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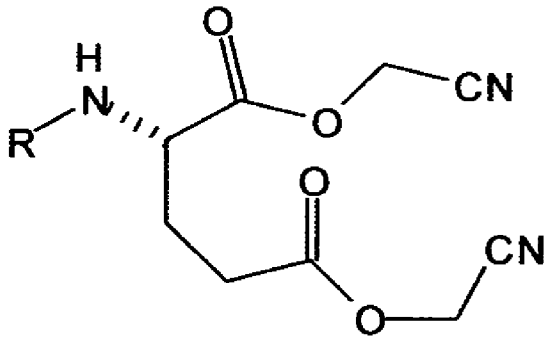
(54) Title: A NEW METHOD FOR PRODUCING ANTIFOLATE AGENTS HAVING GLUTAMIC ACID PART IN THEIR STRUCTURE



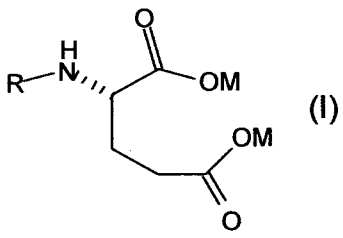
(II)

(57) Abstract: A new method for producing antifolate agents having glutamic acid part in their structure is developed by protecting carboxyl groups of glutamic acid or its N-subsituted derivatives as cyanomethyl ester to give compounds of formula (II) which are hydrolyzed under very mild conditions to afford antifolate agents in high yield with high analytical and optical purity.

DESCRIPTION

A NEW METHOD FOR PRODUCING ANTIFOLATE AGENTS HAVING GLUTAMIC ACID PART IN THEIR STRUCTURE

This invention relates to a new method for producing antifolate agents having glutamic acid part in their structure or salt thereof with the general formula

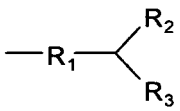


(I)

Wherein

M is a monovalent or divalent cation selected from group consisting of Na^+, K^+, $1/2Ca^{++}$ or $1/2Mg^{++}$; and

R is



with

Ri being a carbonyl group; and

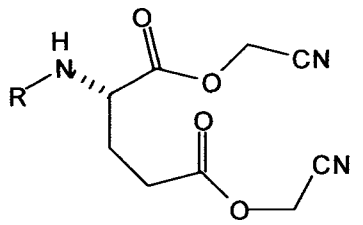
R_2 and R_3 being the same or different and being selected from

- straight-chain or branched, saturated or unsaturated Ci-C_{20}-heteroalkyl groups, which can optionally be substituted with amino groups;
- aromatic or aliphatic C_3-C^-hydrocarbon rings, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;

- aromatic or aliphatic C_3-C_{18}-heterocycles, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;

whereby R_2 and R_3 together can form an aromatic or aliphatic C_3-C_{18}-heterocycle, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;

compressing reacting a compound of the following formula

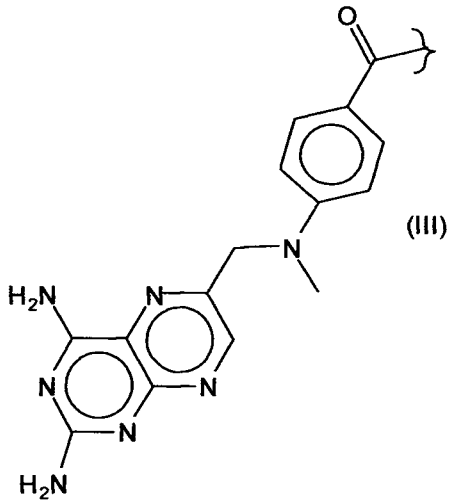


(II)

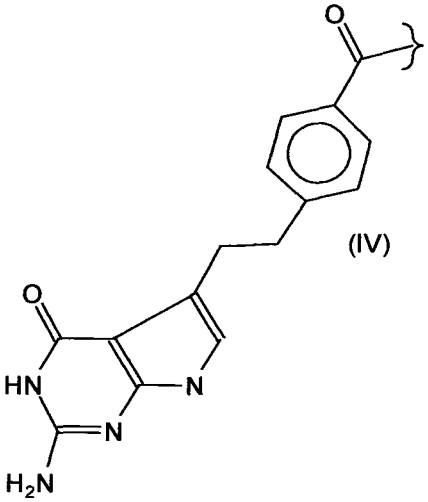
Wherein R is the same as in Formula (I), with an acidor basein an solvent; and

the compounds of formula (II) are obtained from reacting glutamic acid, N-subsituted glutamic acids or their salts with chlorocetonitrile.

