)

- b) reacting the compound of formula (IV) with a compound of formula (V),



Formula (V)

wherein X is a leaving group
to obtain a compound of formula (VII),

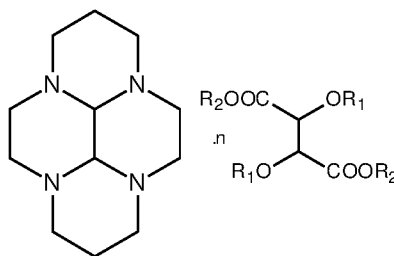


Formula (VII)

- wherein X^- is ion of the leaving group, and
c) reacting the compound of formula (VII) with hydroxylamine or hydroxylamine hydrochloride in the presence of tertiary amine or tertiary akoxide.

Another aspect of the present invention is to provide a process for the preparation of compound of formula (I) using the compound of formula (VI).

Another aspect of the invention is to provide a compound of formula (VI),



Formula (VI)

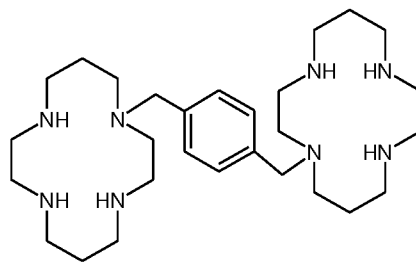
- wherein $n=1,2$ and R_1, R_2 may be independently selected from hydrogen, optionally substituted alkyl, aryl, acyl, alkylaryl or arakyl group.

In another aspect, the present invention provides a process for the preparation of the compound of formula (VI).

DETAILED DESCRIPTION OF THE INVENTION

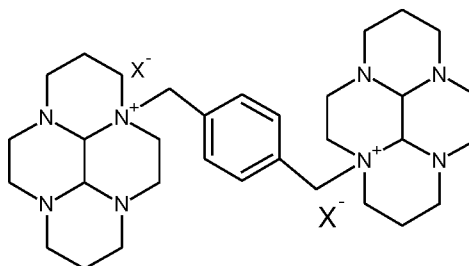
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In one aspect, a process for the preparation of a compound of formula (I),



Formula (I)

comprising, the reaction of the compound of formula (VII),



Formula (VII)

wherein X^- is ion of a leaving group

with hydroxylamine or hydroxylamine hydrochloride in the presence of tertiary amine or tertiary alkoxide is provided.

15 The reaction may optionally be carried out in the presence of a solvent.

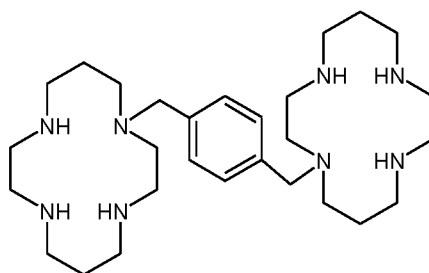
The solvent used in this reaction may be selected from the group comprising of water, alcohols like methanol, ethanol, isopropyl alcohol or halogenated hydrocarbons like dichloromethane, chloroform or esters like methyl acetate, ethyl acetate or ketones like methyl ethyl ketone, acetone, isobutyl ketone or
20 hydrocarbons like hexane, heptanes, toluene or polar aprotic solvents, polar protic solvents, ethers or mixtures thereof. Preferably the reaction is carried out in the presence of, methanol, ethanol or isopropyl alcohol. Most preferably the reaction is carried out in the presence of isopropyl alcohol.

The tertiary amine may be selected from triethylamine or diisopropylethyamine. Tertiary alkoxides may be selected from sodium tertiary butoxide or potassium tertiary butoxide.

The methods for the preparation of plerixafor reported in prior art involve the use of tedious purification techniques or the use of hazardous chemicals and the product obtained has low yield and purity.

The inventors have found that the above mentioned process, which comprises of deprotection reaction with hydroxylamine or hydroxyamine hydrochloride in the presence of tertiary amine or tertiary alkoxide, provides plerixafor in high yield and purity.

