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SUPERINDUSTRIA Y COMERCIO

Radicacion : 00090146 00000008

Fecha (AMD): 2003-10-21 15:56:53

Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION

Folios: 2

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
MINISTERIO DE DESARROLLO ECONOMICO

REF: EXPEDIENTE : **00090148**

SOLICITANTE: SUGEN, INC

FECHA DE LA SOLICITUD: NOVIEMBRE 24, 2000

TITULO: FORMULACIONES PARA AGENTES FARMACEUTICOS...

ASUNTO: SOLICITUD ESTUDIO DE FONDO

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial N°.527 de fecha Abril 30, 2003 se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente, No. 03.72.688

Agradezco continuar con el presente trámite.

Señor Jefe,

DILIA RODRÍGUEZ D'ALEMAN
T.P.No. 20824 del CSJ

P-382

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SUPERINDUSTRIA Y COMERCIO

Radicacion : 00090148 00000000

Folios: 2

Fecha (AMD) : 2003-10-21 15:56:53

Tramite : 002 PATENTES D 1 REGISTRO/ 530 PETICION

MIT 800176099

RECIBO OFICIAL DE CAJA 03 - 72 688
FECHA OCTUBRE 6 DE 2003

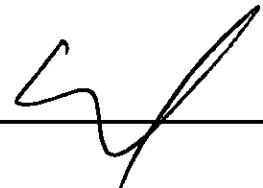
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	8897067	06/10/2003	3 046 000 00

***** C O N C E P T O *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	335 000 00
		TOTAL :	\$ 335 000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE . 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

484
302

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

302

2020/
Bogotá, D.C.,

Doctora
Dilia María Rodríguez
Apoderada

Oficio N° 3711

REFERENCIA	Radicación	00 90148
	Trámite	002
	Evento	001
	Actuación	430
	Folios	015

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 90148, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 4-165
- . Ejemplos: folios 165-305
- . Capítulo reivindicatorio estudiado: folios 306-321
- . Se reivindica prioridad, presentada en Estados Unidos el 24.11.99, bajo el número 60/167544

Objeto de la invención

Según las reivindicaciones 1 a 84 de la presente solicitud, se refiere a una formulación adecuada par administración parenteral u oral que comprende una indolinona sustituida ionizable y un vehículo aceptable para uso farmacéutico.

Clasificación internacional de patentes A 61 K 31/404

Claridad de la solicitud

El art. 30 de la decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

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El término "indolinona sustituida ionizable" de la reivindicación 1 abarca una gran cantidad de compuestos que cumplen con este término y que pueden no encontrarse sustentados por la descripción"

Los términos utilizados en la reivindicación 2 como "compuestos de polihidrocarbilo", "conservantes", "antioxidantes", "alcoholes", "soluciones", "aceites", "liposomas", "lípidos poliglilizados", "agentes de granulación", "diluyentes", "aglutinantes", "desintegrantes", "lubricantes", "incrementadores de flujo" y "agentes de suspensión" son muy generales y abarcan prácticamente TODOS los auxiliares de formulación que, obviamente, no se encuentran sustentados en la descripción. Se le recuerda al solicitante que una composición se debe definir por sus componentes específicos y la proporción de los mismos para que se diferencien de manera clara de las existentes en el estado de la técnica.

Los términos "prodroga", "derivado" y "análogo" usados en las reivindicaciones son vagos y poco claros y dejan en el lector en duda sobre el significado técnico y el alcance de la materia que se desea proteger.

Excepciones a la patentabilidad

El artículo 20d de la decisión 486 de la comisión de la comunidad andina establece que: *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 78-84, que trata de "Un método de prevenir o tratar...", no es patentable.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 24.11.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	US 5886020	"3-(4'-dimetilaminobencilidenil)-2-indolinonas y sus análogos para el tratamiento de enfermedades"	23.03.99
2	US 5883116	"3-(2'-alcoxibencilidenil)-2-indolinonas y sus análogos para el tratamiento de enfermedades"	16.03.99
3	US 5883113	"3-(4'-bromobencilidenil)-2-indolinonas y sus análogos para el tratamiento de enfermedades"	16.03.99
4	WO 9850365	"Preparación de alcaloides policíclicos fusionados por cerramiento del anillo de ilidas de azometina, compuestos novedosos que los contienen y su uso como agentes quimioterapéuticos"	13.11.98
5	WO 9807695	"Series de indolinonas combinatorias y productos relacionados para el tratamiento de enfermedades"	26.02.98

486
488

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que:
"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El art. 16 de la decisión 486 contempla que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

El documento US 5886020 revela indolinonas ionizables que son moduladores de la traducción de la señal de la tirosina quinasa y composiciones que las contienen.

