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SUPERINDUSTRIA Y COMERCIO

Radicación: 00020444 00000033

Fecha (AMD): 2002-08-13 16:45:35

Traite: 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 2

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. **00.020.444.**

Solicitud de Patente de Invención Titulada:

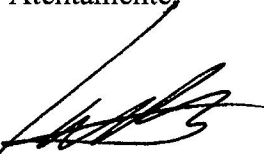
“PROCEDIMIENTO E INTERMEDIOS PARA
PREPARAR COMPUESTOS ANTICANCEROSOS
DERIVADOS DE QUINAZOLINA”.

Solicitante: **PFIZER PRODUCTS INC.**

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 516**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 318.000 pesos para cubrir la tasa correspondiente, según la Resolución 44691 del año 2001.

Atentamente,


CARLOS R. OLARTE
C.C. No. 79'782.747 de Bogotá
T.P. 74.295

Anexos: Recibo por \$ 318.000 pesos

FTT/P2000-000034 090802.DOC

174 102

NIT : 800176089-2

SUPERINTENDENCIA DE REGISTRO

Radicacion : 00020444 00000003
Fecha (AMD): 2002-06-13 16:45:35

Folios: 2

RECIBO OFICIAL DE CAJA : 02 - 37,064
FECHA : JUNIO 7 DE 2002

Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

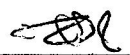
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	9226066	07/06/2002	28,841,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
			318,000.00
		TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

145 183

2005-02-17
375

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC,

Apoderado: Carlos reinaldo Olarte

Oficio:

12122

ASUNTO

Radicación: 00-20444

Trámite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- ◆capítulo descriptivo, folios 104 a 146;
- ◆capítulo reivindicatorio modificado, folios 147 a 157;
- ◆1° examen de forma, folios 168 y 169;
- ◆respuesta técnica al 1° examen de forma, folios 173 a 175;
- ◆solicitud de la cual se reivindica prioridad, junto con su traducción, folios 16 a 102;
- ◆2° examen de forma, folio 179;
- ◆solicitud del examen de patentabilidad 181 a 182.

Objeto de la invención:

El título de la invención es "PROCEDIMIENTO E INTERMEDIOS PARA PREPARAR COMPUESTOS ANTICANCEROSOS DERIVADOS DE QUINAZOLINA "

El objeto de la presente solicitud se refiere a procedimiento para obtener compuestos derivados de quinazolina los cuales son útiles para inhibir las erbB de proteínas tirosina quinasas oncogénicas.

Evaluación de la unidad de invención:

El artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."

La presente solicitud no tiene unidad inventiva presentando los siguientes grupos de invenciones:

- a) Reivindicaciones 1-10, 11-13 (parcialmente porque es una mezcla) y 17, las cuales se tratan de un proceso para obtener N(3-etilfenil)-4-

quinolinamina

- b) Reivindicaciones 14 a 16, 11 a 13 (parcialmente , porque es una mezcla de las dos invenciones), se refieren a un proceso para la obtener derivados de 6,7-dialcoxi-4-anilino- quinazolin

Por lo tanto la solicitud no cumple con el requisito exigido en el Art. 25 de la Decisión 486.

Determinación del estado de la técnica:

Considerando que la fecha de presentación de la primera solicitud de patente, de la cual se reivindica prioridad es 31-mar-99, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

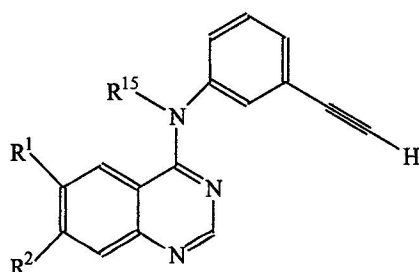
Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones establecidas en el artículo 17 de la misma.

Consultadas la fuente de información con que cuenta este despacho se encontraron los siguientes documentos, anteriores a la fecha de la prioridad invocada

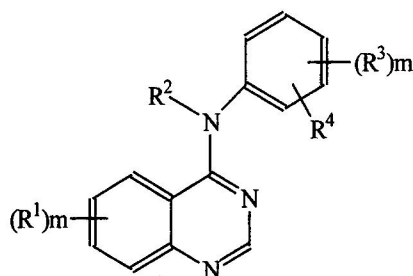
Item	Documento N°	Publicación	Titulo
D1	US 5747498	29-05-1996	Alkynyl and azido-substituted 4-anilinoquinazolines

Evaluación de Novedad:

Esta se evaluó por comparación entre lo reclamado como nuevo y los documentos citados arriba y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina, y se determino la solicitud en estudio basa su novedad en un proceso para obtener los compuestos conocidos del estado de la técnica con la fórmula (I).



-La anterioridad D1 describe los procesos para obtener los compuestos derivados alquinil y azido-4 sustituido 4-anilinoquinazolininas de formula (I):



Especialmente los procesos descritos especialmente en los ejemplos 2, 3, 7, 13 y 47, de esta anterioridad.

El proceso para la obtención de los compuestos de formula (I) reclamado en la solicitud en estudio, esta descrito en la anterioridad, y como proceso es igual al que descrito por la anterioridad, porque son llevados a cabo en las mismas etapas, para obtener los mismos compuestos, por lo tanto no se observa el aporte tecnológico al estado de la técnica.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado
D1	US 5747498	1 a 17	Novedad

En cumplimiento del artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL.

Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 17 FEB. 2005.

CONCEPTO TÉCNICO No. 222	EXAMINADOR TÉCNICO Código: 202012
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US005747498A

United States Patent [19]
Schnur et al.

[11] **Patent Number:** 5,747,498
 [45] **Date of Patent:** May 5, 1998

[54] **ALKYNYL AND AZIDO-SUBSTITUTED 4-ANILINOQUINAZOLINES**

[75] **Inventors:** Rodney Caughren Schnur, Noank, Conn.; Lee Daniel Arnold, Westborough, Mass.

[73] **Assignee:** Pfizer Inc., New York, N.Y.

[21] **Appl. No.:** 653,786

[22] **Filed:** May 28, 1996

Related U.S. Application Data

[63] Continuation-in-part of PCT/IB95/00436, Jun. 6, 1995.

[51] **Int. Cl.⁶** A61K 31/495; A61K 31/505; C07D 239/70; C07D 239/94

[52] **U.S. Cl.** 514/259; 544/283; 544/293

[58] **Field of Search** 544/283, 293; 514/259

[56] References Cited

U.S. PATENT DOCUMENTS

5,256,781	10/1993	Primean	514/259
5,457,105	10/1995	Barker	514/259
5,475,001	12/1995	Barker	514/259

FOREIGN PATENT DOCUMENTS

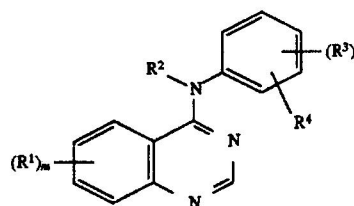
520722	12/1992	European Pat. Off.
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566226	10/1993	European Pat. Off.
602851	6/1994	European Pat. Off.
635498	1/1995	European Pat. Off.
WO92/20642	11/1992	WIPO
WO95/15758	6/1995	WIPO

Primary Examiner—Matthew V. Grumbling
Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; Bryan C. Zielinski

[57] ABSTRACT

The invention relates to compounds of the formula



and to pharmaceutically acceptable salts thereof, wherein R^1 , R^2 , R^3 , R^4 , n and m are as defined herein. The compounds of formula I are useful in the treatment of hyperproliferative diseases, such as cancer. The invention further relates to processes of making the compounds of formula I and to methods of using such compounds in the treatment of hyperproliferative diseases.

