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- (71) **Applicant (for all designated States except US):** SE-
QUENT SCIENTIFIC LIMITED [IN/IN]; STAR - II,
Opp. to Indian Institute of Management, Bannerghatta
Road, Bangalore 560076 (IN).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** ARULMOLI,
Thangavel [IN/IN]; STAR - II, Opp. to Indian Institute of
Management, Bannerghatta Road, Bangalore 560076 (IN).
SURESH, Ramasamy [IN/IN]; STAR - II, Opp. to Indian
Institute of Management, Bannerghatta Road, Bangalore
560076, Karnataka (IN). MUTHULINGAM, Arunagiri
[IN/IN]; STAR - II, Opp. to Indian Institute of Manage-
ment, Bannerghatta Road, Bangalore 560076, Karnataka
(IN). SENTHILKUMAR, Annadurai, Marimuthu
[IN/IN]; STAR - II, Opp. to Indian Institute of Manage-
ment, Bannerghatta Road, Bangalore 560076, Karnataka
(IN). SWAMINATHAN, Dhanabal [IN/IN]; STAR - II,
Opp. to Indian Institute of Management, Bannerghatta
Road, Bangalore 560076 (IN). SARAVANAKUMAR,
Kasiyappan, Gurusamy [IN/IN]; STAR - II, Opp. to Indi-
an Institute of Management, Bannerghatta Road, Bangalore
560076, Karnataka (IN). YOGARAJAN, Nachiappan
[IN/IN]; STAR - II, Opp. to Indian Institute of Manage-

ment, Bannerghatta Road, Bangalore 560076, Karnataka
(IN).

- (74) **Agent:** KUMAR, Ramesh; SeQuent Scientific Limited,
120 A & B, Industrial Area, Baikampady, Mangalore
575011, Karnataka (IN).

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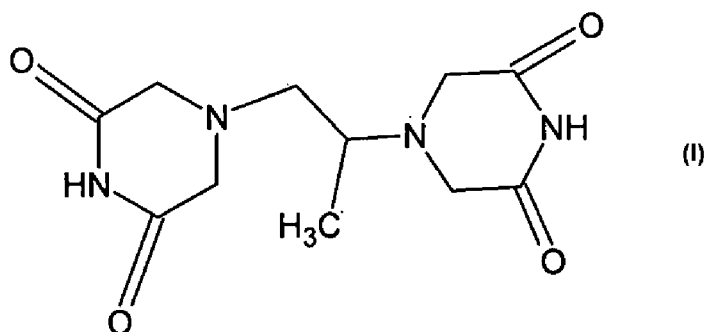
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- (54) **Title:** A PROCESS FOR PREPARATION OF 4,4'-(1-METHYL-1,2-ETHANDIYL)-BIS-(2,6-PIPERAZINEDIONE)



- (57) **Abstract:** The present invention relates to a new method for preparing 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) or its enantiomers. More specifically this invention relates to a new process for preparing 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione), which gives better yield and purity and involves new intermediate.

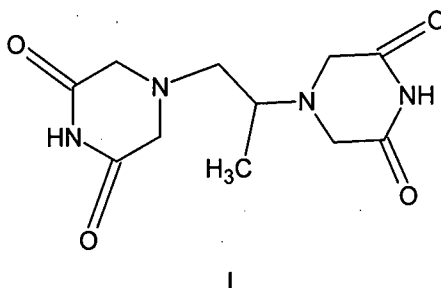
A Process for Preparation of 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione)

Field of Invention

The present invention relates to a new method for preparing 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione). More specifically this invention relates to a new process for preparing 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione), which gives better yield and purity and involves new intermediate.

Background of the Invention

4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) has the general formula (I)



The compound of the formula (I) may be present in the form of two enantiomers like (S)-(+)-4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) called Dexrazoxane, and (R)-(-)-4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) called Levorazoxane, as well as in the form of a racemate, (S,R)-4,4'-(1-methyl-1,2-ethandiyl)-bis(2,6-piperazinedione) called Razoxane. For the purpose of this invention a "compound of the formula (I)" or "4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-p-piperazinedione)", refers to the S-enantiomer, the R-enantiomer as well as to the racemate.

The compound of the formula (I) has an antitumor effect. The S-enantiomer of the compound of the formula (I), Dexrazoxane is known to prevent cardiomyopathy in cancer patients receiving high dose of the anthacycline agent, doxorubicin. It is also useful as a synergist in combination with other anticancer agents. Particularly with regard to sarcoma, lymphosarcoma and leukaemia, it has

been found that Dexrazoxane shows an activity and is particularly effective when used in a regime together with Adriamycin.