El documento US 5883116 revela indolinonas ionizables que son moduladores de la traducción de la señal de la tirosina quinasa y composiciones que las contienen.

El documento US 5883113 revela indolinonas ionizables que son moduladores de la traducción de la señal de la tirosina quinasa y composiciones que las contienen

La publicación WO 9850365 revela indolinonas ionizables, su método de preparación y composiciones farmacéuticas que las contienen,

La publicación WO 9807695 se relaciona con indolinonas ionizables que son inhibidores de la tirosina quinasa y composiciones que las contienen.

Comparando elemento por elemento, las composiciones de las reivindicaciones 1, 2, 4, 6-11, 20, 21, 23, 24, 26-28, 30, 31, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47-50, 52-58, 60-63 y 65-67 de la presente solicitud son iguales a las de los documentos citados y pueden afectar la novedad de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

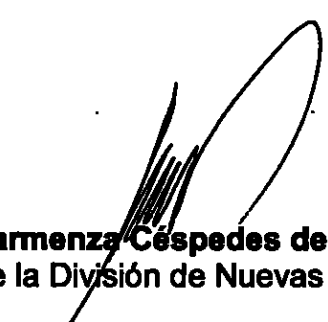
Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5886020	1, 2, 4, 6-11, 20, 21, 23, 24, 26-28, 30, 31, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47-50, 52-58, 60-63 y 65-67	Novedad
2	US 5883116		
3	US 5883113		
4	WO 9850365		
5	WO 9807695		

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar

187

respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 30 MAR. 2006

CONCEPTO TÉCNICO Número 0462	EXAMINADOR TÉCNICO Código 202024
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US005886020A

United States Patent [19]

Tang et al.

[11] Patent Number: 5,886,020

[45] Date of Patent: Mar. 23, 1999

[54] 3-(4'-DIMETHYLAMINO BENZYLIDENYL)-2-INDOLINONE AND ANALOGUES THEREOF FOR THE TREATMENT OF DISEASE

[75] Inventors: Peng Cho Tang, Moraga; Li Sun, Foster City; Gerald McMahon, Kenwood, all of Calif.

[73] Assignee: Sugan, Inc., Redwood City, Calif.

[21] Appl. No.: 655,226

[22] Filed: Jun. 5, 1996

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 485,323, Jun. 7, 1995.

[51] Int. Cl.⁶ A61K 31/40; C07D 209/34

[52] U.S. Cl. 514/418; 548/486

[58] Field of Search 548/486; 514/418

[56] References Cited

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4,966,849	10/1990	Vallee et al.	435/199
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5,322,950	6/1994	Sircar et al.	548/253
5,330,992	7/1994	Eissenstat et al.	514/312
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Translation of Neber et al., "On the action of Benzaldehydes on the Free Aminophenylacetic Acid (II)" *Chem. Institute of the Univ. of Tubingen* 1-8 (1923).

Translation of Szanatay et al., "Process for Preparing Spiro-oxindole Derivatives and of Drug Preparation Containing Same" 1-29 (1992).

Beilstein Reg. No.: 252929 Beilstein (1923).

Andreani et al., "Potential Antitumor Agents. 25[1]. Synthesis and Cytotoxic Activity of 3-(2-Chloro-3-Indolylmethylene) 1,3-Dihydroindol-2-Ones," *AntiCancer Research* 16:3585-3588 (1996).

Terrett et al., "Combinatorial Synthesis—The Design of Compound Libraries and their Application to Drug Discovery," *Tetrahedron* 51(30):8135-8173 (1995).

(List continued on next page.)

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Lyon & Lyon LLP

[57] ABSTRACT

The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

45 Claims, No Drawings

2) Administer the compound; and

3) Measure the tumor growth at various time points.

