Abstract: The present invention is related to an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 with high purity and high yield. The present invention also relates to purification of dasatinib crystalline Neat form N-6.
AN IMPROVED PROCESS FOR THE PREPARATION OF DASATINIB POLYMORPH

Field of the Invention:
The present invention is related to an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 with high purity and high yield. The present invention also relates to purification of dasatinib crystalline Neat form N-6.

Background of the Invention:
Dasatinib is an inhibitor of multiple tyrosine kinases, chemically known as N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-1,4-pyrimidinyl]amino]-5-thiazolecarboxamide, and structurally as represented as below:

![Dasatinib Formula-I](https://example.com)

Dasatinib is first disclosed in US 6596746 and marketed as dasatinib monohydrate under the brand name SPRYCEL® and it is indicated for the treatment of chronic myeloid leukemia (CML).

US 6596746 has disclosed the process for the preparation of dasatinib by reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine at 80°C to get dasatinib.
US 7491725 patent has disclosed Crystalline dasatinib monohydrate (HI-7) and butanol solvate (BU-2) also describes two ethanol solvates (E2-1; T1E2-1) and two anhydrous forms (N-6; T1H1-7). As per this patent anhydrous crystalline Neat form N-6 has prepared by reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-y1) amino] thiazole-5-carboxamide with hydroxy ethyl piperazine in presence of IPEA and NMP.

WO20 14086326 application discloses preparation of dasatinib crystalline Neat form N-6 with use of acetonitrile and propionitrile as a co-solvent.

The inventors of the present invention have developed an improved process for the preparation of dasatinib crystalline Neat form N-6 with high yield and purity. The present process is cost effective and feasible in large scale production also.

**Summary of the Invention:**

One aspect of the present invention is to provide an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:

a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-y1) amino] thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of C3-C5 alcohol,

b) adding the methanol to the reaction mass,

c) isolating the dasatinib crystalline Neat form N-6,

d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.
Another aspect of the present invention is to provide an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:

a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-propanol,
b) adding the methanol to the reaction mass,
c) isolating the dasatinib crystalline Neat form form N-6,
d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

Yet another aspect of the present invention is to provide an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:

a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-pentanol,
b) adding the methanol to the reaction mass,
c) isolating the dasatinib crystalline Neat form form N-6,
d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

**Detailed description of the Invention:**
The present invention relates to an improved process for the preparation of dasatinib crystalline Neat form N-6, wherein one step is related to preparation of dasatinib crystalline Neat form N-6 and other step is related to purification of dasatinib form N-6.

One embodiment of the present invention is related to an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:
a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of C3-C5 alcohol,
b) adding the methanol to the reaction mass,
c) isolating the dasatinib crystalline Neat form N-6,
d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

Another embodiment of the present invention is to provide an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:

a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-propanol,
b) adding the methanol to the reaction mass,
c) isolating the dasatinib crystalline Neat form N-6,
d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

Yet another embodiment of the present invention is to provide an improved process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:

a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-pentanol,
b) adding the methanol to the reaction mass,
c) isolating the dasatinib crystalline Neat form N-6,
d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.
According to the present invention, N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-propanol, reaction mass temperature is raised to 100-110°C, after completion of the reaction, reaction mass temperature was cooled to 25-35°C and added 1-propanol. Reaction mass is maintained at same temperature for 30-45 mins. Transferred the reaction mass and washed with 1-propanol, methanol is added to the wet material an raised the reaction mass temperature to 60-65°C and maintained to 60-90 mins, cooled the reaction mass to 25-35°C and maintain for 30-45 mins, dried the compound.

To the above dried compound methanol and toluene is added and the reaction mass temperature is raised to 60-65°C maintained to 20-30 mins, cooled the reaction mass to 25-35°C and maintain for 45-60 mins suck dried the compound and reaction mass temperature is raised to 60-65°C maintained to 20-30 mins, cooled the reaction mass to 25-35°C and maintain for 45-60 mins and washed with methanol and dried the compound to get crystalline Neat form N-6 of dasatinib.