32 Claims, No Drawings

(6,7-diethoxy-quinazolin-4-yl)-(3-ethynyl-5-fluoro-phenyl)-amine;
 (6,7-diethoxy-quinazolin-4-yl)-(3-ethynyl-4-fluoro-phenyl)-amine;
 (6,7-diethoxy-quinazolin-4-yl)-(5-ethynyl-2-methyl-phenyl)-amine;
 (6,7-diethoxy-quinazolin-4-yl)-(3-ethynyl-4-methyl-phenyl)-amine;
 (6-aminomethyl-7-methoxy-quinazolin-4-yl)-(3-ethynyl-phenyl)-amine;
 (6-aminomethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylmethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylmethyl-7-ethoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylethyl-7-ethoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylmethyl-7-isopropoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylmethyl-7-propoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylmethyl-7-methoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine;
 (6-aminocarbonylethyl-7-isopropoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine; and
 (6-aminocarbonylethyl-7-propoxy-quinazolin-4-yl)-(3-ethynylphenyl)-amine.
 Other specific preferred compounds of formula I include the following:
 (6,7-diethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
 (3-ethynylphenyl)-[6-(2-hydroxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-1-yl]-amine;
 [6,7-bis-(2-hydroxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine;
 [6,7-bis-(2-methoxy-ethoxy)-quinazolin-1-yl]-(3-ethynylphenyl)-amine;
 (6,7-dimethoxyquinazolin-1-yl)-(3-ethynylphenyl)-amine;
 (3-ethynylphenyl)-(6-methanesulfonylamino-quinazolin-1-yl)-amine; and
 (6-amino-quinazolin-1-yl)-(3-ethynylphenyl)-amine.

The invention further relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

The invention further relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

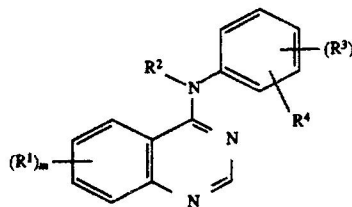
In a preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is cancer.

In another preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is said cancer is brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, gynecological or thyroid cancer.

In another preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is noncancerous.

In another preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is a benign hyperplasia of the skin or prostate.

The invention further relates to a process for preparing a compound of the formula



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

m is 1, 2, or 3;

each R¹ is independently selected from the group consisting of hydrogen, halo, hydroxy, hydroxyamino, carboxy, nitro, guanidino, ureido, cyano, trifluoromethyl, and -(C₁-C₄ alkylene)-W-(phenyl) wherein W is a single bond, O, S or NH;

or each R¹ is independently selected from R⁹ and (C₁-C₄)-alkyl substituted by cyano, wherein R⁹ is selected from the group consisting of R⁵, -OR⁶, -NR⁶R⁶, -C(O)R⁷, -NHOR⁵, -OC(O)R⁶, cyano, A and -YR⁵; R⁵ is C₁-C₄ alkyl; R⁶ is independently hydrogen or R⁵; R⁷ is R⁵, -OR⁶ or -NR⁶R⁶; A is selected from piperidino, morpholino, pyrrolidino, 4-R⁶-piperazin-1-yl, imidazol-1-yl, 4-pyridon-1-yl, -(C₁-C₄ alkylene)(CO₂H), phenoxy, phenyl, phenylsulfanyl, C₂-C₄ alkenyl, and -(C₁-C₄ alkylene)C(O)NR⁶R⁶; and Y is S, SO, or SO₂; wherein the alkyl moieties in R⁵, -OR⁶ and -NR⁶R⁶ are optionally substituted by one to three substituents independently selected from halo and R⁹, and wherein the alkyl moieties of said optional substituents are optionally substituted by halo or R⁹, with the proviso that two heteroatoms are not attached to the same carbon atom, and with the further proviso that no more than three R⁹ groups may comprise a single R¹ group;

or each R¹ is independently selected from -NHSO₂R⁵, phthalimido-(C₁-C₄)-alkylsulfonylamino, benzamido, benzenesulfonylamino, 3-phenylureido, 2-oxopyrrolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, and R¹⁰-(C₂-C₄)-alkanoylamino wherein R¹⁰ is selected from halo, -OR⁶, C₂-C₄ alkanoyloxy, -C(O)R⁷, and -NR⁶R⁶; and wherein the foregoing R¹ groups are optionally substituted from halo, C₁-C₄ alkyl, cyano, methanesulfonyl and C₁-C₄ alkoxy;

or two R¹ groups are taken together with the carbons to which they are attached to form a 5-8 membered ring that includes 1 or 2 heteroatoms selected from O, S and N;

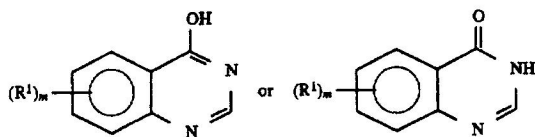
R² is hydrogen or C₁-C₆ alkyl optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkoxy, -NR⁶R⁶, and -SO₂R⁵;

n is 1 or 2 and each R³ is independently selected from hydrogen, halo, hydroxy, C₁-C₆ alkyl, -NR⁶R⁶, and C₁-C₄ alkoxy, wherein the alkyl moieties of said R³ groups are optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkoxy, -NR⁶R⁶, and -SO₂R⁵; and,

R⁴ is azido or -(ethynyl)-R¹¹ wherein R¹¹ is hydrogen or C₁-C₆ alkyl optionally substituted by hydroxy, -OR⁶, or -NR⁶R⁶, which comprises

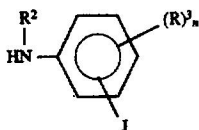
7

a) treating a compound of the formula



wherein R^1 and m are as defined above, with CCl_4 and $(C_6-C_{10}aryl)_3P$, optionally supported on an inert polymer, wherein the aryl moieties of said $(C_6-C_{10}aryl)_3P$ are optionally substituted by C_1-C_6 alkyl; and

b) treating the product of step a) with a compound of the formula



wherein R^2 , R^3 and n are as defined above, and J is Y or R^4 , wherein R^4 is as defined above and wherein Y is NH_2 , Br , I or trifluoromethanesulfonyloxy, with the proviso that when J is Y then the product of step b) must further be treated with an alkyne where Y is Br , I or trifluoromethanesulfonyloxy, or an azide where Y is NH_2 .

Preferred processes for preparing the compound of formula I include those wherein each aryl group is selected from phenyl, naphth-1-yl and naphth-2-yl.

Other preferred processes for preparing the compound of formula I include those wherein each Ar in $(C_6-C_{10}aryl)_3P$ is phenyl.

Other preferred processes for preparing the compound of formula I include those wherein said $(C_6-C_{10}aryl)_3P$ is supported on an inert polymer.

Other preferred processes for preparing the compound of formula I include those wherein said inert polymer is a divinylbenzene-cross-linked polymer of styrene.

The term "halo", as used herein, unless otherwise indicated, means chloro, bromo, iodo, or fluoro.

