

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 August 2008 (28.08.2008)

PCT

(10) International Publication Number
WO 2008/102369 A1

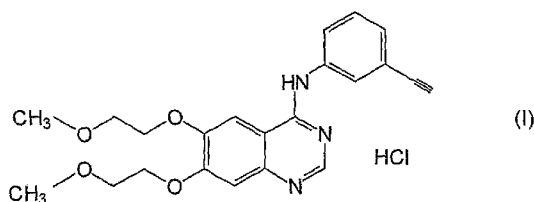
- (51) International Patent Classification:
C07D 239/94 (2006.01) *A61P 35/00* (2006.01)
A61K 31/517 (2006.01)
- (21) International Application Number:
PCT/IN2007/000407
- (22) International Filing Date:
11 September 2007 (11.09.2007)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
349/CHE/2007 21 February 2007 (21.02.2007) IN
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

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, 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, 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.

- (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, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, 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

(54) Title: NOVEL POLYMORPHS OF ERLOTINIB HYDROCHLORIDE AND METHOD OF PREPARATION

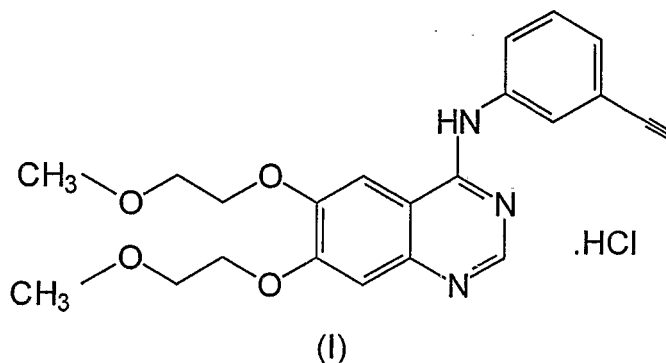


(57) Abstract: The present invention relates to three novel crystalline forms of Erlotinib hydrochloride and method of preparation thereof. Erlotinib hydrochloride is N-(3-ethynylphenyl)-6,7-bis(2-methoxy ethoxy)-4-quinazolinamine hydrochloride of formula-(I). The present invention provides stable novel crystalline forms of Erlotinib hydrochloride designated as Form-M, Form-N and Form-P, and processes for the preparation of the same. Erlotinib hydrochloride can be used as medicament for the treatment of hyperproliferative disorders, such as cancers, in humans.

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NOVEL POLYMORPHS OF ERLOTINIB HYDROCHLORIDE AND METHOD OF PREPARATION

The present invention relates to three novel polymorphic forms Form-M, Form-N and
5 Form-P of Erlotinib Hydrochloride of formula-(I). Erlotinib is N-(3-ethynylphenyl)-6,7-
bis(2-methoxy ethoxy)-4-quinazolinamine and is an inhibitor of the erbB family of
oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor
receptor (EGFR). It is therefore useful in the treatment of proliferative disorders, such as



cancers, in humans and often used as its hydrochloride salt (I).

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BACKGROUND OF THE PRESENT INVENTION:

Erlotinib having the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-
quinazolinamine, is reported in PCT Publication No. WO. 96/30347 and its equivalent
15 Patent US. 5,747,498 (1998). Although, the preparation of its hydrochloride
salt is mentioned in this patent, its Polymorphic forms and their properties are not
discussed. None of its solid state properties excepting melting point are disclosed in this
patent.

20 Subsequently, PCT Publication No. WO. 01/34574 and its equivalent patent US
6,900,221 (2005) described polymorphic Forms-A and B of Erlotinib HCl, and
mentioned that the polymorphic form 'B' is thermodynamically more stable. This patent,
also identified that the product of US 5,747,498 was a mixture of polymorphic Forms A
and B. A method of preparing pure polymorphic Form-B of Erlotinib. HCl (I) free of the

polymorphic Form-A is also claimed in US 6,900,221. The powder XRD data of both the crystal Forms A and B are disclosed in this patent.

The patent WO 2004/072049 corresponding to the International Application No PCT/EP 5 2004/001244 discloses a novel polymorph E along with its DSC and XRD characteristics and claims improved stability over the polymorph A. However, this polymorphic form E is prepared in (α,α,α)-trifluorotoluene which is highly flammable and dangerous for the environment. It is also an expensive solvent and not convenient to handle on an industrial scale.

