Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-067531- -00000-0000

Fecha: 2008-07-02 15:05:24 Dep: 2020 NUECREACION
Tra: 11 PATENTEYII Eve: 378 FASENACIONAL I
Act: 411 PRESENTACION Folios: 141

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1. SOLICITUD DE:

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capitulo I [ ] Capitulo II

2. SOLICITANTE (71)

Nombre: **1.- ARRAY BIOPHARMA, INC**
2.- ASTRAZENECA AB

Dirección: 1.- 3200 Walnut Street, Boulder, CO. 80301
2.- SE 151 85 Sodertalje, Sweden

Nacionalidad o Domicilio:
1.- Boulder, Colorado 80301, Estados Unidos
2.- SE 151 85 Sodertalje, Sweden

Lugar de Constitución: **1.- DELAWARE, EE.U.**

Teléfono Fax:
E-mail:

IDENTIFICACION

C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número: ____

3. REPRESENTANTE O APODERADO

Nombre: **CARLOS ORLANDO MAYA RODRIGUEZ**
Dirección: **Cr. 13 A No 28-38, Mz 2 Bufete 245. Parque Central Bavaria**

Teléfono **3419841** Fax: **3368592**

E-mail: pct@tmtamayo.net

IDENTIFICACION

C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número: **17.117.818** TP: **17.402**

4. INVENTOR(ES) (72)

Nombres: 1.- SQUIRE, Christopher, John
2.- DEMATTEI, John

Dirección: 1.- ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, cheshire SK10 4TG, Gran Bretaña
2.- 3200 WALNUT STREET, Boulder, CO 80301; EE.UU.

Nacionalidad o Domicilio: 1.- Ciudadano de Gran Bretaña
2.- Ciudadano de EE.UU

OTROS INVENTORES EN HOJA ANEXA

5. PCT (86)

Solicitud internacional No. **PCT/US2006/061895** Fecha: **12/12/2006**

Publicación internacional No. **WO 2007/076245 A3** Fecha: **05/07/2007**

6. Titulo (54)

SAL DE SULFATO DE HIDRÓGENO NOVEDOSA

7. Clasificación Internacional (51) A61K31/4184 // A61P37/00

8. Prioridad

Si [X] No [ ]

(33) País de Origen	(32) Fecha	(31) Número deSolicidud
EE.UU.	Diciembre 21/2005	60/752,781

9. Comprobante de pago No. **08-52453** Fecha **JULIO 02/2008**

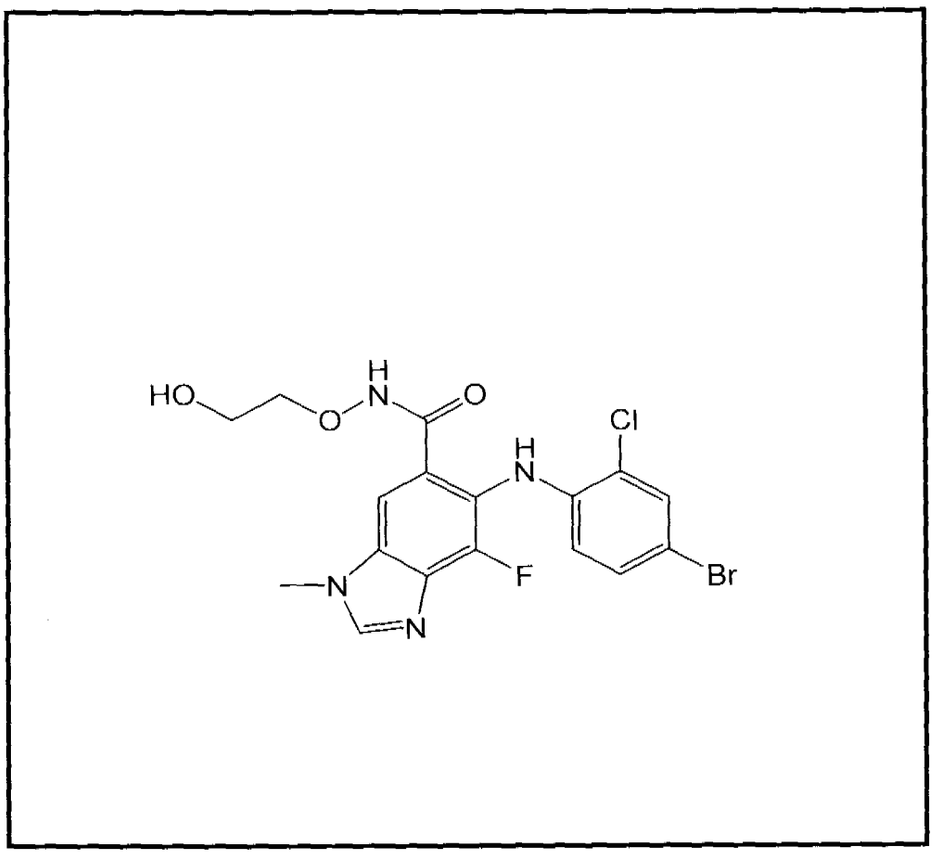
HOJA ANEXA INVENTORES

4.	Nombres:	3 **ROBERTS, Ronald, John** 4 **CHUANG, Tsung-hsun** 5 **SHARMA-SINGH, Gorkhn** 6 **PERVEZ, Mohammed** 7 **FORD, James, Gair** 8 **STOREY, Richard, Anthony** 9 **DICKINSON, Paul, Alfred**
INVENTOR(ES) **(72)**	Dirección:	3 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 4 3200 WALNUT STREET, Boulder, CO 80301; EE.UU. 5 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 6 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 7 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 8 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 9 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña.
	Nacionalidad o Domicilio:	3 Ciudadano de Gran Bretaña; 4 Ciudadano de TAI 5 Ciudadano de Gran Bretaña; 6 Ciudadano de Gran Bretaña; 7 Ciudadano de Gran Bretaña; 8 Ciudadano de Gran Bretaña; 9 Ciudadano de Gran Bretaña;

10. **Anexos**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [ ] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud Internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extrajero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [ ]

11. **FIGURA CARACTERISTICA**



12. Solicito la concesión de la patente,

NOMBRE: **CARLOS ORLANDO MAYA RODRIGUEZ**

FIRMA:

C.C **17.117.818** TP **17.402**

ACTUACION NOTARIAL

N 003948149

LEGALIZACION 040914295263 14/09/2004 10:41:40 $20.00

FOLIO 1.265.- PRIMERA COPIA.- ESCRITURA NUMERO SEISCIENTOS CUARENTA Y DOS.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a diez de septiembre de dos mil cuatro, ante mi, Escribano Autorizante, COMPARECE el Doctor **Daniel GOYTIA**, argentino, mayor de edad, casado, L.E. número 4.526.965, domiciliado en Avenida Leandro N. Alem 449, 3° piso, de esta Ciudad.- El compareciente es persona hábil y de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura de fecha 11 de junio de 2003, pasada al folio 1048 del Protocolo de este mismo Registro, a mi cargo, se protocolizó un **PODER** otorgado por **ARRAY BIOPHARMA, INC.**, domiciliado en 1885 33rd Street, Boulder, Colorado 80301, USA, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para si las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Maya Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Mayerling Rocio Castelblanco S.**, con domicilio en Carrera 13A N° 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en dicho país con las siguientes facultades: "...poder amplio y suficiente para recabar de las autoridades nacionales que corresponda sean estas administrativas y/o judiciales la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES",** y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; de desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir do-

02 JUL. 2008

N 003948149

cumentos y otros valores; justificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 1.265 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 003948149 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

ALEJANDRO M LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

02 JUL. 2008

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION
LEY 404

L 006178443

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº** 040914295263/2 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Martes 14 de Septiembre de 2004

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ESC. LUIS FEDERICO BERUTI
COLEGIO DE ESCRIBANOS
CONSEJERO

02 JUL. 2008

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. PAIS ARGENTINA

El presente documento público

2. Ha sido firmado por Luis F. Benito

3. Quien actúa en calidad de Notario

4. Lleva el sello/timbre de Colegio

Escribanos

5. En BUENOS AIRES 6. El día 14 SEP 2004

7. Por UNIDAD DE COORDINACION LEGALIZACIONES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

8. Sello/Timbre 37576

9. Dr. SEGUNDO ACUÑA
Unidad de Coordinación Legalizaciones
Ministerio de Relaciones Exteriores,
Comercio Internacional y Culto

10. Firma

02 JUL. 2008

N 008663340

FOLIO 2.502.- PRIMERA COPIA.- ESCRITURA NUMERO MIL DOSCIENTOS ONCE.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a veintisiete de noviembre de dos mil siete, ante mí, Escribano Autorizante. COMPARECE don **Daniel GOYTIA**, argentino, mayor de edad, casado, Libreta de Enrolamiento número 4.526.965, domiciliado en Bartolomé Mitre 226, 4° piso, de esta Ciudad.- El compareciente es persona de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura de fecha 26 de junio de 2006, pasada ante mí, al folio 1.070 del Protocolo de este Registro, se protocolizó un **Poder** otorgado por **AstraZeneca AB**, con domicilido en SE-151 85 Södertälje, Sweden, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para sí las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Mava Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Maverling Rocio Castelblanco S.**, con domicilio en Carrera 13A Nº 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en dicho país con las siguientes facultades: "... poder amplio y suficiente para recabar de las autoridades nacionales que corresponda, sean estas administrativas y/o judiciales, la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES"**, y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir documentos y otros valores, jus-

LEGALIZACION 0711290585664 12:05:20 $20.00 29/11/2007

0711290647700 12:05:29 $39.00 29/11/2007

Como Notario Público [illegible] de esta FOTOCOPIA coincide con su original que he tenido a la vista
24 ENE. 2008
Gonzalo Gabriel Zain
NOTARIA DIECIOCHO
BOGOTA, D.C.

N 008663340

tificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue. Este documento tiene validez a partir del 9 de mayo de 2006...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 2.502 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 008663340 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

24 ENE. 2008

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 007941103

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE obrantes en el documento anexo, presentado en el día de la fecha bajo el N° 071129585664/3

La presente legalización no juzga sobre el contenido y forma del documento.

Buenos Aires, Jueves 29 de Noviembre de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ESC. FERNANDO PEÑA ROBIROSA
COLEGIO DE ESCRIBANOS
LEGALIZADOR

24 ENE. 2008

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00148607

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por FERNANDO PEÑA ROBIROSA

3. Quien actúa en calidad de LEGALIZADOR

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 29/11/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: **071129064700**

9. Sello / Timbre

COLEGIO DE ESCRIBANOS · APOSTILLA · CAPITAL FEDERAL - REPUBLICA ARGENTINA

10. Firma

Como Notaria Dieciocho (E) d... Circulo, Pago constar que la ... COPIA coincide con su ... que he tenido a la vista

24 ENE. 2008

Gonzalo Gomez Quintana

NOTARIA DIECIOCHO BOGOTA, D.C.

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. *Country: United States of America*

This public document:

2. *has been signed by Harriet Smith Windsor*

3. *acting in the capacity of Secretary of State of Delaware*

4. *bears the seal/stamp of Office of Secretary of State*

Certified

5. *at Dover, Delaware*

6. *the nineteenth day of November, A.D. 2003*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0213520*

9. *Seal/Stamp:*

10. *Signature:*

Harriet Smith Windsor

Secretary of State

CECBA - LEY404 GCBA
LEGALIZACION
0409142952 65

02 JUL 2008

$20.00

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "ARRAY BIOPHARMA INC.", FILED IN THIS OFFICE ON THE TWENTY-FIRST DAY OF NOVEMBER, A.D. 2000, AT 9 O'CLOCK A.M.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

2856233 8100

030744564

AUTHENTICATION: 2759720

DATE: 11-19-03

02 JUL 2008

ALEJANDRO M. LIPORACE
MATRICULA 3847
ESCRIBANO PUBLICO

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 11/21/2000
001585524 – 2856233

AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF ARRAY BIOPHARMA INC.

Robert Conway hereby certifies that:

ONE: He is the duly elected and acting Chief Executive Officer of Array BioPharma Inc., a Delaware corporation originally incorporated as of February 6, 1998.

TWO: This Amended and Restated Certificate of Incorporation was duly adopted by the Board of Directors of the Corporation in accordance with the provisions of Sections 242 and 245 of the Delaware General Corporation Law and was duly adopted by vote of the stockholders of the Corporation in accordance with the provisions of Sections 228 and 242 of the Delaware General Corporation Law.

THREE: The Certificate of Incorporation of this corporation is hereby amended and restated in its entirety to read as follows:

Article 1. NAME

The name of the corporation is Array BioPharma Inc. (the "**Corporation**").

Article 2. REGISTERED OFFICE AND AGENT

The registered office of the Corporation shall be located at Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801 in the County of New Castle. The registered agent of the Corporation at such address shall be The Corporation Trust Company.

Article 3. PURPOSE AND POWERS

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware (the "**Delaware General Corporation Law**"). The Corporation shall have all power necessary or convenient to the conduct, promotion or attainment of such acts and activities.

Article 4. CAPITAL STOCK

4.1 Authorized Shares. The total number of shares of all classes of stock that the Corporation shall have the authority to issue is 70,000,000, of which 60,000,000 shall be Common Stock, all of one class, having a par value of $.001 per share (the "**Common Stock**"), and 10,000,000 of such shares shall be Preferred Stock, having a par value of $.001 per share (the "**Preferred Stock**").

02 JUL. 2008

ALEJANDRO M. LIPORACE
MATRICULA 3897
ESCRIBANO PUBLICO

4.2 Common Stock.

4.2.1 Relative Rights. The Common Stock shall be subject to all of the rights, privileges, preferences and priorities of the Preferred Stock as set forth in the certificate of designations filed to establish the respective series of Preferred Stock. Each share of Common Stock shall have the same relative rights as and be identical in all respects to all the other shares of Common Stock. The Board of Directors is authorized, subject to the limitations prescribed by the Delaware General Corporation Law and the provisions of this Amended and Restated Certificate of Incorporation, to provide, by resolution or resolutions from time to time for the issuance of shares of Common Stock.

4.2.2 Dividends. Whenever there shall have been paid, or declared and set aside for payment, to the holders of shares of any class of stock having preference over the Common Stock as to the payment of dividends, the full amount of dividends and of sinking fund or retirement payments, if any, to which such holders are respectively entitled in preference to the Common Stock, then dividends may be paid on the Common Stock and on any class or series of stock entitled to participate therewith as to dividends, out of any assets legally available for the payment of dividends thereon, but only when and as declared by the Board of Directors of the Corporation.

4.2.3 Dissolution, Liquidation, Winding Up. In the event of any dissolution, liquidation, or winding up of the Corporation, whether voluntary or involuntary, the holders of the Common Stock, and holders of any class or series of stock entitled to participate therewith, in whole or in part, as to the distribution of assets in such event, shall become entitled to participate in the distribution of any assets of the Corporation remaining after the Corporation shall have paid, or provided for payment of, all debts and liabilities of the Corporation and after the Corporation shall have paid, or set aside for payment, to the holders of any class of stock having preference over the Common Stock in the event of dissolution, liquidation or winding up the full preferential amounts (if any) to which they are entitled.

4.2.4 Voting Rights. Each holder of shares of Common Stock shall be entitled to attend all special and annual meetings of the stockholders of the Corporation and, share for share and without regard to class, together with the holders of all other classes of stock entitled to attend such meetings and to vote (except any class or series of stock having special voting rights), to cast one vote for each outstanding share of Common Stock so held upon any matter or thing (including, without limitation, the election of one or more directors) properly considered and acted upon by the stockholders.

4.3 Preferred Stock. The Board of Directors is authorized, subject to limitations prescribed by the Delaware General Corporation Law and the provisions of this Amended and Restated Certificate of Incorporation, to provide, by resolution or resolutions from time to time and by filing a certificate of designations pursuant to the Delaware General Corporation Law, for the issuance of the shares of Preferred Stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the powers, designations,

02 JUL. 2008

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

preferences and relative, participating, optional or other special rights of the shares of each such series and to fix the qualifications, limitations or restrictions thereof.

4.4 Preemptive Rights. Ownership of shares of any class of the capital stock of the Corporation shall not entitle the holders thereof to any preemptive right to subscribe for or purchase or to have offered to them for subscription or purchase any additional shares of capital stock of any class of the Corporation or any securities convertible into any class of capital stock of the corporation, whether now or hereafter authorized, however acquired, issued or sold by the corporation, it being the purpose and intent hereof that the Board of Directors shall have the full right, power and authority to offer for subscription or sell or to make any disposal of any or all unissued shares of the capital stock of the Corporation or any securities convertible into stock or any or all shares of stock or convertible securities issued and thereafter acquired by the Corporation, for such consideration, in money or property, as the Board of Directors in its sole discretion shall determine.

Article 5. BOARD OF DIRECTORS

5.1 Staggered Board, Number, Election. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended, covering the offer and sale of Common Stock to the public (the "**Initial Public Offering**"), the directors shall be divided into three classes, as nearly equal in number as possible, designated as Class I, Class II and Class III, respectively. Directors shall be assigned to each class in accordance with a resolution or resolutions adopted by the Board of Directors. At the first annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

The number of directors constituting the whole Board or Directors shall not be fewer than three or more than fifteen. The number of directors may be altered from time to time as provided in the Bylaws. Unless and except to the extent that the Bylaws of the Corporation shall otherwise require, the election of directors of the Corporation need not be by written ballot. Except as otherwise provided in this Amended and Restated Certificate of Incorporation, each director of the Corporation shall be entitled to one vote per director on all matters voted or acted upon by the Board of Directors.

02 JUL 2008

ALEJANDRO M. LIPORACE
MATRICULA 3887
ESCRIBANO PUBLICO

5.2 Vacancies. Vacancies and newly created directorships resulting from any increase in the authorized number of directors may be filled by the affirmative vote of a majority of the directors then in office, although fewer than a quorum, or by a sole remaining director. A director shall hold office for the remainder of the term of the class of director to which the vacancy occurred or the new directorship was created Whenever the holders of any class or classes of stock or series thereof are entitled to elect one or more directors by the provisions of this Amended and Restated Certificate of Incorporation, vacancies and newly created directorships of such class or classes or series may be filled by the affirmative vote of a majority of the directors elected by such class or classes or series thereof then in office, or by a sole remaining director so elected. Each director so chosen shall hold office until the next election of directors of the class to which such director was appointed, and until such director's successor is elected and qualified, or until the director's earlier death, resignation or removal. In the event that one or more directors resign from the Board of Directors, effective at a future date, a majority of the directors then in office, including those who have so resigned, shall have power to fill such vacancy or vacancies, the vote thereon to take effect when such resignation or resignations shall become effective, and each director so chosen shall hold office until the next election of directors for such class or series, and until such director's successor is elected and qualified, or until the director's earlier death, resignation or removal.

5.3 Removal of Directors. A director may be removed only for cause and only by an affirmative vote of at least the holders of two-thirds of the outstanding stock entitled to vote thereon.

5.4 Management of Business and Affairs of the Corporation. The business and affairs of the Corporation shall be managed by or under the direction of the Board of Directors.

5.5 Limitation of Liability. No director of the Corporation shall be liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, provided that this provision shall not eliminate or limit the liability of a director (a) for any breach of the director's duty of loyalty to the Corporation or its stockholders; (b) for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law; (c) under Section 174 of the Delaware General Corporation Law; or (d) for any transaction from which the director derived an improper personal benefit. Any repeal or modification of this Section 5.5 shall be prospective only and shall not adversely affect any right or protection of, or any limitation of the liability of, a director of the Corporation existing at, or arising out of facts or incidents occurring prior to, the effective date of such repeal or modification.

