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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2008 (14.08.2008)

PCT

(10) International Publication Number
WO 2008/096987 A1

(51) International Patent Classification:
C07D 401/14 (2006.01)

(21) International Application Number: PCT/KR2008/000639

(22) International Filing Date: 1 February 2008 (01.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2007-0011556 5 February 2007 (05.02.2007) KR

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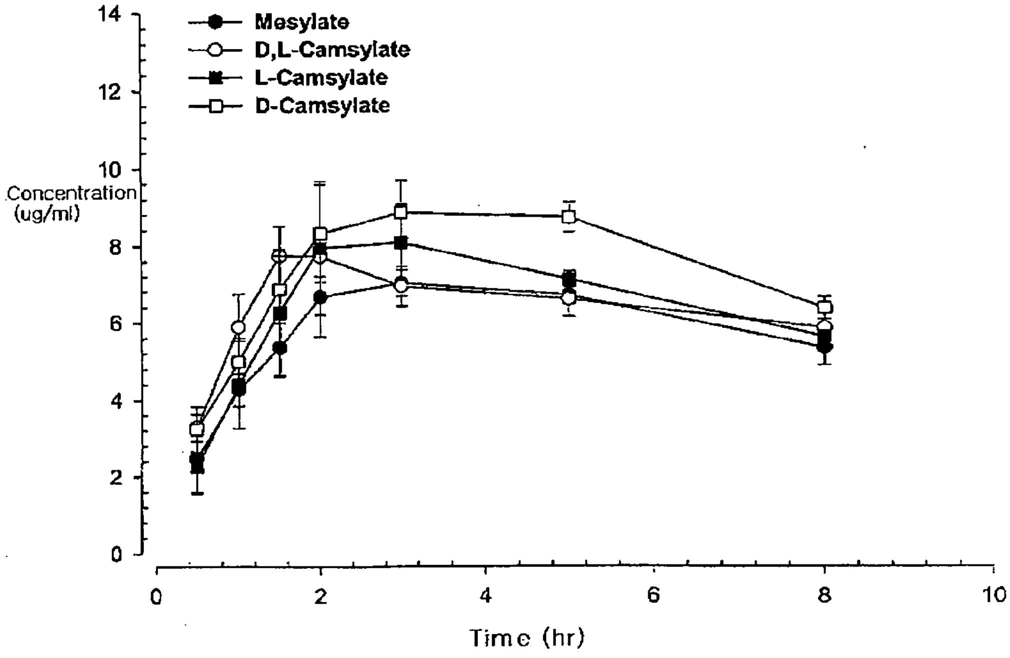
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

[Continued on next page]

(54) Title: NOVEL IMATINIB CAMSYLATE AND METHOD FOR PREPARING THEREOF

[Fig. 1]



(57) Abstract: The present invention relates to a novel imatinib camsylate and a method for preparing the same. Imatinib camsylate according to the present invention has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics, and further has excellent water solubility, as compared to commercially available imatinib mesylate.

WO 2008/096987 A1

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

Published:

— *with international search report*

Description

NOVEL IMATINIB CAMSYLATE AND METHOD FOR PREPARING THEREOF

Technical Field

[1] The present invention relates to a novel imatinib camsylate and a method for preparing the same.

Background Art

[2] Imatinib is a common name of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]benzamide, and is the first anticancer agent that has little effect on normal cells but effect on leukemia cells having an abnormal chromosome called the philadelphia chromosome (due to a reciprocal translocation between chromosomes 9 and 22), so as to inhibit tumor cell proliferation and promote tumor cell death.

[3] US Patent No. 5,521,184 discloses imatinib and a preparation method thereof. For pharmaceutical use, imatinib is suitably administered as a pharmaceutically acceptable acid salt thereof. For example, imatinib is currently marketed under the brand name GLIVEC (or GLEEVEC) as monomethanesulfonate salt (imatinib mesylate) in many countries.

[4] Subsequently, WO 2005/075454 A2 applied by Novartis discloses various pharmaceutically acceptable salt forms of imatinib, which are exemplified by a tartrate salt (D,L), a hydrochloride salt, a citrate salt, a malate salt, a D-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1, 5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, a (S)-lactate salt, a mandelate salt, an (R)-(-)-mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, an (L)-ascorbate salt and a sulfate salt, and discloses a preparation method thereof and their water solubility. However, there is no mention of salts being excellent in terms of various properties, in particular, pharmacokinetic properties.

[5] Meanwhile, there has been no report on D-(+)-camsylate, L-(-)-camsylate and D,L-(±)-camsylate of imatinib, among various acid addition salts of imatinib.

[6] Accordingly, the present inventors have prepared imatinib camsylate by using relatively low toxic 10-camphorsulphonic acid. They found that the prepared imatinib camsylate has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics, and further has excellent water solubility, as compared to commercially available imatinib mesylate, thereby completing the present invention.

Disclosure of Invention

Technical Problem

[7] It is an object of the present invention to provide a novel imatinib camsylate and a method for preparing the same.

Advantageous Effects

[8] Imatinib camsylate according to the present invention has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics, and further has excellent water solubility, as compared to commercially available imatinib mesylate.