10

SUMMARY OF THE INVENTION:

Our continued efforts on the investigation of stable polymorphic forms of Erlotinib HCl resulted in the invention of three novel stable crystal forms designated as Form-M, 15 Form-N and Form-P. The three new polymorphic forms Form-M, Form-N and Form-P are surprisingly and unexpectedly very stable in the solid state at room temperature (30°-35°C) and also at higher temperatures of the order of 60°-120°C. The novel polymorphic forms mentioned can be easily prepared by employing inexpensive and commercially available solvents like isopropanol, methanol and methylene chloride 20 which are suitable for large scale manufacture. Thus the novel Form-M of Erlotinib HCl is prepared by treating Erlotinib base in methanol with a solution of HCl in dry methanol or isopropanol. Similarly the novel form-N is prepared by treating erlotinib base in isopropanol with isopropanolic HCl and Form-P is prepared by treating Erlotinib base in methylene chloride with isopropanolic HCl. The three novel forms, Form-M, 25 Form-N and Form-P of Erlotinib HCl are characterized by Powder XRD pattern and are very stable in solid state.

Therefore the main objective of the present invention is to provide stable novel crystalline forms of Erlotinib HCl designated as Form-M, Form-N and Form-P.

30

Another objective of the present invention is to provide processes for the preparation of stable novel crystalline forms of Erlotinib HCl designated as Form-M, Form-N and Form-P.

- 5 Accordingly the present invention provides novel stable crystalline forms of Erlotinib HCl designated as Form-M, Form-N and Form-P, having the characteristics as given below.:

X-ray Powder Diffraction Pattern :

10

(i) **Form-M:** having typical characteristic peaks at about 6.2, 7.9, 9.6, 11.4, 12.5, 13.4, 14.7, 15.7, 17.0, 17.6, 19.2, 20.2, 20.7, 21.1, 21.9, 22.4, 23.0, 23.9, 24.4, 25.1, 25.9, 26.8, 29.0, 29.7, 31.7, 32.7, 34.8, 40.2 on the 2θ scale as shown in Fig-1.

15

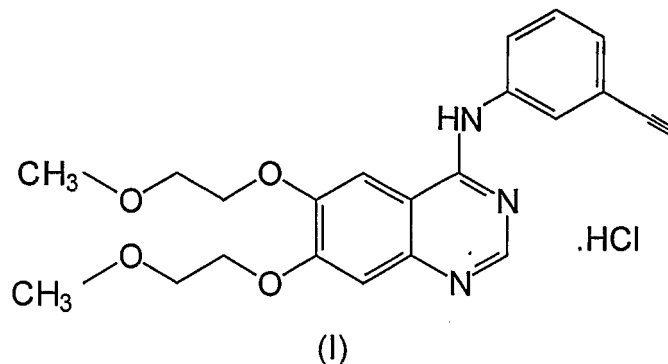
(ii) **Form-N:** having typical characteristic peaks at about 5.56, 9.72, 11.25, 12.82, 18.84, 19.38, 21.01, 22.74, 23.46, 24.23, 25.34, 26.70, 29.17, 32.77, 37.21, 39.96, 45.66 on the 2θ scale as shown in Fig-2.

20

(iii) **Form-P:** having typical characteristic peaks at about 2.97, 5.80, 6.36, 9.97, 10.54, 11.48, 15.00, 15.80, 16.64, 17.11, 17.62, 18.15, 18.58, 19.06, 19.78, 20.74, 22.14, 22.96, 23.72, 24.45, 25.67, 26.40, 27.30, 28.14, 28.76, 29.44, 30.15, 30.82, 32.21, 32.95, 33.99, 34.59, 40.49, 40.64, 42.02, 43.87 on the 2θ scale as shown in Fig-3.

25

According to another feature of the present invention, there are provided processes for the preparation of the novel crystalline forms Form-M, Form-N and Form-P of Erlotinib Hydrochloride of formula-(I), having the above mentioned characteristics which



comprise:

- 5 (i) Dissolving Erlotinib base (prepared according to the process given in International Publication No. : WO. 2007/060691) in dry methanol and adding a solution of dry HCl gas in methanol or isopropanol. The crystals of Erlotinib HCl thus obtained are dried and designated as Form-M.
- 10 (ii) Dissolving Erlotinib base (prepared according to the process given in International Publication No. : WO. 2007/060691) in dry isopropanol and adding a solution of dry HCl gas in isopropanol. The crystals of Erlotinib HCl are filtered and dried and designated as Form-N.
- 15 (iii) Dissolving Erlotinib base (prepared according to the process given in International Publication No. : WO. 2007/060691) in dry methylene chloride and adding a solution of dry HCl gas in isopropanol. The crystals of Erlotinib HCl are filtered and dried and designated as Form-P.