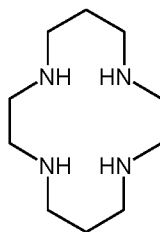
Another aspect of the present invention is to provide a process for the preparation of a compound of formula (I),



Formula (I)

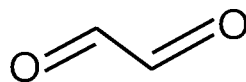
comprising the steps of:

a) reacting a compound of formula (II),



Formula (II)

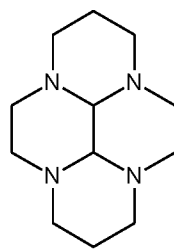
with a compound of formula (III),



Formula (III)

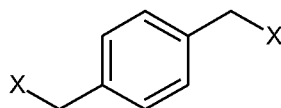
to obtain a compound of formula (IV) or its salts,

5



Formula (IV)

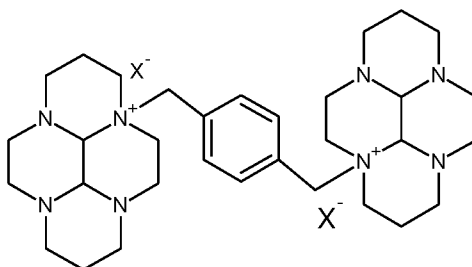
- 10 b) reacting the compound of formula (IV) with a compound of formula (V),



Formula (V)

wherein X is a leaving group

- 15 to obtain a compound of formula (VII),



Formula (VII)

wherein X^- is ion of the leaving group, and

c) reacting the compound of formula (VII) with hydroxylamine or hydroxylamine hydrochloride in the presence of tertiary amine or tertiary alkoxide.

- 5 The product obtained by this process has higher yield and purity and there is no need for the use of column chromatography or expensive and hazardous chemicals.

In one embodiment, the reaction of compound of formula (II) with the compound of formula (III) in step a) is carried out in the presence of a solvent.

- 10 In a preferred embodiment, the solvent used in step a) may be selected from the group comprising of water, alcohols like methanol, ethanol, isopropyl alcohol or halogenated hydrocarbons like dichloromethane, chloroform or esters like methyl acetate, ethyl acetate or ketones like methyl ethyl ketone, acetone, isobutyl ketone or hydrocarbons like hexane, heptanes, toluene or polar aprotic solvents, polar
15 protic solvents, ethers or mixtures thereof. Preferably, the reaction is carried out in the presence of methanol, ethanol or isopropyl alcohol. Most preferably the reaction is carried out in the presence of methanol

As discussed above, the reaction of compound of formula (IV) with a compound of formula (V) is carried out to produce a compound of formula (VII) in step b).

- 20 In the compound of formula (V), X is a leaving group, preferably, a halogen or mesyl or tosyl, more preferably the leaving group is a halogen and most preferably the leaving group is bromine.

- The reaction may be carried out in the presence of solvents selected from the group comprising of halogenated hydrocarbons like dichloromethane,
25 dichloroethane or chloroform, polar aprotic solvents like dimethylformamide, dimethylacetamide or dimethylsulfoxide, nitriles like acetonitrile or propionitrile. Preferably, the reaction is carried out in the presence acetonitrile, propionitrile, dimethylformamide or dimethylsulfoxide. Most preferably, the reaction is carried out in the presence of acetonitrile.

In step c) of the first embodiment, the compound of formula (VII) is reacted with hydroxylamine or hydroxylamine hydrochloride in the presence of tertiary amine or tertiary alkoxide.

The tertiary amine may be selected from triethylamine or diisopropylethylamine.

- 5 Tertiary alkoxides may be selected from sodium tertiary butoxide or potassium tertiary butoxide.

It was found that the purity and yield of the product are much improved when hydroxylamine or hydroxylamine hydrochloride is used in the presence of tertiary amines or tertiary alkoxides, unlike the methods reported in literature which lead
10 to the formation of impure product.

Data on purity of the product obtained using hydroxylamine hydrochloride reagent in the presence of various bases is given in table- 1.