The tumors can also be analyzed for the presence of a receptor such as HER2, by Western and immunohistochemical analyses. Using techniques known in the art, one skilled in the art can vary the above procedures, for example through the use of different treatment regimes.

6.3.4. Tumor Invasion Model

The following tumor invasion model has been developed and may be used for the evaluation of therapeutic value and efficacy of the compounds identified to selectively inhibit KDR/FLK-1 receptor.

6.3.4.1. Procedure

8 week old nude mice (female) (Simonsen Inc.) were used as experimental animals. Implantation of tumor cells was performed in a laminar flow hood. For anesthesia, Xylazine/Ketamine Cocktail (100 mg/kg ketamine and 5 mg/kg) are administered intraperitoneally. A midline incision is done to expose the abdominal cavity (approximately 1.5 cm in length) to inject 10^7 tumor cells in a volume of 100 μ l medium. The cells are injected either into the duodenal lobe of the pancreas or under the serosa of the colon. The peritoneum and muscles are closed with a 6-0 silk continuous suture and the skin was closed by using wound clips. Animals were observed daily.

6.3.4.2. Analysis

After 2-6 weeks, depending on gross observations of the animals, the mice are sacrificed, and the local tumor metastases, to various organs (lung, liver, brain, stomach, spleen, heart, muscle) are excised and analyzed (measurements of tumor size, grade of invasion, immunochemistry, and in situ hybridization).

6.3.5. RESULTS

Results for various compounds obtained from the above-described in vivo assays are set forth at Table 5, below:

TABLE 5

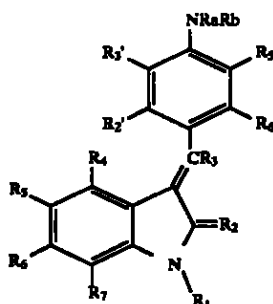
COMPOUND	In Vivo Data	
	EphA-VEGF	% inhibition @ mg/kg
SU4312	56% @ 75	
	50% @ 75	
	63% @ 50	
SU4932	42% @ 75	
	42% @ 50/50	
SU4942	46% @ 50	
	47% @ 25	
SU5416	50% @ 25	
	57% @ 37.5/37.5	
SU5424	45% @ 50	
	65% @ 50	
SU5427	47% @ 50	
	65% @ 50	

The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

All references cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is H or alkyl;

R_2 is O or S;

R_3 is hydrogen;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

R_2' , R_3' , R_4' , and R_6' are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

n is 0-3;

R is H, alkyl or aryl;

R' is H, alkyl or aryl; and

R_a and R_b are each independently selected from the group consisting of H, alkyl and $C(O)R$, or NR_aR_b taken together are a heterocyclic ring of from 3 to 8 atoms optionally substituted at one or more positions with hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_3R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

with the provisos that:

(i) when R_a and R_b are both H, at least one of R_4 , R_5 , R_6 , R_7 , R_2' , R_3' , R_4' or R_6' must be other than hydrogen provided that R_2' is not methyl;

(ii) when R_1 is methyl and one of R_a and R_b is methyl and the other is isooctyl, at least one of R_4 , R_5 , R_6 , R_7 , R_2' or R_3' must be other than hydrogen;

(iii) if one of R_a and R_b is H or lower alkyl, the other of R_a and R_b is not lower alkyl; and

(iv) if one of R_a or R_b is $C(O)R$, at least one of R_2' , R_3' , R_4' , R_6' is not H.

2. The compound of claim 1 wherein:

R_3' is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, halogen, aryl and OR, where R is H, alkyl or aryl; and

R_5' is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, halogen, aryl and OR, where R is H, alkyl or aryl.

3. The compound of claim 1, wherein NR_aR_b taken together are a heterocyclic ring of from 3 to 8 atoms



US005883116A

United States Patent [19]
Tang et al.

[11] Patent Number: 5,883,116
[45] Date of Patent: Mar. 16, 1999

[54] 3-(2'-ALKOXYBENZYLIDENYL)-2-INDOLINONE AND ANALOGUES THEREOF FOR THE TREATMENT OF DISEASE

[75] Inventors: Peng Cho Tang, Moraga; Li Sun, Foster City; Gerald McMahon, Kenwood, all of Calif.

[73] Assignee: Sugen, Inc., Redwood City, Calif.