According to the present invention, N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-pentanol, reaction mass temperature is raised to 90-100°C, after completion of the reaction, reaction mass temperature was cooled to 25-35°C and added 1-pentanol. Reaction mass is maintained at same temperature for 30-45 mins. Transferred the reaction mass and methanol is added to the wet material and dried the compound.

To the above dried compound methanol and toluene is added and the reaction mass temperature is raised to 60-65°C maintained to 20-30 mins, cooled the reaction mass to 25-35°C and maintain for 45-60 mins suck dried the compound and reaction mass temperature is raised to 60-65°C maintained to 20-30 mins, cooled the reaction mass to 25-35°C and maintain for 45-60 mins and washed with methanol and dried the compound to get crystalline Neat form N-6 of dasatinib.
According to the present invention C3-C5 alcohol is selected form the group consisting from 1-propanol, 2-propanol, butanol, and 1-pentanol preferably 1-propanol and 1-pentanol.

**Brief description of drawings:**

**Fig-1:** Powder X-ray diffractogram of dasatinib anhydrous crystalline Neat form N-6.

The following examples are provided for illustrative purpose only and are not intended to limit the scope of invention in anyway.

**Examples:**

**Example-1: Preparation of 2-(6-chloro-2-methylpyrimidine-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide**

a) preparation of ethyl 2-tert-butoxy-carbonylamino-thiazole-5-carboxylate

![Diagram]

Into a clean and dry 1.0 L 4-neck RB flask connected to a mechanical stirrer, condenser, thermometer socket is charged Ethyl2-aminothiazole-5-carboxylate (50gm), DMAP (3.2gm), DIBOC (95gm), DMF (250ml) in presence of N2 atmosphere at 25-30°C, maintained the reaction mass temperature at 25-30°C for 24hrs, after completion of the reaction, transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 100.0 ml of acetonitrile, suck dried for 10-15 min. Transfered the wet material into a clean and dry petridish, dried the above wet material in drier at temperature 60-65°C for 4-6 hrs.
b) **purification of ethyl 2-tert-butoxy-carbonylamino-thiazole-5-carboxylate**

Into a clean and dry 1.0 L 4-neck RB flask, charged ethyl 2-tert-butoxy-carbonylamino-thiazole-5-carboxylate (60 gm) and acetonitrile (300 ml, Lot-I) under stirring at temperature 25-30°C. Raised the reaction mass temperature to 75-80°C. Maintained the reaction mass temperature at 75-80°C for 45-60 min. Cooled the reaction mass temperature to 25-30°C. Transferred the reaction mass into a Buchner funnel and flask kept under plant vacuum. Washed the wet cake with 25.0 ml of acetonitrile. Sucked dried thoroughly for 10-15 min. Transferred the wet material into a clean and dry petridish. Dried the above wet material in drier at temperature 60-65°C for 4-6 hrs.

Weight: 59 gm

c) **preparation of 2-tert-butoxycarbonylamino-thiazole-5-carboxylic acid**

Into a clean and dry 2.0 L 4-neck RB flask charged 600 ml of 6N-NaOH solution. Slowly added ethyl 2-tert-butoxy-carbonylamino-thiazole-5-carboxylate (20 gm) to the 6N-NaOH solution at temperature 25-30°C within 30-60 min period. Maintained the reaction mass temperature at 25-30°C for 24 hrs. after completion of the reaction, added 6N-HCl solution to the reaction mass at temperature 25-30°C within 60-90 min period, maintained the reaction mass at temperature 25-30°C for 60-90 min period, transferred the reaction mass into a Buchner funnel and flask kept under lant vacuum. Wash the wet cake with 100.0 ml DM Water, sucked dried thoroughly for 30-45 min. Transferred the wet material into a clean and dry petridish. Dried the above wet material in drier at temperature 60-65°C for 6-8 hrs.