Article 6. STOCKHOLDER ACTION

6.1 Action Without a Meeting by Unanimous Written Consent. Any action required or permitted to be taken at a stockholders' meeting may be taken without a meeting only by the unanimous written consent of all stockholders entitled to vote on such matter. The action must be evidenced by one or more written consents describing the action taken, signed by all of

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the stockholders entitled to vote on such action, and delivered to the Corporation in the manner prescribed by the Delaware General Corporation Law for inclusion in the minute book.

6.2 **Special Meetings.** Unless the Delaware General Corporation Law shall provide otherwise, no stockholder or any group thereof shall have the right to call a special meeting of the stockholders.

Article 7. BUSINESS COMBINATIONS WITH INTERESTED STOCKHOLDERS

The Corporation by this provision hereby elects to be governed by Section 203 of the Delaware General Corporation Law.

Article 8. COMPROMISE OR ARRANGEMENTS

Whenever a compromise or arrangement is proposed between the Corporation and its creditors or any class of them and/or between the Corporation and its stockholders or any class of them, any court of equitable jurisdiction within the State of Delaware may, on the application in a summary way of the Corporation or of any creditor or stockholder thereof or on the application of any receiver or receivers appointed for the Corporation under the provisions of Section 291 of Title 8 of the Delaware Code or on the application of trustees in dissolution or of any receiver or receivers appointed for the Corporation under the provisions of Section 279 of Title 8 of the Delaware Code order a meeting of the creditors or class of creditors, and/or of the stockholders or class of stockholders of the Corporation, as the case may be, to be summoned in such manner as the said court directs. If a majority in number representing three-fourths in value of the creditors or class of creditors, and/or of the stockholders or class of stockholders of the Corporation, as the case may be, agree to any compromise or arrangement and to any reorganization of the Corporation as a consequence of such compromise or arrangement, the said compromise or arrangement and the said reorganization shall, if sanctioned by the court to which the said application has been made, be binding on all the creditors or class of creditors, and/or on all the stockholders or class of stockholders, of the Corporation, as the case may be, and also on the Corporation.

Article 9. ACQUISITION PROPOSALS

In determining whether the acquisition proposal is in the long-term best interests of the Corporation and its stockholders, the Board of Directors may consider the effect of both an acquisition proposal and a potential acquisition on creditors, customers and employees of the Corporation and on the community in general, the risks of non-consummation of an acquisition proposal, the identity, prior background and other business experiences of the person or entity making an acquisition proposal, and the business plans of both the Corporation and the person or entity making an acquisition proposal and their respective effects on stockholder interests. The Board of Directors is authorized to take such action as it may determine to be reasonably necessary or desirable to encourage any person or entity to enter into negotiations with the Board of Directors and management of the Corporation respecting any transaction that may result in a change of control and to contest or oppose any such transaction that the Board of Directors

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determines to be unfair, abusive or otherwise undesirable to the Corporation or its stockholders, business, customers, employees or other constituencies.

Article 10. AMENDMENT OF BYLAWS

In furtherance and not in limitation of the powers conferred by the Delaware General Corporation Law, the Board of Directors of the Corporation is expressly authorized and empowered to adopt, amend and repeal the Bylaws of the Corporation by an affirmative vote of at least two-thirds of the directors then in office. The Bylaws of the Corporation may also be adopted, amended or repealed upon the affirmative vote of the holders of at least two-thirds of the outstanding stock entitled to vote thereon, voting together as a single class.

Article 11. RESERVATION OF RIGHT TO AMEND CERTIFICATE OF INCORPORATION

The Corporation reserves the right at any time, and from time to time, to amend, alter, change, or repeal any provision contained in this Amended and Restated Certificate of Incorporation, and other provisions authorized by the laws of the State of Delaware at the time in force may be added or inserted, in the manner now or hereafter prescribed by law; and all rights, preferences, and privileges of any nature conferred upon stockholders, directors, or any other persons by and pursuant to this Amended and Restated Certificate of Incorporation in its present form or as hereafter amended are granted subject to the rights reserved in this Article 11. With respect to action to be taken by the stockholders to amend Sections 4.3 and 4.4, and Articles 5, 6, 7, 9, 10 and 11 of this Amended and Restated Certificate of Incorporation, upon the affirmative vote of the holders of at least two-thirds of the outstanding stock entitled to vote thereon, voting together as a single class.

* * * * * * *

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TRADUCCIÓN.----------

[Página 1].----------

APOSTILLA.----------

(Convención de La Haya del 05 de octubre de 1961).---------

1. País: Estados Unidos de América.----------

El presente documento público----------

2. ha sido firmado por Harriet Smith Windsor----------

3. en su carácter de Secretaria de Estado de Delaware------

4. lleva el sello / la estampilla de la Oficina de la Secretaría de Estado----------

ha sido ***CERTIFICADO***----------

5. en Dover, Delaware----------

6. el diecinueve de noviembre de 2003----------

7. por la Secretaria de Estado, Departamento de Estado de Delaware----------

8. con el Número: *0159991*.----------

9. Sello/estampilla: [Aparece una estampilla dorada que reza:] OFICINA DE LA SECRETARIA DE DELAWARE, 1793-1855.----

10. Firma: [Se observa una firma ilegible debajo de la cual se lee:] Secretaria de Estado.----------

[Página 2].----------

DELAWARE. PRIMER ESTADO.----------

[En el margen superior derecho se lee:] Página 1.----------

Yo, Harriet Smith Windsor, Secretaria de Estado del Estado de Delaware, por la presente certifico que el documento

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adjunto es copia fiel y exacta del Acta Constitutiva Modificada de "Array BioPharma, Inc.", presentada ante esta Oficina el veintiuno de noviembre de 2000, a las 9 horas a.m.----------

[Aparece una estampilla dorada que reza:] OFICINA DE LA SECRETARIA DE DELAWARE, 1793-1855. [A su derecha aparece una firma ilegible debajo de la cual se lee:] Harriet Smith Windsor, Secretaria de Estado.----------

2856233 8100 030744564.----------

Certificación: 2759720. Fecha: 19-11-03.----------

[Página 3].----------

[En el margen superior derecho se lee:] ESTADO DE DELAWARE - SECRETARIA DE ESTADO - SECTOR SOCIEDADES. PRESENTADO: 21/11/2000, 09:00 a.m. 001585524 - 2856233.----------

ACTA CONSTITUTIVA MODIFICADA DE ARRAY BIOPHARMA, INC.------

Robert Conway por la presente certifica que:----------

PRIMERO: Quien declara es Gerente General, debidamente elegido y en ejercicio, de Array BioPharma, Inc., sociedad de Delaware originalmente constituida desde el 06 de febrero de 1998.----------

SEGUNDO: La presente Acta Constitutiva Modificada fue debidamente adoptada por el Directorio de la Sociedad en conformidad con las disposiciones de las Secciones 242 y 245 de la Ley General de Sociedades de Delaware y fue debidamente adoptada por el voto de los accionistas de la

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Sociedad en conformidad con las disposiciones de las Secciones 228 y 242 de la Ley General de Sociedades de Delaware.----------

TERCERO: Por el presente se modifica el Acta Constitutiva de la sociedad, que quedará redactada, en su totalidad, de la siguiente forma:----------

Artículo 1. NOMBRE.----------

El nombre de la sociedad es Array BioPharma, Inc. (en adelante la "**Sociedad**").----------

Artículo 2. DOMICILIO SOCIETARIO CONSTITUIDO Y AGENTE DE REPRESENTACIÓN.----------

El domicilio constituido de la Sociedad es Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801, en el Condado de New Castle. El agente de representación de la Sociedad en dicho domicilio es The Corporation Trust Company.----------

Artículo 3. OBJETO Y FACULTADES.----------

El objeto de la Sociedad es desarrollar todo tipo de actividad o realizar todo tipo de acto lícitos para los cuales pueden constituirse las sociedades según la Ley General de Sociedades del Estado de Delaware (en adelante la "**Ley General de Sociedades de Delaware**"). La Sociedad gozará de todas las facultades necesarias o convenientes para la gestión, promoción o consecución de tales actos y actividades.----------

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Artículo 4. CAPITAL ACCIONARIO.----------

4.1. Acciones Autorizadas. El número total de acciones, incluidas todas las clases, que la Sociedad estará facultada a emitir es de 70.000.000, de las cuales 60.000.000 serán Acciones Ordinarias, todas de una sola clase, con un valor par de $0,001 por acción (en adelante llamadas **"Acciones Ordinarias"**), y 10.000.000 serán Acciones Preferidas, con un valor par de $0,001 por acción (en adelante llamadas **"Acciones Preferidas"**).----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 4].----------

4.2. Acciones Ordinarias.----------

4.2.1. Derechos Relativos.----------

Las Acciones Ordinarias gozarán de todos los derechos, privilegios, preferencias y prioridades de las Acciones Preferidas según se establezca en el certificado de designaciones presentado para determinar las series respectivas de Acciones Preferidas. Cada una de las Acciones Ordinarias tendrá los mismos derechos relativos que y serán iguales, en todos los respectos, a todas las demás Acciones Ordinarias. El Directorio está autorizado, con sujeción a las limitaciones establecidas por la Ley General de Sociedades de Delaware y las disposiciones de la presente Acta Constitutiva Modificada, a disponer, mediante

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resolución, la emisión periódica de Acciones Ordinarias.---

4.2.2. Dividendos.----------

Una vez que se hubiera realizado el pago de dividendos, o se hubieran declarado y reservado para el pago, a los tenedores de acciones de cualquier clase con preferencia sobre las Acciones Ordinarias en cuanto al pago de dividendos, la cantidad total de dividendos y de fondos de amortización o pagos de rescate, si hubiera, a los cuales tales tenedores tienen derecho en preferencia a las Acciones Ordinarias, entonces podrán pagarse los dividendos a las Acciones Ordinarias y a cualquier clase o serie de acciones con derecho a participar en los dividendos, de los activos legalmente disponibles para el pago de dividendos, pero sólo cuando y en la forma que lo declare el Directorio de la Sociedad.----------

4.2.3. Disolución y liquidación.----------

En caso de disolución o liquidación de la Sociedad, sea voluntaria o involuntaria, los tenedores de Acciones Ordinarias, y los tenedores de cualquier clase o serie de acciones con derecho a participar, en todo o en parte, en la distribución de los bienes en tal circunstancia, tendrán derecho a participar en la distribución de los bienes de la Sociedad que quedaran una vez que la Sociedad haya pagado, o dispuesto el pago de, todas las deudas y obligaciones de la Sociedad y una vez que la Sociedad haya pagado, o

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reservado para el pago, a los tenedores de cualquier clase de acciones con preferencia sobre las Acciones Ordinarias en caso de disolución o liquidación, la totalidad del monto preferencial (si correspondiere) al cual dichos tenedores tienen derecho.----------

4.2.4. Derecho de Voto.----------

Cada tenedor de Acciones Ordinarias tendrá derecho a participar de todas las asambleas anuales y especiales de accionistas de la Sociedad y, acción por acción sin distinción de clases, junto con los otros tenedores de todas las demás clases de acciones con derecho a participar de tales asambleas y a votar (excepto las clases o series de acciones con derecho especial de voto), a ofrecer un voto por cada Acción Ordinaria en circulación que posean con relación a cualquier cuestión o tema (incluyendo, aunque no taxativamente- la elección de uno o más miembros del Directorio), que recibiera adecuada consideración y tratamiento por los accionistas.----------

4.3. Acciones Preferidas.----------

El Directorio queda autorizado, con sujeción a las limitaciones establecidas por la Ley General de Sociedades de Delaware y las disposiciones de la presente Acta Constitutiva Modificada, a disponer, por resolución, en forma periódica y mediante la presentación de un certificado de designaciones en virtud de la Ley General de

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Sociedades de Delaware, la emisión de Acciones Preferidas en una o más series, a establecer periódicamente la cantidad de acciones a incluir en cada una de tales series, a establecer las facultades, designaciones, preferencias y derechos relativos, de participación, opcionales y otros que correspondan a cada una de tales series, y a establecer las calificaciones y las limitaciones o restricciones que les corresponderán.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 5].----------

4.4. Derechos de Preferencia.----------

La titularidad de las acciones de cualquier clase de la Sociedad no otorgará a sus tenedores ningún derecho de preferencia para suscribir o comprar ni para que se les ofrezca la suscripción o compra de acciones adicionales de capital de cualquier clase de la Sociedad ni de valores convertibles en cualquier clase de acciones de capital de la Sociedad, que se encontrare actualmente autorizada o se autorizare en el futuro, aunque hubieran sido adquiridas, emitidas o vendidas por la Sociedad, siendo el objeto y la intención de la presente disposición que el Directorio goce de plenos derechos, facultades y autoridad para ofrecer la suscripción o venta o para disponer de cualquier forma de la totalidad o parte de las acciones de la Sociedad no

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emitidas o de cualquier valor convertible en acción o de la totalidad o parte de las acciones de capital o valores convertibles emitidos y luego adquiridos por la Sociedad, a cambio de la contraprestación, monetaria o en especie, que el Directorio, a su sola discreción, determine.----------

Artículo 5. DIRECTORIO.----------

5.1. Directorio Renovable. Número. Elección.----------

Con sujeción a los derechos de los tenedores de cualquier serie de Acciones Preferidas de elegir directores adicionales en circunstancias específicas, con posterioridad al cierre de la oferta pública inicial en virtud de una declaración de registro efectiva en conformidad con la Ley de Valores de 1933, con sus modificaciones, que cubra la oferta y venta de Acciones Ordinarias al público (en adelante llamada la **"Oferta Pública Inicial"**), los directores se dividirán en tres clases, cada una de ellas con igual número de directores o con un número de directores lo más cercano posible entre sí, designados como Clase I, Clase II y Clase III, respectivamente. Los directores serán asignados a cada clase en conformidad con una resolución o resoluciones adoptadas por el Directorio. En la primera asamblea anual de accionistas que sigue al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase I y se elegirán directores de la Clase I que ocuparán el

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cargo por un período de tres años. En la segunda asamblea anual de accionistas posterior al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase II y se elegirán directores de la Clase II que ocuparán su cargo por un período completo de tres años. En la tercera asamblea anual de accionistas siguiente al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase II y se elegirán directores de la Clase III que ocuparán sus cargos por un período completo de tres años. En cada asamblea anual de accionistas subsiguiente, los directores se elegirán por períodos de tres años para suceder a los directores de la clase cuyos mandatos concluyen en tal asamblea anual.------

El número de directores que constituirá el directorio completo no será inferior a tres ni excederá de quince. El número de directores podrá modificarse periódicamente según lo establecido en el Estatuto. A menos que y en la medida que el Estatuto de la Sociedad disponga lo contrario, la elección de los directores de la Sociedad no deberá realizarse necesariamente por votación escrita. Salvo que la presente Acta Constitutiva Modificada establezca lo contrario, cada director de la Sociedad tendrá derecho a un voto por director sobre todas las cuestiones sometidas a votación o acción del Directorio.----------

[En el margen inferior izquierdo aparece una leyenda que

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resulta ilegible].----------

[Página 6].----------

5.2. Vacantes.----------

Las vacantes y los nuevos cargos de director que se generen por un aumento en el número autorizado de directores podrán llenarse por el voto afirmativo de la mayoría de los directores entonces en funciones, aunque inferior el número exigido para lograr quórum, o por el único director en funciones. Un director podrá ocupar el cargo por el período que reste del mandato correspondiente al director de la Clase que generó la vacante o por el período para el cual el nuevo cargo fue creado. Cuando los tenedores de cualquier clase, clases o serie de acciones tengan derecho a elegir uno o más directores según lo establecido en la presente Acta Constitutiva Modificada, las vacantes y los nuevos cargos de director que se creen para tal clase, clases o series podrán llenarse por el voto afirmativo de la mayoría de los directores elegidos por tal clase, clases o series, entonces en funciones, o por el único director entonces en funciones que así hubiere sido elegido. Cada director así elegido ocupará el cargo hasta la próxima elección de directores de la clase a la cual tal director fue designado, y hasta que el sucesor de tal director haya sido elegido y habilitado, o hasta la remoción, renuncia o muerte temprana del director. En caso de que uno o más

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directores renuncien al Directorio, con efectos a partir de fecha futura, la mayoría de los directores entonces en funciones, incluyendo aquellos que han renunciado, tendrán derecho a llenar tal vacante o vacantes, la votación que se realice tendrá efectos la renuncia o las renuncias se hagan efectivas, y cada director así elegido ocupará el cargo hasta la siguiente elección de directores de dicha clase o serie, y hasta que el sucesor del director hayas sido elegido y habilitado, o hasta la remoción, renuncia o muerte temprana del director.----------

5.3. Remoción de los Directores.----------

Un director podrá ser removido únicamente con causa y por el voto afirmativo de por lo menos dos tercios de los tenedores de acciones en circulación con derecho a voto sobre el tema.----------

5.4. Gestión de los Negocios y Asuntos de la Sociedad.-----

Los negocios y otros asuntos de la Sociedad serán administrados por y bajo la dirección del Directorio.------

5.5. Límites a la Responsabilidad.----------

Ningún director de la Sociedad será responsable ante la Sociedad ni sus accionistas por daños monetarios originados por incumplimiento del deber fiduciario como director, entendiéndose que esta disposición no desconoce la responsabilidad de un director (a) por incumplimiento del deber de lealtad del director a la Sociedad y a sus

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accionistas; (b) por actos u omisiones de mala fe o que involucren un comportamiento ilícito intencional o la violación de una ley, con conocimiento de ello; (c) en virtud de la Sección 174 de la Ley General de Sociedades de Delaware; o (d) por cualquier transacción de la cual el director haya derivado un beneficio personal irregular. Toda revocación o modificación de esta Sección 5.5. será sólo eventual y no afectará negativamente los derechos ni la protección de, ni los límites a la responsabilidad de, un director de la Sociedad existentes, o emergentes de los hechos o incidentes que ocurran con anterioridad, a la fecha efectiva de tal revocación o modificación.----------

Artículo 6. ACCIONAR DE LOS ACCIONISTAS.----------

6.1. Accionar sin Asamblea y por Consentimiento Escrito Unánime.----------

Cualquier acción cuya realización sea requerida o permitida a los accionistas en asamblea podrá realizarse sin necesidad de celebrar una asamblea únicamente si mediare el consentimiento escrito unánime de todos los accionistas con derecho a voto sobre el tema en cuestión. La acción deberá evidenciarse en uno o más consentimientos por escrito que describa la acción a seguir, firmado por todos los accionistas con derecho a voto sobre tal acción, y entregado a la Sociedad en la forma establecida por la Ley General de Sociedades de Delaware para su inclusión en el

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libro de minutas.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 7].----------

6.2. Asambleas Especiales.----------

A menos que la Ley General de Sociedades de Delaware establezca lo contrario, ningún accionista ni grupo de ellos podrá convocar a una asamblea especial de accionistas.----------

Artículo 7. ASOCIACIÓN DE NEGOCIOS CON ACCIONISTAS INTERESADOS.----------

La Sociedad se somete a las disposiciones de la Sección 203 de la Ley General de Sociedades de Delaware.----------

Artículo 8. ACUERDOS Y TRANSACCIONES.----------

Cuando se proponga un acuerdo o transacción entre la Sociedad y sus acreedores o cualquier clase de ellos y/o entre la Sociedad y sus accionistas o cualquier clase de ellos, cualquier tribunal del régimen de Equity[1] dentro del Estado de Delaware podrá, a pedido en forma sumaria de la Sociedad o de cualquier acreedor o accionista de ella, o a pedido de cualquier administrador o administradores designados por la Sociedad en conformidad con lo dispuesto en la Sección 291 del Título 8 del Código de Delaware, o a

[1] NT: Sistema de derecho o rama de la justicia reparadora administrado por tribunales distintos de los que aplican las normas del sistema del Common Law y que están facultados para decretar "equidad" en el sentido de justicia equitativa o imparcial.

