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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2012 (23.08.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/111027 A2

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/IN2012/000103

(22) International Filing Date:
14 February 2012 (14.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
434/CHE/2011 15 February 2011 (15.02.2011) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: PROCESS FOR PEMETREXED DISODIUM

(57) **Abstract**: The present invention provides a process for the preparation of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester or salts thereof. The present invention also provides a process for the preparation of pemetrexed disodium substantially free of enatiomeric impurity.

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PROCESS FOR PEMETREXED DISODIUM

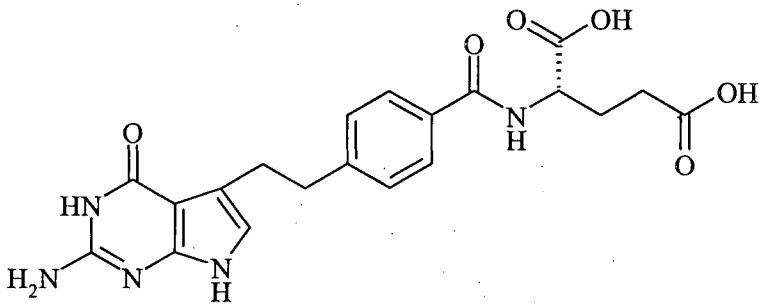
This application claims the benefit of Indian Patent Application No. 434/CHE/2011, filed on February 15, 2011, which is incorporated herein by reference.

Filed of the Invention

The present invention provides a process for the preparation of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester or salts thereof. The present invention also provides a process for the preparation of pemetrexed disodium substantially free of enatiomeric impurity.

Background of the Invention

Pemetrexed is chemically, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid. Pemetrexed is represented by the following structure:



Pemetrexed is an anti-neoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. It is believed to work by inhibiting three enzymes that are required in purine and pyrimidine biosynthesis-thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT). Pemetrexed is available in the market under the brand name ALIMTA® and marketed by Eli Lilly.

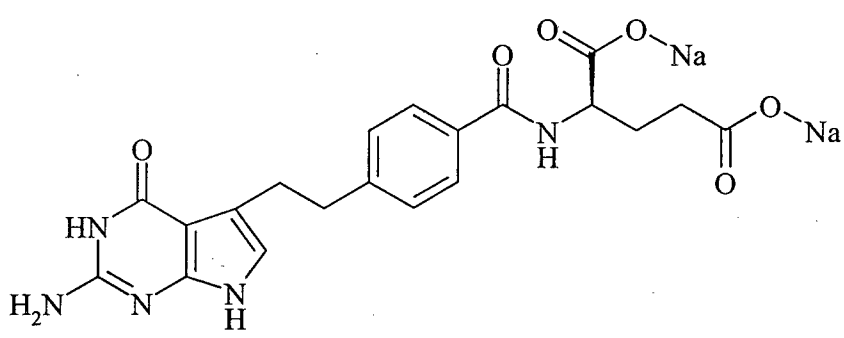
The therapeutic uses of pemetrexed and related compounds were disclosed in US Patent No. 5,344,932 and EP Patent No. 432,677.

PCT publication No. WO 01/14379 ('379 patent) disclosed pemetrexed disodium crystalline hydrate form I. According to the '379 patent, pemetrexed disodium crystalline hydrate form I can be prepared by stirring a solution of 4-(2-(2-amino-4(1H)-oxo-4,7-dihydropyrrolo[2,3-d]pyrimidin-5-yl]ethyl]benzoyl-L-glutamic acid diethyl ester in sodium hydroxide and water, pH of the reaction mass was adjusted to 7.7, heated to 60 to 70^{0}C and then added ethanol, and isolating.

