



No. 12-056781- -00005-0000

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Act. 329 CTOINFORMACION Folios: 83

As. 120.340

Señor

DIRECTOR DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente No. **12.056.781** solicitud de patente de invención a favor de
CELGENE CORPORATION Título **PROCESOS PARA LA PREPARACION**
DE 2-(1-FENILETIL)-ISOINDOLIN-1-ONA

PETICION TRAMITE ACELERADO DE PATENTES

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito presentar los siguientes documentos para participar en el programa de trámite acelerado de patentes. La solicitud de examen de patentabilidad fue radicada el 11 de marzo de 2013.

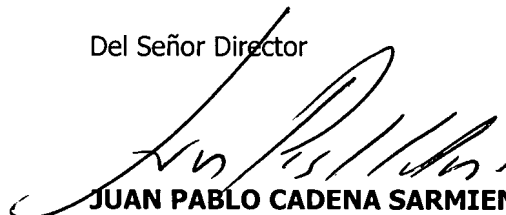
- a. Copia de la acción oficial de patentabilidad emitida por la USPTO junto con la traducción al español.
- b. Copia del arte previo citado en la acción oficial US 7,034,052.
- c. Copia de la respuesta presentada por el solicitante en respuesta a la acción oficial junto con las reivindicaciones modificadas junto con la traducción al español.
- d. Copia de la notificación de concesión (notice of allowability) en donde se establece que las reivindicaciones concedidas son las 1-17.
- e. Notificación de aceptación en donde se establece que la solicitud ha sido examinada y aceptada para conceder la patente.
- f. Tabla de correspondencia entre las reivindicaciones concedidas por la USPTO y las reivindicaciones modificadas en Colombia el 14 de marzo de 2013.

Conclusión

De acuerdo a los documentos adjuntos, las reivindicaciones pendientes actualmente en Colombia corresponden a las reivindicaciones patentadas en Estados Unidos teniendo en cuenta que el alcance es idéntico.

En consecuencia, solicitamos a su Despacho tener en cuenta el examen de patentabilidad y las reivindicaciones concedidas por la USPTO y proceder con la concesión de la patente para la solicitud en Colombia.

Del Señor Director


JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

- a. Copia de la acción oficial de patentabilidad emitida por la USPTO junto con la traducción al español.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/901,338	10/08/2010	Anthony J. Frank	9516-895-999	9825
84802 7590 05/09/2012 JONES DAY for Celgene Corporation 222 E. 41ST. STREET NEW YORK, NY 10017			EXAMINER YOUNG, SHAWQUIA	
			ART UNIT	PAPER NUMBER
			1626	
			MAIL DATE	DELIVERY MODE
			05/09/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	12/901,338		FRANK ET AL.	
	Examiner		Art Unit	
Shawquia Young		1626		

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on ____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5) ☒ Claim(s) 1-17 is/are pending in the application.

 5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☒ Claim(s) 1-17 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date ____.

4) ☐ Interview Summary (PTO-413)
 Paper No(s)/Mail Date. ____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: ____.

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DETAILED ACTION

Claims 1-17 are currently pending in the instant application. Claims 1-17 are rejected in this Office Action.

I. **Priority**

The instant application claims benefit of US Provisional Application 61/250,421, filed on October 9, 2009.

II. **Information Disclosure Statement**

Applicants have not filed an information disclosure statement (IDS) in the instant application.

III. **Rejections**

35 USC § 103 - OBVIOUSNESS REJECTION

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

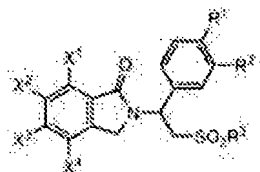
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. § 103(a). See *Graham v. John Deere Co.*, 383 U.S. 1, 148

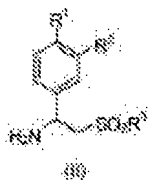
USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

- 1. Determining the scope and contents of the prior art.
- 2. Ascertaining the differences between the prior art and the claims at issue.
- 3. Resolving the level of ordinary skill in the pertinent art.
- 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

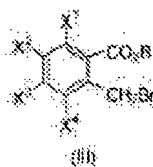
Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Man, et al.* (US Patent 7,034,052). Applicants claim a process for preparing a compound of formula



or a pharmaceutically acceptable salt, solvate, or polymorph thereof, comprising the step of reacting a primary amine of formula (II)



or a salt thereof, with a 2-(bromomethyl)benzoic acid ester of formula (III),



in the presence of an inorganic base, wherein:

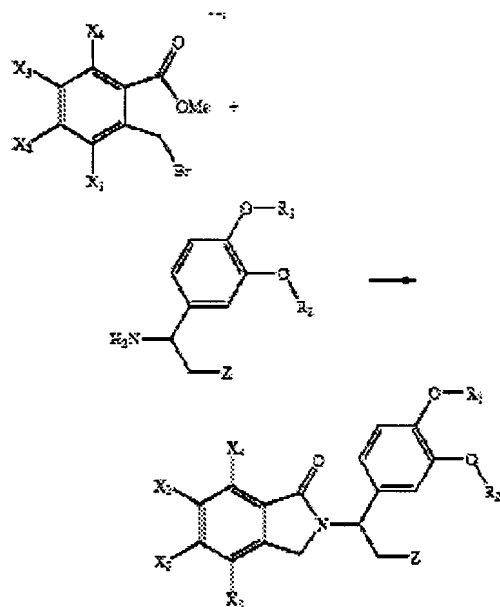
all variables are as defined in claim 1.

The Scope and Content of the Prior Art (MPEP §2141.01)

Man, et al. teaches a process for preparing 7-amido-isoindolyl compounds. The invention is represented by the process:

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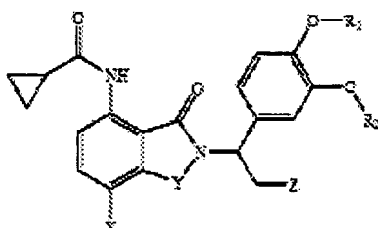


(see column 32) wherein the

variables are as defined

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wherein:

Y is $-\text{C}(\text{O})-$, $-\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{O})-$ or $-\text{SO}_2-$;

X is H;

Z is $(\text{C}_{2-6}\text{-alkyl})-\text{C}(\text{O})\text{R}^3$, $\text{C}_{1-6}\text{-alkyl}$, $(\text{C}_{2-6}\text{-alkyl})-\text{OH}$, $(\text{C}_{1-6}\text{-alkyl})-\text{O}-(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})-\text{SO}_2(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{2-6}\text{-alkyl})-\text{SO}(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{2-6}\text{-alkyl})-\text{NH}_2$, $(\text{C}_{2-6}\text{-alkyl})-\text{N}(\text{C}_{1-6}\text{-alkyl})_2$, $(\text{C}_{2-6}\text{-alkyl})-\text{N}(\text{H})(\text{OH})$, $(\text{C}_{2-6}\text{-alkyl})$ -dichloropyridine, or $\text{CH}_2\text{NSO}_2(\text{C}_{1-6}\text{-alkyl})$;

R_1 and R_2 are independently $\text{C}_{1-6}\text{-alkyl}$, cycloalkyl, or $(\text{C}_{1-6}\text{-alkyl})$ -cycloalkyl;

R^3 is, NR^4R^5 , OH, or $\text{O}-(\text{C}_{1-6}\text{-alkyl})$;

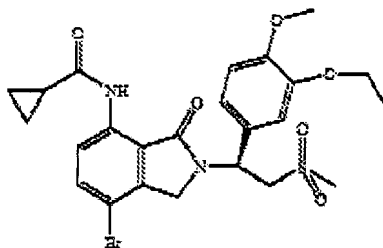
R^4 is H;

R^5 is $-\text{OH}$, or $-\text{O}-\text{C}(\text{O})\text{R}^6$;

R^6 is $\text{C}_{2-6}\text{-alkyl}$, amino- $(\text{C}_{2-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})-(\text{C}_{2-6}\text{-cycloalkyl})$, $\text{C}_{3-6}\text{-cycloalkyl}$, phenyl, benzyl, or aryl;

(see column 11) and teaches the

19



various species such as
20).

(see table 1, columns 19-

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of *Man, et al.* and the instant invention is that there is homologous subject matter. Not all of the substituents are taught, however there is overlap between the substituents disclosed especially in view of the preferred

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embodiments taught by the prior art. The difference is that the instant process uses an inorganic base whereas the prior art teaches the process broadly and in the examples use an organic base.

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

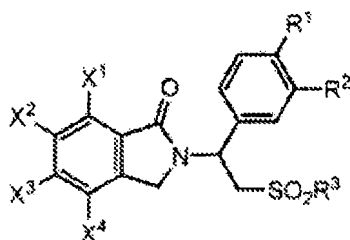
In In re Durden, 763 F.2d 1405, 226 USPQ 359 (Fed. Cir. 1985)), it was well established that the chemical process that is occurring is an expected reaction. The use of a novel and unobvious starting material or a novel and unobvious final product, does not render an obvious, predictable process patentable. In a chemical process, all of the evidence must be considered on the subject matter as a whole from the view point of one skilled in the art, in the determination of obviousness, and not simply to the patentability of one of the starting materials or final products in the process. The process is deemed obvious to one of ordinary skill in the art since it involves a predictable and expected reaction. For example, it is obvious to prepare an isoindolyl compound of the formula in claim 1 using an inorganic base when the art teaches a similar process using an organic base with a reasonable expectation of success. Specifically, an inorganic base and an organic base are still bases and have the same function in the process and are considered obvious absent unexpected results. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to make the above modification based on the teachings of the preferred embodiments in the prior art and perform the same type of reaction.. A strong prima facie obviousness has been established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula



does not reasonably provide enablement for solvates and polymorphs of the said compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

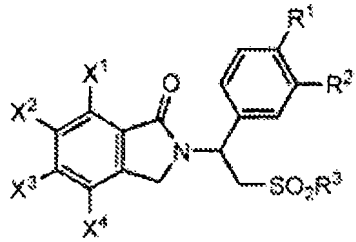
In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a process for preparing a compound of the formula



but does not provide any teachings for a solvate or polymorph of the above compound.

The state of the prior art

It is the state of the prior art that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. The water molecule, because of its small size, can easily fill structural voids and because of its multidirectional hydrogen bonding capability, is also ideal for linking a majority of drug molecules into stable crystal structures. The mere presence of water in a system is not a sufficient reason to expect hydrate formation, because some compounds, though they are soluble in water, do not form hydrates. Predicting the formation of hydrates of a compound and the number of molecules of water incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the

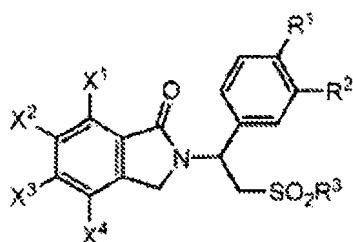
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possible formation of hydrates and hence generalizations cannot be made for a series of related compounds (Vippagunta, et al. 2001).

The amount of direction or guidance present and the presence or absence of working examples

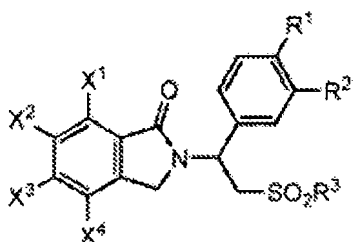
There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what solvates or polymorphs are being included in the elected invention. Applicants have not provided any data to characterize solvates or polymorphs of the compound of formula



. Also, Applicants have not shown how to prepare a solvate form or a polymorph form of the above compound.

The breadth of the claims

The breadth of the claims is a process for preparing a compound of formula



or a pharmaceutically acceptable salt, solvate or polymorph thereof.

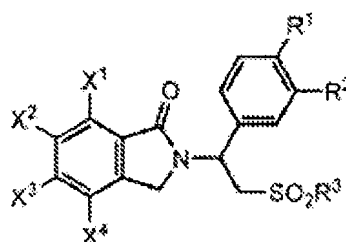
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The level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation.

The level of skill in the art is high without showing or guidance as to how to make



the solvates or polymorphs of the compound it would require undue experimentation to figure out the amount of water, drying temperatures and drying times that would provide all of the possible solvates and polymorphs of the above compound or to determine if the above compound can actually form solvates or polymorphic forms.

To overcome this rejection, Applicant should submit an amendment deleting the term "solvate" and "polymorph".

IV. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/
Primary Examiner, Art Unit 1626

Acción detallada

Las reivindicaciones 1-17 son rechazadas en esta acción oficial.

I. Prioridad

La presente solicitud reivindica beneficio de la solicitud provisional 61/250,421 presentada el 9 de octubre de 2009.

II. Declaración de información revelada

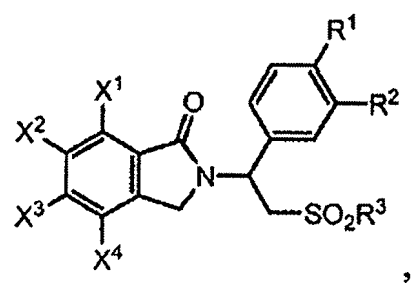
Los solicitantes no han revelado el IDS en la solicitud

III. Objeciones

OBJECION DE OBVIEDAD

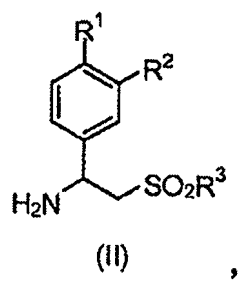
Las reivindicaciones 1-17 se rechazan bajo 35 U.S.C. 103 teniendo en cuenta que no Son patentables en vista de Man et al (US Patent 7,034,052). Los solicitantes reivindican un proceso para preparar compuestos de formula:

1.- Un procedimiento para preparar un compuesto de fórmula:



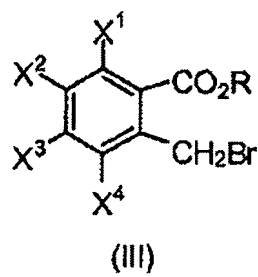
o una sal, solvato o polimorfo farmacéuticamente aceptable de los mismos,

que comprende el paso de hacer reaccionar una amina primaria de fórmula (II)



o una sal del mismo,

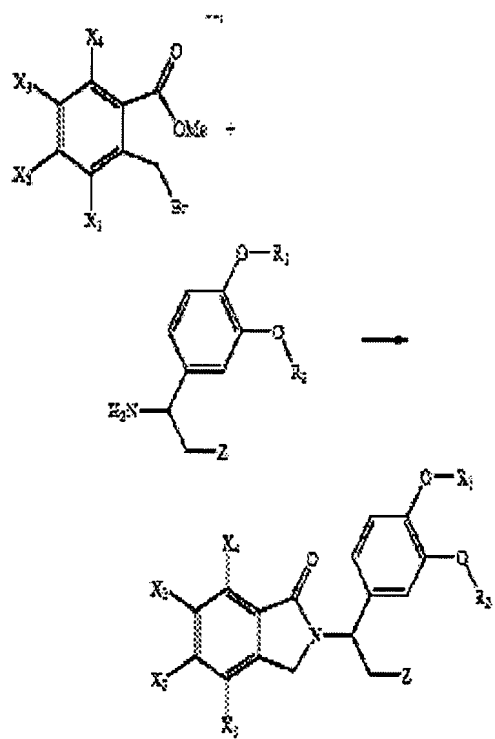
con un éster del ácido 2-(bromometil) benzoico de la Fórmula (III).



en presencia de una base inorgánica, en donde:

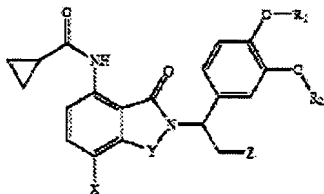
El alcance y contenido del arte previo

Man et al enseñan un proceso para la obtención de compuestos 7-amido-isoindolil. La invención es representada como sigue:

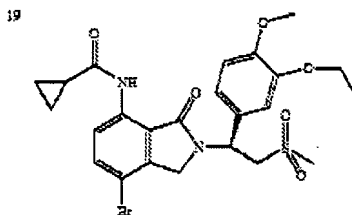


(see column 32) wherein the

variables are as defined



wherein:
Y is $-\text{C}(\text{O})-$, $-\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{O})-$ or $-\text{SO}_2-$;
X is H;
Z is $(\text{C}_{1-6}\text{-alkyl})-\text{C}(\text{O})\text{R}^3$, $\text{C}_{1-6}\text{-alkyl}$, $(\text{C}_{1-6}\text{-alkyl})-\text{OH}$,
 $(\text{C}_{1-6}\text{-alkyl})-\text{O}-(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})-\text{SO}_2(\text{C}_{1-6}\text{-alkyl})$,
 $(\text{C}_{1-6}\text{-alkyl})-\text{SO}(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})-\text{NH}_2$,
 $(\text{C}_{1-6}\text{-alkyl})-\text{N}(\text{C}_{1-6}\text{-alkyl})_2$, $(\text{C}_{1-6}\text{-alkyl})-\text{N}(\text{H})(\text{OH})$,
 $(\text{C}_{1-6}\text{-alkyl})$ -dichloropyridine, or $\text{CH}_3\text{NSO}_2(\text{C}_{1-6}\text{-alkyl})$;
 R_1 and R_2 are independently $\text{C}_{1-6}\text{-alkyl}$, cycloalkyl, or
 $(\text{C}_{1-6}\text{-alkyl})$ -cycloalkyl;
 R^3 is, NR^4R^5 , OH, or $\text{O}-(\text{C}_{1-6}\text{-alkyl})$;
 R^4 is H;
 R^5 is $-\text{OH}$, or $-\text{O}-\text{C}(\text{O})\text{R}^6$;
 R^6 is $\text{C}_{1-6}\text{-alkyl}$, amino- $(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})$ -(C_{3-6} -cy-
cloalkyl), C_{3-6} -cycloalkyl, phenyl, benzyl, or aryl; (see column 11) and teaches the



La diferencia entre el arte previo y las reivindicaciones

La diferencia entre el arte previo y la invención está en que existe materia homologa. No se enseñan todos los sustituyentes, sin embargo, hay materia que se traslapa especialmente entre los sustituyentes preferidos en el arte previo. La diferencia está en que el proceso de la invención utiliza una base inorgánica mientras que el arte previo enseña que el proceso utiliza bases orgánicas.

Obviedad Prima facie

In In re Durden, se estableció claramente que el proceso químico que está ocurriendo es una reacción esperada.

El uso de un material de partida novedoso y no obvio o un producto final novedoso y no obvio no hace a un proceso patentable.

En un proceso químico se debe considerar toda la evidencia sobre la materia reivindicada desde el punto de vista del versado en la materia y no simplemente la patentabilidad de uno de los materiales de partida o productos finales del proceso.

El proceso es obvio para un versado en la materia porque involucra una reacción predecible y esperada.

Por ejemplo, es obvio preparar un compuesto iosindolil de la fórmula de la reivindicación 1 utilizando una base inorgánica cuando el art previo enseña un proceso similar usando una base orgánica con expectativa de éxito razonable.

Específicamente, una base inorgánica y una base orgánica son bases y tienen la misma función en el proceso y se consideran obvias en ausencia de efectos inesperados.

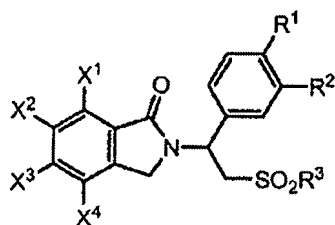
Por lo tanto habría sido obvio para un versado en la materia el proceso de la invención en vista de las enseñanzas del arte previo.

Rechazo de las reivindicaciones – 35 USC 112

La siguiente es un aparte del primer párrafo de 35 USC 112.

La descripción deberá contener una descripción escrita de la invención y de la manera y proceso para llevarla a cabo en una forma completa. Clara y concisa que permita a una versado en la materia reproducirla y usarla y deberá contemplar el mejor modo contemplado por el inventor para llevar a cabo la invención.

Las reivindicaciones 1-17 se rechazan bajo 35 U.S.C porque la descripción si bien sustenta un compuesto de formula



no proporciona sustento para los solvatos y polimorfos.

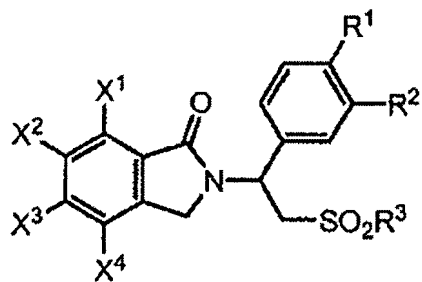
La descripción no permite aun versado en la materia llevar a cabo la invención con el alcance reivindicado.-

In In re Wands, los factores a considerase para determinar si las enseñanzas de la descripción permiten llevar a cabo la invención son:

1. Naturaleza de la invención
2. Estado del arte previo
3. Predictibilidad en el arte
4. Cantidad de direcciones o guía presente
5. Presencia o ausencia de ejemplos
6. Amplitud de las reivindicaciones
7. Cantidad de experimentación necesaria y
8. Nivel del versado en la materia

Naturaleza de la invención

La naturaleza de la invención es un proceso para la obtención de un compuesto de formula:



Pero no proporciona ninguna enseñanza de un solvato o polimorfo de este compuesto.

El estado del arte previo

En el arte previo aproximadamente un tercio de las sustancias activas son capaces de formar hidratos. La molécula de agua debido a su tamaño puede formar vacíos y debido a su capacidad de puentes de hidrogeno es ideal para unir la mayoría de fármacos en estructuras estables.

La sola presencia de agua en un sistema no es suficiente para esperar la formación de hidratos, porque algunos compuestos, aunque solubles en agua no forman hidratos.

Predecir la formación de hidratos de un compuestos y el número de moléculas de agua incorporados en un compuestos es complejo y difícil.

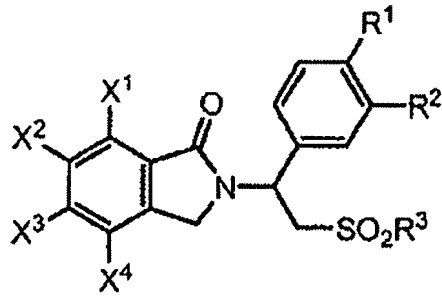
Cada compuesto solido responde de manera única a la posible formación de hidratos y por lo tanto no se pueden hacer generalizaciones para una serie de compuestos.

La cantidad de sustento y la presencia o ausencia de ejemplos

No existe sustento en la solicitud o ejemplos que definan o se relacionen con solvatos o polimorfos. Los solicitantes no han proporcionado datos que caractericen solvatos o polimorfos del compuesto reivindicado.

Amplitud de las reivindicaciones

La amplitud de las reivindicaciones es un proceso para la obtención de un compuesto de formula



O una sal farmacéuticamente aceptable, solvato o polimorfo.

El nivel del versado en la materia

Aun cuando el nivel del versado en al arte farmacéutico es elevado, la cantidad de experimentación necesaria es excesiva.

Necesitaría conocer la cantidad de agua, temperatura y tiempos de secado que proporcionaran los solvatos o polimorfos del compuesto de la invención.

Para superar la objeción, el solicitante deberá eliminar los términos solvato o polimorfo.

b. Cópia del arte previo citado en la acción oficial US 7,034,052



US07034052B2

(12) United States Patent
Man et al.

(10) Patent No.: US 7,034,052 B2
(45) Date of Patent: Apr. 25, 2006

(54) 7-AMIDO-ISOINDOLYL COMPOUNDS AND
THEIR PHARMACEUTICAL USES

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(US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 67 days.

(21) Appl. No.: 10/798,317

(22) Filed: Mar. 12, 2004

(55) Prior Publication Data
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12, 2003.

