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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

Division de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No 04-16685

54 TITULO Derivados de Iden [1,2c] Isoq o/na y
metodos para usar los mismos

51 CLASIFICACION INTERNACIONAL C07D AG1V31/47

71 SOLICITANTE Inotek pharmaceuticals corporation

DOMICILIO Massachusetts, Estados Unidos

74 APODERADO J/la M a Rodriguez D Aleman

22 BOGOTA D C febrero 25, 2004

Handwritten signature/initials

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)	Nombre: INOTEK PHARMACEUTICALS CORPORATION Dirección: 100 Cummings Center, Beverly, MA 01915, Estados Unidos Nacionalidad o domicilio: Massachusetts, Estados Unidos Lugar de constitución: Massachusetts, Estados Unidos		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D'ALEMAN Dirección: Carrera 11 N°. 93-43 Of. 404 Santafé de Bogotá D.C. Teléfono: 6350835 Fax: 6350824 E. Mail: clarkemodet@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
4) INVENTOR (ES) (72)	Nombre: 1. JAGTAP, Prakash, G.; 2. BALOGLU, Erkan; 3. VAN DUZER, John, H.; 4. SZABO, Csaba; 5. SALZMAN, Andrew, L. Dirección: 1. 5 Pinehurst Avenue, Beverly, MA 01915 USA; 2. 75 St. Alphonsus Street, Apt.#1204, Boston, MA 02120 USA; 3. 102 Thurlow Street, Georgetown, MA 01833 USA; 4. 30 Starknought Heights, Gloucester, MA 01930 USA; 5. 483 Pleasant Street, Apt.#1, Belmont, MA 02078 USA. Nacionalidad o Domicilio: Todos los anteriores, Estadounidenses		
5) PCT (86) Solicitud Internacional No. PCT/US02/27585 Fecha: Agosto 30, 2002 Publicación Internacional No.WO 03/020700 A2 Fecha: Marzo 13, 2003			
6) Título (54) DERIVADO DE INDENO [1,2-C] ISOQUINOLINA Y MÉTODOS PARA USAR LOS MISMOS			
7) Clasificación Internacional: C07D A61K31/49			
8) PRIORIDAD SI ☒ NO ☐	33) País de Origen	(32) Fecha	(31) Número de Solicitud
	Estados Unidos	Agosto 31, 2001	09/944,524
9) Comprobante de pago N°. 04-10,464 Fecha: Febrero 10, 2004			
Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

82

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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RECIBO OFICIAL DE CAJA : 04 - 10,464
FECHA : FEBRERO 10 DE 2004

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE NOBET Y CD. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	8895702	10/02/2004	4,236,000.00

CONCEPTO

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

10546

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar 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 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☐ Otros
 1. Comunicación internacional de países designados
 2. Publicación Internacional WO 03/020700 A2
 3. Hoja de cálculo PCT
 4. Notificación de transmisión del reporte de búsqueda
 5. Examen De búsqueda internacional
 6. Notificación de solicitud de examen preliminar internacional

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DIEIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta página

MAR 31 2003

From the INTERNATIONAL BUREAU

RECEIVED TO-2

PCT

**NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

To:

INSOGNA, Anthony, M.
Pennie & Edmonds LLP
1155 Avenue of the Americas
New York, NY 10036
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

13 March 2003 (13.03.03)

Applicant's or agent's file reference

11078-25-228

IMPORTANT NOTICE

International application No.

PCT/US02/027585

International filing date (day/month/year)

30 August 2002 (30.08.02)

Priority date (day/month/year)

31 August 2001 (31.08.01)

Applicant

INOTEK PHARMACEUTICALS CORPORATION

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

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

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 13 March 2003 (13.03.03) under No. WO 03/020700.

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Judith Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.91.11

(19) World Intellectual Property Organization
International Bureau



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

PCT

(10) International Publication Number
WO 03/020700 A2

(51) International Patent Classification⁷: C07D

(74) Agents: INSOGNA, Anthony, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(21) International Application Number: PCT/US02/27585

(22) International Filing Date: 30 August 2002 (30.08.2002)

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

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09/944,524 31 August 2001 (31.08.2001) US

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

(71) Applicant: INOTEK PHARMACEUTICALS CORPORATION (US/US); 100 Cummings Center, Beverly, MA 01915 (US).

Published:
— without international search report and to be republished upon receipt of that report

(72) Inventors: JAGTAP, Prakash, G.; 5 Pinchurst Avenue, Beverly, MA 01915 (US). BALOGLU, Erkan; 75 St. Alphonsus Street, Apt. #1204, Boston, MA 02120 (US). VAN DUZER, John, H.; 102 Thurlow Street, Georgetown, MA 01833 (US). SZABO, Csaba; 30 Starknought Heights, Gloucester, MA 01930 (US). SALZMAN, Andrew, L.; 483 Pleasant Street, Apt. #1, Belmont, MA 02078 (US).

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



WO 03/020700 A2

(54) Title: SUBSTITUTED INDENO[1,2-c]ISOQUINOLINE DERIVATIVES AND METHODS OF USE THEREOF

(57) Abstract: The invention provides novel classes of substituted Indeno[1,2-c]isoquinoline Compounds. Pharmaceutical compositions and methods of making and using the compounds, are also described.

**SUBSTITUTED INDENO[1,2-c]ISOQUINOLINE
DERIVATIVES AND METHODS OF USE THEREOF**

This application is a continuation-in-part of U.S. Application No. 09/944,524, filed August 31, 2001, which is incorporated by reference herein in its entirety.

1. FIELD OF THE INVENTION

The invention relates to indeno[1,2-c]isoquinoline compounds; compositions comprising an indeno[1,2-c]isoquinoline compound; and methods for treating or preventing an inflammatory disease or a reperfusion disease.

2. BACKGROUND OF THE INVENTION

Inflammatory diseases, such as arthritis, colitis, and autoimmune diabetes, typically manifest themselves as disorders distinct from those associated with reperfusion diseases, *e.g.*, stroke and heart attack, and can clinically manifest themselves as different entities. However, there can be common underlying mechanisms between these two types of disorders. In particular, inflammatory disease and reperfusion disease can induce proinflammatory cytokine and chemokine synthesis which can, in turn, result in production of cytotoxic free radicals such as nitric oxide and superoxide. NO and superoxide can react to form peroxynitrite (ONOO⁻) (Szabó *et al.*, Shock 6:79-88, 1996).

The ONOO⁻-induced cell necrosis observed in inflammatory disease and in reperfusion disease involves the activation of the nuclear enzyme poly (ADP-ribose) synthetase (PARS). Activation of PARS is thought to be an important step in the cell-mediated death observed in inflammation and reperfusion disease (Szabó *et al.*, Trends Pharmacol. Sci. 19: 287-98, 1998).

A number of PARS inhibitors have been described in the art. See, *e.g.*, Banasik *et al.*, J. Biol. Chem., 267:1569-75, 1992, and Banasik *et al.*, Mol. Cell. Biochem., 138:185-97, 1994; WO 00/39104; WO 00/39070; WO 99/59975; WO 99/59973; WO 99/11649; WO 99/11645; WO 99/11644; WO 99/11628; WO 99/11623; WO 99/11311; WO 00/42040; Zhang *et al.*, Biochem. Biophys. Res. Commun., 278:590-98, 2000; White *et al.*, J. Med. Chem., 43 :4084-4097, 2000; Griffin *et al.*, J. Med. Chem., 41:5247-5256, 1998; Shinkwin *et al.*, Bioorg. Med. Chem., 7:297-308, 1999; and Soriano *et al.*, Nature Medicine, 7:108-113, 2001. Adverse effects associated with administration of PARS inhibitors have been discussed in Milan *et al.*, Science, 223:589-591, 1984.

Indeno[1,2-c]isoquinoline derivatives have been previously discussed in the art. For example, cytotoxic non-camptothecin topoisomerase I inhibitors are reported in Cushman *et al.*, J. Med. Chem., 43:3688-3698, 2000 and Cushman *et al.*, J. Med. Chem. 42:446-57, 1999; indeno[1,2-c]isoquinolines are reported as antineoplastic agents in Cushman *et al.*, WO 00/21537; and as neoplasm inhibitors in Hrbata *et al.*, WO 93/05023.

Syntheses of indeno[1,2-c]isoquinoline derivatives have been reported. For example, see Wawzonek *et al.*, Org. Prep. Proc. Int. 14:163-8, 1982; Wawzonek *et al.*, Can. J. Chem. 59:2833, 1981; Andoi *et al.*, Bull. Chem. Soc. Japan, 47:1014-17, 1974; Dusemund *et al.*, Arch. Pharm (Weinheim, Ger.), 3 17:381-2, 1984; and Lal *et al.*, Indian J. Chem., Sect. B, 38B:33-39, 1999.

There remains, however, a need in the art for compounds useful for treating or preventing inflammatory diseases or reperfusion diseases.

Citation of any reference in Section 2 of this application is not an admission that the reference is prior art.

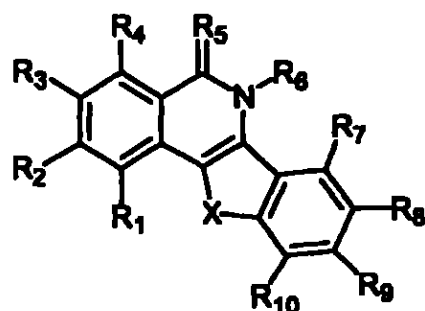
3. SUMMARY OF THE INVENTION

The invention is based in part on the discovery of novel substituted tetracyclic benzamide derivatives and their demonstrated effects in the treatment of inflammation, cell death and in treating shock and reperfusion diseases.

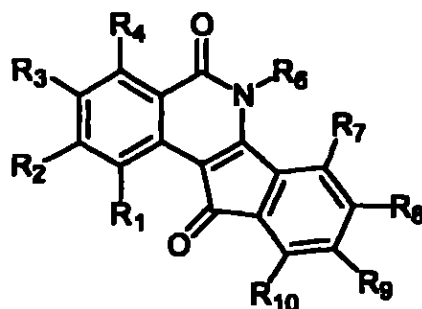
Accordingly, in one aspect the invention includes a compound of Formula I, Formula Ia, Formula Ib, Formula II or Formula III, or a pharmaceutically acceptable salt or hydrate thereof (an "Indeno[1,2-c]isoquinoline Compound") as set forth below in the Detailed Description of the Invention.

Also provided by the invention is a method for treating or preventing an inflammatory disease or a reperfusion disease in a subject, comprising administering to a subject in need of such treatment or prevention an effective amount of an Indeno[1,2-c]isoquinoline Compound.

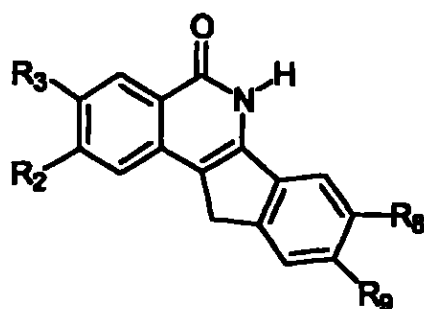
In a further aspect, the invention also includes a method for making an Indeno[1,2-c]isoquinoline Compound.



(I, Ia and Ib)



(II)



(III)

The Indeno[1,2-c]isoquinoline Compounds can be used to treat or prevent a variety of conditions and diseases, including, but not limited to, an inflammatory disease or a reperfusion disease.

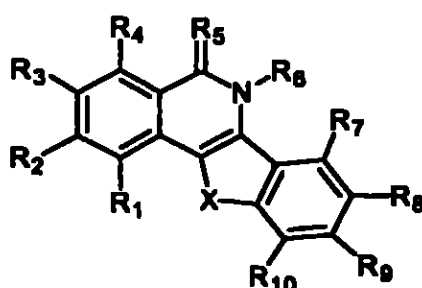
The invention also includes pharmaceutical compositions that comprise an effective amount of an Indeno[1,2-c]isoquinoline Compound and a pharmaceutically acceptable

carrier. The compositions are useful for treating or preventing an inflammatory disease or a reperfusion disease. The invention includes an Indeno[1,2-c]isoquinoline Compound when provided as a pharmaceutically acceptable prodrug, a hydrated salt, such as a pharmaceutically acceptable salt, or mixtures thereof.

The details of the invention are set forth in the accompanying description below. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated by reference.

4. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel class of Indeno[1,2-c]isoquinoline Compounds according to Formula I, Formula Ia, Formula Ib, Formula II and Formula II, as set forth below:



(I)

and pharmaceutically acceptable salts and hydrates thereof,
wherein:

R_5 is O, NH or S;

R_6 is -H or C_1 - C_4 alkyl;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arylene-, -O-, -NH-, -S- or -CH(NR₁₁R₁₂)-, wherein n is an integer ranging from 0-5;

R_{11} and R_{12} are independently -hydrogen or - C_1 - C_9 alkyl, or N, R_{11} and R_{12} are taken together to form a heterocyclic amine;

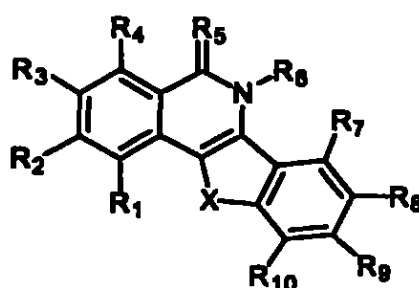
R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently -hydrogen, -halo, -hydroxy, -O-(C_1 - C_3 alkyl), - C_1 - C_{10} alkyl, -alkylhalo, - C_2 - C_{10} alkenyl, - C_3 - C_8 carbocycle, -aryl, - NH_2 , -alkylamino, -C(O)OH, -C(O)O(C_1 - C_3 alkyl), -OC(O)(C_1 - C_3 alkyl), NO_2 or -A-B;

wherein A is - SO_2 -, - SO_2NH -, - $NHCO$ -, - $NHCONH$ -, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C_1 - C_4 alkyl)-, -NH-, - CH_2 -, -S- or -C(S)-;

B is - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, -heterocycle, - C_3 - C_8 carbocycle, -aryl, - NZ_1Z_2 , -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH, -C(O)O-(C_1 - C_3 alkyl) or -C(O)O-phenyl, any of which are unsubstituted or substituted with one or more of -O-(C_1 - C_3 alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, - NO_2 , - NH_2 , -aminoalkyl, -aminodialkyl, -heterocyclic amine, - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, - C_2 - C_{10} alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy, - C_1 - C_3 alkylene-C(O)O- C_1 - C_3 alkyl or - C_1 - C_3 alkylene-OC(O)- C_1 - C_3 alkyl groups; and

Z_1 and Z_2 are independently -H or - C_1 - C_{10} alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or - $N(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, -H or - C_1 - C_3 alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or - NH_2 ; or N, Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

The invention also relates to a compounds of formula (Ia):



(Ia)

and pharmaceutically acceptable salts and hydrates thereof,

wherein:

R_3 is NH or S;

R_6 is -H or C_1 - C_4 alkyl;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arylene-, -O-, -NH-, -S- or -CH(NR₁₁R₁₂)-, wherein n is an integer ranging from 0-5;

R_{11} and R_{12} are independently -hydrogen or - C_1 - C_9 alkyl, or N, R_{11} and R_{12} are taken together to form a heterocyclic amine;

R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently -hydrogen, -halo, -hydroxy, -O-(C_1 - C_3 alkyl), - C_1 - C_{10} alkyl, -alkylhalo, - C_2 - C_{10} alkenyl, - C_3 - C_8 carbocycle, -aryl, -NH₂, -alkylamino, -C(O)OH, -C(O)O(C_1 - C_3 alkyl), -OC(O)(C_1 - C_3 alkyl), NO₂ or -A-B;

wherein A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C_1 - C_4 alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, -heterocycle, - C_3 - C_8 carbocycle, -aryl, -NZ₁Z₂, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH, -C(O)O-(C_1 - C_3 alkyl) or -C(O)O-phenyl, any of which are unsubstituted or substituted with one or more of -O-(C_1 - C_3 alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, -NO₂, -NH₂, -aminoalkyl, -aminodialkyl, -heterocyclic amine, - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, - C_2 - C_{10} alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy, - C_1 - C_3 alkylene-C(O)O- C_1 - C_3 alkyl or - C_1 - C_3 alkylene-OC(O)- C_1 - C_3 alkyl groups; and

Z_1 and Z_2 are independently -H or - C_1 - C_{10} alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z_3)(Z_4), where Z_3 and Z_4 are independently, -H or - C_1 - C_3 alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

In one embodiment, A is -SO₂-.

In another embodiment, R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently arylalkyl.

In other illustrative embodiments R^5 and X in a compound of formula Ia are as set forth below:

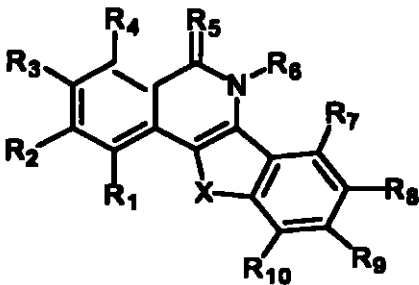
R^5	X
NH	-C(O)-

12

NH	-CH ₂ -
NH	-CH(halo)-
NH	-CH(OH)(CH ₂) _n -
NH	-CH(arylene)(OH)-
NH	-O-
NH	-NH-
NH	-S-
NH	-CH(NR ¹¹ R ¹²)-

<u>R^s</u>	<u>X</u>
S	-C(O)-
S	-CH ₂ -
S	-CH(halo)-
S	-CH(OH)(CH ₂) _n -
S	-CH(arylene)(OH)-
S	-O-
S	-NH-
S	-S-
S	-CH(NR ¹¹ R ¹²)-

The invention also relates to compounds of Formula Ib:



(Ib)

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and pharmaceutically acceptable salts and hydrates thereof,

wherein:

R_3 is O, NH or S;

R_4 is -H or C_1 - C_4 alkyl;

X is $-CH_2-$, $-CH(halo)-$, $-CH(OH)(CH_2)_n-$, $-CH(OH)-arylene-$, $-O-$, $-NH-$, $-S-$ or $-CH(NR_{11}R_{12})-$, wherein n is an integer ranging from 0-5;

R_{11} and R_{12} are independently -hydrogen or $-C_1$ - C_9 alkyl, or N, R_{11} and R_{12} are taken together to form a heterocyclic amine.

R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently -hydrogen, -halo, -hydroxy, $-O-(C_1-C_3 \text{ alkyl})$, $-C_1-C_{10}$ alkyl, -alkylhalo, $-C_2-C_{10}$ alkenyl, $-C_3-C_8$ carbocycle, -aryl, $-NH_2$, -alkylamino, $-C(O)OH$, $-C(O)O(C_1-C_3 \text{ alkyl})$, $-OC(O)(C_1-C_3 \text{ alkyl})$, NO_2 or -A-B;

wherein A is $-SO_2-$, $-SO_2NH-$, $-NHCO-$, $-NHCONH-$, $-O-$, $-CO-$, $-OC(O)-$, $-C(O)O-$, $-CONH-$, $-CON(C_1-C_4 \text{ alkyl})-$, $-NH-$, $-CH_2-$, $-S-$ or $-C(S)-$;

B is $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, -heterocycle, $-C_3-C_8$ carbocycle, -aryl, $-NZ_1Z_2$, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, $-C(O)OH$, $-C(O)O-(C_1-C_3 \text{ alkyl})$ or $-C(O)O$ -phenyl, any of which are unsubstituted or substituted with one or more of $-O-(C_1-C_3 \text{ alkyl})$, -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, $-NO_2$, $-NH_2$, -aminoalkyl, -aminodialkyl, -heterocyclic amine, $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-C_2-C_{10}$ alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy, $-C_1-C_3$ alkylene- $C(O)O-C_1-C_3$ alkyl or $-C_1-C_3$ alkylene- $OC(O)-C_1-C_3$ alkyl groups; and

Z_1 and Z_2 are independently -H or $-C_1-C_{10}$ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or $-N(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, -H or $-C_1-C_3$ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or $-NH_2$; or N, Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

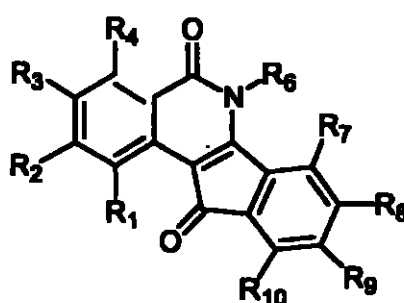
In one embodiment, A is $-SO_2-$.

In another embodiment, R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently arylalkyl.

In illustrative embodiments R^3 and X in a compound of formula Ib are as set forth below:

$\underline{R^3}$	$\underline{X}$
O	-CH ₂ -
O	-CH(halo)-
O	-CH(OH)(CH ₂) _n -
O	-CH(arylene)(OH)-
O	-O-
O	-NH-
O	-S-
O	-CH(NR ¹¹ R ¹²)-

The invention also relates to compounds of Formula II:



(II)

and pharmaceutically acceptable salts and hydrates thereof,
wherein:

R_6 is -H or C₁-C₄ alkyl;

R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 , and R_{10} are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₃ alkyl), -C₁-C₁₀ alkyl, -alkylhalo, -C₂-C₁₀ alkenyl, -C₃-C₈ carbocycle, -aryl, -NH₂, -alkylamino, -C(O)OH, -C(O)O(C₁-C₃ alkyl), -OC(O)(C₁-C₃ alkyl), NO₂ or -A-B; wherein at least one of R^1 , R^4 and R^{10} is other than hydrogen;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -heterocycle, -C₃-C₈ carbocycle, -aryl, -NH₂, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH,

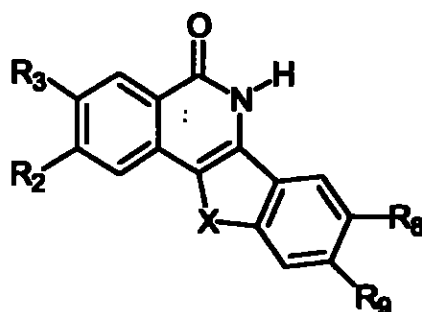
$-\text{C}(\text{O})\text{O}-(\text{C}_1-\text{C}_3 \text{ alkyl}), -\text{C}(\text{O})\text{O}-\text{phenyl}$ or $-\text{NZ}_1\text{Z}_2$; and

Z_1 and Z_2 are independently $-\text{H}$ or $-\text{C}_1-\text{C}_{10}$ alkyl, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{OH}$ or $-\text{N}(\text{Z}_3)(\text{Z}_4)$, where Z_3 and Z_4 are independently, $-\text{H}$ or $-\text{C}_1-\text{C}_3$ alkyl, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{hydroxy}$ or $-\text{NH}_2$; or N , Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N , Z_1 and Z_2 are taken together to form a heterocyclic amine.

In one embodiment, B is a heterocyclic amine.

In another embodiment, B is arylalkyl.

The invention also relates to compounds of Formula III:



(III)

and pharmaceutically acceptable salts and hydrates thereof,

wherein:

X is $-\text{CH}_2-$ or $-\text{O}-$;

R_2 and R_3 are independently $-\text{hydrogen}$, $-\text{halo}$, $-\text{alkylhalo}$, $-\text{hydroxy}$, $-\text{O}-(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{CONH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{OC}(\text{O})-\text{C}_1-\text{C}_3 \text{ alkyl}$ or $-\text{C}(\text{O})\text{O}-\text{C}_1-\text{C}_3 \text{ alkyl}$;

R_8 and R_9 are independently $-\text{hydrogen}$ and $-\text{A-B}$;

A is $-\text{SO}_2-$, $-\text{SO}_2\text{NH}-$ or $-\text{NHCO}-$; and

B is $-\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{NZ}_1\text{Z}_2$, $-\text{heterocycle}$ or $-\text{alkylamino}$, each unsubstituted or substituted with one or more of $-\text{alkanol}$, $-\text{alkylamino}$, $-\text{aminoalkyl}$, $-\text{aminodialkyl}$ or $-\text{heterocycle}$, each unsubstituted or substituted with $-\text{C}_1-\text{C}_{10} \text{ alkyl}$ or $-\text{alkanol}$; and

Z_1 and Z_2 are independently -hydrogen or $-C_1-C_4$ alkyl, which is unsubstituted or substituted with one or more of -hydroxy or $-NZ_3Z_4$, where Z_3 and Z_4 are independently -H or $-C_1-C_3$ alkyl, which is unsubstituted or substituted with one or more of -hydroxy or $-NH_2$, or N, Z_3 and Z_4 are taken together to a heterocyclic amine, or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

In one embodiment, -X- is $-CH_2-$.

In another embodiment, -X- is $-O-$.

In one embodiment, R^8 is hydrogen and R^9 is -A-B.

In another embodiment, R^8 is -A-B and R^9 is hydrogen.

In one embodiment, either R^8 is hydrogen and R^9 is -A-B, or R^8 is -A-B and R^9 is hydrogen.

In one embodiment, R^3 , R^8 and R^9 are hydrogen and R^2 is -A-B, wherein A is $-NHC(O)-$.

In another embodiment, R^2 , R^8 and R^9 are hydrogen and R^3 is -A-B, wherein A is $-NHC(O)-$.

In still another embodiment R^2 , R^3 and R^8 are hydrogen and R^9 is -A-B, wherein A is $-SO_2-$ or $-SO_2NH-$.

4.1 DEFINITIONS

" C_1-C_3 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-3 carbon atoms. Examples of a C_1-C_3 alkyl group include, but are not limited to, methyl, ethyl, propyl and isopropyl

" C_1-C_4 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C_1-C_4 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl.

" C_1-C_5 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C_1-C_5 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl and neopentyl.

" C_1-C_8 alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-8 carbon atoms. Examples of a C_1-C_8 alkyl group include, but are not limited to, methyl,

ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl, neopentyl, isohexyl, isoheptyl and isooctyl.

"C₁-C₉ alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-9 carbon atoms. Examples of a C₁-C₉ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl, neopentyl, isohexyl, isoheptyl, isooctyl and isononyl.

"C₁-C₁₀ alkyl" refers to a straight or branched chain saturated hydrocarbon containing 1-10 carbon atoms. Examples of a C₁-C₁₀ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl, isopentyl, neopentyl, isohexyl, isoheptyl, isooctyl, isononyl and isodecyl.

"C₂-C₁₀ alkenyl" refers to a straight or branched chain unsaturated hydrocarbon containing 2-10 carbon atoms and at least one double bond. Examples of a C₂-C₁₀ alkenyl group include, but are not limited to, ethylene, propylene, 1-butylene, 2-butylene, isobutylene, *sec*-butylene, 1-pentene, 2-pentene, isopentene, 1-hexene, 2-hexene, 3-hexene, isohexene, 1-heptene, 2-heptene, 3-heptene, 1-octene, 2-octene, 3-octene, 4-octene, 1-nonene, 2-nonene, 3-nonene, 4-nonene, 1-decene, 2-decene, 3-decene, 4-decene and 5-decene.

"C₂-C₁₀ alkynyl" refers to a straight or branched chain unsaturated hydrocarbon containing 2-10 carbon atoms and at least one triple bond. Examples of a C₂-C₁₀ alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, isobutyne, *sec*-butyne, 1-pentyne, 2-pentyne, isopentyne, 1-hexyne, 2-hexyne, 3-hexyne, isohexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne, 4-octyne, 1-nonyne, 2-nonyne, 3-nonyne, 4-nonyne, 1-decyne, 2-decyne, 3-decyne, 4-decyne and 5-decyne.

"C₁-C₄ alkylene" refers to a C₁-C₄ alkyl group in which one of the C₁-C₄ alkyl group's hydrogen atoms has been replaced with a bond. Examples of a C₁-C₄ alkylene include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂-.

"C₁-C₉ alkylene" refers to a C₁-C₉ alkyl group in which one of the C₁-C₉ alkyl group's hydrogen atoms has been replaced with a bond. Examples of a C₁-C₉ alkylene include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂-. Examples of a C₁-C₄ alkylene include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂-.

"Alkylhalo" refers to a C₁-C₄ alkyl group, as defined above, wherein one or more of the C₁-C₄ alkyl group's hydrogen atoms has been replaced with -F, -Cl, -Br or -I.

Representative examples of an alkylhalo group include, but are not limited to -CH₂F, -CCl₃, -CF₃, -CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CH₂CH₂CH₂F, -CH₂CH₂CH₂Cl, -CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂I, -CH₂CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂CH₂I, -CH₂CH(Br)CH₃, -CH₂CH(Cl)CH₂CH₃, -CH(F)CH₂CH₃ and -C(CH₃)₂(CH₂Cl).

"Alkylamino" refers to a C₁-C₄ alkyl group, as defined above, wherein one or more of the C₁-C₄ alkyl group's hydrogen atoms has been replaced with -NH₂. Representative examples of an alkylamino group include, but are not limited to -CH₂NH₂, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH(NH₂)CH₂CH₃, -CH(NH₂)CH₂CH₃ and -C(CH₃)₂(CH₂NH₂).

"Aminoalkyl" refers to an -NH group, the nitrogen atom of said group being attached to a C₁-C₄ alkyl group, as defined above. Representative examples of an aminoalkyl group include, but are not limited to -NHCH₃, -NHCH₂CH₃, -NHCH₂CH₂CH₃, -NHCH₂CH₂CH₂CH₃, -NHCH(CH₃)₂, -NHCH₂CH(CH₃)₂, -NHCH(CH₃)CH₂CH₃ and -NH-C(CH₃)₃.

"Aminodialkyl" refers to a nitrogen atom which has attached to it two C₁-C₄ alkyl groups, as defined above. Representative examples of a aminodialkyl group include, but are not limited to, -N(CH₃)₂, -N(CH₂CH₃)(CH₃), -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -N(CH₂CH₂CH₂CH₃)₂, -N(CH(CH₃)₂)₂, -N(CH(CH₃)₂)(CH₃), -N(CH₂CH(CH₃)₂)₂, -NH(CH(CH₃)CH₂CH₃)₂, -N(C(CH₃)₃)₂ and -N(C(CH₃)₃)(CH₃).

"Aryl" refers to a phenyl or pyridyl group. Examples of an aryl group include, but are not limited to, phenyl, N-pyridyl, 2-pyridyl, 3-pyridyl and 4-pyridyl. An aryl group can be unsubstituted or substituted with one or more of the following groups:

-C₁-C₄ alkyl, halo, -alkylhalo, hydroxy, -O-C₁-C₄ alkyl, -NH₂, -aminoalkyl, -aminodialkyl, -COOH, -C(O)O-(C₁-C₄ alkyl), -OC(O)-(C₁-C₄ alkyl), -N-amidoalkyl, -C(O)NH₂, -carboxamidoalkyl, or -NO₂.

"Arylalkyl" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with a C₁-C₄ alkyl group, as defined above.

Representative examples of an arylalkyl group include, but are not limited to, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-propylphenyl, 3-propylphenyl, 4-propylphenyl, 2-butylphenyl, 3-butylphenyl, 4-butylphenyl, 2-pentylphenyl, 3-pentylphenyl, 4-pentylphenyl, 2-isopropylphenyl, 3-

isopropylphenyl, 4-isopropylphenyl, 2-isobutylphenyl, 3-isobutylphenyl, 4-isobutylphenyl, 2-sec-butylphenyl, 3-sec-butylphenyl, 4-sec-butylphenyl, 2-t-butylphenyl, 3-t-butylphenyl and 4-t-butylphenyl,

"Arylamido" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with one or more $-C(O)NH_2$ groups.

