OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Seæores
SUPER1NTENDENCIA DE INDUSTRIA Y COMEP-__
SLJL

DIVISION DE NUEVAS CREACIONES

RIN I LNDLNCIA DL INDUS I HIA Y COMENCIO

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Act 449 Eve: 379 FASLNACIOLII RESPULSOpOSICI Folios 12

Re: Expediente No. 06-078.330
Solicitud de patente de invención titulada: "PIRAZOLOPIRIMIDINAS
NOVEDOSAS COMO INI11BIDORES DE QU1NASA CICLINA DEPENDIENTES Solicitante: SCREWING CORPORATION AND PHARMACOPEIA DRUG DISCOVERY, INC.
Nuestra Ref.: P2006/000156

RESPUESTA A LA OPOSICION NOTIFICADA MEDIANTE OFICIO No 11282 MEDIANTE FIJACION EN LISTA No. 289 DE FECHA 5 DE SEPTIEMBRE DE 2008.

CARLOS R. OLARTE, mayor de edad y vecino de Bogota, identificado tal como aparece al pie de nil firma, en mi carÆcter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente, dentro del plazo legal previsto en el artfculo 43 de la Decision 486, ante la oposición interpuesta por el doctor JosØ Luis Reyes Villamizar, actuando como apoderado de la sociedad

LAFRANCOL S.A.

En primer lugar y con Ænimo de brindar mayor claridad a la materia reivindicada, me permito presentar un Capitulo Reivmdicatorio Modificado, que reemplaza las Reivindicaciones presentadas al momento de radicar la presente solicitud. Para tal efecto, adjunto un recibo de pqgo que cubre la tasa de modificación correspondiente.

El Capitulo Reivindicatorio contiene los siguientes cambios:
Reivindicación
original

Modificaciones

1-30 Eliminadas.
31 Nueva Reivindicación 1.
32-42 Eliminadas.

World Trade Center - Torre A, Calle11

100 No. 8A - 37, Piso 10, Bogota D.C., Colombia

Tel + 57 1601-7700, Fax + 57 1601-7799, office@olarteraisbeCk.00m. yi,olatteiiSbeCk.COfli

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43-54 Nuevas Reivindicaciones 2 a 13
55-70 Eliminadas

Valga anotar que las modificaciones efectuadas al Capitulo Reivin4icatorio cumplen a cabalidad con lo estipulado en ci ArtIculo 34 de la Decision 486, ya que Østas de ninguna manera implican
una ampliación de la protecciOn correspondiente a la divulgaciOn contenida en la solicitud inicial;
por el contrario, la materia ôontenida en el CapItulo Reivindicatorio Modificado corresponde a
una drÆstica limitación del alcance originalmente pretendido.

2. a- El Opositor argumenta que las Reivindicaciones 32 a 40 no son patentables puesto
que reclaman mØtodos de tratamiento.

-) b- Considero superada la anterior objeción en tanto que las Reivindicaciones 32 a 40
han sido eliminadas del Capitulo Reivindicatoijo Modificado.

3. a- El Opositor argumenta que los siguientes documentos afectan la patentabilidad de
la presente invenciOn:
No Documento
Dl US 6.099.593
D2 US 2003/191086
D3 W002/076484

El Opositor anota que Dl revela compuestos y composiciones que comprenden derivados de pirazolo [1,5-a]pirimicjina para la tinciOn oxidativa de fibras de queratina y especificamete el Ejemplo 4 revela el compuesto 7-n- hidroxietilamino-5-metiipirazolo [1,5-a]pirimidina clorhidrato, el cual afecta la novedad de la presente invenciOn.

El Opositor tambiØn indica que la presente invenciOn intenta proteger un segundo uso, que corresponde al empleo de compuestos conocidos en el tratamiento del cancer.
El Opositor igualmente argumenta que D2 revela derivados heterociclicos (pirrolopirimidinas, pirazolopirimidinas, purinas e imidazopiridinas), ütiles çomo inhibidores de CDK y coma agentes anticancerIgenos. Adicionalmente, el Opositor anota que una persona medianamente versada en la materia sabria que los derivados de pirazopirimidinas son activos como inhibidores de CDK, los cuales adicionalmente pueden potencial la actividad de otros agentes anticancerigenos. Asimismo, el Opositor anota que si bien los compuestos revelados en D2 no son idØnticos a aquellos reclamados en la presente invenciOn, son similares estructuralmente y su actividad biológica es comparable. El Opositor concluye que la presente solicitud no es inventiva respecto
aD2.

