

(12) 按照专利合作条约所公布的国际申请

(19) 世界知识产权组织
国际局

(43) 国际公布日
2013 年 11 月 14 日 (14.11.2013)



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C12P 13/04 (2006.01) A61K 31/4409 (2006.01)
C12N 15/53 (2006.01) A61K 31/4402 (2006.01)
C12N 15/63 (2006.01) A61K 31/4406 (2006.01)
A61K 31/381 (2006.01) A61K 31/415 (2006.01)
A61K 31/444 (2006.01)

(21) 国际申请号: PCT/CN2013/078154

(22) 国际申请日: 2013 年 6 月 27 日 (27.06.2013)

(25) 申请语言: 中文

(26) 公布语言: 中文

(71) 申请人: 凯莱英医药集团(天津)股份有限公司 (ASYMCHEM LABORATORIES (TIANJIN) CO., LTD) [CN/CN]; 中国天津市经济技术开发区洞庭三街 6 号, Tianjin 300457 (CN)。 凯莱英生命科学技术(天津)有限公司 (ASYMCHEM LIFE SCIENCE (TIANJIN) CO., LTD) [CN/CN]; 中国天津市经济技术开发区第七大街 71 号, Tianjin 300457 (CN)。 天津凯莱英制药有限公司 (TIANJIN ASYMCHEM PHARMACEUTICAL CO., LTD) [CN/CN]; 中国天津市经济技术开发区, Tianjin 300000 (CN)。 凯莱英医药化学(阜新)技术有限公司 (ASYMCHEM LABORATORIES (FUXIN) CO., LTD) [CN/CN]; 中国辽宁省阜新市经济技术开发区 E 路 42 号, Liaoning 123000 (CN)。 吉林凯莱英医药化学有限公司 (JILIN ASYMCHEM LABORATORIES CO., LTD)

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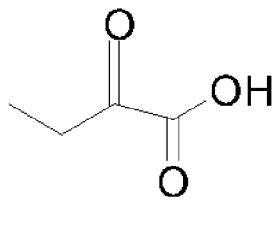
(81) 指定国 (除另有指明, 要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, 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) 指定国 (除另有指明, 要求每一种可提供的地区保护): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA,

[见续页]

(54) Title: SYNTHESIS METHOD FOR L-HETEROCYCLIC AMINO ACID AND PHARMACEUTICAL COMPOSITION HAVING SAID ACID

(54) 发明名称: L-杂环氨基酸的合成方法及具有其的药物组合物



(57) Abstract: A synthesis method for L-heterocyclic amino acid and a pharmaceutical composition thereof are provided. The method comprises: step a.) preparing heterocyclic keto acid, wherein the heterocycle of the heterocyclic keto acid is selected from a five-membered heterocycle, a six-membered heterocycle, a seven-membered heterocycle, an alkyl-substituted five-membered heterocycle, an alkyl-substituted six-membered heterocycle, and an alkyl-substituted seven-membered heterocycle; step b.) mixing the heterocyclic keto acid with ammonium formate, phenylalanine dehydrogenase, formate dehydrogenase and coenzyme NAD⁺ to generate L-heterocyclic amino acid, wherein the phenylalanine dehydrogenase amino acid sequence is SEQ ID No. 1. The synthesis method allows for a high conversion rate of raw materials and high chiral selectivity.