(51) Int. Cl.
C07D 309/46 (2006.01)
A61K 31/0035 (2006.01)
(52) U.S. Cl. 514/429; 548/469; 548/415

(58) Field of Classification Search 548/469;
548/415; 514/429
See application file for complete search history.

(56) References Cited

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U.S. Appl. No. 10/748,085; Man, Hsin-Wah, George W.
Muller, Weihong Zhang *

* cited by examiner

Primary Examiner—Joseph K. McKase
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(57) ABSTRACT

The invention encompasses 7-amido-isoindolyl compounds
and methods of using these compounds and compositions in
mammals for treatment, prevention or management of vari-
ous diseases and disorders. Examples include, but are not
limited to, cancer, inflammatory bowel disease and myelo-
dysplastic syndrome.

13 Claims, No Drawings

US 7,034,052 B2

1
7-AMIDO-ISOINDOLYL COMPOUNDS AND
THEIR PHARMACEUTICAL USES

This application claims the benefit of U.S. Provisional
Application No. 60/454,155, filed Mar. 12, 2003, which is
incorporated herein in its entirety by reference.

1. FIELD OF THE INVENTION

The invention encompasses novel 7-amido-substituted
isoindolyl compounds, pharmaceutical compositions of
these compounds, and methods of using these compounds
and compositions in mammals for the treatment, prevention
and management of diseases mediated by PDE4 inhibition,
associated with abnormal TNF- α levels and/or mediated by
MMP inhibition.

2. BACKGROUND OF THE INVENTION

2.1. TNF- α
Tumor necrosis factor alpha (TNF- α) is a cytokine that is
released primarily by inflammation and mononuclear phago-
cytes in response to immunostimulants. TNF- α is capable
of enhancing most cellular processes, such as differentiation,
recruitment, proliferation, and proteolytic degradation. At
low levels, TNF- α confers protection against infective
agents, tumors, and tissue damage. However, TNF- α also
has role in many diseases. When administered to mammals
such as humans, TNF- α causes or aggravates inflammation,
fever, cardiovascular effects, hemorrhage, coagulation, and
acute phase responses similar to those seen during acute
infectious and shock states. Enhanced or unregulated TNF- α
production has been implicated in a number of diseases and
medical conditions, for example, cancers, such as solid
tumors and blood-borne tumors; heart disease, such as con-
gestive heart failure; and viral, genetic, inflammatory, aller-
gic, and autoimmune diseases.

Cancer is a particularly devastating disease, and increases
in blood TNF- α levels are implicated in the risk of and the
spreading of cancer. Normally, in healthy subjects, cancer
cells fail to survive in the circulatory system, one of the
reasons being that the lining of blood vessels acts as a barrier
to tumor-cell extravasation. However, increased levels of
cytokines have been shown to substantially increase the
adhesion of cancer cells to endothelium in vitro. One expla-
nation is that cytokines, such as TNF- α stimulate the bio-
synthesis and expression of a cell surface receptor called
ELAM-1 (endothelial leukocyte adhesion molecule).
ELAM-1 is a member of a family of calcium-dependent cell
adhesion receptors, known as LEC-CAMs, which includes
LECAM-1 and GMP-140. During an inflammatory
response, ELAM-1 on endothelial cells functions as a "bind-
ing receptor" for leukocytes. ELAM-1 on endothelial cells
was shown to mediate the increased adhesion of colon
cancer cells to endothelium treated with cytokines (Rice et
al., 1989, Science 246:1303-1306).

Inflammatory diseases such as arthritis, related arthritis
conditions (e.g., osteoarthritis and rheumatoid arthritis),
inflammatory bowel disease, sepsis, psoriasis, chronic
obstructive pulmonary diseases and chronic inflammatory
pulmonary diseases are also prevalent and problematic al-
lments. TNF- α plays a central role in the inflammatory
response and the administration of their antagonists block
chronic and acute responses in animal models of inflama-
tory disease.

Enhanced or unregulated TNF- α production has been
implicated in viral, genetic, inflammatory, allergic, and

autoimmune diseases. Examples of such diseases include,
but are not limited to: HIV; hepatitis; adult respiratory
distress syndrome; bone-resorption diseases; chronic
obstructive pulmonary diseases; chronic pulmonary inflam-
matory diseases; dermatitis; cystic fibrosis; septic shock;
sepsis; endotoxic shock; hemodynamic shock; sepsis syn-
drome; post ischemic reperfusion injury; meningitis; pro-
nitis; fibrotic disease; cachexia; graft versus host disease
(GVHD); graft rejection; auto-immune disease; rheumatoid
arthritis; rheumatoid spondylitis and osteoarthritis; osteoporosis;
inflammatory-bowel disease; Crohn's disease; ulcerative
colitis; multiple sclerosis; systemic lupus erythematosus;
ENL; in leprosy; radiation damage; arthritis; and hyperoxic
abductor injury. Tracey et al., 1987, Nature 330:662-664 and
Hitchcock et al., 1990, Circ. Shock 30:279-292 (endotoxic
shock); Derube et al., 1990, Lancet, 335:662 (cachexia);
Miller et al., 1989, Lower 2:712-714 and Ferrn-Balviera et
al., 1989, Arch. Surg. 124:1400-1405 (adult respiratory
distress syndrome); Bernstein et al., 1986, Nature 319:
516-518; Johnson et al., 1989, Endocrinology 124:1424-1427;
Holler et al., 1990, Blood 75:1011-1016, and Grzes et al., 1990, N. Engl. J. Med. 320:1586-1591 (bone
resorption diseases); Pignat et al., 1990, Nature 344:243-247;
Blancome et al., 1989, Inflammation 13:329-339 and Baughman et al., 1990, J. Lab. Clin. Med.
115:36-42 (chronic pulmonary inflammatory diseases);
Elliot et al., 1995, Int. J. Pharmac. 17:141-145 (rheumatoid
arthritis); von Dilleken et al., 1995, Gastroenterology 109:
129-135 (Crohn's disease); Dai et al., 1989, Proc. Nat.
Acad. Sci. 86:5972-5979; Poll et al., 1990, Proc. Nat. Acad.
Sci. 87:782-785; Monto et al., 1990, Blood 79:2670; Close
et al., 1989, J. Immunol. 142, 431-438; Poll et al., 1992,
AIDS Res. Hum. Retrovirus 191-197; Poll et al., 1990, Proc.
Nat. Acad. Sci. 87:782-786; Toles et al., 1989, Proc. Natl.
Acad. Sci. 86:2365-2368 (HIV and opportunistic infections
resulting from HIV).

2.2. PDE4
Adenosine 3',5'-cyclic monophosphate (cAMP) also plays
a role in many diseases and conditions, such as, but not
limited to asthma and inflammation (Lowe and Cheng,
Drug of the Future, 17(5), 795-807, 1992). It has been
shown that the elevation of cAMP in inflammatory leuko-
cytes inhibits their activation and the subsequent release of
inflammatory mediators, including TNF- α and nuclear fac-
tor κ B (NF- κ B). Increased levels of cAMP also lead to the
relaxation of airway smooth muscle.

It is believed that primary cellular mechanism for the
inactivation of cAMP is the breakdown of cAMP by a family
of isoenzymes referred to as cyclic nucleotide phosphodi-
esterases (PDE) (Beavo and Reimzyer, Trends in Pharm.,
11, 150-155, 1990). There are twelve known members of the
family of PDEs. It is recognized that the inhibition of PDE
type IV (PDE4) is particularly effective in both the inhibition
of inflammatory mediated release and the relaxation of
airway smooth muscle (Verghese, et al., Journal of Pharm-
macology and Experimental Therapeutics, 272(3),
1313-1320, 1995). Thus, compounds that specifically
inhibit PDE4 may inhibit inflammation and aid the relax-
ation of airway smooth muscle with a minimum of unwanted
side effects, such as cardiovascular or anti-platelet effects.

The PDE4 family that is specific for cAMP is currently
the largest and is composed of at least 4 isoenzymes (a-d), and
multiple splice variants (Hinslay, M. D. et al. in Advances
in Pharmacology 44, eds. J. August et al., p. 225, 1998).
There may be over 20 PDE4 isoforms expressed in a cell
specific pattern regulated by a number of different proto-

TABLE 1-continued

No. Compound	Name
4	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
5	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
6	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
7	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
8	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
9	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide

TABLE 1-continued

No. Compound	Name
10	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
11	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
12	(1R)-2-(4-Chloro-2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
13	(1R)-2-(4-Chloro-2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide
14	(1R)-Cyclopropylmethyl 2-oxo-2-(2-ethoxy-4-methoxyphenyl)-5-oxo-5-phenyl-3-oxo-2,3-dihydro-1H-isoindol-4-yl) amide

TABLE I-continued

No. Compound	Name
15	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-hydroxy-2-methylpropanoate (4-y)] enantiomer
16	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-hydroxy-2-methylpropanoate (4-y)] enantiomer
17	(1R)-Cyclopropanecarboxylic acid [2-[2-acetoxycarbonyl-5-(3-ethoxy-4-methoxyphenyl)-2-methylpropanoate]-3-methoxy-2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl] enantiomer
18	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-methylpropanoate (4-y)] enantiomer
19	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-methylpropanoate (4-y)] enantiomer

TABLE I-continued

No. Compound	Name
20	Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-hydroxy-2-methylpropanoate (4-y)] enantiomer
21	Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-hydroxy-2-methylpropanoate (4-y)] enantiomer
22	Cyclopropanecarboxylic acid [2-[2,5-dichloro-4-(1-ethyl-4-methoxyphenyl)-3-methoxy-2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl] enantiomer
23	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-methylpropanoate (4-y)] enantiomer
24	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-methylpropanoate (4-y)] enantiomer
25	(1R)-Cyclopropanecarboxylic acid [2-[4-ethoxy-2-(2,3-dihydro-1H-imidazo[4,5-f]quinoxalin-6-yl)-5-methoxyphenyl]-2-methylpropanoate (4-y)] enantiomer

TABLE 1-continued

No. Compound	Name
26	(1R)-Cyclopropylmethoxycarbonyl acid [2-[2-(2,2-dimethyl-3-methyl-5-oxo-1H-indol-3-yl)-4-methoxyphenyl]-ethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl] amide
27	(1R)-Cyclopropylmethoxycarbonyl acid [2-[2-(2,2-dimethyl-3-methyl-5-oxo-1H-indol-3-yl)-4-methoxyphenyl]-ethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl] amide
28	(1R)-Cyclopropylmethoxycarbonyl acid [2-[2-(2,2-dimethyl-3-methyl-5-oxo-1H-indol-3-yl)-4-methoxyphenyl]-ethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl] amide
29	(1R)-3-[7-Chloro-2-[2-(2-ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-1,3-dimethyl-5-oxo-1H-indole
30	(1R)-N-[7-Chloro-2-[2-(2-ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-2-methyl-5-oxo-1H-indole

TABLE 1-continued

No. Compound	Name
31	(1R)-N-[7-Chloro-2-[2-(2-ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-2-methyl-5-oxo-1H-indole
32	(1R)-N-[7-Chloro-2-[2-(2-ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-2-methyl-5-oxo-1H-indole
33	N-[2-[1-(2-Ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-2,2-dimethyl-5-oxo-1H-indole
34	N-[2-[1-(2-Ethoxy-4-methoxyphenyl)-2-methoxyethyl]-3-methyl-2,3-dihydro-1H-acridol-4-yl]-2-methyl-5-oxo-1H-indole

Compounds of the invention generally exist in solid form and can be recrystallized according to well-known methods affording high-purity crystals, preferably, in greater than 95% purity, more preferably, in greater than 98% purity. A narrow melting point range is often an indication of purity. Thus, preferred compounds of the invention have a melting point within a range of 3° C. to 4° C., more preferably, within a range of 2° C.

Various compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses the use of stereoisomerically pure forms of such compounds, as well as the use of mixtures of these forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., *Resolution* 33:2725

(1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 208 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind., 1972).

Compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers and geometric isomers. Chemical structures and portions of chemical structures depicted herein, that do not indicate stereochemistry encompass all of their enantiomers and stereoisomers, e.g., both the enantiomerically pure forms stereoisomeric mixtures.

As used herein, and unless otherwise indicated, the term "stereoisomeric mixture" encompasses racemic mixtures as well as enantiomerically enriched mixtures (e.g., 8:50-50/70, 35:65, 40:60, 45:55, 55:45, 60:40, 65:35 and 70:30).

As used herein, and unless otherwise indicated, the term "stereoisomerically pure" or "enantiomerically pure" means that a compound is one stereoisomer and is substantially free of its counter stereoisomer or enantiomer. For example, a compound is stereoisomerically or enantiomerically pure

when the compound contains 80%, 90%, or 95% or more of one stereoisomer and 20%, 10%, or 5% or less of the counter stereoisomer. In certain cases, a compound of the invention is considered optically active or stereoisomerically/chemically pure (i.e., substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 80% ee (enantiomeric excess) or greater, preferably, equal to or greater than 90% ee with respect to a particular chiral center, and more preferably 95% or with respect to a particular chiral center. Thus, the invention encompasses all enantiomerically pure, enantiomerically enriched, and racemic mixtures of compounds of Formula I, II, or III.

In one embodiment, the invention encompasses an enantiomerically S isomer of a compound of Formula I, II or III, substantially free of its R isomer, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof.

In another embodiment, the invention also encompasses an enantiomerically R isomer of a compound of Formula I, II or III, substantially free of its S isomer, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof.

Enantiomeric and stereoisomeric mixtures of compounds of the invention can be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereoisomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

The invention further encompasses prodrugs of compounds encompassed by Formulae I, II and III. As used herein, and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of compounds of the invention that comprise biodegradable moieties such as biodegradable amides, biodegradable esters, biodegradable carbonates, biodegradable carbamates, biodegradable ureasides, and biodegradable phosphates analogues. Other examples of prodrugs include derivatives of compounds of the invention that comprise —NO₂, —NO, —ONO, or —ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 349-352 (Mastel F, Wolff et al., 5th ed, 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York 1983).

As used herein and unless otherwise indicated, the terms "biodegradable amide," "biodegradable ester," "biodegradable carbonate," "biodegradable carbamate," "biodegradable urea," "biodegradable urea," "biodegradable phosphate" mean an amide, ester, carbonate, carbamate, urea, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biodegradable esters include, but are not limited to, lower alkyl esters, lower alkoxyalkyl esters (such as acetoxyethyl, acetoxyethyl, aminocarbonyloxyethyl, pivaloxyloxyethyl, and pivaloxyloxyethyl esters), isobutoxy esters (such as pivaloyloxyethyl and

thiopropylalcohol esters), lower alkoxyalkoxyalkyl esters (such as methoxycarbonyloxyethyl, ethoxycarbonyloxyethyl, and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biodegradable amides include, but are not limited to, lower alkyl amides, amine amides, alkoxyalkyl amides, and alkoxyalkylaminoalkyl amides. Examples of biodegradable carbonates include, but are not limited to, lower alkylamides, substituted ethylenediamines, amineamides, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is to be accorded more weight.

This invention provides pharmaceutical compositions comprising a therapeutically effective or a prophylactically effective amount of one or more compounds of the invention and a pharmaceutically acceptable vehicle or carrier. A pharmaceutically acceptable vehicle or carrier can comprise an excipient, diluent, or a mixture thereof. The term "therapeutically effective amount" means the amount of a compound of the invention that will elicit the biological or medical response in a mammal that is being treated by the veterinarian or clinician. The term "prophylactically effective" means the amount of a compound of the invention that will prevent or inhibit affliction or mitigate affliction of a mammal with a medical condition that a veterinarian or clinician is trying to prevent, inhibit, or mitigate.

In another embodiment, the invention encompasses a method of inhibiting HIV in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In another embodiment, the invention encompasses a method of modulating the production or lowering the levels of TNF- α in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In yet another embodiment, the invention encompasses a method of inhibiting MMP in a mammal comprising administering to said mammal an effective amount of a compound of the invention.

In yet another embodiment, the invention encompasses a method of testing undesired angiogenesis in a mammal comprising administering to said mammal an effective amount of a compound of the invention. Diseases associated with angiogenesis are well known in the art.

A separate embodiment of the invention encompasses methods of treating, preventing and managing Myeloplastic Syndrome (MDS) which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. MDS refers to a diverse group of hematopoietic stem cell disorders. MDS is characterized by a cellular marrow with impaired morphology and maturation (dysmyelopoiesis), peripheral blood cytopenias, and a variable risk of progression to acute leukemia, resulting from ineffective blood cell production. *The Merck Manual* 953 (17th ed, 1999) and List et al., 1990, *J. Clin. Oncol.* 8:1424.

Another separate embodiment of the invention encompasses methods of treating, preventing and managing MDS-

lar Degeneration (MD), which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. MD refers to an eye disease that destroys central vision by damaging the macula.

A separate embodiment of the invention encompasses methods of treating, preventing and managing Myocardial Ischemic Disease (MID) which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. MID refers to a group of disorders characterized by clinical abnormalities of the hemopoietic stem cell. See e.g., *Current Medical Diagnosis & Treatment*, pp. 499 (17th ed., Tenney et al. ed, Appleton & Lange, 1998).

The invention also encompasses a method of treating, preventing and managing Complex Regional Pain Syndrome (CRPS), which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during or after surgery or physical therapy directed at reducing or avoiding a symptom of complex regional pain syndrome in the patient.

In another embodiment, this invention encompasses a method of treating, preventing and managing a Central Nervous System (CNS) disorder, which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In another embodiment, this invention encompasses a method of treating, preventing or managing an autoimmune-related disease or disorder, which comprises administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. Autoimmune-related disease or disorder refers to a disease or disorder caused by an exposure to autoantigens.

In still another embodiment, the invention encompasses methods of treating, preventing and managing cancer in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention. The compounds of the invention can be used to treat, prevent or manage any cancer, for example, solid tumors and blood-borne tumors. Specific examples of cancers treatable, preventable or manageable by compounds of the invention include, but are not limited to: cancers of the skin, such as melanoma, lymph node, breast; cervix; uterine; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testis; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are particularly useful for treating, preventing or managing cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias. The compounds of the invention can be used for treating, preventing or managing either primary or metastatic tumors.

In yet one more embodiment, the invention encompasses methods of treating, preventing and managing cancer in a mammal, comprising administering to a mammal in need thereof, a therapeutically effective amount of a compound of the invention and another therapeutic agent.

In yet another embodiment, the invention encompasses methods of treating, preventing and managing inflammatory disorders in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention. The compounds of the invention are especially effective to treat, prevent or manage inflammatory diseases related to the up-regulation of TNF- α including, but not limited to, arthritic conditions, such as rheumatoid arthritis, and osteoarthritis; rheumatoid spondylitis; psoriasis; post ischemic perfusion injury; inflammatory bowel disease; and chronic inflammatory pulmonary disease.

In one more embodiment still, the invention encompasses methods of treating, preventing and managing inflammatory disorders in a mammal, comprising administering to a mammal in need thereof, a therapeutically effective amount of a compound of the invention and another anti-inflammatory agent.

In a further embodiment, the invention encompasses methods of treating, preventing and managing heart disease in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention. For example, the compounds of the invention can be used to treat, prevent or manage congestive heart failure, cardiomyopathy, pulmonary edema, endothelin-mediated acute shock, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

In an additional embodiment, the invention encompasses methods of treating, preventing and managing osteoporosis in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention.

In a further embodiment, the invention encompasses methods of treating, preventing and managing viral, genetic, allergic, and autoimmune diseases. For example, the compounds are useful to treat, prevent or manage diseases including, but not limited to, HIV hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic perfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, DM, in hepatitis, radiation damage, cancer, asthma, or hyperoxic alveolar injury in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention.

In still another embodiment, the invention encompasses methods of treating, preventing and managing malaria, myocardial infection, or an opportunistic infection resulting from HIV in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention.

In still one more embodiment, the invention relates to treating, preventing or managing mammals having more than one of the conditions treatable by a compound of the invention.

In the above embodiments, it is preferable that the mammal be in need of the treatment, prevention or management, that is, the mammal is actually suffering from a medical condition or at risk of a medical condition for which a

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compound of the invention can provide treatment, prevention or management. However, the compounds of the invention can also be administered to test animals that do not necessarily require such treatment, prevention or management.

In a further embodiment, the invention encompasses a method of modulating the production, preferably inhibiting, or lowering the level of P75^{F4} in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or tissue.

In a further embodiment, the invention encompasses a method of modulating the production or lowering the level of RMP in a mammalian cell or tissue comprising contacting an effective amount of a compound of the invention with said mammalian cell or tissue.

In these embodiments, the term "effective amount" means the amount of the compound that will induce the biological response sought by the researcher, veterinarian, physician, or clinician. It should be understood that the cell can be in a cell culture or a tissue culture (in vitro) or in an organism (in vivo) including a human.

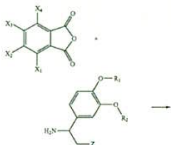
The present invention may be understood by reference to the detailed description and examples that are intended to exemplify non-limiting embodiments of the invention.

4.1. Preparation of the Compounds

The compounds can be prepared using methods which are known in general for the preparation of itins and 2,3-dihydro-1H-indolizines. However, the present invention also pertains to an improvement in the formation of the final compounds, as discussed below in greater detail.

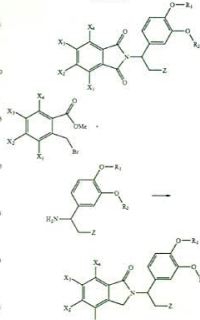
As N-alkylcarbamoylins and an amine then are allowed to react in the presence of a base such as sodium carbonate or sodium bicarbonate substantially as described by Shealy et al., Chem. & Ind., (1953) 1030-1031 and Shealy et al., J. Pharm. Sci., 57, 757-764 (1968) to yield the N-substituted imide. Alternatively, a cyclic acid anhydride can be reacted with an appropriate amine to form an imide.

Formation of a cyclic imide also can be accomplished by refluxing a solution of an appropriately substituted dicarboxylic acid monomide in anhydrous tetrahydrofuran with N-alkylcarbamoylins. Also, a 2-bromomethyl-benzonic ester can be reacted with an appropriate amine to form a 2,3-dihydro-1H-indolizine as shown below.



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-continued



Other methods of formation are described in U.S. Pat. No. 3,605,914 and International Publication No. WO 01/34006 A1 which are incorporated herein by reference.

4.2. Pharmaceutical Compositions

This invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, excipient or diluent and one or more compounds of the present invention.

One embodiment provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline, methylcellulose solutions, detergent solutions or other medium, water, gelatin, oils, etc. The compounds or compositions may be administered alone or in combination with any convenient carrier, diluent, etc. and such administration may be provided in single or multiple dosages. The compositions are sterile, particularly when used for parenteral delivery. However, oral unit dosage forms need not be sterile. Useful carriers include water soluble and water insoluble solids, fatty acids, mixtures, inverse micelles, liposomes and semi-solid or liquid media, including aqueous solutions and non-toxic organic solvents. All of the above formulations may be treated with ultrasound, stirred, mixed, high-shear mixed, heated, ground, milled, aerosolized, pulverized, lyophilized, etc., to form pharmaceutically acceptable compositions.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically

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acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cactets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powder, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compressed in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cactets and lozenges are included. Tablets, powders, capsules, pills, cactets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solutions.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cactet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, preferably 1.0 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

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The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of metabolic disorders, cardiovascular diseases, inflammatory conditions or neoplastic diseases and pathologies associated therewith (e.g., diabetic neuropathy) or other adjacent. In many instances, compositions which include a compound of the invention and an alternative agent have additive or synergistic effects when administered.