The compounds of Formula (I) form among others the backbone of a number of known antifolate agents, in which R is for example



(III)



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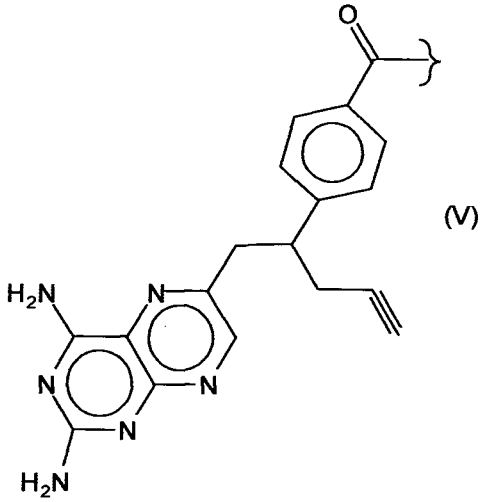

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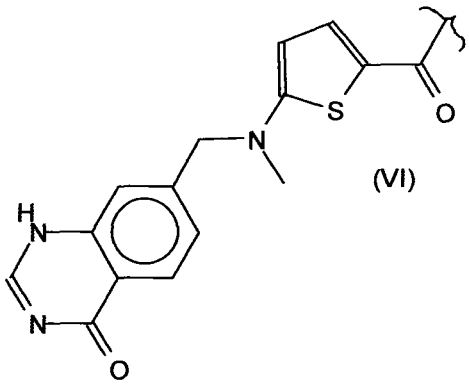

(VI)

Folic acid inhibitors comprising such a heterocyclic aromatic backbone belong to a group of antimetabolites which are generally referred to as "antifolates". Antifolates which show such a heterocyclic aromatic backbone include Methotrexate (R is III), Pemetrexed (R is IV), Pralatrexate (R is V) and Raltitrexed (R is VI).

These agents work by inhibiting the action of key enzymes thymidylate synthase and dihydrofolate reductase and have found clinical utility as

antitumor and antineoplastic agents. These agents inhibit both purine and pyrimidine synthesis by blocking enzyme functions and cause cell death. They have a greater toxic effect on rapidly dividing cell like cancer cells.

The new method for producing optically pure forms of the active pharmaceuticals can increase quality of the drug substances.

The compounds of Formula (II) include precursors to the above antifolates that are protected as a cyanomethyl ester and can be obtained deprotection of the cyanomethyl group on the glutamate moiety by using a basic or acidic agent.

US patent no 4,067,867 describes preparing well known potent folic acid antagonist methotrexate. In the last step of methotrexate synthesis diethyl N-[p[[(2-amino-3-cyano-5-pyrizinyl)methyl] memylamino]benzoyl]glutamate reacted with quanidine acetate in DMF to give Methotrexate diethyl ester. After purification it was found that the compound is completely racemic.

DE patent no 2824011 discloses preparation of p-(N-methyl-N-formyl)-aminobenzoyl-L-glutamic acid which is precursor in the synthesis of methotrexate. In the last step of the synthesis formyl group is removed under basic conditions. They could not use strong alkali conditions and high temperature with long reaction time to remove formyl group because of the racemisation risk of the glutamic acid part of the molecule.