Representative examples of an arylamido group include 2- $C(O)NH_2$ -phenyl, 3- $C(O)NH_2$ -phenyl, 4- $C(O)NH_2$ -phenyl, 2- $C(O)NH_2$ -pyridyl, 3- $C(O)NH_2$ -pyridyl and 4- $C(O)NH_2$ -pyridyl,

"Alkylheterocycle" refers to a C_1 - C_3 alkyl group, as defined above, wherein one of the C_1 - C_3 alkyl group's hydrogen atoms has been replaced with a heterocycle.

Representative examples of an alkylheterocycle group include, but are not limited to, $-CH_2CH_2$ -morpholine, $-CH_2CH_2$ -piperidine, $-CH_2CH_2CH_2$ -morpholine and $-CH_2CH_2CH_2$ -imidazole.

"Alkylamido" refers to a C_1 - C_3 alkyl group, as defined above, wherein one of the C_1 - C_3 alkyl group's hydrogen atoms has been replaced with a $-C(O)NH_2$ group. Representative examples of an alkylamido group include, but are not limited to, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH(C(O)NH_2)CH_3$, $-CH_2CH(C(O)NH_2)CH_2CH_3$, $-CH(C(O)NH_2)CH_2CH_3$ and $-C(CH_3)_2CH_2C(O)NH_2$.

"Alkanol" refers to a C_1 - C_3 alkyl group, as defined above, wherein one of the C_1 - C_3 alkyl group's hydrogen atoms has been replaced with a hydroxyl group. Representative examples of an alkanol group include, but are not limited to, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2CH_2OH$, $-CH_2CH(OH)CH_3$, $-CH_2CH(OH)CH_2CH_3$, $-CH(OH)CH_2CH_3$ and $-C(CH_3)_2CH_2OH$.

"Alkylcarboxy" refers to a C_1 - C_3 alkyl group, as defined above, wherein one of the C_1 - C_3 alkyl group's hydrogen atoms has been replaced with a $-COOH$ group. Representative examples of an alkylcarboxy group include, but are not limited to, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2CH_2CH_2COOH$, $-CH_2CH_2CH_2CH_2COOH$, $-CH_2CH(COOH)CH_3$, $-CH_2CH_2CH_2CH_2CH_2COOH$, $-CH_2CH(COOH)CH_2CH_3$, $-CH(COOH)CH_2CH_3$ and $-C(CH_3)_2CH_2COOH$.

"N-amidoalkyl" refers to a $-NHC(O)-$ group in which the carbonyl carbon atom of said group is attached to a C_1 - C_3 alkyl group, as defined above. Representative examples of a N-amidoalkyl group include, but are not limited to, $-NHC(O)CH_3$, $-NHC(O)CH_2CH_3$,

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-NHC(O)CH₂CH₂CH₃, -NHC(O)CH₂CH₂CH₂CH₃, -NHC(O)CH₂CH₂CH₂CH₂CH₃,
 -NHC(O)CH(CH₃)₂, -NHC(O)CH₂CH(CH₃)₂, -NHC(O)CH(CH₃)CH₂CH₃, -NHC(O)-
 C(CH₃)₃ and -NHC(O)CH₂C(CH₃)₃.

"Carboxamidoalkyl" refers to a -C(O)NH- group in which the nitrogen atom of said group is attached to a C₁-C₃ alkyl group, as defined above. Representative examples of a carboxamidoalkyl group include, but are not limited to, -C(O)NHCH₃, -C(O)NHCH₂CH₃, -C(O)NHCH₂CH₂CH₃, -C(O)NHCH₂CH₂CH₂CH₃, -C(O)NHCH₂CH₂CH₂CH₂CH₃, -C(O)NHCH(CH₃)₂, -C(O)NHCH₂CH(CH₃)₂, -C(O)NHCH(CH₃)CH₂CH₃, -C(O)NH-C(CH₃)₃ and -C(O)NHCH₂C(CH₃)₃.

An "Arylene" group is a phenyl group in which one of the phenyl group's hydrogen atoms has been replaced with a bond. An arylene group may be in an ortho, meta, or para configuration and may be unsubstituted or independently substituted with one or more of the following groups: -C₁-C₃ alkyl, halo, -alkylhalo, hydroxy, -O-C₁-C₃ alkyl, -NH₂, -aminoalkyl, -aminodialkyl, -COOH, -C(O)O-(C₁-C₃ alkyl), -OC(O)-(C₁-C₃ alkyl), -N-amidoalkyl, -C(O)NH₂, -carboxamidoalkyl or -NO₂.

A "C₃-C₈ Carbocycle" is a non-aromatic, saturated hydrocarbon ring containing 3-8 carbon atoms. Representative examples of a C₃-C₈ carbocycle include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. A C₃-C₈ carbocycle may be unsubstituted or independently substituted with one or more of the following groups: -C₁-C₃ alkyl, halo, -alkylhalo, hydroxy, -O-C₁-C₃ alkyl, -NH₂, -aminoalkyl, -aminodialkyl, -COOH, -C(O)O-(C₁-C₃ alkyl), -OC(O)-(C₁-C₃ alkyl), -N-amidoalkyl, -C(O)NH₂, -carboxyamidoalkyl or -NO₂.

"Heterocycle" refers to a 5- to 10-membered aromatic or non-aromatic carbocycle in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. Representative examples of a heterocycle group include, but are not limited to, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, triazinyl, tetrazinyl, imidazolyl, benzimidazolyl, tetrazolyl, indolyl, isoquinolinyl, quinolinyl, quinazolinyl, pyrrolidinyl, purinyl, isoxazolyl, benzisoxazolyl, furanyl, furazanyl, pyridinyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, thiophenyl, pyrazolyl, triazolyl, benzodiazolyl, benzotriazolyl, pyrimidinyl, isoindolyl and indazolyl. A heterocycle group may be unsubstituted or substituted with one or more of the following groups: -C₁-C₃ alkyl, halo, -alkylhalo, hydroxy, -O-C₁-C₃ alkyl, -NH₂, -aminoalkyl, -aminodialkyl, -COOH, -C(O)O-(C₁-C₃ alkyl), -OC(O)-(C₁-C₃ alkyl),

-N-amidoalkyl, -C(O)NH₂, -carboxamidoalkyl or -NO₂.

A "Heterocyclic amine" is a heterocycle, defined above, having 1-4 ring nitrogen atoms. Representative examples of heterocyclic amines include, but are not limited to, piperidinyl, piperazinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, triazinyl, tetrazinyl, imidazolyl, benzimidazolyl, tetrazolyl, indolyl, isoquinolinyl, quinolinyl, quinazolinyl, pyrrolidinyl, purinyl, isoxazolyl, benzisoxazolyl, pyridinyl, oxazolyl, benzoxazolyl, thiazolyl, benzthiazolyl, pyrazolyl, triazolyl, benzodiazolyl, benzotriazolyl, pyrimidinyl, isoindolyl, indazolyl and morpholinyl; each of which may be unsubstituted or substituted with one or more of -N-(C₁-C₃ alkyl), -C(O)-(C₁-C₃ alkyl), -N-C(O)(C₁-C₄ alkyl), -O-(C₁-C₃ alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, -NO₂, -NH₂, -aminoalkyl, -aminodialkyl, -heterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy, -COOH, -C₁-C₃ alkylene-OC(O)-C₁-C₃ alkyl, -C₁-C₃ alkylene-C(O)O-C₁-C₃ alkyl, or a heterocycle or C₃-C₆ carbocycle which may be unsubstituted or substituted with one or more of -C₁-C₁₀ alkyl, -O-(C₁-C₃ alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, -NO₂ or -NH₂.

"Halo" is -F, -Cl, -Br or -I.

A "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate.

The invention also includes pharmaceutical compositions comprising an Indeno[1,2-c]isoquinoline Compound and a pharmaceutically acceptable carrier. The invention includes an Indeno[1,2-c]isoquinoline Compound when provided as a pharmaceutically acceptable prodrug, hydrated salt, such as a pharmaceutically acceptable salt, or mixtures thereof.

Representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camsylate, carbonate, chloride, citrate, clavuliate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate,

p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

An "effective amount" when used in connection an Indeno[1,2-c]isoquinoline Compound is an amount effective for treating or preventing an inflammatory disease or a reperfusion disease.

The following abbreviations are used herein and have the indicated definitions:

AcOH is acetic acid, CEP is Cecal Ligation and Puncture, DMEM is Dulbecco's Modified Eagle Medium, DMF is *N,N*-dimethylformamide, DMSO is dimethylsulfoxide, EtOAc is ethyl acetate, EtOH is ethanol, HEPES is 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, LPS is lipopolysaccharide, MeOH is methanol, MS is mass spectrometry, NMR is nuclear magnetic resonance, PBS is phosphate-buffered saline (pH 7.4), PARS is poly(ADP-ribose)synthetase, Py is pyridine, SDS is dodecyl sulfate (sodium salt), STZ is streptozotocin, TCA is trichloroacetic acid, TFA is trifluoroacetic acid, TLC is thin-layer chromatography, TNF is tumor necrosis factor and TRIS is Tris(hydroxymethyl)aminomethane.

Methods for using Indeno[1,2-c]isoquinoline Compounds

The invention also includes methods for inhibiting PARS in a cell. PARS, which is also known as poly(ADP-ribose)synthetase, PARP ((poly(ADP-ribose) polymerase, EC 2.4.99) and ADP-ribosyltransferase (ADPRT, EC 2.4.2.30), is a nuclear enzyme that catalyzes a transfer of the ADP ribose moiety of NAD⁺ to an acceptor protein.

In one embodiment the method comprises contacting a cell with an Indeno[1,2-c]isoquinoline Compound in an amount sufficient to inhibit PARS in the cell. In general, any cell having, or capable of having, PARS activity or capable of expressing PARS can be used. The cell can be provided in any form. For example, the cell can be provided *in vitro*, *ex vivo*, or *in vivo*. PARS activity can be measured using any method known in the art, *e.g.*, methods as described in Banasik *et al.*, *J. Biol. Chem.* 267:1569-75 (1991). Illustrative examples of cells capable of expressing PARS include, but are not limited to muscle, bone, gum, nerve, brain, liver, kidney, pancreas, lung, heart, bladder, stomach, colon, rectal, small intestine, skin, esophageal, eye, larynx, uterine, ovarian, prostate, tendon, bone marrow, blood, lymph, testicular, vaginal and neoplastic cells.

Also provided in the invention is a method for inhibiting, preventing, or treating inflammation or an inflammatory disease in a subject. The inflammation can be associated

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with an inflammatory disease. Inflammatory diseases can arise where there is an inflammation of the body tissue. These include local inflammatory responses and systemic inflammation. Examples of such diseases include: organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp et al. J. Mol. Cell Cardiol. 31:297-303 (1999)) including, but not limited to, transplantation of the following organs: heart, lung, liver and kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin including sclerodermitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy, such as microalbuminuria and progressive diabetic nephropathy, polyneuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, mononeuropathies, autonomic neuropathy, foot ulcers, joint problems, and a skin or mucous membrane complication, such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabetorum; immune-complex vasculitis, systemic lupus erythematosus (SLE); inflammatory diseases of the heart such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer. The inflammatory disease can also be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, e.g., shock associated with pro-inflammatory cytokines.

Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

In one embodiment, a reoxygenation injury resulting from organ transplantation occurs during the organ transplantation.

The invention also includes methods for treating, preventing, or otherwise inhibiting reperfusion disease in a subject in need of treatment, prevention, or inhibition thereof. The method comprises administering an Indeno[1,2-c]isoquinoline Compound in an amount sufficient to treat, prevent or inhibit reperfusion disease in the subject. Reperfusion refers to the process whereby blood flow in the blood vessels is resumed following ischemia, such as occurs following constriction or obstruction of the vessel. Reperfusion disease can result following a naturally occurring episode, such as a myocardial infarction, stroke, or during a surgical procedure where blood flow in vessels is intentionally or unintentionally blocked.

In some embodiments, the subject is administered an effective amount of an Indeno[1,2-c]isoquinoline Compound.

The invention also includes pharmaceutical compositions useful for treating or preventing an inflammatory disease or a reperfusion disease, or for inhibiting PARS activity, or more than one of these activities. The compositions can be suitable for internal use and comprise an effective amount of an Indeno[1,2-c]isoquinoline Compound and a pharmaceutically acceptable carrier. The Indeno[1,2-c]isoquinoline Compounds are especially useful in that they demonstrate very low peripheral toxicity or, no peripheral toxicity.

The Indeno[1,2-c]isoquinoline Compounds can be administered in amounts that are sufficient to treat or prevent an inflammatory disease or a reperfusion disease and/or prevent the development thereof in subjects.

Administration of the Indeno[1,2-c]isoquinoline Compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or thelike, preferably in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both

bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those skilled in the pharmaceutical arts.

Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising an Indeno[1,2-c]isoquinoline Compound and a pharmaceutically acceptable carrier, such as a) a diluent, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also c) a binder, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone; if desired d) a disintegrant, *e.g.*, starches, agar, methyl cellulose, bentonite, xanthan gum, algiic acid or its sodium salt, or effervescent mixtures; and/or e) absorbent, colorant, flavorant and sweetener.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the Indeno[1,2-c]isoquinoline Compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension.

The Indeno[1,2-c]isoquinoline Compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

The Indeno[1,2-c]isoquinoline Compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in United States Patent No. 5,262,564.

Indeno[1,2-c]isoquinoline Compounds can also be delivered by the use of monoclonal antibodies as individual carriers to which the Indeno[1,2-c]isoquinoline Compound molecules are coupled. The Indeno[1,2-c]isoquinoline Compounds can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol,

polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the Indeno[1,2-c]isoquinoline Compounds can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

One embodiment for parenteral administration employs the implantation of a slow-release or sustained-released system, according to U.S. Pat. No. 3,710,795, incorporated herein by reference.

The compositions can be sterilized or contain non-toxic amounts of adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure pH buffering agents, and other substances, including, but not limited to, sodium acetate or triethanolamine oleate. In addition, they can also contain other therapeutically valuable substances.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, preferably from about 1% to about 70% of the Indeno[1,2-c]isoquinoline Compound by weight or volume.

The dosage regimen utilizing the Indeno[1,2-c]isoquinoline Compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular Indeno[1,2-c]isoquinoline Compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

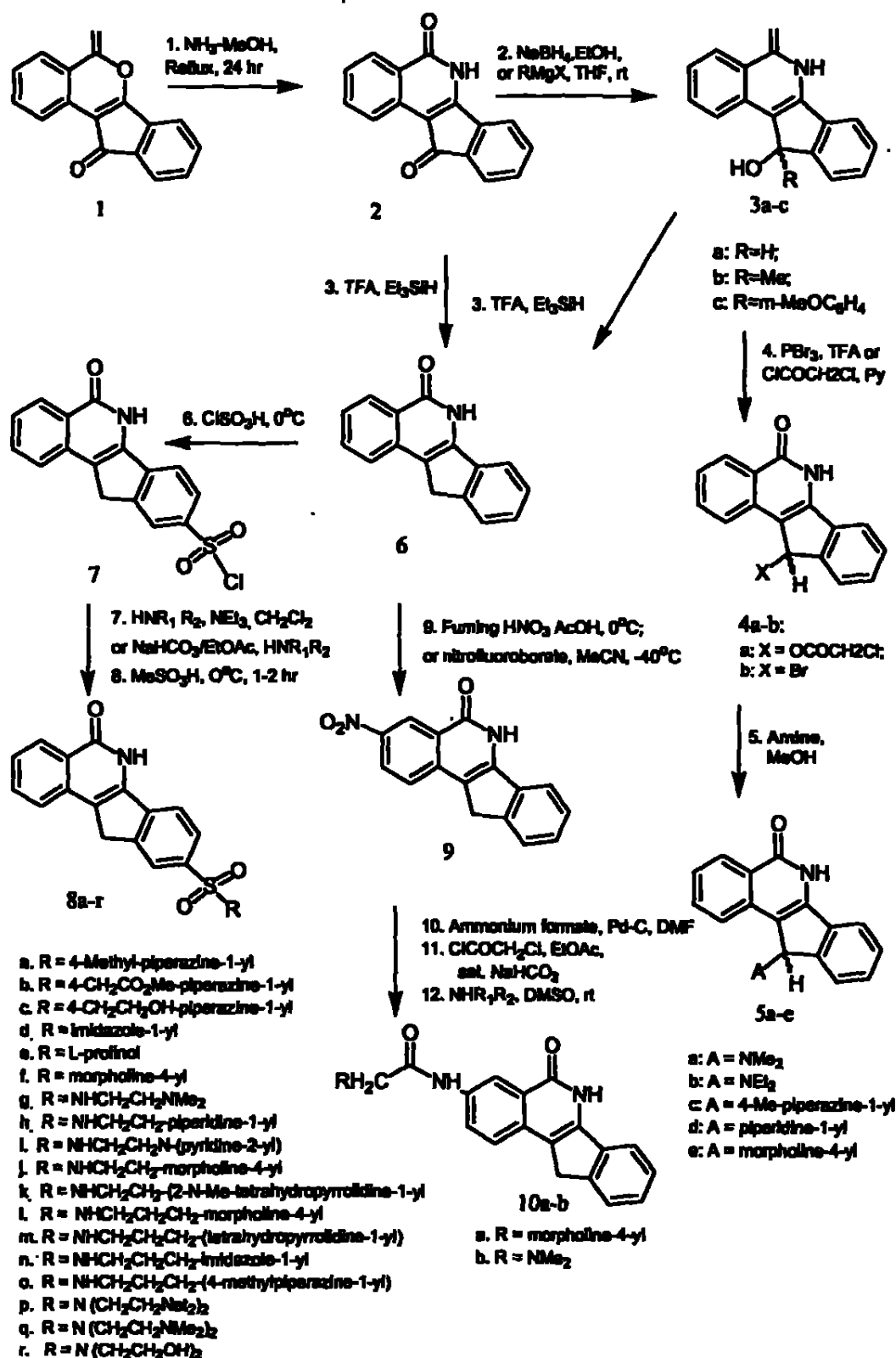
Effective dosage amounts of the present invention, when used for the indicated effects, range from about 0.05 to about 1000 mg of Indeno[1,2-c]isoquinoline Compound per day. The compositions can contain about 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100.0, 250.0, 500.0 or 1000.0 mg of Indeno[1,2-c]isoquinoline Compound. In one embodiment,

the compositions are in the form of a tablet that can be scored. Effective plasma levels of the Indeno[1,2-c]isoquinoline Compounds can range from about 0.002 mg to about 50 mg per kg of body weight per day.

Indeno[1,2-c]isoquinoline Compounds can be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, Indeno[1,2-c]isoquinoline Compounds can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration can be continuous rather than intermittent throughout the dosage regimen. Other illustrative topical preparations include creams, ointments, lotions, aerosol sprays and gels, wherein the concentration of Indeno[1,2-c]isoquinoline Compound ranges from about 0.1% to about 15%, w/w or w/v.

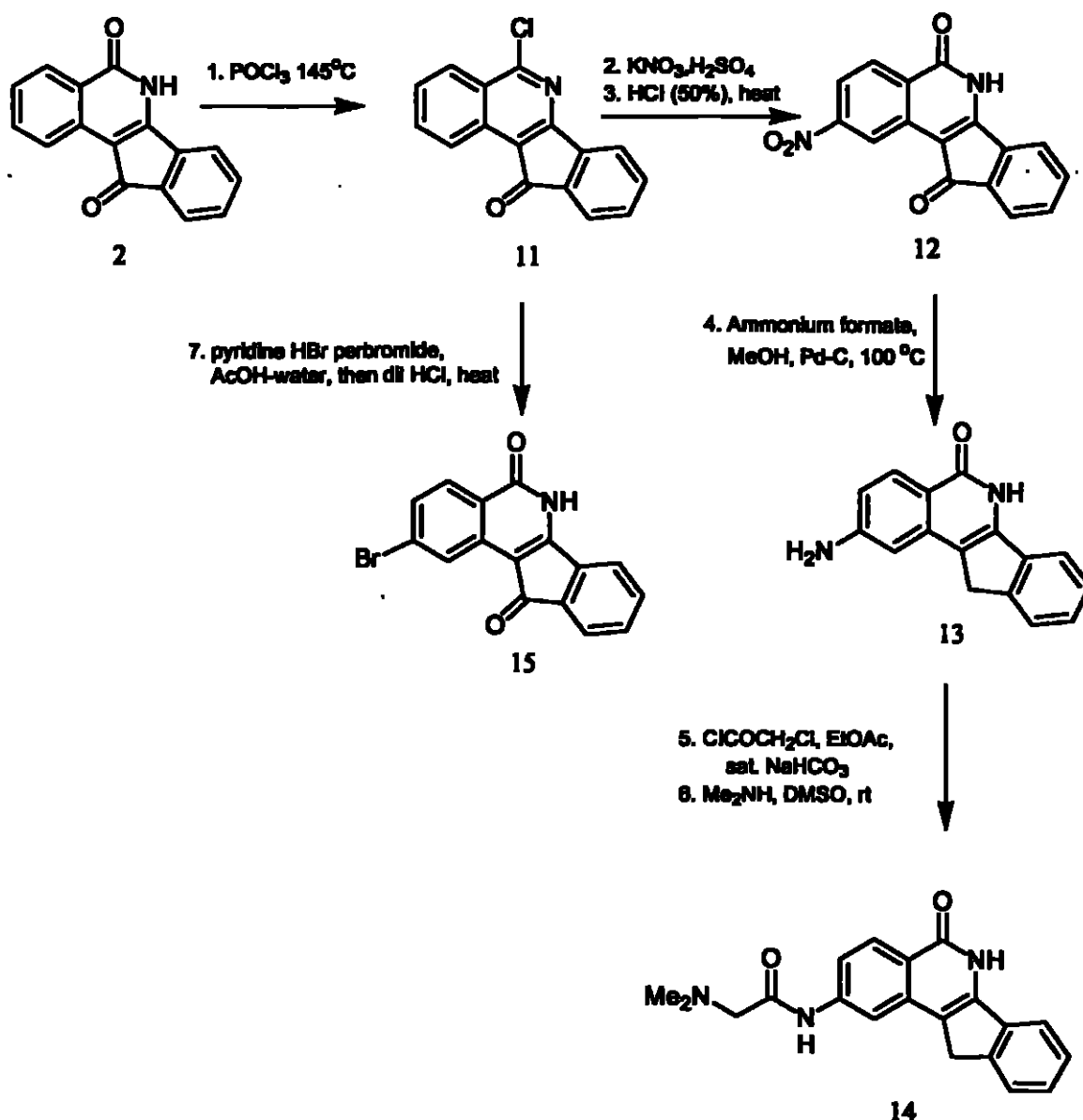
Methods for making Indeno[1,2-c]isoquinoline Compounds

Examples of synthetic pathways useful for making Indeno[1,2-c]isoquinoline Compounds are set forth in the Examples, below and generalized in Schemes 1 and 2.



Scheme 1

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Scheme 2

5,6-dihydro-5,11-diketo-11H-indeno[1,2-c]isoquinoline was prepared by reacting compound 1 (Aldrich Chemical, Milwaukee, WI) with ammonia in methanol.

(±) 11-hydroxy-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (3a) was prepared by reacting 2 with NaBH_4 in ethanol.

(±) 11-hydroxy-11-methyl-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (3b) was prepared by reacting 2 with MeMgI .

(±) 11-hydroxy-11-(*m*-methoxyphenyl)-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (3c) was prepared from 2 using *m*- $\text{MeO-C}_6\text{H}_4\text{MgI}$.

(±) 11-*N,N*-dimethylamino-5,6-dihydro-5-oxo-11*H*-indeno [1,2-*c*]isoquinoline (5a) was prepared from 3a using chloroacetylchloride followed by reacting with dimethylamine. Similarly prepared are: (±) 11-*N,N*-diethylamino-5,6-dihydro-5-oxo-11*H*-indeno [1,2-*c*]isoquinoline (5b), (±) 11-*N*-(piperidino-1-yl)-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*] isoquinoline (5d), (±) 11-*N*-(4-methylpiperazino-1-yl)-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*] isoquinoline (5e), (±) 11-*N*-(morpholino-4-yl)-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (5e). (+) 11-*N*-(morpholino-4-yl)-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (5e) was also prepared from (±) 11-bromo-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (4b).

5,6-Dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (6) is prepared by reduction of 5,6-dihydro-5,11-diketo-11*H*-indeno[1,2-*c*]isoquinoline (2) or (±) 11-hydroxy-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (3a) using CF_3COOH /triethylsilane.

9-Chlorosulphonyl-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*] isoquinoline (7) was prepared by chlorosulfonation of 5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (6).

9-[*N*-(4-methylpiperazine-1-yl)sulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*] isoquinoline (8a) was prepared from 9-chlorosulphonyl-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (7), and *N*-methylpiperazine. Similarly prepared are: 9-[*N*-(4-carbomethoxymethylenepiperazino-1-yl)sulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8b), 9-[*N*-(4-(2-hydroxyethyl)piperazino-1-yl)-sulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8c), 9-[*N*-(imidazolo-1-yl)sulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8d), 9-[*N*-(2-hydroxypropyl) sulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8e), 9-[*N*-morpholinesulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8f), 9-[*N*-(2-[*N,N*-dimethylamino]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8g), 9-[*N*-(2-[piperidino-1-yl]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8h), 9-[*N*-(2-(pyridino-2-yl)-ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8i), 9-[*N*-(2-[morpholino-4-yl]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinoline (8j), 9-[*N*-(2-[*N*-methyltetrahydropyrrolidino-1-yl]ethyl) aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8k), 9-[*N*-(3-[morpholino-4-yl]propyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8l), 9-[*N*-(3-[tetrahydropyrrolodino-1-yl]propyl)aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*] isoquinoline (8m), 9-[*N*-(3-[imidazolo-1-yl]propyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11*H*-indeno-[1,2-*c*]isoquinoline (8n), 9-[*N*-(3-(4-

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methylpiperazino-1-yl]propyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11H-indeno-[1,2-c]isoquinoline (8e), 9-[*N,N*-di-(2-[*N,N*-diethylamino]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11H-indeno-[1,2-c]isoquinoline (8p), 9-[*N,N*-di-(2-[*N,N*-dimethylamino]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11H-indeno-[1,2-c]isoquinoline (8q), and 9-[*N,N*-di-(2-[*N,N*-dihydroxyethylamino]ethyl)-aminosulphonyl]-5,6-dihydro-5-oxo-11H-indeno-[1,2-c]isoquinoline (8r).

The amide derivatives 3-morpholin-4-yl-*N*-(5-oxo-5,11-dihydro-6*H*-indeno[1,2-c]isoquinolin-3-yl)-acetamide (10a), 3-dimethylamino-*N*-(5-oxo-5,11-dihydro-6*H*-indeno[1,2-c]isoquinolin-3-yl)-acetamide (10b) and 2-dimethylamino-*N*-(5-oxo-5,11-dihydro-6*H*-indeno[1,2-c]isoquinolin-2-yl)-acetamide (14) were prepared from 5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (6) and 5-chloro-11H-indeno[1,2-c]isoquinoline (11) using nitration, then reduction, and followed by amination of the chloroacetamide intermediate. 2-bromo-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (15) was prepared by bromination of chloroamide 11.

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims. The following examples illustrate the synthesis of illustrative Indeno[1,2-c]isoquinoline Compounds of the invention, and demonstrates their usefulness for treating or preventing an inflammatory disease or reperfusion disease.

5. EXAMPLES

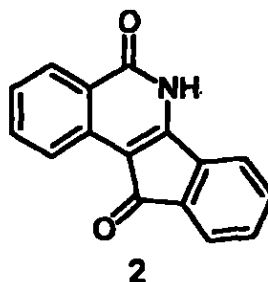
Example 1: Synthesis of Illustrative Indeno[1,2-c]isoquinoline Compounds

a) General Methods

Proton NMR spectra were obtained using a Varian 300 MHz spectrophotometer and chemical shift values (δ) are reported in parts per million (ppm). TLC was performed using TLC plates precoated with silica gel 60 F-254, and preparative TLC was performed using precoated Whatman 60A TLC plates. All intermediates and final compounds were characterized on the basis of ¹H NMR and MS data.

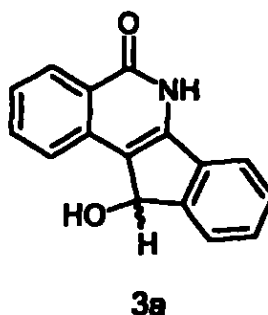
b) Synthesis of 5,6-dihydro-5,11-diketo-11*H*-indeno [1,2-c]isoquinoline (2):

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A stirred suspension of 1 (55 g, 0.22 mol) in NH_3/MeOH (7.0N, 700 mL) was refluxed 15 for 24 h. The reaction mixture was then allowed to cool to room temperature and was filtered and washed thoroughly with MeOH to provide 46 g of the orange colored above-titled product in 84% yield. ^1H NMR ($\text{DMSO}-d_6$): δ 7.48-7.61 (m, 4H), 7.80-7.88 (m, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 8.22 (d, $J = 8.4$ Hz, 1H), 8.44 (d, $J = 7.5$ Hz, 1H), 13.05 (s, 1H); ^{13}C NMR ($\text{DMSO}-d_6$): δ 106.33, 121.63, 122.94, 123.27, 124.80, 128.45, 132.17, 133.60, 134.03, 134.68, 134.68, 134.81, 137.09, 156.41, 163.76, 190.57; MS (ES^+): m/z 246.2 (M-1); Anal. Calcd for $\text{C}_{16}\text{H}_9\text{NO}_2$: C, 77.72; H, 3.67; N, 5.67; Found: C, 77.54; H, 3.69, N, 5.69.

c) Synthesis of ($\pm$) 11-hydroxy-5,6-dihydro-5-oxo-11H-indeno[1,2-c] isoquinoline (3a):

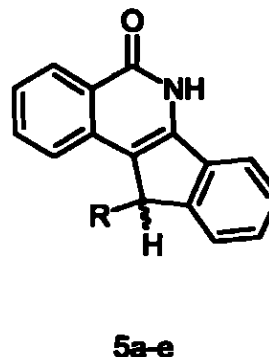
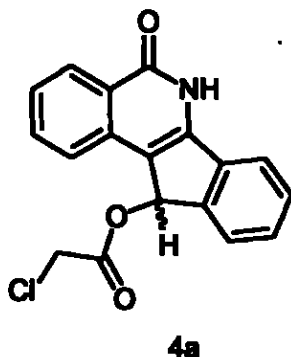


To a stirred suspension of 2 (2.5 g, 0.01 mol) in EtOH (25 mL) was added NaBH_4 (3.75 g, 0.1 mol) at room temperature in small portions over 30 min. The reaction mixture was stirred for an additional 2 h and then cooled to 0°C where it was triturated with dilute HCl (10% soln.). The resulting solid precipitated was filtered and washed with water and MeOH to provide 3a (2.326 g, 92%). ^1H NMR ($\text{DMSO}-d_6$): δ 5.58 (d, $J = 8.1$ Hz, 1H), 5.78 (d, $J = 8.7$ Hz, 1H), 7.33-7.89 (m, 6H), 7.95 (d, $J = 7.8$ Hz, 1H), 8.22 (d, $J = 7.8$ Hz, 1H), 12.29 (s, 1H); ^{13}C NMR ($\text{DMSO}-d_6$): δ 77.44, 118.81, 120.15, 124.28, 125.04, 125.67, 126.34, 128.46, 128.64, 128.95, 133.27, 135.62, 136.12, 139.93, 148.55, 163.69; MS (ES^+):

m/z 250.1 (M+1); Anal. Calcd for C₁₆H₁₁NO₂: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.01; H, 4.57, N, 5.59.