4.3. Methods of Treatment, Prevention and Management

In accordance with the invention, a compound or composition of the invention is administered to a mammal, preferably a human, with or at risk of a disease or medical condition, for example, cancer, such as solid tumors and blood-borne tumors. Specific examples of cancers treatable, preventable or manageable by administering compounds of the invention include, but are not limited to, disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus. Specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangioendothelioma, multiple brain metastases, glioblastoma multiforme, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Duke's C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, kaposi's sarcoma, kaposi's sarcoma, Kaposi's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, cutaneous B-cell lymphoma, diffuse large B-cell lymphoma, low grade follicular lymphoma, metastatic melanoma (localized melanoma, including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion, mesothelioma syndrome, petiole cancer, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, sarcoma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrosarcoma, osteosarcoma, progressive, hormone refractory prostate cancer, metastatic high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenström's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistant to chemotherapy or radiation, in particular, refractory to thalidomide.

The compounds of the invention are also useful to treat, prevent or manage heart disease, such as congestive heart failure, cardiomyopathy, pulmonary edema, endocarditis, myocardial infarction, acute viral myocarditis, cardiac allograft rejection, and myocardial infarction.

The compounds of the invention can also be used to treat, prevent or manage viral, genetic, inflammatory, allergic, and autoimmune diseases. For example, the compounds are useful to treat, prevent or manage diseases including, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone-resorption diseases, chronic obstructive pulmonary disease, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic

embodiment of the invention, nonmotor symptoms are treated, prevented or managed using the methods of the invention, including, but not limited to, disorders of mood, cognition, defective long-term memory, sensation, sleep, dementia, and depression. In other embodiment of the invention, secondary forms of parkinsonism are treated, prevented or managed by the methods of the invention, including, but not limited to, drug induced parkinsonism, vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, disorders with primary tau pathology, cortical basal ganglia degeneration, parkinsonism with dementia, hyperkinetic disorders, chorea, Huntington disease, dystonia, Wilson disease, Tourette syndrome, essential tremor, myoclonus, and tardive movement disorders. In other embodiment of the invention, other central nervous system disorders are treated, prevented or managed by the methods of the invention, including, but not limited to, Alzheimer disease, mild cognitive impairment, Amyotrophic Lateral Sclerosis (ALS) and CNS trauma.

The compounds of the invention are also useful for treating, preventing or managing an asbestos-related disease or disorder and related symptoms. Examples of asbestos-related diseases or disorders include, but are not limited to, malignant mesothelioma, asbestosis, malignant pleural effusion, benign pleural effusion, pleural plaques, pleural calcification, diffuse pleural thickening, round atelectasis, and bronchogenic carcinoma. It further encompasses methods of treating patients who have been previously treated for asbestos-related diseases or disorders but were not sufficiently responsive or were non-responsive, as well as those who have not previously been treated for the diseases or disorders. Because patients have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents and types of physical therapy that can be effectively used to treat an individual patient.

Symptoms of asbestos related diseases or disorders include, but are not limited to, dyspnea, obliteration of the diaphragm, radiolucent sheet-like encasement of the pleura, pleural effusion, pleural thickening, decreased size of the chest, chest discomfort, chest pain, easy fatigability, fever, sweats and weight loss. Examples of patients at risk of asbestos-related diseases or disorders include, but are not limited to, those who have been exposed to asbestos in the workplace and their family members who have been exposed to asbestos embedded in the worker's clothing. Patients having familial history of asbestos-related diseases or disorders are also preferred candidates for preventive regimes.

4.4. Pharmaceutical Formulations

Administration of compounds of the invention can be systemic or local. In most instances, administration to a mammal will result in systemic delivery of the compounds of the invention (i.e., into the bloodstream). Methods of administration include enteral routes, such as oral, buccal, sublingual, and rectal; topical administration, such as transdermal and intradermal; and parenteral administration. Suitable parenteral routes include injection via a hypodermic needle or catheter, for example, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intracranial, intravitreal, intrathecal, and intracerebral injection and non-injection routes, such as intravaginal, rectal, or nasal administration. Preferably, the compounds and compositions of the invention are administered orally. In specific embodiments, it may be desirable to administer one or more

compounds of the invention locally to the area in need of treatment. This may be achieved, for example, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as silastic membranes, or fibers.

The compounds of the invention can be administered via typical as well as non-standard delivery systems, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, etc. For example, the compounds and compositions of the invention can be delivered in a vehicle, in particular a liposome (see Langer, 1990, *Science* 249:1227-1233); Trutt et al., in *Liposomes in Therapy of Infectious Disease and Cancer* (Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*). In another example, the compounds and compositions of the invention can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Schiff, 1987, *CRC Crit. Rev. Biomed. Eng.* 14:201; Buchwald et al., 1980, *Surgery* 88:507; Sankit et al., 1989, *N. Engl. J. Med.* 321:374). In another example, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Press, Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolles and Hall (eds.), Wiley, New York (1984); Ranger and Peppas, 1989, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy et al., 1985, *Science* 228:1390; Doring et al., 1989, *Ann. Neurol.* 25:351; Howard et al., 1989, *J. Neurosurg.* 71:105). In still another example, a controlled-release system can be placed in proximity of the target area to be treated, e.g., the liver, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, *Science* 249:1227-1233) can be used.

When administered as a composition, a compound of the invention will be formulated with a suitable amount of a pharmaceutically acceptable vehicle or carrier so as to provide the form for proper administration to a mammal. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the invention is formulated for administration to a mammal. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum, mastic, gelatin, starch, pectin, tale, keratin, colloidal silica, urea, and the like. In addition, emulsifying, thickening, lubricating and coloring agents may be used. Preferably, when administered to a mammal, the compounds and compositions of the invention and pharmaceutically acceptable vehicles, excipients, or diluents are sterile. An aqueous medium is a preferred vehicle when the compound of the invention is administered intravenously, such as water, saline solutions, and aqueous dextrose and glycerol solutions.

The present compounds and compositions can take the form of capsules, tablets, pills, pellets, lozenges, powders, granules, syrups, elixirs, solutions, suspensions, emulsions,

suppositories, or sustained-release formulations thereof, or any other form suitable for administration to a mammal. In a preferred embodiment, the compounds and compositions of the invention are formulated for administration in accordance with routine procedures as a pharmaceutical composition adapted for oral or intravenous administration to humans. In one embodiment, the pharmaceutically acceptable vehicle is a hard gelatin capsule. Examples of suitable pharmaceutical vehicles and methods for formulation thereof are described in Remington: *The Science and Practice of Pharmacy*, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, Chapters 86, 87, 88, 91, and 92, incorporated herein by reference.

Compounds and compositions of the invention formulated for oral delivery, are preferably in the form of capsules, tablets, pills, or any compressed pharmaceutical form. Moreover, where in tablet or pill form, the compounds and compositions may be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active diving compound are also suitable for orally administered compounds and compositions of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the diving compound that swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the typical profile of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles, excipients, and diluents, such as magnesium stearate, sodium lauryl sulfate, cellulose, magnesium carbonate, lactose, dextrose, saccharose, sorbitol, mannitol, starch, gum, acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents, such as talc, magnesium stearate, mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoate. Such vehicles are preferably of pharmaceutical grade. Orally administered compounds and compositions of the invention can optionally include one or more sweetening agents, such as fructose, aspartame or saccharin; one or more flavoring agents such as peppermint, oil of wintergreen, or cherry; or one or more coloring agents to provide a pharmaceutically palatable preparation.

A therapeutically effective dosage regimen for the treatment of a particular disorder or condition will depend on its nature and severity, and can be determined by standard clinical techniques according to the judgment of a medical practitioner. In addition, *in vivo* or *in vitro* assays can be used to help identify optimal dosages. Of course, the amount of a compound of the invention that constitutes a therapeutically effective dose also depends on the administration route. In general, suitable dosage ranges for oral administration are about 0.001 milligrams to about 20 milligrams of a compound of the invention per kilogram body weight per day, preferably, about 0.7 milligrams to about 6 milligrams, more preferably, about 1.5 milligrams to about 4.5 milligrams. In a preferred embodiment, a mammal, preferably a human is orally administered about 0.01 mg to about 1000 mg of a compound of the invention per day, more preferably, about 0.1 mg to about 300 mg per day, or about 1 mg to about 100 mg in single or divided doses. The dosage amounts described herein refer to total amounts administered, that is, if more than one compound of the invention is

administered, the preferred dosages correspond to the total amount of the compounds of the invention administered. Oral compositions preferably contain 10% to 95% of a compound of the invention by weight. Preferred unit oral dosage forms include pills, tablets, and capsules, more preferably capsules. Typically such unit-dosage forms will contain about 0.01 mg, 0.1 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 100 mg, 250 mg, or 500 mg of a compound of the invention, preferably, from about 1 mg to about 200 mg of compound per unit dosage.

In another embodiment, the compounds and compositions of the invention can be administered parenterally (e.g., by intramuscular, intrathecal, intravenous, and intracranial routes), preferably, intravenously. Typically, compounds and compositions of the invention for intravenous administration are solutions in sterile isotonic aqueous vehicles, such as water, saline, Ringer's solution, or dextrose solution. Where necessary, the compositions may also include a stabilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. For intravenous administration, the compounds and compositions of the invention can be supplied as a sterile, dry lyophilized powder or water-free concentrate in a hermetically sealed container, such as an ampule or sachette, the container indicating the quantity of active agent. Such a powder or concentrate is then diluted with an appropriate aqueous medium prior to intravenous administration. An ampule of sterile water, saline solution, or other appropriate aqueous medium can be provided with the powder or concentrate for dilution prior to administration. Or the compositions can be supplied in pre-mixed form, ready for administration. Where a compound or composition of the invention is to be administered by intravenous infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical-grade water, saline, or other suitable medium.

Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter, modified vegetable oils, and other fatty bases. Suppositories can be formulated by well-known methods using well-known formulations, for example see *Remington: The Science and Practice of Pharmacy*, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, pp. 1591-1597, incorporated herein by reference.

To formulate and administer topical dosage forms, well-known transdermal and intradermal delivery mediums such as lotions, creams, and ointments and transdermal delivery devices such as patches can be used (Gibbs, T. K., Pitter, W. R., Yun, S. I., *Transdermal and Topical Drug Delivery Systems*, Interscience Press, Inc. p. 249-297, incorporated herein by reference). For example, a reservoir type patch design can comprise a backing film coated with an adhesive, and a reservoir compartment comprising a compound or composition of the invention, that is separated from the skin by a semipermeable membrane (e.g., U.S. Pat. No. 4,615,699, incorporated herein by reference). The adhesive coated backing layer extends around the reservoir's boundaries to provide a concentric seal with the skin and hold the reservoir adjacent to the skin.

Mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays and aerosols, or other forms known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton Pa. (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or

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as oral gels. In one embodiment, the aerosol comprises a carrier. In another embodiment, the aerosol is carrier free. The compounds of the invention may also be administered directly to the lung by inhalation. For administration by inhalation, a compound of the invention can be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI") which utilizes containers that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotrifluoroethane, carbon dioxide or other suitable gas can be used to deliver a compound of formula I directly to the lung. MDI devices are available from a number of suppliers such as 3M Corporation, Aventis, Boehringer Ingelheim, Forest Laboratories, Glaxo-Welcome, Schering Plough and Vectura.

Alternatively, a Dry Powder Inhaler (DPI) device can be used to administer a compound of the invention to the lung (See, e.g., Ral Singh et al., *Proc. Amer. Assoc. Cancer Research Annual Meeting*, 1999, 40, 337, which is herein incorporated by reference). DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which can then be inhaled by the patient. DPI devices are also well known in the art and can be purchased from a number of vendors which include, for example, Flutax, Glaxo-Welcome, Inhaler Therapeutic Systems, MI, Laboratories, Qdos and Vectura. A popular variation is the multiple dose DPI ("MDPI") system, which allows for the delivery of more than one therapeutic dose. MDPI devices are available from companies such as AstraZeneca, GlaxoWellcome, INXN, Schering Plough, SkyPharma and Vectura. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch for these systems.

Another type of device that can be used to deliver a compound of the invention to the lung is a liquid spray device supplied, for example, by Aerding Corporation. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung.

In a preferred embodiment, a nebulizer device is used to deliver a compound of the invention to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form the particles that can be readily inhaled (See e.g., Vercrooye et al., *British J. Cancer*, 1999, 80, Suppl. 2, 96, which is herein incorporated by reference). Examples of nebulizers include devices supplied by Sheffield Systems Pulmonary Delivery Ltd. (See, Azner et al., U.S. Pat. No. 5,954,047; van der Linden et al., U.S. Pat. No. 5,950,619; van der Linden et al., U.S. Pat. No. 5,970,074, which are herein incorporated by reference), Aventa and Bantell Pulmonary Therapeutics.

In a particularly preferred embodiment, an electrodynamic ("EHD") aerosol device is used to deliver a compound of the invention to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see e.g., Nokes et al., U.S. Pat. No. 4,765,519; Coffey, U.S. Pat. No. 4,962,851; Coffey, PCT Application, WO 94/12285; Coffey, PCT Application, WO 94/14543; Coffey, PCT Application, WO 95/24234; Coffey, PCT Application, WO 95/26235; Coffey, PCT Application, WO 95/32807, which are herein incorporated by reference). The electrochemical properties of the formulation containing compounds of the invention may be important parameters to optimize when delivering this drug to the lung with an EHD aerosol device and such optimization is routinely performed

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by one of skill in the art. EHD aerosol devices may more efficiently deliver drugs to the lung than existing pulmonary delivery technologies. Other methods of intra-pulmonary delivery will be known to the skilled artisan and are within the scope of the invention.

Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include a pharmaceutically acceptable carrier. Preferably, the pharmaceutically acceptable carrier is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of a compound of the invention. Preferably, this material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspensions suitable for use in aerosol devices are known to those of skill in the art (See, e.g., Bawalki, U.S. Pat. No. 5,112,598; Bawalki, U.S. Pat. No. 5,555,631, which are herein incorporated by reference). A compound of the invention can also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, a compound of the invention can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneous or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively, other pharmaceutical delivery systems can be employed. Liposomes and emulsions are well known examples of delivery vehicles that can be used to deliver compounds of the invention. Certain organic solvents such as dimethylsulfoxide can also be employed, although usually at the cost of greater toxicity. A compound of the invention can also be delivered in a controlled release system. In one embodiment, a pump can be used (Seeffox, CRC Crit. Ref. Biomed. Eng., 1987, 14, 201; Buchwald et al., *Surgery*, 1980, 88, 507; Suddick et al., *N. Engl. J. Med.*, 1989, 321, 574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Press, Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Rieger and Peppers, *J. Macromol. Sci. Rev. Macromol. Chem.*, 1983, 23, 61; see also Levy et al., *Science*, 1985, 228, 190; Daring et al., *Ann. Neurol.*, 1989, 25, 331; Howard et al., 1989, *J. Neurosurg.*, 71, 105). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds of the invention, e.g., the lung, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115 (1984)). Other controlled-release systems can be used (see e.g., Langer, *Science*, 1990, 249, 1527).

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular site or method which a given pharmaceutical composition or dosage form will be administered. With that in mind, typical excipients include, but are not limited to, water, ethanol, ethylhex glycol, propylene glycol, benzene-1,

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3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, which are non-toxic and pharmaceutically acceptable. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th edn., Mack Publishing, Easton Pa. (1990).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, can also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or viscosity can be adjusted to improve delivery. Compounds such as steroids can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, steroids can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

The invention also provides pharmaceutical packs or kits comprising one or more containers filled with one or more compounds of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In one embodiment, the kit contains more than one compound of the invention. In another embodiment, the kit comprises a compound of the invention and another biologically active agent.

The compounds of the invention are preferably assayed *in vitro* and *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific compound of the invention or a combination of compounds of the invention is preferred. The compounds and compositions of the invention may also be demonstrated to be effective and safe using animal model systems. Other methods will be known to the skilled artisan and are within the scope of the invention.

4.5. Combination Therapy

In certain embodiments, a compound of the invention is administered to a mammal, preferably a human, concurrently with one or more other therapeutic agents, or with one or more other compounds of the invention, or with both. By "concurrently," it is meant that a compound of the invention and the other agent are administered to a mammal in a sequence and within a time interval such that the compound of the invention can act together with the other agent to provide an increased or synergistic benefit that if they were administered otherwise. For example, each component may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently closely in time so as to provide the desired treatment effect. Preferably, all components are administered at the same time, and if not administered at the same time, preferably, they are all administered from about 6 hours to about 12 hours apart from one another.

When used in combination with other therapeutic agents, the compounds of the invention and the therapeutic agent can act additively or, more preferably, synergistically. In one embodiment, a compound or a composition of the invention is administered concurrently with another therapeutic agent in the same pharmaceutical composition. In another embodi-

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ment, a compound or a composition of the invention is administered concurrently with another therapeutic agent in separate pharmaceutical compositions. In still another embodiment, a compound or a composition of the invention is administered prior or subsequent to administration of another therapeutic agent. As many of the disorders for which the compounds and compositions of the invention are useful in treating are chronic disorders, in one embodiment combination therapy involves alternating between administering a compound or a composition of the invention and a pharmaceutical composition comprising another therapeutic agent, e.g., to minimize the toxicity associated with a particular drug. In certain embodiments, when a composition of the invention is administered concurrently with another therapeutic agent that potentially produces adverse side effects including, but not limited to toxicity, the therapeutic agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited. Additional therapeutic agents include, but are not limited to, hematopoietic growth factors, cytokines, cytotoxic cancer agents, antibiotics, immunosuppressive agents, steroids, antihistamines, leukotriene inhibitors and other therapeutics discussed herein.

Preferred additional therapeutic agents include, but are not limited to, Remicade™, docetaxel, Celecoxib™, methotrexate, dexamethasone, steroids, gemcitabine, cisplatin, temozolomide, etoposide, cyclophosphamide, tenoside, carboplatin, plicicarbazine, glatir, tamoxifen, topotecan, methotrexate, Arava®, Taxol™, taxotene, fluorouracil, leucovorin, irinotecan, adriamycin, CPT-11, interferon alpha, pegylated interferon alpha, cyclosporine, cisplatin, diazepam, budesonide, carboplatin, liposomal daunorubicin, cytarabine, doxorubicin, paclitaxel, valproic acid, IL-2, GM-CSF, dexamethasone, vinorelbine, meloxicam acid, polmitrenate, baxatin, busulfan, prednisone, hydrophosphamide, arsenic trioxide, PEG-INTRON-A, doxil, vincristine, decadron, doxorubicin, paclitaxel, ganciclovir, adriamycin, estramustine, flucytosine, and etoposide.

The invention further encompasses mutants and derivatives (e.g., modified forms) of naturally occurring proteins that exhibit, *in vivo*, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term "mutants" are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (e.g., sugar-cleaved forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG2 to the protein or active portion of the protein of interest. See, e.g., Pincchet, M. L. and Morrison, S. L., *J. Immunol. Methods*, 248:91-101 (2001).

Recombinant and mutated forms of G-CSF can be prepared as described in U.S. Pat. Nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference. Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. Pat. Nos. 5,391,445; 5,933,470; and 5,229,496; all of which are incorporated herein by reference. In fact, recombinant forms of G-CSF and GM-CSF are currently sold in the United States for the treatment of symptoms associated with specific chemotherapies. A recombinant form of G-CSF known as filgrastim is sold in the United States under the trade name NIVONORM®, and is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients

with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. Physicians' Desk Reference, 587-592 (56th ed., 2002). A recombinant form of GM-CSF known as sargramostim is also sold in the United States under the trade name LEUKINE®. LEUKINE® is indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery. Physicians' Desk Reference, 1755-1760 (56th ed., 2002). A recombinant form of EPO known as epoetin alfa is sold in the United States under the trade name EPOGEN®. EPOGEN® is used to stimulate red cell production by stimulating division and maturation of committed red cell precursor cells. Physicians' Desk Reference, 582-587 (56th ed., 2002).

A growth-factor or cytokine such as G-CSF, GM-CSF and EPO can also be administered in the form of a vaccine. For example, vaccines that secrete, or cause the secretion of, cytokines such as G-CSF and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. See, e.g., Emens, L. A., et al, *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

[illegible][illegible][illegible]

phagocyte antigens CD4, CD8, CD11b, CD14, CD15, CD16, CD18, CD19, CD20, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42, CD43, CD44, CD45, CD46, CD47, CD48, CD49, CD50, CD51, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CD60, CD61, CD62, CD63, CD64, CD65, CD66, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD76, CD77, CD78, CD79, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120, CD121, CD122, CD123, CD124, CD125, CD126, CD127, CD128, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140, CD141, CD142, CD143, CD144, CD145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD157, CD158, CD159, CD160, CD161, CD162, CD163, CD164, 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51 Reactions are incubated at 30° C. for 30 minutes and terminated by boiling for 2 minutes. The amount of phosphotransferase IV containing extract used for these experiments is predetermined such that reactions are within the linear range and consumed less than 15% of the total substrate. Following termination of reaction, samples are chilled at 4° C. and then treated with 10 µl 10 mg/ml snake venom for 15 min at 50° C. Unsued substrate then is removed by adding 200 µl of a quaternary ammonium ion exchange resin (AG1-X8, BioRad) for 15 minutes. Samples then are spun at 3000 rpm, 5 min and 50 µl of the aqueous phase are taken for counting. Each data point is carried out in duplicate and activity is expressed as percentage of control. The IC₅₀ of the compound then is determined from dose response curves of a minimum of three independent experiments.

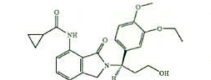
The following examples are offered by way of illustration and are not intended to limit the scope of the invention.

5. EXAMPLES

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wis., USA). ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker AC 250 MHz NMR spectrometer. Significant peaks are tabulated in the order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; coupling constants) in Hertz (Hz) and number of protons.

5.1. Example 1

(1R)-Cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-hydroxy-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide

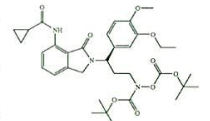


A solution of (1R)-3-amino-3-(3-ethoxy-4-methoxy-phenyl)-propan-1-ol (1.1 g, 4.9 mmol), 2-bromoethyl-4-cyclopropylcarboxyl-amine)benzoic acid methyl ester (1.5 g, 4.9 mmol) and triethylamine (0.75 mL, 5.4 mmol) in DMF (10 mL) was heated at 100° C. for 18 hrs. The solvent was removed in vacuo. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with HCl (1N, 50 mL), brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (5 mL) and hexane (5 mL) to give a suspension. The suspension was filtered to give (1R)-cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-hydroxy-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (1.3 g, 46% yield); mp, 103–105° C.; ¹H NMR (CDCl₃) δ 0.86–0.93 (m, 2H, CH₂), 1.08–1.12 (m, 2H, CH₂), 1.44 (t, 3H, CH₃), 1.64–1.73 (m, 1H, CH), 2.11–2.32 (m, 2H, CH₂), 3.37 (dd,

52 J=4.9 Hz, 1H, OH), 3.50–3.59 (m, 1H, CH), 3.74–3.79 (m, 2H, NCH₂CH₂), 3.80 (s, 3H, CH₃), 4.06 (q, 2–7 Hz, 2H, CH₂), 4.16 (d, 2–18 Hz, 1H, NCH₂), 6.65 (dd, 2–4, 11 Hz, 1H, NCH₂), 6.83–6.99 (m, 4H, Ar), 7.44 (t, 2–8 Hz, 1H, Ar), 8.45 (d, 2–8 Hz, 1H, Ar), 10.52 (s, 1H, NH); ¹³C NMR (CDCl₃) δ 8.35, 14.77, 16.22, 33.85, 46.23, 50.52, 55.98, 58.59, 64.55, 111.36, 112.99, 116.77, 116.99, 117.93, 119.37, 130.73, 133.37, 138.05, 141.49, 148.62, 149.25, 170.33, 172.76; Anal. Calcd for C₂₄H₂₉N₂O₅: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.92; H, 6.67; N, 6.37.

