



(51) International Patent Classification:
C07D 471/04 (2006.01) *C07D 519/00* (2006.01)
C07D 471/00 (2006.01)

(21) International Application Number:
PCT/CN2010/070925

(22) International Filing Date:
9 March 2010 (09.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (*for all designated States except US*):
F.HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAO, Hongjun** [CN/CN]; 88 Jiangling Road, Binjiang District, Hangzhou City, Zhejiang 310051 (CN). **HILDBRAND, Stefan** [CH/CH]; Loerenweg 7, 4460 Gelterkinden (CH). **HOEFLER, Christoph** [DE/DE]; Am Hochgericht 5c, 79618 Mannheim (DE). **YE, Wenfa** [CN/CN]; 99 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang 318000 (CN). **ZHU, Guoliang** [CN/CN]; 99 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang 318000 (CN).

(74) Agent: **ZHONGZI LAW OFFICE**; 7F, New Era Building, 26 Pinganli Xidajie, Beijing 100034 (CN).

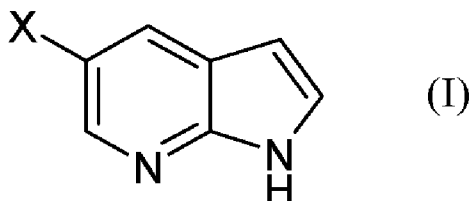
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, 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, RO, RS, RU, 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, 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, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

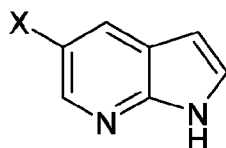
(54) Title: NOVEL PROCESS FOR THE MANUFACTURE OF 5-HALOGENATED-7-AZAINDOLES



(57) Abstract: The present invention provides a novel method for manufacturing the compound of formula (I) wherein X is -Cl or -Br.

Novel process for the manufacture of 5-halogenated-7-azaindoles

The present invention relates to a new process for the manufacture of 5-bromo-7-azaindole (CAS 183208-35-7) or 5-chloro-7-azaindole (CAS 866546-07-8) of formula (I).



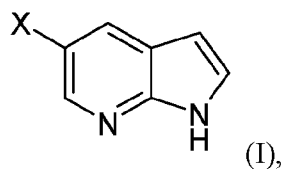
X=Cl, Br (I)

The compounds of general formula (I) are valuable starting materials in the synthesis of more complex heterocyclic molecules, which may be used in many different commercial products, and inter alia as medicaments.

10 Current methods for the synthesis of the compounds of formula (I) are disclosed in US 2006/0183758 and WO03/082869. The disclosed processes are multistep synthesis routes which use environmentally hazardous reagents and/or require the use of heavy metals which are difficult to remove in the subsequent steps.

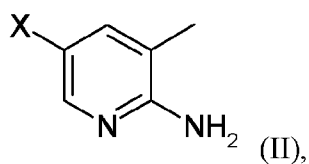
15 It is therefore an object of the present invention to provide a process for manufacturing the compounds of formula (I) which uses few reaction steps, in particular 2 steps, and less hazardous reagents. The present process is thus particularly useful in large scale manufacturing of the compounds of formula (I).

The present invention provides a process for the manufacture of the compound of formula I



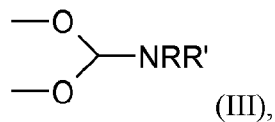
wherein,

5 (a) the compound of formula (II)

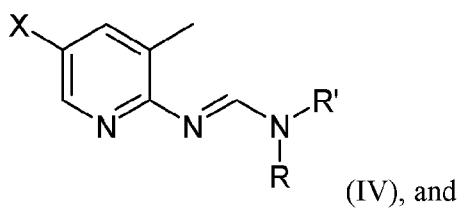


is reacted in the presence of the compound of formula (III)

10



to give the compound of formula (IV)



15 (b) said compound of formula (IV) is further reacted in the presence of a strong base to give the compound of formula (I), and wherein

R and R' are independently selected from C1-4 alkyl; and

X is -Cl or -Br.