Brief Description of the Drawings

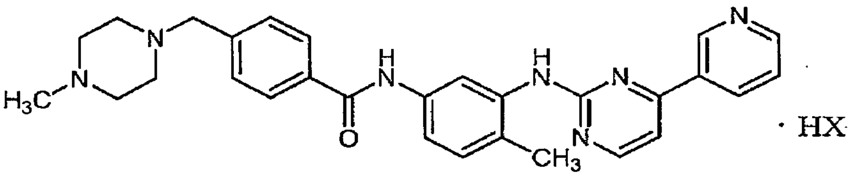
[9] Fig.1 is a graph showing pharmacokinetic properties of D-(+)-camsylate, L-(-)-camsylate, and D,L-(±)-camsylate of imatinib according to the present invention.

Best Mode for Carrying Out the Invention

[10] The present invention provides imatinib camsylate represented by the following Formula 1:

[11] [Formula 1]

[12]



[13] wherein HX is D-(+)-camphorsulphonic acid, L-(-)-camphorsulphonic acid or D,L-(±)-camphorsulphonic acid.

[14] Further, the present invention provides a method for preparing imatinib camsylate of Formula 1, comprising the steps of:

[15] 1) solubilizing imatinib of the following Formula 2 in an organic solvent;

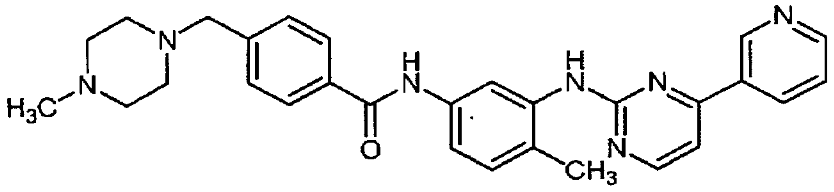
[16] 2) adding one acid selected from the following Formulae 3 and 4 or a mixture (1:1) thereof, or adding the acid or mixture solubilized in an organic solvent to the reaction solution of step 1) to prepare a mixture;

[17] 3) stirring the mixture and filtering precipitated solids to form acid addition salts; and

[18] 4) if necessary, dissolving the acid addition salts in an organic solvent to re-crystallize and purify the acid addition salts.

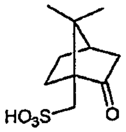
[19] [Formula 2]

[20]



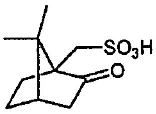
[21] [Formula 3]

[22]



[23] [Formula 4]

[24]



[25] Preferably, in the preparation method, both step 3) of forming the acid addition salts and step 4) of purifying the acid addition salts may further comprise the steps of washing and drying the resulting solid after filtration.

[26] In order to effectively promote crystallization in step 1), imatinib is preferably used in a concentration of 2 to 60% by weight, and more preferably 5 to 20% by weight, based on the total weight of the reaction solution.

[27] In step 2), as an acid, D-(+)-10-camphorsulphonic acid of Formula 3, L-(−)-10-camphorsulphonic acid of Formula 4, or racemic D,L-(±)-10-camphorsulphonic acid, which is a mixture (1:1) of Formulae 3 and 4, is preferably used. Camphorsulphonic acid is a safe acid that is widely used in medicine, and a stable colorless solid having no moisture absorption and corrosiveness. Further, camphorsulphonic acid is harmless to human, thereby being safely and easily used for mass-production. Camphorsulphonic acid is preferably used in an amount of 0.5 to 3 molar equivalent, and more preferably 1.0 to 1.3 molar equivalent, based on 1 molar equivalent of imatinib.

[28] Examples of the organic solvent used in steps 1), 2) and 4) may include C_1~C_4 lower alcohol such as methanol, ethanol, isopropanol, etc.; hydrocarbons such as pentane, hexane, cyclohexane, etc.; ethers such as tetrahydrofuran, 1,4-dioxane, etc.; polar solvents such as acetone, dimethylformamide, dimethylsulfoxide, etc.; and mixtures thereof.

[29] In steps 3) and 4), the formation and purification of acid addition salts are preferably performed in a temperature range of -10 to 120°C, and more preferably in a temperature range of 25 to 90°C.

[30] Imatinib camsylate according to the present invention has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics, and further has excellent water solubility, as compared to commercially available imatinib mesylate.

[31] Hereinafter, the preferred Examples are provided for better understanding. However, these Examples are for the illustrative purpose only, and the invention is not intended to be limited by these Examples.

Mode for the Invention

[32] **Example 1 : Preparation of imatinib D,L-(±)-camphorsulphonic acid salt**

[33] 5 g of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]-benzamide was added to 20 ml of methanol. While stirring, 2.4 g of D,L-(±)-camphorsulphonic acid and 0.1 g of activated carbon were slowly added to the mixture, and further stirred at room temperature for 1 hr. The solution was filtered, washed with 5 ml of methanol, and then distilled off under reduced pressure. Then, 50 ml of isopropanol was added thereto, and stirred at room temperature for 1 hr. The solid mixture was filtered and washed with 10 ml of isopropanol, and then dried under reduced pressure to give 6.7 g of solid (91.1%).

[34] Melting point (m.p.): 144~148℃

[35] **Example 1-1 : Another preparation of imatinib D,L-(±)-camphorsulphonic** acid salt

[36] 5 g of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]-benzamide was added to 20 ml of tetrahydrofuran. While stirring, 2.4 g of D,L-(±)-camphorsulphonic acid was added to the mixture, and further stirred at room temperature for 1 hr. 10 ml of tetrahydrofuran was added to the reaction solution, and refluxed under stirring for 1 hr. Then, the solution was cooled, and filtered. The resultant was washed with 10 ml of tetrahydrofuran, and dried under reduced pressure to give 6.9 g of solid (93.8%).