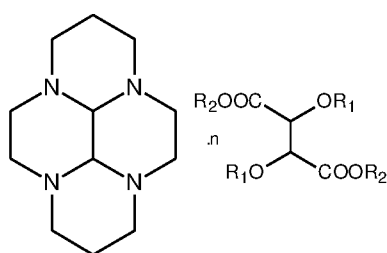
Table- 1

S. No	Base used	Reagent used	HPLC Purity of crude product (%)
1	Triethylamine	Hydroxylamine hydrochloride	91.31
2	Diisopropylethylamine	Hydroxylamine hydrochloride	92.56
3	Potassium tert. butoxide	Hydroxylamine hydrochloride	84.93
4	Sodium ethoxide	Hydroxylamine hydrochloride	62.78
5	Without base	Hydroxylamine hydrochloride	No product formed

- 15 The solvent used in this reaction may be selected from the group comprising of water, alcohols like methanol, ethanol, isopropyl alcohol or halogenated

hydrocarbons like dichloromethane, chloroform or esters like methyl acetate, ethyl acetate or ketones like methyl ethyl ketone, acetone, isobutyl ketone or hydrocarbons like hexane, heptanes, toluene or polar aprotic solvents, polar protic solvents, ethers or mixtures thereof. Preferably the reaction is carried out in the presence of, methanol, ethanol or isopropyl alcohol. Most preferably the reaction is carried out in the presence of isopropyl alcohol.

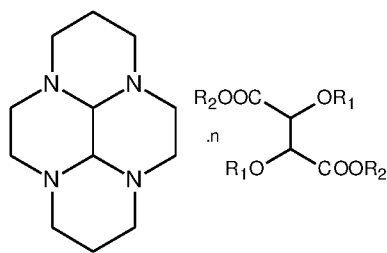
In another embodiment, the reaction of a salt of compound of formula (IV) with a compound of formula (V) to obtain a compound of formula (VII) is provided. The salt of compound of formula (IV) is a compound of formula (VI),



Formula (VI)

wherein n is 1 or 2; and R_1 , R_2 may be independently selected from hydrogen, optionally substituted alkyl, aryl, acyl, alkylaryl or aralkyl group.

The present invention also relates to a compound of formula (VI).

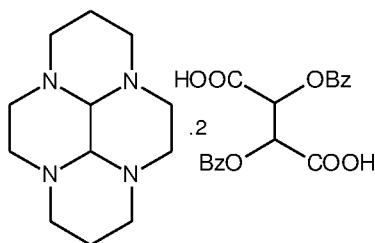


Formula (VI)

wherein R_1 and R_2 and n are as defined above.

The compound of formula (VI) is a salt of compound of formula (IV) which is a hygroscopic, low melting compound that cannot be purified except by column chromatography. But the substituted tartaric acid salts can be isolated and purified.

In a preferred embodiment, the compound of formula (VI) is a compound of formula (X),



Formula (X)

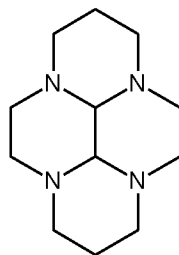
5 wherein Bz is benzoyl group.

The compound of formula (X) is the Dibenzoyl-L- tartaric acid salt of compound of formula (IV). The compound of formula (IV), glyoxal protected cyclam, is a low melting, hygroscopic solid which is difficult to isolate or purify. Further various salts of this compound are also difficult to isolate as either these salts do
 10 not precipitate and if they precipitate, they are highly soluble in most organic solvents and water and therefore cannot be purified.

However, the substituted tartaric acid salts, especially dibenzoyl-L- tartaric acid salt is unique as this salt can be isolated, purified and also shows greater stability compared to the free base or other salts of this compound. Various acids, organic
 15 and inorganic, were used to isolate the stable salt of compound of formula (IV). For example: hydrochloric acid, tartaric acid, p-toluenesulfonic acid, acetic acid, benzoic acid etc. But only the substituted tartaric acids, represented by formula (VII), were found to give stable, non-hygroscopic salts of compound of formula (IV).