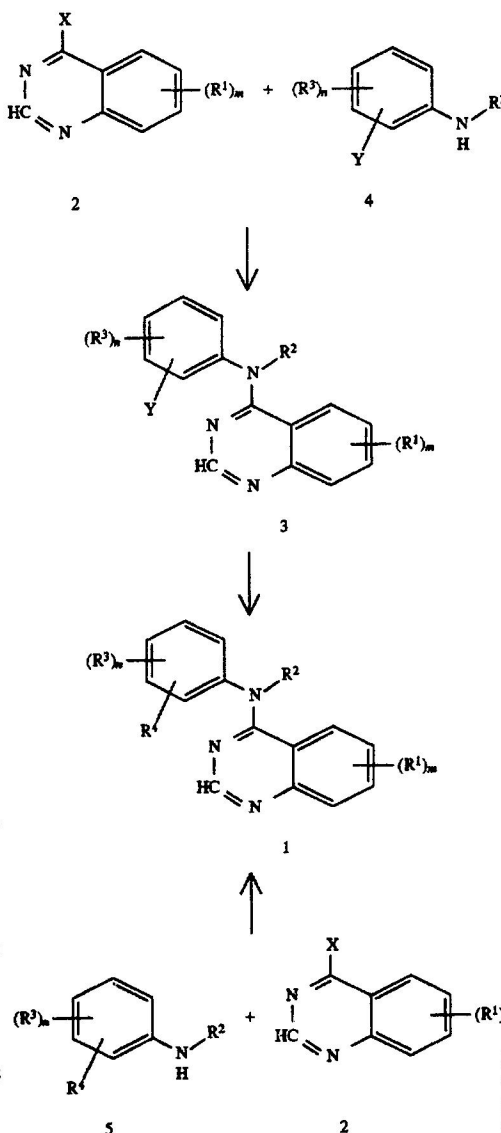
The term "alkyl", as used herein, unless otherwise indicated, means straight chained, cyclic or branched, saturated or unsaturated hydrocarbon moiety with the proviso that said alkyl must comprise three or more carbon atoms if it is branched or cyclic.

As used herein, the expression "reaction-inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Other features and advantages will be apparent from the specification and claims which describe the invention.

8

SCHEME



DETAILED DESCRIPTION OF THE INVENTION

The Formula I compounds, pharmaceutically acceptable salts and prodrugs thereof (hereafter the active compounds) may be prepared by any process known to be applicable to the preparation of chemically-related compounds.

In general the active compounds may be made from the appropriately substituted quinazoline using the appropriately substituted amine.

As shown in the Scheme the appropriate 4-substituted quinazoline 2 wherein X is a suitable displaceable leaving

cleavage reaction may be carried out, for example, by treatment of the protected quinazoline derivative with an alkali metal (C₁-C₄)alkylsulphide, such as sodium ethanethiolate or by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. The cleavage reaction may also, conveniently, be carried out by treatment of the protected quinazoline derivative with a boron or aluminum trihalide such as boron tribromide. Such reactions are preferably carried out in the presence of a reaction-inert solvent at a suitable temperature.

Compounds of formula I, wherein R¹ or R² is a (C₁-C₄)alkylsulphinyl or (C₁-C₄)alkylsulphonyl group are preferably prepared by oxidation of a formula I compound wherein R¹ or R² is a (C₁-C₄)alkylsulfanyl group. Suitable oxidizing agents are known in the art for the oxidation of sulfanyl to sulphinyl and/or sulphonyl, e.g., hydrogen peroxide, a peracid (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxy sulphate (such as potassium peroxy monosulphate), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible using the stoichiometric amount of oxidizing agent in order to reduce the risk of over oxidation and damage to other functional groups. In general, the reaction is carried out in a suitable solvent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature from about -25° to 50° C., preferably at or near ambient temperature, i.e., in the range of 15° to 35° C. When a compound carrying a sulphinyl group is desired a milder oxidizing agents should be used such as sodium or potassium metaperiodate, conveniently in a polar solvent such as acetic acid or ethanol. The compounds of formula I containing a (C₁-C₄)alkylsulphonyl group may be obtained by oxidation of the corresponding (C₁-C₄)alkylsulphinyl compound as well as of the corresponding (C₁-C₄)alkylsulfanyl compound.

Compounds of formula I wherein R¹ is optionally substituted (C₂-C₄)alkanoylamino, ureido, 3-phenylureido, benzamido or sulfonamido can be prepared by acylation or sulfonylation of a corresponding compound wherein R¹ is amino. Suitable acylating agents are any agents known in the art for the acylation of amino to acylamino, for example, acyl halides, e.g., a (C₂-C₄)alkanoyl chloride or bromide or a benzoyl chloride or bromide, alkanoyl acid anhydrides or mixed anhydrides (e.g., acetic anhydride or the mixed anhydride formed by the reaction of an alkanoyl acid and a (C₁-C₄)alkoxycarbonyl halide, for example (C₁-C₄)alkoxycarbonyl chloride, in the presence of a suitable base. For the production of those compounds of Formula I wherein R¹ is ureido or 3-phenylureido, a suitable acylating agent is, for example, a cyanate, e.g., an alkali metal cyanate such as sodium cyanate, or an isocyanate such as phenyl isocyanate. N-sulfonylations may be carried out with suitable sulfonyl halides or sulfonylanhydrides in the presence of a tertiary amine base. In general the acylation or sulfonylation is carried out in a reaction-inert solvent and at a temperature in the range of about -30° to 120° C., conveniently at or near ambient temperature.

Compounds of Formula I wherein R¹ is (C₁-C₄)alkoxy or substituted (C₁-C₄)alkoxy or R¹ is (C₁-C₄)alkylamino or substituted mono-N- or di-N,N-(C₁-C₄)alkylamino, are prepared by the alkylation, preferably in the presence of a suitable base, of a corresponding compound wherein R¹ is hydroxy or amino, respectively. Suitable alkylating agents include alkyl or substituted alkyl halides, for example, an optionally substituted (C₁-C₄)alkyl chloride, bromide or iodide, in the presence of a suitable base in a reaction-inert

solvent and at a temperature in the range of about 10° to 140° C., conveniently at or near ambient temperature.

For the production of those compounds of Formula I wherein R¹ is an amino-, oxy- or cyano-substituted (C₁-C₄)alkyl substituent, a corresponding compound wherein R¹ is a (C₁-C₄)alkyl substituent bearing a group which is displaceable by an amino-, alkoxy-, or cyano group is reacted with an appropriate amine, alcohol or cyanide, preferably in the presence of a suitable base. The reaction is preferably carried out in a reaction-inert solvent or diluent and at a temperature in the range of about 10° to 100° C., preferably at or near ambient temperature.

Compounds of Formula I, wherein R¹ is a carboxy substituent or a substituent which includes a carboxy group are prepared by hydrolysis of a corresponding compound wherein R¹ is a (C₁-C₄)alkoxycarbonyl substituent or a substituent which includes a (C₁-C₄)alkoxycarbonyl group. The hydrolysis may conveniently be performed, for example, under basic conditions, e.g., in the presence of alkali metal hydroxide as illustrated in the accompanying Examples.

Compounds of Formula I wherein R¹ is amino, (C₁-C₄)alkylamino, di-[(C₁-C₄)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(C₁-C₄)alkylpiperazin-1-yl or (C₁-C₄)alkylsulfanyl, may be prepared by the reaction, in the presence of a suitable base, of a corresponding compound wherein R¹ is an amine or thiol displaceable group with an appropriate amine or thiol. The reaction is preferably carried out in a reaction-inert solvent or diluent and at a temperature in the range of about 10° to 180° C., conveniently in the range 100° to 150° C.

Compounds of Formula I wherein R¹ is 2-oxopyrrolidin-1-yl or 2-oxopiperidin-1-yl are prepared by the cyclisation, in the presence of a suitable base, of a corresponding compound wherein R¹ is a halo-(C₂-C₄)alkanoylamino group. The reaction is preferably carried out in a reaction-inert solvent or diluent and at a temperature in the range of about 10° to 100° C., conveniently at or near ambient temperature.

For the production of compounds of Formula I in which R¹ is carbamoyl, substituted carbamoyl, alkanoyloxy or substituted alkanoyloxy, the carbamoylation or acylation of a corresponding compound wherein R¹ is hydroxy is convenient.