[37] Melting point (m.p.): 144~148℃

[38] **Example 2 : Preparation of imatinib D-(+)-camphorsulphonic acid salt**

[39] 5 g of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]-benzamide was added to 20 ml of methanol. While stirring, 2.4 g of D-(+)-camphorsulphonic acid and 0.1 g of activated carbon were slowly added thereto, and further stirred at room temperature for 1 hr. The solution was filtered, washed with 5 ml of methanol, and then distilled off under reduced pressure. Then, 50 ml of isopropanol was added thereto, and stirred at room temperature for 1 hr. The solid mixture was filtered and washed with 10 ml of isopropanol, and then dried under reduced pressure to give 4.8 g of solid (65.2%).

[40] Melting point (m.p.): 130~132℃

[41] **Example 3 : Preparation of imatinib L-(-)-camphorsulphonic acid salt**

[42] 5 g of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridyl)-2-pyrimidinyl]amino]phenyl]-benzamide was added to 20 ml of methanol. While stirring, 2.4 g of L-(-)-camphorsulphonic acid and 0.1 g of activated carbon were slowly added thereto,

and further stirred at room temperature for 1 hr. The solution was filtered, washed with 5 ml of methanol, and then distilled off under reduced pressure. Then, 50 ml of isopropanol was added thereto, and stirred at room temperature for 1 hr. The solid mixture was filtered and washed with 10 ml of isopropanol, and then dried under reduced pressure to give 5.8 g of solid (78.5%).

[43] Melting point (m.p.): 135~136℃

[44]

[45] **Experimental Example 1 : Pharmacokinetic properties of imatinib** camsylate

[46] In order to confirm the pharmacokinetic properties of imatinib camsylate according to the present invention, the following experiment was performed.

[47] Male SD rats (body weight of 180~220 g) were orally administered with 50 mg/kg of each imatinib camsylate prepared in Examples 1 to 3. After 0.5, 1, 1.5, 2, 2.5, 3, 5, and 8 hrs, blood samples were collected from the rats to isolate blood plasma. HPLC was performed to determine the concentration of imatinib in blood plasma. As a control group, commercially available imatinib mesylate was used. The animals used in the experiment were fasted for 16 hrs before drug administration. The concentration of imatinib according to time after drug administration is shown in Table 1 and Fig. 1.

[48]

[49] Table 1

[Table 1]

[Table]

Time (hr)	Salt of imatinib			
	Mesylate	D,L-((±)-camsylate	L-(-)-camsylate	D-(+)-camsylate
0.5	2.444	3.275	2.237	3.231
1.0	4.253	5.877	4.387	4.979
1.5	5.334	7.728	6.262	6.860
2.0	6.646	7.704	7.930	8.308
3.0	7.009	6.926	8.075	8.849
5.0	6.691	6.591	7.112	8.731
8.0	5.304	5.829	5.326	6.339

[50]

[51] As shown in Table 1 and Fig. 1, it was found that imatinib camsylate according to the present invention has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics than commercially available imatinib mesylate.

[52]

[53] **Experimental Example 2 : Solubility test**

[54] Water solubility of each imatinib camsylate prepared in Examples 1 to 3 was measured at 25℃. As a control group, commercially available imatinib mesylate was used.

[55] The results are shown in Table 2.

[56]

[57] Table 2

[Table 2]

[Table]

Example	Salt	Solubility (mg/ml)
1	D,L-(±)-camphorsulphonic acid	≥ 3000
2	D-(+)-camphorsulphonic acid	≥ 3000
3	L-(-)-camphorsulphonic acid	≥ 3000
Control group	methanesulphonic acid	≥ 1200

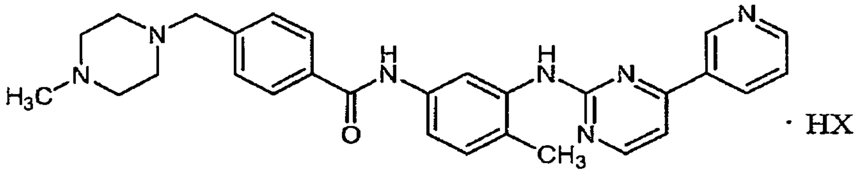
[58]

[59] As shown in Table 2, it was found that imatinib camsylate according to the present invention had much higher solubility than commercially available imatinib mesylate.

Claims

[1] Imatinib camsylate represented by the following Formula 1:

<Formula 1>



wherein HX is D-(+)-camphorsulphonic acid, L-(-)-camphorsulphonic acid, or D,L-(±)-camphorsulphonic acid.

[2] The imatinib camsylate according to claim 1, wherein imatinib camsylate is D-(+)-camsylate, L-(-)-camsylate, or D,L-(±)-camsylate of imatinib.