5.2. Example 2

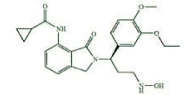
(1R)-tert-Butyl-N-[3-[7-(cyclopropylcarboxylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propyl]carboxylamide)tert-butylfluorinate



A solution of (1R)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-(3-ethoxy-4-methoxyphenyl)propyl]tert-butylcarboxylamine)tert-butylfluorinate (4.1 g, 7.2 mmol), cyclopropylcarboxyl chloride (0.80 mL, 8.8 mmol) and triethylamine (1.3 mL, 9.3 mmol) in THF (20 mL) was heated at reflux for 2 hrs. The solution was extracted with ethyl acetate (100 mL) and sodium hydrogen carbonate (50 mL). The organic layer was washed with sodium hydrogen carbonate (sat, 50 mL), brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo to give (1R)-tert-butyl-N-[3-[7-(cyclopropylcarboxylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propyl]carboxylamine)tert-butylfluorinate as a white solid (4.4 g, 95% yield); mp, 133–135° C.; ¹H NMR (CDCl₃) δ 0.84–0.92 (m, 2H, CH₂), 1.06–1.13 (m, 2H, CH₂), 1.42 (s, 9H, 3CH₃), 1.43 (t, 3H, CH₃), 1.50 (s, 9H, 3CH₃), 1.65–1.73 (m, 1H, CH), 2.23–2.45 (m, 2H, CH₂), 2.99 (t, 2–7 Hz, 2H, CH₂), 3.85 (s, 3H, CH₃), 3.95 (d, 2–16 Hz, 1H, NCH₂), 4.06 (q, 2–7 Hz, 2H, CH₂), 4.26 (d, 2–16 Hz, 1H, NCH₂), 5.97 (dd, 2–6, 10 Hz, 1H, NCH₂), 6.81–6.99 (m, 4H, Ar), 7.41 (t, 2–8 Hz, 1H, Ar), 8.42 (d, 2–8 Hz, 1H, Ar), 10.57 (s, 1H, NH); ¹³C NMR (CDCl₃) δ 8.27, 14.77, 16.19, 29.83, 45.79, 50.40, 51.45, 55.96, 64.57, 111.44, 112.84, 116.73, 117.59, 117.73, 119.52, 131.27, 133.13, 137.99, 141.86, 148.62, 149.18, 169.55, 172.72; Anal. Calcd for C₃₂H₄₁N₃O₅: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.30; H, 6.63; N, 9.21.

5.3. Example 3

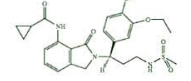
(1R)-Cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-hydroxy-amino-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide



A solution of (1R)-tert-butyl-N-[3-[7-(cyclopropylcarboxylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propyl]carboxylamine)tert-butylfluorinate (4.1 g, 7.2 mmol) in methylene chloride (20 mL) and methanoromethylacetic acid (9 mL) was stirred at room temperature for 1.5 hrs. The solvent was removed in vacuo to give a yellow oil. The oil was extracted with ethyl acetate (50 mL) and sodium hydrogen carbonate (sat, 50 mL). The organic layer was washed with brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (15 mL) to give a suspension. The suspension was filtered to give (1R)-cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-hydroxy-amino-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (2.1 g, 75% yield); mp, 136–138° C.; ¹H NMR (CDCl₃) δ 0.84–0.91 (m, 2H, CH₂), 1.06–1.14 (m, 2H, CH₂), 1.43 (t, 3H, CH₃), 1.44–1.71 (m, 1H, CH), 2.23–2.45 (m, 2H, CH₂), 2.99 (t, 2–7 Hz, 2H, CH₂), 3.85 (s, 3H, CH₃), 3.95 (d, 2–16 Hz, 1H, NCH₂), 4.06 (q, 2–7 Hz, 2H, CH₂), 4.26 (d, 2–16 Hz, 1H, NCH₂), 5.97 (dd, 2–6, 10 Hz, 1H, NCH₂), 6.81–6.99 (m, 4H, Ar), 7.41 (t, 2–8 Hz, 1H, Ar), 8.42 (d, 2–8 Hz, 1H, Ar), 10.57 (s, 1H, NH); ¹³C NMR (CDCl₃) δ 8.27, 14.77, 16.19, 29.83, 45.79, 50.40, 51.45, 55.96, 64.57, 111.44, 112.84, 116.73, 117.59, 117.73, 119.52, 131.27, 133.13, 137.99, 141.86, 148.62, 149.18, 169.55, 172.72; Anal. Calcd for C₃₂H₄₁N₃O₅: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.30; H, 6.63; N, 9.21.

5.4. Example 4

(1R)-Cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-methanoylcarboxylamine-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide



To a solution of (1R)-cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide (0.45 g, 1.1 mmol) and

triethylamine (0.3 mL, 2.2 mmol) in methylene chloride (10 mL) was added methanoyl chloride (0.10 mL, 1.3 mmol) at 0° C. After 3 hrs, the mixture was extracted with methylene chloride (20 mL) and water (20 mL). The organic layer was washed with HCl (1N, 20 mL), sodium hydrogen carbonate (sat, 20 mL), brine (20 mL), and dried over MgSO₄. The solvent was removed in vacuo to give a solid, which was purified with chromatography (Silica Gel) to give (1R)-cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-methanoylcarboxylamine-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (320 mg, 58% yield); mp, 93–95° C.; ¹H NMR (CDCl₃) δ 0.89–0.93 (m, 2H, CH₂), 1.08–1.10 (m, 2H, CH₂), 1.42 (t, 3H, CH₃), 1.65–1.72 (m, 1H, CH), 2.27–2.32 (m, 2H, CH₂), 2.94 (s, 3H, CH₃), 2.97–3.06 (m, 1H, CH₂), 3.85 (s, 3H, CH₃), 3.50 (d, 2–7 Hz, 1H, NCH₂), 4.04 (q, 2–7 Hz, 2H, CH₂), 4.18 (d, 2–7 Hz, 1H, NCH₂), 5.59 (dd, 2–6, 9 Hz, 1H, NCH₂), 5.60–5.62 (m, 1H, NH), 6.81–6.99 (m, 4H, Ar), 7.42 (t, 2–8 Hz, 1H, Ar), 8.42 (d, 2–8 Hz, 1H, Ar), 10.47 (s, 1H, NH); ¹³C NMR (CDCl₃) δ 8.35, 14.76, 16.19, 32.26, 40.24, 40.65, 45.05, 51.12, 55.98, 64.63, 111.50, 112.83, 116.86, 116.94, 117.84, 119.64, 130.33, 133.43, 138.02, 141.44, 148.72, 149.41, 170.07, 172.72; Anal. Calcd for C₃₂H₃₇N₂O₅: C, 65.31; H, 5.92; N, 8.77; H₂O 1.26. Found: C, 59.42; H, 6.16; N, 8.05; H₂O 1.24.

5.5. Example 5

(1R)-Cyclopropylcarboxylic acid [2-[1-amino-1-(3-ethoxy-4-methoxy-phenyl)-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide

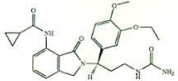


To a solution of triphenyl phosphine (1.4 g, 5.2 mmol), (1R)-cyclopropylcarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-3-hydroxy-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide (1.5 g, 3.4 mmol) and tert-butyl(tert-butylcarboxylamine)formate (2.3 g, 10 mmol) in THF (15 mL) was added a solution of DEAD (1 mL, 5.1 mmol) in THF (10 mL) at room temperature. After 1.5 hrs, the residue was purified with chromatography (Silica Gel) to give (1R)-tert-butyl-N-[3-[7-(cyclopropylcarboxylamino)-1-oxoisindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propyl]-tert-butylcarboxylamine)formate as an oil (2.4 g). The oil in trifluoroacetic acid (5 mL) and methylene chloride (5 mL) was stirred at room temperature for 1 hr. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (10 mL) to give a suspension. The suspension was filtered to give (1R)-cyclopropylcarboxylic acid [2-[1-amino-1-(3-ethoxy-4-methoxy-phenyl)-propyl]-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide (CF₃COOH salt) as a white solid (1.1 g, 57% yield); mp, 169–177° C.; ¹H NMR (DMSO-d₆) δ 0.89–0.94 (m, 4H, 2CH₂), 1.31 (t, 3H, CH₃), 1.72–1.79 (m, 1H, CH), 2.31–2.41 (m, 2H, CH₂), 2.80–2.82 (m, 2H, CH₂), 3.74 (s, 3H, CH₃), 3.99–4.09 (m, 3H, CH₂), 4.53 (d, 2–18 Hz, 1H, NCH₂), 5.35 (dd, 2–6, 9 Hz, 1H, NCH₂), 6.91–6.99 (m, 4H, Ar), 7.19 (d, 2–8 Hz, 1H, Ar), 7.51 (t, 2–8 Hz, 1H, Ar), 7.80 (br s, 3H, NH), 8.23 (d, 2–8 Hz, 1H, Ar), 10.54 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 8

7.78, 14.70, 15.48, 29.20, 36.69, 45.99, 51.58, 55.49, 63.84, 112.81, 112.55, 116.91, 117.19, 117.59, 119.59, 130.87, 132.89, 136.85, 142.32, 149.05, 149.74, 168.15, 171.69. Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot 1.2$ CF₃COOH: C, 56.59; H, 5.43; N, 7.50. Found: C, 56.65; H, 5.59; N, 7.26.

5.6. Example 6

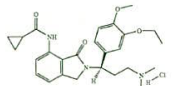
(1R)-Cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide



To a solution of (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide CF₃COOH (0.40 g, 0.74 mmol) in HCl (10 mL, 0.5 M) was added a solution of potassium cyanate (240 mg, 3 mmol) in water (3 mL). The suspension was heated at 50° C. overnight. The mixture was extracted with ethyl acetate (50 mL) and water (20 mL). The organic layer was washed with HCl (1N, 50 mL), brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo to give a solid, which was purified with prep HPLC to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (220 mg, 65% yield; mp, 162–164° C.; ¹H NMR (DMSO-*d*₆) δ 0.88 (d, J=6 Hz, 4H, CH₂), 1.31 (t, J=7 Hz, 3H, CH₃), 1.72–1.79 (m, 1H, CH), 2.11–2.25 (m, 2H, CH₂), 2.90–2.99 (m, 2H, CH₂), 3.79 (s, 3H, CH₃), 3.79–4.13 (s, 3H, CH₃), 4.57 (d, J=17 Hz, 1H, NCH), 5.28 (t, J=9 Hz, 1H, NH), 5.48 (d, 2H, NH), 6.00 (t, J=5 Hz, 1H, NCH), 6.88–6.94 (m, 3H, Ar), 7.17 (d, J=8 Hz, 1H, Ar), 7.48 (t, J=8 Hz, 1H, Ar), 8.22 (d, J=8 Hz, 1H, Ar), 16.59 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 7.75, 14.72, 15.48, 31.97, 36.81, 45.89, 51.74, 55.45, 63.78, 111.07, 112.34, 116.79, 117.33, 117.52, 119.67, 131.93, 132.68, 136.95, 142.29, 147.96, 148.46, 159.69, 168.27, 171.68. Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot 0.6$ H₂O: C, 62.91; H, 4.55; N, 11.74. H₂O 2.25. Found: C, 62.69; H, 6.32; N, 11.56. H₂O 1.20.

5.7. Example 7

(1R)-Cyclopropanecarboxylic acid [2-(1-(3-dimethylamino-1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl)-amide hydrochloride

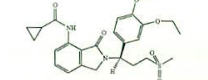


A mixture of (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide CF₃COOH (0.56 g,

1.0 mmol), Pd/C (150 mg) and formaldehyde (400 mg, 5 mmol) in methanol (40 mL) was shaken under hydrogen (50 psi) overnight. The suspension was filtered thru a pad of Celite. The solvent was removed in vacuo. The residue was extracted with methylene chloride (50 mL) and sodium hydrogen carbonate (sat, 50 mL). The organic layer was washed with brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo to give a solid, which was purified with prep HPLC to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-dimethylamino-1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl)-amide hydrochloride as a white solid (229 mg, 48% yield; mp, 119–121° C.; ¹H NMR (DMSO-*d*₆) δ 0.88 (d, J=6 Hz, 4H, CH₂), 1.12 (t, J=7 Hz, 3H, CH₃), 1.71–1.79 (m, 1H, CH), 2.42–2.59 (m, 2H, CH₂), 2.76 (s, 3H, CH₃), 2.78 (s, 3H, CH₃), 3.05–3.10 (m, 2H, CH₂), 3.74 (s, 3H, CH₃), 3.99–4.06 (m, 3H, NCH), 4.29 (d, J=17 Hz, 1H, NCH), 5.32 (dd, J=5, 10 Hz, 1H, NH), 6.96 (brs, 3H, Ar), 7.19 (d, J=8 Hz, 1H, Ar), 7.51 (t, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.46 (brs, 1H, HCl), 10.54 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 7.79, 14.71, 15.47, 23.86, 42.00, 42.05, 45.72, 51.54, 54.07, 55.49, 63.89, 111.96, 122.29, 116.88, 117.22, 117.51, 118.75, 130.64, 132.85, 136.99, 142.37, 148.07, 148.75, 168.42, 171.72. Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot H_2O \cdot Cl$: C, 61.71; H, 7.17; N, 8.30; Cl, 7.01. H₂O 1.56. Found: C, 61.85; H, 7.26; N, 7.99; Cl, 7.52. H₂O 3.36.

5.8. Example 8

(1R)-Cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-methanesulfonyl-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide

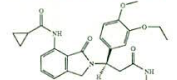


To a solution of triphenyl phosphine (0.61 g, 2.4 mmol) in THF (10 mL) was added DIAD (0.47 mL, 2.4 mmol) at 0° C. After 10 min, (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide (0.93 mL, 2.2 mmol) was added as solid. After 5 min, sodium thiomethoxide (180 mg, 2.4 mmol) was added. After 20 min, the cold bath was removed and the mixture was stirred at room temperature for 1.5 hrs. To the mixture was added water (15 mL), methanol (15 mL), and oxone (5.4 g, 8.4 mmol) and kept for 16 h. The mixture was extracted with methylene chloride (100 mL) and water (50 mL). The organic layer was dried over MgSO₄. The solvent was removed in vacuo to give a solid. The solid was purified with prep HPLC to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-methanesulfonyl-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (50 mg, 5% yield; mp, 148–150° C.; ¹H NMR (CDCl₃) δ 0.89–0.94 (m, 2H, CH₂), 1.10–1.13 (m, 2H, CH₂), 1.46 (t, J=7 Hz, 3H, CH₃), 1.65–1.73 (m, 1H, CH), 2.60–2.69 (m, 2H, CH₂), 2.96 (s, 3H, CH₃), 3.02–3.22 (m, 2H, CH₂), 3.97 (s, 3H, CH₃), 5.99 (d, J=17 Hz, 1H, NCH), 6.07 (t, J=7 Hz, 1H, CH₂), 4.30 (d, J=17 Hz, 1H, NCH), 4.48 (s, J=8 Hz, 1H, NCH), 6.84–7.02 (m, 4H, Ar), 7.46 (t, J=8 Hz, 1H, Ar), 8.45 (d, J=8 Hz, 1H, Ar), 10.49 (s, 1H, NH). ¹³C NMR (CDCl₃) δ 8.30, 14.75, 16.19, 23.78, 41.24, 45.95, 51.99, 53.01, 56.00,

64.65, 111.60, 112.37, 116.88, 117.00, 117.89, 119.46, 129.82, 133.52, 138.09, 141.29, 148.87, 149.53, 169.79, 172.66. Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot 1.2$ CF₃COOH: C, 56.59; H, 5.43; N, 7.50. Found: C, 61.33; H, 6.19; N, 5.59.

5.9. Example 9

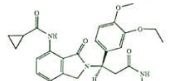
(1R)-Cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide



A solution of (1R)-3-(7-cyclopropanecarboxyl-aminio)-1-oxo-1,3-dihydro-isindol-2-yl)-1-(3-ethoxy-4-methoxyphenyl)propionic acid (300 mg, 0.65 mmol) and CDI (130 mg, 0.91 mmol) in THF (3 mL) was stirred at room temperature for 2 hrs. To the mixture was added hydroxybenzylamine HCl (59 mg, 1 mmol) and kept for overnight. Water (20 mL) was added to the mixture. The suspension was filtered to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (220 mg, 71% yield; mp, 160–162° C.; ¹H NMR (DMSO-*d*₆) δ 0.88–0.92 (m, 4H, CH₂), 1.31 (t, J=7 Hz, 3H, CH₃), 1.72–1.81 (m, 1H, CH), 2.85 (d, J=4 Hz, 2H, CH₂), 3.73 (s, 3H, CH₃), 4.01 (t, J=7 Hz, 2H, CH₂), 4.16 (d, J=18 Hz, 1H, NCH), 4.57 (d, J=18 Hz, 1H, NCH), 5.68 (t, J=8 Hz, 1H, NCH), 6.86–6.95 (m, 3H, Ar), 7.19 (d, J=8 Hz, 1H, Ar), 7.49 (t, J=8 Hz, 1H, Ar), 8.22 (d, J=8 Hz, 1H, Ar), 8.83 (s, 1H, NH), 10.56 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 7.77, 14.72, 15.47, 35.09, 46.44, 51.33, 55.45, 63.81, 111.93, 112.16, 116.81, 117.36, 117.51, 119.37, 131.45, 132.74, 136.96, 142.21, 147.94, 148.55, 165.93, 167.97, 171.11. Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.24; H, 5.95; N, 8.91.

5.10. Example 10

(1R)-Cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide

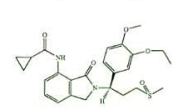


A solution of (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide and acetic anhydride (0.09 mL, 1 mmol) in acetonitrile/methylene chloride (6 mL, each) was stirred at room temperature for 21 hrs.

EtBr (10 mL) and hexane (10 mL) was added to give a suspension. The suspension was filtered to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (270 mg, 63% yield; mp, 140–142° C.; ¹H NMR (DMSO-*d*₆) δ 0.88–0.92 (m, 4H, CH₂), 1.30 (t, J=7 Hz, 3H, CH₃), 1.75–1.81 (m, 1H, CH), 2.09 (s, 3H, CH₃), 1.03–1.07 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 4.01 (t, J=7 Hz, 2H, CH₂), 4.18 (d, J=18 Hz, 1H, NCH), 4.60 (d, J=18 Hz, 1H, NCH), 5.67 (t, J=8 Hz, 1H, NCH), 6.86–6.95 (m, 3H, Ar), 7.18 (d, J=8 Hz, 1H, Ar), 7.49 (t, J=8 Hz, 1H, Ar), 8.21 (d, J=8 Hz, 1H, Ar), 10.54 (s, 1H, NH), 11.86 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 7.75, 14.70, 15.46, 17.95, 17.95, 34.55, 46.53, 51.06, 55.44, 63.76, 111.87, 111.99, 116.77, 117.29, 117.47, 119.23, 131.17, 132.74, 136.94, 142.25, 147.92, 148.52, 166.48, 168.02, 168.32, 171.70. Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot 0.1$ H₂O: C, 62.79; H, 5.92; N, 8.45. H₂O, 0.36. Found: C, 62.44; H, 5.82; N, 8.37. H₂O, 0.30.

5.11. Example 11

(1R)-Cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-methanesulfonyl-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide

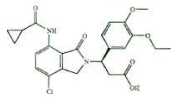


To a solution of (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide (5.7 g, 13 mmol), triphenyl phosphine (7.1 g, 2.4 mmol) and thioctic acid (2.2 mL, 31 mmol) in THF (50 mL) was added a solution of DIAD (5.5 mL, 28 mmol) in THF (50 mL) at room temperature. After 4 hrs, methanol (5 mL) was added to the solution. The solvent was removed in vacuo. The residue was purified with Chromatography to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl)-amide (5.7 g, 13 mmol), triphenyl phosphine (7.1 g, 2.4 mmol) and thioctic acid (2.2 mL, 31 mmol) in THF (50 mL) was added a solution of DIAD (5.5 mL, 28 mmol) in THF (50 mL) at room temperature. After 4 hrs, methanol (5 mL) was added to the solution. The solvent was removed in vacuo. The residue was purified with Chromatography to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl)-amide (5.7 g, 13 mmol), triphenyl phosphine (7.1 g, 2.4 mmol) and thioctic acid (2.2 mL, 31 mmol) in THF (50 mL) was added a solution of DIAD (5.5 mL, 28 mmol) in THF (50 mL) at room temperature. After 2 hrs, to the mixture was added water (40 mL), hydrazine (5N, 4.2 mL, 21 mmol) at room temperature. After 2 hrs, to the mixture was added water (40 mL), methylene chloride (20 mL), and oxone (11 g, 29 mmol) and kept for 1.5 hrs. The mixture was extracted with methylene chloride (100 mL) and water (50 mL). The organic layer was washed with Na₂S₂O₅ (10% 50 mL), brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo. The residue was purified with chromatography (Silica Gel) to give (1R)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-3-methanesulfonyl-propyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (320 mg,

6% yield) mp. 122–125° C.; ¹H NMR (CDCl₃) δ 0.86–0.93 (m, 2H, CH₃), 1.08–1.14 (m, 2H, CH₃), 1.45 (t, J=7 Hz, 3H, CH₃), 1.63–1.72 (m, 1H, CH), 2.58 and 2.59 (2d, 3H, CH₃), 2.60–2.82 (m, 4H, CH₂CH₂), 3.86 (s, 3H, CH₃), 3.97 (d, J=17 Hz, 1H, NCHH), 4.06 (q, J=7 Hz, 2H, CH₂), 4.31 and 4.35 (2 sets of d, J=17 Hz, 1H, NCHH), 5.50–5.59 (m, 1H, NCH), 6.84–7.02 (m, 4H, Ar), 7.41–7.61 (m, 1H, Ar), 8.43 (d, J=8 Hz, 1H, Ar), 10.54 (s, 1H, NH); ¹³C NMR (CDCl₃) δ 8.28, 14.76, 16.18, 24.28, 24.76, 38.05, 45.71, 45.89, 51.22, 51.42, 51.07, 53.01, 55.99, 64.64, 111.54, 112.49, 116.89, 117.19, 117.80, 119.54, 130.38, 130.48, 133.37, 138.04, 141.36, 148.77, 149.48, 169.79, 169.82, 172.66; Anal. Calcd. for C₂₁H₂₅N₂O₅·8+0.8 H₂O: C, 61.93, H, 6.57, N, 5.78, H₂O, 2.97. Found: C, 61.83; H, 6.62; N, 5.81; H₂O, 2.19.