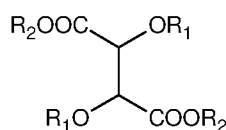
20 Another aspect of the present invention is to provide a process for the preparation of compound of formula (I) using the compound of formula (VI).

Yet another aspect of the present invention is to provide a process for the preparation of the compound of formula (VI), comprising the reaction of a compound of formula (IV),



Formula (IV)

with a compound of formula (VIII),



Formula (VIII)

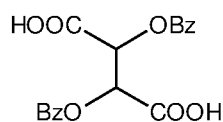
5

wherein R_1 and R_2 may be independently selected from hydrogen, optionally substituted alkyl, aryl, acyl, alkylaryl or arakyl group to obtain the compound of formula (VI).

The reaction may be carried out in the presence of suitable solvent. Suitable solvent may be selected from a group comprising of water, alcohols like methanol, ethanol, isopropyl alcohol or halogenated hydrocarbons like dichloromethane, chloroform or esters like methyl acetate, ethyl acetate or ketones like methyl ethyl ketone, acetone, isobutyl ketone or hydrocarbons like hexane, heptanes, toluene or polar aprotic solvents, polar protic solvents, ethers or mixtures thereof. Preferably the reaction is carried out in the presence of acetone or methyl acetate or ethyl acetate. Most preferably the reaction is carried out in the presence of ethyl acetate.

15

Preferably, the compound of formula (VIII) is a compound of formula (IX),

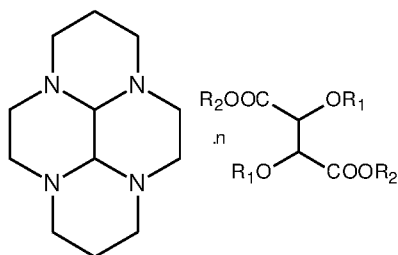


Formula (IX)

20

wherein Bz is benzoyl.

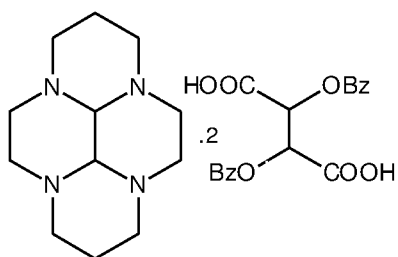
In a further aspect, a compound of formula (VI) is provided,



Formula (VI)

wherein $n=1,2$ and R_1 , R_2 may be independently selected from hydrogen,
 5 optionally substituted alkyl, aryl, acyl, alkylaryl or arakyl group.

Preferably, the compound of formula (VI) is a compound of formula (X),



Formula (X)

10 wherein Bz is benzoyl group.

EXPERIMENTAL

Detailed experimental parameters suitable for the preparation of plerixafor according to the present invention are provided by the following examples, which
 15 are intended to be illustrative and not limiting of all possible embodiments of the invention.

Example-1

Preparation of (2*R*, 3*R*)-2,3-bis(benzoyloxy)butanedioic acid-decahydro-1*H*,6*H*-3*a*,5*a*,8*a*,10*a*-tetraazapyrene (Compound of formula VI)

20 To a stirred solution of 1,4,8,11-tetraazacyclotetradecane (50.0g, 0.249 mole) in methanol (1625 ml) at -5°C was added a solution of glyoxal (44.2 g, 0.304 mole)

in methanol (250 ml) dropwise. After complete addition the reaction temperature was raised to 30°C and stirred for 4 hrs. Methanol was distilled off and the residue was stirred with ethyl acetate (750 ml) and filtered through celite bed. The filtrate was added dropwise to a stirred solution of dibenzoyl-L- tartaric acid (205.7g, 5 0.574 mole) in ethyl acetate (1500 ml) and the reaction mixture was stirred for 3 hrs at 30°C. The reaction mixture was filtered and solid obtained was washed with ethyl acetate. The crude product was dried under vacuum at 55°C for 20 hrs. The crude product was again slurry washed with water and dried to give the title compound.