[3] A method for preparing imatinib camsylate of the following Formula 1, comprising the steps of:

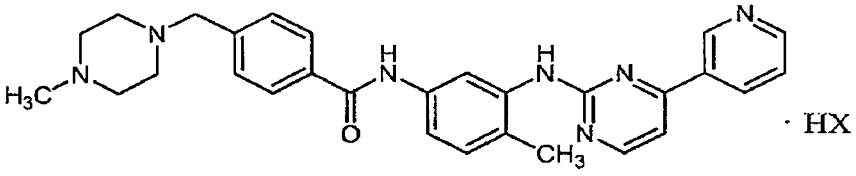
1) solubilizing imatinib of the following Formula 2 in an organic solvent;

2) adding one acid selected from the following Formulae 3 and 4 or a mixture (1:1) thereof, or adding the acid or mixture solubilized in an organic solvent to the reaction solution of step 1) to prepare a mixture;

3) stirring the mixture and filtering precipitated solids to form acid addition salts; and

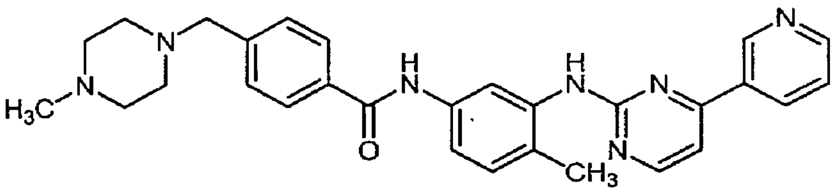
4) if necessary, dissolving the acid addition salts in an organic solvent to re-crystallize and purify the acid addition salts.

<Formula 1>

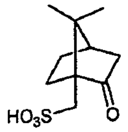


wherein HX is D-(+)-camphorsulphonic acid, L-(-)-camphorsulphonic acid, or D,L-(±)-camphorsulphonic acid.

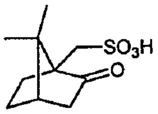
<Formula 2>



<Formula 3>



<Formula 4>



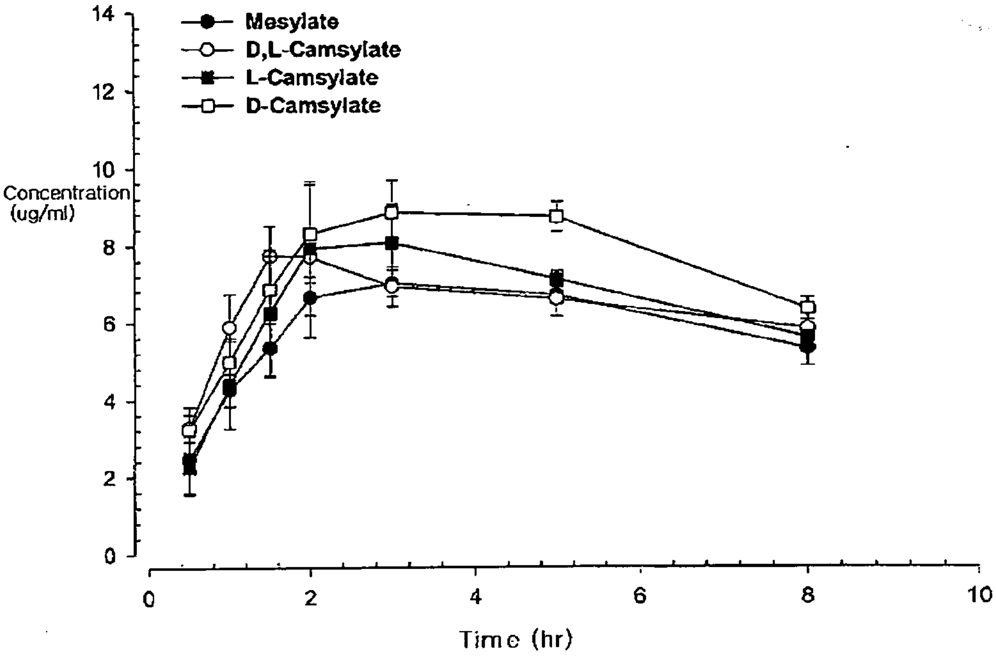
[4] The method for preparing imatinib camsylate according to claim 3, wherein in step 1), imatinib is used in a concentration of 2 to 60% by weight, based on the total weight of the reaction solution.

[5] The method for preparing imatinib camsylate according to claim 3, wherein in step 2), acid is used in an amount of 0.5 to 3 molar equivalent, based on 1 molar equivalent of imatinib.

[6] The method for preparing imatinib camsylate according to claim 3, wherein in steps 1), 2), and 4), the organic solvent is selected from the group consisting of methanol, ethanol, isopropanol, pentane, hexane, cyclohexane, tetrahydrofuran, 1,4-dioxane, acetone, dimethylformamide, dimethylsulfoxide, and mixtures thereof.

[7] The method for preparing imatinib camsylate according to claim 3, wherein in steps 3) and 4), the formation and purification of acid addition salts are performed in a temperature range of -10 to 120°C.

[Fig. 1]


Mesylate
D,L-Camsylate
L-Camsylate
D-Camsylate
Concentration (ug/ml)
0
2
4
6
8
10
12
14
Time (hr)
0
2
4
6
8
10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2008/000639

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/14(2006.01)i

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)

IPC 8 as above

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)

eKIPASS, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005-075454 A2 (NOVARTIS AG) 18 Aug. 2005 See the abstract.	1-7
A	US 5521184 A (CIBA-GEIGY CORPORATION) 28 May 1996 See the abstract.	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search 29 MARCH 2008 (29.03.2008)	Date of mailing of the international search report **31 MARCH 2008 (31.03.2008)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer YANG, In Soo Telephone No. 82-42-481-5049

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2008/000639

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		ZA9302397A	04.10.1993

[19] 中华人民共和国国家知识产权局

[51] Int. Cl.
C07D 401/14 (2006.01)

