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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-008204-00002-0000
Fec: 2006-05-24 10:40:52 Dep. 2020 NUECREACIONES
Tm. 11 PATENTEYB
Evo: 378 FASENACIONAL
Act 329 CTINFORMACION Folios: 184

E. _____ S. _____ D. _____

Re: P1.-WYETH HOLDINGS CORPORATION.-Solicitud de Patente de Invención en Fase Nacional PCT para "USO DE UNA COMBINACIÓN DE UN INHIBIDOR DE LA CINASA DEL RECEPTOR DEL FACTOR DE CRECIMIENTO EPIDÉRMICO Y AGENTES CITOTÓXICOS PARA EL TRATAMIENTO E INHIBICIÓN DEL CÁNCER".-Clase A61K 45/06.-Expediente número 06.008.204.-

1. Me refiero a la solicitud de patente de la referencia, radicada ante ese Despacho el 30 de Enero de 2006.
2. Atentamente me permito presentar a usted documentos completos del Reporte de Búsqueda Internacional y la Opinión Escrita de la Autoridad de Búsqueda Internacional, expedidos el 18 de Enero de 2006, correspondiente a la solicitud internacional número PCT/US2004/024478, actualmente en trámite de Fase Nacional en ese despacho, bajo el número de la referencia y los Documentos anexos a dicho Reporte de Búsqueda Internacional.
3. En consecuencia, ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


ALICIA LLOREDA RICAURTE

T.P. 53.215

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL
(PCT Artículo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente AM101430	PARA FUTURAS ACCIONES ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el ítem 5 a continuación.	
Solicitud internacional No. PCT/US2004/024478	Fecha de registro internacional (día/mes/año) 28/07/2004	Fecha de Prioridad (Primera) (día/mes/año) 01/08/2003
Solicitante WYETH HOLDINGS CORPORATION		
Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante Según el Artículo 18. Una copia será transmitida a la Oficina Internacional. Este Reporte de Búsqueda Internacional consta de un total de <u>5</u> hojas. ☐ También está acompañado de una copia de cada documento técnico anterior citado en este reporte.		
1. Bases del reporte a. Respecto al lenguaje, la búsqueda internacional se llevó a cabo según la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otro modo en este ítem. ☐ la búsqueda internacional se llevó a cabo según la traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23.1(b)). b. ☐ Respecto a una secuencia de ácido nucleótido y/o amino revelado en la solicitud internacional, ver casillo 1. 2. ☒ Ciertas reivindicaciones no pudieron localizarse (Ver Recuadro II). 3. ☒ Falta unidad de invención (ver Recuadro III). 4. Respecto al título, ☒ El texto es aprobado según lo presenta el solicitante. ☐ Esta Autoridad ha establecido que el texto se lea así: 5. Respecto al resumen, ☒ El texto es aprobado según lo presenta el solicitante. ☐ Esta Autoridad ha establecido el texto de acuerdo con la Norma 38.2(b), según aparece en el Recuadro III. El solicitante puede, un mes después de la fecha de haber enviado por correo este reporte de búsqueda internacional, presentar comentarios a esta Autoridad. 6. Respecto a los dibujos, a. la figura de los dibujos que se publicará con el resumen es la Figura No. _____ ☐ como lo sugirió el solicitante. ☐ como lo sugirió la Autoridad, porque el solicitante no sugirió una figura. ☐ como lo sugirió la autoridad, porque esta figura caracteriza mejor a la invención- b. ☒ Ninguna de las figuras se publicará en el resumen.		

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud internacional No.
PCT/US2004/024478

Casilla II Observaciones donde ciertas reivindicaciones fueron inescrutables (Continuación del Item 2 de la primera hoja)

Este reporte de búsqueda internacional no ha sido establecido respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones:

1. ☒ Reivindicaciones Nos.:
porque se relacionan con un asunto que no es necesario que esta Autoridad busque, a saber:

Aunque las reivindicaciones 10 y 11 están dirigidas al método de tratamiento del cuerpo humano/animal, la búsqueda ha sido llevada a cabo y basada en los efectos de los compuesto/composición.

2. ☐ Reivindicaciones Nos.:

porque se relacionan con partes de la solicitud internacional que no cumplen con los requisitos prescritos hasta tal grado que no se puede llevar a cabo una búsqueda internacional significativa, específicamente:

3. ☐ Reivindicaciones No.:
porque son reivindicaciones dependientes y no están diseñadas de acuerdo con la segunda y tercera oración de la Regla 6.4(a).

Casilla No. III Observaciones donde falta unidad de invención (Continuación del Item 3 de la primera hoja)

Esta Autoridad de Búsqueda Internacional encontró invenciones múltiples en esta solicitud internacional, así:
ver hoja adicional

1. ☐ Puesto que todos los derechos de búsqueda adicionales requeridos fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre todas las reivindicaciones investigables.
2. ☐ Puesto que todas las reivindicaciones investigables pudieron investigarse sin esfuerzo que justifique derechos adicionales, esta Autoridad no solicitó pago de derechos adicionales.
3. ☐ Puesto que sólo algunos de los derechos de búsqueda adicionales fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre únicamente aquellas reivindicaciones para las cuales se pagaron derechos, específicamente las reivindicaciones Nos.:
4. ☒ El solicitante no pagó oportunamente los derechos de búsqueda adicionales requeridos. Por consiguiente, este informe de búsqueda internacional se restringe a la primera invención mencionada en las reivindicaciones; está cubierto por las reivindicaciones Nos.:
1-5, 10, 11 (todas parcialmente), 6

Comentario sobre Protesta ☐ Los derechos de búsqueda adicionales estuvieron acompañados por la protesta del solicitante.

☐ El pago de los derechos de búsqueda adicionales no estuvo acompañado por una protesta.

Información Continuada de PCT/ISA/210

Esta Autoridad de Búsqueda Internacional encontró múltiples (grupos de) invenciones en esta solicitud internacional, como sigue:

1. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 6

Una combinación de un agente citotóxico que es capecitabina y un inhibidor de quinasa EGFR.

2. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 7

Una combinación de un agente citotóxico que es paclitaxel y un inhibidor de quinasa EGFR.

3. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 8

Una combinación de un agente citotóxico que es 5-FU y un inhibidor de quinasa EGFR.

4. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 12

Una combinación de un agente citotóxico que es FOLFIRI y un inhibidor de quinasa EGFR.

5. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 13

Una combinación de un agente citotóxico que es FOLFOX4 y un inhibidor de quinasa EGFR.

6. Reivindicaciones: 1-5, 10, 11 (todas parcialmente), 9

Una combinación de un agente citotóxico que es es cisplatín y un inhibidor de quinasa EGFR.

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/US2004/024478

A. CLASIFICACION DE MATERIA INV. A61K45/06 A61K 31/47 A61P35/00		
Según la Clasificación de Patentes Internacional (CPI) o según la clasificación nacional y la CPI		
B. CAMPOS BUSCADOS		
Documentación mínima buscada (sistema de clasificación seguido de símbolos de clasificación)		
A61K		
Documentación buscada fuera de documentación mínima hasta donde dichos documentos se incluyan en los campos buscados		
Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea práctico, buscar términos usados)		
EPO-Interno, Base CHEM ABS, Base WPI, BIOSIS		
C. DOCUMENTOS CONSIDERADOS RELEVANTES		
Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
X	WO 03/020266 A (WYETH) 13 de marzo de 2003 (2003-03-13) página 8, parágrafo 2-página 9, parágrafo 1	1-6,10, 11
X	WO 03/050090 A (WYETH HOLDINGS CORPORATION) 19 de junio de 2003 (2003-06-19) página 34, parágrafo 2 página 36, parágrafo 2	1-5,10, 11
X	US 6 384 051 B1 (FROST PHILIP ET AL) 7 de mayo de 2002 (2002-05-07) citado en la solicitud columna 17, parágrafo 3	1-5,10, 11
☐ En el recuadro C se enumeran más documentos. ☒ En el anexo se enumeran miembros de la familia de patentes.		
* Categorías especiales de documentos citados:		
'A' documento que define el estado general de la técnica el cual no se considera de relevancia		
'E' documento anterior pero publicado en o después de la fecha de presentación internacional		
'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)		
'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios		
'I' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada		
'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustenta la invención		
'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo		
'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica		
'Z' documento miembro de la misma familia de patentes		
Fecha de la terminación real de la búsqueda internacional 18 de Enero de 2006		Fecha de envío por correo del reporte de búsqueda internacional 13.04.2006
Nombre y dirección de correo de ISA European Patent Office, P.B. 5818 Patentlaan 2 NL- 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Funcionario autorizado Leherte, C

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/US2004/024478

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
WO 03020266	A 13-03-2003	AT 314069 T BR 0211769 A CA 2455126 A1 CN 1538842 A DK 1414438 T3 EP 1414438 A1 HK 1061204 A1 HU 0401089 A2 JP 2005505549 T MX PA04001118 A NO 20040558 A ZA 200401801 A	15-01-2006 27-07-2004 13-03-2003 20-10-2004 27-03-2006 06-05-2004 03-03-2006 28-09-2004 24-02-2005 20-05-2004 06-02-2004 06-06-2005
WO 03050090	A 19-06-2003	AU 2002359489 A1 BR 0214485 A CA 2467573 A1 CN 1659145 A EP 1440531 A1 HU 0402228 A2 JP 2005514384 T MX PA04004969 A	23-06-2003 14-09-2004 19-06-2003 24-08-2005 25-08-2004 28-02-2005 19-05-2005 11-08-2004
US 6384051	B1 07-05-2002	NINGUNA	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101430	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2004/024478	International filing date (day/month/year) 28/07/2004	(Earliest) Priority Date (day/month/year) 01/08/2003
Applicant WYETH HOLDINGS CORPORATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).3. ☒ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/024478

Box 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:
Although claims 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, 10, 11 (all partially), 6

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

- 1. claims: 1-5, 10, 11 (all partially), 6**

A combination of a cytotoxic agent which is capecitabine and an EGFR kinase inhibitor.

- 2. claims: 1-5, 10, 11 (all partially), 7**

A combination of a cytotoxic agent which is paclitaxel and an EGFR kinase inhibitor.

- 3. claims: 1-5, 10, 11 (all partially), 8**

A combination of a cytotoxic agent which is 5-FU and an EGFR kinase inhibitor.

- 4. claims: 1-5, 10, 11 (all partially), 12**

A combination of a cytotoxic agent which is FOLFIRI and an EGFR kinase inhibitor.

- 5. claims: 1-5, 10, 11 (all partially), 13**

A combination of a cytotoxic agent which is FOLFOX4 and an EGFR kinase inhibitor.

- 6. claims: 1-5, 10, 11 (all partially), 9**

A combination of a cytotoxic agent which is cisplatin and an EGFR kinase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/024478

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K45/06 A61K31/47 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)

A61K

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, CHEM ABS Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/020266 A (WYETH) 13 March 2003 (2003-03-13) page 8, paragraph 2 - page 9, paragraph 1 -----	1-6,10, 11
X	WO 03/050090 A (WYETH HOLDINGS CORPORATION) 19 June 2003 (2003-06-19) page 34, paragraph 2 page 36, paragraph 2 -----	1-5,10, 11
X	US 6 384 051 B1 (FROST PHILIP ET AL) 7 May 2002 (2002-05-07) cited in the application column 17, paragraph 3 -----	1-5,10, 11

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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
- "a" document member of the same patent family

Date of the actual completion of the International search

18 January 2006

Date of mailing of the International search report

13. 04 2006

Name and mailing address of the ISA

European Patent Office, P.B. 6516 Patentplan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 851 apo nl,
Fax (+31-70) 340-3018

Authorized officer

Leherte, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/024478

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03020266	A	13-03-2003	AT 314069 T	15-01-2006
			BR 0211769 A	27-07-2004
			CA 2455126 A1	13-03-2003
			CN 1538842 A	20-10-2004
			DK 1414438 T3	27-03-2006
			EP 1414438 A1	06-05-2004
			HK 1061204 A1	03-03-2006
			HU 0401089 A2	28-09-2004
			JP 2005505549 T	24-02-2005
			MX PA04001118 A	20-05-2004
			NO 20040558 A	06-02-2004
			ZA 200401801 A	06-06-2005

WO 03050090	A	19-06-2003	AU 2002359489 A1	23-06-2003
			BR 0214485 A	14-09-2004
			CA 2467573 A1	19-06-2003
			CN 1659145 A	24-08-2005
			EP 1448531 A1	25-08-2004
			HU 0402228 A2	28-02-2005
			JP 2005514384 T	19-05-2005
			MX PA04004969 A	11-08-2004

US 6384051	B1	07-05-2002	NONE	

DOCUMENTOS ANEXOS AL REPORTE DE BÚSQUEDA INTERNACIONAL

1. WO 03/020266 A1 (13-03-2003)
2. WO 03/050090 A1 (19-06-2003)
3. US 6,384,051 B1 (07-05-2002)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/020266 A1

(51) International Patent Classification⁷: A61K 31/395,
A61P 35/00, A61K 31/4706 // (A61K 31/395, 31:4706)

(21) International Application Number: PCT/US02/24841

(22) International Filing Date: 6 August 2002 (06.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/310,646 7 August 2001 (07.08.2001) US

(71) Applicant: WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(81) Designated States (*national*): AR, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

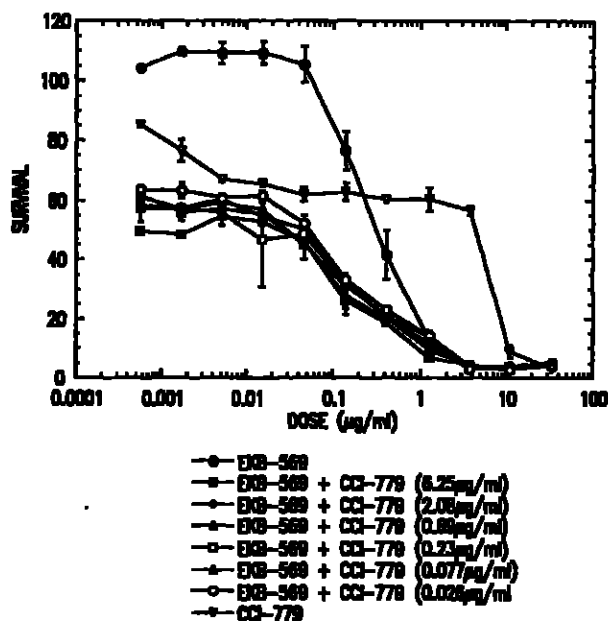
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors: RABINDRAN, Sridhar, Krishna; 2 Pamela Drive, Chestnut Ridge, NY 10977 (US). GIBBONS, James, J., Jr.; 33 Terrace Drive, Westwood, NJ 07675 (US).

(74) Agents: MILOWSKY, Arnold, S.; Wyeth, Patent Law Dept., Five Giralda Farms, Madison, NJ 07940-0874 et al. (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTINEOPLASTIC COMBINATIONS



(57) Abstract: This invention provides the use of a combination of CCI-779 and EKB-569 in the treatment of neoplasms.

WO 03/020266 A1

ANTINEOPLASTIC COMBINATIONS

BACKGROUND OF THE INVENTION

This invention relates to the use of combinations of rapamycin 42-ester with
5 3-hydroxy-2-(hydroxymethyl)-2-methylproplonic acid (CCI-779) and 4-dimethylamino-
but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-
amide (EKB-589).

Rapamycin is a macrocyclic triene antibiotic produced by Streptomyces
10 hygroscopicus, which was found to have antifungal activity, particularly against
Candida albicans, both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721
(1975); S.N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot.
31, 539 (1978); U.S. Patent 3,929,992; and U.S. Patent 3,993,749]. Additionally,
rapamycin alone (U.S. Patent 4,885,171) or in combination with picibanil (U.S. Patent
15 4,401,853) has been shown to have antitumor activity.

The immunosuppressive effects of rapamycin have been disclosed in FASEB
3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have
been shown to be effective as immunosuppressive agents, therefore useful in
preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989);
20 R. Y. Calne et al., Lancet 1183 (1978); and U.S. Patent 5,100,899]. R. Martel et al.
[Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in
the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in
the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited
the formation of IgE-like antibodies.

25 Rapamycin is also useful in preventing or treating systemic lupus
erythematosus [U.S. Patent 5,078,999], pulmonary inflammation [U.S. Patent
5,080,899], insulin dependent diabetes mellitus [U.S. Patent 5,321,009], skin
disorders, such as psoriasis [U.S. Patent 5,286,730], bowel disorders [U.S. Patent
5,286,731], smooth muscle cell proliferation and intimal thickening following vascular
30 injury [U.S. Patents 5,288,711 and 5,518,781], adult T-cell leukemia/lymphoma
[European Patent Application 525,980 A1], ocular inflammation [U.S. Patent
5,387,589], malignant carcinomas [U.S. Patent 5,206,018], cardiac inflammatory
disease [U.S. Patent 5,496,832], and anemia [U.S. Patent 5,561,138].

Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is ester of rapamycin which has demonstrated significant inhibitory effects on tumor growth in both in vitro and in vivo models. The preparation and use of hydroxyesters of rapamycin, including CCI-779, are disclosed in U.S. Patent 5,362,718.

CCI-779 exhibits cytostatic, as opposed to cytotoxic properties, and may delay the time to progression of tumors or time to tumor recurrence. CCI-779 is considered to have a mechanism of action that is similar to that of sirolimus. CCI-779 binds to and forms a complex with the cytoplasmic protein FKBP, which inhibits an enzyme, mTOR (mammalian target of rapamycin, also known as FKBP12-rapamycin associated protein [FRAP]). Inhibition of mTOR's kinase activity inhibits a variety of signal transduction pathways, including cytokine-stimulated cell proliferation, translation of mRNAs for several key proteins that regulate the G1 phase of the cell cycle, and IL-2-induced transcription, leading to inhibition of progression of the cell cycle from G1 to S. The mechanism of action of CCI-779 that results in the G1 S phase block is novel for an anticancer drug.

In vitro, CCI-779 has been shown to inhibit the growth of a number of histologically diverse tumor cells. Central nervous system (CNS) cancer, leukemia (T-cell), breast cancer, prostate cancer, and melanoma lines were among the most sensitive to CCI-779. The compound arrested cells in the G1 phase of the cell cycle.

In vivo studies in nude mice have demonstrated that CCI-779 has activity against human tumor xenografts of diverse histological types. Gliomas were particularly sensitive to CCI-779 and the compound was active in an orthotopic glioma model in nude mice. Growth factor (platelet-derived)-induced stimulation of a human glioblastoma cell line in vitro was markedly suppressed by CCI-779. The growth of several human pancreatic tumors in nude mice as well as one of two breast cancer lines studied in vivo also was inhibited by CCI-779.

Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to tyrosine residue located on protein substrates. Protein tyrosine kinases clearly play a role in normal cell growth. Many of the growth factor receptor proteins function as tyrosine kinases and it is by this process that they effect signaling. The interaction of growth factors with these receptors is a necessary event in normal regulation of cell growth. However, under certain conditions, as a

result of either mutation or overexpression, these receptors can become deregulated; the result of which is uncontrolled cell proliferation which can lead to tumor growth and ultimately to the disease known as cancer [Wilks A.F., *Adv. Cancer Res.*, 60, 43 (1993) and Parsons, J.T.; Parsons, S.J., *Important Advances in Oncology*, DeVita V.T. Ed., J.B. Lippincott Co., Phila., 3 (1993)]. Among the growth factor receptor kinases and their proto-oncogenes that have been identified and which are targets of the compounds of this invention are the epidermal growth factor receptor kinase (EGF-R kinase, the protein product of the erbB oncogene), and the product produced by the erbB-2 (also referred to as the neu or HER2) oncogene. Since the phosphorylation event is a necessary signal for cell division to occur and since overexpressed or mutated kinases have been associated with cancer, an inhibitor of this event, a protein tyrosine kinase inhibitor, will have therapeutic value for the treatment of cancer and other diseases characterized by uncontrolled or abnormal cell growth. For example, overexpression of the receptor kinase product of the erbB-2 oncogene has been associated with human breast and ovarian cancers [Slamon, D. J., et. al., *Science*, 244, 707 (1989) and *Science*, 235, 1146 (1987)]. Deregulation of EGF-R kinase has been associated with epidermoid tumors [Reiss, M., et. al., *Cancer Res.*, 51, 6254 (1991)], breast tumors [Macias, A., et. al., *Anticancer Res.*, 7, 459 (1987)], and tumors involving other major organs [Gullick, W.J., *Brit. Med. Bull.*, 47, 87 (1991)]. Because of the importance of the role played by deregulated receptor kinases in the pathogenesis of cancer, many recent studies have dealt with the development of specific PTK inhibitors as potential anti-cancer therapeutic agents [some recent reviews: Burke, T.R., *Drugs Future*, 17, 119 (1992) and Chang, C.J.; Geahlen, R.L., *J. Nat. Prod.*, 55, 1529 (1992)].

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4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide (EKB-569) is an EGFR kinase inhibitor which has significant inhibitory effects on tumor growth in both in vitro and in vivo models. The preparation and use of EGFR kinase inhibitors, such as EKB-569, are disclosed in U.S. Patent 6,002,008.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows cytotoxicity curves of EKB-569, CCI-779, and combinations of EKB-569 + CCI-779 in HCT116 cells.

5 FIG. 2 shows isobolograms (at the 50% effect level) of a EKB-569 + CCI-779 combination.

FIG. 3 shows isobolograms for EKB-569 + CCI-779 combinations derived from different endpoints ranging from 50-65%.

FIG. 4 shows a 3-dimensional analysis of the synergistic interaction of a EKB-569 + CCI-779 combination.

10 FIG. 5 shows a contour plot of the 3-dimensional synergy plot of a EKB-569 + CCI-779 combination.

DESCRIPTION OF THE INVENTION

15 This invention provides the use of combinations of CCI-779 and EKB-569 as antineoplastic combination chemotherapy. In particular, these combinations are useful in the treatment of renal cancer, soft tissue cancer, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioma, non-small lung cell cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, colon cancer, 20 esophageal cancer, gastric cancer, leukemia, colorectal cancer, and unknown primary cancer. This invention also provides combinations of CCI-779 and EKB-569 for use as antineoplastic combination chemotherapy, in which the dosage of either CCI-779 or EKB-569 or both are used in subtherapeutically effective dosages.

25 As used in accordance with this invention, the term "treatment" means treating a mammal having a neoplastic disease by providing said mammal an effective amount of a combination of CCI-779 and EKB-569 with the purpose of inhibiting growth of the neoplasm in such mammal, eradication of the neoplasm, or palliation of the mammal.

30 As used in accordance with this invention, the term "providing," with respect to providing the combination, means either directly administering the combination, or administering a prodrug, derivative, or analog of one or both of the components of the combination which will form an effective amount of the combination within the body.



The preparation of CCI-779 is described in U.S. Patent 5,362,718, which is hereby incorporated by reference. An improved preparation of CCI-779 is disclosed in US patent application SN 09/670,358, which is hereby incorporated by reference. When CCI-779 is used as an antineoplastic agent, it is projected that initial i.v.

5 Infusion dosages will be between about 0.1 and 100 mg/m² when administered on a daily dosage regimen (daily for 5 days, every 2-3 weeks), and between about 0.1 and 1000 mg/m² when administered on a once weekly dosage regimen. Oral or intravenous infusion are the preferred routes of administration, with intravenous being more preferred.

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EKB-569 can be prepared according to the procedures described in US Patent 6,002,008, which is incorporated by reference. Preferred procedures for the preparation of EKB-569 are provided herein. When EKB-569 is used as an antineoplastic agent it is projected that the initial oral dosage will be between 1 and 100 mg per day. Depending on patient tolerance, EKB-569 can be administered daily for a treatment period, such as 14 days, followed by a rest period (no drug administered), or can be administered on a continuous basis for a longer treatment period (for example, 6 months or longer).

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20 The antineoplastic activity of the CCI-779 plus EKB-569 combination was confirmed in *in vitro* standard pharmacological test procedure; the following briefly describes the procedure used and the results obtained.

Cell Proliferation Procedure - HCT 116 colon adenocarcinoma cells were maintained in RPMI 1640 medium (Life Technologies, Inc., Gaithersburg, MD) supplemented with 10% fetal bovine serum (FBS, Life Technologies) and 50 µg/ml gentamicin (Life Technologies) under 7% CO₂ at 37°C. Cells were plated in 96-well microtiter dishes (8000 cells/well) in 200 µl RPMI 1640 medium containing 5% FBS and 50 µg/ml gentamicin and incubated overnight at 37°C. Compound dilutions were prepared in the same medium, at 5X final concentration, and 50 µl of the drug dilution was added to the cell-containing wells. For studies involving combinations of two drugs, serial dilutions of one compound were prepared in the presence of a fixed dose of a second compound. Alternatively, a checkerboard dilution series was employed. Cells were cultured for three days in the presence of the drugs. Untreated cells were

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Included as controls. The percentage of surviving cells was determined using sulforhodamine B (SRB, Sigma-Aldrich, St Louis, MO), a protein binding dye. Cellular protein was precipitated in each well by the addition of 50 μ l of 50% cold trichloroacetic acid. After 1 hour, the plates were washed extensively in water and
5 dried. SRB dye reagent (0.4% SRB in 1% acetic acid, 80 μ l per well) was added and plates were kept at room temperature for ten minutes. Plates were then washed thoroughly in 1% acetic acid and dried. Cell-associated dye was dissolved in 10 mM Tris (150 μ l) and the absorbance was read at 540 nm in a microtiter plate reader. The concentration of compound that caused a fixed percentage inhibition of growth was
10 determined by plotting cell survival (relative to untreated cells) against the compound dose.

Synergy Evaluation - Isobolograms were used to study the interaction of two pharmacological agents. Here, the concentration of each drug alone which produces a certain endpoint (e.g 50% inhibition of cell growth, IC_{50}), is plotted on the two
15 graphical axes. The straight line connecting the two points represents equally effective concentrations of all combinations of the two drugs if the interaction is purely additive. A shift of the isobologram to the left of the predicted cytotoxicity (curve with concave side up) represents a synergistic interaction. Conversely, a shift to the right (isobologram with the convex side up) represents an antagonistic interaction. When
20 isobolograms for different endpoints were plotted on the same graph, the concentration of each drug was expressed as the fraction of the concentration of each drug alone that produced the same effect. This produces a symmetrical isobologram with unit-less measures on each axis, and allows a direct comparison of different endpoints.

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A second model for studying drug interactions was proposed by Prichard and Shipman [Antiviral Research. 14: 181-206 (1990)]. This is a 3-dimensional model: one for each drug and the third for the biological effect. Theoretical additive interactions are calculated from the individual dose-response curves, based on a
30 dissimilar sites model of additivity (Bliss Independence). The calculated additive surface, representing predicted cytotoxicity is subtracted from the experimental surface to reveal areas of enhanced toxicity (synergy) or reduced toxicity (antagonism). The resulting surface appears as a horizontal plane at 0% inhibition

above the calculated additive surface, if the interaction is additive. Peaks and valleys deviating from this plane are indicative of synergy and antagonism, respectively. MacSynergyII, a Microsoft Excel-based software was used to perform all calculations automatically. This spreadsheet calculates the theoretical additive interactions, and
5 locates and quantifies synergistic or antagonistic interactions that are significant at the 95% confidence levels. The results were plotted as a 3-dimensional plot, or as a contour plot.

Results - HCT 116 cells were chosen as they express low, but detectable
10 levels of EGFR, and are sensitive to inhibition by EGFR inhibitors. The cells are somewhat resistant to CCI-779, but are inhibited by high doses (5-10 µg/ml) of this drug. HCT-116 cells were cultured in the presence of EKB-569 alone, CCI-779 alone, or a dilution series of EKB-569 with fixed doses of CCI-779. Following growth for 3 days, cell survival was determined using the SRB test procedure. Cytotoxicity curves
15 are shown in Fig. 1. EKB-569 produced an IC_{50} value of 0.31 µg/ml in HCT116 cells. When this compound was combined with 2.08 µg/ml CCI-779 (which caused 41% inhibition of growth when administered alone), the IC_{50} value is reduced to 0.03 µg/ml, a 10-fold decrease. When combined with 0.028 µg/ml CCI-779 (which alone inhibits cell proliferation by 36 %), the IC_{50} value dropped to 0.051 µg/ml, a 6-fold decrease.
20 Similar results were observed when dose-response curves were produced with CCI-779 in the presence of fixed doses of EKB-569. To identify the nature of this drug interaction, isobolograms (at 50% effect level) of the combination of EKB-569 and CCI-779 were generated (Fig. 2). The isobologram was deeply indented with the concave side up, indicating a substantial synergistic interaction between the two
25 drugs. At the most synergistic point, 0.03 µg/ml of EKB-569 combined with 0.077 µg/ml CCI-779 was iso-effective with 0.31 µg/ml of EKB-569 alone or 4.3 µg/ml CCI-779 alone (IC_{50} for each drug alone). Thus, a 10-fold reduction in the dose of EKB-569 and a 50-fold reduction in the dose of CCI-779 was required to inhibit cell proliferation by 50% when the drugs were combined, compared to either drug alone.
30 Isobolograms derived from different endpoints, ranging from 50 to 65% were also examined. As shown in Fig 3., the isobolograms produced were almost superimposable, indicating synergy at all effect levels tested.

The interaction between EKB-589 and CCI-779 was also evaluated using a 3-dimensional analysis. Here, pharmacological interactions are presented in a 3-dimensional plot with the plane at 0% representing additive interaction, and peaks and valleys representing areas of synergy or antagonism, respectively, between the two drugs. In Fig. 4, the combination of EKB-589 and CCI-779 resulted in a broad area of synergistic interaction, consistent with the results shown in the isobologram studies. A contour plot of the 3-dimensional synergy plot facilitates the identification of the concentrations of drugs at which greatest synergistic toxicity occurs (Fig. 5). A broad area of synergy was observed at 0.0005 to 3 $\mu\text{g/ml}$ CCI-779 and 0.16 to 0.4 $\mu\text{g/ml}$ EKB-589. Within this area, two peaks of maximum synergy occurred at 0.0005 to 0.003 $\mu\text{g/ml}$ and 0.05 to 0.3 $\mu\text{g/ml}$ of CCI-779 and 0.25 to 0.37 $\mu\text{g/ml}$ EKB-589.

Based on the results of these standard pharmacological test procedures, combinations of CCI-779 plus EKB-589 acted synergistically together, and are useful as antineoplastic therapy. More particularly, these combinations are useful in the treatment of renal carcinoma, soft tissue sarcoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, head and neck cancer, glioma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, colon cancer, esophageal cancer, gastric cancer, leukemia, colorectal cancer, and unknown primary cancer. As these combinations contain at least two active antineoplastic agents, the use of such combinations also provides for the use of combinations of each of the agents in which one or both of the agents is used at subtherapeutically effective dosages, thereby lessening toxicity associated with the individual chemotherapeutic agent.

In providing chemotherapy, multiple agents having different modalities of action are typically used as part of a chemotherapy "cocktail." It is anticipated that the combinations of this invention will be used as part of a chemotherapy cocktail that may contain one or more additional antineoplastic agents depending on the nature of the neoplasia to be treated. For example, this invention also covers the use of the CCI-779/EKB-923 combination used in conjunction with other chemotherapeutic agents, such as antimetabolites (i.e., 5-fluorouracil, floxuridine, thioguanine,

cytarabine, fludarabine, 6-mercaptopurine, methotrexate, gemcitabine, capecitabine, pentostatin, trimetrexate, or cladribine); DNA crosslinking and alkylating agents (i.e., cisplatin, carboplatin, streptozoln, melphalan, chlorambucil, carmustine, methchloroethamine, lomustine, bisulfan, thiotapa, ifofamide, or cyclophosphamide);
5 hormonal agents (i.e., , tamoxifen, toremifene, anastrozole, or letrozole);
antibiotics (i.e., plicamycin, bleomycin, mitoxantrone, idarubicin, daclinomycin, mitomycin, doxorubicin or daunorubicin); immunomodulators (i.e., Interferons, IL-2, or BCG); antimitotic agents (i.e., estramustine, paclitaxel, docetaxel, vinblastine, vincristine, or vinorelbine); topoisomerase inhibitors (i.e., topotecan, irinotecan,
10 etoposide, or teniposide.); and other agents (i.e., hydroxyurea, trastuzumab, altretamine, retuximab, L-asparaginase, or gemtuzumab ozogamicin).

As used in this invention, the combination regimen can be given simultaneously or can be given in a staggered regimen, with CCI-779 being given at a
15 different time during the course of chemotherapy than EKB-923. This time differential may range from several minutes, hours, days, weeks, or longer between administration of the two agents. Therefore, the term combination does not necessarily mean administered at the same time or as a unitary dose, but that each of the components are administered during a desired treatment period. The agents may
20 also be administered by different routes. For example, in the combination of CCI-779 plus EKB-569, it is anticipated that the CCI-779 will be administered orally or parenterally, with parenterally being preferred, while the EKB-569 may be administered parenterally, orally, or by other acceptable means. These combination can be administered daily, weekly, or even once monthly. As typical for
25 chemotherapeutic regimens, a course of chemotherapy may be repeated several weeks later, and may follow the same timeframe for administration of the two agents, or may be modified based on patient response.

As typical with chemotherapy, dosage regimens are closely monitored by the
30 treating physician, based on numerous factors including the severity of the disease, response to the disease, any treatment related toxicities, age, health of the patient, and other concomitant disorders or treatments.

Based on the results obtained with the CCI-779 plus EKB-569 combinations, it is projected that the initial i.v. infusion dosage of CCI-779 will be between about 0.1

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and 100 mg/m², with between about 2.5 and 70 mg/m² being preferred. It is also preferred that the CCI-779 be administered by i.v., typically over a 30 minute period, and administered about once per week. The initial daily dosages of EKB-589 will be between about 1 and 100 mg, with between 5 and 75 mg being preferred. After one
5 or more treatment cycles, the dosages can be adjusted upwards or downwards depending on the results obtained and the side effects observed.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal
10 forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may
15 be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium,
20 polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying
25 agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral
30 formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

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The compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in
5 glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of
10 sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol
15 (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such
20 administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

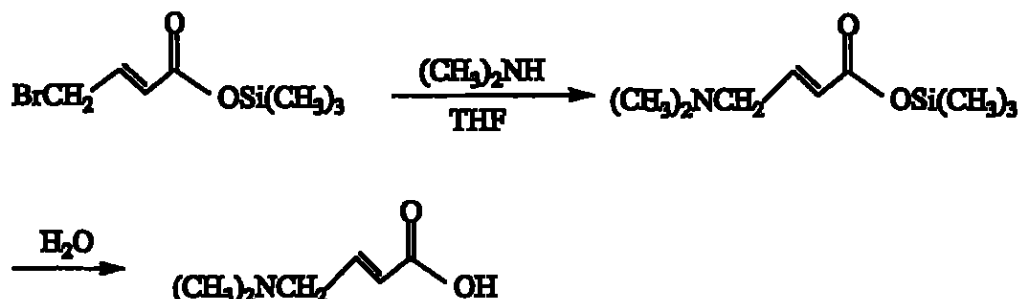
Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the
25 active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in
30 petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

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The following provides the preparation of EKB-589 from commercially available starting materials or starting materials that can be made according to available literature procedures.

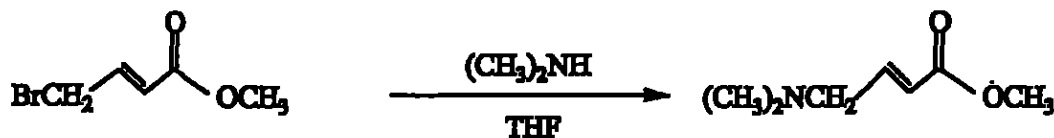
10 Preparation of 4-dimethylaminocrotonic acid from TMS-4-bromocrotonate



211 ml dimethylamine (2M in THF, 0.422 moles) was added drop-wise to a solution of 50 g TMS-4-bromocrotonate (0.211 moles, 75.9% by GC-MS) in 250 ml of THF at 0-50°C under N₂. The reaction mixture was stirred at room temperature for 30 minutes.

- 15 A white solid by-product was filtered off. 2 ml water was added to the filtrate followed by seeding. The crystals formed were filtered and washed with ether to give 18.3 g (from two crops) off-white solid product. Yield was 67.2% (98% purity by GC-MS, NMR was consistent with the structure).

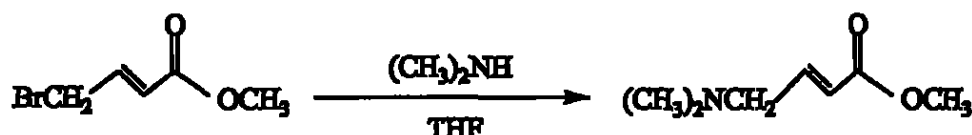
20 Preparation of methyl 4-dimethylaminocrotonate from methyl-4-bromocrotonate



120 ml dimethylamine (2M in THF, 0.24 moles) was added drop-wise to a solution of 20 g methyl 4-bromocrotonate (85% purity, 0.095 moles) in 150 ml of THF at 0-50°C under N₂. The reaction mixture was stirred for 15 minutes at room temperature. TLC

(9:1 CH₂Cl₂: MeOH with few drops of Et₃N) showed residual methyl 4-bromocrotonate. The reaction mixture was heated to 40-45°C for 15 minutes. A white solid by-product was filtered off. The filtrate was evaporated to give a yellow oil (14 g). The yellow oil was dissolved in 100 ml CH₂Cl₂ and washed with H₂O twice. The aqueous layer was back extracted with 100 ml CH₂Cl₂. The CH₂Cl₂ layers were combined, dried over MgSO₄ and filtered. The filtrate was evaporated to give an oil (12 g). Yield was 88%. NMR indicated desired product with trace methyl 4-bromocrotonate.

Preparation of Methyl 4-N,N-dimethylaminocrotonate hydrochloride on large scale:

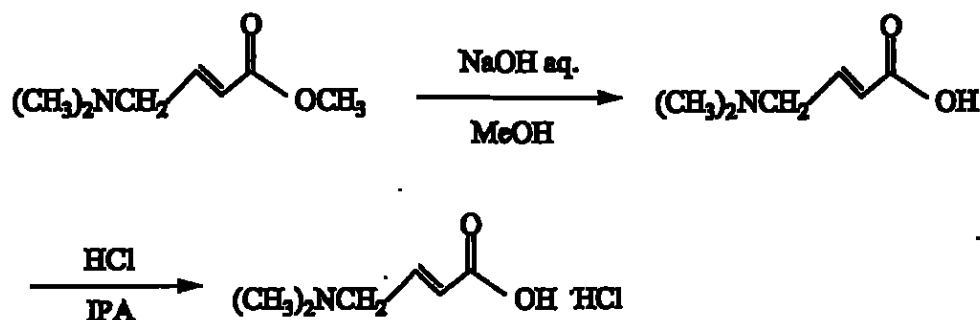


A 3L flask was charged with tetrahydrofuran (0.71 kg, 0.80 L). Methyl 4-bromocrotonate (0.20 kg, 0.13 L, d = 1.522 g/mL) was added and rinsed with tetrahydrofuran (0.18 kg, 0.20 L). The solution was stirred and cooled to 0-10°C. An additional funnel was charged with a solution of dimethylamine in tetrahydrofuran and added over (1 h 15 min) keeping the temperature at 0-10°C. The mixture was stirred for a minimum of 30 mins and checked for reaction completion by TLC. The reaction was complete when there is ≤ 2% detectable starting material (methyl 4-bromocrotonate) present. The mixture was filtered cold on a Buchner funnel into a 3 L multi-neck flask, rinsed with pre-chilled (0-10°C) tetrahydrofuran (2 x 0.18 kg, 2 x 0.20 L), and suction maintained until dripping stops. The flask was equipped with an agitator, thermometer, and a setup for vacuum distillation. The solution was concentrated by distillation under a reduced pressure of (125-200 mm Hg) and at a maximum pot temperature of (40°C) to a pot volume of (200 mL). Isopropanol (0.22 kg, 0.28 L) was added and the mixture cooled to 0-10°C. The distillation stillhead was replaced with an addition funnel charged with a solution of HCl in isopropanol, which was added over 45 min until pH of 2.0-3.0 was reached, while maintaining a temperature 0-10°C. The mixture was held for a minimum 30 min, and filtered cold on a Buchner funnel, rinsed with isopropanol (2 x 0.12 kg, 2 x 0.15 L). The filter cake was dammed and

suction maintained until dripping stopped. The product was dried in a vacuum oven at 50°C and 10 mm Hg for 18-20 h.

Preparation of 4-dimethylaminocrotonic acid hydrochloride from methyl

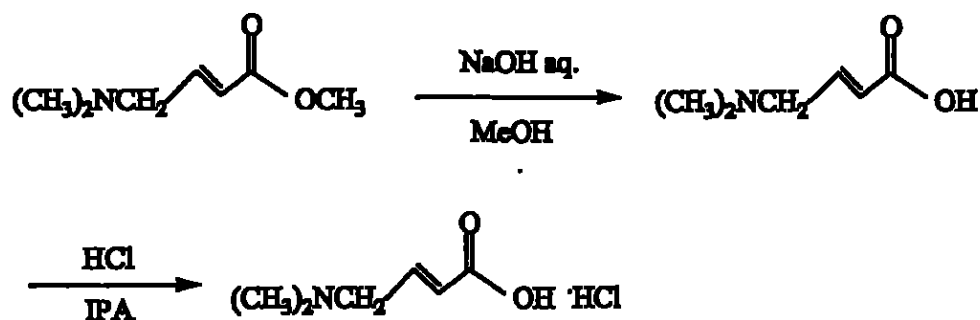
5 4-dimethylaminocrotonate



A NaOH solution (3.35 g in 25 ml H₂O, 0.084 moles) was added drop-wise to a solution of 12 g methyl 4-dimethylaminocrotonate (0.084 moles) in 100 ml MeOH at room temperature. The reaction mixture was heated to 40-45°C for 1 hour then cooled to room temperature. The pH was adjusted to 1-2 with 5 N HCl. The mixture was concentrated to a thick oil which was triturated with dehydrated alcohol to form a solid. The solid by-product was filtered off. The filtrate was evaporated to an oil which was triturated with IPA. Seven (7.0) g of white solid product was obtained. Yield was 50% with the purity 86.3 % by GC-MS.

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Preparation of 4-N,N-dimethylaminocrotonic acid hydrochloride on large scale

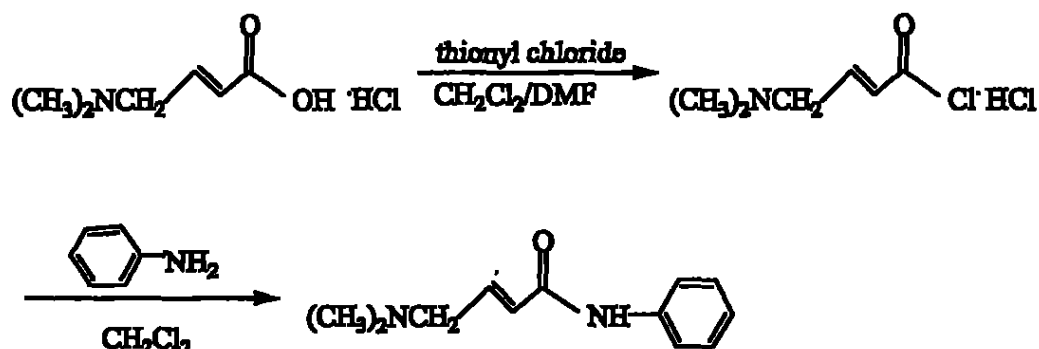


A 2 L multi-neck flask was equipped with agitator, thermometer, addition funnel, and nitrogen protection. The flask was charged with ethanol (0.39 kg, 0.50 L). Methyl 4-N,N-dimethylamino crotonate hydrochloride (0.125 kg) was added and rinsed with

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ethanol (0.10 kg, 0.125 L). The suspension was stirred and cooled to 0-10°C. The addition funnel was charged with sodium hydroxide (50%) (0.11 kg, 0.072 L, d=1.53 g/mL) and added over 20 min keeping the temperature at 0-10°C. A slight exotherm was observed and the mixture turned yellow. The mixture was stirred for a minimum of 15 min, and then warmed to 18-22°C, and held for a minimum of 4 h. The reaction was checked for completion by TLC. The reaction is complete when there is $\leq 2\%$ detectable starting material (methyl 4-N,N-dimethylaminocrotonate hydrochloride) present. The mixture was cooled to 0-10°C. An addition funnel was charged with a solution of HCl in isopropanol and added over 40 min until pH 2.0-3.0 was attained, while maintaining the pot temperature of 0-10°C. The mixture was stirred for a minimum of 30 min, and filtered cold on a Buchner funnel into a 2 L multi-neck flask, rinsed with cold ethanol (0-10°C) (2 x 0.05 kg, 2 x 0.063 L) with suction maintained until dripping stops. The flask was equipped with an agitator, thermometer, and setup for vacuum distillation. Solvent was removed under a reduced pressure of 50-100 mm Hg and at a maximum pot temperature of (40°C) to a pot volume of 160-180 mL. Isopropanol (0.049 kg, 0.063 L) was added, and the mixture warmed to 35-40°C over 10 min. Acetone (0.10 kg, 0.13 L) was added over 20 min while maintaining the pot temperature at 35-40°C. The mixture was seeded and cooled to ambient temperature 20-25°C, and held there for a minimum of 12-18 h. The mixture was cooled to 0-10°C, held there for a minimum of 1 h. A mixture of isopropanol (0.049 kg, 0.063 L) and acetone (0.10 kg, 0.13 L) was prepared, stirred to homogenize, and cooled to 0-10°C. The mixture was filtered cold on a Buchner funnel, rinsed with isopropanol/acetone (2 x 0.074 kg, 2 x 0.096 L), and the filter cake dammed while maintaining suction until dripping stopped. The product was dried in a vacuum oven at 50°C and 10 mm Hg for 18-20 h.

Preparation of 4-dimethylaminocrotonyl anilide from 4-dimethylaminocrotonic acid hydrochloride



Thionyl chloride (0.36 ml, 0.005 moles) was added drop-wise to a solution of 0.33 g 4-dimethylaminocrotonic acid hydrochloride (0.002 moles) in 15 ml CH_2Cl_2 containing 2 drops of DMF at 0°C under N_2 . The reaction mixture was refluxed for 30 min. Then 0.72 ml aniline (0.008 moles) was added drop-wise to the reaction mixture at 0°C and stirred for 1 hour at room temperature. A solid by-product was filtered. The filtrate was evaporated to give an oil (0.6 g). GC-MS data shows that the oil is 11.7% 4-dimethylaminocrotonic acid hydrochloride and 85% of desired product.

Preparation and isolation of 4-N,N-dimethylaminocrotonoylchloride hydrochloride

A well stirred suspension 4-dimethylaminocrotonic acid hydrochloride (5.0 g, 30 mmol) in cold (0°C) THF (40 mL) and DMF (2 pipet drops) was treated with oxalyl chloride (3.15 mL, 36 mmol). The mixture was stirred at $20-25^\circ\text{C}$ for 3 h then cooled to 0°C and held for 30 min. The solids were collected on Buchner funnel (under a blanket of nitrogen) and washed with cold (0°C) THF (3 x 5 mL). The product was dried under vacuum (~ 1 torr) at $40-50^\circ\text{C}$ for 3 h to give 4.0 g of 4-dimethylaminocrotonoyl chloride hydrochloride. This material is characterized as its methyl ester by treatment of the solid with methanol.

Alternatively, the title compound can be prepared in CH_3CN and used directly for the coupling step:

Preparation of EKB-569

A 3 L multi-neck flask was equipped with an agitator, thermometer, dip tube, and nitrogen protection. The flask was charged with N-methyl pyrrolidinone (0.77 kg, 0.75 L, $d=1.033$ g/mL). At ambient temperature, 4-[3-chloro-4-fluorophenyl]amino-6-amino-3-cyano-7-ethoxy quinoline (0.0748 kg) [see, US Patent 6,002,008] was added and the mixture stirred while heating to 40-45 °C and hold for 15 min. The flask was cooled to 0-10°C. The mixture containing 4-N,N-dimethylaminocrotonoyl chloride hydrochloride was transferred via dip tube and positive nitrogen pressure to the 3 L flask over 30-45 min, while maintaining 0-10°C. The mixture was kept at 0-10°C for a minimum of 2 h. The reaction was checked for completion by HPLC. The reaction is complete when there is $\leq 2\%$ of the starting material (4-[3-chloro-4-fluorophenyl]amino-6-amino-3-cyano-7-ethoxy quinoline) present. A 12 L multi-neck flask equipped with agitator, thermometer, dip tube, and nitrogen protection was charged with water (2.61 kg, 2.61 L). Sodium bicarbonate (0.209 kg) was added and stirred until a solution was obtained. The solution was cooled to 20-24°C. The NMP-CH₃CN mixture was transferred, via dip tube and positive nitrogen pressure, to the 12 L flask over 45-60 min, while maintaining 20-24°C. The mixture was maintained at 20-24°C for a minimum of 1 h, and filtered on a Buchner funnel, and rinsed with water (3 x 0.40 kg, 3 x 0.40 L) with suction being maintained until dripping stops. The product was dried in a vacuum oven at 50°C and 10 mm Hg for 28-30 h to give 78.5 g (86% yield) of product.

CLAIMS

1. A method of treating a neoplasm in a mammal in need thereof, which
5 comprises providing to said mammal an effective amount of a combination comprising
CCI-779 and EKB-589.
2. The method according to claim 1, wherein the neoplasm is renal cancer.
- 10 3. The method according to claim 1, wherein the neoplasm is soft tissue
sarcoma.
4. The method according to claim 1, wherein the neoplasm is breast
cancer.
- 15 5. The method according to claim 1, wherein the neoplasm is a
neuroendocrine tumor of the lung.
6. The method according to claim 1, wherein the neoplasm is cervical
20 cancer.
7. The method according to claim 1, wherein the neoplasm is uterine
cancer.
- 25 8. The method according to claim 1, wherein the neoplasm is a head and
neck cancer.
9. The method according to claim 1, wherein the neoplasm is glioma.
- 30 10. The method according to claim 1, wherein the neoplasm is non-small
cell lung cancer.
11. The method according to claim 1, wherein the neoplasm is prostate
cancer.

12. The method according to claim 1, wherein the neoplasm is pancreatic cancer.
- 5 13. The method according to claim 1, wherein the neoplasm is lymphoma.
14. The method according to claim 1, wherein the neoplasm is melanoma.
15. The method according to claim 1, wherein the neoplasm is small cell
10 lung cancer.
16. The method according to claim 1, wherein the neoplasm is ovarian cancer.
- 15 17. The method according to claim 1, wherein the neoplasm is colon cancer.
18. The method according to claim 1, wherein the neoplasm is esophageal cancer.
20
19. The method according to claim 1, wherein the neoplasm is gastric cancer.
20. The method according to claim 1, wherein the neoplasm is leukemia.
25
21. The method according to claim 1, wherein the neoplasm is colorectal cancer.
22. The method according to claim 1, wherein the neoplasm is unknown
30 primary cancer.
23. A method according to any one of Claims 1 to 22 which comprises providing to said mammal an effective amount of a combination comprising CCI-779

and EKB-569, wherein either CCI-779, EKB-569, or both are provided in subtherapeutically effective amounts.

24. A method according to claim 23 in which CCI-779 is provided in a
5 subtherapeutically effective amount.

25. A method according to claim 23 in which EKB-569 is provided in a subtherapeutically effective amount.

10 26. A method according to claim 23 in which both CCI-779 and EKB-569 are provided in subtherapeutically effective amounts.

27. An antineoplastic combination which comprises an antineoplastic effective amount of a combination of CCI-779 and EKB-569.
15

28. A composition according to claim 27 in which CCI-779 is provided in a subtherapeutically effective amount.

29. A composition according to claim 27 in which EKB-569 is provided in a
20 subtherapeutically effective amount.

30. A composition according to claim 27 in which both CCI-779 and EKB-569 are provided in subtherapeutically effective amounts.

25 31. A product comprising CCI-779 and EKB-569 as a combined preparation for simultaneous, separate or sequential use in the treatment of a neoplasm in a mammal

32. A product according to claim 31 in which the neoplasm is one of the
30 following: renal cancer, soft tissue sarcoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, a head and neck cancer, glioma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, colon cancer, esophageal cancer, gastric cancer, leukemia, colorectal cancer or unknown primary cancer.

33. Use of CCI-779 and EKB-569 in the preparation of a medicament for the treatment of neoplasm in a mammal.

5 34. A use according to claim 33 in which the neoplasm is one of the following: renal cancer, soft tissue sarcoma, breast cancer, neuroendocrine tumor of the lung, cervical cancer, uterine cancer, a head and neck cancer, glioma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, colon cancer, esophageal cancer, gastric cancer, 10 leukemia, colorectal cancer or unknown primary cancer.

35. A use according to claim 33 or 34 in which CCI-779 is provided in a subtherapeutically effective amount.

15 36. A use according to claim 33 or 34 in which EKB-569 is provided in a subtherapeutically effective amount.

37. A use according to claim 33 or 34 in which both CCI-779 and EKB-569 are provided in subtherapeutically effective amounts.

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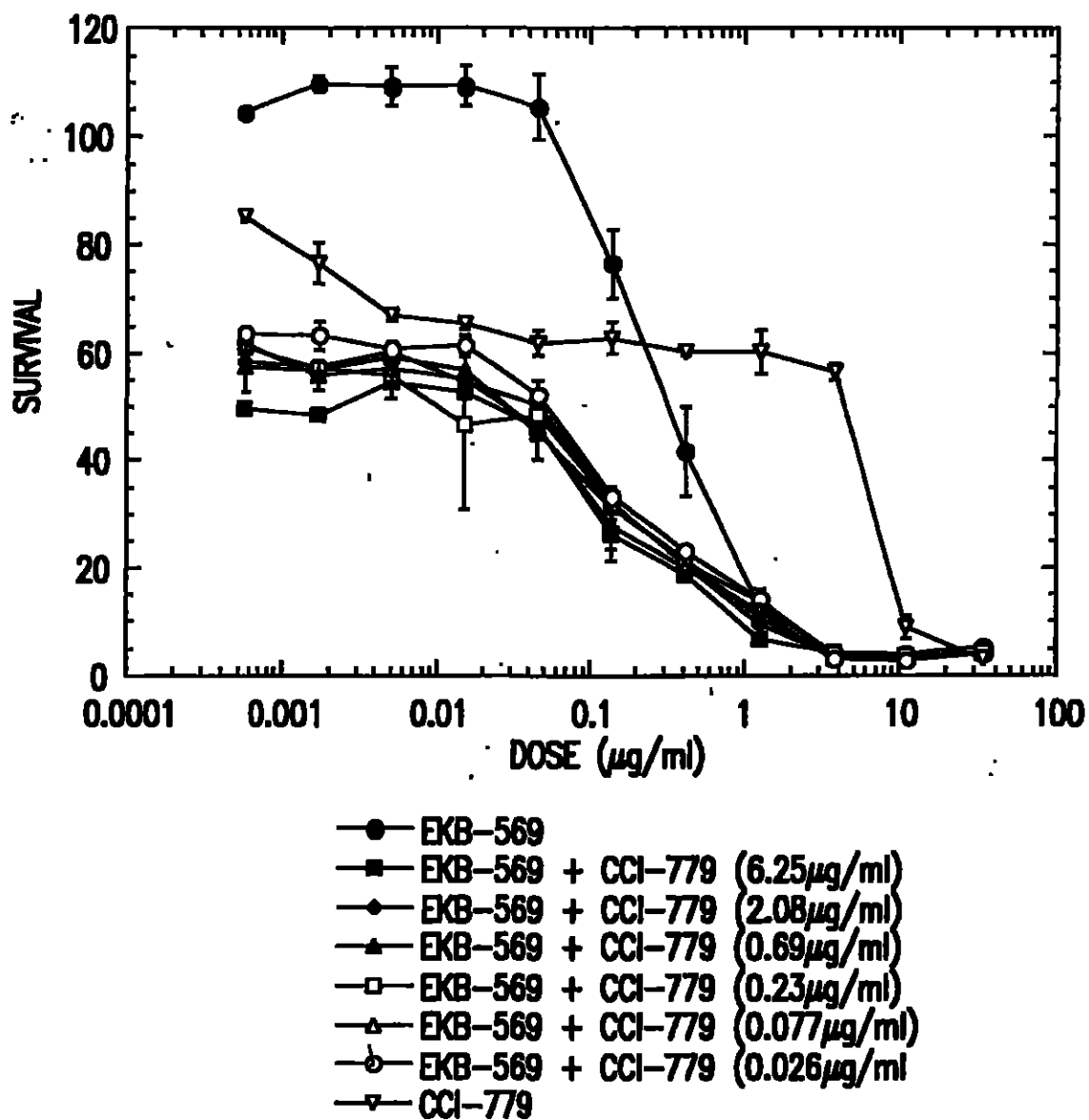


FIG.1

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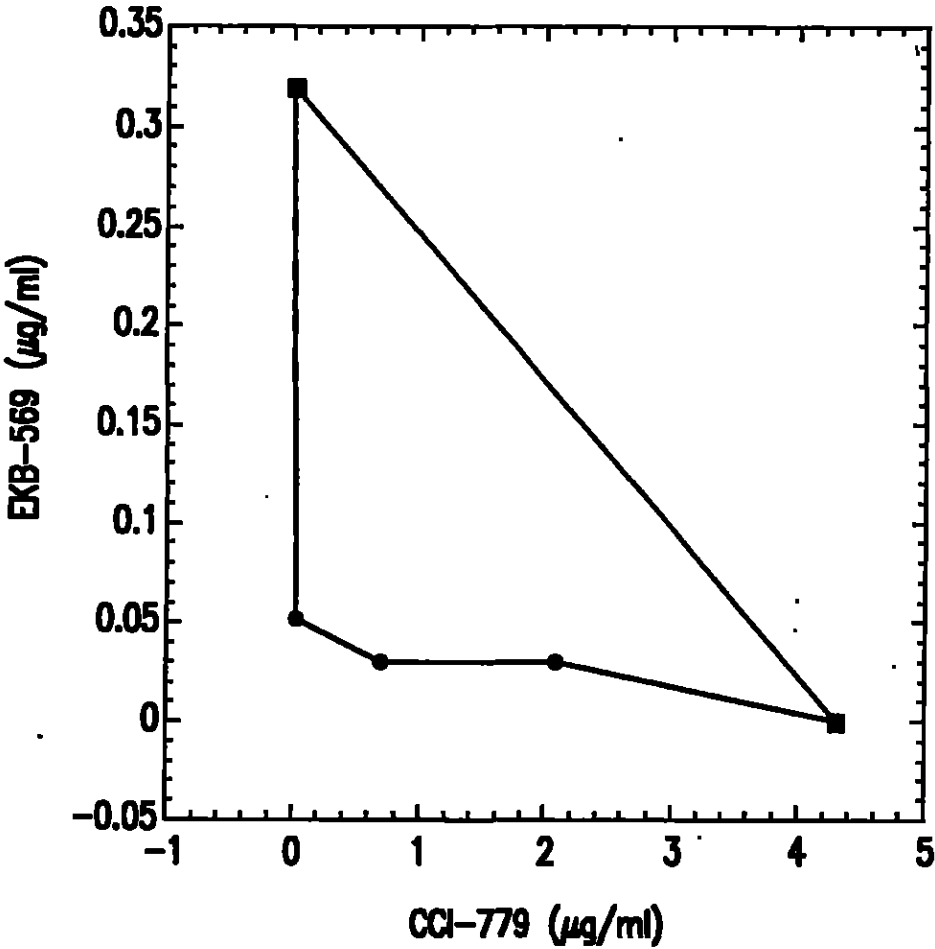


FIG.2

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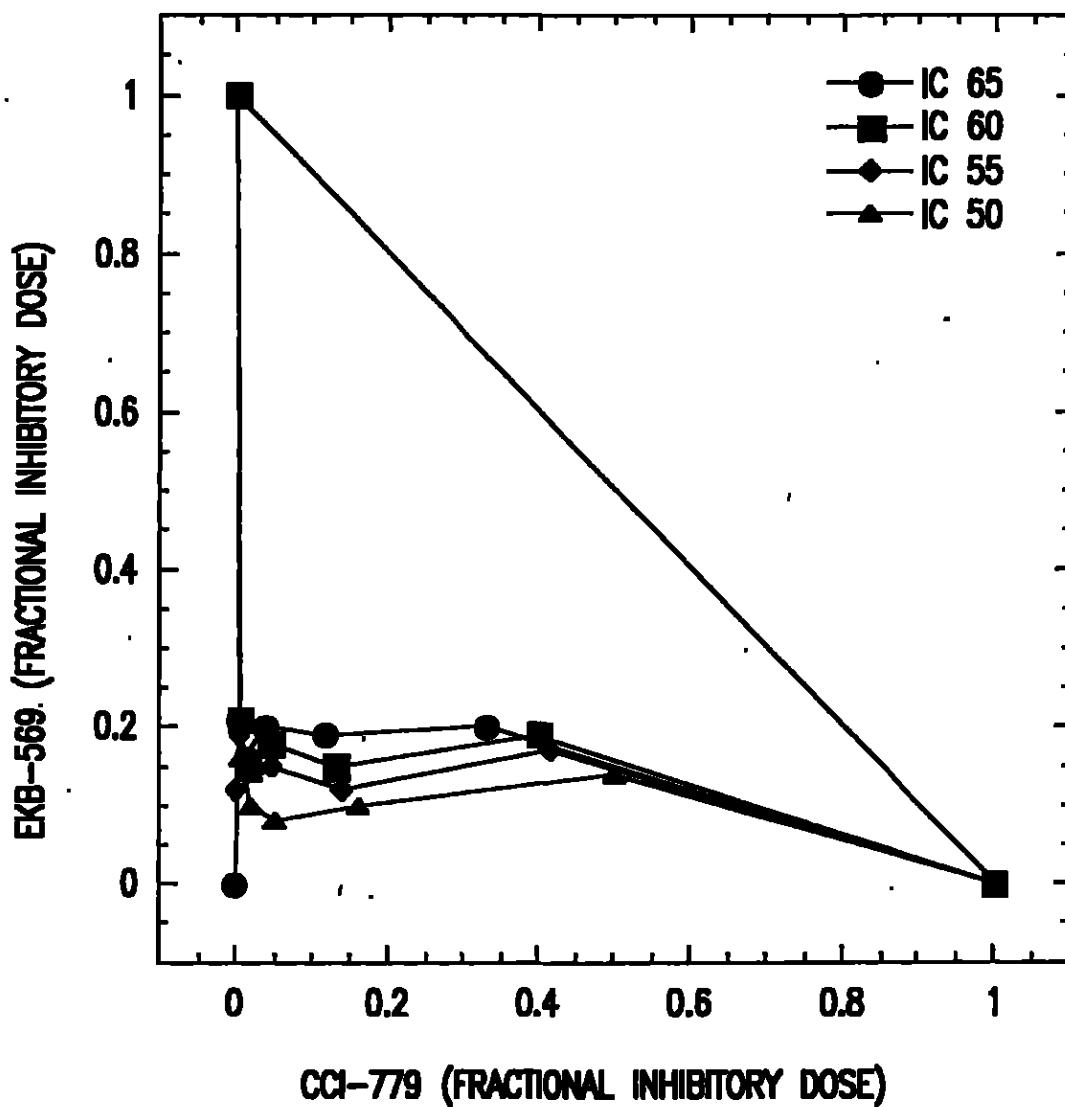
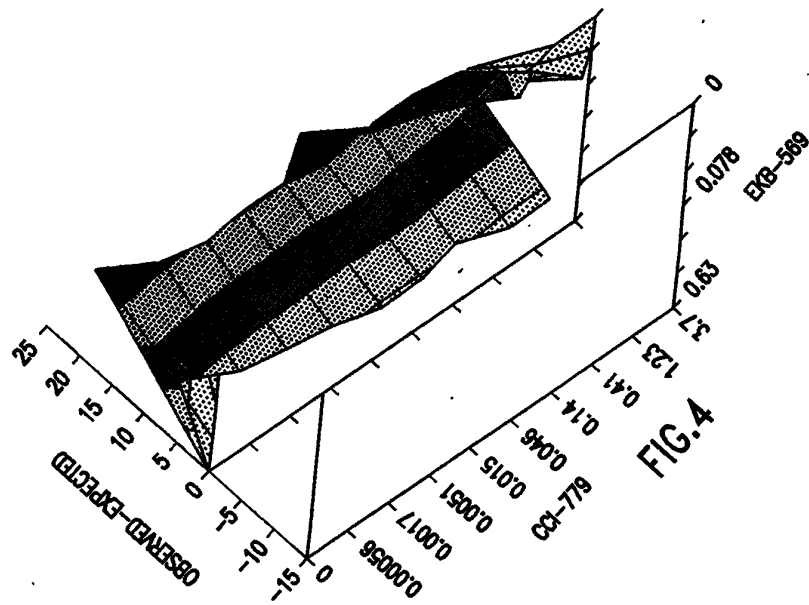
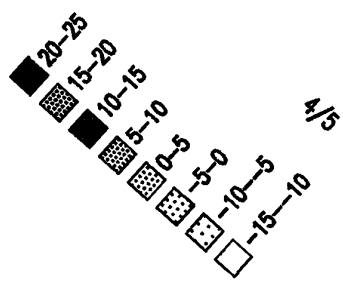


FIG.3

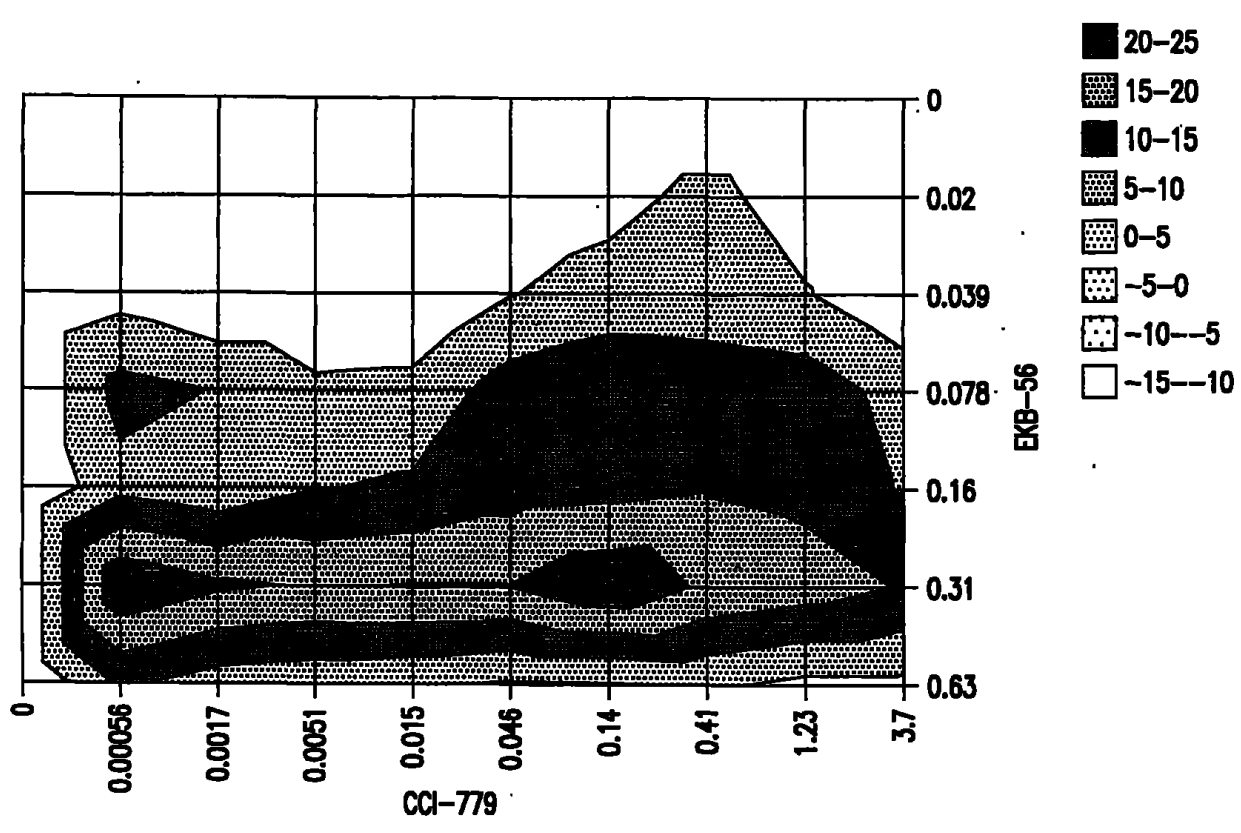
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102

INTERNATIONAL SEARCH REPORT

PCT/US 02/24841

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/395 A61P35/00 A61K31/4706 //(A61K31/395,31:4706)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
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) MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ, SCISEARCH		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Classification of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUPTA R A ET AL: "Combinations for cancer prevention." NATURE MEDICINE, (2000 SEP) 6 (9) 974-5., XP002223840 the whole document, especially from page 974, right-hand column, line 17 to page 975, left-hand column, line 18	1-37
A	TORRANCE C J ET AL: "Combinatorial chemoprevention of intestinal neoplasia." NATURE MEDICINE, (2000 SEP) 6 (9) 1024-8, XP002223841 the whole document	1-37
-/-		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in 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 claims or which is cited to establish the publication date of another citation or other special reason (see specification) "O" document relating 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 maintained 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. "Z" document member of the same patent family		
Date of the actual completion of the international search 9 December 2002		Date of mailing of the international search report 10/01/2003
Name and mailing address of the ISA European Patent Office, P.O. 6816 Patenkassen 2 NL - 6200 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 661 epo nl, Fax (+31-70) 340-3010		Authorized officer Venturini, F

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INTERNATIONAL SEARCH REPORT

PCT/US 02/24841

C.(Continued) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GREENBERGER L M (REPRINT) ET AL: "EKB - 569: a new irreversible inhibitor of epidermal growth factor receptor tyrosine kinase for the treatment of cancer." CLINICAL CANCER RESEARCH, (NOV 2000) VOL. 6, SUPP. 'S1, PP. 388-388. PUBLISHER: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202. ISSN: 1078-0432., XP001120789 MYETH AYERST RES, PEARL RIVER, NY 10965 abstract	1-37
A	GEOERGER B ET AL: "ANTITUMOR ACTIVITY OF THE RAPAMYCIN ANALOG CCI-779 IN HUMAN PRIMITIVE NEUROECTODERMAL TUMOR/MEDULLOBLASTOMA MODELS AS SINGLE AGENT AND IN COMBINATION CHEMOTHERAPY" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 4, no. 61, 15 February 2001 (2001-02-15), pages 1527-1532, XP001079526 ISSN: 0008-5472 the whole document	1-37
A	US 5 066 493 A (SEHGAL SURENDRA N ET AL) 19 November 1991 (1991-11-19) the whole document	1-37
P,A	WO 02 13802 A (AMERICAN HOME PROD) 21 February 2002 (2002-02-21) the whole document	1-37

INTERNATIONAL SEARCH REPORT

PCT/US 02/24841

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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:
Although claims 1-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 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 II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US 02/24841

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5066493	A	19-11-1991	US 5206018 A	27-04-1993
			US 4885171 A	05-12-1989
			BE 877700 A1	14-01-1980
			JP 55073616 A	03-06-1980
			ZA 7905449 A	26-11-1980
WO 0213802	A	21-02-2002	AU 8313901 A	25-02-2002
			WO 0213802 A2	21-02-2002
			US 2002045638 A1	18-04-2002

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A61K 31/47, A61P 35/00(74) Agent: MORAN, Daniel, R.; Wyeth, Patent Law Dept.,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
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SON, Bernard, Dean; 47 Park Road, Stony Point, NY
10980 (US). OVERBEEK-KLUMPERS, Elsiebe, Geraldine;
Plantage 5, NL-3742 DL Baarn (NL).