US 4,136,101 describes for preparing dialkyl(p-methylaminobezoyl)glutamates from zinc N-(p-aminobezoyl)glutamates which is an intermediate in the synyhesis of Methotrexate. In the patent it states that due to the crystalline nature of zinc salt of the intermediate is cleaner than other metal salts. For example, the purity of the zinc N-(p-

aminobezoyl)-L-glutamate is about 80-90% versus about 55-70% for the corresponding disodium salt. In this patent as lower alcohol like methanol, ethanol, 2-propanol and 1-butanol are used as solvent and treated with gaseous HC1 under anhydrous conditions to get corresponding ester. Although this approach seems good there is still a racemization risk of the glutamate part during the hydrolysis of the ester moieties and use off corresive gaseous HC1 together with expensive absolute alcohols makes this process unsuitable for a large scale synthesis.

There are also other patents and articles for preparing methotrexate directly from N-(jp-aminobezoyl)-L-glutamic acid or its salts as an intermediate but in this case crude methotrexate obtained is not pure and need to be crystallized many times. These processes reduce the yield dramatically, (for example, the yield is below 6%, see J. Am. Chem. Soc. 1949, 71, 1753, the yield is 7%, see US Patent No. 3,989,703).

According to literatures given above it is difficult to produce Methotrexate in good yields with high analytical and optical purity. There is still a need to develop new synthetic routes for the preparation of antifolate agents.

Some of the compounds with different alkyl ester of the formula (II) are used as intermediates in the synthesis of the corresponding antifolates of formula (I) and need to be deprotected by hydrolysis at higher temperature under strong basic conditions to get active drug substances or their salt. But under these conditions there is a racemization risk at the alfa carbon of glutamic acid part and formation of the degradation products. When glutamic acid or their metal salts are used in the coupling reaction to get the antifolates, the yields are very low as mentioned above.

It is therefore an object of this invention to describe a new method for producing antifolate agents of formula (I) from compounds of formula (II)

under very mild reaction conditions in good yield with high analytical and optical purity.

It was now surprisingly found that cyanomethyl group can be successfully used to protect carboxyl group of glutamic acid compounds of formula (II) which are intermediates in the synthesis of antifolates.

Cyanomethyl esters can be removed under very mild reaction conditions even serve as a living group in the coupling reaction of unnatural amino acids to dinucleotides during the preparation of misacylated transfer RNAs (Arslan et. al. J. Am. Chem. Soc. **1997,** 119, 10877).

To get different alkyl ester of the formula (II) from the metal salt of glutamic acid, for example from zinc salt, it was necessary to carry out the reaction in absolute alcohol which is expensive and as acid source very corrosive gaseous HC1 which is not convenient for large scale synthesis are used.

Another object of this invention is that cyanomethyl ester of the compounds of formula (II) or their intermediates having glutamic acid part can be easily prepared starting from metal salt of glutamic acid or from its N-substituted derivatives by reacting with chloroacetonitrile in a polar solvent.

Metal salts of glutamic acid that used as intermediates in the synthesis of compounds (I) can not be obtained in pure form, for example, the purity of the zinc N-(p-aminobezoyl)-L-glutamate is about 80-90% versus about 55-70% for the corresponding disodium salt during the synthesis of methotrexate.

When cynomethyl ester of N-(p-aminobezoyl)-L-glutamate was prepared and isolated following the simple procedure in this invention, the purity of

the intermediate is higher than 98% (^{1}H-NMR). The coupling reaction with pure intermediates gives pure compounds of formula (II) in the case of methotrexate with high yield

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It is yet an object of this invention is that cyanomethyl groups of formula (II) can be hydrolyzed under very mild basic or acidic conditions to give desired active substances or their salts in high yield with high analytical and optical purity.

Cyanomethyl ester act as protecting group of carboxyl functionalities of formula (II) but easily hydrolyzed at a more moderate pH value than previously used alkyl esters. They make also possible to obtain pure form of compounds (II) which result in pure antifolate agents of formula (I).

It is an embodiment of the invention, precursors of the antifolate agents having glutamic acid part is protected as dicynaomethyl esters reacting with chloroacetonitrile in a polar solvent and then coupled with other suitable intermediates to give protected antifolate agents as compounds of formula (II).