[12] 发明专利申请公布说明书

[21] 申请号 200880002870.5

[43] 公开日 2009 年 11 月 25 日

[11] 公开号 CN 101589035A

[22] 申请日 2008.2.1
[21] 申请号 200880002870.5
[30] 优先权
[32] 2007.2.5 [33] KR [31] 10－2007－0011556
[86] 国际申请 PCT/KR2008/000639 2008.2.1
[87] 国际公布 WO2008/096987 英 2008.8.14
[85] 进入国家阶段日期 2009.7.22
[71] 申请人 同和药品工业株式会社
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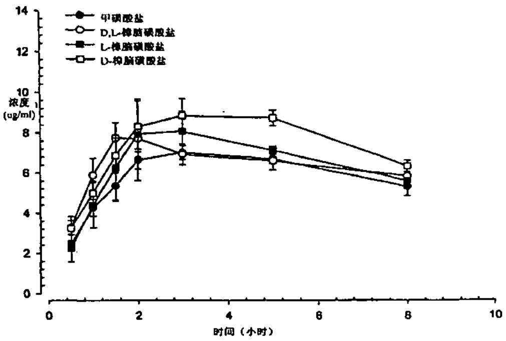
[54] 发明名称

新型伊马替尼樟脑磺酸盐及其制备方法

[57] 摘要

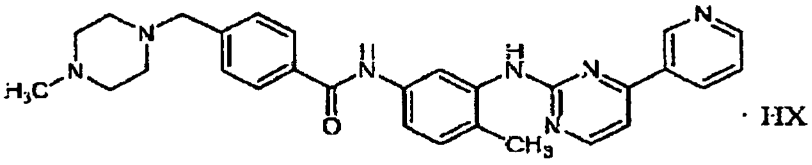
本发明涉及一种新型伊马替尼樟脑磺酸盐及其制备方法。根据本发明的伊马替尼樟脑磺酸盐与商业上可获得的伊马替尼甲磺酸盐相比，在药代动力学方面具有更快的吸收速率和更高的吸收浓度，并且还具有良好的水溶性。



权 利 要 求 书

1. 由下面式 1 所示的伊马替尼樟脑磺酸盐：

式 1：



其中 HX 是 D-(+)-樟脑磺酸、L-(-)-樟脑磺酸或 D,L-(±)-樟脑磺酸。

2. 根据权利要求 1 所述的伊马替尼樟脑磺酸盐，其中伊马替尼樟脑磺酸盐是伊马替尼的 D-(+)-樟脑磺酸盐、L-(-)-樟脑磺酸盐或 D,L-(±)-樟脑磺酸盐。

3. 制备下面式 1 的伊马替尼樟脑磺酸盐的方法，包括以下步骤：

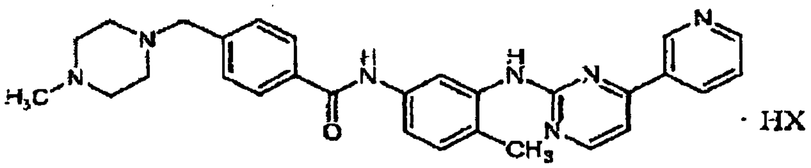
1）在有机溶剂中溶解下面式 2 的伊马替尼；

2）加入选自下面式 3 或者式 4 的一种酸或者其混合物（1:1），或者加入溶解在有机溶剂中的所述酸或者混合物到步骤 1）的反应溶液，以制备混合物；

3）搅拌所述混合物并过滤沉淀的固体以形成酸加成盐；以及

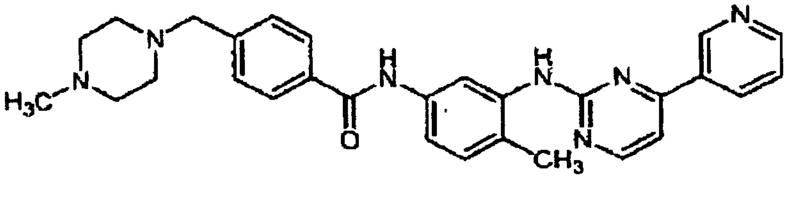
4）如果需要，在有机溶剂中溶解所述酸加成盐以重结晶并纯化所述酸加成盐，

式 1：



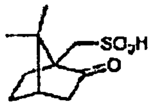
其中 HX 是 D-(+)-樟脑磺酸、L-(-)-樟脑磺酸或 D,L-(±)-樟脑磺酸，

式 2：



式 3：

式 4：



。

4. 根据权利要求 3 所述的制备伊马替尼樟脑磺酸的方法，其中在步骤 1）中，基于所述反应溶液的总重量，伊马替尼按重量计以 2%至 60%的浓度使用。

5. 根据权利要求 3 所述的制备伊马替尼樟脑磺酸的方法，其中在步骤 2）中，基于 1 摩尔当量的伊马替尼，酸以 0.5 至 3 摩尔当量的量使用。

6. 根据权利要求 3 所述的制备伊马替尼樟脑磺酸的方法，其中在步骤 1）、2）和 4）中，所述有机溶剂选自：甲醇、乙醇、异丙醇、戊烷、己烷、环己烷、四氢呋喃、1,4-二噁烷、丙酮、二甲基甲酰胺、二甲亚砜以及其混合物。

7. 根据权利要求 3 所述的制备伊马替尼樟脑磺酸的方法，其中在步骤 3）和 4）中，酸加成盐的形成和纯化在-10℃至 120℃的温度范围内进行。

新型伊马替尼樟脑磺酸盐及其制备方法

技术领域

[1] 本发明涉及一种新型伊马替尼(右旋)樟脑磺酸盐（imatinib camsylate）及其制备方法。

背景技术

[2] 伊马替尼是 4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[4-(3-吡啶基)-2-嘧啶基]氨基]苯基]苯甲酰胺的通用名称，并且是第一种对正常细胞影响较少但对具有称为费城染色体的异常染色体（由于第 9 号染色体和第 22 号染色体之间的相互易位所致）的白血病细胞有效的抗癌药物，从而抑制肿瘤细胞增生并促进肿瘤细胞死亡。