Several methods for preparation of the compound of the formula (I) have been reported in the prior art. For example, US patent no. 3,941,790 and 4,275,063 describe three methods for preparing bisdiketopiperazines including the compounds of the formula (I). In the first method, (S)-1,2-diaminopropane is reacted with chloroacetic acid to form (S)-1,2-diaminopropane-tetraacetic acid. Subsequently tetraacetic acid is reacted with formamide under nitrogen at an elevated temperature to give the corresponding compound of the formula (I). In the second method tetraacetic acid is prepared as previously described, converted to the corresponding tetraacetic acid amide by reacting with ammonia and the latter subsequently cyclised to compound of formula I using polyphosphorous acid or phenol by heating. This method is said to be particularly beneficial, when the tetraacetic acid tends to decarboxylate during heating. In the third method tetranitrile is reacted with sodium amide in formamide and the subsequent treating of the resulting product with hydrogen chloride in methanol is mentioned. This patent mentions that this alternative method has the benefit to be a low-temperature technique. All these methods are stereoselective methods, i.e. therefore the employed intermediate compounds in the form of tetraacetic acid, tetraamide or tetranitrile should already be available in the stereochemical configuration desired for the compound of the formula (I).

The intermediate compounds employed in the above methods, such as tetraacetic acid, may be prepared in different ways. British Patent No. 978724 describes a method for forming tetraacetic acid wherein diamines are reacted with formaldehyde and hydrogen cyanide to form a tetranitrile, which is saponified. US patent 2,461,519 teaches a method for preparing 1,2-diaminopropane-tetracarboxylic acid by reacting 1,2-diaminopropane with formaldehyde and sodium cyanide at an alkaline pH-value.

A major drawback in the known process of preparation of compound of formula I is the need of purification of intermediate compounds, which is costly and difficult to achieve on a commercial scale. By most of the methods, intermediate compounds, such as tetraacetic acid, are obtained together with high amounts of

alkali metal salts as a by-product, which needs to be separated prior to cyclisation to form the compound of the formula (I).

US patent publication 2010/0152447 describes a process for preparation of compound of formula (I) by cyclising a 1,2-diaminopropane-N,N,N',N'-tetraacetic acid alkyl ester with ammonia in formamide.

A lot of problems arise while purifying the precursor compound in known preparation methods, which are described in detail in PCT Application No. 93/08172.

Thus, to overcome these problems, there is a need to develop a process for the preparation of compound of formula (I), especially, a process for preparation of Dexrazoxane, which gives better purity and better yield without necessitating purification prior to cyclisation to form Dexrazoxane.

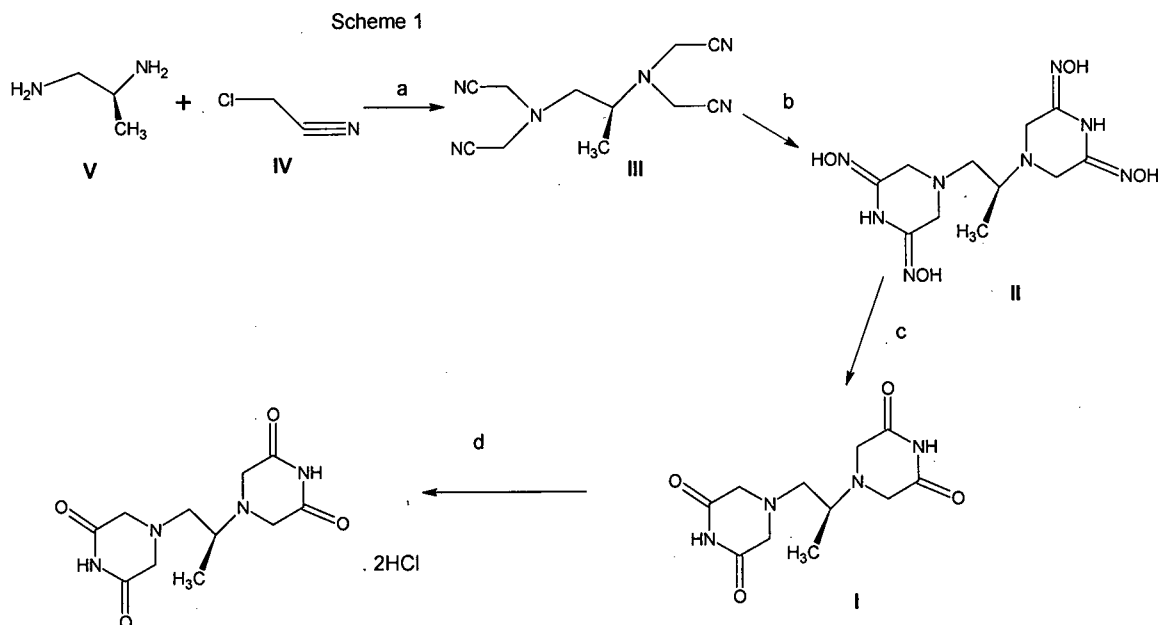
It is an objective of the present invention to provide a method for preparing the compound of the formula (I), which enables the preparation of this compound in good yield and good purity in a cost effective way on a commercial scale and overcomes most of the problems of the existing methods of preparation of compound of formula (I).