The term "strong base" as used herein means strong organic bases like for example alkali metal amides, in particular lithium diisopropylamide (LDA), *n*-butyl lithium (*n*-BuLi).

5 The term "C1-4 alkyl" means a saturated, linear or branched hydrocarbon containing from 1 to 4 carbon-atoms. An especially preferred group is the methyl group.

The reaction step (a) as disclosed herein is preferably carried out using a solvent selected from heptane, toluene, xylene, dimethylsulfoxide (DMSO), dimethylformamide (DMF), chlorobenzene, o-dichlorobenzene, p-dichlorobenzene, m-dichlorobenzene, 2-methyltetrahydrofuran, N-methyl-2-pyrrolidone. The reaction may be carried out at
10 temperatures within the range of 60 to 120 °C.

The reaction step (b) as disclosed herein is preferably carried out using a solvent selected from diethyl ether, methyl *t*-butyl ether, *n*-hexane and tetrahydrofuran (THF). The reaction may be carried out at temperatures ranging from -85 to 30 °C.

15 The term "strong base" as used in reaction step (b) herein means lithium diethylamide, potassium diisopropylamide (KDA), lithium hexamethyldisilazide (LHMDS), Sodium hexamethyldisilazide (NaHMDS), *n*-butyl lithium (*n*-BuLi), *s*-Butyl lithium (*s*-BuLi), *t*-butyl lithium (*t*-BuLi), lithium isopropyl cyclohexylamide (LICA), lithium 2,2,6,6-tetramethylpiperidide (TMPLi), ((trimethylsilyl)methyl)lithium (TMSCH₂Li), lithium *di*-(trimethylsilyl)methyl amide (TMS₂CHLi), and the like.

20

In a particularly preferred embodiment of the present invention, X is -Br (compound 1).

In another particularly preferred embodiment of the present invention, X is -Cl (compound 1a).

25 In still another preferred embodiment of the present invention, X is -Br; R and R' are both methyl, and the strong base in reaction step (b) is LDA.

In still another preferred embodiment of the present invention, X is -Cl; R and R' are both methyl, and the strong base in reaction step (b) is LDA.

30 A particularly preferred embodiment according to the present invention is the synthesis of the compound of formula (I) wherein X is -Br, starting from the compound of formula (2) and using the specific reaction conditions described in Examples 1 and 2a.

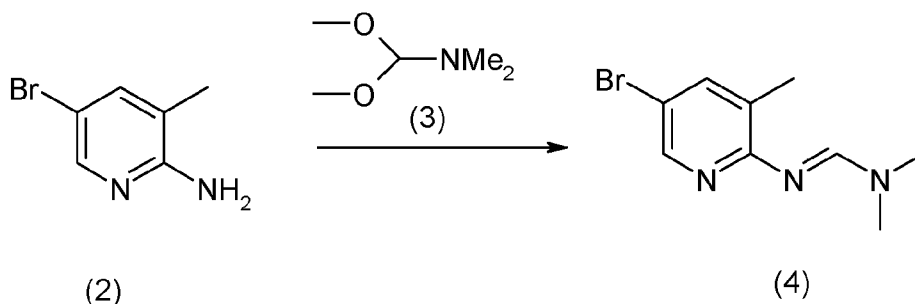
Another particularly preferred embodiment according to the present invention is the

synthesis of the compound of formula (I), wherein X is -Br, starting from the compound of formula (2) and using the specific reaction conditions described in Examples 1 and 2b.

The invention is now illustrated by the accompanying working examples, which are not meant to limit the scope of the present invention.