5.12. Example 12

(R)-3-[4-(chloro-7-(cyclopropanecarbonyl)amino)-1-oxo-1,3-dihydro-isindol-2-yl]-3-(3-ethoxy-4-methoxy-phenyl)-propionic acid

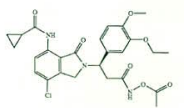


To a solution of (R)-3-[4-(chloro-7-(cyclopropanecarbonyl)amino)-1-oxo-1,3-dihydro-isindol-2-yl]-3-(3-ethoxy-4-methoxy-phenyl)-propionic acid methyl ester (3.0 g, 8.7 mmol) in DMF (25 ml) was added 2-bromomethyl-3-chloro-6-(cyclopropanecarbonyl-amino)-benzoic acid methyl ester (2.2 g, 8.6 mmol) and triethyl amine (2.4 ml, 17 mmol). The mixture was heated at 90° C. overnight. The solvent was removed in vacuo. The resulting oil was extracted with ethyl acetate (50 ml) and water (50 ml). The organic layer was washed with water (50 ml), brine (50 ml) and dried over magnesium sulfate. The solvent was removed in vacuo and the resulting oil was purified by silica gel column to give (R)-3-[4-(chloro-7-(cyclopropanecarbonyl)amino)-1-oxo-1,3-dihydro-isindol-2-yl]-3-(3-ethoxy-4-methoxy-phenyl)-propionic acid methyl ester as a white solid (1.5 g, 37%). mp. 158–160° C.; ¹H NMR (CDCl₃) δ 0.86–0.93 (m, 2H, CH₃), 1.07–1.13 (m, 2H, CH₃), 1.46 (t, J=7 Hz, 3H, OCH₂CH₃), 1.64–1.71 (m, 1H, CH), 2.58, 3.00, 3.06, 3.07, 3.08, 3.10, 3.11, 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, 3.19, 3.20, 3.21, 3.22, 3.23, 3.24, 3.25, 3.26, 3.27, 3.28, 3.29, 3.30, 3.31, 3.32, 3.33, 3.34, 3.35, 3.36, 3.37, 3.38, 3.39, 3.40, 3.41, 3.42, 3.43, 3.44, 3.45, 3.46, 3.47, 3.48, 3.49, 3.50, 3.51, 3.52, 3.53, 3.54, 3.55, 3.56, 3.57, 3.58, 3.59, 3.60, 3.61, 3.62, 3.63, 3.64, 3.65, 3.66, 3.67, 3.68, 3.69, 3.70, 3.71, 3.72, 3.73, 3.74, 3.75, 3.76, 3.77, 3.78, 3.79, 3.80, 3.81, 3.82, 3.83, 3.84, 3.85, 3.86, 3.87, 3.88, 3.89, 3.90, 3.91, 3.92, 3.93, 3.94, 3.95, 3.96, 3.97, 3.98, 3.99, 4.00, 4.01, 4.02, 4.03, 4.04, 4.05, 4.06, 4.07, 4.08, 4.09, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20, 4.21, 4.22, 4.23, 4.24, 4.25, 4.26, 4.27, 4.28, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.37, 4.38, 4.39, 4.40, 4.41, 4.42, 4.43, 4.44, 4.45, 4.46, 4.47, 4.48, 4.49, 4.50, 4.51, 4.52, 4.53, 4.54, 4.55, 4.56, 4.57, 4.58, 4.59, 4.60, 4.61, 4.62, 4.63, 4.64, 4.65, 4.66, 4.67, 4.68, 4.69, 4.70, 4.71, 4.72, 4.73, 4.74, 4.75, 4.76, 4.77, 4.78, 4.79, 4.80, 4.81, 4.82, 4.83, 4.84, 4.85, 4.86, 4.87, 4.88, 4.89, 4.90, 4.91, 4.92, 4.93, 4.94, 4.95, 4.96, 4.97, 4.98, 4.99, 5.00, 5.01, 5.02, 5.03, 5.04, 5.05, 5.06, 5.07, 5.08, 5.09, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17, 5.18, 5.19, 5.20, 5.21, 5.22, 5.23, 5.24, 5.25, 5.26, 5.27, 5.28, 5.29, 5.30, 5.31, 5.32, 5.33, 5.34, 5.35, 5.36, 5.37, 5.38, 5.39, 5.40, 5.41, 5.42, 5.43, 5.44, 5.45, 5.46, 5.47, 5.48, 5.49, 5.50, 5.51, 5.52, 5.53, 5.54, 5.55, 5.56, 5.57, 5.58, 5.59, 5.60, 5.61, 5.62, 5.63, 5.64, 5.65, 5.66, 5.67, 5.68, 5.69, 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17.74, 17.75, 17.76, 17.77, 17.78, 17.79, 17.80, 17.81, 17.82, 17.83, 17.84, 17.85, 17.86, 17.87, 17.88, 17.89, 17.90, 17.91, 17.92, 17.93, 17.94, 17.95, 17.96, 17.97, 17.98, 17.99, 18.00, 18.01, 18.02, 18.03, 18.04, 18.05, 18.06, 18.07, 18.08, 18.09, 18.10, 18.11, 18.12, 18.13, 18.14, 18.15, 18.16, 18.17, 18.18, 18.19, 18.20, 18.21, 18.22, 18.23, 18.24, 18.25, 18.26, 18.27, 18.28, 18.29, 18.30, 18.31, 18.32, 18.33, 18.34, 18.35, 18.36, 18.37, 18.38, 18.39, 18.40, 18.41, 18.42, 18.43, 18.44, 18.45, 18.46, 18.47, 18.48, 18.49, 18.50, 18.51, 18.52, 18.53, 18.54, 18.55, 18.56, 18.57, 18.58, 18.59, 18.60, 18.61, 18.62, 18.63, 18.64, 18.65, 18.66, 18.67, 18.68, 18.69, 18.70, 18.71, 18.72, 18.73, 18.74, 18.75, 18.76, 18.77, 18.78, 18.79, 18.80, 18.81, 18.82, 18.83, 18.84, 18.85, 18.86, 18.87, 18.88, 18.89, 18.90, 18.91, 18.92, 18.93, 18.94, 18.95, 18.96, 18.97, 18.98, 18.99, 19.00, 19.01, 19.02, 19.03, 19.04, 19.05, 19.06, 19.07, 19.08, 19.09, 19.10, 19.11, 19.12, 19.13, 19.14, 19.15, 19.16, 19.17, 19.18, 19.19, 19.20, 19.21, 19.22, 19.23, 19.24, 19.25, 19.26, 19.27, 19.28, 19.29, 19.30, 19.31, 19.32,

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5.17. Example 17

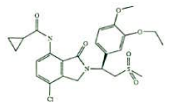
(1*R*)-Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)ethyl]-7-chloro-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide



To the solution of cyclopropanecarboxylic acid [7-chloro-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-hydroxyacetyl]-5-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide (0.45 g, 0.92 mmol) in CH_3CN (50 ml) was added acetic anhydride (0.1 ml, 0.92 mmol) at room temperature. The mixture was stirred overnight. The solvent was removed in vacuo and the resulting acid was stirred with ether (10 ml) for 2 hrs. The suspension was filtered and the solid was dried in oven to give (1*R*)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)-2-hydroxyacetyl]-5-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide (0.4 g, 80%) mp 139-141° C. ^1H NMR (CDCl_3): δ 0.85-0.92 (m, 2H, e-CH_3), 1.05-1.11 (m, 2H, e-CH_3), 1.42 (t, $\text{J}=7.5$ Hz, 3H, OCH_2CH_3), 1.62-1.69 (m, 1H, e-CH_2), 2.12 (s, 3H, CH_3), 3.02 (dd, $\text{J}=5, 16$ Hz, 1H, CHH), 3.50 (dd, $\text{J}=5, 16$ Hz, 1H, CHH), 3.85 (s, 3H, OCH_3), 4.08 (s, $\text{J}=7.5$ Hz, 2H, OCH_2CH_3), 4.12 (d, $\text{J}=17$ Hz, 1H, CHH), 4.38 (d, $\text{J}=17$ Hz, 1H, CHH), 5.61-5.65 (m, 1H, CHH), 6.81-6.94 (m, 3H, Ar), 7.31 (d, $\text{J}=10$ Hz, 1H, Ar), 8.38 (d, $\text{J}=10$ Hz, 1H, Ar), 10.41 (s, 1H); ^{13}C NMR (CDCl_3): δ 50.9, 9.1, 15.3, 16.7, 18.7, 36.8, 48.2, 54.4, 56.5, 65.2, 112.2, 112.8, 119.7, 119.8, 120.2, 122.4, 131.1, 133.5, 137.2, 139.8, 149.3, 150.1, 167.0, 169.0, 170.0, 175.5; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{ClNO}_6$: C, 58.92; H, 5.33; N, 7.93. Found: C, 58.58; H, 5.00; N, 7.76.

5.18. Example 18

(1*S*)-Cyclopropanecarboxylic acid [7-chloro-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide



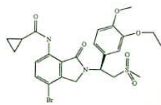
To a solution of (1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine (1.4 g, 3.1 mmol) in DMF (20 ml) was added 2-bromomethyl 3-chloro-6-(cyclopropanecarboxylamino)benzoic acid methyl ester (1.6 g, 4.6

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mmol) and triethyl amine (5 ml, 14 mmol). The mixture was heated at 90° C. overnight. The solvent was removed in vacuo. The resulting oil was extracted with ethyl acetate (50 ml) and water (50 ml). The organic layer was washed with water (50 ml), brine (50 ml) and dried over magnesium sulfate. The solvent was removed in vacuo and the resulting oil was purified by silica gel column to give (1*S*)-cyclopropanecarboxylic acid [7-chloro-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide as a white solid (550 mg, 30%) mp 197-199° C. ^1H NMR (CDCl_3): δ 0.89-0.93 (m, 2H, e-CH_3), 1.06-1.12 (m, 2H, e-CH_3), 1.44 (t, $\text{J}=7.0$ Hz, 3H, OCH_2CH_3), 1.62-1.69 (m, 1H, e-CH_2), 2.97 (s, 3H, CH_3), 3.70 (dd, $\text{J}=5, 13$ Hz, 1H, CHH), 3.87 (s, 3H, OCH_3), 4.09-4.23 (m, 4H, $\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$), 4.41 (d, $\text{J}=17$ Hz, 1H, CHH), 5.75-5.81 (m, 1H, CHH), 6.86-6.96 (m, 3H, Ar), 7.30 (d, $\text{J}=10$ Hz, 1H, Ar), 8.46 (d, $\text{J}=10$ Hz, 1H, Ar), 10.36 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 8.5, 14.2, 16.2, 41.6, 46.9, 51.3, 55.5, 58.0, 64.7, 111.7, 112.3, 118.6, 119.3, 119.7, 121.8, 129.1, 133.2, 136.8, 139.0, 149.0, 149.9, 169.2, 172.6; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{ClNO}_6\text{S}$: C, 56.86; H, 5.37; N, 5.53. Found: C, 56.81; H, 5.26; N, 5.56.

5.19. Example 19

(1*S*)-Cyclopropanecarboxylic acid [7-bromo-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide

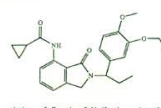


To a solution of (1*S*)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethylamine (0.55 g, 1.2 mmol) in DMF (10 ml) was added 2-bromomethyl 3-bromo-6-(cyclopropanecarboxylamino)benzoic acid methyl ester (0.43 g, 1.1 mmol) and triethyl amine (0.5 ml, 3.3 mmol). The mixture was heated at 90° C. overnight. The solvent was removed in vacuo. The resulting oil was extracted with ethyl acetate (50 ml) and water (50 ml). The organic layer was washed with water (50 ml), brine (50 ml) and dried over magnesium sulfate. The solvent was removed in vacuo and the resulting oil was purified by silica gel column to give (1*S*)-cyclopropanecarboxylic acid [7-bromo-2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide as a white solid (430 mg, 74%) mp 219-221° C. ^1H NMR (CDCl_3): δ 0.89-0.93 (m, 2H, e-CH_3), 1.06-1.14 (m, 2H, e-CH_3), 1.47 (t, $\text{J}=7.0$ Hz, 3H, OCH_2CH_3), 1.65-1.70 (m, 1H, e-CH_2), 2.98 (s, 3H, CH_3), 3.50 (dd, $\text{J}=5, 13$ Hz, 1H, CHH), 3.87 (s, 3H, OCH_3), 4.06-4.14 (m, 3H, $\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$), 4.19 (dd, $\text{J}=10, 15$ Hz, 1H, CHH), 4.59 (d, $\text{J}=17$ Hz, 1H, CHH), 5.75-5.81 (m, 1H, CHH), 6.86-6.96 (m, 3H, Ar), 7.53 (d, $\text{J}=10$ Hz, 1H, Ar), 8.46 (d, $\text{J}=10$ Hz, 1H, Ar), 10.36 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 9.1, 9.2, 15.4, 16.0, 42.2, 49.1, 52.0, 56.1, 56.7, 65.3, 110.1, 112.3, 112.8, 118.5, 119.5, 120.7, 129.7, 136.8, 138.1, 142.0, 149.6, 150.5, 170.0, 173.3; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{BrNO}_6\text{S}$: C, 52.27; H, 4.94; N, 5.08. Found: C, 52.57; H, 4.98; N, 4.95.

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5.20. Example 20

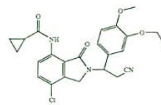
Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)propyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide



A solution of 7-amino-2-[1-(3-ethoxy-4-methoxy-phenyl)propyl]-2,3-dihydro-isotindol-1-one (1.0 g, 2.9 mmol) and cyclopropanecarboxyl chloride (0.32 ml, 3.5 mmol) in THF (10 ml) was heated to reflux for 40 min. The solvent was removed in vacuo. The residue was extracted with ethyl acetate (50 ml) and sodium hydrogen carbonate (sat, 50 ml). The organic layer was washed with brine (50 ml) and dried over MgSO_4 . The solvent was removed in vacuo and the residue was purified with chromatography (Silica Gel) to give cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxy-phenyl)propyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide as a white solid (900 mg, 70% yield) mp 107-109° C. ^1H NMR (CDCl_3): δ 0.84-0.92 (m, 2H, CH_3), 0.99 (t, $\text{J}=7$ Hz, 3H, CH_3), 1.02-1.13 (t, 2H, CH_2), 1.44 (t, $\text{J}=7$ Hz, 3H, CH_3), 1.64-1.73 (m, 1H, CH), 2.00-2.16 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.00 (d, $\text{J}=17$ Hz, 1H, CHH), 4.08 (s, $\text{J}=7$ Hz, 2H, CH_2), 4.27 (d, $\text{J}=17$ Hz, 1H, NCHH), 5.33 (dd, $\text{J}=7, 9$ Hz, 1H, NCH), 6.83-6.95 (m, 3H, Ar), 7.00 (d, $\text{J}=8$ Hz, 1H, Ar), 7.42 (t, $\text{J}=8$ Hz, 1H, Ar), 8.42 (d, $\text{J}=8$ Hz, 1H, Ar), 10.07 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 8.19, 11.18, 14.78, 16.18, 24.54, 45.04, 55.53, 55.97, 58.58, 111.64, 112.91, 116.08, 117.67, 119.51, 131.90, 132.94, 138.02, 141.37, 148.54, 149.04, 169.53, 172.70; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_6$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.54; H, 6.91; N, 6.86.

5.21. Example 21

Cyclopropanecarboxylic acid [7-chloro-2-[2-cyano-1-(3-ethoxy-4-methoxy-phenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide



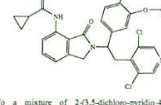
To the DMF solution (20 ml) of 3-Amino-3-(3-ethoxy-4-methoxy-phenyl)propanenitrile (0.55 g, 7 mmol) was added Et_3N (1.6 ml, 12 mmol) followed by 2-bromomethyl 3-chloro-6-(cyclopropanecarboxylamino)benzoic acid methyl ester (2.42 g, 7 mmol). The mixture was heated at 90° C. for 12 hrs then cooled to room temperature. The

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mixture was extracted with EtOAc (50 ml) and water (50 ml). The organic layer was washed with water (50 ml) and brine (50 ml), dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was purified by silica gel chromatography to give cyclopropanecarboxylic acid [7-chloro-2-[2-cyano-1-(3-ethoxy-4-methoxy-phenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide as white solid (2.4 g, 80%) mp 200-202° C. ^1H NMR (CDCl_3): δ 0.90-0.94 (m, 2H, e-CH_3), 1.09-1.14 (m, 2H, e-CH_3), 1.45 (t, $\text{J}=7.0$ Hz, 3H, CH_3), 1.64-1.70 (m, 1H, e-CH_2), 1.12-1.32 (m, 2H, CH_2), 1.84 (s, 3H, CH_3), 1.99-2.12 (m, 3H, $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$), 4.37 (d, $\text{J}=18$ Hz, 1H, CHH), 5.62-5.68 (m, 1H, NCH), 6.87-6.98 (m, 3H, Ar), 7.40 (d, $\text{J}=10$ Hz, 1H, Ar), 8.47 (d, $\text{J}=10$ Hz, 1H, Ar), 10.34 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 8.5, 14.7, 16.2, 21.2, 46.4, 51.8, 56.0, 64.7, 111.7, 112.2, 116.5, 118.4, 119.1, 119.8, 121.9, 127.9, 133.3, 136.8, 138.5, 149.9, 150.5, 169.0, 172.7; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{ClNO}_6$: C, 63.50; H, 5.33; N, 9.26. Found: C, 63.43; H, 5.31; N, 9.01.

5.22. Example 22

Cyclopropanecarboxylic acid [2-[2-(3,5-dichloropyridin-4-yl)-1-(3-ethoxy-4-methoxy-phenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide

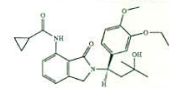


To a mixture of 2-(3,5-dichloro-pyridin-4-yl)-1-(3-ethoxy-4-methoxy-phenyl)-ethanol (500 mg, 1.5 mmol) and PPh_3 (0.60 g, 2.3 mmol), was added DIAD (0.44 mL, 2.2 mmol) at 0° C. After 5 min, PPh_3/POM was added to the mixture at 0° C. The mixture was allowed to warm to room temperature overnight. To the mixture was added PPH_3 (0.9 g, 3.3 mmol) and water (2 mL). The mixture was heated to reflux for 6 hrs. The mixture was extracted with ether (25 mL) and 1*N* HCl (2x25 mL). The aqueous layer was basified with 1*N* sodium hydroxide until pH=14. The aqueous layer was extracted with methylene chloride (2x50 mL). The combined organic layer was concentrated in vacuo. A mixture of the resulting oil, 2-bromomethyl 6-(cyclopropanecarboxylamino)benzoic acid methyl ester (100 mg, 0.64 mmol) and triethyl amine (0.1 mL, 0.7 mmol) in DMF (5 mL) was heated at 90° C. for 27 hrs. The solvent was removed in vacuo. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The solvent was removed in vacuo. The residue was purified with Preparative HPLC to give cyclopropanecarboxylic acid [2-[2-(3,5-dichloro-pyridin-4-yl)-1-(3-ethoxy-4-methoxy-phenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isotindol-4-yl]-amide (0.100 mg, 16% yield) mp 159-161° C. ^1H NMR (CDCl_3): δ 0.81-0.91 (m, 2H, CH_3), 1.01-1.09 (m, 2H, CH_2), 1.45 (t, $\text{J}=7.7$ Hz, 3H, CH_3), 1.56-1.63 (m, 1H, CH), 3.38 (dd, $\text{J}=4, 13$ Hz, 1H, CHH), 3.75 (dd, $\text{J}=1, 13$ Hz, 1H, CHH), 3.91 (d, $\text{J}=17$ Hz, 1H, NCHH), 4.08 (s, $\text{J}=7.7$ Hz, 2H, CH_2), 4.56 (d, $\text{J}=17$ Hz, 1H, NCHH), 5.64 (dd, $\text{J}=4, 11$ Hz, 1H, NCH), 6.86 (m, 4H, Ar), 7.41 (t, $\text{J}=8$ Hz, 1H, Ar), 8.40 (d, $\text{J}=8$ Hz, 1H, Ar), 8.43 (s, 2H, py), 10.28 (s, 1H, NH); ^{13}C

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NMR (CDCl₃) δ 8.27, 14.76, 16.09, 33.22, 46.71, 52.63, 56.00, 64.66, 111.44, 112.69, 116.62, 116.95, 117.67, 119.52, 130.65, 133.11, 133.19, 137.96, 141.40, 142.89, 147.59, 148.75, 149.52, 169.32, 172.75; Anal. Calcd for C₂₄H₂₅N₃O₄Cl₂: C, 62.23; H, 5.04; N, 7.78. Found: C, 61.95; H, 5.09; N, 7.43.

5.25 Example 25

(1R)-Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-3-methylbutyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide

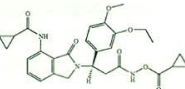


Step 1: To a solution of (1R)-[1-(3-ethoxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (1 g, 3 mmol) in THF (10 mL) was added a solution of methyl iodide (4 mL, 3M, 12 mmol) at 0° C. To the mixture was added methanol (5 mL). The residue was extracted with ethyl acetate (50 mL) and NH₄Cl (sat, 25 mL). The organic layer was washed with brine (100 mL) and dried over MgSO₄. The solvent was removed in vacuo. The residue was purified with preparative HPLC to give (1R)-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-3-methylbutyl]-carbanic acid tert-butyl ester (150 mg, 14% yield).

Step 2: To a solution of (1R)-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-3-methylbutyl]-carbanic acid tert-butyl ester (150 mg, 0.42 mmol) in methylene chloride (5 mL), added a solution of HCl in dioxane (0.5 mL, 4N, 2 mmol). After 2 hrs, the solvent was removed and the crude oil was used in the next step without further purification. A mixture of the resolved oil, 2-bromoethyl-6-cyclopropanecarboxyl-amin)-benzoic acid methyl ester (130 mg, 0.42 mmol) and triethyl amine (0.12 mL, 0.86 mmol) in DMF (1 mL) was heated at 80° C. for 2 hrs. The solvent was removed in vacuo. The residue was extracted with ethyl acetate (50 mL) and NH₄Cl (50 mL). The organic layer was washed with HCl (50 mL), brine (50 mL), and dried over MgSO₄. The solvent was removed in vacuo. The residue was purified with preparative HPLC to give (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxy-3-methylbutyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (100 mg, 51% yield; mp, 90-92° C.; ¹H NMR (CDCl₃) δ 0.85-0.93 (m, 2H, CH₂), 1.96-1.13 (m, 2H, CH₂), 1.25 (s, 3 H, CH₃), 1.34 (s, 3H, CH₃), 1.45 (t, 3H, CH₃), 1.67-1.74 (m, 1H, CH), 2.18 (dd, J=4, 14 Hz, 1H, CH), 2.32 (dd, J=9, 14 Hz, 1H, CH), 2.38 (s, 1H, CH), 2.38 (s, 1H, CH), 3.94 (d, J=7 Hz, 1H, NCH), 4.07 (s, J=7 Hz, 2H, CH₂), 4.36 (d, J=7 Hz, 1H, NCH), 5.70 (dd, J=4, 9 Hz, 1H, NCH), 6.82-6.99 (m, 4H, Ar), 7.41 (t, J=8 Hz, 1H, Ar), 8.42 (d, J=8 Hz, 1H, Ar), 10.28 (s, 1H, NH), ¹³C NMR (CDCl₃) δ 8.27, 14.78, 16.10, 20.08, 30.22, 41.95, 46.13, 50.96, 55.98, 64.60, 70.02, 111.43, 112.90, 116.71, 117.51, 117.69, 119.72, 132.48, 133.16, 137.99, 141.50, 148.50, 149.12, 169.63, 172.72; Anal. Calcd for C₂₄H₂₅N₃O₄•1.1 H₂O: C, 66.11; H, 7.50; N, 5.93. Found: C, 65.75; H, 6.90; N, 5.82.