[3] 美国专利 5,521,184 公开了伊马替尼及其制备方法。对于制药用途，伊马替尼适合以其药学上可接受的酸式盐给予。例如，在很多国家伊马替尼目前作为单甲磺酸盐（伊马替尼甲磺酸盐）以商品名称 GLIVEC（或者 GLEEVEC）出售。

[4] 后来，由 Novartis 申请的 WO2005/075454 A2 公开了多种药学上可接受的伊马替尼盐形式，其例子为酒石酸盐(D,L)、盐酸盐、柠檬酸盐、苹果酸盐、D-苹果酸盐、富马酸盐、琥珀酸盐、苯甲酸盐、苯磺酸盐、噻嘧啶盐(pamoate salt)、甲酸盐、丙二酸盐、1,5-萘二磺酸盐、水杨酸盐、环己烷氨基磺酸盐、乳酸盐、(S)-乳酸盐、杏仁酸盐、(R)-(-)杏仁酸盐、戊二酸盐、己二酸盐、方酸盐(squarate salt)、香子兰酸盐、草酰乙酸盐、抗坏血酸盐、(L)-抗坏血酸盐以及硫酸盐，并公开了其制备方法和它们的水溶性。然而，未提到在多种性质特别是药代动力学性质方面优秀的盐。

[5] 同时，在伊马替尼的各种酸加成盐中，没有关于伊马替尼的 D-(+)-樟脑磺酸盐、L-(-)-樟脑磺酸盐、D,L-(±)-樟脑磺酸盐的报道。

[6] 因此，本发明人通过使用毒性相对低的 10-樟脑磺酸制备了伊

马替尼樟脑磺酸盐。他们发现其制备的伊马替尼樟脑磺酸盐与商业上可获得的伊马替尼甲磺酸盐相比，在药代动力学方面具有更快的吸收速率和更高的吸收浓度，并且还具有良好的水溶性，因此完成本发明。

发明内容

技术问题

[7] 本发明的目的是提供新型伊马替尼樟脑磺酸盐及其制备方法。

有利效果

[8] 根据本发明的伊马替尼樟脑磺酸盐与商业上可获得的伊马替尼甲磺酸盐相比，在药代动力学方面具有更快的吸收速率和更高的吸收浓度，并且进一步具有良好的水溶性。

附图简述

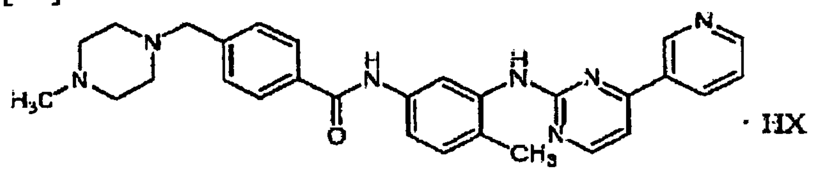
[9] 图 1 是显示根据本发明的伊马替尼的 D-(+)-樟脑磺酸盐、L-(-)-樟脑磺酸盐以及 D,L-(±)-樟脑磺酸盐的药代动力学性质的图。

本发明优选实施方式

[10] 本发明提供由下面式 1 所示的伊马替尼樟脑磺酸盐：

[11] [式 1]

[12]



[13] 其中 HX 是 D-(+)-樟脑磺酸、L-(-)-樟脑磺酸或 D,L-(±)-樟脑磺酸。

[14] 进一步，本发明提供制备式 1 的伊马替尼樟脑磺酸盐的方法，其包括以下步骤：

[15] 1）在有机溶剂中溶解下面式 2 的伊马替尼；

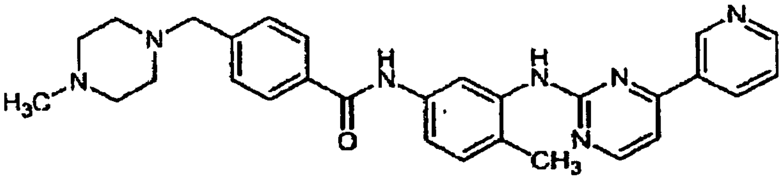
[16] 2）加入选自下面式 3 或者 4 的一种酸或者其混合物（1:1），或者加入溶解在有机溶剂中的该酸或者混合物到步骤 1）的反应溶液中以制备混合物；

[17] 3）搅拌该混合物并过滤沉淀的固体以形成酸加成盐；以及

[18] 4）如果需要，在有机溶剂中溶解该酸加成盐以重结晶并纯化该酸加成盐。

[19] 式 2

[20]

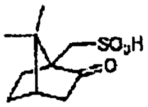


[21] 式 3

[22]

[23] 式 4

[24]



[25] 优选地，在制备方法中，形成酸加成盐的步骤 3）和纯化酸加成盐的步骤 4）可以进一步包括在过滤后洗涤和干燥所得固体的步骤。

[26] 为了有效地促进步骤 1）中的结晶，伊马替尼的使用浓度优选地为按重量计 2-60%，更优选地按重量计 5-20%，这基于反应溶液的总重量。

[27] 步骤 2）中，优选地使用式 3 的 D-(+)-10-樟脑磺酸、式 4 的 L-(-)-10-樟脑磺酸或外消旋 D,L-(±)-10-樟脑磺酸——其为式 3 和式 4 的混合物（1:1）——作为酸。樟脑磺酸是广泛用于药物中的安全的酸，并且是没有吸湿性和腐蚀性的稳定的无色固体。此外，樟脑磺酸对人体无害，因此可以安全地且方便地用于大批量生产。基于 1 摩尔当量伊马替尼，樟脑磺酸优选地以 0.5-3 摩尔当量，更优选地 1.0-1.3 摩尔当量的量使用。