PÆgina 2 de 4

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III

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El Opositor tambiØn argumenta que D3 revela combinaciones de tÆxanos con flavopiridol, cicual es un inhibidor de CDK, y cita artIculos en los que se ilustra la asociación de pirazolopirimidinas con ingredientes activos adicionales para el tratamiento del cancer, las cuales afectan el nivel inventivo de las combinaciones de las Reivindicaciones 41 y 42.

b- i) En primer lugar, me permito seæalar que el Capitulo Reivindicatorio
Modificado ha sido limitado drÆsticamente, eliminando toda posible coincidencia con los compuestos divulgados en Dl. Se eliminaron las antiguas reivindicaciones 1 a 30 y la antigua Reivindicación 31, que es la nueva Reivindicación 1, reclama compuestos que difieren estructuralmente de manera significativa de aquelios revelados en Dl. AsI las cosas, toda objeción referente la novedad de la presente invención respecto a Dl, queda superada.

ii) En cuanto a las combinaciones de las Reivindicaciones 41 y 42, Østas han
sido eliminadas del Capitulo Reivindicatorio Modificado, con to que se supera la objeción

elevada en relación con D3.

iii) Por otra parte, y respecto at nivel inventivo de la presente invención, debo
seflalar que ci arte previo citado por ci opositor (Dl y/o D2) no proporciona ensefianzas concretas que hubiesen conducido a la persona medianamente versada en la materia, justamente at desarrollo de los compuestos reclamados en las nuevas Reivindicaciones 1 a 13, esperando obtener compuestos activos como inhibidores de CDK. Es decir, la persona versada en la tØcnica estarla predispuesta a emplear ünicamente las pirazolopirimidinas que presentan la configuración estructural descrita en dichos documentos, pero no encuentra ninguna indicación que Ic permitiese liegar a la estructura especifica de los compuestos que se reclaman en la solicitud actual, ni mucho menos a esperar que los mismos serlan activos como inhibidores de CDK.

En conclusion, ci arte previo citado por el Opositor no proporciona ensefianzas que pudieran conducir a una persona medianamente versada en la materia al desarrotlo de la materia reivindicada.

4. Finalmente, deseo mencionar que la solicitud Estadounidense equivalente a la presente solicitud Colombians, fue concedida bajo ci nÆmeroUS 7.119,200.
-e--’-

Si bien es cierto que las concesiones de patentes en oficinas de otros palses rfo son vincuiantes en
ci sentido que obliguen a la Superintendencia a tomar una decisiOn en ci mismo sentido,

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considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de
la materia revindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la Superintendencia debe emplear.
Tan cierto es lo anterior, que ci Manual Andino de Patentes, al comentar el ArtIculo 46 de la Decision 486, establece que una Oficina nacional competente podrÆ reconocer los resultadosde exÆmenes de novedad o de patentabilidad efectuados respecto a la solicitud extranjera equivalente, como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad.’

5. Por todo lo anterior, considero que las observaciones presentadas por el Opositor han sido superadas y solicito respetuosamente se proceda con el examen de fondo de la presente

invención.

Atentamente,

V

CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogota
T.P. 74.295

Anexos:

CapItulo Reivindicatorio Modificado
Recibo de pago correspondiente a la tasa de modificación.

’Manual Andino de Patentes. SecciOn 7.3.

Pagina 4 de 4

Me

Expediente No. 06-078-330

CAPITULO REIVINDICATORIO MODIFICADO

1. Un compuesto de formula:

H H ll

OH HN

Nb,,
0

N -;N

-

OH
HN11

?NIC

QNNJ

DH HN

LNO

ON N

(

NJ
OH HN.

NN

ON N

NH2

(

NJ
OH HN

11/ I

/N

OH HN

NIO

OH HN

N
y

N
NH

Izz, N
OH HN

/N

Pagina 1 de 7

Expediente No. 06-078-330

H Br H

ciN

OH HN OH HN

NN’

HO-..
H Br

HN

NH2

HO HBr
NyN
*N’-’/

HM

0,,,
OH H141-, OH HI

rp

H Br H Br N HO HO’

HN HN

HNy..N HN(..N-
01 01

19(

Pagina 2 de 7

Expediente No. 06-078-330 /7Z
Br

Br 9 H Br

HO
HLX>Y- 1

H

0 N 6,"tON N Br

HO BrNI

ONC.,,NyN_A H
/

P4o una sat aceptabte para uso farmaceutico o solvato del mismo. 51
2
2. Un compuesto de la ReMndicaciOn I en forma purificada.
/

3. Un compuesto de formula:

0 N N

""/
I N
HHN

o una sat farmacØuticamente aceptabte del mismo.

Pagina 3 de 7

Expediente No. 06-078-330
4. Un compuesto de formula:

o una sal farmaceuticamente aceptable del mismo.

5. Un compuesto de fOrmula:

ON
OH HN

Nt0-
o una sal farmacØuticamente aceptable del mismo.
6. Un compuesto de fOrmula:

o una sat farmacØuticamerite aceptable del mismo.

PÆgina4de7

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Expediente No. 06-078-330
7. Un compuesto de fOrmula:

OH HN
N... /
o una sal farmacØuticamente aceptable del mismo.

8. Un compuesto de fOrmula: H
0 N N

OH HN

NO("
o una sal farmacØuticamente aceptable del mismo.
9. Un compuesto de fOrmula:

OHHN y

N 0
o una sal farmaceuticamente aceptable del mismo.

Pagina 5 de 7

10. Un compuesto de fOrmula:
QBr

HN

o una sal farmacØuticamente aceptable del mismo.

11. Un compuesto de fOrmula:

Br

HN

1i-0-
oqy-
o una sal farmaceuticamente aceptable del mismo.