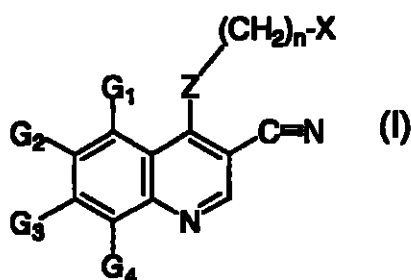
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 03/050090 A1

(54) Title: 3-CYANOQUINOLINES AS INHIBITORS OF EGF-R AND HER2 KINASES

(57) Abstract: This invention provides compounds of Formula (I), represented
by the structure wherein G₁, G₂, G₃, G₄, Z, X and n are defined herein, or a phar-
macologically acceptable salt thereof which are useful as antineoplastic agents
and in the treatment of polycystic kidney disease.

3-CYANOQUINOLINES AS INHIBITORS OF EGF-R AND HER2 KINASES**FIELD OF THE INVENTION**

5

This invention relates to certain substituted 3-cyanoquinoline compounds as well as the pharmaceutically acceptable salts thereof. The compounds of the present invention inhibit the action of certain growth factor receptor protein tyrosine kinases (PTK) and other protein kinases thereby inhibiting the abnormal growth of certain
10 cell types. The compounds of this invention are therefore useful for the treatment of certain diseases that are the result of deregulation of these PTKs. The compounds of this invention are anti-cancer agents and are useful for the treatment of cancer in mammals. In addition, the compounds of this invention are useful for the treatment of polycystic kidney disease in mammals. This invention also relates to the manufacture
15 of said 3-cyanoquinolines, their use for the treatment of cancer and polycystic kidney disease, and the pharmaceutical preparations containing them.

BACKGROUND OF THE INVENTION

20

Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP to a tyrosine residue located on a protein substrate. Protein tyrosine kinases clearly play a role in normal cell growth. Many of the growth factor receptor proteins function as tyrosine kinases and it is by this process that they effect signaling. The interaction of growth factors with these receptors is a necessary
25 event in normal regulation of cell growth. However, under certain conditions, as a result of either mutation or overexpression, these receptors can become deregulated. The result of this is uncontrolled cell proliferation which can lead to tumor growth and ultimately to the disease known as cancer [Wilks A.F., *Adv. Cancer Res.*, 60, 43 (1993) and Parsons, J.T.; Parsons, S.J., *Important Advances in Oncology*, DeVita V.T. Ed., J.B. Lippincott Co., Phila., 3 (1993)]. Among the growth factor receptor
30 kinases and their proto-oncogenes that have been identified and which are targets of the compounds of this invention are the epidermal growth factor receptor kinase (EGF-R kinase, the protein product of the erbB oncogene), and the product produced

by the Her2 (also referred to as the *neu* or *erbB-2*) oncogene. Since the phosphorylation event is a necessary signal for cell division to occur and since overexpressed or mutated kinases have been associated with cancer, an inhibitor of this event, a protein tyrosine kinase inhibitor, will have therapeutic value for the treatment of cancer and other diseases characterized by uncontrolled or abnormal cell growth. For example, overexpression of the receptor kinase product of the Her2 oncogene has been associated with human breast and ovarian cancers [Slamon, D. J., et al., *Science*, 244, 707 (1989) and *Science*, 235, 1146 (1987)]. Deregulation of EGF-R kinase has been associated with epidermoid tumors [Reese, M., et al., *Cancer Res.*, 51, 6254 (1991)], breast tumors [Macias, A., et al., *Anticancer Res.*, 7, 459 (1987)], and tumors involving other major organs [Gullick, W.J., *Brit. Med. Bull.*, 47, 87 (1991)]. Because of the importance of the role played by deregulated receptor kinases in the pathogenesis of cancer, many recent studies have dealt with the development of specific PTK inhibitors as potential anti-cancer therapeutic agents [some recent reviews: Burke, T.R., *Drugs Futura*, 17, 119 (1992) and Chang, C.J.; Geahlen, R.L., *J. Nat. Prod.*, 55, 1529 (1992)]. The compounds of this invention inhibit the kinase activity of EGF-R and Her2 and are therefore useful for treating certain disease states, such as cancer, that result, at least in part, from deregulation of these receptors. The compounds of this invention are also useful for the treatment and prevention of certain pre-cancerous conditions, such as the growth of colon polyps, that result, at least in part, from deregulation of these receptors.

It is also known that deregulation of EGF receptors is a factor in the growth of epithelial cysts in the disease described as polycystic kidney disease [Du J., Wilson P. D., *Amer. J. Physiol.*, 269(2 Pt 1), 487 (1995); Nauta, J., et al., *Pediatric Research*, 37(6), 755 (1995); Gattone, V.H., et al., *Developmental Biology*, 169(2), 504 (1995); Wilson, P.D., et al., *Eur. J. Cell Biol.*, 61(1), 131, (1993)]. The compounds of this invention, which inhibit the catalytic function of the EGF receptors, are consequently useful for the treatment of this disease.

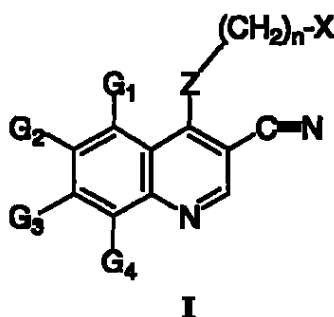
Some 3-cyanoquinoline derivatives are inhibitors of tyrosine kinases and are described in the application WO9843960 (US 6,002,008). These 3-cyanoquinolines may be substituted at carbon-5 through carbon-8 with an unsubstituted phenyl, alkene or alkynes group. Applications WO0018761 and WO0018740 also describe 3-cyanoquinoline inhibitors. A 3-cyanoquinoline with a 4-(2-methylanilino) substituent

having gastric (H⁺/K⁺)-ATPase inhibitory activity at high concentrations has been described [Ife, R., *J. Med. Chem.*, 35(18), 3413 (1992)].

The compounds of the present invention are 3-cyanoquinolines which inhibit the activity of protein kinases that are required for cell growth and differentiation and are therefore useful for the treatment of certain diseases that result from activity of these protein kinases. In particular, the compounds of this invention inhibit the kinase activity of EGF-R and Her2 kinases. The compounds of this invention are anti-cancer agents and are useful for the treatment of cancer in mammals. Further, the compounds of this invention are useful for the treatment of polycystic kidney disease in mammals.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided compounds represented by Formula (I):



wherein:

Z is -NH-, -O-, -S-, or -NR-;

R is alkyl of 1 to 6 carbon atoms, or carboalkyl of 2 to 7 carbon atoms;

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl groups of 1 to 6 carbon atoms; or

X is pyridinyl, pyrimidinyl, or aryl and may optionally be mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon

atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl
 of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1
 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkylC₁-C₆)S-, hydroxy,
 trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms,
 5 carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6
 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6
 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8
 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8
 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9
 10 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-
 alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10
 carbon atoms, mercapto, and benzoylamino; or

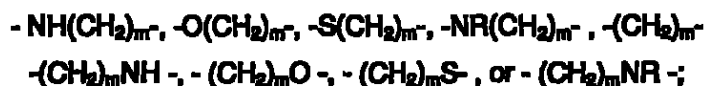
X is a bicyclic aryl or bicyclic heteroaryl ring system of 8 to 12 atoms, where the
 bicyclic heteroaryl ring contains 1 to 4 heteroatoms independently selected
 15 from N, O, and S; wherein the bicyclic aryl or bicyclic heteroaryl ring may be
 optionally mono-, di-, tri-, or tetra-substituted with a substituent selected from
 the group consisting of halogen, oxo, thio, alkyl of 1 to 6 carbon atoms,
 alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido,
 hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7
 20 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6
 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkylC₁-C₆)S-, hydroxy,
 trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms,
 carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C₆H₄S-),
 benzoyl, benzyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2
 25 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1 to 6
 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8
 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8
 carbon atoms, aminoalkyl of 1 to 5 carbon atoms, N-alkylaminoalkyl of 2 to 9
 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-
 30 alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10
 carbon atoms, mercapto, and benzoylamino; or

X is the radical —E—T—L ;

11)

E is pyridinyl, pyrimidinyl, or aryl optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;

T is substituted on E at carbon and is



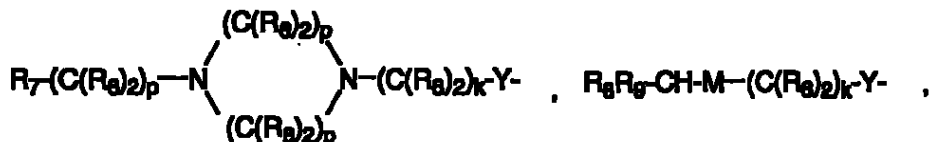
L is an aryl ring optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9

carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino; or

- 5 L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms independently selected from N, O, and S; wherein the heteroaryl ring may be optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C₆H₅S-), benzoyl, benzyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1 to 5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;
- 10 Pyridinyl, pyrimidinyl, or aryl are pyridinyl, pyrimidinyl, or aryl radicals, respectively, optionally mono- di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms,
- 15 20 25 30

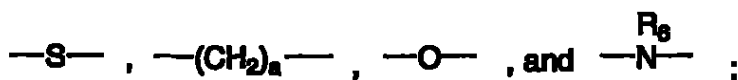
N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;

- 5 G₁, G₂, G₃, and G₄ are each, independently, hydrogen, halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, alkenyloxy of 2 to 6 carbon atoms, alkynyloxy of 2 to 6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 2 to 6 carbon atoms, alkenoyloxy of 3 to 6 carbon atoms, alkynoyloxy of 3 to 6 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkenoyloxymethyl of 4 to 9 carbon atoms, alkynoyloxymethyl of 4 to 9 carbon atoms, alkoxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, alkylsulphinyl of 1 to 6 carbon atoms, alkylsulphonyl of 1 to 6 carbon atoms, alkylsulfonamido of 1 to 6 carbon atoms, alkenylsulfonamido of 2 to 6 carbon atoms, alkynylsulfonamido of 2 to 6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C₆H₅S-), benzyl, amino, hydroxyamino, alkoxyamino of 1 to 4 carbon atoms, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6 to 12 carbon atoms, phenylamino, benzylamino, R₂NH,



- 25 $R_7-(C(R_6)_2)_p-Y-$, $R_7-(C(R_6)_2)_p-M-(C(R_6)_2)_k-Y-$, or $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_k-Y-$,
provided that either G₂ or G₃ or both G₂ and G₃ are R₂NH;

Y is a divalent radical selected from the group consisting of



R₇ is -NR₆R₆, -OR₆, -J, -N(R₆)₃⁺Q⁻, or -NR₆(OR₆) ;

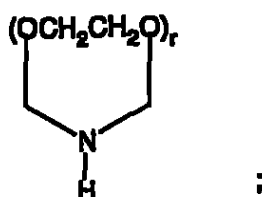
M is $>NR_6$, $-O-$, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$;

W is $>NR_6$, $-O-$ or is a bond;

Het is a heterocyclic radical selected from the group consisting of morpholine,

thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide,

5 piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane, tetrahydropyran, and



10

which may be optionally mono- or di-substituted on carbon with R_6 , hydroxy,

$-N(R_6)_2$, $-OR_6$, $-(C(R_6)_2)_8OR_6$ or $-(C(R_6)_2)_8N(R_6)_2$;

optionally mono-substituted on nitrogen with R_6 ; and

15 optionally mono or di-substituted on a saturated carbon with divalent radicals $-O-$ or $-O(C(R_6)_2)_8O-$;

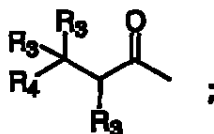
R_6 is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl

of 2 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, carboxyalkyl 2 to 7 carbon atoms, phenyl, or phenyl optionally

20 substituted with one or more halogen, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, amino, alkylamino of 1 to 3 carbon atoms, dialkylamino of 2 to 6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl C_1-C_6)S-, hydroxy, carboxyl, carboalkoxy of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C_6H_5S-), benzoyl, benzyl,

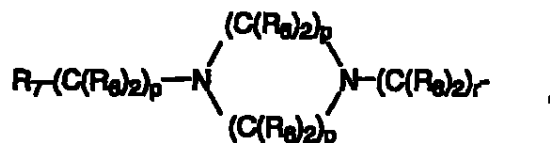
25 phenylamino, benzylamino, alkanoylamino of 1 to 6 carbon atoms, or alkyl of

1 to 6 carbon atoms; provided that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;
 R_2 is selected from the group consisting of



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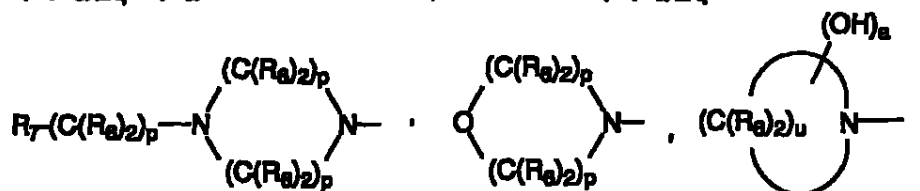
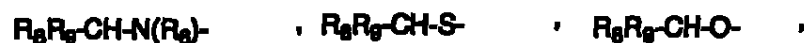
R_3 is hydrogen, alkyl of 1 to 6 carbon atoms, carboxy, carboalkoxy of 1 to 6 carbon atoms, phenyl, carboalkyl of 2 to 7 carbon atoms,



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$R_8 R_9 - CH - M - (C(R_8)_2)_r$, or $Het - (C(R_8)_2)_q - W - (C(R_8)_2)_r$;

R_4 is $-NR_8 R_9$, $-OR_8$, $-SR_8$,



15 cysteine, or a peptide comprised of 2 to 10 native amino acid residues containing at least one unoxidized cysteine residue wherein R_4 is bound to the rest of the molecule through the sulfur atom of one or more of the cysteine residues;

R_8 and R_9 are each, independently, $-(C(R_8)_2)_rNR_9R_8$ or $-(C(R_8)_2)_rOR_9$;

J is independently hydrogen, chlorine, fluorine, or bromine;

a is an integer of 0-1;

g is an integer of 1-8;

5 k is an integer of 0-4;

n is an integer of 0-1;

m is an integer of 0-3;

p is an integer of 2-4;

q is an integer of 0-4;

10 r is an integer of 1-4;

s is an integer of 1-6

u is an integer of 2-6;

Q^- is a counterion selected from salts formed from organic and inorganic acids;

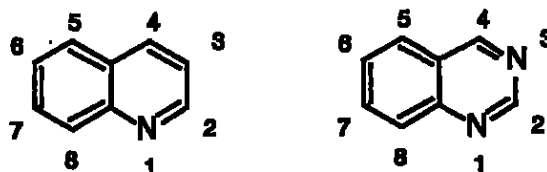
provided that:

- 15 a. when R_6 is alkenyl of 2 to 7 carbon atoms or alkynyl of 2 to 7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;
- b. when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+Q^-$, or $-NR_6(OR_6)$, then g is an integer of 2 to 6;
- 20 c. when M is $-O-$ and R_7 is $-OR_6$ then p is an integer of 1 to 4;
- d. when Y is $-NR_6-$ then k is an integer of 2 to 4;
- e. when Y is $-O-$ and M or W is $-O-$ then k is an integer of 1 to 4;
- f. when W is not a bond with Het bonded through a nitrogen atom then q is an integer of 2 to 4 and when W is a bond with Het bonded through a
- 25 nitrogen atom and Y is $-O-$ or $-NR_6-$ then k is an integer of 2 to 4;

or a pharmaceutically acceptable salt thereof.

The compounds of this invention are certain substituted 3-cyanoquinolines.

Throughout this patent application, the quinoline and quinazoline ring systems will be numbered as indicated in the formulas below.



Preferred bicyclic aryl or bicyclic heteroaryl ring systems include naphthalene, 1,2,3,4-tetrahydronaphthalene, tetralin, indane, 1-oxo-indane, 1,2,3,4-
 5 tetrahydroquinoline, naphthyridine, benzofuran, 3-oxo-1,3-dihydroisobenzofuran, benzothiadiphenene, 1,1-dioxobenzothiadiphenene, indole, 2,3-dihydroindole, 1,3-dioxo-2,3-dihydro-1H-isolindole, benzotriazole, 1H-indazole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, phthalimide, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyridine,
 10 pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, pyrido[3,4-b]pyridine, 1H-pyrazole[3,4-d]pyrimidine, 1,4-benzodioxane, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 2-oxo-2,3-dihydrobenzthiazole, 1,2-methylenedioxycyclohexene, 2-oxindole, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzazine, phthalazine, 1,4-dioxo-1,2,3,4-
 15 tetrahydrophthalazine, 2-oxo-1,2-dihydroquinoline, 2,4-dioxo-1,4-dihydro-2H-benzo[d][1,3]oxazine, 2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine, or cinchonine.

A preferred cysteine containing peptide is glutathione.

20 When L is a 5 or 6-membered heteroaryl ring, preferred heteroaryl rings include pyridine, pyrimidine, imidazole, thiazole, thiazolidine, pyrrole, furan, thiophene, oxazole, or 1,2,4-triazole.

25 Either or both rings of the bicyclic aryl or bicyclic heteroaryl group may be fully unsaturated, partially saturated, or fully saturated. An oxo substituent on the bicyclic aryl or bicyclic heteroaryl moiety means that one of the carbon atoms has a carbonyl group. A thio substituent on the bicyclic aryl or bicyclic heteroaryl moiety means that one of the carbon atoms has a thiocarbonyl group. When a compound of this
 30 invention contains a moiety which contains a heteroaryl ring, such heteroaryl ring does not contain O-O, S-S, or S-O bonds in the ring.

When L is a 5 or 6-membered heteroaryl ring, it may be fully unsaturated, partially saturated, or fully saturated. The heteroaryl ring can be bound to T via carbon or

nitrogen. An oxo substituent on the heteroaryl ring means that one of the carbon atoms has a carbonyl group. A thio substituent on the heteroaryl ring means that one of the carbon atoms has a thiocarbonyl group.

- 5 The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxymethyl, alkanoyloxymethyl, alkylsulphinyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, carboxyalkyl, carboalkoxyalkyl, alkanoylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkylaminoalkoxy, and N,N-dialkylaminoalkoxy include both straight chain as well as branched carbon chains of 1 to 6 carbon atoms. The alkenyl
- 10 portion of the alkenyl, alkenoyloxymethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains of 2 to 6 carbon atoms and one or more sites of unsaturation and all possible configurational isomers. The alkynyl portion of the alkynyl, alkynoyloxymethyl, alkynylsulfonamido, alkynyloxy, substituents include both straight chain as well as branched carbon
- 15 chains of 2 to 6 carbon atoms and one or more sites of unsaturation. Carboxy is defined as a $-CO_2H$ radical. Carboalkoxy of 2 to 7 carbon atoms is defined as a $-CO_2R^a$ radical, where R^a is an alkyl radical of 1 to 6 carbon atoms. Carboxyalkyl is defined as a HO_2C-R^b radical where R^b is a divalent alkyl radical of 1 to 6 carbon atoms. Carboalkoxyalkyl is defined as a $R^cO_2C-R^d$ radical where R^d is a divalent
- 20 alkyl radical and where R^a and R^b together have 2 to 7 carbon atoms. Carboalkyl is defined as a $-COR^e$ radical, where R^e is an alkyl radical of 1 to 6 carbon atoms. Alkanoyloxy is defined as a $-OCOR^f$ radical, where R^f is an alkyl radical of 1 to 6 carbon atoms. Alkanoyloxymethyl is defined as a $R^gCO_2CH_2$ radical, where R^g is an alkyl radical of 1 to 6 carbon atoms. Alkoxymethyl is defined as a R^hOCH_2
- 25 radical, where R^h is an alkyl radical of 1 to 6 carbon atoms. Alkylsulphinyl is defined as a R^iSO radical, where R^i is an alkyl radical of 1 to 6 carbon atoms. Alkylsulphonyl is defined as a R^jSO_2 radical, where R^j is an alkyl radical of 1 to 6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as a R^kSO_2NH radical, where R^k is an alkyl radical of 1 to 6 carbon atoms, an
- 30 alkenyl radical of 2 to 6 carbon atoms, or an alkynyl radical of 2 to 6 carbon atoms, respectively. N-alkylcarbamoyl is defined as a R^lNHCO radical, where R^l is an alkyl radical of 1 to 6 carbon atoms. N,N-dialkylcarbamoyl is defined as a R^mR^nNCO

radical, where R^* is an alkyl radical of 1 to 6 carbon atoms, R^1 is an alkyl radical of 1 to 6 carbon atoms and R^1 and R^* may be the same or different. When X is substituted, it is preferred that it is mono-, di-, or tri-substituted, with mono- and di-substituted being most preferred. It is preferred that of the substituents G_1 and G_4 , at least one is hydrogen and it is most preferred that both be hydrogen. It is also preferred that X is a phenyl ring optionally substituted, Z is $-NH-$, and n is an integer of 0.

Het is a heterocycle, as defined above which may be optionally mono- or di-substituted on carbon with R_6 , optionally mono-substituted on nitrogen with R_6 , optionally mono- or di-substituted on carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on carbon with $-(C(R_6)_2)_3OR_6$ or $-(C(R_6)_2)_3N(R_6)_2$, and optionally mono or di-substituted on a saturated carbon with divalent $-O-$ or $-O(C(R_6)_2)_3O-$ (carbonyl and ketal groups, respectively); In some cases when Het is substituted with $-O-$ (carbonyl), the carbonyl group can be hydrated. Het may be bonded to W when q is an integer of 0 via a carbon atom on the heterocyclic ring, or when Het is a nitrogen containing heterocycle which also contains a saturated carbon-nitrogen bond, such heterocycle may be bonded to carbon, via the nitrogen when W is a bond. When q is an integer of 0 and Het is a nitrogen containing heterocycle which also contains an unsaturated carbon-nitrogen bond, that nitrogen atom of the heterocycle may be bonded to carbon when W is a bond and the resulting heterocycle will bear a positive charge. When Het is substituted with R_6 , such substitution may be on a ring carbon, or in the case of a nitrogen containing heterocycle, which also contains a saturated carbon-nitrogen bond, such nitrogen may be substituted with R_6 or in the case of a nitrogen containing heterocycle, which also contains an unsaturated carbon-nitrogen bond, such nitrogen may be substituted with R_6 in which case the heterocycle will bear a positive charge.

Preferred heterocycles include pyridine, 2,6-disubstituted morpholine, 2,5-disubstituted thiomorpholine, 2-substituted imidazole, substituted thiazole, N-substituted imidazole, N-substituted 1,4-piperazine, N-substituted piperidine, and N-substituted pyrrolidine.

The peptides included among the R_4 substituents are comprised of 2 to 10 native amino acid residues containing at least one unoxidized cysteine residue. The N-terminus of these peptides can be acylated with a C_1 - C_5 alkanoyl group and/or the C-terminus can be esterified with a C_1 - C_5 alkoxy group. In those cases where there are more than one cysteine residue, each cysteine can optionally be bound to a 3-cyanoquinoline through the sulfur atom.

Z may be for example $-NH-$. An example of n is 0. In some embodiments X may be for example $-E-T-L$. E may be for example optionally substituted aryl. T may be $O(CH_2)_m-$ wherein m is 0 or 1. L may be for example optionally substituted aryl or optionally substituted heteroaryl such as pyridine, pyrimidine, imidazole, thiazole, thiazolidine, pyrrole, furan, thiophene, oxazole and 1,2,4-triazole.

In some embodiments X is optionally substituted aryl, e.g., optionally substituted phenyl.

In other embodiments X may be substituted or unsubstituted bicyclic aryl or bicyclic heteroaryl ring system such as naphthalene, 1,2,3,4-tetrahydronaphthalene, indane, 1-oxo-indane, 1,2,3,4-tetrahydroquinoline, naphthyridine, benzofuran, 3-oxo-1,3-dihydroisobenzofuran, benzothiadaphene, 1,1-dioxobenzothiadaphene, indole, 2,3-dihydroindole, 1,3-dioxo-2,3-dihydro-1H-isoindole, benzotriazole, 1H-indazole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole, purine, phthalimide, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyridine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, pyrido[3,4-b]pyridine, 1H-pyrazole[3,4-d]pyrimidine, 1,4-Benzodioxane, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 2-oxo-2,3-dihydrobenzthiazole, 1,2-methylenedioxybenzene, 2-oxindole, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzazine, phthalazine, 1,4-dioxo-1,2,3,4-tetrahydrophthalazine, 2-oxo-1,2-dihydroquinoline, 2,4-dioxo-1,4-dihydro-2H-benzo[d][1,3]oxazine, 2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine and cinnoiline.

Optional substituent(s) may be for example selected from halogen, eg chlorine and phenyl.

In some embodiments G_1 and G_4 are both H.

5

R_4 may be for example NR_6R_8 or a peptide of 2 to 10 native amino acid residues containing at least one unoxidized cysteine residue wherein R_4 is bound to the rest of the molecule through the sulfur atom of one or more of the cysteine residues.

10

Each R_5 may be selected from hydrogen, alkyl of 1 to 6 carbon atoms, R_7 , $(C(R_6)_2)_n$ wherein R_7 is NR_6R_8 and $Het-(C(R_6)_2)_q-W-(C(R_6)_2)_r$.

15

In the compounds of the invention each R_6 may be selected from hydrogen and alkyl of 1 to 6 carbon atoms.

Preferred compounds of this invention are described below. Except as otherwise indicated below, the substituents are as defined above.

20 A. Compounds according to Formula (I), wherein Z is $-NH-$, n is an integer of 0, and X is aryl optionally substituted or a pharmaceutically acceptable salt thereof.

B. Compounds according to Formula (I), wherein Z is $-NH-$, n is an integer of 0, X is phenyl optionally substituted or a pharmaceutically acceptable salt thereof.

25

C. Compounds according to Formula (I), wherein Z is $-NH-$, n is an integer of 0, X is aryl optionally substituted and G_1 and G_4 are H or a pharmaceutically acceptable salt thereof.

30 D. Compounds according to Formula (I), wherein Z is $-NH-$, n is an integer of 0, X is substituted or unsubstituted bicyclic aryl or bicyclic heteroaryl ring system, or a pharmaceutically acceptable salt thereof.

E. Compounds according to Formula (I), wherein Z is -NH-, n is an integer of 0, X is phenyl optionally substituted and G₁ and G₄ are H or a pharmaceutically acceptable salt thereof.

5

Specifically preferred compounds of this invention or a pharmaceutically acceptable salt thereof include:

10 N-(4-{3-chloro-4-[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]anilino}-3-cyano-7-methoxy-6-quinoliny)-3,4-bis(dimethylamino)-2-butanamide,

N-{4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl}-3,4-bis-(3-hydroxy-pyrrolidin-1-yl)-butanamide,

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N-{4-(3-Chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinoliny)-3-(dimethylamino)butanamide,

20 N-{4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny)-3,6-bis(dimethylamino)hexanamide,

N-{4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny)-3,4-di(1-pyrrolidinyl)butanamide,

25 (2R)-2-amino-5-({2-[(carboxymethyl)amino]-1-[(3-[[4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinoliny]amino]-1-[(dimethylamino)methyl]-3-oxopropyl)sulfanyl)methyl]-2-oxoethyl}amino)-5-oxopentanoic acid, and

30 N-{4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny)-3,4-bis(dimethylamino)butanamide,
or a pharmaceutically acceptable salt thereof.

The compounds of this invention may contain one or more asymmetric carbon atoms; in such cases, the compounds of this invention include the individual diastereomers, the racemates, and the individual R and S enantiomers thereof.

Some of the compounds of this invention may contain one or more double bonds; in such cases, the compounds of this invention include each of the possible configurational isomers as well as mixtures of these isomers. When a compound of this invention contains a moiety containing the same substituent more than once (for example, when R_7 is $-NR_8R_9$), each substituent (R_8 in this example) may be the same or different.

For the compounds of Formula (I) defined above and referred to herein, unless otherwise noted, the following terms are defined:

Halogen, as used herein means chloro, fluoro, bromo and iodo.

Alkyl as used herein means a branched or straight chain having from 1 to 6 carbon atoms. Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl optionally substituted with phenyl, phenyl optionally substituted with one or more substituents preferably from one to three substituents independently selected from alkyl, alkoxy, perhaloalkyl, halogen, nitro, hydroxy, amino, carboxy, carboxyalkyl, alkylamino and dialkylamino, thioalkyl, alkoxycarbonyl and acyl.

Alkenyl as used herein means a branched or straight chain having from 2 to 6 carbon atoms, the chain containing at least one carbon-carbon double bond and all possible configurational isomers. Alkenyl, may be used synonymously with the term olefin and includes alkylidenes. Exemplary alkenyl groups include ethenyl, propenyl, 1,4-butadienyl, 3-hexen-1-yl and the like optionally substituted with phenyl, phenyl optionally substituted with one or more substituents preferably from one to three substituents independently selected from alkyl, alkoxy, perhaloalkyl, halogen, nitro, hydroxy, amino, carboxy, carboxyalkyl, alkylamino and dialkylamino, thioalkyl, alkoxycarbonyl and acyl.

An alkynyl group is defined as straight or branched carbon chain of 2 to 6 carbon atoms that contains at least one carbon-carbon triple bond and includes propynyl and the like optionally substituted with phenyl, phenyl optionally substituted with one or more substituents preferably from one to three substituents independently selected from alkyl, alkoxy, perhaloalkyl, halogen, nitro, hydroxy, amino, carboxy, carboxyalkyl, alkylamino and dialkylamino, thioalkyl, alkoxycarbonyl and acyl.

Alkoxy as used herein means an alkyl-O- group in which the alkyl group is as previously described. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, t-butoxy and polyethers including $-O-(CH_2)_2OCH_3$.

Cycloalkyl as used herein means a simple carbocycle having a saturated ring having from 3 to 7 carbon atoms and more preferably from 3 to 6 carbon atoms optionally substituted with 1 to 3 independently selected alkyl groups of 1 to 6 carbon atoms. Exemplary cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl and the like.

Aryl as used herein means a mono or bicyclic aromatic ring having from 6 to 12 carbon atoms. Monocyclic rings preferably have 6 members and bicyclic rings preferably have 8, 9, 10 or 12 membered ring structures. Exemplary aryl groups include phenyl, alpha-naphthyl, beta-naphthyl, indene, and the like independently substituted with one or more substituents and more preferably with 1 to 3 substituents. Phenyl as used herein refers to a 6-membered aromatic ring optionally mono, di or tri-substituted.

Heteroaryl denotes an unsubstituted or optionally substituted monocyclic 5 or 6 membered ring, which contains 1 to 4, or particularly 1 or 2 heteroatoms which may be the same or different. Nitrogen, oxygen and sulfur are the preferred heteroatoms, provided that the heteroaryl does not contain O-O, S-S or S-O bonds. Specific examples include thiophene, furan, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiazole, oxazole, isothiazole, isoxazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine and 1,3,5-triazine. The heteroaryl ring may be oxidized when a heteroatom is a nitrogen atom

to provide the corresponding N-oxide, including pyridine -N-oxide. The heteroaryl ring may be oxidized on a sulfur atom to provide the corresponding sulfoxide or sulfone, including thiophene -1-oxide. The heterocyclic ring may contain a carbonyl group on one of the carbon atoms, such as 1,3,4-oxadiazol-2-one.

5

Bicyclic heteroaryl as used herein refers to saturated or partially unsaturated bicyclic fused rings having 8 to 20 ring atoms containing 1 to 4 heteroatoms which may be the same or different independently selected from nitrogen, oxygen and sulfur optionally substituted with 1 to 3, independently selected substituents which may be the same or different provided that the bicyclic heteroaryl does not contain O-O, S-S or S-O bonds. Specific examples include: indole, 2,3-dihydroindole, 2-indazole, isindazole, quinoline, isoquinoline, tetrahydroquinoline, benzofuran, benzothiophene, benzimidazole, benzotriazole, benzothiazole, benzoxazole, benzisoxazole, 1,2-benzopyran, cinnoline, phthalazine, quinazoline, 1,8-
10 naphthyridine, pyrido[3,2-b]pyridine, pyrido[3,4-b]pyridine, pyrido[4,3-b]pyridine, pyrido[2,3-d]pyrimidine, purine, and pteridine and the like. Either or both rings of the bicyclic ring system may be partially saturated, or fully saturated. The bicyclic group may be oxidized on a nitrogen atom to provide the corresponding N-oxide, such as quinoline -N-oxide. The bicyclic group may be oxidized on a sulfur atom to provide
15 the corresponding sulfoxide or sulfone, such as benzothiophene-1-oxide. The bicyclic ring system may contain a carbonyl group on one of the carbon atoms, such as 2-indanone.

20

Where terms are used in combination, the definition for each individual part of the combination applies unless defined otherwise. For instance, perhaloalkyl refers to an alkyl group, as defined above and perhalo refers to all hydrogen atoms on the alkyl group being substituted with a halogen as defined above. An example is trifluoromethyl.

25

30 Some of the compounds of the invention have centers of asymmetry. The compounds may, therefore, exist in at least two and often more stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with other stereoisomers in any proportion

and thus includes, for instance, racemic mixture of enantiomers as well as the diastereomeric mixture of isomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography. Optically active isomers may be prepared, for example, by resolving racemic derivatives or by asymmetric syntheses. The resolution can be carried out by the methods known to those skilled in the art such as in the presence of a resolving agent, by chromatography, or combinations thereof.

The compounds of Formula (I) may be obtained as inorganic or organic salts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH publishers, 411-415, 1989). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility.

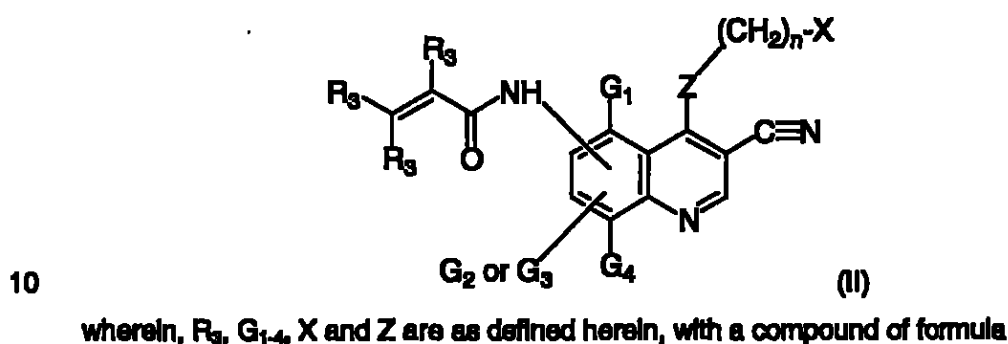
Pharmaceutically acceptable salts of the compounds of Formula (I) with an acidic moiety may be formed from organic and inorganic bases. For example with alkali metals or alkaline earth metals such as sodium, potassium, lithium, calcium, or magnesium or organic bases and N-tetraalkylammonium salts such as N-tetrabutylammonium salts. Similarly, when a compound of this invention contains a basic moiety, salts may be formed from organic and inorganic acids (i.e. $-N(R_6)_3Q^+$). For example salts may be formed from acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphoresulfonic, and similarly known acceptable acids. Q^+ is a counterion which includes but is not limited to acetate, chloride, bromide and nitrate. The compounds can also be used in the form of esters, carbamates and other conventional prodrug forms, which when administered in such form, convert to the active moiety in vivo.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

In addition to the utilities, described herein some of the compounds of this invention are intermediates useful for the preparation of other compounds of this invention.

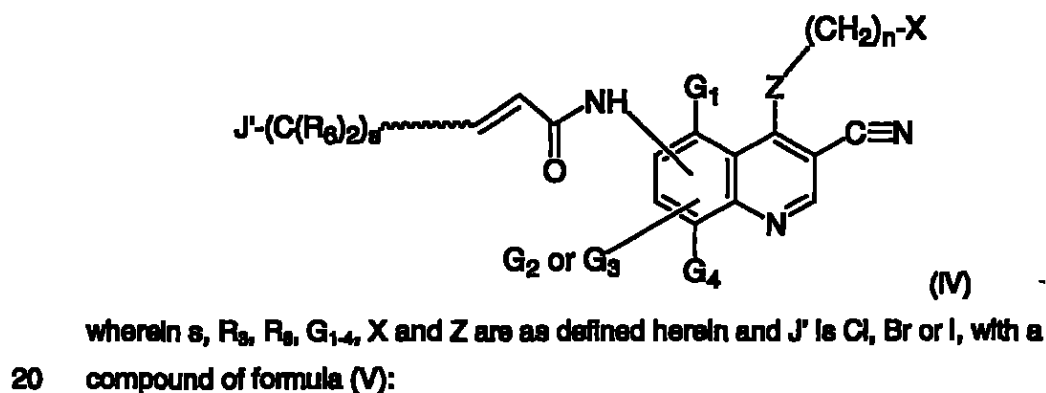
- 5 This invention also provides processes for preparing the compounds of formula (I) which processes comprise one of the following:

a) reacting a compound of formula (II)

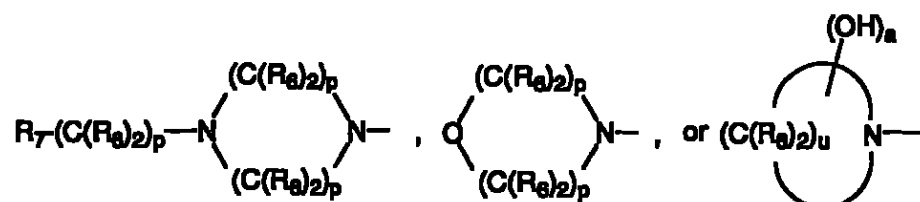
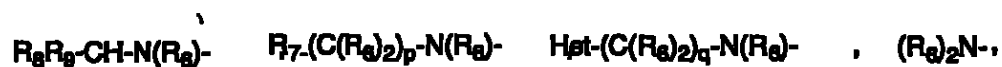


- 15 wherein R_4 is as defined herein, to give a corresponding compound of formula (I);
or

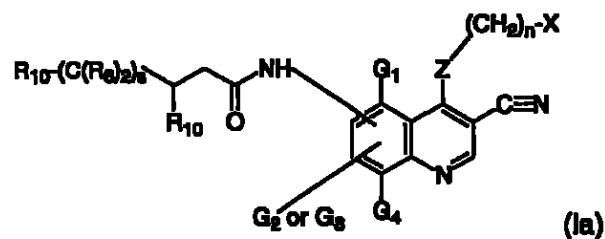
b) reacting a compound of formula (IV)



wherein wherein R_{10} is a radical selected from the group:



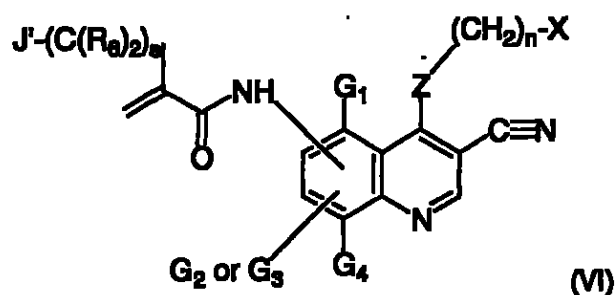
wherein a, R₆, R₇, R₈, R₉, p, u, and q are as defined herein, to give a corresponding compound of formula (Ia)



5

or

c) reacting a compound of formula (VI):

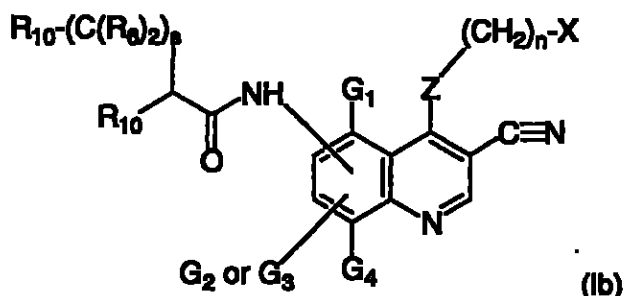


10

wherein s , R_9 , R_8 , G_{1-4} , X and Z are as defined herein and J' is Cl, Br or I, with a compound of formula (V):



15 wherein R_{10} is as defined above, to give a corresponding compound of formula (1b):



If necessary in any of the reactions described herein reactive substituent groups or sites may be protected prior to the reaction and released thereafter.

5

The compounds of this invention may conveniently be prepared from: (a) commercially available starting materials (b) known starting materials which may be prepared as described in literature procedures or (c) new intermediates described in the schemes and experimental procedures herein.

10 Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This may necessitate judgement as to the order of synthetic steps. Appropriate
15 consideration must be made as to the protection of reactive functional groups to prevent undesired side reactions.

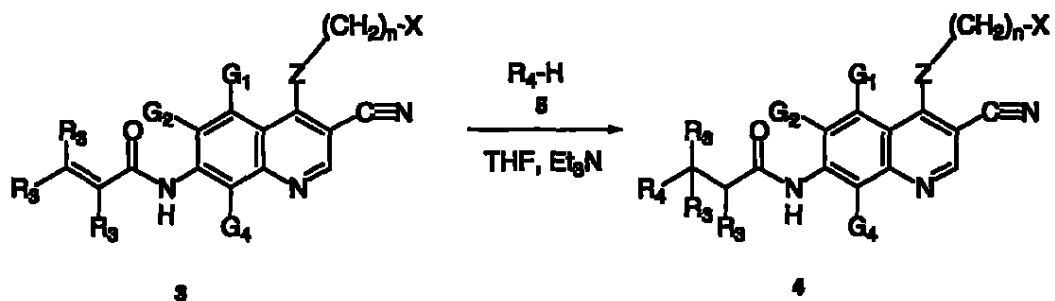
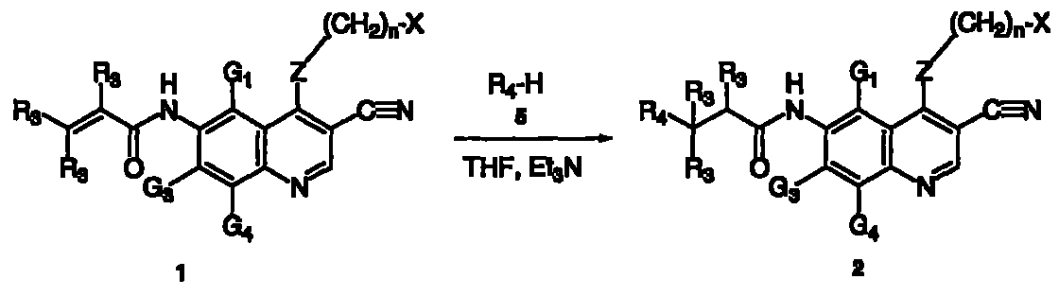
Substituents on the starting materials may be incompatible with some of the reaction conditions. Such restrictions to the substituents which are compatible with the reaction conditions will be apparent to one skilled in the art. Reactions were run under inert atmospheres where appropriate.

The preparation of the compounds of this invention encompassed by formulas 2 and 4 is illustrated below in Flowsheet 1 where Z, X, n, R₃, R₄, G₁, G₂, G₃, and G₄ are as described above. Treatment of the unsaturated amide of formula 1 or 2 with an alcohol, amine, mercaptan, or cysteine containing peptide of formula 5 in an inert solvent such as tetrahydrofuran in the presence of a basic catalyst such as triethylamine and the like results in a Michael addition reaction producing the compounds of this invention represented by formulas 2 and 4. In some case where

the compounds 1 or 3 already contain a basic functional group, it may not be necessary to add an additional basic catalyst to obtain the compounds of this invention 2 and 4, respectively. In those cases where the product contains more than one asymmetric carbon atom, the resulting diastereomers can be separated by

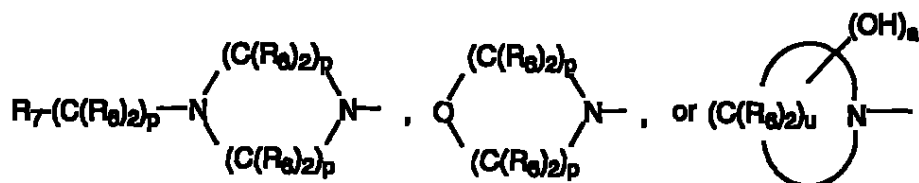
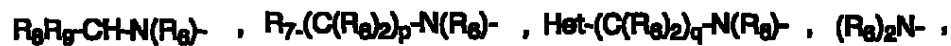
5 chromatographic methods.

Flowsheet 1



5

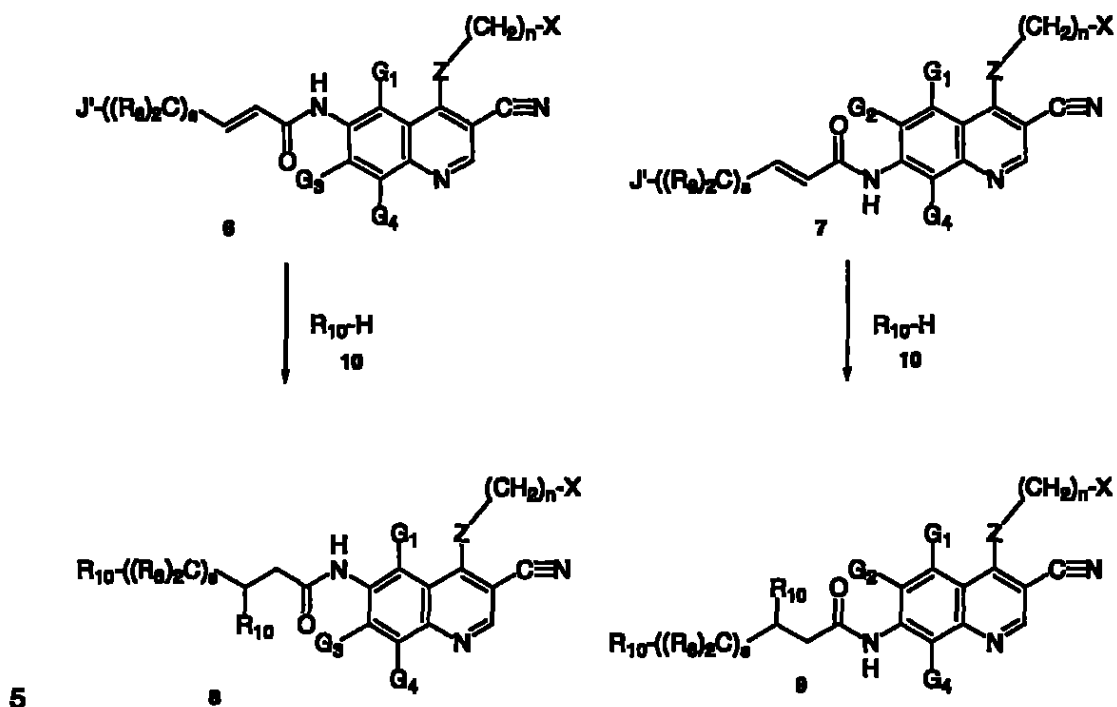
Compounds of this invention represented by formulas 8 and 9 may also be prepared as shown below in Flowsheet 2 wherein Z, X, n, R₃, R₄, G₁, G₂, G₃, and G₄ are as described above. J' is the halogen atom Br, I, or Cl and 10 is a primary or secondary amine wherein R₁₀ is a radical selected from the group:



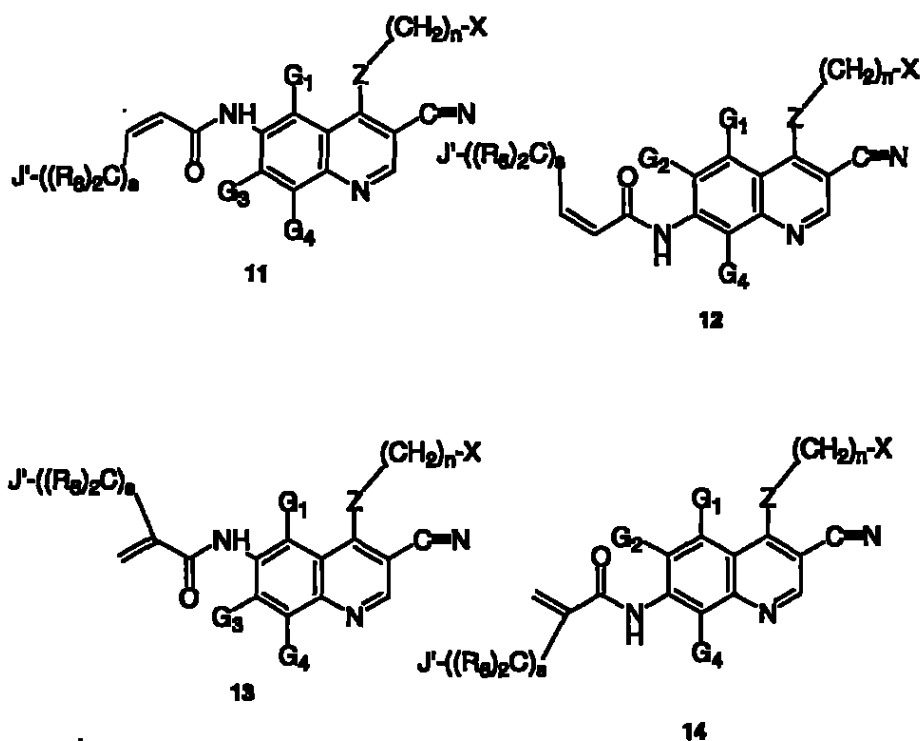
wherein R₆, R₇, R₈, R₉, p, u, and q are as defined above. The reaction of compounds 6 or 7 with an amine 10 in an inert solvent such as tetrahydrofuran or acetonitrile results in a two step process involving displacement of the halogen atom with the

amine and a Michael addition of the amine to the double bond of the unsaturated amide giving the compounds of this invention 8 or 9, respectively.

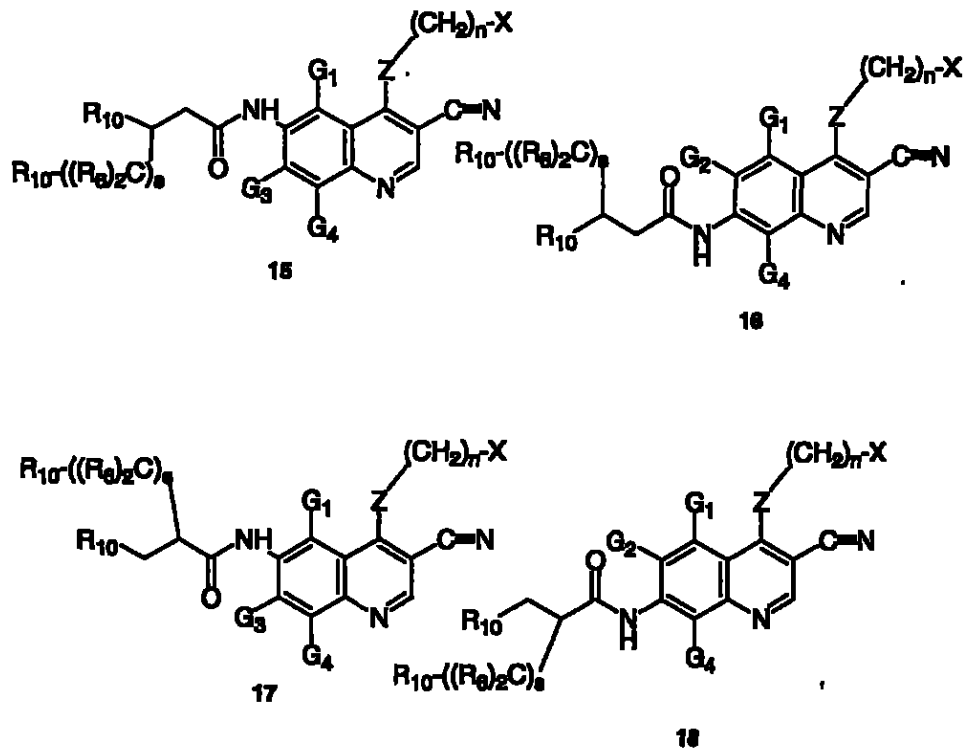
Flowsheet 2



Similar chemistry may be applied to the isomeric intermediates 11-14 to give other compounds of this invention 15-18.



The starting materials 1, 3, 6, 7, and 11-14 needed to prepare the compounds of this invention may be prepared as described in the patent US 6,002,008 and in the applications WO0018761 and WO0018740.



Representative compounds of this invention were evaluated in several standard pharmacological test procedures that showed that the compounds of this invention possess significant activity as inhibitors of protein kinases and are antiproliferative agents. Disease states which can be treated or inhibited by protein kinase inhibitors include those in which the etiology is at least in part caused by a defect upstream in a signaling pathway from a protein kinase (i.e., colon cancer); those in which the etiology is at least in part caused by an overexpressed protein kinase (i.e., lung cancer and colonic polyps); and those in which the etiology is at least in part caused by a dysregulated protein kinase (gene turned on at all times; glioblastoma).

Based on the activity shown in the standard pharmacological test procedures, the compounds of this invention are therefore useful as antineoplastic agents. In particular, these compounds are useful in treating, inhibiting the growth of, or eradicating neoplasms such as those of the breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, lung, pancreas, liver, prostate and skin.

In addition to having antineoplastic properties, the compounds of the present invention are useful in treating or inhibiting a variety of protein tyrosine kinase-associated disorders including: polycystic kidney disease, colonic polyps, restenosis;

atherosclerosis; angiofibromas; hemangiomas; diabetes; acute and chronic nephropathies; Kaposi's sarcoma; neovascularization associated with macular degeneration; rheumatoid arthritis; osteoarthritis; transplant rejection; psoriasis; lupus; graft versus host disease; glomerulonephritis; respiratory and skin allergies; 5 autoimmune alopecia; Autoimmune Hyperthyroidism; multiple sclerosis; atopic dermatitis; and systemic sclerosis; and are useful as antibacterial and antiviral agents.

As used in accordance with this invention, neoplasm and tumor are used interchangeably and mean an abnormal growth of tissue serving no physiological 10 function.

As used in accordance with this invention, the term providing an effective amount of a compound means either directly administering such compound, or administering a prodrug, derivative, or analog which will form an effective amount of the compound within the body.

15 In addition to the above utilities some of the compounds of this invention are useful for the preparation of other compounds of this invention.

The test procedures used and results obtained are shown below.

STANDARD PHARMACOLOGICAL TEST PROCEDURES

20

Representative compounds of this invention were evaluated in several standard pharmacological test procedures that showed that the compounds of this invention possess significant activity as inhibitors of protein tyrosine kinases and are antiproliferative agents. Based on the activity shown in the standard pharmacological 25 test procedures, the compounds of this invention are therefore useful as antineoplastic agents. The test procedures used and results obtained are shown below.

INHIBITION OF EPIDERMAL GROWTH FACTOR RECEPTOR KINASE (EGF-R) AND HER2 USING RECOMBINANT ENZYMES

30

A 1.7 kb cDNA encoding human HER2 cytoplasmic domain (HER2-CD, amino acid 676-1255) and 1.6 kb cDNA for EGFR cytoplasmic domain (EGFR-CD,

amino acid 645-1186) were cloned into baculoviral expression vectors, pBlueBacHis2B (Invitrogen) and pFASTBacHTc (GIBCO), separately. A sequence encoding (His)₆ is located at the 5' end upstream to HER2 and EGFR sequences. Sf-9 cells were infected at moi=10 for 3 days for protein expression. Sf-9 cell pellets

5 were solubilized on ice in buffer containing 50 mM HEPES, pH 7.4, 10 mM NaCl, 1% Triton, 10 μ M ammonium molybdate, 100 μ M sodium vanadate, 10 μ g/ml aprotinin, 10 μ g/ml leupeptin, 10 μ g/ml pepstatin, and 16 μ g/ml benzamidin HCl for 20 min followed by 20 min centrifugation. Crude extract supernatant was passed through equilibrated NI-NTA superflow packed column (QIAGEN, Valencia, CA) and wash with

10 10 mM, and 100 mM imidazole to remove unspecific binding. Histidine-tagged proteins were eluted with 250 mM and 500 mM imidazole and dialyzed against 50 mM NaCl, 20 mM HEPES, 10% glycerol and 1 μ g/ml each of aprotinin, leupeptin and pepstatin for 2 h. All the purification procedure was performed at 4°C or on ice. Purified materials were subjected for electrophoresis followed by Coomassie blue

15 stain to determine the purity of the preparation and Western blot for the identity of protein. Enzymes were aliquoted and stored at -80°C.