[28] 步骤 1)、2)和 4)中使用的有机溶剂的例子可以包括 C_1-C_4 低级醇比如甲醇、乙醇、异丙醇等；烃类比如戊烷、己烷、环己烷等；醚类比如四氢呋喃、1,4-二噁烷等；极性溶剂诸如丙酮、二甲基甲酰胺、二甲亚砜等；以及它们的混合物。

[29] 在步骤 3)和 4)中，酸加成盐的形成和纯化优选地在-10 到 120℃，更优选地在 25 到 90℃的温度范围内进行。

[30] 根据本发明的伊马替尼樟脑磺酸盐与商业上可获得的伊马替尼甲磺酸盐相比，在药代动力学方面具有更快的吸收速率和更高的吸收浓度，并且进一步具有良好的水溶性。

[31] 下面，提供了优选实施方式以获得更好的理解。然而，这些实施例仅仅用于说明的目的，并且本发明将不局限于这些实施例。

本发明的实施方式

[32] 实施例 1：伊马替尼 D,L-(±)-樟脑磺酸盐的制备

[32] 向 20mL 甲醇中加入 5g 的 4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[4-(3-吡啶基)-2-嘧啶基]氨基]苯基]苯甲酰胺。搅拌的同时，向该混合物中缓慢加入 2.4g 的 D,L-(±)-樟脑磺酸和 0.1g 活性碳，并且在室温下进一步搅拌 1 小时。过滤该溶液，用 5mL 甲醇洗涤，然后减压蒸馏。然后，向其加入 50mL 异丙醇，并在室温下搅拌 1 小时。过滤固体混合物并用 10mL 异丙醇洗涤，然后减压干燥得到 6.7g 固体(91.1%)。

[34] 熔点（m.p.）：144-148℃

[35] 实施例 1-1：伊马替尼 D,L-(±)-樟脑磺酸盐的另一种制备

[36] 向 20mL 四氢呋喃加入 5g 的 4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[4-(3-吡啶基)-2-嘧啶基]氨基]苯基]苯甲酰胺。搅拌的同时，向该混合物中加入 2.4g 的 D,L-(±)-樟脑磺酸，并且在室温下进一步搅拌 1 小时。向该反应溶液中加入 10mL 四氢呋喃，并且搅拌下回流 1 小时。然后，冷却该溶液，并过滤。产物用 10mL 四氢呋喃洗涤，并减压干燥得到 6.9g 固体（93.8%）。

[37] 熔点（m.p.）：144-148℃

[38] 实施例 2：伊马替尼 D -(+)-樟脑磺酸盐的制备

[39] 向 20mL 甲醇中加入 5g 的 4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[4-(3-吡啶基)-2-嘧啶基]氨基]苯基]苯甲酰胺。搅拌的同时，向该混合物中缓慢加入 2.4g 的 D -(+)-樟脑磺酸和 0.1g 活性碳，并且在室温下进一步搅拌 1 小时。过滤该溶液，用 5mL 甲醇洗涤，然后减压蒸馏。然后，向其加入 50mL 异丙醇，并在室温下搅拌 1 小时。过滤固体混合物并用 10mL 异丙醇洗涤，然后减压干燥得到 4.8g 固体（65.2%）。

[40] 熔点（m.p.）：130-132℃

[41] 实施例 3：伊马替尼 L -(-)-樟脑磺酸盐的制备

[42] 向 20mL 甲醇中加入 5g 的 4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[4-(3-吡啶基)-2-嘧啶基]氨基]苯基]苯甲酰胺。搅拌的同时，向该混合物中缓慢加入 2.4g 的 L -(-)-樟脑磺酸和 0.1g 活性碳，并且在室温下进一步搅拌 1 小时。过滤该溶液，用 5mL 甲醇洗涤，然后减压蒸馏。然后，向其加入 50mL 异丙醇，并在室温下搅拌 1 小时。过滤固体混合物并用 10mL 异丙醇洗涤，然后减压干燥得到 5.8g 固体（78.5%）。

[43] 熔点（m.p.）：135-136℃

[44]

[45] 实验性实施例 1：伊马替尼樟脑磺酸盐的药代动力学性质

[46] 为了确定根据本发明的伊马替尼樟脑磺酸盐的药代动力学性质，进行下面的实验。

[47] 雄性 SD 大鼠（体重 180-220g）口服给予 50mg/kg 实施例 1 到 3 中制备的每种伊马替尼樟脑磺酸盐。0.5、1、1.5、2、2.5、3、5 和 8 小时后，从大鼠中采集血液样本以分离血浆。进行 HPLC 以测定血浆中伊马替尼的浓度。作为对照组，使用商业上可获得的伊马替尼甲磺酸盐。实验中使用的动物在给药前禁食 16 小时。根据给药后时间的伊马替尼的浓度在表 1 和图 1 中显示。

[48]