The compounds of the formula (II) are formed as intermediates in the synthesis of the corresponding antifolate agents of formula (I). In a further step, they need to be deprotected to form the desired active compounds of formula (I).

Preferably, R_2 and R_3 either together form a phenyl or thiophene ring, which are substituted with an alkyl group or alkyl group containing hetero atoms and alkyl groups are further substituted with bicyclic or heterocyclic aromatic ring systems containing structures like purines or pyrimidenes.

R_1 is preferably carbonyl.

Compounds of such a structure are known to show biological activity and therefore are of interest in the synthesis of drug substances for various pharmaceuticals

In an embodiment of the invention, the compound of Formula (I) is a compound that shows antifolate activity and is used treating different type of cancers. Preferably, it is selected from the group consisting of Methotrexate, Pemetrexed, Pralatrexate and Raltitrexed whereby Methotrexate and Pemetrexed are particularly preferred.

Such compounds are anticancer drugs and therefore are of high commercial interest.

In a further embodiment of the reaction, chloroacetonitrile which is an inexpensive and commercially availably material is used in the esterification reaction for producing the compounds of formula (II) or their precursors.

The esterification reaction is carried in a polar solvent, more preferably in a water miscible polar solvent, especially a solvent selected from the group consisting of dimethylformamide, dimethylacetamide, dimethylsulfoxide, a ketono like acetone or methylisobutyl ketone and acetonitrile or mixtures thereof.

It has been shown that for this kind of reaction, particularly DMF, give the best results with regard to yield as well as solubility of the starting materials or their salts. After formation of cyanometester of formula (II) or their intermediates, water can be added to reaction mixture and the corresponding ester is precipitated and isolated by filtration.

Precipitation is a particularly preferred method for isolating the formed cyanomethylesters of formula (II) or their intermediates since it can be affected by simply stirring the mixture at room temperature without the need for more complex purification technique such as column chromatography.

In a further embodiment of the invention, glutamic acid precursors of compounds of formula (II) are reacted with the chloroacetonitrile at a temperature from 20 to 120 °C, preferably from 50 to 80 °C.

In another embodiment of the invention, the cyanomethyl ester of glutamic acid or its N-substituted derivatives are coupled with other intermediates containing heterocyclic rigs having haloalkyl or carboxyl groups to give compounds of formula (II).

The coupling reaction are carried out in water or in an organic solvent, especially polar solvents give the best results with regard to yield as well as solubility of all agents involved. Dimethylformamide, dimethylacetamide, and water, have thereby been shown to be the most suitable solvents at a temperature from 0 to 100 °C, preferably from 50 to 75 °C.

When water is used as a solvent compounds of formula (II) directly precipitated from the reaction mixtures in a pH range about 1 to about 6, preferably in a pH range about 2 to about 5, especially pH about 4.0 at a temperature from 0 to 60 °C, preferably from 0 to 25 °C.

It has been found that in the above-named temperature ranges, the reactions can be performed in 0.5 to 4.5 hours, preferably 1 hour for obtaining a good yield.

In a further embodiment of the invention, the compound of formula (II) are reacted with the metal hydroxide, earth alkali hydroxides or carbonates to give the compounds of formula (I) or their salts.

The hydrolysis reaction is carried out in a water/alcohol mixture in the presence of 1 to 3 equivalents, especially 2 equivalents of metal hydroxide, alkaline earth metal hydroxides or carbonates. Polar solvents give the best results with regard to yield as well as solubility of all agents involved. Hydrolysis of cyanomethyl groups is done at a temperature from 0 to 100 °C, preferably from 20 to 25 °C.

It has been found that in the above-named time ranges a virtually complete hydrolysis reaction is achieved leading to high yields with high analytical and optical purity of the compound of formula (I) or their pharmaceutically useful salts.

The salt form of the compounds of formula (I) are obtained by suspending the compounds of formula (I) into water, adjusting the pH to about 10 with corresponding metal hydroxide and then adding them to a ketone such as acetone to precipitate.

It is understood that the above features and the features described below can be used not only in their described combination but also in other combinations or in isolation without departing from the scope of the invention.

