

PROVISIONAL APPLICATION COVER SHEET

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This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

	Docket Number	PC10677	Type a plus sign (+) inside this box	+
INVENTOR(s)/APPLICANT(s)				
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)	
Norris	Timothy	-	Gales Ferry, Connecticut	
Raggon	Jeffrey	W.	Unicasville, Connecticut	
TITLE OF THE INVENTION (280 characters max)				
STABLE POLYMORPH OF N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE AND METHOD OR PRODUCTION				
CORRESPONDENCE ADDRESS				
Paul H. Ginsburg Pfizer Inc 235 East 42nd Street New York, NY 10017-5755				
ENCLOSED APPLICATION PARTS (check all that apply)				
<input checked="" type="checkbox"/> Specification 16 Number of Pages		<input checked="" type="checkbox"/> Claim(s) Number of Pages 6 pages		
<input type="checkbox"/> Drawing(s) Number of Sheets		<input checked="" type="checkbox"/> Other (specify) Abstract 1 page		
METHOD OF PAYMENT (check one)				
<input type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees		PROVISIONAL FILING FEE AMOUNT(\$)		
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- No.
 Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE 

DATE: November 11, 1999

TYPED or PRINTED NAME Israel Nissenbaum

REGISTRATION NO: 27,582

(if appropriate)

- Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

CERTIFICATE OF MAILING - EXPRESS MAIL

PFIZER DOCKET NO: PC10677

TITLE: STABLE POLYMORPH OF N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE AND METHOD OR PRODUCTION

APPLICANT: Timothy Norris et al.

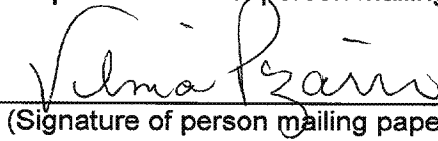
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Pfizer, Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755

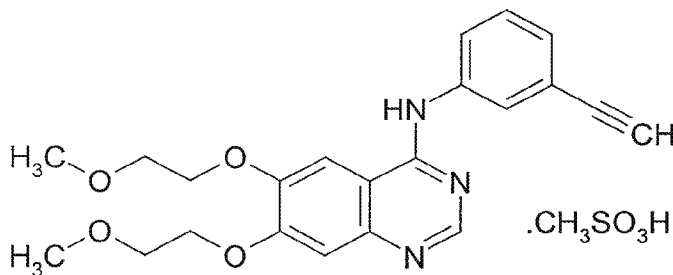
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STABLE POLYMORPH OF N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE AND METHOD OF PRODUCTION

Background of the Invention

5 The present invention relates to polymorphs and methods for the selective production of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochlorides, particularly in the stable polymorph form. These compounds are useful in the treatment of hyperproliferative disorders, such as cancers, in mammals. United States Patent No. 5,747,498, issued May 5, 1998, which is incorporated herein by reference in its entirety, refers, in Example 20, to [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride, which, the patent discloses, is an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders, such as cancers, in humans.

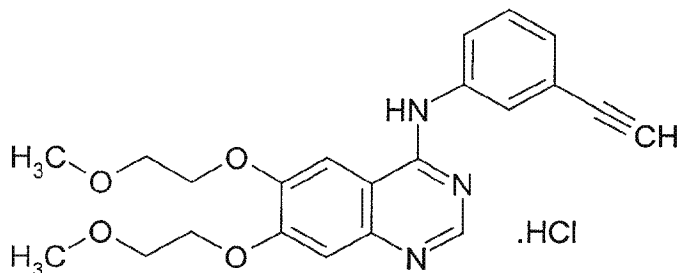
15 The mesylate compound (formula 1):



20 described in co-pending USSN 09/355534, filed April 8, 1999 (the entire disclosure of said application being incorporated herein by reference thereto), and assigned to a common assignee, is useful and more preferred for the treatment of proliferative disorders, with parenteral methods of administration, as compared to the hydrochloride compound, i.e. with greater effectiveness in solution. The mesylate compounds are more soluble in aqueous compositions than the hydrochloride compound, and thus the mesylate compounds are easily delivered according to parenteral methods of administration. The hydrochloride compound is however preferred with respect to solid administration such as with tablets and oral administration.

Summary of the Invention

30 It is accordingly an object of the present invention to provide a method for the production of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine in HCl form (Formula 2):



2 (Polymorph form A and B)

making it more suitable for tablet and oral administration and consisting essentially of the stable polymorphic form (polymorph form B) as well as the compound in such polymorph B form and the intermediate polymorph A in essentially pure form.