12. Un compuesto de fOrmula:

Expediente No. 06-078-330

I

CN

HFJ/
H7

t_ F0_
o una sal -v Cl/cq farmacØuticamente aceptable del mism. 3 _

Pagina 6 de 7

13. Un compuesto de formula:

Expediente No. 06-078-330

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Pagina 7 de 7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DMSION DE NUEVAS CREACIONES

202012

Bogota, D.C., 28 de enero de 2010

Apoderado: Carlos Reinaldo Olarte Garcia

ASUNTO Radicaciôn 06-78330
TrÆmite 002
Evento 001
Actuaciôn 430
Oficio
Folios

Patente de Invención 0

Via PCT (fase nacional) 0 Cap.l 0

No. Sol. Internacional PCT2005/003859
Fecha de Presentación Internal. I 1/mar/2005

Cap. II El

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de la Decision 486 de la Comisiôn de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. DescripciOn: Folios: 326 a 928 Como se radicØ inicialmente.

1.2. Reivindicaciones: Folios 929 a 970 Como se radicO inicialmente.

Folios 1170 a1175 Modificado.

1.3. Prioridad: Folio 2: DE 102004014620.6, 06/oct/2005

1.4. Oposiciones: Folios 1127 a 1163
Opositor(es): LAFRANCOL S.A
1.5 Respuesta del solicitante: Folios: 1165 a 1175.

2. Objeto de la invenciôn

TItulo de la solicitud: PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINAZA CICLINA-DEPENDIENTES

El objeto de la presente solicitud s amina que caen bajo el alcance de

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El objeto de la solicitud se compuestos especificos.

Reivindicaciones 1-2: 39 compuestos ReivindicaciOn 3: un compuesto espe Reivindicaciôn 4: un compuesto espe Reivindicaciôn 5: un compuesto espe ReMndicación 6: un compuesto espe Reivindicaciôn 7:un compuesto espec ReiviAdicaciôn 8: un compuesto espe ReMndicaciôn 9: un compuesto espe Reivindicaciôn 10: un compuesto esp Reivindicacion 11: un compuesto esp
Reivindicaciôn 12: un compuesto esp
Reivindicación 13: un compuesto esp

2%) los denvados de pirazolo[1,5-a]pirlmidin-7-

formula Markush:

tal como aparece los folios 1170-1175,

Se catalogô la invenciôn, segUn la Cl*sificaciön Internacional de Patentes (IPC.): C07D487/04, A61 K31/519 H C07D48704.

3. De la solicitud de Patente

3.1. Rºivindicaciones (articulo 30 486 de Ia C.A.N.)

La reivindicaciôn 2, es una redundanci de la reMndicaciôn 1, puesto que se reclama "Ids compuestos de Ia reWindicación 1 en forma purificadà" ytal como aparece la reivindicación son molØculas 6nicas eparas, puras, por eso son identificables inequlvocamente mediante su fOrmulaestructuraL

Concluir indicando que no cumplen
30 de la Decision 486.ylo art.22 Tr,n-

4. AnÆlisis de la(s)Oposiciôn(es):

el requisito de concision, de acuerdo al art.
PCT.

43 D. 486 de Ia CAN):

Los documentos patente citados porel opositor son documentos citados por la autoridad intemacional de bUsqueda n su informa del estado de la tØcnica, y la

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respuesta que se dio es la misma respuesta que dio el interesado en la fase internacional, al igual que el misma modificaciôn al capitulo reivindicatorio enviado en esa respuesta, pero aqul le agregaron nueve compuestos a la reivindicación I y agregaron el compuesto de la reivindicaciôn 13.

5. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el estado de la tØcnica fecha de presentaciôn de la solicitud de la cual se reclama prioridad, I 1/febI2004. Teniendo en cuenta la fecha indicada se realizó la büsqueda del estado de la tØcnica, en bases de datos en las que esta oficina tiene acceso libre, en büsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrÆndose los siguientes documentos mÆsrelevantes:

NO Documento TItulo Fecha de

presentación

DI W02004022561

____

Pyr&olopyrimidines as cyclin- 03-sep-2003 dependent kinase inhibitors
rD2 W02004022559 Pyrazolopyrimidines as cyclin- 03-sep-2003 dependent kinase inhibitors

6. AnÆlisisde patentabilidad (segün requisito) (artIculo 14 D486)

12.1 Novedad (articulo 16 D486 de la C.A.N.

los derivados de pirazolo[1,5-a]pirimidin-7-amina que caen bajo el alcance de la formula Markush:

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Pero analizado para las nuevas reivindicaciones 1-13 (compuestos especificos, folios 1170-1175)

- Las anterioridades Dl y D2 describen los compuestos de fOrmula:

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Comprenden la misma descripción referente a los derivados pirazolo[1,5-a]pirimidin-7-amina de la formula representada, que la presente solicitud, entonces teniendo la misma información en materia tØcnica, comprende los mismos compuestos que la solicitud en estudio. (VØase DI. PÆgs. 1-603,especialmente los ejemplos; D2 vØase Pagsl -80), donde se demuestra qiie los compuestos reclamados en la presente solicitud no cumplen con el requisito exigido en el articulo 16 D486 de la C.A.N.