Summary of the Invention

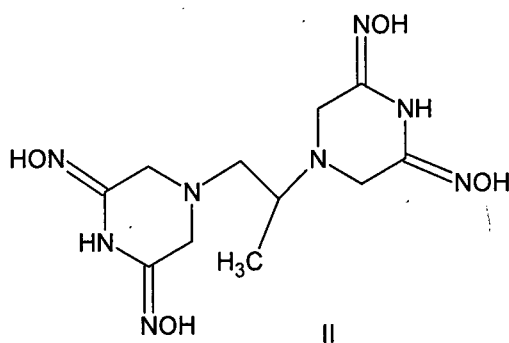
The primary aspect of the invention is to provide a process for the preparation of compound of formula (I) or its pharmaceutically acceptable salts, which comprises:

- a) reacting propanediamine with chloroacetonitrile to obtain propanediamine tetraacetonitrile of formula (III);
- b) cyclising propanediamine tetraacetonitrile in presence of a base and presence or absence of solvent to obtain 4,4'-(methyl-1,2-ethanediyl)-tetrakis-(hydroxylimino)piperazine of formula (II);
- c) hydrolysing 4,4'-(methyl-1,2-ethanediyl)-tetrakis-(hydroxylimino)piperazine in presence of a sodium nitrite, acetic acid and a solvent to obtain 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I); and
- d) optionally converting to a pharmaceutically acceptable salt.

The present invention can be illustrated by below scheme 1:



In another aspect, the present invention uses 4,4'-(methyl-1,2-ethanediyloxy)-tetrakis-(hydroxylimino)piperazine of formula (II) or its enantiomer to obtain the compound of formula (I). The compound of the formula (II) or its enantiomer, which is valuable precursor compound for the compound of the formula (I), is a novel compound.



In yet another aspect, the present invention provides a process for preparation of compound of formula (I) or its pharmaceutically acceptable salts, which comprises:

- a) converting propane diaminetetra acetic acid or its enantiomer to propane diaminetetra[1-imidazolyl carbonyl methyl] or its enantiomer in an organic solvent in presence of carbonyl diimidazole;
- b) cyclising propane diaminetetra[1-imidazolyl carbonyl methyl] in presence of ammonia to obtain 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione); and
- c) optionally converting to a pharmaceutically acceptable salt.

Detail Description of the Invention

Accordingly, in an embodiment of the invention, propane diamine is reacted with chloroacetonitrile in presence of a base preferably alkali metal carbonate and more preferably potassium carbonate, a solvent selected from dichloromethane, Acetone, Acetonitrile, Dimethyl formamide, Dimethyl sulphoxide, Dimethyl acetamide, water or the mixture thereof.

In another embodiment of the invention, cyclisation of propanediamine tetraacetonitrile is carried out in presence of a base preferably alkali metal carbonate and more preferably potassium carbonate. The solvent for the cyclisation is preferably selected from aqueous alcoholic solvent, preferably aqueous methanol in order to obtain 4,4'-(methyl-1,2-ethandiyl)-tetrakis-(hydroxylimino)piperazine of formula II. The compound of formula (II) and its enantiomer are novel and form an embodiment of the present invention. 4,4'-(Methyl-1,2-ethandiyl)-tetrakis-(hydroxylimino)piperazine of formula (II) or its enantiomer may be crystallised by aqueous alcohol preferably aqueous ethanol.

In another embodiment of the invention, the hydrolysis of 4,4'-(Methyl-1,2-ethandiyl)-tetrakis-(hydroxylimino)piperazine of formula (II) is carried out in an aqueous weak organic acid preferably in aqueous acetic acid and sodium nitrite to give an oily residue of 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I). The obtained 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) is crystallised from an alcohol preferably from ethanol.