5.24 Example 24

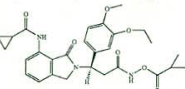
(1R)-Cyclopropanecarboxylic acid [2-[2-(cyclopropanecarboxylonylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide



To a solution of (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (500 mg, 1.1 mmol) in acetonitrile (5 mL) was added cyclopropanecarboxyl chloride (0.15 mL, 1.7 mmol) at room temperature and kept for 24 hrs. The solution was extracted with ethyl acetate (50 mL) and sodium hydrogen carbonate (50 mL, sat). The organic layer was dried over MgSO₄. Filtration and removal of solvent gave (1R)-cyclopropanecarboxylic acid [2-[2-(cyclopropanecarboxylonylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (380 mg, 66% yield); mp, 130-132° C.; ¹H NMR (DMSO-d₆) δ 0.81-1.01 (2 m, 8H, 4CH₂), 1.31 (s, 3H, CH₃), 1.70-1.80 (m, 1H, CH), 2.27-3.69 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.97-4.04 (m, 2H, CH₂), 4.37 (d, J=18 Hz, 1H, NCH), 4.57 (d, J=18 Hz, 1H, NCH), 5.66 (s, J=8 Hz, 1H, NCH), 6.87-6.94 (m, 3H, Ar), 7.18 (d, J=8 Hz, 1H, Ar), 7.49 (d, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.54 (s, 1H, NH), 12.00 (s, 1H, NH), ¹³C NMR (DMSO-d₆) δ 7.77, 8.92, 10.28, 14.69, 15.46, 34.61, 46.60, 51.11, 55.48, 63.80, 111.94, 112.11, 116.61, 117.31, 117.49, 119.27, 131.22, 132.77, 136.96, 142.25, 147.94, 148.57, 166.59, 168.85, 171.72, 172.41; Anal. Calcd for C₂₄H₂₅N₃O₄•0.7 H₂O: C, 62.96; H, 6.11; N, 7.87. Found: C, 62.84; H, 5.89; N, 7.78.

5.25 Example 25

(1R)-Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-isobutylcarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide



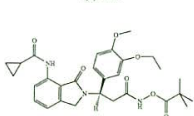
To a solution of (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (500 mg, 1.1 mmol) in acetonitrile (5 mL) was added isobutyl chloride (0.15 mL, 1.4 mmol) at room temperature and kept for 24 hrs. The solution was extracted with ethyl acetate (50 mL) and sodium hydrogen carbonate (50 mL, sat). The organic layer was dried over MgSO₄. Filtration and removal of solvent gave (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-isobutylcarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (380 mg, 66% yield); mp, 130-132° C.; ¹H NMR (DMSO-d₆) δ 0.81-1.01 (2 m, 8H, 4CH₂), 1.31 (s, 3H, CH₃), 1.70-1.80 (m, 1H, CH), 2.27-3.69 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.97-4.04 (m, 2H, CH₂), 4.37 (d, J=18 Hz, 1H, NCH), 4.57 (d, J=18 Hz, 1H, NCH), 5.66 (s, J=8 Hz, 1H, NCH), 6.87-6.94 (m, 3H, Ar), 7.18 (d, J=8 Hz, 1H, Ar), 7.49 (d, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.54 (s, 1H, NH), 12.00 (s, 1H, NH), ¹³C NMR (DMSO-d₆) δ 7.77, 8.92, 10.28, 14.69, 15.46, 34.61, 46.60, 51.11, 55.48, 63.80, 111.94, 112.11, 116.61, 117.31, 117.49, 119.27, 131.22, 132.77, 136.96, 142.25, 147.94, 148.57, 166.59, 168.85, 171.72, 172.41; Anal. Calcd for C₂₄H₂₅N₃O₄•0.7 H₂O: C, 62.96; H, 6.11; N, 7.87. Found: C, 62.84; H, 5.89; N, 7.78.

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ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (380 mg, 66% yield); mp, 107-109° C.; ¹H NMR (DMSO-d₆) δ 0.86-0.89 (m, 4H, 2CH₂), 1.10 (d, J=7 Hz, 6H, 2CH₃), 1.31 (s, J=7 Hz, 3H, CH₃), 1.73-1.81 (m, 1H, CH), 2.62-2.75 (m, 1H, CH), 3.02-3.05 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.96-4.05 (m, 2H, CH₂), 4.19 (d, J=18 Hz, 1H, NCH), 4.59 (d, J=18 Hz, 1H, NCH), 5.67 (s, J=8 Hz, 1H, NCH), 6.86-6.94 (m, 3H, Ar), 7.19 (d, J=8 Hz, 1H, Ar), 7.50 (d, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.54 (s, 1H, NH), 11.86 (s, 1H, NH), ¹³C NMR (DMSO-d₆) δ 7.76, 14.69, 15.46, 18.65, 31.27, 34.64, 46.59, 51.07, 55.47, 63.80, 111.93, 112.09, 116.82, 117.32, 117.50, 119.27, 131.25, 132.77, 136.98, 142.25, 147.95, 148.58, 166.61, 168.86, 171.72, 174.29; Anal. Calcd for C₂₄H₂₅N₃O₄•0.11 H₂O: C, 63.99; H, 6.37; N, 8.00; H₂O, 0.38. Found: C, 63.64; H, 6.37; N, 7.70; H₂O, 0.39.

5.26 Example 26

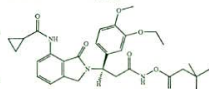
(1R)-Cyclopropanecarboxylic acid [2-[2-(2,2-dimethylpropionylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide



To a solution of (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (180 mg, 0.4 mmol) in acetonitrile (2 mL) was added 2,2-dimethylpropionyl chloride (0.064 mL, 0.5 mmol) at room temperature and kept for 24 hrs. The solution was extracted with ethyl acetate (15 mL) and sodium hydrogen carbonate (15 mL, sat). The organic layer was dried over MgSO₄. Filtration and removal of solvent gave (1R)-cyclopropanecarboxylic acid [2-[2-(2,2-dimethylpropionylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (90 mg, 42% yield); mp, 146-148° C.; ¹H NMR (DMSO-d₆) δ 0.87-0.89 (m, 4H, 2CH₂), 1.19 (s, 3H, CH₃), 1.30 (d, J=7 Hz, 3H, CH₃), 1.76-1.82 (m, 1H, CH), 3.04 (d, J=8 Hz, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.97-4.05 (m, 2H, CH₂), 4.19 (d, J=18 Hz, 1H, NCH), 4.58 (d, J=18 Hz, 1H, NCH), 5.66 (s, J=8 Hz, 1H, NCH), 6.87-6.94 (m, 3H, Ar), 7.19 (d, J=8 Hz, 1H, Ar), 7.50 (d, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.55 (s, 1H, NH), 11.82 (s, 1H, NH), ¹³C NMR (DMSO-d₆) δ 7.77, 14.69, 15.46, 26.71, 34.63, 37.63, 46.61, 51.03, 55.46, 63.78, 111.91, 112.07, 116.82, 117.32, 117.51, 119.24, 131.24, 132.76, 136.96, 142.24, 147.92, 148.55, 166.66, 168.00, 171.71, 175.41; Anal. Calcd for C₂₄H₂₅N₃O₄: C, 64.79; H, 6.50; N, 7.82. Found: C, 64.91; H, 6.50; N, 7.84.

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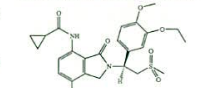
(1R)-Cyclopropanecarboxylic acid [2-[2-(3,3-dimethylbutyrylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide



To a solution of (1R)-cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-hydroxycarbonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (500 mg, 1.1 mmol) in acetonitrile (5 mL) was added 3,3-dimethylbutyryl chloride (0.2 mL, 1.4 mmol) at room temperature and kept for 24 hrs. The solution was extracted with ethyl acetate (50 mL) and sodium hydrogen carbonate (50 mL, sat). The organic layer was dried over MgSO₄. Filtration and removal of solvent gave (1R)-cyclopropanecarboxylic acid [2-[2-(3,3-dimethylbutyrylcarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide (500 mg, 59% yield); mp, 118-120° C.; ¹H NMR (DMSO-d₆) δ 0.87-0.89 (m, 4H, 2CH₂), 0.98 (s, 3H, CH₃), 1.31 (t, J=7 Hz, 3H, CH₃), 1.73-1.80 (m, 1H, CH), 2.27 (s, 3H, CH₃), 3.03-3.06 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 3.97-4.03 (m, 2H, CH₂), 4.18 (d, J=18 Hz, 1H, NCH), 4.59 (d, J=18 Hz, 1H, NCH), 5.67 (s, J=8 Hz, 1H, NCH), 6.86-6.94 (m, 3H, Ar), 7.18 (d, J=8 Hz, 1H, Ar), 7.49 (d, J=8 Hz, 1H, Ar), 8.23 (d, J=8 Hz, 1H, Ar), 10.53 (s, 1H, NH), 11.82 (s, 1H, NH), ¹³C NMR (DMSO-d₆) δ 7.75, 14.70, 15.46, 29.12, 30.53, 34.67, 44.24, 46.62, 51.11, 55.47, 63.80, 111.94, 112.09, 116.78, 117.33, 117.48, 119.25, 131.23, 132.73, 136.98, 142.26, 147.95, 148.56, 166.54, 168.06, 169.34, 171.70; Anal. Calcd for C₂₄H₂₅N₃O₄•0.1 H₂O: C, 65.11; H, 6.78; N, 7.59. Found: C, 64.87; H, 6.87; N, 7.48.

5.28 Example 28

(1S)-Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoxindol-4-yl]-amide



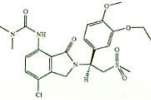
To a solution of 2-bromomethyl-6-(cyclopropanecarboxyl-amin)-3-fluoro-benzoic acid methyl ester (1 g, 3 mmol) and Et₃N (1.25 mL, 9 mmol) in DMF (10 mL) was added (1S)-[1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl]amine (870 mg, 3.2 mmol). The mixture was heated at 90° C. for 20 hrs. The reaction mixture was cooled to room temperature and extracted with water (50 mL) and EtOAc (50 mL). The organic layer was washed with water (50 mL), brine

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(25 ml), dried over Na_2SO_4 and concentrated. The residual oil was purified by chromatography to give (1S)-cyclopropanecarboxylic acid [2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide as a white solid (800 mg, 55% yield); mp. 126–128°C; ^1H NMR (CDCl_3) δ 0.68–0.92 (m, 2H, c-propylCH_2), 1.09–1.12 (m, 2H, c-propylCH_2), 1.47 (t, $J=7.6$ Hz, 3H, OCH_2CH_3), 1.64–1.68 (m, 1H, c-propylCH), 2.58 (s, 3H, CH_3), 3.63–3.73 (m, 1H, CHHSO_2), 3.87 (s, 3H, CH_3), 4.05–4.28 (m, 4H, CHHSO_2 , $\text{CNHCH}_2\text{OCH}_2\text{CH}_3$), 4.49 (d, $J=1.8$ Hz, 1H, CHHN), 6.85–6.92 (m, 1H, NCH), 6.86–6.93 (m, 3H, Ar), 7.04 (t, $J=8$ Hz, 1H, Ar), 8.45–8.55 (m, 1H, Ar), 10.32 (s, 1H, NHCO); ^{13}C NMR (CDCl_3) δ 8.26, 8.27, 14.47, 16.04, 41.50, 44.47, 51.39, 53.39, 55.96, 64.65, 111.63, 112.21, 118.95, 119.26, 119.68, 119.92, 125.43, 126.76, 128.89, 134.48, 134.53, 148.08, 149.88, 150.31, 154.22, 168.89, 172.38. Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_6\text{S}$: C, 58.76; H, 5.55; N, 5.71. Found: C, 58.60; H, 5.33; N, 5.65.

529 Example 29

(1S)-3-[7-Chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-1,1-dimethyl-urea

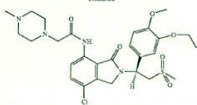


To (1S)-7-amino-4-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-2,3-dihydro-1H-isindol-1-one (800 mg, 1.82 mmol) was added dimethylcarbamyl chloride (3 ml). The mixture was heated at 100°C. for 20 hrs. The reaction mixture was cooled to room temperature and extracted with water (50 ml) and EtOAc (50 ml). The organic layer was washed with water (50 ml), brine (25 ml), dried over Na_2SO_4 and concentrated. The residual oil was purified by chromatography to give (1S)-3-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-1,1-dimethyl-urea as a white solid (800 mg, 70% yield); mp. 205–207°C; ^1H NMR (CDCl_3) δ 1.47 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 3.54 (s, 3H, CH_3), 3.61 (s, 6H, NCH_3), 3.72 (d, $J=5$, 15 Hz, 1H, CHHSO_2), 3.88 (s, 3H, CH_3), 4.05–4.22 (m, 4H, CHHSO_2 , $\text{CNHCH}_2\text{OCH}_2\text{CH}_3$), 4.49 (d, $J=1.5$ Hz, 1H, CHHN), 6.86–6.96 (m, 3H, Ar), 7.36 (d, $J=9$ Hz, 1H, Ar), 8.55 (s, 1H, Ar), 9.77 (s, 1H, NHCO); ^{13}C NMR (CDCl_3) δ 14.68, 36.27, 41.51, 46.96, 51.47, 55.75, 55.97, 64.64, 111.64, 111.67, 112.28, 118.20, 118.54, 119.31, 120.08, 120.13, 133.54, 138.58, 138.77, 148.94, 149.88, 155.01, 169.72. Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_6\text{S}$: C, 54.32; H, 5.65; N, 8.12. Found: C, 54.16; H, 5.42; N, 7.82.

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530 Example 30

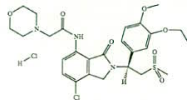
(1S)-N-[7-Chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-(4-methyl-piperazin-1-yl)-acetamide



To a solution of (1S)-2-chloro-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-acetamide (250 mg, 0.48 mmol) in CH_3CN (10 ml) was added 1-methylpiperazine (0.21 ml, 1.9 mmol). The mixture was heated at 70°C. for 2 hrs. The reaction mixture was concentrated on *rotavap* and extracted with water (50 ml) and EtOAc (50 ml). The organic layer was washed with water (50 ml), brine (25 ml), dried over Na_2SO_4 and concentrated. The residual oil was purified by chromatography to give (1S)-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-(4-methyl-piperazin-1-yl)-acetamide as a white solid (70 mg, 25% yield); mp. 205–207°C; ^1H NMR (CDCl_3) δ 1.47 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 2.36 (s, 3H, CH_3), 2.54 (broad, 8H, CH_2 on piperazine ring), 2.99 (s, 3H, NCH_3), 3.21 (d, $J=2$ Hz, 2H, CH_2NCO), 3.73 (d, $J=5$, 15 Hz, 1H, CHHSO_2), 3.88 (s, 3H, CH_3), 4.05–4.20 (m, 4H, CHHSO_2 , $\text{CNHCH}_2\text{OCH}_2\text{CH}_3$), 4.39 (d, $J=1.5$ Hz, 1H, CHHN), 5.74–5.80 (m, 1H, NCH_2), 6.86–6.98 (m, 3H, Ar), 7.40 (d, $J=8$ Hz, 1H, Ar), 8.55 (d, $J=8$ Hz, 1H, Ar), 11.45 (s, 1H, NHCO); ^{13}C NMR (CDCl_3) δ 14.73, 41.15, 46.11, 46.81, 51.57, 52.46, 54.81, 55.76, 55.98, 62.18, 64.62, 111.61, 112.42, 119.46, 119.77, 119.87, 122.32, 129.20, 132.95, 135.98, 139.21, 148.63, 149.87, 168.50, 170.01. Anal. Calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_5\text{O}_6\text{S}$: C, 56.00; H, 6.09; N, 9.67. Found: C, 55.82; H, 5.75; N, 9.42.

531 Example 31

(1S)-N-[7-Chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-morpholin-4-yl-acetamide Hydrochloride



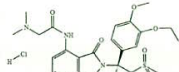
To a solution of (1S)-2-chloro-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-acetamide (250 mg,

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0.48 mmol) in CH_3CN (10 ml) was added morpholine (0.17 ml, 1.94 mmol). The mixture was heated at 70°C. for 2 hrs. The reaction mixture was concentrated on *rotavap* and extracted with water (50 ml) and EtOAc (50 ml). The organic layer was washed with water (50 ml), brine (25 ml), dried over Na_2SO_4 and concentrated. The residual oil was purified by chromatography to give an oil which was stirred with HCl in ether (3 ml) to give (1S)-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-morpholin-4-yl-acetamide hydrochloride as a white solid (200 mg, 60% yield); mp. 198–200°C; ^1H NMR (CDCl_3 , with D_2O added) δ 1.46 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 2.68 (broad, 4H, CH_2NCH_2 on morpholine ring), 2.99 (s, 3H, NCH_3), 3.24 (broad, 2H, CH_2NCO), 3.72 (d, $J=5$, 15 Hz, 1H, CHHSO_2), 3.87–3.92 (m, 3H, $\text{OCH}_2\text{CH}_2\text{OCH}_3$ on morpholine ring), 4.05–4.23 (m, 4H, CHHSO_2 , $\text{CNHCH}_2\text{OCH}_2\text{CH}_3$), 4.49 (d, $J=1.5$ Hz, 1H, CHHN), 5.71–5.77 (m, 1H, NCH_2), 5.86–6.97 (m, 3H, Ar), 7.40 (d, $J=8$ Hz, 1H, Ar), 8.52 (d, $J=8$ Hz, 1H, Ar); ^{13}C NMR (CDCl_3) δ 14.75, 41.71, 47.00, 51.22, 51.59, 55.99, 56.02, 63.81, 64.10, 64.81, 105.68, 111.67, 112.28, 119.32, 120.0, 120.27, 124.03, 128.81, 133.26, 134.72, 139.41, 149.05, 150.01, 168.55. Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{ClN}_3\text{O}_6\text{S}$: C, 51.02; H, 5.61; N, 6.87. Found: C, 50.70; H, 5.38; N, 6.76, 0.98% H_2O .

532 Example 32

(1S)-N-[7-Chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-dimethylamino-acetamide Hydrochloride



To a solution of (1S)-2-chloro-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-acetamide (600 mg, 0.78 mmol) in CH_3CN (10 ml) was added dimethylamine (2N in MeOH, 1.6 ml, 3.2 mmol). The mixture was heated at 70°C. for 2 hrs. The reaction mixture was concentrated on *rotavap* and extracted with water (50 ml) and EtOAc (50 ml). The organic layer was washed with water (50 ml), brine (25 ml), dried over Na_2SO_4 and concentrated. The residual oil was purified by chromatography to give an oil which was stirred with HCl in ether (3 ml) to give (1S)-N-[7-chloro-2-(1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonyl-ethyl)-3-oxo-2,3-dihydro-1H-isindol-4-yl]-2-dimethylamino-acetamide hydrochloride as a white solid (300 mg, 60% yield); mp. 199–200°C; ^1H NMR ($\text{DMSO}-d_6$) δ 1.32 (t, $J=7.5$ Hz, 3H, OCH_2CH_3), 2.87 (s, 6H, NCH_3), 3.04 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.94–4.16 (m, 4H, OCH_2CH_3 , $\text{NCH}_2\text{HCH}_2\text{SO}_2$), 4.36–4.50 (m, 3H, CHHSO_2), CH_2NCO), 4.73 (d, $J=1.8$ Hz, 1H, CHHN), 5.85–5.91 (m, 1H, NCH_2), 6.58 (s, 2H, Ar), 7.05 (s, 1H, Ar), 7.69 (d, $J=8$

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Hz, 1H, Ar), 8.18 (d, $J=8$ Hz, 1H, Ar), 10.21 (bs, 1H, NH), 10.45 (s, 1H, NHCO); ^{13}C NMR ($\text{DMSO}-d_6$) δ 15.17, 23.25, 41.51, 43.86, 46.03, 49.41, 53.88, 56.00, 58.52, 64.41, 112.50, 112.80, 120.25, 121.25, 123.35, 130.22, 133.21, 134.72, 140.60, 148.55, 149.46, 154.53, 167.02, 180.13. Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{ClN}_3\text{O}_6\text{S}$: C, 50.78; H, 5.65; N, 7.40. Found: C, 50.81; H, 5.55; N, 7.18; H_2O , 1.30.

533 Example 33

50 mg Solid Tablets

Tablets, each containing 50 mg of (1R)-Cyclopropanecarboxylic acid [2-(2-carbamoyl-1-(3-ethoxy-4-methoxyphenyl)-ethyl)-7-chloro-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide, can be prepared in the following manner:

Constituents (for 1000 tablets)	
(1R)-Cyclopropanecarboxylic acid [2-(2-carbamoyl-1-(3-ethoxy-4-methoxyphenyl)-ethyl)-7-chloro-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide	50.0 g
lactose	35.0 g
microcrystalline cellulose	7.5 g
polyethylene glycol 6000	5.0 g
silicic acid	3.0 g
magnesium stearate	1.0 g
total	100.0 g

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 ml. of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml. of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

534 Example 34

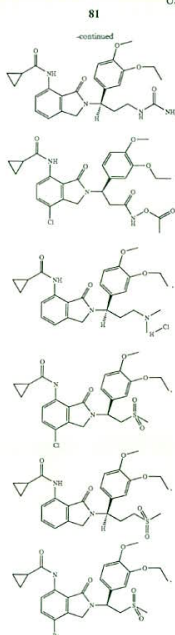
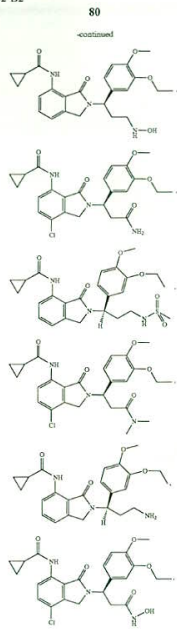
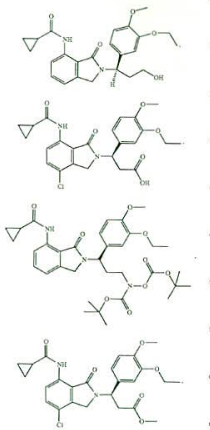
100 mg Solid Tablets

Tablets, each containing 100 mg of (1R)-Cyclopropanecarboxylic acid [2-(2-carbamoyl-1-(3-ethoxy-4-methoxyphenyl)-ethyl)-7-chloro-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide, can be prepared in the following manner:

Constituents (for 1000 tablets)	
(1R)-Cyclopropanecarboxylic acid [2-(2-carbamoyl-1-(3-ethoxy-4-methoxyphenyl)-ethyl)-7-chloro-3-oxo-2,3-dihydro-1H-isindol-4-yl]-amide	100.0 g
lactose	100.0 g
microcrystalline cellulose	47.0 g
magnesium stearate	3.0 g

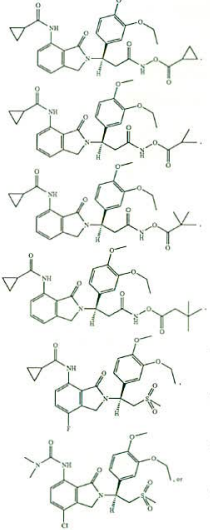
All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 ml. of water and this suspension is added to 100 ml. of boiling water. The

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(1R)-Cyclopropanecarboxylic acid [2-[2-(2,2-dimethyl-
propionyl oxy carbonyl)-1-(3-ethoxy-4-methoxy-phenyl)
ethyl]-3-oxo-2,3-dihydro-1H-indol-4-yl]-
amide,
(1R)-Cyclopropanecarboxylic acid [2-[2-(3,3-dimethyl-
butyryl oxy carbonyl)-1-(3-ethoxy-4-methoxy-phenyl)
ethyl]-3-oxo-2,3-dihydro-1H-indol-4-yl]-
amide,
(1S)-Cyclopropanecarboxylic acid [2-[1-(3-ethoxy-4-
methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-
dihydro-1H-indol-4-yl]-amide,
(1S)-N-[2-[1-(3-ethoxy-4-methoxy-phenyl)-2-
methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-indol-4-yl]-
1,1-dimethyl-urea, or
(1S)-N-[2-[1-(3-ethoxy-4-methoxy-phenyl)-2-
methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-indol-4-yl]-
2-dimethylamino-acetamide hydrochloride
9. A compound of the formula:



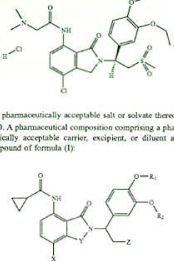
83

-continued-



84

-continued-



13 or a pharmaceutically acceptable salt or solvate thereof.
18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient, or diluent and a compound of formula (I):

wherein:
Y is $-\text{C}(\text{O})-\text{CH}_2-$, $-\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{O})-$ or $-\text{SO}_2-$;
X is H;
Z is $(\text{C}_{1-6}\text{-alkyl})\text{C}(\text{O})\text{R}^1$, $\text{C}_{1-6}\text{-alkyl}$, $(\text{C}_{1-6}\text{-alkyl})\text{OH}$, $(\text{C}_{1-6}\text{-alkyl})\text{O}-\text{C}(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})\text{SO}_2\text{C}_{1-6}\text{-alkyl}$, $(\text{C}_{1-6}\text{-alkyl})\text{SO}_2\text{C}_{1-6}\text{-alkyl}$, $(\text{C}_{1-6}\text{-alkyl})\text{NH}_2$, $(\text{C}_{1-6}\text{-alkyl})\text{N}(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})\text{N}(\text{C}_{1-6}\text{-alkyl})\text{OH}$, or $\text{CH}_2\text{NSO}_2-\text{C}_{1-6}\text{-alkyl}$;
 R^1 and R^2 are independently $\text{C}_{1-6}\text{-alkyl}$, cycloalkyl, or $(\text{C}_{1-6}\text{-alkyl})\text{cycloalkyl}$;
 R^3 is NH^+R^4 , OH , or $\text{O}-\text{C}(\text{C}_{1-6}\text{-alkyl})$;
 R^4 is H;
 R^5 is $-\text{OH}$ or $-\text{O}-\text{C}(\text{O})\text{R}^6$;
 R^6 is $\text{C}_{1-6}\text{-alkyl}$, amino- $(\text{C}_{1-6}\text{-alkyl})$, $(\text{C}_{1-6}\text{-alkyl})\text{C}_{1-6}\text{-alkyl}$, cycloalkyl, $\text{C}_{1-6}\text{-cycloalkyl}$, phenyl, benzyl, or aryl;
or a pharmaceutically acceptable salt or solvate thereof.
11. The compound of claim 1, wherein said solvate is a hydrate.
12. The enantiomerically pure S isomer of claim 6, wherein said solvate is a hydrate.
13. The enantiomerically pure R isomer of claim 7, wherein said solvate is a hydrate.