Similarly, by reacting 2 with MeMgI and m-MeO-C₆H₄MgBr, respectively, compounds (±) 11-hydroxy-11-methyl-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (3b) and (±) 11-hydroxy-11-(m-methoxyphenyl)-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (3c) were prepared.

d) Synthesis of 11-substituted 5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinolines (5a-e):



5a: R = NMe₂

5b: R = NEt₂

5c: R = -piperidine-1-yl

5d: R = -N-methyl-piperidin-4-yl

5e: R = -morpholin-1-yl

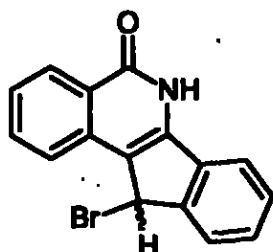
To a stirred suspension of 3a (0.5 g, 0.002 mol) in pyridine (10 mL) was added chloroacetyl chloride (0.81 g, 0.006 mol) at 0°C. The reaction mixture was allowed to warm to room temperature and stir for 24 h. The reaction mixture was then poured on ice and extracted with EtOAc. The organic layer was separated, dried and concentrated to provide crude compound 4a, which was treated further with dimethylamine and stirred at room temperature for 24 h. The reaction mixture was poured on ice, and treated with 10% HCl. The resulting mixture was then basified using saturated aqueous NaHCO₃ and the resulting solid was filtered to provide the desired product 5a. ¹H NMR (DMSO-D₆): δ 2.31 (s, 6H), 5.00 (s, 1H), 7.28-7.45 (m, 3H), 7.68 - 7.73 (m, 2H), 7.95 (d, J = 6.9 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 12.26 (s, 1H); ¹³C NMR (DMSO-D₆): δ 68.09,

116.28, 120.52, 124.58, 125.74, 126.27, 126.34, 127.68, 128.64, 133.02, 136.27, 144.45, 163.80; MS (ES⁺): m/z 277.2 (M+1).

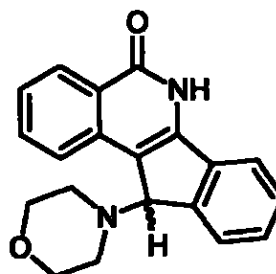
The following compounds were also prepared by reacting 4a as above with diethylamine, piperidine, N-methylpiperidine and morpholine, respectively:

- (±) 11-diethylamino-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (5b)
- (±) 11-piperidino-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (5c)
- (±) 11-(N-methylpiperazino)-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (5d)
- (±) 11-morpholino-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinoline (5e).

e) Synthesis of (±) 11-morpholino-5,6-dihydro-5-oxo-11H-indeno[1,2-c]isoquinolines (5e) from 4b



4b



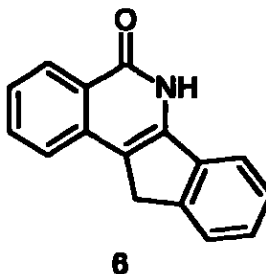
5e

To a stirred suspension of 3a (0.6 g, 2.4 mmol) in trifluoroacetic acid (5 mL) was added phosphorus tribromide (1.0 M soln. in CH₂Cl₂, 3 mL) at room temperature, and the reaction mixture was stirred for 8 h. The reaction mixture was poured on ice and the resulting solid was filtered to provide bromo compound 4b (0.61 gm, 76%). ¹H NMR (DMSO-D₆): δ 7.35-7.50 (m, 3H), 7.61 (d, J = 6.6 Hz, 1H), 7.73-7.82 (m, 2H), 7.94 (d, J = 6.6 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 12.41 (s, 1H); ¹³C NMR (DMSO-D₆): δ 52.06, 79.35, 114.43, 120.56, 123.58, 125.27, 125.50, 126.68, 128.55, 128.86, 129.66, 133.73, 135.91, 136.61, 141.39, 143.95, 163.74.

Compound 4b (0.5 g) was suspended in MeOH (10 mL) and treated with excess morpholine (~10 eq.) at room temperature and stirred at 60°C for 3 h. The reaction mixture was poured on ice, and diluted with ethyl acetate (40 mL). The organic layer was separated and extracted in dil. HCl (10% soln.), the aqueous layer was then basified with sat. aq. NaHCO₃ and the resulting solid precipitated was filtered and dried to provide 5e (0.46 g, 90%). ¹H NMR (DMSO-D₆): δ 2.56 (m, 4H), 3.49 (m, 4H), 5.04 (s, 1H), 7.31-7.45 (m, 3H),

7.65 -7.76 (m, 2H), 7.96 (d, $J = 7.2$ Hz, 1H), 8.20-8.24 (m, 2H), 12.29 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 49.36, 67.62, 68.11, 115.20, 120.60, 124.47, 125.84, 126.34, 126.41, 127.76, 128.30, 128.72, 133.09, 136.30, 136.96, 140.35, 144.44, 163.67.

f) Synthesis of 5,6-dihydro-5-oxo-11H-indeno [1,2-c] isoquinoline (6):

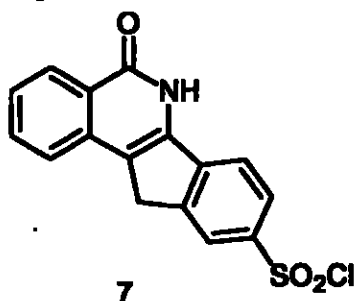


Method I: To a stirred solution of the alcohol 3a (0.35 g, 1.4 mmol) in trifluoroacetic acid (10 mL) was added at room temperature triethylsilane (0.812 g, 7 mmol) and the reaction mixture was stirred for 24 h. Trifluoroacetic acid was evaporated in vacuo and EtOAc was added to the resulting crude product. The resulting solid was filtered and washed with H_2O and EtOAc to provide the above-titled compound 6 (0.285 g, 87 %). ^1H NMR (DMSO- D_6): δ 3.89 (s, 2H), 7.30 - 7.47 (m, 3H), 7.59 (d, $J = 6.9$ Hz, 1H), 7.72 - 7.74 (m, 2H), 7.98 (d, $J = 7.8$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 12.31 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 33.51, 116.50, 120.19, 124.01, 125.51, 125.55, 126.42, 127.50, 127.68, 128.56, 133.45, 136.39, 137.53, 140.18, 143.80, 163.46; MS (ES $^+$): m/z 232.1 (M-1); Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{NO}$: C, 82.38; H, 4.75; N, 6.00. Found: C, 81.79; H, 4.45; N, 5.99.

Method II: To a stirred suspension of 2 (40 g, 0.16 mol) in trifluoroacetic acid (2.5 L) was added triethylsilane (94 g, 0.8 mol) in small portions at room temperature and the reaction mixture was stirred for 96 h, during which time the reaction progress was monitored using TLC (eluent - 5% MeOH/ CH_2Cl_2). The reaction mixture was slowly poured on ice, filtered, washed with copious amounts of H_2O and MeOH and dried in vacuo to provide the above-titled compound 6 (33.1 g, 88 %), whose spectral data were identical to those of a sample of compound 6 that was obtained using Method I.

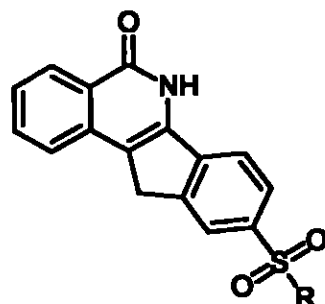
g) Synthesis of 9-chlorosulfonyl-5,6-dihydro-5-oxo-11H-indeno[1,2-c] isoquinoline (7):

3625



Compound 6 (40 g, 0.17 mol) was added in small portions to chlorosulfonyl chloride (112 mL, 1.71 mol) at 0°C and the reaction mixture was allowed to warm to room temperature and stir for 2 h. The reaction mixture was slowly poured on ice and the resulting yellow solid was filtered, washed thoroughly with water and EtOAc and dried in vacuo to provide the above-titled product 7 (52 g, 92 %). ¹H NMR (DMSO-D₆): δ 3.91 (s, 2H), 7.43 - 7.48 (m, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.74 - 7.76 (m, 2H), 7.79 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), Anal. Calcd for C₁₆H₁₂ClNO₄S: C, 54.94; H, 3.46; N, 4.00. Found: C, 55.28; H, 3.43, N, 3.68, Karl-Fisher, 2.95.

b) Synthesis of 9-sulphonamido derivatives of 5,6-dihydro-5-oxo-11*H*-indeno[1,2-*c*]isoquinolines (8a-r) from 7:



8a-r

- a. R = -N-(4-Methyl-piperazine-1-yl)
- b. R = -N-(4-CH₂CO₂Me)-piperazine-1-yl
- c. R = -N-(4-CH₂CH₂OH)-piperazine-1-yl
- d. R = -N-imidazole-1-yl
- e. R = -N-L-prolinyl
- f. R = -N-morpholin-4-yl
- g. R = -NHCH₂CH₂NMe₂
- h. R = -NHCH₂CH₂-piperidine-1-yl
- i. R = -NHCH₂CH₂-(pyridine-2-yl)
- j. R = -NHCH₂CH₂-morpholin-4-yl
- k. R = -NHCH₂CH₂-(2-N-Me-tetrahydropyrrolidine-1-yl)
- l. R = -NHCH₂CH₂CH₂-morpholin-4-yl
- m. R = -NHCH₂CH₂CH₂-(tetrahydropyrrolidine-1-yl)
- n. R = -NHCH₂CH₂CH₂-imidazole-1-yl
- o. R = -NHCH₂CH₂CH₂-(4-methylpiperazine-1-yl)
- p. R = -N(CH₂CH₂NMe₂)₂
- q. R = -N(CH₂CH₂NMe₂)₂
- r. R = -N(CH₂CH₂OH)₂

Method I: To a stirred suspension of 3-(4-morpholino)-1-propylamine (17.28 g, 0.12 mol) in EtOAc was added sat. aq. NaHCO₃ (300 mL), and the mixture was allowed to stir for 15 min. Compound 7 (4.0 g, 0.012 mol) was then introduced in small portions at room temperature. The reaction mixture was stirred for 24h; filtered and washed with H₂O, EtOAc and MeOH; refluxed in MeOH for 30 min; filtered while still warm; and washed with MeOH to provide the above-titled product 8l as a free base (2.330 g, 44%). ¹H NMR(DMSO-D₆): δ 1.47-1.52 (m, 2H), 2.16-2.21 (m, 4H), 2.47-2.48 (m, 2H), 3.44-3.48 (m, 2H), 3.23 (m, 4H), 4.02 (s, 2H), 7.49 - 7.58 (m, 1H), 7.78-7.82 (m, 3H), 7.97 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 9.59 (s, 1H), 12.42 (s, 1H).

The free bases of 8d, 8g, 8h, 8j, 8l, 8m-8r were also prepared by Method I, but substituting 3-(4-morpholino)-1-propylamine with imidazole, 2-dimethylamino-ethylamine,

2-(*N*-piperidinyl)-ethylamine, 2-(*N*-morpholinyl)-ethylamine, 3-(*N*-morpholinyl)-propylamine, 3-(*N*-tetrahydropyrrolidinyl)-propylamine, 3-(*N*-imidazolyl)-propylamine, 3-(*N*-(4-methylpiperazinyl)-propylamine, di-(2-(diethylamino)-ethyl)amine, di-(2-(dimethylamino)-ethyl)amine and di-(2-hydroxyethyl)amine, respectively.

9-(*N*-sulphonylimidazole)-5,6-dihydro-5oxo-11*H*-indeno[1,2-*c*]isoquinolines (8a-r):

Method II: To a stirred suspension of 3-(4-morpholino)-1-propylamine (4.250 g) in CH₂Cl₂ (100 mL) was added 7 (1.950 g, 5.89 mmol) and the resulting mixture was stirred for 5 minutes. Subsequently, triethylamine (3 mL) was added and the reaction mixture was stirred for 24 hr at room temperature. After this time the precipitate was collected and washed with MeOH (2 x 100 mL) and the crude solid product transferred to a round bottom flask. This material was diluted with MeOH (200 mL), heated to reflux for 30 min. and filtered while still warm. The resulting filtercake was washed with MeOH (200 mL) to provide the desired product as the free base of 8I (1.460 g, 56%).

The free bases of compounds 8a-r were prepared using Method II, but substituting 3-(4-morpholino)-1-propylamine with imidazole, 2-dimethylamino-ethylamine, 2-(*N*-piperidinyl)-ethylamine, 2-(*N*-morpholinyl)-ethylamine, 3-(*N*-morpholinyl)-propylamine, 3-(*N*-tetrahydropyrrolidinyl)-propylamine, 3-(*N*-imidazolyl)-propylamine, 3-(*N*-(4-methylpiperazinyl)-propylamine, di-(2-(diethylamino)-ethyl)amine, di-(2-(dimethylamino)-ethyl)amine and di-(2-hydroxyethyl)amine, respectively.

i) General procedure for the preparation of mesylate salts of 8a-r:

Free base 8I was added to methanesulfonic acid at 0°C and the resulting mixture was allowed to warm to room temperature and stir for 2 h. The reaction mixture was then poured into cold MeOH (between -10°C and 0°C) and the precipitated solid was filtered, washed with MeOH (100 mL) and dried in vacuo. The dried solid was then dissolved in water (~200 mL) and lyophilized to provide the methanesulfonate monohydrate salt 8I. (1.020 g, 84%). ¹H NMR (DMSO-D₆): δ 1.75-1.85 (m, 2H), 2.35 (s, 3H), 2.78-2.84 (m, 2H), 2.96-3.12 (m, 4H), 3.36 (d, *J* = 12.3 Hz, 2H), 3.61 (t, *J* = 11.4 Hz, 2H), 3.94 (d, *J* = 12.9 Hz, 2H), 4.03 (s, 2H), 7.49 - 7.55 (m, 1H), 7.76-7.84 (m, 3H), 7.99 (d, *J* = 0.9 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 9.59 (s, 1H), 12.42 (s, 1H); ¹³C NMR (DMSO-D₆): δ 24.27, 33.86, 51.89, 54.51, 64.02, 119.70, 120.39, 123.53, 126.09, 126.45, 128.63,

133.66, 135.80, 138.71, 141.21, 144.57, 163.29; Anal. Calcd for $C_{24}H_{31}N_3O_4S_2$: C, 52.06; H, 5.46; N, 7.59, Karl-Fisher, 3.36. Found: C, 51.85; H, 5.35, N, 7.30, Karl-Fisher, 4.32. Similarly, HCl, H_2SO_4 , CH_3COOH , and succinic acid salts of 8l were prepared by substituting methanesulfonic acid with HCl, H_2SO_4 and CH_3COOH , respectively.

Example 2. Effect of Illustrative Indeno[1,2-c]isoquinoline Compounds on PARS activity in cultured macrophages, using a whole-cell based assay and a purified enzyme assay.

Demonstration of illustrative Indeno[1,2-c]isoquinoline Compounds' ability to inhibit PARS and prevent peroxynitrite induced cytotoxicity was shown using methods described in Virag et al., *Br J Pharmacol.* 1999, 126(3):769-77; and *Immunology* 1998, 94(3):345-55. RAW mouse macrophages were cultured in DMEM medium with high glucose and supplemented with 10% fetal bovine serum. Cells were used at 80% confluence in 12-well plates. Cells were pretreated with various concentrations (100 nM - 1 μ M) of an Indeno[1,2-c]isoquinoline Compound for 10 min. Peroxynitrite, a prototypical oxidant which induces DNA single strand breakage, was used to induce PARS activation. Peroxynitrite was diluted in phosphate buffered saline (PBS) (pH 11.0) and added to the cells in a bolus of 50 μ l. Cells were then incubated for 20 min. Peroxynitrite was decomposed by incubation for 30 min at pH 7.0, used as a control, and failed to influence the parameter studied. After the 20 min incubation, the cells were spun, the medium was aspirated and the cells were resuspended in 0.5 ml assay buffer (56 mM HEPES pH 7.5, 28 mM KCl, 28 mM NaCl, 2 mM $MgCl_2$, 0.01 % w/v digitonin and 0.125 μ M NAD^+ and 0.5 μ Ci/ml ^3H - NAD^+). Following an incubation in assay buffer, (10 min at 37 $^{\circ}C$), PARS activity was measured as follows: 200 μ l ice cold 50 % w/v TCA was added and the samples were incubated for 4 hours at 4 $^{\circ}C$. Samples were then spun (10 min @ 10,000 g) and pellets washed twice with ice cold 5 % w/v TCA and solubilized overnight in 250 μ l 2 % w/v SDS/0.1 N NaOH at 37 $^{\circ}C$. The contents of the tubes were added to 6.5 ml ScintiSafe Plus scintillation liquid (Fisher Scientific) and radioactivity was determined using a liquid scintillation counter (Wallac, Gaithersburg, MD). The results shown in Table 1 demonstrate that the illustrative Indeno[1,2-c]isoquinoline Compounds significantly and dose-dependently inhibit the activation of PARS in the macrophage assay.

Table 1. Inhibitory effect of various novel substituted indeno[1,2-c]isoquinolines on PARS activation in cultured murine macrophages.

Compound No.	% PARS inhibition at 1 μ M	% PARS inhibition at 300 nM	% PARS inhibition at 100 nM
2	60	NT	16
3a	67	NT	8
3b	25	0	NT
3c	21	9	NT
4b	88	NT	51
5a	55	NT	10
5b	33	NT	0
5c	24	NT	0
5d	48	NT	0
5e	21	NT	0
6	65	NT	30
7	50	NT	0
8a	NT	47	NT
8b	NT	NT	NT
8c	NT	27	NT
8d	NT	82	77
8e	NT	68	NT
8f	NT	NT	NT
8g	NT	55	34
8h	NT	76	56
8j	NT	76	34
8k	NT	38	24
8l	NT	84	34
8m	NT	50	NT
8n	NT	82	74
8o	NT	55	48

8p	NT	45	27
8q	NT	28	20
8r	NT	28	20
10a	NT	59	55
10b	NT	17	17

NT = Not tested

The potency of inhibition on purified PARS enzyme was subsequently determined for selected Indeno[1,2-c]isoquinoline Compounds, and the potency was compared with that of 3-aminobenzamide, a prototypical benchmark PARS inhibitor. The assay was performed in 96 well ELISA plates according to instructions provided with a commercially available PARS inhibition assay kit (Trevigen, Gaithersburg, MD). Briefly, wells were coated with 1 mg/mL histone (50 μ l/well) at 4°C overnight. Plates were then washed four times with PBS and then blocked by adding 50 μ l Strep-Diluent (supplied with the kit). After incubation (1h, room temperature), the plates were washed four times with PBS. Appropriate dilutions of PARS inhibitors were combined with 2x PARS cocktail (1.95 mM NAD⁺, 50 μ M biotinylated NAD⁺ in 50 mM TRIS pH 8.0, 25 mM MgCl₂) and high specific activity PARS enzyme (both were supplied with the kit) in a volume of 50 μ l. The reaction was allowed to proceed for 30 min at room temperature. After 4 washes in PBS, incorporated biotin was detected by peroxidase-conjugated streptavidin (1:500 dilution) and TACS Sapphire substrate. The assay confirmed the results of the macrophage-based PARS assay. For example, the PARS inhibitor 8l exerted 50% inhibition of PARS activity in this assay at 3 nM, and thus was approximately 50,000 times more potent than the reference compound 3-aminobenzamide.

Example 3: Effects of illustrative Indeno[1,2-c]isoquinoline Compounds in various models of inflammatory disease and reperfusion disease

a: Effects of illustrative Indeno[1,2-c]isoquinoline Compounds on in vitro cell disease models

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In additional *in vitro* studies in isolated thymocytes, cells were exposed to peroxynitrite or hydrogen peroxide (toxic oxidant species) to induce cytotoxicity. In this system the toxicity is, at least in part, related to activation of the nuclear enzyme PARS. In this oxidant-stimulated thymocyte assay (described, in detail, in Virag et al., *Immunology* 94(3):345-55, 1998), the compounds tested prevented the oxidant-induced suppression of the viability of the cells and did so at the low nanomolar concentration range. An example of this response (Compound 8l) is shown in Table 2. This assay represents an *in vitro* model of cells dying because of exposure to pro-oxidant species, as it occurs in during the reperfusion of ischemic organs.

Table 2. Reduction of peroxynitrite induced cytotoxicity by 30 nM - 3 μ M of the Indeno[1,2-c]isoquinoline Compound 8l.

	Control	+8l 30 nM	+8l 100 nM	+8l 300 nM	+8l 1 μ M	+8l 3 μ M
Cytotoxicity	98%	74%	39%	2%	0%	0%

b: Effect of illustrative Indeno[1,2-c]isoquinoline Compounds on *in vivo* models of inflammatory diseases

In order to substantiate the efficacy of the compounds in inflammatory diseases, the effect of illustrative Indeno[1,2-c]isoquinoline Compounds was demonstrated in a systemic inflammatory model induced by bacterial lipopolysaccharide (LPS), which is reported to be responsible for causing reperfusion diseases and inflammatory diseases such as septic shock and systemic inflammatory response syndrome in animals (*see* Parrillo, *N. Engl. J. Med.*, 328:1471-1478 (1993) and Lamping, *J. Clin. Invest.* 101:2065-2071 (1998). In a series of experiments, mice were pretreated with intraperitoneal injection of 0.1 and 1 mg/kg of compounds 8l, 8p and 8j, and LPS at 10 mg/kg was injected i.p., and TNF- α was measured in the plasma at 90 minutes. As shown in Table 3, all compounds substantially reduced TNF production, indicative of the compounds' anti-inflammatory activity.

Table 3. Reduction of LPS induced TNF production by 0.1 -1 mg/kg intraperitoneal injection of the PARS inhibitor compounds 8L, 8P and 8J in mice *in vivo*

	8j (0.1 mg/kg)	8j (1.0 mg/kg)	8p (0.1 mg/kg)	8p (1.0 mg/kg)	8l (0.1 mg/kg)	8l (1.0 mg/kg)	Vehicle
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TNF	3831.6	5038.8	4470.0	5090.8	3714.6	3509.8	6994.0
(ng/ml)	± 385.2	± 377.1	± 184.4	± 203.7	± 300.9	± 311.5	± 904.4

All compounds markedly suppressed LPS induced TNF production when compared to control.

At high doses, LPS causes multiple organ dysfunction resembling of septic shock, and ultimately death (in part because of the early release of TNF-alpha). Similarly, in a model induced by cecal ligation and puncture (CLP), the live bacteria that derive from the intestinal flora induce systemic inflammation and shock. Agents that inhibit inflammatory mediator production, PARS activation, and cell death in this model prevent mortality induced by LPS or CLP. In experiments with Balb/c mice, injection of 100 mg/kg LPS intraperitoneally caused death in 50% of the animals over 24 h, whereas treatment of the animals with 3 mg/kg/day of compound 8l reduced the endotoxin-induced mortality to 10% under the same experimental conditions. In response to CLP induced shock, compound 8l (3 mg/kg/day) caused a reduction in the mortality from 100% death to 60% death over 24 hours.

The data demonstrating the reduction of TNF production by illustrative Indeno[1,2-c]isoquinoline Compounds in animals subjected to an inflammation model, coupled with the fact that TNF production is an important trigger of inflammation in various inflammatory diseases (such as, for example, colitis, arthritis and neuroinflammation and shock) indicate that the Indeno[1,2-c]isoquinoline Compounds have therapeutic effects in various systemic and local inflammatory diseases, including the rejection of transplanted organs, which entails both an inflammatory disease component and a reperfusion disease component and, accordingly, are useful for treating or preventing an inflammatory disease or a reperfusion disease.

c: Effect of illustrative Indeno[1,2-c]isoquinoline Compounds on *in vivo* models of reperfusion disease

In order to substantiate the efficacy of the Indeno[1,2-c]isoquinoline Compounds in ischemia-reperfusion conditions, the effect of an illustrative Indeno[1,2-c]isoquinoline Compound in a mouse model of ischemic and reperfused gut was tested. The superior

mesenteric artery was occluded for 45 min, followed by a reperfusion for 1 h. Following the end of the reperfusion, gut permeability was measured with the FD4 method in everted gut sacks (Liaudet et al; *Shock* 2000, 14(2):134-41). Ischemia-reperfusion increased the permeability of the gut from 11 ± 4 to 216 ± 27 ml/min/cm², indicative of severe damage of the reperfused gut. Treatment with Compound 81 (3 mg/kg i.v., injected 10 min. prior to initiation of reperfusion) reduced the increase in the permeability of the gut by approximately 73%, indicating a marked maintenance of the gut function. The ischemia-reperfusion studies in the gut were associated with a 80% mortality over 12 hours, whereas only 15% mortality was noted in the animals treated with 81.

In another set of experiments, the effect of Compound 81 in a rat model of middle cerebral artery occlusion/reperfusion was assayed as described in Abdelkarim et al., *Int J Mol Med*. 2001, 7(3):255-60. Occlusion lasted for 2 hours, followed by reperfusion for 24 hours. Infarct size was quantified with tetrazolium staining. Compound 81 was administered at 3 mg/kg/day in 3 divided intraperitoneally injected doses, the first dose being administered 10 min. prior to the initiation of reperfusion. There was an approximately 80% reduction in the degree of cortical necrosis and neuronal death in the animals administered with 81, when compared to vehicle-treated controls. This protection also translated into functional benefit, such as neurological improvements in the PARS inhibitor treated group.

These data indicate that the Indeno[1,2-c]isoquinoline Compounds have therapeutic effects in various systemic and local conditions of reperfusion diseases, including the rejection of transplanted organs, which entails both an inflammatory disease component and a reperfusion disease component and, accordingly, are useful for treating or preventing an inflammatory disease or a reperfusion disease.

d: Effect of illustrative Indeno[1,2-c]isoquinoline Compounds in a diabetes model

PARS inhibitors and PARS deficiency are known to reduce the development of diabetes and the incidence of diabetic complications (Mabley et al., *Br J Pharmacol*. 2001, 133(6):909-9; and Soriano et al., *Nat Med*. 2001, 7(1):108-13). In order to substantiate the efficacy of the Indeno[1,2-c]isoquinoline Compounds in a diabetes model, a single high-dose streptozotocin model of diabetes was conducted as previously described. Briefly, 160 mg/kg streptozotocin was injected to mice treated with vehicle or with illustrative

Indeno[1,2-c]isoquinoline Compounds intraperitoneally (3 mg/kg) and 3 days later blood sugar levels were determined using a blood glucose meter. The data shown in Table 4 demonstrate that the illustrative Indeno[1,2-c]isoquinoline Compounds attenuate the streptozotocin-induced onset of diabetes as they reduce the hyperglycemia.

Table 4. Reduction of streptozotocin (STZ) induced hyperglycemia by 3 mg/kg intraperitoneal injection of the PARS inhibitor compounds 8l, 8p and 8j in mice *in vivo*

	Basal	STZ + Vehicle	STZ + 8j	STZ + 8p	8l
Glucose (mg/ml)	153 ± 21	320 ± 13	253 ± 24	264 ± 24	244 ± 21

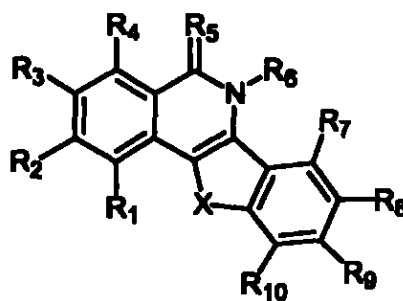
Accordingly, the Indeno[1,2-c]isoquinoline Compounds are useful for treating or preventing diabetes or a diabetic complication.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which have been incorporated herein in their entirety.

What is claimed is:

1. A compound of the formula



(Ia)

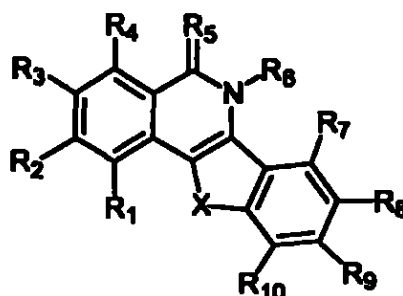
or a pharmaceutically acceptable hydrate or salt thereof,

wherein:

 R_5 is NH or S; R_6 is -H or C_1 - C_4 alkyl; X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arylene-, -O-, -NH-, -S- or -CH(NR₁₁R₁₂)-, wherein n is an integer ranging from 0-5; R_{11} and R_{12} are independently -hydrogen or - C_1 - C_4 alkyl, or N, R_{11} and R_{12} are taken together to form a heterocyclic amine; R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently -hydrogen, -halo, -hydroxy, -O-(C_1 - C_4 alkyl), - C_1 - C_{10} alkyl, -alkylhalo, - C_2 - C_{10} alkenyl, - C_3 - C_8 carbocycle, -aryl, -NH₂, -alkylamino, -C(O)OH, -C(O)O(C_1 - C_4 alkyl), -OC(O)(C_1 - C_4 alkyl), NO₂ or -A-B;wherein A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C_1 - C_4 alkyl)-, -NH-, -CH₂-, -S- or -C(S)-; B is - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, -heterocycle, - C_3 - C_8 carbocycle, -aryl, -NZ₁Z₂, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH, -C(O)O-(C_1 - C_4 alkyl) or -C(O)O-phenyl, any of which are unsubstituted or substituted with one or more of -O-(C_1 - C_4 alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, -NO₂, -NH₂, -aminoalkyl, -aminodialkyl, -heterocyclic amine, - C_1 - C_{10} alkyl, - C_2 - C_{10} alkenyl, - C_2 - C_{10} alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy, - C_1 - C_4 alkylene-C(O)O- C_1 - C_4 alkyl or - C_1 - C_4 alkylene-OC(O)- C_1 - C_4 alkyl groups; and

Z_1 and Z_2 are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z_3)(Z_4), where Z_3 and Z_4 are independently, -H or -C₁-C₃ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

2. A compound of the formula



(Ib)

or a pharmaceutically acceptable hydrate or salt thereof,
wherein:

R_3 is O, NH or S;

R_4 is -H or C₁-C₄ alkyl;

X is -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arylene-, -O-, -NH-,
-S- or -CH(NR₁₁,R₁₂)-, wherein n is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₃ alkyl, or N, R₁₁ and R₁₂ are taken together to form a heterocyclic amine.