Inhibition of EGFR and HER2 kinase autophosphorylation was measured by a DELFIA/time-resolved fluorometry assay. Compounds were dissolved in 100% DMSO and diluted to the appropriate concentrations with 25 mM HEPES, pH 7.4. In

20 each well, 10 μ l of compound was incubated with 10 μ l of recombinant EGF-R or HER2 enzyme (1:80 dilution in 100 mM HEPES) for 10 min at room temperature. Then, 10 μ l of 5x buffer (containing 20 mM HEPES, 2 mM MnCl₂, 100 μ M Na₃VO₄ and 1 mM DTT) and 20 μ l of 0.1 mM ATP/50 mM MgCl₂ was added for 1 h. Positive and negative controls were included in each plate by incubation of enzyme with or

25 without ATP/MgCl₂. At the end of incubation, liquid was aspirated and washed three times with wash buffer. 75 μ l (400 ng) of europium-labeled anti-phosphotyrosine antibody was added to each well for another hour of incubation. After wash, enhancement solution was added and the signal was detected by Victor (Wallac Inc) with excitation at the wavelength of 340 nm and emission at the wavelength of 615

30 nm. All reagents were supplied by Wallac Inc (Wallac/Perkin-Elmer). Percentage of autophosphorylation inhibition by compound was calculated by $100 - [(text - negative control) / (positive control - negative control)]$. IC₅₀ values were obtained from curves of

percentage inhibition with 8 doses of compound. The results of these determinations for the compounds of this invention are shown below in Table 1.

Table 1

5 Inhibition of HER2 and EGF-R Kinases (IC_{50} μ g/mL)

Example	HER2 IC_{50} (μ g/mL)	HER2 %Inhibition at 2 μ g/mL	EGF-R IC_{50} (μ g/mL)
1	0.888		
1	0.529		3.2
1		63	
2		57	
3	4.7		0.33
5	1		1.0
7	0.022		
8	0.662		1.7

INHIBITION OF CANCER CELL GROWTH

- 10 Four human carcinoma cell lines, A431 (epidermoid carcinoma), SKBR3 (breast carcinoma), SW620 (colon carcinoma), and MDA-MB435 (breast carcinoma), BT474 (breast carcinoma), and two murine lines, 3T3 (murine fibroblasts) and HER2-3T3 (murine fibroblasts transfected with human HER2) were used for cell proliferation assays. Cells were maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum. Cells were plated in 96-well plates at the densities of 2.5×10^4 /ml for 3T3 and 3T3/HER2 and 5.0×10^4 /ml for the rest of the cell lines. On the next day, compounds were dosed at 0.5, 5, 50, 500, and 5000 ng/ml and cultured for 2 days. At the end of incubation, cell survival was determined by the sulforhodamine B assay as previously described (Skehan, P; Stornet, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica D., Warren, J.; Bokbosch, H.; Kenny, S.; Boyd, M. New Colorimetric Cytotoxic Assay for Anticancer-Drug Screening. *J. Natl. Cancer Inst.* 1990, 82, 1107-1112). The IC_{50} values (the concentration needed to inhibit cell growth by 50%) were
- 20

obtained from the growth curves and are shown below in Table 2 where the results of multiple determinations are included.

Table 2

5 Inhibition of Cancer Cell Growth *in vitro* (IC₅₀ μ g/mL)

Example	MDA-MB435	SW620	A431	SKBR3	3T3	HER2-3T3	BT474
1	0.42	0.67	0.242	0.006	0.76	0.041	
1	0.6	0.34	0.37	0.009	0.7	0.04	0.02
1	0.09	>5	0.28	0.003	0.57	0.03	
2	3.25	2.58	0.468	0.128	4.39	0.702	
2	4.05	2.95	0.572	0.129	4.47	1.26	
3	7.1		0.48	0.11			
3	2.8	1.1	0.27	0.17	1.3	1.7	
5	0.36		0.87	0.58			
5	0.49	0.19	0.73	0.14	0.42	1.1	
7	0.48		0.13	0.0025			
7	0.22	0.23	0.09	0.0025	0.35	0.017	
7		0.28	0.057	0.0011	0.37	0.014	
8	>5	>5		0.098	>5	2.24	
8	3.5	>5	0.2	0.107	>5	0.4	
8	1.9	>5	0.21	0.208	>5	0.35	

IN VIVO INHIBITION OF THE GROWTH OF MURINE 3T3 CELLS TRANSFECTED WITH HER2

10

Representative compounds of this invention (listed below) were evaluated in an *in vivo* standard pharmacological test procedure which measures their ability to inhibit tumor growth in nude mice. Murine 3T3 fibroblasts, transfected with Her2 were grown *in vitro*. Athymic nu/nu female mice (Charles River, Wilmington, MA) were

15 used in this *in vivo* standard pharmacological test procedure. A unit of 2×10^6 cells

- was injected SC into mice (day zero). Beginning on day 1, mice were treated IP every other day for a total of 11 days with a dose of 30mg/kg/dose of the compound to be evaluated in 0.5% Methocel/0.4% Tween 80. Control animals received vehicle alone. Tumor mass was determined every 7 days $[(\text{length} \times \text{width}^2)/2]$ for a period of 21 days. Absolute tumor growth in mgs, (mean tumor mass on days 7, 14 and 21), is calculated for each treatment group. Statistical analysis (Student t-test) of Mean Tumor Mass compares treated versus control groups. A p-value of ≤ 0.05 indicates a statistically significant reduction in tumor growth of treated group compared to the vehicle control.
- 10 The compound of Example 7 was evaluated for its ability to inhibit the growth of a murine fibroblast tumor that was transfected with human HER2 *in vivo* using the standard pharmacological test procedure described above. The results obtained are shown in Table 3.

Table 3

- 15 *In Vivo* Inhibition of the Growth of Tumors Composed of Murine Fibroblasts Transfect with Human HER2 in Mice by the Compound of Example 7.

a	b	c	d	b	c	d	b	e
Treatment	Day 7	% T/C	(p)	Day 14	% T/C	(p)	Day 21	S/T
Control (0.5% Methocel 0.4% Tween 80)	260			2222				0/20*
Compound of Example 7	39	15	<0.01	261	12	<0.01	1849	10/10

All compounds administered on days 1,3,5,7,9 and 11.

b) Mean Tumor Weight in mg.

c) $\%T/C = \frac{\text{Mean Tumor Weight of Treated Group}}{\text{Mean Tumor Weight of Placebo Group}} \times 100$

- 20 d) Statistical analysis (Student's t-test) of Tumor Weight. A p-value of ≤ 0.05 indicates a statistical significant reduction in Tumor Weight of Treated Group, compared to Placebo Control.
- e) S/T = No. Survivors/No. on Day +28 post tumor cell implantation
- 25 * Sacrificed on Day 14 due to tumor size.

As shown in Table 3, the compound of Example 7 significantly inhibited tumor growth. At 30 mg/kg (administered i.p.) on day 14, the tumors in the control mice were on average 8.5 times larger than the tumors in the mice that were treated with the compound of Example 7.

5 Based on the results obtained for representative compounds of this invention, the compounds of this invention are antineoplastic agents which are useful in treating, inhibiting the growth of, or eradicating neoplasms. In particular, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms that express EGFR such as those of the breast, kidney,
10 bladder, mouth, larynx, esophagus, stomach, colon, ovary, or lung. In addition, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms of the breast that express the receptor protein produced by the erbB2 (Her2) oncogene. Based on the results obtained, the compounds of this invention are also useful in the treatment of polycystic kidney disease.

15 The compounds of this invention may function *in vivo* as prodrugs. By the result of either a chemical reaction or metabolism, the compounds of this invention can be converted to other compounds that are useful for the treatment of cancer and polycystic kidney disease.

 The compounds of this invention may be formulated neat or may be
20 combined with one or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from
25 about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 80% by weight.

30 The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from

about 0.5 to about 1000 mg/kg of body weight, optionally given in divided doses two to four times a day, or in sustained release form. The total daily dosage is projected to be from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound

5 In intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The compounds of this invention may be administered orally as well as by
10 Intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants
15 customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-
20 filled or liquid-filled capsules. Oral administration of the compounds is preferred.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free
25 base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

30 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the

conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the treatment of cancer, the compounds of this invention can be administered in combination with other antitumor substances or with radiation therapy. These other substances or radiation treatments can be given at the same or at different times as the compounds of this invention. These combined therapies may effect synergy and result in improved efficacy. For example, the compounds of this invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cisplatin or cyclophosphamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antitumor angiogenic agents such as angiostatin, and antiestrogens such as tamoxifen.

The compounds of this invention and their preparation are illustrated by the following non-limiting examples.

Example 1

N-(4-(3-chloro-4-((4-phenyl-1,3-thiazol-2-yl)sulfanylanilino)-3-cyano-7-methoxy-6-quinolinyl)-3,4-bis(dimethylamino)-2-butanamide

A 12 ml portion of a 2M solution of dimethylamine in tetrahydrofuran was cooled in an ice bath, and 3.28 g (4.95 mmole) of N-(4-(3-chloro-4-((4-phenyl-1,3-thiazol-2-yl)sulfanylanilino)-3-cyano-7-methoxy-6-quinolinyl)-4-bromo-2-butanamide in 30 ml of N,N-dimethylformamide was added dropwise. The reaction warmed to come to room temperature, and stirred for a total of about 24 hours. The reaction was poured onto ice, and the resulting mixture was extracted with 1:1 (v/v) ethyl acetate-tetrahydrofuran. The solvents were removed *in vacuo*, and the residue was chromatographed on silica gel. The column was washed with 1:19 (v/v) methanol-ethyl acetate, then the product was eluted with 84:5:1 (v/v/v) ethyl acetate-methanol-triethylamine as a mixture of the title compound and N-(4-(3-chloro-4-((4-phenyl-1,3-thiazol-2-yl)sulfanylanilino)-3-cyano-7-methoxy-6-quinolinyl)-4-(dimethylamino)-2-butanamide. This mixture was re-chromatographed on silica gel, and the title

compound was eluted with 99:1 (v/v) methylene chloride-triethylamine. This gave 724 mg (23%) of N-(4-(3-chloro-4-((4-phenyl-1,3-thiazol-2-yl)sulfanylanilino)-3-cyano-7-methoxy-6-quinolinyl)-3,4-bis(dimethylamino)-2-butanamide. Electrospray MS (M+H) = 672.2, (M+2H) = 336.8.

5

Example 2

N-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-8-yl]-3,4-bis-(3-hydroxy-pyrrolidin-1-yl)-butyramide

10 N-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-6-quinolinyl]-4-bromo-2-butenamide (150 mg, 0.3 mmol) in 0.7 mL of DMF was reacted with (R)-(+)-3-pyrrolidinol (0.2 mL, 2.4 mmol) at room temperature. After reacting for 4 hours, the reaction solution was added into saturated sodium bicarbonate solution. The resulting precipitate was filtered and washed with water and ether consecutively to give 150 mg of the title compound as a light brown solid, mp 139-143° C; MS (ES) 15 m/z calcd. 583.2236, found 583.2242 (M+1).

Example 3

N-[4-(3-Chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinolinyl]-3-(dimethylamino)butanamide

20 To a stirred solution of N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinolinyl]-2-butenamide (0.212 g, 0.50 mmol) in 25 ml of 2.0 M dimethylamine in tetrahydrofuran was added 0.02 ml of 40% aqueous Triton B. After 66 h at 25°C the solution was concentrated, and the residue was partitioned between methylene chloride and water. The residue from the organic layer was dissolved in ether, and 25 the solution was passed onto a pad of Magnesol. The pad was washed with ether and ethyl acetate to give the product as an amber foam after evaporation (0.23 g). Mass spectrum (electrospray, m/e) 469.9 (M+H)⁺, 235.5 (M+2H)²⁺.

30

Example 4

N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]6-chloro-2-hexenamide

To a stirred solution of 6-amino-4-[4-(benzyloxy)-3-chloroanilino]-7-ethoxy-3-quinolinecarbonitrile (0.89 g, 2.0 mmol) and diisopropylethylamine (0.47 ml, 2.7 mmol) in 18 ml of tetrahydrofuran at 0°C was added a freshly-prepared solution of 6-chloro-2-hexenoyl chloride in 4 ml of tetrahydrofuran during 30 s. The mixture was then stirred at 25°C for 2.5 h and partitioned between ethyl acetate and water. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel with methylene chloride-ethyl acetate to give 0.83 g of amber solid; mass spectrum (electrospray, m/e) 574.8 (M+H)⁺.

Example 5

N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,6-bis(dimethylamino)hexanamide

A stirred mixture of N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]6-chloro-2-hexenamide (0.58 g, 1.0 mmol), NaI (0.15 g, 1.0 mmol), tetrabutylammonium iodide (74 mg, 0.20 mmol), 4.0 ml of dimethylformamide, and 10 ml of 2.0 M dimethylamine in tetrahydrofuran was heated at 50°C for 8 h. After the addition of 5 ml more 2.0 M dimethylamine in tetrahydrofuran the mixture was heated at 50°C for an additional 8 h. After evaporation of the dimethylamine and tetrahydrofuran, the mixture was stirred in water, brought to pH ~ 9 with potassium carbonate, and filtered. The crude product was washed with water, dried, and chromatographed on silica gel with methylene chloride-ethyl acetate-methanol-triethylamine to give 484 mg of the title compound as an off-white solid; mass spectrum (electrospray, m/e) 628.9 (M+H)⁺, 315.1 (M+2H)¹².

Example 6

(E)-N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-chloro-2-butenamide and (E)-N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-bromo-2-butenamide

A mixture of 3.4 g (7.68 mmol) of 6-amino-4-[4-(benzyloxy)-3-chloroanilino]-7-ethoxy-3-quinolinecarbonitrile and N,N-diisopropylethylamine (2.65 mL, 15.3 mmol), were

stirred in 68 mL of tetrahydrofuran, and cooled to 0°C. To this 4-bromo-but-2-enoylchloride (1.13 mL, 9.95 mmol) was added dropwise over a period of one hour. After stirring for 30 minutes, the solvent was evaporated, and the resulting oil was stirred with saturated sodium bicarbonate, and extracted with ethyl acetate. The layers were separated, and the organic layer was dried over sodium sulfate and evaporated to an oil. Purification was carried out by flash chromatography (50% ethyl acetate in methylene chloride), to give a tan solid (7.3 g, 80% yield), consisting of 50% of (E)-N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-chloro-2-butanamide and 50% of (E)-N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-bromo-2-butanamide, mp 117-120°C; MS (ESI) 547.1 (M+1), 593.0 (M+1).
Analyte for (50% C₂₉H₂₄BrClN₄O₃ + 50% C₂₉H₂₄Cl₂N₄O₃)·0.8H₂O:
Found: C, 59.32; H, 4.07; N, 9.45.
Calcd: C, 59.64; H, 4.42; N, 9.59.

15

Example 7

N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,4-di(1-pyrrolidinyl)butanamide

An amount of 612 mg (1.1 mmol) of (E)-N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-chloro-2-butanamide, and (E)-N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-4-bromo-2-butanamide, were stirred in 6 mL of N,N-dimethylformamide and cooled to -50°C. Pyrrolidine (55µL, 0.66 mmol), was added dropwise over a period of 30 min. After stirring for 2 hrs at -50°C, another 0.250 mL (3.0 mmol) of pyrrolidine was added dropwise over a period of 1.5 hrs, and the reaction mixture was warmed to room temperature for 16 hrs. A solution of saturated sodium bicarbonate was added, and the product was extracted with ethyl acetate and methylene chloride. Both organic layers were combined, dried over sodium sulfate, poured over a Magnesol plug, and evaporated to an oil. Purification was carried out by flash chromatography (40:4:2 = ethyl acetate: methanol: ammonium hydroxide), and preparative thin layer chromatography (40:4:1 = ethyl acetate: methanol: triethylamine), to give the title compound as an orange solid (284 mg, 40%), mp 85-87°C; ¹H NMR (DMSO-d₆) δ 10.59 (bs, 1H), 9.57 (s, 1H), 9.01 (s, 1H), 8.46 (s, 1H), 7.51-7.33 (m, 7H), 7.26-7.16 (m, 2H), 5.21 (s, 2H), 4.23 (q, 2H),

30

2.98 (bs, 1H), 2.71-2.80 (m, 8H), 2.49 (m, 2H) 1.74 (m, 5H), 1.64 (m, 5H), 1.43 (t, 3H); HRMS (ESI-FTMS) 653.29959 (M+1).

Example 8

5 (2R)-2-amino-5-((2-((carboxymethyl)amino)-1-(((3-((4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinolinyl)amino)-1-((dimethylamino)methyl)-3-oxopropyl)sulfanyl)methyl)-2-oxoethyl)amino)-5-oxopentanoic acid

A mixture of 0.50 g (1.07 mmol) of 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide, 0.328 g (1.07 mmol) of
10 glutathione, and 0.2 mL of triethylamine in a solvent mixture consisting of 10 mL of methanol, 4 mL of water, and 4 mL of tetrahydrofuran was stirred for 7 h and then stored overnight in the refrigerator. The solvents were removed at reduced pressure at 30°C. Ethanol was added and removed three times giving 0.81 g of the title compound as a tan powder. A sample of this was purified by HPLC. The product was
15 then isolated as the trifluoroacetate salt. Analysis for $C_{34}H_{40}N_5O_8ClFS + (C_2HF_3O_2)_n$: calcd: C, 43.00, H, 3.88, N, 10.03, Cl, 3.17; found: C, 42.23, H, 4.17, N, 10.03, Cl, 3.23.

Example 9

20 N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinolinyl]-3,4-bis(dimethylamino)butanamide

A solution of (E)-N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butanamide (400 mg, 0.719 mmol) and 1.5 mL of 2N dimethylamine in THF was heated at 36 °C in a sealed tube for 20 hours. After the volatile solvents were stripped off, the residue was treated with 1.5 mL of 2N
25 dimethylamine in THF, and heated again at 36 °C in a sealed tube for 20 hours. After the solvent was removed, the residue was purified by preparatory TLC (developed in ethyl acetate:methanol:triethylamine = 10:1:1) to yield 260 mg of the title compound as a yellow solid (yield: 60%), mp 102-104 °C; MS (ES) 601.3 (M+1).

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Example 10

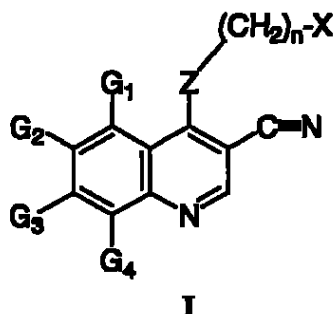
N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7ethoxy-6-quinoliny]-3,4-
bis(dimethylamino)butanamide

5 A solution of N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7ethoxy-6-quinoliny]-3,4-
bis(dimethylamino)butanamide (400 mg, 0.719 mmol) and 1.5 mL of 2N
dimethylamine in THF was heated at 36 °C in a sealed tube for 20 hours. After the
volatile solvents were stripped off, the residue was treated with 1.5 mL of 2N
dimethylamine in THF, and heated again at 36 °C in a sealed tube for 20 hours. After
10 the solvent was removed, the residue was purified by preparatory TLC (developed in
ethyl acetate:methanol:triethylamine = 10:1:1) to yield 260 mg of a yellow solid (yield:
60%), mp 102-104 °C; MS (ES) 601.3 (M+1).

WHAT IS CLAIMED IS:

1. A compound of Formula (I) represented by the structure:

5



wherein:

Z is -NH-, -O-, -S-, or -NR-;

- 10 R is alkyl of 1 to 6 carbon atoms, or carboalkyl of 2 to 7 carbon atoms;

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl groups of 1 to 6 carbon atoms; or

- X is pyridinyl, pyrimidinyl, or aryl which may optionally be mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxyethyl of 2 to 7 carbon atoms, alkanoyloxyethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkylC₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino; or
- 15
- 20
- 25

X is a bicyclic aryl or bicyclic heteroaryl ring system of 8 to 12 atoms, where the bicyclic heteroaryl ring contains 1 to 4 heteroatoms independently selected from N, O, and S; wherein the bicyclic aryl or bicyclic heteroaryl ring may be optionally mono-, di-, tri-, or tetra-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C₆H₅S-), benzoyl, benzyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1 to 5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino; or

X is the radical —E—T—L ;

E is pyridinyl, pyrimidinyl, or aryl optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-

alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;

T is substituted on E at carbon and is

- 5 b) $\text{NH}(\text{CH}_2)_m$, $-\text{O}(\text{CH}_2)_m$, $-\text{S}(\text{CH}_2)_m$, $-\text{NR}(\text{CH}_2)_m$, $-(\text{CH}_2)_m$,
 $-(\text{CH}_2)_m\text{NH}$ -, $-(\text{CH}_2)_m\text{O}$ -, $-(\text{CH}_2)_m\text{S}$ -, or $-(\text{CH}_2)_m\text{NR}$ -;

L is an aryl ring optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms ($\text{alkyl}(\text{C}_1-\text{C}_6)\text{S}$ -, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino; or

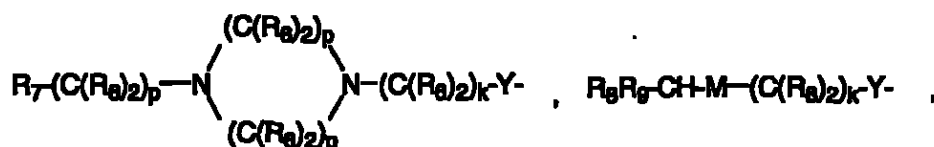
L is a 5- or 6-membered heteroaryl ring where the heteroaryl ring contains 1 to 3 heteroatoms independently selected from N, O, and S; wherein the heteroaryl ring may be optionally mono- or di-substituted with a substituent selected from the group consisting of halogen, oxo, thio, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms ($\text{alkyl}(\text{C}_1-\text{C}_6)\text{S}$ -, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy ($\text{C}_6\text{H}_4\text{S}$ -), benzoyl, benzyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1 to 6

carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1 to 5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;

Pyridinyl, pyrimidinyl, or aryl are pyridinyl, pyrimidinyl, or aryl radicals, respectively, optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, azido, hydroxyalkyl of 1 to 6 carbon atoms, halomethyl, alkoxymethyl of 2 to 7 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, benzoyl, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1 to 6 carbon atoms, alkenoylamino of 3 to 8 carbon atoms, alkynoylamino of 3 to 8 carbon atoms, carboxyalkyl of 2 to 7 carbon atoms, carboalkoxyalkyl of 3 to 8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2 to 9 carbon atoms, N,N-dialkylaminoalkyl of 3 to 10 carbon atoms, N-alkylaminoalkoxy of 2 to 9 carbon atoms, N,N-dialkylaminoalkoxy of 3 to 10 carbon atoms, mercapto, and benzoylamino;

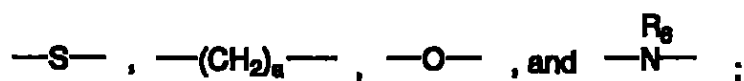
G₁, G₂, G₃, and G₄ are each, independently, hydrogen, halogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, alkenyloxy of 2 to 6 carbon atoms, alkynyloxy of 2 to 6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 2 to 6 carbon atoms, alkenoyloxy of 3 to 8 carbon atoms, alkynyloxy of 3 to 8 carbon atoms, alkanoyloxymethyl of 2 to 7 carbon atoms, alkenoyloxymethyl of 4 to 9 carbon atoms, alkynyloxymethyl of 4 to 9 carbon atoms, alkoxymethyl of 2 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkylthio of 1 to 6 carbon atoms (alkyl(C₁-C₆)S-, alkylsulphinyl of 1 to 6 carbon atoms, alkylsulphonyl of 1 to 6 carbon atoms, alkylsulfonamido of 1 to 6 carbon atoms, alkenylsulfonamido of 2 to 6 carbon atoms, alkynylsulfonamido of 2 to 6 carbon atoms, hydroxy,

- 5 trifluoromethyl, trifluoromethoxy, cyano, nitro, carboxy, carboalkoxy of 2 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms, phenoxy, phenyl, thiophenoxy (C_6H_4S-), benzyl, amino, hydroxyamino, alkoxyamino of 1 to 4 carbon atoms, alkylamino of 1 to 6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 8 to 12 carbon atoms, phenylamino, benzylamino, R_2NH ,



- 10 $R_7(C(R_8)_2)_q-Y-$, $R_7(C(R_8)_2)_p-M-(C(R_8)_2)_k-Y-$, or $Het-(C(R_8)_2)_q-W-(C(R_8)_2)_k-Y-$,
provided that either G_2 or G_3 or both G_2 and G_3 are R_2NH ;

Y is a divalent radical selected from the group consisting of

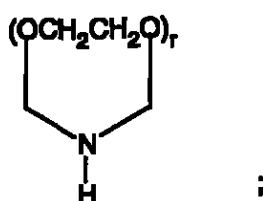


R_7 is $-NR_8R_8$, $-OR_8$, $-I$, $-N(R_8)_3^+Q^-$, or $-NR_8(OR_8)$;

- 15 M is $>NR_8$, $-O-$, $>N-(C(R_8)_2)_pNR_8R_8$, or $>N-(C(R_8)_2)_p-OR_8$;

W is $>NR_8$, $-O-$ or is a bond;

- 20 Het is a heterocyclic radical selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine, tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane, tetrahydropyran, and;



which may be optionally mono- or di-substituted on carbon with R_6 , hydroxy, $-N(R_6)_2$, $-OR_6$, $-(C(R_6)_2)_8OR_6$ or $-(C(R_6)_2)_8N(R_6)_2$;

optionally mono-substituted on nitrogen with R_6 ; and

- 5 optionally mono or di-substituted on a saturated carbon with divalent radicals $-O-$ or $-O(C(R_6)_2)_8O-$;

each R_6 is the same or different selected from hydrogen, alkyl of 1 to 6 carbon

atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms,

cycloalkyl of 3 to 7 carbon atoms, carboalkyl of 2 to 7 carbon atoms,

- 10 carboxyalkyl 2 to 7 carbon atoms, phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1 to 6 carbon atoms, trifluoromethyl, amino, alkylamino of 1 to 3 carbon atoms, dialkylamino of 2 to 6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2 to 7 carbon atoms,

- 15 alkanoyloxymethyl of 2 to 7 carbon atoms, alkylthio of 1 to 6 carbon atoms

(alkyl C_1-C_6)S-, hydroxy, carboxyl, carboalkoxy of 2 to 7 carbon atoms,

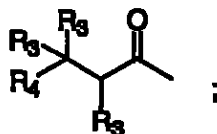
phenoxy, phenyl, thiophenoxy (C_6H_5S-), benzoyl, benzyl, phenylamino,

benzylamino, alkanoylamino of 1 to 6 carbon atoms, or alkyl of 1 to 6 carbon

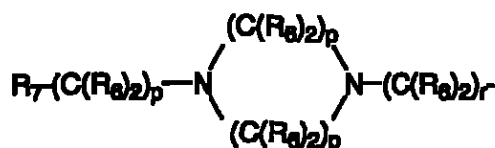
atoms; provided that the alkenyl or alkynyl moiety is bound to a nitrogen or

oxygen atom through a saturated carbon atom;

- 20 R_2 is selected from the group consisting of

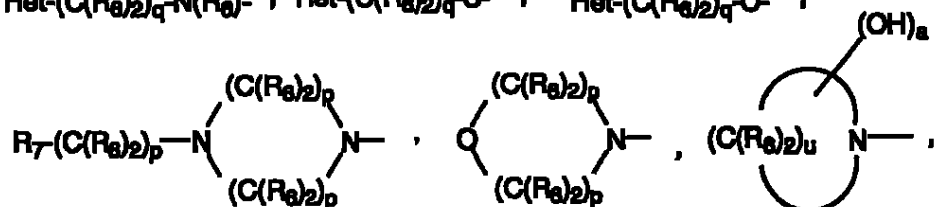


- 25 each R_3 is the same or different selected from hydrogen, alkyl of 1 to 6 carbon atoms, carboxy, carboalkoxy of 1 to 6 carbon atoms, phenyl, carboalkyl of 2 to 7 carbon atoms,





R_4 is $-NR_8R_9$, $-OR_8$, $-SR_8$,



- 5 cysteine, or a peptide comprised of 2 to 10 native amino acid residues containing at least one unoxidized cysteine residue wherein R_4 is bound to the rest of the molecule through the sulfur atom of one or more of the cysteine residues;

R_8 and R_9 are each, independently, $-(C(R_8)_2)_rNR_8R_9$, or $-(C(R_8)_2)_rOR_8$;

- 10 J is independently hydrogen, chlorine, fluorine, or bromine;

a is an integer of 0-1;

g is an integer of 1-6;

k is an integer of 0-4;

n is an integer of 0-1;

- 15 m is an integer of 0-3;

p is an integer of 2-4;

q is an integer of 0-4;

r is an integer of 1-4;

s is an integer of 1-6

- 20 u is an integer of 2-6;

Q^- is a counterion selected from salts formed from organic and inorganic acids;

provided that:

- a. when R_6 is alkenyl of 2 to 7 carbon atoms or alkynyl of 2 to 7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;
- 5 b. when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+Q^-$, or $-NR_6(OR_6)$, then g is an integer of 2 to 6;
- c. when M is $-O-$ and R_7 is $-OR_6$ then p is an integer of 1 to 4;
- d. when Y is $-NR_6-$ then k is an integer of 2 to 4;
- e. when Y is $-O-$ and M or W is $-O-$ then k is an integer of 1 to 4;
- 10 f. when W is not a bond with Het bonded through a nitrogen atom then q is an integer of 2 to 4 and when W is a bond with Het bonded through a nitrogen atom and Y is $-O-$ or $-NR_6-$ then k is an integer of 2 to 4;
- or a pharmaceutically acceptable salt thereof.

- 15 2. A compound according to claim 1 wherein Z is $-NH-$.
3. A compound according to claim 1 or claim 2 wherein n is an integer of 0.
4. A compound according to any one of claims 1 to 3 wherein X is $-E-T-L$.
- 20 5. A compound according to claim 3 wherein E is optionally substituted aryl.
6. A compound according to claim 3 or claim 4 wherein T is $O(CH_2)_m-$ wherein m is 0 or 1.
- 25 7. A compound according to any one of claims 4 to 6 wherein L is optionally substituted aryl.
8. A compound according to any one of claims 4 to 6 wherein L is optionally substituted heteroaryl.
- 30

9. The compound according to claim 8 wherein the heteroaryl ring is selected from pyridine, pyrimidine, imidazole, thiazole, thiazolidine, pyrrole, furan, thiophene, oxazole and 1,2,4-triazole.
- 5 10. A compound according to any one of claims 1 to 3 wherein X is optionally substituted aryl.
11. A compound according to any one of claims 1 to 10 wherein optionally substituted aryl is optionally substituted phenyl.
- 10 12. A compound according to any one of claims 1 to 3 wherein X is substituted or unsubstituted bicyclo aryl or bicyclic heteroaryl ring system.
13. A compound according to claim 12 wherein the bicyclic aryl or bicyclic
15 heteroaryl ring system is selected from the group consisting of naphthalene, 1,2,3,4-tetrahydronaphthalene, indane, 1-oxo-indane, 1,2,3,4-tetrahydroquinoline, naphthyridine, benzofuran, 3-oxo-1,3-dihydroisobenzofuran, benzothiadiazine, 1,1-dioxobenzothiadiazine, indole, 2,3-dihydroindole, 1,3-dioxo-2,3-dihydro-1H-isindole, benzotriazole, 1H-indazole, indoline, benzopyrazole, 1,3-benzodioxole, benzoxazole,
20 purine, phthalimide, coumarin, chromone, quinoline, tetrahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyridine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, pyrido[3,4-b]pyridine, 1H-pyrazole[3,4-d]pyrimidine, 1,4-Benzodioxane, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 2-oxo-2,3-dihydrobenzthiazole, 1,2-methylenedioxybenzene, 2-oxindole, 1,4-benzisoxazine, benzothiazole, quinoxaline,
25 quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzazine, phthalazine, 1,4-dioxo-1,2,3,4-tetrahydrophthalazine, 2-oxo-1,2-dihydroquinoline, 2,4-dioxo-1,4-dihydro-2H-benzo[d][1,3]oxazine, 2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine and cinnoline.
- 30 14. A compound according to any one of claims 1 to 13 wherein optional substituent(s) is/are selected from halogen, eg chlorine, and phenyl.

15. A compound according to any one of claims 1 to 14 wherein G_1 and G_4 are both H.
- 5 16. A compound according to any one of claims 1 to 15 wherein R_4 is NR_6R_8 or a peptide of 2 to 10 native amino acid residues containing at least one unoxidized cysteine residue wherein R_4 is bound to the rest of the molecule through the sulfur atom of one or more of the cysteine residues.
- 10 17. A compound according to any one of claims 1 to 16 wherein each R_9 is selected from hydrogen, alkyl of 1 to 6 carbon atoms, $R_7-(C(R_8)_2)_n$ wherein R_7 is NR_6R_8 and $Het-(C(R_8)_2)_q-W-(C(R_8)_2)_r$.
- 15 18. A compound according to any one of claims 1 to 17 wherein each R_9 is selected from hydrogen and alkyl of 1 to 6 carbon atoms.
19. The compound according to claim 1, which is:
N-[4-{3-chloro-4-[(4-phenyl-1,3-thiazol-2-yl)sulfanyl]anilino}-3-cyano-7-methoxy-6-quinoliny]-3,4-bis(dimethylamino)-2-butanamide or a pharmaceutically acceptable salt thereof.
- 20 20. The compound according to claim 1, which is:
N-[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-3,4-bis-(3-hydroxy-pyrrolidin-1-yl)-butyramide or a pharmaceutically acceptable salt thereof.
- 25 21. The compound according to claim 1, which is:
N-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinoliny]-3-(dimethylamino)butanamide or a pharmaceutically acceptable salt thereof.
- 30 22. The compound according to claim 1, which is:
N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,6-bis(dimethylamino)hexanamide or a pharmaceutically acceptable salt thereof.

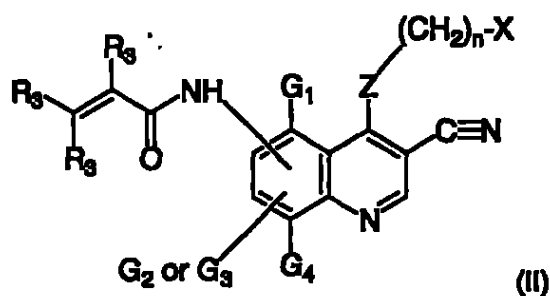
23. The compound according to claim 1, which is:
N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,4-di(1-pyrrolidinyl)butanamide or a pharmaceutically acceptable salt thereof.
- 5 24. The compound according to claim 1, which is:
(2R)-2-amino-5-({2-[(carboxymethyl)amino]-1-[(3-[4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-quinoliny]amino)-1-(dimethylamino)methyl]-3-oxopropyl)sulfanyl)methyl]-2-oxoethyl)amino)-5-oxopentanoic acid or a pharmaceutically acceptable salt thereof.
- 10 25. The compound according to claim 1, which is:
N-[4-[4-(benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,4-bis(dimethylamino)butanamide or a pharmaceutically acceptable salt thereof.
- 15 26. A method of treating, inhibiting the growth of, or eradicating neoplasms in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) as claimed in any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.
- 20 27. The method according to claim 26 wherein the neoplasm is selected from the group consisting of breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary and lung.
28. A method of treating, inhibiting the progression of, or eradicating polycystic
25 kidney disease in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) as claimed in any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.
29. A method of treating, inhibiting, or eradicating colonic polyps in a mammal in
30 need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) as claimed in any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition which comprises a compound of Formula (I) as claimed in any one of claims 1 to 25 or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable carriers.

5 31. A composition according to Claim 30, in which the compound of formula (I) is N-[4-[4-(Benzyloxy)-3-chloroanilino]-3-cyano-7-ethoxy-6-quinoliny]-3,4-bis(dimethylamino)butanamide or a pharmaceutically acceptable salt thereof.

10 32. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 25 which comprises one of the following:

a) reacting a compound of formula (II)



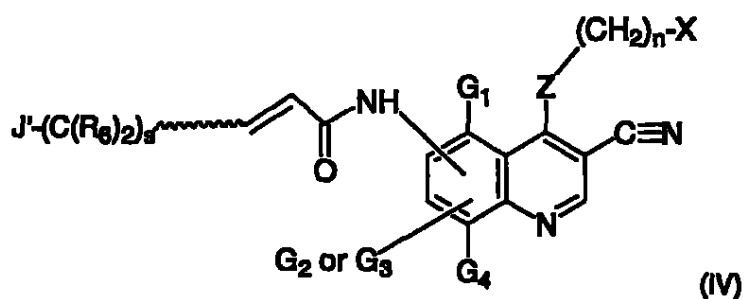
15 wherein, R_3 , G_{1-4} , X and Z are as defined in claim 1, with a compound of formula



20 wherein R_4 is as defined in claim 1, to give a corresponding compound of formula (I); or

b) reacting a compound of formula (IV)

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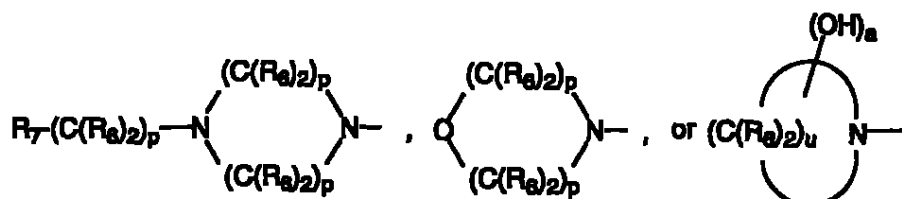
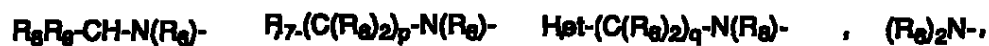


wherein s , R_8 , R_9 , G_{1-4} , X and Z are as defined in claim 1 and J' is Cl, Br or I, with a compound of formula (V):

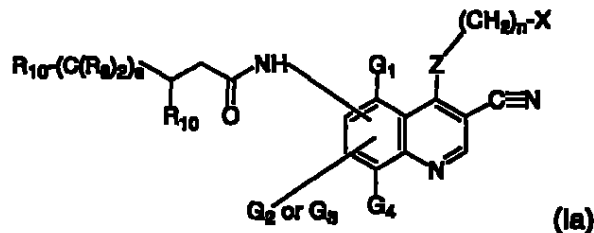
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wherein wherein R_{10} is a radical selected from the group:

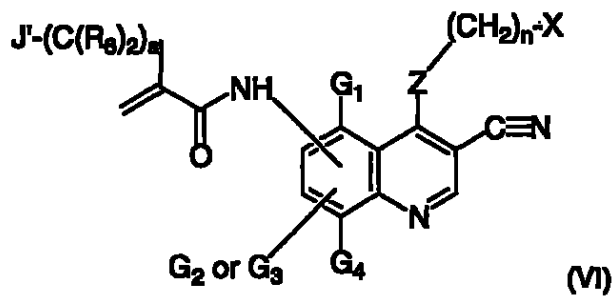


10 wherein a , R_8 , R_7 , R_8 , R_9 , p , u , and q are as defined in claim 1, to give a corresponding compound of formula (Ia)



15 or

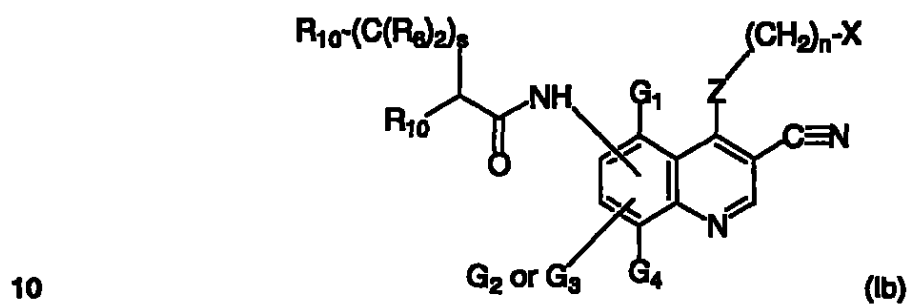
c) reacting a compound of formula (VI):



wherein a , R_8 , R_9 , G_{1-4} , X and Z are as defined in claim 1 and J' is Cl, Br or I, with a
 5 compound of formula (V):



wherein R_{10} is as defined above, to give a corresponding compound of formula (Ib):



or

d) converting a basic compound of formula (I) to a pharmaceutically acceptable
 salt thereof.

15

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D215/54 A61K31/47 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) IPC 7 C07D A61K A61P		
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, CHEM ABS Data, WPI 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 47892 A (AMERICAN HOME PROD) 5 July 2001 (2001-07-05) examples 51,52 ---	1-32
Y	WO 98 43960 A (AMERICAN CYANAMID CO) 8 October 1998 (1998-10-08) cited in the application claim 1; examples 147,148,171-175 ---	1-32
Y	WO 00 18740 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06) cited in the application claim 1; examples ---	1-32
Y	WO 00 18761 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06) cited in the application claim 1 ---	1-32
-/-		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in 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 relating 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 "A" document member of the same patent family		
Date of the actual completion of the international search 11 February 2003		Date of mailing of the international search report 21/02/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 851 epo nl, Fax (+31-70) 340-3018		Authorized officer Lauro, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/37918

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 02 44166 A (FOOTE KEVIN MICHAEL ;ASTRAZENECA UK LTD (GB); BOYLE FRANCIS THOMAS) 6 June 2002 (2002-06-06) examples 10,13 -----	1-32

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/37918

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

PCT/US 02/37918

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 9843960	A	08-10-1998	AU 750906 B2 AU 6877798 A CN 1259125 T EP 0973746 A1 HU 0002112 A2 JP 2001519788 T NO 994798 A NZ 337782 A PL 335999 A1 SK 135799 A3 TR 9902946 T2 WO 9843960 A1 ZA 9802771 A	01-08-2002 22-10-1998 05-07-2000 26-01-2000 28-09-2000 23-10-2001 24-11-1999 27-04-2001 05-06-2000 16-05-2000 21-03-2000 08-10-1998 01-10-1999
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WO 0018761	A	06-04-2000	AU 6159399 A BR 9914167 A CA 2344169 A1 CN 1320121 T CZ 20011038 A3 EP 1117659 A1 HU 0103520 A2 JP 2002525369 T NO 20011575 A PL 346934 A1 SK 4132001 A3 WO 0018761 A1	17-04-2000 19-06-2001 06-04-2000 31-10-2001 12-09-2001 25-07-2001 28-02-2002 13-08-2002 28-05-2001 11-03-2002 07-01-2002 06-04-2000
WO 0244166	A	06-06-2002	AU 1071402 A WO 0244166 A1 AU 9579101 A WO 0236570 A1	11-06-2002 06-06-2002 15-05-2002 10-05-2002



US006384051B1

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(12) **United States Patent**
Frost et al.

(10) Patent No.: **US 6,384,051 B1**
(45) Date of Patent: **May 7, 2002**

(54) **METHOD OF TREATING OR INHIBITING COLONIC POLYPS**

(75) Inventors: **Phillip Frost, Morris Township, NJ (US); Carolyn M. DiCesanti-Marro, Corlandt Manor, NY (US)**

(73) Assignee: **American Cyanamid Company, Madison, NJ (US)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/805,070**

(22) Filed: **Mar. 13, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/304,198, filed on Mar. 13, 2001.

(51) Int. Cl.⁷ **A61K 31/47**

(52) U.S. Cl. **514/313; 514/311**

(58) Field of Search **514/313, 311**

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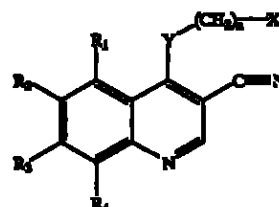
Primary Examiner—Zohreh Fay

Assistant Examiner—Brian-Yong Kwon

(74) *Attorney, Agent, or Firm*—John W. Hogan, Jr.

(57) **ABSTRACT**

This invention provides a method of treating or inhibiting colonic polyps which comprises providing a compound of formula 1



wherein:

R₁, R₂, R₃, R₄, X, Y, and n are as defined hereinbefore, or a pharmaceutically acceptable salt thereof.

21 Claims, No Drawings

METHOD OF TREATING OR INHIBITING COLONIC POLYPS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/304,198, which was converted from U.S. patent application Ser. No. 09/524,196, filed Mar. 13, 2000, pursuant to a petition filed Aug. 2, 2000 under 37 C.F.R. 1.53(c)(2).

This invention relates to the use of certain cyanoquinoline compounds in the treatment and inhibition of colonic polyps.

Colonic Polyps occur in both a familial pattern (Familial Adenomatous Polyps (FAP) and sporadically. FAP afflicts approximately 25,000 patients in the U.S.; while it is estimated that sporadic adenomatous polyps (SAP) occur in approximately 2 million people per year in the U.S. alone. All these patients are at risk for developing adenocarcinoma of the colon. In the case of FAP, that risk is virtually 100% and these patients usually undergo a colectomy at an early age. Patients with sporadic polyps are treated with polypectomy and require periodic colonoscopic examination because of their inherent risk of developing recurrent polyps. In fact, parents and siblings of these patients are also at increased risk for developing colorectal cancer.

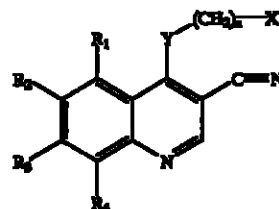
The genetic basis for FAP has been linked to the presence of mutations in the APC gene. Similar APC mutations have been found in patients with sporadic polyps. Biochemically, the APC mutation occurs in conjunction with the increased expression of cyclooxygenase enzymes, particularly COX-2. These enzymes are essential for the production of prostenooids, (prostaglandin's; (PG's)) that mediate a number of functions in the bowel including motility, vascular tone, angiogenesis and mucosal protection. PG's are also purported to discourage apoptosis and this is proposed as an explanation for polyp formation.

The therapy of FAP and SAP has focused on inhibiting COX enzymes. Considerable evidence exists for the efficacy of COX inhibitors in reducing polyp formation. These COX inhibitors are predominantly NSAID's such as cloniril, salindac, piroxicam and etodolac, all of which appear to be equivalent in their action. A major problem with NSAID therapy has been the development of serious side effects including peptic ulceration, and cholestatic hepatitis and renal papillary necrosis. Long term therapy with NSAIDs for the treatment of polyps is therefore considered to be impractical. It has recently been proposed that the activation and overexpression of COX-2 in adenomatous polyps is due to activation of the epidermal growth factor receptor (EGFR). EGFR stimulation by one of it's ligands-amphiregulin (AR), induces the nuclear targeting of COX-2, release of PG's and subsequent mitogenesis, in polarized colonic epithelial cells. COX-2 inhibitors have been shown to prevent this series of events.

DESCRIPTION OF THE INVENTION

This invention provides a method of treating or inhibiting colonic polyps in a mammal in need thereof which comprises providing to said mammal an effective amount of a

compound of formula 1:



wherein:

X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkanoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

n is 0-1;

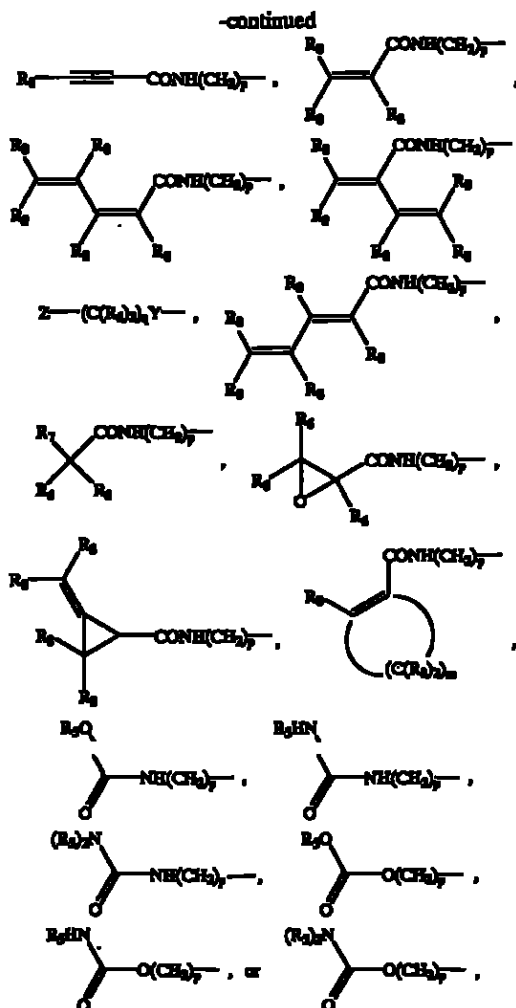
Y is -NH-, -O-, -S-, or -NR-;

R is alkyl of 1-6 carbon atoms;

R1, R2, R3, and R4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkanoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, aminoalkyl of 1-4 carbon atoms, N-alkylaminoalkyl of 2-7 carbon atoms, N,N-dialkylaminoalkyl of 3-14 carbon atoms, phenylamino, benzylamino,



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atoms, dialkylamino wherein each of the alkyl moieties is of 1-6 carbon atoms, morpholino, piperazino, N-alkylpiperazino wherein the alkyl moiety is of 1-6 carbon atoms, or pyrrolidino;

$m=1-4$, $q=1-3$, and $p=0-3$;

any of the substituents R_1 , R_2 , R_3 , or R_4 that are located on contiguous carbon atoms can together be the divalent radical $-O-C(R_a)_2-O-$;

or a pharmaceutically acceptable salt thereof with the proviso that when Y is $-NH-$, R_1 , R_2 , R_3 , and R_4 are hydrogen, and n is 0, X is not 2-methylphenyl.

The pharmaceutically acceptable salts are those derived from such organic and inorganic acids as: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkoxyethyl, alkanoyloxyethyl, alkylsulphinyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, alkanoylamino aminoalkyl, alkylaminoalkyl, N,N-dicycloalkylaminoalkyl, hydroxyalkyl, and alkoxyalkyl substituents include both straight chain as well as branched carbon chains. The cycloalkyl portions of N-cycloalkyl-N-alkylaminoalkyl and N,N-dicycloalkylaminoalkyl substituents include both simple carbocycles as well as carbocycles containing alkyl substituents. The alkenyl portion of the alkenyl, alkenoyloxyethyl, alkenyloxy, alkenylsulfonamido, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. The alkynyl portion of the alkynyl, alkynoyloxyethyl, alkynylsulfonamido, alkynyloxy, substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. Carboxy is defined as a $-CO_2H$ radical. Carboalkoxy of 2-7 carbon atoms is defined as a $-CO_2R^*$ radical, where R^* is an alkyl radical of 1-6 carbon atoms. Carboalkyl is defined as a $-COR^*$ radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkanoyloxy is defined as a $-OCOR^*$ radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkanoyloxyethyl is defined as $R^*CO_2CH_2-$ radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkenoyloxy is defined as R^*OCH_2- radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkylsulphinyl is defined as R^*SO- radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as R^*SO_2- radical, where R^* is an alkyl radical of 1-6 carbon atoms. Alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido are defined as R^*SO_2NH- radical, where R^* is an alkyl radical of 1-6 carbon atoms, an alkenyl radical of 2-6 carbon atoms, or an alkynyl radical of 2-6 carbon atoms, respectively. N-alkylcarbamoyl is defined as R^*NHCO- radical, where R^* is an alkyl radical of 1-6 carbon atoms. N,N-dialkylcarbamoyl is defined as R^*RNCO- radical, where R^* is an alkyl radical of 1-6 carbon atoms, R' is an alkyl radical of 1-6 carbon atoms and R' , and R' may be the same or different. When X is substituted, it is preferred that it is mono-, di-, or tri-substituted, with monosubstituted being most preferred. It is preferred that of the substituents R_1 , R_2 , R_3 , and R_4 , at least one is hydrogen and it is most preferred that two or three be hydrogen. An azacycloalkyl-N-alkyl substituent refers to a monocyclic heterocycle that contains a nitrogen atom on which is substituted a straight or

branched chain alkyl radical. A morpholino-N-alkyl substituent is a morpholine ring substituted on the nitrogen atom with a straight or branch chain alkyl radical. A piperidino-N-alkyl substituent is a piperidine ring substituted on one of the nitrogen atoms with a straight or branch chain alkyl radical. A N-alkyl-piperidino-N-alkyl substituent is a piperidine ring substituted on one of the nitrogen atoms with a straight or branched chain alkyl group and on the other nitrogen atom with a straight or branch chain alkyl radical.

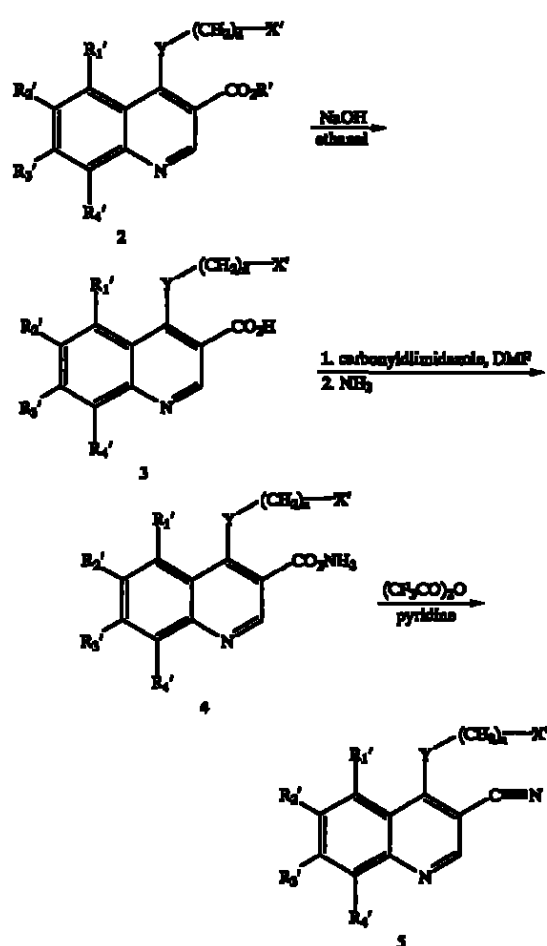
The compounds of this invention may contain an asymmetric carbon; in such cases, the compounds of this invention cover the racemate and the individual R and S enantiomers, and in the case where more than one asymmetric carbon exists, the individual diastereomers, their racemates and individual enantiomers.

As used in accordance with this invention, the term providing an effective amount means either directly administering such a compound of this invention, or administering a prodrug, derivative, or analog which will form an effective amount of the compound of this invention within the body.

The preparation of the compounds of this invention encompassed by Formula 5 is described below in Flowsheet A where Y and n are as described above and X' is cycloalkyl or phenyl optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogeno, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, halomethyl, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, trifluoromethyl, cyano, nitro, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, dialkylamino of 2 to 12 carbon atoms. R₁', R₂', R₃', and R₄' are each, independently, hydrogen, halogeno, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, trifluoromethyl, cyano, nitro, carboxy, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, alkoxyamino of 1-4 carbon atoms, dialkylamino of 2 to 12 carbon atom, N,N-dialkylaminoalkyl of 3-14 carbon atoms, phenylamino, benzylamino, N-alkylcarbamoyl of 1-6 carbon atoms, N,N-dialkylcarbamoyl of 2-12 carbon atoms. Any of the substituents R₁', R₂', R₃', or R₄' that are located on contiguous carbon atoms can together be the divalent radical —O—C(R_n)₂—O—. According to the sequence of reaction outlined in flowsheet A, a quinoline-3-carboxylic acid ester of Formula 2 is hydrolyzed with base to furnish a carboxylic acid of Formula 3. The carboxylic acid group of 3 is converted to an acyl imidazole by heating it with carbonyl-diimidazole in an inert solvent such as dimethylformamide (DMF) followed by the addition of ammonia to give the amide 4. Dehydration of the amide functional group with a dehydrating agent such as trifluoroacetic anhydride in pyridine, phosphorous pentoxide in an inert solvent, or the like gives the 3-cyano quinolines, 5, of this invention. In those cases where any of the intermediates have an asymmetric carbon atom, they can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and

S optically active forms, respectively. The quinoline-3-carboxylic acid esters of Formula 2, the quinoline-3-carboxylic acids of Formula 3, and the quinoline-3-carboxylic amides of Formula 4 needed to prepare the compounds of this invention are either already known to the art or can be prepared by procedures known in the art as detailed in the following references: Sarges, Reinhard; Gallagher, Andrea; Chambers, Timothy J.; Yeh, Li An, *J. Med. Chem.*, 36, 2828 (1993); Savini, Luisa; Massarelli, Paola; Pellarano, Cesare; Bruni, Giancarlo, *Farmaco*, 48(6), 805 (1993); Ife, Robert J.; Brown, Thomas H.; Keeling, David J.; Leach, Colin, *J. Med. Chem.*, 35, 3413 (1992); Hanifin, J. William; Capuzzi, Rosemary; Cohen, Elliott, *J. Med. Chem.*, 12(5), 1096 (1969); Marecki, Paul E.; Bambury, Ronald E., *J. Pharm. Sci.*, 73(8), 1141 (1984); Pellarano, C.; Savini, L.; Massarelli, P.; Bruni, G.; Finelli, A. I., *Farmaco*, 45(3), 269, (1990); Marecki, Paul E.; Bambury, Ronald E., *J. Pharm. Sci.*, 73(8), 114 (1984); patent application WO 8908105; U.S. Pat. No. 4,343,804; U.S. Pat. No. 3,470,186.

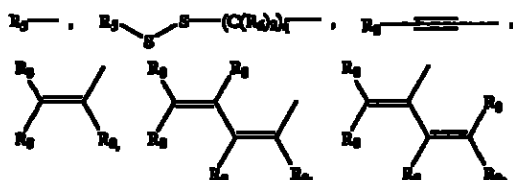
Flowsheet A



The preparation of the compounds of this invention encompassed by Formula 10 and Formula 11 are described below in Flowsheet B where Y, p, and n are as described above. X' is selected from the group consisting of cycloalkyl

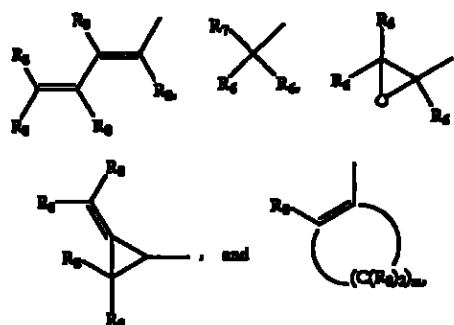
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or phenyl optionally substituted with one or more substituents selected from the group consisting of hydrogen, halogeno, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino. Each R_9 is independently hydrogen, phenyl, or alkyl of 1-6 carbon atoms. The moieties $(R_{10})_2$ represent 1 to 3 substituents on the aromatic ring that can be the same or different and are selected independently from the group hydrogen, halogeno, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphanyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, trifluoromethyl, cyano, nitro, carboxy, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, alkoxyamino of 1-4 carbon atoms, dialkylamino of 2 to 12 carbon atom, N,N -dialkylaminoalkyl of 3-14 carbon atoms, phenylamino, benzylamino, N -alkylcarbamoyl of 1-6 carbon atoms, N,N -dialkylcarbamoyl of 2-12 carbon atoms. R_{11} is a radical and is selected from the group:



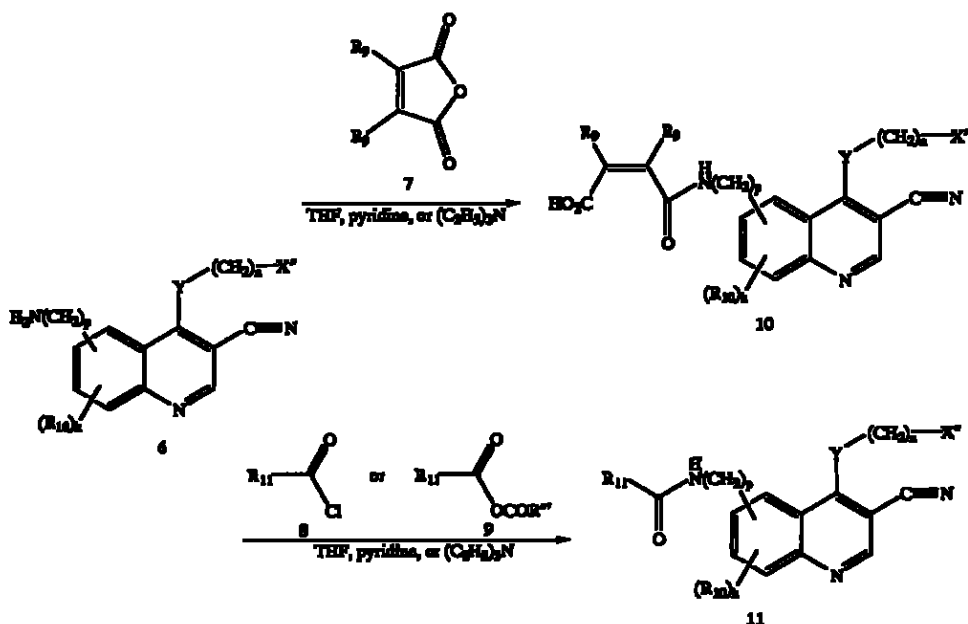
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-continued



wherein q , R_6 , R_7 , and R_8 are as defined above. R'' is alkyl from 1 to 6 carbon atoms preferably isobutyl. According to the sequence of reactions outlined in Flowchart B, acylation of 6 with either an acid chloride of Formula 8 or a mixed anhydride of Formula 9 (which is prepared from the corresponding carboxylic acid) in an inert solvent such as tetrahydrofuran (THF) in the presence of an organic base such as pyridine, triethylamine, or N -methyl morpholine gives the compounds of this invention represented by Formula 11. In those cases where 8 or 9 have an asymmetric carbon atom, they can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and S optically active forms, respectively. Acylation of 6 with a cyclic anhydride of Formula 7 in an inert solvent such as tetrahydrofuran in the presence of a basic catalyst such as pyridine or triethylamine gives the compounds of the invention of Formula 10. The compounds of Formula 6 with $p=0$ can be prepared from the aromatic nitro substituted compounds by reducing the nitro group with a reducing agent such as iron and ammonium chloride in alcohol, sodium hydrosulfite in an aqueous mixture, or the like.