The invention is now further illustrated by means of examples. These examples are not intended to limit the scope of the invention any way.

EXAMPLE 1

Preparation of N-[4-(methylamino)benzoyl]-L-glutamic acid disodium salt from N-[4-(methyIamino)benzoyl]-L-glutamic acid zinc salt

A l 1erlenmayer equipped with magnetic stirrer was charged with 500 ml of water and 50 gr (0.15 mol) of N-[4-(methylamino)benzoyl]-L-glutamic acid zinc salt(~.85% pure) at room temperature. The pH of the mixture was adjusted to 8.0 by using 0.2M Na_2C0_3. The precipitate Zinc oxide was isolated via filtration. The pH of the solution was adjusted to 6.2 by using dilute HC1. The solvent evaporated under reduced pressure and the residue was dried under vacuum at 50 °C for 5-6 hours to give 36.1 g (0.1 16 mol) of N-[4-(methylamino)benzoyl]-L-glutamic acid disodium salt in 90% yield as a red foam.

EXAMPLE 2

Preparation of Dicyanomethyl N-[4-(methylamino)benzoyl]-L-glutamic acid from N-[4-(methyIamino)benzoyl]-L-glutamic acid disodium salt

A I L flask was equipped with magnetic stirrer, thermometer and condenser. The flask was charged with 250 ml of DMF, 30g (0.096 mol) of N-[4-(methylamino)benzoyl]-L-glutamic acid disodium salt and 20 ml (0.31 mol) of chloroacetonitrile at room temperature. The suspension was stirred at 60 °C for 4-5 hours. The solution was cooled to room temperature and 250 ml of water was added. The mixture was stirred for 15-20 minutes, a white precipitate was formed. The solid was isolated via filtration and washed with 20 ml of water. The solid was dried under vacuum at 50 °C for 3 hours and Dicyanomethyl N-[4-(methylamino)benzoyl]-L-glutamic acid_was obtained 27 g (0.078 mol) as a white solid in 81% yield. According to 1H-NMR the product was very clean.

1H-NMR (DMSO) δ 2 07(m, 2H), 2.55(t, 2H), 2.70(d, 3H), 4.45(m, 1H), 4.9 l(s, 2H), 4.97 (s, 2H), 6.23(q, 1H), 6.53(d, 2H), 7.65(d, 2H), 8.43(d, 1H).

EXAMPLE 3

Preparation of Dicyanomethyl N-[4[[(2,4-diamino-6-pteridinyl)methyl] methylamino]benzoyl]-L-glutamate (Methotrexate Dicyanomethyl ester)

A I L flask was equipped with magnetic stirrer, thermometer and condenser. The flask was charged with 143 ml of water and 10 g (0.029 mol) of 2,4-Diarnino-6-(bromomethyl)pteredine hydrobromide at room temperature. To this suspension was added 13 g (0.037 mol) of Dicyanomethyl N-[4-(methylamino) benzoyl]-L-glutamic acid at room temperature. The pH of the mixture was 2.40. The mixture was heated to 58-62 C and stirred there for 1 hour. The progress of the reaction was followed by TLC (EtOAc:MeOH, 4:1) and it was completed. The mixture was cooled to room temperature and the solid was isolated by filtration. The solid cake was washed with 15 ml of water and dried under vacuum at 50 °C for 5-6 hours to give 13.2 g (0.029 mol) of Methotrexate Dicyanomethyl ester as a yellow solid in 87% yield. According to 1H-NMR the product was very clean.

1H-NMR (DMSO) δ 2 08(m, 2H), 2.55(t, 2H), 3.23(s, 3H), 4.46(m, 1H), 4.82(d, 2H), 4.94(s, 2H), 4.98 (s, 2H), 6.82(d, 2H), 7.35(m, 2H), 7.72(d, 2H), 8.30(s, 1H), 8.52(d, 2H), 8.64(s, 1H).