7. Conclusion:

Los requisitos de patentabilidad de Ia presente solicitud se encuentran afectados as!:

Documento No Reivindicaciones afectadas Requisito que afecta Dl 1-13 Novedad
D2 1-13 Novedad

En cumplimiento del artIculo 45 de la DecisiOn 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de 60 dIas contados a partir de la fecha de notificaciOn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impØdimØntôs para la concesiOn, se denegarÆla patente.

Notifiquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capitulo quinto del tItulo Ømep-d)a Circular Unica No 10 de 2001.

ALIX CARMENZAJCEPEDES DE VERGEL
Directora de Nu as Creaciones (c)

El anterior requerimiento fue notificado por fijaciôn en lista, de fecha

ycoNcEPTo TECNICO-No5e Z IEXAMINADOR TECNICO COd. N°202012

E-0

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date (10) International Publication Number
18 March 2004 (18.03.2004) PCT WO 2004/022561 Al

(51) International Patent Classification7: C07D 487/04, NJ 08540 (US). JAMES, Ray, Anthony; 1036 Radcliffe
A61K 31/51911 (CO7D 487/04,239:00,231:00) Street, Bristol, PA 19007 (US). PARK, Haengsoon; 8910
Tamarron Drive, Plainsboro, NJ 08536 (US). PARAD-

(21) International Application Number: KAR, Vidyadliar, M.; 3 Pine Ridge Drive, Somerville, NJ
PCF/US2003/027555 08876 (US). HOBBS, Douglas, Walsh; 1330 University
Drive, Yardley, PA 19067 (US).

(22) International Filing Date:
3 September 2003 (03.09.2003) (74) Agent: KALYANARAMAN, Palalyurj S.; Schering Cor-

poration, Patent Department K-6-1 1990, 2000 Galloping
Hill Road, Kenilworth, NJ 07033-0530 (US).
(25) Filing Language: English

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(26) Publication Language: English AZ, BA, BB, BG, BR,, BY, BZ, CA, CH,CNpJR, CZ,
DE, DK, DM, DZ, EC, BE, ES, FL, GB, GD, GE, HE, HU,

(30) Priority Data: ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, IT, LU, LV,
60/408,027 4 September2002 (04.09.2002) US 7t, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH,
60/421,959 29 October 2002 (29.10.2002) USJ V PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
IT, T4 UA, UZ, VC, VN, YU, ZA, ZM.

(71) Applicants: SCHERING CORPORATION [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530
(US). PHARMACOPEIA, INC. [US/US]; 3000 Eastpark
Boulevard, Cranbury, NJ 08512 (US).

(72) Inventors: GUZI, Timothy, J.; 48 Red Road, Chatham, NJ 07928 (US). PARUCII, Kamil; 20 Third Avenue, Garwood, NJ 07027 (US). DWYER, Michael, P.; 235 Katherine Street, Scotch Plains, NJ 07076 (US). DOLL, Ronald, J.; 8 Concord Lane, Convent Station, NJ 07960 (US). GJRJJAVALLABHAN, Vlyyoor, Moopil; 10 Maplewood Drive, Parsippany, NJ 07054 (US). MAL-LAMS, Alan; 147 Kings Highway, RR3, Hackettstown, NJ 07840 (US). ALVAREZ, Carmen, S.; 121 Walnut Street, Livingston, NJ 07039 (US). KEERTIKAR, Kar-tik, M.; 24 Columbia Avenue, East Windsor, NJ 08520 (US). RIVERA, Jocelyn; 72 Regal Drive, Monmouth Junction, NJ 08852 (US). CHAN, Tin-Yau; 26 Barlow Road, Edison, NJ 08817 (US). MADISON, Vincent; 12 Ronarm Drive, Mountain Lakes, NJ 07046 (US). FISCHMANN, Thlerry, 0.; 2700 Sky Top Drive, Scotch Plains, NJ 07076 (US). DILLARD, Lawrence, W.; 278 Spring Hill Road, Skillman, NJ 08558 (US). TRAN, Vlnh, D.; 17374 Winemast Street, Fountain Valley, CA 92708 (US). HE, Then Mm; 5 Pennoyal Court, Princeton,

(84) Designated States (regional): ARIPO patent (Gil, GM, KB, LS, MW, MZ, SD, SL, SZ, rZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, (2, DE, DK, EE, ES, F!, FR, GB, GR, HU, IB, rr, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NB, SN, TD, TG).

Declarations under Rule 4.17:

- as to the applicant’s entitlement to claim the priority ofthe
earlier application (Rule 4.17(iii))for all designations
- asto the applicant’s entitlement to claim the priority ofthe
earlier application (Rule 4.17(iii))for all designations
- as to the applicant’s entitlement to claim the priority ofthe
earlier application (Rule 4.17(iii))for all designations
- asto the applicant’s entitlement to claim the priority ofthe
earlier application (Rule 4.17(iii))for all designations

Published:
- with international search report

Fortwo-letter codes and other abbreviations, referto the "Guid-
ance Notes on Codes andAbbreviations" appearing at the begin-
ning ofeach regular issue ofthe PCT Gazette.