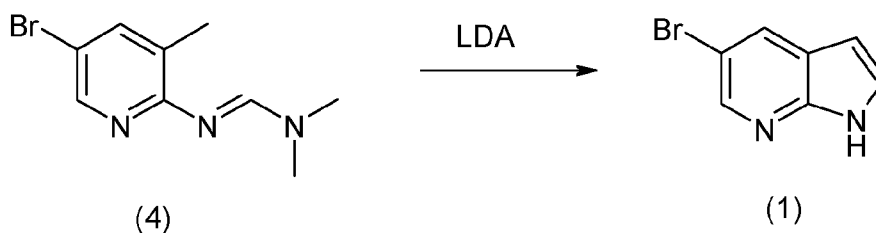
Examples

Example 1: Synthesis of *N'*-(5-bromo-3-methyl-pyridin-2-yl)-*N,N*-dimethyl-formamidine (4):



A mixture of 37.4 g (0.20 mol) of 2-amino-5-bromo-3-methylpyridine and 33 mL (0.25 mol) of *N,N*-dimethylformamide dimethyl acetal (3) was heated to reflux temperature for about 15 h (until the disappearance of the starting material was indicated by HPLC analysis). The reaction mixture was cooled and then concentrated under vacuum (35-40 mmHg) at 55°C to constant weight. Heptane (45 mL) was added in one portion and the mixture stirred for 30 min. The mixture was cooled to -20°C and then kept at this temperature for 5 h for crystallization. The crystals were filtered, washed with 30 g of cold heptane and dried under vacuum at room temperature to afford 44.55 g (92%) of compound 4 with a purity of >99 area% (HPLC).

Example 2a: Synthesis of 5-bromo-7-azaindole (1):



A four-necked flask fitted with a thermometer, adding funnel, and mechanical stirring was flushed with nitrogen for 3 times before use. To this flask, 75 mL of LDA (2.0 M in THF, 0.15 mol) was added and then cooled to -30 ± 2°C. In a separate vessel, 24.2 g (0.10 mol) of compound 4 was dissolved in 121 mL of dry THF and then the solution was injected into the adding funnel. This solution was added slowly within about 2 h. The reaction mixture was then kept at the same temperature for 5-6 h until the disappearance of the compound 4 was shown by

HPLC analysis. A mixture of 20 ml (0.35 mol) of acetic acid and THF (50 mL) was then added drop wise with further vigorous stirring for 10 min. Then 150 mL of water was injected until two clear phases appeared. The organic layer was separated and the aqueous phase was extracted with 4×100 mL of hot toluene (40°C). The organic layers were combined and THF was removed under vacuum at 45°C. The residual toluene solution was washed with 3×150 mL of water and 2×150 mL of saturated sodium chloride solution, and dried over 8 g MgSO₄ for 1 h. After filtration, the mixture was concentrated under vacuum to furnish 20.5 g of a black, sticky oil. This oil was heated in 40 mL of toluene until complete dissolution, and was subsequently cooled to room temperature (rt). The mixture was kept at this temperature for 10 h, then cooled and kept at 0°C for 2 h for crystallization. After filtration, the solid was washed by a small amount of toluene and dried at 50°C for 6 h. The dried solid was dissolved in 15 mL toluene and refluxed with charcoal for 1 h. After filtration, charcoal was washed with toluene. The solutions were combined, cooled to 0°C and kept at this temperature for 2 h for crystallization. The crystals were isolated by filtration, washed with cold toluene and dried at 50°C for 8 h under vacuum to afford 2.1 g of the title compound (1) with a purity of ≥99 % (HPLC). All filtrates were combined and concentrated. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate 10:1 as eluent to afford additional 1.4 g of the title compound (1) with a purity of ≥98.9 % (HPLC). In total 3.5 g (18%) of 5-bromo-7-azaindole (1) were obtained.

HPLC retention time of compound 1: 12.307 min.

Conditions:

Column: Zorbax Eclipse Plus C18, 150 mm*4.6 mm, particle size 3.5 μm

Column Temperature: 50°C

Mobile Phase:

Phase A: 10 mM KH₂PO₃, which was adjusted to pH 2.5 with H₃PO₄

Phase B: Acetonitrile

Gradient:

T (min)	Phase A (% v/v)	Phase B (% v/v)
0.0	95	5
2.0	95	5
20.0	20	80
25.0	20	80
25.1	95	5
30.0	95	5

Flow rate: 2.0 mL/min

Wavelength: UV 230 nm

Injection volume: 5 μl

Preparation of sample solution: A suitable amount of compound 1, about 5.4-6.2 mg, was

accurately weighed and dissolved in a 25 mL volumetric flask with solvent by ultrasound.