Suitable acylating agents known in the art for acylation of hydroxyaryl moieties to alkanoyloxyaryl groups include, for example, (C₂-C₄)alkanoyl halides, (C₂-C₄)alkanoyl anhydrides and mixed anhydrides as described above, and suitable substituted derivatives thereof may be employed, typically in the presence of a suitable base. Alternatively, (C₂-C₄)alkanoic acids or suitably substituted derivatives thereof may be coupled with a Formula I compound wherein R¹ is hydroxy with the aid of a condensing agent such as a carbodiimide. For the production of those compounds of Formula I in which R¹ is carbamoyl or substituted carbamoyl, suitable carbamoylating agents are, for example, cyanates or alkyl or arylisocyanates, typically in the presence of a suitable base. Alternatively, suitable intermediates such as the chloroformate or carbonylimidazolyl derivative of a compound of Formula I in which R¹ is hydroxy may be generated, for example, by treatment of said derivative with phosgene (or a phosgene equivalent) or carbonylimidazole. The resulting intermediate may then be reacted with an appropriate amine or substituted amine to produce the desired carbamoyl derivatives.

Compounds of formula I wherein R¹ is aminocarbonyl or a substituted aminocarbonyl can be prepared by the aminolysis of a suitable intermediate in which R¹ is carboxy.

The activation and coupling of formula I compounds wherein R¹ is carboxy may be performed by a variety of methods known to those skilled in the art. Suitable methods include activation of the carboxyl as an acid halide, azide, symmetric or mixed anhydride, or active ester of appropriate reactivity for coupling with the desired amine. Examples of such types of intermediates and their production and use in couplings with amines may be found extensively in the literature; for example M. Bodansky and A. Bodansky, "The Practice of Peptide Synthesis", Springer-Verlag, New York, 1984. The resulting formula I compounds may be isolated and purified by standard methods, such as solvent removal and recrystallization or chromatography.

The starting materials for the above described reaction schemes (e.g., amines, quinazolines and amine protecting groups) are readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, the preparation of 2,3-dihydro-1,4-benzoxazine derivatives are described in R. C. Elderfield, W. H. Todd, S. Gerber, Ch. 12 in "Heterocyclic Compounds", Vol. 6, R. C. Elderfield ed., John Wiley and Sons, Inc., N.Y., 1957. Substituted 2,3-dihydrobenzothiazinyl compounds are described by R. C. Elderfield and E. E. Harris in Ch. 13 of Volume 6 of the Elderfield "Heterocyclic Compounds" book.

Certain Formula I quinazolines can exist in solvated, as well as unsolvated forms, such as the hydrated forms. It is to be understood that the invention encompasses all such solvated, as well as unsolvated forms, which possess activity against hyperproliferative diseases.

A suitable pharmaceutically-acceptable salt of a compound of formula I is, for example, an acid-addition salt of a corresponding compound which is sufficiently basic, e.g., an acid-addition salt with, for example, an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, phosphoric, methanesulfonic, benzenesulfonic, trifluoroacetic, citric, lactic or maleic acid. A suitable pharmaceutically-acceptable base-addition salt of a compound of formula I which is acidic is an alkali metal salt, for example, a lithium, sodium or potassium salt; an alkaline earth metal salt, for example, a calcium or magnesium salt; an ammonium salt; or a salt with an organic base which affords a physiologically-acceptable cation for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered by filtration; by precipitation with a non-solvent, preferably an etheral or hydrocarbon solvent, followed by filtration and by evaporation of a solvent, or, in the case of aqueous solutions, by lyophilization.

Some of the compounds of Formula I have asymmetric carbon atoms. Such diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known per se., for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers mixtures and pure enantiomers are considered as part of the invention.

The active compounds of this invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. In particular, the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors), and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., BPH). It is, in addition, expected that a quinazoline of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

The active compounds may also be expected to be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions, activation or signalling events related to various protein tyrosine kinases, whose activity is inhibited by the agents of Formula I, are involved.

Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, and other glandular, macrophagal, epithelial, stromal, and blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases may be involved. In addition, compounds of Formula I may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases which are inhibited by compounds of Formula I.

The in vitro activity of the active compounds in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response, e.g., cancer) may be determined by the procedure detailed below.

Activity of the active compounds, in vitro, can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., Lys₃-Gastrin or polyGluTyr (4:1) random copolymer (I. Posner et. al., J. Biol. Chem. 267 (29), 20638-47 (1992)) on tyrosine by epidermal growth factor receptor kinase by a test compound relative to a control. Affinity purified, soluble human EGF receptor (96 ng) is obtained according to the procedure in G. N. Gill, W. Weber, *Methods in Enzymology* 146, 82-88 (1987) from A431 cells (American Type Culture Collection, Rockville, Md.) and preincubated in a microfuge tube with EGF (2 µg/ml) in phosphorylation buffer+vanadate (PBV: 50 mM HEPES, pH 7.4; 125 mM NaCl; 24 mM MgCl₂; 100 µM sodium orthovanadate), in a total volume of 10 µl, for 20-30 minutes at room temperature. The test compound, dissolved in dimethylsulfoxide (DMSO), is diluted in PBV, and 10 µl is mixed with the EGF receptor /EGF mix, and incubated for 10-30 minutes at 30° C. The phosphorylation reaction is initiated by addition of 20 µl ³³P-ATP/substrate mix (120 µM Lys₃-Gastrin (sequence in single letter code for amino acids, KKKGPWL EEEEEAYGWLDF), 50 mM Hepes pH 7.4, 40 µM ATP, 2 µCi γ-[³³P]-ATP) to the EGF/EGF mix and incubated for 20 minutes at room temperature. The reaction is stopped by addition of 10 µl stop solution (0.5M EDTA, pH 8; 2mM ATP) and 6 µl 2N HCl. The tubes are centrifuged at 14,000 RPM, 4° C., for 10 minutes. 35 µl of supernatant from each tube is pipetted onto a 2.5 cm circle of Whatman P81 paper, bulk washed four times in 5% acetic acid, 1 liter per wash, and then air dried. This results in the binding of substrate to the paper with loss of free ATP on washing. The [³³P] incorporated is measured by liquid scintillation counting. Incorporation in the absence of substrate (e.g., lys₃-gastrin) is subtracted from all values as a

background and percent inhibition is calculated relative to controls without test compound present.

Such assays, carried out with a range of doses of test compounds, allow the determination of an approximate IC_{50} value for the in vitro inhibition of EGFR kinase activity. Although the inhibitory properties of the compounds of Formula I vary with structural change as expected, the activity generally exhibited by these agents, determined in the manner described above, is in the range of IC_{50} =0.0001–30 μ M.