R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₃ alkyl), -C₁-C₁₀ alkyl, -alkylhalo, -C₂-C₁₀ alkenyl, -C₃-C₈ carbocycle, -aryl, -NH₂, -alkylamino, -C(O)OH, -C(O)O(C₁-C₃ alkyl), -OC(O)(C₁-C₃ alkyl), NO₂ or -A-B;

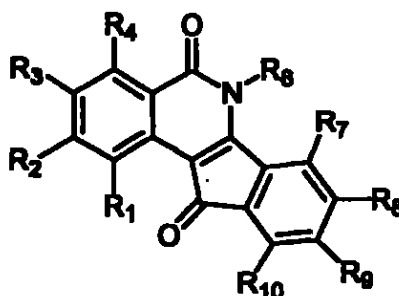
wherein A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -heterocycle, -C₃-C₈ carbocycle, -aryl, -NZ₁Z₂, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH, -C(O)O-(C₁-C₃ alkyl) or -C(O)O-phenyl, any of which are unsubstituted or substituted with one or more of

-O-(C₁-C₃ alkyl), -halo, -alkylhalo, -alkanol, -alkylamino, -hydroxy, -NO₂, -NH₂,
 -aminoalkyl, -aminodialkyl, -heterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl,
 -C₂-C₁₀ alkynyl, -aryl, -benzyl, -alkylamido, -alkylcarboxy,
 -C₁-C₃ alkylene-C(O)O-C₁-C₃ alkyl or -C₁-C₃ alkylene-OC(O)-C₁-C₃ alkyl groups; and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₃ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z₁ and Z₂ are taken together to form a heterocyclic amine.

3. A compound of the formula



(II)

or a pharmaceutically acceptable hydrate or salt thereof,
 wherein:

R₆ is -H or C₁-C₄ alkyl;

R₁, R₂, R₃, R₄, R₇, R₈, R₉, and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₃ alkyl), -C₁-C₁₀ alkyl, -alkylhalo, -C₂-C₁₀ alkenyl, -C₃-C₈ carbocycle, -aryl, -NH₂, -alkylamino, -C(O)OH, -C(O)O(C₁-C₃ alkyl), -OC(O)(C₁-C₃ alkyl), NO₂ or -A-B; wherein at least one of R₁, R₄ and R₁₀ is other than hydrogen;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -heterocycle, -C₃-C₈ carbocycle, -aryl, -NH₂, -alkylamino, -aminodialkyl, -alkylheterocycle, -arylamido, -C(O)OH, -C(O)O-(C₁-C₃ alkyl), -C(O)O-phenyl or -NZ₁Z₂; and

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Z_1 and Z_2 are independently -H or $-C_1-C_{10}$ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or $-N(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, -H or $-C_1-C_3$ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or $-NH_2$; or N, Z_3 and Z_4 are taken together to form an unsubstituted or substituted heterocyclic amine; or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

4. The compound of claim 1, 2 or 3 wherein R_5 is O, and R_6 is hydrogen.
5. The compound of claim 1 wherein R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 , and R_{10} are independently hydrogen, methyl, ethyl, halo, $-NO_2$, hydroxy, methoxy, ethoxy, $-NH_2$, -aminoalkyl, -aminodialkyl or -A-B.
6. The compound of claim 5, wherein either R_8 or R_9 , but not both, is -A-B.
7. The compound of claim 6 wherein R_1 , R_2 , R_3 , R_4 , R_7 , and R_{10} are hydrogen.
8. The compound of claim 1, wherein R_9 is -A-B.
9. The compound of claim 5, wherein R_9 is -A-B.
10. The compound of claim 7, wherein R_9 is -A-B and R_8 is hydrogen.
11. The compound of claim 6, wherein A is $-SO_2-$, $-SO_2NH-$ or $-NHCO-$.
12. The compound of claim 7, wherein A is $-SO_2-$, $-SO_2NH-$ or $-NHCO-$.
13. The compound of claim 8, wherein A is $-SO_2-$, $-SO_2NH-$ or $-NHCO-$.
14. The compound of claim 9, wherein A is $-SO_2-$, $-SO_2NH-$ or $-NHCO-$.
15. The compound of claim 10, wherein A is $-SO_2-$, $-SO_2NH-$ or $-NHCO-$.

16. The compound of claim 1, wherein R₉ is -A-B and B is -C₁-C₈ alkyl, -heterocycle, -C₃-C₈ carbocycle, -aryl, -alkylamino, -alkanol or -alkylheterocycle.

17. The compound of claim 16, wherein B is -C₁-C₈ alkyl.

18. The compound of claim 5, wherein A is -SO₂- and B is -NZ₁Z₂, and Z₁ and Z₂ are independently hydrogen, or -C₁-C₈ alkyl, unsubstituted or substituted with -halo, -hydroxy or -NZ₃Z₄; wherein Z₃ and Z₄ are independently -hydrogen, -C₁-C₈ alkyl, unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂, or wherein N, Z₁ and Z₂, taken together, form a heterocyclic amine.

19. The compound of claim 18, wherein Z₁ and Z₂ are -(CH₂)_nD; wherein n is an integer ranging from 1-5, and D is hydrogen, hydroxy, heterocyclic amine or -NZ₃Z₄; wherein Z₃ and Z₄ are independently hydrogen, methyl or ethyl.

20. The compound of claim 18, wherein B is a heterocycle, which may be unsubstituted or substituted with one or more of methyl, ethyl, or -alkanol.

21. The compound of claim 18, wherein Z₁ is hydrogen and Z₂ is -NZ₃Z₄, wherein n is an integer ranging from 1-5, and Z₃ and Z₄ are independently methyl or ethyl, or, taken together, NZ₃Z₄ forms a heterocyclic amine.

22. The compound of claim 15, wherein X is -CH₂-, A is -SO₂- and B is -NZ₁Z₂; wherein Z₁ and Z₂ are independently hydrogen, -C₁-C₈ alkyl unsubstituted or substituted with halo, hydroxy or -NZ₃Z₄; wherein Z₃ and Z₄ are independently hydrogen, -C₁-C₈ alkyl, unsubstituted or substituted with halo, hydroxy or -NH₂; or wherein Z₁ and Z₂, taken together, form a heterocyclic amine.

23. The compound of claim 22, wherein Z₁ and Z₂ are -(CH₂)_nD, wherein n is an integer ranging from 1-5, and D is hydrogen, hydroxy, a heterocyclic amine or -NZ₃Z₄; wherein Z₃ and Z₄ are independently hydrogen, methyl or ethyl.

24. The compound of claim 18, wherein B is a heterocycle, unsubstituted or substituted with methyl, ethyl or -alkanol.

25. The compound of claim 18, wherein Z_1 is hydrogen and Z_2 is $-(CH_2)_nNZ_3Z_4$, wherein n is 2 or 3, and Z_3 and Z_4 are independently methyl or ethyl, or, taken together, NZ_3Z_4 form a heterocyclic amine.

26. The compound of claim 1 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$, $-CH_2-$ or $-CH(NR_{11}R_{12})-$ wherein R_{11} and R_{12} are hydrogen, $-C_1-C_9$ alkyl, or $NR_{11}R_{12}$, taken together, form a heterocycle.

27. The compound of claim 6 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$, $-CH_2-$ or $-CH(NR_{11}R_{12})-$ wherein R_{11} and R_{12} are hydrogen, $-C_1-C_9$ alkyl, or $NR_{11}R_{12}$, taken together, form a heterocycle.

28. The compound of claim 8 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$, $-CH_2-$ or $-CH(NR_{11}R_{12})-$ wherein R_{11} and R_{12} are hydrogen, $-C_1-C_9$ alkyl, or $NR_{11}R_{12}$, taken together, form a heterocycle.

29. The compound of claim 9 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$, $-CH_2-$ or $-CH(NR_{11}R_{12})-$ wherein R_{11} and R_{12} are hydrogen, $-C_1-C_9$ alkyl, or $NR_{11}R_{12}$, taken together, form a heterocycle.

30. The compound of claim 10 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$, $-CH_2-$ or $-CH(NR_{11}R_{12})-$ wherein R_{11} and R_{12} are hydrogen, $-C_1-C_9$ alkyl, or $NR_{11}R_{12}$, taken together, form a heterocycle.

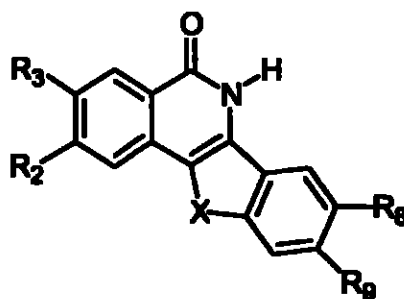
31. The compound of claim 6 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$ or $-CH_2-$.

32. The compound of claim 6 wherein X is $-CH_2-$.

33. The compound of claim 8 wherein X is $-C(O)-$, $-CH(OH)-$, $-CH(Br)-$ or $-CH_2-$.

34. The compound of claim 8 wherein X is $-\text{CH}_2-$.
35. The compound of claim 9 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
36. The compound of claim 9 wherein X is $-\text{CH}_2-$.
37. The compound of claim 10 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
38. The compound of claim 10 wherein X is $-\text{CH}_2-$.
39. The compound of claim 13 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
40. The compound of claim 13 wherein X is $-\text{CH}_2-$.
41. The compound of claim 14 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
42. The compound of claim 14 wherein X is $-\text{CH}_2-$.
43. The compound of claim 18 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
44. The compound of claim 18 wherein X is $-\text{CH}_2-$.
45. The compound of claim 19 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
46. The compound of claim 19 wherein X is $-\text{CH}_2-$.
47. The compound of claim 20 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
48. The compound of claim 20 wherein X is $-\text{CH}_2-$.
49. The compound of claim 21 wherein X is $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{Br})-$ or $-\text{CH}_2-$.
50. The compound of claim 21 wherein X is $-\text{CH}_2-$.

51. A compound of the formula



(III)

or a pharmaceutically acceptable hydrate or salt thereof,

wherein:

X is $-\text{CH}_2-$ or $-\text{O}-$;

R_2 and R_3 are independently -hydrogen, -halo, -alkylhalo, -hydroxy, $-\text{O}-(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{CONH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{OC}(\text{O})-\text{C}_1-\text{C}_3 \text{ alkyl}$ or $-\text{C}(\text{O})\text{O}-\text{C}_1-\text{C}_3 \text{ alkyl}$;

R_8 and R_9 are independently -hydrogen and -A-B;

A is $-\text{SO}_2-$, $-\text{SO}_2\text{NH}-$ or $-\text{NHCO}-$; and

B is $-\text{C}_1-\text{C}_3 \text{ alkyl}$, $-\text{NZ}_1\text{Z}_2$, -heterocycle or -alkylamino, each unsubstituted or substituted with one or more of -alkanol, -alkylamino, -aminoalkyl, -aminodialkyl or -heterocycle, each unsubstituted or substituted with $-\text{C}_1-\text{C}_{10} \text{ alkyl}$ or -alkanol; and

Z_1 and Z_2 are independently -hydrogen or $-\text{C}_1-\text{C}_3 \text{ alkyl}$, which is unsubstituted or substituted with one or more of -hydroxy or $-\text{NZ}_3\text{Z}_4$, where Z_3 and Z_4 are independently -H or $-\text{C}_1-\text{C}_3 \text{ alkyl}$, which is unsubstituted or substituted with one or more of -hydroxy or $-\text{NH}_2$, or N, Z_3 and Z_4 are taken together to a heterocyclic amine, or N, Z_1 and Z_2 are taken together to form a heterocyclic amine.

52. The compound of claim 51, wherein A is $-\text{SO}_2-$ and B is $-\text{NZ}_1\text{Z}_2$.

53. The compound of claim 52, wherein Z_1 and Z_2 are independently hydrogen, or $-\text{C}_1-\text{C}_3 \text{ alkyl}$, unsubstituted or substituted with hydroxy or $-\text{NZ}_3\text{Z}_4$, or, taken together, $-\text{NZ}_1\text{Z}_2$ form a heterocyclic amine.

54. The compound of claim 53, wherein Z_3 and Z_4 are independently hydrogen, or $-C_1-C_3$ alkyl, unsubstituted or substituted with hydroxy or $-NH_2$, or, taken together, NZ_3Z_4 form a heterocyclic amine.

55. The compound of claim 54, wherein the heterocyclic amine is selected from the group consisting of an unsubstituted piperidine, piperazine or morpholine group, or a piperazine, pyrrolidine or imidazole group which may be unsubstituted or substituted with $-N-(C_1-C_3 \text{ alkyl})$ or $-N-C(O)(C_1-C_3 \text{ alkyl})$.

56. The compound of claim 53, wherein either NZ_1Z_2 or NZ_3Z_4 is a heterocycle, unsubstituted or substituted with $-C_1-C_3$ alkyl, $-alkanol$ or $-alkylamino$.

57. A method for inhibiting poly(ADP)-ribose synthase activity in a cell, the method comprising contacting said cell with the compound or pharmaceutically acceptable hydrate or salt of a compound of any one of claims 1, 2, 3 or 51 in an amount sufficient to inhibit poly (ADP)-ribose-synthase in said cell.

58. The method of claim 57 wherein the cell is an *in vivo* cell.

59. A method for treating or preventing an inflammatory disease in a subject, the method comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable hydrate or salt of a compound of any one of claims 1, 2, 3 or 51 in an amount sufficient to treat or prevent the inflammatory disease.

60. The method of claim 59, wherein said subject is a human.

61. The method of claim 59, wherein said inflammatory disease is an inflammatory disease of a joint, a chronic inflammatory disease of the gum, an inflammatory bowel disease, an inflammatory lung disease, an inflammatory disease of the central nervous system, or an inflammatory disease of the eye.

62. The method of claim 59, wherein said inflammatory disease is gram-positive shock, gram negative shock, hemorrhagic shock, anaphylactic shock, traumatic shock and chemotherapeutic shock.

63. A method for treating or preventing a reperfusion disease in a subject, the method comprising administering to a subject in need thereof the compound or pharmaceutically acceptable hydrate or salt of a compound of any one of claims 1, 2, 3 or 51 in an amount sufficient to treat or prevent the reperfusion disease.

64. The method of claim 63, wherein the reperfusion disease is myocardial infarction.

65. The method of claim 63, wherein the reperfusion disease is stroke.

66. The method of claim 63, wherein the subject is a human.

67. A method for treating or preventing diabetes or a diabetic complication in a subject, the method comprising administering to a subject in need thereof the compound or pharmaceutically acceptable hydrate or salt of a compound of any one of claims 1, 2, 3 or 51 in an amount sufficient to treat or prevent diabetes or the diabetic complication.

68. A method for treating or preventing reoxygenation injury resulting from organ transplantation, the method comprising administering to a subject in need thereof the compound or pharmaceutically acceptable hydrate or salt of a compound of any one of claims 1, 2, 3 or 51 in an amount sufficient to treat or prevent the reoxygenation injury.

69. A composition comprising a compound or pharmaceutically acceptable salt or hydrate of the compound of claim 1 and a pharmaceutically acceptable carrier.

70. A composition comprising a compound or pharmaceutically acceptable salt or hydrate of the compound of claim 2 and a pharmaceutically acceptable carrier.

71. A composition comprising a compound or pharmaceutically acceptable salt or hydrate of the compound of claim 3 and a pharmaceutically acceptable carrier.

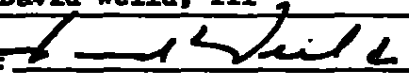
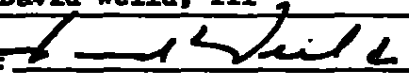
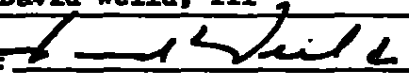
72. A composition comprising a compound or pharmaceutically acceptable salt or hydrate of the compound of claim 51 and a pharmaceutically acceptable carrier.

73. The compound or pharmaceutically acceptable salt or hydrate of claim 51, wherein either R⁸ is hydrogen and R⁹ is -A-B, or R⁸ is -A-B and R⁹ is hydrogen.

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/27585	For International Preliminary Examining Authority use only																		
Applicant's or agent's file reference 11078-25-228	Date stamp of the IPEA																		
Applicant INOTEK PHARMACEUTICALS CORPORATION																			
CALCULATION OF PRESCRIBED FEES <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 60%;">1. Preliminary examination fee</td><td style="width: 20%; text-align: right; border: 1px solid black;">490.00</td><td style="width: 20%; text-align: center; border: 1px solid black;">P</td></tr><tr><td colspan="3"> </td></tr><tr><td>2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)</td><td style="text-align: right; border: 1px solid black;">146.00</td><td style="text-align: center; border: 1px solid black;">H</td></tr><tr><td colspan="3"> </td></tr><tr><td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td><td style="text-align: right; border: 1px solid black;">636.00</td><td></td></tr><tr><td></td><td colspan="2" style="text-align: center; border: 1px solid black;">TOTAL</td></tr></table>		1. Preliminary examination fee	490.00	P				2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	146.00	H				3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	636.00			TOTAL	
1. Preliminary examination fee	490.00	P																	
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3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	636.00																		
	TOTAL																		
MODE OF PAYMENT <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%; vertical-align: top;">☒ authorization to charge deposit account with the IPEA (see below) ☐ cheque ☐ postal money order ☐ bank draft</td><td style="width: 50%; vertical-align: top;">☐ cash ☐ revenue stamps ☐ coupons ☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account with the IPEA (see below) ☐ cheque ☐ postal money order ☐ bank draft	☐ cash ☐ revenue stamps ☐ coupons ☐ other (specify):																
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AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%; vertical-align: top;">☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.</td><td style="width: 50%; vertical-align: top;">IPEA/ US Deposit Account No.: 16-1150 Date: 26 MARCH 2003 Name: David Weild, III Signature: </td></tr></table>		☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ US Deposit Account No.: 16-1150 Date: 26 MARCH 2003 Name: David Weild, III Signature: 																
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The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 11078-25-228
International application No. PCT/US02/27585	International filing date (day/month/year) 30 August 2002 (30.08.02)	(Earliest) Priority date (day/month/year) 31 August 2001 (31.08.01)
Title of invention SUBSTITUTED INDENO[1,2-c]ISOQUINOLINE DERIVATIVES AND METHODS OF USE THEREOF		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) INOTEK PHARMACEUTICALS CORPORATION 100 Cummings Center Beverly, MA 01915 US		Telephone No.
		Facsimile No.
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)		
State (that is, country) of nationality:		State (that is, country) of residence:
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)		
State (that is, country) of nationality:		State (that is, country) of residence:
☐ Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)INSOGNA, Anthony M.
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, NY 10036
US

Telephone No.

212-790-9090

Facsimile No.

212-860-8864

Teleprinter No.

66141 PENNIE

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received not received

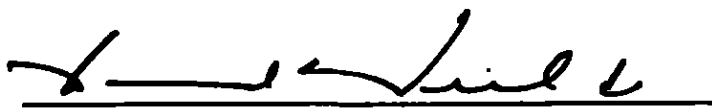
- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


 David Weild, III
 Agent for Applicants

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
ANTHONY M. INSOGNA
PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

*Amend Prior Pub 11/2/03
CK US IDS Refs 12/2/03*

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 11078-25-228	Date of Mailing (day/month/year) 9/2/03
International application No. PCT/US02/27585	International filing date (day/month/year) 30 August 2002 (30.08.2002)
Applicant INOTEK PHARMACEUTICALS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer <i>Jaime Brudger</i> Armin P. Manabhan Telephone No. 703.308.0198
--	---

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
ANTHONY M. INSOGNA
PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing (day/month/year) 02 SEP 2003	
Applicant's or agent's file reference 11078-25-228	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/27585	International filing date (day/month/year) 30 August 2002 (30.08.2002)
Applicant INOTEK PHARMACEUTICALS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.33

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1430 Alexandria, Virginia 22313-1430 Facsimile No. (703)305-5230	Authorized officer <i>John P. Brudger</i> John P. Brudger Telephone No. 703.308.0198
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Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 11078-25-228	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/27585	International filing date (day/month/year) 30 August 2002 (30.08.2002)	(Earliest) Priority Date (day/month/year) 31 August 2001 (31.08.2001)
Applicant INOTEK PHARMACEUTICALS CORPORATION		

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

This international search report consists of a total of 2 sheets.



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

1. Basis of the Report

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



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

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



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

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27585

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/435, 31/00; C07D 221/18
US CL : 514/232.8, 226.5, 255, 285, 309, 372

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/232.8, 226.5, 255, 285, 309, 372

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN-CAPLUS, REGISTRY, PCTFULL, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,997,831A (MICHALSKY et al.) 28 January 1997 (28.01.1997), abstract, column 1-2, claims 1-5.	1-73
Y	US 5,260,316 A (VAN DUZER et al.) 09 November 1993 (09.11.1993), abstract, column 1-2, claims 1-21.	1-73
Y	US 5,079,246 A (FORBES et al.) 07 January 1992 (07.01.1992), abstract, column 9-10, claims 1-15.	1-73
Y	WO 99/11649 (GUILFORD PHARMACEUTICALS INC.) 11 March 1999 (11.03.1999), abstract, pages 11-12 and 55-67, claims 1-171.	1-73

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" another application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"T" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

12 August 2003 (12.08.2003)

Date of mailing of the international search report

02 SEP 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1430
Alexandria, Virginia 22313-1430
Facsimile No. (703)305-3230

Author and officer

Search Partnerabhan

Telephone No. 703.308.0198

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except when, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where and to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

When a demand for international preliminary examination has been filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be numbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether:

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

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NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 44.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 300 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It should not contain any disparaging comments on the international search report or the relevance of citations contained in the report. References to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequences if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(e), first sentence).

Consequences with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
ANTHONY M. INSOGNA
PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036

PCT

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year) **25 SEP 2003**

Applicant's or agent's file reference
11078-25-228

IMPORTANT NOTIFICATION

International application No.
PCT/US02/27585

International filing date (day/month/year)
30 Aug 2002

Priority date (day/month/year)
31 Aug 2001

Applicant
INOTEK PHARMACEUTICALS CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

28 Mar 2003

2. That date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IP/EA/406), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide, Volume II*.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Authorized officer
Valerie Jackson

Facsimile No. 703-305-3230
Form PCT/IP/EA/402 (July 1998)

Telephone No. 703-305-3756

**DERIVADOS DE INDENO [1, 2-C] ISOQUINOLINA Y MÉTODOS PARA
USAR LOS MISMOS.**

Esta solicitud es una continuación en parte de la
5 solicitud U.S. 09/944.524, presentada el 31 de agosto de
2001, que es aquí incorporada completamente como
referencia.

1. Campo de la invención

10

Esta invención se relaciona con compuestos de indeno
[1,2-c] isoquinolina; y métodos para tratar o prevenir
enfermedades inflamatorias o una enfermedad reperfusión.

15 2. Antecedentes de la invención

Las enfermedades inflamatorias, como la artritis,
colitis, y la diabetes auto inmune, se manifiestan
típicamente como desórdenes diferentes de aquellos
20 asociados con las enfermedades de reperfusión, por
ejemplo, apoplejías y ataques de cardiacos, y se puede
manifestar clínicamente como entidades diferentes.

Sin embargo, pueden haber mecanismos subyacentes comunes
entre estos dos tipos de desórdenes. En particular, las
25 enfermedades inflamatorias y las enfermedades de
reperfusión pueden inducir la síntesis de citoquina
proinflamatoria y quemoquina, que a su vez, resultan en
la producción de radicales libres citotóxicos como óxido
nitríco y súper óxido. NO y súper óxido pueden
30 reaccionar para formar peroxinitrito (ONOO⁻) (Szabó et
al, SOC 6:79-88, 1996).

6a

La necrosis celular inducida por ONOO^- que se observa en enfermedades inflamatorias y en enfermedades de reperfusión involucra la activación de la enzima nuclear poli (ADP-ribosa) sintetasa (PARS). Se piensa que la
5 activación del PARS es un paso importante en la muerte celular observada en enfermedades inflamatorias y de reperfusión (Szabó et al, Trends Pharmacol. Sci. 19:28798, 1998).

10 Se han descrito un número de inhibidores de PARS en la técnica. Ver, por ejemplo, Banasik et al., J. Biol. Chem, 167:156978, 1992, y Banasik et al., Mol. Cell Biochem., 138:18597, 1994: WO 00/39104; WO 00/39070; WO 99/59975; WO 99/59973; WO 99/11649; WO 99/11645; WO
15 99/11644; WO 99/11628; WO 99/11623; WO 99/11311; WO 00/42040; Zhang et al., Biochem. Biophys. Res. Commun., 278:590-98,2000; White et al., J. Med. Chem; 43:4084-4097,2000; Griffin et al., J. Med. Chem., 41:5247-5256,1998 ; Shinkwin et al., Bioorg. Med. Chem., 7:297-
20 308,1999; and Soriano et al., Nature Medicine, 7:108-113,2001. Los efectos adversos de asociados a inhibidores de PARS han sido discutidos en Milan et al, Science, 223:589-591,1984.

25 Derivados de Indeno[1,2-c]isoquinolina han sido previamente discutidos en la técnica. Por ejemplo, Inhibidores citotóxicos no-campotecina topoisomerasa, han sido reportados en Cushman et al., J. Med. Chem. 43:3688-3698,2000 y Cushman et al., J. Med. Chem.
30 42:446-57, 1999; Indeno[1,2-c]isoquinolinas se han reportado como agentes antineoplásicos en Cushman et al., WO 93/05023.

La síntesis de derivados de Indeno[1,2-c]isoquinolina ha sido reportada. Por ejemplo, ver Wawzonek et al., Org. Prep. Proc. Int. 14:163-8, 1982; Wawzonek et al., Can. J. Chem. 59:2833, 1981; Andoi et al., Bull. Chem. Soc. Japan, 47:1014-17, 1974; Dusemund et al., Arch. Pharm. (Weinheim), Ger.), 3 17:381-2, 1984; y Lal et al., Indian J. Chem., Sect. B, 38B:33-39, 1999.

10 Sin embargo, ha permanecido la necesidad de encontrar compuestos útiles para tratamiento o la prevención enfermedades inflamatorias o enfermedades de reperusión.

15 La cita de cualquier referencia en esta sección de esta aplicación, no significa admitir que dichas referencias corresponden arte previo.

3. Resumen de la invención.

20

Esta invención se basa en parte en el descubrimiento de nuevos derivados tetracíclicos de benzamida y sus efectos demostrados en el tratamiento de inflamación, muerte celular y en el tratamiento de apoplejías
25 enfermedades de reperusión.

De acuerdo a lo anterior, un aspecto de la invención incluye un compuesto de fórmula I, fórmula Ia, fórmula Ib, fórmula II o fórmula III, o una sal
30 farmacéuticamente aceptable de los mismos (un "compuesto de indeno [1,2-c] isoquinolina "), como un se propone a

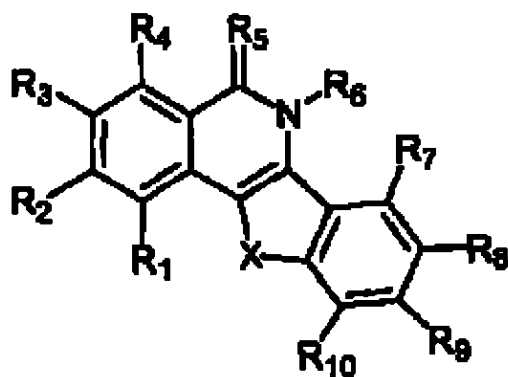
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continuación en la descripción detallada de la invención.

La invención también provee un método para tratar o
5 prevenir una enfermedad inflamatoria o una enfermedad de
reperfusión en un sujeto, comprendiendo la
administración a un sujeto con necesidad de dicho
tratamiento una cantidad efectiva de un compuesto indeno
[1,2-c] isoquinolina.

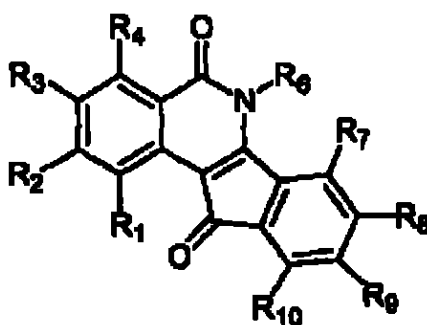
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En un aspecto adicional, la invención también incluye un
método para producir un compuesto indeno [1,2-c]
isoquinolina.

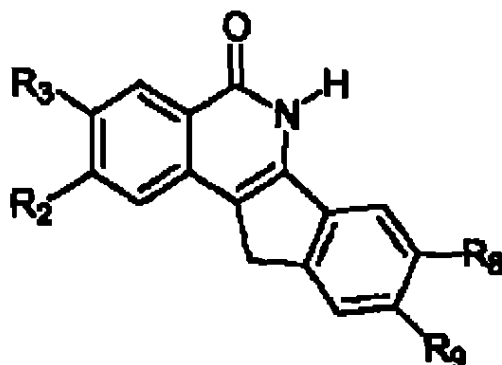


15

(I Ia y Ib)



(II)



(III)

Los compuestos de indeno [1,2-c] isoquinolina, pueden ser usados para prevenir una variedad de condiciones
5 enfermedades como la enfermedad inflamatoria o la enfermedad de reperfusión, sin limitarse a éstas.

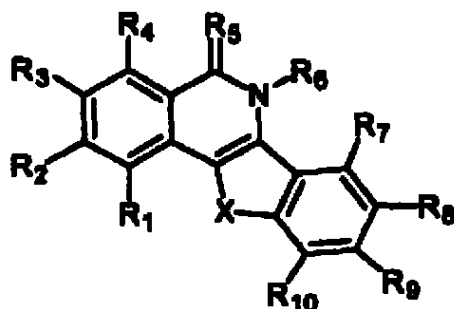
La invención también incluye una composición farmacéutica que comprende una cantidad efectiva de un compuesto de indeno [1,2-c] isoquinolina y un vehículo
10 farmacéuticamente aceptado. La composición es útil para tratar o prevenir una enfermedad inflamatoria o una enfermedad de reperfusión. La invención también incluye un compuesto de indeno [1,2-c] isoquinolina provisto como un profármaco farmacéuticamente aceptable, una sal
15 hidratada, como una sal farmacéuticamente aceptable, o mezclas de los mismos.

Los detalles de la invención se proponen a continuación en la descripción siguiente. Aunque cualquier método y
20 material similar o equivalente a los aquí escritos pueden ser usados en la práctica o los ensayos de la presente invención, ahora se describirán métodos y materiales ilustrativos. Otras características, objetos y ventajas de la invención resultaran aparentes en la

descripción y en las reivindicaciones. En la descripción y en las reivindicaciones las formas singulares también incluyen las formas plurales a menos que el contexto lo dictamine de otra forma. A menos que se defina de otra forma, todos los términos técnicos y científicos usados aquí, tienen el mismo significado comúnmente entendido por una persona versada en la materia a la que esta invención pertenece. Todas las patentes y publicaciones citadas en esta descripción se incorporan a manera de referencia.