Weight: 17.0 gm
d) preparation of 2-tert-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride

\[
\begin{align*}
\text{2-tert-Butoxycarbonylamino-thiazole-5-carboxylic acid} & \quad \rightarrow \\
\text{2-tert-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride}
\end{align*}
\]

Into a clean and dry 1.0 L 4-neck RB charged 2-tert-Butoxycarbonylamino-thiazole-5-carboxylic acid (25 gm) and THF (litr, Lot-I) and DMF (10 ml) at temperature 25-30°C under stirring. Charged thionyl chloride (22.5 ml, dissolved in 125 ml of dichloromethane-Lot-I) to the mass at temperature 25-30°C, maintained the mass at temperature 25-30°C for 4-6 hrs., after completion of the reaction, distilled-off solvent completely under plant vacuum at temperature not crossing 50°C, charged THF (125 ml, Lot-II) to reaction mass. Stirr the mass for 10-15 min. Distilled-off solvent completely under plant vacuum at temperature not crossing 40°C, charged dichloromethane (125 ml, Lot-II) to reaction mass. Stirred the mass for 10-15 min. Distilled-off solvent completely under plant vacuum at temperature not crossing 40°C. Distilled-off solvent completely under plant vacuum at temperature not crossing 60°C. Crude acid chloride is directly taken to next stage in-situ.

Weight: 27 gm

e) preparation of 2-tert-butoxy-carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

\[
\begin{align*}
\text{2-tert-Butoxycarbenylnlamino-thiazole-5-carboxylic acid chloride} & \quad + \\
\text{2-Chloro-6-methyl aniline} & \quad \rightarrow \\
\text{2-tert-Butoxy-carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide}
\end{align*}
\]

Into a clean and dry 3.0 L 4-neck RB flask charged 2-tert-Butoxycarbonylamino-thiazole-5-carboxylic acid chloride crude (28 gm) and methylene chloride (750 ml) under stirring, cooled the reaction mass to temperature to 0-5°C. Added 2-Chloro-6-methyl aniline (23 gm) to the reaction mass at temperature 0-5°C within
30-45 min period. Diisopropyl ethylamine (55 gm) was added to the reaction mass at temperature 0-5° C in 30-45 min period, reaction mass temperature was raised to 25-30°C and maintained for 24 hrs, after completion of the reaction, distilled off the solvent completely under plant vacuum at temperature not crossing 50°C. charged 2NHCl to the reaction mass and stirred for 15-30 min, transferred the reaction mass into a buchner funnel and flask kept under plant Vacuum. Wet cake was washed with 250.0 ml of water and suck dried thoroughly for 30-45 min, wet material was transferred into a clean and dry petridish. Dried the above wet material in drier at temperature 60-65° C for10-12 hrs.

Weight: 20gm

f) purification of 2-tert-butoxy- carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide

Into a clean and dry 3.0L 4-neck RB flask charged 2-tert-butoxy- carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide crude(20gm), methanol (250ml, Lot-1) and Isopropyl ether(200ml) under stirring temperature 25-30°C, reaction mass temperature was raised to 60-65°C and maintained for 45-60 min. cooled the reaction mass temperature to 25-30°C and transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 20.0 ml of methanol (LOT-II) and suck dried for 10-15min, and dried the compound in drier at temperature 60-65 C for 4-6 hrs.

Weight: 16.0 g

g) preparation of 2-amino-N-(2-chloro-6-methyl phenyl)-5-thiazole-1-carboxamide

![Chemical structure](image)

Into a clean and dry 2.0L 4-neck RB flask is charged 2-tert-butoxy- carbonyl amino-N-(2-chloro-6-methylphenyl)-5-thiazolecarboxamide(50gm),
trifluoroacetic acid (500 ml) under stirring, the reaction mass at temperature was maintained at 25-30°C for 3-5 hrs, after completion of the reaction, distilled off trifluoroacetic acid completely under vacuum at temperature not crossing 50°C, ethylacetate (2 ltr) was added into reaction mass and washed the reaction mass with 5% Aq KHCO₃ (2x2.0l) solution. Transferred the reaction mass into a separating funnel. Transferred the organic layer into a clean and dry conical flask. Dry with sodium sulphate. Transferred the dry organic layer into a clean and dry single neck RB flask. Distilled off the solvent completely under plant vacuum at temperature not crossing 50°C. Cooled the reaction mass temperature to 25-30°C. Charged acetonitrile (150 ml) and isopropyl ether (400.0 ml) and stirred for 60 min at 25-30°C. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 100.0 ml of ether. Sucked dried thoroughly for 30-45 min, transferred the wet material into a petridish. Dried the above wet material in a drier at temperature 60-65°C for 4-6 hrs.