(57) 摘要: 提供了一种 L-杂环氨基酸的合成方法及其药物组合物。该方法包括: 步骤 A: 制备杂环酮酸, 其中, 杂环酮酸中的杂环选自五元单杂环、六元单杂环、七元单杂环、五元烷基取代单杂环、六元烷基取代单杂环、七元烷基取代单杂环; 步骤 B: 将杂环酮酸与甲酸铵、苯丙氨酸脱氢酶、甲酸脱氢酶以及辅酶 NAD⁺ 混合, 从而生成 L-杂环氨基酸, 其中, 苯丙氨酸脱氢酶的氨基酸序列为 SEQ ID No.1。所述合成方法的原料转化率高, 手性选择性强。



RW, SD, SL, SZ, TZ, UG, ZM, ZW), 欧亚 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 欧洲 (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, KM, ML, MR, NE, SN, TD, TG)。

- 在修改权利要求的期限届满之前进行，在收到该修改后将重新公布(细则 48.2(h))。
- 根据申请人的请求，在条约第 21 条(2)(a)所规定的期限届满之前进行。
- 包括说明书序列表部分(细则 5.2(a))。

本国际公布:

- 包括国际检索报告(条约第 21 条(3))。

(88) 国际检索报告公布日期: 2014 年 4 月 3 日

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/078154**A. CLASSIFICATION OF SUBJECT MATTER**

See the extra sheet

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: C12P 13/-, C12N 15/-, A61K 31/-

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)

CNPAT, CNKI, EPODOC, WPI, CASREACT (STN), REGISTRY (STN), CAPLUS (STN): ASYMCHEM, heterocyclic ring, heterocyclic, amino acid, keto acid, ammonium formate, formate dehydrogenase, phenylalanine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	CN 103276025 A (ASYMCHEM LABORATORIES (TIANJIN) CO., LTD. et al.), 04 September 2013 (04.09.2013), see claims 1-10	1-10
X	CHEN, Yijun et al., Enzymatic Preparation of an (S)-Amino Acid from a Racemic Amino Acid, ORGANIC PROCESS RESEARCH & DEVELOPMENT, 2011, vol. 15, no. 1, pages 241-248, ISSN: 1083-6160	1-10
X	CN 101903010 A (AVON PRODUCTS, INC.), 01 December 2010 (01.12.2010), see description, pages 4-16, and figures 1-4	10
A	CN 102250976 A (ASYMCHEM LABORATORIES (TIANJIN) CO., LTD. et al.), 23 November 2011 (23.11.2011), see the whole description	1-10

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

* Special categories of cited documents:	“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
“A” document defining the general state of the art which is not considered to be of particular relevance	“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
“E” earlier application or patent but published on or after the international filing date	“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
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&” document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 10 January 2014 (10.01.2014)	Date of mailing of the international search report 13 February 2014 (13.02.2014)
Name and mailing address of the ISA/CN: State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No.: (86-10) 62019451	Authorized officer KANG, Lei Telephone No.: (86-10) 61648356

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/078154

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☒ in electronic form
 - b. (time)
 - ☒ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2013/078154

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 103276025 A	04.09.2013	None	
CN 101903010 A	01.12.2010	WO 2009079126 A1	25.06.2009
		TW 200930412 A	16.07.2009
		EP 2229138 A1	22.09.2010
		CA 2707768 A1	25.06.2009
		US 2010261769 A1	14.10.2010
		MX PA 10006986 A	31.07.2010
		JP 2011507864 A	10.03.2011
		HK 1145982 A0	13.05.2011
		US 8168212 B2	01.05.2012
CN 102250976 A	23.11.2011	None	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/078154

CONTINUATION: A. CLASSIFICATION OF SUBJECT MATTER

C12P 13/04 (2006.01) i

C12N 15/53 (2006.01) i

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A61K 31/444 (2006.01) i

A61K 31/4409 (2006.01) i

A61K 31/4402 (2006.01) i

A61K 31/4406 (2006.01) i

A61K 31/415 (2006.01) i

A. 主题的分类

参见附加页

按照国际专利分类(IPC)或者同时按照国家分类和 IPC 两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

IPC: C12P 13/-, C12N 15/-, A61K 31/-

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称, 和使用的检索词(如使用))

CNPAT, CNKI, EPODOC, WPI, CASREACT(STN), REGISTRY(STN), CAPLUS(STN): 凯莱英, 杂环, 氨基酸, 酮酸, 甲酸铵, 甲酸脱氢酶, 苯丙氨酸, heterocyclic, amino acid, keto acid, ammonium formate, formate dehydrogenase, phenylalanine