The following examples are given for the purpose of illustrating the process of the present invention and therefore should not be considered to limit the scope or spirit of the
20 invention.

Example-1

Preparation of Erlotinib HCl polymorphic form-M :

- 5 Into a 2 Lt. four necked round-bottomed flask provided with a mechanical stirrer, thermometer socket, reflux condenser etc are charged 1340 mL of methanol, followed by Erlotinib base 60 g. (Prepared according to the process given in Example-(1) of PCT international publication No. WO2007/060691). The reaction mass is warmed to around 40°C so that Erlotinib base completely dissolves. To this reaction mass, carbon
- 10 treatment is given and the filtrate is transferred to another 2 Lt. four necked flask. To this solution isopropanolic HCl (HCl content as 100% is 6.12g) is added in one lot and the reaction mass is stirred at 30-35°C for about 90 minutes and filtered. The product is washed with fresh methanol and dried the wet cake to get 55.2 g of Erlotinib hydrochloride as a white crystalline powder.
- 15 XRPD: Form-M (Fig-1)

Example-2

Preparation of Erlotinib HCl polymorphic form-N :

- 20 Into a 1 Lt. four necked round-bottomed flask provided with a mechanical stirrer, thermometer socket, reflux condenser etc, are charged 325 mL of isopropyl alcohol, followed by 25.0 g of Erlotinib base (Prepared according to the process given in Example-(1) of PCT international publication No. WO2007/060691) at 70-75°C so that Erlotinib base completely dissolves in the solvent. Then carbon treatment is given and the
- 25 filtrate is transferred to another 1 Lt. four-necked round bottomed flask provided with all the necessary accessories. To this solution isopropanolic HCl (HCl content as 100% is 2.548 g) is added in one lot at 60-65°C and maintained at this temperature for about 1 hour. The reaction mass is cooled to room temperature and filtered. The product is washed with fresh isopropyl alcohol and dried to get 25.0 g of Erlotinib hydrochloride as
- 30 a white crystalline powder.
- XRPD: Form-N (Fig-2)

Example-3**Preparation of Erlotinib HCl polymorphic form-P :**

5 Into a 3 Lt. four necked round-bottomed flask provided with a mechanical stirrer, thermometer socket, reflux condenser etc, are charged 2400 mL of methylene chloride, followed by 120 g of Erlotinib base (Prepared according to the process given in Example-(1) of PCT international publication No. WO2007/060691) under stirring. The reaction mass is slightly warmed up to $37\pm 1^\circ\text{C}$, so that the Erlotinib base completely
10 dissolves in the solvent. Then carbon treatment is given and the filtrate is transferred to 5 Lt three necked round bottomed flask, provided with a mechanical stirrer and other accessories. To this filtrate, Isopronolic HCl. (HCl content as 100% is 13.90 g) is added in one lot at $30\text{-}35^\circ\text{C}$ and then the reaction mass is refluxed for about 3 hrs. Afterwards, the reaction mass is cooled to room temperature and filtered. The product is washed with
15 methylene chloride and the wet cake is dried to get 119 g of Erlotinib hydrochloride as a white crystalline powder.

XRPD: Form-P (Fig-3)

Example-4**Preparation of Erlotinib Hydrochloride, polymorphic form-P :**

- 5 (i) **Preparation of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (Erlotinib base).**

For the preparation of Erlotinib base, the starting intermediate N-(3-ethynyl phenyl)-6,7-dihydroxy-4-quinazolinamine, is obtained from the process described in steps (i) to (v) of Example-(1) of PCT international publication No. WO 2007/060691.

10

Into a clean and dry stainless steel reactor, are charged 250 Lts of dimethyl formamide, followed by 30 Kgs of potassium carbonate (anhydrous) and 10 Kgs of N-(3-ethynyl phenyl)-6,7-dihydroxy-4-quinazolinamine under nitrogen atmosphere. To this reaction mixture 14.0 Kgs of 2-Iodo ethyl methyl ether is added and maintained at 45-50°C for
15 about 12 hrs and the reaction is found to be completed by HPLC –Test. Then the reaction mass is cooled to room temperature and the mass is centrifuzed to remove the inorganic salt .