Activity of the active compounds, in vivo, can be determined by the amount of inhibition of tumor growth by a test compound relative to a control. The tumor growth inhibitory effects of various compounds are measured according to the methods of Corbett T. H., et al. "Tumor Induction Relationships in Development of Transplantable Cancers of the Colon in Mice for Chemotherapy Assays, with a Note on Carcinogen Structure", *Cancer Res.*, 35, 2434–2439 (1975) and Corbett, T. H., et al., "A Mouse Colon-tumor Model for Experimental Therapy", *Cancer Chemother. Rep. (Part 2)*, 5, 169–186 (1975), with slight modifications. Tumors are induced in the left flank by s.c. injection of 1×10^6 log phase cultured tumor cells (human MDA-MB-468 breast or human HN5 head and neck carcinoma cells) suspended in 0.10 ml RPMI 1640. After sufficient time has elapsed for the tumors to become palpable (2–3 mm in diameter) the test animals (athymic mice) are treated with active compound (formulated by dissolution in DMSO typically at a concentration of 50 to 100 mg/mL followed by 1:9 dilution into saline or, alternatively, 1:9 dilution into 0.1% Pluronic® P105 in 0.9% saline) by the intraperitoneal (ip) or oral (po) routes of administration twice daily (i.e., every 12 hours) for 5 consecutive days. In order to determine an anti-tumor effect, the tumor is measured in millimeters with Vernier calipers across two diameters and the tumor size (mg) is calculated using the formula: Tumor weight=(length $\times$ width) $^2/2$, according to the methods of Geran, R. I., et al. "Protocols for Screening Chemical Agents and Natural Products Against Animal Tumors and Other Biological Systems", Third Edition, *Cancer Chemother. Rep.*, 3, 1–104 (1972). Results are expressed as percent inhibition, according to the formula: Inhibition (%)=($TuW_{control}-TuW_{test}$)/ $TuW_{control} \times 100\%$. The flank site of tumor implantation provides reproducible dose/response effects for a variety of chemotherapeutic agents, and the method of measurement (tumor diameter) is a reliable method for assessing tumor growth rates.

Administration of the active compounds can be effected by any method which enables delivery of the compounds to the site of action (e.g., cancer cells). These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical administration, etc.

The amount of active compound administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgement of the prescribing physician. However an effective dosage is in the range of approximately 0.001–100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses. For an average 70 kg human, this would amount to 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day.

The composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream

or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Pharmaceutical compositions according to the invention may contain 0.1%–95% of the compound, preferably 1%–70%. In any event, the composition or formulation to be administered will contain a quantity of active compound in an amount effective to alleviate or reduce the signs in the subject being treated, i.e., hyperproliferative diseases, over the course of the treatment.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences., Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The hyperproliferative disease treatment described above may be applied as a sole therapy or may involve, in addition to the active compound, one or more other antitumor substances. Such conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment.

High pressure liquid chromatography (HPLC) used in the following examples and preparations was effected according to the following method unless modified in specific examples. Perkin-Elmer Pecosphere® 3 $\times$ 3C cartridge column (3mm $\times$ 3cm, C18; available from Perkin Elmer Corp., Norwalk, Conn. 06859) with a Brownlee (trademark) RP-8Newguard precolumn (7 micron, 3.2 mm $\times$ 15 mm, available from Applied Biosystems Inc. San Jose, Calif. 95134) which was previously equilibrated in pH 4.50, 200 mM ammonium acetate buffer. Samples were eluted using a linear gradient of 0–100% acetonitrile/pH4.50, 200 mM NH_4 acetate over 10 minutes with a flow rate of 3.0 mL/min. Chromatograms were generated over the range 240–400 nm using a diode array detector.

It should be understood that the invention is not limited to the particular embodiments shown and described herein, but

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that various changes and modifications may be made without departing from the spirit and scope of the invention as defined by the claims.

EXAMPLE 1

(4-Azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine Hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (250 mg, 1.12 mmol) and 4-azidoaniline hydrochloride (200 mg, 1.11 mmol) were refluxed in 10 mL of isopropyl alcohol for 0.5 hour, cooled and filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo, at 70° C., 392 mg (98%); mp 200°–205° C. (dec).

EXAMPLE 2

(6,7-Dimethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine Hydrochloride

4-Chloro-6,7-dimethoxyquinazoline (250 mg, 1.12 mmol) and 3-ethynylaniline (137 mg, 1.17 mmol) were refluxed in 10 mL of isopropyl alcohol for 0.5 hour, cooled and filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo, at 70° C., 338 mg (99%); mp 269°–270° C.

EXAMPLE 3

(6,7-Dimethoxyquinazolin-4-yl)-[3-(3'-hydroxypropyn-1-yl)phenyl]-amine

A mixture of (3'-bromophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine hydrochloride (250 mg, 0.591 mmol), tetrakis(triphenylphosphine)palladium (100 mg), propargyl alcohol (600 μ L), 7 mL of dry, nitrogen purged diethylamine and cuprous iodide (10 mg) was refluxed for 5 hours, cooled and filtered to afford solid title product which was washed two times with 2 mL of 50% diethylamine:methanol; 136 mg. The solid was recrystallized from methanol to give pure title product after drying, in vacuo, at 70° C., 73 mg (37%); mp 267°–268° C.

EXAMPLE 4

[3-(2'-Aminomethyl-ethynyl)phenyl]-(6,7-dimethoxyquinazolin-4-yl)-amine Hydrochloride

The title product of Example 3 (50 mg, 0.149 mmol), triphenylphosphine (60 mg, 0.225 mmol), phthalimide (165 mg, 1.12 mmol) and diethyl azodicarboxylate (36 μ L, 0.228 mmol) were stirred at room temperature in 3 mL of dry tetrahydrofuran for 16 hours. The reaction mixture was concentrated to a solid and flash chromatographed on silica gel eluted with 15% acetone:methylene chloride to afford pure solid [3-(2'-{phthalimidomethyl}-ethynyl)phenyl]-(6,7-dimethoxyquinazolin-4-yl)amine which was converted to its hydrochloride salt by addition of 1 mL of anhydrous 1M HCl in methanol followed by 3 mL of isopropyl alcohol. The salt was collected by filtration, dried and used immediately in the next step; 15 mg. This 15 mg, 0.0323 mmol was treated with 0.5 mL of hydrazine hydrate and 1 mL of methanol for 0.5 hours. The reaction mixture was evaporated, in vacuo, and the product isolated by flash chromatography eluted with 10% methanol in methylene chloride. Pure title product was isolated after conversion to its hydrochloride salt with 1 mL of 1M HCl in methanol, precipitation with isopropyl alcohol and diethyl ether and drying, in vacuo; 5.6 mg (47%) mp 275° C. dec.

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EXAMPLE 5

(3-Ethynylphenyl)-(6-nitroquinazolin-4-yl)-amine Hydrochloride

4-Chloro-6-nitroquinazoline (1.06 g, 5.00 mmol) and 3-ethynylaniline (1.00 g, 5.30 mmol) were refluxed in 10 mL of isopropyl alcohol for 3 hours, cooled and, after 16 hours at room temperature, filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo, at 70° C., 1.27 g (78%); mp 255°–256° C.

EXAMPLE 6

(6,7-Dimethoxyquinazolin-4-yl)-(4-ethynylphenyl)-amine

The title product was prepared in the following three step sequence without purification of the intermediates. 4-Chloro-6,7-dimethoxyquinazoline (250 mg, 1.113 mmol) and 4-iodoaniline (268 mg, 1.224 mmol) were refluxed in 10 mL of isopropyl alcohol for 3 hours, cooled to room temperature and filtered to afford solid (4-iodophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine hydrochloride which was washed with 10 mL of isopropyl alcohol and dried in vacuo at 70° C., 396 mg (76%). A mixture consisting of (4-iodophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine hydrochloride (250 mg, 0.564 mmol), tetrakis(triphenylphosphine)palladium (50 mg), trimethylsilylacetylene (160 μ L, 1.13 mmol), 4 mL of dry, nitrogen purged diethylamine and cuprous iodide (10 mg) was refluxed for 2 hours, cooled and concentrated in vacuo, to afford a residue which was partitioned between chloroform and 1N HCL. Solid [4-(2'-{trimethylsilyl}-ethynyl)phenyl]-(6,7-dimethoxyquinazolin-4-yl)amine formed at the interface of the two liquid phases and was filtered and dried in vacuo; 170 mg (80%).