Process for the preparation of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid diethyl ester 4-methylbenzenesulfonic acid was reported in *Organic Process Research & Development, 1999, 3,184-188*. According to the journal, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid diethyl ester 4-methylbenzenesulfonic acid can be prepared by reacting 4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid with 2-chloro-4,6-dimethoxy-1,3,5-triazine and L-glutamic acid diethyl ester hydrochloride in the presence of dimethylformamide and N-methylmorpoline at 25^{0}C to obtain a solid. The obtained solid was reacted with p-toluenesulfonic acid in ethanol and then added dimethyl sulfoxide, heating to 80^{0}C, cooling and isolating

U.S. patent no. 7,138,521 disclosed pemetrexed disodium heptahydrate crystal form. According to the patent, pemetrexed disodium heptahydrate crystal form can be prepared by crystallizing pemetrexed disodium from a solution of pemetrexed disodium in water and acetone.

N-[4-[2-(2-Amino-4,7-dihydro-4-oxo-3H-pyrrolo-[2,3,d]-pyrimidin-5-yl)ethyl]benzoyl]-D-glutamic acid disodium salt is enatiomeric impurity of pemetrexed disodium. The chemical formula of enatiomeric impurity may be represented as:



The present invention is intended to enhance the purity of pemetrexed disodium. In particular, the present invention is directed to reduce or remove enantiomeric impurity from pemetrexed disodium.

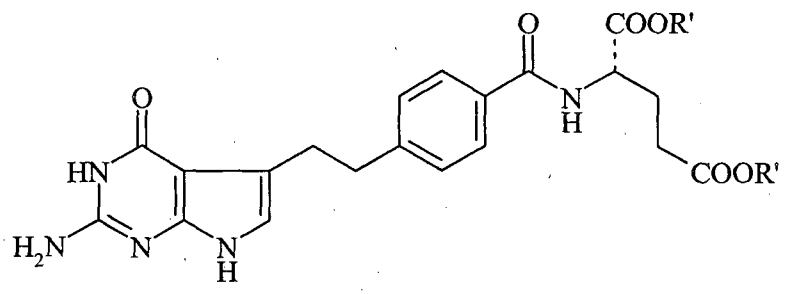
We have discovered a process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity.

Thus, one object of the present invention is to provide a process for the preparation of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester or salts thereof.

Another object of the present invention is to provide a novel process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity.

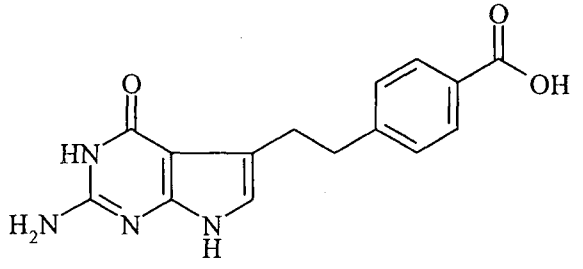
Summary of the Invention

In one aspect, the present invention provides a process for the preparation of substantially pure compound of formula I or salts thereof,



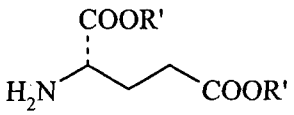
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which comprises, reacting activated 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo-[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid of formula II



---------- II

with a compound of formula III.



---------- III

Wherein the R' is independently a lower alkyl.

In another aspect, the present invention provides a process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity, which comprises:

a) stirring a solution of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid with a mixture of sodium hydroxide and water at below 30^0C;

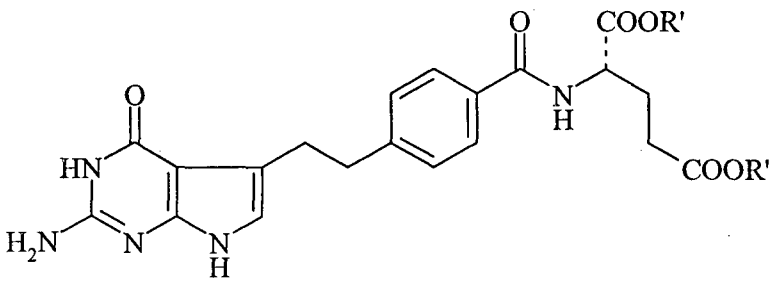
b) adjusting the pH of the reaction mass to above 7.2 with an acid;

c) adding an organic solvent to the solution obtained in step (b) at below 30^0C; and

d) isolating the pemetrexed disodium substantially free of enantiomeric impurity.