4. Descripción detallada de la invención.

La presente invención provee una nueva clase de compuestos indeno [1,2-c] isoquinolinas, de acuerdo a la fórmula I, fórmula Ia, fórmula Ib, fórmula II, fórmula III, como se ilustra abajo:



(I)

20

Y sales farmacéuticamente aceptables e hidratos del mismo,

Donde:

24

R₅ es O, NH o S;

R₆ es -H o alquil C₁-C₄;

X es -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-
 5 arileno-, -O-, -NH-, -S-, o -CH(NR₁₁R₁₂), donde n es un
 entero de 0-5;

R₁₁ y R₁₂ son independientemente -hidrógeno o alquil-
 C₁-C₉, o N, R₁₁ y R₁₂ se toman juntos para formar una
 amina heterocíclica;

10

R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son independientemente
 -hidrógeno, -halo, -hidroxi, -O-alquil (C₁-C₅), alquil-C₁-
 C₁₀, -haloalquil, alquenil-C₂-C₁₀, carbocíclo-C₃-C₈, -
 arilo, -NH₂, -alquilamino, -C(O)OH, -C(O)O(alquil C₁-
 15 C₅), -OC(O)(alquil C₁-C₅), NO₂ o -A-B; donde A es -SO₂-, -
 SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -
 CONH-, -CON(alquil C₁-C₄), -NH-, -CH₂-, -S- o -C(S)-;

B es alquil-C₁-C₁₀, alquenil-C₂-C₁₀, - heterocíclo,
 20 carbocíclo-C₃-C₈, - arilo, -NZ₁Z₂, alquilamino,
 aminodialquil, alquilheterocíclo, arilamido, -C(O)OH, -
 C(O)O-(alquil C₁-C₅) o -C(O)O- fenil, cualquiera de los
 cuales está sin sustituir o sustituido con uno o más
 grupos -O-(alquil C₁-C₅), - halo, haloalquil, alcanol,
 25 alquilamino, hidroxi, -NO₂, -NH₂, alquilamino,
 aminodialquil, amina heterocíclica, alquil-C₁-C₁₀,
 alquenil-C₂-C₁₀, alquinil-C₂-C₁₀, arilo, bencil,
 alquilamido, alquilcarboxi, alquilenno-C₁-C₅-C(O)O-
 alquil-C₁-C₅ o alquilenno-C₁-C₅-OC(O) alquil -C₁-C₅; y

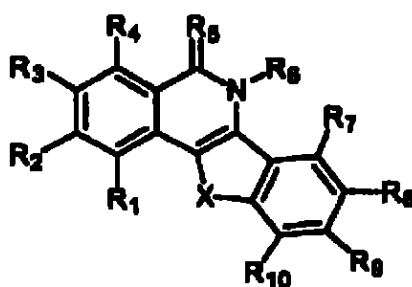
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Z₁ y Z₂ son independientemente -H o alquil-C₁-C₁₀, que
 están no sustituidos o sustituidos con uno o más - halo,

75

-OH o $-N(Z_3)(Z_4)$, donde Z_3 y Z_4 son independientemente -H, alquil- C_1-C_5 , que están no sustituidos o sustituidos con uno o más - halo, hidroxí o $-NH_2$; o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

La invención también se refiere a compuestos de fórmula (Ia):



(Ia)

10

Y sales farmacéuticamente aceptables e hidratos del mismo,

Donde:

15

R_5 es NH o S;

R_6 es -H o alquil- C_1-C_4 ;

X es $-C(O)-$, $-CH_2-$, $-CH-$ halo, $-CH(OH)(CH_2)_n-$, $-CH(OH)-$ arileno, $-O-$, $-NH-$, $-S-$, o $-CH(NR_{11}R_{12})-$, donde n es un entero de 0 a 5;

20

R_{11} y R_{12} son independientemente - hidrógeno o alquil- C_1-C_9 , o N, R_{11} y R_{12} se toman juntos para formar una amina heterocíclica;

26

$R_1, R_2, R_3, R_4, R_7, R_8, R_9$ y R_{10} son independientemente -hidrógeno, -halo, -hidroxi, -O-alquil (C_1-C_5), alquil- C_1-C_{10} , -haloalquil, alquénil- C_2-C_{10} , carbociclo- C_3-C_8 , -arilo, - NH_2 , -alquilamino, - $C(O)OH$, - $C(O)O$ (alquil C_1-C_5), - $OC(O)$ (alquil C_1-C_5), NO_2 o -A-B; donde A es - SO_2 -, - SO_2NH -, - $NHCO$ -, - $NHCONH$ -, -O-, -CO-, - $OC(O)$ -, - $C(O)O$ -, -CONH-, -CON(alquil C_1-C_4), -NH-, - CH_2 -, -S- o -C(S)-;

B es alquil- C_1-C_{10} , alquénil- C_2-C_{10} , - heterociclo, carbociclo- C_3-C_8 , - arilo, - NZ_1Z_2 , alquilamino, aminodialquil, alquilheterociclo, arilamido, - $C(O)OH$, - $C(O)O$ -(alquil C_1-C_5) o - $C(O)O$ - fenil, cualquiera de los cuales está sin sustituir o sustituido con uno o más grupos -O-(alquil C_1-C_5), - halo, haloalquil, alcohol, alquilamino, hidroxil, - NO_2 , - NH_2 , alquilamino, aminodialquil, amina heterocíclica, alquil- C_1-C_{10} , alquénil- C_2-C_{10} , alquínil- C_2-C_{10} , arilo, bencil, alquilamido, alquilcarboxi, alquilenio- $C_1-C_5-C(O)O$ -alquil- C_1-C_5 o alquilenio- $C_1-C_5-OC(O)$ alquil - C_1-C_5 ; y

20

Z_1 y Z_2 son independientemente -H o alquil- C_1-C_{10} , que están no sustituidos o sustituidos con uno o más - halo, -OH o - $N(Z_3)(Z_4)$, donde Z_3 y Z_4 son independientemente -H, alquil- C_1-C_5 , que están no sustituidos o sustituidos con uno o más - halo, hidroxil o - NH_2 ; o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

30

En una modalidad, A es - SO_2 -.

27

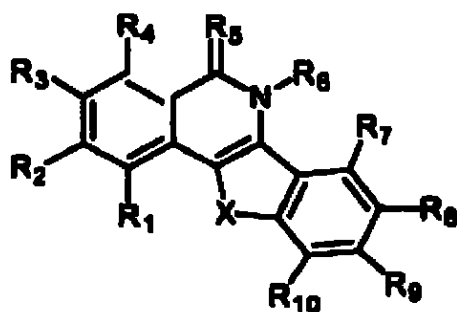
En otra modalidad $R_1, R_2, R_3, R_4, R_7, R_8, R_9$ y R_{10} son independientemente arilalquil.

En otras modalidades ilustrativas R^5 y X , en un compuesto de fórmula Ia, son como se proponen como a continuación:

R^5	X
NH	-C(O)-
NH	-CH ₂ -
NH	-CH(halo)-
NH	-CH(OH)(CH ₂) _n -
NH	-CH(arylene)(OH)-
NH	-O-
NH	-NH-
NH	-S-
NH	-CH(NR ¹¹ R ¹²)-
R^5	X
S	-C(O)-
S	-CH ₂ -
S	-CH(halo)-
S	-CH(OH)(CH ₂) _n -
S	-CH(arylene)(OH)-
S	-O-
S	-NH-
S	-S-
S	-CH(NR ¹¹ R ¹²)-

10

la invención también se relaciona con compuestos de fórmula Ib:



(Ib)

y sales e hidratos farmacéuticamente aceptables de éstos.

5 Donde:

R₅ es O, NH o S;

R₆ es -H o alquil-C₁-C₄;

X es CH₂-, -CH(halo), -CH(OH)(CH₂)_n- arileno-, -O-, -
10 NH-, -S-, o -CH(NR₁₁R₁₂)-, donde n es un entero de 0 a 5;

R₁₁ y R₁₂ son independientemente - hidrógeno, alquil-C₁-C₉, o N, R₁₁ y R₁₂ se toman juntos para formar una amina heterocíclica.

15

R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son independientemente -hidrógeno, -halo, -hidroxi, -O-alquil (C₁-C₅), alquil-C₁-C₁₀, -haloalquil, alquenil-C₂-C₁₀, carbocíclo-C₃-C₈, -
arilo, - NH₂, -alquilamino, -C(O)OH, -C(O)O(alquil C₁-C₅), -OC(O)(alquil C₁-C₅), NO₂ o -A-B; donde A es -SO₂-, -
20 SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(alquil C₁-C₄), -NH-, -CH₂-, -S- o -C(S)-;

7A

B es alquil-C₁-C₁₀, alquenil-C₂-C₁₀, - heterociclo, carbociclo-C₃-C₈, - arilo, -NZ₁Z₂, alquilamino, aminodialquil, alquilheterociclo, arilamido, -C(O)OH, -C(O)O-(alquil C₁-C₅) o -C(O)O- fenil, cualquiera de los
 5 cuales está sin sustituir o sustituido con uno o más grupos -O-(alquil C₁-C₅), - halo, haloalquil, alcanol, alquilamino, hidroxil, -NO₂, -NH₂, alquilamino, aminodialquil, amina heterocíclica, alquil-C₁-C₁₀, alquenil-C₂-C₁₀, alquinil-C₂-C₁₀, arilo, bencil,
 10 alquilamido, alquilcarboxi, alquilen-C₁-C₅-C(O)O-alquil-C₁-C₅ o alquilen-C₁-C₅-OC(O) alquil -C₁-C₅; y

Z₁ y Z₂ son independientemente -H o alquil-C₁-C₁₀, que están no sustituidos o sustituidos con uno o más - halo,
 15 -OH o -N(Z₃)(Z₄), donde Z₃ y Z₄ son independientemente -H, alquil-C₁-C₅, que están no sustituidos o sustituidos con uno o más - halo, hidroxil o -NH₂; o N, Z₃ y Z₄ tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z₁ y Z₂ tomados juntos forman una
 20 amina heterocíclica.

En una modalidad, A es -SO₂-.

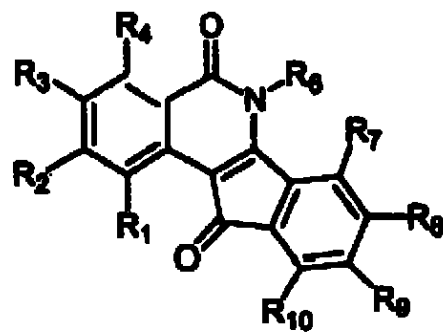
en otra modalidad R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son
 25 independientemente arilalquil.

En otras modalidades ilustrativas R⁵ y X, en un compuesto de fórmula Ib, son como se proponen como a continuación:

80

R^s	X
O	-CH ₂ -
O	-CH(halo)-
O	-CH(OH)(CH ₂) _n -
O	-CH(arylene)(OH)-
O	-O-
O	-NH-
O	-S-
O	-CH(NR ¹¹ R ¹²)-

La invención también se relaciona con compuestos de fórmula II:



(II)

5

Y sales e hidratos farmacéuticamente aceptables de éstos.

10 Donde:

R₆ es H, alquil- C₁-C₄;

R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son independientemente -hidrógeno, -halo, -hidroxi, -O-alquil (C₁-C₅), alquil-C₁-C₁₀, -haloalquil, alquenil-C₂-C₁₀, carbociclo-C₃-C₈, -
 15 arilo, - NH₂, -alquilamino, -C(O)OH, -C(O)O(alquil C₁-

21

C₅), -OC(O)(alquil C₁-C₅), NO₂ o -A-B; donde al menos uno de R₁ y R₄ es diferente de hidrógeno;

A es -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -
5 OC(O)-, -C(O)O-, -CONH-, -CON(alquil C₁-C₄), -NH-, -CH₂-,
-S- o -C(S)-;

B es alquil-C₁-C₁₀, alquenil-C₂-C₁₀, - heterociclo,
carbociclo-C₃-C₈, -arilo, NH₂, alquilamino, aminodialquil,
10 alquilheterociclo, arilamido, -C(O)OH, -C(O)O-(alquil
C₁-C₅) o -C(O)O- fenil, o -NZ₁Z₂; y

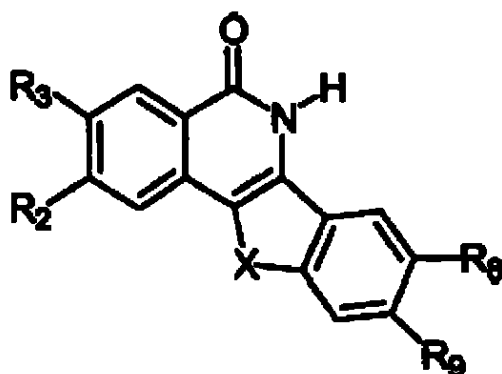
Z₁ y Z₂ son independientemente -H o alquil-C₁-C₁₀, que
están no sustituidos o sustituidos con uno o más - halo,
15 -OH o -N(Z₃)(Z₄), donde Z₃ y Z₄ son independientemente -
H, alquil-C₁-C₅, que están no sustituidos o sustituidos
con uno o más - halo, hidroxil o -NH₂; o N, Z₃ y Z₄
tomados juntos forman una amina heterocíclica sustituida
o no sustituida; o N, Z₁ y Z₂ tomados juntos forman una
20 amina heterocíclica.

En una modalidad, B es una amina heterocíclica

en otra modalidad, B es arilalquil

25

La invención también se relaciona con compuestos de
fórmula III:



(III)

Y sales e hidratos farmacéuticamente aceptables de éstos.

5

Donde:

X es $-\text{CH}_2-$ o $-\text{O}-$;

R_2 y R_3 son independientemente - hidrógeno, halo, -
10 haloalquil, hidroxil, $-\text{O}-(\text{alquil}-\text{C}_1-\text{C}_5)$, $\text{alquil}-\text{C}_1-\text{C}_3$, -
 NO_2 , $-\text{NH}_2$, $-\text{CONH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{OC}(\text{O})-\text{alquil}-\text{C}_1-\text{C}_5$, o $-\text{C}(\text{O})\text{O}-$
 $\text{alquil}-\text{C}_1-\text{C}_5$;

R_8 y R_9 son independientemente -hidrógeno y A-B;

15

A es $-\text{SO}_2-$, $\text{SO}_2\text{NH}-$ o $\text{NHCO}-$; and

B es $\text{alquil}-\text{C}_1-\text{C}_3$, $-\text{NZ}_1\text{Z}_2$, -heterociclo o alquilamino,
cada uno no sustituido o sustituido por uno o más -
20 alcohol, - alquilamino, - aminoalquil, -aminodialquil, o
- heterociclo, cada uno no sustituido o sustituido con -
 $\text{alquil}-\text{C}_1-\text{C}_{10}$ o - alcohol; y

Z_1 y Z_2 son independientemente - hidrógeno o alquil- C_1-C_8 , que están no sustituidos o sustituidos con uno o más - hidroxil o $-NZ_3Z_4$, donde Z_3 y Z_4 son independientemente -H, alquil- C_1-C_3 , que están no
 5 sustituidos o sustituidos con uno o más hidroxil o $-NH_2$, o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

10 En una modalidad, -X- es $-CH_2-$.

En otra modalidad, -X- es -O-.

En otra modalidad, R_8 es hidrógeno y R_9 es A-B.

En otra modalidad, R_8 es -A-B y R_9 es hidrógeno.

En una modalidad, cada R_8 es hidrógeno y R_9 es -A-B.

15 o R_8 es -A-B- y R_9 es hidrógeno.

En una modalidad, R_3 , R_8 y R_9 son hidrógeno y R_2 es -A-B, donde A es $-NHC(O)-$,

en otra modalidad, R_2 , R_8 y R_9 son hidrógeno y R_3 es -A-B, donde A es $-NHC(O)-$,

20 aún en otra modalidad, R_2 , R_3 y R_8 son hidrógeno y R_9 es -A-B, donde A es $-SO_2-$ o $-SO_2NH$.

4.1. DEFINICIONES

25 "alquil- C_1-C_3 " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 3 átomos de carbono. Ejemplos de alquil- C_1-C_3 incluyen, pero no están limitados a metil, etil, propil e isopropil.

30

"alquil- C_1-C_4 " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 4

átomos de carbono. Ejemplos de alquil- C_1-C_4 incluyen, pero no están limitados a metil, etil, propil, butil, isopropil, isobutil, sec-butil, ter-butil.

- 5 "alquil- C_1-C_5 " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 5 átomos de carbono. Ejemplos de alquil- C_1-C_5 incluyen, pero no están limitados a metil, etil, propil, butil, pentil, isopropil, isobutil, sec-butil, ter-butil,
10 isopentil y neopentil.

- "alquil- C_1-C_8 " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 8 átomos de carbono. Ejemplos de alquil- C_1-C_8 incluyen,
15 pero no están limitados a metil, etil, propil, butil, pentil, hexil, heptil, octil, isopropil, isobutil, sec-butil, ter-butil, isopentil, neopentil, isohexil, isoheptil e isooctil.

- 20 "alquil- C_1-C_9 " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 9 átomos de carbono. Ejemplos de alquil- C_1-C_9 incluyen, pero no están limitados a metil, etil, propil, butil, pentil, hexil, heptil, octil, nonil, isopropil,
25 isobutil, sec-butil, ter-butil, isopentil, neopentil, isohexil, isoheptil, isooctil e isononil.

- "alquil- C_1-C_{10} " se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 1 a 10
30 átomos de carbono. Ejemplos de alquil- C_1-C_{10} incluyen, pero no están limitados a metil, etil, propil, butil, pentil, hexil, heptil, octil, nonil, decil, isopropil,

isobutil, sec-butil, ter-butil, isopentil, neopentil, isohexil, isoheptil, isooctil, isononil e isodecil.

5 "alquenal-C₂-C₁₀" se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 2 a 10 átomos de carbono y al menos un doble enlace. Ejemplos de alquenal-C₂-C₁₀ incluyen, pero no están limitados a etileno, propileno, 1-butileno, 2-butileno, isobutileno, sec-butileno, 1-penteno, 2-penteno, isopenteno, 1-
10 hexeno, 2-hexeno, 3-hexeno, isohexeno, 1-hepteno, 2-hepteno, 3-hepteno, 1-octeno, 2-octeno, 3-octeno, 4-octeno, 1-noneno, 2-noneno, 3-noneno, 4-noneno, 1-deceno, 2-deceno, 3-deceno, 4-deceno y 5-deceno.

15 "alquini-C₂-C₁₀" se refiere a una cadena lineal o ramificada saturada de hidrocarburo que contiene 2 a 10 átomos de carbono y al menos un triple enlace. Ejemplos de alquini-C₂-C₁₀ incluyen, pero no están limitados a acetileno, propino, 1-butino, 2-butino, isobutino, sec-
20 butino, 1-pentino, 2-pentino, isopentino, 1-hexino, 2-hexino, 3-hexino, isohexino, 2-heptino, 3-heptino, 1-octino, 2-octino, 3-octino, 4-octino, 1-nonino, 2-nonino, 3-nonino, 4-nonino, 1-decino, 2-decino, 3-decino, 4-decino y 5-decino.

25

"alquilen-C₁-C₄" se refiere a un grupo alquil-C₁-C₄ en el que uno de los grupos de átomos de hidrógeno del alquil-C₁-C₄ ha sido reemplazado por un enlace. Ejemplos de un alquilen-C₁-C₄ incluyen -CH₂-, -CH₂CH₂-, -
30 CH₂CH₂CH₂- y -CH₂CH₂CH₂CH₂-.

"alquilenno-C₁-C₅" se refiere a un grupo alquil-C₁-C₅ en el que uno de los grupos de átomos de hidrógeno del alquil-C₁-C₅ ha sido reemplazado por un enlace. Ejemplos de un alquilenno-C₁-C₅ incluyen -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂- y -CH₂CH₂CH₂CH₂CH₂-

"haloalquil" se refiere a grupos alquil-C₁-C₅, como los definidos arriba, donde uno o más hidrógeno del grupo alquil-C₁-C₅ han sido reemplazados con F, Cl, Br o I. Ejemplos representativos de grupos haloalquil incluyen, pero no se limitan a -CH₂F, -CCl₃, CF₃, -CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CH₂CH₂CH₂F, -CH₂CH₂CH₂Cl, -CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂I, -CH₂CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂CH₂I, -CH₂CH(Br)CH₃, -CH₂CH(Cl)CH₂CH₃, -CH(F)CH₂CH₃ y -C(CH₃)₂(CH₂Cl).

"Alquilamino" se refiere a grupos alquil-C₁-C₄, como los definidos arriba, donde uno o más de los átomos de hidrógeno del grupo alquil-C₁-C₄ se reemplazado con -NH₂. Ejemplos representativos de grupos alquilamino incluyen, pero no se limitan a -CH₂NH₂, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH(NH₂)CH₂CH₃, -CH(NH₂)CH₂CH₃ y -C(CH₃)₂(CH₂NH₂)

"aminoalquil" se refiere a un grupo -NH, en el que el átomo de nitrógeno de dicho grupo se une a un grupo alquil-C₁-C₄, como los definidos arriba. Ejemplos representativos de grupos aminoalquil incluyen, pero no se limitan a -NHCH₃, -NHCH₂CH₃, NHCH₂CH₂CH₃, -NHCH₂CH₂CH₂CH₃, -NHCH(CH₃)₂, -NHCH₂CH(CH₃)₂, -NHCH(CH₃)CH₂CH₃ y -NHC(CH₃)₃.

- "Aminodialquil" se refiere a un átomo de nitrógeno al que se encuentran unidos los grupos alquilo-C₁-C₄, como los definidos arriba. Ejemplos representativos de grupos aminoalquil incluyen, pero no se limitan a -NH(CH₃)₂, -
- 5 N(CH₂CH₃)(CH₃), -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -
 N(CH₂CH₂CH₂CH₃)₂, -N(CH(CH₃)₂)₂, -N(CH(CH₃)₂)(CH₃), -
 N(CH₂CH(CH₃)₂)₂, -NH(CH(CH₃)CH₂CH₃)₂, -N(C(CH₃)₃)₂ y -
 N(C(CH₃)₃)(CH₃)
- 10 "aril" se refiere a un grupo fenil o piridin. Ejemplos de un grupo arilo incluyen, pero no se limitan a fenil, N-piridin, 2-piridin, 3-piridin y 4-piridin. El grupo arilo puede estar sin sustituir o sustituido con uno o más de los siguientes grupos: alquilo-C₁-C₅, Halo, -
- 15 haloalquil, hidroxil, -O-alquilo-C₁-C₅, -NH₂, aminoalquil, aminodialquil, -COOH, -C(O)O-(alquilo-C₁-C₅), -OC(O)-(alquilo-C₁-C₅), N-amidoalquil, -C(O)NH₂, carboxamidoalquil, o NO₂,
- 20 "alquilarilo" se refiere a un grupo arilo, como los definidos arriba, donde uno de los hidrógenos del grupo arilo ha sido reemplazado con un grupo alquilo-C₁-C₅ como se definen arriba. Ejemplos representativos de un grupo alquilarilo incluyen, pero no se limitan a 2-
- 25 metilfenil, 3-metilfenil, 4-metilfenil, 2-etilfenil, 3-etilfenil, 4-etilfenil, 2-propilfenil, 3-propilfenil, 4-propilfenil, 2-butilfenil, 3-butilfenil, 4-butilfenil,, 2-pentilfenil, 3-pentilfenil, 4-pentilfenil, 2-isopropilfenil, 3-isopropilfenil, 4-isopropilfenil, 2-
- 30 isobutilfenil, 3-isobutilfenil, 4-isobutilfenil, 2-sec-butilfenil, 3-sec-butilfenil, 4-sec-butilfenil, 2-t-butilfenil, 3-t-butilfenil, y 4-t-butilfenil,

"arilamido" se refiere a un grupo arilo, como el definido arriba, donde uno de los hidrógenos del grupo arilo se han reemplazado con uno o más grupos $-C(O)NH_2$,
 5 Ejemplos representativos de de un grupo arilamido incluyen, $2-C(O)NH_2$ -fenilo, $3-C(O)NH_2$ -fenilo, $4-C(O)NH_2$ -fenilo, $4-C(O)NH_2$ -fenilo, $2-C(O)NH_2$ -piridin, $3-C(O)NH_2$ -piridin y $4-C(O)NH_2$ -piridin,

10 "alquilheterociclo" se refiere a un grupo alquil- C_1-C_5 , como los definidos arriba, donde uno de los hidrógenos del grupo alquil- C_1-C_5 se ha reemplazado por un heterociclo. Ejemplos representativos de grupos alquilheterociclos incluyen, pero no se limitan a -
 15 CH_2CH_2 -morfolina, $-CH_2CH_2$ -piperidina, $-CH_2CH_2CH_2$ -morfolina y $-CH_2CH_2CH_2$ -imidazol.

"alquilamido" se refiere a un grupo alquil- C_1-C_5 , como los definidos arriba, donde uno de los hidrógenos del
 20 grupo alquil- C_1-C_5 se ha reemplazado por un grupo $-C(O)NH_2$. Ejemplos representativos de grupos alquilamido incluyen, pero no se limitan a $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH_2CH_2CH_2CH_2C(O)NH_2$, $-CH_2CH(C(O)NH_2)CH_3$, $-CH_2CH(C(O)NH_2)CH_2CH_3$, $-CH(C(O)NH_2)CH_2CH_3$ y $C(CH_3)_2CH_2C(O)NH_2$.
 25

"alcanol" se refiere a un grupo alquil- C_1-C_5 , como los definidos arriba, donde uno de los hidrógenos del grupo
 30 alquil- C_1-C_5 se ha reemplazado por un grupo hydroxilo. Ejemplos representativos de grupos alcanol incluyen, pero no se limitan a $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, -

$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$ y $-\text{C}(\text{CH}_3)_2\text{CHOH}$.

"Alquilcarboxi" se refiere a un grupo alquil- $\text{C}_1\text{-C}_5$, en donde alquil- $\text{C}_1\text{-C}_5$, como los definidos arriba, donde uno
5 de los hidrógenos del grupo alquil- $\text{C}_1\text{-C}_5$ se ha reemplazado por un grupo $-\text{COOH}$. Ejemplos representativos de grupos alquilcarboxi incluyen, pero no se limitan a $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}(\text{COOH})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}(\text{COOH})\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{COOH})\text{CH}_2\text{CH}_3$ y $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{COOH}$.
10

"N-amidoalquil" se refiere a un grupo $-\text{NHC}(\text{O})-$ en donde el carbonil de un átomo de carbono de dicho grupo se encuentra unido a un grupo alquil- $\text{C}_1\text{-C}_5$, como los
15 definidos arriba. Ejemplos representativos de grupos N-amidoalquil incluyen, pero no se limitan a $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{NHC}(\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{NHC}(\text{O})\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{C}(\text{CH}_3)_3$ y $-\text{NHC}(\text{O})\text{CH}_2\text{C}(\text{CH}_3)_3$.
20

"Alquilcarboxamida" se refiere a un grupo $-\text{C}(\text{O})\text{NH}-$ en donde el átomo de nitrógeno de dicho grupo se encuentra unido a un grupo alquil- $\text{C}_1\text{-C}_5$, como los definidos
25 arriba. Ejemplos representativos de grupos alquilcarboxamida incluyen, pero no se limitan a $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{NHCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NHCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NH}-\text{C}(\text{CH}_3)_3$ y $-\text{C}(\text{O})\text{NHCH}_2\text{C}(\text{CH}_3)_3$.
30

Un grupo "Arileno" es un grupo fenil en donde uno de los átomos de hidrógeno de dicho grupo ha sido reemplazado con un enlace. Un grupo amileno puede estar en configuración orto, meta, o para y puede estar sin
 5 sustituir o independientemente sustituido con uno o más de los siguientes grupos: alquil-C₁-C₅, halo, -haloalquil, hidroxil, -O-C₁-C₅-alquil, -NH₂, -aminoalquil, -aminodialquil, -COOH, -C(O)O-(alquil-C₁-C₅), -OC(O)-(alquil-C₁-C₅), -N-amidoalquil, -C(O)NH₂, -
 10 carboxiamidoalquil o NO₂.

Un "Carbociclo C₃-C₈" es un anillo de hidrocarburos no aromático saturado que contiene 3 a 8 átomos de carbono. En los representativos de carbociclo C₃-C₈, incluyen pero
 15 no se limitan a ciclopropil, ciclobutil, ciclopentil, ciclohexil, cicloheptil y ciclooctil. Un Carbociclo C₃-C₈ puede estar sin sustituir o independientemente sustituido con uno o más de los siguientes grupos: alquil-C₁-C₅, halo, haloalquil, hidroxil, -O-alquil-C₁-C₅-
 20 NH₂, aminoalquil, aminodialquil, -COOH, -C(O)O-(alquil-C₁-C₅), -OC(O)-(alquil-C₁-C₅), -N-amidoalquil, -C(O)NH₂, -Carboxiamidoalquil o -NO₂.

"Heterociclo" se refiere a un carbociclo aromático o no
 25 aromático en el que uno a cuatro de los átomos de carbono del anillo han sido reemplazados independientemente con un átomo N, O o S. Ejemplos representativos de grupos heterociclos no incluyen, pero no se limitan a: piperidinil, piperazinil, morfolinil,
 30 pirrolil, oxazolil, tiazolil, diazolil, triazolil, tetrazolil, imidazolil, bencimidazolil, tetrazolil, indolil, isoquinolinil, quinolinil, quinazolinil,

pirrolidinil, purinil, isoxazolil, bencisoxazolil, furanil, furazanil, piridinil, oxazolil, benzoxazolil, tiazolil, benzotiazolil, tiofenil, pirazolil, triazolil, benzodiazolil, benzotriazolil, pirimidinil, isoindolil e
 5 indazolil. Un grupo heterociclo puede estar sin sustituir o sustituido con uno o más de los siguientes grupos: alquil-C₁-C₅, halo, haloalquil, hidroxil, -O-alquil-C₁-C₅, NH₂, -aminoalquil, -aminodialquil, -COOH, -C(O)O-(alquil-C₁-C₅), -OC(O)-(alquil-C₁-C₅), -N-
 10 amidoalquil, -C(O)NH₂, -Carboxamidoalquil o -NO₂.

Una "amina heterocíclica" es un heterociclo, como los definidos arriba, que tiene 1 a 4 átomos de nitrógeno en el anillo. Ejemplos representativos de aminas heterocíclicas incluyen, pero no se limitan a:
 15 piperidinil, piperazinil, pirrolil, oxazinil, tiazinil, diazinil, triazinil, tetrazinil, imidazolil, bencimidazolil, tetrazolil, indolil, isoquinolinil, quinolinil, quinazolinil, pirrolidinil, purinil, isoxazolil, bencisoxazolil, piridinil, oxazolil, benzoxazolil, tiazolil, benzotiazolil, pirazolil, triazolil, benzodiazolil, benzotriazolil, pirimidinil, isoindolil e indazolil y morfolinil; cada uno de los
 20 cuales estar sin sustituir o sustituido con uno o más: -N-(alquil-C₁-C₅), -C(O)-(alquil-C₁-C₅), -N-C(O)(alquil-C₁-C₄), -O-(alquil-C₁-C₅), -halo, -haloalquil, -alcanol, -alquilamino, -hidroxil, -NO₂, -NH₂, -aminoalquil, aminodialquil, -aminaheterocíclica, -alquil-C₁-C₁₀, -alquenil-C₂-C₁₀, -alquinil-C₂-C₁₀, -aril, -bencil, -aquilamido, -alquilcarboxil, -COOH, -alquilenil-C₁-C₅-
 30 OC(O)-alquil-C₁-C₅, -alquilenil-C₁-C₅-C(O)O-alquil-C₁-C₅, o un heterociclo o carbociclo-C₃-C₈, el cual puede estar sin sustituir o sustituido con uno o más: alquil-C₁-C₁₀,

-O-(alquil-C₁-C₅), -halo, -haloalquil, -alcanol, -alquilamino, hidroxí, -NO₂ o -NH₂.