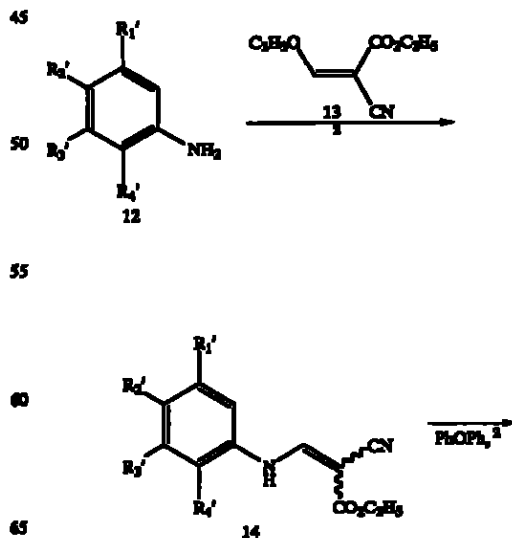
FLOWSHEET B



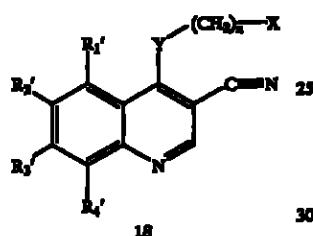
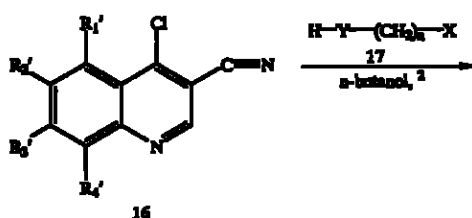
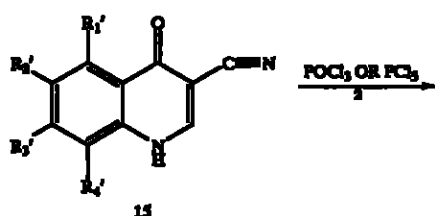
The preparation of the compounds of this invention encompassed by Formula 18 is described below in Flow-sheet C where X, Y, n, R_1' , R_2' , R_3' , and R_4' are as described above. The substituted aniline of Formula 12 is heated with or without a solvent with the reagent 13 to give intermediate 14 as a mixture of isomers. Thermolysis of 14 in a high boiling solvent such as diphenyl ether at 200–350° C. gives the 3-cyano quinolones of Formula 15; these intermediates may also exist in the 4-hydroxy quinoline tautomeric form. In those cases where R_4' is a hydrogen atom, the intermediates 15 may be formed as a mixture of two regioisomers. These isomers can be separated by methods well known in the art including, but not limited to, fractional crystallization and chromatographic methods. The separated isomers can then be converted separately to the compounds of the invention. Alternatively, the isomers can be separated at a later stage of the synthesis. Heating compounds 15 with or without solvent with a chlorinating agent such as phosphorous oxychloride or phosphorous pentachloride gives the 4-chloro-3-cyano quinolones of Formula 16. Condensation of 16 with a nucleophilic amine, aniline, mercaptan, thiophenol, phenol, or alcohol reagent of Formula 17 gives the 3-cyano quinolones of this invention of Formula 18; this condensation can be accelerated by heating the reaction mixture or by using basic catalysts such as trialkylamines, sodium hydride in an inert solvent, sodium or potassium alkoxides in an alcohol solvents, and the like. In those cases where the substituents X, R_1' , R_2' , R_3' , and R_4' may contribute an asymmetric carbon atom, the intermediates can be used as the racemate or as the individual R or S enantiomers in which case the compounds of this invention will be in the racemic or R and S optically active forms, respectively. In cases where the substituents X, R_1' , R_2' , R_3' , and R_4' may

contribute more than one asymmetric carbon atoms, diastereomers may be present; these can be separated by methods well known in the art including, but not limited to, fractional crystallization and chromatographic methods.

FLOWSHEET C

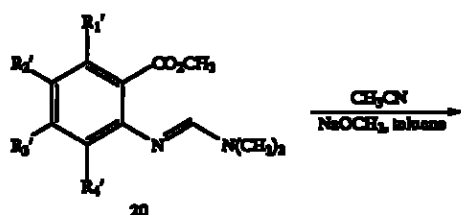
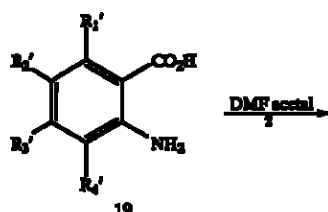


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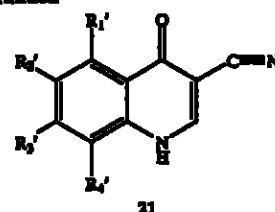


The preparation of intermediate 21 (identical to intermediate 15 of Flowchart C) can also be prepared as describe below in Flowchart D. Heating the substituted aniline of Formula 19 with dimethylformamide dimethyl acetal with or without a solvent gives intermediates for Formula 20. The reaction of 20 with one to ten equivalents of acetonitrile using a base such as sodium methoxide or the like in an inert solvent gives the 3-cyano quinolones, 21, or the 3-cyano-4-hydroxy quinoline tautomers thereof which can be converted to the compounds of this invention using the procedures outlined above in Flowchart C.

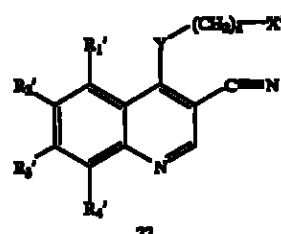
FLOWCHART D



12
-continued



Formula 22 is given below wherein R_1 , R_2 , R_3 , R_4 , n , and X' are as defined above.



Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a nitro group, it can be converted to the corresponding amino group by reduction using a reducing agent such as iron in acetic acid.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is an amino group, it can be converted to the corresponding dialkylamino group of 2 to 12 carbon atoms by alkylation with at least two equivalents of an alkyl halide of 1 to 6 carbon atoms by heating in an inert solvent.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a methoxy group, it can be converted to the corresponding hydroxy group by reaction with a demethylating agent such as boron tribromide in an inert solvent or by heating with pyridinium chloride with or without solvent.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is an amino group, it can be converted to the corresponding alkylsulfonamido, alkenylsulfonamido, or alkynylsulfonamido group of 2 to 6 carbon atoms by the reaction with an alkylsulfonyl chloride, alkenylsulfonyl chloride, or alkynylsulfonyl chloride, respectively, in an inert solvent using a basic catalyst such as triethylamine or pyridine. Alternatively, when one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is an amino group, it can be converted to the corresponding alkylsulfonamido group by the reaction with a reagent $Cl-C(R'_1)_2-CH(R'_2)SO_2Cl$, wherein R'_1 is hydrogen or alkyl of 1-4 carbon atoms, in an inert solvent using an excess of an organic base such as triethylamine.

Where two of R_1 , R_2 , R_3 , or R_4 of Formula 22 are contiguous methoxy groups, the corresponding compound with contiguous hydroxy groups can be prepared by using a demethylating agent such as boron tribromide in an inert solvent or by heating with pyridinium chloride with or without solvent.

Where two of R_1 , R_2 , R_3 , or R_4 of Formula 22 are contiguous hydroxy groups, they can be converted to the compound where together the two contiguous R_1 , R_2 , R_3 , or R_4 groups are the divalent radical $-O-C(R_5)_2-O-$ wherein R_5 is defined above by the reaction with a reagent, $J-C(R_6)_2-J$, wherein J is chloro, bromo, or iodo, and each J can be the same or different, using a base such as cesium carbonate or potassium carbonate in an inert solvent and heating as required.

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Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is an amino group, it can be converted to the corresponding alkylamino group of 1 to 6 carbon atoms by alkylation with one equivalent of an alkyl halide of 1 to 6 carbon atoms by heating in an inert solvent or by reductive alkylation using an aldehyde of 1 to 6 carbon atoms and a reducing agent such as sodium cyanoborohydride in a protic solvent such as water or alcohol, or mixtures thereof.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is hydroxy, it can be converted to the corresponding alkanoxyloxy group of 1-6 carbon atoms by reaction with an appropriate carboxylic acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is hydroxy, it can be converted to the corresponding alkanoxyloxy group of 1-6 carbon atoms by reaction with an appropriate carboxylic acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst.

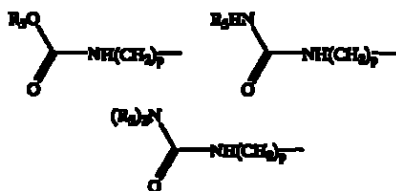
Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is hydroxy, it can be converted to the corresponding alkanoxyloxy group of 1-6 carbon atoms by reaction with an appropriate carboxylic acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is carboxy or a carboalkoxy group of 2-7 carbon atoms, it can be converted to the corresponding hydroxymethyl group by reduction with an appropriate reducing agent such as borane, lithium borohydride, or lithium aluminum hydride in an inert solvent; the hydroxymethyl group, in turn, can be converted to the corresponding halomethyl group by reaction in an inert solvent with a halogenating reagent such as phosphorous tribromide to give a bromomethyl group, or phosphorous pentachloride to give a chloromethyl group. The hydroxymethyl group can be acylated with an appropriate acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst to give the compounds of this invention with the corresponding alkanoxyloxymethyl group of 2-7 carbon atoms, alkanoxyloxymethyl group of 2-7 carbon atoms, or alkynoxyloxymethyl group of 2-7 carbon atoms.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a halomethyl group, it can be converted to an alkoxymethyl group of 2-7 carbon atoms by displacing the halogen atom with a sodium alkoxide in an inert solvent.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a halomethyl group, it can be converted to an aminomethyl group, N-alkylaminomethyl group of 2-7 carbon atoms or N,N-dialkylaminomethyl group of 3-14 carbon atoms by displacing the halogen atom with ammonia, a primary, or secondary amine, respectively, in an inert solvent.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a $H_2N(CH_2)_p$ group, it can be converted to the corresponding groups:

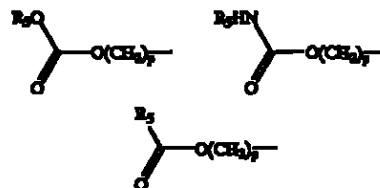


wherein R_3 and p are as defined above by reacting with phosphene in an inert solvent such as toluene in the presence

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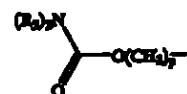
of a base such as pyridine to give an isocyanate which, in turn, is treated with an excess of the alcohol R_5-OH or amines R_5-NH_2 or $(R_5)_2NH$, respectively.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a $HO-(CH_2)_p$ group, it can be converted to the corresponding groups:



wherein R_5 and p are as defined above by the reaction, in an inert solvent using a basic catalyst such as pyridine, with an appropriate alkyl or phenyl chloroformate, $R_5-OCOCl$, alkyl or phenyl substituted isocyanate, $R_5-N=C=O$, or alkyl or phenyl substituted carboxylic acid chloride, R_5-COCl , respectively.

Where one or more of R_1 , R_2 , R_3 , or R_4 of Formula 22 is a $HO-(CH_2)_p$ group, it can be converted to the corresponding group:



wherein R_5 and p are as defined above by the reaction, in an inert solvent using a basic catalyst such as pyridine, with a reagent $(R_5)_2NCOCl$.

The ability of the compounds of this invention to treat or inhibit colonic polyps was demonstrated in an in vivo standard pharmacological test procedure as described below. The compound of Example 399 was evaluated in this procedure, which emulates familial adenomatous polyps (FAP) in humans, as a representative compound of this invention. The min mouse used in this test procedure, currently the best available model for FAP, is a strain that has lost both copies of the APC gene. These animals develop multiple intestinal polyps (adenomas). The polyps that develop in min mice express EGFR and have activated COX-2. NSAID's such as sulindac and etodolac can reduce (but not eradicate) intestinal polyp formulation in these animals indicating that COX-2 and the ultimate production of PG's is likely responsible for these effects. The following briefly describes the procedure used and the results obtained in this standard pharmacological test procedure.

The compound of Example 399 was blended with a standard murine chow and animals were given ad libitum access to the food for 60 days. Based on estimated food consumption, the compound of Example 399 was added at concentration commensurate with animals ingesting either 5 mg/kg/day or 150 mg/kg/day. At day 61, 10-15 animals in each treatment group+10-15 control (chow alone) animals corresponding to each treatment group were sacrificed and assessed for polyp number. The following table summarizes the results.

Treatment Group	Mean # Polyps ± S.D.	P-Value vs Control
Group I		
Control	32.6 ± 19.1	
5 mg/kg/day Example 399	15.6 ± 6.0	p < 0.01
Group II		
Control	19.5 ± 14.1	
150 mg/kg/day Example 399	2.6 ± 1.6	p < 0.001

These data demonstrate that the compounds of this invention effectively inhibit polyp formation in animals having mutations in their APC genes. Based on the results obtained in this standard pharmacological test procedure, the compounds of this invention are useful in treating or inhibiting the formation of colonic polyps.

The ability of an EGFR kinase inhibitor to treat or inhibit colonic polyps was demonstrated in an in vivo standard pharmacological test procedure as described below, using (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide as a representative EGFR kinase inhibitor. The preparation and activity of (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide as an EGFR kinase inhibitor are described in U.S. Pat. No. 6,002,008. This potent EGFR Kinase inhibitor, (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide, has proven to be effective in significantly reducing polyp numbers in mice.

The procedure described below emulates familial adenomatous polyps (FAP) in humans using the Min mouse (C57BL/6J-Min⁺), which is a strain of mice that has a mutation in the APC (*Adenomatous Polyposis Coli*) Gene. These animals develop multiple intestinal polyps (adenomas) when raised on a high fat diet that ultimately lead to death by 120 days of age due to anemia and/or intestinal blockage. The polyps that develop in Min mice express EGFR and have activated COX-2. The following briefly describes the procedure used and the results obtained in this standard pharmacological test procedure.

Test animals were divided into two treatment groups: Group I, control and Group II, (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide. The test compound administered to Group II was blended with AIN-93G murine chow (BioServe, Frenchtown, N.J.) and animals were given ad libitum access to the food, in quantities corresponding to the approximate daily dose of 20 mg/kg (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide. The animals were treated for 60 days. The food was weighed once per week to determine consumption, and the animals also weighed weekly. On day 61, the animals were euthanized with CO₂ inhalation, and the entire intestinal tract from stomach to anus was removed. The intestinal tract was injected with Bouins fixative, and allowed to fix for several days. The intestinal tracts were then opened and the number of polyps counted. Statistical analysis was performed using the Student's t-Test; a p-value of ≤0.05 is considered statistically significant.

The following table summarizes the results that were obtained.

Treatment Group	Number of Polyps	P value
Group I	19.5 ± 14.1	
Group II	2.6 ± 1.6	<0.001

The results obtained in this standard pharmacological test procedure showed that treatment with (4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide alone reduced polyp numbers 87 percent when compared to the AIN-93G control diet alone.

The compounds of this invention may formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of animal body weight, optionally given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The compounds of this invention may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

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The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the treatment of cancer, the compounds of this invention can be administered in combination with other antitumor substances or with radiation therapy. These other substances or radiation treatments can be given at the same or at different times as the compounds of this invention. These combined therapies may effect synergy and result in improved efficacy. For example, the compounds of this invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cisplatin or cyclophosphamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, and antiestrogens such as tamoxifen.

The preparation of representative examples of the compounds of this invention is described below.

EXAMPLE 1

1,4-Dihydro-7-methoxy-4-oxo-3-quinolinecarbonitrile

A mixture of 30.2 g (245.2 mmol) of 3-methoxy aniline and 41.5 g (245.2 mmol) of ethyl(ethoxymethylene) cyanoacetate was heated in the absence of solvent to 140° C. for 30 minutes. To the resulting oil was added 1200 ml of Dowtherm. The solution was refluxed with stirring under nitrogen for 22 hours. The mixture was cooled to room temperature and solid was collected and washed with hexanes. The solid was recrystallized from acetic acid to give 17 g of 1,4-dihydro-7-methoxy-4-oxo-3-quinolinecarbonitrile: mass spectrum (electrospray, m/e): M+H 200.9.

EXAMPLE 2

4-Chloro-7-methoxy-3-quinolinecarbonitrile

A mixture of 4.0 g (20 mmol) of 1,4-dihydro-7-methoxy-4-oxo-3-quinolinecarbonitrile and 8.3 g (40 mmol) of phosphorous pentachloride was heated at 165° C. for 3 hours. The mixture was diluted with hexanes and the solid was collected. The solid was mixed with brine and dilute sodium hydroxide solution and extracted several times with a mixture of tetrahydrofuran and ethyl acetate. The solution was dried over magnesium sulfate and filtered through a pad of silica gel giving 3.7 g of 4-chloro-7-methoxy-3-quinolinecarbonitrile as a white solid: mass spectrum (electrospray, m/e): M+H 218.9.

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EXAMPLE 3

4-[(3-Bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile

A solution of 2.97 g (13.6 mmol) of 4-chloro-7-methoxy-3-quinolinecarbonitrile and 4.67 g (27.2 mmol) of 3-bromo aniline in 76 ml of methoxyethanol was refluxed under nitrogen for 5 hours. The solution was cooled and diluted with ether. Solid was collected and washed with ether. The solid was stirred with a hot mixture of ethyl acetate and sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was recrystallized from a chloroform-ethyl acetate mixture giving 1.6 g of 4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile as a white solid: mass spectrum (electrospray, m/e): M+H 354.1, 356.1.

EXAMPLE 4

1,4-Dihydro-7-methoxy-6-nitro-4-oxo-3-quinolinecarbonitrile

To a suspension of 10 g (49.6 mmol) of 1,4-dihydro-7-methoxy-4-oxo-3-quinolinecarbonitrile in 160 ml of trifluoroacetic anhydride was added 6 g (74.9 mmol) of ammonium nitrate over a period of 3 hours. The mixture was stirred an additional two hours. Excess anhydride was removed at reduced pressure at 45° C. The residue was stirred with 500 ml of water. The solid was collected and washed with water. The solid was dissolved in 1000 ml of boiling acetic acid and the solution was treated with decolorizing charcoal. The mixture was filtered and concentrated to a volume of 300 ml. Cooling gave a solid which was collected giving 5.4 g of 1,4-dihydro-7-methoxy-6-nitro-4-oxo-3-quinolinecarbonitrile as a brown solid: mass spectrum (electrospray, m/e): M+H 246.

EXAMPLE 5

4-Chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile

A mixture of 5.3 g (21.6 mmol) of 1,4-dihydro-7-methoxy-6-nitro-4-oxo-3-quinolinecarbonitrile and 9 g (43.2 mmol) of phosphorous pentachloride was heated at 165° C. for 2 hours. The mixture was diluted with hexanes and the solid was collected. The solid was dissolved in 700 ml ethyl acetate and washed with cold dilute sodium hydroxide solution. The solution was dried over magnesium sulfate and filtered through a pad of silica gel giving 5.2 g of 4-chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile as a tan solid.

EXAMPLE 6

4-[(3-Bromophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile

A solution of 5.2 g (19.7 mmol) of 4-chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile and 3.7 g (21.7 mmol) of 3-bromo aniline in 130 ml of methoxyethanol was refluxed under nitrogen for 4 hours. The reaction mixture was poured into dilute sodium bicarbonate solution. Solid was collected and washed with water and dried in air. The solid was chromatographed on silica gel eluting with chloroform-ethyl acetate 9:1. Solvent was removed from product fractions giving 1.2 g of 4-[(3-bromophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile as a yellow solid: mass spectrum (electrospray, m/e): M+H 399.0, 402.0.

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EXAMPLE 7

6-Amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile

A mixture of 2.05 g (5.1 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile, 1.37 g (25.7 mmol) of ammonium chloride, and 0.86 g (15.4 mmol) of powdered iron was stirred at reflux in 26 ml water and 26 ml methanol for 2 hours. The mixture was diluted with ethyl acetate and the hot mixture was filtered. The organic layer was separated from the filtrate and dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel eluting with mixtures of chloroform and ethyl acetate. Product fractions were combined to give 1.3 g of 6-amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile as a yellow solid: mass spectrum (electrospray, m/e): M+H 369.1, 371.1.

EXAMPLE 8

N-[4-[(3-Bromophenyl)amino]-3-cyano-7-methoxy-6-quinoliny]-2-butyramide

To a solution of 1.44 g (17.14 mmol) of 2-butyric acid and 2.26 g (16.5 mmol) of isobutyl chloroformate in 30 ml of tetrahydrofuran at 0° C., with stirring, was added 3.1 g (3.4 mmol) of N-methyl morpholine. This solution of the mixed anhydride was added to a stirred solution of 1.13 g (3.06 mmol) of 6-amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile in 30 ml tetrahydrofuran in three portions over a 24 hour period. The solvent was removed. The residue was stirred with dilute sodium bicarbonate solution. Solid was collected and washed with water and ether. This was recrystallized from 1-butanol. The resulting solid was taken up in hot tetrahydrofuran and filtered through silica gel. The filtrate was concentrated and diluted with hexanes to give 0.71 g of N-[4-[(3-bromophenyl)amino]-3-cyano-7-methoxy-6-quinoliny]-2-butyramide as a yellow powder: mass spectrum (electrospray, m/e): M+H 437.1, 438.1.

EXAMPLE 9

N-[4-[(3-Bromophenyl)amino]-3-cyano-7-methoxy-6-quinoliny]-2-propenamide

To a solution of 1.5 g (4.06 mmol) of 6-Amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile and 0.45 ml of N-methylmorpholine in 30 ml of tetrahydrofuran was added at 0° C., under nitrogen, with stirring, 0.42 g (4.7 mmol) of acryloyl chloride of a 15 minute period. After 1 hour at 0° C., the solution was diluted with 200 ml ethyl acetate. The mixture was washed with saturated sodium bicarbonate solution and then dried over magnesium sulfate. The solvent was removed. The residue was chromatographed on silica gel eluted with chloroform-ethyl acetate mixtures to give 0.5 g of the title compound as a light yellow solid powder: mass spectrum (electrospray, m/e): M+H 423.1, 425.1.

EXAMPLE 10

2-Cyano-3-(4-nitrophenylamino)acrylic Acid Ethyl Ester

4-Nitroaniline (60.0 g, 0.435 mol) and ethyl (ethoxymethylene) cyanoacetate (73.5 g, 0.435 mol) were mixed mechanically in a flask. The mixture was heated at 100° C. for 0.5 h after it had melted and resolidified. A 114

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g portion of the crude product was recrystallized from dimethylformamide to give 44.2 g of yellow crystals; mp 227-228.5° C.

EXAMPLE 11

1,4-Dihydroquinoline-6-Nitro-4-oxo-3-carbonitrile

A slurry of 25.0 g (95.8 mmol) of 2-cyano-3-(4-nitrophenylamino)acrylic acid ethyl ester in 1.0 L of Dowtherm A was heated at 260° C. under N₂ for 12.5 h. The cooled reaction was poured into 1.5 L of hexane. The product was collected, washed with hexane and hot ethanol and dried in vacuo. There was obtained 18.7 g of brown solid. An analytical sample was obtained by recrystallization from dimethylformamide/ethanol: mass spectrum (electrospray, m/e): M+H 216.

EXAMPLE 12

4-Chloro-6-nitro-3-quinolinecarbonitrile

A mixture of 31.3 g (0.147 mol) of 6-nitro-4-oxo-1,4-dihydro-3-quinolinecarbonitrile and 160 mL of phosphorous oxychloride was refluxed for 5.5 h. The phosphorous oxychloride was removed in vacuo and the residue was poured over ice and neutralized with sodium bicarbonate. The product was collected, washed with water and dried in vacuo (500° C.). There was obtained 33.5 g of tan solid; solid: mass spectrum (electrospray, m/e): M+H 234.

EXAMPLE 13

4-[(3-Bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 17.0 g (73.1 mmol) of 4-chloro-6-nitro-3-quinolinecarbonitrile and 15.1 g (87.7 mmol) of 3-bromoaniline in 425 mL of ethanol was refluxed for 5 h. Saturated sodium bicarbonate was added and then all volatile material was removed in vacuo. The residue was slurried with hexane and the product was collected and washed with hexane. The crude product was washed with water and dried in vacuo (60° C.). There was obtained 22.5 g of yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate; mp 258-259° C.

EXAMPLE 14

6-Amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile

A mixture of 4.00 g (10.8 mmol) of 4-[(3-bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile and 12.2 g (54.2 mmol) of SnCl₄ dihydrate in 160 mL of ethanol was refluxed under N₂ for 1.3 h. After cooling to 250° C., ice water and sodium bicarbonate were added and the mixture was stirred for 2 h. Extraction with chloroform, treatment with Darco, drying (magnesium sulfate) and solvent removal gave 3.9 g of brown crystals: mass spectrum (electrospray, m/e): M+H 339.

EXAMPLE 15

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-2-butyramide

Isobutyl chloroformate (0.788 g, 5.75 mmol) and N-methylmorpholine (0.581 g, 5.75 mmol) were added to an ice cold solution of 0.485 g (5.75 mmol) of 2-butyric acid

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in 20 mL of tetrahydrofuran under N_2 . After stirring for 10 min, a solution of 1.50 g (4.42 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 10 mL of tetrahydrofuran was added and the mixture was stirred overnight at 25° C. A second equivalent of preformed mixed anhydride was then added. After 6 h, the reaction was poured into saturated sodium bicarbonate and brine. The product was collected and washed with hot ethyl acetate and ethanol and dried in vacuo to give 0.638 g of yellow solid; mp 283–285° C. (dec).

EXAMPLE 16

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]acetamide

Triethylamine (0.359 g, 3.55 mmol) and acetyl chloride (0.277 mg, 3.55 mmol) were added to an ice cold solution of 1.00 g (2.96 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 8 mL of methylene chloride and 6 mL of tetrahydrofuran under N_2 . After stirring overnight at 25° C., volatile material was removed, and the residue was slurried with water and collected. Recrystallization from ethanol gave 0.543 g of brown solid; mp 258–261° C. (dec).

EXAMPLE 17

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]butanamide

Triethylamine (0.359 g, 3.55 mmol) and butyryl chloride (0.380 g, 3.55 mmol) were added to an ice cold solution of 1.00 g (2.96 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 12 mL of tetrahydrofuran under N_2 . After stirring overnight at 25° C., volatile material was removed, and the residue was slurried with water and collected. The residue was washed with boiling methanol and dried in vacuo to give 0.773 g of brown powder; mp 276–277° C. (dec).

EXAMPLE 18

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-2-propenamide

Triethylamine (0.359 g, 3.55 mmol) and acryloyl chloride (0.321 g, 3.55 mmol) were added to an ice cold solution of 1.00 g (2.96 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 12 mL of tetrahydrofuran under N_2 . After stirring overnight at 25° C., volatile material was removed and the residue was slurried with water and collected. Recrystallization from ethanol gave 0.580 g of brown solid; mass spectrum (electrospray, m/e): M+H 393, 395.

EXAMPLE 19

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-2-chloroacetamide

Triethylamine (0.359 g, 3.55 mmol) and chloroacetyl chloride (0.402 g, 3.55 mmol) were added to an ice cold solution of 1.00 g (2.96 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 12 mL of tetrahydrofuran under N_2 . After stirring overnight at 25° C., volatile material was removed and the residue was slurried in water and collected. Recrystallization from methanol gave 0.540 g of tan solid; mass spectrum (electrospray, m/e): M+H 415, 417.

EXAMPLE 20

4-[(3,4-Dibromophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 6.20 g (26.6 mmol) of 4-chloro-6-nitro-3-quinolinecarbonitrile and 8.00 g (31.9 mmol) of 3,4-

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dibromoaniline in 160 mL of ethanol was refluxed under N_2 for 5 h. Saturated sodium bicarbonate was added and volatile material was removed. The residue was slurried with hexane, collected, washed with hexane and water and dried. The insoluble material was repeatedly extracted with boiling ethyl acetate and the solution was then filtered through silica gel. The solvent was removed to give 3.80 g of green solid; mass spectrum (electrospray, m/e): M+H 449.

EXAMPLE 21

6-Amino-4-[(3,4-dibromophenyl)amino]-3-quinolinecarbonitrile

A mixture of 4.90 g (10.9 mmol) of 4-[(3,4-dibromophenyl)amino]-6-nitro-3-quinolinecarbonitrile and 12.4 g (54.7 mmol) of $SnCl_2$ dihydrate in 200 mL of ethanol was refluxed under N_2 for 1.5 h. After cooling to 25° C., the reaction was diluted with ice water, neutralized with sodium bicarbonate and stirred for 2 h. This solution was then extracted with chloroform, treated with Darco, dried (magnesium sulfate) and evaporated. After drying in vacuo (40° C.), there was obtained 1.25 g of brown solid; mass spectrum (electrospray, m/e): M+H 417, 419, 421.

EXAMPLE 22

N-[4-[(3,4-dibromophenyl)amino]-3-cyano-6-quinolinyl]-2-butyramide

Isobutyl chloroformate (0.984 g, 7.18 mmol) and N-methylmorpholine (0.725 g, 7.18 mmol) were added to an ice cold solution of 0.604 g (7.18 mmol) of 2-butyric acid in 25 mL of tetrahydrofuran. After 10 min, a solution of 1.20 g (2.87 mmol) of 6-amino-4-[(3,4-dibromophenyl)amino]-3-quinolinecarbonitrile in 12 mL of tetrahydrofuran was added dropwise. After stirring overnight at 25° C., volatile material was removed and the residue was slurried in water and filtered. The crude product was washed with boiling EtOAc and ethanol and dried in vacuo (50° C.) to give 0.651 g of brown solid; mass spectrum (electrospray, m/e): M+H 485.

EXAMPLE 23

6-Nitro-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile

A mixture of 10.6 g (45.7 mmol) of 4-chloro-6-nitro-3-quinolinecarbonitrile and 8.82 g (54.8 mmol) of 3-(trifluoromethyl)aniline in 270 mL of ethanol was refluxed under N_2 for 5 h. The reaction was diluted with ethanol, neutralized with acid sodium bicarbonate and evaporated. The residue was slurried with hexane, collected, washed with hexane and water and dried in vacuo (60° C.) to give 10.9 g of yellow solid. A 2.00 g sample was recrystallized from ethanol to give 1.20 g of bright yellow solid; mp 260–261° C.

EXAMPLE 24

6-Amino-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile

A slurry of 6.00 g (16.8 mmol) of 6-nitro-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile and 18.9 g (83.3 mmol) of $SnCl_2$ dihydrate in 240 mL of ethanol was refluxed under N_2 for 1 h. After cooling to 25° C., the reaction was diluted with ice water, neutralized with sodium bicarbonate and stirred for 2 h. The product was extracted

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with chloroform, treated with Darco, dried (magnesium sulfate) and evaporated. The residue was filtered through silica gel (10% methanol in chloroform), evaporated and dried in vacuo (40° C.) to give 4.87 g of brown solid: mass spectrum (electrospray, m/e): M+H 329.

EXAMPLE 25

N-[4-[(3-Trifluoromethylphenyl)amino]-3-cyano-6-quinolinyl]-2-butyramide

Isobutyl chloroformate (1.56 g, 11.4 mmol) and N-methylmorpholine (1.15 g, 11.4 mmol) were added to an ice cold solution of 0.961 g (11.4 mmol) of 2-butyric acid in 40 mL of tetrahydrofuran under N₂. After stirring for 10 min, a solution of 1.50 g (4.57 mmol) of 6-amino-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile in 12 mL of tetrahydrofuran was added dropwise. After stirring at 25° C. overnight, volatile material was removed and the residue was slurried in water and filtered. The crude product was washed 3 times with small portions of hot ethyl acetate and then dried in vacuo (45° C.) to give 0.831 g of yellow solid: mass spectrum (electrospray, m/e): M+H 395.

EXAMPLE 26

3-Carboethoxy-4-hydroxy-6,7-dimethoxyquinoline

A mixture of 30.6 g of 4-aminoveratrole and 43.2 g of diethyl ethoxymethylenemalonate was heated at 100 for 2 h and at 165° C. for 0.75 h. The intermediate thus obtained was dissolved in 600 ml of diphenyl ether, and the resulting solution was heated at reflux temperature for 2 h, cooled, and diluted with hexane. The resulting solid was filtered, washed with hexane followed by ether, and dried to provide the title compound as a brown solid, mp 275–285° C.

EXAMPLE 27

3-Carboethoxy-4-chloro-6,7-dimethoxyquinoline

A mixture of 28.8 g of 3-carboethoxy-4-hydroxy-6,7-dimethoxyquinoline and 16.6 ml of phosphorous oxychloride was stirred at 110° C. for 30 min, cooled to 0° C., and treated with a mixture of ice and ammonium hydroxide. The resulting grey solid was filtered, washed with water and ether, and dried, mp 147–150° C.

EXAMPLE 28

4-[(3-Bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxylic Acid, Ethyl Ester

A mixture of 14.8 g of 3-carboethoxy-4-chloro-6,7-dimethoxyquinoline, 9.46 g of 3-bromoaniline, 4.05 ml of pyridine, and 150 ml of ethanol was refluxed for 30 min, evaporated to remove ethanol, and partitioned with dichloromethane-aq sodium bicarbonate. The organic layer was washed with water, dried, and concentrated. The residue was recrystallized from ethanol to give a white solid, mp 155–158° C.

EXAMPLE 29

4-[(3-Bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxylic Acid

A mixture of 13 g of 4-[(3-bromophenyl)amino]-3-quinolinecarboxylic acid, ethyl ester, 15 ml of 10 N sodium hydroxide, and 300 ml of ethanol was refluxed for 2 h. After

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evaporation of most ethanol, the residue was diluted with water and acidified with sodium dihydrogen phosphate to pH 7. The resulting white solid was filtered, washed with water, and dried, mp 282–285° C.

EXAMPLE 30

4-[(3-Bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxamide

A mixture of 4.03 g of 4-[(3-bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxylic acid, 3.24 g of carbonyldiimidazole, and 100 ml of dimethylformamide was heated at 55 for 30 m, cooled to 0° C., and saturated with ammonia gas. After warming to 25 the resulting solution was stirred for 45 m, heated at 50, and evaporated to remove dimethylformamide. The residue was stirred with water, and the resulting solid was filtered, washed with water, and dried. Recrystallization from acetone gave a grey solid, mp 239–242° C.

EXAMPLE 31

4-[(3-Bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

To a stirred mixture of 3.02 g of 4-[(3-bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxamide, 2.43 ml of pyridine, and 22.5 ml of dichloromethane at 0° C. was added 3.18 ml of trifluoroacetic anhydride during 3 min. The reaction mixture was warmed to 25° C., stirred for 60 min, and concentrated. The residue was dissolved in 38 ml of methanol. The resulting solution was treated with 15 ml of 5 N NaOH at 25° C. After 5 m the solution was acidified with carbon dioxide and evaporated free of methanol. The residue was partitioned with dichloromethane-water. The organic layer was washed with water, dried, and evaporated to give a white solid. Recrystallization from ethyl acetate-hexane gave mp 224–228° C.

EXAMPLE 32

Ethyl 2-cyano-3-(3,4-dimethoxyphenylamino)acrylate

A mixture of 7.66 g of 4-aminoveratrole, 8.49 g of ethyl ethoxymethylenecyanoacetate, and 20 ml of toluene was heated at 100° C. for 90 min. The toluene was evaporated to give a solid, mp 150–155° C.

EXAMPLE 33

1,4-Dihydro-6,7-dimethoxy-4-oxo-3-quinolinecarbonitrile

A mixture of 40 g of ethyl 2-cyano-3-(3,4-dimethoxyphenylamino)acrylate and 1.2 L of Dowtherm® A was refluxed for 10 h, cooled, and diluted with hexane. The resulting solid was filtered, washed with hexane followed by dichloromethane, and dried; mp 330–350° C. (dec).

EXAMPLE 34

4-Chloro-6,7-dimethoxy-3-quinolinecarbonitrile

A stirred mixture of 20 g of 1,4-dihydro-6,7-dimethoxy-4-oxo-3-quinolinecarbonitrile and 87 ml of phosphorous oxychloride was refluxed for 2 h, cooled, and evaporated free of volatile matter. The residue was stirred at 0° C. with dichloromethane-water as solid sodium carbonate was

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added until the aqueous layer was pH 8. The organic layer was separated, washed with water, dried and concentrated. Recrystallization from dichloromethane gave a solid, mp 220-223° C.

EXAMPLE 35

4-[(3-Fluorophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile

A mixture of 1.00 g of 4-chloro-6,7-dimethoxy-3-quinolinecarboxitrile, 0.89 g of 3-fluoroaniline, 0.32 ml of pyridine, and 12 ml of ethoxyethanol was stirred at reflux temperature for 4 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate to give a solid, mp 226-230° C.

EXAMPLE 36

Methyl 2-(dimethylaminomethyl)amino)benzoate

To a stirred solution of 7.56 g of methyl anthranilate in 50 ml of dimethylformamide at 0° C. was added 5.6 ml of phosphorous oxychloride during 15 m. The mixture was heated at 55 for 45 m, cooled to 0, and diluted with dichloromethane. The mixture was basified at 0° C. by slow addition of cold 1N NaOH to pH 9. The dichloromethane layer was separated, washed with water, dried and concentrated to an oil.

EXAMPLE 37

1,4-Dihydro-4-oxo-3-quinolinecarboxitrile

A stirred mixture of 1.03 g of methyl 2-(dimethylaminomethyl)amino)benzoate, 0.54 g of sodium methoxide, 1.04 ml of acetonitrile, and 10 ml of toluene was refluxed for 18 h. The mixture was cooled, treated with water, and brought to pH 3 by addition of dilute HCl. The resulting solid was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was recrystallized from ethanol to give a solid, mp 290-300° C.

EXAMPLE 38

4-(Cyclohexylamino)-6,7-dimethoxy-3-quinolinecarboxitrile

A solution of 1.24 g (5 mmole) of 4-chloro-6,7-dimethoxy-3-quinolinecarboxitrile, 1.14 ml (0.99 g; 10 mmole) of cyclohexylamine, and 0.4 ml (0.39 g) of pyridine in 10 ml of methyl cellosolve was refluxed in an oil bath at 148° C. for 3 hours. The reaction was poured into 25 ml of saturated aqueous sodium bicarbonate, and the resulting solid was filtered. This solid was dissolved in methylene chloride, and the solution was passed through Magnesol. Hexanes were added to the filtrate, and this solution was evaporated on a hot plate until crystals formed. Cooling gave 1.54 g of 4-(cyclohexylamino)-6,7-dimethoxy-3-quinolinecarboxitrile melting at 193-195° C.: mass spectrum (electrospray, m/e): M+H 312.1.

EXAMPLE 39

4-[(3-Bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarboxitrile

5.11 g of 4-[(3-bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile and 30.74 g of pyridine hydrochloride

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were intimately mixed and then heated under nitrogen at 207° C. for an hour. On cooling the reaction was treated with about 100 ml of water and the solid was filtered. This solid was digested with methyl cellosolve and washed with ether to give 3.00 g of 4-[(3-bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarboxitrile: mass spectrum (electrospray, m/e): M+H 356, 358.

EXAMPLE 40

8-[(3-Bromophenyl)amino]-[1,3]-dioxolo[4,5-g]quinoline-7-carboxitrile

A mixture of 2.17 g (6.09 mmole) of 4-[(3-bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarboxitrile, 0.59 ml (1.18 g; 9.14 mmole) of bromochloromethane and 2.98 g (9.14 mmole) of cesium carbonate in 20 ml of N,N-dimethylformamide was heated and stirred for 2 hours in an oil bath at 111° C. The reaction was poured into 75 ml of water and extracted with four 50 ml portions of methylene chloride. The combined methylene chloride extracts were washed with several portions of water. This solution was taken to an oil in vacuo and this was dissolved in ethyl acetate. This solution was washed repeatedly with water, then with brine. The solution was dried over anhydrous magnesium sulfate, and taken to a solid in vacuo to give 0.95 g of 8-[(3-bromophenyl)amino]-[1,3]-dioxolo[4,5-g]quinoline-7-carboxitrile, m.p. 201-205° C.: mass spectrum (electrospray, m/e): M+H 368.1, 370.1.

EXAMPLE 41

4-[(3-Chlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile

A mixture of 0.5 g of 4-chloro-6,7-dimethoxy-3-quinolinecarboxitrile, 0.51 g of 3-chloroaniline, 0.16 ml of pyridine, and 6 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 6 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate-hexanes to give 0.37 g of 4-[(3-chlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile as a solid, mp 214-217° C.

EXAMPLE 42

4-[(3-Trifluoromethylphenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile

A mixture of 1.24 g of 4-chloro-6,7-dimethoxy-3-quinolinecarboxitrile, 1.61 g of 3-trifluoromethylaniline, 0.4 ml of pyridine, and 15 ml of ethoxyethanol was stirred, under nitrogen, at reflux temperature for 5 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate-hexanes to give 1.34 g of 4-[(3-trifluoromethylphenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile as a solid, mp 190-193° C.

EXAMPLE 43

4-[(3,4-Dimethoxyphenyl)amino]-6,7-dimethoxy-3-quinolinecarboxitrile

A mixture of 1.0 g of 4-chloro-6,7-dimethoxy-3-quinolinecarboxitrile, 1.22 g of 3,4-dimethoxyaniline, 0.32 ml of pyridine, and 12 ml of ethoxyethanol was stirred,

under nitrogen, at reflux temperature for 5 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate to give 0.96 g of 4-[(3,4-dimethoxyphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile as a solid, mp 230–240° C.

EXAMPLE 44

4-[(Methylphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 0.86 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.86 g of N-methylaniline, 0.32 ml of pyridine, and 12 ml of ethoxyethanol was stirred, under nitrogen, at reflux temperature for 24 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate-hexanes to give 0.54 g of 4-[(methylphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile as a solid, mp 137–141° C.

EXAMPLE 45

4-[(3-Cyanophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 0.5 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.47 g of 3-aminobenzonitrile, 0.16 ml of pyridine, and 12 ml of ethoxyethanol was stirred, under nitrogen, at reflux temperature for 22 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate-hexanes to give 0.59 g of 4-[(3-cyanophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile as a solid, mp 285–288° C.

EXAMPLE 46

4-[(4-Fluorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 0.5 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.44 g of 4-fluoroaniline, 0.16 ml of pyridine, and 6 ml of ethoxyethanol was stirred, under nitrogen, at reflux temperature for 4 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ethyl acetate to give 0.59 g of 4-[(4-fluorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile as a solid, mp 282–285° C.

EXAMPLE 47

4-[(3-Bromophenyl)amino]-6,7-diethoxy-3-quinolinecarbonitrile

A mixture of 0.36 g of 4-[(3-bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarbonitrile, 0.32 ml of ethyl iodide and 0.55 g of potassium carbonate in 4 ml of dimethylsulfoxide was stirred for 3 hours in an oil bath with heating. Most of the solvent was removed at reduced pressure. The mixture was mixed with ethyl acetate and water. The organic layer was washed with water and dried over magnesium sulfate. Solvent was removed to give 0.23 g of 4-[(3-bromophenyl)amino]-6,7-diethoxy-3-quinolinecarbonitrile

which after recrystallization from ethyl acetate gave mp=173–175° C.

EXAMPLE 48

4-[(3-(hydroxymethyl)phenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 1.0 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.98 g of 3-aminobenzyl alcohol, 0.32 ml of pyridine, and 12 ml of ethoxyethanol was stirred, under nitrogen, at reflux temperature for 3 h. The mixture was cooled and partitioned with dichloromethane and aqueous sodium bicarbonate. The organic layer was washed with water, dried and evaporated. The residue was washed with hot methanol to give 1.16 g of 4-[(3-(hydroxymethyl)phenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile as a solid, mp 250–255° C.

EXAMPLE 49

4-(3-Bromophenoxy)-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 0.16 g of 88% KOH and 1.73 g of 3-bromophenol at 50° C. was treated with 0.50 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile. The resulting mixture was heated to 170° C. during 30 min, cooled, and treated at 0° C. with 40 ml of 0.1N NaOH. The solid which resulted was filtered, washed with water, and dissolved in methylene chloride. The solution was washed with 0.5 N NaOH and water, dried, and concentrated. The resulting solid was recrystallized from methylene chloride-hexane to give 4-(3-bromophenoxy)-6,7-dimethoxy-3-quinolinecarbonitrile as a white solid, mp 187–190° C.

EXAMPLE 50

4-[(4-Bromophenyl)sulfonyl]-6,7-dimethoxy-3-quinolinecarbonitrile

To 1.89 g of 4-bromothiophenol at 25 under argon was added 0.16 g of 88% KOH. The resulting mixture was heated at 85° C. for 15 minutes, treated with 0.50 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, and heated at 140° C. for 1 hour and 160° C. for 15 minutes. The mixture was cooled and stirred at 0° C. with 40 ml of 0.1 N NaOH. The resulting solid was filtered, washed with water, and dissolved in methylene chloride. The solution was washed with 0.2 N NaOH and water, dried, and concentrated. The residue which resulted was recrystallized from ethyl acetate to give 4-[(3-bromophenyl)sulfonyl]-6,7-dimethoxy-3-quinolinecarbonitrile as a an off-white solid, mp 173–175° C.

EXAMPLE 51

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-3(E)-chloro-2-propenamide and

EXAMPLE 52

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinoliny]-3(Z)-chloro-2-propenamide

A mixture of 3 g (28.2 mmol) of cis-3-chloro acrylic acid and 3.3 ml (37.5 mmol) of oxalyl chloride in 30 ml of methylene chloride containing one drop of dimethylformamide was stirred for 2.5 hours. The solvent was removed to give the acid chloride as a mixture of cis and trans isomers.

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To a solution of 0.5 g (1.5 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile and 0.24 g (1.8 mmol) of *N,N*-diisopropylethylamine in 5 ml tetrahydrofuran was added at 0° C., under nitrogen, with stirring, 0.21 g (1.7 mmol) of 3-chloro acryloyl chloride isomer mixture over a 4 minute period. After 40 min at 0° C., the solution was diluted with ether. The solid was collected and dissolved in a mixture of tetrahydrofuran and ethyl acetate. The mixture was washed with brine and then dried over magnesium sulfate. The solvent was removed. The residue was chromatographed on silica gel eluted with chloroform-ethyl acetate. Two products were obtained. The less polar product is *N*-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-3(E)-chloro-2-propenamide: mass spectrum (electrospray, *m/e*): *M*+*H* 424.9, 427.0. The more polar product is *N*-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-3(Z)-chloro-2-propenamide: mass spectrum (electrospray, *m/e*): *M*+*H* 425.0, 427.0.

EXAMPLE 53

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-2-methyl-2-propenamide

To a solution of 0.5 g (1.48 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile and 0.194 g (1.92 mmol) of triethylamine in 6 ml tetrahydrofuran was added at 0° C., under nitrogen, with stirring, 0.21 g (1.92 mmol) of 2-methyl acryloyl chloride over a 10 minute period. The solution was stirred at room temperature overnight. The mixture was poured into water. The solid was collected and air dried. The solid was washed with boiling ethyl acetate and air dried giving 0.32 g of *N*-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-2-methyl-2-propenamide: mass spectrum (electrospray, *m/e*): *M*+*H* 407, 409.

EXAMPLE 54

N-[4-[(3,4-Dibromophenyl)amino]-3-cyano-6-quinolinyl]-2-propenamide

To a solution of 0.75 g (1.79 mmol) of 6-amino-4-[(3,4-dibromophenyl)amino]-3-quinolinecarbonitrile and 0.22 g (2.15 mmol) of triethylamine in 10 mL of tetrahydrofuran was added dropwise 0.195 g (2.15 mmol) of acryloyl chloride. After stirring overnight at 25° C., volatile material was removed and the residue was slurried in water and solid was collected. The crude product was washed with boiling ethyl acetate dried in vacuo (50° C.) to give 0.609 g of brown solid: high resolution mass spectrum (*m/e*): 470.9457.

EXAMPLE 55

N-[4-[(5-bromo-3-pyridinyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile

A mixture of 249 mg (1 mmole) of 3-cyano-4-chloro-6,7-dimethoxy quinoline, 346 mg (2 mmole) of 3-amino-5-bromo pyridine and 20 mg (about 0.1 mmole) of *p*-toluenesulfonic acid monohydrate in 5 ml of 2-methoxy ethanol was stirred and refluxed in an oil bath at 153° C. for 7 hours. On cooling overnight to room temperature, the solid was filtered and washed with ethanol, then with ether to give 287 mg (74.5%) of *N*-[4-[(5-bromo-3-pyridinyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile, which melted at 272–275° C. mass spectrum (electrospray, *m/e*) *M*+*H*=384.9, 386.8.

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EXAMPLE 56

4-[(3-Bromophenyl)amino]-6,7-bis(methoxymethoxy)-3-quinolinecarbonitrile

A mixture of 0.36 g of 4-[(3-bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarbonitrile, 0.30 ml of 2-chloromethyl methyl ether and 0.55 g of potassium carbonate in 4 ml of dimethylformamide was stirred for 6 hours at 0° C. Most of the solvent was removed at reduced pressure. The mixture was mixed with ethyl acetate and water and the pH was adjusted to 8 with dilute hydrochloric acid. The organic layer was washed with water and dried over magnesium sulfate. Solvent was removed to give 4-[(3-bromophenyl)amino]-6,7-bis(methoxymethoxy)-3-quinolinecarbonitrile which was purified by column chromatography on silica gel: mass spectrum (electrospray, *m/e*): *M*+*H* 356, 358.

EXAMPLE 57

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-hydroxy-2-butyramide

Isobutyl chloroformate (0.214 g, 1.57 mmol) and *N*-methylmorpholine (0.190 g, 1.88 mmol) were added to an ice cold solution of 0.336 g (1.57 mmol) of 4-(*tert*-butyl-dimethyl-silanyloxy)-2-butyric acid in 15 mL of tetrahydrofuran under N₂. After stirring for 30 min, it was transferred to an additional funnel plugged with a glass wool and added dropwise to a solution of 0.4 g (1.18 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 3 mL of tetrahydrofuran and 1.5 ml of pyridine. The mixture was stirred at 25° C. for 1 h. The reaction solution was poured into ethyl acetate and washed with saturated sodium bicarbonate and brine. The product was collected and purified by flash column chromatography (60% ethyl acetate in hexane) to give 0.220 g of

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(*tert*-butyl-dimethyl-silanyloxy)-2-butyramide as a yellow solid (35%); ESMS *m/z* 535.1 (*M*+*H*⁺); mp ° C. (dec). *N*-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(*tert*-butyl-dimethylsilanyloxy)-2-butyramide (0.120 g, 0.224 mmol) was dissolved in a 25 ml solution (acetic acid:tetrahydrofuran:water=3:1:1) and stirred overnight at 25° C. The reaction was poured into ethyl acetate and washed with saturated sodium bicarbonate and brine. The product was collected, washed with ethyl acetate, and dried in vacuo to give 0.085 g of yellow solid (90%); ESMS *m/z* 421.2 (*M*+*H*⁺); mp 253–254° C. (dec).

EXAMPLE 58

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-morpholino-2-butyramide

Isobutyl chloroformate (0.161 g, 1.18 mmol) and *N*-methylmorpholine (0.150 g, 1.48 mmol) were added to an ice cold solution of 0.250 g (1.48 mmol) of 4-morpholino-2-butyric acid in 10 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 0.250 g (0.74 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 8 mL of pyridine was added and the mixture was stirred at 0° C. for 2 h. The reaction was quenched with ice water and then poured into saturated sodium bicarbonate and brine. The product was collected, washed with ethyl acetate, and dried in vacuo to give 0.096 g (27%) of yellow solid; ESMS *m/z* 490.1 (*M*+*H*⁺); mp 112–115° C.

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EXAMPLE 59

N-[4-(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butyramide

Isobutyl chloroformate (0.260 g, 1.91 mmol) and N-methylmorpholine (0.594 g, 5.88 mmol) were added to an ice cold solution of 0.370 g (2.94 mmol) of 4-dimethylamino-2-butyric acid in 50 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 0.500 g (0.147 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 10 mL of pyridine was added and the mixture was stirred at 0° C. for 2 h. The reaction was quenched with ice water, and then poured into saturated sodium bicarbonate and brine. The product was collected, washed with ethyl acetate, and dried in vacuo to give 0.144 g (21%) of yellow solid; ESMS m/z 448.0 (M+H⁺); mp 114–118° C.

EXAMPLE 60

N-[4-(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-2-butyramide

Isobutyl chloroformate (0.410 g, 3.0 mmol) and N-methylmorpholine (0.910 g, 9.0 mmol) were added to an ice cold solution of 0.680 g (6.0 mmol) of 4-methoxy-2-butyric acid in 20 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 0.500 g (0.147 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 10 mL of pyridine was added and the mixture was stirred at 0° C. for 2 h. The reaction was quenched with ice water, and then poured into saturated sodium bicarbonate and brine. The product was collected, washed with ethyl acetate, and dried in vacuo to give 0.200 g (35%) of yellow solid; ESMS m/z 435.1 (M+H⁺); mp 198–202° C. (dec).

EXAMPLE 61

4-(3-Bromophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

A stirred mixture of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile (0.69 g, 2.5 mmol), 3-bromobenzylamine (0.78 g, 3.5 mmol), diisopropylethyl amine (1.05 mL, 6.0 mmol), and 7.5 mL of ethoxyethanol was refluxed for 4 h, cooled, and stirred with a mixture of hexane and water containing 0.4 g of potassium carbonate for 3 h. The resulting solid was filtered, washed with water, and dried. Recrystallization from acetone-hexane gave 0.73 g of off-white solid, mp 156–159° C.

EXAMPLE 62

4-(3-Phenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 61 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with benzylamine gave the title compound as an off-white solid, mp 150–153° C.

EXAMPLE 63

4-(3,4-Dimethoxyphenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 61 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3,4-dimethoxybenzylamine gave the title compound as a tan solid, mp 200–204° C.

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EXAMPLE 64

4-(3,4-Dichlorophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 61 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3,4-dichlorobenzylamine gave the title compound as a tan solid, mp 163–165° C.

EXAMPLE 65

4-Methoxy-but-2-enoic Acid [4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide

To a solution of 1.0 g (2.95 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile and 0.57 g (4.42 mmol) of diisopropylethyl amine at 0° C. with stirring was added 0.43 g (3.24 mmol) of 4-methoxycrotonyl chloride. After 1.5 hr at 0° C., the mixture was poured into a saturated solution of sodium bicarbonate and then extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and the solvent was removed. The residue was recrystallized from 1-butanol giving 1.3 g of 4-Methoxy-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide as a yellow solid; mass spectrum (electrospray, m/e): M+H 436.4, 438.9.

EXAMPLE 66

4-(3-Chloro-propoxy)-5-methoxy-benzoic Acid Methyl Ester

A mixture of 102.4 g (411.7 mmol) of 3-chloropropyl p-toluene sulfonate, 75 g (411.7 mmol) of 4-hydroxy-5-methoxy-benzoic acid methyl ester, 75.7 g (547.5 mmol) of potassium carbonate, and 1.66 g (4.1 mmol) of methyl-tricapryl ammonium chloride in 900 mL of acetone was stirred rapidly at reflux for 18 hr. The mixture was filtered and the solvent was removed giving 106 g of the title compound after recrystallization from a chloroform-hexane mixture.

EXAMPLE 67

4-(2-Chloro-ethoxy)-5-methoxy-benzoic Acid Methyl Ester

By using an identical method as above 77 g of 4-hydroxy-5-methoxy-benzoic acid methyl ester, 99.2 g of 2-chloroethyl p-toluene sulfonate, 77.7 g of potassium carbonate, and 1.7 g (4.1 mmol) of methyl-tricapryl ammonium chloride was converted to 91.6 g of the title compound; mass spectrum (electrospray, m/e): M+H 245.0

EXAMPLE 68

4-(3-Chloro-propoxy)-5-methoxy-2-nitro-benzoic Acid Methyl Ester

To a solution of 100 g (386.5 mmol) 4-(3-chloro-propoxy)-5-methoxy-benzoic acid methyl ester in 300 mL acetic acid was added dropwise 100 mL of 70% nitric acid. The mixture was heated to 50° C. for 1 hr and then poured into ice water. The mixture was extracted with chloroform. The organic solution was washed with dilute sodium hydroxide and then dried over magnesium sulfate. The solvent was removed. Ether was added and the mixture was stirred until solid was deposited. The solid was collected by filtration giving 98 g of 4-(3-Chloro-propoxy)-5-methoxy-

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2-nitro-benzoic acid methyl ester as white crystals: mass spectrum (electrospray, m/e): M+H 303.8; 2M+NH₄ 623.9.

EXAMPLE 69

4-(2-Chloro-ethoxy)-5-methoxy-2-nitro-benzoic Acid Methyl Ester

By using an identical method as above 85 g of 4-(2-Chloro-ethoxy)-5-methoxybenzoic acid methyl ester was nitrated to give 72 g of the title compound: mass spectrum (electrospray, m/e): 2M+NH₄ 595.89

EXAMPLE 70

2-Amino-4-(3-chloro-propoxy)-5-methoxy-benzoic Acid Methyl Ester

A mixture of 91 g (299.6 mmol) of 4-(3-chloro-propoxy)-5-methoxy-2-nitro-benzoic acid methyl ester and 55.2 g (988.8 mmol) of iron was mechanically stirred at reflux in a mixture containing 60.1 g ammonium chloride, 500 ml water, and 1300 ml methanol for 5.5 hr. The mixture was concentrated and mixed with ethyl acetate. The organic solution was washed with water and saturated sodium bicarbonate. The solution was dried over magnesium sulfate and filtered through a short column of silica gel. The solvent was removed and the residue mixed with 300 ml of ether-hexane 2:1. After standing 73.9 g of the title compound was obtained as a pink solid: mass spectrum (electrospray, m/e): 2M-HCl+H 511.0; M+H 273.8

EXAMPLE 71

2-Amino-4-(2-chloro-ethoxy)-5-methoxy-benzoic Acid Methyl Ester

A mixture of 68.2 g (235.4 mmol) of 4-(2-chloro-ethoxy)-5-methoxy-2-nitro-benzoic acid methyl ester and 52.6 g (941.8 mmol) of iron was mechanically stirred at reflux in a mixture containing 62.9 g ammonium chloride, 393 ml water, and 1021 ml methanol for 15 hr. The mixture was concentrated and mixed with ethyl acetate. The organic solution was washed with water and saturated sodium bicarbonate. The solution was dried over magnesium sulfate and filtered through a short column of silica gel. The solution was concentrated to 200 ml and diluted with 250 of hot hexane. After standing 47.7 g of the title compound was obtained as a solid: mass spectrum (electrospray, m/e) M+H 259.8.

EXAMPLE 72

7-(2-Chloro-ethoxy)-4-hydroxy-6-methoxy-quinoline-3-carbonitrile

A mixture of 25 g (96.3 mmol) of 2-amino-4-(2-chloro-ethoxy)-5-methoxy-benzoic acid methyl ester and 17.2 g (144.4 mmol) of dimethylformamide dimethylacetal was heated to reflux for 1.5 hr. Excess reagents were removed at reduced pressure leaving 30.3 g of a residue which was dissolved in 350 ml of tetrahydrofuran.

In a separate flask, to a stirred solution of 80.9 ml of 2.5M n-butyl lithium in hexane in 300 ml of tetrahydrofuran at -78° C. was added dropwise 8.3 g (202.1 mmol) of acetonitrile over 40 min. After 30 min, the above solution of amidine was added dropwise over 45 min at -78° C. After 1 hr, 27.5 ml of acetic acid was added and the mixture was allowed to warm to room temperature. The solvent was removed and water was added. Solid was collected by

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filtration and washed with water and ether. After drying in vacuum, 18.5 g of the title compound was obtained as a tan powder: mass spectrum (electrospray, m/e) M+H 278.8.

EXAMPLE 73

7-(3-Chloro-propoxy)-4-hydroxy-6-methoxy-quinoline-3-carbonitrile

By using the above method, starting with 6.01 g of the corresponding amidine, 1.58 g of acetonitrile, and 15.35 ml of n-butyl lithium solution, 3.7 g of the title compound was obtained as a tan powder: mass spectrum (electrospray, m/e) M+H 292.8; 2M+H 584.2

EXAMPLE 74

7-(3-Chloro-propoxy)-4-chloro-6-methoxy-quinoline-3-carbonitrile

A mixture of 3.5 g (12 mmol) of 7-(3-chloro-propoxy)-4-hydroxy-6-methoxy-quinoline-3-carbonitrile and 28 ml of phosphorous oxychloride was refluxed for 1.5 hr. Excess reagent was removed at reduced pressure. The residue was mixed with ice cold dilute sodium hydroxide and ethyl acetate. The mixture was extracted with a combination of ethyl acetate and tetrahydrofuran. The combined extracts were washed with a saturated solution of sodium bicarbonate, dried over magnesium sulfate, and filter through a short column of silica gel. Solvents were removed giving 3.2 g of the title compound as a pink solid that is used with additional purification.

EXAMPLE 75

7-(3-Chloro-ethoxy)-4-chloro-6-methoxy-quinoline-3-carbonitrile

A solution of 8 g (28.7 mmol) of 7-(3-chloro-ethoxy)-4-hydroxy-6-methoxy-quinoline-3-carbonitrile and 18.2 g (143.5 mmol) of oxalyl chloride in 80 ml of methylene chloride containing 0.26 g of dimethylformamide was stirred at reflux for 2.5 hr. The solvent was removed. The residue was mixed with cold dilute sodium hydroxide and extracted several time with ethyl acetate and tetrahydrofuran. The combined extracts were dried over magnesium sulfate and the solution was passed through a short silica gel column. The solvents were removed giving 6.0 g of the title compound as an off-white solid that is used without additional purification.

EXAMPLE 76

4-(4-Chloro-2-fluoro-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile

A mixture of 3.1 g (9.96 mmol) of 7-(3-Chloro-propoxy)-4-chloro-6-methoxy-quinoline-3-carbonitrile, 1.6 g (10.96 mmol) of 4-chloro-2-fluoro-aniline, and 1.2 g (10 mmol) of pyridine hydrochloride in 31 ml of 2-ethoxyethanol was stirred at reflux for 1.5 hr. The mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic solution was dried and solvent was removed. The residue was purified on a silica gel column eluting with chloroform-ether mixtures to give 2.88 g of the title compound as an off-white solid powder: mass spectrum (electrospray, m/e) M+H 419.7.

EXAMPLE 77

7-(2-Chloro-ethoxy)-4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-3-carbonitrile

By using the above method, starting with 3 g of 7-(2-chloro-ethoxy)-4-chloro-6-methoxy-quinoline-3-

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carbonitrile, 1.37 g of 3-hydroxy-4-methyl-aniline, and 1.2 g of pyridine hydrochloride in 31 ml of 2-ethoxyethanol, 2.6 g of the title compound was obtained as a crystalline solid: mass spectrum (electrospray, m/e) M+H 383.9.

EXAMPLE 78

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile

By using the above method, starting with 3 g of 7-(3-chloro-propoxy)-4-chloro-6-methoxy-quinoline-3-carbonitrile, 2.35 g of the methyl carbonate of 4-chloro-2-fluoro-5-hydroxy-aniline, and 1.1 g of pyridine hydrochloride in 30 ml of 2-ethoxyethanol, 1.7 g of the title compound was obtained as a crystalline solid: mass spectrum (electrospray, m/e) M+H 435.8, 437.8.

EXAMPLE 79

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-(2-chloro-ethoxy)-6-methoxy-quinoline-3-carbonitrile

By using the above method, starting with 3 g of 7-(2-chloro-ethoxy)-4-chloro-6-methoxy-quinoline-3-carbonitrile, 2.46 g of the methyl carbonate of 4-chloro-2-fluoro-5-hydroxy-aniline, and 1.18 g of pyridine hydrochloride in 31 ml of 2-ethoxyethanol, 2.2 g of the title compound was obtained as a tan solid: mass spectrum (electrospray, m/e) M+H 421.9.

EXAMPLE 80

4-(4-Chloro-2-fluoro-phenylamino)-7-(3-dimethylaminopropoxy)-6-methoxy-quinoline-3-carbonitrile

A mixture of 1 g (2.38 mmol) of 4-(4-chloro-2-fluoro-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile and 0.07 g of sodium iodide in 17.85 ml of 2M dimethylamine in tetrahydrofuran was placed in a sealed tube and heated to 125° C. for 3.5 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and ether was added. One standing, the crystals were deposited giving 0.93 g of the title compound as a white solid: mass spectrum (electrospray, m/e) M+H 428.9.