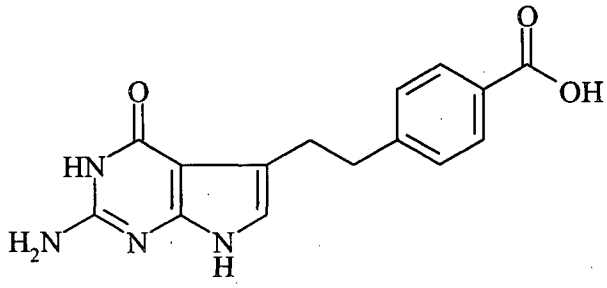
Detailed Description of the Invention

According to one aspect of the present invention, there is provided a process for the preparation of substantially pure compound of formula I or salts thereof,



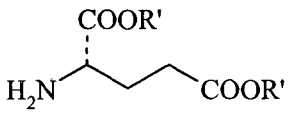
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which comprises reacting activated 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo-[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid of formula II



---------- II

with a compound of formula III.



---------- III

Wherein the R' is independently a lower alkyl.

The term "lower alkyl" refers to $C_1 - C_4$ alkyl such as methyl, ethyl, propyl and butyl, and preferable alkyl is methyl or ethyl. More preferable alkyl is methyl.

The reaction may preferably be carried out in a solvent system comprising a solvent or mixture of solvents selected from dimethylformamide, dimethyl sulfoxide, methylene chloride, N-methylpyrrolidone and dimethylformamide, and more preferably the solvents are dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone and methylene chloride.

According to another aspect of the present invention, there is provided a process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity, which comprises:

a) stirring a solution of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid with a mixture of sodium hydroxide and water at below 30^0C;

b) adjusting the pH of the reaction mass to above 7.2 with an acid;

c) adding an organic solvent to the solution obtained in step (b) at below 30^0C; and

d) isolating the pemetrexed disodium substantially free of enantiomeric impurity.

The term "pemetrexed disodium substantially free of enantiomeric impurity" refers to pemetrexed disodium having the content of enantiomeric impurity in equal to or less than about 0.3% by weight, preferably equal to or less than about 0.2% by weight

and more preferably equal to or less than about 0.1% by weight. The contents of pemetrexed disodium and the enantiomeric impurity are determined by High performance liquid chromatography (HPLC).

Preferably the reaction in step (a) may be carried out at below 25^0C.

Preferably the pH of the reaction mass in step (b) may be adjusted to above 7.5.

Preferably the acid used in step (b) may be a mineral acid or an organic acid and more preferably the acid is mineral acid selected from hydrochloric acid, sulfuric acid or phosphoric acid. Still more preferably the acid is hydrochloric acid.

The organic solvent used in step (c) may preferably be a solvent or mixture of solvents selected from the group consisting of methanol, ethanol, isopropanol, isobutanol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone, and more preferably the organic solvents are methanol, ethanol, isopropanol and acetone.

Preferably the reaction in step (c) may be carried out at below 25^0C.

Isolation of pemetrexed disodium in step (d) can be performed by conventional methods such as cooling, removal of solvents, concentrating the reaction mass, adding an anti-solvent, extraction with a solvent and the like.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Reference example

Preparation of 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid

Step-I: Preparation of 4-(4-hydroxy-1-butynyl)benzoic acid methyl ester

To a mixture of methyl 4-bromobenzoate (100 gm) and ethyl acetate (1000 ml) were added palladium(II)chloride (4.2 gm), triphenylphosphine (6.1 gm), cuprous iodide (4.5 gm), triethylamine (80 gm) and 3-butyn-1-ol (42 gm). The contents were heated to 70^0C and then maintained for 4 hours. The reaction mass was then cooled to 50^0C and filtered. The separated organic layer was dried with sodium sulfate and the solvent was distilled off under reduced pressure to obtain a residual solid. To the residual solid was added n-hexane (1000 ml) and then cooled to 0 to 5^0C. The reaction mass was stirred for

2 hours at 0 to 5^{0}C and filtered. The solid obtained was dried to give 80 gm of 4-(4-hydroxy-1-butynyl)benzoic acid methyl ester.