"Halo" es -F, -Cl, -Br o -I-

5

Un " sujeto " es un mamífero, por ejemplo un humano, ratón, rata, cerdo de Guinea, perro, gato, caballo, vaca, cerdo, o un primate no humano.

- 10 La invención también incluye composiciones que comprenden un compuesto de indeno [1,2-c] isoquinolina y un vehículo farmacéuticamente aceptable. La invención incluye un un compuesto de indeno [1,2-c] isoquinolina provisto como un profármaco farmacéuticamente aceptable,
- 15 una sal hidratada, como un sal farmacéuticamente aceptable, o mezclas de los mismos.

- Representantes de "una sal farmacéuticamente aceptable" incluyen, por ejemplo, sales solubles en agua e
- 20 insolubles en agua, tales como: el acetato, amsonato (4,4-diaminoestilbeno-2,2-disulfonato), bencensulfonato, bezonato, bicarbonato, bisulfato, bitartrato, borato, bromuro, butirato, Edeteato de Calcio, Camsilato, carbonato, cloruro, citrato, clavulariato,
- 25 dihidrocloruro, edeteato, edisilato, estolato, esilato, fiunarato, gluceptato, gluconato, glutamato, glicolilarsanilato, hexafluorofosfato, hexilresorcinato, hidrabamina, hidrobromuro, hidrocioruro, hidroxinaptoato, yoduro, isotionato, lactato,
- 30 lactobionato, laurato, malato, maleato, mandelato, mesilato, metilbromuro, metilnitrato, metilsulfato, mucato, napsilato, nitrato, sal amónica de N-

metilglucamina, 3-hidroxi-2-naptoato, oleato, ocalato, palmitato, pamoato(1,1-meteno-bis-2-hidroxi-3-naptoato, einbonato), pantotenato, fosfato/difosfato, priorato, poligalacturonato, propianato, p-toluensulfonato, 5 salicilato, estearato, subacetato, siccinato, sulfato, sufosaliculado, suramato, tanato, tartrato, teoclato, tosilato, trietiodinato y sal valerato.

Una " cantidad efectiva" cuando se usa en relación a un 10 compuesto indeno [1,2-c] isoquinolina, es una cantidad efectiva para tratar o prevenir una enfermedad inflamatoria o una enfermedad de reperusión.

Las siguientes abreviaciones se usan aquí y tienen las 15 siguientes definiciones: AcOH es ácido acético, CEP es Punción y ligadura cecal, DMEM es Dulbecco's modified Eagle Médium, DMF es N,N-dimetilformamida, DMSO es dimetilsulfóxido, EtOAc es acetato de etilo, EtOH es etanol, HEPES es ácido 4-(2-hidroxietil)-1- 20 piperazinetanosulfónico, LPS es lipopolisacárido, MeOH metanol, MS es esctrometría de masas, MNR resonancia magnética nuclear, PBS es buffer salino de fosfato(pH 7.4), PARS es poli(ADP-ribosa)sitetasa, Py es piridina, SDS es sulfato de docecil (sal de sodio), STZ es 25 estreptozotocin, TCA es ácido tricloroacético, TFA es ácido trifluoroacético, TLC Cromatografía de capa delgada, TNF es factor de necrosis tumoral y TRIS es Tris(hidroximetil)aminometano.

30

Metodo para utilizar compuestos de indeno [1,2-c] isoquinolina

La invención también incluyen métodos para inhibir PARS en una célula. PARS, que también se conoce como poli(ADP-ribosa) sintetasa, PARP ((poli(ADP-ribosa)polimerasa, EC 2.4.99) y ADP-ribosiltransferasa (ADPRT, EC 2.4.2.30), es una enzima nuclear que cataliza la transferencia de una fracción de ADP ribosa de NAD⁺ a una proteína aceptora.

10 En una modalidad el método comprende contactar una célula con un compuesto indeno [1,2-c] isoquinolina en una cantidad suficiente para inhibir el PARS en la célula. En general, cualquier célula que tenga, o sea capaz de tener actividad de PARS o capaz de expresar

15 PARS, puede usarse. La célula puede ser suministrada en cualquier forma. Por ejemplo, la célula puede ser suministrada *in vitro*, *ex vivo* o *in vivo*. La actividad de PARS se puede medir usando un método conocido en el arte, por ejemplo como los métodos descritos en Banasik et al., J. Biol. Chem. 267:1569-75 (1991). Ejemplos

20 ilustrativos de células capaces de expresar PARS incluyen, pero no se limitan a músculo, hueso, encía, nervio, cerebro, hígado, riñón, páncreas, pulmón, corazón, vejiga, estómago, Colon, rectal, intestino

25 delgado, piel, esofagal, ojo, laringe, uterina, ovario, próstata, tendón, médula ósea, sangre, linfa, testicular, vaginal y células neoplásicas.

En la invención también se provee un método para

30 inhibir, prevenir, o tratar la inflamación o una enfermedad inflamatoria en un sujeto. La inflamación puede asociarse con un enfermedad inflamatoria. Las

enfermedades inflamatorias puede surgir donde exista una inflamación en un tejido del cuerpo. Éstas incluyen respuestas inflamatorias locales e inflamaciones sistémicas. Ejemplos de dichas enfermedades incluyen:

5 rechazo de transplante de órganos; lesión de reoxigenación producida por el trasplante de un órgano (ver Grupp et. Al. J. Mol. Cell Cardiol. 31:297-303 (1999)) incluyendo, pero no limitándose a trasplantes de los siguientes órganos: corazón, pulmón, hígado y riñón;

10 enfermedad inflamatoria crónica de las articulaciones, incluyendo artritis, artritis reumatoidea, osteoartritis y enfermedades óseas asociadas con resorción incrementada del hueso; enfermedad inflamatoria intestinal como ileitis, colitis ulcerativa, síndrome de

15 Barreto, enfermedad de Crohn; enfermedad inflamatoria de los pulmones como el asma, síndrome del sufrimiento respiratorio del adulto, y enfermedad obstructiva crónica de las vías respiratorias; enfermedades inflamatorias del ojo incluyendo distrofia corneal,

20 tracoma, oncocercosis, uveitis, oftalmitis simpática y endoftalmitis; tuberculosis; lepra; enfermedad inflamatoria del riñón incluyendo complicaciones urémicas, glomerulonefritis, nefrosis; enfermedades inflamatorias de la piel incluyendo esclerodermatitis,

25 psoriasis y eczema; enfermedades inflamatorias del sistema nervioso central, incluyendo enfermedades crónicas de desmielinización del sistema nervioso, esclerosis múltiple, neurodegeneración relacionada con el sida y la enfermedad de Alzheimer, meningitis

30 infecciosa, encefalomielitis, enfermedad de Parkinson, enfermedad de Huntington, esclerosis amiotrófica lateral y encefalitis viral o auto inmune; enfermedades auto

inmunes incluyendo diabetes mellitas tipo I y tipo II, complicaciones diabéticas, incluyendo, pero no limitándose a, cataratas diabéticas, glaucoma, retinopatía, neuropatía, como microalbuminuria y

5 nefropatía diabética progresiva, polineuropatía, gangrena del pie, enfermedad arterial coronaria aterosclerótica, enfermedad arterial periférica, coma hiperglicémico-hiperosmolar no cetónico, mononeuropatías, neuropatía autonómica, úlceras en el

10 pie, problemas de articulación, y complicaciones en membranas mucosas o piel, como una infección, acné, una infección por *Candida* o necrobiosis lipoidica diabetorum; vasculitis del complejo inmune, lupus eritematoso sistémico (SLE); enfermedades inflamatorias

15 del corazón como cardiomiopatía, enfermedad cardíaca isquémica hipercolesterolemica, y aterosclerosis; así como muchas otras enfermedades que tienen componentes inflamatorios significativos, incluyendo preclampsia; falla renal crónica, trauma cerebral y de la médula

20 espinal, y cáncer. La enfermedad inflamatoria también puede ser una inflamación sistémica del cuerpo, ejemplificada por shock gram-positivo o gram-negativo, shock hemorrágico o anafiláctico, o shock inducido por quimioterapia anticancerígena en respuesta a citoquinas

25 pro inflamatorias, por ejemplo, shock asociado con citoquinas pro inflamatorias. Dichos shocks pueden ser inducidos, por ejemplo, por un agente quimioterapéutico que es administrado como tratamiento para el cáncer.

30 En una modalidad, una lesión de reoxigenación resultante del trasplante de un órgano ocurre durante el trasplante del órgano.

La invención también incluye métodos para tratar, prevenir, o de otra forma inhibir enfermedades de reperfusión en un sujeto con necesidad de tratamiento, prevención, o inhibición de la misma. El método comprende la administración de un compuesto indeno [1,2-c] isoquinolina en una cantidad suficiente para tratar, prevenir o inhibir enfermedades de reperfusión en un sujeto. La reperfusión se refiere al proceso donde el flujo sanguíneo en los vasos sanguíneos se reanuda luego de una isquemia, como ocurre luego de una constricción o obstrucción de un vaso. La enfermedad de reperfusión puede darse luego de un episodio de ocurrencia natural, como un infarto del miocardio, un derrame, o durante un procedimiento quirúrgico donde el flujo sanguíneo en los vasos es bloqueado intencionalmente o no intencionalmente.

En algunas modalidades, se le administra al sujeto una cantidad efectiva de un compuesto indeno [1,2-c] isoquinolina.

La invención también incluye composiciones farmacéuticas útiles para el tratamiento o prevención de una enfermedad inflamatoria o una enfermedad de reperfusión, o para inhibir la actividad del PARS, o más de una de estas actividades. Las composiciones pueden ser adecuadas para uso interno y comprender una cantidad efectiva de un compuesto indeno [1,2-c] isoquinolina y un vehículo farmacéuticamente aceptable. Los compuestos indeno [1,2-c] isoquinolina son especialmente útiles ya

que ellos demuestran muy baja toxicidad periférica o, ninguna toxicidad periférica.

Los compuestos indeno [1,2-c] isoquinolina pueden ser
5 administrados en cantidades que sean suficientes para tratar o prevenir una enfermedad inflamatoria o una enfermedad de reperfusión y/o prevenir el desarrollo de las mismas en sujetos.

10 La administración de compuestos indeno [1,2-c] isoquinolina puede ser llevada a cabo por cualquier modo de administración de agentes terapéuticos. Estos modos incluyen administración sistémica o local tal como oral, nasal, parenteral, transdermal, subcutánea, vaginal,
15 bucal, rectal, o tópicamente.

Dependiendo del modo deseado de administración, las composiciones pueden estar en formas de dosificación sólidas, semi sólidas o líquidas, tales como por
20 ejemplo, inyectables, tabletas, supositorios, píldoras, cápsulas de liberación retardada, elixires, tinturas, emulsiones, jarabes, polvos, líquidos, suspensiones, como bolsitas de té, preferiblemente en dosis unitarias y consistentes con las prácticas farmacéuticas
25 convencionales. De la misma forma, éstas también pueden ser administradas vía intravenosa (en bolo o infusión), intraperitoneal, en forma subcutánea o intramuscular, todas éstas usando formas bien conocidas para aquellos versados en las artes farmacéuticas.

30

Composiciones farmacéuticas ilustrativas son tabletas y cápsulas de gelatina que comprenden un compuesto indeno

[1,2-c] isoquinolina y un vehículo farmacéuticamente aceptable, como es a) un diluyente, por ejemplo, lactosa, dextrosa, sucrosa, manitol, sorbitol, celulosa, sodio, sacarina, glucosa y/o glicina; b) un lubricante, por ejemplo, silica, talco, ácido esteárico, su sal magnésica o cálcica, oléato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio y/o polietilenglicol; para tabletas también c) un aglutinante, por ejemplo, silicato de magnesio aluminio, pasta de almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa sódica, carbonato de magnesio, azúcares naturales como glucosa o beta lactosa, endulzantes de maíz, gomas naturales y sintéticas como la acacia, tragacanto o alginato de sodio, ceras y/o polivinilpirrolidona; si se desea d) un desintegrante, por ejemplo almidones, agar, metil celulosa, bentonita, goma xantana, ácido algico o su sal de sodio, o mezclas efervescentes; y/o e) absorbentes, colorantes, saborizantes y endulzantes.

Composiciones líquidas, particularmente inyectables, pueden, por ejemplo, ser preparadas por disolución, dispersión, etc. Por ejemplo, el compuesto indeno [1,2-c] isoquinolina se disuelve en o se mezcla con un solvente farmacéuticamente aceptable, como por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol, y similares, para así formar una solución o suspensión inyectable isotónica.

Compuestos de indeno [1,2-c] isoquinolina también pueden ser formulados como supositorios que se pueden preparar

desde emulsiones o suspensiones oleosas; usando polialquilen glicoles como el propilen glicol, como vehículo.

- 5 Los compuestos de indeno [1,2-c] isoquinolina también pueden administrarse en forma de sistemas de entrega de liposomas, como pequeñas vesículas unilamelares, grandes vesículas unilamelares y vesículas multilamelares. Los liposomas pueden formarse a partir de una variedad de
10 fosfolípidos, que contienen colesterol, estearilamina o fosfatidilcolinas. En algunas modalidades, una película de componente lípido se hidrata con una solución acuosa del fármaco a una forma de capa lipídica encapsulando el fármaco, como se describe en la patente de Estados
15 Unidos Núm. 5.262.564.

- Compuestos de indeno [1,2-c] isoquinolina también se pueden entregar mediante el uso de anticuerpos monoclonales como vehículos individuales a los que las
20 moléculas del compuesto indeno [1,2-c] isoquinolina se unen. Los compuestos indeno [1,2-c] isoquinolina también se pueden unir con polímeros solubles como vehículos transportadores de fármacos. Estos polímeros pueden incluir polivinilpirrolidona, copolímero de pirano,
25 polihidroxipropilmetacrilamida-fenol, polihidroxietilaspanamidafenol, o polietilenoxidepolilisina sustituida con residuos de palmitoil. También, los compuestos de indeno [1,2-c] isoquinolina se pueden unir a una clase de polímeros
30 biodegradables útiles para lograr la liberación controlada de un fármaco, por ejemplo ácido poliláctico, caprolactona poliepsilon, ácido polihidroxibutírico,

poliortoesteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de hidrogel de unión cruzada o antipáticos.

5 La administración inyectable parenteral se usa generalmente para inyecciones e infusiones subcutáneas, intramusculares, o intravenosas. Los inyectables pueden ser preparados de forma convencional, como soluciones líquidas o suspensiones o en formas sólidas adecuadas
10 para disolverse en líquidos antes de la inyección.

Una modalidad para la administración parenteral emplea el implante de un sistema de liberación lenta o liberación sostenida, de acuerdo a la patente de Estados
15 Unidos Núm. 3.710.795, incorporada aquí como referencia.

Las composiciones pueden ser esterilizadas o contener cantidades no tóxicas de adyuvantes, como preservantes, estabilizantes, humidificantes o agentes emulsionantes,
20 promotores de solución, sales para regular la presión osmótica agentes reguladores de pH, y otras sustancias, incluyendo, pero no limitándose a, acetato de sodio o oleato de trietanolamina. Adicionalmente, éstas también pueden contener otras sustancias valiosas
25 terapéuticamente.

Las composiciones pueden ser preparadas de acuerdo al mezclado convencional, granulado o métodos de cubrimiento, respectivamente, y las presentes
30 composiciones farmacéuticas pueden contener cerca de 0.1% a cerca de 99%, preferiblemente cerca de 1% a cerca

de 70% del compuesto indeno [1,2-c] isoquinolina por peso o volumen.

El régimen de dosis de utilización del compuesto indeno
5 [1,2-c] isoquinolina se selecciona de acuerdo con una
variedad de factores incluyendo tipo, especie, edad,
peso, sexo y condición médica del paciente; la severidad
de la condición a ser tratada; la ruta de
administración; la función renal o hepática del
10 paciente; y el compuesto indeno [1,2-c] isoquinolina
particular empleado. Un médico o veterinario de
entrenamiento usual en el arte, puede fácilmente
determinar y prescribir la cantidad efectiva del fármaco
requerido para prevenir, contraatacar o detener el
15 progreso de la condición.

Cantidades de dosis efectiva de la presente invención,
cuando se usa para los efectos indicados, tiene un rango
de cerca de 0.05 a cerca de 1000 mg del compuesto indeno
20 [1,2-c] isoquinolina por día. Las composiciones pueden
contener cerca de 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0,
50.0, 100.0, 250.0, 500.0 o 1000.0 mg del compuesto
indeno [1,2-c] isoquinolina. En una modalidad, las
composiciones están en forma de tabletas que pueden ser
25 valoradas. Los niveles efectivos plasmáticos de
compuestos indeno [1,2-c] isoquinolina pueden
encontrarse en rangos desde cerca de 0.002 mg a cerca de
50 mg por kilogramo de peso corporal por día.

30 Los compuestos indeno [1,2-c] isoquinolina pueden ser
administrados en una única dosis diaria, o la dosis
diaria total puede ser administrada en dosis divididas

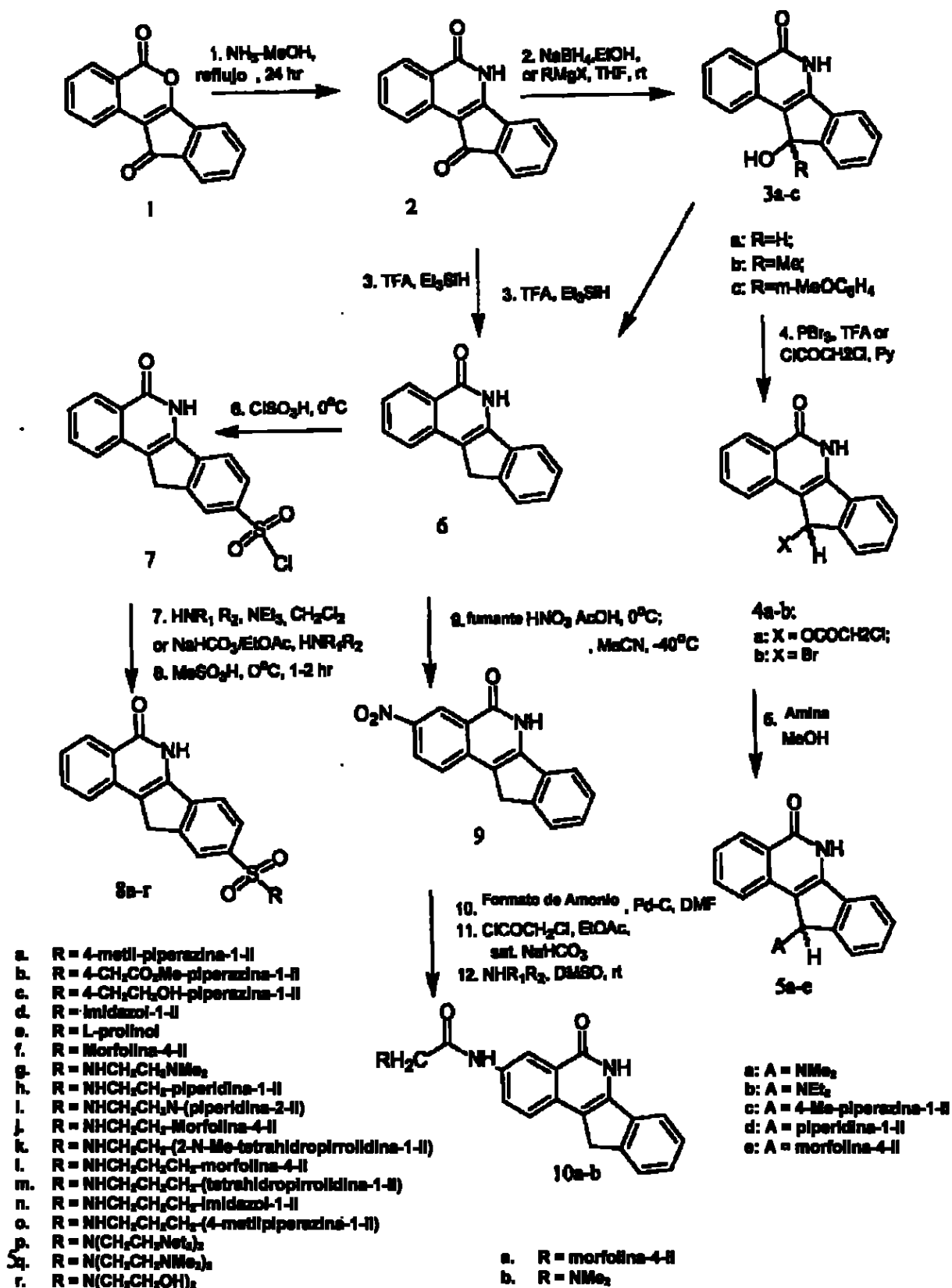
de dos, tres, o cuatro veces diariamente. Igualmente, los compuestos indeno [1,2-c] isoquinolina pueden ser administrados de forma intranasal por uso de la vía tópica de vehículos intranasales adecuados, o por vías transdermales, usando esas formas de parches de piel transdermales bien conocidas por aquellos versados en el arte. Para ser administrados en forma de sistemas de entrega transdermal, la dosis de administración puede ser continua más que intermitente durante el régimen de dosificación. Otras preparaciones tópicas ilustrativas incluyen cremas, ungüentos, lociones, aerosoles y geles, donde la concentración del compuesto indeno [1,2-c] isoquinolina está en un rango de cerca de 0.1% a cerca de 15%, p/p o p/v.

15

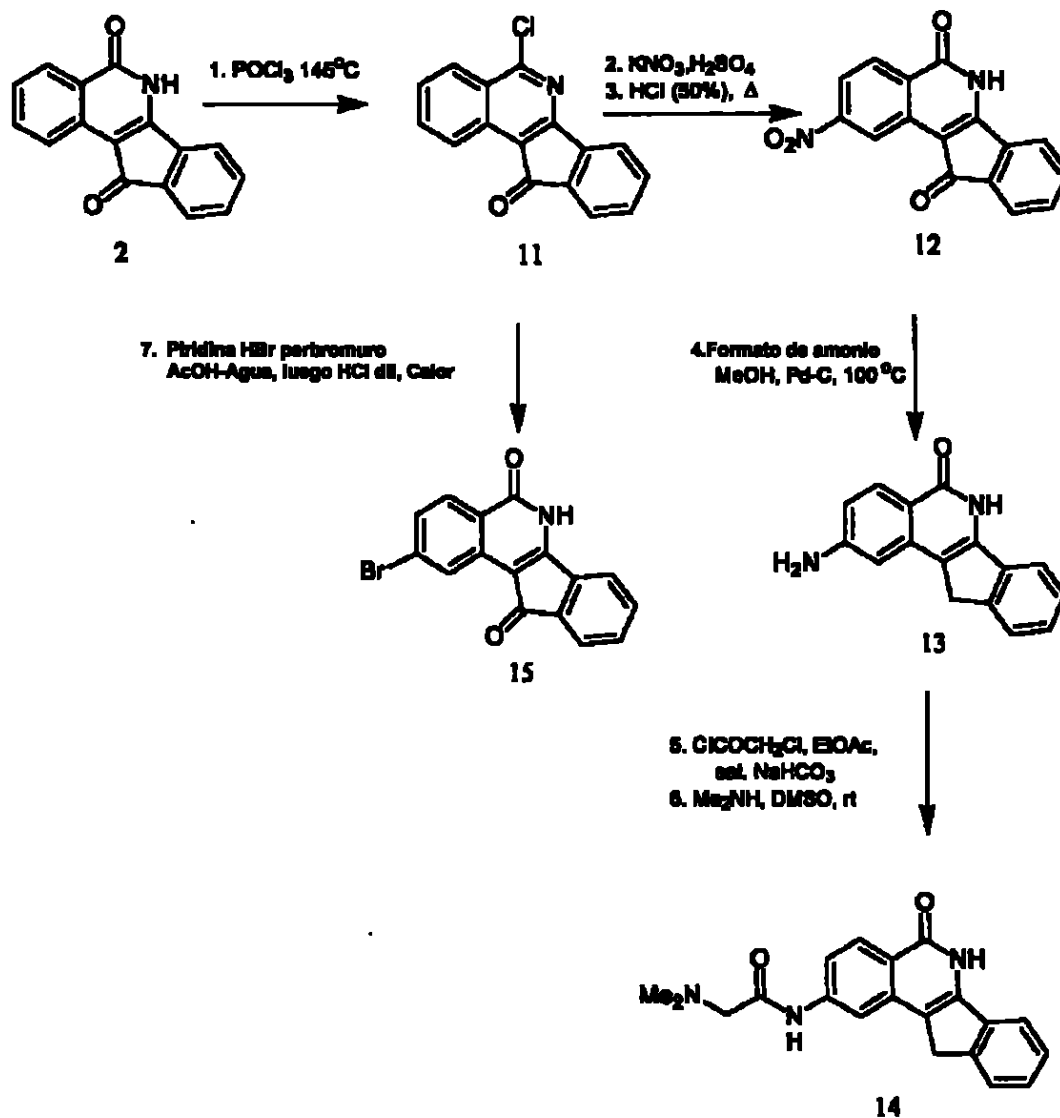
Métodos para preparar compuestos indeno [1,2-c] isoquinolina

Ejemplos de vías sintéticas para preparar compuestos indeno [1,2-c] isoquinolina, se proponen en los ejemplos siguientes y los esquemas generalizados 1 y 2.

20



Esquema 1



5

Esquema 2

5,6-dihidro-5,11-diceto-11H-indeno[1,2-c] isoquinolina, se preparó por reacción el compuesto 1 (Aldrich Chemical, Milwaukee, WI) con amino en metanol.

10

(±)11-hidroxi-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (3a) se preparó por reacción de 2 con NaBH_4 en etanol.

(±)11-hidroxi-11-metil-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (3b) se preparó por reacción de 2 con MeMgI.

(±)11-hidroxi-11-(m-metoxifenil)-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (3c) ha sido preparado desde 2, usando m-MeO-C₆H₄MgI.

(±)11-N,N-dimetilamino-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (5a) se preparó desde 3a usando cloroacetilcloruro seguido por reacción con demetilamina.

Se preparan similarmente: (±)11-N,N-dietilamino-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (5b), (±)11-N-(piperidin-1-il)-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (5d), (±)11-N-(4-metilpiperazino-1-il)-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (5c), (±)11-N-(morfolin-4-il)-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (5e), (+)11-N-(morfolin-4-il)-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (4b).

5,6-Dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (6), se prepara por reducción de 5,6-dihidro-5,11-diceto-11H-indeno[1,2-c] isoquinolina (2) o (±)11-hidroxi-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (3a) usando CF₃COOH/trietilsilano. 9-clorosulfonil-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (7) se preparó por clorosulfonación de 5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (6). 9-[N-(4-metilpiperazina-1-il)sulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c]

isoquinolina (8a) se preparó a partir de 9-clorosulfonil-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (7), y N-metilpiperazina. De manera similar se preparan: 9-[N-(4-carbometoximetilenpiperazino-1-il)sulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8b), 9-[N-4-(2-hidroxietilpiperazino-1-il)-sulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8c), 9-[N-(imidazol-1-il)sulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8d), 9-[N-(2-hidroxiprolinil)sulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8e), 9-[N-morfolinsulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8f), 9-[N-(2-[N,N-dimetilamino)etil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8g), 9-[N-(2-[piperidino-1-il]etil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8h), 9-[N-(2-(piridino-2-il)-etil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8i), 9-[N-(2-[morfolino-4-il]etil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8j), 9-[N-(2-[N-metiltetrahidropirrolidina-1-il]etil)aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8k), 9-[N-(3-[morfolino-4-il]propil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8l), 9-[N-(3-[tetrahidropirrolidina-1-il]propil)aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8m), 9-[N-(3-[imidazol-1-il]propil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8n), 9-[N-(3-(4-metilpiperazino-1-il)propil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8o), 9-[N,N-di-(2-[N,N-dietilamino]etil)-aminosulfonil]-5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8p), 9-

[N,N-di-(2-[N,N-dimetilamino]etil)-aminosulfonil] -5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8q), y 9-[N,N-di-(2-[N,N-dihidroxi-etilamino]etil)-aminosulfonil] -5,6-dihidro-5-oxo-11H-indeno[1,2-c] isoquinolina (8r).

5

Los derivados amínicos de 3-morfolin-4-il-N-(5-oxo-5,11-dihidro-6H-indeno[1,2-c]isoquinolina-3-il)-acetamida (10a), 3-dimetilamino-N-(5-oxo-5,11-dihidro-6H-indeno[1,2-c]isoquinolina-3-il)-acetamida (10b) y 2-dimetilamino-N-(5-oxo-5,11-dihidro-6H-indeno[1,2-c]isoquinolina-2-il)-acetamida (14) se preparó desde 5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (6) y 5-Cloro-11H-indeno[1,2-c]isoquinolina (11), usando nitración, luego reducción y seguido por aminación del intermediario cloroacetamida. 2-Bromo-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (15) se preparó por bromación de cloroamidato (11).

La invención adicionalmente se describe en los siguientes ejemplos, los cuales no limitan el alcance de la invención descrita en las reivindicaciones. Los siguientes ejemplos ilustran la síntesis ilustrativa de compuestos indeno[1,2-c]isoquinolina de la invención, y demuestran su utilidad para tratar o prevenir una enfermedad inflamatoria o enfermedad de reperfusión.