EXAMPLE 81

4-(4-Chloro-2-fluoro-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

A mixture of 1 g (2.38 mmol) of 4-(4-chloro-2-fluoro-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile, 3.1 g (35.7 mmol) of morpholine, and 0.07 g of sodium iodide in 20 ml ethylene glycol dimethyl ether refluxed for 7 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and ether-hexane was added. One standing, the crystals were deposited giving 1.1 g of the title compound as a off-white solid: mass spectrum (electrospray, m/e) M+H 470.9.

EXAMPLE 82

7-(2-Dimethylamino-ethoxy)-4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-3-carbonitrile

A mixture of 1 g (2.38 mmol) of 7-(2-chloro-ethoxy)-4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-

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3-carbonitrile and 0.078 g of sodium iodide in 19.5 ml of 2M dimethylamine in tetrahydrofuran was placed in a sealed tube and heated to 125° C. for 14 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was chromatographed on silica gel eluting with ethyl acetate-methanol-triethylamine 70:30:2.5 giving 0.89 g of the title compound as a light yellow solid: mass spectrum (electrospray, m/e) M+H 393.0; (M+2H)⁺ 196.9.

EXAMPLE 83

4-(3-Hydroxy-4-methyl-phenylamino)-6-methoxy-7-(2-morpholin-4-yl-ethoxy)-quinoline-3-carbonitrile

A mixture of 1 g (2.38 mmol) of 7-(2-chloro-ethoxy)-4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-3-carbonitrile, 3.4 g (39 mmol) of morpholine, and 0.08 g of sodium iodide in 22 ml ethylene glycol dimethyl ether refluxed for 34 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was chromatographed on silica gel eluting with ethyl acetate-methanol-triethylamine 70:30:2.5 giving 1.05 of the title compound as a light orange solid: mass spectrum (electrospray, m/e) M+H 435.0; (M+2H)⁺ 218.0.

EXAMPLE 84

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-(3-dimethylamino-propoxy)-6-methoxy-quinoline-3-carbonitrile

A mixture of 0.8 g (1.83 mmol) of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile and 0.055 g of sodium iodide in 15.6 ml of 2M dimethylamine in tetrahydrofuran was placed in a sealed tube and heated to 125° C. for 2.5 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was treated with with ethyl acetate-ether depositing a solid and giving 0.51 g of the title compound as a off-white solid: mass spectrum (electrospray, m/e) M+H 445.0; (M+2H)⁺ 243.4.

EXAMPLE 85

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

A mixture of 0.8 g (1.83 mmol) of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile, 2.4 g (27.5 mmol) of morpholine, and 0.11 g of sodium iodide in 15 ml ethylene glycol dimethyl ether refluxed for 7 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was recrystallized from ethyl acetate-carbon tetrachloride giving 0.63 of the title compound as a light tan solid: mass spectrum (electrospray, m/e) M+H 487.0; (M+2H)⁺ 243.9.

EXAMPLE 86

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-(2-dimethylamino-ethoxy)-6-methoxy-quinoline-3-carbonitrile

A mixture of 0.8 g (1.83 mmol) of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(2-chloro-ethoxy)-6-methoxy-

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quinoline-3-carbonitrile and 0.11 g of sodium iodide in 16.1 ml of 2M dimethylamine in tetrahydrofuran was placed in a sealed tube and heated to 135° C. for 14 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was chromatographed on silica gel eluting with ethyl acetate-methanol-triethylamine 60:40:3 giving 0.41 g of the title compound as a tan solid: mass spectrum (electrospray, m/e) M+H 430.9; (M+2H)⁺ 216.0.

EXAMPLE 87

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-7-(2-morpholin-4-yl-ethoxy)-quinoline-3-carbonitrile

A mixture of 0.8 g (1.83 mmol) of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(2-chloro-ethoxy)-6-methoxyquinoline-3-carbonitrile, 2.4 g (27.5 mmol) of morpholine, and 0.11 g of sodium iodide in 15 ml ethylene glycol dimethyl ether heated in a sealed tube at 135° C. for 12 hr. The solvent was removed and the residue was mixed with warm ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was chromatographed on silica gel eluting with ethyl acetate-methanol-triethylamine 70:30:1 giving 0.43 g of the title compound as a tan solid: mass spectrum (electrospray, m/e) M+H 470.0; (M+2H)⁺ 237.0.

EXAMPLE 88

N-[3-Cyano-4-(3-fluorophenylamino)quinolin-6-yl]acrylamide

A solution of 1.00 g (3.60 mmol) of 6-amino-4-(3-fluorophenylamino)quinoline-3-carbonitrile in 12 mL of THF under N₂ was chilled in ice. Triethylamine (0.436 g, 4.32 mmol) was added followed by 0.393 g (4.32 mmol) of acryloyl chloride and the reaction was stirred at 25° C. overnight. The solvent was removed and the residue was slurried with water and filtered. The crude product was washed with water, dried, washed with hot ethyl acetate and dried in vacuo (50° C.). This yielded 0.862 g of N-[3-cyano-4-(3-fluorophenylamino)quinolin-6-yl]acrylamide as a brown solid: mass spectrum (electrospray, m/e): M+H 333.1.

EXAMPLE 89

6,7-Dimethoxy-4-(3-nitrophenylamino)quinoline-3-carbonitrile

A solution of 0.500 g (2.00 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile and 0.332 g (2.41 mmol) of 3-nitroaniline in 6 mL of methyl cellosolve was refluxed under N₂ for 8 hr. Methanol was added, followed by satd NaHCO₃ (pH 8) and volatile material was removed. The residue was slurried with water, collected by filtration and dried. Recrystallization from ethanol gave 0.480 g of 6,7-dimethoxy-4-(3-nitrophenylamino)quinoline-3-carbonitrile as yellow crystals: mass spectrum (electrospray, m/e): M+H 351.0.

EXAMPLE 90

4-(3-Bromophenylamino)-6-ethoxy-7-methoxyquinoline-3-carbonitrile

A mixture of 1.00 g (3.82 mmol) of 4-chloro-6-ethoxy-7-methoxyquinoline-3-carbonitrile and 0.788 g (4.58 mmol)

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of 3-bromoaniline in 20 mL of ethanol was refluxed under N₂ for 7 h. Saturated NaHCO₃ was added, volatile material was removed and the residue was azeotroped with ethanol. The crude product was slurried with hexane, filtered, washed with water and dried. Recrystallization from ethanol gave 1.31 g of 4-(3-bromophenylamino)-6-ethoxy-7-methoxyquinoline-3-carbonitrile as tan crystals: mass spectrum (electrospray, m/e): M+H 397.9, 399.8.

EXAMPLE 91

4-Chloro-6-ethoxy-7-methoxyquinoline-3-carbonitrile

A mixture of 7.95 g (32.6 mmol) of 6-ethoxy-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile and 50 mL of phosphorous oxychloride was refluxed for 3 h 40 min. The phosphorous oxychloride was removed in vacuo and the residue was slurried with ice water. Solid NaHCO₃ was added (pH8) and the product was collected by filtration, washed well with water and dried in vacuo (40° C.). The yield was 7.75 g of 4-chloro-6-ethoxy-7-methoxyquinoline-3-carbonitrile as a tan solid: mass spectrum (electrospray, m/e): M+H 262.8, 264.8.

EXAMPLE 92

6-Ethoxy-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile

A solution of 10.2 g (45.3 mmol) of methyl 2-amino-5-ethoxy-4-methoxy benzoate and 10.8 g (90.7 mmol) of dimethylformamide dimethyl acetal in 50 mL of dimethylformamide was refluxed for 3 h. Volatile material was removed and the residue was azeotroped with toluene and dried in vacuo to give the formamidine as a purple syrup. n-Butyllithium (100 mmol) in hexane was diluted with 60 mL of tetrahydrofuran at -78° C. A solution of 4.18 g (102 mmol) of acetonitrile in 80 mL of tetrahydrofuran was added over 15 min and the solution was stirred for 20 min. The crude formamidine was dissolved in 80 mL of tetrahydrofuran and added dropwise to the cold solution over 0.5 h. After stirring for 2 h, the reaction was quenched at -78° C. with 13 mL of acetic acid. It was allowed to warm to room temperature and volatile material was removed in vacuo. The residue was slurried with water and the crude product was collected by filtration washed with water and dried. This material was then washed with chloroform and dried to give 7.95 g of 6-ethoxy-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile as yellow crystals: mass spectrum (electrospray, m/e): M-H 243.2.

EXAMPLE 93

Methyl 2-Amino-5-ethoxy-4-methoxybenzoate

A mixture of 17.0 g (66.7 mmol) of methyl 5-ethoxy-4-methoxy-2-nitrobenzoate, 13.1 g (233 mmol) of powdered iron and 17.7 g (334 mmol) of ammonium chloride in 95 mL of water and 245 mL of methanol was refluxed for 4.5 h. An additional 13.1 g of iron was added followed by refluxing for 2.5 h. Then an additional 13.1 g of iron and 17.7 g of ammonium chloride was added and refluxing was continued for 12 h. The reaction was filtered through Celite and methanol was removed from the filtrate. The filtrate was extracted with chloroform and the extracts were treated with Darco, evaporated and dried in vacuo (50° C.). The yield was 11.0 g of methyl 2-amino-5-ethoxy-4-methoxybenzoate as tan crystals: mass spectrum (electrospray, m/e): M+H 225.9.

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EXAMPLE 94

Methyl 5-Ethoxy-4-methoxy-2-nitrobenzoate

A mixture of 15.0 g (74.1 mmol) of methyl 3-ethoxy-4-methoxybenzoate in 45 mL of acetic acid was treated with 15 mL of conc nitric acid dropwise over 12 min. The reaction was kept at 55° C. for 45 min, cooled to 25° C. and poured into ice water. The product was extracted into methylene chloride and the extracts were washed with water and dil sodium hydroxide, dried and evaporated. The yield was 17.8 g of methyl 5-ethoxy-4-methoxy-2-nitrobenzoate as yellow crystals; mass spectrum (electrospray, m/e): M+H 256.0.

EXAMPLE 95

Methyl 3-Ethoxy-4-methoxybenzoate

A mixture of 24.3 g (134 mmol) of methyl 3-hydroxy-4-methoxybenzoate, 36.8 g (267 mmol) of anhyd potassium carbonate and 31.4 g (201 mmol) of ethyl iodide in 500 mL of dimethylformamide was stirred at 100° C. for 5.5 h. An additional amount of ethyl iodide (31.4 g) and potassium carbonate (18.4 g) was added and heating was continued for 2 h more. The reaction was filtered and volatile material was removed from the filtrate in vacuo. The residue was slurried with water and filtered to collect the product which was washed with water and dried. Recrystallization from heptane gave 15.6 g of methyl 3-ethoxy-4-methoxybenzoate as white crystals; mass spectrum (electrospray, m/e): M+H 210.9.

EXAMPLE 96

Methyl 3-Hydroxy-4-methoxybenzoate

A solution of 30.8 g (183 mmol) of 3-hydroxy-4-methoxybenzoic acid and 6 mL of conc sulfuric acid in 600 mL of methanol was refluxed overnight. Most of the solvent was removed and the remaining solution was poured into 600 mL of water containing 25 g of sodium bicarbonate. The product was extracted into ether, treated with Darco, dried and evaporated. The yield was 31.8 g of methyl 3-hydroxy-4-methoxybenzoate as pale yellow crystals.

EXAMPLE 97

6-Ethoxy-4-(3-hydroxy-4-methylphenylamino)-7-methoxyquinoline-3-carbonitrile

A mixture of 1.00 g (3.82 mmol) of 4-chloro-6-ethoxy-7-methoxyquinoline-3-carbonitrile and 0.563 g (4.58 mmol) of 3-hydroxy-4-methylaniline in 20 mL of ethanol was refluxed under N₂ for 8 h. Saturated NaHCO₃ was added, volatile material was removed and the residue was azeotroped with ethanol. The crude product was slurried with hexane, filtered, washed with water and cold ethanol and dried. Recrystallization from ethanol gave 0.632 g of 6-ethoxy-4-(3-hydroxy-4-methylphenylamino)-7-methoxyquinoline-3-carbonitrile as light yellow crystals; mass spectrum (electrospray, m/e): M+H 349.9.

EXAMPLE 98

4-Bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide

A solution of 1.65 grams (0.01 mole) of 4-bromo crotonic acid (Giza Braun, J. Am. Chem. Soc. 52, 3167 1930) in 15 mL of dichloromethane was treated with 1.74 mL (0.02

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moles) of oxalyl chloride and 1 drop of N, N-dimethylformamide. After an hour the solvents were removed on the rotary evaporator. The residual oil was taken up in 25 mL of tetrahydrofuran, and 3.39 grams of 6-Amino-4-(3-bromo-phenylamino)-quinoline-3-carbonitrile in 25 mL of tetrahydrofuran was added dropwise. This was followed by the dropwise addition of 1.92 mL (0.011 moles) of diisopropylethylamine. After the addition of 25 mL of water and 50 mL of ethyl acetate, the layers were separated. The organic layer was dried over anhydrous sodium sulfate, and taken to a solid in vacuo. This solid was digested for an hour with refluxing ethyl acetate then filtered from the ethyl acetate while still hot. Thus was obtained 3.31 grams (68%) of 4-bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide.

EXAMPLE 99

4-Dimethylamino-but-2-enoic Acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide

Fifteen milliliters of a 2 molar solution of dimethylamine in tetrahydrofuran was cooled in an ice bath and a solution of 729 mg (1.5 mmol) of 4-bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide in 5 mL of N,N-dimethylformamide was added dropwise. Stirring and cooling were continued for 2 hours. Then 25 mL of water and 15 mL of ethyl acetate were added. The layers were separated and the organic layer was extracted with an additional 25 mL of water. The combined aqueous layers were extracted with 2-25 mL portions of 1:1 tetrahydrofuran-ethyl acetate. The combined organic layers were absorbed onto silica gel and chromatographed on silica gel. The column was eluted with a gradient of 1:19 to 1:4 methanol-methylene chloride. Obtained was 381 mg (56%) of 4-Dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide which melted at 209-211 deg.; mass spectrum (electrospray, m/e): M+H 225.5, 226.2.

EXAMPLE 100

4-Diethylamino-but-2-enoic Acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide

A solution of 3.15 mL (30 mmol) of diethylamine in 15 mL of tetrahydrofuran was cooled in an ice bath and a solution of 729 mg (1.5 mmol) of 4-bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide in 5 mL of N,N-dimethylformamide was added dropwise. Stirring and cooling were continued for 2 hours. Then 25 mL of water and 15 mL of ethyl acetate were added. The layers were separated and aqueous layer was extracted with 2-15 mL portions of 1:1 tetrahydrofuran-ethyl acetate. The combined organic layers were absorbed onto silica gel and chromatographed on silica gel. The column was eluted with a gradient of 1:19 to 1:4 methanol-methylene chloride to give 367 mg (51%) of 4-Diethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide. The compound melted at 141-145 deg; mass spectrum (electrospray, m/e): M+H 478.0, 480.0.

EXAMPLE 101

4-Methylamino-but-2-enoic Acid [4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide

Fifteen milliliters of a 2 molar solution of methylamine in tetrahydrofuran was cooled in an ice bath and a solution of

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729 mg (1.5 mmol) of 4-bromo-but-2-enoic acid[4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-amide in 5 ml of *N,N*-dimethylformamide was added dropwise. Stirring and cooling were continued for 2 hours. Then 25 ml of water and 15 ml of ethyl acetate were added. The layers were separated aqueous layer was extracted with 2-15 ml portions of 1:1 tetrahydrofuran-ethyl acetate. The combined organic layers were absorbed onto silica gel and chromatographed on silica gel. The column was eluted with a gradient of 1:19 to 1:1 methanol-methylene chloride. Obtained was 210 mg (32%) of 4-Methylamino-but-2-enoic acid[4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide which slowly went to a tar in the range of 194-202 deg.: mass spectrum (electrospray, *m/z*): *M*+*H* 437.9; *M*+2*H* 219.5.

EXAMPLE 102

2-Cyano-3-(2-methyl-4-nitrophenyl)acrylic Acid Ethyl Ester

A mixture of 2-methyl-4-nitroaniline (38.0 g, 250 mmol), ethyl (ethoxymethylene)cyanoacetate (50.8 g, 300 mmol), and 200 ml of toluene was refluxed for 24 h, cooled, diluted with 1:1 ether-hexane, and filtered. The resulting white solid was washed with hexane-ether and dried to give 63.9 g, mp 180-210° C.

EXAMPLE 103

1,4-Dihydroquinoline-8-methyl-6-nitro-3-carbonitrile

A stirred mixture of 64 g (230 mmol) of 2-cyano-3-(2-methyl-4-nitrophenyl)acrylic acid ethyl ester and 1.5 L of Dowtherm A was heated at 260° C. for 12 h, cooled, diluted with hexane, and filtered. The gray solid thus obtained was washed with hexane and dried to give 51.5 g, mp 295-305° C.

EXAMPLE 104

4-Chloro-8-methyl-6-nitro-3-quinolinecarbonitrile

A stirred mixture of 1,4-dihydroquinoline-8-methyl-6-nitro-3-carbonitrile (47 g, 200 mmol) and 200 ml of phosphorous oxychloride was refluxed for 4 h. The phosphorous oxychloride was removed in vacuo, and the residue was stirred with methylene chloride at 0° C. and treated with a slurry of ice and sodium carbonate. The organic layer was separated and washed with water. The solution was dried and concentrated to a volume of 700 ml. The product was precipitated by the addition of hexane and cooling to 0° C. The white solid was filtered off and dried to give 41.6 g, mp 210-212° C.

EXAMPLE 105

4-[(3-Bromophenyl)amino]-8-methyl-6-nitro-3-quinolinecarbonitrile

A stirred mixture of 4-chloro-8-methyl-6-nitro-3-quinolinecarbonitrile (14.8 g, 60 mmol), 3-bromoaniline (12.4 g, 72 mmol), pyridine hydrochloride (6.93 g, 60 mmol), and 180 ml of ethoxyethanol was refluxed for 1.5 h, cooled, poured into a stirred mixture of water and an amount of sodium carbonate to give a pH of 8-9. The resulting yellow solid was filtered, washed with water, dried, digested in boiling ether, filtered, and dried to give 22.6 g, mp 263-267° C.

EXAMPLE 106

4-[(3-Bromophenyl)-*N*-acetylamino]-8-methyl-6-nitro-3-quinolinecarbonitrile

A stirred mixture of 4-[(3-bromophenyl)amino]-8-methyl-6-nitro-3-quinolinecarbonitrile (15.3 g, 40 mmol),

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0.37 g (3 mmol) of dimethylaminopyridine, 40 ml of acetic anhydride, and 80 ml of pyridine was refluxed for 3 h and concentrated at 50° C. under vacuum. The residue was stirred with methylene chloride and 0.1 N HCl. After filtration through Celite, the organic layer was washed with water, dried and concentrated. The residue was subjected to chromatography on silica gel with 1% acetic acid in methylene chloride to give 11.2 g of an amber glass, NMR (CDCl₃) δ 2.29 (*N*-acetyl group).

EXAMPLE 107

8-Bromomethyl-4-[(3-bromophenyl)-*N*-acetylamino]-6-nitro-3-quinolinecarbonitrile

A stirred mixture of 4-[(3-bromophenyl)-*N*-acetylamino]-8-methyl-6-nitro-3-quinolinecarbonitrile (10.6 g, 25 mmol), *N*-bromosuccinimide (6.68 g, 37.5 mmol), 0.30 g of dibenzoyl peroxide, and 200 ml of carbon tetrachloride was refluxed for 2 h, treated with an additional 0.30 g of dibenzoyl peroxide, and refluxed an additional 2.5 h, cooled, diluted with methylene chloride, and stirred with aqueous sodium bisulfite. The organic layer was separated and washed successively with water, sodium bicarbonate solution, and water. The solution was dried and evaporated to give 15 g of a white foam, NMR (CDCl₃) δ 5.19 (dd, C H₂Br).

EXAMPLE 108

4-[(3-Bromophenyl)amino]-8-dimethylaminomethyl-6-nitro-3-quinolinecarbonitrile

To a stirred solution of dimethylamine in THF (2.0 M; 115 ml; 230 mmol) at 0° C. was added a solution of 8-bromomethyl 4-[(3-bromophenyl)-*N*-acetylamino]-6-nitro-3-quinolinecarbonitrile (11.6 g, 23 mmol) in 115 ml of THF during 15 m. After warming to 25° C. the mixture was stirred for 2 h. The THF was evaporated off, and the residue was refluxed in 230 ml of methanol with 12.7 g (92 mmol) of potassium carbonate for 1 h. The mixture was cooled, saturated with CO₂, and concentrated. The residue was partitioned with methylene chloride and water. The organic layer was washed with water, dried, and concentrated. The residue was subjected to chromatography on silica gel with methylene chloride-ethyl acetate-methanol-triethylamine to give 6.0 g yellow solid, mp 223-226° C.

EXAMPLE 109

6-Amino-4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-3-quinolinecarbonitrile

A stirred mixture of 4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-6-nitro-3-quinolinecarbonitrile (5.98 g, 14.1 mmol), iron powder (2.76 g, 49 mg-atoms), acetic acid (5.67 ml, 99 mmol), and 70 ml of methanol was refluxed for 2 h and then evaporated to remove methanol. The residue was stirred with water for 10 m, and the orange solid was filtered off and washed with 2% acetic acid. The total filtrate was basified to pH 10 with 5 N sodium hydroxide. The resulting precipitate was extracted with methylene chloride. The extract was washed with water, dried, and concentrated. The residue was subjected to chromatography on silica gel with ethyl acetate-methanol-triethylamine to give 3.34 g of amber solid; mass spectrum (electrospray, *m/z*) *M*+*H* 396.2, 398.1.

EXAMPLE 110

N-{4-[(3-Bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinoliny]-2-butyramide

To a stirred mixture of 2-butyric acid (0.42 g, 5.0 mmol) and *N*-methylmorpholine (0.66 ml, 6.0 mmol) in 4.0 ml of

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THF at 0° C. was added *i*-butyl chloroformate (0.52 ml, 4.0 mmol) during 10 m. After 10 m a solution of 6-amino-4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-3-quinolinecarbonitrile (0.79 g, 2.0 mmol) in 4.0 ml of THF was added during 60 s. The mixture was warmed to 25° C., stirred for 2 h, and diluted with water. The μ_{H} was adjusted to 9–10 with potassium carbonate, and the resulting solid was filtered off, washed with water, stirred with methylene chloride, and filtered. The latter filtrate was concentrated to give a solid which was subjected to chromatography on silica gel with methylene chloride-ethyl acetate-methanol-triethylamine to give an amber solid; mass spectrum (electrospray, *m/e*) *M*+*H* 462, 464.

EXAMPLE 111

N-[4-[(3-Bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinolinyl]-2-propenamide

To a stirred solution of 6-amino-4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-3-quinolinecarbonitrile (0.20 g, 0.50 mmol) and *N,N*-diisopropylethylamine (0.13 ml, 0.75 mmol) in 3.4 ml of THF at 0° C. was added acryloyl chloride (0.045 ml, 0.55 mmol) during 5 m. After stirring for 3 h at 0° C. the mixture was diluted with sodium bicarbonate solution. The resulting solid was filtered off, washed with water, dried, and subjected to chromatography on silica gel with methylene chloride-ethyl acetate-methanol-triethylamine to give a yellow solid; mass spectrum (electrospray, *m/e*) *M*+*H* 449.9, 452.0.

EXAMPLE 112

N-[4-[(3-Bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinolinyl]acetamide

To a stirred mixture of 6-amino-4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-3-quinolinecarbonitrile (0.20 g, 0.50 mmol) and 1.5 ml of acetic acid at 25° C. was added 0.14 ml (1.5 mmol) of acetic anhydride. After 60 m volatile matter was evaporated off under vacuum. The residue was stirred with sodium bicarbonate solution. The resulting solid was filtered off, washed with water, dried, and recrystallized from isopropanol-hexane to give a light yellow solid, mp 162–167° C.

EXAMPLE 113

N'-[2-Carbethoxy-4,5-bis(2-methoxyethoxy)phenyl]-*N,N*-dimethylformamidine

To a stirred solution of 15.7 g (50 mmol) of ethyl 2-amino-4,5-bis(2-methoxyethoxy)benzoate (Pfizer patent WO 96130347) in 50 ml of DMF at 0° C. was added phosphorous oxychloride (5.6 ml, 60 mmol) during 15 m. The resulting solution was heated at 55° C. for 45 m, cooled, diluted with methylene chloride, and treated at 0° C. with 200 ml of *N*/1 sodium hydroxide during 2 m. The organic layer was separated and washed at 0° C. with water. The solution was dried and evaporated with added toluene present to give 18.4 g of amber oil; NMR (CDCl₃) δ 3.02 (s, Me₂N).

EXAMPLE 114

1,4-Dihydroquinoline-5,6-bis(2-methoxyethoxy)-3-carbonitrile

To a stirred solution of *n*-butyllithium (44 ml of 2.5 M in hexane; 110 mmol) in 65 ml of THF at –78° C. was added

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a solution of acetonitrile (5.85 ml, 112 mmol) in 110 ml of THF during 10 m. After stirring at –78° C. for 15 m, the mixture was treated with a solution of *N*'-[2-carbethoxy-4,5-bis(2-methoxyethoxy)phenyl]-*N,N*-dimethylformamidine in 75 ml of THF during 20 m. After 30 m at –78° C. the stirred mixture was treated with acetic acid (14.3 ml, 250 mmol). The mixture was warmed to 25° C. and stirred for 2 h. The mixture was evaporated to dryness, and diluted with water. The resulting white solid was filtered, washed with water, and dried to give 10.7 g; mass spectrum (electrospray, *m/e*) *M*+*H* 319.2.

EXAMPLE 115

4-Chloro-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile

A stirred mixture of 1,4-dihydroquinoline-5,6-bis(2-methoxyethoxy)-3-carbonitrile 9.68 g, 30.4 mmol) and 30 ml of phosphorous oxychloride was refluxed for 1.5 h. The resulting solution was concentrated under vacuum, and the residue was stirred with methylene chloride at 0° C. as ice-water and sodium carbonate were added until pH of mixture was 8–9. The organic layer was separated, washed with water, dried and concentrated to give a tan solid; mass spectrum (electrospray, *m/e*) *M*+*H* 337.1, 339.1.

EXAMPLE 116

4-[(3-Ethynylphenyl)amino]-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile

A stirred mixture of 4-Chloro-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile (2.52 g, 7.5 mmol), pyridine hydrochloride (0.87 g, 9.0 mmol), 3-ethynylaniline (1.06 g, 9.0 mmol), and ethoxyethanol (22 ml) was refluxed for 1.5 h, cooled, diluted with water containing potassium carbonate to give pH–9, and extracted with ethyl acetate. The extract was washed well with water, dried, and concentrated. The resulting solid was recrystallized from ethyl acetate to give an off-white solid, mp 150–153°.

EXAMPLE 117

4-[3-Dimethylaminophenyl]amino]-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile

A stirred mixture of 4-Chloro-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile (0.67 g, 2.0 mmol), pyridine (0.39 ml, 4.8 mmol), 3-dimethylaminoaniline dihydrochloride (0.50 g, 2.4 mmol), and ethoxyethanol (6.0 ml) was refluxed for 2 h, cooled, and partitioned with ethyl acetate and water containing potassium carbonate to give pH–9–10. The organic layer was washed with water, dried and concentrated. The residue was chromatographed on silica gel with methylene chloride-ethyl acetate-methanol to give an amber glass; mass spectrum (electrospray, *m/e*) *M*+*H* 437.0.

EXAMPLE 118

4-[(3-Acetylphenyl)amino]-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile

In the manner of Example 116, 4-Chloro-5,6-bis(2-methoxyethoxy)-3-quinolinecarbonitrile was reacted with 3-aminoacetophenone to give the title compound; recrystallized from ethanol to give off-white solid, mp 250–253 (dec).

EXAMPLE 119

Methyl 4-Methoxy-3-(3-morpholin-4-yl-propoxy)benzoate

A stirred mixture of methyl isovanillate (22.6 g, 124 mmol), *N*-(3-chloropropyl)-morpholine (25.4 g, 155 mmol),

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potassium carbonate (18.8 g, 136 mmol), tetrabutylammonium iodide (0.92 g, 2.5 mmol), and 248 ml of 2-butanone was refluxed for 20 h. The 2-butanone was evaporated off, and the residue was stirred with water at 0° C. The resulting white solid was filtered off, washed successively with water and hexane, and dried; mp 90–94° C.

EXAMPLE 120

Methyl 4-methoxy-5-(3-morpholin-4-yl-propoxy)-2-nitrobenzoate

To a stirred solution of methyl 4-methoxy-3-(3-morpholin-4-yl-propoxy)benzoate (30.9 g, 100 mmol) in 100 ml of acetic acid at 25° C. was added 50 ml of 70% nitric acid during 30 m. The solution was heated to 45° C. at which point the reaction started and was self-sustaining at that temperature. After a total of 1.5 h at 45–50° C. the mixture was cooled to 0° C., treated with ice-water and 240 g (1.75 mol) of potassium carbonate, and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated to give a yellow solid, mp 78–82° C.

EXAMPLE 121

Methyl 2-Amino-4-methoxy-5-(3-morpholin-4-yl-propoxy)benzoate

A solution of methyl 4-methoxy-3-(3-morpholin-4-yl-propoxy)-2-nitrobenzoate (32.5 g, 91.7 mmol) in 110 ml of methanol and 220 ml of ethyl acetate was hydrogenated at 55 psi in the presence of 2.0 g of 10% Pd on carbon catalyst at 25° C. After 4 h the mixture was filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from acetone-hexane to give a tan solid, mp 78–82° C.

EXAMPLE 122

Ethyl 2-(Dimethylaminomethyleneamino)-4-methoxy-5-(3-morpholin-4-yl-propoxy)benzoate

A mixture of methyl 2-amino-4-methoxy-5-(3-morpholin-4-yl-propoxy)benzoate (6.49 g, 20 mmol) and dimethylformamide dimethyl acetal (4.25 ml, 30 mmol) was heated at 100° C. for 1.5 h. All volatile materials were evaporated off directly at 70° C. to give a syrup; mass spectrum (electrospray, m/e) M+H 380.5.

EXAMPLE 123

1,4-Dihydroquinoline-7-methoxy-6-(3-morpholin-4-yl-propoxy)-4-oxo-3-carbonitrile

To a stirred solution of n-butyllithium (17.6 ml of 2.5 M in hexane; 44 mmol) in 26 ml of THF at –78° C. was added a solution of acetonitrile (1.85 ml, 45 mmol) in 44 ml of THF during 10 m. After stirring at –78° C. for 15 m, the mixture was treated with a solution of ethyl 2-(dimethylaminomethyleneamino)-4-methoxy-5-(3-morpholin-4-yl-propoxy)benzoate (7.6 g, 20 mmol) in 30 ml of THF during 20 m. After 90 m at –78° C. the mixture was treated with carbon dioxide while warming slowly to 25° C. and then evaporated to dryness. The residue was partitioned with n-butanol (200 ml) and half-saturated NaCl solution (40 ml). The organic layer was separated, washed with saturated NaCl solution, and evaporated to dryness. The resulting solid was triturated successively with boiling acetone and methanol, filtered, and dried to give a tan solid, mp 255–260° C.

EXAMPLE 124

4-Chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile

A stirred mixture of 1,4-Dihydroquinoline-7-methoxy-6-(3-morpholin-4-yl-propoxy)-4-oxo-3-carbonitrile (4.75 g,

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13.8 mmol), 0.10 ml of DMF, and 55 ml of thionyl chloride was refluxed for 3 h. Volatile matter was removed by evaporation at 30° C., and the residue was stirred at 0° C. with a mixture of methylene chloride and water containing potassium carbonate to give pH 9–10. The organic layer was separated, washed with water, dried and concentrated to give a brown solid; mass spectrum (electrospray, m/e) M+H 362.4, 364.4.

EXAMPLE 125

4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile

A stirred mixture of 4-chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile (1.8 g, 5.0 mmol), 3-chloro-4-fluoroaniline (0.87 g, 6.0 mmol), pyridine hydrochloride (1.15 g, 10 mmol), and 15 ml of ethoxyethanol was refluxed for 2 h, cooled, and stirred with hexane and water containing potassium carbonate to give pH 10. The resulting brown solid was filtered off, washed with water and hexane, and dried. Recrystallization from ethanol gave an off-white solid, mp 240–244° C.

EXAMPLE 126

4-[(3-Bromophenyl)amino]-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile

In the manner of Example 125, 4-chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile was reacted with 3-bromoaniline to give the title compound; recrystallized from methanol to give an off-white solid, mp 208–212° C.

EXAMPLE 127

4-[(4-Chloro-2-fluorophenyl)amino]-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile

In the manner of Example 125, 4-chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile was reacted with 4-chloro-2-fluoroaniline to give the title compound; recrystallized from methanol to give an off-white solid, mp 207–212° C.

EXAMPLE 128

4-[(3-Hydroxy-4-methylphenyl)amino]-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile

In the manner of Example 125, 4-chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile was reacted with 3-hydroxy-4-methylaniline to give the title compound; recrystallized from ethyl acetate to give an amber solid, mp 222–227° C. (dec).

EXAMPLE 129

N-[3-Cyano-4-[(3-iodophenyl)amino]-6-quinolinyl]-2-propenamide

Dissolved 500 mg (1.29 mmol) 6-amino-4-[(3-iodophenyl)amino]-3-quinolinecarbonitrile in 1.0 ml of DMF and added 6 ml THF. Chilled to 0° C. under N₂ and added 200 μ l (1.43 mmol) triethyl amine and 120 μ l (1.44 mmol) acryloyl chloride. Removed ice bath at 15 minutes. At 1.5 hours stripped solvent. Stirred residue with water and dilute sodium bicarbonate. Collected, washed with

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water, air dried. Boiled solids in ethyl acetate. Filtered off solids, removed solvent of the filtrate, and dried in vacuo, giving 391 mg of orange-brown solid: mass spectrum (electrospray m/e): M+H=441.1.

EXAMPLE 130

6-Amino-4-[(3-iodophenyl)amino]-3-quinolinecarbonitrile

A mixture of 6.70 g (16.1 mmol) 4-[(3-iodophenyl)amino]-6-nitro-3-quinolinecarbonitrile, 300 ml ethanol, and 18.2 g (80.5 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 2 hours, added ice water. Added sodium bicarbonate until pH was basic, forming a thick yellow mixture. Stirred for 2.5 hours. Extracted with chloroform, stirred organic portion with Darco and filtered through magnesium sulfate. Stripped solvent and dried in vacuo, giving 3.48 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H=387.0.

EXAMPLE 131

4-[(3-iodophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 3.10 ml (25.7 mmol) 3-iodoaniline, 200 ml ethanol, and 5.00 g (21.4 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile was heated to reflux under N₂ for 3.5 hours. Cooled and made basic with a saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Shurried residue with hexane and collected. Air dried, washed solids with water, and dried in vacuo. Dissolved solids in 400 ml ethyl acetate, stirred with Darco, filtered and removed solvent. Dried solids in vacuo to give 7.38 g of yellow solid: mass spectrum (electrospray m/e): M+H=417.0.

EXAMPLE 132

N-{3-Cyano-4-[(3-methylphenyl)amino]-6-quinolinyl}-2-butyramide

Dissolved 597 mg (7.10 mmol) 2-butyric acid in 25 ml THF under N₂ and chilled to 0° C. Added 950 μl (7.30 mmol) isobutyl chloroformate and 780 μl (7.10 mmol) N-methylmorpholine and stirred for 10 minutes. Added dropwise a solution of 778 mg (2.84 mmol) 6-amino-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile, stirred for 15 minutes at 0° C. and then at 25° C. overnight. Stripped solvent and slurried residue with water, drying the gummy solid in vacuo briefly. Boiled solid in ethyl acetate and collected. Recrystallized from DMF, using ethanol to crash out the product, and dried in vacuo, giving 401 mg of yellow-brown solid: mass spectrum (electrospray m/e): M+H=341.2.

EXAMPLE 133

6-Amino-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile

Added 253 mg 10% palladium on carbon to a round bottom flask under N₂ and covered catalyst with 140 ml ethanol. To this added 2.49 g (8.18 mmol) 6-nitro-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile and 640 μl (20.4 mmol) anhydrous hydrazine. The mixture was heated to reflux for 2 hours 15 minutes and filtered hot through celite. Stripped solvent and dried in vacuo, giving 2.455 g of yellow solid: mass spectrum (electrospray m/e): M+H=275.2.

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EXAMPLE 134

6-Nitro-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 2.75 ml (25.7 mmol) 3-toluidine was heated to reflux for 4.5 hours. Cooled and added a saturated sodium bicarbonate until pH was basic. Stripped solvents and azeotroped with ethanol. Slurried with hexane, collected, and air dried. Washed with water and dried in vacuo. Boiled in ethyl acetate, stirred with Darco and filtered. Stripped solvent and dried in vacuo to give 4.82 g of yellow-orange solid: mass spectrum (electrospray m/e): M+H=305.2.

EXAMPLE 135

N-{4-[(3-Chlorophenyl)amino]-3-cyano-6-quinolinyl}-2-propenamide

Dissolved 430 mg (1.46 mmol) 6-amino-4-[(3-chlorophenyl)amino]-3-quinolinecarbonitrile in 4 ml DMF, added 10 ml THF and chilled to 0° C. under N₂. Added 224 μl (1.60 mmol) triethylamine and 133 μl (1.60 mmol) acryloyl chloride. Removed ice bath at 15 minutes, reaction complete at this time, but stirred overnight at 25° C. Stripped solvent, added a dilute sodium bicarbonate to the residue and collected solids. Washed with water and dried in vacuo. Boiled in ethyl acetate, collected solids and dried in vacuo, giving 200 mg of orange solid: mass spectrum (electrospray m/e): M+H=349.0, 351.0.

EXAMPLE 136

6-Amino-4-[(3-chlorophenyl)amino]-3-quinolinecarbonitrile

A mixture of 6.30 g (19.4 mmol) 4-[(3-chlorophenyl)amino]-6-nitro-3-quinolinecarbonitrile, 300 ml ethanol, and 21.9 g (97 mmol) SnCl₂ dihydrate were heated to reflux under N₂. Removed heat at 2.5 hours, added ice water and made basic with sodium bicarbonate. Stirred for 2 hours and extracted with chloroform. Dried organic layer with sodium sulfate, filtered, stripped solvent and dried residue in vacuo, giving 5.74 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H=295.1, 297.1.

EXAMPLE 137

4-[(3-Chlorophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 10.0 g (42.9 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 260 ml ethanol, and 5.40 ml 3-chloroaniline was heated to reflux under N₂. Removed heat at 4 hours, cooled to 25° C. and added saturated sodium bicarbonate until the pH was basic. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane, collected solid, and air dried. Washed solids with water and dried in vacuo. Dissolved in boiling ethyl acetate, stirred with Darco, and filtered. Stripped solvent and dried residue in vacuo, giving 6.5 g of yellow solid: mass spectrum (electrospray m/e): M+H=325.0, 327.0.

EXAMPLE 138

N-{3-Cyano-4-[(3-methoxyphenyl)amino]-6-quinolinyl}-2-propenamide

Dissolved 500 mg (1.72 mmol) 6-amino-4-[(3-methoxyphenyl)amino]-3-quinolinecarbonitrile in 2 ml hot

DMF, added 6 ml THF, and chilled to 0° C. Added 264 μ l (1.90 mmol) triethylamine and 158 μ l (1.90 mmol) acryloyl chloride. Removed ice bath at 15 minutes. Stripped solvent at 2 hours. Washed residue with dilute sodium bicarbonate, collected solids, washed with water, and air dried. Boiled solids in ethyl acetate, collected and dried in vacuo, giving 288 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=345.2.

EXAMPLE 139

N-{3-Cyano-4-[(3-methoxyphenyl)amino]-6-quinolinyl}-2-butyramide

Dissolved 362 mg (4.31 mmol) acid in 20 ml THF under N₂ and chilled to 0° C. Added 560 μ l (4.30 mmol) isobutyl chloroformate and 475 μ l (4.31 mmol) N-methylmorpholine and stirred for 10 minutes. Dissolved 500 mg (1.72 mmol) 6-amino-4-[(3-methoxyphenyl)amino]-3-quinolinecarbonitrile in 2 ml hot DMF and added 10 ml THF. Added this to the mixed anhydride dropwise, stirred for 15 minutes at 0° C. and at 25° C. overnight. Stripped solvent, slurried residue with water, collected solids, and air dried. Recrystallized from ethyl acetate and dried in vacuo, giving 270 mg of yellow solid: mass spectrum (electrospray m/e): M+H=357.1.

EXAMPLE 140

N-{3-Cyano-4-[(3-methoxyphenyl)amino]-6-quinolinyl}-4-piperidino-2-butyramide

Partially dissolved 1.21 (7.22 mmol) 4-piperidino-2-butyric acid in 100 ml THF and chilled to 0° C. under N₂. Added 955 μ l (8.67 mmol) N-methylmorpholine and 750 μ l (5.78 mmol) isobutyl chloroformate. Stirred for 40 minutes and added a solution of 840 mg (2.89 mmol) 6-amino-4-[(3-methoxyphenyl)amino]-3-quinolinecarbonitrile dissolved in 10 ml hot pyridine. At 2 hours, poured into ice water and made basic with saturated sodium bicarbonate. Extracted with ethyl acetate, dried with sodium sulfate, and stripped down to a small volume, which was loaded onto a column of silica gel. Eluted with 10% methanol/ethyl acetate, stripped solvent of desired fractions, and dried in vacuo, giving 970 mg of green solid: mass spectrum (electrospray m/e): M+H=440.1.

EXAMPLE 141

6-Amino-4-[(3-methoxyphenyl)amino]-3-quinolinecarbonitrile

325 mg of 10% palladium on carbon was added to a round bottom flask under N₂ and covered with 165 ml ethanol. Added 3.29 g (10.3 mmol) 4-[(3-methoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile and 800 μ l anhydrous hydrazine and heated mixture to reflux. At 1.5 hours, filtered hot through celite, stripped solvent and dried in vacuo, giving 2.876 g of yellow solid: mass spectrum (electrospray m/e): M+H=291.2.

EXAMPLE 142

4-[(3-Methoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.0 ml (26.0 mmol) m-anisidine was heated to reflux under N₂. Removed heat at 4.5 hours and made basic with saturated sodium

bicarbonate. Stripped solvents and azeotroped with ethanol. Slurried with hexane and collected crystals. Washed with water, dried in vacuo. Dissolved 5.94 g of crude product in 320 ml boiling ethyl acetate, stirred with Darco, filtered, stripped solvent, and dried in vacuo, giving about 5 g of yellow-orange solid: mass spectrum (electrospray m/e): M+H=291.1.

EXAMPLE 143

N-{4-[(3-Chloro-4-fluoro-phenyl)amino]-3-cyano-6-quinolinyl}-2-butyramide

Dissolved 336 mg (4.00 mmol) 2-butyric acid in 20 ml of THF and chilled to 0° C. under N₂. Added 520 μ l (4.00 mmol) isobutyl chloroformate and 440 μ l (4.00 mmol) N-methylmorpholine and stirred for 10 minutes. Added a solution of 500 mg (1.60 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile, stirred for 15 minutes at 0° C. and then at 25° C. overnight. Stripped solvent, washed with water, collected and dried in vacuo. Recrystallized from ethyl acetate, giving 148 mg of a yellow solid: mass spectrum (electrospray m/e): M+H=379.1, 381.1.

EXAMPLE 144

N-{4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-2-propenamide

Dissolved 1.00 g (3.20 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile in 2 ml hot DMF, added 12 ml THF and chilled to 0° C. under N₂. Added 490 μ l (3.52 mmol) triethyl amine and 295 μ l (3.52 mmol) acryloyl chloride. Removed ice bath at 15 minutes, and at 1.5 hours stripped solvent. Slurried residue with a dilute sodium bicarbonate, collected solids, and washed with water. Recrystallized from ethyl acetate, giving 215 mg of yellow solid: mass spectrum (electrospray m/e): M+H=367.1, 369.1.

EXAMPLE 145

N-{4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-2-butanamide

Dissolved 1.50 g (4.80 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile in 50 ml THF, added 836 μ l (4.80 mmol) N,N-diisopropylethylamine, and chilled to 0° C. under N₂. Added 500 μ l (4.80 mmol) 4-bromo-but-2-enoyl chloride and after 1 hour dropwise added the mixture to 10 ml of a 2M solution (19 mmol) of dimethylamine in THF cooled to -78° C. At 2 hours, added 5 ml (9.5 mmol) more of dimethyl amine solution and warmed to 25° C. After 1 hour, poured onto a cold solution of sodium bicarbonate. Extracted with ethyl acetate, dried organics with brine and sodium sulfate, reduced to small volume and loaded onto a column of silica gel. Eluted with 70% methanol/ethyl acetate, stripped solvent of desired fractions and dried in vacuo, giving 427 mg of yellow solid: mass spectrum (electrospray m/e): M+H=424.0, 426.0.

EXAMPLE 146

N-{4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-diethylamino-2-butanamide

Added 500 μ l (4.80 mmol) 4-bromo-but-2-enoyl chloride to a solution of 1.50 g (4.80 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile and 836 μ l

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(4.80 mmol) *N,N*-diisopropylethylamine in 50 ml THF at 0° C. under N₂. At 1 hour added the mixture dropwise to 1.26 ml (24 mmol) diethylamine in 11 ml THF chilled to -78° C. Removed dry ice bath after complete addition, and at 2 hours, 45 minutes poured onto a mixture of ice and saturated sodium bicarbonate. Extracted with ethyl acetate, dried organic layer with brine and sodium sulfate, and stripped solvent. Loaded compound onto a column of silica gel, eluted with 35% methanol/ethyl acetate, stripped solvent from desired fractions, and dried in vacuo, giving 292 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=452.4, 454.4.

EXAMPLE 147

N-{4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-morpholino-2-butenamide

Added 500 μ l (4.80 mmol) 4-bromo-but-2-enoyl chloride to a solution of 1.50 g (4.80 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile and 836 μ l (4.80 mmol) *N,N*-diisopropylethylamine in 50 ml THF at 0° C. under N₂. At 1 hour added the mixture dropwise to 2.09 ml (24 mmol) morpholine in 10 ml THF at 0° C. Removed ice bath upon complete addition and at 3 hours, poured reaction onto a mixture of ice and saturated sodium bicarbonate. Extracted with ethyl acetate, dried organic layer with brine and sodium sulfate, and stripped solvent. Loaded compound onto a column of silica gel, eluted with 12% methanol/ethyl acetate, stripped solvent from desired fractions, and dried in vacuo, giving 798 mg of yellow solid: mass spectrum (electrospray m/e): M+H=466.4, 468.4.

EXAMPLE 148

N-{4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-2-morpholin-4-ylmethyl-2-propenamide

Partially dissolved 1.37 g (8.00 mmol) 2-morpholin-4-ylmethyl-2-propenoic acid in 50 ml THF and chilled to 0° C. under N₂. Added 1.06 ml (9.6 mmol) *N*-methylmorpholine and 833 μ l (6.4 mmol) isobutyl chloroformate. Stirred at 0° C. for 1 hour and added a solution of 1.00 g (3.20 mmol) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile in 5 ml pyridine. Stirred overnight at 25° C. Poured onto a mixture of ice and saturated sodium bicarbonate, extracted with ethyl acetate, dried organic layer with brine and sodium sulfate, and stripped solvent to a small volume. Loaded onto a column of silica gel, eluted with 1% methanol/ethyl acetate, stripped solvent from desired fractions and dried under vacuum, giving 139 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=465.8, 468.0.

EXAMPLE 149

6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile

A mixture of 5.360 g (15.6 mmol) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol, and 17.67 g (78.2 mmol) SnCl₄ dihydrate was heated to reflux under N₂. Removed heat at 1.5 hours and added ice water. Made basic with sodium bicarbonate. Stirred for 2 hours extracted with chloroform. Added brine to the separatory funnel to help separate layers. Stirred organic layer with Darco and dried with sodium sulfate. Filtered, stripped solvent and dried in vacuo, giving 4.460 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H=312.9, 315.0.

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EXAMPLE 150

4-[(3-Chloro-4-fluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.75 g (25.8 mmol) 3-chloro-4-fluoroaniline was heated to reflux under N₂. Removed heat at 3.5 hours and added a solution of saturated sodium bicarbonate until mixture was basic. Stripped solvents and azeotroped with ethanol. Stirred residue with hexane, collected solids, washed with water and dried in vacuo. Dissolved solids in 250 ml boiling ethyl acetate, stirred with Darco, and filtered. Stripped solvent and dried in vacuo, giving 6.036 g of yellow solid: mass spectrum (electrospray m/e): M+H=343.1, 345.1.

EXAMPLE 151

N-{4-[(4-Bromophenyl)amino]-3-cyano-6-quinolinyl}-2-propenamide

Dissolved 500 mg (1.47 mmol) 6-amino-4-[(4-bromophenyl)amino]-3-quinolinecarbonitrile in 1 ml hot DMF, added 6 ml THF and chilled to 0° C. under N₂. Added 226 μ l (1.62 mmol) triethylamine and 135 μ l (1.62 mmol) acryloyl chloride. Removed ice bath at 15 minutes. At 1.5 hours, stripped solvent, stirred residue in dilute sodium bicarbonate, collected solids, and dried in vacuo. Boiled solids in ethyl acetate, collected, and dried in vacuo, giving 194 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=393.1, 395.1.

EXAMPLE 152

6-Amino-4-[(4-bromophenyl)amino]-3-quinolinecarbonitrile

A mixture of 3.10 g (8.40 mmol) 4-[(4-bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile, 155 ml ethanol, and 9.47 g (42.0 mmol) SnCl₄ dihydrate was heated to reflux under N₂. After 4 hours, removed heat and added ice water. Made basic with sodium bicarbonate and stirred for 2 hours. With mixture still basic, extracted with chloroform, stirred organic layer with Darco and dried with sodium sulfate. Filtered, stripped solvent and dried in vacuo, giving 2.265 g of brown-yellow solid: mass spectrum (electrospray m/e): M+H=339.0, 341.0.

EXAMPLE 153

4-[(4-Bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 4.42 g (25.8 mmol) *p*-bromoaniline was heated to reflux under N₂ for 3 hours. Removed heat and added saturated sodium bicarbonate until basic. Stripped solvents and azeotroped with ethanol. Stirred residue with hexane, collected solids, and air dried. Washed with water and dried in vacuo. Boiled in 1.4 liters ethyl acetate, and without completely dissolving all solids, stirred with Darco, and filtered. Stripped solvent and dried in vacuo, giving 3.524 g of yellow solid: mass spectrum (electrospray m/e): M+H=369, 370.9.

EXAMPLE 154

N-{3-Cyano-4-[(3,4-difluorophenyl)amino]-6-quinolinyl}-2-propenamide

Dissolved 1.00 g (3.37 mmol) 6-amino-4-[(3,4-difluorophenyl)amino]-3-quinolinecarbonitrile in 2 ml

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DMF, added 12 ml THF, and chilled to 0° C. under N₂. Added 517 µl (3.71 mmol) triethylamine and 310 µl (3.72 mmol) acryloyl chloride. Removed ice bath a 15 minutes. At 3.5 hours stripped solvent and slurried residue with dilute sodium bicarbonate. Collected solids, washed with water, and air dried. Boiled in ethyl acetate, collected solids and dried in vacuo, giving 332 mg of yellow solid: mass spectrum (electrospray m/e): M+H=351.1.

EXAMPLE 155

6-Amino-4-[(3,4-difluorophenyl)amino]-3-quinolinecarbonitrile

A mixture of 4.53 g (13.9 mmol) 4-[(3,4-difluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol and 15.72 g (69.4 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 1.5 hours, added ice water and made basic with sodium bicarbonate. Stirred for 2 hours and extracted with chloroform. Stirred organic layer with Darco, dried with sodium sulfate and filtered. Stripped solvent and dried in vacuo, giving 3.660 g of yellow-green solid: mass spectrum (electrospray m/e): M+H=297.1.

EXAMPLE 156

4-[(3,4-Difluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol and 2.55 ml (25.8 mmol) 3,4-difluoroaniline was heated to reflux under N₂. Removed heat at 3.5 hours and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane, collected solids and air dried. Washed with water and dried in vacuo. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving 5.02 g of yellow solid: mass spectrum (electrospray m/e): M+H=327.1.

EXAMPLE 157

N-[4-[(3-Chloro-4-thiophenoxyphenyl)amino]-3-cyano-6-quinolinyl]-2-butyramide

Dissolved 314 mg (3.72 mmol) 2-butyric acid in 40 ml THF under N₂. Chilled to 0° and added 409 µl (3.72 mmol) N-methylmorpholine and 485 µl (3.72 mmol) isobutyl chloroformate and stirred for 10 minutes. Added dropwise a solution that was prepared by dissolving 1.00 g (2.48 mmol) 6-amino-4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-quinolinecarbonitrile in 2.0 ml hot DMF and adding 20 ml THF. Stirred mixture for 15 minutes at 0° and 25° C. overnight. To drive reaction to completion, added 1.24 mmol of the mixed anhydride (104 mg acid, 136 µl NMM, and 161 µl isobutyl chloroformate) in 15 ml THF. Stirred overnight. Stripped solvent, dried in vacuo. Recrystallized from ethyl acetate, dried in vacuo, giving 284 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=469.2, 471.2.

EXAMPLE 158

6-Amino-4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-quinolinecarbonitrile

A mixture of 6.753 g (15.6 mmol) 4-[(3-chloro-4-thiophenoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile,

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250 ml ethanol, and 17.66 g (78.0 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 2 hours, added large volume of ice water, and made basic with sodium bicarbonate. Stirred for 2 hours and with mixture still basic, extracted with chloroform. Stirred organic layer with Darco, dried with sodium sulfate, filtered, stripped solvent and dried in vacuo, giving 5.996 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H=403.1, 405.1.

EXAMPLE 159

4-[(3-Chloro-4-thiophenoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol, and 6.07 g (25.6 mmol) 3-chloro-4-thiophenoxyaniline was heated to reflux under N₂. Removed heat at about 8 hours, made basic with saturated sodium bicarbonate, stripped solvents and azeotroped with ethanol. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Dissolved nearly completely in 400 ml ethyl acetate, stirred with Darco and filtered. Stripped solvent and boiled in hexane to remove last of the excess aniline. Dried in vacuo, giving 6.90 g of red solid: mass spectrum (electrospray m/e): M+H=433.1, 435.1.

EXAMPLE 160

N-[3-Cyano-4-[(3-cyanophenyl)amino]-6-quinolinyl]-2-propenamide

Dissolved 729 mg (2.56 mmol) 6-amino-4-[(3-cyanophenyl)amino]-3-quinolinecarbonitrile in 2 ml hot DMF, added 12 ml THF and cooled to 0° C. under N₂. Added 392 µl (2.81 mmol) triethylamine and 234 µl (2.81 mmol) acryloyl chloride. Removed ice bath after 15 minutes and stripped solvent at 2 hours. Washed residue with water and collected solids. Recrystallized from ethyl acetate and dried in vacuo, giving 318 mg of yellow solid: mass spectrum (electrospray m/e): M+H=340.1.

EXAMPLE 161

N-[3-Cyano-4-[(3-cyanophenyl)amino]-6-quinolinyl]-4-piperidino-2-butyramide

Partially dissolved 1.46 g (8.75 mmol) 4-piperidino-2-butyric acid in 100 ml THF and chilled to 0° C. under N₂. Added 1.16 ml (10.5 mmol) N-methylmorpholine and 911 µl (7.00 mmol) isobutyl chloroformate and stirred for 30 minutes. Added a solution of 1.00 g (3.50 mmol) 6-amino-4-[(3-cyanophenyl)amino]-3-quinolinecarbonitrile in 8 ml pyridine. At 3.5 hours poured onto ice bath and made basic with saturated sodium bicarbonate. Extracted with ethyl acetate, dried organic layers with magnesium sulfate, filtered, and reduced solvent to a small volume. Loaded compound onto a column of silica gel and eluted with 7% methanol/ethyl acetate. Stripped solvent from desired fractions and dried in vacuo, giving 1.008 g of off-white solid: mass spectrum (electrospray m/e): 435.0.

EXAMPLE 162

6-Amino-4-[(3-cyanophenyl)amino]-3-quinolinecarbonitrile

Added 100 mg of 10% palladium on carbon to a round bottom flask under N₂ and covered with 50 ml ethanol.

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Added 1.00 g (3.17 mmol) 4-[(3-cyanophenyl)amino]-6-nitro-3-quinolinecarbonitrile and 250 μ l (7.39 mmol) anhydrous hydrazine and heated to reflux. Removed heat at 2 hours and filtered hot through celite. Stripped solvent and dried in vacuo, giving 887 mg of yellow solid: mass spectrum (electrospray m/e): M+H=286.2.

EXAMPLE 163

4-[(3-Cyanophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.04 g (25.8 mmol) 3-aminobenzonitrile was heated to reflux. Removed heat at 3.5 hours and made basic with saturated sodium bicarbonate. Stripped solvents and air dried. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Boiled in large volume ethyl acetate, collected solids and dried in vacuo, giving 5.15 g of yellow-brown solid: mass spectrum (electrospray m/e): 316.0.

EXAMPLE 164

N-[3-Cyano-4-[(3-ethylphenyl)amino]-6-quinolinyl]-2-butyramide

Dissolved 370 mg (4.40 mmol) 2-butyric acid in 20 ml THF under N₂ and chilled to 0° C. Added 484 μ l (4.40 mmol) N-methylmorpholine and 572 μ l (4.40 mmol) isobutyl chloroformate and stirred for 10 minutes. Added a solution of 500 mg (1.76 mmol) 6-amino-4-[(3-ethylphenyl)amino]-3-quinolinecarbonitrile in 1 ml DMF and 10 ml THF. Removed ice bath at 15 minutes and stirred overnight at 25° C. Stripped solvent, slurried residue with water, collected solids, and dried in vacuo. Boiled in ethyl acetate, collected solids and dried in vacuo, giving 494 mg of yellow solid: mass spectrum (electrospray m/e): M+H=350.9.

EXAMPLE 165

N-[3-Cyano-4-[(3-ethylphenyl)amino]-6-quinolinyl]-2-propenamide

Dissolved 1.00 g (3.52 mmol) 6-amino-4-[(3-ethylphenyl)amino]-3-quinolinecarbonitrile in 2 ml hot DMF, added 12 ml THF and chilled to 0° C. under N₂. Added 539 μ l (3.87 mmol) triethylamine and 322 μ l (3.87 mmol) acryloyl chloride. Removed ice bath at 15 minutes and stripped solvent at 1.5 hours. Slurried residue in water, collected solids and air dried overnight. Recrystallized from ethyl acetate, dried in vacuo, giving 302 mg of orange solid: mass spectrum (electrospray m/e): 339.1.

EXAMPLE 166

N-[3-cyano-4-[(3-ethylphenyl)amino]-6-quinolinyl]-4-piperidino-2-butyramide

Partially dissolved 1.03 g (6.16 mmol) 4-piperidino-2-butyric acid in 70 ml THF and chilled to 0° C. under N₂. Added 812 μ l (7.38 mmol) N-methylmorpholine and 640 μ l (4.92 mmol) isobutyl chloroformate. After 0.5 hour stirring, added a solution of 700 mg (2.46 mmol) 6-amino-4-[(3-ethylphenyl)amino]-3-quinolinecarbonitrile dissolved in 5 ml pyridine. At 1 hour poured onto ice bath and made basic with a saturated solution of sodium bicarbonate. Extracted with ethyl acetate, dried organics with sodium sulfate, reduced to a small volume and loaded onto a column

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of silica gel. Eluted with 8% methanol in ethyl acetate. Stripped solvent of desired fractions and dried in vacuo, giving 641 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=434.2.

EXAMPLE 167

6-Amino-4-[(3-ethylphenyl)amino]-3-quinolinecarbonitrile

A mixture of 2.00 g (6.36 mmol) 4-[(3-ethylphenyl)amino]-6-nitro-3-quinolinecarbonitrile, 100 ml ethanol, and 7.19 g (31.8 mmol) SnCl₂ dihydrate was heated to reflux under N₂. Removed heat at 3.5 hours and added ice water. Made basic with sodium bicarbonate and stirred for 2 hours. Extracted with chloroform, stirred organic layer with Darco, dried with sodium sulfate, filtered, stripped solvent, and dried in vacuo, giving 1.737 g of yellow-brown solid: mass spectrum (electrospray m/e): M+H=285.2.

EXAMPLE 168

4-[(3-Ethynylphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.82 g (32.6 mmol) 3-ethynylaniline was heated to reflux under N₂. Removed heat at 3.5 hours and added a solution of saturated sodium bicarbonate until basic. Stripped solvents and azeotroped with ethanol. Slurried residue with hexane and collected solids. Washed with water and dried in vacuo. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving 4.544 g of yellow solid: mass spectrum (electrospray m/e): M+H=315.1.

EXAMPLE 169

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-piperidino-2-butyramide

Partially dissolved 1.23 g (7.37 mmol) 4-piperidino-2-butyric acid in 40 ml THF and chilled to 0° C. under N₂. Added 973 μ l (8.4 mmol) N-methylmorpholine and 768 μ l (5.9 mmol) isobutyl chloroformate. Stirred 10 minutes and added a solution of 1.00 g (2.95 mmol) 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 2 ml DMF and 10 ml THF. Removed ice bath at 15 minutes and at 5 hours added 2.95 mmol more of mixed anhydride (0.493 g acid, 487 μ l NMM, and 384 μ l isobutyl chloroformate), stirred overnight at 25° C. Stripped solvent, slurried residue with water, and collected solids. Boiled in ethyl acetate and collected. Dissolved in 20% methanol/chloroform and coated 5 g of silica gel. Flash chromatographed with 20% methanol/ethyl acetate, stripped solvent of desired fractions and dried in vacuo, giving 122 mg of brown solid: mass spectrum (electrospray m/e): M+H=488.0, 489.9.

EXAMPLE 170

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-dipropylamino-2-butyramide

Partially dissolved 1.28 g (7.0 mmol) 4-dipropylamino-2-butyric acid in 100 ml THF and chilled to 0° C. under N₂. Added 974 μ l (8.85 mmol) N-methylmorpholine 768 μ l (5.90 mmol) isobutyl chloroformate and stirred for 30 minutes. Added a solution of 1.00 g (2.95 mmol) 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 8 ml pyridine. At two hours, quenched with ice water and

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extracted with ethyl acetate. Dried organic layer with magnesium sulfate, reduced solvent to a small volume and loaded onto a column of silica gel. Eluted with ethyl acetate, stripped solvent from desired fractions and dried in vacuo, giving 764 mg of yellow solid: mass spectrum (electrospray m/e): M+H=504, 506.4.

EXAMPLE 171

N-{4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl}-2-morpholin-4-ylmethyl-2-propanamide

Partially dissolved 1.26 g (7.37 mmol) 2-morpholin-4-ylmethyl-2-propanoic acid in 40 ml THF and chilled to 0° C. under N₂. Added 810 μ l (7.37 mmol) N-methylmorpholine and 950 μ l (7.37 mmol) isobutyl chloroformate. After stirring 10 minutes, added a solution of 1.00 g (2.95 mmol) 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 2.5 ml DMF and 20 ml THF. Stripped solvent at 2 hours, slurried residue with water, collected solids, and dried in vacuo. Recrystallized from ethyl acetate and dried in vacuo, giving 334 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=492, 494.3.