EXAMPLE 3

Preparation of N-[4[[(2,4-diamino-6-pteridinyl)methyl] methylamino]benzoyl]-L-glutamic acid disodium salt from Methotrexate Dicyanomethyl ester

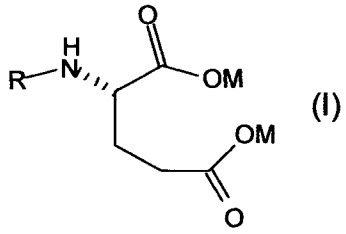
A I L flask was equipped with magnetic stirrer, thermometer and condenser. The flask was charged with 160 ml of methanol, 80 ml of water and 1.75 g (0.03 mol) of KOH. The solution was stirred at rt for 5-10 minutes. To this solution was added 10 g (0.019 mol) of Methotrexate Dicyanomethyl ester at room temperature. The solution was stirred for 20 min at room temperature. The progress of the reaction was followed by TLC (EtOAc.MeOH 4:1) and it was completed. The solution was concentrated under reduced pressure. The pH of the solution was adjusted to 4.2 with

dilute HC1 and a yellow solid was precipitated. The crude methotrexate was isolated by filtration and washed with water. The wet cake was suspended into 75 ml water and the pH was adjusted to 10 with 2N NaOH,. a clear solution was obtained. To the solution 2 g of charcoal was added stirred for 5 min. and filtered. The solution containing methotrexate disodium was added at room temperature into 500 ml of acetone while stirring. A yellowish solid was formed and isolated by filtration. The solid was dried under vacuum at 50 ℃ for 8-10 hours to yield 8.3 g (0.017 mol, 89% yield) of Methotrexate Disodium with a purity of higher than 99.8% determined by HPLC.

1H-NMR (D_20) δ 1.88(m, 1H), 1.98(m, 1H), 2.17(m, 2H), 2.89(s, 3H), 4.14(m, 1H), 4.37(s, 2H), 6.53(d, 2H), 7.46(d, 2H), 8.27(s, 1H).

CLAIMS

1. A new method for producing antifolate agents having glutamic acid part in their structure or salt thereof with the general formula

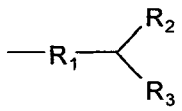


(I)

Wherein

M is a monovalent or divalent cation selected from group consisting of Na^+, K^+, $1/2Ca^{++}$ or $1/2Mg^{++}$; and

R is



with

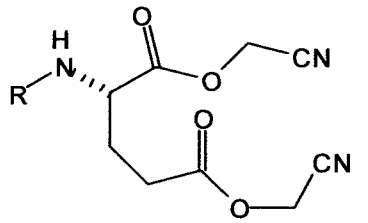
R_1 being a carbonyl group; and

R_2 and R_3 being the same or different and being selected from

- straight-chain or branched, saturated or unsaturated C_1-C_{20}-heteroalkyl groups, which can optionally be substituted with amino groups;
- aromatic or aliphatic C_3-C_{18}-hydrocarbon rings, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;
- aromatic or aliphatic C_3-C_{18}-heterocycles, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;

whereby R_2 and R_3 together can form an aromatic or aliphatic **C3-C18**-heterocycle, which can optionally be substituted with one or more selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, amine, nitro, thiol, sulfoxy, sulfone groups, which can optionally be substituted and/or form further rings;

compresing reacting a compound of the following formula



(II)

Wherein R is the same as in Formula (I), with an acid or base in a solvent; and

the compounds of formula (II) are obtained from reacting glutamic acid, N-subsituted glutamic acids or their salts with chlorocetonitrile.

2. Method according to claim 1, characterized in that R_2 and R_3 either together form a phenyl or thiophene ring, which can be substituted with an alkyl group or alkyl group containing hetero atoms and alkyl groups can be further substituted with a bicyclic or heterocyclic ring systems containing structures like purines or pyrimidenes.

3. Method according to any one of claims 1 to 2, characterized in that Ri is carbonyl.

4. Method according to any one of claims 1 to 3, characterized in that the compound of formula (I) is a compound that shows antifolate activity and used treating different type of cancers.