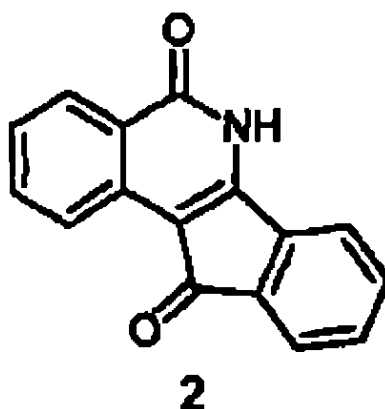
5. EJEMPLOS

Ejemplo 1: síntesis ilustrativa de compuestos indeno[1,2-c]isoquinolina

a) métodos generales

El espectro NMR protónico se obtuvo usando un espectrofotómetro Varian 300 MHz y las variaciones químicas de valor (δ) se reportan en partes por millón(ppm). Se llevaron a cabo TLC, usando placas de TLC precubiertas con silicagel 60 F-254, y la TLC preparatoria se llevó cabo usando placas precubiertas con Whatman 60^a. Todos los compuestos intermediarios y finales se caracterizaron con base en datos de ^1H NMR y MS.

b) síntesis de 5,6-dihidro-5,11-diceto-11H-indeno[1,2-c]isoquinolina (2):

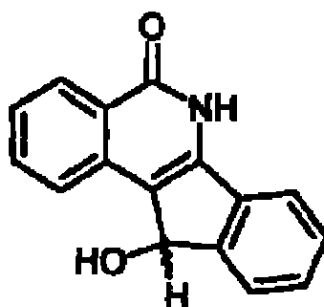


15

Una suspensión agitada de 1 (55 gr, 0,22 mol) en NH_3/MeOH (7,0N, 700 ml) se pusieron en reflujo 15 por 24 horas. La mezcla de reacción se dejó enfriar a temperatura ambiente y se filtró y se lavó totalmente con MeOH para dar 46 gramos del producto de color naranja arriba titulado con un rendimiento de 84%. ^1H NMR ($\text{DMSO}-d_6$): δ 7,48-7,61 (m, 4H), 7,80-7,88 (m, 1H), 7,86 (d, $J=8,7$ Hz, 1H), 8,22 (d, $J=8,4$ Hz, 1H), 8,44 (d,

J=7.5 Hz, 1H), 13,05 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 106,33, 121,63, 122,94, 123,27, 124,80, 128,45, 132,17, 133,60, 134,03, 134,68, 134,68, 134,81, 137,09, 156,41, 163,76, 190,57; MS (ES^-): m/z 246,2 (M-1); Anal. Calcd para $\text{C}_{16}\text{H}_9\text{NO}_2$: C, 77,72; H, 3,67; N, 5,67; encontrado: C, 77,54; H, 3.69, N, 5.69.

c) síntesis de (±)11-hidroxi-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (3a):



3a

10

A una suspensión agitada de 2 (2,5 g, 0,01 mol) en etanol (25 ml) se adicionó NaBH_4 (3,75 gramos, 0,1 mol) a temperatura ambiente en pequeñas porciones cada 30 minutos. La mezcla de reacción fue agitada por un tiempo adicional de dos horas y luego enfriada a 0°C donde fue precipitado con ácido clorhídrico (solución 10%). El sólido resultante se filtró y se lavó con agua en metanol para dar 3a (2,326 g, 92%). ^1H NMR (DMSO- D_6): δ 5.58 (d, $J=8.1$ Hz, 1H), 5.78 (d, $J=8.7$ Hz, 1H), 7.33-7.89 (m, 6H), 7.95 (d, $J=7.8$ Hz, 1H), 8.22 (d, $J=7.8$ Hz, 1H), 12.29 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 77,44, 118,81, 120,15, 124,28, 125,04, 125,67, 126,34, 128,46, 128,64, 128,95, 133,27, 135,62, 136,12, 139,93, 148,55, 163,69.; MS (ES^+): m/z 250,1 (M+1); Anal. Calcd para $\text{C}_{16}\text{H}_{11}\text{NO}_2$: C,

15

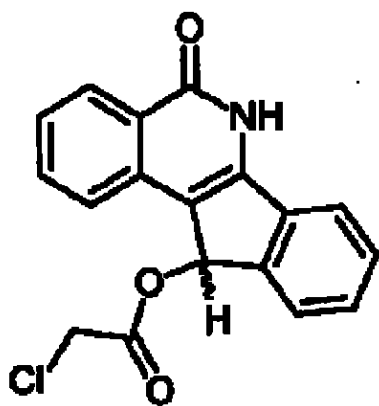
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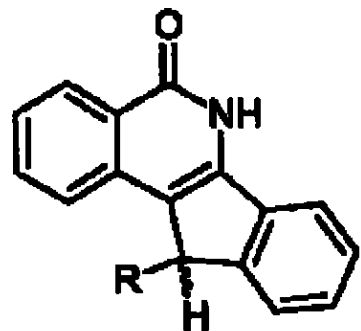
77,10; H, 4.45; N, 5,62. Encontrado: C, 77.01; H, 4,57; N, 5,59.

Similarmente, se prepararon por reacción de 2 con MeMgI y m-MeO-C₆H₄MgBr respectivamente, los compuestos (±)11-hidroxi-11-metil-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (3b) y (±)11-hidroxi-11-(m-metoxifenil)-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (3c).

10 d) Síntesis de 11-sustituido-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (5a-e):



4a



5a-e

5a: R = NMe₂

5b: R = Net₂

5c: R = -piperidina-1-il

5d: R = -N-metil-piperadín-4-il

5e: R = -morfolín-1-il

15

20 A una suspensión agitada de 3a (0,5 gramos, 0,002 mol) en piridina (10 ml) se adicionó cloruro de cloroacetil (0,81 gramos, 0,006 mol) a 0°C. Se permitió que la mezcla de reacción se calentara a temperatura ambiente y

si agitara por 24 horas. Luego la mezcla de reacción se
virtió en hielo y se extrajo con EtOAc. La fase orgánica
se separó, se secó y se concentró para dar el compuesto
crudo 4a el cual se trató luego con dimetilamina y se
5 agitó a temperatura ambiente por 24 horas. La mezcla de
reacción se virtió en hielo y se trató con ácido
clorhídrico a 10%. La mezcla de reacción se alcalinizó
usando NaHCO₃ acuoso saturado y el sólido resultante se
filtró para dar el producto deseado 5^a. ¹H NMR (DMSO-
10 D₆): δ 2,31 (s, 6H), 5,00 (s, 1H), 7,28-7,45 (m, 3H),
7,68-7,73 (m, 2H), 7,95 (d, J=6,9 Hz, 1H), 8,10 ((d,
J=7,8 Hz, 1H), 8,21 (d, J=8,1 Hz, 1H), 12,26 (s, 1H);
¹³C NMR (DMSO-D₆): δ 68,09, 116,28, 120,52, 124,58,
125,74, 126,27, 126,34, 127,68, 128,64, 133,02, 136,27,
15 144,45, 163,80; MS (ES⁺): m/z 277,2 (M+1)

También se prepararon los siguientes compuestos por
reacción de 4a como arriba con dietilamina, piperidina,
N-metilpiperidina y morfolina, respectivamente:

20

(±) 11-dietilamino-5,6-dihidro-5-oxo-11H-indeno[1,2-
c]isoquinolina (5b)

(±) 11-piperidin-5,6-dihidro-5-oxo-11H-indeno[1,2-
c]isoquinolina (5c)

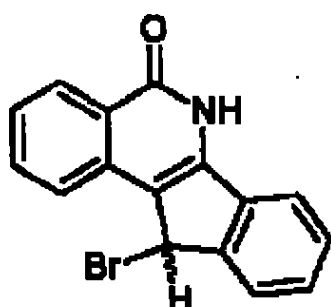
25

(±) 11-m-metilpiperazin-5,6-dihidro-5-oxo-11H-
indeno[1,2-c]isoquinolina (5d)

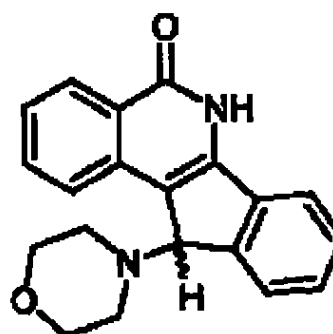
(±) 11-morfolin-5,6-dihidro-5-oxo-11H-indeno[1,2-
c]isoquinolina (5e)

30

**e) síntesis de (±) 11-morfolin-5,6-dihidro-5-oxo-11H-
indeno[1,2-c]isoquinolina (5e) a partir de 4b**



4b



5e

a una suspensión agitada de 3a (0,6 gramos, 2,4 mol) en ácido trifluoroacético (5 ml) se adicionó tribromuro fosfórico (1,0M sln. en CH₂Cl₂, 3 ml) a temperatura ambiente, y la mezcla de reacción fue agitada por ocho horas. La mezcla reacción se virtió en hielo y el sólido resultante se filtró para dar el compuesto bromado 4b (0,61 gramos, 76%). ¹H NMR (DMSO-D₆): δ 7,35-7,50 (m, 3H), 7,61 (d, J=6,6 Hz, 1H), 7,73-7,82 (m, 2H), 7,94 (d, J=6,6 Hz, 1H), 8,23 (d, J=7,8 Hz, 1H), 12,41 (s, 1H); ¹³C NMR (DMSO-D₆): δ 52,06, 79,35, 114,43, 120,56, 123,58, 125,27, 125,50, 128,55, 128,86, 129,66, 133,73, 135,91, 136,61, 141,39, 143,95, 163,74.

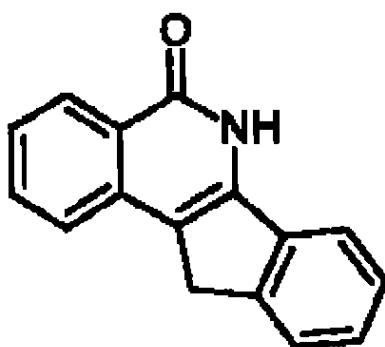
15

El compuesto 4b (0,5 gramos) se suspendió en MeOH (10 ml) y se trató con exceso de morfolina (~10 eq.) a temperatura ambiente y se agitó a 60°C por tres horas. La mezcla de reacción se virtió en hielo y se diluyó con acetato de etilo (40 ml). La fase orgánica se separó y se extrajo en HCl diluido (10% sln.), la fase acuosa se alcalinizó con NaHCO₃ acuoso saturado, y el sólido resultante precipitado se filtró y se secó para producir

20

5e (0,46 gramos, 90%). ^1H NMR (DMSO- D_6): δ 2,56 (m, 4H), 3,49 (m, 4H), 5,04 (s, 1H), 7,31-7,45 (m, 3H), 7,65-7,76 (m, 2H), 7,96 (d, $J=7,2$ Hz, 1H), 8,20-8,24 (m, 2H), 12,29 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 49,36, 67,62, 68,11, 115,20, 120,60, 124,47, 125,84, 126,34, 126,41, 127,76, 128,30, 128,72, 133,09, 136,30, 136,96, 140,35, 144,44, 163,67.

f) **síntesis de 5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (6)**



6

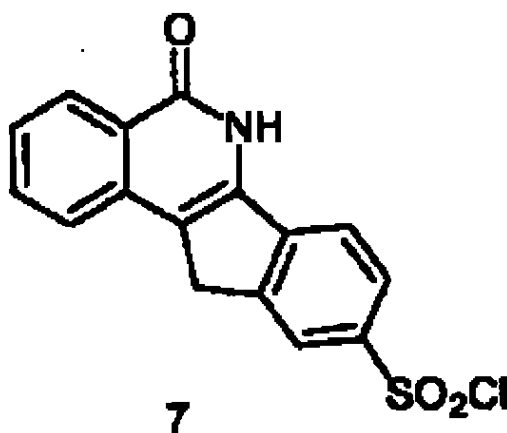
Método 1: a una solución agitada del alcohol 3a (0,35 gramos, 1,4 mmol) en ácido trifluoroacético (10 ml) se
15 adicionó a temperatura ambiente trietilsilano (0,812 gramos, 7 mmol) y la mezcla reacción se agitó por 24 horas. El ácido trifluoroacético se evaporó al vacío y se adicionó EtOAc al producto crudo resultante. El sólido resultante se filtró y se lavó con agua y EtOAc
20 para dar el compuesto arriba titulado 6 (0,285 gramos, 87%). ^1H NMR (DMSO- D_6): δ 3,89 (s, 2H), 7,30-7,47 (m, 3H), 7,59 (d, $J=6,9$ Hz, 1H), 7,72-7,74 (m, 2H), 7,98 (d, $J=7,8$ Hz, 1H), 8,23 (d, $J=8,4$ Hz, 1H), 12,31 (s, 1H); ^{13}C NMR (DMSO- D_6): δ 33,51, 116,50, 120,19, 124,01,

125,51, 125,55, 126,42, 127,50, 127,68, 158,56, 133,45, 136,39, 137,53, 140,18, 143,80, 163,46; MS (ES⁻): m/z 232,1 (M-1); Anal. Calcd para C₁₆H₁₁NO₂: C, 81,38; H, 4.75; N, 6,00. Encontrado: C, 81,79; H, 4,45; N, 5,99.

5

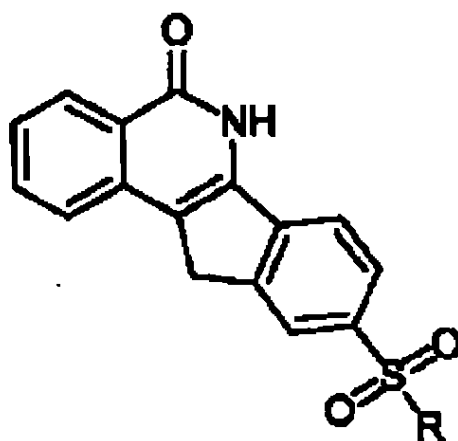
Método 2: a una suspensión agitada de 2 (40 gramos, 0,16 mol) en ácido trifluoroacético (2,5 L.) se adicionó trietilsilano (94 gramos, 0,8 mol) en pequeñas porciones a temperatura ambiente y la mezcla de reacción se agita por 96 hrs., tiempo durante el cuál el progreso de la reacción se monitoreo usando TLC (eluyente- 5%MeOH/CH₂Cl₂). La mezcla de reacción se virtió lentamente en hielo, se filtró, se lavó repetidamente con cantidades de agua y metanol y se secó al vacío para dar el compuesto arriba titulado 6 (33,1 gramos, 88%) cuyos datos de espectro fueron idénticos a los de la muestra de compuesto 6 que se obtuvo originalmente usando el método 1.

20 **g) síntesis de 9-clorosulfonil-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (7)**



El compuesto 6 (40 gramos, 0,17 mol) se adicionó en
pequeñas porciones a clorosulfonil cloruro (112 ml, 1,71
mol) a 0°C y la mezcla de reacción se dejó calentar a
temperatura ambiente y se agitó por dos horas. La mezcla
5 de reacción fue vertida lentamente en hielo y el sólido
amarillo resultante se filtró, se lavó completamente con
agua y etanol y se secó al vacío para dar el compuesto
arriba titulado 7 (52 g, 92%). ¹H NMR (DMSO-D₆): δ 3,91
(s, 2H), 7,43-7,48 (m, 1H), 7,60 (d, J=7,2 Hz, 1H),
10 7,74-7,76 (m, 2H), 7,79 (s, 1H), 7,90 (d, J=7,5 Hz, 1H),
8,23 (d, J=7,8 Hz, 1H), Anal. Calcd para C₁₆H₁₂ClNO₄S:
C, 54,94; H, 3,46; N, 4,00. Encontrado: C, 55,28; H,
3,43; N, 3,68, Karl.Fischer, 2,95.

15 h) síntesis de derivados de 9-sulfonamido-5,6-dihidro-5-
oxo-11H-indeno[1,2-c]isoquinolina (8a-r) a partir de 7:



8a-r

- 20 a. R = -N-(4-Metil-piperazina-1-il)
b. R = -N-(4-CH₂CO₂Me)-piperazina-1-il)
c. R = -N-(4-CH₂CH₂OH)-piperazina-1-il)
d. R = -N-imidazol-1-il

- e. R = -N-L-prolinil
- f. R = -N-morfolin-4-il
- g. R = -NHCH₂CH₂NMe₂
- h. R = -NHCH₂CH₂-piperidin-1-il
- 5 i. R = -NHCH₂CH₂-(piridin-2-il)
- j. R = -NHCH₂CH₂-morfolin-4-il
- k. R = -NHCH₂CH₂-(2-N-Me-tetrahidropirrolidina-1-il)
- l. R = -NHCH₂CH₂CH₂-morfolin-4-il
- m. R = -NHCH₂CH₂CH₂-(tetrahidropirrolidina-1-il)
- 10 n. R = -NHCH₂CH₂CH₂-imidazol-1-il
- o. R = -NHCH₂CH₂CH₂-(4-metilpiperazina-1-il)
- p. R = -N(CH₂CH₂Net₂)₂
- q. R = -N(CH₂CH₂NMe₂)₂
- r. R = -N(CH₂CH₂OH)₂

15

Método 1: a una suspensión agitada de 3-(4-morfolino)-1-propilamina (17.28 g, 0.12 mol) en EtOAc se le adicionó NaHCO₃ saturado acuoso (300 ml), y la mezcla se dejó agitar por 15 minutos. El compuesto 7 (4,0 gramos, 0,012 mol) se adicionó entonces en pequeñas porciones a temperatura ambiente. La mesa de reacción fue agitada por 24 horas; filtrada y lavada con agua, EtOAc y metanol; se puso en reflujo en metanol por 30 minutos, se filtró aún caliente; y se lavó con metanol para proveer el compuesto arriba titulado 81 como base libre (2,330 gramos, 44%). ¹H NMR (DMSO-D₆): δ 1,47-1,52 (m, 2H), 2,16-2,21 (m, 4H), 2,47-2,48 (m, 2H), 3,44-3,48 (m, 2H), 3,23 (m, 4H), 4,02 (s, 2H), 7,49-7,58 (m, 1H), 7,78-7,82 (m, 3H), 7,97 (s, 1H), 8,14 (d, J=7,8 Hz, 1H), 8,26 (d, J=7,8 Hz, 1H), 9,59 (s, 1H), 12,42 (s, 1H).

La base libre de 8d, 8g, 8h, 8j, 8l, 8m-8r también se prepararon por el Metodo I, pero sustituyendo el 3-(4-morfolino)-1-propilamina con imidazol, 2-dimetilamino-etilamina, 2-(N-piperidinil)-etilamina, 2-(N-morfolinil)-etilamina, 3-(N-morfolinil)-propilamina, 3-(N-tetrahidropirrollidinil)-propilamina, 3-(N-imidazolil)-propilamina, 3-(N-(4-metilpiperazinil)-propilamina, di-(2-(dietilamino)-etil)amina, di-(2-(dimetilamino)-etil)amina y di-(2-hidroxietil)amina, respectivamente.

9-(N-sulfonilimidazol)-5,6-dihidro-5-oxo-11H-indeno[1,2-c]isoquinolina (8a-r):

Método 2: a una suspensión agitada de 3-(4-morfolino)-1-propilamina (4, 250 gramos) en CH_2Cl_2 (100 ml) se adicionó 7 (1,950 gramos, 5,89 mmol) en la mezcla resultante se agitó por cinco minutos. Subsecuentemente, se adicionaron 3 ml de trietilamina y la mezcla de reacción se agitó por 24 horas a temperatura ambiente. Luego este tiempo se recolectó el precipitado y se lavó con metanol (2 x 100 ml) y el producto sólido crudo se transfirió a un balón de fondo redondo. Este material se diluyó con metanol (200 ml), se calentó a reflujo por 30 minutos y se filtró estando aún caliente. La pasta de filtrada resultante se lavó con metanol (200 ml) para proveer el producto deseado como base libre de 8l (1, 460 gramos, 56%).

Las bases libres del compuesto 8a-r se prepararon usando el método 2, pero sustituyendo la 3-(4-morfolina)-1-propilamina con imidazol, 2-dimetilamino-etilamina, 2-

(N-piperidinil)-etilamina, 2-(N-morfolinil)-etilamina,
 3-(N-morfolinil)-propilamina, 3-(N-tetrahidropirrollidinil)-propilamina, 3-(N-imidazolil)-
 propilamina, 3-(N-(4-metilpiperazinil)-propilamina, di-
 5 (2-(dietilamino)-etil)amina, di-(2-(dimetilamino)-
 etil)amina y di-(2-hidroxietil)amina, respectivamente.

i) procedimientos general para la preparación de la sal mesilato de 8a-r:

10

Se adicionó la base libre 8l a ácido metanosulfónico a 0°C y luego se dejó enfriar la mezcla resultante a temperatura ambiente y se agitó por dos horas. La mezcla de reacción fue entonces vertida en metanol frío (entre
 15 -10°C y 0°C) y el sólido precipitado se filtró, se lavó con metanol (100 ml) y se secó al vacío. El sólido secó seis odio en agua (~200 ml) y se liofilizó para dar la sal monohidrato de metanosulfonato 8l.

20 (1,020 gramos, 84%). ¹H NMR (DMSO-D₆): δ 1,75-1,85 (m, 2H), 2,35 (s, 3H), 2,78-2,84 (m, 2H), 2,96-3,12 (m, 4H), 3,36 (d, J= 12,3 Hz, 2H), 3,61 (t, J= 11,4 Hz, 2H), 3,94 (d, J= 12,9 Hz, 2H), 4,03 (s, 2H), 7,49-7,55 (m, 1H), 7,76-7,84 (m, 3H), 7,99 (d, J= 0,9 Hz, 1H), 8,15 (d, J= 8,4 Hz, 1H), 8,25 (d, J= 8,4 Hz, 1H), 9,59 (s, 1H),
 25 12,42 (s, 1H); ¹³C NMR (DMSO-D₆): δ 24,27, 33,86, 51,89, 54,51, 64,02, 119,70, 120,39, 123,53, 126,09, 126,45, 128,63, 133,66, 135,80, 138,71, 141,21, 144,57, 163,29; Anal. Calcd para C₂₄H₃₁N₃O₈S₂: C, 52,06; H, 5,46; N, 7,59m
 30 Kart-Fisher, 3,36. Encontrado: C, 51,85; H, 5,35; N, 7,30, Kart.Fischer, 4,32. Similarmente se prepararon sales de HCl, H₂SO₄, CH₃COOH, y de ácido succínico, por

sustitución del ácido metanosulfónico con HCl, H₂SO₄ y CH₃COOH.

Ejemplo 2. Efecto de compuestos ilustrativos de indeno[1,2-c]isoquinolina en la actividad de PARS en macrofagos cultivados, usando un ensayo basado en cero las enteras en ensayo enzimas purificadas

La demostración de la habilidad de compuestos ilustrativos de indeno[1,2-c]isoquinolina para inhibir PARS y prevenir la cito toxicidad inducida por peroxidonitrito, se enseñó usando métodos descritos Virag et al., Br J Pharmacol. 1999, 126 (3): 769-77; y Immunology 1998, 94 (3): tres 345-55. RAW más prófugos de ratón se cultivaron en un medio DMEM con alta glucosa y suplementado con 10% de suero bovino fetal. Las células fueron usadas al 80% de confluencia en platos de 12-pozos. Las células fueron pretratadas con varias concentraciones (100 nM-uno µM) de un compuesto indeno[1,2-c]isoquinolina por diez minutos. Peroxinitrito, un oxidante prototipo que induce el rompimiento en una hebra sencilla de DNA, se usó para inducir la activación PARS. El Peroxinitrito se diluyó en buffer de de fosfato salino (PBS) (pH 11,0) y se adicionó a las células en un bolo de 50µl. Luego las células se incubaron por 20 minutos. El Peroxinitrito se descompuso por incubación de 30 minutos a pH 7. 0, usado como control, y falló para influenciar el parámetro estudia. Después de 20 minutos de incubación, las células fueron centrifugadas, el medio se respiró y las células se resuspendieron en 0,5 ml del buffer de ensayo (56mM HEPES pH 7,5, 28mM KCl, 28mM NaCl, 2mM MgCl₂,

121

pero, 0,01% p/v digitonina y 0,125 μM NAD^+ y 0,5 $\mu\text{M}/\text{ml}$ $^3\text{H-NAD}^+$). Continuando con una incubación de buffer de ensayo (10 minutos a 37°C), la actividad de PARS fue medida como sigue: 200 μl helado 50% p/v de TCA se
5 adicionó y las muestras fueron incubadas por 4 horas a 4°C. Las muestras se centrifugaron (10 minutos @ 10.000 g) y el sólido se lavó dos veces con 50% p/v de TCA helado visualizado durante la noche en 250 μl 2% p/v SDS/0,1N NaOH a 37°C. Al contenido de los tubos se
10 agregaron 6,5 ml de ScintiSafe Plus scintillation liquid (Fisher Scientific) que la radioactividad se determinó usando un líquido centelleante contador (Wallac, Gaithersburg, MD). Los resultados mostrados en la tabla 1 demuestran que los compuestos ilustrativos de
15 indeno[1,2-c]isoquinolina, significativamente y dependiendo de la dosis inhiben la activación de PARS en ensayo de macrofagos.

Tabla 1. Efecto inhibidor de varios indeno[1,2-c]isoquinolina sustituidos novedosos, en la activación de PARS en macrofagos de murina cultivados.

20

Compuesto	% PARS inhibición a 1 μ M	% PARS inhibición a 300 nM	% PARS inhibición a 100 nM
2	60	NT	16
3a	67	NT	8
3b	25	0	NT
3c	21	9	NT
4b	88	NT	51
5a	55	NT	10
5b	33	NT	0
5c	24	NT	0
5d	48	NT	0
5e	21	NT	0
6	65	NT	30
7	50	NT	0
8a	NT	47	NT
8b	NT	NT	NT
8c	NT	27	NT
8d	NT	82	77
8e	NT	68	NT
8f	NT	NT	NT

8g	NT	55	34
8h	NT	76	56
8j	NT	76	34
8k	NT	38	24
8l	NT	84	34
8m	NT	50	NT
8n	NT	82	74
8o	NT	55	48
8p	NT	45	27
8q	NT	28	20
8r	NT	28	20
10a	NT	59	55
10b	NT	17	17

NT = No probado.

5

Prepotencia de inhibición en enzimas PARS purificadas se determinó subsecuentemente para compuestos indeno[1,2-c]isoquinolina seleccionados, y la potencia se comparó con la del 3-aminobenzamida, un inhibidor de PARS prototipo de prueba. El ensayo se lleva cabo en 96 platos de pozos de ELISA de acuerdo con instrucciones provistas con un kit de ensayo disponible para la inhibición de PARS (Trevigen, Gaithersburg, MD). En breve, los pozos fueron cubiertos con 1mg/mL de histona (50 μ L/pozo) a 4°C durante la noche. Los platos se lavaron cuatro veces con PBS y luego se bloquearon por la edición de 50 μ L de diluyente-Strep (provisto con el

10

15

kit). Luego de la incubación (una hora a temperatura ambiente), los platos se lavaron cuatro veces con PBS. De ilusiones apropiadas de inhibidores de PARS se combinaron con un cóctel 2x PARS (1,95mM NAD⁺, 50mM biotinilado NAD⁺ en 50mM TRIS pH 8,0, 25mM MgCl₂) y enzima de alta especificidad para la actividad de PARS (ambas fueron previstos con el kit) en un volumen de 50μL. se permitió suceder la reacción por 30 minutos a temperatura ambiente. Después se lavó cuatro veces en PBS, la biotina incorporada se detectó streptavidina peroxidasa conjugada (dilución 1:500) y sustratoTACS Sapphire. El ensayo confirmó el resultado del ensayo PARS basado en macrofagos. Por ejemplo, el inhibidor PARS 81 ejerció 50% de inhibición de actividad de PARS en este ensayo a 3nM, y así fue aproximadamente 50.000 veces más potente que el compuesto de referencia 3-aminobenzamida.

Ejemplo 3: efectos de compuestos ilustrativos de indeno[1,2-c]isoquinolina en varios modelos de enfermedad inflamatoria y enfermedad de reperfusión

a: efectos de compuestos ilustrativos de indeno[1,2-c]isoquinolina en modelos de células in-vitro de la enfermedad

En estudios adicionales in-vitro en timocitos aislados, las células se expusieron a Peroxinitrito o peróxido de hidrógeno (especies oxidantes tóxicas) para inducir citotoxicidad. En este sistema la toxicidad, al menos en parte, se relaciona con activación de la enzima nuclear PARS. En este ensayo de timocito oxidante estimulado

(escrito en detalle en Virag et al., Immunology 94 (3): 345-55, 1998), los compuestos ensayados previnieron la supresión de la oxidación inducida de la viabilidad de las células y también lo hicieron a rangos de baja
 5 concentración nanomolar. Un ejemplo de esta respuesta (compuesto 81) se muestra en la tabla 2. Este ensayo representa un modelo in-vitro de células muertas por la exposición a especies pro oxidantes, como ocurre durante la reperfusion o isquémica de los órganos.

10

Tabla 2. Reducción de la citotoxicidad inducida por Peroxinitrito por 30nM-3µM del compuesto indeno[1,2-c]isoquinolina 81.

	Control	+81 30 nM	+81 100 nM	+81 300 nM	+81 1 µM	+81 3 µM
Cytotoxicity	98%	74%	39%	2%	0%	0%

15

b: efectos de compuestos ilustrativos indeno[1,2-c]isoquinolina en modelos in-vivo de enfermedades inflamatorias

20

Para documentar la eficacia de los compuestos en enfermedades inflamatorias, el efecto de compuestos ilustrativos de indeno[1,2-c]isoquinolina se demostró en un modelo inflamatorio sistémico un inducido por
 25 lipopolisacárido bacteriano (LPS), que se reporta como responsable de causar enfermedades de reperfusion e inferior enfermedades inflamatorias como el shock séptico y el síndrome de respuesta de inflamación sistémica en animales (ver Parrillo, N. Engl. J. Med.,
 30 328: 1471-1478 (1993) y Lamping, J. Clin Invest. 101:

2065-2071 (1998). En una serie de experimentos, ratones fueron pretratados con una inyección intraperitoneal de 0,1 y 1 mg/Kg de compuestos 8l, 8p y 8j, y LPS a 10 mg/Kg se inyectó i.p., y se midió alfa-TNF en el plasma a los 90 minutos. Como se muestra en la tabla 3, todos los compuestos redujeron sustancialmente la producción de TNF, indicando la actividad antiinflamatoria de los compuestos.

10 **Tabla 3. Reducción de la producción de TNF inducida por LPS por una inyección intraperitoneal de 0,1-1 mg/Kg de un compuesto 8l, 8p y 8j inhibidor de PARS, in-vivo en ratón.**

15

	8j (0.1 mg/kg)	8j (1.0 mg/kg)	8p (0.1 mg/kg)	8p (1.0 mg/kg)	8l (0.1 mg/kg)	8l (1.0 mg/kg)	Vehicle
TNF (ng/ml)	3831.6 ± 385.2	5038.8 ± 377.1	4470.0 ± 184.4	5090.8 ± 203.7	3714.6 ± 300.9	3509.8 ± 311.5	6994.0 ± 904.4

Todos los compuestos suprimieron la producción de TNF inducida por LPS, cuando se compararon con el control.

20 A altas dosis, LPS causa la disfunción de múltiples órganos asemejando el shock séptico, y en últimas la muerte (en parte debido a la liberación temprana de alfa-TNF). Similarmente, en un modelo inducido por unión secal y punciones (CLP), la bacteria viva derivada de la flora intestinal induce inflamación sistémica y shock.

25 Agentes que inhiben la producción del mediador de la inflamación, activación PARS, y la muerte celular en este modelo previenen la mortalidad inducida por LPS o

CLP. En experimentos con ratón Balb/c, una inyección intraperitoneal de 100 mg/Kg LPS causó la muerte en 50% de los animales en 24 horas, mientras que el tratamiento de animales con 3 mg/kg/día del compuesto 81 redujo la mortalidad inducida por endotoxina al 10% bajo las mismas condiciones experimentales. En respuesta al shock inducido por CLP, el compuesto 81 (3 mg/kg/día) causó una reducción en la mortalidad del 100% al 60% en 24 horas.

10

Los datos que demuestran la reducción de la producción de TNF por compuestos ilustrativos de indeno[1,2-c]isoquinolina en animales sometidos al modelo de inflamación, coinciden con el hecho de que la producción de TNF es un desencadenante de la inflamación en varias enfermedades inflamatorias (como por ejemplo, colitis, artritis y neuroinflamación y shock) indicando que los compuestos de indeno[1,2-c]isoquinolina tienen efecto terapéutico en varias enfermedades inflamatorias sistémicas y locales, incluyendo el rechazo de órganos transplantados, que se implican un componente de enfermedad inflamatoria y un componente de enfermedad de reperfusión y, por lo tanto, son útiles para tratar o prevenir una enfermedad inflamatoria o una enfermedad de reperfusión.

25

c: efecto de compuestos ilustrativos de indeno[1,2-c]isoquinolina en modelos invivo de enfermedad de reperfusión.