Step-II: Preparation of 4-(4-hydroxybutyl)benzoic acid methyl ester

4-(4-Hydroxy-1-butynyl)benzoic acid methyl ester (75 gm) was added to methanol (700 ml) under nitrogen atmosphere. To the mixture was added raney nickel (30 gm) in methanol (50 ml) and the resulting mixture was stirred under 45 psig of hydrogen for 5 hours. The reaction mass was filtered and the solvent was distilled off under reduced pressure at below 40^{0}C to obtain 69 gm of 4-(4-hydroxybutyl)benzoic acid methyl ester.

Step-III: Preparation of 4-(4-oxobutyl)benzoic acid methyl ester

A solution of 4-(4-hydroxybutyl)benzoic acid methyl ester (73 gm) in methylene chloride (3650 ml) was added to a solution of potassium bromide (4.1 gm) in water (70 ml). The solution was cooled to 0 to 5^{0}C and then added 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1.7 gm). To the solution was added sodium hypochlorite (12%, 270 ml (adjusted to pH by the addition of 20% acetic acid)) at 0 to 10^{0}C. The layers were separated and the organic layer was dried over sodium sulfate. The methylene chloride solvent was distilled off under reduced pressure to obtain 39 gm of 4-(4-oxobutyl)benzoic acid methyl ester.

Step-IV: Preparation of 4-(3-bromo-4-oxobutyl)benzoic acid methyl ester

A solution of 4-(4-oxobutyl)benzoic acid methyl ester (58 gm) in methylene chloride (58 ml) was added to a mixture of 5,5-dibromo barbituric acid (6.4 gm) and hydrobromic acid in acetic acid (33% HBr, 160 ml) in methylene chloride (720 ml) slowly for 1 hour at 25 to 30^{0}C. The reaction mixture was stirred for 6 hours at 25 to 30^{0}C and the mixture was then filtered through celite bed. The layers were separated and the organic layer was dried over sodium sulfate. The solvent was distilled off under reduced pressure at below 40^{0}C to obtain 44 gm of 4-(3-bromo-4-oxobutyl)benzoic acid methyl ester.

Step-V: Preparation of 4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid methyl ester

A mixture of sodium acetate (3.4 gm) in water and 2,4-diamino-6-hydroxy pyrimidine (26 gm) was added to a solution of (4-(3-bromo-4-oxobutyl)benzoic acid methyl ester (59 gm) in isopropanol (290 ml) at 25 to 30^{0}C. The contents were heated to 40^{0}C and maintained for 3 hours, filtered. The wet solid obtained was slurried in isopropanol (290 ml) at 60 to 65^{0}C for 1 hour. The separated solid was filtered and dried to obtain 3.9 gm of 4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid methyl ester.

Step-VI: Preparation of 4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid

4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid methyl ester (49 gm) was suspended in methanol (320 ml) and then cooled to 0 to 5^{0}C. A solution of sodium hydroxide (63 gm) in water (100 ml) was added to the above slurry slowly at 0 to 10^{0}C. The reaction mass was stirred for 2 hours at 0 to 5^{0}C and pH of the reaction mass was adjusted to 3.5 with hydrochloric acid (6N, 95 ml). The reaction mass was stirred for 30 minutes at 0 to 5^{0}C and filtered. The solid obtained was dried to obtain 44 gm of 4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid.

Examples

Example 1:

Preparation of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid

4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5yl)ethyl]benzoic acid (49 gm) as obtained in reference example was suspended in dimethylformamide (500 ml) and dimethyl sulfoxide (100 ml) and then added N-methylmorpholine (98 gm). The mixture was then cooled to -15 to -10^{0}C and then added 2-chloro-4,6-dimethoxy-1,3,5-triazine (64 gm). The mixture was stirred for 1 hour at -15 to -10^{0}C and then added a solution of L-glutamic acid dimethyl ester (85 gm) in methylene chloride (300 ml).