To the collected filtrate, demineralized water is slowly added, under stirring below 35°C,
20 so that the product is crystallized out. Then the product is centrifuged and washed with water and the wet cake is dried to get 9.8 Kgs (69% by theory) of Erlotinib base as a brownish yellow coloured crystalline solid.

Purity : 99.17% (by HPLC)

Melting range: 151-153°C

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- (ii) **Purification of Erlotinib base**

Erlotinib base of high purity is obtained by adopting the following purification method. Into a clean and dry All Glass Reactor, are charged 90 Lts of methylethyl ketone, followed by 9 Kgs of Erlotinib base obtained by the process described in Step-(i) above.
30 The temperature is raised to 60-65°C to dissolve the solid completely. Carbon treatment is given and the filtrate is cooled to 10°C and centrifuged the crystallized product and

washed the cake with methylethyl ketone and the wet cake is dried to get 5.9 Kgs of Erlotinib base of high purity, as a pale yellow coloured crystalline solid.

Purity : 99.74% (by HPLC)

Melting range: 154-155°C

5 (iii) **Preparation of Erlotinib Hydrochloride, Polymorphic form-P.**

Into a clean and dry All Glass Reactor, are charged 110 Lts of methylene chloride, followed by 5.5 Kgs of Erlotinib base as obtained from step-(ii) above. The temperature is raised to $37\pm 1^\circ\text{C}$ so that the solid completely dissolves. To this carbon treatment is given and the filtrate is transferred into another clean and dry All glass reactor. To this reaction mass isoproponolic HCl (HCl content as 100% is 0.6371 Kg) is added in one lot at $25-35^\circ\text{C}$ and then the reaction is maintained at reflux condition for 3 hrs. The reaction mass is cooled to room temperature and centrifused. The product cake is washed with methylene chloride and dried to get 5.5 Kgs of Erlotinib hydrochloride as a white crystalline powder.

Purity : 99.82% (by HPLC)

XRPD : Form-P (identical to Fig-3)

ADVANTAGES OF THE PRESENT INVENTION:

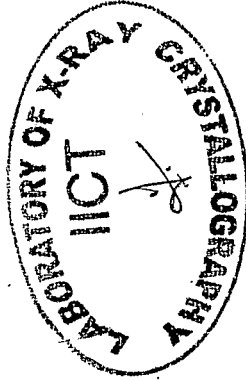
- 1) The novel polymorphic forms, Form-M, Form-N and Form-P of Erlotinib hydrochloride are prepared easily and are very stable at room temperature (30-35°C) and also at elevated temperatures like 60-120°C.
- 2) The novel polymorphic forms, Form-M, Form-N and Form-P are prepared in inexpensive solvents like isopropanol and methanol and methylene chloride and can be easily scaled-up to manufacturing level.
- 3) The procedures for preparing the new polymorphic form of Erlotinib hydrochloride (Form-M, Form-N and Form-P) are consistently reproducible.
- 4) The novel polymorphs M, Form-N and Form-P of Erlotinib hydrochloride are prepared from Erlotinib base purified by a crystallization technique and devoid of any cumbersome chromatographic methods.

We claim :