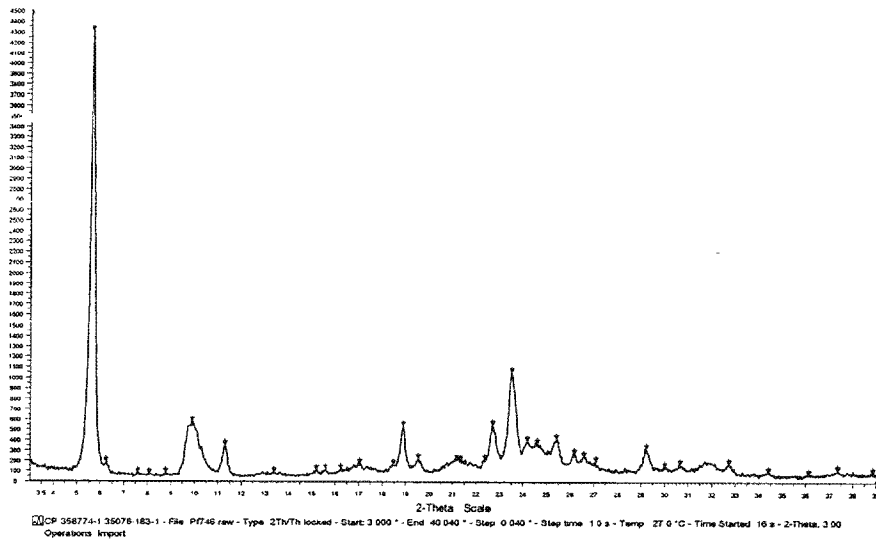
It is a further object of the present invention to provide such stable polymorph form B in a pharmaceutical orally administered composition.

Stability of the hydrochloride compound is of concern for use thereof in the treatment of patients for the enumerated conditions since variations will affect effective dosage level and administration. It has been discovered that the hydrochloride of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exists in two polymorph states, polymorph A and B. This contrasts with the mesylate compounds which exist in three polymorph states (mesylate polymorphs A, B and C). Polymorph B of the hydrochloride was found to be the thermodynamically most stable and desirable form and the present invention comprises the polymorph B compound in the substantially pure polymorphic B form and pharmaceutical compositions of the substantially pure form of polymorph B, particularly in tablet form and a method of the selective production of the compound.

The hydrochloride compound disclosed in the aforementioned patent actually comprised a mixture of the polymorphs A and B, which, because of its partially reduced stability (i.e., from the polymorph A component) was not more preferred for tablet form than the mesylate salt forms.

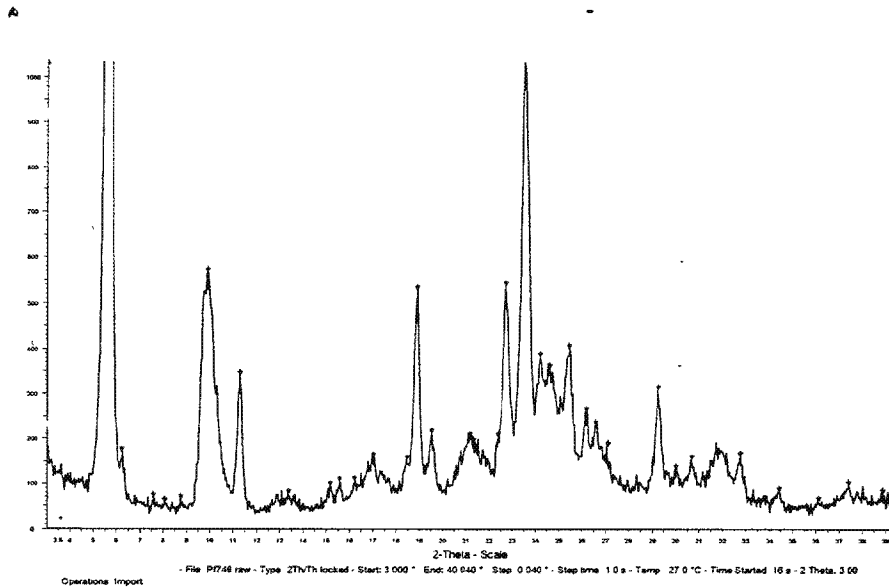
Specifically, the present invention relates to methods of producing the hydrochloride compound forms of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine and for producing the stable form B in high yield. The mesylate salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine has been discovered to exist in at least three polymorphic forms which have been designated A, B, and C, of increasing stability with different X-ray powder diffraction patterns. The X-ray powder diffraction patterns for the hydrochloride polymorph A (A₁ and A₂) and B (B₁ and B₂) forms are as follows (Graphs A₁ and B₁ are over a larger range to show the first peaks respectively and A₂ and B₂ are over a shorter range to show more detail):

X-ray Powder diffraction pattern of polymorph A, the thermodynamically less stable form:



A₁

5



A₂

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