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pedido de los liquidadores en caso de disolución o de cualquier administrador o administradores designados por la Sociedad en virtud de lo dispuesto en la Sección 279 del Título 8 del Código de Delaware, ordenar una reunión de los acreedores o clase de acreedores, y/o de los accionistas o clase de accionistas de la Sociedades, según fuera el caso, que se convocará en la forma en que el tribunal disponga. Si una mayoría en número que represente tres cuartos en el valor de los acreedores o clase de acreedores, y/o de los accionistas o clase de accionistas de la Sociedad, según fuere el caso, acuerdan celebrar un acuerdo o transacción y acuerdan la reorganización de la Sociedad como consecuencia de tal acuerdo o transacción, dicho acuerdo a transacción y la reorganización resultante, si fuera sancionada por el tribunal a quien se elevó la solicitud, será vinculante para todos los acreedores o clase de acreedores, y/o para todos los accionistas o clase de accionistas, de la Sociedad, según fuera el caso, como así también para la Sociedad.----------

Artículo 9. PROPUESTAS DE ADQUISICIÓN.----------

A fin de determinar si la propuesta de adquisición será a largo plazo beneficiosa para la Sociedad y sus accionistas, el Directorio deberá considerar los efectos que tendrían tanto una propuesta de adquisición como una potencial propuesta de adquisición sobre los acreedores, clientes, y

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empelados de la Sociedades y sobre la comunidad en general, los riesgos de la no consumación de una propuesta de adquisición, la identidad, los antecedentes y otras experiencias comerciales de la persona o entidad que realiza la propuesta de adquisición, y los planes comerciales tanto de la Sociedad como de la persona o entidad que formula la propuesta de adquisición y sus respectivos efectos sobre los intereses de los accionistas. El Directorio está autorizado para realizar todas las acciones que considere razonablemente necesarias o deseables para alentar a que cualquier persona o entidad entre en negociaciones con el Directorio y la administración de la Sociedad con relación a cualquier transacción que pudiera resultar en un cambio en el control y para impugnar u oponerse a las transacciones que el Directorio considere injustas, abusivas o no deseables para la Sociedad y sus accionistas, negocios, clientes, empleados u otros involucrados.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 8].----------

Artículo 10. MODIFICACIÓN DEL ESTATUTO.----------

A fin de ampliar sin limitar las facultades conferidas por la Ley General de Sociedades de Delaware, el Directorio queda expresamente autorizado y facultado para adoptar,

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modificar y revocar el Estatuto de la Sociedad con el voto afirmativo de por lo menos dos tercios de los directores entonces en funciones. El Estatuto de la Sociedad podrá también adoptarse, modificarse o revocarse con el voto afirmativo de los tenedores de por lo menos dos tercios de las acciones en circulación con derecho a voto sobre la cuestión, en votación conjunta como clase única.----------

Artículo 11. RESERVA DEL DERECHO A MODIFICAR EL ACTA CONSTITUTIVA.----------

La Sociedad se reserva el derecho de, en cualquier, y periódicamente, modificar, enmendar, cambiar o revocar cualquier disposición contendida en la presente Acta Constitutiva Modificada; asimismo, otras disposiciones autorizadas por las leyes del Estado de Delaware actualmente vigentes podrán agregarse o incorporarse en la forma dispuesta por ley en el presente o en el futuro; y todos los derechos, preferencias y privilegios de cualquier naturaleza conferidos a los accionistas, directores, o cualquier otra persona por y en conformidad con la presente Acta Constitutiva Modificada en su forma actual o en la forma que resulte de modificaciones futuras, se otorgan con sujeción a los derechos reservados en este Artículo 11. Con respecto a la acción que deberán realizar los accionistas para modificar las Secciones 4.3 y 4.4, y los Artículos 5, 6, 7, 9, 10, y 11 de la presente Acta Constitutiva

02 JUL. 2008

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

Modificada, la misma podrá realizarse con el voto afirmativo de los tenedores de por lo menos dos tercios de las acciones e circulación con derecho a voto sobre el tema en cuestión, actuando conjuntamente como una sola clase.---

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 9].----------

EN PRUEBA DE CONFORMIDAD, Array BioPharma, Inc. Celebra la presente Acta Constitutiva Modificada a través de su Gerente General, quien en este acto declara que los hechos aquí anteriormente descriptos has sido establecidos con exactitud, a los 21 días del mes de noviembre del año 2000.

Array BioPharma, Inc.----------

A través de: [Aparece una firma ilegible debajo de la cual se lee:] Robert Conway, Gerente General.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[En el margen inferior, en el centro, se lee:] Página de Firma.----------

Es traducción fiel al idioma español del documento original redactado en idioma inglés, que he tenido a la vista y adjunto a la presente, en la Ciudad de Buenos Aires, a los seis días del mes de diciembre del año dos mil tres.-------

---

02 JUL. 2008

SILVIA P. PLANKENHORN
TRADUCTORA PUBLICA
INGLES
MAT. T XIII - F 459 - CAP. FED.
INSCRIP. C.T.P.C.B.A. Nº 4854

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

CERTIFICACION DE REPRODUCCIONES
LEY 404

T 002409825

Buenos Aires, 9 de diciembre de 2003.-

En mi carácter de Escribano Titular del Registro 1331 de Capital Federal.-

CERTIFICO que la reproducción anexa, extendida en Veintiseis.-

foja/s, que sello y firmo, es COPIA FIEL de su original, que tengo a la vista, doy fe.

El Autorizante deja constancia que el documento cuyas fotocopias se certifican se encuentra redactado en idioma extranjero con su correspondiente traducción al español y consiste en un **ACTA CONSTITUTIVA MODIFICADA DE ARRAY BIOPHARMA, INC.-**

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

RO M. LIPORACE
TRICULA 3837
ANO PUBLICO

02 JUL. 2009

37

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 006178202

ESCRIBANOS de la Ciudad de BUENOS AIRES

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº** 040914295265/2 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Martes 14 de Septiembre de 2004

ESC. LUIS FEDERICO BERUTI
COLEGIO DE ESCRIBANOS
CONSEJERO

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

02 JUL. 2008

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. PAIS ARGENTINA

El presente documento público

2. Ha sido firmado por Luis F Benedi

3. Quien actúa en calidad de [illegible]

4. LLeva el sello/timbre de Colegio [illegible]

5. En BUENOS AIRES 6. El día 14 SEP 2004

7. Por UNIDAD DE COORDINACION LEGALIZACIONES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

8. bajo el No. 175510

9. Sello y Firma

Dr. SEGUNDO ACUÑA
Unidad de Coordinación Legalizaciones
Ministerio de Relaciones Exteriores,
Comercio Internacional y Culto

10. Firma

02 JUL 2008

BE IT KNOWN that I, ADRIAN PETER MARK WATNEY of 33 Queen Street, Maidenhead, Berkshire SL6 1NB, United Kingdom, a duly authorised Notary Public

CERTIFY ONLY that Blair Consular Services Limited on behalf of their client

ASTRAZENECA AB

have this day presented to me the hereto annexed document

COPY ARTICLES OF ASSOCIATION

and that the said Blair Consular Services Limited have represented to me by such presentation that their said client has represented to them that the said annexed document is a true copy of the corresponding original document.

SIGNED AND SEALED at 33 Queen Street, Maidenhead, Berkshire SL6 1NB, United Kingdom, on 20th February 2008.

Adrian Peter Mark Watney
Notary Public

02 JUL. 2008

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **Adrian Peter Mark Watney**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres

   Certified/Attesté
6. the/le **22 February 2008**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H688744**

9. Stamp: / timbre:

10. Signature: **R Shilton**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

02 JUL. 2008

Approved 19 December 2005

ARTICLES OF ASSOCIATION

§ 1 The Company's name is AstraZeneca AB. The Company is a public company (publ).

§ 2 The object of the Company shall be to engage in the manufacture of, and trade in, products for health care and medical care; to conduct financial activities; to own and manage real and personal property, including stocks and interests in other companies; and to conduct other activities which are compatible with the above-mentioned business activities.

§ 3 The Company's registered office shall be situated in Södertälje, Sweden.

§ 4 The share capital shall be not less than seven hundred and fifty million kronor (SEK 750,000,000) and not more than three billion kronor (SEK 3,000,000,000).

§ 5 The number of shares shall be no less than 600,000,000 and no more than 2,400,000,000.

§ 6 The Board of Directors shall consist of no less than three members and no more than twelve members and no more than three alternate members.

§ 7 Two auditors and two deputy auditors or one or two certified accounting firms shall be appointed by the meeting of shareholders.

§ 8 General meetings of the shareholders shall be held in Södertälje, Stockholm, Gothenburg, Mölndal, Malmö or Lund on or before June 30.

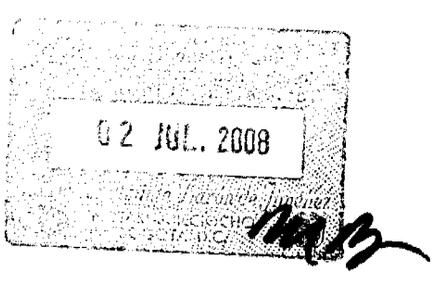
The following business shall be addressed at the annual meeting:

1) election of a chairman for the meeting;

2) preparation and attestation of voting register;
3) approval of agenda;
4) election of one or two persons who shall attest the minutes of the meeting;
5) determination of whether the meeting was duly convened;
6) submission of the annual report and report of the auditors and the consolidated annual report and report of the auditors for the group;
7) resolution regarding:
    a. adoption of the profit and loss accounts and balance sheet and the consolidated profit and loss accounts and consolidated balance sheet;
    b. allocation of the Company's profits or losses according to the adopted balance sheet;
    c. release of the members of the Board of Directors and the managing director from liability;
8) determination of the number of members of the Board of Directors and alternate members;
9) determination of fees for the Board of Directors and the auditors;
10) election of members of the Board of Directors and alternate members;
11) where applicable, election of auditors and alternate auditors;
12) resolutions regarding other matters which are prescribed in the Companies Act or the Company's Articles of Association.

§ 9 Notice to shareholders of general meetings of the shareholders shall be given either by letter posted in the public postal service or by publication in Post- och Inrikes Tidningar and Dagens Nyheter.

§ 10 The financial year of the Company shall be the calendar year.



TRADUCCIÓN PÚBLICA----------

[Página 1]----------

Sépase que, yo Adrian Peter Mark Watney de 33 Queen Street, Maidenhead, Berkshire SL6 1NB, Reino Unido, un Notario Público debidamente autorizado.----------

CERTIFICO SOLAMENTE que Blair Consular Services Limited a nombre de su cliente ASTRAZENECA AB han presentado este día el documento al presente adjunto COPIA DE LOS ARTÍCULOS DE ASOCIACIÓN y que dicha Blair Consular Services Limited me ha representado mediante dicha presentación que su cliente les ha representado que dicho documento adjunto es una copia fiel del correspondiente documento original.----------

FIRMADO Y SELLADO en 33 Queen Street, Maidenhead, Berkshire SL6 1NB, Reino Unido, a los 20 días del mes de Febrero 2008.---------

[Aparece una firma ilegible] Adrian Peter Mark Watney. Notario Público. ----------

[Aparece una estampilla parcialmente legible. En su parte legible reza:] Notario Público.----------

[Aparece un sello de puntos parcialmente ilegible, en su parte legible reza: Oficina del Commonwealth.----------

[Reverso de la Página 1]----------

APOSTILLA----------

02 JUL. 2008

[Aparece una Apostilla redactada en inglés y otro idioma, en su parte en inglés reza:]----------

Convención de la Haya del 5 de octubre de 1961----------

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE----------

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte-----

El presente documento público ----------

2. ha sido firmado por **Adrian Peter Mark Watney** ----------

3. actuando en carácter de Notario Público ---------- -----

4. lleva el sello/ timbre de Dicho Notario Público----------

CERTIFICADO ----------

5. en Londres ----------

6. a los 22 días del mes de febrero de 2008 ----------

7. por el Secretario Principal de su Majestad del Estado para Asuntos Externos y Commonwealth----------

8. No. H688744 ----------

9. Sello/ Timbre: Oficina de Commonwealth y Exterior. Londres---

10. Firma: [Aparece una firma ilegible debajo de la cual se lee:] Por el Secretario de Estado. ----------

Si el presente documento se utiliza en un país que no es parte de la Convención de la Haya del 5 de octubre de 1961, debe presentarse en la sección consular de la misión que representa aquel país. Una apostilla o certificado de legalización solamente confirma que la firma, sello y estampilla en el documento son

02 JUL. 2008

ALCIJA TRA... AZCÁRATE PUBLICA... Cap. Fed. ... Nº 0573

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-067531- -00000-0000

Fecha: 2008-07-02 15:05:24 Dep: 2020 NUEVA CREACION
Tra: 11 PATENTE(YII Eve: 378 FASE NACIONAL I
Act: 411 PRESENTACION Folios: 141

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1. SOLICITUD DE:

[X] Patente de Invención [ ] Patente de Modelo de Utilidad

[X] Capitulo I [ ] Capitulo II

2. SOLICITANTE (71)

Nombre: **1.- ARRAY BIOPHARMA, INC**
2.- ASTRAZENECA AB
Dirección: 1.- 3200 Walnut Street, Boulder, CO. 80301
2.- SE 151 85 Sodertalje, Sweden
Nacionalidad o Domicilio:
1.- Boulder, Colorado 80301, Estados Unidos
2.- SE 151 85 Sodertalje, Sweden
Lugar de Constitución: **1.- DELAWARE, EE.U.**

Teléfono Fax:
E-mail:

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número: ____

3. REPRESENTANTE O APODERADO

Nombre: **CARLOS ORLANDO MAYA RODRIGUEZ**
Dirección: **Cr. 13 A No 28-38, Mz 2 Bufete 245. Parque Central Bavaria**
Teléfono **3419841** Fax: **3368592**
E-mail: pct@tmtamayo.net

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número: **17.117.818** TP: **17.402**

4. INVENTOR(ES) (72)

Nombres: 1.- SQUIRE, Christopher, John
2.- DEMATTEI, John
Dirección: 1.- ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, cheshire SK10 4TG, Gran Bretaña
2.- 3200 WALNUT STREET, Boulder, CO 80301; EE.UU.
Nacionalidad o Domicilio: 1.- Ciudadano de Gran Bretaña
2.- Ciudadano de EE.UU
OTROS INVENTORES EN HOJA ANEXA

5. PCT (86)
Solicitud internacional No. **PCT/US2006/061895** Fecha: **12/12/2006**
Publicación internacional No. **WO 2007/076245 A3** Fecha: **05/07/2007**

6. Título (54)
SAL DE SULFATO DE HIDRÓGENO NOVEDOSA

7. Clasificación Internacional (51) A61K31/4184 // A61P37/00

8. Prioridad Si [X] No [ ]

(33) País de Origen	(32) Fecha	(31) Número deSolicidud
EE.UU.	Diciembre 21/2005	60/752,781

9. Comprobante de pago No. **08-52453** Fecha **JULIO 02/2008**

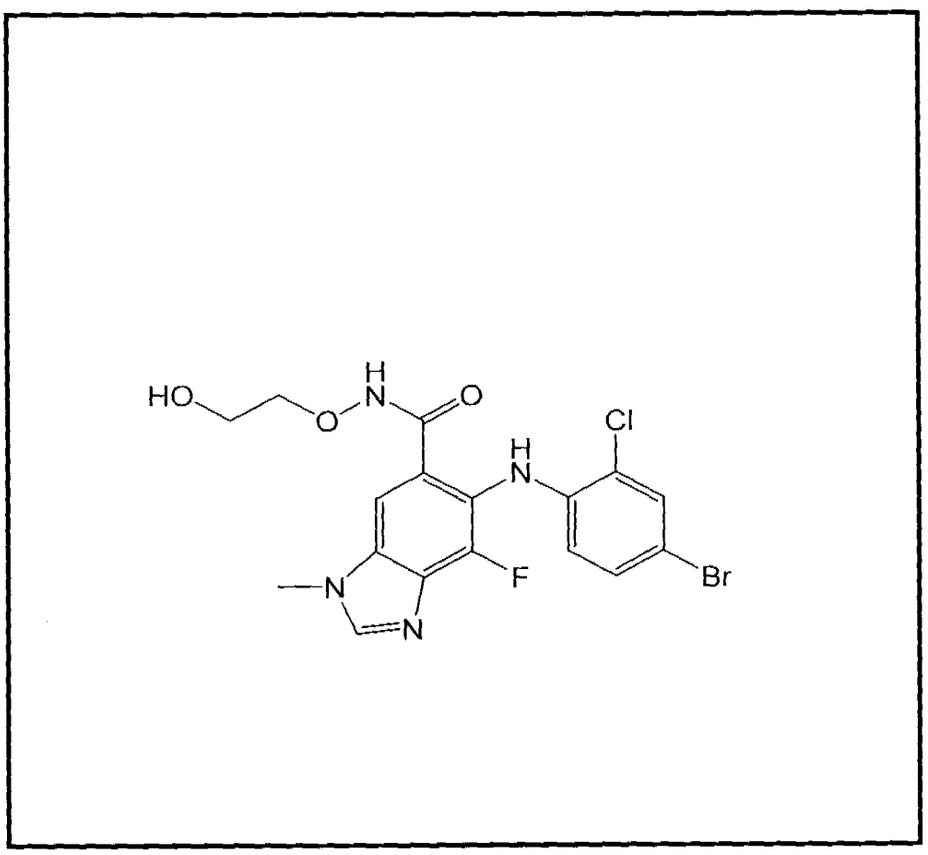
HOJA ANEXA INVENTORES

4.	Nombres:	3 **ROBERTS, Ronald, John** 4 **CHUANG, Tsung-hsun** 5 **SHARMA-SINGH, Gorkhn** 6 **PERVEZ, Mohammed** 7 **FORD, James, Gair** 8 **STOREY, Richard, Anthony** 9 **DICKINSON, Paul, Alfred**
INVENTOR(ES) **(72)**	Dirección:	3 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 4 3200 WALNUT STREET, Boulder, CO 80301; EE.UU. 5 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 6 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 7 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 8 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña. 9 ASTRAZENECA R & D ALDERLEY, ALDERLEY PARK, Macclesfield, Cheshire SK10 4TG, Gran Bretaña.
	Nacionalidad o Domicilio:	3 Ciudadano de Gran Bretaña; 4 Ciudadano de TAI 5 Ciudadano de Gran Bretaña; 6 Ciudadano de Gran Bretaña; 7 Ciudadano de Gran Bretaña; 8 Ciudadano de Gran Bretaña; 9 Ciudadano de Gran Bretaña;

10. **Anexos**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [ ] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud Internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extrajero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [ ]

11. **FIGURA CARACTERISTICA**



12. Solicito la concesión de la patente,

NOMBRE: **CARLOS ORLANDO MAYA RODRIGUEZ**

FIRMA:

C.C **17.117.818** TP **17.402**

N 003948149

FOLIO 1.265.- PRIMERA COPIA.- ESCRITURA NUMERO SEISCIENTOS CUARENTA Y DOS.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a diez de septiembre de dos mil cuatro, ante mi, Escribano Autorizante, COMPARECE el Doctor **Daniel GOYTIA**, argentino, mayor de edad, casado, L.E. número 4.526.965, domiciliado en Avenida Leandro N. Alem 449, 3º piso, de esta Ciudad.- El compareciente es persona hábil y de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura de fecha 11 de junio de 2003, pasada al folio 1048 del Protocolo de este mismo Registro, a mi cargo, se protocolizó un **PODER** otorgado por **ARRAY BIOPHARMA, INC.**, domiciliado en 1885 33rd Street, Boulder, Colorado 80301, USA, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para si las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Maya Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Mayerling Rocio Castelblanco S.**, con domicilio en Carrera 13A Nº 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en dicho país con las siguientes facultades: "...poder amplio y suficiente para recabar de las autoridades nacionales que corresponda sean estas administrativas y/o judiciales la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES"**, y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; de desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir do-

N 003948149

cumentos y otros valores; justificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 1.265 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 003948149 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

02 JUL. 2008

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION
LEY 404

L 006178443

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el N°** 040914295263/2 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Martes 14 de Septiembre de 2004

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ESC. LUIS FEDERICO BERUTI
COLEGIO DE ESCRIBANOS
CONSEJERO

02 JUL. 2008

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. PAIS ARGENTINA

El presente documento público

2. Ha sido firmado por Luis F. Benedi

3. Quien actúa en calidad de Habil

4. LLeva el sello/timbre de Colegio 4

5. En BUENOS AIRES 6. El día 14 SEP 2004

7. Por UNIDAD DE COORDINACION LEGALIZACIONES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

8. Sello/Timbre 17576

9.