In another embodiment of the invention, 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) may be prepared alternatively, by converting propane diaminetetra acetic acid or its enantiomer to propane diamine tetra[1-

imidazolyl carbonyl methyl] or its enantiomer in an organic solvent selected from dichloromethane, Acetone, Acetonitrile, Dimethyl formamide, Dimethyl sulphoxide, Dimethyl acetamide, preferably in dichloromethane and in presence of carbonyl diimidazole and further cyclising propane diamine tetra[1-imidazolyl carbonyl methyl] in presence of ammonia to obtain 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione).

In another embodiment of the invention, 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) may be converted to hydrochloride salt by refluxing it in an alcoholic hydrochloric acid preferably ethanolic hydrochloric acid.

In the preferred embodiment, the process of the present invention is stereoselective, i.e. the precursor compound must be available in the configuration desired for the compound of the formula (I).

Further aspects of the present invention can be learned from the following examples, which are given for illustration purposes and not to limit the invention. Those skilled in the art should appreciate that the details of the method, which are described in the following examples, may be modified within the scope of the present invention. For example, the method given in example has been described for the S-enantiomer i.e. for Dexrazoxane, the R-enantiomer, Levorazoxane, and the racemate may be prepared as well.

Example

Process for preparation of S-(+) –4, 4' (Methyl-1,2-ethane diyl) –bis-2,6-piperazinedione hydrochloride:

a) Preparation of S-(+) – Propane diamine tetraacetonitrile

S-(+) – Propane diamines (5g), Potassium carbonate (13.87g), water (15mL) and Dichloromethane (40mL) were mixed and stirred. The reaction mass was cooled to 0-5°C, (21.2g) of Chloro acetonitrile were added slowly and the temperature was allowed to return to ambient temperature. The reaction mixture was maintained at the same temperature for 2 hours. The organic layer was separated and the aqueous layer was extracted twice with Dichloromethane. The combined organic phase left an oily residue after evaporation which was further crystallized in cyclohexane.

Yield: 14.0g (90.32%)

b) Preparation of S-(+) -4, 4' (Methyl-1, 2-ethane diyl) -tetrakis (hydroxyimino) Piperazine

Methanol (20mL) and 7.5mL of water were added to a mixture of hydroxylamine hydrochloride (11.65g) and potassium carbonate (2.9 g). The mixture was stirred and S-(+) – Propane diamine tetraacetonitrile (5g) was added into it in portion. The mixture was refluxed in an inert atmosphere for 2-3 hours. After cooling the crystals were filtered. The crystals so obtained were crystallized further in ethanol and water.

Yield: 7.50g (83.8%)

c) Preparation of S-(+) -4, 4' (Methyl-1,2-ethane diyl) –bis- 2,6-piperazinedione

S-(+) -4, 4' (Methyl-1,2-ethane diyl) -tetrakis (hydroxyimino) Piperazine (5 g) was suspended in a mixture of water (20 mL) and acetic acid (20 mL). After cooling the reaction medium to 0-5°C, a solution of sodium nitrite (5 g) in 25 mL of water was added drop wise in an inert atmosphere. The mixture was left for 24 hours at ambient temperature. The reaction mixture was evaporated and the residue was extracted with ethyl acetate, washed with water. The oily residue obtained after evaporation of ethyl acetate layer was crystallized from ethanol.

Yield: 2.80g (87.50%)

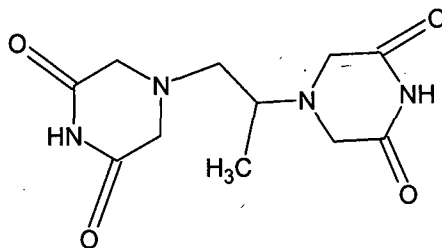
d) Preparation of S-(+) -4, 4' (Methyl-1,2-ethane diyl) –bis-2,6-piperazinedione hydrochloride

S-(+) -4,4' (Methyl-1,2-ethane diyl) –bis-2,6-piperazinedione (5g) was suspended in ethanol (20 mL) and hydrochloric acid (2.2mL) was added and refluxed for 1 hour. The reaction mixture was cooled to 0-5°C and filtered to obtain S-(+) -4, 4' (Methyl-1,2-ethane diyl) –bis-2,6-piperazinedione hydrochloride.