EXAMPLE 172

N-{4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-2-butenamide

Made 2.25 mmol of 5-bromo-but-2-enoyl chloride by mixing 386 μ l (2.25 mmol) trimethylsilyl 4-bromo-but-2-enoate, 10 ml methylene chloride, 294 μ l (3.38 mmol) oxalyl chloride, and 2 drops of DMF. After bubbling had subsided, removed solvent and dissolved in 10 ml THF. This solution was added to a mixture of 800 mg (2.25 mmol) 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-3-quinolinecarbonitrile, 50 ml THF, and 392 μ l (2.25 mmol) N,N-diisopropylethylamine chilled to 0° C. under N₂. At 1 hour, added dropwise to a solution of 5.62 ml of 2.0M dimethyl amine in THF (11.2 mmol) at -78° C. Removed dry ice bath after complete addition. After 2 hours, poured into a cold solution of sodium bicarbonate, extracted with ethyl acetate, dried organic layer with sodium sulfate and reduced solvent to a small volume. Loaded onto a column of silica gel and eluted with 50% methanol/ethyl acetate. Stripped solvent of desired fractions and dried in vacuo, giving 386 mg of yellow solid: mass spectrum (electrospray m/e): M+H=467.9, 469.9.

EXAMPLE 173

N-{4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-diethylamino-2-butenamide

Made 2.25 mmol of 5-bromo-but-2-enoyl chloride by mixing 386 μ l (2.25 mmol) trimethylsilyl 4-bromo-but-2-enoate, 10 ml methylene chloride, 294 μ l (3.38 mmol) oxalyl chloride, and 2 drops of DMF. After bubbling had subsided, removed solvent and dissolved in 10 ml THF. This solution was added to a mixture of 800 mg (2.25 mmol) 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-3-quinolinecarbonitrile, 50 ml THF, 3 ml DMF (failed to dissolve amine) and 392 μ l (2.25 mmol) N,N-diisopropylethylamine chilled to 0° C. under N₂. Removed ice bath at 20 minutes. At 1 hour added dropwise to a solution of 1.2 ml (11.2 mmol) diethylamine in 4.4 ml THF chilled to -78° C. Removed dry ice bath after complete addition and stirred for 3 hours. Poured into a mixture of ice

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and saturated sodium bicarbonate, extracted with ethyl acetate, dried organic layer with sodium sulfate and reduced solvent to a small volume. Loaded compound onto a column of silica gel, eluted with 30% methanol/ethyl acetate, stripped solvent from desired fractions and dried in vacuo, giving 321 mg of yellow-brown solid: mass spectrum (electrospray m/e): M+H=496.0, 497.9.

EXAMPLE 174

N-{4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-morpholino-2-butenamide

Made 2.25 mmol of 5-bromo-but-2-enoyl chloride by mixing 386 μ l (2.25 mmol) trimethylsilyl 4-bromo-but-2-enoate, 10 ml methylene chloride, 294 μ l (3.38 mmol) oxalyl chloride, and 2 drops of DMF. After bubbling had subsided, removed solvent and dissolved in 10 ml THF. This solution was added to a mixture of 800 mg (2.25 mmol) 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-3-quinolinecarbonitrile, 50 ml THF, and 392 μ l (2.25 mmol) N,N-diisopropylethylamine chilled to 0° C. under N₂. At 1 hour, added the mixture dropwise to a solution of 1 ml (11.2 mmol) morpholine in 4.5 ml THF chilled to 0° C. After complete addition, removed the ice bath, and at 2 hours poured onto a mixture of ice and saturated sodium bicarbonate. Extracted with ethyl acetate, dried organic layer with sodium sulfate and reduced solvent to a small volume. Loaded onto a column of silica gel, eluted with 12% methanol/ethyl acetate, stripped solvent from desired fractions and dried in vacuo, giving 369 mg of yellow solid: mass spectrum (electrospray m/e): M+H=509.9, 511.9.

EXAMPLE 175

N-{4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl}-4-morpholino-2-butenamide

Made 2.07 mmol of 5-bromo-but-2-enoyl chloride by mixing 363 μ l (2.07 mmol) trimethylsilyl 4-bromo-but-2-enoate, 8 ml methylene chloride, 270 μ l (3.10 mmol) oxalyl chloride and 2 drops of DMF. Removed solvent when bubbling subsided and dissolved in 10 ml THF. The acid chloride solution was added to a mixture of 800 mg (2.07 mmol) 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-7-methoxy-3-quinolinecarbonitrile, 50 ml THF, and 721 μ l (4.14 mmol) N,N-diisopropylethylamine chilled to 0° C. under N₂. At 1.5 hours added this mixture to a solution of 900 μ l (10.4 mmol) morpholine in 4.3 ml THF at 0° C. Warmed to 25° C. after complete addition, and at 2 hours added 900 μ l more morpholine. At 3 hours, poured onto a mixture of ice and saturated sodium bicarbonate, extracted with ethyl acetate, dried with sodium sulfate, and reduced solvent to a small volume. Loaded compound onto a column of silica gel, eluted with 12% methanol/ethyl acetate, stripped solvent from desired fractions, and dried in vacuo, giving 287 mg of orange-brown solid: mass spectrum (electrospray m/e): M+H=539.9, 541.9.

EXAMPLE 176

4-[(3-Bromophenyl)amino]-7-ethoxy-6-methoxy-3-quinolinecarbonitrile

A mixture of 500 mg (1.90 mmol) 4-chloro-7-ethoxy-6-methoxy-3-quinolinecarbonitrile, 20 ml ethanol, and 250 μ l (2.28 mmol) 3-bromoaniline was heated to reflux under N₂. At 3 hours, added 103 μ l (0.95 mmol) and 10 ml ethanol and refluxed overnight. Removed heat and made basic with

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saturated sodium bicarbonate. Stripped solvent, slurried residue with hexane, collected solids, and dried. Washed with water and dried in vacuo, giving 554 mg of tan solid: mass spectrum (electrospray m/e): M+H=398, 399.8.

EXAMPLE 177

7-Ethoxy-4-[(3-hydroxy-4-methylphenyl)amino]-6-methoxy-3-quinolinecarbonitrile

A mixture of 500 mg (1.90 mmol) 4-chloro-7-ethoxy-6-methoxy-3-quinolinecarbonitrile, 30 ml ethanol, and 281 mg (2.28 mmol) 3-hydroxy-4-methylamine was heated to reflux under N₂ overnight. Removed heat and made basic with saturated sodium bicarbonate. Stripped solvents and slurried residue in hexane. Collected solids, washed with water, and dried in vacuo, giving 364 mg off-white solid: mass spectrum (electrospray m/e): M+H=349.9.

EXAMPLE 178

4-Chloro-7-ethoxy-6-methoxy-3-quinolinecarbonitrile

Mixed 122 mg (0.50 mmol) 7-ethoxy-1,4-dihydro-6-methoxy-4-oxo-3-quinolinecarbonitrile and 2.0 ml methylene chloride under N₂ and kept temperature near 25° C. Added 218 µl (2.5 mmol) oxalyl chloride and 10 µl (0.125 mmol) DMF. Stirred overnight, diluted with chloroform and stirred in saturated sodium bicarbonate until basic. Separated layers and dried organics with magnesium sulfate, stripped solvent and dried in vacuo, giving 117 mg of tan solid: mass spectrum (electrospray m/e): M+H=262.8, 264.8.

EXAMPLE 179

7-Ethoxy-1,4-dihydro-6-methoxy-4-oxo-3-quinolinecarbonitrile

Added 54.0 ml (135 mmol) n-butyl lithium to 150 ml THF and chilled to -78° C. under N₂. Added dropwise over 20 minutes 7.05 ml (135 mmol) acetonitrile in 200 ml THF. Stirred 15 minutes and added a solution of 17.99 g (64.2 mmol) methyl 4-ethoxy-5-methoxy-2-(dimethylaminomethyleneamino)benzoate in 150 ml THF dropwise over 20 minutes. Let stir for 0.5 hour at -78° C. Added 11.0 ml (193 mmol) acetic acid and warmed gradually to 25° C. After 2.5 hours, stripped solvent, slurried residue with water, collected solids and dried in vacuo, giving 13.025 g of yellow solid: mass spectrum (electrospray m/e): M+H=245.2.

EXAMPLE 180

Methyl 4-Ethoxy-5-methoxy-2-(dimethylaminomethyleneamino)benzoate

A mixture of 15.056 g (66.9 mmol) methyl 2-amino-4-ethoxy-5-methoxybenzoate and 14.1 ml (100 mmol) N,N-dimethylformamide dimethylacetal was heated to 100° C. under N₂. At 4.5 hours added 4.7 ml (33.3 mmol) more DMF/DMA and removed heat at 5 hours. Stripped solvent, azeotroped with toluene, and dried in vacuo, giving 18.211 g of grey-brown solid: mass spectrum (electrospray m/e): M+H=281.3.

EXAMPLE 181

Methyl 2-Amino-4-ethoxy-5-methoxybenzoate

A mixture of 24.110 g (94.5 mmol) methyl 4-ethoxy-5-methoxy-2-nitrobenzoate, 15.81 g (283 mmol) iron powder,

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25.28 g (472 mmol) ammonium chloride, 135 ml water, and 350 ml methanol was heated to reflux under N₂. At both 3 and 5.5 hours added the same amount of iron and ammonium chloride. Removed heat at 6.5 hours, added ethyl acetate and saturated sodium bicarbonate, filtered through celite and separated layers. Washed organic layer with saturated sodium bicarbonate, dried with magnesium sulfate, stripped solvent, and dried in vacuo, giving 17.594 g of pink solid: mass spectrum (electrospray m/e): M+H=226.2.

EXAMPLE 182

Methyl 4-Ethoxy-5-methoxy-2-nitrobenzoate

Dissolved 5.00 g (23.7 mmol) methyl 4-ethoxy-3-methoxybenzoate in 25 ml acetic acid under N₂ and added 6.1 ml (95.1 mmol) 69% nitric acid dropwise over 30 minutes. Heated to 50° C. for 1.5 hours and poured onto ice bath. Extracted with chloroform, washed with dilute sodium hydroxide solution and filtered through magnesium sulfate. Stripped solvent and dried in vacuo, giving 5.268 g of off-white solid: mass spectrum (electrospray m/e): M+H=255.8.

EXAMPLE 183

Methyl 4-Ethoxy-3-methoxybenzoate

A mixture of 25.0 g (137 mmol) methyl vanillate, 38.87 g (274 mmol) potassium carbonate, 500 ml DMF, and 16.5 ml (206 mmol) ethyl iodide was heated to 100° C. under N₂. At 2.5 hours, cooled and removed solids. Stripped solvent, and partitioned between water and methylene chloride. Stripped solvent and dried in vacuo, giving 25.85 g of white solid: mass spectrum (EI m/e): M=210.0.

EXAMPLE 184

N-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-(Z)-2-butenamide

A mixture of 0.05 g (0.118 mmol) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butenamide and 6 mg of Lindlar catalyst in 10 mL of methanol was hydrogenated at room temperature overnight. The mixture was filtered through a pad of Celite. After the solvent was removed, the residue was purified by thin-layer chromatography eluted with 30% methanol in ethyl acetate. The product was dried to give 0.018 g (36%) pale yellow solid; HRMS m/z 423.1270 (M⁺).

EXAMPLE 185

N-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-(Z)-2-butenamide

A mixture of 0.05 g (0.118 mmol) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-2-butenamide and 6 mg of Lindlar catalyst in 15 mL of methanol was hydrogenated at room temperature for 5.5 hrs. The mixture was filtered through a pad of Celite. The solvent was removed to give 0.05 g (99.7%) yellow solid; HRMS m/z 410.0928 (M⁺).

EXAMPLE 186

4-[[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-amino]-2-methylene-4-oxo-butanoic Acid

Itaconic anhydride (0.14 g, 1.25 mmol) was added portionwise to a solution of 0.1 g (0.30 mmol) of 6-amino-

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4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 2 mL of ethyl acetate under N_2 . After stirring at room temperature overnight, the reaction solution was added into ice water and hexane. The product was collected, washed with water, ether and hexane, and dried in vacuo to give 0.09 g (68%) of yellowish brown solid; ESMS m/z 451.2 ($M+H^+$).

EXAMPLE 187

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-diethylamino-2-butyramide

Isobutyl chloroformate (0.261 g, 1.91 mmol) was dropwise added into an ice cold solution of 4-diethylamino-2-butyric acid (0.456 g, 2.94 mmol) and N-methylmorpholine (0.294 g, 2.94 mmol) in 50 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 0.5 g (1.47 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 3 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 15% methanol in ethyl acetate. The product was collected, and dried in vacuo to give 0.2 g (28.5%) of pale greenish yellow solid; ESMS m/z 476.2, 478.2 ($M+H^+$); mp 133–135° C.

EXAMPLE 188

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(N-ethylpiperazino)-2-butyramide

Isobutyl chloroformate (0.785 g, 5.75 mmol) was dropwise added into an ice cold solution of 4-(N-ethylpiperazino)-2-butyric acid (1.75 g, 8.85 mmol) and N-methylmorpholine (1.3453 g, 13.3 mmol) in 50 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 1.5 g (4.42 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 10 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 1.07 g (46%) of light brown solid; ESMS m/z 517.1, 519.1 ($M+H^+$); mp 161° C. (dec).

EXAMPLE 189

N-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-diethylamino-2-butyramide

Isobutyl chloroformate (0.061 g, 0.448 mmol) was dropwise added into an ice cold solution of 4-diethylamino-2-butyric acid (0.104 g, 0.672 mmol) and N-methylmorpholine (0.068 g, 0.672 mmol) in 10 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 0.1 g (0.32 mmol) of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile in 1.5 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 1.5 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 15% methanol in ethyl acetate. The product was collected, and dried in vacuo to give 0.046 g (32%) of light brown solid; ESMS m/z 450.2, ($M+H^+$); mp 117–120° C.

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EXAMPLE 190

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(N-methylpiperazino)-2-butyramide

Isobutyl chloroformate (0.785 g, 5.75 mmol) was dropwise added into an ice cold solution of 4-(N-methylpiperazino)-2-butyric acid (1.65 g, 8.85 mmol) and N-methylmorpholine (1.36 g, 13.3 mmol) in 10 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 1.5 g (4.42 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 10 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 15% methanol in ethyl acetate. The product was collected, and dried in vacuo to give 0.37 (16%) of yellow solid; ESMS m/z 503, 505, ($M+H^+$); mp 190° C. (dec).

EXAMPLE 191

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-(N-isopropyl-N-methylamino)-2-butyramide

Isobutyl chloroformate (0.785 g, 5.75 mmol) was dropwise added into an ice cold solution of 4-(N-isopropyl-N-methylamino)-2-butyric acid (1.4 g, 8.84 mmol) and N-methylmorpholine (0.94 g, 9.3 mmol) in 80 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 1.5 g (4.42 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 15 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.65 (31%) of reddish brown solid; ESMS m/z 476.0, 478.0 ($M+H^+$); mp 124–126° C.

EXAMPLE 192

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-diisopropylamino-2-butyramide

Isobutyl chloroformate (0.785 g, 5.75 mmol) was dropwise added into an ice cold solution of 4-diisopropylamino)-2-butyric acid (1.65 g, 8.85 mmol) and N-methylmorpholine (0.94 g, 9.3 mmol) in 100 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 1.5 g (4.42 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 15 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 1.08 (48%) of light brown solid; ESMS m/z 504.1, 506.1 ($M+H^+$); mp 130° C. (dec).

EXAMPLE 193

N-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butyramide

Isobutyl chloroformate (0.85 g, 6.2 mmol) was dropwise added into an ice cold solution of 4-dimethylamino-2-

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butynoic acid (1.85 g, 14.4 mmol) and N-methylmorpholine (1.5 g, 14.8 mmol) in 100 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 1.5 g (4.79 mmol) of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarboxitrile in 15 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.47 (23%) of reddish brown solid; ESMS m/z 422.0 (M+H⁺); mp 225° C. (dec).

EXAMPLE 194

N-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-2-butyramide

Isobutyl chloroformate (0.85 g, 6.2 mmol) was dropwise added into an ice cold solution of 4-methoxy-2-butyric acid (1.1 g, 9.6 mmol) and N-methylmorpholine (1.02 g, 10 mmol) in 100 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 1.5 g (4.79 mmol) of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarboxitrile in 15 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 3 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.73 (37%) of light yellowish brown solid; ESMS m/z 409(M+H⁺); mp 170-171).

EXAMPLE 195

4-[(3-Bromo-4-fluorophenyl)amino]-6-nitro-3-quinolinecarboxitrile

A mixture of 3.8 g (16.33 mmol) of 4-chloro-6-nitro-3-quinolinecarboxitrile and 3.7 g (20 mmol) of 3-bromo-4-fluoroaniline in 200 mL of ethanol was refluxed for 3 hr. After the solvent was removed, the residue was dissolved in ethyl acetate and washed with sodium bicarbonate. The product was collected as a pale yellow solid, 6.5 g (71%); ESMS m/z 387.3, 389.2, mp 269-270° C. (dec).

EXAMPLE 196

6-amino-4-[(3-Bromo-4-fluorophenyl)amino]-3-quinolinecarboxitrile

A mixture of 8 g (20.67 mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-3-quinolinecarboxitrile, 4 g (72.35 mmol) of iron dust and 8.9 g (165.36 mmol) of ammonium chloride in 240 mL of methanol and water (2:1 ratio) was refluxed for 4 hr. The mixture was filtered hot and washed with methanol and water. The product precipitated from the filtrate upon cooling. The solid was collected and dried in vacuo to give 5.8 g (79%) yellowish brown solid; ESMS m/z 356.8, 358.8, mp 210-212° C.

EXAMPLE 197

N-[4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butyramide

Isobutyl chloroformate (0.373 g, 2.73 mmol) was dropwise added into an ice cold solution of 4-dimethylamino-2-butyric acid (0.8 g, 6.3 mmol) and N-methylmorpholine

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(0.658 g, 6.5 mmol) in 80 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 10.65 g (2.1 mmol) of 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-3-quinolinecarboxitrile in 10 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2.5 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by flash column chromatography. The product fractions were collected, and dried in vacuo to give 0.33 (33%) of yellow solid; ESMS m/z 465.9, 467.9(M+H⁺); mp 228-231° C.

EXAMPLE 198

4-Dimethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 1.9 g (5.1 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-amino-3-quinolinecarboxitrile and 5.3 ml (31 mmol) of Hunig's base in 110 ml of dry THF at 0° C., with stirring, was added a THF solution containing 5.7 g (31 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 0.5 hour after addition. 100 ml of saturated sodium chloride solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and then was added to 40 ml of dimethyl amine solution (2.0 M in THF) at 0° C. dropwise. The solution was stirred an additional 0.5 hour. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate. Chromatography gave 1.4 g of beige solid; mass spectrum (electrospray, m/e): M+H 480.0 and 481.9.

EXAMPLE 199

4-Diethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 0.5 g (1.36 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-amino-3-quinolinecarboxitrile and 0.48 ml (2.7 mmol) of Hunig's base in 50 ml of dry THF at 0° C., with stirring, was added a THF solution containing 0.50 g (2.7 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 0.5 hour after addition and then was added to a solution of 4.2 ml (40.8 mmol) diethyl amine in 50 ml of THF at 0° C. dropwise. The solution was stirred for an additional 0.5 hour. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate. Chromatography gave 0.2 g of white solid; mass spectrum (electrospray, m/e): M+H 508.1 and 510.8.

EXAMPLE 200

4-Morpholin-4-yl-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 0.69 g (1.87 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-amino-3-quinolinecarboxitrile and 0.98 ml (5.6 mmol) of Hunig's base in 50 ml of dry THF at 0° C., with stirring, was added a THF solution containing 0.86 g (5 mmol) of 4-bromocrotonyl chloride dropwise. The mixture was stirred for an additional 0.5 hour and then was added to a solution of

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4.89 ml (56 mmol) morpholine in 50 ml THF at 0° C. dropwise. The solution was stirred an additional 0.5 hour and then the mixture was poured into diluted sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate. The residue was chromatographed to give 0.38 g of grey solid: mass spectrum (electrospray, m/e): M+H 521.9 and 523.8.

EXAMPLE 201

4-(3-Chloro-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 4.4 g (16.7 mmol) of 4-chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile and 2.67 g (18.3 mmol) of 3-chloro-4-fluoro aniline in 110 ml of methoxyethanol was refluxed under nitrogen for 4 hours. The reaction mixture was diluted with ethyl acetate and wash with sodium bicarbonate solution and sodium chloride solution. The organic layer was dried over sodium sulfate and then the solvent was removed under vacuum. The residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 3 g yellow solid: mass spectrum (electrospray, m/e): 372.9.

EXAMPLE 202

6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile

A mixture of 4.88 g (13 mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile, 5.2 g (97.5 mmol) of ammonium chloride, and 3.3 g (58.5 mmol) iron was stirred at reflux in 60 ml of water and 60 ml of methanol for 4.5 hours. The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution and then the organic layer was dried over sodium sulfate. The solvent was removed and the residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 3.38 g of yellow solid: mass spectrum (electrospray, m/e): M+H 343.4.

EXAMPLE 203

4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 1.08 g (3.1 mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-amino-quinoline-3-carbonitrile and 1.7 ml (9.7 mmol) of Hunig's base in 30 ml of dry THF at 0° C., with stirring, was added a THF solution containing 1.99 g (9.3 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 0.5 hour at 0° C. under nitrogen. 50 ml of saturated sodium chloride solution was introduced to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was separated and dried over sodium sulfate and then it was added to 31 ml of dimethyl amine solution (2.0 M in THF) at 0° C. dropwise. After addition, the solution was stirred for another hour at room temperature. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was separated and the residue was chromatographed to give 0.86 grams of white solid: mass spectrum (electrospray, m/e).

EXAMPLE 204

4-Diethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 1.1 g (3.2 mmol) of 4-(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-amino-3-

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quinolinecarbonitrile and 2.24 ml (12.8 mmol) of Hunig's base in 40 ml of dry THF at 0° C., with stirring, was added a THF solution containing 2.34 g (12.8 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 0.5 hour at 0° C. 50 ml of saturated sodium chloride solution was added to the reaction mixture and then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and added to a solution of 6.6 ml (64 mmol) diethyl amine in 5 ml of THF at 0° C. dropwise. The solution was stirred an additional hour at 0° C. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was separated and dried over sodium sulfate. The residue was chromatographed and followed by recrystallization to give 0.62 grams of white solid: mass spectrum (electrospray, m/e): M+H 482.0.

EXAMPLE 205

4-Morpholin-4-yl-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 1.2 g (3.5 mmol) of 4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-amino-quinoline-3-carbonitrile and 2.44 ml (14 mmol) of Hunig's base in 50 ml of dry THF at 0° C., with stirring, was added a THF solution containing 2.57 g (14 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for an additional hour at 0° C. 50 ml of saturated sodium chloride solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and then was added to a solution of 4.58 ml (52.5 mmol) morpholine in 5 ml of THF at 0° C. dropwise. The solution was stirred an overnight at 0° C. The mixture was poured into diluted sodium bicarbonate solution. The organic layer dried over sodium sulfate. Chromatography gave 0.83 grams off-white solid: mass spectrum (electrospray, m/e): M+H 496.0.

EXAMPLE 206

4-(3-Bromo-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 3.52 g (9.7 mmol) of 4-chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile and 2.0 g (10.7 mmol) of 3-bromo-4-fluoro aniline in 150 ml of methoxyethanol was refluxed under nitrogen for 5.5 hours. The reaction mixture was diluted with ethyl acetate and wash with sodium bicarbonate solution and sodium chloride solution. The organic layer was dried with sodium sulfate and then solvent was removed under vacuum. The residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 3 g of yellow solid: mass spectrum (electrospray, m/e): 416.8 and 418.8.

EXAMPLE 207

6-Amino-4-(3-bromo-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile

A mixture of 2.9 g (6.95 mmol) of 4-[(3-bromo-4-fluorophenyl)amino]-7-methoxy-6-nitro-quinoline-3-carbonitrile, 6.5 g (121.6 mmol) of ammonium chloride and 4.05 g (73 mmol) of iron in 50 ml of water and 50 ml of methanol for 6 hours. The mixture was diluted with hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution then the organic layer was dried over sodium sulfate. The solvent was

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removed and the residue was chromatographed on silica gel eluting with mixture of ethyl acetate and methanol to give 2.11 g of light yellow solid: mass spectrum (electrospray, m/e): M+H 386.7 and 388.8.

EXAMPLE 208

4-Dimethylamino-but-2-enoic acid [4-(3-bromo-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 0.77 g (1.98 mmol) of 4-(3-bromo-4-fluorophenyl)amino]-7-methoxy-6-amino-quinoline-3-carbonitrile and 3.5 ml (20 mmol) of Hunig's base in 35 ml of dry THF at 0° C., with stirring, was added a THF solution containing 2.2 g (12 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 30 minutes at 0° C. 50 ml of saturated sodium chloride solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and then was added to 15 ml of dimethyl amine (2.0 M in THF) at 0° C. dropwise. The solution was stirred an additional hour at room temperature. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. The residue was chromatographed gave 0.55 g beige solid: mass spectrum (electrospray, m/e): M+H 498.0 and 500.0.

EXAMPLE 209

4-Diethylamino-but-2-enoic acid [4-(3-bromo-4-fluoro-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

To a mixture of 0.77 g (1.98 mmol) of 4-(3-bromo-4-fluorophenyl)amino]-7-methoxy-6-amino-quinoline-3-carbonitrile and 3.5 ml (20 mmol) of Hunig's base in 35 ml of dry THF at 0° C., with stirring, was added a THF solution containing 2.2 g (12 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 30 minutes at 0° C. 50 ml of saturated NaCl solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and then was added to a solution of 3.1 ml (30 mmol) of diethyl amine in 5 ml of THF at 0° C. dropwise. The solution was stirred an additional hour at 0° C. and 30 minutes at room temperature. The mixture was poured into diluted sodium bicarbonate solution. The organic layer was dried over sodium sulfate and solvent was removed under vacuum. The residue was chromatographed to give 0.4 g off-white solid: mass spectrum (electrospray, m/e): M+H 525.9 and 527.9.

EXAMPLE 210

7-Ethoxy-4-hydroxy-quinoline-3-carbonitrile

A mixture of 10 g (73 mmol) of 3-ethoxy aniline and 12.3 g (73 mmol) of ethyl (ethoxymethylene) cyanoacetate was heated in 90 ml of Dowther at 140° C. for 7 hours. To this mixture was added 250 ml of Dowtherm. The solution was stirred and refluxed under nitrogen for 12 hours with periodically distilling out the eliminated ethanol. The mixture was cooled to room temperature and the solid was collected and washed with hexane. The crude solid was treated with boiling ethanol and then filtered to give 9.86 g of brown solid: mass spectrum (electrospray, m/e): M+H 214.7.

EXAMPLE 211

7-Ethoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile

To a suspension of 5 g (23 mmol) of 7-Ethoxy-4-hydroxy-quinoline-3-carbonitrile in 75 ml of trifluoroacetic anhydride

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was added 5.5 g (69 mmol) of ammonium nitrate over a period of 6 hours at room temperature. Excess anhydride was removed at reduced pressure at 45° C. The residue was stirred with 300 ml of water. The solid was collected and treated with boiling ethanol to give 3.68 g of tin solid: mass spectrum (electrospray, m/e) M+H 259.8.

EXAMPLE 212

4-Chloro-7-ethoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 3.45 g (13 mmol) of 7-Ethoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile, 5.55 g (26 mmol) of phosphorous pentachloride, and 10 ml of phosphorous oxychloride was refluxed for 3 hours. The mixture was diluted with hexane and the solid was collected. The solid was dissolved in 500 ml of ethyl acetate and washed with cold diluted sodium hydroxide solution. The solution was dried over magnesium sulfate and filtered through a pad of silica gel. The solvent was removed giving 2.1 g of beige solid: mass spectrum (electrospray, m/e) M+H 277.7.

EXAMPLE 213

4-(3-Bromo-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 2.1 g (7.6 mmol) of 4-chloro-7-ethoxy-6-nitro-3-quinolinecarbonitrile and 0.91 ml (8.3 mmol) of 3-bromo aniline in 100 ml ethanol was refluxed under nitrogen for 4.5 hours. The reaction mixture was poured into diluted sodium bicarbonate solution. Ethanol was removed under vacuum. The mixture was diluted with ethyl acetate and the organic layer was separated and dried over sodium sulfate. The solution was concentrated and solid was collected and then washed with hexane. Upon drying, 2.6 g of yellow solid obtained: mass spectrum (electrospray, m/e) M+H 412.8 and 414.9.

EXAMPLE 214

6-Amino-4-(3-bromo-phenylamino)-7-ethoxy-quinoline-3-carbonitrile

A mixture of 2.5 g (6 mmol) of 4-(3-bromophenyl)amino]-7-ethoxy-6-nitro-quinoline-3-carbonitrile, 2.4 g (45 mmol) of ammonium chloride, and 1.5 g (27 mmol) iron was stirred at reflux in 40 ml of water and 40 ml of methanol for 4 hours. The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution and then the organic layer was dried over sodium sulfate. The solution was concentrated and 1.5 of beige solid was collected: mass spectrum (electrospray, m/e): M+H 382.8 and 384.8.

EXAMPLE 215

4-Bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

To a mixture of 1.34 g (3.5 mmol) of 4-(3-bromo-phenyl)amino]-7-ethoxy-6-amino-3-quinolinecarbonitrile and 3.66 ml (21 mmol) of Hunig's base in 80 ml of dry THF at 0° C., with stirring, was added a THF solution containing 3.85 g (21 mmol) of 4-bromo crotonyl chloride dropwise. The mixture was stirred for additional 30 minutes at 0° C. 50 ml of saturated sodium chloride solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and

then the drying agent was filtered off. This solution was used without further characterization.

EXAMPLE 216

4-Dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 18 was added dropwise to 8.75 ml (17.5 mmol) of dimethyl amine at 0° C. The mixture was stirred for an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 0.32 g beige solid: mass spectrum (electrospray, m/e) M+H, 494.0 and 496.0.

EXAMPLE 217

4-Diethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 18 was added dropwise to a solution of 1.81 ml (17.5 mmol) of diethyl amine in 5 ml of THF at 0° C. The mixture was stirred for an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 0.22 g beige solid: mass spectrum (electrospray, m/e) M+H, 522.0 and 524.0.

EXAMPLE 218

4-Morpholin-4-yl-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 18 was added dropwise to a solution of 1.57 ml (18 mmol) of morpholine in 5 ml of THF at 0° C. The mixture was stirred for an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 0.37 g white solid: mass spectrum (electrospray, m/e) M+H, 535.9 and 538.0.

EXAMPLE 219

8-Methoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile

A mixture of 12.6 g (75 mmol) of 2-methoxy-4-nitro aniline and 12.7 g (75 mmol) of ethyl (ethoxymethylene) cyanoacetate was heated in 100 ml of Dowther at 120° C. for overnight and 180° C. for 20 hours. To this mixture was added 300 ml of Dowther. The solution was stirred and refluxed under nitrogen for 12 hours with periodically distilling out the eliminated ethanol. The mixture was cooled to room temperature and the solid was collected and washed with hexane. The crude solid was treated with boiling ethanol and then filtered to give 12 g of brown solid: mass spectrum (electrospray, m/e): M+H 245.8.

EXAMPLE 220

4-Chloro-8-methoxy-6-nitro-quinoline-3-carbonitrile

A mixture of 4 g (16 mmol) of 8-Methoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile, 6.66 g (32 mmol) of phos-

phorous pentachloride, and 15 ml of phosphorous oxychloride was refluxed for 2.5 hours. The mixture was diluted with hexane and the solid was collected. The solid was dissolved in 500 ml of ethyl acetate and washed with cold diluted sodium hydroxide solution. The solution was dried over magnesium sulfate and filtered through a pad of silica gel. The solvent was removed giving 2.05 g of tan solid: mass spectrum (electrospray, m/e) M+H 263.7.

EXAMPLE 221

6-nitro-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile

A mixture of 1.9 g (7.6 mmol) of 4-chloro-8-methoxy-6-nitro-quinoline-3-carbonitrile and 0.86 ml (8.3 mmol) of 3-bromo aniline in 95 ml ethanol was refluxed under nitrogen for 5 hours. The reaction mixture was poured into diluted sodium bicarbonate solution. Ethanol was removed under vacuum. The mixture was diluted with ethyl acetate and the organic layer was separated and dried over sodium chloride. The solution was concentrated and solid was collected and then washed with hexane. Upon drying, 2.3 g of yellow solid obtained: mass spectrum (electrospray, m/e) M+H 398.8 and 400.8.

EXAMPLE 222

6-Amino-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile

A mixture of 2.15 g (5 mmol) of 4-[(3-bromophenyl) amino]-8-methoxy-6-nitro-quinoline-3-carbonitrile, 1.95 g (37.5 mmol) of ammonium chloride, and 1.26 g (22.5 mmol) iron was stirred at reflux in 40 ml of water and 40 ml of methanol for 3 hours. The mixture was diluted with 500 ml of hot ethyl acetate and the hot mixture was filtered. The filtration was washed with saturated sodium chloride solution and then the organic layer was dried over sodium sulfate. The solution was concentrated and 0.43 of dark yellow solid was collected: mass spectrum (electrospray, m/e): M+H 368.9 and 370.9.

EXAMPLE 223

4-Bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide

To a mixture of 1.05 g (2.8 mmol) of 4-(3-bromo-phenyl) amino]-8-methoxy-6-amino-3-quinolinecarbonitrile and 3.9 ml (22.4 mmol) of Hunig's base in 50 ml of dry THF at 0° C., with stirring, was added a THF solution containing 4.11 g (22.4 mmol) of 4-bromo crotonylchloride dropwise. The mixture was stirred for additional 1 hour at 0° C. 50 mL of saturated sodium chloride solution was added to the reaction mixture, then it was extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and then the drying agent was filtered off. This solution was used without further characterization.

EXAMPLE 224

amino)-4-Dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 26 was added dropwise to a solution of 7 ml (14 mmol) of dimethyl amine (2.0 M in THF) at 0° C. The mixture was stirred for

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an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 0.22 g tin solid: mass spectrum (electrospray, m/e) M+H, 480.0 and 482.0.

EXAMPLE 225

4-Diethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 26 was added dropwise to a solution of 1.4 ml (14 mmol) of diethyl amine in 5 ml of THF at 0° C. The mixture was stirred for an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 95 mg tin solid: mass spectrum (electrospray, m/e) M+H, 509.9 and 511.0.

EXAMPLE 226

4-Morpholin-4-yl-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide

A one-third portion of the solution from example 26 was added dropwise to a solution of 1.2 ml (14 mmol) of morpholine in 5 ml of THF at 0° C. The mixture was stirred for an additional 30 minutes at 0° C. The mixture was diluted with sodium bicarbonate solution and then the organic layer was separated and dried. The solvent was removed under vacuum and the residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and methanol giving 0.21 g yellow solid: mass spectrum (electrospray, m/e) M+H, 522.0 and 524.0.

EXAMPLE 227

4-Dimethylamino-but-2-ynoic acid [4-(3-bromo-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide

Isobutyl chloroformate 6.9 ml (5.4 mmol) and N-methylmorpholine 1.19 ml (10.8 mmol) were added to an ice-cold solution of 1.37 g (10.8 mmol) of 4-dimethylamino-2-butynoic acid in 60 ml of THF. After stirring for 10 minutes, a solution of 1 g (2.7 mmol) 4-[(3-bromophenyl)amino]-7-methoxy-6-amino-quinoline-3-carbonitrile in 10 ml of pyridine was introduced. The reaction mixture was stirred overnight at 0° C. The solvent was evaporated and the residue was stirred in diluted sodium bicarbonate. The solution was then extracted with ethyl acetate. The ethyl acetate solution was dried and removed under vacuum. The residue was chromatographed to give 0.18 g of tin solid: mass spectrum (electrospray, m/e) 478.0 and 480.0.

EXAMPLE 228

4-(4-Chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 2.0 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 1.46 g of 4-chloro-2-fluoroaniline, 0.925 g of pyridine hydrochloride, and 125 ml of ethoxy-

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ethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 1000 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried to give 2.61 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 139–141° C.; mass spectrum (electrospray, m/e): M+H 357.9.

EXAMPLE 229

4-(3-Hydroxy-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 2.98 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 1.85 g of 5-amino-o-cresol, 1.39 g of pyridine hydrochloride, and 200 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 1000 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried to give 3.27 g of 4-(3-hydroxy-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 222–224° C.; mass spectrum (EI, m/e): M 335.1269.

EXAMPLE 230

4-Hydroxy-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 4.82 g of methyl 3,4,5-trimethoxyanthranilate in 20 ml of N,N-dimethylformamide dimethyl acetal was refluxed for 18 hours and concentrated *in vacuo*. The crude amidine product was used in the next step without further purification.

To 25 ml of tetrahydrofuran at –78° C. was added 17.6 ml of 2.5M n-butyllithium in hexanes. Then 2.35 ml of acetonitrile in 45 ml of tetrahydrofuran was added dropwise. The mixture was stirred at –78° C. for 15 minutes. Then a solution of the crude amidine in 30 ml of tetrahydrofuran was added dropwise. The mixture was stirred at –78° C. for 30 minutes, then 5.7 ml of acetic acid was added. The mixture was warmed to room temperature, and 100 ml of water was added. The product was collected, washed with water, and dried to give 4.14 g of 4-hydroxy-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 280° C. (decomposed); mass spectrum (electrospray, m/e): M+H 261.2.

EXAMPLE 231

4-Chloro-6,7,8-trimethoxy-quinoline-3-carbonitrile

A stirred mixture of 1.30 g of 4-hydroxy-6,7,8-trimethoxy-quinoline-3-carbonitrile, 10 ml of phosphorous oxychloride, and 1 drop of N,N-dimethylformamide was refluxed for 10 minutes and evaporated free of volatile matter. The residue was stirred with 20 ml of 5% methyl alcohol in ethyl acetate. The product was collected and dried to give 1.12 g of 4-chloro-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 161–163° C.; mass spectrum (EI, m/e): M 278.0452.

EXAMPLE 232

4-(3-Dimethylamino-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 0.279 g of 4-chloro-6,7,8-trimethoxy-quinoline-3-carbonitrile, 0.23 g of N,N-dimethyl-1,3-phenylenediamine dihydrochloride, 0.2 ml of pyridine, and 15 ml of ethoxyethanol was stirred under nitrogen, at reflux

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temperature for 30 minutes. The mixture was cooled and added to 100 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried to give 0.251 g of 4-(3-dimethylamino-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 142-144° C.; mass spectrum (EI, m/e): M 378.1685.

EXAMPLE 233

4-(3-Hydroxy-4-methyl-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 0.279 g of 4-chloro-6,7,8-trimethoxy-quinoline-3-carbonitrile, 0.148 g of 5-amino-o-cresol, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 100 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried to give 0.279 g of 4-(3-hydroxy-4-methyl-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 200° C. (decomposed); mass spectrum (EI, m/e): M 365.1356.

EXAMPLE 234

4-(4-Chloro-2-fluoro-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 0.279 g of 4-chloro-6,7,8-trimethoxy-quinoline-3-carbonitrile, 0.177 g of 4-chloro-2-fluoroaniline, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 100 ml of water. To this mixture was added sodium carbonate to pH 9. The product was extracted with ethyl acetate, washed with water, dried and concentrated in vacuo. The solid thus obtained was chromatographed on silica gel eluting with hexanes-ethyl acetate 9:1 to 2:1. Solvent was removed from product fractions giving 0.261 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile as a yellow solid: mp 166-168° C.; mass spectrum (EI, m/e): M 387.0777.

EXAMPLE 235

2-(Dimethylamino-methyleneamino)-3,6-dimethoxy-benzoic Acid Methyl ester

A mixture of 3.46 g of 2-amino-3,6-dimethoxybenzoic acid (Manouchehr Azadi-Ardakani and Timothy W. Wallace, *Tetrahedron*, Vol. 44, No. 18, pp. 5939 to 5952, 1988) in 20 ml of *N,N*-dimethylformamide dimethyl acetal was refluxed for 18 hours and concentrated in vacuo. To the residue was added 180 ml of ethyl acetate. The mixture was filtered, and 200 ml of hexanes was added to the filtrate. The mixture was then concentrated to 100 ml. The product was collected and dried to give 3.25 g of 2-(dimethylamino-methyleneamino)-3,6-dimethoxy-benzoic acid methyl ester as a solid, mp 81-83° C.; mass spectrum (EI, m/e): M 266.1263.

EXAMPLE 236

4-Hydroxy-5,8-dimethoxy-quinoline-3-carbonitrile

To 12.5 ml of tetrahydrofuran at -78° C. was added 8.8 ml of 2.5M *n*-butyllithium in hexanes. Then 1.18 ml of acetonitrile in 25 ml of tetrahydrofuran was added dropwise. The mixture was stirred at -78° C. for 15 minutes. Then a solution of 2-(dimethylamino-methyleneamino)-3,6-dimethoxy-benzoic acid methyl ester in 62 ml of tetrahydro-

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furan was added dropwise. The mixture was stirred at -78° C. for 10 minutes, then warmed to room temperature in 15 minutes. Acetic acid (3 ml) was added, followed by 200 ml of water. The product was collected, washed with water, and dried to give 1.57 g of 4-hydroxy-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 300-305° C.; mass spectrum (EI, m/e): M 230.0685.

EXAMPLE 237

4-Chloro-5,8-dimethoxy-quinoline-3-carbonitrile

A stirred mixture of 1.30 g of 4-hydroxy-5,8-dimethoxy-quinoline-3-carbonitrile, 10 ml of phosphorous oxychloride, and 2 drops of *N,N*-dimethylformamide was refluxed for 10 minutes and evaporated free of volatile matter. The residue was stirred with 50 ml of water. The product was collected and dried to give 1.74 g of 4-chloro-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 165-167° C.; mass spectrum (EI, m/e): M 248.0346.

EXAMPLE 238

4-(4-Chloro-2-fluoro-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.148 g of 4-chloro-5,8-dimethoxy-3-quinolinecarbonitrile, 0.102 g of 4-chloro-2-fluoroaniline, and 5 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 50 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, dried, and washed with 10 ml of hexanes-ethyl acetate (4:1) to give 0.168 g of 4-(4-chloro-2-fluoro-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 197-199° C.; mass spectrum (EI, m/e): M 329.7609.

EXAMPLE 239

4-(3-Hydroxy-4-methyl-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.148 g of 4-chloro-5,8-dimethoxy-3-quinolinecarbonitrile, 0.087 g of 5-amino-o-cresol, and 5 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 50 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, dried, and washed with 10 ml of hexanes-ethyl acetate (4:1) to give 0.168 g of 4-(3-hydroxy-4-methyl-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 240-242° C.; mass spectrum (EI, m/e): M 335.1260.

EXAMPLE 240

4-(3-Bromo-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.148 g of 4-chloro-5,8-dimethoxy-3-quinolinecarbonitrile, 0.12 g of *m*-bromoaniline, and 5 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 50 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, dried, and washed with 10 ml of hexanes-ethyl acetate (4:1) to give 0.213 g of 4-(3-bromo-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 72-74° C.; mass spectrum (EI, m/e): M 383.0265.

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EXAMPLE 241

4-(3-Bromo-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 0.167 g of 4-chloro-6,7,8-trimethoxy-3-quinolinecarbonitrile, 0.12 g of m-bromoaniline, and 5 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 50 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, dried, and washed with 10 ml of hexanes-ethyl acetate (4:1) to give 0.212 g of 4-(3-bromo-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 211–213° C.; mass spectrum (EI, m/e): M 413.0377.

EXAMPLE 242

4-(3-Dimethylamino-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.148 g of 4-chloro-5,8-dimethoxy-3-quinolinecarbonitrile, 0.146 g of N,N-dimethyl-1,3-phenylenediamine dihydrochloride, 0.2 ml of pyridine, and 5 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. Then the mixture was partitioned between ethyl acetate and saturated sodium chloride solution. The organic layer was dried and concentrated in vacuo. The residue thus obtained was chromatographed on silica gel eluting with ethyl acetate. Solvent was removed from product fractions giving 0.160 g of 4-(3-dimethylamino-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 103–105° C.; mass spectrum (EI, m/e): M 348.1588.

EXAMPLE 243

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.223 g of 4-chloro-5,8-dimethoxy-3-quinolinecarbonitrile, 0.22 g of the methyl carbonate of 4-chloro-2-fluoro-5-hydroxy-aniline, and 15 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 100 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried.

The solids thus obtained were dissolved in a mixture of 30 ml of methyl alcohol and 20 ml of acetone. To this mixture was added 1.5 ml of 28–30% ammonium hydroxide solution. The mixture was heated at 50° C. for 30 minutes and concentrated. The product was collected, washed with ethyl acetate, and dried to give 0.237 g of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile as a solid, mp 240° C. (decomposed); mass spectrum (electrospray, m/e): M+H 373.9.

EXAMPLE 244

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile

A mixture of 0.279 g of 4-chloro-6,7,8-trimethoxy-3-quinolinecarbonitrile, 0.22 g of the methyl carbonate of 4-chloro-2-fluoro-5-hydroxy-aniline, and 15 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 100 ml of water. To this mixture was added sodium carbonate to pH 9. The product was collected, washed with water, and dried.

The solids thus obtained were dissolved in a mixture of 30 ml of methyl alcohol and 20 ml of acetone. To this mixture

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was added 1.5 ml of 28–30% ammonium hydroxide solution. The mixture was heated at 50° C. for 30 minutes and concentrated. The product was collected, washed with ethyl acetate, and dried to give 0.162 g of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile as a solid, mp 223–225° C.; mass spectrum (EI, m/e): M 403.0731.

EXAMPLE 245

4-(3-Hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.123 g of 3-amino-o-cresol, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.174 g of 4-(3-hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 255–257° C.; mass spectrum (electrospray, m/e): M+H 335.9.

EXAMPLE 246

4-(2-Hydroxy-6-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.123 g of 2-amino-m-cresol, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.216 g of 4-(2-hydroxy-6-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 245–247° C.; mass spectrum (electrospray, m/e): M+H 336.1363.

EXAMPLE 247

3-(3-Cyano-6,7-dimethoxy-quinolin-4-ylamino)-benzamide

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.136 g of 3-aminobenzamide, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.321 g of 3-(3-cyano-6,7-dimethoxy-quinolin-4-ylamino)-benzamide as a solid, mp 253–255° C.; mass spectrum (electrospray, m/e): M 349.1301.

EXAMPLE 248

4-(3-Bromo-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.186 g of 3-bromo-4-methylaniline, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and

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concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.286 g of 4-(3-bromo-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 292–294° C; mass spectrum (EI, m/e): M 397.0446.

EXAMPLE 249

4-(3-Chloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.144 g of 4-amino-2-chlorophenol, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.256 g of 4-(3-chloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 230–232° C; mass spectrum (EI, m/e): M 355.0719.

EXAMPLE 250

6,7-Dimethoxy-4-(2-methylsulfa-phenylamino)-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.139 g of 2-(methylmercapto)aniline, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.184 g of 6,7-dimethoxy-4-(2-methylsulfa-phenylamino)-quinoline-3-carbonitrile as a solid, mp 245–247° C; mass spectrum (EI, m/e): M 351.1051.

EXAMPLE 251

Methyl 2-(dimethylaminomethyleneamino)-4,5-diethoxybenzoate

To a stirred solution of methyl 2-amino-4,5-diethoxybenzoate (4.79 g, 20 mmol) in 20 ml of DMF at 0° C. was added phosphorous oxychloride (2.24 ml, 24 mmol) during 15 m. The mixture was warmed to 55° C. and stirred for 45 m. The resulting solution was diluted with methylene chloride, cooled to 0° C., and treated with 80 ml of pre-cooled N/1 sodium hydroxide during 5 m. The organic layer was separated and washed at 0° C. with water. The solution was dried and concentrated to give an amber oil; NMR (CDCl₃) δ 3.00(s, Me₂N).

EXAMPLE 252

1,4-Dihydroquinoline-6,7-diethoxy-4-oxo-3-carbonitrile

To a stirred solution of n-butyllithium (17.6 ml of 2.5 M in hexane; 44 mmol) in 25 ml of THF at –78° C. was added a solution of acetonitrile (2.35 ml, 45 mmol) in 44 ml of THF during 10 m. After stirring at –78° C. for 15 m, the mixture was treated with a solution of ethyl 2-(dimethylaminomethyleneamino)-4,5-diethoxybenzoate (5.83 g, 19.8 mmol) in 30 ml of THF during 30 m. After 30 m at –78° C. the mixture was treated with 5.7 ml (100 mmol) of acetic acid and evaporated to dryness. The residue was

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stirred in water, and the resulting precipitate was filtered off, washed with water, and dried to give 4.01 g of off-white solid; NMR (DMSO-d₆) δ 8.58(s, 2-H).

EXAMPLE 253

4-Chloro-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 115 treatment of 1,4-dihydroquinoline-6,7-diethoxy-4-oxo-3-carbonitrile with phosphorous oxychloride gave the title compound as a pink solid, mp 170–175° C.

EXAMPLE 254

4-[3-Chloro-4-(phenylthio)phenylamino]-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3-chloro-4-(phenylthio)aniline gave the title compound as a tan solid, mp 88–94° C.

EXAMPLE 255

4-[3-Chloro-4-(phenylthio)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile with 3-chloro-4-(phenylthio)aniline gave the title compound as a tan solid, mp 124–130° C.

EXAMPLE 256

4-(3-Chloro-4-fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3-chloro-4-fluoroaniline gave the title compound as an off-white solid, mp 194–198° C.

EXAMPLE 257

4-(3-Acetylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3-aminoacetophenone gave the title compound as an off-white solid, mp 191–194° C.

EXAMPLE 258

4-(N-Methylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with N-methylaniline gave the title compound as a tan solid, mp 153–155° C.

EXAMPLE 259

4-(Phenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with aniline gave the title compound as a tan solid, mp 168–170° C.

EXAMPLE 260

4-(4-Fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 4-fluoroaniline gave the title compound as a tan solid, mp 177–181° C.

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EXAMPLE 261

4-(4-Fluoro-2-methylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 4-fluoro-3-methylaniline gave the title compound as a tan solid, mp 105–108° C.

EXAMPLE 262

4-(3-Chlorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 4-fluoroaniline gave the title compound as a tan solid, mp 188–190° C.

EXAMPLE 263

4-(3-Fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 105 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3-fluoroaniline gave the title compound as a tan solid, mp 192–195° C.

EXAMPLE 264

4-(3-Aminophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile

A stirred mixture of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile (3.73 g, 15 mmol), 1,3-diaminobenzene (4.86 g, 45 mmol), pyridine (1.21 ml, 15 mmol), and 45 ml of ethoxyethanol was refluxed for 30 m, cooled, and stirred with aqueous sodium bicarbonate. The resulting solid was filtered, washed with water, and dried. Recrystallization from ethanol gave a brown solid, mp 222–228° C.

EXAMPLE 265

4-(3-Acetamidophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile

To a stirred solution of 4-(3-aminophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile (0.96 g, 3.0 mmol) in 9.0 ml of acetic acid at 25° C. was added 0.85 ml (9.0 mmol) of acetic anhydride. After 2 h the solution was evaporated to dryness, and the residue was stirred with methanol. This solution was evaporated, and the residue was recrystallized from ethanol to give 0.50 g of amber solid, mp 147–150° C.

EXAMPLE 266

4-[3-(2-Butynoylamino)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

Isobutyl chloroformate (0.26 ml, 2.0 mmol) and N-methylmorpholine (0.22 ml, 2.0 mmol) were added to an ice-cold solution of 2-butyric acid (0.21 g, 2.5 mmol) in 8.5 ml of THF. After 10 m a suspension of 4-(3-aminophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile (0.32 g, 1.0 mmol) in 6.5 ml of THF was added, and the resulting mixture was stirred at 25° C. for 16 h and diluted with water. The resulting solid was filtered off, washed with water, dried, and recrystallized from methanol to give 0.12 g of off-white solid, mp 193–196° C.

EXAMPLE 267

4-[3-(Hydroxymethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

A stirred mixture of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile (7.46 g, 30 mmol), 3-aminobenzyl

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alcohol (7.39 g, 60 mmol), pyridine (2.43 ml, 30 mmol), and 90 ml of ethoxyethanol was refluxed for 5 h, cooled, and stirred with aqueous sodium bicarbonate. The resulting solid was filtered, washed with water, and dried. Recrystallization from methanol gave a brown solid, mp 250–255° C.

EXAMPLE 268

4-[3-(Chloromethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

To 14 ml of DMF was added phosphorous trichloride (0.70 ml, 8.0 mmol) with stirring at 25–30° C. After 60 m, the mixture was cooled to 0° C., and a suspension of 4-[3-(hydroxymethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile (1.34 g, 4.0 mmol) in 6 ml of DMF was added. The mixture was warmed to 25° C., stirred 15 m, recooled in ice bath, and partitioned with methylene chloride-aqueous sodium bicarbonate. The organic layer was washed with water, dried, and concentrated to give 1.15 g of an amber solid; NMR (CDCl₃) δ 4.79(s, CH₂Cl).

EXAMPLE 269

4-[3-(Acetylthiomethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

To a stirred solution of 4-[3-(chloromethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile (0.97 g, 2.7 mmol) in 5.4 ml of DMF was added potassium thioacetate (0.93 g, 8.1 mmol) at 25° C. After 30 m the mixture was partitioned with methylene chloride and water. The organic layer was washed with water, dried, and concentrated. The residue was recrystallized from ethyl acetate to give 0.43 g of yellow solid, mp 172–177° C.

EXAMPLE 270

4-[3-(Thiomethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile

A stirred mixture of 4-[3-(acetylthiomethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile (1.23 g, 3.13 mmol), 12.5 ml of concentrated ammonium hydroxide, 63 ml of ethanol, and 32 ml of DMF was heated at 85° C. for 2.5 h and then concentrated to dryness. The residue was partitioned with methylene chloride and water. The organic layer was washed with water, dried, and concentrated. The residue was subjected to chromatography on silica gel with methylene chloride-ethyl acetate-methanol to give an off-white solid; mass spectrum (electrospray, m/e) M+H 352.1.

EXAMPLE 271

2-(Dimethylamino-methyleneamino)-3-methoxybenzoic acid methyl ester

A reaction mixture of 5.0 g (29.9 mmol) of 2-amino-3-methoxybenzoic acid in 25.0 mL of DMF-DMA was heated at 100–105° C. for 2.5 hr, and then the solvent was removed to give a red-purple viscous oil. After standing in a refrigerator, the oil solidified to give 5.8 g of the product as a red-purple solid in 82.8% yield, mass spectrum (electrospray, m/e): M+H 236.9

EXAMPLE 272

1,4-Dihydro-8-methoxy-4-oxo-3-quinolinecarbonitrile

To 35.0 mL of THF was added 26.6 mL (66.4 mmol) of n-BuLi solution during 5 min at –78° C. To the stirred

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solution was added a solution of 3.55 mL (67.9 mmol) of CH_3CN in 65 mL of THF during 10 min which time the solution became white suspension, and then continued to stir for 15 min at -78°C . To the suspension was added a solution of 5.8 g (24.5 mmol) of 2-(Dimethylamino-methyleamino)-3-methoxy-benzoic acid methyl ester in 45 mL of THF during 30 min, and then continued to stir 30 min at -78°C . during which time the mixture gradually became clear. The solution was quenched with 8.5 mL of HOAc. The resulting thick slurry was stirred and warmed to room temperature. After most of the solvent was evaporated, the residue was diluted with cold water. The separate solid was collected by filtration and washed with water. After drying in vacuo, this afforded 3.8 g of the product as an off white solid in 77.6% of yield, m.p. 270°C . (dec.), mass spectrum (electrospray, m/e): M+H 201.1

EXAMPLE 273

4-Chloro-8-methoxy-3-quinolinecarbonitrile

A mixture of 3.8 g (19 mmol) of 1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarbonitrile and 40 mL of phosphorous oxychloride and 5 drops of DMF was refluxed for 0.5 hours. The mixture was evaporated to dryness and diluted with hexanes. The solid was collected and mixed with cold dilute sodium carbonate solution and extracted several times with ethyl acetate. The organic layer was dried over sodium sulfate and filtered through a pad of silica gel. Removal of the solvent gave 3.8 g of 4-chloro-8-methoxy-3-quinolinecarbonitrile as an off white solid in 91% yield, mass spectrum (electrospray, m/e): M+H 219.1.

EXAMPLE 274

4-[(3-Bromophenyl)amino]-8-methoxy-3-quinolinecarbonitrile

A solution of 328.0 mg (1.5 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 309.7 mg (1.8 mmol) of 3-bromoaniline and 173.3 mg (1.5 mmol) of pyridine hydrochloride in 15 mL of 2-ethoxyethanol was refluxed under nitrogen for 0.5 hours. The solvent was removed and the residue was diluted with water followed by neutralization to pH 7-8 with diluted sodium carbonate solution. The precipitate was collected and washed with ether and dried in vacuo to give 476.1 mg (89.6%) of the product as a yellow solid, m.p. $210-212^\circ\text{C}$; mass spectrum (electrospray, m/e): M+H 353.8, 355.8.

EXAMPLE 275

4-(4-Chloro-2-fluoro-phenylamino)-8-methoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 328.0 mg (1.5 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 173.3 mg (1.5 mmol) of pyridine hydrochloride and 240.0 mg (1.7 mmol) of 2-fluoro-4-chloro-aniline in 15 mL of 2-ethoxyethanol was heated at 100°C . for 2 hr. After the work up, 431.3 mg (87.9%) of the product was obtained as an off white solid, m.p. 127°C . (dec.), mass spectrum (electrospray, m/e): M+H 327.8, 329.9.

EXAMPLE 276

4-(3-Hydroxy-4-methyl-phenylamino)-8-methoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 328.0 mg (1.5 mmol) of

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4-chloro-8-methoxy-3-quinolinecarbonitrile, 173.3 mg (1.5 mmol) of pyridine hydrochloride and 203.2 mg (1.7 mmol) of 3-hydroxy-4-methyl-aniline in 15 mL of 2-ethoxyethanol was heated at 100°C . for 1.5 hr. After the work up, 407.7 mg (89.4%) of the product was obtained as a yellow solid, m.p. $148-150^\circ\text{C}$., mass spectrum (electrospray, m/e): M+H 306.9.

EXAMPLE 277

4-(3-Dimethylamino-phenylamino)-8-methoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 250.0 mg (1.1 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 273.3 mg (3.0 mmol) of pyridine and 261.4 mg (1.25 mmol) of 3-dimethylaminoaniline hydrochloride in 10 mL of 2-ethoxyethanol was heated at 100°C . for 1.5 hr. The work up gave 294.8 mg (73.4%) of the product as a deep greenish yellow solid, m.p. $222-225^\circ\text{C}$., mass spectrum (electrospray, m/e): M+H 319.0.

EXAMPLE 278

4-(4-Bromo-3-hydroxy-phenylamino)-8-methoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 250.0 mg (1.1 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 131.7 mg (1.1 mmol) of pyridine hydrochloride and 286.7 mg (1.3 mmol) of 4-bromo-3-hydroxy-aniline in 10 mL of 2-ethoxyethanol was heated at 100°C . for 1.5 hr. The work up gave 374.1 mg (88.6%) of the product as a pink solid, m.p. 146°C . (dec.), mass spectrum (electrospray, m/e): M+H 369.9.

EXAMPLE 279

4-(3-Hydroxy-4-methoxy-phenylamino)-8-methoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 200.0 mg (0.92 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 105.7 mg (0.92 mmol) of pyridine hydrochloride and 140.6 mg (1.0 mmol) of 5-amino-2-methoxy-phenol in 10 mL of 2-ethoxyethanol was heated at 100°C . for 2 hr. The work up gave 261.6 mg (89.0%) of the product as a deep yellow solid, m.p. $138-140^\circ\text{C}$. (dec.), mass spectrum (electrospray, m/e): M+H 321.9.

EXAMPLE 280

8-Methoxy-4-(2,4,6-trifluoro-phenylamino)-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 274. A reaction mixture of 200.0 mg (0.92 mmol) of 4-chloro-8-methoxy-3-quinolinecarbonitrile, 105.7 mg (0.92 mmol) of pyridine hydrochloride and 148.6 mg (1.0 mmol) of 2,4,6-trifluoro-aniline in 10 mL of 2-ethoxyethanol was heated at 100°C . for 2 hr. The work up gave 112.6 mg (37.4%) of the product as a yellow solid, m.p. 297°C . (dec.), mass spectrum (electrospray, m/e): M+H 330.0.

EXAMPLE 281

4-(3-Hydroxy-4-methyl-phenylamino)-7-methoxy-quinoline-3-carbonitrile

To a suspension of 200 mg (0.91 mmol) of 4-chloro-7-methoxy-3-quinolinecarbonitrile and 135.5 mg (1.10 mmol)

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of 5-amino-o-cresol in 10 mL of 2-ethoxy ethanol was added 105.6 mg (0.91 mmol) of pyridine hydrochloride. The resulting reaction mixture was refluxed for 1 hr, and then the solvent was removed to give a residue. To the residue was added about 30 mL of water and neutralized to pH 7-8 by addition of diluted sodium carbonate solution. The precipitate was collected by filtration and washed with water and ether. After drying in vacuo, this afforded 277 mg (99%) of the product as a yellow solid, m.p. >250° C., mass (electrospray, m/e): M+H 305.9.

EXAMPLE 282

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-methoxy-quinoline-3-carbonitrile

The method of Example 281 was used with 218.6 mg (1.0 mmol) of 4-chloro-7-methoxy-3-quinolinecarbonitrile, 263.5 mg (1.2 mmol) of the aniline and 115.6 mg (1.0 mmol) of pyridine hydrochloride in 10 mL of 2-ethoxyethanol. This afforded a red oil residue. To the residue was added 10 mL of methanol and 1 mL of NH₄OH (28-30%). The resulting mixture was heated at 50° C. for 30 min, and then the solvent was removed to give a residue. To the residue was added water. The separated solid was collected by filtration and washed with water and ether/ethyl acetate (1:1). After drying in vacuo, 142.1 mg (41.4%) of the product was obtained as a brown solid, m.p. 240° C. (dec.); mass (electrospray, m/e): M+H 343.9, 345.8.

EXAMPLE 283

4-(4-Chloro-2-fluoro-phenylamino)-6-methoxy-quinoline-3-carbonitrile

The method of Example 281 was used with 218.6 mg (1 mmol) of 4-chloro-6-methoxy-3-quinolinecarbonitrile, 174.7 mg (1.2 mmol) of 4-chloro-2-fluoro-aniline and 115.6 mg (1 mmol) of pyridine hydrochloride in 10 mL of 2-ethoxyethanol. This afforded 319.8 mg of the product as a yellow solid, m.p. >250° C., mass (electrospray, m/e): M+H 325.9, 327.9

EXAMPLE 284

4-(3-Hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-3-carbonitrile

To a suspension of 218.6 mg (1.0 mmol) of 4-chloro-6-methoxy-3-quinolinecarbonitrile and 147.8 mg (1.20 mmol) of 5-amino-o-cresol in 10 mL of 2-ethoxyethanol was added 115.6 mg (1.0 mmol) of pyridine hydrochloride. The resulting reaction mixture was refluxed for 1 hr, and then the solvent was removed to give a residue. To the residue was added about 30 mL of water and neutralized to pH 7-8 by addition of diluted sodium carbonate solution. The precipitate was collected by filtration and washed with water and ether. After drying in vacuo, this afforded 278.3 mg (91%) of the product as a yellow solid, m.p. >250° C. (dec.), mass (electrospray, m/e): M+H 305.9.