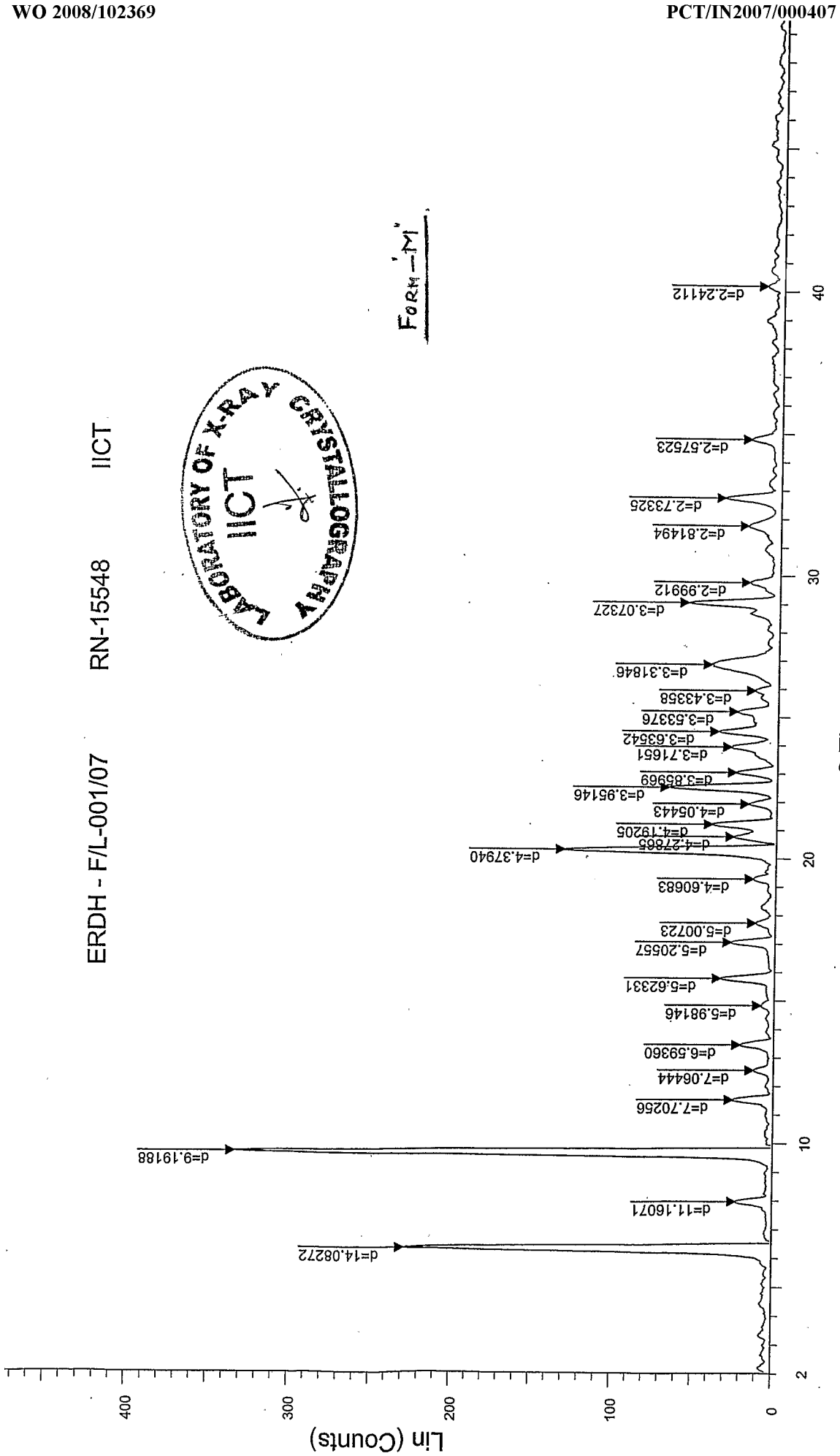
1. A novel stable crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)6,7-bis(2-methoxy ethoxy)-4-quinazolinamine designated as **Form-M**, which is characterized by an x-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately. 6.2, 7.9, 9.6 ,11.4, 12.5, 13.4, 14.7,15.7,17.0,17.6, 19.2, 20.2, 20.7, 21.1, 21.9, 22.4, 23.0, 23.9, 24.4, 25.1, 25.9, 26.8, 29.0, 29.7, 31.7, 32.7, 34.8, 40.2.
2. The crystalline polymorph of Claim-1, characterized by the x-ray powder diffraction pattern shown in Figure-1.
3. A novel stable crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)6,7-bis(2-methoxy ethoxy)-4-quinazolinamine designated as **Form-N**, which is characterized by an x-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately. 5.56, 9.72, 11.25, 12.82, 18.84, 19.38, 21.01, 22.74, 23.46, 24.23, 25.34, 26.70, 29.17, 32.77, 37.21, 39.96, 45.66.
4. The crystalline polymorph of Claim-3, characterized by the x-ray powder diffraction pattern shown in Figure-2.
5. A novel stable crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)6,7-bis(2-methoxy ethoxy)-4-quinazolinamine designated as **Form-P**, which is characterized by an x-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately. 2.97, 5.80, 6.36, 9.97, 10.54, 11.48, 15.00, 15.80, 16.64, 17.11, 17.62, 18.15, 18.58, 19.06, 19.78, 20.74, 22.14, 22.96, 23.72, 24.45, 25.67, 26.40, 27.30, 28.14, 28.76, 29.44, 30.15, 30.82, 32.21, 32.95, 33.99, 34.59, 40.49, 40.64, 42.02, 43.87
6. The crystalline polymorph of Claim-5, characterized by the x-ray powder diffraction pattern shown in Figure-3
7. A process for the manufacture of a crystalline polymorph **Form-M**, as defined in claims 1 to 2, which comprises dissolving N-(3-ethynylphenyl)6,7-bis(2-methoxyethoxy)-4-quinazolinamine or Erlotinib base in dry methanol and reacting it with a solution of dry hydrogen chloride gas in methanol or isopropanol.