(54) Title: PYRAZOLOPYRIMIDINES AS CYCUN-DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

WO 2004/022561 PCT/US2003/027555

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In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula HI:

HNR

Formula Ill
wherein:

R is H, alkyl, alkenyl. alkynyl, arylalkyl, arylalkenyl, cycloalkyl,
cycloalkylalkyl, alkenylalkyl, alkynylalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl (including. N-oxide of said heteroaryl), -(CHR5)-aryl, -(CHR5)-

10 heteroaryl, . (CHR5) NR5R8 171
_ /-\
(CHR5)n_,1NR8 _(CHR5)n_Nj _

(CHR5)/\
\j or

: (cHR5)n_NçJ

wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl can be unsubstituted or optionally substituted with one or more
15 moieties which can be the same or different, each moiety being independently
selected from the group consisting of halogen, alkyl, aryl, cycloalkyl,
heterocyclylalkyl, CF3, OCF3, CN, -0115, -NR5R10, -C(R4R5)-R9,
- N(R5)Boc, -(CR4R5)OR51. -C(02)R5, -C(0)W, -C(0)NR5R10, -S03H, -SR10,
- S(02)R7, -S(02)NR5R’°, -N(R5)S(02)R7, -N(R5)C(0)R7 and -N(R5)C(0)NR5R’°;
20 R2 is selected from the group consisting of R9, alkyl, alkenyl, alkynyl, CF3, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, aryl, arylalkyl, heteroarylalkyl, alkynylalkyl, cycloalkyl, heteroaryl, alkyl substituted with 1-6 R9 groups which can
be the same or different and are independently selected from the list of R9
shown below, aryl substituted with 1-3 aryl or heteroaryl groups which can be the
25 same or different and are independently selected from phenyl, pyridyl,

II

WO 2004/022561 PCT/US2003/027555

PYRAZOLOPYRIMIDINES AS CYCLIN-DEPENDENT KINASE INHIBITORS

Field of the Invention

The present invention relates to pyrazolo[1,5-a]pyrimidine compounds
useful as protein kinase inhibitors (such as for example, the inhibitors of the
5 cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK),
glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as
10 Alzheimers disease, cardiovascular diseases, and fungal diseases. This.

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application claims benefit of priority from U.S. provisional patent applications, Serial No. 60/408,027 filed September 4, 2002, and Serial No. 60/421,959 filed October 29, 2002.

Background of the Invention
Protein kinase inhibitors include kinases such as, for example, the
inhibitors of the cydin-dependent kinases (CDKs), mitogen activated protein
kinase (MAPKIERK), glycogen synthase kinase 3 (GSK3beta), and the like.
Protein kinase. inhibitors are described, for example, by M. Hale et al in
20 W002/22610 Al and by Y. Mettey et al in J. Med. Chem., (2003)46222-236.
The cyclin-dependent kinases are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK’s, such
as, CDKI, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8 and the like,
perform distinct roles in cell cycle progression and can be classified as either GI,
25 S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer
cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through Gi to the S phase of the cell cycle,
30 and CDK2 is one of the key components of the 01 checkpoint. Checkpoints
serve to maintain the proper sequence of cell cycle events and allow the cell to

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Table I

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"Patient" includes both human and animals.
"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about

1 to about 20 carbon atoms in the chain.
5 Preferred alkyl groups contain about

1tabout 12 carbon atoms in the chain.
More preferred alkyl groups contain about Ito about

6 carbon atoms in the

chain. Branched means that one or more lower alkyl groups such as methyl,
ethyl or propyl, are attached to

a linear alkyl chain. "Lower alkyl" means

a group
having about

I to about

6 carbon atoms in the chain which may be straight or
10 branched. The term "substituted alkyr means that the alkyl group may be
substituted by one or more substituents which may be the same or different,
each substituent being independently selected from the group consisting of halo, alkyl, aryl, cydoalkyl, cyano, hydroxy, aikoxy, aikyithio, amino, -NH(alkyl),

-

NH(cycloalkyi), -N(alkyl)2. carboxy and C(0)0-alkyl. Non-limiting examples of
15 suitable aikyl groups Include methyl, ethyl, n-propyt, isopropyl and

1-butyl.
"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and
comprising about

2 to about 15 carbon atoms in the chain. Preferred alkynyl
groups have about

2 to about 12 carbon atoms In the chain; and more preferably
20 about

2 to about

4 carbon atoms In the chain. Branched means that one or more
lower alkyl groups such as methyl, ethyl or propyl, are attached to

a linear

alkynyl chain. "Lower alkynyr means about

2 to about

6 carbon atoms In the

chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The
25. term "substituted alkynyl" means that the alkynyl group may be substituted by
one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cydoalkyl.
"Aryl" means an aromatic monocyclic or multicyclic ring system
30 comprising about

6 to about 14 carbon atoms, preferably about

6 to about 10

carbon atoms. The aryl group can be optionally substituted with one or more
ring system substituents" which may be the same or different, and are as

- ’O

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Table 32

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Ex. Column

2 Columnl Column

4 CMPD
3

398 /Th Br MS: MW=419
M.P. 102-105°C

OHrNN

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MS: MH421
M.P. 79-81 °C

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MS: MW 433

M.P. 226-231 °C HO9 N’ HO

HN6

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S r402 MS: MW 447

M. P. N H 97-102°C

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M.P.