Solvent: Acetonitrile/H₂O 20:80 (v/v)

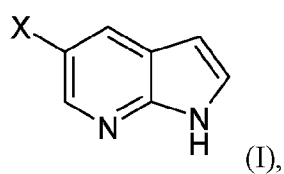
Example 2b: Synthesis of 5-bromo-7-azaindole (1):

- 5 150 mL of LDA (2.0 M in THF, 0.30 mol) was added into a flask and cooled to -30°C. Then 24.2 g (0.10 mol) of the compound of formula (4) was dissolved in 121 mL of dry THF and the solution was slowly added (within about 2 h) to keep the reaction at constant temperature for 5-6 h until the disappearance of the compound 4 was shown by HPLC analysis. Then, 37.2 mL (0.65 mol) of acetic acid in 90 mL of THF was slowly added and the resulting solution was further
- 10 vigorously stirred for 10 min. Then, 150 mL of water was injected until two clear phases appeared. The organic layer was separated and the aqueous phase was extracted with 4×100 mL of hot toluene (40°C). The organic phases were combined and THF was removed under vacuum at 45°C. The residual toluene solution was washed with 3×150 mL of water and 2×150 mL of saturated sodium chloride solution, and then dried over 8 g magnesium sulfate for 1 h. After
- 15 filtration, the mixture was concentrated under vacuum to furnish 22 g of a black, sticky oil. This oil was heated in 40 mL toluene until complete dissolution, and was then cooled to room temperature. The mixture was kept at this temperature for 10 h and then cooled and kept at 0°C for 2 h for crystallization. After filtration, the solid was washed by a small amount of toluene and dried at 50°C for 8 h to furnish 2.8 g of the title compound (1) with a HPLC purity of ≥99 %. All
- 20 filtrates were combined and concentrated. The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate 10:1 as eluent to afford additional 2.2 g of the title compound (1) with a purity of ≥98.9 % (HPLC). In total 5.0 g (26%) of 5-bromo-7-azaindole (1) were obtained.

Claims

1. A process for the manufacture of the compound of formula (I)

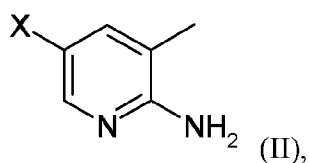
5



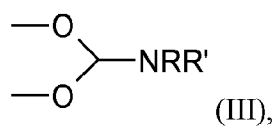
wherein,

- (a) the compound of formula (II)

10

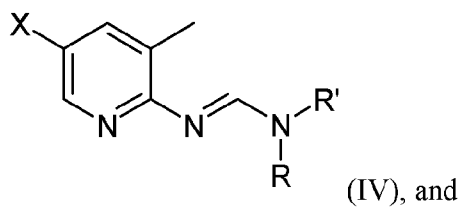


is reacted in the presence of the compound of formula (III)



to give the compound of formula (IV)

15



- (b) said compound of formula (IV) is further reacted in the presence of a strong base to give the compound of formula (I), and wherein

R and R' are independently selected from C1-4 alkyl; and

X is -Cl or -Br.

2. The process according to claim 1, wherein X is -Br.

5

3. The process according to claim 1, wherein X is -Cl.

4. The process according to claim 2 or 3, wherein

R and R' are both methyl; and

10

the strong base used in reaction step (b) is lithium diisopropylamide (LDA).

5. The novel process substantially as described herein before.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070925

A. CLASSIFICATION OF SUBJECT MATTER

See 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: C07D 471/-; C07D 519/-

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)

WPI; WPODOC; CNPAT; CNKI; CA: azaindole azaindiol bromo chloro pyridine acetal 183208-35-7
866546-07-8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2005095400 A1(VERTEX PHARMACEUTICALS INCORPORATED ET AL) 13 Oct. 2005(13.10.2005) pages 342, 343-345 of the description	1-4
A	WO0147922 A2(AVENTIS PHARMA LIMITED ET AL) 05 Jul. 2001(05.07.2001) pages 172-173 of the description	1-4
A	WO03000688 A1(AVENTIS PHARMA LIMITED ET AL) 03 Jan. 2003(03.01.2003) pages 98-99 of the description	1-4
A	US20060183758 A1(CHARLES, D. B. ET AL) 17 Aug. 2006(17.08.2006) the whole document	1-4