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- c. Copia de la respuesta presentada por el solicitante en respuesta a la acción oficial junto con las reivindicaciones modificadas junto con la traducción al español.

Electronic Filing

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Frank <i>et al.</i>	Confirmation No.:	9825
Serial No.:	12/901,338	Art Unit:	1626
Filed:	October 8, 2010	Examiner:	Young, Shawquia
For:	PROCESSES FOR THE PREPARATION OF 2-(1-PHENYLETHYL)ISOINDOLIN-1-ONE COMPOUNDS	Attorney Docket No.:	9516-895-999
		(CAM:	501872-999895)

AMENDMENT AND RESPONSE

Mail Stop Amendment
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, VA 22313-1450

Sir:

In response to the non-final Office Action mailed May 9, 2012, please enter the following amendments and remarks into the file of the above-referenced application.

An extension of time for a period of one month, the fee for which will be paid via EFS Web, is respectfully requested herein.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

REMARKS

I. Status of Claims

Claims 1–17 are pending. Claim 1 is amended to delete the terms “solvate” and “polymorph” without prejudice or disclaimer. The definition for certain variables in the formulas recited by claim 1 is also amended solely for the sake of clarity. The support for the amendment can be found, for example, in paragraph [035] on pages 9–10 of the specification as originally filed. Claim 13 is amended to make it depend from claim 12. No new matter is introduced. Applicants respectfully submit that all of the pending claims are allowable for at least the reasons set forth below.

II. The Rejections under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1–17 are rejected under 35 U.S.C. § 103(a) for being allegedly obvious over U.S. Patent No. 7,034,052 by Man *et al.* (“Man”). Specifically, it is alleged in the Office Action that: (i) Man allegedly discloses a general process that a 2-bromomethyl-benzoic ester can be reacted with an appropriate amine to form a 2,3-dihydro-1H-isoindolinone; (ii) Man allegedly discloses a few examples of the said general process using an organic base (*i.e.*, triethylamine); (iii) the process recited by the pending claims allegedly differs from the process disclosed in Man only in that an inorganic base is used in place of the organic base; and (iv) it is allegedly *prima facie* obvious to substitute an inorganic base for an organic base in a process. Office Action, pages 4–6. Applicants respectfully disagree with each of these allegations and submit that the obviousness rejection should be withdrawn for at least the reasons set forth below.

(1) The Office has not established a *prima facie* case of obviousness

The general process for the preparation of 2,3-dihydro-1H-isoindolinones, as described in the reaction scheme in column 32 of Man, does not specify any reaction conditions, much less the requirement of an inorganic base, or any base at all. Nor does the disclosure of the general process contain any teaching that would have led those skilled in the art to believe that an inorganic base is required or preferred for carrying out the reaction. Moreover, Applicants respectfully point out that the substituents on the phenyl ring of the benzoic ester starting material (*i.e.*, X¹–X⁴) are not expressly defined in Man, thus, the difference between the process

recited by the pending claims and the general process disclosed in Man, to the extent any specific chemical compounds are concerned, cannot clearly be ascertained by those skilled in the art. For at least this reason, Applicants respectfully submit that the general process disclosed in Man cannot be used as a basis for the assessment of the obviousness of the pending claims.

Man also purportedly provides a few examples in which 2,3-dihydro-1H-isoindolinones are prepared by reacting corresponding 2-bromomethyl-benzoic esters with an aminosulfone intermediate in the presence of triethylamine. See Man, columns 63–64, Examples 18 and 19. It is alleged in the Office Action that the difference between these examples and the process recited by the pending claims is that the examples use an organic base while the process recited by the pending claims uses an inorganic base. Office Action, page 6. However, even assuming, *arguendo*, that such an allegation were true, Applicants respectfully submit that merely pointing to such a difference alone is insufficient to establish a *prima facie* case of obviousness for the pending claims.

It is well-settled that substitution of one known element for another known element alone is insufficient to establish a *prima facie* case of obviousness. See MPEP § 2143 (stating that “Exemplary rationales that may support a conclusion of obviousness include . . . (B) Simple substitution of one known element for another to obtain predictable results. . . .”) (emphasis added). What is required in the obviousness inquiry, which is precisely the element missing from the analysis provided in the Office Action, is the predictability of the results. Specifically, the Office appears to allege that substitution of an inorganic base for an organic base would yield predictable results because they are both bases and have the same function in the process. Office Action, page 6. However, if such a general assertion were to be held true, it would be equally applicable to any reaction involving a base, regardless of the properties of the reactants and the nature of the reaction. Applicants respectfully submit that it is well-accepted in the art that, absent evidence to the contrary, the results of chemical reactions are generally considered unpredictable.

Specifically, it is well-known in the art that inorganic bases and organic bases are different types of bases, and are often preferred for different types of reactions. In this regard, Applicants respectfully invite the Examiner’s attention to Nishikubo *et al.*, *J. Polym. Sci. A Polym. Chem.*, 1996, 34, 3531–3537 (“Nishikubo”), the abstract of which is attached hereto as

Exhibit A. Nishikubo was published prior to the priority date of this application and would provide insight as to what was known in the art prior to this application. Nishikubo discloses an esterification reaction between poly(methacrylic acid) (PMAA) and certain alkyl halides including substituted or unsubstituted benzyl bromides. Nishikubo, Abstract. The esterification reaction is similar to the process recited by the pending claims in at least two aspects: (i) both processes involve a starting material bearing a benzyl bromide moiety; and (ii) the benzyl bromide is displaced by a nucleophile. Nishikubo further discloses that the esterification reactions were carried out smoothly using organic bases such as DBU, triethylamine, and pyridines. *Id.* However, the degree of esterification was “much lower” when inorganic bases such as sodium carbonate and potassium carbonate were used. *Id.* Thus, Applicants respectfully submit that, in view of what was known at the time of this application, as represented by Nishikubo, those skilled in the art would not have expected that an organic base and an inorganic base can be used interchangeably, with reasonable expectation of success, in a benzyl bromide displacement reaction, if any reaction at all.

Furthermore, Applicants respectfully submit that claims 11–17 are even more nonobvious over Man. This is because, among other things, in addition to the difference in the bases used, the 2-bromomethyl-benzoic ester starting material of the process recited by claims 11–17 bears at its 6-position a nitro group, which is different from the corresponding acylated amino group in Examples 18 and 19 of Man. Applicants respectfully submit that the Office has not pointed to any teaching in Man that would have led those skilled in the art to believe that the process disclosed in Examples 18 and 19 of Man can be applied to a different starting material with reasonable expectation of success. To the contrary, it is well-known in the art that a minor change in the structure of a compound could potentially lead to drastic difference in its chemical reactivities as shown in Man itself. For example, the only difference between the starting materials in Example 18 and Example 19 of Man is the halogen at the 3-position of the 2-bromomethyl-benzoic ester (*i.e.*, Cl in Example 18 and Br in Example 19), but the yields are drastically different (*i.e.*, 30% for Example 18 and 74% for Example 19). In view of this, Applicants respectfully submit that those skilled in the art would not have been able to predict the results of applying the process disclosed in Man to the starting materials recited by claims 11–17.

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For at least the reasons discussed above, Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness for the pending claims, and thus, the rejection under 35 U.S.C. § 103(a) should be withdrawn.

(2) The unexpected results rebut any *prima facie* obviousness

Even assuming, *arguendo*, that those skilled in the art would have somehow been motivated to apply the process described in Man to the starting materials recited by the pending claims, at the same time to replace the organic base with an inorganic base, the unexpected results disclosed in the instant application would rebut any presumption of obviousness that may have been established. For example, Examples 4A and 4B of the specification disclose that the reaction yields are 78% when sodium hydrogen carbonate is used as the base and 93% when potassium carbonate is used, which are much higher than the reaction yields in Examples 18 and 19 of Man (*i.e.*, 30% and 74%, respectively). This result would have been especially surprising and unexpected to those skilled in the art in view of the disclosure in Nishikubo, where use of inorganic bases leads to much lower yields than use of organic bases does for an esterification reaction involving benzyl bromides. Thus, for this additional reason, Applicants respectfully request that the obviousness rejection to the pending claims be withdrawn.

III. The Rejections under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 1–17 are rejected under 35 U.S.C. §112, first paragraph for allegedly not enabled. In particular, it is alleged that the preparation of a solvate or polymorph of a compound of the formula recited by claim 1 is not enabled. Office Action, pages 7–10. Although Applicants respectfully disagree with the substances of this rejection, the terms “solvate” and “polymorph” are deleted from claim 1 solely to expedite the prosecution of this application. In view of this, Applicants respectfully request that the rejection be withdrawn.

IV. Conclusion

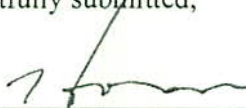
In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Favorable consideration and allowance of the application are respectfully requested.

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No fees, other than the fee required for the extension of time, are believed due for the submission of this paper. If any fees are required, however, the Commissioner is hereby authorized to charge such fees to Jones Day Deposit Account No. 503013 (Ref. 501872-999895).

Respectfully submitted,

Date: September 7, 2012



Hoon Choi Reg. No. 64,214
For: Anthony M. Insogna Reg. No. 35,203

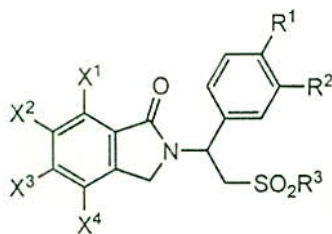
JONES DAY
12265 El Camino Real, Suite 200
San Diego, CA 92130
(858) 314-1200

AMENDMENTS TO THE CLAIMS

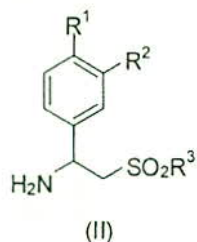
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A process for preparing a compound of formula:

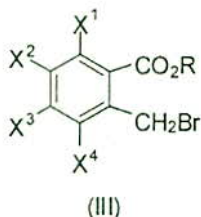


or a pharmaceutically acceptable salt, ~~solvate, or polymorph~~ thereof, comprising the step of reacting a primary amine of formula (II)



or a salt thereof,

with a 2-(bromomethyl)benzoic acid ester of formula (III).



in the presence of an inorganic base, wherein:

R is alkyl or aryl;

each of R¹ and R² is independently hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of 3 to 18 carbon atoms;

R³ is hydroxyl, alkyl of 1 to 8 carbon atoms, ~~phenyl~~ phenyl, benzyl or NR⁴R⁵;

each of X^1 , X^2 , X^3 and X^4 is independently hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxyl, or $-NR^4R^5-NR^{4'}R^{5'}$; or any two of X^1 , X^2 , X^3 and X^4 on adjacent carbon atoms, together with the depicted phenylene ring, form naphthylidene;

each of R^4 and R^5 is independently hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl; or

one of R^4 and R^5 is hydrogen, and the other is $-COR^6$, or $-SO_2R^6$; or

R^4 and R^5 taken together are tetramethylene, pentamethylene, hexamethylene, or

$-CH_2CH_2X^5CH_2CH_2-$ in which X^5 is $-O-$, $-S-$, or $-NH_2-$ $-NH-$;

each of $R^{4'}$ and $R^{5'}$ is independently hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl; or

one of $R^{4'}$ and $R^{5'}$ is hydrogen and the other is $-COR^{6'}$, or $-SO_2R^{6'}$; or

$R^{4'}$ and $R^{5'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or

$-CH_2CH_2X^5CH_2CH_2-$ $-CH_2CH_2X^{5'}CH_2CH_2-$ in which X^5 $X^{5'}$ is $-O-$, $-S-$, or $-NH_2-$ $-NH-$;

and

each of R^6 and $R^{6'}$ is independently hydrogen, alkyl of 1 to 8 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, or phenyl.

2. (Original) The process of claim 1, wherein the inorganic base is a metal hydroxide, a metal carbonate, a metal hydrogen carbonate, a metal hydride, or a combination thereof.

3. (Original) The process of claim 2, wherein the metal hydroxide is potassium hydroxide or sodium hydroxide.

4. (Original) The process of claim 2, wherein the metal carbonate is potassium carbonate or sodium carbonate.

5. (Original) The process of claim 2, wherein the metal hydrogen carbonate is potassium hydrogen carbonate or sodium hydrogen carbonate.

6. (Original) The process of claim 1, wherein the solvent in which the reaction between (II) and (III) occurs is acetonitrile.
7. (Original) The process of claim 6, wherein the reaction temperature is the boiling point of acetonitrile.
8. (Original) The process of claim 1, wherein the mole ratio of Formula (III) to Formula (II) is from about 1:0.8 to about 1:1.3.
9. (Original) The process of claim 1, wherein an enantiomerically pure (S)-isomer of Formula (II) is used.
10. (Original) The process of claim 1, wherein an enantiomerically pure (R)-isomer of Formula (II) is used.
11. (Original) The process of claim 1, wherein X^1 is nitro.
12. (Original) The process of claim 11, further comprising the step of reducing the nitro using a reducing agent to obtain a 7-aminoisoindolin-1-one compound of the following formula (VII):



13. (Currently Amended) The process of claim ~~13~~ 12, wherein the reducing agent is Pd/C and hydrogen.

14. (Original) The process of claim 12, further comprising the step of reacting Formula (VII) with an acyl halide ($R^{6'}\text{-C(O)-halogen}$) to obtain an amide compound of the following formula (VIII):



15. (Original) The process of claim 14, wherein an enantiomerically pure (S)-isomer of Formula (VII) is used.

16. (Original) The process of claim 14, wherein an enantiomerically pure (R)-isomer of Formula (VII) is used.

17. (Original) The process of any one of claims 11, 12 and 14-16, wherein $X^2\text{-}X^4$ are all hydrogen, R^1 is methoxy, R^2 is ethoxy, and R^3 is methyl.

Comentarios

I. Status de las reivindicaciones

Las reivindicaciones 1-17 están pendientes en la solicitud. La reivindicación 1 ha sido modificada para eliminar los términos solvato y polimorfo sin perjuicio.. la definición de ciertas variables en las formulas descritas por la reivindicación 1 también se modifica solamente con fines de claridad.

El sustento para estas modificaciones se puede encontrar, por ejemplo, en el párrafo (035] paginas 9-10 de la descripción tal como fue presentada. La reivindicación 13 ha sido modificada para hacerla dependiente de la reivindicación 12. No se ha incluido nueva materia.

El solicitante respetuosamente establece que las reivindicaciones pendientes son patentables por las siguientes razones:

II. La objeción bajo 35 U.S.C. 103 debe retirarse

Las reivindicaciones 1-17 son objetadas bajo US 35 por ser obvias sobre la solicitud US 7,034,0152 de Man et al ("Man") específicamente, se la acción oficial establece lo siguiente:

Man revela un procesos general en el cual un éster 2-bromometil benzoico se puede hacer reaccionar con una amina apropiada para formar una 2,3-dihidro-1H-isoindolina.; (ii) Man revela pocos ejemplos de dicho procesos general usando una base orgánica (i.e trietilamina); (iii) el proceso descrito por las reivindicaciones pendientes difiere del proceso descrito por Man en que se utiliza una base inorgánica en lugar de una base orgánica, y ((iv) es obvio prima facie sustituir una base inorgánica por una orgánica en un proceso.

El solicitante respetuosamente disiente de estas objeciones y solicita que se retire la objeción por las siguientes razones:

(1) La acción oficial no ha establecido la obviedad prima facie

El proceso general de preparación de 2,3 dihidro-1H-isonindolinonas como se describe en el esquema de reacción en la columna 32 de Man, no especifica ninguna condición de reacción, mucho menos el requerimiento de una base inorgánica o de cualquier base.

Tampoco revela un proceso general que contenga alguna enseñanza que motivara al versado en la materia a creer que base inorgánica se requería o preferiría para llevar a cabo la reacción.

Es más. El solicitante señala que los sustituyentes sobre el anillo del éster benzoico (ie X1-X4) no se definen expresamente en Man. Así, la diferencia entre el proceso de las reivindicaciones pendientes y el proceso general revelado en Man no se puede establecer con claridad por el versado en la materia en lo relacionado con compuestos químicos específicos. Por esta razón, el solicitante considera que el proceso general revelado en Man no puede utilizarse como base para la evaluación de la obviedad de las reivindicaciones pendientes.

Man además proporciona muy pocos ejemplos en los cuales 2,3-dihidro-1H-isoindolinonas se preparen mediante la reacción de esteres 2-bomometilbenzoicos con un intermediario aminosulfona en presencia de trietilamina. Ver Man, columnas 63,64, ejemplos 18 y 19.

La acción oficial establece que la diferencia entre los ejemplos y el proceso de la invención es el uso de una base inorgánica. Sin embargo, aun asumiendo que esto fuera cierto, los solicitantes establecen que solo señalar esta diferencia no es suficiente para concluir la obviedad de la invención.

Se ha establecido claramente que la sustitución de un elemento conocido por otro no es suficiente para establecer la obviedad prima facie. Ver MPEP 2143 (establece que racionales ejemplarizantes pueden sustentar una conclusión de obviedad (B) simple sustitución de un elemento por otro para obtener resultados predecibles).

Lo que se requiere en un análisis de obviedad que es precisamente el elemento ausente según el análisis del oficio, es la predictibilidad de los resultados.

Específicamente, el oficio técnico parece concluir que la sustitución de una base inorgánica por una base orgánica produciría resultados predecibles porque ambas son bases y tienen la misma función dentro del proceso.

Sin embargo, si dicha afirmación fuera cierta, sería igualmente aplicable a cualquier reacción que conlleva una base sin importar las propiedades de los reactivos y la naturaleza de la reacción.

Los solicitantes establecen respetuosamente que en ausencia de evidencia en lo contrario, los resultados de las reacciones químicas son considerados generalmente impredecibles.

Específicamente, es bien conocido en el arte que las bases inorgánicas y orgánicas son diferentes tipos de bases y son a menudo preferidas para diferentes tipos de reacciones. En este sentido, los solicitantes invitan respetuosamente la atención del examinador al artículo Nishikubo et al., J. Polym. Sci. A polym chem, 1996, 34, 3531-3537 (Nishikubo), cuyo resumen adjuntamos como Adjunto A.

Nishikubo fue publicado antes de la fecha de prioridad de la presente solicitud y proporciona una percepción de lo que se conocía en el arte previo de esta solicitud.

Nishikubo revela una reacción de esterificación entre poli (ácido metacrílico) (PMAA) y ciertos haluros de alquilo que incluyen bromuros de bencilo sustituidos y no sustituidos.

La reacción de esterificación es similar al proceso de la invención en al menos dos aspectos:

- i. Ambos procesos involucran **un material de** partida que conlleva una molécula de bromuro de bencilo; y
- ii. El bromuro de bencilo es desplazado por un nucleófilo

Nishikubo revela además que las reacciones de esterificación se llevaron a cabo ligeramente usando bases orgánicas como DBU, trietilamina y piridinas.

Sin embargo, el grado de esterificación era "mucho menor" cuando se utilizaban bases inorgánicas como carbonato de sodio y potasio.

De acuerdo a lo anterior, los solicitantes establecen que un versado en la materia o habría esperado que una base orgánica y una base inorgánica puedan utilizarse de manera intercambiable con una expectativa real de éxito en una reacción de desplazamiento de bromuro de bencilo.

Adicionalmente, los solicitantes establecen que las reivindicaciones 11-17 son no obvias en vista de Man. Esto porque entre otras cosas, adicionalmente a la diferencia en las bases utilizadas, el éster 2-bromometilbenzoico del proceso de las reivindicaciones 11-17 lleva en la posición 6 un grupo nitro, el cual es diferente del correspondiente grupo amino acetilado de los ejemplos 18 y 19 de Man.

Se establece respetuosamente que la acción oficial no ha señalado ninguna enseñanza en Man que motivara a un versado en la materia a creer que los procesos revelados en los ejemplos 18 y 19 pudieran aplicarse a un material de partida diferente con expectativa real de éxito.

Por el contrario, en el arte se conoce muy bien que una cambio menor en la estructura de un compuesto puede llevar a una diferencia drástica en las reactividades química como lo muestra Man.

Por ejemplo, la única diferencia entre los compuestos de partida en el ejemplo 18 y ejemplo 19 de Man es el halógeno en la posición 3 del éster 2-bromometilbenzoico (Cl en el ejemplo 18 y Br en el ejemplo 19), pero los rendimientos son drásticamente diferentes)30 % para el ejemplo 18 y 74 % para el ejemplo 19).

En vista de estos, los solicitantes establecen que los versados en la materia no habrían podido predecir los resultados de aplicar el proceso revelado en Man a los materiales de partida revelados en las reivindicaciones 11-17.

Por las razones arriba discutidas, consideramos que la oficina no ha establecido un caso prima facie de obviedad de las reivindicaciones pendientes y por lo tanto se solicita el retiro de la objeción bajo 35 U.S.C..

(2) Los resultados inesperados refutan cualquier obviedad prima facie.

Aun asumiendo que el versado en la materia estuviera motivado a aplicar el proceso descrito por Man a los materiales de partida de la invención, al reemplazar una base orgánica por una inorgánica, los resultados inesperados revelados en la presente solicitud refutan cualquier conclusión de obviedad que pudiera establecerse.

Por ejemplo, los ejemplos 4A y 4B de la descripción revelan que la reacción dio un rendimiento de 78 % cuando se utilizó carbonato de sodio y 93 % cuando se utilizó carbonato de potasio los cuales son más elevados que los rendimientos alcanzados por Man en los ejemplos 18 y 19 (30 % y 74 %, respectivamente).