5. Method according to claim 4, characterized in that the compound of formula (I) is selected from the group of consisting of Methotrexate, Pemetrexed, Pralatrexate and Raltitrexed.

6. Method according to claim 5, characterized in that the compound of the formula (I) is selected from the group consisting of Methotrexate and Pemetrexed.

7. Method according to any one of the claimsl to 6, characterized in that the protecting group is an ester.

8. Method according to claims 7, characterized in that the ester is cyanomethyl ester.

9. Method according to any one of the claimsl to 8, characterized in that cyanomethyl ester of the compounds of formula (II) or their intermediates having glutamic acid part are easily prepared starting from metal salt of glutamic acid or from its N-substituted derivatives by reacting with chloroacetonitrile.

10. Method according to claim 9, characterized in that the esterification reaction is carried in a polar solvent, more preferably in a water miscible polar solvent.

11. Method according to claim 10, characterized in that the solvent selected from the group consisting of dimethylformamide, dimethylacetamide, dimethylsulfoxide, a ketono like acetone or methylisobutyl ketone and acetonitrile or mixtures thereof.

12. Method according to any one of the claims 1 to 11, characterized in that the cyanomethyl ester of glutamic acid or its N-substituted derivatives are coupled with other intermediates containing heterocyclic rigs having haloalkyl or carboxyl groups to give compounds of formula (II).

13. Method according to claim 12, characterized in that the coupling reaction affording compounds of formula (II) are carried out in water or in an organic solvent, such as dimethylformamide and dimethylacetamide.

14. Method according to claim 13, characterized in that the coupling reaction is carried out at a temperature from 0 to 100 °C, preferably from 50 to 75 °C.

15. Method according to any one of the claims 1 to 14, characterized in that the compound of formula (II) are reacted with the metal hydroxide, alkaline earth metal hydroxides or carbonates to give the compounds of formula (I) or their salts.

16. Method according to the claims 15, characterized in that the hydrolysis reaction is carried out in a water/alcohol mixture in the presence of 1 to 3 equivalents, especially 2 equivalents of metal hydroxide, earth alkali hydroxides or carbonates.

17. Method according to claim 16, characterized in that when a water/Ci^ alcohol mixture used as solvent best results are achieved.

18. Method according to claim 17, characterized in that hydrolysis of cyanomethyl groups is done at a temperature from 0 to 100 °C, preferably from 20 to 25 °C.

19. Method according to any one of the claims 1 to 18, characterized in that the salt form of the compounds of formula (I) are obtained by suspending the compounds of formula (I) into water, adjusting the pH to about 10 with corresponding metal hydroxide and then adding them to a ketone such as acetone to precipitate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2010/000235

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D475/08
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, 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.
A	WO 2006/014706 A2 (SERENEX INC [US] ; HANSON GUNNAR J [US] ; BARTA THOMAS E [US] ; VEAL JAME) 9 February 2006 (2006-02-09) page 1, paragraph 1 scheme on page 10; page 9, lines 10-24; claim 1; example 1	1-19
A	US 3 035 041 A (ROBERT SCHWYZER ET AL) 15 May 1962 (1962-05-15) columns 1,2; claim 1; example 24	1-19

-/- .

[X] Further documents are listed in the continuation of Box C.

[X] 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

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2011	09/08/2011

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	Guspanova, Jana

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2010/000235

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LOEFFLER L J ET AL: "Anti neopl asti c Agents . 2. Structure-Acti vity Studi es on N-Protected Vi nyl , 1,2-Di bromoethyl , and Cyanomethyl Esters of Several Ami no Aci ds", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCI ETY, US, vol . 20, no. 12 , 1 December 1977 (1977-12-01) , pages 1584-1588, XP002113237 , ISSN : 0022-2623 , DOI : D0I : 10. 1021/JM00222A009 compound 17 i n Tabl e I compound 18 i n tabl e I I ; page 1584, col umn 2, l i nes 3-7 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2010/000235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 20060 14706 A2	09-02 -2006	NON E	
US 303504 1 A	15-05 - 1962	NON E	