Dr. SEGUNDO ACUÑA
Unidad de Coordinación Legalizaciones
Ministerio de Relaciones Exteriores,
Comercio Internacional y Culto

10. Firma

02 JUL. 2008

N 008663340

FOLIO 2.502.- PRIMERA COPIA.- ESCRITURA NUMERO MIL DOSCIENTOS ONCE.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a veintisiete de noviembre de dos mil siete, ante mí, Escribano Autorizante, COMPARECE don **Daniel GOYTIA**, argentino, mayor de edad, casado, Libreta de Enrolamiento número 4.526.965, domiciliado en Bartolomé Mitre 226, 4° piso, de esta Ciudad.- El compareciente es persona de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura de fecha 26 de junio de 2006, pasada ante mí, al folio 1.070 del Protocolo de este Registro, se protocolizó un **Poder** otorgado por **AstraZeneca AB**, con domicilido en SE-151 85 Södertälje, Sweden, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para si las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Mava Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Maverling Rocio Castelblanco S.**, con domicilio en Carrera 13A Nº 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en dicho país con las siguientes facultades: "... poder amplio y suficiente para recabar de las autoridades nacionales que corresponda, sean estas administrativas y/o judiciales, la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES"**, y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir documentos y otros valores; sus

LEGALIZACION 07112958566 4 $20.00 12:05:20 29/11/2007

LEGALIZACION 07112906470 0 $39.00 12:05:29 29/11/2007

Como Notario Público de este Distrito hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
24 ENE. 2008
Gonzalo Osvaldo Daino
NOTARIA DECIMA
BOGOTA D.C.

N 008663340

tificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue. Este documento tiene validez a partir del 9 de mayo de 2006...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 2.502 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 008663340 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

ALEJANDRO M. LIPORACE
MATRICULA 3887
ESCRIBANO PUBLICO

24 ENE. 2008

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 007941103

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el N°** 071129585664/3

La presente legalización no juzga sobre el contenido y forma del documento.

Buenos Aires, Jueves 29 de Noviembre de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ESC. FERNANDO PEÑA ROBIROSA
COLEGIO DE ESCRIBANOS
LEGALIZADOR

24 ENE. 2008

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00148607

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por FERNANDO PEÑA ROBIROSA

3. Quien actúa en calidad de LEGALIZADOR

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 29/11/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: **071129064700**

9. Sello / Timbre

COLEGIO DE ESCRIBANOS · APOSTILLA · CIUDAD DE BUENOS AIRES · REPUBLICA ARGENTINA

10. Firma

Como Notaria Dieciocho (E) de Bogotá, D.C., consta que la FOTOCOPIA coincide con su original que he tenido a la vista y devuelto al interesado.

24 ENE. 2008

Gonzalo Gaviria Quintana

NOTARIA DIECIOCHO

BOGOTA, D.C.

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. *Country: United States of America*

This public document:

2. *has been signed by Harriet Smith Windsor*

3. *acting in the capacity of Secretary of State of Delaware*

4. *bears the seal/stamp of Office of Secretary of State*

Certified

5. *at Dover, Delaware*

6. *the nineteenth day of November, A.D. 2003*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0213520*

9. *Seal/Stamp:*

10. *Signature:*

Harriet Smith Windsor

Secretary of State

CECBA - LEY 404 GCBA
LEGALIZACION
0409142952 65

02 JUL 2003

$20.00

14/09/2009 10:41:48

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "ARRAY BIOPHARMA INC.", FILED IN THIS OFFICE ON THE TWENTY-FIRST DAY OF NOVEMBER, A.D. 2000, AT 9 O'CLOCK A.M.

Harriet Smith Windsor

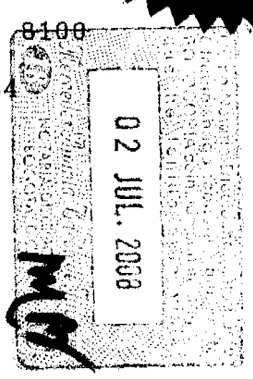
Harriet Smith Windsor, Secretary of State

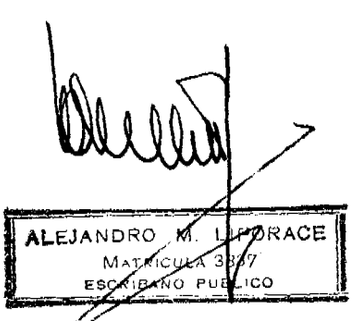
2856233 8100

030744564

AUTHENTICATION: 2759720

DATE: 11-19-03





STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 11/21/2000
001585524 – 2856233

AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF ARRAY BIOPHARMA INC.

Robert Conway hereby certifies that:

ONE: He is the duly elected and acting Chief Executive Officer of Array BioPharma Inc., a Delaware corporation originally incorporated as of February 6, 1998.

TWO: This Amended and Restated Certificate of Incorporation was duly adopted by the Board of Directors of the Corporation in accordance with the provisions of Sections 242 and 245 of the Delaware General Corporation Law and was duly adopted by vote of the stockholders of the Corporation in accordance with the provisions of Sections 228 and 242 of the Delaware General Corporation Law.

THREE: The Certificate of Incorporation of this corporation is hereby amended and restated in its entirety to read as follows:

Article 1. NAME

The name of the corporation is Array BioPharma Inc. (the "**Corporation**").

Article 2. REGISTERED OFFICE AND AGENT

The registered office of the Corporation shall be located at Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801 in the County of New Castle. The registered agent of the Corporation at such address shall be The Corporation Trust Company.

Article 3. PURPOSE AND POWERS

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware (the "**Delaware General Corporation Law**"). The Corporation shall have all power necessary or convenient to the conduct, promotion or attainment of such acts and activities.

Article 4. CAPITAL STOCK

4.1 Authorized Shares. The total number of shares of all classes of stock that the Corporation shall have the authority to issue is 70,000,000, of which 60,000,000 shall be Common Stock, all of one class, having a par value of $.001 per share (the "**Common Stock**"), and 10,000,000 of such shares shall be Preferred Stock, having a par value of $.001 per share (the "**Preferred Stock**").

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4.2 Common Stock.

4.2.1 Relative Rights. The Common Stock shall be subject to all of the rights, privileges, preferences and priorities of the Preferred Stock as set forth in the certificate of designations filed to establish the respective series of Preferred Stock. Each share of Common Stock shall have the same relative rights as and be identical in all respects to all the other shares of Common Stock. The Board of Directors is authorized, subject to the limitations prescribed by the Delaware General Corporation Law and the provisions of this Amended and Restated Certificate of Incorporation, to provide, by resolution or resolutions from time to time for the issuance of shares of Common Stock.

4.2.2 Dividends. Whenever there shall have been paid, or declared and set aside for payment, to the holders of shares of any class of stock having preference over the Common Stock as to the payment of dividends, the full amount of dividends and of sinking fund or retirement payments, if any, to which such holders are respectively entitled in preference to the Common Stock, then dividends may be paid on the Common Stock and on any class or series of stock entitled to participate therewith as to dividends, out of any assets legally available for the payment of dividends thereon, but only when and as declared by the Board of Directors of the Corporation.

4.2.3 Dissolution, Liquidation, Winding Up. In the event of any dissolution, liquidation, or winding up of the Corporation, whether voluntary or involuntary, the holders of the Common Stock, and holders of any class or series of stock entitled to participate therewith, in whole or in part, as to the distribution of assets in such event, shall become entitled to participate in the distribution of any assets of the Corporation remaining after the Corporation shall have paid, or provided for payment of, all debts and liabilities of the Corporation and after the Corporation shall have paid, or set aside for payment, to the holders of any class of stock having preference over the Common Stock in the event of dissolution, liquidation or winding up the full preferential amounts (if any) to which they are entitled.

4.2.4 Voting Rights. Each holder of shares of Common Stock shall be entitled to attend all special and annual meetings of the stockholders of the Corporation and, share for share and without regard to class, together with the holders of all other classes of stock entitled to attend such meetings and to vote (except any class or series of stock having special voting rights), to cast one vote for each outstanding share of Common Stock so held upon any matter or thing (including, without limitation, the election of one or more directors) properly considered and acted upon by the stockholders.

4.3 Preferred Stock. The Board of Directors is authorized, subject to limitations prescribed by the Delaware General Corporation Law and the provisions of this Amended and Restated Certificate of Incorporation, to provide, by resolution or resolutions from time to time and by filing a certificate of designations pursuant to the Delaware General Corporation Law, for the issuance of the shares of Preferred Stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the powers, designations,

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preferences and relative, participating, optional or other special rights of the shares of each such series and to fix the qualifications, limitations or restrictions thereof.

4.4 Preemptive Rights. Ownership of shares of any class of the capital stock of the Corporation shall not entitle the holders thereof to any preemptive right to subscribe for or purchase or to have offered to them for subscription or purchase any additional shares of capital stock of any class of the Corporation or any securities convertible into any class of capital stock of the corporation, whether now or hereafter authorized, however acquired, issued or sold by the corporation, it being the purpose and intent hereof that the Board of Directors shall have the full right, power and authority to offer for subscription or sell or to make any disposal of any or all unissued shares of the capital stock of the Corporation or any securities convertible into stock or any or all shares of stock or convertible securities issued and thereafter acquired by the Corporation, for such consideration, in money or property, as the Board of Directors in its sole discretion shall determine.

Article 5. BOARD OF DIRECTORS

5.1 Staggered Board, Number, Election. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended, covering the offer and sale of Common Stock to the public (the "**Initial Public Offering**"), the directors shall be divided into three classes, as nearly equal in number as possible, designated as Class I, Class II and Class III, respectively. Directors shall be assigned to each class in accordance with a resolution or resolutions adopted by the Board of Directors. At the first annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

The number of directors constituting the whole Board or Directors shall not be fewer than three or more than fifteen. The number of directors may be altered from time to time as provided in the Bylaws. Unless and except to the extent that the Bylaws of the Corporation shall otherwise require, the election of directors of the Corporation need not be by written ballot. Except as otherwise provided in this Amended and Restated Certificate of Incorporation, each director of the Corporation shall be entitled to one vote per director on all matters voted or acted upon by the Board of Directors.

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5.2 Vacancies. Vacancies and newly created directorships resulting from any increase in the authorized number of directors may be filled by the affirmative vote of a majority of the directors then in office, although fewer than a quorum, or by a sole remaining director. A director shall hold office for the remainder of the term of the class of director to which the vacancy occurred or the new directorship was created. Whenever the holders of any class or classes of stock or series thereof are entitled to elect one or more directors by the provisions of this Amended and Restated Certificate of Incorporation, vacancies and newly created directorships of such class or classes or series may be filled by the affirmative vote of a majority of the directors elected by such class or classes or series thereof then in office, or by a sole remaining director so elected. Each director so chosen shall hold office until the next election of directors of the class to which such director was appointed, and until such director's successor is elected and qualified, or until the director's earlier death, resignation or removal. In the event that one or more directors resign from the Board of Directors, effective at a future date, a majority of the directors then in office, including those who have so resigned, shall have power to fill such vacancy or vacancies, the vote thereon to take effect when such resignation or resignations shall become effective, and each director so chosen shall hold office until the next election of directors for such class or series, and until such director's successor is elected and qualified, or until the director's earlier death, resignation or removal.

5.3 Removal of Directors. A director may be removed only for cause and only by an affirmative vote of at least the holders of two-thirds of the outstanding stock entitled to vote thereon.

5.4 Management of Business and Affairs of the Corporation. The business and affairs of the Corporation shall be managed by or under the direction of the Board of Directors.

5.5 Limitation of Liability. No director of the Corporation shall be liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, provided that this provision shall not eliminate or limit the liability of a director (a) for any breach of the director's duty of loyalty to the Corporation or its stockholders; (b) for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law; (c) under Section 174 of the Delaware General Corporation Law; or (d) for any transaction from which the director derived an improper personal benefit. Any repeal or modification of this Section 5.5 shall be prospective only and shall not adversely affect any right or protection of, or any limitation of the liability of, a director of the Corporation existing at, or arising out of facts or incidents occurring prior to, the effective date of such repeal or modification.

Article 6. STOCKHOLDER ACTION

6.1 Action Without a Meeting by Unanimous Written Consent. Any action required or permitted to be taken at a stockholders' meeting may be taken without a meeting only by the unanimous written consent of all stockholders entitled to vote on such matter. The action must be evidenced by one or more written consents describing the action taken, signed by all of

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the stockholders entitled to vote on such action, and delivered to the Corporation in the manner prescribed by the Delaware General Corporation Law for inclusion in the minute book.

6.2 Special Meetings. Unless the Delaware General Corporation Law shall provide otherwise, no stockholder or any group thereof shall have the right to call a special meeting of the stockholders.

Article 7. BUSINESS COMBINATIONS WITH INTERESTED STOCKHOLDERS

The Corporation by this provision hereby elects to be governed by Section 203 of the Delaware General Corporation Law.

Article 8. COMPROMISE OR ARRANGEMENTS

Whenever a compromise or arrangement is proposed between the Corporation and its creditors or any class of them and/or between the Corporation and its stockholders or any class of them, any court of equitable jurisdiction within the State of Delaware may, on the application in a summary way of the Corporation or of any creditor or stockholder thereof or on the application of any receiver or receivers appointed for the Corporation under the provisions of Section 291 of Title 8 of the Delaware Code or on the application of trustees in dissolution or of any receiver or receivers appointed for the Corporation under the provisions of Section 279 of Title 8 of the Delaware Code order a meeting of the creditors or class of creditors, and/or of the stockholders or class of stockholders of the Corporation, as the case may be, to be summoned in such manner as the said court directs. If a majority in number representing three-fourths in value of the creditors or class of creditors, and/or of the stockholders or class of stockholders of the Corporation, as the case may be, agree to any compromise or arrangement and to any reorganization of the Corporation as a consequence of such compromise or arrangement, the said compromise or arrangement and the said reorganization shall, if sanctioned by the court to which the said application has been made, be binding on all the creditors or class of creditors, and/or on all the stockholders or class of stockholders, of the Corporation, as the case may be, and also on the Corporation.

Article 9. ACQUISITION PROPOSALS

In determining whether the acquisition proposal is in the long-term best interests of the Corporation and its stockholders, the Board of Directors may consider the effect of both an acquisition proposal and a potential acquisition on creditors, customers and employees of the Corporation and on the community in general, the risks of non-consummation of an acquisition proposal, the identity, prior background and other business experiences of the person or entity making an acquisition proposal, and the business plans of both the Corporation and the person or entity making an acquisition proposal and their respective effects on stockholder interests. The Board of Directors is authorized to take such action as it may determine to be reasonably necessary or desirable to encourage any person or entity to enter into negotiations with the Board of Directors and management of the Corporation respecting any transaction that may result in a change of control and to contest or oppose any such transaction that the Board of Directors

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determines to be unfair, abusive or otherwise undesirable to the Corporation or its stockholders, business, customers, employees or other constituencies.

Article 10. AMENDMENT OF BYLAWS

In furtherance and not in limitation of the powers conferred by the Delaware General Corporation Law, the Board of Directors of the Corporation is expressly authorized and empowered to adopt, amend and repeal the Bylaws of the Corporation by an affirmative vote of at least two-thirds of the directors then in office. The Bylaws of the Corporation may also be adopted, amended or repealed upon the affirmative vote of the holders of at least two-thirds of the outstanding stock entitled to vote thereon, voting together as a single class.

Article 11. RESERVATION OF RIGHT TO AMEND CERTIFICATE OF INCORPORATION

The Corporation reserves the right at any time, and from time to time, to amend, alter, change, or repeal any provision contained in this Amended and Restated Certificate of Incorporation, and other provisions authorized by the laws of the State of Delaware at the time in force may be added or inserted, in the manner now or hereafter prescribed by law; and all rights, preferences, and privileges of any nature conferred upon stockholders, directors, or any other persons by and pursuant to this Amended and Restated Certificate of Incorporation in its present form or as hereafter amended are granted subject to the rights reserved in this Article 11. With respect to action to be taken by the stockholders to amend Sections 4.3 and 4.4, and Articles 5, 6, 7, 9, 10 and 11 of this Amended and Restated Certificate of Incorporation, upon the affirmative vote of the holders of at least two-thirds of the outstanding stock entitled to vote thereon, voting together as a single class.