10 Yield: 78.9% (185g)

GC Purity: 99.87%

Example-2

Preparation of 3a,3a'-(benzene- 1,4-diyl dimethanediyl)bisdecahydro- 1H,6H- 5a,8a,10a-triaza-3a-azonia pyrene dibromide (Compound of formula VII)

15 To a stirred solution of (2*R*, 3*R*)-2, 3-bis(benzoyloxy)butanedioic acid-decahydro- 1*H*,6*H*-3a,5a,8a,10a-tetraazapyrene (1000g, 1.065 mole) in dichloromethane (10000 ml) was added a solution of potassium carbonate (588.8g, 4.260 mole) in water at room temperature. The reaction mixture was stirred for 15 minutes and the layers were separated. The solvent was distilled off and acetonitrile (4500ml) 20 and a, a'-dibromo-p-xylene (115.3g, 0.436 mole) were added. The reaction mixture was stirred at room temperature for 30 hrs. The solid obtained was filtered and dried under vacuum and finally recrystallized from a mixture of methanol and IPA to obtain the title compound.

Yield: 72.3% (273.0g)

25 HPLC Purity: 98.65%

Example-3

Preparation of Plerixafor

To a stirred solution of hydroxylamine hydrochloride (760g, 10.937 mole) in isopropyl alcohol (5000 ml) was added triethylamine (1071g, 10.584 mole) at room temperature and the reaction mixture was stirred for 1.5 hrs. To this was added the product of example-2 (250g, 0.353 mole) and the reaction mixture was heated to 90°C and stirred at same temperature for 24 hrs. The solvent was distilled off and water (2500 ml) was added. An aqueous solution of sodium hydroxide was added and reaction mass was stirred. The layers were allowed to separate and dichloro methane was added to the organic layer. The organic layer was then washed with water. The organic solvent was distilled off and product was crystallized from toluene.

Yield: 52% (92.4 g)

HPLC Purity: 99.25%

Example-4

Purification of Plerixafor

To a stirred mixture of acetone (2250 ml) and water (250 ml) was added crude plerixafor (250g) and reaction mixture was heated to 60°C and stirred for 15 minutes. The solution obtained was filtered through 5 micron filter paper and the filtrate was stirred at 20°C for 2.5 hrs. The solution was further cooled to 0°C and stirred for 2 hrs. The solid obtained was filtered and dried under vacuum.

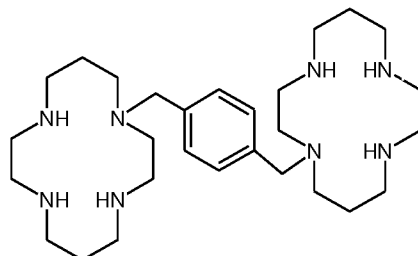
Yield: 91.6% (229g)

HPLC Purity: 99.80%

¹H NMR (400MHz, CDCl₃) δ: 1.646-1.656 (m, 4H), 1.842-1.852 (m, 4H), 2.446-2.456 (m, 4H), 2.517-2.531 (m, 4H), 2.545-2.560 (m, 4H), 2.602-2.615 (m, 4H), 2.627-2.652 (m, 4H), 2.663-2.710 (m, 4H), 2.720-2.736 (m, 4H), 2.750-2.804 (m, 4H), 2.966 (s, 4H), 3.352 (s, 2H), 3.511 (s, 4H), 7.276 (s, 4H).