C. 相关文件

类 型*	引用文件, 必要时, 指明相关段落	相关的权利要求
E	CN 103276025 A (凯莱英医药集团(天津)股份有限公司 等), 04. 9 月 2013 (04.09.2013) 参见权利要求 1-10	1-10
X	CHEN, Yijun 等, Enzymatic Preparation of an (S)-Amino Acid from a Racemic Amino Acid, Organic Process Research & Development, 2011 年, 第 15 卷, 第 1 期, 第 241-248 页, ISSN: 1083-6160	1-10
X	CN 101903010 A (雅芳产品公司), 01. 12 月 2010 (01.12.2010) 参见说明书第 4-16 页, 附图 1-4	10
A	CN 102250976 A (凯莱英医药化学(天津)有限公司 等), 23. 11 月 2011 (23.11.2011) 参见说明书全文	1-10



其余文件在 C 栏的续页中列出。



见同族专利附件。

* 引用文件的具体类型:

“A” 认为不特别相关的表示了现有技术一般状态的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

“L” 可能对优先权要求构成怀疑的文件, 或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件(如具体说明的)

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“P” 公布日先于国际申请日但迟于所要求的优先权日的文件

“T” 在申请日或优先权日之后公布, 与申请不相抵触, 但为了理解发明之理论或原理的在后文件

“X” 特别相关的文件, 单独考虑该文件, 认定要求保护的发明不是新颖的或不具有创造性

“Y” 特别相关的文件, 当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时, 要求保护的发明不具有创造性

“&” 同族专利的文件

国际检索实际完成的日期

10. 1 月 2014 (10.01.2014)

国际检索报告邮寄日期

13.2 月 2014 (13.02.2014)

ISA/CN 的名称和邮寄地址:

中华人民共和国国家知识产权局

中国北京市海淀区蓟门桥西土城路 6 号 100088

传真号: (86-10)62019451

受权官员

康蕾

电话号码: (86-10) 61648356

第I栏 核苷酸和/或氨基酸序列(续第 1 页第 1.c 项)

1、关于国际申请中所公开的任何对要求保护的发明必要的核苷酸和/或氨基酸序列, 国际检索是在下列基础上进行的:

a. 序列表的提交或提供

☐ 纸件形式

☒ 电子形式

b. 提交或提供时间

☐ 包含在申请提交时的国际申请中

☒ 以电子形式与国际申请一起提交

☐ 为检索之用随后提交本单位

2、☐ 另外, 在提交/提供了多个版本或副本的序列表的情况下, 提供了关于随后提交的或附加的副本中的信息与申请时提交的申请中的信息相同或未超出申请时提交的申请中的信息范围(如适用)的所需声明。

3. 补充意见

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2013/078154

检索报告中引用的 专利文件	公布日期	同族专利	公布日期
CN 103276025 A	04.09.2013	无	
CN 101903010 A	01.12.2010	WO 2009079126 A1	25.06.2009
		TW 200930412 A	16.07.2009
		EP 2229138 A1	22.09.2010
		CA 2707768 A1	25.06.2009
		US 2010261769 A1	14.10.2010
		MX PA10006986 A	31.07.2010
		JP 2011507864 A	10.03.2011
		HK 1145982 A0	13.05.2011
		US 8168212 B2	01.05.2012
CN 102250976 A	23.11.2011	无	

续: A. 主题的分类

C12P 13/04 (2006.01) i

C12N 15/53 (2006.01) i

C12N 15/63 (2006.01) i

A61K 31/381 (2006.01) i

A61K 31/444 (2006.01) i

A61K 31/4409 (2006.01) i

A61K 31/4402 (2006.01) i

A61K 31/4406 (2006.01) i

A61K 31/415 (2006.01) i