Este resultado habría sido especialmente sorprendente e inesperado para el versado en la materia en vista de Nishikubo en donde el uso de bases inorgánicas produjo un rendimiento mucho menor que el uso de bases orgánicas en una reacción de esterificación.

III. Las objeciones bajo 35 U.S.C. primer párrafo deben retirarse

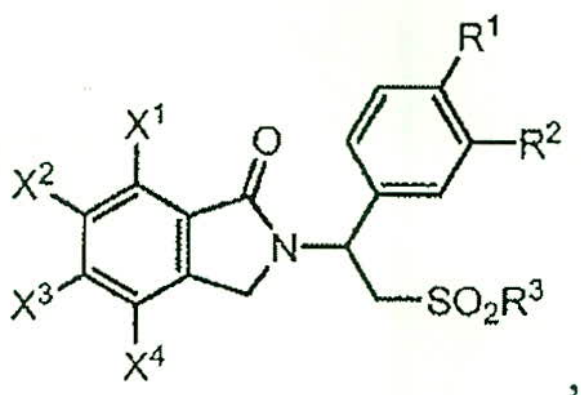
Las reivindicaciones 1-17 son rechazadas ya que la preparación de un solvato o polimorfo de un compuestos no se puede llevar a cabo. Aunque el solicitante no está de acuerdo con esta objeción, los términos solvato y polimorfo han sido eliminados con el ánimo de acelerar el trámite.

IV. Conclusión

En vista de lo anterior, consideramos que la solicitud está en condiciones de ser concedida.

**TRADUCION REIVINDICACIONES PRESENTADAS EN RESPUESTA A LA ACCION
OFICIAL USPTO**

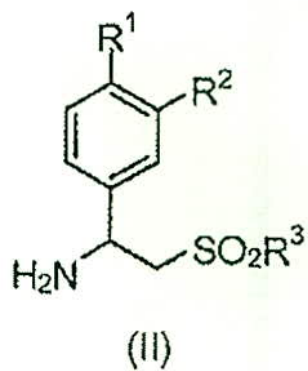
1.- Un procedimiento para preparar un compuesto de fórmula:



o una sal, solvato o polimorfo farmacéuticamente aceptable de los mismos,

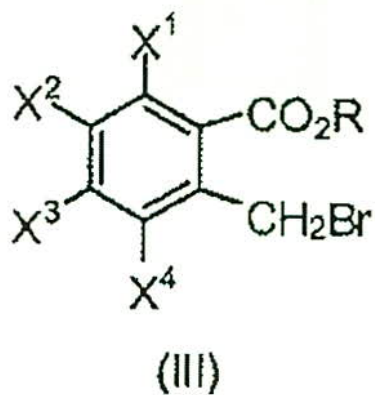
que comprende el paso de hacer reaccionar una amina primaria de fórmula

(II)



o una sal del mismo,

con un éster del ácido 2-(bromometil) benzoico de la Fórmula (III).



en presencia de una base inorgánica, en donde:

R es alquilo o arilo;

cada uno de R^1 y R^2 es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, ciano, o cicloalcoxi de 3 a 18 átomos de carbono;

R^3 es hidroxilo, alquilo de 1 a 8 átomos de carbono, fenilo, bencilo o NR^4R^5 ;

cada uno de X^1 , X^2 , X^3 y X^4 es independientemente hidrógeno, halo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, nitro, ciano, hidroxilo, o - NR^4R^5 , NR^4R^5 o dos cualesquiera de X^1 , X^2 , X^3 y X^4 en átomos de carbono adyacentes, junto con el anillo de fenileno representado, forma naftilidieno;

cada uno de R^4 y R^5 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o

uno de R^4 y R^5 es hidrógeno, y el otro es $-COR^6$, o $-SO_2R^6$; o

R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o

$-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es $-O-$, $-S-$, o $-NH_2$ $-NH-$

cada uno de R^4 y R^5 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o

uno de R^4 y R^5 es hidrógeno y el otro es $-COR^6$, o SO_2R^6 ; o

R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o $-CH_2CH_2X^5CH_2CH_2-$ $-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es $-O-$, $-S-$, o $-NH_2$; $-NH-$ y

cada uno de R^6 y R^6 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o fenilo.

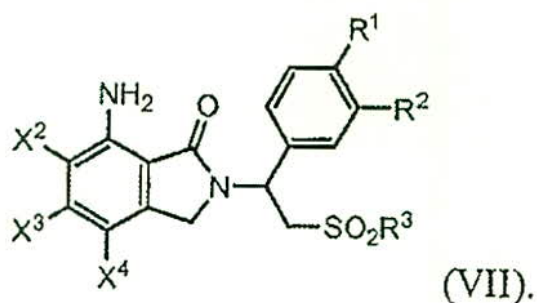
2.- El proceso de la reivindicación 1, donde la base inorgánica es un hidróxido de metal, un carbonato de metal, un carbonato de metal de hidrógeno, un hidruro metálico, o una combinación de los mismos.

3.- El proceso de la reivindicación 2, en el que el hidróxido de metal es el hidróxido de potasio o hidróxido de sodio.

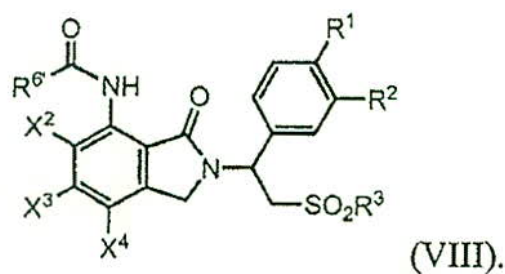
4.- El proceso de la reivindicación 2, en el que el carbonato de metal es el carbonato de potasio o carbonato de sodio.

5.- El proceso de la reivindicación 2, en donde el hidrógeno carbonato de metal es hidrógeno carbonato de potasio o carbonato ácido de sodio.

- 6.- El proceso de la reivindicación 1, caracterizado porque el disolvente en el que la reacción que se produce entre (II) y (III) es acetonitrilo.
- 7.- El proceso de la reivindicación 6, en el que la temperatura de reacción es el punto de ebullición de acetonitrilo.
- 8.- El proceso de la reivindicación 1, en donde la relación molar de Fórmula (III) a la Fórmula (II) es de aproximadamente 1:0.8 a aproximadamente 1:1.3.
- 9.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (II).
- 10.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (II).
- 11.- El proceso de la reivindicación 1, en donde X^1 es nitro.
- 12.- El proceso de la reivindicación 11, que comprende además el paso de reducir a nitro usando un agente reductor para obtener un compuesto 7-aminoisindolin-1-ona de la siguiente Fórmula (VII):



- 13.- El proceso de la reivindicación 12, en donde el agente reductor es Pd/C e hidrógeno.
- 14.- El proceso de la reivindicación 12, que comprende además el paso de hacer reaccionar Fórmula (VII) con un haluro de acilo ($R^6-C(O)-\text{halógeno}$) para obtener un compuesto de amida de la siguiente Fórmula (VIII):



15.- El proceso de la reivindicación 14, en el que se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (VII).

16.- El proceso de la reivindicación 14, en el que se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (VII).

17.- El proceso de cualquiera de las reivindicaciones 11, 12 y 14-16, en donde X^2 - X^4 son todos hidrógeno, R^1 es metoxi, R^2 es etoxi, y R^3 es metilo.

Exhibit A

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Article

Synthesis of polymers in aqueous solutions: Esterification reaction of poly(methacrylic acid) with alkyl halides using DBU in aqueous solutions

1. Tadatomi Nishikubo*,
2. Atsushi Kameyama,
3. Youji Yamada,
4. Yuichi Yoshida

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Issue



Journal of Polymer Science Part A: Polymer Chemistry

Volume 34, Issue 17, pages 3531–3537, December 1996

Additional Information

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Nishikubo, T., Kameyama, A., Yamada, Y. and Yoshida, Y. (1996), Synthesis of polymers in aqueous solutions: Esterification reaction of poly(methacrylic acid) with alkyl halides using DBU in aqueous solutions. *J. Polym. Sci. A Polym. Chem.*, 34: 3531–3537. doi: 10.1002/(SICI)1099-0518(199612)

[http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1099-0518\(199612\)34:17%3C3531::AID...](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1099-0518(199612)34:17%3C3531::AID...) 8/20/2012

34:17<3531::AID-POLA7>3.0.CO;2-X

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Publication History

1. Issue published online: 21 JAN 2000
2. Article first published online: 21 JAN 2000
3. Manuscript Accepted: 22 APR 1996
4. Manuscript Received: 24 NOV 1995

- Abstract
- [References](#)
- [Cited By](#)

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Keywords:

esterification; poly(methacrylic acid); various alkyl halides; DBU; water and aqueous solution

Abstract

A convenient esterification reaction of poly(methacrylic acid) (PMAA) with certain alkyl halides was performed using 1,8-diazabicyclo-[5.4.0]-7-undecene (DBU) as a base in aqueous solution or in water. The esterification reaction of PMAA with propargyl bromide (PB) proceeded very smoothly and quantitatively at 30°C to give corresponding poly(propargyl methacrylate), although the rate of the reaction decreased with increasing water. The reaction of PMAA with benzyl bromide, *o*-nitrobenzyl bromide, and *p*-nitrobenzyl bromide gave corresponding poly(methacrylic ester) using DBU under suitable reaction conditions in water. The esterification reactions of PMAA with PB were carried out using certain organic bases such as triethylamine, 4(*N,N*-dimethylamino)pyridine and pyridine. Inorganic bases such as sodium carbonate, sodium hydroxide, potassium carbonate, and potassium hydroxide were also tried under the same conditions as with DBU. However, the degrees of esterification with all these bases was much lower than that with DBU. © 1996 John Wiley & Sons, Inc.

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- [Youji Yamada](#)
- [Yuichi Yoshida](#)
- [All Authors](#)

- d. Copia de la notificación de concesión (notice of allowability) en donde se establece que las reivindicaciones concedidas son las 1-17

Notice of Allowability	Application No.	Applicant(s)	
	12/901,338	FRANK ET AL.	
	Examiner	Art Unit	
	Shawquia Young	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to an amendment filed on September 7, 2012.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 1-17. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has **THREE MONTHS FROM THE "MAILING DATE"** of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in **ABANDONMENT** of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☒ Notice of References Cited (PTO-892) | 5. ☐ Examiner's Amendment/Comment |
| 2. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date <u>9/7/12</u> | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other ____. |
| 4. ☐ Interview Summary (PTO-413),
Paper No./Mail Date ____. | |

/Shawquia Young/
Primary Examiner, Art Unit 1626

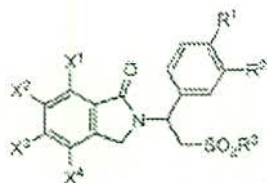
DETAILED ACTION

Applicants have amended claims 1 and 13-16 in the amendment filed on September 7, 2012. The claims 1-17 are considered allowable. The IDS filed on September 7, 2012 has been fully considered.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

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



comprising the step as defined in claim 1 and wherein all variables are defined in claim 1. The closest prior art is Man, et al. (US Patent 7,034,052). The above process is neither taught nor suggested by the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

at

Application/Control Number: 12/901,338
Art Unit: 1626

Page 3

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

Primary Examiner, Art Unit 1626

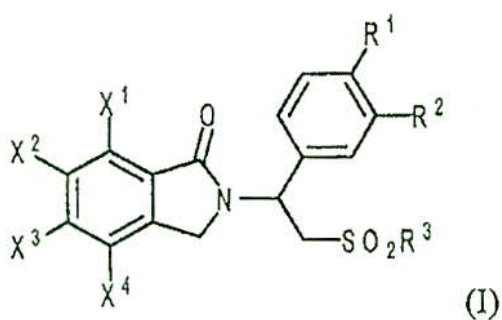
ACCION DETALLADA

Los solicitantes han modificado las reivindicaciones 1 y 13 en la modificación presentada el 7 de septiembre de 2012. Las reivindicaciones 1-17 se concedieran patentables. EL IDS presentado el 7 de septiembre de 2012 ha sido considerado.

Razones para la concesión

Las siguientes son las razones para la concesión:

La invención se refiere a un proceso para la obtención de un compuesto de formula



que comprende la etapa como se define en la reivindicación 1 y en donde todas las variables se definen en la reivindicación 1. El estado de la técnica más cercano es Man, et al (US 7,034,052). El proceso arriba descrito no se revela ni sugiere en el arte previo.

- e. Notificación de aceptación (Notice of allowance) en donde se establece que la solicitud ha sido examinada y aceptada para conceder la patente.



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NOTICE OF ALLOWANCE AND FEE(S) DUE

84802 7590 12/12/2012
JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	PAPER NUMBER

1626
DATE MAILED: 12/12/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/901,338	10/08/2010	Anthony J. Frank	9516-895-999/501872-895	9825

TITLE OF INVENTION: Processes for the Preparation of 2-(1-Phenylethyl)isoindolin-1-one Compounds

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1770	\$300	\$0	\$2070	03/12/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

- I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or
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Complete and send this form, together with applicable fee(s), to: **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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84802 7590 12/12/2012
JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

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(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/901,338	10/08/2010	Anthony J. Frank	9516-895-999/501872-895	9825

TITLE OF INVENTION: Processes for the Preparation of 2-(1-Phenylethyl)isoindolin-1-one Compounds

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1770	\$300	\$0	\$2070	03/12/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
YOUNG, SHAWQUIA	1626	548-415000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 1 _____ 2 _____ 3 _____
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE _____ (B) RESIDENCE: (CITY and STATE OR COUNTRY) _____

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted: ☐ Issue Fee ☐ Publication Fee (No small entity discount permitted) ☐ Advance Order - # of Copies _____	4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above) ☐ A check is enclosed. ☐ Payment by credit card. Form PTO-2038 is attached. ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).
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5. Change in Entity Status (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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Typed or printed name _____	Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/901,338	10/08/2010	Anthony J. Frank	9516-895-999/501872-895	9825
84802	7590	12/12/2012	EXAMINER	
JONES DAY for Celgene Corporation			YOUNG, SHAWQUA	
222 E. 41ST. STREET			ART UNIT	PAPER NUMBER
NEW YORK, NY 10017			1626	

DATE MAILED: 12/12/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 124 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 124 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

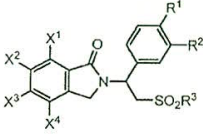
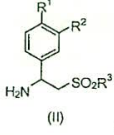
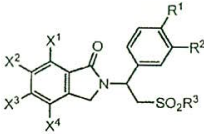
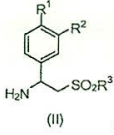
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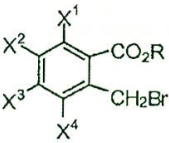
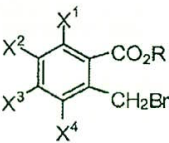
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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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- f. Tabla de correspondencia entre las reivindicaciones concedidas por la USPTO y las reivindicaciones presentadas en Colombia.

TABLA DE CORRESPONDENCIA ENTRE LAS REIVINDICACIONES CONCEDIDAS POR LA USPTO Y LAS REIVINDICACIONES PENDIENTES EN COLOMBIA

Reivindicaciones patentadas Estados Unidos	Reivindicaciones modificadas y pendientes en Colombia	Explicación de la correspondencia
1.- Un procedimiento para preparar un compuesto de fórmula:  o una sal, farmacéuticamente aceptable del mismo. que comprende el paso de hacer reaccionar una amina primaria de fórmula (II)  (II) , o una sal del mismo,	1.- Un procedimiento para preparar un compuesto de fórmula:  o una sal, farmacéuticamente aceptable del mismo. que comprende el paso de hacer reaccionar una amina primaria de fórmula (II)  (II) , o una sal del mismo,	El alcance en ambos casos es idéntico

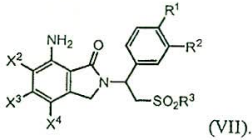
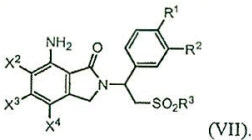
con un éster del ácido 2-(bromometil) benzoico de la Fórmula (III).  (III) en presencia de una base inorgánica, en donde: R es alquilo o arilo; cada uno de R¹ y R² es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, ciano, o cicloalcoxi de 3 a 18 átomos de carbono; R³ es hidroxilo, alquilo de 1 a 8 átomos de carbono, fenilo, bencilo o NR⁴R⁵; cada uno de X¹, X², X³ y X⁴ es independientemente hidrógeno, halo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, nitro, ciano, hidroxilo, o -NR⁴R⁵ o dos cualesquiera de X¹, X², X³ y X⁴ en átomos de carbono adyacentes, junto con el anillo de fenileno representado, forma naftilidieno; cada uno de R⁴ y R⁵ es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o	con un éster del ácido 2-(bromometil) benzoico de la Fórmula (III).  (III) en presencia de una base inorgánica, en donde: R es alquilo o arilo; cada uno de R¹ y R² es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, ciano, o cicloalcoxi de 3 a 18 átomos de carbono; R³ es hidroxilo, alquilo de 1 a 8 átomos de carbono, fenilo, bencilo o NR⁴R⁵; cada uno de X¹, X², X³ y X⁴ es independientemente hidrógeno, halo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, nitro, ciano, hidroxilo, o -NR⁴R⁵ o dos cualesquiera de X¹, X², X³ y X⁴ en átomos de carbono adyacentes, junto con el anillo de fenileno representado, forma naftilidieno; cada uno de R⁴ y R⁵ es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o
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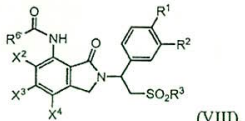
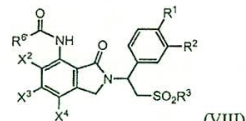
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uno de R^4 y R^5 es hidrógeno, y el otro es $-COR^6$, o $-SO_2R^6$; o R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o $-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es -O-, -S-, o -NH- cada uno de R^4 y R^5 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o uno de R^4 y R^5 es hidrógeno y el otro es $-COR^6$, o SO_2R^6; o R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o $-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es -O-, -S-, o -NH- y cada uno de R^6 y R^6 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o fenilo.	uno de R^4 y R^5 es hidrógeno, y el otro es $-COR^6$, o $-SO_2R^6$; o R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o $-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es -O-, -S-, o -NH- cada uno de R^4 y R^5 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, fenilo, o bencilo; o uno de R^4 y R^5 es hidrógeno y el otro es $-COR^6$, o SO_2R^6; o R^4 y R^5 tomados juntos son tetrametileno, pentametileno, hexametileno, o $-CH_2CH_2X^5CH_2CH_2-$ en el que X^5 es -O-, -S-, o -NH- y cada uno de R^6 y R^6 es independientemente hidrógeno, alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, o fenilo.	
2.- El proceso de la reivindicación 1, donde la base inorgánica es un hidróxido de metal, un carbonato de metal, un carbonato de metal de hidrógeno, un hidruro metálico, o una combinación de los mismos.	2.- El proceso de la reivindicación 1, donde la base inorgánica es un hidróxido de metal, un carbonato de metal, un carbonato de metal de hidrógeno, un hidruro metálico, o una combinación de los mismos.	El alcance en ambos casos es idéntico
3.- El proceso de la reivindicación 2, en el que el hidróxido de metal es el hidróxido de potasio o hidróxido de sodio.	3.- El proceso de la reivindicación 2, en el que el hidróxido de metal es el hidróxido de potasio o hidróxido de sodio.	El alcance en ambos casos es idéntico

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4.- El proceso de la reivindicación 2, en el que el carbonato de metal es el carbonato de potasio o carbonato de sodio.	4.- El proceso de la reivindicación 2, en el que el carbonato de metal es el carbonato de potasio o carbonato de sodio.	El alcance en ambos casos es idéntico
5.- El proceso de la reivindicación 2, en donde el hidrógeno carbonato de metal es hidrógeno carbonato de potasio o carbonato ácido de sodio.	5.- El proceso de la reivindicación 2, en donde el hidrógeno carbonato de metal es hidrógeno carbonato de potasio o carbonato ácido de sodio.	El alcance en ambos casos es idéntico
6.- El proceso de la reivindicación 1, caracterizado porque el disolvente en el que la reacción que se produce entre (II) y (III) es acetonitrilo.	6.- El proceso de la reivindicación 1, caracterizado porque el disolvente en el que la reacción que se produce entre (II) y (III) es acetonitrilo.	El alcance en ambos casos es idéntico
7.- El proceso de la reivindicación 6, en el que la temperatura de reacción es el punto de ebullición de acetonitrilo.	7.- El proceso de la reivindicación 6, en el que la temperatura de reacción es el punto de ebullición de acetonitrilo.	El alcance en ambos casos es idéntico
8.- El proceso de la reivindicación 1, en donde la relación molar de Fórmula (III) a la Fórmula (II) es de aproximadamente 1:0.8 a aproximadamente 1:1.3.	8.- El proceso de la reivindicación 1, en donde la relación molar de Fórmula (III) a la Fórmula (II) es de aproximadamente 1:0.8 a aproximadamente 1:1.3.	El alcance en ambos casos es idéntico
9.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (II).	9.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (II).	El alcance en ambos casos es idéntico
10.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (II).	10.- El proceso de la reivindicación 1, caracterizado porque se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (II).	El alcance en ambos casos es idéntico

11.- El proceso de la reivindicación 1, en donde X ¹ es nitro.	11.- El proceso de la reivindicación 1, en donde X ¹ es nitro.	El alcance en ambos casos es idéntico
12.- El proceso de la reivindicación 11, que comprende además el paso de reducir a nitro usando un agente reductor para obtener un compuesto 7-aminoisindolin-1-ona de la siguiente Fórmula (VII):  (VII).	12.- El proceso de la reivindicación 11, que comprende además el paso de reducir a nitro usando un agente reductor para obtener un compuesto 7-aminoisindolin-1-ona de la siguiente Fórmula (VII):  (VII).	El alcance en ambos casos es idéntico
13.- El proceso de la reivindicación 12, en donde el agente reductor es Pd/C e hidrógeno.	13.- El proceso de la reivindicación 12, en donde el agente reductor es Pd/C e hidrógeno.	El alcance en ambos casos es idéntico
14.- El proceso de la reivindicación 12, que comprende además el paso de hacer reaccionar Fórmula (VII) con un haluro de acilo (R ⁶ -C(O)-halógeno) para obtener un compuesto de amida de la siguiente Fórmula (VIII):	14.- El proceso de la reivindicación 12, que comprende además el paso de hacer reaccionar Fórmula (VII) con un haluro de acilo (R ⁶ -C(O)-halógeno) para obtener un compuesto de amida de la siguiente Fórmula (VIII):	El alcance en ambos casos es idéntico

 (VIII).	 (VIII).	
15.- El proceso de la reivindicación 14, en el que se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (VII).	15.- El proceso de la reivindicación 14, en el que se utiliza un (S)-isómero enantioméricamente puro de la Fórmula (VII).	El alcance en ambos casos es idéntico
16.- El proceso de la reivindicación 14, en el que se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (VII).	16.- El proceso de la reivindicación 14, en el que se utiliza un (R)-isómero enantioméricamente puro de la Fórmula (VII).	El alcance en ambos casos es idéntico
17.- El proceso de cualquiera de las reivindicaciones 11, 12 y 14-16, en donde X ² -X ⁴ son todos hidrógeno, R ¹ es metoxi, R ² es etoxi, y R ³ es metilo.	17.- El proceso de cualquiera de las reivindicaciones 11, 12 y 14-16, en donde X ² -X ⁴ son todos hidrógeno, R ¹ es metoxi, R ² es etoxi, y R ³ es metilo.	El alcance en ambos casos es idéntico