The reaction mass was stirred for 3 hours at -10 to -15^{0}C and filtered. The organic layer was separated and the solvent was distilled off under reduced pressure at below 35^{0}C to obtain a residual solid. To the residual solid was dissolved in methanol (2000 ml) and then added a solution of p-toluene sulfonic acid monohydrate (64 gm) in methanol (2000 ml). The contents were heated to reflux and maintained for 3 hours. The reaction mass was then cooled to 40^{0}C and filtered. The solid obtained was dried to obtain 110 gm of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid.

Example 2:

Preparation of pemetrexed disodium 2.5 hydrates

N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzensulfonic acid (102 gm) as obtained in example 1 was added to a solution of sodium hydroxide (29 gm) in water (720 ml) under stirring at 25 to 30^{0}C to obtain a solution. The pH of the solution was adjusted to 7.8 to 8.1 with hydrochloric acid (1N, 200 ml) and the reaction mass was then filtered through celite bed. To the filtrate obtained was added ethanol (150 ml) at 25 to 30^{0}C, stirred for 1 hour and filtered. The solid obtained was dried to give 45 gm of pemetrexed disodium 2.5 hydrates.

Chromatographic purity of pemetrexed disodium: 99.75%; and

Content of enatiomeric impurity: 0.08%.

Example 3:

Preparation of pemetrexed disodium 2.5 hydrates

N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzensulfonic acid (5 gm) was added to a solution of sodium hydroxide (1.4 gm) in water (36 ml) at 20 to 25^{0}C. The pH of the reaction mass was adjusted to 8.3 to 8.6 with hydrochloric acid (1N, 9 ml) and the reaction mass was then filtered through celite bed. To the filtrate obtained was added isopropanol (300 ml) at 20 to 25^{0}C and stirred for 1 hour. The separated solid was

filtered and dried under vacuum at 40 to 45^{0}C to obtain 2 gm of pemetrexed disodium 2.5 hydrates.

Chromatographic purity of pemetrexed disodium: 99.84%; and

Content of enatiomeric impurity: 0.06%.

Example 4:

Preparation of pemetrexed disodium 2.5 hydrates

N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzensulfonic acid (5 gm) was added to a solution of sodium hydroxide (1.4 gm) in water (36 ml) under stirring at 0 to 5^{0}C. The pH of the reaction mass was adjusted to 7.9 to 8.2 with hydrochloric acid (1N, 10 ml) and the reaction mass was then filtered through celite bed. To the filtrate obtained was added methanol (300 ml) at 0 to 5^{0}C and stirred for 1 hour under nitrogen atmosphere, filtered. The solid obtained was washed with methanol and dried under vacuum at 40 to 45^{0}C to obtain 0.8 gm of pemetrexed disodium 2.5 hydrates.

Chromatographic purity of pemetrexed disodium: 99.75%; and

Content of enatiomeric impurity: 0.09%.

Example 5:

Preparation of pemetrexed disodium 2.5 hydrates

N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzensulfonic acid (10 gm) was added to a solution of sodium hydroxide (3 gm) in water (72 ml) at 15 to 20^{0}C. The pH of the solution was adjusted to 8.1 to 8.3 with hydrochloric acid (1N, 20 ml) and the reaction mass was then filtered through celite bed. To the filtrate obtained was added ethanol (15 ml) at 15 to 20^{0}C and stirred for 1 hour under nitrogen atmosphere. The separated solid was filtered and dried under vacuum at 40 to 45^{0}C to obtain 5 gm of pemetrexed disodium 2.5 hydrates.

Chromatographic purity of pemetrexed disodium: 99.85%; and

Content of enatiomeric impurity: 0.06%.