[4-(2'-{Trimethylsilyl}ethynyl)phenyl]-(6,7-dimethoxyquinazolin-4-yl)amine (100 mg, 0.265 mmol) and anhydrous potassium carbonate (125 mg, 0.906 mmol) were stirred in 3 mL of methanol and 1 mL of water at room temperature for 2.5 hours. The reaction mixture was concentrated in vacuo, and partitioned between 20 mL of chloroform and 20 mL of 1N hydrochloric acid. The organic layer was dried with magnesium sulfate, filtered and vacuum evaporated to give the title product which was triturated with diethyl ether and dried in vacuo at 70° C.; 81 mg (90%) mp 239° C. dec.

EXAMPLE 7

(6,7-Dimethoxyquinazolin-4-yl)-(3-ethynyl-2-methylphenyl)-amine

The title product was prepared in the following three step sequence without purification of the intermediates. A mixture consisting of 3-bromo-2-methylaniline (1.00 g, 5.37 mmol), tetrakis(triphenylphosphine)palladium (200 mg), trimethylsilylacetylene (1.053 g, 10.75 mmol), 10 mL of dry, nitrogen purged diethylamine and cuprous iodide (910 mg) was refluxed for 16 hours, cooled and concentrated, in vacuo, to afford a residue which was partitioned between chloroform and 1N HCL. The organic layer was washed with brine, dried with magnesium sulfate and vacuum evaporated to yield a residue. 3-[2'-(trimethylsilyl)ethynyl]-2-methylaniline which was purified by flash chromatography on silica gel eluted with 1:1 hexanes:methylene chloride; 200 mg (18%).

4-Chloro-6,7-dimethoxyquinazoline (104 mg, 0.466 mmol) and 3-[2'-(trimethylsilyl)ethynyl]-2-methylaniline

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Handwritten notes and diagrams on the right margin of page 18. The notes include "no + over" and "H₁₂". There are also several small chemical structures and arrows drawn, including a structure that appears to be a quinazoline derivative with an ethynyl group and a methyl group, and arrows indicating a sequence of steps or transformations.

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(100 mg, 0.491 mmol) were refluxed in 3 mL of isopropyl alcohol for 16 hours, cooled to room temperature and filtered to afford a residue of solid {3-[2'-(trimethylsilyl)ethynyl]-2'-methylphenyl}-(6,7-dimethoxyquinazolin-4-yl)amine hydrochloride which was washed with 10 mL of isopropyl alcohol and triturated for 16 hours with diethyl ether. Thin layer chromatography on silica gel eluted with 9:1 chloroform:methanol indicated that the residue was impure product. The residue was purified by flash chromatography on silica gel eluted with 9:1 methylene chloride:methanol to afford after concentration and drying, in vacuo, pure product, 64 mg (33%). The product was dissolved in 3 mL of methanol and treated with 64 mg of anhydrous potassium carbonate at room temperature for 3 hours. The reaction mixture was concentrated in vacuo and partitioned between 1N HCl and chloroform. Solid title product formed at the interface of the two liquid phases and was filtered and dried, in vacuo; 40 mg (84%) mp 225° C. dec.

EXAMPLE 8

(6-Amino-quinazolin-4-yl)-(3-ethynylphenyl)-amine

(3-Ethynyl-phenyl)-(6-nitro-quinazolin-4-yl)-amine hydrochloride (500 mg, 1.50 mmol) was dissolved in 10 mL of formic acid and treated portion-wise with sodium dithionite (1.10 g, 6.28 mmol) at room temperature. After 2 hours the mixture was quenched with 120 mL of water and filtered. The filtrate was evaporated in vacuo to a residue which was dissolved in 100 mL of 1:1 methanol:chloroform, filtered and evaporated in vacuo to a second residue. This was triturated with 200 mL of 5% sodium bicarbonate for 30 minutes, filtered, washed with water and dried in vacuo for 16 hours. Flash chromatography on silica gel eluted with ethyl acetate afforded pure (6-aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine; 140 mg (34%); mp 165° C. dec.

EXAMPLE 9

(3-Ethynylphenyl)-(6-methanesulfonylaminoquinazolin-4-yl)-amine

The title product of Example 8 (100 mg, 0.384 mmol), pyridine (140 μ L, 1.68 mmol) and methanesulfonyl chloride (99 μ L, 1.26 mmol) were refluxed in 10 mL of 1,2-dichloroethane for 7 hours. The reaction mixture was cooled and evaporated in a vacuo to a residue which was triturated in 10 mL of 1N HCl, filtered and dried in vacuo to yield (3-ethynylphenyl)-(6-methanesulfonylaminoquinazolin-4-yl)amine; 102 mg (78%) mp 248° C. dec.

EXAMPLE 10

(3-Ethynylphenyl)-(6,7-methylenedioxyquinazolin-4-yl)-amine Hydrochloride

4-Chloro-6,7-methylenedioxyquinazoline (200 mg, 1.04 mmol) and 3-ethynylaniline (127 mg, 1.09 mmol) were refluxed in 5 mL of isopropyl alcohol for 16 hours, cooled and filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo at 70° C., 266 mg (79%); mp >350° C.

EXAMPLE 11

((6,7-Dimethoxyquinazolin-4-yl)-3-ethynyl-6-methylphenyl)-amine Hydrochloride

The title product was prepared in the following three step sequence without purification of the intermediates. A mixture

consisting of 4-bromo-2-nitrotoluene (1.50 g, 6.94 mmol) tetrakis(triphenylphosphine)palladium (750 mg), trimethylsilylacetylene (3.00 mL, 21.21 mmol) and cuprous iodide (20 mg) in 20 mL of nitrogen purged, dry diethylamine was refluxed for 2 hours, cooled and concentrated, in vacuo, to afford a residue which was partitioned between 100 mL of ethyl acetate and 100 mL of 1N HCl. The organic layer was washed two times with 50 mL of 1N HCl followed by brine, dried with magnesium sulfate and vacuum evaporated to a residue. The residue was dissolved in 10 mL of ethyl acetate and diluted with 200 mL of petroleum ether. The solids were filtered off and the oil, obtained upon vacuum evaporation of the filtrate, solidified to give 4-[2'-(trimethylsilyl)ethynyl]-2-nitrotoluene. This product was reduced to the amino product by treatment with iron powder (1.76 g, 98.5 mmol) in 30 mL of methanol and 5 mL of concentrated hydrochloric acid at 80° C. for 2 hours. The cooled reaction mixture was filtered through Celite® and the filtrate was evaporated in vacuum. The residue was partitioned between ethyl acetate and 5% aqueous sodium bicarbonate. The organic layer was washed with brine, dried with magnesium sulfate, filtered and vacuum evaporated to yield an oil, 5-[2'-(trimethylsilyl)ethynyl]-2-methylaniline which solidified upon standing; 1.37 g.

The above product (185 mg, 0.909 mmol) and 4-chloro-6,7-dimethoxyquinazoline (200 mg, 0.890 mmol) were refluxed in tert-butyl alcohol for 16 hours. After cooling the reaction mixture was filtered to yield pure [2-methyl-5-(2'-(trimethylsilyl)ethynyl)-phenyl]-(6,7-dimethoxyquinazolin-4-yl)-amine hydrochloride after washing with ether and drying in vacuum; 326 mg (85%). The trimethylsilyl group was removed by dissolving the above product in 5 mL of methanol and 1 mL of water and treatment with potassium carbonate (320 mg). After stirring for 1 hour the mixture was filtered and concentrated in vacuo. The residue thus obtained was partitioned between 100 mL of methylene chloride and 100 mL of 1N HCl. The aqueous layer was extracted with an additional 100 mL of methylene chloride. The pooled organic layers were dried with magnesium sulfate, filtered and vacuum evaporated to a residue which was dissolved in anhydrous 1N HCl in methanol, concentrated and precipitated with ether. The solid title product was collected by filtration and washed with diethyl ether then dried in vacuo at 70° C.; 236 mg (88%) mp 266°-267° C.