* * * * * * *

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TRADUCCIÓN.----------

[Página 1].----------

APOSTILLA.----------

(Convención de La Haya del 05 de octubre de 1961).---------

1. País: Estados Unidos de América.----------

El presente documento público----------

2. ha sido firmado por Harriet Smith Windsor----------

3. en su carácter de Secretaria de Estado de Delaware------

4. lleva el sello / la estampilla de la Oficina de la Secretaría de Estado----------

ha sido ***CERTIFICADO***----------

5. en Dover, Delaware----------

6. el diecinueve de noviembre de 2003----------

7. por la Secretaria de Estado, Departamento de Estado de Delaware----------

8. con el Número: *0159991*.----------

9. Sello/estampilla: [Aparece una estampilla dorada que reza:] OFICINA DE LA SECRETARIA DE DELAWARE, 1793-1855.----

10. Firma: [Se observa una firma ilegible debajo de la cual se lee:] Secretaria de Estado.----------

[Página 2].----------

DELAWARE. PRIMER ESTADO.----------

[En el margen superior derecho se lee:] Página 1.----------

Yo, Harriet Smith Windsor, Secretaria de Estado del Estado de Delaware, por la presente certifico que el documento

02 JUL. 2008

ALEJANDRO M. LAPORAGE
MATRICULA 3837
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adjunto es copia fiel y exacta del Acta Constitutiva Modificada de "Array BioPharma, Inc.", presentada ante esta Oficina el veintiuno de noviembre de 2000, a las 9 horas a.m.----------

[Aparece una estampilla dorada que reza:] OFICINA DE LA SECRETARIA DE DELAWARE, 1793-1855. [A su derecha aparece una firma ilegible debajo de la cual se lee:] Harriet Smith Windsor, Secretaria de Estado.----------

2856233 8100 030744564.----------

Certificación: 2759720. Fecha: 19-11-03.----------

[Página 3].----------

[En el margen superior derecho se lee:] ESTADO DE DELAWARE - SECRETARIA DE ESTADO - SECTOR SOCIEDADES. PRESENTADO: 21/11/2000, 09:00 a.m. 001585524 - 2856233.----------

ACTA CONSTITUTIVA MODIFICADA DE ARRAY BIOPHARMA, INC.------

Robert Conway por la presente certifica que:----------

PRIMERO: Quien declara es Gerente General, debidamente elegido y en ejercicio, de Array BioPharma, Inc., sociedad de Delaware originalmente constituida desde el 06 de febrero de 1998.----------

SEGUNDO: La presente Acta Constitutiva Modificada fue debidamente adoptada por el Directorio de la Sociedad en conformidad con las disposiciones de las Secciones 242 y 245 de la Ley General de Sociedades de Delaware y fue debidamente adoptada por el voto de los accionistas de la

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Sociedad en conformidad con las disposiciones de las Secciones 228 y 242 de la Ley General de Sociedades de Delaware.----------

TERCERO: Por el presente se modifica el Acta Constitutiva de la sociedad, que quedará redactada, en su totalidad, de la siguiente forma:----------

Artículo 1. NOMBRE.----------

El nombre de la sociedad es Array BioPharma, Inc. (en adelante la "**Sociedad**").----------

Artículo 2. DOMICILIO SOCIETARIO CONSTITUIDO Y AGENTE DE REPRESENTACIÓN.----------

El domicilio constituido de la Sociedad es Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801, en el Condado de New Castle. El agente de representación de la Sociedad en dicho domicilio es The Corporation Trust Company.----------

Artículo 3. OBJETO Y FACULTADES.----------

El objeto de la Sociedad es desarrollar todo tipo de actividad o realizar todo tipo de acto lícitos para los cuales pueden constituirse las sociedades según la Ley General de Sociedades del Estado de Delaware (en adelante la "**Ley General de Sociedades de Delaware**"). La Sociedad gozará de todas las facultades necesarias o convenientes para la gestión, promoción o consecución de tales actos y actividades.----------

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ALEJANDRO M. LIBORACE
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Artículo 4. CAPITAL ACCIONARIO.----------

4.1. Acciones Autorizadas. El número total de acciones, incluidas todas las clases, que la Sociedad estará facultada a emitir es de 70.000.000, de las cuales 60.000.000 serán Acciones Ordinarias, todas de una sola clase, con un valor par de $0,001 por acción (en adelante llamadas "**Acciones Ordinarias**"), y 10.000.000 serán Acciones Preferidas, con un valor par de $0,001 por acción (en adelante llamadas "**Acciones Preferidas**").----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 4].----------

4.2. Acciones Ordinarias.----------

4.2.1. Derechos Relativos.----------

Las Acciones Ordinarias gozarán de todos los derechos, privilegios, preferencias y prioridades de las Acciones Preferidas según se establezca en el certificado de designaciones presentado para determinar las series respectivas de Acciones Preferidas. Cada una de las Acciones Ordinarias tendrá los mismos derechos relativos que y serán iguales, en todos los respectos, a todas las demás Acciones Ordinarias. El Directorio está autorizado, con sujeción a las limitaciones establecidas por la Ley General de Sociedades de Delaware y las disposiciones de la presente Acta Constitutiva Modificada, a disponer, mediante

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resolución, la emisión periódica de Acciones Ordinarias.---

4.2.2. Dividendos.----------

Una vez que se hubiera realizado el pago de dividendos, o se hubieran declarado y reservado para el pago, a los tenedores de acciones de cualquier clase con preferencia sobre las Acciones Ordinarias en cuanto al pago de dividendos, la cantidad total de dividendos y de fondos de amortización o pagos de rescate, si hubiera, a los cuales tales tenedores tienen derecho en preferencia a las Acciones Ordinarias, entonces podrán pagarse los dividendos a las Acciones Ordinarias y a cualquier clase o serie de acciones con derecho a participar en los dividendos, de los activos legalmente disponibles para el pago de dividendos, pero sólo cuando y en la forma que lo declare el Directorio de la Sociedad.----------

4.2.3. Disolución y liquidación.----------

En caso de disolución o liquidación de la Sociedad, sea voluntaria o involuntaria, los tenedores de Acciones Ordinarias, y los tenedores de cualquier clase o serie de acciones con derecho a participar, en todo o en parte, en la distribución de los bienes en tal circunstancia, tendrán derecho a participar en la distribución de los bienes de la Sociedad que quedaran una vez que la Sociedad haya pagado, o dispuesto el pago de, todas las deudas y obligaciones de la Sociedad y una vez que la Sociedad haya pagado, o

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ALEJANDRO M. [illegible]
MATRICULA 3837
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reservado para el pago, a los tenedores de cualquier clase de acciones con preferencia sobre las Acciones Ordinarias en caso de disolución o liquidación, la totalidad del monto preferencial (si correspondiere) al cual dichos tenedores tienen derecho.----------

4.2.4. Derecho de Voto.----------

Cada tenedor de Acciones Ordinarias tendrá derecho a participar de todas las asambleas anuales y especiales de accionistas de la Sociedad y, acción por acción sin distinción de clases, junto con los otros tenedores de todas las demás clases de acciones con derecho a participar de tales asambleas y a votar (excepto las clases o series de acciones con derecho especial de voto), a ofrecer un voto por cada Acción Ordinaria en circulación que posean con relación a cualquier cuestión o tema (incluyendo, -aunque no taxativamente- la elección de uno o más miembros del Directorio), que recibiera adecuada consideración y tratamiento por los accionistas.----------

4.3. Acciones Preferidas.----------

El Directorio queda autorizado, con sujeción a las limitaciones establecidas por la Ley General de Sociedades de Delaware y las disposiciones de la presente Acta Constitutiva Modificada, a disponer, por resolución, en forma periódica y mediante la presentación de un certificado de designaciones en virtud de la Ley General de

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ALEJANDRO M. LLORENTE
MATRICULA 3837
ESCRIBANO PUBLICO

Sociedades de Delaware, la emisión de Acciones Preferidas en una o más series, a establecer periódicamente la cantidad de acciones a incluir en cada una de tales series, a establecer las facultades, designaciones, preferencias y derechos relativos, de participación, opcionales y otros que correspondan a cada una de tales series, y a establecer las calificaciones y las limitaciones o restricciones que les corresponderán.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 5].----------

4.4. Derechos de Preferencia.----------

La titularidad de las acciones de cualquier clase de la Sociedad no otorgará a sus tenedores ningún derecho de preferencia para suscribir o comprar ni para que se les ofrezca la suscripción o compra de acciones adicionales de capital de cualquier clase de la Sociedad ni de valores convertibles en cualquier clase de acciones de capital de la Sociedad, que se encontrare actualmente autorizada o se autorizare en el futuro, aunque hubieran sido adquiridas, emitidas o vendidas por la Sociedad, siendo el objeto y la intención de la presente disposición que el Directorio goce de plenos derechos, facultades y autoridad para ofrecer la suscripción o venta o para disponer de cualquier forma de la totalidad o parte de las acciones de la Sociedad no

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emitidas o de cualquier valor convertible en acción o de la totalidad o parte de las acciones de capital o valores convertibles emitidos y luego adquiridos por la Sociedad, a cambio de la contraprestación, monetaria o en especie, que el Directorio, a su sola discreción, determine.----------

Artículo 5. DIRECTORIO.----------

5.1. Directorio Renovable. Número. Elección.----------

Con sujeción a los derechos de los tenedores de cualquier serie de Acciones Preferidas de elegir directores adicionales en circunstancias específicas, con posterioridad al cierre de la oferta pública inicial en virtud de una declaración de registro efectiva en conformidad con la Ley de Valores de 1933, con sus modificaciones, que cubra la oferta y venta de Acciones Ordinarias al público (en adelante llamada la "**Oferta Pública Inicial**"), los directores se dividirán en tres clases, cada una de ellas con igual número de directores o con un número de directores lo más cercano posible entre sí, designados como Clase I, Clase II y Clase III, respectivamente. Los directores serán asignados a cada clase en conformidad con una resolución o resoluciones adoptadas por el Directorio. En la primera asamblea anual de accionistas que sigue al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase I y se elegirán directores de la Clase I que ocuparán el

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cargo por un período de tres años. En la segunda asamblea anual de accionistas posterior al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase II y se elegirán directores de la Clase II que ocuparán su cargo por un período completo de tres años. En la tercera asamblea anual de accionistas siguiente al cierre de la Oferta Pública Inicial, expirará el mandato de los directores de la Clase II y se elegirán directores de la Clase III que ocuparán sus cargos por un período completo de tres años. En cada asamblea anual de accionistas subsiguiente, los directores se elegirán por períodos de tres años para suceder a los directores de la clase cuyos mandatos concluyen en tal asamblea anual.------

El número de directores que constituirá el directorio completo no será inferior a tres ni excederá de quince. El número de directores podrá modificarse periódicamente según lo establecido en el Estatuto. A menos que y en la medida que el Estatuto de la Sociedad disponga lo contrario, la elección de los directores de la Sociedad no deberá realizarse necesariamente por votación escrita. Salvo que la presente Acta Constitutiva Modificada establezca lo contrario, cada director de la Sociedad tendrá derecho a un voto por director sobre todas las cuestiones sometidas a votación o acción del Directorio.----------

[En el margen inferior izquierdo aparece una leyenda que

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resulta ilegible].----------

[Página 6].----------

5.2. Vacantes.----------

Las vacantes y los nuevos cargos de director que se generen por un aumento en el número autorizado de directores podrán llenarse por el voto afirmativo de la mayoría de los directores entonces en funciones, aunque inferior el número exigido para lograr quórum, o por el único director en funciones. Un director podrá ocupar el cargo por el período que reste del mandato correspondiente al director de la Clase que generó la vacante o por el período para el cual el nuevo cargo fue creado. Cuando los tenedores de cualquier clase, clases o serie de acciones tengan derecho a elegir uno o más directores según lo establecido en la presente Acta Constitutiva Modificada, las vacantes y los nuevos cargos de director que se creen para tal clase, clases o series podrán llenarse por el voto afirmativo de la mayoría de los directores elegidos por tal clase, clases o series, entonces en funciones, o por el único director entonces en funciones que así hubiere sido elegido. Cada director así elegido ocupará el cargo hasta la próxima elección de directores de la clase a la cual tal director fue designado, y hasta que el sucesor de tal director haya sido elegido y habilitado, o hasta la remoción, renuncia o muerte temprana del director. En caso de que uno o más

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directores renuncien al Directorio, con efectos a partir de fecha futura, la mayoría de los directores entonces en funciones, incluyendo aquellos que han renunciado, tendrán derecho a llenar tal vacante o vacantes, la votación que se realice tendrá efectos la renuncia o las renuncias se hagan efectivas, y cada director así elegido ocupará el cargo hasta la siguiente elección de directores de dicha clase o serie, y hasta que el sucesor del director hayas sido elegido y habilitado, o hasta la remoción, renuncia o muerte temprana del director.----------

5.3. Remoción de los Directores.----------

Un director podrá ser removido únicamente con causa y por el voto afirmativo de por lo menos dos tercios de los tenedores de acciones en circulación con derecho a voto sobre el tema.----------

5.4. Gestión de los Negocios y Asuntos de la Sociedad.-----

Los negocios y otros asuntos de la Sociedad serán administrados por y bajo la dirección del Directorio.------

5.5. Límites a la Responsabilidad.----------

Ningún director de la Sociedad será responsable ante la Sociedad ni sus accionistas por daños monetarios originados por incumplimiento del deber fiduciario como director, entendiéndose que esta disposición no desconoce la responsabilidad de un director (a) por incumplimiento del deber de lealtad del director a la Sociedad y a sus

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accionistas; (b) por actos u omisiones de mala fe o que involucren un comportamiento ilícito intencional o la violación de una ley, con conocimiento de ello; (c) en virtud de la Sección 174 de la Ley General de Sociedades de Delaware; o (d) por cualquier transacción de la cual el director haya derivado un beneficio personal irregular. Toda revocación o modificación de esta Sección 5.5. será sólo eventual y no afectará negativamente los derechos ni la protección de, ni los límites a la responsabilidad de, un director de la Sociedad existentes, o emergentes de los hechos o incidentes que ocurran con anterioridad, a la fecha efectiva de tal revocación o modificación.----------

Artículo 6. ACCIONAR DE LOS ACCIONISTAS.----------

6.1. Accionar sin Asamblea y por Consentimiento Escrito Unánime.----------

Cualquier acción cuya realización sea requerida o permitida a los accionistas en asamblea podrá realizarse sin necesidad de celebrar una asamblea únicamente si mediare el consentimiento escrito unánime de todos los accionistas con derecho a voto sobre el tema en cuestión. La acción deberá evidenciarse en uno o más consentimientos por escrito que describa la acción a seguir, firmado por todos los accionistas con derecho a voto sobre tal acción, y entregado a la Sociedad en la forma establecida por la Ley General de Sociedades de Delaware para su inclusión en el

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libro de minutas.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 7].----------

6.2. Asambleas Especiales.----------

A menos que la Ley General de Sociedades de Delaware establezca lo contrario, ningún accionista ni grupo de ellos podrá convocar a una asamblea especial de accionistas.----------

Artículo 7. ASOCIACIÓN DE NEGOCIOS CON ACCIONISTAS INTERESADOS.----------

La Sociedad se somete a las disposiciones de la Sección 203 de la Ley General de Sociedades de Delaware.----------

Artículo 8. ACUERDOS Y TRANSACCIONES.----------

Cuando se proponga un acuerdo o transacción entre la Sociedad y sus acreedores o cualquier clase de ellos y/o entre la Sociedad y sus accionistas o cualquier clase de ellos, cualquier tribunal del régimen de Equity[1] dentro del Estado de Delaware podrá, a pedido en forma sumaria de la Sociedad o de cualquier acreedor o accionista de ella, o a pedido de cualquier administrador o administradores designados por la Sociedad en conformidad con lo dispuesto en la Sección 291 del Título 8 del Código de Delaware, o a

[1]NT: Sistema de derecho o rama de la justicia reparadora administrado por tribunales distintos de los que aplican las normas del sistema del Common Law y que están facultados para decretar "equidad" en el sentido de justicia equitativa o imparcial.

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NOTARIA DIECIOCHO
BOGOTA, D.C.

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pedido de los liquidadores en caso de disolución o de cualquier administrador o administradores designados por la Sociedad en virtud de lo dispuesto en la Sección 279 del Título 8 del Código de Delaware, ordenar una reunión de los acreedores o clase de acreedores, y/o de los accionistas o clase de accionistas de la Sociedades, según fuera el caso, que se convocará en la forma en que el tribunal disponga. Si una mayoría en número que represente tres cuartos en el valor de los acreedores o clase de acreedores, y/o de los accionistas o clase de accionistas de la Sociedad, según fuere el caso, acuerdan celebrar un acuerdo o transacción y acuerdan la reorganización de la Sociedad como consecuencia de tal acuerdo o transacción, dicho acuerdo a transacción y la reorganización resultante, si fuera sancionada por el tribunal a quien se elevó la solicitud, será vinculante para todos los acreedores o clase de acreedores, y/o para todos los accionistas o clase de accionistas, de la Sociedad, según fuera el caso, como así también para la Sociedad.----------

Artículo 9. PROPUESTAS DE ADQUISICIÓN.----------

A fin de determinar si la propuesta de adquisición será a largo plazo beneficiosa para la Sociedad y sus accionistas, el Directorio deberá considerar los efectos que tendrían tanto una propuesta de adquisición como una potencial propuesta de adquisición sobre los acreedores, clientes, y

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33.

empelados de la Sociedades y sobre la comunidad en general, los riesgos de la no consumación de una propuesta de adquisición, la identidad, los antecedentes y otras experiencias comerciales de la persona o entidad que realiza la propuesta de adquisición, y los planes comerciales tanto de la Sociedad como de la persona o entidad que formula la propuesta de adquisición y sus respectivos efectos sobre los intereses de los accionistas. El Directorio está autorizado para realizar todas las acciones que considere razonablemente necesarias o deseables para alentar a que cualquier persona o entidad entre en negociaciones con el Directorio y la administración de la Sociedad con relación a cualquier transacción que pudiera resultar en un cambio en el control y para impugnar u oponerse a las transacciones que el Directorio considere injustas, abusivas o no deseables para la Sociedad y sus accionistas, negocios, clientes, empleados u otros involucrados.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 8].----------

Artículo 10. MODIFICACIÓN DEL ESTATUTO.----------

A fin de ampliar sin limitar las facultades conferidas por la Ley General de Sociedades de Delaware, el Directorio queda expresamente autorizado y facultado para adoptar,

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modificar y revocar el Estatuto de la Sociedad con el voto afirmativo de por lo menos dos tercios de los directores entonces en funciones. El Estatuto de la Sociedad podrá también adoptarse, modificarse o revocarse con el voto afirmativo de los tenedores de por lo menos dos tercios de las acciones en circulación con derecho a voto sobre la cuestión, en votación conjunta como clase única.----------

Artículo 11. RESERVA DEL DERECHO A MODIFICAR EL ACTA CONSTITUTIVA.----------

La Sociedad se reserva el derecho de, en cualquier, y periódicamente, modificar, enmendar, cambiar o revocar cualquier disposición contendida en la presente Acta Constitutiva Modificada; asimismo, otras disposiciones autorizadas por las leyes del Estado de Delaware actualmente vigentes podrán agregarse o incorporarse en la forma dispuesta por ley en el presente o en el futuro; y todos los derechos, preferencias y privilegios de cualquier naturaleza conferidos a los accionistas, directores, o cualquier otra persona por y en conformidad con la presente Acta Constitutiva Modificada en su forma actual o en la forma que resulte de modificaciones futuras, se otorgan con sujeción a los derechos reservados en este Artículo 11. Con respecto a la acción que deberán realizar los accionistas para modificar las Secciones 4.3 y 4.4, y los Artículos 5, 6, 7, 9, 10, y 11 de la presente Acta Constitutiva

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Modificada, la misma podrá realizarse con el voto afirmativo de los tenedores de por lo menos dos tercios de las acciones e circulación con derecho a voto sobre el tema en cuestión, actuando conjuntamente como una sola clase.--- [En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[Página 9].----------

EN PRUEBA DE CONFORMIDAD, Array BioPharma, Inc. Celebra la presente Acta Constitutiva Modificada a través de su Gerente General, quien en este acto declara que los hechos aquí anteriormente descriptos has sido establecidos con exactitud, a los 21 días del mes de noviembre del año 2000.

Array BioPharma, Inc.----------

A través de: [Aparece una firma ilegible debajo de la cual se lee:] Robert Conway, Gerente General.----------

[En el margen inferior izquierdo aparece una leyenda que resulta ilegible].----------

[En el margen inferior, en el centro, se lee:] Página de Firma.----------

Es traducción fiel al idioma español del documento original redactado en idioma inglés, que he tenido a la vista y adjunto a la presente, en la Ciudad de Buenos Aires, a los seis días del mes de diciembre del año dos mil tres.-------

---

02 JUL. 2008

SILVIA P. PLANKENHORN
TRADUCTORA PUBLICA
INGLES
MAT. T XIII - F 459 - CAP. FED.
INSCRIP. C.T.P.C.B.A. Nº 4854

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA ·

CERTIFICACION DE REPRODUCCIONES
LEY 404

T 002409825

ALEJANDRO M. LIPORACE
MATRICULA 3837
ESCRIBANO PUBLICO

Buenos Aires, 9 de diciembre de 2003.-

En mi carácter de Escribano Titular del Registro 1331 de Capital Federal.-

CERTIFICO que la reproducción anexa, extendida en Veintiseis.-

foja/s, que sello y firmo, es COPIA FIEL de su original, que tengo a la vista, doy fe.