EXAMPLE 285

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile

The method of Example 282 was used with 218.6 mg (1.0 mmol) of 4-chloro-6-methoxy-3-quinolinecarbonitrile and 263.5 mg (1.2 mmol) of the aniline (cat 800906) in 10 mL of 2-ethoxyethanol was added 115.6 mg (1.0 mmol) of

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pyridine hydrochloride. This afforded a dark oil residue. To the residue was added 10 mL of methanol and 1 mL of NH₄OH (28-30%). The resulting mixture was heated at 50° C. for 30 min, and then the solvent was removed and the residue was triturated with water and ether in an ice bath. The separated solid was filtered off and washed with water and ether. After drying in vacuo, 83.2 mg (24.2%) of the product was obtained as a light brown solid, m.p. 228-230° C., mass (electrospray, m/e): M+H 343.8, 345.8.

EXAMPLE 286

4-(3,5-Dichloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A reaction mixture of 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 213.6 mg (1.2 mmol) of 4-amino-2,6-dichlorophenol and 115.6 mg (1 mmol) of pyridine hydrochloride in 10 mL of 2-ethoxyethanol was refluxed under N₂ for 1 hr. After removal of the solvent, the residue was diluted with water and neutralized to pH 7-8 with diluted sodium carbonate solution. The precipitate was filtered and washed with water and ether/ethyl acetate (1:1). After drying in vacuo this yielded 346.7 mg (88.8%) of the product as a yellow solid, m.p. >250° C., mass (electrospray, m/e): M+H 389.8, 391.8.

EXAMPLE 287

4-(2-Hydroxy-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 10 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 147.8 mg (1.2 mmol) of 6-amino-m-cresol to give 287.5 mg (85.8%) of the product as a light brown solid, m.p. >250° C., mass (electrospray, m/e): M+H 335.9.

EXAMPLE 288

4-(4-Hydroxy-3,5-dimethyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 10 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 164.6 mg (1.2 mmol) of 4-amino-2,5-dimethylphenol to give 232.9 mg (66.7%) of the product as a light brown solid, m.p. 234-236° C., mass (electrospray, m/e): M+H 349.9.

EXAMPLE 289

4-(3-Cyano-6,7-dimethoxy-quinolin-4-ylamino)-benzamide

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 10 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 163.4 mg (1.2 mmol) of 4-amino-benzamide to give 255.7 mg (73.4%) of the product as a light yellow solid, m.p. >250° C., mass (electrospray, m/e): M+H 348.9.

EXAMPLE 290

4-(5-Chloro-2-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-

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dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 172.3 mg (1.2 mmol) of 2-amino-chlorophenol to give 326.4 mg (91.9%) of the product as a yellow solid, m.p. >250° C., mass (electrospray, m/e): M+H 355.8.

EXAMPLE 291

4-(3,5-Dibromo-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 320.3 mg (1.2 mmol) of 4-amino-2,6-dibromophenol to give 427.1 mg (89.2%) of the product as a gray solid, m.p. >250° C., mass (electrospray, m/e): M+H 479.7, 481.6.

EXAMPLE 292

4-(4-Hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 147.8 mg (1.2 mmol) of 4-amino-m-cresol to give 304.6 mg (90.9%) of the product as a salmon solid, m.p. >250° C., mass (electrospray, m/e): M+H 335.9

EXAMPLE 293

6,7-Dimethoxy-4-(pyridin-3-ylamino)-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 112.9 mg (1.2 mmol) of 3-amino-pyridine to give 60.6 mg (19.8%) of the product as an orange solid, m.p. 231-233° C., mass (electrospray, m/e): M+H 306.8.

EXAMPLE 294

6,7-Dimethoxy-4-(3-methylsulfanyl-phenylamino)-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 167.1 mg (1.2 mmol) of 3-(methylthio)aniline to give 134.1 mg (38.2%) of the product as an off white solid, m.p. >250° C., mass (electrospray, m/e): M+H 351.9.

EXAMPLE 295

4-(2-Hydroxy-5-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-

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dimethoxy-3-quinolinecarbonitrile, in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 147.8 mg (1.2 mmol) of 2-amino-p-cresol to give 315.0 mg (94.0%) of the product as a yellow solid, m.p. 198-200° C., mass (electrospray, m/e): M+H 335.8.

EXAMPLE 296

4-(2-Chloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 15 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 270.1 mg (1.5 mmol) of 4-amino-3-chlorophenol to give 299.2 mg (84.3%) of the product as a light brown solid, m.p. >250° C., mass (electrospray, m/e): M+H 355.8, 357.8.

EXAMPLE 297

2-(3-Cyano-6,7-dimethoxy-quinolin-4-ylamino)-benzamide

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 177.0 mg (1.3 mmol) of anthranilamide to give 292.4 mg (84.0%) of the product as a deep yellow solid, m.p. 238-240.5° C., mass (electrospray, m/e): M+H 348.9.

EXAMPLE 298

6,7-Dimethoxy-4-(4-methylsulfanyl-2benalamino)-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 181.0 mg (1.3 mmol) of 4-(methylmercapto)aniline to give 334.1 mg (95.2%) of the product as a yellow solid, m.p. 235-237° C., mass (electrospray, m/e): M+H 351.9, 352.9, 353.8, 354.9.

EXAMPLE 299

4-[4-(2-Hydroxy-ethyl)-phenylamino]-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 178.3 mg (1.3 mmol) of 4-aminophenethyl alcohol to give 327.8 mg (93.9%) of the product as an off white yellow solid, m.p. 208-210° C., mass (electrospray, m/e): M+H 349.9.

EXAMPLE 300

4-(2,4-Dihydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-

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dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 210.0 mg (1.3 mmol) of 4-aminoresorcinol to give 330.4 mg (98.0%) of the product as a deep purple solid, m.p. >250° C., mass (electrospray, m/e): M+H 337.9.

EXAMPLE 301

4-[2-(2-Hydroxy-ethyl)-phenylamino]-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in Example 286, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 178.3 mg (1.3 mmol) of 2-aminophenethyl alcohol to give 218.4 mg (64.4%) of the product as a pink solid, m.p. 159–162° C., mass (electrospray, m/e): M+H 349.9.

EXAMPLE 302

4-(3-Bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile

A stirred mixture of 4-(3-bromophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile (15.4 g, 40 mmol) and 100 g of pyridine hydrochloride was heated at 210° C. for 20 m, cooled to 0° C., treated with 100 ml of concentrated ammonium hydruide, and concentrated to dryness. The residue was stirred with 1 L of water, and the resulting amber solid was filtered off, washed with water, and dried; mass spectrum (electrospray, m/e) M+H 356.1, 358.1.

EXAMPLE 303

4-(3-Bromophenylamino)-6,7-di-n-propoxy-3-quinolinecarbonitrile

To a stirred mixture of 4-(3-bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile (1.07 g, 3.0 mmol), potassium carbonate (1.66 g, 12.0 mmol), and 12 ml of DMF at 0° C. was added 1-iodopropane (1.17 ml, 12.0 mmol). The mixture was warmed to 25° C., stirred for 5 h, and then partitioned at 0° C. with ethyl acetate and water containing HCl to give pH=8. The organic layer was separated, washed with water, dried, and concentrated. The residue was subjected to chromatography on silica gel with methylene chloride-ethyl acetate-acetic acid to give an amorphous solid; mass spectrum (electrospray, m/e) M+H 440.2, 442.2.

EXAMPLE 304

4-[(3-Bromophenyl)-N-acetylamino]-6,7-dihydroxy-3-quinolinecarbonitrile

A solution of 4-(3-bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile (1.78 g, 5.0 mmol), dimethylaminopyridine (60 mg, 0.50 mmol), 5.0 ml of acetic anhydride, and 10 ml of pyridine was stirred at reflux temperature for 1.5 h and concentrated to dryness. The residue was stirred with 50 ml of methanol, 5 ml of water, and sodium bicarbonate (2.1 g, 25 mmol) at 25° C. for 16 h and concentrated to dryness. The residue was stirred with water containing acetic acid to give pH=4–5, and the resulting solid was filtered off, washed with water, and dried. A solution of the resulting solid in THF was passed through a pad of silica gel; the filtrate was concentrated to give a tan solid; mass spectrum (electrospray, m/e) M–H 396.3, 398.3.

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EXAMPLE 305

4-(3-Bromophenylamino)-6,7-di-n-butoxy-3-quinolinecarbonitrile

A stirred mixture of 4-[(3-bromophenyl)-N-acetylamino]-6,7-dihydroxy-3-quinolinecarbonitrile (0.40 g, 1.0 mmol), 1-bromobutane (0.41 g, 3.0 mmol), potassium carbonate (0.30 g, 2.2 mmol), and 2.0 ml of DMF was stirred at 65–70° C. for 5 h, concentrated to dryness, and partitioned with ethyl acetate and water containing acetic acid to give pH=6. The organic layer was washed with water, dried and concentrated. The residue was stirred with potassium carbonate (0.55 g, 4.0 mmol), and 10 ml of methanol at reflux temperature for 60 m and then evaporated to dryness. The residue was partitioned with methylene chloride and water saturated with carbon dioxide (pH=8–9). The organic layer was separated and washed with water, dried, and concentrated. A solution of the residue in 60:30:1 heptane-ethyl acetate-acetic was filtered through a pad of silica gel. The filtrate was evaporated to give an amorphous solid; mass spectrum (electrospray, m/e) M+H 467.9, 469.9.

EXAMPLE 306

4-Chloro-7-methoxy-3-quinolinecarbonitrile

In the manner of Example 115 treatment of 1,4-dihydroquinolin-7-methoxy-4-oxo-3-carbonitrile with phosphorus oxychloride gave the title compound as a tan solid; mass spectrum (electrospray, m/e) M+H 219.2, 221.2.

EXAMPLE 307

4-(4-Chloro-2-fluorophenylamino)-7-methoxy-3-quinolinecarbonitrile

In the manner of Example 274 reaction of 4-chloro-7-methoxy-3-quinolinecarbonitrile with 4-chloro-2-fluoroaniline gave the title compound as an amber solid, mp 208–210° C.

EXAMPLE 308

4-(4-Chloro-2-fluorophenylamino)-7-hydroxy-3-quinolinecarbonitrile

In the manner of Example 302 reaction of 4-(4-chloro-2-fluorophenylamino)-7-methoxy-3-quinolinecarbonitrile with pyridine hydrochloride at 210° C. gave the title compound, mp 295–305° C.

EXAMPLE 309

4-[(4-Chloro-2-fluorophenylamino)-N-acetylamino]-7-hydroxy-3-quinolinecarbonitrile

In the manner of Example 304 peracetylation of 4-(4-chloro-2-fluorophenylamino)-7-hydroxy-3-quinolinecarbonitrile with acetic anhydride in the presence of dimethylaminopyridine followed by de-O-acetylation with sodium bicarbonate in aqueous methanol gave the title compound as an amber solid, mp 182–191° C.

EXAMPLE 310

4-(4-Chloro-2-fluorophenylamino)-7-ethoxy-3-quinolinecarbonitrile

In the manner of Example 305 alkylation of 4-[(4-Chloro-2-fluorophenylamino)-N-acetylamino]-7-hydroxy-3-

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quinolinecarbonitrile with ethyl iodide in the presence of potassium carbonate in DMF followed by de-N-acetylation with potassium carbonate in aqueous methanol gave the title compound as a white solid, mp 221–224° C.

EXAMPLE 311

4-[(3-Bromophenyl)amino]-6,7-bis(2-methoxyethoxy)-3-quinolinecarbonitrile

In the manner of Example 305 alkylation of 4-(3-bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile with 2-bromoethyl methyl ether in the presence of potassium carbonate in DMF gave the title compound as a light yellow solid, mp 135–138° C.

EXAMPLE 312

4-(4-Hydroxy-2-methyl-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

A mixture of 0.3 g of 4-chloro-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile derivative, 0.12 g of 4-amino-m-cresol, 0.1 g of pyridine hydrochloride and 4 ml of 2-ethoxy ethanol was stirred under nitrogen at reflux temperature for 1.5 hr. The mixture was cooled and added to the mixture of ethyl acetate and saturated solution of sodium bicarbonate, stirred for 15 minutes. Following separation of layers, the organic layer was dried over anhydrous sodium sulfate, filtered and filtrate was evaporated to yield dark oil. The oil was purified by silica gel flash chromatography utilizing a gradient of methylene chloride/methanol (95:5 to 90:10) to give 0.23 g of the title compound as a tan solid, mp 120–126°C; mass spectrum (electrospray, m/e): M+H 449.

EXAMPLE 313

4-(3-Bromo-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

The method of Example 312 was used as well as 0.3 g of 4-chloro-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile, 0.12 ml of 3-bromo aniline, 0.1 g of pyridine hydrochloride and 4.0 ml of 2-ethoxy ethanol. This afforded an oil which was purified by silica gel flash chromatography utilizing a gradient of methylene chloride/methanol (96:4 to 92:8) to give 0.22 g of the title compound as an off white solid, mp 115–118 C; mass spectrum (ES, m/e): M+H 499.

EXAMPLE 314

6-Methoxy-4-(2-methylsulfanyl-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

The method of Example 312 was used as well as 0.3 g of 4-chloro-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile, 0.14 ml of 2-(methyl mercapto) aniline, 0.1 g of pyridine hydrochloride and 4.0 ml of 2-ethoxy ethanol. This afforded an oil which was purified by silica gel flash chromatography [methylene chloride/methanol (96:4)] to give 0.16 g of the title compound as an off white solid, mp 179–180 C; mass spectrum (ES, m/e): M+H 465.

EXAMPLE 315

4-(4-Hydroxy-3,5-dimethyl-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile

The method of Example 312 was used as well as 0.25 g of 4-chloro-6-methoxy-7-(3-morpholin-4-yl-propoxy)-

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quinoline-3-carbonitrile, 0.12 ml of 4-amino, 2-5 dimethyl phenol, 0.1 g of pyridine hydrochloride and 4.0 ml of 2-ethoxy ethanol. This afforded an oil which was purified by silica gel flash chromatography utilizing a gradient of methylene chloride/methanol (96:4 to 92:8) to give 0.20 g of the title compound as a tan foam, mp 122–125 C; mass spectrum (ES, m/e): M+H 481.

EXAMPLE 316

4-(2-Aminophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 61 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 2-aminobenzylamine gave the title compound as an off-white solid, mp 173–177° C.

EXAMPLE 317

4-(3,4-Difluorophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile

In the manner of Example 61 reaction of 4-chloro-6,7-diethoxy-3-quinolinecarbonitrile with 3,4-difluorobenzylamine gave the title compound as a tan solid, mp 167–169° C.

EXAMPLE 318

4-Methoxy-but-2-enoic acid [4-(3-bromophenylamino)-quinazolin-6-yl]-amide

To a solution of 1 g (3.17 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile and 0.6 g of diisopropylethylamine in 21 ml of tetrahydrofuran was added 0.47 g (3.5 mmol) of 4-methoxycrotonoyl chloride at 0° C. with stirring. After 1.5 hr at 0° C. another 0.15 g of acid chloride was added. The mixture was diluted with 75 ml of tetrahydrofuran and stirred with a mixture of brine and saturated sodium bicarbonate. 50 ml of ethyl acetate was added and the organic layer was separated and dried over magnesium sulfate. Solvent was removed and the residue was purified by chromatography on silica gel. Recrystallization from 1-butanol gave 1.25 g of a yellow powder; mass spectrum (electrospray, m/e): M+H 415.0 and 415.9.

EXAMPLE 319

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.25 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.195 g of 4-chloro-2-fluoro-5-hydroxyaniline, 0.116 g of pyridine hydrochloride, and 3 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 10 ml of water. To this mixture was added sodium carbonate until pH 9. The product was collected, washed with water, and dried to give 0.327 g of 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, dec>260° C; mass spectrum (electrospray, m/e): M+H 373.9.

EXAMPLE 320

7-Benzoyloxy-4-hydroxy-6-methoxy-quinoline-3-carbonitrile

To a stirred solution of 26.9 ml of n-butyllithium (2.5 M in hexane) in 50 ml of THF at –78° C. was added a 3.51 ml

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of acetonitrile in 20 ml of THF during 10 min. After stirring at -78°C . for 30 min, the mixture was treated with 10 g of L17741-150 (B. Floyd) in 20 ml of THF during 5 min. After 15 min at -78°C . the stirred mixture was warmed to 0°C . for a further 30 min. It was then treated with 5 ml of acetic acid, warmed to 25°C . and stirred for 30 min. The mixture was evaporated to dryness, and diluted with aqueous sodium bicarbonate. The resulting off-white solid was filtered, washed with water, ethyl acetate and ether. After drying, 4.5 g of 7-benzyloxy-4-hydroxy-6-methoxy-quinoline-3-carbonitrile was obtained as an off-white solid, dec $>255^{\circ}\text{C}$; mass spectrum (electrospray, m/e) $\text{M}+\text{H}$ 307.

EXAMPLE 321

7-Benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile

To a stirred suspension of 1 g of 7-benzyloxy-4-hydroxy-6-methoxy-quinoline-3-carbonitrile in 10 ml of methylene chloride was added 5 ml of oxalyl chloride (2M in methylene chloride), and 2 drops of *N,N*-dimethylformamide. The mixture was refluxed for 20 min and to it was slowly added aqueous sodium bicarbonate until the bubbling ceased. Following separation of the layers, the organic layer was evaporated to a small volume, then passed through a plug of magnesium. Elution with 50 ml methylene chloride, followed by evaporation provided 0.6 g of 7-benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile as a pale yellow solid, mp $282-284^{\circ}\text{C}$; mass spectrum (electrospray, m/e) $\text{M}+\text{H}$ 325.

EXAMPLE 322

7-Benzyloxy-4-(4-chloro-2-fluoro-phenylamino)-6-methoxy-quinoline-3-carbonitrile

A mixture of 0.200 g of 7-benzyloxy-4-chloro-6-methoxy-quinoline-3-carbonitrile 0.108 g of 4-chloro-2-fluoroaniline, 0.071 g of pyridine hydrochloride, and 3 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 10 ml of water. To this mixture was added sodium carbonate until pH 9. The product was collected, washed with water, and dried to give 0.150 g of 7-benzyloxy-4-(4-chloro-2-fluoro-phenylamino)-6-methoxy-quinoline-3-carbonitrile hydrochloride as a solid, mp $241-243^{\circ}\text{C}$; mass spectrum (electrospray, m/e): $\text{M}+\text{H}$ 433.9.

EXAMPLE 323

4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-methoxy-6-(3-morpholin-4-yl)-propoxyl-quinoline-3-carbonitrile

A mixture of 0.35 g of 4-chloro-7-methoxy-6-(3-morpholin-4-yl-propoxy)-3-quinolinecarbonitrile, 0.188 g of 4-chloro-2-fluoro-5-hydroxyaniline, 0.112 g of pyridine hydrochloride, and 4 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 1 h. The mixture was cooled and added to 10 ml of water. To this mixture was added sodium carbonate until pH 9. The product was collected, washed with water, and dried to give 0.210 g of 4-(4-Chloro-2-fluoro-5-hydroxy-phenylamino)-7-methoxy-6-(3-morpholin-4-yl)-propoxyl-quinoline-3-carbonitrile as a solid, mp $125-128^{\circ}\text{C}$; mass spectrum (electrospray, m/e): $\text{M}+\text{H}$ 487.0.

EXAMPLE 324

4-(3-Acetylphenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile

In the manner of Example 274 reaction of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile with

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3-aminoacetophenone gave the title compound as a tan solid, mp $204-206^{\circ}\text{C}$.

EXAMPLE 325

4-(3-Bromophenylamino)-6,7-di-methoxymethyl-3-quinolinecarbonitrile

In the manner of Example 305 treatment of 4-(3-bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile with potassium carbonate and chloromethyl ether in dimethylformamide gave the title compound as a yellow solid; mp $113-116^{\circ}\text{C}$.

EXAMPLE 326

N-[4-(3-Bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(E) acrylamide and

EXAMPLE 327

N-[4-(3-Bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(Z)-acrylamide

To a solution of 0.5 g (1.47 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile and 0.24 g (1.8 mmol) of diisopropylethyl amine in 3 ml of tetrahydrofuran at 0°C . with stirring was added 0.21 g (1.7 mmol) of 3-chloro-acryloyl chloride (cis/trans mixture) in 2 ml of tetrahydrofuran. After 40 min at 0°C ., the mixture was poured into a saturated solution of sodium bicarbonate and then extracted ether. The organic solution was dried over magnesium sulfate and the solvent was removed. The residue chromatographed on silica gel giving 0.16 g of N-[4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(E) acrylamide; mass spectrum (electrospray, m/e): $\text{M}+\text{H}$ 424.9, 427.0, and 0.12 g of N-[4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(Z) acrylamide; mass spectrum (electrospray, m/e): $\text{M}+\text{H}$ 425.0, 427.0.

EXAMPLE 328

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-morpholino-2-butyramide

Isobutyl chloroformate (0.161 g, 1.18 mmol) was dropwise added into an ice cold solution of 4-morpholino-2-butyric acid (0.25 g, 1.48 mmol) and *N*-methylmorpholine (0.15 g, 1.48 mmol) in 8 mL of tetrahydrofuran under N_2 . After stirring for 30 min, a solution of 0.25 g (0.74 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile in 6 mL of pyridine was added dropwise and the mixture was stirred at 0°C . for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 15% methanol in ethyl acetate. The product was collected, and dried in vacuo to give 0.096 g (27%) of yellow solid; mass spectrum (electrospray, m/e): 490.1, 492.1 ($\text{M}+\text{H}^+$); mp $145-148^{\circ}\text{C}$.

EXAMPLE 329

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butyramide

Isobutyl chloroformate (0.342 g, 2.5 mmol) was dropwise added into an ice cold solution of 4-dimethylamino-2-

butynoic acid (0.9 g, 3.8 mmol) and N-methyl-morpholine (0.384 g, 3.8 mmol) in 50 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 0.644 g (1.9 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarboxitrile in 10 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2.5 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 15% methanol in ethyl acetate. The product was collected, and dried in vacuo to give 0.144 g (21%) of yellow solid; mass spectrum (electrospray, m/e): 447.9, 450.2 (M+H⁺); mp 180° C. (dec.).

EXAMPLE 330

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-2-butyramide

Isobutyl chloroformate (0.432 g, 3.2 mmol) was dropwise added into an ice cold solution of 4-methoxy-2-butyric acid (0.72 g, 6.32 mmol) and N-methylmorpholine (0.959 g, 9.78 mmol) in 20 mL of tetrahydrofuran under N₂. After stirring for 30 min, a solution of 0.5 g (1.58 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarboxitrile in 8 mL of pyridine was added dropwise and the mixture was stirred at 0° C. for 2 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by thin-layer chromatography eluted with 5% methanol in chloroform. The product was collected, and dried in vacuo to give 0.27 g (41%) of yellow solid; mass spectrum (electrospray, m/e): 435.1, 437.0 (M+H⁺); mp 197° C. (dec.).

EXAMPLE 331

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-*t*-butyldimethylsiloxy-2-butyramide

Isobutyl chloroformate (0.214 g, 1.57 mmol) was dropwise added into an ice cold solution of 4-*t*-butyldimethylsiloxy-2-butyric acid (0.336 g, 1.57 mmol) and N-methylmorpholine (0.19 g, 1.88 mmol) in 15 mL of tetrahydrofuran under N₂. After stirring for 30 min, the reaction mixture was added dropwise into a solution of 0.4 g (1.18 mmol) of 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarboxitrile in 3 mL of tetrahydrofuran and 1.5 mL of pyridine and stirred at 0° C. for 1 hr. The reaction was quenched with ice water, poured into saturated sodium bicarbonate and brine, and extracted with ethyl acetate. The ethyl acetate layer was concentrated and purified by column chromatography eluted with 60% ethyl acetate in hexane. The product was collected, and dried in vacuo to give 0.22 g (35%) of yellow solid; mass spectrum (electrospray, m/e): 535.1189 (M⁺).

EXAMPLE 332

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-hydroxy-2-butyramide

N-[4-[(3-Bromophenyl)amino]-3-cyano-6-quinolinyl]-4-*t*-butyldimethylsiloxy-2-butyramide (60 mg, 0.122 mmol) was dissolved in a solution of acetic acid, tetrahydrofuran and water (3:1:1) and stirred overnight at room temperature. The solution was diluted with ethyl acetate and washed with

saturated sodium bicarbonate and brine. The ethyl acetate was concentrated to give 42.2 mg (90%) of yellow solid; mass spectrum (electrospray, m/e): 421.0311 (M⁺).

EXAMPLE 333

4-(3-Hydroxymethyl-2-methylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.151 g (1.1 mmol) of 3-amino-2-methylbenzyl alcohol, 0.116 g (1 mmol) pyridine hydrochloride and 12 mL of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 6 hours; progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 mL of water followed by 5 mL of 1M NaHCO₃, approximately pH 8. The resulting precipitate was collected, washed with water and diethyl ether, and dried in vacuo at 65° C. to give 0.32 g (91.5%) of the desired product as light tan crystals. MP 123–125° C.; mass spectrum (electrospray, m/e): 349.9(M+H)⁺.

EXAMPLE 334

4-(2-Amino-4,5-dimethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.410 g (3.0 mmol) of 4,5-dimethyl-1,2-diphenylenediamine, 0.116 g (1 mmol) pyridine hydrochloride and 12 mL of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 1 hour; progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 mL of water followed by 5 mL of 1M NaHCO₃, approximately pH 8. The resulting precipitate was collected, washed with water and diethyl ether, and dried in vacuo at 65° C. to give 0.587 g of the desired product (impure). The impure product was digested with 50 mL of chloroform and 50 mL of ethyl acetate for 0.5 hour, collected, washed with chloroform and dried to give 0.307 g (88%) of the desired pure product as yellow crystals. MP 260–262° C.; mass spectrum (electrospray, m/e): 348.1582(HR).

EXAMPLE 335

4-(4-Ethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.14 mL (1.1 mmol) of 4-ethylamine, 0.116 g (1 mmol) pyridine hydrochloride and 12 mL of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 1 hour; progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 mL of water followed by 5 mL of 1M NaHCO₃, approximately pH 8. The resulting precipitate was collected, washed with water and diethyl ether, and dried in vacuo at 65° C. to give 0.325 g (97.5%) of the desired product as light cream crystals. MP 248–250° C.; mass spectrum (electrospray, m/e): 333.1462.

EXAMPLE 336

4-(4-Chloro-2-methylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.156 g (1.1 mmol) of

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4-chloro-2-methylaniline, 0.116 g (1 mmol) pyridine hydrochloride and 12 ml of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 24 hours; progress of the reaction was monitored by TLC. After 24 hours an additional 0.156 g of 4-chloro-2-methylaniline was added and the heating continued for 24 hours. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 ml of water followed by 5 ml of 1M NaHCO₃, approximately pH 8. The gummy solid was dissolved in chloroform and passed through a pad of hydrous magnesium silicate. The liquid was concentrated in vacuo and the residue triturated 5 times with hexane. The resulting precipitate was collected, washed with hexane, and dried in vacuo at 65° C. to give 0.250 g (71%) of the desired product as brown crystals. MP 227–229° C.; mass spectrum (electrospray, m/e): 353.8(M+H)⁺.

EXAMPLE 337

6,7-Dimethoxy-4-(3-phenoxyphenylamino)quinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.204 g (1.1 mmol) of 3-phenoxyaniline, 0.116 g (1 mmol) pyridine hydrochloride and 12 ml of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 3 hours; progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 ml of water followed by 5 ml of 1M NaHCO₃, approximately pH 8. The resulting precipitate was collected, washed with water and diethyl ether, and dried in vacuo at 65° C. to give 0.309 g (78%) of the desired product as cream crystals. MP 253–254° C.; mass spectrum (electrospray, m/e): 397.0(M+H)⁺.

EXAMPLE 338

4-(4-Chloro-3-trifluoromethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

A mixture of 0.248 g (1 mmol) of 4-chloro-6,7-dimethoxyquinoline-3-carbonitrile, 0.215 g of 4-chloro-3-trifluoromethylaniline, 0.116 g (1 mmol) pyridine hydrochloride and 12 ml of 2-ethoxyethanol was heated in a 138–140° C. oil bath for 1.5 hours; progress of the reaction was monitored by TLC. When TLC indicated the disappearance of starting material, the reaction was cooled and concentrated in vacuo to a thick oil. To this oil was added 50 ml of water followed by 5 ml of 1M NaHCO₃, approximately pH 8. The resulting precipitate was collected, washed with water and diethyl ether, and dried in vacuo at 65° C. to give 0.266 g (65.5%) of the desired product as cream crystals. MP 265–267° C.; mass spectrum (electrospray, m/e): 408.2(M+H)⁺.

EXAMPLE 339

4-(3-Hydroxy-phenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

Using the method described in Example 105, 0.7 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile and 0.38 g of 3-aminophenol was converted to 0.83 g of the title compound: mass spectrum (electrospray, m/e): 321.9, 322.8 (M+H)⁺.

EXAMPLE 340

4-(4-methyl-phenylamino)-6,7-dimethoxyquinoline-3-carbonitrile

Using the method described in Example 105, 0.7 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile and 0.317 g

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of 4-methylphenol was converted to 0.79 g of the title compound: MP=128–130° C.

EXAMPLE 341

4-(3-Hydroxy-4-methyl-phenylamino)-8-methoxy-6-nitroquinoline-3-carbonitrile

Using the method described in Example 105, 0.5 g of 4-chloro-8-methoxy-6-nitro-3-quinolinecarbonitrile and 0.28 g of 3-hydroxy-4-methylphenol was converted to 0.3 g of the title compound: mass spectrum (electrospray, m/e): 350.9, 351.9 (M+H)⁺.

EXAMPLE 342

4-(4-Chloro-2-fluoro-phenylamino)-8-methoxy-6-nitroquinoline-3-carbonitrile

Using the method described in Example 105, 0.5 g of 4-chloro-8-methoxy-6-nitro-3-quinolinecarbonitrile and 0.25 ml of 4-chloro-2-fluoro phenol was converted to 0.08 g of the title compound: mass spectrum (electrospray, m/e): 372.8, 374.8 (M+H)⁺.

EXAMPLE 343

4-(3-Hydroxy-4-methoxy-phenylamino)-8-methoxy-6-nitroquinoline-3-carbonitrile

Using the method described in Example 105, 0.5 g of 4-chloro-8-methoxy-6-nitro-3-quinolinecarbonitrile and 0.31 g of 3-hydroxy-4-methoxy phenol was converted to 0.21 g of the title compound: mass spectrum (electrospray, m/e): 366.9, 367.9 (M+H)⁺.

EXAMPLE 344

6-Amino-4-(3-hydroxy-4-methyl-phenylamino)-8-methoxyquinoline-3-carbonitrile

Using the method described in Example 196, 0.2 g of 4-(3-hydroxy-4-methyl-phenylamino)-8-methoxy-6-nitroquinoline-3-carbonitrile and 0.1 g of iron was converted to 0.14 g of the title compound: MP=227° C. (dec)

EXAMPLE 345

6-Amino-4-(3-hydroxy-4-methoxy-phenylamino)-8-methoxyquinoline-3-carbonitrile

Using the method described in Example 196, 0.1 g of 4-(3-hydroxy-4-methoxy-phenylamino)-8-methoxy-6-nitroquinoline-3-carbonitrile and 0.09 g of iron was converted to the title compound: MP=215° C. (dec)

EXAMPLE 346

N-[4-[(3-Bromo-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-bromo-2-butanamide

By using the method described in EXAMPLE 172 and not reacting with dimethylamine, a portion of 6-amino-4-(3-bromo-4-fluoro-phenylamino)-7-methoxyquinoline-3-carbonitrile was converted to the title compound: mass spectrum (electrospray, m/e): 532.8, 534.8, 536.8 (M+H)⁺.

EXAMPLE 347

N-[4-[(3-Bromophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-chloro-2-butanamide

In the method described in EXAMPLE 198, a side product was isolated that proved to be the title compound: mass spectrum (electrospray, m/e): 471.25, 473.3(M+H)⁺.

EXAMPLE 348

N-{3-Cyano-4-[(3-iodophenyl)amino]-6-quinolinyl}-2-butyramide

5 Dissolved 275 mg (3.27 mmol) 2-butyric acid in 20 ml THF under N_2 and chilled to 0° C. Added 420 μ l (3.23 mmol) isobutyl chloroformate and 355 μ l (3.24 mmol) N-methylmorpholine and stirred for 10 minutes. Added dropwise a solution of 500 mg (1.30 mmol) 6-amino-4-[(3-iodophenyl)amino]-3-quinolinecarbonitrile and after 15 minutes, removed ice bath and stirred overnight at 25° C. Stripped solvent, washed with water and collected solids. Boiled in ethyl acetate, collected, and dried in vacuo, giving 228 mg of orange-brown solid: mass spectrum (electrospray m/e): M+H=453.1.

EXAMPLE 349

N-{3-Cyano-4-[(3-methylphenyl)amino]-6-quinolinyl}-2-propenamide

Dissolved 500 mg (1.82 mmol) of 6-amino-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile in 1.0 ml DMF and 6 ml THF and chilled to 0° C. under N_2 . Added 280 μ l (2.00 mmol) triethylamine and 166 μ l (2.00 mmol) acryloyl chloride. Removed ice bath at 15 minutes and at 1 hour, stripped solvent and slurried residue with dilute sodium bicarbonate. Collected crystals and washed with water. Boiled solids in ethyl acetate, collected and dried in vacuo, giving 238 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=329.1.

EXAMPLE 350

N-{4-[(4-Bromophenyl)amino]-3-cyano-6-quinolinyl}-2-butyramide

5 Dissolved 310 mg (3.68 mmol) 2-butyric acid in 20 ml THF and chilled to 0° C. under N_2 . Added 480 μ l (3.68 mmol) isobutyl chloroformate and 410 μ l (3.72 mmol) N-methylmorpholine. Stirred for 20 minutes and dropwise added a solution of 500 mg (1.47 mmol) 6-amino-4-[(4-bromophenyl)amino]-3-quinolinecarbonitrile in 1 ml DMF and 10 ml THF. Removed ice bath after 15 minutes and stirred at 25° C. overnight. Stripped solvent, slurried residue with water and collected solids. Boiled solids in ethyl acetate, collected, and dried in vacuo, giving 341 mg of yellow solid: mass spectrum (electrospray m/e): M+H=405.1, 407.1.

EXAMPLE 351

N-{4-[(3-Chloro-4-thiophenoxyphenyl)amino]-3-cyano-6-quinolinyl}-2-propenamide

10 Dissolved 1.00 g (2.48 mmol) 6-amino-4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-quinolinecarbonitrile in 2.0 ml DMF and 12 ml THF and chilled to 0° C. under N_2 . Added 380 μ l (2.73 mmol) triethylamine and 227 μ l (2.73 mmol) acryloyl chloride. Removed ice bath at 15 minutes and at 1.5 hours stripped solvent and slurried residue with dilute sodium bicarbonate. Collected solids and washed with water. Recrystallized from ethyl acetate and dried in vacuo, giving 293 mg of yellow-orange solid: mass spectrum (electrospray m/e): M+H=457.3, 459.3.

EXAMPLE 352

N-{3-Cyano-4-[(3,4-difluorophenyl)amino]-6-quinolinyl}-2-butyramide

Dissolved 425 mg (5.06 mmol) 2-butyric acid in 40 ml THF and chilled to 0° C. under N_2 . Added 556 μ l (5.06

mmol) N-methylmorpholine and 658 μ l (5.06 mmol) isobutyl chloroformate and stirred for 10 minutes. Added dropwise a solution of 1.00 g (3.37 mmol) 6-amino-4-[(3,4-difluorophenyl)amino]-3-quinolinecarbonitrile in 2.0 ml hot DMF and 20 ml THF. Removed ice bath at 15 minutes and stirred at 25° C. overnight. Stripped solvent, slurried residue with water, and collected solids. Boiled in ethyl acetate, collected solids, and dried in vacuo, giving 735 mg of yellow solid: mass spectrum (electrospray m/e): M+H=363.3

EXAMPLE 353

N-{4-[(3-Chlorophenyl)amino]-3-cyano-6-quinolinyl}-2-butyramide

15 Dissolved 428 mg (5.09 mmol) 2-butyric acid in 40 ml THF and chilled to 0° C. under N_2 . Added 560 μ l (5.09 mmol) N-methylmorpholine and 662 μ l (5.09 mmol) isobutyl chloroformate and stirred for 10 minutes. Added dropwise a solution of 1.00 g (3.39 mmol) 6-amino-4-[(3-chlorophenyl)amino]-3-quinolinecarbonitrile in 2 ml DMF and 20 ml THF. Removed ice bath at 15 minutes and stirred at 25° C. overnight. Stripped solvent, slurried residue with water and collected solids. Boiled in ethyl acetate, collected and dried in vacuo, giving 975 mg of yellow solid: mass spectrum (electrospray m/e): M+H=361.1, 363.2.

EXAMPLE 354

N-{3-Cyano-4-[(3-isopropylphenyl)amino]-6-quinolinyl}-2-butyramide

20 Dissolved 695 mg (8.27 mmol) 2-butyric acid in 40 ml THF and chilled to 0° C. under N_2 . Added 1.08 ml (8.30 mmol) isobutyl chloroformate and 910 μ l (8.27 mmol) N-methylmorpholine and stirred for 10 minutes. Dropwise added a solution of 1.00 g (3.31 mmol) 6-amino-4-[(3-isopropylphenyl)amino]-3-quinolinecarbonitrile in 2.0 ml DMF and 15 ml THF. Removed ice bath at 15 minutes and stirred at 25° C. overnight. Stripped solvent, slurried residue with water, and collected solid. Recrystallized from ethyl acetate and dried in vacuo, giving 329 mg of yellow-green solid: mass spectrum (electrospray m/e): M+H=369.2.

EXAMPLE 355

N-{3-Cyano-4-[(3-isopropylphenyl)amino]-6-quinolinyl}-2-propenamide

25 Dissolved 1.00 g (3.31 mmol) 6-amino-4-[(3-isopropylphenyl)amino]-3-quinolinecarbonitrile in 2.0 ml hot DMF, added 12 ml THF, and chilled to 0° C. under N_2 . Added 507 μ l (3.64 mmol) triethylamine and 303 μ l (3.64 mmol) acryloyl chloride. Removed ice bath at 15 minutes and at 1 hour stripped solvent. Slurried residue with dilute sodium bicarbonate, collected solids and washed with water. Recrystallized from ethyl acetate and dried in vacuo, giving 366 mg of orange solid: mass spectrum (electrospray m/e): M+H=357.1.

EXAMPLE 356

6-Amino-4-[(3-isopropylphenyl)amino]-3-quinolinecarbonitrile

30 Added 0.5 g 10% palladium on carbon to a flask under N_2 and covered with 250 ml ethanol. To this added 4.818 g (14.5 mmol) 4-[(3-isopropylphenyl)amino]-6-nitro-3-quinolinecarbonitrile and 1.14 ml (36.2 mmol) anhydrous hydrazine and heated to reflux. At 1.5 hours, filtered hot

mixture through celite, stripped solvent, and dried in vacuo, giving 4.30 g of yellow solid: mass spectrum (electrospray m/e): M+H=303.1.

EXAMPLE 357

4-[(3-Isopropylphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.48 g (25.8 mmol) 3-isopropylaniline was heated to reflux under N₂. At 4 hours, removed heat and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Stirred residue with hexane and collected solids. Dissolved in ethyl acetate, stirred with Darco, filtered through celite, stripped solvent and dried in vacuo, giving 5.289 g of yellow solid: mass spectrum (electrospray m/e): M+H=333.1.

EXAMPLE 358

4-(3-Bromo-phenylamino)-6-(3-pyrrolidin-1-yl-propylamino)-quinoline-3-carbonitrile

Dissolved 0.64 g (3.69 mmol) 3-(pyrrolidin-1-yl)propionaldehyde dimethyl acetal in 10 ml water and acidified to pH 1 with concentrated HCl. Heated to 40° C. for 90 minutes, removed heat and neutralized with sodium bicarbonate. Dissolved 500 mg (1.47 mmol) 6-amino-4-(3-bromo-phenylamino)-quinoline-3-carbonitrile in 100 ml ethanol and added acetic acid until pH was 3 to 4. Added the deprotected aldehyde to the amine solution and stirred at 25° C. for 0.5 hour. Gradually added 94 mg (1.47 mmol) sodium cyanoborohydride and stirred overnight. Stripped solvent, partitioned between chloroform and water. Washed organic layer with brine and dried with sodium sulfate. Stripped solvent and filtered through a pad of silica gel, first with 10% methanol/chloroform, then 20% methanol/chloroform/1% ammonium hydroxide. Stripped solvent and dried in vacuo, giving 143 mg of yellow-brown solid: mass spectrum (electrospray m/e): M+H=450, 452.1.

EXAMPLE 359

4-(3-Azido-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Dissolved 643 mg (2.00 mmol) 4-(3-amino-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile in 25 ml 80% acetic acid in water. Chilled to 0° C. and added 152 mg (2.21 mmol) sodium nitrile in 2.2 ml water. After 10 minutes, added 144 mg (2.21 mmol) sodium azide in 2.2 ml water. At 1.5 hours stripped solvent and dissolved residue in hot ethyl acetate. Washed with saturated sodium bicarbonate, water and brine and dried with sodium sulfate. Stripped solvent and redissolved in 60% ethyl acetate/methylene chloride and filtered through a pad of silica gel. Stripped solvent and dried in vacuo, giving 526 mg of brown solid: mass spectrum (electrospray m/e): M+H=347.1.

EXAMPLE 360

6-Amino-4-[(4-Chloro-2-fluorophenyl)amino]-7-methoxy-3-quinolinecarbonitrile

A mixture of 500 mg (1.34 mmol) 4-[(4-chloro-2-fluorophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile, 20 ml ethanol and 1.52 ml (6.71 mmol) tin chloride dihydrate was heated to reflux under N₂. At 3 hours, removed heat, added ice water and made basic

with sodium bicarbonate. Stirred for several hours and extracted with chloroform. Dried organic layer with sodium sulfate, stripped solvent and dried in vacuo, giving 350 mg of green solid: mass spectrum (electrospray m/e): M+H=342.9, 344.8.

EXAMPLE 361

4-[(4-Chloro-2-fluorophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile

A mixture of 5.017 g (19.0 mmol) 4-chloro-7-methoxy-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol, and 2.55 ml (22.8 mmol) 4-chloro-2-fluoroaniline was heated to reflux under N₂. At 3.5 hours, removed heat and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Stirred residue with hexane, collected solids, and washed with water. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent, and dried in vacuo, giving 6.54 g of yellow solid: mass spectrum (electrospray m/e): M+H=372.8, 374.8.

EXAMPLE 362

4-[(3,4-Dichlorophenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol, and 4.17 g (25.6 mmol) 3,4-dichloroaniline was heated to reflux under N₂. At 3.5 hours, removed heat and made basic with saturated sodium bicarbonate. Stripped solvents and azeotroped with ethanol. Stirred residue with hexane, collected solids and washed with water. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent and dried in vacuo, giving 2.106 g of yellow solid: mass spectrum (electrospray m/e): M+H=359.1, 361.0.

EXAMPLE 363

6-Amino-4-[(3-methylsulfanyphenyl)amino]-3-quinolinecarbonitrile

A mixture of 4.55 g (13.5 mmol) 4-[(3-methylsulfanyphenyl)amino]-6-nitro-3-quinolinecarbonitrile, 250 ml ethanol, 0.46 g 10% palladium on carbon, and 1.06 ml (33.8 mmol) anhydrous hydrazine was heated to reflux. At 4 hours, added 0.5 equivalents of hydrazine, and at 5 hours, filtered the hot mixture through celite. Stripped the solvent and dried in vacuo, giving 4.068 g brown solid: mass spectrum (electrospray m/e): M+H=307.1.

EXAMPLE 364

4-[(3-Methylsulfanyphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.18 ml (25.8 mmol) 3-methylsulfanylaniline was heated to reflux under N₂. At 2 hours, removed heat and made basic with saturated sodium bicarbonate. Stripped solvents and air dried. Washed residue with hexane, collected solids and washed with water. Dissolved in ethyl acetate, stirred with Darco, stripped solvent and dried in vacuo, giving 4.848 g of yellow solid: mass spectrum (electrospray m/e): M+H=337.1.

EXAMPLE 365

4-[(3-Trifluoromethoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile

A mixture of 5.00 g (21.5 mmol) 4-chloro-6-nitro-3-quinolinecarbonitrile, 200 ml ethanol, and 3.4 ml (25.3

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mmol) 3-trifluoromethoxyaniline was heated to reflux. At 5 hours, removed heat and made basic with saturated sodium bicarbonate. Stripped solvents, slurried residue with hexane, collected, and washed with water. Dissolved in ethyl acetate, stirred with Darco, filtered, stripped solvent, and dried in vacuo, giving 4.537 g of yellow-orange solid: mass spectrum (electrospray m/e): M+H=374.8.

EXAMPLE 366

4-(3-Dimethylamino-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A 1.25 gram (5 mmole) portion of 4-chloro, 6,7-dimethoxy-quinoline-3-carbonitrile and a 1.05 gram (5 mmole) portion of N,N-dimethyl-1,3-phenylenediamine in 1 ml of 2-methoxyethanol were refluxed for 2 hours in an oil bath at 154 deg. Cooling gave a solid which was recrystallized from water to give 0.4 grams (19%) of 4-(3-Dimethylamino-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile which melted at 246-249° C.: mass spectrum (electrospray m/e): (M+H)=349.2, (M+2H)⁺=174.9.

EXAMPLE 367

6,7-Dimethoxy-4-(4-methoxy-2-methyl-phenylamino)-quinoline-3-carbonitrile

A reaction mixture of 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 164.6 mg (1.2 mmol) of 4-methoxy-2-methyl-aniline and 115.6 mg (1 mmol) of pyridine hydrochloride in 10 mL of 2-ethoxyethanol was refluxed under N₂ for 3 hr. After removal of the solvent, the residue was diluted with water and neutralized to pH 7-8 with diluted sodium carbonate solution. The precipitate was filtered and washed with water and ether. After drying in vacuo, this yielded 250.2 mg (71.7%) of the product as a off red solid, m.p.>131° C. (dec.), mass (electrospray, m/e): M+H 349.9.

EXAMPLE 368

3-(3-Cyano-6,7-dimethoxy-quinolin-4-ylamino)-2-methyl-benzoic acid

Using an analogous procedure to that described in EXAMPLE 367, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 196.5 mg (1.3 mmol) of 3-amino-2-methylbenzoic acid to give 89.6 mg (24.7%) of the product as a gray solid, m.p. 242-245° C., mass (electrospray, m/e): M+H 364.0.

EXAMPLE 369

4-(3-Hydroxy-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in EXAMPLE 367, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 10 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 167.0 mg (1.2 mmol) of 5-amino-2-methoxyphenol to give 313.3 mg (89.3%) of the product as a gray solid, m.p. 254-256° C., mass (electrospray, m/e): M+H 351.2.

EXAMPLE 370

4-(3-Chloro-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in EXAMPLE 367, 248.7 mg (1 mmol) of 4-chloro-6,7-

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dimethoxy-3-quinolinecarbonitrile in 10 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 170.0 mg (1.2 mmol) of 2-chloro-4-amino-toluene to give 350.9 mg (99.4%) of the product as a yellow solid, m.p.>250° C., mass (electrospray, m/e): M+H 353.9, 355.8.

EXAMPLE 371

6,7-Dimethoxy-4-(4-phenoxy-phenylamino)-quinoline-3-carbonitrile

Using an analogous procedure to that described in EXAMPLE 367, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 222.3 mg (1.2 mmol) of 4-phenoxyaniline to give 283.0 mg (71.3%) of the product as a light yellow solid, m.p. 239-241° C., mass (electrospray, m/e): M+H 397.9.

EXAMPLE 372

4-(5-Chloro-2-methoxyphenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

Using an analogous procedure to that described in EXAMPLE 367, 248.7 mg (1 mmol) of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile in 12 mL of 2-ethoxyethanol and in the presence of 115.6 mg (1 mmol) of pyridine hydrochloride was reacted with 189.1 mg (1.2 mmol) of 5-chloro-o-anisidine to give 240.5 mg (65.0%) of the product as a cream solid, m.p. 200-202° C., mass (electrospray, m/e): M+H 369.9, 371.8.

EXAMPLE 373

4-(4-Chloro-2-fluoro-phenylamino)-6,7-dihydroxy-quinoline-3-carbonitrile

A mixture of 0.358 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile and 3 g of pyridine hydrochloride was stirred under nitrogen at 210-220° C. for 20 minutes. The mixture was cooled and added to 50 ml of 3% ammonium hydroxide solution. The product was collected, washed with water, and dried to give 0.302 g of 4-(4-chloro-2-fluoro-phenylamino)-6,7-dihydroxy-quinoline-3-carbonitrile as a solid, mp 270-272° C.: mass spectrum (EI, m/e): M 329.0363.

EXAMPLE 374

4-(3-Hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.123 g of 3-amino-o-cresol, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.174 g of 4-(3-hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 255-257° C.; mass spectrum (electrospray, m/e): M+H 335.9.

EXAMPLE 375

4-(3-Chloro-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.158 g of 3-chloro-p-anisidine, 20

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mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.324 g of 4-(3-chloro-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile as a solid, mp 278-280° C.; mass spectrum (EI, m/e): M 369.0860.

EXAMPLE 376

6,7-Dimethoxy-4-(4-trifluoromethyl-phenylamino)-quinoline-3-carbonitrile

A mixture of 0.249 g of 4-chloro-6,7-dimethoxy-3-quinolinecarbonitrile, 0.322 g of 4-(trifluoromethyl)aniline, 20 mg of pyridine hydrochloride, and 10 ml of ethoxyethanol was stirred under nitrogen, at reflux temperature for 30 minutes. The mixture was cooled and added to 40 ml of water. To this mixture was added sodium carbonate and concentrated hydrogen chloride to adjust pH to 7. The product was collected, washed with water, and dried to give 0.268 g of 6,7-dimethoxy-4-(4-trifluoromethyl-phenylamino)-quinoline-3-carbonitrile as a solid, mp 116-118° C.; mass spectrum (EI, m/e): M 373.1031.

EXAMPLE 377

4-(3,4-Dibromophenylamino)-6-nitroquinoline-3-carbonitrile

A mixture of 6.20 g (26.6 mmol) of 4-chloro-6-nitroquinoline-3-carbonitrile and 8.00 g (31.9 mmol) of 3,4-dibromoaniline in 160 mL of EtOH was refluxed under N₂ for 5 hr. Satd NaHCO₃ was added and volatile material was removed. The residue was slurried with hexane, collected, washed with hexane and H₂O and dried. The insoluble material was repeatedly extracted with boiling EtOAc and the solution was then filtered through silica gel. The solvent was removed to give 3.80 g of 4-(3,4-dibromophenylamino)-6-nitroquinoline-3-carbonitrile as a green solid; mass spectrum (electrospray, m/e): M+H 448.9.

EXAMPLE 378

6-Amino-4-(3-trifluoromethylphenylamino)quinoline-3-carbonitrile

A mixture of 6.0 g (16.8 mmol) of 6-nitro-4-(3-trifluoromethylphenylamino)quinoline-3-carbonitrile and 18.9 g (83.8 mmol) of SnCl₄·2H₂O in 240 mL of EtOH was refluxed under N₂ for 1 hr. Ice water was added followed by NaHCO₃ to pH 8. The mixture was stirred for 2 hr and then extracted with CHCl₃. Darco was added and the extracts were filtered through anhyd MgSO₄ and evaporated. The residue was filtered through silica gel with 10% MeOH in CHCl₃. Solvent evaporation and drying in vacuo (40° C.) gave 4.87 g of 6-amino-4-(3-trifluoromethylphenylamino)quinoline-3-carbonitrile as a brown solid; mass spectrum (electrospray, m/e): M+H 329.1.

EXAMPLE 379

6-Amino-4-(3,4-dibromophenylamino)quinoline-3-carbonitrile

Prepared from 4.90 g of 4-(3,4-dibromophenylamino)-6-nitroquinoline-3-carbonitrile and 12.4 g of SnCl₄·2H₂O in the same manner as EXAMPLE 378. There was obtained

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1.25 g of 6-amino-4-(3,4-dibromophenylamino)quinoline-3-carbonitrile as a brown solid; mass spectrum (electrospray, m/e): M+H 416.9, 418.9.

EXAMPLE 380

N-[3-Cyano-4-(3,4-dibromophenylamino)quinolin-6-yl]acrylamide

6-Amino-4-(3,4-dibromophenylamino)quinoline-3-carbonitrile (0.750 g, 1.79 mmol) in 10 mL of THF was treated with 0.217 g (2.15 mmol) of Et₃N and 0.195 g (2.15 mmol) of acryloyl chloride at 0° C. under N₂. After stirring overnight at 25° C., the solvent was evaporated and the residue was slurried with water and collected. The residue was boiled twice with EtOAc and then dried in vacuo (50° C.) to give 0.609 g of N-[3-cyano-4-(3,4-dibromophenylamino)quinolin-6-yl]acrylamide as a brown solid; mass spectrum (electrospray, m/e): 470.9, 472.9.

EXAMPLE 381

N-[4-(3-Bromophenylamino)-3-cyanoquinolin-6-yl]propionamide

Prepared from 1.00 g of 6-amino-4-(3-bromophenylamino)quinoline-3-carbonitrile, 0.359 g of Et₃N and 0.328 g of propionyl chloride in the same manner as EXAMPLE 380. The yield of N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]propionamide was 0.722 g as a yellow solid; mass spectrum (electrospray, m/e): M+H 395.1, 397.0.

EXAMPLE 382

(E)-But-2-enoic Acid [4-(3-Bromophenylamino)-3-cyanoquinolin-6-yl]amide

A solution of 0.637 g (7.40 mmol) of E-but-2-enoic acid in 25 mL of THF under N₂ was chilled in ice. Isobutyl chloroformate (1.01 g, 7.40 mmol) and N-methylmorpholine (0.747 g, 7.40 mmol) were added and the solution was stirred cold for 10 min. A slurry of 1.00 g (2.96 mmol) of 6-amino-4-(3-bromophenylamino)quinoline-3-carbonitrile in 15 mL of THF was added and the mixture was stirred at 25° C. overnight. The mixture was evaporated and the residue was slurried in water, collected and dried. The residue was boiled twice with EtOAc and dried in vacuo (50° C.) to give 0.965 g of (E)-but-2-enoic acid [4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]amide as a yellow solid; mass spectrum (electrospray, m/e): M+H 406.9, 408.9.

EXAMPLE 383

N-[4-(3-Bromophenylamino)-3-cyanoquinolin-6-yl]-2-methylacrylamide

Prepared from 0.500 g of 6-amino-4-(3-bromophenylamino)quinoline-3-carbonitrile, 0.194 g of Et₃N and 0.202 g of methacryloyl chloride in the same manner as EXAMPLE 380. There was obtained 0.317 g of N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]-2-methylacrylamide as a yellow solid; mass spectrum (electrospray, m/e): M+H 406.8, 408.8.

EXAMPLE 384

4-(3-Fluorophenylamino)-6-nitroquinoline-3-carbonitrile

Prepared from 5.00 g of 4-chloro-6-nitroquinoline-3-carbonitrile and 2.86 g of 3-fluoroaniline in the same manner

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as EXAMPLE 377. The crude product was dissolved in a large volume of EtOAc, treated with Darco and filtered through Celite. Solvent removal and drying in vacuo (50° C.) gave 5.77 g of 4-(3-fluorophenylamino)-6-nitroquinoline-3-carbonitrile as a yellow-orange solid: mass spectrum (electrospray, m/e): M+H 309.2

EXAMPLE 385

6-Amino-4-(3-fluorophenylamino)quinoline-3-carbonitrile

Prepared from 5.04 g of 4-(3-fluorophenylamino)-6-nitroquinoline-3-carbonitrile and 18.5 g of SnCl₄·2H₂O in the same manner as EXAMPLE 378. Filtration through silica was unnecessary. There was obtained 4.30 g of 6-amino-4-(3-fluorophenylamino)quinoline-3-carbonitrile as yellow-brown crystals: mass spectrum (electrospray, m/e): M+H 279.1.

EXAMPLE 386

4-(3-Dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile

Prepared from 5.00 g of 4-chloro-6-nitroquinoline-3-carbonitrile, 5.38 g of 3-dimethylaminoaniline dihydrochloride and 5.17 g of triethylamine in the same manner as EXAMPLE 377. The crude product was taken up in EtOAc, treated with Darco, filtered through Celite, evaporated and dried in vacuo (50° C.). The yield of 4-(3-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile was 5.62 g as brick red crystals: mass spectrum (electrospray, m/e): M+H 334.2.

EXAMPLE 387

4-(4-Dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile

Prepared from 5.00 g of 4-chloro-6-nitroquinoline-3-carbonitrile, 5.38 g of 4-dimethylaminoaniline dihydrochloride and 5.17 g of triethylamine in the same manner as EXAMPLE 386. The yield of 4-(4-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile was 5.58 g as brick red crystals: mass spectrum (electrospray, m/e): M+H 334.2.

EXAMPLE 388

6-Amino-4-(3-dimethylaminophenylamino)quinoline-3-carbonitrile

A mixture of 5.00 g (15.0 mmol) of 4-(3-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile, 1.20 g (37.5 mmol) of anhyd hydrazine and 0.5 g of 10% Pd/C in 250 mL of EtOH was refluxed under N₂ for 1.3 hr. The reaction was filtered through Celite, the Celite was washed with EtOH and the filtrate and washes were combined. Solvent evaporation and drying in vacuo (50° C.) gave 6-amino-4-(3-dimethylaminophenylamino)quinoline-3-carbonitrile as a red brown solid: mass spectrum (electrospray, m/e): 303.9.

EXAMPLE 389

6-Amino-4-(4-dimethylaminophenylamino)quinoline-3-carbonitrile

Prepared from 4-(4-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile (5.00 g), 1.20 g of anhyd

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hydrazine and 0.500 g of 10% Pd/C in the same manner as EXAMPLE 388 155179. After washing first with MeOH (discarded), the product was eluted with DMF. The latter solvent was collected separately, evaporated and the residue was dried in vacuo (50° C.). The yield of 6-amino-4-(4-dimethylaminophenylamino)quinoline-3-carbonitrile was 4.00 g as a yellow solid: mass spectrum (electrospray, m/e): M+H 303.9.

EXAMPLE 390

But-2-ynoic Acid [4-(3-Fluorophenylamino)-3-cyanoquinolin-6-yl]amide

Prepared from 0.756 g of but-2-ynoic acid, 1.23 g of isobutyl chloroformate, 0.908 g of N-methylmorpholine and 1.00 g of 6-amino-4-(3-fluorophenylamino)quinoline-3-carbonitrile in the same manner as EXAMPLE 382. The yield of but-2-ynoic acid [4-(3-fluorophenylamino)-3-cyanoquinolin-6-yl]amide was 1.07 g as a yellow solid: mass spectrum (electrospray, m/e): 345.1.

EXAMPLE 391

N-[3-Cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]acrylamide

Prepared from 1.00 g of 6-amino-4-(3-dimethylaminophenylamino)quinoline-3-carbonitrile, 0.400 g of triethylamine and 0.360 g of acryloyl chloride in the same manner as EXAMPLE 88. The yield of N-[3-cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]acrylamide was 0.880 g as an orange solid: mass spectrum (electrospray, m/e): 358.1.

EXAMPLE 392

N-[3-Cyano-4-(4-dimethylaminophenylamino)quinolin-6-yl]acrylamide

Prepared from 1.00 g of 6-amino-4-(4-dimethylaminophenylamino)quinoline-3-carbonitrile, 0.400 g of triethylamine and 0.360 g of acryloyl chloride in the same manner as EXAMPLE 380. The yield of N-[3-cyano-4-(4-dimethylaminophenylamino)quinolin-6-yl]acrylamide was 0.990 g of brown-orange solid: mass spectrum (electrospray, m/e): 358.2.

EXAMPLE 393

But-2-ynoic Acid [3-Cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]amide

Prepared from 0.694 g of but-2-ynoic acid, 1.13 g of isobutyl chloroformate, 0.833 g of N-methylmorpholine and 1.00 g of 6-amino-4-(3-dimethylaminophenylamino)quinoline-3-carbonitrile in the same manner as EXAMPLE 382. The yield of but-2-ynoic acid [3-cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]amide was 0.967 g as an orange solid: mass spectrum (electrospray, m/e): M+H 370.2.

EXAMPLE 394

But-2-ynoic Acid [3-Cyano-4-(4-dimethylaminophenylamino)quinolin-6-yl]amide

Prepared from 0.694 g of but-2-ynoic acid, 1.13 g of isobutyl chloroformate, 0.833 g of N-methylmorpholine and 1.00 g of 4-(4-dimethylaminophenylamino)quinoline-3-

carbonitrile in the same manner as EXAMPLE 382. The yield of but-2-ynoic acid [3-cyano-4-(4-dimethylaminophenylamino)quinolin-6-yl]amide was 1.13 g as a brick red solid: mass spectrum (electrospray, m/e): M+H 370.2.

EXAMPLE 395

4-(3-Bromophenylamino)-6-dimethylaminoquinoline-3-carbonitrile Hydrochloride

Prepared from 0.400 g of 4-chloro-6-dimethylaminoquinoline-3-carbonitrile and 3-bromoaniline in the same manner as EXAMPLE 377. The crude product was boiled twice with EtOAc and dried in vacuo (50° C.). The yield of 4-(3-bromophenylamino)-6-dimethylaminoquinoline-3-carbonitrile hydrochloride was 0.621 g as a brown powder: mass spectrum (electrospray, m/e) M+H 366, 368.9.

EXAMPLE 396

6-Dimethylamino-4-(3-methoxyphenylamino)quinoline-3-carbonitrile Hydrochloride

Prepared from 0.400 g of 4-chloro-6-dimethylaminoquinoline-3-carbonitrile and 0.256 g of 3-methoxyaniline in the same manner as EXAMPLE 395. The yield of 6-dimethylamino-4-(3-methoxyphenylamino)quinoline-3-carbonitrile was 0.532 g of brown powder: mass spectrum (electrospray, m/e): M+H 318.9.

EXAMPLE 397

2-Bromo-N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]acetamide

Prepared from 1.50 g of 6-amino-4-(3-bromophenylamino)quinoline-3-carbonitrile, 0.538 g of triethylamine and 1.08 g of bromoacetyl bromide in the same manner as EXAMPLE 380. The yield of 2-bromo-N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]acetamide was 1.55 g as a yellow-brown solid: mass spectrum (electrospray, m/e): M+H 458.9, 460.9.

EXAMPLE 398

6-Iodo-4-(3-methoxyphenylamino)quinoline-3-carbonitrile

Prepared from 1.00 g of 4-chloro-6-iodoquinoline-3-carbonitrile and 0.469 g of 3-methoxyaniline in the same manner as EXAMPLE 377. The crude product was filtered through silica gel with 20% EtOAc in CH₂Cl₂, evaporated and dried in vacuo (50° C.). The yield of 6-iodo-4-(3-methoxyphenylamino)quinoline-3-carbonitrile was 1.09 g as yellow crystals: mass spectrum (electrospray, m/e): M+H 401.9.

EXAMPLE 399

4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

5-Methoxy-2-methyl-4-nitroacetanilide

A solution of 182.1 g (1.0 mol) of 5-methoxy-2-methyl-4-nitroaniline in 400 ml acetic acid was heated to reflux. To the hot solution was added 320 ml of acetic anhydride. The mixture was refluxed for 1/2 hr and then poured onto ice.