EXAMPLE 12

(3-Ethynylphenyl)-(7-nitroquinazolin-4-yl)-amine Hydrochloride

4-Chloro-7-nitroquinazoline (7.97 g, 38.0 mmol) and 3-ethynylaniline (4.54 g, 38.8 mmol) were refluxed in 125 mL of tert-butyl alcohol for 3 hours, cooled to room temperature and filtered to afford the title product as a solid which was washed with 10 mL of isopropyl alcohol and dried in vacuo at 70° C., 9.95 g (80%); mp 209°-210° C. dec.

EXAMPLE 13

(3-Ethynylphenyl)-[6-(4'-toluenesulfonylamino)-quinazolin-4-yl]-amine Hydrochloride

The title product of example 8 (0.201 mg, 0.774 mmol) and 4-toluenesulfonyl chloride (0.441 mg, 2.31 mmol) were refluxed in 3 mL of 1,2-dichloroethane and 0.5 mL of pyridine for 5 minutes. The reaction mixture was cooled to

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room temperature, diluted with 75 mL of ethyl acetate and washed two times with 75 mL of water once with 75 mL of 3% sodium bicarbonate and once with 75 mL of brine. The organic layer was dried with magnesium sulfate, filtered and vacuum evaporated to a residue which was purified by chromatography using a Chromatotron (trademark) eluted with ethyl acetate, to afford solid title product; 86.7 mg (27%) mp 220°–222° C.

EXAMPLE 14

(3-Ethynylphenyl)-{6-[2'-phthalimido-ethan-1'-ylsulfonylamino]quinazolin-4-yl}-amine Hydrochloride

The title product of example 8 (0.20 mg, 0.768 mmol) and 2-phthalimido-1-ethanesulfonyl chloride (0.615 mg, 2.25 mmol) were refluxed in 2 mL of 1,2-dichloroethane and 0.5 mL of pyridine for 16 hours, cooled to room temperature, diluted with 100 mL of chloroform and washed with 50 mL of 3% sodium bicarbonate and 50 mL of brine. The organic layer was dried with magnesium sulfate, filtered and vacuum evaporated to a residue which was dissolved in minimal methylene chloride and precipitated with petroleum ether, 188 mg. The precipitate was purified by chromatography using Chromatotron® eluted with ethyl acetate, to afford the title product as a solid; 53.4 mg (14%) mp 197°–200° C.

EXAMPLE 15

(3-Ethynylphenyl)-(6-guanidinoquinazolin-4-yl)-amine Hydrochloride

The title product of example 8, (0.302 mg, 1.16 mmol) and 3,5-dimethylpyrazole-1-carboxamidine (0.328 mg, 2.36 mmol) were refluxed in 10 mL of 1,2-dichloroethane and 0.97 mL of acetic acid for 24 hours, cooled to room temperature and filtered to yield the crude acetate of the title product. The product was dissolved in 35 mL of methanol and treated with 15 mL of anhydrous 1N HCl in methanol for 15 minutes and then precipitated with 75 mL of diethyl ether. Solid title product was collected by filtration and dried in vacuo at 70° C.; 91.2 mg (23%) mp >400° C.

EXAMPLE 16

(7-Aminoquinazolin-4-yl)-(3-ethynylphenyl)-amine

The title product of example 12 (1.039 g, 3.18 mmol) was dissolved in 50 mL of tetrahydrofuran, 10 mL of methanol and 5 mL of chloroform at 50° C. Sodium dihydrogen phosphite (NaH₂PO₂, 3.822 g, 36 mmol) and 10% palladium on carbon (0.19 g) were added followed by dropwise addition of 10 mL of water. When 3 mL of water had been added the mixture became noticeably more homogeneous. After 1 hour the mixture was filtered through Celite. The Celite was washed thoroughly with methanol and chloroform. The combined organic solutions were vacuum evaporated to a residue which was triturated with water, 3% aqueous sodium bicarbonate and filtered. The solid title product was washed with water then diethyl ether and dried in vacuo, 1.054 gm (127%, wet). A portion of the above product was recrystallized from a minimum amount of hot ethanol and water to give, after removal of a small first crop of impure material, pure title product, (43%), mp 180° C. (dec).

EXAMPLE 17

(3-Ethynylphenyl)-(7-methoxyquinazolin-4-yl)-amine Hydrochloride

4-Chloro-7-methoxyquinazoline (274 mg, 3.72 mmol) and 3-ethynylaniline (436 mg, 3.72 mmol) were refluxed in

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15 mL of tert-butyl alcohol for 3 hours, cooled and filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo at 70° C., 977 mg (84%); mp 229°–231° C.

EXAMPLE 18

(6-Carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine Hydrochloride

4-Chloro-6-carbomethoxyquinazoline (100 mg, 0.450 mmol) and 3-ethynylaniline hydrochloride (53.4 mg, 0.456 mmol) were refluxed in 2 mL of tert-butyl alcohol for 2 hours, cooled, diluted with 2 mL of isopropyl alcohol and filtered to afford solid title product which was washed with 10 mL of diethyl ether and dried, in vacuo, at 70° C., 122 mg (80%); mp 232°–233° C. (dec).

EXAMPLE 19

(7-Carbomethoxyquinazolin-4-yl)-(3-ethynylphenyl)-amine Hydrochloride

4-Chloro-7-carbomethoxyquinazoline (202 mg, 0.907 mmol) and 3-ethynylaniline (110 mg, 0.939 mmol) were refluxed in 4 mL of tert-butyl alcohol for 2 hours, cooled, diluted with 4 mL of isopropyl alcohol and filtered to afford solid title product which was washed with 10 mL of diethyl ether and dried, in vacuo, at 70° C., 248 mg (80%); mp 219.5°–221° C.

EXAMPLE 20

[6,7-Bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine Hydrochloride

3-Ethynylaniline (37 mg, 0.32 mmol), and 4-chloro-6,7-bis-(2-methoxy-ethoxy)quinazoline (90 mg, 0.29 mmol) were added to isopropanol (1.5 mL) containing pyridine (25 µL, 0.32 mmol) and the mixture was refluxed 4 hours under an atmosphere of dry nitrogen. The solvent was removed, in vacuo, and the residue partitioned between 10% methanol in CHCl₃ and saturated aqueous NaHCO₃. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was flash chromatographed on silica using 30% acetone in hexanes to afford 81 mg of the free base of the title product as a pale yellow solid. The free-base was dissolved in a minimum volume of CHCl₃, diluted with several volumes of ether, and titrated with 1M HCl in ether to precipitate the title product as its hydrochloride salt; 90 mg; 71%; mp 228°–230° C.