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MB: MW 388

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Organization
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as to the app!leant’s entitlement to claim thepriority ofthe
earlier application (Rate 4.17(lli))for all designations
- asic the app!leant’s entitlement to claim thepriorityofthe
earlier application (Rate 4.17(lll))fcr all designations

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For eec-letter codes andother abbreviations, refer to the "Guid-
ance Note., on Codes andAbbreviations’ appearing at the begin-
ning ofeach regular Issue ofthe PCTGown,- azette.

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It)

(54) Title: PYRAZOLOPYRIMIDINES AS CYCLIN DBPENDENT KINASE INHIBiTORS

(57) Abstract: In its many emlndtmenu, the present Invention provides a novel class of pyrezolo[t,5-a]pyrtmldtne compounds as Inhibitors of cyclin dependent kineses, methods of preparing such compounds, pharmaceutical compositions containing one or
more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods
of treatment, prevention, Inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or phannaceutlesl compositions.

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K S. Kim etal. J. Med. Chem. 45(2002) 3905-3927 and WO 02110162

disclose certain amlnothiazole compounds as CDK Inhibitors. Pyrazoiopyzimidlnes are known. For Example, W092118504, W002150079, W095135298, W002140485, EP94304104.6, EP0628559 (equivalent to US

5 Patents 5,602,136. 5,602,137 and 5,571,813), U.S. 6,383,790. Chem. Phann.

Suit., (1999) 4Z 928, J. Med. Chem., (1977) 2. 296, J. Med. Chem., (1976) i. 517 and Chem. Pharm. Bull., (1962) jQ 620 dIsclose various pyrazotopyrimidines. There is a need for new compounds, formulations, treatments and

therapies to treat diseases and disorders associated with CDKs. It is, therefore, an

10 object of this Invention to provide compounds useful In the treatment or prevention
or amelioration of such diseases and disorders.

Summary of the Invention

In its many embodiments, the present Invention provides a novel class of

15 pyrazolo[l,5-a]pyrimidlne compounds as Inhibitors of cyclin dependent kineses,

methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, Inhibition or amelioration of one or more diseases associated with the CDKs using

20 such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown In Formula Ill:

R3N

25 Formula Ill

wherein:

R Is heteroazyl, wherein said heteroaryl can be unsubstltuted or optionally Independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of

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7 68

CLAIMS
1-2 What Is claimed Is:
Re N1

1. A compound represented by the structural tenaula:
1-2 and
R3
1-2

vl-2 HNR

wherein said alkyl. aryl, heteroal)1, heterocycI4 and cycloalkyl for R3 are 5 whereim
unsubstltuted or optionally Independently substituted with one or more moieties R Is heteroaryl. wherein said heteroaryl can be unsubstituted or optionally
5 which can be the same or different, each moiety being Independently selected independently substituted with one or more moieties which can be the same or
from the group consisting of halogen, CF3. OCF3, lower alkyl. CN and OR8. different, each moiety being Independently selected from the group consisting of
In another embodiment, R4 is H, halo, orlower alkyl. halogen, alk)l, aryl, cycloalkyl, CF3. OCF3, CN, -OR5, -NR5R8, -C(R4R5)OR5, -
In another embodiment, R51s H orlower alkyl. 10 C(02)R8. -C(0)W, -C(0)NR5R6, -SW, -S(02)R7, -S(02)NR5R8, -N(R5)S(02)RT,
In another embodiment, m Is lo 2. 44(R8)C(0)R7 and -N(R5)C(0)NR5R8;
10 in another embodiment, n Is Ito 2. R2 Is selected from the group consisting of W. alkyl, alkynyl, 00)4.
In an additional embodiment. R is 2-pyildyl, 4-pylid)i, 3-pyildyl, 4-pyrldyl-N- heteroaryl, CF, hetemcyd)4aik)1, alkyn)4alk)1, cycloalkyl, -C(0)0R4, alkyl
odds, 3-pyrld)l-N-oxlde. 1,3-thlazol-2-yl, pyrlmldln-5-yl, pyiazln-3-yl and pyildazln- substituted with 1-6 R9 groups which can be the some or different and are
3-yl. 15 independently selected from the Hat of R9 shown later below,

In an additional embodiment, F, Cl, Br. CF3. CN, lower alkyl, cycloalkyl or- CH2)nrP(j)4_R8 \ACH2)fl)Re J_ari()-. 15 (CH2),10R8.
In an additional embodiment. R3 Is H, lower alkyl, cycloalkyl, bcarC)_Rs
and
12

wherein the aryl in the above-noted definitions for R2 can be unsubstituted or

(OR8, aryl, hetema, loalal,Nl or optionally substituted with one or more moieties which can be the same or
12

20 different, each moiety being Independently selected from the group consisting of
QN halogen. CN, -014, SR8. -CH2O, R5 -C(0)Ft, -SH, -S(02)R8, -S(02)NR8R°,

wherein each of said lower alkyl, cycloalkyl, hethma and

- NR°, (0)NR8R8. -CF3. and CF3;

R3 Is selected from the group consisting of H, halogen, -NR5R°, -C(o)OR, aryl are unsubstituted or optionally Independently substituted with one or more -C(0)NR8R6, alkyl, alkynyl, cyc1oalkl, cdoaik)4aik)4, ar)l, az)Iaik)1, heterocycl)l, 20 moieties which can be the same or different, each moIety being Independently 25 heterocydylalk)l. heteroaryl. selected from the group consisting of halogen, CF3, lower alkyl, Me and CN.