The solid was collected and washed twice with water and once with conc. NH₄OH (this step converts any di-acetate to mono-acetate). The solid is then air dried. The solid is dissolved in 1400 ml of boiling chloroform, treated with MgSO₄ and Norite, and filtered while hot. The filtrate was boiled and 500 ml of hexanes were added. The mixture was cooled in an ice bath. Solid was collected giving 145.9 g (65%) of the product as an orange solid.

5-Ethoxy-2-methyl-4-nitroacetanilide

A mixture of 186 g (830 mmol) of 5-methoxy-2-methyl-4-nitroacetanilide and 105.5 g (2.49 mol) of LiCl in 1115 ml of DMF was mechanically stirred at reflux for 12 hr without using a condenser. The dark orange solution was allowed to cool to room temperature and then allowed to stand overnight. To the stirring solution was added 114.65 g (830 mmol) of powdered K₂CO₃ and 265.4 ml (3.32 mol) of ethyl iodide. The mixture was slowly heated with stirring. At about 70° C a rapid gas evolution ensues (probably ethyl chloride). After most gas has evolved, heating is continued to reflux temperature. The mixture is refluxed for 5 hr and then poured onto ice water. The solid is collected, washed several times with water, and air dried. The solid is dissolved in 2 L of boiling chloroform, treated with MgSO₄, and filtered while hot. The filtrate is boiled and diluted with 1.5 L hexanes. The mixture is cooled and solid is collected giving 105 g of a yellow solid (53%).

2-Acetylmino-4-ethoxy-5-nitro-benzoic acid

A solution of 217.3 g of potassium permanganate and 75.23 g of magnesium sulfate in 5000 ml of water was heated to 80° C. Then 119 g (0.5 moles) of 5-ethoxy-2-methyl-4-nitroacetanilide was added in one portion. Heating at reflux was continued. After about 45 minutes (the disappearance of the permanganate color) an additional 37.62 g of magnesium sulfate and then 108.65 g of potassium permanganate were added. After about 45 minutes of additional reflux (the disappearance of the permanganate color) the reaction was filtered hot. The manganese dioxide cake was reserved. Acidification of the filtrate with concentrated hydrochloric acid gave product. The reserved manganese dioxide was boiled with 2000 ml of water, and filtered. Acidification of the filtrate gave additional product. The products were combined and dried to give 68.19 g (50.8%) of the desired product. Starting material could be extracted from the manganese dioxide cake with acetone.

3-Ethoxy-4-nitroaniline

To 600 ml of H₂O was slowly added 400 ml conc. H₂SO₄. To the hot mixture was added 118.5 g (0.44 mol) of 2-acetylmino-4-ethoxy-5-nitro-benzoic acid. The mixture was heated to 110-112° C. with stirring. Initially there was a vigorous gas evolution. After 1 hr., the mixture was poured onto ice. The mixture was made basic with conc. ammonium hydroxide (an exothermic reaction ensued). The mixture was allowed to cool to room temperature and the solid was collected by filtration. The solid was washed several times with 500 ml portions of water and then dried in vacuum and then extracted several times with warm ethyl acetate. The extracts were filtered and solvent was removed giving 57.8 g (71%) of the product.

2-(2-Cyano-2-ethoxycarbonyl-vinylamino)-4-ethoxy-5-nitro-benzoic Acid

A mixture of 58.96 g (0.324 moles) of 3-ethoxy-4-nitroaniline and 77.22 g (0.456 moles) of ethyl (ethoxymethylene) cyano acetate in 210 ml of toluene was refluxed for about 16 hours (overnight). The reaction was cooled in an ice bath, and the product was filtered. It was washed with three portions of ether, then dried to give 94.33 g (95.8%) of the desired product. This can be recrystallized in about 80% yield from methyl cellosolve.

7-Ethoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile

The yellow starting material 2-(2-cyano-2-ethoxycarbonyl-vinylamino)-4-ethoxy-5-nitro-benzoic acid (37.5 g, 0.123 mol), which had been recrystallized from 2-methoxyethanol, was added as a solid to 2.5L of refluxing (256° C.) Dowtherm in a 5L three-necked flask equipped with a mechanical stirrer and a thermometer under nitrogen. The reaction mixture was stirred vigorously at this temperature for 1.25 hrs, and then allowed to cool to room temperature. The thick reaction mixture was diluted with 2L of ether, filtered and washed with ether to yield 24.2 g of the cyclized product 7-ethoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile as an off-white solid with a yield of 76%.

The filtrate was evaporated to remove ether and then treated with hexane. The resulting yellow precipitate was collected and washed with hexane to yield 10-15% unreacted starting material, which could be recycled to generate more cyclized product. The resulting filtrate was evaporated to remove hexane and then passed through a thin pad of silica gel to remove colored impurities to regenerate the Dowtherm for more cyclization reactions.

4-Chloro-7-ethoxy-6-nitro-quinoline-3-carbonitrile

In a 1L round-bottomed flask, the nitro compound 7-ethoxy-4-hydroxy-6-nitro-quinoline-3-carbonitrile (20 g, 77 mmol) was refluxed with 120 ml of phosphorus oxychloride under nitrogen for 2.5 hrs. TLC (ethyl acetate: hexane=1:1) showed no starting material left. The volatile reagents were removed by rotary evaporation and further azeotropically removed with toluene at 50° C. The flask containing the solid residue was cooled in an ice bath, and 600 ml of methylene chloride was added to dissolve the residue. The resulting cold methylene chloride solution was added into a vigorously stirred solution of 250 ml ice-cold saturated potassium carbonate solution (53.3 g, 5 eq) and stirred for 30 min. The organic layer was separated, washed and dried to give 18.58 g of 4-chloro-7-ethoxy-6-nitro-quinoline-3-carbonitrile with a yield of 86.9%.

4-(3-Chloro-4-fluoro-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile

4-Chloro-7-ethoxy-6-nitro-quinoline-3-carbonitrile (26.8 g 96.5 mmol) and 3-chloro-4-fluoroaniline 14.05 g 96.5 mmol) in 900 ml of iso-propanol were refluxed under N₂ for 3.5 hrs. TLC (ethyl acetate: hexane=1:1) showed no starting material left. After standing at room temperature overnight, the hydrochloride salt was filtered off and washed with isopropanol and ether giving 4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile 38.6 g (95%) as a yellow hydrochloride salt.

6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile

4-(3-Chloro-4-fluoro-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile hydrochloride (38.6 g 91.2 mmol) was mixed with 35.7 g (638 mmol) of iron powder. A solution of 43.9 g (820 mmol) of ammonium chloride in 280 ml of water was added followed by 985 ml of methanol. The mixture was reflux with mechanical stirring under nitrogen for 4 hr at which time TLC indicated complete reduction. The reaction mixture was filtered hot and solids were washed with 500 ml of boiling methanol. After the combined filtrate was evaporated, the residue was partitioned between 1.5L of warm ethyl acetate and 700 ml of saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, treated with Norita, filtered and evaporated to give a solid which was recrystallized from CHCl₃-hexanes giving 29.0 g (89%) of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile as a light green solid.

4-Bromo-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-quinolin-6-yl]-amide

To 14.98 g (63.17 mmol) of trimethylsilyl 4-bromo-2-butenolate (prep.: *Synthesis* 745 1983) in 36 ml of methylene chloride, was added 8.82 g (69.5 mmol) of oxalyl chloride, followed by 1 drop of dried DMR. After the solution was stirred for 2 hr, the solvent was evaporated, and further azeotropically distilled with carbonyl tetrachloride to yield the acid chloride. 6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile (19.6 g, 54.9 mmol) was mixed with 11.46 ml (65.91 mmol) of N,N-diisopropylethylamine in 366 ml of anhydrous THF under nitrogen in an ice bath. A solution of the acid chloride prepared above in 183 ml of THF was added over 15 minutes, and then stirred for half an hour at 0° C. The reaction vessel was sealed and stored in the freezer overnight. The reaction solution was rotary evaporated and the residue was partitioned between saturated sodium bicarbonate and ethyl acetate. The organic layer was separated, washed, dried with magnesium sulfate and passed through a thin layer of silica gel to give 32 g of the crude product as an orange solid. The crude product was refluxed with 400 ml of methanol for half an hour. After cooling to room temperature, the solid was collected and washed with methanol followed by hexane to give 21.3 g of beige solid with a yield of 76.5%. It is a mixture of the bromo and chloro compounds. More product could be isolated from the mother liquor.

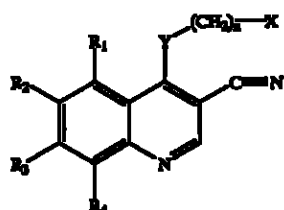
4-Dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide

The bromo/chloro compounds (19.88 g, 39.53 mmol) were dissolved in 800 ml of THF at 0° C. and 2 equivalent of 2M dimethylamine (39.54 ml, 79.07 mmol) in THF was added in one portion. The reaction solution was stirred at room temperature overnight. Another equivalent of dimethylamine was added. After stirring overnight at room temperature, only 10% of chloro compound was unreacted. The reaction solution was rotary evaporated and the residue was partitioned between ethyl acetate and saturated potassium bicarbonate. The organic layer was dried, filtered and evaporated to give 17 g of orange glass. The crude product was taken up in acetone and purified by column chromatography using acetone as the eluant. The main fractions were pooled and evaporated to give 9.8 g of a yellow glass. It was then dissolved in 350 ml of hot ethyl acetate and evaporated to a concentrated solution. A few drops of methanol was added to assist recrystallization. After standing at room temperature overnight, the beige crystals were filtered to yield 7.09 g of pure 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide (mp 196-198° C.) with a yield of 38.7%. A lot of product remained in the mother liquors in the steps of chromatography and recrystallization, and could be isolated. The expected yield is about 60%.

We claim:

1. A method of treating or inhibiting colonic polyps in a mammal susceptible to the formation of colonic polyps which comprises providing to said mammal an effective amount of a compound of the formula

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wherein:

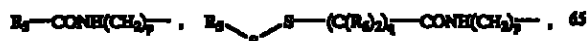
X is cycloalkyl of 3 to 7 carbon atoms, which may be optionally substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a pyridinyl, pyrimidinyl, or phenyl ring; wherein the pyridinyl, pyrimidinyl, or phenyl ring may be optionally mono-, di-, or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxyethyl of 2-7 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, and benzoylamino;

n is 0-1;

Y is $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, or $-\text{NR}-$;

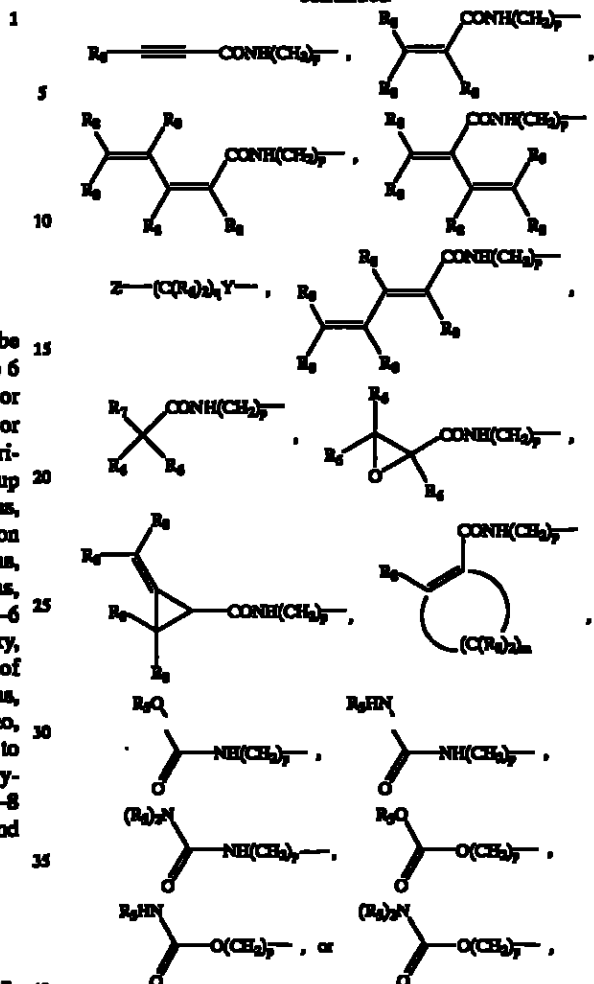
R is alkyl of 1-6 carbon atoms;

R_1 , R_2 , R_3 , and R_4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, halomethyl, alkanoyloxy of 1-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxyethyl of 2-7 carbon atoms, alkenoyloxyethyl of 4-9 carbon atoms, alkynoyloxyethyl of 4-9 carbon atoms, alkoxyethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, aminoalkyl of 1-4 carbon atoms, N-alkylaminoalkyl of 2-7 carbon atoms, N,N-dialkylaminoalkyl of 3-14 carbon atoms, phenylamino, benzylamino,



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-continued



R_5 is alkyl of 1-6 carbon atoms, alkyl optionally substituted with one or more halogen atoms, phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, nitro, cyano, or alkyl of 1-6 carbon atoms groups;

R_6 is hydrogen, alkyl of 1-6 carbon atoms, or alkenyl of 2-6 carbon atoms;

R_7 is chloro or bromo

R_8 is hydrogen, alkyl of 1-6 carbon atoms, aminoalkyl of 1-6 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-12 carbon atoms, N-cycloalkylaminoalkyl of 4-12 carbon atoms, N-cycloalkyl-N-alkylaminoalkyl of 5-18 carbon atoms, N,N-dicycloalkylaminoalkyl of 7-18 carbon atoms, morpholino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, piperidino-N-alkyl wherein the alkyl group is 1-6 carbon atoms, N-alkyl-piperidino-N-alkyl wherein either alkyl group is 1-6 carbon atoms, azacycloalkyl-N-alkyl of 3-11 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-8 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms, chloro, fluoro, or bromo;

Z is amino, hydroxy, alkoxy of 1-6 carbon atoms, alkylamino wherein the alkyl moiety is of 1-6 carbon

atoms, dialkylamino wherein each of the alkyl moieties is of 1-6 carbon atoms, morpholino, piperazino, N-alkylpiperazino wherein the alkyl moiety is of 1-6 carbon atoms, or pyrrolidino;

m=1-4, q=1-3, and p=0-3;

any of the substituents R_1 , R_2 , R_3 , or R_4 that are located on contiguous carbon atoms can together be the divalent radical $-O-C(R_5)_2-O-$;

or a pharmaceutically acceptable salt thereof with the proviso that when Y is $-NH-$, R_1 , R_2 , R_3 , and R_4 are hydrogen, and n is 0, X is not 2-methylphenyl.

2. The method according to claim 1 wherein Y is $-NH-$ and n=0 or a pharmaceutically acceptable salt thereof.

3. The method according to claim 2 wherein X is optionally substituted phenyl or a pharmaceutically acceptable salt thereof.

4. The method according to claim 3 wherein R_1 and R_4 are hydrogen or a pharmaceutically acceptable salt thereof.

5. The method according to claim 1 in which 4-[(3-bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile or a pharmaceutically acceptable salt thereof is provided.

6. The method according to claim 1 in which 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluorophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

7. The method according to claim 1 in which 4-diethylamino-but-2-enoic acid [4-(3-chloro-4-fluorophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

8. The method according to claim 1 in which 4-dimethylamino-but-2-enoic acid [4-(3-bromo-4-fluorophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

9. The method according to claim 1 in which 4-dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

10. The method according to claim 1 in which 4-diethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

11. The method according to claim 1 in which 4-morpholin-4-yl-but-2-enoic acid [4-(3-chloro-4-fluorophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

12. The method according to claim 1 in which 4-dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

13. The method according to claim 1 in which N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-4-methoxy-2-butanamide or a pharmaceutically acceptable salt thereof is provided.

14. The method according to claim 1 in which N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butanamide or a pharmaceutically acceptable salt thereof is provided.

15. The method according to claim 1 in which 4-dimethylamino-but-2-enoic acid [4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide or a pharmaceutically acceptable salt thereof is provided.

16. The method according to claim 1 in which

a) 4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile;

b) 4-[(3-bromophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile;

c) 6-amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile;

d) N-[4-[(3-bromophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-2-butanamide;

e) N-[4-[(3-bromophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-2-propenamide;

f) 4-[(3-bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile;

g) 6-amino-4-[(3-bromophenyl)amino]-3-quinolinecarbonitrile;

h) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-2-butanamide;

i) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]acetamide;

j) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]butanamide;

k) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-2-propenamide;

l) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-2-chloroacetamide;

m) 4-[(3,4-dibromophenyl)amino]-6-nitro-3-quinolinecarbonitrile;

n) 6-amino-4-[(3,4-dibromophenyl)amino]-3-quinolinecarbonitrile;

o) N-[4-[(3,4-dibromophenyl)amino]-3-cyano-6-quinolinyl]-2-butanamide;

p) 6-nitro-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile;

q) 6-amino-4-[(3-trifluoromethylphenyl)amino]-3-quinolinecarbonitrile;

r) N-[4-[(3-trifluoromethylphenyl)amino]-3-cyano-6-quinolinyl]-2-butanamide;

s) 4-[(3-bromophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

t) 4-[(3-fluorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

u) 4-(cyclohexylamino)-6,7-dimethoxy-3-quinolinecarbonitrile;

v) 4-[(3-bromophenyl)amino]-6,7-dihydroxy-3-quinolinecarbonitrile;

w) 8-[(3-bromophenyl)amino]-[1,3]-dioxolo[4,5-g]quinoline-7-carbonitrile;

x) 4-[(3-chlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

y) 4-[(3-trifluoromethylphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

z) 4-[(3,4-dimethoxyphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

aa) 4-[(methylphenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

bb) 4-[(3-cyanophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

cc) 4-[(4-fluorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

dd) 4-[(3-(hydroxymethyl)phenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;

ee) 4-(3-bromophenoxy)-6,7-dimethoxy-3-quinolinecarbonitrile;

ff) 4-[(4-bromophenyl)sulfanyl]-6,7-dimethoxy-3-quinolinecarbonitrile;

gg) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-3(E)-chloro-2-propenamide;

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- hh) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-3(Z)-chloro-2-propenamide;
ii) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-2-methyl-2-propenamide;
jj) N-[4-[(3,4-dibromophenyl)amino]-3-cyano-6-quinoliny]-2-propenamide;
kk) N-[4-[(5-bromo-3-pyridinyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile;
ll) 4-[(3-bromophenyl)amino]-6,7-bis(methoxymethoxy)-3-quinolinecarbonitrile;
mm) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-4-hydroxy-2-butyramide;
nn) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-4-morpholino-2-butyramide;
oo) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-4-dimethylamino-2-butyramide;
pp) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinoliny]-4-methoxy-2-butyramide;
qq) 4-(3-bromophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
rr) 4-(3-phenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
ss) 4-(3,4-dimethoxyphenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
tt) 4-(3,4-dichlorophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
uu) 4-methoxy-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide;
vv) 4-(4-chloro-2-fluoro-phenylamino)-7-(3-chloro-propoxy)-6-methoxy-quinoline-3-carbonitrile;
ww) 4-(4-chloro-2-fluoro-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile;
xx) 7-(2-dimethylamino-ethoxy)-4-(3-hydroxy-4-methylphenylamino)-6-methoxy-quinoline-3-carbonitrile;
yy) 4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-7-(2-morpholin-4-yl-ethoxy)-quinoline-3-carbonitrile; or
zz) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(3-dimethylamino-propoxy)-6-methoxy-quinoline-3-carbonitrile;
or a pharmaceutically acceptable salt thereof is provided.
17. The method according to claim 1 in which
a) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile;
b) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-(2-dimethylamino-ethoxy)-6-methoxy-quinoline-3-carbonitrile;
c) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-7-(2-morpholin-4-yl-ethoxy)-quinoline-3-carbonitrile;
d) N-[3-cyano-4-(3-fluorophenylamino)quinolin-6-yl]acrylamide;
e) 6,7-dimethoxy-4-(3-nitrophenylamino)quinoline-3-carbonitrile;
f) 4-(3-bromophenylamino)-6-ethoxy-7-methoxyquinoline-3-carbonitrile;
g) 6-ethoxy-4-(3-hydroxy-4-methylphenylamino)-7-methoxyquinoline-3-carbonitrile;
h) 4-dimethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide;
i) 4-diethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide;

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- j) 4-methylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-quinolin-6-yl]-amide;
k) 4-[(3-bromophenyl)amino]-8-methyl-6-nitro-3-quinolinecarbonitrile;
l) 4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-6-nitro-3-quinolinecarbonitrile;
m) 6-amino-4-[(3-bromophenyl)amino]-8-dimethylaminomethyl-3-quinolinecarbonitrile;
n) N-[4-[(3-bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinoliny]-2-butyramide;
o) N-[4-[(3-bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinoliny]-2-propenamide;
p) N-[4-[(3-bromophenyl)amino]-3-cyano-8-dimethylaminomethyl-6-quinoliny]acetamide;
q) 4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-(morpholinopropoxy)-3-quinolinecarbonitrile;
r) 4-[(3-bromophenyl)amino]-7-methoxy-6-(morpholinopropoxy)-3-quinolinecarbonitrile;
s) 4-[(4-chloro-2-fluorophenyl)amino]-7-methoxy-6-(morpholinopropoxy)-3-quinolinecarbonitrile;
t) 4-[(3-hydroxy-4-methylphenyl)amino]-7-methoxy-6-(morpholinopropoxy)-3-quinolinecarbonitrile;
u) N-[3-cyano-4-[(3-iodophenyl)amino]-6-quinoliny]-2-propenamide;
v) 6-amino-4-[(3-iodophenyl)amino]-3-quinolinecarbonitrile;
w) 4-[(3-iodophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
x) N-[3-cyano-4-[(3-methylphenyl)amino]-6-quinoliny]-2-butyramide;
y) 6-amino-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile;
z) 6-nitro-4-[(3-methylphenyl)amino]-3-quinolinecarbonitrile;
aa) N-[4-[(3-chlorophenyl)amino]-3-cyano-6-quinoliny]-2-propenamide;
bb) 6-amino-4-[(3-chlorophenyl)amino]-3-quinolinecarbonitrile;
cc) 4-[(3-chlorophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
dd) N-[3-cyano-4-[(3-methoxyphenyl)amino]-6-quinoliny]-2-propenamide;
ee) N-[3-cyano-4-[(3-methoxyphenyl)amino]-6-quinoliny]-2-butyramide;
ff) N-[3-cyano-4-[(3-methoxyphenyl)amino]-6-quinoliny]-4-piperidino-2-butyramide;
gg) 6-amino-4-[(3-methoxyphenyl)amino]-3-quinolinecarbonitrile;
hh) 4-[(3-methoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile;
ii) N-[4-[(3-chloro-4-fluoro-phenyl)amino]-3-cyano-6-quinoliny]-2-butyramide;
jj) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinoliny]-2-propenamide;
kk) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinoliny]-4-diethylamino-2-butenamide;
ll) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinoliny]-4-morpholino-2-butenamide;
mm) N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinoliny]-2-morpholin-4-ylmethyl-2-propenamide;
nn) 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-3-quinolinecarbonitrile;

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- oo) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- pp) N-{4-[(4-bromophenyl)amino]-3-cyano-6-quinolinyl}-2-propenamide;
- qq) 6-amino-4-[(4-bromophenyl)amino]-3-quinolinecarbonitrile;
- rr) [(4-bromophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- ss) N-{3-cyano-4-[(3,4-difluorophenyl)amino]-6-quinolinyl}-2-propenamide;
- tt) 6-amino-4-[(3,4-difluorophenyl)amino]-3-quinolinecarbonitrile;
- uu) 4-[(3,4-difluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- ww) N-{4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-cyano-6-quinolinyl}-2-butyramide;
- xx) 6-amino-4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-quinolinecarbonitrile;
- yy) 4-[(3-chloro-4-thiophenoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile; or
- zz) N-{3-cyano-4-[(3-cyanophenyl)amino]-6-quinolinyl}-2-propenamide;
- or a pharmaceutically acceptable salt thereof.
18. The method according to claim 1 in which
- a) N-{3-cyano-4-[(3-cyanophenyl)amino]-6-quinolinyl}-4-piperidino-2-butyramide;
- b) 6-amino-4-[(3-cyanophenyl)amino]-3-quinolinecarbonitrile;
- c) 4-[(3-cyanophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- d) N-{3-cyano-4-[(3-ethynylphenyl)amino]-6-quinolinyl}-2-butyramide;
- e) N-{3-cyano-4-[(3-ethynylphenyl)amino]-6-quinolinyl}-2-propenamide;
- f) N-{3-cyano-4-[(3-ethynylphenyl)amino]-6-quinolinyl}-4-piperidino-2-butyramide;
- g) 6-amino-4-[(3-ethynylphenyl)amino]-3-quinolinecarbonitrile;
- h) 4-[(3-ethynylphenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- i) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-piperidino-2-butyramide;
- j) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-dipropylamino-2-butyramide;
- k) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-2-morpholin-4-ylmethyl-2-propenamide;
- l) N-{4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-2-butanamide;
- m) N-{4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-diethylamino-2-butanamide;
- n) N-{4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-morpholino-2-butanamide;
- o) N-{4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl}-4-morpholino-2-butanamide;
- p) 4-[(3-bromophenyl)amino]-7-ethoxy-6-methoxy-3-quinolinecarbonitrile;
- q) 7-ethoxy-4-[(3-hydroxy-4-methylphenyl)amino]-6-methoxy-3-quinolinecarbonitrile;
- r) N-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-(z)-2-butanamide;
- s) N-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-methoxy-(z)-2-butanamide;

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- t) 4-[(4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl)amino]-2-methylene-4-oxo-butanolic acid;
- u) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-diethylamino-2-butyramide;
- v) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-(n-ethylpiperazino)-2-butyramide;
- w) N-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-diethylamino-2-butyramide;
- x) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-(n-methylpiperazino)-2-butyramide;
- y) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-(n-isopropyl-n-methylamino)-2-butyramide;
- z) N-{4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl}-4-diisopropylamino-2-butyramide;
- aa) N-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-2-butyramide;
- bb) N-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-methoxy-2-butyramide;
- cc) 4-[(3-bromo-4-fluorophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
- dd) 6-amino-4-[(3-bromo-4-fluorophenyl)amino]-3-quinolinecarbonitrile;
- ee) N-{4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-6-quinolinyl}-4-dimethylamino-2-butyramide;
- ff) 4-diethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide;
- gg) 4-morpholin-4-yl-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide;
- hh) 4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile;
- ii) 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile;
- jj) 4-(3-bromo-4-fluoro-phenylamino)-7-methoxy-6-nitro-quinoline-3-carbonitrile;
- kk) 6-amino-4-(3-bromo-4-fluoro-phenylamino)-7-methoxy-quinoline-3-carbonitrile;
- ll) 4-diethylamino-but-2-enoic acid [4-(3-bromo-4-fluorophenylamino)-3-cyano-7-methoxy-quinolin-6-yl]-amide;
- mm) 4-(3-bromo-phenylamino)-7-ethoxy-6-nitro-quinoline-3-carbonitrile;
- nn) 6-amino-4-(3-bromo-phenylamino)-7-ethoxy-quinoline-3-carbonitrile;
- oo) 4-bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide;
- pp) 4-morpholin-4-yl-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-amide;
- qq) 6-amino-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
- rr) 6-amino-4-(3-bromo-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
- ss) 4-bromo-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide;
- tt) 4-dimethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide;
- uu) 4-diethylamino-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide;
- vv) 4-morpholin-4-yl-but-2-enoic acid [4-(3-bromophenylamino)-3-cyano-8-methoxy-quinolin-6-yl]-amide;

- ww) 4-dimethylamino-but-2-ynoic acid [4-(3-bromo-phenylamino)-3-cyano-7-methoxy-quinol-6-yl]-amide;
 xx) 4-(4-chloro-2-fluoro-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 yy) 4-(3-hydroxy-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile; or
 zz) 4-(3-dimethylamino-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile;
 or a pharmaceutically acceptable salt thereof is provided.
 19. The method according to claim 1 in which
 a) 4-(3-hydroxy-4-methyl-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile;
 b) 4-(4-chloro-2-fluoro-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile;
 c) 4-(4-chloro-2-fluoro-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile;
 d) 4-(3-hydroxy-4-methyl-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile;
 e) 4-(3-bromo-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile;
 f) 4-(3-bromo-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile;
 g) 4-(3-dimethylamino-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile;
 h) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-5,8-dimethoxy-quinoline-3-carbonitrile;
 i) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6,7,8-trimethoxy-quinoline-3-carbonitrile;
 j) 4-(3-hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 k) 4-(2-hydroxy-6-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 l) 4-(3-bromo-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 m) 4-(3-chloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 n) 6,7-dimethoxy-4-(2-methylsulfanyl-phenylamino)-quinoline-3-carbonitrile;
 o) 1,4-dihydroquinoline-6,7-diethoxy-4-oxo-3-carbonitrile;
 p) 4-[3-chloro-4-(phenylthio)phenylamino]-6,7-diethoxy-3-quinolinecarbonitrile;
 q) 4-[3-chloro-4-(phenylthio)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 r) 4-(3-chloro-4-fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 s) 4-(3-acetylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 t) 4-(n-methylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 u) 4-(phenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 v) 4-(4-fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 w) 4-(4-fluoro-2-methylphenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 x) 4-(3-chlorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 y) 4-(3-fluorophenylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
 z) 4-(3-aminophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile;

- aa) 4-(3-acetamidophenylamino)-6,7-dimethoxy-3-quinolinecarbonitrile;
 bb) 4-[3-(2-butyrylamino)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 cc) 4-[3-(hydroxymethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 dd) 4-[3-(chloromethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 ee) 4-[3-(acetylthiomethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 ff) 4-[3-(thiomethyl)phenylamino]-6,7-dimethoxy-3-quinolinecarbonitrile;
 gg) 4-[(3-bromophenyl)amino]-8-methoxy-3-quinolinecarbonitrile;
 hh) 4-(4-chloro-2-fluoro-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 ii) 4-(3-hydroxy-4-methyl-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 jj) 4-(3-dimethylamino-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 kk) 4-(4-bromo-3-hydroxy-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 ll) 4-(3-hydroxy-4-methoxy-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 mm) 8-methoxy-4-(2,4,6-trifluoro-phenylamino)-quinoline-3-carbonitrile;
 nn) 4-(3-hydroxy-4-methyl-phenylamino)-7-methoxy-quinoline-3-carbonitrile;
 oo) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-methoxy-quinoline-3-carbonitrile;
 pp) 4-(4-chloro-2-fluoro-phenylamino)-6-methoxy-quinoline-3-carbonitrile;
 qq) 4-(3-hydroxy-4-methyl-phenylamino)-6-methoxy-quinoline-3-carbonitrile;
 rr) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-6-methoxy-quinoline-3-carbonitrile;
 ss) 4-(3,5-dichloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 tt) 4-(2-hydroxy-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 uu) 4-(4-hydroxy-3,5-dimethyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 vv) 4-(5-chloro-2-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 ww) 4-(3,5-dibromo-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 xx) 4-(4-hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 yy) 6,7-dimethoxy-4-(pyridin-3-ylamino)-quinoline-3-carbonitrile; or
 zz) 6,7-dimethoxy-4-(3-methylsulfanyl-phenylamino)-quinoline-3-carbonitrile;
 or a pharmaceutically acceptable salt thereof is provided.
 20. The method according to claim 1 in which
 a) 4-(2-hydroxy-5-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 b) 4-(2-chloro-4-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 c) 6,7-dimethoxy-4-(4-methylsulfanyl-phenylamino)-quinoline-3-carbonitrile;
 d) 4-[4-(2-hydroxy-ethyl)-phenylamino]-6,7-dimethoxy-quinoline-3-carbonitrile;

- e) 4-(2,4-dihydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- f) 4-(2-(2-hydroxy-ethyl)-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- g) 4-(3-bromophenylamino)-6,7-dihydroxy-3-quinolinecarbonitrile;
- h) 4-(3-bromophenylamino)-6,7-di-n-propoxy-3-quinolinecarbonitrile;
- i) 4-[(3-bromophenyl)-n-acetylamino]-6,7-dihydroxy-3-quinolinecarbonitrile;
- j) 4-(3-bromophenylamino)-6,7-di-n-butoxy-3-quinolinecarbonitrile;
- k) 4-(4-chloro-2-fluorophenylamino)-7-methoxy-3-quinolinecarbonitrile;
- l) 4-(4-chloro-2-fluorophenylamino)-7-hydroxy-3-quinolinecarbonitrile;
- m) 4-[(4-chloro-2-fluorophenylamino)-n-acetylamino]-7-hydroxy-3-quinolinecarbonitrile;
- n) 4-(4-chloro-2-fluorophenylamino)-7-ethoxy-3-quinolinecarbonitrile;
- o) 4-[(3-bromophenyl)amino]-6,7-bis(2-methoxyethoxy)-3-quinolinecarbonitrile;
- p) 4-(2-aminophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
- q) 4-(3,4-difluorophenylmethylamino)-6,7-diethoxy-3-quinolinecarbonitrile;
- r) 4-methoxy-but-2-enoic acid [4-(3-bromophenylamino)quinazolin-6-yl]-amide;
- s) 7-benzyloxy-4-(4-chloro-2-fluoro-phenylamino)-6-methoxy-quinoline-3-carbonitrile;
- t) 4-(4-chloro-2-fluoro-5-hydroxy-phenylamino)-7-methoxy-6-(3-morpholin-4-yl)-propoxyl-quinoline-3-carbonitrile;
- u) N-[4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(e) acrylamide;
- v) N-[4-(3-bromo-phenylamino)-3-cyano-quinolin-6-yl]-3-chloro-(z)-acrylamide;
- w) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-4-morpholino-2-butyramide;
- x) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-4-dimethylamino-2-butyramide;
- y) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-4-t-butylidimethylsiloxy-2-butyramide;
- z) N-[4-[(3-bromophenyl)amino]-3-cyano-6-quinolinyl]-4-hydroxy-2-butyramide;
- aa) 4-(3-hydroxymethyl-2-methylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile;
- bb) 4-(2-amino-4,5-dimethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile;
- cc) 4-(4-ethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile;
- dd) 4-(4-chloro-2-methylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile;
- ee) 6,7-dimethoxy-4-(3-phenoxyphenylamino)quinoline-3-carbonitrile;
- ff) 4-(4-chloro-3-trifluoromethylphenylamino)-6,7-dimethoxyquinoline-3-carbonitrile;
- gg) 4-(3-hydroxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- hh) 4-(4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- ii) 4-(3-hydroxy-4-methyl-phenylamino)-8-methoxy-6-nitro-quinoline-3-carbonitrile;

- jj) 4-(4-chloro-2-fluoro-phenylamino)-8-methoxy-6-nitro-quinoline-3-carbonitrile;
 - kk) 4-(3-hydroxy-4-methoxy-phenylamino)-8-methoxy-6-nitro-quinoline-3-carbonitrile;
 - ll) 6-amino-4-(3-hydroxy-4-methyl-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 - mm) 6-amino-4-(3-hydroxy-4-methoxy-phenylamino)-8-methoxy-quinoline-3-carbonitrile;
 - nn) N-[4-[(3-bromo-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-bromo-2-butanamide;
 - oo) N-[4-[(3-bromophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-chloro-2-butanamide;
 - pp) N-[3-cyano-4-[(3-iodophenyl)amino]-6-quinolinyl]-2-butyramide;
 - qq) N-[3-cyano-4-[(3-methylphenyl)amino]-6-quinolinyl]-2-propenamide;
 - rr) N-[4-[(4-bromophenyl)amino]-3-cyano-6-quinolinyl]-2-butyramide;
 - ss) N-[4-[(3-chloro-4-thiophenoxyphenyl)amino]-3-cyano-6-quinolinyl]-2-propenamide;
 - tt) N-[3-cyano-4-[(3,4-difluorophenyl)amino]-6-quinolinyl]-2-butyramide;
 - uu) N-[4-[(3-chlorophenyl)amino]-3-cyano-6-quinolinyl]-2-butyramide;
 - vv) N-[3-cyano-4-[(3-isopropylphenyl)amino]-6-quinolinyl]-2-butyramide;
 - ww) N-[3-cyano-4-[(3-isopropylphenyl)amino]-6-quinolinyl]-2-propenamide;
 - xx) 6-amino-4-[(3-isopropylphenyl)amino]-3-quinolinecarbonitrile;
 - yy) 4-[(3-isopropylphenyl)amino]-6-nitro-3-quinolinecarbonitrile; or
 - zz) 4-(3-bromo-phenylamino)-6-(3-pyrrolidin-1-yl-propylamino)quinoline-3-carbonitrile;
- or a pharmaceutically acceptable salt thereof.
21. The method according to claim 1 in which
- a) 4-(3-azido-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 - b) 6-amino-4-[(4-chloro-2-fluorophenyl)amino]-7-methoxy-3-quinolinecarbonitrile;
 - c) 4-[(4-chloro-2-fluorophenyl)amino]-7-methoxy-6-nitro-3-quinolinecarbonitrile;
 - d) 4-[(3,4-dichlorophenyl)amino]-6-nitro-3-quinolinecarbonitrile;
 - e) 6-amino-4-[(3-methylsulfanyphenyl)amino]-3-quinolinecarbonitrile;
 - f) 4-[(3-methylsulfanyphenyl)amino]-6-nitro-3-quinolinecarbonitrile;
 - g) 4-[(3-trifluoromethoxyphenyl)amino]-6-nitro-3-quinolinecarbonitrile;
 - h) 4-(3-dimethylamino-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 - i) 6,7-dimethoxy-4-(4-methoxy-2-methyl-phenylamino)-quinoline-3-carbonitrile;
 - j) 4-(3-hydroxy-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 - k) 4-(3-chloro-4-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
 - l) 6,7-dimethoxy-4-(4-phenoxy-phenylamino)-quinoline-3-carbonitrile;
 - m) 4-(5-chloro-2-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;

- n) 3-(3-cyano-6,7-dimethoxy-quinolin-4-ylamino)-2-methyl-benzoic acid;
- o) 4-(4-chloro-2-fluoro-phenylamino)-6,7-dihydroxy-quinoline-3-carbonitrile;
- p) 4-(3-hydroxy-2-methyl-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- q) 4-(3-chloro-4-methoxy-phenylamino)-6,7-dimethoxy-quinoline-3-carbonitrile;
- r) 6,7-dimethoxy-4-(4-trifluoromethyl-phenylamino)-quinoline-3-carbonitrile;
- s) 4-(3,4-dibromophenylamino)-6-nitroquinoline-3-carbonitrile;
- t) 6-amino-4-(3-trifluoromethylphenylamino)quinoline-3-carbonitrile;
- u) 6-amino-4-(3,4-dibromophenylamino)quinoline-3-carbonitrile;
- v) N-[3-cyano-4-(3,4-dibromophenylamino)quinolin-6-yl]acrylamide;
- w) N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]propionamide;
- x) (e)-but-2-enoic acid [4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]amide;
- y) N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]-2-methylacrylamide;
- z) 4-(3-fluorophenylamino)-6-nitroquinoline-3-carbonitrile;
- aa) 6-amino-4-(3-fluorophenylamino)quinoline-3-carbonitrile;
- bb) 4-(3-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile;
- cc) 4-(4-dimethylaminophenylamino)-6-nitroquinoline-3-carbonitrile;
- dd) 6-amino-4-(3-dimethylaminophenylamino)quinoline-3-carbonitrile;

- ee) 6-amino-4-(4-dimethylaminophenylamino)quinoline-3-carbonitrile;
 - ff) but-2-ynoic acid [4-(3-fluorophenylamino)-3-cyanoquinolin-6-yl]amide;
 - gg) N-[3-cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]acrylamide;
 - hh) N-[3-cyano-4-(4-Dimethylaminophenylamino)quinolin-6-yl]acrylamide;
 - ii) but-2-ynoic acid [3-cyano-4-(3-dimethylaminophenylamino)quinolin-6-yl]amide;
 - jj) but-2-ynoic acid [3-cyano-4-(4-dimethylaminophenylamino)quinolin-6-yl]amide;
 - kk) 4-(3-bromophenylamino)-6-dimethylaminoquinoline-3-carbonitrile hydrochloride;
 - ll) 6-dimethylamino-4-(3-methoxyphenylamino)quinoline-3-carbonitrile hydrochloride;
 - mm) 2-bromo-N-[4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]acetamide;
 - nn) 6-iodo-4-(3-methoxyphenylamino)quinoline-3-carbonitrile;
 - oo) 4-(4-hydroxy-2-methyl-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile;
 - pp) 4-(3-bromo-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile;
 - qq) 6-methoxy-4-(2-methylsulfanyl-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile; or
 - rr) 4-(4-hydroxy-3,5-dimethyl-phenylamino)-6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinoline-3-carbonitrile;
- or a pharmaceutically acceptable salt thereof is provided.

* * * * *

TRATADO DE COOPERACION DE PATENTES

De la
AUTORIDAD DE BUSQUEDA INTERNACIONAL

Para:

ver forma PCT/ISA/220

PCT

OPINION ESCRITA DE LA
AUTORIDAD DE BUSQUEDA INTERNACIONAL

(PCT Regla 43bis.1)

		Fecha de envío por correo (día/mes/año) ver forma PCT/ISA/210 (segunda página)	
Registro de referencia del solicitante o agente ver forma PCT/ISA/220		PARA FUTURAS ACCIONES Ver el párrafo 2 a continuación	
Solicitud Internacional No. PCT/US2004/024478	Fecha de registro internacional (día/mes/año) 28.07.2004	Fecha de prioridad (día/mes/año) 01.08.2003	
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC INV. A61K45/06 A61K31/47 A61P35/00			
Solicitante WYETH HOLDINGS CORPORATION			
1. Esta opinión contiene indicaciones relacionadas con los siguientes ítems: ☒ Casilla No. I Bases del Reporte ☐ Casilla No. II Prioridad ☒ Casilla No. III No establecimiento de opinión respecto a novedad, nivel inventivo y aplicabilidad Industrial. ☒ Casilla No. IV Falta de unidad de invención ☒ Casilla No. V Afirmación razonada de conformidad con la Regla 43bis.1(a)(i) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citas y explicaciones que sustentan dicha afirmación. ☐ Casilla No. VI Ciertos documentos citados ☐ Casilla No. VII Ciertos defectos en la solicitud internacional ☐ Casilla No. VIII Ciertas observaciones sobre la solicitud internacional 2. ACCIONES FUTURAS Si se hace una demanda para examen preliminar internacional, esta opinión generalmente será considerada como una opinión escrita de la Autoridad Examinadora Preliminar ("IPEA"). Sin embargo, esto no aplica cuando el solicitante escoge una Autoridad diferente a ésta para que sea la IPEA y la IPEA escogida le ha notificado a la Oficina Internacional de conformidad con la Regla 66.1bis(b) que no se considerarán las opiniones escritas de esta Autoridad Examinadora Preliminar. Si esta opinión es, según se estipula anteriormente, considerada una opinión escrita de la IPEA, se invita al solicitante a presentar ante la IPEA una respuesta escrita junto, cuando sea apropiado, con modificaciones, antes de la fecha de expiración de tres meses desde la fecha de envío por correo de la Forma PCT/ISA/220 o antes de la fecha de expiración de 22 meses desde la fecha de prioridad, la que expire más tarde. Para opciones futuras, ver la Forma PCT/ISA/220 3. Para detalles adicionales, ver las notas a la Forma PCT/ISA/220			
Nombre y dirección de correo de ISA: European Patent Office-P.B 5818 Patentlaan 2 NL-2280 HV Rijswijk-Pays Bas Tel. +31 70 340-2040 Tx: 31 651 epo nl Fax: +31 70 340-3016		Funcionario Autorizado Leherte, C Teléfono No. +31 70 340-2748	

**OPINION ESCRITA DE LA
AUTORIDAD DE BUSQUEDA INTERNACIONAL**

Solicitud Internacional No.
PCT/US2004/024478

Casilla No. I. Bases de la opinión

1. Respecto al idioma, esta opinión se ha establecido según la solicitud internacional en el idioma en el cual se presentó, a menos que se indique de otro modo bajo este ítem.
☐ Esta opinión se ha establecido según una traducción del idioma original al siguiente idioma, que es el idioma de una traducción proporcionada para la búsqueda internacional (bajo las Reglas 12.3 y 23.1(b)).
2. Respecto a cualquier nucleótido y/o secuencia aminoácida revelada en la solicitud internacional y necesaria para la invención reivindicada, esta opinión se ha establecido según:
 - a. tipo de material:
☐ un listado de secuencia
☐ tabla(s) relacionada con el listado de secuencia
 - b. formato de material:
☐ en formato escrito
☐ en formato legible por computador
 - c. tiempo de presentación/suministro:
☐ contenido en la solicitud internacional según se registró
☐ registrada junto con la solicitud internacional en formato legible por computador
☐ proporcionada subsiguientemente a esta Autoridad para la búsqueda.
3. ☐ Además, en el caso en que más de una versión o copia de un listado de secuencia y/o tabla relacionada con ello se haya registrado o proporcionado, las declaraciones requeridas de que la información en las copias subsiguientes o adicionales es idéntica a aquella en la solicitud según se presentó o no va más allá de la solicitud según se registró, según lo apropiado, fueron suministradas.
4. Comentarios adicionales:

OPINION ESCRITA DE LA
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Casilla No. III No establecimiento de opinión respecto a novedad, nivel inventivo o aplicabilidad industrial

Las preguntas de si la invención reivindicada parece ser novedosa, comprender un paso inventivo (ser no obvia) o ser aplicable industrialmente no se han examinado respecto a:

- ☐ toda la solicitud internacional,
☒ reivindicaciones Nos. 1-5, 7-13

porque:

☒ dicha solicitud internacional, o dichas reivindicaciones Nos. 10,11 (con respecto a la aplicabilidad industrial) (Regla 67.1 (iv) PCT) se relacionan con la siguiente materia objeto que no requiere un examen preliminar internacional (*especifique*):

ver hoja separada

☐ la descripción, reivindicaciones o dibujos (*indique los elementos particulares a continuación*) de dichas reivindicaciones Nos son tan poco claros que no se podría formar una opinión significativa (*especifique*):

☐ las reivindicaciones, o dichas reivindicaciones Nos. son sustentadas tan inadecuadamente por la descripción que no se podría formar una opinión significativa.

☒ no se ha establecido ningún reporte de búsqueda internacional para toda la solicitud o para dichas reivindicaciones Nos 1-5,10, 11 (todas parcialmente), 7-8, 12, 13.

☐ El nucleótido y/o lista de secuencia aminoácida no cumple con el estándar proporcionado en el Anexo C de las Instrucciones Administrativas en que:

la forma escrita

☐ no se ha proporcionado

☐ no cumple con el estándar

el formato legible por computador

☐ no se ha proporcionado

☐ no cumple con el estándar

☐ las tablas relacionadas con el nucleótido y/o lista de secuencia aminoácida, si están en formato legible por computador únicamente, no cumplen con los requerimientos técnicos proporcionados en el Anexo C-bis de las Instrucciones Administrativas.

☐ Ver la hoja separada para más detalles.

OPINION ESCRITA DE LA
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Solicitud internacional No.
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Casilla No. IV Falta de Unidad en la invención

1. ☒ En respuesta a la invitación (Forma PCT/ISA/206) para pagar tasas adicionales, el solicitante ha:
- ☐ Pagado tasas adicionales
 - ☐ Pagado tasas adicionales bajo protesta
 - ☒ Ni pagado tasas adicionales
2. ☐ Esta Autoridad encontró que el requisito de unidad de invención no se cumple y decidió, no invitar al solicitante a pagar tasas adicionales.
3. Esta Autoridad considera que el requisito de unidad de invención de acuerdo con las Reglas 13.1, 13.2 y 13.3 es:
- ☐ Cumplido
 - ☒ No cumplido por las siguientes razones:
ver siguiente hoja
4. En consecuencia, este reporte ha sido establecido con respecto a las siguientes partes de la solicitud internacional:
- ☐ Todas la partes
 - ☒ Las partes que se relacionan a las reivindicaciones Nos. 1-6, 10 11

Casilla No. V Afirmación razonada bajo el Artículo 43bis.1 (a) (i) respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación

1. Afirmación

Novedad (N)	Si: Reivindicaciones
	No: Reivindicaciones 1-6,10,11
Nivel inventivo (IS)	Si: Reivindicaciones
	No: Reivindicaciones 1-6, 10,11
Aplicabilidad industrial (IA)	Si: Reivindicaciones ver hoja separada
	No: Reivindicaciones

2. Citaciones y explicaciones
ver hoja separada

Re Item III

No establecimiento de opinión respecto a novedad, paso inventivo y aplicabilidad industrial

Las reivindicaciones 1-3, 5, 10 y 11 comprenden géneros de compuestos definidos únicamente por su función ("agente citotóxico") e "inhibidor de quinasa EGFR"), donde la relación entre las características estructurales de los miembros del género y dicha función no han sido definidos. En ausencia de dicha relación ya sea revelados en las solicitudes según se presentó o que se hubiese reconocido con base en información fácilmente disponible a una persona versada en la técnica, la persona versada no sabría cómo hacer y usar compuestos a los que les falta definición estructural.

El hecho de que uno hubiese podido ensayar un compuesto de interés usando los ensayos reivindicados no supera este defecto puesto que uno no tendría conocimiento anticipado en cuanto a si un compuesto dado (fuera de aquellos que podrían ser revelados particularmente en una solicitud) caería dentro del alcance de lo que se reivindica. Se requeriría experimentación indebida (ser una carga indebida) para investigar al azar compuestos indefinidos para la actividad reivindicada.

Las reivindicaciones cubren todas las combinaciones de agentes citotóxicos e inhibidores de quinasa EGFR, mientras que la solicitud proporciona apoyo dentro del significado del Artículo 6 PCT y/o revelación dentro del significado del Artículo 5 PCT para únicamente un número muy limitado de dichas combinaciones.

En el presente caso, a las reivindicaciones les falta soporte, y a la solicitud le falta revelación, tanto que es imposible una búsqueda significativa sobre todo el alcance reivindicado.

Por consiguiente, se ha llevado a cabo la búsqueda para aquellas partes de las reivindicaciones que parecen ser claras, sustentadas y reveladas, a saber, aquellas partes relacionadas con las composiciones farmacéuticas, que contienen capecitabina y EKB-569.

Las reivindicaciones 10 y 11 se relacionan con la materia objeto que esta Autoridad considera que están cubiertas por las disposiciones de la Regla 67.1(iv) PCT. Por consiguiente, no se formulará ninguna opinión respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(i) PCT).

No se dará ninguna opinión de la presente Autoridad respecto a la materia objeto que no está cubierta por el reporte de búsqueda (Regla 66.1(e) PCT).

Re Item IV

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Falta de unidad de invención

Las invenciones/grupos separados de invenciones son:

Invención 1: reivindicaciones 1-5, 10, 11 (todas parcialmente), 6,

Una combinación de un agente citotóxico que es capecitabina y un inhibidor de quinasa EGFR.

Invención 2: reivindicaciones 1-5, 10, 11 (todas parcialmente), 7,

Una combinación de un agente citotóxico que es paclitaxel y un inhibidor de quinasa EGFR.

Invención 3: reivindicaciones 1-5, 10, 11 (todas parcialmente), 8,

Una combinación de un agente citotóxico que es 5-FU y un inhibidor de quinasa EGFR.

Invención 4: reivindicaciones 1-5, 10, 11 (todas parcialmente), 12,

Una combinación de un agente citotóxico que es FOLFIRI y un inhibidor de quinasa EGFR.

Invención 5: reivindicaciones 1-5, 10, 11 (todas parcialmente), 13,

Una combinación de un agente citotóxico que es FOLFOX4 y un inhibidor de quinasa EGFR.

Invención 6: reivindicaciones 1-5 y 10, 11 (todas parcialmente), 9,

Una combinación de un agente citotóxico que es cisplatín y un inhibidor de quinasa EGFR.

Están así unidas para formar un único concepto inventivo general (Regla 13.1 PCT) por las siguientes razones:

El problema que hay que solucionar por medio de la presente solicitud es proporcionar un medicamento para el tratamiento de las enfermedades.

La solución a este problema propuesta en la presente solicitud es usar una combinación de agentes farmacéuticos que comprenden un agente citotóxico y un inhibidor de quinasa EGFR.

WO 03/020266 se relaciona con el uso de combinaciones de CCI-779 y EKB-569 (el inhibidor de quinasa EGFR particularmente preferido de esta invención) y el uso de estas combinaciones como parte de una mezcla de quimioterapia que pueden contener uno o más agentes antineoplásicos adicionales (v.g. 5-fluorouracil, capecitabina, cisplatín y paclitaxel), dependiendo de la naturaleza de la neoplasia que será tratada.

WO 03/050090 y US 6 384 051 proporcionan compuestos de Fórmula (I), de esta invención, que son útiles como agentes antineoplásicos. Para el tratamiento de cáncer, los compuestos de estas invenciones pueden administrarse en combinación con otras sustancias antitumorales.

Por consiguiente, la idea de usar un inhibidor de quinasa EGFR con otro agente citotóxico en medicina es conocida en el estado de la técnica, y no puede servir como un único concepto inventivo, que une las combinaciones para uso en medicina.

Capecitabina, paclitaxel, 5-FU, FOLFIRI, FOLFOX4, y cisplatín comparten la propiedad común de ser agentes citotóxicos, pero no comparten un elemento estructural significativo, ni pertenecen a una sola clase reconocida de compuestos químicos en la técnica a la cual pertenece la invención: De hecho, cada uno de estos compuestos individuales forman ellos mismos distintas clases individuales reconocidas de compuestos químicos en la técnica farmacológica. No hay expectativa del conocimiento en la técnica de que miembros de todas estas clases se comportarán de la misma manera en el contexto de las invenciones reivindicadas. Tampoco hay expectativa en la técnica de que cada miembro de cada una de estas clases pueda ser sustituido por el otro, con la expectativa de que el mismo resultado pretendido se obtuviese.

En esta solicitud, no pueden distinguirse características técnicas adicionales que puedan considerarse como una "característica técnica especial" comprendida en la relación técnica entre las diferentes invenciones.

Por consiguiente, a esta solicitud le falta unidad de invención y las diferentes soluciones que no pertenecen a un concepto inventivo común se especifican como invenciones diferentes anteriormente mencionadas. Cada una de las invenciones enumeradas es una invención diferente, caracterizada por su propia característica especial, que define la contribución que cada una de las invenciones reivindicadas, considerada como un todo, traspasa la técnica anterior, es decir, las características específicas de los compuestos individuales.

Como el solicitante no ha tenido un reporte de búsqueda elaborado sobre las otras invenciones, la solicitud será procesada según la invención respecto de la cual se ha llevado a cabo una búsqueda, en otras palabras la invención mencionada primero en las reivindicaciones.

Re Item V

Afirmación razonada respecto a novedad, paso inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación

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PCT/US2004/024478**

Se llama la atención al hecho de que esta declaración expresada en cuanto a novedad, paso inventivo y aplicabilidad industrial se refiere únicamente a la materia objeto para la cual se ha redactado un Reporte de Búsqueda Internacional (es decir, únicamente para composiciones farmacéuticas, que contienen compuestos que se revelan explícitamente en las reivindicaciones).

1) DOCUMENTOS USADOS EN EL EXAMEN

Se hace referencia a los siguientes documentos en esta comunicación:

- D1: WO 03/020266 A (WYETH) 13 de marzo de 2003
- D2: WO 03/050090 A (WYETH HOLDINGS CORPORATION) 19 de junio de 2003
- D3: US 6 384 051 B1 (FROST PHILIP ET AL) 7 de mayo de 2002

A menos que se indique lo contrario, se hace referencia en el reporte de búsqueda.

2) NOVEDAD

Esta solicitud no cumple con los requerimientos del Artículo 33(2) PCT porque la materia objeto de las reivindicaciones 1-6, 10 y 11 no es nueva.

El documento D1 describe el uso de combinaciones de CCI-779 y EKB-596 (el inhibidor de quinasa EGFR particularmente preferido de la presente invención) y en cuanto al uso de estas combinaciones como parte de la mezcla de quimioterapia que puede contener uno o más agentes antineoplásicos adicionales (v.g. capecitabina).

Por lo tanto, D1 es perjudicial para la novedad de las reivindicaciones 1-6, 10 y 11.

3) NIVEL INVENTIVO

La presente solicitud no cumple con los criterios del Artículo 33(1) PCT porque la materia objeto de las reivindicaciones 1-6, 10 y 11 (en cuanto a novedad) no comprende un paso inventivo en el sentido del Artículo 33(3) PCT, en cuanto a la materia objeto de las reivindicaciones parece ser una alternativa obvia sobre los documentos D1-D3.

Aún más, el uso de una combinación de dos o más ingredientes activos con un uso terapéutico idéntico conocido puede considerarse únicamente como inventivo cuando un efecto sorprendente, por ejemplo un gran efecto sinérgico inesperado o efectos secundarios reducidos puedan

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signarse en relación al uso terapéutico reivindicado. A este respecto, a esta solicitud le falta evidencia que la sustente.

4) APLICABILIDAD INDUSTRIAL

Estas reivindicaciones 10 y 11 comprenden composiciones o sustancias en un método de tratamiento de un cuerpo humano/animal. Para la evaluación de dichas reivindicaciones sobre la pregunta de si son aplicables industrialmente, no existen criterios unificados en los Estados Contratantes del PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como aplicable industrialmente la materia objeto de las reivindicaciones en cuanto al uso de un compuesto en el tratamiento médico, pero puede permitir, sin embargo, reivindicaciones a un compuesto conocido para primer uso en el tratamiento médico y el uso de dicho compuesto para la elaboración de un medicamento para un nuevo tratamiento médico.

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/024478

International filing date (day/month/year)
28.07.2004

Priority date (day/month/year)
01.08.2003

International Patent Classification (IPC) or both national classification and IPC
INV. A61K4506 A61K3147 A61P3500

Applicant
WYETH HOLDINGS CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one in the IPEA and the chosen IPEA has notified the International Bureau under Rule 86.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



European Patent Office - P.O. 5818 Patentlaan 2
NL-2200 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2140 Telex 31 651 epo nl
Fax +31 70 340 - 3016

Authorized Officer

Leherte, C

Téléphone Fax. +31 70 340-2748



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

239
International application No.
PCT/US2004/024478

Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. III Non establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5, 7-13

because:

☒ the said international application, or the said claims Nos. 10, 11 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-5, 10, 11 (all partially), 7-8, 12, 13

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/200) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the International application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-6 10 11

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- | | | |
|-------------------------------|-------------|--------------------|
| Novelty (N) | Yes: Claims | |
| | No: Claims | 1-6, 10, 11 |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-6, 10, 11 |
| Industrial applicability (IA) | Yes: Claims | see separate sheet |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/024478

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-3, 5, 10 and 11 encompass genera of compounds defined only by their function ("cytotoxic agent" and "EGFR kinase inhibitor"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

The claims cover all combinations of cytotoxic agents and EGFR kinase inhibitors, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the pharmaceutical compositions, containing capecitabine and EKB-569.

Claims 10 and 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

No opinion of the present Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV

Lack of unity of invention

The separate inventions/groups of inventions are:

Invention 1: claims 1-5, 10, 11 (all partially), 6,
A combination of a cytotoxic agent which is capecitabine and an EGFR kinase inhibitor.

Invention 2: claims 1-5, 10, 11 (all partially), 7,
A combination of a cytotoxic agent which is paclitaxel and an EGFR kinase inhibitor.

Invention 3: claims 1-5, 10, 11 (all partially), 8,
A combination of a cytotoxic agent which is 5-FU and an EGFR kinase inhibitor.

Invention 4: claims 1-5, 10, 11 (all partially), 12
A combination of a cytotoxic agent which is FOLFIRI and an EGFR kinase inhibitor.

Invention 5: claims 1-5, 10, 11 (all partially), 13,
A combination of a cytotoxic agent which is FOLFOX4 and an EGFR kinase inhibitor.

Invention 6: claims 1-5 and 10, 11 (all partially), 9,
A combination of a cytotoxic agent which is cisplatin and an EGFR kinase inhibitor.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCI)
for the following reasons:

The problem to be solved by the present application is to provide a medicament for the
treatment of diseases.

The solution to this problem proposed in the present application is to use a combination
of pharmaceutical agents which comprises a cytotoxic agent and an EGFR kinase
inhibitor.

WO 03/020266 relates to the use of combinations of CCI-779 and EKB-569 (the
particularly preferred EGFR kinase inhibitor of the present invention) and to the use of
these combinations as part of a chemotherapy cocktail that may contain one or more
additional antineoplastic agents (e.g. 5-fluorouracil, capecitabine, cisplatin and
paclitaxel), depending on the nature of the neoplasia to be treated.

WO 03/050090 and US 6 384 051 provide compounds of Formula (I), of the present invention, which are useful as antineoplastic agents. For the treatment of cancer, the compounds of these inventions can be administered in combination with other antitumor substances.

Consequently the idea to use EGFR kinase inhibitor with another cytotoxic agent in medicine is known in the state of the art, and cannot serve as a single inventive concept, linking the combinations for use in medicine.

Capecitabine, paclitaxel, 5-FU, FOLFIRI, FOLFOX4, and cisplatin share the common property of being cytotoxic agents, but they do not share a significant structural element, nor do they belong to a single recognized class of chemical compounds in the art to which the invention pertains: In fact, each of these individual compounds form themselves distinct individual recognized classes of chemical compounds in the pharmacological art. There is no expectation from the knowledge in the art that members of all these classes will behave in the same way in the context of the claimed inventions. There is also no expectation in the art that each member of each of these classes can be substituted one for the other, with the expectation that the same intended result would be achieved.

In the present application no further technical features can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Consequently, the present application lacks unity of invention and the different solutions not belonging to a common inventive concept are detailed as the different inventions listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art, i.e. the specific features of the individual compounds.

As the applicant has not had a search report drawn up on the other inventions, the application will be prosecuted on the basis of the invention in respect of which a search has already been carried out, in other words the invention first mentioned in the claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international Search Report has been drawn up (i.e. only for pharmaceutical compositions, containing compounds explicitly disclosed in the claims).

1) DOCUMENTS USED IN EXAMINATION

The following documents are referred to in this communication:

D1 : WO 03/020266 A (WYETH) 13 March 2003

D2 : WO 03/050090 A (WYETH HOLDINGS CORPORATION) 19 June 2003

D3 : US 6 384 051 B1 (FROST PHILIP ET AL) 7 May 2002

Unless indicated otherwise reference is made to the documents mentioned herein in the search report.

2) NOVELTY

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1-6, 10 and 11 is not new.

Document D1 describes the use of combinations of CCI-779 and FKR-589 (the particularly preferred EGFR kinase inhibitor of the present invention) and to the use of these combinations as part of a chemotherapy cocktail that may contain one or more additional antineoplastic agents (e.g. capecitabine).

Therefore D1 is prejudicial to the novelty of claims 1-6, 10 and 11.

3) INVENTIVE STEP

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6, 10 and 11 (as far as novel) does not involve an inventive step in the sense of Article 33(3) PCT, as the subject matter of the claims appears to be an obvious alternative over documents D1-D3.

Even more the use of a combination of two or more active ingredients with known identical therapeutic use can only be considered as inventive when a surprising effect, an unexpected high synergistic effect or reduced side effects for example, can be

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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assigned in relation to the claimed therapeutic use. In this respect, the present application lacks supportive evidence.

4) INDUSTRIAL APPLICABILITY

Present claims 10 and 11 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.