EXAMPLE 21

(3-Azidophenyl)-(6,7-dimethoxyquinazolin-4-yl)-amine

4-Chloro-6,7-dimethoxyquinazoline (5.01 g, 22.3 mmol) was added in portions, over 1.5 hours, to m-phenylenediamine (2.66 g, 24.6 mmol) in refluxing isopropanol (100 mL) under an atmosphere of dry nitrogen. After the addition was complete the mixture was heated at reflux for 4 hours. The mixture was cooled to 20° C., and the precipitate was filtered, washed with chilled isopropanol and dried in vacuo to afford 6.97 g (93%) of (3-aminophenyl)-(6,7-dimethoxyquinazolin-4-yl)amine hydrochloride (LC-MS: 297 (MH⁺)). To a solution of the above product (50 mg, 0.169 mmol) in 80% acetic acid/H₂O (2 mL), at 0° C., was added a solution of NaNO₂ (18.4 mg, 0.186 mmol) in H₂O (100 µL). After stirring 10 minutes at 0° C. a solution of

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carbon tetrachloride were refluxed for 16 hours. The reaction mixture was concentrated in vacuo to a residue which was diluted with 3 mL of isopropyl alcohol and 3-ethynylaniline (66 mg, 0.563 mmol) and refluxed for 3 hours. The cooled reaction mixture was filtered to afford solid title product which was washed with 10 mL of isopropyl alcohol and dried in vacuo at 70° C., 140 mg (75%); mp 269°-270° C.

EXAMPLE 43

(6,7-Diethoxy-quinazolin-4-yl)-(3-ethynyl-2-methyl-phenyl)-amine Hydrochloride

4-Chloro-6,7-diethoxyquinazoline (200 mg, 0.792 mmol) and 3-(2'-trimethylsilylethynyl-2-methyl-aniline (168 mg, 0.871 mmol) in 4 mL of tert-butyl alcohol was refluxed for 16 hours. The cooled reaction mixture was diluted with 5 mL of ethyl ether and filtered to afford solid (6,7-diethoxy-quinazolin-4-yl)-(3-(2'-trimethylsilyl-ethynyl)-2-methyl-phenyl)-amine hydrochloride which was washed with 10 mL of ethyl ether and dried in vacuo at 70° C. This material was desalted directly by treatment with 2 mL of methanol containing 1 drop of water and 100 mg of potassium carbonate for 0.5 hours. The heterogeneous reaction mixture was filtered through Celite and vacuum evaporated to a residue which was dissolved in excess 1N HCl in methanol, precipitated with ethyl ether, filtered and dried in vacuo at 70° C. to afford the title product; 160 mg (75%); mp 258°-259.5° C.

EXAMPLE 44

(3-Ethynyl-phenyl)-(6-methyl-quinazolin-4-yl)-amine Hydrochloride

6-Methyl-quinazolin-4-one (350 mg, 2.18 mmol) was added to a suspension of polymer-supported triphenylphosphine (from Fluka, 3.63 g of about 3 mmol P/g resin; 10.9 mmol) in a mixture of CCl₄ (3.35 g, 21.80 mmol) and 1,2-dichloroethane (10 mL). The mixture was heated to 60° C. for 2 hours and then the polymer was removed by filtration and washed with dichloroethane. The filtrate was collected in a flask containing 3-ethynyl-aniline (0.644 g, 2.18 mmol) and concentrated to 5 mL by evaporation. After 4 hours reflux under N₂, followed by cooling to 20° C., the title product was collected by filtration (551 mg; 86%; M.P. 256°-257° C.; LC-MS: 260 (MH⁺); anal. RP-HPLC RT: 4.41 min).

EXAMPLE 45

2-{2-[4-(3-Ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethylsulfanyl}-propionic Acid Ammonium Salt

The title product of Example 34 (150 mg, 0.34 mmol) was added to a solution of thiolactic acid (100 μL, 1.14 mmol) and KOH (150 mg, 2.7 mmol) in degassed DMF (5 mL)/H₂O (0.5 mL). The reaction mixture was stirred at 50° C. under an atmosphere of N₂ for 72 hours and then cooled to room temperature. The pH of the mixture was adjusted to about 4.0 with acetic acid and then partitioned between CHCl₃ and brine. The organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by preparative RP18 HPLC utilizing a gradient of 15% to 100% CH₃CN/pH 4.5, 50 mM ammonium acetate followed by lyophilization of the appropriate pure fractions to afford the title product (28 mg; 18%; M.P. 95°-103° C. (dec); LC-MS: 468 (MH⁺); anal. RP-HPLC RT: 3.57 min).

EXAMPLE 46

{2-[4-(3-Ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethylsulfanyl}-acetic Acid Ammonium Salt

The title product was prepared from the title product of Example 34 and mercaptoacetic acid according to the

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method of Example 45. (3%; LC-MS: 454 (MH⁺); anal. RP-HPLC RT: 3.37 min).

EXAMPLE 47

4-(3-Ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-ol

This product was isolated as a more lipophilic product (by preparative RP18 HPLC) from the reaction used to generate the title product of Example 46 (5%; LC-MS: 336 (MH⁺); anal. RP-HPLC RT: 3.60 min).

EXAMPLE 48

(3-ethynyl-phenyl)-[7-(2-methoxy-ethoxy)-6-vinyloxy-quinazolin-4-yl]-amine and [6-(2-ethoxy-ethoxy)-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-3-ethynyl-phenyl)-amine Hydrochloride

The title product of Example 30 (107 mg, 0.245 mmol) was treated with sodium ethoxide (0.582 mmol) in refluxing ethanol (3 mL) for 24 hours. The solvent was removed in vacuo and the product was isolated by flash chromatography on silica using 10% acetone/CH₂Cl₂ to provide 30 mg of the 6-vinyloxy product (33%; M.P. 113°-114° C.; LC-MS: 362 (MH⁺); anal. RP-HPLC RT: 4.84 min). The 6-(2-ethoxy-ethoxy) derivative eluted as a more polar product (45 mg) and was converted to its HCl salt according to the procedure described for Example 28 (43%; M.P. 220°-225° C. (dec); LC-MS: 408 (MH⁺); anal. RP-HPLC RT: 4.35 min).

EXAMPLE 49

4-(3-Ethynyl-phenylamino)-7-(2-methoxy-ethoxy)-quinazolin-6-ol Hydrochloride

(3-Ethynyl-phenyl)-[7-(2-methoxy-ethoxy)-6-vinyloxy-quinazolin-4-yl]-amine (20 mg; from Example 48) was hydrolyzed by treatment with 6M HCl/methanol (30:70; 3 mL) at 50° C. for 5 days. The solution was concentrated in vacuo, and the residue was partitioned between CHCl₃ and brine at a pH of about 7. The organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to afford the title product as its free base (15 mg), which was converted to its HCl salt according to the procedure described for Example 28 (M.P. 135°-150° C. (dec); LC-MS: 336 (MH⁺); anal. RP-HPLC RT: 3.77 min).

EXAMPLE 50

1-{2-[4-(3-Ethynyl-phenylamino)-6-(2-methoxy-ethoxy)-quinazolin-7-yloxy]-ethyl}-1H-pyridin-4-one Hydrochloride

NaH (30 mg of 60% in mineral oil, 0.77 mmol) was added to anhydrous DMF (2.0 mL) followed by pyrid-4-one (79 mg, 0.83 mmol). The mixture was stirred 40 minutes at 22° C. until all solids dissolved and the evolution of H₂ ceased. The title product of Example 34 (120 mg, 0.28 mmol) and tetrabutylammonium iodide (15 mg) were added and the reaction mixture was stirred at 22° C. for 7 days under N₂. Additional pyrid-4-one (79 mg) and NaH (30 mg of 60%) were dissolved in DMF (2 mL) and the solution was added to the reaction mixture. After another 4 days stirring the mixture was partitioned between CHCl₃ and brine. The organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica utilizing 10% methanol/CH₂Cl₂ to afford 65 mg of the free base of the title product which was converted to the mono-hydrochloride salt according to the procedure described for Example 28 (66 mg; M.P. 240°-248° C. (dec); LC-MS: 457 (MH⁺); anal. RP-HPLC RT: 3.23 min)