[21] Appl. No.: 655,224

[22] Filed: Jun. 5, 1996

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 485,323, Jun. 7, 1995.

[51] Int. Cl.⁶ A61K 31/40; C07D 209/34

[52] U.S. Cl. 514/418; 548/486

[58] Field of Search 548/486; 514/418

[56] References Cited

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(List continued on next page.)

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Lyon & Lyon LLP

[57] ABSTRACT

The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

26 Claims, No Drawings

J. Steroid Biochem. 30:311-314. More specifically, the following procedure can be used to measure the inhibitory effect of a compound on the HER2 receptor:

- 1) Implant, at various concentrations, MDA-MB-231 and MCF-7 cells transfected with HER-2 into the axillary mammary fat pads of female athymic mice;
- 2) Administer the compound; and
- 3) Measure the tumor growth at various time points.

The tumors can also be analyzed for the presence of a receptor such as HER2, by Western and immunohistochemical analyses. Using techniques known in the art, one skilled in the art can vary the above procedures, for example through the use of different treatment regimes.

6.3.4. Tumor Invasion Model

The following tumor invasion model has been developed and may be used for the evaluation of therapeutic value and efficacy of the compounds identified to selectively inhibit KDR/FLK-1 receptor.

6.3.4.1. Procedure

8 week old nude mice (female) (Simonsen Inc.) were used as experimental animals. Implantation of tumor cells was performed in a laminar flow hood. For anesthesia, Xylazine/Ketamine Cocktail (100 mg/kg ketamine and 5 mg/kg) are administered intraperitoneally. A midline incision is done to expose the abdominal cavity (approximately 1.5 cm in length) to inject 10^7 tumor cells in a volume of 100 μ l medium. The cells are injected either into the duodenal lobe of the pancreas or under the serosa of the colon. The peritoneum and muscles are closed with a 6-0 silk continuous suture and the skin was closed by using wound clips. Animals were observed daily.

6.3.4.2. Analysis

After 2-6 weeks, depending on gross observations of the animals, the mice are sacrificed, and the local tumor metastases, to various organs (lung, liver, brain, stomach, spleen, heart, muscle) are excised and analyzed (measurements of tumor size, grade of invasion, immunochemistry, and in situ hybridization).

6.3.5. RESULTS

Results for various compounds obtained from the above-described in vivo assays are set forth at Table 5, below:

TABLE 5

COMPOUND	In Vivo Data	
	EpH4-VEGF	% inhibition @ mg/kg
SU4312	56% @ 75	
	50% @ 75	
	63% @ 50	
SU4932	42% @ 75	
	—	
SU4942	42% @ 50/50	
	46% @ 50	
	47% @ 25	
SU5416	50% @ 25	
	—	
SU5424	57% @ 37.5/37.5	
	45% @ 50	
SU5427	65% @ 50	
	47% @ 50	
	65% @ 50	

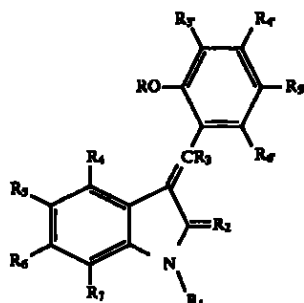
The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein

will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

All references cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is H or alkyl;

R_2 is O or S;

R_3 is hydrogen;

R_4 , R_5 , R_6 , and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_2R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

R_3' , R_4' , R_5' , and R_6' are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, $S(O)R$, SO_2NRR' , SO_2R , SR , NO_2 , NRR' , OH , CN , $C(O)R$, $OC(O)R$, $NHC(O)R$, $(CH_2)_nCO_2R$, and $CONRR'$;

n is 0-3;

R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

with the provisos that:

- (i) when OR at the 2-position of the benzylidenyl moiety is methoxy, R_5 is not OH or methoxy;
- (ii) OR at the 2-position of the benzylidenyl moiety is not OH;
- (iii) said compound is not 3-[2,5-dimethoxybenzylidenyl]-2-indolinone or 3-[2-methoxybenzylidenyl]-2-indolinone, and
- (iv) if R_6' is NRR' , then R and R' are not alkyl substituted with $N(CH_3)_2$ amino.

2. The compound of claim 1 wherein:

R_3' is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, halogen, aryl and OR, where R is H, alkyl or aryl; and

R_5' is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, halogen, aryl and OR, where R is H, alkyl or aryl.