8. A process for the manufacture of a crystalline polymorph **Form-N**, as defined in claims 3 to 4, which comprises dissolving N-(3-ethynylphenyl)6,7-bis(2-methoxyethoxy)-4-quinazolinamine or Erlotinib base in dry isopropanol. and reacting it with a solution of dry hydrogen chloride gas in isopropanol.
- 5 9. A process for the manufacture of a crystalline polymorph **Form-P**, as defined in claims 5 to 6, which comprises dissolving N-(3-ethynylphenyl)6,7-bis(2-methoxyethoxy)-4-quinazolinamine or Erlotinib base in dry methylene chloride and reacting it with a solution of dry hydrogen chloride gas in methanol or isopropanol.
10. Pharmaceutical compositions useful for anticancer activity comprising the novel
10 stable crystalline **Form-M** of Erlotinib Hydrochloride as claimed in claims 1 to 2 and a Pharmaceutically acceptable carrier and /or adjuvant.
11. Pharmaceutical compositions useful for anticancer activity comprising the novel stable crystalline **Form-N** of Erlotinib Hydrochloride as claimed in claims 3 to 4 and a Pharmaceutically acceptable carrier and /or adjuvant.
- 15 12. Pharmaceutical compositions useful for anticancer activity comprising the novel stable crystalline **Form-P** of Erlotinib Hydrochloride as claimed in claims 5 to 6 and a Pharmaceutically acceptable carrier and /or adjuvant.
13. A process for the preparation of a novel crystalline **Form-M**, having the above mentioned characteristics, as claimed in claims 1 to 2, of Erlotinib Hydrochloride of
20 Formula-I, substantially as herein described with reference to Example-1.
14. A process for the preparation of a novel crystalline **Form-N**, having the above mentioned characteristics, as claimed in claims 3 to 4, of Erlotinib Hydrochloride of Formula-I, substantially as herein described with reference to Example-2
15. A process for the preparation of a novel crystalline **Form-P**, having the above
25 mentioned characteristics, as claimed in claims 5 to 6, of Erlotinib Hydrochloride of Formula-I, substantially as herein described with reference to Example-3 and 4.