Weight: 30.0 g

h) preparation of 2-(6-chloro-2-methylpyrimidine-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide

![Chemistry structure](image)

Into clean and dry 5.0 L 4-neck RB flask charged 2-amino-N-(2-chloro-6-methylphenyl)-5-thiazole-1-carboxamide (200 gm), 4,6-dichloro-2-methylpyrimidine (146 gm), 2.0 L of THF under nitrogen atmosphere. Clear solution formation was observed. Cooled the reaction mass to temperature 10-20°C, added 30% sodium-t-butoxide (845 gm) solution to the reaction mass over a period of 60-75 min at temperature 10-20°C. Brown coloured solution formation was observed. Reaction mass temperature was raised to 25-30°C and maintained the reaction mass temperature to 25-30°C for 90-120 min, cooled the mass to temperature 0-5°C and added 2N HCl solution to the reaction mass over a period of 60-90 min at
0-5°C and maintained for 105-120 min. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 600.0 ml of water. Sucked dried thoroughly for 45-60 min and dried the wet material in a drier at a temperature of 60-65°C for 8-10 hrs.

Weight: 210 gm

Example-2: Preparation of Dasatinib crystalline neat form N-6 from 1-propanol

Into clean and dry 1.0L 4-neck Rb flask charged 2-(6-chloro-2-methylpyrimidine-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (50 gm), N-2-(hydroxyethyl) piperazine (150 gm) and 1-Propanol (100 ml, Lot-I) under stirring. Reaction mass temperature was raised to 100-110°C and maintained it for 180-240 min, after completion of the reaction, mass temperature was cooled to 25-35°C and charged 1-Propanol (100 ml, Lot-II) maintained the reaction mass at 25-35°C for 30-45 mins., transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 50.0 ml of 1-propanol (50 ml, lot-III). Sucked dried thoroughly for 20-30 mins, transferred the wet material into clean 1.0lt 4N RBF and charged Methanol (600 ml, lot-I), raise the mass temperature to 60-65°C and maintain for 60-90 mins. Cooled the mass temperature to 25-35°C and maintain for 30-45 mins. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with 50.0 ml of methanol. Sucked dried thoroughly for 20-30 mins. Dried the wet material in a drier at temperature 60-65°C for 8-10 hrs.

Weight: 50.0 g

Example-3: Preparation of Dasatinib crystalline neat form N-6 from 1-pentanol
Into a clean and dry 4N RBF is charged 2-(6-chloro-2-methylpyrimidine-4-ylamino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (50 gm), N-(2-hydroxyethyl) piperazine (150 gm) and 1-pentanol (100 ml, Lot-L). Reaction mass temperature was raised to 90-100°C and maintained for 180-240 mins, after completion of the reaction cooled the mass temperature to 25-35°C and added 1-pentanol (100 ml, lot-II) and maintained for 30-45 mins. Filtered the mass and wash with 1-pentanol (50 ml, Lot-III), suck dried for 20-30 mins, transferred the wet material into clean 1.0 L 4N RBF and charged Methanol lot-I (600 ml). Raised the mass temperature to 60-65°C and maintained for 60-90 mins. Cooled the mass temperature to 25-35°C and maintained for 45-60 mins. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum at temperature 60-65°C. Raised the mass temperature to 60-65°C and maintain for 20-30 mins. Cooled the mass temperature to 25-35°C and maintain for 45-60 mins. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with methanol (50 ml, Lot-II). Suck dried thoroughly for 20-30 mins. Transferred the wet material into a clean and dry 1.0L 4N RBF and charged methanol (300 ml, Lot-III). Raised the mass temperature to 60-65°C and maintained for 45-60 mins. Cooled the mass temperature to 25-35°C and maintain for 45-60 mins, Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with methanol (50 ml, Lot-IV) and Suck dried for 20-30 mins. Dried the wet compound at temperature 65-70°C for 12-15 hrs.