Yield: 5.0g (89.28%)

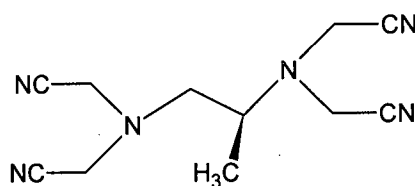
We claim:

1. A process for the preparation of compound of formula (I) or its pharmaceutically acceptable salts, which comprises:



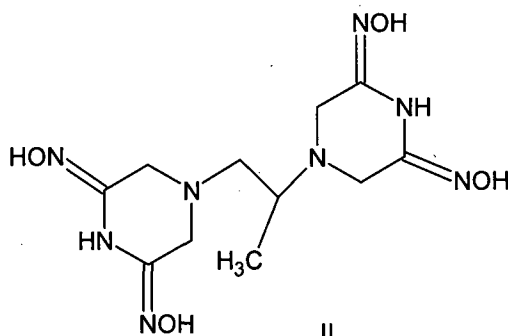
I

- a) reacting propanediamine with chloroacetonitrile to obtain propanediamine tetraacetonitrile of formula (III);



III

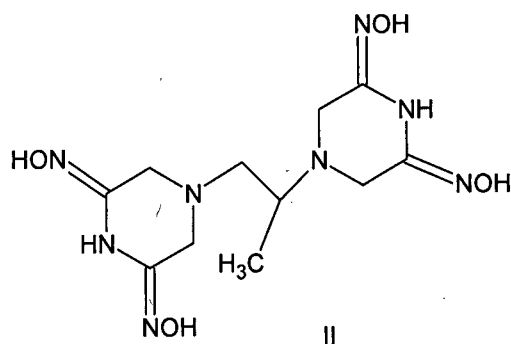
- b) cyclising propanediamine tetraacetonitrile in presence of a base and presence or absence of solvent to obtain 4,4'-(methyl-1,2-ethandiyl)-tetrakis-(hydroxylimino)piperazine of formula (II);



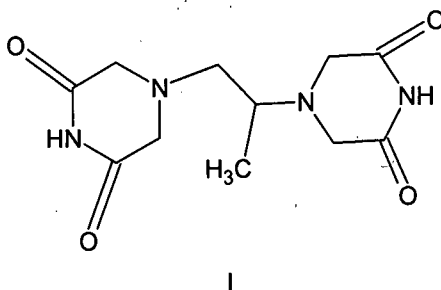
II

- c) hydrolysing 4,4'-(methyl-1,2-ethandiyl)-tetrakis-(hydroxylimino)piperazine in presence of a sodium nitrite, acetic acid and a solvent to obtain 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I); and
- d) optionally converting to a pharmaceutically acceptable salt.

2. A process according to claim 1, wherein propanediamine is reacted with chloroacetonitrile in step (a) in presence of a base such as alkali metal carbonate.
3. A process according to claim 1, wherein propanediamine is reacted with chloroacetonitrile in step (a) in presence of a base potassium carbonate.
4. A process according to claim 1, wherein propanediamine is reacted with chloroacetonitrile in step (a) in presence a solvent selected from dichloromethane, Acetone, Acetonitrile, Dimethyl formamide, Dimethyl sulphoxide, Dimethyl acetamide, water or the mixture thereof.
5. A process according to claim 1, wherein cyclisation of propanediamine tetraacetonitrile is carried out in presence of a base alkali metal carbonate.
6. A process according to claim 1, wherein cyclisation of propanediamine tetraacetonitrile is carried out in presence of a base potassium carbonate.
7. A process according to claim 1, wherein cyclisation of propanediamine tetraacetonitrile is carried out in presence of a solvent selected from aqueous alcoholic solvent, preferably aqueous methanol.
8. A process according to claim 1, wherein 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) in step (d) is converted to hydrochloride salt by refluxing it in an alcoholic hydrochloric acid.
9. A process according to claim 1, wherein 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione) of formula (I) in step (d) is converted to hydrochloride salt by refluxing it in ethanolic hydrochloric acid.
10. A compound of the formula (II).



11. The use of compound of formula (II) for the preparation of 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione).
12. A process for preparation of compound of formula (I) or its pharmaceutically acceptable salts, which comprises:



- a) converting propane diaminetetra acetic acid or its enantiomer to propane diamine tetra[1-imidazolyl carbonyl methyl] or its enantiomer in an organic solvent in presence of carbonyl diimidazole;
 - b) cyclising propane diamine tetra[1-imidazolyl carbonyl methyl] in presence of ammonia to obtain 4,4'-(1-methyl-1,2-ethandiyl)-bis-(2,6-piperazinedione); and
 - c) optionally converting to a pharmaceutically acceptable salt.
13. A process according to claim 12, wherein an organic solvent is selected from dichloromethane, Acetone, Acetonitrile, Dimethyl formamide, Dimethyl sulphoxide, Dimethyl acetamide.
14. A process according to claim 12, wherein an organic solvent used is dichloromethane.