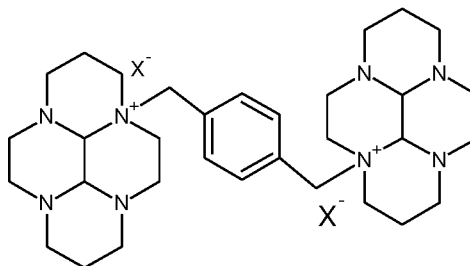
WE CLAIM:

1. A process for the preparation of a compound of formula (I),



Formula (I)

comprising the reaction of the compound of formula (VII),

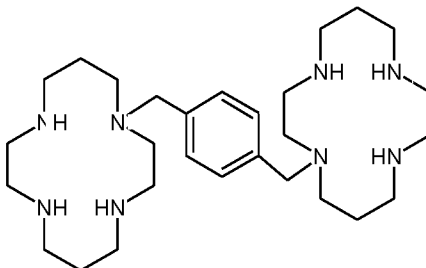


Formula (VII)

wherein X^- is ion of a leaving group

with hydroxylamine or hydroxykmine hydrochloride in the presence of tertiary amine or tertiary akoxide.

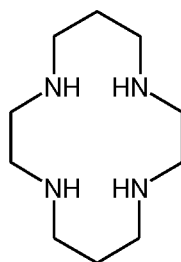
2. A process according to claim 1, for the preparation of a compound of formula (I),



Formula (I)

further comprising the steps of:

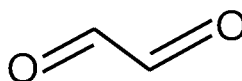
- d) reacting a compound of formula (II),



Formula (II)

with a compound of formula (III),

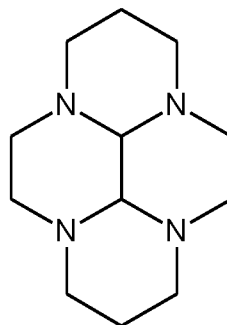
5



Formula (III)

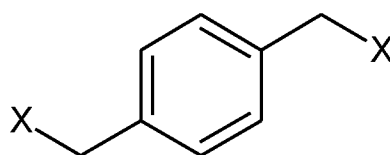
to obtain a compound of formula (IV) or its salts,

10



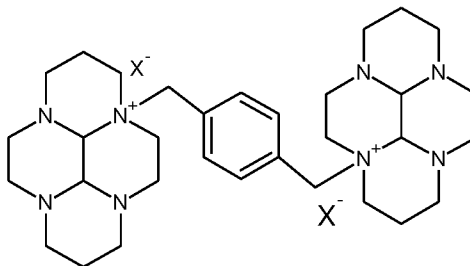
Formula (IV)

- 15 e) reacting the compound of formula (IV) with a compound of formula (V),



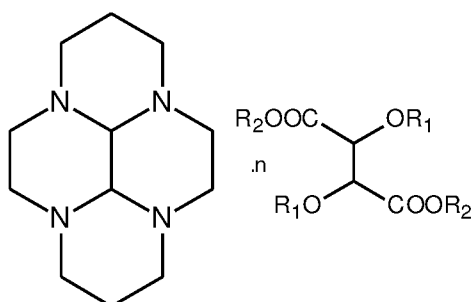
Formula (V)

wherein X is a leaving group
to obtain a compound of formula (VII),



Formula (VII)

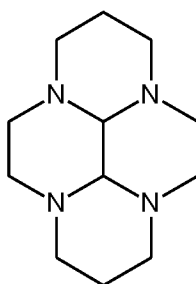
- 5 wherein X⁻ is ion of the leaving group.
3. The process according to claim 1 or 2, wherein the leaving group is halogen, preferably bromine.
- 10 4. The process according to any of claims 1-3, wherein the tertiary amine is selected from triethylamine, diisopropylethylamine and the tertiary akoxide is potassium tertiary butoxide.
5. The process according to claims 2-4, wherein step a) is carried out in the
15 presence of a solvent selected from a group of methanol, ethanol or isopropyl alcohol, preferably methanol.
6. The process according to claims 2-5, wherein step b) is carried out in the
presence of a solvent selected from a group of acetonitrile, propionitrile,
20 dimethylformamide or dimethylsulfoxide, preferably acetonitrile.
7. The process according to claim 1, wherein the reaction is carried out in the
presence of a solvent selected from a group of methanol, ethanol or isopropyl
alcohol, preferably isopropyl alcohol
- 25 8. The process according to claims 2-6, wherein the salt of compound of
formula (IV) is a compound of formula (VI),



Formula (VI)

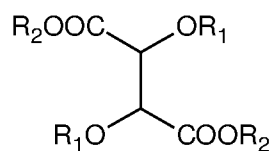
wherein n is 1 or 2; and R_1 , R_2 may be independently selected from hydrogen,
 5 optionally substituted alkyl, aryl, acyl, alkylaryl or arakyl group.