30

Para documentar la eficacia de compuestos de indeno[1,2-c]isoquinolina en condiciones de isquemia-reperfusión,

el efecto de un compuesto ilustrativo de indeno[1,2-c]isoquinolina se probó en un modelo de ratón isquémico e intestino en reperfusión. La arteria superior mesentérica se ocluyó por 45 minutos, seguido por una reperfusión de una hora. Luego del final de la reperfusión, se midió la permeabilidad del intestino con el método FD4 en sacos uniformes de intestino (Liaudet et al; Shock 2000, 14 (2): 134-41). La isquemia-reperfusión incrementó la permeabilidad del intestino de 11 ± 4 a 216 ± 27 ml/min/cm², indicando el severo daño del intestino reperfundido. El tratamiento con el compuesto 81 (3 mg/kg i.v., inyectado 10 minutos antes de la iniciación de la reperfusión) reduce el incremento de la permeabilidad del intestino en aproximadamente 73%, indicando un marcado mantenimiento de la función del intestino. Los estudios de isquemia-reperfusión en el intestino se asociaron con una mortalidad del 80% en 12 horas, mientras que sólo una mortalidad del 15% se notó en animales tratados con 81.

20

En otra serie de experimentos, el efecto del compuesto 81 en ratas con el modelo de la arteria cerebral media en oclusión/reperfusión, se ensayo como se describe en Abdelkarim et al., Int J Mol Med. 2001, 7(3): 255-60. La oclusión que duró por dos horas, seguida por la reperfusión de 24 horas. El tamaño del infarto se cuantificó con manchado de tetrazolium. El compuesto 81 se han ministro a 3 mg/kg/día en tres dosis divididas inyectadas intraperitonealmente, siendo administrada la primera 10 minutos antes de la iniciación de la reperfusión. Se encontró una reducción aproximada del 80% en el grado de la necrosis cortical y la muerte

neuronal en los animales administrados con 81, cuando se comparó con los controles tratados con el vehículo. Esta protección también se trasladó en un beneficio funcional, como el mejoramiento neurológico en el grupo
5 tratado con los inhibidores de PARS.

Estos datos indican que los compuestos de indeno[1,2-c]isoquinolina tienen efectos terapéuticos en varias condiciones de enfermedades de reperfusión sistémicas y
10 locales, incluyendo el rechazo de órganos transplantados, lo que conduce tanto a componentes de enfermedad inflamatoria como a componentes de enfermedad de reperfusión, por lo tanto, resultan útiles para tratar o prevenir una enfermedad inflamatoria o una
15 enfermedad de reperfusión.

d: efecto de compuestos ilustrativos de indeno[1,2-c]isoquinolina en modelos de diabetes.

20 Se conoce que la inhibición de PARS y la deficiencia de PARS reduce el desarrollo de diabetes y la incidencia de complicaciones diabéticas (Mabley et al., Br J Pharmacol. 2001, 133 (6): 909-9; y Soriano et al., Nat Med. 2001, 7 (1): 108-13). Para documentar la eficacia
25 de los compuestos de indeno[1,2-c]isoquinolina en un modelo de diabetes, una dosis única del modelo de estreptozotocina de diabetes se llevó a cabo como se describió anteriormente. En breve, 160 mg/kg de estreptozotocina se inyectó aún ratón tratado con
30 vehículo o con el compuesto ilustrativo de indeno[1,2-c]isoquinolina intraperitonealmente (3 mg/kg) y tres días después se determinó el nivel de azúcar en la

sangre usando un medidor de glucosa en la sangre. Los
datos mostrados en la tabla 4 demuestran que los
compuestos ilustrativos de indeno[1,2-c]isoquinolina
atenuan el comienzo de diabetes inducida por
5 estreptozotocina así como reduce la hiperglicemia.

Tabla 4. Reducción de hiperglicemia inducida con
estreptozotocina (STZ) por inyección intraperitoneal de
3 mg/kg del compuesto inhibidor de PARS 8l, 8p y 8j en
10 ratón in-vivo.

	Basal	STZ + Vehicle	STZ + 8j	STZ + 8p	8l
Glucose (mg/ml)	153 ± 21	320 ± 13	253 ± 24	264 ± 24	244 ± 21

En concordancia, los compuestos de indeno[1,2-
15 c]isoquinolina son útiles para tratar o prevenir la
diabetes o una complicación diabética.

La presente invención no se limita en alcance por las
modalidades específicas reveladas en los ejemplos que
20 solamente tienen la intención de ilustrar unos pocos
aspectos de la invención y cualquier modalidad que sea
funcionalmente equivalente se encuentra dentro del
alcance de esta invención. De hecho, varias
modificaciones de la invención adicionales a las
25 mostradas y descritas aquí serán aparentes para aquellos
versados en el arte y se tiene la intención de que caiga
dentro del alcance de las reivindicaciones siguientes.

Un número de referencias han sido citadas, la revelación completa de las que han sido aquí incorporadas en su totalidad.

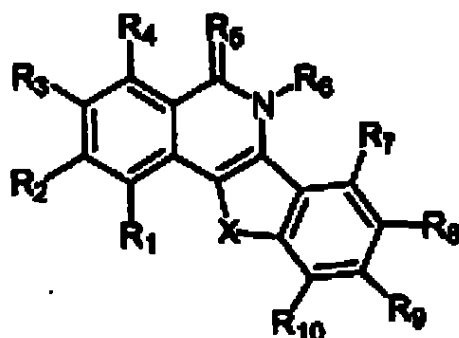
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10

15

Lo que se reivindica es:

1. Un compuesto de la fórmula



(Ia)

5

Y sales farmacéuticamente aceptables e hidratos del mismo,

Donde:

10

R₅ es NH O S;

R₆ es -H O C₁-C₄ alquil;

X es -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arileno-, -O-, -NH-, -S- o -CH(NR₁₁R₁₂)-,
donde n es un entero de 0-5;

15

R₁₁ y R₁₂ son independientemente -hidrogeno o -C₁-C₉ alquil, o N, R₁₁ y R₁₂ tomados juntos forman una amina heterocíclica;

20

R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son independientemente -hidrógeno, -halo, -hidroxy, -O-(C₁-C₃ alquil), -C₁-C₁₀ alquil, -haloalquil, -C₂-C₁₀ alquenil, -C₃-C₈ carbociclo, -aril, -NH₂, -

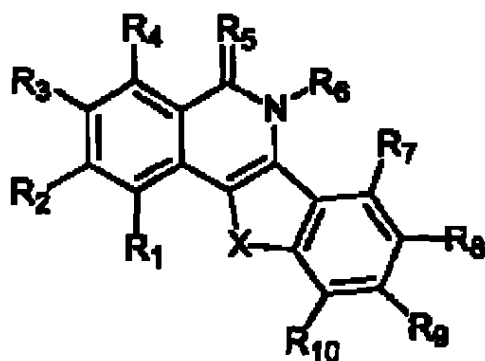
alquilamino, $-C(O)OH$, $-C(O)O(C_1-C_5 \text{ alquil})$, $-OC(O)(C_1-C_5 \text{ alquil})$, NO_2 o $-A-B$;

donde A es $-SO_2-$, $-SO_2NH-$, $-NHCO-$, $-NHCONH-$, $-O-$, $-CO-$, $-OC(O)-$, $-C(O)O-$, $-CONH-$, $CON(C_1-C_4 \text{ alquil})-$, $-NH-$, $-CH_2-$, $-S-$ o $-C(S)-$;

B es $-C_1-C_{10}$ alquil, $-C_2-C_{10}$ alquenil, $-heterociclo$, $-C_3-C_8$ carbociclo, $-aril$, $-NZ_1Z_2$, $-alquilamino$, $-aminodialquil$, $-alquilheterociclo$, $-arilamido$, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alquil})$ o $-C(O)O-fenil$, donde ninguno de los cuales están no-sustituídos o sustituidos con uno o mas de $-O-(C_1-C_5 \text{ alquil})$, $-halo$, $-haloalquil$, $-alcanol$, $-alquilamino$, $-hidroxi$, $-NO_2$, $-NH_2$, $-aminoalquil$, $-aminodialquil$, $-amina heterocíclica$, $-C_1-C_{10}$ alquil, $-C_2-C_{10}$ alquenil, $-C_2-C_{10}$ alquinil, $-aril$, $-benzil$, $-alquilamido$, $-alquilcarboxi$, $-C_1-C_5$ alquilenio- $-C(O)O-C_1-C_5$ alquil o grupos $-C_1-C_5$ alquilenio- $-OC(O)-C_1-C_5$ alquil; y

Z_1 y Z_2 son independientemente $-H$ o $-C_1-C_{10}$ alquil, los cuales están no-sustituídos o sustituidos con uno o mas de $-halo$, $-OH$ o $-N(Z_3)(Z_4)$, donde Z_3 y Z_4 son independientemente, $-H$ o $-C_1-C_5$ alquil, donde están no-sustituídos o sustituidos con uno o mas de $-halo$, $-hidroxi$ o $-NH_2$; o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

2. Un compuesto de la fórmula



(1b)

Y sales farmacéuticamente aceptables e hidratos del mismo,

5

Donde:

R₅ es O, NH o S;

R₆ es -H o C₁-C₄ alquil;

10 X es -CH₂-, -CH(halo)-, -CH(OH)(CH₂)_n-, -CH(OH)-arileno-, -O-, -NH-, -S- o -CH(NR₁₁R₁₂)-, donde n es un entero de 0-5;

15 R₁₁ y R₁₂ son independientemente -hidrogeno o -C₁-C₉ alquil, o N, R₁₁ y R₁₂ tomados juntos forman una amina heterocíclica;

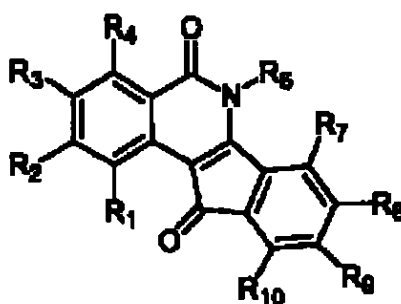
20 R₁, R₂, R₃, R₄, R₇, R₈, R₉ y R₁₀ son independientemente -hidrógeno, -halo, -hidroxy, -O-(C₁-C₅ alquil), -C₁-C₁₀ alquil, -haloalquil, -C₂-C₁₀ alquenil, -C₃-C₈ carbociclo, -aril, -NH₂, -alquilamino, -C(O)OH, -C(O)O(C₁-C₅ alquil), -OC(O)(C₁-C₅ alquil), NO₂ o -A-B;

donde A es -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, CON(C₁-C₄ alquil)-, -NH-, -CH₂-, -S- o -C(S)-;

B es $-C_1-C_{10}$ alquil, $-C_2-C_{10}$ alquenil, -heterociclo, $-C_3-C_8$ carbociclo, -aril, $-NZ_1Z_2$, -alquilamino, -aminodialquil, -alquilheterociclo, -arilamido, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alquil})$ o $-C(O)O$ -fenil, donde
 5 ninguno de los cuales están no-sustituídos o sustituidos con uno o mas de $-O-(C_1-C_5 \text{ alquil})$, -halo, -haloalquil, -alcanol, -alquilamino, -hidroxi, $-NO_2$, $-NH_2$, -aminoalquil, -aminodialquil, -amina heterocíclica, $-C_1-C_{10}$ alquil, $-C_2-C_{10}$ alquenil, $-C_2-C_{10}$
 10 alquinil, -aril, -benzil, -alquilamido, -alquilcarboxi, $-C_1-C_5$ alquilenos $-C(O)O-C_1-C_5$ alquil o grupos $-C_1-C_5$ alquilenos $-OC(O)-C_1-C_5$ alquil; y

Z_1 y Z_2 son independientemente $-H$ o $-C_1-C_{10}$ alquil, los cuales están no-sustituídos o sustituidos con uno o mas de -halo, $-OH$ o $-N(Z_3)(Z_4)$, donde Z_3 y Z_4
 15 son independientemente, $-H$ o $-C_1-C_5$ alquil, donde están no-sustituídos o sustituidos con uno o mas de -halo, -hidroxi o $-NH_2$; o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no
 20 sustituida; o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

3. Un compuesto de la fórmula



(II)

Y sales farmacéuticamente aceptables e hidratos del mismo,

Donde:

5

R_6 es -H o C_1-C_4 alquil;

10 $R_1, R_2, R_3, R_4, R_7, R_8, R_9$ y R_{10} son independientemente -hidrógeno, -halo, -hidroxy, -O- (C_1-C_5 alquil), - C_1-C_{10} alquil, -haloalquil, - C_2-C_{10} alquenil, - C_3-C_8 carbociclo, -aril, - NH_2 , -alquilamino, -C(O)OH, -C(O)O(C_1-C_5 alquil), -OC(O)(C_1-C_5 alquil), NO_2 o -A-B; donde por lo menos uno de R^1, R^4 y R^{10} es diferente de hidrógeno;

15 A es - SO_2 -, - SO_2NH -, - $NHCO$ -, - $NHCONH$ -, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, $CON(C_1-C_4$ alquil)-, -NH-, - CH_2 -, -S- o -C(S)-;

20 B es - C_1-C_{10} alquil, - C_2-C_{10} alquenil, -heterociclo, - C_3-C_8 carbociclo, -aril, - NH_2 , -alquilamino, -aminodialquil, -alquilheterociclo, -arilamido, -C(O)OH, -C(O)O-(C_1-C_5 alquil) o -C(O)O-fenil o - NZ_1Z_2 ; y

25 Z_1 y Z_2 son independientemente -H o - C_1-C_{10} alquil, los cuales están no-sustituídos o sustituidos con uno o mas de -halo, -OH o - $N(Z_3)(Z_4)$, donde Z_3 y Z_4 son independientemente, -H o - C_1-C_5 alquil, donde están no-sustituídos o sustituidos con uno o mas de -halo, -hidroxí o - NH_2 ; O N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica sustituida o no sustituida; o N, Z_1 y Z_2 tomados juntos forman una
30 amina heterocíclica.

4. El compuesto de la reivindicación 1, 2 o 3 donde R_5 es O, y R_6 es hidrógeno.
- 5 5. El compuesto de la reivindicación 1 donde $R_1, R_2, R_3, R_4, R_7, R_8, R_9$ y R_{10} son independientemente hidrógeno, metil, etil, halo, $-NO_2$, hidroxil, metoxi, etoxi, $-NH_2$, -aminoalquil, -aminodialquil o -A-B.
- 10 6. El compuesto de la reivindicación 5, donde cualquiera de los dos R_8 o R_9 pero no juntos son -A-B.
- 15 7. El compuesto de la reivindicación 6 donde R_1, R_2, R_3, R_4, R_7 y R_{10} son hidrógeno.
8. El compuesto de la reivindicación 1, donde R_9 es -A-B.
- 20 9. El compuesto de la reivindicación 5, donde R_9 es -A-B.
10. El compuesto de la reivindicación 7, donde R_9 es -A-B y R_8 es hidrógeno.
- 25 11. El compuesto de la reivindicación 6, donde A es $-SO_2-$, $-SO_2NH-$ o $-NHCO-$.
12. El compuesto de la reivindicación 7, donde A es $-SO_2-$, $-SO_2NH-$ o $-NHCO-$.
- 30 13. El compuesto de la reivindicación 8, donde A es $-SO_2-$, $-SO_2NH-$ o $-NHCO-$.

14. El compuesto de la reivindicación 9, donde A es -SO₂-, -SO₂NH- o -NHCO-.
- 5 15. El compuesto de la reivindicación 10, donde A es -SO₂-, -SO₂NH- o -NHCO-.
- 10 16. El compuesto de la reivindicación 1, donde R₉ es -A-B y B es -C₁-C₈ alquil, -heterociclo, -C₃-C₈ carbociclo, -aril, -alquilamino, -alcanol o -alquilheterociclo.
17. El compuesto de la reivindicación 16, donde B es -C₁-C₅ alquil.
- 15 18. El compuesto de la reivindicación 5, donde A es -SO₂- y B es -NZ₁Z₂ y Z₁ y Z₂ son independientemente hidrógeno, o -C₁-C₅ alquil, no-sustituido o sustituido con -halo, -hidroxi o -NZ₃Z₄; donde Z₃ y Z₄ son independientemente -hidrógeno, -C₁-C₅ alquil, no-sustituido o sustituido con uno o mas de -halo, -hidroxi o -NH₂, o donde N, Z₁ y Z₂ tomados juntos forman una amina heterocíclica.
- 20 19. El compuesto de la reivindicación 18, donde Z₁ y Z₂ son -(CH₂)_nD; donde n es un entero de 1-5, y D es hidrógeno, hidroxi, amina heterocíclica o -NZ₃Z₄; donde Z₃ y Z₄ son independientemente hidrógeno, metil o etil.
- 25 20. El compuesto de la reivindicación 18, el cual puede ser no sustituido o sustituido con uno o más de metil, etil, o -alcanol.
- 30

21. El compuesto de la reivindicación 18, donde Z_1 es hidrógeno y Z_2 es $-NZ_3Z_4$ donde n es un entero de 1-5, y Z_3 y Z_4 son independientemente metil o etil, o, tomados juntos, NZ_3Z_4 forman una amina heterocíclica.
5
22. El compuesto de la reivindicación 15, donde X es $-CH_2-$, A es $-SO_2-$ y B es $-NZ_1Z_2$; donde Z_1 y Z_2 son independientemente hidrógeno, $-C_1-C_5$ alquil no-sustituido o sustituido con halo, hidroxí o $-NZ_3Z_4$ donde Z_3 y Z_4 son independientemente hidrógeno, $-C_1-C_5$ alquil no-sustituido o sustituido con halo, hidroxí o $-NH_2$; o donde Z_1 y Z_2 , tomados juntos, forman una amina heterocíclica.
10
15
23. El compuesto de la reivindicación 22, donde Z_1 y Z_2 son $-(CH_2)_nD$, donde n es un entero de 1-5, y D es hidrógeno, hidroxí, una amina heterocíclica o $-NZ_3Z_4$; donde Z_3 y Z_4 son independientemente hidrógeno, metil o etil.
20
24. El compuesto de la reivindicación 18, donde B es un heterociclo, no-sustituido o sustituido con metil, etil o -alcanol.
25
25. El compuesto de la reivindicación 18, donde Z_1 es hidrógeno y Z_2 es $-(CH_2)_nNZ_3Z_4$, donde n es 2 o 3, y Z_3 y Z_4 son independientemente metil o etil, o, tomados juntos, NZ_3Z_4 , forman una amina heterocíclica.
30
26. El compuesto de la reivindicación 1 donde X es $-C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$ o $-CH(NR_{11}R_{12})-$ donde

R_{11} y R_{12} son hidrógeno, $-C_1-C_9$ alquil, o $NR_{11}R_{12}$, tomados juntos, forman un heterociclo.

27. El compuesto de la reivindicación 6 donde X es -
5 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$ o $-CH(NR_{11}R_{12})-$ donde R_{11} y R_{12} son hidrógeno, $-C_1-C_9$ alquil, o $NR_{11}R_{12}$, tomados juntos, forman un heterociclo.

28. El compuesto de la reivindicación 8 donde X es -
10 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$ o $-CH(NR_{11}R_{12})-$ donde R_{11} y R_{12} son hidrógeno, $-C_1-C_9$ alquil, o $NR_{11}R_{12}$, tomados juntos, forman un heterociclo.

29. El compuesto de la reivindicación 9 donde X es -
15 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$ o $-CH(NR_{11}R_{12})-$ donde R_{11} y R_{12} son hidrógeno, $-C_1-C_9$ alquil, o $NR_{11}R_{12}$, tomados juntos, forman un heterociclo.

30. El compuesto de la reivindicación 10 donde X es -
20 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$ o $-CH(NR_{11}R_{12})-$ donde R_{11} y R_{12} son hidrógeno, $-C_1-C_9$ alquil, o $NR_{11}R_{12}$, tomados juntos, forman un heterociclo.

31. El compuesto de la reivindicación 6 donde X es -
25 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$.

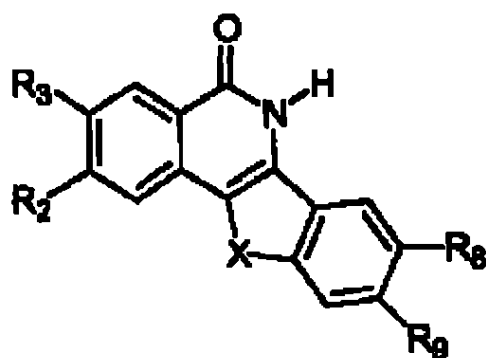
32. El compuesto de la reivindicación 6 donde X es $-CH_2-$.

33. El compuesto de la reivindicación 8 donde X es es -
30 $C(O)-$, $-CH(OH)$, $-CH(Br)-$, $-CH_2-$.

34. El compuesto de la reivindicación 8 donde X es $-CH_2-$.

35. El compuesto de la reivindicación 9 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
- 5 36. El compuesto de la reivindicación 9 donde X es -CH₂-.
37. El compuesto de la reivindicación 10 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
- 10 38. El compuesto de la reivindicación 10 donde X es -
CH₂-.
39. El compuesto de la reivindicación 13 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
- 15 40. El compuesto de la reivindicación 13 donde X es -
CH₂-.
41. El compuesto de la reivindicación 14 donde X es -
20 C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
42. El compuesto de la reivindicación 14 donde X es -
CH₂-.
- 25 43. El compuesto de la reivindicación 18 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
44. El compuesto de la reivindicación 18 donde X es -
CH₂-.
- 30 45. El compuesto de la reivindicación 19 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.

46. El compuesto de la reivindicación 19 donde X es -
CH₂-.
- 5 47. El compuesto de la reivindicación 20 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
48. El compuesto de la reivindicación 20 donde X es -
CH₂-.
- 10 49. El compuesto de la reivindicación 21 donde X es -
C(O)-, -CH(OH), -CH(Br)-, -CH₂-.
50. El compuesto de la reivindicación 21 donde X es -
15 CH₂-.
51. Un compuesto de la fórmula



(III)

20

Y sales farmacéuticamente aceptables e hidratos del mismo,

Donde:

X es $-\text{CH}_2-$ o $-\text{O}-$;

5 R_2 y R_3 son independientemente -hidrógeno, -halo, -haloalquil, -hidroxi, $\text{O}-(\text{C}_1-\text{C}_5 \text{ alquil})$, $-\text{C}_1-\text{C}_3$ alquil, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{CONH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{OC}(\text{O})-\text{C}_1-\text{C}_5$ alquil o $-\text{C}(\text{O})\text{O}-\text{C}_1-\text{C}_5$ alquil;

R_4 y R_5 son independientemente -hidrógeno y -A-B;

A es $-\text{SO}_2-$, $-\text{SO}_2\text{NH}-$, o $-\text{NHCO}-$; y

10 B es $-\text{C}_1-\text{C}_3$ alquil, $-\text{NZ}_1\text{Z}_2$, -heterociclo o -alcamino, cada uno no-sustituido o sustituido con uno o más de -alcanol, -alquilamino, -aminoalquil, -aminodialquil o -heterociclo, cada uno no-sustituido o sustituido con $-\text{C}_1-\text{C}_{10}$ alquil o -alcanol; y

15 Z_1 y Z_2 son independientemente -hidrógeno o $-\text{C}_1-\text{C}_8$ alquil, los cuales están no-sustituidos o sustituidos con uno o mas de -hidroxi o $-\text{NZ}_3\text{Z}_4$, donde Z_3 y Z_4 son independientemente, -H o $-\text{C}_1-\text{C}_3$ alquil, donde están no-sustituidos o sustituidos con uno o
20 mas de -hidroxi o $-\text{NH}_2$, o N, Z_3 y Z_4 tomados juntos forman una amina heterocíclica, o N, Z_1 y Z_2 tomados juntos forman una amina heterocíclica.

25 52. El compuesto de la reivindicación 51, donde A es $-\text{SO}_2-$, y B es $-\text{NZ}_1\text{Z}_2$.

30 53. El compuesto de la reivindicación 52, donde Z_1 y Z_2 son independientemente hidrógeno, o $-\text{C}_1-\text{C}_5$ alquil, no-sustituido o sustituido con hidroxi o NZ_3Z_4 , o, tomados juntos, $-\text{NZ}_1\text{Z}_2$ forman una amina heterocíclica.

54. El compuesto de la reivindicación 53, donde Z_3 y Z_4 son independientemente hidrógeno, o $-C_1-C_5$ alquil, no-sustituido o sustituido con hidroxilo o $-NH_2$, o, tomados juntos, NZ_3Z_4 forman una amina heterocíclica.
55. El compuesto de la reivindicación 54, donde la amina heterocíclica es seleccionada desde el grupo basado de una piperidina no-sustituida, grupo de piperazina o morfolina, o un grupo de piperazina, pirrolidina o imidazole el cual puede estar sin sustituir o sustituido con $-N-(C_1-C_5 \text{ alquil})$ o $-N-C(O)(C_1-C_5 \text{ alquil})$.
56. El compuesto de la reivindicación 53, donde NZ_1Z_2 o NZ_3Z_4 es un heterociclo, no-sustituido o sustituido con $-C_1-C_5$ alquil, -alcohol o -alquilamino.
57. Un método para inhibir la actividad de la poli(ADP)-ribosa sintetasa en una célula, el método comprende poner en contacto dicha célula con el compuesto o su sal o hidratos farmacéuticamente aceptables, de cualquiera de las reivindicaciones 1,2,3 o 51 en una cantidad suficiente para inhibir la poli(ADP)-ribosa sintetasa en dicha célula.
58. El método de la reivindicación 57 donde la célula es una célula in-vivo.
59. El método para tratar o prevenir una enfermedad inflamatoria en un sujeto, que comprende la administración a un sujeto con la necesidad del compuesto o una sal o hidratos farmacéuticamente

aceptables de un compuesto de cualquiera de las reivindicaciones 1,2,3 o 51 en una cantidad suficiente para tratar o prevenir la enfermedad inflamatoria.

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60. El método de la reivindicación 59, donde dicho sujeto es un humano.

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61. El método de la reivindicación 59, donde dicha enfermedad inflamatoria es una enfermedad inflamatoria de las articulaciones, una enfermedad inflamatoria crónica de la encía, una enfermedad inflamatoria del intestino, una enfermedad inflamatoria de los pulmones, una enfermedad inflamatoria del sistema nervioso central, o una enfermedad inflamatoria del ojo.

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62. El método de la reivindicación 59, lo donde dicha enfermedad inflamatoria es un shock gram-positivo, gram- negativo, un shock hemorrágico, un shock anafiláctico, un shock traumático y un shock quimioterapéutico.

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63. Un método para tratar o prevenir una enfermedad de reperfusion en un sujeto, que comprende la administración a un sujeto con necesidad del mismo del compuesto o sal o hidrato farmacéuticamente aceptables de un compuesto de cualquiera de las reivindicaciones 1,2,3 o 51 en una cantidad suficiente para tratar o prevenir la enfermedad de reperfusion.

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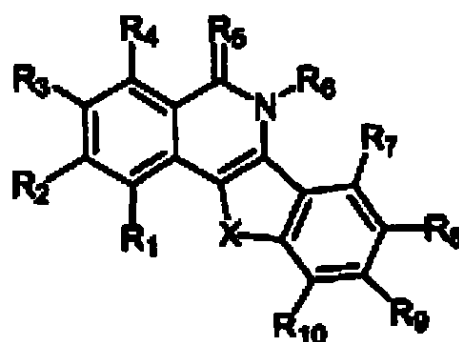
30

64. El método de la reivindicación 63, donde la enfermedad de reperfusión es un infarto del miocardio.
- 5 65. El método de la reivindicación 63, donde la enfermedad de reperfusión es una apoplejía.
66. El método de la reivindicación 63, donde el sujeto es un humano.
- 10 67. Un método para tratar o prevenir diabetes o una complicación diabética en un sujeto, que comprende administrar a un sujeto con necesidad del mismo del compuesto o hidrato o sal farmacéuticamente aceptables de cualquiera de las reivindicaciones
- 15 1,2,3 o 51 en una cantidad suficiente para tratar o prevenir diabetes o la complicación diabética.
68. Un método para tratar o prevenir una lesión de reoxigenación resultante por un trasplante de
- 20 órgano, que comprende la administración a un sujeto con la necesidad del mismo del compuesto o sal o hidratos farmacéuticamente aceptable de cualquiera de las reivindicaciones 1,2,3 o 51 en una cantidad
- 25 suficiente para tratar o prevenir la lesión de reoxigenación.
69. Una composición que comprende un compuesto o su sal o hidrato farmacéuticamente aceptables, de la
- 30 reivindicación 1 y un vehículo farmacéuticamente aceptable.

70. Una composición que comprende un compuesto o su sal o hidrato farmacéuticamente aceptables, de la reivindicación 2 y un vehículo farmacéuticamente aceptable.
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71. Una composición que comprende un compuesto o su sal o hidrato farmacéuticamente aceptables, de la reivindicación 3 y un vehículo farmacéuticamente aceptable.
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72. Una composición que comprende un compuesto o su sal o hidrato farmacéuticamente aceptables, de la reivindicación 51 y un vehículo farmacéuticamente aceptable.
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73. El compuesto o su sal o hidrato farmacéuticamente aceptable de la reivindicación 51, donde R^8 es hidrógeno y R^9 es $-A-B$, o R^8 $-A-B$ y R^9 es hidrógeno.

RESUMEN

5 Esta invención se relaciona con compuestos de indeno [1,2-c] isoquinolina, de fórmula:



(Ia)

Igualmente se describen composiciones farmacéuticas de
10 éstos, y su utilización terapéutica para tratar o
prevenir enfermedades inflamatorias o una enfermedad
reperfusión.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
Indicacion de que solicita el concesio de un patente	()	()
Datos d Identificaci3n del solicitant d l perso que p sent l solicitud	()	()
Descrip i3n de l invenci3n	()	()
Dibujos d lo pertinente	()	()
Co proba te d Pag d la tasa establecida	()	()
COMPLETA ()	INCOMPLETA ()	()

DISEÑO INDUSTRIAL ()		
Id i3n de q oil lta l registro d Di ñ i dustri l	()	()
Dat d de tificaci3n d l licita t d l pers q pres nta l licit d	()	()
Repres taci3n gráfca y fotograf íca d l Di ñ i d tr l m estra del M ter l q incorpora el diseñ	()	()
C mproba t d pag d l tasas establ ida	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()		
Id i3n de q licita el registro d Esquema de trazad	()	()
Datos de Identifi aci3n del solicitante d la persona qu pres nta l licit d	()	()
R p es t ci3n gráfca del quem d trazad	()	()
Comprobante de pag d l tasas establecida	()	()
COMPLETA ()	INCOMPLETA ()	()

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Dependencia 2020 DIVISION DE NUEVAS CREATIVIDADES



2020
Bogotá, D.C.,

Doctor:
DILIA MARIA RODRIGUEZ D'ALEMAN
Apoderado
INOTEK PHARMACEUTICALS CORPORATION

Oficio N° 03492

ASUNTO:	Radicación N°	04-16685
	Solicitud Internacional	PCT/US02/27585
	Fecha Inicio fase nacional	31/03/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

- 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).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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 Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de
fecha 1-2 APR 2004.

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