[49] 表 1

时间（hr）	伊马替尼的盐			
	甲磺酸盐	D,L-(±)-樟	L -(-)-樟脑	D-(+)-樟脑

		脑磺酸盐	磺酸盐	磺酸盐
0.5	2.444	3.275	2.237	3.231
1.0	4.253	5.877	4.387	4.979
1.5	5.334	7.728	6.262	6.860
2.0	6.646	7.704	7.930	8.308
3.0	7.009	6.926	8.075	8.849
5.0	6.691	6.591	7.112	8.731
8.0	5.304	5.829	5.326	6.339

[50]

[51] 如表 1 和图 1 所示，发现根据本发明的伊马替尼樟脑磺酸盐比商业上可获得的伊马替尼甲磺酸盐在药代动力学方面具有更快的吸收速率和更高的吸收浓度。

[52]

[53] 实验性实施例 2：溶解度试验

[54] 在 25℃下测定实施例 1-3 中制备的每种伊马替尼樟脑磺酸盐的水溶解度。作为对照组，使用商业上可获得的伊马替尼甲磺酸盐。

[55] 其结果在表 2 中显示。

[56]

[57] 表 2

实施例	盐	溶解度（mg/ml）
1	D,L-(±)-樟脑磺酸	≥3000
2	D-(+)-樟脑磺酸	≥3000
3	L-(-)-樟脑磺酸	≥3000
对照组	甲磺酸	≥1200

[58]

[59] 如表 2 所示，发现根据本发明的伊马替尼樟脑磺酸盐比商业上可获得的伊马替尼甲磺酸盐具有更高的溶解度。

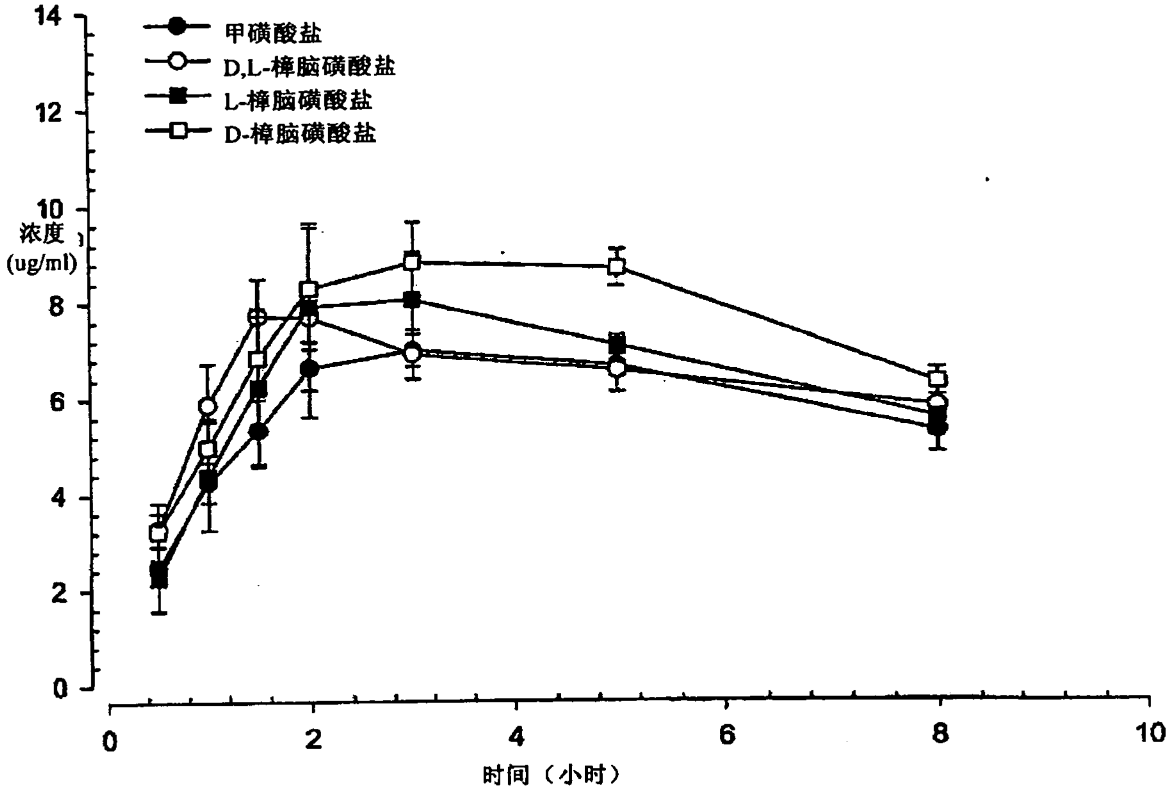

14
12
10
8
6
4
2
0
浓度
(ug/ml)
甲磺酸盐
D,L-樟脑磺酸盐
L-樟脑磺酸盐
D-樟脑磺酸盐
0
2
4
6
8
10
时间（小时）

图 1

新型伊马替尼樟脑磺酸盐及其制备方法

摘要

本发明涉及一种新型伊马替尼樟脑磺酸盐及其制备方法。根据本发明的伊马替尼樟脑磺酸盐与商业上可获得的伊马替尼甲磺酸盐相比，在药代动力学方面具有更快的吸收速率和更高的吸收浓度，并且还具有良好的水溶性。

Novel Imatinib Camsylate and Method for Preparing Thereof

ABSTRACT

The present invention relates to a novel imatinib camsylate and a method for preparing the same. Imatinib camsylate according to the present invention has a faster absorption rate and higher absorption concentration in terms of pharmacokinetics, and further has excellent water solubility, as compared to commercially available imatinib mesylate.