El Autorizante deja constancia que el documento cuyas fotocopias se certifican se encuentra redactado en idioma extranjero con su correspondiente traducción al español y consiste en un **ACTA CONSTITUTIVA MODIFICADA DE ARRAY BIOPHARMA, INC.-**

ALEJANDRO M. LIPORACE
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ESCRIBANO PUBLICO

02 JUL. 2008

LEGALIZACION
LEY 404

L 006178202

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE

obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº 040914295265/2 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Martes 14 de Septiembre de 2004

ESC. LUIS FEDERICO BERUTI
COLEGIO DE ESCRIBANOS
CONSEJERO

02 JUL. 2008

APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. PAIS ARGENTINA

El presente documento público

2. Ha sido firmado por Luis E Beade

3. Quien actúa en calidad de

4. LLeva el sello/timbre de Colegio

5. En BUENOS AIRES 6. El día 14 SEP 2004

7. Por UNIDAD DE COORDINACION LEGALIZACIONES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

8. bajo el número: 175510

9. Sello / Timbre

Dr. SEGUNDO ACUÑA
Unidad de Coordinación Legalizaciones
Ministerio de Relaciones Exteriores,
Comercio Internacional y Culto
10. Firma

07 JUL. 2008

BE IT KNOWN that I, ADRIAN PETER MARK WATNEY of 33 Queen Street, Maidenhead, Berkshire SL6 1NB, United Kingdom, a duly authorised Notary Public

CERTIFY ONLY that Blair Consular Services Limited on behalf of their client

ASTRAZENECA AB

have this day presented to me the hereto annexed document

COPY ARTICLES OF ASSOCIATION

and that the said Blair Consular Services Limited have represented to me by such presentation that their said client has represented to them that the said annexed document is a true copy of the corresponding original document.

SIGNED AND SEALED at 33 Queen Street, Maidenhead, Berkshire SL6 1NB, United Kingdom, on 20th February 2008.

Adrian Peter Mark Watney
Notary Public

02 JUL. 2008

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **Adrian Peter Mark Watney**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

Certified/Attesté

5. at London/à Londres

6. the/le **22 February 2008**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H688744**

9. Stamp: / timbre:

10. Signature: **R Shilton**

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

02 JUL. 2008

Approved 19 December 2005

ARTICLES OF ASSOCIATION

§ 1 The Company's name is AstraZeneca AB. The Company is a public company (publ).

§ 2 The object of the Company shall be to engage in the manufacture of, and trade in, products for health care and medical care; to conduct financial activities; to own and manage real and personal property, including stocks and interests in other companies; and to conduct other activities which are compatible with the above-mentioned business activities.

§ 3 The Company's registered office shall be situated in Södertälje, Sweden.

§ 4 The share capital shall be not less than seven hundred and fifty million kronor (SEK 750,000,000) and not more than three billion kronor (SEK 3,000,000,000).

§ 5 The number of shares shall be no less than 600,000,000 and no more than 2,400,000,000.

§ 6 The Board of Directors shall consist of no less than three members and no more than twelve members and no more than three alternate members.

§ 7 Two auditors and two deputy auditors or one or two certified accounting firms shall be appointed by the meeting of shareholders.

§ 8 General meetings of the shareholders shall be held in Södertälje, Stockholm, Gothenburg, Mölndal, Malmö or Lund on or before June 30.

The following business shall be addressed at the annual meeting:

1) election of a chairman for the meeting;

2) preparation and attestation of voting register;
3) approval of agenda;
4) election of one or two persons who shall attest the minutes of the meeting;
5) determination of whether the meeting was duly convened;
6) submission of the annual report and report of the auditors and the consolidated annual report and report of the auditors for the group;
7) resolution regarding:
   a. adoption of the profit and loss accounts and balance sheet and the consolidated profit and loss accounts and consolidated balance sheet;
   b. allocation of the Company's profits or losses according to the adopted balance sheet;
   c. release of the members of the Board of Directors and the managing director from liability;

8) determination of the number of members of the Board of Directors and alternate members;
9) determination of fees for the Board of Directors and the auditors;
10) election of members of the Board of Directors and alternate members;
11) where applicable, election of auditors and alternate auditors;
12) resolutions regarding other matters which are prescribed in the Companies Act or the Company's Articles of Association.

§ 9 Notice to shareholders of general meetings of the shareholders shall be given either by letter posted in the public postal service or by publication in Post- och Inrikes Tidningar and Dagens Nyheter.

§ 10 The financial year of the Company shall be the calendar year.

TRADUCCIÓN PÚBLICA----------

[Página 1]----------

Sépase que, yo Adrian Peter Mark Watney de 33 Queen Street, Maidenhead, Berkshire SL6 1NB, Reino Unido, un Notario Público debidamente autorizado.----------

CERTIFICO SOLAMENTE que Blair Consular Services Limited a nombre de su cliente ASTRAZENECA AB han presentado este día el documento al presente adjunto COPIA DE LOS ARTÍCULOS DE ASOCIACIÓN y que dicha Blair Consular Services Limited me ha representado mediante dicha presentación que su cliente les ha representado que dicho documento adjunto es una copia fiel del correspondiente documento original.----------

FIRMADO Y SELLADO en 33 Queen Street, Maidenhead, Berkshire SL6 1NB, Reino Unido, a los 20 días del mes de Febrero 2008.---------

[Aparece una firma ilegible] Adrian Peter Mark Watney. Notario Público. ----------

[Aparece una estampilla parcialmente legible. En su parte legible reza:] Notario Público.----------

[Aparece un sello de puntos parcialmente ilegible, en su parte legible reza: Oficina del Commonwealth.----------

[Reverso de la Página 1]----------

APOSTILLA----------

02 JUL. 2008

[Aparece una Apostilla redactada en inglés y otro idioma, en su parte en inglés reza:]----------

Convención de la Haya del 5 de octubre de 1961----------

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE----------

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte-----

El presente documento público ----------

2. ha sido firmado por **Adrian Peter Mark Watney** ----------

3. actuando en carácter de Notario Público ----------

4. lleva el sello/ timbre de Dicho Notario Público----------

CERTIFICADO ----------

5. en Londres ----------

6. a los 22 días del mes de febrero de 2008 ----------

7. por el Secretario Principal de su Majestad del Estado para Asuntos Externos y Commonwealth----------

8. No. H688744 ----------

9. Sello/ Timbre: Oficina de Commonwealth y Exterior. Londres---

10. Firma: [Aparece una firma ilegible debajo de la cual se lee:] Por el Secretario de Estado. ----------

Si el presente documento se utiliza en un país que no es parte de la Convención de la Haya del 5 de octubre de 1961, debe presentarse en la sección consular de la misión que representa aquel país. Una apostilla o certificado de legalización solamente confirma que la firma, sello y estampilla en el documento son

02 JUL. 2008

ALCALDÍA TRÁ AZCÁRATE PÚBLICA Cap. Fed. Nº 0075

genuinas. No significa que los contenidos del documento sean correctos o que la Oficina de Commonwealth y Exterior aprueba los contenidos.----------

[Página 2]----------

Aprobado el 19 de diciembre de 2005----------

Artículos de Asociación----------

1. El nombre de la Empresa es AstraZeneca AB. La empresa es una empresa pública (pública)----------

2. El objeto de la Empresa deberá comprometerse en la fabricación, y comercialización, de productos para el cuidado médico y sanitario; a realizar actividades financieras; a poseer y manejar bienes personales y raíces, incluyendo acciones e intereses en otras empresas; y a conducir otras actividades que sean compatibles con las actividades comerciales anteriormente mencionadas.----------

3. La oficina registrada de la Empresa se situará en Sodertalje, Suecia.----------

4. El capital accionario no deberá ser menor a setecientos cincuenta millones de Coronas (SEK 750.000.000) ni mayor a tres billones de Coronas (SEK 3.000.000.000).----------

5. El número de acciones no deberá ser menos a 600.000.000 ni mayor a 2.400.000.000.----------

02 JUL. 2008

6. La Junta Directiva no se formará con menos de tres miembros ni con más de doce miembros y no más de tres miembros alternativos.-

7. La junta de accionistas designará no más de dos auditores y dos sub auditores o uno o dos contadores certificados.----------

8. Las juntas generales de los accionistas se realizarán en Sodertalje, Estocolmo, Gothenburg, Molndal, Malmo o Lund el 30 de junio o antes.----------

Los siguientes temas serán abordados en la junta anual:----------

1) elección de un presidente de la junta;----------

2)preparación y certificación de un registro electoral;----------

3) aprobación de la agenda;----------

4) elección de una o dos personas que certificarán los minutos de duración de la junta;----------

5) determinación sobre si la junta se convocó debidamente;-------

6) entrega de un informe anual e informe de los auditores y el informe anual consolidado de los auditores del grupo;----------

7) resolución con respecto a:----------

a) adopción de cuentas de pérdidas y ganancias y balance y cuentas de pérdidas y ganancias consolidados y balance consolidado;----------

b) distribución de pérdidas y ganancias de la Empresa de acuerdo con el balance adoptado;----------

c) liberación de responsabilidad de los miembros de la Junta Directiva y del director gerente;----------

8) determinación del número de miembros de la Junta Directiva y miembros alternativos;----------

9)determinación de aranceles para la Junta Directiva y los auditores;----------

10) elección de los miembros de la Junta Directiva y miembros alternativos;----------

11) cuando corresponda, elección de auditores y auditores alternativos;----------

12) resoluciones con respecto a los asuntos que se prescriben en el Acta Corporativa o Artículos de Asociación de la Empresa.-----

9. Se deberá notificar a los accionistas sobre reuniones generales de dichos accionistas ya sea mediante cartas enviadas por servicio postal público o mediante publicación en Post-och Inrikes Tidningar y Dagens Nyheter.----------

10. El año financiero de la Empresa será el año calendario.-----

ES TRADUCCIÓN FIEL AL ESPAÑOL DE LA PARTE PERTINENTE REDACTADA EN INGLES DEL DOCUMENTO ORIGINAL REDACTADO EN INGLES Y OTRO QUE HE TENIDO A LA VISTA Y AL CUAL ME REMITO EN LA CIUDAD DE BUENOS AIRES, A LOS VEINTE DEL MES DE MARZO DE 2008.----------

02 JUL. 2008

ALEJANDRA AZCÁRATE
TRADUCTORA PÚBLICA
INGLÉS
Mat. Tº XV Fº 408 Cap. Fed.
Inscripción C.T.P.C.B.A. Nº 5575

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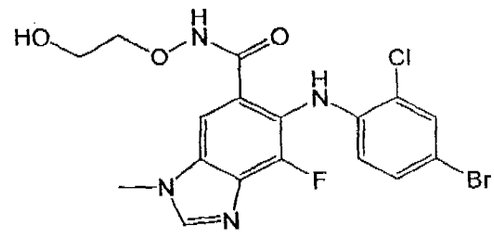

(I)

(57) Abstract: The present invention relates to Compound I hydrogen sulfate salt and solvates, crystalline forms and amorphous forms thereof, and to processes for their preparation.

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NOVEL HYDROGEN SULFATE SALT

BACKGROUND OF THE INVENTION

[0001] **Related Application**

[0002] The present application claims priority of U.S. Provisional Application Serial No. 60/752,781 filed December 21, 2005, which is incorporated herein in its entirety by this reference.

[0003] **Field of the Invention**

[0004] The present invention relates to a novel salt and, more particularly, to a novel salt of 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide (hereinafter referred to as "Compound 1"), which is a MEK inhibitor that is useful in the treatment and/or prophylaxis of proliferative disease states, such as cancer, in a mammal. More specifically, the present invention relates to a hydrogen sulfate salt of Compound 1 and to processes for the preparation of said salt. Also provided are pharmaceutical compositions containing a hydrogen sulfate salt of Compound 1, and the use of the salt in the manufacture of medicaments for treatment and/or prophylaxis of proliferative disease states, such as cancer, in the human or animal body, and methods of treating proliferative disease states, such as cancer, in a mammal by administering a therapeutically effective amount of a hydrogen sulfate salt of Compound 1.

[0005] **Description of the state of the art**

[0006] Cell signaling through growth factor receptors and protein kinases is an important regulator of cell growth, proliferation and differentiation. In normal cell growth, growth factors, through receptor activation (i.e., PDGF or EGF and others), activate MAP kinase pathways. One of the most important and most well understood MAP kinase pathways involved in normal and uncontrolled cell growth is the Ras/Raf kinase pathway. Active GTP-bound Ras results in the activation and indirect phosphorylation of Raf kinase. Raf then phosphorylates MEK1 and 2 on two serine residues (S218 and S222 for MEK1 and S222 and S226 for MEK2) (Ahn et al., *Methods in Enzymology*, 2001, **332**:417-431). Activated MEK then phosphorylates its only known substrates, the MAP kinases ERK1 and 2. ERK phosphorylation by MEK occurs on Y204 and T202 for ERK1 and Y185 and T183 for ERK2 (Ahn et al., *Methods in Enzymology* 2001, **332**:417-431). Phosphorylated ERK dimerizes and

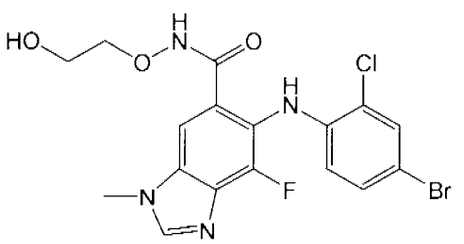
then translocates to the nucleus where it accumulates (Khokhlatchev et al., *Cell* 1998, **93**:605-615). In the nucleus, ERK is involved in several important cellular functions, including but not limited to nuclear transport, signal transduction, DNA repair, nucleosome assembly and translocation, and mRNA processing and translation (Ahn et al., *Molecular Cell*, 2000, **6**:1343-1354). Overall, treatment of cells with growth factors leads to the activation of ERK1 and 2 which results in proliferation and, in some cases, differentiation (Lewis et al., *Adv. Cancer Res.* 1998, **74**: 49-139).

[0007] In proliferative diseases, genetic mutations and/or overexpression of the growth factor receptors, downstream signaling proteins, or protein kinases involved in the ERK kinase pathway lead to uncontrolled cell proliferation and, eventually, tumor formation. For example, some cancers contain mutations which result in the continuous activation of this pathway due to continuous production of growth factors. Other mutations can lead to defects in the deactivation of the activated GTP-bound Ras complex, again resulting in activation of the MAP kinase pathway. Mutated, oncogenic forms of Ras are found in *50%* of colon and >90% pancreatic cancers as well as many others types of cancers (Kohl et al., *Science*, 1993, **260**:1834-1837). Recently, bRaf mutations have been identified in more than 60% of malignant melanoma (Davies, H., et al., *Nature* 2002, **417**:949-954). These mutations in bRaf result in a constitutively active MAP kinase cascade. Studies of primary tumor samples and cell lines have also shown constitutive or overactivation of the MAP kinase pathway in cancers of pancreas, colon, lung, ovary and kidney (Hoshino, R., et al., *Oncogene* 1999, **18**:813-822). Hence, there is a strong correlation between cancers and an overactive MAP kinase pathway resulting from genetic mutations.

[0008] As constitutive or overactivation of MAP kinase cascade plays a pivotal role in cell proliferation and differentiation, inhibition of this pathway is believed to be beneficial in hyperproliferative diseases. MEK is a key player in this pathway as it is downstream of Ras and Raf. Additionally, it is an attractive therapeutic target because the only known substrates for MEK phosphorylation are the MAP kinases, ERK1 and 2. Inhibition of MEK has been shown to have potential therapeutic benefit in several studies. For example, small molecule MEK inhibitors have been shown to inhibit human tumor growth in nude mouse xenografts, (Sebolt-Leopold et al., *Nature-Medicine* 1999, **5(7)**:810-816; Trachet et al., AACR April 6-10, 2002, Poster #5426; Tecle, H., IBC 2nd International Conference of Protein Kinases, September 9-10, 2002), block static allodynia in animals (WO 01/05390) and inhibit growth of acute myeloid leukemia cells (Milella et al., *J. Clin. Invest.* 2001, **108 (6)**:851-859).

[0009] Small molecule inhibitors of MEK have been disclosed. At least thirteen patent applications have appeared in the last several years: US 5,525,625; WO 98/43960; WO 99/01421; WO 99/01426; WO 00/41505; WO 00/42002; WO 00/42003; WO 00/41994; WO 00/42022; WO 00/42029; WO 00/68201; WO 01/68619; and WO 02/06213.

[0010] Inhibitors of the MEK are also described in WO 03/077914. 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide, or "Compound 1", is exemplified in WO 03/077914 and possesses the following structural formula:



Compound 1

[0011] Compound 1 has been shown to possess inhibitory activity against MEK and therefore to be useful in the treatment of a hyperproliferative disease such as cancer.

[0012] WO 03/077914 discloses, in general terms, certain pharmaceutically acceptable salts of the compounds disclosed therein. Specifically, it is stated in WO 03/077914 that pharmaceutically acceptable salts of the compounds disclosed therein that possess a sufficiently basic moiety may form acid addition salts containing pharmaceutically acceptable anions, and a range of such anions are listed. Similarly, suitable salts of the compounds possessing an acidic moiety are to be formed by treatment of a compound with a basic compound and particularly an inorganic base.

[0013] The form of a pharmaceutically active compound which is used in medicaments is suitably one that provides for reasonable handling properties, which allow it to be processed and formulated. However, it is also necessary to ensure that the biological properties of the final formulation, such as dissolution rate of tablets and bioavailability of active ingredient are optimized, and there is frequently compromises to be made in selecting a particular form which best fulfils all these various requirements. However, in some cases, salts do not form easily and/or are not stable, which is probably due to low pKa values. The pKa value expresses the strength of acids and base, i.e., the tendency for an acid to lose a

proton or a base to add a proton (Bronsted J.N., *Rec. Trav. Chim.* (1923) **47**:718). This is particularly true for Compound 1.

SUMMARY OF THE INVENTION

[0014] The present invention provides a hydrogen sulfate salt (1:1 drug:H_2SO_4) of Compound 1 and various forms thereof, all of which are included within the scope of the invention. The salt may be in various forms, all of which are included within the scope of the invention. These forms include anhydrous forms as well as solvates. A further form may be produced by desolvating solvates. In a particular embodiment the salt is in the anhydrous form.

[0015] In a further aspect the present invention provides a method of using a hydrogen sulfate salt of Compound 1 as a medicament to treat a hyperproliferative disease or condition.

[0016] An additional aspect of the invention is the use of a hydrogen sulfate salt of Compound 1 in the preparation of a medicament for the treatment or prevention of a hyperproliferative disease or condition.

[0017] Additional advantages and novel features of this invention shall be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the invention. The advantages of the invention may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0018] The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate non-limiting embodiments of this invention, and together with the description, serve to explain the principles of the invention.

In the Figures:

[0019] Figure 1 shows the XRPD of the hydrogen sulfate salt of Compound 1:

[0020] Figure 2 shows the infrared spectrum of the hydrogen sulfate salt of Compound 1 obtained using the DRIFTS sampling technique; and

[0021] Figure 3 shows the results of plasma concentration levels of Compound 1 following administration of 150 mg free base equivalent oral dispersion doses of Compound 1 (×) and the hydrogen sulfate salt to fasted dogs (▲).