Weight: 55.0 gm

Example-4: Purification of Dasatinib

Into clean and dry 2.0 L-neck RB flask Charged Dasatinib (50 gm), methanol (500 ml, Lot-I) and toluene (500 ml). Reaction mass temperature was raised to 60-65°C and maintained for 20-30 mins. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum at temperature 60-65°C. Raised the mass temperature to 60-65°C and maintain for 20-30 mins. Cooled the mass temperature to 25-35°C and maintain for 45-60 mins. Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with methanol (50 ml, Lot-II). Suck dried thoroughly for 20-30 mins. Transferred the wet material into a clean and dry 1.0L 4N RBF and charged methanol (300 ml, Lot-III). Raised the mass temperature to 60-65°C and maintained for 45-60 mins. Cooled the mass temperature to 25-35°C and maintain for 45-60 mins, Transferred the reaction mass into a buchner funnel and flask kept under plant vacuum. Washed the wet cake with methanol (50 ml, Lot-IV) and Suck dried for 20-30 mins. Dried the wet compound at temperature 65-70°C for 12-15 hrs.

Weight: 35 gm
CLAIMS

1. A process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:
   a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of C3-C5 alcohol,
   b) adding the methanol to the reaction mass,
   c) isolating the dasatinib crystalline Neat form N-6,
   d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

2. The process according to claim 1, wherein the C3-C5 alcohol is selected from the group consisting of 1-propanol, 2-propanol, butanol, and 1-pentanol.

3. A process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:
   a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-propanol,
   b) adding the methanol to the reaction mass,
   c) isolating the dasatinib crystalline Neat form N-6,
   d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.

4. A process for the preparation of dasatinib anhydrous crystalline Neat form N-6 comprising the steps of:
   a) reacting N-(2-chloro-6-methyl-phenyl)-2-[(6-chloro-2-methyl-pyrimidin-4-yl) amino]thiazole-5-carboxamide with N-2-hydroxy ethyl piperazine in presence of 1-pentanol,
   b) adding the methanol to the reaction mass,
   c) isolating the dasatinib crystalline Neat form N-6,
   d) optionally purifying dasatinib crystalline Neat form N-6 using methanol and toluene.
Fig-1: Powder X-ray diffractogram of dasatinib anhydrous crystalline Neat form N-6.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/12

ADD.

According to International Patent Classification (IPC) into 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wo 2014/086326 AI (ZENTIVA K S [CZ]) 12 June 2014 (2014-06-12) cited in the application claims 1,3,4, 12</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>wo 2010/139981 A2 (GENERICS UK LTD [GB]; MYLAN INDIA PRIVATE LTD [IN]; GORE VINAYAK GOVIN) 9 December 2010 (2010-12-09) claim 17</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>wo 2010/139979 A2 (GENERICS UK LTD [GB]; MYLAN INDIA PRIVATE LTD [IN]; GORE VINAYAK GOVIN) 9 December 2010 (2010-12-09) claims 29-32</td>
<td></td>
</tr>
</tbody>
</table>

[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

**E** earlier application or patent but published on or after the international filing date

**L** document which may throw doubts on priority claim(s) on which the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**O** document referring to an oral disclosure, use, exhibition or other means to the claimed invention

**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

**Z** document member of the same patent family

Date of the actual completion of the international search: 22 June 2017

Date of mailing of the international search report: 06/07/2017

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: Fanni, Stefano
### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2014086326 A1</td>
</tr>
<tr>
<td>WO 2010139981 A2</td>
<td>09-12-2010</td>
<td>NONE</td>
</tr>
<tr>
<td>WO 2010139979 A2</td>
<td>09-12-2010</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2508523 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2537847 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2565521 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 6081763 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010539156 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2013047238 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20100058660 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20120033357 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2010256158 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2009053854 A2</td>
</tr>
</tbody>
</table>