Example 6:

Preparation of pemetrexed disodium heptahydrate

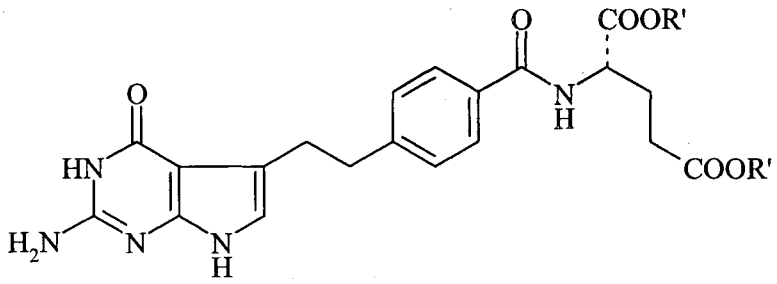
N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid (10 gm) was added to sodium hydroxide solution (72 ml; sodium hydroxide in water) at 25 to 30^0C under stirring. The pH of the reaction mass was adjusted to 7.7 to 8.0 with hydrochloric acid (1N, 20 ml) and then added acetone (600 ml). The reaction mass was maintained for 1 hour at 25 to 30^0C and filtered. The solid obtained was dried to give 11 gm of pemetrexed disodium heptahydrate.

Chromatographic purity of pemetrexed disodium: 99.8%; and

Content of enatiomeric impurity: 0.08%.

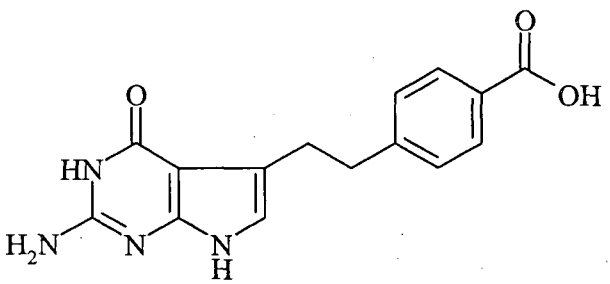
We claim:

1. A process for the preparation of substantially pure compound of formula I or salts thereof,



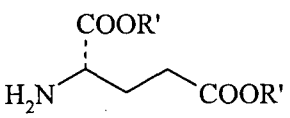
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which comprises reacting activated 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo-[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid of formula II



---------- II

with a compound of formula III.



---------- III

Wherein the R' is independently a lower alkyl.

2. The process as claimed in claim 1, wherein the R' is methyl, ethyl, propyl or butyl.
3. The process as claimed in claim 2, wherein the R' is methyl or ethyl.
4. The process as claimed in claim 3, wherein the R' is methyl.
5. The process as claimed in claim 1, wherein the reaction is carried out in a solvent system comprising a solvent or mixture of solvents selected from dimethylformamide, dimethyl sulfoxide, methylene chloride, N-methylpyrrolidone and dimethylformamide.

6. The process as claimed in claim 5, wherein the solvents are dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone and methylene chloride.
7. A process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity, which comprises:
   a. stirring a solution of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4-methylbenzenesulfonic acid with a mixture of sodium hydroxide and water at below 30^0C;
   b. adjusting the pH of the reaction mass to above 7.2 with an acid;
   c. adding an organic solvent to the solution obtained in step (b) at below 30^0C; and
   d. isolating the pemetrexed disodium substantially free of enantiomeric impurity.
8. The process as claimed in claim 7, wherein the reaction in step (a) is carried out at below 25^0C.
9. The process as claimed in claim 7, wherein the pH of the reaction mass in step (b) is adjusted to above 7.5.
10. The process as claimed in claim 7, wherein the acid used in step (b) is a mineral acid or an organic acid.
11. The process as claimed in claim 10, wherein the acid is mineral acid selected from hydrochloric acid, sulfuric acid or phosphoric acid.
12. The process as claimed in claim 11, wherein the acid is hydrochloric acid.
13. The process as claimed in claim 7, wherein the organic solvent used in step (c) is a solvent or mixture of solvents selected from the group consisting of methanol, ethanol, isopropanol, isobutanol, n-butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone.
14. The process as claimed in claim 13, wherein the organic solvents are methanol, ethanol, isopropanol and acetone.
15. The process as claimed in claim 7, wherein the reaction in step (c) is carried out at below 25^0C.