US005883113A

United States Patent [19]
Tang et al.

[11] Patent Number: 5,883,113
[45] Date of Patent: Mar. 16, 1999

[54] 3-(4'-BROMOBENZYLINDENYL)-2-
INDOLINONE AND ANALOGUES THEREOF
FOR THE TREATMENT OF DISEASE

[75] Inventors: Peng Cho Tang, Moraga; Li Sun,
Foster City; Gerald McMahon,
Kenwood, all of Calif.

[73] Assignee: Sugan, Inc., Redwood City, Calif.

[21] Appl. No.: 659,191

[22] Filed: Jun. 5, 1996

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 485,323, Jun. 7, 1995.

[51] Int. Cl.⁶ A61K 31/40; C07D 209/34

[52] U.S. Cl. 514/418; 548/486

[58] Field of Search 548/486; 514/418

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(List continued on next page.)

Primary Examiner—Richard L. Raymond

Attorney, Agent, or Firm—Lyon & Lyon LLP

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The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

27 Claims, No Drawings

mary cell lines, including MCF-7, have been grown in the mammary fat pad of athymic mice. Shafie and Grantham, 1981, *Natl. Cancer Instit.* 67:51-56; Gottardis et al., 1988, *J. Steroid Biochem.* 30:311-314. More specifically, the following procedure can be used to measure the inhibitory effect of a compound on the HER2 receptor:

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TABLE 5-continued

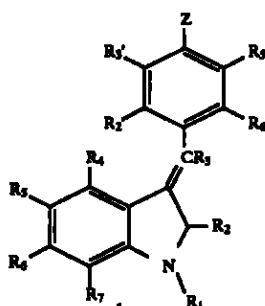
In Vivo Data	
COMPOUND	EpH4-VEGF % inhibition @ mg/kg
SUS416	50% @ 25
	57% @ 37.5/37.5
SUS424	45% @ 50
	65% @ 50
SUS427	47% @ 50
	65% @ 50

The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

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What is claimed is:

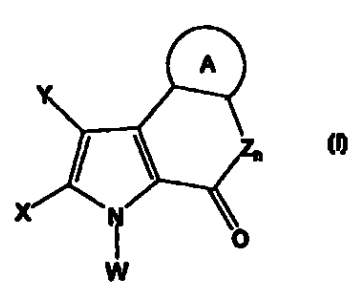
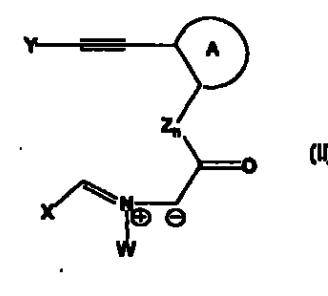
1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

- R₁ is H or alkyl;
 - R₂ is O or S;
 - R₃ is hydrogen;
 - R₄, R₅, R₆, and R₇ are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)₂CO₂R, and CONRR';
 - R₈, R₉, R₁₀, and R₁₁ are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO₂NRR', SO₃R, SR, NO₂, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH₂)_nCO₂R, and CONRR';
 - n is 0-3;
 - Z is Br, Cl, F, I, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl;
 - R is H, alkyl or aryl;
 - R' is H, alkyl or aryl; and
- with the provisos that:

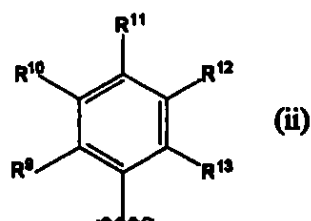
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 217/20, 217/24, 487/14, 491/147, A61K 31/47	A1	(11) International Publication Number: WO 98/50365 (43) International Publication Date: 12 November 1998 (12.11.98)
(21) International Application Number: PCT/AU98/00312 (22) International Filing Date: 1 May 1998 (01.05.98) (30) Priority Data: PO 6565 2 May 1997 (02.05.97) AU (71) Applicant (for all designated States except US): THE AUSTRALIAN NATIONAL UNIVERSITY [AU/AU]; Acton, ACT 2601 (AU). (72) Inventors; and (75) Inventors/Applicants (for US only): BANWELL, Martin, Gerhardt [AU/AU]; 6 Marawa Place, Aranda, ACT 2614 (AU). FLYNN, Bernard, Luke [AU/AU]; 103 Canberra Avenue, Griffith, ACT 2603 (AU). (74) Agents: HUGHES, E., John, L. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PREPARATION OF FUSED POLYCYCLIC ALKALOIDS BY RING CLOSURE OF AZOMETHINE YLIDES, NOVEL COMPOUNDS THEREOF AND THEIR USE AS CHEMOTHERAPEUTIC AGENTS (57) Abstract A method for the preparation of a compound of general Formula (I) comprising the step of cyclizing an azomethine ylide of general Formula (II) wherein A is a cyclic group being an optionally substituted aryl group or an aromatic heterocyclic group; or A is a cyclic group $R^{A1}R^{A2}C-CR^{A3}R^{A4}$ wherein R^{A2} and R^{A3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group and R^{A1} and R^{A4} are as defined below or together form a bond; or A is a non-cyclic group $R^{A1}R^{A2}C-CR^{A3}R^{A4}$ wherein $R^{A1} - R^{A4}$ are as defined below and R^{A2} and R^{A3} may optionally together form a bond; Z is a carbon or a heteroatom; n is selected from 0, 1, 2 or 3; and $R^{A1} - R^{A4}$, W, X and Y may be the same or different and each are selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano, or W and X, together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group; or pharmaceutically acceptable derivatives and salts, racemates, isomers and/or tautomers thereof.  (I)  (II)		

12. A method according to claim 8, wherein Z is oxygen.

13. A method according to claim 1, wherein Y is an optionally substituted phenyl group of Formula (ii)

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wherein $R^9 - R^{13}$ are as defined for $R^1 - R^4$ and R^{14} in claim 5.

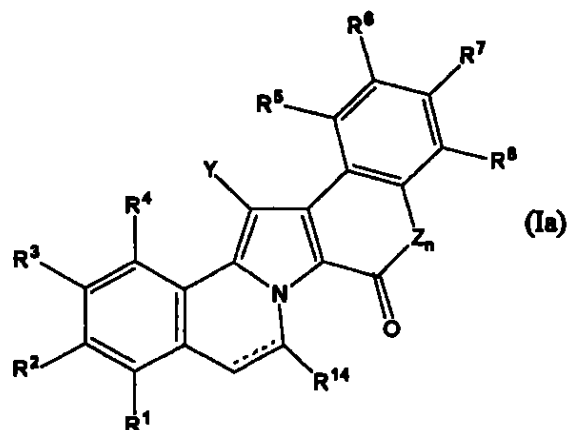
14. A method according to claim 13, wherein $R^9 - R^{13}$ are selected from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, or

15 acyloxy.

15. A method according to claim 14, wherein the $R^9 - R^{13}$ are selected from hydrogen, hydroxy, methoxy, isopropoxy, methyl or acetoxy.

20 16. A method for the preparation of a compound of Formula (Ia):

25



30 comprising the step of cyclizing an azomethine ylide of general Formula (IIa):