ERDH - F/L-001/07 RN-15548 IICT



Form-M



2-Theta - Scale

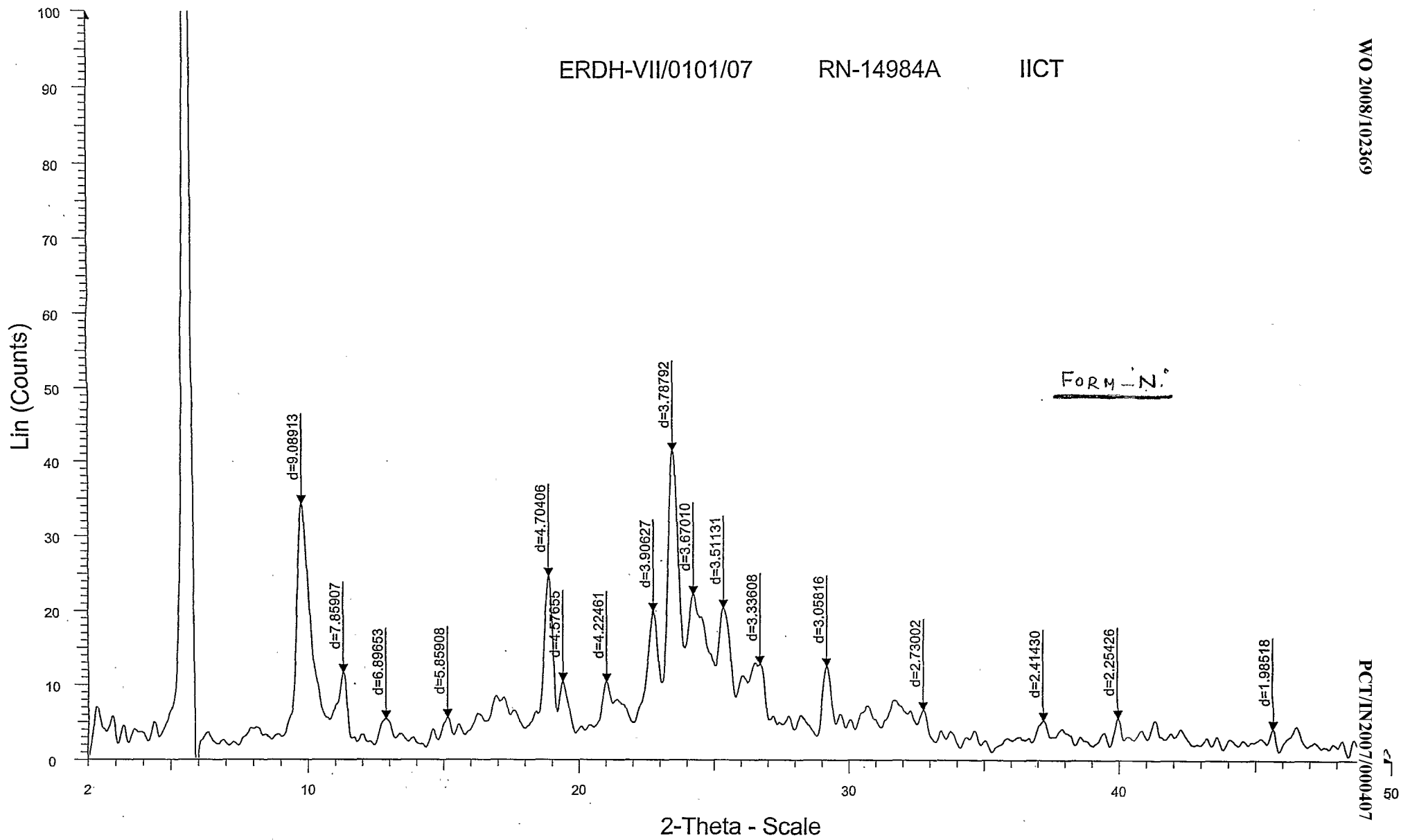
FIGURE - 1

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ERDH-VII/0101/07

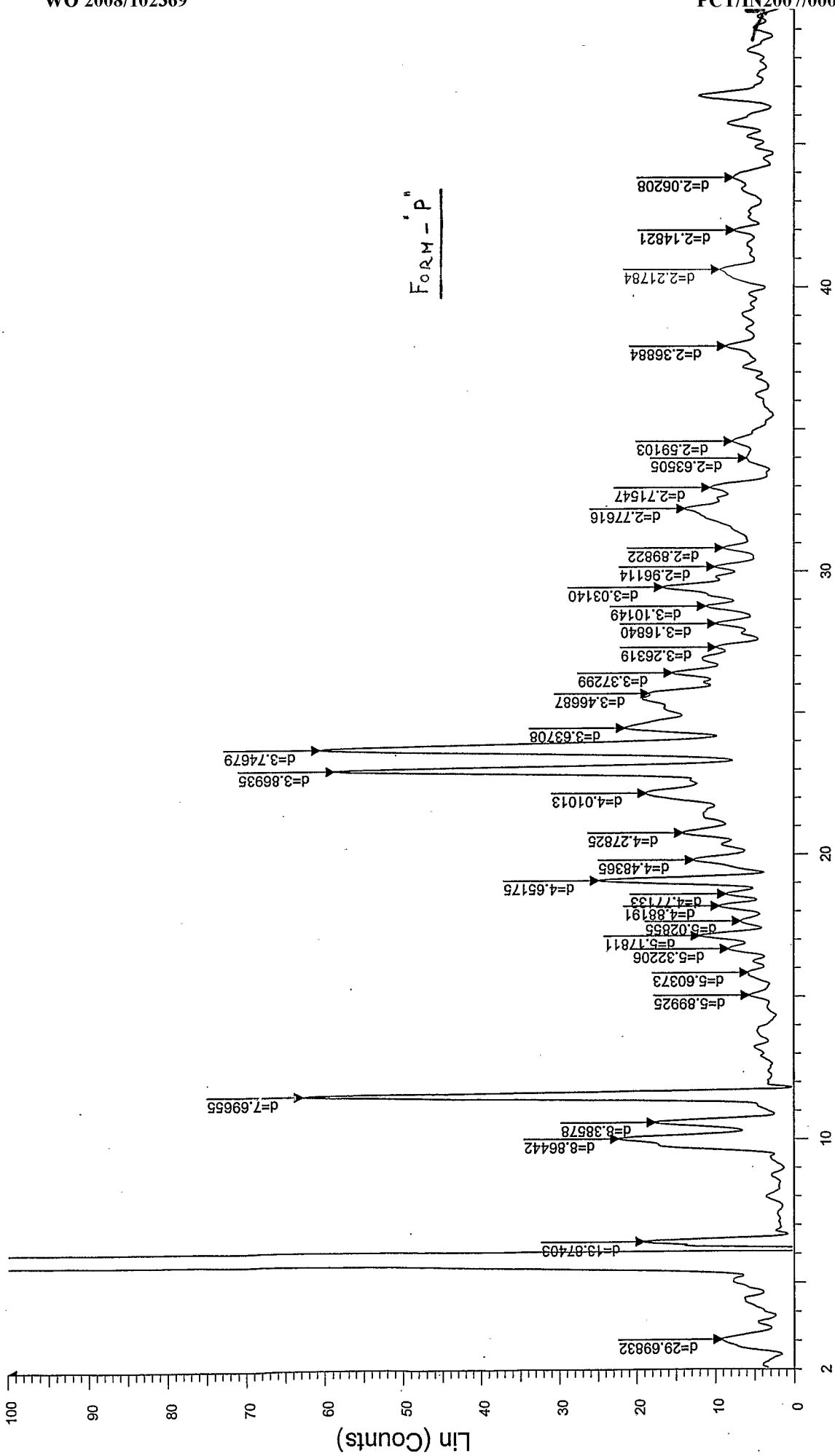
RN-14984A

IICT



ERDH-VII/0101/07 - File: RN-14984A.RAW - Start: 2.000 ° - End: 50.000 ° - Step: 0.030 ° - Step time: 0.5 s - WL1: 1.5406 - Creation: 1/17/07 3:56:39 PM
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FIGURE - 2.



FORM - P

2-Theta - Scale

FIGURE - 3.

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Operations: Smooth 0.193 | Smooth 0.193 | Background 0.000,0.000 | Import

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2007/000407

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/94 A61K31/517 A61P35/00

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)
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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/34574 A (OSI PHARM INC [US]) 17 May 2001 (2001-05-17) cited in the application Polymorph A and B	1-15
X	WO 2004/072049 A (HOFFMANN LA ROCHE [CH]; BUBENDORF ANDRE GERARD [FR]; HENNIG MICHAEL [D] 26 August 2004 (2004-08-26) cited in the application claim 1	1-15
X	US 6 476 040 B1 (NORRIS TIMOTHY [US] ET AL) 5 November 2002 (2002-11-05) examples 7,10,11	1-15
	-/--	

 Further documents are listed in the continuation of Box C. 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 document but published on or after the international filing date
- *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)
- *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

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.

& document member of the same patent family

Date of the actual completion of the international search

24 April 2008

Date of mailing of the international search report

14/05/2008

Name and mailing address of the ISA/

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Authorized officer

Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2007/000407

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2007/060691 A (NATCO PHARMA LTD [IN]; JYOTHI PRASAD RAMANADHAM [IN]; NAGESHWAR RAO B0) 31 May 2007 (2007-05-31) example 2	1-15
E	WO 2007/138613 A (VITTAL MALLYA SCIENT RES FOUND [IN]; CHANDREGOWDA VENKATESHAPPA [IN];) 6 December 2007 (2007-12-06) page 13, line 11 - line 17	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2007/000407

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.:
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:

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:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,2,7,10,13

form M

2. claims: 3,4,8,11,14

form N

3. claims: 5,6,9,12,15

form P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2007/000407

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