DETAILED DESCRIPTION

[0022] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0023] The present invention provides a hydrogen sulfate salt (1:1 drug to H_2SO_4) of Compound 1 and various forms thereof, all of which are included within the scope of the invention. The salt may be in various forms, all of which are included within the scope of the invention. These forms include anhydrous forms as well as solvates. A further form may be produced by desolvating solvates. In a particular embodiment, the salt is anhydrous hydrogen sulfate salt of Compound 1. Further, the present invention provides a hydrogen sulfate salt form of Compound 1 which shows unique physical and pharmaceutical properties that make it particularly suitable for use in medicaments.

[0024] In certain embodiments, salts of Compound 1 are crystalline. The crystalline salts have been found to be better than the free base in terms in their handling properties from a manufacturing point of view, in particular their static and flow properties. The formation of salts may provide a means of purification, as process impurities can be separated and salts are generally easier to isolate than the free base.

[0025] In one embodiment of the invention the hydrogen sulfate salt of Compound 1 is a crystalline salt, which has surprisingly been found to possess improved pharmaceutical properties when compared to the free base of Compound 1 and certain other salt forms of Compound 1. In particular, the dissolution rate of this crystalline salt, as well as its bioavailability has been found to be particularly high as compared to the free base and other salts, as illustrated in the examples hereinafter. The enhanced bioavailability of the hydrogen sulfate salt of Compound 1 over the free base has been shown to be independent of the formulation used for administration. The bioavailability of the free base and hydrogen sulfate

forms have been compared herein when dosed in the same dispersion formulations, but similar differences in bioavailability were also observed for simple tablet formulations.

[0026] When it is stated that the present invention relates to a salt of Compound 1 which is a crystalline salt the degree of crystallinity is conveniently greater than about 60%, more conveniently greater than about 80%, preferably greater than about 90% and more preferably greater than about 95%. Most preferably the degree of crystallinity is greater than about 98%.

[0027] The extent of enhanced bioavailability offered by the hydrogen sulfate salt is surprising and is particularly useful, since the free base of Compound 1 has been classified as a BCS Class 4 compound. BCS Class 4 compounds normally have low bioavailability due to both low dissolution rate and permeability, and the limitation of permeability on absorption means that such salts would not usually be expected exert a substantial impact on absorption (See for example: Dressman et al. (2001) *Pharm Tech.* July: 68).

[0028] Suitable solvates of the hydrogen sulfate salt of Compound 1 are formed from a wide range of solvents, in particular organic solvents such as tetrahydrofuran (THF), acetonitrile (ACN), ethanol (EtOH) and methanol (MeOH). Suitable organic solvents include esters such as C_{1-6} alkyl esters, for example ethyl acetate, and ketones such as C_{1-6} alkyl ketones, for example methyl ethyl ketone (2-butanone).

[0029] Preparation of the salt can be effected by reacting a slurry of Compound 1 in an organic solvent and water with sulfuric acid. For preparation of a 1:1 salt approximately 1 equivalent of sulfuric acid is used. Thus in a further aspect, the invention provides a method for preparing a hydrogen sulfate salt of Compound 1, said method comprising:

[0030] (i) reacting a slurry of Compound 1 in an organic liquid and water with approximately 1 equivalent of sulfuric acid;

[0031] (ii) recovering the salt from the resultant solution; and

[0032] (iii) thereafter, if desired or necessary, forming a solvate thereof.

[0033] The mole ratio of the amount of sulfuric acid to Compound 1 is suitably in the range of from 1.00:1 to 2:1, for example in a range from 1.05:1 to 1.15:1. The sulfuric acid used is suitably in the form of concentrated sulfuric acid. In a particularly embodiment, the mole ratio of sulfuric acid to Compound 1 is 1.10:1.0.

[0034] Suitably the amount of water added in step (i) is restricted to that necessary to ensure that the salt is formed. The precise amounts used will depend upon the particular nature of the solvent, the concentration of the sulfuric acid etc., but typically, the water will be present in an amount of less than 20% v/v of the total liquid present, for example from 13-

17% v/v.

[0035] In a particular embodiment, the organic solvent used in step (i) is 2-butanone (methyl ethyl ketone), water is approximately 15% of the liquid volume, and the total amount of liquid used relative to Compound 1 is approximately 8 mL per gram of Compound 1.

[0036] Suitably, addition of sulfuric acid in step (i) is carried out in a controlled manner, for example at a temperature below 10 °C, and the remainder of step (i) is then carried out at elevated temperature, for example from 30-90 °C, as a further example in a range between 55-75 °C, and as a further example at about 65 °C.

[0037] Suitable organic liquids include organic solvents in which Compound 1 and its salts are sparingly soluble. As used herein, the expression "sparingly soluble" means having a solubility less than 100 mL of solvent per gram of solute, for example between 30 and 100 mL of solvent per gram of solute. These solvents include alkyl ketones, for example C_{1-6} alkyl ketones such as 2-butanone, alcohols such as C_{1-6} alcohols, for example methanol or ethanol, and esters such as C_{1-6} alkyl esters, for example as ethyl acetate. In one embodiment, the organic solvent is methyl ethyl ketone (2-butanone).

[0038] Suitably, the reaction mixture is filtered between steps (i) and (ii) to remove any extraneous material. The residue is optionally washed, for example with a mixture of the organic liquid and water, and the desired salt crystallized from the filtrate, which may optionally be combined with the wash solution.

[0039] In certain embodiments, the hydrogen sulfate salt is recovered in step (ii) by cooling the reaction mixture, optionally with the addition of further organic liquid, so that the hydrogen sulfate salt is precipitated. The further organic liquid may be the same organic liquid as used in step (i), or it may be a different organic liquid, provided this acts as an anti-solvent for the hydrogen sulfate salt of Compound 1. Seeding of the solution with crystals of the hydrogen sulfate salt of Compound 1 may assist in the precipitation process.

[0040] In one embodiment, prior to cooling, the filtrate is first subjected to a distillation step to remove water and to ensure that the salt is recovered in an acceptable yield. In a particular embodiment the solvent is 2-butanone and the filtrate is distilled at atmospheric pressure.

[0041] On cooling, the salt can be recovered from the resultant slurry for example by filtration. The recovered material may then be dried for example at elevated temperature, for example of from 40-60 °C, and as another example at about 50°C, until constant weight is achieved. If the product is a solvate with the organic liquid such as methanol, it may be de-

solvated if desired at this time by heating.

[0042] The physical properties of the hydrogen sulfate salt were investigated and are described further in the Examples.

[0043] The invention also includes isotopically-labeled compounds, which are identical to those recited in the present invention, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. The hydrogen sulfate salt of Compound 1 and polymorphs thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and carbon-14, i.e., ^{14}C, isotopes are particularly widely used as a result of their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be utilized in some particular circumstances. Isotopically labeled salts of the present invention can generally be prepared by carrying out procedures disclosed in WO 03/077914 by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent during the preparation, or if desired, using an isotopically labeled sulfuric acid in the preparation of the salt.

[0044] The composition may be in a form suitable for oral administration (for example as tablets, lozenges, hard or soft capsules, emulsions, dispersible powders or granules, syrups, elixirs or oily or extemporaneously prepared aqueous suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder), for parenteral injection (for example as a sterile solution, suspension or emulsion for intravenous, subcutaneous, intramuscular, intravascular or infusion dosing), for topical administration (for example as creams, ointments, gels, oily solutions or suspensions or extemporaneously prepared aqueous suspensions), or for rectal administration (for example as a suppository). In one embodiment, the hydrogen sulfate salt of Compound 1 is administered orally. In general the above compositions may be prepared in a conventional manner using

conventional excipients.

[0045] The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.01 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.7 to 7000 mg/day, preferably about 70 to about 2500 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day. A unit dosage form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient, and preferably 5-420 mg of active ingredient. Preferably a daily dose in the range of 0.03-6 mg/kg is employed.

[0046] According to a further aspect of the present invention there is provided a hydrogen sulfate salt of Compound 1 as defined herein for use in a method of treatment or prophylaxis of the human or animal body by therapy. A further feature of the present invention is hydrogen sulfate salt of Compound 1 as defined herein for use as a medicament. In a further aspect, the present invention provides hydrogen sulfate salt of Compound as defined herein for use as a medicament for the treatment of disease states mediated through MEK, in particular proliferative disorders, or abnormal cell growth, such as cancer, in a warm-blooded mammal such as a human. Accordingly, a further aspect of the invention provides the use of hydrogen sulfate salt of Compound 1 as defined herein in the manufacture of a medicament for use in the treatment of disease states mediated through the MEK, in particular proliferative disorders, or abnormal cell growth, such as cancer, in a warm-blooded mammal such as a human.

[0047] According to a further feature of the invention there is provided a method for treating disease states mediated through the MEK, in particular proliferative disorders, or abnormal cell growth, such as cancer, in a warm-blooded mammal, such as a human, in need of such treatment which comprises administering to said mammal an effective amount of an hydrogen sulfate salt of Compound 1 hydrogen sulfate salt as herein, or a pharmaceutical composition as defined herein.

[0048] Particular examples of proliferative disorders, which may be treated using the salts or compositions of the invention, include hyperproliferative disorders in a mammal. Particular cancers are brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head,

neck, renal, kidney, ovarian, prostate, colorectal, esophageal, testicular, gynecological or thyroid cancer.

[0049] However, the compounds and compositions of the invention may also be used in the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

[0050] Other examples of MEK mediated diseases, which may be treated using the compounds, or compositions of the invention include pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) or the treatment of pain in a mammal.

[0051] The compounds and compositions may also be used for the prevention of blastocyte implantation in a mammal, or for treating a disease related to vasculogenesis or angiogenesis in a mammal. Such diseases may include tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[0052] The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application and refer to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes, for example, the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or over expression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

[0053] The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

[0054] Thus patients that can be treated with compounds or compositions of the present invention include, for example, patients that have been diagnosed as having psoriasis, restenosis, atherosclerosis, BPH, lung cancer, non small cell lung cancer, bone cancer,

CMML, pancreatic cancer, colorectal, skin cancer, cancer of the head and neck, melanoma (in particular cutaneous or intraocular melanoma), uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, testicular, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), ovarian cancer, multiple myeloma, hepatocellular carcinoma, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, in particular acute myeloid leukaemia solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

[0055] The hydrogen sulfate salt of Compound 1 may be applied as a sole therapy or may involve, in addition to the hydrogen sulfate salt of Compound 1, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to Compound 1 hydrogen sulfate salt may be surgery, radiotherapy or chemotherapy. Such chemotherapy may cover categories of therapeutic agent such as:

[0056] (i) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by different mechanisms from those defined herein (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxin, thalidomide, MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-

metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors), and

[0057] (ii) vascular targeting agents (for example combretastatin phosphate and compounds disclosed in WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213, and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166, (for example N-acetylcolchinol-O-phosphate));

[0058] (iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, and exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, and cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, leuprorelin, and buserelin), inhibitors of 5α-reductase (for example finasteride);

[0059] (iv) anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanese;

[0060] (v) inhibitors of growth factor function (such growth factors include for example platelet derived growth factor and hepatocyte growth factor), such inhibitors include growth factor antibodies, growth factor receptor antibodies, (for example the anti-erbb2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [C225]), and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005. Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors such as inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)- quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy) quinazolin-4-amine (CI 1033)) and erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529,

VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

[0061] (vi) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates such as methotrexate, fluoropyrimidines such as 5-fluorouracil, tegafur, purine and adenosine analogues, and cytosine arabinoside, hydroxyurea or, for example, one of the anti-metabolites specifically disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino-2-thenoyl)-L-glutamic acid;; antitumour antibiotics (for example anthracyclines such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, and mithramycin); platinum derivatives (for example cisplatin, and carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, and thiotepa); antimitotic agents (for example vinca alkaloids such as vincristine, vinblastine, vindesine, and vinorelbine, and taxoids such as taxol and taxotere); topoisomerase inhibitors (for example epipodophyllotoxins such as etoposide and teniposide, amsacrine, topotecan, camptothecin and irinotecan); enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);

[0062] and additional types of chemotherapeutic agent including:

[0063] (vii) biological response modifiers (for example interferon);

[0064] (viii) antibodies (for example edrecolomab);

[0065] (ix) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

[0066] (x) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

[0067] (xi) immunotherapy approaches, including for example *ex-vivo* and *in vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0068] For example, a hydrogen sulfate salt of Compound I may be used in

conjunction with an effective amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

[0069] In a particular embodiment, anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a Compound 1 hydrogen sulfate salt of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloprotienase inhibitors are described in WO 96/33172, WO 96/27583, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, U.S. Patent 5,863,949, and U.S. Patent 5,861,510, all of which are incorporated herein in their entireties by reference. Suitable MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. In particular, those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e., MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13) are used. Particular examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.

[0070] Therefore, a further aspect of the present invention the hydrogen sulphate salt of Compound 1 in combination with any one of the anti tumour agents listed under (i) – (xi) herein above. A further aspect of the present invention provides the hydrogen sulphate salt of Compound 1 in combination with one or more of the anti tumour agents listed under (i) – (xi) herein above. A further aspect of the present invention provides the hydrogen sulphate salt of Compound 1 in combination with any one of the classes of anti-tumour agents listed under (i) (xi) herein above.

[0071] Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[0072] According to a further aspect of the present invention there is provided a kit comprising the hydrogen sulphate salt of Compound 1 in combination with an anti-tumour agent selected from one listed under (i) – (xi) herein above.

[0073] According to a further aspect of the present invention there is provided a kit comprising:

a) the hydrogen sulphate salt of Compound 1 in a first unit dosage form:

b) an anti-tumour agent selected from one listed under (i) - (xi) herein above: in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

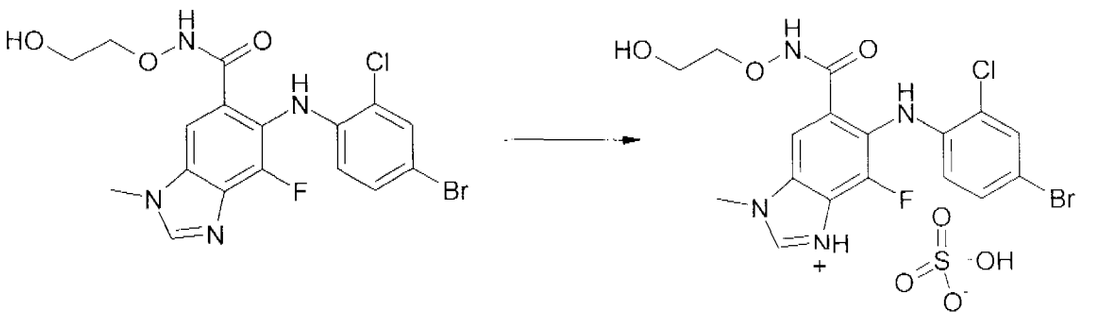
[0074] Compound 1 has been found to have activity in the following assay. N-terminal 6 His-tagged, constitutively active MEK1 (2-393) is expressed in *E. coli* and protein is purified by conventional methods (Ahn et al., *Science* 1994, 265:966-970). The activity of MEK1 is assessed by measuring the incorporation of γ-^{33}P-phosphate from γ-^{33}P-ATP onto N-terminal His tagged ERK2, which is expressed in *E. coli* and is purified by conventional methods, in the presence of MEK1. The assay is carried out in 96-well polypropylene plate. The incubation mixture (100 µL) comprises of 25 mM Hepes, pH 7.4, 10 mM $MgCl_2$, 5 mM β-glycerolphosphate, 100 µM sodium orthovanadate, 5 mM DTT, 5 nM MEK1, and 1 µM ERK2. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1% DMSO. Reactions are initiated by the addition of 10 µM ATP (with 0.5 µCi γ-^{33}P-ATP/well) and incubated at ambient temperature for 45 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP washed off using a Tomtec MACH III harvestor. Plates are allowed to air-dry prior to adding 30 µL/well of Packard Microscint 20, and plates are counted using a Packard TopCount. In this assay, Compound 1 exhibited an IC_{50} of less than 50 micromolar.

EXAMPLES

[0075] In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Yields are given for the Examples as performed and could likely be enhanced through further development. The ^{1}H NMR spectrum (400 MHz) was referenced to TMS (0.00 ppm), ^{13}C NMR spectrum (100 MHz) was referenced to the NMR solvent (39.5 ppm) and the ^{19}F NMR spectrum was referenced to trichlorofluoromethane (0.00 ppm). FTIR spectra were obtained on a Nicolet Magna 860 ESP FTIR Spectrometer in various ways including from a 2% w/w dispersion of this material in powdered KBr, using the DRIFTS sampling technique, over the 4,000 – 400 cm^{-1} mid-infrared spectral region.

Example 1

Preparation of the Hydrogen sulfate salt of Compound 1



[0076] To a stirred suspension of 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide (100 g, 0.206 mol) (obtainable as described in Example 10 of WO 03/077914, which is incorporated herein by reference and as described below) in 2-butanone (680 mL) and water (115 mL) at 0-5 °C was added sulfuric acid (12.3 mL, 0.226 mol) followed by water (5 mL) maintaining a temperature of 10 °C or lower. The stirred mixture was heated to 65 °C and held for 30 minutes before filtering to remove any extraneous matter. The filter was washed with a mixture of 2-butanone (85 mL) and water (15 mL). The combined filtrates were heated to 72 °C before adding 2-butanone (500 mL) maintaining a temperature of between 60-72 °C. The resulting mixture was distilled at atmospheric pressure (approximate distillation temperature 73-74°C) until 500 mL of distillate had been collected.

[0077] A second aliquot of 2-butanone (500 mL) was added, maintaining the temperature of the mixture above 70 °C. The resulting mixture was distilled again until 250 mL of distillate had collected. The mixture was cooled to 0-5 °C over approximately 1 hour. The resulting slurry was filtered, washed with 2-butanone (240 mL) and dried under reduced pressure at 50 °C, until a constant weight was achieved, to give 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide hydrogen sulfate (103.5 g, 0.186 mol, 90% yield) as an off white crystalline solid. ^{1}H NMR (400 MHz, D_6 DMSO) δ 3.58 (2H, t, CH_2OH), 3.89 (2H, t, CH_2ON), 3.99 (3H, s, CH_3), 6.47 (1H, dd, ArH), 7.29 (1H, dd, ArH), 7.63 (1H, d, ArH), 7.91 (1H, s, ArH), 7.96 (3H, br, ROH, NH, SOH), 8.10 (1H, br, ArNH), 8.94 (1H, s, NCHN), 11.79 (1H, s, ONH). ^{13}C NMR (100 MHz, D_6 DMSO) δ 32.1 (CH_3), 58.5 (CH_2OH), 77.3 (CH_2ON), 108.2 (CH), 109.6 (CBr), 115.8 (CH), 120.6 (CCl), 122.0 (C), 125.0 (CC=O), 129.4 (C), 130.5 (CH), 131.1 (CH), 132.3 (C), 140.6 (C), 145.8 (CF), 146.5 (CH), 164.2 (C=O).

|0078| The results of the infrared analysis are shown in Figure 2. Spectral assignments are summarized in Table 1.