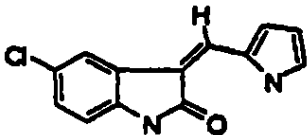
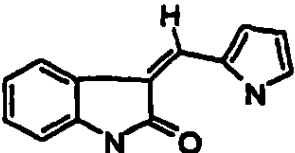
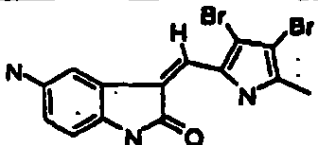
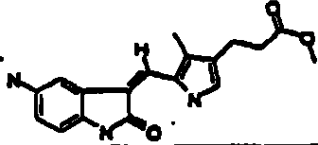
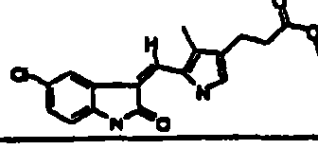
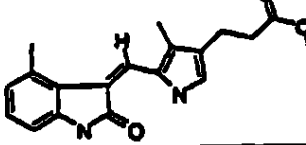
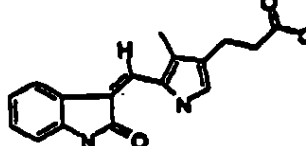
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 209/34, 409/06, 403/06, A61K 31/40		A1	(11) International Publication Number: WO 98/07695
			(43) International Publication Date: 26 February 1998 (26.02.98)
(21) International Application Number: PCT/US97/14736		Road, Kenwood, CA 95452 (US). HIRTH, Klaus, Peter [DE/US]; 334 Collingwood Street, San Francisco, CA 94114 (US). SHAWVER, Laura, Kay [US/US]; 216 Cotter Street, San Francisco, CA 94112 (US).	
(22) International Filing Date: 20 August 1997 (20.08.97)			
(30) Priority Data:		(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West 5th Street, Los Angeles, CA 90071-2066 (US).	
08/702,232	23 August 1996 (23.08.96) US	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
60/031,586	5 December 1996 (05.12.96) US		
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60/045,566	5 May 1997 (05.05.97) US		
60/045,715	5 May 1997 (05.05.97) US		
60/045,714	5 May 1997 (05.05.97) US		
60/046,843	5 May 1997 (05.05.97) US		
60/045,565	5 May 1997 (05.05.97) US		
(71) Applicant (for all designated States except US): SUGEN, INC. [US/US]; 351 Galveston Drive, Redwood City, CA 94063-4720 (US).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventors; and (75) Inventors/Applicants (for US only): TANG, Peng, Cho [US/US]; 827 Camino Ricardo, Moraga, CA 94556 (US). SUN, Li [CN/US]; 64 Rockharbor Lane, Foster City, CA 94404 (US). McMAHON, Gerald [US/US]; 1800 Schultz			
(54) Title: INDOLINONE COMBINATORIAL LIBRARIES AND RELATED PRODUCTS AND METHODS FOR THE TREATMENT OF DISEASE			
(57) Abstract			
The present invention relates to organic molecules capable of modulating, regulating and/or inhibiting protein kinase signal transduction. Such compounds are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis and restenosis and metabolic diseases such as diabetes. The present invention features indolinone compounds that potently inhibit protein kinases and related products and methods. Inhibitors specific to the <i>FLK</i> protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3-yl)methylene]-2-indolinone, in particular at the 1' position of the indole ring. Indolinone compounds that specifically inhibit the <i>FLK</i> and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano-b-pyrrol moiety. Indolinone compounds that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosoluble indolinone compounds that are tyrosine kinase inhibitors and related products and methods.			

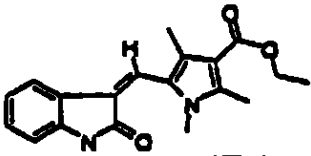
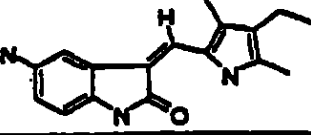
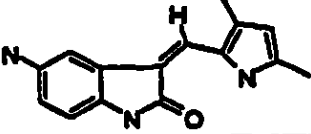
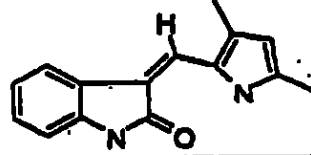
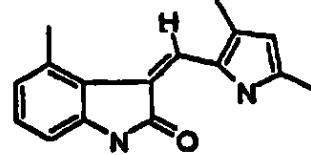
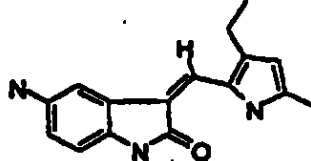
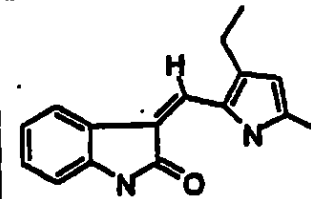
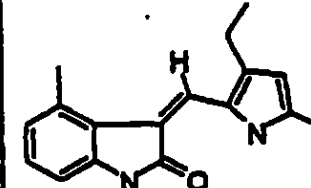
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TABLE 10 SHEET 1 OF 5

FLK Kinase IC50 (μ M)	STRUCTURES	METHOD
1.6		A
2.6		A
1.9		B
4.7		B
5.6		B
10.8		B
12.5		A

498
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TABLE 10 SHEET 2 OF 5

0.97		B
1.5		B
1.1		B
3.5		A
7.3		A
5.6		B
8.1		A
17.3		A