In an additional embodiment, R3 Is:

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R8i,N1 R4-
1-2 and

L1
R8

wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl,
heterocyciylaikyi, heteroaryl and heteroarylalkyl for R3 and the heterocyclyl
5 moieties whose structures are shown immediately above for R3 can be substituted
or optionally independently substituted with one or more moieties which can be
the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl. CF3. CN, -OCF3, -(CR4R5)OR5, -OR5,
- NR5R6, -(CR4RNR5R6, -C(02)R8, -C(0)R5, -C(0)NR5R6, -SW, -S(02)R°,
10 -S(02)NR5R°, -N(R)S(02)R7, -N(R5)C(0)R7 and -N(R5)C(0)NR5R6;
R4 is H, halo or alkyl;
R5 is H or alkyl;
R° is selected from the group consisting of H, alkyl, aryl. arylalkyl,
cycloalkyl, heterocyclyl, heterocyclyialkyl, heteroaryl, and heteroarylalkyl, wherein
15 each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl,
heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being Independently selected from the group consisting of halogen, alkyl, aryl,
cycloalkyl, CF3. OCF3. CN. -OR5, -NR5R10, -N(R6)Boc, -(CR4ROR5, -C(02)R5,
20 -C(0)R5, -C(0)NR5R10, -SO3H, -SR10, -S(02)R1, -S(02)NR5R10, -N(R5)S(02)R7,
- N(R5)C(0)R1 and -N(R5)C(0)NR5R’°;
R1° Is selected from the group consisting of H, alkyl, aryl, arylalkyl,
cycloalkyl, heterocyclyl, heterocyclyiaikyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl. heterocyclylaikyi,
25 heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with
one or more moieties which can be the same or different, each moiety being

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Independently selected from the group consisting of halogen, alkyl, aryl,
cycloalkyl, CF3. OCF3, CN, -OW, -NR4R5, -N(R5)Boc, -(CR4R5),10R5, -C(02)R8,
- C(0)NR4R8, -C(0)R5, -SO3H, -SW, -S(02)R7, -8(02)NR4R5, -N(R)S(02)R7,
- N(R5)C(0)R7 and -N(R5)C(0)NR4R5;
5 or optionally (I) R5 and R1° in the moiety -NR8R10, or (II) R5 and R° in the moiety -NR5R°, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with one or more R9 groups;
R7is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl,
10 arylalkyl and heteroarylalkyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl,
aryl, heteroaryl and arylalkyl for R7 can be unsubstituted or optionally
Independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF3. OCF3, CN, -OR8, -NR5R10, -CH2OR5, -

15 C(020, -C(0)NR5R10, -C(0)W. -SR10. -8(02)R10, -S(02)NR5R10, -N(R8)S(02)R10,
- N(R8)C(0)R1° and -N(R)C(0)NR8R10;
R8 Is selected from the group consisting of R°, -C(0)NR8R10, -CH2OR8,
- C(0)0R6, -C(0)R7and -S(02)R7;
R9 Is selected from the group consisting of halogen, -CN, -NR8R6,
20 -(CH2)OR8, -C(02)R6, -C(0)NR5R6, -OW, -SW, -S(02)R7, -S(02)NR8R8,
- N(R5)S(02)R7, -N(R8)C(0)R1and -N(R)C(0)NR6R6;
m IsO to 4; and
n Is to 4.

2. The compound of claim 1, wherein R Is selected from the group consisting
25 of 2-pyndyi, 4-pyildyl, 3-pyridyl, 4-pyiidyl-N-oxlde, 3-pyrldyl-N-odde, 1,3-thlazol-2-
yl, pyrimidin-5-yl, pyrazin-3-yI and pyridazln-3-yl wherein each of said pyiidyl, thlazolyl, pyilmidinyl, pyrazinyl and pyridazinyl moieties can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group
30 consisting of halogen, alkyl, aryiCF3, OCF3, CN, -OW, -NR6R6, -CH20R5, -
C(02)R5, -C(0)NR511°. -S(02)NR5R6, and -N(R)S(02)R’
R2 Is halogen, CF3. CN, lower alkyl, cycloalkyl, -OW, -C(0)OR8,
-(CH2)OR°, aryl or heteroaryl;

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Br Br

°ç rN

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or

a pharmaceutically acceptable salt or solvate thereof.
27.

A method of inhibiting one or more cyclin dependent kinases, comprising
10 administering

a therapeutically effective amount of at least one compound of claim
1t

a patient In need of such inhibition.
28.