9. A process for the preparation of the compound of formula (VI), comprising
 the reaction of a compound of formula (IV),



Formula (IV)

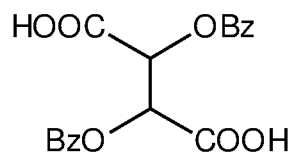
with a compound of formula (VIII),



Formula (VIII)

wherein R_1 and R_2 may be independently selected from hydrogen, optionally
 substituted alkyl, aryl, acyl, alkylaryl or aralkyl group
 to obtain the compound of formula (VI).

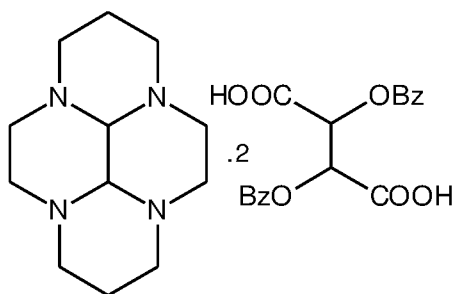
10. The process according to claim 9, wherein the compound of formula (VIII) is a compound of formula (IX),



Formula (IX)

wherein Bz is benzoyl.

11. The process according to claim 8, wherein the compound of formula (VI) is a compound of formula (X),

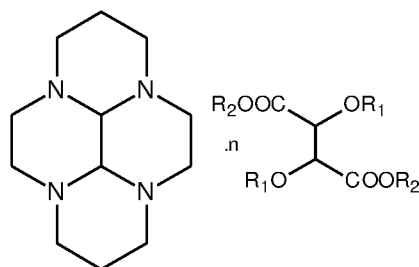


Formula (X)

wherein, Bz is benzoyl group.

12. A process for the preparation of compound of formula (I) using the compound of formula (VI).

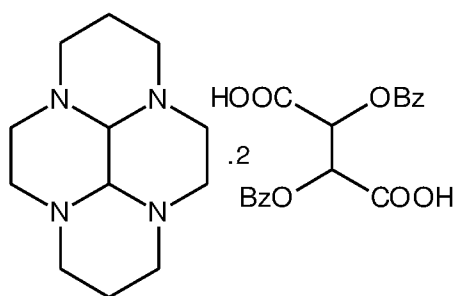
13. A compound of formula (VI),



Formula (VI)

wherein $n=1,2$ and R_1 , R_2 may be independently selected from hydrogen, optionally substituted alkyl, aryl, acyl, alkylaryl or aralkyl group.

14. A compound according to claim 13, wherein the compound of formula (VI) is
5 a compound of formula (X),



Formula (X)

wherein Bz is benzoyl group.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/055215

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D257/02 C07D519/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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 , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BACCON LE M ET AL: "BIS-AMINALS: EFFICIENT TOOLS FOR BIS-MACROCYCLE SYNTHESIS", NEW JOURNAL OF CHEMISTRY, ROYAL SOCIETY OF CHEMISTRY, GB, vol . 25, 1 January 2001 (2001-01-01) , pages 1168-1174, XPQ01157093 , ISSN : 1144-0546, DOI : 10. 1039/B103995B page 1168, scheme 1; page 1171, scheme 4 table 2; compound 9e page 1172 , left col umn, synthesi s of 9e page 1172 , right col umn, preparati on of 9'e page 1171 , synthesi s of compound 2 -----	1-8



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

17 October 2016

Date of mailing of the international search report

23/12/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Gutke, Hans-Jurgen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055215

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

process to prepare compound of formula I

2. claims: 9-14

salt of formula VI, method of its preparation and use thereof