☐ 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 22 Nov. 2010(22.11.2010)	Date of mailing of the international search report 16 Dec. 2010 (16.12.2010)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WANG, Qingeng Telephone No. (86-10)82245406

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070925

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 5 is unclear to such an extent that no meaningful international search can be carried out.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2010/070925

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2005095400A1	13.10.2005	NO20064852A	24.10.2006
		EP1730146A1	13.12.2006
		US2007043063A1	22.02.2007
		AU2005228904A1	13.10.2005
		INKOLNP200602852E	08.06.2007
		MXPA06011327A	01.01.2007
		KR20070027542A	09.03.2007
		CN1938303A	28.03.2007
		BRPI0509369A	11.09.2007
		JP2007531760T	08.11.2007
		JP2008156370A	10.07.2008
		US7507826B2	24.03.2009
		ZA200607981A	25.06.2008
		US2009176763A1	09.07.2009
		TW200602052A	16.01.2006
		CN100569772C	16.12.2009
		CN101676285A	24.03.2010
		CN101676286A	24.03.2010
		KR20100039913A	16.04.2010
		NZ549880A	30.04.2010
WO0147922A2	05.07.2001	AU2209401A	09.07.2001
		NO20023032A	21.06.2002
		CZ20022207A3	13.11.2002
		EP1263759A2	11.12.2002
		KR20020062663A	26.07.2002
		BR0017038A	07.01.2003
		HU0203895A2	28.02.2003
		SK9012002A3	01.04.2003
		CN1413213A	23.04.2003
		JP2003519144T	17.06.2003
		MXPA02006338A	01.01.2003
		ZA200204126A	29.10.2003
		US2004009983A1	15.01.2004
		NZ519121A	28.05.2004
		US6770643B2	03.08.2004
		US2004198737A1	07.10.2004
		AU777717B2	28.10.2004
		CN1615873A	18.05.2005
		INCHENP200200965E	04.03.2005
		NO20066017A	21.06.2002
		US7227020B2	05.06.2007
		NO323766B1	02.07.2007
		MX243510B	26.01.2007
		KR20070050103A	14.05.2007

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CN2010/070925

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO03000688A1	03.01.2003	KR100755622B1	04.09.2007
		CN100379734C	09.04.2008
		EP1990343A2	12.11.2008
		EP1990343A3	10.12.2008
		KR100910488B1	04.08.2009
		MX270499B	01.10.2009
		IN227429B	06.03.2009
		CZ301750B6	09.06.2010
		CZ301751B6	09.06.2010
		CA2699568A1	05.07.2001
		EP1397360A1	17.03.2004
		US2004053931A1	18.03.2004
		CZ20033444A3	17.03.2004
		BR0210507A	15.06.2004
		SK15902003A3	08.06.2004
		KR20040018284A	02.03.2004
		AU2002302849A1	08.01.2003
		JP2004534826T	18.11.2004
		MXPA04000188A	01.04.2004
		HU0400247A2	28.01.2005
		INCHENP200302023E	11.12.2004
		US6897207B2	24.05.2005
		ZA200309648A	25.05.2005
		US2005267304A1	01.12.2005
		CN1665809A	07.09.2005
		NZ529205A	28.04.2006
		NZ545741A	28.09.2007
		SG135051A1	28.09.2007
		MX245809B	14.05.2007
		RU2326880C2	20.06.2008
		KR20090035650A	09.04.2009
		AU2009200024A1	05.02.2009
		INCHENP200800530E	14.08.2009
		KR100915289B1	03.09.2009
		MX267489B	16.06.2009
		CN100509811C	08.07.2009
		JP4409938B2B2	03.02.2010
US20060183758 A1	17.08.2006	none	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2010/070925

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i

C07D 471/00(2006.01)i

C07D 519/00(2006.01)i