A method of treating one or more diseases associated with cyclin
dependent idnase, comprising administering

a therapeutically effective amount of
at least one compound of claim Ito

a patient In need of such treatment
15 29. The method of claim 28, wherein said cyclin dependent kinase is CDK2.
30. The method of claim 28 wherein said disease Is selected from the group consisting ot cancer of the bladder, breast, colon, kidney, Over, lung, small cell
lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid,

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prostate, and skin, squamous cell carcinoma; leukemia, acute lymphocytic leukemia, acute iymphobiastic leukemia,

B-cell lymphoma, T- cell lymphoma,
Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, Burketts lymphoma; acute and chronic myologenous leukemia, myelodyspiastic syndrome,
5 promyelocytic leukemia; fibrosarcoma, rhabdomyosarcoma; astrocytoma,
neurobiastoma, glioma and schwannomas; melanoma, seminoma,
teratocarclnoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposrs sarcoma
31.

A method of treating one or more diseases associated with cyclin
10 dependent kinase, comprising administering to

a mammal in need of such
treatment
an amount of

a first compound, which is

a compound of claim 1, or

a

pharmaceutically acceptable salt or solvate thereof
and

15 an amount of at least one second compound, said second compound being
an anti-cancer agent,
wherein the amounts ofthe first compound and said second compound
result in

a desired therapeutic eficct.
32. The method of claim 31, further comprising radiation therapy.
20 33. The method of claim 31, wherein said anti-cancer agent Is selected from
the group consisting of

a cytostatic agent, clsplatln, doxorubicin, taxotere, taxol,
etoposide, Irinotecan (or CPT-1 1), camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxlfen, 5-fluorouracil, methoxtrexate, 5-Fiuorouradll,
temozolomide, cyciophosphamide, 4-12-14-[(I IR)-3,10-dlbromo-8-diloro-6,1 1-
26 dlhydro-5H-benzo[5,6]cyclohepta[I,2-b]pytldin-I 1-yl-]-I-piperidiny11-2-oxoehtyl-I-
piperidinecarboxamide, tipifamib, L778,123 (a famesyl protein transferase
Inhibitor), BMS 214662 (a famesyl protein transferase Inhibitor), Iressa, Tarceva, antibodies to EGFR. Gleevec, lntron, are-C, adrlamycln, cytoxan, gemcltabine,
Uradll mustard, Chlormethine, lfosfamide. Meiphalan, Chlorambucil, Pipobroman,
30 Trlethylenemeiamine, Triethylenethlophosphoramine, Busulfan, Carmustine,
Lomustine, Streptozocin, Dacarbazine, Floxurldlne, Cytarabine, 6-Mercaptopurine, 6-Thloguanine, Fludarabine phosphate, oxallplatln, leucovirin, oxallplatin, Pentostatine, Vinblastlne, Vincristine, Vindesine, Bieomycin, Dactinomycln,

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Daunorubicin, Doxorubicin, Epirubicin, Idarublcin, Mlthramycin, Deoxycoformycin, Mitomycln-C, L-Asparaginase, Teniposide 17u-EthhiIestradIol, Diethyistilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone proplonate, Testolactone, Megestrolacetate, Meth)4prednlsolone, Methyltestoserone, Prednisotone, Triamclnoione, Chlorotiianlsene, Hydroxyprogesterone, Anilnoglutethlmlde, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelln, Cisplatin, Carboplatin. Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Naveibene, Anastrazole, Letruzole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamhie.
34. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim I In combination with at least one pharmaceutically acceptable carrier.
35. The pharmacØullcal compositich of claim 34, additionally comprising one or more anti-cancer agents selected from the group consisting of cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-1 1, irinotecan, Camptostar, topotecan, paciltaxel, docetaxel, epothliones, tamoxifen, 5-fluorouracli, methoxtrexate, 5-fluorouracli, temozolomide, cyclophosphamide. 4-[2-14-1(11 R)- 3,1
’rrIdhiyl]:2-oxoehtyl1-1-pIperIdh1ecarboxam1de, Zamestrafi (tipitamib), rhlbeso proteinbnsferase Inhibitor), BMS 214662 (a tamesyi

proteintltor),Iressa, Tameva, antibodies to EGFRI Gleevec, Intron, are-C,
ytoxän, gemcltabine. Uradil mustard, Chlomiethlne, Ifosfamide,

/ hteranbuclt, Pipobroman, Trlethyienemelamlne,
ophchoramlne, Busuifan, Carmustine, Lomustine, Streptozocin,
Floxi‰rldIne,Cytambine, 6-Mercaptopurine, 6-Thioguanine,
4.hospate,Pentostaflne Vinblastine, Vinctistine, Vindesine,
.%cflnonydn, DauorubicIn. Doxorubicin, Ephubicin, Idarublcin,
eofórmyafniiiycln-C, L-Asparaginase, Teniposide 11cr.-

1i 91 yistllbestrol, Testosterone, Prednisone, Fluoxymesterone,
30 DromóstnJ proplonate, Testolactone, Megestrolacetate, Methyiprednlsotone, Methyitetoen, Prednlsolóne, Trlamclnolone, Chiorotrlanlsene,
Arninoglutethlmlde, Estramustlne,

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Medroxypragesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cleplatin, Carboplatln,Hydroxyuree, Anisacrine, Procarbazine, Mitotane, Mltoxantivne, Levamisole, Naveibene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafino, or Hexamethylmetarnlrre.
5 38. A compound of claIm 1, In Isolated and purified form.