Table 1

Wavenumber (cm^{-1})	Assignment
3,255	Includes the O-H stretching vibration of the primary alcohol group and the N-H stretching vibrations of the secondary aromatic amine and secondary amide groups.
3,200 - 2,700	Includes =C-H stretching vibrations of the aromatic ring and benzimidazole group and the aliphatic C-H stretching vibrations.
2,700 - 2,300	Includes the multiple NH^+ stretching vibrations of the benzimidazole 1:1 sulfate salt group.
1,673	C=O stretching vibrations of the secondary amide group where
1,653	the carbonyl group is subject to different environmental effects such as hydrogen bonding.
1,640 - 1,370	Includes the C=C aromatic ring stretching vibrations, the C -C and C=N stretching vibrations of the benzimidazole group, the O-H deformation vibration of the primary alcohol group and the aliphatic C-H deformation vibrations.
1,570	The CNH combination band of the secondary amide group.
1,506	Includes the CNH bending vibration of the secondary aromatic amine group.
1,213	The aryl C-F stretching vibration.
1,189	The asymmetric SO_3^- stretching vibration of the benzimidazole 1:1 sulfate salt group.
1,100 - 1,000	Includes the C-O stretching vibration of the primary alcohol group and the aryl C-Br stretching vibration.
1,011	The symmetric SO_3^- stretching vibration of the benzimidazole 1:1 sulfate salt group.
920 - 600	Includes the C-H wag vibrations and C=C ring bending vibrations of the 1,2,4-trisubtituted aromatic ring and the benzimidazole group.
888	Includes the S-O(H) stretching vibration of the benzimidazole 1:1 sulfate salt group.

Example 1A

Preparation of the Hydrogen sulphate salt of Compound 1

[0079] Sulfuric acid (1.52 ml, 27.86 mmol) was added to a stirred suspension of 6-(4-bromo-2-chlorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide (10 g, 0.0214 mol) (obtainable as described in Example 10 of WO 03/077914, which is incorporated herein by reference and as described below) in tetrahydrofuran (THF) (62 ml) and water (8 ml) whilst maintaining a temperature of 10 °C or lower. The stirred mixture was heated to 65 °C and held for 30 minutes before filtering to remove any extraneous matter. THF (150 ml) was then added to the mixture maintaining the temperature above 60 °C. The mixture was then cooled to 0-5 °C over approximately 2 hour. The resulting slurry was filtered, washed with THF (30 ml) and dried under reduced pressure at 50 °C until a constant weight was achieved, to give 6-(4-bromo-2-chlorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide hydrogen sulfate (9.81g, 0.17 mol, 82% yield) as an off white crystalline solid. The material was the same as that produced in Example 1 above.

Example 1B

Preparation of 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethoxy)-amide

[0080] Step A: 2,3,4-Trifluoro-5-nitro-benzoic acid: A 3 litre three neck round bottom flask was charged with 125 ml H_2SO_4. Fuming nitric acid was added (8.4 ml, 199 mmol) and the mixture gently stirred. 2,3,4-Trifluorobenzoic acid (25 g, 142 mmol) was added in 5 g portions over 90 minutes. The dark brownish yellow solution was stirred for 60 minutes at which time the reaction was complete. The reaction mixture was poured into 1 litre of an ice:water mixture and extracted with diethyl ether (3 x 600 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow solid. The solid was suspended in hexanes and stirred for 30 min after which time it was filtered to give 29 g (92%) of clean desired product as an off-yellow solid: MS APCI (-) *m/z* 220 (M-1) detected.

[0081] Step B: 4-Amino-2,3-difluoro-5-nitro-benzoic acid: Ammonium hydroxide solution (~30% in water) (35 ml, 271 mmol) was added to a solution of 2,3,4-trifluoro-5-nitro-benzoic acid (15 g, 67.8 mmol) in 30 ml water at 0 °C with stirring. Upon completion of the ammonium hydroxide addition, the reaction mixture was warmed to room temperature with stirring. After 2.5 hours, the reaction mixture was cooled to 0 °C and concentrated HCl was carefully added until pH of reaction mixture was 0. The reaction mixture was diluted

with water (30 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 14 g (95%) of pure desired product: MS APCI (-) *m/z* 217 (M-1) detected.

[0082] Step C: 4-amino-2,3-difluoro-5-nitrobenzoic acid methyl ester: A 2 M solution of tetramethylsilane (TMS) diazomethane in hexanes (6.88 ml, 13.75 mmol) was added to a suspension of 4-amino-2,3-difluoro-5-nitrobenzoic acid (2.00 g, 9.17 mmol) in 25 ml of 4:1 Tetrahydrofuran (THF):MeOH at 0 °C under nitrogen atmosphere. Upon completion of addition, reaction mixture was warmed to room temperature. After 0.5 hours, excess TMS diazomethane was destroyed by the careful addition of acetic acid. The reaction was then concentrated under reduced pressure and dried *in vacuo* 1.95 g (92%) of pure desired product: MS APCI (-) *m/z* 231 (M-1) detected.

[0083] Step D: 4-Amino-3-fluoro-5-nitro-2-phenylamino-benzoic acid methyl ester: 4-Amino-2,3-difluoro-5-nitrobenzoic acid methyl ester (23.48 g, 101.1 mmol) was suspended in xylenes (125 ml) and aniline (92 ml, 1011 mmol) was added. The reaction mixture was stirred at 125 °C for 16 hours under N_2. The reaction mixture was cooled to room temperature and solids precipitated out of solution. The solids were collected by filtration and washed with xylenes and then diethyl ether. Recovered 22.22 g (72.78 mmol) of yellow solid which was pure desired product. The filtrate was concentrated under reduced pressure, redissolved in methylene chloride and flushed through a plug of silica gel eluting with methylene chloride. The desired fractions were concentrated under reduced pressure to give a brown solid which was triturated with diethyl ether to give 5.47 g (17.91 mmol) of yellow solid which was pure desired product. Combined product yield was 27.69 g (90%). MS APCI (-) *m/z* 304 (M-1) detected.

[0084] Step E: 7-Fluoro-6-phenylamino-3H-benzoimidazole-5-carboxylic acid methyl ester: 4-Amino-3-fluoro-5-nitro-2-phenylamino-benzoic acid methyl ester (16.70 g, 54.71 mmol), formic acid (250 ml, 6.63 mol) and 20% $Pd(OH)_2/C$ (9.00 g, 16.91 mmol) in ethanol (250 mL) were stirred at 40 °C for two hours under N_2 and then at 95 °C for 16 hours. The reaction mixture was cooled to room temperature and filtered through Celite rinsing with ethyl acetate. The filtrate was concentrated under reduced pressure to give a yellow solid. The solid was triturated with diethyl ether to give 13.47 g (86%) of the desired product as a tan solid. MS APCI (+) *M/Z* 286 (M+1) detected; MS APCI (-) *m/z 284* (M-1) detected.

[0085] Step F: 6-(4-Bromo-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester: 7-Fluoro-6-phenylamino-3*H*-benzoimidazole-5-carboxylic acid methyl ester (4.99 g, 17.51 mmol) was dissolved in *N,N*-dimethylformamide (275 ml). N-

bromosuccinimide (3.15 g, 17.70 mmol) was added as a solid and the reaction mixture was stirred at room temperature under N_2. After 30 minutes, the reaction mixture was quenched by the addition of aqueous saturated sodium bisulfite solution. The reaction mixture was then poured into a separatory funnel, diluted with water and ethyl acetate and the layers separated. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed three times with water, once with brine and then dried (Na_2SO_4) and concentrated under reduced pressure to yield 6.38 g (100%) of the pure desired product as a tan solid. MS ESI (+) *m/z* 364, 366 (M+ Br pattern) detected.

[0086] Step G: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester: 6-(4-Bromo-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboyxlic acid methyl ester (6.38 g, 17.51 mmol), was dissolved in N,N-dimethylformamide (275 mL). N-chlorosuccinimide (2.36 g, 17.70 mmol) was added as a solid and the reaction mixture was stirred at room temperature under N_2 until the reaction is complete (5-6 days). The reaction mixture was quenched by the addition of aqueous saturated sodium bisulfite solution to give a suspension. The resulting solids were collected by filtration, washed with water and diethyl ether and dried under reduced pressure to yield 6.07 g (87%) of the pure desired product as a beige solid. MS ESI (+) *m/z* 398, 400 (M+ Br pattern) detected.

[0087] Step H: 6-(4-Bromo-2-chlorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid methyl ester and 6-(4-Bromo-2-chlorophenylamino)-7-fluoro-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester: A solution of 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3H-benzoimidazole-5-carboxylic acid methyl ester (150 mg, 0.38 mmol), iodomethane (28 µL, 0.45 mmol) and potassium carbonate (78 mg, 0.56 mmol) in dimethylformamide (1.5 mL) was stirred at 75°C for one hour. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous potassium carbonate (2x), brine and dried (Na_2SO_4). Flash column chromatography (20:1 methylene chloride/ethyl acetate) provided 56 mg (36%) of the more mobile 6-(4-bromo-2-chlorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid methyl ester as a white solid. ^{19}F NMR (376 MHz, CD_3OD) - 133.5(s). MS APCI (+) *m/z* 412, 414 (M+, Br pattern) detected. Also isolated is 54 mg (35%) of 6-4(-bromo-2-chloro-phenylamino)-7-fluoro-1-methyl-1H-benzoimidazole-5- carboxylic acid methyl ester as a white solid. ^{19}F NMR (376 MHz, CD_3OD) – 139.9 (s). MS APCI(+) *m/z* 412, 414 (M+, Br pattern) detected.

[0088] Step I: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-

benzoimidazole-5-carboxylic acid: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid methyl ester (56 mg, 0.14 mmol) was dissolved into 2:1 THF/water (3 mL) and NaOH (0.55 ml, 1.0 M aqueous solution, 0.55 mmol) was added. After stirring for two hours the reaction was reduced to one quarter initial volume via rotary evaporation and the remainder diluted to 50 ml with water. The aqueous solution was acidified to pH 2 by the addition of 1.0 M aqueous HCl and extracted with 1:1 tetrahydrofuran/ethyl acetate (3x), dried (Na_2SO_4) and concentrated under reduced pressure to provide 43 mg (79%) pure carboxylic acid as an off white solid. MS ESI (+) *m/z* 397, 398 (M+, Br pattern) detected.

[0089] Step J: 6-(4-Bromo-2 chloro-phenylamino-7-fluoro-3-methyl-3H-benzoimidazole-5-carboyxlic acid (2-vinyloxy-ethoxy)-amide: 6-(4-Bromo-2- chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2.00 g, 5.0 mmol), O-(2-vinloxy-ethyl)-hydroxylamine (0.776 g, 7.5 mmol), HOBt (0.88 g, 6.5 mmol), triethylamine (1.61 mL, 2.3 mmol) and EDCI (1.3 g, 6.5 mmol) were dissolved in dimethylformamide (52 mL), and stirred at room temperature for 48 hours. The reaction mixture was diluted with ethyl acetate, washed with water (3x), saturated potassium carbonate (2x), saturated ammonium chloride (2x), brine, dried (Na_2SO_4) and concentrated under reduced pressure to an off-white solid. Trituration of the solid with diethyl ether provided 2.18 g (90%) desired product as an off-white solid. MS ESI (=) *m/z* 483, 485 (M+ Br pattern) detected.

[0090] Step K: 6-(4-Bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboyxlic acid (2-hydroxy-ethoxy)-amide: Hydrochloric acid (14 mL, 1.0 M aqueous solution, 14 mmol) was added to a suspension of 6-(4-bromo-2-chloro-phenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboyxlic acid (2-vinyloxyethoxy)-amide (2.18 g, 4.50 mmol) in ethanol (50 mL) and the reaction mixture allowed to stir for 24 hours. The reaction mixture was concentrated to dryness by rotary evaporation and the solids partitioned between 3:1 ethyl acetate/tetrahydrofuran and saturated potassium carbonate. The aqueous phase was extracted with 3:1 ethyl acetate/tetrahydrofuran (3x), the combined organics dried (Na_2SO_4), and concentrated to provide 2.11 g (100%) 6-(4-bromo-2-chlorophenylamino)-7-fluoro-3-methyl-3H-benzoimidazole-5-carboxylic acid (2-hydroxyethoxy)-amide as an off-white solid. MS ESI (+) m/z 457, 459 (M+, Br pattern) detected. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.26 (s, 1H), 7.78 (s, 1H), 7.57 (d, 1H), 7.24 (dd, 1H), 6.40 (dd, 1H), 3.86 (s, 3H), 3.79 (m, 2H), 3.49 (m, 2H). ^{19}F NMR (376 MHz, MeOH-d_4)

-133.68 (s).

Example 2

Investigation of the physical properties of the hydrogen sulfate salt

[0091] The product of Example 1 was subject to the following tests to determine its physical properties.

[0092] Powder X-ray diffraction (PXRD)

[0093] All samples were run on a Bruker D5000 diffractometer. The X-ray powder diffraction spectra were determined by mounting a sample of the crystalline salt on Siemens single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 2 mm antiscatter slit and a 0.2 mm detector slit. The sample was exposed for 1 second per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 31 minutes and 41 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffract+ software.

[0094] Data were collected over the range 2-theta 2 - 40°, in increments of 2-theta 0.02° with 4s per increment and are categorized in Table 2, with relative intensities derived from diffractograms measured with fixed slits.

Table 2

% Relative Intensity	Definition
25-100	VS - Very Strong
10-25	S - Strong
3-10	M – Medium
1-3	W –Weak

[0095] The results of the scan are shown in Figure 1, where the upper grey line represents the XRPD of the hydrogen sulfate salt of Compound 1 and the lower black line represent the free form. The most intense peaks, starting with most intense, are given in Table 3. The peak at 24.59° is particularly strong.

Table 3

2 theta scale	Relative intensity
24.59	VS
20.97	VS
23.99	S
27.65	S
12.24	S
23.49	S
24.30	S
17.02	S
25.91	S
22.50	M

[0096] Persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values (see Jenkins, R. & Snyder, R.L., "Introduction to X-Ray Powder Diffractometry", John Wiley & Sons, 1996, for further information).

Example 3

In-vivo investigation: Study of salts versus free base in dispersed formulation

[0097] A study was performed in dogs to measure plasma levels of Compound 1 in fasted dogs following administration of 150 mg free base equivalent oral doses in 7.5 mL various dispersion formulations in pharmaceutically acceptable dispersing agents with Compound 1 contained as the free form or hydrogen sulfate salt.

[0098] Single doses of 150 mg were administered orally to fasted beagle dogs weighing 12-17 kg and about 2 to 6 years old on each of three dosing days. Each dosing day was 1 week apart.

[0099] All formulations were prepared extemporaneously just prior to dosing by adding 7.5 mL of the appropriate dispersing solution via a 10 mL disposable syringe, to vials containing 150 mg free base equivalents of the appropriate drug form, capping and vortex

mixing for 30 seconds to form a dispersion.

[00100] The dispersion was removed from the vial using the disposable syringe and dosed to the animal via a gavage tube positioned into the stomach. The vials were rinsed twice by adding, for each of the two rinses, a separate 15 mL aliquot of water (total rinse volume – 30 mL) via a 20 mL disposable syringe, capping, vortex mixing for 5 seconds, removing the wash solution from the vial using the disposable syringe and dosing to the animal via the gavage tube.

[00101] Dogs were fed about 400 g of Special Diet Services Laboratory Diet A each day and allowed water ad libitum. Whole blood (2 mL) in lithium heparin tubes were taken from the jugular vein immediately prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 hours. The blood was centrifuged at 3000 rpm for 15 minutes and plasma was removed into plain blood tubes and the plasma stored at -20°C until analysis.

[00102] Plasma (50 mcL) was analyzed for Compound 1 concentration. Two dogs were excluded from the analysis as they had vomited just after dosing. Mean plasma concentration profiles for Compound 1 seen after oral dosing are shown in Figure 3 where the line represented by ▲ illustrates a formulation which included the hydrogen sulfate salt of Compound 1, and the line represented by × shows the results of Compound 1 free base in the same formulation.

[00103] It appears that formulation changes had a relatively small affect on exposure (results not shown). However when Compound 1 was dosed as the hydrogen sulfate salt, a substantial approximately 4 to 8 fold increase in exposure was produced.

[00104] The foregoing description is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will be readily apparent to those skilled in the art, it is not desired to limit the invention to the exact construction and process shown as described above. Accordingly, all suitable modifications and equivalents may be resorted to falling within the scope of the invention as defined by the claims that follow.

[00105] The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

What is claimed is:

1. A hydrogen sulfate salt of Compound 1.

2. A hydrogen sulfate salt of Compound 1 according to claim 1 in anhydrous form.

3. A hydrogen sulfate salt of Compound 1 according to claim 1 in the form of a solvate.

4. A hydrogen sulfate salt of Compound 1 according to any one of the previous claims which is crystalline.

5. A hydrogen sulfate salt of Compound 1 according to claim 4, wherein said hydrogen sulfate salt of Compound 1 has an X-ray powder diffraction pattern with at least one specific peak at about 24.59°.

6. A hydrogen sulfate salt of Compound 1 according to claim 5, wherein said hydrogen sulfate salt of Compound 1 has an X-ray powder diffraction pattern with specific peaks at about 2-theta equal to 24.59°, 20.97°, 23.99°, 27.65°, 12.24°, 23.49°, 24.30°, 17.02°, 25.91° and 22.50°.

7. A hydrogen sulfate salt of Compound 1 according to claim 1 which has a powder X-ray diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 1.

8. A hydrogen sulfate salt of Compound 1 according to claim 1 or claim 2 in amorphous form.

9. A method for preparing a hydrogen sulfate salt of Compound 1 according to any one of claims 1 to 8, said method comprising

(i) reacting a slurry of Compound 1 in an organic liquid with at least a stoichiometric amount of sulfuric acid and water;

(ii) recovering the salt from the resultant solution; and

(iii) thereafter, if desired or necessary, forming a solvate thereof.

10. The method according to claim 9 wherein the amount of water added in step (i) is restricted to that amount necessary to ensure that the salt is formed.

11. The method according to claim 9 or claim 10 wherein step (i) is carried out at a temperature of from 40-80 °C.

12. The method according to any one of claims 9 to 11 wherein the organic liquid is a C_{1-6} alkyl ketone.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
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(21) N° de solicitud:	(51) Int Cl:
22) Fecha de solicitud: **02/07/2008**	(71)Solicitante(s) **1.- ARRAY BIOPHARMA, INC.** **2.- ASTRAZENECA AB**
(30) Prioridad (31) ***No. Priodidad*** 32) ***Fecha*** (33) ***País*** S! **60/752,781** **21/12/2005** **US**	(72) Inventor(es) **SQUIRE, Christopher, John** **DEMATTEI, John** **ROBERTS, Ronald, John** **CHUANG, Tsung-hsun** **SHARMA-SINGH, Gorkhn** **PERVEZ, Mohammed** **FORD, James, Gair** **STOREY, Richard, Anthony** **DICKINSON, Paul, Alfred**
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(85) Fecha limite inicio fase nacional: (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **Diciembre 12/2006** No. de solicitud **PCT/US2006/061895**	(87) Publicación internacional Fecha: **5-07-2007** N° publicación: **WO 2007/076245 A3**
(54) Titulo: **SAL DE SULFATO DE HIDRÓGENO NOVEDOSA**	

Reivindicación(es):

Una sal de sulfato de hidrógeno del Compuesto 1.

Una sal de sulfato de hidrógeno del Compuesto 1 de acuerdo con la reivindicación 1, en forma anhidra.

Una sal de sulfato de hidrógeno del Compuesto 1 de acuerdo con la reivindicación 1, en la forma de un solvato.

Una sal de sulfato de hidrógeno del Compuesto 1 de acuerdo con cualquiera de las reivindicaciones anteriores que es cristalina.

Una sal de sulfato de hidrógeno del Compuesto 1 de acuerdo con la reivindicación 4, en donde la sal de sulfato de hidrógeno del Compuesto 1 tiene un patrón de difracción de polvo de rayos X con por lo menos un pico específico a 24,59°.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

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Firma Responsable

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

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Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.

2. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9). Se sugiere al solicitante señalar el nombre del compuesto orgánico respectivo.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

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